[*n* + 1] Annulation Route to Highly Substituted Cyclic Ketones with Pendant Ketone, Nitrile, and Ester Functionality

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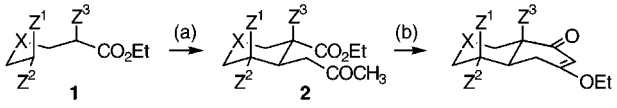
Two carbon acids connected by a tether containing a ketone undergo two Michael reactions to 3-butyn-2-one to afford highly substituted and functionalized cyclic ketones with pendant ketone, nitrile, and ester functionality. The stereochemical courses of the double Michael reactions vary remarkably with the structure of the starting material. Double Michael adducts with equatorially disposed cyano groups can be hydrogenated to afford trans-fused bicyclic amines.

The stereoselective assembly of complex architectures from simple ones in just a few steps and in good yield remains a challenging goal in organic synthesis.[1,2] We have recently shown that tethered carbon acids **1** containing at least one CN group undergo a double Michael reaction[3−6] with 3-butyn-2-one, formally an [*n* + 1] annulation, to give functionalized cycloalkanes **2** containing two new quaternary centers (Scheme 1).[7] Compound **2** can then undergo a Dieckmann reaction to give a *trans*-decalin or hydrindane or, when Z^2 = CN, can be hydrogenated to a *trans*-perhydroisoquinoline. We have already described double Michael reactions using tethered carbon acids bearing only CN and CO_2Et groups and an unfunctionalized tether. In this paper, we describe the double Michael reactions of tethered carbon acids in which one of the acidifying groups, a ketone, is contained in the tether.

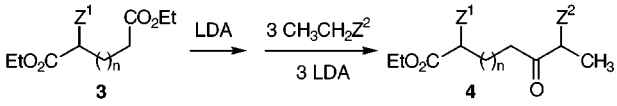
The requisite starting materials **4a**−**e** are prepared in moderate to excellent yield by mixed Claisen condensations of **3a**−**d**[8−11] with the enolate of propionitrile or ethyl propionate (Scheme 2).[12] Prior deprotonation of the most acidic carbon of **3** ensures that only its isolated CO_2Et group is subject to nucleophilic attack. Three equivalents of the nucleophile are required because the first equivalent undergoes Claisen condensation to give **4**, the second equivalent deprotonates **4**, and the third equivalent undergoes a Thorpe or Claisen reaction with the neutralized second equivalent to give 2-cyano-3-pentanone or ethyl 2-methyl-3-oxopentanoate. This byproduct is easily separated from **4** by distillation. After the effort required to develop high-yielding syntheses of **1**,[13] the swift preparation of **4a**−**e** using established methodology has been very gratifying.

Scheme 1[a]



[a] Z = CN or CO_2Et; X = CH_2 or nothing. (a) HC≡CCOCH$_3$, catalytic NaH or *t*-BuOK. (b) NaOEt; EtOH, TsOH.

Scheme 2



3	Z^1	n
a	CN	1
b	CO_2Et	1
c	CN	0
d	CO_2Et	0

4	Z^1	Z^2	n	yield
a	CN	CN	1	86%
b	CO_2Et	CN	1	85%
c	CN	CO_2Et	1	50%
d	CN	CN	0	63%
e	CO_2Et	CN	0	61%

We initially tried to catalyze the double Michael additions of **4** to 3-butyn-2-one with bases such as NaH, Et_3N, Cs_2CO_3, Hünig's base, and pyridine. Either products derived from addition of deprotonated 3-butyn-2-one to the tethered carbon acid were obtained along with small amounts of double Michael adducts, or starting material was recovered unchanged. Our attention was then drawn to Ph_3P, which had been found to efficiently catalyze Michael additions of α-cyanoester nucleophiles.[14]

When **4a**, **4d**, or **4e** is combined with 3-butyn-2-one and 10% Ph_3P in CH_3CN at room temperature, the double Michael reaction occurs smoothly (Table 1). The reaction of **4a** and 3-butyn-2-one gives all four possible diastereomers (17:5:2:1 dr by GC−MS) in 83% combined yield. The dr is not improved when the reaction is executed at lower temperature. The major isomer, **5a**, can be isolated

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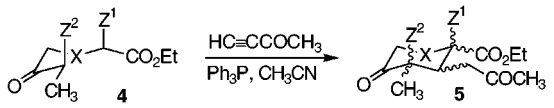
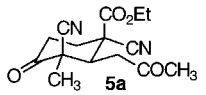
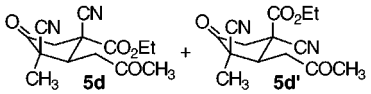
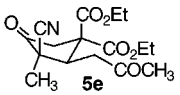
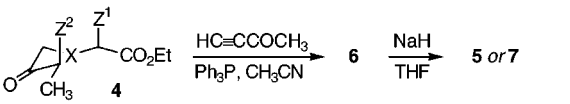
Table 1

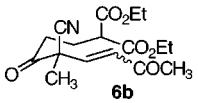
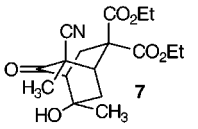
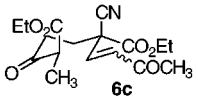
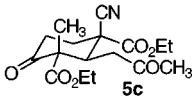


4	Major product 5	dr[a]	Yield[b]
a		17:5:2:1	34% (pure **5a**), 83% (mixture)
d			30% (**5d**), 25% (**5d′**)
e		4:1	46%

[a] Determined by GC−MS of the crude reaction mixture. [b] Isolated yield of the major isomer in >95% purity.

Table 2



4	Product of first Michael reaction	Yield[a]	Product of second Michael reaction	Yield[b]
b		74%		38%
c		63%		59-69%

[a] Isolated yield of the diastereomeric mixture. [b] Isolated yield of the major isomer in >95% purity.

in pure form in 34% yield. X-ray crystallographic analysis of **5a** shows that only one CN group is axial, which is rather surprising. By contrast, the double Michael reaction of **4d** provides nearly equal amounts of only two diastereomers, **5d** and **5d′**, in 30% and 25% yields, respectively. X-ray crystallographic analysis of **5d** shows that the CN and acetonyl groups are all cis. We have been unable to solve the X-ray structure of **5d′**, but its NOESY spectrum shows that the ring Me and methine H are cis, establishing that **5d′** differs from **5d** only in the stereochemistry of the α-cyanoester group. Meanwhile, the double Michael reaction of **4e** affords a 4:1 mixture of two cyclopentanones, from which the major isomer **5e** is isolated in 46% yield. Clearly the proximity of the ketone to the malonate group in **4e** increases the acidity of the latter sufficiently that it can react under Ph_3P catalysis, as its homolog **4b** undergoes only a single Michael addition to 3-butyn-2-one under Ph_3P catalysis (vide infra). X-ray crystallographic analysis of **5e** shows that the CN and acetonyl groups are cis, as expected.

When **4b** and **4c** are treated with 3-butyn-2-one and catalytic Ph_3P, "mono-Michael adducts" **6b** and **6c** are obtained as diastereomeric mixtures in 74% and 63% yields, respectively (Table 2). Upon treatment of the inseparable mixture of (*E*)- and (*Z*)-**6b** with a catalytic amount of NaH, highly functionalized bicyclo[2.2.2]-octanone **7** is obtained as a single stereoisomer in 38% yield, along with 3% of a monocyclic compound (Figure 1). The structure and stereochemistry of **7** have been established by X-ray crystallographic analysis. The formation of **7** by an intramolecular aldol condensation requires that nascent double Michael adduct **5b** has an axial acetonyl group, a very surprising result. Less surprisingly, **5b** must also have an axial CN group. The high acidity of the α-cyanoketone moiety of **5b** may contribute to the facility of the intramolecular aldol reaction. By contrast, (*E*)- and (*Z*)-**6c** are separable, and both undergo intramolecular Michael addition under NaH catalysis to give the same double Michael adduct **5c** as a single stereoisomer in 59% and 69% yields, respectively (Figure 2). X-ray crystallography shows that **5c** has axial CN and Me groups. The Me group is undoubtedly placed in the axial position because the carbonyl O atoms of the β-ketoester moiety of the enolate of **6c** have to be oriented in the same direction so that they can chelate the Na^+ counterion.

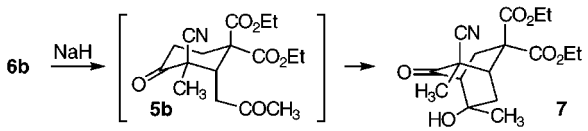


Figure 1.

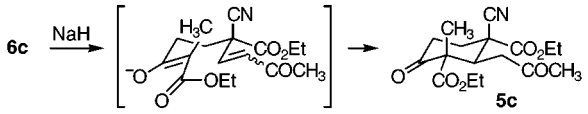
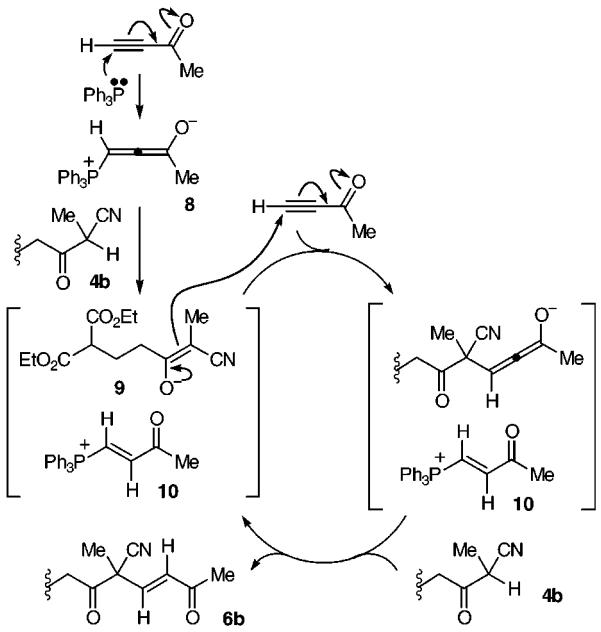


Figure 2.

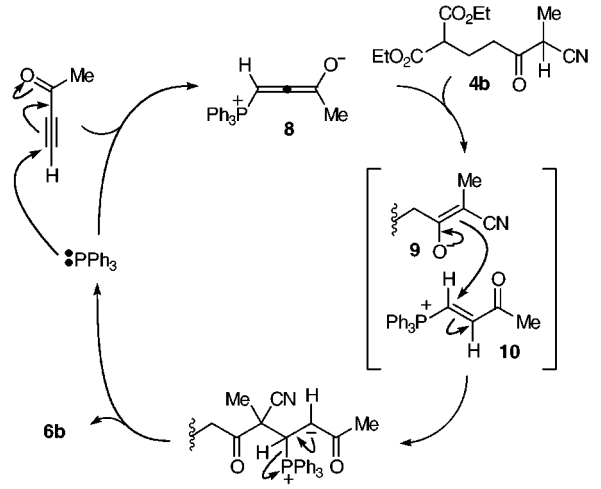
In light of the fact that tethered carbon acids **1** undergo double Michael reactions with good (and readily understood) stereoselectivity,[7] why do tethered carbon acids **4** show such diverse stereochemical results in their double Michael reactions? We believe that compounds **5** are formed irreversibly and under kinetic control, because the nonbasic or weakly basic conditions under which they are prepared should not promote retro-Michael reactions, and no evidence for such reactions has been observed. If this is the case, then the strength of 1,3-diaxial interactions in the TS for the second Michael reaction of **4** controls the stereoselectivity of the double Michael reaction. The ketone in the tether of **4** reduces the steric encumbrance to an axial acetonyl group in the TS of the second Michael reaction, creating a much finer kinetic balance among the different diastereomeric TSs. Weak stereoselectivities that are difficult to rationalize are observed as a result.

Two reasonable mechanisms can be drawn for the Ph_3P-catalyzed Michael reactions. Consider the Ph_3P-catalyzed reaction of **4b** with 3-butyn-2-one to give **6b**. The first mechanism begins with conjugate addition of Ph_3P to 3-butyn-2-one to give zwitterion **8** (Scheme 3). Compound **8** then deprotonates the most acidic site of **4b** to give enolate **9** and β-phosphonioenone **10**, the first participants in the catalytic cycle. Enolate **9** undergoes conjugate addition to 3-butyn-2-one, and the nascent dienolate deprotonates another equivalent of **4b** to give **6b** and to regenerate **9**. In this mechanism, β-phosphonioenone **10** serves merely as a counterion for **9**. In the second mechanism, on the other hand, the catalytic cycle begins immediately with conjugate addition of Ph_3P to 3-butyn-2-one to give zwitterion **8**, which then deprotonates **4b** to give enolate **9** and β-phosphonioenone **10**

Scheme 3



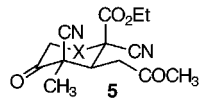
Scheme 4

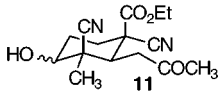
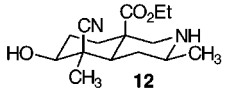
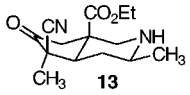


(Scheme 4). Enolate **9** then undergoes an addition−elimination reaction with **10** to give **6b** and to regenerate Ph_3P. In this mechanism, β-phosphonioenone **10** is the actual electrophile with which enolate **9** reacts. Although we have not carried out detailed mechanistic studies, we favor the second mechanism for the following reasons. If zwitterion **8** is acting merely as a base, it is difficult to understand why the product distribution obtained from reactions catalyzed by Ph_3P is so different from that obtained from reactions catalyzed by bases such as Et_3N and NaH. Furthermore, the inductive effect of the phosphonio group should make **10** more electrophilic than 3-butyn-2-one. Experiments to exclude either mechanism conclusively are underway.

The double Michael adducts **5** are potentially useful starting materials for a range of mono- and bicyclic compounds. The ring ketone of **5a** is selectively hydrogenated over PtO_2 in slightly acidic EtOAc, affording alcohol **11** in 73% yield and ca. 1:1 dr (Table 3). When the catalyst and solvent are changed to Pd/C in AcOH, the equatorial CN group of **5a** undergoes reduction to the amine, which subsequently undergoes intramolecular reductive alkylation. The axial CN group remains unchanged under these conditions, but the ring ketone is partly reduced to give an inseparable mixture of ketone and alcohol products. Further hydrogenation over PtO_2 cleanly affords *trans*-perhydroisoquinolinol **12** in 60% yield. The axial orientations of the new methine H atoms in the major diastereomer of **12** are indicated by the coupling constants in the ^{1}H NMR spectrum, and the IR spectrum indicates that the equatorial CN group of **5a** is reduced.[15] The inertness of the axial CN group of **5a** is consistent with what we have observed previously.[7] Compound **12** is contaminated with a small amount (ca. 6%) of a compound that appears to be the lactone derived from **12**: 1 equiv of EtOH with respect to the impurity is also observed, and a small IR absorbance at 1755 cm^{-1} is seen.

Table 3



Double Michael adducts	Conditions	Major product	Yield[a]
5a	H_2, PtO_2, 10:1 EtOAc:AcOH	 **11**	73%
5a	H_2, Pd/C, AcOH; H_2, PtO_2, 10:1 EtOAc:AcOH	 **12**	60%
5d'	H_2, Pd/C, AcOH	 **13**	74%

[a] Isolated yield of the major isomer in >95% purity.

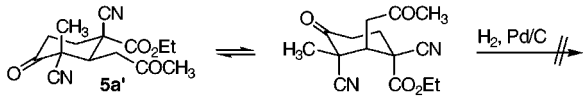


Figure 3.

Certain *trans*-perhydroisoquinolines with quaternary centers at C5 and C8a are potent inhibitors of 2,3-oxidosqualene cyclase.[16−19] Only a handful of these compounds have been prepared, and none have the level of substitution and functionality of **12**.

The three diastereomers of **5a** are not reduced under the conditions under which **5a** is reduced, even though one of them must have an equatorial CN group. This isomer, **5a′**, may prefer to exist in a conformation in which the equatorial CN group is cis to a sterically encumbering axial acetonyl group (Figure 3).

Cyclopentanone **5d′** is also hydrogenated to *trans*-perhydro-5-azaindanone **13** as a single regio- and stereoisomer in 74% yield (Table 3). No reduction of the ring ketone is observed in this case. Again, the axial orienta-

(15) The carbonyl IR absorbances of **12** (1714 cm^{-1}) and **13** (1762, 1721 cm^{-1}) are most consistent with products that do not retain an α-cyanoester moiety.

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tion of the new methine H in **13** is indicated by the coupling constants in the ^{1}H NMR spectrum, and the IR spectrum indicates that the pseudoequatorial CN group of **5d′** is reduced,[15] as expected.[7] A Beilstein search reveals no *trans*-perhydro-5-azaindanones with the substitution pattern of **13** in the literature. Compound **13** is contaminated with a small amount (ca. 10%) of a compound that appears to be derived from reduction of the CN group of **13** and crossannular lactamization: three isolated AB pairs are observed in the ^{1}H NMR spectrum, and an IR absorbance at 1670 cm^{-1} is also seen. It is not terribly surprising that reduction of a pseudoaxial CN group can occur in the more flexible cyclopentane system.

In conclusion, we have extended the double Michael and double annulation reactions to tethered carbon acids that have a ketone group in the tether. Our method is distinguished by the ready availability of the starting materials, inexpensive and environmentally friendly reagents used in catalytic amounts, experimental simplicity, and atom economy (the only byproduct is H_2O); its stereochemical temperamentality is an obvious drawback. We have shown that the dense functionalization of the double Michael adducts **5** does not prevent selective transformation of certain groups in these compounds. In future papers we will describe the double annulations of nucleophiles with other acidifying groups and of electrophiles other than 3-butyn-2-one. We are also exploring ways of transforming the highly substituted and functionalized double annulation products into biologically active natural products.

Experimental Section

General Procedure for Mixed Claisen Condensation. *n*-Butyllithium (3 equiv) was added to a solution of *i*-Pr$_2$NH (3 equiv) in dry THF (0.3 M) at 0 °C under N_2. The solution was allowed to stir for 30 min, and then it was cooled to −78 °C. Propionitrile or ethyl propionate (3 equiv) was added, and the solution was allowed to stir for 30 min more. Ester **3** (1 equiv) was added to LDA (1 equiv, prepared as above) at −78 °C and allowed to stir for 30 min. This solution was then added to the first solution by cannula. The reaction mixture was allowed to warm to room temperature. The reaction was quenched with 6 N HCl and extracted with ether. The ether layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The product was purified by Kugelrohr distillation.

Ethyl 2,6-Dicyano-5-oxopentanoate (4a). The general procedure was followed using propionitrile and diethyl 2-cyanoglutarate (**3a**) (8.52 g, 40.0 mmol) to afford **4a** (7.32 g, 34.4 mmol, 86% yield) as a colorless oil, 99% pure by GC−MS. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.28 (q, 7.2 Hz, 2H), 3.70 (m, 1H), 3.54 and 3.52 (two q, 7.3 Hz each, 1H total), 2.99 (m, 2H), 2.31 (m, 2H), 1.53 (d, 7.3 Hz, 3H), 1.34 (t, 6.9 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 13.8, 13.9, 14.0, 23.1, 35.9, 36.6, 37.7, 37.8, 63.1, 115.9, 117.8, 165.5, 199.5. IR (neat): 2249, 1731, 1454, 1375, 1258 cm^{-1}. $C_{11}H_{14}N_2O_3$.

Diethyl 5-Cyano-4-oxohexane-1,1-dicarboxylate (4b). The general procedure was followed using propionitrile and triethyl 1,1,3-propanetricarboxylate (**3b**) (3.90 g, 15.0 mmol) to afford **4b** (3.46 g, 12.8 mmol, 85% yield) as a colorless oil, 99% pure by GC−MS. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.21 (q, 7.0 Hz, 4H), 3.49 (q, 7.4 Hz, 1H), 3.41 (t, J = 7.4 Hz, 1H), 2.85 (m, 2H), 2.21 (q, 7.0 Hz, 2H), 1.50 (d, 7.4 Hz, 3H), 1.28 (t, 7.4 Hz, 6H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 13.9, 22.0, 37.4, 50.1, 61.6, 200.0, 168.9, 118.0. IR (neat): 2248, 1731, 1448, 1371 cm^{-1}. $C_{13}H_{19}NO_5$.

Diethyl 2-Cyano-6-methyl-5-oxopimelate (4c). The general procedure was followed using ethyl propionate and diethyl 2-cyanoglutarate (**3a**) (4.47 g, 21.0 mmol) to afford **4c** (2.79 g, 10.4 mmol, 50% yield) as a colorless oil, 99% pure by GC−MS. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.24 (m, 4H), 3.69 (m, 1H), 3.56 and 3.54 (two q, 7.1 Hz each, 1H total), 2.85 (m, 2H), 2.10 (m, 2H), 1.35 (d, 7.0 Hz; 3H), 1.33 (t, 7.2 Hz, 3H), 1.28 (t, 7.2 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 204.0, 203.9, 170.0, 165.6, 116.0, 62.7, 61.4, 61.3, 52.5, 52.4, 37.5, 37.3, 36.0, 23.2, 13.7, 12.4, 12.3. IR (neat): 2250, 1742, 1718, 1451, 1371, 1256 cm^{-1}. $C_{13}H_{19}NO_5$·

Ethyl 2,5-Dicyano-4-oxohexanoate (4d). The general procedure was followed using propionitrile and diethyl 2-cyanosuccinate (**3c**) (1.99 g, 10.0 mmol) to afford **4d** (1.31 g, 6.29 mmol, 63% yield) as a colorless oil, 99% pure by GC−MS. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.30 (q, 6.9 Hz, 1H), 4.29 (q, 7.2 Hz, 1H), 4.01 (m, 1H), 4.43 (m, 3H), 1.58, 1.57, 1.56 and 1.54 (four s, 3H total), 1.35 and 1.35 (two t, 7.2 Hz each, 3H total). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 196.7, 196.6, 164.7, 164.6, 117.3, 115.3, 63.6, 39.1, 39.0, 37.6, 37.5, 31.6, 31.5, 13.8, 13.7, 13.6. IR (neat): 2250, 1739, 1453, 1370 cm^{-1}. $C_{10}H_{12}N_2O_3$.

Diethyl 4-Cyano-3-oxopentane-1,1-dicarboxylate (4e). The general procedure was followed using propionitrile and triethyl 1,1,3-ethanetricarboxylate (**3d**) (2.46 g, 10.0 mmol) to afford **4e** (1.56 g, 6.11 mmol, 61% yield) as a colorless oil, 99% pure by GC−MS. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.22 (q, 7.2 Hz, 2H), 4.21 (q, 7.2 Hz, 2H), 3.89 (t, 7.0 Hz, 1H), 3.61 (q, 7.2 Hz, 1H), 3.28 (d, 7 Hz, 2H), 1.54 (d, 7.4 Hz, 3H), 1.28 (t, 7.4 Hz, 6H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 198.4, 168.2, 168.0, 117.6, 61.9, 46.8, 38.9, 37.7, 13.8, 13.7. IR (neat): 2251, 1734, 1452, 1390 cm^{-1}. $C_{12}H_{17}NO_5$.

General Procedure for the First Michael Addition. To a mixture of Michael donor **4a**−**e** (5.00 mmol) and triphenylphosphine in CH_3CN (15.0 mL) at rt was added 3-butyn-2-one (0.40 mL, 5.10 mmol). The resulting solution was stirred at rt for 10 min. The solvent was removed under vacuum, and the residue was purified by flash chromatography (gradient of 20%, 25%, 30%, and 35% ethyl acetate in petroleum ether as eluant) to give the stated products.

Ethyl (1*R,2*S*,3*S*)-1,3-Dicyano-3-methyl-2-(2-oxopropyl)-4-cyclohexanone-1-carboxylate (5a).** Compound **5a** (487 mg, 1.68 mmol, 34% yield) was obtained from **4a** as a colorless solid, mp 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.38 (m, 2H), 3.31 (dd, 2.9 Hz, 6.6 Hz, 1H), 3.27 (dd, 2.9 Hz, 19.7 Hz, 1H), 3.06 (ddd, 6.2 Hz, 11.1 Hz, 15.9 Hz, 1H), 3.00 (dd, 6.6 Hz, 19.7 Hz, 1H), 2.80 (ddd, 4.6 Hz, 6.2 Hz, 14.0 Hz, 1H), 2.73 (ddd, 4.6 Hz, 6.1 Hz, 15.9 Hz, 1H), 2.34 (ddd, 6.1 Hz, 11.1 Hz, 14.0 Hz, 1H), 2.29 (s, 3H), 1.48 (s, 3H), 1.40 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 203.5, 198.1, 165.5, 117.8, 117.5, 64.2, 49.0, 45.0, 44.3, 43.9, 33.6, 30.9, 29.7, 22.0, 13.0. IR (KBr): 2248, 1735, 1728, 1711 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.24. Found: C, 61.75; H, 6.24. A mixture (20:7:2:1 by GC−MS) of four compounds.with similar retention times and mass spectra was also isolated (710 mg, 2.45 mmol, 49% yield); the least abundant component of this mixture was the title compound.

Diethyl 5-Cyano-5-methyl-6-nonene-4,8-dione-1,1-dicarboxylate (6b). Compound **6b** (1.24 g, 3.68 mmol, 74% yield) was obtained from **4b** as a colorless oil and as an inseparable 1:1 diastereomeric mixture. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.49 and 6.45 (two d, 4.2 Hz, 11.0 Hz, 1H), 6.25 and 5.92 (two d, 4.2 Hz, 11.0 Hz, 1H), 4.22 (m, 4H), 3.15−3.50 (m, 2H), 2.91 (m, 1H), 2.40 and 2.28 (two s, 3H), 2.21 (m, 2H), 1.71 and 1.62 (two s, 3H), 1.29 (t, 6.9 Hz, 6H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 200.9, 200.6, 197.4, 196.9, 169.2, 169.0, 140.3, 129.8, 129.0, 119.4, 118.8, 61.4, 50.3, 50.2, 48.9, 47.2, 35.9, 35.8, 31.0, 30.7, 25.9, 25.5, 22.3, 22.0, 21.0, 13.9. IR (KBr): 2238, 1828, 1730, 1679, 1448, 1370 cm^{-1}. $C_{17}H_{23}NO_6$.

Diethyl *trans*- and *cis*-6-Cyano-7-decene-3,9-dione-2,6-dicarboxylate (*trans*- and *cis*-6c). Compounds *trans*-**6c** (534 mg, 1.59 mmol, 32% yield) and *cis*-**6c** (518 mg, 1.54 mmol, 31% yield) were obtained from **4c** as colorless oils.

Compound *trans*-6c. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.68 (d, 15.7 Hz, 1H), 6.55 (d, 15.7 Hz, 1H), 4.31 (q, 6.9 Hz, 2H), 4.20 (q, 5.1 Hz, 2H), 3.52 (q, 6.9 Hz, 1H), 2.60−2.95 (m, 2H), 2.15−2.50 (m, 2H), 2.32 (s, 3H), 1.30 (m, 9H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 203.0, 196.2, 170.0, 165.8, 137.8, 132.5,

115.9, 63.9, 61.6, 52.7, 50.9, 36.6, 30.8; 30.7, 28.4, 13.8, 12.5. IR (neat): 2248, 1741, 1725, 1710, 1680, 1628, 1475, 1449 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87. Found: C, 60.30; H, 6.83.

Compound *cis*-6c. ^1H NMR (200 MHz, $CDCl_3$): δ 6.49 (d, 11.3 Hz, 1H), 5.91 (d, 11.7 Hz, 1H), 4.21 (m, 4H), 3.55 (q, 7.3 Hz, 1H), 2.60−3.10 (m, 2H), 2.20−2.50 (m, 2H), 2.30 (s, 3H), 1.30 (m, 9H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 203.4, 197.5, 170.1, 166.5, 137.3, 131.1, 116.5, 62.9, 61.5, 47.0, 46.9, 36.8, 32.8, 30.9, 28.3, 13.9, 13.7. IR (KBr): 2253, 1743, 1726, 1710, 1619, 1449 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87. Found: C, 60.22; H, 6.93.

Ethyl (1*R,2*R*,3*R*)- and (1*R**,2*S*,3*S*)-1,3-Dicyano-3-methyl-2-(2-oxopropyl)-4-cyclopentanone-1-carboxylate (5d and 5d′).** Compounds **5d** (413 mg, 1.50 mmol, 30% yield) and **5d′** (345 mg, 1.25 mmol, 25% yield) were obtained from **4d** as colorless solids.

Compound 5d. Mp 128 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 4.31 (m, 2H), 3.36 (m, 1H), 3.26 (s, 2H), 3.11 (m, 2H), 2.32 (s, 3H), 1.57 (s, 3H), 1.35 (t, 7.1 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 204.1, 201.1, 166.5, 115.8, 115.6, 64.4, 47.8, 47.5, 46.5, 45.8, 42.8, 30.0, 21.6, 13.6. IR (KBr): 2926, 2253, 2238, 1759, 1722, 1372, 1234 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.83. Found: C; 61.12; H, 5.85.

Compound 5d′. Mp 119 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 4.43 (dq, J_d = 7.3 Hz, J_q = 14.3 Hz, 1H), 4.32 (dq, J_d = 7.3 Hz, J_q = 14.3 Hz, 1H), 3.31 (dd, 3.2 Hz, 9.8 Hz, 1H), 3.14 (d, 17.5 Hz, 1H), 3.09 (dd, 3.4 Hz, 18.3 Hz, 1H), 2.98 (d, 17.7 Hz, 1H), 2.93 (dd, 9.8 Hz, 18.4 Hz, 1H), 2.31 (s, 3H), 1.71 (s, 3H), 1.38 (t, 7.1 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 203.7, 201.2, 166.0, 116.7, 64.5, 48.0, 46.5, 46.0, 44.4, 42.2, 30.2, 25.2, 13.6. IR (KBr): 2238, 1770, 1756, 1716, 1378, 1316, 1244, 1200 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.83. Found: C, 60.84; H, 5.85.

Ethyl (2*R,3*R*)-3-Cyano-3-methyl-2-(2-oxopropyl)-4-cyclopentanone-1,1-dicarboxylate (5e).** Compound **5e** (746 mg, 2.31 mmol, 46% yield) was obtained from **4e** as a colorless solid, mp 124 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 4.28 (m, 4H), 3.31 (t, 2.8 Hz, 1H), 3.28 (dd, 2.4 Hz, 5.6 Hz, 1H), 3.09 (d, 18.0 Hz, 1H), 2.88 (dd, 10.0 Hz, 18.8 Hz, 1H), 2.76 (d, 18.0 Hz, 1H), 2.26 (s, 3H), 1.64 (s, 3H), 1.33 (t, 6.8 Hz, 3H), 1.28 (t, 7.2 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 205.0, 203.9, 168.9, 168.8, 117.5, 62.9; 62.4, 56.9, 48.2, 44.9, 43.8, 43.3, 30.1, 24.9, 13.8, 13.6. IR (KBr): 2241, 1767, 1750, 1715, 1468, 1450 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_6$: C; 59.43; H, 6.54. Found: C, 59.38; H, 6.64.

General Procedure for the Second Michael Addition. The enone **6b** or **6c** (5.00 mmol) was dissolved in dry THF (20 mL) under an atmosphere of N_2 and was cooled to −78 °C. A small amount of NaH was added. The reaction was allowed to warm to rt, when it was quenched with 6 N HCl and extracted with ether. The ether layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash chromatography (gradient of 20%, 25%, 30%, and 35% ethyl acetate in petroleum ether as eluant) to afford the stated products.

Diethyl (1*R,4*S*,6*S*,8*R*)-6-Cyano-8-hydroxy-6,8-dimethylbicyclo[2.2.2]octan-5-one-1,1-dicarboxylate (7).** Compound **7** (636 mg, 1.89 mmol, 38% yield) was obtained from **6b** as a white solid, mp 165−166 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 4.24 (m, 4H), 3.25 (t, 2.7 Hz, 1H), 2.95 (dd, 16.1 Hz, 2.9 Hz, 1H), 2.67 (dd, 16.1 Hz, 3.2 Hz, 1H), 2.47 (t, 3.0 Hz, 1H), 2.16 (dd, 16.0 Hz, 3.4 Hz, 1H), 1.88 (dd + br s, 16.1 Hz, 2.3 Hz, 2H), 1.76 (s, 3H), 1.35 (s, 3H), 1.29 (t, 7.1 Hz, 3H), 1.28 (t, 7.1 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 204.6, 169.7, 168.8, 118.9, 70.9, 62.9, 62.6, 55.2, 55.1, 43.3, 42.3, 34.2, 28.9, 25.3, 22.6, 13.8, 13.4. IR (KBr): 3474, 2250, 1740, 1710 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87. Found: C, 60.39; H, 6.72.

Diethyl (1*R,2*S*,3*R*)-1-Cyano-3-methyl-2-(2-oxopropyl)-4-cyclohexanone-1,3-dicarboxylate (5c).** Compound **5c** (991 mg, 2.94 mmol, 59% yield from (*E*)-**6c**; 1.15 g, 3.43 mmol, 69% yield from (*Z*)-**6c**) was obtained as a white solid, mp 86−87 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 4.21 (m, 4H), 3.80 (dd, 7.6 Hz, 3.3 Hz, 1H), 2.96 (dd, 18.0 Hz, 7.7 Hz, 1H), 2.84 (ddd, 5.2 Hz, 5.8 Hz, 17.8 Hz, 1H), 2.68 (ddd, 4.4 Hz, 5.1 Hz, 15.8 Hz, 1H), 2.56 (ddd, 4.2 Hz, 10.0 Hz, 16.8 Hz, 1H), 2.41 (dt, J_t = 5.2; J_d = 5.2 Hz, 1H), 2.36 (dd, 18.0 Hz, 3.4 Hz, 1H); 2.15 (s, 3H), 1.55 (s, 3H), 1.34 (t, 7.1 Hz, 3H), 1.24 (t, 7.1 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 205.2, 203.7, 170.8, 167.6, 118.4, 63.8, 62.1, 60.4, 47.2, 43.1, 40.6, 33.9, 31.0, 29.6; 16.6, 13.8, 13.6. IR (KBr): 2243, 1754, 1732, 1714, 1367 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87. Found: C, 60.55; H, 6.84.

Ethyl (1*R,2*S*,3*S*,4*RS*)-1,3-Dicyano-4-hydroxy-3-methyl-2-(2-oxopropyl)cyclohexane-1-carboxylate (11).** Compound **5a** (70 mg, 0.24 mmol) was dissolved in a 1:10 mixture of acetic acid and ethyl acetate (10.0 mL). PtO_2 (20 mg, 0.08 mmol) was added, and the mixture was hydrogenated in a Parr shaker at 45 psi for 4 d. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated. Purification by flash chromatography (35% ethyl acetate in petroleum ether as eluant) afforded **11** (51 mg, 0.18 mmol, 73% yield) as a 1:1 diastereomeric mixture and as a colorless solid, mp 78 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 4.34 (m, 4H), 3.96 (m, 1H), 3.49 (t, 7.8 Hz, 1H), 3.34 (d and dd superimposed, 2H), 3.25 (d, 19.0 Hz, 1H), 3.04 (dd, 7.5 Hz, 19.5 Hz, 1H), 2.96 (dd, 7.6 Hz, 19.3 Hz, 2H), 2.68 (dt, J_d = 13.7 Hz, J_t = 3.5 Hz, 1H), 2.39 (m, 2H), 2.32 (m, 3H), 2.29 and 2.27 (two s, 6H total), 2.05 (m, 2H), 1.92 (m, 2H), 1.40 and 1.39 (two t, 7.2 Hz each, 6H total), 1.32 and 1.30 (two s, 6H total). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 204.9 and 204.7, 165.9 and 165.4, 120.8 and 119.4, 119.0 and 118.6, 73.8 and 69.8, 63.6 and 63.4, 45.6 and 45.3, 45.1 and 43.6, 43.4 and 42.1, 41.4 and 36.9, 30.8 and 29.6, 28.2, 26.8 and 26.7, 22.5 and 22.1, 13.5. IR (KBr): 3485, 2236, 1731, 1716, 1450, 1421 cm^{-1}. Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.89. Found: C, 61.83; H, 7.13.

Ethyl (1*R,4*S*,6*S*,7*S*,8*S*)-7-Cyano-8-hydroxy-4,7-dimethyl-3-azabicyclo[4.4.0]decane-1-carboxylate (12).** Compound **5a** (200 mg, 0.68 mmol) was dissolved in acetic acid (10 mL), and 5% Pd/C (50 mg) was added. The mixture was hydrogenated in a Parr shaker at 60 psi for 3 d. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated. The crude product was dissolved in a 1:10 mixture of acetic acid and EtOAc (10.0 mL), PtO_2 (40 mg, 0.16 mmol) was added, and the mixture was hydrogenated in a Parr shaker at 60 psi for 24 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated. Purification by flash chromatography (40% MeOH in CH_2Cl_2 as eluant) afforded **12** (116 mg, 0.41 mmol, 60% yield) as a pale yellow glass. ^1H NMR (400 MHz, $CDCl_3$): δ 4.70 (s, 1H), 4.23 (m, 2H), 3.30 (dd, 7.0 Hz, 9.2 Hz, 1H), 3.05 (d, 13.7 Hz, 1H), 2.82 (m, 1H), 2.51 (d, 13.9 Hz, 1H), 2.21 (dt, J_d = 13.2 Hz, J_t = 3.2 Hz, 1H), 1.96 (s + m, 4H), 1.69 (dt, J_d = 13.1 Hz, J_t = 3.5 Hz, 1H), 1.44 (s, 3H), 1.39 (dd, 3.5 Hz, 12.9 Hz, 1H), 1.34 (t, 7.1 Hz, 3H), 1.24 (d, 6.3 Hz, 3H), 1.06 (m, 1H). $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 173.0, 120.4, 75.6, 61.3, 55.5, 51.6, 49.3, 44.1, 43.8, 31.5, 30.0, 29.8, 21.5, 21.3, 13.9. IR (KBr): 3310, 3219, 2236, 1714, 1559, 1447, 1384 cm^{-1}. $C_{15}H_{24}N_2O_3$. A small amount (ca. 6%) of an impurity identified as the lactone derived from **12** is also seen along with 1 equiv of EtOH. ^1H NMR: δ 3.93 (m, 1H), 3.36 (d, 14.3 Hz, 1H), 2.45 (d, 13.9 Hz, 1H), 1.56 (s, 3H), 1.15 (d, 6.4 Hz, 3H). $^{13}C\{H\}$ NMR: δ 176.3, 120.2, 79.4, 51.1, 46.9, 38.3, 26.1, 24.4, 22.4, 21.7, 21.2. IR: 1755 cm^{-1}.

Ethyl (1*R,4*S*,6*S*,7*S*)-7-Cyano-4,7-dimethyl-3-azabicyclo-[4.3.0]nonane-8-one-1-carboxylate (13).** Compound **5d′** (276 mg, 1.00 mmol) was dissolved in acetic acid (10 mL), and 5% Pd/C (50 mg) was added. The mixture was hydrogenated in a Parr shaker at 55 psi for 24 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated. Purification by flash chromatography (50% ethyl acetate in petroleum ether as eluant) afforded **13** (196 mg, 0.74 mmol, 74%) as a thick oil. ^1H NMR (400 MHz, $CDCl_3$): δ 4.32 (dq, J_d = 17.6 Hz, J_q = 6.8 Hz, 1H), 4.13 (dq, J_d = 17.6 Hz, J_q = 6.8 Hz, 1H), 3.58 (d, 13.4 Hz, 1H), 2.86 (m, 1H), 2.83 (d + br s, J_d = 17.2 Hz, 2H), 2.64 (d, 13.4 Hz, 1H), 2.05 (d, 17.2 Hz, 1H), 2.00 (dd, 13.0 Hz, 3.0 Hz, 1H), 1.88 (dt, J_d = 12.8 Hz, J_t = 3.2

Hz, 1H), 1.55 (ddd, partly obscured, 1H), 1.53 (s, 3H), 1.29 (t, 7.2 Hz, 3H), 1.23 (d, 6.4 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 205.4, 172.7, 117.7, 61.8, 56.4, 53.9, 52.1, 47.4, 45.8, 44.8, 31.8, 22.9, 22.0, 13.3. IR (neat): 3339, 2234, 1762, 1721, 1574, 1448, 1412 cm^{-1}. $C_{14}H_{20}N_2O_3$. A small amount (ca. 10%) of a compound derived from reduction of the CN group of **13** and crossannular lactamization is also seen. ^1H NMR: δ 3.93 (d, 12.5 Hz, 1H), 3.22 (d, 11.6 Hz, 1H), 3.11 (dd, 11.5 Hz, 2.0 Hz, 1H), 2.55 (d, 18.4 Hz 1H), 2.48 (d, 12.8 Hz, 1H), 2.18 (d, 18.2 Hz, 1H), 2.00 (s, 1H), 1.93 (dd, 13.2 Hz, 3.6 Hz, 1H), 1.84 (dt, J_d = 13.2 Hz, J_t = 3.0 Hz, 1H), 1.19 (d, 6.4 Hz, 3H), 1.09 (s, 3H). IR: 1670 cm^{-1}.

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Supporting Information Available: X-ray crystallographic information for **5a**, **5c**, **5d**, **5e**, and **7** and ^1H and ^{13}C NMR spectra for **6b**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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