Nitro Compounds in the Double Annulation Route to Trans-Fused Bicyclic Compounds

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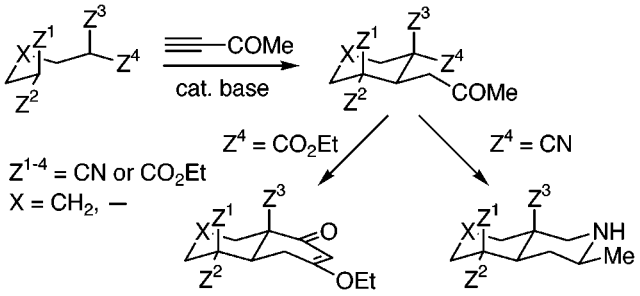
Tethered carbon acids bearing nitro groups undergo a double Michael reaction with 3-butyn-2-one, and the cyclic products thereby obtained can be transformed into trans-fused bicyclic compounds with high levels of substitution and functionality. Three new C−C or C−N bonds, two new rings, two to four new stereocenters, and one or two new quaternary centers are created in this novel *double annulation* of two acyclic, readily available starting materials. Examples of the synthesis of *trans*-decalins, *trans*-hydrindanes, and *trans*-perhydroindoles are presented. Methods for converting the nitro groups in the double Michael and double annulation products into other groups are also described.

The development of methods for assembling complex compounds from simple ones in as few synthetic steps as possible is a continuing theme in organic synthesis. Methods that allow for the formation of multiple C−C bonds efficiently and stereoselectively are especially valuable.[1,2] We have recently reported a novel "double annulation" method for the synthesis of trans-fused bicyclic compounds, especially *trans*-decalins, that meets these criteria.[3] Our method begins with a double Michael reaction[4−6] (formally an [*n* + 1] annulation) of two tethered carbon acids and 3-butyn-2-one to give a cycloalkane with a pendant acetonyl group. The double Michael reaction may be followed by a Dieckmann reaction[7,8] or an intramolecular reductive amination to afford a trans-fused bicyclic compound such as a *trans*-decalin or *trans*-perhydroisoquinoline. Three new C−C or C−N bonds, two new rings, two to four new stereocenters, and one or two new quaternary centers are created from two acyclic, readily available starting materials with nearly perfect atom-economy.



Because α-cyanoesters, which work so well in the double Michael and double annulation reactions,[3] have acidities (EtO_2CCH_2CN: $pK_a = 9$) comparable to those of aliphatic nitro compounds (CH_3NO_2: $pK_a = 10$), we thought that nitro compounds might also be good substrates for these reactions. Such substrates might allow the preparation of some interesting, highly substituted cyclic nitro compounds by the double Michael reaction. Although aliphatic nitro compounds are rarely found among ultimate synthetic targets, their synthetic versatility—they can be reduced to amines, converted to ketones, or replaced with H or radical acceptors[9,10]—makes them valuable synthetic intermediates. We now describe the double Michael reactions and double annulations of nitro-group-containing tethered carbon acids, along with some transformations of the cyclic products.

Results and Discussion

The nitro-containing tethered carbon acids required for the double Michael reaction, **3a**−**c**, are prepared using protecting group methodology that we have reported.[11] The Knoevenagel adduct of ethyl cyanoacetate and 3-pentanone[12] is alkylated with an excess of a 1,3- or 1,4-dibromide in DMF to give a monobromide **1**, and substitution of **1** with $NaNO_2$ affords the monoprotected tethered carbon acid **2**.[13] Deblocking of **2** is then carried out by ozonolysis and acidic alcoholysis (retro-Claisen

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(12) The literature procedure for the preparation of this compound (**i**) uses 3-pentanone (**ii**) and a slight excess of ethyl cyanoacetate (**iii**), but the close boiling points of **i** and **iii** make their separation difficult. When an excess of **ii** is used instead, all of the **iii** is consumed, the excess **ii** is removed upon solvent evaporation, and the distillation of **i** becomes much easier. Cope, A. C.; Hancock, E. M. *Org. Synth., Coll. Vol. III* **1955**, 399.

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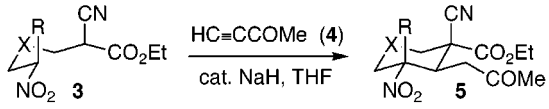
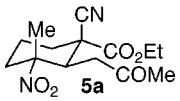
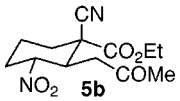
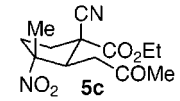
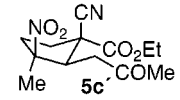
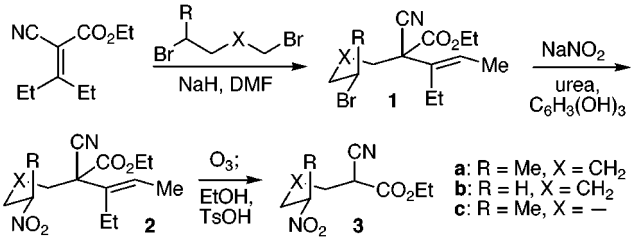
Table 1.



3	5	dr[a]	Yield[b]
a		11:1.5:1	58%
b		26:1	46%
c			37%
			19%

[a] Determined by GC−MS of the crude reaction mixture. [b] Isolated yield of >95% chemically and diastereomerically pure products.

reaction). The ozonolysis does not affect the nitro group. So far we have prepared only **3a**−**c**, but it is not difficult to see that a wide variety of tethered carbon acids can potentially be prepared with this methodology.



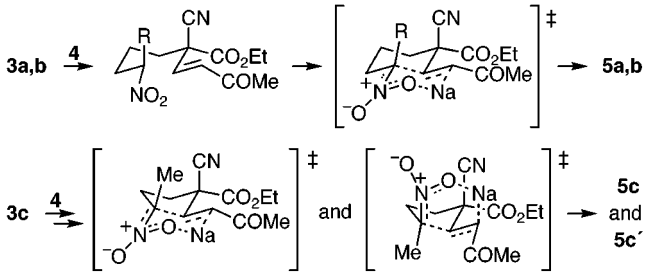
Nitro compounds **3a** and **3b** undergo double Michael addition to 3-butyn-2-one (**4**) under NaH catalysis to give cyclohexanes **5a** and **5b** in 58% and 46% yields, respectively, with good to excellent stereoselectivity (Table 1).[14] Nitro compound **3c** also undergoes double Michael addition to **4** to give cyclopentanes **5c** and **5c′** in 37% and 19% yields, respectively.[14] The stereochemistries of all of the double Michael adducts **5** have been established by X-ray crystallography. The acetonyl and CN groups are cis in compounds **5a**, **5b**, and **5c**, as are the CO_2Et and NO_2 groups, whereas in minor isomer **5c′**, the nitro, acetonyl, and CN groups are all cis. Two new C−C bonds, a new ring, and one or two new quaternary centers are created in these operationally simple, atom-economical reactions.

The stereochemical results are most sensibly explained by the following conjectures.

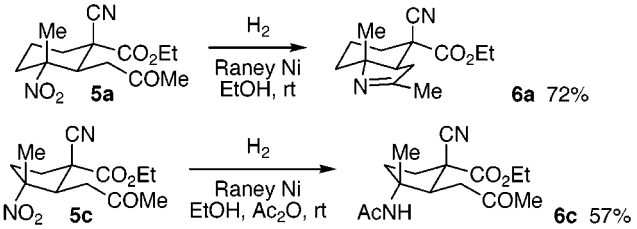
• The double Michael reaction of **3c** is kinetically controlled. Augmented MM2 and semiempirical calculations show that minor isomer **5c′** is much lower in energy than **5c**, and **5c** is isomerized completely to **5c′** with catalytic *t*-BuOK in CH_2Cl_2. Different types of calculations of the relative energies of **5a** and its diastereomers give disparate answers, but by analogy, the double Michael reaction of **3a** is probably kinetically controlled, too. The double Michael reaction of **3b**, on the other hand, is consistent with either kinetic or thermodynamic control, as **5b** is clearly lower in energy than its diastereomers, and it has a low-energy pathway for isomerization of its nitro-substituted stereocenter.

• The α-cyanoester group of **3b** undergoes a Michael addition to **4** before the nitro group does. If the nitro group were to add to **4** first, the nascent, very acidic vinylogous nitroketone would be deprotonated immediately, and the double Michael reaction would stop in its tracks. It seems reasonable to assume that the α-cyanoester groups of **3a** and **3c** also undergo the Michael addition to **4** before their nitro groups do.

• The enone intermediates in the double Michael reactions of **3a** and **3c** undergo the second, intramolecular Michael addition from a bicyclic TS in which the nitronate and enone groups are both coordinated to the Na^+ ion. When a six-membered ring is being formed (**3a**), the *trans*-decalin-like TS is considerably lower in energy than the *cis*-decalin-like TS, and the product (**5a**) with an equatorial NO_2 group is obtained predominantly. When a five-membered ring is being formed (**3c**), the *cis*- and *trans*-hydrindane-like TSs are close in energy, and the products with both axial and equatorial orientations of the NO_2 group (**5c** and **5c′**) are obtained in nearly equal amounts.



Nitro compounds **5** serve as versatile starting materials for the synthesis of a range of mono- and bicyclic compounds. Hydrogenation of **5a** over Raney Ni in EtOH[15] affords *trans*-hexahydroindole **6a** in 72% yield. The C=N π bond of **6a** is unexpectedly not reduced under the reaction conditions. To the best of our knowledge, compound **6a** is the first synthetic *trans*-4,4,7a-trialkylperhydroindole (with or without N−C(2) unsaturation) to be described in the literature. Similarly, hydrogenation of **5c** over Raney Ni in the presence of Ac_2O affords highly substituted acetamide **6c** in 57% yield. Although the hydrogenation of **5c** proceeds in the absence of Ac_2O, the product decomposes upon attempted isolation. However, imine **6a** is obtained from **5a** regardless of whether Ac_2O is present.

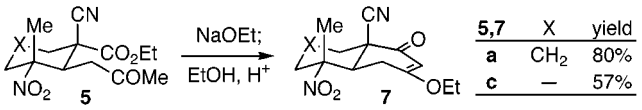


When **5a** or **5c** is heated in absolute EtOH with an excess of NaOEt, a Dieckmann reaction occurs to form a

(14) All yields refer to isolated, diastereomerically pure material.

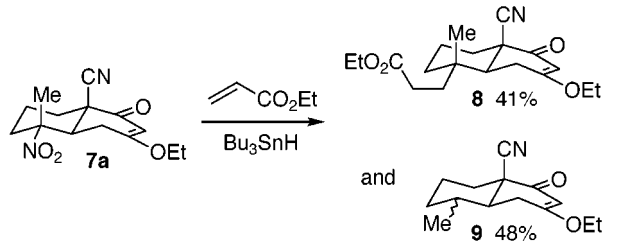
(15) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1998**, *63*, 10052.

new, six-membered ring.[7,8] Treatment of the immediate product with TsOH and EtOH in benzene then affords enol ether **7a** or **7c** in the indicated yields. Assuming that the stereochemistry of the starting materials is preserved in the products,[3] both **7a** and **7c** must have trans ring fusions. This conclusion is confirmed by the large coupling constants (12.1 and 12.4 Hz, respectively) between the methine hydrogens of **7a** and **7c** and their trans vicinal neighbors. The stereochemistry of **7c** is also confirmed by a NOESY experiment. The regiochemistry of enol ether formation is assigned by analogy to known compounds.[3] The good yield of *trans*-hydrindane **7c** is particularly gratifying, as these somewhat strained compounds are not particularly easy to prepare in good yield.[3,16]

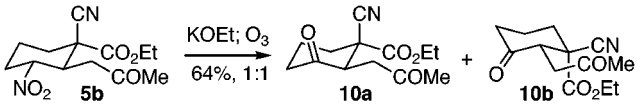


5,7	X	yield
a	CH_2	80%
c	—	57%

The nitro group of **7a** can be replaced with a functionalized alkyl group in another C−C bond-forming reaction by treatment with Bu_3SnH in the presence of an excess of the radical acceptor, ethyl acrylate.[10] Compound **8** is obtained as a >10:1 mixture of diastereomers in 41% yield along with another 48% of the simple reduction product **9** as a ca. 1:1 mixture of two diastereomers. The observation of NOE from the axial allylic H to the CH_3 group in the NOESY spectrum of **8** establishes the axial orientation of the CH_3 group in the major isomer with certainty. The reaction leading to **8** retains the high level of substitution of **7a** while removing all traces of the functionality used to create the quaternary center adjacent to the ring fusion in the double Michael reaction.



Finally, ozonolysis of secondary nitro compound **5b** in EtOK/EtOH affords an inseparable 1:1 mixture of diketones **10a** and **10b** in 64% yield.[17] At first glance, this result may seem surprising, because **3a**−**c** are prepared by ozonolysis, and their nitro groups are not affected. However, **3a**−**c** are prepared by ozonolysis under neutral conditions, whereas **5b** is ozonolyzed as its nitronate. The epimerization of the tertiary carbon of **10a** is facile because the ring ketone reduces the 1,3-diaxial resistance to the axial positioning of the CO_2Et group, as in **10b**.



Conclusion

Easily prepared nitro-containing tethered carbon acids undergo the double Michael reaction to give products that feature two new C−C bonds, one or two new quaternary centers, and multiple functionality with good stereoselectivity. The double Michael adducts are versatile starting materials for the preparation of fused bicyclic compounds such as *trans*-decalins, *trans*-hydrindanes, and *trans*-perhydroindoles by C−C or C−N bond-forming reactions. The nitro group can also be replaced with a functionalized alkyl side chain or converted to a ketone. In this era of higher environmental awareness, the inexpensive and innocuous nature of almost all of the reagents used in this work and the perfect atom-economy of the double Michael reaction should make these procedures very attractive to those working on a large scale. Future papers will describe the use of the double Michael reaction in the preparation of naturally occurring compounds and further extension of the scope of the reaction.

Experimental Section

Standard Alkylation Procedure. Ethyl (3-pentylidene)-cyanoacetate[12] (10−150 mmol) was added slowly to a vigorously stirred solution of clean NaH (1.1 equiv) in dry DMF (20−250 mL) under N_2. (**CAUTION**! Foaming and evolution of flammable H_2 occurs.) The dibromide (10−100 mmol) was added, and the reaction was allowed to stir for 2−12 h at a temperature between 20 and 80 °C. The reaction was quenched with AcOH (ca. 2 mL), and the solvent, excess AcOH, and excess bromide were removed by vacuum distillation. The residue was suspended in ether, and the resulting mixture was extracted four times with water, dried over $MgSO_4$, and evaporated. Excess alkylidene compound was removed by Kugelrohr distillation, and the material that remained (80−90% pure by GC−MS) was purified further by distillation.

Ethyl 8-Bromo-4-cyano-3-ethyl-2-nonene-4-carboxylate (1a). Ethyl (3-pentylidene)cyanoacetate (9.59 mL, 50.0 mmol) was alkylated with 1,4-dibromopentane (7.53 mL, 55.0 mmol). Compound **1a** (13.86 g, 42.0 mmol, 84% yield, 96% pure by GC−MS) was obtained as a colorless liquid and as a mixture of two diastereomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.90 (q, 7.0 Hz, 1H), 4.25 (q, 7.7 Hz, 2H), 4.11 (m, 1H), 2.18 (q, 7.7 Hz, 2H), 2.04 (m, 1H), 1.86 (m, 3H), 1.72 (d, 7.0 Hz, 3H), 1.71 (d, 6.6 Hz, 3H), 1.61 (m, 2H), 1.31 (t, 7.7 Hz, 3H), 1.00 (t, 7.7 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 167.8, 134.9, 125.3, 118.5, 62.8, 55.3, 50.3 and 50.2, 40.5 and 40.4, 34.3 and 34.2, 26.3 and 26.2, 23.6 and 23.5, 20.9, 13.8, 13.6, 13.4. IR (neat): 2233, 1740, 1582, 733 cm^{-1}. $C_{15}H_{24}BrNO_2$.

Ethyl 8-Bromo-4-cyano-3-ethyl-2-octene-4-carboxylate (1b). Ethyl (3-pentylidene)cyanoacetate (7.6 mL, 40 mmol) was alkylated with 1,4-dibromobutane (14.4 mL, 120 mmol). Compound **1b** (9.38 g, 29.6 mmol, 74% yield, 96% pure by GC−MS) was obtained as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.86 (q, 7.0 Hz, 1H), 4.25 (q, 7.0 Hz, 2H), 3.41 (t, 6.6 Hz, 2H), 2.16 (m, 3H), 1.92 (m, 3H), 1.72 (d, 7.0, 3H), 1.61 (m, 2H), 1.31 (t, 7.0 Hz, 3H), 1.00 (t, 7.3 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 167.8, 134.9, 125.3, 118.5, 62.8, 55.3, 34.2, 32.6, 32.2, 23.9, 20.9, 13.8, 13.6, 13.4. IR (neat): 2243, 1743, 1588, 734 cm^{-1}. $C_{14}H_{22}BrNO_2$.

Ethyl 7-Bromo-4-cyano-3-ethyl-2-octene-4-carboxylate (1c). Ethyl (3-pentylidene)cyanoacetate (9.55 mL, 50.0 mmol) was alkylated with 1,3-dibromobutane (7.53 g, 55.0 mmol). Compound **1c** (13.12 g, 41.4 mmol, 82% yield, 95% pure by GC−MS) was obtained as a colorless oil and as a mixture of two diastereomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.88 (overlapping q's, 6.7 Hz, 1H), 4.25 (m, 2H), 4.12 (m, 1H), 2.19 (m, 3H), 1.92 (m, 3H), 1.74 (overlapping d's, 6.7, 6H), 1.31 (t, 7.0 Hz, 3H), 1.02 (t, 7.4 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 167.7 and 167.6, 134.8 and 134.6, 125.7 and 125.5, 118.4, 62.9, 54.8 and 54.7, 50.1 and 49.8, 36.4 and 36.3, 33.4 and 33.3, 26.5 and 26.2, 21.0 and 20.8, 13.8, 13.6, 13.4 and 13.3. IR (neat): 2243, 1742, 1588, 732 cm^{-1}. $C_{14}H_{22}BrNO_2$.

Standard Nitration Procedure.[13] The aliphatic bromide (10−40 mmol) was added to a stirring solution of sodium nitrite (1.8 equiv), urea (2.2 equiv) and phloroglucinol (1.2

(16) Jankowski, P. *Tetrahedron* **1998**, *54*, 12071.
(17) McMurry, J. E.; Melton, J.; Padgett, H. *J. Org. Chem.* **1974**, *39*, 259.

equiv) in DMF (10−100 mL). The reaction was allowed to stir at room temperature for 6−8 h (primary bromide) or 60−72 h (secondary bromide). When the starting material was consumed, the reaction mixture was poured into 10−100 mL of ice water and then extracted three times with ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and evaporated. The product was purified by flash chromatography (6% or 8% EtOAc in petroleum ether as eluant) followed by distillation.

Ethyl 4-Cyano-3-ethyl-8-nitro-2-nonene-4-carboxylate (2a). Compound **2a** (6.33 g, 21.4 mmol, 51% yield, 97% pure by GC−MS) was obtained from **1a** (13.86 g, 42.0 mmol) as a colorless liquid and as a mixture of two diastereomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.85 (q, 6.6 Hz, 1H), 4.59 (m, 1H), 4.24 (q, 7.0 Hz, 2H), 2.11 (m, 3H), 1.84 (m, 3H), 1.72 (d, 6.6 Hz, 3H), 1.54 (d, 6.6 Hz, 3H), 1.45 (m, 2H), 1.30 (t, 7.0 Hz, 3H), 0.99 (t, 7.3 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 167.6, 134.7 and 134.6, 125.5 and 125.4, 118.3, 82.9 and 82.7, 62.9, 55.1, 34.4 and 34.3, 21.6 and 21.5, 20.8 and 20.8, 19.1, 18.9, 13.7, 13.6, 13.3. IR (neat): 2238, 1740, 1552, 1391 cm^{-1}. $C_{15}H_{24}N_2O_4$.

Ethyl 4-Cyano-3-ethyl-8-nitro-2-octene-4-carboxylate (2b). Compound **2b** (13.1 g, 46.3 mmol, 55% yield, 99% pure by GC−MS) was obtained from **1b** (26.7 g, 84.2 mmol) as a colorless liquid and as a mixture of two diastereomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.85 (q, 6.9 Hz, 1H), 4.40 (t, 7.3 Hz, 2H), 4.24 (q, 7.0 Hz, 2H), 2.16 (m, 4H), 1.86 (m, 2H), 1.72 (d, 7.0 Hz, 3H), 1.51 (m, 2H), 1.31 (t, 7.3 Hz, 3H), 1.00 (t, 7.7 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 167.6, 134.7, 125.6, 118.3, 74.9, 62.9, 55.1, 34.3, 26.8, 22.2, 20.8, 13.8, 13.6, 13.4. IR (neat): 2238, 1749, 1550, 1376 cm^{-1}. $C_{14}H_{22}N_2O_4$.

Ethyl 4-Cyano-3-ethyl-7-nitro-2-octene-4-carboxylate (2c). Compound **2c** (5.96 g, 21.1 mmol, 53% yield, 99% pure by GC−MS) was obtained from **1c** (12.50 g, 39.4 mmol) as a colorless liquid and as a mixture of two diastereomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.86 and 5.85 (overlapping q's, 7.0 Hz, 1H), 4.60 (m, 1H), 4.25 and 4.26 (overlapping q's, 7.0 Hz, 2H), 2.16 (m, 4H), 1.92 (m, 2H), 1.73 and 1.72 (overlapping d's, 7.0 Hz, 3H), 1.58 (d, 6.6 Hz, 3H), 1.32 and 1.31 (overlapping t's, 7.0 Hz, 3H), 0.99 and 0.98 (overlapping t's, 7.6 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 167.3 and 167.1, 134.5 and 134.2, 126.0 and 125.8, 118.0 and 117.9, 82.8 and 82.7, 63.1, 54.8 and 54.7, 31.1, 30.6 and 30.5, 20.9 and 20.7, 19.4 and 19.0, 13.7, 13.6, 13.3 and 13.2. IR (neat): 2243, 1742, 1552, 1357 cm^{-1}. $C_{14}H_{22}N_2O_4$.

Ethyl 2-Cyano-6-nitroheptanoate (3a). Ozonolysis and acidic alcoholysis[11] of **2a** (417 mg, 1.40 mmol) followed by distillation afforded **3a** (252 mg, 1.10 mmol, 78% yield, 99% pure by GC−MS) as a colorless oil and as a mixture of two diastereomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.58 (m, 1H), 4.28 (q, 7.3 Hz, 2H), 3.52 (t, 8.1 Hz, 1H), 2.02 (m, 3H), 1.82 (m, 1H), 1.59 (m, 2H), 1.56 (d, 7.0 Hz, 3H), 1.33 (t, 7.3 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 165.7, 116.1, 82.8 and 82.7, 63.0, 37.1 and 37.0, 34.0 and 33.9, 28.9 and 28.8, 23.0 and 22.9, 19.1 and 19.0, 13.8. IR (neat): 2248, 1747, 1560, 1386 cm^{-1}. $C_{10}H_{16}N_2O_4$.

Ethyl 2-Cyano-6-nitrohexanoate (3b). Ozonolysis and acidic alcoholysis[11] of **2b** (2.20 g, 7.80 mmol) followed by flash chromatography (10% EtOAc in petroleum ether as eluant) and by distillation afforded **3b** (1.33 g, 6.21 mmol, 80% yield, 99% pure by GC−MS) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.43 (t, 6.5 Hz, 2H), 4.28 (q, 7.3 Hz, 2H), 3.59 (t, 7.0 Hz, 1H), 2.09 (m, 4H), 1.61 (m, 2H), 1.33 (t, 7.3 Hz, 3H). ^{13}C-{H} NMR (50 MHz, $CDCl_3$): δ 165.7, 116.1, 74.8, 63.0, 37.1, 28.8, 26.4, 23.5, 13.9. IR (neat): 2251, 1743, 1552, 1376 cm^{-1}. $C_9H_{14}N_2O_4$.

Ethyl 2-Cyano-5-nitrohexanoate (3c). Ozonolysis and acidic alcoholysis[11] of **2c** (4.82 g, 17.1 mmol) followed by flash chromatography (6% EtOAc in petroleum ether as eluant) and distillation afforded **3c** (3.01 g, 14.0 mmol, 82% yield, 98% pure by GC−MS) as a colorless liquid and as a mixture of two diastereomers. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.61 (m, 1H), 4.28 (q, 6.0 Hz, 2H), 3.60 (m, 1H), 2.18 (m, 1H), 2.01 (m, 3H), 1.60 (d, 6.6 Hz, 3H), 1.33 (t, 6.0 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 165.3 and 165.2, 115.7, 82.4 and 82.2, 63.1, 36.7 and 36.6, 31.6 and 31.4, 25.7 and 25.5, 19.1 and 19.0, 13.8. IR (neat): 2248, 1747, 1556, 1363 cm^{-1}. $C_9H_{14}N_2O_4$.

Standard Procedure for the Double Michael Reaction. Compound **3** was dissolved in freshly distilled THF (0.25 M), and NaH (0.1−0.2 equiv) was added. The flask was cooled to −78 °C. A solution of 3-butyn-2-one (1.05 equiv) in THF (1.0 M) was added slowly to the reaction mixture. The reaction was allowed to warm to room temperature. The progress of the reaction was monitored by GC; it was usually complete within 1 hr. The solvent was evaporated, and the residue was taken up in ether. This solution was shaken once with saturated aqueous NH_4Cl and then twice with water. The aqueous layers were combined and back-extracted twice with ether. The organic layers were combined, shaken once with brine, and allowed to dry over $MgSO_4$. The product was purified by flash chromatography (20%, then 25% EtOAc in petroleum ether as eluant) and recrystallized from hot EtOH.

Ethyl (1*R,2*S*,3*S*)-1-Cyano-3-methyl-3-nitro-2-(2-oxopropyl)-1-cyclohexanecarboxylate (5a).** Compound **5a** (1.38 g, 4.66 mmol, 58% yield) was obtained from **3a** (2.06 g, 9.03 mmol) as a white solid, mp 102−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.16 (m, 2H), 3.59 (dd, 7.7 Hz, 2.6 Hz, 1H), 2.83 (dd, 17.9 Hz, 7.7 Hz, 1H), 2.43 (dd, 17.9 Hz, 2.6 Hz, 1H), 2.21 (m, 3H), 2.14 (s, 3H), 2.13 (m, 1H), 2.00 (m, 1H), 1.83 (s, 3H), 1.80 (m, 1H), 1.33 (t, 7.2 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 203.3, 167.3, 118.3, 91.5, 63.9, 50.1, 42.7, 40.6, 37.5, 33.0, 29.3, 19.2, 18.3, 13.7. IR (KBr): 2238, 1755, 1725, 1551, 1356 cm^{-1}. Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.74; H, 6.80. Found: C, 56.60; H, 6.97.

Ethyl (1*R,2*S*,3*S*)-1-Cyano-3-nitro-2-(2-oxopropyl)-1-cyclohexanecarboxylate (5b).** Compound **5b** (547 mg, 1.95 mmol, 46% yield) was obtained from **3b** (872 mg, 4.07 mmol) as a white solid, mp 89−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.53 (dt, J_d = 12.0 Hz, J_t = 4.4 Hz, 1H), 4.23 (dq, J_d = 10.8 Hz, J_q = 7.2 Hz, 1H), 4.20 (dq, J_d = 10.8 Hz, J_q = 7.2 Hz, 1H), 3.27 (ddd, 12.0 Hz, 6.0 Hz, 4.4 Hz, 1H), 2.76 (dd, 18.4 Hz, 6.0 Hz, 1H), 2.63 (dd, 18.4 Hz, 4.4 Hz, 1H), 2.36 (m, 1H), 2.19 (m, 1H), 2.13 (s, 3H), 2.10 (m,1H), 2.07 (m, 1H), 2.04 (m, 1H), 1.82 (m, 1H), 1.32 (t, 7.2 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 203.0, 166.8, 116.7, 87.0, 63.7, 51.2, 43.8, 39.2, 32.5, 30.3, 29.5, 20.2, 13.7. IR (KBr): 2239, 1733, 1715, 1558, 1354 cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43. Found: C, 54.93; H, 6.29.

Ethyl (1*R,2*S*,3*S*)- and (1*R**,2*S*,3*R*)-1-Cyano-3-methyl-3-nitro-2-(2-oxopropyl)-1-cyclopentanecarboxylate (5c and 5c′).** Compounds **5c** (536 mg, 1.90 mmol, 37% yield) and **5c′** (283 mg, 1.00 mmol, 19% yield) were obtained from **3c** (1.11 g, 5.18 mmol) as white solids. Compound **5c**: mp 87−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 (q, 7.2 Hz, 2H), 3.81 (dd, 9.7 Hz, 6.2 Hz, 1H), 2.96 (dd, 18.8 Hz, 6.2 Hz, 1H), 2.92 (dd, 18.8 Hz, 9.7 Hz, 1H), 2.77 (ddd, 14.0 Hz, 8.2 Hz, 6.6 Hz, 1H), 2.57 (dt, 13.6 Hz, 8.2 Hz, 1H), 2.45 (ddd, 13.6 Hz, 7.1 Hz, 6.6 Hz, 1H), 2.22 (s, 3H), 2.20 (ddd, 14.0 Hz, 7.1 Hz, 8.2 Hz, 1H), 1.66 (s, 3H), 1.36 (t, 7.2 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 204.8, 167.8, 117.8, 93.2, 69.5, 52.2, 49.2, 41.4, 38.2, 34.8, 29.7, 21.7, 13.8. IR (KBr): 2243, 1739, 1712, 1543, 1356 cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.42. Found: C, 55.04; H, 6.60. Compound **5c′**: mp 107−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.35 (dq, J_d = 14.3 Hz, J_q = 7.2 Hz, 1H), 4.33 (dq, J_d = 14.3 Hz, J_q = 7.2 Hz, 1H), 3.27 (dd, 10.6 Hz, 3.4 Hz, 1H), 2.94 (dd, 18.9 Hz, 10.6 Hz, 1H), 2.82 (ddd, 13.8 Hz, 11.9 Hz, 6.6 Hz, 1H), 2.78 (dd, 18.9 Hz, 3.4 Hz, 1H), 2.61 (ddd, 14.7 Hz, 7.7 Hz, 2.6 Hz, 1H), 2.45 (ddd, 13.8 Hz, 8.7 Hz, 2.6 Hz, 1H), 2.23 (s, 3H), 2.20 (ddd, 14.7 Hz, 11.9 Hz, 8.7 Hz, 1H), 1.72 (s, 3H), 1.37 (t, 7.2 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 205.3, 170.2, 117.6, 96.6, 63.5, 51.9, 51.4, 41.4, 38.5, 36.8, 29.8, 23.0, 13.8. IR (KBr): 2243, 1734, 1718, 1537, 1366 cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.42. Found: C, 55.16; H, 6.63.

Ethyl (1*R,2*S*,6*R*)-2-Cyano-6,8-dimethyl-7-azabicyclo-[4.3.0]non-7-ene-2-carboxylate (6a).** Compound **5a** (296 mg, 1.00 mmol) was dissolved in EtOH (ca. 80 mL), and Raney Ni (ca. 300 mg) was added. The mixture was stirred in a Parr bomb under 1400 psi H_2 at room temperature. After completion of the reaction (4 h, GC check), the mixture was filtered

through Celite, rinsed with EtOAc, and the solvent was evaporated. The residue was purified by flash chromatography (gradient of 0%, 10%, 20%, and 50% EtOAc in CH_2Cl_2 as eluant) to afford **6a** (178 mg, 0.72 mmol, 72% yield) as a white solid, mp 48−49 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.27 (q, 7.0 Hz, 2H), 2.58 (ddd, 15.6 Hz, 12.7 Hz, 0.7 Hz, 1H), 2.34 (dd, 15.6 Hz, 6.6 Hz, 1H), 2.31 (dt, J_d = 12.3 Hz, J_t = 2.9 Hz, 1H), 2.13 (dt, J_d = 12.3 Hz, J_t = 3.3 Hz, 1H), 2.05 (s, 3H), 2.07 (dd, 12.7 Hz, 6.6 Hz, 1H), 1.97 (m, 1H), 1.93 (m, 1H), 1.87 (m, 1H), 1.56 (dt, J_t = 12.0 Hz, J_d = 5.0 Hz, 1H), 1.33 (t, 7.0 Hz, 3H), 1.16 (s, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 173.7, 168.7, 118.2, 70.4, 62.9, 50.7, 45.2, 37.3, 36.3, 34.9, 21.0, 20.3, 17.7, 13.9. IR (KBr): 3222, 2243, 1741, 1623 cm^{-1}. Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12. Found: C, 67.76; H, 8.16.

Ethyl (1*R,2*S*,3*S*)-3-Acetamido-1-cyano-3-methyl-2-(2-oxopropyl)-1-cyclopentanecarboxylate (6c).** Prepared from **5c** (100 mg, 0.35 mmol) over Raney Ni (ca. 100 mg) in EtOH (ca. 40 mL) by the procedure used for **6a**, except that acetic anhydride (50 μL, 0.40 mmol) was also added to the reaction mixture. Compound **6c** (59 mg, 0.20 mmol, 57% yield) was obtained as a white solid, mp 66−67 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 (bs, 1H), 4.29 (q, 7.2 Hz, 2H), 3.09 (dd, 8.90 Hz, 5.7 Hz, 1H), 3.08 (dd, 19.3 Hz, 8.9 Hz, 1H), 2.88 (dd, 19.3 Hz, 5.7 Hz, 1H), 2.43 (m, 2H), 2.28 (m, 2H), 2.24 (s, 3H), 1.94 (s, 3H), 1.39 (s, 3H), 1.34 (t, 7.2 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 207.6, 169.9, 168.9, 118.8, 63.1, 61.6, 51.3, 50.0, 41.9, 37.7, 34.9, 29.9, 23.9, 21.5, 13.8. IR (KBr): 3277, 3211, 3088, 2239, 1745, 1710, 1643, 1562 cm^{-1}. Anal. Calcd for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53. Found: C, 61.32; H, 7.54.

Ethyl (1*R,6*S*,7*S*)-4-Ethoxy-7-methyl-7-nitrobicyclo-[4.4.0]dec-3-en-2-one-1-carbonitrile (7a).** Compound **5a** (400 mg, 1.35 mmol) was added to a solution of Na (36 mg, 1.62 mmol) in dry EtOH (6 mL), and the mixture was heated to reflux. After 1 h, all of the starting material had been consumed (TLC). Benzene (ca. 25 mL) and *p*-toluenesulfonic acid monohydrate (361 mg, 1.90 mmol) were added to the reaction mixture. The solution was allowed to reflux overnight while water was azeotropically removed. The solvent was evaporated, and the residue was taken up in ether, shaken twice with saturated aqueous $NaHCO_3$ solution, and shaken twice with water. The aqueous layers were combined and back-extracted twice with ether. All of the organic fractions were combined, shaken with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by by flash chromatography (20% EtOAc in petroleum ether as eluant). Recrystallization from CH_2Cl_2/petroleum ether afforded **7a** (319 mg, 1.15 mmol, 80% yield) as a white solid, mp 97−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40 (d, 1.6 Hz, 1H), 3.97 (m, 2H), 2.95 (dd, 12.1 Hz, 3.6 Hz, 1H), 2.80 (ddd, 17.2 Hz, 12.1 Hz, 1.6 Hz, 1H), 2.57 (dm, 14.0 Hz, 1H), 2.27 (dd, 17.2 Hz, 3.6 Hz, 1H), 2.10 (m, 1H), 2.05 (m, 2H), 1.89 (s, 3H), 1.83 (m, 1H), 1.61 (dt, J_d = 14.0 Hz, J_t = 3.6 Hz, 1H), 1.39 (t, 7.0 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 188.4, 176.5, 117.9, 99.7, 91.0, 65.5, 46.1, 43.9, 38.2, 30.0, 28.9, 19.3, 17.7, 13.9. IR (KBr): 2242, 1734, 1718, 1537, 1366 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.51. Found: C, 60.29; H, 6.56.

Ethyl (1*R,6*S*,7*S*)-4-Ethoxy-7-methyl-7-nitrobicyclo-[4.3.0]dec-3-en-2-one-1-carbonitrile (7c).** Prepared from **5c** (282 mg, 1.00 mmol) by the procedure used for **7a**. Purification by flash chromatography (12% EtOAc in petroleum ether as eluant) afforded **7c** (151 mg, 0.06 mmol, 57% yield) as a white solid, mp 66−67 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40 (d, 1.4 Hz, 1H), 3.99 (q, 7.0 Hz, 2H), 3.05 (dd, 12.4 Hz, 4.3 Hz, 1H), 2.91 (ddd, 17.5 Hz, 12.4 Hz, 4.3 Hz, 1H), 2.94 (ddd, 14.8 Hz, 8.1 Hz, 0.8 Hz, 1H), 2.79 (dd, 17.5 Hz, 4.3 Hz, 1H), 2.43 (ddd, 13.2 Hz, 7.4 Hz, 0.8 Hz, 1H), 2.30 (ddd, 14.8 Hz, 11.4 Hz, 7.4 Hz, 1H), 2.16 (ddd, 13.2 Hz, 11.4 Hz, 8.1 Hz, 1H), 1.87 (s, 3H), 1.41 (t, 7.0 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 188.0, 177.9, 117.5, 100.9, 92.6, 66.0, 51.8, 51.0, 37.0, 29.5, 29.4, 23.9, 13.9. IR (KBr): 2229, 1718, 1683, 1585, 1347 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10. Found: C, 59.19; H, 6.18.

(1*R,6*R*,7*R*)-3-Ethoxy-7-(2-ethoxycarbonylethyl)-7-methylbicyclo[4.4.0]dec-3-en-2-one-1-carbonitrile (8) and (1*R**,6*R*,7*RS*)-3-Ethoxy-7-methylbicyclo[4.4.0]dec-3-en-2-one-1-carbonitrile (9).** Compound **7a** (150 mg, 0.54 mmol) was dissolved in benzene (0.60 mL) and ethyl acrylate (1.30 mL, 12.0 mmol), and AIBN (90 mg, 0.54 mmol) and tributyltin hydride (0.36 mL, 1.38 mmol) were added. The mixture was heated at 80 °C for 10 min. It was then cooled to room temperature and filtered through a silica gel column (5% EtOAc in petroleum ether, then 20% EtOAc). Further purification by flash chromatography (20% EtOAc in petroleum ether as eluant) afforded **8** as a colorless oil (73 mg, 0.22 mmol, 41% yield) and as a >10:1 mixture of diastereomers (^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (d, 1.7 Hz, 1H), 4.12 (q, 7.2 Hz, 2H), 3.85 (q, 7.0 Hz, 2H), 2.74 (ddd, 17.8 Hz, 12.2 Hz, 1.7 Hz, 1H), 2.52 (dd, 17.8 Hz, 3.8 Hz, 1H), 2.48 (dm, 14.1 Hz, 1H), 2.25 (m, 2H), 1.80 (m, 3H), 1.71 (dd, 12.2 Hz, 3.8 Hz, 1H), 1.74 (m, 2H), 1.38 (m, 1H), 1.39 (t, 7.2 Hz, 3H), 1.26 (t, 7.0 Hz, 3H), 1.24 (m, 1H), 1.18 (s, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 190.9, 177.8, 173.6, 119.4, 99.5, 65.0, 60.5, 46.1, 45.6, 37.1, 36.0, 35.7, 30.8, 28.6, 28.2, 18.5, 18.2, 14.0, 13.9. IR (neat): 2224, 1733, 1672, 1606 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16. Found: C, 68.36; H, 8.31. Compound **9** was also isolated as a colorless oil (60 mg, 0.26 mmol, 48% yield) and as a 1:1 mixture of diastereomers (GC−MS). A small amount of one of the diastereomers (**9a**) could be separated from the mixture. Compound **9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.39 (d, 1.5 Hz, 1H), 3.95 (q, 7.2 Hz, 2H), 2.63 (dd, 18.1 Hz, 4.7 Hz, 1H), 2.50 (ddd, 18.1 Hz, 11.5 Hz, 1.5 Hz, 1H), 2.47 (dm, 14.2 Hz, 1H), 1.76 (m, 4H), 1.58 (m, 1H), 1.41 (m, 1H), 1.39 (t, 7.2 Hz, 3H), 1.24 (m, 1H), 0.98 (d, 6.4 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 190.8, 177.1, 118.0, 100.4, 64.9, 48.1, 46.1, 34.1, 33.9, 31.6, 30.3, 22.0, 18.7, 14.0. MS (*m*/*z*, rel intensity): 233 (M^+, 10), 112 (100), 84 (68), 69 (42). Selected data for **9b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (d, 1.7 Hz, 1H), 2.94 (ddd, 17.8 Hz, 12.1 Hz, 1.7 Hz, 1H), 2.25 (dd, 17.8 Hz, 3.6 Hz, 1H), 2.06 (m, 2H), 1.84 (m, 3H), 1.23 (d, 5.3 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 191.3, 177.9, 119.6, 99.8, 64.9, 44.6, 42.4, 32.4, 32.0, 31.8, 31.0, 17.3, 13.9, 13.5. MS (*m*/*z*, rel intensity): 233 (M^+, 8), 112 (100), 84 (70), 69 (42). Mixture of **9a** and **9b**: IR (neat): 2225, 1734, 1670, 1603 cm^{-1}. $C_{14}H_{19}NO_2$.

Ethyl 1-Cyano-2-(2-oxopropyl)-3-cyclohexanone-1-carboxylate (10a and 10b). Potassium *tert*-butoxide (159 mg, 1.42 mmol) was added to a solution of **5a** (400 mg, 1.42 mmol) in absolute ethanol (4 mL) and allowed to stir for 10 min at room temperature to form the nitronate salt. The solution was cooled to −78 °C, and a stream of O_3 was passed through (1 L/min, 80 V). After completion of the reaction (TLC check, 30 min), the reaction mixture was purged with O_2 and then slowly allowed to warm to room temperature. It was then filtered through Celite, washed with ethyl acetate. The filtrate was concentrated, and the crude products were purified by flash chromatography (15% ethyl acetate in petroleum ether as eluant). Recrystallization from CH_2Cl_2/petroleum ether afforded an inseparable 1:1 mixture (^{1}H NMR) of the title compounds **10a** and **10b** as a white solid (228 mg, 0.91 mmol, 64% yield), mp 87−89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31 (m, 4H), 3.59 and 3.37 (ddd, 9.5 Hz, 2.7 Hz, 1.0 Hz and ddd, 9.7 Hz, 2.0 Hz, 0.9 Hz, 2H), 3.23 and 3.19 (two dd, 9.2, 17.6, and 9.4 Hz, 17.4 Hz, 2H), 2.50 (m, 6H), 2.35 (m, 4H), 2.26 and 2.24 (two s, 6H), 2.22 (m, 1H), 2.15 (dd, 2.8 Hz, 17.2 Hz, 1H), 2.10 (m, 1H), 1.80 (m, 1H), 1.34 and 1.33 (two t, 7.2 Hz, 6H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 204.6 and 204.6, 205.0 and 202.0, 167.0 and 166.6, 118.0 and 116.2, 63.6 and 63.5, 52.8 and 50.5, 49.7 and 49.6, 40.3 and 39.6, 39.5 and 39.2, 34.1 and 33.6, 30.8 and 30.0, 23.1 and 21.3, 14.0. IR (KBr): 2246, 1735, 1713 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82. Found: C, 62.14; H, 6.82.

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Supporting Information Available: All crystallographic data regarding **5a**, **5b**, **5c**, and **5c′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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