Double Annulation Route to Highly Substituted and Functionalized cis Bicyclic and Tricyclic δ-Lactams and Imides

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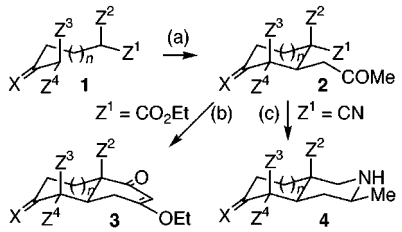
Recent reports from this laboratory have established the wide scope of the double Michael reaction between a tethered carbon diacid **1** and 3-butyn-2-one (Scheme 1).[1−4] We have shown that the highly substituted and functionalized double Michael adducts **2** undergo further transformations such as Dieckmann reactions and intramolecular reductive aminations in a chemo-, regio- and, diastereoselective manner to give trans bicyclic "double annulation" products such as *trans*-decalins and *trans*-hydrindans **3**,[1,2,4] *trans*-perhydroisoquinolines and *trans*-perhydro-2-pyrindines **4**,[1,3] and *trans*-hexahydroindoles.[2]

The double Michael reaction proceeds only when **1** has at least one CN group, which becomes axial in the adducts **2** (Z^2 or Z^3 in Scheme 1). The further transformation of **2** into **3** or **4** does not affect that group. For example, when **2** with one axial and one equatorial CN group is hydrogenated over Pd/C to give **4**, the equatorial CN group is reduced and the axial CN group remains unaffected.[1,3] By contrast, when **2** with two axial CN groups is hydrogenated under various conditions, either no reaction occurs or no identifiable products are obtained. We have been eager to find conditions under which the axial CN groups are converted into other functionalities, as the utility of our method for the synthesis of natural products or potential pharmaceuticals would otherwise be greatly circumscribed. We now report that axial CN groups in **2**−**4** and related compounds are smoothly hydrated to $CONH_2$ groups in 75−80% concentrated H_2SO_4 in absolute EtOH, and these groups condense with pendant carbonyl functionality to provide a variety of highly substituted and functionalized cis bicyclic and bridged tricyclic δ-lactams and imides in moderate to good yield. The H_2SO_4-mediated hydration of nitriles to amides has of course been known for a very long time,[5] but the reaction is rarely applied to compounds as highly functionalized as **2**−**4**, and it is rather surprising that such harsh reaction conditions applied to these compounds give such clean products.

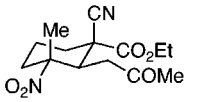
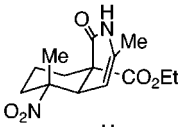
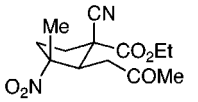
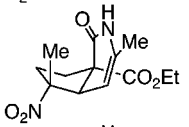
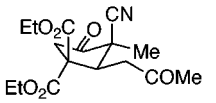
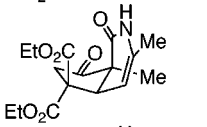
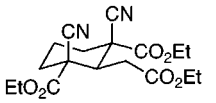
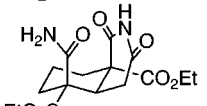
Adducts **2** with one axial CN group and an equatorial acetonyl group are hydrated to *cis*-hexahydroisoquinolin-1-ones and *cis*-tetrahydro-2-pyrindin-1-ones in good yields (Table 1, entries 1−3), nicely complementing our previously reported route to the corresponding trans compounds **4**.[1,3,6] Similarly, hydration of a compound with two axial CN groups and an equatorial CH_2CO_2Et group affords a cis bicyclic amide-imide, reminiscent of the Kemp's triacid-derived U-turn compounds of Rebek,[7] in good yield (Table 1, entry 4). Even when a coaxial CO_2Et or CN group is available in the 3-position (entries 3 and 4), attack of the nascent axial $CONH_2$ group on this group is much slower than attack on an equatorial carbonyl group in the 2-position. The direct conversion of a 4-cyanoketone into a 3,4-dihydropyridin-2-one has been described in the literature only a handful of times.[8−12] Of course, the conversion of a 4-carbamoyl ketone to a 3,4-dihydropyridin-2-one is relatively common, so the transformation reported here is not remark-

Scheme 1[a]



[a] X = O or H,H; Z^{1-4} = CN, CO_2Et, NO_2, or Me (at least Z^2 or Z^3 = CN); *n* = 0 or 1. (a) HC≡CCOMe, cat. NaH in THF or *t*-BuOK in CH_2Cl_2 or Ph_3P in CH_3CN; (b) NaOEt; EtOH, cat. TsOH, $-H_2O$; (c) 2−4 atm H_2, 5% Pd/C.

Table 1. cis Bicyclic Unsaturated δ-Lactams and Imides via Hydration of 2

Entry	Double Michael adduct	Hydration Product	Yield
1			59%
2			56%
3			74%
4			79%

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(5) The earliest mention of this reaction seems to be in: Engelhardt, A. *Ann.* **1858**, *108*, 341.
(6) Only one conformer of each compound is shown in the table; however, the two chair conformers of each bicyclic compound are close in energy, and conformational flexibility is expected.
(7) For example: Wintner, E. A.; Conn, M. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8877.
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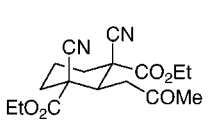
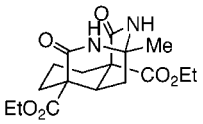
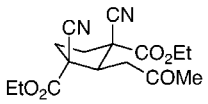
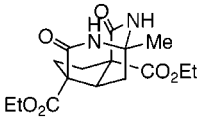
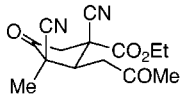
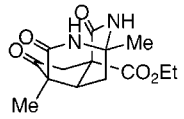
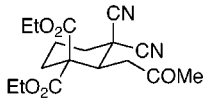
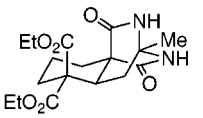
Table 2. Tricyclic *N,N′*-Diacylaminals via Hydration of 2

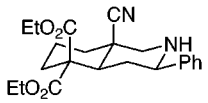
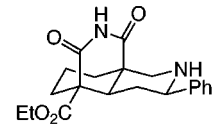
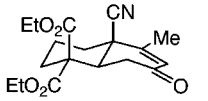
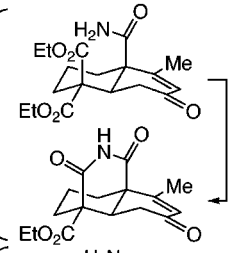
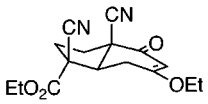
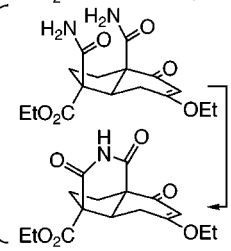
Entry	Double Michael adduct	Hydration Product	Yield
1			43%
2			46%
3			54%
4			41%

able in itself. Still, it is somewhat surprising that despite abundant opportunities for side reactions involving the other functional groups in the starting materials (retro-Claisen and retro-Dieckmann reactions or hydrolysis of the CO_2Et or $CONH_2$ groups and subsequent decarboxylation), the reported products are obtained cleanly and in good yield.

Adducts **2** with two CN groups and an acetonyl group are hydrated to tricyclic *N,N′*-diacylaminals in moderate yield (Table 2). The structures of the aminals are assigned from their spectral characteristics, including their symmetry in the ^1H and ^{13}C NMR spectra (entries 1 and 2), the absence of ketone and CN resonances in the ^{13}C NMR and IR spectra, the upfield shift of the ^{13}C NMR resonance of the former pendant ketone (ca. 140 ppm) and the upfield shift of the ^1H NMR resonance of the Me group adjacent to it (ca. 0.7 ppm), and the presence of NMR and IR absorbances characteristic of CO_2Et groups and secondary amides. In addition, the structure of one tricyclic *N,N′*-diacylaminal (entry 2) was confirmed by X-ray crystallography. A plausible mechanism for the formation of the aminals involves hydrolysis of one CN group to the amide, condensation of the amide with the pendant ketone to give the bicyclic *N*-acylimine, hydrolysis of the second CN group, and closure to the tricyclic product. Again, attack of a nascent axial $CONH_2$ group on the acetonyl group or the *N*-acylimine is much faster even than attack on a coaxial CO_2Et group (entry 4). *N,N′*-Diacylaminals with bicyclo[2.2.2]octane skeletons such as the product in entry 4 have occasionally appeared in the literature,[13−15] as have fused bicyclic *N,N′*-diacylaminals,[16−20] but the products in entries 1−3 are to our knowledge the first such compounds with a cage structure.

We have shown previously that the transformation of **2** into rigid, trans bicyclic "double annulation" products

Table 3. Bicyclic Primary Amides and Bridged Tricyclic Imides via Hydration of trans Bicyclic Compounds

Entry	Doubly annulated substrate	Hydration Product(s)	Yield
1			50%
2			32%[a,b] 45%[a,c]
4			32% 30%

[a] A 2:1 mixture of amide and imide is obtained initially. [b] Isolated yield of pure amide after chromatography; a 1:1 mixture of amide and imide is also obtained. [c] Isolated yield of pure imide derived from further hydration of a 1:1 mixture of amide and imide.

3 and **4** (Scheme 1) leaves the axial CN group of the starting materials unchanged.[1−4] Geometric constraints require that the nascent axial $CONH_2$ group obtained upon hydration of such trans bicyclic compounds combine with a coaxial group or with no group at all (Table 3). Thus, hydration of a *trans*-perhydroisoquinoline with coaxial CO_2Et and CN groups affords a tricyclic imide (entry 1). Hydration of a *trans*-octalone with coaxial CO_2Et and CN groups under the same conditions and for the same period of time affords mostly a bicyclic amide, along with some of the tricyclic imide (entry 2), but the amide is converted completely to the imide after standing longer in ethanolic H_2SO_4. Attack of the nascent $CONH_2$ group on the coaxial CO_2Et group probably occurs more slowly in entry 2 than in entry 1 because of the electron-withdrawing effect of the alkenone, as molecular models show no differences in the spatial orientations of the $CONH_2$ and CO_2Et groups in the two cases. Similarly, hydration of a *trans*-hydrindanone with two coaxial CN groups affords a 1:1 mixture of a bicyclic diamide and a tricyclic imide, which are separated by chromatography (entry 3). The tricyclic imide is slightly contaminated with a small amount of a similar compound that is probably the transposed *β*-ethoxy enone. The bicyclic diamide is also slightly contaminated with a small amount of a greasy impurity, but attempted repurification on silica gel causes its partial conversion to the imide.

As noted above, it is not difficult to imagine a host of side reactions that could occur when the very highly functionalized **2**−**4** are dissolved in ethanolic H_2SO_4. Instead, smooth reactions occur to afford highly functionalized bicyclic and tricyclic compounds in moderate to good yield. The new compounds described herein may be useful scaffolds for displaying functionalized side

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chains in fixed mutual orientations. Future reports from this laboratory will describe the synthesis of natural products via **2** and **3** and further extension of the scope of the double annulation reaction.

Experimental Section

Starting materials were reported previously,[1−3] with the exception of the following compounds.

Diethyl (1*R*,2*r*,3*S*)-1,3-Dicyano-2-(2-ethoxycarbonylethyl)-1,3-cyclohexanedicarboxylate (Table 1, entry 4 starting material). To a solution of KOH (150 mg, 2.58 mmol) in EtOH (3 mL) was added a solution of diethyl 2,6-dicyanopimelate[21] (2.15 g, 8.08 mmol) in THF (10 mL). The resulting solution was allowed to stir at room temperature for 20 min, and it was then diluted with THF (10 mL). After the reaction mixture cooled to 0 °C, ethyl propiolate (920 μL, 8.9 mmol) was slowly added. The reaction was allowed to warm at room temperature and was allowed to stir overnight. The solvent was evaporated, and the residue was taken up in ether. This solution was shaken once with dilute HCl and then twice with water. The aqueous layers were combined and extracted twice with ether. The organic layers were combined, shaken once with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (15% EtOAc in petroleum ether as eluant), and further recrystallization from hot ethanol afforded the title compound (1.35 g, 3.72 mmol, 46% yield) as a white solid, mp 60−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25 (dq, J_d = 10.7 Hz, J_q = 7.2 Hz, 2H), 4.24 (dq, J_d = 10.7 Hz, J_q = 7.2 Hz, 2H), 4.08 (q, 7.2 Hz, 2H), 3.16 (t, 5.3 Hz, 1H), 2.70 (d, 5.3 Hz, 2H), 2.34 (m, 1H), 2.31 (m, 1H), 2.00 (m, 4H), 1.32 (t, 7.2 Hz, 6H), 1.24 (t, 7.2 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 169.9, 167.5 (× 2), 116.1 (× 2), 63.7 (× 2), 61.3, 49.3 (× 2), 38.8, 36.6, 33.5 (× 2), 18.5, 13.9, 13.7 (× 2). IR (KBr): 2239, 1752, 1737, 1728 cm^{-1}. Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64. Found: C, 59.20; H, 6.78.

Diethyl (1*R,6*R*,9*R*)-6-Cyano-9-phenyl-8-azabicyclo[4.4.0]-decane-2,2-dicarboxylate (Table 3, entry 1 starting material).** This compound was prepared in two steps from diethyl (4,4-dicyanobutyl)malonate[1,21] and phenyl ethynyl ketone[22] using procedures analogous to those previously reported for the preparation of diethyl (1*R**,6*R*,9*S*)-6-cyano-9-methyl-8-azabicyclo-[4.4.0]decane-2,2-dicarboxylate.[1] Details will be reported in a future publication.[23]

Diethyl (1*R,6*R*)-6-Cyano-7-methylbicyclo[4.4.0]dec-7-en-9-one-2,2-dicarboxylate (Table 3, entry 2 starting material).** A solution of diethyl (*1R*,6S*)-6-cyano-9-ethoxybicyclo-[4.4.0]dec-8-en-7-one-2,2-dicarboxylate[1] (400 mg, 1.10 mmol) in dry THF (10 mL) at −78 °C was treated with a 1.6 M solution of MeLi in ether (0.7 mL, 1.1 mmol). The reaction mixture was allowed to warm to room temperature. The mixture was acidified with 6 N HCl (2 mL) and allowed to stir for 24 h. When the reaction was complete (TLC check),[24] the solution was extracted twice with ether. The combined ether layers were shaken with brine, dried over $MgSO_4$, and evaporated, and the residue was purified by flash chromatography (15% EtOAc in petroleum ether as eluant) to give the title compound (298 mg, 894 μmol, 81% yield) as a white solid, mp 152−153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.00 (quintet, 1.1 Hz, 1H), 4.34 (dq, J_d = 11.8 Hz, J_q = 7.1 Hz, 1H), 4.28 (dq, J_d = 11.8 Hz, J_q = 7.1 Hz, 1H), 4.24 (dq, J_d = 12.0 Hz, J_q = 7.1 Hz, 1H), 4.17 (dq, J_d = 12.0 Hz, J_q = 7.1 Hz, 1H), 3.06 (dd, 17.7 Hz, 14.0 Hz, 1H), 2.74 (dd, 14.0 Hz, 2.6 Hz, 1H), 2.71 (ddd, 17.7 Hz, 2.6 Hz, 1.1 Hz, 1H), 2.59 (ddt, J_d = 13.5 Hz, J_t = 3.4 Hz, J_d = 1.4 Hz, 1H), 2.45 (dm, J_d = 13.5 Hz, 1H), 2.26 (m, 1H), 2.07 (d, 1.4 Hz, 3H), 1.59 (m, 1H), 1.50 (dt, J_d = 13.4 Hz, J_t = 4.0 Hz, 1H), 1.46 (dt, J_d = 13.4 Hz, J_t = 4.0 Hz, 1H), 1.33 (t, 7.1 Hz, 3H), 1.25 (7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 196.6, 170.7, 168.5, 155.7, 129.5, 117.7, 62.2, 61.9, 56.5, 44.1, 41.5, 39.5, 33.2, 33.0, 20.0, 19.4, 19.3, 13.8. IR (KBr): 2229, 1744, 1725, 1675, 1627 cm^{-1}. Anal. Calcd for $C_{18}H_{23}N_2O_5$: C, 64.85; H, 6.95. Found: C, 64.77; H, 6.99.

General Procedure for Hydration. Concentrated sulfuric acid (4 mL) was slowly added to a solution of the substrate in absolute ethanol (1 mL) with constant stirring at 0 °C. The reaction mixture was then allowed to warm to room temperature. After 15−48 h, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution and extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated to give a white solid. Recrystallization from hot ethanol or flash chromatography afforded the pure hydration product.

Ethyl (1*R,6*S*,7*S*)-4,7-Dimethyl-7-nitro-3-azabicyclo[4.4.0]-decan-2-one-1-carboxylate (Table 1, entry 1).** Hydration of ethyl (1*R**,2*S*,3*S*)-1-cyano-3-methyl-3-nitro-2-(2-oxopropyl)-1-cyclohexanecarboxylate[2] (100 mg, 0.34 mmol) afforded the title compound (59 mg, 0.20 mmol, 59% yield) as a white solid, mp 132−133 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (s, 1H), 4.78 (dm, J_d = 6.3 Hz, 1H), 4.21 (m, 2H), 3.72 (d, 6.2 Hz, 1H), 2.67 (d, 11.6 Hz, 1H), 2.09 (m, 2H), 1.82 (s, 3H), 1.79 (m, 1H), 1.62 (m, 2H), 1.54 (s, 3H), 1.23 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 171.3, 169.3, 135.9, 100.0, 91.2, 62.1, 53.6, 42.0, 37.3, 28.9, 19.6, 18.7, 17.7, 13.9. IR (KBr): 3437, 3214, 1736, 1696, 1675 cm^{-1}. Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80. Found: C, 56.81; H, 6.75.

Ethyl (1*R,6*S*,7*S*)-4,7-Dimethyl-7-nitro-3-azabicyclo[4.3.0]-nonan-2-one-1-carboxylate (Table 1, entry 2).** Hydration of ethyl (1*R**,2*S*,3*S*)-1-cyano-3-methyl-3-nitro-2-(2-oxopropyl)-1-cyclopentanecarboxylate[2] (82 mg, 0.29 mmol) afforded the title compound (46 mg, 0.16 mmol, 56% yield) as a white solid, mp 125−126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 (s, 1H), 4.85 (d quintet, J_d = 6.1 Hz, $J_{quintet}$ = 1.3 Hz, 1H), 4.20 (m, 2H), 3.73 (dm, J_d = 5.0 Hz, 1H), 2.68 (m, 1H), 2.57 (m, 2H), 1.97 (dd, 13.1 Hz, 6.3 Hz, 1H), 1.91 (t, 1.3 Hz, 3H), 1.47 (s, 3H), 1.25 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 170.9, 168.6, 134.6, 96.7, 95.8, 62.3, 56.7, 51.4, 37.3, 31.2, 21.2, 19.1, 13.9. IR (KBr): 3241, 1733, 1673 cm^{-1}. Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43. Found: C, 55.19; H, 6.47.

Diethyl (1*R,6*R*)-1,4-Dimethyl-3-azabicyclo[4.3.0]nonane-2,9-dione-7,7-dicarboxylate (Table 1, entry 3).** Hydration of ethyl (2*R**,3*R*)-3-cyano-3-methyl-2-(2-oxopropyl)-4-cyclopentanone-1,1-dicarboxylate[3] (100 mg, 0.31 mmol) afforded the title compound (73 mg, 0.23 mmol, 74% yield) as a white solid, mp 153−154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (broad, 1H), 5.02 (d quintet, J_d = 5.8 Hz, $J_{quintet}$ = 1.3 Hz, 1H), 4.22 (m, 4H), 3.21 (dd, 5.8 Hz, 1.1 Hz, 1H), 3.05 (d, 18.9 Hz, 1H), 2.51 (d, 18.9 Hz, 1H), 1.83 (t, 1.1 Hz, 3H), 1.41 (s, 3H), 1.29 (t, 7.1 Hz, 3H), 1.21 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 207.9, 170.3, 170.1, 167.3, 133.8, 96.5, 62.1, 61.9, 59.1, 52.5, 48.8, 43.0, 23.8, 18.9, 13.9, 13.8. IR (KBr): 3221, 3175, 3099, 1766, 1736, 1663 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55. Found: C, 59.25; H, 6.50.

Diethyl (1*R,5*S*,6*R*)-5-Aminocarbonyl-9-azabicyclo[4.4.0]-decane-8,10-dione-1,5-dicarboxylate (Table 1, entry 4).** Hydration of diethyl (*1R,2R,3S*)-1,3-dicyano-2-(2-ethoxycarbonylethyl)-1,3-cyclohexanedicarboxylate (200 mg, 551 μmol) afforded the title compound (151 mg, 426 μmol, 79% yield) as a white solid, mp 205−206 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.19 (s, 1H), 7.41 (s, 1H), 7.25 (s, 1H), 4.13 (dq, J_d = 14.1 Hz, J_q = 7.1 Hz, 1H), 4.11 (dq, J_d = 14.1 Hz, J_q = 7.1 Hz, 1H), 3.97 (dq, J_d = 11.2 Hz, J_q = 7.2 Hz, 1H), 3.94 (dq, J_d = 11.2 Hz, J_q = 7.2 Hz, 1H), 3.48 (dd, 13.3 Hz, 4.3 Hz, 1H), 2.80 (dd, 16.8 Hz, 13.3 Hz, 1H), 2.20 (dd, 16.8 Hz, 4.3 Hz, 1H), 2.06 (m, 1H), 1.88 (m, 1H), 1.74 (m, 3H), 1.60 (m, 1H), 1.17 (t, 7.2 Hz, 3H), 1.13 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, DMSO-d_6): δ 173.5, 171.6, 171.1, 170.5, 170.0, 61.2, 61.1, 56.9, 53.1, 35.5, 30.8, 26.0, 24.4, 18.7, 13.7, 13.6. IR (KBr): 3440, 3203, 1744, 1721, 1708, 1681, 1642 cm^{-1}. Anal. Calcd for $C_{16}H_{22}N_2O_7$: C, 54.23; H, 6.25. Found: C, 53.98; H, 6.20.

Diethyl(1*R*,5*S*,11*r*)-8-Methyl-7,9-diazatricyclo[6.2.2.0^{5,11}]-dodecane-6,10-dione-1,5-dicarboxylate (Table 2, entry 1). Hydration of diethyl (*1R,2r,3S*)-1,3-dicyano-2-(2-oxopropyl)-1,3-cyclohexanedicarboxylate[1] (580 mg, 1.74 mmol) afforded the title compound (265 mg, 752 μmol, 43% yield) as a white solid, mp 179−181 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (s, 2H), 4.22 (m, 4H), 3.23 (t, 3.2 Hz, 1H), 2.72 (dm, 13.2 Hz, 2H), 2.21

(21) Grossman, R. B.; Varner, M. A. *J. Org. Chem.* **1997**, *62*, 5235.
(22) Prepared by Jones oxidation of commercially available 1-phenyl-3-propyn-1-ol.
(23) Grossman, R. B.; Maggard, R. K. Unpublished results.
(24) If the reaction is not allowed to proceed for enough time or the conditions are insufficiently acidic, the undehydrated aldol is isolated also.

(d, 3.2 Hz, 2H), 1.67 (m, 3H), 1.47 (s, 3H), 1.27 (t, 7.1 Hz, 6H), 1.08 (broad q, 13.7 Hz, 1H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 172.1, 170.3, 66.6, 62.3, 54.4, 37.5, 32.2, 30.6, 27.0, 19.2, 13.9. IR (KBr): 3448, 3336, 3262, 3200, 1733, 1691, 1652 cm^{-1}. $C_{17}H_{24}N_2O_6$.

Diethyl(1*R*,4*S*,10*r*)-7-Methyl-6,8-diazatricyclo[5.2.2.0^{4,10}]-undecane-5,9-dione-1,4-dicarboxylate (Table 2, entry 2). Hydration of diethyl (*1R*,*2r*,*3S*)-1,3-dicyano-2-(2-oxopropyl)-1,3-cyclopentanedicarboxylate[1] (1.82 g, 5.68 mmol) in concentrated sulfuric acid (18 mL) and EtOH (6 mL) afforded the title compound (876 mg, 2.59 mmol, 46% yield) as a white solid, mp 193 °C (dec). ^1H NMR (400 MHz, $CDCl_3$): δ 6.96 (s, 2H, chemical shift varies with concentration), 4.23 (m, 4H), 2.87 (t, 3.4 Hz, 1H), 2.62 (~q, 6.8 Hz, 2H), 2.40 (d, 3.2 Hz, 2H), 2.19 (~q, 7.1 Hz, 2H), 1.59 (s, 3H), 1.28 (t, 7.2 Hz, 6H). $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 170.6, 170.6, 65.9, 62.1, 59.7, 45.9, 33.3, 31.9, 27.5, 14.0. IR (KBr): 3202, 1742, 1686 (w), 1652 cm^{-1}. Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55. Found: C, 56.78; H, 6.83.

Ethyl (1*R,4*S*,7*S*,10*R*)-4,7-Dimethyl-6,8-diazatricyclo-[5.2.2.0^{4,10}]undecane-3,5,9-trione-1-carboxylate (Table 2, entry 3).** Hydration of ethyl (1*R**,2*R*,3*R*)-1,3-dicyano-3-methyl-2-(2-oxopropyl)-4-cyclopentanone-1-carboxylate[3] (298 mg, 1.05 mmol) afforded the title compound (172 mg, 584 μmol, 54% yield) as a white solid, mp 238−239 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.59 (s, 1H), 4.26 (m, 2H), 3.37 (d, 20.2 Hz, 1H), 3.18 (d, 20.2 Hz, 1H), 2.73 (t, 3.2 Hz, 1H), 2.59 (dd, 13.5 Hz, 2.8 Hz, 1H), 2.19 (dd, 13.4 Hz, 2.5 Hz, 1H), 1.62 (s, 3H), 1.43 (s, 3H), 1.31 (t, 7.1 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 207.5, 170.4, 170.1, 167.1, 65.7, 62.8, 57.1, 54.0, 45.8, 45.2, 30.6, 27.2, 22.7, 14.1. IR (KBr): 3205, 3071, 1754, 1731, 1683, 1644 cm^{-1}. Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16. Found: C, 56.93; H, 6.30.

Diethyl 8-Methyl-9,12-diazatricyclo[6.2.2.0^{1,6}]dodecane-10,11-dione-5,5-dicarboxylate (Table 2, entry 4). Hydration of diethyl 3,3-dicyano-2-(2-oxopropyl)-1,1-cyclohexanedicarboxylate[1] (280 mg, 838 μmol) afforded the title compound (121 mg, 343 μmol, 41% yield) as a white solid, mp 251−252 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.08 (s, 1H), 4.15 (m, 4H), 2.72 (dd, 12.6 Hz, 5.8 Hz, 1H), 2.48 (dd, 10.2 Hz, 5.7 Hz, 1H), 2.35 (m, 2H), 2.17 (dd, 12.5 Hz, 10.3 Hz, 1H), 1.83 (m, 3H), 1.61 (s, 3H), 1.56 (dd, 13.8 Hz, 3.4 Hz, 1H), 1.25 (t, 7.2 Hz, 3H), 1.24 (t, 7.2 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 174.3, 171.9, 171.4, 169.3, 65.2, 61.7, 61.2, 56.9, 53.6, 39.8, 39.2, 32.7, 22.9, 21.6, 18.4, 13.9, 13.8. IR (KBr): 3435, 3189, 1728, 1668 cm^{-1}. Anal. Calcd for $C_{17}H_{24}N_2O_6$: C, 57.94; H, 6.86. Found: C, 57.90; H, 7.06.

Ethyl (1*R,2*R*,4*R*,7*R*)-4-Phenyl-5,9-diazatricyclo[5.3.3.0^{2,7}]-tridecane-8,10-dione-1-carboxylate (Table 3, entry 1).** Hydration of diethyl (1*R**,6*R*,9*R*)-6-cyano-9-phenyl-8-azabicyclo-[4.4.0]decane-2,2-dicarboxylate (384 mg, 1.00 mmol) afforded the title compound (179 mg, 503 μmol, 50% yield) as a white solid, mp 197−198 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.48 (broad, 1H), 7.29 (broad, 1H), 7.28 (m, 5H), 4.21 (q, 7.2 Hz, 1H), 4.20 (q, 7.1 Hz, 1H), 3.81 (d, 12.2 Hz, 1H), 3.65 (dd, 11.3 Hz, 2.8 Hz, 1H), 2.58 (d, 12.2 Hz, 1H), 2.19 (m, 2H), 2.15 (dd, 12.7 Hz, 4.1 Hz, 1H), 1.84 (m, 3H), 1.54 (m, 3H), 1.23 (t, 7.2 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 174.3, 170.7, 169.4, 143.1, 128.4, 127.5, 126.4, 61.6, 61.0, 56.2, 53.4, 45.8, 44.8, 35.1, 32.9, 32.8, 19.1, 14.0. IR (KBr): 3315, 3170, 1731, 1698 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79. Found: C, 67.24; H, 6.94.

Diethyl (1*R,6*R*)-6-Aminocarbonyl-7-methylbicyclo[4.4.0]-dec-7-en-9-one-2,2-dicarboxylate and Ethyl (1*R**,2*R*,7*R*)-6-Methyl-9-azatricyclo[5.3.3.0^{2,7}]tridec-5-ene-4,8,10-trione-1-carboxylate (Table 3, entry 2).** Hydration of diethyl (1*R**,6*R*)-6-cyano-7-methylbicyclo[4.4.0]dec-7-en-9-one-2,2-dicarboxylate (80 mg, 0.24 mmol) and chromatographic purification afforded the amide (27 mg, 77 μmol, 32% yield) as a white solid, mp 221−223 °C, plus a 1:1 mixture of the amide and the imide. Further hydration of this mixture afforded pure imide (33 mg, 0.11 mmol, 45% yield) as a white solid, mp 214−215 °C.

Data for the Amide. ^1H NMR (300 MHz, $CDCl_3$): δ 5.99 (s, 1H), 5.71 (broad, 2H), 4.18 (m, 4H), 3.47 (dd, 17.8 Hz, 14.1 Hz, 1H), 2.79 (dd, 14.1 Hz, 3.4 Hz, 1H), 2.55 (m, 3H), 2.37 (dm, J_d = 12.2 Hz, 1H), 2.01 (d, 1.4 Hz, 3H), 1.75 (m, 1H), 1.57 (dt, J_t = 13.1 Hz, J_d = 4.2 Hz, 1H), 1.37 (dt, J_t = 13.4 Hz, J_d = 4.5 Hz, 1H), 1.28 (t, 7.2 Hz, 3H), 1.23 (t, 7.1 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 198.6, 171.8, 171.2, 168.9, 162.1, 128.1, 61.0, 60.1, 55.8, 49.5, 44.8, 38.0, 33.0, 32.1, 19.7, 19.5, 13.4, 13.2. IR (KBr): 3380, 3174, 1750 (w), 1723, 1693, 1646 cm^{-1}. $C_{18}H_{25}NO_6$.

Data for The Imide. ^1H NMR (300 MHz, $CDCl_3$): δ 8.34 (s, 1H), 6.04 (d, 1.3 Hz, 1H), 4.28 (q, 7.2 Hz, 1H), 4.27 (q, 7.1 Hz, 1H), 2.52 (m, 4H), 2.26 (d, 1.4 Hz, 3H), 2.21 (m, 1H), 2.04 (m, 1H), 1.65 (m, 3H), 1.32 (t, 7.2 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 195.0, 171.7, 169.9, 168.7, 160.7, 128.8, 62.2, 55.8, 47.9, 44.7, 38.2, 32.3, 32.1, 22.3, 19.4, 13.9. IR (KBr): 3241, 1743, 1692, 1673 cm^{-1}. $C_{16}H_{19}NO_5$.

Ethyl (1*R,6*R*,7*R*)-1,7-Bis(aminocarbonyl)-4-ethoxybicyclo[4.3.0]non-3-en-2-one-7-carboxylate and Ethyl (1*R**,-2*R*,7*R*)-4-Ethoxy-9-azatricyclo[5.3.2.0^{2,7}]dodec-4-ene-6,8,10-trione-1-carboxylate (Table 3, entry 3).** Hydration of ethyl (1*R**,6*S*,7*S*)-1,7-dicyano-4-ethoxybicyclo[4.3.0]non-3-en-2-one-7-carboxylate (100 mg, 331 μmol) afforded the diamide (27 mg, 80 μmol, 32% yield) as a white solid, mp 170−171 °C, and the imide (24 mg, 75 μmol, 30% yield) as a white solid, mp 128−129 °C.

Data for the Diamide. ^1H NMR (400 MHz, $CDCl_3$): δ 6.08 (s, 2H), 5.48 (s, 2H), 5.32 (d, 1.5 Hz, 1H), 4.21 (m, 2H), 3.93 (m, 2H), 3.49 (dd, 17.2 Hz, 12.3 Hz, 1H), 2.90 (dd, 12.4 Hz, 4.6 Hz, 1H), 2.78 (dd, 17.2 Hz, 4.6 Hz, 1H), 2.54 (dd, 10.5 Hz, 4.3 Hz, 1H), 2.25 (dt, J_d = 12.5 Hz, J_t = 4.3 Hz, 1H), 1.92 (m, 2H), 1.37 (t, 7.0 Hz, 3H), 1.27 (t, 7.1 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 197.9, 181.2, 173.5, 172.4, 171.8, 101.8, 65.4, 63.1, 62.1, 61.2, 48.2, 32.1, 31.0, 14.0, 13.9, one resonance obscured. IR (KBr): 3442, 3348, 1730, 1671 cm^{-1}. $C_{16}H_{22}N_2O_6$.

Data for the Imide. ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 5.46 (d, 1.6 Hz, 1H), 4.31 (q, 7.3 Hz, 1H), 4.30 (q, 7.1 Hz, 1H), 3.92 (q, 7.0 Hz, 2H), 2.96 (dd, 17.6 Hz, 4.7 Hz, 1H), 2.73 (dd, 11.8 Hz, 4.8 Hz, 1H), 2.61 (m, 2H), 2.37 (m, 2H), 2.21 (m, 1H), 1.36 (t, 7.1 Hz, 3H), 1.34 (t, 7.1 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 192.1, 175.6, 170.7, 170.4, 168.2, 102.7, 65.4, 62.2, 60.3, 60.2, 46.5, 30.7, 30.1, 26.4, 14.1, 14.0. IR (KBr): 3227, 3103, 1733, 1705, 1670 cm^{-1}. $C_{16}H_{19}NO_6$.

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Supporting Information Available: A thermal ellipsoid plot of the product in Table 2, entry 2, and ^1H and ^{13}C NMR spectra of all compounds for which elemental analyses are not reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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