Intramolecular Ketone−Nitrile Reductive Coupling Reactions Promoted by Samarium(II) Iodide

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Samarium(II) iodide (SmI_2) has been successfully utilized as a reducing agent for the intramolecular coupling of ketones with nitriles. The use of visible light to promote the reductive coupling represents an improvement over previously reported protocols. The procedure also avoids overreduction of the resulting α-hydroxy ketones. Monocyclic, fused bicyclic, and bridged bicyclic α-hydroxy ketones composed of a number of substitution patterns have been synthesized in moderate to excellent yield via this method. A sequential reaction consisting of a nucleophilic acyl substitution followed by a ketyl−nitrile coupling has also been accomplished.

Introduction

Carbonyl coupling reactions passing through a ketyl intermediate constitute an important class of reactions in organic chemistry. Samarium(II) iodide (SmI_2) has been shown to promote a wide variety of these reactions, including ketyl−olefin couplings[1] and intramolecular pinacolic coupling reactions.[1b,c,e] Ketyl formation can also be achieved with other reductants[1d,2] and by electrochemical[3] and photochemical processes.[4] The high degree of chemoselectivity exhibited by SmI_2, however, provides several advantages over the aforementioned methods. For instance, a large number of organic functional groups are tolerated under the mild reaction conditions. Furthermore, the Sm(III) Lewis acid generated during the course of the reaction can be used as a template to control stereochemistry in appropriately designed substrates.[1e,5] Differential reactivity of various reducible groups permits the sequencing of organic reactions with this reductant. Thus, complex products can be accessed from relatively simple precursors in a one-pot process.[1j,k,6]

Ketyls have also been coupled with nitriles, providing the same α-hydroxy ketone products as generated by an acyloin condensation. Although the acyloin condensation itself is an effective method for generating medium- and large-membered rings, it employs harsh reaction conditions and generally gives low yields when forming five- and six-membered rings.[7] This method also suffers from poor regiochemical and stereochemical control.[7a,b,8] An intramolecular SmI_2-promoted version of the acyloin condensation, employing an acyl anion derived from a carboxylic acid chloride, has also been studied.[9] Synthesis of α-hydroxycyclopentanones by this route was not

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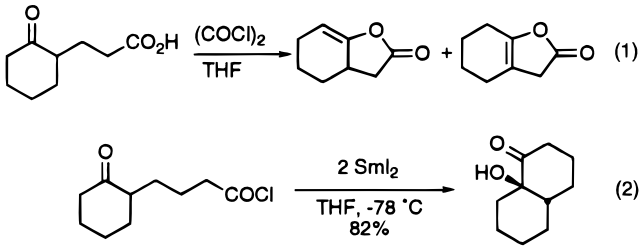
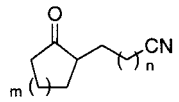
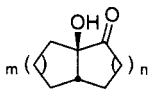
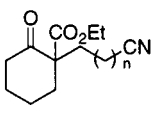
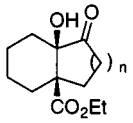
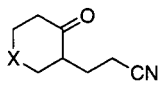
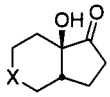
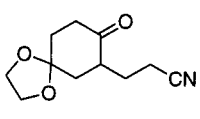
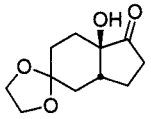
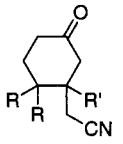
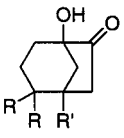
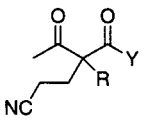
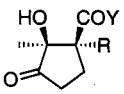
possible because the conditions required for the generation of the requisite acid chlorides enolized the ketones, leading to the formation of enol lactones (eq 1).[9] However, construction of six-membered rings was achieved in yields ranging from 36 to 82% (eq 2), as these substrates were not as prone to enolization.[9]



Ketyl−nitrile coupling reactions have been mediated by Zn/TMSCl,[2f] by SmI_2,[1e,10] and by electrochemical methods.[11] Photochemically promoted ketyl−nitrile coupling reactions have proven unsuccessful.[4b] In some instances the SmI_2-promoted reaction proceeds with much better stereochemical control than identical reactions promoted by electrochemical processes.[11b] The Sm(III) Lewis acid that is generated during the course of the reaction can chelate substrates to control the stereochemistry of the cyclization. Chelation control has not been studied in the Zn/TMSCl procedure, where only a single result has been reported.[2f] Although the SmI_2 method generally proceeds with excellent diastereoselectivity,[1e,10] the yields utilizing past experimental protocols were less than satisfactory (<50%). Although overreduction of the α-hydroxy ketone product was viewed as one potential problem,[12] it appeared more likely that the low yields were the result of a low equilibrium concentration of the ketyl radical donor in the presence of the modestly reactive nitrile acceptor. Electron transfer from SmI_2 to ketone carbonyls has been postulated to be highly reversible.[13]

It had been previously reported that irradiation of THF solutions of SmI_2 enhanced the reactivity of this reductant in reactions with organic chlorides.[14] This phenomenon was ascribed to more facile electron transfer from a photoexcited SmI_2 species. If a low concentration of the ketyl was indeed problematic in the ketone−nitrile coupling reactions, it seemed reasonable that an increase in the reducing power of the SmI_2 might improve the yields of the desired products. We now report that illuminating keto nitriles with a 250 W floodlamp in the presence of SmI_2 enhances the yields of these reactions. The sequencing of multiple reductive coupling reactions has also been briefly investigated.

Table 1. Samarium(II) Iodide-Promoted Ketyl−Nitrile Couplings

entry	substrate	product	% isolated yield
			
1	**1a** m = 2, n = 1	**2a**	89
2	**1b** m = 1, n = 2	**2b**	34
3	**1c** m = 1, n = 1	**2c**	80
			
4	**1d** n=1	**2d**	96
5	**1e** n=2	**2e**	37
			
6	**1f** X = O	**2f**	88
7	**1g** X = NBn	**2g**	71
8	**1h** X = S	**2h**	67
9	**1i** X = $Si(CH_3)_2$	**2i**	50
10			93
	1j	**2j**	
			
11	**1k** R = H, R' = Me	**2k**	62
12	**1l** R = Me, R' = H	**2l**	42
			
13	**1m** R = Me, Y = OEt	**2m**	65
14	**1n** R = H, Y = OEt	**2n**	0
15	**1o** R = H, Y = NEt_2	**2o**	89

Results and Discussion

A variety of reaction conditions were surveyed to optimize the synthesis of α-hydroxy ketones from a test keto nitrile. Treatment of keto nitrile **1a** (Table 1) with 2.2 equiv of SmI_2 and 2.1 equiv of *t*-BuOH gave no reaction after 24 h. Addition of HMPA[15] or NiI_2[16] to the reaction mixtures gave incomplete conversion to the desired product. When the same reaction was carried out in the presence of a 250 W floodlamp with 2.05 equiv of SmI_2 and 2.1 equiv of *t*-BuOH, the starting material was completely consumed to provide an 89% yield of α-hydroxy ketone **2a** (entry 1, Table 1). Quenching the reaction with Rochelle's salt[17] was necessary to liberate

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the product from the samarium salts. A number of differentially substituted keto nitriles were then subjected to the cyclization conditions to probe the generality of the reaction method, the results of which are summarized in Table 1.

Substrates **1a** and **1c** were both cyclized in good yield. For comparison, when Zn/TMSCl was utilized as the reductant, **1a** was cyclized to **2a** in 79% yield.[2f] When the photoinduced SmI_2 protocol was utilized, keto nitrile **1b** gave only a 34% yield of the desired product. Evidently, the 6-exo cyclization is so slow that the ketyl is not persistent enough to allow for an efficient annulation. This result was not unexpected because the rate of cyclization of the 4-cyanobutyl radical, generating cyclopentanone (following hydrolysis), is 4.0×10^3 s^{-1} at 25 °C.[18] This rate is approximately 2 orders of magnitude slower than the 5-hexenyl radical cyclization. In the case of **1b**, the ketyl must also cyclize through a 6-exo mode which is inherently slower than a 5-exo annulation. Therefore, one would expect the more distal cyano group to be an extremely inefficient ketyl trap. The cis stereochemistry of **2a**−**c** was determined by comparison of their ^{13}C NMR spectra with the reported data[11] and is reasonable considering the strain of the transition structure leading to trans-fused bicyclo[3.3.0] or -[4.3.0] systems.

Keto nitriles **1d** and **1e** both possess a β-keto ester functional array that has been shown to act as a template for controlling stereochemistry in SmI_2-promoted cyclizations.[1e,5] Both substrates gave the cis diastereomer exclusively because of the chelating nature of the Sm(III) Lewis acid that is generated during the course of the reaction. Again, the cis stereochemistry of **2d** and **2e** was determined by comparison of their ^{13}C NMR spectra with the reported data.[11b] In the formation of the bicyclo[4.4.0] system in entry **5**, only the cis diastereomer could be detected, and it was isolated in 37% yield. This is the outcome predicted by chelate direction during cyclization. This result is in stark contrast to the 2:1 ratio of diastereomers formed electrochemically.[11b] No evidence for a retro-aldol equilibration of diastereomers was observed during the course of the SmI_2-promoted reaction. Additionally, 2 equiv of a proton source (*t*-BuOH in this case) has been shown to hinder the retro-aldol pathway by destroying the Sm(III) chelate, allowing the kinetic product to be isolated.[1e]

Entries 6−10 (Table 1) demonstrate that a wide variety of functional groups remain untouched by the reaction conditions. Ethers, tertiary amines, thioethers, quaternary silanes, and ethylene glycol protected ketones are compatible with the reductive coupling reaction. α-Hydroxy ketones **2f**−**j** were all isolated as single diastereomers and assigned the cis stereochemistry by analogy to **2a**.

Entries 11 and 12 (Table 1) serve to demonstrate that bridged bicyclic α-hydroxy ketones can also be synthesized using this method. α-Hydroxy ketone **2k** was formed in 62% yield, whereas **2l** was formed in only 42% yield. This variance in yield results from the respective conformational preferences of these substrates. Overlap between the ketone and nitrile is optimal when the cyanomethyl group occupies an axial rather than an equatorial orientation (Figure 1). Keto nitrile **1k** has a methyl substituent in the 3-position that causes the cyanomethyl moiety to populate the axial and equatorial orientations equally, while **1l** has a hydrogen in this position, leading to a conformation in which the cyanomethyl group preferentially occupies an equatorial orientation that is unfavorably disposed for efficient cyclization.

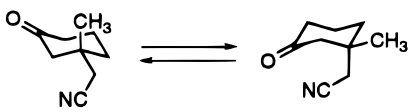

Figure 1. Axial and equatorial conformations of **1k**.

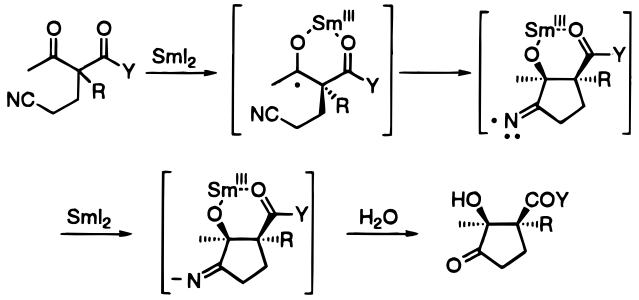

Figure 2. SmI_2-mediated cyclization of β-dicarbonyl substrates.

Under nonphotolytic conditions with SmI_2, substrate **1m** was cyclized in only 45% yield.[1e] By employing the current protocol, several acyclic keto nitriles were cyclized in good yields with excellent control of stereochemistry, as evidenced by the examples presented in entries 13−15 (Table 1). Thus keto nitriles **1m** and **1o** were both cyclized in good yield as single diastereomers. The relative stereochemistry of these products was determined by comparing their ^{13}C NMR spectra with the literature data.[1e] The cis selectivity in forming the β-hydroxy carbonyl functional group array stems from the chelating nature of the Sm(III) Lewis acid generated during the course of the reaction (Figure 2). As in entries 4 and 5 (Table 1), no evidence was observed for a retro-aldol equilibration of diastereomers. Keto nitrile **1o** cyclized more efficiently because of the stronger Lewis basicity of the β-keto amide compared to that of the β-keto ester. This attribute allows the β-keto amide to form a tighter chelate with the SmI_2. Substrate **1n** was recovered in quantitative yield after being subjected to SmI_2, suggesting that enolizable keto nitriles are not compatible with this method.

The SmI_2-promoted ketyl−nitrile coupling has been incorporated within a sequential process (eq 3). Thus a nucleophilic acyl substitution reaction followed by the ketyl−nitrile coupling reaction developed herein permits the facile, one-step construction of functionalized, bicyclic α-hydroxy ketones. Catalytic NiI_2 was added to facilitate the reduction of the organic iodide to the organosamarium species,[16] which then condensed with the ester, liberating a ketone. The ketone was then reduced to the ketyl, which underwent a 5-exo cyclization with the nitrile to afford **4** in 49% yield after hydrolysis. The cis stereochemistry was assigned on the basis of the previous examples presented in this work. This one-pot transformation demonstrates that the 5-exo ketyl−nitrile coupling can be sequenced with other SmI_2-promoted reac-

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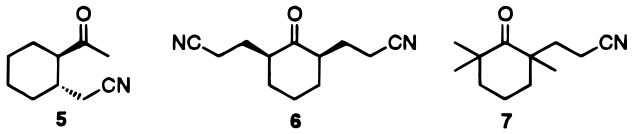
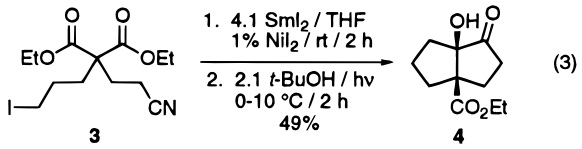


Figure 3. Keto nitriles that failed to cyclize.

tions to synthesize complex molecules from comparatively simple precursors.



(3)

Keto nitriles **5**−**7** (Figure 3) failed to provide the desired products. The major product from the reduction of substrate **5** appeared to be an isomeric mixture resulting from the reduction of the ketone to the corresponding alcohol. Keto nitrile **6** was treated with 4.1 equiv of SmI_2 in order to perform a ketyl−nitrile coupling followed by an imino−nitrile coupling. The ketyl−nitrile coupling appeared to be successful, but the imino−nitrile coupling did not proceed as anticipated. Rather than being reduced to the radical anion and then cyclizing onto the remaining nitrile, a mixture of isomers was isolated resulting from the cleavage of the newly formed α-hydroxyl group. Substrate **7** appeared to be reduced in a manner similar to that of keto nitrile **5**. This suggests that the annulation is sensitive to steric effects because although electron transfer to the ketone was achieved, cyclization onto the nitrile was not observed.

Conclusions

The light-induced, SmI_2-promoted 5-exo coupling of various keto nitriles affords a variety of α-hydroxy ketones in fair to excellent yield. Unfortunately, the analogous 6-exo cyclization is too slow, and the corresponding α-hydroxycyclohexanones are obtained in low yields. The mild reaction conditions are compatible with esters, amides, ethers, tertiary amines, thioethers, quaternary silanes, and ethylene glycol protected ketones. The method developed is complementary to other procedures, including the SmI_2-promoted cyclization of keto carboxylic acid chlorides. A sequential reaction consisting of a nucleophilic acyl substitution followed by a ketyl−nitrile coupling has also been accomplished.

Experimental Section

Tetrahydrofuran (THF) was distilled from $LiAlH_4$, stored over benzophenone ketyl, and distilled from benzophenone ketyl immediately prior to use. Samarium metal was purchased from Aldrich and was stored under an inert atmosphere. Standard benchtop techniques were employed for handling air-sensitive reagents,[19] and all reactions were carried out under Ar. Substrates **1a**,[20] **1c**,[20] **5**,[21] and **6**[20] were prepared according to literature procedures.

***cis*-6-Hydroxybicyclo[4.3.0]nonan-7-one (2a). General Procedure for the SmI_2-Promoted Reactions of Keto Nitriles.** To Sm (0.452 g, 3.00 mmol) was added I_2 (0.690 g, 2.72 mmol). Then 28 mL of dry THF was added. The resultant orange slurry was stirred vigorously for 2 h at rt. The resulting SmI_2 solution had a deep blue-green color. Keto nitrile **1a** (0.2006 g, 1.327 mmol) and *t*-BuOH (0.2015 g, 2.786 mmol) were added as a 0.05 M solution in dry THF in one portion. The reaction mixture was then cooled to 0 °C and irradiated with a 250 W flood lamp. The reaction mixture was maintained at 0−10 °C for 2 h. After this period, the reaction mixture was subjected to TLC/GC analysis and the reaction was found to be complete. The reaction was quenched with Rochelle's salt[13] and subjected to an aqueous workup. The crude product was purified by flash chromatography (30% EtOAc/hexanes) followed by Kugelrohr distillation (ot 95−100 °C at 13 mmHg) to afford 0.1812 g of **2a** (89% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49−2.09 (m, 4H), 1.89−1.42 (m, 9H), 1.30−1.24 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.83, 77.76, 40.80, 33.17, 29.31, 24.38, 20.95, 20.71, 20.66; IR (neat) 3447.9, 2931.5, 2859.4, 1742.8 cm^{-1}; LRMS (EI$^+$) *m*/*z* 154 (19), 98 (100), 70 (43), 55 (26); HRMS (EI$^+$) calcd for $C_9H_{14}O_2$ 154.0994, found 154.0980. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.84; H, 9.35.

***cis*-6-Hydroxybicyclo[4.3.0]nonan-5-one (2b). 2b** was prepared from keto nitrile **1b** according to the general procedure for **2a**. Purification by flash chromatography (30% EtOAc/hexanes) and Kugelrohr distillation (ot 95−100 °C at 12 mmHg) afforded **2b** in 34% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 1H), 2.57−2.42 (m, 2H), 2.20−1.86 (m, 6H), 1.75−1.52 (m, 4H), 1.40−1.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.50, 86.57, 52.78, 37.41, 37.28, 30.71, 30.16, 26.25, 21.45; IR ($CHCl_3$) 3488.4, 2938.0, 2867.1, 1705.9 cm^{-1}; LRMS (EI$^+$) *m*/*z* 154 (24), 136 (12), 110 (49), 97 (100), 84 (93); HRMS (EI$^+$) calcd for $C_9H_{14}O_2$ 154.0994, found 154.1011. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.95; H, 9.18.

***cis*-5-Hydroxybicyclo[3.3.0]octan-6-one (2c). 2c** was prepared from keto nitrile **1c** according to the general procedure for **2a**. Purification by flash chromatography (35% EtOAc/hexanes) and Kugelrohr distillation (ot 110−115 °C at 20 mmHg) afforded **2c** in 80% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 1H), 2.53−1.34 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.88, 88.14, 48.22, 37.43, 34.97, 32.08, 24.43, 23.99; IR (neat) 3435.9, 2956.8, 2872.3, 1740.4 cm^{-1}; LRMS (EI$^+$) *m*/*z* 140 (28), 97 (15), 84 (100); HRMS (EI$^+$) calcd for $C_8H_{12}O_2$ 140.0837, found 140.0841. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.42; H, 8.63.

Ethyl *cis*-6-Hydroxy-7-oxobicyclo[4.3.0]nonanecarboxylate (2d). 2d was prepared from keto nitrile **1d** according to the general procedure for **2a**. Purification by flash chromatography (30% EtOAc/hexanes) and Kugelrohr distillation (ot 70−80 °C at 0.01 mmHg) afforded **2d** in 96% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (q, J = 7.15 Hz, 2H), 3.15 (s, 1H), 2.52−2.36 (m, 2H), 2.09−1.98 (m, 3H), 1.66−1.41 (m, 7H), 1.21 (t, J = 7.15 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.83, 175.65, 79.25, 61.07, 51.50, 31.46, 30.63, 27.39, 24.82, 21.01, 20.38, 13.99; IR (CH_2Cl_2) 3466.2, 2936.4, 2863.7, 1751.6 cm^{-1}; LRMS (EI$^+$) *m*/*z* 170 (100), 124 (72); HRMS (EI$^+$) calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1188. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.75; H, 8.07.

Ethyl *cis*-6-Hydroxy-7-oxobicyclo[4.4.0]decanecarboxylate (2e). 2e was prepared from keto nitrile **1e** according to the general procedure for **2a**. Purification by flash chromatography (25% EtOAc/hexanes) and Kugelrohr distillation (ot 70−80 °C at 0.01 mmHg) afforded **2e** in 37% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (q, J = 7.08 Hz, 2H), 3.94 (s, 1H), 2.54−2.30 (m, 3H), 2.02−1.51 (m, 10H), 1.37−1.21 (m, 1H), 1.20−1.15 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.32, 174.71, 77.61, 60.68, 53.85, 35.64, 33.42, 29.06, 28.84, 21.55, 20.58, 20.33, 13.96; IR (neat) 3477.4, 2936.6, 2867.6, 1723.7 cm^{-1}; LRMS (EI$^+$) *m*/*z* 212 (45), 170 (84), 138 (37), 122 (100); HRMS (EI$^+$) calcd for $C_{13}H_{20}O_4$ 240.1362, found 240.1363. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.33; H, 8.62.

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***cis*-6-Hydroxy-3-oxabicyclo[4.3.0]nonan-7-one (2f). 2f** was prepared from keto nitrile **1f** according to the general procedure for **2a**. Purification by flash chromatography (75% EtOAc/hexanes) and Kugelrohr distillation (ot 60−70 °C at 0.01 mmHg) afforded **2f** in 88% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82−3.59 (m, 4H), 3.21 (s, 1H), 2.51−1.74 (m, 6H), 1.23−1.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.61, 75.10, 65.44, 62.95, 40.85, 33.20, 29.13, 19.32; IR (neat) 3396.0, 2953.4, 2858.0, 1744.2 cm^{-1}; LRMS (EI$^+$) *m/z* 156 (25), 138 (28), 100 (59), 56 (100); HRMS (EI$^+$) calcd for $C_8H_{12}O_3$ 156.0786, found 156.0801. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.90; H, 7.91.

***cis*-3-Aza-3-benzyl-6-hydroxybicyclo[4.3.0]nonan-7-one (2g). 2g** was prepared from keto nitrile **1g** according to the general procedure for **2a**. Purification by flash chromatography (50% EtOAc/hexanes) and Kugelrohr distillation (ot 100−110 °C at 0.01 mmHg) afforded **2g** in 71% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.19 (m, 5H), 3.55−3.45 (m, 2H), 2.75−1.79 (m, 11H), 1.35−1.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.54, 138.57, 128.71, 128.16, 126.92, 76.07, 62.77, 51.99, 48.54, 41.69, 33.17, 30.16, 20.28; IR (neat) 3445.4, 3083.9, 3060.6, 3026.3, 2944.0, 2915.8, 2807.3, 1744.0 cm^{-1}; LRMS (EI$^+$) *m/z* 245 (30), 228 (33), 91 (100); HRMS (EI$^+$) calcd for $C_{15}H_{19}NO_2$ 245.1416, found 245.1402. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.67; H, 7.91; N, 5.80.

***cis*-6-Hydroxy-3-thiabicyclo[4.3.0]nonan-7-one (2h). 2h** was prepared from keto nitrile **1h** according to the general procedure for **2a**. Purification by flash chromatography (40% EtOAc/hexanes) afforded **2h** in 67% yield: mp 84−85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23 (dd, J = 14.16, 3.91 Hz, 1H), 2.94−2.85 (m, 1H), 2.57−2.19 (m, 7H), 1.90−1.80 (m, 2H), 1.51−1.44 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.61, 76.26, 39.73, 32.85, 29.65, 26.77, 22.42, 19.26; IR (CH_2Cl_2) 3391.8, 2958.2, 2944.6, 2919.6, 2901.2, 2876.6, 2819.2, 1741.2 cm^{-1}; LRMS (EI$^+$) *m/z* 172 (60), 154 (10), 116 (69), 83 (67), 27 (100); HRMS (EI$^+$) calcd for $C_8H_{12}O_2S$ 172.0558, found 172.0556. Anal. Calcd for $C_8H_{12}O_2S$: C, 55.78; H, 7.02; S, 18.62. Found: C, 55.85; H, 7.07; S, 18.60.

***cis*-3,3-Dimethyl-6-hydroxy-3-silabicyclo[4.3.0]nonan-7-one (2i). 2i** was prepared from keto nitrile **1i** according to the general procedure for **2a**. Purification by flash chromatography (30% EtOAc/hexanes) and Kugelrohr distillation (ot 70−75 °C at 0.01 mmHg) afforded **2i** in 50% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42−2.32 (m, 3H), 2.24−2.16 (m, 1H), 2.02−1.96 (m, 1H), 1.72−1.62 (m, 2H), 1.53−1.48 (m, 1H), 0.98−0.88 (m, 2H), 0.67−0.63 (m, 1H), 0.57−0.52 (m, 1H), 0.12 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 220.13, 80.08, 41.79, 33.34, 26.14, 25.49, 12.38, 6.72, −1.17, −1.63; IR (neat) 3450.9, 2952.1, 2901.7, 1744.4 cm^{-1}; LRMS (EI$^+$) *m/z* 198 (19), 170 (7), 142 (52), 75 (100); HRMS (EI$^+$) calcd for $C_{10}H_{18}O_2Si$ 198.1076, found 198.1088. Anal. Calcd for $C_{10}H_{18}O_2Si$: C, 60.56; H, 9.15. Found: C, 60.62; H, 9.34.

***cis*-6-Hydroxybicyclo[4.3.0]nonane-3,7-dione, 3-Ethylene Glycol Acetal (2j). 2j** was prepared from keto nitrile **1j** according to the general procedure for **2a**. Purification by flash chromatography (50% EtOAc/hexanes) and recrystallization from hexanes afforded **2j** in 93% yield: mp 99−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97−3.87 (m, 4H), 2.50−1.79 (m, 9H), 1.66−1.56 (m, 2H), 1.41−1.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.53, 108.11, 77.12, 64.46, 63.84, 41.80, 33.37, 33.11, 29.27, 27.67, 21.81; IR (CH_2Cl_2) 3436.0, 2952.9, 2886.3, 1743.8 cm^{-1}; LRMS (EI$^+$) *m/z* 171 (9), 156 (9), 112 (48), 99 (86), 86 (100); HRMS (EI$^+$) calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1056. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.43; H, 7.79.

5-Hydroxy-1-methylbicyclo[3.2.1]octan-6-one (2k). 2k was prepared from keto nitrile **1k** according to the general procedure for **2a**. Purification by flash chromatography (40% EtOAc/hexanes) and Kugelrohr distillation (ot 110−115 °C at 5 mmHg) afforded **2k** in 62% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95 (br s, 1H), 2.15−1.94 (m, 2H), 1.79−1.62 (m, 5H), 1.47−1.34 (m, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.02, 80.79, 49.14, 47.49, 36.82, 36.76, 34.76, 27.29, 20.11; IR (neat) 3424.2, 2947.1, 2868.1, 1748.9 cm^{-1}; LRMS (EI$^+$) *m/z* 154 (49), 126 (30), 111 (88), 98 (88), 83 (58), 69 (100); HRMS (EI$^+$) calcd for $C_9H_{14}O_2$ 154.0994, found 154.0979. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.22; H, 9.31.

5-Hydroxy-2,2-dimethylbicyclo[3.2.1]octan-6-one (2l). 2l was prepared from keto nitrile **1l** according to the general procedure for **2a**. Purification by flash chromatography (40% EtOAc/hexanes) and Kugelrohr distillation (ot 100−105 °C at 0.01 mmHg) afforded **2l** in 42% yield, >99% pure by gas chromatographic analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (s, 1H), 2.39−2.19 (m, 3H), 2.06−1.67 (m, 3H), 1.52−1.23 (m, 3H), 1.10 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.91, 79.09, 40.30, 39.07, 37.52, 34.06, 32.69, 32.10, 28.88, 26.23; IR (neat) 3425.9, 2953.0, 2933.0, 2869.5, 1747.9 cm^{-1}; LRMS (EI$^+$) *m/z* 168 (36), 112 (57), 97 (100); HRMS (EI$^+$) calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1145.

Ethyl (1*R, 2*R**)-2-Hydroxy-1,2-dimethyl-3-oxocyclopentanecarboxylate (2m). 2m** was prepared from keto nitrile **1m** according to the general procedure for **2a**. Purification by flash chromatography (40% EtOAc/hexanes) and Kugelrohr distillation (ot 55−65 °C at 0.01 mmHg) afforded **2m** in 65% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15−4.07 (m, 2H), 2.85 (br s, 1H), 2.55−2.21 (m, 3H), 1.79−1.68 (m, 1H), 1.27 (s, 3H), 1.19 (t, J = 7.22 Hz, 3H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.07, 175.13, 80.71, 61.07, 52.08, 31.65, 29.13, 19.30, 17.44, 13.93; IR (neat) 3480.0, 2981.1, 2941.2, 1738.2 cm^{-1}; LRMS (EI$^+$) *m/z* 155 (8), 144 (100), 98 (85), 43 (57); HRMS (EI$^+$) calcd for $C_{10}H_{16}O_4$ 200.1049, found 200.1059. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.70; H, 8.07.

(1*R,2*R**)-*N*,*N*-Diethyl-2-hydroxy-2-methyl-3-oxocyclopentanecarboxylate (2o). 2o** was prepared from keto nitrile **1o** according to the general procedure for **2a**. Purification by flash chromatography (100% EtOAc) and Kugelrohr distillation (ot 90−95 °C at 0.01 mmHg) afforded **2o** in 89% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (br s, 1H), 3.33−3.19 (m, 4H), 2.89−2.86 (m, 1H), 2.50−2.43 (m, 1H), 2.21−2.14 (m, 1H), 2.06−1.99 (m, 2H), 1.16 (s, 3H), 1.12−1.09 (m, 3H), 1.01−0.99 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.52, 173.17, 77.53, 46.65, 42.05, 40.17, 32.24, 22.04, 21.08, 14.52, 12.75; IR (neat) 3237.0, 2975.1, 2934.9, 1752.2, 1684.0 cm^{-1}; LRMS (EI$^+$) *m/z* 157 (71), 142 (27), 43 (65); HRMS (CI$^+$) calcd for $C_{11}H_{20}NO_3$ (M + H)$^+$ 214.1443, found 214.1457. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.18; H, 9.22; N, 6.96.

Ethyl *cis*-5-Hydroxy-4-oxobicyclo[3.3.0]octanecarboxylate (4). To Sm (0.740 g, 4.92 mmol) was added I_2 (1.125 g, 4.43 mmol). Then 45 mL of dry THF was added. The resultant orange slurry was stirred vigorously for 2 h at rt. NiI_2 (0.014 g, 0.044 mmol) was then added to the freshly generated SmI_2. The resulting SmI_2 solution had a deep blue-green color. Keto nitrile **3** (0.401 g, 1.05 mmol) was added dropwise as a 0.05 M solution in dry THF. After 2 h, TLC showed complete consumption of the starting material. *t*-BuOH (0.163 g, 2.20 mmol) was added, and the reaction mixture was cooled to 0 °C. The reaction mixture was irradiated with a 250 W flood lamp for 2 h at 0−10 °C. After 2 h, the reaction was found to be complete by TLC. The reaction was quenched with Rochelle's salt,[13] and the mixture was subjected to an aqueous workup. The crude product was purified by flash chromatography (40% EtOAc/hexanes) and Kugelrohr distillation (ot 70−80 °C at 0.01 mmHg) to afford 0.110 g of **4** (49% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, J = 7.08 Hz, 2H), 3.00 (br s, 1H), 2.53−2.40 (m, 3H), 2.32−2.23 (m, 1H), 2.11−1.69 (m, 6H), 1.20 (t, J = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.36, 173.87, 89.58, 61.00, 36.84, 33.47, 33.05, 27.55, 22.86, 14.05; IR (neat) 3469.7, 2970.6, 1737.9 cm^{-1}; LRMS (EI$^+$) *m/z* 156 (100), 110 (78), 97 (23); HRMS (EI$^+$) calcd for $C_{11}H_{16}O_4$ 212.1049, found 212.1054. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.17; H, 7.84.

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Supporting Information Available: Experimental details and characterization for substrates **1b**, **1d**−**o**, **3**, **7**, and their precursors and ^{1}H and ^{13}C NMR spectra for compounds without reported elemental analyses (52 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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