# Unsaturated Nitriles: Precursors for a Domino Ozonolysis−Aldol Synthesis of Oxonitriles

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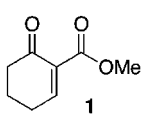
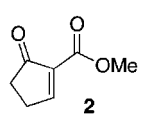
Cyclic five-, six-, and seven-membered oxonitriles are prepared by a tandem ozonolysis−aldol sequence. Cyclopentenylacetonitrile (**4**) and cyclohexenylacetonitrile (**12**) afford the ring-expanded oxonitriles **3** (98%) and **17** (58%), respectively, in highly efficient one-pot syntheses. Homologous five-membered oxonitriles **22a**−**c** are prepared by analogous ozonolysis-aldol cyclizations employing $\omega$-alkenyl $\beta$-ketonitriles. The method tolerates various substitution patterns and allows for the synthesis of $\beta,\beta$-disubstituted oxonitriles (**22c**). The reaction conditions are essentially neutral providing the $\beta$-hydroxyoxonitriles **22d** and **22e** with only trace amounts of the aromatic dehydration product.

Doubly activated alkenes bearing two electron-withdrawing groups on the same carbon are exceptionally reactive electrophiles.[1] The highly polarized $\pi$-bond allows Michael reactions[2] and Diels−Alder cycloadditions[3] that are otherwise unsuccessful with comparable monoactivated alkenes. Several syntheses have exploited this reactivity, both to assemble sterically demanding intermediates[4] and to successfully complete reactions in otherwise unreactive substrates.[2,3]

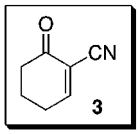
The extensive use of doubly activated alkenes has stimulated a number of excellent syntheses, particularly of cycloalkenones containing an additional electron-withdrawing group on the α-carbon.[5] Historically, many doubly activated alkenes have been prepared by Knoevanagel condensations,[6] although some products are incompatible with the reaction conditions. For example, **1** and **2** rapidly decompose[7] and are frequently prepared by selenation−selenoxide elimination[1b] sequences. The resultant crude alkene is often used without purification since decomposition commonly occurs during silica gel chromatography.[8]




**1**




**2**




**3**

Unsaturated oxonitriles, such as **3**, represent an ideal compromise between stability and high reactivity. Most unsaturated oxonitriles are relatively stable to chromatography and storage and are ideal intermediates for carbocyclic[9] and heterocyclic syntheses.[10,11] Importantly, unsaturated oxonitriles maintain an exceptional reactivity in Diels−Alder reactions[12] and photochemical cycloadditions.[13] Michael reactions of unsaturated oxonitriles exhibit a similar heightened reactivity, giving *conjugate* addition products with Grignard reagents,[14] allyl silanes,[15] and radicals.[11] Biological nucleophiles, particularly sulfides present at enzymatic active sites, react conjugately with unsaturated oxonitriles, making these Michael acceptors potential irreversible enzyme inhibitors.[16]

The exceptional reactivity of unsaturated oxonitriles stimulated us to develop a rapid and general synthesis of this class of compounds. We previously reported our successful synthesis of several substituted unsaturated oxonitriles[17] and fully describe the scope of this method in this paper.

(1) (a) Gololobov, Y. G.; Gruber, W. *Russ. Chem. Rev.* **1997**, *66*, 953. For doubly activated alkenes prepared by selenoxide elimination, see: (b) Reich, H. J.; Wollowitz, S. *Org. React.* **1993**, *44*, 1−296 and Table 11 (pp 254−272) in particular. (c) Liu, H.-J.; Yeh, W.-L.; Browne, E. N. C. *Can. J. Chem.* **1995**, *73*, 1135.

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(3) (a) Liu, H.-J.; Browne, E. N. C. *Can. J. Chem.* **1987**, *65*, 1262. (b) Caine, D.; Harrison, C. R.; VanDerveer, D. G. *Tetrahedron Lett.* **1983**, *24*, 1353.

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(7) Liu, H.; Ngooi, T.; Browne, E. N. C. *Can. J. Chem.* **1988**, *66*, 3143.

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(12) (a) Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904. (b) Bogdanowicz-Szwed, K.; Palasz, A. *Monatsh.* **1995**, *126*, 1341. (c) Lee, I.; Han, E. S. *Hsksurwon Nonmunjip, Cha'yon Kwahak P'yon* **1983**, *22*, 43; *Chem. Abstr.* **1984** *101*, #109891.

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(15) Pan, L.-R.; Tokoroyama, T. *Chem. Lett.* **1990**, 1999.

(16) Brillon, D.; Sauve, G. *J. Org. Chem.* **1992**, *57*, 1838.

(17) Fleming, F. F.; Huang, A.; Sharief, V. A.; Pu, Y. *J. Org. Chem.* **1997**, *62*, 3036.

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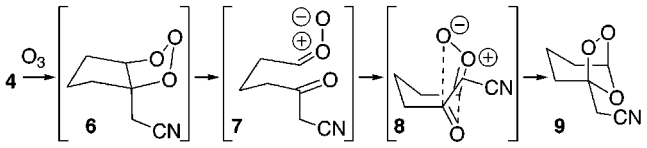
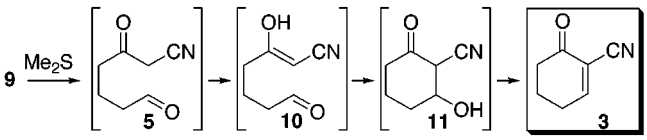
**Scheme 1**

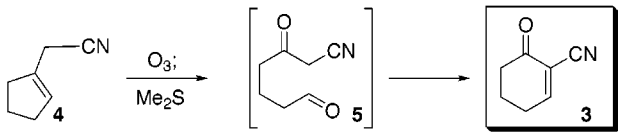


**Scheme 2**



## Results and Discussion

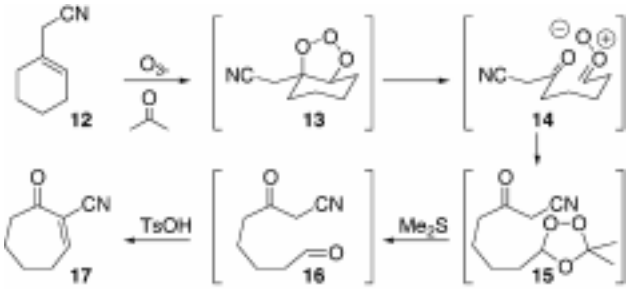
Our strategy for assembling cyclic 2-oxocycloalkenecarbonitriles was based on an attractive domino ozonolysis−aldol sequence[18] (**4** → **3**). Cyclopenteneacetonitrile (**4**) represented an ideal substrate to test this sequence since **4** is readily available and relatively inexpensive.[19] The resultant oxonitrile **3** is particularly valuable both as a substitute for the less stable ester **1** and for *uncatalyzed* conjugate addition reactions with Grignard reagents.[14]



Ozonolysis of cyclopenteneacetonitrile generates a surprisingly stable ozonide **9** (Scheme 1). Careful displacement of excess ozone and solvent removal provides the pure ozonide **9** (71% yield) as a highly crystalline solid, whose structure was determined by X-ray analysis.[20] Formation of **9** involves several complex stereoselective reactions that directly impinge on the efficiency of the reaction. The cycloaddition reaction affords a primary ozonide **6** that is predicted[21] to adopt a conformation with the trioxo bridge in an endo fold. Fragmentation from this conformation dictates the formation of the *cis*-carbonyl oxide **7**. Intramolecular cycloaddition proceeds smoothly since the *cis*-carbonyl oxide readily achieves a conformation (**8**) where there is effective orbital overlap between the 4$\pi$ and 2$\pi$ components.

Dimethyl sulfide reduction of the ozonide **9** triggers a cascade of reactions that generates the oxonitrile **3** in 91% yield (Scheme 2). Formation of **3** is surprisingly easy given the number of proton transfers involved in the conversion of the initial intermediate **5** to the oxonitrile **3**. Enolization of oxonitriles is usually quite facile[22] and, in the case of **5**, provides the intermediate enol **10** that is ideally poised for the ensuing aldol condensation. Spontaneous dehydration of the resultant aldol is particularly facile since **11** is both an aldol and a $\beta$-hydroxy nitrile, functionalities that are particularly prone to dehydration.[23]

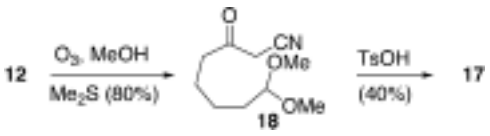
**Scheme 3**



The successful reduction−cyclization of **9** implied that a more efficient one-pot synthesis of the oxonitrile **3** should be possible. In fact, ozonolysis of a dichloromethane solution of cyclopenteneacetonitrile (**4**) followed by the removal of excess ozone and addition of dimethyl sulfide affords the oxonitrile **3** in 98% yield after chromatography. This reaction has been performed numerous times on a 1−5 g scale[24] and consistently affords the oxonitrile **3** in yields greater than 90%. Oxonitrile **3** is remarkably stable to storage with only trace decomposition being observed after several weeks at −4 °C.

Formation of the analogous seven-membered ring oxonitrile is readily achieved from commercially available cyclohexeneacetonitrile (**12**). Ozonolysis of an acetone solution of **12** affords an intermediate ozonide that is redissolved in $CH_2Cl_2$ and reduced with $Me_2S$ providing the intermediate **16** (Scheme 3). Cyclization is induced by treating **16** with a catalytic amount of TsOH in $CH_2Cl_2$ to provide the desired oxonitrile **17** in 58% overall yield.

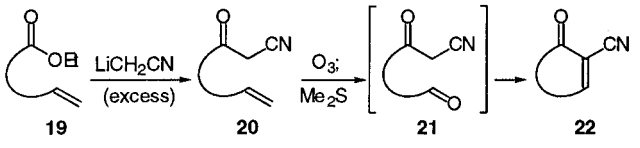
The ozonolysis of **12** must be performed in acetone in order to efficiently intercept the *trans*-carbonyl oxide **14** in an *intermolecular* cycloaddition. The trans geometry of the carbonyl oxide is determined by fragmentation from an exocyclic conformation of the primary ozonide **13**.[21] Unlike the homologous *cis*-carbonyl oxide **7**, the *trans*-carbonyl oxide **14** is unable to achieve a conformation for intramolecular cycloaddition and polymerizes in the absence of a suitable 2$\pi$ reactant. Cleavage of the intermediate ozonide **13** must position the electron-deficient carbonyl oxide on the electron-releasing terminal carbon[21] since the terminal acetal **18** is obtained (80% yield) when the ozonolysis is performed in methanol. Exposure of the acetal to TsOH induces cyclization of the resultant aldehyde and provides **17**, although the yield is modest because of the instability of **17** to the prolonged acid exposure required to cleave the acetal.

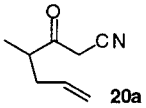
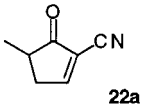
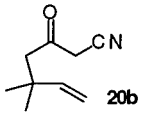
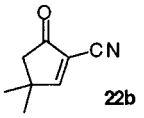
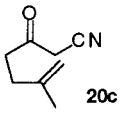
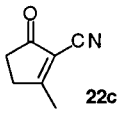
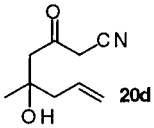
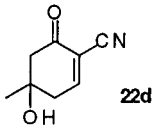
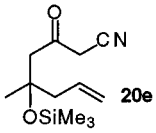
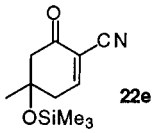


The synthesis of oxonitriles more substituted than **3** or **17** is readily achieved from the corresponding $\omega$-alkenyl esters (Table 1), many of which are commercially available. The classical procedure[25] for converting esters

(18) Kretchmer, R. A.; Thompson, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 3379.
(19) Oakwood Products supplies cyclopenteneacetonitrile at $1.21/g for 100 g quantities.
(20) Tzou, J.-R.; Huang, A.; Fleming, F. F.; Norman, R. E.; Chang, S.-C. *Acta Crystallogr. Sect. C.* **1996**, *C52*, 1012.
(21) Bunnelle, W. H. *Adv. Cycloaddit.* **1993**, *3*, 67.
(22) Elnagdi, M. H.; Elmoghayar, M. R. H.; Elgemeie, G. E. H. *Synthesis* **1984**, 1.
(23) DiBiase, S. A.; Lipisko, B. A., Haag, A.; Wolak, R. A.; Gokel, G. W. *J. Org. Chem.* **1979**, *44*, 4640.
(24) $^1$H NMR spectra of concentrated solutions of **3** (165 mg/mL) exhibit significant spectral shifts ($\Delta\nu = 0.5$ ppm for the olefinic proton) relative to more dilute spectra (~10 mg/mL), which suggests the presence of dimeric aggregates: Ilich, P.; Mishra, P. K.; Macura, S.; Burghardt, T. P. *Spectrochim. Acta A* **1996**, *52*, 1323.
(25) Eby, C. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1957**, *79*, 723.

**Table 1. Tandem Ozonolysis−Aldol Cyclization of Unsaturated Ketonitriles**



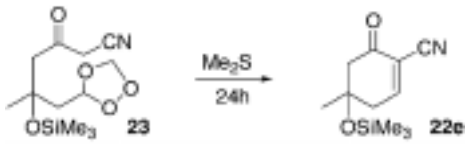

| Entry | Ketonitrile | Yield (%) | Oxonitrile | Yield (%) |
|---|---|---|---|---|
| 1 |  **20a** | 81 |  **22a** | 83[b] |
| 2 |  **20b** | 73 |  **22b** | 91[b] |
| 3 |  **20c** | 71 |  **22c** | 91[c] |
| 4 |  **20d** | 70 |  **22d** | 53 |
| 5 |  **20e** | 58[a] |  **22e** | 57 |

[a] Prepared by silylation of **19d**. [b] The intermediate aldehydes cyclize during silica gel chromatography. [c] The intermediate ketone is cyclized by sequential treatment with $CaH_2$ and aqueous $NH_4Cl$.

to oxonitriles employs sodium amide to deprotonate acetonitrile, but in our experience, this procedure is sometimes unpredictable. Cleaner, more reliable deprotonation is achieved with butyllithium,[26] which consistently affords good yields of the corresponding oxonitriles and is particularly effective for labile systems. The advantage of using $LiCH_2CN$ is seen in the formation of **20d** (Table 1, entry 4) where a significantly lower yield is obtained with $NaCH_2CN$ (70% and 46%, respectively).[27]

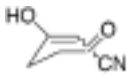
Ozonolysis of the $\beta$-ketonitriles **20a**−**c** occurs readily in $CH_2Cl_2$ at −78 °C to provide the corresponding ozonides. Excess ozone is removed by purging the solution with $N_2$, followed by the addition of $Me_2S$. Careful $^1H$ NMR monitoring of the ozonide reduction indicates that the reaction is initially quite rapid, affording several unidentified side products when performed at room temperature. We assume that the reduction of the ozonide is exothermic and therefore add the dimethyl sulfide slowly at −78 °C.

The ozonides from **20d** and **20e** were significantly more difficult to reduce. Steric crowding has a profound effect on the stability of ozonides,[28] and in our case, the diastereomeric ozonides **23** are sufficiently stable to be separated by chromatography. Reduction of **23** in neat dimethyl sulfide provides the cyclic oxonitrile **22e** in 62% yield, although the preparative formation of **22e** is best achieved using the more efficient one-pot procedure (Table 1, entry 5).

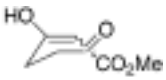



The six-membered oxonitriles cyclize more easily than the five- and seven-membered ring oxonitriles. Monitoring the reactions after the dimethyl sulfide addition reveals that the six-membered oxonitriles are formed with only a small accumulation of the intermediate aldehydes. For the five-membered ring precursors **20a** and **20b** the dimethyl sulfide reduction affords primarily the aldehyde intermediates that cyclize during radial silica gel chromatography.[16] Cyclization of **20c** is even more difficult with chromatography providing the corresponding ketone. The most effective method for obtaining the oxonitrile **22c** is to treat the intermediate ketone with calcium hydride followed by stirring with ammonium chloride to eliminate the presumed aldol intermediate.

Geometric constraints retard the cyclization rate of the five- and seven-membered aldehydes **21**. Cyclization of **20a**−**c** through the enol **24** requires a rather difficult orbital alignment since the double bond rigidifies the carbon framework. A further impediment is the 120° angle of the enol that results in a difficult alignment for the aldehyde and enolic carbons. Presumably, the use of silica gel or $CaH_2$ generates more reactive oxonium or enolate intermediates capable of overcoming these steric constraints. Cyclization of the keto ester **25**[29] is even slower (8 days, *p*-TsOH, rt), possibly as a consequence of the slower enolization of keto esters compared to keto nitriles.[9] The cyclization of **25** affords the desired keto ester **2**, but the instability of this material to silica gel chromatography[8] prevents this from being a viable preparative procedure.



**24**



**25**

Collectively, the examples in Table 1 show that the method is quite general for assembling substituted oxonitriles. The method tolerates various substitution patterns and allows for the synthesis of $\beta,\beta$-disubstituted systems (entry 3). The cyclization conditions are essentially neutral, allowing the synthesis of the rather sensitive nitriles **22d** and **22e** with only trace amounts of the aromatic dehydration product. Preparation of gram quantities of **22d** revealed a sensitivity of this material to dehydration on silica gel. Consequently, trace impurities were removed by rapid radial chromatography, allowing for the preparation of **22d** in slightly greater than 50% yield, although on one occasion the yield was as high as 98%.

(26) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1.

(27) The reaction of $NaCH_2CN$ with **19e** affords only trace amounts (8%) of **20e**. The main component is tentatively assigned as the conjugated enoate resulting from elimination of trimethylsiloxide. For a related example, see: Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.-B.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965.

(28) Mayr, H.; Baran, J.; Will, E.; Yanakoshi, H.; Teshima, K.; Nojima, M. *J. Org. Chem.* **1994**, *59*, 5055.

(29) Prepared by ozonolysis of commercially available methyl 3-oxo-6-octenoate.

## Conclusion

The tandem ozonolysis−aldol reaction of unsaturated nitriles is an efficient method for preparing cyclic five-, six-, and seven-membered oxonitriles. In the case of cyclopentene- and cyclohexeneacetonitrile (**3** and **17**, respectively) the sequence represents a new method for ring expansion that converts $\beta,\gamma$-unsaturated nitriles into highly reactive oxonitriles. The conditions are extremely mild, allowing for the synthesis of a diverse range of oxonitriles.

## Experimental Section[30]

**General Procedure for Preparing 3-Oxonitriles (20a−d).** Neat acetonitrile (2.0 equiv) was added to a cold (−78 °C), stirred, THF solution (0.1 M) of *n*-butyllithium (~1 M in hexanes, 2.0 equiv). A white suspension formed that was stirred for 1 h before the slow addition (5−10 min) of a THF solution (0.1 M) of the alkenylester (1.0 equiv). The resultant yellow mixture was warmed to −45 °C and stirred for 2 h, and then aqueous hydrochloric acid (2 M) was added until the solution was neutral to pH paper. The organic phase was separated, washed with brine, dried over $Na_2SO_4$, and concentrated under reduced pressure. Radial chromatography of the crude product (2:8 EtOAc/hexanes) provided the corresponding 3-oxonitrile.

**4-Methyl-3-oxo-6-heptenenitrile (20a).** The general procedure was employed with acetonitrile (28.1 mmol, 1.47 mL), *n*-butyllithium (28.1 mmol, 1.43 M), and ethyl 2-methyl-4-pentenoate (14.1 mmol, 2.29 mL). Radial chromatography of the crude product (4 mm silica gel plate, 2:8 EtOAc/hexanes) provided 1.57 g (81%) of the nitrile **20a** as a yellow oil: IR (film) 3079, 2261, 1732, 1641 $cm^{-1}$; $^1H$ NMR $\delta$ 1.15 (d, $J$ = 6.9 Hz, 3H), 2.12−2.22 (m, 1H), 2.35−2.46 (m, 1H), 2.79 (sextet, $J$ = 6.9 Hz, 1H), 3.51 (s, 2H), 5.04−5.11 (m, 2H), 5.71 (ddt, $J$ = 17.3, 9.8, 7.1 Hz, 1H); $^{13}C$ NMR $\delta$: 15.6 (q), 31.0 (t), 36.6 (t), 45.5 (d), 113.7 (s), 117.9 (t), 134.2 (d), 200.6 (s).

**5,5-Dimethyl-3-oxo-6-heptenenitrile (20b).** The general procedure was employed with acetonitrile (14.0 mmol, 0.73 mL), *n*-butyllithium (14.0 mmol, 1.36 M), and methyl 3,3-dimethyl-4-pentenoate (7.02 mmol, 1.11 mL). Radial chromatography of the crude product (4 mm silica gel plate, 2:8 EtOAc/hexanes) gave 770 mg (73%).

**6-Methyl-3-oxo-6-heptenenitrile (20c).** The general procedure was employed with acetonitrile (14.0 mmol, 0.73 mL), *n*-butyllithium (14.0 mmol, 1.15 M), and ethyl 4-methyl-4-pentenoate (6.95 mmol, 1.11 mL). Radial chromatography of the crude product (4 mm silica gel plate, 2:8 EtOAc/hexanes) gave 683 mg (71%).

**5-Hydroxy-5-methyl-3-oxo-7-octenenitrile (20d).** This oxonitrile was prepared from ethyl 3-hydroxy-3-methyl-5-hexenoate (**19d**), which was prepared by a modification of the literature procedure:[31] Dry ethyl acetoacetate (110 $\mu$L, 0.86 mmol) and allyl bromide (407.1 mg, 3.37 mmol) were added, sequentially, to a stirred, THF suspension (1 mL) of grannular zinc (236.9 mg, 3.62 mmol). The resultant mixture was heated to reflux for 0.5 h, allowed to cool to room temperature, and then filtered through a plug of cotton wool. The filtrate was diluted with EtOAc (20 mL) and vigorously stirred, and then aqueous HCl (1%, 20 mL) was added. After 5 min, the mixture was filtered through a plug of Celite, extracted with EtOAc (3 × 10 mL), dried, and concentrated. Radial chromatography of the crude product (1 mm plate, 1:9 then 1:5 EtOAc/hexane), followed by concentration of the appropriate fractions, provided 104.1 mg (58%) of **19d** whose spectral data have not previously been published: IR (film) 3454, 3079, 2979, 1714, 1641 $cm^{-1}$; $^1H$ NMR $\delta$: 1.22 (s, 3H), 1.25 (t, $J$ = 7.1 Hz, 3H), 2.27 (br d, $J$ = 7 Hz, 2H), 2.43 (ABq, $\Delta\nu$ = 30.6, $J$ = 15.6 Hz, 2H), 3.61 (br s, 1H), 4.15 (q, $J$ = 7.1 Hz, 2H), 5.02−5.11 (m, 2H), 5.75−5.90 (m, 1H); $^{13}C$ NMR $\delta$ 14.1, 26.7, 44.3, 46.4, 60.5, 70.6, 118.4, 133.6, 172.8; MS *m/e* 173 ($MH^+$).

Standard silylation (TMSCl, 1.5 equiv; $Et_3N$, 2.5 equiv; $CH_2Cl_2$) of **19d** afforded **19e** in 58% yield as an oil: IR (film) 3078, 2960, 1737, 1641 $cm^{-1}$; $^1H$ NMR $\delta$ 0.12 (s, 9H), 1.25 (t, $J$ = 7.1 Hz, 3H), 1.35 (s, 3H), 2.33−2.37 (m, 2H), 2.43 (ABq, $\Delta\nu$ = 16.9, $J$ = 13 Hz, 2H), 4.11 (q, $J$ = 7.1 Hz, 2H), 5.03−5.06 (m, 1H), 5.09 (s, 1H), 5.76−5.90 (m, 1H); $^{13}C$ NMR $\delta$ 2.42, 14.2, 27.6, 46.8, 47.3, 60.0, 74.6, 117.9, 134.4, 171.0; MS *m/e* 229 ($M - CH_3^+$).

Formation of **20d** was achieved using the general procedure with acetonitrile (2.92 mL, 56 mmol), *n*-butyllithium (56 mmol), and **19d** (2.756 g, 16 mmol). Radial chromatography of the crude product (4 mm silica gel plate, 1:3 EtOAc/hexanes) gave 1.88 g (70%) of the nitrile **20d** as a yellow oil: IR (film) 3455, 3078, 2978, 2920, 2260, 2210, 1726, 1641 $cm^{-1}$; $^1H$ NMR $\delta$ 1.26 (s, 3H), 2.26−2.34 (m, 3H), 2.68 (ABq, $\Delta\nu$ = 44.2, $J$ = 15.3 Hz, 2H), 3.61 (ABq, $\Delta\nu$ = 23.6, $J$ = 19.7 Hz, 2H), 5.08−5.19 (m, 2H), 5.74−5.88 (m, 1H); $^{13}C$ NMR $\delta$ 27.0, 33.8, 46.7, 51.6, 71.6, 113.7, 119.7, 132.8, 198.2; MS *m/e* 168 ($MH^+$).

**5-Methyl-5-trimethylsilyloxy-3-oxo-7-octenenitrile (20e).** Neat triethylamine (67 $\mu$L, 0.48 mmol) and trimethylsilyl chloride (37 $\mu$L, 0.29 mmol) were sequentially added to a dichloromethane solution (1 mL) of ethyl 3-hydroxy-3-methyl-5-hexenoate (**19d**) at room temperature. After 21 h, saturated, aqueous $NaHCO_3$ was added, the phases were separated, and the organic phase was extracted with EtOAc (3 × 10 mL). The combined extracts were dried ($MgSO_4$), concentrated, and then purified by radial chromatography (1:9 then 1:5 EtOAc/hexanes) to provide 26.8 mg (58%) of **20e** as an oil: IR (film) 3079, 2958, 2259, 2213, 1731, 1641 $cm^{-1}$; $^1H$ NMR $\delta$ 0.16 (s, 9H), 1.33 (s, 3H) 2.25 (dd, $J$ = 13.7, 7.9 Hz, 1H), 2.39 (dd, $J$ = 13.7, 6.9 Hz, 1H), 2.58 (ABq, $\Delta\nu$ = 84.3, $J$ = 12.5 Hz, 2H), 3.58 (ABq, $\Delta\nu$ = 27.9, $J$ = 19.5 Hz, 2H), 5.07−5.15 (m, 2H), 5.70−5.84 (m, 1H); $^{13}C$ NMR $\delta$ 2.4, 27.6, 34.2, 47.6, 52.9, 75.9, 114.0, 119.1, 133.3, 197.4; MS *m/e* 224 ($M - CH_3^+$).

**General Ozonolysis Procedure.** A stream of ozone was bubbled through a cold (−78 °C), dichloromethane solution of the unsaturated nitrile until the distinctive blue color of ozone was clearly observed. Ozonolysis was then terminated, and excess ozone was displaced by passing a stream of nitrogen through the solution for 5−10 min. The solution was allowed to warm to room temperature, and then neat dimethyl sulfide was added.

**1-Cyanomethyl-6,7,8-trioxabicyclo[3.2.1]octane.** Ozonolysis of a dichloromethane (5 mL) solution of **4** (112.3 mg, 1.05 mmol) was performed according to the general procedure except that the solution was concentrated after purging with nitrogen. Crystallization occurred during concentration to provide 115.4 mg (71%) of the ozonide **9** as colorless crystals (mp 50−51 °C): IR (KBr) 2259, 1105 $cm^{-1}$; $^1H$ NMR $\delta$ 1.71−2.04 (m, 5H), 2.18−2.32 (m, 1H), 2.90 (s, 2H), 5.89 (s, 1H). $^{13}C$ NMR $\delta$ 15.5 (t), 24.9 (t), 28.5 (t), 31.8 (t), 103.7 (d), 105.2 (s), 114.1 (s).

**2-Oxo-6-cyclohexenecarbonitrile (3). (a) From Ozonide 9.** Neat $Me_2S$ (0.2 mL) was added to a dichloromethane solution (4 mL) of the ozonide **9** (91.9 mg, 0.592 mmol) at room temperature. The resultant solution was stirred at room temperature for 35 h, and then the solvent was removed under reduced pressure. Chromatography of the crude product (1 mm plate, elution with EtOAc/hexane 4:6) followed by concentration of the appropriate fractions gave 65.1 mg (91%) of **3** as a yellow oil: IR (film) 2233, 1698, 1615 $cm^{-1}$; $^1H$ NMR $\delta$ 2.10 (br quintet, $J$ = 6 Hz, 2H), 2.53−2.61 (m, 4H), 7.75 (t, $J$ = 4.2 Hz, 1H): $^{13}C$ NMR $\delta$ 21.2 (t), 26.3 (t), 36.9 (t), 114.0 (s), 117.3 (s), 163.4 (d), 192.0 (s). MS *m/e* 122 ($M + H^+$).

**(b) From 4 without Isolation of the Ozonide 9.** Ozonolysis of a dichloromethane (5 mL) solution of **4** (128.4 mg, 1.20 mmol) was performed according to the general procedure using 0.2 mL of dimethyl sulfide. The resultant mixture was stirred at room temperature for 30 h, and then the solvent was removed under reduced pressure. Radial chromatography of the crude product (1 mm silica gel plate) with rapid elution (3:2 EtOAc/hexane, 4 mm solvent delivery tip), and concentra-

(30) For general experimental procedures, see: Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305.

(31) Wilson, W. K.; Baca, S. B.; Barber, Y. J.; Scallen, T. J.; Morrow, C. J. *J. Org. Chem.* **1983**, *48*, 3960.

tion of the appropriate fractions under reduced pressure gave 142.3 mg (98%) of **3**.

**2-Oxo-6-cycloheptenecarbonitrile (17). (a) From 12.** Ozonolysis of an acetone (5 mL) solution of **12** (504.0 mg, 4.16 mmol) was performed according to the general procedure using 0.6 mL of dimethyl sulfide. The resultant mixture was stirred overnight and was then concentrated. The resultant material was dissolved in dry $CH_2Cl_2$ (5 mL), TsOH (44.1 mg, 0.23 mmol) was added, and the solution was then stirred overnight. The solvent was removed under reduced pressure, and the crude product was purified by radial chromatography (1 mm silica gel plate, 6:4 EtOAc/hexane) to provide 326.7 mg (58%) of **17** as a yellow oil: IR (film) 2229, 1684, 1616 $cm^{-1}$; $^1H$ NMR $\delta$ 1.81−1.86 (m, 4H), 2.64−2.72 (m, 4H), 7.49 (t, $J$ = 6.0 Hz, 1H); $^{13}C$ NMR $\delta$ 20.9 (t), 24.9 (t), 30.1 (t), 42.7 (t), 115.9 (s), 120.9 (s), 160.0 (d), 196.7 (s); MS *m/e* 136 ($MH^+$).

**(b) From 18.** TsOH (13.0 mg, 68.3 $\mu$mol) was added to a dichloromethane solution (5 mL) of **18** (135.8 mg, 0.68 mmol), and the resultant solution was stirred for 30 h at room temperature. Concentration of the resultant crude product followed by chromatography on silica gel ($CH_2Cl_2$) gave 36.8 mg (40%) of **17** as a yellow oil.

**8,8-Dimethoxy-3-oxooctanenitrile (18).** Ozonolysis of a dichloromethane-methanol solution (5 mL, 4:1, v/v) of **12** (103.2 mg, 0.85 mmol) was performed according to the general procedure using 0.2 mL of dimethyl sulfide. The resultant mixture was stirred for 30 h, and then the solvent was removed under reduced pressure. Radial chromatography of the crude product with rapid elution (1 mm silica plate, elution with EtOAc/hexane 4:6, 4 mm solvent delivery tip), and concentration of the appropriate fractions gave 135.8 mg (80%) of **18** as a colorless oil: IR (film) 2208, 1732 cm-1; $^1H$ NMR $\delta$ 1.33−1.42 (m, 2H), 1.57−1.70 (m, 4H), 2.62 (t, $J$ = 7.2 Hz, 2H), 3.31 (s, 6H), 3.45 (s, 2H), 4.34 (t, $J$ = 5.6 Hz, 1H); $^{13}C$ NMR $\delta$ 23.0, 23.7, 31.9, 32.1 41.9, 52.8, 104.2, 113.8, 197.4.

**3-Methyl-2-oxo-5-cyclopentenecarbonitrile (22a).** Ozonolysis of a dichloromethane (6 mL) solution of **20a** (102.4 mg, 0.75 mmol) was performed according to the general procedure, terminating the ozonolysis immediately upon observation of the distinctive blue color of ozone. Neat dimethyl sulfide (2.5 mL) was then added, dropwise, at −78 °C. The resultant mixture was allowed to warm to room temperature and stirred for 4 h, and then the solvent was removed under reduced pressure. Chromatography of the crude product (1 mm silica gel plate, 3:2 EtOAc/hexanes) and concentration of the appropriate fractions under reduced pressure gave 75.0 mg (83%) of **22a** as a colorless oil: IR (film) 3074, 2974, 2936, 2234, 1729, 1647 $cm^{-1}$; $^1H$ NMR $\delta$ 1.23 (d, $J$ = 7.5 Hz, 3H), 2.43−2.61 (m, 2H), 3.14 (br ddd, $J$ = 21, 7, 3 Hz, 1H), 8.28 (t, $J$ = 3 Hz, 1H); $^{13}C$ NMR $\delta$ 15.7, 37.3, 39.5, 111.9, 120.4, 172.8, 203.9; MS *m/e* 121 ($M^+$).

**4,4-Dimethyl-2-oxo-5-cyclopentenecarbonitrile (22b).** Ozonolysis of a dichloromethane (6 mL) solution of **20b** (102.0 mg, 0.67 mmol) was performed according to the general procedure, terminating the ozonolysis immediately upon observation of the distinctive blue color of ozone. Neat dimethyl sulfide (2.5 mL) was then added, dropwise, at −78 °C. The resultant mixture was allowed to warm to room temperature and stirred for 22 h, and then the solvent was removed under reduced pressure. Chromatography of the crude product (1 mm silica gel plate, 1:1 EtOAc/hexanes) and concentration of the appropriate fractions under reduced pressure gave 83.0 mg (91%) of **22b** as a colorless oil: IR (film) 3056, 2974, 2236, 1702, 1654 $cm^{-1}$; $^1H$ NMR $\delta$ 1.31 (s, 6H), 2.40 (s, 2H), 8.04 (s, 1H); $^{13}C$ NMR $\delta$ 27.3, 41.5, 49.1, 111.5, 118.4, 181.8, 200.5; GC/MS *m/e* 136 (MH).

**5-Methyl-2-oxo-5-cyclopentenecarbonitrile (22c).** Ozonolysis of a dichloromethane solution (2.5 mL) of **20c** (89.0 mg, 0.65 mmol) was performed according to the general procedure, terminating the ozonolysis immediately upon observation of the distinctive blue color of ozone. The solution was concentrated and redissolved in dimethyl sulfide (1 mL). The resultant solution was stirred for 12 h, and then the solvent was removed under reduced pressure. The crude ketone was dissolved in THF (5 mL), and solid calcium hydride (35.5 mg, 0.84 mmol) was added. After 3 h, saturated aqueous ammonium chloride (3.0 mL) was cautiously added and stirring continued for 1 h. The organic phase was separated, dried over $MgSO_4$, and concentrated under reduced pressure. Radial chromatography of the crude product (1 mm silica gel plate, EtOAc) afforded 64.0 mg (81%) of **22c** as a colorless oil: IR (film) 2919, 2229, 1719, 1633 $cm^{-1}$; $^1H$ NMR $\delta$ 2.41 (s, 3H), 2.57 (br t, $J$ = 5 Hz, 2 H), 2.78−2.82 (m, 2H); $^{13}C$ NMR $\delta$ 19.6, 33.0, 34.8, 111.8, 118.0, 189.3, 201.0; GC/MS *m/e* 122 (M + 1).

**4-Hydroxy-4-methyl-2-oxo-6-cyclohexenecarbonitrile (22d).** Ozonolysis of a dichloromethane (2 mL) solution of **20d** (45.4 mg, 0.27 mmol) was performed according to the general procedure. The solvent was removed, and the resultant material was dissolved in dimethyl sulfide (1 mL) with the aid of sonication. The solution was allowed to stir for 15 h and was then concentrated and purified by radial chromatography (1 mm plate, 3:2 EtOAc/hexanes) to afford 21.9 mg (53%) of **22d** as an oil: IR (film) 3473, 2972, 2929, 2235, 1698, 1616 $cm^{-1}$; $^1H$ NMR $\delta$ 1.43 (s, 3H); 2.68 (ABq, $\Delta\nu$ = 37.9, $J$ = 16.4 Hz, 2H), 2.72−2.84 (m, 2H), 7.64 (dd, $J$ = 4.9, 3.4 Hz, 1H); $^{13}C$ NMR $\delta$ 29.5, 40.5, 51.0, 71.4, 113.9, 117.3, 159.1, 191.4; MS *m/e* 134 ($M - OH^+$).

**4-Methyl-2-oxo-4-trimethylsilyloxy-6-cyclohexenecarbonitrile (22e).** Ozonolysis of a dichloromethane (1 mL) solution of **20e** (25.6 mg, 0.11 mmol) was performed according to the general procedure. The solvent was removed, and the resultant material was dissolved in dimethyl sulfide (1 mL) with the aid of sonication. The solution was allowed to stir for 15 h and was then concentrated and purified by radial chromatography (1 mm plate, 1:4 EtOAc/hexanes) to afford 13.7 mg (57%) of **22e** as an oil: IR (film) 2976, 2234, 1703, 1619 $cm^{-1}$; $^1H$ NMR $\delta$ 0.09 (s, 9H), 1.42 (s, 3H), 2.36−2.80 (m, 4H), 7.56 (dd, $J$ = 5.0, 3.3 Hz, 1H); $^{13}C$ NMR $\delta$ 2.2, 29.1, 42.0, 52.1, 74.1, 114.0, 117.4, 158.6, 191.2.

**5-Methyl-5-trimethylsilyloxy-6-(2,3,5-trioxacyclopentyl)-3-oxohexanenitrile (23).** Ozonolysis of a dichloromethane (1 mL) solution of **20e** (17.3 mg, 72.4 $\mu$mol) was performed according to the general procedure. The solvent was removed, and the resultant material was purified by radial chromatography (1 mm plate, 1:4 EtOAc/hexanes) to afford 2.3 mg (11%) of a fast eluting diastereomer **23a** as an oil: IR (film) 2960, 2260, 1732 $cm^{-1}$; $^1H$ NMR $\delta$ 0.16 (s, 9H), 1.45 (s, 3H), 1.97 (dd, $J$ = 14.8, 6.8 Hz, 1H), 2.08 (dd, $J$ = 14.8, 3.3 Hz, 1H), 2.76 (AB$q$, $J$ = 14.7, $\Delta\nu_{AB}$ = 34.0 Hz, 2H), 3.55 (AB$q$, $J$ = 19.3, $\Delta\nu_{AB}$ = 26.8 Hz, 2H), 5.08 (d, $J$ = 18.9, 2H), 5.33 (dd, $J$ = 6.8, 3.3 Hz, 1H); $^{13}C$ NMR $\delta$ 2.4, 28.7, 33.9, 43.6, 53.1, 73.4, 93.7, 101.2, 113.7, 196.2; MS *m/e* 286 ($M - H^+$). Chromatography also afforded 3.0 mg (14%) of a slow-eluting diastereomer **23b** as an oil: IR (film) 2959, 2260, 1732 $cm^{-1}$; $^1H$ NMR $\delta$ 0.16 (s, 9H), 1.47 (s, 3H), 1.95−2.04 (m, 2H), 2.81 (AB$q$, $J$ = 15.0, $\Delta\nu_{AB}$ = 27.7 Hz, 2H), 3.53 (AB$q$, $J$ = 19.4, $\Delta\nu_{AB}$ = 24.2 Hz, 2H), 5.00 (s, 1H), 5.19 (s, 1H), 5.29 (t, $J$ = 4.9 Hz, 1H); $^{13}C$ NMR $\delta$ 2.4, 28.8, 33.7, 42.9, 53.2, 73.4, 93.9, 101.1, 113.7, 196.1; MS *m/e* 286 ($M - H^+$).

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**Supporting Information Available:** $^1H$ NMR and $^{13}C$ NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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