JOC*Article*

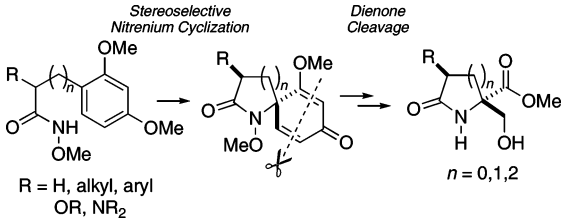
Nitrenium Ion Azaspirocyclization−Spirodienone Cleavage: A New Synthetic Strategy for the Stereocontrolled Preparation of Highly Substituted Lactams and *N*-Hydroxy Lactams

Duncan J. Wardrop* and Matthew S. Burge

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607

wardropd@uic.edu

Received June 17, 2005



Although 1,4-cyclohexadienes **2**, obtained through the Birch reduction of arenes **1**, have found widespread use as masked β-oxo carbonyl synthons **3**, the possibility that 2,5-cyclohexadienones **5** might also be employed to the same end has been overlooked despite their ready availability. As part of our ongoing investigation of the synthetic chemistry of nitrenium ions, we have developed a novel and efficient strategy for the stereoselective preparation of di- and trisubstituted azetidinone, pyrrolidinone, and piperidinone derivatives, which features the ozonolytic cleavage of azaspirocyclic 2,5-cyclohexadienones **12**. For example, ozonolysis of spirodienone **12c** in CH_2Cl_2 and reductive workup with dimethyl sulfide generated unstable β-formyl ester **21**, whereas cleavage in MeOH followed by reduction with thiourea led to hemiacetal **22**. While both **21** and **22** partially decompose upon exposure to silica gel, they can be trapped in situ, with a variety of weakly basic nucleophiles, to usefully substituted products. The requisite spirodienone substrates are readily accessible through the nitrenium ion cyclization of alkyl ω-arylhydroxamates **10**, which proceeds with moderate to high diastereoselectivity.

Introduction

The synthetic equivalency of benzenoid systems and carbonyl-based functional groups[1] has been widely exploited since Woodward's biosynthetically inspired use of a veratryl group as a masked hexa-2,4-dienedioic acid during his total synthesis of strychnine.[2] Among the numerous reports concerning the oxidative cleavage of aromatic and heteroaromatic rings to form carboxylic acids, lactones and other related functionality,[3] the use of disubstituted arenes **1** as latent 1,3-dicarbonyl groups **3** has proven to be particularly fruitful (Scheme 1). Rather than involving a direct oxidation, in this case, Birch reduction of **1** and cleavage of one or both double bonds in the resulting dihydroaromatic compound **2**, most commonly through ozonolysis, serves to unmask the latent dicarbonyl system.[4] This two-step protocol is tolerant of a wide range of aryl substituents (R^1, R^2) and has successfully been applied to the synthesis of β-keto

* To whom correspondence should be addressed. Tel: 312-996-8542. Fax: 312-996-0431.

(1) Ho, T.-L. *Tactics of Organic Synthesis*, 1st ed.; Wiley: New York, 1994; pp 50−53.

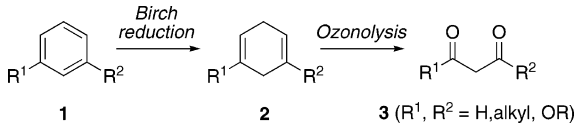
(2) (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. (b) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *Tetrahedron* **1963**, *19*, 247.

(3) For recent, representative reports concerning the oxidative degradation of benzenoid systems, see: (a) Audouard, C.; Barsukov, I.; Fawcett, J.; Griffith, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A. *Chem. Commun.* **2004**, 1526 (b) Lee, Y.-S.; Choung, W.-K.; Kim, K. H.; Kang, T. W.; Ha, D.-C. *Tetrahedron* **2004**, *60*, 867. (c) Miranda, L. S. M.; Vasconcellos, M. L. A. A. *Synthesis* **2004**, 1767. (d) Demir, A.; Sesenoglu, O.; Ulku, D.; Arici, C. *Helv. Chim. Acta* **2003**, *86*, 91. (e) Jaroch, S.; Holscher, P.; Rehwinkel, H.; Sulzle, D.; Burton, G.; Hillmann, M.; McDonald, F. M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1981. (f) Mander, L. N.; Williams, C. M. *Tetrahedron* **2003**, *59*, 1105 and references therein. (g) Colletti, S. L.; Li, C.; Fisher, M. H.; Wyvratt, M. J.; Meinke, P. T. *Tetrahedron Lett.* **2000**, *41*, 7825. (h) Bringmann, G.; Munchbach, M.; Michel, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3167. (i) Zhou, W.-S.; Lu, Z.-H.; Xu, Y.-M.; Liao, L.-X.; Wang, Z.-M. *Tetrahedron* **1999**, *55*, 11959.

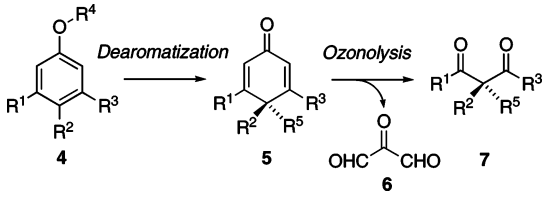
(4) Birch, A. J.; Fitton, F.; Smith, D. C. C.; Steere, D. E.; Stelfox, A. R. *J. Chem. Soc.* **1963**, 2209.

10.1021/jo051252r CCC: $30.25
Published on Web 11/12/2005

SCHEME 1. 1,3-Disubstituted Arenes as Masked *β*-Oxo Carbonyl Synthons



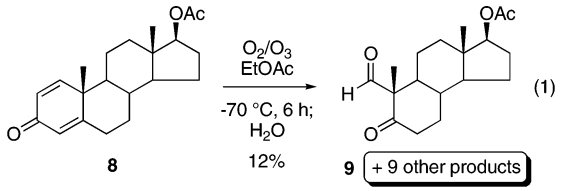
SCHEME 2. 2,5-Cyclohexadienones as Potential Masked *β*-Oxo Carbonyl Synthons



esters,[5] ω-formyl esters,[6] malonate esters,[7] β-diketones,[8] β-formyl ketones,[9] and even higher order polyketides.[10]

In contrast to cyclohexadienes **2**, there are only a handful of accounts documenting the ozonolytic cleavage of 2,5-cyclohexadienones **5**, their electron-deficient congeners, to form 1,3-dicarbonyl compounds **7** (Scheme 2).[11] Given the complex nature of the reaction between dienones and ozone, the absence of reports concerning this transformation is perhaps understandable. The ozonolysis of cross-conjugated ketones was first studied by Harries, who noted that while treatment of phorone with excess ozone formed mesoxaldialdehyde (**6**) and acetone,[12] exposure of this substrate to 1 equiv of ozone resulted in anomalous ozonolysis[13] to produce β,β-dimethylacrylic acid.

More recently, Caspi[11a–c] and Rodig[11d] have independently investigated the ozonolysis of steroidal $\Delta^{1,4}$–3-ketones and found the outcome of this reaction to be similarly complex. Ozonolysis of 1-dehydrotestosterone acetate (**8**) in ethyl acetate,[11c] for example, provided keto aldehyde **9** in low yield together with *nine other products*, which were proposed to arise through anomalous ozonolysis of **8**, Baeyer–Villiger oxidation of aldehyde **9**,[14] and the partial ozonolytic cleavage of the dienone ring.[15]



Notwithstanding these unpromising observations, successful ozonolytic cleavage of systems such as **5** remains synthetically appealing for a number of reasons, not least of which is the prospect that a route to 1,3-dicarbonyl systems, which bear an asymmetric quaternary stereocenter at C-2, might be established through the ozonolysis of differentially 4,4-disubstituted 2,5-cyclohexadienones **5**.[16] That the requisite dienones precursors **5** are readily available, through with the oxidation of phenols **4** and other electron-rich arenes,[17] is an additionally attractive feature of this type of transformation.

Our interest in the ozonolytic cleavage of 2,5-cyclohexadienones was spurred by this laboratory's ongoing study of the synthetic application of acyl nitrenium ions.[18–20] We have recently reported a stereoselective nitrenium ion spirocyclization involving the treatment of α- and β-substituted methyl 3-(methoxyphenyl)propiohydroxamates **10** (n = 1) with phenyliodine(III) bis-(trifluoroacetate) (PIFA) to provide spirolactams **12** with useful levels of diastereoselectivity (Scheme 3).[21]

(5) (a) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 3119. (b) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M. and Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741. (c) Rao, A. V. R.; Gurjar, M. K.; Islam, A. *Tetrahedron Lett.* **1993**, *34*, 4993.

(6) (a) Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. J. *Am. Chem. Soc.* **1968**, *90*, 5618. (b) Moody, C. J.; Toczek, J. *Tetrahedron Lett.* **1986**, *27*, 5253. (c) Moody, C. J.; Toczek, J. *J. Chem. Soc.-Perkin Trans. 1* **1988**, 1397. (d) Kammler, R.; Polborn, K.; Wanner, K. T. *Tetrahedron* **2003**, *59*, 3359.

(7) (a) Mittelbach, M.; Poklukar, N.; Junek, H. *Liebigs Ann. Chem.* **1990**, 185. (b) Bringmann, G.; Kuenkel, G.; Geuder, T. *Synlett* **1990**, 253. (c) Bringmann, G.; Geuder, T. *Synthesis* **1991**, 829.

(8) (a) Wipf, P.; Lim, S. *J. Am. Chem. Soc.,* **1995**, *117*, 558. (b) Wipf, P.; Reeves, J. T. *Chem. Commun.* **2002**, 2066. (c) Jung, I. C. *Eur. J. Org. Chem.* **2001**, 1899.

(9) (a) Zvilichovsky, G.; Gurvich, V. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2509. (b) Zvilichovsky, G.; Gurvich, V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1069 (c) Zvilichovsky, G.; Gurvich, V. *Tetrahedron* **1995**, *51*, 5479. (d) Gbara-Haj-Yahia, I.; Zvilichovsky, G.; Seri, N. *J. Org. Chem.* **2004**, *69*, 4135.

(10) (a) Kirkemo, C. L.; White, J. D. *J. Org. Chem.*, **1985**, *50*, 1316. (b) Bringmann, G. *Liebigs Ann.*, *Chem.* **1985**, 2105.

(11) For reports concerning the ozonolysis of 2,5-cyclohexadienones, see: (a) Caspi, E.; Schmid, W.; Khan, B. T. *Tetrahedron* **1962**, *18*, 767. (b) Caspi, E.; Khan, B. T.; Balasubrahmanyam, S. N. *Tetrahedron* **1962**, *18*, 1013. (c) Balasubrahmanyam, S. N.; Caspi, E.; Khan, B. T. *J. Chem. Soc.* **1963**, 761. (d) Rodig, O. R.; Zanati, G. *J. Org. Chem.* **1968**, *33*, 914. (e) Okamoto, K.; Nitta, I.; Shingu, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1768. (f) Bailey, P. S.; Ferrell, T. M. *J. Org. Chem.* **1981**, *46*, 5028.

(12) (a) Harries, C.; Turk, H. *Chem. Ber.* **1905**, *38*, 1630. (b) Harries, C. *Ann.* **1910**, *374,* 288. (c) For an account of Harries' introduction of ozone into organic chemistry, see: Rubin, M. B. *Helv. Chim. Acta* **2003**, *86*, 930.

(13) Bailey, P. S. *Ozonation in Organic Chemistry*, *Vol. 1*; Trahanovsky, W., Ed.; Academic Press: New York, 1978; Vol. I, pp 153–162.

(14) Story, P. R.; Burgess, J. R. *Tetrahedron Lett.* **1968**, 1287.

(15) (a) Shibata, K.; Takegawa, S.; Koizumi, N.; Yamakoshi, N.; Shimazawa, E. *Chem. Pharm. Bull.* **1992**, *40*, 935. (b) Koizumi, N.; Takegawa, S.; Mieda, M.; Shibata, K. *Chem. Pharm. Bull.* **1996**, *44*, 2162. (c) Cambie, R. C.; Higgs, P. I.; Read, C. M.; Rutledge, P. S.; Ryan, G. R.; Woodgate, P. D. *Aust. J. Chem.* **1990**, *43*, 681.

(16) For reviews covering the formation of quaternary stereogenic center, see: (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

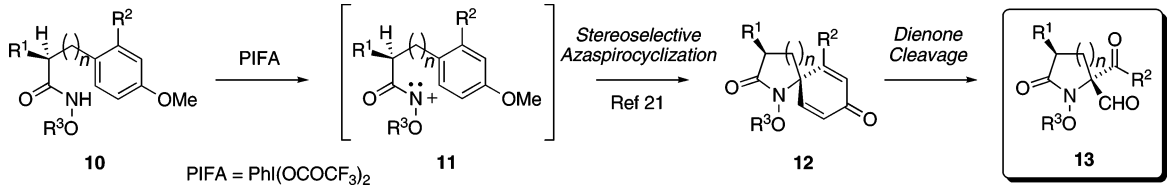
(17) For recent reviews of phenolic oxidation, see: (a) Wirth, T. In *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Springer: Berlin, 2003; Vol. 224. (b) Moriarty, R. M.; Prakash, O. *Org. React.* **2001**, *57*, 327. (c) Pelter, A.; Ward, R. S. *Tetrahedron* **2001**, *57*, 273.

(18) (a) Wardrop, D. J.; Basak, A. *Org. Lett.*, **2001**, *3*, 1053. (b) Wardrop, D. J.; Zhang, W. *Org. Lett*., **2001**, *3*, 2353. (c) Wardrop, D. J.; Landrie, C. L.; Ortíz, J. A. *Synlett*, **2003**, 1352.

(19) For reviews concerning the chemistry of nitrenium ions, see: (a) Falvey, D. E. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jones, M., Eds.; Wiley-Interscience: Hoboken, NJ, 2004; Chapter 13. (b) Kikugawa, Y. *Rev. Heteroatom Chem.* **1996**, *15*, 263. (c) Abramovitch, R. A.; Jeyaraman, R. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Eds.; Academic Press: Orlando, FL, 1984; Chapter 6.

(20) For the intramolecular reaction acylnitrenium ions and related electron-deficient species with arenes, see: (a) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2255. (b) Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728. (c) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *Tetrahedron* **1987**, *43*, 2577. (d) Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394. (e) Cherest, M.; Lusinchi, X. *Tetrahedron Lett.* **1989**, *30*, 715. (f) Glover, S. A.; Rowbottom, C. A.; Scott, A. P.; Schoonraad, J. L. *Tetrahedron* **1990**, *46*, 7247. (g) Prata, J. V.; Clemente, D. T. S.; Prabhakar, S.; Lobo, A. M.; Mourato, I.; Branco, P. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 513. (h) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *Heterocycles* **2003**, *59*, 149. (i) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Org. Chem.* **2003**, *68*, 5429. (j) Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. *J. Org. Chem.* **2003**, *68*, 6739.

SCHEME 3. Spirocyclic Lactams as Masked Heterocyclic β-Oxo Carbonyl Synthons



10 11 12 13

Given the ease with which spirocycles **12** can be accessed and our ability to control the configuration of the spirocyclic center, we were prompted to consider the possibility that ozonolytic cleavage of the dienone ring would offer convenient access to lactams **13** that possess a nitrogen-bearing quaternary stereogenic center. Since spiroazetidinone, pyrrolidinone and piperidinone systems **12** (n = 0, 1, 2) are all accessible through the oxidative cyclization of alkyl hydroxamates **10**,[19b] and given the fact that this reaction is tolerant of a wide range of aryl and side chain substituents, this strategy potentially offers a route to a diverse array of target molecules. Among the heterocyclic systems that might potentially be accessed through application of the two-step sequence outlined in Scheme 3, the targets shown in Figure 1 are of particular interest.

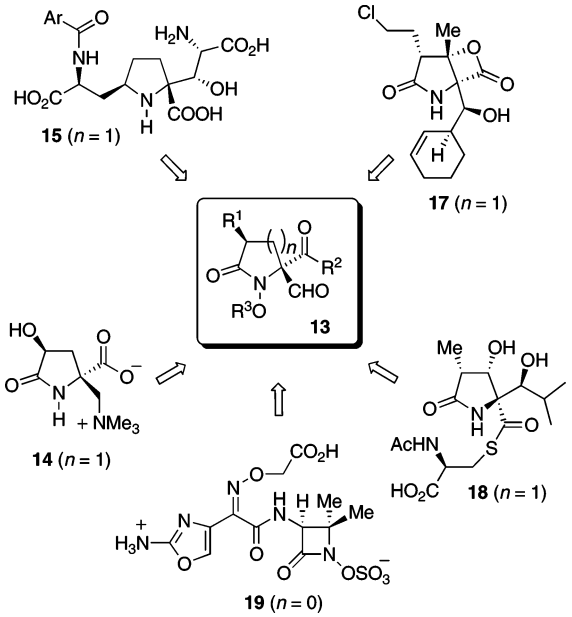


FIGURE 1. Synthetic targets potentially accessible via nitrenium ion cyclization–dienone cleavage strategy.

The marine natural product (−)-dysibetaine (**14**) is a neuroexcitotoxin, which is believed to bind to the glutamate receptors present in the central nervous system of mice,[22,23] while kaitocephalin (**15**), an AMPA/NMDA antagonist isolated from the fungus *Eupenicillium shearii* PF1191, protects hippocampal neurons from kainate toxicity.[24] Salinosporamide (**17**) and lactacystin (**18**), on the other hand, are both inhibitors of the proteasome, while the latter is additionally a potent cytotoxic agent.[25] That the dienone cleavage strategy might also lend itself to the development of an expedient synthetic route to 4,4-disubstituted β-lactams (**13**, n = 0) is also appealing in view of the pharmacological importance of these systems. Tigemonam (**19**), for example, is a potent oral antibiotic that is resistant to β-lactamase-mediated hydrolysis.[26]

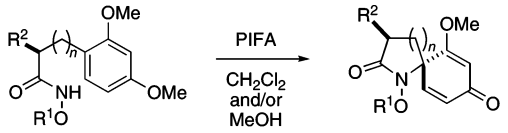
Having recently reported the application of the reaction sequence shown in Scheme 3 to the total synthesis of (−)-dysibetaine,[27] in this paper, we now disclose a full account of our development of two complementary strategies for the ozonolytic cleavage of spirolactams 2,5-cyclohexadienones **12** and the implementation of this transformation, together with the stereoselective nitrenium ion spirocyclization reaction, as a valuable strategy for the synthesis of di- and trisubstituted lactams and *N*-hydroxy lactams.

Results and Discussion

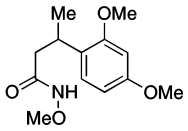
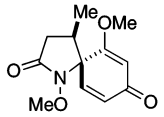
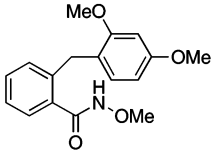
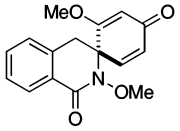
1. Substrate Preparation. Given Caspie and Rodig's observations concerning the cleavage of steroidal systems, our initial choice of spirodienone substrate was guided by the recognition that in order to promote efficient ozonolysis, it would be necessary to address the inherent electron-deficiency of these cross-conjugated ketones. Since it is well-known that electron-releasing substituents increase the reactivity of alkenes toward ozone,[28,29] we opted to examine the cleavage of dienone substrates activated by the presence of a β-methoxy substituent. Our investigation therefore commenced with the preparation of a series of dienones **12**, which where accessed through the oxidative spirocyclization of alkyl hydroxamates **10**,[30]

(21) Wardrop, D. J.; Burge, M. S.; Zhang, W.; Ortíz, J. A. *Tetrahedron. Lett.*, **2003**, *44*, 2587.
(22) Sakai, R.; Oiwa, C.; Takaishi, K.; Kamiya, H.; Tagawa, M. *Tetrahedron Lett.* **1999**, *40*, 6941.
(23) For syntheses of dysibetaine, see: (a) Langlois, N.; Le Nguyen, B. K. *J. Org. Chem.* **2004**, *69*, 7558. (b) Le Nguyen, B. K.; Langlois, N. *Tetrahedron Lett.* **2003**, *44*, 5961. (c) Snider, B. B.; Gu, Y. *Org. Lett.* **2001**, *3*, 1761.
(24) (a) Shin-ya, K.; Kim, J. S.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 7079. (b) Okue, M.; Kobayashi, H.; Shinya, K.; Furihata, K.; Hayakawa, Y.; Seto, H.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **2002**, *43*, 857.
(25) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355.
(26) (a) Gordon, E. M.; Ondetti, M. A.; Pluscec, J.; Cimarusti, C. M.; Bonner, D. P.; Sykes, R. B. *J. Am. Chem. Soc.* **1982**, *104*, 6053. (b) Koster, W. H.; Bonner, D. P. In *Frontiers of Antibiotic Research*; Umezawa, H., Ed.; Academic Press: New York, 1987; p 211
(27) Wardrop, D. J.; Burge, M. S. *Chem. Commun.* **2004**, 1230.
(28) (a) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396. (b) Keul, H.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1984**, *106*, 5370. (c) Keul, H.; Kuczkowski, R. L.; Choi, H.-S. *J. Org. Chem.* **1985**, *50*, 3365. (d) Wojciechowski, B. J.; Pearson, W. H.; Kuczkowski, R. L. *J. Org. Chem.* **1989**, *54*, 115. (e) Griesbaum, K.; Kim, W. S.; Nakamura, N.; Mori, M.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* **1990**, *55*, 6153. (f) Bunnelle, W. H. *Chem. Rev.* **1991**, *91*, 335. (g) Griesbaum, K.; Kim, W. S. *J. Org. Chem.* **1992**, *57*, 5574. (h) Hillers, S.; Niklaus, A.; Reiser, O. *J. Org. Chem.* **1993**, *58*, 3169. (i) Schank, K.; Beck, H.; Pistorius, S. *Helv. Chim. Acta* **2004**, *87*, 2025.
(29) For reports of the efficient ozonolysis of dihydropyrones, see: (a) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 360. (b) Sugiyama, T.; Yamakoshi, H.; Nojima, M. *J. Org. Chem.* **1993**, *58*, 4212.

TABLE 1. Preparation of Dienone Substrates 12 through Spirocyclization of Alkyl Hydroxamates 10[a]



10 **12**

entry	substrate	*n*	R^1	R^2	product	yield (%)[b]	dr[c]
1	**10a**	0	Me	H	**12a**	53[d]	-
2	**10a**	0	Me	H	**12a**	67[e]	-
3	**10b**	0	Bn	H	**12b**	86[e]	-
4	**10c**	1	Me	H	**12c**	81	-
5	**10d**	1	Bn	H	**12d**	98	-
6	**10e**	2	Me	H	**12e**	92	-
7	**10f**	2	Bn	H	**12f**	83	-
8	**10g**	1	Me	Me	**12g**	85[f]	92:8
9	**10h**	1	Me	*t*-Bu	**12h**	82[f]	87:13
10	**10i**	1	Me	Bn	**12i**	98[g]	92:8
11	**10j**	1	Me	Ph	**12j**	85[h]	91:9
12	**10k**	1	Me	OTIPS	**12k**	99[i]	90:10
13	**10l**	1	Me	NHBz	**12l**	85[f]	91:9
14	 **10m**	-	-	-	 **12m**	90[f]	80:20
15	 **10n**	-	-	-	 **12n**	94	-

[a] Reaction conditions: PIFA (1.2 equiv), CH_2Cl_2–MeOH (1:1), −78 → −15 °C, 1.5 h; H_2O, 10 min. [b] Isolated yield, after purification by flash chromatography. [c] Diastereomeric ratio (dr) determined by NMR analysis of the appropriate, characteristic proton signals in the unpurified product mixture. [d] Methanol adduct 20 (26%) was also isolated.[31] [e] Reaction performed in the absence of MeOH. [f] Isolated yield of *anti* diastereomer, after separation by flash chromatography and recrystallization. [g] Isolated yield of inseparable 92:8 mixture of *anti* and *syn* diastereomers. [h] Isolated yield of an inseparable 93:7 mixture of *anti* and *syn* diastereomers. [i] Isolated yield of an inseparable 90:10 mixture of *anti* and *syn* diastereomers.

under conditions previously developed in this laboratory (Table 1).[21] Thus, upon treatment of a solution of **10** in CH_2Cl_2 at −78 °C with 1.2 equiv of phenyliodine(III) bis(trifluoroacetate) (PIFA) in methanol followed by warming to −15 °C, spirocyclization took place smoothly to afford the desired azaspirans **12** in good to excellent yield.[31]

As anticipated from our investigation of the stereochemistry of this reaction,[21] substrates **10g**–**m** underwent spirocyclization to provide the *anti* spirolactam diastereomers with reasonable selectivity. Figure 2 shows a possible rationale for this general observation. We believe that spirocyclization of the nitrenium ion generated from **10** preferentially proceeds via conformer **B** to form *anti*-**12**. Conformer **A**, on the other hand, is destabilized due to nonbonding interactions (benzylic strain)[32]

(30) For details of the preparation of **10**, see the Supporting Information.

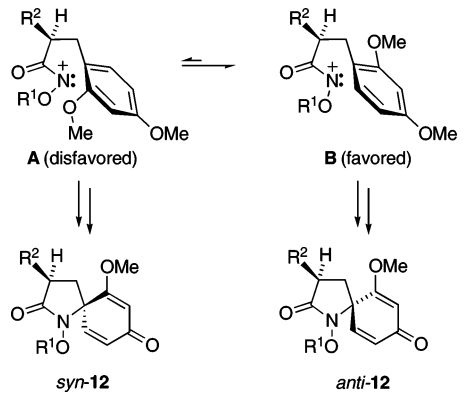


FIGURE 2. Benzylic strain in the putative nitrenium ion intermediate leads to selective formation of *anti*-**12**.

between the substituents on the side chain and the ortho position of the aromatic ring.[33]

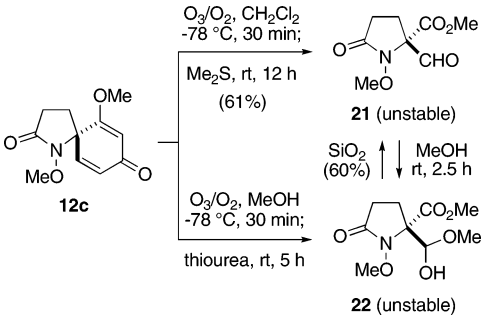
After separation by chromatography and/or crystallization, the relative stereochemistry of the individual diastereomers was readily assigned on the basis of correlations observed in the 2D-NOESY spectra. In the case of products **12i** and **12k**, separation of the individual spirodienone diastereomers was not possible, and consequently, the mixtures were used in the subsequent step.

The successful cyclization of benzyl hydroxamates[34] **10b**, **10d**, and **10f** is noteworthy from a synthetic standpoint since it adds additional flexibility to our methodology: in these cases, hydrogenolysis of the benzyl ether, after dienone cleavage, provides access to *N*-hydroxy lactams, which are important bioactive targets (vide infra).[35]

2. Exploratory Dienone Ozonolysis Studies. Proceeding now to examine cleavage of the dienone system, we chose spiropyrrolidinone **12c** for the purposes of this exploratory study (Scheme 4).

Exposure of a solution of **12c** in CH_2Cl_2 (0.12 M) at −78 °C to a stream of ozonated oxygen for 30 min resulted in complete consumption of starting material

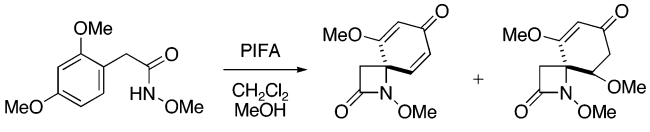
SCHEME 4. Exploratory Dienone Ozonolysis Studies



and the formation of a less polar product, as indicated by thin-layer chromatography. Subsequent reduction of this ozonide intermediate with dimethyl sulfide (10 equiv) at room temperature for 12 h gave, upon concentration of the reaction mixture, *β*-formyl ester **21**. While the spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, and MS) from this compound were fully consistent with the structure assigned, purification of **21** by flash chromatography resulted in partial decomposition, and the product was isolated in moderate yield. The instability of **21** was further apparent from its rapid decomposition, upon standing at room temperature, to form an intractable mixture of products. That the sterically congested aldehyde group in this compound is highly reactive is also evident from its spontaneous reaction with methanol to generate adduct **22**. Ozonolysis of **12c** in methanol, followed by reduction of the putative α-methoxy hydroperoxide intermediate[36] with thiourea (1.25 equiv),[37] proceeded cleanly to yield hemiacetal **22** as a 1:1 mixture of epimers. While this reaction was highly efficient, as evidenced by NMR analysis of the crude product mixture, attempts to purify **22** by flash chromatography resulted in loss of methanol and formation of aldehyde **21**, which was also isolated in diminished yield (60%). Fortunately in this case, there was no need for purification since filtration of the reaction mixture through a plug of Celite after ozonolysis served to remove the precipitated thiourea *S*-dioxide and provided material of sufficient purity to be utilized in subsequent manipulations. In view of the instability of both aldehyde **21** and hemiacetal **22**, we now examined the possibility that these compounds might be intercepted in situ, either through reduction or reaction with nucleophiles in general, to provide more tractable products (Scheme 5).

Encouragingly, ozonolysis of **12c** in methanol, reduction with thiourea, and then treatment of the reaction

(31) (a) In the case of substrate **10a** (entry 1), the formation of *β*-lactam **12a** was also accompanied by compound **20**, which arises from the conjugate addition of methanol to the dienone system.[31b] Although isolated as a single diastereomer, we were unable to unequivocally establish the relative stereochemistry of **20** via spectroscopic means. The formation of this undesired byproduct was simply avoided by carrying out the cyclization of **10a** and **10b** in CH_2Cl_2, in the absence of methanol (entries 2 and 3).



(b) Nilsson, A.; Ronlán, A.; Parker, V. D. *Tetrahedron Lett.* **1975**, 1107.

(32) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(33) Analogous rationalizations of *π*-facial diastereoselectivity are proposed in: (a) Wender, P, A.; Ternansky, R. J. *Tetrahedron Lett.* **1985**, *26*, 2625. (b) Adam, W.; Peters, E. M.; Peters, K.; Prein, M.; von Schnering, H. G. *J. Am. Chem. Soc.* **1995**, *117*, 6686. (c) Kamikawa, K.; Furusyo, M.; Uno, T.; Sato, Y.; Konoo, A.; Bringmann, G.; Uemura, M. *Org. Lett.* **2001**, *3*, 3667.

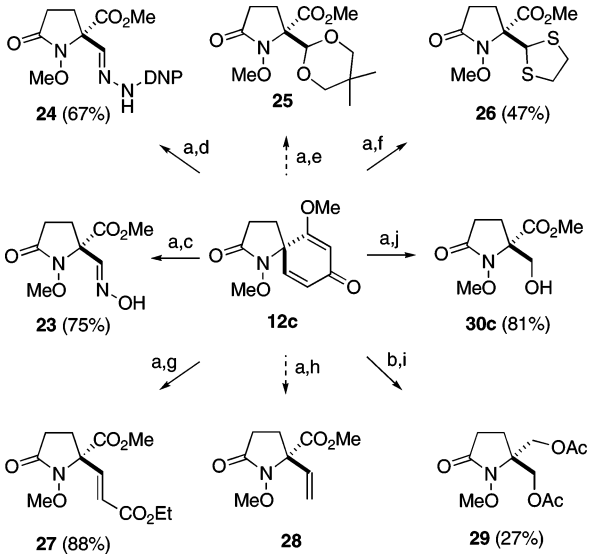
(34) The oxidative Ar_2-5 cyclization of 3-substituted 3-aryl-1-benzyloxyureas has previously been noted: Romero, A. G.; Darlington, W. H.; Jacobsen, E. J.; Mickelson, J. W. *Tetrahedron Lett.* **1996**, *37*, 2361 (footnote 7).

(35) For examples of biologically active *N*-hydroxy lactams and their derivatives, see: (a) Higashide, E.; Horii, S.; Ono, H.; Mizokami, N.; Yamazaki, T.; Shibata, M.; Yoneda, M. *J. Antibiot.* **1985**, *38*, 285. (b) Schlemminger, I.; Mole, D. R.; McNeill, L. A.; Dhanda, A.; Hewitson, K. S.; Tian, Y. M.; Ratcliffe, P. J.; Pugh, C. W.; Schofield, C. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1451. (c) Wendenbaum, S.; Demange, P.; Dell, A.; Meyer, J. M.; Abdallah, M. A. *Tetrahedron Lett.* **1983**, *24*, 4877. (d) Swarén, P.; Massova, I.; Bellettini, J. R.; Bulychev, A.; Maveyraud, L.; Kotra, L. P.; Miller, M. J.; Mobashery, S.; Samama, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 5353. (e) Bulychev, A.; O'Brien, M. E.; Massova, I.; Teng, M.; Gibson, T. A.; Miller, M. J.; Mobashery, S. *J. Am. Chem. Soc.* **1995**, *117*, 5938. (f) Bulychev, A.; Bellettini, J. R.; O'Brien, M.; Crocker, P. J.; Samama, J.-P.; Miller, M. J.; Mobashery, S. *Tetrahedron* **2000**, *56*, 5719.

(36) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

(37) Gupta, D.; Soman, R.; Dev, S. *Tetrahedron* **1982**, *38*, 3013.

SCHEME 5. One-Pot Dienone Ozonolysis and Trapping[a]



[a] Reagents and conditions: (a) O_3/O_2, MeOH, −78 °C, 30 min; thiourea, −78 °C → rt, 30 min; (b) O_3/O_2, CH_2Cl_2, −78 °C, 30 min; Me_2S, −78 °C→rt, 4 h; (c) $H_2NOH{\cdot}HCl$, NaOAc, MeOH, rt, 3 h (75%); (d) 2,4-DNPH, HCl (concd), MeOH, 3 Å ms, reflux, 3 h (67%); (e) $Me_2C(CH_2OH)_2$, TsOH, 3 Å ms, CH_2Cl_2, reflux, 16 h dec; (f) $(CH_2SH)_2$, HCl (concd), rt, 16 h (47%); (g) $Ph_3P{=}CHCO_2Et$, $PhCH_3$, reflux, 2 h (88%); (h) $Ph_3P{=}CH_2$, THF, rt, 14 h dec; (i) $LiBH_4$, THF, rt, 16 h then Ac_2O, py, rt 24 h (27%); (j) $NaBH(OAc)_3$, AcOH, rt, 20 h (81%).

mixture with hydroxylamine hydrochloride (2.4 equiv) and sodium acetate (1.8 equiv) provided stable aldoxime **23** in good yield (75%). Likewise, hemiacetal **22** also underwent condensation with 2,4-dinitrophenylhydrazine to form hydrazone **24**, albeit under somewhat more forcing conditions. Although attempts to prepare 4,4-dimethyldioxane acetal **25** under a variety of dehydrating conditions were unsuccessful, treatment of **22** with 1,2-ethanedithiol in the presence of concentrated hydrochloric acid did provide 1,2-dithiolane **26** albeit in modest yield (47%). Homologation of **22**, on the other hand, proved to be more successful. Horner−Wittig reaction of **22** with (carboethoxymethylene)triphenylphosphorane (2.2 equiv) proceeded efficiently to provide enoate **27** as a single geometrical isomer.[38] In this case, the ozonolysis reaction mixture was concentrated to remove methanol, and the carboethoxymethylenation was then carried out in toluene. Interestingly, **22** did not undergo methylenation with the ylide generated from methyltriphenylphosphonium bromide and *n*-butyllithium. In fact, treatment of either **21** or **22** with strongly basic nucleophiles, including Grignard and organozinc reagents, failed to provide the expected addition products. This general observation may be due to decomposition of these substrates through retro-aldol or retro-Claisen processes, which could occur upon deprotonation of the hydroxyl group, in the case of **22**, or upon nucleophilic addition to the aldehyde group in **21**.[39]

We next turned our attention to the reduction of the initial ozonolysis products and, in particular, to the transformation of these compounds to β-hydroxy ester **30c** via selective reduction of the aldehyde and hemiacetal groups. While attempts to generate **30c** through in situ reduction of **21** with sodium borohydride gave unsatisfactory results, concentration of the ozonolysis reaction mixture and reduction with $LiBH_4$ in THF provided the corresponding bis(hydroxymethyl)pyrrolidinone,[40] which because of its polarity was converted to bis-*O*-acetate **29** prior to purification. Treatment of hemiacetal **22** with $NaBH_4$ or $LiBH_4$, on the other hand, failed to provide any useful results. Reasoning that a weaker reducing agent might prove selective for the hemiacetal group, without affecting the methyl ester or promoting decomposition, sodium triacetoxyborohydride in acetic acid was evaluated.[41] Thus, after ozonolysis of **12c** and reductive workup with thiourea, the reaction mixture was concentrated under reduced pressure and then treated with $NaBH(OAc)_3$ (4 equiv) in acetic acid. Reduction of latent aldehyde **22** proceeded smoothly at room temperature and was complete within 24 h. Treatment of the reaction mixture with aqueous HCl for 20 min, extractive workup and purification by flash chromatography then provided β−hydroxy ester **30c** in 81% overall yield from **12c** (Table 2, entry 3).

3. Establishing the Scope and Limitations of Dienone Cleavage. Having successfully established the practical viability of dienone cleavage and in situ derivatization, we now proceeded to extend our study to include the remaining dienone substrates **12** in order to evaluate the scope and limitations of this chemistry. In view of the synthetic value of β-hydroxy esters of general structure **30**, as both masked 2-hydroxymethyl amino acids[42] and potential building blocks for the preparation of the natural products dysibetaine (**14**) and lactacystin (**18**), we opted to focus our attention on in situ reduction of the ozonolysis products with sodium triacetoxyborohydride. The results of this study are detailed in Table 2.

Encouragingly, the reactivity of spiropyrrolidinone **12c** toward ozone appeared to be general: cleavage of the homologous azaspiro[3.5]nonadienone (entries 1 and 2) and azaspiro[5.5]undecadienone (entries 5 and 6) systems proceeded to furnish the respective disubstituted azetidinone and piperidinone products **30**. The successful ozonolysis of spiroazetidinones **12a** and **12b** is of particular note since this transformation provides expedient access to usefully functionalized 4,4-disubstituted β-lactams.[43] The disparity in yield observed during the formation of **30a** and **30b** appears to result from the greater polarity of the former product, which hampers its purification by flash chromatography. While the beneficial

(38) Duhamel, P.; Kotera, M.; Monteil, T.; Marabout, B.; Davoust, D. *J. Org. Chem.* **1989**, *54*, 4419.

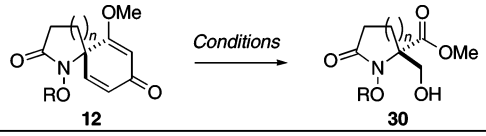
(39) The instablity of related systems to basic conditions has been noted: (a) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230. (b) Trancard, D.; Tout, J.-B.; Giard, T.; Chichaoui, I.; Cahard, D.; Plaquevent, J.-C. *Tetrahedron Lett.* **2000**, *41*, 3843. (c) Duhamel, P.; Kotera, M. *J. Org. Chem.* **1982**, *47*, 1688.

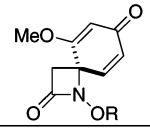
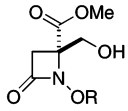
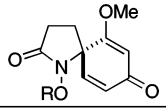
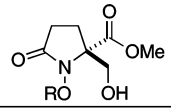
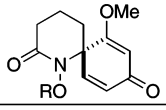
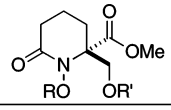
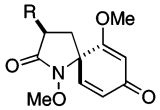
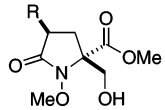
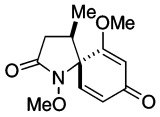
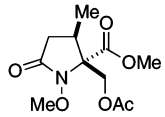
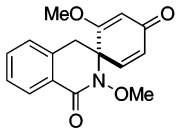
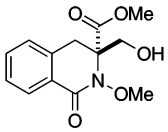
(40) Bis(hydroxymethyl)pyrrolidinones and their derivatives are of interest as neuraminidase inhibitors: (a) Brouillette, W. J.; Bajpai, S. N.; Ali, S. M.; Velu, S. E.; Atigadda, V. R.; Lommer, B. S.; Finley, J. B.; Luo, M.; Air, G. M. *Bioorg. Med. Chem.* **2003**, *11*, 2739. (b) Schieweck, F.; Altenbach, H. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3409. (c) Atigadda, V. R.; Brouillette, W. J.; Duarte, F.; Ali, S. M.; Babu, Y. S.; Bantia, S.; Chand, P.; Chu, N.; Montgomery, J. A.; Walsh, D. A.; Sudbeck, E. A.; Finley, J.; Luo, M.; Air, G. M.; Laver, G. W. *J. Med. Chem.* **1999**, *42*, 2332.

(41) (a) Ishmuratov, G. Y.; Kharisov, R. Y.; Yakovleva, M. P.; Botsman, O. V.; Muslukhov, R. R.; Tolstikov, G. A. *Russ. J. Org. Chem.* **2001**, *37*, 37. (b) Gribble, G. W. *Chem. Soc. Rev.* **1998**, *27*, 395.

(42) Zhang, J.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Org. Chem.* **2001**, *66*, 7555.

TABLE 2. Ozonolytic Cleavage of Spirodienones 12 and In Situ Reduction



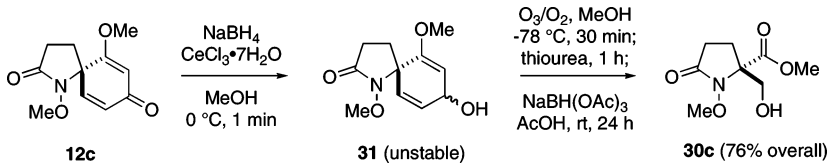
entry	substrate	R	product	method A[a] time[c]	method A[a] % yield[d]	method B[b] time[c]	method B[b] % yield[d]
							
1	**12a**	Me	**30a**	10 min	53	30 min	0[e]
2	**12b**	Bn	**30b**	20 min	82	30 min	0[e]
							
3	**12c**	Me	**30c**	1 h	81	30 min	76
4	**12d**	Bn	**30d**	1 h	98	30 min	94
							
5	**12e**	Me	**30e**	3 h	58 (R' = Ac)[f]	30 min	70 (R' = H)
6	**12f**	Bn	**30f**	2 h[f]	56 (R' = Ac)[f]	30 min	65 (R' = H)
							
7	**12g**	Me	**30g**	1 h	53	30 min	67
8	**12h**	*t*-Bu	**30h**	1 h	59	30 min	84
9	**12i**	Bn	**30i**	1 h	91	30 min	84
10	**12j**	Ph	**30j**	30 min	81	30 min	98
11	**12k**	OTIPS	**30k**	1 h	91[g]	30 min	89
12	**12l**	NHBz	**30l**	1 h	46	30 min	84
13	 **12m**	-	 **30m**	3.5 h	0[h]	1 h	31[i]
14	 **12n**	-	 **30n**	30 min	84	30 min	38

[a] Method A: O_3/O_2, MeOH, −78 °C, 30 min; thiourea, −78 °C → rt; $NaBH(OAc)_3$, AcOH, rt, 24 h. [b] Method B: $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 1 min; O_3/O_2, MeOH, −78 °C, 30 min; thiourea, −78 °C → rt, 1 h; $NaBH(OAc)_3$, AcOH, rt, 24 h. [c] Duration of ozonolysis. [d] Overall, isolated yield, after purification of the final product by flash chromatography. [e] A complex, intractable mixture of products was isolated after ozonolysis and reduction. [f] Isolated yield, after conversion of alcohol to the corresponding *O*-acetate derivative and purification by flash chromatography. [g] Isolated as a 91:9 mixture of diastereomers. [h] A complex, intractable mixture of products was recovered. [i] Ozonolysis carried out for 1 h and the product converted to acetate **30m** derivative before purification.

effect of *O*-benzyl groups, upon the efficiency of dienone cleavage, was also apparent during the ozonolysis of spiropyrrolidinones **12c** and **12d**, this effect did not extend to compounds **12e** and **12f**.

A remarkable structure–reactivity relationship emerged during the cleavage of substrates **12a–e**. While the reaction of spiroazetidinones **12a** and **12b** with ozone was complete within 30 min, ozonolysis of the corresponding

SCHEME 6. Alternative, Two-Step Protocol for the Cleavage of Spirodienone Lactams 12



pyrrolidinones **12c** and **12d** was significantly slower, requiring 1 h. Even more strikingly, piperidinones **12e** and **12f** reacted very sluggishly with cleavage not reaching completion even after exposure to ozone for 3 h. Purification of the product mixtures, in the case of this latter pair of substrates, also proved to be problematic due to the presence of several minor byproducts. Fortunately, acetylation of the reaction mixtures, using Ac_2O in pyridine, provided the corresponding *O*-acetate derivatives, which where more amenable to purification by flash chromatography. Rather unexpectedly, spiropiperidinone **12n** proved to be considerably more reactive toward ozone than either **12e** or **12f** and underwent rapid ozonolysis to provide **30n** in excellent yield, after in situ reduction. The successful cleavage of **12n** is notable since it opens a possible route to quaternary tetrahydroisoquinoline-3-carboxylic acid (Tic) derivatives,[44] which are of interest as conformationally restricted amino acids. A more detailed discussion of the possible origins of this structure−reactivity pattern is presented in section 5.

Having established the viability of cleavage in unsubstituted 4-, 5-, and 6-membered spirolactams, attention now turned to the α- and *β*-substituted spiropyrrolidinones **30g**−**l**. We were encouraged to find, in fact, that the presence of α-substituents in the pyrrolidinone ring was tolerated with cleavage giving the corresponding 2,4-disubstituted pyroglutamate derivatives with moderate to excellent efficiency. That attempts to ozonize **12m**, the isomer of compound **12g**, failed to provide any trace of compound **30m** is likely a consequence of the increased steric encumbrance imposed upon the dienone ring by the *β*-methyl substituent in this substrate.

4. An Alternative Strategy for Dienone Cleavage. The extended reaction times and modest yields encountered during the ozonolysis of substrates **12e** and **12f**, coupled with the failure of *β*-substituted spiropyrrolidinone **12m** to undergo cleavage, prompted a search for an alternative, more efficient strategy for cleavage of the dienone ring system. Given the greater reactivity of 1,4-cyclohexadienes toward ozone as compared to their electron-deficient congeners, the logical course of action at this stage seemed to be to reduce the dienone carbonyl group and subject the resulting dienylic alcohol(s) **31** to ozonolysis (Scheme 6).

Although the 1,2-reduction of 2,5-cyclohexadienones is well documented,[45] a potential caveat with this plan was the propensity of the reduction products **31** to potentially undergo rearrangement during purification.[46] Fortunately, reduction of dienone **12c**, under Luche conditions ($NaBH_4$, $CeCl_3$, MeOH),[47] proceeded rapidly at 0 °C to give a mixture of diastereomers **31**, which could be isolated with excellent mass recovery. As these alcohols proved to be highly acid sensitive and decomposed upon exposure to silica gel, they were immediately submitted to ozonolysis without further purification (Table 2).

Gratifyingly, ozonolysis of diene **31** in CH_2Cl_2 at −78 °C occurred rapidly, with the starting material being consumed within 30 min as opposed to 1 h for dienone **12c**. Sequential reduction of the peroxidic intermediates with thiourea (1.25 equiv) and sodium triacetoxyborohydride (5 equiv) in acetic acid then proceeded without incident to furnish *β*-hydroxy ester **30c** in good yield. While this two-step protocol was slightly less efficient than direct dienone ozonolysis in this case (76 vs 81%), its application to the remaining substrates in Table 2 proved to be considerably more rewarding. With the exception of **12a**, **12b**, and **12n**, improvements in yield and a decrease in reaction time were observed in all cases. Indeed, ozonolysis of the intermediate dienylic alcohols was complete within 30 min for all substrates, including spiropiperidinones **12e** and **12f**. The transformation of hindered **12m** to compound **30m**,[48] albeit in low yield, under these conditions is also of note, since this product could not be prepared through direct ozonolysis of the dienone system. In the case of compounds **12a** and **12n**, complex mixtures of products where obtained, which we believe arise from decomposition of the intermediate dienylic alcohols prior to ozonolysis.

5. Assessment of Spirodienone Structure−Reactivity Relationships. Steric effects are known to play a significant role in determining the rate of 1,3-dipolar cycloaddition between ozone and unsaturated systems, including alkenes and arenes.[49] We have rationalized the marked variation in reactivity toward ozone displayed by spirodienones **12** in terms of steric hindrance above

(43) For selected routes to 4,4-disubtituted azetidinones, see: (a) Ageno, G.; Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Riva, R.; Rocca, V. *Tetrahedron* **1995**, *51*, 8121. (b) DeKimpe, N.; Tehrani, K. A.; Fonck, G. *J. Org. Chem.* **1996**, *61*, 6500. (c) Palomo, C.; Aizpurua, J. M.; García, J. M.; Galarza, R.; Legido, M.; Urchegui, R.; Román, P.; Luque, A.; Server-Carrio, J.; Linden, A. *J. Org. Chem.* **1997**, *62*, 2070. (d) Gerona-Navarro, G.; Garcia-López, M. T.; González-Mniz, R. *J. Org. Chem.* **2002**, *67*, 3953. (e) Campomanes, P.; Menendez, M. I.; Sordo, T. L. *J. Org. Chem.* **2003**, *68*, 6685.

(44) For the preparation of quaternary tetrahydroisoquinoline-3-carboxylic acid derivatives, see: (a) Vicario, J. L.; Badia, D.; Carrillo, L.; Etxebarria, J. *Curr. Org. Chem.* **2003**, *7*, 1775. (b) Kawabata, T.; Ozturk, O.; Suzuki, H.; Fuji, K. *Synthesis* **2003**, 505. (c) Alezra, V.; Bonin, M.; Micouin, L.; Husson, H. P. *Tetrahedron Lett.* **2001**, *42*, 2111. (d) Chinchilla, R.; Galindo, N.; Najera, C. *Synthesis* **1999**, 704. (e) Ma, D.; Ma, Z.; Kozikowski, A. P.; Pshenichkin, S.; Wroblewski, J. T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2447. (f) Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215. (g) Bajgrowicz, J.; El Achquar, A.; Roumestant, M.-L.; Pigière, C.; Viallefont, P. *Heterocycles* **1986**, *24*, 2165.

(45) (a) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4219. (b) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Synthesis* **1993**, 920. (c) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678. (d) Blades, K.; Cockerill, G. S.; Easterfield, H. J.; Lequeux, T. P.; Percy, J. M. *Chem. Commun.* **1996**, 1615.

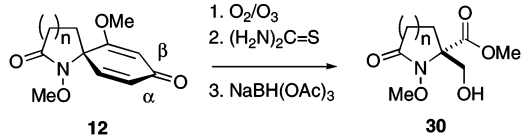
(46) Banerjee, A. K.; Azocar, J. A.; Vera, W. *Synth. Commun.* **1999**, *29*, 2995.

(47) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Abruscato, G. J.; Tidwell, T. T. *J. Org. Chem.* **1972**, *37*, 4151.

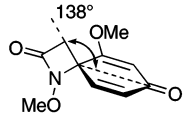
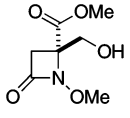
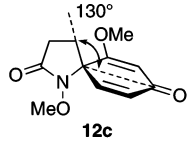
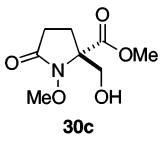
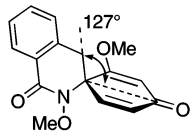
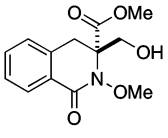
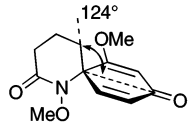
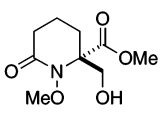
(48) Acetylation of the crude product was necessary in this case to facilitate chromatographic purification.

(49) Nakagawa, T. W.; Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc.* **1960**, *82*, 269.

TABLE 3. Relationship between Spirodienone Reactivity and Structure



12 30

substrate[a]	time (min)[b]	product
 12a	10	 30a
 12c	30	 30c
 12n	30	 30n
 12e	180	 30e

[a] Optimized geometries were obtained through the MMMF force field implemented in Spartan. [b] Duration of ozonolysis.

(β) and below (α) the plane of the dienone ring system, which varies as a function of the size of the adjoining lactam ring (Table 3).

Notwithstanding possible dipole and stereoelectronic effects,[50] we believe that ozone approaches the spirocyclic cyclohexadienones from the α face, *anti* to the *N*-methoxyl group, which in all substrates bisects the dienone ring and thereby disfavors β attack. Our assumption that the N-OMe group is more sterically demanding than the methylene group appears to be born out by the observation that substrate **12m**, which possesses a methyl substituent at the β position of the pyrrolidinone ring, is quite inert to ozone. Molecular mechanics minimization (MMMF) of the geometries of dienones **12a**, **12c**, **12e**, and **12n** using the SPARTAN computational interface[51] reveals that methylene group attached to the spirocenter progressively shields the β face of the adjoining dienone ring from ozone cycloaddition as the lactam ring increases in size. The increasing steric influence played by the methylene group in going from azetidinone to piperidinone is apparent from the decrease in the angle (ϕ) formed between the methylene group, spirocenter and the carbonyl carbon of the dienone ring. That the dienone rings in spiroazetidinones **12a** and **12b** are more accessible to attack is also evident from the fact only these substrates undergo conjugate addition of methanol during azaspirocyclization. While the dramatic increase in reactivity of dienylic alcohols **31**, as compared to their corresponding dienone partners can be rationalized in terms of the attenuation of the electron-withdrawing properties of the carbonyl group, it is not immediately apparent why this should result in loss of the structure reactivity relationship.

6. Reductive Cleavage of *N*-Methoxy and *N*-Benzyloxy Lactams. To confirm the practical utility of the nitrenium ion cyclization−dienone cleavage strategy, it was necessary now to address the issue of N−O bond scission in the cleavage products **30**. Although the reduction of hydroxylamines, hydroxamic acids, and *N*-hydroxy lactams can readily be accomplished with a variety of reagents, metal ion-mediated reduction of *N*-alkoxy lactams is often more demanding since these systems lack an acidic chelation site.[52] While this transformation has been accomplished with a number of reagents, including hydrogenolysis over heterogeneous catalysts[53] or reduction with Raney nickel,[54] SmI_2,[55] sodium[56] and aluminum amalgam,[57] LDA,[58] *tert*-butyldimethylsilyl triflate,[59] Li/4,4′-di-*tert*-butylbiphenyl,[60] and Birch reduction,[61] few are entirely general. From previous studies, we have found the most dependable reducing agent for our relatively hindered substrates to be molybdenum hexacarbonyl.[62]

Reductive cleavage of **30** proceeds most efficiently when the substrate is heated with 1.2 equiv of $Mo(CO)_6$ in a degassed mixture of acetonitrile and water (15:1) for 24 h and the reaction then exposed to air at room temperature for an equivalent period of time (Table 4). Concentration of the black reaction mixture and purification of the residue by flash chromatography then provides the desired lactams **32** in good yield. Exposure of the reaction mixture to air greatly facilitates purification, and failure to carry out this step often results in the con-

(50) (a) Wipf, P.; Jung, J.-K. *Chem. Rev.* **1999**, *99*, 1469. (b) Ohkata, K.; Tamura, Y.; Shetuni, B. B.; Takagi, R.; Miyanaga, W.; Kojima, S.; Paquette, L. A. *J. Am. Chem. Soc.* **2004**, *126*, 16783.

(51) The calculations were performed with Spartan′04 for Macintosh, Wavefunction Inc., Irvine, CA 92612.

(52) Mattingly, P. G.; Miller, M. J. *J. Org. Chem.* **1980**, *45*, 410.

(53) (a) Chang, C. Y.; Yang, T. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2081. (b) Romero, A. G.; Darlington, W. H.; McMillan, M. W. *J. Org. Chem.* **1997**, *62*, 6582.

(54) Qabar, M. N.; Kahn, M. *Tetrahedron Lett* **1996**, *37*, 965.

(55) (a) Chiara, J. L.; Destabel, C.; Gallego, P.; Marco-Contelles, J. *J. Org. Chem.* **1996**, *61*, 359. (b) Yang, H. W.; Romo, D. *J. Org. Chem.* **1999**, *64*, 7657. (c) Keck, G. E.; Wager, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755

(56) (a) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358. (b) Blakemore, P. R.; Kim, S.-K.; Schulze, V. K.; White, J. D.; Yokochi, A. F. T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1831. (c) Chow, C. P.; Shea, K. J.; Sparks, S. M. *Org. Lett.* **2002**, *4*, 2637

(57) (a) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089. (b) Malpass, J. R.; Smith, C. *Tetrahedron Lett.* **1992**, *33*, 273.

(58) (a) Graham, S. L.; Scholz, T. H. *Tetrahedron Lett.* **1990**, *31*, 6269. (b) Anderson, J. C.; Flaherty, A.; Swarbrick, M. E. *J. Org. Chem.* **2000**, *65*, 9152.

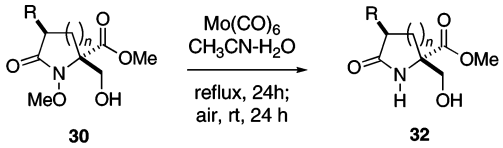
(59) Keck, G. E.; McHardy, S. F.; Murry, J. A. *Tetrahedron Lett.* **1994**, *34*, 6215

(60) Yus, M.; Radivoy, G.; Alonso, F. *Synthesis* **2001**, 914

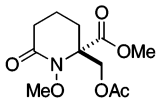
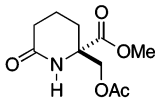
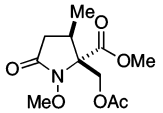
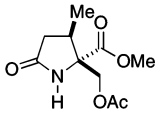
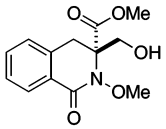
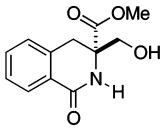
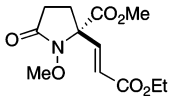
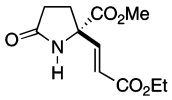
(61) (a) Cardani, S.; Gennari, C.; Scolastico, C.; Villa, R. *Tetrahedron* **1989**, *45*, 7397. (b) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073.

(62) (a) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351. (b) Gouverneur, V.; Ghosez, L. *Tetrahedron Lett.* **1991**, *32*, 5349. (c) Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4602.

TABLE 4. Reductive N–O Bond Cleavage of *N*-Methoxy Lactams 30



30 32

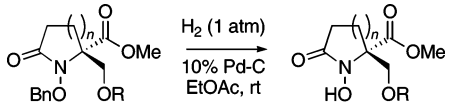
entry[a]	substrate	R	*n*	product	yield (%)[b]
1	**30a**	H	0	**32a**	75
2	**30c**	H	1	**32c**	88
3	**30g**	Me	1	**32g**	70
4	**30h**	*t*-Bu	1	**32h**	59
5	**30i**	Bn	1	**32i**	73
6	**30j**	Ph	1	**32j**	65
7	**30k**	OTIPS	1	**32k**	90
8	**30l**	NHBz	1	**32l**	77
9		-	-		76
	30e			**32e**	
10		-	-		86
	30m			**32m**	
11		-	-		74
	30n			**32n**	
12		-	-		73
	27			**33**	

[a] Reaction conditions: $Mo(CO)_6$ (1.2 equiv), CH_3CN, H_2O reflux, 24 h; air, rt, 24 h. [b] Isolated yield, after purification by flash chromatography.

tamination of the lactam products with unidentified, nonpolar molybdenum complexes. As documented in Table 4, reductive cleavage of the *N*-methoxy lactams proceeded without incident to provide the corresponding pyroglutamate derivatives in good to excellent yield. The successful reduction of *N*-methoxy-2-azetidinone **30a** under these mild conditions is notable since direct cleavage of this class of substrate has previously only been accomplished under more stringent conditions involving alkali metals in ammonia.[61]

N-Hydroxy lactams are important synthetic targets, imbued with a wide range of biological activities, for which there are relatively few methods of preparation available.[63] In this regard, the successful cyclization of the benzyl hydroxamate substrates **12b**, **12d**, and **12f** and the subsequent compatibility of the *O*-benzyl groups

TABLE 5. Hydrogenolysis of *N*-Benzyloxy Lactams 30



entry	substrate	R	*n*	product	reaction time (h)	yield[a] (%)
1	**30b**	H	0	**34b**	0.1	99
2	**30d**	H	1	**34d**	0.5	90
3	**30f**	Ac	2	**34f**	1.5	99

[a] Isolated yield, after purification by flash chromatography.

with the dienone cleavage protocol now provided an opportunity to access these target molecules, through selective hydrogenolysis of the benzyl ether in *N*-benzyloxy lactams **30** (Table 5).

Hydrogenation of **30b**, **30d** and **30f** in ethyl acetate proceeded smoothly at atmospheric pressure, in the presence of 10% Pd–C, to provide the desired *N*-hydroxy lactams **34** in excellent yield. In all cases, the reaction stopped after debenzylation, and no trace of the lactam products, resulting from N–O bond cleavage,[64] could be detected.

Conclusions

In conclusion, we have reported a novel and efficient strategy for the stereoselective preparation of di- and trisubstituted azetidinone, pyrrolidinone, and piperidinone derivatives, which features the ozonolytic cleavage of azaspirocyclic 2,5-cyclohexadienones. Notable features of this methodology include (a) the rapidity with which structural complexity is established; (b) flexibility (4-, 5-, and 6-membered lactams and *N*-hydroxy lactams can be accessed); and (c) the accessibility of the spirodienone substrates, which can be prepared through the nitrenium ion cyclization of alkyl ω-arylhydroxamates with excellent efficiency and moderate to high diastereoselectivity. The results presented herein demonstrate, for the first time, that the ozonolytic cleavage of 2,5-cyclohexadienones is a synthetically viable and potentially powerful method. Since, in addition to the cyclization of nitrenium ions, spirocyclic 2,5-cyclohexadienones, including lactones, lactams, and oxazolines, are readily accessible, through the oxidative spirocyclization of phenol derivatives, we anticipate that the chemistry reported herein may offer a general route to α,α-disubstituted heterocycles. Future directions for this work will include application of the current method to the synthesis of the natural products lactacystin and kaitocephalin as well as an examination of dienone cleavage in the context of other types of spirodienone.

Experimental Section

Reagents. Flash column chromatography was performed according to the method of Still[65] using silica gel 60 (mesh 230–400). Phenyliodine(III) bis(trifluoroacetate) (PIFA) was prepared according to the procedure reported by Loudon.[66] Solutions of sodium triacetoxyborohydride were prepared freshly by reacting sodium borohydride with acetic acid.

General Procedure A (Preparation of Spirodienones 12 in CH_2Cl_2). (±)-1,5-Methoxy-1-azaspiro[3.5]nona-5,8-diene-2,7-dione (12a) (Entry 2, Table 1). To a stirred suspension of phenyliodine(III) bis(trifluoroacetate) (PIFA) (580 mg, 1.35 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL), under an atmosphere of N_2 at −78 °C, was added a cold (−78 °C) solution of alkyl hydroxamate **10a** (253 mg, 1.12 mmol) in CH_2Cl_2 (5 mL) via cannula. The reaction mixture was then allowed to warm to −15 °C (bath temperature) over 1.5 h, whereupon H_2O (3 mL) was added and the cooling bath removed. After being stirred for 10 min, the biphasic mixture was partitioned between CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a yellow oil. Purification by flash chromatography (SiO_2, EtOAc/hexanes, 1:3) then afforded **12a** (158 mg, 67%): white crystals; mp 100–103 °C (EtOAc/hexanes); R_f 0.55 (EtOAc); FTIR (film) ν_{max} 1785, 1676, 1600, 1222 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, J = 9.9 Hz, 1 H), 6.36 (dd, J = 1.6, 9.9 Hz, 1 H), 5.78 (d, J = 1.6 Hz, 1 H), 3.84 (s, 3 H), 3.74 (s, 3 H), 3.15 (d, J = 13.7 Hz, 1 H), 2.83 (d, J = 13.7 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.7, 169.3, 163.4, 142.2, 132.0, 105.7, 65.4, 61.2, 56.7, 43.8; HRMS-ESI calcd for $C_{10}H_{11}NO_4Na$ $[M + Na]^+$ 232.0586, found 232.0591.

General Procedure B (Preparation of Spirodienones 12 in CH_2Cl_2–MeOH). (±)-1,6-Dimethoxy-1-azaspiro[4.5]-deca-6,9-diene-2,8-dione (12c) (Entry 4, Table 1). To a suspension of phenyliodine(III) bis(trifluoroacetate) (PIFA) (863 mg, 2.01 mmol, 1.2 equiv) in MeOH (2 mL), under an atmosphere of N_2 at −78 °C, was added a cold (−78 °C) solution of **10c** (400 mg, 1.67 mmol) in CH_2Cl_2 (8 mL) via cannula. The reaction mixture was then allowed to warm to −20 °C (internal temperature) over 1.5 h, whereupon H_2O (3 mL) was added and the cooling bath removed. After being stirred for 10 min, the biphasic mixture was partitioned between CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). After separation, the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil. Purification by flash chromatography over silica gel (EtOAc) then afforded **12c** (301 mg, 81%): white crystals; mp 133–135 °C (EtOAc/hexanes); R_f 0.24 (EtOAc); FTIR (film) ν_{max} 1728, 1665, 1633, 1602, 1369, 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, J = 9.9 Hz, 1 H), 6.28 (dd, J = 1.5, 9.9 Hz, 1 H), 5.61 (d, J = 1.5 Hz, 1 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 2.65–2.55 (m, 1 H), 2.48–2.40 (m, 1 H), 2.26–2.19 (m, 1 H), 2.16–2.08 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 173.2, 172.7, 144.3, 130.3, 103.2, 64.7, 62.8, 56.2, 27.3, 26.2; HRMS-ESI calcd for $C_{11}H_{13}NO_4Na$ $[M + Na]^+$ 246.0742, found 246.0750.

Methyl (±)-2-Formyl-1-methoxy-5-oxopyrrolidine-2-carboxylate (21). A stream of oxygen and ozone was passed through a solution of **12c** (83 mg, 0.37 mmol) in CH_2Cl_2 (3 mL) at −78 °C for 30 min. The blue solution was then purged with a stream of argon for 5 min, Me_2S (546 μL, 7.44 mmol) added,

(63) (a) Black, D. S. C.; Brown, R. F. C.; Wade, A. M. *Aust. J. Chem.* **1972**, *25*, 2155. (b) Black, D. S. C.; Brown, R. F. C.; Wade, A. M. *Aust. J. Chem.* **1972**, *25*, 2429. (c) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007. (d) Crossley, M. J.; Crumbie, R. L.; Fung, Y. M.; Potter, J. J.; Pegler, M. A. *Tetrahedron Lett.* **1987**, *28*, 2883. (e) Baldwin, J. E.; Adlington, R. M.; Gollins, D. W.; Schofield, C. J. *J. Chem. Soc., Chem. Commun.* **1990**, 720. (f) Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R. A.; Gollins, D. W.; Schofield, C. J. *Tetrahedron* **1991**, *47*, 5835 (g) Leeson, P. D.; Williams, B. J.; Rowley, M.; Moore, K. W.; Baker, R.; Kemp, J. A.; Priestley, T.; Foster, A. C.; Donald, A. E. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 71. (h) Tiecco, M.; Testaferri, L.; Tingoli, M.; Marini, F. *J. Chem. Soc., Chem. Commun.* **1994**, 221. (i) Thomas, A.; Rajappa, S. *Tetrahedron* **1995**, *51*, 10571. (j) Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E.; Morganti, S.; Rizzato, E.; Spinelli, D.; Dell'Erba, C.; Petrillo, G.; Tavani, C. *Tetrahedron* **2004**, *60*, 11011.

(64) Dong, L.; Miller, M. J. *J. Org. Chem.* **2002**, *67*, 4759.

(65) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(66) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272.

the cooling bath removed, and the mixture stirred room temperature for 12 h. The reaction mixture was then concentrated under reduced pressure and the residual oil purified by flash chromatography (SiO_2, EtOAc) to provide a crude sample of unstable **21** (45 mg, 61%): yellow oil; R_f 0.23 (EtOAc); IR (film) ν_{max} 2951, 1734, 1296, 1246, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1 H, CHO), 3.94 (s, 3 H), 3.89 (s, 3 H), 2.49−2.26 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 172.6, 168.9, 64.5, 53.5, 42.6, 25.6, 23.3; HRMS-ESI calcd for $C_8H_{11}NO_5Na$ $[M + Na]^+$ 224.0535, found 224.0538.

Methyl (2*S,6*RS**)-2-(Hydroxymethoxymethyl)-1-methoxy-5-oxopyrrolidine-2-carboxylate (22).** A stream of oxygen and ozone was passed through a solution of **12c** (160 mg, 0.72 mmol) in MeOH (5 mL) at −78 °C for 30 min. The blue solution was then purged with a stream of argon for 5 min, thiourea (68 mg, 0.90 mmol, 1.25 equiv) was added, the cooling bath was removed, and the solution was stirred at room temperature for 5 h. The reaction mixture was then filtered through a pad of Celite and the filtrate concentrated under reduced pressure to provide crude **22** (180 mg) as an approximately 1:1 mixture of hemiacetal diastereomers (by ^1H NMR): colorless oil; R_f 0.50 (EtOAc); IR (film) ν_{max} 3373 (br), 1741, 1702, 1694, 1440, 1253, 1059 cm-1; ^1H NMR (500 MHz, CD_3OD) δ (mixture of diastereomers) δ 5.11 (s, 0.5 H), 5.09 (s, 0.5 H), 3.80 (s, 3.8 H), 3.79 (s, 2.2 H), 3.42 (s, 1.2 H), 3.35 (s 1.5 H), 2.35−2.31 (m, 5 H); ^{13}C NMR (125 MHz, CD_3OD) δ (mixture of diastereomers) 174.5, 174.4, 170.8, 170.7, 96.5, 96.3, 71.7, 71.4, 63.4, 63.3, 55.1, 54.8, 52.3, 49.0, 26.2, 26.1, 20.7, 20.1; HRMS-ESI calcd for $C_9H_{15}NO_6Na$ $[M + Na]^+$ 256.0797, found 256.0791.

(±)-2-(Hydroxyiminomethyl)-1-methoxy-5-oxopyrrolidine-2-carboxylic Acid Methyl Ester (23). A stream of oxygen and ozone was passed through a solution of **12c** (200 mg, 0.90 mmol) in MeOH (5 mL) at −78 °C for 30 min. The blue solution was then purged with a stream of argon for 10 min, thiourea (85 mg, 1.11 mmol) added, and the mixture then allowed to warm to room temperature over 40 min. Sodium acetate (132 mg, 1.61 mmol) and $NH_2OH{\cdot}HCl$ (149 mg, 2.15 mmol) were added and the mixture stirred at room temperature for 3 h. The reaction mixture was then concentrated under reduced pressure and the residue purified by flash chromatography (SiO_2, EtOAc/hexane, 1:1) to provide **23** (146 mg, 75%) as a 12:1 mixture of geometrical isomers: yellow oil; R_f 0.68 (EtOAc); IR (film) ν_{max} 3293 (br), 1745, 1703, 1439, 1268, 1070, 974 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (major isomer) 8.96 (br s, 1 H), 7.74 (s, 1 H), 3.89 (s, 3 H), 3.83 (s, 3 H), 2.59−2.51 (m, 1 H), 2.47−2.42 (m, 2 H), 2.26−2.19 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major isomer) 173.1, 170.3, 145.9, 68.3, 64.4, 53.5, 26.0, 25.1; HRMS-ESI calcd for $C_8H_{12}N_2O_5Na$ $[M + Na]^+$ 239.0644, found 239.0647.

(±)-2-[(2,4-Dinitrophenyl)hydrazonomethyl]-1-methoxy-5-oxopyrrolidine-2-carboxylic Acid Methyl Ester (24). A stream of oxygen and ozone was passed through a solution of **12c** (178 mg, 0.80 mmol) in MeOH (4 mL) at −78 °C for 30 min. The blue solution was then purged with a stream of argon for 10 min, thiourea (76 mg, 1.00 mmol) added, the cooling bath removed, and the solution allowed to warm to room temperature over 40 min. After the reaction mixture was filtered through a plug of Celite, the filtrate was sequentially treated with activated 3 Å molecular sieve beads (500 mg), 2,4-dinitrophenylhydrazine (316 mg, 1.59 mmol), and concentrated HCl (300 μL). The reaction mixture was then heated at reflux for 1.5 h, whereupon it was cooled to room temperature, filtered through a plug of Celite, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (SiO_2, EtOAc/hexanes, 1:5) to provide hydrazone **24** (204 mg, 67%): orange crystals; mp 174−176 °C (EtOAc/hexanes); R_f 0.67 (EtOAc); FTIR (film) ν_{max} 3296 (br), 1735, 1616, 1593, 1514, 1431, 1335, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.26 (s, 1 H), 9.10 (d, J = 2.5 Hz, 1 H), 8.34 (dd, J = 2.5, 9.5 Hz, 1 H), 7.89 (s, 1H, NH), 7.87 (d, J = 9.5 Hz, 1 H), 3.94 (s, 3 H), 3.90 (s, 3 H), 2.72−2.65 (m, 1 H), 2.61−2.45 (m, 2 H), 2.40−2.33 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 170.1, 144.6, 144.3, 138.9, 130.3, 129.8, 123.2, 116.6, 69.3, 64.5, 53.7, 25.9, 25.4; HRMS-ESI calcd for $C_{14}H_{14}N_5O_8$ $[M - H]^-$ 380.0842, found 380.0844.

(±)-2-[1,3]Dithiolan-2-yl-1-methoxy-5-oxopyrrolidine-2-carboxylic Acid Methyl Ester (26). A stream of oxygen and ozone was passed through a solution of **12c** (123 mg, 0.55 mmol) in MeOH (3 mL) at −78 °C for 30 min. The blue solution was then purged with a stream of argon for 10 min, thiourea (52 mg, 0.69 mmol) added, the cooling bath removed, and the solution then allowed to warm to room temperature over 40 min. The reaction mixture was then filtered through a plug of Celite and the filtrate concentrated under reduced pressure. The resulting colorless oil was taken up in CH_2Cl_2 (6 mL), and ethane-1,2-dithiol (58 μL, 0.69 mmol) and concentrated HCl (300 μL) were added sequentially. The reaction mixture was stirred for 16 h at room temperature, concentrated under reduced pressure, and purified by flash chromatography (SiO_2, EtOAc/hexanes, 1:5) to provide dithioacetal **26** (72 mg, 47%): colorless oil; R_f 0.66 (EtOAc); FTIR (film) ν_{max} 1735, 1433, 1271, 1057 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.37 (s, 1 H), 3.90 (s, 3 H), 3.81 (s, 3 H), 3.32−3.19 (m, 4 H), 2.51−2.46 (m, 2 H), 2.38−2.29 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 171.5, 72.0, 64.2, 55.5, 53.2, 39.4, 39.0, 26.4, 21.8; HRMS-ESI calcd for $C_{10}H_{16}NO_4S_2$ $[M + H]^+$ 278.0521, found 278.0526.

Methyl (±)-*E*-2-(2-Ethoxycarbonylvinyl)-1-methoxy-5-oxopyrrolidine-2-carboxylate (27). A stream of oxygen and ozone was passed through a solution of **12c** (200 mg, 0.90 mmol) in MeOH (5 mL) at −78 °C for 30 min. The blue solution was then purged with a stream of argon for 10 min, thiourea (85 mg, 1.11 mmol) added, the cooling bath removed, and the solution then allowed to warm to room temperature over 40 min. The reaction mixture was then concentrated under reduced pressure to provide **22** as an oil, which was dissolved in toluene (5 mL). (Carbethoxymethylene)triphenylphosphorane (687 mg, 1.97 mmol) was then added and the mixture heated at reflux for 2 h. The reaction was then cooled and concentrated under reduced pressure and the resulting oil partitioned between CH_2Cl_2 (10 mL) and saturated aqueous NH_4Cl (7 mL). The organic phase was separated and the aqueous portion extracted with CH_2Cl_2 (3 × 10 mL), The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure, and the residue was purified by flash chromatography (SiO_2, EtOAc/hexanes, 1:1) to provide **27** (213 mg, 88%) as a single geometrical isomer: yellow oil; R_f 0.52 (EtOAc); IR (film) ν_{max} 1726, 1659, 1313, 1266, 1184, 1053, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 16.0 Hz, 1 H), 6.10 (d, J = 16.0 Hz, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 3.93 (s, 3 H), 3.82 (s, 3 H), 2.44−2.15 (m, 4 H), 1.28 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 170.3, 165.5, 142.0, 123.5, 69.6, 64.2, 60.9, 53.4, 28.4, 25.7, 14.1; HRMS-ESI calcd for $C_{12}H_{17}NO_6Na$ $[M + Na]^+$ 294.0954, found 294.0945.

Acetic Acid (±)-2-Acetoxymethyl-1-methoxy-5-oxopyrrolidin-2-ylmethyl Ester (29). A stream of oxygen and ozone was passed through a solution of **12c** (148 mg, 0.66 mmol) in CH_2Cl_2 (4 mL) at −78 °C for 30 min. The blue solution was then purged with a stream of argon for 10 min, Me_2S (730 μL, 9.94 mmol) added, the cooling bath removed, and the mixture stirred at room temperature for 4 h. The reaction mixture was then concentrated under reduced pressure, the residue dissolved in Et_2O (5 mL), and this solution then treated with $LiBH_4$ (72 mg). After being stirred at room temperature for 16 h, the reaction was quenched with H_2O (4 mL) and then stirred for an additional 1 h. The organic layer was then separated and the aqueous layer extracted with EtOAc (5 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered through Celite, and concentrated under reduced pressure. The resulting solid was dissolved in pyridine (1 mL) and Ac_2O (500 μL), and this mixture then stirred at room temperature for 24 h. The reaction mixture was then concentrated

under reduced pressure and the resulting residue purified by flash chromatography (SiO_2, EtOAc) to provide **29** (47 mg, 27%): colorless oil; R_f 0.32 (EtOAc); IR (film) ν_{max} 1743, 1724, 1225, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (d, J = 11.6 Hz, 2 H), 4.12 (d, J = 11.6 Hz, 2 H), 3.84 (s, 3 H), 2.38 (m, 2 H), 2.10 (s, 6 H), 2.03 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 170.3, 64.3, 64.2, 63.8, 26.3, 22.6, 20.7; HRMS-ESI calcd for $C_{11}H_{17}NO_6Na$ $[M + Na]^+$ 282.0954, found 282.0958.

Methyl (±)-2-Hydroxymethyl-1-methoxy-5-oxopyrrolidine-2-carboxylate (30c). A stream of oxygen and ozone was passed through a solution of **12c** (139 mg, 0.62 mmol) in CH_2Cl_2 (7 mL) at −78 °C for 30 min. The blue solution was then purged with a stream of argon for 10 min, Me_2S (686 μL, 9.34 mmol) added, the cooling bath removed, and the mixture stirred at room temperature for 4 h. The reaction mixture was then filtered through a plug of Celite and the filtrate concentrated under reduced pressure. The resulting residue was dissolved in AcOH (2 mL) and this mixture added to a solution of $NaBH(OAc)_3$ in AcOH (0.8 M, 7.8 mL). After being stirred for 24 h at room temperature, the reaction was concentrated under reduced pressure, the residual oil diluted with CH_2Cl_2 (5 mL), and 2 M aqueous HCl (2 mL) added. After being allowed to stand for 10 min, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were concentrated under reduced pressure, and the resulting oil was purified by flash chromatography (SiO_2, EtOAc) to provide **30c** (62 mg, 49%): colorless oil; R_f 0.32 (EtOAc); FTIR (film) ν_{max} 3410 (br), 1737, 1706, 1432, 1251, 1056, 969 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.97 (d, J = 11.9 Hz, 1 H), 3.87 (d, J = 11.9 Hz, 1 H), 3.84 (s, 3 H), 3.73 (s, 3 H), 3.35 (br s, 1 H), 2.38−2.34 (m, 2 H), 2.28−2.22 (m, 1 H), 2.08−2.03 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 172.2, 70.0, 64.3, 62.9, 53.2, 26.7, 24.1; HRMS-EI calcd for $C_8H_{14}NO_5$ $[M + H]^+$ 204.0872, found 204.0881

General Procedure C (Ozonolysis−Reduction of Spirodienones 12). Methyl (±)-2-Hydroxymethyl-1-methoxy-4-oxoazetidine-2-carboxylate (30a) (Entry 1, Table 2). A stream of oxygen and ozone was passed through a solution of **12a** (50 mg, 0.24 mmol) in MeOH (3 mL) at −78 °C for 30 min. The blue solution was then purged with a stream of argon for 10 min, thiourea (23 mg, 0.30 mmol) was added, and the solution then allowed to warm to room temperature over 30 min. After being stirred for an additional 10 min, the reaction was concentrated under reduced pressure, the residue dissolved in AcOH (500 μL), and this mixture added to a solution of $NaBH(OAc)_3$ in AcOH (0.51 M, 2 mL). After being stirred for 24 h at room temperature, the reaction was concentrated under reduced pressure, the residual oil diluted with CH_2Cl_2 (5 mL), and 2 M aqueous HCl (2 mL) added. After being allowed to stand for 10 min, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were concentrated under reduced pressure, and the resulting oil was purified by flash chromatography (SiO_2, EtOAc) to provide **30a** (35 mg, 78%): colorless oil; R_f 0.44 (EtOAc); IR (film) ν_{max} 3445 (br), 1778, 1742, 1072, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (d, J = 12.4 Hz, 1 H), 4.02 (d, J = 12.4 Hz, 1 H), 3.90 (s, 3 H; OCH_3), 3.84 (s, 3 H; OCH_3), 2.93 (d, J = 13.8 Hz, 1 H), 2.88 (d, J = 13.8 Hz, 1 H) 2.51 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 164.4, 67.5, 65.0, 61.4, 53.0, 39.6; HRMS-ESI calcd for $C_7H_{11}NO_5Na$ $[M + Na]^+$ 212.0535, found 212.0543.

General Procedure D (Ozonolysis−Reduction−Acetylation of Spirodienones 12). Methyl (±)-2-Acetoxymethyl-1-methoxy-6-oxopiperidine-2-carboxylate (30e) (Entry 5, Table 2). A stream of oxygen and ozone was passed through a solution of **12e** (50 mg, 0.21 mmol) in MeOH (5 mL) at −78 °C for 3 h. The blue solution was then purged with a stream of argon for 10 min, thiourea (20 mg, 0.26 mmol) was added in one portion, and the solution was then allowed to warm to room temperature over 30 min. After being stirred for an additional 10 min, the reaction was concentrated under reduced pressure and the residue dissolved in AcOH (500 μL). This solution was added to a solution of $NaBH(OAc)_3$ in AcOH (0.17 M, 5 mL). After being stirred for 24 h at room temperature, the reaction was concentrated under reduced pressure and the residue dissolved in pyridine (1 mL) and acetic anhydride (500 μL, 5 mmol). The mixture was stirred at room temperature for 8 h and then concentrated under reduced pressure and the residue purified by flash chromatography (SiO_2, EtOAc) to provide **30e** (32 mg, 58%) and starting material **12e** (18 mg): white crystals; mp 72−74 °C (EtOAc/hexanes); R_f 0.37 (EtOAc); FTIR (film) ν_{max} 1745, 1689, 1238, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.54 (d, J = 11.9 Hz, 1 H), 4.49 (d, J = 11.9 Hz, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 2.54−2.47 (m, 2 H), 2.19−2.16 (m, 1 H), 2.12 (s, 3 H), 2.11−2.05 (m, 1 H), 1.82−1.78 (m 2 H); ^{13}C NMR (125 MHz, CD_3OD) δ 171.0 (2 C), 170.7, 70.9, 63.9, 63.7, 53.5, 33.5, 31.3, 21.2, 18.1; HRMS-ESI calcd for $C_{11}H_{17}NO_6Na$ $[M + Na]^+$ 282.0954, found 282.0958.

General Procedure E (Luche Reduction−Ozonolysis of Spirodienones 12). Methyl (2*S,4*S**)-2-Hydroxymethyl-1-methoxy-5-oxo-4-phenylpyrrolidine-2-carboxylate (30j) (Entry 10, Table 2).** To a solution of **12j** (117 mg, 0.39 mmol) and $CeCl_3 \cdot 7H_2O$ (117 mg, 0.39 mmol) in MeOH (8 mL) at 0 °C was added $NaBH_4$ (16 mg, 0.41 mmol). After being stirred for 1 min, the reaction was quenched with water (2 mL) and concentrated under reduced pressure and the remaining aqueous portion extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to provide the unstable dienylic alcohol as a colorless oil, which was immediately subjected to ozonolysis. Thus, a stream of oxygen and ozone was passed through a solution of the dienylic alcohol in MeOH (4 mL) at −78 °C for 30 min. The blue solution was then purged with a stream of argon for 10 min, thiourea (37 mg, 0.49 mmol, 1.25 equiv) was added, and the solution was then allowed to warm to room temperature over 30 min. After being stirred for an additional 30 min, the reaction was concentrated under reduced pressure, the residue dissolved in AcOH (1 mL), and this mixture added to a solution of $NaBH(OAc)_3$ in AcOH (0.65 M, 3 mL, 5 equiv). After being stirred for 24 h at room temperature, the reaction was concentrated under reduced pressure, the residual oil diluted with CH_2Cl_2 (10 mL), and 2 M aqueous HCl (5 mL) added. After being allowed to stand for 20 min, the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were concentrated under reduced pressure, and the resulting oil was purified by flash chromatography (SiO_2, EtOAc) to provide **30j** (107 mg, 98%).

General Procedure F (Reductive Cleavage of *N*-Methoxy Lactams). Methyl (±)-2-Hydroxymethyl-4-oxoazetidine-2-carboxylate (32a) (Entry 1, Table 4). A mixture of **30a** (210 mg, 1.11 mmol) and $Mo(CO)_6$ (352 mg, 1.33 mmol, 1.2 equiv) in degassed CH_3CN-H_2O (15:1, 5 mL) was heated at reflux, under N_2, for 24 h, whereupon the black reaction mixture was cooled to room temperature, opened to the atmosphere, and stirred for 24 h. The reaction was then concentrated under reduced pressure and the resulting residue purified by flash chromatography (SiO_2, EtOAc) to yield **32a** (133 mg, 75%): colorless oil; R_f 0.37 (EtOAc); FTIR (film) ν_{max} 3312 (br), 1750, 1277, 1228, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (br s, 1 H), 4.14 (d, J = 11.7 Hz, 1 H), 3.85−3.82 (m, 4 H), 3.12 (d, J = 14.9 Hz, 1 H), 3.04 (d, J = 14.9 Hz, 1 H), 2.71 (br s, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.4, 167.1, 65.1, 59.3, 53.5, 45.2; HRMS-ESI calcd for $C_6H_9NO_4$ $[M + Na]^+$ 182.0429, found 182.0426.

General Procedure G (Hydrogenolysis of *N*-Benzyloxy Lactams). Methyl (±)-1-Hydroxy-2-hydroxymethyl-4-oxoazetidine-2-carboxylate (34b) (Entry 1, Table 5). A mixture of **30b** (40 mg, 0.15 mmol) and 10% Pd/C (2 mg) in EtOAc (2 mL) was stirred under an atmosphere of H_2 for 10

min and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue purified by flash chromatography (SiO_2, EtOAc) to yield **34b** (26 mg, 99%): colorless oil; R_f 0.25 (EtOAc); FTIR (film) ν_{max} 3390 (br), 1770, 1745, 1247, 1037 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 4.02 (d, J = 12.4 Hz, 1 H), 3.95 (d, J = 12.4 Hz, 1 H), 3.79 (s, 3 H), 2.89 (d, J = 13.2 Hz, 1 H), 2.82 (d, J = 13.2 Hz, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.0, 164.7, 67.9, 58.4, 51.7, 38.0; HRMS-ESI calcd for $C_6H_9NO_5Na$ $[M + Na]^+$ 198.0378, found 198.0373.

Acknowledgment. We thank the National Institutes of Health (GM-67176) for financial support.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051252R