Synthesis of Substituted Pyridines via Regiocontrolled [4 + 2] Cycloadditions of Oximinosulfonates

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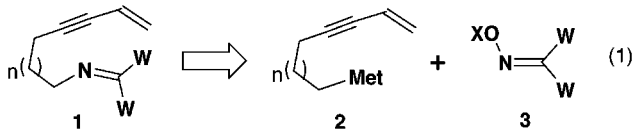
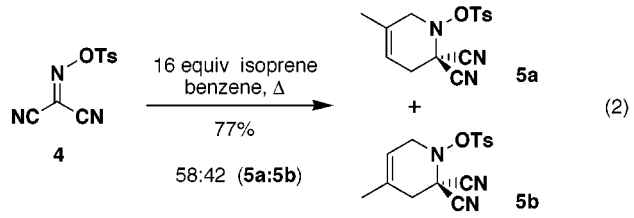
Diels−Alder cycloadditions of oximinosulfonate **8** with a variety of 1,3-dienes proceed with regiochemistry *opposite* to that observed with conventional imino dienophiles, providing expeditious synthetic routes to substituted pyridines, tetrahydropyridines, and pyrrolines. The oximinosulfonate **8** is prepared in one convenient synthetic operation from Meldrum's acid and reacts with conjugated dienes at −78 °C in the presence of 2 equiv of dimethylaluminum chloride to afford [4 + 2] cycloadducts in good to excellent yield. Exposure of these cycloadducts to the action of NaOMe and *N*-chlorosuccinimide in methanol−THF at room temperature then produces substituted pyridines. The utility of this new two-step annulation protocol is demonstrated in total syntheses of the pyridine alkaloids fusaric acid and (*S*)-(+)-fusarinolic acid. Heating the [4 + 2] cycloadducts derived from **8** in a mixture of acetonitrile and pH 7 phosphate buffer induces an unusual Stieglitz-type rearrangement leading to the formation of interesting spirobicyclic pyrrolines.

In connection with our investigations of [4 + 2] cycloadditions of conjugated enynes,[1] we became interested in activated imine derivatives with the ability to function as reactive 2π components in these and related cycloadditions. Of particular interest have been systems such as **1** (eq 1), which we envisioned might be available via the transition-metal-mediated coupling of an organometallic species **2** (Met = Cu, Zn, B, Sn, etc.) with a readily available oxime building block of type **3** (X = Ts, Tf, etc.). Oxime derivatives of type **3** are themselves of some interest as cycloaddition partners, and we report herein our studies of the scope of the intermolecular [4 + 2] cycloadditions of one class of such compounds, oximinosulfonates derived from Meldrum's acid. We have found that cycloadditions of these species proceed with regiochemistry *opposite* to that observed with conventional imino dienophiles,[2] providing expeditious synthetic routes to substituted pyridines, tetrahydropyridines, and pyrrolines.



In contrast to imines, the application of oxime derivatives as dienophiles for the Diels−Alder reaction has attracted relatively little attention. Most of the work in this area has been reported by Fleury,[3] who described the synthesis and cycloadditions of a variety of oximino esters and nitriles during the 1970s. Most useful among the compounds examined was the bis-nitrile **4**, which reacts with cyclopentadiene[3b] and a number of acyclic dienes[3d] in generally good yield. Unfortunately, these cycloadditions appear to proceed with poor regioselectivity (eq 2), and the scope of this chemistry is further limited by the instability of **4** above 90 °C and the apparent need to use excess diene in these reactions. A useful feature of the resulting cycloadducts, however, is that they undergo aromatization to form pyridines in good yield simply upon heating in ethanol.[3d]



In related studies, Breitmaier has reported cycloadditions of oximinosulfonate **4** with oxygenated dienes and conversion of the cycloadducts to pyridines, albeit in low yield.[4] More recently, Katagiri and co-workers studied the reaction of the Meldrum's acid-derived oximinoacetate **6** with cyclopentadiene and 2,3-substituted butadienes, finding that most of these cycloadditions require the application of high-pressure techniques (eq 3).[5] Cycloadditions involving unsymmetrical dienes were not investigated in this study. The modest Diels−Alder reactivity of dienophile **6** stands in contrast to the related, unreactive diesters investigated by Fleury[3b] (i.e., **3**, W = CO_2Et, X = Ts, Ms), which fail to combine with even the most reactive dienes such as cyclopentadiene. Greater

(1) Danheiser, R. L.; Gould, A. E.; Fernández de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514.

(2) For reviews of azadienophiles in the Diels−Alder reaction, see: (a) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 401−413. (b) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949. (c) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087. (d) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987; Chapter 2.

(3) (a) Biehler, J.-M.; Perchais, J.; Fleury, J.-P. *Bull. Soc. Chim. Fr.* **1971**, 2711. (b) Biehler, J.-M.; Fleury, J.-P. *J. Heterocycl. Chem.* **1971**, *8*, 431. (c) Perchais, J.; Fleury, J.-P. *Tetrahedron* **1972**, *28*, 2267. (d) Fleury, J.-P.; Desbois, M.; See, J. *Bull. Soc. Chim. Fr.* **1978**, II-147.

(4) Dormagen, W.; Rotscheidt, K.; Breitmaier, E. *Synthesis* **1988**, 636.

(5) Katagiri, N.; Nochi, H.; Kurimoto, A.; Sato, H.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 1251.

(6) For reviews of the chemistry of Meldrum's acid and its derivatives see: (a) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345. (b) Chen, B.-C. *Heterocycles* **1991**, *32*, 529.

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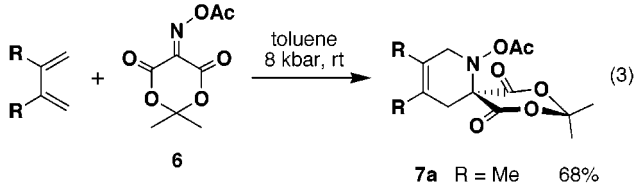
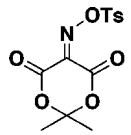
orbital overlap between the carbonyl groups and the oximino π-bond in the cyclic Meldrum's acid[6] derivative leads to enhanced dienophilicity in **6** relative to the related acyclic diesters.



6

7a R = Me 68%
7b R = MeO 62%

In this article we report on Diels–Alder reactions of the previously unknown oximinosulfonate **8** and the facile transformation of the resulting cycloadducts to pyridines. Overall, this process provides a valuable regiocontrolled [4 + 2] annulation strategy for the synthesis of substituted pyridines, one of the most important classes of



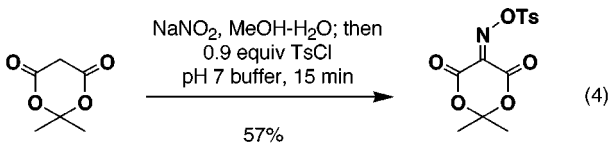
8

aromatic nitrogen heterocycles.[7] The structures of a number of natural products[8] incorporate the pyridine ring system, as do important commercial compounds including herbicides, insecticides, fungicides, and a variety of medicinal agents.[7b] Pyridine–metal complexes[7c] find an important place in coordination chemistry, and recently the pyridine ring system has figured prominently in the design of molecules with important roles in supramolecular chemistry.[9] The development of improved synthetic routes to pyridines consequently continues to be a problem of great interest.[7d] Pyridine syntheses based on the Diels–Alder reaction are especially powerful, as their intrinsic convergent nature often permits the rapid assembly of complex substituted systems. Both azadienes and azadienophiles have found application in the synthesis of pyridines. Heteroaromatic azadienes employed in pyridine synthesis include oxazoles, triazenes, and diazenes,[10] and recently Boger[11] and Ghosez[12] have developed methods based on *acyclic* azadienes which have been applied in elegant total syntheses of natural products.[13] Although a variety of azadienophiles[2] have been used for the synthesis of tetrahydropyridines, few examples of their application in the synthesis of pyridines have previously been reported.

Our investigation of the previously unknown oximinosulfonate **8** was founded on the expectation that the Diels–Alder reactions of this system would enjoy several advantages over the previously reported oximino dienophiles **4** and **6** (vide infra). Most importantly, we anticipated that cycloadditions involving **8** would be subject to Lewis acid promotion, thus permitting highly regioselective cycloadditions with an expanded range of diene substrates under relatively mild reaction conditions. The expectation that cycloadducts of **8** could be transformed to pyridines in a single synthetic operation also made this system an attractive candidate for our investigation.

Results and Discussion

Preparation of Oximinosulfonate 8. We have developed a convenient one-pot procedure for the preparation of oximinosulfonate **8** (eq 4). Nitrosation of Meldrum's acid (**9**) with 1.0 equiv of sodium nitrite in methanol–water proceeds smoothly at room temperature[14] to afford an oxime which is sulfonylated in the same flask by neutralization[15] of the solution with pH 7 phosphate buffer followed by addition of tosyl chloride (0.9 equiv) at 0 °C. The solid oximinosulfonate **8** precipitates almost immediately, and is collected by filtration, washed with cold methanol, and dried in a desiccator over P_2O_5. This simple procedure provides multigram quantities of **8** in high purity as an easily handled white solid (mp 155–156 °C) which can be transferred in air and is stable for months when stored under argon in a refrigerator.



9 **8**

Thermal [4 + 2] Cycloadditions. As anticipated, oximinosulfonate **8** exhibits dienophilicity in thermal

(7) For general reviews of the synthesis and chemistry of pyridines, see: (a) Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 2, Part 2A, pp 165–314. (b) Yates, F. S. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 2, Part 2A, pp 511–524. (c) Tomasik, P.; Ratajewicz, Z. In *Pyridine-Metal Complexes*; Newkome, G. R., Strekowski, L., Eds.; The Chemistry of Heterocyclic Compounds; Wiley: New York, 1985; Vol. 14, Part 6A. (d) Jones, G. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J.; McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 2, Part 2A, pp 395–510. (e) *Pyridine and its Derivatives*; Newkome, G. R., Ed; The Chemistry of Heterocyclic Compounds; Wiley: New York, 1984; Vol. 14, Part 5.

(8) (a) Enzell, C. R.; Wahlberg, I. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Grisebach, H.; Kirby, G. W., Eds.; Springer-Verlag: New York, 1977; Vol. 34, p 1. (b) Birkinshaw, J. H.; Stickings, C. E. In *Progress in the Chemistry of Organic Natural Products*; Zechmeister, L., Ed.; Springer-Verlag: Vienna, 1962; Vol. 20, p 1. (c) Cordell, G. A. *Introduction to Alkaloids*; Wiley: New York, 1981; Chapters 3 and 5.

(9) For reviews see: (a) Chambron, J.-C.; Dietrich-Buchecker, C.; Sauvage, J.-P. In *Comprehensive Supramolecular Chemistry*; Sauvage, J.-P., Hosseini, M. W., Eds.; Pergamon: New York, 1996; Vol. 9, pp 43–84. (b) Amabilino, D. B.; Raymo, F. M.; Stoddart, J. F. In *Comprehensive Supramolecular Chemistry*; Sauvage, J.-P., Hosseini, M. W., Eds.; Pergamon: New York, 1996; Vol. 9, pp 85–130. (c) Baxter, P. N. W. In *Comprehensive Supramolecular Chemistry*; Sauvage, J.-P., Hosseini; M. W., Eds.; Pergamon: New York, 1996; Vol. 9, pp 165–212.

(10) (a) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (b) Boger, D. L. *Bull. Soc. Chim. Belg.* **1990**, *99*, 599.

(11) (a) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1990**, *55*, 5439. (b) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713. (c) Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1993**, *58*, 2068.

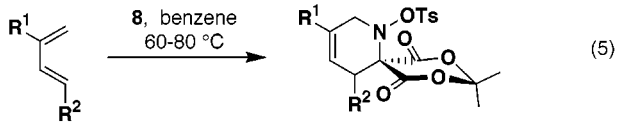
(12) (a) Demoulin, A.; Gorissen, H.; Hesbain-Frisque, A.-M.; Ghosez, L. *J. Am. Chem. Soc.* **1975**, *97*, 4409. (b) Sainte, F.; Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428. (c) Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261. (d) Bayard, P.; Ghosez, L. *Tetrahedron Lett.* **1988**, *29*, 6115.

(13) (a) Boger, D. L.; Nakahara, S. *J. Org. Chem.* **1991**, *56*, 880. (b) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 4051. (c) Waldner, A. *Synth. Commun.* **1989**, *19*, 2371.

(14) Meldrum's acid is itself sufficiently acidic to catalyze the nitrosation reaction. For the first report of the nitrosation of Meldrum's acid, see: Eistert, B.; Geiss, F. *Chem. Ber.* **1961**, *94*, 929.

(15) Neutralization before the addition of TsCl helps prevent the acid-promoted addition of methanol to **8** (the product is obtained in 35% yield if buffer is not used).

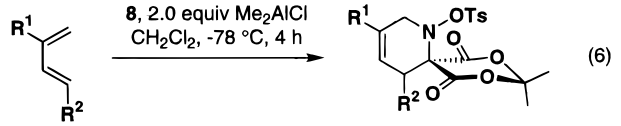
Diels–Alder reactions comparable to Fleury's bis-nitrile **4**, and considerably greater than that of the corresponding diesters and the oximinoacetate **6**. Thus, reaction of **8** with penta-1,3-diene in refluxing benzene produced the expected cycloadduct **10** (eq 5), the regiochemical assignment for which is based on the observation of a methylene resonance at 4.04 ppm (CH_2N) and a methine resonance at 3.31 ppm ($CH(CH_3)$) in the ^{1}H NMR spectrum. The more reactive 2-(triisopropylsiloxy)buta-1,3-diene reacts similarly at only 55–65 °C to provide cycloadduct **11** in 46–56% yield. Noteworthy is the regiochemical outcome of these Diels–Alder reactions, in which the carbonyl substituents direct the cycloaddition to generate products with regiochemistry opposite to that which would be observed with conventional imino dienophiles.[2]



(5)

10 R^1 = H, R^2 = Me 32%
11 R^1 = *i*-Pr_3SiO, R^2 = H 46-56%

Lewis Acid-Promoted Cycloadditions. When a purified sample of cycloadduct **10** was heated at reflux in benzene, a number of new compounds were produced and a brown tar formed on the inside of the reaction flask. This observation suggests that the modest yield obtained in the reaction of **8** with penta-1,3-diene is due, at least in part, to the instability of the cycloadduct at elevated temperature. Consequently, we next turned our attention to the promotion of cycloadditions of **8** using Lewis acids, and after some experimentation, we were pleased to find that Me_2AlCl is quite effective at promoting the desired [4 + 2] cycloaddition. Thus, as outlined in eq 6, reaction of oximinosulfonate **8** with isoprene or penta-1,3-diene (3.0 equiv) and Me_2AlCl (2.0 equiv) in dichloromethane at −78 °C for 4 h provided the desired cycloadducts **12** and **13** in high yield and in each case as a single regioisomer. Once again, the cycloaddition of **8** produces heterocycles with substitution patterns that cannot be accessed using standard imino Diels–Alder



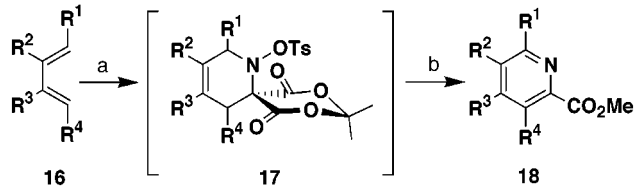
(6)

12 R^1 = Me, R^2 = H 84-91%
13 R^1 = H, R^2 = Me 76-78%

methodology. Also significant is our finding that Lewis acids fail to promote cycloadditions involving Fleury's bis-nitrile oximinosulfonate **4** and the Meldrum's acid-derived oximinoacetate **6** described by Katagiri. In both cases we observed only decomposition when these dienophiles were exposed to Me_2AlCl and other Lewis acids under conditions that lead to successful cycloadditions with oximinosulfonate **8**.

Other reagents such as $TiCl_4$, $ZnCl_2$, $AlCl_3$, methanesulfonic acid, and camphorsulfonic acid proved less effective than Me_2AlCl in promoting the desired cycloaddition; in most cases either decomposition of the starting materials or no significant rate enhancement was observed. A series of experiments in which Me_2AlCl stoichiometry was varied from 0.1 to 2.5 equiv relative

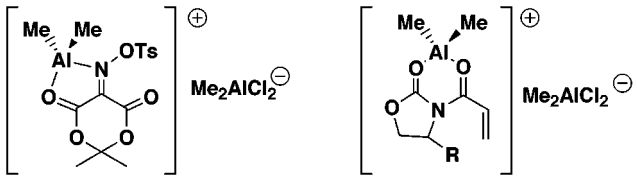
Scheme 1



16 **17** **18**

(a) **8**, 2.0 equiv Me_2AlCl, CH_2Cl_2, -78 °C; (b) 3.0 equiv NaOMe, 1.0 equiv NCS, MeOH-THF (1:1), rt

to **8** established the requirement that a full 2.0 equiv of the Lewis acid is necessary for these reactions. It is likely that the second equivalent of Me_2AlCl serves to promote ionization of chloride from an initial 1:1 Lewis acid–**8** complex, thereby generating the more reactive ionic 2:1 complex **14**. This type of Lewis acid behavior has previously been noted by Lehmkuhl and Kobs,[16] and more recently has been observed by Evans in Diels–Alder reactions of oxazolidinone-metal complexes such as **15**.[17]

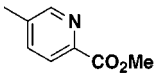
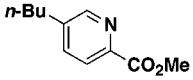
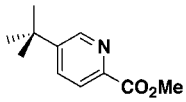
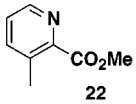
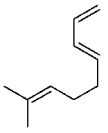
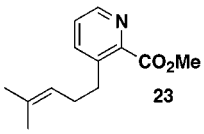
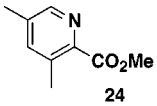
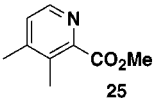
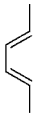
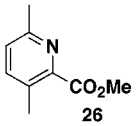
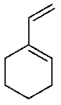
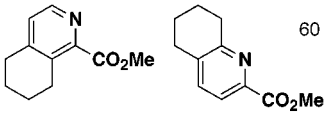


14 **15**

Synthesis of Substituted Pyridines. Encouraged by the efficiency and regioselectivity of these cycloadditions, we next turned our attention to their application in the context of a regiocontrolled synthesis of substituted pyridines. Initially, we set as our goal the identification of conditions for the conversion of the tetrahydropyridine cycloadducts (**17**) to pyridines in a single synthetic operation. It was our expectation that the desired transformation might be achieved through the simultaneous action of a nucleophilic alkoxide reagent and suitable oxidizing agent on the cycloadducts **17**. After having little success with oxidants such as DDQ, O_2, and air, we ultimately found that the combination of *N*-chlorosuccinimide (NCS) and sodium methoxide is especially effective at bringing about the desired transformation.[18] Thus, treatment of a cooled (0 °C) solution of **17** in methanol-THF (1:1) with 3.0 equiv of NaOMe and 1.0 equiv of NCS, followed by stirring overnight at room temperature, affords the desired pyridines in generally excellent yield after chromatographic purification[19] (Scheme 1). The mechanism of this multistage reaction presumably involves initial cleavage of the dioxandione ring by methoxide with concomitant elimination of acetone and carbon dioxide. β-Elimination of tosylate from the resulting ester enolate then generates a dihydropyridine, and subsequent chlorination by NCS and elimination of HCl finally provides the desired aromatic product. Optimal yields are obtained by converting the cycloadducts **17** directly to pyridines without purification,

(16) Lehmkuhl, H.; Kobs, H.-D. *Liebigs. Ann. Chem.* **1968**, *719*, 11.
(17) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
(18) NCS in conjunction with NaOMe has recently been used for the oxidation of tetrahydropyridines to pyridines: De Kimpe, N.; Keppens, M.; Fonck, G. *Chem. Commun.* **1996**, 635.
(19) Care must be exercised to avoid strongly basic workup conditions since the pyridine esters are sensitive to hydrolysis. This difficulty was circumvented by performing a neutral workup with pH 7 phosphate buffer.

Table 1. [4 + 2] Pyridine Annulations[a]

entry	diene[b]	pyridine	% yield[c]
1		 **19**	77
2		 **20**	72
3		 **21**	73
4		 **22**	56-57
5		 **23**	60
6		 **24**	70
7		 **25**	40
8[d]		 **26**	40
9		 **27** 83 : 17 **28**	60

[a] Conditions: (a) **8**, 2.0 equiv of Me_2AlCl, CH_2Cl_2, −78 °C, 2-4 h; (b) 3.0 equiv MeONa, 1.0 equiv of NCS, MeOH−THF (1:1), rt, 14-16 h. [b] 1.5-3.0 equiv of diene was employed. [c] Isolated overall yield for two steps. [d] 5.0 equiv of NaOMe and 4.0 equiv of NCS were used.

especially in the case of tetrahydropyridines that are prone to undergo rearrangement upon purification (vide infra). Overall, this two-stage protocol comprises a new regiocontrolled [4 + 2] annulation strategy for the synthesis of substituted pyridines from 1,3-dienes.

Table 1 delineates the scope of the [4 + 2] pyridine annulation. A variety of monosubstituted dienes participate in the reaction, with the exception of (*Z*)-dienes, which as usual do not undergo efficient Diels−Alder cycloaddition. Reactions involving disubstituted 1,3-dienes provide convenient access to trisubstituted pyridines, although in some cases (e.g., entries 7 and 8) lower yields are obtained due to competing Stieglitz-type rearrangement processes (vide infra). Cycloadducts derived from 2,3-disubstituted dienes are particularly prone to this rearrangement and cannot be employed in the pyridine annulation. Finally, the preparation of pyridine **23** in good yield demonstrates the compatibility of alkene functionality with the cycloaddition and chlorination conditions. Structural assignments for the pyridine annulation products are based on NMR spectroscopic analyses, and data for the known pyridines **19**,[20] **20**,[21] **22**[22], and **24**[23] are fully consistent with that previously reported for these compounds.

Total Synthesis of Fusaric Acid and (*S*)-(+)-Fusarinolic Acid. The [4 + 2] pyridine annulation described herein provides a particularly powerful method for the construction of 5-alkylpicolinic acid derivatives, an important class of biologically active alkaloids. The following syntheses of fusaric acid (**32**) and (*S*)-(+)-fusarinolic acid (**36**) illustrate the utility of the new annulation strategy as applied to this class of naturally occurring pyridines.

The phytotoxin fusaric acid is produced by several species of plant-pathogenic fungi belonging to the genus *Fusarium*.[24] In nature, fusaric acid acts as a plant growth inhibitor causing leaf and stem necrosis and inhibiting root elongation. It has recently been suggested that fusaric acid might have utility as a herbicide for the control of the parasitic weed *Striga hermonthica* (witchweed).[24h] Fusaric acid is also a potent inhibitior[25] of dopamine β-hydroxylase and possesses significant hypotensive activity in mammals.[24c,e] In comparison to fusaric acid, much less is known about the oxygenated derivative (*S*)-(+)-fusarinolic acid (**36**). This alkaloid was isolated from *Gibberella fujikuroi*[26] (the same species of fungus from which fusaric and dehydrofusaric acid had previously been extracted[24b]) and displays much lower phytotoxicity than fusaric acid in tomato plant assays.[26] Several syntheses of fusaric acid (**32**) and (*S*)-(+)-fusarinolic acid (**36**) have previously been reported,[26−28] including two which involve strategies based on hetero Diels−Alder reactions of azadiene derivatives.[27e,f] Despite the rather simple structure of these alkaloids, most of the reported routes require five to ten synthetic steps. The application of an *azadienophile*-based hetero Diels−Alder strategy to the synthesis of these natural products has not previously been reported.

(20) Deady, L. W.; Harrison, P. M.; Topsom, R. D. *Org. Magn. Reson.* **1975**, *7*, 41.

(21) Capasso, R.; Evidente, A.; Cutignano, A.; Vurro, M.; Zonno, M. C.; Bottalico, A. *Phytochemistry* **1996**, *41*, 1035.

(22) (a) Hromatka, O.; Binder, D.; Stanetty, P.; Marischler, G. *Monatsh. Chem.* **1976**, *107*, 233. (b) Subramanyam, C.; Chattarjee, S.; Mallamo, J. P. *Tetrahedron Lett.* **1996**, *37*, 459.

(23) Blank, B.; DiTullio, N. W.; Krog, A. J.; Saunders: H. L. *J. Med. Chem.* **1979**, *22*, 840.

(24) (a) Yabuta, T.; Kambe, K.; Hayashi, T. *J. Agric. Chem. Soc. Jpn.* **1934**, *10*, 1059. (b) Grove, J. F.; Jeffs, P. W.; Mulholland, T. P. C. *J. Chem. Soc.* **1958**, 1236. (c) Hidaka, H.; Nagatsu, T.; Takeya, K. *J. Antibiot.* **1969**, *22*, 228. (d) Nagatsu, T.; Hidaka, H.; Kuzuya, H.; Takeya, K.; Umezawa, H.; Takeuchi, T.; Suda, H. *Biochem. Pharmacol.* **1970**, *19*, 35. (e) Suda, H.; Takeuchi, T.; Nagatsu, T.; Matsuzaki, M.; Matsumoto, I.; Umezawa, H. *Chem. Pharm. Bull.* **1969**, *17*, 2377. (f) Claydon, N.; Grove, J. F.; Pople, M. *Phytochemistry* **1977**, *16*, 603. (g) Abraham, W.-R.; Hanssen, H.-P. *Tetrahedron* **1992**, *48*, 10559. (h) Capasso, R.; Evidente, A.; Cutignano, A.; Vurro, M.; Zonno, M. C.; Bottalico, A. *Phytochemistry* **1996**, *41*, 1035.

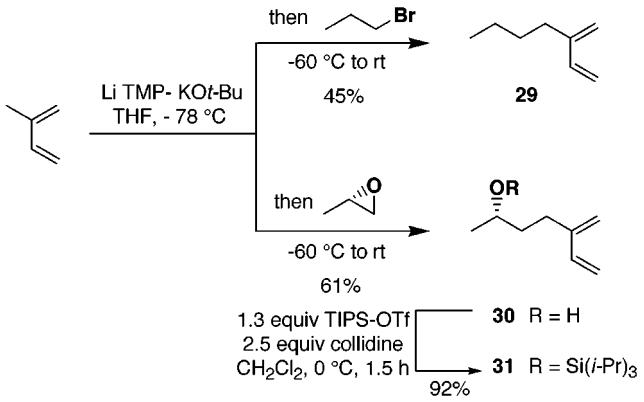
(25) Fusaric acid is a nanomolar inhibitor of dopamine β-hydroxylase ($IC_{50} = 3.0 \times 10^{-8}$ M), see: ref 24d.

(26) Steiner, K.; Graf, U.; Hardegger, E. *Helv. Chim. Acta* **1971**, *54*, 845.

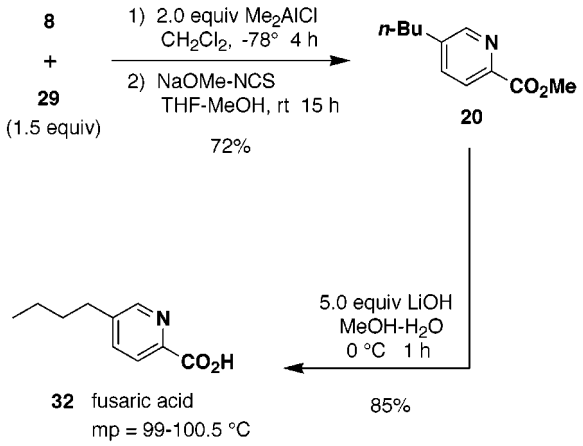
(27) (a) Plattner, Pl. A.; Keller, W.; Boller, A. *Helv. Chim. Acta* **1954**, *37*, 1379. (b) Hardegger, E.; Nikles, E. *Helv. Chim. Acta* **1957**, *40*, 1016. (c) Vogt, H.; Mayer, H. *Tetrahedron Lett.* **1966**, 5887. (d) Tschesche, R.; Führer, W. *Chem. Ber.* **1978**, *111*, 3502. (e) Sagi, M.; Amano, M.; Konno, S.; Yamanaka, H. *Heterocycles* **1989**, *29*, 2249. (f) Waldner, A. *Synth. Commun.* **1989**, *19*, 2371. (g) Langhals, E.; Langhals, H.; Rüchardt, C. *Liebigs Ann. Chem.* **1982**, 930.

(28) Büyük, G.; Hardegger, E. *Helv. Chim. Acta* **1975**, *58*, 682.

Scheme 2



Scheme 3

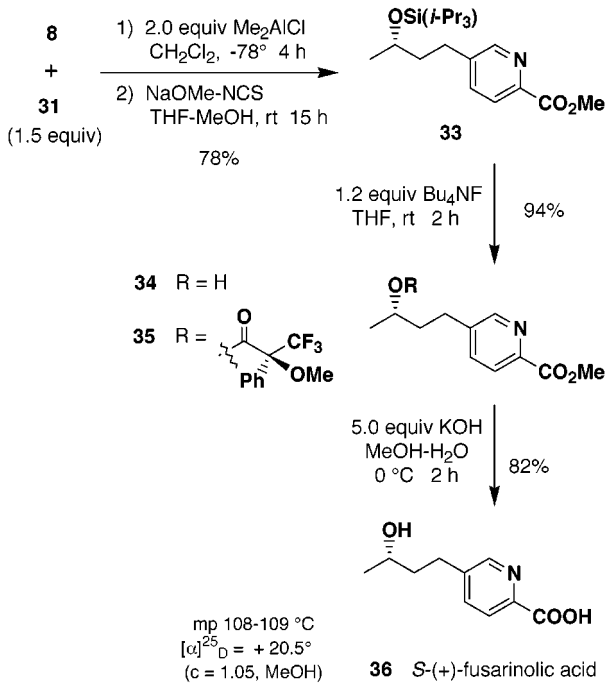


Our approach to the synthesis of fusaric acid and (*S*)-(+)-fusarinolic acid begins with the synthesis of the conjugated dienes **29** and **31** (Scheme 2). Metalation of isoprene with LiTMP−potassium *tert*-butoxide[29] and alkylation with bromopropane furnished **29**[30] in 45% yield as material (ca. 90% purity) suitable for use in the subsequent Diels−Alder reaction without further purification. Alkylation of isoprene with (*S*)-(−)-propylene oxide provided **30**, which was protected as the corresponding triisopropylsilyl ether (**31**) under standard conditions.

Scheme 3 outlines the remainder of the synthesis of fusaric acid. Reaction of oximinosulfonate **8** with 1.5 equiv of diene **29** according to our standard annulation protocol provided methyl fusarate (**20**) in good overall yield as a single regioisomer, and ester hydrolysis then furnished synthetic fusaric acid in 85% yield following purification by sublimation (0.1 mmHg, 110 °C). Spectroscopic and physical data (mp, ^{1}H and ^{13}C NMR, IR, EA) for this material was fully consistent with that previously reported for fusaric acid isolated from natural sources.[24b,g]

Scheme 4 outlines the conversion of diene **31** to (*S*)-(+)-fusarinolic acid. Reaction of oximinosulfonate **8** with 1.5 equiv of this diene using our standard annulation procedure afforded the expected pyridine **33** in excellent

Scheme 4



overall yield following chromatographic purification. Unreacted diene **31** could be recovered in essentially quantitative yield from this reaction. Desilylation of **33** with tetrabutylammonium fluoride next gave (*S*)-(+)-methyl fusarinolate (**34**) in 94% yield. Analysis of the Mosher ester (**35**) derived from **34** by ^{1}H and ^{19}F NMR revealed only one diastereomer within the detection limits of the spectrometer.[31] The synthesis of (*S*)-(+)-fusarinolic acid was then completed by hydrolysis of methyl ester **34** with KOH in aqueous methanol.[32] Attempted crystallization (dichloromethane−methanol) of the crude product gave an oil which subsequently crystallized, providing synthetic (*S*)-(+)-fusarinolic acid in 82% yield. Spectral data (^{1}H and ^{13}C NMR, IR, EA) for **36** was fully consistent with that of (*S*)-(+)-fusarinolic acid, and the melting point of the (+)-camphorsulfonate salt of synthetic **36** (188−189 °C) was in good agreement with that previously reported (187−188 °C) for the same derivative prepared from authentic natural product.[26]

In summary, total syntheses of fusaric acid and (*S*)-(+)-fusarinolic acid were completed in four and six steps and in 35 and 33% overall yield, respectively. The efficiency of these new synthetic routes compares very favorably to those reported previously, highlighting the utility of this approach to the synthesis of substituted pyridines.

Rearrangement of Oximinosulfonate Cycloadducts to Pyrrolines. As mentioned earlier, in the course of our exploratory cycloaddition studies we observed that the cycloadducts derived from certain disubstituted 1,3-dienes undergo a facile rearrangement upon attempted purification. Exposure of the cycloaddition product from the reaction of **8** with hexa-2,4-diene to

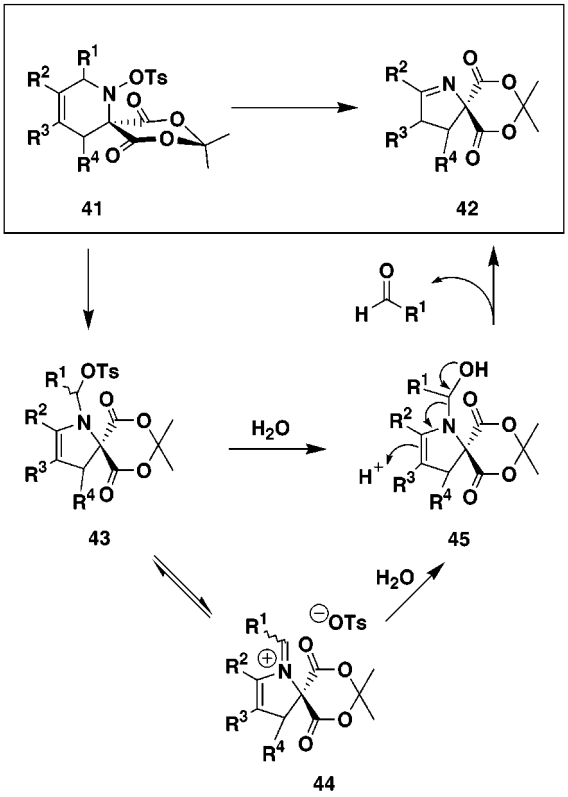
(29) Klusener, P. A. A.; Hommes, H. H.; Verkruijsse, H. D.; Brandsma, L. *Chem. Commun.* **1985**, 1677.

(30) For previous multistep routes to **29**, see: (a) Korobova, L. M.; Livshits, I. A. *Zh. Obshch. Khim.* **1964**, *34*, 3419. (b) Ueno, Y.; Sano, H.; Aoki, S.; Okawara, M. *Tetrahedron Lett.* **1981**, *28*, 2675. (c) Dzhemilev, U. M.; Ibragimov, A. G. *J. Organomet. Chem.* **1994**, *466*, 1.

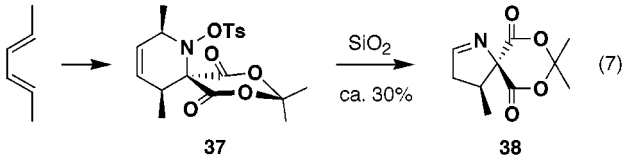
(31) The Mosher ester of *racemic* **34** was also prepared, and the diastereomers were found to be well resolved by both ^{1}H and ^{19}F NMR spectroscopy.

(32) The isolation of (*S*)-(+)-fusarinolic acid was complicated by its high solubility in aqueous solution. Fortunately, (*S*)-(+)-fusarinolic acid could be recovered from an appropriately buffered (pH 2.5) aqueous solution by continuous liquid−liquid extraction with dichloromethane for 2 days.

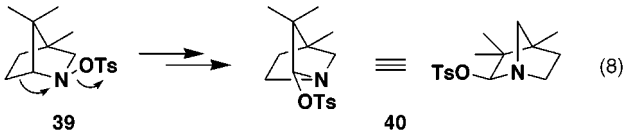
Scheme 5



silica gel, for example, resulted in formation of the spirobicyclic pyrroline **38** (eq 7). This transformation, which appears to involve migration of the vinylic carbon in **37** to nitrogen with displacement of tosylate, is reminiscent of the well-known Stieglitz rearrangement

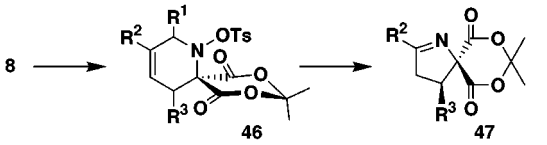


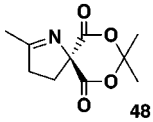
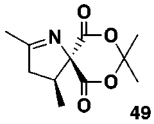
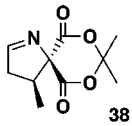
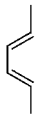
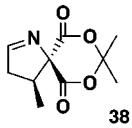
of *N*-chloroamines and hydroxylamine derivatives (e.g., N−OSO_2Ar, N−OC(O)R). Stieglitz rearrangements involving bridged bicyclic systems (e.g., eq 8) often proceed under very mild conditions, and have been the subject of extensive studies by Gassman[33] and Hoffman,[34] among others.



Scheme 5 outlines a likely mechanism to account for the rearrangement of the oximinosulfonate cycloadducts **41** to pyrrolines. Vinyl migration to nitrogen is most likely concerted with ionization of tosylate, leading to an iminium ion (**44**) or, alternatively, the product of ion pair collapse (**43**). Addition of water then generates the hemiaminal **45**, which fragments as shown to produce

Table 2. Synthesis of Pyrrolines[a]



diene	rearrangement[b]	pyrroline	% yield[c]
	15 min	 **48**	42
	45 min	 **49**	45
	2 h	 **38**	24
	< 5 min	 **38**	35

[a] Conditions: (a) 3.0 equiv of diene, 2.0 equiv of Me_2AlCl, 1.0 equiv of **8**, CH_2Cl_2, −78 °C; (b) CH_3CN−pH 7 phosphate buffer (10:1), 80 °C. [b] Reaction time for rearrangement step b. [c] Isolated overall yield for two steps.

the observed pyrroline products **42**. Note that this mechanism is consistent with our observation that cycloadducts incorporating R^1-substitution have the greatest propensity to undergo rearrangement.[35]

As summarized in Table 2, we have found that under the proper conditions a wide range of oximinosulfonate Diels−Alder adducts can be converted to these interesting pyrroline derivatives. Since it appeared likely that the Stieglitz-type rearrangement is triggered by ionization of the N−OTs bond, we focused our attention on conditions that might promote ionization by stabilizing charge separation. Initial experiments were carried out on the cycloadduct derived from isoprene (**12**), which does not rearrange under normal conditions. After some experimentation, we found that heating this cycloadduct in a mixture of acetonitrile and pH 7 phosphate buffer (10:1) produces the desired pyrroline **48** in 55% yield. Table 2 presents the results of the application of this cycloaddition−rearrangement protocol to several dienes; yields shown are overall isolated yields for the two-step sequence. As expected, ketimines **48** and **49** are formed in higher yield than the less stable aldimine **38**. Note that both penta-1,3-diene and hexa-2,4-diene produce the same pyrroline product, as expected, since the carbon bearing R^1 is lost during rearrangement.

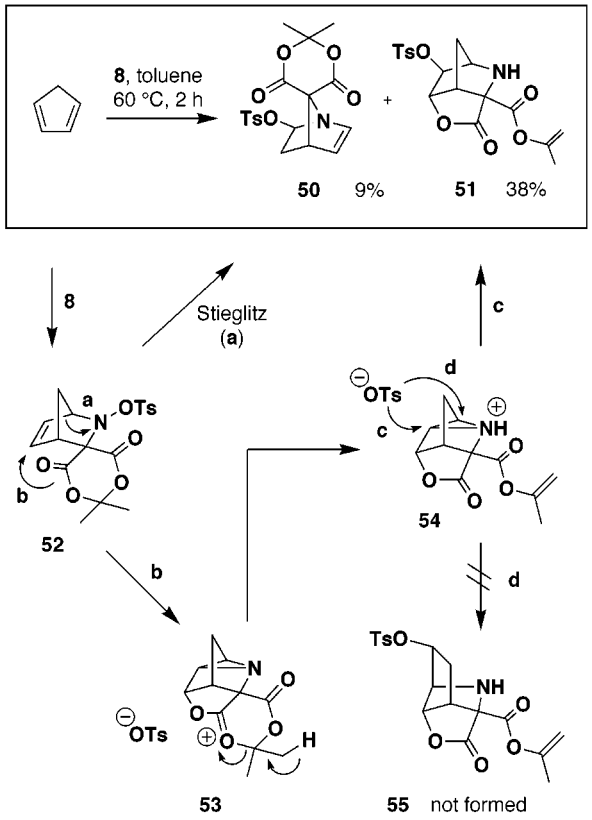
Reaction of Oximinosulfonate 8 with Cyclopentadiene. The reaction of oximinosulfonate **8** with cyclo-

(33) (a) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26 and references therein. (b) Gassman, P. G.; Hartman, G. D. *J. Am. Chem. Soc.* **1973**, *95*, 449.

(34) Hoffman, R. V.; Kumar, A.; Buntain, G. A. *J. Am. Chem. Soc.* **1985**, *107*, 4731.

(35) We briefly conducted experiments with the aim of trapping the putative intermediate **44** with cyanide ion. A variety of cyanide sources and solvents were examined, but only the normal pyrroline product could be isolated. Attack of cyanide at the sulfonyl group of **43** may be responsible for pyrroline formation in these reactions.

Scheme 6



pentadiene led to the formation of a novel rearranged product of a type not observed with any other dienes we have examined to date. Thus, heating **8** with 5 equiv of cyclopentadiene in toluene at 60 °C (sealed tube) for 2 h produced two products, neither of which was the expected cycloadduct (Scheme 6). The minor compound **50** was identified as the product resulting from Stieglitz rearrangement of the Diels−Alder adduct **52**, analogous to the rearranged cycloadduct observed previously by Fleury in the reaction of the bis-nitrile **4** with cyclopentadiene.[36] The major product of the reaction (38% yield) was not so easily identified, and inspection of its ^{1}H and ^{13}C NMR spectra indicated that a major structural rearrangement had occurred. An NMR DEPT experiment revealed the presence of two methyl, two methylene, eight methine, and six quaternary carbons, and these data, along with 2-D ^{1}H NMR (TOCSY) data, eventually allowed the assignment shown below for **51**.

Scheme 6 presents a possible mechanistic pathway for the transformation of the initially formed cycloadduct **52** to rearranged products **50** and **51**. Ionization of the N−OTs bond with anchimeric assistance by the alkene generates a carbocation that is trapped by the *endo* carbonyl group to produce the aziridine intermediate **53**. Elimination opens the dioxanedione ring, and attack of tosylate on the resulting aziridinium ion **54** via pathway c then generates the observed product **51**. Interestingly, no products derived from the alternative mode of cleavage of the aziridinium ion (pathway d) were detected in this reaction. This departure from normal Stieglitz-rearrangement chemistry is novel and most likely results from the presence of an auspiciously situated nucleophile (the *endo* carbonyl) in **52**. Although the yield of **51** is modest, it is nonetheless striking that a product of such structural complexity is formed in a single step from cyclopentadiene.

(36) (a) Fleury, J.-P.; Biehler, J.-M.; Desbois, M. *Tetrahedron Lett.* **1969**, 4091. (b) Biehler, J.-M.; Fleury, J.-P. *Tetrahedron* **1971**, *27*, 3171. (c) Fleury, J.-P.; Desbois, M. *J. Heterocycl. Chem.* **1978**, *15*, 1005.

Summary

The Me_2AlCl-promoted cycloaddition of the new oximinosulfonate **8** with conjugated dienes serves as the key step in a regiocontrolled method for the synthesis of substituted pyridines. Diels−Alder reactions of dienophile **8** are highly regioselective and provide cycloadducts with regiochemistry opposite to that obtained in hetero Diels−Alder reactions involving imino dienophiles. The utility of this new annulation strategy has been demonstrated in efficient total syntheses of fusaric acid and (*S*)-(+)-fusarinolic acid. Upon heating in a mixture of acetonitrile and pH 7 phosphate buffer, the cycloadducts also undergo an interesting Stieglitz-type rearrangement producing novel substituted pyrrolines.

Experimental Section

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Methanol, toluene, benzene, dichloromethane, acetonitrile, collidine, 2,2,6,6-tetramethylpiperidine, and triisopropylsilyl trifluoromethanesulfonate were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium benzophenone ketyl. *N*-Chlorosuccinimide was recrystallized from acetic acid. Meldrum's acid was recrystallized from acetone−water. Tosyl chloride was recrystallized from diethyl ether at −78 °C. Isoprene was distilled at atmospheric pressure prior to use. 2-*tert*-Butylbuta-1,3-diene and 1-vinylcyclohex-1-ene were prepared as described by Korotkov and Roguleva[37] except that the dehydration was effected according to the general method of Traynelis.[38] 2-(Triisopropylsilyloxy)buta-1,3-diene was prepared as described previously.[39] Cyclopentadiene was prepared by thermal cracking of the dimer and stored at −60 °C until needed. Sodium methoxide solution was freshly prepared before use by the addition of sodium to methanol at 0 °C.

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of argon and stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated by using a Büchi rotary evaporator at 15−20 mmHg. Column chromatography was performed on EM Science silica gel 60 (35−75 μm). Deactivated silica gel was prepared by passing acetone through a column of silica gel followed by drying in an oven at 120−130 °C for 2−4 h.

5-(Tosyloxyimino)-2,2-dimethyl-1,3-dioxane-4,6-dione (8). A 25-mL, round-bottomed flask equipped with an argon inlet adapter and solid addition funnel was charged with Meldrum's acid (2.61 g, 18.1 mmol) and 13 mL of methanol. To this suspension was added in one portion a solution of sodium nitrite (1.25 g, 18.1 mmol) in 10 mL of water. The reaction mixture was stirred for 2 h at room temperature to give a deep red solution which was treated with 2.5 mL of pH 7 phosphate buffer and then cooled to 0 °C. Tosyl chloride (3.11 g, 16.9 mmol) was added over 3 min via the solid addition funnel, the cooling bath was removed, and the resulting peach-colored mixture was stirred for 30 min and then filtered with the aid of 30 mL of cold methanol. The resulting solid was dried at 0.2 mmHg over P_2O_5 for 2 h to provide 3.02 g (57% based on TsCl) of **8** as a white solid: mp 155−156 °C; IR

(37) Korotkov, A. A.; Roguleva, L. F. *Zh. Org. Khim.* **1965**, *1*, 1180.
(38) Traynelis, V. J.; Hergenrother, W. L.; Livingston, J. R.; Valicenti, J. A. *J. Org. Chem.* **1962**, *27*, 2377.
(39) Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y.-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677.

($CHCl_3$) 3020, 1790, 1765, 1596, 1400, 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (s, 6 H), 2.46 (s, 3 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.93 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 28.1, 106.8, 129.5, 130.1, 130.2, 138.8, 147.1, 149.6, 154.7. Anal. Calcd for $C_{13}H_{13}NO_7S$: C, 47.70; H, 4.00; N, 4.28; Found: C, 47.76; H, 4.02; N, 4.22.

9-(Triisopropylsiloxy)-3,3-dimethyl-1,5-dioxo-7-(tosyloxy)-7-aza-2,4-dioxaspiro[5.5]undec-9-ene (11). A solution of 2-(triisopropylsiloxy)buta-1,3-diene (0.366 g, 1.37 mmol) and oximinosulfonate **8** (0.150 g, 0.458 mmol) in 8 mL of benzene was heated at 55−60 °C for 24 h, cooled to room temperature, and then concentrated to give a brown oil which was purified by column chromatography on 10 g of deactivated silica (elution with 0−25% ethyl acetate−hexane) to provide 0.142 g (56%) of **11** as a yellow oil: IR ($CHCl_3$) 2950, 2370, 1755, 1390, 1310 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, J = 5.7 Hz, 18 H), 1.05−1.15 (m, 3 H), 1.72 (s, 3 H), 1.93 (s, 3 H), 2.47 (s, 3 H), 2.74 (m, 2 H), 3.87 (d, J = 1.5 Hz, 2 H), 4.75 (m, 1 H), 7.36 (d, J = 8.1 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 17.7, 21.7, 28.6, 29.2, 30.5, 56.2, 66.7, 95.3, 106.4, 129.3, 129.7, 131.2, 144.5, 146.0, 163.8.

General Procedure for Lewis Acid-Promoted Reaction of Oximinosulfonate 8 with Dienes. Preparation of 3,3,9-Trimethyl-1,5-dioxo-7-(tosyloxy)-7-aza-2,4-dioxaspiro[5.5]undec-9-ene (12). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and rubber septum was charged with a solution of oximinosulfonate **8** (0.327 g, 1.00 mmol) and isoprene (0.204 g, 3.00 mmol) in 14 mL of dichloromethane. The solution was cooled at −78 °C while Me_2AlCl solution (1.0 M in hexane, 2.0 mL, 2.0 mmol) was added dropwise via syringe over 4 min. The resulting orange solution was stirred for 4 h at −78 °C to give a yellow solution which was quenched by addition of 3 mL of saturated sodium potassium tartrate solution. The resulting mixture was allowed to warm to 0 °C, 15 mL of dichloromethane and 15 mL of water were added, and the aqueous phase was separated and extracted with three 20-mL portions of dichloromethane. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide an orange oil. Column chromatography on silica gel (elution with 1% methanol−dichloromethane) provided 0.354 g (90%) of **12** as a white foam: IR ($CHCl_3$) 3020, 1780, 1750, 1385, 1300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (s, 3 H), 1.69 (s, 3 H), 1.88 (s, 3 H), 2.48 (s, 3 H), 2.72 (br dd, J = 1.2, 3.3 Hz, 2 H), 3.93 (s, 2 H), 5.33 (br dd, J = 1.2, 3.6 Hz, 1 H), 7.36 (d, J = 8.7 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 21.7, 28.5, 29.3, 32.8, 57.4, 66.3, 106.2, 113.9, 129.2, 129.55, 129.62, 131.2, 145.9, 164.0.

3,3,11-Trimethyl-1,5-dioxo-7-(tosyloxy)-7-aza-2,4-dioxaspiro[5.5]undec-9-ene (13). Reaction of oximinosulfonate **8** (1.22 g, 3.73 mmol) with *trans*-penta-1,3-diene (0.761 g, 11.2 mmol) and Me_2AlCl (1.0 M in hexane, 7.5 mL, 7.5 mmol) in 37 mL of dichloromethane at −78 °C for 4 h according to the general procedure furnished 1.15 g (78%) of cycloadduct **13** as a white solid: mp (dec) 133−145 °C; IR ($CHCl_3$) 3005, 1780, 1750, 1380, 1290 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, J = 7.5 Hz, 3 H), 1.70 (s, 3 H), 1.86 (s, 3 H), 2.47 (s, 3 H), 3.28−3.34 (m, 1 H), 4.03−4.09 (m, 2 H), 5.35−5.39 (dm, J = 10.3 Hz, 1 H), 5.60−5.65 (dm, J = 10.1 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 2 H), 7.81 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 21.8, 29.2, 29.5, 40.5(br), 54.3, 71.6, 106.5, 122.0, 125.5, 129.4, 129.6, 131.1, 146.0, 161.6, 164.9.

General Procedure for Two-Step Pyridine Annulation. Preparation of Methyl 5-Methylpyridine-2-carboxylate (19). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and rubber septum was charged with a solution of oximinosulfonate **8** (0.450 g, 1.37 mmol) and isoprene (0.281 g, 4.13 mmol) in 19 mL of dichloromethane. The solution was cooled at −78 °C while Me_2AlCl solution (1.0 M in hexane, 2.7 mL, 2.7 mmol) was added dropwise via syringe over 4 min. The resulting orange solution was stirred for 3 h at −78 °C to give a yellow solution which was quenched by addition of 4 mL of saturated sodium potassium tartrate solution. The resulting mixture was allowed to warm to 0 °C, 20 mL of dichloromethane and 20 mL of water were added, and the aqueous phase was separated and extracted with three 25-mL portions of dichloromethane. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide the cycloadduct as an orange foam.

A 100-mL, round-bottomed flask equipped with an argon inlet adapter was charged with a solution of the cycloadduct (prepared above) in 13 mL of THF and 13 mL of methanol. The solution was cooled at 0 °C while NaOMe solution (1.51 M in methanol, 2.7 mL, 4.1 mmol) was added via syringe over 1 min followed by the addition of *N*-chlorosuccinimide (0.183 g, 1.37 mmol) in one portion. After the cooling bath was removed, the solution was stirred in the dark for 16 h, concentrated to ca. 5 mL, and then diluted with 30 mL of ethyl acetate and 30 mL of pH 7 phosphate buffer. The aqueous phase was separated and extracted with two 25-mL portions of ethyl acetate, and the combined organic phases were extracted with three 25-mL portions of 1.0 N HCl. The combined acidic extracts were neutralized by the slow addition of solid $NaHCO_3$ and then extracted with three 30-mL portions of ethyl acetate. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated onto 1 g of silica gel. The free-flowing powder was placed at the top of a column of 10 g of silica gel and eluted with 0−25% ethyl acetate−1% triethylamine-hexane to provide 0.159 g (77%) of the pyridine **19** as a colorless solid: mp 54−55 °C (petroleum ether); IR ($CHCl_3$) 2950, 1695, 1420, 1295, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 4.00 (s, 3H), 7.64 (dd, J = 7.8, 2.0 Hz, 1 H), 8.05 (d, J = 8.3 Hz, 1 H), 8.57 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 52.6, 124.6, 137.1, 137.3, 145.2, 150.2, 165.6. Anal. Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00, N, 9.27; Found: C, 63.57, H, 6.24, N, 9.20.

Methyl 5-*n*-Butylpyridine-2-carboxylate (Methyl Fusarate) (20). Reaction of oximinosulfonate **8** (0.419 g, 1.28 mmol) with 3-methylenehept-1-ene (**29**) (0.200 g, 1.92 mmol) and Me_2AlCl (1.0 M in hexane, 2.6 mL, 2.6 mmol) in 11 mL of dichloromethane at −78 °C for 4 h according to the general procedure provided the crude cycloadduct as an orange foam. Reaction of this material with NaOMe (1.42 M in methanol, 2.7 mL, 3.8 mmol) and NCS (0.171 g, 1.28 mmol) in 12 mL of THF and 12 mL of methanol at room temperature for 15 h according to the general procedure furnished 0.179 g (72%) of pyridine **20** as a pale yellow oil: IR (film) 2990, 1725, 1440, 1310, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (tr, J = 7.5 Hz, 3 H), 1.31−1.35 (app hex, 2 H), 1.56−1.66 (app quint, 2 H), 2.65−2.70 (tr, J = 7.5 Hz, 2 H), 3.98 (s, 3 H), 7.62 (dd, J = 8.1, 1.9 Hz, 1 H), 8.04 (d, J = 7.8 Hz, 1 H), 8.54 (d, J = 1.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 22.1, 32.6, 32.8, 52.6, 124.8, 136.5, 142.1, 145.4, 149.9, 165.7. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25; Found: C, 68.08; H, 7.91; N, 7.22.

Methyl 5-*tert*-Butylpyridine-2-carboxylate (21). Reaction of oximinosulfonate **8** (0.545 g, 1.66 mmol) with 2-*tert*-butylbuta-1,3-diene (0.275 g, 2.49 mmol) and Me_2AlCl (1.0 M in hexane, 3.3 mL, 3.3 mmol) in 14 mL of dichloromethane at −78 °C for 3.5 h according to the general procedure provided the crude cycloadduct as a pink foam. Reaction of this material with NaOMe (1.52 M in methanol, 3.3 mL, 5.0 mmol) and NCS (0.222 g, 1.66 mmol) in 15 mL of THF and 15 mL of methanol at room temperature for 14 h according to the general procedure furnished 0.234 g (73%) of pyridine **21** as a pale yellow oil: IR (film) 2960, 1740, 1720, 1435, 1315, 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9 H), 4.01 (s, 3 H), 7.82 (dd, J = 8.1, 2.4 Hz, 1 H), 8.07 (d, J = 8.1 Hz, 1 H), 8.79 (d, J = 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.7, 33.9, 52.6, 124.5, 133.8, 145.1, 147.7, 149.9, 165.7.

Methyl 3-Methylpyridine-2-carboxylate (22). Reaction of oximinosulfonate **8** (0.45 g, 1.37 mmol) with *trans*-penta-1,3-diene (0.280 g, 4.12 mmol) and Me_2AlCl (1.0 M in hexane, 2.7 mL, 2.7 mmol) in 20 mL of dichloromethane at −78 °C for 3 h according to the general procedure provided the crude cycloadduct as a pink solid. Reaction of this material with NaOMe (1.53 M in methanol, 2.7 mL, 4.1 mmol) and NCS

(0.183 g, 1.37 mmol) in 13 mL of THF and 13 mL of methanol at room temperature for 16 h according to the general procedure furnished 0.117 g (57%) of pyridine **22** as a clear colorless oil: IR (film) 2975, 1725, 1440, 1310, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.60 (s, 3H), 3.99 (s, 3 H), 7.31 (dd, $J = 7.8$, 3.9 Hz, 1 H), 7.58 (dd, $J = 7.8$, 2.9 Hz, 1 H), 8.51 (dd, $J = 4.4$, 1.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 52.3, 125.8, 135.4, 139.7, 146.7, 146.8, 166.3.

Methyl 3-(4-Methylpent-3-enyl)pyridine-2-carboxylate (23). Reaction of oximinosulfonate **8** (0.384 g, 1.17 mmol) with 8-methylnona-1,3(*E*),7-triene (0.240 g, 1.76 mmol) and Me_2AlCl (1.0 M in hexane, 2.3 mL, 2.3 mmol) in 16 mL of dichloromethane at −78 °C for 3 h according to the general procedure provided the crude cycloadduct as an orange oil. Reaction of this material with NaOMe (1.40 M in methanol, 2.5 mL, 3.5 mmol) and NCS (0.156 g, 1.17 mmol) in 11 mL of THF and 11 mL of methanol at room temperature for 20 h according to the general procedure furnished 0.139 g (54%) of pyridine **23** as a clear colorless oil: IR (film) 2960, 2930, 1730, 1450, 1430, 1305, 1200, 1135, 1110, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 3 H), 1.61 (s, 3 H), 2.25 (app q, $J = 8$ Hz, 2 H), 2.91 (t, $J = 8$ Hz, 2 H), 3.93 (s, 3 H), 5.09 (t, $J = 7$ Hz, 1 H), 7.30 (dd, $J = 5$, 8 Hz, 1 H), 7.55 (d, $J = 7$ Hz, 1 H), 8.49 (d, $J = 5$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 25.5, 29.4, 32.7, 52.5, 122.7, 125.7, 132.9, 139.0, 139.1, 146.7, 147.2, 166.4.

Methyl 3,5-Dimethylpyridine-2-carboxylate (24). Reaction of oximinosulfonate **8** (0.450 g, 1.37 mmol) with a 70:30 mixture of *trans*-2-methylpenta-1,3-diene and 4-methylpenta-1,3-diene (0.452 g, 5.5 mmol) and Me_2AlCl (1.0 M in hexane, 2.7 mL, 2.7 mmol) in 20 mL of dichloromethane at −78 °C for 1 h according to the general procedure provided the crude cycloadduct as a yellow foam. Reaction of this material with NaOMe (1.53 M in methanol, 2.7 mL, 4.4 mmol) and NCS (0.183 g, 1.37 mmol) in 15 mL of THF and 15 mL of methanol at room temperature for 16 h according to the general procedure furnished 0.159 g (70%) of pyridine **24** as a colorless solid: mp 42−43 °C (petroleum ether); IR ($CHCl_3$) 2960, 1710, 1440, 1305, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 2.56 (s, 3 H), 3.94 (s, 3 H), 7.39 (s, 1 H), 8.35 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 20.0, 52.4, 135.6, 136.4, 140.4, 144.1, 147.4, 166.5. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48; Found: C, 64.59; H, 6.80; N, 8.40.

Methyl 3,4-Dimethylpyridine-2-carboxylate (25). Reaction of oximinosulfonate **8** (0.452 g, 1.38 mmol) with 3-methylpenta-1,3-diene (0.340 g, 4.14 mmol) and Me_2AlCl (1.0 M in hexane, 2.8 mL, 2.8 mmol) in 19 mL of dichloromethane at −78 °C for 2.5 h according to the general procedure provided the crude cycloadduct as an orange foam. Reaction of this material with NaOMe (1.52 M in methanol, 2.7 mL, 4.1 mmol) and NCS (0.184 g, 1.38 mmol) in 12 mL of THF and 12 mL of methanol at room temperature for 14 h according to the general procedure furnished 0.091 g (40%) of pyridine **25** as a pale yellow oil: IR ($CHCl_3$) 2900, 1725, 1440, 1300, 1190, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3 H), 2.43 (s, 3 H), 3.96 (s, 3 H), 7.19 (d, $J = 4.9$ Hz, 1 H), 8.36 (d, $J = 4.9$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 19.9, 52.5, 127.0, 133.1, 146.3, 147.8, 148.8, 167.3.

Methyl 3,6-Dimethylpyridine-2-carboxylate (26). Reaction of oximinosulfonate **8** (0.600 g, 1.83 mmol) with *trans,trans*-hexa-2,4-diene (0.451 g, 5.49 mmol) and Me_2AlCl (1.0 M in hexane, 3.7 mL, 3.7 mmol) in 25 mL of dichloromethane at −78 °C for 1.5 h according to the general procedure provided the crude cycloadduct as a pink foam. Reaction of this material in 20 mL of THF and 20 mL of methanol at room temperature with NaOMe in *three portions* (1.51 M in methanol, 6.0 mL total, 9.2 mmol, *5.0 equiv*) and NCS in *two portions* (0.489 g, 7.3 mmol, *4.0 equiv*) for 13 h according to the general procedure furnished 0.120 g (40%) of pyridine **26** as a colorless oil: IR (film) 2950, 1725, 1435, 1320, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3 H), 2.59 (s, 3 H), 3.97 (s, 3H), 7.20 (d, $J = 8.0$ Hz, 1 H), 7.49 (d, $J = 7.8$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 23.9, 52.4, 125.6, 131.8, 140.0, 146.5, 155.6, 166.7.

Methyl 5,6,7,8-Tetrahydroquinoline-2-carboxylate (28) and Methyl 5,6,7,8-tetrahydroisoquinoline-1-carboxylate (27). Reaction of oximinosulfonate **8** (0.635 g, 1.94 mmol) with 1-vinylcyclohex-1-ene (0.315 g, 2.91 mmol) and Me_2AlCl (1.0 M in hexane, 3.9 mL, 3.9 mmol) in 16 mL of dichloromethane at −78 °C for 4 h according to the general procedure provided the crude cycloadduct as an orange foam. Reaction of this material with NaOMe (1.51 M in methanol, 3.9 mL, 5.8 mmol) and NCS (0.259 g, 1.94 mmol) in 18 mL of THF and 18 mL of methanol at room temperature for 16 h according to the general procedure furnished 0.039 g (11%) of pyridine **28** as a pale yellow oil and 0.184 g (50%) of pyridine **27** as a pale yellow solid. For pyridine **28**: IR ($CHCl_3$) 2940, 1720, 1435, 1320, 1130 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.82−1.94 (m, 4 H), 2.84 (tr, $J = 6.4$ Hz, 2 H), 3.03 (tr, $J = 6.7$ Hz, 2 H), 3.98 (s, 3 H), 7.49 (d, $J = 7.8$ Hz, 1 H), 7.88 (d, $J = 7.8$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 22.8, 29.0, 32.7, 52.7, 122.5, 136.7, 137.4, 145.1, 158.0, 166.1. For pyridine **27**: mp 68−69 °C (petroleum ether) IR ($CHCl_3$) 3020, 2970, 1720, 1435, 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.79−1.82 (m, 4 H), 2.80−2.84 (m, 2 H), 3.02−3.06 (m, 2 H), 3.96 (s, 3 H), 7.13 (d, $J = 4.8$ Hz, 1 H), 8.36 (d, $J = 4.8$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 22.4, 25.9, 29.5, 52.4, 126.6, 134.5, 145.6, 147.5, 148.2, 166.8. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32; Found: C, 69.10; H, 6.98; N, 7.23.

3-Methylenehept-1-ene (29). A solution of KO*t*-Bu (1.65 g, 14.7 mmol) and 2,2,6,6-tetramethylpiperidine (2.08 g, 14.7 mmol) in 12 mL of THF was cooled at −65 °C while *n*-BuLi solution (2.5 M in hexane, 5.9 mL, 14.7 mmol) was added dropwise via syringe over 2 min. The resulting orange solution was cooled at −78 °C while isoprene (1.50 g, 22.1 mmol) was added dropwise via syringe over 10 min. The resulting red solution was stirred for 10 min at −78 °C, and then a solution of 1-bromopropane (2.72 g, 22.1 mmol) in 3 mL of THF was added dropwise via cannula over 30 s. The resulting yellow suspension was stirred for 20 min at −50 °C, the cooling bath was removed, and the solution was allowed to warm to 0 °C. The yellow suspension was then quenched by addition of 40 mL of water, and the resulting solution was extracted with three 25-mL portions of ether. The combined organic phases were washed with two 20-mL portions of 1 N HCl solution and 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and then concentrated by distillation at atmospheric pressure. The pale yellow residue was purified by column chromatography (elution with pentane), and the resulting pentane solution was concentrated by distillation at atmospheric pressure to give 0.687 g (45%, ca. 90% pure) of the diene **29** as a colorless oil, used in the next step without further purification.

5-*n*-Butylpyridine-2-carboxylic Acid (Fusaric Acid) (32). To a solution of methyl fusarate (**20**) (0.126 g, 0.652 mmol) in 2 mL of methanol and 0.5 mL of water at 0 °C was added $LiOH-H_2O$ (0.239 g, 3.26 mmol) in one portion. The resulting mixture was stirred for 1 h at 0 °C, and then the cooling bath was removed and the solution was diluted with 2 mL of water, acidified to pH 2 by slow addition of 1.0 N HCl, and then extracted with eight 10-mL portions of EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to provide a white solid. Sublimation at 0.1 mmHg and ca. 100 °C provided 0.099 g (85%) of fusaric acid (**32**) as a white solid: mp 99−100.5 °C; IR ($CHCl_3$) 2960, 2930, 1765, 1410, 1355, 1295 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, $J = 7.3$ Hz, 3 H), 1.35−1.45 (app hex, $J = 7.3$ Hz 2 H), 1.60−1.70 (m, 2 H), 2.73 (t, $J = 7.6$ Hz, 2 H), 7.75 (dd, $J = 8.0$, 2.1 Hz, 1 H), 8.14 (d, $J = 8.0$, 1 H), 8.44 (d, $J = 1.5$ Hz, 1 H), 11.8 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 22.2, 32.7, 32.8, 124.5, 138.5, 143.0, 145.0, 147.6, 165.3. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82; Found: C, 67.10; H, 7.27; N, 7.66.

(*S*)-5-Methylenehept-6-en-2-ol (30). A solution of KO*t*-Bu (0.310 g, 2.75 mmol) and 2,2,6,6-tetramethylpiperidine (0.388 g, 2.75 mmol) in 3 mL of THF was cooled at −60 °C while *n*-BuLi solution (2.55 M in hexane, 1.1 mL, 2.8 mmol) was added dropwise via syringe over 2 min. The resulting orange solution was cooled at −78 °C while isoprene (0.28 g, 4.1 mmol) was added dropwise via syringe over 5 min. The

resulting red solution was stirred for 10 min at −60 to −70 °C, and then a solution of (*S*)-propylene oxide (0.240 g, 4.13 mmol) in 1 mL of THF was added dropwise via cannula over 2 min. The resulting deep red solution was stirred for 10 min at −50 °C and allowed to warm to room temperature, and the mixture was then quenched by addition of 10 mL of water and extracted with six 10-mL portions of ether. The combined organic phases were washed with two 10-mL portions of 0.5 N HCl solution, and the combined acidic phases were back-extracted with two 10-mL portions of ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated onto 1.4 g of silica gel. This free-flowing powder was transferred to the top of a column of 16 g of silica gel and eluted with 0−25% ethyl acetate-0.1% methanol−hexane to provide 0.212 g (61%) of the diene **30** as a pale yellow oil: $[\alpha]^{25}_D$ +16° ($CHCl_3$, c = 2.70); IR (film) 3340, 2960, 2925, 1595, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, J = 6.3 Hz, 3 H), 1.43 (br s, 1H), 1.62−1.69 (app quart, J = 7.8 Hz, 2 H), 2.24−2.40 (m, 2 H), 3.82−3.88 (app hex, J = 6.0 Hz, 1 H), 5.03 (s, 2 H), 5.08 (d, J = 10.8 Hz, 1 H), 5.26 (d, J = 17.4 Hz, 1 H), 6.38 (dd, J = 17.7, 11.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5, 27.5, 37.6, 67.8, 113.3, 115.7, 138.7, 146.1.

(*S*)-2-(Triisopropylsiloxy)-5-methylenehept-6-ene (31). A solution of diene **30** (0.349 g, 2.76 mmol) in 4 mL of dichloromethane was cooled at 0 °C while collidine (0.836 g, 6.90 mmol) was added dropwise via syringe over 2 min followed by the addition of triisopropylsilyl trifluoromethanesulfonate (1.1 g, 0.97 mL, 3.6 mmol) over 10 min. The resulting solution was stirred for 1.5 h at 0 °C, diluted with 20 mL of dichloromethane, and then washed with 20 mL of 1.0 N HCl. The acid extracts were back-extracted with 10 mL of dichloromethane, and the combined organic phases were washed with 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give a colorless oil. Purification by column chromatography on silica gel (elution with 1% triethylamine−hexane) provided 0.720 g (92%) of the diene **31** as a colorless oil: $[\alpha]^{25}_D$ +2.6° ($CHCl_3$, c = 2.8); IR (film) 2940, 1595, 1460, 1095 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 21 H), 1.20 (d, J = 6.0 Hz, 3 H), 1.58−1.72 (m, 2 H), 2.23−2.31 (m, 2 H), 3.96−4.02 (app hex, J = 5.9 Hz, 1H), 5.00 (s, 2 H), 5.06 (d, J = 10.8 Hz, 1 H), 5.24 (d, J = 17.7 Hz, 1 H), 6.37 (dd, J = 17.7, 10.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 18.1, 18.2, 23.5, 27.1, 38.5, 68.4, 113.2, 115.4, 138.9, 146.6.

(*S*)-Methyl 5-(3-(Triisopropylsiloxy)butyl)pyridine-2-carboxylate (33). Reaction of oximinosulfonate **8** (0.494 g, 1.51 mmol) with diene **31** (0.640 g, 2.27 mmol) and Me_2AlCl (1.0 M in hexane, 3.0 mL, 3.0 mmol) in 13 mL of dichloromethane at −78 °C for 3 h according to the general procedure provided the crude cycloadduct as an orange oil. Reaction of this material with NaOMe (1.44 M in methanol, 3.1 mL, 4.5 mmol) and NCS (0.202 g, 1.51 mmol) in 15 mL of THF and 15 mL of methanol at room temperature for 16 h according to the general procedure furnished 0.428 g (78%) of pyridine **33** as a pale yellow oil: $[\alpha]^{25}_D$ +0.86° ($CHCl_3$, c = 1.97); IR (film) 2940, 1745, 1720, 1310 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 21 H), 1.24 (d, J = 6.0 Hz, 3 H), 1.76−1.83 (m, 2 H), 2.76−2.81 (m, 2 H), 4.00 (s, 3 H), 4.04 (app hex, J = 5.9 Hz, 1 H), 7.65 (dd, J = 8.0, 1.7 Hz, 1 H), 8.06 (d, J = 8.0 Hz, 1 H), 8.57 (d, J = 2.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 18.11, 18.07, 23.3, 28.5, 40.9, 52.7, 67.6, 124.9, 136.5, 142.3, 145.5, 150.0, 165.8.

(*S*)-Methyl 5-(3-Hydroxybutyl)pyridine-2-carboxylate ((*S*)-Methyl Fusarinolate) (34). A solution of pyridine **33** (0.079 g, 0.22 mmol) in 2.2 mL of THF was treated with tetrabutylammonium fluoride solution (1.0 M in THF, 0.24 mL, 0.24 mmol) dropwise via syringe over 1 min. The resulting orange solution was stirred for 2 h at room temperature and then quenched by addition of 2 mL of saturated NH_4Cl solution. The resulting mixture was stirred for 15 min, diluted with 10 mL of water, and extracted with eight 5-mL portions of EtOAc. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated onto 0.4 g of silica gel. This free-flowing powder was transferred to the top of a column of 5 g of silica gel and eluted with 1% triethylamine−0.1% methanol−ethyl acetate to furnish 0.042 g (93%) of (*S*)-methyl fusarinolate (**34**) as a colorless oil: $[\alpha]^{25}_D$ +17.9° ($CHCl_3$, c = 1.13); IR (film) 3370, 2960, 1725, 1570, 1310 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J = 6.2 Hz, 3 H), 1.52 (br s, 1 H), 1.74−1.82 (m, 2 H), 2.72−2.93 (m, 2 H), 3.80−3.86 (app hex, J = 6.2 Hz, 1 H), 3.99 (s, 3 H), 7.67 (dd, J = 8.0, 2.3 Hz, 1 H), 8.06 (d, J = 8.0 Hz, 1 H), 8.59 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 29.2, 39.9, 52.6, 66.9, 124.9, 136.6, 141.6, 145.7, 150.0, 165.7.

(*S*)-5-(3-Hydroxybutyl)pyridine Carboxylic Acid ((*S*)-Fusarinolic Acid) (36). A flask charged with (*S*)-methyl fusarinolate **34** (0.128 g, 0.610 mmol) was cooled at 0 °C while KOH solution (1.0 M in methanol, 4.6 mL, 4.6 mmol) and then 1.2 mL of water was added. The resulting solution was stirred for 2 h at 0 °C, concentrated to ca. 1 mL, and treated with 10 mL of pH 2.5 phosphate buffer. The resulting solution was subjected to continuous liquid−liquid extraction with 20 mL of dichloromethane for 2 days. The dichloromethane phase was dried over Na_2SO_4, filtered, and concentrated to give 0.120 g of a colorless oil. Attempted recrystallization from dichloromethane−methanol gave an oil which solidified upon drying at 0.1 mmHg to provide 0.097 g (82%) of (*S*)-fusarinolic acid (**36**) as colorless crystals: mp 108−109 °C; $[\alpha]^{25}_D$ +20.5° (MeOH, c = 1.05); IR (KBr) 3265, 2870, 2420, 1660 cm^{-1}; ^1H NMR (300 MHz, DMSO-*d*6) δ 1.08 (d, J = 6.0 Hz, 3 H), 1.60−1.67 (app quart, J = 6.2 Hz, 2 H), 2.62−2.82 (m, 2 H), 3.53−3.61 (app hex, J = 6.0 Hz, 1 H), 4.2−4.8 (br s, 1 H), 7.79 (dd, J = 8.1, 1.9 Hz, 1 H), 7.95 (d, J = 8.1 Hz, 1 H), 8.54 (d, J = 1.7, 1 H), 11.8−13.2 (br s, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 23.7, 30.3, 41.2, 67.7, 126.4, 140.1, 144.4, 146.9, 149.6, 167.2. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.24; H, 6.71; N, 7.03.

General Procedure for Two-Step Pyrroline Annulation. Preparation of 2,8,8-Trimethyl-6,10-dioxo-1-aza-7,9-dioxaspiro[4.5]dec-1-ene (48). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and rubber septum was charged with a solution of oximinosulfonate **8** (0.328 g, 1.00 mmol) and isoprene (0.204 g, 3.00 mmol) in 12 mL of dichloromethane. The solution was cooled at −78 °C while Me_2AlCl solution (1.0 M in hexane, 2.0 mL, 2.0 mmol) was added dropwise via syringe over 4 min. The resulting orange solution was stirred for 3 h at −78 °C to give a yellow solution which was quenched by addition of 3 mL of saturated sodium potassium tartrate solution. The resulting mixture was allowed to warm to 0 °C, 20 mL of dichloromethane and 20 mL of water were added, and the aqueous phase was separated and extracted with three 20-mL portions of dichloromethane. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide the crude cycloadduct as a yellow foam.

A 100-mL, round-bottomed flask equipped with an argon inlet adapter and reflux condenser was charged with a solution of the crude cycloadduct in 21 mL of acetonitrile and 2.5 mL of pH 7 phosphate buffer. The resulting solution was heated at 80 °C for 30 min, allowed to cool to room temperature, and concentrated to ca. 2 mL. The residue was diluted with 15 mL of dichloromethane and 15 mL of water, and the aqueous phase was separated and extracted with three 20-mL portions of dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated onto 1 g of deactivated silica gel. This free-flowing powder was transferred to the top of a column of 10 g of deactivated silica gel and eluted with 0−25% ethyl acetate−hexane to provide 0.089 g (42%) of the pyrroline **48** as a colorless oil: IR ($CHCl_3$) 3015, 1745, 1635, 1300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (s, 3 H), 2.05 (s, 3 H), 2.12 (s, 3 H), 2.58 (tr, J = 7.5 Hz, 2 H), 2.94 (tr, J = 7.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 28.5, 28.8, 31.7, 41.5, 81.0, 106.4, 167.7, 183.2.

2,4,8,8-Tetramethyl-6,10-dioxo-1-aza-7,9-dioxaspiro-[4.5]dec-1-ene (49). Reaction of oximinosulfonate **8** (0.328 g, 1.00 mmol) with a 70:30 mixture of *trans*-2-methylpenta-1,3-diene and 4-methylpenta-1,3-diene (0.329 g, 4.00 mmol) and Me_2AlCl (1.0 M in hexane, 2.0 mL, 2.0 mmol) in 12 mL of dichloromethane at −78 °C for 1 h according to the general procedure provided the crude cycloadduct as an orange foam.

Heating this material in 21 mL of acetonitrile and 2.5 mL of pH 7 phosphate buffer at 80 °C for 45 min according to the general procedure furnished 0.102 g (45%) of pyrroline **49** as a white solid: mp 108−109 °C; IR ($CHCl_3$) 2990, 1780, 1750, 1630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, J = 6.9 Hz, 3 H), 1.76 (s, 3H), 1.90 (s, 3 H), 2.14 (s, 3 H), 2.76 (dd, J = 16.8, 9.6 Hz, 1 H), 2.85 (dd, J = 16.8, 8.4 Hz, 1 H), 3.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.1, 27.8, 29.9, 44.1, 47.4, 83.1, 105.8, 165.9, 168.8, 184.9. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22; Found: C, 58.79; H, 6.68; N, 6.02.

4,8,8-Trimethyl-6,10-dioxo-1-aza-7,9-dioxaspiro[4.5]dec-1-ene (38). Reaction of oximinosulfonate **8** (0.328 g, 1.00 mmol) with *trans*-hexa-2,4-diene (0.246 g, 3.00 mmol) and Me_2AlCl (1.0 M in hexane, 2.0 mL, 2.0 mmol) in 12 mL of dichloromethane at −78 °C for 3 h according to the general procedure provided the crude cycloadduct as a yellow foam. Heating this material in 20 mL of acetonitrile and 2.5 mL of pH 7 phosphate buffer at 80 °C for 10 min according to the general procedure furnished 0.073 g (35%) of pyrroline **38** as a white solid: mp 102−106 °C; IR ($CHCl_3$) 2990, 1780, 1745, 1620 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, J = 7.2 Hz, 3 H), 1.79 (s, 3 H), 1.93 (s, 3H), 2.69 (dd, J = 17.4, 9.0 Hz, 1 H), 2.98 (dd, J = 18.6, 8.7 Hz, 1 H), 3.12 (m, 1 H), 7.99 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 27.8, 29.8, 42.5, 45.6, 83.1, 106.0, 165.1, 168.2, 175.5.

7-Oxo-1-(propenoxycarbonyl)-4-(tosyloxy)-3,8-methano-2-aza-6-oxabicyclo[3.2.1]octane (51) and 3,3-Dimethyl-1,5-dioxo-8-(tosyloxy)-7,10-etheno-7-aza-2,4-dioxaspiro-[5.4]decane (50). A threaded Pyrex tube (ca. 50 mL capacity) equipped with a rubber septum and argon inlet needle was charged with oximinosulfonate **8** (0.198 g, 0.605 mmol), cyclopentadiene (0.200 g, 3.02 mmol), and 20 mL of toluene. The tube was then sealed with a Teflon cap and heated at 60 °C for 2 h. After cooling to room temperature, the resulting orange solution was concentrated, and the residual orange oil was purified by column chromatography on 12 g of silica gel (elution with 25% ethyl acetate−hexane) to provide 0.090 g (38%) of 7-oxo-1-(propenoxycarbonyl)-4-(tosyloxy)-3,8-methano-2-aza-6-oxabicyclo[3.2.1]octane (**51**) as a white solid and 0.021 g (9%) of 3,3-dimethyl-1,5-dioxo-8-tosyloxy-7,10-etheno-7-aza-2,4-dioxaspiro[5.4]decane (**50**). For 7-oxo-1-(propenoxycarbonyl)-4-(tosyloxy)-3,8-methano-2-aza-6-oxabicyclo[3.2.1]octane (**51**): mp 135−137 °C; IR ($CHCl_3$) 3345, 3030, 1800, 1755, 1375, 1175, 995 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (dq, J = 12.1, 1.8 Hz, 1H), 1.94 (s, 3 H), 2.17 (d, J = 12.9 Hz, 1 H), 2.48 (s, 3 H), 2.5−2.7 (br s, 1 H), 3.61 (dq, J = 5.1, 1.4 Hz, 1 H), 3.76 (s, 1 H), 4.31 (app t, J = 1.7 Hz, 1 H), 4.68 (dd, J = 5.1, 1.4 Hz, 1 H), 4.77 (s, 2 H), 7.39 (d, J = 7.8 Hz, 2 H), 7.81 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 21.8, 33.2, 50.1, 59.9, 66.4, 81.9, 82.6, 102.8, 127.8, 130.2, 132.4, 145.6, 152.4, 166.0, 172.2. For 3,3-dimethyl-1,5-dioxo-8-(tosyloxy)-7,10-etheno-7-aza-2,4-dioxaspiro[5.4]decane **(50)**: IR ($CHCl_3$) 3020, 1780, 1740, 1380, 1320, 1180, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.71 (s, 3 H), 1.94 (dd, J = 12.9, 6.7 Hz, 1 H), 2.21 (s, 3 H), 2.45 (s, 3 H), 2.66 (dtr, J = 12.9, 2.6 Hz, 1 H), 3.43 (tr, J = 3.0 Hz, 1 H), 5.23 (dd, J = 6.7, 2.4 Hz, 1 H), 6.04 (d, J = 3.8 Hz, 1 H), 6.65 (dd, J = 3.8, 3.0 Hz, 1 H), 7.34 (d, J = 7.9 Hz, 2 H), 7.76 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 26.7, 30.0, 30.5, 44.5, 82.3, 93.9, 108.3, 127.5, 129.8, 133.9, 134.5, 140.1, 145.1, 162.34, 162.32.

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Supporting Information Available: ^1H NMR spectra for all pyridine and pyrroline annulation products, as well as compounds **30**, **31**, **32**, **34**, **36**, **50**, and **51** (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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