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# Development of an Oxazole Conjunctive Reagent and Application to the Total Synthesis of Siphonazoles

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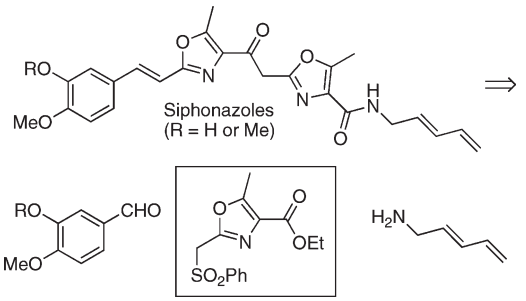


The preparation of 4-carbethoxy-5-methyl-2-(phenylsulfonyl)methyloxazole and its use in the elaboration of more complex oxazoles are described. A total synthesis of the unique natural products siphonazoles A and B, illustrates an application of this building block. A discussion of the biological activity of the siphonazoles is also presented.

## Introduction

Siphonazole, **1**, and its methylated relative **2** (Figure 1) are structurally novel natural products isolated from a *Herpetosiphon* species.[1] They are the first, and so far the only, naturally occurring substances known that incorporate oxazole subunits connected by a two-carbon tether. Prior to their discovery, only arrangements comprising directly linked oxazoles[2] (e.g., muscoride A, **3**), or oxazole pairs separated by a one-carbon bridge[3] (cf. bengazole A, **4**) had been observed among polyoxazole natural products.[4] We propose to distinguish the two substances with the names siphonazole A (**1**) and B (**2**). While the unusual structure of these compounds provides sufficient cause to embark in a total synthesis, lack of knowledge concerning their bioactivity adds an incentive to do so. Indeed, numerous polyoxazole natural products, and certainly so the bengazoles, display remarkable antibiotic and cytotoxic activity: it seemed likely that **1** and **2** may also possess useful biological properties.

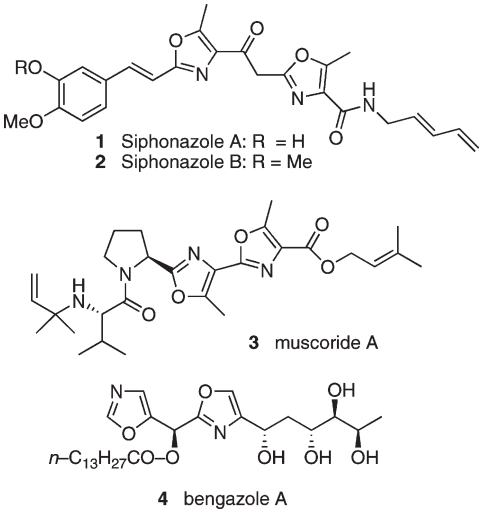


**FIGURE 1.** Structures of siphonazoles, muscoride A, and bengazole A.

Chemical efforts in the siphonazole area culminated in 2007 with Moody's landmark total synthesis of **1** and **2**[5] from advanced intermediates **5** and **6** and dienic amine **7** (Scheme 1). Key aspects of this work are the assembly of oxazole units via the reaction of a Rh−ketocarbenoid with an amide[6] or a nitrile[7] and the construction of the central (2-oxazolyl)methyl ketone motif by acylation of an organozinc agent derived from 4-carbomethoxy-2-iodomethyl-5-methyloxazole. A later study by Feng produced fragment **9** through a Wittig reaction of phosphorane **8**.[8]

(1) Nett, M.; Erol, Ö.; Kehrhaus, S.; Köck, M.; Krick, A.; Eguereva, E.; Neu, E.; König, G. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3863.



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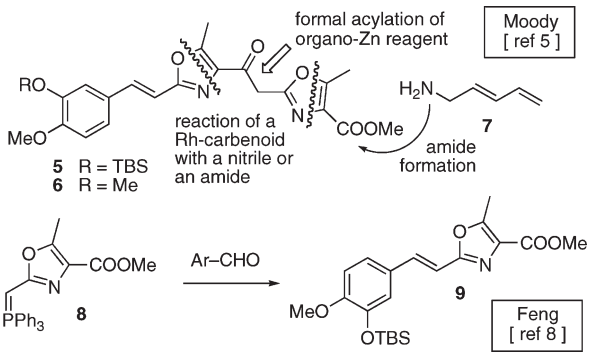
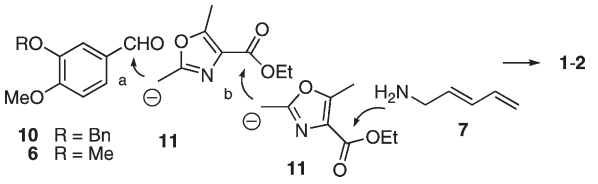
**SCHEME 1**

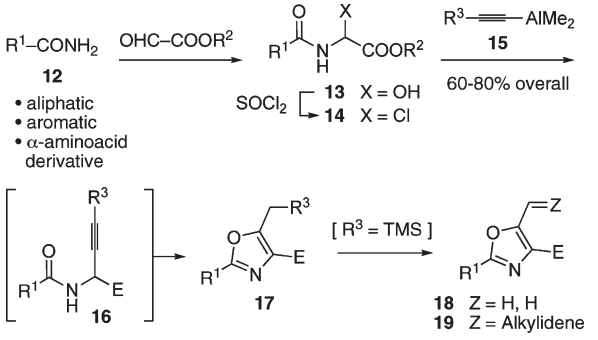



In 2009, we described a second total synthesis[9] involving the iterative use of a conjunctive oxazole building block that acts as a carrier of synthon **11**, as shown in Scheme 2. This diagram captures the essence of our synthetic strategy. At a chemical level, the solutions devised during this effort promise to be of value beyond the siphonazole problem. In the biological domain, our work permitted a preliminary investigation of the activity of the natural products, whereupon moderate cytoxicity was unveiled for **1**. This paper provides full details of our chemical and biological investigations.

**SCHEME 2**




**SCHEME 3**




**Background.** We perceived that an oxazole-forming reaction devised in these laboratories (Scheme 3)[10] could be advantageously utilized in the synthesis of **1** and **2**. This chemistry relies on the condensation of an aluminum acetylide, **15**, with an α-chloroglycinate **14**, available in high yield from a generic primary amide **12** by Ben-Ishai addition to a glyoxylate ester[11] and $SOCl_2$ treatment of the resultant **13**. The alkynylglycinate intermediates **16** are isolable, but they are more conveniently allowed to cyclize in situ to oxazoles **17**. The use of an organoaluminum reagent derived from TMS-acetylene results in formation of a product **17** in which $R^3 = SiMe_3$. Such an oxazole is amenable to desilylation (cf. **18**) or, more interestingly, to conversion into an alkylidene derivative through a Peterson reaction (cf. **19**).[12] Of course, the facile cyclization of **16** to **17** is consonant with Nagao's observation that *N*-acyl alkynylglycinates isomerize easily to oxazoles.[13] The overall process embodies a special case of a general class of oxazole-forming reactions that involve the cycloisomerization of an *N*-propargylamide. Pioneering

(2) Representative bis-oxazoles of this type: Muscoride A (isolation): (a) Nagatsu, A.; Kajitani, H.; Sakakibara, J. *Tetrahedron Lett.* **1995**, *36*, 4097. Synthesis: (b) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1996**, *61*, 6517. (c) Muir, J. C.; Pattenden, G.; Thomas, R. M. *Synthesis* **1998**, 613. (d) Ref 10. Hennoxazole (isolation): (e) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173. (f) Higa, T.; Tanaka, J.; Kitamura, A.; Koyama, T.; Takahashi, M.; Uchida, T. *Pure Appl. Chem.* **1994**, *66*, 2227. Synthesis: (g) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558. (h) Wipf, P.; Lim, S. *Chimia* **1996**, *50*, 157–167. (i) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924. (j) Yokokawa, F.; Asano, T.; Shioiri, T. *Tetrahedron* **2001**, *57*, 6311 as well as ref 21. Synthetic studies: (k) Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, 415. Diazonamides (isolation): (l) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303. (n) Fernandez, R; Martin, M. J.; Rodriguez-Acebes, R.; Reyes, F.; Francesch, A.; Cuevas, C. *Tetrahedron Lett.* **2008**, *49*, 2283. Synthesis: (o) Li, J.; Jeong, S.; Esser, L.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4765. (p) Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770. (q) Nicolaou, K. C.; Chen, D. Y.-K.; Huang, X.; Ling, T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888. (r) Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897. For higher polyoxazoles of this type, see the following leading references: (s) Dalisay, D. S.; Rogers, E. W.; Edison, A. S.; Molinski, T. F. *J. Nat. Prod.* **2009**, *72*, 732. (t) Deeley, J.; Bertram, A.; Pattenden, G. *Org. Biomol. Chem.* **2008**, *6*, 1994. (u) Hernandez, D.; Vilar, G.; Riego, E.; Canedo, L. M.; Cuevas, C.; Albericio, F.; Alvarez, M. *Org. Lett.* **2007**, *9*, 809. (v) Petchprayoon, C.; Asato, Y.; Higa, T.; Garcia-Fernandez, L. F.; Pedpradab, S.; Marriott, G.; Suwanborirux, K.; Tanaka, J. *Heterocycles* **2006**, *69*, 447. (w) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464. (x) Doi, T.; Yoshida, M.; Shin-ya, K.; Takahashi, T. *Org. Lett.* **2006**, *8*, 4165. (y) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995. (z) Matsunaga, S.; Fusetani, N.; Hashimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 847.

(3) This substructure is characteristic of the bengazoles, a group of about 20 marine substances with remarkable bioactivity. Isolation: (a) Adamczeski, M.; Quinoa, E.; Crews, P. *J. Am. Chem. Soc.* **1988**, *110*, 1598. (b) Rodriguez, J.; Nieto, R. M.; Crews, P. *J. Nat. Prod.* **1993**, *56*, 2034. (c) Rudi, A.; Kashman, Y.; Benayahu, Y.; Schleyer, M. *J. Nat. Prod.* **1994**, *57*, 829. (d) Groweiss, A.; Newcomer, J. J.; O'Keefe, B. R.; Blackman, A.; Boyd, M. R. *J. Nat. Prod.* **1999**, *62*, 1691. (e) Fernandez, R.; Dherbomez, M.; Letourneux, Y.; Nabil, M.; Verbist, J. F.; Biard, J. F. *J. Nat. Prod.* **1999**, *62*, 678. (f) Searle, P. A.; Richter, R. K.; Molinski, T. F. *J. Org. Chem.* **1996**, *61*, 4073. Total syntheses: (g) Mulder, R. J.; Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1999**, *64*, 4995. (h) Bull, J. A.; Balskus, E. P.; Horan, R. A. J.; Langner, M.; Ley, S. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 6714. () Bull, J. A.; Balskus, E. P.; Horan, R. A. J.; Langner, M.; Ley, S. V. *Chem.—Eur. J.* **2007**, *13*, 5515. Synthetic studies: (i) Mulder, R. J.; Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1999**, *64*, 4995. (j) Shafer, C. M.; Molinski, T. F. *Tetrahedron Lett.* **1998**, *39*, 2903. (k) Shafer, C. M.; Molinski, T. F. *Heterocycles* **2000**, *53*, 1167. (l) Hodges, J. C.; Patt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991**, *56*, 449. (m) Vedejs, E.; Monahan, S. D. *J. Org. Chem.* **1996**, *61*, 5192. (n) Chittari, P.; Hamada, Y.; Shioiri, T. *Synlett* **1998**, 1022. (o) Chittari, P.; Hamada, Y.; Shioiri, T. *Heterocycles* **2003**, *59*, 465.

(4) Review: (a) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995. See also: (b) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, *23*, 26.

(5) (a) Linder, J.; Moody, C. J. *Chem. Commun.* **2007**, 1508. (b) Linder, J.; Blake, A. J.; Moody, C. J. *Org. Biomol. Chem.* **2008**, *6*, 3908.

(6) Davies, J. R.; Kane, P. D.; Moody, C. J. *Tetrahedron Lett.* **2004**, *60*, 3967 See ref 5 for a thorough bibliography.

(7) Connell, R. D.; Tebbe, M.; Helquist, P.; Åkermark, B. *Tetrahedron Lett.* **1991**, *32*, 17. See also ref 28b.

(8) Zhu, Y.; Hu, L.; Tan, W.; Feng, Y. *Jingxi Huagong Zhongjianti* **2008**, *38*, 42.

(9) Zhang, J.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 2389.

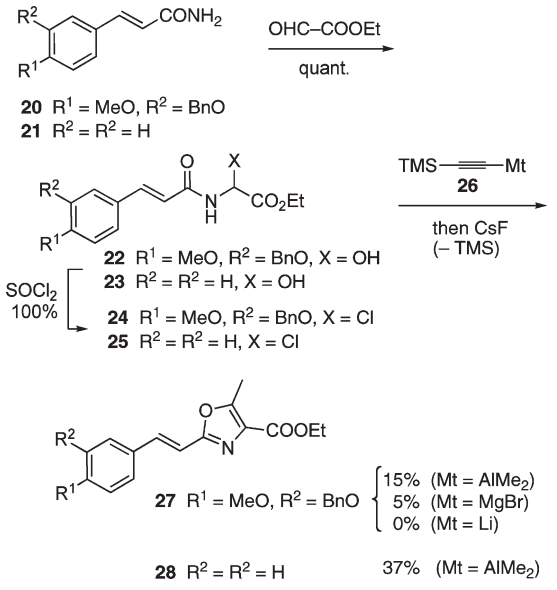
(10) Coqueron, P. Y.; Didier, C.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1411. This paper provides a thorough bibliography of oxazole-forming reactions through early 2003.

(11) (a) Zoller, U.; Ben-Ishai, D. *Tetrahedron* **1975**, *31*, 863. (b) Ben-Ishai, D.; Sataty, I.; Bernstein, Z. *Tetrahedron* **1976**, *32*, 1571. (c) Bernstein, Z.; Ben-Ishai, D. *Tetrahedron* **1977**, *33*, 881.

(12) Chau, J.; Zhang, J.; Ciufolini, M. A. *Tetrahedon Lett.* **2009**, *50*, 6163.

(13) (a) Nagao, Y.; Kweon, K.; Sano, S.; Kakegawa, H.; Lee, W. S.; Shimizu, H.; Shiro, M.; Katunuma, N. *Tetrahedron Lett.* **1996**, *37*, 861. (b) Sano, S.; Shimizu, H.; Kim, K.; Lee, W. S.; Shiro, M.; Nagao, Y. *Chem. Pharm. Bull.* **2006**, *54*, 196.

**SCHEME 4**

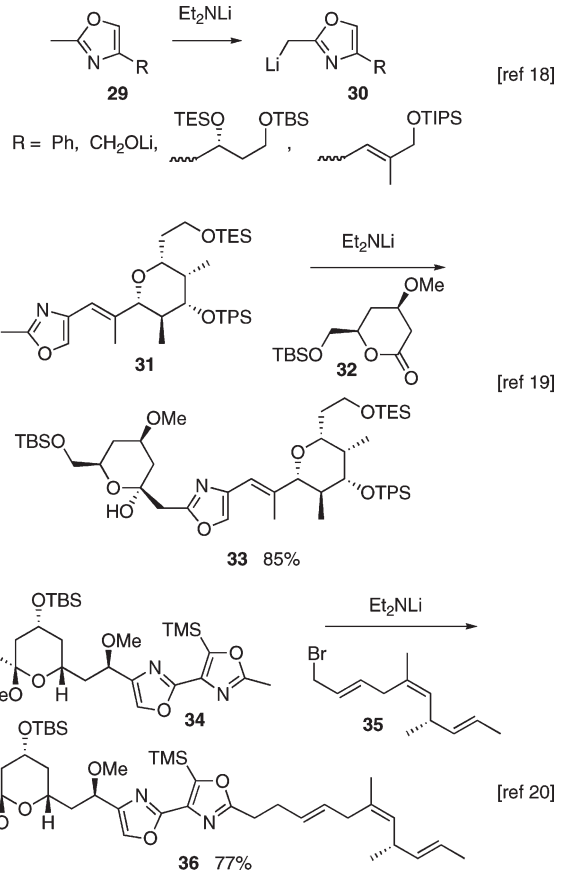



work by Hacksell demonstrated early instances of base-promoted transformations of this type,[14] notable examples of which were later described by Wipf.[15] More recently, transition-metal catalysis has proven to be of value in this transformation.[16]

Initial efforts endeavored to reach **27** from chloride **24**, which was prepared in high yield from isoferulamide benzyl ether, **20** (Scheme 4).[17] Regrettably, **24** performed poorly in the oxazole-forming reaction, and it afforded **27** in no more than 15% yield. While analogous chlorides obtained from aliphatic, aromatic, or α-amino acid-derived primary amides generally participate in the above sequence to furnish oxazoles in good to excellent yield, those resulting from conjugated amides had never before been investigated. A control experiment revealed that cinnamamide-derived **25** also produces oxazole **28** in an abnormally low 37% overall yield. Evidently, conjugated amides are poor substrates for the reaction; moreover, the protected catechol moiety present in **24** may well sequester the organometallic agent, thereby retarding the substitution step and further diminishing the yield.

An ultimately successful alternative materialized upon recognition that **1** and **2** could result through the union of an aromatic aldehyde, dienic amine **7**, plus two molecules of the same oxazole-centered nucleophile, **11** (Scheme 2), even though the prognosis for the viability of this approach

**SCHEME 5**




seemed to be quite unfavorable at the onset of our investigations. To wit, the generation of nucleophiles similar to **11**, but lacking a carbonyl substituent at the oxazole C-4 position, entails the deprotonation of a 2-methyloxazole. Notable in this respect is the work of Evans, who discovered that lithium diethylamide is the base of choice for such a purpose.[18] Thus, substrates **29** are smoothly lithiated to **30** (Scheme 5), which efficiently participate in carbonyl addition and nucleophilic substitution reactions. This chemistry performs well even in complex systems, as evident from key steps in the Evans synthesis of phorboxazole (Scheme 5, **31** → **33**)[19] and in the Smith synthesis of hennoxazole A (Scheme 5, **34** → **36**).[20]

The landscape changes dramatically in the presence of a 4-carboxy substituent on the oxazole ring. As first shown by Meyers,[21] the action of strong base upon 2-methyloxazole-4-carboxylic acid induces exclusive deprotonation at the C-5 ring position (Scheme 6). The same is true for the corresponding methyl[22] or *tert*-butyl[23] esters. This defeats all attempts to generate a C-2 lithiomethyl intermediate by

(14) (a) Nilsson, B. M.; Hacksell, U. *J. Heterocycl. Chem.* **1989**, *26*, 269. (b) Nilsson, B. M.; Vargas, H. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1992**, *35*, 285.

(15) (a) Wipf, P.; Rahman, L. T.; Rector, S. R. *J. Org. Chem.* **1998**, *63*, 7132. (b) Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593.

(16) (a) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (b) Milton, M. D.; Inada, Y.; Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2004**, 2712. (c) Hashmi, A. S. K.; Rudolph, M.; Schymura, S.; Visus, J.; Frey, W. *Eur. J. Org. Chem.* **2006**, 4905. (d) Kang, J.-E.; Kim, H.-B.; Lee, J.-W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537. (e) Merkul, E.; Grotkopp, O.; Müller, T. J. J. *Synthesis* **2009**, 502. It is important to note that among these methods only the chemistry of refs 10 and 13 permits access to the 2,5-dialkyloxazole-4-carboxylate series.

(17) The preparation of this material is provided as Supporting Information.

(18) Evans, D. A.; Cee, V. J.; Smith, T. E.; Santiago, K. J. *Org. Lett.* **1999**, *1*, 87.

(19) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033. See also ref 18.

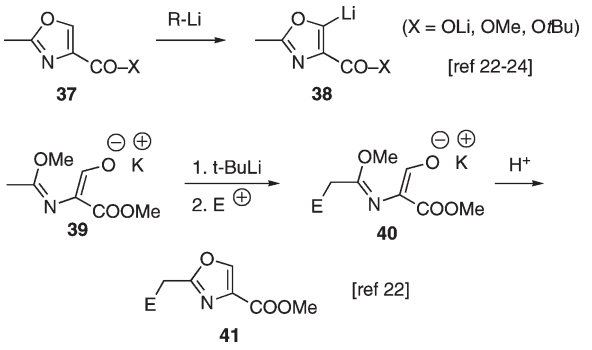
(20) Smith, T. E.; Kuo, W.-H.; Bock, V. D.; Roizen, J. L.; Balskus, E. P.; Theberge, A. B. *Org. Lett.* **2007**, *9*, 1153.

(21) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1981**, *22*, 3163.

(22) Meyers, A. I.; Lawson, J. P.; Walker, D. G.; Lindermann, R. J. *J. Org. Chem.* **1986**, *51*, 5111.

(23) Nagao, Y.; Yamada, S.; Fujita, E. *Tetrahedron Lett.* **1983**, *24*, 2291.

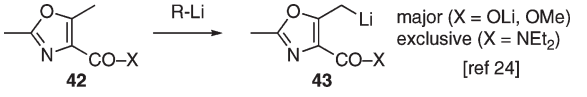
**SCHEME 6**




direct deprotonation. Indeed, a surrogate of the nucleophile in question may be accessed only by lithiation of Cornforth imidate **39** *prior to* oxazole ring formation.

Additional complications materialize upon the introduction of a methyl substituent at the oxazole C-5 position. Knight determined that 2,5-dimethyloxazole-4-carboxylic acid, **42**, undergoes preferential metalation (ca. 2:1) at the C-5 methyl group, while the corresponding diethylamide is

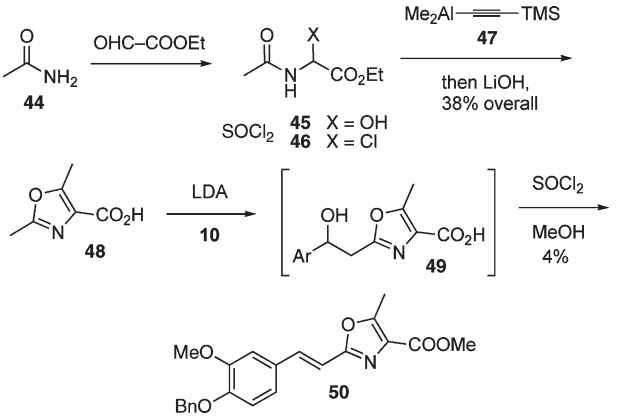
**SCHEME 7**




deprotonated exclusively there (Scheme 7).[24] Under particular conditions, it is possible to generate a 1:1 mixture of C-2 lithiomethyl and C-5 lithiomethyl derivatives of the 4-carboxylate salt. However, in Knight's words, "*this lack of regioselectivity renders the method of little synthetic value*." Moody and collaborators had an opportunity to reexamine this chemistry during their synthesis of siphonazoles, but they could only confirm Knight's conclusions. Thus, the Nottingham team observed poor selectivity and disappointing yields in the attempted derivatization of the C-2 methyl group via the dianions of 2,5-dimethyloxazole-4-carboxylic acid or of the corresponding diethyl amide, even under Evans[18,19] conditions. Further confirmation of such a problematic state of affairs is borne out of our own observation that generation of the dianion of 2,5-dimethyloxazole-4-carboxylic acid, addition thereof to aldehyde **10** and treatment of the resultant complex mixture of products with $MeOH/SOCl_2$ affords **50** in a meager 4% yield after chromatography. In summary, the 4-COOR substituent in such oxazoles fiercely opposes metalation at the C-2 Me group.[25]

In principle, one could bypass the foregoing obstacles by activating the C-2 Me group with an appropriate anion-stabilizing unit, logical choices for which would be a phosphorus- or a sulfur-centered functionality. In the first case,

**SCHEME 8**




bond-forming sequence *a* (Scheme 2) entails a Wittig-type reaction, whereas step *b* could proceed through an acylation-dephosphorylation[26] sequence. The pursuit of this strategy was terminated at an early stage on the basis of the following results. First, phosphorane **8**[8] (Scheme 1) appears to be the sole example recorded in the CAS database of an olefination agent of general structure **51**. By contrast, many compounds

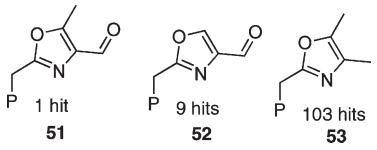



**FIGURE 2.** Phosphorylated oxazole substructures recorded in the CAS database.

of the type **52**[27] and **53** (Figure 2) are known,[28] the latter mostly in the patent literature.[29] The preparation of **8** required five steps from dichloroacetonitrile and threonine. The reaction of chloroglycinates **55** or **58** with alkynylaluminum agents might have offered a more direct avenue to phosphonate **59**; however, neither substrate provided any of the desired oxazoles when treated with organoalane **47** (Scheme 9).[30] No attempt was made to obtain the bromo analogue of **56** through radical bromination of the corresponding dimethyloxazole. While the radical bromination of

(24) Cornwall, P.; Dell, C. P.; Knight, D. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2417.

(25) This is imputable to the unfavorable positioning of the 4-COOR substituent: the 5-COOR isomer is smoothly deprotonated at the C-2 Me group (ref 24), presumably because of good resonance stabilization of the ensuing anion.

(26) (a) Fox, D. J.; Parris, S.; Pedersen, D. S.; Tyzack, C. R.; Warren, S. *Org. Biomol. Chem.* **2006**, *4*, 3102. (b) Fox, D. J.; Pedersen, D. S.; Warren, S. *Org. Biomol. Chem.* **2006**, *4*, 3108. (c) Hawkins, M. J.; Powell, E. T.; Leo, G. C.; Gauthier, D. A.; Greco, M. N.; Maryanoff, B. *Org. Lett.* **2006**, *8*, 3429. (d) Hong, J. E.; Shin, W. S.; Jang, W. B.; Oh, D. Y. *J. Org. Chem.* **1996**, *61*, 2199.

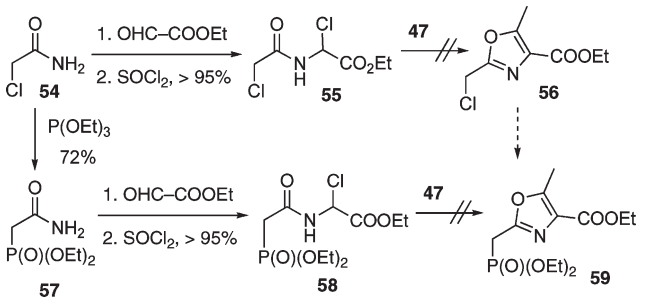
(27) (a) Pattenden, G.; Ashweek, N. J.; Baker-Glenn, C. A. G.; Kempson, J.; Walker, G. M.; Yee, J. G. K. *Org. Biomol. Chem.* **2008**, *6*, 1478. (b) Wolbers, P; Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1999**, *40*, 4527. (c) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185. (d) Crimmin, M. J.; O'Hanlon, P.; Rogers, N. H.; Walker, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2047. See also literature cited therein.

(28) E.g.: (a) Schroeder, D. C.; Corcoran, P. O.; Holden, C. A.; Mulligan, M. C. *J. Org. Chem.* **1962**, *27*, 1098. (b) Meanwell, N. A.; Rosenfeld, M. J.; Wright, J. J. K.; Brassard, C. L.; Buchanan, J. O.; Federici, M. E.; Fleming, J. S.; Gamberdella, M.; Hartl, K. S.; Zavoico, G. B.; Seiler, S. M. *J. Med. Chem.* **1993**, *36*, 3871.

(29) E.g.: (a) Fischer, C.; Munoz, B.; Rivkin, A. A. *PCT Int. Appl.* **2008**, WO 2008097538 A1 20080814. (b) Kudo, Y.; Suzuki, M.; Suemoto, T.; Okamura, N.; Shiomitsu, T.; Shimazu, H. *PCT Int. Appl.* **2005**, WO 2005016888 A1 20050224. (c) Talley, J. J.; Bertenshaw, S.; Rogier, D. J., Jr.; Graneto, M.; Brown, D. L.; Devadas, B.; Lu, H.-F.; Sikorski, J. A. *PCT Int. Appl.* **1996**, WO 9636617 A1. (d) Hoffman, J. M., Jr.; Rooney, C. S.; Saari, W. S.; Wai, J. S.; Williams, T. M.; Bamberger, D. L.; Jones, J. H. *Eur. Pat. Appl.* **1991**, EP 462800 A2 19911227.

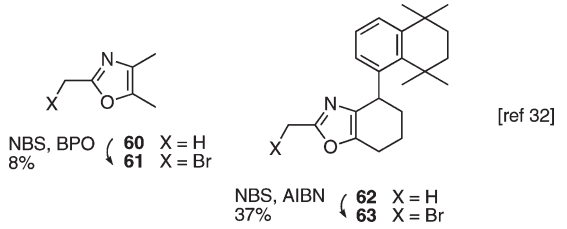
(30) Conceivably, **56** could be made by Rh(II)-mediated condensation of diethyl cyanomethyl-phosphonate with ethyl diazoacetoacetate according to Hoffmann, et al. (ref 27b). However, the modest yield (18%) obtained by these authors in a similar reaction of phosphonoacetonitrile with diethyl diazomalonate discouraged us from researching this possibility.

**SCHEME 9**



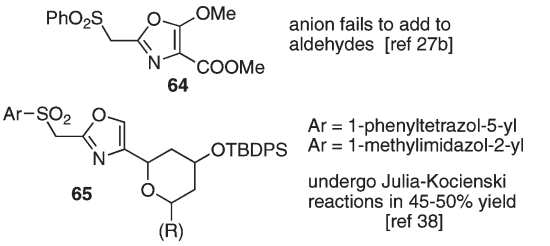

2-methyloxazole-4-carboxylic esters is efficient,[31] that of oxazoles incorporating multiple benzylic-type sites is notoriously problematic. Instructive examples appear in Scheme 10.[32]

**SCHEME 10**




The sulfone alternative entails the creation of bond *a* in a Julia mode[33] and that of bond *b* through a Fujita-type acylation,[34] followed by desulfonylation.[35] Precedent indicated that such an approach was perilous. While a limited volume of literature exists concerning the chemistry of 2-(sulfonyl)methyloxazole-4-carboxylates,[36] the anions of these species are known to be poor nucleophiles. For instance, Hoffmann discovered that the metalated **64** (Scheme 11) fails to add to aldehydes,[27b,37] precluding the occurrence of Julia reactions. Once again, the COOMe

**SCHEME 11**

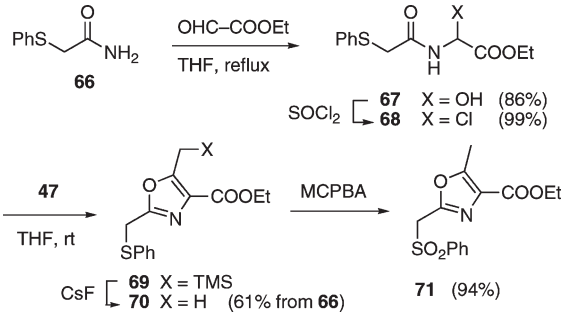



substitutent must be responsible for such a behavior, for Williams demonstrated that sulfonyloxazoles lacking such a group, e.g., **65**, do undergo Julia–Kocienski reactions, albeit in only 45–50% yield.[38]

## Results and Discussion

We anticipated that the reluctance of metalated sulfones of the type **64** to add to aldehydes could be overcome by activating the carbonyl receptor with an appropriate Lewis acid. We thus set out to prepare sulfone **71** and study its condensation with carbonyl compounds. Contrary to the case of **54** and **57**, α-(phenylthio)acetamide, **66**, performed well in the oxazole-forming reaction, affording **70** in 61% overall yield. Subsequent *m*-CPBA oxidation produced the desired **71**, a white crystalline solid with mp 154–155 °C, in 94% yield (Scheme 12).

**SCHEME 12**




In accord with Hoffmann,[27b,37] the anion of **71**, generated by deprotonation with NaH à la Fujita,[34] failed to add to aldehydes. More significantly, even the presumably more reactive lithio derivative of **70**, prepared by deprotonation with LDA, added to aldehydes inefficiently, underscoring the unfavorable influence of the 4-COOR group. However, activation of the carbonyl receptor with $TiCl_4$ enabled smooth Knoevenagel-type condensations of **71** with aldehydes and even with ketones. Aromatic aldehydes reacted efficiently at room temperature in THF–$CH_2Cl_2$ in the presence of $TiCl_4$ and $Et_3N$ (Table 1), giving rise to the expected products **72** mostly or exclusively as the *E*-isomers (shown), except in the case of cinnamaldehyde (entry **h**), which reacted nonstereoselectively. The stereochemical assignment of the major/exclusive product of these reactions rests on the observation of a nuclear Overhauser enhancement of the signals of the *ortho*-protons on the $PhSO_2$ group,

(31) Examples appear in ref 23 as well as in: White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Synth.* **2003**, *79*, 244.

(32) For **60**: (a) Kim, K. S.; Kimball, S. D.; Misra, R. N.; Rawlins, D. B.; Hunt, J. T.; Xiao, H.-Y.; Lu, S.; Qian, L.; Han, W.-C.; Shan, W.; Mitt, T.; Cai, Z.-W.; Poss, M. A.; Zhu, H.; Sack, J. S.; Tokarski, J. S.; Chang, C. Y.; Pavletich, N.; Kamath, A.; Humphreys, W. G.; Marathe, P.; Bursuker, I.; Kellar, O. K. A.; Roongta, U.; Batorsky, R.; Mulheron, J. G.; Bol, D.; Fairchild, C. R.; Lee, F. Y.; Webster, K. R. *J. Med. Chem.* **2002**, *45*, 3905. (b) For **62**: Haffner, C. D.; Lenhard, J. M.; Miller, A. B.; McDougald, D. L.; Dwornik, K.; Ittoop, O. R.; Gampe, R. T., Jr.; Xu, H. E.; Blanchard, S.; Montana, V. G.; Consler, T. G.; Bledsoe, R. K.; Ayscue, A.; Croom, D. *J. Med. Chem.* **2004**, *47*, 2010.

(33) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833. Reviews: (b) Kelly, S. E. Alkene Synthesis. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 1, pp 729–817. (c) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563.

(34) Nagao, Y.; Yamada, S.; Fujita, E. *Tetrahedron Lett.* **1983**, *24*, 2287. See also ref 32a.

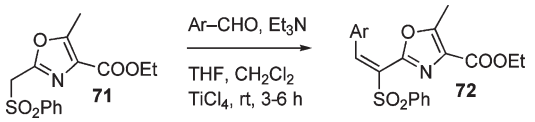
(35) Reviews: (a) Simpkins, N. *Tetrahedron* **1990**, *46*, 6951. (b) Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547.

(36) Comprehensive bibliography: refs 9, 27b, 31, and 37, as well as: (a) Fujita, E. *Heterocycles* **1984**, *21*, 41. (b) Yokoyama, M.; Menjo, Y.; Ubukata, M.; Irie, M.; Watanabe, M.; Togo, H. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2219. (c) White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Synth* **2003**, *79*, 244. The following patents describe the preparation of some 2-(arylsulfonyl)methyloxazole-4-carboxylic esters: (d) *Jpn. Kokai Tokkyo Koho* JP 59108772 A 19840623 Showa (Taiho Pharmaceutical Co., Ltd.), 1984; CAN 101:171238. (e) Dehmlow, H.; Kuhn, B.; Masciadri, R.; Panday, N.; Ratni, H.; Wright, M. B. *U.S. Pat. Appl. Pub.* US 2005215577 A1 20050929, 2005; CAN 143:347051.

(37) Ref 27b as well as: Wolbers, P.; Misske, A.; M.; Hoffmann, H. M. R. *Synlett* **1999**, 1808.

(38) Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291. However, this study also revealed that a Wadsworth–Emmons olefination mode is distinctly superior.

**TABLE 1. Condensation of Sulfonyl Oxazole 71 with Aromatic Aldehydes**



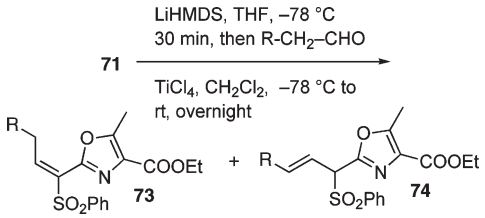

| entry | Ar | reaction time (h) | *E*/*Z* ratio | yield (%) |
|---|---|---|---|---|
| **a** | $C_6H_5$ | 3 | *E* only | 85 |
| **b** | 4-MeO-$C_6H_4$ | 3 | 7:1 | 93 |
| **c** | 4-HO-$C_6H_4$ | 3 | *E* only | 89 |
| **d** | 4-Cl-$C_6H_4$ | 3 | *E* only | 88 |
| **e** | 2-Me-$C_6H_4$ | 6 | *E* only | 88 |
| **f** | 2-furyl | 6 | 3:1 | 83 |
| **g** | 2-thienyl | 6 | 7:1 | 92 |
| **h** | (*E*)-$C_6H_5$-CH=CH | 6 | 1:1 | 76 |

as well as of those on the Ar substituent, upon irradiation of the olefinic proton. The preferential formation of the *E*-isomer is consistent with the relative steric demand of an aryl, phenylsulfonyl, and 2-oxazolyl substituent.[39]

The foregoing conditions are reminiscent of the Masamune-Roush protocol[40] for Wadsworth-Emmons olefinations. However, the literature seems to contain no record of like procedures for the Knoevenagel-like reaction of sulfones. Indeed, such transformations are normally carried out with stronger bases such as NaOH,[41] tBuOK,[42] NaH,[43] LiHMDS,[44] or BuLi,[45] though in one case an activated sulfone was successfully condensed with PhCHO in the presence of piperidine,[46] and in a second one, in the presence of TBAF, but in modest yield.[47]

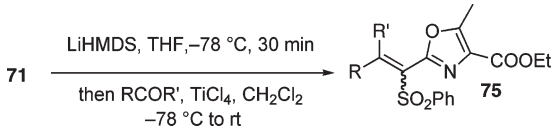
Aliphatic aldehydes (Table 2) and ketones (Table 3) reacted best when exposed to the action of lithiated **71** (prepared by treatment with LHMDS) and $TiCl_4$ in THF$-CH_2Cl_2$ at $-78$ °C, followed by gradual warming to room temperature overnight. Under these conditions, enolizable aldehydes afforded mixtures of the expected **73** (major product, *E*-isomer only) and its deconjugated isomer **74** (*E*-isomer only, Table 2), except propionaldehyde (entry **b**), which delivered exclusively a product of the type **73**. Compounds **73** and **74** were separable (silica gel chromatography)

**TABLE 2. Condensation of Sulfonyl Oxazole 71 with Enolizable Aliphatic Aldehydes**




| | | | yield (%) of | |
|---|---|---|---|---|
| entry | R | ratio **73**/**74** | **73** | **74** |
| **a** | $C_6H_5-CH_2$ | 2:1 | 60 | 30 |
| **b** | Me | **73** only | 87 | |
| **c** | *n*-$C_5H_{11}$ | 4:1 | 66 | 17 |

**TABLE 3. Condensation of Sulfonyl Oxazole 71 with Ketones**




| entry | RCOR′ | reaction time (h) | isomeric ratio[a] | yield (%) |
|---|---|---|---|---|
| **a** | acetone | 24 | | 81 |
| **b** | 2-heptanone | 24 | 5:1 | 78 |
| **c** | cyclohexanone | 24 | | 85 |
| **d** | acetophenone | 36 | 4:1 | 44 |

[a]Ratio of unassigned isomers; major product believed to be the *E*-isomer.

and were individually characterized. No product of either type was formed in the absence of $TiCl_4$. The LHMDS-based procedure was also suitable for the condensation of **71** with aromatic aldehydes, but it was less efficient than the $TiCl_4-Et_3N$ method detailed in Table 1. For instance, benzaldehyde gave **72** (*E*-isomer only) in a diminished 78% yield under these conditions (cf. 85%, Table 1). Not surprisingly, enolizable ketones reacted more slowly than aldehydes (24−36 h vs 12 h) but yielded exclusively conjugated sulfones **75** (Table 3). Products arising from unsymmetrical ketones were obtained as mixtures of geometric isomers. While these remained unassigned, the major product is believed to be the (*E*)-isomer, by analogy with earlier cases. Again, no product was formed in the absence of $TiCl_4$.

The application of the above findings to a synthesis of siphonazoles is subordinate to the identification of a technique for the desulfonylation of compounds **72**, **73**, and **75** under mild conditions. Among the various reagents that were examined for that purpose (Na/Hg, Mg/EtOH, Mg/TMSCl, $SmI_2$, Zn/$NH_4Cl$), metallic Zn in the presence of $NH_4Cl$ buffer proved to be optimal for the desulfonylation of products **72** and **73**. The latter substrates presented a special challenge, in that they were found to isomerize easily to allylsulfones **74**.[48] The combination of Zn and $NH_4Cl$ largely suppressed this unwanted isomerization. It should be

(39) As gauged from their *A* values: 2.9 kcal/mol for a $PhSO_2$ group (Juaristi, E.; Labastida, V.; Antunez, S. *J. Org. Chem.* 2000, 65, 969); 2.8 kcal/mol for a Ph group (Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 697); approximately 1.3 kcal/mol for a 4-carbomethoxy-5-methyl-2-oxazolyl group (estimated by MM+ structural optimization of the axial and equatorial conformer of the corresponding 2-cyclohexyl derivative).

(40) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, 2183.

(41) (a) Parpani, P.; Zecchi, G. *J. Org. Chem.* **1987**, *52*, 1417. (b) Nacci, V.; Filacchioni, G.; Porretta, G. C. *Farmaco* **1972**, *27*, 1003.

(42) Garst, M. E.; Dolby, L. J.; Esfandiari, S.; Okrent, R. A.; Avey, A. A. *J. Org. Chem.* **2006**, *71*, 553.

(43) Cabanal-Duvillard, I.; Berrien, J.-F. *Heterocycl. Commun.* **1999**, *5*, 257.

(44) (a) Orita, A.; Hasegawa, D.; Nakano, T.; Otera, J. *Chem.—Eur. J.* **2002**, *8*, 2000. (b) Babu, G.; Orita, A.; Otera, J. *Org, Lett.* **2005**, *7*, 4641.

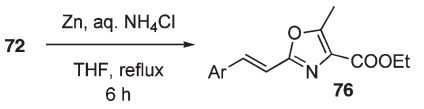
(45) (a) Ager, D. J. *Chem. Commun.* **1984**, 486. (b) Ager, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 183. (c) Antelo, B.; Castedo, L.; Delamano, J.; Gomez, A.; Lopez, C.; Tojo, G. *J. Org. Chem.* **1996**, *61*, 1188. (d) Uno, H.; Inoue, K.; Inoue, T.; Fumoto, Y.; Ono, N. *Synthesis* **2001**, 2255. (e) Orita, A.; Ye, F.; Doumoto, A.; Otera, J. *Chem. Lett.* **2003**, *32*, 104. (f) Ye, F.; Orita, A.; Doumoto, A.; Otera, J. *Tetrahedron* **2003**, *59*, 5635.

(46) Nikolae, A.; Florea, S.; Rudorf, W.-D.; Perjessy, A. *Rev. Chim.* **2005**, *56*, 524 (CAN 144:412344).

(47) Antelo, B.; Castedo, L.; Delamano, J.; Gomez, A.; Lopez, C.; Tojo, G. *J. Org. Chem.* **1996**, *61*, 1188.

(48) For an excellent discussion of the vinylsulfone−allylsulfone isomerization, see: El-Awa, A.; Noshi, M. N.; Mollat du Jourdin, X.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315 and literature cited therein. See especially pp 2331 ff.

**TABLE 4. Desulfonylation of Vinyl Sulfones Derived from Aromatic Aldehydes**[a]




| entry | Ar | yield (%) |
|---|---|---|
| **a** | $C_6H_5$ | 100 |
| **b** | 4-MeO-$C_6H_4$ | 94 |
| **c** | 4-HO-$C_6H_4$ | 57 |
| **d** | 4-Cl-$C_6H_4$ | 91 |
| **e** | 2-Me-$C_6H_4$ | 93 |
| **f** | 2-furyl | 89 |
| **g** | 2-thienyl | 93 |

[a]The reaction may be carried out at rt for 30 min; however, the product is then a mixture of *E*- and *Z*-isomers.

noted that the use of Zn/$NH_4Cl$ for the desulfonylation of olefinic sulfones such as **72** appears to be undocumented.

Results obtained in the desulfonylation of compounds **72** are summarized in Table 4. One aspect of this chemistry merits comment. Conducting the reaction in refluxing THF afforded only the *E*- isomer of olefins **76** (within the limits of 300 MHz $^1$H NMR spectroscopy). By contrast, mixtures of *E*- and *Z*-olefins were obtained when the reaction was carried out at room temperature for 30 min. The desulfonylation of compound **72h** had to be run at room temperature for 30 min in order to avoid overreduction of the sensitive diene **76h**, which was obtained in 45% yield (Scheme 13). Interestingly, this product emerged substantially only as the *E,Z*-isomer (shown),[49] even though the starting **72h** was a 1:1 mixture of geometric isomers.

**SCHEME 13**

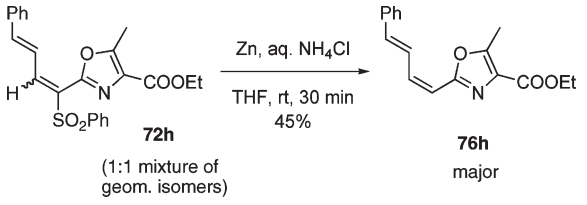
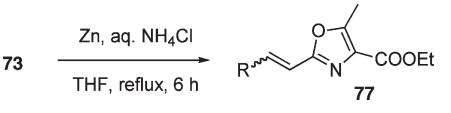


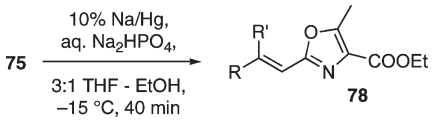

Table 5 illustrates the results observed in the desulfonylation of products **73**. The emerging **77** were produced as mixtures of chromatographically separable *E* and *Z* isomers, with the latter being dominant. Geometric isomers were thus individually characterized. Sulfones **75** obtained from aliphatic ketones were resistant to desulfonylation with Zn/$NH_4Cl$. Conversion into **78** required the more vigorous

**TABLE 5. Desulfonylation of Vinyl Sulfones Derived from Enolizable Aliphatic Aldehydes**




| entry | R | *E*/*Z* isomeric ratio | yield (%) | |
|---|---|---|---|---|
| **a** | $C_6H_5$-$(CH_2)_2$ | 1:3.5 | 20 (*E*) | 70 (*Z*) |
| **b** | Et | 1:3 | 23 (*E*) | 70 (*Z*) |
| **c** | *n*-$C_6H_{13}$ | 1:3 | 22 (*E*) | 66 (*Z*) |

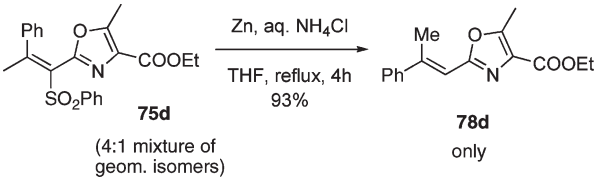
**TABLE 6. Desulfonylation of Vinyl Sulfones Derived from Ketones**




| entry | R | R | isomeric ratio | yield (%) |
|---|---|---|---|---|
| **a** | Me | Me | | 42 |
| **b** | *n*-$C_5H_{11}$ | Me | 1:1 | 48 |
| **c** | $(CH_2)_5$ | | | 49 |

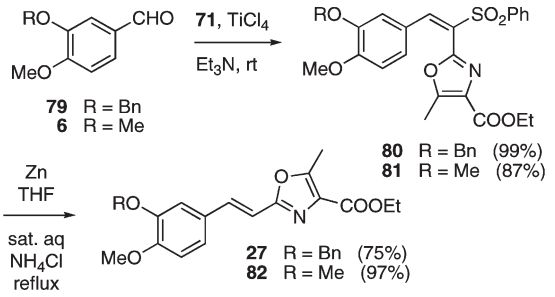
reductant, 10% Na/Hg amalgam, which, however, promoted some overreduction of the double bond. Results of the desulfonylation of ketone-derived vinylsulfones are summarized in Table 6. On the other hand, acetophenone-derived sulfone **75d** was smoothly desulfonylated with Zn/$NH_4Cl$ to furnish **78d** as the *E*-isomer only (Scheme 14).

**SCHEME 14**




With the above results in hand, intermediates **27** and **82** were rapidly assembled in good overall yield as detailed in Scheme 15. Thus, condensation of **71** with aldehydes **79** and **6** over 6 h provided alkylidene derivatives **80** (75%) and **81** (87%), respectively, as the *E*-isomers only (within the limits

**SCHEME 15**

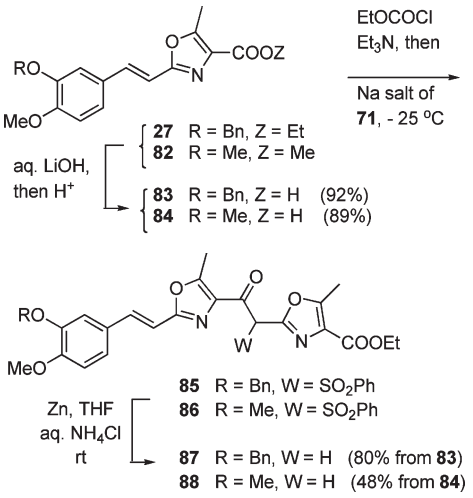



of 300 MHz $^1$H NMR spectroscopy). Conducting the reaction for only 3 h had no effect on the yield, but it furnished **80** as a 5:1 mixture of *E*- and *Z*-isomers and **81** as a 4:5 mixture of *E*- and *Z*-isomers, respectively.[9] Evidently, equilibration of the product mixture to the thermodynamically favored isomer takes place upon prolonged contact time. Desulfonylation with Zn dust in refluxing THF afforded olefins **27** and **82** as the *E*-isomers only.

The union of a second molecule of **71** with intermediates **27** and **82** (Scheme 16) was realized under Fujita conditions,[34] since the anion of **71** is insufficiently nucleophilic to condense directly with esters. Accordingly, hydrolysis of **27**

(49) Selective formation of *Z*-olefins in the desulfonylation of vinylsulfones is documented; e.g.: Bremner, J.; Julia, M.; Launay, M.; Stacino, J.-P. *Tetrahedron Lett*. **1982**, *23*, 3265. See also ref 36a and literature cited therein.

**SCHEME 16**

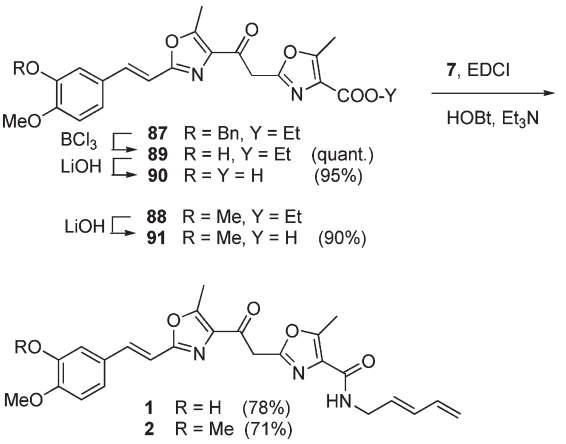



and **82** with LiOH provided the corresponding acids **83** and **84** (Scheme 16). The latter were not thoroughly characterized. Instead, they were directly converted into α-sulfonylketones **85** and **86** by sequential reaction with EtOCOCl and $Et_3N$ (activation as mixed anhydrides), followed by the sodium salt of **71**, which had been prepared separately by deprotonation of the parent compound with NaH. The resulting **85** and **86** existed as mixtures of keto (shown) and enol tautomers in a ratio that appeared to be a function of solvent, moisture content, time and pH. Inferior results were obtained in this step when the acids were activated as the corresponding acyl chlorides ($SOCl_2$) or imidazole derivatives (CDI).[50] Desulfonylation of **85** and **86** was once again best carried out by treatment with $Zn/NH_4Cl$.

Contrary to the case of compounds **72**, **73**, and **75**, the desulfonylation of α-sulfonyl ketones by this method finds precedent in the work of Holton.[51] Reductants like Na/Hg amalgam or $SmI_2$ performed poorly in the present case. Ketones **87** and **88** existed in equilibrium with the relative enols, the proportion of which once again varied as a function of solvent, temperature, etc. The same was true also for later compounds incorporating these fragments, including the final **1** and **2**.

The synthesis was completed uneventfully as delineated in Scheme 17. Compound **87** was debenzylated ($BCl_3$) to afford ester **89**. The latter as well as its relative **88** underwent saponification to the corresponding acids, **90** and **91**, which were condensed with dienic amine **7**[52] in the presence of EDCI. This delivered fully synthetic siphonazoles, which existed mostly as the keto tautomers (NMR),[53] and that

**SCHEME 17**




produced $^1H$ and $^{13}C$ NMR spectra[54] identical to those recorded in the literature for the natural products.[1,5]

The biological evaluation[55] of synthetic siphonazoles revealed no antibiotic activity against the following pathogens: *Candida albicans*, *Acinetobacter junii*, *Citrobacter freundii*, *Bacillus cereus*, *Comamonas testosteroni*, *Enterobacter cloacae*, *Escherichia coli* 0157:H7, *Klebsiella oxitoca*, *Mycobacterium neoaurum*, *Pseudomonas aeruginosa*, *Pseudomonas cepacia*, and *Staphylococcus aureus*. Tests were carried out at a concentration of 10 μg/mL (in accord with the NIH standard; equivalent to $2.2 \times 10^{-5}$ M for **1** and $2.1 \times 10^{-5}$ M for **2**) using both the paper disk and the soft agar techniques. Compounds **1** and **2** were also tested for cytotoxic activity using the following cell lines: human colon adenocarcinoma (Caco-2), human hepatocellular carcinoma (hepG2), human prostate adenocarcinoma (PC3), human breast carcinoma (HTB-129), human acute T-cell leukemia (TIB-152), mouse lymphoma (ML), and Chinese hamster ovarian cancer (CHO). Both **1** and **2** exhibited cytotoxic activity against human breast carcinoma (HTB-129) and, especially, human acute T-cell leukemia (TIB-152) cells, but they proved to be inactive against hepatocellular carcinoma (hepG2), prostate cancer (PC3), colon adenocarcinoma (Caco-2), and Chinese hamster ovarian cancer (CHO) cell lines at the same concentrations. The lack of activity toward hepG2 cells could be a promising feature, indicating a probable lack of toxicity to normal human liver cells. Compound **1** was also cytotoxic against the mouse lymphoma cell line.

As apparent from Figures 3 and 4, siphonazole A, **1**, is significantly more cytotoxic than its congener **2**. Thus, compound **1** induced cell death in human TIB-152 leukemia and mouse lymphoma cells with an $IC_{50}$ value equal to 16 μg/mL ($3.5 \times 10^{-5}$ M) and in breast carcinoma HTB-129 with an $IC_{50}$ of 20 μg/mL ($4.2 \times 10^{-5}$ M). Furthermore, compound **1** exhibited a good dose−response curve against human acute T cell leukemia TIB-152 (Figure 4). In conclusion, the present synthesis of siphonazoles served as a vehicle to develop the chemistry of sulfone **71** as an oxazole conjunctive agent. The results described herein resolve the difficulties previously experienced with the use of a similar oxazolyl sulfone and provide a solution to the long-standing problem of generating nucleophilic synthon **11**. As indicated

(50) (a) Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351. (b) Review: Armstrong, A.; Li, W. N,N'-Carbonyldiimidazole. in *e-EROS Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 2006. http://www.mrw.interscience.wiley.com/eros/articles/rc024/frame.html; DOI 10.1002/047084289X.rc024.pub2.

(51) Holton, R. A.; Crouse, D. J.; Williams, A. D.; Kennedy, R. M. *J. Org. Chem.* **1987**, *52*, 2317.

(52) Grieco, P. A.; Galatsis, P.; Spohn, R. F. *Tetrahedron* **1986**, *42*, 2847. See also ref 5.

(53) The enol tautomer of **1**−**2** was recognizable from a characteristic $^{13}C$ signal at 85 ppm. See the spectra provided in the Supporting Information.

(54) The appearance of the $^1H$ NMR spectrum of **1** depended strongly on the nature of the solvent used. Thus, a spectrum recorded in $CDCl_3$ solution differed significantly from one obtained from acetone-$d_6$. Published spectra of **1** were recorded in the latter solvent. Accordingly, the spectra of **1** shown in the Supporting Information were also obtained from acetone-$d_6$ solutions.

(55) Relevant experimental protocols are provided as Supporting Information.

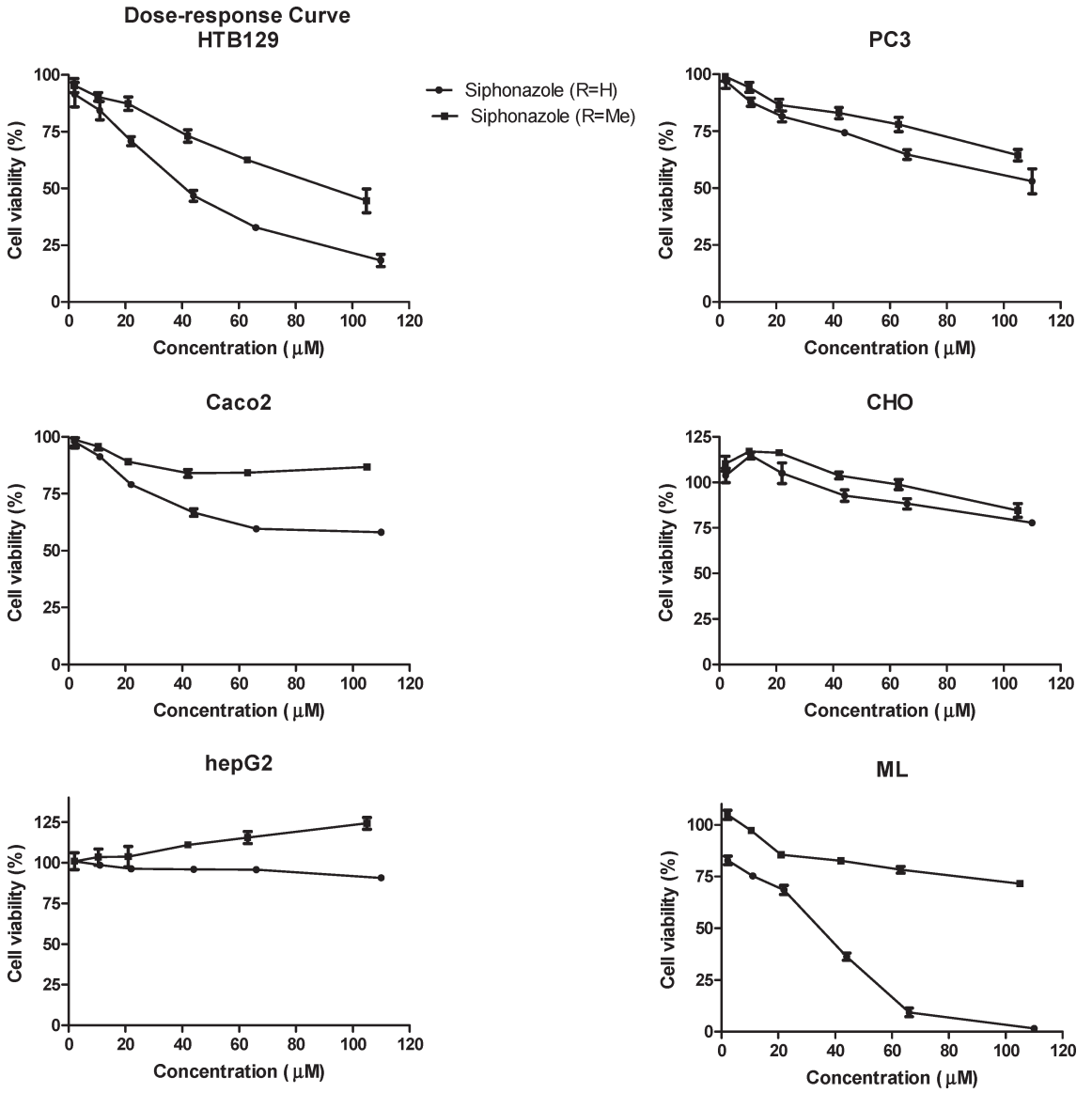



**FIGURE 3.** Cytotoxic effect of synthetic **1** and **2** on human breast carcinoma (HTB-129), prostate cancer (PC3), colon adenocarcinoma (Caco-2), Chinese hamster ovarian cancer (CHO), human hepatocellular carcinoma (hepG2), and mouse lymphoma. Values are means ± SEM of two independent experiments, each performed in triplicate.

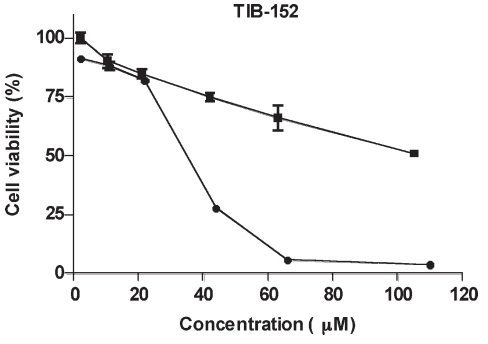
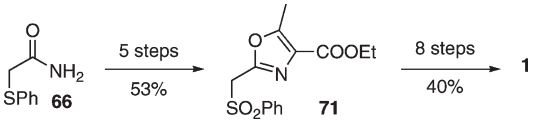



**FIGURE 4.** Dose−response curve of human acute T cell leukemia (TIB-152) against siphonazoles 1(-●-) and 2(-■-). Values are means ± SEM of two independent experiments, each performed in triplicate.

in Scheme 18, siphonazole A was reached in eight steps and in 40% yield from **71**, which in turn may be prepared in five

**SCHEME 18**




steps and 53% yield from **66**. Synthetic siphonazoles were devoid of antimicrobial activity, but they showed appreciable and selective cytotoxicity against human breast carcinoma HTB-129 and acute T-cell leukemia TIB-152, with **1** being significantly more active than **2**.

## Experimental Section

**Experimental Protocols.**[56] Unless otherwise stated, $^{1}$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded at room

(56) Additional details are provided as Supporting Information.

temperature from $CDCl_3$ solutions. Chemical shifts are reported in parts per million (ppm) on the $\delta$ scale, and coupling constants, $J$, are in hertz (Hz). Multiplicities are reported as "s" (singlet), "d" (doublet), "dd" (doublet of doublets), "ddd" (doublet of doublets of doublets), "t" (triplet), "q" (quartet), "m" (multiplet), and further qualified as "app" (apparent) and "br" (broad). Flash chromatography was performed on 230−400 mesh silica gel.

**Ethyl 2-Hydroxy-2-(2-(phenylthio)acetamido)acetate (67).** A solution of 2-(phenylthio)acetamide (3.3 g, 20.0 mmol) and ethyl glyoxylate (5.2 mL, 50% in toluene, 26.0 mmol) in THF (30 mL) was refluxed overnight, whereupon TLC (30% EtOAc/hexanes) indicated complete conversion. The mixture was concentrated in vacuo, and the residue was triturated with $Et_2O$ and then with 30% EtOAc in hexanes to yield **67** as a white solid (4.6 g, 86%). Mp: 104−105 °C. IR: 3326, 1743, 1660. $^1$H: 8.07 (d, 1H, $J$ = 7.8), 7.36−7.14 (m, 5H), 5.55 (d, 1H, $J$ = 7.8), 5.03 (br, 1H), 4.17 (q, 2H, $J$ = 7.1), 3.61 (s, 2H), 1.29 (t, 3H, $J$ = 7.1); $^{13}$C: 169.5, 169.4, 134.4, 129.2, 129.0, 127.0, 72.0, 62.5, 37.8, 14.0. HRMS: calcd for $C_{12}H_{15}NO_4SNa$ $[M + Na]^+$ 292.0619, found 292.0613.

**Ethyl 2-Chloro-2-(2-(phenylthio)acetamido)acetate (68).** A solution of **67** (4.0 g, 15.0 mmol) and $SOCl_2$ (3.3. mL, 45.0 mmol) in $CH_2Cl_2$ (30 mL) was stirred at rt overnight, and then it was concentrated in vacuo. The residue was dried under high vacuum for several hours to afford **68** as a yellow foam (4.3 g, quant), which was used for next step without purification. $^1$H: 7.97 (d, 1H, $J$ = 9.8), 7.40−7.22 (m, 5H), 6.20 (d, 1H, $J$ = 9.8), 4.31 (q, 2H, $J$ = 7.2), 3.68 (s, 2 H), 1.33 (t, 3H, $J$ = 7.2).

**Ethyl 5-Methyl-2-(phenylthiomethyl)oxazole-4-carboxylate (70).** Commercial *n*-BuLi (1.6 M in hexanes, 7.9 mL, 12.6 mmol) was added to a solution of trimethylsilylacetylene (1.8 mL, 12.6 mmol) in THF (16 mL) at −78 °C. The mixture was stirred at −78 °C for 20 min, and then dimethylaluminum chloride (1.0 M in hexanes, 12.6 mL, 12.6 mmol) was added. The mixture was stirred at 0 °C for 1 h, and then a solution of **68** (3.4 g, 12.0 mmol) in THF (16 mL) was added slowly. The resulting mixture was stirred at rt for 3 h and then diluted with $CHCl_3$, filtered through silica gel (elution with EtOAc), and concentrated in vacuo. The residue was redissolved in THF/$H_2O$ (15 mL/15 mL) and treated with $NaHCO_3$ (2.0 g, 24.0 mmol) at rt overnight. The reaction mixture was diluted with $H_2O$ (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with $H_2O$ (30 mL) and brine (30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a crude oil, which was further dissolved in EtOH (20 mL) and treated with CsF (2.0 g, 13.2 mmol). The resulting mixture was stirred at rt for 6 h, and the solvent was removed in vacuo. The residue was diluted with $H_2O$ (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with $H_2O$ (30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (30% EtOAc/hexanes) afforded **70** as a yellow oil (2.0 g, 61%). IR: 1713. $^1$H: 7.42−7.37 (m, 2H), 7.32−7.20 (m, 3H), 4.36 (q, 2H, $J$ = 7.1), 4.17 (s, 2H), 2.57 (s, 3H), 1.37 (t, 3H, $J$ = 7.1). $^{13}$C: 162.1, 158.9, 156.9, 134.3, 130.6, 129.1, 127.7, 127.3, 60.9, 31.0, 14.4, 12.0. HRMS: calcd for $C_{14}H_{15}NO_3SNa$ $[M + Na]^+$ 300.0670, found 300.0667.

**Ethyl 5-Methyl-2-(phenylsulfonylmethyl)oxazole-4-carboxylate (71).** Solid *m*-CPBA (7.16 g, 50−60% purity, ~41.5 mmol) was added in portions to a cold (0 °C; ice bath) solution of **70** (2.3 g, 8.3 mmol) in $CH_2Cl_2$. The ice bath was removed, and the suspension was stirred at rt for 6 h; The suspension was sequentially washed with saturated $NaHCO_3$ solution (3 × 30 mL), $H_2O$ (30 mL), and brine (30 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (30% EtOAc/hexanes) to yield **71** as a white solid (2.4 g, 94%). Mp: 154−155 °C. IR: 1717. $^1$H: 7.86−7.78 (m, 2H), 7.73−7.65 (m, 1H), 7.60−7.52 (m, 2H), 4.55 (s, 2H), 4.36 (q, 2H, $J$ = 7.1), 2.62 (s, 3H), 1.37 (t, 3H, $J$ = 7.1). $^{13}$C: 161.6, 158.2, 151.0, 137.9, 134.5, 129.4, 128.6, 128.4, 61.1, 55.5, 14.3, 12.1. HRMS: calcd for $C_{14}H_{15}NO_5SNa$ $[M + Na]^+$ 332.0569, found 332.0576.

**(*E*)-Ethyl 2-(2-(3-(Benzyloxy)-4-methoxyphenyl)-1-(phenylsulfonyl)vinyl)-5-methyloxazole-4-carboxylate (80).** A solution of **71** (93 mg, 0.3 mmol), 3-(benzyloxy)-4-methoxybenzaldehyde (**79**, 73 mg, 0.3 mmol), $Et_3N$ (0.2 mL, 1.5 mmol), and $TiCl_4$ (1.0 M in $CH_2Cl_2$, 1.5 mL, 1.5 mmol) in THF (3 mL) was stirred at rt for 6 h, and then the mixture was quenched with saturated aq $NH_4Cl$ (10 mL) and extracted with EtOAc (15 mL). The organic layer was sequentially washed with $H_2O$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was filtered through a plug of silica gel (50% EtOAc/hexanes), and the eluate was concentrated to afford **80** (165 mg, 99%) as a yellow solid. Mp: 147−149 °C. IR: 1721, 1321, 1150. $^1$H: 8.08 (s, 1H), 7.89−7.86 (m, 2H), 7.63−7.58 (m, 1H), 7.53−7.48 (m, 2H), 7.34−7.27 (m, 5H), 6.96−6.93 (m, 2H), 6.83 (d, 1H, $J$ = 9.0), 4.91 (s, 2H), 4.32 (q, 2H, $J$ = 7.1), 3.87 (s, 3H), 2.57 (s, 3H), 1.32 (t, 3H, $J$ = 7.1). $^{13}$C: 161.7, 157.7, 153.0, 152.1, 148.1, 146.2, 139.6, 136.2, 133.7, 129.1, 128.8, 128.6, 128.5, 128.0, 127.2, 126.8, 125.8, 124.0, 114.1, 111.3, 70.6, 61.1, 56.0, 14.3, 12.2. HRMS: calcd for $C_{29}H_{27}NO_7SNa$ $[M + Na]^+$ 556.1406, found 556.1418.

**(*E*)-Ethyl 2-(2-(3,4-Dimethoxyphenyl)-1-(phenylsulfonyl)-vinyl)-5-methyloxazole-4-carboxylate (81).** This compound was prepared from **71** (558 mg, 1.8 mmol) and 3,4-dimethoxybenzaldehyde (**6**, 300 mg, 1.8 mmol) following the procedure described above for **80**. Yellow solid, mp 135−137 °C, 87% after chromatography (50% EtOAc/hexanes). $^1$H: 8.12 (s, 1H), 7.90 (d, 2H, $J$ = 7.4), 7.64−7.59 (m, 1H), 7.55−7.49 (m, 2H), 6.97 (dd, 1H, $J$ = 8.3, 1.4), 6.88 (d, 1H, $J$ = 1.4), 6.82 (d, 1H, $J$ = 8.3), 4.35 (q, 2H, $J$ = 7.1), 3.87 (s, 3H), 3.68 (s, 3H), 2.61 (s, 3H), 1.36 (t, 3H, $J$ = 7.1). $^{13}$C: 161.7, 157.6, 152.4, 152.2, 148.9, 146.1, 139.6, 133.6, 129.0, 128.8, 128.6, 126.6, 125.9, 124.2, 111.8, 110.8, 61.1, 56.0, 55.6, 14.3, 12.1. HRMS: calcd for $C_{23}H_{23}NO_7SNa$ $[M + Na]^+$ 480.1093, found 480.1103.

**(*E*)-Ethyl 2-(3-(Benzyloxy)-4-methoxystyryl)-5-methyloxazole-4-carboxylate (27).** A suspension of **80** (160 mg, 0.3 mmol), zinc dust (1.2 g, 18.0 mmol), and saturated aq $NH_4Cl$ (8 mL) in THF (8 mL) was refluxed for 6 h, and then it was cooled to rt and filtered through Celite. The filtrate was diluted with $H_2O$ (10 mL) and extracted with EtOAc (15 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by flash chromatography (30% EtOAc/hexanes) afforded **27** as a yellow solid (88 mg, 75% over two steps). Mp: 107−109 °C. IR: 1712. $^1$H: 7.48−7.28 (m, 6H), 7.09 (dd, 1H, $J$ = 8.3, 1.9), 7.05 (d, 1H, $J$ = 1.9), 6.90 (d, 1H, $J$ = 8.3), 6.68 (d, 1H, $J$ = 16.4), 5.19 (s, 2H), 4.40 (q, 2H, $J$ = 7.1), 3.92 (s, 3H), 2.66 (s, 3H), 1.40 (t, 3H, $J$ = 7.1). $^{13}$C: 162.4, 159.6, 155.7, 151.0, 148.3, 136.7, 136.7, 128.7, 128.6, 128.1, 128.0, 127.2, 121.7, 111.9, 111.6, 111.1, 71.0, 61.0, 56.1, 14.4, 12.1. HRMS: calcd for $C_{23}H_{23}NO_5Na$ $[M + Na]^+$ 416.1474, found 416.1468.

**(*E*)-Ethyl 2-(3,4-Dimethoxystyryl)-5-methyloxazole-4-carboxylate (82).** This compound was prepared from **81** following the procedure described above for **27**. The product, 97% yield, was obtained as a yellow solid. Mp: 79−81 °C. IR: 1711. $^1$H: 7.43 (d, 1H, $J$ = 16.4), 7.05 (dd, 1H, $J$ = 8.3, 1.6), 7.01 (d, 1H, $J$ = 1.6), 6.89 (d, 1H, $J$ = 8.3), 6.75 (d, 1H, $J$ = 16.4), 4.37 (q, 2H, $J$ = 7.1), 3.89 (s, 3H), 3.88 (s, 3H), 2.64 (s, 3H), 1.38 (t, 3H, $J$ = 7.1). $^{13}$C: 162.4, 159.6, 155.7, 150.4, 149.2, 136.7, 128.6, 128.2, 121.2, 111.2, 111.1, 109.0, 60.9, 55.9, 55.8, 14.4, 12.1. HRMS: calcd for $C_{17}H_{20}NO_5$ $[M + H]^+$ 318.1341, found 318.1346.

**(*E*)-2-(3-(Benzyloxy)-4-methoxystyryl)-5-methyloxazole-4-carboxylic acid (83).** A suspension of **27** (95 mg, 0.24 mmol) and LiOH (14 mg, 0.33 mmol) in THF/$H_2O$ (2 mL/2 mL) was stirred at rt overnight, whereupon TLC (50% EtOAc/hexanes) indicated complete conversion. The mixture was diluted with $H_2O$ (10 mL), acidified to pH = 3 with aq 1 N HCl, and then extracted with

EtOAc (3 × 10 mL). The combined extracts were sequentially washed with $H_2O$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to afford **83** (81 mg, 92%) as a white solid. Mp: 185−186 °C. IR: 3052, 2947, 1689. $^1$H ($CD_3OD$): 7.52−7.28 (m, 6H), 7.26 (d, 1H, $J$ = 1.3), 7.15 (dd, 1H, $J$ = 8.3, 1.3), 6.98 (d, 1H, $J$ = 8.3), 6.74 (d, 1H, $J$ = 16.3), 5.14 (s, 2H), 3.87 (s, 3H), 2.64 (s, 3H). $^{13}$C ($CD_3OD$): 163.4, 160.0, 155.7, 151.4, 148.4, 137.4, 137.1, 128.2, 128.1, 127.6, 127.4, 122.0, 112.0, 111.6, 109.9, 70.7, 55.0, 10.6. HRMS: calcd for $C_{21}H_{19}NO_5Na$ $[M + Na]^+$ 388.1161, found 388.1166.

**(*E*)-2-(3,4-Dimethoxystyryl)-5-methyloxazole-4-carboxylic Acid (84).** The title compound was prepared from **82** (480 mg, 1.5 mmol) following the procedure described above for **83**. The product was obtained as a white solid (390 mg, 89%). Mp 222−224 °C. IR: 3055, 2835, 1694. $^1$H ($CD_3OD$): 7.49 (d, 1H, $J$ = 16.4), 7.23 (s, 1H), 7.16 (d, 1H, $J$ = 8.2), 6.98 (d, 1H, $J$ = 8.2), 6.82 (d, 1H, $J$ = 16.4), 3.90 (s, 3H), 3.87 (s, 3H), 2.66 (s, 3H). $^{13}$C ($CD_3OD$): 163.4, 160.0, 155.7, 150.7, 149.4, 137.5, 128.2, 121.6, 111.3, 109.9, 109.4, 55.1, 55.0, 10.6. HRMS: calcd for $C_{15}H_{14}NO_5$ ($[M - H]^-$) 288.0872, found 288.0870.

**(*E*)-Ethyl 2-(2-(2-(3-(Benzyloxy)-4-methoxystyryl)-5-methyloxazol-4-yl)-2-oxo-1-(phenylsulfonyl)ethyl)-5-methyloxazole-4-carboxylate (85).** A solution of **71** (495 mg, 1.60 mmol) and NaH (211 mg, 60% dispersion in mineral oil, 5.30 mmol) in THF (10 mL) was stirred at −10 °C for 1 h, and then it was cooled to −25 °C. In parallel, a solution of **83** (643 mg, 1.80 mmol), EtOCOCl (185 μL, 1.94 mmol), and $Et_3N$ (270 μL, 1.94 mmol) in THF (10 mL) was stirred at 0 °C for 1 h, and then it was filtered through a plug of Celite to remove precipitated $Et_3N \cdot HCl$. The filtrate, presumed to contain the mixed anhydride of **83**, was added dropwise to the first solution. The resulting mixture was stirred at −25 °C for 8 h, and then it was quenched with saturated aq $NH_4Cl$ (30 mL) and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo to yield **85** (1.12 g) as a yellow foam, which was used in next step without further purification. $^1$H: 7.86−7.80 (m, 2H), 7.70−7.28 (m, 9H), 7.14−7.00 (m, 3H), 6.91 (d, 1H, $J$ = 8.2), 6.51 (d, 1H, $J$ = 16.3), 5.21 (s, 2H), 4.35 (q, 2H, $J$ = 7.1), 3.93 (s, 3H), 2.65 (s, 3H), 2.64 (s, 3H), 1.36 (t, 3H, $J$ = 7.1). MS: 679.3 $[M + Na]^+$.

**(*E*)-Ethyl 2-(2-(2-(3,4-Dimethoxystyryl)-5-methyloxazol-4-yl)-2-oxo-1-(phenylsulfonyl)ethyl)-5-methyloxazole-4-carboxylate: Mixture of Keto and Enol Tautomers (86).** The compound was prepared from **71** (310 mg, 1.0 mmol) and **84** (318 mg, 1.1 mmol) following the procedure described above for **85**. The product, a yellow foam (720 mg), was obtained as a 5:4 mixture of keto and enol tautomers, and it was used in next step without further purification. $^1$H keto tautomer: 7.85−7.82 (m, 2H), 7.72−7.46 (m, 3H), 7.40 (d, 1H, $J$ = 16.3), 7.12−7.08 (m, 1H), 7.06 (d, 1H, $J$ = 1.7), 6.90 (d, 1H, $J$ = 8.3), 6.62 (d, 1H, $J$ = 16.3), 4.55 (s, 1H), 4.33 (q, 2H, $J$ = 7.1), 3.96 (s, 3H), 3.93 (s, 3H), 2.66 (s, 3H), 2.64 (s, 3H), 1.36 (t, 3H, $J$ = 7.1); enol tautomer: 7.83−7.79 (m, 2H), 7.72−7.46 (m, 3H), 7.43 (d, 1H, $J$ = 16.3), 7.12−7.08 (m, 1H), 7.06 (d, 1H, $J$ = 1.7), 7.03 (s, 1H), 6.89 (d, 1H, $J$ = 8.3), 6.70 (d, 1H, $J$ = 16.3), 4.37 (q, 2H, $J$ = 7.1), 3.93 (s, 3H), 3.92 (s, 3H), 2.69 (s, 3H), 2.61 (s, 3H), 1.36 (t, 3H, $J$ = 7.1). MS: 581.2 $[M + H]^+$.

**(*E*)-Ethyl 2-(2-(2-(3-(Benzyloxy)-4-methoxystyryl)-5-methyloxazol-4-yl)-2-oxoethyl)-5-methyloxazole-4-carboxylate: Mixture of Keto and Enol Tautomers (87).** A solution of **85** (1.1 g, 1.7 mmol), zinc dust (6.8 g, 10.5 mmol), and saturated aq $NH_4Cl$ (100 mL) in THF (50 mL) was refluxed for 6 h, and then it was cooled to rt and filtered through Celite. The filtrate was concentrated in vacuo, diluted with $H_2O$ (50 mL), and then extracted with $CH_2Cl_2$ (100 mL). The extract was washed with brine (50 mL), dried ($MgSO_4$), and evaporated. Purification of the crude (flash chromatography, 50% EtOAc/hexanes/$Et_3N$) afforded **87** (yellow solid, 0.66 g, 80% over two steps) as a 1:3 mixture of keto and enol tautomers. IR: 1736, 1650. $^1$H keto tautomer: 7.50−7.28 (m, 6H), 7.14−7.08 (m, 2H), 6.92 (d, 1H, $J$ = 8.2), 6.68 (d, 1H, $J$ = 16.3), 5.19 (s, 2H), 4.50 (s, 2H), 4.38 (q, 2H, $J$ = 7.1), 3.93 (s, 3H), 2.65 (s, 3H), 2.64 (s, 3H), 1.39 (t, 3H, $J$ = 7.1); enol tautomer: 7.50−7.28 (m, 6H), 7.14−7.08 (m, 2H), 6.90 (d, 1H, $J$ = 8.9), 6.68 (d, 1H, $J$ = 16.3), 6.22 (s, 1H), 5.19 (s, 2H), 4.38 (q, 2H, $J$ = 7.1), 3.92 (s, 3H), 2.66 (s, 3H), 2.63 (s, 3H), 1.40 (t, 3H, $J$ = 7.1). $^{13}$C (mixture of tautomers): 189.4, 162.3, 162.0, 161.7, 159.6, 159.1, 157.7, 157.1, 156.4, 155.4, 153.3, 151.2, 150.9, 148.8, 148.4, 148.4, 137.1, 136.8, 136.7, 136.0, 134.4, 131.2, 128.6, 128.4, 128.0, 128.0, 127.9, 127.3, 127.3, 126.3, 121.8, 121.6, 111.9, 111.8, 111.7, 111.4, 110.8, 84.2, 71.0, 71.0, 60.8, 56.0, 39.6, 14.4, 14.3, 12.3, 12.2, 12.1, 12.0. HRMS: calcd for $C_{29}H_{29}N_2O_7$ $[M + H]^+$, 517.1975, found 517.1979.

**(*E*)-Ethyl 2-(2-(2-(3,4-Dimethoxystyryl)-5-methyloxazol-4-yl)-2-oxoethyl)-5-methyloxazole-4-carboxylate (88).** This compound was prepared from **86** (395 mg, 0.68 mmol) following the procedure described above for **87**, and it was obtained as a yellow oil (145 mg, 48%; keto tautomer only). IR: 1713, 1691. $^1$H: 7.45 (d, 1H, $J$ = 16.3), 7.09 (dd, 1H, $J$ = 8.2, 1.9), 7.07 (d, 1H, $J$ = 1.9), 6.89 (d, 1H, $J$ = 8.2), 6.75 (d, 1H, $J$ = 16.3), 4.50 (s, 2H), 4.38 (q, 2H, $J$ = 7.1), 3.93 (s, 3H), 3.92 (s, 3H), 2.66 (s, 3H), 2.63 (s, 3H), 1.38 (t, 3H, $J$ = 7.1). $^{13}$C: 189.4, 162.3, 159.1, 157.2, 156.4, 155.5, 150.5, 149.3, 137.2, 134.4, 129.4, 128.1, 121.5, 111.1, 110.8, 108.9, 60.9, 56.0, 55.9, 39.6, 14.4, 12.3, 12.1. HRMS: calcd for $C_{23}H_{25}N_2O_7$ ($[M + H]^+$) 441.1662, found 441.1657.

**(*E*)-Ethyl 2-(2-(2-(3-Hydroxy-4-methoxystyryl)-5-methyloxazol-4-yl)-2-oxoethyl)-5-methyloxazole-4-carboxylate (89).** A cold (−78 °C) solution of **87** (100 mg, 0.19 mmol) and $BCl_3$ (1.0 M in $CH_2Cl_2$, 1.0 mL, 1.0 mmol) in $CH_2Cl_2$ (3 mL) was stirred for 30 min, and then it was warmed to rt and stirred for another 30 min. Water (5 mL) was added to quench the reaction, and the mixture was stirred for another 15 min and then extracted with $CH_2Cl_2$ (10 mL). The extract was washed with brine (5 mL), dried ($MgSO_4$), and evaporated in vacuo to yield **89** as a yellow solid (85 mg, quant), which was used in next step without further purification. IR: 3211, 1716, 1691. $^1$H: 7.41 (d, 1H, $J$ = 16.3), 7.15 (d, 1H, $J$ = 2.0), 7.04 (dd, 1H, $J$ = 8.4, 2.0), 6.87 (d, 1H, $J$ = 8.4), 6.73 (d, 1H, $J$ = 16.3), 5.67 (s, 1H), 4.50 (s, 2H), 4.38 (q, 2H, $J$ = 7.1), 3.94 (s, 3H), 2.66 (s, 3H), 2.64 (s, 3H), 1.39 (t, 3H, $J$ = 7.1). $^{13}$C: 189.5, 162.3, 159.1, 157.1, 156.5, 155.5, 147.9, 145.9, 137.1, 134.4, 128.8, 127.9, 120.7, 112.4, 111.2, 110.7, 60.8, 56.0, 39.6, 14.4, 12.3, 12.1. HRMS: calcd for $C_{22}H_{22}N_2O_7Na$ $[M + Na]^+$ 449.1325, found 449.1314.

**(*E*)-2-(2-(2-(3-Hydroxy-4-methoxystyryl)-5-methyloxazol-4-yl)-2-oxoethyl)-5-methyloxazole-4-carboxylic Acid (90).** A suspension of **89** (84 mg, 0.20 mmol) and LiOH (28 mg, 0.65 mmol) in THF/$H_2O$ (3 mL/3 mL) was stirred at rt overnight, whereupon TLC (50% EtOAc/hexanes) indicated complete conversion. The solvent was removed in vacuo; the residue was diluted with $H_2O$ (10 mL), then the solution was acidified to pH = 3 with aq 1 N HCl. The mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), and the combined extracts were washed with $H_2O$ (10 mL), dried ($MgSO_4$), and concentrated in vacuo to afford **90** (74 mg, 95%) as a yellow solid. Mp: 186−188 °C. IR: 3407, 1712, 1690. $^1$H: 7.41 (d, 1H, $J$ = 16.1), 7.15 (s, 1H), 7.04 (d, 1H, $J$ = 8.3), 6.87 (d, 1H, $J$ = 8.3), 6.73 (d, 1H, $J$ = 16.1), 4.51 (s, 2H), 3.93 (s, 3H), 2.66 (s, 6H). $^{13}$C: 189.2, 164.6, 159.2, 158.1, 156.7, 155.6, 148.0, 145.9, 137.2, 134.4, 128.8, 127.2, 120.7, 112.4, 111.1, 110.7, 56.0, 39.5, 12.4, 12.1. HRMS: calcd for $C_{20}H_{17}N_2O_7$ $[M - H]^-$ 397.1036, found 397.1028.

**(*E*)-2-(2-(2-(3,4-Dimethoxystyryl)-5-methyloxazol-4-yl)-2-oxoethyl)-5-methyloxazole-4-carboxylic Acid (91).** This compound was prepared from **88** (95 mg, 0.22 mmol) following the procedure described above for **90**. The product was obtained as a yellow solid (80 mg, 90%). Mp: 168−170 °C. IR: 2922, 1694, 1660. $^1$H: 7.46 (d, 1H, $J$ = 16.3), 7.10 (dd, 1H, $J$ = 8.2, 1.8), 7.08 (d, 1H, $J$ = 1.8), 6.89 (d, 1H, $J$ = 8.2), 6.77 (d, 1H, $J$ = 16.3), 4.51 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 2.67 (s, 3H), 2.66 (s, 3H). $^{13}$C: 189.1, 164.9, 159.2, 158.2, 156.7, 155.6, 150.5, 149.3, 137.2, 134.4, 128.1,

127.2, 121.5, 111.1, 110.8, 108.9, 56.0, 55.9, 39.5, 12.4, 12.1. HRMS: calcd for $C_{21}H_{19}N_2O_7$ $[M - H]^-$ 411.1192, found 411.1198.

**Siphonazole A (1).** A solution of **90** (20.0 mg, 0.05 mmol), (*E*)-penta-2,4-dien-1-ylamine (9.1 mg, 0.11 mmol), EDCI (21.0 mg, 0.11 mmol), HOBt (15.0 mg, 0.11 mmol), and $Et_3N$ (15.3 $\mu$L, 0.11 mmol) in $CH_2Cl_2$ (2 mL) was stirred at rt overnight. The mixture was then quenched with $H_2O$ (5 mL) and extracted with EtOAc (10 mL). The extract was washed with $H_2O$ (10 mL), dried ($MgSO_4$), and evaporated. Purification of the residue by flash chromatography (70% EtOAc/hexanes) afforded **1** as a yellow solid (18 mg, 78%; mostly keto form). IR: 3399, 1690. $^1$H (keto tautomer, acetone-$d_6$): 7.83 (s, 1H), 7.65−7.52 (m, 1H), 7.47 (d, 1H, $J$ = 16.4), 7.23 (d, 1H, $J$ = 2.1), 7.16 (dd, 1H, $J$ = 8.3, 2.1), 7.01 (d, 1H, $J$ = 8.3), 6.85 (d, 1H, $J$ = 16.4), 6.45−6.31 (m, 1H), 6.28−6.18 (m, 1H), 5.82 (dt, 1H, $J$ = 15.0, 6.0), 5.21−5.15 (m, 1H), 5.05−5.02 (m, 1H), 4.44 (s, 2H), 4.04−4.00 (m, 2H), 3.91 (s, 3H), 2.65 (s, 3H), 2.60 (s, 3H). $^{13}$C (acetone-$d_6$): 190.1, 162.0, 160.0, 156.8, 155.9, 153.8, 150.0, 147.8, 138.2, 137.6, 135.3, 132.7, 131.9, 130.5, 129.4, 121.4, 117.0, 113.9, 112.4, 111.5, 56.3, 40.7, 40.0, 12.2, 11.5. HRMS: calcd for $C_{25}H_{25}N_3O_6Na$ $[M + Na]^+$ 486.1641, found 486.1639.

**Siphonazole B (2).** The title compound was prepared from **91** (21 mg, 0.05 mmol) following the procedure described for **1**. The product was obtained as a yellow solid (17 mg, 71%, mostly keto form). IR: 1690, 1659. $^1$H (keto tautomer, acetone-$d_6$): 7.56 (br, 1H), 7.50 (d, 1H, $J$ = 16.4), 7.40 (d, 1H, $J$ = 2.0), 7.23 (dd, 1H, $J$ = 8.3, 2.0), 7.01 (d, 1H, $J$ = 8.3), 6.95 (d, 1H, $J$ = 16.4), 6.44−6.32 (m, 1H), 6.26−6.19 (m, 1H), 5.82 (dt, 1H, $J$ = 15.1, 5.9), 5.21−5.15 (m, 1H), 5.05−5.02 (m, 1H), 4.44 (s, 2H), 4.05−4.00 (m, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 2.65 (s, 3H), 2.60 (s, 3H). $^{13}$C (acetone-$d_6$): 190.0, 161.9, 160.0, 156.8, 155.9, 153.8, 152.0, 150.7, 138.1, 137.6, 135.3, 132.7, 131.9, 130.5, 129.1, 122.7, 117.0, 112.5, 111.5, 110.5, 56.1, 56.1, 40.7, 40.0, 12.2, 11.5. HRMS: calcd for $C_{26}H_{27}N_3O_6Na$ $[M + Na]^+$ 500.1798, found 500.1787.

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**Supporting Information Available:** Experimental procedures and characterization data; hardcopy NMR ($^1$H and $^{13}$C) spectra. This material is available free of charge via the Internet at http://pubs.acs.org.