Total Synthesis of Dimethyl Sulfomycinamate†

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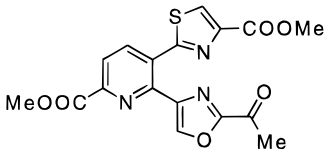
Dimethyl sulfomycinamate (**1**), a methanolysis product from the natural antibiotic sulfomycin I, is synthesized in 11 steps (Scheme 19). The chemistry of various pyridine, thiazole, and oxazole heterocycles and their coupling reactions under palladium catalysis are examined. The key transformations in the synthesis are the selective palladium-catalyzed coupling reactions on doubly activated pyridine **62** and the condensation reaction between bromo ketone **69** and amide **28** to form the oxazole moiety **76**. The first preparation of oxazole triflates is described, as are some of their chemical properties.

Introduction

In 1978, Abe et al.[1] reported the isolation of dimethyl sulfomycinamate from the methanolysis product of the antibiotic sulfomycin I. The structure of dimethyl sulfomycinamate was determined by X-ray crystallography to be **1**.



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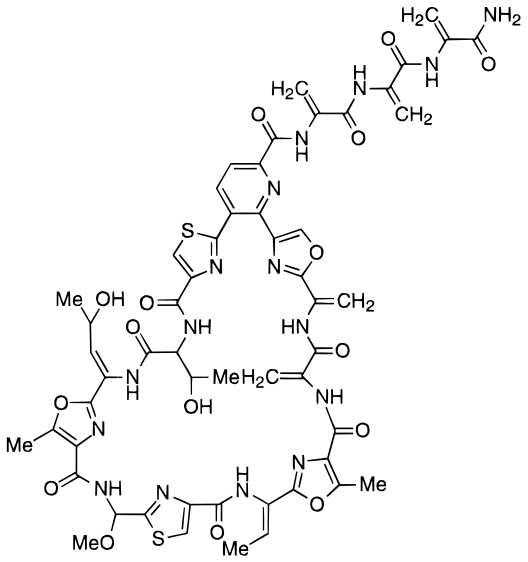
The sulfomycins were first isolated from *Streptomyces viridochromogenes* by Egawa et al.[2] They exhibit strong inhibitory activity against Gram-positive bacteria. The three main components isolated were given the names sulfomycin I, II, and III. After careful investigation of the fragments of various hydrolyses of sulfomycin I, combined with FAB-MS data and results from extensive NMR studies, the total structure of sulfomycin I was assigned as **2** by Abe et al.[3] in 1988. The structure features a sulfur-containing macrocycle linked by several peptide bonds. Sulfomycin I (**2**) represents a fast-growing family of compounds known as the thiopeptide antibiotics. Related structures have also been found in the antibiotics berninamycin A (**3**),[3,4] B, C, and D,[5] thioxamycin,[6] A10255,[7] geninthiocin,[8] thioactin,[9] thiotipin,[10] diazonamide A,[11] amythiamicin B, C, and D,[12] GE37468 A,[13] GE2270A,[14] nosiheptide,[15] and thiostreptone.[16] The pronounced antibiotic activity and the unique structure



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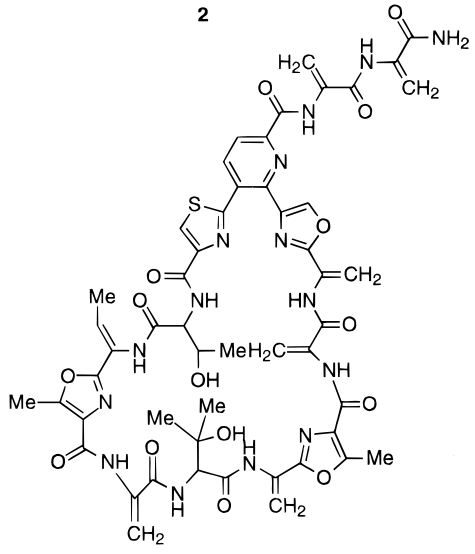

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† Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

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(1) Abe, H.; Takaishi, T.; Okuda, T. *Tetrahedron Lett.* **1978**, 2791.
(2) Egawa, Y.; Umino, K.; Tamura, Y.; Shimizu, M.; Kaneko, K.; Sakurazawa, M.; Awataguchi, S.; Okuda, T. *J. Antibiot.* **1969**, *22*, 12.
(3) Abe, H.; Kushida, K.; Shiobara, Y.; Kodama, M. *Tetrahedron Lett.* **1988**, *29*, 1401.
(4) Liesch, J. M.; Rinehart, K. L. *J. Am. Chem. Soc.* **1977**, *99*, 1645.
(5) Lau, R. C. M.; Rinehart, K. L. *J. Antibiot.* **1994**, *47*, 1466.
(6) Matsumoto, M.; Kawamura, Y.; Yasuda, Y.; Tanimoto, T.; Matsumoto, K.; Yoshida, T.; Shoji, J. *J. Antibiot.* **1989**, *42*, 1465.
(7) Debono, M.; Molloy, R. M.; Occolowitz, J. L.; Paschal, J. W.; Hunt, A. H.; Michel, K. H.; Martin, J. W. *J. Org. Chem.* **1992**, *57*, 5200.
(8) Yun, B.-S.; Hidaka, T.; Furihata, K.; Seto, H. *J. Antibiot.* **1994**, *47*, 969.
(9) Yun, B.-S.; Hidaka, T.; Furihata, K.; Seto, H. *J. Antibiot.* **1994**, *47*, 1541.
(10) Yun, B.-S.; Hidaka, T.; Furihata, K.; Seto, H. *Tetrahedron* **1994**, *50*, 11659.
(11) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303.
(12) Shimanaka, K.; Takahashi, Y.; Linuma, H.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 1153. Shimanaka, K.; Takahashi, Y.; Linuma, H.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 1145.
(13) Ferrari, P.; Colombo, L.; Stella, S.; Selva, E.; Zerilli, L. F. *J. Antibiot.* **1995**, *48*, 1304.
(14) Kettenring, J.; Colombo, L.; Ferrari, P.; Tavecchia, P.; Nebuloni, M.; Vekey, K.; Gallo, G. G.; Selva, E. *J. Antibiot.* **1991**, *44*, 702.

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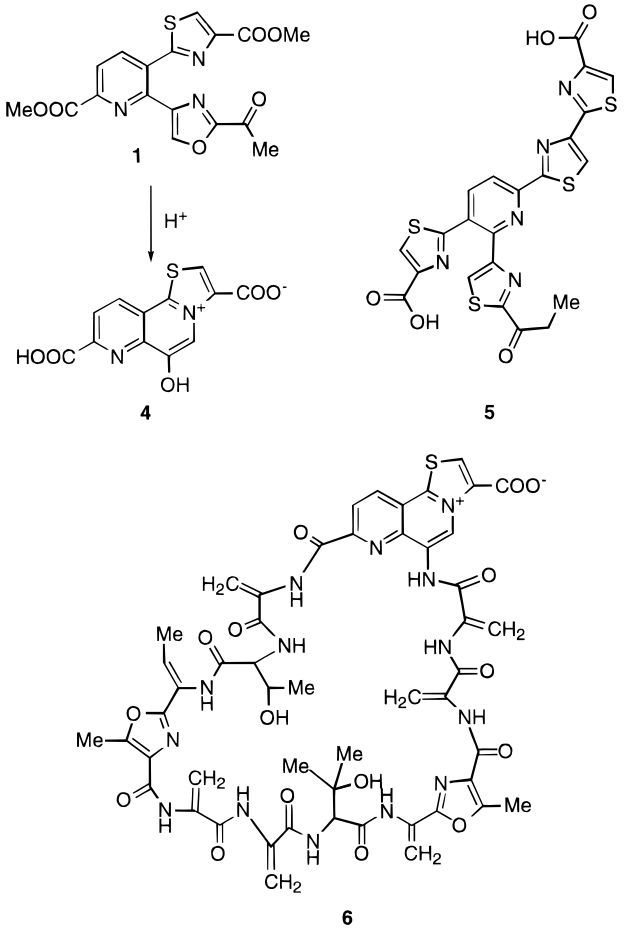
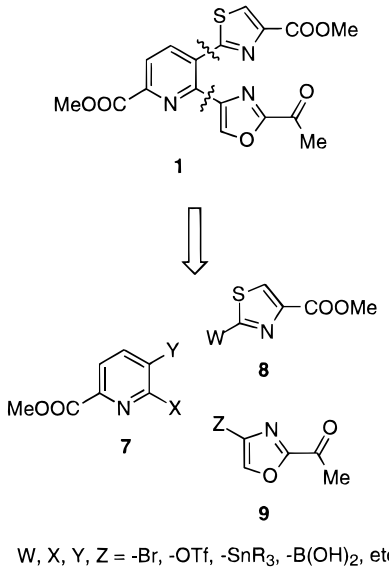
of this family attracted interest in its mode of action[17] and its biosynthesis.[15,16,18–20] Research on the synthesis of the thiopeptides is relatively limited; to our knowledge the only reports to date have been the syntheses of berninamycinic acid (**4**)[21a] and micrococcinic acid (**5**),[21b] both accomplished in this laboratory, and the synthesis of some small subunits of nosiheptide.[22] The synthesis of **4** was achieved in 1984.[21a] At that time, the structure of berninamycin A was proposed to be **6**.[4] However, the discovery by Abe[3] that both sulfomycin I (**2**) and dimethyl sulfomycinamate (**1**) give berninamycinic acid (**4**) under acidic hydrolysis conditions raised doubts about the proposed structure **6**. Further investigation led in 1988[3] to the total structure of sulfomycin I (**2**) and a revised structure for berninamycin A (**3**).



The synthesis of micrococcinic acid (**5**) was accomplished in 1991[21b] and demonstrated the versatility of palladium-catalyzed cross-coupling reactions[23] in the formation of heterobiaryl bonds.

Scheme 1. Retrosynthetic Analysis of Dimethyl Sulfomycinamate (1)



The central tris-heterocyclic unit of sulfomycin I (**2**) and berninamycin A (**3**), which gives dimethyl sulfomycinamate (**1**) upon methanolysis, also appears in several other thiopeptide antibiotics. Dimethyl sulfomycinamate (**1**) bears some resemblance to micrococcinic acid (**5**), but the presence of the oxazole ring in **1** clearly distinguishes it from **5** and renders **1** a synthetic challenge in its own right. We now report the first total synthesis of **1**.[24]

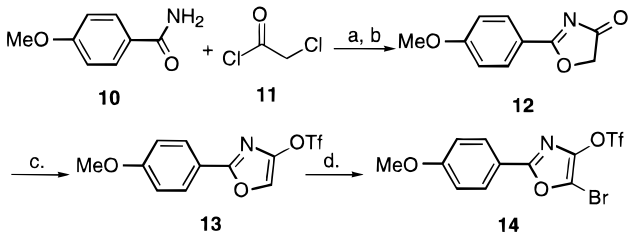
Results and Discussion

Since the synthesis of micrococcinic acid (**5**) was achieved by using palladium-catalyzed cross-coupling reactions for the formation of all the biaryl bonds, it was of interest to explore whether the same strategy could be extended to the construction of dimethyl sulfomycinamate (**1**). Disconnection of two biaryl bonds divides the target molecule (**1**) into three parts with about equal complexity (Scheme 1).

With respect to this strategy, pyridine and thiazole moieties were used in the micrococcinic acid (**5**)[21b] synthesis and in other syntheses[25–27] from this laboratory; consequently, in-house experience with their chemistry and behavior in palladium-catalyzed cross-coupling reactions was available. In contrast, however, oxazole moieties having structure **9** had not been reported in the literature. Moreover, at the outset of this project, there was only one example of biaryl bond formation between oxazole and pyridine units.[28] Although it may seem that the behavior of oxazole compounds should resemble that of their thiazole counterparts, the chemistry of oxazoles is much less developed compared to that of the thiazoles. Electrophilic substitution and functional group transfor-

(15) Mocek, U.; Knaggs, A. R.; Tsuchiya, R.; Nguyen, T.; Beale, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1993**, *115*, 7557.
(16) Mocek, U.; Zeng, Z.; O'Hagan, D.; Zhou, P.; Fan, L.-D. G.; Beale, J. M.; Floss, H. G. *J. Am. Chem. Soc.* **1993**, *115*, 7992.
(17) Reusser, H. *Biochemistry* **1969**, *8*, 3303.
(18) Pearce, C. J.; Rinehart, K. L. *J. Am. Chem. Soc.* **1979**, *101*, 5069.
(19) Lau, R. C. M.; Rinehart, K. L. *J. Am. Chem. Soc.* **1995**, *117*, 7606.
(20) Favret, M. E.; Paschal, J. W.; Elzey, T. K.; Boeck, L. D. *J. Antibiot.* **1992**, *45*, 1499.
(21) (a) Kelly, T. R.; Echavarren, A.; Chandrakumar, N. S.; Köksal, Y. *Tetrahedron Lett.* **1984**, *25*, 2127. (b) Kelly, T. R.; Jagoe, C. T.; Gu, Z. *Tetrahedron Lett.* **1991**, *32*, 4263.
(22) (a) Iwakawa, M.; Kobayashi, Y.; Ikuta, S.; Yoshimura, J. *Chem. Lett.* **1982**, 1975. (b) Koerber-Pié, K.; Massiot, G. *Synlett* **1994**, 759. (c) Umemura, K.; Tate, T.; Yamaura, M.; Yoshimura, J.; Yonezawa, Y.; Shin, C. *Synthesis* **1995**, 1423. (d) Shin, C.; Nakamura, Y.; Yamada, Y.; Yonezawa, Y.; Umemura, K.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3151. (e) Shin, C.; Yamada, Y.; Hayashi, K.; Yonezawa, Y.; Umemura, K.; Tanji, T.; Yoshimura, J. *Heterocycles* **1996**, *43*, 891.
(23) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
(24) For preliminary reports, see: (a) Kelly, T. R.; Lang, F. *Tetrahedron Lett.* **1995**, *36*, 5319. (b) Kelly, T. R.; Lang, F. *Tetrahedron Lett.* **1995**, *36*, 9293.
(25) Kelly, T. R.; Bowyer, M. C.; Bhaskar, K. V.; Bebbington, D.; Garcia, A.; Lang, F.; Kim, M. H.; Jette, M. P. *J. Am. Chem. Soc.* **1994**, *116*, 3657.
(26) Kelly, T. R.; Kim, M. H. *J. Org. Chem.* **1992**, *57*, 1593.
(27) Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024.
(28) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A; Pedrini, P. *Synthesis* **1987**, 693.

Scheme 2. Synthesis and Bromination of Oxazole Triflate 13[a]



[a] Reaction conditions: (a) 110 °C, neat; (b) NaH, DME; (c) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 5 h, 75%; (d) Br_2, benzene, rt, 1 h, 45%.

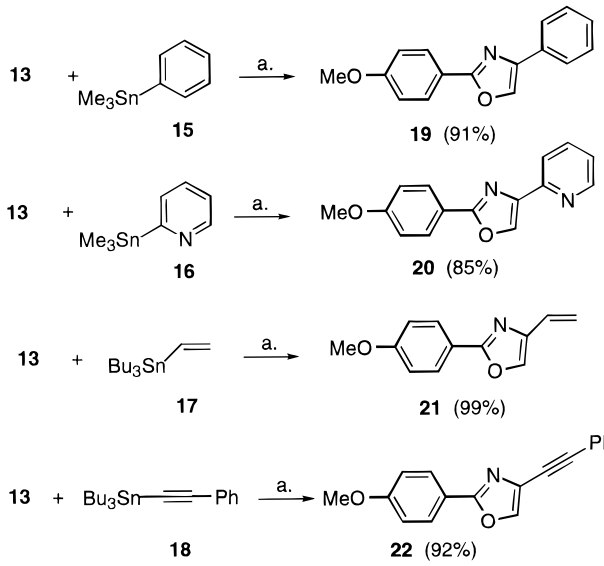
mation on the oxazole ring[29] are infrequently seen. Recent developments in marine natural product chemistry[30,31] have heightened interest in oxazole chemistry as more marine natural products are found to contain the oxazole moiety. We regarded the most challenging part of the synthesis of **1** to be the formation of the oxazole moiety and its connection to the pyridine ring. A model study on the oxazole was considered to be a good starting point for the synthesis of dimethyl sulfomycinamate (**1**).

The model studies started from the known oxazolone **12**, which was secured by a literature procedure.[32] Oxazole triflate **13** was prepared in 75% yield from **12** using trifluoromethanesulfonic anhydride (Tf_2O) and 2,6-lutidine; the triflate **13** thus obtained is a white solid and easy to purify by flash column chromatography on silica gel (Scheme 2). To our knowledge, **13** is the first reported oxazole triflate. In order to learn more about the properties of oxazole triflates, an electrophilic substitution reaction was carried out on **13**. Bromination of **13** using bromine in benzene afforded **14** in 45% yield (88% yield based on consumed starting material **13**), with recovery of 49% of **13**. The use of NBS in benzene for the bromination of **13** also gave **14** but in a lower yield (~35%, low conversion, recovered starting material). Both **13** and **14** seemed suitable for palladium-catalyzed cross-coupling reactions; **14** could potentially couple twice to put two different groups on the oxazole ring.[33]

With the oxazole triflate **13** in hand, several organostannanes including phenyltrimethyltin (**15**),[34a] 2-pyridyltrimethyltin (**16**),[34b] vinyltributyltin (**17**), and (phenylethynyl)tributyltin (**18**) were tested for the palladium-catalyzed cross-coupling reactions. When tetrakis(triphenylphosphine)palladium(0) was used as the catalyst, in the presence of over 3 equiv of anhydrous lithium chloride in dioxane solution, triflate **13** coupled with the stannanes (**15**−**18**) in good yield (85%−99%). To our knowledge, this was the first time that an oxazole triflate was either made or coupled with stannanes to form carbon−carbon bonds (Scheme 3).

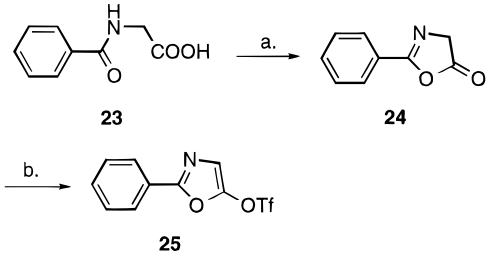
The encouraging chemistry of 4-oxazole triflate **13** led us to the investigation of 5-oxazolones, especially **24**,

Scheme 3. Coupling of Triflate 13 with Stannanes[a]



[a] Reaction conditions: (a) $Pd(PPh_3)_4$, LiCl, dioxane, 100 °C, overnight.

Scheme 4. Synthesis of 5-Oxazole Triflate 25[a]



[a] Reaction conditions: (a) Ac_2O; (b) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 40 min, 52%.

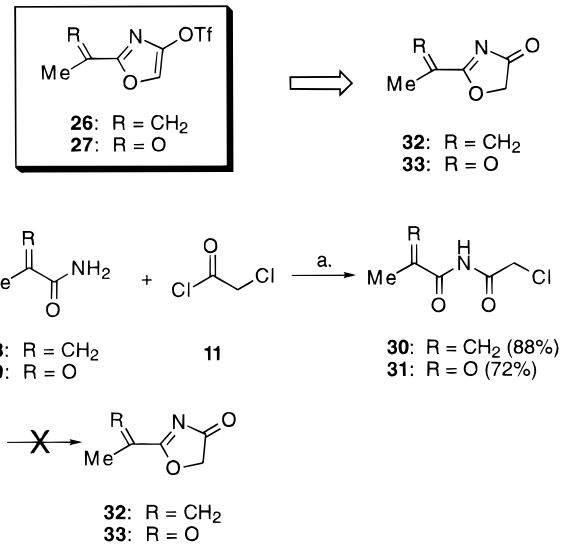
which could be prepared easily from **23** following a literature procedure.[35] It was found that oxazolone **24** could be transformed in moderate yield to the desired triflate **25** (Scheme 4). However, **25** was only stable when stored in a freezer; it decomposed into red insoluble material after a few days at room temperature. Attempted coupling reactions of **25** with stannanes under similar conditions as used for the coupling of **13** failed because of the decomposition of **25**.

With an eye toward the construction of dimethyl sulfomycinamate (**1**), we then sought to apply the triflate strategy to the synthesis of **26** or **27**. Starting from amides **28** and **29**,[36] reaction with chloroacetyl chloride (**11**) afforded imides **30** and **31**. We were, however, unable to cyclize either **30** or **31** to form the corresponding oxazolones **32** or **33**, which were to serve as the precursors for the desired oxazole triflate **26** and/or **27** (Scheme 5).

As the attempts at the preparation of oxazole triflates **26** and **27** were unsuccessful, other possibilities for constructing the oxazole moiety were investigated. Condensation of an amide and an α-bromo ketone is usually the method of choice to build 4-substituted oxazoles[37−39]

(29) Turchi, I. J., Ed. Oxazoles; J. Wiley: New York, 1986; pp 2−136.
(30) (a) Faulkner, D. J. *Nat. Prod. Rep.* **1993**, *10*, 497. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1994**, *11*, 355. (c) Lewis, J. R. *Nat. Prod. Rep.* **1993**, *10*, 29. (d) Lewis, J. R. *Nat. Prod. Rep.* **1994**, *11*, 395.
(31) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115.
(32) Rodehorst, R. M.; Koch, T. H. *J. Am. Chem. Soc.* **1975**, *97*, 7298.
(33) Coupling of **14** with phenyltrimethyltin (**15**) using tetrakis(triphenylphosphine)palladium(0) (5%) and anhydrous LiCl (3−5 equiv) in dioxane at 100 °C overnight in a sealed tube selectively afforded 5-bromo-2-(4-methoxyphenyl)-4-phenyloxazole in 95% yield. (Unpublished results from Dr. W. Xu in this laboratory.)
(34) (a) Eaborn, C.; Waters, J. A. *J. Chem. Soc.* **1962**, 1131. (b) For the preparation of 2-lithiopyridine, see: Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, 1485.
(35) Vandenberg, G. E.; Harrison, J. B.; Carter, H. E.; Magerlein, B. J. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol **V**, 946.
(36) Anker, H. S. *J. Biol. Chem.* **1948**, 1333.
(37) Turchi, I. J., Ed. *Oxazoles*; J. Wiley: New York, NY, 1986; pp 11−12.

Scheme 5. Attempts To Make Triflate 26 or 27[a]



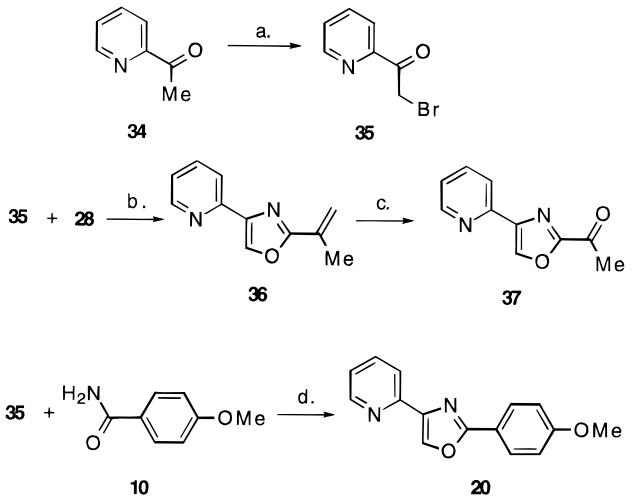
[a] Reaction conditions: (a) toluene, reflux, 3 h.

because of the easy accessibility of amides and the general effectiveness of this methodology. To explore this strategy, condensation of methacrylamide (**28**) and bromo ketone **35** was used as a model for the synthesis. Bromo ketone **35** was prepared from 2-acetylpyridine (**34**) using a known[40] procedure. To our delight, **28** and **35** reacted smoothly to give the desired oxazole product **36** in 62% yield. Oxidative cleavage[41] of the olefin in **36** using OsO_4 and $NaIO_4$ in a 1:1 dioxane/water solution at room temperature afforded acetyloxazole **37** in 86% yield. The presumed[37] regiochemical outcome of the condensation reaction between **35** and **28** was corroborated by the reaction of bromo ketone **35** and amide **10** to give the already (Scheme 3) known **20** (Scheme 6). Condensation of **35** with pyruvamide (**29**) was also attempted in the hope of producing acetyloxazole **37** directly, but no **37** was formed under reaction conditions analogous to those affording **36**.

The actual synthesis of dimethyl sulfomycinamate (**1**) started with the pyridine unit. The pyridine building block **7** (see Scheme 1) was designed to have functional groups −X and −Y at the 2- and 3-positions of the pyridine. It was preferred that −X and −Y should be different to provide selectivity in the coupling reactions. The requirement for −X and −Y is that they should be compatible with the palladium-coupling reactions. In the pyridine system, the obvious choice was bromine and triflate because they could be easily synthesized. Starting from 6-amino-2-picoline (**38**), acetylation[42] gave a quantitative yield of the acetamide **39**. The acetamide **39** was then oxidized by $KMnO_4$ in aqueous solution at 75 °C to give the corresponding acid. Esterification (and simultaneous amide cleavage) was achieved by refluxing the acid in MeOH saturated with HCl afforded methyl ester **40** in 52% yield from **39** (Scheme 7).

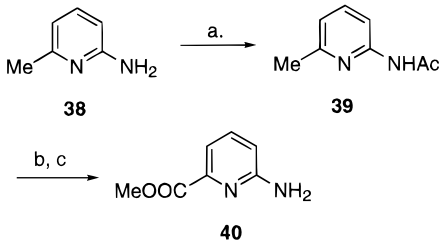
Bromination of aminopyridine **40** using bromine in chloroform was not regioselective. The desired product

Scheme 6. Formation of Pyridyloxazole 37: A Successful Model[a]



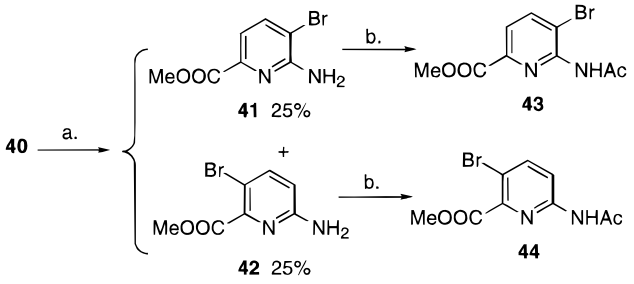
[a] Reaction conditions: (a) Br_2, AcOH; (b) sealed-tube, THF, 100 °C, 3 days, 62%; (c) OsO_4, $NaIO_4$, dioxane, H_2O, rt, 3 h, 86%; (d) toluene, reflux, 3 days, 68%.

Scheme 7. Preparation of Methyl Ester 40[a]



[a] Reaction conditions: (a) Ac_2O, 60−70 °C, 1.5 h, 100%; (b) $KMnO_4$, H_2O, 75 °C, 3 h; (c) MeOH/HCl, reflux, overnight, 52% from **39**.

Scheme 8. Bromination of Aminopyridine 40[a]

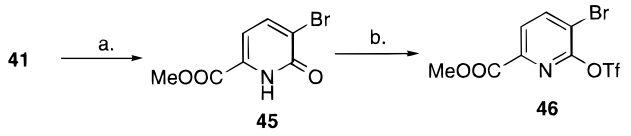


[a] Reaction conditions: (a) bromine, $CHCl_3$; (b) Ac_2O, 60−70 °C, 1.5 h.

41 was obtained in ~25% yield along with the undesired isomer **42** (~25%) and a dibrominated product (Scheme 8). Several other brominating reagents were also tried and similar results obtained. When bromination was carried out on **38** or **39**, the bromine went primarily to the position para to the amino group, and the resulting undesired isomer was the dominant product. The regiochemistry of **41** and **42** was assigned by acetylation of the amino group on pyridines **41** and **42**. We anticipated a larger chemical shift change for the aromatic protons going from **42** to **44** than going from **41** to **43**, because of the proximity of the acetyl unit to the ring protons in **42**. A large chemical shift change was observed going from **42** to **44** (**42**: δ 6.50, 7.64; **44**: δ 7.94, 8.23), compared with going from **41** to **43** (**41**: δ 7.36, 7.78; **43**:

(38) Vaccaro, H. A.; Levy, D. E.; Sawabe, A.; Jaetsch, T.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1937.
(39) Zhao, Z.; Scarlato, G. R.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609.
(40) Clemo, G. R.; Morgan, W. M.; Raper, R. *J. Chem. Soc.* **1937**, 965.
(41) Demuth, M.; Ritterskamp, P.; Weigt, E.; Schaffner, K. *J. Am. Chem. Soc.* **1986**, *108*, 4149.
(42) Meyer, H. *Recl. Trav. Chim. Pays-Bas* **1925**, *44*, 323.

Scheme 9. Preparation of Bromotriflate 46[a]



[a] Reaction conditions: (a) 9 M H_2SO_4, $NaNO_2$, 0 °C, 15 min, 85%; (b) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 10 min, 100%.

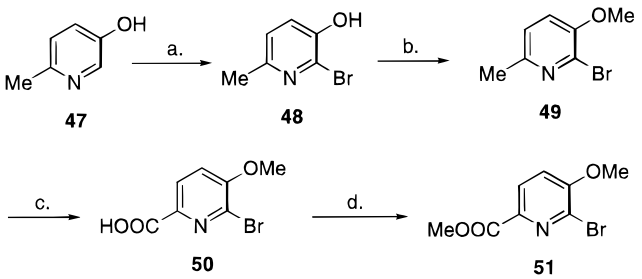
δ 7.75, 8.02), which allowed us to assign the regiochemistry of **41** and **42**.[43]

Even though the bromination of **40** was not regioselective, the desired **41** could still be prepared in fairly large amounts (grams). Since the starting material **38** is inexpensive, the preparation of **41** is economical by this method. The difficulty in this sequence is to separate **41** from the byproduct **42**, which is formed in about an equal amount in the bromination reaction. Aminopyridine **41** could be converted into pyridone **45** in 85% yield by diazotization, and **45** was transformed to the corresponding triflate **46** in 100% yield by using trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 2,6-lutidine in CH_2Cl_2 at 0 °C (Scheme 9).

Bromotriflate **46** might have served in the synthesis of **1**, but a more efficient approach involving compound **51** was ultimately developed. The 2,3,6-substitution pattern in **46** is also present in **51**, but the latter possesses only one site activated for a coupling reaction, although the methoxy group could be converted into a triflate later. The presence in **51** of only one functionality available for coupling helped to eliminate the potential ambiguity in the selectivity for the coupling of bromotriflate **46**. The synthesis of **51** started from commercially available 5-hydroxy-2-methylpyridine (**47**); bromination using bromine in pyridine gave **48** regioselectively in 77% yield,[44] and methylation of **48** by iodomethane and K_2CO_3 in refluxing acetone gave methyl ether **49** in 88% yield (the less convenient literature method[45] for the preparation of **49** is to methylate **48** by using diazomethane in 2-methyl-2-propanol and ether at −15 °C). Oxidation of the methyl group in **49** using $KMnO_4$ in aqueous solution at 90 °C afforded the acid **50**; subsequent esterification[46] of **50** in CH_2Cl_2 using methyl chloroformate in the presence of 4-(dimethylamino)-pyridine (DMAP) and triethylamine provided methyl ester **51** in 65% yield from **49** (Scheme 10). The overall yield of this four-step sequence is 44%. Following this sequence, **51** can be produced in 5−10 g quantities without much difficulty.

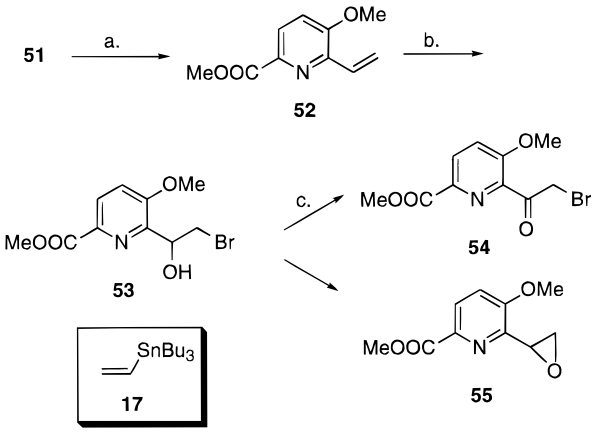
To synthesize the desired bromo ketone **54**, bromopyridine **51** was coupled with vinyltributyltin (**17**) using bis-(triphenylphosphine)palladium(II) chloride as the catalyst in dioxane at 100 °C overnight, and vinylpyridine **52** was formed in 92% yield. It was then converted into bromo ketone **54** in two steps without isolation of the intermediate bromohydrin **53**. In the first step, bromohydrin **53** was formed regioselectively; **53** was only stable under weakly acidic conditions. One side reaction was the formation of epoxide **55** from the bromohydrin **53**; under neutral or basic conditions **53** changed into **55**. The bromo ketone **54** tended to decompose when exposed to

Scheme 10. Modified Pyridine Synthesis[a]



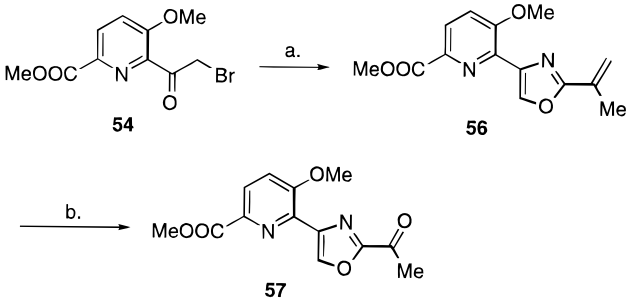
[a] Reaction conditions: (a) Br_2, pyridine, rt, 77%; (b) MeI, K_2CO_3, acetone, reflux, overnight, 88%; (c) $KMnO_4$, H_2O, 90 °C, 3 h; (d) ClCOOMe, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 2 h, 65% from **49**.

Scheme 11. Synthesis of Bromo Ketone 54[a]



[a] Reaction conditions: (a) **17**, $Pd(PPh_3)_2Cl_2$, dioxane, 100 °C, overnight, 92%; (b) NBS, THF/H_2O, rt, 10 min; (c) CrO_3, H^+, H_2O, EtOAc, 3 h, 47% from **52**.

Scheme 12. Formation of Pyridyloxazole 57[a]



[a] Reaction conditions: (a) **28**, THF, sealed tube, 100 °C, 3 days, 62%; (b) OsO_4, $NaIO_4$, dioxane, H_2O, rt, 1 h, 86%.

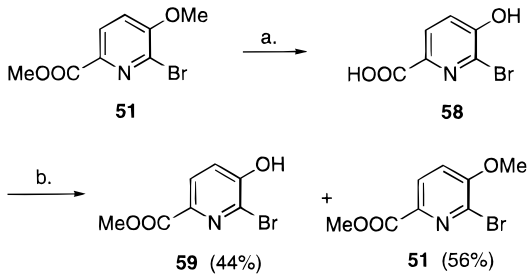
an acidic environment for a prolonged period. A poor yield of **54** was observed when either Jones reagent in acetone/water or pyridinium dichromate (PDC) in CH_2Cl_2 was used for the oxidation. The best conditions we found were to carry out the oxidation in two phases using CrO_3 as the oxidant under acidic conditions in ethyl acetate and water. The bromohydrin **53** was oxidized in an aqueous phase in an acidic environment, and the bromo ketone **54** mostly stayed in the organic phase to minimize its decomposition. Under these conditions, **54** was formed in 47% yield from **52** (Scheme 11).

Reaction of bromo ketone **54** with methacrylamide (**28**) gave the desired oxazole **56** in 62% yield. Oxidative cleavage of the olefin in **56** by OsO_4 and $NaIO_4$ gave **57** in 86% yield (Scheme 12).

In order to achieve the biaryl connection between the pyridine and thiazole moieties for the synthesis of **1**, the

(43) This assignment is corroborated by the formation of **64** from **41** (via **46**).
(44) Undheim, K.; Nordal, V.; Tjonneland, K. *Acta. Chem. Scand.* **1969**, *23*, 1704.
(45) Undheim, K.; Tveita, P. O. *Acta. Chem. Scand.* **1969**, *23*, 2065.
(46) Kim, S.; Lee, I. J.; Kim, Y. C. *J. Org. Chem.* **1985**, *50*, 560.

Scheme 13. Cleavage of Methyl Ether 51[a]

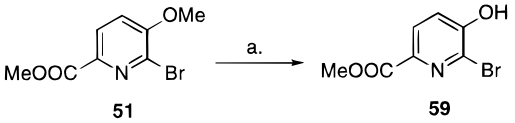


[a] Reaction conditions: (a) $AlCl_3$/NaCl; 150 °C, 2 min, 98%; (b) Et_2O, CH_2N_2, 0 °C.

methoxy group in **57** must eventually be changed into a triflate but first into a free hydroxy group. However, the seemingly trivial demethylation turned out to be troublesome. Despite attempts with various demethylation reagents, we found it impossible to cleave the methyl ether in either **57** or **56** without destroying the oxazole moiety. This result forced us to remove the methyl group at an earlier stage.

Given the difficulties stated above, we tried the cleavage of the methyl ether in **51**. Aluminum trichloride was found to be a good reagent for the demethylation. When a mixture of **51**, $AlCl_3$, and NaCl was heated to 150 °C for 2 min,[47] a clean reaction was observed and acid **58** was produced in 98% yield. When acid **58** was subjected to CH_2N_2 in Et_2O, the desired product **59** was obtained in 44% yield along with **51** in 56% yield (Scheme 13).

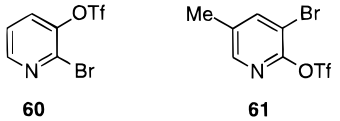
Later, it was observed that when **51** was mixed with $AlCl_3$ at room temperature, a slow reaction occurred to give **59** cleanly. Optimized reaction conditions for the selective cleavage of the methyl ether in the presence of the methyl ester in **51** involve reacting **51** and $AlCl_3$ in refluxing CH_2Cl_2[48,49] (eq 1). The desired product **59** was obtained in 93% yield by this method. Pyridinol **59** was then converted to triflate **62** in 97% yield using Tf_2O and 2,6-lutidine.



(eq. 1)

Reaction conditions: a) $AlCl_3$, CH_2Cl_2, reflux, 2 days, 93%.

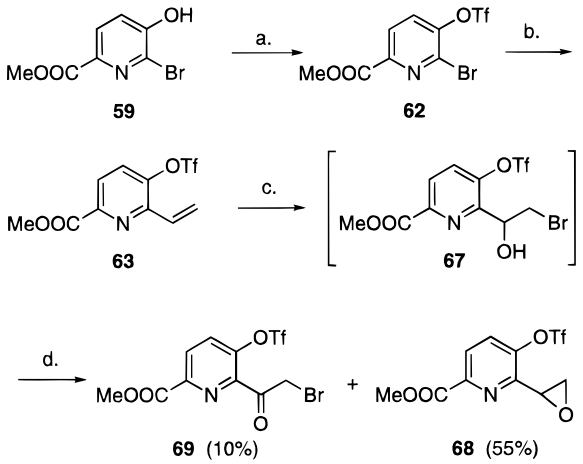
In an independent study,[50] the reactivity of pyridines doubly substituted with bromine and triflate at the 2- and 3-positions has been investigated. In particular, compounds **60**[51a] and **61**[51b] were made in order to test their reactivity toward palladium-catalyzed cross-coupling reactions. It was found that, regardless of the leaving group, the 2-position was more reactive than the 3-position of the pyridine in both **60** and **61**. Accordingly,



bromotriflate **62** was coupled with exactly 1 equiv of vinyltributyltin (**17**) with excellent selectivity to give **63** in 91% yield (Scheme 14). When 2 equiv of **17** was used

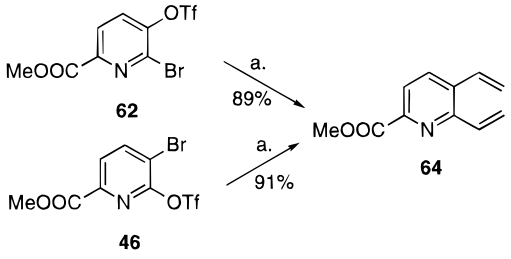
(47) (a) Cameron, D. W.; Deutscher, D. J.; Feutrill, G. I.; Griffiths, P. G. *Aust. J. Chem.* **1981**, *34*, 2401. (b) Kelly, T. R.; Xu, W.; Ma, Z.; Li, Q.; Bhushan, V. *J. Am. Chem. Soc.* **1993**, *115*, 5843.

Scheme 14. Selective Coupling Reaction of 62 and the Synthesis of 69[a]



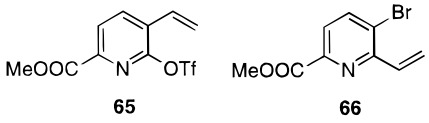
[a] Reaction conditions: (a) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 5 min, 95%; (b) **17**, $Pd(PPh_3)_2Cl_2$, dioxane, 100 °C, 12 h, 91%; (c) NBS, THF/H_2O, rt, 10 min; (d) CrO_3, H^+, H_2O, EtOAc, 3 h.

in the coupling reaction, the double-coupled product **64** was obtained in 89% yield. To compare the reactivity of **62** and **46**, **46** was also coupled with vinyltributyltin (**17**). When 1 equiv of **17** was used, a clean and selective reaction occurred and afforded a single product that, surprisingly, given the reactivity of **61**, is **65**, not **66**. With 2 equiv of vinyltributyltin (**17**), **46** coupled at both possible coupling positions to give **64** in 91% yield (eq 2).



(eq. 2)

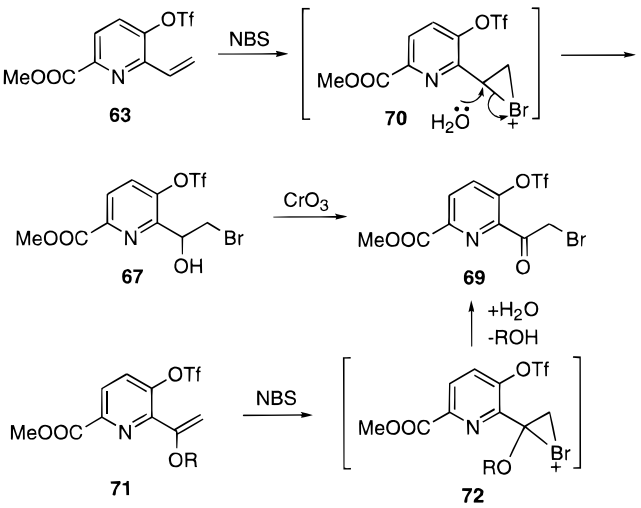
Reaction conditions: a) vinyltributyltin (**17**, 2 equivalents), $Pd(PPh_3)_2Cl_2$, dioxane, 100 °C, overnight.



The results indicated that both the 2- and 3-positions and both bromine and triflate in compounds **62** and **46** could be coupled with stannanes effectively. Still, for **62**, the reactivity at both positions was sufficiently different to provide excellent selectivity for the preparation of **63** in the coupling reaction. Reaction of **63** with NBS and water in THF followed by two-phase oxidation with CrO_3 under weakly acidic conditions gave, however, only 10% of the desired bromo ketone **69**; instead, the epoxide **68** was obtained as the major product (55%) (Scheme 14).

(48) Li, T.; Wu, Y. L. *J. Am. Chem. Soc.* **1981**, *103*, 7007.
(49) Li, T.; Ellison, R. H. *J. Am. Chem. Soc.* **1978,** *100*, 6263.
(50) Unpublished results obtained in conjunction with: Kelly, T. R.; Bowyer, M. C.; Bhaskar, K. V.; Bebbington, D.; Garcia, A.; Lang, F.; Kim, M. H.; Jette, M. P. *J. Am. Chem. Soc.* **1994**, *116*, 3657.
(51) (a) Synthesized by triflation (Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C to rt) of the commercially available 2-bromo-3-hydroxypyridine. (b) Synthesized in three steps (NBS, CH_2Cl_2; 9 M H_2SO_4, $NaNO_2$, 0 °C; Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C) from 2-amino-5-methylpyridine.

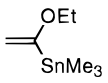
Scheme 15. Analysis of the Reaction Mechanism Toward 69



This result was disappointing but easy to understand. The problem in this sequence was the instability of the bromohydrin **67**, which was easily changed into byproduct **68** under the reaction conditions. A similar side product (**55**) was observed previously in the preparation and oxidation of bromohydrin **53**. Unfortunately, in the case of triflate **63**, byproduct **68** became the major product.

To overcome the difficulties in the synthesis of **69**, the mechanism of the **63** → **67** → **69** sequence was analyzed. In the transformation from **63** to **67**, bromonium ion **70** is presumably involved; ring opening of **70** by the nucleophilic attack of water gives bromohydrin **67**. Intramolecular nucleophilic displacement of the bromide by the hydroxy group then resulted in the formation of epoxide **68**. A solution to this problem would be to avoid the bromohydrin intermediate **67**. If an oxygen were attached to the vinyl substituent on the pyridine ring as in **71**, and similar transformations were possible, the desired bromo ketone **69** should be obtainable without going through bromohydrin intermediate **67** (Scheme 15).

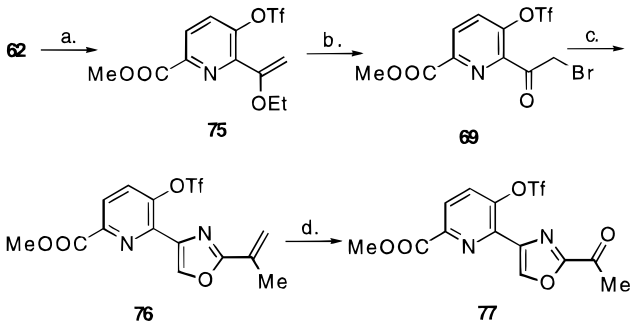
Following this analysis, vinylstannane **74**[52] was substituted for **17**. The coupling reaction between **62** and **74** proceeded in a highly selective manner to give **75** in 97% yield when exactly 1 equiv of **74** was used. Reaction of **75** with NBS and water in THF provided, as predicted, bromo ketone **69** directly in high (95%) yield. Condensation of **69** with methacrylamide (**28**) went smoothly to afford oxazole **76** in 63% yield. Oxidative cleavage of the olefin in **76** by OsO_4 and $NaIO_4$ furnished **77** in 85% yield, which was ready to couple with the thiazole moiety (Scheme 16).



74

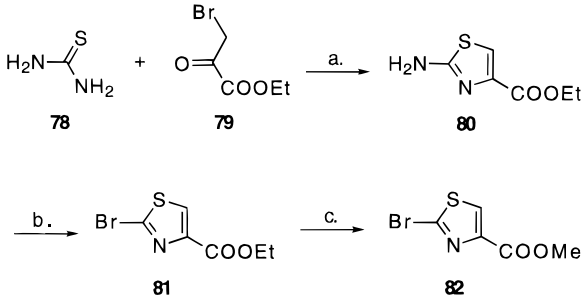
The synthesis of the thiazole moiety started with the condensation of thiourea (**78**) and ethyl bromopyruvate (**79**) to give aminothiazole **80**. Without purification, **80** was converted into bromothiazole **81** via diazotization in the presence of NaBr and $CuSO_4$. The yield of this two-step transformation is 75%. Transesterification (methyl bromopyruvate is not commercially available) in methanol with a catalytic amount of concentrated sulfuric acid gave methyl ester **82** in 85% yield (Scheme 17).

Scheme 16. Synthesis of Triflate 77[a]



[a] Reaction conditions: (a) **74**, $Pd(PPh_3)_2Cl_2$, dioxane, 100 °C, overnight, 97%; (b) NBS, THF, H_2O, rt, 10 min, 95%; (c) **28**, THF, sealed-tube, 100 °C, 3 days, 65%. (d) OsO_4, $NaIO_4$, dioxane, H_2O, rt,3 h, 85%.

Scheme 17. Preparation of Bromothiazole 82[a]

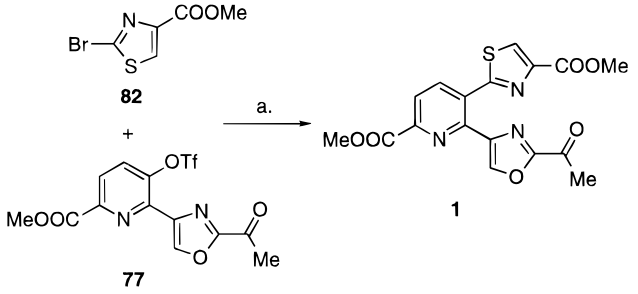


[a] Reaction conditions: (a) 100 °C, neat, 45 min; (b) H_3O^+, $NaNO_2$, $CuSO_4$, NaBr, 0 °C, 75% two steps; (c) MeOH, H_2SO_4, reflux overnight, 85%.

In an effort to couple triflate **77** and bromothiazole **82**, we sought to convert one of them into the corresponding stannane. Bromothiazole **82** was reacted with bis(tributyltin) ($Bu_3SnSnBu_3$) in the presence of bis(triphenylphosphine)palladium(II) chloride in dioxane to give dimer **83** and debrominated product **84** as the major products. On the basis of NMR analysis, the desired product **85** was not present in the reaction mixture. Nonetheless, the formation of **83** strongly suggests the generation of **85** during the course of the reaction. However, bromothiazole **82** is apparently more reactive than bis(tributyltin) toward the coupling reaction conditions; the dimerized product **83** is formed to the exclusion of **85** even when an excess amount (5 equiv) of bis(tributyltin) was used. The coupling of triflate **77** with bis(tributyltin) in the presence of tetrakis(triphenylphosphine)palladium(0) and 3 equiv of LiCl in dioxane led to the slow conversion of the starting material **77** to an unidentified product without formation of the desired stannane **86**. Finally, we succeeded in coupling triflate **77** and bromothiazole **82** by trapping stannane **85** *in situ* with **77**. Experimentally, the *in situ* trapping was accomplished by mixing **77** with bis(tributyltin), anhydrous LiCl, tetrakis(triphenylphosphine)palladium(0), and bis(triphenylphosphine)palladium(II) chloride in dioxane, heating the mixture at reflux, and then adding a solution of **82** in dioxane very slowly (4−6 h) *via* syringe pump; this procedure afforded dimethyl sulfomycinamate (**1**) in 35% yield (Scheme 18). The identity of synthetic

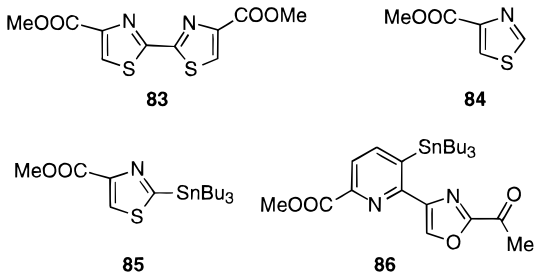
(52) Cheney, D. L.; Paquette, L. A. *J. Org. Chem.* **1989**, *54*, 3334.

Scheme 18. Synthesis of Dimethyl Sulfomycinamate (1)[a]



[a] Reaction conditions: (a) Sn_2Bu_6, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, LiCl, dioxane, 100 °C, 35%.

1 with authentic, naturally derived material[53] was established by direct comparison of spectral and physical properties, and chromatographic behavior and by a mixture melting point determination.

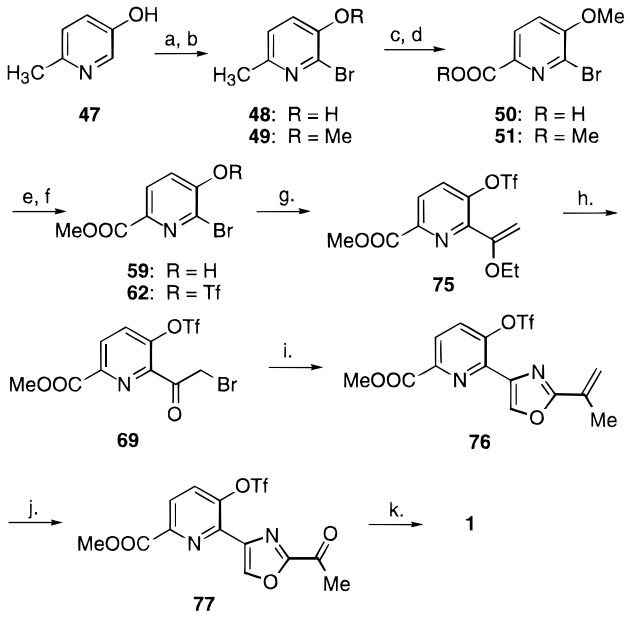


In conclusion, we have thus completed the first total synthesis of dimethyl sulfomycinamate (**1**) by the route summarized in Scheme 19. The longest linear sequence in the synthesis is only 11 steps.

Experimental Section

General Procedures. All reagents, including palladium catalysts, are commercially available materials used without purification unless otherwise stated. Anhydrous dioxane, dimethylformamide (DMF), toluene, and ethylene glycol dimethyl ether (DME) were purchased from Aldrich in Sure/Seal bottles and used as received. Anhydrous ethyl ether and THF were obtained by distillation from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Petroleum ether refers to the fraction boiling between 35 and 60 °C. Anhydrous lithium chloride used in the coupling reactions was dried in a pistol under vacuum (~2 Torr) at 130 °C overnight and stored in a desiccator. Flash column chromatography was conducted according to the procedure of Still et al.[54] on silica gel purchased from Baxter Scientific Products (S/P brand silica gel 60 A, 230−400 mesh). Neutral alumina (activated, Brockmann I) was purchased from Aldrich (catalog no. 19,997-4). The phrase "solvent was evaporated" or equivalent phrases mean that solvent was removed on a rotary evaporator under house vacuum (ca. 40−100 Torr) and that remaining traces of volatiles were then removed on a vacuum pump. The phrase "*in vacuo*" refers to house vacuum. NMR spectra were obtained from 300, 400, or 500 MHz spectrometers. Infrared spectra were recorded using KBr disks or in CH_2Cl_2 solution. Whatman polyester-backed silica gel GF plates were used for analytical TLC and visualized using a short and longwave UV lamp. For preparative TLC, Analtech silica gel GF plates (200−1000 μm) were employed; after elution, compounds were extracted from the silica gel by using

Scheme 19. Total Synthesis of Dimethyl Sulfomycinamate (1)[a]



[a] Reaction conditions: (a) Br_2, pyridine, rt, 77%; (b) MeI, K_2CO_3, acetone, reflux, overnight 88%; (c) $KMnO_4$, 90 °C, 3 h; (d) ClCOOMe, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 2 h, 65% from **49**; (e) $AlCl_3$, CH_2Cl_2, reflux, 2 days, 93%; (f) Tf_2O, 2,6-lutidine, CH_2Cl_2, 0 °C, 5 min, 95%; (g) **74**, $Pd(PPh_3)_2Cl_2$, dioxane, 100 °C, overnight 97%; (h) NBS, THF, H_2O, rt 10 min, 95%; (i) **28**, THF sealed tube, 100 °C, 3 days, 65%; (j) OsO_4, $NaIO_4$, dioxane, H_2O, rt 3 h, 85%; (k) **82**, Sn_2Bu_6, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, LiCl, dioxane, 100 °C, overnight, 35%.

CH_2Cl_2/MeOH (95:5). Melting points (uncorrected) were measured on a Fisher-Johns melting point apparatus. Elemental analyses were performed by Robertson Microlit Labs, Inc., Madison, NJ. High-resolution mass spectra (HRMS) were performed by the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois, Urbana, IL.

General Procedure for Sealed-Tube Reactions. Reagents and solvents were placed in an oven-dried, glass, disposable, sealable (Carius) tube containing a magnetic stir bar. The tube was filled with nitrogen and then evacuated under house vacuum (ca. 40−100 Torr). This process was repeated twice. Finally, the tube was evacuated (the negative pressure inside the tube gives a better seal) and sealed. The mixture was heated at the desired temperature with stirring until completion of reaction.

2-(4-Methoxyphenyl)-4-oxazolyl Trifluoromethanesulfonate (13). To a solution of oxazolone **12**[32] (1.28 g, 6.70 mmol) and 2,6-lutidine (1.28 mL, 11.0 mmol) in distilled CH_2Cl_2 (50 mL) at 0 °C was added trifluoromethanesulfonic anhydride (1.70 mL, 10.0 mmol) dropwise over 15 min; the reaction mixture was allowed to reach room temperature gradually over 30 min and stirred for 5 h. When the reaction was complete (TLC, CH_2Cl_2, R_f of **13** = 0.7), the solvent was evaporated at room temperature under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (CH_2Cl_2), giving 1.62 g (75%) **13** as a white solid: mp 37.2−38.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, s), 6.98 (2H, d, J = 9.0 Hz), 7.68 (1H, s), 7.95 (2H, d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 55.3, 114.3, 114.8, 117.3, 118.7, 119.9, 122.4, 125.5, 128.2, 145.9, 159.8, 162.2; IR (KBr) ν 3184, 2966, 1435, 1218 cm^{-1}. Anal. Calcd for $C_{11}H_8NO_5SF_3$: C, 40.87; H, 2.49; N, 4.33, found C, 40.65; H, 2.33; N, 4.26.

General Procedure for Coupling Reactions between Triflate 13 and Stannanes 15−18. In a sealable tube were mixed triflate **13** (336 mg, 1.04 mmol), the corresponding stannane (1.25 mmol), tetrakis(triphenylphosphine)palladium-(0) (37 mg, 3 mol %), anhydrous LiCl (3−5 equiv), and anhydrous dioxane (10 mL). The tube was sealed and heated at 100 °C overnight. After being cooled to room temperature,

(53) We thank L. B. Crandall and M. H. Niedenthal of Lilly Research Laboratories for a sample of A10255B,[7] from which an authentic sample of **1** was prepared.

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

the tube was opened and the solvent evaporated. The residue was then purified by flash column chromatography on silica gel to give the cross-coupled product.

2-(4-Methoxyphenyl)-4-phenyloxazole (19). Prepared in 91% yield by a coupling reaction between **13** and **15** using the general procedure described above. Purification of **19** by flash column chromatography on silica gel (petroleum ether:CH_2Cl_2 = 1:1) afforded **19** as a white solid: mp 97.5−99.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, s), 6.99 (2H, d, J = 8.8 Hz), 7.33 (1H, t, J = 7.5 Hz), 7.43 (2H, t, J = 7.5 Hz), 7.81 (2H, d, J = 7.5 Hz), 7.92 (1H, s), 8.05 (2H, d, J = 8.8 Hz). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.58, found C, 76.38; H, 5.31; N, 5.32.

2-(4-Methoxyphenyl)-4-(2-pyridyl)oxazole (20). (1) Prepared in 85% yield by a coupling reaction between **13** and **16** using the general procedure described above. Purification of **20** by flash column chromatography on silica gel (petroleum ether:ethyl acetate = 2:1) afforded **20** as a white solid: mp 131.0−132.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 7.00 (2H, d, J = 9.0 Hz), 7.22 (1H, dd, J = 7.5, 7.8 Hz), 7.78 (1H, t, J = 7.8 Hz), 8.01 (1H, d, J = 7.8 Hz), 8.07 (2H, d, J = 9.0 Hz), 8.27 (1H, s), 8.60 (1H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 55.3, 114.2, 120.2, 120.3, 122.6, 128.2, 136.1, 136.7, 142.0, 149.4, 151.0, 161.5, 162.1; IR (KBr) ν 2910 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10, found C, 71.36; H, 4.96; N, 10.96.

(2) Into a sealable tube were introduced bromo ketone **35** (100 mg, 0.50 mmol), amide **10** (150 mg, 1.0 mmol), and anhydrous toluene (10 mL). The tube was sealed and heated at 100 °C for 3 days. After evaporation of the solvent, the residue was purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate = 7:3) to give 85 mg (68%), **20**, which was identical with the product from the coupling reaction of **13** and **16**.

2-(4-Methoxyphenyl)-4-vinyloxazole (21). Prepared in 94% yield by a coupling reaction between **13** and **17** using the general procedure described above. Purification of **21** by flash column chromatography on silica gel (petroleum ether:ethyl acetate = 7:3) afforded **21** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s), 5.35 (1H, dd, J = 1.5, 10.5 Hz), 6.00 (1H, dd, J = 1.5, 16.8 Hz), 6.55 (1H, dd, J = 10.5, 16.8 Hz), 6.96 (2H, d, J = 9.0 Hz), 7.56 (1H, s), 8.00 (2H, d, J = 9.0 Hz).

2-(4-Methoxyphenyl)-4-(phenylethynyl)oxazole (22). Prepared in 92% yield by a coupling reaction between **13** and **18** using the general procedure described above. Purification of **22** by flash column chromatography on silica gel (petroleum ether:ethyl acetate = 2:1) afforded **22** as a white solid: mp 113.8−115.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.86 (3H, s), 6.98 (2H, d, J = 8.9 Hz), 7.36 (3H, m), 7.56 (2H, m), 7.87 (1H, s), 8.02 (2H, d, J = 8.9 Hz); ^{13}C NMR ($CDCl_3$) δ 55.4, 79.3, 92.6, 114.2, 119.5, 122.4, 124.8, 128.3, 128.7, 131.6, 140.5, 161.7, 161.8. Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09, found C, 78.26; H, 4.89; N, 4.69.

2-(1-Methylethenyl)-4-(2-pyridyl)oxazole (36). Bromo ketone **35**[40] (211 mg, 1.05 mmol) and methacrylamide (**28**) (178 mg, 2.1 mmol) were dissolved in THF (20 mL, freshly distilled) in a sealable tube. The tube was sealed and the mixture heated at 100 °C for 3 days. After being cooled to room temperature, the tube was opened and solvent evaporated. The resulting solid was purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate = 7:3) to give 120 mg (62%) of **36** as a white solid: mp 60.2−60.8 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, d), 5.43 (1H, d, J = 1.3 Hz), 6.02 (1H, d, J = 1.3 Hz), 7.20 (1H, dt, J = 1.3, 8.7 Hz), 7.77 (1H, dt, J = 1.0, 8.7 Hz), 7.93 (1H, d, J = 5.9 Hz), 8.20 (1H, s), 8.59 (1H, dd, J = 1.0, 5.9 Hz); IR (KBr) ν 3121 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04, found C, 70.68; H, 5.33; N, 14.91.

2-Acetyl-4-(2-pyridyl)oxazole (37). To a solution of **36** (20 mg, 0.11 mmol) in 10 mL of 1:1 dioxane/water under a nitrogen atmosphere were added one drop (ca. 0.03 mL) of an OsO_4 solution in CH_3CN (500 mg of OsO_4 in 25 mL of CH_3CN) and sodium periodate (44 mg, 0.20 mmol). The mixture was stirred at room temperature for 1 h. The solution was extracted with CH_2Cl_2, washed with aqueous $Na_2S_2O_5$ solution, water, and brine, and then dried over Na_2SO_4 and evaporated to dryness. Purification by flash column chromatography on silica gel (CH_2Cl_2:MeOH = 95:5) gave 17.8 mg (86%) **37** as a white solid: mp 122.0−123.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.75 (3H, s), 7.28 (1H, ddd, J = 1.2, 4.8, 7.6 Hz), 7.81 (1H, dt, J = 1.8, 7.6 Hz), 8.00 (1H, m), 8.42 (1H, s), 8.62 (1H, m); IR (CH_2Cl_2) ν 1706 cm^{-1}; HRMS calcd for $C_{10}H_8N_2O_2$ 188.0586, found 188.0586.

Methyl 6-Amino-2-pyridinecarboxylate (40). A mixture of *N*-(6-methyl-2-pyridyl)acetamide[42] (**39**, 20.0 g, 0.13 mol) and water (200 mL) was heated at 75 °C until a homogeneous solution was formed. Then $KMnO_4$ (50.0 g, 0.31 mol) was added in small portions over 40 min with vigorous magnetic stirring. The purple reaction mixture was kept at 75 °C for a further 3 h. The reaction mixture was then filtered through Celite while still hot. The filtrate was concentrated to about 50 mL. Concentrated HCl was then added to adjust the pH of the solution to 4−5 (pH paper), whereupon a large amount of white solid formed. The white solid was collected by filtration and dried under vacuum to afford 16.5 g of crude material. This crude product was mixed with a methanol solution saturated with HCl (200 mL) and refluxed overnight. The solvent was removed *in vacuo* and the residue partitioned between water and CH_2Cl_2. Solid sodium bicarbonate was added to the two-layer mixture until gas evolution (CAUTION) ceased. The organic layer was then separated, dried over sodium sulfate, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2:ethyl acetate = 1:1) to give 10.27 g (52%) of **40** as a white solid: mp 84.6−85.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.96 (3H, s), 4.72 (2H, br, s), 6.68 (1H, d, J = 8.0 Hz), 7.48−7.60 (2H, m); ^{13}C NMR ($CDCl_3$) δ 33.3, 113.3, 116.4, 138.9, 146.9, 159.0, 166.6; IR (CH_2Cl_2) ν 3382, 1724 cm^{-1}. Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41, found C, 54.91; H, 5.51; N, 18.18.

Methyl 6-Amino-5-bromo-2-pyridinecarboxylate (41) and Methyl 6-Amino-3-bromo-2-pyridinecarboxylate (42). To a solution of **40** (11.8 g, 77.6 mmol) in $CHCl_3$ (500 mL) was added a solution of bromine (4.00 mL, 77.6 mmol) in $CHCl_3$ (100 mL) over 1 h. The reaction mixture was stirred at room temperature for 40 h. Then the reaction mixture was washed with saturated aqueous sodium thiosulfate solution (100 mL) and water (100 mL). The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate = 2:1) to give 4.48 g (25%) of **41**, 4.48 g (25%) of **42**, and 2.95 g (25%) of recovered **40**. **41**: white solid; mp 144.2−145.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.96 (3H, s), 5.29 (2H, br, s), 7.36 (1H, d, J = 7.9 Hz), 7.78 (1H, d, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 53.4, 109.7, 117.0, 141.5, 145.8, 156.1, 166.0; IR (CH_2Cl_2) ν 3275, 1742 cm^{-1}. Anal. Calcd for $C_7H_7BrN_2O_2$: C, 36.39; H, 3.05; N, 12.12, found C, 36.42; H, 2.99; N, 12.01. **42**: white solid; mp 94.1−95.2 °C; ^{1}H NMR ($CDCl_3$) δ 3.97 (3H, s), 4.68 (2H, br, s), 6.50 (1H, d, J = 8.7 Hz), 7.64 (1H, d, J = 8.7 Hz); IR (CH_2Cl_2) ν 3466, 1730 cm^{-1}. Anal. Calcd for $C_7H_7BrN_2O_2$: C, 36.39; H, 3.05; N, 12.12, found C, 36.57; H, 2.95; N, 11.92.

Methyl 6-(*N*-Acetylamino)-5-bromo-2-pyridinecarboxylate (43). A solution of **41** (5 mg) in Ac_2O (0.5 mL) was heated at 60−70 °C for 1.5 h. Then the solvent was removed *in vacuo*, which resulted in a white solid (~5 mg). A small sample of **43** was purified by recrystallization from CH_2Cl_2/hexane as a white solid: mp 167.5−169.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.53 (3H, s), 3.98 (3H, s), 7.75 (1H, d, J = 8.1 Hz), 7.92 (1H, br, s), 8.02 (1H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 25.4, 53.7, 122.5, 143.4, 145.9, 149.2, 165.4, 171.4; IR (CH_2Cl_2) ν 3240, 1724, 1682 cm^{-1}.

Methyl 6-(*N*-Acetylamino)-3-bromo-2-pyridinecarboxylate (44). A solution of **42** (5 mg) in Ac_2O (0.5 mL) was heated at 60−70 °C for 1.5 h. Then the solvent was removed *in vacuo*, which gave **44** as a white solid (~5 mg): mp 140−141 °C; ^{1}H NMR ($CDCl_3$) δ 2.19 (3H, s), 3.98 (3H, s), 7.94 (1H, d, J = 8.8 Hz), 8.06 (1H, br, s), 8.23 (1H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 25.3, 53.8, 113.4, 117.8, 144.8, 147.3, 150.3, 165.6, 169.4; IR (CH_2Cl_2) ν 3222, 1742, 1665 cm^{-1}.

3-Bromo-6-carbomethoxy-2(1*H*)-pyridinone (45). To a solution of **41** (0.942 g, 4.3 mmol) in 9 N sulfuric acid (100 mL) at 0 °C was added a solution of sodium nitrite (0.940 g, 13.6 mmol) in water (10 mL) dropwise over 10 min. The

reaction mixture was stirred at 0 °C for 15 min (completion checked by TLC), brought near neutrality by adding a solution of 36 g of sodium hydroxide in 200 mL of water, and then neutralized with saturated sodium bicarbonate solution until gas evolution ceased; the pH at this point was 7−8 (pH paper). The mixture was extracted with CH_2Cl_2 (3 × 300 mL). The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel (CH_2Cl_2:ethyl acetate = 2:1) to give 0.805 g (85%) of **45** as a white solid: mp 190−210 °C; ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 6.86 (1H, d, J = 7.4 Hz), 7.87 (1H, d, J = 7.4 Hz), 9.71 (1H, br, s); ^{13}C NMR ($CDCl_3$) δ 54.2, 110.0, 124.8, 133.6, 142.2, 158.9, 161.6; IR (CH_2Cl_2) ν 2955, 1730, 1659 cm^{-1}. Anal. Calcd for $C_7H_6NO_3Br$: C, 36.24; H, 2.61; N, 6.04, found C, 35.92; H, 2.42; N, 5.85.

Methyl 5-Bromo-6-[(trifluoromethanesulfonyl)oxy]-2-pyridinecarboxylate (46). To a solution of pyridone **45** (50 mg, 0.23 mmol) in CH_2Cl_2 (distilled, 20 mL) at 0 °C was added 2,6-lutidine (39.8 μL, 0.34 mmol) and trifluoromethanesulfonic anhydride (45.8 μL, 0.27 mmol). The reaction mixture was stirred at 0 °C for 10 min, after which time the solvent was evaporated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2) gave 80.3 mg (100%) **46** as a white solid: mp 33.2−34.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.99 (3H, s), 8.04 (1H, d, J = 8.0 Hz), 8.23 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 53.9, 114.4, 116.3, 117.6, 120.8, 124.0, 126.8, 145.9, 146.2, 152.8, 164.0; IR (CH_2Cl_2) ν 1730, 1427, 1219 cm^{-1}. Anal. Calcd for $C_8H_5BrF_3NO_5S$: C, 26.39; H, 1.38; N, 3.85, found C, 26.38; H, 1.39; N, 3.87.

2-Bromo-3-methoxy-6-methylpyridine (49). A mixture of 2-bromo-3-hydroxy-6-methylpyridine (**48**) (prepared in 77% yield from **47**,[44] 2.62 g, 13.9 mmol), anhydrous potassium carbonate (3.87 g, 28.0 mmol), and iodomethane (1.30 mL, 20.8 mmol) in 80 mL of acetone was refluxed overnight. The reaction mixture was cooled to room temperature and filtered through Celite. Evaporation of the solvent followed by silica gel chromatography (petroleum ether:ethyl acetate = 7:3) afforded the known **49** (2.48 g, 88%) as a white solid: mp 52.5−53.8 °C (lit.[45] mp 54 °C); ^{1}H NMR ($CDCl_3$) δ 2.48 (3H, s), 3.87 (3H, s), 7.05 (2H, s).

6-Bromo-5-methoxy-2-pyridinecarboxylic Acid (50). To a solution of 2-bromo-3-methoxy-6-methylpyridine (**49**) (5.00 g, 24.7 mmol) in 100 mL of water at 90 °C was added $KMnO_4$ (11.6 g, 73.0 mmol) in small portions over a 30 min period with vigorous magnetic stirring. A dark purple solution resulted. This solution was kept at 90 °C for a further 3 h and filtered through Celite while still hot to give a colorless filtrate. After cooling, the aqueous solution was acidified to pH 1−2 by adding 6 N HCl, and a white solid precipitated. The white solid was collected by filtration to give 4.41 g (77%) of crude **50**, which was ordinarily used in the next reaction without further purification. An analytical sample was obtained by recrystallization from methanol to give **50** as a white solid: mp 220−237 °C; ^{1}H NMR (DMSO-d_6) δ 3.45 (1H, br, s), 4.06 (3H, s), 7.68 (1H, d, J = 8.5 Hz), 8.14 (1H, d, J = 8.5 Hz); ^{13}C NMR (DMSO-d_6) δ 57.0, 119.8, 126.4, 131.1, 140.0, 155.1, 164.6; IR (KBr) ν 3445, 1728 cm^{-1}. Anal. Calcd for $C_7H_6BrNO_3$: C, 36.24; H, 2.61; N, 6.04, found C, 36.00; H, 2.44; N, 5.88.

Methyl 6-Bromo-5-methoxy-2-pyridinecarboxylate (51). The crude acid **50** (4.41 g, 19.0 mmol) was partially dissolved in 150 mL of CH_2Cl_2 and cooled at 0 °C. Triethylamine (10 mL, 72 mmol), methyl chloroformate (10.0 mL, 129 mmol), and 4-(dimethylamino)pyridine (DMAP) (8.00 g, 65 mmol) were sequentially introduced. The reaction mixture was gradually brought to room temperature over 30 min and stirred for another 2 h. It became a homogeneous solution when the reaction was complete. Evaporation of the solvent followed by flash column chromatography on silica gel (petroleum ether: ethyl acetate = 7:3) gave 3.95 g (65% from **49**) of **51** as a white solid. An analytical sample of **51** was obtained by recrystallization from acetone/hexane as colorless crystals: mp 143.0−144.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 4.00 (3H, s), 7.20 (1H, d, J = 8.7 Hz), 8.11 (1H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$): 164.3, 155.7, 139.6, 132.5, 126.1, 117.8, 56.6, 52.8; IR (KBr) ν 1731 cm^{-1}. Anal. Calcd for $C_8H_8BrNO_3$: C, 39.05; H, 3.28; N, 5.69, found C, 39.21; H, 3.23; N, 5.50.

Methyl 5-Methoxy-6-vinyl-2-pyridinecarboxylate (52). Into a sealable tube were introduced bromopyridine **51** (167 mg, 0.68 mmol), vinyltributyltin (**17**) (0.30 mL, 1.0 mmol), bis-(triphenylphosphine)palladium(II) chloride (47.7 mg, 0.068 mmol), and anhydrous dioxane (10 mL). The tube was sealed and heated at 100 °C for 48 h. Dioxane was removed *in vacuo* and the residue purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate = 3:2) to give 120 mg (92%) of **52** as an oil. A pure sample of **52** was obtained by precipitation with hexane at 0 °C as a white solid: mp 87.5−89.2 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (3H, s), 3.97 (3H, s), 5.58 (1H, dd, J = 1.8, 11.1 Hz), 6.50 (1H, dd, J = 1.8, 17.4 Hz), 7.18 (1H, dd, J = 11.1, 17.4 Hz), 7.23 (1H, d, J = 8.7 Hz), 8.05 (1H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 52.6, 55.6, 117.3, 120.7, 125.5, 130.2, 139.1, 145.4, 155.5, 165.7; IR (KBr) ν 1735 cm^{-1}.

Methyl 2-Bromo-3-hydroxy-6-pyridinecarboxylate (59). (1) By Demethylation of 51. To a solution of **51** (3.34 g, 13.6 mmol) in 200 mL of freshly distilled CH_2Cl_2 under a nitrogen atmosphere was added $AlCl_3$ (22.0 g, 0.165 mol), and the cloudy solution was refluxed for 2 days. This mixture was slowly poured into 100 mL of 1 N HCl to destroy excess $AlCl_3$ (CAUTION!), extracted with CH_2Cl_2, and dried over Na_2SO_4. Evaporation of the solvent followed by silica gel chromatography (CH_2Cl_2:ethyl acetate = 3:1) gave 2.92 g (93%) of **59** as a white solid. An analytical sample of **59** was prepared by recrystallization from Et_2O/hexane affording colorless needles: mp 190−200 °C; ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 5.98 (1H, br, s), 7.39 (1H, d, J = 8.2 Hz), 8.07 (1H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 52.8, 122.5, 126.3, 130.8, 140.1, 152.0, 163.9; IR (KBr) ν 3290, 1712 cm^{-1}. Anal. Calcd for $C_7H_6BrNO_3$: C, 36.24; H, 2.61; N, 6.04, found C, 36.46; H, 2.61; N, 6.08.

(2) By Reaction of Diazomethane with Acid 58. To a solution of acid **58** (100 mg, 0.46 mmol) in ethyl ether (20 mL) at 0 °C, was added a solution of diazomethane in ether[55] dropwise. TLC was checked for the complete disappearance of starting material **58**, whereupon the ether solution was evaporated and the residue purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate = 1:1) to give 47 mg (44%) of **59** and 63 mg (56%) of **51**.

Methyl 6-Bromo-5-[(trifluoromethanesulfonyl)oxy]-2-pyridinecarboxylate (62). To a solution of pyridinol **59** (600 mg, 2.59 mmol) and 2,6-lutidine (0.45 mL, 3.9 mmol) in 25 mL of distilled CH_2Cl_2 at 0 °C under a nitrogen atmosphere was added trifluoromethanesulfonic anhydride (0.87 g, 0.52 mL, 3.1 mmol) dropwise over 15 min. The solution was gradually warmed to room temperature and stirred for 5 min. Evaporation of the solvent and purification by flash column chromatography on silica gel (CH_2Cl_2) gave 894 mg (95%) of **62** as a white solid. An analytical sample of **62** was obtained as colorless crystals by recrystallization from ethyl acetate/hexane: mp 54.5−56.0 °C; ^{1}H NMR ($CDCl_3$) δ 4.03 (3H, s), 7.75 (1H, d, J = 8.4 Hz), 8.20 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 53.5, 114.7, 117.2, 119.7, 122.2, 125.6, 131.2, 135.8, 146.8, 147.3, 163.1; IR (KBr) ν 1746, 1433, 1230 cm^{-1}. Anal. Calcd for $C_8H_5BrF_3NO_5S$: C, 26.39; H, 1.38; N, 3.85, found C, 26.61; H, 1.41; N, 3.75.

Methyl 6-(2-Bromoacetyl)-5-[(trifluoromethanesulfonyl)oxy]-2-pyridinecarboxylate (69). To a solution of **75** (550 mg, 1.7 mmol) in 30 mL of THF and 2 mL of water was added *N*-bromosuccinimide (303 mg, 1.7 mmol) in one portion. The solution was stirred at room temperature for 10 min. Evaporation of the solvent and purification by flash column chromatography on silica gel (CH_2Cl_2) gave 656 mg (95%) **69** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.05 (3H, s), 4.84 (2H, s), 7.89 (1H, d, J = 8.6 Hz), 8.41 (1H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 32.8, 54.1, 119.2 (q, J = 320 Hz), 130.9, 133.3, 144.3, 147.2, 147.6, 163.9, 190.0; IR (KBr) ν 1727, 1432, 1218 cm^{-1}; HRMS calcd for $C_{10}H_7BrF_3NO_6S$ 404.9129, found 404.9091.

Methyl 6-(1-Ethoxyethenyl)-5-[(trifluoromethanesulfonyl)oxy]-2-pyridinecarboxylate (75). Into a sealable tube were introduced **62** (760 mg, 2.09 mmol), vinylstannane **74**[52] (520 mg, 2.21 mmol), bis(triphenylphosphine)palladium(II)

(55) Prepared from Diazald and potassium hydroxide in aqueous ethanol, see: Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; J. Wiley: New York, NY, 1967, Vol. 1, pp 191−192.

chloride (74 mg, 5 mol %), and 10 mL of anhydrous dioxane. The tube was sealed and the reaction mixture heated at 100 °C overnight. After being cooled to room temperature, the mixture was filtered through Celite, washed with CH_2Cl_2, and evaporated; the residue was purified by flash column chromatography on silica gel (CH_2Cl_2) to give 650 mg (97%) of **75** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t, J = 7.0 Hz), 3.99 (2H, q, J = 7.0 Hz), 4.01 (3H, s), 4.63 (1H, d, J = 2.8 Hz), 5.07 (1H, d, J = 2.8 Hz), 7.72 (1H, d, J = 8.4 Hz), 8.17 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.7, 53.9, 64.9, 91.2, 119.2 (q, J = 320 Hz), 126.7, 132.0, 146.6, 147.3, 149.1, 156.9, 164.9; IR (KBr) ν 1730, 1432, 1215 cm^{-1}; HRMS (MH^+) calcd for $C_{12}H_{13}F_3NO_6S$ 356.0413, found 356.0406.

Methyl 6-[(1-Methylethenyl)-4-oxazolyl]-5-[(trifluoromethanesufonyl)oxy]-2-pyridinecarboxylate (76). Into a sealable tube were introduced **69** (300 mg, 0.74 mmol), methacrylamide (126 mg, 1.48 mmol), and 10 mL of freshly distilled THF. The tube was sealed, and the reaction mixture was heated at 100 °C for 3 days. Evaporation of the solvent and purification by flash column chromatography on silica gel (CH_2Cl_2:MeOH = 95:5) gave 188 mg (65%) of **76** as a white solid: mp 75.1−78.1 °C; ^{1}H NMR ($CDCl_3$) δ 2.23 (3H, s), 4.00 (3H, s), 5.50 (1H, s), 6.07 (1H, s), 7.80 (1H, d, J = 8.6 Hz), 8.14 (1H, d, J = 8.6 Hz), 8.38 (1H, s); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 18.8, 53.1, 118.6 (q, J = 320 Hz), 119.3, 125.0, 131.2, 131.5, 137.5, 140.1, 144.1, 145.1, 147.2, 163.2, 164.1; IR (KBr) ν 1739, 1434 cm^{-1}; HRMS calcd for $C_{14}H_{11}F_3N_2O_6S$ 392.0290, found 392.0285.

Methyl 6-(2-Acetyl-4-oxazolyl)-5-[(trifluoromethanesulfonyl)oxy]-2-pyridinecarboxylate (77). To a solution of **76** (40 mg, 0.10 mmol) in 10 mL of 1:1 dioxane/water was added two drops (ca. 0.06 mL) of an OsO_4 solution in CH_3CN (500 mg of OsO_4 in 25 mL of CH_3CN), then sodium periodate (44 mg, 0.20 mmol) was introduced. The mixture was stirred at room temperature for 1 h and extracted with CH_2Cl_2; the extract was washed with aqueous $Na_2S_2O_5$ solution, water, and brine, dried over Na_2SO_4, and evaporated to dryness. Purification by flash column chromatography on silica gel (CH_2Cl_2:MeOH = 95:5) gave 34 mg (85%) of **77** as a white solid: mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 2.78 (3H, s), 4.02 (3H, s), 7.83 (1H, d, J = 8.6 Hz), 8.20 (1H, d, J = 8.6 Hz), 8.62 (1H, s); ^{13}C NMR ($CDCl_3$) δ 26.6, 53.2, 118.6 (q, J = 320 Hz), 125.9, 131.7, 138.4, 143.0, 143.1, 145.1, 147.3, 157.7, 163.8, 185.8; IR (KBr) ν 1728, 1703, 1440 cm^{-1}; HRMS calcd for $C_{13}H_9F_3N_2O_7S$ 394.0083, found 394.0077.

Ethyl 2-Amino-4-thiazolecarboxylate (80). Ethyl bromopyruvate **79** (Aldrich, 90%, 2.00 mL, ~14 mmol) and thiourea **78** (1.10 g, 14.3 mmol) were mixed and heated slowly to 100 °C and maintained at that temperature for 20 min. The reaction mixture became a homogeneous solution at 70 °C, whereupon a rapid, exothermic reaction was observed (careful temperature control is necessary to avoid a violent reaction). After cooling, 2.56 g of a pale brown solid was obtained which was of sufficient purity to be used directly in the next reaction. A pure sample of **80** was obtained by recrystallization from petroleum ether and ethyl acetate (9:1) as a white solid: mp 179−180 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, t, J = 7.2 Hz), 4.35 (2H, q, J = 7.2 Hz), 5.75 (2H, br, s), 7.41 (1H, s); ^{13}C NMR ($CDCl_3$) δ 15.0, 61.8, 118.3, 143.8, 162.1, 168.4; IR (CH_2Cl_2) ν 3394, 3215, 1705 cm^{-1}.

Ethyl 2-Bromo-4-thiazolecarboxylate (81). To a mixture of crude **80** (2.56 g), $CuSO_4$ (6.84 g, 43 mmol), and NaBr (5.89 g, 57 mmol) in 30 mL of 9 M sulfuric acid in an ice−salt bath at −5 to 0 °C (internal temperature) was added a solution (precooled to 0 °C) of $NaNO_2$ (1.18 g, 17 mmol) in 10 mL of H_2O dropwise over 30 min. The internal temperature was maintained below 0 °C during the addition. After being stirred at 0 °C for 20 min, the reaction mixture was gradually warmed to room temperature over 1 h period and stirred for another 30 min. The mixture was then diluted with 30 mL of water and extracted with ethyl ether (3 × 30 mL). To thoroughly extract the product, the water layer was basified with 20% NaOH solution to pH = 9 and extracted further with ethyl ether (2 × 30 mL). The combined ether extracts were dried over sodium sulfate and evaporated to dryness. Purification by flash column chromatography on silica gel (CH_2Cl_2) gave 2.53 g (75%, two steps) of **81** as a white solid. An analytical sample of **81** was obtained by recrystallization from acetone/hexane as colorless flakes: mp 68.5−69.2 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (3H, t, J = 7.2 Hz), 4.43 (2H, q, J = 7.2 Hz), 8.13 (1H, s); ^{13}C NMR ($CDCl_3$) δ 14.9, 62.5, 131.4, 137.4, 148.0, 160.8; IR (KBr) ν 3091, 1719 cm^{-1}. Anal. Calcd for $C_6H_6BrNO_2S$: C, 30.53; H, 2.56; N, 5.93, found C, 30.65; H, 2.59; N, 5.76.

Methyl 2-Bromo-4-thiazolecaboxylate (82). A solution of ethyl ester **81** (1.14 g, 4.83 mmol) and 5 drops of concentrated sulfuric acid in 30 mL methanol was refluxed for 3 h (checked by TLC for completion). The solvent was evaporated, and the residue was neutralized with saturated sodium bicarbonate solution and extracted with CH_2Cl_2. The extract was dried over sodium sulfate and evaporated to dryness. Purification of the residue by flash column chromatography on silica gel (CH_2Cl_2) gave 0.91 g (85%) of **82** as a white solid. An analytical sample of **82** was obtained by recrystallization from acetone/hexane as colorless crystals: mp 128.2−129.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.96 (3H, s), 8.14 (1H, s); ^{13}C NMR ($CDCl_3$) δ 53.3, 131.6, 137.6, 147.6, 161.2; IR (KBr) ν 1715 cm^{-1}. Anal. Calcd for $C_5H_4BrNO_2S$: C, 27.05; H, 1.82; N, 6.31, found C, 27.01; H, 1.80; N, 6.23.

Dimethyl Sulfomycinamate (1). Into an oven-dried, two-necked flask fitted with a condenser and an argon atmosphere were introduced triflate **77** (18.5 mg, 0.047 mmol), tetrakis(triphenylphosphine)palladium(0) (5.4 mg, 10 mol %), bis(triphenylphosphine)palladium(II) chloride (3.3 mg, 10 mol %), anhydrous LiCl (20 mg), bis(tributyltin) (28 μL, 0.056 mmol), and 2 mL of anhydrous dioxane. The mixture was heated to reflux, and a solution of bromide **82** (13.3 mg, 0.071 mmol) in 1 mL of anhydrous dioxane was added via syringe pump very slowly over 4−6 h. The mixture was then refluxed overnight. After cooling, the mixture was filtered through Celite, and the Celite washed with CH_2Cl_2. The combined filtrate and wash were evaporated and purified by flash column chromatography on silica gel (CH_2Cl_2:MeOH = 95:5) to give 6.3 mg (35%) of **1** as a white solid. A pure sample of **1** was obtained by recrystallization from ethyl ether/hexane as colorless crystals, mp 157.3−160.2 °C (lit.[1] mp 160.5−161.0 °C). A mixture of synthetic **1** and the naturally derived material[7,53] (mp 158.0−160.5 °C) melted at 157.5−160.8 °C. The synthetic **1** was identical to the authentic sample by TLC analyses (CH_2Cl_2:MeOH = 9:1; ethyl acetate) including cospotting: IR (CH_2Cl_2) ν 1726 cm^{-1}; HRMS (MH^+) calcd for $C_{17}H_{14}N_3O_6S$ 388.0603, found 388.0600. The ^{1}H NMR of synthetic and naturally derived **1** are identical and in agreement with literature values.[1,7]

Supporting Information Available: Photocopies of ^{1}H NMR spectra of all compounds and experimental details of the preparation and characterization of some compounds (**14**, **25**, **30**, **31**, **53**, **54**, **56**−**58**, **63**−**65**, **67**, and **68**) only peripherally related to the synthesis of **1** (45 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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