JOC*Article*

Use of Thiazoles in the Halogen Dance Reaction: Application to the Total Synthesis of WS75624 B

Eric L. Stangeland and Tarek Sammakia*

Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

sammakia@colorado.edu

Received July 30, 2003

The total synthesis of the pyridine−thiazole-containing natural product WS75624 B (**1**) is described. This synthesis proceeds via the Stille coupling of appropriately functionalized pyridine and thiazole components, and this paper details our studies on the use of the halogen dance reaction to prepare the desired thiazole. Various halogen dance reactions on thizoles are described, including a novel one-pot multistep reaction in which 2-bromothiazole is treated with LDA in the presence of a silyl chloride at −78 °C and quenched with an electrophile to provide the highly functionalized thiazole derivatives **27**.

WS75624 A and B (Figure 1) are two related compounds that were isolated from the fermentation broth of *Saccharothrix* sp. No. 75624.[1] The structures of these compounds differ at the hydroxyl-bearing carbon of their aliphatic side chain; WS75624 A has a tertiary alcohol and one less methylene in the chain, while WS75624 B has a secondary alcohol of which the stereochemistry is unknown. These compounds are potent endothelin converting enzyme (ECE) inhibitors and are potential antihypertensive agents.[2] We recently described the synthesis of a structurally related molecule, caerulomycin C (Figure 1, **3**), in which we made extensive use of the halogen dance reaction[3] to prepare a suitably functionalized pyridine subunit.[4] The similarity of these molecules suggests that the synthesis of WS75624 B could be accomplished using a similar disconnection. In this paper, we describe the synthesis and determination of the absolute stereochemistry of WS75624 B and, in the context of this synthesis, the use of thiazoles in the halogen dance reaction.

There are two reported syntheses of WS75624 B in the literature, the first by Patt and Massa[5] and the second

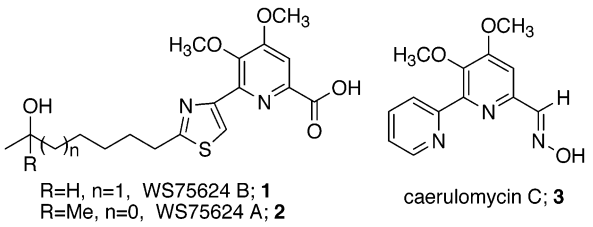


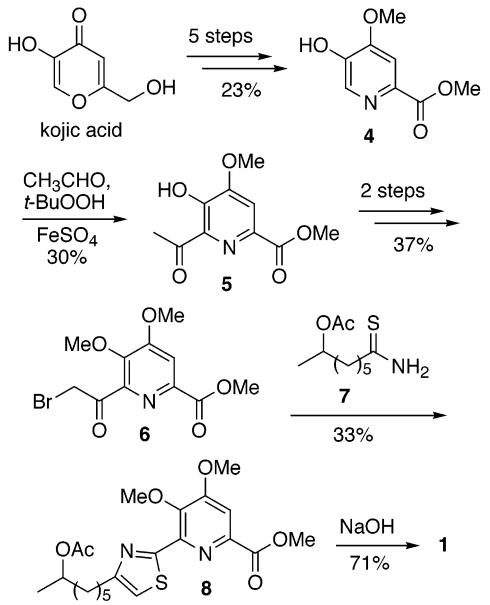
FIGURE 1. The structures of WS75624 A and B and caerulomycin C.

by Huang and Gordon,[6] and one synthesis of the structurally related molecule WS75624 A.[7] In Patt and Massa's synthesis, the pyridine ring is derived from kojic acid (Scheme 1). Thus, conversion of kojic acid to the substituted pyridine derivative **4** took five steps and proceeded in 23% yield. This compound contains three of the four pyridyl substituents, and incorporation of the fourth substituent proceeded by a radical acylation procedure involving acetaldehyde, *tert*-butyl hydroperoxide, and ferrous sulfate to provide compound **5** in a modest 30% yield. Conversion of **5** to bromo ketone **6** required two steps and proceeded in 37% yield. Treatment of this compound with racemic thioamide **7** provided the desired thiazole (**8**) in 33% yield along with a major ring-demethylated byproduct, the structure of which was not fully characterized. Conversion of this material to the natural product occurred uneventfully by alkaline hydrolysis in 71% yield. This synthesis is notable in its use of a starting material, kojic acid, which contains much of the required functionality of the pyridine of the molecule but suffers from a problematic installation of the thiazole moiety and several low-yielding transformations.

(1) Yoshimura, S.; Tsuruni, T.; Takase, S.; Okuhara, M. J. *Antibiotics* **1995**, *48*, 1073.
(2) Tsuruni, Y.; Ueda, H.; Hayashi, K.; Takase, S.; Nishikawa, M.; Kiyoto, S.; Okuhara, M. *J. Antibiotics* **1995**, *48*, 1066.
(3) For reviews of the halogen dance reaction, see: (a) Bunnett, J. F. *Acc. Chem. Res.* **1972**, *5*, 139. (b) Fröhlich, J. *Bull. Soc. Chim. Belg.* **1996**, *105*, 615. (c) Fröhlich, J. In *Progress in Heterocyclic Chemistry;* Suschitzky, H., Scriven, E. F. V., Eds.; Oxford: New York, 1994; Vol 6, pp 1−35. For leading references to more recent work, see: (d) Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 1371. (e) Trecourt, F.; Gervais, B.; Mallet, M.; Queguiner, G. *J. Org. Chem.* **1996**, *61*, 1673. (f) Comins, D. L.; Saha, J. K. *Tetrahedron Lett.* **1995**, *36*, 7995. (g) Trécourt, F.; Mallet, M.; Mongin, O.; Quéguiner, G. *J. Org. Chem.* **1994**, *59*, 6173. (h) Guillier, F.; Nivoliers, F.; Godard, A.; Marsais, F.; Quéguiner, G. *Tetrahedron Lett.* **1994**, *35*, 6489. (i) Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1993**, *58*, 7832. (j) Marsais, F.; Pineau, P.; Nivolliers, F.; Mallet, M.; Turck, A.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1992**, *57*, 565.
(4) Sammakia, T.; Stangeland, E. L.; Whitcomb, M. C. *Org. Lett.* **2002**, *4*, 2385.
(5) (a) Patt, W. C.; Massa, M. A. *Tetrahedron Lett.* **1997**, *38*, 1297. (b) Massa, M. A.; Patt, W. C.; Ahn, K.; Sisneros, A. M.; Herman, S. B.; Doherty, A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2117.
(6) Huang, S.-T.; Gordon, D. M. *Tetrahedron Lett.* **1998**, *39*, 9335.
(7) Bach, T.; Heuser, S. *Synlett* **2002**, 2089.

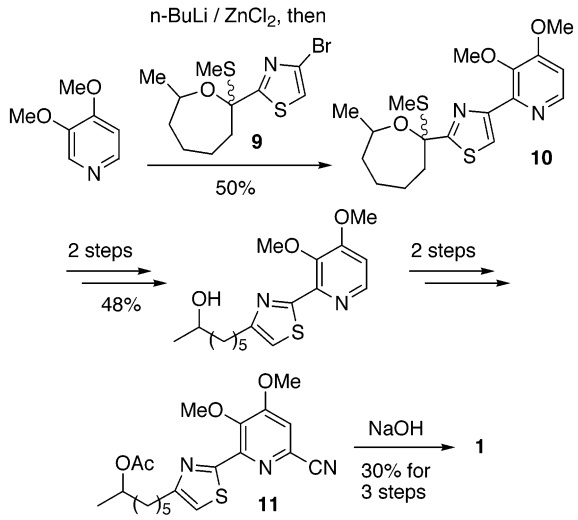
10.1021/jo0351217 CCC: $27.50
Published on Web 02/26/2004

SCHEME 1



Huang and Gordon's synthesis (Scheme 2) begins with 3,4-dimethoxypyridine, which is known to undergo metalation/Negishi coupling at the 2-position.[3e] Thus, coupling

SCHEME 2



with bromothiazole **9**, which was prepared in three steps and 75% yield from 2,4-dibromothiazole, provided **10** in 50% yield. Compound **10** requires reduction of the mixed thioketal, and this proceeds in two steps and 48% yield. Incorporation of the required carboxylic acid proceeded in two steps by a Reissert−Hanze reaction via the *N*-oxide. This provided nitrile **11**, which was hydrolyzed to the racemic natural product in 30% overall yield for three steps. This synthesis is notable for its brevity, convergency, and lack of use of protecting groups, but it suffers from a few steps that proceed in modest yields.

Our retrosynthetic analysis of WS75624 B is similar to that for our synthesis of caerulomycin C.[4] We first disconnected the thiazole from the pyridine, simplifying our precursors to the 6-iodopyridine derivative **13** and the substituted 4-stannyl thiazole **12** (Figure 2). We previously described the synthesis of **13**[4] and now re-

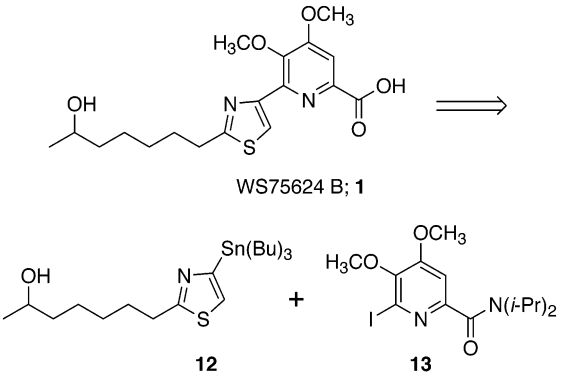
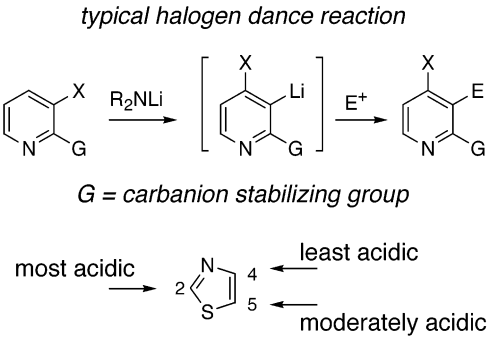


FIGURE 2. Coupling fragments for the synthesis of WS75624 B.

SCHEME 3



quired an efficient synthesis of the thiazole component (**12**), and we turned to the halogen dance reaction to accomplish this task. The halogen dance reaction proceeds by a metalation to form a lithio aromatic species, followed by a transposition of the lithio and halogen moieties to produce a new organolithium (Scheme 3).[8] The driving force for this reaction is the formation of a more stable organolithium, and typically, the added stability is derived from having the lithium flanked by the halogen and an additional carbanion stabilizing group. However, this is not a required component of the reaction; if a substrate contains sites that differ in acidity, there exists a thermodynamic driving force for the rearrangement of a lithio species to the more acidic site.[9] This is the case with thiazoles. Thiazole is most acidic at the 2-position, less acidic at the 5-position, and least acidic at the 4-position (Scheme 1).[10] For our synthesis of WS75624 B, we required a substituent at the least acidic position of the thiazole (the 4-position), and we therefore wished to force a metalation at this position and migrate a halogen from either the 2-position or the 5-position to this site.

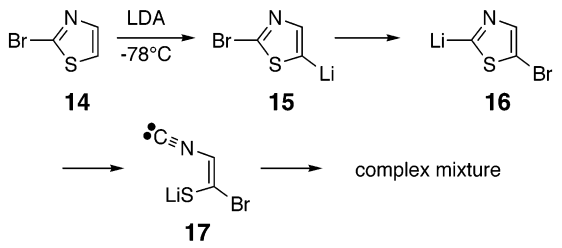
To test the viability of the halogen dance reaction on a simple thiazole substrate, we studied the reactivity of 2-bromothiazole (**14**, Scheme 4). This compound was treated with LDA at −78 °C in ethereal solvents and then subjected to an aqueous workup; however, under all

(8) For leading references on the mechanism of this reaction, see ref 4 and references therein.

(9) For examples of halogen dance reactions that are driven by differential acidities on thiophenes, see ref 11a and the following: Sauter, F.; Fröhlich, H.; Kalt, W. *Synthesis* **1989**, 771.

(10) For a review of the chemistry of lithio thiazole, see: Iddon, B. *Heterocycles* **1995**, *41*, 533.

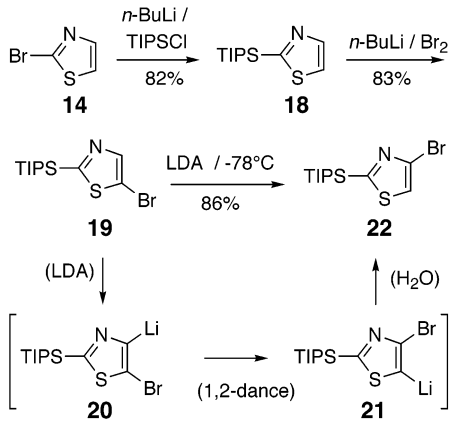
SCHEME 4



14 15 16 17

conditions examined a dark intractable product was produced. We suspect that this is a result of lithiation at the moderately acidic 5-position to produce **15**, followed by a halogen dance reaction to produce 2-lithio-5-bromothiazole (**16**). This species can then undergo an α-elimination and open to the unstable isocyanide (**17**), which decomposes to a complex mixture. Although the parent 2-lithiothiazole is known to be stable at −78 °C,[9] we postulate that the electron-withdrawing nature of the bromine at the 5-position stabilizes the thiolate of **17** and facilitates the ring opening. We therefore decided to block the 2-position of the thiazole and examine the halogen dance reaction between the 4- and 5-positions, and we prepared 2-silyl-5-bromothiazole derivatives by treating 2-bromothiazole with *n*-BuLi and trapping with a variety of chlorotrialkylsilanes at −78 °C. The 2-silyl species were then metalated with LDA and quenched with bromine (Scheme 5). Of the silanes we examined (trimethylsilyl,

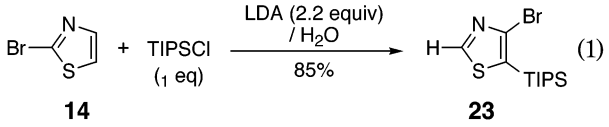
SCHEME 5



14 18 19 22 20 21

triethylsilyl, *tert*-butyldimethylsilyl, and triisopropylsilyl), we found that only the triisopropylsilyl (TIPS) derivate (**18**) underwent the bromination reaction without desilylation. When 2-triisopropylsilyl-5-bromothiazole (**19**) was subjected to the halogen dance conditions by treatment with LDA at −78 °C, it smoothly rearranged to the 4-bromo derivative **22** in 86% yield (Scheme 5). This reaction likely proceeds by a deprotonation at the 4-position to provide **20**, followed by a 1,2-dance to provide the 4-bromo-5-lithio product (**21**) in which the lithium is at the more acidic site. Confident that the halogen dance is viable on thiazole derivatives, we returned to examining the use of 2-bromothiazole as a starting material.

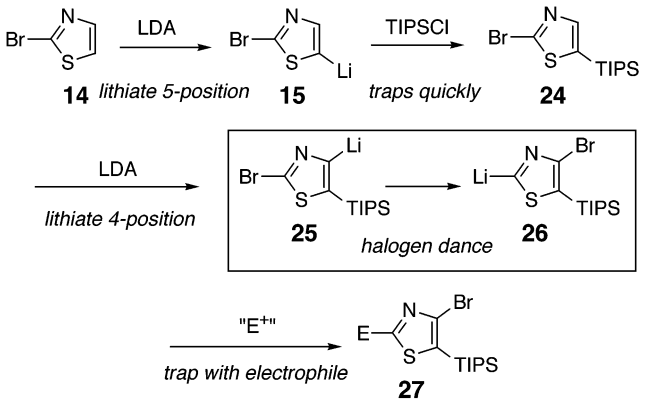
Our previous attempts at the use of 2-bromothiazole as a partner in this reaction suffered from the lability of the 2-lithiothiazole that is produced by the halogen dance. As previously mentioned, it is likely that this lability is enhanced by the presence of a halogen at the 5-position of the thiazole, and we sought to stabilize this species by the installation of an electron-donating group at that position. We therefore conducted a reaction wherein 2-bromothiazole was treated with 2.2 equiv of LDA at −78 °C in the presence of 1 equiv of TIPSCl. After an aqueous workup, 5-triisopropylsilyl-4-bromothiazole (**23**) was isolated in 85% yield (eq 1). This remarkable reaction



14 23 (1)

likely proceeds by the mechanism shown in Scheme 6. The reaction is conducted at −78 °C, and at this temperature, LDA does not react with TIPSCl. Thus, the first

SCHEME 6



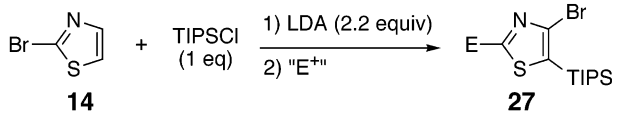
14 15 24 25 26 27

equivalent of LDA deprotonates the thiazole at the more acidic 5-position to produce 5-lithio-2-bromothiazole (**15**). This compound can either undergo a halogen dance reaction or be trapped by the TIPSCl. The latter is a more facile process, and 5-triisopropylsilyl-2-bromothiazole (**24**) is produced.[11] Compound **24** can then be deprotonated by the second equivalent of LDA in solution to produce the substituted 4-lithothiazole **25**. Since all the TIPSCl is consumed after the first metalation, **25** can only undergo a 1,3-halogen dance reaction to produce the substituted 2-lithiothiazole **26**. Compound **26** is now stable at −78 °C and can be trapped with reactive electrophiles. Table 1 shows the results of trapping with a variety of common electrophiles. In cases that display diminished yields, the balance of the material consists of the protonated product **23**.

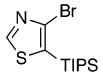
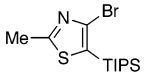
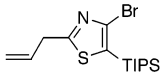
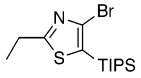
This reaction is remarkably clean considering its complexity and the lability of many of the intermediates. A drawback, however, is the low nucleophilicity of the 2-lithiothiazole **26**; at −78 °C, **26** does not react with hindered lactones and typical alkyl halides, though it will react with more reactive alkyl halides, such as methyl

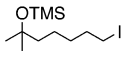
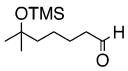
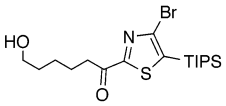
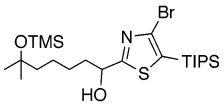
(11) For other examples where an in situ trapping with a silyl chloride proceeds faster than a halogen dance, see: (a) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *Heterocycles* **1983**, *20*, 2035. (b) Bury, P.; Hareau, G.; Kocienski, P.; Dhanak, D. *Tetrahedron* **1994**, *50*, 8793. (c) Cochennec, C.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Synthesis* **1995**, 321. (d) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Heterocycles* **1999**, *50*, 215.

TABLE 1. Thiazole Halogen Dance and Subsequent Trapping with Electrophiles

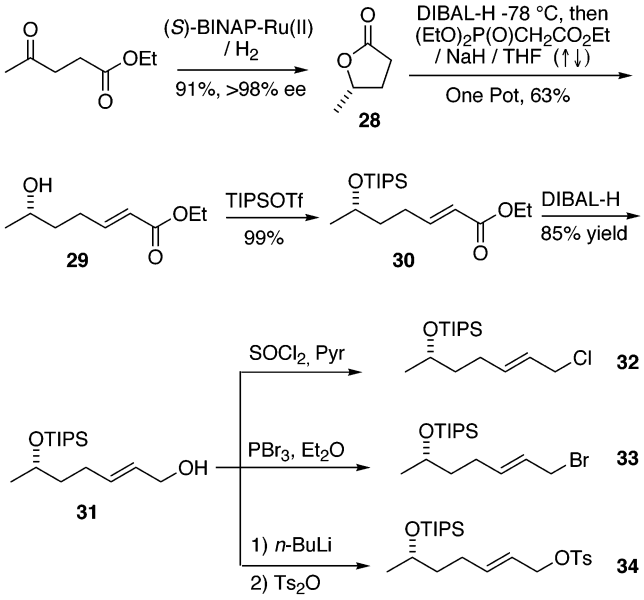


14 **27**

"E+"	H_2O	CH_3I		CH_3CH_2I
Product				
Yield	85%	82%	20%	<10%

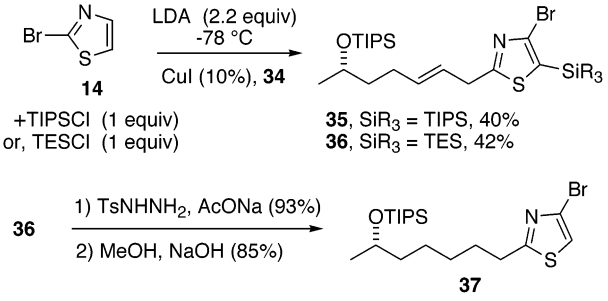
"E+"				
Product	--		--	
Yield	0%	57%	0%	60%

SCHEME 7



28 **29** **30** **31** **32** **33** **34**

SCHEME 8



14 **36** **37**

iodide, and with aldehydes.[12] At temperatures above about −70 °C, it is unstable and undergoes decomposition faster than alkylation.

To complete the synthesis of WS75624 B, we were faced with the problem of appending the side chain at the 2-position of the thiazole. Since alkylation of **26** with simple primary alkyl halides proceeded in low yields, we sought to increase the reactivity of the alkylating agent and rendered the leaving group allylic. The synthesis of our coupling partner proceeded as shown in Scheme 7 beginning with ethyl levulinate. Noyori hydrogenation using the (*S*)-BINAP-derived catalyst provided (*S*)-lactone **28** in 91% yield and >98% ee.[13] This compound was converted to enoate **29** in 63% yield in a one-pot procedure in which the lactone was reduced with diisobutylaluminum hydride at −78 °C and then subjected to an in situ Horner−Emmons olefination.[14] The secondary alcohol was protected as a TIPS ether, and the ester was reduced with diisobutylaluminum hydride to alcohol **31**, which was then activated as the chloride (**32**), bromide (**33**), or tosylate (**34**). Activation as the tosylate using tosyl chloride was problematic, due to competing displacement of the tosylate by chloride ion. This could be suppressed using *p*-toluenesulfonic anhydride and deprotonating the alcohol with *n*-BuLi.[15]

With the activated electrophiles in hand, we attempted a coupling reaction between them and lithothiazole **26**. As expected, the reaction was sluggish and did not provide usable quantities of the desired product. However, in the presence of 10% CuI, a 42% yield of the coupled product was obtained with allylic tosylate **34** (Scheme 8). The corresponding bromide (**33**) and chloride (**32**) provided diminished yields and significant amounts of the S_N2' coupling product under a variety of conditions. Diimide reduction of the alkene of **34** occurred smoothly;

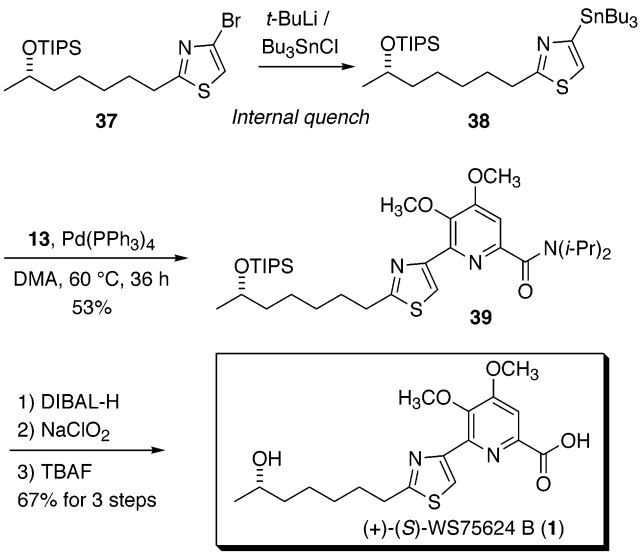
(12) For a review of nucleophilic reactions of 2-lithiothiazole, see: Dondoni, A. *Synthesis* **1998**, 1681.

(13) Ohkuma, T.; Kitamura, M.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 5509.

(14) For a related transformation, see: Burke, S. D.; Deaton, D. N.; Olsen, R. J.; Armistead, D. M.; Blough, B. E. *Tetrahedron Lett.* **1987**, *28*, 3905.

(15) This reaction requires prior purification of the anhydride by recrystallization from ethyl acetate in order to minimize the formation of several byproducts.

SCHEME 9



however, the TIPS blocking group on the thiazole proved difficult to remove without extensive decomposition. We therefore repeated the sequence starting from **14** using a triethylsilyl (TES) blocking group instead and found that it was smoothly removed upon stirring in basic methanol (Scheme 8).

Completion of the synthesis proceeded as shown in Scheme 9. Compound **37** was converted to the tributylstannyl derivative by treatment with *t*-BuLi with an in situ quench with tributyltin chloride to provide **38**. Due to the steric hindrance of the *t*-BuLi, halogen−metal exchange is more facile than attack on the tributyltin chloride, allowing the use of the tin electrophile as an internal quenching agent. If the tributyltin chloride is not present during the halogen−metal exchange, diminished yields of product are observed, presumably due to deprotonation of the α-methylene of the thiazole. Coupling of **38** with iodopyridine **13** (see Figure 2) was then accomplished using $Pd(PPh_3)_4$ in dimethylacetamide at 60 °C for 36 h and provided **39** in 53% yield. Conversion of **39** to WS75624 B simply required hydrolysis of the amide to the acid and deprotection of the silyl group. However, we were unable to accomplish the hydrolysis in a single step and resorted to the two-step procedure of diisobutylaluminum hydride reduction of the amide to the aldehyde followed by Lindgren oxidation[16] to the carboxylic acid. Finally, deprotection of the TIPS group with TBAF provided (*S*)-WS75624 B in 67% yield for three steps. The optical rotation of our material was determined to be $[\alpha]_D = +3.1$ ($c = 8.0$ mg/mL, CH_3OH), while that of the natural product was reported as being $[\alpha]_D = +3$ ($c = 8.0$ mg/mL, CH_3OH).[1] This allows us to assign the stereochemistry of the natural product as the (*S*)-configuration at the carbon bearing the secondary alcohol.

Conclusions. We have described the asymmetric synthesis of WS75624 B and the use of thiazoles as substrates for the halogen dance reaction. With appropriately functionalized thiazoles, this reaction can provide high yields of compounds that are difficult to obtain by other methods. In the course of our synthesis, we utilized a novel, one-pot functionalization of 2-bromothiazole in which the halogen dance reaction plays a key role. Studies to further extend the scope of these reactions are currently in progress.

Acknowledgment. We thank the National Institutes of Health (GM48498), Array Biopharma, and Pharmacia (graduate fellowship to E.L.S.) for financial support of this research. NMR instrumentation used in this work was supported in part by the National Science Foundation CRIF program (CHE-0131003).

Supporting Information Available: Spectroscopic and analytical data as well as experimental procedures for the synthesis of all compounds shown in Schemes 5, 7, 8, and 9. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0351217

(16) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888; Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.