Pergamon

Tetrahedron Letters 39 (1998) 9335–9338

TETRAHEDRON LETTERS

Total Synthesis of Endothelin-Converting Enzyme Antagonist WS75624 B

Sheng-Tung Huang and Dana M. Gordon*

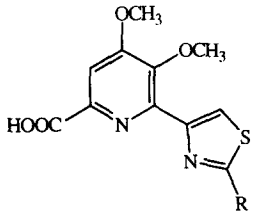
Department of Chemistry, Brandeis University, Waltham, MA 02454-9110 USA

Received 23 September 1998; revised 6 October 1998; accepted 7 October 1998

Abstract: A concise synthesis of endothelin-converting enzyme antagonist WS75624 B is reported. The natural product was prepared in seven steps from 2,4-dibromothiazole.

Endothelin-1 (ET-1), a twenty-one amino acid peptide, has been isolated from cultured endothelial cells, and has been shown to be a potent vasoconstrictor both *in vitro* and *in vivo*.[1] ET-1 is derived *in vivo* from a two-hundred-and-three amino acid precursor peptide that is cleaved proteolytically to produce a thirty-eight amino acid peptide termed big endothelin-1 (big ET-1). Big ET-1 is then degraded by endothelin-converting enzyme (ECE) to produce ET-1. Big ET-1 has approximately one hundredth the vasoconstrictive activity of ET-1. Inhibitors of ECE, possibly administered in concert with endothelin receptor antagonists, hold promise as therapeutics for a wide range of disorders in which vasoconstriction plays a significant role, including hypertension, congestive heart failure, and stroke.[2]

Two novel inhibitors of ECE, WS75624 A and B (**1** and **2**, respectively), were isolated recently from a fermentation broth of *Saccharothrix* sp. No 75624.[3] Both compounds are highly potent inhibitors of ECE with IC_{50} values of 0.03 μg/mL. The structures of WS75624 A and B were assigned based on their physical and spectral characteristics.[4] Both natural products comprise a tetra-substituted pyridine ring, a thiazole ring, and a seven-carbon hydroxyalkyl moiety. The two natural products are constitutional isomers that differ only in the architecture of their hydroxyalkyl moieties: the hydroxyalkyl moiety of **1** is a 5-hydroxy-5-methylhexyl group; and the hydroxyalkyl moiety of **2** is a 6-hydroxyheptyl group.

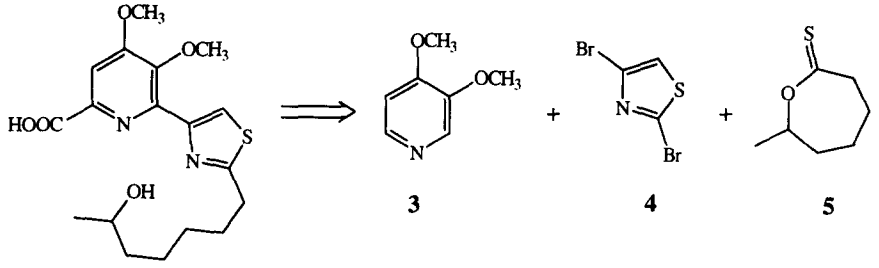


WS75624 A (**1**) R = $(CH_2)_4C(OH)(CH_3)_2$
WS75624 B (**2**) R = $(CH_2)_5CH(OH)CH_3$

0040-4039/98/$ - see front matter
PII: S0040-4039(98)02158-3

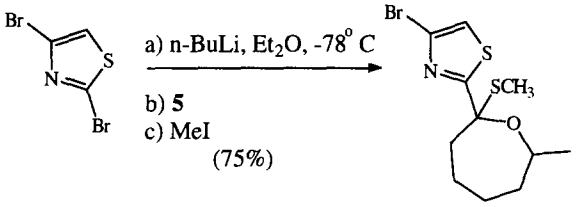
These compounds are compelling due to their ECE antagonist activity, the synthetic challenges posed by their structures, and their status as potential new leads in drug discovery efforts. The first total synthesis of WS75624 B was disclosed in 1997, and consisted of 15 steps.[5] The total synthesis of WS75624 B disclosed herein is significantly more concise, requiring only seven steps from three known starting materials: 3,4-dimethoxypyridine[6] (**3**); 2,4-dibromothiazole[7] (**4**); and thionolactone **5**.[8] An outline of our retrosynthetic analysis of **2** is shown in Scheme I. A retrosynthetic analysis of this type, if reduced to practice, promised to provide ready access to **2** and analogues thereof.

Scheme I



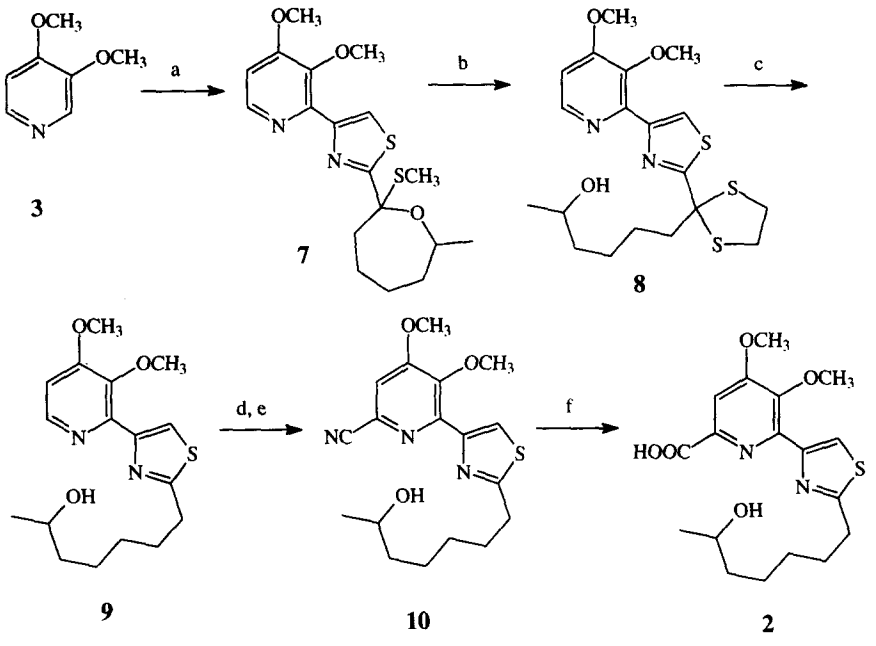
The first step in the synthesis of **2** was the preparation of mixed ketal **6** from **4** and **5** (Scheme II). Treatment of **4** with a single equivalent of *n*-butyllithium generated 4-bromo-2-lithiothiazole;[9] addition of 4-bromo-2-lithiothiazole to **5**, followed by trapping the resulting tetrahedral intermediate with iodomethane, yielded mixed ketal **6** in 75% yield based on **4**. Trapping of the tetrahedral intermediate formed upon addition of the lithiothiazole to the thiocarbonyl moiety served to protect the hydroxyl group required for **2** without the need to resort to cumbersome protecting group chemistry.

Scheme II



Tricycle **7** was prepared from **3** and **6** via a palladium-catalyzed cross-coupling of **6** with an organozinc reagent derived from **3** (Scheme III). Specifically, pyridine **3** underwent regioselective lithiation, upon treatment with two equivalents of *n*-butyllithium, to generate 2-lithio-3,4-dimethoxypyridine;[10] *in situ* transmetallation of the lithiopyridine intermediate, with excess zinc chloride (2.5 equivalents), gave the corresponding organozinc reagent; and palladium-catalyzed cross-coupling of the organozinc reagent with **6** (1.9 equivalents) gave **7** in 53% yield based on **3**.

Scheme III



(a) n-BuLi, THF, -78 °C; $ZnCl_2$; **6**, $Pd(PPh_3)_4$ (50%). (b) $(HSCH_2)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2 (95%). (c) $NiCl_2$, $NaBH_4$, H_3BO_3 (50%). (d) MMPP, MeOH (80%). (e) TMSCN, Me_2NCOCl, CH_2Cl_2 (61%). (f) 1 N NaOH, MeOH; 1 N HCl (60%).

Naively, we believed that a simple hydrogenation would suffice to reduce the mixed ketal resident in **7** to the methylene group required for the natural product; reduction of **7** to **9**, however, proved to be highly problematic. Numerous attempts to reduce **7** under transition metal-catalyzed hydrogenation conditions failed to produce **9**. Clemmensen reduction conditions likewise failed to provide **9**. Moreover, attempts to reduce the recalcitrant carbon via ketal hydrolysis followed by carbonyl reduction were not productive. Ultimately, a different two step approach provided **9**. Treatment of **7** with 1,2-ethanedithiol and $BF_3{\cdot}OEt_2$ gave **8** in 95% yield.[11] Dithiolane **8** was then reduced with nickel boride to give **9** in 50% yield.[12] This reduction sequence unveiled the hydroxyalkyl moiety required for natural product.

The carboxylic acid moiety required for **2** was then installed. Oxidation of **9** with MMPP at room temperature gave the corresponding pyridine *N*-oxide in 80% yield.[13,14] The pyridine *N*-oxide underwent a Reissert-Hanze reaction with dimethylcarbamyl chloride and TMSCN to give nitrile **10** in 61% yield.[15] Hydrolysis of **10** produced the natural product WS75624 B (**2**) in 60% yield. The spectral and physical characteristics (IR, ^1H NMR, ^{13}C NMR, and melting point) of synthetic **2** were identical to the published data.[3] The synthesis disclosed herein provided WS75624 B (**2**) in seven steps from 2,4-dibromothiazole (**4**). The one pot procedure for forming the mixed ketal is a convenient way to protect the required hydroxyl

functionality without the need to resort to protecting group manipulations. The synthetic strategy exploited for the preparation of **2** should serve as a basis for the preparation of **1** and analogues of both natural products.

Acknowledgment: We thank Brandeis University and Procter & Gamble for their generous financial support of this research. S.-T.H. acknowledges partial support from an NIH Training Grant to the Bioorganic Chemistry Program at Brandeis University.

REFERENCES

1. Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Yazakai, T.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411.
2. Simonson, M. S.; Dunn, M. J. *Lab. Clin. Med.* **1992**, *119*, 622.
3. Tsurumi, Y.; Ueda, H.; Hayashi, K.; Takase, S.; Nishikawa, M., Kiyoto, S.; Okuhara, M. *J. Antibiot.* **1995**, *48*, 1066.
4. Yoshimura, S.; Tsurumi, Y.; Takase, S.; Okuhara, M. *J. Antibiot.* **1995**, *49*, 1073.
5. Patt, C. W.; Massa, A. M. *Tetrahedron Lett.* **1997**, *39*, 1297.
6. Trecout, F.; Mallet, M.; Mengin, O.; Gervais, B.; Queguiner, G. *Tetrahedron* **1993**, *49*, 8373.
7. Reynaud, P.; Robba, M.; Moreau, R. C. *Bull. Soc. Chim. France* **1962**, 1735.
8. Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C..A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263.
9. Dondoni, A.; Mastellari, A. R.; Medici, A.; Negrini, E.; Pedrini, P. *Synthesis* **1986**, 757.
10. Trecout, F.; Gervais, B; Mallet, M.; Queguiner, G. *J. Org. Chem.* **1996**, *61*, 1673.
11. James, Z. S.; Voss, D.; Decamp, D. L.; Li, J.; Craik, C. S.; Ortiz de Montellano, P. R. *Synthesis* **1993**, 803.
12. Boar, R. B.; Hawkins, D. W.; McGhie, J. F. *J. Chem. Soc., Perkin Trans I* **1973**, 655.
13. Dondoni, A.; Merino, P. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996, 373.
14. Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synth. Commun.* **1987**, 1015.
15. Fife, W. F. *J. Org. Chem.* **1983**, *48*, 1375.