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The Total Synthesis of the Natural Product Endothelin Converting Enzyme (ECE) Inhibitor, WS75624 B

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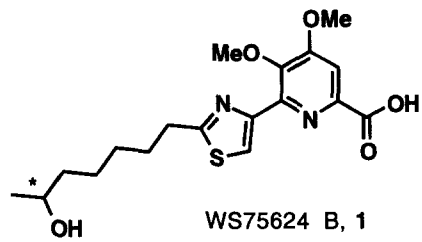
Abstract: The first total synthesis of WS75624 B, **1**, an endothelin converting enzyme inhibitor produced in a fermentation broth of *Saccharothrix* sp. No. 75624 is reported herein. WS75624 B is synthesized in 14 steps from commercially available kojic acid, **2**. The synthetic methodology allows for facile substitution at multiple sites on the molecule. © 1997 Elsevier Science Ltd. All rights reserved.

WS75624 B, **1**, is one of two closely related bi-aryl endothelin converting enzyme inhibitors which were first reported in 1994.[1] WS75624 B was isolated from a fermentation broth of *Saccharothrix* sp. No. 75624. The structure was elucidated and reported by the same group of scientists.[2] The compound is of interest since it is one of the first non-peptide, small molecule inhibitors of the recently discovered endothelin converting enzyme (ECE)[3-4], IC_{50}= 0.03 μg/ml. Due to its ECE activity and its rather interesting chemical structure[5], we undertook the synthesis of this molecule. This bi-aryl molecule contains a 2,4,5,6-tetra-substituted pyridine and a (2-alkyl)thiazol-4-yl ring. In this paper we shall describe a novel strategy and demonstrate versatility in the synthesis of WS75624 B.

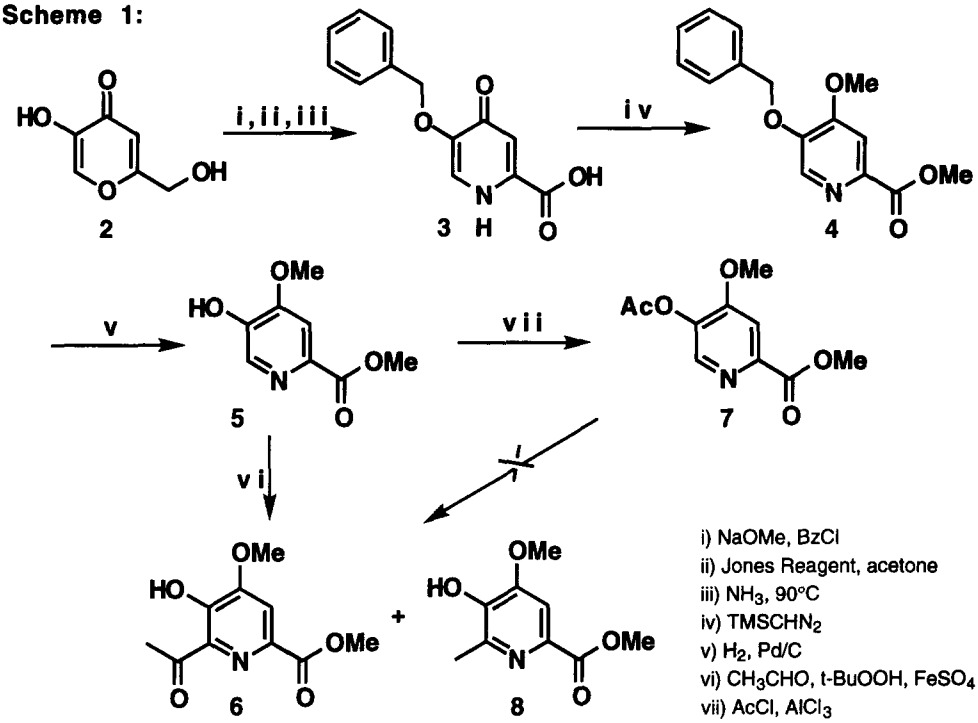


WS75624 B, **1**

As a starting material we chose kojic acid **2**. This commercially available pyrone contains precursors to three of the four needed substitutions required in the final product. Additionally, there already existed in the literature, methodology to convert the pyrone to the pyridone, as well as methods for conversion of the two exocyclic pyrone oxygens to alkoxys. This left as the remaining synthetic obstacle, how to incorporate the thiazole ring at the other alpha position on the pyridyl ring. Our route is shown in Schemes 1-3.

The ring hydroxyl of compound **2** was converted to the benzyl ether with benzyl chloride and sodium methoxide in methanol according to a literature procedure (70% yield).[6] The hydroxy methyl group was then oxidized to the carboxylic acid with Jones reagent in acetone (63% yield).[7] The pyrone was then converted quantitatively to the pyridone **3** by reaction with concentrated ammonium hydroxide in a sealed flask at 90°C.[8]

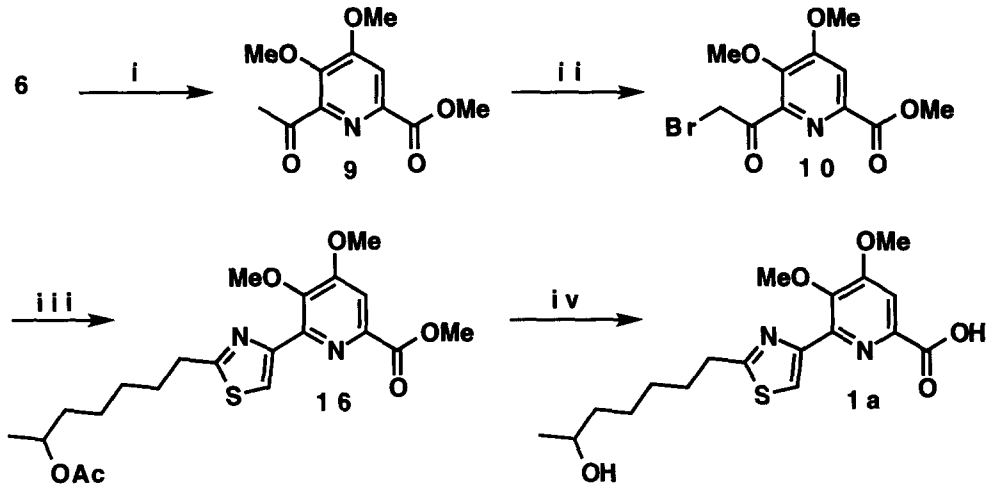
Scheme 1:



Methylation of both the carboxyl and phenolic oxygens was accomplished with trimethylsilyl-diazomethane in 20% methanol in toluene affording the dialkoxy ester **4** in 54% yield. Hydrogenolysis of the benzyl ether with Pd/C in methanol proceeded nicely to give the new phenolic compound **5** in 97% yield. At this point we attempted a Friedel-Crafts acylation to give compound **6**. However, after unsuccessfully trying several conditions with various catalysts and acylating reagents this method was abandoned. The only products isolated from these routes were the O-acyl derivative **7** and the product resulting from ester hydrolysis. Attempted Fries rearrangement of the O-acyl derivative **7** also failed. Fortunately, radical acylation proceeded fairly smoothly.[9] Reacting **5** with acetaldehyde, t-butyl hydroperoxide and iron sulfate in sulfuric acid gave two products. The required acylated material **6** was isolated in 30% yield while a ring methylated byproduct **8** was isolated in 8% yield.

The phenolic oxygen of **6** was methylated with trimethylsilyldiazomethane in 20% methanol in toluene to give the tetrasubstituted pyridine compound **9** in 49% yield (Scheme 2). The acetyl methyl was brominated using pyridinium bromide perbromide in dilute HBr in acetic acid affording the bromide **10** in 75% yield.

Scheme 2:



i) $TMSCHN_2$; ii) pyridine•Br_3, HBr/HOAc; iii) **11**, acetone, r.t.; iv) NaOH

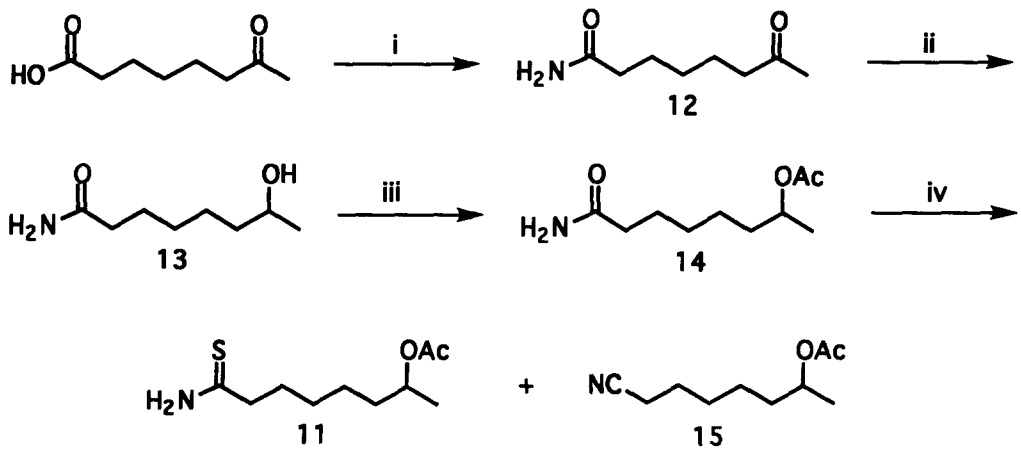
With the pyridine ring ready for subsequent transformations we now needed to synthesize the alkyl thioamide **11**, Scheme 3. 7-Oxooctanoic acid was converted to the amide **12** via the acid chloride in 88% yield. The ketone group of **12** was reduced to the alcohol derivative **13** with sodium borohydride in methanol (65% yield). The hydroxy group was then acylated with acetic anhydride in pyridine giving the protected amide **14** (89% yield). This amide was then converted to the thioamide **11** with Lawessons reagent. This reaction was problematic as a large amount of the nitrile **15** was isolated in virtually every attempt. Under many conditions the nitrile was not only the major product isolated, but the only product isolated. However, we were able to isolate the acetylated thioamide **11** in 60% yield using Lawessons reagent in THF at room temperature for 2 hours.

Coupling of the thioamide **11** with the bromide **10** gave the diprotected penultimate compound **16** in 33% yield, Scheme 2. A major byproduct is formed in this reaction which appears to be a ring demethylated analogue, although the structure has yet to be fully characterized. Basic hydrolysis of the esters gave racemic WS75624 B **1a** in 71% yield. Our compound **1a** has identical ^1H NMR and MS properties[10] to those reported by the Fujisawa group.

This synthetic route can be used to produce analogs at both ring alkoxys and the 2'-position of the thiazole ring. The natural product **1** is suspected to be one enantiomer at the hydroxy position based upon an observed optical rotation reported in the original publication. The absolute configuration has not been reported,

our compound is racemic at this position. In our hands an authentic sample of WS75624 B[11] and our compound **1a** had identical activity against the ECE[12] enzyme.

Scheme 3:



i) $C_2O_2Cl_2$, NH_3; ii) $NaBH_4$; iii) Ac_2O, pyridine; iv) Lawesson's reagent

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10. ^1H NMR (CD_3OD): δ 8.35 (1H, s), δ 7.83 (1H, s), δ 4.08 (3H, s), δ 3.99 (1H, s), δ 3.67 (1H, m), δ 3.11 (2H, m), δ 1.84 (2H, m), δ 1.4 (6H, br m), δ 1.10 (3H, d J= 6Hz). MS (APCI) $[M=1]^+$= 381. Microanalysis: ($C_{18}H_{24}N_2O_5S \cdot 0.5$ H_2O) found C=55.68, H=6.33, N=6.84. HPLC: 98.7%, C18 reverse phase, 1:1(H_2O:CH_3CN), ret.time= 2.4 min.
11. Authentic sample was obtained from Fujisawa Pharmaceutical Co.
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