Pergamon

Tetrahedron Letters 41 (2000) 4061–4064

TETRAHEDRON LETTERS

Synthesis of the novel antibacterial 6,8-dihydroxy-7-propyl-9*H*-pyrrolo[1,2-*b*][1,3]-benzoxazin-9-one

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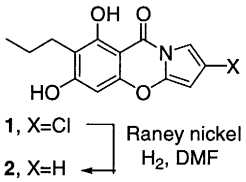
Received 24 January 2000; revised 22 March 2000; accepted 23 March 2000

Abstract

The total synthesis of 6,8-dihydroxy-7-propyl-9*H*-pyrrolo[1,2-*b*][1,3]benzoxazin-9-one, a novel antibacterial agent, is described. The key step in the synthesis is achieved via an oxidative cyclization of a phenol to the 2-position of a pyrrole using stoichiometric $Pd(OAc)_2$. This provides a straightforward approach to the tricyclic structure of this prevously unreported template and future derivatives.

Increasing resistance to existing antibacterial agents necessitates the identification of new templates with activity against resistant strains of bacteria.[1] The novel natural product 2-chloro-6,8-dihydroxy-7-propyl-9*H*-pyrrolo[1,2-*b*][1,3]benzoxazin-9-one (**1**, XR 587) was isolated from *Streptomyces rimosus* during a microbial extract screening program to identify inhibitors of bacterial histidine kinase.[2] This compound demonstrates promising Gram-positive antibacterial activity against both wild-type and resistant strains of bacteria.[3–5] The dechlorination of **1** with Raney nickel in DMF provides 6,8-dihydroxy-7-propyl-9*H*-pyrrolo[1,2-*b*][1,3]benzoxazin-9-one (**2**), which exhibits similar antibacterial activity.[5]



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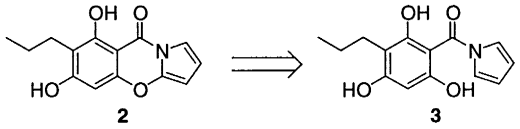
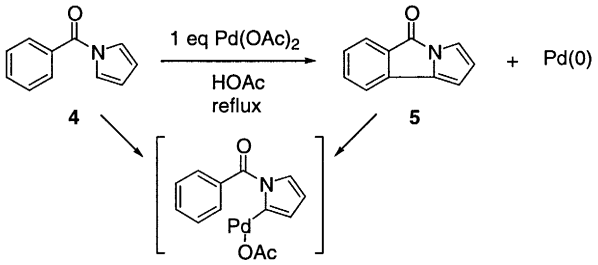
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00590-6

In the course of studying the structure–activity relationships of **2**, we needed to develop a rapid synthetic pathway into this previously unreported ring system. We envisioned the key step into this heterocyclic system to be ring closure of **3** to provide **2** (Scheme 1). The reaction of a phenol coupling to the 2-position of an *N*-acylpyrrole is, to the best of our knowledge, unknown in the literature.



Scheme 1.

Treatment of 1-benzoylpyrroles and 1-acetylindoles with arenes and stoichiometric $Pd(OAc)_2$ is known to give rise to 2-aryl-substituted pyrroles and indoles.[6a] These reactions are proposed to occur via palladation of the 2-position of the electron rich pyrrole or indole rings followed by subsequent attack of the aroyl moiety generating Pd(0) as a by-product as exemplified by the cyclization of **4** to provide **5** (Scheme 2).

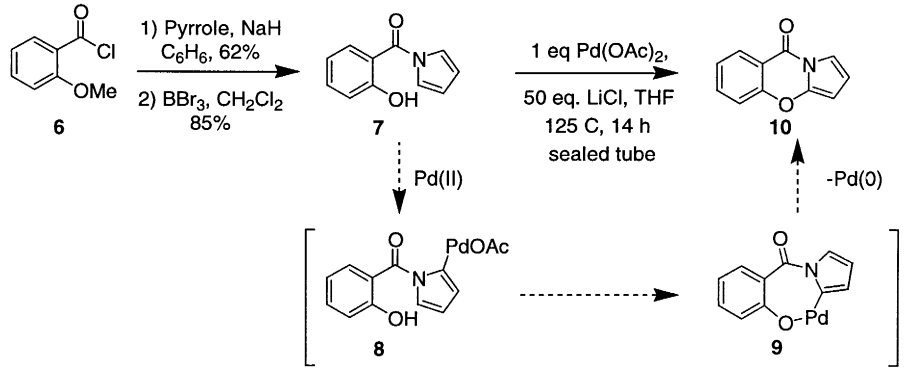


Scheme 2.

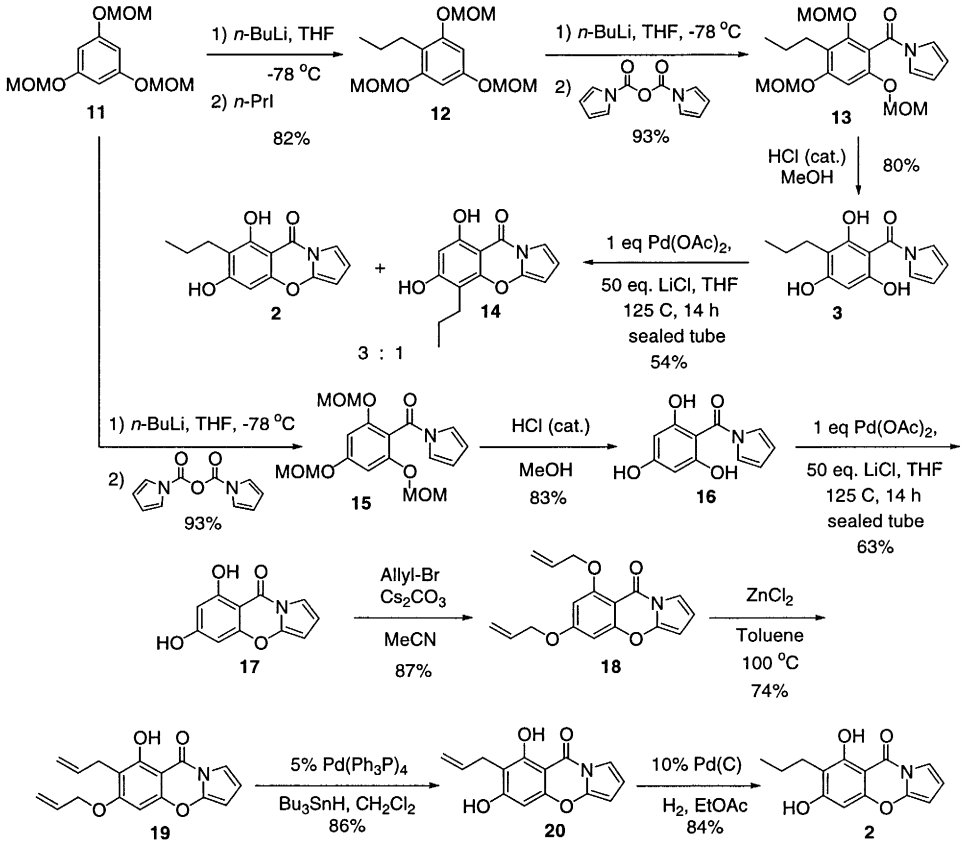
We anticipated that a phenol, under similar conditions, might also serve as an effective coupling partner based on the work of Buchwald and co-workers (Scheme 3).[6b] It was anticipated that **7** would cyclize, via **8** and **9**, to afford **10** upon treatment with a Pd(II) catalyst, the rate determining step presumably being the palladation of the pyrrole ring. We found that treatment of a THF solution of **7**, prepared by the coupling of **6** with pyrrole and subsequent deprotection, with one equivalent of $Pd(OAc)_2$ and 50 equivalents of lithium chloride[7a,b] at 125°C provides the desired cyclized **10** in 54% yield. Other palladium reagents such as $Pd(TFA)_2$ and $PdCl_2$ were less efficient, each producing **10** in less than 10% yield. It was observed that using fewer numbers of equivalents of LiCl (0–10 equiv.) that significantly lower yields were obtained (0–10% yield) suggesting that the ionic strength of the solvent[7b,c] rather than the Lewis acidity of LiCl influences the efficiency of the reaction. The use of bases such as K_2CO_3, KO-*t*-Bu or amine bases provided little reaction and/or decomposition of the substrate. Attempts to make this process catalytic by using 10 mol% of $Pd(OAc)_2$ with $Cu(OAc)_2$ and/or air as oxidants have been unsuccessful.[8]

Using this methodology, our synthesis of **2** began with MOM-protected phloroglucinol (**11**).[9] *ortho*-Directed metallation[10] with *n*-BuLi, followed by treatment with *n*-propyl iodide provided **12** that was then metallated and quenched with 1-pyrrolecarboxylic anhydride[11] to provide the benzoylpyrrole derivative **13** in high yield. Acidic deprotection afforded **3**. Intramolecular cyclization of **3** was carried out as described above to provide a mixture of **2** and **14** in a 3:1 ratio (54% yield). Recrystallization from $CHCl_3$ gave the desired isomer (**2**) as a white crystalline solid (Scheme 4).[12]

In order to avoid isomer formation of the palladium mediated cyclization step, an alternative approach introducing the *n*-propyl group late in the synthesis was undertaken. This synthesis of **2** also began with the *ortho*-directed metallation[10] of MOM-protected phloroglucinol (**11**),[9] followed by treatment



Scheme 3.



Scheme 4.

with 1-pyrrolecarboxylic anhydride[11] to provide the benzoylpyrrole derivative **15** in 93% yield. Acidic deprotection of **15** afforded **16**. The key intramolecular cyclization[13] was carried out to provide the desired ring system **17** in 63% yield. The *n*-propyl side-chain was then introduced by allylation of both phenols to provide **18** that upon treatment with $ZnCl_2$ underwent a Claisen rearrangement generating **19** in good yield. The allyl ether at the 8-position was subsequently cleaved by treatment with Bu_3SnH/5% $Pd(Ph_3P)_4$ to give **20**, which was hydrogenated to generate **2**. Compound **2** was spectroscopically identical to that prepared by semisynthesis (vide supra).[12]

In summary, we have accomplished the first total synthesis of the novel antibacterial agent **2**. The key step involved a palladium mediated cyclization of 1-(2-hydroxybenzoyl)pyrrole to provide the previously unknown pyrrolobenzoxazine ring system. This synthetic methodology has allowed us to explore structure–activity relationships associated with the antibacterial activities of this ring system. These will be reported in due course.

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12. ^{1}H NMR ($CDCl_3$) of **2**: δ 11.48 (s, 1H, 8-OH), 7.19 (m, 1H), 6.46 (m, 1H), 6.29 (s, 1H), 5.82 (m, 1H), 5.48 (s, 1H, 6-OH), 2.64 (t, J=7.6 Hz, 2H), 1.61 (sex., J=7.6 Hz, 2H), 0.99 (t, J=7.6 Hz, 3H).
13. Intramolecular cyclization of **16** was carried out in the following fashion: A pressure bottle charged with 1-(2,4,6-trihydroxybenzoyl)pyrrole (200 mg, 0.912 mmol), $Pd(OAc)_2$ (205 mg, 0.912 mmol), anhydrous LiCl (1.933 g, 45.6 mmol) and THF (5 ml) was heated and stirred at 125°C for 4 h. The mixture was filtered and the solid residue washed with EtOAc. The combined organic phase was washed with brine and dried on Na_2SO_4. Flash chromatography on a silica column with 35% EtOAc/hexane as the eluent afforded the product **17** (124 mg, 63%) as a white crystalline solid. Mp: 201–202°C. ^{1}H NMR ($CDCl_3$): δ 7.20 (dd, J=3.8 Hz, J=1.8 Hz, 1H), 6.47 (t, J=3.7 Hz, 1H), 6.29 (d, J=2.4 Hz, 1H), 6.26 (d, J=2.4 Hz, 1H), 5.84 (dd, J=3.8 Hz, J=1.8 Hz, 1H), 5.48 (s, 1H, -OH).