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PRACTICAL TOTAL SYNTHESIS OF A NATURALLY OCCURRING THIELOCIN VIA THE REGIOSELECTIVE ARYLATION OF A CYCLIC BORONATE

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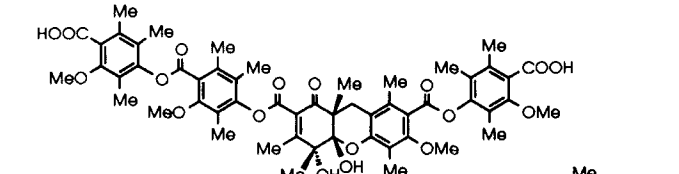
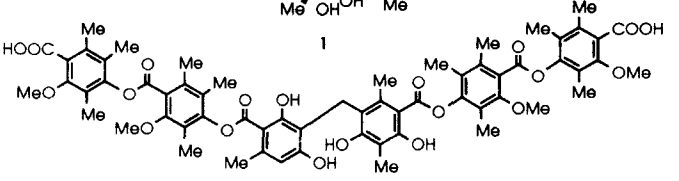
Abstract: *The first total synthesis of thielocin B (2) has been achieved. Lewis acid-catalyzed arylation of the readily available cyclic boronate 8 provided the central portion of the molecule in a regiocontrolled manner. The desired natural compound 2 was then obtained in 7 steps and 31% yield from the intermediate 5.*

We have recently described the first total synthesis of thielocin A1β (**1**) (Figure 1) showing unique inhibitory activities towards secretory phospholipase A_2s.[1] We now wish to report the first total synthesis of another naturally occuring thielocin, termed thielocin B (**2**), isolated from the culture liquors of the same *Thielavia terricola* ascomycetes.[2]

Thielocin B (**2**) (Figure 1) and **1** possess in common the highly substituted phenolic esters characteristic of the depsides. However, **2** lacks the hydroxy diketone moiety (partially masked as an hemiketal) of **1** and could therefore be considered as a reduced analog of thielocin A1β (**1**).

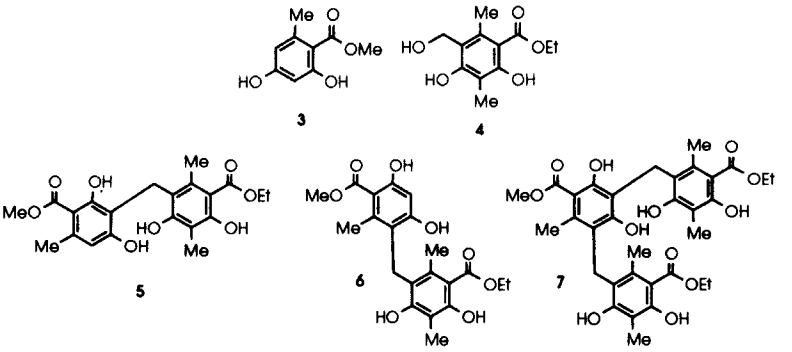
Figure 1





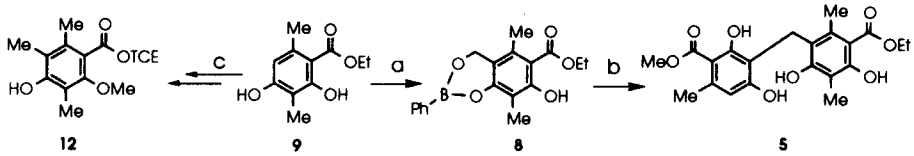
We first focused our studies on an efficient approach to the central portion of the target molecule **2**. A synthesis of related methylene bridged diaromatic structures has been described where a benzylic cation derived by acid-catalyzed decomposition of the corresponding acetate was trapped with a dihydroxybenzene counterpart.[3] Application of this procedure (PTSA, dioxane, reflux) to an equimolar mixture of methyl orsellinate **3**[4] (Figure 2) and benzylic alcohol **4**[5] yielded a mixture of the two possible regioisomers **5** and **6** (50%) along with the diadduct **7** (10%).[6] ^{1}H NMR analysis allowed us to identify the major regioisomer (70/30 ratio) as the desired product **5**. These modest preliminary results as well as the low availability of the alcohol **4**[5] prompted us to develop a more efficient route.

Figure 2



Cyclic boronate **8** (Scheme 1) appeared to be the precursor of choice for the required arylation. Preparation and reactivity of similar species towards various nucleophiles has been well studied by Cheuk K. Lau and collaborators.[7] In particular, Lewis acid-catalyzed arylation by a phenol has been described. Key intermediate **8** was obtained as a stable solid in 90% yield from the readily available orsellinate **9**[4] ($PhB(OH)_2$, $(CHO)_n$, $EtCO_2H$, toluene, reflux). We then investigated the coupling reaction with phenol **3**. Optimization of the experimental conditions showed that treatment of cyclic boronate **8** with three equivalents of **3**[8] (2.2 equiv. of $BF_3{\cdot}Et_2O$, $CHCl_3$, -10 °C) yielded the desired regioisomer **5** (93/7 ratio) with 77% isolated yield.[9]

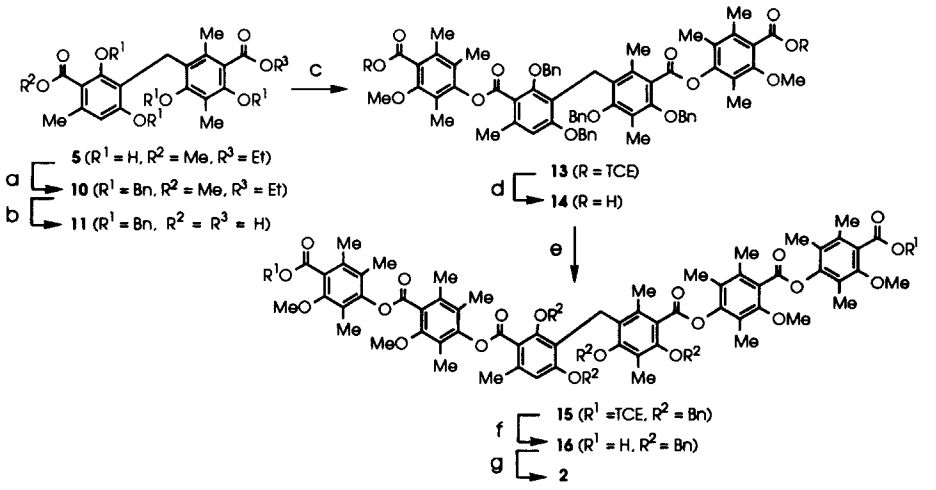
Scheme 1



Reagents and conditions: a) $PhB(OH)_2$, $(CHO)_n$, $EtCO_2H$, toluene, reflux, 1h, 90% b) **3**, $BF_3{\cdot}Et_2O$, $CHCl_3$, -10 °C, 15h, 77% c) TCE= 2,2,2-trichloroethyl, 4 steps and 49% overall yield from **9**: see ref. 1

Having in hand a direct and efficient access to the central portion of the desired thielocin B (**2**) we further elaborated the polyphenolic side chains. After perbenzylation (BnBr, K_2CO_3, acetone, reflux), the protected diester **10** (78%) (Scheme 2) was hydrolyzed (KOH, DMSO, 90 °C)[10] to the corresponding dicarboxylic acid **11** (79%). We then formed the phenolic ester bonds in a sequential manner: although less convergent, this approach presented the double advantage of 1) avoiding the preparation of the otherwise required phenolic dimer[11] and 2) providing access to potentially interesting simplified analogs of **2**. Bis-esterification of **11** with appropriately protected phenolic monomer **12**[12] (TFAA, toluene)[13] afforded the tetrameric derivative **13** (92%). Subsequent hydrolysis of the two 2,2,2-trichloroethyl (TCE) esters (Cd, DMF/AcOH)[14] followed by bis-esterification of the resulting dicarboxylic acid **14** (94%) with **12** (TFAA, toluene) gave protected thielocin **15** (80%). Due to their potential sensitivity to hydrogenation[15] the TCE esters were removed first. Thus, hexameric dicarboxylic acid **16** (85%) was obtained from **15** (Cd, DMF/AcOH) and final hydrogenolysis of the benzyl ethers (Pd/C 10%, H_2, AcOH) provided title compound **2** (85%). Thielocin B (**2**), which gave physical and spectral data consistant with the published data,[16] was thus obtained in nine steps and 21% overall yield from the orsellinate precursor **9**.

Scheme 2



Reagents and conditions: a) BnBr, K_2CO_3, acetone, reflux, 4h, 78% b) KOH, DMSO, 90 °C, 8h, 79% c) **12**, TFAA, toluene, 25 °C, 2h, 92% d) Cd, DMF/AcOH, 25 °C,, 1h, 94% e) **12**, TFAA, toluene, 25 °C, 2h, 80% f) Cd, DMF/AcOH, 25 °C, 1h, 85% g) Pd/C 10%, H_2, atm. pressure, AcOH, 25 °C, 4h, 85%

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References and Notes:

1. Génisson, Y.; Tyler, P. C.; Young, R. N. *J. Am. Chem. Soc.* **1994**, *116*, 759.
2. JP App. No 2-285599 (22.10.90).
3. Elix, J. A.; Evans, J. E.; Parker, J. L. *Aust. J. Chem.* **1987**, *40*, 2129.
4. Compounds **3** and **9** were prepared in two steps from commercially available ethyl crotonate and respectively ethyl acetoacetate or methyl propionylacetate: Dyke, H. J.; Elix, J. A.; Marcuccio, S. M.; Whitton, A. A. *Aust. J. Chem.* **1987**, *40*, 431.
5. Intermediate **4** was obtained in 15% yield by reduction ($NaBH_4$, MeOH) of the corresponding aldehyde previously described in ref. 1. This alcohol was found to be sensitive to acid-promoted decomposition during purification (SiO_2).
6. The Lewis acid-catalyzed version of this coupling ($ZnCl_2$, CH_2Cl_2, 25 °C) gave the same product distibution.
7. Chambers, J. D.; Crawford, J.; Williams, H. W. R.; Dufresne, C.; Scheigetz, J.; Bernstein, M. A.; Lau, C. K. *Can. J. Chem.* **1992**, *70*, 1717 and references cited therein.
8. Unreacted material could be simply recovered by flash chromatography.
9. Reactions monitored by HPLC (column Nova-pak® C18, eluent MeOH/0.2% aq. AcOH (81:19), flow 1mL/min, λ 270 nm): three equivalents of **3** were sufficient to prevent formation of diadduct **7**. A greater excess of $BF_3{\cdot}Et_2O$ resulted in a important loss of selectivity ($SnCl_4$, $Ti(OEt)_4$, Et_2AlCl, $EtAlCl_2$, ZnI_2 or TFA in CH_2Cl_2 gave either no reaction or decomposition). No obvious solvent effect could be observed and only $CHCl_3$ gave a slightly better product ratio (CH_2ClCH_2Cl, CCl_4, 1,2-dichlorobenzene and toluene were tried with $BF_3{\cdot}Et_2O$). A lower reaction temperature led to unacceptably long reaction times.
10. Elix, J. A.; Norfolk, S. *Aust. J. Chem.* **1975**, *28*, 1113.
11. This sequence requires consecutive silylation and desilylation of the phenol present on the precursor **12**.
12. Prepared in four steps and 49% overall yield from orsellinate **9**: see ref. 1.
13. Parish, R. C.; Stock, L. M. *J. Org. Chem.* **1965**, *30*, 927.
14. Hancock, G.; Galpin, I. J.; Morgan, B. A. *Tetrahedron Lett.* **1982**, *23*, 249. These conditions gave cleaner results than Zn in AcOH.
15. Reduction of trichloroethyl ester to ethyl ester was observed during catalytic hydrogenation in AcOH of a monomeric related aromatic derivative: Génisson, Y.; Young, R. N. unpublished results.
16. HRMS, IR and mp (198-201 °C (lit. 194-197 °C)) were found essentially identical to those reported: see ref 2.
    ^1H NMR (400MHz, $CDCl_3/CD_3OD$ (9:1)) δ 6.38 (s, 1H, arom. H), 4.00 (s, 2H, CH_2), 3.82-3.74 (m, 12H, 4OMe), 2.86 (s, 3H, Me), 2.61 (s, 3H, Me), 2.35 (s, 6H, 2Me), 2.24 (s, 6H, 2Me), 2.20 (s, 6H, 2Me), 2.17 (s, 6H, 2Me), 2.13 (s, 3H, Me), 2.12 (s, 3H, Me), 2.09 (s, 3H, Me), 2.08 (s, 3H, Me), 2.07 (s, 3H, Me)
    ^{13}C NMR (100MHz, $CDCl_3/CD_3OD$ (9:1)) δ 170.3, 170.0, 166.4, 166.3, 163.6, 161.0, 160.1, 159.2, 154.2, 152.6, 149.8, 149.3, 148.6, 141.6, 139.3, 133.3, 133.3, 131.8, 129.1, 126.2, 125.7, 125.6, 125.4, 121.9, 121.8, 121.6, 118.3, 111.6, 111.2, 109.8, 104.5, 103.1, 61.9, 61.6, 24.5, 20.0, 19.4, 16.9, 16.3, 12.9, 12.8, 12.6, 10.8, 9.96, 9.81, 8.04.

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