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TOTAL SYNTHESIS OF A MARINE ALKALOID, RIGIDIN

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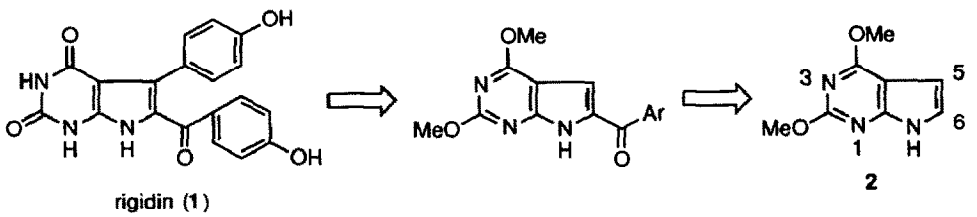
Abstract: Rigidin, a marine alkaloid, was synthesized by the combination of acylation *via* lithiation and arylation by palladium-catalyzed reaction starting from 2,4-dimethoxypyrrolo[2,3-*d*]pyrimidine.

Rigidin (**1**), a marine alkaloid, was isolated and characterized in 1990 by Kobayashi, *et al.* from the Okinawan marine tunicate *Eudistoma* cf. *rigida* and was found to inhibit calmodulin activated brain phosphodiesterase.[1] In connection with our studies on the pyrrole fused heteroaromatics synthesis,[2] we are intrigued by the novel structure and biological activity of rigidin. We wish to report here a concise total synthesis of rigidin. Recently, the first total synthesis starting from 6-chlorouracil was reported by Edstrom, *et al.*,[3] which starts from the pyrrole ring formation.[2] In our synthesis, we chose readily available 2,4-dimethoxypyrrolo[2,3-*d*]pyrimidine (**2**) as a starting material. We have reported a facile synthesis of pyrrolo[2,3-*d*]pyrimidines from aminohalopyrimidines and (*Z*)-1-ethoxy-2-(tributylstannyl)ethene by palladium-catalyzed reaction as a key step[2d] and the compound **2** could be prepared by our method[2d] or classical pyrimidine ring construction method.[4]

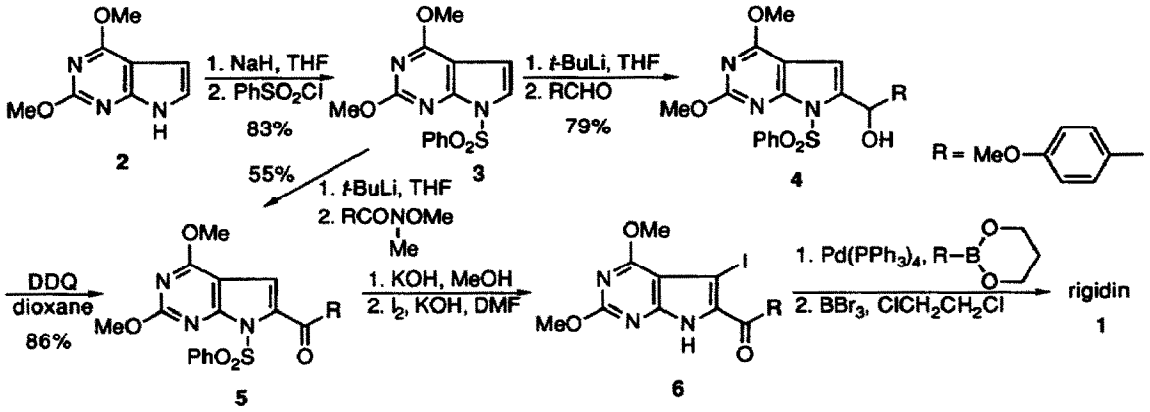


rigidin (**1**)

Our strategy to synthesize rigidin consists of the acylation *via* lithiation at the 6-position and the palladium-catalyzed arylation at the 5-position of 2,4-dimethoxypyrrolo[2,3-*d*]pyrimidine (**2**).

In order to acertain favorable directed metallation group (DMG) for the lithiation at the 6-position of **2**, some 2,4-dimethoxypyrrolo[2,3-*d*]pyrimidines having DMGs at the 7-position were reacted with *tert*-butyllithum in tetrahydrofuran (THF) at -78°C and quenched with deuterium oxide. As a result, 7-phenylsulfonyl group was found to be a better DMG than *tert*-butoxycarbonyl or lithiooxycarbonyl group. Based on the results, 7-phenylsulfonyl derivative (**3**) was converted to the carbinol (**4**) by the lithiation with *tert*-butyllithium and the subsequent reaction with 4-methoxybenzaldehyde in 79% yield. The carbinol (**4**) was transformed by the oxidation with dichlorodicyano-1,4-benzoquinone (DDQ) to the 4-methoxybenzoyl derivative (**5**)[5] in 86 % yield. Compound **5** was also obtained directly from **3** by the lithiation and the subsequent acylation with *N*-(4-methoxybenzoyl)-*N*,*O*-dimethylhydroxylamine. The 5-(4-methoxybenzoyl) derivative (**5**) was treated with potassium hydroxide in

aqueous methanol to give the desulfonylated pyrrolopyrimidine which was iodinated with iodine in the presence of potassium hydroxide in dimethylformamide (DMF) to yield 5-iodo derivative (**6**)[5] in 78% overall yield.



Suzuki reaction[6] was effective for introducing the aromatic ring at the 5 position, and compound **6** was reacted with 2-(4-methoxyphenyl)-1,3,2-dioxaborinane in the presence of tetrakis(triphenylphosphine)palladium in DMF at 100°C to give the 5-(4-methoxyphenyl) derivative in 60% yield which was demethylated with boron tribromide in 1,2-dichloroethane to afford rigidin (**1**)[5] in 41% yield, which spectral data was superimposable with the reported data.[1] Thus we accomplished a total synthesis of rigidin in only 6 steps from the known, readily available material **2**.

References and Notes

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3. Edstrom, E. D.; Wei, Y. *J. Org. Chem.*, **1993**, *58*, 403.
4. Seela, F.; Liman, U. *Liebigs Ann. Chem.* **1984**, 273.
5. Compound **5**: mp 199-200°C; IR ($CHCl_3$) cm^{-1}: 1600; ^{1}H-NMR ($CDCl_3$) δ : 3.91 (3H, s), 4.06 (3H, s), 4.15 (3H, s), 6.78 (1H, s), 6.99 (2H, d, *J*=8.8), 7.6-7.7 (3H, m), 8.02 (2H, d, *J*=8.8), 8.50 (2H, d, *J*=7.0).
Compound **6**: mp 214-216°C (decomp.); IR ($CHCl_3$) cm^{-1}: 3400; ^{1}H-NMR ($CDCl_3$) δ : 3.90 (3H, s), 4.03 (3H, s), 4.15 (3H, s), 6.99 (2H, d, *J*=8.4), 7.83 (2H, d, *J*=8.8), 9.34 (1H, brs).
Compound **1** (rigidin): mp > 300°C; IR (KBr) cm^{-1}: 3200, 1700; ^{1}H-NMR (DMSO-d_6) δ : 6.45 (1H, d, *J*=8.1), 6.47 (1H, d, *J*=7.3), 6.95 (2H, d, *J*=8.8), 7.29 (2H, d, *J*=7.3), 9.25 (1H, brs), 10.0 (1H, brs), 10.6 (1H, brs), 11.2 (1H, brs), 11.8 (1H, brs)
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