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Total Syntheses of the Marine Pyrrole Alkaloids Polycitone A and B

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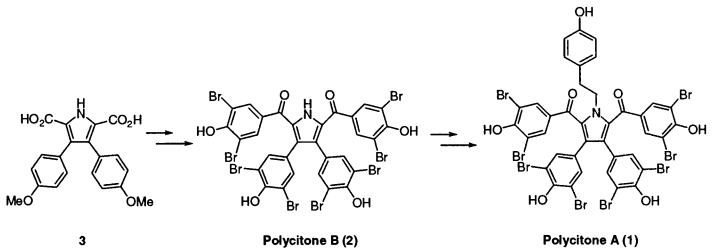
ABSTRACT



Polycitone B (2) was obtained in four steps from pyrrole dicarboxylic acid 3, including Friedel–Crafts reaction of the corresponding acid chloride with anisole. The conversion of 2 into polycitone A (1) was achieved in two steps via Mitsunobu alkylation of the pyrrolic NH group. The synthesis of polycitone A proceeds in 18% overall yield and offers the possibility of varying the substituents on the pyrrole ring.

The polycitones A and B (**1** and **2** respectively) are polybrominated pyrrole alkaloids and were isolated by Kashman and co-workers[1,2] from marine ascidians of the genus *Polycitor*. Polycitone A was found to be a potent inhibitor of retroviral reverse transcriptases (i.e., human immundeficiency virus type 1) and cellular DNA polymerases.[3] In a continuation of our studies on the biomimetic synthesis of marine 3,4-diarylpyrrole alkaloids,[4] we now report the first total syntheses of the polycitones A and B. Our syntheses commence with dicarboxylic acid **3** used previously for the preparation of polycitrin A.[5] Compound **3** is easily obtained in 72% yield by oxidative coupling of

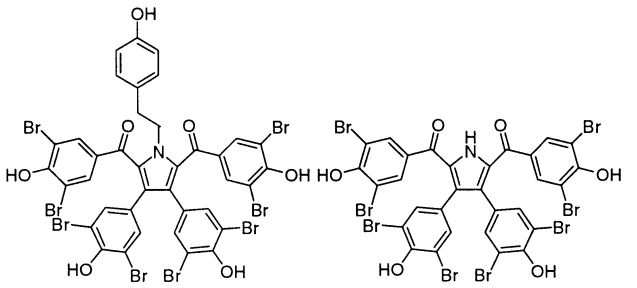


Figure 1.

the dianion of 3-(4-methoxyphenyl)pyruvic acid and cyclization of the resulting 1,4-dicarbonyl intermediate with ammonia. Treatment of dicarboxylic acid **3** with oxalyl chloride followed by removal of the solvent and rigorous drying yielded the crude acid chloride **4**, which reacted with anisole

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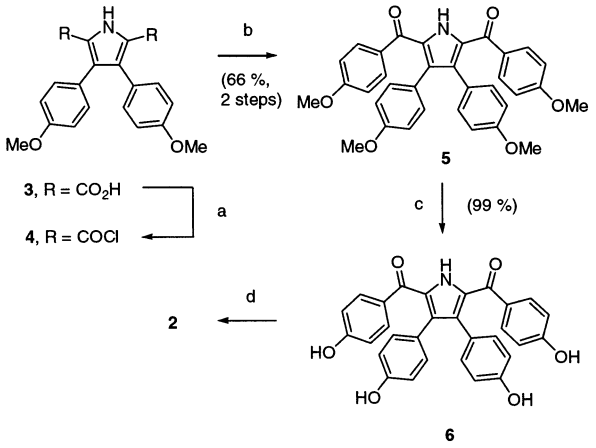
under Friedel−Crafts conditions to afford the diketone **5** in 66% yield (Scheme 1). Surprisingly, this convenient method

Scheme 1. Synthesis of Polycitone B[a]



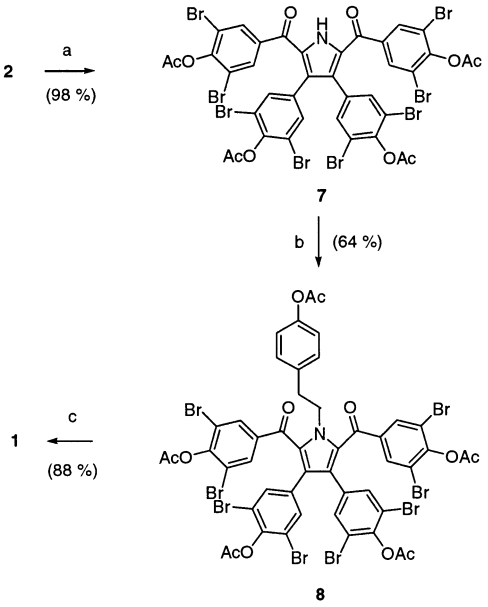
[a] Reagents and conditions: (a) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C, 2 h; (b) $AlCl_3$, PhOMe, CH_2Cl_2, rt, 12 h; (c) AlI_3 (freshly prepared from Al powder and I_2), *n*-$Bu_4N^+I^-$, PhH, reflux, 12 h; (d) Br_2, AcOH, rt, 48 h.

for the synthesis of a 2,5-dibenzoylpyrrole[6] from the corresponding pyrrole dicarboxylic acid chloride[7] has not been used before.

Attempted cleavage of the methoxy groups with BBr_3, $AlBr_3$, EtSNa, or pyridine hydrochloride gave only partially demethylated products. These difficulties were solved by using freshly prepared AlI_3[8] in the presence of *n*-$Bu_4N^+I^-$ as a phase transfer catalyst.[9] The resulting tetraphenol **6** was then brominated in acetic acid at room temperature to provide polycitone B (**2**) in 83% yield. The ^1H NMR data derived from the synthetic material were in close correspondence with those reported in the literature.[2] The chemical shifts in the ^{13}C NMR spectra exhibited small differences that may be explained by solvent effects.

For the synthesis of polycitone A (**1**) (Scheme 2), polycitone B (**2**) was converted into the tetraacetate **7**, which upon treatment with 2-(4-acetoxyphenyl)ethanol under Mitsunobu conditions in refluxing THF afforded peracetylpolycitone A (**8**) in 64% yield after purification by column chromatography (in contrast, unbrominated analogues of compound **7** could be alkylated already at room temperature and provided the corresponding *N*-alkyl derivatives in much better yields). The acetyl groups in **8** were removed under

Scheme 2. Synthesis of Polycitone A[a]



[a] Reagents and conditions: (a) AcCl (10 equiv), NEt_3 (6 equiv), CH_2Cl_2, rt, 12 h; (b) 2-(4-acetoxyphenyl)ethanol (4 equiv), PPh_3 (4 equiv), DEAD (4 equiv), dry THF, reflux, 2 h; (c) $N_2H_4 \cdot H_2O$ (20 equiv), dry MeOH, rt, 45 min.

mild conditions with hydrazine monohydrate in dry methanol[10] to give polycitone A (**1**), as a yellow solid, in 88% yield. Whereas the free phenol **1** exhibited small differences from the reported ^{13}C NMR data for the natural product, the data of the permethyl derivative[1] obtained from synthetic **1** by treatment with Me_2SO_4 and K_2CO_3 were in complete agreement.

In summary our synthesis afforded polycitone A in eight steps and 22% overall yield from 3-(4-methoxyphenyl)-pyruvic acid. The synthesis is very flexible and can be easily adapted to the preparation of analogues. Attempts to shorten our syntheses by oxidative coupling of benzylic 1,2-diketones and subsequent cyclization with ammonia or amines to 2,5-dibenzoylpyrroles have been unsuccessful.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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