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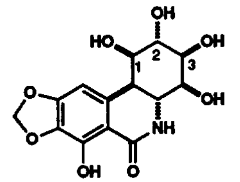
Quinone Methide Initiated Cyclization Reactions: Studies Toward The Synthesis of (+)-Pancratistatin

Steven R. Angle* and Michael S. Louie[1]

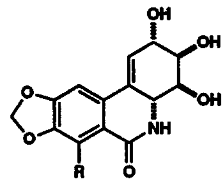
Department of Chemistry, University of California-Riverside
Riverside, California 92521-0403

Abstract: The synthesis of highly functionalized cyclohexenone **15**, a possible precursor for (+)-pancratistatin, was accomplished in 15 steps (10% yield) from aldehyde **4** via a quinone methide initiated cyclization reaction.

(+)-Pancratistatin, **1**, is a phenanthridone alkaloid that was isolated by Pettit and coworkers from the root of the native Hawaiian plant, *Pancratium littorale*.[2] It is structurally similar to the previously known biologically active anhydro and anhydrodeoxy *Amaryllidaceae* alkaloids narciclasine,[3] **2**, and lycoricidine,[4] **3**, which are also obtained from the same extract. Interest in pancratistatin was stimulated by its particularly promising efficacy in several antineoplastic test screens.[2] Although pancratistatin was found to exhibit pronounced *in vivo* antineoplastic activity in animal models, and demonstrated significantly higher therapeutic indices than its congeners **2** and **3**,[2] preclinical development has been impeded by the paucity of the natural product. Conversion of readily available narciclasine to pancratistatin has not been successful to date.[5]



1 Pancratistatin



2 Narciclasine, R = OH
3 Lycoricidine, R = H

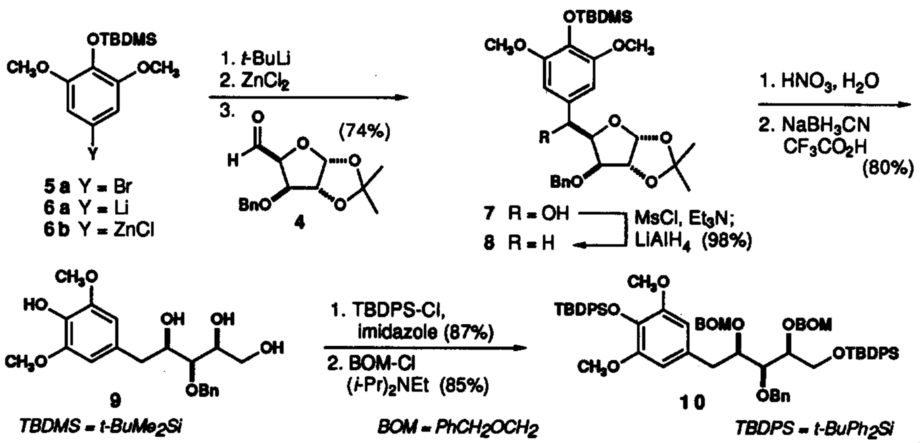
The limited availability of (+)-pancratistatin for further biological evaluation has stimulated synthetic efforts by several groups. Danishefsky and Lee have reported the only total synthesis thus far.[5] Their synthesis is a landmark first effort in this area and provided racemic pancratistatin in 0.13% overall yield via a 26 step route. Groups led by Hudlicky,[3b] Kallmerten,[6] and Clark[7] have reported synthetic approaches to pancratistatin.

Previous work from our laboratory has shown quinone methide initiated cyclization reactions can be used to assemble 5, 6, and 7-membered carbocycles with pendant aromatic rings.[8] Application of this methodology to the synthesis of (+)-pancratistatin requires the synthesis of a highly functionalized quinone methide which would allow us to examine the synthesis, stability, and chemistry of complex quinone methides. We report here the initial results of our studies toward the synthesis of (+)-pancratistatin.

The carbohydrate like appearance of pancratistatin, led us to consider carbohydrates as starting materials.[9] The absolute stereochemistry at C(1), C(2) and C(3) of (+)-pancratistatin corresponds to C(2), C(3) and C(4) of glucose. A survey of the literature showed that aldehyde **4** (Scheme 1), a suitably functionalized starting material, had been prepared from diacetone glucose in 3 steps by Wolfrom and Hanessian.[10]

Treatment of readily available aryl bromide **5**[11] with *t*-butyl lithium at -78 °C afforded aryl lithium **6a** which was found to have very limited stability (half-life *ca.* 0.75 h at -78 °C).[12] However, transmetalation of **6a** with $ZnCl_2$ afforded aryl zinc **6b** which was found to be much more stable.[12] Condensation of **6b** with aldehyde **4**,[10] afforded alcohol **7** in 74% yield as a single diastereomer (Scheme 1).[13] This high degree of diastereoselectivity agreed with results by Wolfrom and Hanessian in which they observed that organometallic reagents generally add to aldehyde **4** with chelation control, to afford products with excellent stereoselectivity.[10] Deoxygenation was effected by conversion of alcohol **7** to the methanesulfonate followed by reduction with $LiAlH_4$ to afford deoxyxylose derivative **8** in 98% yield. Hydrolysis of the acetonide with 20% aqueous nitric acid in DME (1:1; 50 °C, 3.5 h) afforded the hemiacetal in 86% yield as a 1:2 mixture of α:β anomers. Reduction ($NaBH_3CN$, CF_3CO_2H, CH_3CH_2OH/THF, 25 °C)[14] afforded **9** in 93% yield. Selective protection of the primary alcohol and the phenol was achieved by treatment of **9** with *t*-butyldiphenylsilyl chloride (TBDPS-Cl, imidazole, DMF/CH_2Cl_2, -42 °C) in 87% yield. Treatment of the resulting diol with benzyl chloromethyl ether (BOM-Cl, 6 equiv) in the presence of Hunig's base (6 equiv, no solvent, 25 °C, 22 h) afforded **10** in 85% yield. Overall, the **4** to **10** conversion was achieved in 43% yield (6 steps).

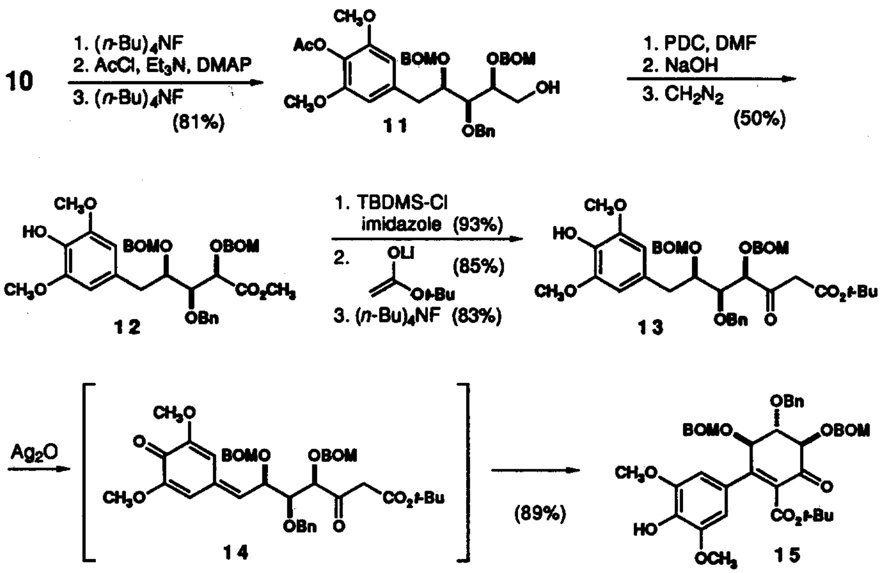
Scheme 1. Synthesis of 10.



Selective deprotection of the phenolic TBDPS ether was accomplished by treatment of **10** with one equiv of (n-Bu)$_4$NF (25 °C, 30 min; 92%, Scheme 2).[15] Treatment of the resulting phenol with acetyl chloride (1.3 equiv, Et_3N, cat. DMAP, CH_2Cl_2; 99%) afforded the acetate which was treated with fluoride ((n-Bu)$_4$NF, 2.0 equiv; THF, 25 °C, 2 h; 89%) to afford primary alcohol **11** in

81% yield for the 3 steps. Oxidation of **11** with PDC (19 equiv) in DMF (25 °C, 19 h), followed by hydrolysis (NaOH, 3 equiv; CH_3OH/H_2O 3:1, 0 °C, 30 min) and esterification (CH_2N_2) afforded **12** in 50% yield. It was necessary to have an electron withdrawing group on the phenol to suppress oxidation of the electron rich aromatic ring; oxidation of the unprotected phenol or the corresponding TBDMS ether afforded products in low yields. Homologation of **12** by condensation with the enolate of *t*-butyl acetate afforded phenol **13** in modest yields (5-15%). A more lengthy, but higher yielding procedure was to protect the phenol of **12** as the TBDMS ether (TBDMS-Cl, 1.1 equiv; imidazole, CH_2Cl_2, 25 °C, 24 h; 93%), carry out the homologation (LDA, 15 equiv; CH_3CO_2t-Bu, 17 equiv; THF, -78 °C, 4 h; 85%), and then deprotect ((*n*-Bu)$_4$NF, 1.1 equiv; THF, 30 min, 25 °C; 83%) the phenol. The large excess of ester enolate was required for a good yield in the acylation. The conversion of **12** to **13** was accomplished in 66% yield by this 3 step procedure. Oxidation of **13** with excess Ag_2O (30 equiv; CH_2Cl_2, 25 °C, 24 h)[8a] afforded **15** in 89% yield.[16]

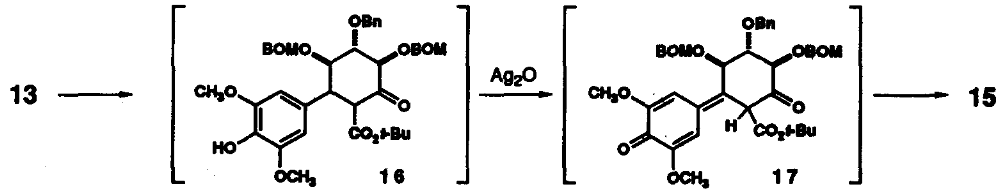
Scheme 2. Cyclization of Quinone Methide 14.



The formation of cyclohexenone **15** was precedented in our earlier work.[8a] The progress of the oxidation was monitored by ^{1}H NMR using 3 equiv of Ag_2O. The disappearance of phenol **13** with concomitant formation of quinone methide **14** was clearly observed. The disappearance of **14** was accompanied by the formation of an intermediate, believed to be cyclohexenone **16** (eq 1). The formation of **15** must occur via oxidation of **16** to quinone methide **17** (which is not observed) followed by loss of the acidic hydrogen activated by both the ketone and the ester moieties.

The high yield of **15** shows the viability of quinone methide initiated cyclization methodology for the synthesis of enantiopure intermediates that might be further elaborated into pancratistatin. Ketone **15** possesses 3 of the stereogenic centers of (+)-pancratistatin in their correct absolute and relative orientations and suitable functionality to allow transformation to the natural product. In

(equation 1)



addition to pursuing this strategy, we are currently investigating alternative approaches that prevent the second oxidation (to **17**) and allow the synthesis of a cyclohexanone with 5 stereogenic centers in the proper orientation required for pancratistatin. Results will be reported in due course.

ACKNOWLEDGMENTS
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11. Bromide **5** was prepared from 2,6-dimethoxyphenol by reaction with dioxane dibromide monohydrate to afford a 1:1 mixture of 3- and 4-bromo-2,6-dimethoxyphenols. The 4-bromo-isomer readily crystallized affording 4-bromo-2,6-dimethoxyphenol (Foley, J. W., U. S. Patent 4,182,912, 1980; *Chem. Abstr.* **1980**, *92*, 163705x) in 50% yield. Silylation (TBDMS-Cl) afforded **5** in 45% overall yield.
12. The stability of **6a/b** was ascertained by quenching an aliquot into D_2O and measuring D incorporation by integration of the ^1H NMR spectrum.
13. All new compounds showed satisfactory ^1H NMR, ^{13}C NMR, IR, and MS spectral data, and HRMS or combustion analysis consistent with the elemental composition.
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16. The stereochemistry of **15** was based on ^1H NMR coupling constants [*J* H(1)-H(2) = 7.8 Hz; *J* H(2)-H(3) = 10.3 Hz] which agree with predicted values determined by MMX calculations (pancratistatin numbering). In addition, irridation of the resonance for H(3) in a difference NOE experiment showed no enhancement of the signal for H(2) and a 2% enhancement of the signal for H(1). This is consistent with the cis diaxial orientation of H(1) and H(3), and the trans orientation of H(3) and H(2). See reference 9 for details.

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