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Synthesis of the Cyclobutylfuran Sector of Providencin via Zirconium-mediated Oxygen Abstraction from a Furanoside

James D. White* and Somnath Jana

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

james.white@oregonstate.edu

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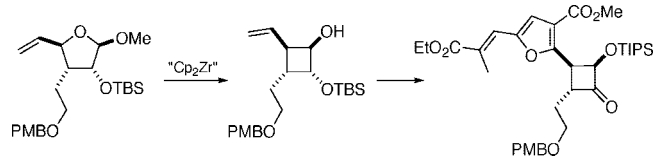
ABSTRACT



A portion of the macrocyclic cembrenoid diterpene providencin possessing conjoined cyclobutane and furancarboxylate units was synthesized from D-glucose using deoxygenative ring contraction methodology to construct the tetrasubstituted cyclobutane and a Knoevenagel condensation of glyceraldehyde to fabricate the trisubstituted furan.

Investigation of chemical constituents of the gorgonian octoral *Pseudoterogorgia kallos* found in shallow waters of the South West Caribbean has brought to light several new cembrenoid diterpenes with interesting biological properties.[1] Recently, Rodriguez et al. isolated a highly oxygenated cembrenoid from this organism that they named providencin[2] and for which X-ray crystallographic analysis revealed the structure and relative configuration represented as **1**.[3] Providencin manifests a unique bicyclo[12.2.0]hexadecane scaffold incorporating a trisubstituted furan linked directly to a tetrasubstituted cyclobutane as well as an unusual α,γ-bridged β,γ-epoxy-γ-lactone. The 1,2,3,4-tetrasubstituted cyclobutane of providencin presents a particularly intriguing synthetic challenge, and it was this feature of the structure that initially drew our interest toward a synthesis of **1**.

Our plan for construction of the providencin skeleton shown in Scheme 1 envisioned dissection of **2** at bonds C9−C10 and C12−C13.[4] For the linked furan-cyclobutane component **3**, we required a blueprint that would place three of the four cyclobutane substituents in a firmly defined,

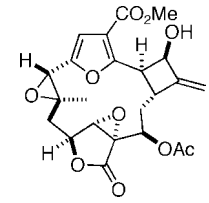


Figure 1. Structure of providencin (**1**).

nonepimerizable configuration while leaving us a "handle" from which the furan could be assembled. This premise led to **4** as our cyclobutane template and to D-glucose (**5**) as the progenitor of **4**.[5] The key transformation of **5** to **4** is predicated upon zirconium-mediated deoxygenative ring contraction of a furanoside, a process first described by Taguchi[6] and subsequently employed by Paquette as an entry to enantiopure cyclobutanols.[7]

(1) Look, S. A; Burch, M. T.; Fenical, W. *J. Org. Chem.* **1985**, *50*, 5741.
(2) Named for the isolation site near the island of Providencia.
(3) Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G. *Org. Lett.* **2003**, *5*, 2551.
(4) Numbering conforms to the cembranoid convention.
(5) For a different approach to this segment of providencin, see: Bray, C. D.; Pattenden, G. *Tetrahedron Lett.* **2006**, *47*, 3937.
(6) (a) Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835. (b) Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 229.

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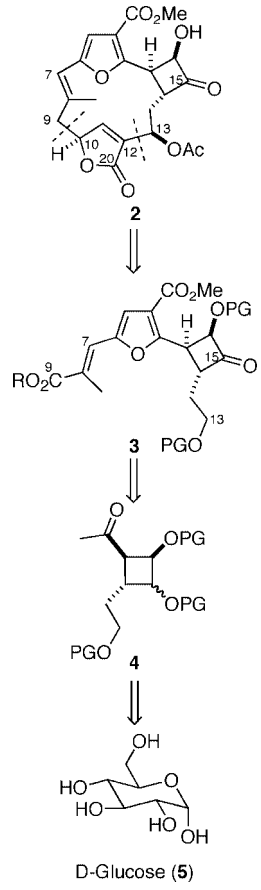
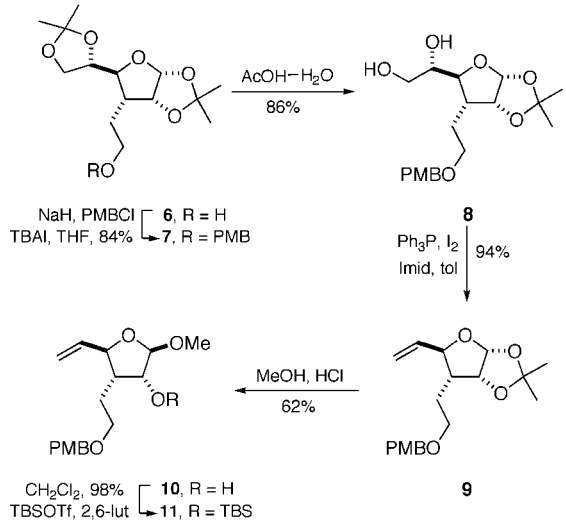
Scheme 1. Retrosynthetic Analysis of Providencin

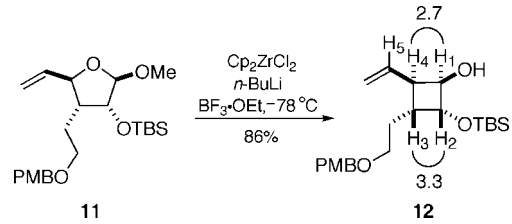


The known alcohol **6**,[8] prepared in four steps from D-glucose (**5**) via its diacetonide,[9] was first protected as its *p*-methoxybenzyl ether **7** (Scheme 2).[10] Selective hydrolysis of the exocyclic acetonide of **7**[8] afforded diol **8** which was treated with iodine, triphenylphosphine, and imidazole in hot toluene to give the 2-vinyltetrahydrofuran **9**.[11] Acid-catalyzed methanolysis of **9** furnished tetrahydrofuranol **10**, which was protected as its silyl ether **11**.

Scheme 2. Synthesis of Furanoside **11**

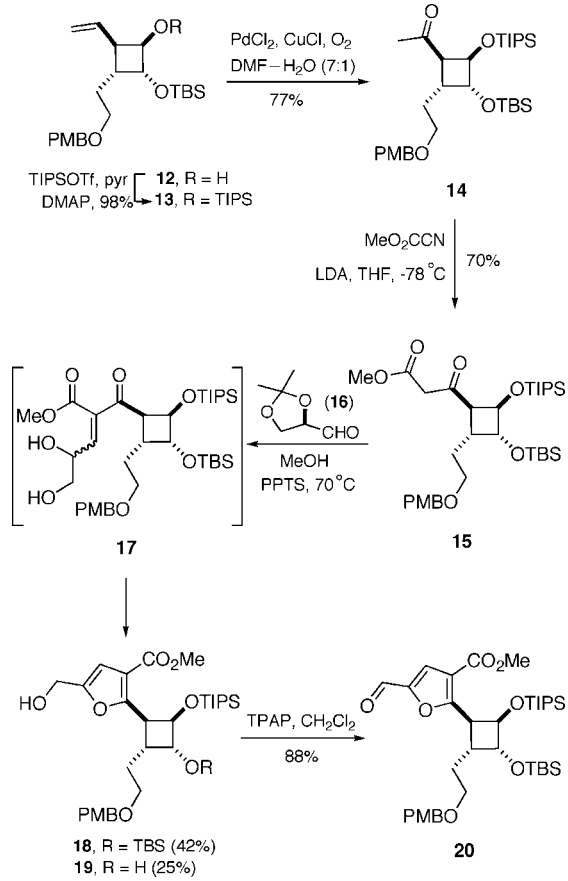


Scheme 3. Oxygen Atom Abstraction from **11** and NOE Correlations of **12**

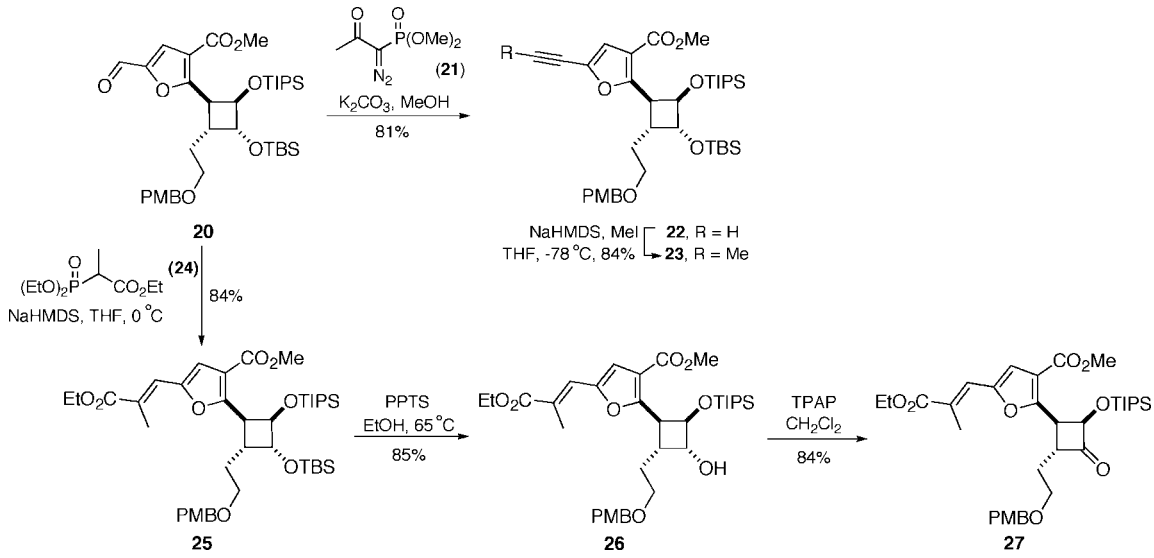


The zirconium reagent, nominally dicyclopentadienylzirconium(0), required for oxygen atom abstraction from **11** was generated by treatment of dicyclopentadienylzirconium dichloride (2 equiv) with *n*-butyllithium in toluene (Scheme 3). Addition of tetrahydrofuran **11** to this mixture followed by boron trifluoride etherate with work up in the presence of dilute hydrochloric acid produced cyclobutane **12** in excellent yield. That all four stereocenters of **11** had been faithfully transcribed into **12** was confirmed by careful

Scheme 4. Synthesis of Cyclobutylfuran **20**



Scheme 5. Synthesis of "Northern Sector" of Providencin

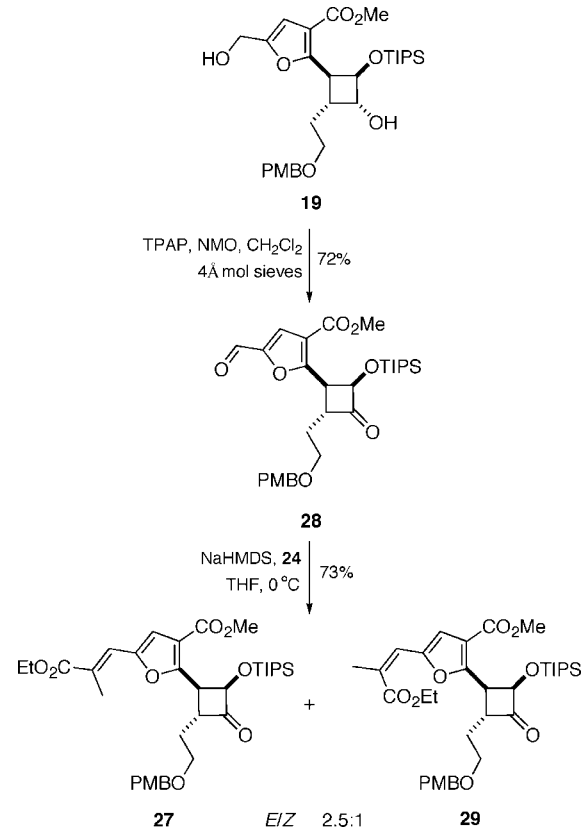


analysis of the ^{1}H NMR spectrum of the cyclobutane which showed NOE's consistent with a cis relationship between H_1 and H_4 and between H_2 and H_3.

After protection of cyclobutanol **12** as its TIPS ether **13**, Wacker oxidation of the vinyl substituent gave methyl ketone **14** with a trace of aldehyde resulting from the alternate regiochemical oxidation[12] (Scheme 4). Exposure of the kinetic lithium enolate of **14** to methyl cyanoformate[13] furnished β-keto ester **15** which was condensed with 2,3-*O*-isopropylidene-D-glyceraldehyde (**16**)[14] under acid catalysis. The initially formed Knoevenagel product **17**, detectable by thin-layer chromatography, was converted slowly to a mixture of **18** and desilylated alcohol **19**.[15] Oxidation of **18** with tetra-*n*-propyl perruthenate[16] then yielded aldehyde **20**.

Our first plan for **20** involved elaboration of this aldehyde into an alkyne that could be used to set in place the (*E*) trisubstituted alkene at C7−C9 of **2**. To this end, aldehyde **20** was reacted with dimethyl 1-diazo-2-oxopropylphosphonate (**21**)[17] in the presence of base to furnish terminal alkyne **22** (Scheme 5). The latter was methylated to give disubstituted alkyne **23**, but all attempts to functionalize this alkyne through hydrozirconation or hydrobromination returned starting material or destroyed the furan. Consequently, we turned to Horner-Wadsworth-Emmons olefination of **20** with ethyl 2-(diethoxyphosphono)propionate (**24**)[18] in order to extend this aldehyde toward **3**. This process gave (*E*)-α,β-unsaturated ester **25** in excellent yield. In anticipation that installation of the

Scheme 6. Alternative Route to Northern Sector **27**



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exo methylene function at C15 of providencin would require a keto group at this site on the cyclobutane, the TBS ether was selectively cleaved from **25** to liberate alcohol **26** and the resulting alcohol was oxidized to cyclobutanone **27**.

Subsequently, it was discovered that more direct access to **27** could be realized through exhaustive oxidation of diol **19** with TPAP to furnish keto aldehyde **28** (Scheme 6). Horner-Wadsworth-Emmons olefination of **28** with phosphonate **24** took place exclusively at the aldehyde but in this case the result was a 2:1 *E*/*Z* mixture of **27** and **29**, respectively, which proved difficult to separate.

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Continuation of our route from **27** toward **1** requires modification of the keto ester in a manner that permits attachment of the γ-lactone unit comprising C10−C12(C20) of providencin. Efforts along this line that change the oxidation level at C9 and C13 are under way.

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

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