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Pectenotoxin-2 Synthetic Studies. 1. Alkoxide Precoordination to [Rh(NBD)(DIPHOS-4)]BF_4 Allows Directed Hydrogenation of a 2,3-Dihydrofuran-3-ol without Competing Furan Production

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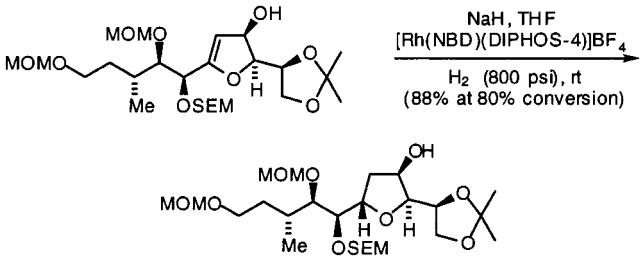
ABSTRACT



The alkoxide-directed hydrogenation shown is reported as a key step in a concise synthesis of a fully functionalized precursor to the C29−C40 F/G sector of pectenotoxin-2.

Recognition that the pectenotoxins (PTXs) are the agents chiefly responsible for the onset of severe diarrhea and liver damage following the ingestion of bivalves (scallops, mussels, clams, etc.) has had significant dietary consequences in Japan and Europe.[1,2] From among the several known members of the PTX family, PTX2 (**1**) has more recently also attracted attention for its selective cytotoxicity properties[3] and its impressive capacity for site-specific interaction with the actin cytoskeleton.[4] The structural complexity of **1** brings a large assortment of challenges to those who attempt its synthesis. Embedded in its framework are 19 stereocenters (of which six are quaternary), a pair of spiroacetals, and several additional oxygenated rings housed in a 33 carbon macrolide ring.

To the present time, only two research groups have documented preliminary studies targeting the PTXs.[5,6] For the above reasons and in keeping with our long-standing interest in marine toxins,[7] we have initiated a synthetic effort aimed at securing **1** in these laboratories.[8] Retrosynthetically, we envisioned **2** to constitute an advanced precursor to its C29−C40 sector that comprises rings F and G. In this

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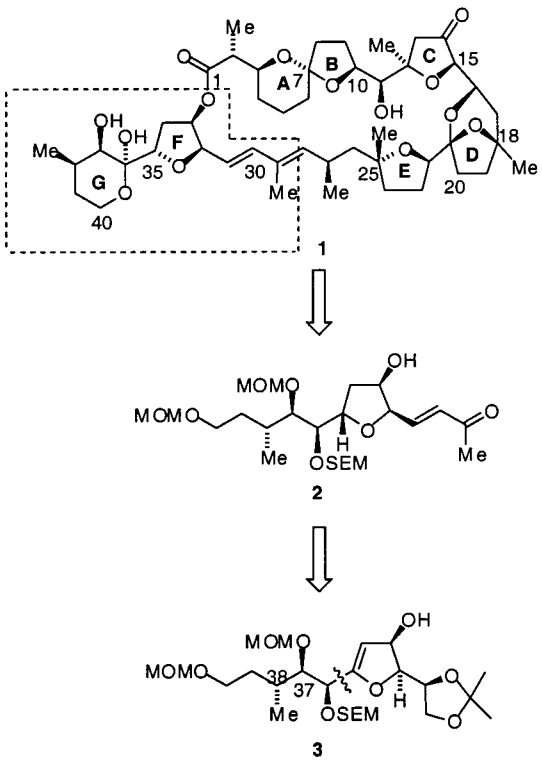
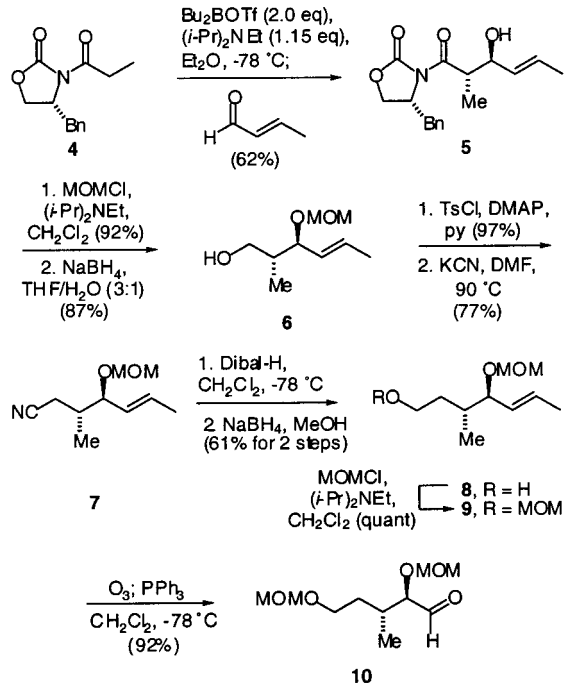
communication, we outline an effective route to **2** that capitalizes on a new, ultramild, alkoxide-directed hydrogenation protocol[24] capable of skirting the flagrant tendency of **3** to experience dehydration.



To set the stage for proper conjoining of the two components of **3** as indicated, the stereochemical relationship of the hydroxyl and methyl substituents at C37 and C38, respectively, was established by an anti aldol reaction.[9] Condensation of the *Z*-enolate of enantiopure oxazolidinone **4**[10] with crotonaldehyde in the presence of dibutylboron triflate[11] afforded **5** as the heavily dominant or exclusive diastereomer depending on the reaction scale (Scheme 1). The magnitude of $J_{H\alpha,H\beta}$ (7.2 Hz) was fully congruent with the stereochemical assignment.[9] Conversion of **5** to its MOM ether followed by reductive cleavage with sodium borohydride[12] then provided alcohol **6**. One-carbon homologation was effected by cyanide ion displacement of the tosylate group. Two-stage reduction of **7** made available the

Scheme 1



primary carbinol **8**. The latter was protected as its MOM derivative prior to ozonolytic degradation leading to aldehyde **10**.

Concurrently, dihydrofuran **11**, which is readily available in quantity from D-mannose,[13] was lithiated with *tert*-butyllithium at −78 °C[14] and the resulting vinyl anion was coupled with **10** (Scheme 2). This reaction was complete within 5 min in the cold to afford **12**, which was immediately protected as the SEM ether **13** in 44% overall yield.[15] ^{13}C NMR analysis of **13** clearly revealed it to consist of two

Scheme 2

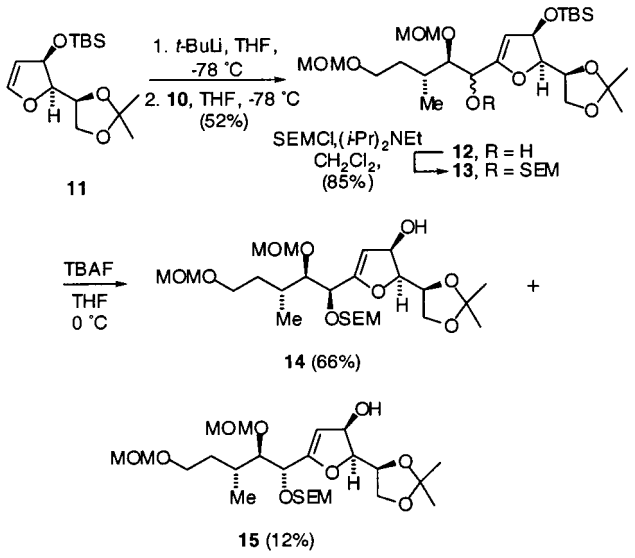


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Table 1. Summary of Hydrogenation Experiments Performed on **14** and **15**[a]

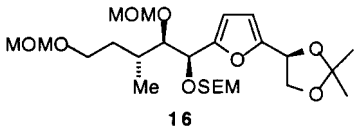
run	substrate	catalyst	base	solvent	products
1	**14**	Rh[b]		CH_2Cl_2	**16** (54%); **18** (11%); **14** (25%)
2	**14**	10% Pd/C		CH_2Cl_2	complex mixture
3	**14**	Ir[c]		CH_2Cl_2	**16** (84%)
4	**14**	Rh[b]	$(i\text{-Pr})_2NEt$	CH_2Cl_2	**17** (46%); **18** (3%); **14** (46%)
5	**15**	Rh[b]	$(i\text{-Pr})_2NEt$	THF	*epi*-**17** (50%); **15** (20%)
6	**15**	Rh[b]		THF	*epi*-**16** (67%); *epi*-**18** (19%)
7	**15**	Rh[b]	KH	THF	*epi*-**17** (7%); *epi*-**18** (53%); **15** (10%)
8	**15**	Rh[b]	KH	CH_2Cl_2	*epi*-**17** (41%); **15** (20%)
9	**14**	Ir[c]		THF	**16** (89%)
10	**14**	Rh[b]	NaH	THF	**18** (43%); **14** (57%)
11	**14**	Rh[b]	NaH	THF	**18** (68%); **14** (20%)[d]

[a] For the general hydrogenation conditions, consult the text. [b] As $[Rh(NBD)(DIPHOS\text{-}4)BF_4$. [c] As $Ir(COD)(py)(PCy_3)PF_6$. [d] Run 10 was allowed to proceed for 3 days.

diastereomers. Although their chromatographic separation could not be achieved at this stage, it proved to be readily accomplished following chemoselective desilylation. The ratio of **14** to **15** was 5:1. The absolute configuration of either SEM ether could not be ascertained. However, since this unidentified chiral center was to be oxidized to the ketone level in one of the final steps of the synthesis, both intermediates are serviceable. For convenience, the major isomer **14**, arbitrarily assigned the β configuration,[16] was utilized for much of the ensuing chemistry.

The stage was now set for a hydroxyl-directed hydrogenation[17] to establish the third chiral center in the tetrahydrofuran ring of **2**. However, when a 2% solution of **14** in CH_2Cl_2 was stirred with 20 mol % $[Rh(NBD)(DIPHOS\text{-}4)]BF_4$[18] under 800 psi of hydrogen for 17 h, the major product was the furan **16** (run 1, Table 1).

The readiness with which water was eliminated was exacerbated when recourse was made to $Ir(COD)(py)(PCy_3)PF_6$[19] (run 3). As expected, the response of **15** was closely comparable, and a switch to THF as the solvent was not beneficial (run 6). The complication was attributed to the Lewis-acidic nature of these catalysts, and recourse was therefore made to the inclusion of 2−3 equiv of Hünig's base in the reaction medium from the outset (runs 4 and 5). While this ploy halted furan formation, the reputed hydroxyl-directing capability of these catalysts did not surface. Thus, **17** and *epi*-**17** were isolated in 46−50% yield as the major products. The stereochemical assignment to **17** was convincingly established by conversion to **19** (NaH, PMBBr) and NOESY analysis in $CDCl_3$. In this solvent system, $H_{5\alpha}$ and $H_{5\beta}$ were cleanly differentiated and their spatial relationship to H_4 and H_6 easily ascertained.



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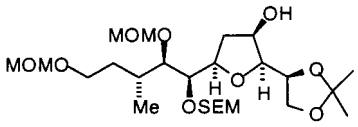

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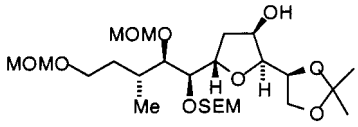

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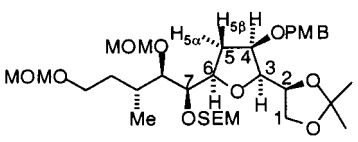
At this point, our attention was drawn to the very early work of Thompson and McPherson who demonstrated that the capacity of Wilkinson's catalyst for π-facial discrimination could be significantly enhanced by *covalent* bonding between an alkoxide and the rhodium center.[20] When these conditions were applied to **14**, no reduction was observed. We were therefore led to examine the merits of *ionic* complexation between alkali metal salts of **14**/**15** and the cationic catalyst $[Rh(NBD)(DIPHOS\text{-}4)]BF_4$. In THF solution, the potassium salt of **15** was transformed into a product mixture consisting predominantly of *epi*-**18** (53%, run 7). None of this product was formed in CH_2Cl_2 (run 8). Alternative use of the sodium salt as in run 10 gave only **18**. Excellent reproducibility and efficiency were ultimately achieved with sodium hydride (1.05 equiv) in THF when the reaction time was extended to 3 days. As before, NOESY analysis of the PMB derivative **20** provided a desirable stereochemical confirmation. We strongly endorse the adoption of these mild, basic conditions in difficult cases such as that faced here.



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(16) This assignment is in line with predominant adherence to the Cram chelate transition state during 1,2-addition to the α-chiral, α-oxygenated aldehyde **10**.

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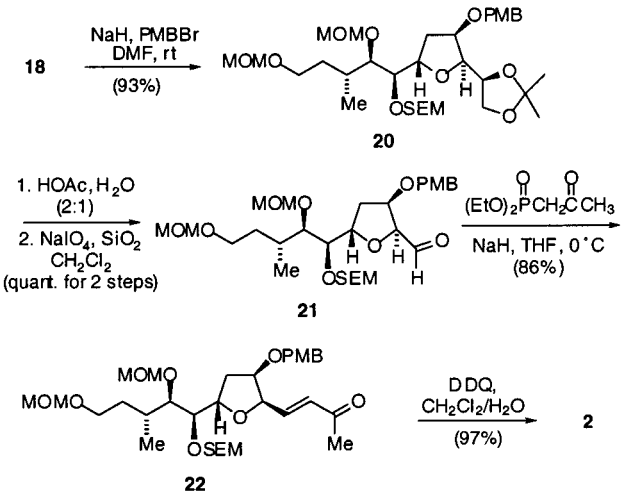
Scheme 3



Completion of the route to **2** involved hydrolytic cleavage of the acetonide with aqueous acetic acid and exposure of the diol to silica gel-supported sodium periodate[21] (Scheme 3). Wadsworth−Horner−Emmons homologation[22] of **21** and exposure of **22** to DDQ oxidation[23] efficiently secured **2** ready for eventual conversion to pectenotoxin-2.[24]

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Supporting Information Available: Copies of the 300 or 500 MHz ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) **Protocol for Alkoxide-Directed Hydrogenation.** To a slurry of sodium hydride (3.9 mg of 60% in oil, 0.098 mmol, 1.05 equiv) in deoxygenated THF (0.50 mL) was added a solution of **14** (50 mg, 0.093 mmol) in the same solvent (0.50 mL). The contents of the vial were stirred for 10 min before a solution of [Rh(NBD)(DIPHOS-4)]BF_4 (13.5 mg, 20 mol %) in deoxygenated THF (1.5 mL) was quickly introduced. The vial was placed in a Parr autoclave, flushed with argon, and pressurized to 800−900 psi of hydrogen. After overnight stirring (17 h), the pressure was released and the reaction mixture was subjected directly to chromatography on silica gel (elution with 2:1 hexanes/ethyl acetate).