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Mukaiyama–Michael Reactions with Acrolein and Methacrolein: A Catalytic Enantioselective Synthesis of the C17–C28 Fragment of Pectenotoxins

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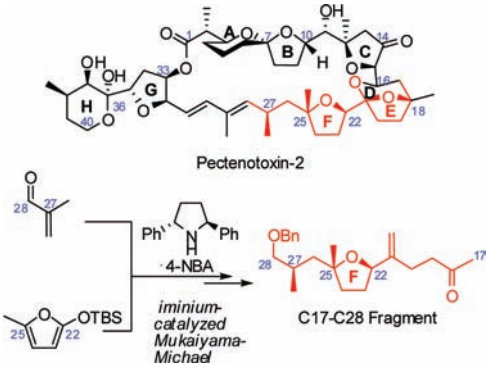
ABSTRACT



Enantioselective iminium-catalyzed reactions with acrolein and methacrolein are rare. A catalytic enantioselective Mukaiyama–Michael reaction that readily accepts acrolein or methacrolein as substrates, affording the products in good yields and 91–97% ee, is presented. As an application of the methodology, an enantioselective route to the key C17–C28 segment of the pectenotoxin using the Mukaiyama–Michael reaction as the key step is described.

The 1985 report by Yasumoto describing the isolation and characterization of a novel marine natural product, pectenotoxin-1 (PTX1),[1] has been followed up by studies characterizing more than 20 structurally related pectenotoxins.[2] Originally isolated from scallops (*Patinopecten yessoensis*),[1] the actual producers of PTXs are the *Dinophysis* dinoflagellates, found in coastal areas worldwide.[3] PTXs are cytotoxic compounds that interact with the actin cytoskeleton;[4] however, for further studies into their biological activity, only microgram amounts of the compounds are commercially available.

PTX4 and PTX8 are the only members of the PTX family that have been produced synthetically.[5] We have previously recorded efforts[6] aimed at the synthesis of the most active congener, PTX2, which bears as an additional synthetic challenge a thermodynamically unstable "non-anomeric" spiroketal.[7]

Our previous work has identified the building blocks such as **2** and **3** as well as a methyl ketone such as **4** (Scheme 1, a) as versatile building blocks that allow the construction of the sensitive AB ring spiroketal in a complex setting.[6d] However, the model methyl ketones used in our previous studies[6b,d] could not realistically be projected to be carried forward in the actual total synthesis route. The installment of the solitary methyl-bearing stereocenter at C27 and the development of a highly stereocontrolled route to the F ring stereochemistry were viewed as key

[†] X-ray crystallography.

(1) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019.

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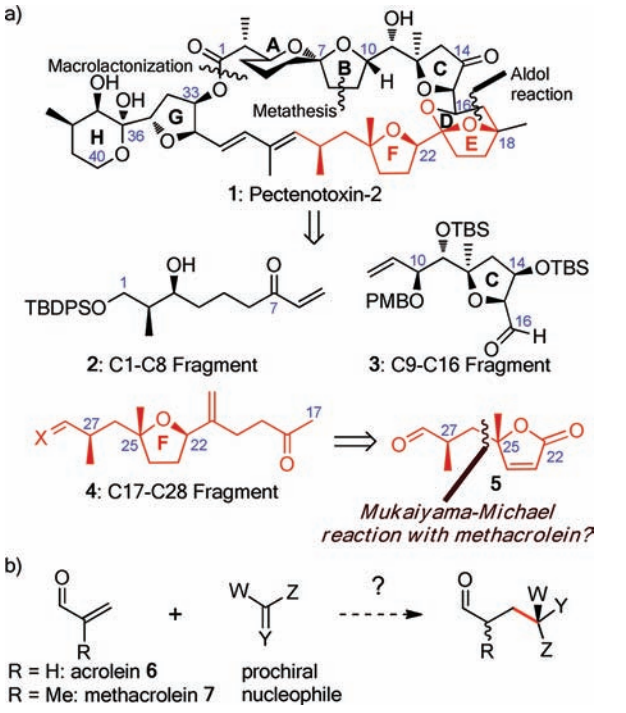
objectives. Herein we present an expedient synthesis of the C17−C28 fragment of the PTXs using an enantioselective iminium-catalyzed Mukaiyama−Michael reaction with methacrolein.

In principle, an iminium-catalyzed Mukaiyama−Michael reaction should allow the construction of a building block such as **5**. However, although a wide range of iminium-catalyzed enantioselective reactions are known,[8] in the vast majority of cases the reactions have been restricted to β-substituted enals,[9] and methacrolein is typically an unreactive substrate.[10] Indeed, only very recently have iminium-catalyzed reactions been expanded to α-substituted enals,[11] but to the best of our knowledge, high enantioselectivities have only been obtained in iminium-catalyzed reactions with β-unsubstituted aldehydes when the *product is cyclized during the reaction*. The process required herein is an example of a noncyclizing iminium-catalyzed process. With acrolein, this process effectively generates new stereogenicity *solely at the nucleophile* (Scheme 1 b).

Scheme 1. (a) Partial Retrosynthetic Analysis of Pectenotoxin-2 and (b) a Missing Link in Enantioselective Catalysis



We reasoned that although it might be difficult to control the stereochemistry at C27 of PTX via protonation, the Mukaiyama−Michael reaction between a silyloxyfuran such as **17** and methacrolein **7** should irreversibly set the stereochemistry at the C25 tertiary center. For this reaction, we screened a number of known iminium/enamine type catalysts and some of their more bulky variants (Table 1).[12]

Although most secondary amine catalysts screened were able to promote the desired reaction, the enantioselectivities were typically only modest (entries 1−8). However, we were delighted to find that the *C*2-symmetric 2,5-diphenylpyrrolidine **16** catalyst[13] afforded the products **18a** and **18b** with excellent enantiopurity.[14] Furthermore, the aldehyde diastereomers **18a** and **18b** were readily separable by chromatography, and the undesired isomer **18a** could

(3) For selected examples, see: (a) Japan: see refs 1, 2a, 2b. (b) Korea: Jung, J. H.; Sim, C. J.; Lee, C.-O. *J. Nat. Prod.* **1995**, *58*, 1722. (c) New Zealand and Norway: see ref 2d. (d) Ireland: see ref 2c. (e) Finland: Kuuppo, P.; Uronen, P.; Petermann, A.; Tamminen, T.; Granéli, E. *Limnol. Oceanogr.* **2006**, *51*, 2300.

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(6) (a) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849. (b) Helmboldt, H.; Aho, J. E.; Pihko, P. M. *Org. Lett.* **2008**, *10*, 4183. (c) Aho, J. E.; Salomäki, E.; Rissanen, K.; Pihko, P. M. *Org. Lett.* **2008**, *10*, 4179. (d) Aho, J. E.; Piisola, A.; Krishnan, K. S.; Pihko, P. M. *Eur. J. Org. Chem.* **2011**, 1682.

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(11) Examples of iminium-catalyzed reactions with α-substituted acroleins where the products are cyclized during the reaction: Epoxidations: (a) Erkkilä, A.; Pihko, P. M.; Clarke, M.-R. *Adv. Synth. Catal.* **2007**, *349*, 802. (b) Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227. Cyclopropanations: (c) Terrasson, V.; van der Lee, A.; de Figueiredo, R. M.; Campagne, J. M. *Chem.—Eur. J.* **2010**, 7875. Cycloadditions: (d) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504. (e) Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2006**, *8*, 2229. (f) Sakakura, A.; Suzuki, K.; Ishihara, K. *Adv. Synth. Catal.* **2006**, *348*, 2457. (g) Ishihara, K.; Nakano, K.; Akakura, M. *Org. Lett.* **2008**, *10*, 2893. (h) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2007**, *129*, 8930. (i) Kano, T.; Tanaka, Y.; Osawa, K.; Yurino, T.; Maruoka, K. *Chem. Commun.* **2009**, *15*, 1956. (j) Aziridinations: Deiana, L.; Dziedzic, P.; Zhao, G.-L.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Córdova, A. *Chem.—Eur. J.* **2011**, *17*, 7904.

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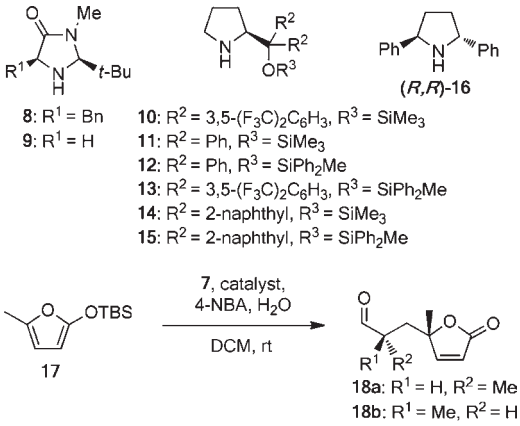
(13) (a) Higashiyama, K.; Inoue, H; Takahashi, H. *Tetrahedron* **1994**, *53*, 1083. (b) For the use of **16** in enamine catalysis, see: Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.

(14) The identification of the diastereomers **18a** and **18b** is based on NMR analysis of their cyclic derivatives (see the Supporting Information).

Table 1. Catalyst Screen for the Mukaiyama–Michael Reaction



entry	cat.	duration (h)	conv (%)[a]	*ee*[b] (%) (**18a/b**)	*dr*[b] (**18a/b**)
1	**8**	23	33	<5/<5	55/45
2	**9**	1.5	>95	37/23	64/36
3	**10**	24	65	20/28	65/35
4	**11**	24	94	54/53	57/43
5	**12**	10	>95	61/63	56/44
6	**13**	24	>95	29/64	59/41
7	**14**	20	>95	59/59	56/44
8	**15**	24	76	30/37	58/42
9	**16**	8	**>95**	**−93/−93**[c]	**56/44**

[a] Determined by GC, monitoring the conversion of silyloxyfuran **17** to **18a**/**18b** during the reaction. [b] Determined by GC (Supelco Astec CHIRALDEX B-DM column). [c] Designates the opposite enantiomers of **18a/18b**.

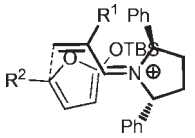
easily be recycled to the thermodynamic 56:44 mixture upon brief exposure to DBU.[15]

A preliminary study of the reaction scope revealed that the scope is not limited to the combination of methacrolein and furan **17**. Acrolein **6** was also a viable electrophile for this reaction, and silyloxyfurans bearing a hydrogen in the α-position could also be used as nucleophiles, affording the products in good enantioselectivities (Table 2).[16,17]

(15) See the Supporting Information for details.

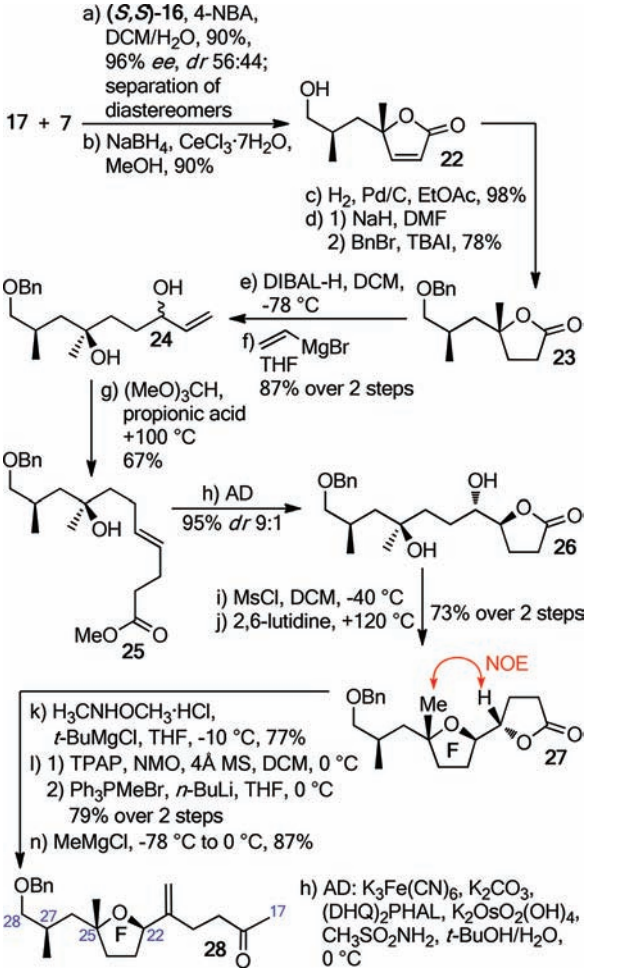
(16) The enantioselectivities were slightly improved when the reaction was carried out at 0 °C instead of rt (see Table 2).

(17) Although several different possible approaches for the union of **17** and **7** consistent with the observed stereochemistry can be presented, the uniformly high enantioselectivities in Table 2 suggest that the stereochemistry-determining step is similar in all cases. A possible rationalization for the observed stereochemistry is depicted below.



(18) The use of Luche conditions was found to prevent a competing Michael addition of the alcohol to the unsaturated lactone. Although the use of Luche conditions results in a slower rate of reduction (as a result of a competing reversible acetal formation reaction), the chemoselectivity of the reduction is improved compared to standard $NaBH_4$ reduction.

Scheme 2. Synthesis of the C_{17}–C_{28} Fragment



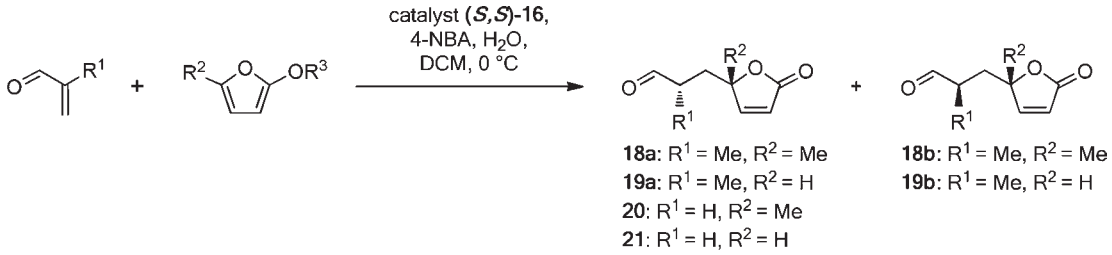
The new methodology was immediately put to use in the synthesis of the F ring fragment **28** of PTXs (Scheme 2). The aldehyde product **18a** was subjected to Luche reduction,[18] hydrogenation, and benzyl protection, affording the saturated lactone **23**. Reduction with DIBAL-H, followed by Grignard reaction with vinylmagnesium bromide, gave the allylic alcohol **24**, setting the stage for a Johnson–Claisen rearrangement cleanly affording the olefin **25** as an essentially pure *E* isomer. The Sharpless asymmetric dihydroxylation with AD-mix α ($(DHQ)_2PHAL$ ligand) led to the formation of the diol **26** in 9:1 diastereoselectivity. The secondary hydroxyl group was then selectively mesylated. Cyclization of the F ring was readily achieved under the conditions reported by Wu and Sun[19] to yield compound **27**. Finally, formation of the Weinreb amide, Ley oxidation, Wittig reaction, and the Weinreb ketone synthesis afforded the ketone **28**.

The stereochemistry of the adducts **18a** and **18b** was assigned by the X-ray analysis of **29**, derived from alternate asymmetric dihydroxylation of olefin **25** with AD-mix

(19) Wu, Y.; Sun, Y.-P. *Org. Lett.* **2006**, *8*, 2831.

(20) Other Mukaiyama–Michael products have been assigned by analogy.

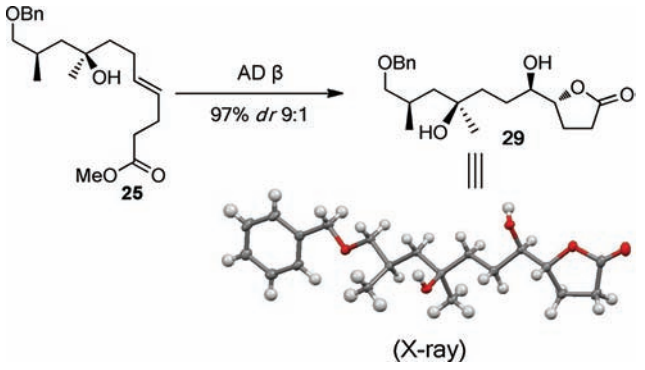
Table 2. Enantioselective Mukaiyama–Michael Reactions with Acrolein or Methacrolein



entry	R^1	R^2	R^3	yield (%)[a]	*ee* (%)[c]	*dr*[d]
1	Me	Me	TBS	90[b] (80)[a]	97/96[e]	55/45
2	Me	H	TBS	65[a]	94/93[e]	50/50
3	H	Me	TBS	65[a]	93	–
4	H	H	TBS	56[a]	91	–
5	H	H	TIPS	71[a]	92	–

[a] Isolated yield of the derived alcohol, after Luche reduction of the aldehyde group. [b] Isolated yield of the aldehyde. [c] Determined by GC (Supelco Astec CHIRALDEX B-DM column). [d] Determined by GC. [e] *ee* reported for both **18a/18b** and **19a/19b**.

Scheme 3. Proof of Stereochemistry



β ((DHQD)$_2$PHAL ligand) (Scheme 3).[20] Furthermore, diagnostic NOE enhancements were observed for compound **27** (Scheme 2), consistent with the depicted stereochemistry.

In summary, we have identified an enantioselective iminium-catalyzed Mukaiyama-Michael-type reaction with acrolein and methacrolein that could be readily applied to the synthesis of the key C17–C28 segment of the pectenotoxins. Efforts toward the total synthesis of pectenotoxin-2 as well as expansion of the scope of catalyst **16** are underway.

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Note Added after ASAP Publication. In the version posted ASAP on February 1, 2012, the descriptors α and β for AD-mix α and AD-mix β were interchanged. This error is now corrected in the paper and in the Supporting Information. The corrected version reposted on February 6, 2012.

Supporting Information Available. Full experimental details, characterization data, X-ray characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.