Natural Products

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Total Synthesis of Pederin**

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Dedicated to Professor Hisashi Yamamoto

Pederin (**1**, Figure 1) has a long and rich history among bioactive natural products.[1] Present in the haemolymph of rove beetles of the genus *Paederus*,[2] this compound was first

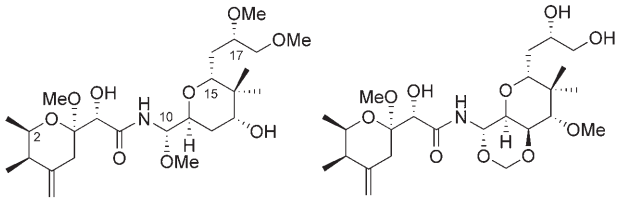

Figure 1. Two members of the pederin family.

obtained in crystalline form in 1919 by Netolitzky and was shown to be a potent vesicant.[3] Pavan and Bo led a massive isolation effort, using 25 million field-collected *Paederus fuscipes* beetles, to secure a sizable quantity of pure pederin,[4] to allow its chemical formula and provisional structure to be determined by Quilico and co-workers in 1965.[5,6] Independently, Matsumoto et al. proposed a slightly modified structure for pederin,[7] one that was subsequently corroborated through X-ray analysis.[8]

Over the years much attention has been accorded to pederin, due in no small part to its impressive and varied biological activities. In addition to its blistering and necrotic properties,[9] pederin displays nanomolar toxicity against a broad range of cancer cell lines.[10] Although the details of its mode of action remain unclear, pederin has been shown to inhibit protein and DNA synthesis without significantly affecting RNA synthesis,[11] and to suppress entry of cells into prophase, thereby blocking mitosis in normal and tumor cells at concentrations of 1–10 ng mL^{-1}.[12] Pederin also slows the growth of sarcoma 180 tumors in mice.[12]

From a chemical perspective, pederin presents a formidable challenge for total synthesis. Its intricate structure, decorated with nine chiral centers, is composed of two tetrahydropyran rings—the pederic acid unit on the left and the pederamine part on the right—connected through an amide bond to a labile aza acetal. The chemical synthesis of pederin has been pursued by many groups, and with successes having been reported by the groups of Matsumoto, Kocienski, and Nakata.[13,14] Despite years of work, fundamental issues about pederin, such as its cellular target or its mode of action, remain unresolved. An efficient synthesis of pederin that proceeds with good diastereoselectivity would enable the preparation of sufficient quantities of the natural product and analogues for such chemical biology studies. In connection with our interest in this family of natural products, we recently reported the total synthesis of mycalamide A (**2**).[15,16] We detail below a synthesis of pederin that is concise, stereocontrolled, and high yielding.

Our synthetic strategy was devised to provide rapid access to pederin and its analogues, and to address the difficult stereochemical issues that plagued earlier syntheses. The plan was to take advantage of a diastereoselective hetero-Diels–Alder reaction (HDA) or a Mukaiyama aldol/cyclization sequence[17] for the convergent assembly of two comparably sized pieces, and thereby generate a functionalized dihydropyran-4-one, in which the stereochemistry at the C15 position would be set as *syn* relative to that at C17. At the outset, the HDA was expected to be complicated by the fact that the required Danishefsky-type diene **4** has a terminal gem-dimethyl moiety, and it would be reacting with an aldehyde in which the existing chirality resides on a carbon atom β to the carbonyl group. Adding to these difficulties was the recognition that the undesired diastereomer would be favored based on both chelation and nonchelation models.[18] In the event, the reaction of **4** and **3a**, catalyzed by traditional Lewis acids, gave the expected pyranone product (**5a,** R = Me; Table 1, entries 1 and 2) in, at best, modest diastereoselectivity, in favor of the undesired *anti* diastereomer.[19] The insensitivity of dimethoxy aldehyde **3a** to even bulky Lewis acids, such as the MAPH complex reported by Yamamoto and Saito (Table 1, entry 3),[20] prompted us to examine a derivative in which the β-alkoxy substituent possessed significantly altered steric and electronic properties.

A solution to the diastereoselectivity problem was found by using TIPS-protected aldehyde **3b**. The reaction of **3b** catalyzed by $BF_3{\cdot}OEt_2$ proceeded with excellent diastereoselectivity, albeit to provide the undesired diastereomer of the pyranone (Table 1, entry 4). Quenching the reaction mixture with HF removed both silyl groups and promoted the cyclization of the Mukaiyama aldol product to provide **5b** (R = H). We were pleased to find that when same reaction was catalyzed with the Yamamoto–Saito Lewis acid,[20] it produced the desired pyranone diastereomer in good yield and selectivity (Table 1, entry 6). Activation of the aluminum

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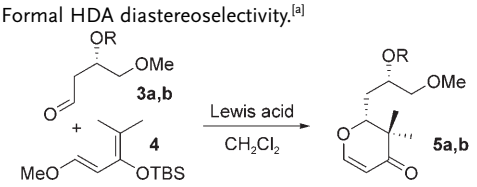
Table 1: Formal HDA diastereoselectivity.[a]

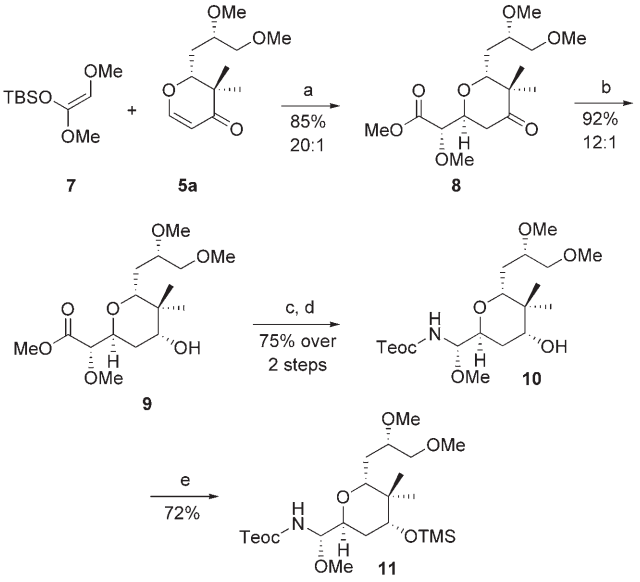


Entry	R	Lewis acid (equiv)	Ratio *syn* (desired)/*anti*	Yield [%]
1	Me	$BF_3{\cdot}OEt_2$ (2)	22:78	75
2	Me	$TiCl_4$ (2)	51:49	62
3	Me	$Al(OAr)_2Me$ (1), TMSOTf (1)	22:78	60
4	TIPS	$BF_3{\cdot}OEt_2$ (2)	6:94	52
5	TIPS	$TiCl_4$ (2)	40:60	nd
6	TIPS	$Al(OAr)_2Me$ (0.2), TMSOTf (2)	92:8	65

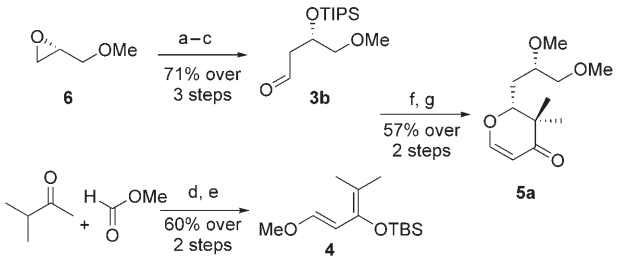
[a] OAr = 2,6-diphenylphenol, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl, TIPS = triisopropylsilyl, TBS = *tert*-butyldimethylsilyl, nd = not determined.

alkoxide with TMSOTf is essential for a successful reaction. The full sequence of reactions leading to pyranone **5b** is shown in Scheme 1. The TIPS-protected aldehyde **3b** was available in three steps from commercially available (*S*)-(+)-glycidyl methyl ether (**6**). Diene **4** was prepared from a vinylogous ester precursor under thermodynamic silation conditions. The free hydroxy group on the pyranone product was methylated to provide **5a**.

Control of the stereochemistry of the C10-methoxy group has plagued the previous routes to pederin. For example, reduction of the methoxyimine of a fully assembled pederin skeleton provided the required aza acetal with around 2:1 diastereoselectivity, in favor of the undesired diastereomer.[13] Our plan was to introduce both the stereocenters at C10 and C11 simultaneously by taking advantage of a diastereoselective Mukaiyama–Michael reaction, in which a carboxylate functionality would serve as the masked form of the C10-nitrogen atom. Thus the conjugate addition reaction of silyl ketene acetal **7** onto pyranone **5a**, when catalyzed by $Sc(OTf)_3$,[21] produced ester **8** in excellent diastereoselectivity. Only the two C11-epimers were observed and the desired diastereomer predominated by a 20:1 ratio (Scheme 2). The observed selectivity can be rationalized by considering the transition states shown in Figure 2, wherein the dimethoxypropane side chain is held in the equatorial orientation. The axial methyl group is expected to disfavor approach of the nucleophile from the bottom face (A and B, Figure 2). Of the remaining two possibilities, transition state C presents fewer steric interactions, as it places the carbonyl carbon atom with its alkoxy groups farther away from the olefinic carbon atoms of the pyranone. Various conditions were examined for the reduction of pyranone **8**, and the best result was obtained with L-selectride, which predominantly afforded the desired diastereomer (**9**, 12:1). We have found that reduction of the ketone functionality at a later stage to be less selective. The required C10-nitrogen atom was expected to be revealed through a Curtius rearrangement, which proceeds stereospecifically. In preparation for this transformation, ester **9** was saponified (NaOH, MeOH) and the resulting acid was subjected to the rearrangement protocol,[22] which gave the Teoc-protected pederamine **10**, with complete retention of the stereochemistry at C10. Silation of the hydroxy group gave **11**.



Scheme 2. Synthesis of Teoc-pederamine (**11**): a) $Sc(OTf)_3$ (10 mol%), CH_2Cl_2, −78 °C to RT; 10% HF/MeCN quench; b) L-selectride, THF, −78 °C; c) 10% NaOH/MeOH, RT; d) DPPA, Et_3N, 2-trimethylsilylethanol, 4-Å MS, THF, reflux; e) TMSCl, imidazole, DMF, RT. DPPA = diphenylphosphoryl azide, DMF = *N*,*N*-dimethylformamide, MS = molecular sieves, Teoc = 2-(trimethylsilyl)ethoxycarbonyl.



Scheme 1. Synthesis of **5a**: a) vinyl Grignard reagent, CuI, THF, −78 °C to 0 °C; b) TIPSCl, imidazole, CH_2Cl_2; c) O_3, CH_2Cl_2; PPh_3 quench; d) NaOMe, Et_2O, reflux; DMSO, Me_2SO_4; e) TBSOTf, Et_3N, Et_2O, 0 °C to RT; f) Al(2,6-diphenyl-phenoxide)$_2$Me (0.4 equiv), TMSOTf (2.1 equiv), CH_2Cl_2, −78 °C to −45 °C; 10% HF/MeCN quench; g) NaHMDS, MeI, THF, −78 °C to 0 °C. DMSO = dimethyl sulfoxide, HMDS = hexamethyldisilazane.

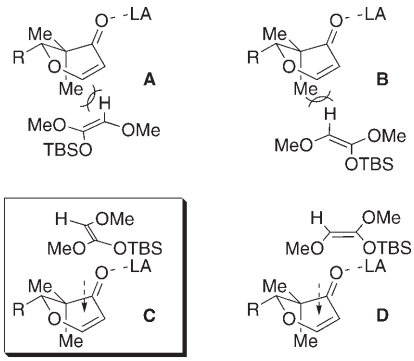
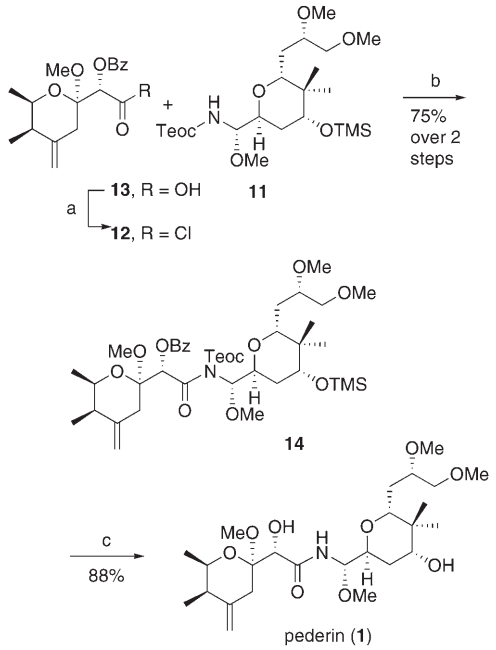


Figure 2. Rationale for Mukaiyama–Michael selectivity. LA = Lewis acid.



Scheme 3. Synthesis of pederin: a) $SOCl_2$, pyridine, CH_2Cl_2, RT; b) LiHMDS, THF, −78 °C to RT; c) TBAF, THF, 0 °C, LiOH/MeOH quench. Bz = benzoyl, TBAF = tetra-*n*-butylammonium fluoride.

Coupling of pederic acid with the aza acetal fragment has been a challenging problem in the pederin family. Indeed, whereas carbamates such as **11** can be coupled to small acid chlorides, their direct coupling to the full pederic acid unit has not been reported.[22]

We were pleased to find the direct coupling strategy to be highly effective for assembling the two halves of pederin (Scheme 3). Pederic acid[15a] was converted into its acid chloride in the presence of an excess of pyridine so as to avoid degradation of the labile acetal moiety.[13a] The addition of a toluene solution of this acid chloride to the lithium anion of **11** gave the protected pederin **14** in 75% yield over two steps. Complete deprotection by treatment with TBAF followed by a hydrolytic quench gave pederin (**1**) in 88% yield.

In conclusion, we have completed a concise, asymmetric total synthesis of pederin. The synthetic route proceeds in 12 steps and 11% overall yield for the longest linear sequence, and it features the diastereocontrolled synthesis of pyranone **5a** and construction of the amide linkage with control of the stereochemistry of the aminal group. Importantly, the strategy is sufficiently general so as to allow the synthesis of not only analogues of pederin, but also many other members of the pederin family. Studies in this regard, as well as those aimed at the identification of the biological target of pederin, are currently underway.[24]

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Keywords: Curtius rearrangement · diastereoselectivity · Mukaiyama–Michael reaction · natural products · total synthesis

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