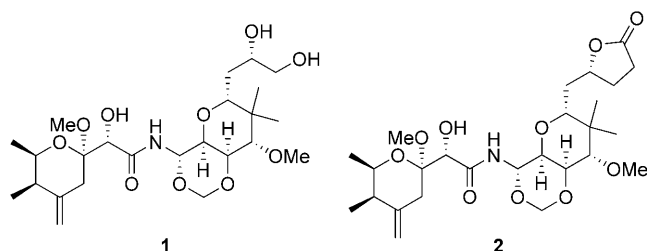


# Total Synthesis of Theopederin D\*\*

Michael E. Green, Jason C. Rech, and Paul E. Floreancig\*

Members of the mycalamide, theopederin, and onnamide families of natural products,<sup>[1]</sup> which are exemplified by mycalamide A (**1**) and theopederin D (**2**; Scheme 1), have

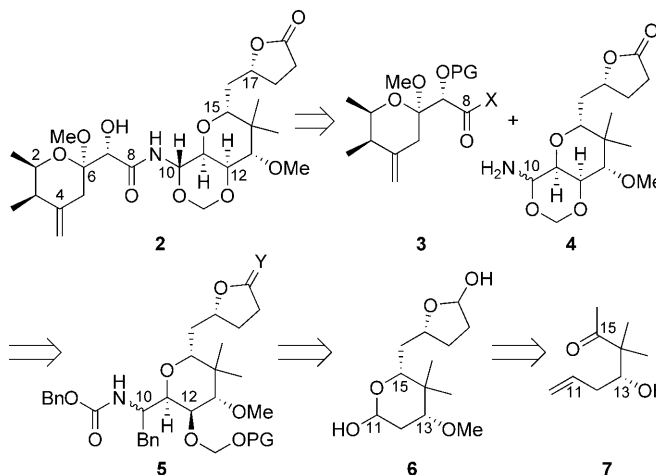


Scheme 1. Mycalamide A (**1**) and theopederin D (**2**).

inspired substantial synthetic studies<sup>[2]</sup> in response to their intriguing structural features, labile functionality, as well as their potent cytotoxic,<sup>[1,3]</sup> immunosuppressive,<sup>[4]</sup> and antiviral<sup>[1]</sup> activities. For example theopederin D, isolated from a marine sponge belonging to the *Theonella* genus found off the coast of Japan, has ten stereocenters, an unusual amido trioxadecalin unit, an acid-labile cyclic  $\beta,\gamma$ -unsaturated acetal fragment, a butyrolactone group, and has an  $IC_{50}$  value of approximately 2 nM against murine P388 leukemia cells.<sup>[1c]</sup> Most synthetic endeavors have been directed toward mycalamide A, but theopederin D, with its additional structural complication of the butyrolactone group, has previously been synthesized only once.<sup>[2d]</sup> Our efforts toward the synthesis of this class of molecules stem from our studies on preparing cyclic acyl aminals,<sup>[5]</sup> including amido trioxadecalins, through electron transfer initiated cyclization (ETIC) reactions.<sup>[6]</sup> In this process cyclic acetals are formed through formaldehyde hemiacetal surrogates that add into acyliminium ions that are generated by oxidation. Herein we report a total synthesis of theopederin D in which we employ ETIC as the key amido trioxadecalin construction step. Other notable transformations include an asymmetric aldehyde/acid chloride condensation, a diastereoselective aldol reaction, a selective func-

tionalization of a tetrahydrofuranol in the presence of a tetrahydropyranol, and a glycol epoxide ring-opening.

We envisioned **2** as arising from subunits **3** and **4** (Scheme 2). This disconnection has proven to be effective for coupling these types of fragments, even though stereo-



Scheme 2. Retrosynthetic analysis of theopederin D. Bn = benzyl, PG = protecting group.

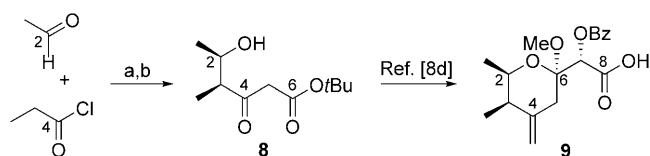
control at C10 is often elusive. Rawal and co-workers, however, reported<sup>[2f]</sup> that the amido trioxadecalin unit of mycalamide A can be constructed with the correct stereochemical orientation at C10 through the coupling of a protected pederic acid unit (C1–C8) with an amino trioxadecalin mediated by 1,3-dicyclohexylcarbodiimide (DCC). The trioxadecalin group of **4** can be prepared through the ETIC reaction of **5**, in which the mixed acetal must contain a group that departs as a highly stable carbocation. This acetal can be derived from bis(hemiacetal) **6**, which in turn can be prepared from the known<sup>[7]</sup> keto alcohol **7**.

Previous synthetic approaches to the pederic acid subunit have relied upon chiral pool materials or chiral auxiliaries to establish stereogenicity.<sup>[2,8]</sup> In considering that the pederic acid unit is needed for the synthesis of all members of this structural family, we felt that development of the first approach to employ asymmetric catalysis as a means of establishing absolute stereocontrol would prove to be of general use. We initiated our route (Scheme 3) with an aldehyde/acid chloride condensation using trimethylsilyl quinidine (TMSQ) and  $LiClO_4$ <sup>[9]</sup> to form a  $\beta$ -lactone, which was opened with the lithium enolate of *tert*-butyl acetate to form **8** in 76% yield and greater than 99% *ee*. We converted **8** into the pederic acid derivative **9** in six steps through a slight modification of Nakata's<sup>[8d]</sup> stereoselective variant of the

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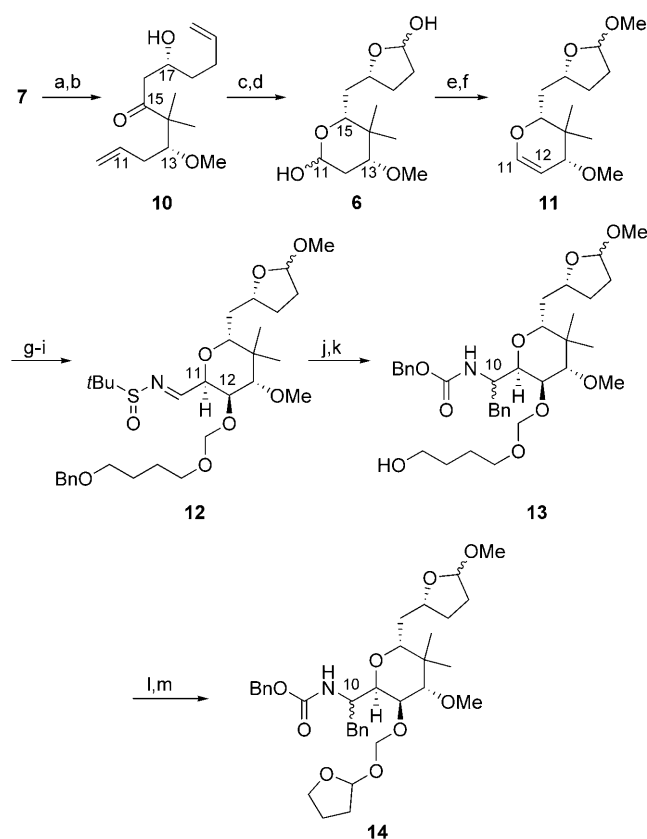
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200802548>.



**Scheme 3.** Synthesis of benzoyl pederic acid **9**. Reagents and conditions: a) TMSQ, LiClO<sub>4</sub>, *i*Pr<sub>2</sub>NEt, Et<sub>2</sub>O; b) LDA, *t*BuOAc, THF, 76 % (over 2 steps). Bz = benzoyl, LDA = lithium diisopropylamide.

Meinwald approach.<sup>[8a]</sup> In our work we discovered that cleavage of a methyl ester mediated by Me<sub>3</sub>SnOH<sup>[10]</sup> (to form the C8 carboxylic acid) was more efficient than the reported cleavage mediated by thiolate.

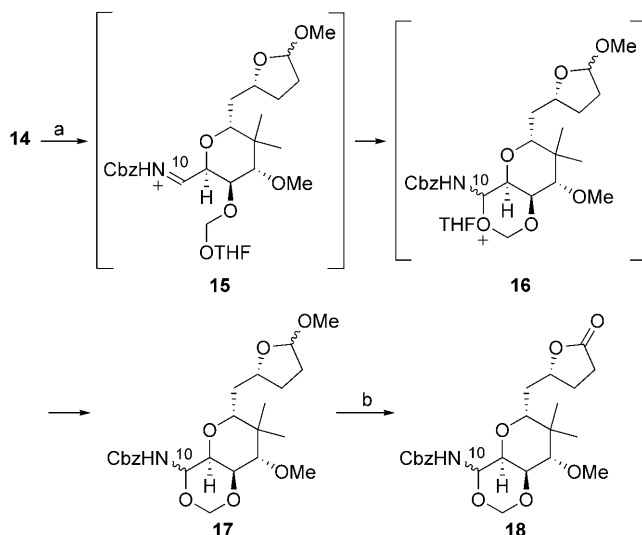
Our initial objective for the construction of the trioxadecalin fragment was to develop a new and selective method for creating the C17 stereocenter (Scheme 4). This stereocenter has most commonly been set through Sharpless dihydroxyla-



**Scheme 4.** Synthesis of the cyclization substrate **14**. Reagents and conditions: a) MeOTf, DTBP, CH<sub>2</sub>Cl<sub>2</sub>, 88 %; b) (+)-Ipc<sub>2</sub>BCl, Et<sub>3</sub>N, Et<sub>2</sub>O; then 5-pentenal, 65 %, d.r. 10:1; c) Et<sub>2</sub>BOMe, THF; then NaBH<sub>4</sub>, MeOH, 77 %; d) OsO<sub>4</sub>, NaIO<sub>4</sub>, THF, H<sub>2</sub>O, 82 %; e) PPTS, MeOH; f) TFAA, *i*Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 92 % (over 2 steps); g) DMDO, acetone; then trivinylalane, CH<sub>2</sub>Cl<sub>2</sub>, 100 %; h) BBMCl, *i*Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 77 %; i) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; then (*R*)-*t*BuS(O)NH<sub>2</sub>, Ti(O*i*Pr)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 50 %, 62 % (based on recovered aldehyde); j) BnMgCl, THF, 65 %; k) HCl, MeOH, 80 %; l) H<sub>2</sub>, Pd/C, MeOH; then CbzCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 70 %; m) PhI(OAc)<sub>2</sub>, *hν*, cyclohexane, 80 %. BBM = benzyloxybutoxymethyl; Cbz = benzyloxycarbonyl, DMDO = 2,2-dimethyldioxirane, Ipc<sub>2</sub>BCl = diisopinocampheyl chloroborane, PPTS = pyridinium *para*-toluenesulfonate, Tf = trifluoromethanesulfonyl, TFAA = trifluoroacetic anhydride.

tion reactions in the syntheses of mycalamide A, even though the terminal alkenes that are used as substrates react with moderate selectivity. We chose to employ an aldol reaction to introduce the C17–C20 unit and to set the stereocenter at C17 through remote induction from the C13 alkoxy group.<sup>[11]</sup> This approach commenced by exposing **7** to MeOTf and 2,6-di-*tert*-butylpyridine (DTBP), and the resulting methyl ether was converted into a boron enolate and coupled with 4-pentenal to provide **10**. Attempts to use the diethylboron enolate resulted in modest selectivity (d.r. 3:1). This result was consistent with reports<sup>[12]</sup> that show methyl ethers to be less effective at promoting 1,5-stereoiduction than sterically more demanding alkyl ethers. Therefore we formed the enolate with (+)-Ipc<sub>2</sub>BCl,<sup>[13]</sup> which improved the d.r. to 10:1 through a matching sense of induction between substrate and reagent control, which has precedence in the synthesis of leucascandolide A developed by Crimmins and Siliphai-vanh.<sup>[14]</sup> *Syn* reduction of the β-hydroxy ketone<sup>[15]</sup> and cleavage of both alkenes under modified Johnson–Lemieux reaction conditions<sup>[16]</sup> provided the highly polar bis(hemiacetal) **6**. The completion of the sequence required that the tetrahydrofuran alcohol and the tetrahydropyran alcohol be distinguished from one another. We reasoned that the tetrahydrofuran alcohol would undergo acid-mediated solvolysis faster than the tetrahydropyran alcohol because of its smaller difference in strain energy between the starting material and the product. Indeed, tetrahydrofuran ethers have been shown to be more labile than tetrahydropyran ethers under acidic conditions.<sup>[17]</sup> Thus, the cyclic hemiacetal groups were differentiated by selectively forming the tetrahydrofuran ether with MeOH and PPTS. The remaining tetrahydropyranol was then dehydrated with TFAA and *i*Pr<sub>2</sub>NEt to yield **11**. Oxygenation at C12 and installation of a vinyl group at C11 with the requisite *syn* arrangement were achieved by treating **11** with DMDO<sup>[18]</sup> and exposure of the resulting crude, labile glycal epoxide to trivinylalane.<sup>[19]</sup> A similar glycal epoxidation in the synthesis of mycalamide A was reported by Nakata et al.<sup>[2b]</sup> The resulting C12 hydroxy group was alkylated with benzyloxybutoxymethyl chloride<sup>[5c]</sup> to introduce the precursor of the formaldehyde hemiacetal surrogate. A nitrogen-containing unit was incorporated into the structure through cleavage of the C11 vinyl group with O<sub>3</sub> followed by conversion of the resulting unstable aldehyde into sulfinyl imine **12** under standard reaction conditions.<sup>[20]</sup> Homobenzylic amine **13** was subsequently constructed through a sequence of BnMgCl addition and cleavage of the sulfinyl group mediated by HCl. Nucleophilic addition gave no stereocontrol at C10, which is evidence that the conformational bias of the substrate overwhelmed the directing effect of the auxiliary. No change in selectivity was observed with the diastereomeric sulfinyl imine, thus indicating that the lack of control did not result from a mismatch between the auxiliary and the substrate. The stereochemistry at this position, however, is inconsequential since it will ultimately be converted into a planar acyliminium ion. The preparation of cyclization substrate **14** was completed by benzyl ether hydrogenolysis, benzyl carbamate formation from the unpurified amino alcohol, and oxidative etherification<sup>[21]</sup> to form the tetrahydrofuran ether.

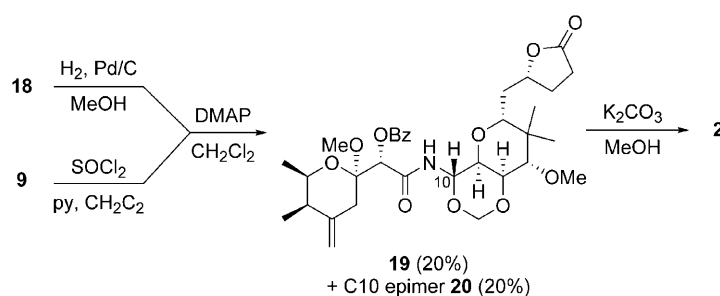
The key cyclization proceeded by irradiation of **14** (medium-pressure mercury lamp, Pyrex filtration) in the presence of 6 mol % of *N*-methylquinolinium hexafluorophosphate (NMQPF<sub>6</sub>) and O<sub>2</sub><sup>[22]</sup> to provide trioxadecalin **17** in 76 % yield as a 2:1 mixture of diastereomers at C10 (Scheme 5). By using these remarkably selective non-acidic oxidative fragmentation conditions, the requisite acyliminium ion **15** was formed in the presence of two highly acid-labile tetrahydrofuranyl ethers. Acetal addition provides oxonium ion **16**, which loses the tetrahydrofuranyl cation to yield **17**. The stereochemical outcome of this



**Scheme 5.** Synthesis of the amido trioxadecalin **18**. Reagents and conditions: a) *hν*, NMQPF<sub>6</sub>, O<sub>2</sub>, NaOAc, Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, toluene, DCE, 76 %; b) Jones reagent, acetone, 64 %. DCE = 1,2-dichloroethane.

reaction, in which the orientation at C10 in the major product is opposite to that of the natural product, is inconsequential for the completion of the synthesis. Hong and Kishi have reported<sup>[2a]</sup> that the amino trioxadecalin which forms from cleavage of the Cbz group is configurationally labile under acidic, basic, or neutral conditions. Treatment of **17** with Jones reagent produced lactone **18** in 64 % yield.

We initially attempted the notoriously difficult fragment coupling by hydrogenolytic cleavage of the Cbz group of **18** and exposing the crude amine **9** to the DCC/DMAP conditions reported by Rawal and co-workers.<sup>[2f]</sup> However, these reaction conditions resulted in a very low yield of the desired amide **19**: the undesired C10 diastereomer **20** was the dominant coupling product, while the aldehyde decomposition product that resulted from amino trioxadecalin opening and β-alkoxy group elimination was a major impurity. We reasoned that the decomposition pathway could be suppressed by using a more reactive acylating agent, therefore we treated **9** with SOCl<sub>2</sub> and pyridine to form the acid chloride<sup>[8b]</sup> and subsequently mixed it with the crude amine in the presence of DMAP. This sequence provided amides **19** and **20** in a combined 40 % yield as a 1:1 mixture (Scheme 6). None



**Scheme 6.** Completion of the synthesis. DMAP = 4-dimethylaminopyridine, py = pyridine.

of the aldehyde decomposition product was isolated, but variable amounts of the diastereomer at C7, resulting from ketene formation in the acylation, were observed. These results are consistent with previous studies<sup>[2]</sup> showing that the intermediate amino trioxadecalin unit is configurationally labile and that the stereochemical outcome of the acylation is quite difficult to control. Studies on related structures in the psymberin/pederin series of natural products have also shown that remote structural differences can cause significant reactivity differences at C10.<sup>[23]</sup> The synthesis was completed through cleavage of the benzoyl group of **19** under standard reaction conditions<sup>[2d]</sup> to yield theopederin D in 66 % yield. Spectroscopic data for the synthetic material<sup>[2d]</sup> matched those reported for the natural product<sup>[1c]</sup>.

We have reported a brief total synthesis of the immunosuppressant and cytotoxic agent theopederin D. The longest linear sequence from **7**, which is available from commercially available material in two steps, requires 16 steps that need purification (or 18 steps by including solvent changes) and in an overall yield of 0.8 %. This sequence compares favorably with the most efficient approaches to any member of this structural class. For comparison, the elegant synthesis of mycalamide A by Rawal and co-workers<sup>[2f]</sup> was accomplished from diethyl tartrate in 20 steps that require purification (or 23 steps by including solvent changes), and the landmark synthesis of theopederin D by Kocienski et al.<sup>[2d]</sup> proceeded in 33 steps from ethyl isobutyrate. Our sequence highlights the capacity of oxidative carbon–carbon bond activation (mediated by electron transfer) to effect highly chemoselective transformations in densely functionalized structures—as indicated by the formation of an acyliminium ion in the presence of two acid-labile tetrahydrofuranyl ethers. The use of the stereoselective aldol reaction to form the C16–C17 bond, while providing a new method for the generation of the C17 stereocenter, makes this route applicable to numerous members of the theopederin and mycalamide families of natural products. The catalytic asymmetric approach to pederic acid will improve the accessibility to this ubiquitous subunit, thereby facilitating subsequent analogue studies.

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