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Total Synthesis of Theopederin D

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Abstract

The total synthesis of the potent cytotoxin theopederin D has been achieved through the use of an oxidative carbon–carbon bond cleavage reaction to form an acyliminium ion in the presence of acid labile acetal groups Other key transformations include an acid mediated functionalization of a tetrahydrofuranyl alcohol in the presence of a tetrahydropyranyl alcohol, a *syn*-selective glycal epoxide opening, and a catalytic asymmetric aldehyde-acid chloride condensation.

Keywords

total synthesis; radical ions; chemoselectivity; cyclization; C–C activation

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

We envisioned **2** as arising (Scheme 1) from subunits **3** and **4**. This disconnection has proven to be effective for coupling the fragments, though stereocontrol at C_{10} is often elusive. Rawal, however, reported[2f] that the amido trioxadecalin of mycalamide A can be constructed with the correct stereochemical orientation at C_{10} through a DCC-mediated coupling of a protected pederic acid (C_1-C_8) unit with an amino trioxadecalin. The trioxadecalin group in **4** can be prepared through the ETIC reaction of **5**, in which the mixed

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acetal must contain a group that depart as a highly stable carbocation. This acetal can be derived from bis-hemiacetal **6** which can be prepared from the known[7] keto-alcohol **7**.

Previous approaches to the pederic acid subunit have relied upon chiral pool materials or chiral auxiliaries to establish stereogenicity.[2,8] In consideration of the the need for this unit for the synthesis of all members of this structural family, we felt that developing 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 2) with an aldehyde-acid chloride condensation using trimethylsilyl quinidine and $LiClO_4$[9] to form a β-lactone that was opened with the lithium enolate of *tert*-butyl acetate to form **8** in 76% yield and >99% ee. We converted **8** to pederic acid derivative **9** in six steps through a slight deviation from Nakata's stereoselective variant[8d] of the Meinwald approach,[8a] in which we discovered that a Me_3SnOH-mediated methyl ester cleavage[10] to form the C_8 carboxylic acid was more efficient than the reported thiolate-mediated cleavage.

Our initial objective for the construction of the trioxadecalin fragment (Scheme 3) was to develop a new and selective method for creating the C_{17} stereocenter. This stereocenter has most commonly been set in the mycalamide A syntheses through Sharpless dihydroxylation reactions, though the terminal alkenes that have been used as substrates react with moderate selectivity. We chose to employ an aldol reaction to introduce the C_{17}–C_{20} unit and to set the stereocenter at C_{17} through remote induction from the C_{13} alkoxy group.[11] This approach commenced by exposing **7** to MeOTf and 2,6-di-*tert*-butyl-pyridine. The resulting methyl ether was converted to a boron enolate and coupled with 4-pentenal to provide **10**. Attempts to use the diethylboron enolate resulted in modest selectivity (dr = 3:1). This result was consistent with reports[12] that methyl ethers are less effective at promoting 1,5-stereoinduction than bulkier alkyl ethers. Therefore we formed the enolate with (+)-$(Ipc)_2BCl$,[13] which improved the dr to 10:1 through a matching sense of induction between substrate and reagent control, as precedented by Crimmins' synthesis of leucascandolide A.[14] *Syn*-reduction of the β-hydroxy ketone[15] and cleavage of both alkenes under modified Johnson-Lemieux conditions[16] provided the highly polar bis hemiacetal **6**. The completion of the sequence required that the tetrahydrofuranyl alcohol and the tetrahydropyranyl alcohol be distinguished. We reasoned that the tetrahydrofuranyl alcohol would undergo acid-mediated solvolysis faster than the tetrahydropyranyl alcohol because of its smaller difference in strain energy between starting material and product. Indeed, tetrahydrofuranyl ethers have been shown to be more labile than tetrahydropyranyl ethers in acidic conditions.[17] Thus, the cyclic hemiacetal groups were differentiated by selectively forming the tetrahydrofuranyl ether with MeOH and PPTs. The remaining tetrahydropyranol was then dehydrated with TFAA and $^{i}Pr_2NEt$ to yield **11**. Introducing oxygenation at C_{12} and a vinyl group at C_{11} with the requisite *syn*-arrangement was achieved by treating **11** with dimethyl dioxirane[18] and exposing the crude, labile glycal epoxide to trivinylalane.[19] A similar glycal epoxidation in the synthesis of mycalamide A was reported by Nakata.[2b] The resulting C_{12} hydroxyl group was alkylated with benzyloxybutoxymethyl chloride[5c] to introduce the precursor of the formaldehyde hemiacetal surrogate. Nitrogen was incorporated into the structure through a sequence of C_{11} vinyl group cleavage with O_3 and converting the resulting unstable aldehyde to sulfinyl imine **12** under standard conditions.[20] Homobenzylic amine **13** was subsequently constructed through a sequence of BnMgCl addition and HCl-mediated sulfinyl group cleavage. No stereocontrol was observed at C_{10} in the nucleophilic addition, showing 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, indicating that the lack of control did not result from a mismatching between the auxiliary and the substrate. The stereochemistry at this position, however, is inconsequential since it will ultimately be converted to 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[21] to form the tetrahydrofuranyl ether.

The key cyclization proceeded (Scheme 4) by irradiating **14** (medium pressure mercury lamp, Pyrex filtration) in the presence of 6 mol% *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$) and O_2[22] to provide trioxadecalin **17** in 76% yield as a 2:1 mixture of diastereomers at C_{10}. By using these remarkably selective non-acidic oxidative fragmentation conditions, the requisite acyliminium ion **15** is 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 reaction, in which the orientation at C_{10} in the major product is opposite to that of the natural product, is inconsequential for the completion of the synthesis. Kishi has reported[2a] that the amino trioxadecalin that forms from cleaving the Cbz-group is configurationally labile under acidic, basic, and neutral conditions. Treating **17** with the Jones reagent produced lactone **18** in 64% yield.

We initially attempted the notoriously difficult fragment coupling by hydrogenolytic cleavage of the Cbz group in **18** and exposing the crude amine to **9** under Rawal's DCC/DMAP conditions.[2f] This, however, resulted in a very low yield of desired amide **19**, with **20**, the undesired C_{10} diastereomer, being the dominant coupling product and the aldehyde that results from amino trioxadecalin opening and β-alkoxy group elimination being formed as a major impurity. Reasoning that the decomposition pathway could be suppressed by using a more reactive acylating agent, we treated **9** with $SOCl_2$ and pyridine to form the acid chloride[8b] and 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 5). None of the aldehyde decomposition product was isolated, but variable amounts of the diastereomer at C_7, resulting from ketene formation in the acylation, were observed. These results are consistent with previous studies[2] showing that the intermediate amino trioxadecalin is configurationally labile and that the stereochemical outcome of the acylation is quite difficult to control. Work on related structures in the psymberin/pederin series has also shown that remote structural differences can cause significant reactivity differences at C_{10}.[23] The synthesis was completed through cleaving the benzoyl group of **19** under standard conditions[2d] to yield theopederin D in 66% yield. Spectral data matched reported values for natural[1c] and synthetic[2d] material.

We have reported a brief total synthesis of the immunosuppressant and cytotoxic agent theopederin D, with a longest linear sequence from **7**, which is available from commercially available material in two operations, of 16 steps that require purification (18 steps that involve 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, Rawal's elegant mycalamide A synthesis[2f] was accomplished from diethyl tartrate in 20 steps that require purification (23 steps that involve solvent changes), and the landmark Kocienski synthesis of theopederin D[2d] proceeded in 33 steps from ethyl isobutyrate. The sequence highlights the capacity of electron transfer-mediated oxidative carbon–carbon bond activation 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 C_{16}–C_{17} bond while providing a new solution to the generation of the C_{17} stereocenter makes this route applicable to numerous members of the theopederin and mycalamide family of natural products. The catalytic asymmetric approach to pederic acid will improve the accessibility of this ubiquitous subunit, thereby facilitating subsequent analog studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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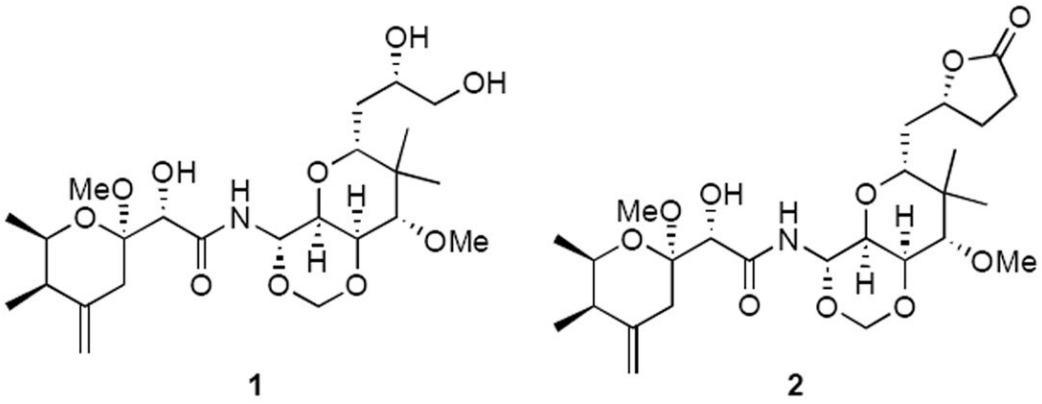
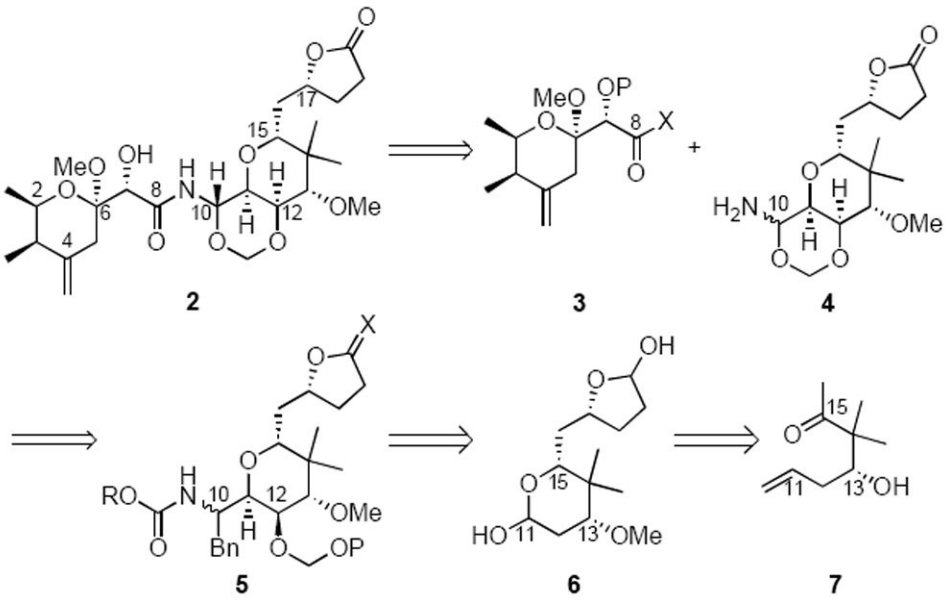
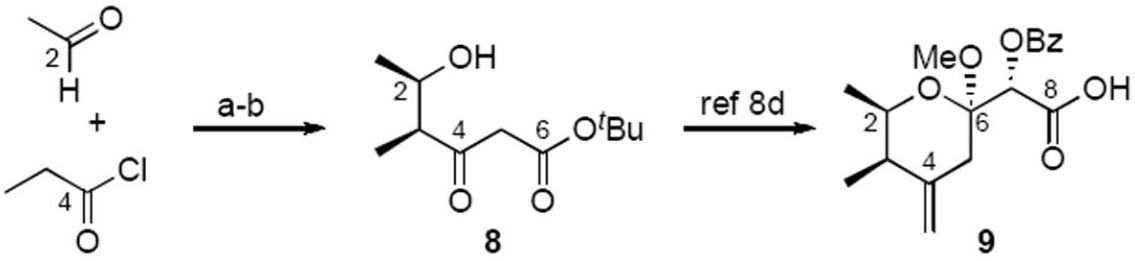


Figure 1.
Mycalamide A and theopederin D.

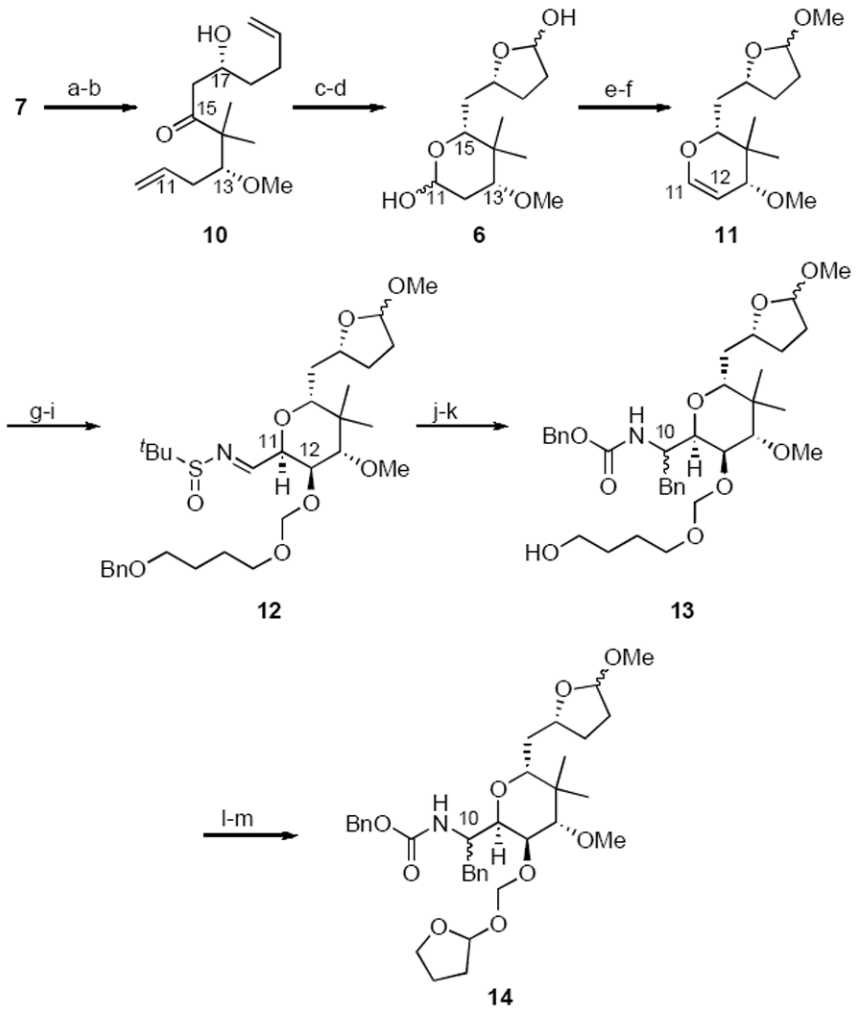


Scheme 1.
Retrosynthetic analysis of theopederin D.



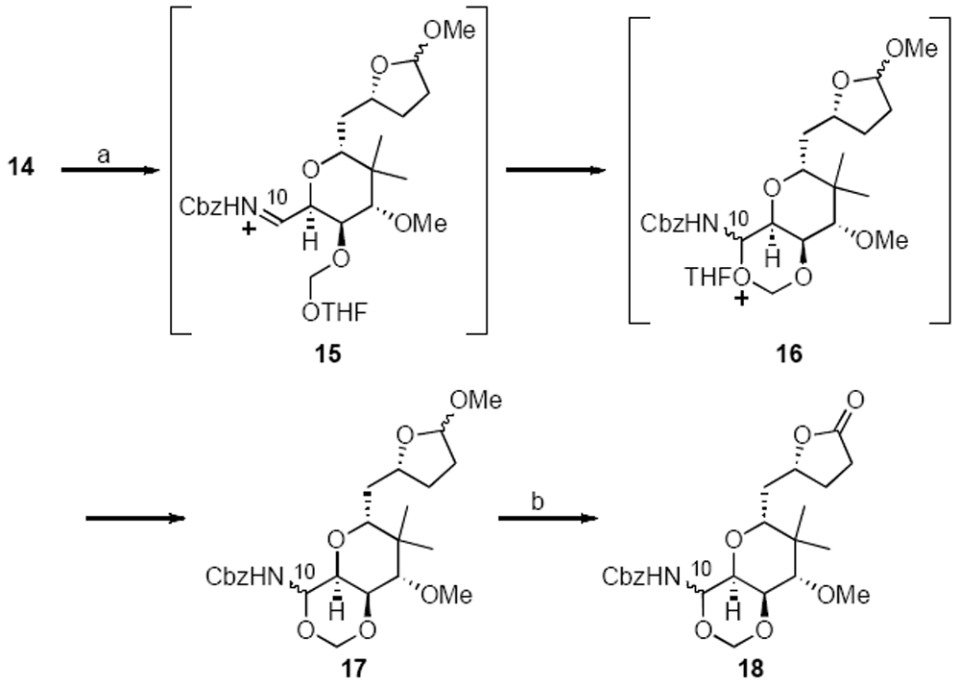
Scheme 2.

Synthesis of benzoyl pederic acid. Reagents and conditions: a) Trimethylsilyl quinidine, $LiClO_4$, $^iPr_2NEt$, Et_2O. b) LDA, ^{t}BuOAc, THF, 76% (two steps).



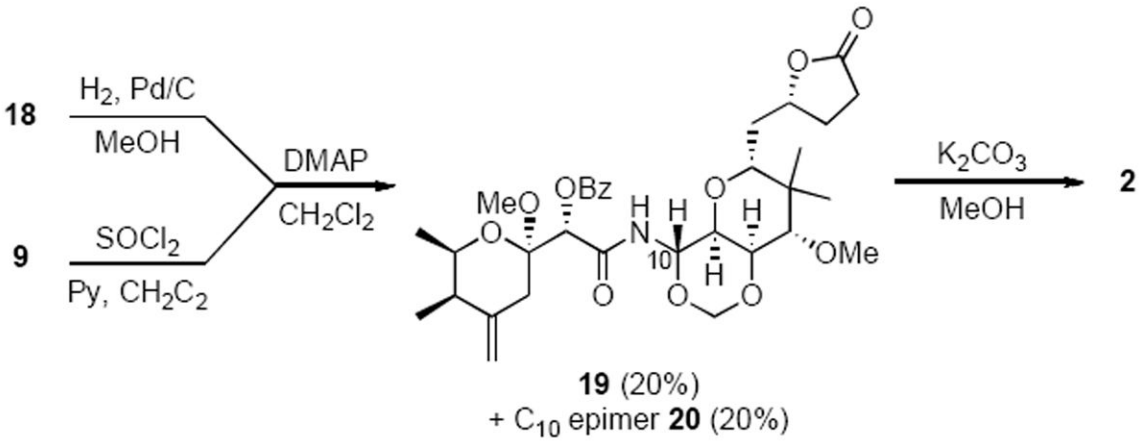
Scheme 3.

Synthesis of the cyclization substrate. Reagents and conditions: a) MeOTf, 2,6-(^{t}Bu)$_2$Py, CH_2Cl_2, 88%. b) (+)-Ipc$_2$BCl, Et_3N, Et_2O, then 5-pentenal, 65%, dr = 10:1. c) Et_2BOMe, THF, then $NaBH_4$, MeOH, 77%. d) OsO_4, $NaIO_4$, NMO, THF, H_2O, 82%. e) PPTs, MeOH. f) TFAA, ^{i}Pr$_2$NEt, CH_2Cl_2, 92%, two steps. g) Dimethyl dioxirane, acetone, then trivinylalane, CH_2Cl_2, 100%. h) Benzyloxybutoxymethyl chloride, ^{i}Pr$_2$NEt, CH_2Cl_2, 77%. i) O_3, CH_2Cl_2, −78 °C, then (*R*)-^{t}BuS(O)NH$_2$, Ti(OEt)$_4$, CH_2Cl_2, 50%, 62% based on recovered aldehyde. j) BnMgCl, THF, 65%. k) HCl, MeOH, 80%. l) H_2, Pd/C, MeOH, then CbzCl, Et_3N, CH_2Cl_2, 70%. m) PhI(OAc)$_2$, *hν*, C_6H_{12}, 80%. Ipc$_2$BCl = diisopinocamphenyl chloroborane, PPTs = pyridinium *para*-toluenesulfonate, TFAA = trifluoroacetic anhydride, CbzCl = benzyl chloroformate.



Scheme 4.

Amido trioxadecalin synthesis. Reagents and conditions: a) *hν*, $NMQPF_6$, O_2, NaOAc, $Na_2S_2O_3$, PhMe, DCE, 76%. b) Jones reagent, acetone, 64%. $NMQPF_6$ = *N*-methylquinolinium hexafluorophosphate, DCE = 1,2-dichloroethane.



Scheme 5.
Completion of the synthesis. DMAP = 4-dimethylamino pyridine.