A Synthesis of Theopederin D and a Formal Synthesis of Pederin

Philip J. Kocienski*[a], Robert Narquizian[a], Piotr Raubo[a], Christopher Smith[a] and F. Thomas Boyle[b]

[a] Department of Chemistry, Glasgow University, Glasgow G12 8QQ, UK

[b]Zeneca Pharmaceuticals, Mereside, Macclesfield, Cheshire, SK10 4TG, UK

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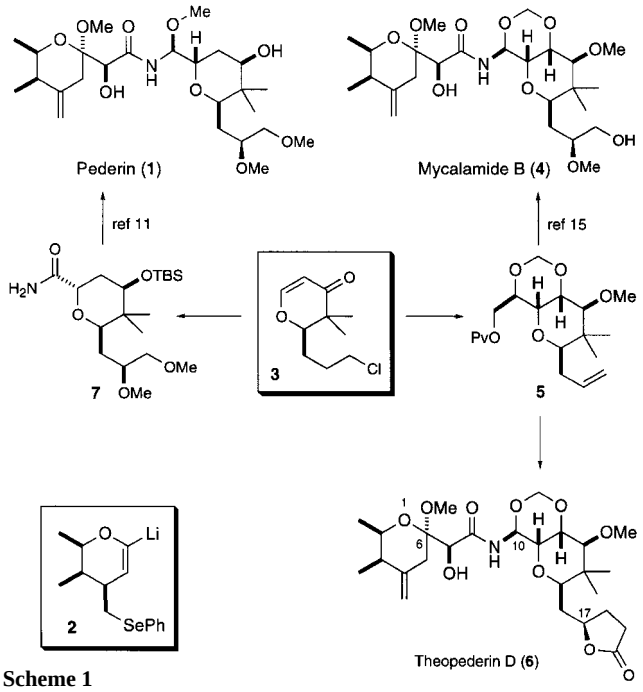
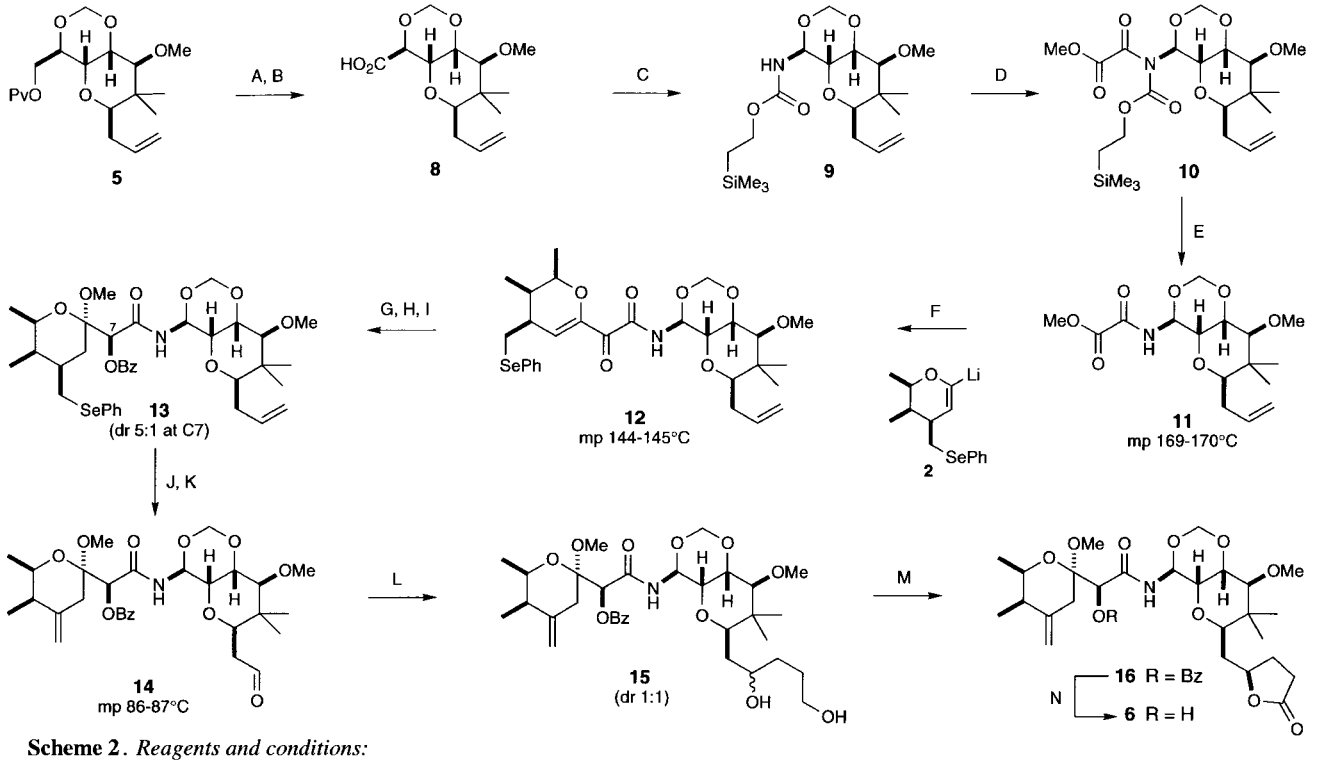
Abstract: Theopederin D, a cytotoxic metabolite from a sponge of the genus *Theonella*, was synthesised in 14 steps (11.1% overall yield) from two advanced intermediates previously used in a synthesis of mycalamide B. A formal synthesis of pederin from similar intermediates is also reported.

Pederin (**1**) was the first and simplest member of a family of secondary metabolites which comprises the mycalamides, onnamides and theopederins. Though pederin was isolated from an insect (*Paederus fuscipes*),[1,2] all the subsequent structures were isolated from sponges of the genus *Mycale* or *Theonella*.[3-7] The potent antitumour and antiviral activities of the marine compounds has stimulated interest in their synthesis because they are only available in minute amounts from natural sources. Total syntheses have been reported for pederin itself,[8-11] mycalamides A[12-14] and B[14,15], and onnamide A.[16] Progress towards theopederin derivatives has been recorded[17,18] but no total syntheses have yet appeared. We recently devised a general approach to all known members of the pederin family based on the metallated dihydropyran **2** (Scheme 1), which is a precursor to the 'left-half' common to all members of the pederin family, and the dihydropyranone **3**, a platform designed for side-chain variation (Note 1). Our strategy was exemplified in a synthesis of mycalamide B (**4**)[15] in which the trioxadecalin intermediate **5** was fabricated from the dihydropyranone **3**, and we now



Scheme 1



Scheme 2. *Reagents and conditions:*

A 98% $NaAlH_2(OCH_2CH_2OMe)_2$, THF, –78 → 0°C, 30 min
B ↓ PDC, DMF, r.t., 24 h
C 58% $(PhO)_2PON_3$, $TMSCH_2CH_2OH$, EtN(i-Pr)$_2$, 4Å MS, PhMe, 65°C, 1 h
D 70% MeO_2C–COCl (5 equiv), DMAP (5 equiv), CH_2Cl_2, r.t., 91 h
E 83% TBAF•$3H_2O$, THF, 0 °C, 2 min
F 78% **2** (3 equiv), TMEDA, THF, –78°C, 30 min
G ↓ *s*-Bu_3BHLi, THF, –95°C, 30 min
H ↓ CSA, MeOH–CH_2Cl_2, r.t., 40 min
I 77% BzCl, DMAP, EtN(i-Pr$_2$), CH_2Cl_2, r.t., 1 h; separate isomers by SGC
J ↓ Sharpless AD
K 69% (a) $NaIO_4$, MeOH–CH_2Cl_2, r.t., 30 min; (b) NEt_3, PhMe, Δ, 2.5 min
L ↓ $ClMgCH_2CH_2CH_2OMgCl$ (2 equiv), THF, –78°C, 2 h
M 85% (a) TPAP, NMO, 4Å MS, CH_2Cl_2-MeCN, r.t., 30 min; (b) separate by TLC
N 79% K_2CO_3, MeOH, r.t., 1 h

disclose the first synthesis of a member of theopederin family, theopederin D (**6**) which likewise uses trioxadecalin intermediate **5**. To further underscore the flexibility of our general strategy, we also report the conversion of dihydropyranone **3** to the amide **7**, a key pederin intermediate.

Theopederin D

Our synthesis of theopederin D began with the reductive cleavage of the pivalate ester in **5** (Scheme 2) using Red-Al followed by oxidation of the primary alcohol with pyridinium dichromate to give the carboxylic acid **8**. A crucial step of the synthesis, introduction of the aminal centre at C10, was performed using a Curtius rearrangement as described by Roush[19] in order to secure the stereochemistry at the aminal centre unambiguously. The sequence entailed preparation of the acyl azide by reaction of carboxylic acid **8** with diphenylphosphoryl azide followed by thermolysis in the presence of 2-(trimethylsilyl)ethanol to trap the intermediate isocyanate as its 2-(trimethylsilyl)ethyl carbamate **9**. No epimerisation of the aminal centre was observed. Acylation of the carbamate **9** with methyl oxalyl chloride in the presence of DMAP occurred slowly but cleanly to give the *N*-acyl oxalamide **10** in 70% yield. The crucial oxalamide ester **11** (Note 2) was then released by fluoride-induced cleavage of the 2-(trimethylsilyl)ethyl carbamate **10.**[20]

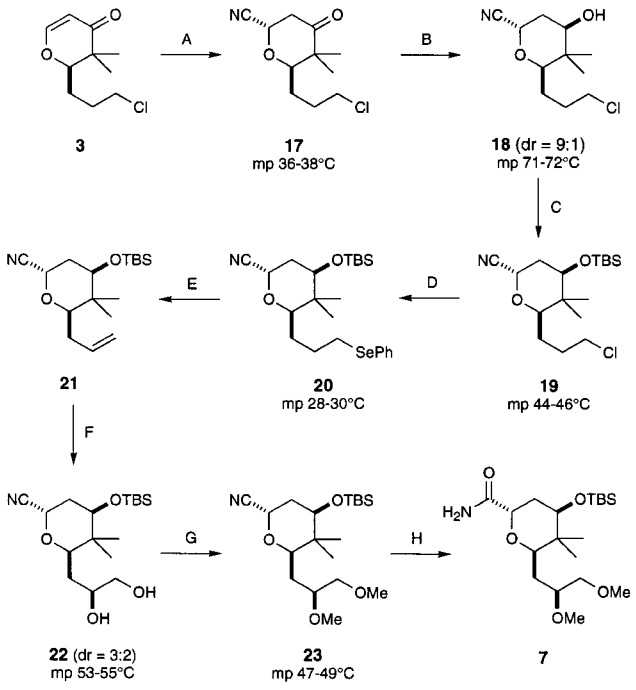
The bridge linking the two ring systems was created by reaction of the oxalamide ester **11** with 3 equivalents of the lithiated dihydropyran **2** in the presence of TMEDA to generate the acyl dihydropyran **12** in 78% yield. A very efficient 3-step sequence completed the construction of the *N*-acyl aminal bridge: (a) reduction of the keto function using L-Selectride at –95°C, (b) acid-catalysed addition of MeOH across the dihydropyran, and finally (c) benzoylation. A 5:1 mixture benzoate esters diastereoisomeric at C7 was obtained which were separated by column chromatography. The overall yield of **13** for the 3-step sequence was 93%.

The terminal alkene function at C17 offers a number of opportunities for side chain elaboration but for the purposes of this synthesis, we opted for a sequence involving oxidative cleavage followed by nucleophilic addition of a 3-carbon nucleophile. Thus Sharpless asymmetric dihydroxylation of alkene **13** using dihydroquinine-9-phenanthryl ether as the ligand[21] selectively oxidised the alkene to a 1:1 mixture of diastereoisomeric diols (Note 3) without complications from the selenium atom. The lack of stereoselectivity in the dihydroxylation was of no consequence since the diol was cleaved to an aldehyde function with concomitant oxidation of the selenium to the selenoxide in a single operation using sodium periodate. Brief thermolysis of the selenoxide in refluxing toluene installed the exocyclic methylene to give aldehyde **14** in 69% overall yield from **13**. The acid sensitivity of the nascent homoallylic acetal imposed significant constraints on the subsequent chemistry. Attempts to introduce a propionate fragment directly by addition of 2-carboethoxyethylzinc[22] or samarium reagents[23] gave complex mixtures. However, the Grignard reagent derived from *unprotected* 3-chloropropan-1-ol[24] underwent clean but stereorandom addition to give a 1:1 mixture of diastereoisomeric adducts **15** at C17. Oxidation of the mixture of 1,4-diols with TPAP[25,26] then gave a mixture of butyrolactones from which the desired diastereoisomer **16** was isolated by preparative TLC. Finally, methanolysis of the benzoate ester using potassium carbonate gave theopederin D (**6**) by comparison of the ^{1}H and ^{13}C NMR spectra (400 and 100 MHz respectively (Note 4) with published data for the natural product.[7] 17-*epi*-Theopederin D prepared by the same method was clearly distinguishable by ^{1}H NMR spectroscopy (Note 5).

A Formal Synthesis of Pederin

A recent biological evaluation of synthetic mycalamide derivatives[27] indicated that pederin was as potent as 18-*O*-methyl mycalamide B[28,29] as an antitumour agent and therefore pederin should be considered a simpler and more readily accessible alternative candidate for development. We have already described a synthesis of pederin from the metallated dihydropyran **2** and the amide **7**.[11] We now report the conversion of dihydropyranone **3** to amide **7** which, together with our much improved synthesis of metallated dihydropyran **2**[15] represents a new formal total synthesis of pederin.

Conjugate addition of trimethylsilyl cyanide to dihydropyranone **3** (Scheme 3) catalysed by TMSOTf gave the nitrile **17** as a single isomer in 92% yield. Luche reduction[30] of the carbonyl group was diastereoselective affording a quantitative yield of diastereoisomeric alcohols (dr = 9:1) from which the pure desired isomer **18** could be obtained by crystallisation. After protection of the hydroxyl as its TBS ether and displacement of chloride with selenide, the alkene was generated by thermolysis of a selenoxide intermediate giving terminal alkene **21**. Sharpless asymmetric dihydroxylation using the dihydroquinine 9-phenanthryl ether ligand[21] as described above gave a 3:2 mixture of diastereoisomeric diols which were separable by column chromatography (Note 6). The desired (17*S*)-diol **22** then methylated and the nitrile function converted to the corresponding amide **7** with a large excess of hydrogen peroxide. Amide **7** was converted to pederin as described previously.[11]



Scheme 3. *Reagents and conditions:*

A 92% TMSCN (1.1 equiv), TMSOTf (0.03 equiv), CH_2Cl_2, 0°C, 1.5 h
B 100% $NaBH_4$ (3 equiv), $CeCl_3 \cdot 7H_2O$ (0.5 equiv), MeOH, –90°C → –30°C, 1.5 h
C 99% TBSOTf (1.1 equiv), 2,6-lutidine (1.2 equiv), CH_2Cl_2, 0°C, 2.5 h
D 91% $NaBH_4$ (1.44 equiv), PhSeSePh (0.65 equiv), EtOH, Δ, 1 h
E 96% (a) $NaIO_4$ (1.5 equiv), MeOH, r.t., 30 min; (b) NEt_3 (10 equiv), PhMe, Δ, 30 min
F 78% Sharpless AD
G 91% NaH (3 equiv), MeI (5 equiv), 18-cr-6 (0.12 equiv), THF, r.t., 24 h
H 87% H_2O_2 (57 equiv), K_2CO_3 (20 equiv), EtOH-H_2O, r.t., 20 h

49% overall (8 steps); 27% overall based on the desired isomer in steps B and F

In conclusion, theopederin D was synthesised in 14 steps in 11.1% overall yield from intermediates **2** and **5**. The route benefits from ready availability of the key intermediates **2** and **3** from cheap starting

materials. Alkene **13** should serve as a flexible platform for further elaboration to other members of the theopederin, mycalamide, and onnamide class of cytotoxic agents. Our improved synthesis of amide **7** from dihydropyranone **3** (49% overall in 8 steps) is capable of delivering gram quantities of pederin and its analogs.

Notes

1. Hong and Kishi's syntheses of onnamide A and mycalamides A and B were also based on modifications of a late terminal alkene intermediate.[14,16]
2. All crystalline compounds were recrystallised from ether-hexanes unless otherwise stated.
3. The (*17S*)-diol corresponds to mycalamide A. However, no attempts were made to separate the diols.
4. NMR data for theopederin D: δ_H (400 MHz, $CDCl_3$) 7.51 (1H, d, *J* 10.3 Hz, NH), 5.80 (1H, t, *J* 9.5 Hz, C10-H), 5.11 (1H, d, *J* 7.0 Hz, OCH_AH_BO), 4.86 (1H, d, *J* 7.0 Hz, OCH_AH_BO), 4.84 (1H, t, *J* 2.0 Hz, $=CH_AH_B$), 4.73 (1H, *J* 1.7 Hz, $=CH_AH_B$), 4.42 (1H, ddd, *J* 14.1, 8.2, 5.9 Hz, C17-H), 4.25 (1H, d, *J* 3.2 Hz, C7-H), 4.19 (1H, dd, *J* 9.7, 6.4 Hz, C12-H), 4.11 (1H, d, *J* 3.2 Hz, C7-OH), 4.01 (1H, dq, *J* 6.6, 2.8 Hz, C2-H), 3.80 (1H, dd, *J* 9.2, 6.4 Hz, C11-H), 3.54 (3H, s, OMe), 3.42 (1H, d, *J* 9.5 Hz, C13-H), 3.40 (1H, d, *J* 9.0, Hz, C15-H), 3.38 (3H, s, OMe), 2.50 (1H, m, C19-H_AH_B), 2.45 (1H, m, C19-H_AH_B), 2.39 (1H, m, C18-H_AH_B), 2.33 (1H, d, *J* 13.9 Hz, C5-H), 2.24 (1H, dq, *J* 7.1, 2.6 Hz, C3-H), 2.18 (1H, d, *J* 14.1 Hz, C5-H), 1.92 (1H, m, C16-H_AH_B), 1.76 (1H, m, C18-H_AH_B), 1.58 (1H, ddd, *J* 14.3, 8.3, 1.3 Hz, C16-H_AH_B) 1.18 (3H, d, *J* 6.6 Hz, C2-Me), 1.00 (3H, s, C14-Me_A), 0.98 (3H, d, *J* 7.1 Hz, C3-Me), 0.86 (3H, s, C14-Me_B).
   δ_C (100 MHz, $CDCl_3$) 177.5 (0, C20), 172.3 (0, C8), 145.0 (0, C4), 111.0 (2, C4=CH_2), 99.8 (0, C6), 86.5 (2, OCH_2O), 79.5 (1, C13), 79.2 (1, C17), 76.0 (1, C15), 74.0 (1, C12), 73.6 (1, C10), 71.6 (1, C7), 69.5 (1, C11), 69.5 (1, C2), 61.7 (3, C12-OMe), 48.5 (3, C6-OMe), 41.3 (1, C3), 41.1 (0, C14), 35.0 (2, C16), 33.3 (2, C5), 28.7 (2, C19), 28.0 (2, C18), 22.6 (3, C14-Me), 18.0 (3, C2-Me), 14.1 (3, C14-Me), 12.0 (3, C3-Me).
5. NMR data for 17-*epi*-theopederin D: δ_H (400 MHz, $CDCl_3$) 7.41 (1H, d, *J* 9.4 Hz, NH), 5.83 (1H, t, *J* 9.2 Hz, C10-H), 5.12 (1H, d, *J* 7.0 Hz, OCH_AH_BO), 4.87 (1H, d, *J* 6.8 Hz, OCH_AH_BO), 4.87 (1H, t, *J* 2.0 Hz, $=CH_AH_B$), 4.75 (1H, *J* 1.7 Hz, $=CH_AH_B$), 4.48 (1H, ddd, *J* 12.1, 9.1, 6.4, C17-H), 4.26 (1H, d, *J* 2.4 Hz, C7-H), 4.19 (1H, dd, *J* 9.7, 6.5 Hz, C12-H), 4.05 (1H, dq, *J* 2.8, 6.6 Hz, C2-H), 3.83 (1H, d, *J* 2.5 Hz, C7-OH), 3.82 (1H, dd, *J* 9.0, 6.5 Hz, C11-H), 3.65 (1H, dd, *J* 9.8, 1.5 Hz, C15-H), 3.54 (3H, s, OMe), 3.44 (1H, d, *J* 9.7 Hz, C13-H), 3.30 (3H, s, OMe), 2.49 (2H, m, C19-H_2), 2.36 (1H, d, *J* 13.9 Hz, C5-H), 2.28 (1H, dq, *J* 7.1, 2.7 Hz, C3-H), 2.20 (1H, m, C18-H_AH_B), 2.16 (1H, bd, *J* 14.1 Hz, C5-H), 1.83-1.70 (2H, m, C16-H_AH_B and C18-H_AH_B), 1.60 (1H, dd, *J* 9.7, 3.0 Hz, C16-H_AH_B), 1.19 (3H, d, *J* 6.6 Hz, C2-Me), 1.02 (3H, s, C14-Me_A), 0.99 (3H, d, *J* 7.1 Hz, C3-Me), 0.84 (3H, s, C14-Me_B).
6. The minor (17*R*)-diol gave mp 36-38°C ($CHCl_3$).

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