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A stannous chloride-induced deacetalisation–cyclisation process to prepare the ABC ring system of 'upenamide

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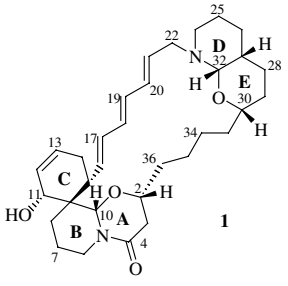
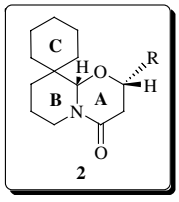
Abstract—A stannous chloride-induced deacetalisation–cyclisation approach to the ABC core of the macrocyclic alkaloid, 'upenamide is reported. The use of a substituted β-lactone to prepare a C-2 substituted 'upenamide analogue is also disclosed.

Upenamide **1** is a unique macrocyclic alkaloid isolated[1] from the branching sponge, *Echinochalina* sp. (Protolithospongia) (order Poecilosclerida) collected from Derawan Island, Indonesia. Due to the scarcity of the natural product the biological activity of 'upenamide has not yet been widely screened although no anticancer activity was seen in in vitro screening. The name 'upenamide is coined from "*upena*', meaning fishing net or trap in Hawaiiwan, and reflects its mesh-like structure consisting of two main core systems (A, B, C and D, E rings) linked in a 20-membered macrocycle.[2] The ABC core comprises a novel spiro-oxaquinolizidinone system and accounts for five of the eight chiral centres within 'upenamide—four of which are contiguous and one quaternary. The D and E ring system is based on a hemiaminal *cis*-decalin-type system and contains the remaining three chiral centres. The C and D ring systems are linked by an all *trans*-triene system and a fully saturated aliphatic chain then completes the 20-membered macrocycle adjoining rings A and E. The architectural complexity and novel structure of 'upenamide make its total synthesis an attractive challenge. As part of our ongoing program to prepare novel natural products, we have turned our attention towards the total synthesis of 'upenamide and herein report a novel diastereoselective approach to the unique ABC spirocyclic core **2**.



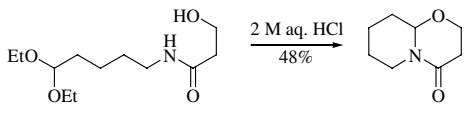
1



2

The ABC ring system appears completely novel in nature and indeed synthesis of oxaquinolizidinone ring systems have received little attention.[3,4] However, Winterfeld and Michael have prepared oxaquinolizidinone **4** in 48% yield by treatment of the diethyl acetal β-hydroxyamide **3** with 2 M aq HCl (Scheme 1).

We hoped to utilise this approach to prepare 'upenamide, and therefore decided to first test its utility to prepare model system **2** (R = H). The ideal cyclisation precursor was identified as protected amide **10**, which was prepared by the route shown in Scheme 2. Thus, cyclohexane carboxaldehyde **5** was converted into *tert*-butyl imine **6**,[5] which was directly transformed into amine **9** using the sequence described by Maison et al.[6] Hence, **6** was alkylated using acrylonitrile and catalytic hydroquinone and the product subjected to acidic deprotection and distillation to give the desired aldehyde



3 **4**

Scheme 1.

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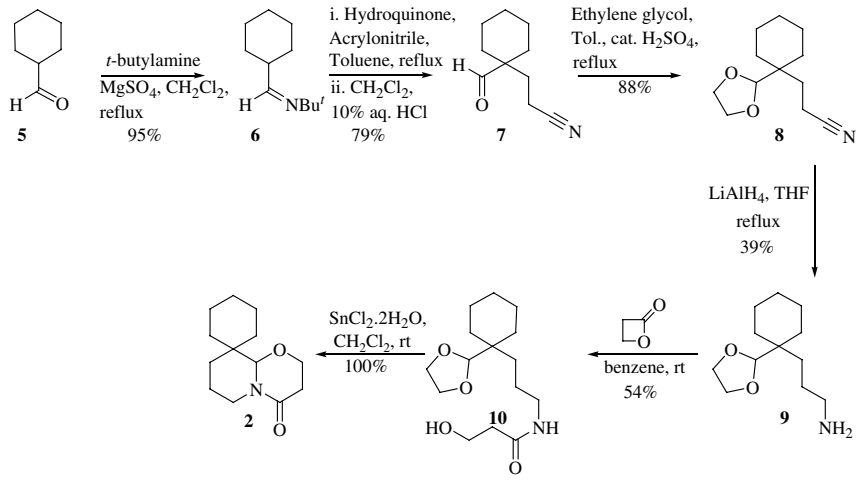


Scheme 2.

7 in 79% yield from **6**. Aldehyde **7** was then protected as the corresponding dioxolane in 88% yield after distillation. With the reactive carbonyl function protected, nitrile **8** was then reduced to afford primary amine **9** using lithium aluminium hydride. Initially, attempts to purify **9** by an acid/base extraction, using 5% aq HCl solution, proved unsuccessful, resulting in degradation. However, switching to 0.1 M tartaric acid allowed amine **9** to be accessed in high purity in a moderate, but unoptimised, 39% yield. With free amine **9** in hand, β-hydroxy amide **10** was then furnished through nucleophilic ring opening of β-propiolactone in an unoptimised 54% yield after silica chromatography (Scheme 2).[7]

With cyclisation precursor **10** in hand, we then proceeded to investigate the deacetalisation–cyclisation to give the ABC model system **2**. Use of Winterfeld's conditions (2 M HCl) gave the expected product **2** in 70% yield after chromatography although the reaction was slow and gave a number of other by-products. The use of stannous chloride dihydrate ($SnCl_2{\cdot}2H_2O$) was then investigated as it is known to hydrolyse effectively dioxolanes under mild conditions[8] and furthermore, it was hoped that the Lewis acidity of $SnCl_2{\cdot}2H_2O$ would then facilitate the cyclisation by activating the intermediate aldehyde. Thus, dioxolane **10** was stirred in dichloromethane at room temperature with 2.3 equiv of $SnCl_2{\cdot}2H_2O$ and, to our delight, furnished spiro-oxaquinolizidinone **2** in quantitative yield after simple filtration and silica column chromatography. These mild conditions represent a new and efficient procedure for the synthesis of spiro-oxaquinolizidinones.

Attention was next turned to the synthesis of C-2 substituted model systems to investigate methods of introducing additional functionality and to ascertain the stereochemical outcome of the cyclisation. It was hoped that the use of substituted β-lactones to alkylate amine **9** would allow several important questions regarding the synthesis of the ABC system in 'upenamide itself. Namely, if we could open the substituted lactone to afford the substituted β-hydroxyamide and, if so, whether the subsequent hydrolysis–cyclisation reaction would still proceed using secondary alcohol **11**. Furthermore it was hoped to gain knowledge of the stereochemical outcome of the cyclisation.

To this end (±)-4-(benzyloxymethyl)oxetan-2-one **12** was prepared using the $Al(SbF_6)_3$ mediated [2+2]-cycloaddition of benzyloxyacetaldehyde and ketene (derived from acetyl chloride), as described by Nelson et al. (Scheme 3)[9] With lactone **12** in hand, nucleophilic ring opening using primary amine **9** then afforded the desired β-substituted-β-hydroxy amide **11** in 72% yield. Stirring dioxolane **11** with $SnCl_2{\cdot}2H_2O$ in CH_2Cl_2 then smoothly afforded the desired cyclisation to furnish spiro-hemiaminal **13** in a near quantitative yield, as a 1:1 mixture of diastereomers.[10] These diastereomers **13a** and **13b** were, however, readily separated by silica column chromatography and the diastereomers crystallised and the relative stereochemistry of **13b** assigned by X-ray crystallography (Fig. 1).[11]

It was, however, postulated that, under the Lewis acid conditions, the hemiaminal cyclisation may be reversible. With this in mind, the cyclisation of **11** was repeated in the presence of an increased quantity of stannous chloride and for an increased reaction time (2 days vs 1 h previously). Pleasingly, this produced an 88% yield of the cyclised product but now in a 96:4 ratio of diastereomers in favour of the 'natural' diastereomer **13b** in which the protons at C-1 and C-8 have a *syn*-relationship. Furthermore, it was found that **13a** could be isomerised to give a 92:8 mixture of diastereomers in

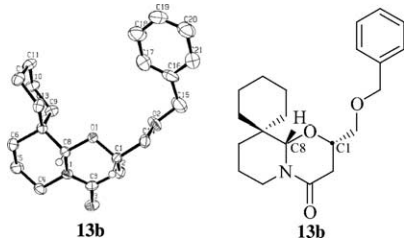
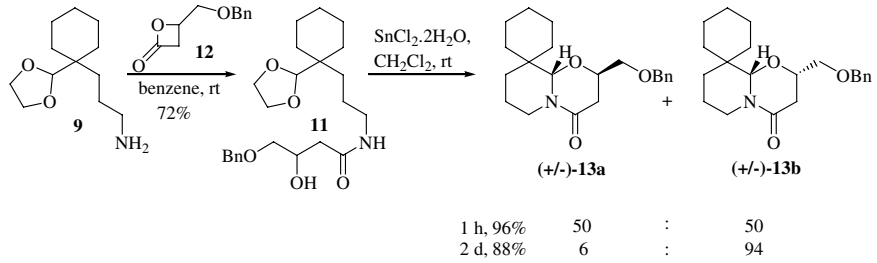


Figure 1. ORTEP drawing of **13b** (50% probability thermal ellipsoids).



Scheme 3.

favour of the desired diastereomer **13b** in 89% yield by stirring in dichloromethane with $SnCl_2{\cdot}2H_2O$ for 46 h. A control experiment was also carried out whereby **13a** was stirred in dichloromethane for 40 h showing no isomerisation and thus confirming that the Lewis acid conditions are essential for the transformation to the thermodynamically more stable **13b**.

In summary, we have developed a novel stannous chloride-induced deacetalisation–cyclisation procedure to spiro-oxaquinolizidinones **2** and **13**. This represents the first approach to the ABC ring system of 'upenamide. We are now applying this methodology to an enantioselective total synthesis of the natural product.

Acknowledgements

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10. To a solution of dioxolane **11** (27 mg, 0.067 mmol) in CH_2Cl_2 (2 mL) was added stannous chloride dehydrate (38 mg, 0.17 mmol). The reaction mixture was then stirred for 1 h at rt and filtered through Celite®, washing with CH_2Cl_2. The filtrate was then concentrated in vacuo to give a colourless residue, which was purified by silica column chromatography (eluting with 50–60% EtOAc/petroleum ether) to afford **13a** (11 mg, 48%) as a colourless solid; mp 90–92 °C (from EtOAc/petroleum ether), R_f 0.39 (EtOAc), which was fully characterised and **13b** (11 mg, 48%) as a colourless solid; mp 85–87 °C (from petroleum ether) R_f 0.29 (EtOAc); IR (neat) 2929, 2858, 1653, 1447 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29–7.19 (5H, m, Ar–H), 4.63 (1H, ddd, app dt, J 13.0, 4.0 Hz, H-6_{eq}), 4.55 (2H, s, benzylic CH_2), 4.23 (1H, s, H-10), 3.86 (1H, m, H-2), 3.50 [1H, dd, (ABX system), J 10.5, 6.0, CH_2OBn], 3.45 [1H, dd, (ABX system), J 10.5, 3.5, CH_2OBn], 2.42 (1H, app td, J 13.0, 4.0, H-6_{ax}), 2.35–2.25 (2 H, m, H-3), 2.16–2.12 (1H, m,CH), 1.76 (1H, app td, J 13.0, 4.5, CH), 1.60–1.07 (11H, m, CH), 0.93 (1H, app td, J 14.0, 4.5, CH); δ_C (100 MHz, $CDCl_3$) 167.1 (C-4), 138.2 (Ar–C), 128.6 (Ar–C), 127.9 (Ar–C), 127.7 (Ar–C), 92.9 (C-10), 73.5 (Benzylic-C), 72.2 (C-2), 71.9 (*C*H_2OBn), 40.5 (C-6), 38.2 (C-9), 35.3 (C-3), 34.2, 30.1, 26.5, 24.0, 21.4, 20.9, 19.5 (C-3, C-4, C-5, C-6, C-7, C-8, C-9); m/z (CI) 344 (MH^+, 100) [HRMS (CI): calcd for $C_{21}H_{30}NO_3$, 344.2226. Found: MH^+, 344.2228 (0.6 ppm error)].
11. Cambridge Crystallographic Data Centre reference no 2341139.