Pergamon

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Total synthesis of cytotoxic sponge alkaloids Motuporamines A and B

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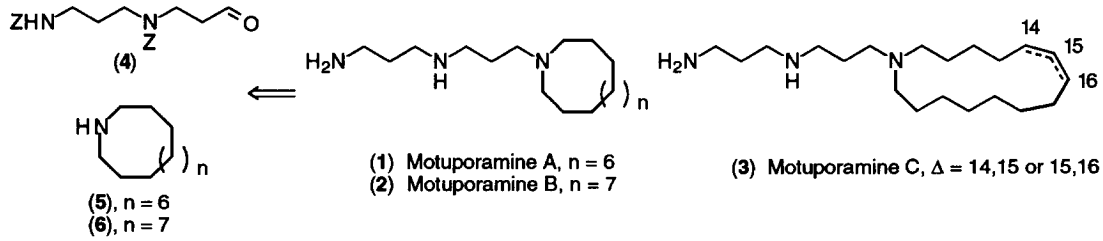
Abstract:

The synthesis of two sponge alkaloids, Motuporamines A and B is reported. The key step involved a reductive amination using sodium triacetoxyborohydride. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords sponge, alkaloids, Motuporamine.

Motuporamines A (**1**), B (**2**) and C (**3**) are a new group of macrocyclic alkaloids isolated as an inseparable mixture from the marine sponge *Xestospongia exigua* (Kirkpatrick) by Andersen *et al.*[1] Subsequent chromatographic purification and structure elucidation of these alkaloids were carried out on their diacetamide derivatives. Biogenetically, the Motuporamines may be related to the 3-alkylpiperidine and 3-alkylpyridine alkaloids which are the postulated precursors [2] of the Manzamine type alkaloids.[3-5] Similar types of azamacrocyclic alkaloids have been isolated in nature, for example Manzamine C,[6] Keramamine C and Keramaphidin C [7] from the *Haliclona sp.*, Haliclorensin [8] and Halitulin [9] from *Haliclona tulearensis*. However the presence of the spermidine-like side chains in the Motuporamines distinguish them from these compounds.



Bioassay of the Motuporamines mixture revealed cytotoxicity against a panel of human solid tumour cell lines. The unusual structures of the Motuporamines and their biological activities together with the lack of pure samples prompted us to investigate the synthesis of these compounds. Herein we describe the synthesis of Motuporamines A and B, the two

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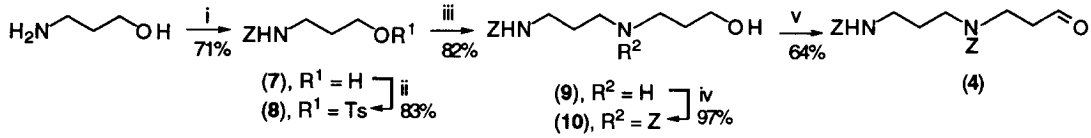
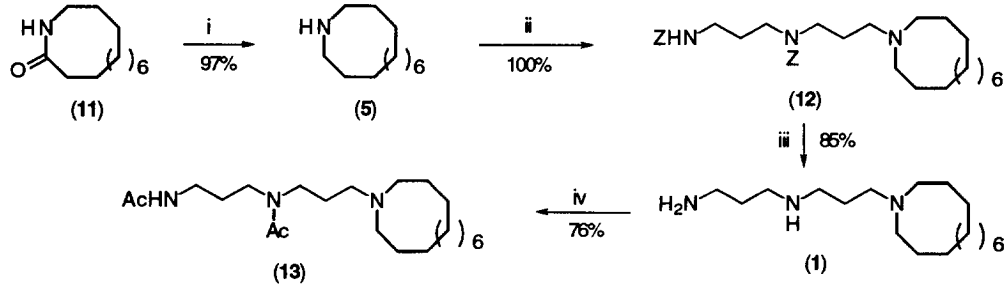
minor components of the Motuporamines mixture. Retrosynthetically, Motuporamines A and B can be derived from reductive amination of a diprotected spermidine-like aldehyde (**4**) with the corresponding macrocyclic amines (**5**) and (**6**) respectively.

Thus 3-amino-1-propanol was converted to its *N*-benzyloxycarbonyl derivative (**7**) in 71% yield by benzylchloroformate and aqueous sodium carbonate solution.[10] Treatment of alcohol (**7**) with tosyl chloride and triethylamine in dichloromethane gave tosylate (**8**) in 83% yield. [11] Reaction of tosylate (**8**) with excess 3-amino-1-propanol in the presence of sodium iodide/sodium carbonate in DMF gave aminoalcohol (**9**) in 82% yield.[12] The secondary amine in (**9**) was protected as its benzyloxycarbonyl derivative (**10**) in 97% yield by benzylchloroformate and sodium hydroxide in THF. Unlike the procedure described by Miller *et al.*[12], we found it is unnecessary to protect the primary alcohol prior to the protection of the secondary amine. Alcohol (**10**) was then oxidised with catalytic tetra-n-propylammonium perruthenate (VII) in the presence of *N*-methylmorpholine *N*-oxide[13, 14] in acetonitrile to give aldehyde (**4**) in 64% yield (Scheme 1).



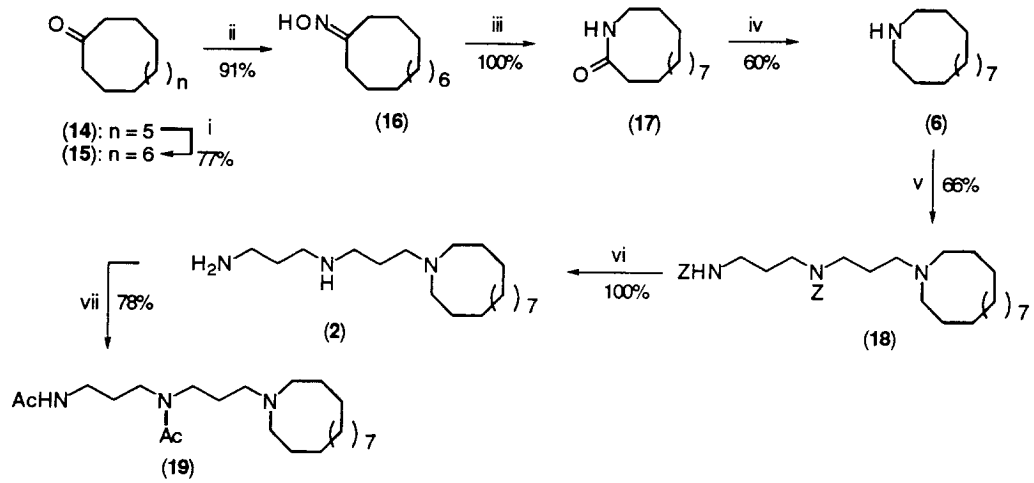
Scheme 1 (i) Z-Cl/ NaOH/ H_2O; (ii) TsCl/ Et_3N/CH_2Cl_2; (iii)3-amino-1-propanol (4 eq.)/ NaI/ Na_2CO_3/ DMF; (iv) Z-Cl/ NaOH/ THF; (v) TPAP(cat.)/ NMO/ molecular sieves/ CH_3CN

With the availability of common intermediate (**4**) the preparation of the corresponding macrocyclic amine component was undertaken. For Motuporamine A, the requisite macrocyclic amine (**5**) was obtained in 97% yield by reduction of the commercially available laurolactam (**11**) with lithium aluminium hydride in THF under reflux.[15] Reductive amination of (**5**) with aldehyde (**4**) using sodium triacetoxyborohydride in 1,2-dichloroethane[16] gave protected triamine (**12**) in quantitative yield. Deprotection of (**12**) by hydrogenolysis gave Motuporamine A (**1**) in 85% yield which was converted to its diacetamide derivative (**13**) in 76% yield by acetic anhydride and triethylamine.



Scheme 2:(i) $LiAlH_4$/ THF/ reflux; (ii) 4/ $NaBH(OAc)_3$, 1,2-dichloroethane; (iii) Pd/ C/ H_2/ MeOH; (iv) Ac_2O, Et_3N.

The synthesis of Motuporamine B (**2**) began with the ring expansion of cyclododecanone (**14**) with trimethylsilyldiazomethane and boron trifluoride etherate[17] to give cyclotridecanone (**15**) in 77% yield. Ketone (**15**) was treated with hydroxylamine hydrochloride and sodium bicarbonate in methanol to give oxime (**16**) in 91% yield after recrystallization. Beckmann rearrangement of (**16**) with concentrated sulphuric acid[15] gave intractable material. However when the reaction was conducted with Eaton's reagent[18], amide (**17**) was obtained in quantitative yield. Reduction of amide (**17**) with lithium aluminium hydride gave amine (**6**) in 60% yield. Reductive coupling of (**6**) and (**4**) gave (**18**) in 66% yield which was deprotected to give Motuporamine B (**2**) in quantitative yield. As before, (**2**) was converted to its diacetamide derivative (**19**) in 78% yield.



Scheme 3: (i) Me_3SiCHN_2/ $BF_3.Et_2O$/ CH_2Cl_2;(ii) $NH_2OH.HCl$/ $NaHCO_3$/ MeOH; (iii) P_2O_5/CH_3SO_3H; (iv) $LiAlH_4$/ THF/ reflux; (v) **4**/ $NaBH(OAc)_3$/ 1,2-dichloroethane; (vi) Pd/ C/ H_2/ MeOH; (vii) Ac_2O/ Et_3N/ pyridine.

The spectroscopic data (^1H and ^{13}C nmr) of diacetamide (**13**) and (**19**) are identical to the data reported by Andersen [1]. In summary, we have achieved the synthesis of two natural products and for the first time pure (**1**) and (**2**) are made available. This should enable the full evaluation of the biological properties of these compounds.

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