Pergamon

Tetrahedron Letters 42 (2001) 851–854

TETRAHEDRON LETTERS

A convergent approach to midpacamide and dispacamide pyrrole-imidazole marine alkaloids

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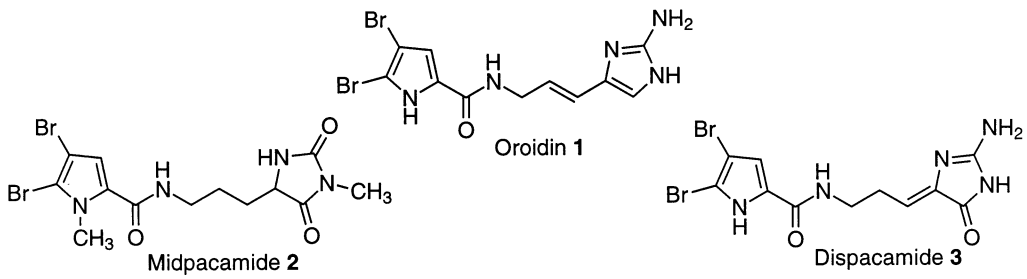
Received 21 September 2000; accepted 16 November 2000

Abstract—A two-step synthesis of the *N*-acylated α-azido-ω-aminovalerate, a common intermediate for the synthesis of midpacamide and dispacamide, is described. This intermediate undergoes cyclization through the corresponding α-ureido ester derivative to give the 3-methylhydantoin ring present in midpacamide, whereas the reaction with triphenylphosphine, tosyl isocyanate and ammonia followed by cyclization of the resulting guanidine derivative provides the 2-aminoimidazole ring present in dispacamide.

Marine sponges have become recognized as a rich source of a structurally diverse and pharmacologically interesting class of $C_{11}N_5$ pyrrole-imidazole alkaloids. Collectively, this group of natural products is known as the 'oroidin group' of which oroidin **1** represents the simplest structural entity.[1] Common structural features for this group of secondary metabolites are a brominated or nonbrominated pyrrole carboxamide unit connected to a functionalized imidazole ring through a functionalized or unfunctionalized three-membered carbon bridge. Among these are midpacamide **2**[2] and dispacamide **3**,[3] which have been isolated from marine sponges of the genus *Agelas*. Midpacamide **2** differs from oroidin **1** by the N-substituent of the pyrrole ring, in the functionalization of the three-carbon chain as well as in the oxidation of the imidazole ring, which is in **2** an unusual 3-methylhydantoyl moiety, whereas dispacamide **3** differs from **1** by isomerization of the double bond position and by an imidazolinone ring. Compound **3** is especially interesting because it shows a potent and selective antagonistic activity against histaminergic receptors as shown in the test performed in vitro on the guinea pig ileum. Two approaches have been reported for the synthesis of midpacamide **2** and dispacamide **3**. The first one, applicable to **2** and **3** is based on the Horner–Wadsworth–Emmons reaction of the 4,5-dibromo *N*-(3-oxopropyl)pyrrole-2-carboxamide with the appropriately substituted hydantoin[4] or 2-thiohydantoin.[5] The second approach for the synthesis of **3** involves the preparation and further acylation of 2-amino-4-(3-aminopropyl)-1*H*-imidazole.[6] In both approaches a conveniently functionalized imidazole ring is needed.

In conjunction with our synthetic efforts on the synthesis of a number of imidazole-containing alkaloids of marine origin,[7] we have devised a reliable approach to the alkaloids **2** and **3**, which is based on the formation



Keywords: aza-Wittig reaction; natural products; sponges; nitrogen heterocycles.

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0040-4039/01/$ - see front matter
PII: S0040-4039(00)02120-1

of the key common α-azido ester intermediate **5**. Slight variations in the cyclization strategy of this novel precursor allow the appropriately substituted imidazole ring to be created.

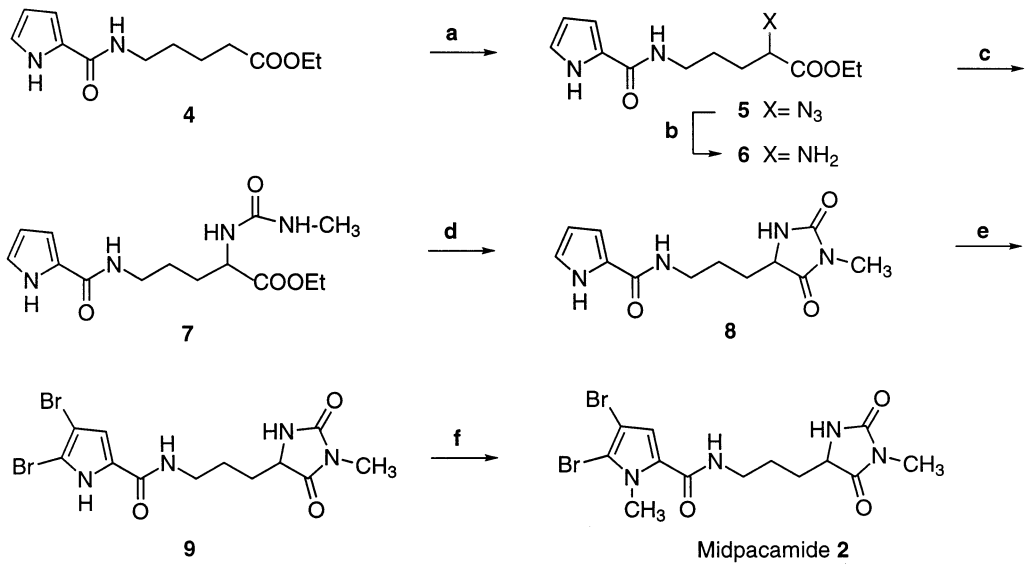
The *N*-acylated amino ester **4** was prepared in 90% yield from the reaction of 2-pyrrolyltrichloromethyl ketone with ethyl 5-aminovalerate hydrochloride in acetonitrile in the presence of triethylamine. The common intermediate α-azido ester **5** was prepared in 70% yield from **4** by the enolate azidation procedure described by Evans[8] using LDA/2,4,6-triisopropylbenzenesulfonyl azide[9] (trisyl azide)/HMPA. Staudinger reaction between the α-azido ester **5** and triphenylphosphine followed by hydrolysis of the resulting iminophosphorane provided the α-amino ester **6** in 80% yield.

Conversion of the α-amino ester **6** into the α-ureido ester **7** was achieved in one step with a 65% yield by sequential treatment with triphosgene and methylamine. When compound **7** was treated with sodium hydroxide in THF at room temperature hydantoin annelation took place to give **8** in almost quantitative yield (95%), thus completing the carbon skeleton of the midpacamide. All that remained for realization of the final goal was the appropriate functionalization of the pyrrole ring. Bromination of **8** with bromine in acetic acid at room temperature provided the expected dibrominated compound **9** in 95% yield, which was converted into midpacamide **2** with 85% yield by selective methylation with methyl iodide in DMF in the presence of potassium carbonate[10] (Scheme 1).

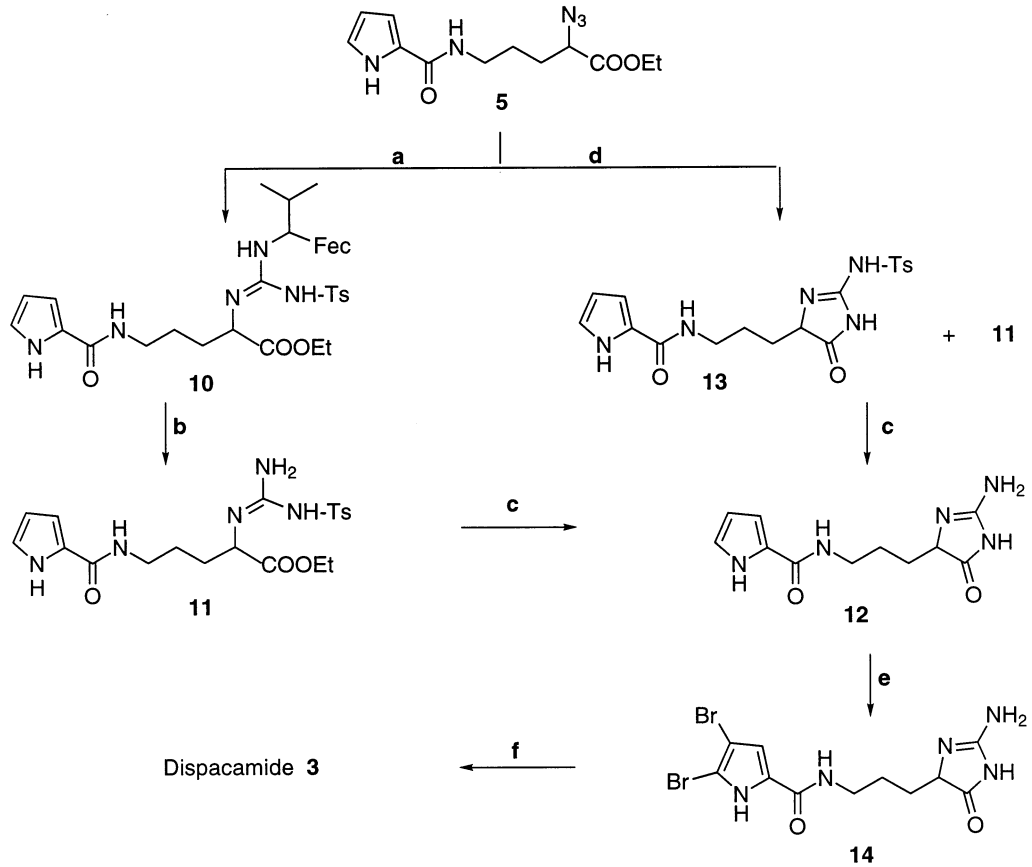
The synthesis of dispacamide **3** required the formation of the 2-aminoimidazolone ring from the α-azido ester **5**. Initial Staudinger reaction between the α-azido ester **5** and triphenylphosphine gave the corresponding iminophosphorane, which was not isolated. An aza-Wittig type reaction between the iminophosphorane and tosyl isocyanate at room temperature afforded the expected carbodiimide (as evidenced by the appearance of a strong band at 2129 cm^{-1} in the IR spectrum). Reaction of the carbodiimide with 1-ferrocenyl-2-methylpropylamine[11] led to the *N*,*N*′,*N*″-trisubstituted guanidine **10** in 47% overall yield, which under the reaction conditions did not undergo cyclization. The 1-ferrocenyl-2-methylpropyl group in compound **10** was removed by the action of trifluoroacetic acid in thioglycolic acid[12] as solvent at −15°C to give the *N*,*N*′-disubstituted guanidine **11** in 80% yield. Removal of the *N*-tosyl protecting group was essential to our objective to prepare dispacamide **3**. On the basis of the reaction conditions used to remove *N*-sulfonyl protecting groups using samarium diiodide,[13] complete deprotection of **11** with concomitant imidazole ring formation was achieved in 90% yield to give **12** by action of an excess of samarium diiodide in THF in the presence of 1,3 - dimethyl - 3,4,5,6 - tetrahydro - 2(1*H*)pyrimidinone (DMPU).

Clearly, the modest yield in the guanidine formation step (**5**→**10**), which is probably due to the hindered nature of the amine, does not make this a practical route to **12**, and we therefore examined the same type of sequence of reactions except that ammonia was used instead of 1-ferrocenyl-2-methylpropylamine in order to increase the yield of the guanidine formation step.

In this context, sequential treatment of the α-azido ester with triphenylphosphine, tosyl isocyanate and ammonia provide a mixture of guanidine **11** (20%) and the cyclized product **13** (40%). When this mixture was submitted to the above *N*-sulfonyldeprotection with samarium diiodide, the 2-amino-imidazolinone **12** was obtained in 92% yield after chromatographic separation. Bromination of **12** with bromine in acetic acid at



Scheme 1. *Reagents and conditions*: (a) i: LDA, THF, −30°C, ii: trisyl azide, HMPA, −78°C, iii: AcOH, rt (70%); (b) i: Ph_3P, Et_2O, rt, ii: H_2O, rt (80%); (c) i: triphosgene, Et_3N, CH_2Cl_2, rt, ii: CH_3NH_2 (65%); (d) NaOH, THF, rt (95%); (e) Br_2, AcOH, rt (95%); (f) CH_3I, K_2CO_3, DMF, rt (85%).



Scheme 2. *Reagents and conditions*: (a) i: Ph_3P, Et_2O, rt, ii: Ts-NCO, rt; iii: 1-ferrocenyl-2-methyl propylamine, rt (47%); (b) TFA, $HSCH_2COOH$, −15°C (80%); (c) SmI_2/DMPU, THF, reflux (90% from **11**; 92% from **11**+**13**); (d) i: Ph_3P, Et_2O, rt, ii: Ts-NCO, rt, iii: NH_3, rt (**11** 20% and **13** 40%); (e) Br_2, AcOH, 0°C (95%); (f) Ref. 6.

room temperature afforded the dihydrodispacamide **14** in 95% yield (Scheme 2).

This constitutes a formal total synthesis of dispacamide **3**, since **14** may be converted into the target alkaloid in a straightforward manner.[6]

In conclusion, convenient syntheses of both midpacamide **2** (five steps) and dispacamide **3** (four steps) have been developed. The utility of the α-azido ester **5** as a common intermediate is demonstrated by the selective formation throughout on appropriate cyclization strategy of the 3-methylhydantoin and 2-aminoimidazolinone rings present in **2** and **3**, respectively.

Acknowledgements

We gratefully acknowledge the financial support of the Dirección General de Investigación Científica y Técnica (PB95-1019). M.A.S. also thanks the 'Fundación Séneca' (CARM) for a studentship.

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