Tetrahedron Letters,Vol.23,No.27,pp 2793-2796,1982 0040-4039/82/272793-04$03.00/0
Printed in Great Britain

A GENERAL SYNTHESIS OF THE ACARNIDINES

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ABSTRACT: A general synthetic route to the biologically active marine natural products, the acarnidines (10a-c),[1] and molecules of the acarnidine type, is presented. The substituted homospermidine skeleton of the acarnidines was synthesised *via* an aldimine intermediate prepared from mono-BOC protected 1,5-diaminopentane (5) and the aldehyde (4).

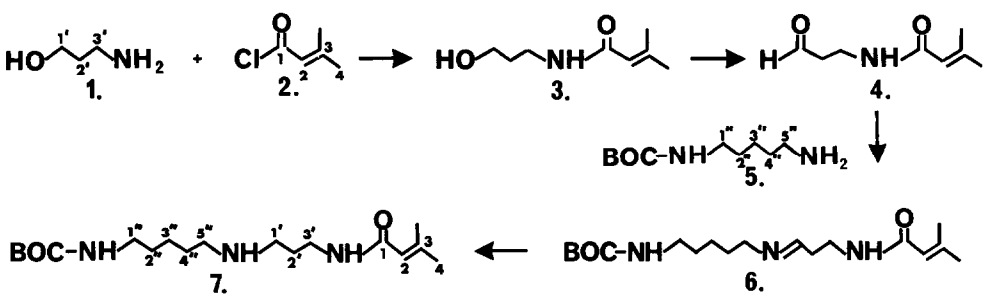
The marine natural products (10a-c), known as the acarnidines, were recently isolated from the sponge *Acarnus erithacus*.[1] These compounds were reported to possess broad antimicrobial activity and modest antiviral activity against *Herpes simplex*, type I. The structures of the acarnidines were elucidated by mass spectrometry, by ^{13}C- and ^{1}H NMR spectroscopy, and by degradative methods,[1] and the skeleton of one of the acarnidines was confirmed by the synthesis of a dimethyl pyrimidyl derivative.[1]

We report here a general synthetic route leading to the acarnidine skeleton and illustrate the route with the preparation of the natural 3,5-acarnidine (10a). The development of the synthetic scheme depended on the ease with which different synthons could be incorporated, without significant changes in method, whilst still maintaining high yields. This aspect of the synthesis was of importance as the overall aim of the synthetic route included the preparation of synthetic analogues of the acarnidines (e.g. 10a; x = 2-6, y = 2-5) for assessment of biological activity. Although there are several reported methods for assembling acyclic triamines[2] and amidoguanidines[3] the synthesis of derivatives has been restricted because of a lack of selectivity, forcing conditions[4] or because terminal bis-products were formed. To overcome these problems a convergent synthetic strategy which made use of a mono-protected diamine (e.g. 5) was adopted to assemble the triamine skeleton. Oxidation of the alcohol (e.g. 3) would lead to the aldehyde (e.g. 4), which could be condensed to the aldimine (e.g. 6) and then readily converted through to the acarnidine type skeleton (10).

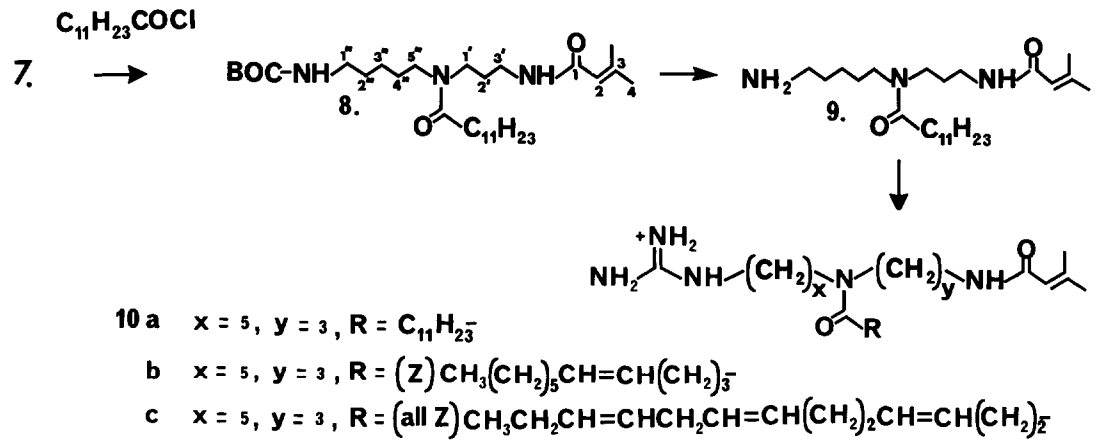
The starting point in the synthesis of the 3,5-acarnidine (10a) was the amidation of 3-aminopropanol (1) with 3,3-dimethylacryloyl chloride (2) in triethylamine and chloroform at 0°. The amido-alcohol (3), bp 100-105°/0.02mm, [ν_{max} 3300, 1665, 1630 cm^{-1}; λ_{max} 218 nm (ε 17,000)] was isolated as an oil in 83% yield.[5,6].

Considerable difficulty was encountered in the oxidation of the amido-alcohol (3) to the amido-aldehyde (4). It was found that over-oxidation to the carboxylic acid occurred with the chromium based oxidation methods, although no useful reaction was observed with pyridinium chloro-chromate/CH_2Cl_2. The Moffat oxidation method and many of its variants, surprisingly, were also not successful with only low yields of the amido-aldehyde being obtained (as measured by comparison of the integral of the formyl proton resonance in the ^1H NMR spectrum with that of either the olefinic proton, or the *gem*-dimethyl proton signals). Of the twelve oxidation methods explored the only truly successful method was that using DMSO/oxalyl chloride at -60°.[7] Using this method the amido-aldehyde (4) (ν_{max} 2740, 1725, 1675, 1640 cm^{-1}) was formed in an 84% yield. It was observed that the relative integral of the formyl proton signal decreased rapidly on storage of the aldehyde even when stored at low temperatures. For this reason the freshly prepared amido-aldehyde was used without purification.[8]

For the synthesis of the 3,5-acarnidines, mono-BOC protected 1,5-diamino-pentane was used. The monoprotection of such an α,ω-diaminoalkane was a key point in the general synthetic scheme. This was achieved in good yield through the use of S-(*tert*-butyloxycarbonyl)-4, 6-dimethyl-2-mercaptopyrimidine.[9] Under carefully controlled conditions it was possible to effect monoprotection of an α,ω-diaminoalkane.[9] An excess of the freshly prepared amido-aldehyde (4) was condensed with the mono-BOC protected diamine (5)[10] in chloroform over 4Å molecular sieves at room temperature. After a reaction time of 45 minutes the chloroform was removed under reduced pressure and the residue dissolved in a suspension of $NaBH_4$ in ethanol and the mixture heated under reflux for 20 minutes. After removal of the ethanol the secondary amine (7) was separated from any neutral material as the hydrochloride in a 71% yield and recrystallised from ethyl acetate/diethyl ether, m.p. 85-86°, (ν_{max} 3350, 1690, 1675, 1640 cm^{-1}). The ^1H and ^{13}C n.m.r. spectra[11] were in keeping with the assignment of structure.



At this point reaction of the secondary amine group with any acyl halide would have been possible, but to synthesise the natural product (10a), lauroyl chloride was used. The secondary amine (7) was acylated in a CH_2Cl_2/triethylamine mixture and the acylation proceeded in good yield (73% recovered yield after chromatography) to give the tertiary amide (8) (ν_{max} 1710, 1680, 1630 cm^{-1}).[12] The BOC protecting group of the diamide (8) was removed by reaction in neat trifluoroacetic acid at 15° and was complete after 40 min. The amine (9) was isolated from the basified reaction mixture (95% yield) as an unstable oil (ν_{max} 3350, 1660, 1630 cm^{-1})[13] which without delay was reacted with S-methylisothiouronium iodide (50% molar excess) in ethanol at room temperature for 24 hours. Trial



10 a x = 5, y = 3, R = $C_{11}H_{23}$-

b x = 5, y = 3, R = (Z)$CH_3(CH_2)_5CH{=}CH(CH_2)_3$-

c x = 5, y = 3, R = (all Z)$CH_3CH_2CH{=}CHCH_2CH{=}CH(CH_2)_2CH{=}CH(CH_2)_2$-

experiments had indicated that such mild conditions were necessary to achieve guanidination of the amine (9 → 10a) in satisfactory yield with the minimum yield of byproducts and minimum decomposition of the amine (9). The 3,5-acarnidine (10a) was isolated and purified by removal of the ethanol and partitioning of the residue between water/chloroform. The chloroform extract, which contained the acarnidine (10a), was further purified by gel chromatography on Fractogel PGM2000 using ethanol as eluent which successfully separated the amine and neutral impurities. The 3,5-acarnidine hydroiodide, which was isolated in a 60% yield, had spectral properties[14] identical with those for the natural product (10a) and the identity and molecular formula of the synthetic material was confirmed by FABMS and HRFABMS.[15]

This general synthetic scheme has been extended successfully to a wide variety of chain lengths (10a; x = 2-6, y = 2-5) to produce a number of synthetic acarnidines which are currently being assessed for the potential for useful biological activity in this general skeletal type.

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ACKNOWLEDGEMENTS. Financial assistance from the N.Z. U.G.C. for the purchase of research equipment and the acquisition of FABMS and HRFABMS by the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois, Urbana, are gratefully acknowledged as is the discussion with Professor A.R. Battersby (Erskine Fellow, University of Canterbury, 1979).

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3. P.L. Barker, P.L. Gendler and H. Rapoport, J. Org. Chem., 46, 2455 (1981).
4. J.S. McManis and B. Ganem, J. Org. Chem., 45, 2042 (1980).
5. Satisfactory analytical and/or HR mass spectral data were obtained for all new compounds reported.
6. 3. $\delta_H(CDCl_3)$ 1.70 (2H,m,2'-H), 1.83 (3H,s,4-H), 2.10 (3H,s,3-CH_3), 3.36 (2H, t,3'-H), 3.62 [3H(1H exchanges with D_2O),t,1'-H], 5.68 (1H,s,2-H), 7.67 [1H(exchanged by D_2O),bs,amide-H] ppm. $\delta_C(CDCl_3)$ 19.8, 27.1, 32.3, 35.9, 59.2, 118.5, 150.8, 168.4 ppm.
7. A.J. Mancuso, S. Huang and D. Swern, J. Org. Chem., 43, 2480 (1978).
8. 4. $\delta_H(CDCl_3)$ 1.83 (3H,s,4-H), 2.12 (3H,s,3-CH_3), 2.72 (2H,t,2'-H), 3.51 (2H, m,3'-H), 5.57 (1H,s,2-H), 6.53 [1H(exchanged by D_2O),bs,amide-H], 9.72 (1H,s, 1'-H) ppm. $\delta_C(CDCl_3)$ 19.7, 27.1, 32.8, 44.0, 118.5, 150.8, 167.4, 201.7 ppm.
9. G.L. Stahl, R. Walter and C.W. Smith, J. Org. Chem., 43, 2285 (1978).
10. 5. HCl. mp 112-113°, ν_{max} 1690 cm^{-1}. $\delta_H(CDCl_3)$ 1.43 (15H,bs,BOC-CH_3,2"-H, 3"-H,4"-H), 4.72 (4H,bt,1"-H,5"-H), 5.1 [1H(exchanged by D_2O),bs,amide-H] ppm. $\delta_C(CDCl_3)$ 23.6, 26.8, 28.5, 29.2, 39.7, 40.3, 79.2, 156.8 ppm.
11. 7. HCl. $\delta_H(CDCl_3)$ 1.45 (17H,bs,BOC-CH_3,2'-H,2"-H,3"-H,4"-H), 1.87 (3H,s,4-H), 2.14 (3H,s,3-CH_3), 2.6-3.5 (8H,bm,1'-H,3'-H,1"-H,5"-H), 4.98 [1H(exchanged by D_2O),bs,BOC-NH], 5.78 (1H,s,2-H), 7.82 [1H(exchanged by D_2O),bs,amide-H], 9.40 [2H(exchanged by D_2O),bs,-NH_2] ppm. $\delta_C(CDCl_3)$ 19.5, 24.3, 26.9, 28.2, 28.9, 29.6, 29.7, 37.5, 40.2, 47.5, 49.3, 78.8, 118.6, 149.7, 156.1, 168.8 ppm.
12. 8. $\delta_H(CDCl_3)$ 0.87 (3H,t,alkyl), 1.27 (26H,bs,alkyl,2'-H,2"-H,3"-H,4"-H), 1.43 (9H,s,BOC-CH_3), 1.82 (3H,s,4-H), 2.13 (3H,s,3-CH_3), 2.32 (2H,t,alkyl), 3.22 (8H, bm,1'-H,3'-H,1"-H,5"-H), 4.70 (1H,bs,BOC-NH), 5.60 (1H,s,2-H), 6.72 (1H,bs, amide-H) ppm. $\delta_C(CDCl_3)$ 14.1, 19.5, 22.6, 24.1, 25.7, 27.1, 28.4, 29.3, 29.5, 29.9, 31.9, 33.2, 35.2, 40.3, 42.2, 47.7, 78.8, 119.0, 149.5, 155.9, 173.7 ppm.
13. 9. $\delta_H(CDCl_3)$ 0.88 (3H,t,alkyl), 1.25 (18H,bs,alkyl), 1.4-1.75 (8H,bm,2'-H, 2"-H,3"-H,4"-H), 1.80 (3H,s,4-H), 2.13 (3H,s,3-CH_3), 2.28 (2H,t,alkyl), 2.75 [4H(2H exchanged by D_2O),1"-H,-NH_2], 2.9-3.5 (6H,bm,1'-H,3'-H,5"-H), 5.60 (1H,s,2-H), 6.82 [1H(exchanged by D_2O),bs,amide-H] ppm. $\delta_C(CDCl_3)$ 13.9, 19.5, 22.5, 24.6, 25.5, 26.8, 27.2, 28.7, 29.1, 29.3, 29.4, 31.7, 33.0, 35.2, 41.5, 42.1, 45.4, 47.6, 118.9, 149.6, 167.0, 173.7 ppm.
14. 10a. HI. $\delta_H(CDCl_3)$ 0.87 (3H,t,alkyl), 1.27 (18H,bs,alkyl), 1.4-1.75 (8H,bm, 2'-H,2"-H,3"-H,4"-H), 1.80 (3H,s,4-H), 2.13 (3H,s,3-CH_3), 2.28 (2H,t,alkyl), 3.25 (8H,bm,1'-H,3'-H,1"-H,5"-H), 5.60 (1H,s,2H), 7.15 [1H(exchanged by D_2O), bs,amide-H], 5.0-8.0 [5H(exchanged by D_2O),vbs,guanidine-NH] ppm. $\delta_C(CDCl_3)$ 13.7, 19.6, 22.3, 25.3, 26.8, 29.0, 29.3, 31.5, 32.9, 35.8, 36.3, 41.6, 43.2, 46.1, 48.1, 118.2, 150.1, 157.1, 167.5, 173.6 ppm.
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(Received in UK 8 March 1982)