Tetrahedron Letters,Vol.30,No.23,pp 3027-3028,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

# SYNTHESIS OF A MODEL DEPSIPEPTIDE SEGMENT OF LUZOPEPTINS (BBM 928), POTENT ANTITUMOR AND ANTIRETROVIRAL ANTIBIOTICS

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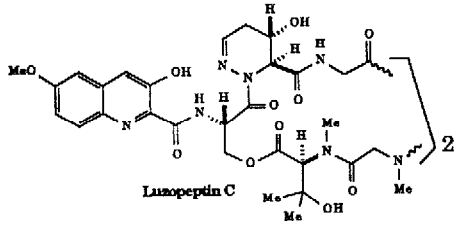
**ABSTRACT:** *A modified Rapoport procedure was used to synthesize a tripeptide containing N-methyl-3-hydroxyvaline, an unusual aminoacid found in Luzopeptins .*

Luzopeptins are cyclodepsipeptide antibiotics isolated from *Actinomadura luzonensis*.[1] Luzopeptin C has recently been identified as a potent inhibitor of HIV reverse transcriptase,[2] a finding of considerable significance for prospective applications of the antibiotic to AIDS therapy. Even before such discovery, the complex architecture of Luzopeptins had stimulated model synthetic studies.[3] During an exploratory phase of our own synthetic work in the luzopeptin area, we have prepared a model tripeptide fragment, **6**, which incorporates the unusual aminoacid, (L)-N-methyl-3-hydroxyvaline.[4] Below, we present a summary of our results.



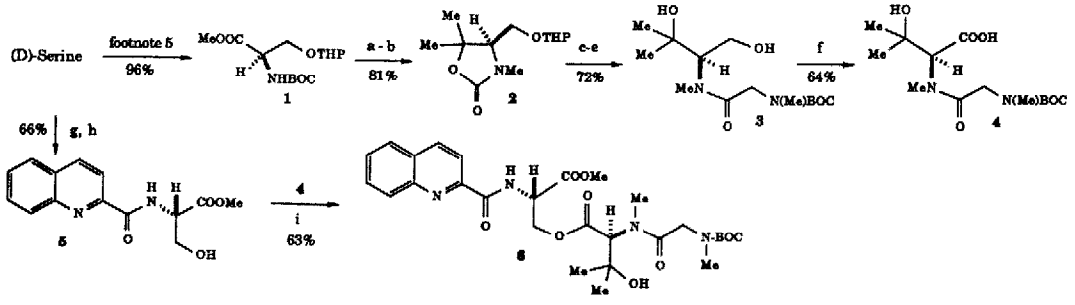

Compound **1**, readily available from inexpensive D-serine,[5] itself a component of luzopeptins, was converted into amide **3** (white foam, $[a]^{23} = +24.3^{o}$, c=3.350, ethanol) *via* the sequence outlined in the scheme below. Compound **3** formed a single diastereomer upon coupling with MTPA,[6] as evident based on high-temperature $^{1}H$ NMR (300 MHz, DMSO-D6, 383° K). Oxidation of the primary alcohol to acid **4**[7] (foam, $[a]^{23} = -29.9^{o}$, c=2.645, ethanol), was smoothly achieved with alkaline permanganate[8] (64% yield; 75% based on recovered alcohol). Compound **4** was coupled to a fragment containing D-serine, in order to demonstrate depsipeptide bond formation. Sequential reaction of (D)-serine with quinaldoyl chloride, under Schötten-Baumann conditions, and with ethereal $CH_2N_2$, afforded **5**, which was uneventfully esterified with acid **4** using DCC in dichloromethane. Tripeptide **6** (m.p. 64-67° C after softening at 62-64° C; $[a]^{23} = -15.6^{o}$, c=1.106, ethanol) was obtained as a white powder in 63% yield, after silica gel chromatography (50% ethyl acetate in hexanes) and crystallization from ether-hexane (-78° C). This work defines a method for the preparation of the rare aminoacid, N-methyl-3-hydroxyvaline in a form suitable for direct incorporation into luzopeptins. Moreover, the feasibility of depsipeptide bond formation using a close model of the natural product has been ascertained.

Because of the importance of compound **4** for future synthetic studies in the luzopeptin area, an experimental procedure for its preparation is provided. An ethereal solution of compound **1** was added over 10 min to a 0.5 M ethereal solution of 4 eq. of MeMgBr cooled to -30° C. The mixture was then brought to gentle reflux, and after 15 min. it was quenched (aq. $NH_4Cl$) and worked up. Without purification, the alcohol was cyclized to the oxazolone using 3 eq. NaH in THF (0.5 M, 50° C, 10 h). The oxazolone, presumably emerging as its N-anion, was methylated *in situ* simply by quenching the reaction with 3 eq. MeI. Compound **2** resulted in 81% overall yield, but as a

mixture of 2 stereoisomers, because of the THP group. Vigorous base hydrolysis (3 eq. KOH, 4:1 ethylene glycol:$H_2O$, 0.5 M soln., refl. 24 h) was necessary to cleave 2 to the aminoalcohol, which was directly coupled with N-*t*BOC serine (1.2 eq.) without protection of the tertiary OH (1.2 eq. DCC, 0.05 M sln. in $CH_2Cl_2$, 25° C, 8 hrs). The crude reaction mixture was filtered through a short plug of silica gel using additional $CH_2Cl_2$, and the amide thus obtained was further de-tetrahydropyranylated by stirring a 0.1 M methanolic solution with a catalytic amount of $TsOH \cdot H_2O$ (72 % overall yield ). A 1 M solution of the diol in distilled water containing 0.75 mol NaOH and 3 mol $KMnO_4$ per mol of alcohol was stirred at 25° C for 12 hr. Saturated aq. $NaHSO_3$ solution was added until disappearance of the purple color, and the solution was extracted (EtOAc) to recover unreacted alcohol. Careful acidification to pH 2 (4 N HCl) and EtOAc extraction afforded acid 4, which was further purified by a second acid-base extraction followed by trituration with hexane (white foam, 65 % yield). The yield is 75 % if recovered alcohol is taken into account.

**Acknowledgement:** we thank the National Science Foundation and the American Foundation for AIDS Research (AmFAR) for their generous support of this work.

**SCHEME 1**




a. xs MeMgBr, ether, -20° C; b. 3 equiv. NaH, THF, refl., add MeI; c. KOH, $(CH_2OH)_2/H_2O$, refl.; d. N-BOC sarcosine, DCC, $CH_2Cl_2$, 25° C; e. TsOH, MeOH, 25° C; f. $KMnO_4$, NaOH, $H_2O$, 25° C, ; g. quinaldoyl chloride, $NaHCO_3$, $H_2O$, 25° C; h. $CH_2N_2$; i. 4, DCC, $CH_2Cl_2$, 25° C.

## REFERENCES AND FOOTNOTES

1. Konishi, M.; Ohkuma, H.; Sakai, F.; Tsuno, T.; Koshiyama, H.; Naito, T.; Kawaguchi, H. *J. Antibiot.* **1981**, *34*, 148; Konishi, M.; Ohkuma, H.; Sakai, F.; Tsuno, T.; Koshiyama, H.; Naito, T.; Kawaguchi, H. *J. Am. Chem. Soc.* **1981**, *103*, 1241; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 1243.
2. Inouye, Y.; Take, Y.; Nakamura, S. *J. Antibiot.* **1987**, *40*, 100.
3. Previous model studies: Olsen, R. K.; Apparao, S.; Bhat, K. L. *J. Org. Chem.* **1986**, *51*, 3079.
4. The racemic aminoacid has been prepared: Izumiya, N.; Nagamatsu, A. *J. Chem. Soc. Jpn.* **1951**, *72*, 336, but the optically active material has apparently never been reported.
5. a. $BOC_2O$, THF, aq. 10% NaOH; b. $CH_2N_2$; c. DHP, PPTS, $CH_2Cl_2$.
6. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. The Mosher ester was easily obtained by coupling with MTPA (DCC, DMAP) in $CH_2Cl_2$.
7. This procedure is clearly patterned along lines pioneered by: Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1094.
8. Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855.

(Received in USA 23 February 1989)