Tetrahedron Letters,Vol.29,No.34,pp 4225-4228,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# TOTAL SYNTHESIS OF THE MIXED PEPTIDE-POLYPROPIONATE BASED CYCLODEPSIPEPTIDE (+)-GEODIAMOLIDE B

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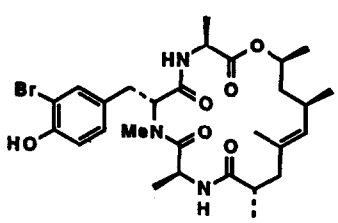
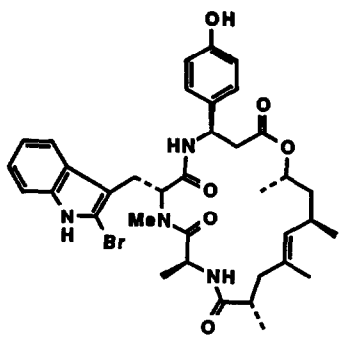
Summary: The first total synthesis of the mixed peptide-polypropionate based cyclodepsipeptide (+)-geodiamolide B (**1**) has been realized via coupling of the polypropionate fragment **4** with the tripeptide unit **3** possessing the unique (R)-3-bromo-N-methyltyrosine.

The novel cyclodepsipeptide geodiamolide B(**1**),[2] isolated from an acetone extract of the marine sponge Geodia sp., is composed of an 11-carbon polypropionate fragment and a tripeptide unit within an 18-membered ring. Of particular interest is the tripeptide segment which possesses the unique (R)-3-bromo-N-methyltyrosine along with two (S)-alanine units. Geodiamolide B, like the closely related cyclodepsipeptide jasplakinolide (**2**)[3,4] (jaspamide), is



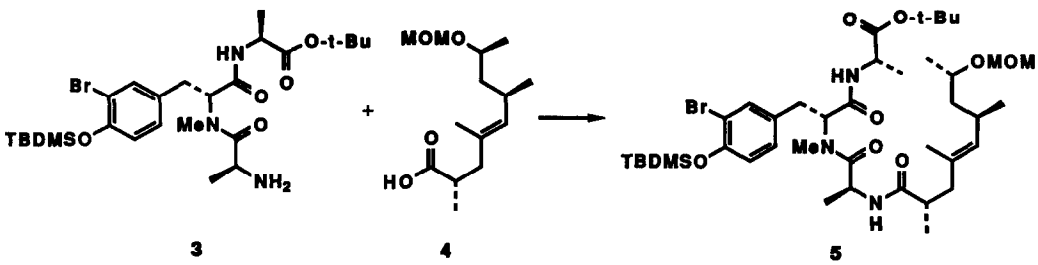

**1**




**2**

active against the fungus Candida albicans. Both **1** and **2** possess the same 11-carbon hydroxy carboxylic acid [(2S, 6R, 8S)-8-hydroxy-2,4,6-trimethyl-4E-nonenoic acid]. We detail below the first total synthesis of (+)-geodiamolide B.

Our approach to the construction of geodiamolide B (**1**) featured




**3** **4** **5**

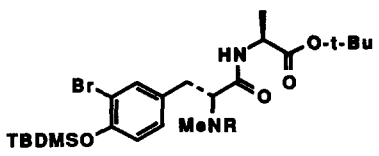
coupling of tripeptide **3** with the known 11-carbon hydroxy nonenoic acid **4**.[5] The preparation of tripeptide **3** required a prior synthesis of the unknown, unnatural amino acid, 3-bromo-O-tert-butyldimethylsilyl-N-methyl-N-t-BOC-D-tyrosine **7**. Toward this end, N-t-BOC-D-tyrosine was protected in essentially quantitative yield as its tert-butyldimethylsilyl ether by exposure


**6** **7**

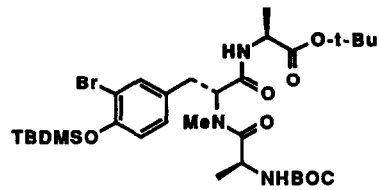
(48 h) to tert-butyldimethylchlorosilane/imidazole in dimethylformamide followed by cleavage of the resultant O-silyl ester with potassium carbonate in water:methanol:tetrahydrofuran, 1:1:2 (1 h). Subsequent N-alkylation (t-BuLi, THF, MeI, -78°C ⟶ room temperature)[6] gave rise in 71% yield to **6**, $[\alpha]_D$ +47.3° (c 0.81, $CHCl_3$). Bromination ($Br_2$, $Hg(OAc)_2$, $CCl_4$, 0°C, 2 h) of **6** afforded 3-bromo-O-tert-butyldimethylsilyl-N-methyl-N-t-BOC-D-tyrosine **7**, $[\alpha]_D$ +38.2° (c 2.23, $CHCl_3$), in 80% yield.

Coupling (DCC, HOBt, $Et_3N$, THF)[7] of the D-tyrosine derivative **7** with L-alanine t-butyl ester hydrochloride provided dipeptide **8**, $[\alpha]_D$ +39.4° (c 3.52, $CHCl_3$) in 81% yield. Cleavage of the N-t-BOC group in **8** in the presence of the tert-butyl ester was achieved in 52% yield employing tert-butyldimethylsilyl triflate (TBDMSOTf)[8] in methylene chloride containing 2,6-lutidine followed

by cleavage of the resultant N-tert-butyldimethylsilyloxycarbonyl group with potassium carbonate in aqueous methanol-THF (1:1:2). Having secured **9**, N-t-



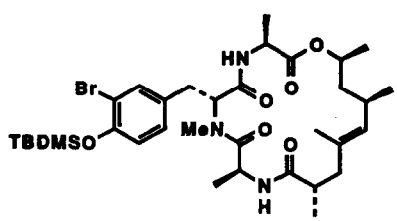

**8** R = BOC
**9** R = H




**10**

BOC-L-alanine was coupled (DCC, HOBt, THF) to **9** providing **10**, $[\alpha]_D$ +30.1° [c 3.70, $CHCl_3$] in 90% yield. Cleavage [(a)TBDMSOTf, $CH_2Cl_2$, 2,6-lutidine; (b) $K_2CO_3$, $H_2O$-MeOH-THF, 1:1:2] of the N-t-BOC group in **10** gave rise (68%) to **3**, $[\alpha]_D$ +54.7°(c 1.83, $CHCl_3$).

Completion of the synthesis of (+)-geodiamolide B was realized by a four step sequence. Coupling [DCC, HOBt, THF] of carboxylic acid **4** with tripeptide **3** was accomplished in 81% yield giving rise to **5**, $[\alpha]_D$ +21.8° (c 1.72,. $CHCl_3$). Simultaneous removal of the methoxymethyl ether and the tert-butyl ester group employing excess ethanedithiol and excess trifluoroacetic acid in methylene chloride (1.25 h) afforded (50%) the corresponding seco acid which upon macrolactonization (DCC, DMAP, DMAP-TFA, $CHCl_3$, reflux)[9] generated




**11**

(ca. 15%) the silylated geodiamolide B **11**, $[\alpha]_D$ +42.3° (c 0.04, $CHCl_3$). Desilylation (TBAF, THF) provided (88%) synthetic (+)-geodiamolide B, mp 197-198°C, $[\alpha]_D$ + 101.8° (c 0.05, $CHCl_3$), which was identical (300 MHz $^1H$ NMR, IR, $[\alpha]_D$ and mp) with an authentic sample of natural material kindly provided by Dr. Percy Manchand.

**Acknowledgements.** Generous support for this work from the National Cancer Institute, National Institutes of Health (Grant CA 28865) is gratefully acknowledged. The 300-MHz NMR instrument (Varian XL-300) used in the above studies was purchased with funds provided by the National Institutes of Health (Grant RR-1882). We are grateful to Dr. Percy Manchand (Hoffmann-La Roche) for a sample of natural geodiamolide B.

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(Received in USA 5 May 1988)