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Studies on Cyclodepsipeptides - Part II : The Total Synthesis of Jaspamide and Geodiamolide-D

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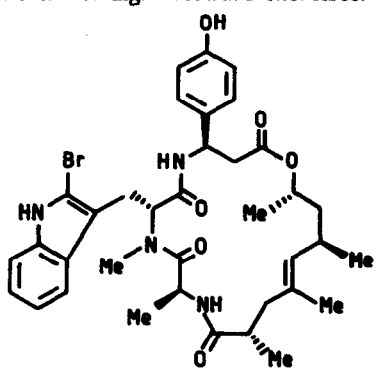
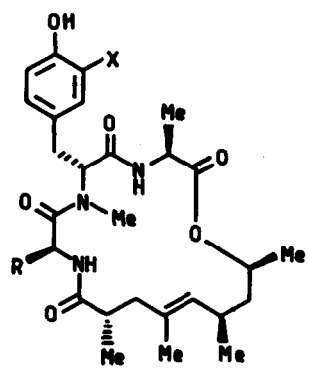
Abstract : The total synthesis of cyclodepsipeptides jaspamide and geodiamolide D have been presented.

In the preceding communication[1], we described a rational synthetic design to construct the C_{12} polyketide (C1-C8) fragment (3), which forms the part structure of jaspamide (1) and geodiamolide A-F (2)[2]. Herein, we report the total synthesis of jaspamide (1) and geodiamolide D (2) for which our basic analogy centered around the preparation of the unusual amino acids and tripeptides (4 and 5). Having had the C_{12} chain ready at hand, we considered that its coupling with respective tripeptides 4 and 5; and finally the macrolactonisation to 1 and 2-D should be the straight forward exercises.



Jaspamide 1



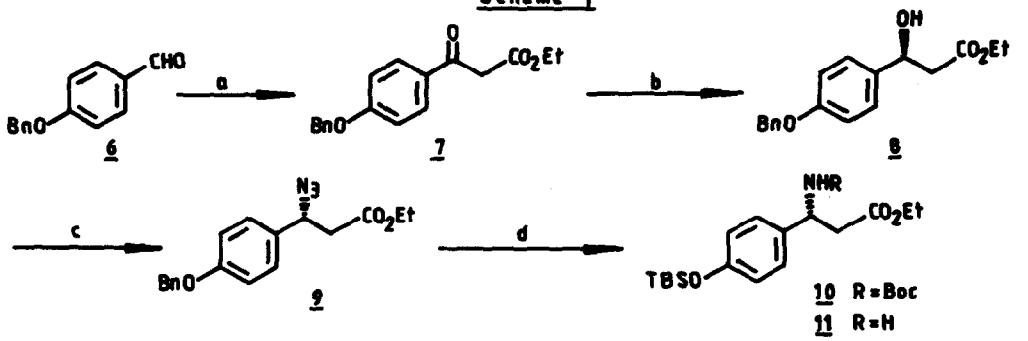
Geodiamolide 2

A X=I, R=Me D X=I, R=H
B X=Br, R=Me E X=Br, R=H
C X=Cl, R=Me F X=Cl, R=H

The desired tripeptide (4) segment of jaspamide (1) was obtained from (R)-β-tyrosine (11). We have developed the protocol to prepare the (R)-β-tyrosine derivative from the β-keto ester (7) (prepared from 6 in two steps) by enantioselective reduction of $Li(O^tBu)_3AlH$ with N,N-dibenzoyl-D-cystine, as a chiral auxiliary (70%)[3]. Its stereochemical assignment was based on earlier literature precedences while the e.e. (90%) was established from the Mosher ester. The nucleophilic displacement reaction of 8 with HN_3 under Mitsunobu condition[4] (DEAD, TPP, C_6H_6) gave the azido derivative (9) (80%) along with 5% of the cinnamic acid derivative. Successive hydrogenation, (Pd-C, H_2, MeOH), N-Boc protection (BOC_2O,THF) and O-TBS formation (TBS-Cl, Imid.) gave 10{ $[\alpha]_D$ +18.2° ($CHCl_3$)}, the N-Boc group of which was selectively

cleaved (CF_3COOH, CH_2Cl_2, 0°) to give **11** (Scheme 1).

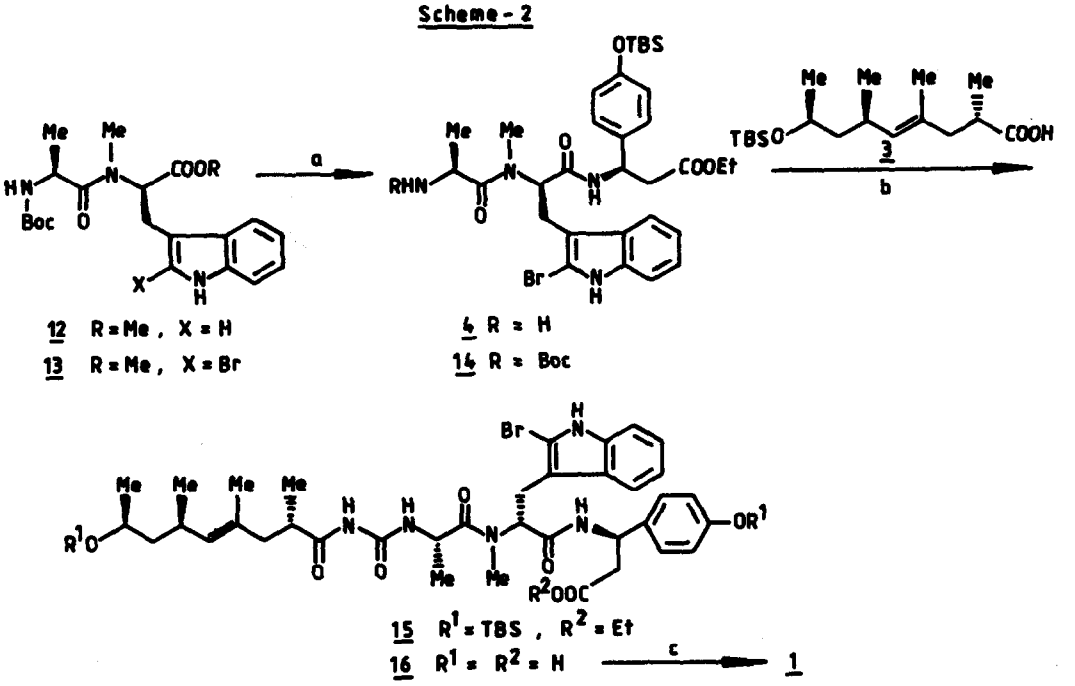
Scheme-1



a) (i) $BrCH_2COOEt$, Zn, Et_2O-C_6H_6, Δ, 1h; (ii) PCC, CH_2Cl_2, RT, 4h; b) $LiBH_4$, tBuOH, THF, N,N'-dibenzoyl-D-cystine, -78°C, 5h; c) HN_3, DEAD, PPh_3, C_6H_6, 0°C to RT, 3h; d) (i) Pd-C, H_2, MeOH, 1 atm, RT, (ii) $(Boc)_2O$, THF, RT, 6h; (iii) TBS-Cl, imid., CH_2Cl_2, RT, 3h; e) CF_3-COOH, CH_2Cl_2, 0°C, 3h.

The dipeptide, N-Boc-(S)-alanine-N-methyl-(R)-tryptophan methyl ester[5] (**12**) was subjected to nuclear bromination with NBS-$(C_6H_5CO)_2O_2$ to afford 2-bromoarbine derivative

Scheme-2



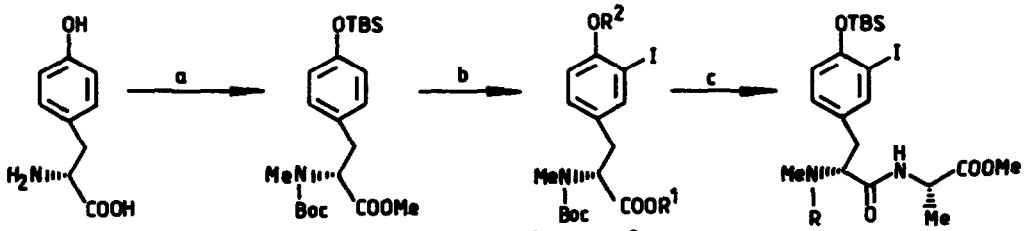
a) (i) NBS, $(C_6H_5$-$CO)_2O_2$, CCl_4, 0.5 h; (ii) LiOH, THF, MeOH, H_2O, 2h; (iii) **11**, DCC, HOBT, CH_2Cl_2, 0°C to RT, 6h; (iv) TBS-OTf, 2,6-lutidine, CH_2Cl_2, RT, 3h; b) (i) **3**, DCC, HOBT, CH_2Cl_2, -5°C, to 0°C, 5h; (ii) HF-pyridine, CH_2Cl_2, RT, 4h; (iii) LiOH-THF-MeOH-H_2O, RT, 3h; c) DCC, DMAP, DMAP.TFA, $CHCl_3$, Δ, 16h.

(13). Hydrolysis of 13 (LiOH, THF, MeOH, H_2O) was followed by coupling with 11 in the presence of DCC-HOBT to give the tripeptide (14) { $[\alpha]_D$ +35.7° ($CHCl_3$)}, the N-Boc group of which was preferentially removed (TBS-OTf, 2,6-lutidine, CH_2Cl_2) to afford 4 (Scheme 2).

The condensation of 4 with 3 promoted by DCC-HOBT gave 15 { $[\alpha]_D$ +24.6° ($CHCl_3$)} which was first desilylated (HF,Py, CH_2Cl_2) and then hydrolysed (LiOH-THF, MeOH, H_2O) to give the seco acid (16). The final macrolactonisation[6] was advanced in the presence DCC, DMAP, DMAP.TFA mixture in refluxing chloroform to give jaspamide (1) (22%). The structure of 1 was supported by comparison of its ^1H NMR, IR spectra, optical rotation values and mobility on TLC with that of the authentic specimen.

The synthetic exploration for geodiamolide (2-D) began with the transformation of (R)-tyrosine (17) into the corresponding N-Boc-N-methyl-O-TBS (R)-tyrosine methyl ester (18) by sequential a) esterification ($SOCl_2$, MeOH), b) N-Boc protection (BOC_2O, THF), c) O-TBS formation (TBS-Cl, Imid.) and d) N-methylation (NaH, MeI (58%). Treatment of 18 with iodine in the presence of $Hg(OAc)_2$ and acetic acid provided the 3-iodo-derivative (19), the methyl ester group of which was typically hydrolysed with LiOH-THF-MeOH-H_2O combination to obtain 20 (80%). Its coupling reaction with N-Boc-(S)-alanine promoted by DCC-HOBT afforded the dipeptide (21) which was selectively deprotected at N-Boc site by using TFA-CH_2Cl_2 at 0° to provide 22 (Scheme 3).

Scheme - 3



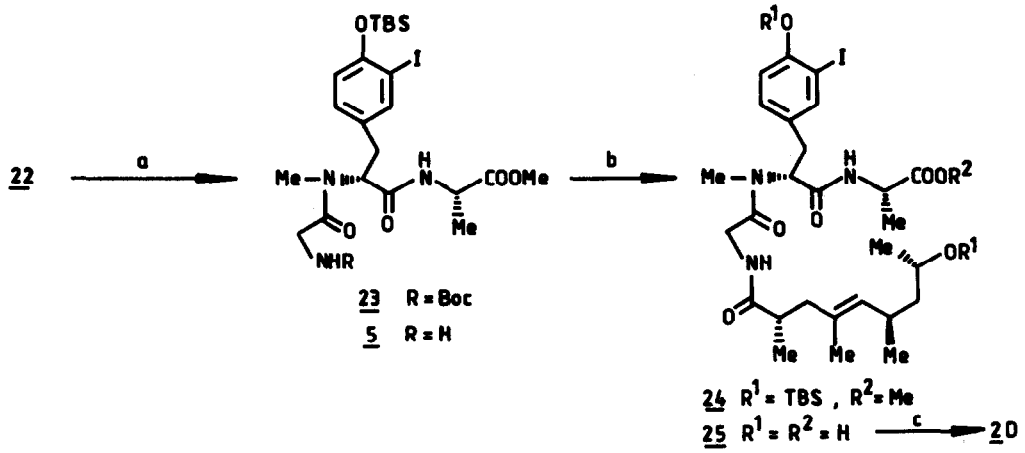
17 18 19 R^1 = Me, R^2 = TBS 20 R^1 = R^2 = H 21 R = Boc 22 R = H

a) (i) $SOCl_2$, MeOH, 0°C to RT, 8h; (ii) $(Boc)_2O$, THF, RT, 3h; (iii) TBS-Cl, imid., CH_2Cl_2, RT, 3h; (iv) NaH, MeI, DMF, RT, 4h; b) (i) I_2, $Hg(OAc)_2$, CH_3COOH, RT, 9h; (ii) LiOH, THF-MeOH-H_2O, 3h, RT; c) (i) (S)-Ala-OMe, DCC, HOBT, CH_2Cl_2, 0°C to RT, 10h, (ii) TBS-Cl, Imid., CH_2Cl_2, RT, 10 h; (iii) CF_3COOH, CH_2Cl_2, 0°C, 5h.

Compound 22 and N-Boc-glycine were then condensed with DCC-HOBT as promoters. From the resulting tripeptide (23)[7] { $[\alpha]_D$ +70.5° ($CHCl_3$)} (80%), the N-Boc group was cleaved, as described above, to provide the free amine 5, ready to be coupled with the C_{12} chain 3. This coupling reaction was performed in the presence of DCC-HOBT to give 24[7] { $[\alpha]_D$ +42.5° ($CHCl_3$)} (68%) from which both the OTBS groups were deprotected by using HF-Py (CH_2Cl_2, RT). The hydrolysis of the ester group (LiOH-THF-MeOH-H_2O) gave the seco-acid (25). The final macrolactonisation of 25 turned out to be a difficult proposition. With DCC-DMAP-DMAP.TFA in refluxing chloroform[6], 25 gave geodiamolide D (2) in an annoyingly low yield (7%) (Scheme 4). The structure of 2 was supported by the ^1H NMR and Mass spectral analysis which

were consistent with the reported data. We thank Prof Philip Crews and Prof R J Andersen for providing the sample of jaspamide and the ^{1}H NMR spectrum of geodiamolide D respectively.

Scheme - 4



a) (i) Boc-glycine, DCC, HOBT, CH_2Cl_2, 0°C to RT, 12h; (ii) CF_3COOH, CH_2Cl_2, 0°C, 3h; b) (i) 3, DCC, HOBT, CH_2Cl_2, -5°C to 0°C, 5h; (ii) HF-pyridine, CH_2Cl_2, RT, 4h; (iii) LiOH-THF-MeOH-H_2O, RT, 3h; c) DCC, DMAP, DMAP.TFA, $CHCl_3$, reflux, 16h.

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7. ^{1}H NMR spectra of some selected compounds: **23** (200 MHz, $CDCl_3$): δ 0.22 (s, 6H), 1.02 (s, 9H), 1.30 (d, 3H, J 7.2 Hz), 1.42 (s, 9H), 2.74 (dd, 1H, J 8.0, 15.2 Hz), 2.88 (s, 3H), 3.21 (dd, 1H, J 8.0, 15.2 Hz), 3.68 (s, 3H), 3.80 (dd, 1H, J 4.4, 18.0 Hz), 3.98 (dd, 1H, J 4.0, 18.0 Hz), 4.48 (dq, 1H), 5.26 (t, 1H, J 8.0 Hz), 5.38 (bs, 1H), 6.52 (d, 1H, J 8.0 Hz), 6.70 (d, 1H, J 8.0 Hz), 7.00 (dd, 1H, J 2.0, 8.0 Hz), 7.56 (d, 1H, J 2.0 Hz); **24** (400 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.25 (s, 6H), 0.88 (s, 18 H), 1.03 (s, 9H), 1.09 (d, 6H, J 6.5 Hz), 1.35 (d, 3H, J 7.5 Hz), 1.58 (s, 3H), 2.70 (dd, 1H, J 7.8, 14.1 Hz), 2.90 (s, 3H), 3.19 (dd, 1H, J 7.8, 14.1 Hz), 3.72 (s, 3H), 4.45 (dq, 1H), 4.90 (bd, 1H), 5.19 (t, 1H, J 7.8 Hz), 6.41 (t, 2H, J 8.0 Hz), 6.61 (d, 1H, J 8.5 Hz), 6.98 (d, 1H, J 8.5 Hz), 7.52 (s, 1H).

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