A TOTAL SYNTHESIS OF THE NOVEL CYCLODEPSIPEPTIDE (+)-GEODIAMOLIDE A

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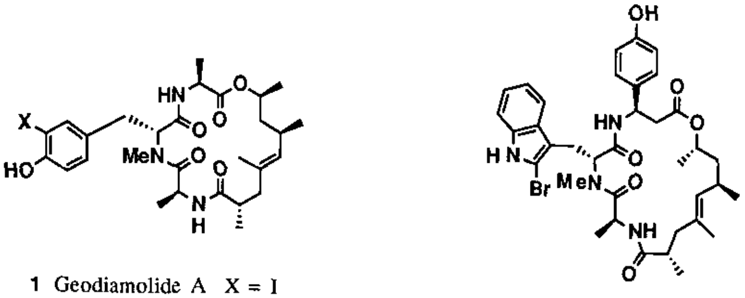
Abstract —— A diastereo-controlled total synthesis of (+)-geodiamolide A (**1**) has been accomplished via a prior synthesis of the tetrapropionate derived fragment **11** and of the iodinated N-methyltyrosyltripeptide **17**, the latter involving direct iodination of the tripeptide, and subsequent coupling of both fragments followed by the trichlorobenzoyl chloride-mediated macrolactonization.

In 1987, Chan and his co-workers[1] announced the isolation and structure elucidation of (+)-geodiamolides A (**1**) and B (**2**) from the marine sponge Geodia sp. as additional members of the sponge cyclodepsipeptide precedented by jaspamide (**3**).[2] Our interest in the total synthesis of these cyclic depsipeptides stemmed not only from their unique structural features but also from their biological activities reported. We now report a diastereo-controlled total synthesis of (+)-geodiamolide A (**1**).[3]



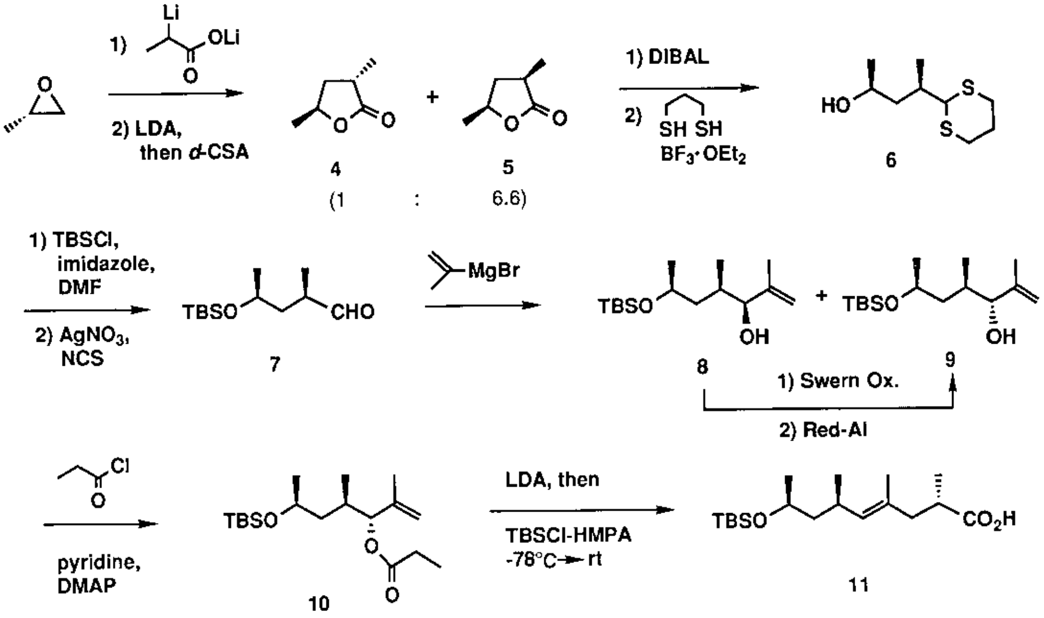
1 Geodiamolide A X = I
2 Geodiamolide B X = Br

3 Jaspamide

Scheme 1.

Geodiamolide A (**1**) is composed of a polypropionate fragment of twelve carbons and a tripeptide unit which contains the unique amino acid moiety 3-iodo-*N*-methyl-*D*-tyrosine in an 18-membered ring. A polypropionate fragment was constructed stereoselectively from (*S*)-(-)-propylene oxide[4] by the following sequence. The ring-opening of (*S*)-(-)-propylene oxide with the dianion of propionic acid gave the lactones (**4**) and (**5**) as a 1:1 mixture of diastereoisomers in 62% combined yield. Treatment of a mixture of the lactones (**4**) and (**5**) with lithium diisopropylamide (LDA) in THF at -78°C followed by protonation with (1*R*)-(-)-10-camphorsulfonic acid at -78°C resulted in preference of **5** over **4** (*ca.* 6.6:1).[5] Reduction of this mixture of **4** and **5** with diisobutylaluminum hydride in toluene at -78°C and subsequent treatment of the resulting lactols with propanedithiol and boron trifluoride etherate afforded the 1,3-dithiane derivative (**6**), $[\alpha]_D^{27}$ + 19.7° (*c* 1.42, $CHCl_3$), in 58% yield along with its diastereoisomer (8% yield). Silylation of **6** [*t*-butyldimethylsilyl chloride (TBSCl), imidazole, DMF] and oxidative hydrolysis of the resulting silyl ether (*N*-chlorosuccinimide and silver nitrate)[6] afforded the aldehyde (**7**), $[\alpha]_D^{26}$ +23.2° (*c* 0.06, $CHCl_3$), in 38% yield. Reaction of **7** with isopropenylmagnesium bromide in THF at -78°C gave the alcohols (**8**) and (**9**) as a mixture (*ca.* 1:1) of diastereoisomers in a combined yield of 95%. Treatment of the ketone, obtained by the Swern oxidation of a mixture of **8** and **9**, with Red-Al in toluene at -78°C gave the alcohol (**9**), $[\alpha]_D^{27}$ +30.4° (*c* 0.90, $CHCl_3$), in 72% yield along with **8** (15% yield). The alcohol (**9**) was then acylated with propionyl chloride and the resulting propionate (**10**) was subjected to the enolate Claisen rearrangement[7] (LDA/THF/-78°C, TBSCl-HMPA, and then warmed to room temperature) to give the acyclic acid (**11**),[8] $[\alpha]_D^{26}$ -9.7°(*c* 1.30, $CHCl_3$), in 77% yield along with its epimer (6% yield).

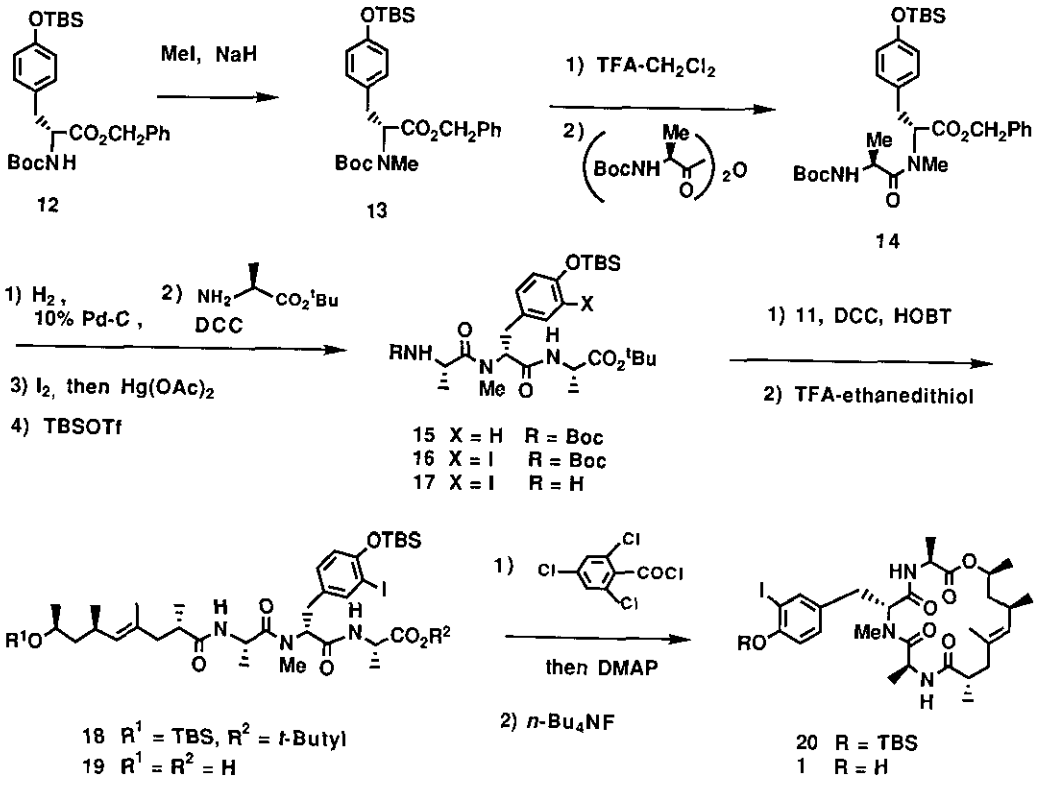
Next we examined a construction of the tripeptide (**17**). Methylation (NaH, MeI, THF) of *O*-*t*-butyldimethylsilyl-*N*-Boc-*D*-tyrosine benzyl ester (**12**), readily available from *D*-tyrosine, provided *N*-methylurethane (**13**) in 82% yield. Removal of the *N*-*t*-butyloxycarbonyl protecting group in **13** [TFA-CH_2Cl_2(1:2), 4 h, 0°C] followed by treatment with *N*-Boc-*L*-alanine anhydride in CH_2Cl_2 in the presence of Et_3N gave the dipeptide (**14**), $[\alpha]_D^{24}$ +25.8° (*c* 1.75, MeOH), in 78% yield.



Scheme 2.

Removal of the benzyl group in **14** (H_2, 10% Pd/C, EtOH) and subsequent dicyclohexylcarbodiimide (DCC)-promoted coupling of the resulting acid with L-alanine t-butyl ester in CH_2Cl_2 in the presence of 1-hydroxybenzotriazole (HOBT) at 0°C for 5 h provided the linear tripeptide (**15**), $[\alpha]_D^{25}$ + 8.0° (c 1.04, MeOH), in 72% yield. Subsequent treatment of **15** with iodine and $Hg(OAc)_2$ afforded the monoiodide (**16**), $[\alpha]_D^{25}$ + 31.5° (c 1.1, $CHCl_3$), in 78% yield. The selective removal of the N-t-butoxycarbonyl group in **16** was effected by treatment with t-butyldimetylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine in CH_2Cl_2, followed by hydrolysis with a saturated NH_4Cl solution[9] to give **17** in 80% yield. The DCC-promoted coupling[10] of **17** with **11** in the presence of HOBT in CH_2Cl_2 for 6 h at 0°C afforded **18**, $[\alpha]_D^{25}$ + 15.7° (c 1.04, $CHCl_3$), in 79% yield. The simultaneous cleavage of the t-butyl ester and partial desilylation of **18** were effected by treatment with TFA-ethanedithiol-CH_2Cl_2 (3:1:12) at 0°C to give the seco acid (**19**), $[\alpha]_D^{26}$ +20.8° (c 0.47, $CHCl_3$), in 59% yield. Lactonization of **19** using the Yamaguchi procedure [2,4,6-trichlorobenzoyl chloride/triethylamine and then 4-dimethylaminopyridine (DMAP)/benzene/reflux][11] afforded the desired 18-membered ring compound (**20**) in 18% yield. Desilylation of **20** with *n*-Bu_4NF in THF furnished (+)-geodiamolide A (**1**), $[\alpha]_D^{26}$ +55.1° (*c* 0.077, $CHCl_3$) [lit.[1] $[\alpha]_D^{25}$ +53°(*c* 0.04, $CHCl_3$)], in 79% yield, whose structure was established by direct comparison with an authentic sample of the natural material.

A synthesis of the bromo congener (**2**)[12] was also accomplished by starting with the direct bromination of the tripeptide **15** with bromine.



Scheme 3.

ACKNOWLEDGMENT

We are grateful to Dr. Manchand (Hoffmann-La Roche) and Professor Chan (University of the West Indies) for kindly providing us with the authentic sample of geodiamolide A and the spectral data for geodiamolide B. We also acknowledge financial support from Pfizer Pharmaceuticals Inc.

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12 The detailed experimental results will be presented in due course

Received, 24th July, 1989