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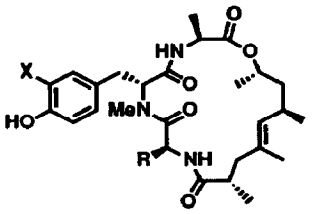
Efficient Syntheses of Geodiamolide A and Jaspamide, Cytotoxic and Antifungal Cyclic Depsipeptides of Marine Sponge Origin

Takayuki Imaeda, Yasumasa Hamada,* and Takayuki Shioiri*

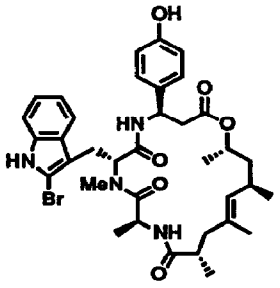
Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467, JAPAN

Abstract: Geodiamolide A (**1a**) and jaspamide (**2**) have been efficiently synthesized by use of the Evans asymmetric alkylation, the Mitsunobu esterification, and the DPPA macrolactamization as key steps.

Geodiamolide A (**1a**), isolated from a Caribbean sponge *Geodia* sp.[1a] and a Papua New Guinean sponge *Pseudaxinyssa* sp.,[1b] is a cyclic depsipeptide containing the tripeptide and polypropionate units. The other geodiamolides B-F (**1b-1f**) which are different each other in the peptide parts are also known in addition to jaspamide[2a] (jasplakinolide[2b]) (**2**), which has been isolated from a south Pacific sponge *Jaspis* sp. As shown in the formula **2**, jaspamide is a cyclic depsipeptide containing the same polypropionate unit as that of geodiamolides. Cytotoxic and antifungal activities have been reported as the biological properties of both geodiamolides and jaspamide, the latter of which has also been found to have insecticidal and anthelmintic properties. These interesting biological activities as well as their structural uniqueness have led several groups to synthesize these depsipeptides.[3-7] However, the stereoefficiencies of these syntheses have not been satisfactory and the yields of the final cyclization through the lactone formation have been low in the synthesis of geodiamolides.[3] These results will preclude the supply of enough quantities of these depsipeptides to investigate their biological profiles in detail. Now, we wish to report efficient stereoselective syntheses of geodiamolide A (**1a**) and jaspamide (**2**), which will promise their large scale production. The key steps of our syntheses are: (1) the asymmetric alkylation using the Evans chiral oxazolidinone to construct the polypropionate unit, (2) the coupling of the tripeptide unit with the polypropionate by the Mitsunobu reaction, and (3) the intramolecular amide bond formation using diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$).

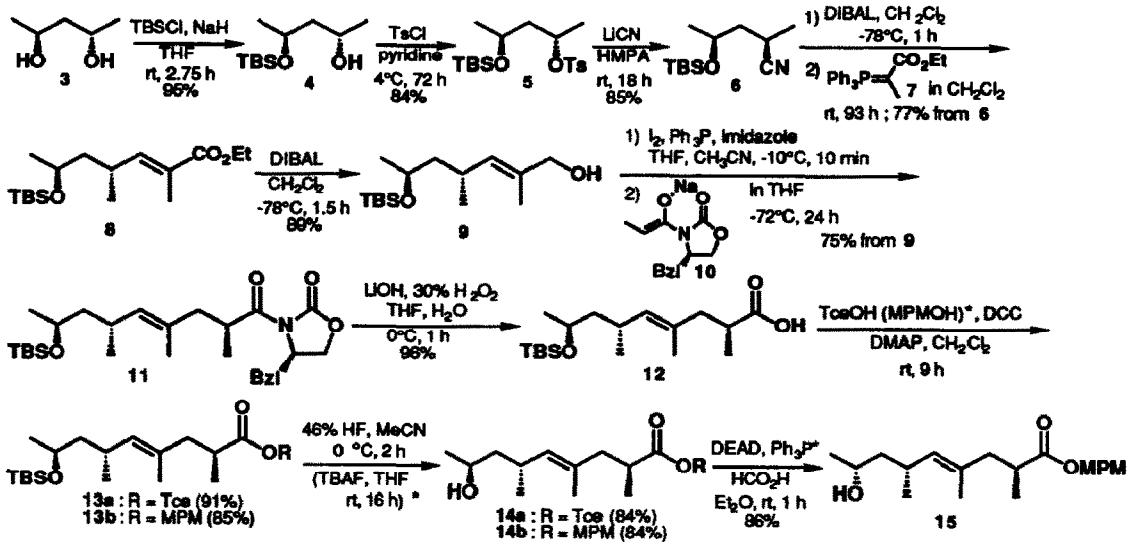


Geodiamolide A (**1a**): R=Me, X=I
B (**1b**): R=Me, X=Br
C (**1c**): R=Me, X=Cl
D (**1d**): R=H, X=I
E (**1e**): R=H, X=Br
F (**1f**): R=H, X=Cl



Jaspamide (Jasplakinolide) (**2**)

The synthesis of the polypropionate unit started from commercially available (2S,4S)-2,4-pentanediol (**3**), as shown in Scheme 1. After protection of one of the hydroxyl function with the t-butyldimethylsilyl (TBS) group, the resulting mono-protected alcohol **4**, $[\alpha]_D^{24}$ +38.2 (c 1.2, $CHCl_3$),[8] was converted to the cyanide **6**, $[\alpha]_D^{24}$ +10.0 (c 1.0, $CHCl_3$),[8] with inversion of configuration through the tosylate **5**, $[\alpha]_D^{24}$ +20.5 (c 0.92, $CHCl_3$), by its treatment with lithium cyanide. Reduction of the cyanide **6** with diisobutylaluminum hydride (DIBAL), followed by the Wittig homologation with the phosphorane **7** afforded the (E)-ester **8**, $[\alpha]_D^{24}$ -15.8 (c 1.0, $CHCl_3$),[8] which was reduced with DIBAL to give the alcohol **9**, $[\alpha]_D^{24}$ -1.6 (c 0.91,

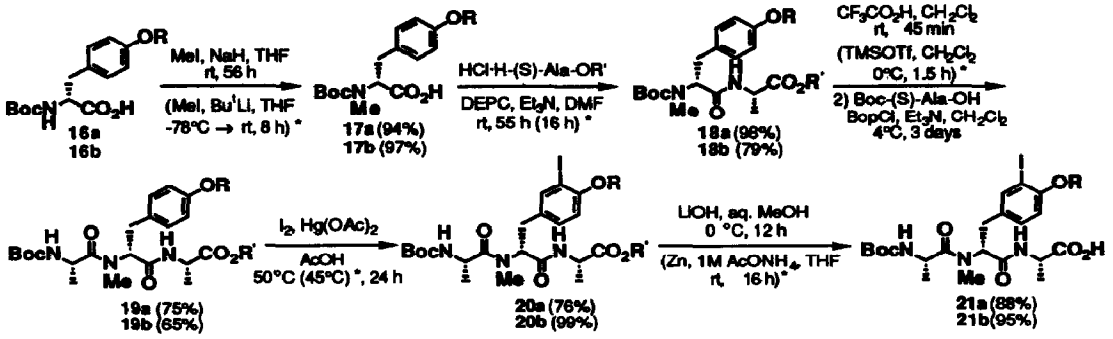


Scheme 1

$CHCl_3$).[8] Although the attempted conversion of the alcohol **9** to the corresponding bromide[5b] gave a mass of products, treatment of **9** with a mixture of iodine, triphenylphosphine, and imidazole afforded the iodide, which was directly used for the asymmetric alkylation[5b] of the sodium enolate **10** of the oxazolidinone derived from (R)-phenylalaninol.[9] The desired polypropionate **11**, $[\alpha]_D^{24}$ -35.2 (c 0.94, $CHCl_3$),[8] was preferentially formed with 94% diastereomeric excess. Removal of the chiral auxiliary from **11** with alkaline hydrogen peroxide[9] furnished the carboxylic acid **12**,[3d] $[\alpha]_D^{24.5}$ -9.2 (c 1.1, $CHCl_3$),[8] which was converted to the trichloroethyl (Tce) ester **13a**, $[\alpha]_D^{24}$ -10.2 (c 1.0, $CHCl_3$).[8] Deprotection of the TBS group of **13a** with hydrofluoric acid yielded the polypropionate alcohol **14a**, $[\alpha]_D^{24}$ -19.2 (c 0.90, $CHCl_3$).[8] As another route, the carboxylic acid **12** was converted to the p-methoxyphenylmethyl (MPM) ester **13b**, $[\alpha]_D^{24}$ -10.0 (c 0.85, $CHCl_3$),[8] which underwent the selective deprotection of its TBS group with tetra-n-butylammonium fluoride (TBAF) to give the polypropionate MPM ester **14b**, $[\alpha]_D^{24}$ -21.7 (c 0.85, $CHCl_3$).[8] The inversion of the hydroxyl function in **14b** was easily carried out under the Mitsunobu reaction conditions using formic acid, diethyl azodicarboxylate (DEAD), and triphenylphosphine to give the polypropionate alcohol **15**, $[\alpha]_D^{24}$ -25.1 (c 0.56, $CHCl_3$).[8]

The preparation of the tripeptide unit was achieved stepwise from the C-terminal (S)-alanine methyl ester, as shown in Scheme 2. Methylation of N-tert-butoxycarbonyl-O-2,6-dichlorobenzyl-(R)-tyrosine (**16a**, Boc-(R)-Tyr(Cl_2Bzl)-OH) with an excess of both methyl iodide and sodium hydride[10] afforded the N-methylamino acid **17a**, mp 103-104°C, $[\alpha]_D^{24.5}$ -37.1 (c 1.0, $CHCl_3$). Coupling of **17a** with (S)-alanine methyl ester was carried out by use of diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$) to give the dipeptide **18a**, mp 35-36°C, $[\alpha]_D^{24.5}$ +62.6 (c 0.93, $CHCl_3$). After removal of the Boc group from **18a** with trifluoroacetic acid, coupling with Boc-(S)-alanine using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BopCl)[11] afforded the tripeptide **19a**, mp 89°C, $[\alpha]_D^{27}$ +42.6 (c 1.1, $CHCl_3$). Iodination of the tyrosine residue in **19a** with iodine in the presence of mercuric acetate furnished the fully protected tripeptide **20a**, mp 62-64°C, $[\alpha]_D^{24.5}$ +26.4 (c 1.1, $CHCl_3$), which underwent the alkaline saponification to give the tripeptide carboxylic acid **21a**, mp 109-110°C, $[\alpha]_D^{24.5}$ +28.3 (c 1.1, $CHCl_3$).

The coupling of the tripeptide unit **21a** with the polypropionate unit **14a** or **14b** was found to be exceptionally difficult to achieve. After several fruitless trials, we finally found that the high pressure reaction conditions were suitable for the esterification. The carboxyl group of **21a** was first activated as the imidazolide, and then the coupling with **14b** under 5000 bar at room temperature gave the ester **22a** in good yield. To our knowledge, this will be the first successful example of the high pressure esterification in such

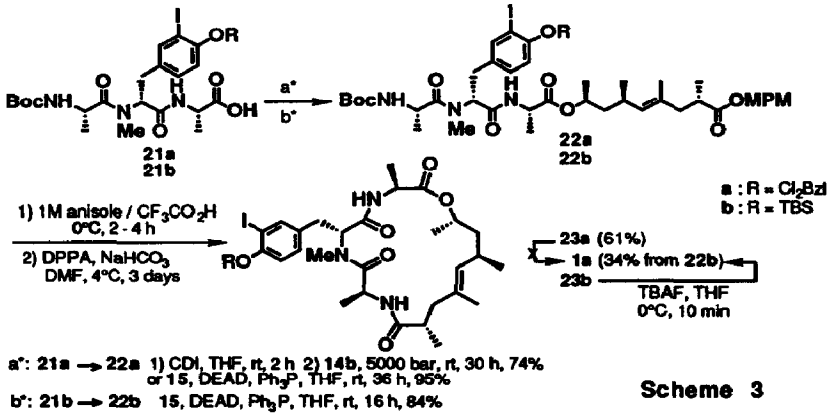


Scheme 2

complicated substrates. Furthermore, the ester **22a** was efficiently obtained by the Mitsunobu reaction of **21a** with **15**, as shown in Scheme 3. After cleavage of the N- and C-terminal protective groups, the intramolecular cyclization with diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$) afforded the O-2,6-dichlorobenzyl derivative **23a** of geodiamolide A in 61% yield. Final deprotection of the 2,6-dichlorobenzyl group from **23a**, however, was revealed to be difficult to achieve. All of the attempted deprotection so far tried have been found to give a mass of products on a TLC plate. Thus, we had to replace the protective group at the tyrosine residue with some other group.

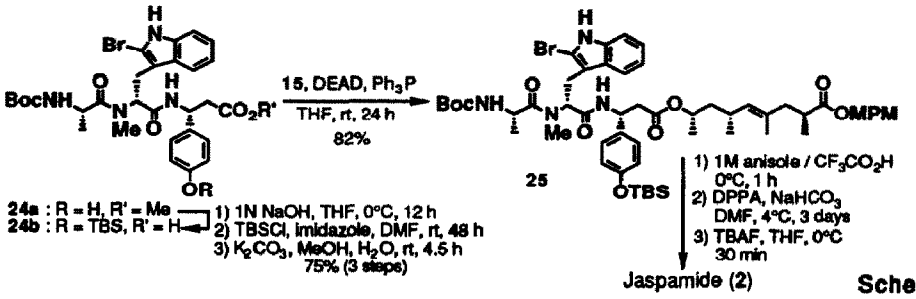
The group we chose was the tert-butyldimethylsilyl (TBS) group, as shown in Scheme 2. Treatment of Boc-(R)-tyrosine with TBSCl followed by alkaline treatment gave the TBS derivative **16b**, which was methylated according to the method of Grieco.[3a] The resulting N-methyl derivative **17b** was coupled with the hydrochloride of (S)-alanine trichloroethyl ester[12] by use of DEPC to give the dipeptide **18b**, mp 90-92°C, $[\alpha]_D^{25}$ +44.8 (c 0.86, $CHCl_3$). After selective deprotection of the Boc group from **18b** with trimethylsilyl triflate (TMSOTf), coupling with Boc-(S)-alanine was achieved again by use of BopCl. The tripeptide **19b** thus obtained as a colorless amorphous solid, $[\alpha]_D^{25}$ +35.4 (c 0.30, $CHCl_3$), was iodinated as before to yield **20b** as a yellow amorphous solid, $[\alpha]_D^{25}$ +41.7 (c 0.27, $CHCl_3$). Removal of the Tce group from the C-terminal with zinc produced the required tripeptide unit **21b**, mp 108-109°C, $[\alpha]_D^{25}$ +31.3 (c 0.40, $CHCl_3$).

Formation of the fully protected linear precursor **22b** of geodiamolide A was achieved by the Mitsunobu reaction of **21b** with **15**, as shown in Scheme 3. The ester **22b**, a colorless amorphous solid, $[\alpha]_D^{25}$ + 17.5°C (c 0.19, $CHCl_3$), easily underwent the deprotection of the N- and C-terminals with trifluoroacetic acid, followed by the DPPA macrolactamization. Final deprotection of the TBS group from the crude cyclized product was easily accomplished this time by use of (TBAF). Geodiamolide A (**1a**), $[\alpha]_D^{25}$ +51.6 (c 0.17, $CHCl_3$), lit.[1a] $[\alpha]_D^{26}$ +53 (c 0.04, $CHCl_3$) thus obtained in 34% yield from **22b** was identical with the authentic sample through spectral comparisons.



Scheme 3

Using the same methodology, we have succeeded in the synthesis of jaspamide (2) utilizing the tripeptide unit **24a** synthesized before.[7b] Alkaline hydrolysis of **24a** followed by treatment with TBSCl and then aqueous potassium carbonate afforded the O-TBS carboxylic acid **24b**, mp 105-107°C, $[\alpha]_D^{27}$ +55.2 (c 0.09, $CHCl_3$), as shown in Scheme 4. Coupling of **24b** with the polypropionate **15** was smoothly achieved by the Mitsunobu reaction to give the linear precursor **25** of jaspamide. Successive treatment with trifluoroacetic acid, DPPA, and then TBAF afforded jaspamide (2), identified by spectral comparisons.



Scheme 4

Thus we could complete the efficient stereoselective syntheses of geodiamolide A (**1a**) and jaspamide (**2**). The overall strategy adopted here can be applied to the synthesis of the other cyclic depsipeptides, especially the other geodiamolides (**1b-1f**).

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References and Notes

1. (a) Chan, W.R.; Tinto, W.F.; Manchand, P.S; Todaro, L.J. *J. Org. Chem.*, **1987**, *52*, 3091. (b) de Silva, E.D.; Andersen, R.J.; Allen, T.M. *Tetrahedron Lett.*, **1990**, *31*, 489.
2. (a) Zabriskie, T.M.; Klocke, J.A.; Ireland, C.M.; Marcus, A.H.; Molinski, T.F.; Faulkner, D.J.; Xu, C.; Clardy, J.C. *J. Am. Chem. Soc.*, **1986**, *108*, 3123. (b) Crews, P.; Manes, L.V.; Boehler, M. *Tetrahedron Lett.*, **1986**, *27*, 2797.
3. Total synthesis of geodiamolides: (a) Grieco, P.A.; Perez-Medrano, A. *Tetrahedron Lett.*, **1988**, *29*, 4225. (b) White, J.D.; Amedio, J.C. *J. Org. Chem.*, **1989**, *54*, 736. (c) Hirai, Y.; Yokota, K.; Sakai, H.; Yamazaki, T.; Momose, T. *Heterocycles*, **1989**, *29*, 1865. (d) Hirai, Y.; Yokota, K.; Yamazaki, T.; Momose, T. *Heterocycles*, **1990**, *30*, 1101.
4. Synthesis of the peptide unit of geodiamolide A: Chiarello, J.; Joullié, M.M. *Synth. Comm.*, **1998**, *18*, 2211.
5. Synthesis of the polypropionate unit: (a) Schmidt, U.; Siegal, W.; Mundinger, K. *Tetrahedron Lett.*, **1998**, *29*, 1269. (b) Kang, S.-K.; Lee, D.-H. *Synlett*, **1991**, 175.
6. Total synthesis of jaspamide: (a) Grieco, P.A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.*, **1998**, *110*, 1630. (b) Chu, K.S.; Negrete, G.R.; Konopelski, J.P. *J. Org. Chem.*, **1991**, *56*, 5196.
7. Synthesis of the peptide unit of jaspamide: (a) Kato, S.; Sugiura, T.; Hamada, Y.; Shioiri, T. *Peptide Chemistry* **1987** (ed. by Shiba, T.; Sakakibara, S.), **1988**, 355. (b) Kato, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.*, **1988**, *29*, 6465. (c) Konopelski, J.P.; Chu, K.S.; Negrete, G.R. *J. Org. Chem.*, **1991**, *56*, 1355.
8. A colorless or pale yellow oil.
9. George, J.R.; Evans, D.A. *Org. Synth.*, **1989**, 89.
10. *Cf.* McDermott, J.R.; Benoiton, N.L. *Can. J. Chem.*, **1973**, *51*, 1915; Cheung, S.T.; Benoiton, N.L. *Can. J. Chem.*, **1977**, *55*, 906.
11. Tung, R.D.; Rich, D.H. *J. Am. Chem. Soc.*, **1985**, *107*, 4342.
12. Prepared from Boc-(S)-alanine by treatment with trichloroethanol by use of N,N'-dicyclohexylcarbodiimide, followed by removal of the Boc group with 4N HCl in dioxane: mp 167-169°C.

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