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Studies on Cyclodepsipeptides - Part I : A Stereoselective Synthesis of C_{12} Polyketide Unit (C1-C8) Present in Jaspamide and Geodiamolide A-F

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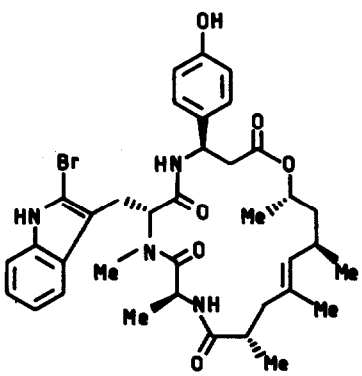
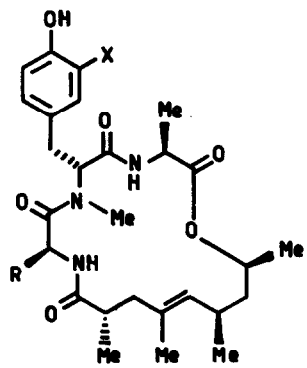
Abstract : An innovative synthetic protocol to obtain the polyketide C_{12} chain in an enantiomerically pure form has been developed.

The structurally novel cyclodepsipeptides represented by jaspamide (1) and geodiamolide A-F (2), isolated from marine sponges, Jaspis sp, geodia sp and pseudaxinyssa sp., exhibit potent insecticidal, antifungal and cytotoxic activities[1]. The total synthesis of these molecules are of considerable interest[2] owing to the unusual tripeptide segment and the characteristic C_{12} polyketide unit locked together in an unprecedented 18-membered macrocyclic ring. Here, we have envisaged a strategy for the C_{12} unit (3) as a part of which we investigated the iodolactonisation of (R)-2-methyl-4-pentenoic acid, as a function of temperature, to influence cis mode of ring closure. This strategy offered enantiomerically pure (EP) allyl alcohol (16), as a key intermediate (without recourse to diastereomeric separation) by employing reductive elimination of epoxy-halide.

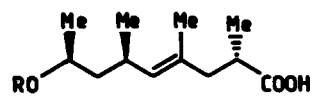


Jaspamide 1



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

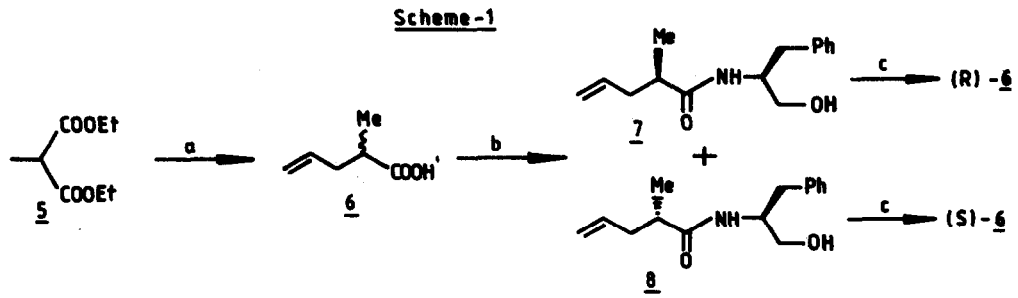


3 R = H
4 R = TBS

The chiral building block (R)-2-methyl-4-pentenoic acid (R-6) was earlier prepared by resolution of (±)-6 (obtained in three modified steps from 5) with quinine in a five times crystallisation process[3]. Since we needed large quantities of this material, we resorted to a simple resolution technique of the corresponding phenylalanilol amides (7 and 8) by MPLC[4]. Subsequent hydrolysis of 7 and 8 under acidic conditions (3N H_2SO_4, Δ) provided EP (R)-6 { $[\alpha]_D$ -10.3°

$(CHCl_3)$ } and S-(6) { $[\alpha]_D$ +10.1° $(CHCl_3)$, lit.[3] $[\alpha]_D$ +10.5° $(CHCl_3)$} respectively (Scheme 1).

Scheme-1



a) i) allyl bromide, K_2CO_3, aliquat 336, EtCOMe, Δ, 12 h; (ii) 14N KOH, EtOH-H_2O; (iii) 160°C followed by distillation ; b) (i) $SOCl_2$, C_6H_6, RT, 4h; (ii) L-phenylalaninol, Et_3N, dioxane, RT, 1h; c) 3N H_2SO_4, dioxane-H_2O (1:1), 90°C, 1h.

The iodolactonization of (R)-6 with I_2-CH_3CN at 0° provided cis lactone 9 and trans lactone 10 in a ratio of 65:35, as judged by HPLC[5]. We studied this critical step at low temperatures as indicated in Table 1. Entry 3 indicated our best efforts with respect to diastereofacial selectivity and chemical yield. The major product 9 { $[\alpha]_D$ +35.0° $(CHCl_3)$} was isolated (70%) by preparative HPLC on silica gel.

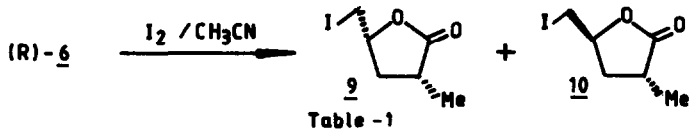
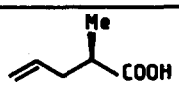
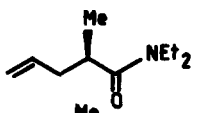
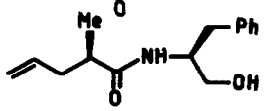


Table-1

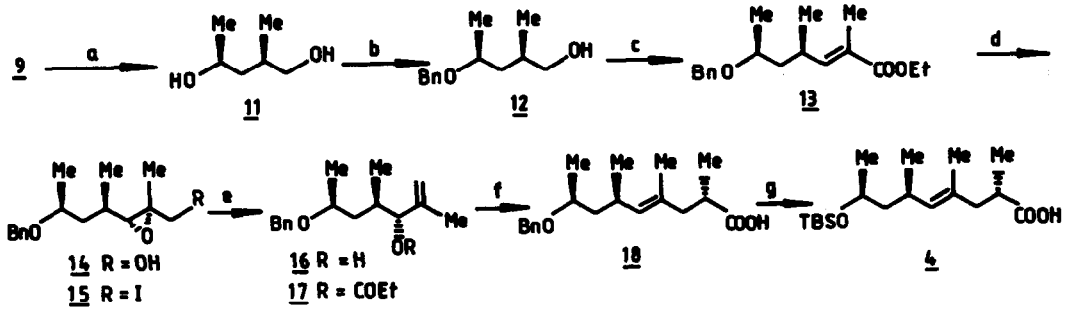
Entry	Substrate	Temp.	Time (h)	cis	trans	Yield (%)
1		0°	1	65	35	90
2		-20°	3	78	22	87
3		-40°	3	85[a]	15	82
4		RT[b]	72	10	90	71
5		RT[b]	72	40	60	72

a - Isolated yield 70% ; b - I_2 - DME - H_2O mixture was employed

Compound **9** was reduced with LAH (THF, RT) to provide the diol (**11**) { $[\alpha]_D$ +36.8° ($CHCl_3$)} whose primarily OH group was temporarily protected as a TBS ether (TBS-Cl, Imid.) while the secondary OH was converted into the benzyl ether (NaH, BnBr, THF) followed by the removal of TBS-ether (Bu_4NF,THF) to give **12** (58%). Subsequent Swern oxidation (DMSO, $(COCl)_2$, Et_3N, -78°) and Wittig reaction (Ph_3P=C(Me)COOEt) gave (E)-α,β-unsaturated ester (**13**) (76%). Reduction of **13** with DIBAL-H (-78° → 0°) was followed by epoxidation with MCPBA (CH_2Cl_2, 0°) to give **14** as a single isomer[6]. Conversion of **14** into the corresponding iodo derivative (**15**) (TsCl, KOH, Et_2O; NaI, MeCOMe) (59%) and reductive elimination (Zn, MeOH) gave the EP-allyl alcohol (**16**) (83%).

The propionate (**17**), obtained (CH_3CH_2COCl, Py, DMAP, CH_2Cl_2, RT) from **16**, underwent Ireland-Claisen rearrangement (LDA, TBSCl, THF, -78° to RT) to give **18** which was debenzylated (Li/NH_3) and silylated (TBSCl, Imid., K_2CO_3, MeOH, H_2O) to give **4** { $[\alpha]_D$ -9.5° ($CHCl_3$). lit.[7] $[\alpha]_D$ -9.7° ($CHCl_3$)} (Scheme 2).

Scheme - 2



a) LAH, THF, RT, 3h; b) (i) TBS-Cl, imid., CH_2Cl_2, 0°C, 3h; (ii) $C_6H_5CH_2Br$, NaH, THF, 6h; (iii) TBAF, THF, RT, 3h; c) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C to -20°C, 2h; (ii) Ph_3P=$C(CH_3)COOEt$, C_6H_6, Δ, 6h; d) (i) DIBAL-H, CH_2Cl_2, -78°C, 0.5 h; (ii) MCPBA, CH_2Cl_2, 0°C, 2h; (iii) TsCl, KOH, Et_2O, 0°C, 0.5h; (iv) NaI, acetone, RT, 3h; e) (i) Zn, MeOH, Δ, 3h; (ii) CH_3CH_2COCl, py., DMAP, CH_2Cl_2, RT, 0.5 h; f) LDA, TBS-Cl, THF, HMPT, -78°C to RT, 8h; g) (i) Li, liq. NH_3, THF, -78°C, 2h; (ii) TBS-Cl, imid., CH_2Cl_2, RT, 3h; (iii) K_2CO_3, MeOH-H_2O, RT, 3h.

Thus, we have developed an efficient stereoselective synthetic approach to the C_{12} polyketide unit, commonly present in cyclodepsipeptide natural products. We have judiciously employed **3** in the total synthesis of jaspamide and geodiamolide D, the results of which are described in the following publication.

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