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A PRACTICAL SYNTHESIS OF THE PEPTIDE PART OF JASPAMIDE (JASPLAKINOLIDE), A CYCLODEPSIPEPTIDE FROM A MARINE SPONGE[1,2]

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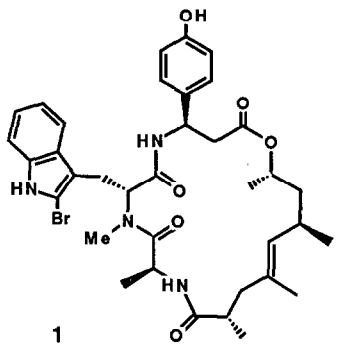
Abstract: (S)-Alanyl-(R)-2-bromoabryl-(R)-β-tyrosine found in jaspamide(**1**) was conveniently synthesized as its protected derivative **2** in good yield.

Jaspamide (jasplakinolide)(**1**)[3] recently isolated from a *jaspis* sponge is a novel cyclodepsipeptide exhibiting potent insecticidal and antifungal activities. Recent reports on synthetic studies including a total synthesis,[4a] syntheses of its non-peptide part[4b] and non-peptide mimetics[4c] have prompted us to record our own results on a practical synthesis of the peptide part of **1** as its protected form **2**.



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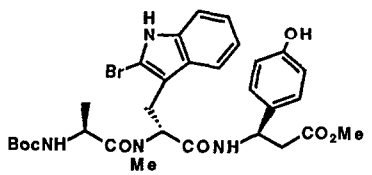
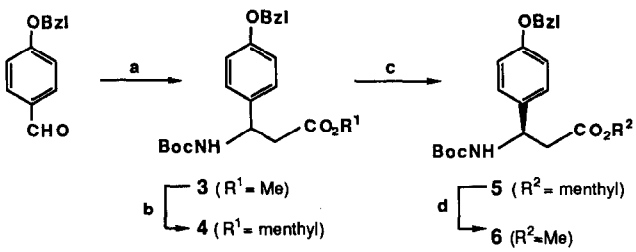
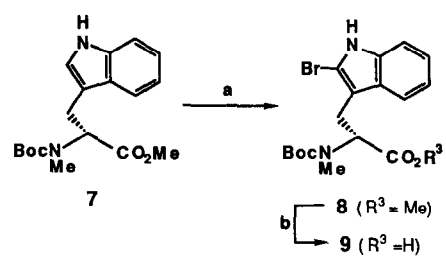


2

(R)-β-Tyrosine derivative **6** was obtained from p-benzyloxybenzaldehyde through the optical resolution of racemic **3** (mp 93-95°C)[5] via the menthyl ester **4**. Less soluble **5** (mp 128.5 - 130°C, $[\alpha]^{23}_D$ -5.0° (c 1, CH_2Cl_2)) was readily separated by repetitive recrystallizations from hexane in 74% yield.[6] The optical purity of **6** (mp 111-113°C, $[\alpha]^{23}_D$ +49.4°(c 1, MeOH)) was determined to be ca.100% by HPLC analysis as its N-3,5-dinitrobenzoyl derivative (CF_3CO_2H, r.t. 30min; 3,5-dinitrobenzoyl chloride, Et_3N, THF, r.t. 2h (93%)) using the chiral phase column.[7] The absolute configuration was established by comparing the optical rotation of the deprotected (R)-β-tyrosine hydrochloride ($[\alpha]^{24}_D$ -3.1°(c 1.65, H_2O)) with the reported one ($[\alpha]_D$ -4.15°).[8] (R)-2-Bromoabrine derivative **8** (mp 146-147°C, $[\alpha]^{24}_D$ +103°(c 1, MeOH)) was prepared by bromination[9] of the (R)-abrine derivative **7** (mp 86-88°C, $[\alpha]^{23}_D$ +113.1°(c 1, MeOH))[10] in 75% yield.

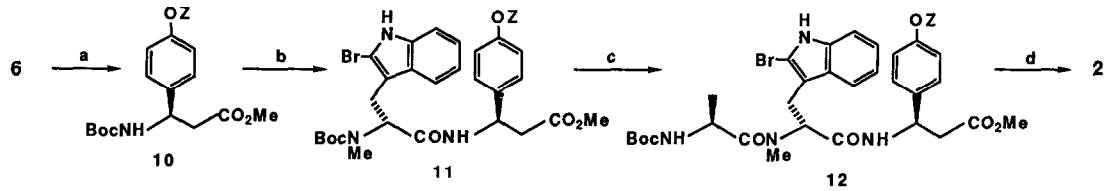


a) malonic acid, $AcONH_4$, EtOH, reflux 5h; Boc_2O, NaOH, aq. dioxane, r.t. 4h ; MeI, $KHCO_3$, DMF, r.t. 29h (43%). b)1.5eq. NaOH, aq. MeOH, r.t. 7h (89%); 1.15eq. L-menthol, 1.3eq. DCC, 0.4eq. DMAP, CH_2Cl_2, 0°C 2h→r.t. 16h (92%). c) 8 recrystallizations from hexane (74%) d) 1.5eq. NaOH, aq. MeOH, reflux 4h (97%); MeI, $KHCO_3$, DMF, r.t. 12h (98%).



a) 1.3eq. NBS, 0.05eq. benzoyl peroxide, CCl_4, reflux, 30min (75%). b) 1.2eq. NaOH, aq. dioxane, r.t. 4h.

Construction of the tripeptide **2** was started from O-benzyloxycarbonyl (Z)-(R)-β-tyrosine derivative **10** (mp 116-118°C, $[\alpha]^{24}_D$ +36.7°(c 1, MeOH)) obtained from **6** by changing the benzyl protective group. Coupling with the carboxylic acid **9** obtained from **8** using diethyl phosphorocyanidate (DEPC) and N-methylmorpholine gave the dipeptide **11** (amorphous solid, $[\alpha]^{22}_D$ +19.1°(c 0.88, CH_2Cl_2)), which was condensed with Boc-(S)-alanine by use of bis(2-oxo-3-oxazolidinyl)phosphinic chloride (Bop-Cl)[11] to give the tripeptide **12** ($[\alpha]^{22}_D$ +16.6°(c 0.9, CH_2Cl_2)) in 78% yield.[12] Use of DEPC afforded **12** in 60% yield. Selective hydrolysis of the phenolic protection quantitatively afforded **2** as an amorphous solid ($[\alpha]^{22}_D$ +19.2°(c 1.13, CH_2Cl_2)).



a) H_2, 5% Pd-C, MeOH, r.t. 3.5h (quant.); 2.6eq. ZCl, 3.1eq. Py, CH_2Cl_2, 0°C 4h (88%). b) 99% HCO_2H, r.t. 3h; **9** from 0.95eq. **8**, 1.2eq. DEPC,1.05eq NMM, DMF, 0°C 2h→r.t. 19h (90%). c) CF_3CO_2H, r.t. 15min; Ⓐ 1.3eq. Boc-L-Ala-OH, 1.5eq. BOP-Cl, 2.4eq. Et_3N, CH_2Cl_2, 0°C 39h (78%). Ⓑ 1.3eq. Boc-L-Ala-OH, 1.6eq. DEPC, 1.4eq. NMM, DMF, 0°C 2h→ r.t. 46h (60%). d) 1.05eq. LiOH, 0°C 1h (97%).

The above synthesis conveniently and efficiently provides the tripeptide **2** useful for the total synthesis of jaspamide(**1**)[13] and the synthesis of mimetics as potential insecticides.

References and Notes

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6 The two diastereoisomers separated on silica gel thin layer chromatograph developed with ether-benzene, but the separation on column was unpractical. The less moved isomer is (R)-isomer.

7 HPLC was carried out under the following conditions : Sumipax OA-1000 (ϕ 4.6 x 250nm, purchased from Sumitomo Chemical Co.,Ltd.) ; mobile phase, ethanol - 1,2-dichloroethane - hexane (1 : 10 : 20); flow rate, 1.5ml/min; detector, 254nm, (R)-isomer (18min), (S)-isomer (35.5min).

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12 Without the protection of the phenolic hydroxyl group, the coupling resulted in low yield (37%).

13 For example, after hydrolysis at its C-terminal, the tripeptide **2** will be esterified with the non-peptide part. Final cyclization of the deblocked linear precursor will produce jaspamide (**1**) as our didemnin synthesis, Y. Hamada, Y. Kondo, M. Shibata, and T. Shioiri,"Peptide Chemistry 1987", ed. by T. Shiba and S. Sakakibara, Protein Research Foundation, Osaka, p.359(1988).

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