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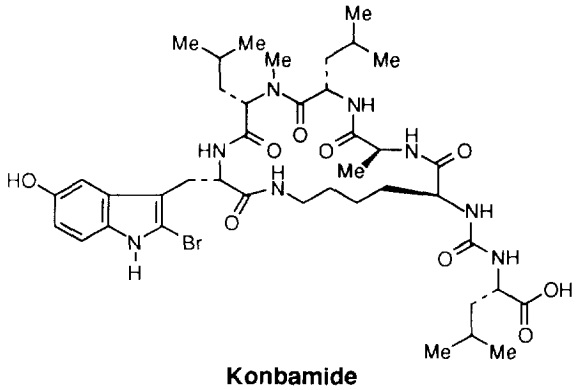
A Concise Synthesis of Optically Active 2-Bromotryptophan Amino Acids Present in Konbamide and Jaspamide *Via* A Regiospecific Bromination Procedure

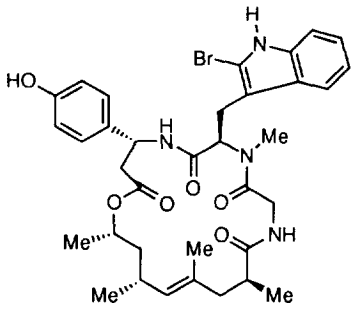
Puwen Zhang, Ruiyan Liu, and James M. Cook*
Department of Chemistry, University of Wisconsin-Milwaukee, Milwaukee, WI 53211

ABSTRACT A highly stereoselective synthesis of optically active 2-bromo-5-hydroxy-tryptophan **1a** and important derivatives **1b** and **1c** as well as their 2-bromotryptophan analogs was achieved in three steps from 2-bromo-3-bromomethylindoles **3a** and **3b**, respectively.

Konbamide, a novel cyclic peptide recently isolated from the Okinawan marine sponge *Theonella* sp.,[1] has been shown to antagonize the effects of calmodulin,[1,2] while jaspamide, a marine cyclodepsipeptide, has exhibited antifungal, antihelminthic, insecticidal and ichthyotoxic activity.[3,4] The biological activity of these marine natural products has promoted Ashworth *et al.*[5] to synthesize jaspamide while the unique 2-bromo-5-hydroxytryptophan unit of konbamide has stimulated our own interest in such molecules. We wish to report here the first stereoselective synthesis of optically active 2-bromo-5-hydroxytryptophan **1a** as well as synthetically important intermediates **1b** and **1c**. Moreover, this route has been employed to prepare 2-bromotryptophan, an amino acid which could be used in the preparation of jaspamide.[5]

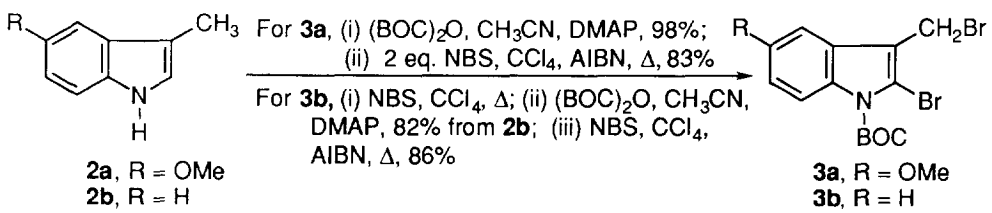


Konbamide



Jaspamide

Scheme I

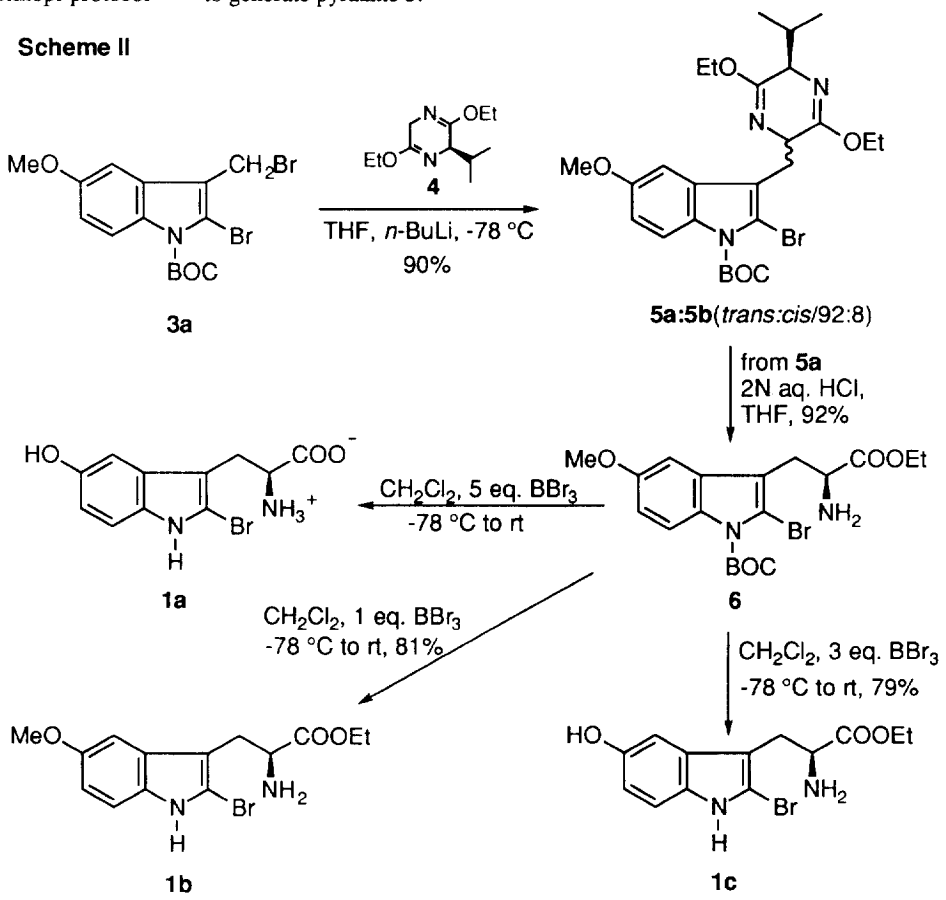


2a, R = OMe
2b, R = H

3a, R = OMe
3b, R = H

As illustrated in Scheme I, 3-methyl-5-methoxyindole **2a**, readily available *via* a Japp-Klingmann/Fischer indole protocol[6-8] was converted into the BOC-protected indole and regiospecifically brominated with NBS.[9] The bifunctional dibromide **3a** provided by this process served as the key intermediate for the synthesis of **1a**, **1b**, and **1c**. Not only did the BOC moiety control the regiochemistry of the bromination sequence but this deactivating group was also required for successful execution of the Schöllkopf protocol[10,11] to generate pyrazine **5**.

Scheme II

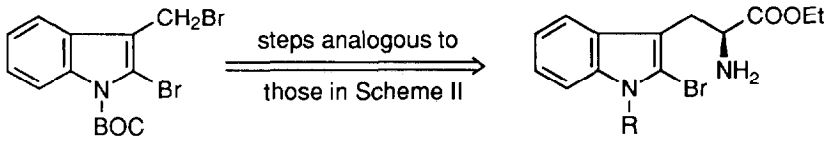


In brief, dibromide **3a** was stirred with the anion of the Schöllkopf chiral auxiliary **4** (derived from D-valine on multihundred gram scale[11-13]) at - 78 °C to provide a mixture of diastereomers **5a** and **5b** in a ratio of 92:8 (C-13 NMR) in 90% yield as illustrated in Scheme II. Although the alkylation was not stereospecific, the desired *trans* isomer **5a** could be easily separated from **5b** by flash chromatography [silica gel, hexane/ethyl acetate (9:1)]. It is important to point out that syntheses of the related pyrazines in the indole-2(H) series were stereospecific[6,12,14] in contrast to the results [indole-2(Br)] observed here. The pure pyrazine **5a** was hydrolyzed under acidic conditions (aq. 2N HCl, THF) to provide the key

intermediate L(+)-1-BOC-2-bromo-5-methoxytryptophan ethyl ester **6** in 92% yield, accompanied by D-valine ethyl ester which was readily recovered by Kugelrohr distillation for reuse. The 2-bromo-5-methoxytryptophan ethyl ester was sequentially converted into amino acid **1a** as well as esters **1b** and **1c** by treatment with varying amounts of BBr_3[15,16] as illustrated in Scheme II. For example, when ester **6** was stirred with 3 equivalents of BBr_3 an 82% yield of L(+)-2-bromo-5-hydroxytryptophan ethyl ester **1c** was realized while use of 5 equivalents of BBr_3 furnished the desired L-amino acid **1a**.[17] The use of the enantiomer of the Schöllkopf chiral auxiliary **4** (derived from L-valine) afforded the D-enantiomer of 2-bromo-5-hydroxytryptophan as well as the related esters with high enantioselectivity.

For the synthesis of L(+)-2-bromotryptophan ethyl ester **7** found in jaspamide the sequence of steps required for the bromination was altered, as illustrated in Scheme I (see **3b**). Conversion of indole **3b** into the desired pyrazine (Scheme III) under conditions previously employed for **3a** followed by the same sequence of reagents in Scheme II provided L(+)-2-bromotryptophan ethyl ester **7**.[18] The D isomers of this amino acid ester could also be prepared *via* this route with the auxiliary again derived from L-valine.

Scheme III



3a

7a R = BOC
7b R = H

In summary, the success of this method rests on the ability to prepare either antipode of the Schöllkopf chiral auxiliary on greater than 500 gram scale[6,12,13] as well as facile preparation of the required 2-bromo-3-bromomethylindoles[19] in regiospecific fashion. The unusual 2-bromotryptophan residues present in these peptides and their important derivatives can now be easily prepared from 2-bromo-3-bromomethyl-5-methoxyindoles **3a** and **3b** as described in this letter. Ready access to these unusual amino acids and their analogs is essential for the total synthesis of konbamide and its congeners as well as for study of structure/activity relationships. Further work in this area will be reported in due course.

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17. Procedure for **6:** To a solution of (3R)-isopropyl-2,5-diethoxypyrazine (0.025mol, 5.34g) in THF (150ml) was added n-butyllithium (2.5M in hexane, 10.4ml, 0.026mol) at -78°C under nitrogen. The solution which resulted was stirred at -78°C for 30min after which a solution of **3a** (0.024mol, 10g) in THF (100ml) under nitrogen was added dropwise. After the mixture was allowed to stir at -78°C for 20 h, the reaction solution was slowly warmed to rt and treated with a saturated aq. solution of $NaHCO_3$. The work up procedure was the same as reported in reference 6. A mixture of **5a** (0.018mol, 10g), THF (100ml), and 2N aq. HCl (50ml) was stirred at rt for 20min after which the mixture was poured into ice/NH_4OH (60ml) to bring the pH to about 8. The THF was removed under reduced pressure and the aq.solution was extracted with ethyl acetate (3x100ml). The combined organic layer was washed with brine and dried (K_2CO_3). The solvent was removed under reduced pressure to afford **6**. Further purification was carried out by a wash column (silica gel, ethyl acetate). The selected data for the L isomers of compounds **5a**, **6** and **1c**: **5a**, ^{13}C NMR (75 MHz, $CDCl_3$)) δ 14.27, 16.59, 19.07, 28.24, 31.07, 31.44, 55.66, 60.53, 60.63, 60.77, 84.40, 102.29, 111.02, 112.48, 115.95, 120.43, 130.46, 131.21, 149.23, 155.76, 126.57, 132.22. **6** (HCl salt), mp 116-120 °C (dec.); $[\alpha]_D^{27}$ = + 12.1 (c = 2.0, in CH_3OH); ^1H NMR (250 MHz, $CDCl_3$) δ 0.98 (t, 3H, J = 7.0 Hz), 1.31 (s, 9H), 3.42 (m, 1H), 3.61 (m, 1H), 3.80 (s, 3H), 3.99 (m, 2H), 4.39 (br, 1H), 6.81 (dd, 1H, J = 9.3, 2.1 Hz), 7.25 (d, 1H, J = 1.7 Hz), 7.89 (d, 1H, J = 9.2 Hz), 9.05 (br, 3H). **1c**, mp 164 -170 (dec.); $[\alpha]_D^{27}$ = + 27.40 (c = 1.0, in CH_3OH); ^1H NMR (250 MHz, $(DMSO)_{d6}$) δ 1.02 (t, 3H, J = 7.1 Hz), 2.10 (br, 2H, D_2O exchangeable), 2.75 (dd, 1H, J = 14.1, 7.4 Hz), 2.87 (dd, 1H, J = 14.1, 7.3 Hz), 3.54 (t, 1H, J = 7.0 Hz), 3.95 (q, 2H, J = 7.2 Hz), 6.58 (dd, 1H, J = 8.7, 2.2 Hz), 6.78 (d, 1H, J = 2.0 Hz), 7.04 (d, 1H, J = 8.5 Hz), 8.70 (s, 1H, D_2O exchangeable), 11.29 (s, 1H, D_2O exchangeable). The physical data for the D enantiomers of the above compounds are in agreement with the data for the L isomers.
18. The selected data for the L isomers of compounds **7a** and **7b**: **7a** (HCl salt), mp 88-90 °C; $[\alpha]_D^{27}$ = + 17.20 (c = 1.0, in CH_3OH); ^1H NMR (250 MHz, $(DMSO)_{d6}$) δ 0.91 (t, 3H, J = 7.0 Hz), 1.63 (s, 9H), 3.09 (m, 1H), 3.19 (m, 1H), 3.41 (m, 1H), 3.96 (q, 2H, J = 7.1 Hz), 7.28 (t, 1H, J = 7.6 Hz), 7.34 (t, 1H, J = 7.6 Hz), 7.76 (d, 1H, J = 7.6 Hz), 7.99 (d, 1H, J = 7.6 Hz), 8.87 (br, 3H, D_2O exchangeable). **7b** (HCl salt), mp 150-152 °C; $[\alpha]_D^{27}$ = + 20.80 (c = 2.0, in CH_3OH); ^1H NMR (250 MHz, $(DMSO)_{d6}$) δ 0.93 (t, 3H, J = 7.2 Hz), 3.12 (m, 1H), 3.24 (m, 1H), 3.29 (m, 1H), 4.01 (m, 2H), 7.05 (t, 1H, J = 7.5 Hz), 7.11 (t, 1H, J = 7.4 Hz), 7.30 (d, 1H, J = 7.9 Hz), 7.53 (m, 1H), 8.60 (br, 3H, D_2O exchangeable), 11.85 (s, 1H, D_2O exchangeable). The physical data for the D enantiomers of the above compounds are in agreement with the data for the L isomers.
19. After indole **2a** was protected with the BOC group followed by treatment with two equivalents of NBS and then heated to reflux for one hour, a mixture of two tribromoindoles (1-BOC-2-bromo-3-bromomethyl-4-bromo-5-methoxyindole and 1-BOC-2-bromo-3-bromomethyl-6-bromo-5-methoxyindole) was obtained. It was found that heating the mixture of BOC protected indole **2a** and one equivalent of NBS in CCl_4 to reflux for one hour followed by addition of another equivalent of NBS and AIBN (5%) afforded greater than 80% yield of the desired dibromoindole **3a**.

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