Communications

New Efficient Method for the Total Synthesis of (*S,S*)-Isodityrosine from Natural Amino Acids

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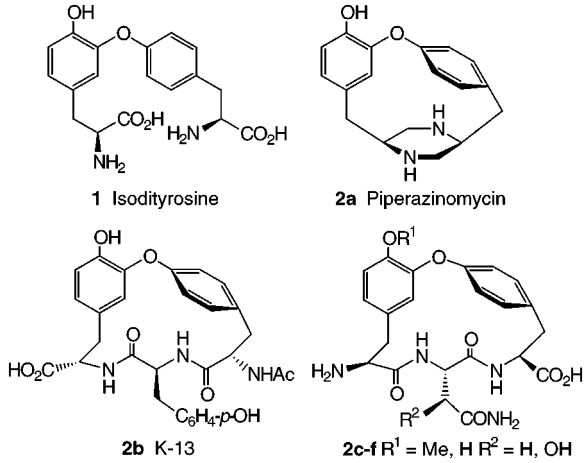
Received February 17, 1999

Isodityrosine[2] (**1**), isolated in the early 1980s from extensin, a plant cell wall glycoprotein, is the key structural unit which defines a large class of biologically active natural products. Piperazinomycin[3] (**2a**) exhibits antimicrobial and antifungal activity, the cyclic tripeptide K-13[4] (**2b**) is a potent inhibitor of angiotensin I converting enzyme (ACE), and OF4949-I-OF4949-IV[5] (**2c**−**f**) are inhibitors of aminopeptidase B and exhibit antitumor and immunopotentiating activity. The bicyclic hexapeptides bouvardin[6] and deoxybouvardin[7,8] are members of a large class of potent antitumor antibiotics, including RA-I−RA-IV.[7]



The construction of the diaryl ether moiety is the foremost synthetic challenge posed by these target molecules, and therefore many chemists[8] have worked at developing new methodology to achieve this goal. Several syntheses of isodityrosine,[9] piperazinomycin,[10] K-13,[11] OF-4949-III,[12] bouvardin,[13] deoxybouvardin,[14] and RA-VII[15] have used a variety of approaches. Several different approaches have been used to build the diaryl ether moiety,[10] e.g., Ullmann-type couplings,[16] nucleophilic displacements of *o*-nitro-substituted aryl fluorides[17] or bromobenzoquinones,[18] oxidative phenol couplings,[19] Diels−Alder reactions,[20] displacement of areneruthenium complexes,[21] etc. We describe herein a new method for the synthesis of isodityrosine which involves a direct coupling of two readily prepared derivatives of the natural amino acids L-phenylalanine and L-tyrosine. This convergent synthesis should permit one to easily prepare the asymmetric isodityrosine derivatives necessary for the synthesis of the more complex natural products in this series.

The first component of this convergent synthesis was avaiable in five steps and reasonable overall yield from tyrosine **3** via the selectively monoprotected L-DOPA derivative **5** prepared by formylation to give **4** followed by benzylation and a Dakin oxidation to give **5**.[22] Formation of the ester afforded **6** in good yield (Scheme 1).

The second component was prepared from the commercially available 4-iodophenylalanine **7** (Scheme 2) (which

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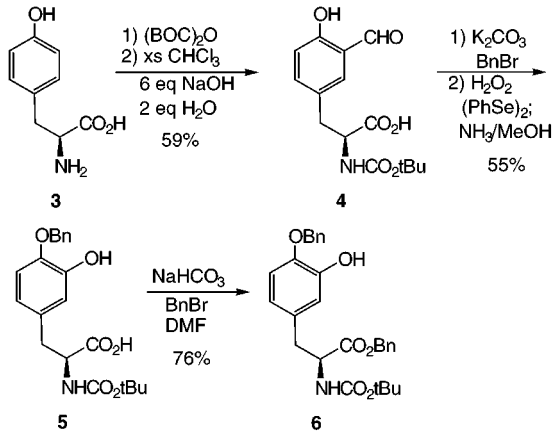
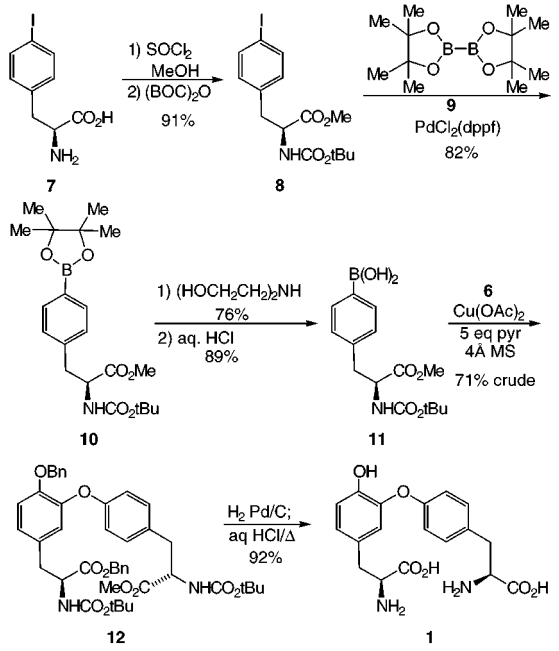
10.1021/jo9902751 CCC: $18.00
Published on Web 04/07/1999

Scheme 1



Scheme 2



can be prepared from phenylalanine by iodination in one step).[23] Protection of both the amine and acid gave **8** in 91% yield. The key process involved the conversion of this iodide into the corresponding boronic acid **11**. This was accomplished by palladium-catalyzed coupling of the iodide **8** with the commercially available bis(boronate) **9** to give the arylboronate **10** in 82% yield.[24] The use of the diphenylphosphoferrocene ligand (dppf) was cruical to the success of this process. Reaction of **10** with diethanolamine gave in 76% yield the cyclic aminoboronate which was hydrolyzed under acidic conditions to the arylboronic acid **11**. The amino acid prepared from this compound, L-(4-boronophenyl)alanine (L-BPA), is used clinically in boron neutron capture therapy (BNCT) for the tretament of brain tumors.[25] Although it has been made previously,[26] this represents the first synthesis of this system from phenylalanine. The key step of this new method is the cupric acetate promoted coupling of an arylboronic acids with phenols developed jointly by Chan, Evans, and Lam.[27] Thus, treatment of the L-DOPA derivative **6** with 1.5 equiv of the arylboronic acid **11** in the presence of cupric acetate, 4 Å powdered molecular sieves, and 5 equiv of pyridine gave the desired aryloxy phenol **12** in 71% crude yield (60% after flash column chromatography). This compound was identical in all respects with authentic material prepared by another route.[9d] Final conversion of **12** to isodityrosine **1** was accomplished in one operation by catalytic hydrogenation followed by acidic hydrolysis to afford **1** in 92% yield.

This ends a very efficient convergent synthesis of **1** in which all of the chirality in the molecule is derived directly from the two aromatic amino acids L-tyrosine and L-phenylalanine. This novel approach opens the door to the synthesis of the many isodityrosine-derived natural products and to unique analogues as well.[28]

Acknowledgment. We thank the National Institutes of Health (GM 31349) and the Agricultural Division of American Cyanamid Company for generous financial support.

Supporting Information Available: Experimental Section, ^{1}H and ^{13}C NMR spectra of all new compounds, and the ^{11}B NMR spectrum of the acid derived from **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9902751

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