Total Synthesis of (+)-Lactacystin, the First Non-Protein Neurotrophic Factor

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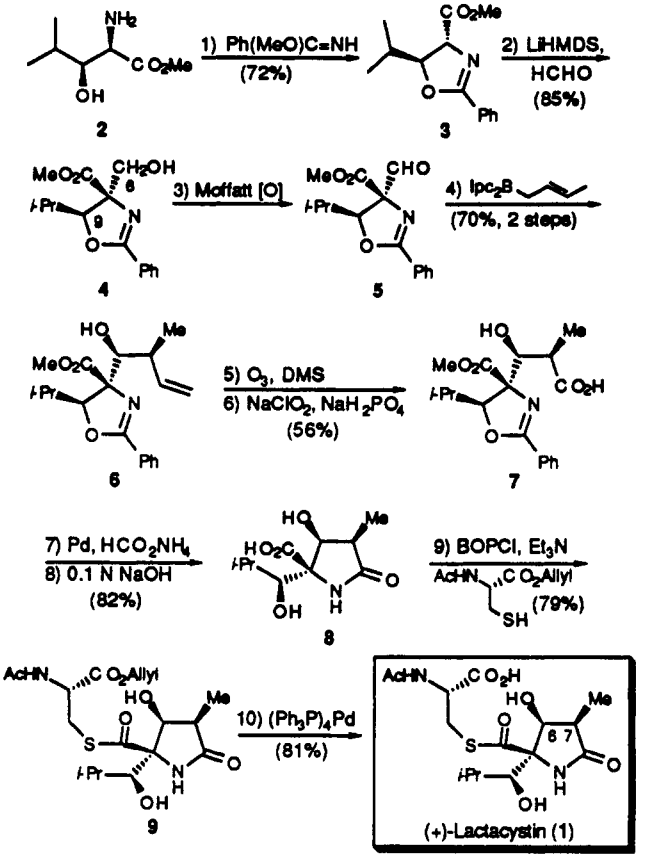
Neurotrophic agents such as nerve growth factor (NGF), a well-characterized protein, are required for the survival and function of neurons.[1] In 1991 we reported the isolation and characterization of the first non-protein neurotrophic factor, (+)-lactacystin (**1**), a novel sulfur-containing γ-lactam produced by a culture broth of *Streptomyces* sp. OM-6519.[2] Lactacystin induces neuritogenesis and causes a transient increase in the intracellular cAMP level in Neuro 2A neuroblastoma cells[2a] and is also active against Sarcoma 180.[3] Corey and Reichard recently reported the first total synthesis of **1**.[4] Herein we describe a concise alternative approach, designed to afford easy access to both the natural product and a variety of analogues. Key steps in the elaboration of the lactam moiety include the stereoselective hydroxymethylation of oxazoline **3** and an asymmetric allylboration which introduces the hydroxyl and methyl substituents at C(6) and C(7), respectively (Scheme I).

As our point of departure, 2(*R*),3(*S*)-β-hydroxyleucine methyl ester[5] (**2**) was treated with methyl benzimidate to furnish the *trans*-disubstituted oxazoline **3**.[6,7] Aldol condensation with formaldehyde via the Seebach protocol[8] then gave **4**[6] exclusively (85% yield, >98% de); the stereochemical assignment was secured by ^{1}H NOE studies.[9] Moffatt oxidation[10] afforded aldehyde **5**,[6] which was subjected without purification to allylboration with (*E*)-crotyldiisopinocampheylborane as described by Brown.[11] The desired β-methyl homoallylic alcohol **6**[6] was thus obtained in 70% yield from **4** after chromatography on silica gel.

Conversion of **6** to carboxylic acid **7**[6] entailed ozonolysis and reductive workup (dimethyl sulfide) followed by selective oxidation

Scheme I



($NaClO_4$, NaH_2PO4, 2-methyl-2-butene; 56% yield from **6**).[12] The key γ-lactam **8**[6] could be elaborated in 82% yield by catalytic transfer hydrogenation[13] of **7** and ester hydrolysis. For the transformation of **8** to **1** we employed a two-step sequence first devised by Corey.[4] The amino side chain was incorporated via thioesterification of **8** with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl)[14] and *N*-acetyl-L-cysteine allyl ester (79%). Finally, deallylation of **9**[6] [$Pd(PPh_3)_4$, HCOOH, Et_3N] gave pure (+)-lactacystin (**1**)[6] in 81% yield as colorless needles. The successful construction of (+)-lactacystin was confirmed by detailed comparison of the synthetic and natural compounds (400-MHz ^{1}H and 100-MHz ^{13}C NMR, IR, HRMS, optical rotation, melting and mixed melting points, and TLC in four solvent systems).

In summary, the development of an economic and versatile synthetic approach to **1** (10 steps, 13% overall yield) should permit the preparation of useful quantities of (+)-lactacystin and its analogues, greatly facilitating the ongoing pharmacological studies of neurotrophic factors.

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Supplementary Material Available: Characterization data for **1–9** (IR, ^{1}H and ^{13}C NMR, MS, mp, optical rotation) (4 pages). Ordering information is given on any current masthead page.

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