Total Synthesis of (+)-Lactacystin from (*R*)-Glutamate

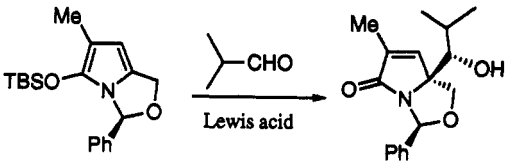
Hidemitsu Uno,† Jack E. Baldwin,* and Andrew T. Russell

The Dyson Perrins Laboratory
South Parks Road, Oxford OX1 3QY, U.K.

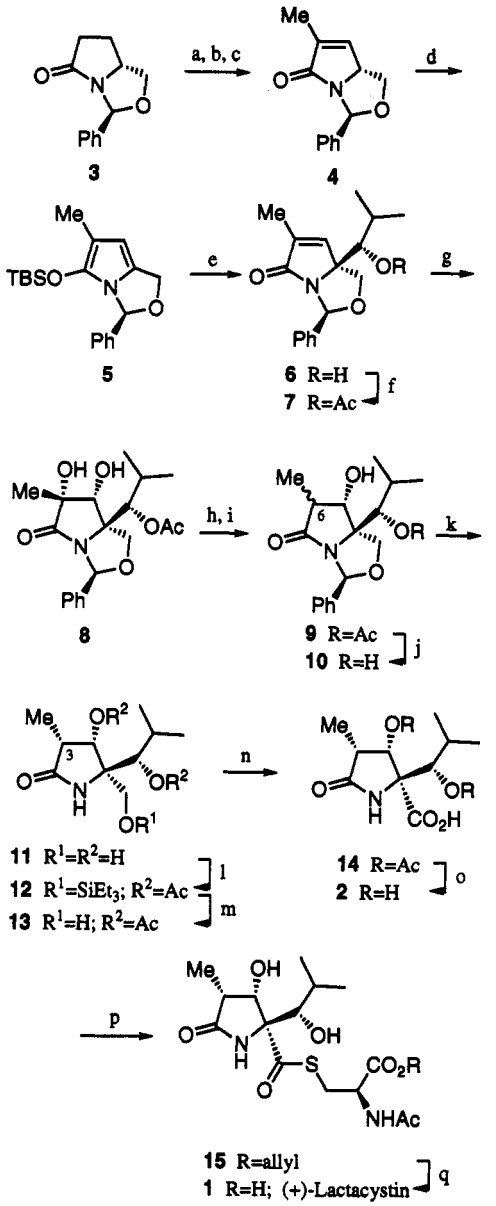
Received October 12, 1993

The discovery by Ōmura[1] of (+)-lactacystin (**1**) in *Streptomyces sp.* OM-6519 and the finding that it possesses neurotrophic activity have created much excitement, since the role of neurotrophic proteins, such as nerve growth factors (NGFs), in diseases is the center of much current interest.[2] This substance consists of two α-amino acids, (*R*)-*N*-acetylcysteine and a novel pyroglutamic acid derivative **2**. The combination of biological activity and the unique structure of lactacystin encouraged us to develop a synthesis which could permit variations of both the substituents and their stereochemistry. During the course of our work two elegant syntheses were reported,[3,4] which are strategically different from our route. The key reaction in our synthesis involves the stereoselective aldol reaction of a siloxypyrrole, readily available from pyroglutamate, with an aldehyde, thereby assembling the quaternary center and secondary alcohol in the correct stereochemical form, Scheme 1. The bicyclic oxazolidine **3** was prepared from (*R*)-glutamic acid in three steps (57%)[5] and was elaborated to the unsaturated derivative **4** by sequential methylation[6] and selenenylation/ozonolysis (65%, Scheme 2). The key siloxypyrrole **5** was obtained as a crystalline solid (89%) by treatment with TBSOTf and 2,6-lutidine.[7] The aldol reaction of **5** with isobutyraldehyde was achieved at −78 °C in ether in the presence of 2 equiv of $SnCl_4$ to afford **6**[8] and its secondary alcohol epimer[8] in the ratio 9:1. The major isomer **6** was obtained as a crystalline solid after chromatography (55% yield). The surprising π-facial selectivity observed here, i.e., addition to the same face as the phenyl substituent, was revealed by X-ray crystallography of the *p*-bromobenzoate derivative of *ent*-**6**.[9] Use of other Lewis acids and solvents led to the formation of other isomers at the quaternary and secondary alcohol centers,[10] thereby permitting access to these substances. Following acetylation **7** was converted to the diol **8** as a single isomer (87%) by osmylation (OsO_4, *N*-methylmorpholine *N*-oxide). The tertiary hydroxyl group was removed *via* the cyclic thiocarbonate with Bu_3SnH in toluene at reflux (AIBN catalyst, 94% yield),[11] which resulted in an approximately equal ratio of the C6 epimers of **9**.[8] However, treatment of this mixture with 0.5 N NaOH in aqueous MeOH

Scheme 1



Scheme 2 [a]



[a] (a) LDA, MeI, THF, −78 °C; 95%. (b) LDA, PhSeBr, THF, −78 °C; 79%. (c) O_3, CH_2Cl_2, −78 °C; pyridine, → room temperature; 87%. (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temperature; 89%. (e) *i*-PrCHO, $SnCl_4$, ether, −78 °C; 55%. (f) Ac_2O, pyridine, room temperature; 99%. (g) OsO_4, *N*-methylmorpholine *N*-oxide, aqueous acetone, room temperature; 87% (two cycles). (h) *N*,*N*′-Thiocarbonyldiimidazole, THF, room temperature; 91%. (i) Bu_3SnH, AIBN, toluene, reflux; 94%. (j) 2N NaOH/MeOH (1:3), 0–3 °C; 94%. (k) H_2, Pd/C, HCl, MeOH, room temperature; 87%. (l) Et_3SiCl, pyridine; Ac_2O, room temperature; 89%. (m) 40% HF, CH_3CN, room temperature; 91%. (n) Jones' reagent, acetone, 0 °C → room temperature; 91%. (o) 0.2 N NaOH, room temperature; quantitative. (p) (*R*)-*N*-Acetylcysteine allyl ester, BOPCl, Et_3N, CH_2Cl_2, room temperature; 60%. (q) $Pd(PPh_3)_4$, HCO_2HNEt_3, THF, room temperature; 88%.

† Ramsay Memorial Fellow (1991–1993). Present address: Advanced Instrumentation Center for Chemical Analysis, Ehime University, Matsuyama 790, Japan.

(1) Ōmura, S.; Fujimoto, T.; Otogurro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot. Chem.* **1991**, *44*, 113. Ōmura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, T.; Nakagawa, A. *Ibid.* **1991**, *44*, 117. Ōmura, S. *Gene* **1992**, *115*, 141.

(2) Henderson, C. E.; Camu, W.; Mettling, C.; Gouin, A.; Poulsen, K.; Karihaloo, M.; Rullamas, J.; Evans, T.; McMahon, S. B.; Armanini, M. P.; Berkemeier, L.; Phillips, H. S.; Rosenthal, A. *Nature* **1993**, *363*, 266. Lohof, A. M.; Ip, N. Y.; Poo, M.-m. *Ibid.* **1993**, *363*, 350. Lin, L.-F. H.; Doherty, D. H.; Lile, J. D.; Bektesh, S.; Collins, F. *Science* **1993**, *260*, 1130. Magal, E.; Burnham, P.; Varon, S. *Dev. Brain Res.* **1991**, *63*, 141. Sendtner, M.; Arakawa, Y.; Stöckli, K. A.; Kreutzberg, G. W.; Thoenen, H. *J. Cell. Sci.* **1991**, S15, 103. Arakawa, Y.; Sendtner, M.; Thoenen, H. *J. Neurosci.* **1990**, *10*, 3507. Barde, Y.-A. *Neuron* **1989**, *2*, 1525.

(3) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677.

(4) Sunazuka, T.; Nagamitsu, T.; Matsuzaki, K.; Tanaka, H.; Ōmura, S.; Smith, A. B., III. *J. Am. Chem. Soc.* **1993**, *115*, 5302.

(5) Thottathil, J. K.; Montiot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissik, T. P. *J. Org. Chem.* **1986**, *51*, 3140. Thottathil, J. K.; Pryzbyla, C.; Malley, M.; Gougoutas, J. Z. *Tetrahedron Lett.* **1986**, *27*, 1533. Saijo, S.; Wada, M.; Himizu, J.; Ishida, A. *Chem. Pharm. Bull.* **1980**, *28*, 1449.

(6) Armstrong, R. W.; Demattei, J. A. *Tetrahedron Lett.* **1991**, *32*, 5749.

(7) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760. Rassu, G.; Casiraghi, G.; Spanu, P.; Pinna, L.; Fava, G. G.; Ferrari, M. B.; Pelosi, G. *Tetrahedron: Asymmetry* **1992**, *3*, 1035.

(8) The relative stereochemistry was determined by NOE experiments. We thank Mrs. E. McGuiness for the measurements.

(9) The analysis using the anomalous dispersion technique was carried out by Dr. Alison Edwards, Chemical Crystallography Laboratory, University of Oxford, 9 Parks Road, Oxford OX1 3PD, U.K.

(10) The detailed study on this reaction will be described elsewhere.

0002-7863/94/1516-2139$04.50/0

at 0–3 °C epimerizes C6 to the more stable and desired *syn*-isomer **10** (*syn*-**10**:*anti*-**10**:*syn*-**9** = 73:10:11, 94%), along with a small amount (5%) of elimination product **6**. This mixture was hydrogenated (10% Pd/C) under acidic conditions to give a mixture of **11** and its C3 epimer (87%). Although recrystallization gave pure **11** in 66% yield, removal of the undesired epimer was more easily achieved by chromatography following the next step. Selective protection of the primary hydroxyl as its Et_3Si ether and the secondary alcohols as acetates was performed in one operation by sequential addition of Et_3SiCl and then excess Ac_2O to a solution of **11** in pyridine to give **12** (89%) after chromatography. On treatment of **12** with 40% HF in CH_3CN, the primary hydroxyl group was regenerated, which was then converted into a carboxylic acid by excess Jones' reagent (91%). Saponification of the diacetate acid **14** with 0.2 N NaOH provided the lactam **2** as white powdery crystals [mp 241–242 °C dec, $[\alpha]_D^{21}$ +18.5° (*c* 1.0, MeOH)]. The spectroscopic data for **2** were identical to those reported previously[3,4] in all respects. Final transformation of **2** into (+)-lactacystin (**1**) was carried out according to Corey's protocol.[3] Coupling of **3** with (*R*)-*N*-acetylcysteine allyl ester[12] (BOPCl, Et_3N) followed by deallylation [$Pd(PPh_3)_4$, HCO_2H, Et_3N] gave (+)-lactacystin (**1**) as colorless needles [mp 235–237 °C dec, $[\alpha]_D^{21}$ +75° (*c* 0.28, MeOH)]. The identity of this compound was confirmed by detailed comparison with the reported data[2–4] and an authentic sample, generously provided by Dr. S. Ōmura.

In summary, we have achieved an efficient total synthesis of (+)-lactacystin (7.5% overall yield from **3**) by a route which should be applicable to the synthesis of a number of its analogues and stereoisomers.

Supplementary Material Available: Selected experimental procedures and all characterization data for **1-15** (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718.

(12) We thank Mr. Ian Churcher for the preparation of this material.