

An enantiocontrolled synthesis of a key intermediate to (+)-lactacystin

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An asymmetric synthesis of a key intermediate **16** to (+)-lactacystin **1** has been established starting from epoxide **2** via intramolecular mercurioamidation of allylic trichloroacetimidate **4** and concomitant addition-reduction of ester **13** by Pr^iMgBr , in which reduction of the intermediate ketone proceeded with complete stereoselectivity.

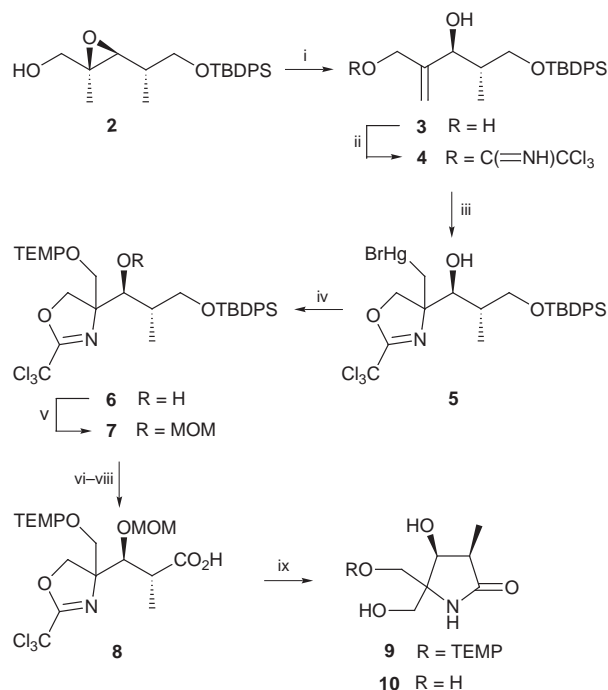
Since neurotrophic factors are responsible for the survival and function of neurons,¹ they might be useful in the treatment of various nerve diseases.² Omura *et al.* screened a number of microbial culture samples to isolate the first non-protein neurotrophic agent (+)-lactacystin **1** from *Streptomyces* sp. OM-6519.³ Its structure, elucidated by NMR spectroscopy and X-ray crystallographic analysis, is composed of (*R*)-*N*-acetylcysteine and a unique pyroglutamic acid via a thioester linkage.⁴ (+)-Lactacystin inhibits cell proliferation, induces neurogenesis and increases the intracellular cAMP level transiently in the Neuro 2A neuroblastoma cell line.^{3,5} Its intriguing structural features as well as potential therapeutic utility have engendered considerable interest in the fields of synthetic and medicinal chemistry. Here we describe a stereoselective synthetic route to (+)-lactacystin.^{6–9} The key steps of our synthesis comprise tertiary amination of the olefinic double bond in allylic trichloroacetimidate **4** via mercurioamidation,¹⁰ facile differentiation of the hydroxymethyl groups in **10** by ring formation and diastereoselective derivatization of ester **13** into alcohol **14**.

The known epoxide **2**,¹¹ $[\alpha]_{\text{D}}^{20} -24.7$ (*c* 1.15, CHCl_3), was treated with LDA to give allylic alcohol **3**, $[\alpha]_{\text{D}}^{21} +10.4$ (*c* 1.44, CHCl_3), in 91% yield (Scheme 1). Only the primary hydroxy group of **3** was functionalized to a trichloroacetimidate. The crude monoimidate **4** was subjected to intramolecular mercurioamidation using mercuric trifluoroacetate with K_2CO_3 to furnish a 1:1 diastereomeric mixture of oxazolines **5** in 92% overall yield after aqueous KBr work-up. Since oxidative demercuration¹² of **5** using O_2 failed under a variety of reaction conditions, it was attempted by exposing **5** to TEMPO in the presence of LiBH_4 to provide the oxidized products **6** in 78% yield. The secondary hydroxy groups of **6** were protected with MeOCH_2Cl (MOMCl) and then the silyl groups were removed to afford the corresponding primary alcohols in 84% overall yield. While PDC oxidation of the alcohols in DMF was sluggish, they were efficiently oxidized to carboxylic acids **8** in 78% yield by Swern oxidation¹³ followed by KMnO_4 oxidation.¹⁴ Complete hydrolysis and the ensuing cyclization were effected by heating **8** at reflux with ethanolic HCl in AcOH. The 2,2,6,6-tetramethylpiperidyl (TEMP) groups of the generated pyrrolidinones **9** were reductively cleaved *in situ* by adding zinc to the hot reaction mixture to produce trihydroxy pyrrolidinone **10**, $[\alpha]_{\text{D}}^{19} +9.5$ (*c* 0.95, MeOH), in 72% overall yield from **8**.

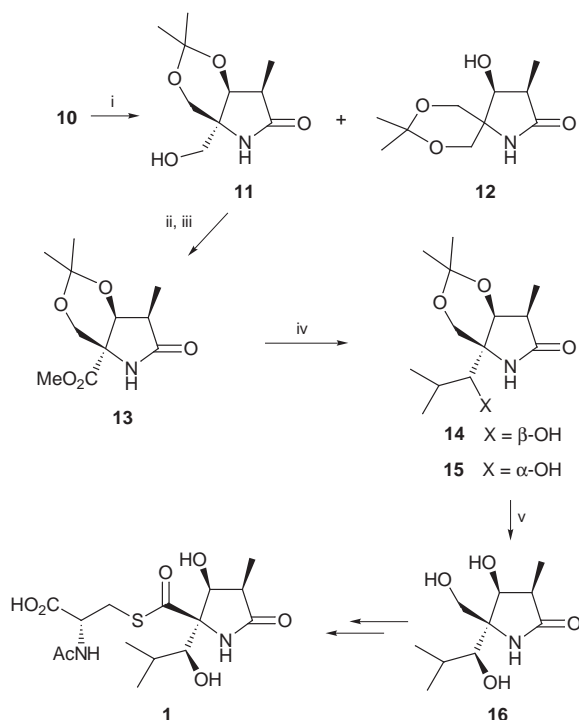
For the appropriate elaboration of the α -hydroxymethyl groups in **10**, it was chemoselectively reacted with acetone under acidic conditions to give a 7:1 mixture of acetonides **11** and **12** in 95% combined yield (Scheme 2). After chromatographic separation, the primary alcohol **11**, $[\alpha]_{\text{D}}^{20} +31.4$ (*c* 1.10, CHCl_3), was oxidized under Swern conditions and the resulting aldehyde reacted with Pr^iMgBr under various reaction conditions to furnish a 1:1 mixture of alcohols **14** and **15** along with an appreciable amount of the reduced starting alcohol **11**.

Owing to the inefficient Grignard addition, **11** was converted into ester **13**, $[\alpha]_{\text{D}}^{21} +57.1$ (*c* 1.70, CHCl_3), in 90% yield. Subjection of **13** to 1 equiv. of Pr^iMgBr provided the corresponding isopropyl ketone in 80% yield, the stereoselective reduction of which was attempted employing several reducing agents such as oxazaborolidine,¹⁵ Ipc_2Cl ,¹⁶ sodium triacetoxyborohydride,¹⁷ NaBH_4 in the presence of diethylmethoxyborane,¹⁸ and so forth. However, the best stereoselectivity turned out to be 5:1 in favor of **14** with NaBH_4 in MeOH at 0 °C. Some experimentation revealed that an excess amount of Pr^iMgBr reduced the generated isopropyl ketone to the alcohol **14**. Accordingly, **13** was treated with >2 equiv. of Pr^iMgBr to give selectively only the desired diastereomeric alcohol **14**, $[\alpha]_{\text{D}}^{20} +40.5$ (*c* 1.20, CHCl_3), in 91% yield. Acidic hydrolysis of **14** yielded trihydroxy pyrrolidinone **16**, mp 198–199 °C (decomp.), $[\alpha]_{\text{D}}^{20} +16.2$ (*c* 0.62, MeOH), quantitatively, the spectroscopic data of which are identical to those reported in the literature and which is a known intermediate to (+)-lactacystin **1**.^{8,19}

We have developed an enantioselective synthetic route to (+)-lactacystin **1** via several crucial steps, including amino hydroxylation of the olefinic double bond in **3**, the hydrolytic cyclization of **8**, and the regio- and stereo-selective functionalization of one hydroxymethyl group in **10**; these should have versatility in the synthesis of its analogues.



Scheme 1 Reagents and conditions: i, LDA, THF, 0–24 °C; ii, Cl_3CCN , DBU, EtCN, –78 °C; iii, $\text{Hg}(\text{O}_2\text{CCF}_3)_2$, K_2CO_3 , THF, 0 °C, then aq. KBr; iv, TEMPO, LiBH_4 , THF, 24 °C; v, MOMCl, Pr^iNEt , CH_2Cl_2 , 0–24 °C; vi, Bu_4NF , H_2O , THF, 45 °C; vii, $(\text{COCl})_2$, DMSO, Et_3N ; viii, 1 M KMnO_4 , 1.25 M NaH_2PO_4 , Bu^iOH , 24 °C; ix, conc. HCl, EtOH, AcOH, reflux, then Zn, reflux



Scheme 2 Reagents and conditions: i, TsOH, acetone, 24 °C; ii, Jones' reagent, acetone, 0 °C; iii, CH₂N₂, THF, 0 °C; iv, PrⁱMgBr, THF, -20 to 0 °C; v, TsOH, MeOH, 60 °C

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Notes and References

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- 19 All new compounds showed satisfactory spectral data. *Selected data for 16*: δ_{H} (300 MHz, CD₃OD) 0.94 (3H, d, *J* 6.7), 1.02 (3H, d, *J* 6.7), 1.11 (3H, d, *J* 7.5), 1.91–2.00 (1H, m), 2.79 (1H, p, *J* 7.5), 3.49 (1H, d, *J* 3.6), 3.78 (2H, s) and 4.40 (1H, d, *J* 7.5); δ_{C} (75.5 MHz, CD₃OD) 9.5, 17.6, 22.7, 30.6, 42.6, 63.4, 70.7, 74.4, 79.1 and 181.6.

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