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

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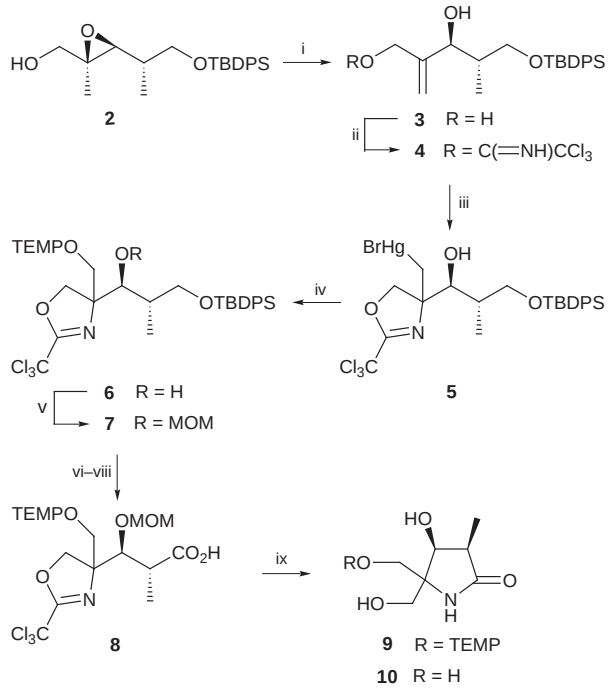
An asymmetric synthesis of a key intermediate 16 to (+)-lactacystin 1 has been established starting from epoxide 2 *via* intramolecular mercurioamidation of allylic trichloroacetimidate 4 and concomitant addition-reduction of ester 13 by Pr^i MgBr, in which reduction of the intermediate ketone proceeded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

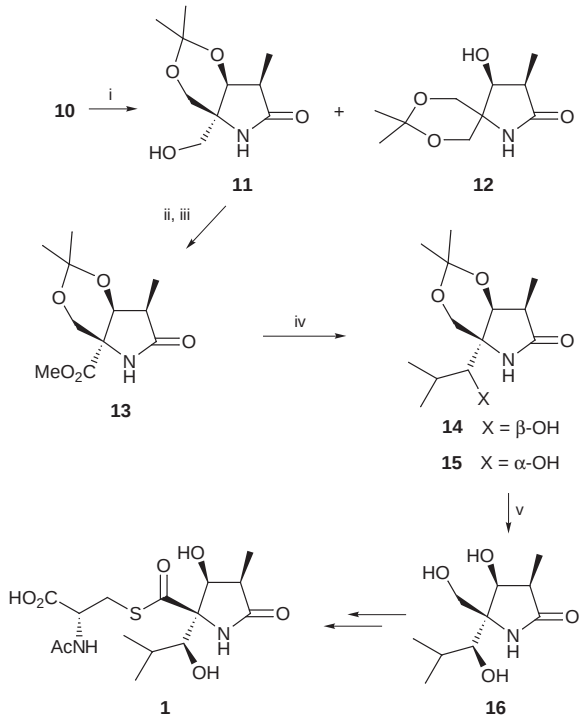
The known epoxide **2**,[11] $[\alpha]_D^{20}$ −24.7 (*c* 1.15, $CHCl_3$), was treated with LDA to give allylic alcohol **3**, $[\alpha]_D^{21}$ +10.4 (*c* 1.44, $CHCl_3$), in 91% yield (Scheme 1). Only the primary hydroxy group of **3** was functionalized to a trichloroacetimidate. The crude monoimidate **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 demercuration[12] 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 oxidation[13] 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**, $[\alpha]_D^{19}$ +9.5 (*c* 0.95, MeOH), in 72% overall yield from **8**.

For the appropriate elaboration of the α-hydoxymethyl 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**, $[\alpha]_D^{20}$ +31.4 (*c* 1.10, $CHCl_3$), was oxidized under Swern conditions and the resulting aldehyde reacted with Pr^{i}MgBr 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**, $[\alpha]_D^{21}$ +57.1 (*c* 1.70, $CHCl_3$), in 90% yield. Subjection of **13** to 1 equiv. of Pr^{i}MgBr 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^{i}MgBr reduced the generated isopropyl ketone to the alcohol **14**. Accordingly, **13** was treated with > 2 equiv. of Pr^{i}MgBr to give selectively only the desired diastereomeric alcohol **14**, $[\alpha]_D^{20}$ +40.5 (*c* 1.20, $CHCl_3$), in 91% yield. Acidic hydrolysis of **14** yielded trihydroxy pyrrolidinone **16**, mp 198–199 °C (decomp.), $[\alpha]_D^{20}$ +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 animo 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, $Hg(O_2CCF_3)_2$, K_2CO_3, THF, 0 °C, then aq. KBr; iv, TEMPO, $LiBH_4$, THF, 24 °C; v, MOMCl, Pr$^i_2$NEt, CH_2Cl_2, 0–24 °C; vi, Bu_4NF, H_2O, THF, 45 °C; vii, $(COCl)_2$, DMSO, Et_3N; viii, 1 M $KMnO_4$, 1.25 M NaH_2PO_4, Bu^{t}OH, 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, CH_2N_2, THF, 0 °C; iv, Pr^iMgBr, 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, CD_3OD) 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, CD_3OD) 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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