Total Synthesis of (+)-Lactacystin from D-Glucose

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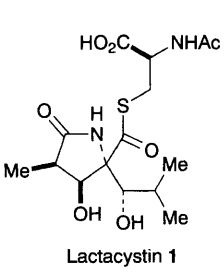
The chiral and stereoselective synthesis of (+)-lactacystin **1**, the first non-protein neurotrophic factor, is described; the γ-lactam portion possessing a quaternary carbon in **1** was constructed stereoselectively from D-glucose using the allylic trichloroacetimidate rearrangement (Overman rearrangement) as the key reaction.

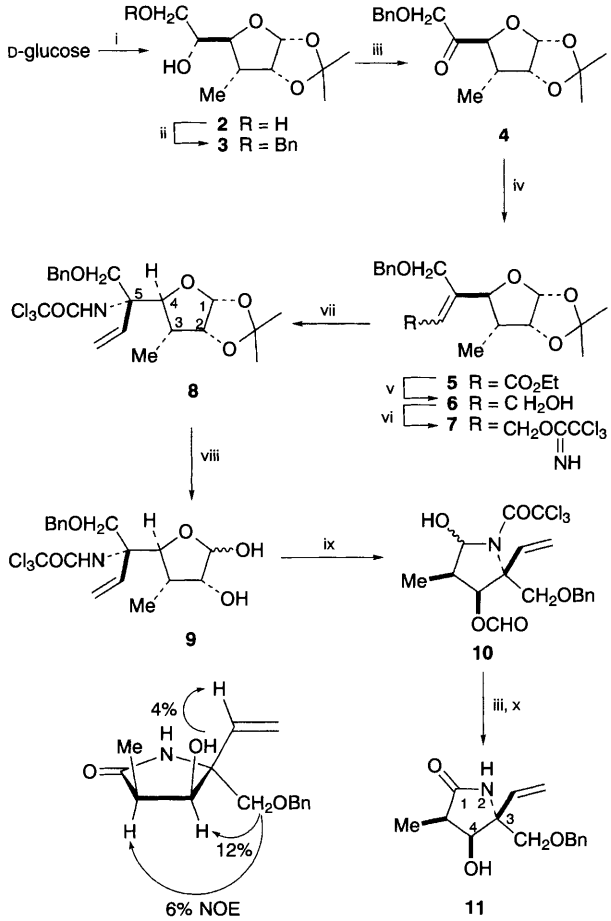
Lactacystin **1** is a novel amino acid derivative isolated from the culture broth of *Streptomyces*[1] and reported to inhibit cell proliferation and induce neurite outgrowth in the mouse neuroblastoma cell line Neuro 2A.[1] Such interesting neurotrophic activity as well as its unique structure[2] attracted synthetic interest and three elegant total syntheses of **1**, all employing amino acids as the starting material, have been reported to date.[3] Recently, reports on the synthesis[4] and the structure–activity relationship study[5] of analogues of **1** have appeared. The structural feature of **1** is the presence of a highly functionalized γ-lactam with four contiguous chiral centres including a quaternary carbon. For construction of the quaternary carbon, previous successful syntheses adopted Seebach's protocol[6] using oxazolidine[3a] and oxazoline[3b] derivatives, and the aldol reaction of the bicyclic siloxypyrrole.[3c] Here we report an alternative approach to **1**, which involves the stereoselective generation of the quaternary carbon by the rearrangement of the allylic trichloroacetimidate (Overman rearrangement),[7,8] starting from D-glucose.

The known 3-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose **2**,[9] prepared from diacetone-D-glucose in four steps, was chosen as the starting material. Reaction of **2** with dibutyltin oxide[10] followed by treatment with benzyl bromide afforded **3** in 66% yield. Jones oxidation of **3** gave **4**, which was subjected to a Wittig reaction to give alkene **5** as an inseparable mixture of (*E*)- and (*Z*)-isomers (1 : 1) in 78% yield from **3**. Reduction of the ester function in **5** with DIBAL-H gave **6**, the substrate for the Overman rearrangement[7] [(*E*) : (*Z*) = 1 : 1], in 90% yield. Allylic alcohol **6** was converted into trichloroacetimidate **7**, which, without isolation, was heated in toluene at 150 °C (in a sealed tube) for 89 h to provide the inseparable mixture of rearranged product **8** and its C(5) epimer in a ratio of 4.8 : 1 (determined by 270 MHz ^{1}H NMR) in 60% yield from **6**. Acid hydrolysis of the mixture followed by chromatographic separation afforded **9** in 72% isolated yield as an anomeric mixture (6 : 1). Periodate oxidation of **9** provided hemiaminal derivative **10**. Jones oxidation of **10** gave the corresponding lactam, whose protecting (*N*-trichloroacetyl and *O*-formyl) groups were cleanly removed by treatment with $NaBH_4$ to furnish the γ-lactam **11** in 75% yield from **9**. The observed NOE in **11** clearly supported the assigned structure, revealing that the newly formed stereocentre at C(3) should be *R* (Scheme 1).

Silylation of the hydroxy group in **11** followed by removal of the *O*-benzyl group gave **12** in 74% yield (Scheme 2). Moffatt oxidation of **12** afforded **13**, which, without isolation, was treated with isopropylmagnesium bromide in THF to give adducts **14a**, **14b** and reduced product **12** in 35, 30 and 21% isolated yields from **12**, respectively, after separation by silica gel chromatography. The undesired isomer **14b** was effectively converted into **14a** by an oxidation–reduction procedure: oxidation of **14b** gave ketone **15** (78% yield), whose reduction with triisobutylaluminium in CH_2Cl_2 at 0 °C proceeded stereoselectively and gave **14a** as the major product in 70% yield (**14b**, 7% yield). Treatment of **14a** with aqueous TFA provided **16** in 76% yield. Ozonolysis of **16** (Me_2S workup) followed by selective oxidation of the resulting aldehyde afforded carboxylic acid **17**, which, without isolation, was coupled with *N*-acetyl-L-cysteine allyl ester by the procedure reported by Corey *et al.*[3a] to provide lactacystin allyl ester **18** {mp 183–185 °C (decomp.), $[\alpha]_D^{23}$ +38 (*c* 0.74, acetone); lit.[3c] mp 181–182 °C (decomp.), $[\alpha]_D^{22}$ +39.8 (*c* 0.55, acetone)} in 36% yield from **16**. The spectral data for **18** were identical to those reported previously[3b,c] in all respects. Finally, removal of the allyl protecting group[3a] gave (+)-lactacystin **1** in 70% yield. The physical properties of synthetic **1** {mp 234–236 °C (decomp.), $[\alpha]_D^{15}$ + 75 (*c* 0.4, MeOH), lit.[2a] mp 237–238 °C

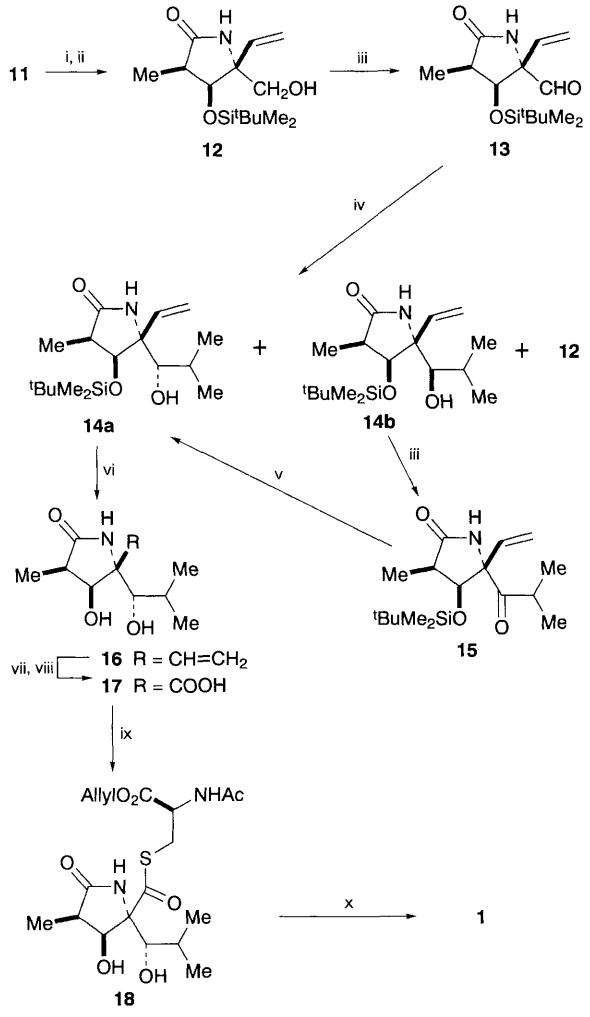


Lactacystin **1**



Scheme 1 *Reagents and conditions*: i, see ref. 9; ii, Bu_2SnO, toluene, reflux, then BnBr, CsF, DMF, room temp.; iii, Jones reagent (CrO_3 in dil. H_2SO_4), acetone, 0 °C; iv, $Ph_3P{=}CHCO_2Et$, toluene, 60 °C; v, DIBAL-H, CH_2Cl_2, −15 °C; vi, trichloroacetonitrile, NaH (60 mol%), Et_2O, room temp.; vii, heat at 150 °C, toluene (in a sealed tube), 89 h; viii, TFA–H_2O (3 : 2), 0 °C; ix, $NaIO_4$, MeOH–H_2O (1 : 1), room temp.; x, $NaBH_4$, MeOH, 0 °C

(decomp.), $[\alpha]_D^{25}$ + 71.3 (*c* 0.5, MeOH)}, as well as spectroscopic data for **1** (^1H and ^{13}C NMR) showed good agreement with those reported for the natural product.[2a]



Scheme 2 *Reagents and conditions*: i, *tert*-butyldimethylsilyl trifluoromethanesulfonate, 2,6-lutidine, CH_2Cl_2, room temp.; ii, Na, liq. NH_3–THF, −78 °C; iii, Me_2SO, DCC, TFA, pyridine, benzene, room temp.; iv, isopropylmagnesium bromide, THF, −20 °C to room temp.; v, triisobutylaluminium, CH_2Cl_2–hexane, 0 °C; vi, TFA–H_2O (4 : 1), 50 °C; vii, O_3, CH_2Cl_2, −78 °C, then Me_2S; viii, $NaClO_2$, NaH_2PO_4, $HOSO_2NH_2$, *tert*-butanol–H_2O, room temp.; ix, bis(2-oxo-3-oxazolidinyl)phosphonic chloride, *N*-acetyl-L-cysteine allyl ester, Et_3N, CH_2Cl_2, 0 °C to room temp.; x, $Pd(PPh_3)_4$, HCO_2H, Et_3N, THF, room temp.

This work provides a novel pathway to lactacystin which should be applicable to the syntheses of its analogues and proved that Overman rearrangement of allylic trichloroacetimidates derived from carbohydrates should be an effective method for the chiral synthesis of α,α′-disubstituted amino acid derivatives.

We thank Professors Satoshi Omura and Toshiaki Sunazuka (The Kitasato Institute, Tokyo, Japan) for providing us with spectral data of natural lactacystin and their synthetic intermediates, and for helpful information. We also thank Professor Amos B. Smith III (University of Pennsylvania, USA) for valuable discussions. Financial support from the Uehara Memorial Foundation is gratefully acknowledged.

Received, 16th January 1995; Com. 5/00269I

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