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A convenient approach to an advanced intermediate for (+)-lactacystin synthesis

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ABSTRACT

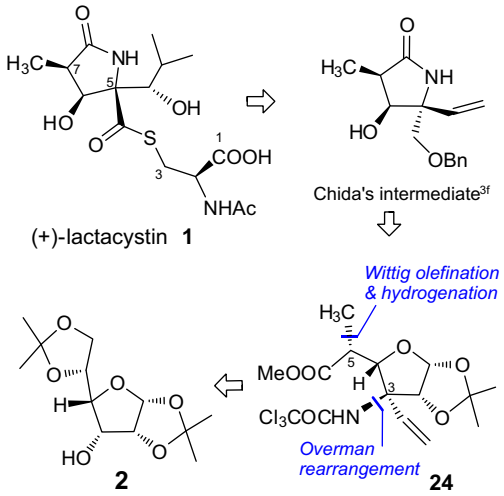
A fully stereoselective preparation of the advanced intermediate **24** for the synthesis of (+)-lactacystin from known 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (**2**), as the source of chirality, has been achieved. The C-5 methyl group was introduced via a Wittig olefination followed by Pd/C-mediated hydrogenation of the conformationally restricted alkene **11** in a highly stereoselective manner. The stereogenic tetrasubstituted carbon centre at C-3, with an amino group, was installed stereoselectively via an Overman rearrangement, which was efficiently controlled by a saccharide environment.

(+)-Lactacystin (**1**) (Scheme 1) is a secondary metabolite that was isolated from a *Streptomyces* strain by Ōmura et al. in 1991 during a screening programme to detect small molecules with nerve growth factor-like activity.[1] This complex amino acid natural product was found to be a specific inhibitor of the 20S proteasome in mammalian and bacterial cells.[2] Its remarkable biological activity and the structural features have made (+)-lactacystin an attractive target for synthetic chemists, and a number of total syntheses of **1** have been reported.[3] The asymmetric installation of the nitrogen-bearing quaternary stereocentre presents the most significant challenge.[4]

Our previous success with the preparation of α-substituted α-amino acids[5] from sugar templates suggested that an aza-Claisen rearrangement of the structurally appropriate chiral allylic imidates and thiocyanates would effectively install a densely functionalized quaternary carbon adjacent to nitrogen. In continuation of the aforementioned study, we decided to extend our methodology to other chiral scaffolds and illustrate its potential for a diastereoselective approach to (+)-lactacystin and its congeners.

In the present paper we describe a practical route to advanced intermediate **24** towards (+)-lactacystin synthesis, in which the stereogenic tetrasubstituted carbon (C-5) with a nitrogen and a methyl group at C-7 were installed with a high level of stereocontrol using the Overman rearrangement, accompanied by a tandem Wittig reaction/hydrogenation of the resulting conformationally restricted substrate. Our strategy is based on the retrosynthetic plan outlined in Scheme 1.

The synthesis of (5*S*)-5-deoxy-1,2-*O*-isopropylidene-5-*C*-methyl-β-L-*lyxo*-hexofuranose (**15**), the key synthon in our route, is presented in Scheme 3. The known 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose[6] (**2**) served as the starting material and was prepared on a large scale applying modifications of the combined literature protocols.[6] The remaining hydroxyl group at the C-3 position in **2** was protected as the corresponding *tert*-butyldimethylsilyl ether using TBDMSCl and imidazole in dry DMF to



Scheme 1. Retrosynthesis of (+)-lactacystin.

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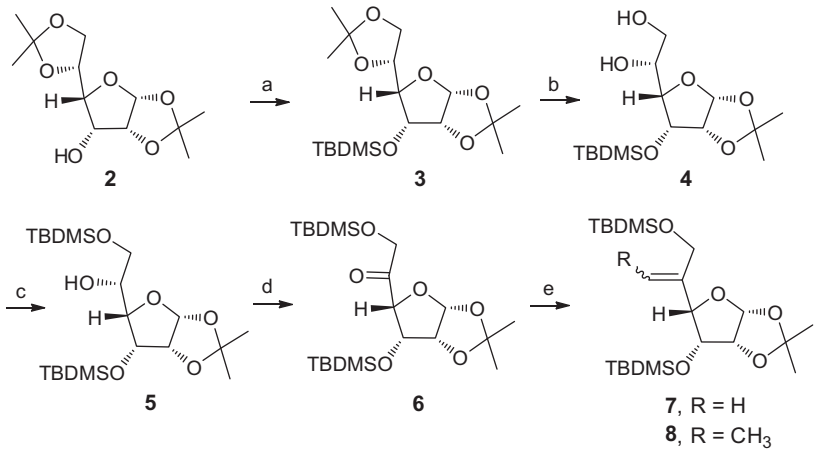
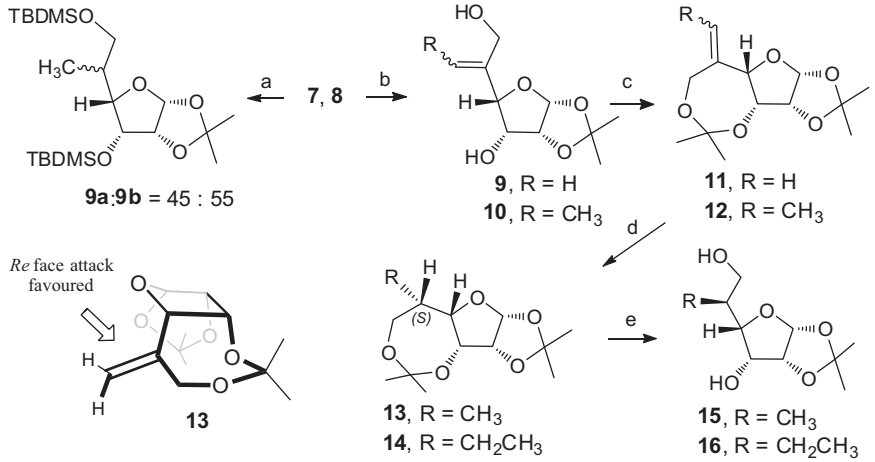


Scheme 2. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, 70 °C, 22 h, 99%; (b) 60% AcOH, 40 °C, 35 min, 91%; (c) TBDMSCl, Et_3N, DMAP CH_2Cl_2, rt, 22 h, 98%; (d) IBX, CH_3CN, 3 h, 88%; (e) CH_3PPh_3I, *n*-BuLi, THF, −75 °C → 20 °C, 5 h, **7**, 90%; or $CH_3CH_2PPh_3I$, **8**, 85%.

furnish **3** in 99% yield (Scheme 1). Subsequently, the 5,6-*O*-isopropylidene moiety in **3** was removed chemoselectively by treatment with 60% aqueous AcOH at 40 °C providing diol **4** (91%). The primary hydroxyl functionality present in **4** was silylated selectively with TBDMSCl in CH_2Cl_2 in the presence of Et_3N and DMAP to afford **5** in 98% yield. Oxidation of **5** with IBX[6] in acetonitrile resulted in the formation of ketone **6** (88%, Scheme 2), which was then treated with the unstabilized ylide derived from methyltriphenylphosphonium iodide (CH_3PPh_3I) using *n*-BuLi as the base in THF to afford alkene **7** in 90% yield. Applying the same conditions, the Wittig olefination of **6** with ethylidenetriphenylphosphorane provided an inseparable mixture of *cis*/*trans* isomers **8** in 85% yield.

Having prepared substrates **7** and **8**, our next task was to develop a suitable procedure for the stereoselective reduction of their C=C functionalities. The catalytic hydrogenation of **7** using conventional conditions (H_2, Pd/C) turned out to be ineffective and led to a mixture of the corresponding diastereoisomers **9a** and **9b** (**9a**:**9b** ≈ 45:55) in 91% yield. To overcome this poor diastereoselectivity, we prepared the conformationally restricted alkenes **11** and **12** in which the double bond is mainly accessible from the *Re* side (Scheme 3). Thus, exposure of both olefins **7** and **8** to tetrabutylammonium fluoride in THF resulted in cleavage of the *tert*-butyldimethylsilyl groups at C-3 and C-5 and gave diols **9** and **10** in 99% and 98% yields, respectively. Subsequent acetonide formation in **9** and **10** using 2,2-dimethoxypropane and a catalytic amount of CSA produced alkenes **11** and **12** in 80% and 86% yields, respectively. Hydrogenation of **11** in the presence of 10% Pd/C in ethanol proceeded from the *Re* face of the double bond providing **13** as the sole diastereoisomer in 91% yield (Scheme 3). The excellent stereoselectivity was attributed to the shielding of the corresponding *Si* face by the sterically bulky saccharide skeleton. All spectroscopic data of **13** were consistent with the obtained structure.[7a] The stereochemistry of **13** was determined by NOE difference experiments. A series of large NOE enhancements between protons H-3, H-4 and H-5 suggested that they all occupied the same face of the tetrahydrofuran core, whilst irradiation of the methyl protons at C-5 resulted in only a 1.37% NOE with proton H-4, and thus confirmed their *trans*-relationship (Fig. 1). The same procedure was also applied for the preparation of **14**, which was obtained in 86% yield (Scheme 3). Our synthetic strategy can also be utilized for the stereoselective installation of various alkyl groups at the C-5 position of the saccharide moiety to enable the preparation of the corresponding analogues of (+)-lactacystin (**1**).

Our next task was to install a densely functionalized quaternary centre with an amino group at the C-3 position of the furanose ring via a stereoselective Overman rearrangement of the corresponding imidate, followed by a deprotection/oxidation protocol



Scheme 3. Reagents and conditions: (a) H_2, 10% Pd/C, Et_3N, EtOH, 0 °C, 6 h, 91%; (b) TBAF, THF, 0 °C → rt, 1 h, **9**, 99%, **10**, 98%; (c) 2,2-dimethoxypropane, CSA, CH_2Cl_2, rt, 1 h, **11**, 80%, **12**, 86%; (d) H_2, 10% Pd/C, Et_3N, EtOH, 0 °C, 6 h, **13**, 91%, **14**, 86%; (e) 10% AcOH, rt, 10 min, **15**, 91%, **16**, 76%.