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A formal synthesis of (+)-lactacystin from 4-hydroxyproline

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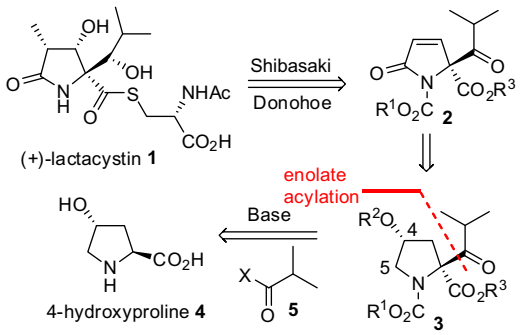
ABSTRACT

A formal synthesis of (+)-lactacystin has been completed from *trans*-4-hydroxyproline, using a diastereoselective enolate acylation reaction as a key step. Diastereoselectivity was seen to vary as a function of the steric bulk of the C4-O-protecting group, and contrary to expectations, the best diastereoselectivities were obtained when the small methyl carbonate protecting group was used. The formal synthesis was then completed by intercepting Shibasaki's route via methyl carbonate deprotection, dehydration, 3-pyrroline to 3-pyrrolinone oxidation, hydrogenation and *N*-CO_2Me deprotection.

The 26S proteasome inhibitor (+)-lactacystin (**1**)[1,2] has been the subject of much synthetic interest and a wide variety of strategies have been employed for its preparation.[3] Stereoselective construction of the embedded α,α-dialkyl-α-amino acid moiety is an essential step in any synthesis of **1**, and we found it surprising that direct functionalization of proline (or proline derivatives) at the α-stereocentre had not been used for this purpose. We therefore decided to examine whether **1** could be accessed from proline derivatives, and these studies have resulted in a new formal synthesis of (+)-lactacystin.

Inspired primarily by the work of Donohoe[3n] and Shibasaki,[3j] disconnection of **1** revealed pyrrolinone **2** as a possible advanced precursor (Scheme 1). We felt that **2** could be accessed from the substituted pyrrolidine **3** via C4-alkoxy group elimination and oxidation at C5. Finally, disconnection of **3** indicated that it could be prepared in a few simple steps from 4-hydroxyproline (**4**), with a diastereoselective enolate acylation reaction being used to construct the α,α-dialkyl-α-amino acid moiety. Although the C2-acylation of 4-hydroxyproline derivatives has not been reported in the literature, Chamberlin has recently demonstrated the utility of C2-acylation of C5-substituted proline derivatives in his total synthesis of keitocephalin,[4] so we were confident that we could develop this chemistry for our purposes. The equivalent C2-alkylation of 4-hydroxyproline derivatives has been examined in some detail,[5] and this work has shown that the level, and sense of diastereocontrol obtained is highly dependent upon both the choice of protecting groups and the electrophile used. Therefore, we began our enolate acylation studies by examining the reactivity of a range of protected 4-hydroxyproline derivatives **6a**–**f**[6] in combination with various acylating agents **5a**–**c**.

Enolate formation from **6a**–**f** was performed using LDA (−78 °C, THF, 2–2.5 h), and we found that addition of the acylating species over a 15 min period was optimal (Table 1). Although acylation was not observed under any conditions with the Weinreb amide **5c**, both the *N*-acyl imidazole **5a** and acid chloride **5b** gave the acylation products **7** and **8** in a variety of yields and diastereomeric ratios. In general, the acid chloride **5b** performs as well, and in some cases better than the *N*-acyl imidazole **5a**, and *N*-CO_2Me protection produces higher yields than *N*-CO_2Bn protection on equivalent examples (cf. entries 2 vs 6 and 3 vs 9, Table 1).[7] Furthermore, the bulky C4-OTBS, -OTIPS and -OBoc groups lead to poor diastereoselectivity (Table 1, entries 1, 2 and 4–7) and the use of a smaller



Scheme 1. Retrosynthetic analysis of lactacystin (**1**).

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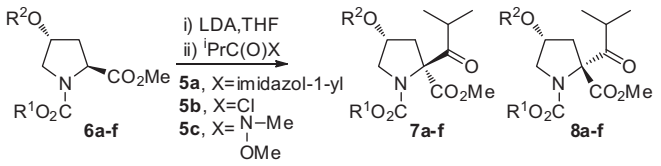
Table 1



Entry	Substrate	R^1	R^2	X	Yield[a] (%)	Ratio **7:8**
1	**6a**	Bn	TBS	Im	47	60:40[b]
2	**6a**	Bn	TBS	Cl	38	71:29[b]
3	**6b**	Bn	CO_2Me	Cl	11	78:22[c]
4	**6c**	Me	TBS	Im	41	55:45[b]
5	**6c**	Me	TBS	Cl	60	56:44[b]
6	**6d**	Me	TIPS	Cl	76	60:40[b]
7	**6e**	Me	Boc	Cl	39	56:44[b]
8	**6f**	Me	CO_2Me	Im	42	88:12[c]
9	**6f**	Me	CO_2Me	Cl	69	83:17[c]

[a] Combined isolated yield.
[b] Ratio of separated products.
[c] Ratio determined by integration of the ^1H NMR spectrum as the products could not be separated by column chromatography.

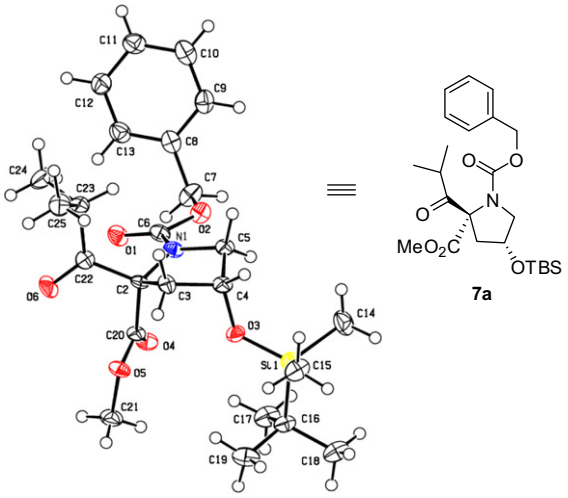
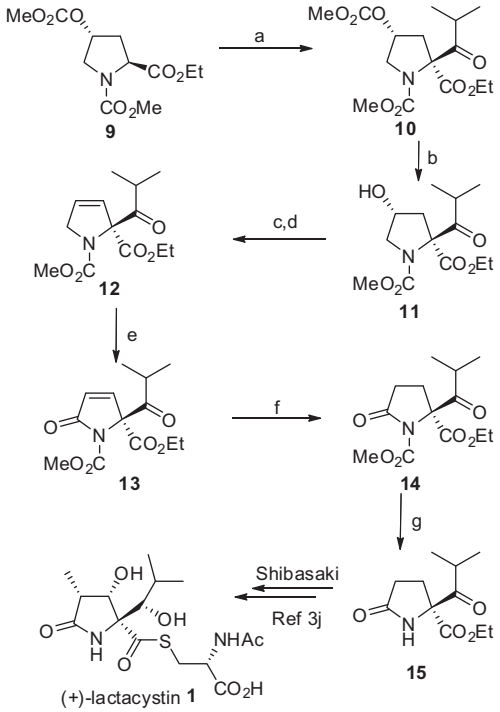


Figure 1. X-ray crystal structure of **7a**.

hydroxyl protecting group (CO_2Me, Table 1, entries 3, 8 and 9) improves the diastereoselectivity. These results show that simple steric hindrance arguments, based upon blocking the α-face with a large group, cannot be used to predict the diastereochemical outcome of the acylation reaction. At first glance, this observation is somewhat surprising, and the X-ray structure of the crystalline product **7a** (Fig. 1) clearly shows that the C4-OTBS substituent provides considerable steric shielding to the lower face of the molecule.

However, further inspection of the X-ray structure of **7a** (Fig. 1) shows that the C2-ester moiety has adopted a pseudo-axial orientation, which places it on the same face as the bulky C4-OTBS group. The steric interaction of the C2-ester and the C4-OTBS is unavoidable if acylation is to occur on what appears to be the 'less hindered' β-face of the molecule, and the only way to avoid this is for acylation to occur on what appears to be the more hindered α-face. In order to favour acylation on the desired β-face therefore, the unfavourable 1,3-interaction between the C2-ester and the C4-protecting group needs to be minimized, and this scenario is satisfied when the C4-protecting group is small (e.g. CO_2Me, entries 8 and 9, Table 1).

Following these results, the best overall acylation reaction, in terms of yield and diastereoselectivity (entry 9, Table 1), was repeated on the corresponding ethyl ester **9**, as this would give quick access to Shibasaki's intermediate to lactacystin **15**.[3j] Thus, acylation of **9** proceeded in acceptable yield to give the desired product **10** as an inseparable 81:19 mixture of diastereoisomers (Scheme 2). The C4-carbonate protecting group was then selectively removed to give alcohol **11** (68%), which could then be separated from the unwanted minor (2*R*,4*R*)-diastereoisomer (4%). This deprotection was particularly satisfying as **10** contains four different carbonyls, each of which could potentially react with LiOH (i.e. ester hydrolysis, carbamate hydrolysis, retro-Claisen condensation) to give a variety of products.



Scheme 2. Reagents and conditions: (a) LDA, THF, −78 °C, 1 h; then ^iPrCOCl, −78 °C, 4 h, 56%; (b) $LiOH{\cdot}H_2O$, EtOH-THF-H_2O (2:2:1), 0 °C, 2.5 h, 72%; (c) PPh_3, I_2, imidazole, CH_2Cl_2, rt, 72 h, 73%; (d) DBU, CH_2Cl_2, rt, 20 h, 82%; (e) pyridine, CrO_3, CH_2Cl_2, rt, 21 h, 84%; (f) H_2, $Pd(OH)_2$, EtOAc, rt, 22 h, 100%; (g) TMSI, CH_2Cl_2, rt, 4 h, 73%.

Having gained access to alcohol **11**, the next synthetic challenge was dehydration to form the 3-pyrroline **12**. Although treatment of **11** with Martin's sulfurane in CH_2Cl_2 gave the desired 3-pyrroline **12**[8] in 53% yield, the isomeric 2-pyrroline product was also formed in 31% yield, and both compounds were contaminated with the diphenylsulfone by-product, which was difficult to remove. Fortunately, hydroxyl to iodide conversion (iodine/PPh_3/imidazole)[9] followed by DBU treatment, gave the desired 3-pyrroline product **12** in good yield as a single regioisomer. Oxidation of **12** using Donohoe's conditions[3n] then gave the desired lactam **13** in good yield. This advanced intermediate was then hydrogenated [H_2, $Pd(OH)_2$] and deprotected [TMSI, CH_2Cl_2] to give Shibasaki's intermediate **15**, whose analytical and spectroscopic data were identical to those reported,[3j] thus completing our formal synthesis of (+)-lactacystin (**1**) (Scheme 2). Work is currently underway in our laboratory to convert the lactam **13** into lactacystin via a new reaction sequence, and these results will be reported in due course.

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Supplementary data

Supplementary data (experimental procedures and characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.076.

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