

Enantioselective total syntheses of (–)-*clasto*-lactacystin β-lactone and 7-*epi*-(–)-*clasto*-lactacystin β-lactone†

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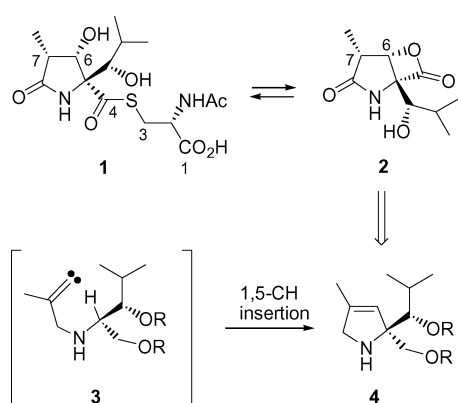
An alkylidene carbene 1,5-CH insertion has been used as a key step in an efficient enantioselective total synthesis of (–)-*clasto*-lactacystin β-lactone, and its C7-epimer. An additional noteworthy feature of the synthesis is the use of a novel oxidative deprotection procedure, utilizing DMDO, for the conversion of a late-stage benzylidene acetal into a primary alcohol and a secondary benzoate ester.

(+)-Lactacystin **1** was isolated from the bacterial strain, *Streptomyces* sp. OM-6519 by Ōmura in 1991 during a screening program for small molecule mimics of nerve growth factors.¹ Lactacystin was later found to be a specific inhibitor of the 20S proteasome found in mammalian and bacterial cells.² The proteasome is responsible for the normal turnover of cellular proteins and degradation of damaged and mutated proteins, and **1** has played a vital role in the study of its function. The remarkable biological activity and intriguing structure of **1** has sparked continued interest over the last 13 years and a number of syntheses have been published to date.³ Lactacystin **1** spontaneously and reversibly forms (–)-*clasto*-lactacystin β-lactone (also known as omuralide) **2** in the extracellular medium, and it is this β-lactone that penetrates the cell and acylates an active site threonine residue, leading to inhibition of the proteasome (Scheme 1). As well as serving as the biologically active form of lactacystin **1**, *clasto*-lactacystin β-

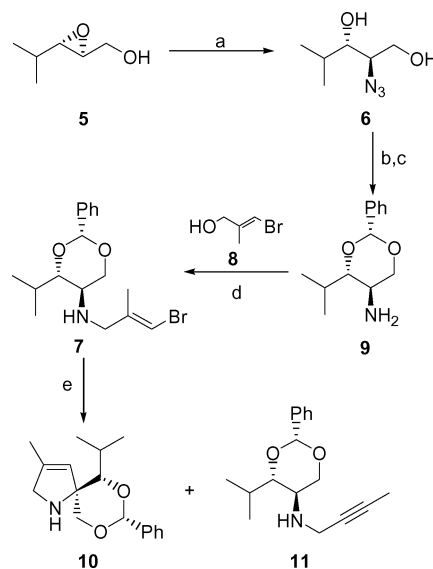
lactone **2** has also served as a synthetic precursor to the natural product **1** itself, and the enantioselective synthesis of **2** has become an important synthetic challenge in its own right.

In 2002 we reported a formal synthesis of (+)-lactacystin **1**,⁴ which used a highly stereoselective alkylidene carbene 1,5-CH insertion reaction as a method to construct the key quaternary stereocentre.^{5,6} In this first generation route we utilized TBS-protecting groups during the CH-insertion step (*vis* **3** → **4**, R = TBS), but in order to mitigate unexpected problems during scale-up we chose to explore an alternative protecting group strategy in a second generation route to **1** and **2**. As the TBS-protecting groups on **3** (Scheme 1) created a highly hindered environment at the site of CH-insertion, we chose to explore the possibility of protecting the 1,3-diol moiety in **3** as a benzylidene acetal. During the preparation of this manuscript, Wardrop independently reported an alkylidene carbene 1,5-CH-insertion approach to **1**,⁷ following an identical approach to that outlined in Scheme 1, which also uses a benzylidene acetal to protect the diol moiety in **3** and **4**. We now wish to report our own results in this area, which have led to a second generation enantioselective total synthesis of *clasto*-lactacystin β-lactone **2** as well as its C7-epimer **22**.

The key vinyl bromide CH-insertion precursor **7** was readily prepared in 4 steps from epoxy alcohol **5** according to the route shown below (Scheme 2).



Scheme 1



Scheme 2 Reagents and conditions: (a) NaN₃, B(OMe)₃, DMF, 50 °C (77%); (b) PhCH(OMe)₂, PPTS, C₆H₆, reflux (78%); (c) H₂, Lindlar cat., MeOH, 20 °C (100%); (d) MnO₂, **8**, DCM, 4 Å mol. sieves, reflux, then NaCNBH₃, AcOH, MeOH, 0 °C (75%); (e) KHMDS, THF, –30 °C (83%).

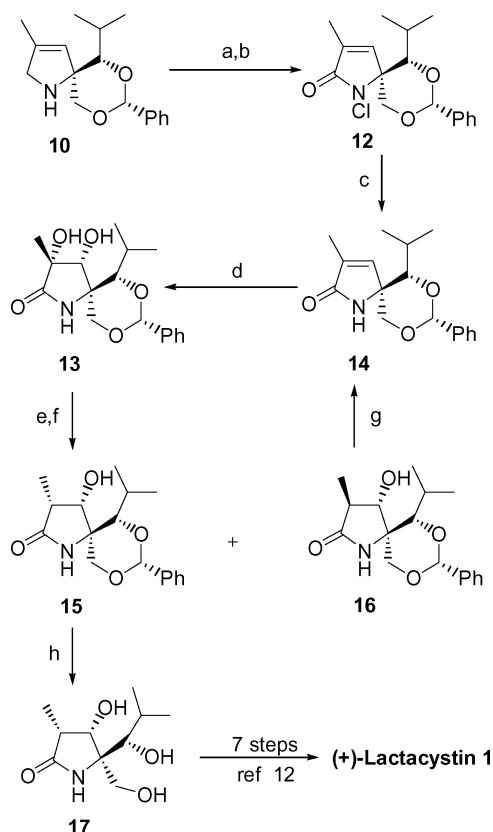
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Thus treatment of the known epoxide **5** under Miyashita's conditions⁸ gave 2-azido-1,3-diol **6** in 77% yield. Acetal protection and hydrogenation next gave the amine **9** in good yield. One-pot MnO₂ oxidation, imine formation and reduction, as described by Taylor,⁹ finally provided the (*E*)-vinyl bromide cyclisation precursor **7** as a single isomer in 59% yield over 3 steps. After careful optimization, exposure of **7** to an excess (2 equiv.) of KHMDS in THF at -30 °C gave the desired 3-pyrroline **10** in a very pleasing 83% isolated yield. The cyclisation of **7** to **10** was also accompanied by the formation of the corresponding but-2-ynyl-amine **11** (13% yield), but this byproduct could be easily removed by column chromatography.

Having secured an efficient route to the 3-pyrroline **10**, we next needed to install the additional oxygenation and remaining stereocentres present in **1** and **2**. Thus, oxidation with TPAP-NMO, and then sodium chlorite first gave the *N*-chlorolactam **12** and treatment with sodium borohydride then provided the desired 3-pyrrolinone **14** in 76% over 3 steps.¹⁰ Dihydroxylation was then accomplished using Sharpless's modified UpJohn conditions¹¹ which cleanly afforded the diol **13** as a single, crystalline diastereoisomer in 96% yield. Formation of the cyclic thiocarbonate, followed by selective deoxygenation with ^tBu₃SnH and AIBN¹² then gave a separable 1 : 3.6 mixture of the **15** and **16** in 94% combined yield (Scheme 3).

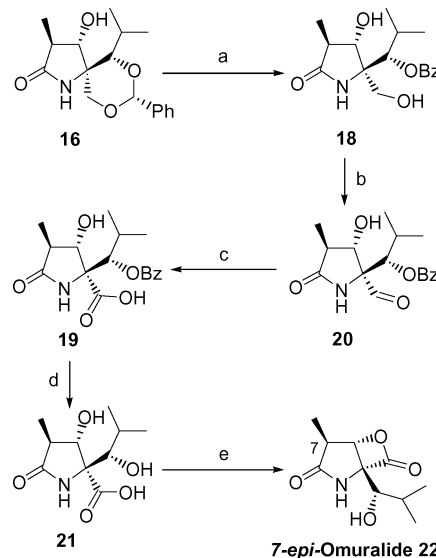


Scheme 3 Reagents and conditions: (a) TPAP, NMO, MeCN, 4 Å mol. sieves (93%); (b) NaClO₂, NaH₂PO₄·2H₂O, 2-methyl-2-butene, ^tBuOH, H₂O, 0 °C; (c) NaBH₄, MeOH, 20 °C (84% over 2 steps); (d) K₂OsO₂(OH)₄, NMO, citric acid, ^tBuOH-H₂O (1 : 1), 20 °C (96%); (e) thiocarbonyl diimidazole, THF, reflux (100%); (f) ^tBu₃SnH, AIBN, toluene, reflux (94%); (g) NaOMe, MeOH; (h) H₂, Pd/C, HCl, MeOH (93%).

Although base-mediated epimerisation of the undesired diastereoisomer **16** proved difficult to achieve in high yield, we found that **16** could be transformed into the 3-pyrrolinone **14** by treatment with NaOMe-MeOH, hence providing a high yielding (90%) method of recycling material through to the desired *cis*-isomer **15**.

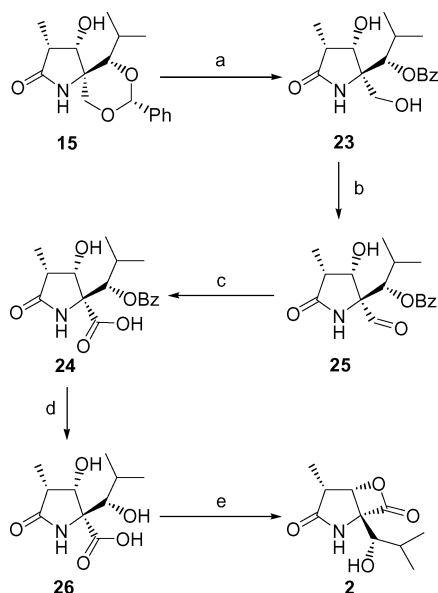
Once we had access to **15**, we were able to complete a formal synthesis of **1** by conversion to the known triol **17** by standard catalytic hydrogenation in 93% yield (Scheme 3). Whilst we were pleased with this initial success, we were aware that 7 steps were still required to convert **17** into the natural product **1**, and we therefore hoped to shorten this sequence by developing a selective deprotection-oxidation strategy from lactam **15**.

As we had access to both **15** and **16**, we first decided to investigate this new 'end-game' approach on the more abundant *trans*-isomer **16** (Scheme 4). Thus, treatment of the benzylidene acetal **16** with DMDO (dimethyldioxirane) caused a selective, oxidative-deprotection to give the alcohol-ester **18**, as a single regioisomer, in quantitative yield.¹³ This remarkable deprotection reaction gives both a free primary alcohol and protected secondary alcohol in one convenient transformation. Selective oxidation of the primary alcohol in **18** to the acid **19** was achieved using sequential Dess-Martin periodinane (63%) and sodium chlorite (81%) oxidations. Deprotection of **19** and formation of the β-lactone by treatment with BOPCl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride) finally afforded 7-*epi*-clasto-lactacystin β-lactone **22**. The spectroscopic data of **22** were identical to those reported by Corey for this compound.¹⁴



Scheme 4 Reagents and conditions: (a) DMDO (3 equiv., 0.06 M), acetone, 0 °C (100%); (b) Dess-Martin periodinane, DCM, 20 °C (63%); (c) NaClO₂, NaH₂PO₄·2H₂O, HOSO₂NH₂, ^tBuOH, H₂O, 20 °C (81%); (d) NaOMe, MeOH, 20 °C (78%); (e) BOPCl, Et₃N, DCM, 20 °C (38%).

Having completed the synthesis of **22**, we then turned our attention to repeating the same chemical steps on the correct diastereoisomer isomer **15** required for the synthesis of (+)-lactacystin **1** (Scheme 5). Thus, selective deprotection according to our newly developed procedure cleanly gave the alcohol-ester



Scheme 5 Reagents and conditions: (a) DMDO (3 equiv. 0.06 M), acetone, 0 °C (90%); (b) Dess-Martin periodinane, DCM, 20 °C (35%); (c) NaClO₂, NaH₂PO₄·2H₂O, HOSO₂NH₂, ^tBuOH, H₂O, 20 °C (95%); (d) NaOMe, MeOH, 20 °C (74%); (e) BOPCl, Et₃N, DCM, 20 °C (45%).

23 in 75% yield. Sequential Dess-Martin periodinane (35%) and sodium chlorite (95%) oxidations then gave the acid **24**. Pleasingly, the ester **24** could be saponified to afford the previously reported acid **26**, which was then converted to *clasto*-lactacystin β-lactone **2** using the known procedure.¹⁵

In summary, we have developed a second generation synthesis of **1** and **2** using an alkylidene carbene 1,5-CH insertion reaction as a key step, and during this work we have also completed a total synthesis of the recently described proteasome inhibitor 7-*epi-clasto*-lactacystin β-lactone **22**. In addition to developing novel methodology for the construction of quaternary stereocentres, we have also utilised a novel procedure for the selective oxidative deprotection of benzylidene acetals using DMDO and we are currently exploring the wider synthetic utility of this particular transformation.

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