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# An enantioselective formal synthesis of the proteasome inhibitor (+)-lactacystin

Martin P. Green,[a] Jeremy C. Prodger[b] and Christopher J. Hayes[a,*]

[a]*The School of Chemistry, The University of Nottingham, University Park, Nottingham NG7 2RD, UK*
[b]*GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK*

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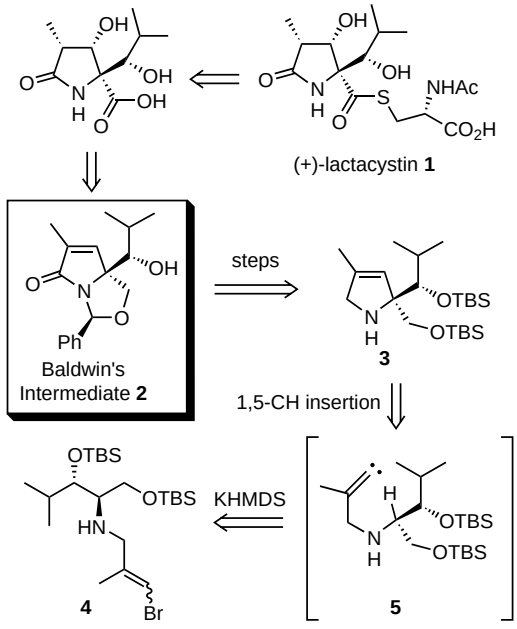
**Abstract**—An enantioselective formal synthesis of the proteasome inhibitor (+)-lactacystin has been achieved using an alkylidene carbene 1,5-CH insertion reaction as a key step. The key cyclisation precursor was synthesised in high diastereomeric excess using a combination of known procedures, with the two key asymmetric centres being introduced via a Sharpless asymmetric epoxidation reaction. KHMDS induced 1,5-CH insertion produced a 3-pyrroline product, which was oxidised to the corresponding 3-pyrrolin-2-one using (1) TPAP/NMO; (2) $NaClO_2$; (3) $NaBH_4$. The formal synthesis was then completed with a few standard functional group interconversions. © 2002 Published by Elsevier Science Ltd.

(+)-Lactacystin (**1**) was isolated from the fermentation broth of *streptomyces* sp. OM-6519 and first attracted interest due to its ability to inhibit cell proliferation and induce neurite outgrowth in the mouse neuroblastoma cell line Neuro 2A.[1] It was subsequently shown that the 20S proteasome was the cellular target of lactacystin,[2] and since this discovery **1** has been used as a tool to study proteasome function. The interesting biological activity and intriguing chemical structure of **1** soon stimulated interest from the synthetic organic chemistry community. Corey and Reichard published the first total synthesis of **1** in 1992[3] and their approach used Seebach-type oxazolidine chemistry to construct the key α,α-dialkyl-α-amino acid moiety. During the following year, Smith et al. published their total synthesis of **1**.[4] Similarly, their route used Seebach-type chemistry to synthesise the α,α-dialkyl-α-amino acid moiety. In 1994, Baldwin et al. successfully completed another synthesis of **1** using a diastereoselective Mukaiyama-type aldol reaction as a key step.[5] Since these early reports, a number of alternative syntheses of **1** have been published,[6] and with the exception of Chida's and Kang's approaches,[7] diastereoselective aldol-type reactions have been employed to construct the quaternary centre (Scheme 1).

Over the last few years, we have been interested in the development of methods for the enantioselective construction of nitrogen-bearing stereocentres, and we have shown that alkylidene carbene 1,5-CH insertion reactions can be used for this purpose.[8] As part of this work, we recently reported our studies on the construction of 3-pyrrolines[9] and we now wish to show how this methodology can be used to complete an enantioselective formal synthesis of **1**.[10]




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

* Corresponding author. Tel.: +44-(0)115-951-3045; fax: +44-(0)115-951-3564; e-mail: chris.hayes@nottingham.ac.uk

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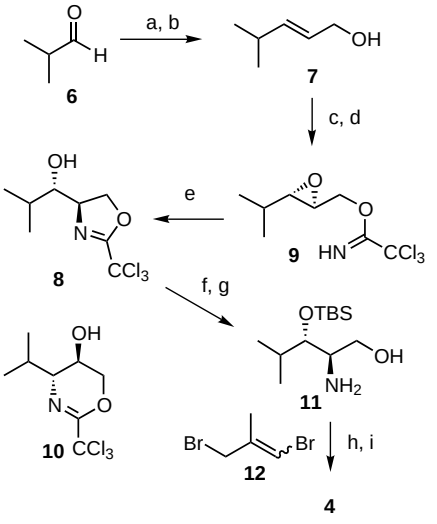
During their total synthesis of **1**, Baldwin et al. showed that the 3-pyrrolin-2-one **2** could be used as a key synthetic intermediate. In contrast to the route chosen by Baldwin et al., we felt that **2** could be accessed from a suitably functionalised 3-pyrroline **3** via a few functional group interconversions. Further disconnection of **3**, via the alkylidene carbene **5**, revealed the 1-bromo-1-alkene **4** as a potential acyclic precursor.

In order to examine the key 1,5-CH insertion reaction, we first had to develop an efficient synthesis of the amine **4** (Scheme 2). Hatakeyama et al. had previously reported the enantioselective synthesis of the oxazoline **8** and we felt that this would be an excellent precursor to **4**. Thus, the *E*-allylic alcohol **7**[11] was synthesised from isobutyraldehyde **6** with excellent stereochemical integrity, and Sharpless asymmetric epoxidation of **7** next afforded the corresponding epoxide in high enantiomeric excess (>95% ee).[12] Formation of the trichloroacetimidate **9**[13] and Lewis acid-mediated ring closure then afforded the oxazoline **8**.[14] In our hands, the isomeric 5-membered **8** and 6-membered **10** heterocycles were obtained in a 5:1 ratio during this cyclisation, but the major isomer **8** was readily separated from **10** by column chromatography and could be isolated in 70% yield as a single diastereoisomer.

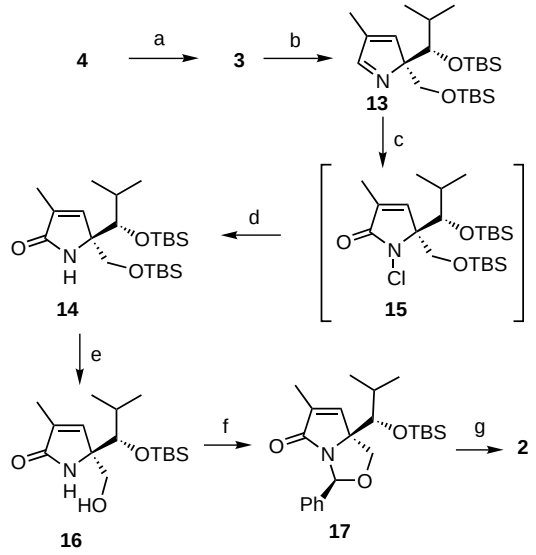
Protection of the secondary hydroxyl in **8** was achieved in near quantitative yield by exposure to TBSOTf, $Et_3N$ in $CH_2Cl_2$, and acid-mediated hydrolysis then afforded the amino alcohol **11** in excellent yield. Selective protection of the primary hydroxyl, and caesium hydroxide-mediated mono-alkylation[15] of the primary amine with **12** (2.3:1, *E*:*Z*)[16] finally produced the desired 1,5-CH insertion precursor **4** as a 2.3:1 mixture of *E*:*Z* isomers.




**Scheme 2.** *Reagents and conditions*: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 0°C (97%); (b) DIBAL-H, THF, −78°C (62%); (c) $Ti(^iPrO)_4$, (+)-DET, $^t$BuOOH (in PhMe), DCM, −20°C (94%); (d) $Cl_3CCN$, DBU, DCM, 0°C (90%); (e) $Et_2AlCl$, DCM, −10°C (70% **8**); (f) TBSOTf, $Et_3N$, DCM, 0°C (98%); (g) HCl (2 M), THF, rt (97%); (h) TBSOTf, $Et_3N$, DCM, 0°C (73%); (i) $CsOH{\cdot}H_2O$, **12**, DMF (72%).

Having established a reliable route to the key cyclisation precursor **4**, we were now ready to examine the key 1,5-CH insertion reaction. Pleasingly, treatment of **4** with KHMDS (2 equiv.) in $Et_2O$[17] resulted in the formation of the desired 3-pyrroline **3** as the major new product (49%)[9,18] (Scheme 3). Analysis of both the $^1H$ and $^{13}C$ NMR spectra of this material confirmed that only one diastereoisomer of the product had been formed, thus showing that the 1,5-CH insertion reaction had proceeded in a highly stereoselective manner. In order to complete a synthesis of Baldwin's intermediate **2**, the last significant synthetic challenge was oxidation of the 3-pyrroline **3** to the corresponding 3-pyrrolin-2-one **14**.

According to our previously developed procedure, **3**[19] was oxidised with TPAP/NMO to afford the cyclic imine **13** (85%) and further oxidation with sodium chlorite then afforded the *N*-chlorolactam **15**. Due to the instability of this material to column chromatography, the *N*-chlorolactam was treated with sodium borohydride and the desired 3-pyrrolin-2-one **14** could be isolated in 73% yield for the two steps. Exposure of **14** to 1 equiv. of TBAF resulted in selective deprotection of the primary TBS ether to afford the alcohol **16**, and aminal formation under standard conditions[20] then afforded the bicyclic lactam **17** as a single diastereoisomer. TBAF-mediated deprotection of **17** produced the desired secondary alcohol **2**, whose data matched that reported by Baldwin et al., thus completing a formal synthesis of (+)-lactacystin **1**. Studies directed at completing a new, shorter total synthesis of **1** from the 3-pyrroline intermediate **3** are currently underway, and the results of this study will be published in due course.




**Scheme 3.** *Reagents and conditions*: (a) KHMDS (0.5 M in PhMe, 2 equiv.), $Et_2O$ (49%); (b) TPAP, NMO, MeCN (85%); (c) $NaClO_2$, $NaH_2PO_4$, $^t$BuOH/$H_2O$; (d) $NaBH_4$, MeOH (73%, two steps); (e) TBAF, THF (87%); (f) $PhCH(OMe)_2$, TsOH, PhMe, Δ (67%); (g) TBAF, THF (66%).

## Acknowledgements

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