An Enantioselective Formal Synthesis of (+)-Lactacystin from Hydroxymethyl Glutamic Acid (HMG)

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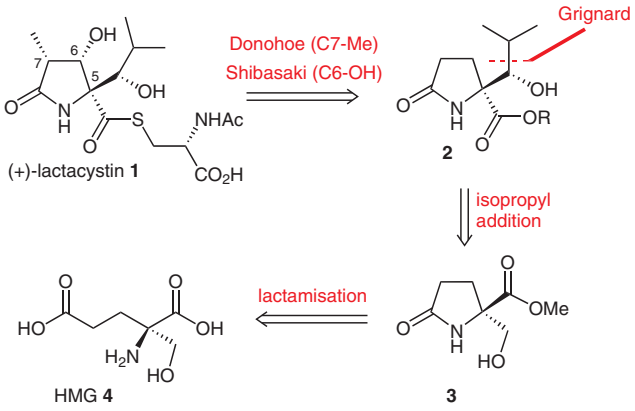
Dedicated to Professor Gerald Pattenden in honour of his many outstanding contributions to organic chemistry

Abstract: A formal synthesis of (+)-lactacystin from hydroxymethylglutamic acid (HMG), with an alkylidene carbene insertion reaction being used to construct the key nitrogen-bearing quaternary centre has been completed. Our route intercepts that of Shibasaki at an advanced pyrrolidinone intermediate, from which the synthesis can be completed following Donohoe's route.

Key words: Lactacystin, hydroxymethyl glutamic acid, alkylidene carbene, CH insertion

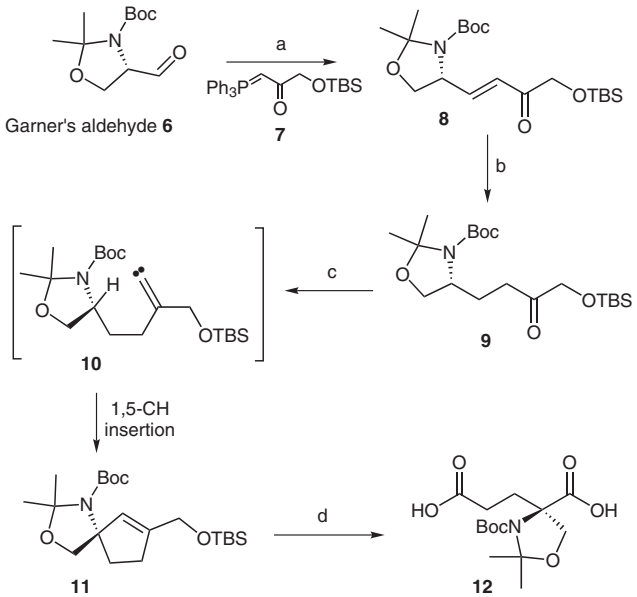
The 26S proteasome inhibitor (+)-lactacystin (**1**)[1,2] has become a classic target for total synthesis and a large number of synthetic studies on this molecule have been reported to date.[3] In this Letter we describe our most recent work on the synthesis of this biologically important target, which has resulted in an enantioselective formal synthesis of **1**.



Scheme 1 Retrosynthetic analysis of lactacystin **1**

Our retrosynthetic analysis of lactacystin (**1**) is shown in Scheme 1. After disconnection of the *N*-acetyl cysteine side-chain, we first chose to remove the methyl group at C7. In our previous synthetic approach to **1**, we experienced difficulties installing this substituent with a high degree of stereocontrol,[4] so in our revised route we chose to utilize Donohoe's excellent method of late-stage enolate alkylation[5] for methyl group introduction. Further disconnection of the C6-hydroxy group using Shibasaki's method[6] revealed the lactam **2** (hereafter referred to as Shibasaki's intermediate) as an advanced precursor to **1**. The isopropyl group in **2** could be installed through a Grignard addition to a suitably functionalized derivative of lactam **3**, with the latter being derived from hydroxymethyl glutamic acid (HMG; **4**) through simple lactamisation.[7]

Although a number of alternative methods exist for the enantioselective preparation of HMG,[8] we chose to use our previously developed synthesis, which utilizes an alkylidene carbene 1,5-CH insertion reaction to install the key nitrogen-bearing quaternary stereocentre (Scheme 2).[9]



Scheme 2 *Reagents and conditions*: (a) CH_2Cl_2, **7**, r.t., 5 d, 83%; (b) H_2, Pd/C, EtOAc, 17 h, 86%; (c) $TMSCHN_2$, THF, *n*-BuLi, –78 °C to r.t., 90 min, 63–69%; (d) $RuCl_3$, $NaIO_4$, MeCN, H_2O, CCl_4, r.t., 88%.

The chemistry shown in Scheme 2 was performed on a multi-gram scale and gave access to large quantities of the protected HMG derivative **12** for use in the synthesis of **1**. Formation of lactam **3** was then achieved by formation of the dimethyl ester **13**,[10] which was then deprotected using sulfuric acid in methanol to afford a nearly equimolar mixture of the ammonium salt **14** and the desired lactam **3** (Scheme 3). This mixture could easily be converted into

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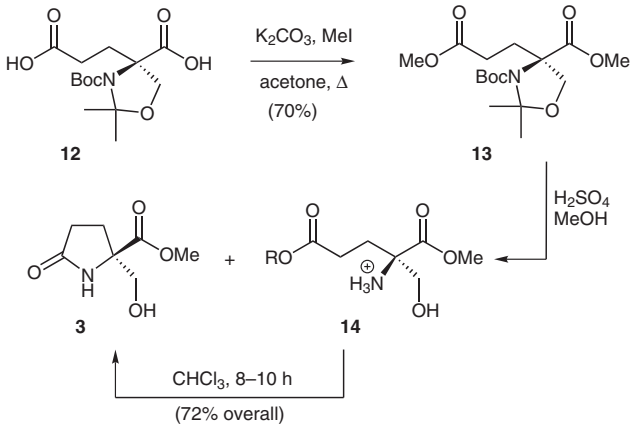
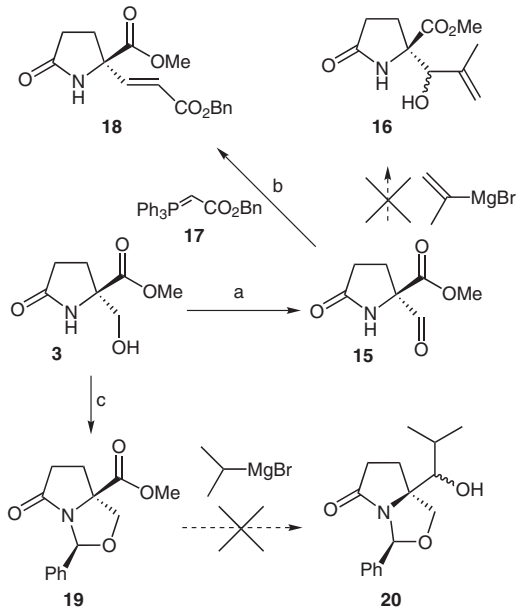
essentially pure **3** in good yield (72%) by simply heating the mixture at reflux in chloroform for 8–10 hours.



Scheme 3

With significant quantities of **3** in hand, we could then examine installation of the isopropyl side-chain. Although this particular batch of **3** was in the wrong enantiomeric series, we decided to explore a very direct method for accessing *ent*-Shibasaki's intermediate (**16**) by adding an organometallic reagent (i.e. Grignard reagent) to aldehyde **15**. Unfortunately the aldehyde **15** proved to be difficult to handle, and we could only produce trace amounts of the desired product **16**. We were confident that the problem lay in the organometallic addition (**15**→**16**) rather than the oxidation step (**3**→**15**), because a Wittig reaction on the crude oxidation product **15**, using the stabilized ylide **17**, afforded the expected product **18** in reasonable overall yield (59%, 2 steps).



Scheme 4 *Reagents and conditions*: (a) DMP, CH_2Cl_2; (b) $Ph_3PCH_2CO_2Bn$, r.t., 3 d (59%, over 2 steps); (c) $PhCH(OMe)_2$, $TsOH{\cdot}H_2O$, toluene, reflux, 100%.

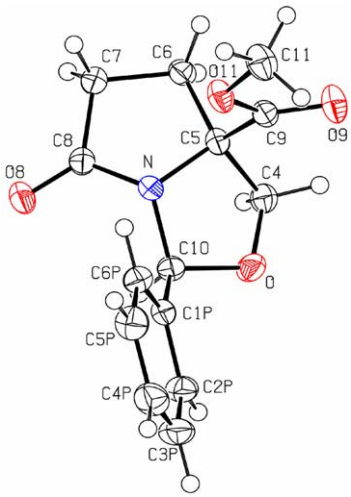


Figure 1 X-ray crystal structure of aminal **19**

A variety of protecting group strategies (Boc, PMB and TBS) were explored (data not shown) in order to overcome this reactivity problem but, unfortunately, no adequate solution could be found. We therefore returned our attention to using the ester present in lactam **3** as the electrophilic centre for isopropyl addition. Thus, *N*,*O*-benzylidene aminal protection of **3** under standard conditions afforded the desired product **19** as a single diastereoisomer. The relative stereochemistry of **19** was confirmed unambiguously by single crystal X-ray diffraction (Figure 1).[11] Direct addition of the isopropyl group to **19** using Kang's method[12] [*i*-PrMgBr (0.5 M in THF), THF, –20 °C to r.t.] unfortunately failed (**19**→**20**; Scheme 4); however, we were able to adopt a stepwise procedure that ultimately led to the desired product (Scheme 5).

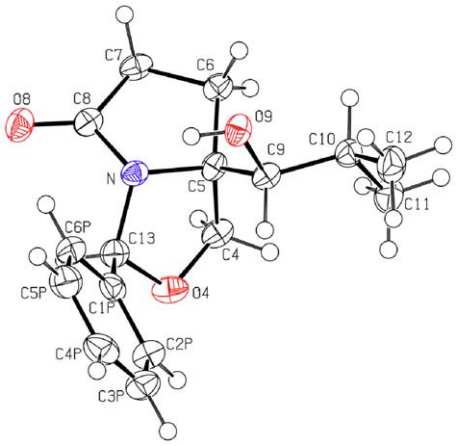
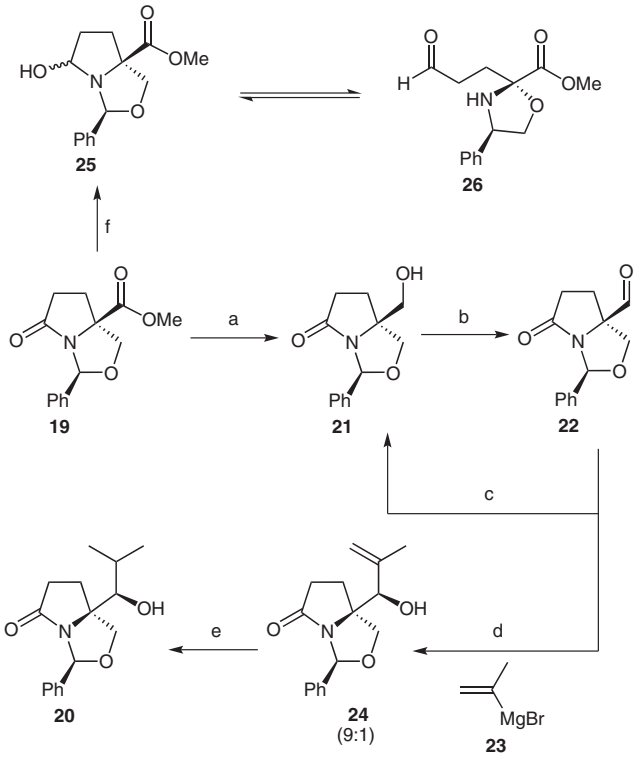


Figure 2 X-ray crystal structure of aminal **20**

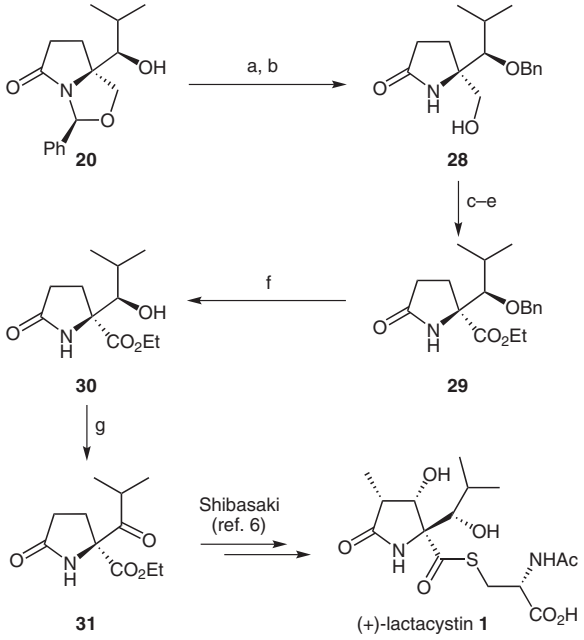
Initial attempts to prepare aldehyde **22** directly from **19** were frustrated by the fact that the lactam carbonyl in **19** was preferentially reduced with DIBAL-H to afford the hemiaminal **25** (and its ring-opened form **26**, as judged by ^1H NMR) in excellent yield. Sodium borohydride ($NaBH_4$, MeOH/THF), however, cleanly reduced the ester to afford the desired alcohol **21** (93%), which was then



Scheme 5 *Reagents and conditions*: (a) $NaBH_4$, MeOH–THF (1:1), 0 °C, 3 h, 93%; (b) DMP, CH_2Cl_2, 2 h, 75%; (c) *i*-PrMgBr (0.5 M in THF), THF, –20 °C to r.t., 38% (**21**) / 35% (**22**); (d) **23** (0.5 M in THF), THF, –78 °C, 5 h, 60% (+ recovered starting material); (e) Pd/C, H_2, EtOH, 2 d, 85%; (f) DIBAL-H, THF, –78 °C, 100%.

oxidized to **22** using Dess–Martin periodinane[13] (75%). Attempted addition of the isopropyl Grignard to **22** led only to reduction (**22**→**21**; Scheme 5), so the isopropyl group was added using Corey's two-step sequence[14] (isopropenyl Grignard addition followed by catalytic hydrogenation), to afford **20** as the major new product. Single crystal X-ray diffraction analysis confirmed the stereochemistry at the newly formed carbinol stereocentre (Figure 2).

The final stages of the formal synthesis of lactacystin (**1**) were completed as shown in Scheme 6 using standard functional group manipulations. Thus, alcohol **20** was protected as its benzyl ether and the aminal was deprotected under Moloney's conditions.[15] The resulting primary alcohol **28** was oxidised (Dess–Martin periodinane then $NaClO_2$) to the corresponding carboxylic acid, which was then esterified (EtI/K_2CO_3) to give ester **29** in good yield (61% over 3 steps). Deprotection of the benzyl group (Pd/C, H_2, EtOH) gave the secondary alcohol **30**, which was oxidised with Dess–Martin periodinane to produce the desired ketone **31**, whose analytical and spectroscopic data were identical to those of the compound synthesised by Shibasaki,[5] thus completing our own formal synthesis.



Scheme 6 *Reagents and conditions*: (a) BnBr, TBAI, NaH (60% in oil), THF, reflux, 15 h, 51% (+ recovered starting material); (b) propanedithiol, CF_3CH_2OH+HCl (1.5% *w*/*v*), 16 h, 82%; (c) DMP, CH_2Cl_2, 2 h; (d) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, HSO_3NH_2, *t*-BuOH–H_2O, r.t., 16 h; (e) EtI, K_2CO_3, acetone, 30–40 °C, 61% (over 3 steps); (f) Pd/C, H_2, EtOH, 2 d, 88%; (g) DMP, CH_2Cl_2, 2 h, r.t., 74%.

References and Notes

(1) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113.
(2) Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. *Science* **1995**, *268*, 726.
(3) (a) Pattenden, G.; Rescourio, G. *Org. Biomol. Chem.* **2008**, *6*, 3428. (b) Legeay, J.-C.; Langlois, N. *J. Org. Chem.* **2007**, *72*, 10108. (c) Yoon, C. H.; Flanigan, D. L.; Yoo, K. S.; Jung, K. W. *Eur. J. Org. Chem.* **2007**, 37. (d) Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631. (e) Balskus, E. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 6810. (f) Wardrop, D. J.; Bowen, E. G. *Chem. Commun.* **2005**, 5106. (g) Ooi, H.; Ishibashi, N.; Iwabuchi, Y.; Ishihara, J.; Hatekeyama, S. *J. Org. Chem.* **2004**, *69*, 7765. (h) Brennan, C. J.; Pattenden, G.; Rescourio, G. *Tetrahedron Lett.* **2003**, *44*, 8757. (i) Green, M. P.; Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6609. (j) Iwama, S.; Gao, W. G.; Shinada, T.; Ohfune, Y. *Synlett* **2000**, 1631. (k) Panek, J. S.; Masse, C. E. *Angew. Chem. Int. Ed.* **1999**, *38*, 1093. (l) Kang, S. H.; Jun, H. S.; Youn, J. H. *Synlett* **1998**, 1045. (m) Corey, E. J.; Li, W. D.; Reichard, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 2330. (n) Corey, E. J.; Li, W. D.; Nagamitsu, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 1676. (o) Chida, N.; Takeoka, J.; Ando, K.; Tsutsumi, N.; Ogawa, S. *Tetrahedron* **1997**, *53*, 16287. (p) Nagamitsu, T.; Sunazuka, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A.; Smith, A. B. *J. Am. Chem. Soc.* **1996**, *118*, 3584. (q) Chida, N.; Takeoka, J.; Tsutsumi, N.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1995**, 793. (r) Uno, H.; Baldwin, J. E.;

Russell, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2139. (s) Sunazuka, T.; Nagamitsu, T.; Matsuzaki, K.; Tanaka, H.; Omura, S.; Smith, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 5302. (t) Corey, E. J.; Reichard, G. A.; Kania, R. *Tetrahedron Lett.* **1993**, *34*, 6977. (u) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677.

(4) (a) Hayes, C. J.; Sherlock, A. E.; Green, M. P.; Wilson, C.; Blake, A. J.; Selby, M. D.; Prodger, J. C. *J. Org. Chem.* **2008**, *73*, 2041. (b) Hayes, C. J.; Sherlock, A. E.; Selby, M. D. *Org. Biomol. Chem.* **2006**, *4*, 193.

(5) (a) Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Ace, K. W.; Guyo, P. M.; Cowley, A.; Harling, J. D. *Chem. Eur. J.* **2005**, *11*, 4227. (b) Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Harling, J. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 2293.

(6) Fukuda, N.; Sasaki, K.; Sastry, T. V. R. S.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2006**, *71*, 1220.

(7) An independent route to lactam **3** has been reported previously en route to (–)-kaitocephaline, see: Kawasaki, M.; Shinada, T.; Hamda, M.; Ohfune, Y. *Org. Lett.* **2005**, *7*, 4165.

(8) (a) Zhang, J.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Org. Chem.* **2001**, *66*, 7555. (b) Choudhury, P. K.; Le Nguyen, B. K.; Langlois, N. *Tetrahedron Lett.* **2002**, *43*, 463. (c) Langlois, N.; Le Nguyen, B. K. *J. Org. Chem.* **2004**, *69*, 7558. (d) Kawasaki, M.; Namba, K.; Tsujishima, H.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2003**, *44*, 1235. (e) Lee, J.; Lee, Y.-I.; Kang, M. J.; Lee, Y.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, M.-J.; Choi, J.-Y.; Ku, J.-M.; Park, H.-G.; Jew, S.-S. *J. Org. Chem.* **2005**, *70*, 4158. (f) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, T.-S.; Lee, J.; Ku, J.-M.; Jew, S.-S.; Park, H.-G. *Org. Lett.* **2005**, *7*, 3207. (g) Battistini, L.; Curti, C.; Zanardi, F.; Rassu, G.; Auzzas, L.; Casiraghi, G. *J. Org. Chem.* **2004**, *69*, 2611. (h) Tang, G.; Tian, H.; Ma, D. *Tetrahedron* **2004**, *60*, 10547.

(9) Hayes, C. J.; Bradley, D. M.; Thomson, N. M. *J. Org. Chem.* **2006**, *71*, 2661.

(10) Welch, S. C.; Chou, C. Y.; Gruber, J. M.; Assercq, J. M. *J. Org. Chem.* **1985**, *50*, 2668.

(11) CCDC 753698 and 753699 contain the supplementary crystallographic data for this paper (for **19** and **20**). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) Kang, S. H.; Jun, H. S. *Chem. Commun.* **1998**, 1929.

(13) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *48*, 4155.

(14) Corey, E. J.; Li, W. D.; Nagamitsu, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 1676.

(15) Andrews, D. M.; Brewster, A. G.; Moloney, M. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 80.