DOI: 10.1002/ejoc.200600835

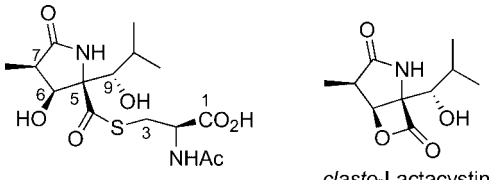
Stereogenic Evolution of *clasto*-Lactacystin β-Lactone from L-Serine

Cheol H. Yoon,[a] David L. Flanigan,[a] Kyung S. Yoo,[a] and Kyung W. Jung*[a]

Keywords: Stereoselctive C–H insertion / Rhodium catalysis / γ-Lactam / Aldol reaction / Lactacystin β-lactone

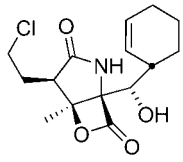
Reported herein is a novel synthesis of *clasto*-lactacystin β-lactone. The γ-lactam core was selectively prepared by an intramolecular C–H insertion to establish the stereocenter, C(6). The ensuing construction of the quaternary C(5) and carbinol C(9) centers was facilitated by aldol with excellent stereoselection. All these new stereochemistries were induced by the inherent chirality of L-serine without employing chiral auxiliaries or reagents.

Recently, a synthetic proteasome inhibitor was approved to treat multiple myeloma, thus validating this new drug mechanism.[1] With such growing interest, substantial efforts have been made toward drug discovery utilizing proteasome inhibition. Lactacystin (**1**) and its analog, *clasto*-lactacystin β-lactone (**2**) are known to induce apoptosis (programmed cell death) in human monoblast cells by specific inhibition of the 20S proteasome, which overcomes the Bcl-2 protective function (Figure 1).[2] A structural congener of lactacystin, salinosporamide A (**3**), isolated from marine sediment, is also a highly selective proteasome inhibitor.[3]



Lactacystin (**1**)

clasto-Lactacystin β-Lactone (**2**)



Salinosporamide A (**3**)

Figure 1. Representative examples of natural 20S-Proteasome inhibitors.

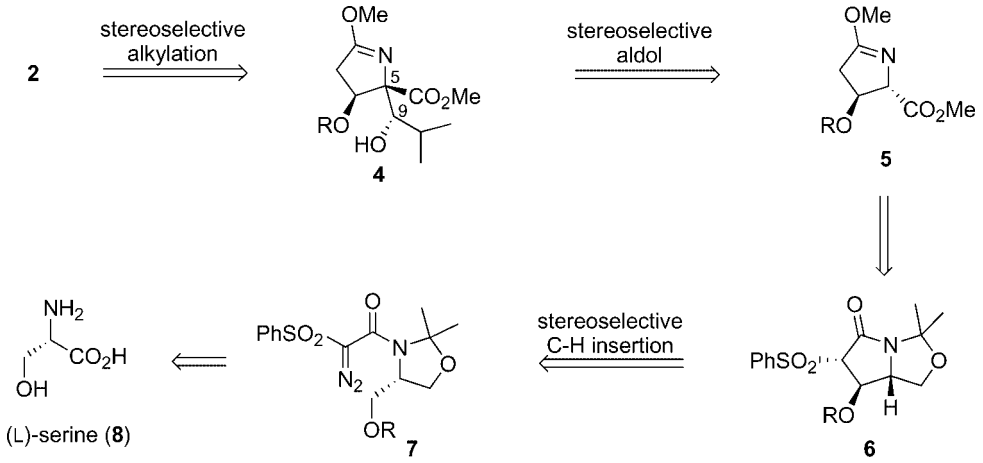
A number of synthetic routes have been explored to supply lactacystin and its β-lactone analog for clinical trials.[4] In these previous syntheses, the C(5) quaternary center was established using aldol or acylation at an early stage, then the formation of γ-lactam was carried out later presumably because the quaternary center was considered to be the most difficult to construct. This strategy required the use of chiral auxiliaries or reagents, and consequently the procedures were relatively cumbersome and costly.

In order to overcome these shortcomings, we embarked on an efficient synthesis by starting with an inexpensive chiral commodity, L-serine. Another noteworthy salient feature was to change the order of key structural and functional manipulations compared to the other known syntheses, where we diastereoselectively introduced the C(5) quaternary center at a relatively late stage. Herein we report a novel synthesis of **2** employing a stereoseletive aldol protocol, resulting in the simultaneous installation of the C(5) and C(9) centers (Scheme 1). The γ-lactam core can be efficiently derived from L-serine by stereoselective C–H insertion into the diazoamide **7**.[5]

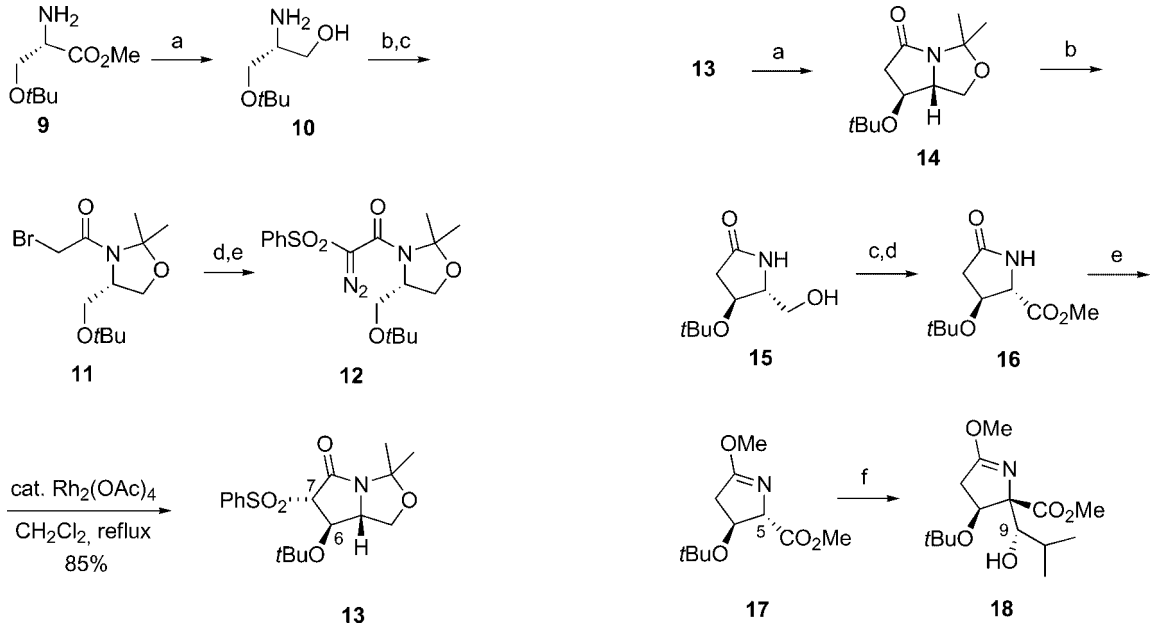
Reduction of *O*-*tert*-butyl serine methyl ester (**9**), prepared from L-serine (**8**) in two steps by known procedures,[6] afforded amino alcohol **10** in a high yield (Scheme 2). The amino alcohol was subjected to N,O-acetonide formation, followed by bromoacetylation to yield **11**. Displacement of the bromide **11** with the phenylsulfonyl group, and subsequent diazo transfer using *p*ABSA produced the diazo compound **12**. This entire series of reactions can be performed on large scales and requires no significant purification efforts. Intramolecular C–H insertion of diazo compound **12** yielded the desired *trans*-γ-lactam **13** in 85% yield with exclusive regio- and stereoselectivities. The configuration of the two newly generated stereocenters at C(6) and C(7) of the γ-lactam **13** was unambiguously elucidated and discussed in our previous report.[5b]

Desulfonylation of the γ-lactam **13** was realized with Na(Hg) in a high yield (Scheme 3). After the acetonide group was cleaved under acidic conditions with Dowex resin, the resulting hydroxy group was subsequently oxid-

[a] Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California,
Los Angeles, California 90089-1661, USA
Fax: +1-213-821-4096
E-mail: kwjung@usc.edu
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 1. Retrosynthetic analysis of **2**.



Scheme 2. Synthesis of γ-lactam **13** by C–H insertion.

Scheme 3. Stereoselective aldol reaction.

ized to give the corresponding carboxylic acid, which was then subjected to esterification to afford the methyl ester **16**. Exposure of **16** to $Me_3O{\cdot}BF_4$ in dichloromethane produced the imino ether **17**, where *O*-methylation was observed exclusively without any concomitant *N*-methylation.

The resultant imino ether compound turned out to be a suitable aldol precursor rather than the corresponding amide because steric congestion was diminished at the C(5) center and the acidity of the C(5) proton was enhanced.[7] Enolization of **17** with LDA followed by the addition of isobutyraldehyde at –78 °C afforded the aldol product **18** as a single isomer.

The aldol was anticipated to take place via closed chair-like transition states, where the isopropyl group would lie in the equatorial position, accounting for the observed excellent stereoselectivity at the C(9) (Figure 2).[8] Additionally, the β-face of **17** would be blocked by the bulky *O*-*tert*-butyl substituent, thus we expected the aldol reaction of **17** to yield the desired product **18** selectively through **17a**. The structure of **18** was confirmed as the desired product by the synthesis of the known final compound **2** derived from **18** (vide infra).

The aldol product **18** was converted into the key intermediate **21** for the selective methylation in 6 steps (Scheme 4). The secondary hydroxy moiety in **18** was protected with an acetyl group. Treatment of the resultant acetate with Dowex resin followed by $BF_3{\cdot}OEt_2$ afforded the hydroxy amide

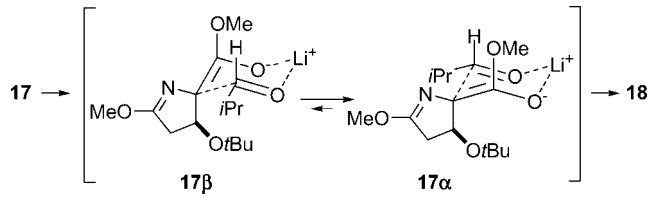
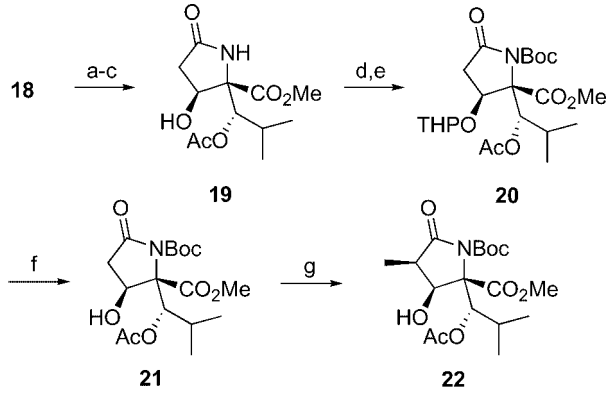


Figure 2. Proposed transition states for the aldol reaction of **17**.

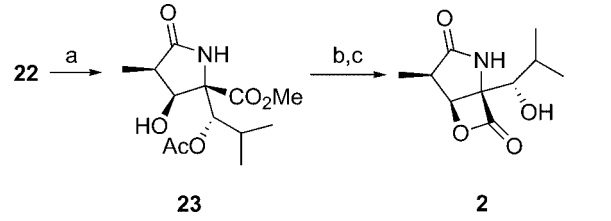
compound **19**. Selective protection of the amide was conducted in a three consecutive step conversion; *O*-THP protection, *N*-Boc protection and hydrolysis of THP group. The lactam **21** underwent methylation stereoselectively to furnish the compound **22** as a single isomer in 88% yield.[4c]



(a) Ac_2O, cat. DMAP, pyridine (93%). (b) Dowex resin, MeOH (79%); (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2 (95%); (d) DHP, cat. *p*TsOH, CH_2Cl_2; (e) Boc_2O, DMAP, CH_2Cl_2 (83% for 2 steps); (f) *p*TsOH, MeOH (85%); (f) LDA, MeI, THF–HMPA, –78 °C (88%).

Scheme 4. Stereoselective C(7) methylation.

The total synthesis of *clasto*-lactacystin β-lactone (**2**) was completed from **22** by following the reported procedures (Scheme 5).[4a] Thus, deprotection of the N-Boc group with TFA, simultaneous hydrolysis of methyl ester and acetate under basic conditions, and lactone formation with BOPCl afforded *clasto*-lactacystin β-lactone (**2**) successfully.



(a) TFA (75%); (b) aq. 0.5 N NaOH, 72 h, r.t.; (c) BOPCl, TEA, CH_2Cl_2 (65% for 2 steps).

Scheme 5. Synthesis of *clasto*-lactacystin β-lactine (**2**).

In summary, this novel synthesis of *clasto*-lactacystin β-lactone (**2**) involves two key steps, γ-lactam formation by Rh^{II}-catalyzed intramolecular C–H activation and stereoselective aldol reaction to form the highly congested quaternary center. An outstanding aspect of the synthesis is that the formation of all four stereocenters was controlled by the inherent chirality of L-serine without employing chiral auxiliaries or chiral inducing reagents throughout. In fact, three stereochemistry generating steps (**12** to **13**, **17** to **18**, and **21** to **22**) are perfectly selective to culminate in one desired isomer. Therefore, we believe that this synthesis is expeditious and convenient to offer an inexpensive and pragmatic approach towards a large scale preparation of *clasto*-lactacystin β-lactone (**2**).

Supporting Information (see also the footnote on the first page of this article): Full experimental details and spectroscopic information (^1H and ^{13}C NMR) are provided for all compounds.

Acknowledgments

We acknowledge generous financial support from the National Institute of General Medical Sciences of the National Institutes of Health (RO1 GM 62767).

[1] a) J. Adams, *Drug Discovery Today* **2003**, *8*, 307–315; b) J. Adams, *Curr. Opin. Oncol.* **2002**, *14*, 628–634.
[2] a) S. Omura, T. Fujimoto, K. Otogura, R. Moroguchi, H. Tanaka, Y. Sasaki, *J. Antibiot.* **1991**, *44*, 113–116; b) S. Omura, K. Matsuzaki, T. Fujumoto, K. Kosuge, T. Furuya, S. Fujita, A. Nakagawa, *J. Antibiot.* **1991**, *44*, 117–118; c) L. R. Dick, A. A. Cruikshank, L. Grenier, F. D. Melandri, S. L. Nunes, R. L. Stein, *J. Biol. Chem.* **1996**, *271*, 7273–7276; d) J. A. Adams, R. Stein, *Annu. Rep. Med. Chem.* **1996**, *31*, 279–288.
[3] R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Cauffman, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed.* **2003**, *42*, 355–357.
[4] Reviews on lactacystin total syntheses, see: a) T. Nagamitsu, T. Sunazuka, H. Tanaka, S. Omura, P. A. Sprengeler, A. B. Smith, *J. Am. Chem. Soc.* **1996**, *118*, 3584–3590; b) E. J. Corey, W.-D. Z. Li, *Chem. Pharm. Bull.* **1999**, *47*, 1–10; c) C. E. Masse, A. J. Morgan, J. Adams, J. S. Panek, *Eur. J. Org. Chem.* **2000**, 2513–2528. For recent total syntheses, see; d) T. J. Donohoe, H. O. Sintim, L. Sisangia, J. D. Harling, *Angew. Chem. Int. Ed.* **2004**, *43*, 2293–2296; e) H. Ooi, N. Ishibashi, Y. Iwabuchi, J. Ishihara, S. Hatakeyama, *J. Org. Chem.* **2004**, *69*, 7765–7768; f) N. Fukuda, K. Sasaki, T. V. R. S. Sastry, M. Kanai, M. Shibasaki, *J. Org. Chem.* **2006**, *71*, 1220–1225; g) C. J. Hayes, A. E. Sherlock, M. D. Selby, *Org. Biomol. Chem.* **2006**, *4*, 193–195; h) E. P. Balskus, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 6810–6812.
[5] a) C. H. Yoon, M. J. Zaworotko, B. Mouton, K. W. Jung, *Org. Lett.* **2001**, *3*, 3539–3542; b) C. H. Yoon, D. L. Flanigan, B.-D. Chong, K. W. Jung, *J. Org. Chem.* **2002**, *67*, 6582–6584; c) D. L. Flanigan, C. H. Yoon, K. W. Jung, *Tetrahedron Lett.* **2005**, *46*, 143–146.
[6] J. G. Adamson, M. A. Blaskovich, H. Groenevelt, G. A. Lajoie, *J. Org. Chem.* **1991**, *56*, 3447–3449.
[7] Aldol reactions of lactam **16**, and their analogs (*N*-protected with *t*Boc, Cbz, benzyl, etc.) afforded β-elimination products predominantly. These results and additional aldols with other sustrates will be reported in a separate full account.
[8] C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, J. Lampe, *J. Org. Chem.* **1980**, *45*, 1066–1081.

Received: September 25, 2006
Published Online: November 13, 2006

