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[11] Alternatively, the regioselective formation of compounds of type **4** by addition of allyl metal reagents to α,β-unsaturated carbonyl compounds has not been definitively addressed. For elegant work on this subject, see T. Ooi, T. Kondo, K. Maruoka, *Angew. Chem.* **1997**, *109*, 1231; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1183.

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[13] An interesting case of C–C bond formation by sequential addition of propargyl alcohol to [ethoxy(phenylethynyl)carbene]pentacarbonylchromium(0) and Claisen rearrangement: A. Segundo, J. M. Moretó, J. P. Viñas, S. Ricart, *Organometallics* **1994**, *13*, 2467.

[14] I. Erden, F.-P. Xu, W.-G. Cao, *Angew. Chem.* **1997**, *109*, 1557; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1516.

[15] This study was also prompted by the fact that undesired oxidation of the carbene to a carbonyl group frequently took place when working with Fischer carbene complexes. The current results suggest that nucleophilic addition/demetalation/hydrolysis processes might be responsible rather than the routinely invoked accidental oxidation by atmospheric oxygen.

treatment of arthritis.[2] The equally potent β-lactone **2** acts by selective acylation of the N-terminal threonine residue of a protein subunit of the cylindrical 20*S* proteasome,[3] a result confirmed by X-ray crystallographic studies at 2.4 Å resolution of the lactacystin inactivated proteasome.[4] Recent mechanistic studies have shown that lactacystin hydrolyzes to the inactive dihydroxy acid through its β-lactone **2**. It is the β-lactone species that subsequently acylates the proteasome and results in its inactivation (Figure 1).[3b] The presence of intracellular levels of glutathione (GSH) converts **2** into lactathione, which is believed to act as a "lactone reservoir".[3c]

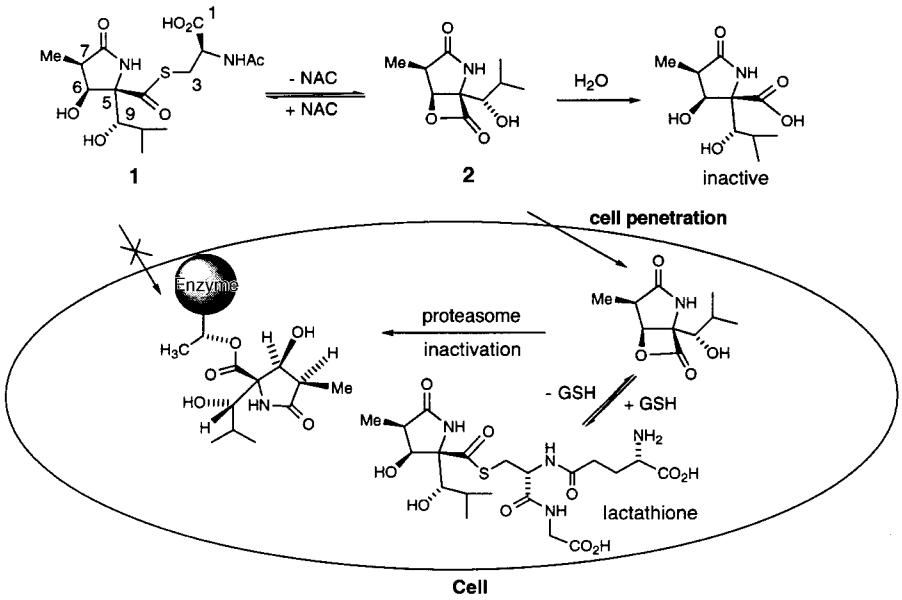

Figure 1. Mechanism of proteasome inhibition by (+)-lactacystin.

Total Synthesis of (+)-Lactacystin**

James S. Panek* and Craig E. Masse

(+)-Lactacystin (**1**) is a metabolite isolated from *Streptomyces sp.* OM-6519 that exhibits significant neurotrophic activity.[1a] The relative and absolute stereochemistry of (+)-lactacystin has been elucidated by ^{1}H and ^{13}C NMR spectroscopy, and single-crystal X-ray analysis.[1b] (+)-Lactacystin has been shown to be a potent proteasome inhibitor, and has led to speculation that it may be therapeutically useful in the

(+)-Lactacystin (**1**) is a unique member of a class of neurotrophic factors since it consists of a nonprotein γ-lactam thioester. Its compact array of five resident stereogenic centers renders (+)-lactacystin a significant target for synthesis; a number of other syntheses of **1** have been reported.[5] A critical issue relative to the synthesis of lactacystin is the fact that most of the structural features of **1** are essential to maintain its unique biological profile. The C4-carboxylic moiety and the C6-hydroxyl group must be *cis* because of the necessity for β-lactone formation to achieve proteasome inactivation.[4] The absolute configuration of the C9-hydroxyl and the isopropyl substituents are also essential for biological activity.[5c] The C7-methyl group is critical to the activity and stability of **1**, although replacement of this group with either ethyl or isopropyl groups does lead to a two- to threefold increase in activity.[5c]

As a consequence of these strict structural and stereochemical requirements any synthesis of **1** must not only be efficient, but also highly selective for the introduction of each of the stereogenic centers. Our approach to lactacystin nicely compliments the synthesis by Smith and co-workers[5e] through the use of the hydroxyleucine-derived oxazoline **5** to set the stage for the critical *anti*-crotylation reaction for the installation of the C6 and C7 stereocenters.

Retrosynthetic analysis of the lactacystin skeleton (Scheme 1) reveals two key operations: a) stereoselective

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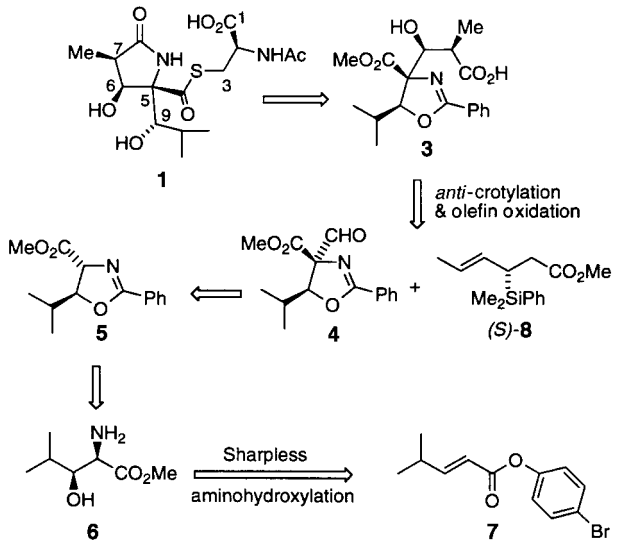
[**] This work was financially supported by the National Institutes of Health (RO1GM55740). C.E.M. is grateful to the American Chemical Society, Division of Medicinal Chemistry, and Hoechst Marion Roussel for a pre-doctoral fellowship. We are grateful to Dr. Julian Adams, Dr. Louis Plamondon, Mr. Louis Grenier, Mr. Francois Soucy, and Mark Behnke of ProScript (Cambridge, MA.) for insightful discussions.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

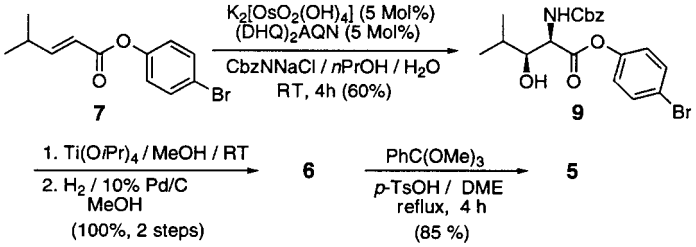


Scheme 1. Retrosynthetic analysis.

generation of the heterocyclic aldehyde **4** derived from a 3-hydroxyleucine derivative and b) an asymmetric crotylsilane addition to aldehyde **4** to generate the fully elaborated stereochemical core of the parent molecule **1**. Earlier efforts in this area[5e] have established that aldol surrogates such as (*E*)-crotylboron or (*E*)-crotylchromium(II) reagents exhibit only modest levels of diastereoselection for the (*6S*)-isomer (dr = 2:1 → 4:1). We anticipated that the chiral silane reagents should be capable of providing enhanced levels of diastereoselection for this double stereodifferentiating reaction since Lewis acid promoted reactions involving allylsilanes proceed through open transition structures.[6] These transition states diminish the destabilizing effects associated with the steric congestion of heterocyclic aldehyde **4**. The first stage of the synthesis involved the development of an efficient stereoselective synthesis of heterocyclic aldehyde **4** that contained the C5 and C9 stereocenters of lactacystin. This required an efficient route to oxazoline **5**. Currently, the most efficient approach to oxazoline **5** requires ten steps with an overall yield of 60% from (*E*)-4-methyl-2-penten-1-ol.[5e]

Our first objective in the development of a more practical synthesis of oxazoline **5** was to devise a concise and stereoselective synthesis of the hydroxyleucine unit. Numerous approaches to the 3-hydroxyleucine synthon **6** have been reported.[7] However, they either lack the flexibility to prepare the various isomers, require the preparation of a chiral catalyst system, or are prohibitively lengthy and impractical for large scale preparation. Given those considerations, the present synthesis of (2*R*,3*S*)-hydroxyleucine methyl ester (**6**) employs commercially available materials and utilizes an asymmetric catalytic aminohydroxylation of (*p*-bromophenyl)-4-methyl-2-pentenoate.

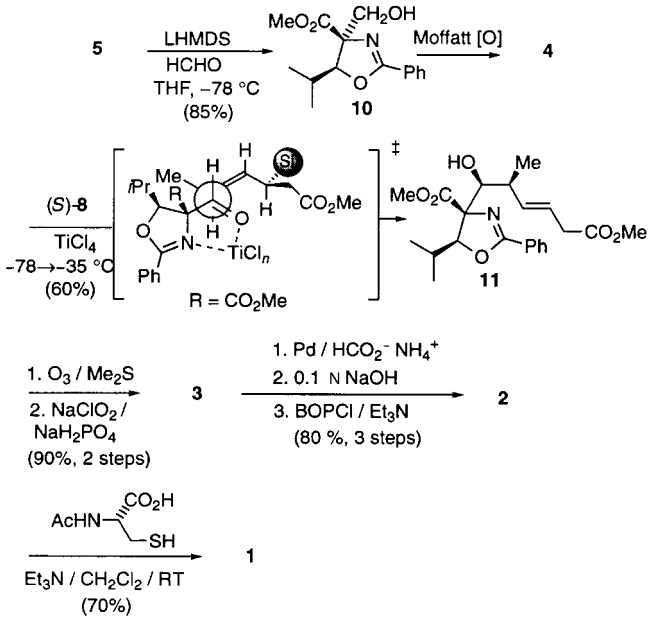
The asymetric aminohydroxylation (AA) of **7** using the benzylcarbamate-based Sharpless reaction[8] and 1,4-bis(dihydroquininyl)anthraquinone $(DHQ)_2AQN$ gave **9** with good levels of regioselectivity (7:1) in favor of the α-amino ester and high levels of enantioselectivity (87% *ee*, Scheme 2). The ratio of regioisomers was determined by ^1H NMR analysis of the crude product and the initial *ee* value of 87% could be



Scheme 2. Preparation of oxazoline **5**. Cbz = "carbobenzoxy" = benzyloxycarbonyl, DME = 1,2-dimethoxyethane.

raised to > 99% by recrystallization (two times) from EtOH/H_2O (1/1). Subsequent transesterification to the methyl ester in the presence of $Ti(OiPr)_4$[9] and removal of the benzyloxycarbonyl group by hydrogenolysis afforded **6**. Finally, treatment of **6** with trimethylorthobenzoate in the presence of *p*-toluenesulfonic acid[10] provided the *trans*-oxazoline **5**. The virtues of this approach are apparent from the concise nature of the synthetic sequence, mild reaction conditions, and the fact that either enantiomer can be prepared by the proper choice of the alkaloid ligand.

The preparation of the heterocyclic aldehyde **4** was accomplished according to a literature precedent established by Smith et al.[5e] Oxazoline **5** was subjected to an aldol condensation with formaldehyde according to the Seebach protocol[11] to afford primary alcohol **10** as a single diastereomer (Scheme 3). The topological bias for this ester enolate was presumably controlled by the chirality of the oxazoline in



Scheme 3. Completion of the synthesis of (+)-lactacystin (**1**). LHMDS = lithium bis(trimethylsilyl)amide.

which the bulky isopropyl group functions as the controller of diastereoselectivity. Oxidation of the primary alcohol using the Moffatt protocol (dicyclohexylcarbodiimide, DMSO, pyridine, trifluoroacetic acid)[12] provided the desired heterocyclic aldehyde **4**. Any attempt to purify this product resulted in deformylation, so this aldehyde was used without purifica-

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tion. The critical *anti*-selective crotylation reaction was then carried out to establish the relative configuration at the C6 and C7 centers. This double stereodifferentiating[13] reaction was readily accomplished with $TiCl_4$ to afford homoallylic alcohol **11** with high levels of diastereoselectivity (*anti*:*syn* > 30:1) and in 50–60% yield. This *anti*-bond construction was presumably achieved through simultaneous coordination of the aldehyde oxygen atom and the nitrogen atom in the oxazoline ring. The 1,3-relationship of the heteroatoms ideally predisposes the more Lewis basic nitrogen atom relative to the aldehyde carbonyl group to generate a 5-membered chelate with $TiCl_4$ via the illustrated synclinal transition state (Scheme 3).[14] Oxidative cleavage of (*E*)-olefin **11** under standard ozonolysis conditions and subsequent oxidation with sodium chlorite[15] furnished carboxylic acid **3**.

The completion of (+)-lactacystin was initiated by catalytic transfer hydrogenation of the oxazoline moiety with Pd-black to give the γ-lactam methyl ester after cyclization. Saponification of the methyl ester under mild conditions afforded the dihydroxy acid, which was directly converted into β-lactone **2** by treatment with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl). We employed the lactone opening strategy developed by Corey et al. to attach the *N*-acetyl-L-cysteine side chain.[5b] Treatment of **2** with *N*-acetyl-L-cysteine/Et_3N furnished synthetic (+)-**1** identical in all respects to the natural product (^1H and ^{13}C NMR, IR spectroscopies, HR-MS, optical rotation, and TLC).[5b]

Received: October 20, 1998 [Z12551]
German version: *Angew. chem.* **1999**, *111*, 1161–1163

Keywords: asymmetric synthesis · enzyme inhibitors · lactacystin · lactones · total synthesis

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Aerobic Oxidation of Primary Alcohols by a New Mononuclear Cu^{II}-Radical Catalyst**

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Recently we reported[1] a dinuclear Cu^{II}-phenoxyl radical complex, which catalyzes efficiently the aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones or to 1,2-glycols by oxidative C–C coupling with concomitant formation of H_2O_2. This complex together with that of Stack et al.[2] are the first reported functional models for the enzyme galactose oxidase (GO).[3] We report here a new mononuclear Cu^{II}-iminosemiquinone catalyst that selectively transforms primary alcohols (e.g. ethanol but not methanol) with O_2 to aldehydes and H_2O_2; secondary alcohols are not at all substrates for the catalyst.

The trifluoroacetate salt of the cation *N*,*N*-bis(2-hydroxy-3,5-di-*tert*-butylphenyl)ammonium $[H_4(L^3)](CF_3CO_2)$ was prepared through the condensation of 3,5-di-*tert*-butylcatechol with NH_3 in *n*-heptane and subsequent acidification with trifluoroacetic acid. It is known[4] that the diamagnetic trianion $(L^3)^{3-}$ (Scheme 1), present as a tridentate ligand in complexes, can be easily oxidized to the radical dianion $(L^2)^{2-}$ and then to the diamagnetic monoanion $(L^1)^{1-}$ in two successive one-electron oxidation steps. Speier and Pierpont et al. have, for example, described the complexes $[Cu^{II}(L^1)_2]$

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[**] This work was supported by the Degussa AG, Frankfurt, and the Fonds der Chemischen Industrie.