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Catalytic Asymmetric Total Synthesis of (+)-Lactacystin

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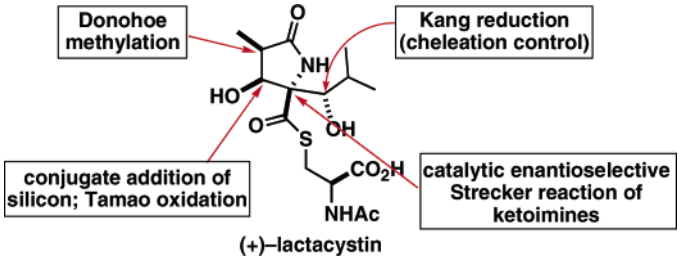

Total synthesis of (+)-lactacystin, a potent and selective proteasome inhibitor, was accomplished using a catalytic enantioselective Strecker reaction of a ketoimine as the initial key step. An enone-derived *N*-phosphinoyl ketoimine **7** was selected as a stable masked α-hydroxy ketoimine analogue. Excellent enantioselectivity (98% ee) and practical catalyst activity were produced under the optimized catalyst preparation method using 2.5 mol % $Gd\{N(SiMe_3)_2\}_3$ as a metal source and 3.8 mol % D-glucose-derived ligand **8**. This reaction was conducted on a 5 g scale. The chiral tetrasubstituted C-5 carbon efficiently controlled the stereochemistry of the other three chiral centers of lactacystin. Chelation-controlled Meerwein-type reduction of ketone **5** using *i*-PrMgBr (originally reported by Kang in a related substrate) selectively produced the desired secondary alcohol at the C-9 position. The C-6 hydroxy and C-7 methyl groups were introduced via a silyl conjugate addition followed by the Tamao oxidation and Donohoe methylation, respectively, in a highly stereoselective manner. A practical amount of enantiomerically pure *clasto*-lactacystin *β*-lactone (**2**), the biologically active form of (+)-lactacystin, can be synthesized using this route. *clasto*-Lactacystin *β*-lactone (**2**) was converted to (+)-lactacystin following the reported procedure.

Introduction

Proteolytic degradation and turnover of cellular proteins are essential processes in living cells. The ubiquitin-proteasome pathway is particularly important for the regulated degradation of various proteins. The 26S proteasome complex is the key catalytic protease and digests a wide variety of ubiquitinated proteins. This complex is composed of catalytically active 20S proteasome and two 19S regulatory complexes. Lactacystin (**1**), isolated from the *streptomyces* sp. by Omura et al.,[1] was the first identified natural 20S proteasome inhibitor. It was initially discovered as a neurite outgrowth inducer of a murine neuroblastoma cell line. Studies to elucidate the molecular basis of its biological activity revealed its target to be the proteasome; radioactive lactacystin covalently binds to the *β*5 subunit of the 20S proteasome.[2] Afterward, the crystal structure of the yeast 20S proteasome−lactacystin complex unequivocally demonstrated that lactacystin selectively binds to the *β*-oxygen atom of the *N*-terminal threonine in the *β*5 subunit through an ester covalent bond.[3] Because this oxygen atom is crucial for the enzymatic activity, lactacystin is an irreversible inhibitor of the proteasome. The actual biologically active acylating species derived from lactacystin is *clasto*-lactacystin *β*-lactone (also known as omuralide; **2**), which is formed by eliminating *N*-acetyl-L-cystein and can penetrate cell membranes.[4] Currently, **1** and **2** are essential tools for biological studies of the proteasome function (Figure 1).

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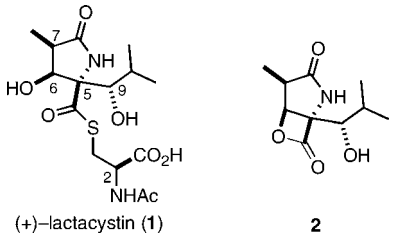
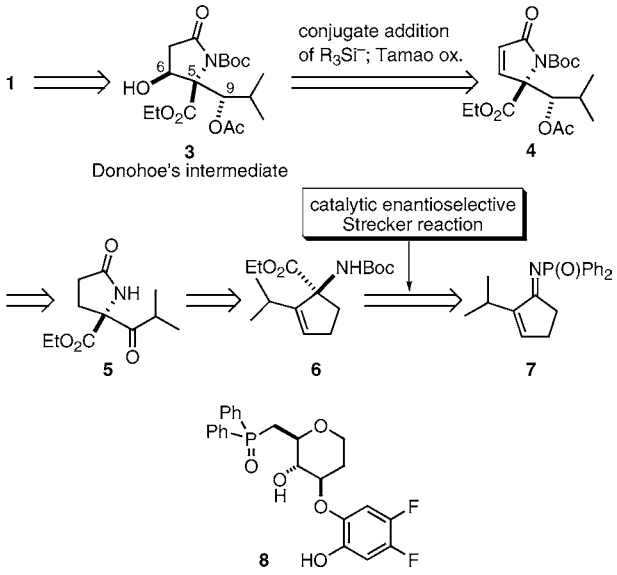


FIGURE 1. Lactacystin (**1**) and *clasto*-lactacystin β-lactone (**2**).

Proteasome targeting has recently emerged as a new modality for the potential treatment of diseases ranging from malaria to cancer. Proteasome inhibitors cause the accumulation of proteasome substrates, including cyclins and transcriptional factors and induce cell cycle arrest with apoptotic program activation.[5] Therefore, even though more than 10 years has passed since the discovery of lactacystin, active research continues to develop new synthetic routes for lactacystin and its analogues[6] and other proteasome inhibitors.[7]

One structural characteristic of lactacystin is its densely gathered chiral centers on a relatively small γ-lactam core, including the chiral tetrasubstituted C-5 carbon. All previous asymmetric syntheses utilized diastereoselective reactions to construct the chirality at the C-5 carbon. Typically, Sharpless

SCHEME 1. Retrosynthetic Analysis



catalytic asymmetric epoxidation,[8] dihydroxylation,[9] or aminohydroxylation[10] to synthesize the hydroxyleucine unit, followed by Seebach-type diastereoselective carbon−carbon bond formation[11] is used for this purpose (Corey, Omura and Smith, Kang, Adams, and Panek syntheses). Diastereoselective Overman rearrangement (Chida), Strecker reaction (Ohfune), carbene insertion to the C−H bond (Hayes), and acetal migration (Hatakeyama) are alternative methods. Some of those syntheses are efficient enough for a preparative scale supply of lactacystin for use as a biological tool. Meanwhile, we developed a practical enantioselective Strecker reaction of ketoimines using a gadolinium (Gd) complex of ligand **8** as a catalyst.[12,13] Thus, we expected that direct construction of the chiral α,α-disubstituted amino acid moiety of lactacystin would be possible using our reaction. Our main aim of this project was to clarify if our reaction is feasible for the practical synthesis of chiral α,α-disubstituted amino acid derivatives with significant structural complexity and important biological activity. We describe herein a total synthesis of (+)-lactacystin, in which the chiral tetrasubstituted C-5 carbon was constructed at the initial stage using the catalytic enantioselective Strecker reaction of a ketoimine.

Results and Discussion

We selected Donohoe's intermediate **3** as a temporary goal in our synthesis (Scheme 1). This intermediate can be converted

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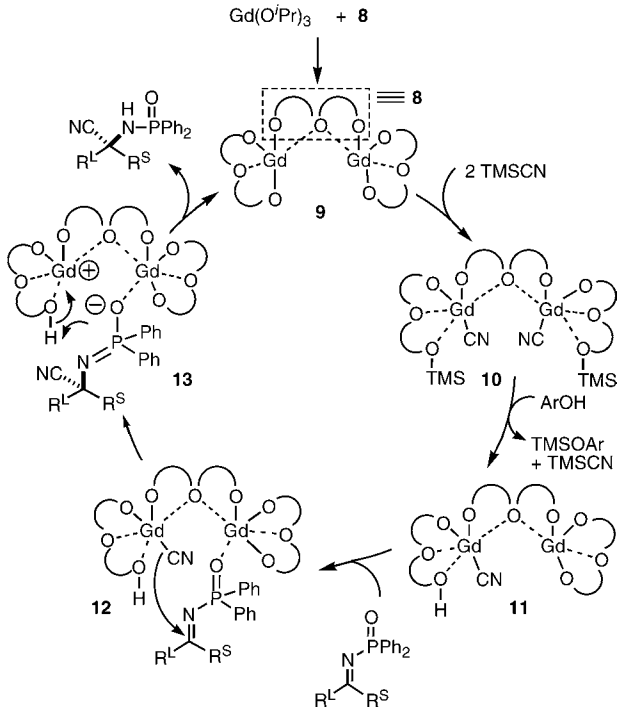
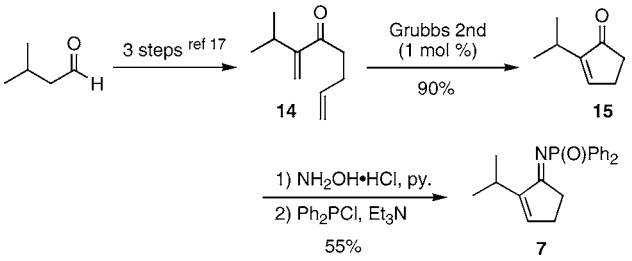


FIGURE 2. Proposed catalytic cycle of the enantioselective Strecker reaction of ketoimines.

to lactacystin (**1**) in five steps with high efficiency.[6n,o] In addition, this intermediate is versatile for lactacystin analogue synthesis because the only replaceable group in the molecule that retains biological activity is the C-7 methyl group.[6t,u] The secondary alcohol at the C-6 position of **3** should be constructed via conjugate addition of a silicon nucleophile to the α,*β*-unsaturated imide **4**, followed by the Tamao oxidation.[14] The sterically hindered acetoxy *iso*-butyl substituent at the C-5 position should block the α-face of the conjugated double bond, thus directing the silicon addition from the desired *β* face. Compound **4** should be synthesized from keto lactam **5** via a Kang-type stereoselective reduction[6j] through chelation control. Compound **5** should be synthesized from a chiral α,α-disubstituted amido ester **6** via ozonolysis and lactam formation. Finally, **6** should be obtained using the catalytic enantioselective Strecker reaction of ketoimine **7**[15] developed by our group.

Our catalytic enantioselective Strecker reaction has several characteristic features: (1) high enantioselectivity and catalyst turnover with broad substrate generality; (2) the active catalyst is generated from Gd(O*i*-Pr)$_3$ and **8** in a 1:2 ratio (the experimentally optimized ratio for catalyst preparation from Gd(O*i*-Pr)$_3$); and (3) protic additives, such as 2,6-dimethylphenol or HCN, dramatically improve the enantioselectivity, the catalyst turnover number, and the turnover frequency. A working hypothesis for the catalytic cycle of the enantioselective Strecker reaction is shown in Figure 2. This mechanism was postulated on the basis of the catalyst composition assessed by ESI-MS, labeling experiments, and kinetic studies.[12b,16] The reaction between Gd(O*i*-Pr)$_3$ and **8** initially generates a chiral alkoxide 2:3 complex **9**, which is converted to a silylated gadolinium cyanide **10** in the presence of TMSCN. The silyl ethers are then cleaved by a protic additive to give complex **11**, the active catalyst of this reaction. The enantioselective Strecker reaction would proceed through a bifunctional mechanism (**12**) in which one of the gadolinium metals in the complex works as a Lewis acid to activate a substrate, and the other gadolinium cyanide works as a nucleophile, giving **13**. The internal proton of the asymmetric catalyst facilitates the catalytic cycle probably by enhancing the product dissociation rate (**13** to **9**). The active catalyst **11** is regenerated from **9** only through silylated complex **10**, and direct protonolysis of **9** to **11** by HCN does not proceed.

SCHEME 2. Synthesis of Ketoimine 7



Ketoimine **7**, the substrate for the catalytic asymmetric Strecker reaction, was synthesized from known ketone **14**[17] via ring closing metathesis, oxime formation, and phosphinoylimine formation[18] (Scheme 2).

Reaction conditions were optimized for the catalytic enantioselective Strecker reaction of ketoimine **7** (Table 1). First, previously optimized conditions were applied (entry 1).[19] The reaction proceeded slowly with 5 mol % catalyst at −40 °C, and the product **16** was obtained in quantitative yield after 7 days with 88% ee. To improve the efficiency, reaction conditions were carefully optimized in this specific case.[20] The enantioselectivity and reaction rate were significantly improved by changing the addition order of the reagents (entry 2); after the alkoxide complex **9** was generated from Gd(O*i*-Pr)$_3$ and **8**, TMSCN and 2,6-dimethylphenol were added prior to the addition of substrate **7**. Because the structure of the lanthanide complex fluctuates and several species can exist under equilibrium, this addition order might generate the active catalyst **11** in higher concentration than the original method without any detrimental effect to **7** in the catalyst preparation step. The ratio

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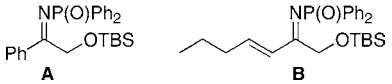
(15) Compound **7** can be used as a masked α-hydroxy ketoimine equivalent. α-Hydroxy phosphinoylketoimines such as **A** or **B** were unstable, and we could not synthesize these compounds in a pure form. For the synthesis of **7**, see Supporting Information for details.



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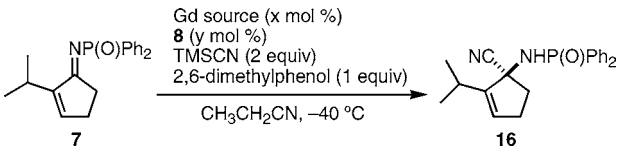
(19) As a result of steric hindrance, substrate **7** had unusually low reactivity, and the Strecker reaction under typical conditions for racemic compound synthesis (TMSCN−ZnI$_2$, Zn(OTf)$_2$, Ln(OTf)$_3$, or HCN-EtOH) did not proceed well (<20% yield). The chiral Gd−**8** complex generally produces significantly higher activity than that of strongly Lewis acidic achiral promoters.

(20) The use of HCN instead of 2,6-dimethylphenol did not improve the catalyst activity and enantioselectivity in this case.

TABLE 1. Catalytic Enantioselective Strecker Reaction of Ketoimine 7



7 16

entry	Gd source (mol %)	Gd:**8**	time (d)	yield[a] (%)	ee[b] (%)
1[c]	Gd(O*i*-Pr)$_3$ (5)	1:2	7	>99	88
2	Gd(O*i*-Pr)$_3$ (5)	1:2	3	94	96
3	Gd(O*i*-Pr)$_3$ (5)	1:2.2	4	>99	92
4	Gd(O*i*-Pr)$_3$ (5)	1:1.8	2	>99	96
5	Gd(O*i*-Pr)$_3$ (5)	1:1.5	4	>99	88
6	Gd(O*i*-Pr)$_3$ (2.5)	1:1.8	6.5	>99	92
7	Gd(HMDS)$_3$ (2.5)	1:1.5	2	>99	98
8[d]	Gd(HMDS)$_3$ (2.5)	1:1.5	2	>99	98

[a] Conversion yield calculated by the ^{1}H NMR of the crude mixture. [b] Determined by chiral HPLC. See Supporting Information for details. [c] Compound **7**, solvent, TMSCN, and 2,6-dimethylphenol were added successively to the gadolinium alkoxide complex **9**. In other entries, solvent, TMSCN, 2,6-dimethylphenol, and **7** were added successively. [d] A 5 g scale reaction. Isolated yield = 94% (see Experimental Section for the isolation procedure of **16**). Other entries were performed on a 100 mg scale.

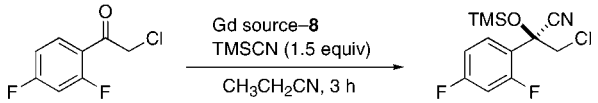
of Gd(O*i*-Pr)$_3$ and ligand **8** when the catalyst was prepared was important for the reaction rate and enantioselectivity (entries 2−5); a catalyst prepared from Gd(O*i*-Pr)$_3$ and **8** in a 1:1.8 ratio produced a synthetically useful reaction rate and enantioselectivity (entry 4). When the catalyst amount was reduced to 2.5 mol %, however, the reaction rate retarded giving slightly lower enantioselectivity (entry 6).

To further improve the catalyst activity, the recent observation in catalytic enantioselective cyanosilylation of ketones using a Gd−**8** complex[21] was considered. A catalyst solution prepared from a Gd(O*i*-Pr)$_3$ and **8** in a 1:2 ratio in the absence of 2,6-dimethylphenol contains two main species observed by ESI-MS, the major 2:3 complex **10** and the minor 4:5 complex. The 4:5 complex was thought to be a less-active catalyst with lower enantioselectivity than the 2:3 complex in the cyanosilylation of ketones because contamination of the 4:5 complex is problematic only in the case of reactive ketones. When the catalyst was prepared from Gd(HMDS)$_3$ (HMDS = hexamethyldisilazane) and **8** in a 2:3 ratio, however, the desired 2:3 complex was the sole species observed by ESI-MS. Thus, the catalyst prepared from Gd(HMDS)$_3$ produced both higher enantioselectivity and reactivity than did the catalyst prepared from Gd(O*i*-Pr)$_3$ in cyanosilylation of reactive ketones.[21] In the catalytic enantioselective Strecker reaction of **7**, optimized results were also obtained using Gd(HMDS)$_3$ as a metal source (entry 7); the reaction was completed in 2 days using 2.5 mol % catalyst, and product **16** was obtained with 98% ee. These conditions were applied to a 5 g scale synthesis, and comparable results were reproducibly obtained (entry 8). After the reaction, ligand **8** was recovered in 90% yield, which was recycled and reused.

The obtained amidonitrile **16** was converted to the corresponding α,α-disubstituted amino acid derivative **6** in high yield (Scheme 3). Ozonolysis, oxidation of the resulting aldehyde to carboxylic acid, and lactam formation under acidic conditions afforded ketone **5**. The stereoselective reduction of **5** was achieved using *i*-PrMgBr as a reducing reagent[6j] through a possible chelation transition state (TS), TS **17** (**18**:**19** = 10:1).[22] After one recrystallization of the crude mixture, the desired **18** was obtained in an enantiomerically and diastereomerically pure form. Interestingly, reversed stereoselectivity (**18**:**19** = 1:>10) was observed using $NaBH_4$ as a reducing reagent. In this case, reduction might proceed through a Felkin−Anh transition state, TS **20**, in which the polarized C−N bond is positioned perpendicular to the carbonyl plane. In both cases, the ethoxycarbonyl group at the tetrasubstituted C-5 carbon acts as a larger substituent than the C-6 methylene group, thus directing the hydride entry to the ketone.

The next key step was the introduction of the C-6 hydroxyl group via the stereoselective conjugate addition of a silyl group and the following Tamao oxidation. The precursor **4** was synthesized from **18** via 4 steps: chemoselective protection of the C-9 hydroxyl group and the lactam nitrogen atom with acetyl and Boc groups, respectively, to give **21**, selenenylation, and elimination. Silyl conjugate addition,[23] followed by the Tamao oxidation,[24] is a reliable synthetic method for the construction of β-hydroxy carbonyl compounds. A silyl anion is highly nucleophilic, even though sterically bulky substituents exist on the silicon atom. This characteristic is advantageous for the stereoselective introduction of an oxygen functionality to sterically hindered positions.[14] Tamao oxidation sometimes requires highly acidic conditions, depending on the silyl group. Therefore, proper selection of silyl reagents is important for the reasonable stability of the conjugate addition products possessing concomitant susceptibility to the Tamao oxidation under mild conditions. In our synthesis, the Et_2NPh_2Si group[25] fulfilled such requirements.[26] Thus, the conjugate addition of the corresponding silyl zincate[25] proceeded with complete stereoselectivity from the desired β side. The excellent stereoselectivity was attributed to the shielding of the α face by the sterically bulky acetoxy isobutyl group at the C-5 chiral center. The hydroxy imide **3** was obtained in 57% yield after the oxidation of the silyl group with *m*-chloroperoxybenzoic acid in the presence of KHF_2. Methylation of **3** was conducted under the conditions reported by Donohoe, and product **22** was obtained as the major isomer in 58% isolated yield (selectivity = >15:1). All the spectroscopic data of **22** completely matched the reported values. The total synthesis of lactacystin was completed from **22** following the reported procedures.[6o,b] Thus, the removal of the *N*-Boc group with TFA, hydrolysis of the ethyl ester under basic conditions, and lactone formation with BOPCl produced *clasto*-lactacystin β-lactone (**2**) in 63% yield. We succeeded in synthesizing **2** on a >100 mg scale by this

(21) Suzuki, M.; Kato, N.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 2527−2530. A typical comparison between the results obtained using catalysts prepared from Gd(O*i*-Pr)$_3$ and Gd(HMDS)$_3$ in cyanosilylation of a reactive ketone is shown in the following scheme.



Gd(O^{i}Pr)$_3$ (5 mol %)–**8** (10 mol %): 85%, 68% ee
Gd(HMDS)$_3$ (2 mol %)–**8** (3 mol %): 93%, 83% ee

(22) Relative stereochemistry was assigned on the basis of the comparison of the ^{1}H NMR charts of **3** and **22** with those of Donohoe's intermediates and the ^{1}H and ^{13}C NMR chemical shifts of **2** with the reported values.

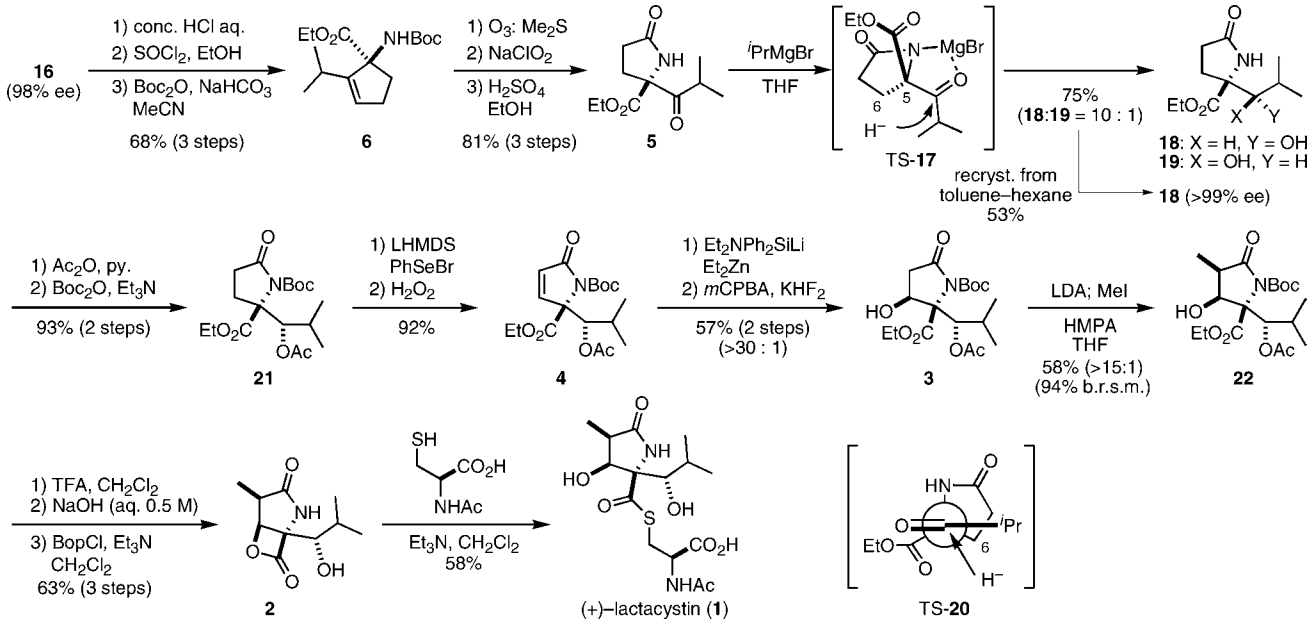
(23) (a) Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520−2526. (b) Fleming, I.; Rowley, M.; Cuadrado, P.; González-Nogal, A. M.; Pulido, F. J. *Tetrahedron* **1989**, *45*, 413−424.

(24) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7662.

(25) Crump, R. A. N. C.; Fleming, I.; Urch, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 701−706.

(26) The $PhMe_2Si$ group could be introduced to **4** with excellent stereoselectivity and yield. The Tamao oxidation, however, did not proceed from this silylated product.

SCHEME 3. Total Synthesis of (+)-Lactacystin (1)



route. Finally, treatment of **2** with *N*-acetyl L-cysteine, according to the reported procedure,[6b] gave (+)-lactacystin (**1**).

Conclusion

We achieved a catalytic asymmetric total synthesis of (+)-lactacystin. Our synthesis is characteristic in that the chiral tetrasubstituted C-5 carbon was constructed at the initial stage of the total synthesis. The practical catalytic enantioselective Strecker reaction of ketoimines developed in our group allowed for this new synthetic route. A cyclic enone-derived ketoimine **7** was used as a masked, stable, α-hydroxy ketoimine equivalent. The enantioselectivity and reaction rate were quite sensitive to the catalyst preparation method. When an asymmetric catalyst was prepared from Gd(HMDS)$_3$ and ligand **8** in a 2:3 ratio, the reaction proceeded using 2.5 mol % of the catalyst, producing the C-5 chiral tetrasubstituted carbon with an excellent enantioselectivity (98% ee) and a useful reaction rate. Other stereocenters were all constructed with excellent selectivity using the steric environment constituted by this tetrasubstituted carbon: chelation-controlled Meerwein-type reduction to construct the secondary alcohol at the C-9 position, conjugate addition of a silicon followed by the Tamao oxidation to construct the secondary alcohol at the C-6 position, and the Donohoe methylation to construct the chiral carbon at the C-7 position. This work demonstrates the utility and practicality of the Gd−**8**-catalyzed enantioselective Strecker reaction of ketoimines in complex molecule synthesis. Because chiral β-hydroxy α,α-disubstituted amino acid derivatives are widely found as a chiral building block of biologically active compounds in natural sources, the method described herein should have general applicability. Efforts are ongoing to extend this methodology to the synthesis of other pharmaceutical leads containing chiral α,α-disubstituted amino acid derivatives.

Experimental Section

(1*S*)-*N*-[1-Cyano-2-isopropylcyclopent-2-en-1-yl]-*P*,*P*-diphenylphosphinic amide (16). Gd(HMDS)$_3$ solution in THF (0.2 M, 2.0 mL, 0.40 mmol) was added to a solution of ligand **8** (276 mg, 0.6 mmol) in THF (16 mL) at 4 °C, and the mixture was stirred at 50 °C for 1 h. The solvent was evaporated, and the residue was dried in vacuo for 2 h at room temperature. The resulting amorphous material was dissolved in EtCN (18.7 mL). After cooling to −40 °C, TMSCN (4.3 mL, 32 mmol) and 2,6-dimethylphenol (1.95 g, 16 mmol) in THF (6 mL + 2 mL for wash) were added. The mixture was stirred for 0.5 h at −40 °C. Then compound **7** (5.2 g, 16 mmol) was added at −40 °C. The reaction mixture was stirred for about 2.5 days. SiO_2 (50 g) was added at −40 °C to quench the reaction (Caution! HCN generation). The slurry was filtrated and washed with a mixture of CH_2Cl_2 (400 mL) and MeOH (20 mL). The combined filtrate was concentrated in vacuo. The solid residue was partially purified by flash column chromatography (EtOAc/hexane, 2:1 → EtOAc/MeOH, 20:1) to afford **16** as a white solid (5.9 g) containing the chiral ligand. The ligand was washed off from the crude mixture with toluene and hexane, as follows. Toluene (117 mL) was added to the mixture (5.9 g) and warmed at 80 °C. To this solution, hexane (47 mL) was added at the same temperature. The solution was cooled gradually to room temperature, and the precipitate was filtered to afford pure **16** (4.6 g) as a white solid. The filtrate was concentrated in vacuo. To the residue, toluene (30 mL) was again added at 80 °C, followed by the addition of hexane (12 mL). After gradually cooling to room temperature, the precipitate was filtered to afford an additional crop of **16** (0.7 g) as a white solid. These two crops were combined, and pure **16** was obtained in a 94% yield (5.3 g) as a white solid. The enantiomeric excess did not change in this washing process. M.p. 132−133 °C; IR (neat, ν_{max}) 2230, 1590, 1437, 894 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.44−7.56 (m, 6H), 5.77 (m, 1H), 3.24 (d, J = 5.8 Hz, 1H), 2.69−2.73 (m, 1H), 2.59 (sept, J = 8.2 Hz, 1H), 2.44−2.47 (m, 1H), 2.34−2.40 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 133.6, 132.5, 132.5, 132.4, 132.2, 131.4, 131.3, 131.1, 129.8, 128.8, 128.7, 128.7, 128.6, 120.4, 62.2, 40.2, 29.4, 26.9, 22.9, 22.7; ^{31}P NMR ($CDCl_3$) δ 20.9. LRMS (FAB) m/z (%): 373 [M$^+$ + Na]. HRMS (FAB) calcd for $C_{21}H_{24}N_2OP^+$ [M$^+$ + H], 351.1621; found, 351.1635. $[\alpha]^{23}_D$ +12.9° (c 0.51, $CHCl_3$, 90% ee). For the determination of the enantiomeric excess, see Supporting Information. Chiral ligand **8** was recovered as follows. The filtrate solution containing ligand **8** was evaporated, and concentrated aq HCl (20 mL) was added to the residue. The mixture was heated at 100 °C for 5 h and poured into water (50

mL). Ligand **8** was extracted with EtOAc (20 mL × 2). The combined organic phase was washed with brine (30 mL), dried (Na_2SO_4), and concentrated. Pure **8** was recovered through a silica gel column chromatography (EtOAc/hexane, 1:1, 90% yield).

Ethyl 2-Isobutyryl-5-oxo-D-prolinate (5). To a solution of **6** (217 mg, 0.73 mmol) in MeOH (12 mL) was bubbled ozone at −78 °C for 30 min. Me_2S (0.54 mL, 7.3 mmol) was then added to reduce the ozonide. The reaction mixture was gradually warmed to room temperature over 4 h and was stirred for 1 h at room temperature. *tert*-Butyl alcohol (8 mL) was added to the reaction mixture. MeOH and Me_2S were evaporated in vacuo. To the solution of the aldehyde in *tert*-butyl alcohol were added water (2 mL), NaH_2PO_4 (234 mg, 1.95 mmol), 2-methyl-2-butene (0.33 mL, 2.92 mmol), and sodium chlorite (132 mg, 1.46 mmol) at room temperature. After 2 h, saturated aq $Na_2S_2O_3$ (20 mL) and 10% aq citric acid (20 mL) were added, and the products were extracted with CH_2Cl_2 (20 mL × 2). The combined organic phase was washed with brine (20 mL), dried (Na_2SO_4), and concentrated to give the crude carboxylic acid. Concentrated H_2SO_4 (20 μL, 0.37 mmol) was added to the residue in EtOH (8 mL). The reaction mixture was heated for 9 h at 80 °C. After cooling to room temperature, the reaction mixture was poured into saturated aq $NaHCO_3$ (20 mL), and the products were extracted with EtOAc (20 mL × 2). The combined organic phase was washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc/hexane 1:1 → 2:1) to afford **5** (134 mg, 81%, 3 steps) as a colorless oil. IR (neat, ν_{max}) 1751, 1706, 1465, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.47 (brs, 1H), 4.23 (q, J = 7.0 Hz, 2H), 2.95 (sept, J = 6.7 Hz, 1H), 2.71−2.72 (m, 1H), 2.33−2.45 (m, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.6, 176.4, 169.1, 73.6, 62.8, 35.8, 29.4, 27.2, 19.8, 19.7, 14.0. LRMS (ESI) *m*/*z* (%): 249.8 [M^+ + Na]. HRMS (FAB) calcd for $C_{11}H_{18}NO_4^+$ [M^+ + H], 228.1230; found, 228.1238. $[\alpha]^{27}_D$ −86.6° (*c* 0.92, $CHCl_3$, >99% ee).

(1*S*,1′*S*)-Ethyl 2-[1′-hydroxy-2′-methylpropyl]-5-oxo-D-prolinate (18). Isopropylmagnesium bromide in THF (0.67 M, 24.8 mL, 16.6 mmol) was added dropwise to **5** (1.08 g, 4.75 mmol) in THF (158 mL) at 4 °C. After stirring for 11 h, 1 N hydrochloric acid (100 mL) was added to the reaction mixture, and the products were extracted with EtOAc (100 mL × 1) and CH_2Cl_2 (100 mL × 3). Saturated aq $NaHCO_3$ was added to the aqueous phase until the pH = 8. The products were again extracted with CH_2Cl_2 (100 mL × 4). The combined organic phase was washed with brine (200 mL), dried (Na_2SO_4), and concentrated. ^1H NMR analysis of this crude mixture indicated that the ratio of **18** and **19** was 10:1. Enantiomerically pure **18** was obtained by recrystallization as follows. After the addition of toluene (6 mL) to the solid residue, the mixture was heated at 80 °C to give a clear solution. Then hexane (7.5 mL) was added, and the slurry was cooled to room temperature. The precipitate was filtered to afford **18** (436 mg, 40%) as a white solid. The enantiomeric excess was checked by chiral HPLC to be >99% ee (DAICEL, Chiralpak AD-H, *i*-PrOH/hexane/trifluoroacetic acid = 20:80:0.1, flow = 1.0 mL/min, 220 nm, t_R = 5.9 min (minor) and 7.1 min (major)). M.p. 122−123 °C; IR (neat, ν_{max}) 3330, 1730, 1697, 1258 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (brs, 1H), 4.20−4.27 (m, 2H), 3.61 (d, J = 5.2 Hz, 1H), 2.49−2.31 (m, 4H), 1.74−1.67 (m, 1H), 1.31 (t, J = 7.5 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 173.2, 80.1, 69.3, 61.8, 31.0, 30.1, 29.9, 20.6, 17.9, 14.0. LRMS (ESI) *m*/*z* (%): 251.8 [M^+ + Na]. HRMS (FAB): calcd for $C_{11}H_{20}NO_4^+$ [M^+ + H], 230.1387; found, 230.1392. $[\alpha]^{25}_D$ +10.2° (*c* 0.95, $CHCl_3$, >99% ee).

1-*tert*-Butyl 2-Ethyl (2*S*,3*S*)-2-[(1*S*)-1-(Acetyloxy)-2-methylpropyl]-3-hydroxy-5-oxopyrrolidine-1,2-dicarboxylate (3). (Diethylamino)diphenylsilylithium in THF solution was prepared from $(Et_2N)Ph_2SiCl$ and Li in an ice bath for 3 h.[14b] This silyllithium in THF (0.233 M, 30 mL, 6.94 mmol) was added to diethyl zinc in hexane (1 M, 6.9 mL, 6.94 mmol) in THF (63 mL) at 0 °C. After 10 min, the solution was cooled to −78 °C and **4** (2.33 g, 6.31 mmol) in THF (28 mL) was added. Two portions of (diethylamino)diphenylsilylithium in THF (0.233 M, 1.1 equiv (30 mL) + 0.5 equiv (13.5 mL)) were added every 30 min before starting material **4** disappeared on TLC. A slurry of NH_4Cl (15 g) in absolute EtOH (65 mL) was added at −78 °C, and the mixture was stirred at room temperature for 12 h. After adding water, the products were extracted with EtOAc (20 mL × 2). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was partially purified by flash column chromatography (EtOAc/hexane 1:4 → 1:1) to obtain the (diethylamino)diphenylsilyl adduct (4.34 g) and the corresponding hydrolyzed silanol (0.96 g). To a solution of the (diethylamino)diphenylsilyl adduct (4.34 g) in DMF (63 mL) were added KHF_2 (982 mg, 12.6 mmol) and 3-chloroperoxybenzoic acid (4.7 g, 18.9 mmol) in a water bath. After 2 h, KHF_2 (982 mg) and 3-chloroperoxybenzoic acid (4.7 g) were further added. After stirring for 2 h at room temperature, the reaction mixture was poured into saturated aq $Na_2S_2O_3$ (30 mL). The products were extracted with EtOAc (40 mL × 2). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1 → 2:1) to afford **3** (1.23 g, 50%, 2 steps). Meanwhile, KHF_2 (327 mg, 4.2 mmol) and 3-chloroperoxybenzoic acid (1.56 g, 6.31 mmol) were added to a solution of the silanol (0.96 g) in DMF (21 mL) in a water bath. After 4 h, the reaction mixture was poured into saturated aq $Na_2S_2O_3$. The workup and purification as described above gave **3** (162 mg, 7%, 2 steps) as a colorless oil (combined yield = 57%). IR (neat, ν_{max}) 3471, 2977, 1790, 1748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (d, J = 4.0 Hz, 1H), 4.87 (dd, J = 8.6 Hz, 1H), 4.18 (q, J = 6.9 Hz, 2H), 2.88, 2.84 (dd, J = 8.6, 9.2 Hz, 1H), 2.74, 2.70 (dd, J = 8.6, 9.2 Hz, 3H), 2.43 (brs, 1H), 2.12 (s, 3H), 1.87 (brs, 1H), 1.82, 1.81 (dsept, J = 3.4, 6.9 Hz, 9H), 1.47 (s, 9H), 1.23 (t, J = 6.9 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 169.2, 169.0, 148.6, 84.7, 75.5, 73.7, 65.6, 61.8, 38.1, 29.1, 27.7, 21.3, 21.0, 17.2, 14.0. LRMS (ESI) *m*/*z* (%): 410.2 [M^+ + Na]. HRMS (FAB): calcd for $C_{18}H_{30}NO_8^+$ [M^+ + H], 388.1966; found, 388.1962. $[\alpha]^{26}_D$ −20.9° (*c* 0.84, $CHCl_3$, >99% ee).

Lactacystin (1). The conversion of **2** to **1** was conducted following the literature procedure.[6b] To a solution of β-lactone **2** (17.5 mg, 0.082 mmol) in CH_2Cl_2 (2 mL) were added triethylamine (31 μL, 0.22 mL) and *N*-acetyl-L-cysteine (9.5 mg, 0.058 mmol), and the mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated and purified twice by flash column chromatography (first, CH_2Cl_2/MeOH/AcOH, 10:2:1; second, EtOAc/MeOH/AcOH, 10:1:1) to afford lactacystin **1** (12.8 mg, 58%). The ^1H NMR data matched data reported in the litrature.[6b,m] ^1H NMR (500 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.79 (brs, 1H), 5.40 (brs, 1H), 5.34 (d, J = 6.9 Hz, 1H), 4.59 (d, J = 6.9 Hz, 1H), 4.05 (dd, J = 5.1, 14.0 Hz, 1H), 3.86−3.79 (m, 1H), 3.47 (dq, J = 7.5, 7.5 Hz, 1H), 2.29−2.21 (m, 1H), 2.03 (s, 3H), 1.56 (d, J = 7.5 Hz, 3H), 1.25 (d, J = 6.9 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H).

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Supporting Information Available: Experimental procedures, determination of enantiomeric excess, and chiral HPLC and NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

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