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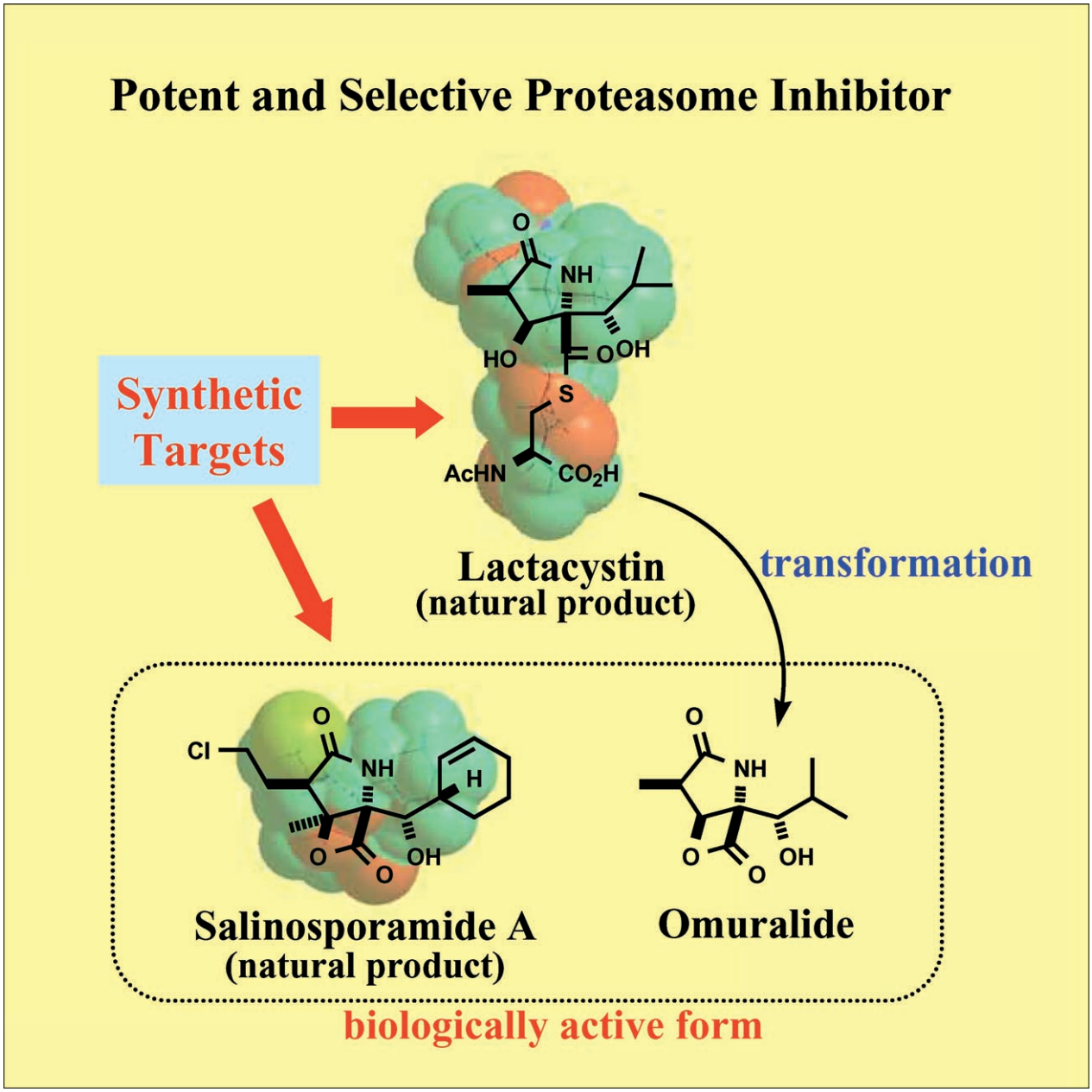
Total Synthesis of Lactacystin and Salinosporamide A

Masakatsu Shibasaki,* Motomu Kanai,* and Nobuhisa Fukuda[a]



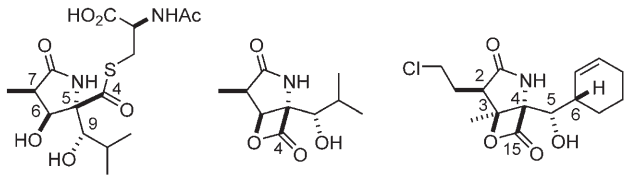
Abstract: Lactacystin and salinosporamide A are fascinating molecules with regard to both their chemical structures and biological activities. These naturally occurring compounds are potent and selective proteasome inhibitors. The molecular structures are characterized by their densely functionalized γ-lactam cores. The structure and biological properties of these two compounds are attracting the attention of many chemists as challenging synthetic targets. We discuss their synthetic strategies in this review.

Keywords: asymmetric synthesis · lactacystin · lactams · natural products · salinosporamide A

1. Introduction

Proteolytic degradation of ubiquitinated cellular proteins by the 20S proteasome is an essential process in living cells.[1] This process is involved in a broad array of cellular functions, such as regulation of the cell cycle and cell division, regulation of transcription factors, and assurance of cellular quality control. Aberrations in the ubiquitin–proteasome system are implicated in the pathogenesis of human disease, such as malignancies and neurodegenerative disorders. Proteasome targeting has recently emerged as a new avenue for the development of mechanism-based drugs that can potentially treat those diseases. For example, proteasome inhibitors can be effective anticancer drugs because these compounds cause the accumulation of proteasome substrates, including cyclins and transcription factors, and induce cell-cycle arrest with apoptotic program activation.

(+)-Lactacystin (**1**) is a potent and selective proteasome inhibitor that was isolated from *Streptomyces sp.* by Omura et al.[2] The cell-permeable, biologically active form derived from lactacystin is (−)-*clasto*-lactacystin (also known as omuralide; **2**),[3] which is generated by lactonization with cystein elimination. The highly strained β-lactone of **2** can acylate the N-terminal threonine of the proteasome, a crucial amino acid for protease activity.[4] Thus, lactacystin is a proteasome inhibitor that covalently blocks the catalytically active site.[5]



(+)-lactacystin (**1**) (−)-*clasto*-lactacystin (**2**) (−)-salinosporamide A (**3**)

Recently, a more-potent proteasome inhibitor, (−)-salinosporamide A (**3**), was isolated from a marine actinomycete by Fenical and co-workers.[6] Salinosporamide A (**3**) inhibits proteasomal proteolytic activity with an IC_{50} value of 1.3 nM. In a parallel assay, the IC_{50} of **2** was 49 nM. Moreover, **3** has potent in vitro cytotoxicity ($LC_{50} < 10$ nM against 4 different cancer cell lines). X-ray crystallographic studies revealed that **3** binds to the same threonine residue of the proteasome that is acylated by **2**.[7] The enhanced activity of **3** relative to **2** is partly attributed to irreversible proteasome inhibition by **3**. On the other hand, proteasomes acylated by **2** are slowly hydrolyzed, resulting in the complete recovery of proteasome activity within 24 h.[8] The irreversibility of proteasome inhibition by **3** is explained as follows: after acylation of the proteasome by **3**, the free C3 alcohol displaces the chloride atom of the C2 side chain to form tetrahydrofuran **4** (Scheme 1); the tetrahydrofuran moiety of **4** occupies the position of a water molecule in the protein, which can otherwise hydrolyze the acylated enzyme, thus preventing the acylated proteasome from being hydrolyzed.

Owing to the potent biological activity and fascinating inhibitory mechanism of **1** and **3**, as well as their complex chemical structure, many synthetic chemists study them as synthetic targets. More than 10 groups have reported total syntheses of lactacystin, and three have reported total syntheses of salinosporamide A. The focus of this review is to discuss the synthetic strategies of these two compounds. There are three excellent reviews of the syntheses and biological studies of **1** and **2** achieved prior to 2000.[9] Therefore, we describe the total syntheses of **1** described in those

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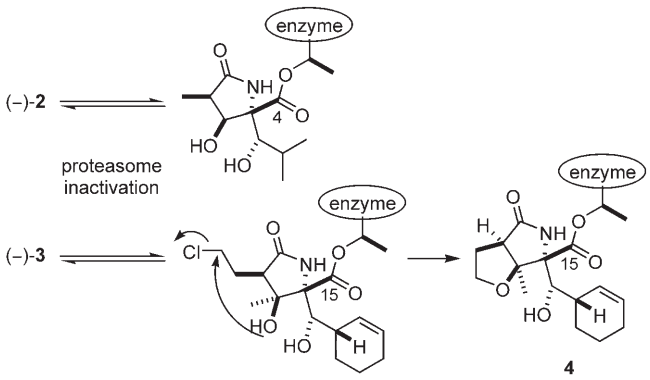


Scheme 1. Action mechanism and comparison of **2** and **3**.

previous reviews only briefly, focusing on the more recently published stereocontrol strategies.

2. Total Synthesis of Lactacystin

2.1 Corey Synthesis

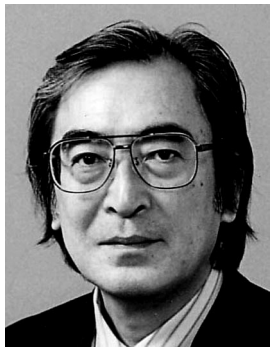
The first total synthesis of lactacystin was achieved by Corey et al. in 1992.[10] Subsequently, two different synthetic routes of lactacystin[11] and its hydrolytically more stable analogue **27** (α-methylomuralide)[12] were reported by the same group.

The first Corey route utilized two aldol reactions to construct four contiguous stereogenic centers (C5, C6, C7, and C9; Scheme 2). The stereochemistry of the tetrasubstituted C5 and trisubstituted C9 was controlled by applying the self-reproduction method of Seebach et al.[13] Thus, the aldol reaction between isobutyraldehyde and oxazolidine **5** in the presence of 5 equivalents of LiBr afforded the desired isomer **6** in 77% yield and with greater than 98% diastereomeric purity by trituration of the crude products. Enantiomerically and diastereomerically pure **6** was obtained in 51% yield after recrystallization. After conversion into aldehyde **7**, an MgI_2-mediated Mukaiyama aldol reaction between **7** and *E* trimethylsilyl enolate **8** produced the desired *anti* product **10** in 77% yield (*anti*/*syn* = 9:1). The face selectivity of the aldehyde was greater than 35:1 in this step. It was proposed that **8** approached the activated aldehyde **7** by chelating Mg from the less-hindered side in a synclinal fashion (**9**). This doubly diastereoselective aldol reaction was applied to the synthesis of lactacystin analogues containing alkyl groups that were longer than the methyl group at C7. After **10** was converted into **11**, *clasto*-lactacystin (**2**) was synthesized through β-lactone formation with BOPCl. Cysteine was introduced directly into **2**, and the total synthesis of lactacystin was completed.

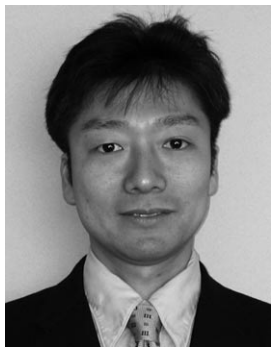
Interest in the biological effects of replacing the C9 isopropyl group with other lipophilic groups led to the development of the second synthetic route from Corey et al., in which the isopropyl group was introduced at a later stage (Scheme 3).[11] This synthesis utilized a bulky thiomethyl group on the γ-lactam as a directing group for the construction of the C5 and C6 stereogenic centers. Asymmetric hydrolysis of **12** by porcine liver esterase followed by recrystallization of the quinine salt of the resulting carboxylic acid produced **13** with 95% *ee*. After conversion into γ-lactam

Abstract in Japanese:

ラクタシスチン（**1**）は，1991 年に大村らによって単離、構造決定された天然物であり，クラストラクタシスチン（オムラリド：**2**）に変換された後に細胞内に取り込まれ，強力かつ選択的なプロテアソーム阻害活性を発現する。また，サリノスポラミドA（**3**）は，2003 年に Fenical によって単離，構造決定された，**1** および **2** よりも高い活性を示すプロテアソーム阻害剤である。これらの化合物はその高い生物活性，比較的小分子でありながら複雑な構造を有している点，医薬への展開の可能性，ユニークな活性発現機構といった観点から，多くの有機合成化学者の関心を集めてきた。本総説では，現在までに発表されているこれらの化合物の全合成ルートについて，立体制御戦略に中心をおいて概説する。

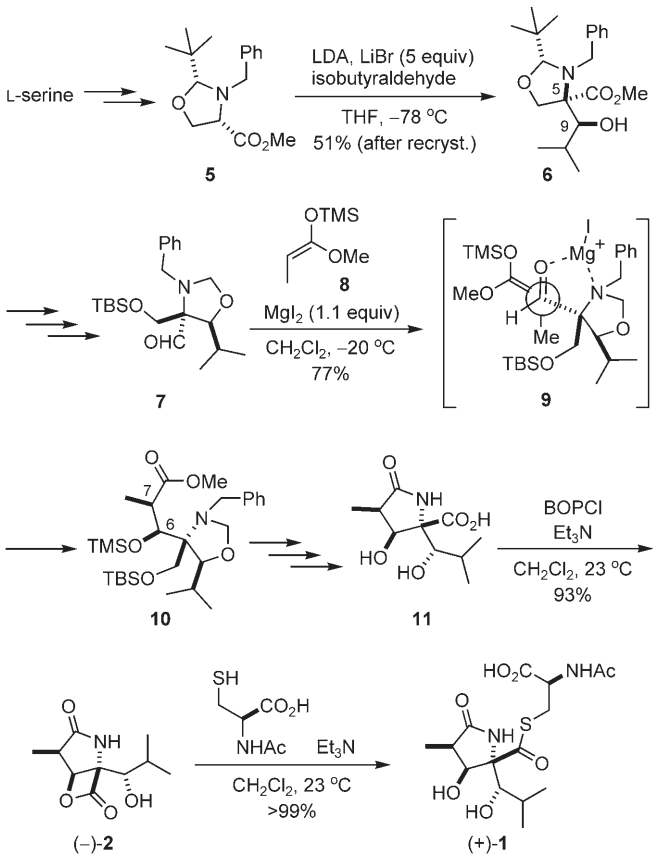


Masakatsu Shibasaki *was born in 1947 in Saitama, Japan, and received his PhD from the Univ. of Tokyo in 1974 with Prof. S. Yamada. After postdoctoral studies with Prof. E. J. Corey at Harvard Univ., he returned to Japan in 1977 and joined Teikyo Univ. as an Associate Prof. In 1983 he moved to Sagami Chemical Research Center as a group leader, and in 1986 took up a professorship at Hokkaido Univ., before returning to the Univ. of Tokyo as a Prof. in 1991. His research interests entail asymmetric catalysis as well as the medicinal chemistry of biologically significant compounds.*



Motomu Kanai *was born in 1967 in Tokyo, Japan, and received his PhD from Osaka Univ. in 1995 under the direction of Prof. Kiyoshi Tomioka before doing postdoctoral studies with Prof. Laura L. Kiessling at the Univ. of Wisconsin. In 1997 he returned to Japan and joined Prof. Shibasaki's group at the Univ. of Tokyo as an assistant professor. He is currently an associate professor in the Shibasaki group. His research interests entail the design and synthesis of functional molecules.*

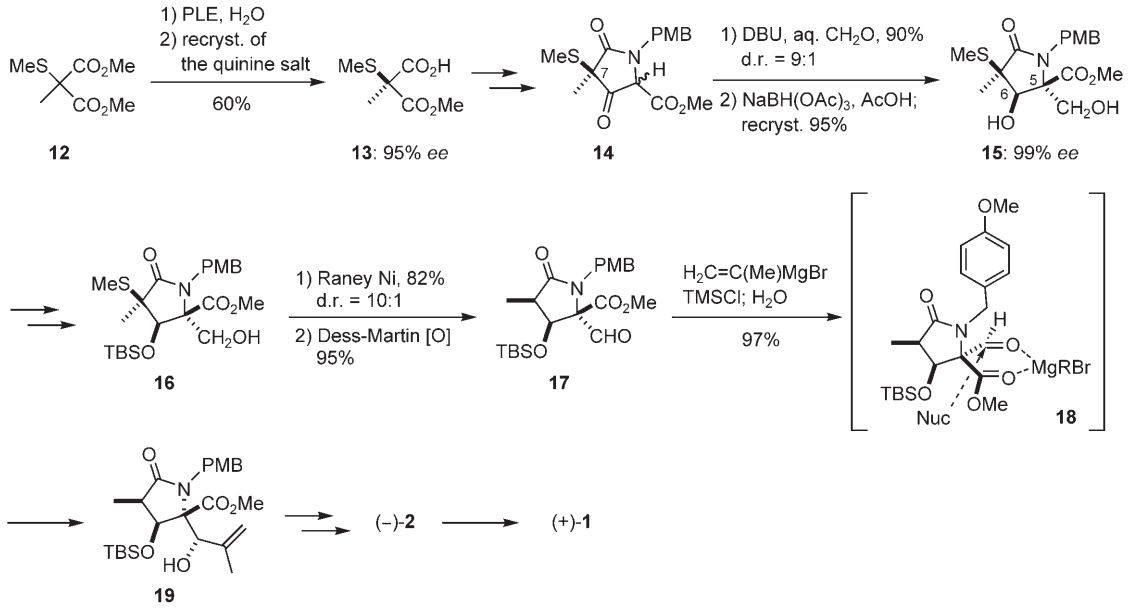
Nobuhisa Fukuda *was born in 1975 in Nara, Japan, and received his BSc (1997) and MSc (1999) from the Univ. of Osaka. He joined Sumitomo Pharma. Co., Ltd. in 1999 and has been with Dainippon Sumitomo Pharma. Co., Ltd. as a researcher since 2005. He is also currently a researcher in Prof. Shibasaki's group at the Univ. of Tokyo, having also joined them in 2005. He is interested in medicinal, organic, and process chemistry.*



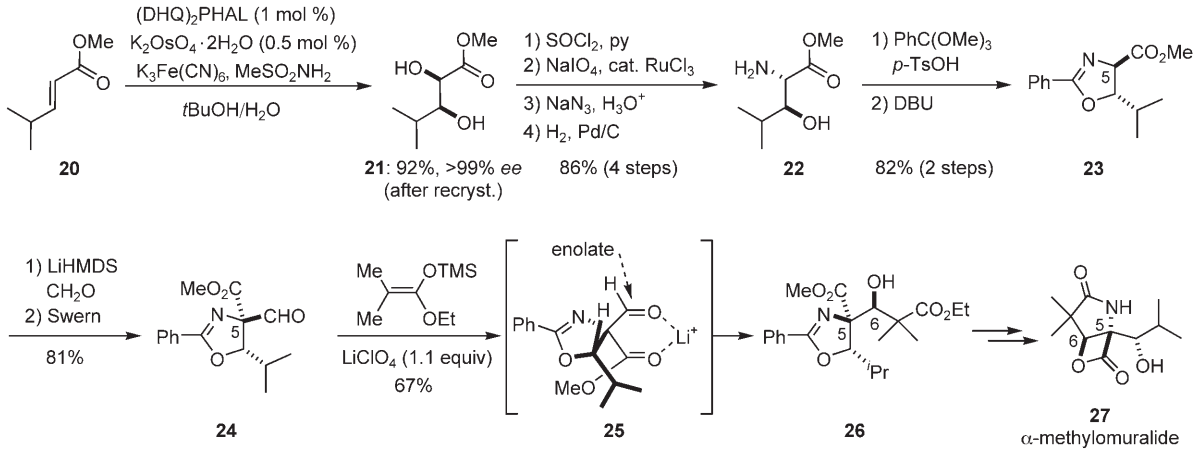
Scheme 2. The first Corey total synthesis of lactacystin. BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, LDA = lithium diisopropylamide, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

14, both the introduction of a hydroxymethyl group at C5 and reduction of the C6 ketone proceeded from the less-hindered side opposite the methylthio group. Enantiomerically pure **15** was obtained through recrystallization. Desulfurization was performed with Raney Ni to produce the desired stereoisomer in a 10:1 ratio. Oxidation of the primary alcohol with Dess–Martin periodinane afforded aldehyde **17**, which was subjected to a Grignard reaction in the presence of TMSCl. The addition of a propenyl group selectively proceeded from the less-hindered side of the presumed six-membered chelate **18** to produce **19** as a single isomer. TMSCl trapped the intermediate magnesium alkoxide to avoid a rapid retroaldol reaction.

The third route (Scheme 4) targeted α-methylomuralide (**27**),[12] which may be superior to **1** and **2** as a proteasome-selective anticancer agent. Sharpless asymmetric dihydroxylation of *E* ester **20** with $(DHQ)_2PHAL$ (1 mol%) and $K_2OsO_4{\cdot}2H_2O$ (0.5 mol%) and stoichiometric $K_3[Fe(CN)_6]$ in *t*BuOH/H_2O (1:1) containing $CH_3SO_2NH_2$[14] gave enantiomerically pure diol **21** in 92% yield after recrystallization. The *syn* diol **21** was converted into *anti*-3-hydroxyleucine **22** via a cyclic sulfate. After two-step conversion from **22** into *trans*-oxazolidine **23** via *cis*-oxazolidine formation and epimerization of C5 with DBU, a hydroxymethyl group was introduced to C5 selectively from the opposite side of the isopropyl group through an aldol reaction. Swern oxidation afforded aldehyde **24**, which was subjected to the Mukaiyama aldol reaction in the presence of $LiClO_4$ to produce **26** selectively in 67% yield. The observed stereoselectivity was explained from the chelation model **25**. Hydrolysis of **26** under acidic conditions concomitant with the construction of the γ-lactam, saponification of the methyl ester, and β-lactone formation produced α-methylomuralide.



Scheme 3. The second Corey total synthesis. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, d.r. = diastereomer ratio, Nuc = nucleophile, PLE = porcine liver esterase, PMB = *p*-methoxybenzyl.



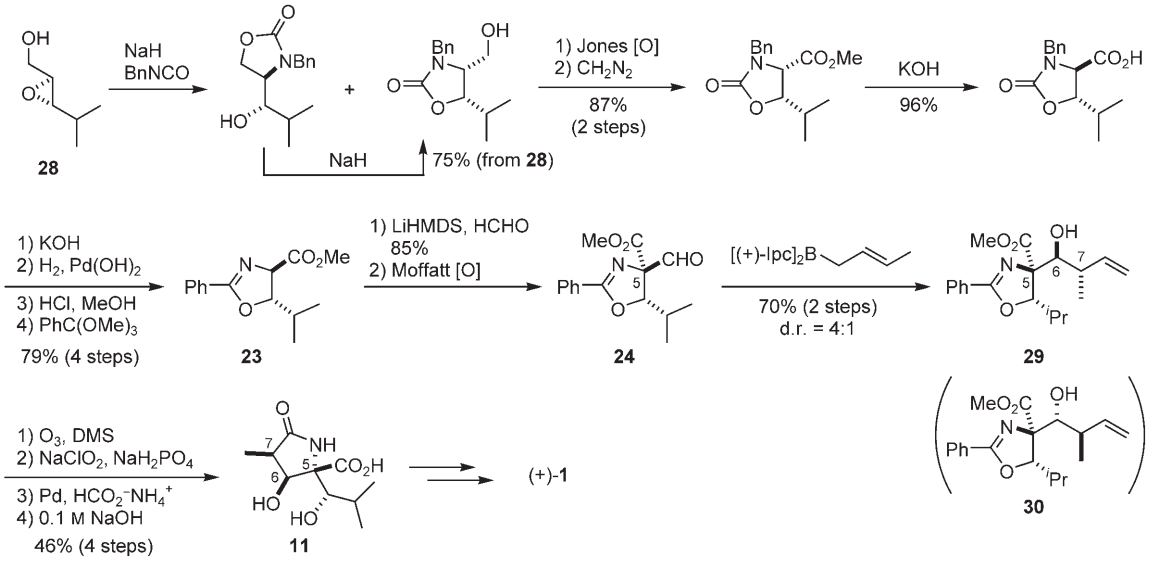
Scheme 4. The Corey α-methylomuralide synthesis. DHQ = dihydroquinino, PHAL = phthalazine, Ts = tosyl.

2.2 Omura and Smith Synthesis

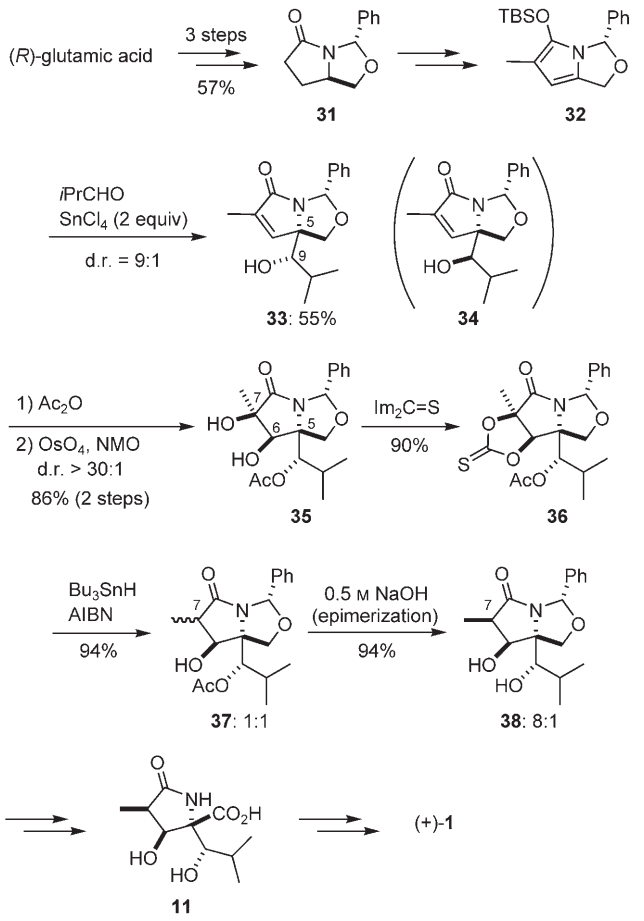
Stereoselective transformation from hydroxyleucine derivative **23** to **24** was initially developed as a key step in the synthesis by Omura, Smith, and co-workers.[15] This transformation is highly reliable and convenient for the construction of the C5 tetrasubstituted carbon atom of **1**, and several groups later utilized this method. In the Omura–Smith synthesis, **23** was produced from enantiomerically enriched (97% *ee*) epoxy alcohol **28**, which was obtained by Sharpless–Katsuki epoxidation (Scheme 5).[16] The asymmetric crotylation of Brown and Bhat[17] using (*E*)-crotyl(diisopinocamphenyl)-borane was applied to aldehyde **24** to produce the contiguous stereocenters at C6 and C7 with a 4:1 ratio (**29**/**30**). Ozonolysis and subsequent perchlorite oxidation followed by transfer hydrogenation and saponification afforded Corey intermediate **11**, which was converted into lactacystin with the Corey protocol.

2.3 Baldwin Synthesis

The synthesis by Baldwin and co-workers commenced with the (*R*)-glutamic acid derived oxazolidine **31**, and the chiral tetrasubstituted C5 was constructed by a vinylogous aldol reaction with excellent stereoselectivity with the self-reproduction method (Scheme 6).[18] α Methylation followed by dienolate formation afforded **32**, which was subjected to a $SnCl_4$-mediated stereoselective vinylogous Mukaiyama aldol reaction to produce **33** in 55% yield. The face selectivity of the enolate was nearly perfect (from the α side *trans* to the phenyl group), while the face selectivity of the aldehyde (**33**/**34**) was 9:1. After protection of the secondary alcohol at C9 by the acetyl group, dihydroxylation with OsO_4 and NMO produced diol **35** with excellent selectivity. The dihydroxylation proceeded from the less-hindered β side of the $\Delta_{6,7}$ olefin, opposite the bulky C5 substituent. The tertiary hydroxy group at C7 was selectively removed via the cyclic thiocarbonate **36** with Bu_3SnH in the presence of AIBN,



Scheme 5. The Omura–Smith synthesis. DMS = dimethylsulfide, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, Ipc = isopinocamphenyl.



Scheme 6. The Baldwin synthesis. AIBN = 2,2′-azobisisobutyronitrile, Im = imidazole, NMO = *N*-methylmorpholine *N*-oxide.

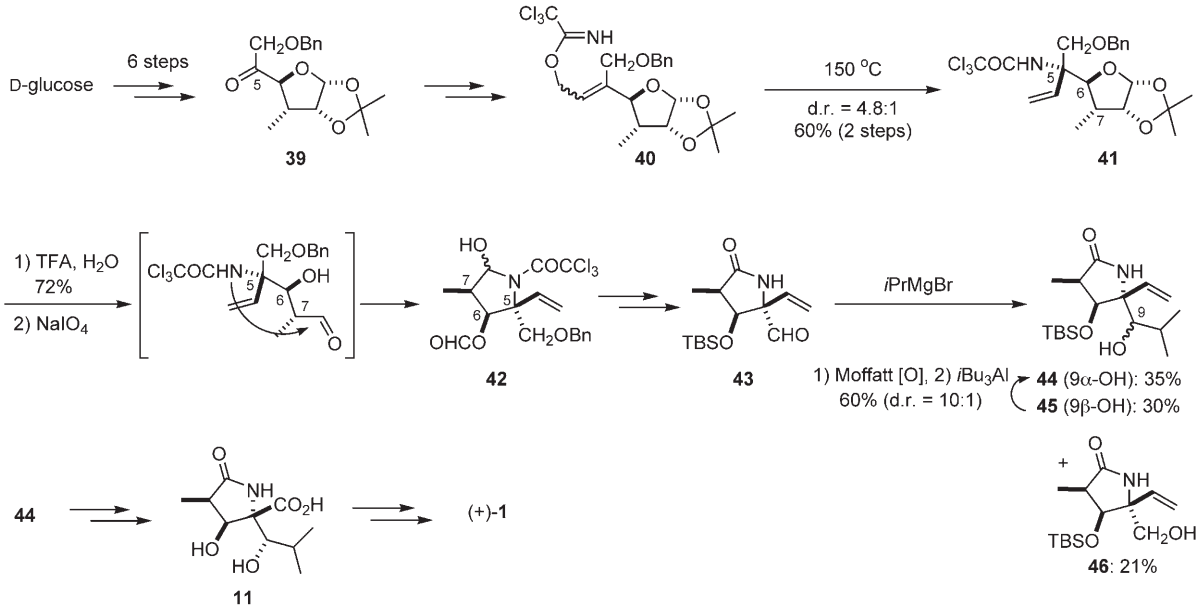
which resulted in an approximately 1:1 mixture of the C7 epimers **37**. Treatment of **37** with base epimerized C7 to the more-stable and desired isomer **38**. Hydrogenolysis of the benzylidene aminal followed by oxidation of the primary alcohol afforded Corey intermediate **11**, which was converted into lactacystin by using a modification of the Corey method.

2.4 Chida Synthesis

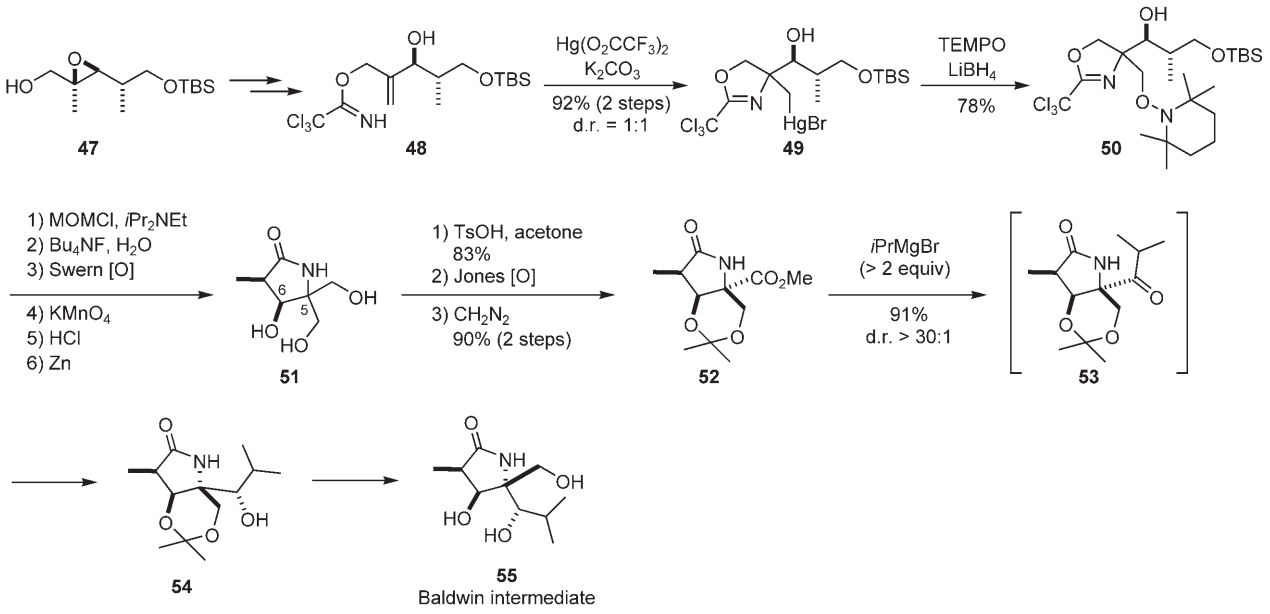
The synthesis by Chida et al.[19] utilized D-glucose derivative **39** as the starting chiral building block for the C6 and C7 contiguous stereogenic centers of lactacystin (Scheme 7). Honor–Wittig olefination of the ketone at C5 ($E/Z = 1:1$) followed by trichloroacetoimidate formation led to allylimidate **40**. Overman rearrangement of **40** produced **41**, which contains the tetrasubstituted C5, in a 4.8:1 ratio with the desired isomer as the major product. Hydrolysis of the acetonide and oxidative cleavage of the resulting diol spontaneously afforded the cyclized product **42**. After **42** was converted into aldehyde **43**, the addition of *i*PrMgBr produced a roughly 1:1 mixture of diastereomers derived from the stereochemistry of the C9 secondary alcohol (**44** and **45**) together with the reduced primary alcohol **46**. The undesired **45** was recycled by oxidation and stereoselective reduction with $i\text{Bu}_3\text{Al}$. Isolated **44** was converted into Corey intermediate **11**, and the total synthesis of **1** was completed by following the Corey and Omura–Smith procedures.

2.5 Kang Synthesis

The synthesis by Kang and Jun started from the known enantiomerically enriched epoxy alcohol **47** (Scheme 8),[20] which can be synthesized by using Sharpless asymmetric ep-



Scheme 7. The Chida synthesis. TFA = trifluoroacetic acid.

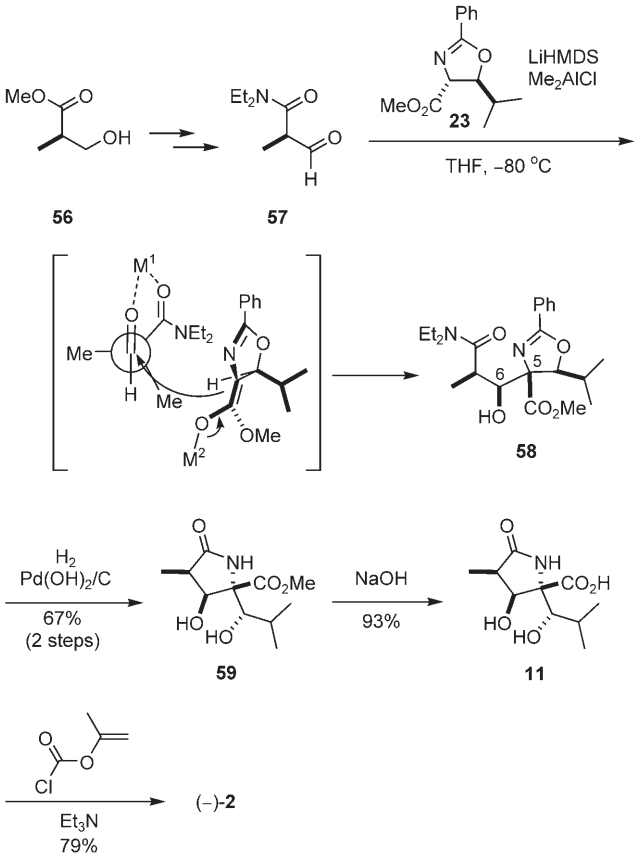


Scheme 8. The Kang synthesis. MOM = methoxymethyl, TEMPO = 2,2,6,6-tetramethylpipedinyloxy.

oxidation. After epoxide opening via deprotonation and selective chloroimidate formation of the primary alcohol, **48** was subjected to intramolecular mercurioamidation to produce oxazoline **49** as a 1:1 mixture of diastereomers. Treatment of **49** with TEMPO and $LiBH_4$[21] afforded **50**, which was converted into γ-lactam **51** over several steps. The two hydroxymethyl groups of **51** were differentiated by six-membered acetal formation using the secondary alcohol at C6, thus producing the desired acetonide in 83% yield. In this reaction, undesired acetonide formation with two primary alcohols also occurred in 8% yield. The free primary alcohol of the desired acetonide was oxidized, and the resulting acid was esterified to give **52**. The addition of more than 2 equivalents of *i*PrMgBr produced the corresponding ketone **53** as the initial product, which was reduced stereoselectively by excess Grignard reagent to give the desired alcohol **54** in 30:1 selectivity. The Kang formal total synthesis was completed by converting **54** into Baldwin intermediate **55**.

2.6 Adams Synthesis

The synthesis of *clasto*-lactacystin by Adams and co-workers utilized a well-designed stereoselective aldol reaction between oxazoline **23** and chiral aldehyde **57** as the initial key step (Scheme 9).[22] This aldol reaction produced a contiguous tetrasubstituted carbon center C5 and trisubstituted carbon center C6 through carbon–carbon bond formation. Oxazoline **23** was synthesized through a related method described in Scheme 4 by using Sharpless dihydroxylation. Aldehyde **57** was synthesized from the known alcohol **56**. Interestingly, **57** was configurationally stable even after 3 months when stored at −20 °C. The crucial aldol reaction proceeded at −80 °C to produce **58** with complete stereoselectivity. The stereochemical outcome of this reaction is explained by considering that bond formation occurs between the less-hindered enantiotopic faces of the *Z* enolate derived from **23** and **57** chelating to a metal. Because **58** is prone to



Scheme 9. The Adams synthesis.

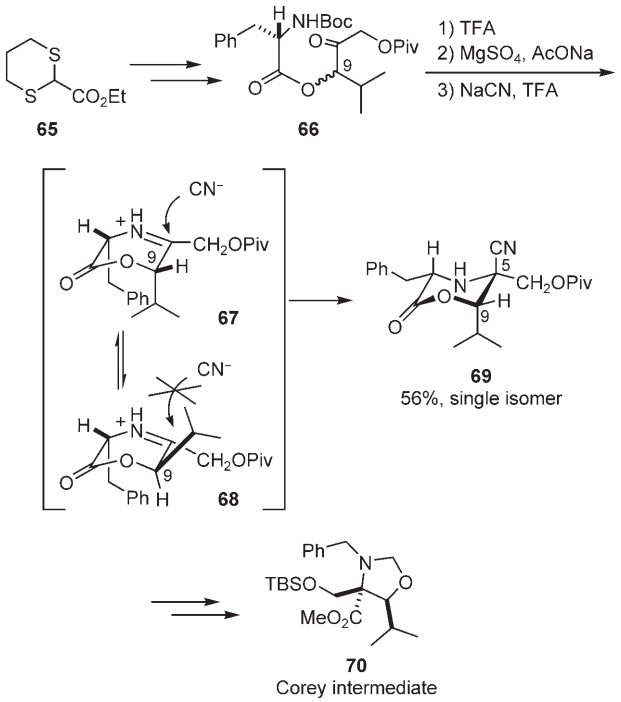
the retroaldol reaction, crude **58** was subjected to hydrogenolysis of the oxazoline by using $Pd(OH)_2$ on carbon as a catalyst. The γ-lactam formed during the hydrogenolysis, and **59** was obtained in one pot. Hydrolysis of the methyl ester under basic conditions produced Corey intermediate **11**, which was converted into **2** by using the mixed anhydride method.

2.7 Panek Synthesis

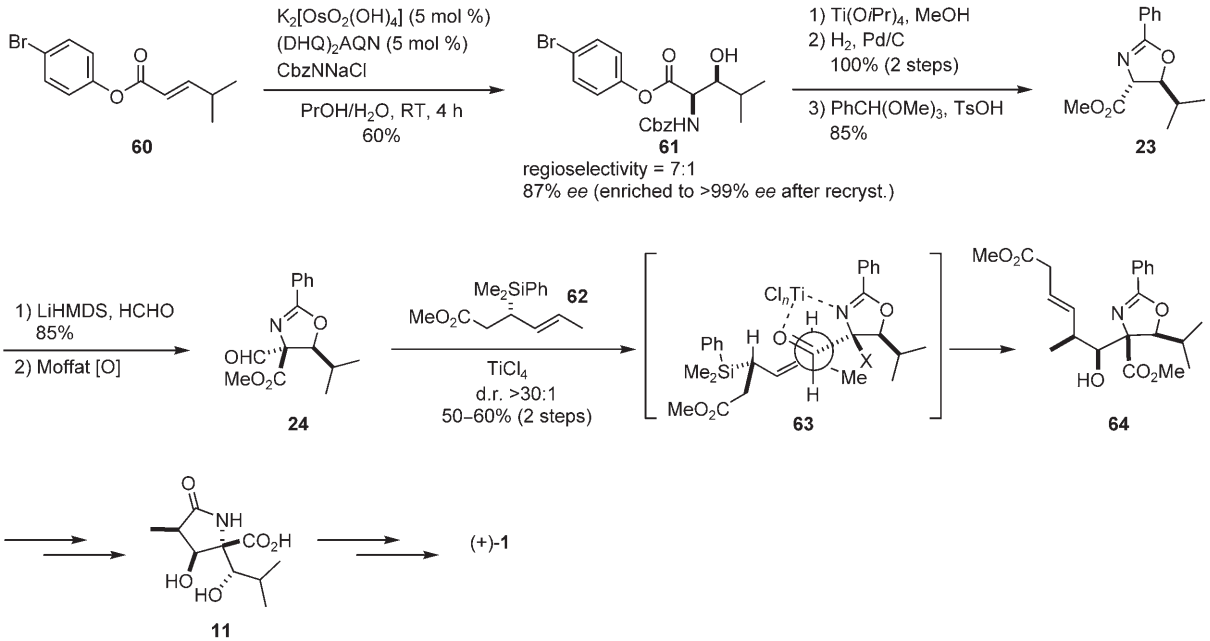
The synthetic strategy of Panek and Masse[23] was similar to that of Omura and Smith, except that Sharpless asymmetric aminohydroxylation[24] was used instead of asymmetric dihydroxylation for the synthesis of **23**, and asymmetric crotylation of aldehyde **24** with chiral crotylsilane **62**[25] instead of the Brown crotylboration was used (Scheme 10). Thus, asymmetric aminohydroxylation of ester **60** proceeded with a 7:1 regioselectivity in favor of the production of α-amino ester **61** with high enantioselectivity (87% *ee*). Enantiomerically pure **61** was obtained through recrystallization. Oxazoline **23**, obtained in three steps from **61**, was transformed into aldehyde **24** via formylation followed by Moffat oxidation. The crucial allylation of **24** with **62** proceeded with excellent diastereoselectivity (>30:1) in the presence of $TiCl_4$ through a presumed linear transition state **63** to give **64**. The common intermediate **11** was produced from **64** over several steps.

2.8 Ohfune Synthesis

The formal synthesis by Ohfune and co-workers utilized a dynamic diastereoselective Strecker reaction to construct the C5 tetrasubstituted stereogenic center.[26] The precursor of this key reaction (**66**) was synthesized from dithiane **65** (Scheme 11). After removal of the *N*-Boc group, the key Strecker reaction proceeded with concomitant epimerization at C9 via imine/enamine tautomerization and a kinetic trap of **67** through a cyanide attack from the less-hindered β side to produce **69** with the desired stereochemistry at C5 and



Scheme 11. The Ohfune synthesis. Boc = *tert*-butoxycarbonyl, Piv = pivaloyl.



Scheme 10. The Panek synthesis. AQN = anthraquinone, Cbz = benzyloxycarbonyl.

C9 in 56% yield as the sole product. From **69**, Corey intermediate **70** was synthesized over several steps.

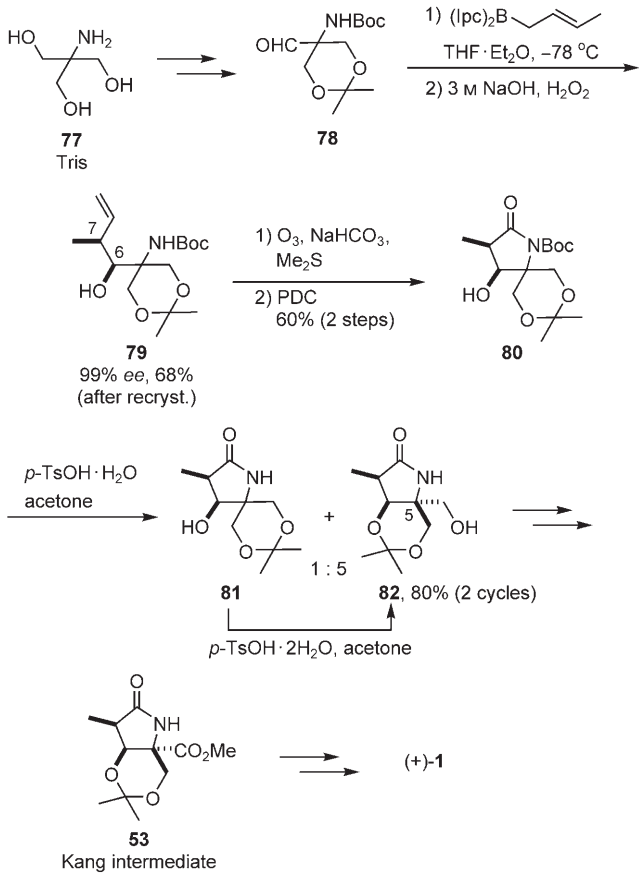
2.9 Pattenden Synthesis

The formal synthesis by Pattenden and co-workers[27] started from Sharpless epoxidation of enyne **71** to produce epoxy alcohol **72** in 66% yield with 90% *ee* (Scheme 12). Trichloromethylimidate formation at the primary alcohol followed by epoxide opening in the presence of Et_2AlCl afforded oxazoline **73**, which was converted into α-bromo amide **74** over several steps, including hydrolysis of the oxazoline and N-acylation with α-bromopropionoyl chloride. The crucial radical cyclization of **74** proceeded with Bu_3SnH in the presence of a catalytic amount of AIBN under toluene reflux conditions to produce γ-lactam **75** in 70% yield as a 2:1 mixture of stereoisomers at C7. The stereochemistry of C7 was adjusted through sulfanylation of the β-ketolactam derived from **75**. Finally, Corey intermediate **15**[11] was synthesized from **76** over three steps, including a stereoselective reduction with $NaBH(OAc)_3$ to construct the C6 secondary alcohol.

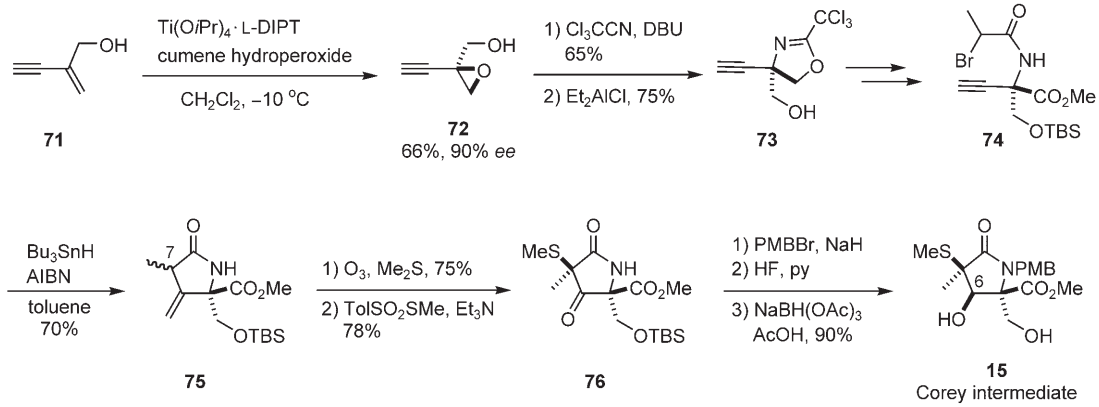
2.10 Hatakeyama Synthesis

As described above, lactacystin synthesis was intensively reported from 1992 to 1999. After an interval of several years, lactacystin is again drawing much attention as a synthetic target (2004–present). There are several reasons for this recent trend: 1) protein degradation by proteasomes is recognized as an essential process for living cells; 2) the proteasome pathway is a new promising drug target; and 3) recent advances of synthetic technology have made it possible to address the difficulty in stereocontrol of lactacystin synthesis by using new approaches.

In the synthesis by Hatakeyama and co-workers,[28] the chirality at the tetrasubstituted C5 was constructed through desymmetrization of acetal **80** by utilizing the secondary alcohol at C6 (Scheme 13). This strategy is similar to that used in the Kang synthesis. Aldehyde **78** was synthesized from Tris (**77**) via Boc protection, acetal formation, and Swern oxidation. Crotylboration of **78** with Brown reagent produced homoallylic alcohol **79**, which contains the correct C6 and C7 stereochemistry with 90% *ee*. Distillation followed by recrystallization afforded the enantiomerically pure **79**. γ-Lactam **80** was obtained from **79** through ozonolysis and oxidation. Treatment of **80** with *p*-TsOH in acetone produced an equilibrium mixture of **81** and **82** with the desired **82** as the major isomer (5:1). Pure **82** was obtained by fractional crystallization of the mixture, and the residue was again subjected to the equilibrium process. After two cycles,



Scheme 13. The Hatakeyama synthesis. PDC = pyridinium dichromate.



Scheme 12. The Pattenden synthesis. DIPT = diisopropyl tartrate, py = pyridine, Tol = *p*-tolyl.

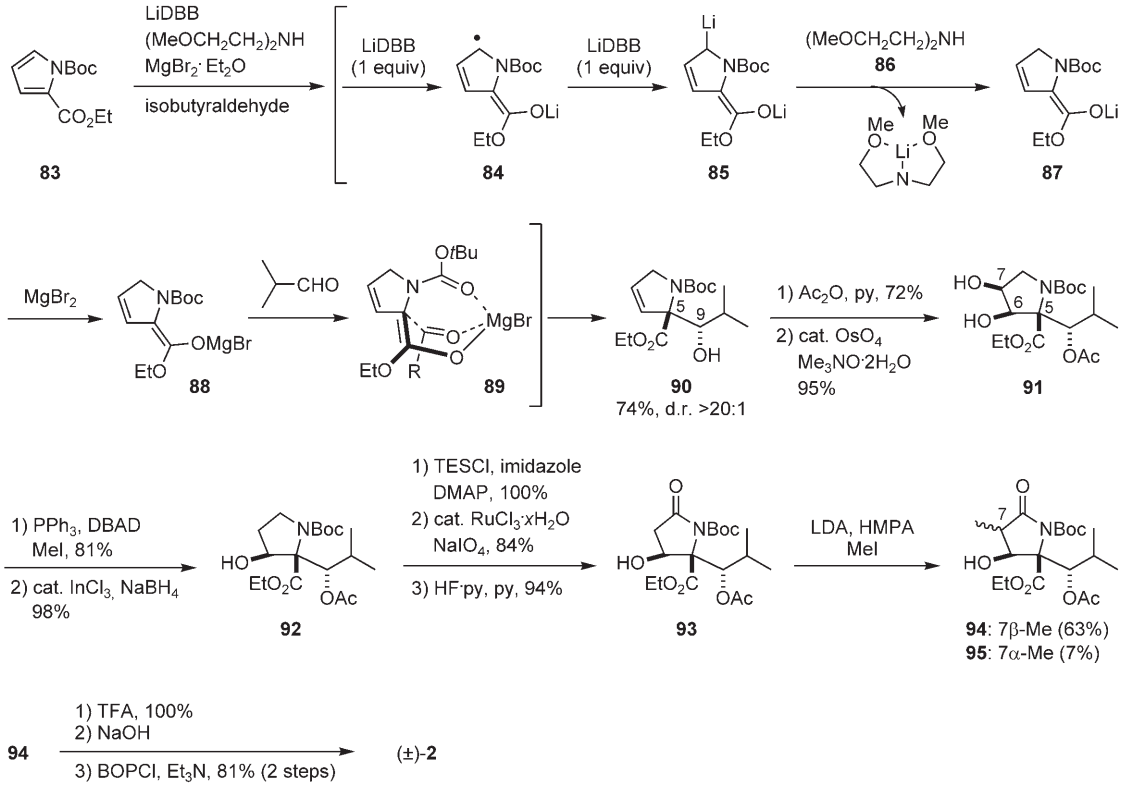
82 was obtained in 80% yield. Notably, no column chromatography was necessary from **77** to **82**. Oxidation of **82** followed by methyl ester formation afforded Kang intermediate **53**, which was converted into lactacystin **1** by following the reported procedures.

2.11 Donohoe Racemic Synthesis

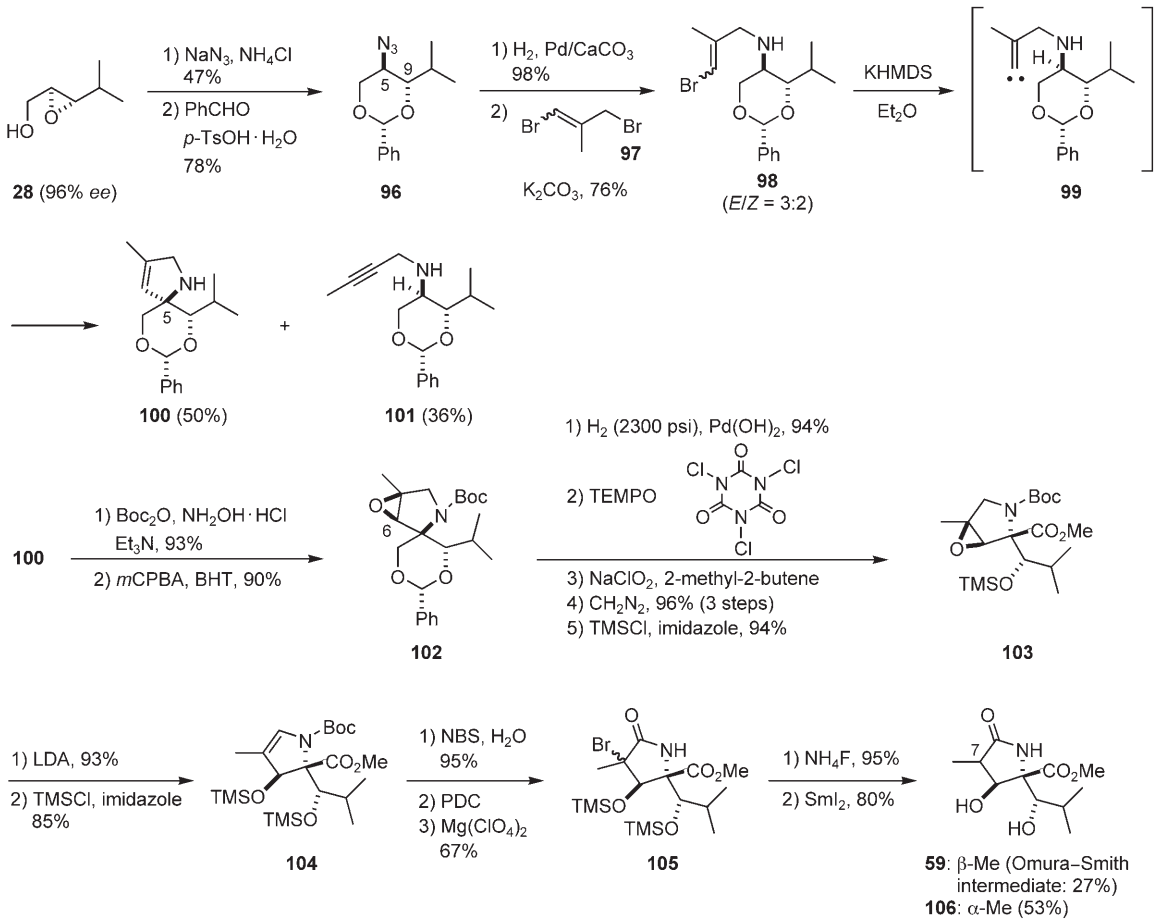
Donohoe et al. reported a short racemic synthesis of *clasto*-lactacystin (**2**) by using a diastereoselective reductive aldol reaction of pyrrole carboxylic acid derivative **83** (Scheme 14).[29] Iterative single-electron transfer from LiDBB to **83** produced dianion **85**, of which the more-reactive carbanion was quenched with bis(methoxyethyl)amine (**86**). After transmetalation of the lithium enolate to magnesium enolate **88**, isobutyraldehyde was added. The aldol reaction proceeded through a boat transition state **89**, and the desired *anti* aldol **90** was obtained in 74% yield with greater than 20:1 diastereoselectivity. Protection of the secondary alcohol at C9 and dihydroxylation with a catalytic amount of OsO_4 in the presence of a stoichiometric amount of Me_3NO selectively afforded diol **91**. The stereochemical outcome of this dihydroxylation step is explained by considering that OsO_4 approaches the olefin from the side opposite to the bulky isobutyloxy group at C5. The less-hindered C7 (relative to C6) is deoxygenated by halogenation under Mitsunobu conditions followed by dehalogenation under radical conditions in the presence of a catalytic amount of $InCl_3$[30] to produce monoalcohol **92**. Oxidation of the pyrrolidine to the γ-lactam with catalytic $RuCl_3{\cdot}xH_2O$ in the presence of $NaIO_4$ was performed after protection of the secondary alcohol at C6 with a triethylsilyl group. Deprotection of the alcohol was essential for the next stereoselective methylation at C7. Otherwise, β elimination occurs when the corresponding enolate is formed. The crucial methylation of **93** proceeded with high diastereoselectivity (9:1) in the presence of HMPA, and the desired β-methyl compound **94** was obtained in 63% yield. Cleavage of the *N*-Boc group with TFA, hydrolysis of the ethyl ester, and lactonization according to the Corey procedure produced **2**.

2.12 Wardrop Synthesis

The formal synthesis by Wardrop and Bowen[31] utilized an intramolecular C–H insertion of an alkylidene carbene[32] (**98**) as a key step (Scheme 15). This reaction transfers the chirality of the readily accessible tertiary stereocenter (C5 of **97**) to that of the tetrasubstituted carbon atom while maintaining the configuration. The synthesis started from enantiomerically enriched epoxy alcohol **28** obtained with 96% *ee* by Sharpless epoxidation. Epoxide opening by NaN_3 occurred regioselectively at the less-hindered site, and the following benzylidene acetal formation produced **96**. Hydrogenolysis of the azide and N-allylation with **97** gave an *E*/*Z* mixture of allyl amines **98**. The key C–H carbene insertion was initiated with alkylidene carbene formation through α



Scheme 14. The Donohoe synthesis. DBAD = di-*tert*-butylazodicarboxylate, DBB = di-*tert*-butylbiphenylide, DMAP = 4-dimethylaminopyridine, HMPA = hexamethylphosphoramide, TES = triethylsilyl.

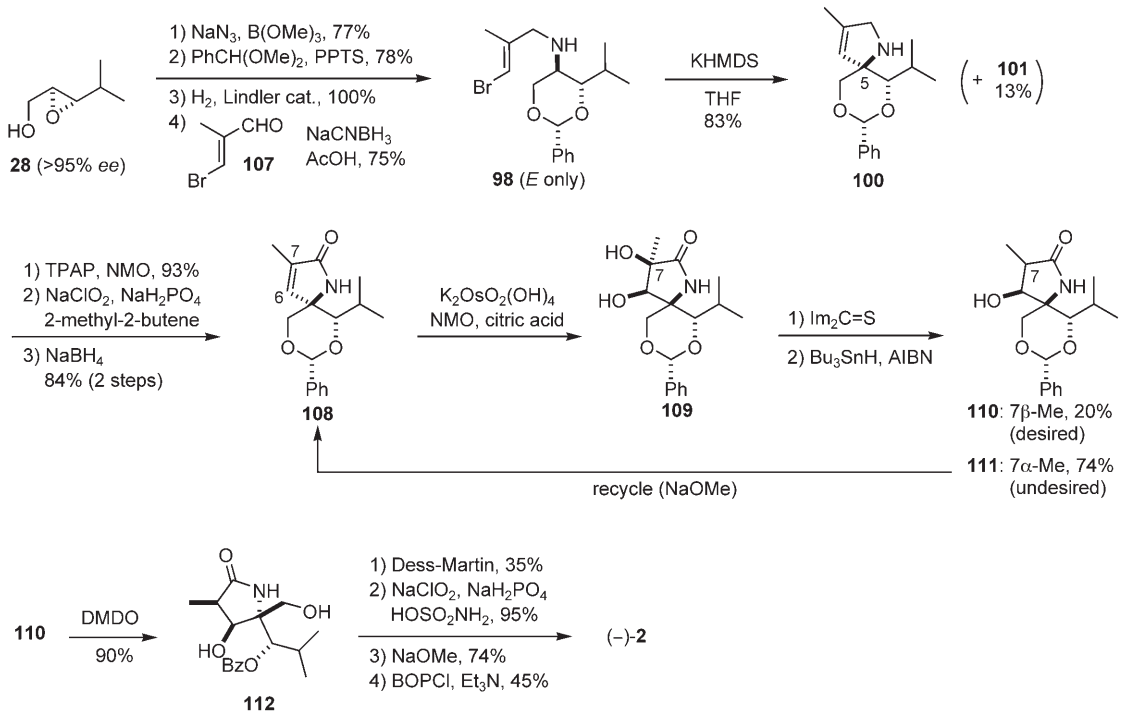


Scheme 15. The Wardrop synthesis. BHT = 2,6-di-*tert*-butyl-4-methylphenol, *m*CPBA = *m*-chloroperbenzoic acid, NBS = *N*-bromosuccinimide.

elimination of vinyl bromide **98** by using KHMDS, and the desired five-membered ring compound **100** was produced in 50% yield. A major side product was propargyl amine **101**, which was derived from 1,2-methyl migration. The efficiency of this cyclization depended on the olefin geometry of **98**. Thus, yields of **100** were 67% and 14% starting from (*E*)-**98** and (*Z*)-**98**, respectively. After *N*-Boc protection of **100**, epoxidation with *m*CPBA proceeded from the less-hindered β side of the olefin to produce **102** in high yield. Hydrogenolysis of the benzylidene acetal and primary-alcohol-selective TEMPO oxidation[33] followed by methyl ester formation and silylation produced **103**. Epoxide opening through deprotonation with LDA selectively produced the endocyclic olefin, possibly due to the directing effect of the *N*-Boc group. The resulting secondary alcohol at C6 was protected with a TMS group, and the following hydrobromination of **104** selectively produced a mixture of α-bromo carbinolamine diastereomers. PDC oxidation followed by Boc cleavage with $Mg(ClO_4)_2$ produced **105**, which was desilylated and debrominated with SmI_2. Unfortunately, undesired C7 α-methyl **106** was the major product in this reaction, and the desired **59**, the Omura and Smith intermediate, was obtained in only 27% yield.

2.13 Hayes Synthesis

The intramolecular C–H insertion of an alkylidene carbene was also a key step in the Hayes synthesis. This strategy was utilized in lactacystin synthesis initially by Hayes and coworkers in 2002.[34a] Later, Wardrop independently developed his original synthetic route with the carbene insertion as described in Section 1.12. In the improved Hayes synthesis reported in 2006,[34b] the key carbene-insertion reaction was conducted with the same substrate **98** as used by Wardrop, but in significantly higher yield. This improved route is described here. The carbene precursor **98** was synthesized from epoxy alcohol **28** by a similar procedure to that used in the Wardrop synthesis (Scheme 16). Wardrop and Bowen had already determined that the carbene insertion proceeds in higher yield from (*E*)-**98** than from (*Z*)-**98**.[31] Therefore, in the Hayes synthesis, (*E*)-**98** was selectively prepared through reductive amination with *E* bromoaldehyde **107**. As expected, the stereoselective C–H insertion proceeded from **98** to produce the spiro pyrroline **100** in 83% yield. The undesired 1,2-methyl migration was minimized to 13%. The significantly higher chemical yield realized in this C–H insertion compared to the case of Wardrop could be attributed to the difference in the reaction solvent: Wardrop conducted the reaction in Et_2O, whereas the solvent of Hayes was



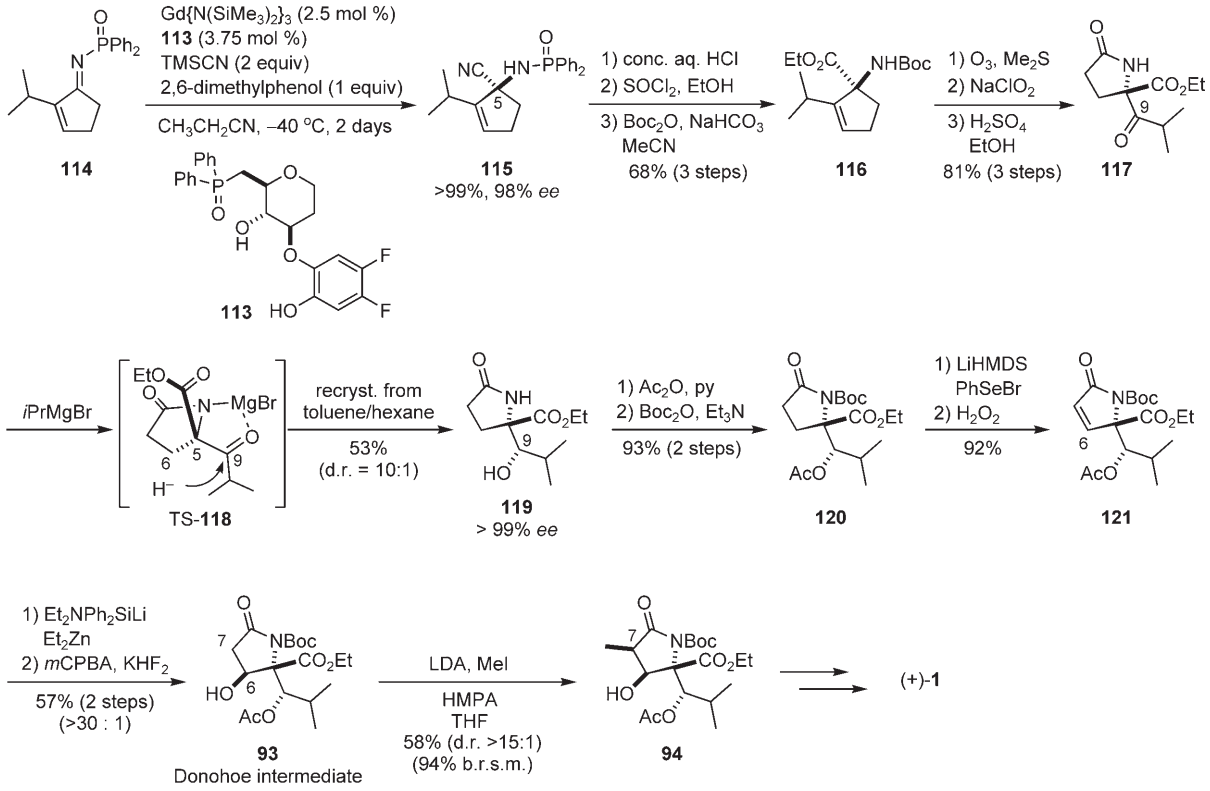
Scheme 16. The Hayes synthesis. DMDO = dimethyldioxirane, PPTS = pyridinium *p*-toluenesulfonate, TPAP = tetra-*n*-propylammonium perruthenate.

THF. α Oxidation of the amine group with TPAP followed by Pinnick oxidation first produced the corresponding *N*-chlorolactam, and subsequent N-dechlorination with $NaBH_4$ gave the desired lactam **108**. Dihydroxylation of the $\Delta_{6,7}$ double bond proceeded from the less-hindered β side. Radical deoxygenation of C7 through the cyclic thiocarbonate, initially utilized in the Baldwin lactacystin synthesis (Scheme 6, **36**→**37**), proceeded in high yield. The major product **111**, however, contained the undesired stereochemistry at C7. Thus, **111** was recycled through conversion into **108** by dehydration. Regioselective oxidative cleavage of the benzylidene acetal with DMDO produced diol **112**. Oxidation of the primary alcohol and lactonization produced *clasto*-lactacystin **2**.

2.14 Shibasaki Synthesis

Our group developed a general catalytic enantioselective Strecker reaction of phosphinoylketoimines by using a gadolinium complex derived from $Gd(O\mathit{i}Pr)_3$ and ligand **113** mixed in a 1:2 ratio (Scheme 17).[35] Additive 2,6-dimethylphenol activates the asymmetric catalyst and facilitates product dissociation from the catalyst.[35b] Products of this reaction can be converted into enantiomerically enriched α,α-disubstituted amino acids through acid hydrolysis of the phosphinoylamide and nitrile. We planned to utilize this reaction for the construction of the tetrasubstituted C5 of lactacystin. Based on our plan, α-hydroxy ketoimines are obvious starting ketoimines. This type of imine, however, is unstable and not isolable in a pure form. Thus, we utilized enone-derived, stable **114** as a masked α-hydroxy ketoimine. Imine **114**, which contains a bulky isopropyl group at the α position, was barely reactive under Strecker reaction conditions, and optimization of the reaction conditions was necessary. Intensive studies revealed that the catalyst generated from $Gd\{N(SiMe_3)_2\}_3$ and **113** in a 2:3 ratio produced higher activity and enantioselectivity than the catalyst prepared from $Gd(O\mathit{i}Pr)_3$. ESI MS analysis and X-ray crystallographic studies of the catalyst revealed that this alternative catalyst preparation method generated the active 2:3 complex of Gd and **113** in a pure form.[36] Under the optimized conditions, the Strecker reaction of **114** completed with 2.5 mol% catalyst in 2 days, and the product **115** was obtained in quantitative yield with 98% *ee* (Scheme 17).

Amidonitrile **115** was converted into protected amino acid derivative **116**, which was further transformed into γ-lactam **117** through ozonolysis, oxidation, and cyclization. Stereoselective reduction of the C9 ketone with *i*PrMgBr (used as a reducing reagent in the Kang synthesis) via a presumed cyclic transition state **118** produced a mixture of C9 diastereomeric secondary alcohols with the desired α-alcohol **119** as the major isomer (d.r. = 10:1). Diastereomerically and enantiomerically pure **119** was obtained by recrystallization of the crude mixture from toluene/hexane. After protection of the secondary alcohol and the lactam nitrogen atom with acetyl and Boc groups, respectively, selenenylation and oxidation produced the α,β-unsaturated lactam **121** in excellent yield. The β-hydroxy group of C6 was introduced via a stereoselective conjugate addition of the Et_2NPh_2Si group from the less-hindered side of the enone, followed by Tamao–Fleming oxidation of the silicon while maintaining the configuration[37] to produce enantiomeri-



Scheme 17. The Shibasaki synthesis. b.r.s.m. = based on reacted starting material.

cally pure Donohoe intermediate **93**. Methylation of **93** at C7 under the conditions developed by Donohoe produced the desired stereoisomer **94**, which was further converted into lactacystin by following the procedures reported by Corey and Donohoe.[38]

2.15 Jacobsen Synthesis

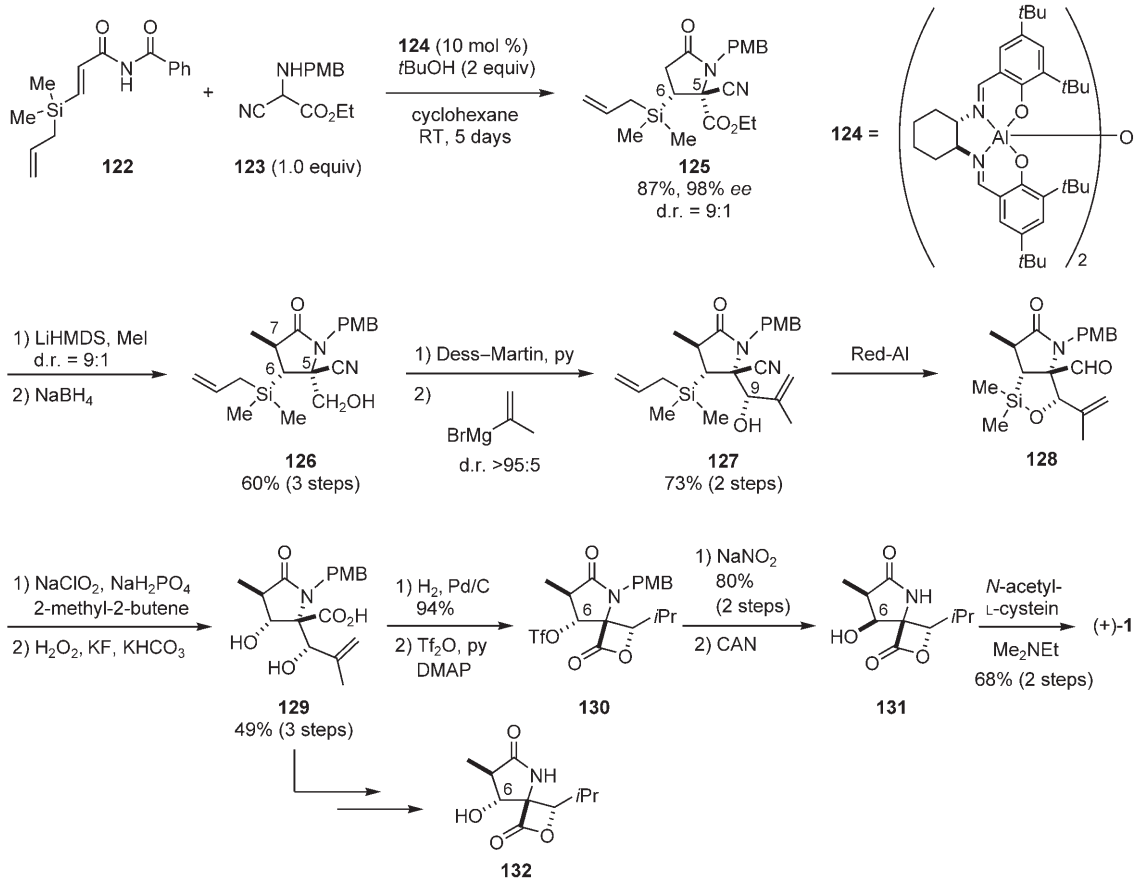
The total synthesis by Balskus and Jacobsen[39] began with a catalytic enantio- and diastereoselective conjugate addition of α-amino cyanoacetate **123** to α,β-unsaturated β-silyl imide **122** with 10 mol% of the μ-oxo dimer of salen–Al complex **124** (salen = *N*,*N*-ethylenebis(salicylideneiminato))[40] to produce γ-lactam **125** with 98% *ee* and 9:1 diastereomeric ratio (Scheme 18). This reaction is noteworthy in that the lactacystin core structure is synthesized in one pot, although the stereochemistry of C6 is opposite to that of the natural compound. After stereoselective methylation of C7, conversion of the C5 ethyl ester into an aldehyde through a reduction–oxidation sequence followed by the stereoselective introduction of a propenyl group to the aldehyde produced **127**. Unexpected allyl-group displacement on the silicon atom occurred during reduction of the nitrile at C5 with Red-Al to afford **128**. Pinnick oxidation followed by Tamao oxidation afforded carboxylic acid **129**, which was subjected to hydrogenation and treatment with triflic anhydride to produce spiro β-lactone **130**. Invertive triflate displacement at C6 was accomplished with $NaNO_2$ without harming the β-lactone. Deprotection of the lactam nitrogen atom by CAN and treatment of the β-lactone with *N*-acetylcystein in the presence of base completed the total synthesis of lactacystin.

The acylating ability of **131** is interesting in terms of its relationship to biological function. It was found that **131** is a comparably potent inhibitor of 26S proteasome relative to *clasto*-lactacystin (**2**). The stereoisomer **132**, however, exhibited no proteasome inhibitory activity. These data indicate that the position of the β-lactone is not important for biological activity, and that the configuration at C6 is critical for reasons other than β-lactone formation.

3. Total Synthesis of Salinosporamide A

3.1 Corey Synthesis

The first total synthesis of salinosporamide A was achieved by Corey and co-workers in 2004.[41] N-Acylation of L-threonine methyl ester and cyclization in the presence of *p*-TsOH produced oxazoline **134**, which was stereoselectively alkylated with benzyloxymethyl chloride to produce **135** with the correct chirality at the tetrasubstituted C4 (Scheme 19). A selective reductive opening of the oxazoline afforded *N*-PMB-protected amino alcohol **136**. Temporary protection of the secondary alcohol of **136** with a trimethylsilyl group, N-acylation with acryloyl chloride, desilylation, and oxidation with Dess–Martin periodinane produced amido ketone **137**. The key Baylis–Hillman reaction with quinuclidine as a cat-



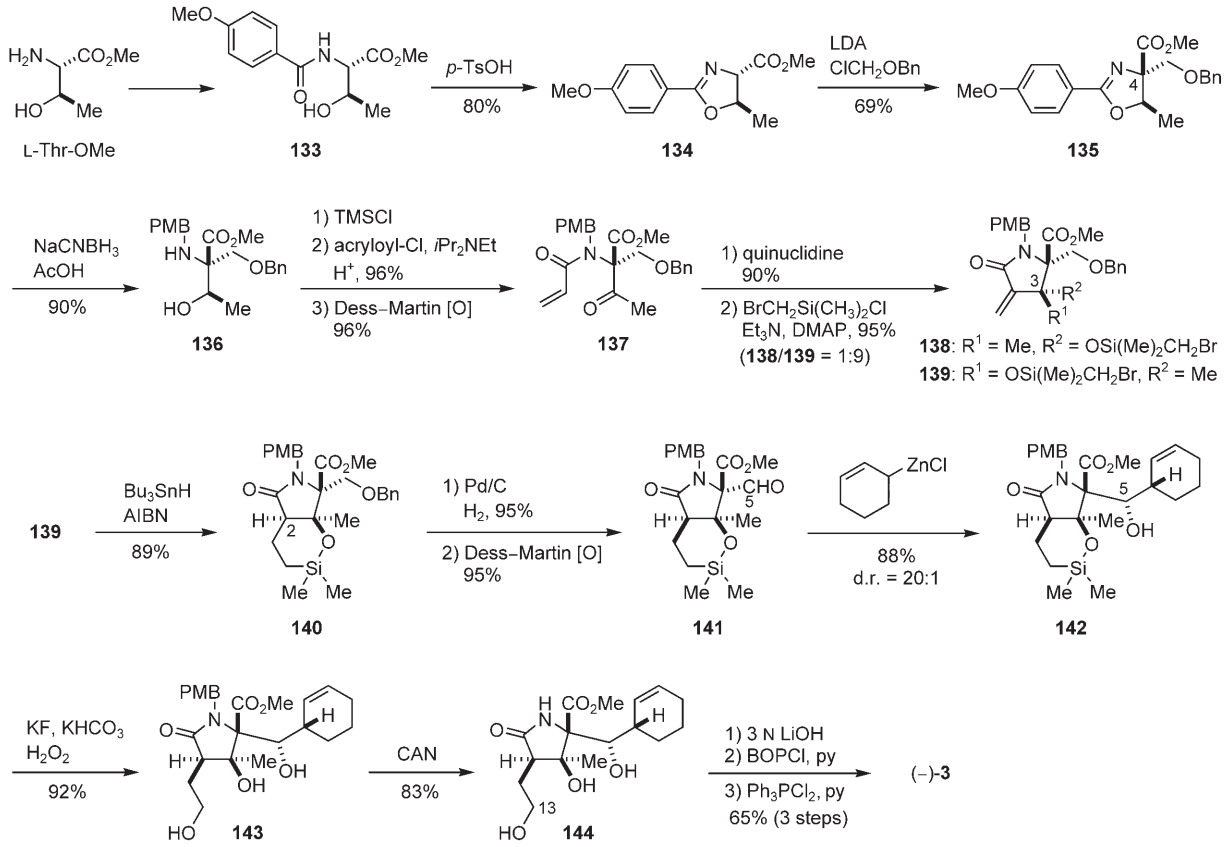
Scheme 18. The Jabobsen synthesis. CAN = ceric ammonium nitrate, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride, Tf = trifluoromethanesulfonyl.

alyst proceeded slowly (7 days) but with high stereoselectivity (9:1), and the desired γ-lactam **139** was obtained after silylation. Radical cyclization of **139** with Bu_3SnH and AIBN to *cis*-fused γ-lactam **140** proceeded in high yield. Cleavage of the benzyl ether and oxidation of the resulting primary alcohol at C5 with Dess–Martin periodinane produced the precursor aldehyde **141** for the key allylation reaction. The allylation reaction from **141** to **142** proceeded with excellent diastereoselectivity with 2-cyclohexenyl zinc reagent, constructing two contiguous stereogenic centers at C5 and C6. Fused bicyclic **142**, which contains the entire carbon skeleton of salinosporamide A was converted into **3** through Tamao–Fleming oxidation, β-lactone formation after PMB cleavage and ester hydrolysis, and displacement of the primary alcohol 13-OH by chloride.

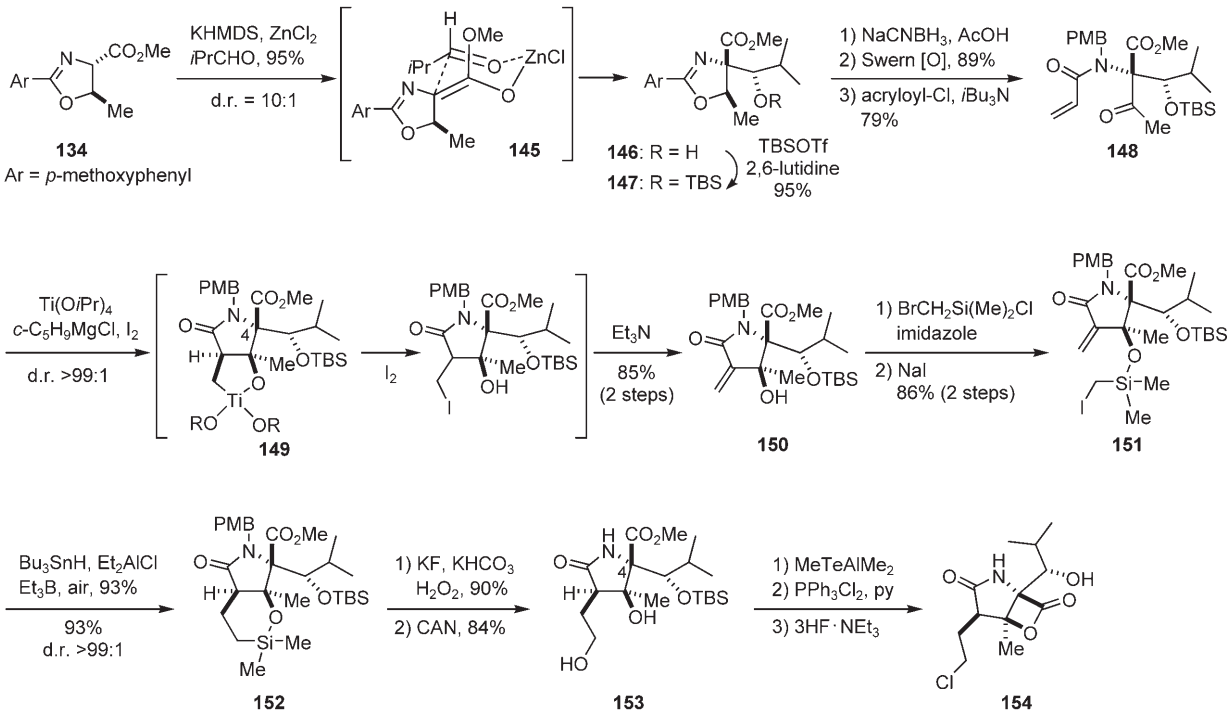
The synthetic efficiency was later improved by using the Kulinkovich reaction,[42] instead of the slow (7 days) Baylis–Hillman reaction from **137** in the previous first total synthesis, as a key step.[43] Thus, keto amide **148** was synthesized from chiral oxazoline **134** through a diastereoselective aldol reaction of a zinc enolate via cyclic chair transition state **145**, reductive oxazoline opening, and acryloyl amide formation (Scheme 20). Treatment of **148** with the Kulinkovich reagent prepared from $Ti(OiPr)_4$ and cyclopentylmagnesium chloride, followed by iodination of the resulting titanacycle **149** and elimination of HI with Et_3N produced **150** in 85% yield with greater than 99:1 selectivity. This excellent diastereoselectivity can be explained by considering the titanacycle formation from the less-hindered side opposite the bulky isobutyl group at C4. The reaction time was only 5 h throughout the sequence. As developed previously, radical cyclization of **151** followed by Tamao oxidation led to γ-lactam **153**. Hydrolysis of the methyl ester at C4 proved to be unusually difficult due to severe steric hindrance. This difficulty was overcome by developing a new demethylation reagent, $(MeTeAlMe_2)_2$, and synthesis of *clasto*-lactacystin–salinosporamide A hybrid **154** was accomplished.

Evaluation of the biological activity of **154** relative to *clasto*-lactacystin (**2**) indicated that the potency of **154** is approximately 2.5 times higher than that of **2**.

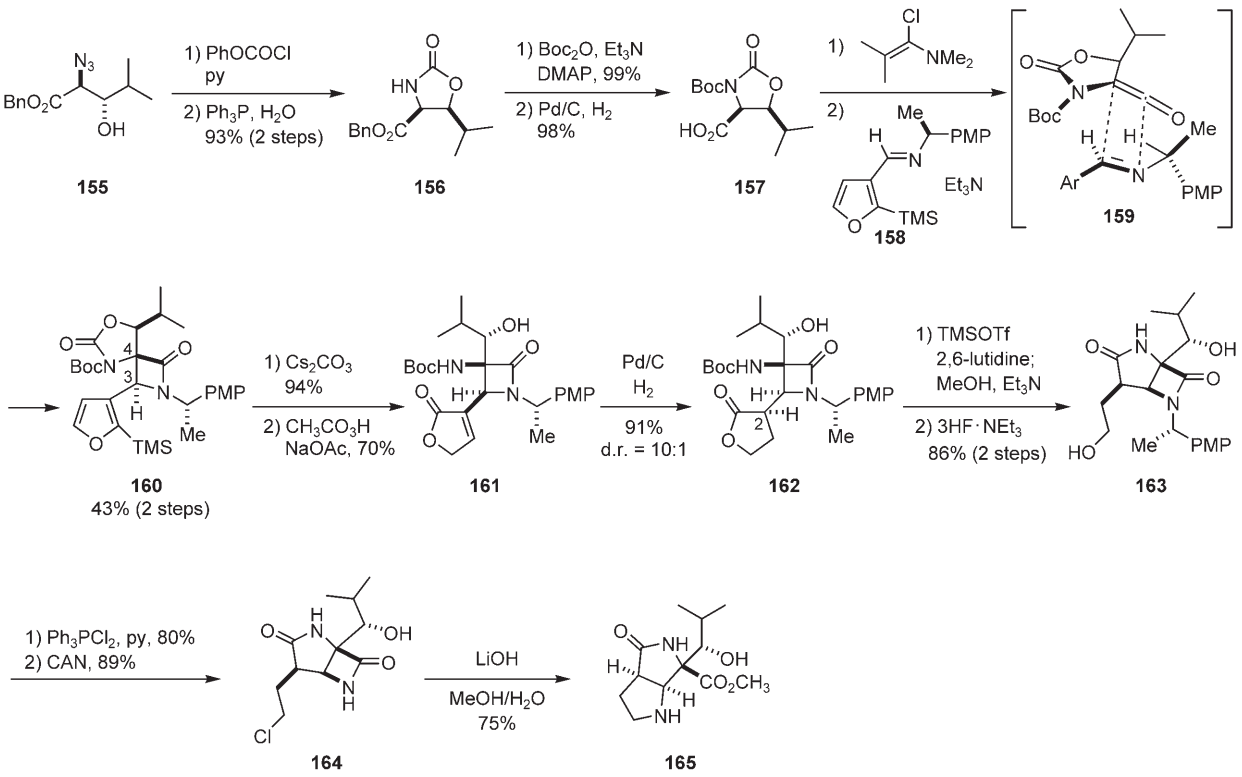
One potential problem in using **2** and **3** as therapeutic agents is their short half-lives in solution at pH 7 or in serum ($t_{1/2} \approx 5$–10 min). Hogan and Corey designed a new analogue **164** containing a β-lactam that is much more stable than the corresponding β-lactone.[44] Synthesis of **164** started from known azido alcohol **155**, which was produced by using Sharpless dihydroxylation as a key step (Scheme 21). After cyclic carbamate formation, *N*-Boc protection and cleavage



Scheme 19. The first Corey total synthesis of salinosporamide A.



Scheme 20. The improved Corey synthesis of salinosporamide A and its analogues.

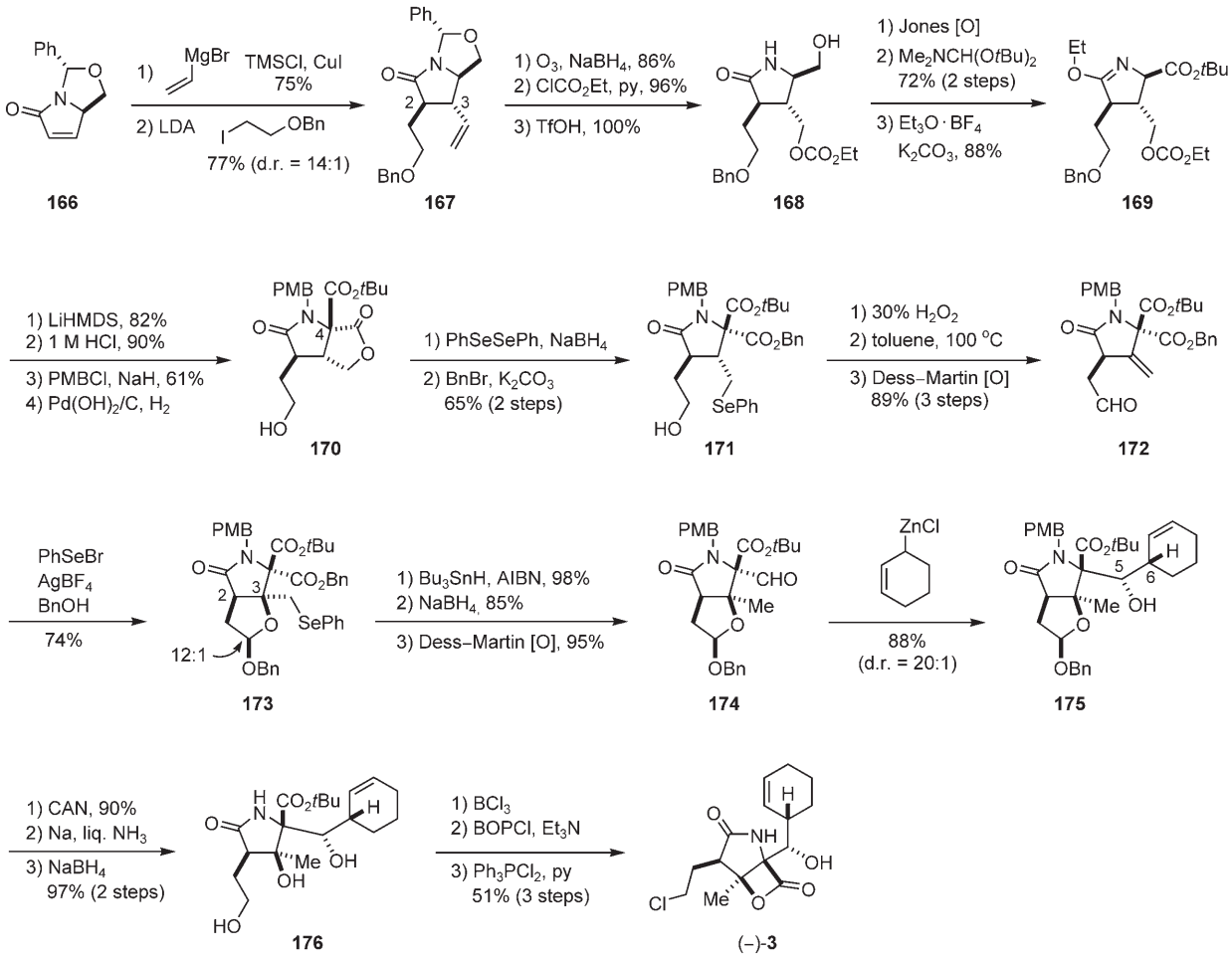


Scheme 21. The Corey synthesis of a stable salinosporamide A analogue. PMP = *p*-methoxyphenyl.

of the benzyl ester produced carboxylic acid **157**. Treatment of **157** with 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, followed by addition of the resulting acid chloride to a solution of chiral imine **158** and Et_3N, led to the formation of β-lactam **160**, which has C3 and C4 of the desired stereochemistry, in 43% yield. The stereoselectivity of this reaction can be explained from the model **159**, in which the auxiliary of **158** is fixed owing to allylic strain, and the bond formations occurred between the less sterically crowded sides of **158** and a ketene derived from **157**. After removal of the cyclic carbamate, regioselective oxidation of trimethylsilylated furan with peracetic acid produced butenolide **161**, which was stereoselectively hydrogenated to butyrolactone **162**. Cleavage of the Boc group was accomplished with TMSOTf in the presence of 2,6-lutidine. Any remaining TMSOTf was quenched with MeOH, and fluoride treatment during the workup provided the desired butyrolactam **163** in 86% yield. Selective conversion of the primary alcohol to chloride followed by oxidative cleavage of the chiral auxiliary produced **164**. As expected, **164** was completely stable at pH 7 and 23 °C for 24 h, and maintained a potent proteasome inhibitory activity. Furthermore, it was expected that proteasome inhibition by **164** would be irreversible due to pyrrolidine formation after proteasome acylation via β-lactam opening. Indeed, pyrrolidine **165** was formed when β-lactam **164** was hydrolyzed under basic conditions.

3.2 Danishefsky Synthesis

The synthesis of salinosporamide A by Endo and Danishefsky started from the bicyclo[2.2.0] compound **166** derived from L-glutamic acid (Scheme 22).[45] Conjugate addition of divinyl cuprate to **166** in the presence of TMSCl proceeded with complete diastereoselectivity from the convex face, and the resulting β-vinyl product was stereoselectively (14:1) alkylated with β-benzyloxy iodoethane to produce **167**. Ozonolysis followed by reductive treatment, carbonate formation, and aminal cleavage afforded alcohol **168**, which was subjected to Jones oxidation to carboxylic acid, *tert*-butyl ester formation, and imidate formation with Meerwein reagent to produce **169**. Internal acylation of C4 with the pendant carbonate proceeded through a lithium enolate derived from **169**. At this stage, the stereogenic center at C4 was constructed. Hydrolysis of the imidate, protection of the lactam with the PMB group, and hydrogenolysis of the benzyl ether produced lactone **170**. A nucleophilic ring opening of the lactone with a phenylselenium anion generated from $(PhSe)_2$ and $NaBH_4$ followed by benzyl ester formation of the resulting carboxylic acid afforded **171**, in which the two carboxylic acids at C4 were differentiated. Oxidation of the selenide and thermolysis produced the exocyclic olefin through β elimination. Oxidation of the primary alcohol with Dess–Martin periodinane afforded aldehyde **172**. Cationic cyclization from **172** proceeded in the presence of PhSeBr, $AgBF_4$, and benzylalcohol to produce acetal **173** with complete stereoselectivity at the C3 tetrasubstituted



Scheme 22. The Danishefsky synthesis of salinosporamide A.

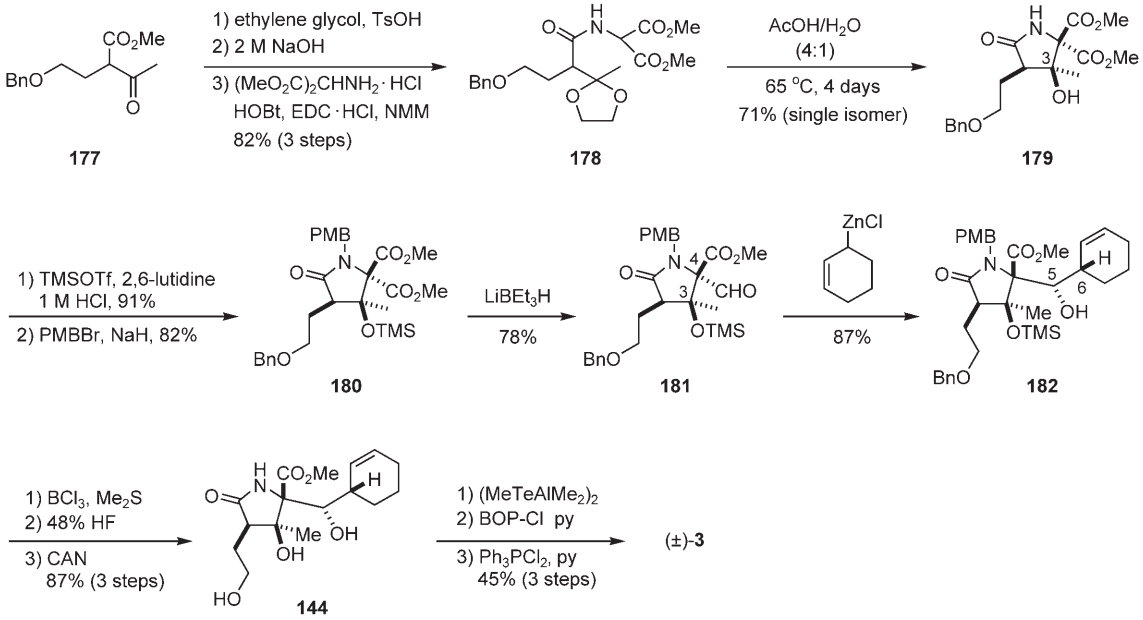
stereogenic center. Deselenenylation with tributyltin radical followed by a selective reduction–Dess–Martin oxidation sequence afforded aldehyde **174**. Stereoselective introduction of the cyclohexenyl group was conducted according to the Corey procedure by using a cyclohexenyl zinc reagent with excellent diastereoselectivity to produce **175**. The *N*-PMB and *O*-Bn groups were successively removed, and the acetal was reduced with $NaBH_4$ to afford diol **176**. The total synthesis of **3** was completed from **176** through cleavage of the *tert*-butyl ester with BCl_3, β-lactone formation, and replacement of the primary alcohol with chloride.

3.3 Pattenden Racemic Synthesis

Recently, Pattenden and co-workers reported a racemic synthesis of salinosporamide A.[46] The ketone **177** was first protected as an acetal, and ester hydrolysis followed by coupling with dimethyl 2-aminomalonate produced amide **178** (Scheme 23). A stereoselective aldol-type cyclization proceeded from **178** in acetic acid/H_2O to lead to γ-lactam **179** in 71% yield as a single diastereomer. The relative stereochemistry of the two stereogenic centers at C2 and C3 is elegantly defined at this stage. After protection of the tertiary alcohol as a trimethylsilyl ether, the lactam nitrogen atom was protected with a PMB group. The resulting diester **180** was subjected to regioselective reduction with superhydride to produce aldehyde **181** in 78% yield. This selectivity is explained by considering that the C4 methoxycarbonyl group *trans* to the C3 trimethylsilyloxy group is sterically less-hindered than that in the *cis* position. By following the Corey procedure, the addition of cyclohexenyl zinc chloride to aldehyde **181** produced **182** with excellent diastereoselectivity. Cleavage of the benzyl ether and trimethylsilyl ether followed by oxidative removal of the *N*-PMB group produced Corey intermediate **144**, which was converted into salinosporamide A according to the Corey procedure.

4. Summary and Outlook

In this review, various synthetic strategies of lactacystin and salinosporamide A are described. Densely functionalized γ-lactams are the characteristic core structure of these molecules. Specifically, the chiral tetrasubstituted carbon centers C5 of lactacystin and C3 and C4 of salinosporamide A constitute the most-crowded part of the molecules. Thus, con-



Scheme 23. The Pattenden racemic synthesis of salinosporamide A. EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = 1-hydroxybenzotriazole, NMM = *N*-methylmorpholine.

struction of the tetrasubstituted carbon center(s) is an important aspect of the synthesis. A reasonable synthetic approach is to start from the peripheral, relatively readily accessible moieties (such as the C9 secondary alcohol of lactacystin accessible with the Sharpless oxidation) followed by construction of the core tetrasubstituted carbon center(s) with the assistance of the stereochemistry of the peripheral carbon atoms. Recent advances in asymmetric catalysis, however, allow for direct introduction of the core tetrasubstituted carbon centers through catalyst control (e.g., our synthesis (Section 1.14) and the Jacobsen synthesis (Section 1.15)). Double stereocontrol of two adjacent stereogenic centers via carbon–carbon bond formation can significantly shorten the synthesis. Remarkable examples are the MgI_2-mediated Mukaiyama aldol reaction in the first Corey total synthesis of lactacystin (Section 1.1), the $SnCl_4$-mediated vinylogous Mukaiyama aldol reaction in the Baldwin synthesis (Section 1.3), the Me_2AlCl-mediated aldol reaction in the Adams synthesis (Section 1.6), the Jacobsen synthesis with a catalytic asymmetric Michael reaction (Section 1.15), and the addition of cyclohexenylzinc chloride to aldehyde, initially utilized in the first Corey total synthesis of salinosporamide A (Sections 2.1 and 2.3). The synthesis of lactacystin, salinosporamide A, and their analogues has a significant role in clarifying the biology of proteasomes. These molecules are excellent pharmaceutical leads. The history of lactacystin synthesis clearly demonstrates that synthetic organic chemistry is a basic science that is required for the advancement of biology and medicine.

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