Total Synthesis of Oxacyclic Macrodiolide Natural Products

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Contents

1. Intoduction

Nature presents us countless numbers of natural products with complex and fascinating structures and useful properties. Macrodiolides belong to one relatively small but interesting class of natural products exhibiting many different bioactivities. In this review, total syntheses of macrodiolides containing oxacyclic rings will be discussed; only those approaches that led to successful total syntheses will be highlighted. Total syntheses of some of the oxacyclic macrodiolides (swinholide A and aplasmomycin) were already discussed in a previous review by Norcross and Patterson;[1] therefore, discussions of the more recent developments will be included here. In discussing total syntheses of these compounds, emphasis is naturally on the methods used for macrocycle formation. The other important facet will be the reactions employed for oxacycle synthesis, particularly for those containing oxolane (tetrahydrofuran) and oxane (tetrahydropyran) moieties.

Pamamycins are the best known macrodiolides containing oxolane moieties. The total synthesis of pamamycin 607 (**1**),[2] the prototype member of the pamamycin family, was achieved recently. A number of other macrodiolides containing oxolane systems are also known, for example, feigrisolide C and D,[3] IKD 8344,[4] and pyrrolizidine alkaloids such as nemorensine,[5] mulgediifoline,[6] and retroisosenine,[7] but total syntheses of these compounds are yet to be reported. More recently, the total synthesis of amphidinolide X (**2**)[8] was reported. Successful synthetic efforts were reported for SCH 351448 (**3**)[9] and swinholide A (**4**),[10] which are 28- and 40-membered symmetric macrodiolides containing oxane and oxene (dihydropyran) moieties. Early synthesis of swinholide A (**4**) was reviewed previously;[1] therefore, this review will deal with the more recent total synthesis. Cycloviracin B_1 (**5**)[11] and glucolipsin A (**6**)[12] possess unique macrodiolide structures incorporating cyclic acetal units, and the recent success stories on total syntheses will be discussed. Macrodiolides such as boromycin (**7**),[13] tartrolon B (**8**),[14] debromoaplysiatoxin (**9**),[15] and aplysiatoxin (**10**)[15] exhibit cyclic hemiketal structural units (Figure 1), and total syntheses of these compounds will be summarized in this review. The total synthesis of aplasmomycin[16] was already discussed in the previous review article[1] and omitted here.

2. Oxolane Macrodiolides

2.1. Pamamycin 607 (1)

Pamamycins were first isolated by McCann and Pogell in 1979 from *Streptomyces alboniger* ATCC 12461 for their aerial mycelium-inducing acitivity[2a] and classified as new family type antibiotics active against Gram-positive bacteria, *Mycobacteria* and *Neurospora*. Isolation of pamamycin 607 (**1**) was reported by Marumo and co-workers in 1987 from *S. alboniger* IFO 12738,[2b] and they were also successful in structure determination studies on the basis of

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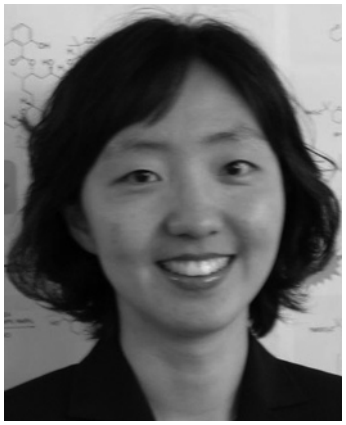
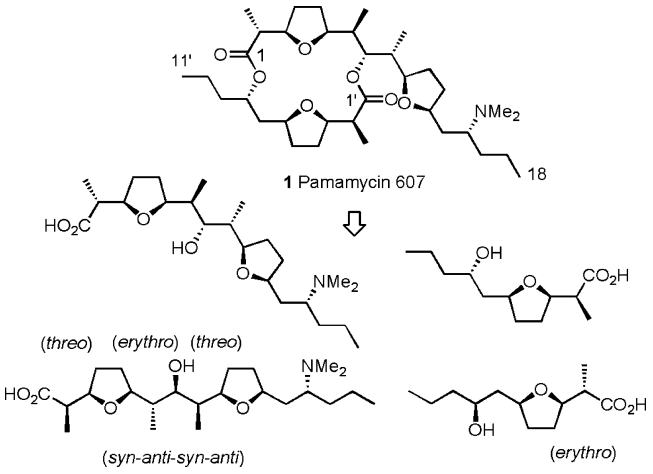


Eun Joo Kang studied Chemistry at Seoul National University, where she received her M.S. in 2001 under the supervision of Professor Eun Lee working on the synthetic studies on oxacyclic natural products, elatenyne and pamamycin-607. She is currently a Ph.D. student at SNU. In 2003, she was a Visiting Researcher in the laboratory of Professor Barry M. Trost at Standford University for the winter quarter. In 2004, she was awarded an IUPAC poster prize at ICOS-15 and also received a certificate of achievement from the Department of Chemistry, SNU, in recognition of her research accomplishment on the total synthesis of SCH 351448. Her research interests focus on the stereoselective synthesis of oxacyclic natural products using radical cyclization reactions.

Eun Lee graduated from Seoul National University in 1969 and studied organic chemistry at Yale University, where he received his Ph.D. degree on the biosynthetic studies on fungal tropolones and vitamin B12 under the supervision of Professor A. I. Scott. After postdoctoral research with Professor K. Nakanishi at Columbia University on α-ecdysone synthesis, he spent a year and half at Zoecon Corporation working on the biosynthesis of insect juvenile hormones. He was appointed as assistant professor at the Chemistry Department, College of Natural Sciences, Seoul National University in 1977 and, since then, was promoted to associate professor in 1981 and professor in 1987. He served as the Chairman of the Department of Chemistry from 1986 to 1988. He spent a year (1985–86) at Dyson Perrins Laboratory, Oxford University, as a visiting professor associated with Professor Sir J. E. Baldwin. His main interest in research is centered on the selectivity of organic reactions involving radical and carbenoid intermediates in conjunction with total synthesis of natural products. He received the Korean Chemical Society Award in 1995 and the Korea Science Award in 1997 and served as the secretary general of the Korean Chemical Society in 1996.

spectroscopic analysis. Subsequent studies by Marumo[17] and other groups[18] on pamamycins led to the discovery of their anionophoric activity and identification of further members of the family as well as evaluation of structure−activity relationships. Pamamycin 607 (**1**) is especially interesting for its potent activity against Gram-positive bacteria including multiple antibiotic resistant strains of *Mycobacterium tuberculosis* as well as against phytopathogenic fungi.[19] Pamamycins are 16-membered macrodiolides incorporating two of the three *cis*-2,5-disubstituted oxolane rings within the macrocycle framework.

Scheme 1. Retrosynthetic Analysis of Pamamycin 607 (1)



In the total synthesis, stereoselective synthesis of the C1−C18 and C1′−C11′ fragments is required (Scheme 1), and correct conditions have to be found for two separate esterification reactions. Stereo control in the synthesis of polypropionate systems incorporating oxacycles is difficult, and the first successful synthesis of the C1−C18 fragment was reported in 2001, which led to successful total synthesis of pamamycin 607 (**1**).

2.1.1. Thomas Total Synthesis[20]

The Thomas approach is based on the intramolecular selenoetherification of (*Z*)-homoallylic alcohols leading to *cis*-2,5-disubstituted oxolanes; the required 1,5-*anti*-(*Z*)-homoallylic alcohols are available stereoselectively from tin(IV) halide-promoted reactions between 4-methyl-5-alkoxy-2-pentenylstannanes and aldehydes via remote asymmetric induction[21] (Scheme 2).

Synthesis of the C1−C18 fragment of pamamycin 607 (**1**) commenced with conjugate addition of lithium (*R*)-(α-methylbenzyl)benzylamide to *tert*-butyl (*E*)-2-hexenoate (**11**),[22] and β-amino ester **12** with excellent enantiomeric excess was obtained by transfer hydrogenolysis. Protection of the nitrogen as its tosyl derivative and methylation gave the amido ester, which was converted into aldehyde **13** by reduction followed by oxidation. Hydroxy acid **15** was obtained from isobutyric acid (**14**) via biological oxidation,[23] which was further converted[21b,24] into allylic stannane **16**. Aldehyde **13** reacted with the trichloroallylstannane generated by transmetalation of stannane **16** to give alcohol **17** with less than 4% of any other diastereoisomers being detected in the product. Cyclization of **17** using phenylselenenyl chloride and 20 mol % of tin(IV) chloride gave the *cis*-2,5-disubstituted oxolane **18** after reductive removal of the phenylselenyl group although the yield of this cyclization was only about 43% because of competing *O*-debenzylation and participation by the tosylamino group to give mixtures of side products that were not

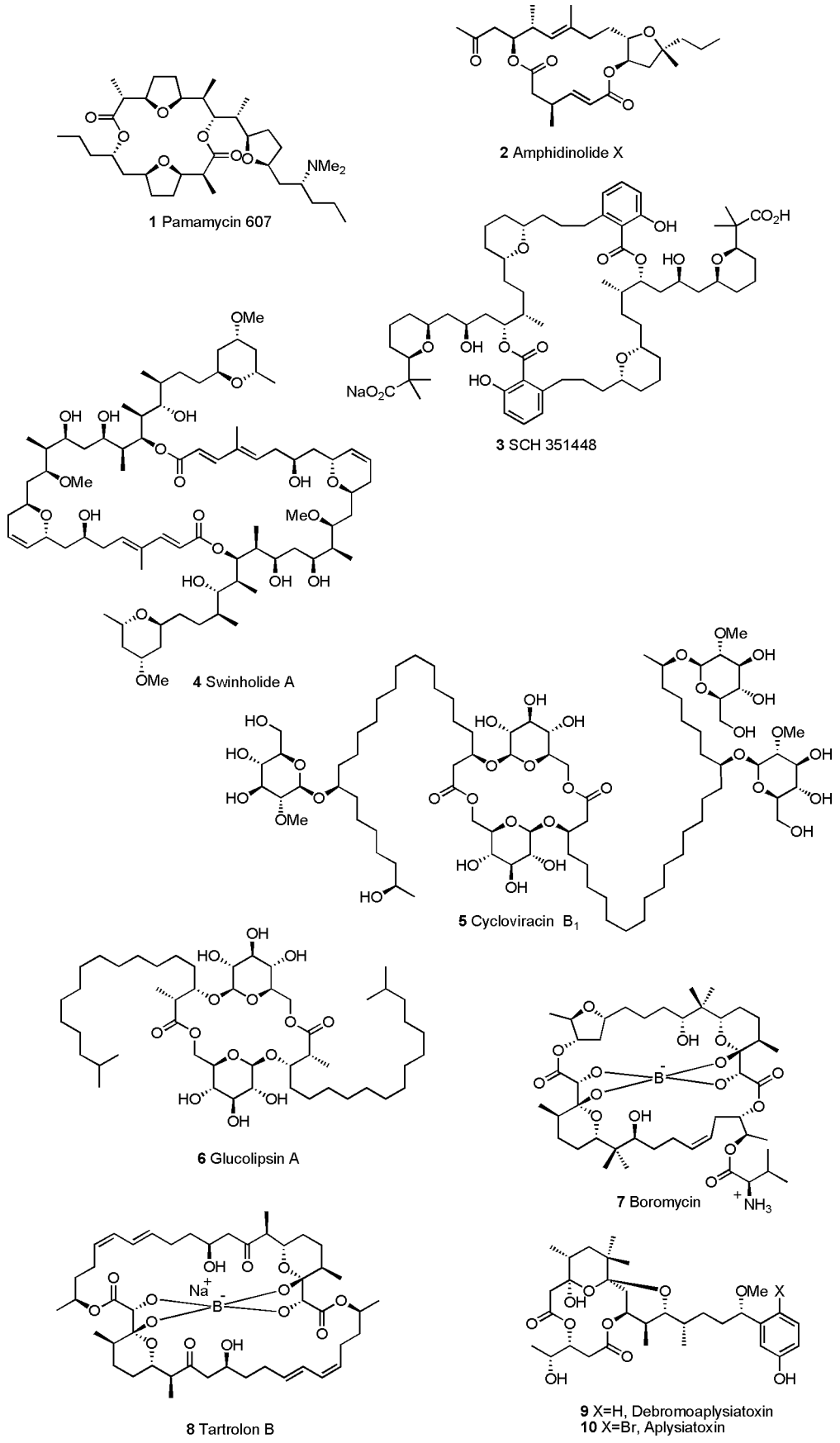
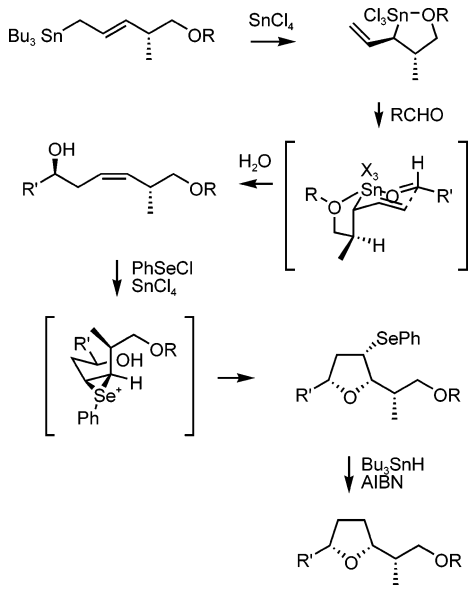


Figure 1. Oxacyclic macrodiolide natural products.

fully identified. Hydrogenolysis and oxidation then gave aldehyde **19**, which was treated with the lithium enolate derived from 2,6-dimethylphenyl propanoate[25] to give a mixture of the aldol products in the ratio of 19:72:9. The structure of the silyl ether **20** prepared from the major aldol product was established as the

Scheme 2. Key Steps in Thomas Total Synthesis



required 2,3-*anti*-3,4-*syn*-diastereoisomer: the preferred formation of the 2,3-*anti*-3,4-*syn*-isomer in the aldol reaction is consistent with addition of the (*Z*)-enolate of the 2,6-dimethylphenyl ester to aldehyde **19** according to the Felkin−Anh model.

Reduction and oxidation of the protected major aldol product **20** gave aldehyde **21**, which reacted with the trichloroallylstannane generated from allyllic stannane **16** to give the (*Z*)-1,5-*anti*-product **22**. Cyclization in this case was best achieved using phenylselenenyl phthalimide in the presence of zinc(II) chloride and gave bis-oxolane **23** in approximately 50% yield from the homoallylic alcohol **22** after reductive removal of the phenylselenyl group. Benzyl ether **23** was taken through to the C1−C18 fragment acid **24** by removal of the tosyl group, reprotection of the nitrogen as its *t*-Boc derivative, hydrogenolysis, and oxidation.

In the synthesis of the C1′−C11′ fragment of pamamycin 607, it was necessary to invert the configuration of the hydroxyl bearing stereogenic center introduced during the allylstannane reaction before cyclization. The tin(IV) chloride-promoted reaction between the protected hydroxy aldehyde **25**[26] and the allylstannane **26** (*ent*-**16**) gave the (*Z*)-1,5-*anti*-product **27** (1,5-anti:1,5-syn ca. 87:13). This was converted into its 1,5-*syn*-diastereoisomer **28** by Mitsunobu inversion using 4-nitrobenzoic acid followed by saponification. Cyclization of the 1,5-*syn*-alcohol **28** using phenylselenenyl phthalimide in the presence of 20 mol % tin(IV) chloride then gave the oxolane (∼60%) together with inseparable side products (10−15%). Reduction of this mixture by tributylstannane and AIBN gave the *cis*-2,5-disubstituted oxolane **29**, which was converted into the alcohol by hydrogenolysis. Oxidation and carboxylate alkylation then gave the benzyl ester, which was desilylated to give the free alcohol **30** corresponding to the C1′−C11′ fragment.

Acid **24** and alcohol **30** were coupled using 2,4,6-trichlorobenzoyl chloride to give the ester.[27] The TBS group was removed using aqueous hydrogen chloride in ethanol. This also removed the *t*-Boc group, which had to be reinstated to yield ester **31**. Hydrogenolysis then gave the *seco*-acid, which was cyclized using 2,4,6-trichlorobenzoyl chloride to give the macrodiolide product in 25% yield accompanied by a dimer. Finally, removal of the *t*-Boc group and *N*-methylation gave pamamycin 607 (**1**) (Scheme 3).

2.1.2. Lee Total Synthesis[28]

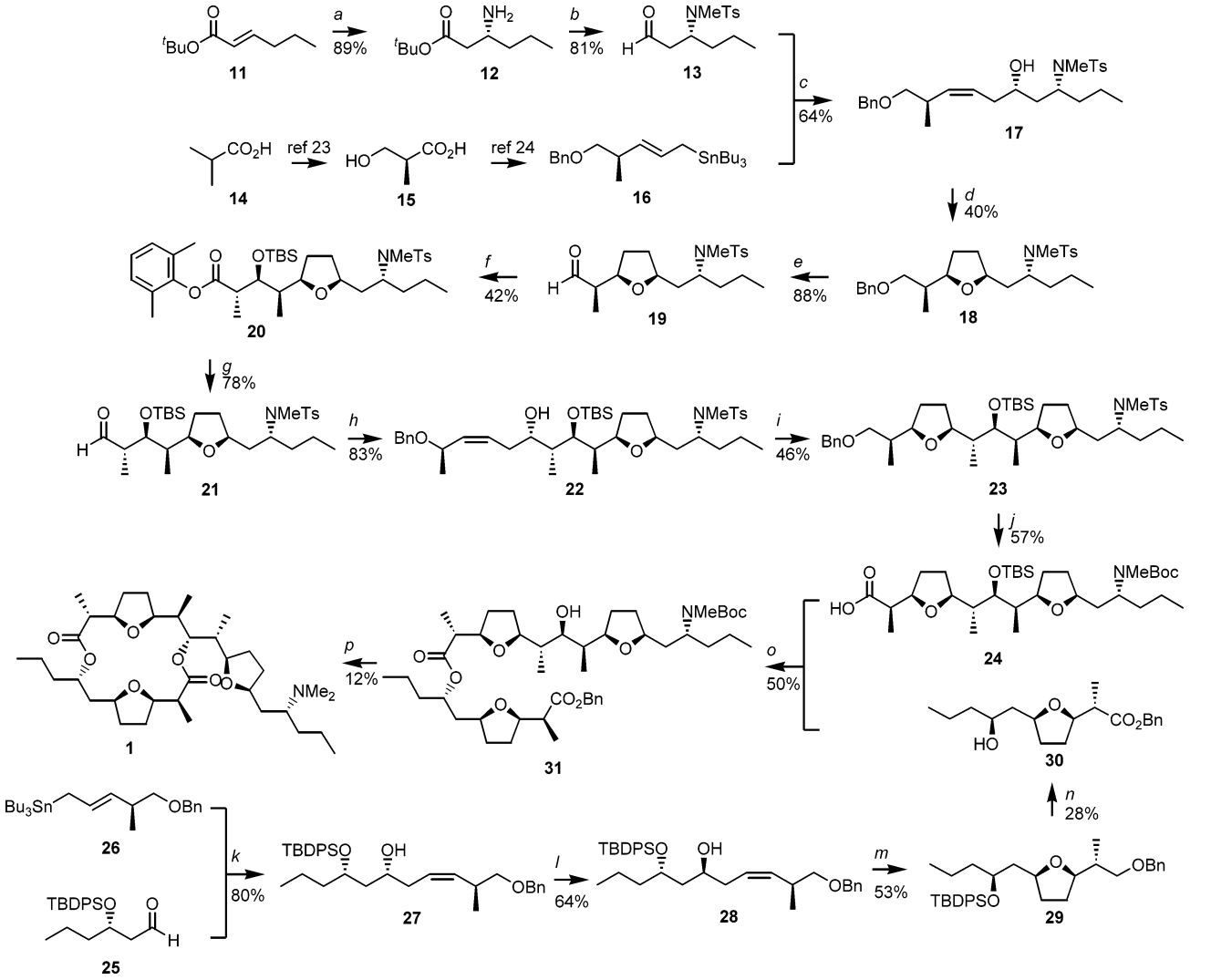
The key step in the Lee total synthesis involves radical cyclization of β-alkoxymethacrylates for the synthesis of 2-(oxolane)propanoate with threo-cis arrangement. Radical cyclization of β-alkoxyacrylates and β-alkoxyvinyl ketones is a highly useful method for stereoselective preparation of *cis*-2,5-disubstituted oxolanes and *cis*-2,6-disubstituted oxanes.[29] In the radical cyclization of β-alkoxymethacrylates, preference for "outside alkoxy" conformation of the intermediate radical species should minimize both allylic 1,3-strain and electrostatic repulsions, and an early transition state for hydrogen abstraction in which attack occurs from the least hindered face of the radical is apparently operative leading to threo products[30] (Scheme 4).

For synthesis of the C1′−C11′ fragment, the PMB-protected 3-hydroxypropanal **32** was reacted with the (*Z*)-boron enolate prepared from the chiral imide **33**.[31] The imide aldol was converted into the corresponding methyl ester **34**, and ester **35** was obtained via PMB deprotection and tosylation. The reaction of **35** with acetal ketone **36** under acidic conditions afforded β-alkoxyvinyl ketone **37** after subsequent iodide substitution. Radical cyclization of **37** in the presence of tributylstannane and AIBN under the standard high-dilution conditions proceeded efficiently to give the keto oxolane product **38** in high yield. Samarium(II) iodide was the reagent of choice[32] for stereoselective reduction of the carbonyl group (8.5:1) in **38**, and carboxylic acid **39** was prepared via TBS protection of the hydroxyl group and basic hydrolysis of the methyl ester moiety.

Synthesis of the C1−C18 fragment commenced with the reaction of **32** with the (*Z*)-boron enolate of imide **40** (*ent*-**33**). The Weinreb amide obtained from the aldol imide was transformed into the BOM derivative **41**, and aldehyde **42** was obtained via DIBAL reduction. Reaction of **42** with the (*Z*)-boron enolate of imide **33** yielded the aldol imide. $NaBH_4$ reduction, protection of the primary hydroxyl group with TBSCl, and benzylation of the secondary hydroxyl group provided the protected tetrahydroxy intermediate **43** in a stereoselective manner. Allylation of aldehyde **44**, which was obtained from **43** via TBS deprotection and oxidation, proceeded stereoselectively upon addition of allyltributylstannane in the presence of the $MgBr_2 \cdot Et_2O$ complex.[33] Homoallylic alcohol **45** thus obtained was converted into dibenzoate **46** via oxidative cleavage of the double bond, $NaBH_4$ reduction, and benzoylation.

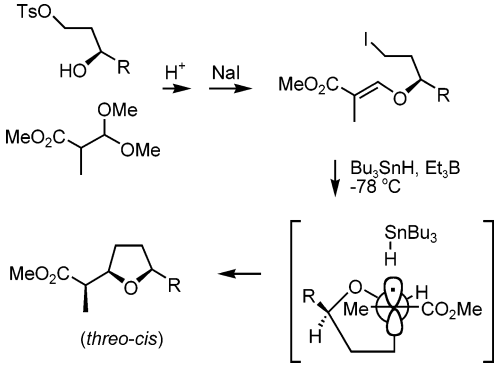
Alcohol **47** was obtained from **46** via PMB deprotection with ceric ammonium nitrate, tosylation of the primary hydroxyl group, and BOM deprotection. The reaction of **47** with excess methyl 3,3-dimethoxy-2-methylpropanoate (**48**) in the presence of an acid

Scheme 3. Thomas Total Synthesis of Pamamycin 607 (1)[a]



[a] Reagents and conditions: (a) (i) (*R*)-BnNH·CHMePh, *n*-BuLi, −78 °C; (ii) $Pd(OH)_2/C$, HCO_2NH_4, HCO_2H. (b) (i) *p*-TsCl, TEA, DMAP; (ii) NaH, MeI; (iii) $LiAlH_4$, Et_2O; (iv) $(COCl)_2$, DMSO, TEA. (c) $SnCl_4$, −78 °C. (d) (i) PhSeCl, 0.2 equiv $SnCl_4$; (ii) *n*-Bu_3SnH, AIBN. (e) (i) H_2, Pd/C, EtOH; (ii) $(COCl)_2$, DMSO, TEA. (f) (i) 2,6-Dimethylphenyl propanoate, LDA, −78 °C; (ii) TBSOTf. (g) (i) DIBAL; (ii) $(COCl)_2$, DMSO, TEA. (h) Compound **16**, $SnCl_4$. (i) (i) PhthSePh, $ZnCl_2$, DCM; (ii) *n*-Bu_3SnH, AIBN. (j) (i) Na, naphth, −60 °C; (ii) Boc_2O, TEA; (iii) H_2, Pd/C; (iv) Dess−Martin periodinane; (v) $NaOCl_2$, NaH_2PO_4. (k) $SnCl_4$. (l) (i) Ph_3P, *p*-NO_2PhCO_2H, DEAD; (ii) NaOH. (m) (i) PhSePhth, $SnCl_4$; (ii) *n*-Bu_3SnH, AIBN. (n) (i) H_2, Pd/C; (ii) Dess−Martin periodinane; (iii) $NaOCl_2$, NaH_2PO_4; (iv) DIPEA, BnBr; (v) concentrated HCl, MeOH. (o) (i) 2,4,6-$Cl_3PhCOCl$, DMAP, DCM; (ii) HCl, EtOH, 40−50 °C; (iii) Boc_2O, TEA. (p) (i) H_2, Pd/C, EtOH; (ii) 2,4,6-$Cl_3PhCOCl$, TEA, DMAP; (iii) TFA, DCM; (iv) CH_2O, $NaBH_3CN$, AcOH.

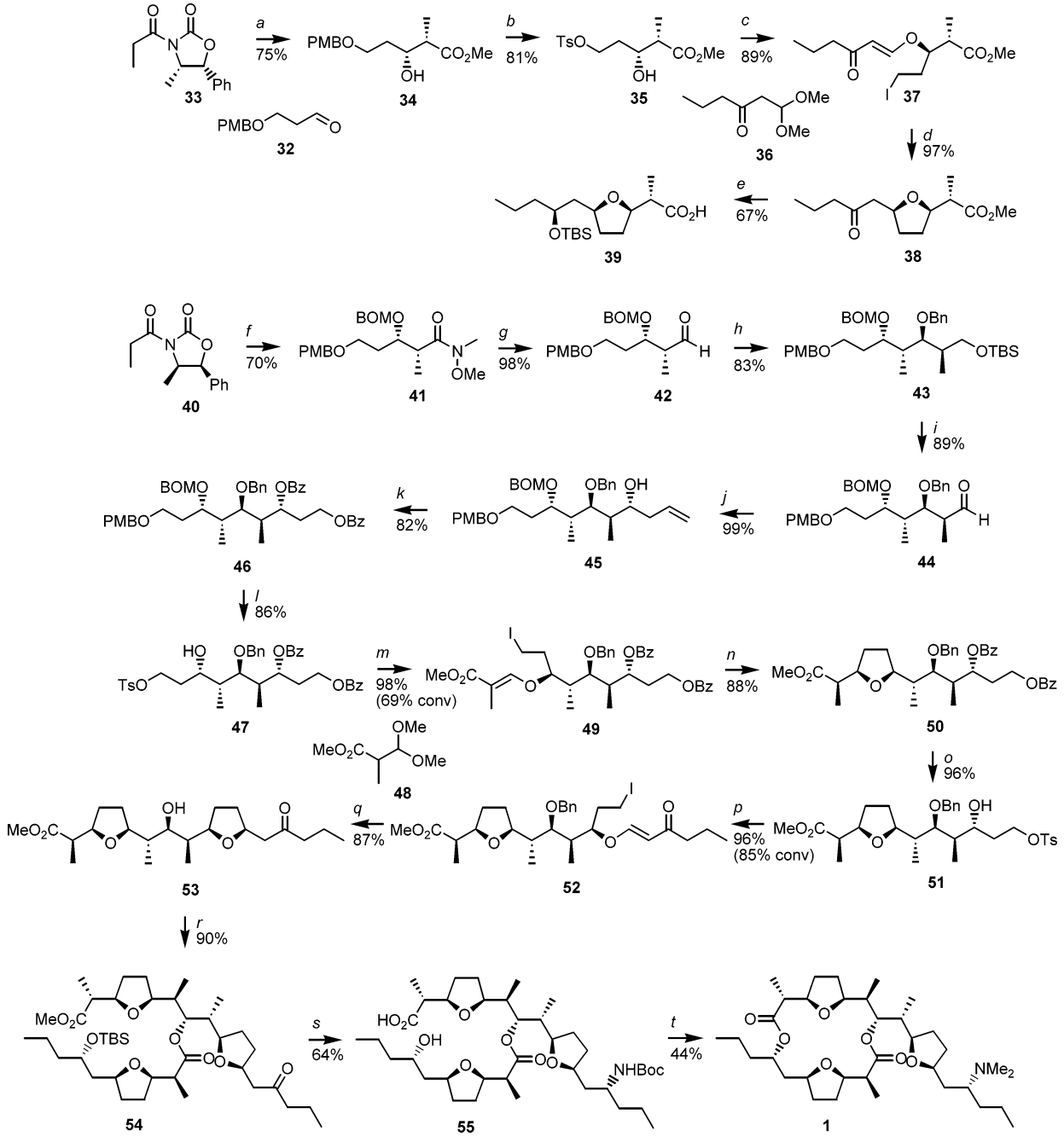
Scheme 4. Key Steps in Lee Total Synthesis



catalyst provided the desired β-alkoxymethacrylate derivative, which was converted into iodide **49** via iodide substitution. Low-temperature radical cyclization reaction of **49** in the presence of triethylborane proceeded efficiently producing a mixture of the oxolane products favoring (10.8:1) the correct threo isomer **50**. The benzoate moieties in **50** were hydrolyzed, and the primary hydroxyl group was tosylated to provide alcohol **51**. Reaction of **51** with acetal ketone **36** proceeded uneventfully, and β-alkoxyvinyl ketone **52** was obtained after iodide substitution. Radical cyclization reaction of **52** under the standard high-dilution conditions in the presence of tributylstannane and AIBN and subsequent debenzylation via hydrogenolysis afforded hydroxy ketone **53** in high yield.

Esterification of carboxylic acid **39** with alcohol **53** was achieved using the Yamaguchi protocol[27a] yielding ester **54** in high yield. Reductive amination of the carbonyl group in **54** and subsequent *t*-Boc protection proceeded stereoselectively, and TBS deprotection and hydrolysis of the methyl ester moiety afforded

Scheme 5. Lee Total Synthesis of Pamamycin 607 (1)[a]



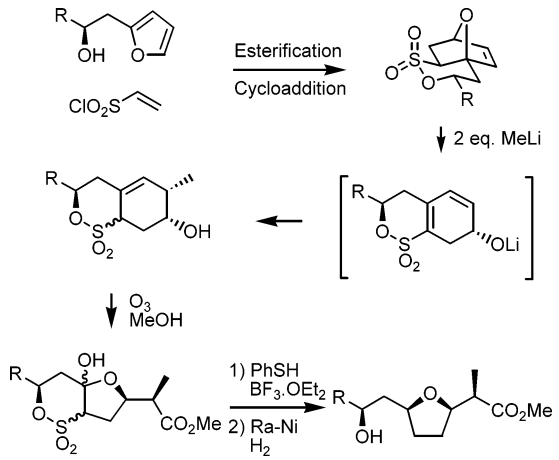
[a] Reagents and conditions: (a) (i) *n*-Bu_2BOTf, TEA, DCM, −40−0 °C, **32**, −78−0 °C; (ii) $Sm(OTf)_3$, MeOH−THF. (b) (i) H_2, Pd/C; (ii) *p*-TsCl, TEA, 0 °C. (c) (i) Compound **36**, TFA, benzene, reflux; (ii) NaI, acetone, reflux. (d) *n*-Bu_3SnH, AIBN. (e) (i) SmI_2, MeOH−THF; (ii) TBSCl, imidazole, DMF; (iii) NaOH, MeOH−H_2O. (f) (i) *n*-Bu_2BOTf, TEA, DCM, −40−0 °C, **32**, −78−0 °C; (ii) MeNH(OMe)·HCl, Me_3Al, THF, −20 °C to room temperature; (iii) BOMCl, DIPEA, TBAI. (g) DIBAL, THF, −78 °C. (h) (i) Compound **33**, *n*-Bu_2BOTf, TEA, DCM, −40−0 °C, **42**, −78−0 °C; (ii) $NaBH_4$, THF−H_2O; (iii) TBSCl, imidazole, DCM, 0 °C; (iv) BnBr, NaHMDS, THF−DMF, 0 °C. (i) (i) TBAF, THF; (ii) SO_3·Pyr, TEA, DMSO−DCM. (j) H_2CCHCH_2Sn*n*-Bu_3, $MgBr_2·Et_2O$, DCM. (k) (i) OsO_4, NMO, acetone−H_2O, $NaIO_4$; (ii) $NaBH_4$, EtOH; (iii) BzCl, pyridine, DMAP, DCM. (l) (i) CAN, MeCN−THF; (ii) *p*-TsCl, TEA, 0 °C; (iii) concentrated HCl−MeCN. (m) (i) Compound **48**, *p*-TsOH, $CHCl_3$, reflux; (ii) NaI, acetone, reflux. (n) *n*-Bu_3SnH, Et_3B, toluene, −78 °C. (o) (i) K_2CO_3, MeOH; (ii) *p*-TsCl, TEA, 0 °C. (p) (i) Compound **36**, TFA, benzene, reflux; (ii) NaI, acetone, reflux. (q) (i) *n*-Bu_3SnH, AIBN, benzene, reflux; (ii) H_2, Pd/C. (r) Compound **39**, 2,4,6-$Cl_3PhCOCl$, TEA, THF; **53**, DMAP, benzene (0.1 M). (s) (i) NH_4OAc, $NaBH_3CN$, 4 Å MS, *i*-PrOH, 0 °C; (ii) Boc_2O, TEA, DCM; (iii) concentrated HCl, MeOH; (iv) LiOH, MeOH−H_2O. (t) (i) DCC, PPTS, pyridine, $ClCH_2CH_2Cl$ (0.001 M), reflux; (ii) TFA, DCM; (iii) H_2, Pd/C, aqueous CH_2O, AcOH, MeOH.

hydroxy carboxylic acid **55**. Dicyclohexylcarbodiimide was the reagent of choice for the crucial macrodiolide ring closure,[34] and the macrodiolide was obtained in 56% yield. Pamamycin 607 (**1**) was obtained via *t*-Boc deprotection and reductive methylation of the free amino group (Scheme 5). In the total synthesis, epimerization at C1 and C1′ was a serious problem in the esterification steps, and screening for milder esterification conditions was indispensable for the successful conclusion.

2.1.3. Metz Total Synthesis[35]

Vinylsulfonates of hydroxyalkyl 1,3-dienes provide sultones stereoselectively via intramolecular Diels−

Scheme 6. Key Steps in Metz Total Synthesis



Alder reaction. Metz and co-workers obtained threo-cis 2-(oxolane)propanoates from sultones by methyllithium addition, ozonolysis, phenylthio substitution, and reductive elimination/hydrogenation (Scheme 6).

Alcohol **58**, readily available from furan (**56**) and (*S*)-1,2-epoxypentane (**57**),[26b] reacted with vinylsulfonyl chloride (**59**) to give sultone **60** by a tandem esterification/cycloaddition[36] with complete diastereoselectivity. Subsequent treatment of **60** with 2 equiv of methyllithium induced a tandem elimination/alkoxide-directed 1,6-addition[37] to yield a mixture of the bicyclic compounds favoring **61**. Ozonolysis of this mixture, followed by eliminative workup, afforded two diastereomeric hemiketals **62**. Lewis acid-catalyzed exchange of the hydroxyl group with a phenylthio group and then tandem reductive elimination/hydrogenation with Raney nickel gave **63** (**63**:6′-*epi*-**63** = 18:1) via a single 2,3-dihydrofuran. Yamaguchi lactonization of the corresponding hydroxy acid readily available by saponification gave a 71:10 mixture of lactones favoring **64** under kinetic control. The configurational inversion at C2 is due to either an equilibration at the stage of the mixed anhydride coupled with a faster cyclization of the (2*S*) compound or the formation of a ketene intermediate coupled with a stereoselective protonation of the enol or enolate resulting from a hydroxy ketene cyclization. Upon treatment of lactone **64** with the lithium alkoxide of benzyl alcohol,[27b] the C1′−C11′ fragment **65** was readily obtained.

TBS protection of the hydroxyl group of **63** followed by reduction of the ester function delivered the monoprotected diol, which was converted into iodide **66**. Halogen−lithium exchange and subsequent addition of 2-acetylfuran (**67**) to the resultant organolithium intermediate yielded two diastereomeric tertiary alcohols (d.r. = 1:1). Upon stirring a chloroform solution of this mixture with catalytic amounts of concentrated aqueous hydrogen chloride, (*E*)-olefin **68** was formed with complete diastereoselectivity.

Hydroboration of **68** followed by standard oxidative workup delivered largely one stereoisomer **69** that was isolated in good yield. Treatment of hydroxyalkylfuran **69** with vinylsulfonyl chloride (**59**) smoothly produced a single sultone **70** via tandem esterification/cycloaddition in high yield. Treatment of sultone **70** with 2 equiv of methyllithium cleanly introduced a methyl group only syn to the hydroxyl substituent via tandem elimination/alkoxide-directed 1,6-addition. Ozonolysis of the resultant mixture favoring the trisubstituted olefin **71** followed by eliminative workup delivered the expected hemiketal **72** as a single stereoisomer in excellent yield. Treatment of hemiketal **72** with thiophenol in the presence of trifluoroborane effected lactol *S*,*O*-acetal interchange and cleavage of the TBS ether moiety on the side chain to give the corresponding alcohol, which was cleanly converted into azide **73** via Mitsunobu reaction with hydrazoic acid. Smooth azide reduction and subsequent double reductive alkylation[38] of the intermediate primary amine took place to deliver the dimethylamino product **74** when azide **73** was subjected to the standard conditions for reductive sultone desulfurization followed by addition of a 35% aqueous formaldehyde solution to the reaction mixture.

Silylation of methyl ester **74** followed by mild saponification yielded the C1−C18 fragment **75** as a single stereoisomer. Subsequent intermolecular Yamaguchi esterification of **75** with **65** then provided the coupling product **76** in high yield. Desilylation of **76** using aqueous HF and reductive debenzylation of the resultant benzyl ester proceeded to give the desired *seco*-acid **77**. Modified Yamaguchi cyclization of **77** (6.4×10^{-3} M) at room temperature in the presence of DMAP in dichloromethane[27b] produced pamamycin 607 (**1**) in 69% yield (Scheme 7). Facile epimerization at C1 and C1′ had to be overcome for successful total synthesis.

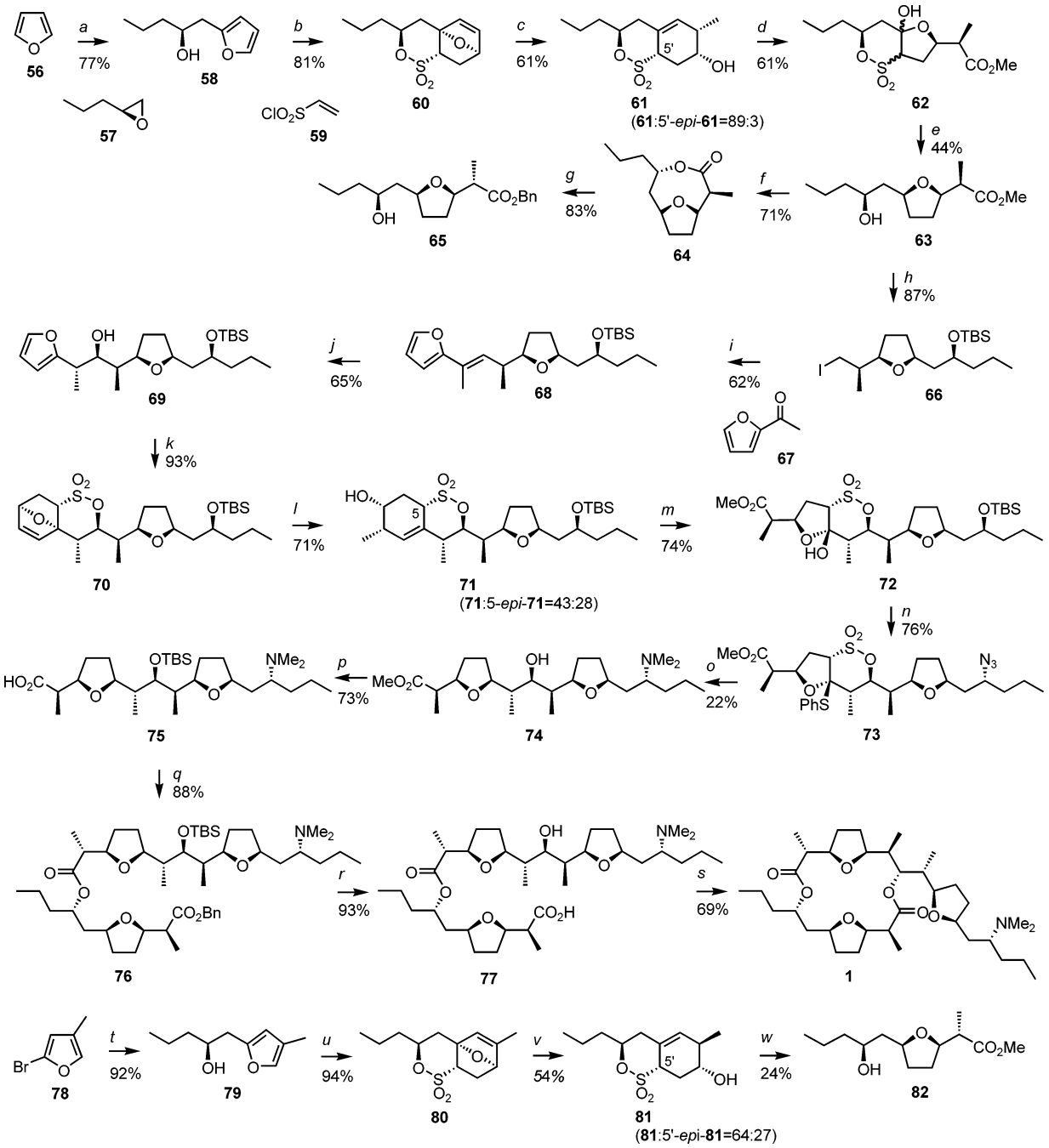
In an alternative synthesis of the C1′−C11′ fragment, sultone **80** was efficiently generated with complete diastereoselectivity from 2-bromo-4-methylfuran (**78**)[39] via intramolecular Diels−Alder reaction of the vinylsulfonate derived from alcohol **79**. Upon subjecting **80** to a tandem elimination/alkoxide-directed 1,6-hydride addition,[40] a mixture of the bicyclic compounds favoring **81** with the required trans relationship of the hydroxyl and the methyl substituent were isolated in good yield. Application of the reaction sequence of tandem ozonolysis/cyclization, Lewis acid-catalyzed hydroxyl/phenylthio exchange, and tandem reductive elimination/hydrogenation finally led to methyl ester **82** with high diastereoselectivity (**82**:6′-*epi*-**82** = 17:1) for the final step.

2.1.4. Kang Total Synthesis[41]

In the total synthesis of Kang and co-workers, stereoselective iodoetherification reaction of γ-triethylsilyloxyalkenes[42] was employed for *cis*-2,5-disubstituted oxolane synthesis. The iodo functionality in the product was used for synthesis of an oxirane intermediate, which in turn was reacted with lithium dimethylcuprate to form the required threo-cis arrangement (Scheme 8).

For preparation of the C1′−C11′ fragment, aldehyde **83** was reacted with the Roush allylboronate **84**[43] and the product alcohol was silylated to yield olefin **85** (78% d.e.), which was then subjected to hydroboration, Mitsunobu reaction, and *m*CPBA oxidation to afford sulfone **86**. Addition of aldehyde

Scheme 7. Metz Total Synthesis of Pamamycin 607 (1)[a]

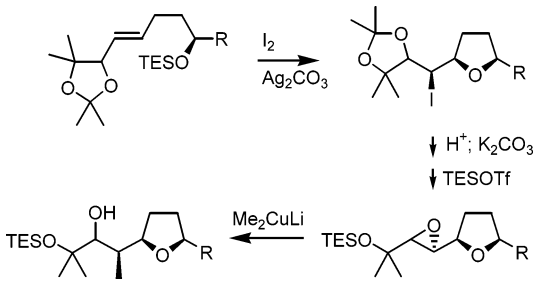


[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 to −15 °C; **57**, −15 to 25 °C. (b) Compound **59**, TEA, THF, 0−25 °C. (c) (i) MeLi, THF, −78 to 0 °C; (ii) NH_4Cl, H_2O, −78 to 25 °C. (d) (i) O_3, $NaHCO_3$, DCM, MeOH, −78 °C; (ii) Ac_2O, pyridine, DCM. (e) (i) PhSH, $BF_3{\cdot}Et_2O$, DCM; (ii) Raney Ni (W2), 50 bar H_2, EtOH. (f) (i) 2 N NaOH; (ii) 2,4,6-Cl_3PhCOCl, TEA, THF; DMAP, toluene, reflux. (g) BnOLi, BnOH, THF. (h) (i) TBSCl, imidazole, DMAP, DMF; (ii) $LiAlH_4$, Et_2O; (iii) I_2, Ph_3P, imidazole, Et_2O, MeCN. (i) (i) *t*-BuLi, Et_2O, −78 °C; (ii) **67**, −78 to 25 °C; (iii) HCl, $CHCl_3$. (j) (i) $BH_3{\cdot}$THF, 0−25 °C; (ii) H_2O_2, NaOH, 0−25 °C. (k) Compound **59**, TEA, THF, 0−25 °C. (l) (i) MeLi, THF, −78 to 0 °C; (ii) NH_4Cl, H_2O, −78 to 25 °C. (m) (i) O_3, $NaHCO_3$, DCM, MeOH, −78 °C; (ii) Ac_2O, pyridine, DCM, 25 °C ∼ reflux. (n) (i) PhSH, $BF_3{\cdot}Et_2O$, DCM; (ii) HN_3, DEAD, Ph_3P, toluene, 0−25 °C. (o) (i) Raney Ni, 50 bar H_2, EtOH; (ii) CH_2O, H_2O. (p) (i) TBSOTf, 2,6-lutidine, DCM; (ii) 0.2 N LiOH, THF, MeOH. (q) 2,4,6-Cl_3PhCOCl, TEA, THF; **65**, DMAP, toluene. (r) (i) Aqueous HF, MeCN; (ii) H_2, Pd/C, THF, MeOH. (s) 2,4,6-Cl_3PhCOCl, DMAP, 4 Å MS, DCM. (t) *t*-BuLi, THF, −78 to −15 °C; **57**, −15 to 25 °C. (u) Compound **59**, TEA, THF, 0−25 °C. (v) (i) Red-Al, toluene; (ii) NH_4Cl, H_2O. (w) (i) O_3, $NaHCO_3$, DCM, MeOH, −78 °C; (ii) Ac_2O, pyridine, DCM; (iii) PhSH, $BF_3{\cdot}Et_2O$, DCM; (iv) Raney Ni (W2), 50 bar H_2, EtOH.

87 to the lithium anion obtained from **86** provided a 1.2:1 mixture of *trans*- and *cis*-alkenes **88**. The mixture **88** was exposed to iodine in the presence of silver carbonate in diethyl ether to provide a 1.2:1 mixture of iodides in 92% yield. Reductive deiodination[44] and debenzylation of the cyclized products gave rise to the oxolane product **89** as the only stereoisomer.

Synthesis of the C1−C18 fragment began with the formation of sulfone **91**, derived from alcohol **90**[45] by Mitsunobu reaction and *m*CPBA oxidation. Coupling of **91** with **87** using KHMDS and subsequent desilylation produced a 7:1 separable mixture favoring the *trans*-alkene. The *trans*-olefinic alcohol was then oxidized to aldehyde **92**. Aldol condensation[46] of **92** with the (*E*)-boron enolate of ethyl ketone **93**[47] mainly

Scheme 8. Key Steps in Kang Total Synthesis



provided the desired *anti*-aldol product **94**. Stereoselective anti reduction[48] of the keto group of **94** and the subsequent deprotection gave predominantly the desired triol **95**. Triol **95** was chemoselectively oxidized[49] to a six-membered lactone, which was subjected to Weinreb-amide formation[50] and regioselective monosilylation to yield Weinreb amide **96**.

The known phosphonate **97**[51] was olefinated with aldehyde **98** to furnish exclusively the *trans*-enone. Reduction of the enone moiety,[52] desilylation, acetonide protection, and iodide substitution gave the racemic iodide **99**. Transmetalation of **99** followed by the addition of amide **96** yielded a β-hydroxy ketone product. Diastereoselective anti reduction of the ketone gave a 20:1 mixture of alcohols favoring the desired product **100**. After disilylation of **100**, double iodoetherification was performed using iodine in the presence of silver carbonate in diethyl ether to supply bis-oxolane product **101** with complete cis stereoselectivity. Acidic deprotection of **101**, oxirane cyclization, reductive deiodination, and silylation provided the oxirane intermediate **102**. The reaction of **102** with lithium dimethylcuprate proceeded regio- and stereoselectively producing tetraol **103** after benzyl and TES deprotection by hydrogenation. Azide substitution of the least hindered hydroxyl group in **103** was possible under Mitsunobu conditions, and carboxylic acid **104** was obtained after oxidative cleavage of the vicinal diol moiety.

The fragments **89** and **104** were coupled under Yamaguchi conditions, and the coupled ester **105** was desilylated and oxidized chemoselectively[53] to yield carboxylic acid **106**. Lactonization of **106** via the corresponding thiopyridyl ester in the presence of cupric bromide[54] gave the macrodiolide product. The azido group was reduced, and in situ addition of formaldehyde to the generated amine under the hydrogenation conditions produced pamamycin 607 (**1**) (Scheme 9).

An alternative synthesis[55] of the C1−C18 fragment of pamamycin 607 (**1**) by Kang began with crotylation of the aldehyde, generated from the known alcohol **107**[56] with (*E*)-crotylboronate **108**[57] to afford alcohol **109** (80% e.e.). Alcohol **109** was subjected to esterification with *N*-Cbz-(*S*)-proline, dihydroxylation, oxidative cleavage, and $NaBH_4$ reduction in sequence to furnish a 9:1 separable mixture of the desired alcohol **110** and its diastereomer. Conversion of **110** into iodide **111** was carried out via a sequence of basic hydrolysis, acetonide protection, debenzylation by dissolving metal reduction, and iodide substitution. Acidic hydrolysis of **111** yielded a labile diol, which was disilylated consecutively with TBDPSCl and TESOTf and then reacted with Ph_3P to render the phosphonium salt **112**. Alcohol **110** was oxidized under Swern conditions, and the resultant aldehyde was reacted with vinyl Grignard reagent to give allylic alcohol **113** in 53% overall yield along with 17% of the diastereomeric alcohol. The aldehyde derived from **113** via acetonide protection and ozonolysis reacted with the ylide generated from **112** with *t*-BuLi to provide only *cis*-alkene **114**. Treatment of **114** with iodine in the presence of Ag_2CO_3 gave rise to the *cis*-disubstituted oxolane **115** as a single stereoisomer.

Conversion of **115** into epoxide **116** was accomplished by acidic deprotection, cyclization, and silylation. Lithium dimethylcuprate reaction of **116** afforded the desired alcohol **117** along with the regioisomer. Hydrogenolysis of **117** was implemented to unmask benzyl and TES groups concurrently. The resulting triol was protected as the 1,3-dioxane and subsequently transformed into the phosphonium salt via the iodide to furnish **118**. Aldehyde **87** was olefinated with the ylide derived from **118** to give a 10:1 mixture of the *cis*- and *trans*-alkenes, which was further converted into bis-TES ether **119** via acidic hydrolysis and silylation. Iodoetherification of **119** and reductive deiodination yielded the bis-oxolane product **120** as the only stereoisomer. Coincident deprotection of the benzyl and the triethylsilyl groups in **120** by hydrogenolysis provided the diol. The sterically less hindered hydroxyl group was chemoselectively converted into an azido group under Mitsunobu conditions, and the remaining one was protected as the PMB ether. Successive desilylation and Jones oxidation afforded the C1−C18 subunit **121** (Scheme 10).

2.2. Amphidinolide X (2)

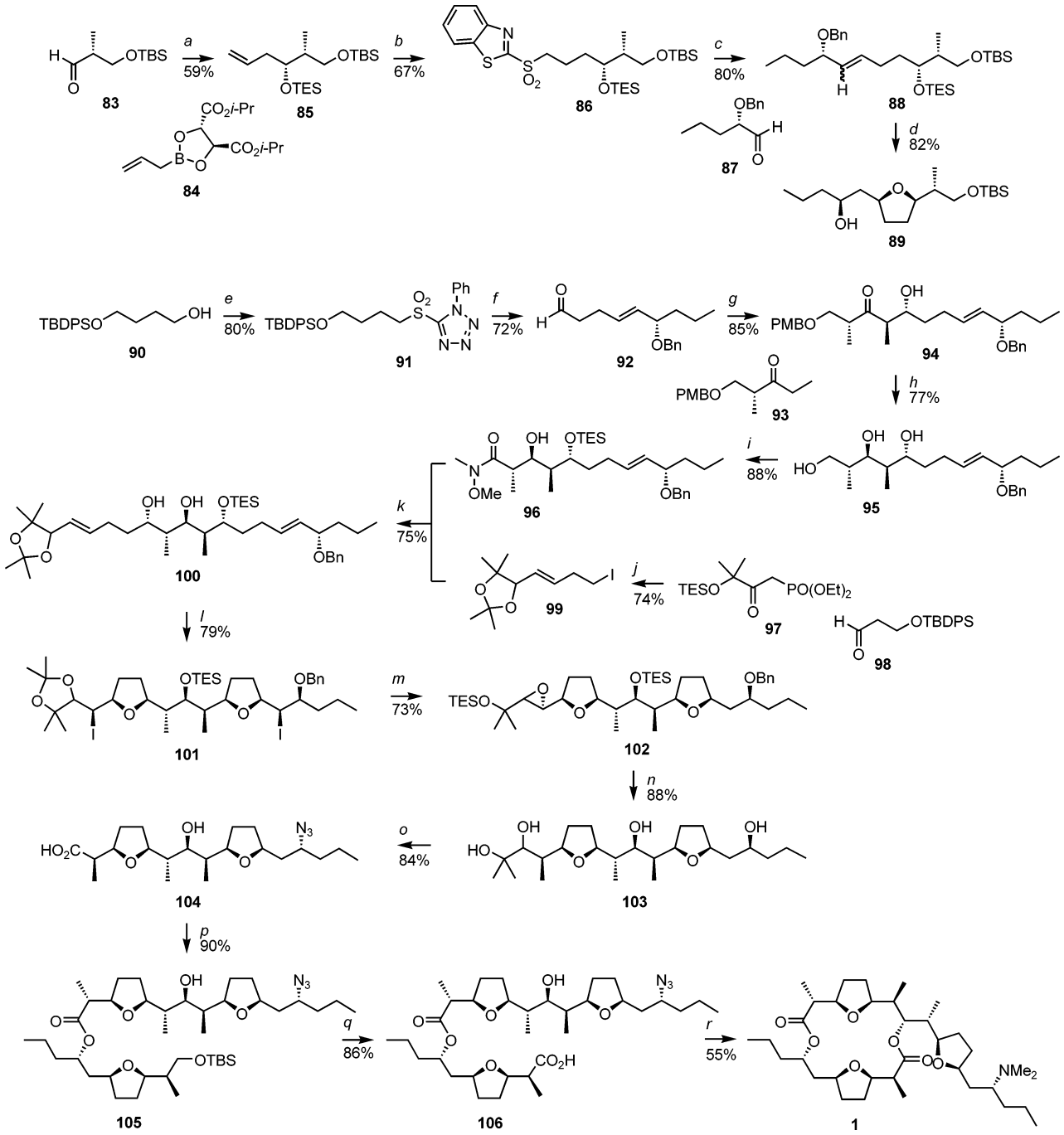
Marine dinoflagellates of the genus *Amphidinium* sp. living in symbiosis with the Okinawan flatworm *Amphiscolops* sp. produce a host of secondary metabolites, which are called amphidinolides.[58] They are endowed with potent cytotoxicity against various cancer cell lines and exhibit highly diverse macrolactone backbones. Possessing high cytotoxicity against murine lymphoma and human epidermoid carcinoma, amphidinolide X (**2**) is a unique member of this class because it has neither the characteristic exomethylene group, nor a vicinal one-carbon branch, nor a 1,3-diene unit found in virtually all other members of this series.[8] Moreover, **2** is the only naturally occurring macrodiolide known to date that consists of a diacid and a diol unit rather than of two hydroxy acid entities.

2.2.1. Fürstner Total Synthesis[59]

In the Fürstner total synthesis, the ester linkages forming the macrodiolide ring presented obvious sites of disconnection, and it was envisaged to assemble the C7−C22 segment by metal-catalyzed cross coupling at the C13−C14 bond (Scheme 11).

Fürstner and co-workers employed a chiral allenol as a latent progenitor of the oxolane ring in amphidinolide X (**2**), which can be formed stereoselectively by an iron-catalyzed reaction of a propargyl epoxide

Scheme 9. Kang Total Synthesis of Pamamycin 607 (1)[a]

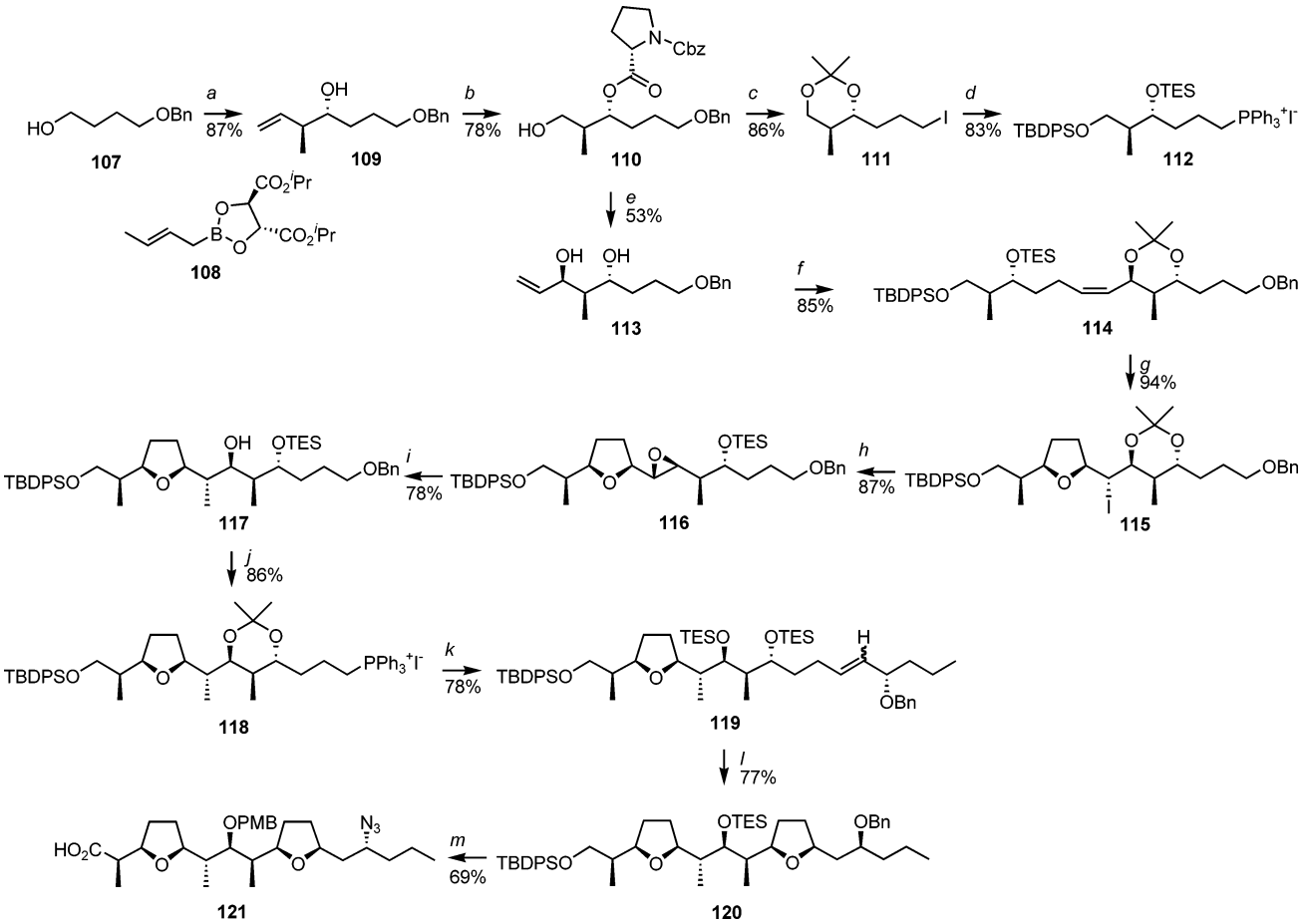


[a] Reagents and conditions: (a) (i) Compound **84**, toluene, 4 Å MS, −78 °C; (ii) TESCl, imidazole, DMF. (b) (i) BH_3·DMS, THF; NaOH, H_2O_2; (ii) Ph_3P, 2-mercaptobenzothiazole, DEAD, THF, 0 °C to room temperature; (iii) *m*CPBA, DCM. (c) LiHMDS, THF, −78 °C; **87**. (d) (i) I_2, Ag_2CO_3, Et_2O; (ii) Ph_3SnH, Et_3B, THF, 0 °C; (iii) H_2, Pd/C, MeOH. (e) (i) 1-Phenyl-1*H*-tetrazole-5-thiol, Ph_3P, DEAD, THF; (ii) *m*CPBA, $NaHCO_3$, DCM. (f) (i) KHMDS, **87**, DME, −78 °C to room temperature; (ii) TBAF, THF; (iii) Swern oxidation. (g) Compound **93**, *c*-Hex_2BCl, TEA, Et_2O, 0 °C; **92**, −78 to −20 °C. (h) (i) $Me_4NBH(OAc)_3$, AcOH, MeCN, −30 to −20 °C; (ii) CAN, MeCN−H_2O, 0 °C. (i) (i) TEMPO, NCS, *n*-Bu_4NCl, aqueous $NaHCO_3$, K_2CO_3 (pH 8.6), DCM; (ii) MeONHMe·HCl, Me_3Al, DCM, −78 °C; (iii) TESCl, imidazole, DCM, −40 °C. (j) (i) Compound **98**, DIPEA, LiCl, MeCN; (ii) $NaBH_4$, $CeCl_3$·$7H_2O$, MeOH, 0 °C; (iii) TBAF, THF; (iv) *p*-TsOH, acetone; (v) I_2, Ph_3P, imidazole, THF, 0 °C to room temperature. (k) (i) Compound **99**, *t*-BuLi, Et_2O, −78 to −20 °C; **96**, −50 to −20 °C; (ii) $Me_4NBH(OAc)_3$, AcOH, MeCN, −20 °C. (l) (i) TESOTf, TEA, DCM, 0 °C; (ii) I_2, Ag_2CO_3, Et_2O. (m) (i) 2 N HCl, MeOH, reflux; K_2CO_3; (ii) Ph_3SnH, Et_3B, THF, 0 °C; (iii) TESOTf, TEA, DCM, −20 °C. (n) (i) Me_2CuLi, Et_2O, 5 °C; (ii) H_2, $Pd(OH)_2$/C, EtOH. (o) (i) HN_3, Ph_3P, DEAD, benzene, 0 °C; (ii) $NaIO_4$, *t*-BuOH, H_2O; 1.25 M NaH_2PO_4, 1 M $KMnO_4$. (p) 2,4,6-$Cl_3PhCOCl$, TEA, THF; **89**, DMAP, benzene. (q) (i) TBAF, THF; (ii) TEMPO, $NaClO_2$, NaH_2PO_4 buffer (pH 6.7), NaOCl, MeCN. (r) (i) $(PyS)_2$, Ph_3P, MeCN; $CuBr_2$, MeCN; (ii) H_2, Pd/C, MeOH; aqueous CH_2O, AcOH.

with a suitable Grignard reagent.[60] This sequence efficiently transfers the central chirality of a readily accessible epoxide to the tetrasubstituted chiral sp^3 center at C19 via the axial chirality of an allene relay (Scheme 12).

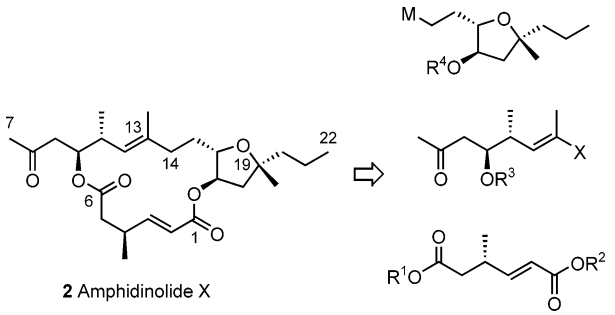
Sharpless epoxidation of allylic alcohol **122**[61] furnished the product **123** in excellent yield (83% e.e.). Swern oxidation of **123** followed by treatment with the Ohira−Bestmann reagent[62] gave a terminal alkyne, which was converted to propargylic epoxide

Scheme 10. Kang Alternative Synthesis of C1−C18 Fragment of Pamamycin 607 (1)[a]



[a] Reagents and conditions: (a) (i) Swern oxidation; (ii) **108**, 4 Å MS, toluene, −78 °C; 2 N NaOH, 0 °C. (b) (i) *N*-Cbz-(*S*)-proline, DCC, DMAP, DCM; (ii) OsO_4, NMO, acetone−H_2O; (iii) $NaIO_4$, THF−H_2O; $NaBH_4$, 0 °C. (c) (i) LiOH, MeOH−H_2O; (ii) PPTS, $Me_2C(OMe)_2$, toluene, reflux; (iii) Li, NH_3(l), THF, −78 °C; (iv) I_2, Ph_3P, imidazole, THF, 0 °C. (d) (i) Concentrated HCl, MeOH, 0 °C; (ii) TBDPSCl, DMAP, TEA, DCM, −15 °C; TESOTf, −15 °C; (iii) Ph_3P, K_2CO_3, MeCN, reflux. (e) (i) Swern oxidation; (ii) $CH_2CHMgBr$, Et_2O, −78 °C; (iii) LiOH, MeOH−H_2O. (f) (i) PPTS, $Me_2C(OMe)_2$, acetone; (ii) O_3, $NaHCO_3$, DCM, MeOH, −78 °C; DMS; (iii) **112**, *t*-BuLi, THF, −78 to −5 °C; aldehyde, 10 °C. (g) I_2, Ag_2CO_3, Et_2O. (h) (i) PPTS, MeOH, THF; K_2CO_3; (ii) TESOTf, 2,6-lutidine, DCM, −78 °C. (i) Me_2CuLi, Et_2O, 10 °C. (j) (i) H_2, $Pd(OH)_2$/C, EtOH; (ii) PPTS, acetone; (iii) I_2, Ph_3P, imidazole, THF, 0 °C; (iv) Ph_3P, K_2CO_3, MeCN, reflux. (k) (i) *n*-BuLi, THF, −78 to −5 °C; **87**, 10 °C; (ii) PPTS, MeOH, THF; (iii) TESOTf, 2,6-lutidine, DCM. (l) (i) I_2, Ag_2CO_3, Et_2O; (ii) Ph_3SnH, Et_3B, THF, 0 °C. (m) (i) H_2, $Pd(OH)_2$/C, EtOH; (ii) HN_3, Ph_3P, DEAD, benzene, 0 °C; (iii) PMBCl, TBAI, DMF, 0 °C; KHMDS, 0 °C; (iv) TBAF, THF; (v) Jones oxidation, 0 °C.

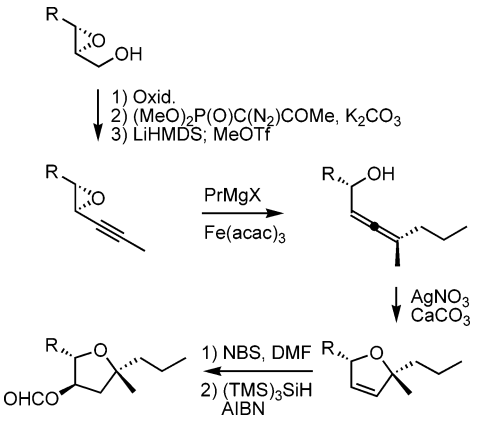
Scheme 11. Retrosynthetic Analysis of Amphidinolide X (2)



2 Amphidinolide X

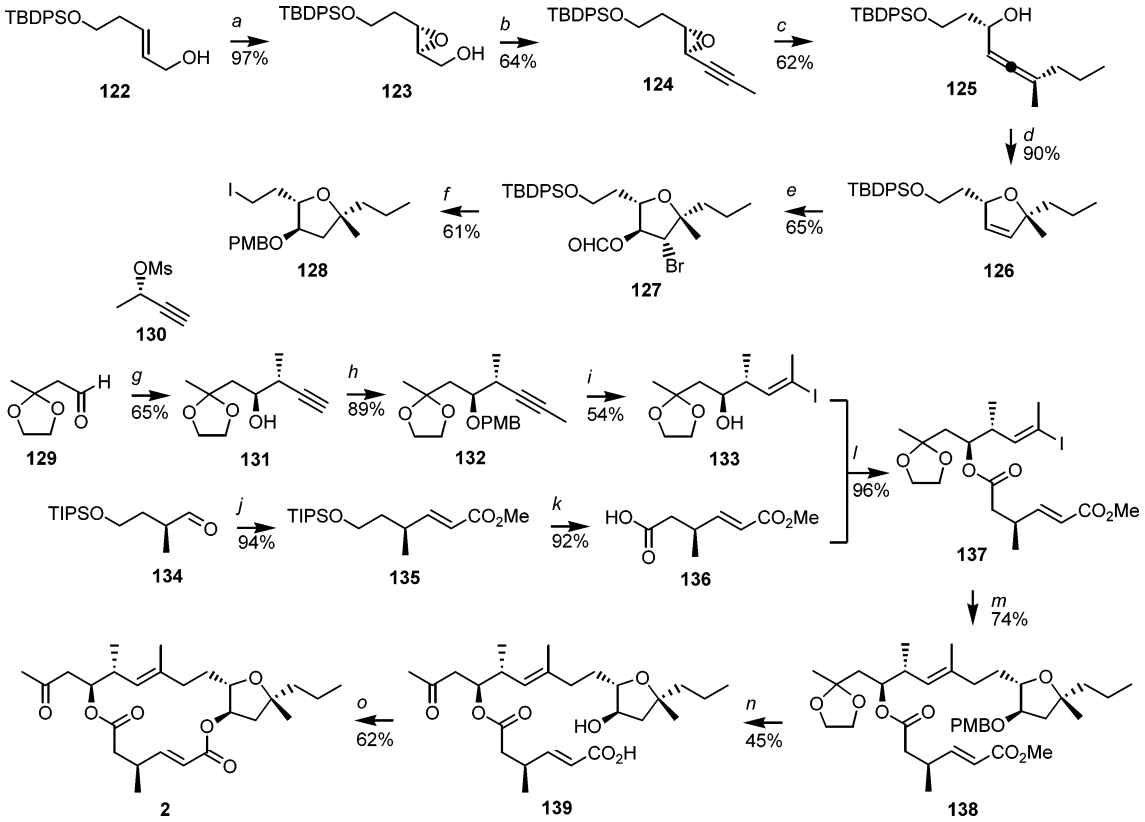
124 on treatment with LiHMDS and MeOTf. Reaction of **124** with PrMgCl in the presence of $Fe(acac)_3$ as the precatalyst furnished a 8:1 mixture of products in favor of the desired allene **125**. The mixture of allene isomers was treated with $AgNO_3$/$CaCO_3$ in aqueous acetone to afford the corresponding dihydrofuran **126** with strict chirality transfer.[63] Bromoesterification of **126** with NBS in aqueous DMF[64]

Scheme 12. Key Steps in Fürstner Total Synthesis



gave bromo formate **127** in satisfactory yield and also allowed the C19 isomers to be separated by flash chromatography. Removal of the bromide functionality in **127** using $(Me_3Si)_3SiH$ and AIBN followed by standard protecting group manipulations furnished iodide **128**.

Scheme 13. Fürstner Total Synthesis of Amphidinolide X (2)[a]



[a] Reagents and conditions: (a) Ti(O*i*-Pr)$_4$, L-(+)-DET, *t*-BuOOH, 4 Å MS, DCM. (b) (i) $(COCl)_2$, DMSO, TEA, DCM; (ii) $(MeO)_2P(O)C(N_2)COMe$, K_2CO_3, MeOH; (iii) LiHMDS, MeOTf, THF. (c) Fe(acac)$_3$, PrMgCl, toluene. (d) $AgNO_3$, $CaCO_3$, acetone−H_2O. (e) NBS, DMF−H_2O. (f) (i) TTMSS, AIBN, toluene; (ii) $NaHCO_3$, MeOH; (iii) $PMBOC(=NH)CCl_3$, PPTS, DCM−cyclohexane; (iv) TBAF, THF; (v) I_2, Ph_3P, imidazole, MeCN−Et_2O. (g) Et_2Zn, $Pd(OAc)_2$, Ph_3P, THF. (h) (i) PMBCl, NaH, TBAI, DMF; (ii) LiHMDS, MeI, THF. (i) (i) Cp_2ZrHCl, benzene; (ii) I_2, DCM; (iii) DDQ, DCM, buffer (pH 7). (j) $(EtO)_2P(O)CH_2CO_2Me$, LiCl, DBU, MeCN. (k) (i) HF·pyridine, MeCN; (ii) $(COCl)_2$, DMSO, TEA, DCM; (iii) $NaClO_2$, NaH_2PO_4, $(CH_3)_2CCHCH_3$, *t*-BuOH. (l) Compound **136**, 2,4,6-$Cl_3PhCOCl$, TEA, toluene; **133**, DMAP. (m) Compound **128**, *t*-BuLi, Et_2O−THF; 9-MeO-9-BBN; **137**, $(dppf)PdCl_2$, Ph_3As, K_3PO_4, DMF−H_2O. (n) (i) LiI, pyridine, 125 °C; (ii) AcOH−H_2O; (iii) DDQ, DCM, buffer (pH 7). (o) 2,4,6-$Cl_3PhCOCl$, TEA, THF; DMAP, toluene.

The second building block was accessed by the palladium-catalyzed, Et_2Zn-mediated addition of the enantiopure propargylic mesylate **130** to aldehyde **129**.[65] The major anti isomer **131** (93% e.e.) was converted into **132** after PMB protection and *C*-methylation. Hydrozirconation/iodination[66] of the triple bond in **132** and PMB deprotection with DDQ produced alcohol **133**. Ester **137** was obtained via Yamaguchi esterification of alcohol **133** with acid **136**, which was derived from the known aldehyde **134**[67] via enoate **135**.

For alkyl−alkenyl cross-coupling[68] of segments **128** and **137**, alkyl iodide **128** was treated with *t*-BuLi at −78 °C followed by addition of excess 9-MeO-9-BBN to give the corresponding borate,[69] which transferred its functionalized alkyl group to the organopalladium species derived from alkenyl iodide **137** and $(dppf)PdCl_2/AsPh_3$, thus delivering the product **138** in 74% isolated yield. Selective cleavage of the methyl ester in diester **138** with LiI in pyridine[70] followed by successive removal of the remaining acetal moiety and the PMB ether gave the *seco*-acid **139**. The final macrocyclization of this compound proceeded smoothly under Yamaguchi conditions, affording amphidinolide X (**2**) in 62% yield (Scheme 13).

3. Oxane/Oxene Macrodiolides

3.1. SCH 351448 (3)

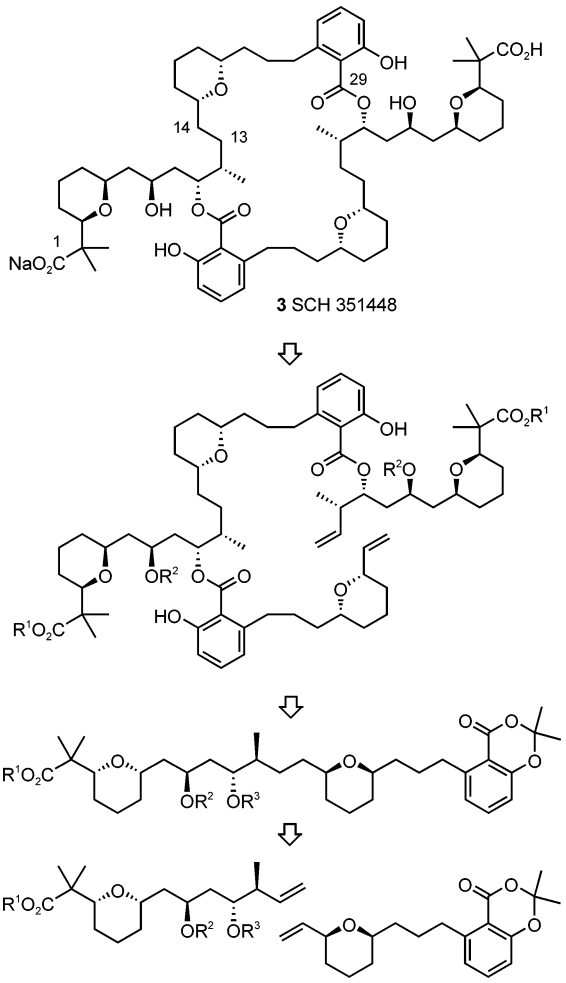
SCH 351448 (**3**) is a novel activator of low-density lipoprotein receptor (LDL-R) promoter with an IC_{50} of 25 μM, which was discovered from the organic extract of the fermentation broth of a *Micromonospora* microorganism.[9] Selective activators of LDL-R transcription may be able to decrease serum LDL levels by increasing LDL uptake by the LDL-R. The structure of **3** features a 28-membered macrodiolide consisting of two identical hydroxy carboxylic acid units.

3.1.1. Lee Total Synthesis[71]

In the Lee synthesis, two olefins representing C1−C13 and C14−C29 segments were prepared as basic modules. These modules were used for synthesis of the monomeric hydroxy acid (C1−C29), which was again derivatized with the modules for the final ring-closing metathesis reaction leading to the macrodiolide structure (Scheme 14).

For the synthesis of the salicylate fragment, selenide **141** obtained from acetonide alcohol **140**[72] was converted into β-alkoxyacrylate **142** via regioselective

Scheme 14. Retrosynthetic Analysis of SCH 351448 (3)



benzylation and reaction with methyl propiolate. Radical cyclization of **142** proceeded smoothly in the presence of tributylstannane and AIBN to provide (oxane)acetate ester **143** in good yield. The aldehyde obtained from ester **143** was converted into the homologous vinylstannane **144** via a modified Corey–Fuchs protocol[73] and hydrostannylation. Efficient Stille coupling[74] of **144** and the known triflate **145**[75] led to an olefinic intermediate **146**, which was transformed into aldehyde **147** after hydrogenation/hydrogenolysis and oxidation. Terminal olefin **148** was prepared from **147** via Wittig reaction.

Synthesis of the complementary fragment started with Mukaiyama aldol reaction of aldehyde **149**[76] mediated by a chiral borane reagent.[77] Secondary alcohol **150** obtained was converted into β-alkoxyacrylate **151** via reaction with methyl propiolate, TBS deprotection, and iodide substitution. Radical cyclization in the presence of hypophosphite and triethylborane in ethanol[78] proceeded efficiently to yield diester **152**. Basic hydrolysis of **152** provided a monocarboxylic acid, and the corresponding aldehyde **153** was converted into the correct homoallylic alcohol (d.r. = 9.6:1) via Brown allylation. Benzyl protection and transesterification with 2-(TMS)ethanol led to a new ester **154**. The aldehyde obtained via oxidative cleavage was converted into homoallylic alcohol **156** (d.r. = 14.1:1) via reaction with the Brown crotylation reagent **155**.[79]

Homoallylic alcohol **156** was converted into sulfone **157** via a five-step sequence, and Julia–Julia olefination of **157** proceeded smoothly with aldehyde **147** to generate the product olefin, from which the monomeric unit **158** was obtained via diimide reduction. The final assembly of the fragments was initiated by the reaction of the sodium alkoxide derived from **156** with **158**. The coupled product was converted into alcohol **159** via TBS deprotection, which was used for the coupling with **148** to produce diester **160**. Intramolecular olefin metathesis of **160** mediated by the second-generation Grubbs catalyst **161**[80] proceeded smoothly, and the macrodiolide was obtained after hydrogenation/hydrogenolysis. (TMS)ethyl ester functionalities were removed by reaction with TBAF, and monosodium salt **3** was obtained when the reaction mixture was equilibrated with 4 N hydrochloric acid saturated with sodium chloride (Scheme 15). SCH 351448 appears to be a remarkably stable sodium carboxylate.

3.2. Swinholide A (4)

Swinholide A (**4**) is a marine natural product isolated from the sponge *Theonella swinhoei*: it was demonstrated that the producer organisms of this natural product are heterotrophic unicellular bacteria.[10] It displays impressive biological properties including antifungal activity and potent cytotoxicity against a number of tumor cells. Its cytotoxicity has been attributed to its ability to dimerize actin and disrupt the actin cytoskeleton.[81] Swinholide A (**4**) is a C_2 symmetric 40-membered macrodiolide, which consists of two conjugated diene, two trisubstituted oxane, and two disubstituted oxene systems. A total of 30 stereogenic centers are present in the carbon backbone of **4**.

3.2.1. Paterson Total Synthesis[82]

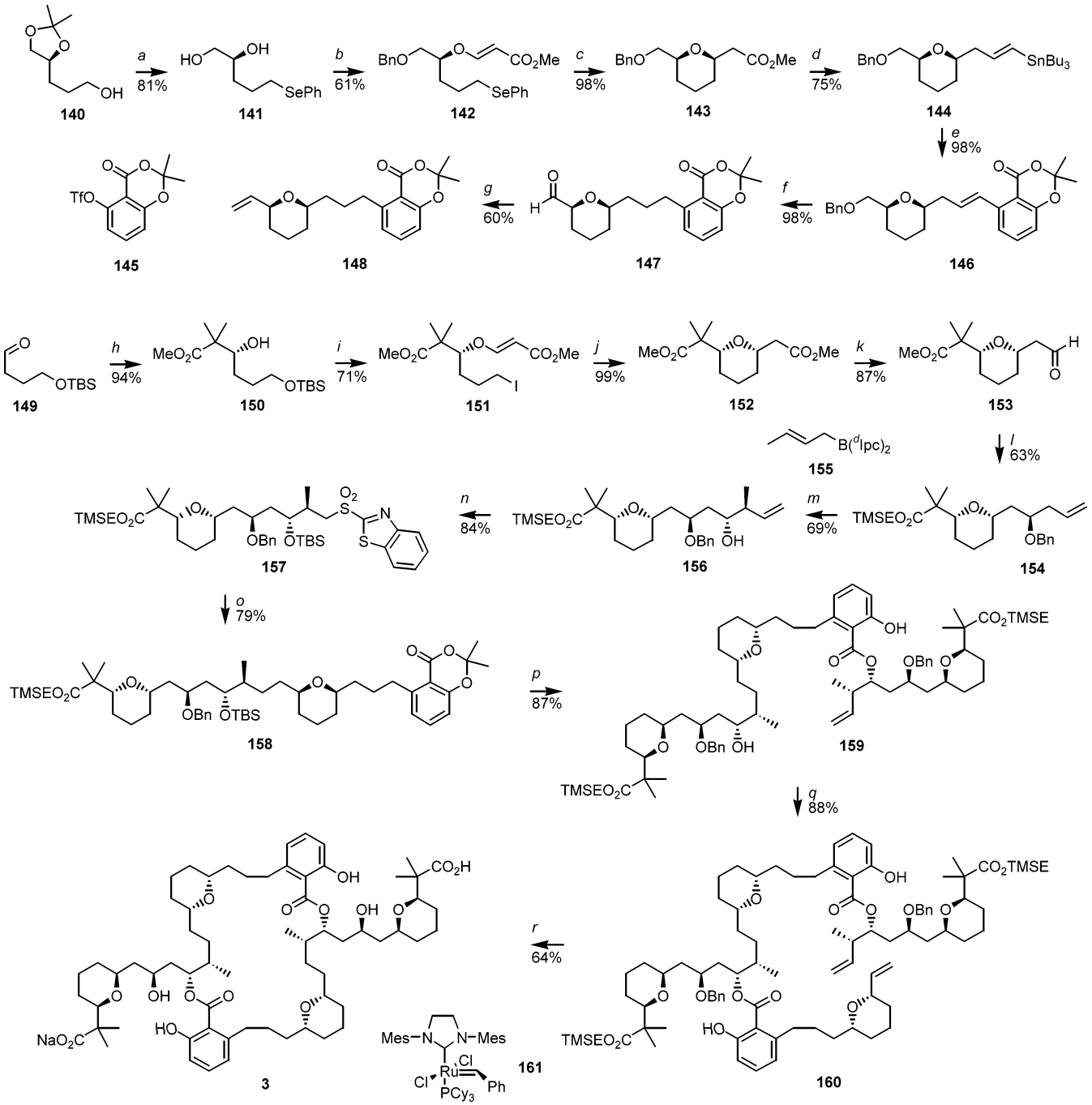
The first total synthesis was reported by Paterson and co-workers in 1994 and already reviewed by Norcross and Paterson.[1]

3.2.2. Nicolaou Total Synthesis[83]

The symmetry of the molecule allowed double disconnection and the adoption of a highly convergent plan using simple building blocks. Sequential disconnection of the two ester linkages in **4** defined a macrolactonization and an esterification as the final key reactions in the synthesis. The Wadsworth–Horner–Emmons reaction pointed to a C3–C32 fragment. Disconnection of the C17–C18 using a retro dithiane–cyclic sulfate coupling reaction allowed the utilization of the two segments C3–C17 and C18–C32 (Scheme 16).

The synthesis started from dimethyl (*S*)-malate (**162**), which upon reduction with BH_3·DMS/$NaBH_4$ gave the corresponding 1,2-diol.[84] Sequential silylation of this diol with TBDPSCl and TBSOTf followed by DIBAL reduction furnished bis-silyl ether aldehyde **163**. Asymmetric crotylboration of **163** using Brown (*Z*)-crotylborane **164**, followed by methylation, led to the formation of homoallylic ether **165** (d.r. = >20:1). Ozonolysis of **165**, followed by reductive work-

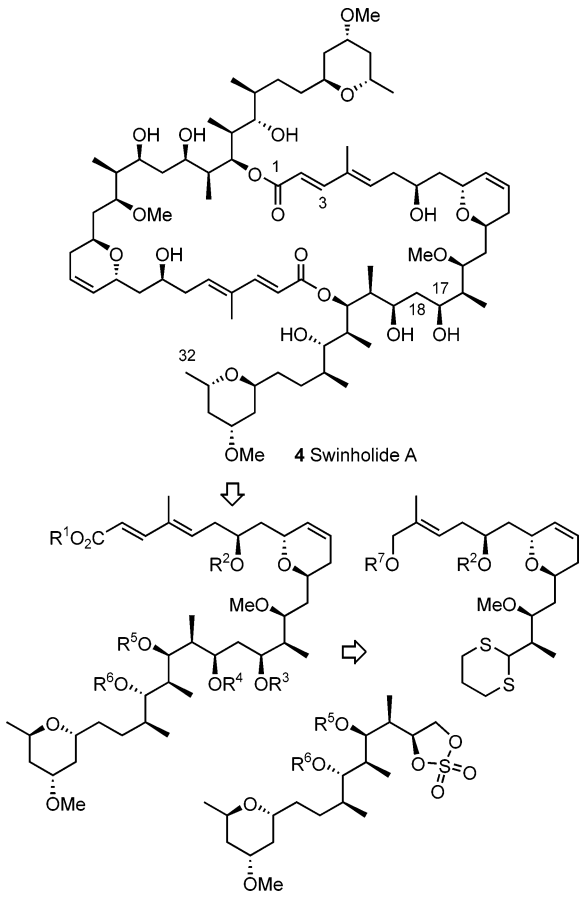
Scheme 15. Lee Total Synthesis of SCH 351448 (3)[a]



[a] Reagents and conditions: (a) (i) *p*-TsCl, TEA, DCM, 0 °C; (ii) PhSeSePh, $NaBH_4$, EtOH; (iii) concentrated HCl, MeOH. (b) (i) *n*-Bu_2SnO, benzene, reflux (−H_2O); BnBr, TBAI, benzene, reflux; (ii) $HCCCO_2Me$, NMM, MeCN. (c) *n*-Bu_3SnH, AIBN, benzene, reflux. (d) (i) LAH, THF, 0 °C; (ii) SO_3·pyr, TEA, DMSO−DCM, 0 °C; (iii) CBr_4, HMPT, THF, −30 °C; (iv) *n*-BuLi, THF, −78 °C; (v) *n*-Bu_3SnH, AIBN, benzene, reflux. (e) $PdCl_2(PPh_3)_2$, **145**, LiCl, Ph_3P, DMF, 120 °C. (f) (i) H_2, Pd/C, MeOH; (ii) SO_3·pyr, TEA, DMSO−DCM, 0 °C. (g) $Ph_3PCH_3^+Br^-$, *n*-BuLi, THF, 0 °C; **147**, −78 °C to room temperature. (h) *N*-tosyl-(*S*)-valine, BH_3·THF, DCM; **149**, $Me_2CC(OMe)(OTMS)$, −78 °C. (i) (i) $HCCCO_2Me$, NMM, MeCN; (ii) concentrated HCl, MeOH; (iii) I_2, Ph_3P, imidazole, THF, 0 °C. (j) H_3PO_2, 1-ethylpiperidine, Et_3B, EtOH. (k) (i) KOH, THF−H_2O−MeOH; (ii) BH_3·DMS, $B(OMe)_3$, THF, 0 °C; (iii) SO_3·pyr, TEA, DMSO−DCM, 0 °C. (l) (i) (+)-DIPCl, CH_2CHCH_2MgBr, THF, −78 °C; **153**, −78 °C to room temperature; NaOH, H_2O_2; (ii) NaHMDS, BnBr, THF−DMF, 0 °C to room temperature; (iii) Ti(O*i*-Pr)$_4$, $TMSCH_2CH_2OH$, DME, 120 °C. (m) (i) OsO_4, NMO, acetone−H_2O; $NaIO_4$; (ii) **155**, THF, −78 °C; NaOH, H_2O_2, −78 °C to room temperature. (n) (i) TBSOTf, 2,6-lutidine, DCM, 0 °C; (ii) OsO_4, NMO, acetone−H_2O; $NaIO_4$; (iii) $NaBH_4$, EtOH; (iv) 2-mercaptobenzothiazole, DIAD, Ph_3P, THF, 0 °C; (v) $(NH_4)_6Mo_7O_{24}$·$4H_2O$, H_2O_2, EtOH, 0 °C to room temperature. (o) (i) NaHMDS, ether, −78 °C; **147**, −78 °C to room temperature; (ii) $TsNHNH_2$, NaOAc, DME−H_2O, reflux. (p) (i) Compound **156**, NaHMDS, THF, 0 °C; **158**; (ii) concentrated HCl, MeOH. (q) NaHMDS, THF, 0 °C; **148**, 0 °C. (r) (i) 10 mol % **161**, DCM (3 mM), 80 °C; (ii) H_2, Pd/C, MeOH−EtOAc; (iii) TBAF, THF; 4 N HCl (saturated with NaCl).

up, protection with PMB trichloroacetimidate,[85] complete desilylation with excess TBAF, and reprotection with TBDPSCl gave secondary alcohol **166**, and epoxide **167** was obtained after mesylation of the secondary hydroxyl group and exposure of the mesylate to anhydrous TBAF. Epoxide **167** was treated with the lithio derivative of methyl 3-phenylsulfonylorthopropionate **168** to afford lactone **169** via subsequent acidic hydrolysis and DBU-induced elimination. DIBAL reduction of **169** led to the corre-

Scheme 16. Retrosynthetic Analysis of Swinholide A (4)



sponding lactol, which was converted into aldehyde **171** (α:β = ~4:1) upon reaction with silyl enol ether **170**[86] in the presence of zinc chloride. Aldehyde **171** was then subjected to a Mukaiyama type aldol reaction using vinylketene acetal **172**[87] and $BF_3{\cdot}Et_2O$ to afford a mixture (~1.4:1) of alcohols favoring **173**. Chromatographic separation and silylation of **173** led to the corresponding silyl ether, which was then converted into dithiane **174** via PMB deprotection, Swern oxidation, and reaction with 1,3-propanedithiol. DIBAL reduction of **174** and silylation led to the formation of the C3−C17 fragment **175**.

Synthesis of the C18−C32 fragment started with peracetylation of L-rhamnose (**176**), and reaction with allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$ and TMSOTf led exclusively to the corresponding α-glycoside,[88] which was subsequently deacetylated completely with NaOMe and then subjected to regioselective methylation[89] using n-Bu_2SnO and MeI in the presence of CsF to afford compound **177**. The conversion of **177** to iodide **178** required bis(xanthate) formation and radical-mediated reduction with tributylstannane, followed by ozonolysis reduction and iodide substitution. Enders alkylation[90] using iodide **178** and SAMP hydrazone **179** and removal of the chiral auxiliary group by ozonolysis furnished ketone **180**. Allyl alcohol (**181**) was benzylated and then ozonized to afford aldehyde **182**. Crotylation of **182** with crotylborane **183** led to homoallylic alcohol **184**, which was converted into aldehyde **185** by benzylation and ozonolysis. Coupling of the two fragments **180** and **185** was accomplished via the chlorotitanium enolate of ketone **180**, leading to the syn aldol product **186**.[91] A samarium(II) iodide-catalyzed intramolecular Tishchenko−Evans reduction[92] of **186** furnished the 1,3-anti diol benzoate, which was silylated with TBSOTf to afford compound **187**. Debenzylation of **187** via hydrogenolysis provided diol **188**, which was converted to the cyclic sulfate **189** upon treatment with $SOCl_2$ in the presence of TEA followed by oxidation with $RuCl_3$ catalyst and $NaIO_4$[93] (Scheme 17).

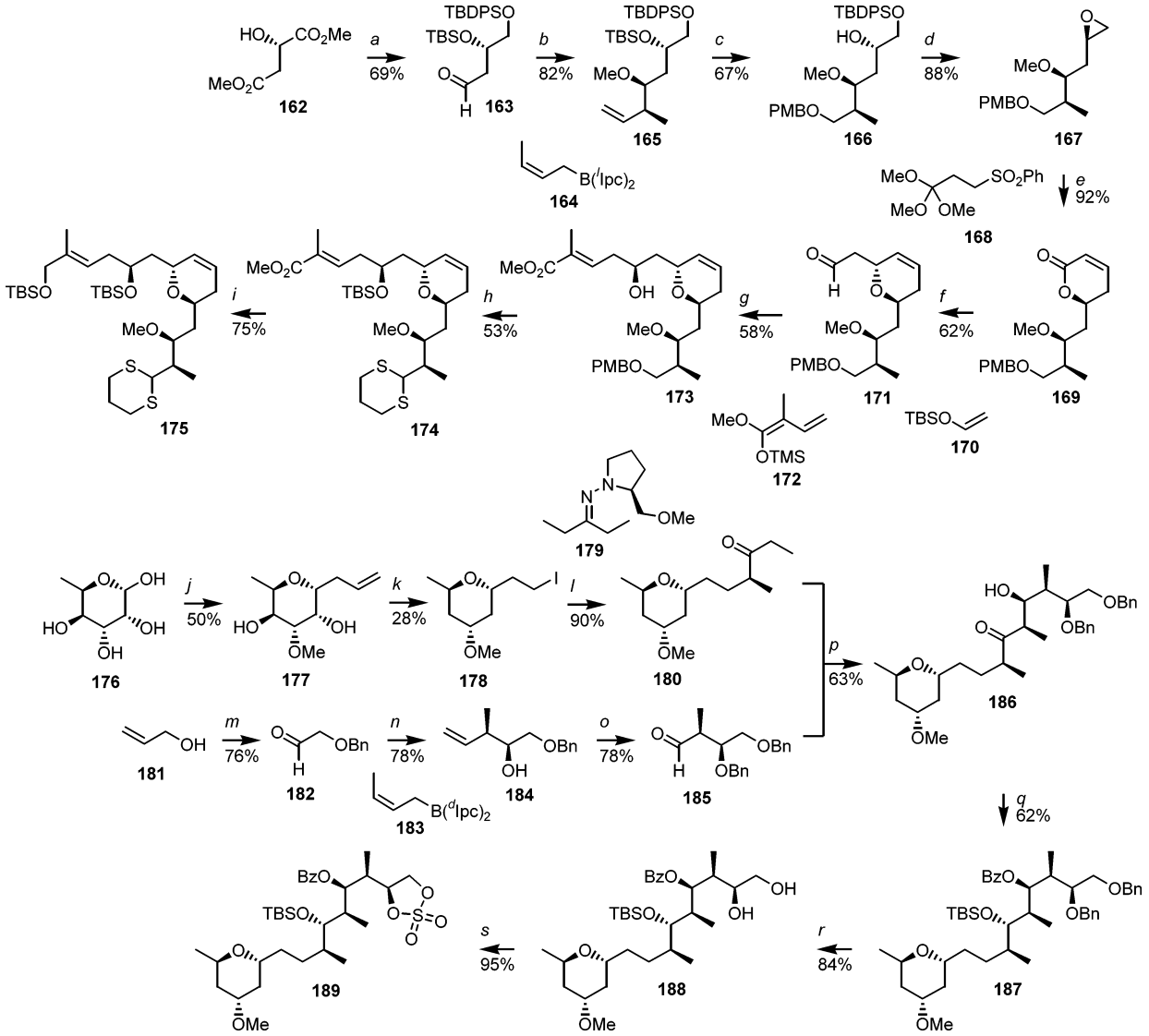
Coupling of sulfate **189** with the lithio derivative of dithiane **175** led to the coupled product, which afforded ketone **190** after removal of the dithiane moiety with NBS and $AgClO_4$.[94] Reduction of **190** with $NaBH_4$ in the presence of n-Bu_3B[95] followed by basic hydrogen peroxide workup gave the requisite 1,3-*syn*-diol, which was reacted with *p*-methoxybenzaldehyde dimethyl acetal and a catalytic amount of CSA to give *p*-methoxybenzylidene acetal **191**. Sequential removal of the benzoate and TBS groups afforded a diol, from which enal **192** was generated by selective oxidation with MnO_2. Extension of enal **192** via a Wadsworth−Horner−Emmons olefination reaction using the lithio derivative obtained from trimethyl phosphonoacetate and n-BuLi furnished selectively (*E*,*E*)-diene ester **193**. Hydrolysis of the methyl ester moiety in **193** was achieved by exposure to NaOH in aqueous MeOH−THF to give the corresponding hydroxy acid from which trimethylsilyl ether **194** was generated by treatment with TMSOTf in the presence of base. Esterification of carboxylic acid **194** with alcohol **193** in the presence of DIC and DMAP at 35 °C gave the coupling product in low yield (4−13%). A higher yield (46%) of the coupling product was obtained when the Yamaguchi procedure (2,4,6-trichlorobenzoyl chloride, TEA, DMAP) was employed affording an ester that had suffered concomitant TMS removal. Selective saponification of the ester provided hydroxy acid **195**, which gave the protected swinholide A (38% yield, based on 75% conversion) following the Yamaguchi protocol. Removal of all the protecting groups by aqueous HF in acetonitrile liberated swinholide A (**4**) in 60% yield (Scheme 18).

4. Cyclic Acetal Macrodiolides

4.1. Cycloviracin B_1 (5)

The actinomycete strain *Kibdelosporangium albatum* so. nov. (R761-7) isolated from a soil sample collected on Mindanao Island, the Philippines, was found to produce a complex glycolipid cycloviracin B_1 (**5**), which exhibits pronounced antiviral activity against the human pathogens herpes simplex virus type 1 (HSV-1), influenza A virus, varicella-zoster virus, and human immunodeficiency virus type 1 (HIV-1).[11] Extensive spectroscopic investigations established the constitution of this metabolite, while the absolute stereochemistry of the six chiral centers along its alkyl chains remained elusive. The structure determination and total synthesis of this remarkable target were recently accomplished by Fürstner and co-workers.

Scheme 17. Nicolaou Total Synthesis of Swinholide A (4): Synthesis of the Fragments[a]



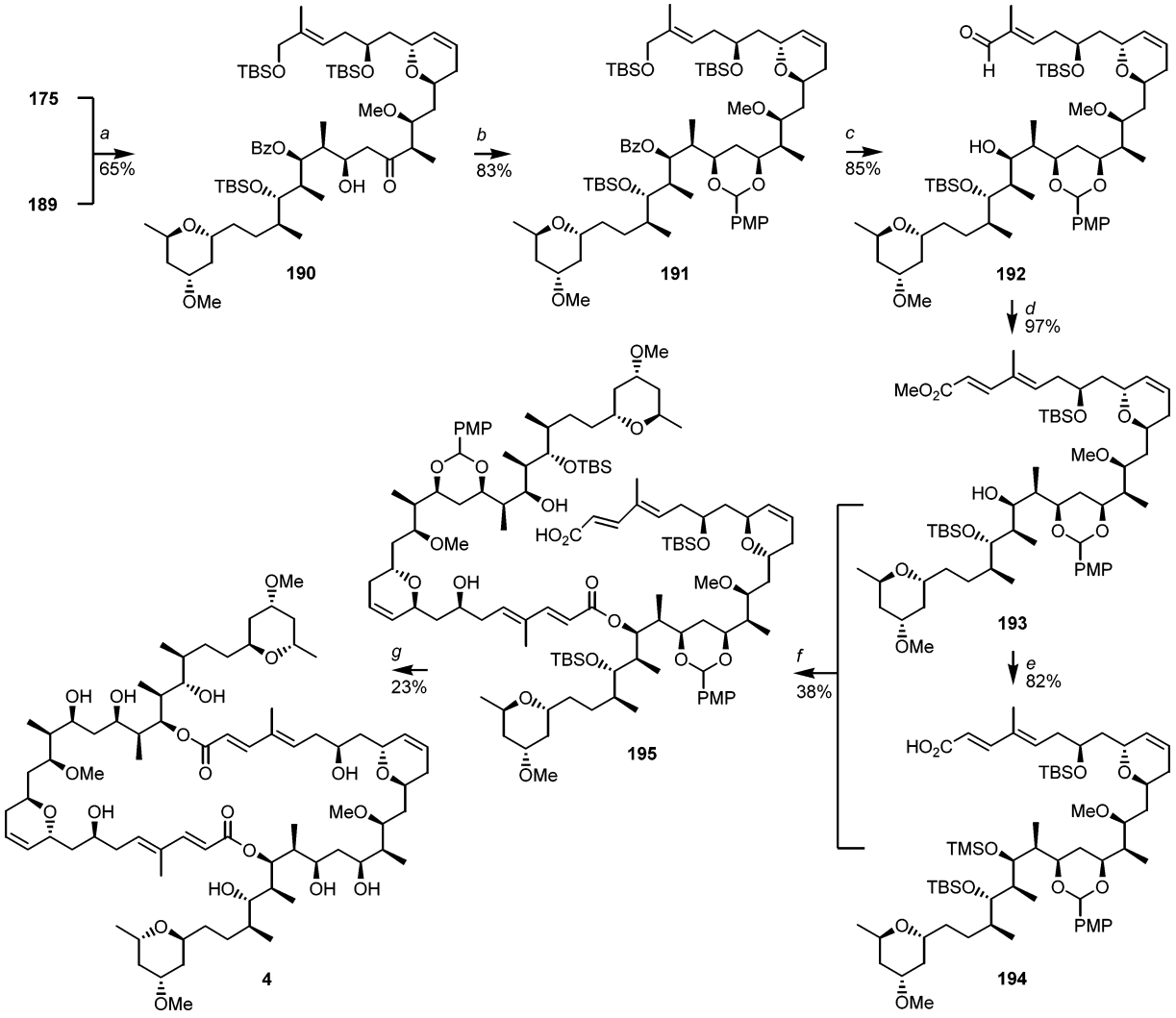
[a] Reagents and conditions: (a) (i) BH_3·DMS, −78 °C; $NaBH_4$, THF, 0 °C; (ii) TBDPSCl, TEA, DMAP, DCM; (iii) TBSOTf, 2,6-lutidine, DCM; (iv) DIBAL, DCM, −78 °C. (b) (i) Compound **164**, THF, −78 °C; NaOH, H_2O_2, −78 °C to reflux; (ii) NaH, MeI, THF, 0 °C. (c) (i) O_3, DCM, MeOH, −78 °C; $NaBH_4$; (ii) PMBOC(=NH)CCl_3, CSA, DCM; (iii) TBAF, THF, 0 °C; (iv) TBDPSCl, TEA, DMAP, DCM. (d) (i) MsCl, TEA, DCM, 0 °C; (ii) TBAF, THF. (e) Compound **168**, DMPU, THF, *n*-BuLi, **167**, −78 to −20 °C; H_2SO_4, 0 °C; *p*-TsOH, DCM; TEA, DBU, −10 °C. (f) (i) DIBAL, DCM, −78 °C; (ii) $ZnCl_2$, **170**, DCM, −20 °C. (g) Compound **172**, BF_3·Et_2O, DCM−Et_2O, −78 °C. (h) (i) TBSOTf, 2,6-lutidine, DCM, −78 °C; (ii) DDQ, DCM−H_2O; (iii) $(COCl)_2$, DMSO, DCM, TEA; (iv) 1,3-propanedithiol, $TiCl_4$, DCM, −78 °C. (i) (i) DIBAL, THF, −78 °C; (ii) TBSOTf, 2,6-lutidine, DCM, −78 °C. (j) (i) Ac_2O, TEA, DMAP, DCM, 0 °C; (ii) CH_2CHCH_2TMS, BF_3·Et_2O, TMSOTf, CH_3CN, 0 °C; (iii) NaOMe, MeOH; (iv) *n*-Bu_2SnO, MeOH, reflux; CsF, MeI, DMF, 50 °C. (k) (i) NaH, CS_2, MeI, imidazole, THF; *n*-Bu_3SnH, AIBN, toluene, 110 °C; (ii) O_3, $NaBH_4$, DCM, MeOH, −78 °C; (iii) I_2, Ph_3P, imidazole, DCM. (l) (i) Compound **179**, LDA, Et_2O, −78 °C; **178**, −110 °C; (ii) O_3, DCM, −78 °C. (m) (i) NaH, BnBr, TBAI, imidazole, THF, 0 °C; (ii) O_3, DCM, −78 °C; DMS. (n) Compound **183**, THF, −78 °C; NaOH, H_2O_2, −78 °C to reflux. (o) (i) KH, BnBr, DMF, 0 °C; (ii) O_3, DCM, −78 °C; Ph_3P, (p) $TiCl_4$, **180**, DCM, TEA, **185**, −78 °C. (q) (i) PhCHO, SmI_2, THF, −10 °C; (ii) TBSOTf, lutidine, DCM. (r) H_2, Pd/C, EtOH. (s) $SOCl_2$, TEA, DCM, 0 °C; $RuCl_3$, $NaIO_4$, CCl_4−CH_3CN−H_2O, 0 °C.

4.1.1. Fürstner Total Synthesis[96]

Fürstner and co-workers assumed that the lactide core of **5** is C_2-symmetrical and adopted a two-directional synthesis strategy.[97] Given the different length of its two lateral chains and their discrete hydroxylation pattern, careful retrosynthetic analysis was necessary. Established methodology should allow one to control the configuration at C17′ generated by coupling the C17′ aldehyde and the C18′−C24′ fragments (M = metal), and formation of the C17−C18 bond would require a highly stabilized nucleophile at C17 bearing X. The lactide core as the key component of this synthesis plan might be assembled by a template-directed cyclodimerization process.[98] The initial target is then a single precursor, which may be derived from a β-selective glycosylation of an aldol derivative with a suitably protected glucosyl donor (Scheme 19).

Ring-opening Claisen condensation of pentadecanolide (**196**)[99] with lithio *tert*-butyl acetate gave rise to β-keto ester **197**. Subsequent hydrogenation of **197** in the presence of Noyori's catalyst[100] afforded the corresponding (*R*)-diol in excellent yield, which was regioselectively silylated at the terminal position with TBDPSCl to give product **198** (98% e.e.).

Scheme 18. Nicolaou Total Synthesis of Swinholide A (4): Completion of Synthesis[a]

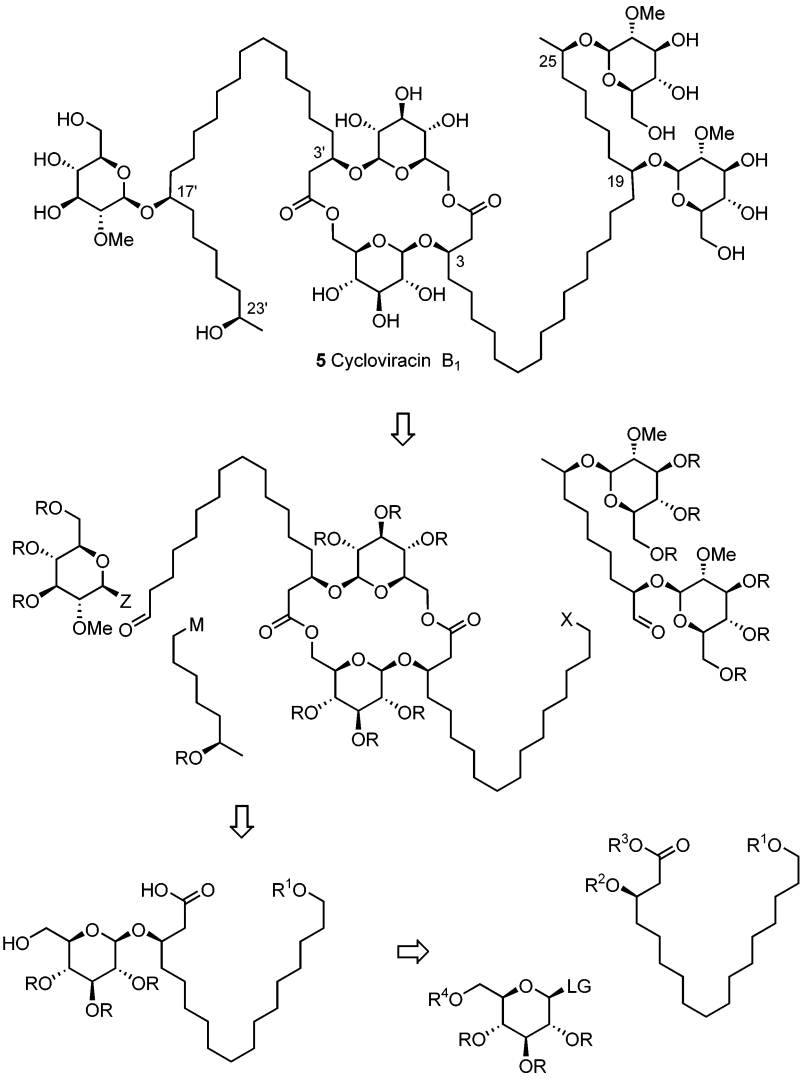


[a] Reagents and conditions: (a) (i) Compound **175**, *t*-BuLi, HMPA, THF, −78 °C; **189**, −78 °C; (ii) H_2SO_4, THF−H_2O; (iii) NBS, $AgClO_4$, acetone−H_2O, 0 °C. (b) (i) *n*-Bu_3B, THF; $NaBH_4$, −78 °C; NaOH, H_2O_2, 0 °C; (ii) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, DCM, 0 °C. (c) (i) DIBAL, DCM, −78 °C; (ii) HF·pyr, pyridine, DCM, 0 °C; (iii) MnO_2, DCM. (d) $(MeO)_2P(O)CH_2CO_2Me$, *n*-BuLi, THF, 0 °C to room temperature. (e) (i) NaOH, MeOH−THF−H_2O; (ii) TMSOTf, DIPEA, DCM, 0 °C to room temperature. (f) (i) Compound **194**, 2,4,6-$Cl_3PhCOCl$, TEA, toluene; **193**, DMAP, 105 °C; (ii) $Ba(OH)_2·8H_2O$, MeOH. (g) (i) 2,4,6-$Cl_3PhCOCl$, TEA, toluene (0.0005 M); DAMP, 110 °C; (ii) aqueous HF, CH_3CN, 0 °C.

Trichloroacetimidate **201**[101] was selected as a precursor for the glucose units to be embedded into the lactide core: It was readily available in four operations from laevoglucosane **199**[102] via acetate **200**. Exposure of **198** and **201** in dichloromethane at low temperature to $BF_3·Et_2O$ provided the corresponding β-glucoside in 62% isolated yield (87% based on recovered starting material, $\alpha:\beta = 1:6$). Subsequent cleavage of the *tert*-butyl ester moiety with trifluoroacetic acid followed by saponification of the residual acetate with NH_3/MeOH led to hydroxy acid **202** in 74% overall yield. When compound **202** was exposed to 2-chloro-1,3-dimethylimidazolinium chloride (**203**)[103] in the presence of DMAP at 0 °C, the desired cyclic dimer **204** (37%) was obtained, accompanied by the cyclic monomer (28%) and other oligomeric byproducts. Addition of KH not only led to a substantially increased reaction rate but also to a significant improvement of the product distribution in favor of **204**, which was obtained in 71% yield under optimized conditions. This outcome appears to reflect the ability of the K^+ cation to preorganize the cyclization precursor **202** (as in **205**) for directed macrodilactonization.

Synthesis of the C18−C26 segment started with α-methylation of cycloheptanone (**206**)[104] followed by Baeyer−Villiger oxidation, which led to lactone **207**. The PLE-catalyzed hydrolysis reaction[105] of lactone **207** after 40% conversion furnished acid **208** in 38% yield (95% e.e.). This compound was then activated with carbonyl diimidazole and reacted with magnesium carboxylate **209**[106] to give the keto ester after aqueous NaOH workup. Asymmetric hydrogenation of this material in the presence of Noyori catalyst afforded diol **210** in almost quantitative yield. Subsequent glycosylation[107] with trichloroacetimidate **211** in the presence of TMSOTf in dichloromethane was completely selective for the β-glycoside due to the anchimeric assistance of the 2-*O*-acetyl group in the donor. Further elaboration of the product thus formed started with an exhaustive $LiAlH_4$ reduction

Scheme 19. Retrosynthetic Analysis of Cycloviracin B_1 (5)



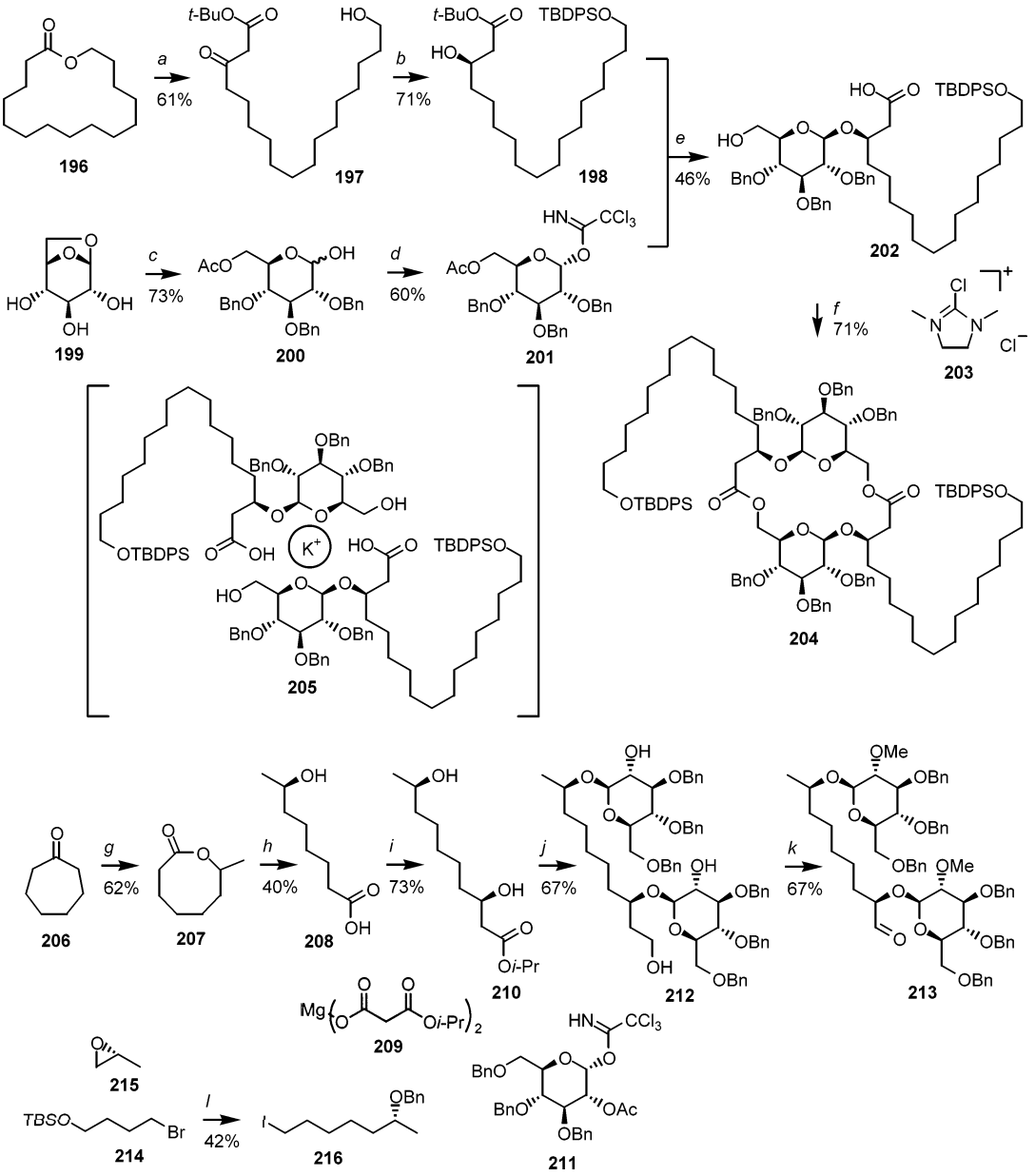
of the three ester moieties to give triol **212**. Only the primary hydroxyl group reacted with *o*-nitrophenylselenocyanate in the presence of Bu_3P to give the corresponding selenide, which was oxidized with aqueous H_2O_2 to the corresponding selenoxide;[108] this compound underwent a clean elimination with the formation of the corresponding alkene in 90% yield. *O*-Methylation of the remaining two hydroxyl groups on the sugar moieties under standard conditions followed by ozonolysis of the alkene afforded the desired aldehyde **213**.

For the synthesis of the C18′−C24′ segment, reaction of the Grignard reagent derived from the protected 4-bromo-1-butanol derivative **214** with (*R*)-propene oxide (**215**)[109] in the presence of a catalytic amount of CuCl(COD) led to efficient ring opening. Protection of the resulting secondary hydroxyl group as a benzyl ether followed by cleavage of the TBS group with TBAF provided the corresponding alcohol in good overall yield, which was converted into the primary iodide **216** under standard conditions (Scheme 20).

For final assembly of the segments, lactide **204** was desymmetrized by cleavage of both terminal silyl groups followed by introduction of a single OTBDPS group. Conversion of the corresponding alcohol to the sulfide on treatment with 1-phenyl-1*H*-tetrazole-5-thiol and Ph_3P[110] proceeded with excellent yield, and sulfone **217** was obtained upon oxidation with H_2O_2 in the presence of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$[111] in a mixed solvent system (EtOH/DCM).

Kocienski−Julia olefination[112] of the lithio sulfone derived from **217** and aldehyde **213** delivered the corresponding alkene in 61% yield (*E*:*Z* = ∼1:1), which was hydrogenated to give the saturated product. Standard deprotection of the residual silyl ether followed by oxidation of the resulting alcohol with PCC afforded the labile aldehyde **218**. Aldehyde **218** reacted at low temperature with the diorganozinc reagent[113] obtained from **216** in the presence of Ti(O*i*-Pr)$_4$ and the (*S*,*S*)-bistriflate **219**[114] to give alcohol **220** in 81% yield as a single diastereomer. Subsequent β-selective glycosidation of **220** with trichloroacetimidate **221** was promoted by TMSOTf in DCM/MeCN. Exhaustive debenzylation of the product thus formed by hydrogenolysis cleanly provided cycloviracin B_1 (**5**) (Scheme 21). The synthesis also confirmed the absolute stereochemistry of the six chiral centers residing on the fatty acid residues as (3*R*,19*S*,25*R*,3′*R*,17′*S*,23′*R*).

Scheme 20. Fürstner Total Synthesis of Cycloviracin B_1 (5): Synthesis of the Fragments[a]



[a] Reagents and conditions: (a) *t*-BuOAc, LDA, THF, −78 °C. (b) (i) H_2, [(*R*)-BINAP)$RuCl_2]_2$·Et_3N, MeOH, 70 °C; (ii) TBDPSCl, imidazole, DMF. (c) (i) NaH, BnBr, DMF; (ii) Ac_2O, NaOAc, H_2SO_4. (d) (i) H_2NNH_2·HOAc, DMF; (ii) NaH, Cl_3CCN, DCM. (e) (i) BF_3·Et_2O, 4 Å MS, DCM, −78 °C to room temperature; (ii) TFA, DCM; (iii) NH_3, MeOH. (f) Compound **203**, DMAP, KH, DCM. (g) (i) LDA, THF, −78 °C; MeI; (ii) *m*CPBA, DCM. (h) Porcine liver esterase, pH 7.2. (i) (i) Carbonyl diimidazole, **209**, THF; (ii) NaOH, THF−H_2O; (iii) H_2, [(*R*)-BINAP)$RuCl_2]_2$·Et_3N, MeOH−THF, 70 °C. (j) (i) Compound **211**, TMSOTf, 4 Å MS, DCM; (ii) $LiAlH_4$, THF. (k) (i) Bu_3P, *o*-$NO_2PhSeCN$, THF; (ii) H_2O_2, THF; (iii) NaH, MeI, DMF; (iv) O_3, DCM, −78 °C; DMS. (l) (i) Mg, THF; (ii) CuCl(COD), **215**; (iii) NaH, BnBr; (iv) TBAF, THF; (v) I_2, imidazole, Ph_3P.

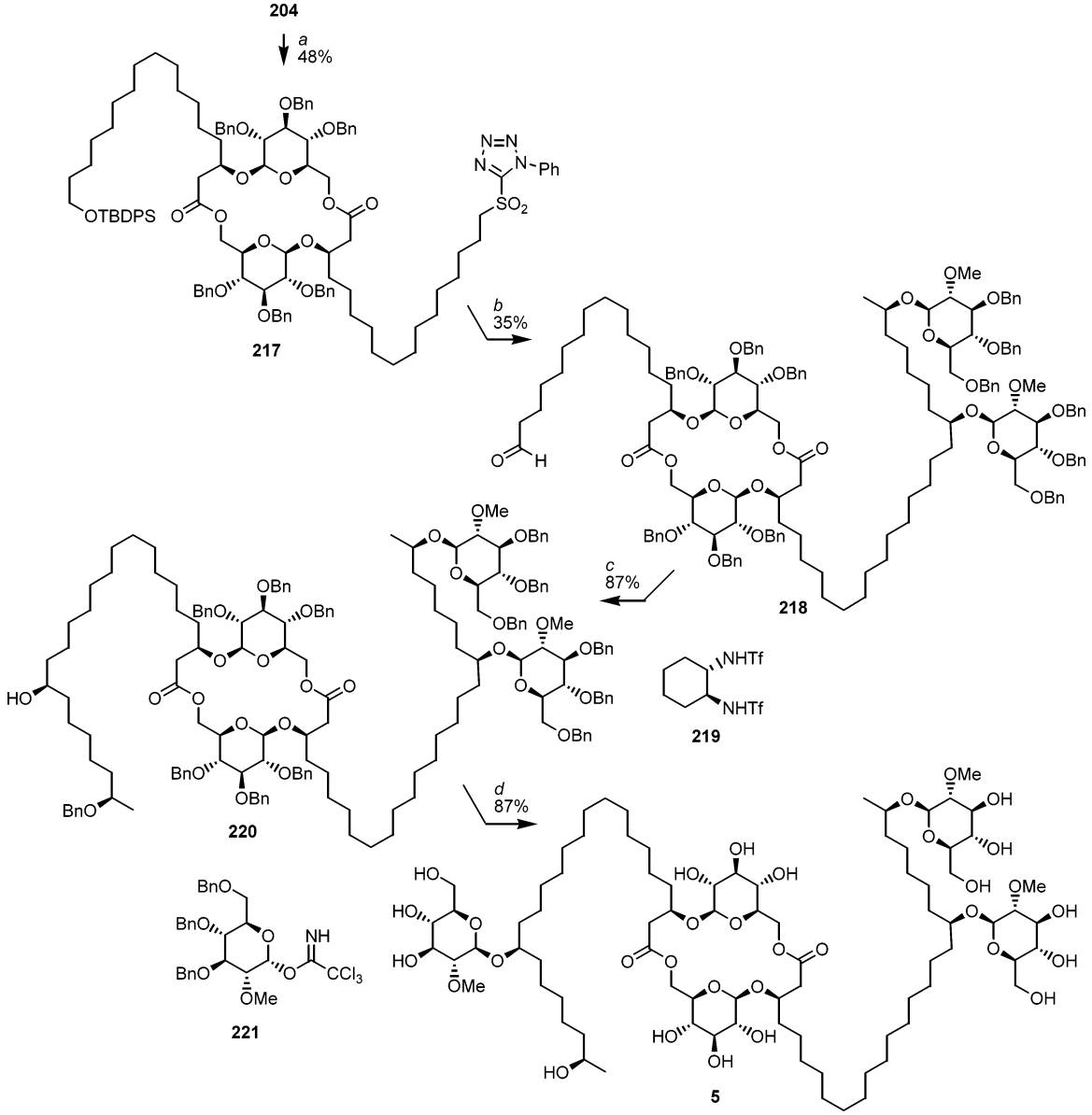
4.2. Glucolipsin A (6)

During a search for natural products able to relieve the inhibitory effects of stearoyl-CoA on glucokinase, a team at Bristol-Myers Squibb discovered the glycoconjugate glucolipsin A (**6**), produced by *Streptomyces purpurogeniscleroticus* and *Nocardia vaccinii* strains.[12] Glucokinase catalyzes phosphorylation of glucose to glucose-6-phosphate, which, in turn, plays a central role in the entire carbohydrate metabolism.[115] It is well-established that glucokinase is allosterically inhibited by long-chain fatty acid-CoA esters. Small molecules that either competitively bind to the fatty acid-CoA cofactor site or sequester these negative effectors would result in an upregulation of glucokinase activity and, as such, might ultimately lead to complementary drugs for therapeutic intervention in diabetes.[116] While spectroscopic investigations unraveled the symmetric structure of **6** and showed the presence of two β-glucose entities within its macrocyclic core, the absolute stereochemistry of the four chiral centers at the periphery remained elusive.

4.2.1. Fürstner Total Synthesis[117]

For an unambiguous assignment of the stereostructure of glucolipsin A (**6**), Fürstner and coworkers prepared all conceivable C_2-symmetrical dimers of this type by a highly integrated synthesis

Scheme 21. Fürstner Total Synthesis of Cycloviracin B_1 (5): Completion of Synthesis[a]



[a] Reagents and conditions: (a) (i) TBAF, THF; (ii) TBDPSCl, TEA, DCM; (iii) 1-phenyl-1*H*-tetrazole-5-thiol, Ph_3P, DIAD; (iv) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, EtOH−DCM. (b) (i) LiHMDS, DME, −78 °C, **213**; (ii) H_2, Pd/C, EtOAc; (iii) TBAF, THF; (iv) PCC, DCM. (c) Compound **216**, Et_2Zn, CuCN; $Ti(Oi\text{-}Pr)_4$, **219**, **218**, toluene. (d) (i) Compound **221**, TMSOTf, DCM−CH_3CN; (ii) H_2, Pd/C, EtOH−EtOAc.

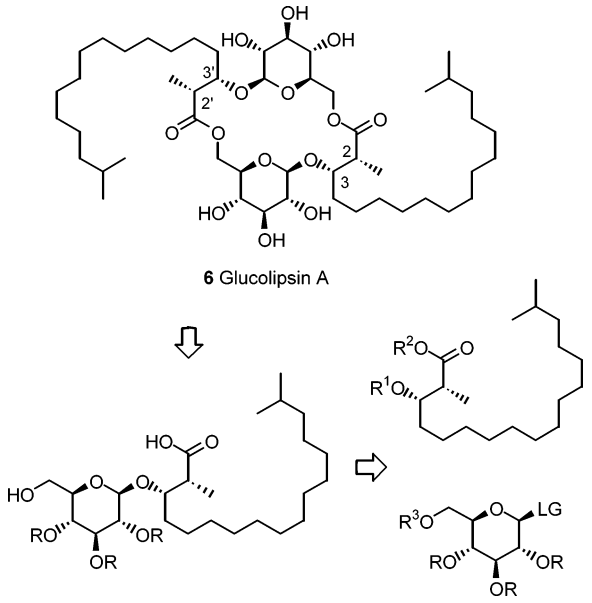
route based on a template-directed cyclodimerization reaction as the key step. This study revealed that the fatty acid moiety of glucolipsin A (**6**) comprises a *syn*-aldol with a (3*S*)-configured stereocenter, *opposite* the (3*R*)-configured motif found in cycloviracin B_1 (**5**) (Scheme 22).

The required aldehyde **224** was prepared from commercially available 12-bromo-1-dodecanol (**222**)[118] by reaction with isobutylmagnesium bromide (**223**) in the presence of Li_2CuCl_4[119] and subsequent PCC oxidation of the resulting alcohol. Reaction of aldehyde **224** with the (*Z*)-boron enolate derived from **40** delivered the (2*R*,3*S*)-configured *syn*-aldol derivative **225** in essentially diastereomerically pure form (99% d.e.) after purification of the crude product by flash chromatography.[120]

Effective yields obtained in the glycosidation of compound **225** remained rather low due to the poor glycosyl acceptor properties of aldol derivatives and their insufficient chemical stability under the required acidic reaction conditions. Best results were obtained with use of an excess (3 equiv) of trichloroacetimidate **201** activated in situ by TMSOTf (20 mol %) in MeCN.[121] Under these conditions, the desired β-anomer was obtained in 45% isolated yield (β:α = 5.2:1). Saponification of the product with aqueous LiOH in THF in the presence of H_2O_2[122] furnished hydroxy acid **226** as the required substrate for the cyclodimerization step by concomitant cleavage of the oxazolidinone and the residual acetate.

A template-directed macrodilactonization reaction of the glycosylated aldol derivative **226** preorganized around a potassium cation (as in **228**) proceeded, and the cyclic dimer **227** was obtained in 54% isolated yield when the reaction was performed with 2-chloro-1,3-dimethylimidazolinium chloride (**203**) as the activating agent in the presence of the admixed potassium cation derived from KH. Hydrogenolytic cleavage

Scheme 22. Retrosynthetic Analysis of Glucolipsin A (6)



of the benzyl ether groups in **227** proceeded quantitatively with $Pd(OH)_2$ as the precatalyst to yield glucolipsin A (**6**) (Scheme 23). The synthesis confirmed the absolute stereochemistry of the four chiral centers residing on the fatty acid residues as (2*R*,3*S*,2′*R*,3′*S*).

5. Cyclic Hemiketal Macrodiolides

5.1. Boromycin (7)

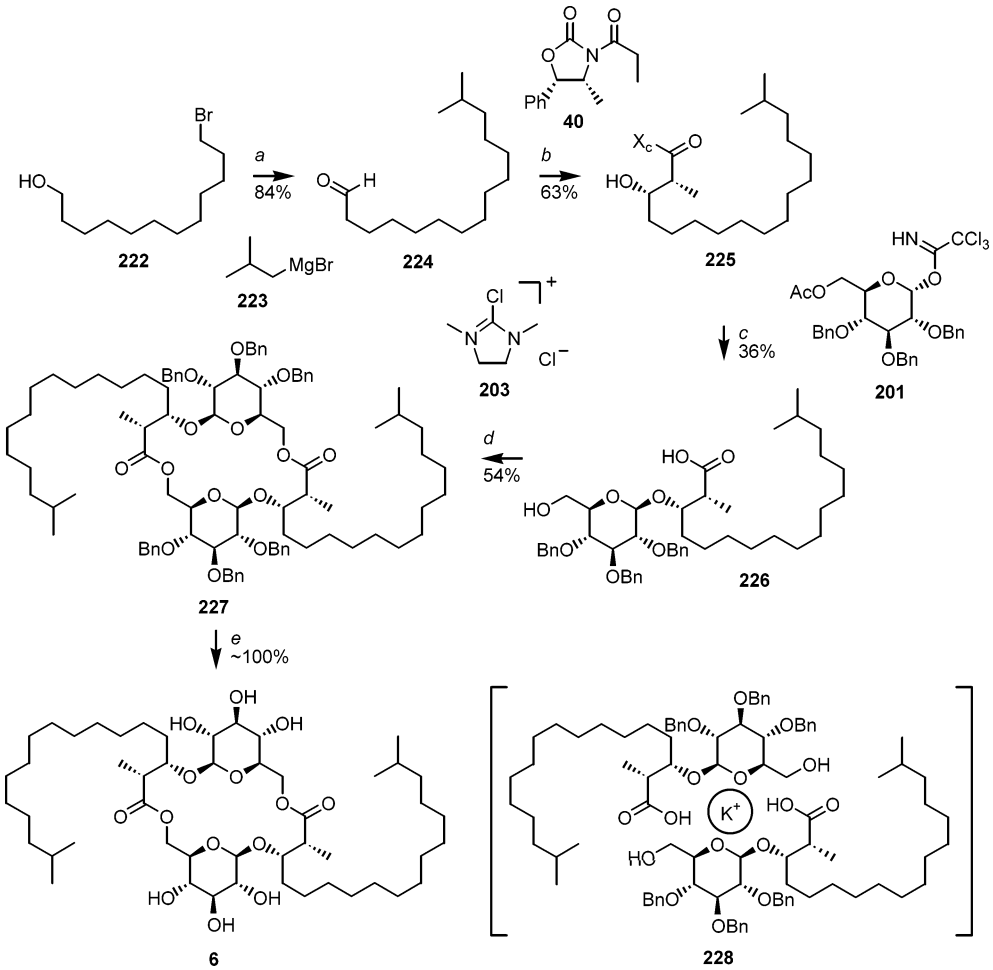
Boromycin (**7**) is an ionophoric metabolite of *Streptomyces antibioticus* (Waksman et Woodruff), which consists of two stereochemically related halves linked head to tail to form a 28-membered macrodiolide, with a borate bridge spanning the macrocycle.[13] Boromycin (**7**) is a D-valine ester, and it was the first natural product discovered to contain boron.

5.1.1. White Total Synthesis[123]

The total synthesis of White and co-workers employed a strategy that elaborated protected versions of the lower (C1−C17) and the upper (C1′−C17′) half structures, and coupled them in head-to-tail fashion via glycolate linkages to produce a 34-membered macrocycle. The finale to this sequence was a ring contraction ("double Chan" reaction) based on the rearrangement of an α-acyloxyacetate to an α,β-enediolate[124] (Scheme 24).

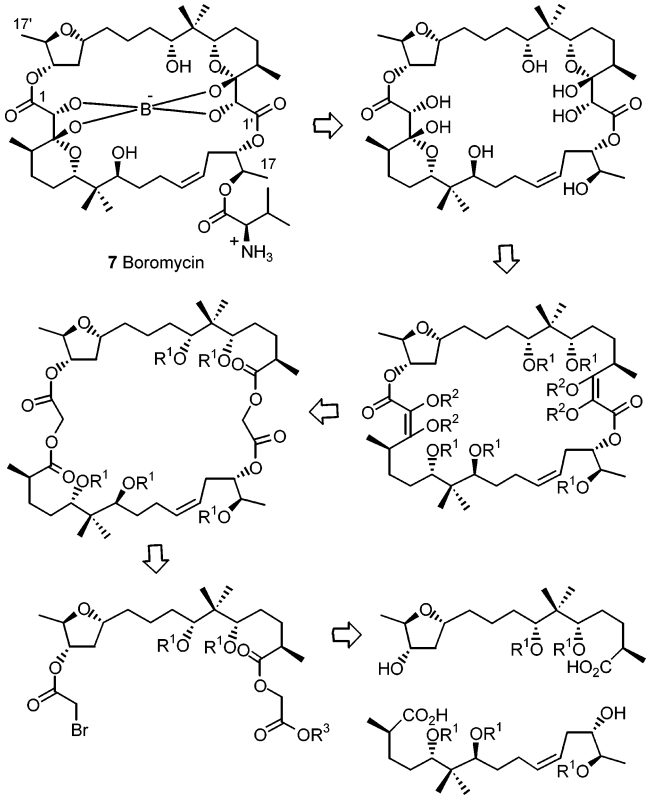
Synthesis of the C11−C17 segment was achieved from 3-buten-2-ol (**229**) via enantioselective epoxi-

Scheme 23. Fürstner Total Synthesis of Glucolipsin A (6)[a]



[a] Reagents and conditions: (a) (i) Compound **223**, Li_2CuCl_4, THF, 0 °C; (ii) PCC, DCM. (b) Compound **40**, *n*-Bu_2BOTf, TEA, DCM, −78 °C. (c) (i) Compound **201**, TMSOTf, MeCN, −30 °C; (ii) LiOH, H_2O_2, THF−H_2O, 55 °C. (d) Compound **203**, KH, DMAP, DCM. (e) H_2, $Pd(OH)_2$, MeOH.

Scheme 24. Retrosynthetic Analysis of Boromycin (7)



dation following Sharpless protocol.[125] The resulting epoxide **230** was alkylated with propargyl THP ether (**231**) to give alkyne **232**. This alkyne was semihydrogenated to afford (*Z*)-olefin **233**, and the latter was converted directly to the corresponding acetonide alcohol, which was then transformed to (*Z*)-allylic chloride **234** with *N*-chlorosuccinimide and dimethyl sulfide.[126]

Synthesis of the C3−C10 moiety began from (*R*)-(+)-pulegone (**235**). Preparation of keto ester **237** was accomplished by methanolysis of the hydrocyanation product **236** and also by conjugate addition of vinylmagnesium bromide to **235**, followed by oxidative cleavage of the vinyl group of **238** with ruthenium tetroxide and esterification of the resulting carboxylic acid with diazomethane. Baeyer−Villiger oxidation of **237** afforded ϵ-lactone **239** with only a trace of the regioisomeric lactone. Lactone **239** was converted to the corresponding diester by methanolysis, and the hydroxyl group was protected as its TBS ether. Reduction of the more exposed ester function with lithium aluminum hydride at low temperature gave a primary alcohol with excellent selectivity. The alcohol was then converted to olefin **240** by elimination of the intermediate *o*-nitrophenylselenoxide.[108b] Oxidative cleavage of the olefin with ruthenium(IV)[127] yielded a carboxylic acid, which was subjected to hydrofluoric acid to furnish lactone **241**. Alternatively, lactone **239** was treated with phenylmagnesium bromide to yield a diol, which provided olefin **242** via acid-catalyzed dehydration. Acetylation of **242** and oxidative cleavage of the double bond furnished an acetoxy carboxylic acid. Methanolysis of the acetate moiety and acidification afforded **241**. Treatment of **241** with (2*R*,3*R*)-(−)-butanediol under acidic conditions afforded the corresponding ortholactone ester. Condensation of the ortholactone ester with the dianion of methyl phenyl sulfone gave keto sulfone **243**.

For preparation of the C3−C17 segment, keto sulfone **243** was alkylated with (*Z*)-allylic chloride **234** to furnish ketone **244** after reductive removal of the sulfonyl group. Reduction of **244** with L-selectride proceeded in favor of the (9*S*)-alcohol (3.5:1), which was purified as its acetate derivative. After reductive removal of the acetate group, triol **245** was obtained upon mild acidic hydrolysis. TBS protection of **245**, saponification, treatment with diazomethane, acidic hydrolysis of the acetonide moiety, selective silylation, and saponification led to hydroxy carboxylic acid **246**.

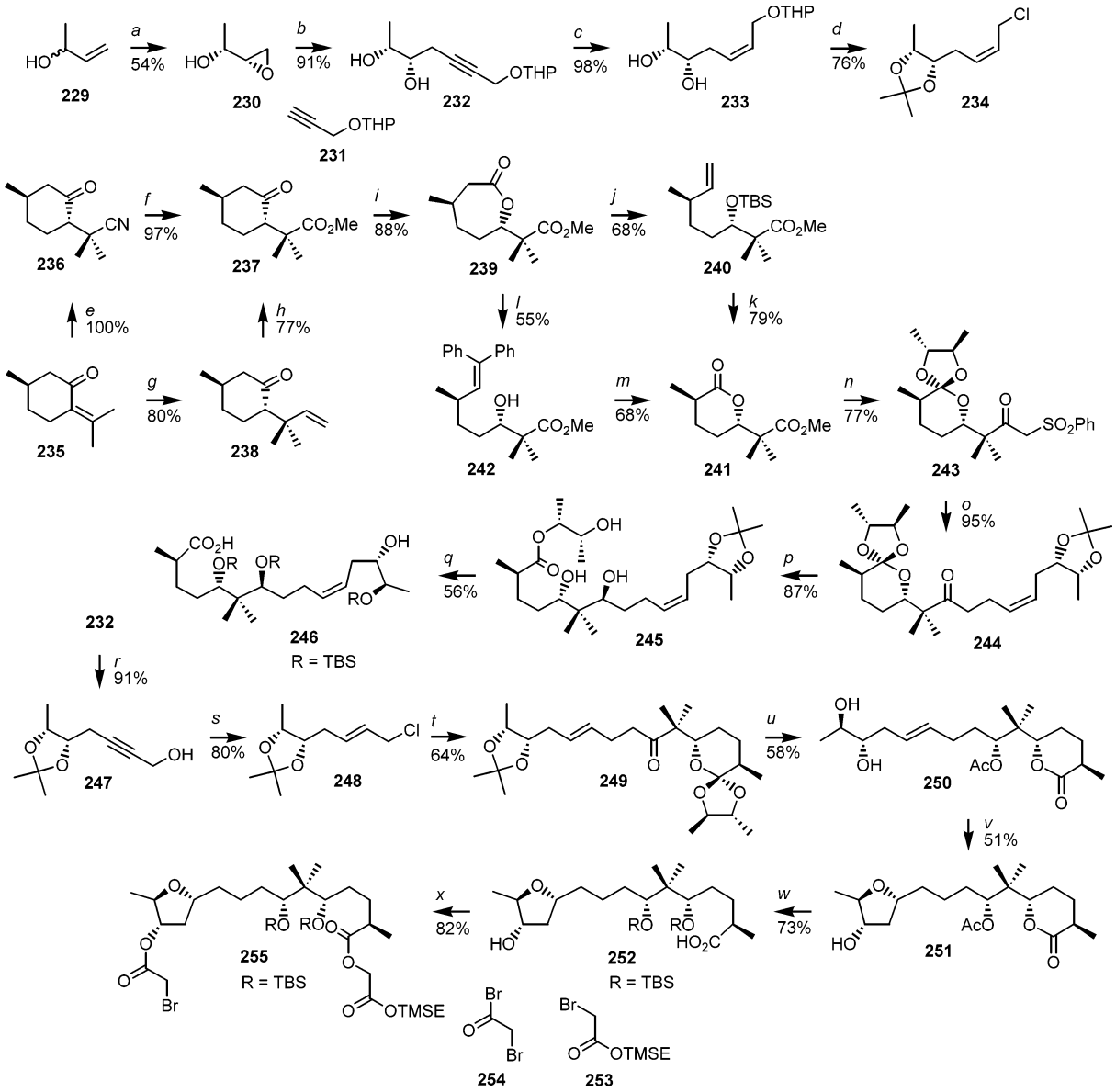
Synthesis of the C3′−C17′ segment required preparation of propargylic alcohol acetonide **247** from diol **232**. Reduction of **247** with lithium aluminum hydride furnished an (*E*)-allylic alcohol, which was transformed to allylic chloride **248**. Alkylation of keto sulfone **243** with (*E*)-allylic chloride **248** and reductive removal of the sulfone unit provided ketone **249**. Ketone **249** was reduced with lithium aluminum hydride at −110 °C to give predominantly the (9′*R*)-alcohol (22:1). The corresponding acetate was subjected to acidic hydrolysis and careful saponification to yield an acid that lactonized readily in the presence of HCl to **250**. Treatment of **250** with *N*-bromosuccinimide effected cyclization[128] to a pair of easily separated bromo oxolanes, and the major isomer was reduced with tributylstannane to give **251**. Saponification of **251**, exhaustive silylation, and brief exposure to TBAF furnished hydroxy acid **252**. Reaction of **252** with 2-(TMS)ethyl bromoacetate (**253**) and then with bromoacetyl bromide (**254**) furnished diester **255** (Scheme 25).

Final assembly started when the potassium carboxylate derived from **246** condensed smoothly with **255** to produce glycolate ester **256**. Treatment of **256** with TBAF furnished a monohydroxy acid, which underwent Mukaiyama lactonization[129] to yield macrocycle **257**. Contraction of **257** was effected with 2 equiv of lithium hexamethyldisilazide at 0 °C, and entrapment of the intermediate enediolate with TMSOTf afforded the unstable dilactone **258** (mixture of *E* and *Z* isomers). Exhaustive desilylation of **258** with TBAF, followed by brief exposure to mineral acid, furnished a heptaol **259** in 36% overall yield from **257**, which afforded desvalinylboromycin **260** upon treatment with anhydrous trimethyl borate in methanol under reflux. Esterification[123a] of **260** with *t*-Boc-D-valine and subsequent *t*-Boc deprotection yielded boromycin (**7**) (Scheme 26).

5.2. Tartrolon B (8)

The tartrolons were first isolated in 1994 by Höfle and Reichenbach from Myxobacterium *Sorangium cellulosum* strain So ce678.[14] The fermentation furnished tartrolon A (**261**) or B (**8**) depending on the fermentation vessel. Glass vessels provide boron and hence allow the formation of **8**, whereas in steel fermenters the boron-free compounds **261** are formed as diastereomeric mixtures. Alternatively, the boron

Scheme 25. White Total Synthesis of Boromycin (7): Synthesis of the Fragments[a]



[a] Reagents and conditions: (a) *t*-BuOOH, Ti(O*i*-Pr)$_4$, (−)-DIPT. (b) Compound **231**, *n*-BuLi, THF, −78 °C to room temperature. (c) H_2, Pd/$BaSO_4$, quinoline, MeOH. (d) (i) 2,2-Dimethoxypropane, *p*-TsOH, MeOH−benzene; (ii) NCS, DMS. (e) NaCN, NH_4Cl. (f) H_2SO_4, MeOH. (g) $CH_2CHMgBr$, CuBr, THF, −20 °C. (h) (i) $RuCl_3$, $NaIO_4$, CH_3CN−CCl_4−H_2O; (ii) CH_2N_2, Et_2O. (i) CF_3CO_3H, DCM. (j) (i) K_2CO_3, MeOH; (ii) TBSOTf, 2,6-lutidine, DCM; (iii) $LiAlH_4$, Et_2O, −78 °C; (iv) *o*-$NO_2PhSeCN$, *n*-Bu_3P, THF; (v) H_2O_2. (k) (i) $RuCl_3$, $NaIO_4$, CH_3CN−CCl_4−H_2O; (ii) 5% HF, CH_3CN. (l) (i) PhMgBr, THF, 0 °C; (ii) PPTS, benzene, reflux. (m) (i) Ac_2O, pyridine, DMAP, DCM; (ii) $RuCl_3$, $NaIO_4$, CH_3CN−CCl_4−H_2O; (iii) K_2CO_3, MeOH, reflux; (iv) 1 N HCl, $CHCl_3$. (n) (i) (2*R*,3*R*)-butanediol, *p*-TsOH; (ii) $PhSO_2Me$, *n*-BuLi, THF, 0 °C. (o) (i) *n*-BuLi, KI, **234**, THF−DMSO, 40 °C; (ii) Al/Hg, THF−H_2O, 75 °C. (p) (i) L-Selectride, THF, 0 °C; (ii) Ac_2O, pyridine, DMAP, DCM; (iii) $LiAlH_4$, THF, 0 °C; (iv) *p*-TsOH, THF−H_2O. (q) (i) TBSOTf, 2,6-lutidine, DCM; (ii) 3 N NaOH, MeOH−THF, reflux; (iii) CH_2N_2, Et_2O, 0 °C; (iv) PPTS, MeOH, reflux; (v) TBSOTf, 2,6-lutidine, DCM, −78 °C; (vi) 3 N NaOH, MeOH−THF, reflux. (r) 2,2-Dimethoxypropane, *p*-TsOH, MeOH−benzene. (s) (i) $LiAlH_4$, $AlCl_3$, THF, reflux; (ii) NCS, DMS. (t) (i) Compound **243**, *n*-BuLi, KI, THF−DMSO, 40 °C; (ii) Al/Hg, THF−H_2O, 75 °C. (u) (i) $LiAlH_4$, Et_2O, −110 °C; (ii) Ac_2O, DMAP; (iii) *p*-TsOH, THF−H_2O; (iv) NaOH, H_2O; (v) 5% HCl, THF. (v) (i) NBS, Et_2O−CH_3CN, −110 °C; (ii) *n*-Bu_3SnH, AIBN, benzene, reflux. (w) (i) 10% NaOH, MeOH; (ii) TBSOTf, 2,6-lutidine, DCM, 0 °C; (iii) *p*-TsOH, hexanes−EtOAc; (iv) TBAF, THF. (x) (i) Compound **253**, K_2CO_3, acetone, reflux; (ii) **254**, pyridine, DMAP, DCM, 0 °C.

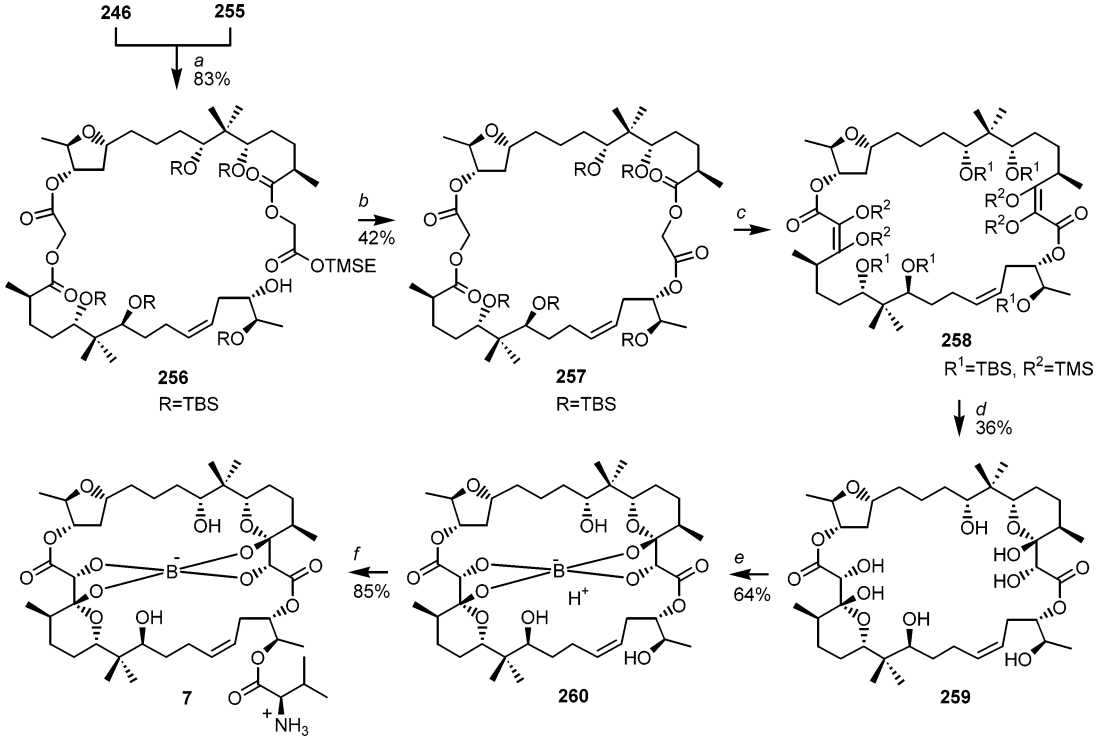
can be incorporated into **261** chemically. This leads to a fixation of the variable stereogenic center at C2 and forces **8** into a C_2-symmetrical structure. Both tartrolon A (**261**) and B (**8**) act as ion carriers, and they are both active against Gram-positive bacteria with MIC values of 1 μg/mL.

5.2.1. Mulzer Total Synthesis[130]

The C_2-symmetrical overall structure of **8** called for cyclodimerization of the monomeric *seco*-acid. The *seco*-acid in its open form suffered from the lability of its β-keto-ester moiety,[130c] and a bicyclic ketal structure was chosen as a more appropriate C1−C10 fragment, which would be coupled with the C11−C21 diene aldehyde fragment via aldol addition. The 9-carbonyl was replaced by a hydroxyl group that could be oxidized in a later step (Scheme 27).

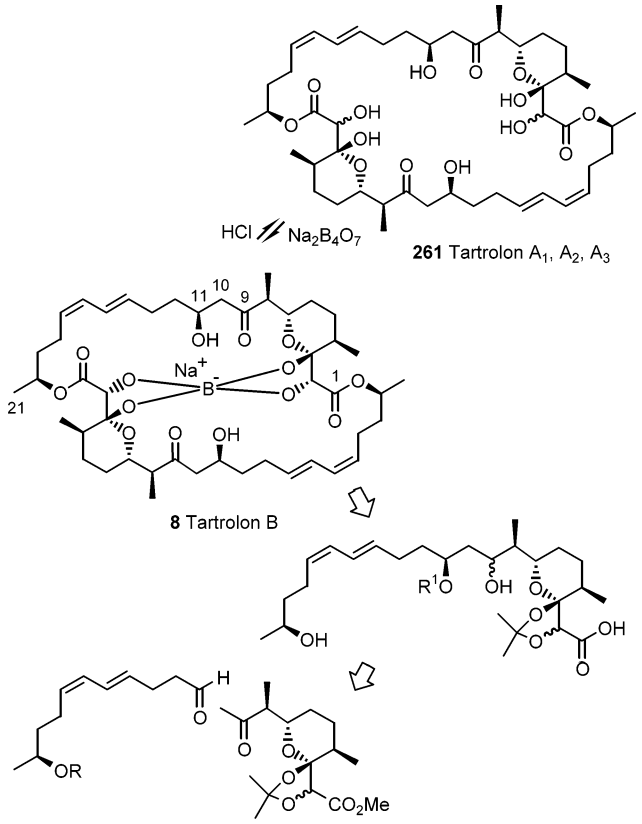
The sequence for the C11−C21 fragment started with *O*-protected lactic ester **262**, which was reduced to the aldehyde and then subjected to a Wadsworth−

Scheme 26. White Total Synthesis of Boromycin (7): Completion of Synthesis[a]



[a] Reagents and conditions: (a) K_2CO_3, acetone, reflux. (b) (i) TBAF, THF, −23 °C; 0 °C; (ii) 2-chloro-1-methylpyridinium iodide, DMAP, CH_3CN. (c) $(TMS)_2NLi$, THF, 0 °C; TMSOTf, 0 °C. (d) TBAF, THF; 1 N HCl. (e) $B(OMe)_3$, MeOH, reflux. (f) (i) *t*-Boc-D-Val, DCC, DMAP, DCM; (ii) TFA, DCM.

Scheme 27. Retrosynthetic Analysis of Tartrolon B (8)



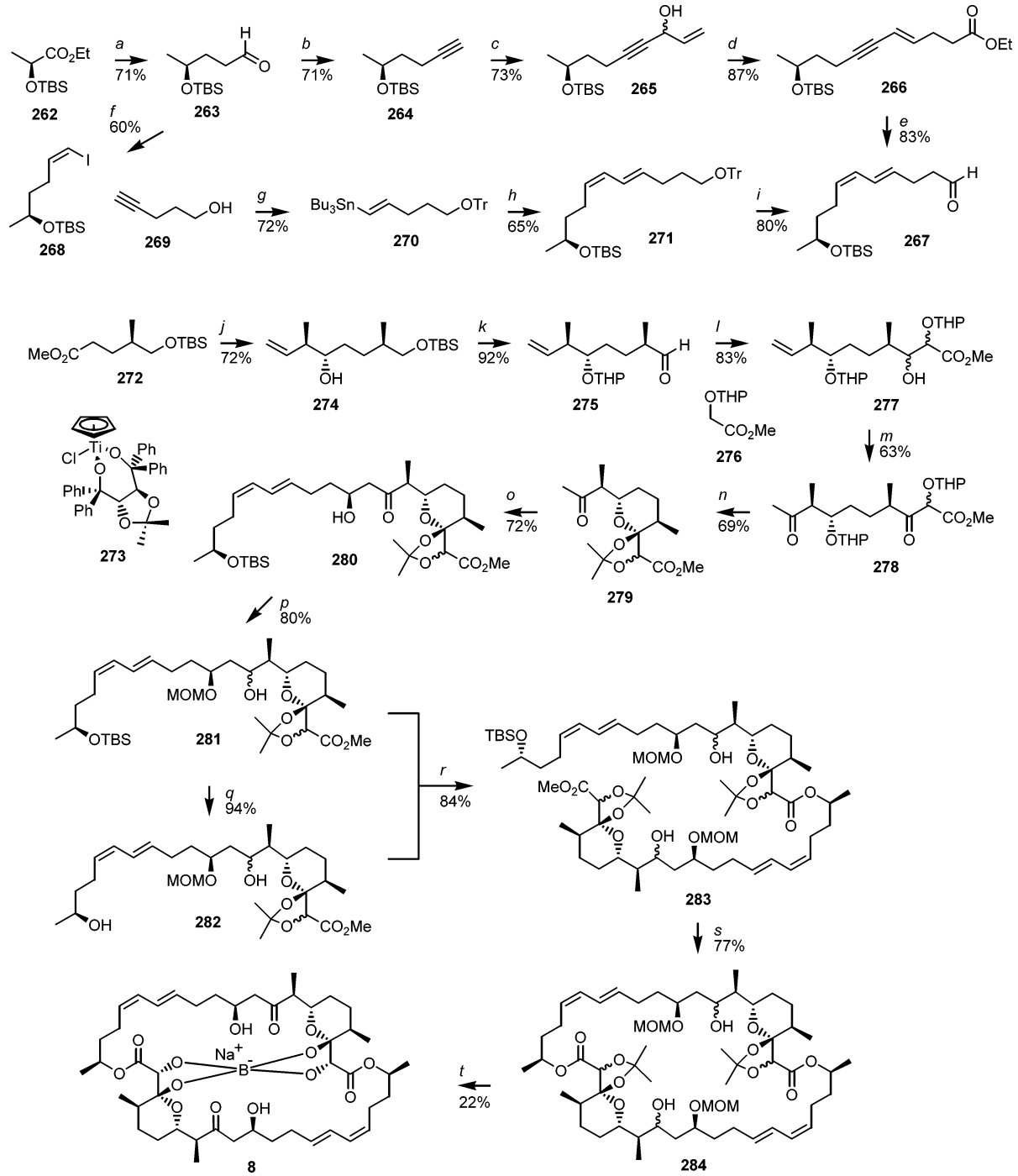
Horner−Emmons olefination to generate the enoate. Hydrogenation of the double bond and reduction of the ester led to aldehyde **263**. Corey−Fuchs chain elongation[131] generated alkyne **264**, which was deprotonated, and, after addition of lithium bromide,[132] was treated with acrolein to furnish enynol **265**. Johnson−Claisen rearrangement[133] occurred exclusively across the olefinic bond and generated (*E*)-enyne ester **266**. (*Z*)-Selective Boland reduction[134] of the alkyne followed by DIBAL reduction delivered aldehyde **267** in high overall yield.

In a second approach, aldehyde **263** was subjected to a (*Z*)-selective Wittig reaction[135] to furnish vinyl iodide **268**. Separately, 4-pentyn-1-ol (**269**) was *O*-tritylated and then converted to (*E*)-vinylstannane **270** by a free radical-induced hydrostannylation. Components **268** and **270** were connected via a Stille coupling[136] to form diene **271**, which was then converted into aldehyde **267**. Both routes exhibit similar (*Z*)-selectivity (6−7:1) and yield.

For synthesis of the C1−C10 fragment, ester **272**[137] was reduced to the corresponding aldehyde and Duthaler−Hafner crotylation[138] was used to form olefin **274** with >95% relative and absolute stereocontrol. Protecting group manipulation and oxidation converted **274** to aldehyde **275**, which was treated with the enolate of glycolate **276**. Aldol adduct **277** was formed as a mixture of the diastereomers. Swern oxidation led to the corresponding keto ester, which was converted via Wacker oxidation[139] to diketone **278** in high yield. The THP groups were removed, and then, acetone was added under strongly acidic conditions to generate the bicyclic ketal **279** in acceptable yield.

Aldol addition of ketone **279** to aldehyde **267** furnished adduct **280** with a 4:1 diastereoselectivity. The hydroxyl group in **280** was protected as the MOM-ether, and the problematic 9-keto functionality

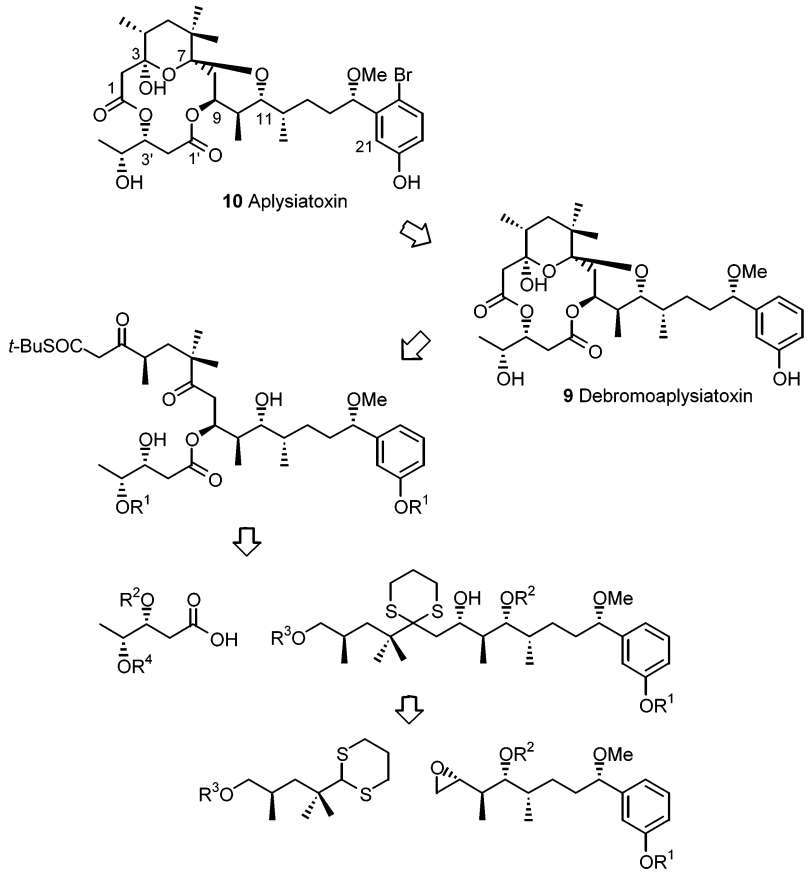
Scheme 28. Mulzer Total Synthesis of Tartrolon B (8)[a]



[a] Reagents and conditions: (a) (i) DIBAL, Et_2O, −78 °C; (ii) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF; (iii) H_2, Raney Ni, MeOH; (iv) DIBAL, Et_2O, −78 °C. (b) (i) Zn, CBr_4, Ph_3P, DCM; (ii) Mg, THF. (c) *n*-BuLi, acrolein, LiBr, THF. (d) $CH_3C(OEt)_3$, $EtCO_2H$, xylenes, reflux. (e) (i) Zn, $BrCH_2CH_2Br$, CuBr, LiBr, MeOH; (ii) DIBAL, Et_2O, −78 °C. (f) $PPh_3{}^+CH_2I_2{}^-$, NaHMDS, THF. (g) (i) NaH, TrCl, THF; (ii) *n*-Bu_3SnH, AIBN, benzene, reflux. (h) Compound **268**, $Pd(dba)_3$, $AsPPh_3$, CuI, DMF, 100 °C. (i) (i) HCO_2H; (ii) NaOH; (iii) $(COCl)_2$, DMSO, DCM, −78 °C; TEA. (j) (i) DIBAL, Et_2O, −90 °C; (ii) **273**, crotylmagnesium chloride, Et_2O, 0 °C; aldehyde, −78 °C. (k) (i) DHP, CSA, DCM; (ii) HF, pyridine, THF; (iii) $(COCl)_2$, DMSO, DCM, −78 °C; TEA. (l) Compound **276**, LDA, THF, −90 °C. (m) (i) $(COCl)_2$, DMSO, DCM, −78 °C; TEA; (ii) $PdCl_2$, THF, DMF, Na_2HPO_4 buffer. (n) (i) *p*-TsOH, MeOH; (ii) P_2O_5, acetone. (o) (−)-DIPCl, TEA, THF, −78 °C; **267**. (p) (i) MOMCl, DIPEA, DCM; (ii) $NaBH_4$, MeOH, THF, −20 to 0 °C. (q) HF, pyridine, THF. (r) (i) Compound **281**, $Ba(OH)_2$, H_2O, MeOH; (ii) 2,4,6-$Cl_3PhCOCl$, TEA, DMAP, toluene; **282**. (s) (i) HF, pyridine, THF; (ii) $Ba(OH)_2$, H_2O, MeOH; (iii) 2,4,6-$Cl_3PhCOCl$, TEA, DMAP, toluene. (t) (i) $(COCl)_2$, DMSO, DCM, −78 °C; TEA; (ii) $(CH_3)_2BBr$, Et_2O, −78 °C; (iii) $Na_4B_2O_7{\cdot}10H_2O$, THF, reflux.

was reduced to furnish alcohol **281**, from which diol **282** was prepared by desilylation. Ester **281** was saponified to the corresponding acid, which was esterified with hydroxy ester **282** to obtain the dimeric ester **283**. For macrolactonization of **283**, the TBS group was first removed, and then, the methyl ester was hydrolyzed with barium hydroxide in methanol[82g] to generate a *seco*-acid, which was lactonized under Yamaguchi conditions[27a] to furnish macrodiolide **284**. Attempts to obtain diolide **284** directly from the hydroxy acid (obtained from **282** via saponification) by a dimerization−cyclization se-

Scheme 29. Retrosynthetic Analysis of Debromoaplysiatoxin (9) and Aplysiatoxin (10)



quence under Yamaguchi conditions in one pot failed. Instead, the corresponding monomacrolactone was obtained in high yield along with only a small amount of diolide **284**.

Reoxidation of the free 9-OH groups in **284** and removal of the acetonide and MOM protective groups with dimethylboron bromide[140] gave a mixture of the tartrolon A diastereomers, which were converted into tartrolon B (**8**) with Borax under the known conditions[14] (Scheme 28).

5.3. Debromoaplysiatoxin (9) and Aplysiatoxin (10)

Debromoaplysiatoxin (**9**) and aplysiatoxin (**10**) were first isolated from the digestive gland of the sea hare *Stylocheilus longicauda* by Kato and Scheuer.[15a] On the basis of spectroscopic and chemical degradation studies, they elucidated the gross structure in 1974. Moore and co-workers isolated aplysiatoxins and structurally related oscillatoxins from the marine blue-green alga *Lyngbya majuscule* and succeeded in establishing the complete structures including the absolute stereochemistry.[15b−d] Aplysiatoxins are causative agents of a severe contact dermatitis and remarkably active tumor promoters.[141]

5.3.1. Kishi Total Synthesis[142]

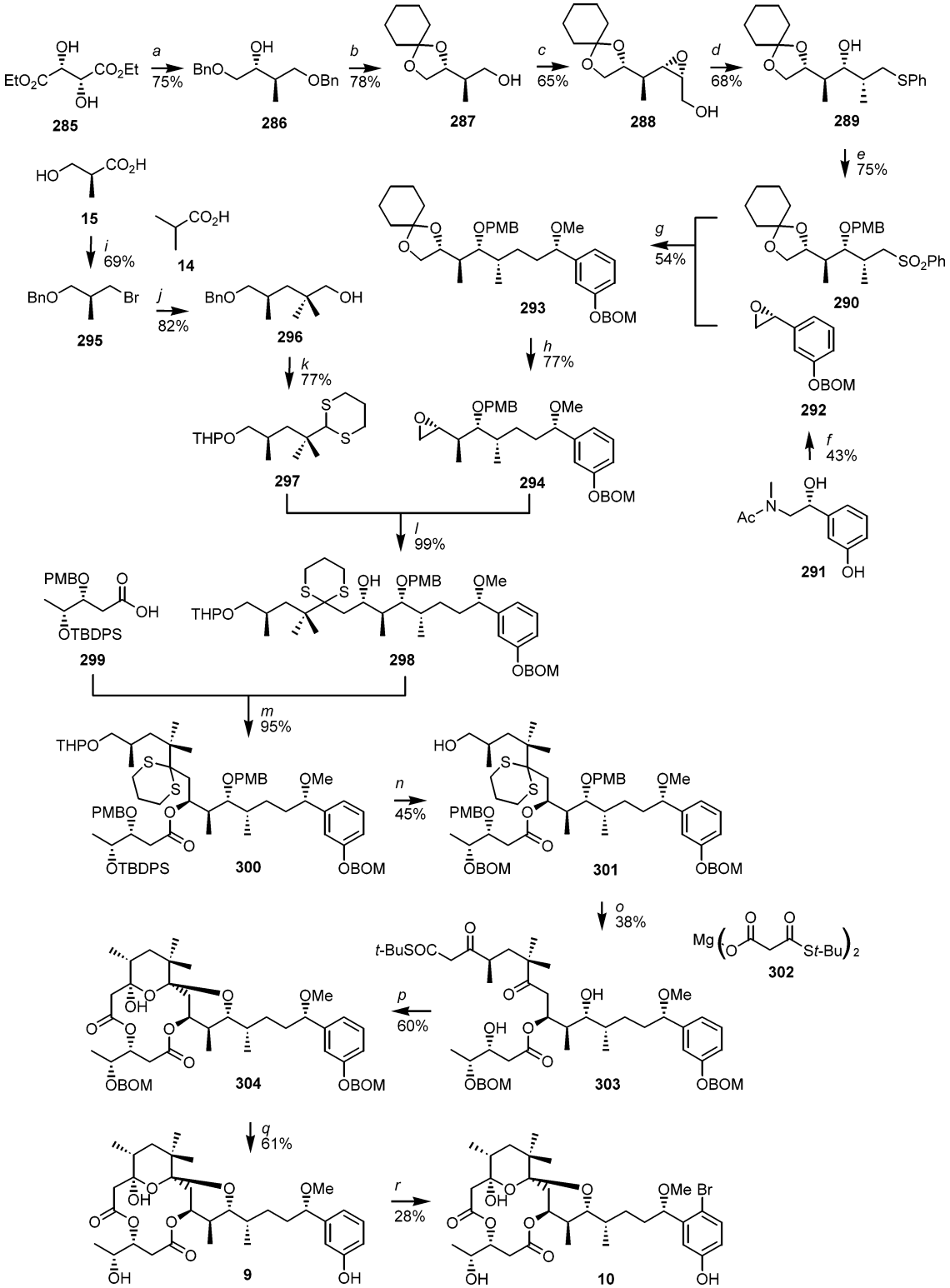
Aplysiatoxin (**10**) was to be prepared from debromoaplysiatoxin (**9**).[15c] Macrolactonization of a thioester intermediate with two carbonyl groups at C3 and C7 and two hydroxyl groups at C11 and C3′ would set the stage for bicyclic hemiketal formation. Coupling of the C3−C7 dithiane and the C8−C21 epoxide fragments would serve as a key step in the synthesis (Scheme 29).

Dibenzyl ether **286** was synthesized from (+)-diethyl L-tartrate (**285**) via a known six-step sequence.[143] The crude triol obtained from **286** via hydrogenolysis was converted into a 6:1 mixture of 1,2- and 1,3-cyclohexylidenes, which were separated as benzyl ethers. The regenerated 1,2-cyclohexylidene **287** was subjected to Swern oxidation, (*Z*)-selective Horner−Emmons reaction,[24a] DIBAL reduction, and stereoselective epoxidation with *m*CPBA to furnish epoxide **288**. Treatment with lithium dimethylcuprate led to a diol product, which was converted into hydroxy sulfide **289** via the corresponding benzenesulfonate. PMB protection of sulfide **289** and peracid oxidation led to sulfone **290**. Selective BOM protection of phenol **291**, lithium aluminum hydride reduction to the corresponding amine, exhaustive methylation, and treatment with KH furnished epoxide **292**.

Coupling reaction of sulfone **290** with epoxide **292** was best achieved through the dianion formation[144] of **290** followed by treatment with **292** at ambient temperature. The resultant diastereomeric mixture of sulfones was subjected to reductive desulfurization and methylation to furnish cyclohexylidene **293** in 54% overall yield from **290**. Ketal deprotection followed by treatment with KH and tosyl chloride transformed **293** into the terminal epoxide **294**.

Acidic benzylation of acid **15**, lithium aluminum hydride reduction, and bromide substitution with

Scheme 30. Kishi Total Synthesis of Debromoaplysiatoxin (9) and Aplysiatoxin (10)[a]



[a] Reagents and conditions: (a) (i) $(EtO)_3CH$, CSA, toluene, reflux; (ii) LAH, THF, 0 °C; (iii) NaH, BnBr, DME, 0−65 °C; (iv) PCl_5, DCM, 0 °C to room temperature; (v) K_2CO_3, MeOH; (vi) $LiCuMe_2$, Et_2O, −78 to −40 °C. (b) (i) H_2, $Pd(OH)_2$/C, EtOH; (ii) cyclohexanone, *p*-TsOH, toluene, 140 °C; (iii) KH, BnBr, THF, 0 °C; (iv) H_2, $Pd(OH)_2$/C, EtOH. (c) (i) $(COCl)_2$, DMSO, DCM, −78 °C; TEA; (ii) $(MeO)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, −78 °C; aldehyde, −78 °C; (iii) DIBAL, Et_2O, −78 °C; (iv) *m*CPBA, K_2CO_3, DCM, 0 °C. (d) (i) MeLi, CuI, Et_2O, −40 to −20 °C; (ii) $PhSO_2Cl$, TEA, DMAP, DCM; (iii) KO*t*-Bu, PhSH, THF. (e) (i) KH, PMBCl, THF; (ii) *m*CPBA, $NaHCO_3$, DCM, 0 °C. (f) (i) BOMCl, $PhMe_3NBr$, DCM, 1 N NaOH; (ii) LAH, THF, 0 °C; (iii) MeI, CH_3CN; KH, THF. (g) (i) *n*-BuLi, **292**, hexane−THF; (ii) Na−Hg, Na_2HPO_4, MeOH; (iii) MeI, KOH, DMSO. (h) (i) AcOH, H_2O, 40 °C; (ii) KH, TsCl, THF. (i) (i) $BnOC(=NH)CCl_3$, TfOH, cyclohexane−DCM; LAH, Et_2O, 0 °C; (ii) NBS, Ph_3P, DCM, 0 °C. (j) (i) LDA, **14**, THF, 0 °C; **295**; (ii) LAH, THF, 0 °C. (k) (i) PCC, DCM; (ii) 1,3-propanedithiol, $BF_3{\cdot}Et_2O$, DCM, −60 °C; (iii) EtSH, $AlCl_3$, DCM, 0 °C; (iv) DHP, PPTS, DCM. (l) Compound **297**, *n*-BuLi, TMEDA, THF, −20 °C; **294**, −20 °C. (m) Compound **299**, TBSCl, imidazole, DMF, 45 °C; $(COCl)_2$, DMF, DCM, 0 °C to room temperature; **298**, DMAP, pyridine. (n) (i) TBAF, THF; (ii) BOMCl, DIPEA, DCM; (iii) AcOH, THF−H_2O, 55 °C. (o) (i) DCC, TFA, pyridine, DMSO, toluene; (ii) NCS, acetone−H_2O; (iii) $NaClO_2$, NaH_2PO_4, $(CH_3)_2C{=}CHCH_3$, *t*-BuOH, H_2O, 0 °C to room temperature; (iv) carbonyl diimidazole, THF; **302**, 40 °C; (v) DDQ, DCM−H_2O. (p) AgOTFA, Na_2HPO_4, benzene. (q) H_2, Pd/C, TEA, EtOH. (r) Br_2 (in aqueous NaBr), MeOH, Na_2HPO_4 buffer (pH 6).

NBS and Ph_3P provided bromide **295**. The dianion of isobutyric acid (**14**) was reacted with bromide **295**, and the product acid was reduced with lithium aluminum hydride to furnish alcohol **296**. Dithiane **297** was prepared from **296** via oxidation, reaction with 1,3-propanedithiol, benzyl deprotection by ethanethiol and aluminum chloride, and THP protection of the primary hydroxyl group.

Treatment of epoxide **294** with the anion generated from dithiane **297** gave alcohol **298** in almost quantitative yield. Introduction of the acid side chain at the hydroxyl group at C9 of **298** was difficult, and the problem was solved when the acid chloride, prepared from the PMB- and TBDPS-protected dihydroxy pentanoic acid **299** under neutral conditions,[145] was reacted with **298** in the presence of DMAP to furnish ester **300** in 95% yield. After adjustment (from TBDPS to BOM) of the hydroxyl protecting group at C4′ of **300**, acid treatment furnished the primary alcohol **301** in 45% overall yield. The unstable dihydroxy β-keto thio ester **303** was prepared from **301** in 38% overall yield via Moffat oxidation,[146] oxidative hydrolysis of the dithiane unit by treatment with NCS,[94a] further oxidation to the corresponding carboxylic acid,[147] Claisen condensation following Masamune protocol[106a] using the magnesium salt **302**, and DDQ treatment. When diol **303** was subjected to the Masamune macrolactonization conditions,[148] the desired product **304** was isolated in 60% yield. BOM deprotection of **304** via hydrogenolysis provided debromoaplysiatoxin (**9**) in 61% yield. Bromination of **9** furnished aplysiatoxin (**10**) (Scheme 30).

6. Conclusions

As stated in the Introduction, stereoselective oxolane synthesis was important in the total synthesis of pamamycin 607 (**1**). Intramolecular selenoetherification of 1,5-*anti*-(*Z*)-homoallylic alcohols (Thomas synthesis),[20] obtained via remote asymmetric induction, and iodoetherification reaction of γ-triethylsilyloxyalkenes followed by epoxide formation/dimethylcuprate reaction (Kang synthesis)[41] were employed for synthesis of threo-cis 2-(oxolane)propanoate functionality. The same structure was obtained via the sultone approach (Metz synthesis):[35d] Sultones were prepared from hydroxyalkyl 1,3-dienes via esterification/cycloaddition and further transformed via methyllithium addition, ozonolysis, phenylthio substitution, and reductive elimination/hydrogenation. Radical cyclization of β-alkoxymethacrylates prepared from β-iodo alcohols directly produced the threo-cis 2-(oxolane)propanoate moiety (Lee synthesis).[28] In the synthesis of amphidinolide X (**2**), the oxolane ring was prepared via silver ion-catalyzed cyclization of a chiral allenol (Fürstner synthesis),[59] which was formed stereoselectively by an iron-catalyzed reaction of a propargyl epoxide with a Grignard reagent.

Radical cyclization of β-alkoxyacrylates furnished *cis*-2,6-disubstituted oxanes in the synthesis of SCH 351448 (**3**) (Lee synthesis).[71] In the synthesis of swinholide A (**4**), the *trans*-2,6-disubstituted oxane and oxene moieties were prepared via electrophilic addition to cyclic oxocarbenium ions (Nicolaou synthesis).[83a,b]

Concerning formation of macrodiolide ring systems, two separate esterification reactions of different monomeric hydroxy carboxylic acids were employed for syntheses of pamamycin 607 (**1**) (Thomas,[20] Lee,[28] Metz,[35f] and Kang[41] syntheses), amphidinolide X (**2**) (Fürstner synthesis),[59] and debromoaplysiatoxin (**9**) (Kishi synthesis).[142] In the syntheses of swinholide A (**4**) (Nicolaou synthesis)[83c] and tartrolon B (**8**) (Mulzer synthesis),[130a,b] the same strategy was adopted with two units of identical monomeric hydroxy acids. The Yamaguchi esterification reaction was frequently the method of choice.

Template-directed cyclodimerization reaction of hydroxy carboxylic acids worked for expedient syntheses of cycloviracin B_1 (**5**) (Fürstner synthesis)[96c] and glucolipsin A (**6**) (Fürstner synthesis).[117] The total synthesis of boromycin (**7**) (White synthesis)[123g] features a ring contraction reaction based on the rearrangement of an α-acyloxyacetate to an α,β-enediolate for macrodiolide formation. Ring-closing metathesis reaction of an open diester intermediate was a key step in the synthesis of SCH 351448 (**3**) (Lee synthesis).[71]

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