Strategy and Methodology Development for the Total Synthesis of Polyether Ionophore Antibiotics†

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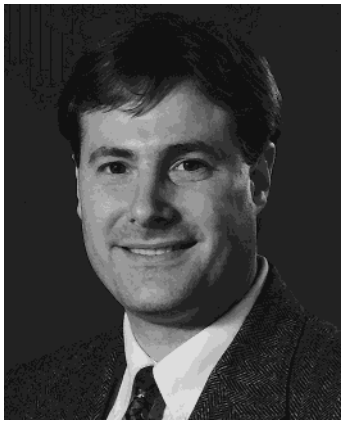
I. Introduction

The polyether antibiotics, a class of compounds isolated from fermentation cultures of *Streptomyces*, characteristically contain a carboxylate group and 2−5 oxygen atoms serving as ligands for the complexation of inorganic cations. Complexes generated from ionophores are exceptionally hydrophobic and facilitate translocation of ions across membrane barriers. The polyether antibiotics induce a range of biological responses that include ruminant growth promotion, anticoccidial activity, and mammalian cardiovascular effects. An excellent monograph edited by Westley provides an in depth summary of the chemistry and biology of this family of natural products.[1]

Over 120 naturally occurring ionophores are known,[2] and 16 have been prepared by total synthesis. The framework of these molecules, dominated by the presence of substituted tetrahydrofurans, tetrahydropyrans, and spiroketal systems, is primarily derived from polypropionate and polyacetate fragments. The structural complexity and diversity of the polyether antibiotics continue to challenge synthetic organic chemists two decades after the landmark synthesis of lasalocid A was reported by Kishi and co-workers.[3]

† Dedicated to Professor David A Evans.

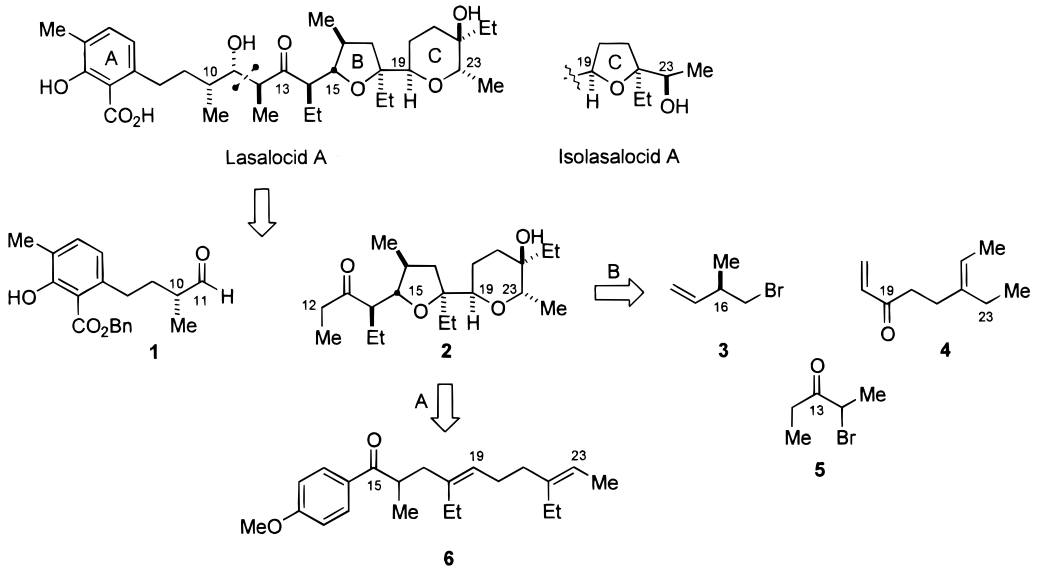
Margaret Faul was born in Co. Kerry, Ireland, in 1964. She completed her B.Sc. and M.Sc. degrees in Science at the University College Dublin, Ireland. She received her Ph.D. degree from Harvard University in 1992, under the supervision of Professor David A. Evans. Her work focused in two major areas: (i) Asymmetric synthesis of chiral organosulfur compounds using *N*-sulfinyl carboximides and (ii) Copper-catalyzed aziridination of olefins by [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane. It was during this time that she became interested in the area of asymmetric synthesis and in particular asymmetric catalysis. Since 1993 she has been working at the Chemical Process Research and Development Laboratories of Eli Lilly and Company in Indianapolis, IN.



Bret Huff was born in Inglewood, CA, in 1962. He earned his Bachelors degree in Chemistry from California State University, Chico, in 1984 and his Ph.D. degree in 1989 from the University of California, Santa Barbara. At UCSB he worked under the direction of Professor Bruce Lipshutz on the functionalization of imidazoles into α-alkylated amino acids and on the total synthesis of cyclopeptide alkaloids. As an NIH postdoctoral fellow in the laboratory of Professor David Evans at Harvard, he worked on the total synthesis of lonomycin A. Since 1991, he has been at Eli Lilly and Company in the department of Chemical Process Research and Development.

Several acyclic methods have been developed to address the problem of polypropionate synthesis. For example, the use of allylic 1,3 strain (A-1,3) by Kishi allowed the synthesis of propionate fragments and tetrahydrofuran formation by hydroboration, epoxidation, and haloetherification.[4] Later, by using Sharpless asymmetric epoxidation, these transformations were carried out to prepare enantiomerically pure propionate fragments.[5] Kishi and Still introduced the use of Cram- and Cram-chelate-controlled addition of nucleophiles to carbonyls to build propionate units as well as assemble propionate fragments.[6] Later, chiral enolate bond constructions developed by Evans made these types of bond constructions even more versatile and efficient. This methodology also allowed the enantioselective synthesis of polyether antibiotics

Scheme 1



without the use of chiral pool elements or resolution of intermediates. Extending the versatility of simple A-1,3 interactions in acyclic systems, Still and Schrieber introduced methods for the stereoselective epoxidation of macrocyclic olefins to prepare the tetrahydrofuran region of the ionophores.

Along with new methods for polypropionate synthesis, several strategies and reactions have been developed for fragment coupling. The aldol reaction is by far the most important and well-studied reaction for this purpose. In addition, the Julia olefination, Horner−Emmons, Wittig, and Diels−Alder reactions have been used in the formation of di- and trisubstituted double bonds as well as fragment couplings.

In this review, the total syntheses of all polyether ionophores prepared to date are presented in order of the year that the synthesis was published. For each synthesis the retrosynthetic approach is presented followed by (i) a table indicating the origin of each stereogenic center; (ii) the synthesis of each fragment, and (iii) the final coupling strategy. Discussion of the fragment synthesis is limited to those reactions that establish stereochemistry by acyclic stereocontrol. Stereogenic centers and fragments that were derived from chiral pool elements are not discussed in detail. In this way, it is hoped the reader can easily compare each synthesis and follow the chronological advances in strategy and methods that have been developed to prepare this class of complex natural products.

II. Survey of the Synthesis of Polyether Ionophores

A. 1978, Lasalocid A and Isolasalocid A (Kishi)

Lasalocid A and isolasalocid A were the first polyether ionophores prepared by total synthesis.[7] Lasalocid A and isolasalocid A contain 10 asymmetric centers and a central tetrahydrofuran B-ring. They differ only in that the C-ring of lasalocid A is a tetrahydropyran while the C-ring of isolasalocid A is a tetrahydrofuran. Aldol disconnection of the C_{11}−C_{12} bond afforded the C_1−C_{11} and C_{12}−C_{24} fragments **1** and **2** (Scheme 1). Further disconnection of the C_{12}−C_{24} fragment **2** was achieved by two complimentary approaches (A and B) that used the highly regio- and stereocontrolled addition of alcohols to epoxides.[8] The stereochemical inventory for Kishi's synthesis of lasalocid A is summarized in Table 1.

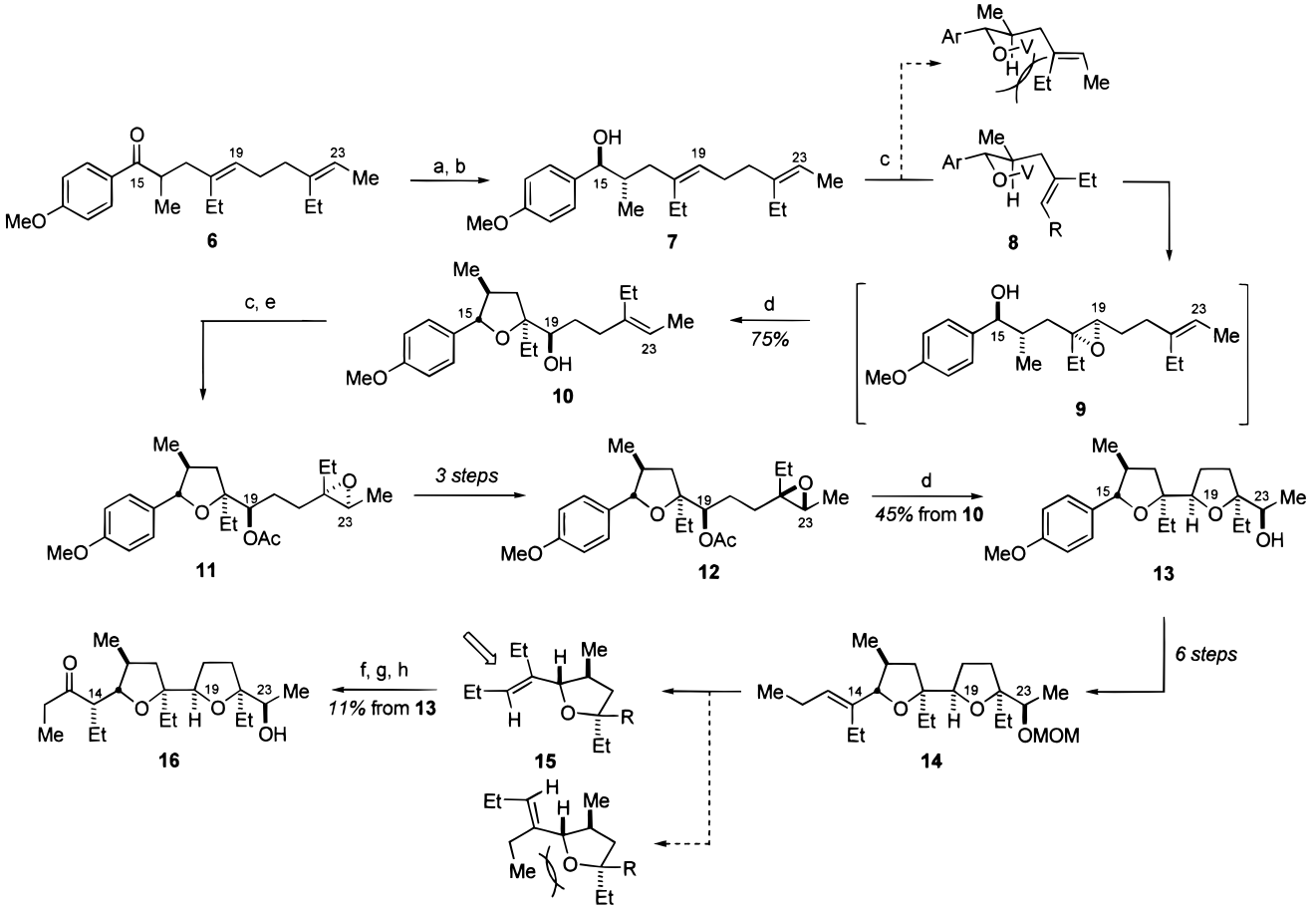
Table 1. Stereochemical Inventory for Kishi's Synthesis of Lasalocid A (Approach B)

carbon	control element	reaction/source
C_{10}	chiral pool	*(S)*-(+)-3-hydroxy-2-methyl-propionic acid
C_{11}	Cram addn	aldol/Zn enolate
C_{12}	Cram addn	aldol/Zn enolate
C_{14}	equilibration	
C_{15}	Cram-chelate	aldol/Mg enolate
C_{16}	chiral pool	*(S)*-(+)-3-hydroxy-2-methyl-propionic acid
C_{18}	Cram-chelate	Grignard addn
C_{19}	directed reduction	hydride/resolution
C_{22}	A-1,3	hydroxyl-directed epoxidation/ resolution
C_{23}	A-1,3	epoxidation/resolution

1. Synthesis of the C_{12}–C_{24} Fragment, Approach A

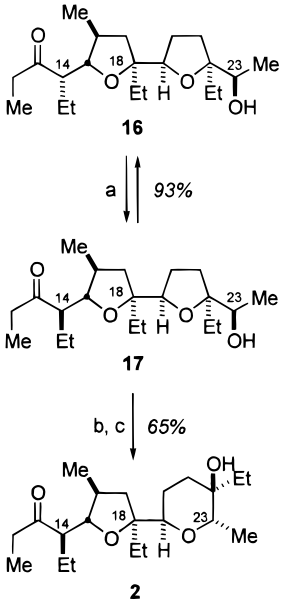
In the syntheses of lasalocid A and isolasalocid A, Kishi demonstrated the power of A-1,3 interactions to prepare tetrahydrofurans by epoxidation of bis-homoallylic alcohols and stereoselective (directed) reduction of ketones followed by epoxide opening.[9] Ketone **6**, prepared by Johnson orthoester−Claisen rearrangement, was reduced with $LiAlH_4$ in the presence of DL-2-(*o*-toluidinomethyl)pyrrolidine to provide **7** as a >10:1 mixture of racemic C_{15} alcohols.[10] The major isomer resulted from Cram addition of hydride to the carbonyl (Scheme 2). Resolution provided optically pure alcohol **7**. Hydroxyl-directed epoxidation of the C_{18}−C_{19} olefin with $VO(acac)_2$ through **8** afforded epoxide **9**. Epoxide **9** was treated directly with HOAc to provide tetrahydrofuran **10** in 75% yield as an 8:1 mixture of C_{19} alcohols. A second hydroxyl-directed epoxidation protocol followed by three-step inversion of the resulting epoxide provided

Scheme 2[a]



[a] (a) $LiAlH_4$, DL-2-(*o*-toluidinomethyl)pyrrolidine; (b) resolution; (c) *t*-BuOOH, $VO(acac)_2$, NaOAc, PhH, rt; (d) HOAc; (e) Ac_2O, pyr; (f) B_2H_6, THF, rt; (g) CrO_3; (h) $TrBF_4$, CH_2Cl_2, rt.

Scheme 3[a]



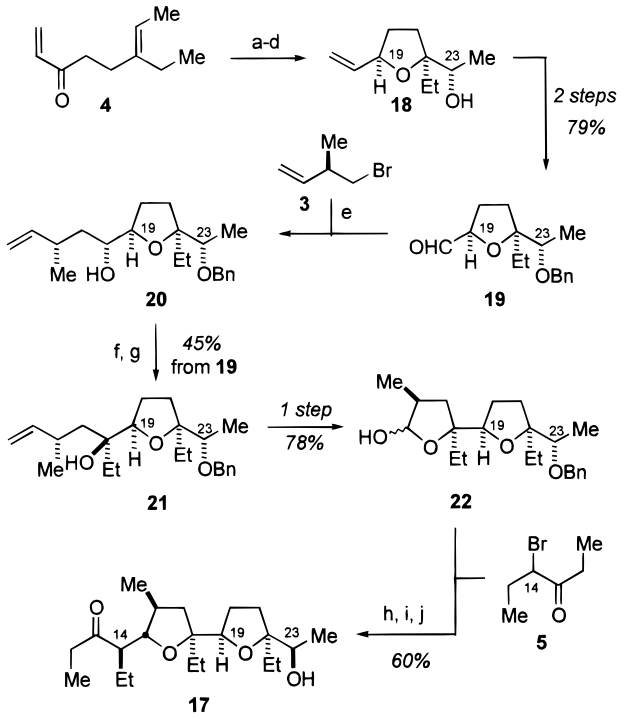
[a] (a) aq NaOH, dioxane; (b) MsCl, pyr, rt; (c) aq acetone, Ag_2CO_3, rt.

12. Treatment of **12** with HOAc afforded tetrahydrofuran **13** as a 5:1 mixture of C_{23} alcohols. Unmasking of the $C_{11}-C_{14}$ carbons contained within the anisole group yielded intermediate olefin **14** in 6 steps. Hydroboration of **14**, followed by oxidation and removal of the MOM group, provided the unnatural C_{14} ethyl epimer **16** exclusively. Hydroboration occurred on the most stable olefin conformer **15** in which A-1,3 interactions were minimized. Equilibration of C_{14} with aqueous NaOH in dioxane provided a 1:1 mixture of **16** and **17** in 93% yield (Scheme 3). The tetrahydrofuran ring corresponding to isolasalocid A was converted to the lasalocid A tetrahydropyran ring **2** in 65% yield by mesylation of the C_{23} hydroxyl followed by ring expansion using Ag_2CO_3 in aqueous acetone.

2. Synthesis of the C_{12}–C_{24} Fragment, Approach B

An alternate approach to the $C_{12}-C_{24}$ fragment was reported by Kishi in 1978 (Scheme 4). Epoxidation of olefin **4** followed by reduction with $LiAlH_4$/toluidine afforded a 10:1 mixture of C_{19} alcohols. The major alcohol was the Cram addition product. Tetrahydrofuran formation with HOAc afforded racemic **18** in 65% isolated yield along with 6% of the isomeric tetrahydrofuran. The absolute stereochemistry of **18** was established by resolution. Grignard addition of optically pure **3**, derived from (*S*)-(+)-3-hydroxy-2-methyl propionic acid, to aldehyde **19** provided the Cram-chelate product **20** as a single isomer. Oxidation of the C_{18} hydroxyl followed by a second Cram-chelate addition of EtMgBr provided **21** as a single isomer in 45% overall yield from **19**. Ozonolysis of **21** yielded lactol **22** in 78% yield. Treatment of **22**

Scheme 4[a]



[a] (a) *t*-BuOOH, $VO(acac)_2$, NaOAc, PhH, rt; (b) $LiAlH_4$, DL-2-(*o*-2-toluidinomethyl)pyrrolidine; (c) HOAc; (d) five-step resolution; (e) Mg, THF; (f) CrO_3; (g) EtMgBr, Et_2O; (h) Mg, THF; (i) *p*-TsOH, PhH; (j) Pd/C, MeOH, H_2.

with the Grignard reagent derived from **5** provided a 3:2 mixture of **16** and the desired C_{14} epimer **17**. As described previously, equilibration of the mixture with NaOH provided a 1:1 mixture of **16** and **17** in 93% yield.

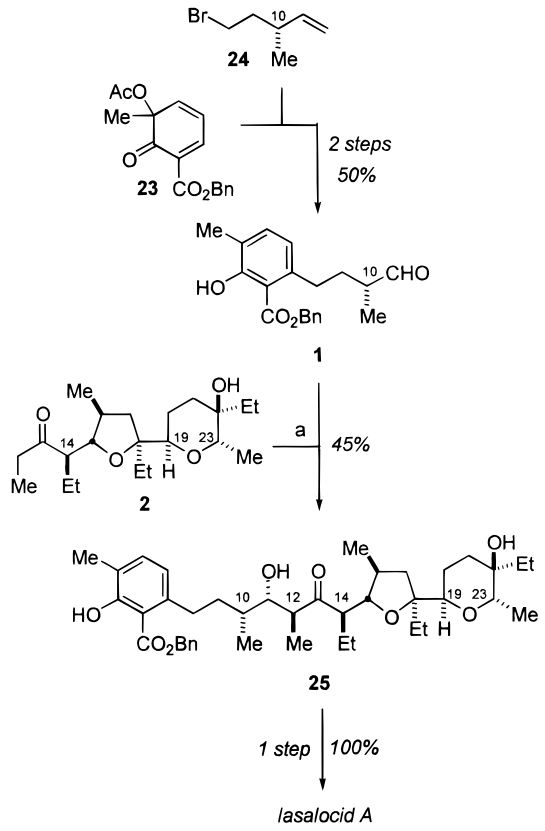
3. Fragment Coupling—The Aldol Reaction

The C_1-C_{12} fragment was prepared in two steps and 50% overall yield from 2-acetoxy-2-methyl-6-carbobenzoxy-3,5-cyclohexadiene-1-one (**23**) and L-1-bromo-3-methyl-4-pentene **24** (Scheme 5). Aldol reaction of the zinc enolate of **2** with aldehyde **1** provided a 40:10:7:3 ratio of isomers in 45% yield. The major product **25**, formed by Cram addition of the enolate to the aldehyde, contained the stereochemistry required for lasalocid A. Catalytic hydrogenation of the benzyl protecting group proceeded in quantitative yield to complete the synthesis of lasalocid A. Similarly, isolasalocid A was prepared by aldol reaction of fragment **17** and **1**.[11]

B. 1979, Monensin A (Kishi)

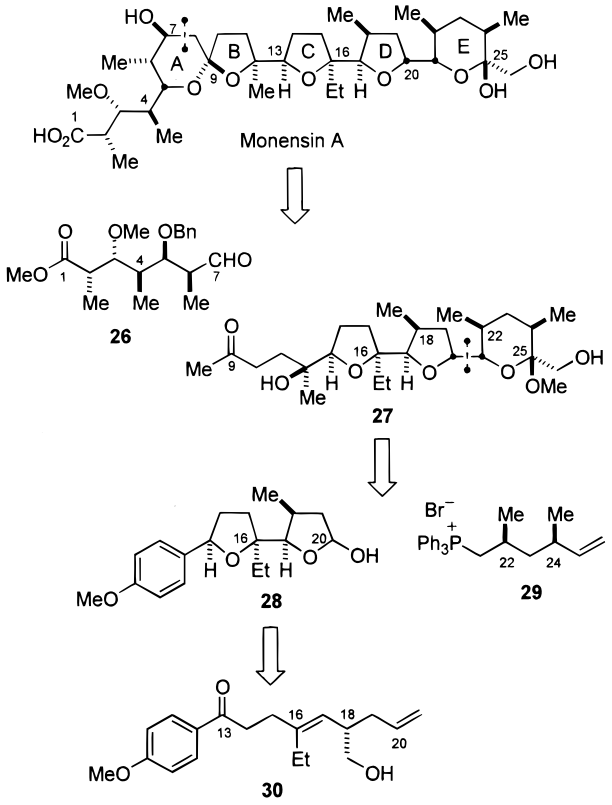
In 1979 both Kishi and Still reported the total synthesis of monensin A.[12] Aldol disconnection of the C_7-C_8 bond afforded the C_1-C_7 and C_8-C_{26} fragments **26** and **27** (Scheme 6). For his synthesis of **26** Kishi developed new methodology for the preparation of propionate fragments using the hydroboration reaction. Further disconnection of the $C_{20}-C_{21}$ bond of **27** by a Wittig reaction afforded the C_9-C_{20} and $C_{21}-C_{26}$ fragments **28** and **29**, respectively. In analogy to his work on the synthesis of lasalocid A, Kishi envisioned that the C_9-C_{20} fragment **28** could be derived from **30** by application of the bishomoallylic

Scheme 5[a]



[a] (a) LDA, $ZnCl_2$, 0 °C.

Scheme 6



alcohol methodology. The absolute stereochemistry of monensin A was derived by resolution of key intermediates. The stereochemical inventory for Kishi's synthesis of monensin A is summarized in Table 2.

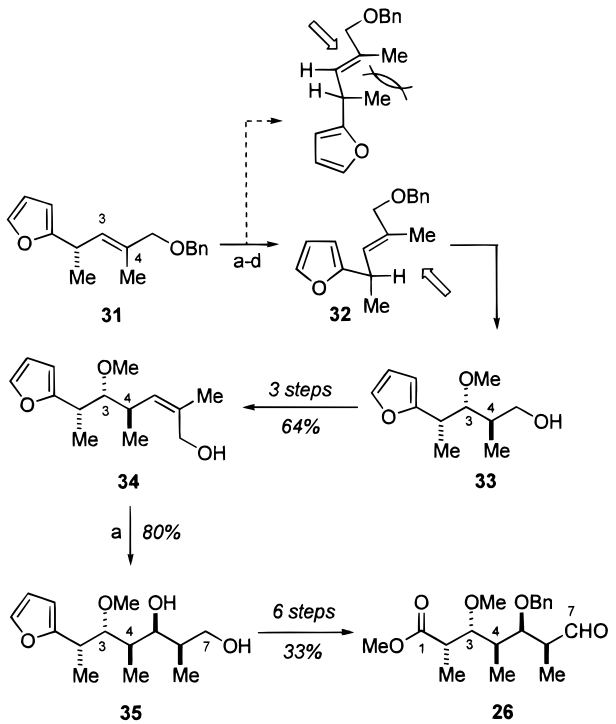
Table 2. Stereochemical Inventory for Kishi's Synthesis of Monensin A

carbon	control element	reaction/source
C_2	resolution	α-methyl benzylamine
C_3	A-1,3	hydroboration
C_4	A-1,3	hydroboration
C_5	A-1,3	hydroboration
C_6	A-1,3	hydroboration
C_7	Cram addn	aldol/Mg enolate
C_9	thermodynamic	equilibration
C_{12}	Cram-chelate	Grignard addn
C_{13}	A-1,3	directed reduction
C_{16}	A-1,3	epoxidation
C_{17}	A-1,3	epoxidation
C_{18}	resolution	α-methyl decylamine
C_{20}	A-1,3	haloetherification
C_{21}	A-1,3	haloetherification
C_{22}	resolution	α-methyl benzylamine
C_{24}	resolution	α-methyl benzylamine
C_{25}	thermodynamic	equilibration

1. Synthesis of the C_1–C_7 Fragment

In the synthesis of the C_1-C_7 fragment, Kishi demonstrated the versatility of acyclic stereocontrol in the hydroboration of olefins to prepare propionate fragments (Scheme 7). Hydroboration of racemic olefin **31** provided **33** as an 8:1 mixture of C_3 alcohols. The desired isomer **33** was formed through conformer **32** that minimized A-1,3 interactions. Hydroboration of **32** occurred from the α-face, opposite the large (furan) group. The absolute stereochemistry of the C_1-C_7 fragment was established by resolution of the diastereomeric urethanes derived from the hydroboration product. A second hydroboration established the stereochemistry of the C_5-C_6 bond. In this case, the desired isomer **35** was obtained in 80% yield as a 12:1 mixture. The C_1-C_7 fragment was completed in six steps by ozonolysis of the furan ring, oxidation of the C_7 alcohol, and protection of the C_5 hydroxyl.[13]

Scheme 7[a]



[a] (a) BH_3, THF, 0 °C, H_2O_2; (b) MeI, KH, DMF; (c) Pd/C, MeOH, H_2; (d) three-step resolution.

2. Synthesis of the C_8–C_{26} Fragment

As in the synthesis of lasalocid A, Kishi used the epoxidation of bishomoallylic alcohols to prepare the C_8-C_{26} fragment of monensin A (Scheme 8). The absolute stereochemistry of the C_8-C_{26} fragment was derived from resolution of the benzyl ether of 2-allyl-1,3-propanediol (**36**). Taking advantage of the symmetry of **36**, each enantiomer was converted separately into olefin **30**. Epoxidation of the bishomoallylic $C_{16}-C_{17}$ olefin with *m*-CPBA followed by tosylation of the primary alcohol provided **38** as a single epoxide isomer. Epoxidation occurred through conformation **37**, which minimized A-1,3 strain. Additionally, *m*-CPBA coordinated with the hydroxymethylene to direct the epoxidation to the desired β-face. The stereochemistry at C_{13} was established by $LiAlH_4$ reduction of the C_{13} carbonyl with concomitant reduction of the C_{18} tosyl group. In this case, the optimal reduction conditions ($LiAlH_4$, DL-2-(*o*-toluidinomethyl)pyrrolidine) used in the synthesis of lasalocid A were unsatisfactory, since the tosyl group was not reduced. However, using $LiAlH_4$ directly, a 7:2 mixture of C_{13} alcohols was obtained and cyclized with CSA to form tetrahydrofuran **39**. Oxidation of the terminal olefin followed by lactol formation gave **28** in 36% overall yield from **30**. Wittig coupling of the $C_{13}-C_{20}$ lactol **28** with phosphonium salt **29** provided *cis* olefin **42** in 78% yield. The $C_{21}-C_{26}$ fragment **29** was prepared in 36% overall yield from racemic *cis*-3,5-dimethylcyclohexanone **40** by resolution in 13 steps.[14]

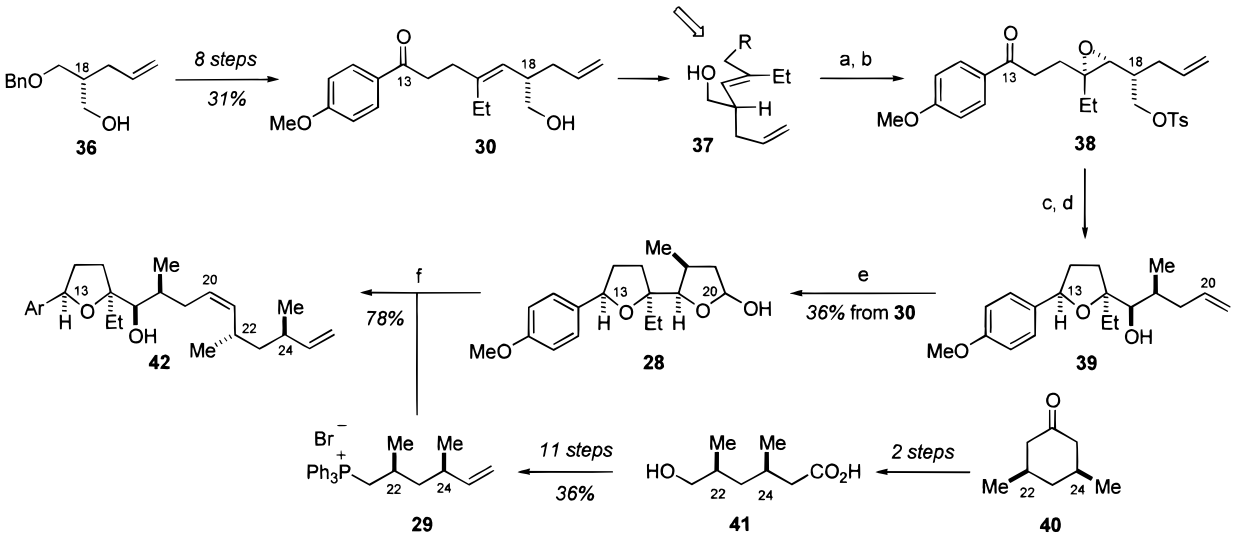
Bromination of olefin **42** was governed by A-1,3 strain where reaction with NBS occurred selectively from the α-face (Scheme 9). Opening of the intermediate bromonium ion from the β-face by the C_{17} hydroxyl group provided the tetrahydrofuran D-ring **43** in 57% yield. The C_{21} bromide **43** was inverted to the C_{21} alcohol **44** with superoxide and cyclized to **45** in four steps. Formation of the E-ring tetrahydropyran and unmasking of the anisole protecting group afforded **47**. Cram-chelate addition of MeMgBr to the C_{12} ketone provided a single tertiary alcohol that cyclized in the presence of HCl to afford lactone **48** in 22% yield from **46**. Ring opening of **48** with MeLi proceeded in quantitative yield to give the completed C_8-C_{26} fragment **27** in 15 steps.

3. Fragment Coupling—The Aldol Reaction

The synthesis of monensin A was completed by acetate aldol coupling of the C_1-C_7 and C_8-C_{26} fragments **26** and **27** using $(i\text{-Pr})_2NMgBr$ to provide a 1:1 mixture of C_7 epimeric alcohols. The desired aldol product **49** was isolated in 36% yield (Scheme 10).

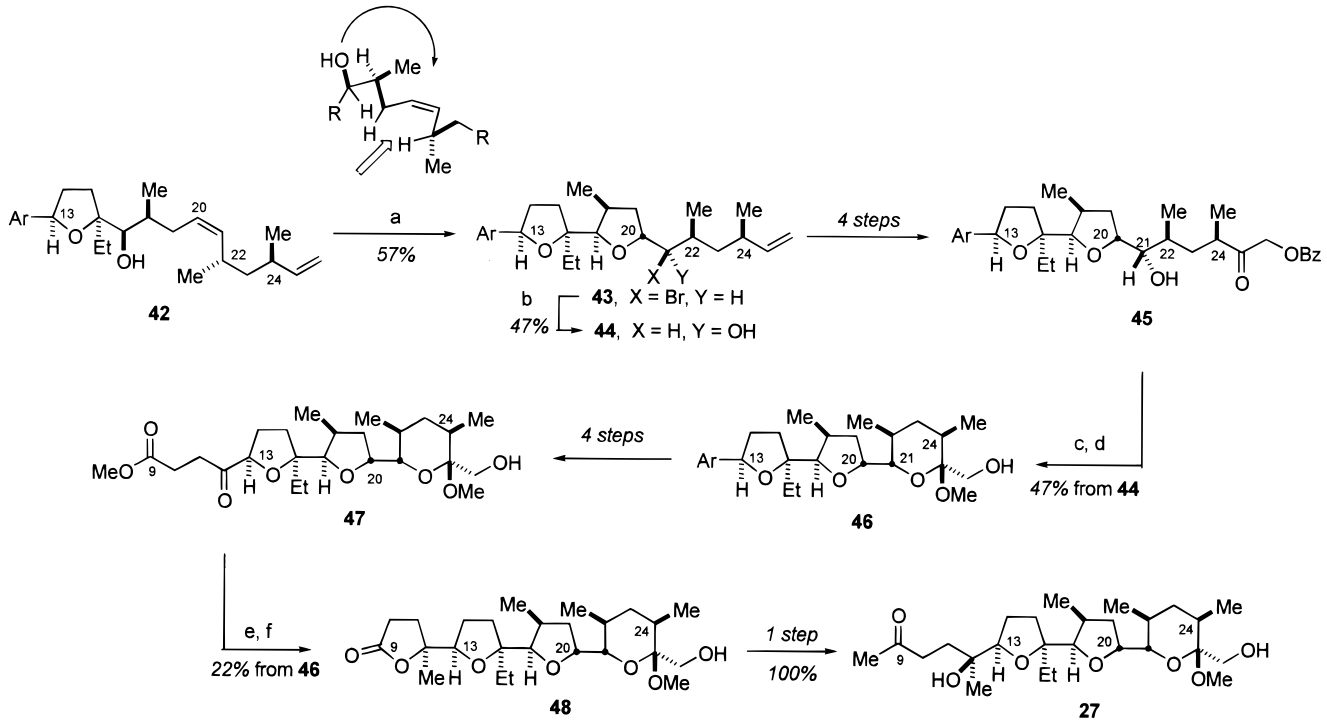
The last remaining hurdle to complete the total synthesis of monensin A was spiroketal formation. In a model system, catalytic hydrogenation of ketone **50** using $Pd/C-H_2$ in the presence of HOAc afforded a 1:1 mixture of spiroketals **51** and **52**. However, when this mixture was treated with catalytic CSA,

Scheme 8[a]



[a] (a) *m*-CPBA, CH_2Cl_2, Na_2CO_3; (b) *p*-TsCl, pyr, 0 °C; (c) $LiAlH_4$, Et_2O, 0 °C; (d) CSA, CH_2Cl_2, rt; (e) $NaIO_4$, OsO_4, dioxane; (f) $Me_2SO^-Na^+$, DMSO.

Scheme 9[a]



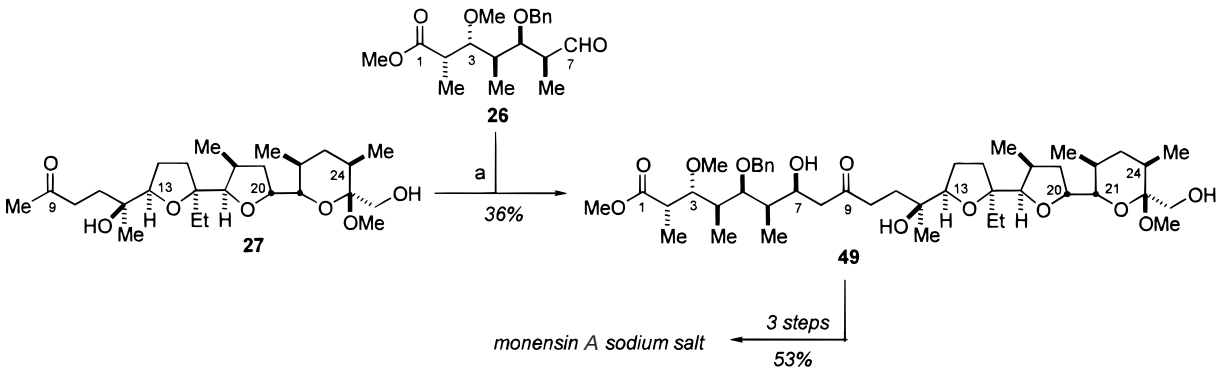
[a] (a) NBS, MeCN, rt; (b) KO_2, DMSO; (c) NaOMe, MeOH, rt; (d) $MeC(OMe)_3$, MeOH, CSA; (e) MeMgBr, Et_2O, rt; (f) conc HCl, MeOH, rt.

the selectivity improved to >20:1 (Scheme 11). Application of these conditions to **49** completed the synthesis of monensin A in 53% overall yield by deprotection of the C_5 benzyl group, formation of the monensin A spiroketal with CSA, and formation of the sodium salt (Scheme 10).

C. 1979, Monensin A (Still)

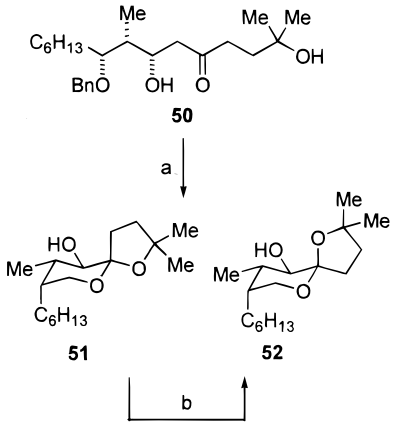
In contrast to Kishi's synthesis of monensin A, Still relied heavily on Cram and Cram-chelate nucleophilic addition reactions to carbonyl compounds to prepare propionate fragments.[15] These reactions were used to set seven stereogenic centers in the total synthesis of monensin A. In analogy to Kishi's synthesis, Still's retrosynthetic approach used an aldol disconnection of the C_7-C_8 bond to generate the C_1-C_7 and C_8-C_{26} fragments **53** and **54** (Scheme 12).[16] Cram-chelate-controlled addition reactions were used to prepare the C_1-C_7 propionate fragment **53**. Further disconnection of the C_8-C_{26} fragment provided two smaller fragments **55** and **56**. Synthesis of fragment **55** relied on Cram-chelate reactions, while the stereogenic centers contained in fragment **56** were assembled using A-1,3 interactions. The stereochemical inventory for Still's synthesis of monensin A is summarized in Table 3.

Scheme 10[a]



[a] (a) $(i\text{-Pr})_2$NMgBr, THF, 0 °C.

Scheme 11[a]



[a] (a) Pd/C, H_2, AcOH; (b) CSA, CH_2Cl_2.

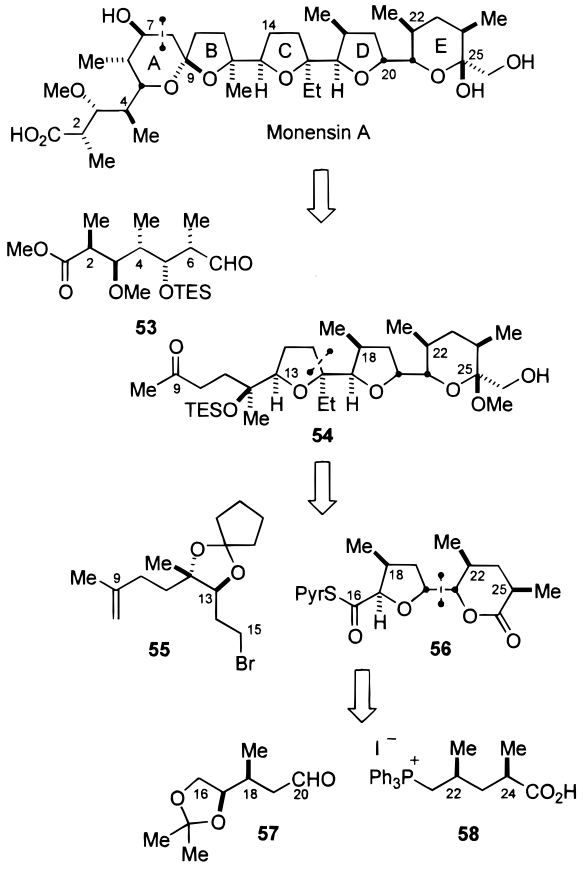
1. Synthesis of the C_1–C_7 Fragment

The C_1-C_7 fragment of monensin A was prepared from BOM-protected (*R*)-*β*-hydroxyisobutyraldehyde (**59**) in 10 steps by two sequential aldol reactions (Scheme 13). Cram-chelate-controlled aldol reaction of aldehyde **59** with 2-methyl-2-trimethylsilyloxy-3-pentanone (**60**) produced a 5:1 mixture of diastereomers in 85% yield. The mixture of diastereomers was oxidized to the *β*-hydroxy acid, the C_3 hydroxyl methylated, and the major diastereomer isolated by chromatography. Removal of the BOM protecting group and oxidation of the C_5 hydroxyl produced aldehyde **61** in 38% overall yield from **59**. A second aldol-like reaction of **61** with *cis*-2-butenyldiethylaluminum proceeded in 3:1 selectivity favoring the Cram (nonchelate) product **62**. Presumably, the Cram product was obtained because the aluminum reagent is not capable of chelating efficiently with the C_3 *β*-alkoxymethyl group. Hydrolysis of lactone **62**, protection of the C_5 hydroxyl, and ozonolysis completed the synthesis of the C_1-C_7 fragment **53** in 10 steps.

2. Synthesis of the C_8–C_{15} Fragment

Chelate-controlled addition reaction of the Grignard reagent derived from 3-methyl-3-butenylbromide (**66**) to ketone **65**, prepared in six steps from (*S*)-malic acid, provided a 50:1 mixture diastereomers that were deprotected to provide **67** in 70% yield (Scheme 14). Diol protection, desilylation, and bromination completed the synthesis of the C_8-C_{15} fragment **55** in 10 steps and 32% overall yield.

Scheme 12



3. Synthesis of the C_{16}–C_{25} Fragment

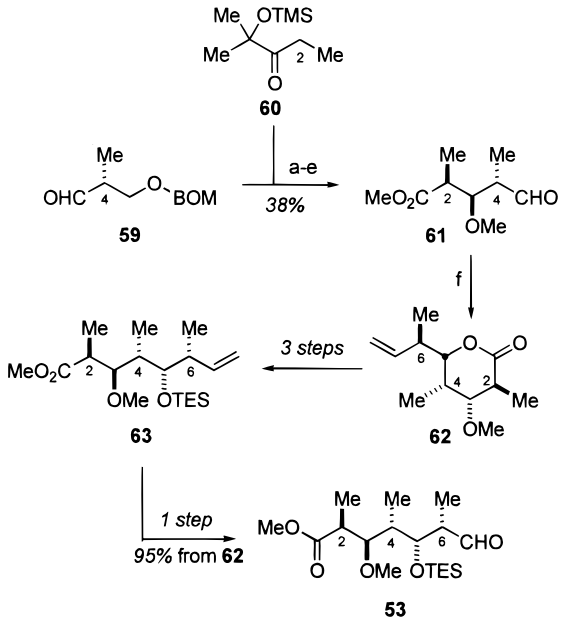
The $C_{16}-C_{25}$ fragment was prepared from two smaller fragments **57** and **58**. Fragment **57**, derived from (*R*)-citronellic acid, was prepared in seven steps by thermodynamic iodolactonization of **68** to provide **69** as a 20:1 mixture of lactones in 89% yield (Scheme 15). Inversion of the C_{17} stereogenic center was achieved by treatment of **69** with the potassium salt of benzyl alcohol followed by hydrogenolysis to afford lactone **70** in 84% yield. Reduction of lactone **70**, acetonide formation, and oxidation of C_{20} afforded the completed $C_{16}-C_{20}$ fragment **57** in seven steps and 60% overall yield.

The $C_{21}-C_{25}$ fragment **58** was prepared from THP-protected (*R*)-*β*-hydroxyisobutyraldehyde (**71**) by

Table 3. Stereochemical Inventory for Still's Synthesis of Monensin A

carbon	control element	reaction/source
C_2	Cram-chelate	aldol/Mg enolate
C_3	Cram-chelate	aldol/Mg enolate
C_4	chiral pool	(*R*)-β-hydroxyisobutyraldehyde
C_5	Cram addn	organoaluminum addn
C_6	Cram addn	organoaluminum addn
C_7	Cram addn	aldol/Mg enolate
C_9	thermodynamic	equilibration
C_{12}	Cram-chelate	Grignard addn
C_{13}	chiral pool	(*S*)-(−)-malic acid
C_{16}	Cram-chelate	Grignard addn
C_{17}	A-1,3	haloetherification
C_{18}	chiral pool	(*R*)-citronellic acid
C_{20}	A-1,3	haloetherification
C_{21}	A-1,3	haloetherification
C_{22}	chiral pool	(*R*)-β-hydroxyisobutyraldehyde
C_{24}	cyclic stereocontrol	hydrogenation
C_{25}	thermodynamic	equilibration

Scheme 13[a]

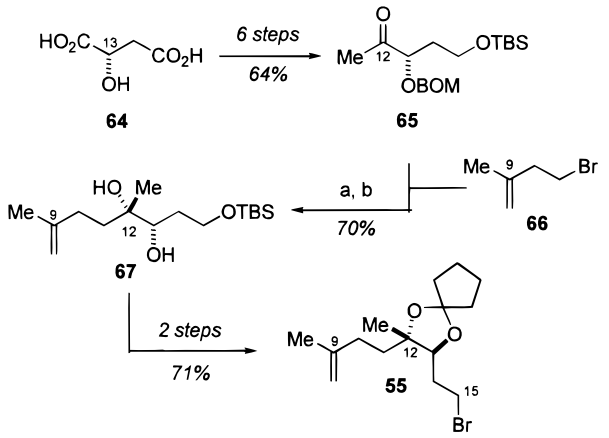


[a] (a) LiN(*i*-Pr)$_2$, THF, MgBr$_2$, −100 °C; (b) H$_5$IO$_6$, MeOH; (c) KN(TMS)$_2$, Me$_2$SO$_4$; (d) 10% Pd/C, H$_2$; (e) CrO$_3$, pyr, CH$_2$Cl$_2$; (f) *cis*-2-butenyldiethylaluminum, THF, −78 °C.

aldol reaction with ethyl propionate and dehydration to provide lactone **72** (Scheme 16). Catalytic hydrogenation of the C_{23}−C_{24} olefin provided an 8:1 mixture of syn:anti isomers. The desired syn isomer was isolated by selective crystallization. Opening of the lactone with HI, followed by phosphonium salt formation completed the synthesis of the C_{21}−C_{25} fragment.

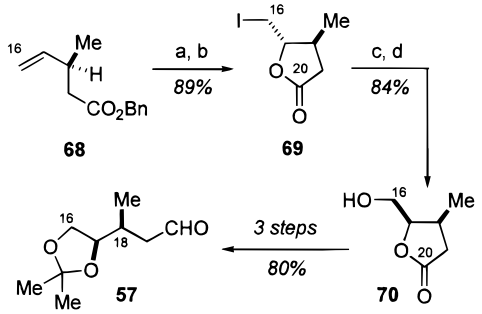
Wittig coupling of **57** and **58** afforded *cis*-olefin **74** in 70% yield (Scheme 17). As in Kishi's synthesis of monensin A, the C_{20}−C_{21} bond was functionalized and the D-ring formed by haloetherification. Hence, treatment of **74** with KI$_3$ provided the intermediate iodonium ion that was selectively intercepted by the C_{25} carboxylic acid from the α-face to provide lactone **76** in 87% yield. Lactonization was controlled by the C_{22} stereogenic center which constrained the C_{25} carboxyl group below the plane of the olefin in conformation **75** and reduced A-1,3 interactions. Hydrolysis of the acetonide and tetrahydrofuran

Scheme 14[a]



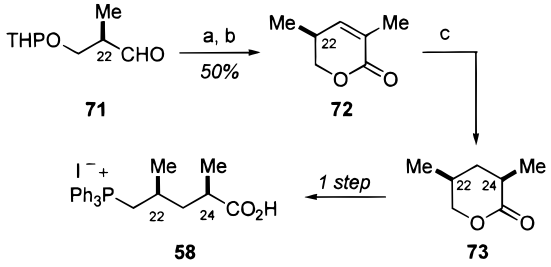
[a] (a) Mg, THF, −78 °C; (b) Li/NH$_3$, −78 C.

Scheme 15[a]



[a] (a) KOH, MeOH; (b) I$_2$, MeCN, −15 °C, 72 h; (c) KOBn, THF, −20 °C; (d) Pd/C, H$_2$, Et$_2$O.

Scheme 16[a]



[a] (a) LDA, THF, −78 °C, ethyl propionate; (b) *p*-TsOH, PhH; (c) Rh/Al$_2$O$_3$, H$_2$, Et$_2$O.

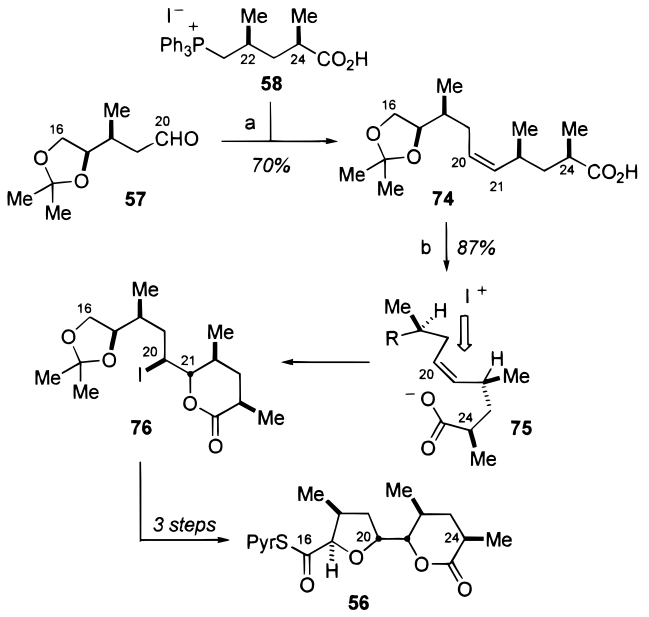
formation by displacement of the C_{20} iodide by the C_{17} hydroxyl provided the D-ring of monensin A with inversion of the C_{20} stereocenter. Activation of the C_{16} ketone as the *S*-pyridyl ester completed the synthesis of the C_{16}−C_{25} fragment.

Coupling of the C_8−C_{15} fragment **55** and C_{16}−C_{25} **56** fragment was accomplished by Grignard reaction in the presence of CuI·PBu$_3$ (Scheme 18). Subsequent chelate-controlled addition of EtMgBr to the C_{16} ketone provided a single tertiary alcohol **77** in 70% overall yield. Deketalization with NBS in the presence of *p*-TsOH followed by mesylation afforded **78**. Methyl ketone **79** was obtained in six steps and 68% yield by inversion of the C_{13} stereocenter.

4. Fragment Coupling—The Aldol Reaction

The final aldol coupling reaction of the magnesium enolate of methyl ketone **79** with the C_1−C_7 aldehyde **53** yielded a 3:1 mixture of aldol diastereomers with

Scheme 17[a]



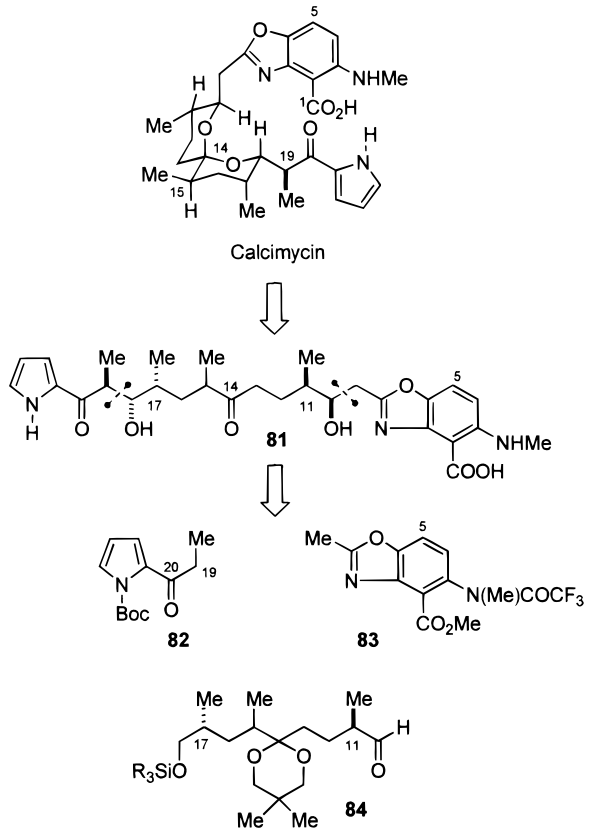
[a] (a) NaH, DMSO, 25 °C; (b) KI_3, $NaHCO_3$.

the Cram product as the major isomer in 75% yield. The bulky TES group presumably precluded chelation by the C_5 oxygen. The conversion of **80** to the sodium salt of monensin A was accomplished by hydrogenolysis of the benzyl group, formation of the spiroketal under equilibrating conditions, and saponification.

D. 1979, Calcimycin (Evans)

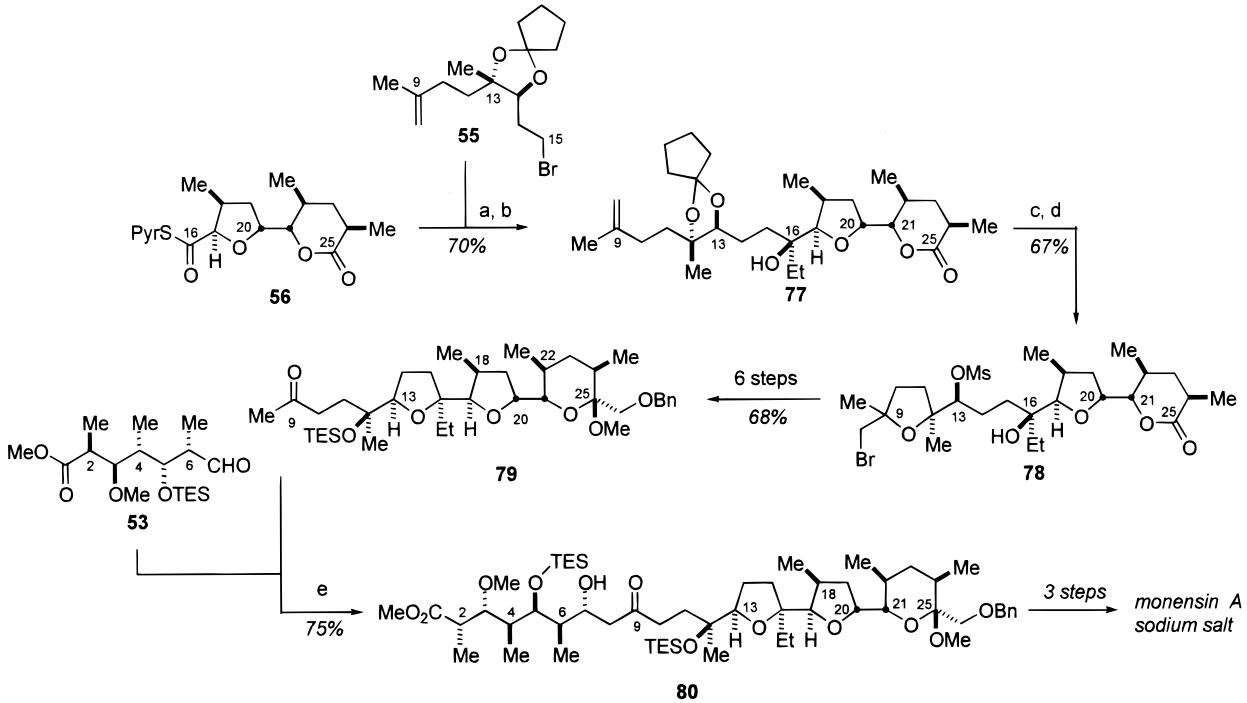
Six syntheses of calcimycin have been reported that focus on the acyclic stereocontrol involved in formation of the spiroketal ring system. The first reported

Scheme 19



synthesis by Evans in 1979 relied on thermodynamic control in the spiroketalization step.[17] Retrosynthetic disconnection of the C_9-C_{10} and $C_{18}-C_{19}$ bonds of **81** afforded the heterocyclic precursors **82**, **83**, and **84** (Scheme 19). The stereochemistry at C_{15} was not considered to be an issue in the synthesis of **81** since

Scheme 18[a]



[a] (a) CuI, PBu_3, THF, −78 °C, Mg; (b) EtMgBr, THF, −78 °C; (c) NBS, *p*-TsOH, CH_2Cl_2, 0 °C; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C; (e) LDA, THF, $MgBr_2$, −78 °C.

Table 4. Stereochemical Inventory for Evan's Synthesis of Calcimycin

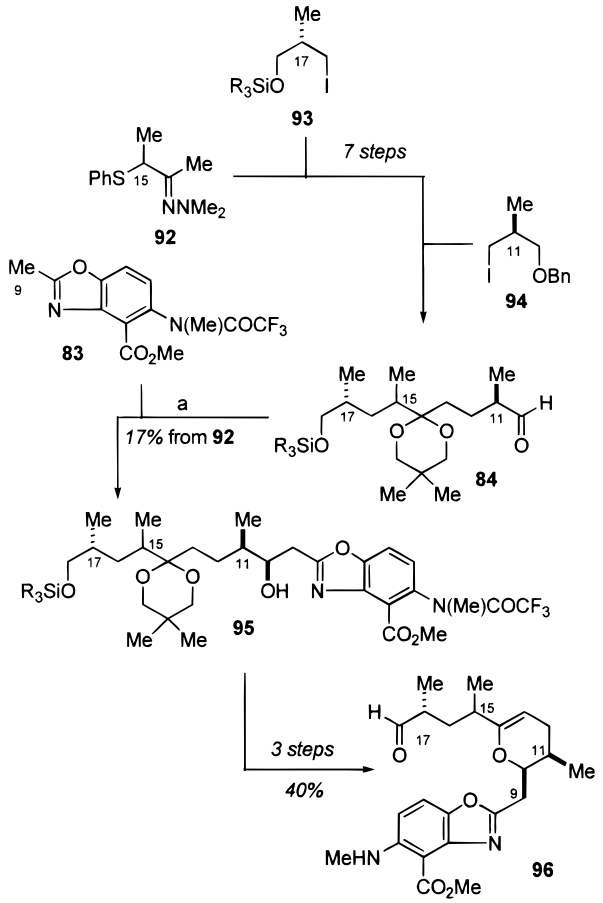
carbon	control element	reaction/source
C_{10}	Cram addn	organolithium addn
C_{11}	chiral pool	(*S*)-(+)-β-hydroxyisobutyric acid
C_{15}	thermodynamic	equilibration
C_{17}	chiral pool	(*S*)-(+)-β-hydroxyisobutyric acid
C_{18}	Cram addn	aldol/Zn enolate
C_{19}	Cram addn	aldol/Zn enolate

it was believed that acid-catalyzed equilibration of this center in the target molecule should afford the desired equitorial diastereomer. The stereochemical inventory for Evan's synthesis of calcimycin is summarized in Table 4.

Evans first demonstrated thermodynamic control in the formation of the spiroketals using the dioxaspirane **85** (Scheme 20).[18] Ketalization of **86** and **87** (when R = H), prepared as a 1:1 mixture of isomers from dihydroanisole, afforded only the desired isomer **88** containing the calcimycin stereochemistry in 89% yield. When R = Me, ketalization of **86** afforded dioxaspirane **88** in 60% yield. The formation of only one of the possible conformations is the consequence of stabilizing anomeric and exo-anomeric effects that direct both C−O bonds to the axial positions of the respective rings. These results are a clear demonstration of how stereoelectronic effects can define the three-dimensional space of polycyclic compounds.[19−21]

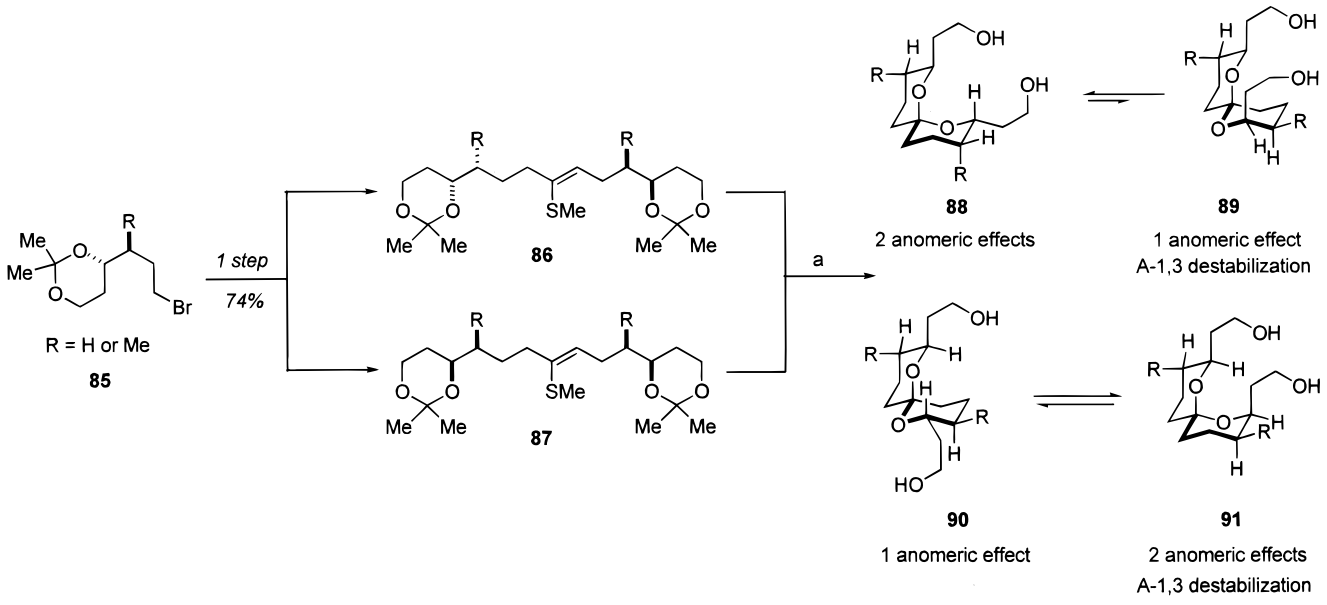
Evans successfully used these results to complete the first total synthesis of calcimycin (Scheme 21). The dioxaspirane subunit **84** was prepared by alkylation of dimethylhydrazone derivative **92**, prepared from α-phenylthioacetone, with chiral iodides **93** and **94** derived from (*S*)-(+)-β-hydroxyisobutyric acid. Cram addition of the anion of benzoxazole **83** to aldehyde **84** introduced the C_{10} stereocenter with 88:12 selectivity. Formation of the minor diastereomer was disfavored due to destabilizing *syn*-pentane interactions. Evans postulated that the outcome of the aldol reaction of **83** and **84** was influenced by remote steric effects, since addition of **83** to aldehyde **97** was stereorandom (Scheme 22). Treatment of acyclic precursor **95** with acid to form the spiroketal, removal of the protecting groups, and oxidation of C_{18} afforded dihydropyran **96** as the major product in 40% yield.

Scheme 21[a]



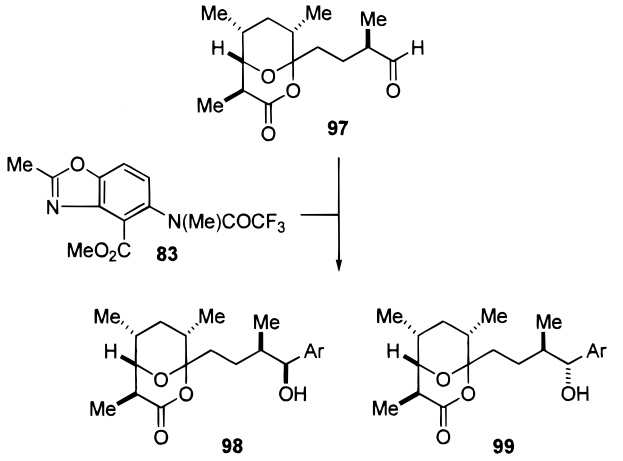
[a] (a) LDA, THF, −100 °C.

Scheme 20[a]



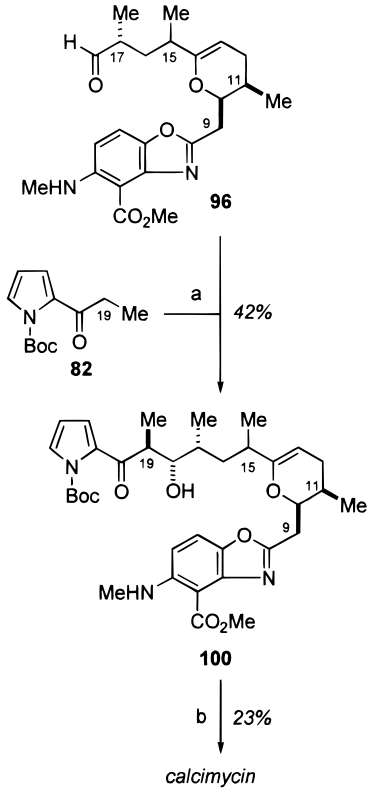
[a] (a) $HgCl_2$, CAN, H_2O. (Reprinted with permission from ref 18. Copyright 1978 Elsevier Sciences Ltd.)

Scheme 22



Aldol reaction of **96** with the enolate of pyrrole **82** afforded the Cram addition product **100** as the predominant diastereomer (Scheme 23). The metal employed in preparation of the enolate was found to have a profound effect on the enolate geometry. The zinc enolate afforded predominantly the *threo* (thermodynamic) product derived from the *E*-enolate. The lithium enolate slightly favored the *Z*-isomer. Treatment of **100** with an acidic ion-exchange resin induced spiroketal formation, equilibration of the diastereomeric C_{15} methyl epimers, and removal of the pyrrole protecting group to afford the methyl ester of calcimycin in 23% yield. Evans' spiroketalization strategy was also successfully employed by Grieco (1982) and Ogawa (1986).

Scheme 23

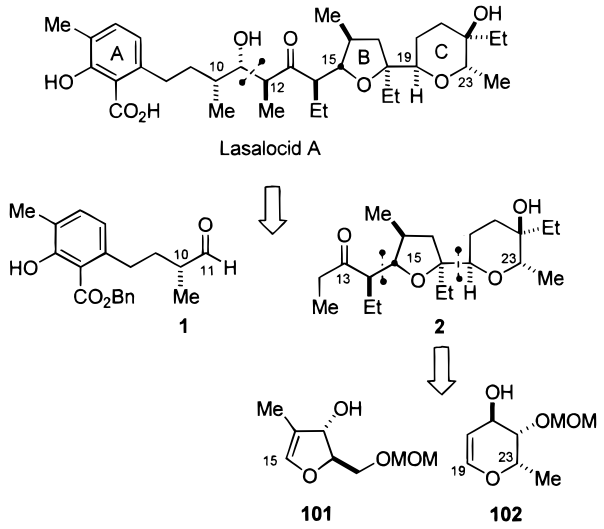


(a) LDA, $ZnCl_2$, 1:1 Et_2O/DME; (b) AG 50W−X8, PhMe, 100 °C.

E. 1980, Lasalocid A (Ireland)

Ireland's retrosynthetic approach to lasalocid A incorporated the first example of the use of the ester−enolate Claisen rearrangement[22] in the synthesis of a polyether ionophore (Scheme 24).[23] As in Kishi's

Scheme 24



synthesis of lasalocid A, Ireland disconnected the C_{11}−C_{12} bond using an aldol reaction to afford the C_1−C_{11} and C_{12}−C_{24} fragments **1** and **2**. Fragment **2** was further disconnected at the C_{14}−C_{15} and C_{18}−C_{19} bonds by dual application of the ester−enolate Claisen rearrangement.[24] Use of Claisen technology enabled the efficient coupling of fully formed tetrahydrofuran and tetrahydropyran subunits derived from carbohydrates. In this way, Ireland used the ester−enolate Claisen rearrangement as a method of fragment coupling and stereochemical transfer. The stereochemical inventory for Ireland's synthesis of lasalocid A is summarized in Table 5.

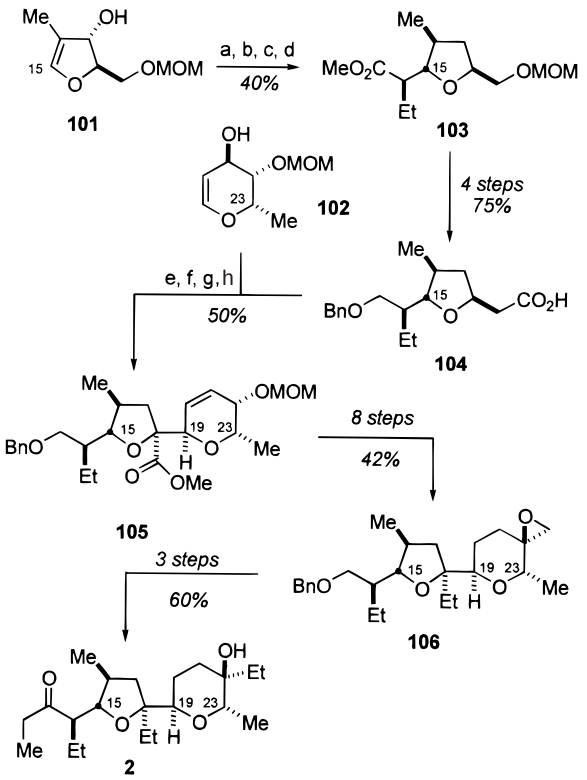
1. Synthesis of the C_{12}–C_{24} Fragment

Two sequential ester−enolate Claisen rearrangements were used in the synthesis of the C_{12}−C_{24} fragment **2** of lasalocid A. Each of the building blocks **101** and **102** were derived from carbohydrate precursors (Scheme 25). Treatment of alcohol **101** with butyryl chloride, followed by ester−enolate Claisen rearrangement using *n*-BuLi and TMSCl provided **103** and its diastereomer as a 3:1 mixture in 40% yield, after hydrogenation of the C_{16}−C_{17} olefin. The

Table 5. Stereochemical Inventory for Ireland's Synthesis of Lasalocid A

carbon	control element	reaction/source
C_{10}	chiral pool	(*R*)-citronellene
C_{11}	Cram addn	aldol/Zn enolate
C_{12}	Cram addn	aldol/Zn enolate
C_{14}	cyclic stereocontrol	ester−enolate Claisen
C_{15}	cyclic stereocontrol	ester−enolate Claisen
C_{16}	cyclic stereocontrol	hydrogenation
C_{18}	chiral pool	D-glucosaccharino-1,4-lactone
C_{19}	cyclic stereocontrol	ester−enolate Claisen
C_{22}	chiral pool	6-deoxy-L-gulose
C_{23}	chiral pool	6-deoxy-L-gulose

Scheme 25[a]

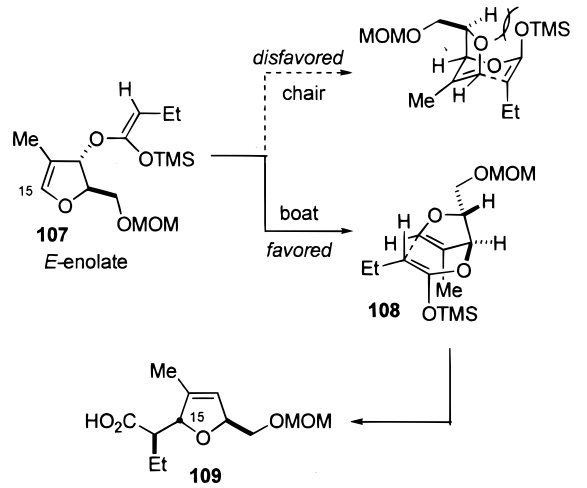


[a] (a) *n*-BuLi, *n*-C_3H_7COCl; (b) LDA, TMSCl, THF/HMPA; (c) H_2, Pt/C, EtOAc; (d) CH_2N_2, Et_2O; (e) $(COCl)_2$, PhH; (f) *n*-BuLi, THF; (g) LDA, TMSCl, THF; (h) CH_2N_2, Et_2O.

stereochemistry at the ethyl-bearing C_{14} stereogenic center was controlled by the *E*/*Z* ratio of enolates. Using a saturated solution of HMPA in THF, the *E*-enolate was favored (Scheme 26). Ireland showed that in cyclic systems the boat transition state **108** is favored over the chair transition state.

Coupling of acid **104** with carbohydrate-derived alcohol **102**, followed by treatment of the resulting ester with *n*-BuLi and TMSCl, initiated a second Claisen rearrangement that provided a 3:1 mixture of **105** in 50% yield. Conversion of **105** to ketone **2** proceeded through epoxide **106** in 11 steps and 25% overall yield. The $C_{12}-C_{24}$ fragment was constructed in 19 steps and 4% overall yield.

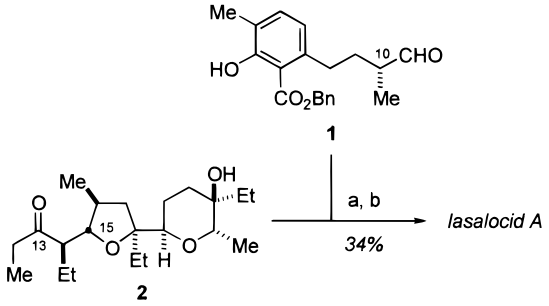
Scheme 26



2. Fragment Coupling—The Aldol Reaction

In analogy to Kishi's synthesis of lasalocid A, Ireland used an aldol reaction for the final fragment coupling. Reaction of optically active aldehyde **1**, derived from (*R*)-citronellene, with the zinc enolate of ketone **2** resulted in a 54:32:10:4 mixture aldol products. The major isomer, isolated in 34% yield, contained the desired stereochemistry required for lasalocid A. Hydrogenation of the benzyl ester provided lasalocid A (Scheme 27).[25]

Scheme 27[a]



[a] (a) LDA, Et_2O, $ZnCl_2$; (b) H_2, Pd/C, EtOH.

F. 1981, Indanomycin (Nicolaou)

All five of the reported total syntheses of indanomycin employ a Diels–Alder reaction for construction of the tetrahyroindan ring system. Nicolaou completed the first total synthesis of indanomycin in 1981.[26] Removal of the pyrrole and disconnection of the $C_{10}-C_{11}$ bond revealed tetrahydropyran **110** and tetrahydroindan **111** as the major fragments. Bromopyran **110** was in turn derived from **112** and **113** (Scheme 28). The stereochemical inventory for Nicolaou's synthesis of indanomycin is summarized in Table 6.

Scheme 28

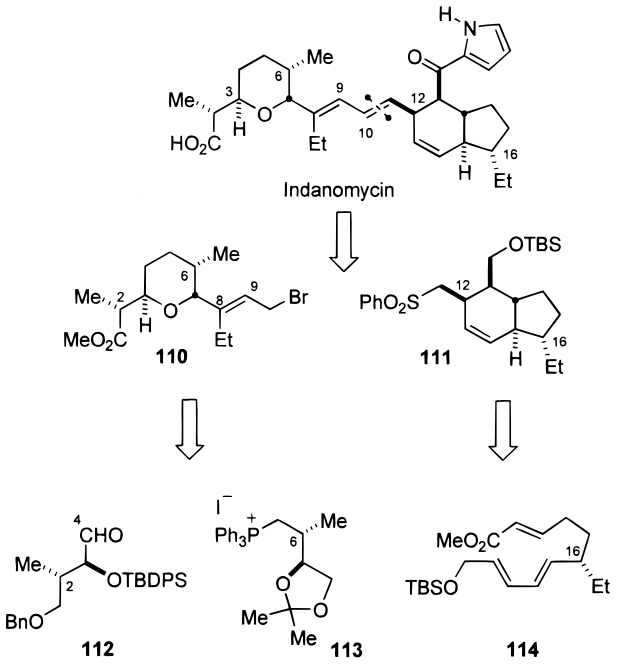


Table 6. Stereochemical Inventory for Nicolaou's Synthesis of Indanomycin

carbon	control element	reaction/source
C_2	chiral pool	D-tartaric acid
C_3	chiral pool	D-tartaric acid
C_6	chiral pool	D-tartaric acid
C_7	chiral pool	D-tartaric acid
C_{12}	cyclic stereocontrol	Diels–Alder
C_{15}	cyclic stereocontrol	Diels–Alder
C_{16}	cyclic-chelate	SAMP hydrazone
C_{19}	cyclic stereocontrol	Diels–Alder
C_{20}	cyclic stereocontrol	Diels–Alder

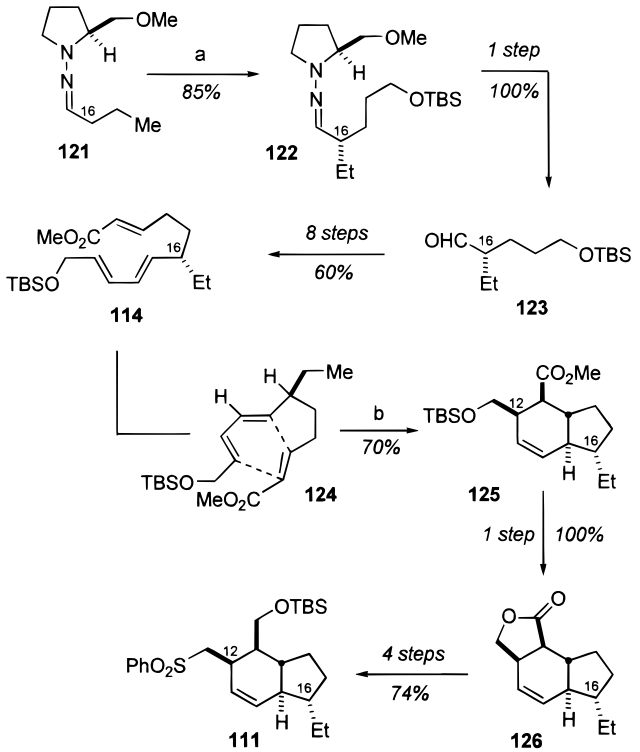
1. Synthesis of the C_1–C_{10} Fragment

The (*R*,*R*)-epoxide **115**, readily prepared in 75% overall yield from (−)-diethyl tartrate, was employed as the starting material for a convergent synthesis of the C_1–C_4 and C_5–C_8 fragments **112** and **113**, respectively (Scheme 29). Wittig reaction of aldehyde **112** with phosphonium salt **113** afforded olefin **116** in 77% yield (*E*:*Z* = 2:1). Since the double bond was hydrogenated later both isomers were carried forward. Treatment of epoxide **117**, generated in five steps from **116**, with CSA effected the critical ring-closure reaction with complete regio- and stereoselectivity and inversion of the epoxide C_7 stereocenter. Oxidation of the intermediate C_8-hydroxymethyl compound provided C_7 aldehyde **118** in 76% yield. The aldehyde was converted into ethyl ketone **119** in four steps and 72% yield. Introduction of the C_9–C_{10} two carbon fragment was achieved by treatment of **119** with vinylmagnesium bromide. The vinyl alcohol **120** was treated with phosphorus tribromide to provide *E*-allylic bromide **110** in 65% yield by a 1,3-rearrangement. The synthesis of the C_1–C_{10} fragment was completed in 31 steps and 3% overall yield from **115**.

2. Synthesis of the C_{11}–C_{21} Fragment

Asymmetric alkylation of aldehydes using optically active SAMP hydrazones, methodology developed by Enders, was employed to introduce the C_{16} ethyl group (Scheme 30).[27] The key intramolecular Diels–Alder reaction was performed by conversion of triene **114** to bicycle **125** by heat in 70% yield. In the Diels–Alder reaction transition state **124** was favored. Deprotection, followed by lactonization, afforded **126**, which was converted into the sulfone **111** prior to the final coupling reaction. The C_{11}–C_{21} fragment was completed in 16 steps and 26% overall yield.

Scheme 30[a]

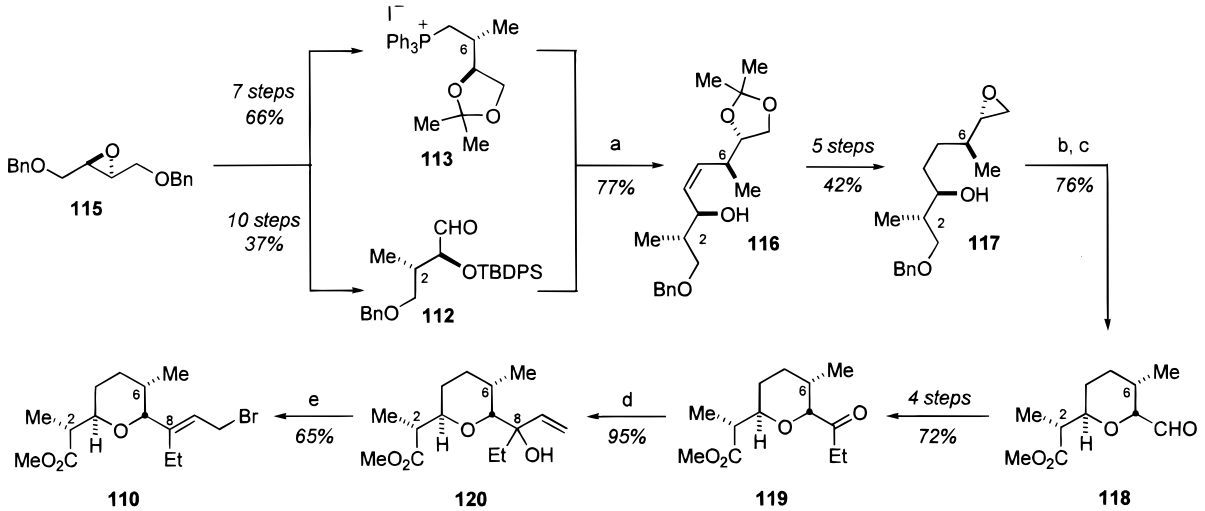


[a] (a) LDA, Et_2O, −78 °C, $I(CH_2)_3OTBS$, 0 °C; (b) PhMe, sealed tube, 130 °C.

3. Fragment Coupling—Julia Olefination

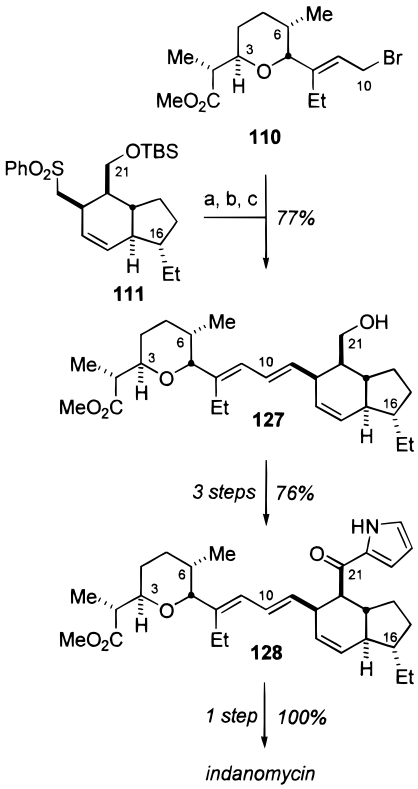
Coupling of bromide **110** with the anion of sulfone **111** was extremely efficient and stereoselective, affording a 10:1 ratio of sulfone diastereomers, which on elimination with Triton B generated the C_{10}–C_{11}

Scheme 29[a]



[a] (a) NaH, DMSO, rt; (b) CSA (cat), CH_2Cl_2, 25 °C; (c) CrO_3·pyr·HCl, NaOAc, CH_2Cl_2; (d) VinylMgBr, THF, −78 °C; (e) PBr_3, Et_2O, −10 °C.

Scheme 31[a]



[a] (a) LDA, THF, −78 °C; (b) 40% Triton B, MeOH, 45 °C; (c) CH_2N_2, Et_2O, 0 °C.

double bond with concomitant deprotection of the hydroxyl and ester groups. Hydrolysis of the methyl ester presumably protects the molecule from potential epimerization of C_2 and cleavage of the tetrahydropyran ring (Scheme 31).

The final steps of the synthesis involved incorporation of the 2-ketopyrrole moiety to **127** by oxidation of C_{21}, activation of the carboxylic acid as its 2-pyridyl ester, and addition of the anion of pyrrole. The methyl ester of indanomycin **128** was obtained in 76% overall yield from **127**. Careful saponification of **128** afforded enantiomerically pure indanomycin in quantitative yield.[28]

G. 1981, Narasin and Salinomycin (Kishi)

For the syntheses of narasin and salinomycin, Kishi used a palette of complimentary methods for the synthesis of propionate fragments from acyclic precursors using hydroboration, epoxidation of bis-homoallylic alcohols, and Sharpless asymmetric epoxidation.[29] In the retrosynthesis of narasin, aldol disconnection of the C_9-C_{10} bond afforded fragments **129** and **130**. Fragment **130** was further disconnected to **133**, **134**, and **135**. The $C_{21}-C_{30}$ fragment **135** resembled the $C_{12}-C_{24}$ lasalocid A fragment described previously. The spiroketal stereochemistry of both narasin and salinomycin was shown in model systems to adopt the desired relative stereochemistry. Kishi proposed that a hydrogen bond stabilizes the spiroketal despite the two C−O bonds being in the less thermodynamically stable conformation (Scheme 32).[30] The stereochemical inventory for Kishi's synthesis of narasin is summarized in Table 7.

1. Synthesis of the Narasin C_1–C_9 Fragment

The C_1-C_9 fragment **131** was prepared entirely from acyclic precursors (Scheme 33). The absolute stereochemistry was derived from **136**. Epoxidation of *cis*-olefin **137** provided epoxide **139** as a single stereoisomer through conformer **138**. Although open-

Scheme 32

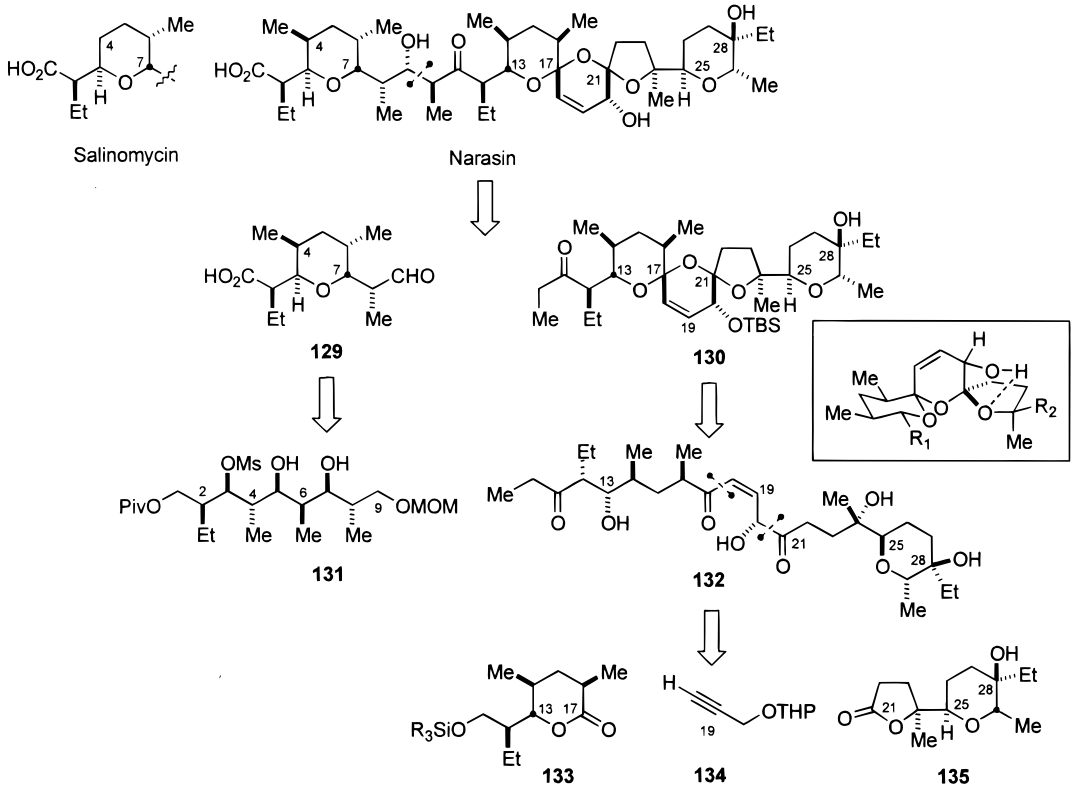


Table 7. Stereochemical Inventory for Kishi's Synthesis of Narasin

carbon	control element	reaction/source
C_2	A-1,3	epoxidation
C_3	A-1,3	epoxidation
C_4	chiral pool	(+)-3-hydroxypropanoic acid
C_6	A-1,3	epoxidation
C_7	A-1,3	Sharpless AE
C_8	A-1,3	Sharpless AE
C_9	Cram addn	aldol/Mg enolate
C_{10}	Cram addn	aldol/Mg enolate
C_{12}	A-1,3	epoxidation
C_{13}	A-1,3	epoxidation
C_{14}	chiral pool	(+)−3-hydroxypropanoic acid
C_{16}	A-1,3	epoxidation
C_{17}	thermodynamic	equilibration
C_{20}	nonselective	alkylithium addn
C_{21}	thermodynamic	equilibration
C_{24}	Cram-chelate	Grignard addn
C_{25}	directed reduction	hydride addn
C_{28}	A-1,3	epoxidation
C_{29}	A-1,3	epoxidation

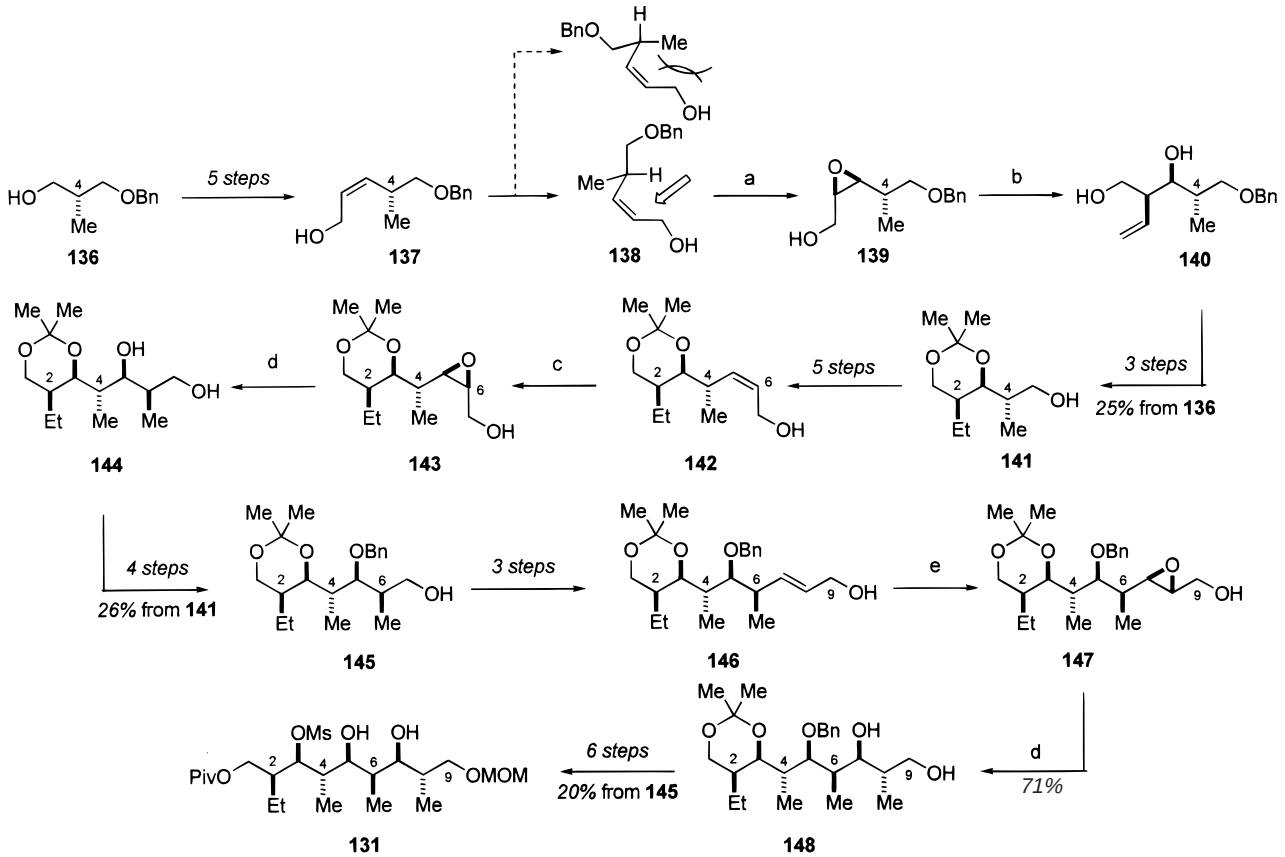
ing of epoxide **139** with EtMgBr occurred with good regio- and stereoselectivity, the yield was unsatisfactory. However, treatment of **139** with vinylmagnesium bromide provided **140** in excellent yield. Protecting-group manipulation and reduction of the C_2 vinyl group provided alcohol **141** in three steps and 25% overall yield from **136**. Conversion of **141** to olefin **142** followed by epoxidation with *m*-CPBA generated epoxide **143**. Opening of epoxide **143** with dimethyl cuprate provided **144** with excellent regio- and stereoselectivity. Following protecting-group manipulation, **145** was isolated in 26% overall yield from **141**. Olefination of **145** provided *trans*-olefin **146**, which was converted by Sharpless asymmetric epoxidation to **147** as a 20:1 mixture of epoxides. Treatment of **147** with dimethyl cuprate provided **148** in 71% and 4:1 regioselectivity. Protecting-group manipulation gave the completed C_1-C_9 fragment in eleven steps and 20% overall yield from **145**.[31] Kishi utilized the Sharpless asymmetric epoxidation reaction for the first time in the total synthesis of a polyether ionophore to prepare the C_1-C_9 fragment of narasin and salinomycin. Subsequent syntheses of polyether ionophores made frequent use of this powerful reaction (vide infra).

Reaction of mesylate **131** with KH provided the A-ring cyclization product **149** in 45% yield, along with C_2-C_3 and C_3-C_4 elimination products (Scheme 34). Deoxygenation of the C_5 hydroxyl using Barton's method provided the narasin A-ring tetrahydropyran **150**. Conversion of **150** to the C_1-C_9 fragment **129** was completed in four steps and approximately 50% yield.[32]

2. Synthesis of the C_{10}–C_{30} Fragment

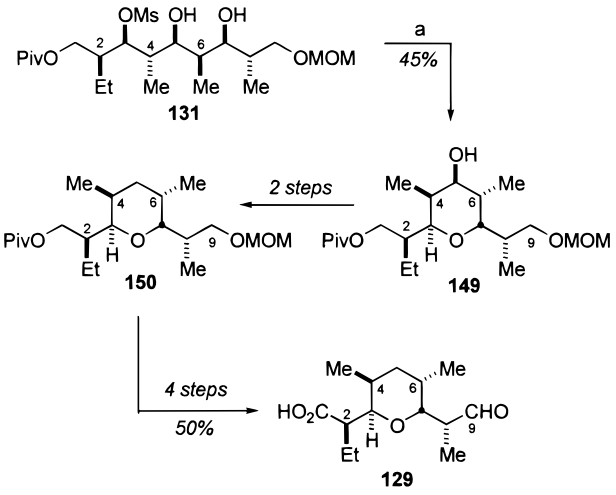
The narasin and salinomycin $C_{21}-C_{30}$ fragment **135** was prepared using the methods described in the synthesis of the lasalocid A $C_{15}-C_{24}$ fragment.[33] Lactone **135** was converted to dithiane **151** in three steps and 76% yield (Scheme 35). Lactone **133** was prepared using the methods described in the synthesis of the C_1-C_{10} fragment (Scheme 33). Aldehyde

Scheme 33[a]



[a] (a) *m*-CPBA, CH_2Cl_2, −78 °C; (b) VinylMgBr, CuI, Et_2O; (c) *m*-CPBA, CH_2Cl_2, 0 °C; (d) $LiCuMe_2$, Et_2O −40 °C; (e) *t*-BuOOH, Ti(O-*i*-Pr)$_4$, diethyl-D-tartrate, −23 °C. (Reprinted with permission from ref 29a. Copyright 1982 Elsevier Sciences Ltd.)

Scheme 34[a]



[a] (a) KH, hex/PhMe, 0 °C.

152 was prepared from **133** in three steps and 92% yield as a 3:1 mixture of β- and α-glycosides. The glycosides were separated and carried through the remainder of the synthesis separately. Aldehyde **152** was treated with the dithiane anion of **151** to provide 37% of the desired C_{20} alcohol epimer **153** and 48% of the undesired C_{20} alcohol. The undesired epimer was recycled to the desired alcohol **153** in 38% yield by oxidation to the C_{20} ketone followed by reduction with $NaBH_4$. Conversion of **153** to **154** proceeded by dethioketalization, intramolecular ketalization of the C_{21} and C_{24} centers, and acetylation of the C_{20} alcohol in 46% overall yield. Both C_{17} α- and β- glycosides provided the same C_{17} stereochemistry. Kishi postulated that equilibration must have occurred in the presence of *p*-TsOH. The acetylenic bond was reduced using Lindlar's catalyst to provide **154**. Bis-spiroketalization in HOAc provided a single isomer of **155** (epimeric at C_{17} with natural narasin and salinomycin) in 21% overall yield from **153**. Finally, deprotection of the silyl protecting group, oxidation of C_{11}, and addition of EtMgBr converted **155** to the completed C_{11}−C_{29} fragment **130**.

3. Fragment Coupling—The Aldol Reaction

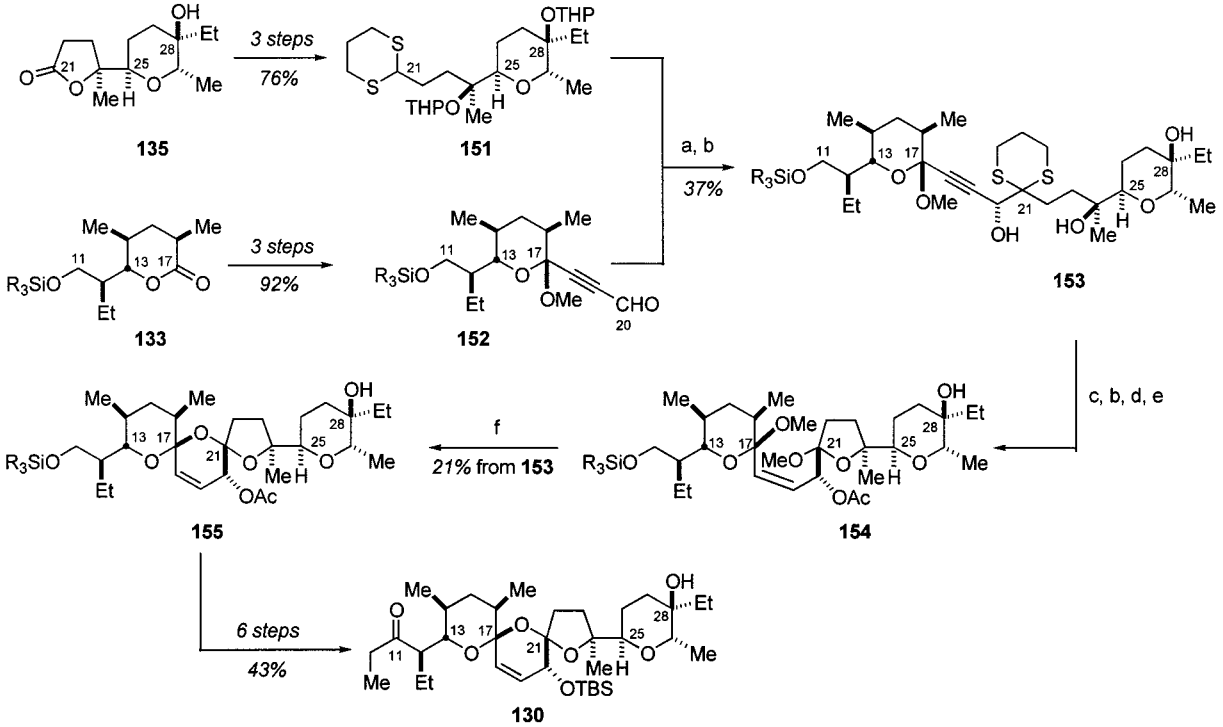
Aldol coupling of fragments **129** and **130** using dicyclohexylaminomagnesium bromide provided, after desilylation, a single isomer of **157** corresponding to *epi*-(C_{17})-narasin (Scheme 36). As in Kishi's lasalocid A synthesis, the stereochemical result of the aldol reaction was explained by Cram approach of the *Z*-enolate **156** to aldehyde **129**. Treatment of **157** with TFA afforded a 7:1 mixture of narasin and **157** in 91% yield. Salinomycin was synthesized similarly using the corresponding C_4-unsubstituted tetrahydropyran in the aldol fragment coupling reaction.

H. 1982, Calcimycin (Grieco)

In analogy to Evans, Grieco reported a synthesis of calcimycin[34] that generated the 1,7-dioxaspiro[5,5]-undecane ring system under thermodynamic control. The benzoxazole **83** was incorporated by Cram addition to the C_{10} aldehyde (Scheme 37). However, the pyrrole group was introduced by addition of the 2-lithio anion of **159** to the C_{20} aldehyde. Therefore, a key target in Grieco's approach to calcimycin was the synthesis of the C_{10}−C_{20} acyclic fragment **160**. The stereochemical inventory for Grieco's synthesis of calcimycin is summarized in Table 8.

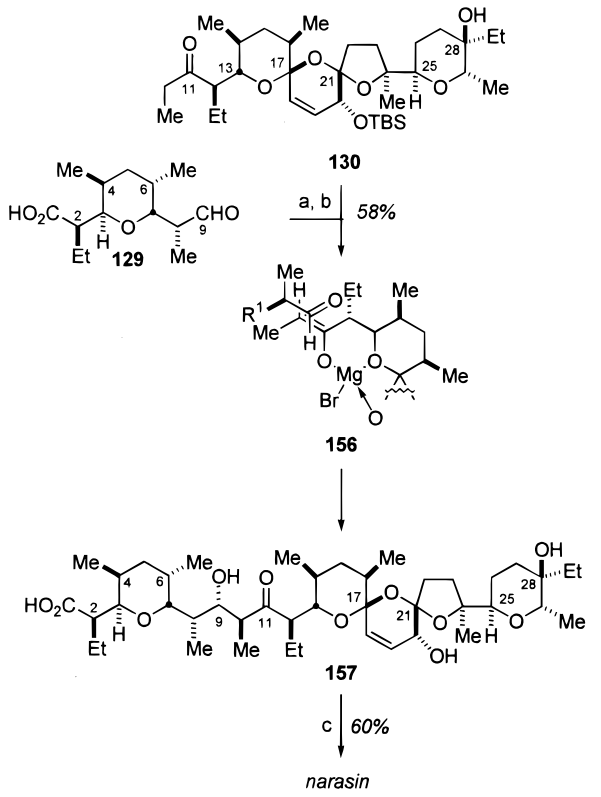
The C_{10}−C_{20} fragment **160** was prepared from bicyclo[2.2.1]heptane **161** by a series of oxidations

Scheme 35[a]



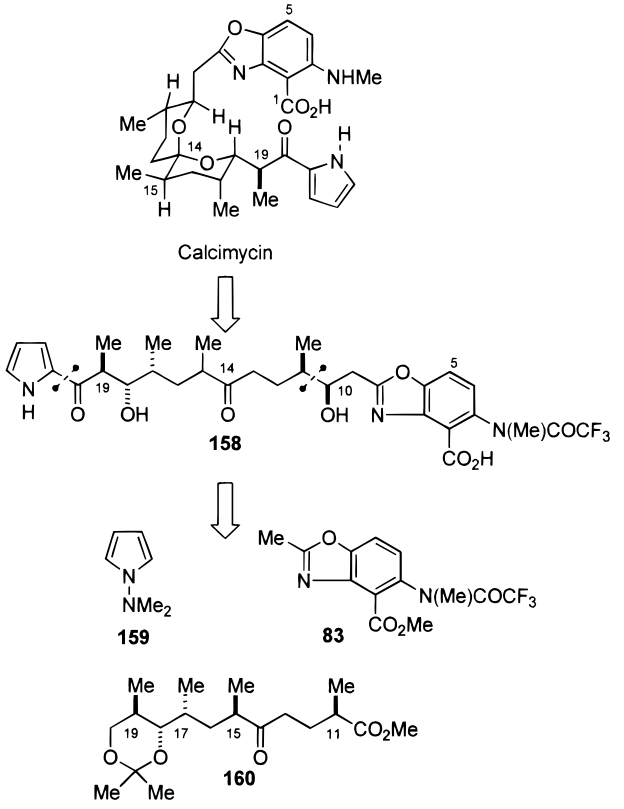
[a] (a) *n*-BuLi, THF, −20 °C; (b) *p*-TsOH, MeOH, rt; (c) NCS, MeOH, rt; (d) Ac_2O, pyr, rt; (e) H_2, Lindlar's cat., MeOH; (f) 80% HOAc, rt. (Reprinted with permission from ref 29a. Copyright 1982 Elsevier Sciences Ltd.)

Scheme 36[a]



[a] (a) $(C_6H_{11})_2NMgBr$, THF, −50 °C; (b) TBAF, THF, rt; (c) TFA, CH_2Cl_2, 3 Å sieves. (Reprinted with permission from ref 29a. Copyright 1982 Elsevier Sciences Ltd.)

Scheme 37



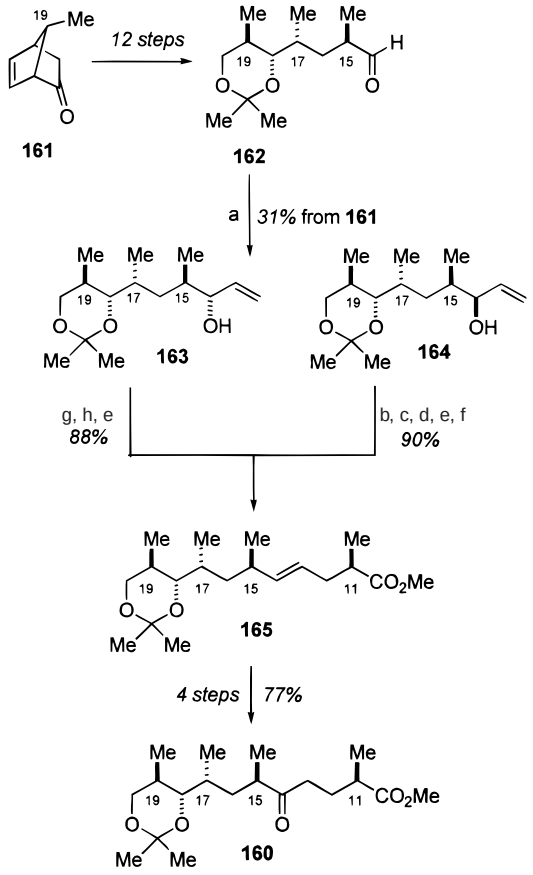
and 1−3 carbon addition reactions (Scheme 38). Cyclic stereocontrol was employed to introduce the C_{15}−C_{19} stereocenters. Addition of vinylmagnesium bromide to aldehyde **162** generated a 2:1 mixture of allylic alcohols **163** and **164** in 31% yield from **161**, favoring the Cram product. Each isomer was separately elaborated to methyl ester **165** using an ester−enolate Claisen rearrangement. In analogy to Ireland's synthesis of lasalocid A, solvent effects were employed to control the enolate geometry in the formation of the silyl ketene acetal of each alcohol diastereomer. Transformation of **165** into **160** was completed in 77% yield by bishydroxylation of the C_{13}−C_{14} olefin, oxidation, reductive cleavage of the C_{13} oxygen bond, and esterification.

The synthesis was completed by introduction of the benzoxazole and pyrrole groups followed by spiroketalization (Scheme 39). Conversion of ketone **160** into the corresponding ketal **166** followed by protecting-group manipulation generated the differentially protected diol **167** in four steps and 88% yield. Formation of the C_{20} aldehyde, condensation with 2-lithio-*N*-(*N*,*N*-dimethylamino)pyrrole, and oxidation gave

Table 8. Stereochemical Inventory for Grieco's Synthesis of Calcimycin

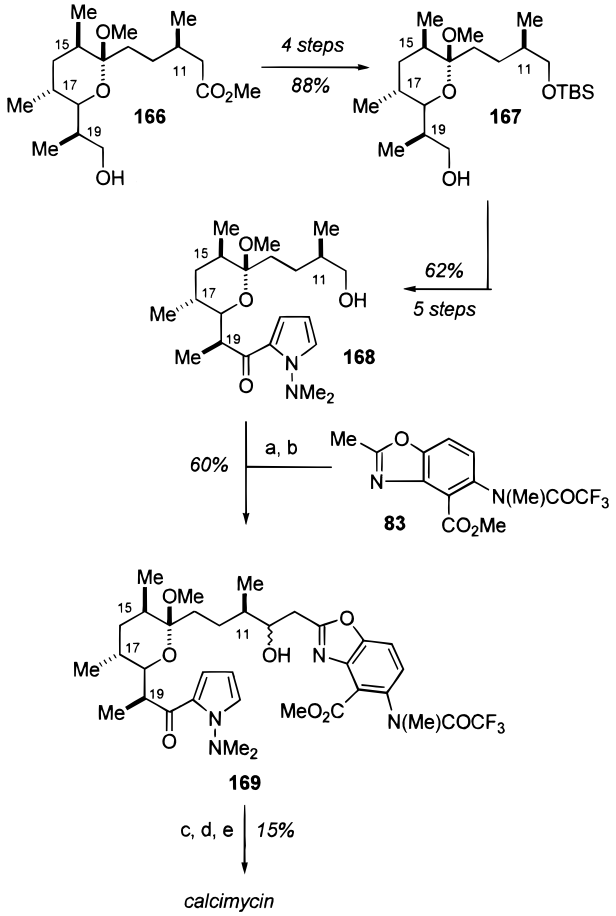
carbon	control element	reaction/source
C_{10}	Cram addn	organolithium addn
C_{11}	cyclic stereocontrol	Claisen rearrangement
C_{15}	thermodynamic	equilibration
C_{17}	cyclic stereocontrol	bicyclo[2.2.1]heptane
C_{18}	cyclic stereocontrol	bicyclo[2.2.1]heptane
C_{19}	cyclic stereocontrol	bicyclo[2.2.1]heptane

Scheme 38[a]



[a] (a) VinylMgBr, THF, −78 °C; (b) C_2H_5COCl, pyr; (c) LDA, THF, −78 °C; (d) TBSCl, HMPA, reflux; (e) TBAF; (f) CH_2N_2, Et_2O; (g) LDA, THF, HMPA, −78 °C; (h) TBSCl, HMPA, reflux.

Scheme 39[a]



[a] (a) CrO_3·2pyr, CH_2Cl_2, 0 °C; (b) LDA, THF, −100 °C; (c) CSA, CH_2Cl_2, −15 °C; (d) $Cr_2(OAc)_4$·$2H_2O$, EtOH; (e) K_2CO_3, MeOH.

168 in 62% overall yield. In a similar manner, oxidation of the alcohol at C_{10} to the aldehyde and condensation with the lithium anion of methyl benzoxazole afforded alcohol **169** in 60% yield. Acid-catalyzed equilibration of **169**, followed by reductive cleavage of the dimethylamino group, yielded the thermodynamically more stable dioxaspirane of calcimycin in 15% yield.

I. 1983, Indanomycin (Ley)

As in Nicolaou's approach to indanomycin, Ley's retrosynthesis disconnected the C_{10}−C_{11} bond to afford fragments **170** and **171**. The tetrahydroindan ring **171** was prepared through **126**. However, in contrast to Nicolaou, the final coupling was performed with the ketopyrrole group present on the tetrahydroindan ring (Scheme 40).[35] The stereochemical inventory for Ley's synthesis of indanomycin is summarized in Table 9.

1. Synthesis of the C_1–C_{10} Fragment

Ester−enolate Claisen rearrangement of *E*-ketene acetal **173**, derived from laevoglucosan **172** in six steps and 60% yield, proceeded through the boat transition state **174** to afford **175** as a 5:1 mixture of C_2 epimers in 73% yield (Scheme 41). Inversion of the C_7 stereochemistry was achieved by hydroboration of exocyclic enol ether **176** with borane. Using

Scheme 40

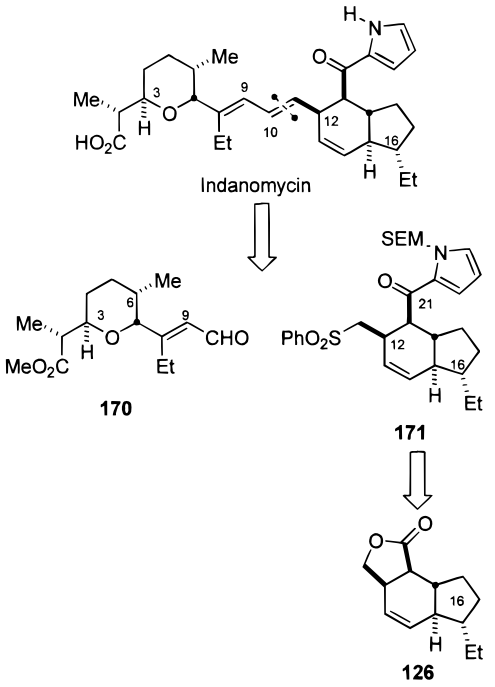


Table 9. Stereochemical Inventory for Ley's Synthesis of Indanomycin

carbon	control element	reaction/source
C_2	cyclic stereocontrol	ester−enolate Claisen
C_3	cyclic stereocontrol	ester−enolate Claisen
C_6	chiral pool	laevoglucosan
C_7	cyclic stereocontrol	hydroboration
C_{12}	cyclic stereocontrol/ resolution	Diels−Alder/α-methyl-benzylamine
C_{15}	cyclic stereocontrol/ resolution	Diels−Alder/α-methyl-benzylamine
C_{16}	cyclic stereocontrol/ resolution	Diels−Alder/α-methyl-benzylamine
C_{19}	cyclic stereocontrol/ resolution	Diels−Alder/α-methyl-benzylamine
C_{20}	cyclic stereocontrol/ resolution	Diels−Alder/α-methyl-benzylamine

methodology developed by Nicolaou, enal **170** was prepared by conversion of **177** to ethyl ketone **119**, followed by addition of vinylmagnesium bromide and oxidative rearrangement with PCC. Synthesis of the C_1−C_{10} fragment **170** was completed in 16 steps and 4% overall yield from laevoglucosan.

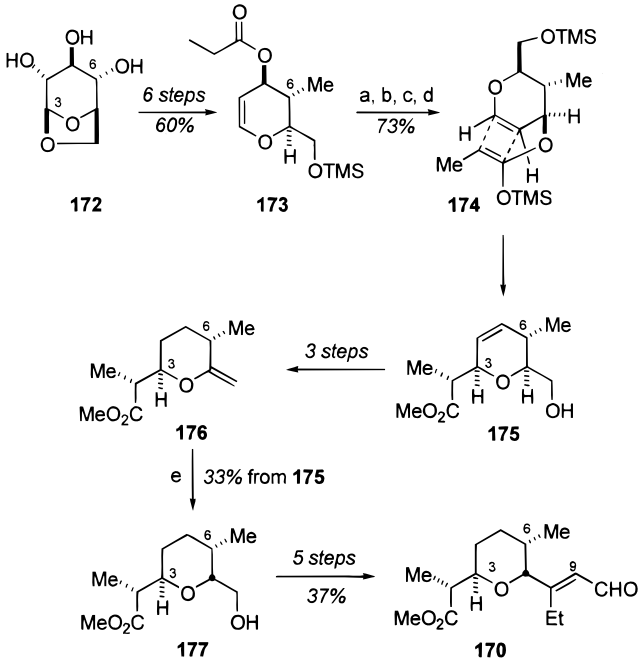
2. Synthesis of the C_{11}–C_{21} Fragment

Tricyclic lactone **126** was prepared from δ-valerolactone **178** and resolved with (*S*)-α-methylbenzylamine (Scheme 42). Introduction of the pyrrole moiety, followed by formation of the phenyl sulfone, completed the synthesis of the SEM-protected derivative **171** in 14 steps and 7% overall yield.

3. Fragment Coupling—Julia Olefination

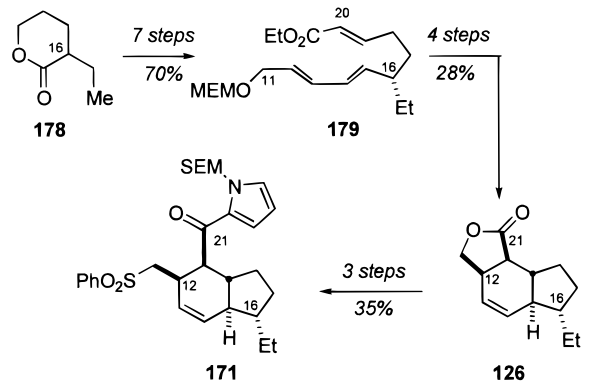
Coupling of fragments **170** and **171** was achieved by the Lythgoe−Kocienski modification of the Julia reaction (Scheme 43).[36] Treatment of **171** with *n*-BuLi and reaction with enal **170** provided, after treatment with benzoyl chloride, the diastereomeric benzoyloxy sulfones **180**. Stereospecific reduction with sodium-

Scheme 41[a]



[a] (a) LDA, THF, −50 °C; (b) TMSCl, Et_3N, THF, 50 °C; (c) TBAF; (d) CH_2N_2; (e) BH_3·THF, NaOH, H_2O_2. (Reprinted with permission from ref 35b. Copyright 1983 Royal Society of Chemistry.)

Scheme 42



amalgam, removal of the SEM protecting group, and hydrolysis of the methyl ester gave indanomycin in 34% yield.

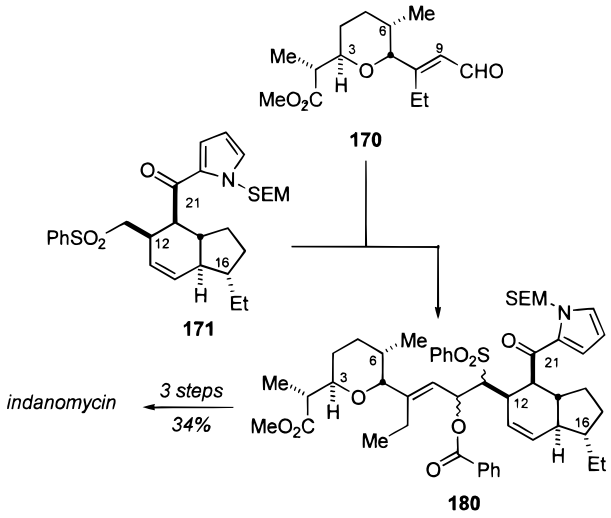
J. 1984, Indanomycin (Roush)

In contrast to the approach of Nicolaou and Ley, Roush disconnected the C_{12}−C_{20} bond of indanomycin by an intramolecular Diels−Alder reaction to afford pentaene **181**.[37] Further disconnection of the C_{10}−C_{11} and C_{19}−C_{20} bonds of **181** by Wittig chemistry yielded fragments **170**, **182**, and **183** (Scheme 44). The stereochemical inventory for Roush's synthesis of indanomycin is summarized in Table 10.

1. Synthesis of the C_{11}–C_{19} Fragment

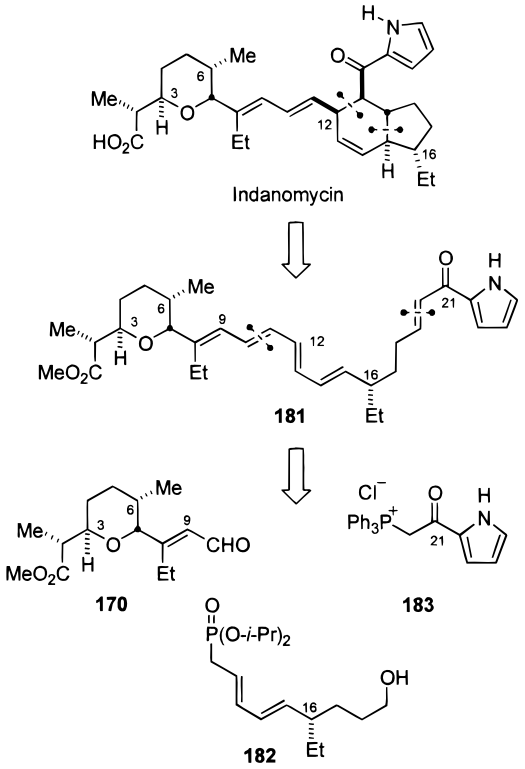
Addition of *Z*-crotylboronate (**185**), derived from acetylene **184**, to D-glyceraldehyde acetonide (**186**) afforded **188** in 55% yield as a 10:1 mixture of stereoisomers (Scheme 45). The stereochemical outcome of this reaction was influenced by steric rather than stereoelectronic effects.[38] The reaction proceeded

Scheme 43[a]



[a] Reprinted with permission from ref 35b. Copyright 1983 Royal Society of Chemistry.

Scheme 44[a]



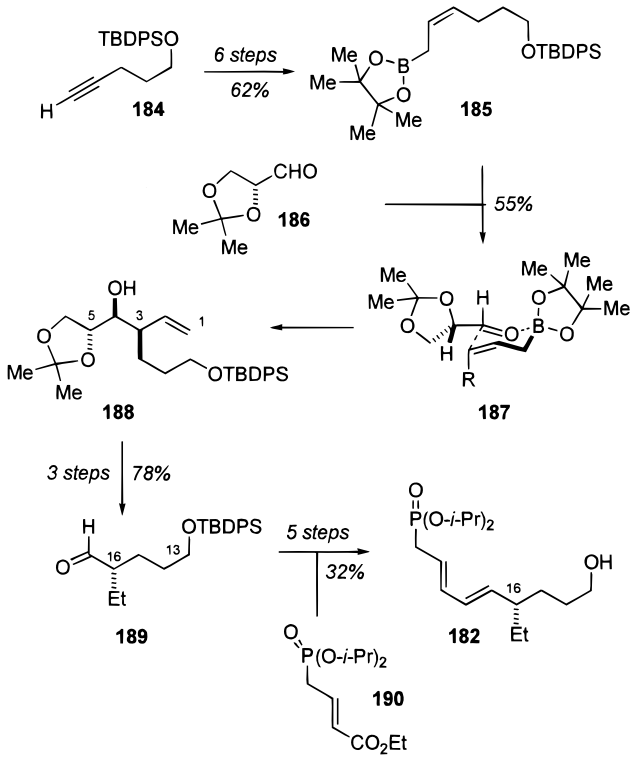
[a] Reprinted with permission from ref 37b. Copyright 1982 Elsevier Sciences Ltd.

through transition state **187** containing fewer nonbonded interactions between the olefinic substituents and the aldehydic C_2 or C_3 substituent. Reduction of the vinyl group with diimide, hydrolysis of the acetonide, and cleavage of the resulting triol afforded aldehyde **189** containing the C_{16} ethyl group in 78% yield. Wittig reaction of **189** with the lithium anion of triethyl 4-phosphonocrotonate (**190**) afforded a diene ester that was reduced directly with $LiAlH_4$ and converted into phosphonate **182** in 32% overall yield. The synthesis of this fragment represented the first reported method to prepare α-chiral aldehydes

Table 10. Stereochemical Inventory for Roush's Synthesis of Indanomycin

carbon	control element	reaction/source
C_2	indanomycin	degradation
C_3	indanomycin	degradation
C_6	indanomycin	degradation
C_7	indanomycin	degradation
C_{12}	cyclic stereocontrol	Diels−Alder
C_{15}	cyclic stereocontrol	Diels−Alder
C_{16}	Cram-chelate	chiral crotyl borane
C_{19}	cyclic stereocontrol	Diels−Alder
C_{20}	cyclic stereocontrol	Diels−Alder

Scheme 45

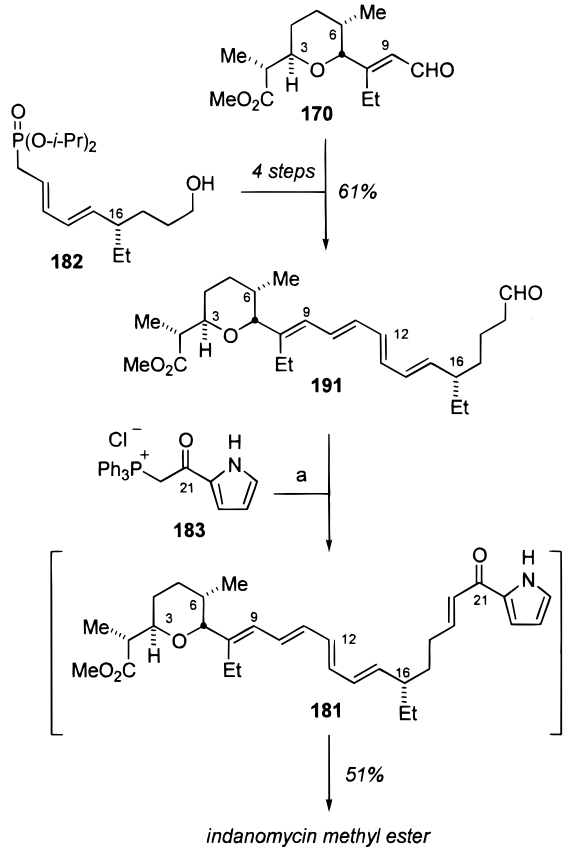


by addition of crotylboronates to α,β-dialkoxy aldehydes.

2. Fragment Coupling—Diels–Alder Reaction

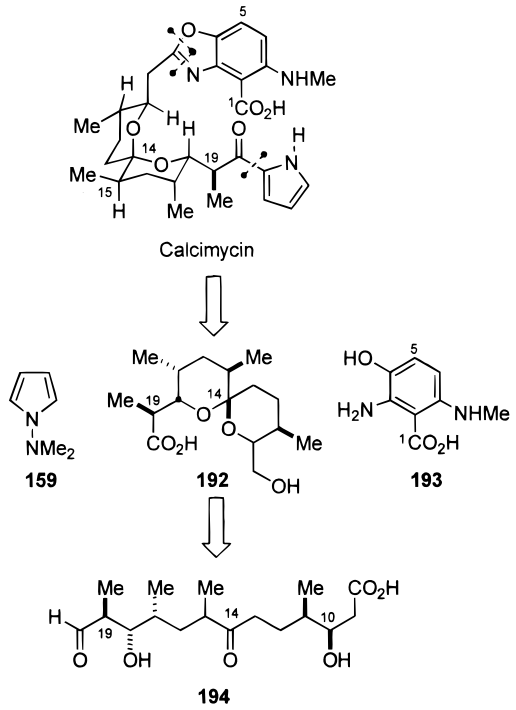
Treatment of enal **170**, prepared by degradation of the natural product (using the procedure established by Nicolaou), and phosphonate **182** with *t*-BuOK gave the corresponding tetraene in 83% yield as an 11:1 mixture of olefin isomers. Swern oxidation of the C_{19} alcohol afforded **191** in 61% yield from **170**. Wittig reaction of **191** with phosphorane **183** afforded the methyl ester of indanomycin in 51% yield along with 5% of the $C_{10}-C_{11}$ *Z*-olefin and 5% of the *cis*-fused cycloadducts (Scheme 46). The transition state for the Diels−Alder reaction is analogous to that reported by Nicolaou.

Scheme 46[a]



[a] (a) $ClCH_2CH_2Cl$, 3 d, 40 °C.

Scheme 47



K. 1986, Calcimycin (Ogawa)

Ogawa developed a synthesis of calcimycin that, in analogy to Evans, performed the spiroketalization under thermodynamic control with concurrent equilibration of the C_{15} stereocenter (Scheme 47).[39] The pyrrole group was introduced using the 2-pyridyl thioester Chemistry as previously reported by Nicolaou in the synthesis of indanomycin. The benzoxazole group was introduced by condensation of amino phenol **193** with the C_8 carboxylic acid **192**. The spiroketal was further disconnected to **194**. The

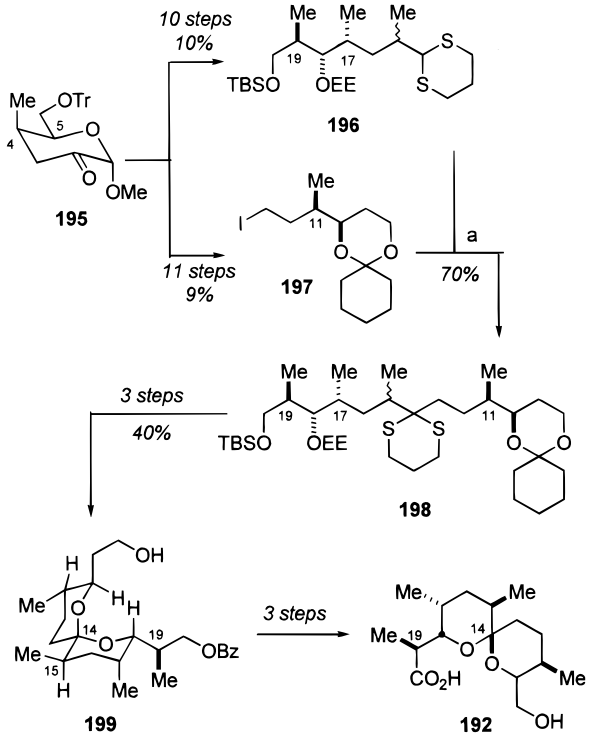
Table 11. Stereochemical Inventory for Ogawa's Synthesis of Calcimycin

carbon	control element	reaction/source
C_{10}	chiral pool	D-glucose
C_{11}	chiral pool	D-glucose
C_{15}	thermodynamic	equilibration
C_{17}	chiral pool	D-glucose
C_{18}	chiral pool	D-glucose
C_{19}	chiral pool	D-glucose

stereochemical inventory for Ogawa's synthesis of calcimycin is summarized in Table 11.

The absolute stereochemistry of the core acyclic C_8-C_{20} unit **194** was derived from the chiral pool. The carbohydrate template **195**, derived from D-glucose, was employed to prepare fragments **196** and **197**, since the (4*R*,5*S*) configuration is identical to that at C_{10},C_{11} and C_{17},C_{18} in calcimycin (Scheme 48).

Scheme 48[a]



[a] (a) *n*-BuLi, HMPA. (Reprinted with permission from ref 39a. Copyright 1986 Elsevier Sciences Ltd.)

Coupling of **196** with **197** followed by protecting-group manipulation of **198** and thermodynamic spiroketal formation provided **199** in 40% yield. Further protecting-group manipulation provided the completed spiroketal **192**. Introduction of the pyrrole and formation of the benzoxazole provided calcimycin.

L. 1986, Indanomycin (Boeckman)

In analogy to Roush, Boeckman disconnected the $C_{19}-C_{20}$ bond of indanomycin by an intramolecular Diels–Alder reaction to reveal pentaene **200** with C_1 at the alcohol oxidation state.[40] Further disconnection of the $C_{10}-C_{11}$ and $C_{19}-C_{20}$ bonds of **200** by Wittig chemistry afforded fragments **201**, **202**, and **183** (Scheme 49). The stereochemical inventory for Boeckman's synthesis of indanomycin is summarized in Table 12.

Scheme 49

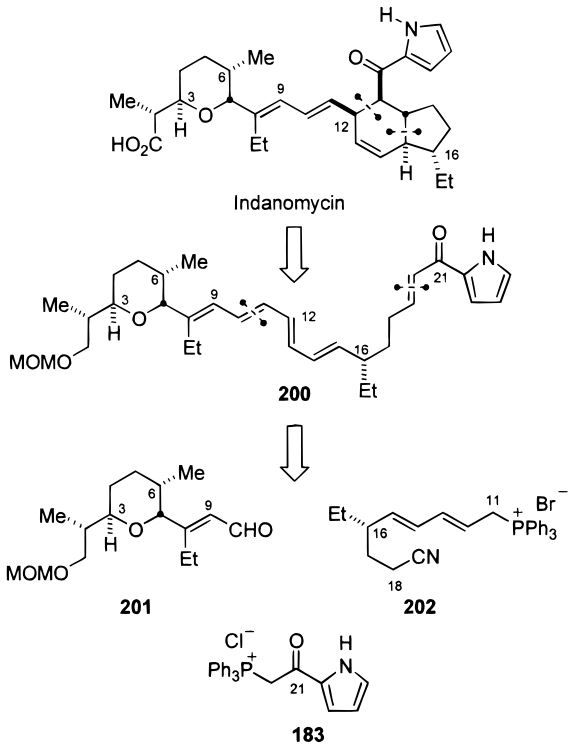


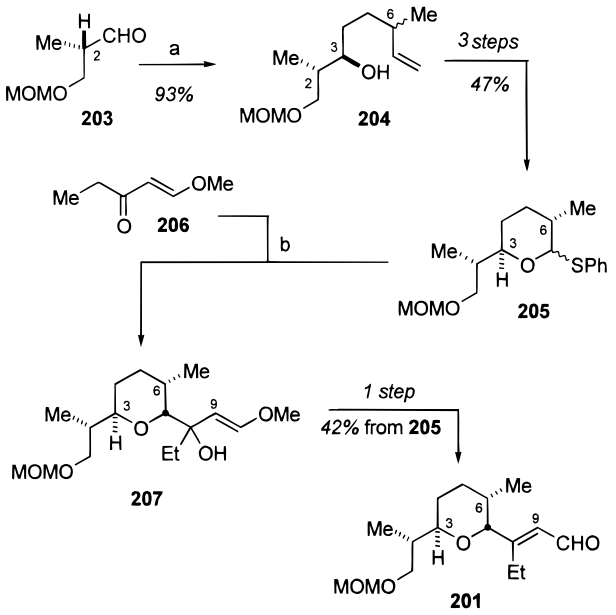
Table 12. Stereochemical Inventory for Boeckman's Synthesis of Indanomycin

carbon	control element	reaction/source
C_2	chiral pool	methyl-(*R*)-(+)-hydroxy-2-methyl propionate
C_3	Cram-chelate	organocuprate addn
C_6	thermodynamic	equilibration
C_7	radical anomeric effect	lithium 4,4′-di-*tert*-butylbiphenylide
C_{12}	cyclic stereocontrol	Diels–Alder
C_{15}	cyclic stereocontrol	Diels–Alder
C_{16}	cyclic stereocontrol	ester–enolate Claisen
C_{19}	cyclic stereocontrol	Diels–Alder
C_{20}	cyclic stereocontrol	Diels–Alder

1. Synthesis of the C_1–C_{10} Fragment

Aldehyde **203** was prepared in three steps and 73% yield from methyl-(*R*)-(+)-hydroxy-2-methyl propionate (Scheme 50). Cram-chelate addition of the lithium dialkylcuprate derived from 1-(bromomethyl)-4-pentene to aldehyde **203** afforded **204** as a 1:1 mixture of diastereomeric alcohols in 93% yield. Ozonolysis of **204** followed by base-catalyzed epimerization of the C_6 methyl group and formation of the thiolactol provided **205** as a 1:3 mixture of anomeric lactols in 47% overall yield from **204**. Reductive lithiation of **205** with lithium 4,4′-di-*tert*-butylbiphenylide generated only the configurationally stable axial lithiopyran. Reaction of the intermediate α-lithiopyran with 1-methoxy-1(*E*)-penten-3-one **(206)** afforded the 1,2-adduct **207** possessing the required axial appendage at C_7. Similar to the method of Nicolaou, treatment of **207** with catalytic PPTS afforded enal **201** in 42% yield as a 3:1 *E*:*Z* mixture of geometric isomers. The C_1-C_{10} fragment was

Scheme 50[a]



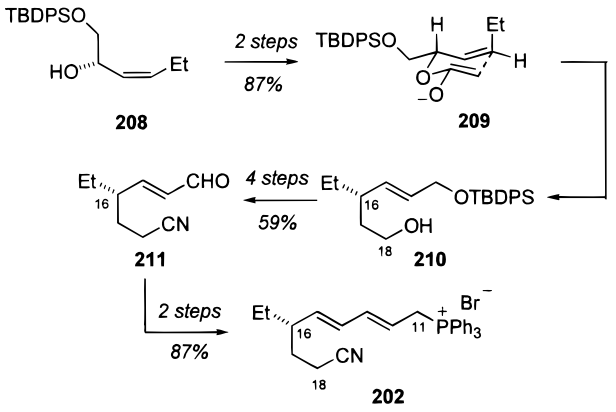
[a] (a) $LiCu[(CH_2)_2CHCH_3CH{=}CH_2)]_2$, Et_2O, −40 °C; (b) LiDBB, −78 °C.

completed in six steps and 18% overall yield from **203**.

2. Synthesis of the C_{11}–C_{19} Fragment

Orthoester Claisen rearrangement of monoprotected diol **208** with trimethylorthoacetate proceeded through transition state **209** to afford the *E*-olefinic alcohol **210** in 87% yield after ester reduction (Scheme 51). Conversion of the C_{18} alcohol to the corresponding nitrile, deprotection, and oxidation produced the α,β-unsaturated aldehyde **211** in 59% yield. Treatment of **211** with vinylmagnesium bromide and reaction with $Ph_3P{\cdot}HBr$ generated exclusively the (*E*,*E*)-dienylphosphonium salt **202** in 87% yield by S_N2' displacement.

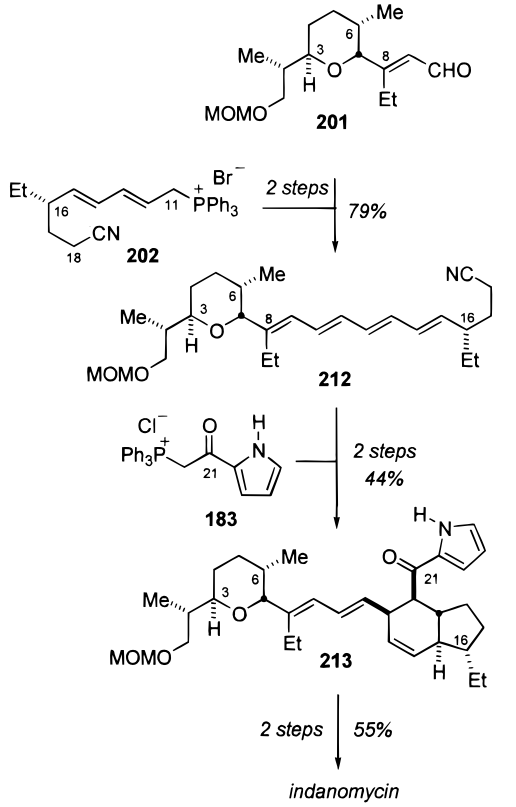
Scheme 51



3. Fragment Coupling—Diels–Alder Reaction

Wittig reaction of **201** with **202** produced a complex mixture of geometric isomers that were directly isomerized to the all-*trans*-tetraenenitrile **212** with I_2. Reduction of the C_{18} nitrile to the aldehyde, followed by treatment with phosphorane **183**, afforded the tetrahydroindan **213** in 44% yield. Deprotection, followed by oxidation of the C_1-alcohol, completed the synthesis of indanomycin in 55% yield from **213** (Scheme 52).

Scheme 52



M. 1987, Calcimycin (Kishi)

In contrast to the previous syntheses of calcimycin by Evans and Ogawa, Kishi employed kinetic control in the spiroketalization reaction.[41] This was achieved using acyclic precursor **214**, where the C_{10} stereocenter was replaced by a C_9−C_{10} double bond (Scheme 53). As in Evans' synthesis of calcimycin, Kishi proposed to introduce the pyrrole **82** by addition to the C_{18} aldehyde. The benzoxazole was introduced using phosphonate ester **216**. The stereochemical inventory for Kishi's synthesis of calcimycin is summarized in Table 13.

The absence of the C_{10} stereocenter facilitated a very rapid synthesis of **214**. The C_{11}, C_{15}, and C_{17} methyl-bearing stereocenters were introduced by cyclic stereocontrol using (*R*)-5-methyl-2-cyclohexen-1-one **(217)**. The benzoxazole moiety was introduced by Wittig reaction of phosphonate **216** with aldehyde **215** to provide **220** as a 19:1 mixture of *E*:*Z* olefins in 88% yield. Formation of the aldehyde at C_{18} and aldol reaction with the magnesium enolate of pyrrole **82** afforded the Cram addition product **214** as the predominant diastereomer in 61% yield (Scheme 54).

The kinetic spiroketalization reaction was performed using the *trans*-olefin **221**, although it was determined that the geometry of the olefinic bond does not alter the outcome of the reaction. Treatment of **221** with catalytic sodium methoxide afforded

Scheme 53

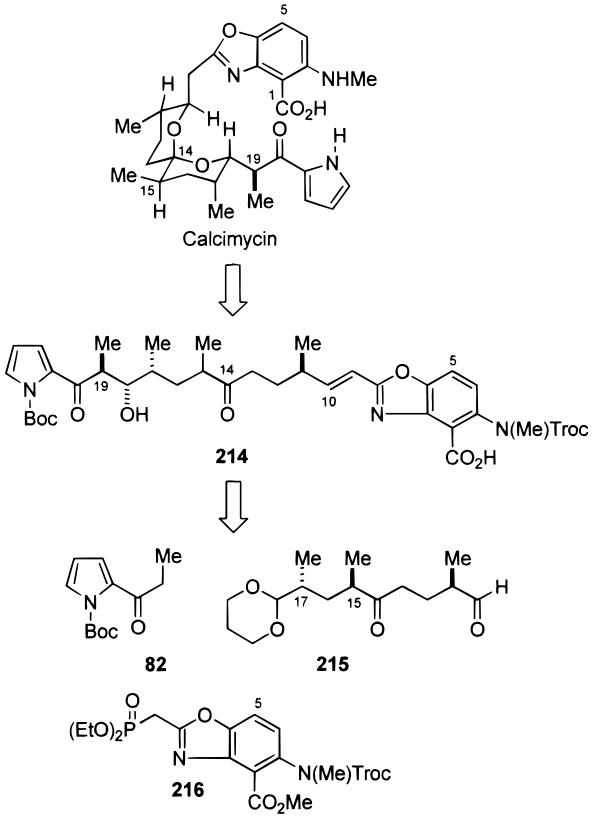


Table 13. Stereochemical Inventory for Kishi's Synthesis of Calcimycin

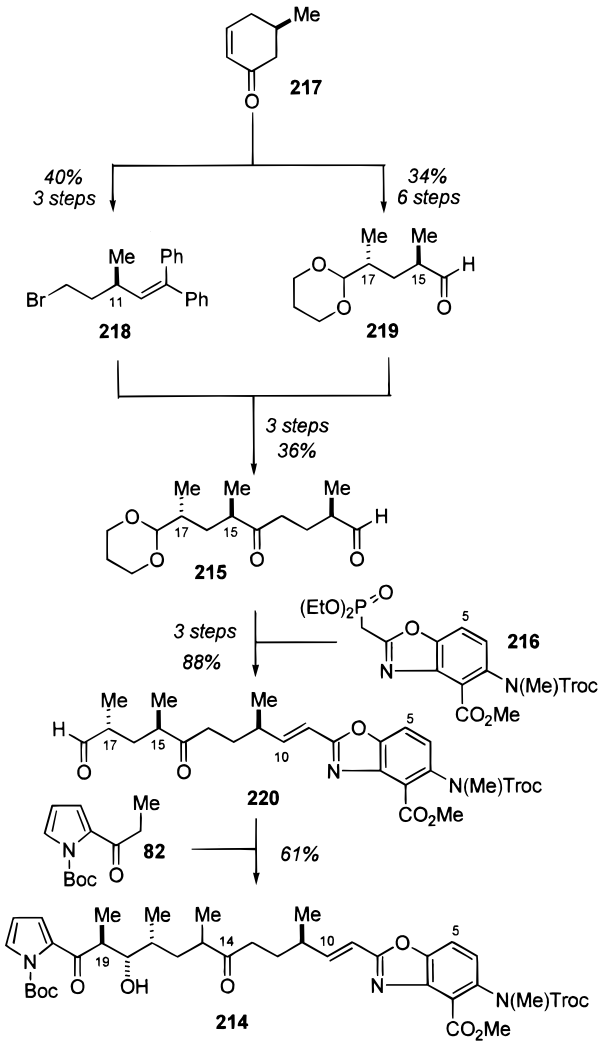
carbon	control element	reaction/source
C_{10}	kinetic	spiroketalization
C_{11}	chiral pool	(*R*)−5-methyl-2-cyclohexen-1-one
C_{15}	chiral pool	(*R*)−5-methyl-2-cyclohexen-1-one
C_{17}	chiral pool	(*R*)−5-methyl-2-cyclohexen-1-one
C_{18}	Cram-chelate	aldol/Mg enolate
C_{19}	Cram-chelate	aldol/Mg enolate

spiroketal **222**. Deprotection provided a 42% yield of the calcimycin methyl ester. Although four spiroketals are possible from the reaction, only **222** and **225** are probable due to severe destabilization of the other two isomers by 1,3-diaxial interactions (Scheme 55). During the ring-closure reaction the ratio of **223** and **224** at equilibrium should reflect their relative thermodynamic stability. Although the two spiroketals are structurally similar, **222** is stabilized by two anomeric effects but has an axial Me group at the C_{11} position whereas **225** is stabilized by only one anomeric effect and has an equatorial methyl group at the C_{11} position. Therefore, under the (kinetic) reaction conditions, the ratio of **223** and **224** should reflect the reaction rate for cyclization of **221** to form **222** or **225**.[42]

N. 1987, Calcimycin/Cezomycin (Boeckman)

Boeckman employed cyclic vinyl ether chemistry to prepare the calcimycin class of antibiotics.[43] His retrosynthetic approach was similar to that of Ogawa for incorporation of the pyrrole and benzoxazole on the spiroketal **226** (Scheme 56). Spiroketal **192** (C_{15} = Me) was derived from a tandem acid-catalyzed spirocyclization of cyclopropane **227**. Acid-catalyzed ring opening of the vinyl ether **228** was employed to prepare cezomycin (C_{15} = H). Vinyl ether **228** was further disconnected to **229** and **230**. The stereochemical inventory for Boeckman's synthesis of calcimycin is summarized in Table 14.

Scheme 54[a]



[a] Reprinted with permission from ref 41. Copyright 1987 Elsevier Sciences Ltd.

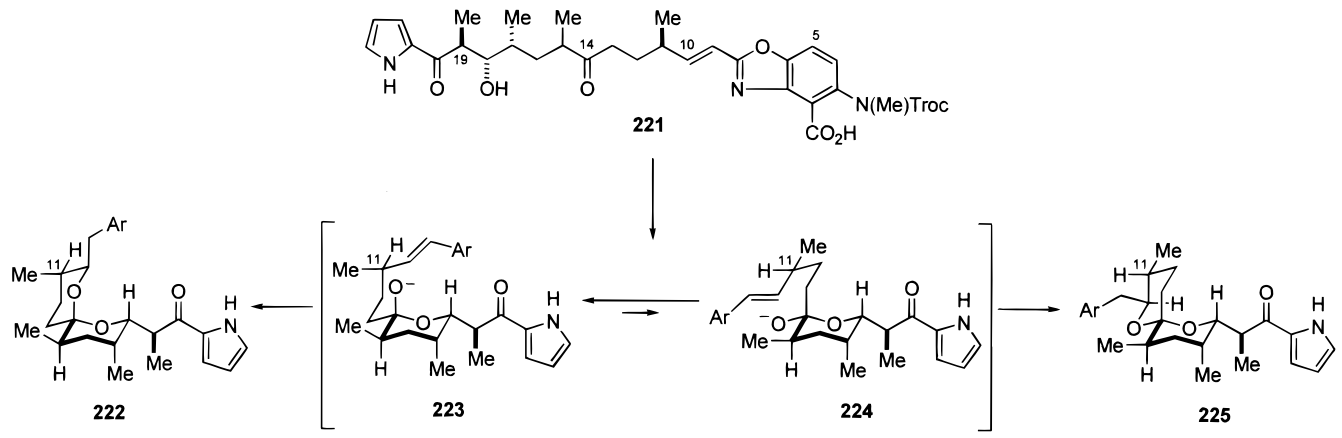
1. Synthesis of the C_8–C_{13} Fragment

Coupling of β-silyloxy aldehyde **232** with *Z*-crotyl diisopinocamphenylborane **(231)** afforded homoallylic alcohol **233** as a single diastereomer in 80% yield (Scheme 57). Protection of the secondary alcohol, hydroboration, and bromination afforded **230** in 92% yield and completed the synthesis of the C_8−C_{13} fragment in four steps and 74% overall yield.

2. Synthesis of the C_{14}–C_{20} Fragment

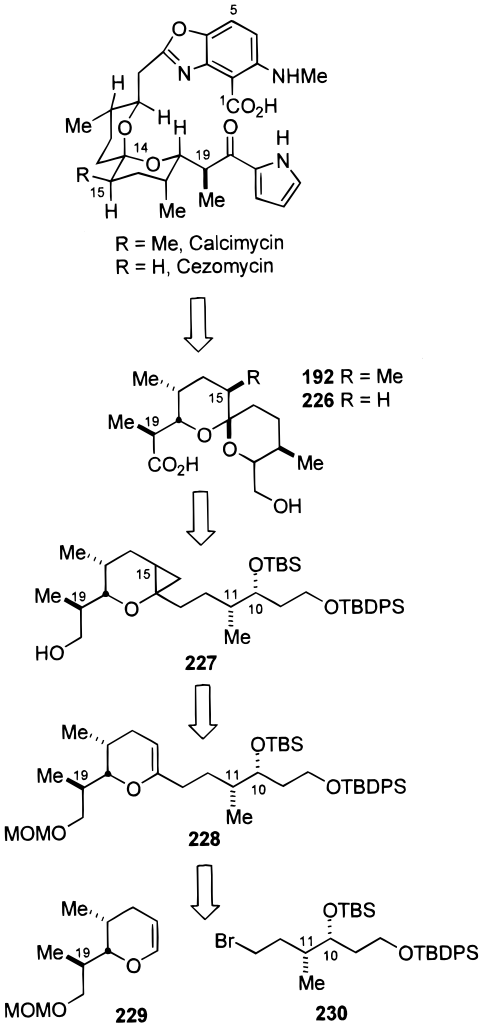
Chelate-controlled addition of tri-*n*-butyl crotylstannane to aldehyde **234**, prepared in three steps and 76% yield from methyl-(*S*)−(+)-hydroxy-2-methylpropionate, afforded **235** as the major diastereomer (6.7:1) in 88% yield. The cyclic vinyl ether **229** was

Scheme 55[a]



[a] Reprinted with permission from ref 41. Copyright 1987 Elsevier Sciences Ltd.

Scheme 56



prepared in 33% overall yield from **235**. This completed an extremely short, six-step stereocontrolled synthesis of the $C_{14}-C_{20}$ fragment (Scheme 58).

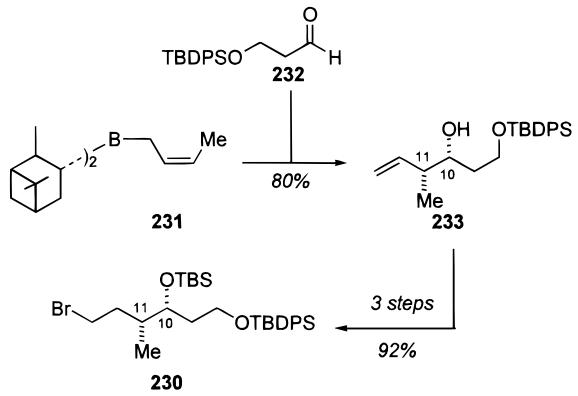
3. Fragment Coupling

Coupling of the lithium anion **229** with bromide **230** afforded a 70% yield of **228** (Scheme 59). Treatment of **228** with *p*-TsOH afforded spiroketal **236**, which was converted to cezomycin in eight steps.

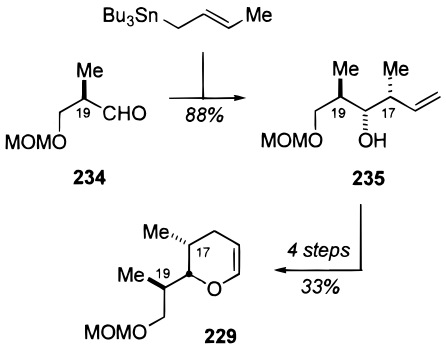
Table 14. Stereochemical Inventory for Boeckman's Synthesis of Calcimycin

carbon	method	reaction/source
C_{10}	Cram addn	chiral crotyl borane
C_{11}	Cram addn	chiral crotyl borane
C_{15}	thermodynamic	equilibration
C_{17}	Cram-chelate	organostannane addn
C_{18}	Cram-chelate	organostannane addn
C_{19}	chiral pool	methyl-(*S*)-(+)-3-hydroxy-2-methylpropionate

Scheme 57

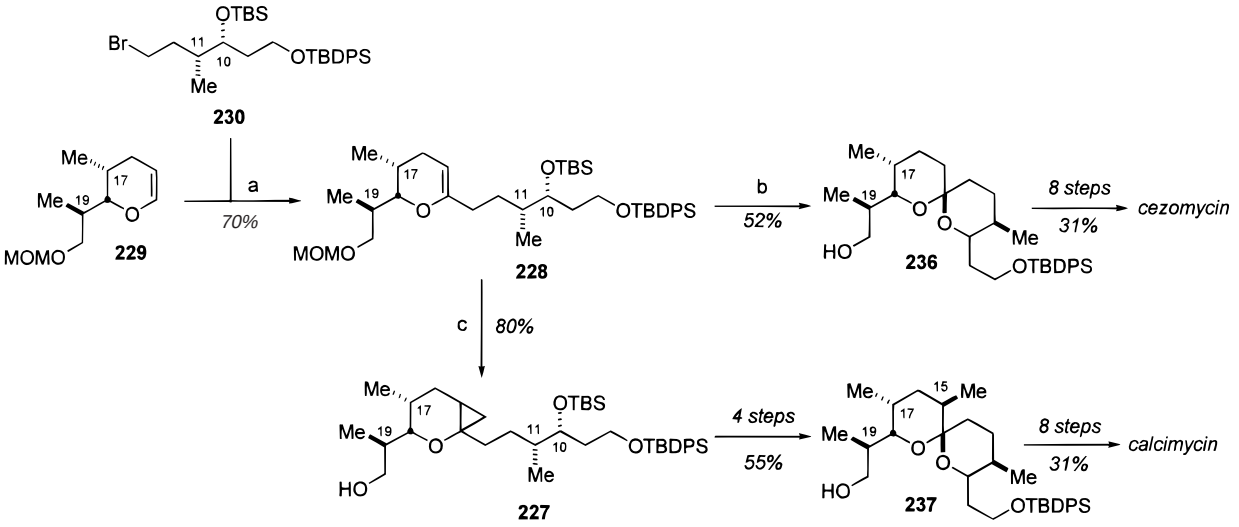


Scheme 58



Alternatively, treatment of **228** with diethylzinc and diiodomethane afforded a 1:1 mixture of cyclopropanes **227** in 80% yield. The calcimycin spiroketal **237** was obtained in 55% yield by a four-step reaction sequence that involved ring opening of the cyclopropane, equilibration of the methyl group at C_{15}, selective desilylation of C_{10}, and spiroketalization.

Scheme 59[a]



[a] (a) *t*-BuOK, *n*-BuLi, THF, −78 °C; Bu_3SnCl; (b) *p*-TsOH·H_2O, PhH, 0−80 °C; (c) Et_2Zn, CH_2I_2, Et_2O.

Introduction of the aromatic moieties completed the synthesis of calcimycin.

O. 1987, Zincophorin (Danishefsky)

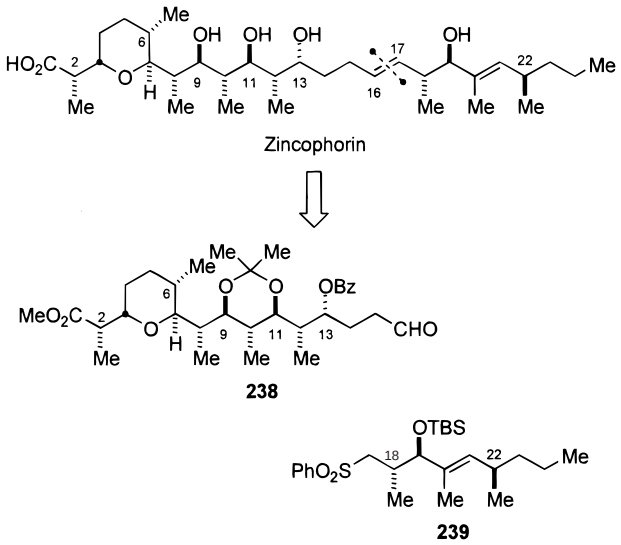
Zincophorin, a zinc-binding antibiotic, contains 13 stereocenters and a *trans*-fused tetrahydropyranoid ring. Danishefsky reported the total synthesis of zincophorin in 1987.[44] Disconnection of the $C_{16}-C_{17}$ double bond using a Julia olefination afforded the C_1-C_{16} and $C_{17}-C_{25}$ fragments **238** and **239**, respectively (Scheme 60).[45] The stereochemical inventory for Danishefsky's synthesis of zincophorin is summarized in Table 15.

1. Synthesis of the C_1–C_{16} Fragment

Danishefsky employed a 2-fold application of the Lewis-acid-induced aldehyde−siloxydiene cyclocondensation reaction to generate 4 of the 10 stereocenters of the C_1-C_{16} fragment.[46] Cyclic stereocontrol was used to install 5 of the remaining stereocenters (Scheme 61).

Cram addition of the Grignard derived from **241** to aldehyde **240**, generated by Sharpless asymmetric epoxidation of *E*-crotyl alcohol, afforded aldehyde **242** in 48% yield. Chelate-controlled cyclocondensation of **242** with siloxydiene **243**, in the presence of $MgBr_2$, generated dihydropyranone **245** in 80% yield as a 7:1 mixture of diastereomers favoring the anti $C_{10}-C_{11}$

Scheme 60



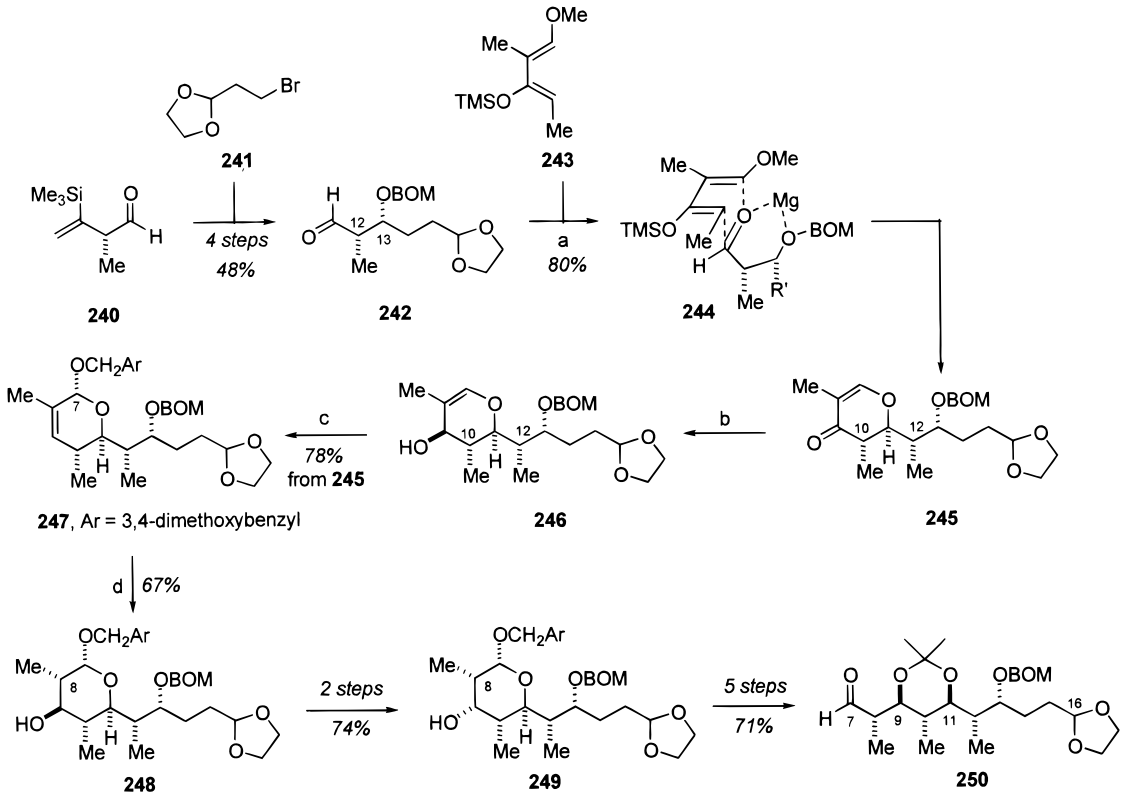
relationship. The stereochemistry was controlled by reaction through **244**, where chelation of magnesium between the aldehyde carbonyl and OBOM group resulted in attack of the diene from the β-face of the aldehyde. The α-face was blocked by the C_{12} methyl and C_{13} alkyl groups.

Reduction of ketone **245** afforded β-alcohol **246**, which was treated with 3,4-dimethoxybenzyl alcohol

Table 15. Stereochemical Inventory for Danishefsky's Synthesis of Zincophorin

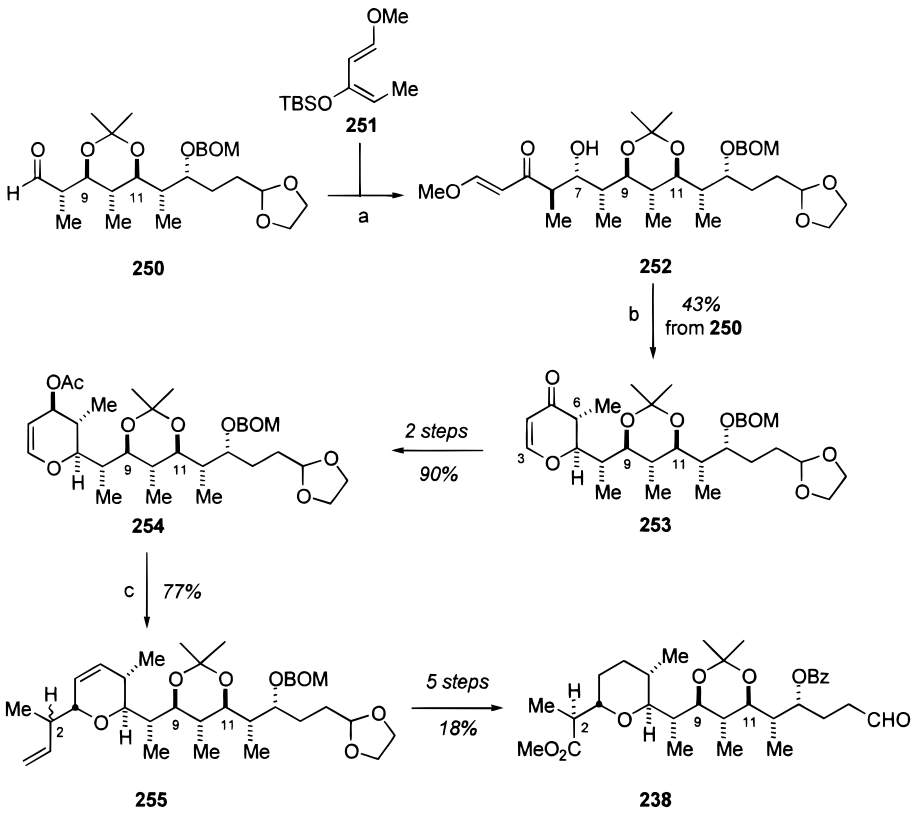
carbon	control element	reaction/source
C_2	cyclic stereocontrol	Ferrier rearrangement
C_3	cyclic stereocontrol	Ferrier rearrangement
C_6	cyclic stereocontrol	Aldehyde siloxydiene cyclocondensation
C_7	cyclic stereocontrol	Aldehyde siloxydiene cyclocondensation
C_8	cyclic stereocontrol	hydroboration
C_9	cyclic stereocontrol	oxidation/reduction
C_{10}	cyclic stereocontrol	Aldehyde siloxydiene cyclocondensation
C_{11}	cyclic stereocontrol	Aldehyde siloxydiene cyclocondensation
C_{12}	A-1,3	Sharpless AE
C_{13}	Cram-chelate	Grignard addn
C_{18}	A-1,3	aldol reaction/(1*R*, 2*S*)-*N*-methylephedrine-*O*-propionate
C_{19}	A-1,3	aldol reaction/(1*R*, 2*S*)-*N*-methylephedrine-*O*-propionate
C_{22}	A-1,3	alkylation/oxazolidinone

Scheme 61[a]



[a] (a) $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, −65 °C; (b) $CeCl_3{\cdot}7H_2O$, $NaBH_4$; (c) 3,4-dimethoxybenzyl alcohol, *p*-TsOH, PhH; (d) $BH_3{\cdot}Me_2S$, THF.

Scheme 62[a]



[a] (a) $BF_3{\cdot}OEt_2$, −78 °C; (b) *p*-TsOH, PhH; (c) *E*-crotyltrimethylsilane, $BF_3{\cdot}OEt_2$.

to generate **247** and introduced the C_7 stereocenter in 70% yield via a Ferrier rearrangement.[47] Hydroboration of the C_8−C_9 double bond occurred from the β-face to yield **248** in 67% yield. This reaction installed the correct C_8 methyl stereocenter, but the configuration of the C_9 hydroxyl group was opposite to that required in zincophorin. This stereochemistry was easily reversed by an oxidation/reduction se-

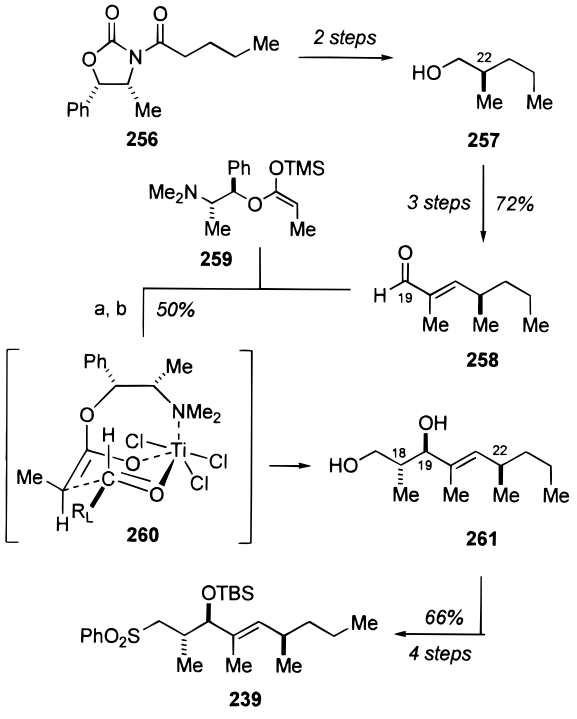
quence to afford the desired axial alcohol **249** in 74% yield. Treatment of **249** with lithium borohydride, acetonide formation, and oxidation afforded the C_7−C_{16} aldehyde **250** for the second cyclocondensation reaction.

Cyclocondensation of aldehyde **250** with siloxy−diene **251** in the presence of BF_3·OEt_2, followed by acid-catalyzed cyclization of **252**, afforded **253** in 43% yield as a 4.5:1 mixture of *trans*:*cis*-substituted dihydropyrones (Scheme 62). Reduction and acylation of the C_5 ketone afforded glycal **254** in 90% yield. Introduction of the C_1−C_2 functionality was achieved using the carbon nucleophilic version of the Ferrier rearrangement.[48] Thus, reaction of **254** with *E*-crotyltrimethylsilane in the presence of BF_3·OEt_2 afforded a 70% yield of a 3.5:1 mixture of the C_2 epimers **255**. Oxidation, esterification, and cleavage of the acetonide completed the synthesis of the C_1−C_{16} fragment in 23 steps and 1% yield from **240**.

2. Synthesis of the C_{17}–C_{25} Fragment[49]

Alkylation of the norephedrine-derived Evans oxazolidinone **256** with methyl iodide introduced the C_{22} stereocenter. Reductive removal of the auxiliary afforded **257**. Elongation of the chain using Wittig chemistry generated aldehyde **258** in 72% yield. The *anti*-stereochemistry at C_{18}−C_{19} was introduced by a $TiCl_4$-mediated aldol reaction of the *E*-silyl ketene acetal **259**, derived from (1*R*,2*S*)-*N*-methylephedrine-*O*-propionate.[50] The transition state of the reaction, **260**, was generated by formation of a 1:1:1 $TiCl_4$:**259**:**258** complex, in which both the aldehyde carbonyl and the ephedrine NMe_2 group are bound to the $TiCl_4$.[51] This reaction afforded an 8:1 mixture of *threo*:*erythro* isomers **261** in 50% yield. Conversion of **261** into sulfone **239** completed the synthesis of the C_{17}−C_{25} fragment in eight steps and 23% yield (Scheme 63).

Scheme 63[a]

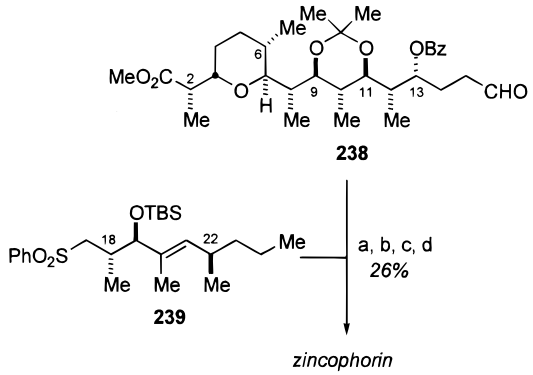


[a] (a) $TiCl_4$, CH_2Cl_2, −78 °C; (b) $LiAlH_4$, Et_2O, 0 °C.

3. Fragment Coupling—Julia Olefination

The final steps of the synthesis involved Julia olefination of aldehyde **238** with sulfone **239**. Thus, lithiation of **239** followed by treatment with $MgBr_2$ and reaction with **238** generated, after reduction of the intermediate hydroxysulfones, an 8:1 mixture of *E*:*Z* isomers at the C_{16}−C_{17} double bond. Removal of protecting groups and hydrolysis of the methyl ester completed the synthesis of zincophorin in 26% yield (Scheme 64).

Scheme 64[a]



[a] (a) 1.75 M *n*-BuLi, THF, −78 °C; $MgBr_2$; (b) 3:1 THF/MeOH, 6% Na−Hg, −40 °C; (c) 1:1:2 1 N HCl:MeOH:THF, 50 °C; (d) 1:1:2 2 N LiOH:MeOH:THF, 50 °C.

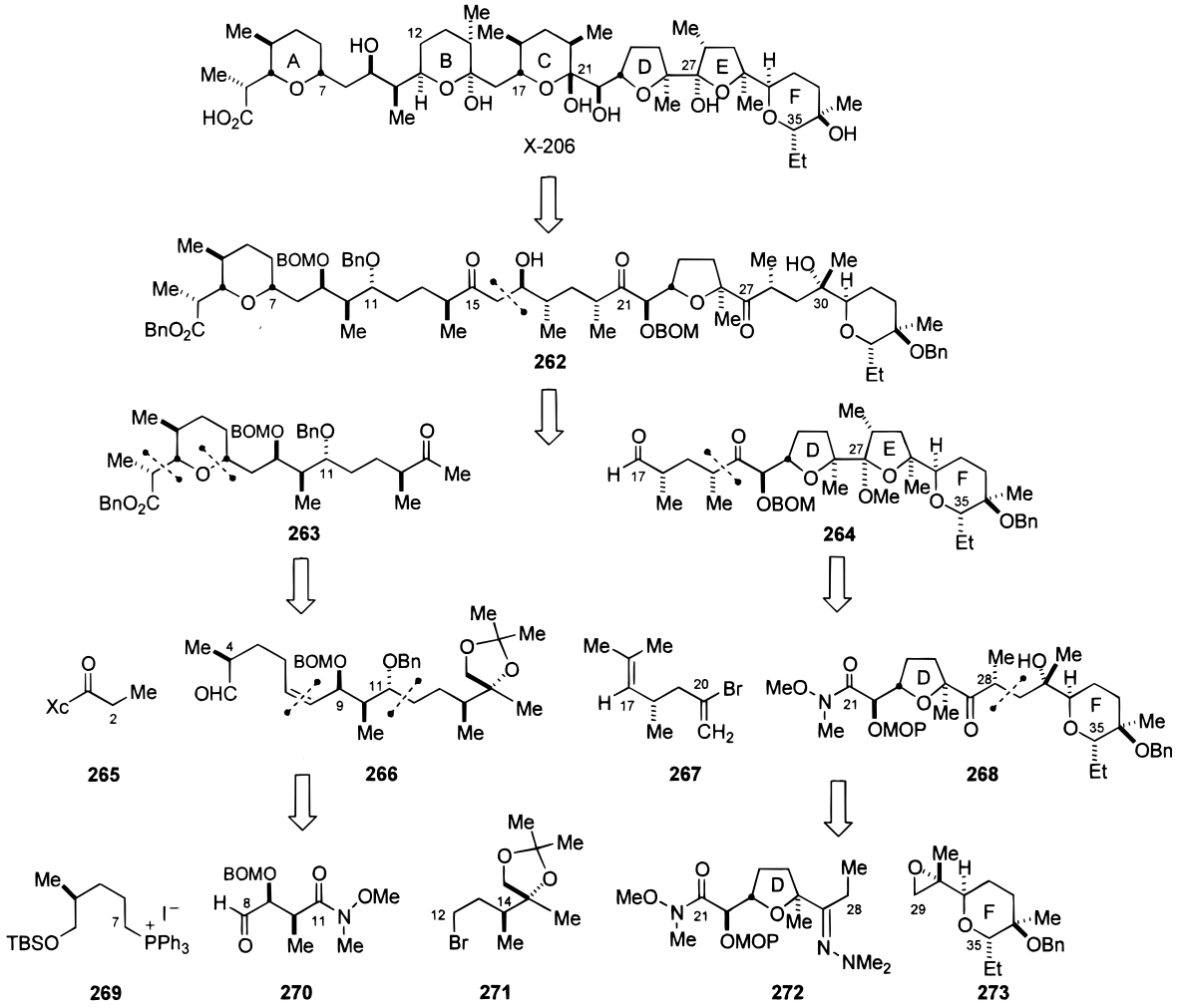
P. 1988, X-206 (Evans)

The D-, E-, and F-rings of the antibiotic X-206 closely resemble the corresponding subunits of lysocellin and lasalocid A, although the presence of three lactol functionalities distinguish it from other members of its class. The total synthesis of X-206 was completed by Evans in 1988.[52] Disconnection of the C_{16}−C_{17} bond of β-hydroxyketone tautomer **262** by a methyl ketone aldol reaction afforded two fragments,

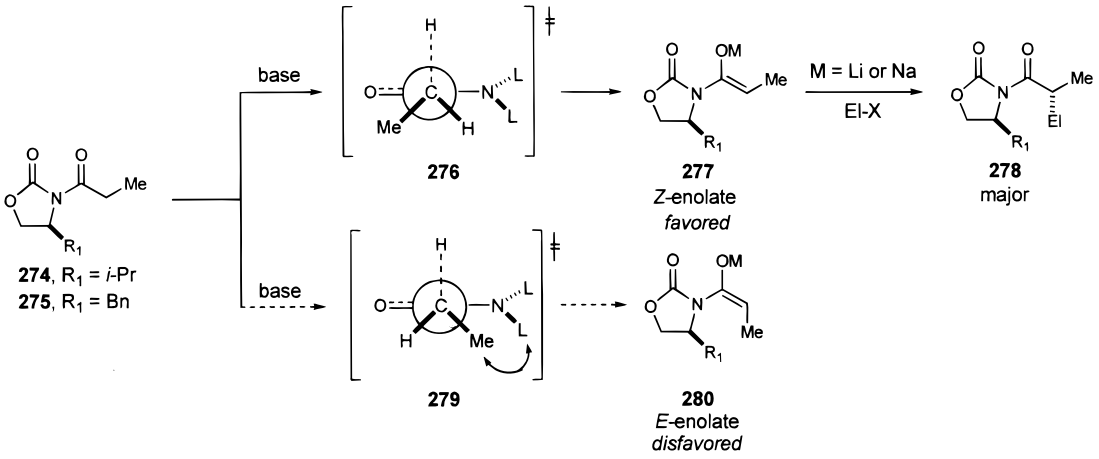
Table 16. Stereochemical Inventory for Evan's Synthesis of X-206

carbon	control element	reaction/source
C_2	A-1,3	boron aldol/oxazolidinone
C_3	A-1,3	boron aldol/oxazolidinone
C_4	A-1,3	alkylation/oxazolidinone
C_7	A-1,3	alkoxymercuration
C_9	A-1,3	boron aldol/oxazolidinone
C_{10}	A-1,3	boron aldol/oxazolidinone
C_{11}	Cram-chelate	organocuprate addn
C_{14}	A-1,3	Sharpless AE
C_{15}	thermodynamic	equilibration
C_{17}	Cram	aldol/Li enolate
C_{18}	A-1,3	alkylation/oxazolidinone
C_{20}	A-1,3	directed hydrogenation
C_{21}	thermodynamic	equilibration
C_{22}	A-1,3	boron aldol/oxazolidinone
C_{23}	A-1,3	boron aldol/oxazolidinone
C_{26}	A-1,3	bishomoallylic alcohol epoxidation
C_{27}	cyclic stereocontrol	THF-formation
C_{28}	Cram-chelate	organolithium addn
C_{30}	A-1,3	Sharpless AE
C_{31}	A-1,3	Sharpless AE
C_{34}	A-1,3	Sharpless AE
C_{35}	A-1,3	Sharpless AE

Scheme 65



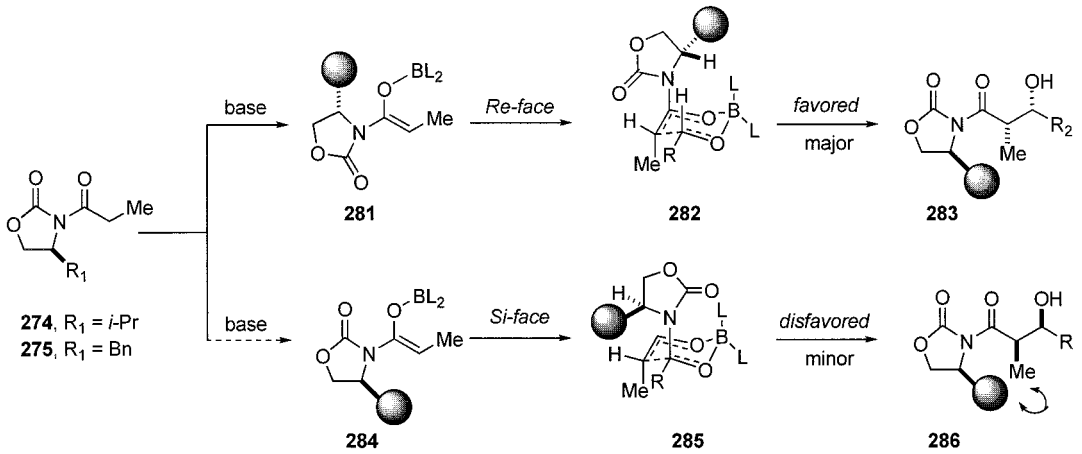
Scheme 66



C_1-C_{16} and $C_{17}-C_{37}$, **263** and **264**, respectively (Scheme 65). Retrosynthetic analysis of **263** afforded four fragments **265** (by aldol disconnection of C_2-C_3 bond), **269** and **270** (by Wittig disconnection of the C_7-C_8 bond), and **271** (by disconnection of $C_{11}-C_{12}$ bond). Retrosynthetic analysis of the $C_{17}-C_{37}$ subunit **264** yielded three fragments **267**, **272**, and **273**. The stereochemical inventory for Evan's synthesis of X-206 is summarized in Table 16.

Evans employed the Sharpless asymmetric epoxidation to introduce 5 of the 22 stereocenters of X-206. He introduced two new methods for asymmetric synthesis using chiral oxazolidinones to incorporate **8** of the remaining 17 stereocenters. The first method involved alkylation of *N*-acyl oxazolidinones derived from valine (X_V) **(274)**, phenylalanine (X_p) **(275)**, and norephedrine **(287)** (X_N). Treatment of **274** or **275** with base generates the *Z*-enolate **277**, due to the

Scheme 67



unfavorable A-1,3 interaction (Me⇄NL_2) interaction, illustrated in **279**, upon formation of the *E*-enolate **280**. Trapping of an electrophile (El-X) on the *Z*-enolate then occurs on the face opposite the C_4 substituent of the oxazolidinone ring (Scheme 66).[53]

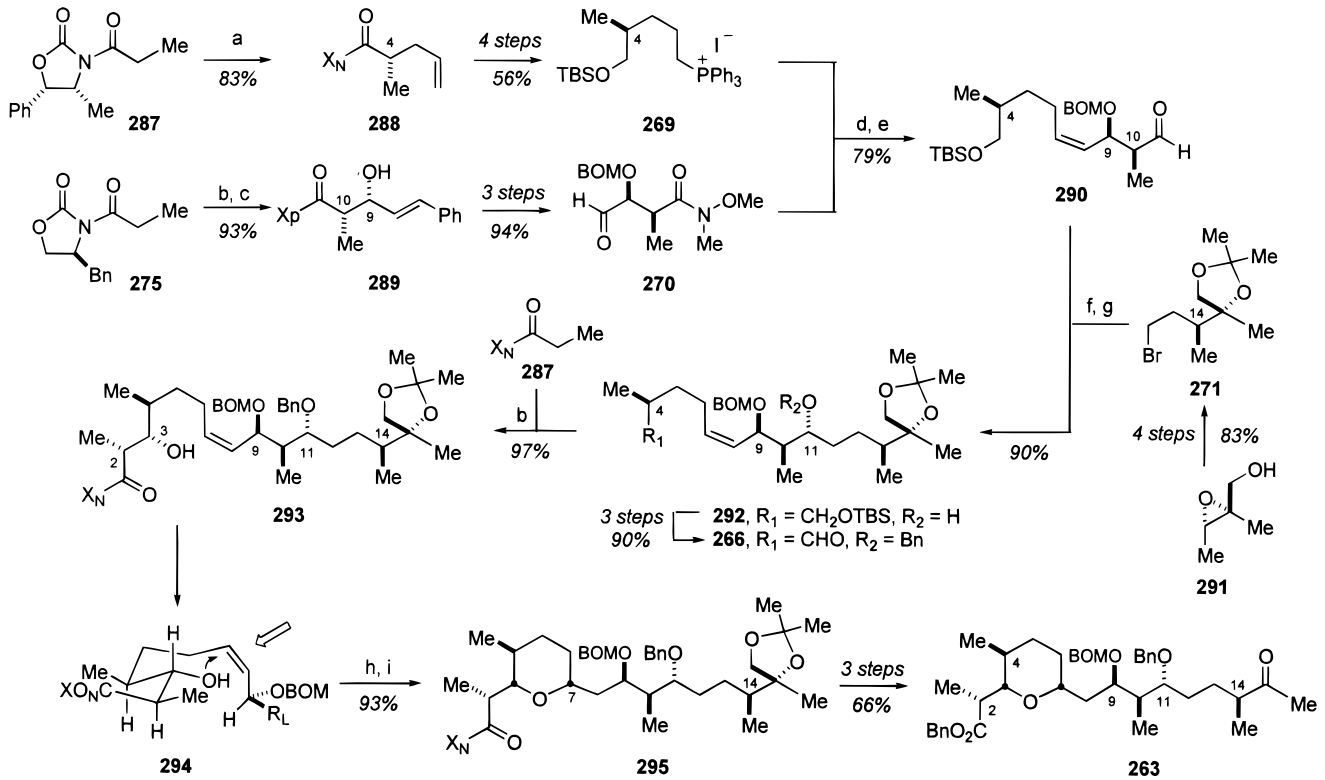
The second method involved aldol reaction of the boron enolate derived from *N*-acyl oxazolidinones **274**, **275**, and **287**.[54] Using the valine- or phenylalanine-derived auxiliaries, **274** or **275**, the reaction occurs with high levels of syn selectivity, due to attack of the aldehyde on the *Re*-face of the *Z*-boron enolate as illustrated in **282** (Scheme 67). As observed in the alkylation, attack on the *Si*-face via **285** was disfavored by steric interactions with the oxazolidinone C_4 substituent. Similar transition states can be drawn for the norephedrine oxazolidinone **(287)** to afford the opposite sense of induction. This new asymmetric methodology proved to be instrumental in the synthesis by Evans of the polyether ionophores X-206, ionomycin, ferensmycin B, and lonomycin A.

1. Synthesis of the C_1–C_{16} Fragment

Alkylation of the sodium enolate of the norephedrine oxazolidinone **287** with allyl iodide afforded **288** in >99% de and 83% yield (Scheme 68). Conversion of **288** to the phosphonium salt **269** completed the synthesis of the C_3–C_7 fragment in five steps and 47% overall yield.

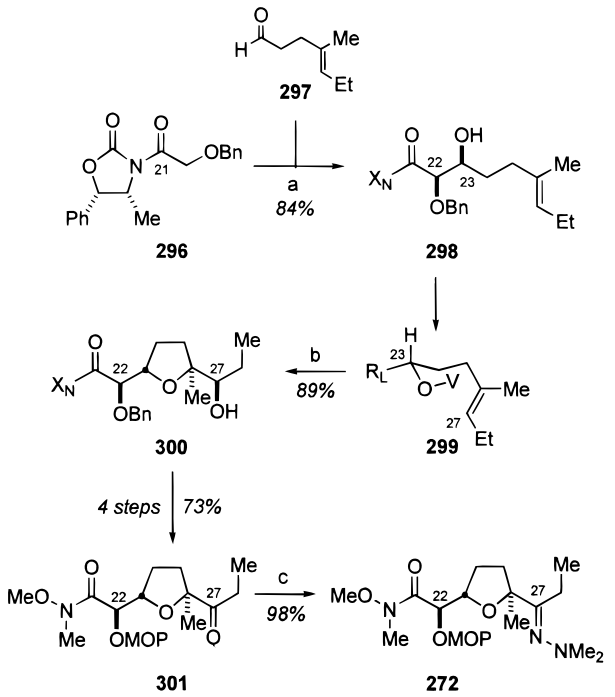
The C_9–C_{10} stereocenters were introduced in 93% yield by boron aldol reaction of **275** with cinnamaldehyde. Conversion of **289** into the Weinreb amide,

Scheme 68[a]



[a] (a) NaHMDS, THF, allyl iodide, −78 °C; (b) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2; (c) PhCH=CHCHO; H_2O_2; (d) $NaN(TMS)_2$, PhMe; (e) DIBAL, THF, −78 °C; (f) 1.6 M *t*-BuLi; (g) CuCN; (h) $Hg(OAc)_2$, CH_2Cl_2; (i) *n*-Bu_3SnH, PhMe.

Scheme 69[a]



[a] (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, H_2O_2; (b) *t*-BuOOH, catalytic $VO(acac)_2$, CH_2Cl_2; (c) Me_2NNH_2, TMSCl, 0 °C.

protection of the alcohol, and ozonolysis afforded aldehyde **270** in six steps and 87% overall yield.

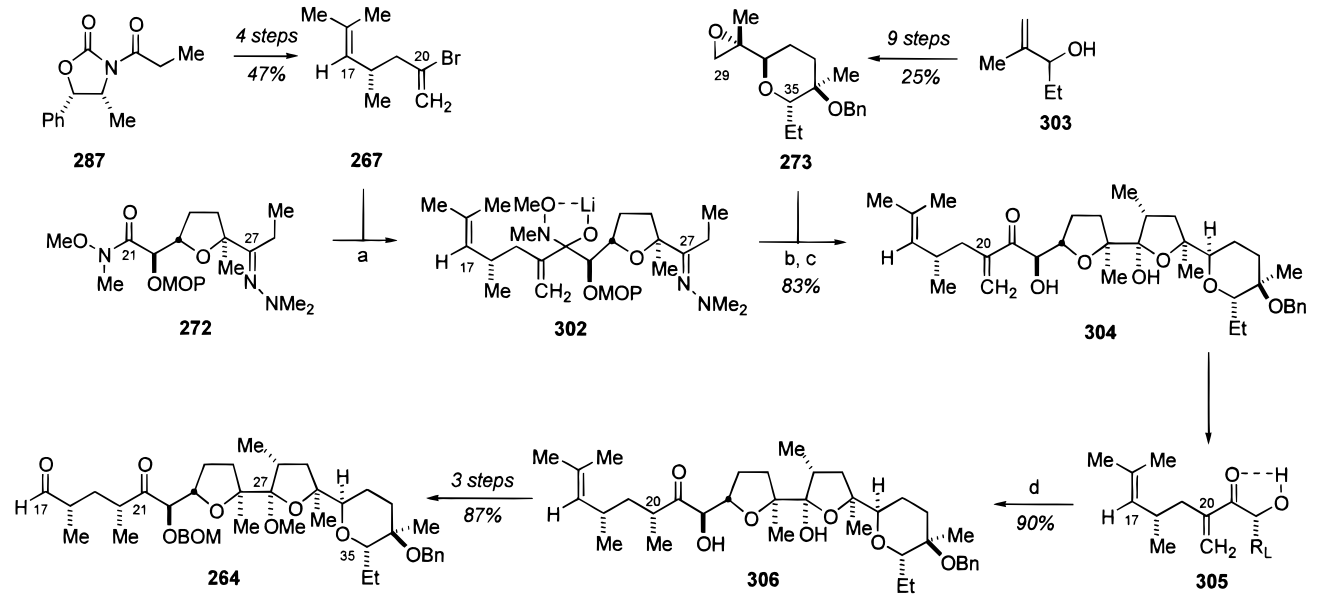
Wittig coupling of aldehyde **270** with phosphorane **269** under "salt-free" conditions, followed by hydride addition to the Weinreb amide, afforded aldehyde **290** in 79% yield. Chelate-controlled addition of the organocuprate derived from bromide **271**, prepared from epoxide **291**, afforded alcohol **292** in 90% yield and introduced the C_{11} stereocenter.[55] Hydrolysis of the TBS ether, protection of the C_{11} alcohol, and oxidation gave aldehyde **266** in 90% yield. A second boron aldol reaction of **266** with the *Z*-enolate of **287** afforded the syn aldol adduct **293** as a single diastereomer in 97% yield. Treatment of **293** with $Hg(OAc)_2$, followed by demercuration, closed the A-ring and afforded **295** as a single C_7 diastereomer in 93% overall yield through the intermediacy of **294**. Removal of the chiral auxiliary, hydrolysis of the acetonide, and oxidative cleavage of the glycol afforded the C_1-C_{16} fragment **263** in 17 steps and 17% overall yield (Scheme 68).

2. Synthesis of the C_{17}–C_{37} Fragment

Boron aldol reaction of oxazolidinone **296** with aldehyde **297** afforded **298** in 84% yield and established the C_{22} and C_{23} stereocenters (Scheme 69). Tetrahydrofuran **300** was prepared using Kishi's bishomoallylic epoxidation methodology. $VO(acac)_2$-catalyzed epoxidation of **298** proceeded through transition state **299** to afford, after acid-catalyzed cyclization, **300** in 95:5 selectivity and 89% yield. Conversion of **300** into **301**, followed by formation of hydrazone **272**, completed the synthesis of the $C_{21}-C_{28}$ fragment in seven steps and 56% yield.

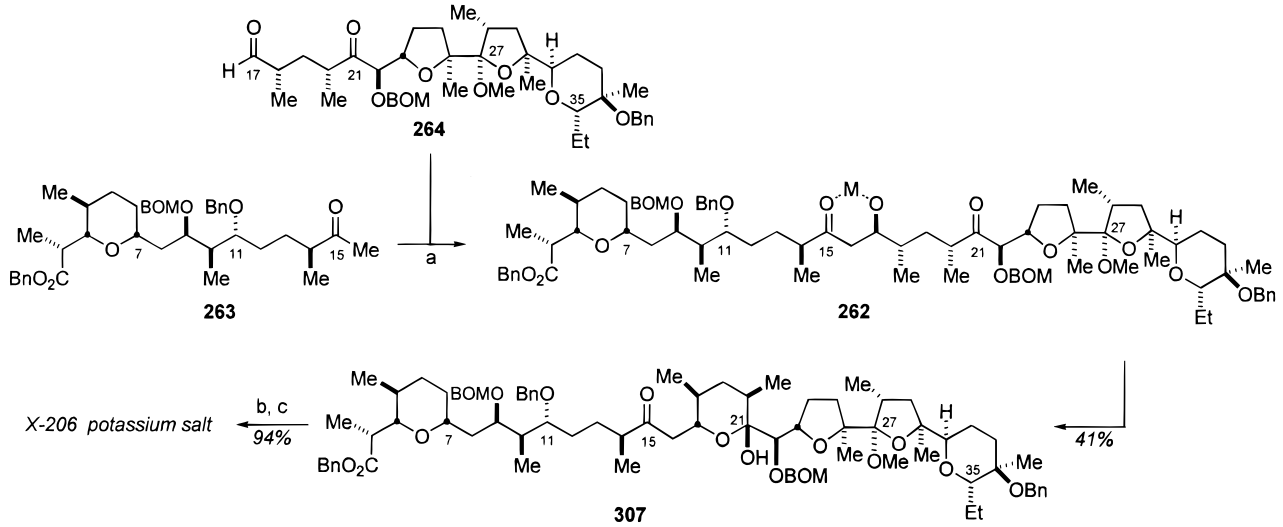
Hydrazone **272** was reacted with bromide **267**, prepared in four steps and 47% yield by alkylation of **287**, to afford the stable tetrahedral intermediate **302** (Scheme 70). Deprotonation of **302** and reaction with **273**, prepared from 2-methyl-1-penten-3-ol **(303)** by 2-fold application of the Sharpless epoxidation, afforded **304** containing the D-, E-, and F-rings of X-206 in 83% yield. The C_{20} stereocenter was introduced in 90% yield by a hydroxyl-directed hydrogenation reaction using Wilkinson's catalyst.[56] Reaction through the hydrogen-bonded *S-trans* conformation **305** provided the sterically accessible *Re*-face for catalyst coordination and gave the desired *R*-diastereomer **306** as the predominant product. Ketalization of the E-ring under nonequilibrating conditions followed by ozonolysis of the isopropylidene moiety afforded aldehyde **264** in 17 steps and 25% overall yield.

Scheme 70



(a) *t*-BuLi (2.0 equiv), Et_2O, −78 to 0 °C; (b) LDA, 0 °C; (c) 1 N aq $NaHSO_4$, 25% CH_2Cl_2/pentane; (d) 1 atm of H_2, $(Ph_3P)_3RhCl$, PhMe.

Scheme 71[a]

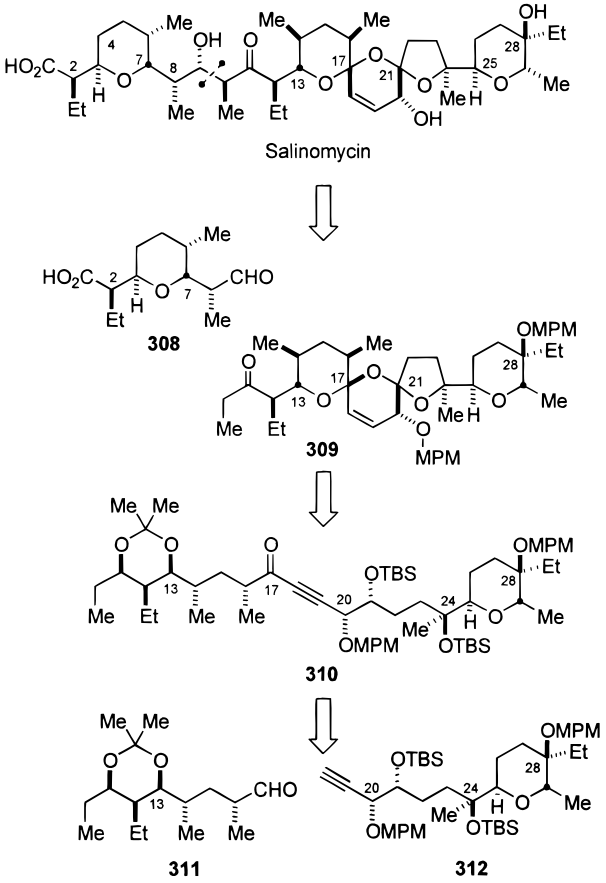


[a] (a) LDA, Et_2O, −78 °C, 5 min; (b) 1 atm of H_2, 10% Pd/C; (c) 0.01 N $HClO_4$ in 80% aqueous THF, 25 °C.

3. Fragment Coupling—The Aldol Reaction

Kinetic aldol condensation of the lithium enolate of ketone **263** with aldehyde **264** afforded a 55:45 mixture of diastereomeric aldol adducts, from which lactol **307** was isolated in 41% yield (Scheme 71). The stereochemical outcome of the reaction slightly favored the undesired diastereomer, a fact consistent with the small diastereofacial bias imposed on the aldehyde by the α-stereocenter in accordance with Cram's rule. Hydrogenolysis of **307** and hydrolysis of the E-ring methyl ketal at C_{28} was achieved in 94% yield to complete the synthesis of X-206.

Scheme 72



Q. 1989, Salinomycin (Horita and Yonemitsu)

Horita and Yonemitsu reported the second total synthesis of salinomycin in 1989.[57] Disconnection of the C_9-C_{10} and $C_{17}-C_{18}$ bonds afforded three fragments (Scheme 72), similar to those prepared by Kishi. The C_1-C_9, $C_{10}-C_{17}$, and $C_{18}-C_{30}$ fragments **308**, **311**, and **312** respectively, were principally derived from D-glucose by extensive use of chelate-controlled addition reactions. The stereochemical inventory for Hortia and Yonemitsu's synthesis of salinomycin is summarized in Table 17.

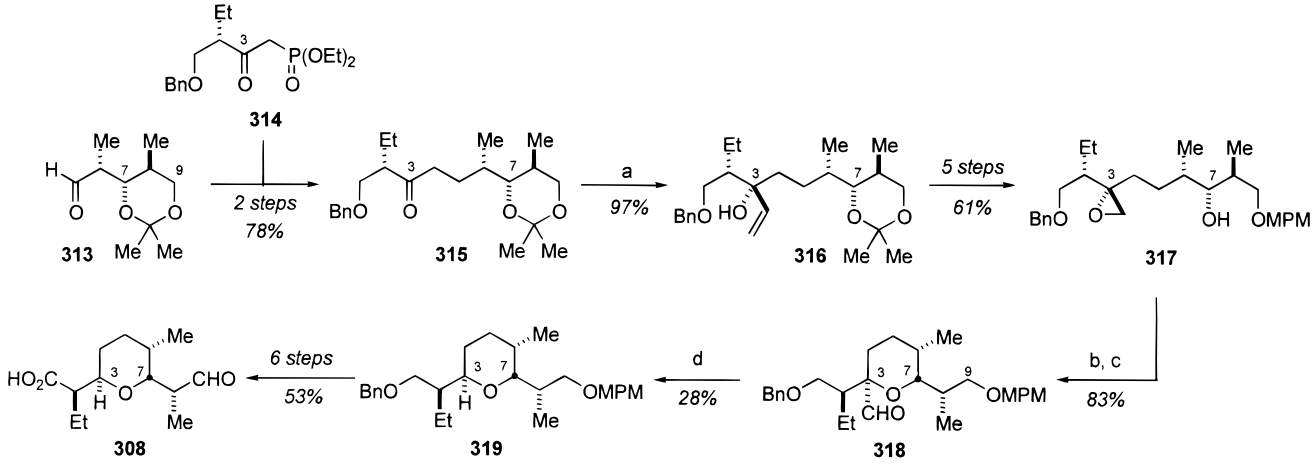
1. Synthesis of the C_1–C_9 Fragment

Wittig−Horner reaction of aldehyde **313** and phosphonate **314**, both derived from D-glucose, gave an intermediate *E*-enone that upon hydrogenation afforded ketone **315** in 78% yield (Scheme 73). Chelate-controlled addition of vinylmagnesium bromide to the C_3 ketone provided alcohol **316** as a 13:1 mixture of stereoisomers in 97% yield. Conversion of **316** into epoxide **317**, with the two primary alcohols differen-

Table 17. Stereochemical Inventory for Horita and Yonemitsu's Synthesis of Salinomycin

carbon	control element	reaction/source
C_2	chiral pool	D-glucose
C_3	Cram-chelate	Grignard addn
C_6	chiral pool	D-glucose
C_7	chiral pool	D-glucose
C_8	chiral pool	D-glucose
C_9	Cram addn	aldol/Mg enolate
C_{10}	Cram addn	aldol/Mg enolate
C_{12}	chiral pool	D-glucose
C_{13}	chiral pool	D-glucose
C_{14}	chiral pool	D-glucose
C_{16}	cyclic stereocontrol	hydrogenation
C_{17}	thermodynamic	equilibration
C_{20}	chiral pool	D-glucose
C_{21}	thermodyanmic	equilibration
C_{24}	Cram-chelate	organolithium addn
C_{25}	chiral pool	D-mannitol
C_{28}	Cram-chelate	Grignard addn
C_{29}	chiral pool	L-lactate

Scheme 73[a]



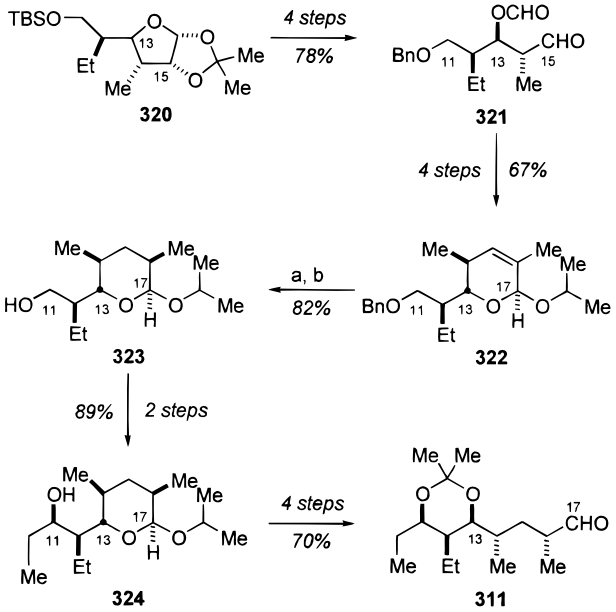
[a] (a) VinylMgBr, THF, −78 °C; (b) CSA, CH_2Cl_2; (c) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N; (d) $(Ph_3P)_3RhCl$, MeCN, 160 °C. (Reprinted with permission from refs 57b and 57g. Copyright 1989 Pharmaceutical Society of Japan and Copyright 1988 Elsevier Sciences Ltd., respectively.)

tially protected as their benzyl and *p*-methoxybenzyl (MPM) ethers, was achieved in five steps and 61% overall yield. Acid-catalyzed cyclization of **317**, followed by Swern oxidation, provided the A-ring tetrahydropyran **318** in 83% yield. Although decarbonylation of the C_3 aldehyde using Wilkinson's catalyst proceeded with retention of configuration, **319** was obtained in only 28% yield due to the severe steric crowding of the carbonyl group. A six step sequence of protecting-group manipulations and adjustment of the C_1 and C_9 oxidation states converted **319** into **308** in 53% yield. The synthesis of the C_1-C_9 fragment was completed in 17 steps and 6% overall yield from **313**.

2. Synthesis of the C_{10}–C_{17} Fragment

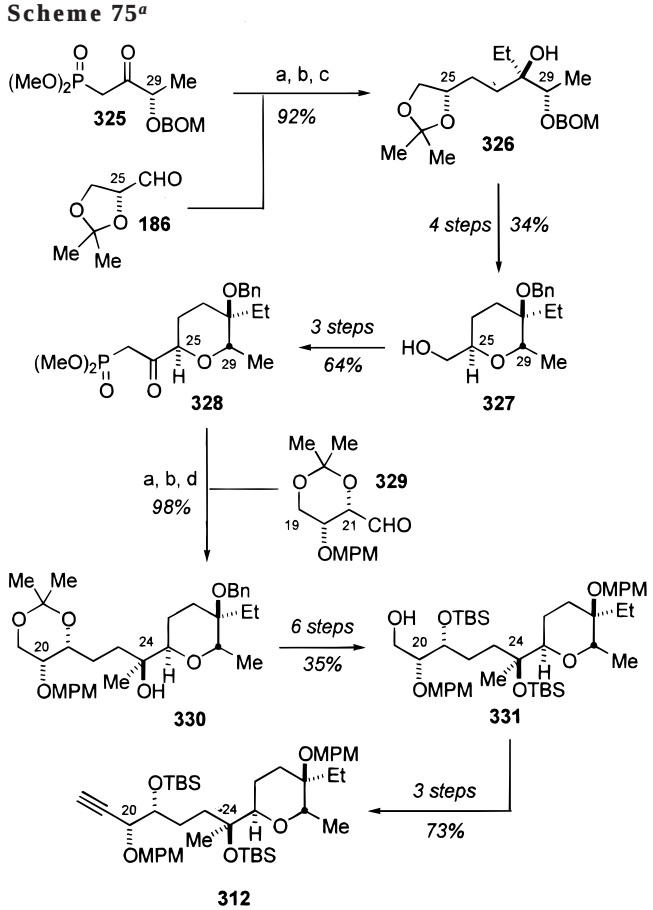
Aldehyde **321** was prepared in four steps and 78% overall yield from **320**, derived from D-glucose (Scheme 74).[58] Wittig−Horner reaction of **321** with trimethyl 2-phosphonopropionate followed by treatment with K_2CO_3 gave an α,β-unsaturated C_{17} lactone. DIBAL reduction and isopropylation afforded **322** in 67% overall yield from **321**. Catalytic hydrogenation of **322** with Raney-Ni, followed by $Rh-Al_2O_3$, afforded **323** in 82% yield and introduced the C_{16} methyl stereocenter with 13:1 selectivity. Swern oxidation of **323** and treatment with EtMgBr gave the Cram addition product **324** in 89% yield. Hydrolysis of the isopropyl group, reduction to the triol, acetonide

Scheme 74[a]



[a] (a) Raney-Ni; (b) Rh/Al_2O_3, H_2, Et_2O. (Reprinted with permission from refs 57b and 57f. Copyright 1989 Pharmaceutical Society of Japan and Copyright 1987 Elsevier Sciences Ltd., respectively.)

Scheme 75[a]



[a] (a) NaH, DMSO/THF, 0 °C; (b) Pd/C, H_2, EtOAc; (c) EtMgBr, THF, −93 °C; (d) MeLi, Et_2O, −93 °C. (Reprinted with permission from ref 57c. Copyright 1989 Pharmaceutical Society of Japan.)

formation, and Swern oxidation completed the synthesis of the $C_{10}-C_{17}$ fragment **311** in 16 steps and 27% overall yield from **320**.

3. Synthesis of the C_{18}–C_{30} Fragment

Wittig−Horner coupling of keto phosphonate **325**, derived from ethyl-L-lactate, with D-glyceraldehyde acetonide **186**, afforded an intermediate enone (Scheme 75). Olefin reduction and chelate-controlled addition of EtMgBr to the C_{28} ketone afforded alcohol **326** as a single isomer in 92% yield. Benzylation, removal of the BOM and acetonide protecting groups, followed by intramolecular cyclization onto a C_{25} tosylate provided **327** in 34% yield. Three steps were required to convert **327** into phosphonate **328**. A second Wittig−Horner coupling with aldehyde **329**, derived from D-glucose, followed by olefin reduction and chelate-controlled addition of MeLi provided **330** in 98% yield as a 33:1 mixture of C_{24} alcohol epimers. Protecting-group manipulation afforded **331** in 35% yield.[59] Oxidation of **331**, followed by reaction with bromodichloromethylphenylmercury and triphenylphosphine, afforded the dichloroolefin. Dechlorination with *n*-BuLi gave acetylene **312** and completed the synthesis of the $C_{18}-C_{30}$ fragment in 22 steps and 4% overall yield from **325**.[60]

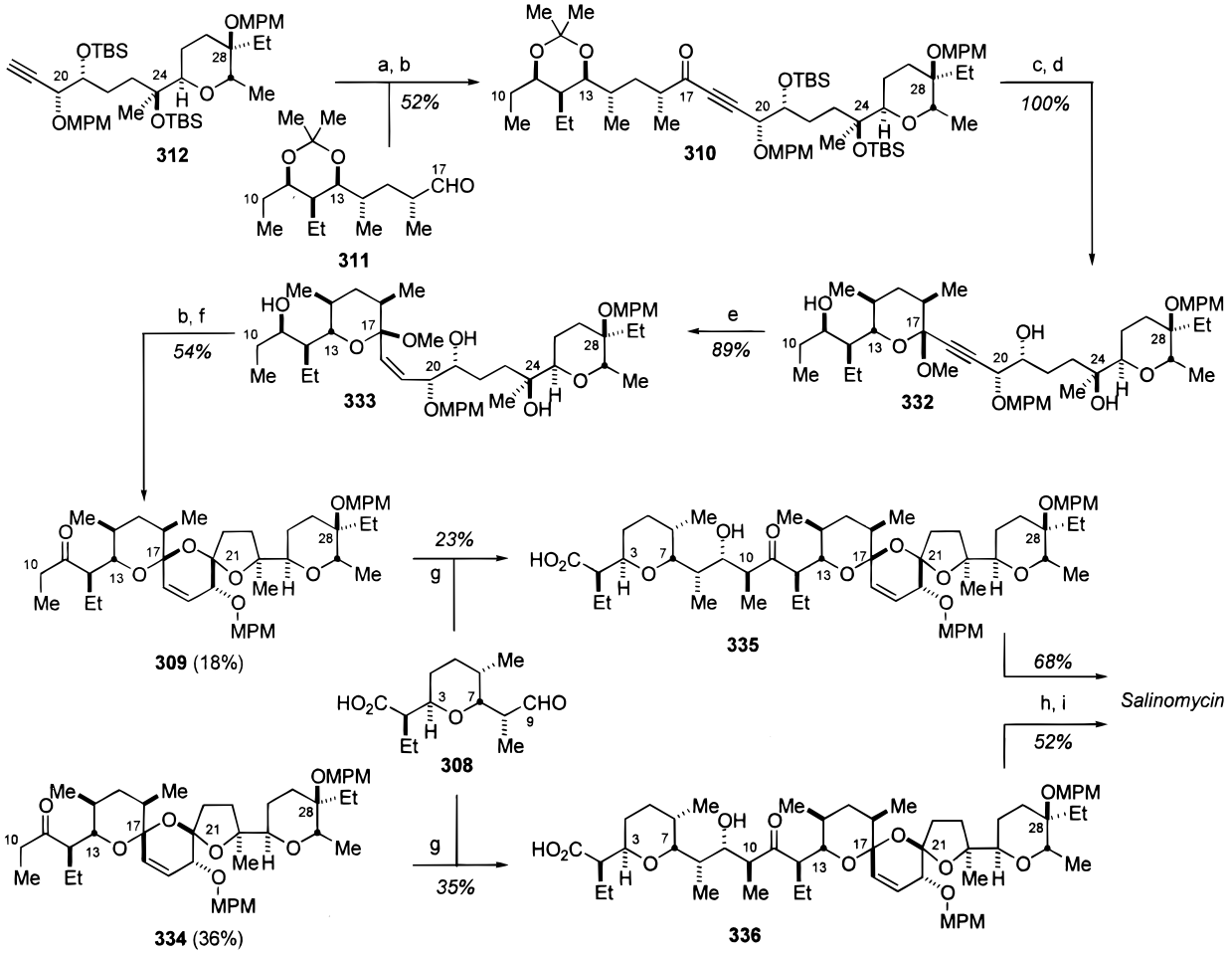
4. Synthesis of the C_{10}–C_{30} Fragment

The acetylenic anion of the $C_{18}-C_{30}$ fragment **312** was coupled with the $C_{10}-C_{17}$ aldehyde **311** affording, after oxidation, the $C_{10}-C_{30}$ fragment **310** in 52% yield (Scheme 76). Removal of the isopropylidene and TBS protecting groups provided the B-ring lactol **332** as a 4:1 mixture of C_{17} stereoisomers. Reduction of acetylene **332** with Lindlar's catalyst gave *cis*-olefin **333** in 89% yield. Swern oxidation of the secondary alcohols, followed by treatment with CSA, afforded the $C_{10}-C_{30}$ fragments **309** and **334** as a 1:1.1 mixture of stereoisomers with respect to the C_{17} and C_{21} positions. The isomers were purified to afford **309** and **334** in 18% and 36% yield, respectively. Each isomer was carried forward separately to salinomycin.[61,62]

5. Fragment Coupling—The Aldol Reaction

Coupling of the magnesium enolate of **309** or **334** with aldehyde **308** provided **335** in 23% yield and **336** in 35% yield. Removal of the MPM groups with DDQ and epimerization of C_{17} of **335** and C_{21} of **336** with trifluoroacetic acid completed the synthesis of salinomycin in 68% yield from **335** and 52% from **336**.

Scheme 76[a]

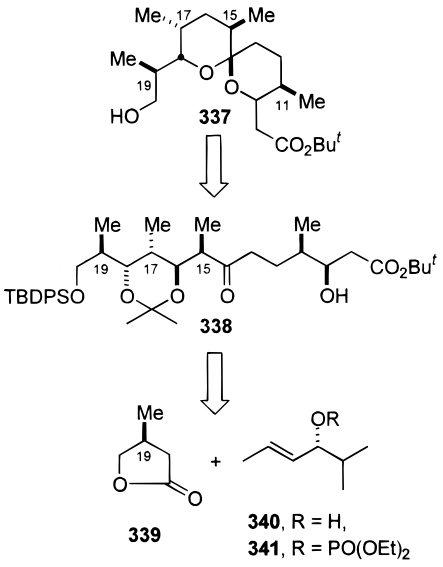


[a] (a) *n*-BuLi, THF, −78 °C; (b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N; (c) CSA, MeOH; (d) TBAF, dioxane/THF, 65 °C; (e) Lindlar's cat., H_2; (f) CSA, CH_2Cl_2; (g) $(C_6H_{11})_2NMgBr$, THF, −55 °C; (h) DDQ, CH_2Cl_2/H_2O; (i) Trifluoroacetic acid, 4 Å sieves, CH_2Cl_2. (Reprinted with permission from refs 57d and 57g. Copyright 1998 Elsevier Sciences Ltd. and Copyright 1989 Pharmaceutical Society of Japan, respectively.)

R. 1989, Calcimycin (Ziegler)

Ziegler completed a formal total synthesis of the calcimycin spiroketal **337**,[63] which in contrast to Ogawa and Boeckman contained C_8 at the carboxylic acid oxidation state (Scheme 77). Spiroketal **337** was

Scheme 77



prepared by thermodynamic spiroketalization of **338**, followed by radical deoxygenation of the C_{16} alcohol. The acyclic precursor **338** was prepared from (*S*)-methyl-γ-butyrolactone **339** and **340** by application of the Claisen rearrangement. The stereochemical inventory for Ziegler's synthesis of calcimycin is summarized in Table 18.

Claisen rearrangement of the allyl vinyl ether prepared from **339** and *S*-alcohol *ent*-**340** afforded a 45:55 mixture of **344** and **345** respectively, generated

Table 18. Stereochemical Inventory for Ziegler's Synthesis of Calcimycin

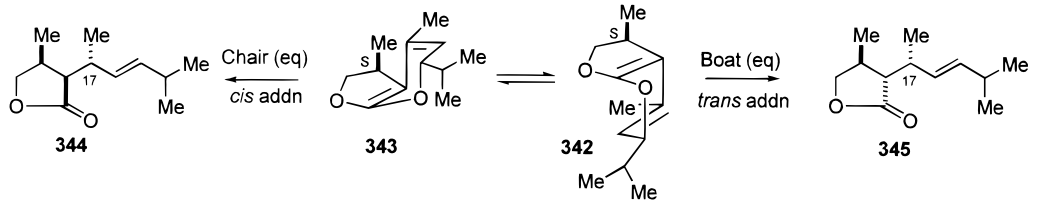
carbon	control element	reaction/source
C_{10}	nonselective	aldol/lithium enolate
C_{11}	cyclic stereocontrol	ester−enolate Claisen
C_{15}	thermodynamic	equilibration
C_{17}	cyclic stereocontrol	ester−enolate Claisen
C_{18}	thermodynamic	equilibration
C_{19}	cyclic stereocontrol	ester−enolate Claisen

from transition states **343** and **342**, containing the isopropyl substituent in the favored equatorial position (Scheme 78).[64] Equilibration of the mixture with *t*-BuOK/*t*-BuOH afforded a 97:3 ratio of **345**:**344** in 100% yield.

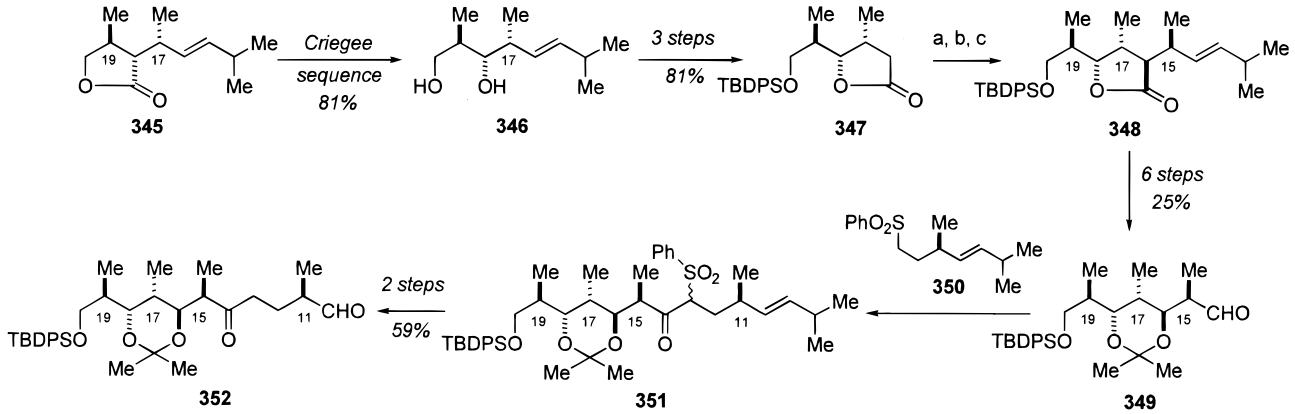
Conversion of **345** into diol **346** was achieved by a Criegee sequence.[65] Ozonolysis followed by relactonization of diol **346** afforded **347** in 81% yield. Palladium-mediated alkylation of **347** with phosphonate **341**, followed by kinetic protonation with NaH, afforded *trans*-lactone **348** in 95:5 selectivity. A six-step sequence involving Baeyer−Villiger oxidation (Criegee sequence), acetonide formation, and ozonolysis of **348** afforded aldehyde **349** in 25% overall yield. Alkylation of **349** with sulfone **350**, generated by orthoester Claisen rearrangement of (*R*)-alcohol **340**, generated four β-hydroxy sulfones that were directly oxidized to keto sulfones **351**. Reductive desulfonation of **351** with sodium amalgam, followed by ozonolysis, afforded the $C_{11}-C_{20}$ aldehyde **352** in 59% yield (Scheme 79).

Completion of the synthesis of **337** was achieved by addition of the lithium enolate of *tert*-butyl acetate to aldehyde **352** to afford a 56:44 ratio of syn:anti adducts **338**:**353** in 92% yield, which existed as the ring-opened and hemiketal forms, respectively (Scheme 80). Attempts to improve the stereoselectivity by use of zinc enolates, additives (HMPA), or

Scheme 78

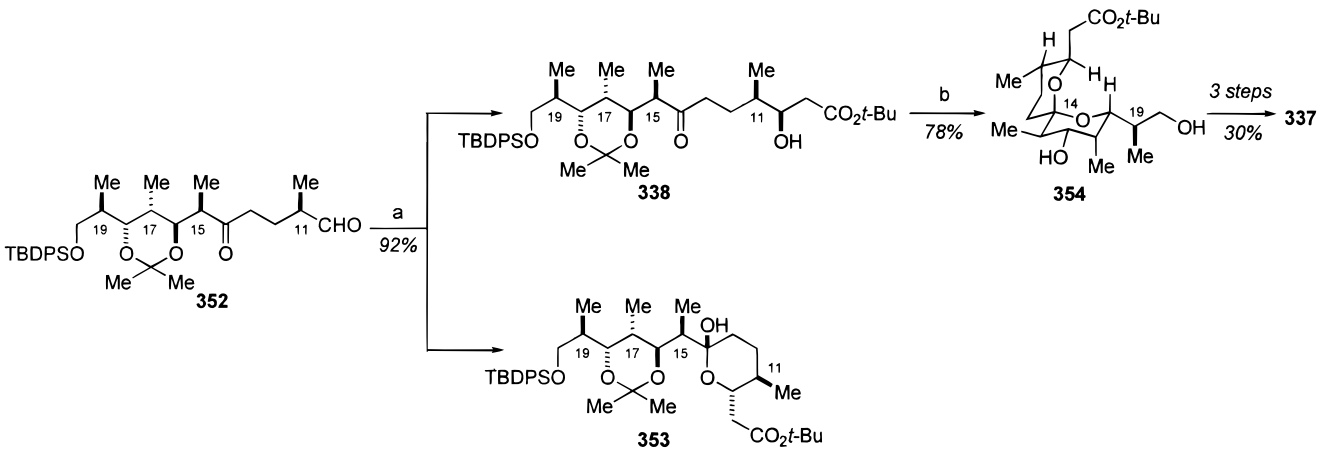


Scheme 79[a]



[a] (a) LDA, $NCCO_2Me$, THF; (b) NaH, $(Ph_3P)_4Pd$, Ph_3P, THF, **341**; (c) LiCl, DMSO/H_2O.

Scheme 80[a]



[a] (a) *i*-Pr_2NH, *n*-BuLi, *tert*-butyl acetate; (b) *p*-TsOH, MeOH.

tert-butyldimethylsilyl-*tert*-butylketene acetal in the presence of $TiCl_4$ were unsuccessful. Treatment of **338** with *p*-TsOH in MeOH afforded spiroketal **354** in 78% yield. A three-step sequence involving radical deoxygenation of the C_{16} alcohol, oxidation of the C_{18} alcohol, and introduction of the pyrrole group was accomplished in 30% overall yield to complete a formal total synthesis of calcimycin.

S. 1990, Lasalocid A and Isolasalocid A (Horita and Yonemitsu)

In anaolgy to the Kishi and Ireland syntheses of lasalocid A and isolasalocid A, Horita and Yonemitsu disconnected the $C_{11}-C_{12}$ bond by an aldol reaction to obtain the C_1-C_{11} and $C_{12}-C_{24}$ fragments **1** and **2** (Scheme 81).[66] However, they developed new methodology for the preparation of tetrahydrofurans and tetrahydropyrans and applied this to the synthesis of fragment **2**. The stereochemical inventory for Horita and Yonemitsu's synthesis of lasalocid A and isolasalocid A is summarized in Table 19.

Scheme 81

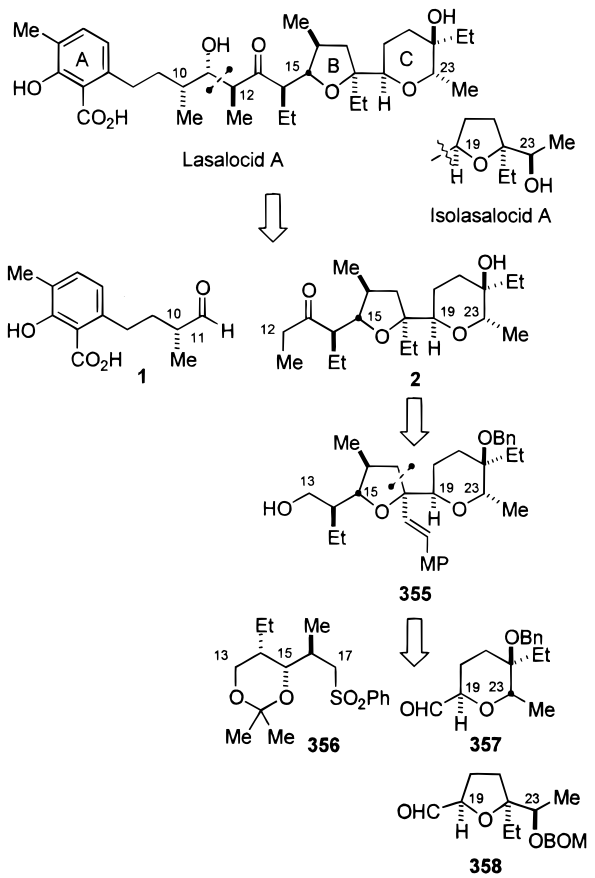


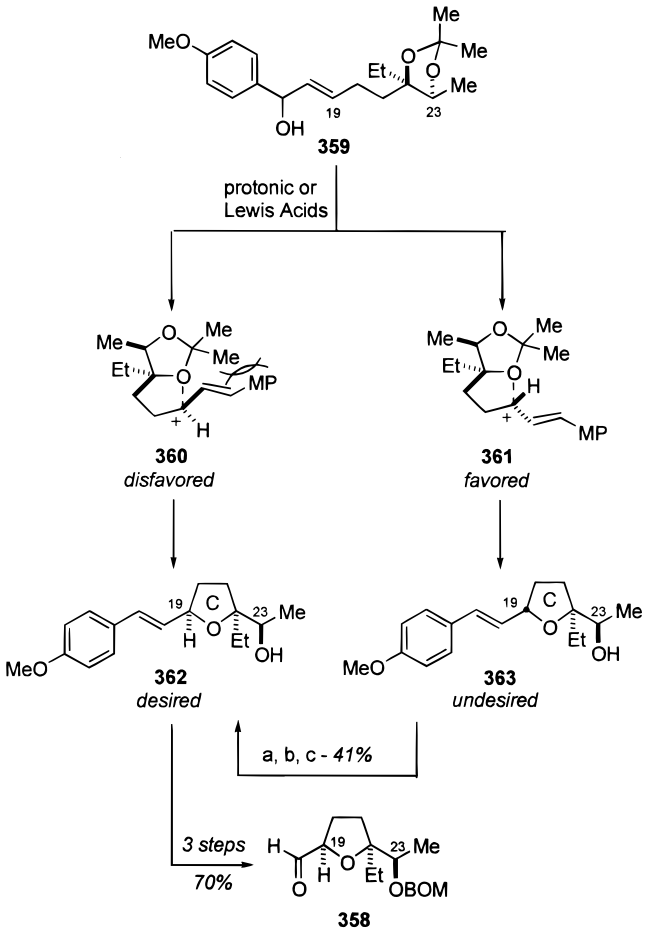
Table 19. Stereochemical Inventory for Horita and Yonemitsu's Synthesis of Lasalocid A and Isolasalocid A

carbon	control element	reaction/source
C_{10}	chiral pool	(*R*)-citronellene
C_{11}	Cram addn	aldol/Zn enolate
C_{12}	Cram addn	aldol/Zn enolate
C_{14}	chiral pool	D-glucose
C_{15}	chiral pool	D-glucose
C_{16}	chiral pool	D-glucose
C_{18}	Cram-chelate	organolithium addn
C_{19}	chelate control	THF/THP formation
C_{22}	chiral pool	D-glucose
C_{23}	chiral pool	D-glucose

1. Synthesis of the C_{18}–C_{24} Fragment

Horita and Yonemitsu developed new methodology for the synthesis of the tetrahydropyran and tetrahydrofuran rings **357** and **358** of lasalocid A and isolasalocid A by acid-catalyzed cyclization of the *p*-methoxyphenyl (MP) allyl alcohols **359** and **364**. For isolasalocid A, treatment of acetonide **359**, derived from D-glucose, with either a protonic or Lewis acid afforded a mixture of tetrahydrofuran rings whose stereoselectivity varied markedly with the reaction conditions (Scheme 82, Table 20). Use of CSA in PhH or THF for 1 h afforded the undesired *trans*-tetrahydrofuran, **363**, in 99:1 selectivity and 60% or 82% yield, respectively (entries 1 and 2). Formation of **363** was kinetically controlled by the steric effect between the isopropylidene and *p*-methoxystyryl groups as shown in transition states **360** and **361**. In CH_2Cl_2, although **363** was the major product after 33 min (entry 3), after 1 h an equilibrium was reached affording **362**:**363** in 89% yield as a 1:2.1 mixture (entry 4). MeOH gave a similar result (entry 5). Lewis acids ($HgBr_2$, $ZnCl_2$, and $ZnBr_2$) were also found to be effective (entries 6−9). In fact, the

Scheme 82[a]



[a] (a) Ac_2O, Et_3N, CH_2Cl_2, rt; (b) CSA, CH_2Cl_2, rt; (c) $LiAlH_4$, Et_2O, 0 °C. (Reprinted with permission from ref 66c. Copyright 1993 Elsevier Sciences Ltd.)

Table 20. Formation of the C-Ring Tetrahydrofuran of Isolasalocid A

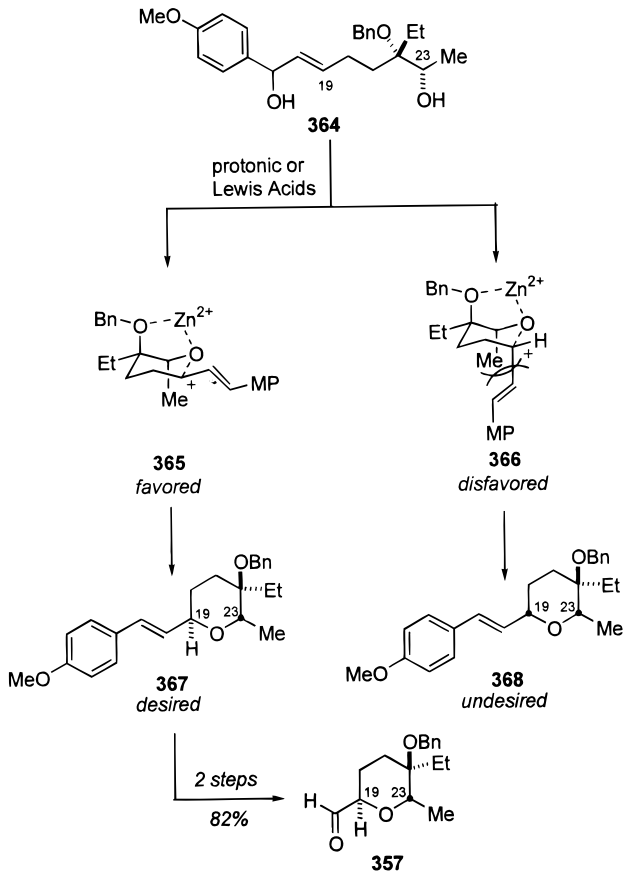
entry	catalyst[a]	time (h)	yield (%)	ratio **362**:**363**
1	CSA[b]	1.0	60	1.0:99
2	CSA[c]	1.0	82	1.0:99
3	CSA	0.3	95	1.0:99
4	CSA	1.0	89	1.0:2.1
5	CSA[d]	1.0	86	1.0:2.3
6	$HgBr_2$	3.0	36	1.0:1.0
7	$ZnCl_2$	3.0	78	1.0:1.6
8	$ZnBr_2$	3.0	96	1.0:1.7
9	$ZnBr_2$	24	99	1.0:1.5

[a] Unless indicated all reactions were performed at room temperature in CH_2Cl_2. [b] Reaction in PhH. [c] Reaction in THF. [d] Reaction in MeOH.

optimum conditions for formation of **362** involved treatment of **359** with $ZnBr_2$ for 24 h at room temperature, which afforded a 99% yield of a 1:1.5 mixture of **362**:**363** (entry 9). The undesired *trans*-tetrahydrofuran **363** was converted into the desired *cis*-tetrahydrofuran **362** by a three-step epimerization of C_{19} that proceeded in 41% yield. Protection of the C_{23} alcohol followed by oxidative cleavage of the MP group completed the synthesis of the $C_{18}-C_{24}$ fragment of isolasalocid A.

Formation of the tetrahydropyran ring of lasalocid A was examined using triol **364** (Scheme 83, Table 21). The desired *trans*-tetrahydropyran **367** was

Scheme 83[a]



[a] Reprinted with permission from ref 66c. Copyright 1993 Elsevier Sciences Ltd.

Table 21. Formation of the C-Ring Tetrahydropyran of Lasalocid A

entry	catalyst[a]	time	yield (%)	ratio **367**:**368**
1	CSA	3 min	54	4.4:1.0
2	CSA	10 min	78	2.0:1.0
3	CSA	12 h	78	1.0:3.3
4	CSA	48 h	60	1.0:4.3
5	$ZnBr_2$	25 min	77	4.5:1.0
6	$ZnBr_2$	12 h	85	3.8:1.0
7	$ZnBr_2$	1.5 h	79	14:1.0[b]

[a] All reactions were performed at room temperature in CH_2Cl_2. [b] Reaction at −20 °C.

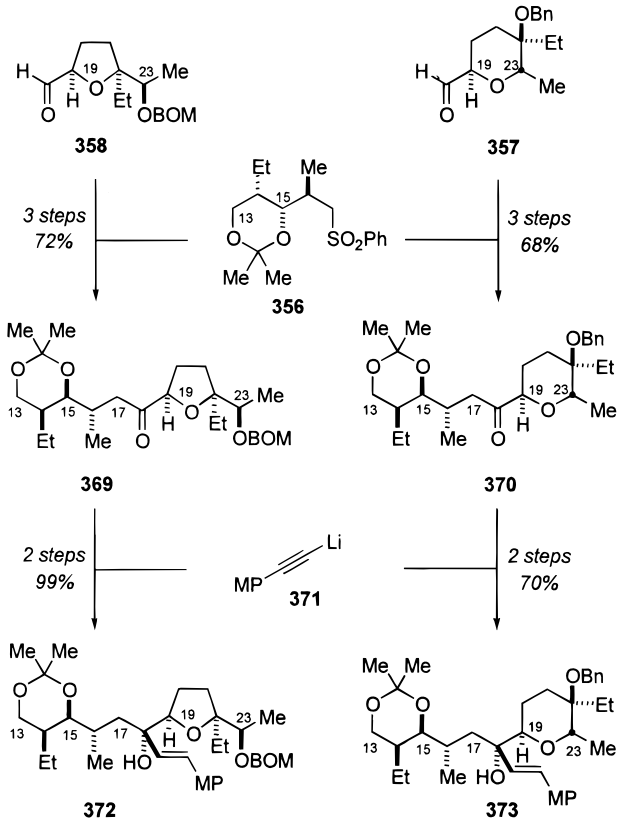
obtained in 54% yield as a 4.4:1 mixture of diastereomers by treatment of **364** with CSA in CH_2Cl_2 (entry 1). However, upon prolonged treatment of **364** with CSA, the kinetic product, **367**, was converted into the undesired *cis*-tetrahydropyran **368** (entries 2−4). The optimum method to generate **367** involved treatment of **364** with $ZnBr_2$ at −20 °C for 1.5 h, which afforded a 79% yield of a 14:1 mixture of **367**:**368** (entry 7). Although **368** is thermodynamically more stable than **367**, **367** was the major product under both kinetic and thermodynamic conditions in the presence of $ZnBr_2$ (entries 5−7). This result was rationalized by reaction through the chelated transition state **365** that does not suffer from a 1,3-diaxial interaction between the C_{24} methyl and the *p*-methoxystyryl group present in **366**. Support for the mechanism was obtained by replacement of the C_{22}−OBn with a bulky TBS protecting group. In this case the reaction

afforded only the nonchelation-controlled product **368**. In analogy to the synthesis of isolasalocid A, oxidative cleavage of the MP group completed the synthesis of the $C_{18}-C_{24}$ fragment of lasalocid A.

2. Synthesis of the $C_{12}-C_{24}$ Fragment

Treatment of the lithium anion of sulfone **356** derived from D-glucose,[67] with aldehyde **358** afforded a mixture of four diastereomeric β-hydroxysulfones. Swern oxidation, followed by desulfurization with aluminum-amalgam, afforded ketone **369** in 72% yield. Chelate-controlled addition of *p*-methoxyphenyl ethynyllithium **371**, followed by alkyne reduction, provided the *trans*-allylic alcohol **372** in 99% yield. In a similar manner aldehyde **357**, was converted into the $C_{13}-C_{24}$ MP *E*-allyl alcohol **373** in 48% overall yield (Scheme 84).

Scheme 84[a]

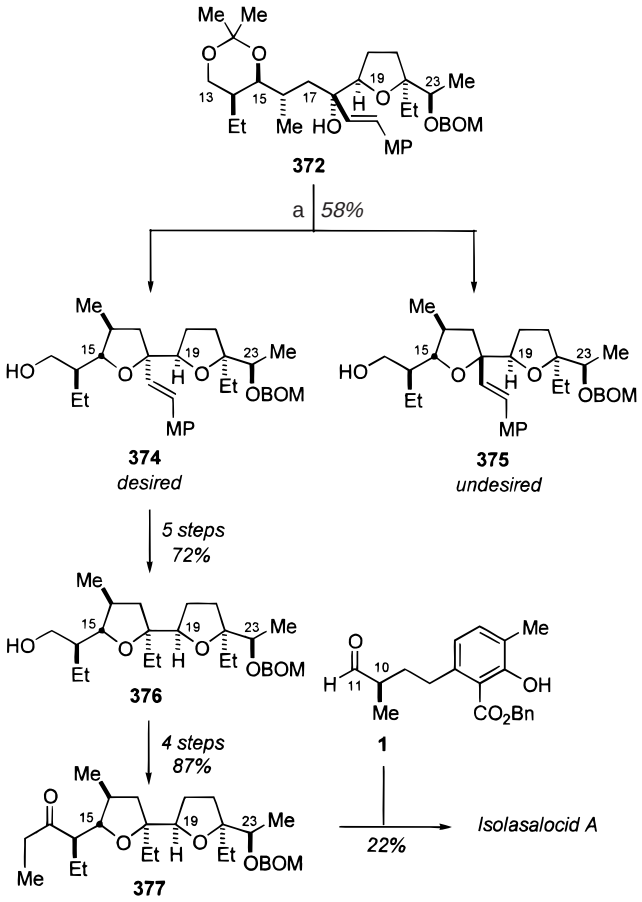


[a] Reprinted with permission from ref 66d. Copyright 1993 Elsevier Sciences Ltd.

A variety of Lewis acids were examined for cyclization of **372** to the bis-tetrahydrofuran **374** required for isolasalocid A (Scheme 85). As observed in the synthesis of the $C_{18}-C_{24}$ fragment, $ZnBr_2$ was found to be the optimal Lewis acid and afforded a 7:1 ratio of **374**:**375** in 58% yield, indicating that **374** was the chelation-controlled cyclization product under thermodynamic conditions. Conversion of the *p*-methoxystyryl group into the C_{18} ethyl, followed by four-step conversion of alcohol **376** into ketone **377**, completed the synthesis of the $C_{12}-C_{24}$ fragment of isolasalocid A.

Similarily, treatment of **373** with $ZnBr_2$ in CH_2Cl_2 afforded the B-ring tetrahydrofuran of lasalocid A in

Scheme 85[a]



[a] (a) $ZnBr_2$, CH_2Cl_2.

90% yield and 35:1 selectivity of **355**:**379** (Scheme 86). The high stereoselectivity obtained in construction of the B-ring tetrahydrofuran was due to a chelation-controlled cyclization under thermodynamic conditions via the double chelation of zinc cations, as illustrated by formation of the thermodynamically stable intermediate **378**. In analogy to the isolasalocid A synthesis, conversion of the *p*-methoxystyryl group into the C_{18} ethyl, followed by four-step conversion of alcohol **380** into ketone **2**, completed the synthesis of the $C_{12}-C_{24}$ fragment of lasalocid A.

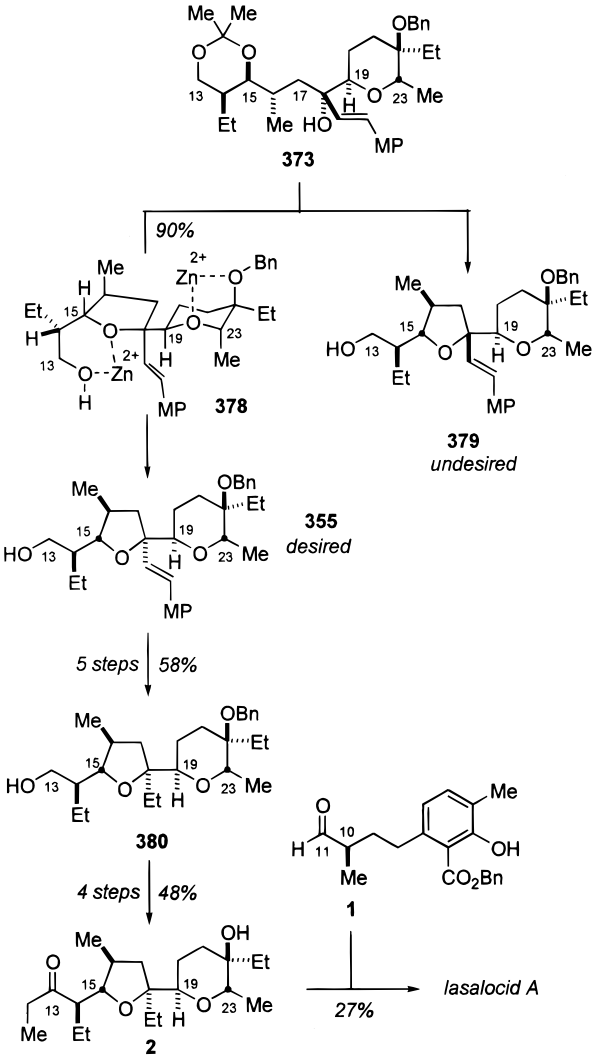
3. Fragment Coupling—The Aldol Reaction

As in the Kishi and Ireland syntheses of lasalocid A, reaction of the zinc enolate of ketone **377** or **2** with aldehyde **1** afforded, after hydrogenation of the C_1 benzyl ester, a 22% isolated yield of isolasalocid A or a 27% yield of lasalocid A, respectively.

T. 1990, Ionomycin (Evans)

Ionomycin, with 14 stereogenic centers, contains two unique architectural features that distinguish it from other members of the family of polyether antibiotics.[68] First, it is the only example of a doubly charged ionophore, thus affording the unique opportunity to form 1:1 charge-neutral hexacoordinate complexes with divalent cations. Second, in addition to the carboxylate ligand, the β-dicarbonyl at C_9-C_{11} provides an additional charged ligation point. A total synthesis of ionomycin was reported by Evans[69] and

Scheme 86[a]



[a] Reprinted with permission from ref 66d. Copyright 1993 Elsevier Sciences Ltd.

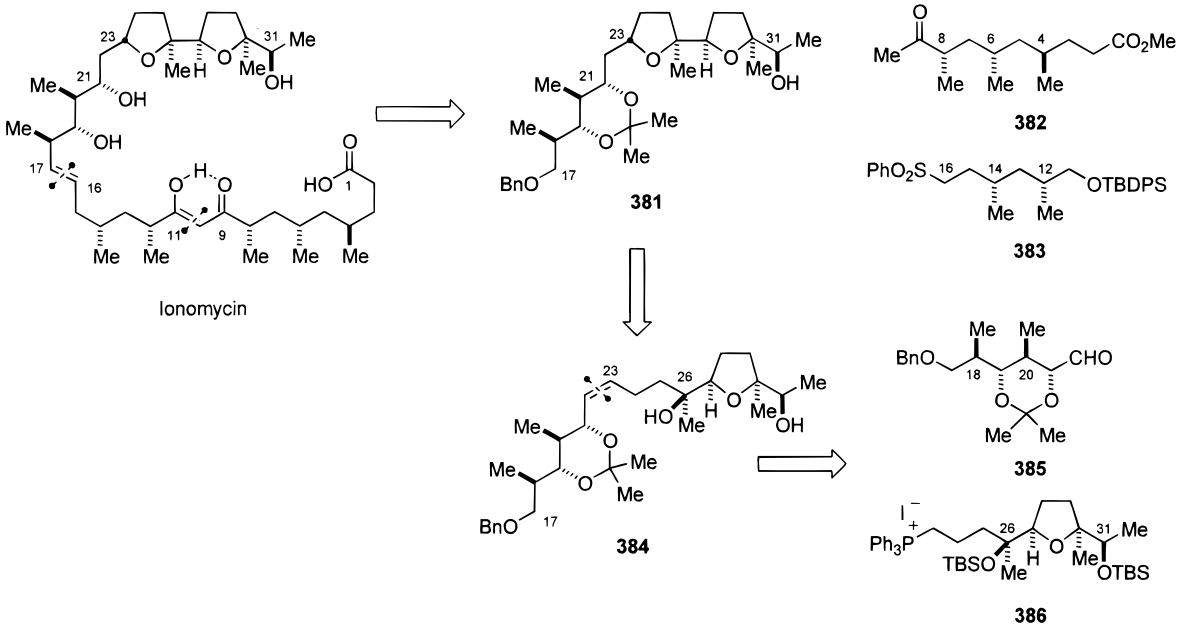
Table 22. Stereochemical Inventory for Evan's Synthesis of Ionomycin

carbon	control element	reaction/source
C_4	A-1,3	alkylation/oxazolidinone
C_6	A-1,3	directed hydrogenation
C_8	A-1,3	boron aldol/oxazolidinone
C_{12}	A-1,3	alkylation/l-prolinol
C_{14}	A-1,3	alkylation/oxazolidinone
C_{18}	chiral pool	β-hydroxyisobutyric acid
C_{19}	A-1,3	boron aldol/oxazolidinone
C_{20}	A-1,3	boron aldol/oxazolidinone
C_{21}	thermodynamic	equilibration
C_{23}	A-1,3	alkoxymercuration
C_{26}	Cram-chelate	Grignard addn
C_{27}	A-1,3	boron aldol/oxazolidinone
C_{30}	non-selective	*m*-CPBA oxidation
C_{31}	non-selective	*m*-CPBA oxidation

Hanessian in 1990, although a number of groups have reported the synthesis of various fragments of this complex ionophore.

Evans' retrosynthetic approach to ionomycin divided the molecule into four major fragments (Scheme 87). Disconnection of the *trans* $C_{16}-C_{17}$ double bond and the β-dicarbonyl C_9-C_{11} afforded the C_1-C_{10}, $C_{11}-C_{16}$ and $C_{17}-C_{32}$ synthons **381**, **382** and **383**, respectively. Fragment **382** is similar to the $C_{21}-C_{26}$ fragment of monensin A prepared by Kishi and Still. Both of these fragments contained the common theme of alternating methyl-bearing stereocenters characteristic of propionate-based natural products. For the $C_{17}-C_{32}$ fragment **381** it was envisioned that the C_{23} stereocenter would be incorporated late in the synthesis during formation of the associated tetrahydrofuran ring through an intramolecular oxymercuration or related haloetherification of the $C_{22}-C_{23}$ *Z*-olefin is **384**. Therefore, the $C_{17}-C_{32}$ fragment **384** was disconnected at the $C_{22}-C_{23}$ bond generating the $C_{17}-C_{22}$ and $C_{23}-C_{32}$ fragments **385** and **386**. Collectively, these two transforms provided four subunits of comparable complexity. The stereochemical inventory for Evan's synthesis of ionomycin is summarized in Table 22.

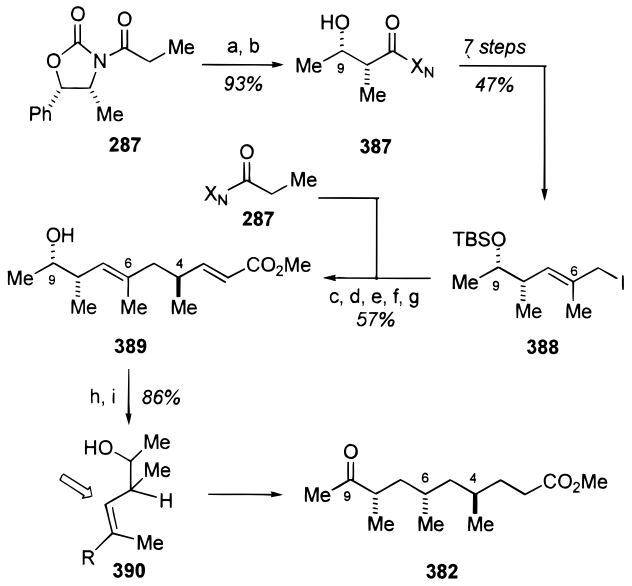
Scheme 87



1. Synthesis of the C_1–C_{10} Fragment[70,71]

Boron aldol reaction of norephedrine oxazolidinone **(287)** with acetaldehyde afforded **387** in 93% yield and introduced the C_8 stereocenter (Scheme 88).

Scheme 88[a]



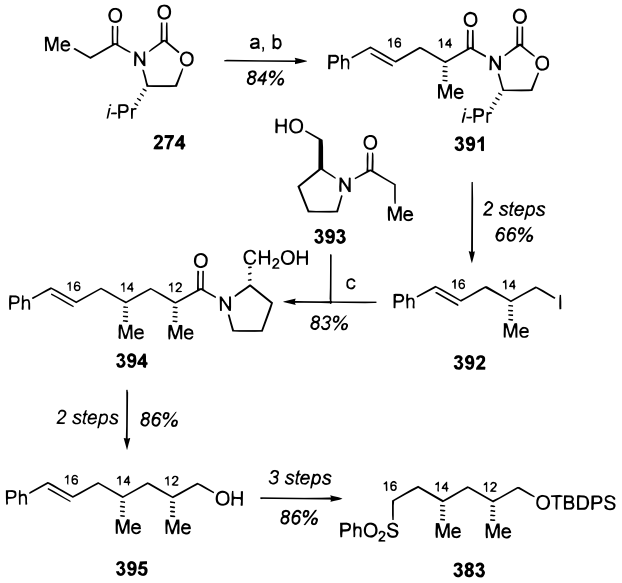
[a] (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C; (b) MeCHO; (c) NaN(TMS)$_2$, THF, −78 to −50 °C; (d) $LiAlH_4$, THF; (e) $(ClCO)_2$, DMSO, Et_3N; (f) $MeO_2CCH{=}PPh_3$, CH_2Cl_2; (g) $HF{\cdot}H_2O$, MeCN; (h) H_2, [Rh(NBD)DIPHOS-4]BF_4, CH_2Cl_2; (i) $Pyr{\cdot}SO_3$, Et_3N, DMSO. (Reprinted with permission from ref 76. Copyright 1986 Elsevier Sciences Ltd.)

Conversion of **387** into iodide **388** was completed in seven steps and 47% yield. A second alkylation of **287** with **388** introduced the C_4 methyl stereocenter. The C_6 methyl stereocenter was introduced with 94:6 selectivity by a directed hydrogenation reaction from the C_9 secondary alcohol in **389** with 5 mol % of a cationic rhodium catalyst. The selectivity of the reaction was controlled by A-1,3 conformational effects through transition state **390**. Oxidation of the C_9 alcohol to ketone **382** completed the synthesis of the C_1−C_9 fragment in 13 steps and 21% overall yield.

2. Synthesis of the C_{11}–C_{16} Fragment[72]

Consecutive alkylation of two propionate enolates generated the *syn*-1,3-dimethyl relationships present in the C_{11}−C_{16} fragment. The C_{14} stereocenter was generated by alkylation of the lithium enolate derived from oxazolidinone **274** with cinnamyl bromide to provide **391** in 84% yield (Scheme 89). Conversion of **391** into iodide **392** was achieved in 66% yield. Although oxazolidinones **274**, **275**, and **287** have proved extremely valuable for the synthesis of polyether ionophores, they are not nucleophilic enough to react with *β*-branched alkyl halides with acceptable levels of diastereoselectivity. Therefore, to successfully incorporate the *syn*-1,3-dimethyl relationships required for ionomycin, Evans employed the chiral propionate enolate derived from L-prolinol **393**. Reaction of the potassium−lithium enolate derived from **393** with iodide **392** afforded an 83% yield of **394** as a 97:3 mixture of C_{12} epimers. Completion of

Scheme 89[a]



[a] (a) LDA, THF, −78 °C; (b) $PhCH{=}CHCH_2Br$, −40 to 0 °C; (c) KH, LDA, HMPA, THF, −78 °C. (Reprinted with permission from ref 76. Copyright 1986 Elsevier Sciences Ltd.)

the synthesis of **383** was accomplished by internally assisted hydrolysis (N to O acyl transfer) of the imide in refluxing NaOH to afford the carboxylic acid. Subsequent reduction with $LiAlH_4$ to the corresponding alcohol **395** was achieved in 86% yield. Conversion of **395** into sulfone **383** was achieved in 86% yield, completing the synthesis of the C_{11}−C_{16} fragment in nine steps and 34% overall yield from **274**.

3. Synthesis of the C_{17}–C_{22} Fragment[73−75]

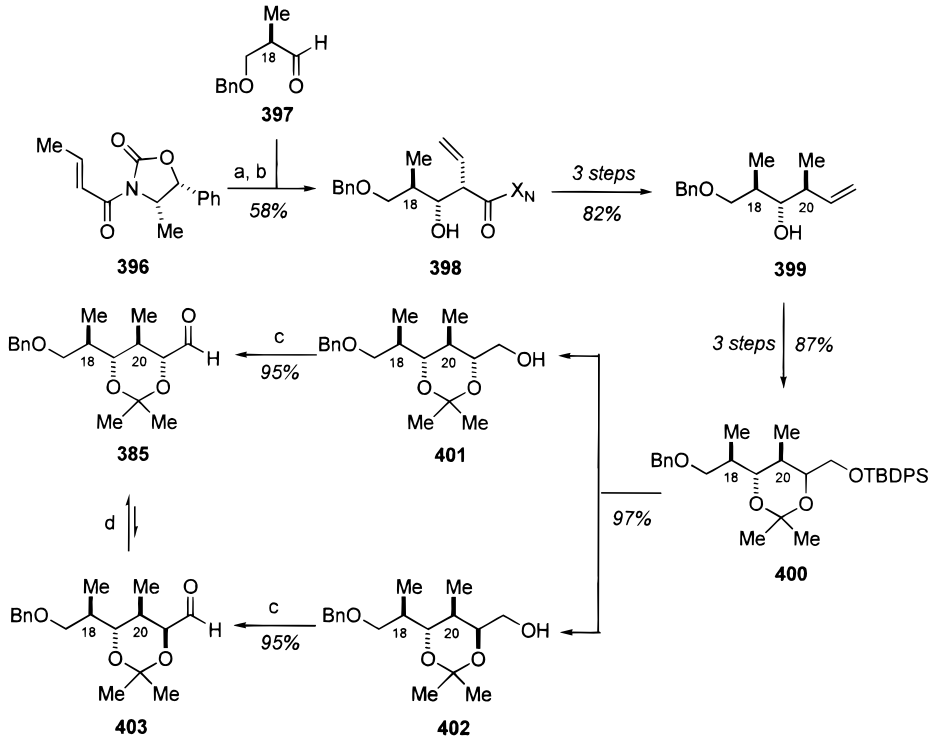
Aldol reaction of the boron enolate derived from crotonimide **396** with aldehyde **397** afforded the *syn*-α-vinyl adduct **398** in 58% yield.[76] Reduction of **398** to the diol, tosylation, and treatment with triethylborohydride introduced the C_{20} methyl group in 82% overall yield (Scheme 90).

Bishydroxylation of **399** introduced the remaining oxygen functionality. Protection of the primary alcohol, acetonide formation, followed by desilylation afforded **401** and **402** as a 78:22 mixture of diastereomers in 85% yield from **399**. The major isomer **401** was isolated by chromatography. Equilibration of the C_{21} stereocenter in the minor diastereomer was achieved by oxidation followed by epimerization (K_2CO_3/methanol) to afford a 92:8 equilibrium mixture of **385** and **403**.

4. Synthesis of the C_{23}–C_{32} Fragment[77,78]

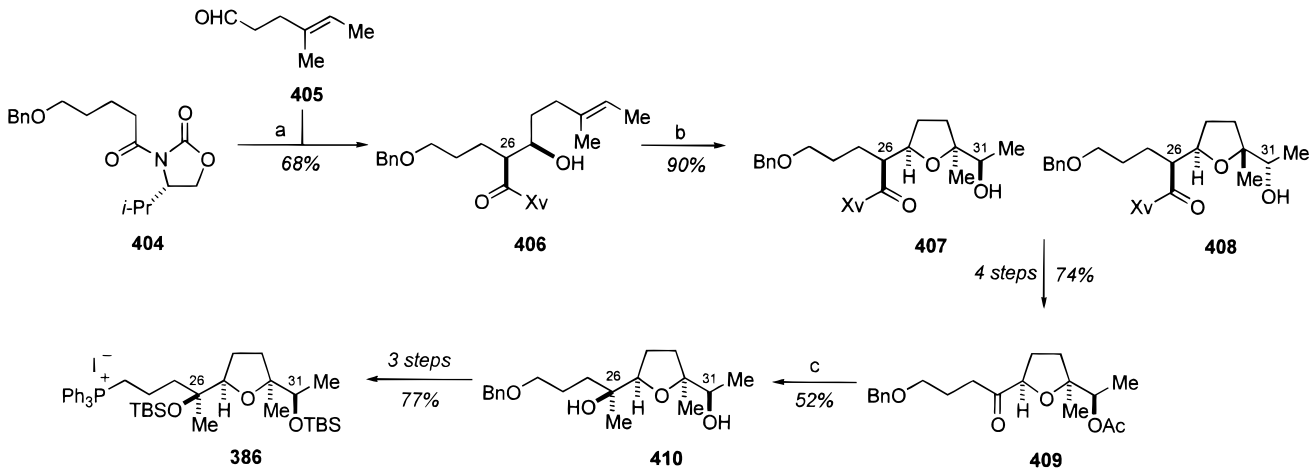
Boron aldol reaction of carboximide **404** with aldehyde **405** provided the aldol adduct **406** in 68% yield and 97% diastereoselectivity (Scheme 91). Epoxidation of **406** with *m*-CPBA, followed by cyclization with HOAc, afforded a 1:1 mixture of tetrahydrofurans **407** and **408** in 90% yield. An alternative approach to **407** using Kishi's bishomoallylic epoxidation technology was unsuccessful. Conversion of **407** to ketone **409** was achieved in four steps and 74% yield. Chelate-controlled addition of MeMgBr to **409** afforded diol **410** in 52% yield. Protection of the C_{31}

Scheme 90[a]



[a] (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C; (b) H_2O_2, MeOH; (c) Pyr·SO_3, Et_3N, DMSO; (d) K_2CO_3, MeOH.

Scheme 91[a]



[a] (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2; (b) *m*-CPBA, HOAc; (c) MeMgBr, CH_2Cl_2/Et_2O, −78 °C.

and C_{26} alcohols, removal of the benzyl protecting group, and formation of phosphonium salt completed the synthesis of the $C_{23}-C_{32}$ fragment **386** in 10 steps and 18% overall yield.

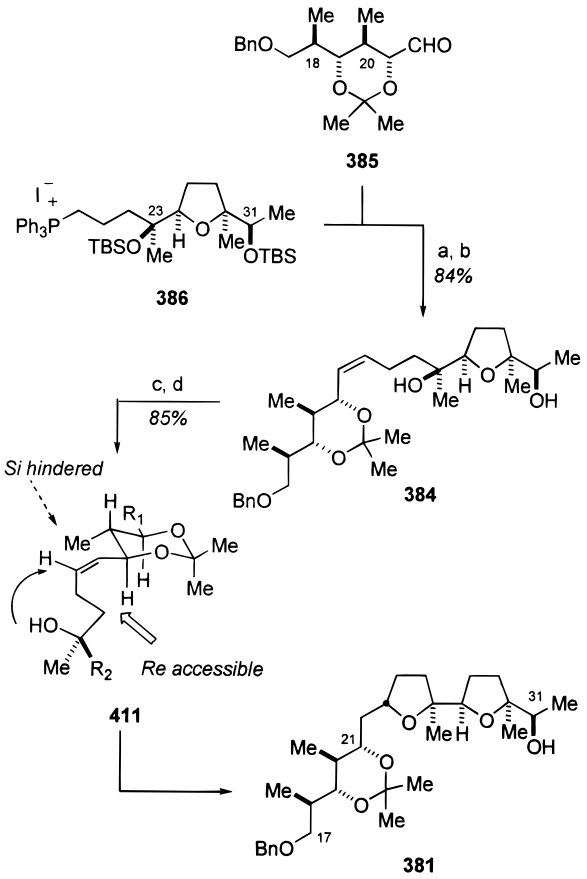
5. Fragment Coupling

Condensation of aldehyde **385** with the ylide derived from **386**, under salt-free conditions, followed by removal of the silyl protecting groups, provided the desired *cis* olefin **384** in 84% yield (97:3 *Z*:*E*). Internal oxymercuration of the $C_{22}-C_{23}$ double bond afforded a 93:7 mixture of C_{23} diastereomers **381** (Scheme 92). The stereochemical course of the electrophile-induced cyclization to form the second tetrahydrofuran ring and the associated C_{23} stereocenter was a consequence of the C_{22} *cis* olefin geometry. The reaction proceeded through **411** with attack of the electrophile occurring on the *Re* face of the olefin since the *Si* face is blocked by the C_{20} methyl.

Protection of the C_{31} hydroxyl group of **381**, removal of the benzyl group by hydrogenolysis, and oxidation afforded aldehyde **412** in 94% yield. Reaction of **412** with the lithium conjugate of sulfone **383** afforded a mixture of β-hydroxysulfones that were quenched with acetic anhydride, reduced with sodium amalgam, and deprotected to yield an 86:14 mixture of *trans*:*cis* olefins in 62% yield favoring **413** (Scheme 93).

Aldol reaction of the enolate derived from **382** with the aldehyde derived from alcohol **413** afforded a 1:1 mixture of diastereomers **414** in 85% yield. Completion of the synthesis was achieved by formation of the β-diketone by oxidation with Collins reagent, deprotection of the C_{31} silyl group and the acetonide,

Scheme 92[a]



[a] (a) $NaN(TMS)_2$, toluene, −78 °C; (b) TBAF, THF, 80 °C; (c) $Hg(OAc)_2$, CH_2Cl_2, −78 to −20 °C; (d) $NaBH_4$, NaOH (aq), MeOH, −78 °C.

and hydrolysis of the methyl ester with LiOH. Ionomycin was isolated as its calcium complex in 51% yield from **414**.

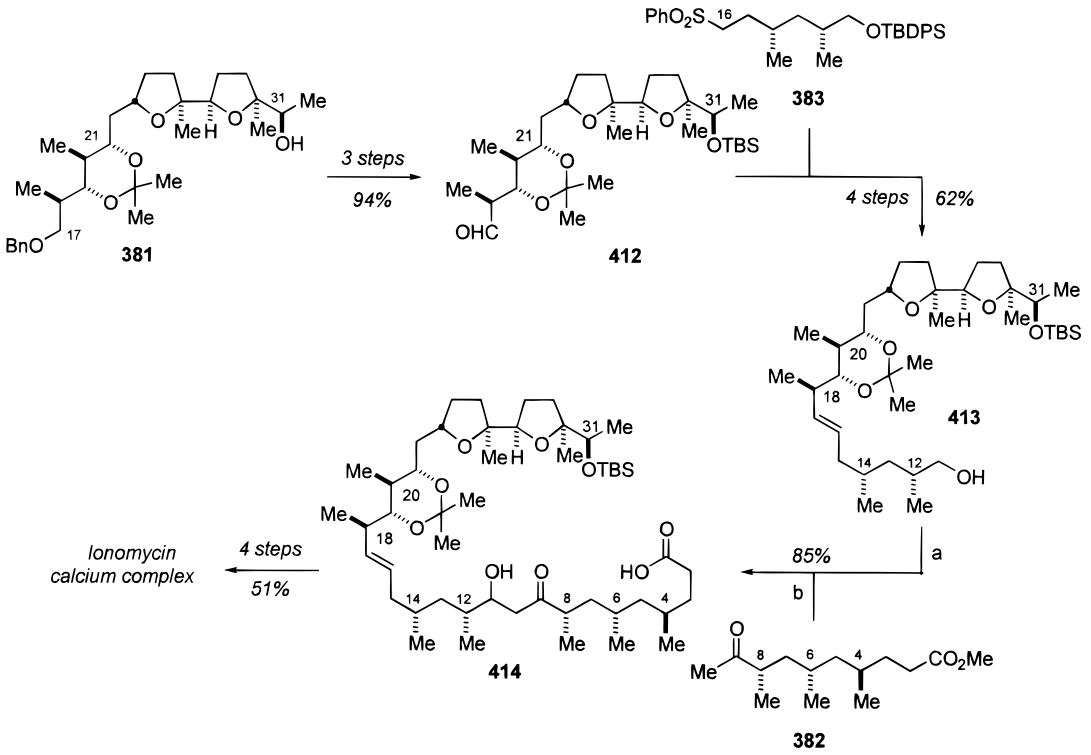
U. 1990, Ionomycin (Hanessian)

A total synthesis of ionomycin was also completed by Hanessian in 1990.[79] The retrosynthetic approach was similar to that employed by Evans, with the primary targets being the C_1-C_{10}, $C_{11}-C_{16}$, $C_{17}-C_{22}$, and $C_{23}-C_{32}$ fragments **382**, **415**, **416**, and **417** (Scheme 94).[80] In contrast to the Evans method, Hanessian employed his lactone replication strategy to synthesize fragments **382**, **415**, and **416** from **(***R***)**- and (*S*)-4-hydroxymethyl-2-buten-4-olides, derived from L-glutamic acid **423**, by cyclic stereocontrol.[81] The stereochemical inventory for Hanessian's synthesis of ionomycin is summarized in Table 23.

1. Synthesis of the C_1–C_{10} and C_{11}–C_{16} Fragments

Michael reaction of **422** with Me_2CuLi afforded lactone **424** in 87% yield and introduced the C_6 (and C_{12}) stereocenters (Scheme 95). The stereochemical control of the reaction was governed by the presence of the bulky C_4 substituent which influences the approach of the incoming nucleophile. Reduction, tritylation, mesylation, and treatment with fluoride ion afforded the inverted epoxide **425** in 84% yield. Addition of the lithium anion of phenylthiomethyl ether to **425** afforded **426** in 89% yield. Sulfur-assisted C-methylation of the C_8 tosylate afforded the 1,3-*syn*-dimethyl compound **427** in 90% yield. The thioether group was essential for this transformation, since elimination was competitive when the corresponding sulfoxide or alkyl chain was present.

Scheme 93[a]



[a] (a) $(ClCO)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (b) *n*-Bu_2BOTf, (*i*-Pr)$_2NEt$, CH_2Cl_2, −78 °C.

Scheme 94[a]

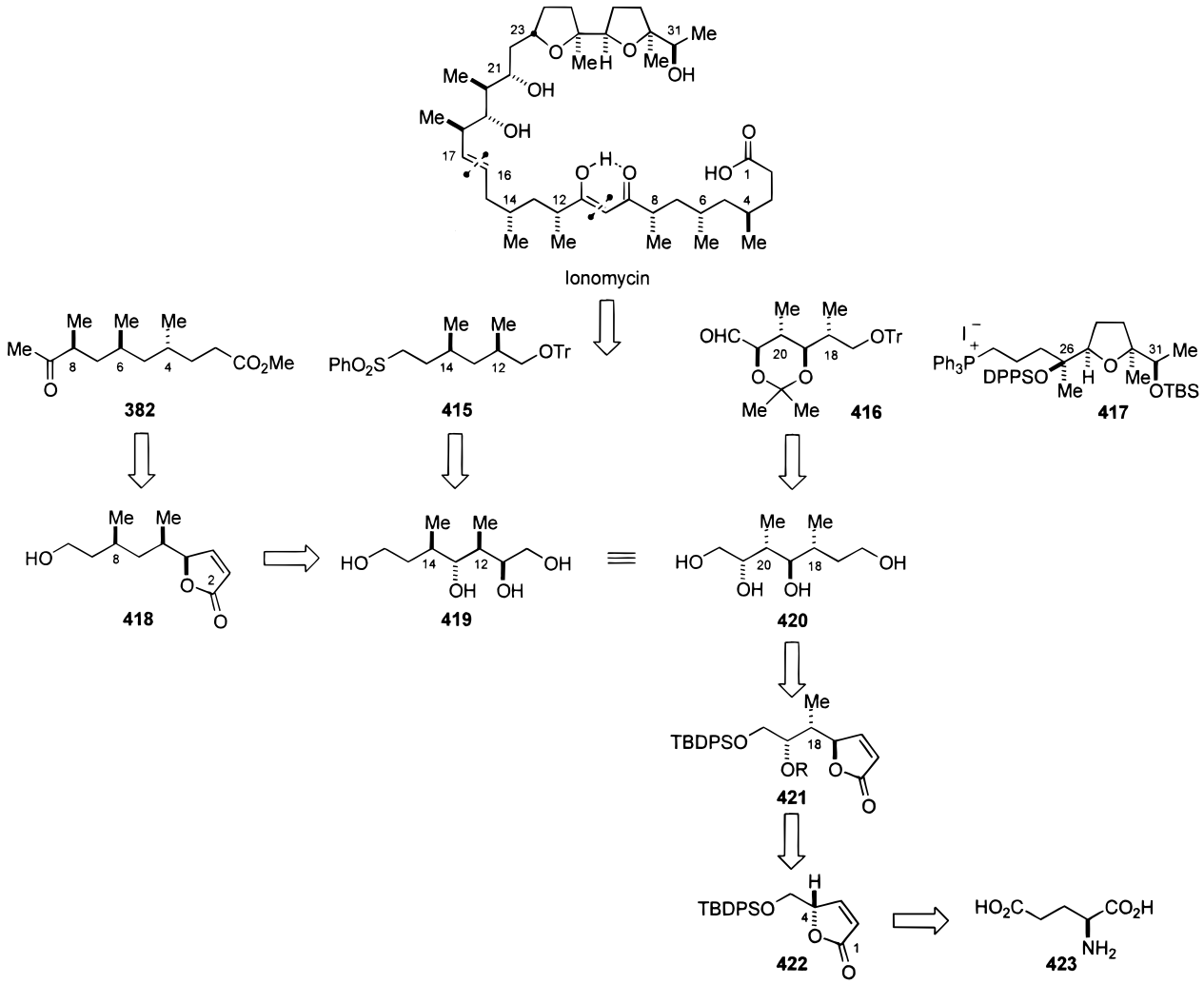


Table 23. Stereochemical Inventory for Hanessian's Synthesis of Ionomycin

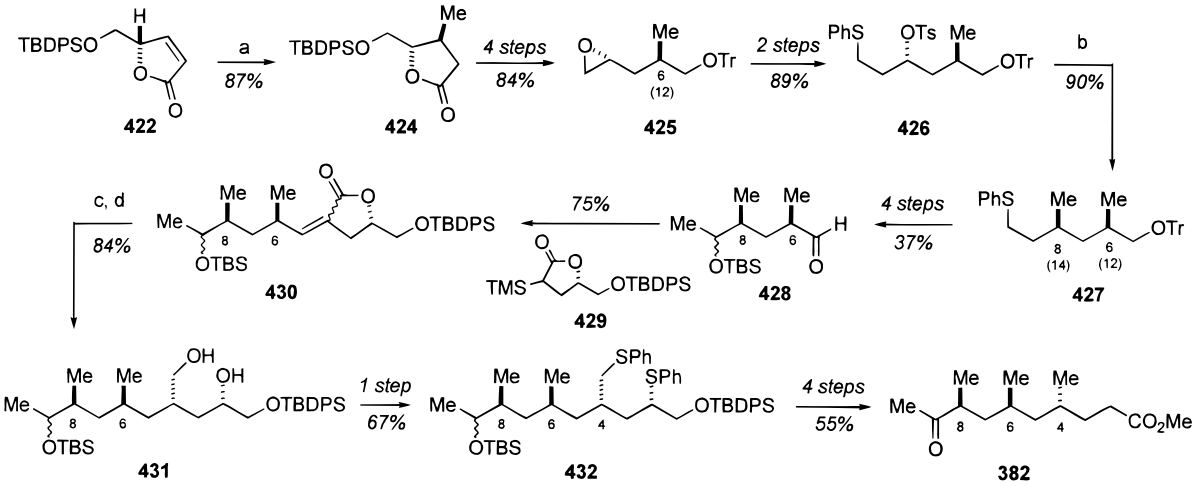
carbon	control element	reaction/source
C_4	chiral pool	L-glutamic acid
C_6	chiral pool	L-glutamic acid
C_8	chiral pool	L-glutamic acid
C_{12}	chiral pool	L-glutamic acid
C_{14}	chiral pool	L-glutamic acid
C_{18}	chiral pool	L-glutamic acid
C_{19}	chiral pool	L-glutamic acid
C_{20}	chiral pool	L-glutamic acid
C_{21}	thermodynamic	equilibration
C_{23}	A-1,3	alkoxymercuration
C_{26}	A-1,3	bishomoallylic alcohol epoxidation
C_{27}	A-1,3	bishomoallylic alcohol epoxidation
C_{30}	A-1,3	Sharpless AE
C_{31}	A-1,3	Sharpless AE

Introduction of the C_1-C_4 carbons was achieved by Peterson olefination of aldehyde **428** with trimethylsilyllactone **429**, also derived from L-glutamic acid. The *E*,*Z*-mixture of olefins **430** was hydrogenated to the corresponding *cis* lactone, then converted into the diol **431** (as a C_9 mixture of epimers). Treatment of **431** with diphenyl disulfide generated the bis(phenylthio)ether **432** in 67% yield. Reduction of **432** with Raney nickel introduced the C_4 methyl group. Desilylation, Jones oxidation, and esterification completed the synthesis of the C_1-C_{10} fragment **382** in 20 steps and 5% yield from **422**.

2. Synthesis of the C_{17}–C_{22} Fragment

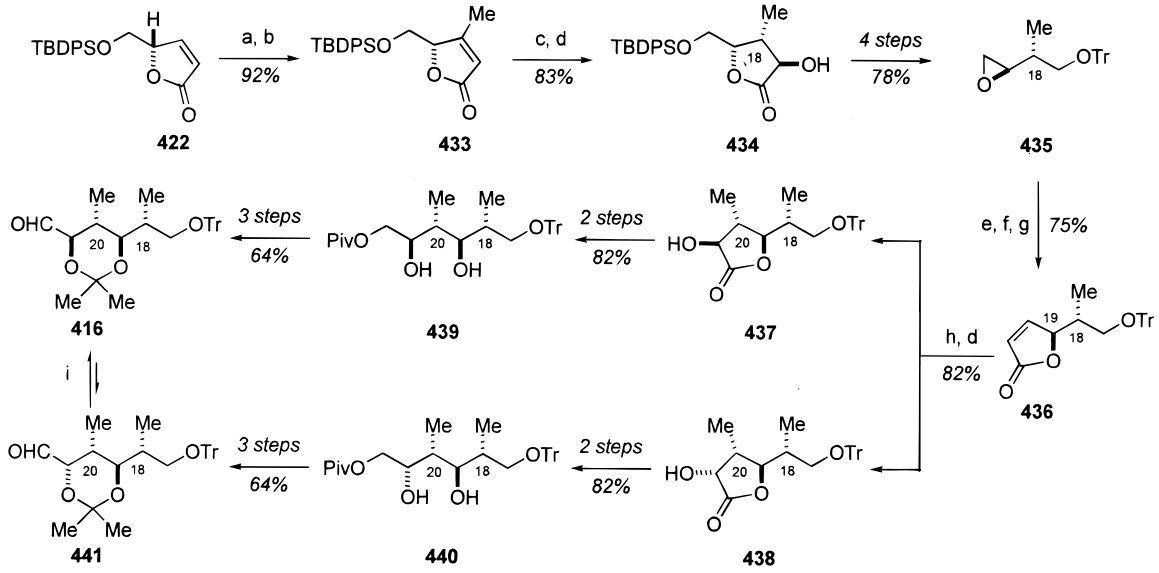
As a further extension of the lactone replication strategy, Hanessian successfully introduced the C_{18}, C_{19}, and C_{20} stereocenters with high selectivity (Scheme 96). Since the conjugate addition method previously employed in the synthesis of the C_1-C_{10} and $C_{11}-C_{16}$ fragments introduced the methyl group from the face opposite the bulky C_4 substituent, Hanessian developed an alternative protocol to provide the corresponding syn derivative. Thus, treatment of **422** with diazomethane afforded an intermediate Δ^2-pyrazoline that upon heating gave the methyl butenolide **433**. Catalytic hydrogenation of **433** was selective, affording only the product containing the desired *syn*-C_3/C_4 relationship. Enolate formation and hydroxylation afforded α-hydroxylactone **434** in 83% yield. Reduction and epoxide formation via the primary sulfonate gave **435** in 78% yield. Two-carbon extension of **435** with dilithio(phenylseleno)-acetate, lactonization, and elimination provided **436**, the replicated template. Reiteration of this sequence afforded lactones **437** and **438** as a 1.7:1 mixture of

Scheme 95[a]



[a] (a) CuBr·Me_2S, Et_2O, MeLi; (b) CuI, MeLi, Et_2O, −78 to −20 °C; (c) H_2, Rh−Al_2O_3, EtOAc; (d) BH_3·Me_2S, THF.

Scheme 96[a]



[a] (a) CH_2N_2, Et_2O, HOAc; (b) $Ca(CO_3)_2$, toluene, reflux; (c) Rh−Al_2O_3, EtOAc; (d) KHMDS, MoOPh, THF; (e) $PhSeCH_2CO_2H$, *n*-BuLi; (f) EDAC·HCl; DMAP; (g) H_2O_2, CH_2Cl_2; (h) CuI, MeLi·LiBr, −20 °C; (i) K_2CO_3.

C_{21} epimers. The minor diastereomer **437** contained the full complement of alternating methyl and hydroxyl groups required for the C_{17}−C_{22} fragment. The problem of low selectivity was overcome by conversion of **438** into the acetonide **441** followed by equilibration to the desired diastereomer **416** using the procedure of Evans. The synthesis of the C_{17}−C_{22} fragment **416** was completed in 19 steps and 19% overall yield from **422**.

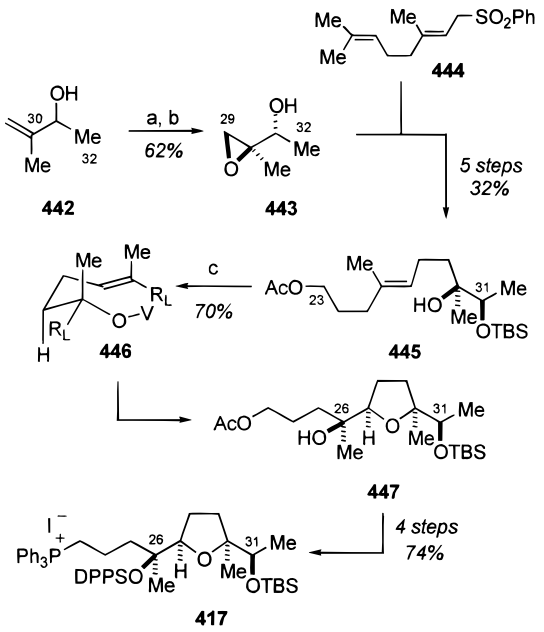
3. Synthesis of the C_{23}–C_{32} Fragment

Sharpless asymmetric epoxidation and Kishi's bishomoallylic alcohol-directed epoxidation were employed in the preparation of the C_{23}−C_{32} fragment **417** (Scheme 97). Epoxide **443** was prepared by Sharpless asymmetric epoxidation of (*R*,*S*)-3-methyl-3-buten-2-ol **(442)** and kinetic resolution. Ring opening of **443** with the lithium anion of sulfone **444** afforded, after protection, ozonolysis and reduction, **445**, the precursor for the epoxidation-cyclization sequence in 32% overall yield. $VO(acac)_2$-catalyzed epoxidation of **445** in hexane afforded the *cis* tetrahydrofuran **447** in 70% yield and 9:1 *cis*:*trans* selectivity. Formation of the *cis* tetrahydrofuran was due to reaction through transition state **446**, which minimizes the steric compression between the vinylic methyl group and the tertiary oxygen bound to the catalyst. This selectivity was best in noncoordinating solvents. In this manner, Hanessian successfully extended the Kishi bishomoallylic epoxidation methodology to tertiary alcohols. Protection, deacylation, and conversion of the alcohol into the phosphonium salt completed the synthesis of the C_{23}−C_{32} fragment **417** in 11 steps and 10% overall yield from **442**.

4. Fragment Coupling

The final coupling strategy employed by Hanessian to complete the synthesis of ionomycin was comparable to that employed by Evans.

Scheme 97[a]



[a] (a) Diisopropyl-D-tartrate, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, 4 Å sieves, −20 °C; (b) then Me_2S, −20 °C; (c) *t*-BuOOH, $VO(acac)_2$, 3 Å mol sieves, hexanes.

V. 1991, Ferensimycin B (Evans)

Ferensimycin B, a member of the lysocellin family of ionophores, shares common structural features with both lonomycin A and X-206. A total synthesis of ferensimycin B was reported by Evans.[82] The methods and strategy used by Evans in the synthesis of the γ- and δ-lactols of X-206 proved to be instrumental in the design of a synthesis for ferensimycin B. In addition, the chemistry employed in the synthesis of the sensitive ring A, the carboxy terminus, and, in particular, the potentially labile stereogenic center at C_2 proved invaluable in Evan's subsequent approach to the synthesis of lonomycin A.

Retrosynthetic analysis of ferensimycin B revealed an aldol disconnection at C_9-C_{10} that divided the molecule into the C_1-C_9 and $C_{10}-C_{23}$ fragments **448** and **449** of comparable complexity (Scheme 98). In analogy to the synthesis of X-206, chiral imide enolate bond constructions were employed to establish 8 of the 16 stereogenic centers of the C_1-C_9 and $C_{10}-C_{23}$ subunits. The stereogenic centers at C_3, C_4, C_9, C_{10}, C_{16}, C_{17}, and C_{18} were established through internal asymmetric induction, while those at C_{20} and C_{21} were established using asymmetric epoxidation methodology. The stereochemical inventory for Evan's synthesis of ferensmycin B is summarized Table 24.

1. Synthesis of the C_1–C_9 Fragment

Chiral imide enolate alkylation and aldol methodology was used to establish five of the six stereocenters in the C_1-C_9 fragment (Scheme 99).[83] Alkylation of the norephedrine-derived oxazolidinone **287** with methallyl iodide gave a 96:4 mixture of diastereomers from which **452** was isolated in 73% yield. Conversion into aldehyde **453** followed by an aldol reaction with **287** afforded **454** in 86% yield as a single diastereomer. Reductive removal of the auxiliary and protection of the diol as the α-naphthylidene acetal yielded **455** in 74% yield. Treatment of **455** with thexylborane followed by an oxidative workup produced an 86:14 mixture of C_4 epimers from which **457** was isolated in 79% yield. The selectivity obtained in the hydroboration of **455** can be rationalized in terms of A-1,3 strain where reaction through transition state **456** is favored.

Scheme 98

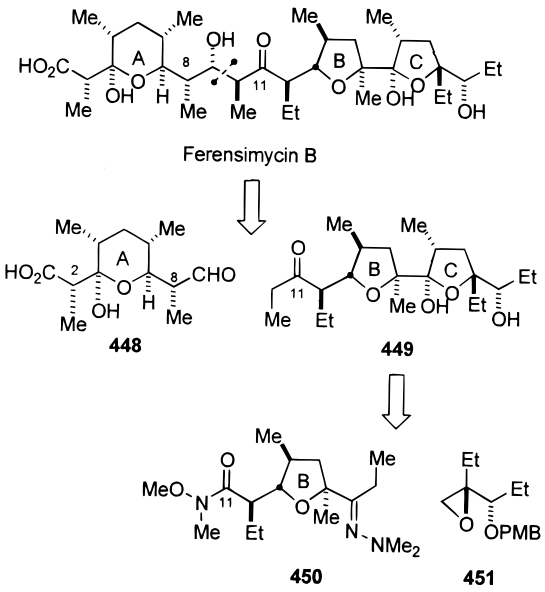
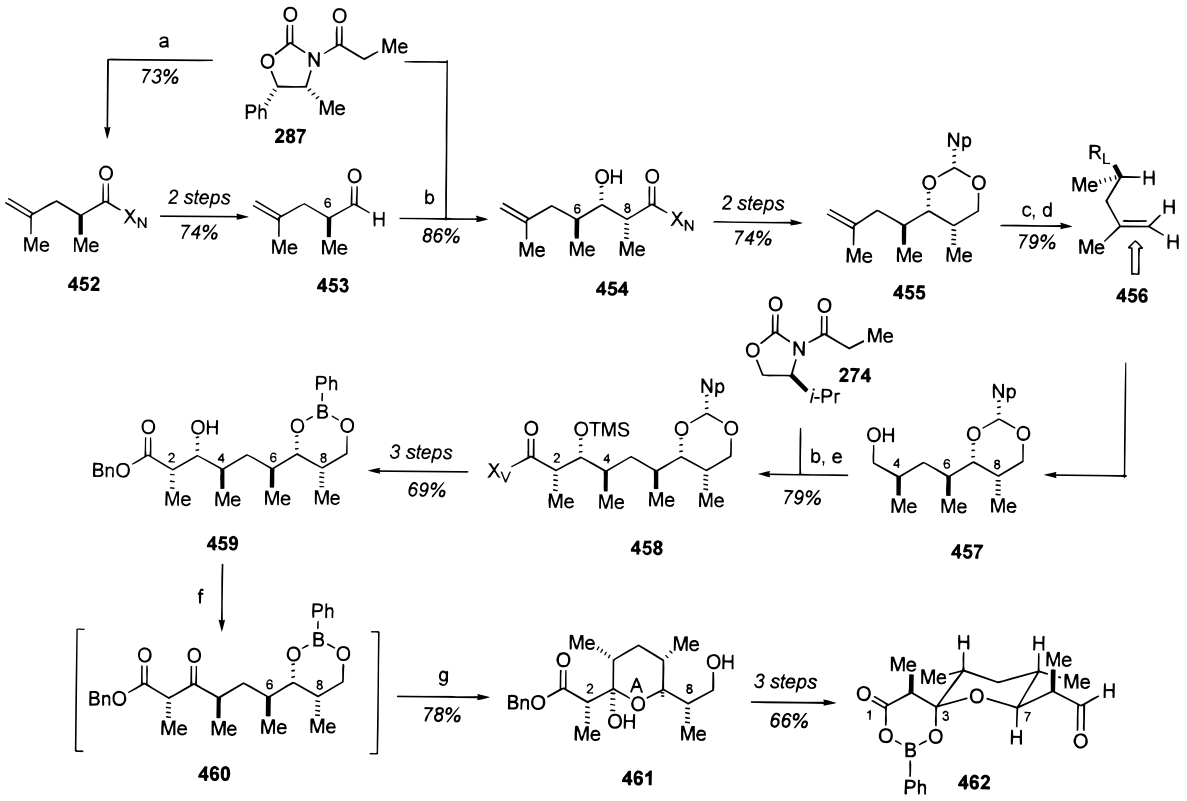


Table 24. Stereochemical Inventory for Evan's Synthesis of Ferensimycin B

carbon	control element	reaction/source
C_2	A-1,3	boron aldol/oxazolidinone
C_3	A-1,3	boron aldol/oxazolidinone
C_4	A-1,3	hydroboration
C_6	A-1,3	alkylation/oxazolidinone
C_7	A-1,3	boron aldol/oxazolidinone
C_8	A-1,3	boron aldol/oxazolidinone
C_9	Cram-chelate	aldol/Zn enolate
C_{10}	Cram-chelate	aldol/Zn enolate
C_{12}	A-1,3	boron aldol/oxazolidinone
C_{13}	A-1,3	boron aldol/oxazolidinone
C_{14}	A-1,3	alkylation/oxazolidinone
C_{16}	A-1,3	bishomoallylic alcohol epoxidation
C_{17}	cyclic stereocontrol	THF-formation
C_{18}	Cram-chelate	organolithium addition
C_{20}	A-1,3	Sharpless AE
C_{21}	A-1,3	Sharpless AE

The remaining carbon skeleton was assembled through a boron aldol reaction of **274** and the aldehyde derived from **457** to provide **458** as a single diastereomer. Due to the liability of β-keto esters such as **460** toward racemization, the acetal protecting group was changed to the more labile C_7-C_9 phenyl boronate. Transesterification of the imide, deprotection of the secondary alcohol, and Swern oxidation afforded the highly sensitive β-keto ester **460**. Deprotection of **460** with aqueous peroxide provided the A-ring lactol **461** in 78% yield from **459**. No evidence of epimerization at C_2 was observed during these transformations. Conversion to the aldehyde followed by hydrogenolysis afforded an unstable acid that was isolated as the boronic ester **462** in 66% yield. The completed C_1-C_9 fragment was prepared in 17 steps and 8% overall yield.

Scheme 99[a]



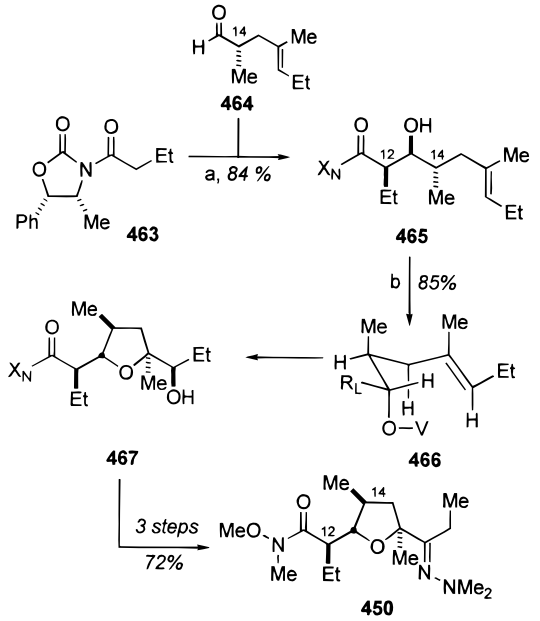
[a] (a) LDA, THF, $CH_2C(Me)CH_2I$, −78 °C; (b) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C; (c) thexylborane, THF, −10 °C, 5 h; (d) H_2O_2, $NaHCO_3$; (e) TMS-imidazole, DMAP, CH_2Cl_2; (f) $(COCl)_2$, DMSO, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, − 50 °C. (g) H_2O_2. (Reprinted with permission from ref 83. Copyright 1986 Elsevier Sciences Ltd.)

2. Synthesis of the C_{10}–C_{23} Fragment

Synthesis of the $C_{10}-C_{23}$ fragment was based on the approach employed by Evans in the synthesis of the $C_{17}-C_{37}$ fragment of X-206. Boron aldol reaction of butyrate imide **463** with aldehyde **464**, generated using chiral imide enolate alkylation methodology, afforded the aldol adduct **465** in 84% yield and >99% diastereoselectivity (Scheme 100). Hydroxy-directed $VO(acac)_2$-catalyzed epoxidation of the bishomoallylic alcohol **465** and subsequent acid-catalyzed ring opening of the intermediate epoxide afforded the desired *trans* tetrahydrofuran **467** in 94:6 selectivity and 85% isolated yield. Swern oxidation of **467** generated the C_{17} ketone, which was converted into the hydrazone **450** in 92% yield as a single diastereomer, completing the synthesis of the B-ring synthon.

Hydrazone **450** was coupled with epoxide **451**, prepared by a Sharpless kinetic resolution of 2-ethyl-1-penten-3-ol, in 76% yield and 90% ee (Scheme 101). In analogy with the synthesis of X-206, the amide was protected as a stable tetrahedral intermediate. Deprotonation of the C_{17} hydrazone with LDA, followed by reaction of the metalloenamine with epoxide **451,** afforded, after direct hydrolysis of the hydrazinyltetrahydrofurans, lactol diastereomers **449** in 48% yield as a 9:1 ratio of C_{18} epimers. Formation of the activated epoxide with $MgBr_2$ was necessary to enhance the rate of the reaction. The $C_{10}-C_{23}$ lactol **449** was prepared in six steps and 25% overall yield from **463**.

Scheme 100[a]

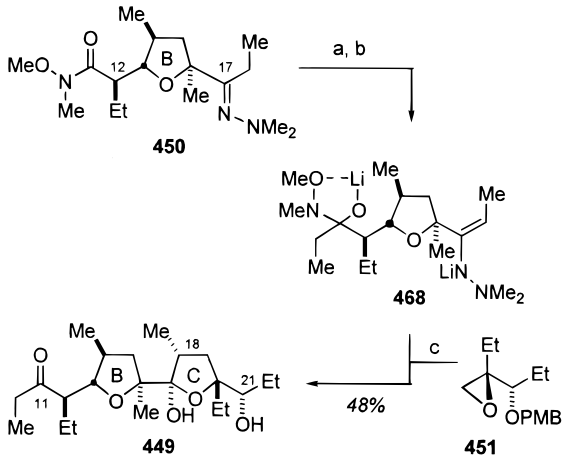


[a] (a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C; (b) $VO(acac)_2$, *t*-BuOOH, PhH, 25 °C; HOAc, 25 °C.

3. Fragment Coupling—The Aldol Reaction

In analogy with the selectivity observed by Kishi in his narasin synthesis, Evans elected to leave the carboxylic portion of the C_1-C_9 fragment unprotected and to take advantage of the inherent metal-ligating properties of the molecule, either kinetically or thermodynamically, to obtain the desired anti rela-

Scheme 101[a]

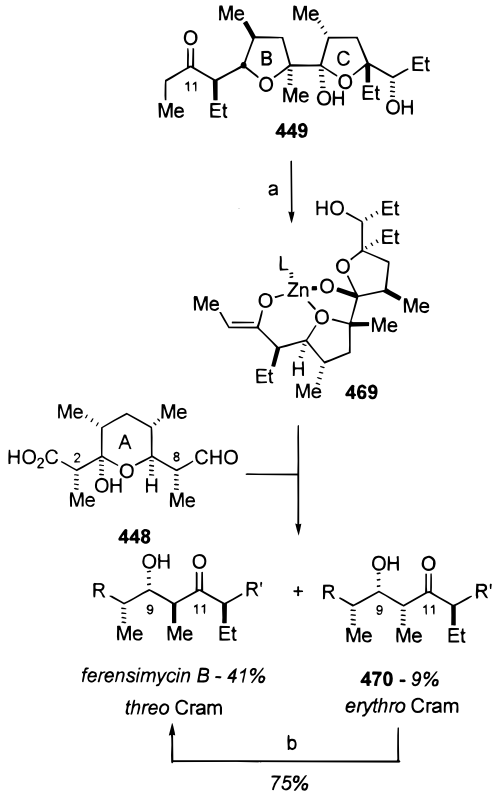


[a] (a) EtLi, Et_2O; (b) Et_2NLi, THF; (c) $MgBr_2$.

tionship between the newly created centers in the final aldol construction. This simplification extended to the C_3 lactol functionality as well. Due to the lability of the C_{10}−C_{23} synthon **449**, particularly toward acidic conditions, a similar decision was made to avoid the use of protecting groups in this fragment. The success of this approach resided in the reactivity of the fragments to be joined. Most importantly, the ligation sites present in the ionophore provided the necessary organization to bias the course of the aldol reaction under kinetic or thermodynamic conditions.

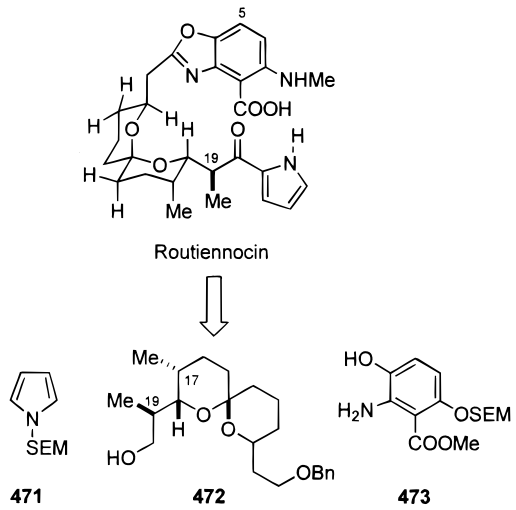
Reaction of zinc enolate trianion **469**, derived from ketone **449**, with aldehyde **448** provided four adducts in a combined yield of 63% and a ratio of 41:11:39:9,

Scheme 102[a]



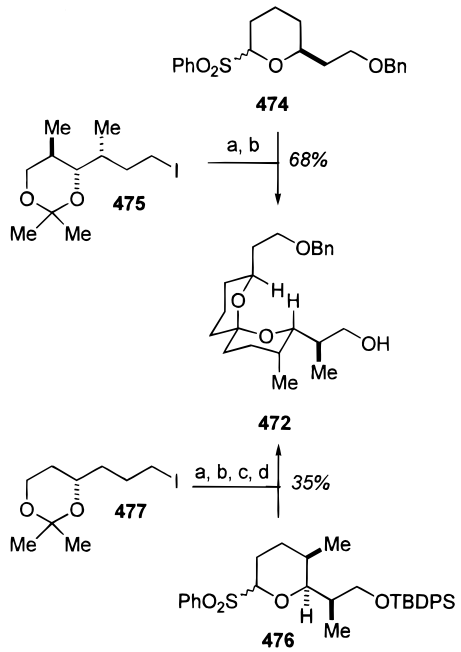
[a] (a) LDA (3.0 equiv), $ZnCl_2$ (1.5 equiv), THF, −78 C; (b) $Ba(OH)_2$, hexane, 25 °C.

Scheme 103



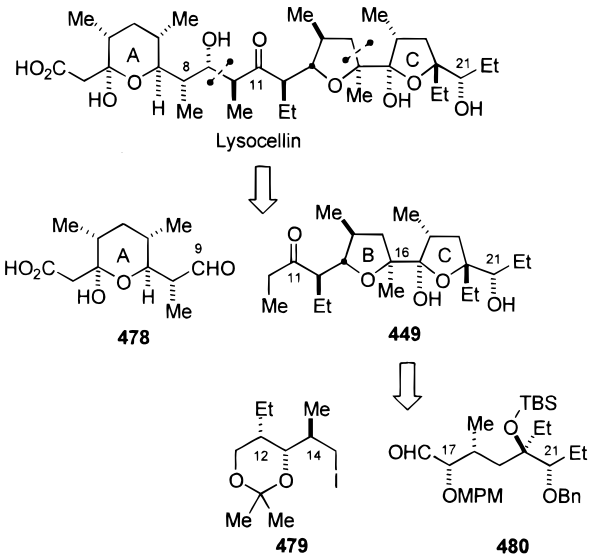
with the major product corresponding to the desired *threo* Cram adduct ferensimycin B (41%) (Scheme 102). It was possible to equilibrate the minor *erythro* Cram adduct **470** to ferensimycin B in 75% yield using $Ba(OH)_2$. The zinc enolate **469** exhibited the desired (and predicted) kinetic bias (4:1) for the stereochemistry of the natural product at the C_{10} stereocenter. The *Re* face was favored over the *Si* face, since the *Si* face was sterically blocked by the C_{12} ethyl group. Attempts to improve the selectivity using alternative solvents or different metal enolates failed to improve the yield of ferensimycin B. Under the optimized conditions for this reaction (zinc enolate trianion with both partners totally unprotected), the combined yield of synthetic ferensimycin B after equilibration was 30%.

Scheme 104[a]



[a] (a) *n*-BuLi, −78 °C, THF; (b) CSA, wet CH_2Cl_2; (c) NaH, BnBr, THF; (d) TBAF, THF. (Reprinted with permission from ref 84c. Copyright 1992 Elsevier Sciences Ltd.)

Scheme 105[a]



[a] Reprinted with permission from refs 88b and 88c. Copyright 1992 and 1996 Elsevier Sciences Ltd.

W. 1992, Routiennocin (Ley)

The total synthesis of routiennocin, a member of the calcimycin family of antibiotics, was completed by Ley in 1992. Retrosynthetic analysis of routiennocin yielded spiroketal **472**, which lacks the C_{15} and C_{11} methyl groups of calcimycin. Incorporation of the aromatic moieties was planned for the final stages of the synthesis (Scheme 103).[84]

Spiroketal **472** was prepared by coupling of phenylsulfonylpyran **474**, prepared using π-allyltricarbonyl iron chemistry,[85] with iodide **475** (Scheme 104).[86] It is interesting to note that **472** can also be prepared using **476** and **477**, in which the functionality on the coupling partners are reversed.[87] Introduction of the pyrrole and benzoxazole groups completed the synthesis of routiennocin.

X. 1992, Lysocellin (Yonemitsu and Horita)

Yonemitsu and Horita reported the first total synthesis of lysocellin in 1992.[88] Aldol disconnection of the C_9-C_{10} bond afforded the C_1-C_9 and $C_{10}-C_{23}$ fragments **478** and **449**, respectively (Scheme 105).

Table 25. Stereochemical Inventory for Horita and Yonemitsu's Synthesis of Lysocellin

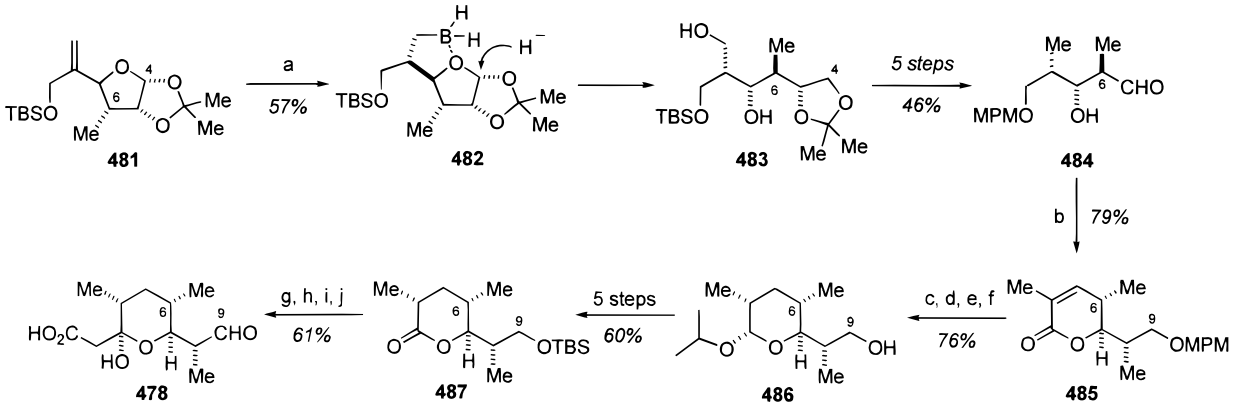
carbon	control element	reaction/source
C_3	thermodynamic	equilibration
C_4	cyclic stereocontrol	hydrogenation
C_6	chiral pool	D-glucose
C_7	chiral pool	D-glucose
C_8	cyclic stereocontrol	hydroboration
C_9	Cram-chelate	aldol/Zn enolate
C_{10}	Cram-chelate	aldol/Zn enolate
C_{12}	chiral pool	D-glucose
C_{13}	chiral pool	D-glucose
C_{14}	chiral pool	D-glucose
C_{16}	Cram-chelate	Grignard addn
C_{17}	thermodynamic	equilibration
C_{18}	Cram-chelate	organocuprate addn
C_{20}	Cram-chelate	Grignard addn
C_{21}	chiral pool	D-mannitol

In analogy to their synthesis of isolasalocid A, fragment **449** was disconnected across the $C_{15}-C_{16}$ bond to provide the $C_{11}-C_{15}$ and $C_{16}-C_{23}$ fragments, **479** and **480**. The stereochemical inventory for Horita and Yonemitsu's synthesis of lysocellin is summarized in Table 25.

1. Synthesis of the C_1–C_9 Fragment

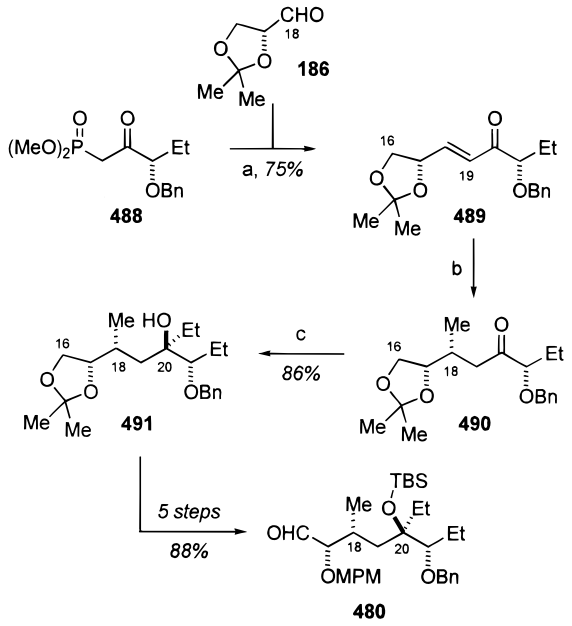
Hydroboration of **481**, derived from D-glucose, afforded alcohol **483** in 57% yield and 11:1 stereoselectivity (Scheme 106). The reaction proceeded according to Still's model[89] via **482**. A second equivalent of borane cleaved the furanose ring. Formation of β-hydroxy aldehyde **484** and Wittig–Horner reaction with dimethyl 1-methoxycarbonylethylphosphonate afforded the α,β-unsaturated-δ-lactone **485** in 79% yield. Formation of the α-lactolide, oxidative removal of the *p*-methoxybenzyl protecting group, and hydrogenation of the C_4-C_5 olefin with $Rh-Al_2O_3$ gave **486** in 76% yield. In analogy to Still's synthesis of monensin introduced A, the C_4 stereocenter was in quantitative yield and 25:1 stereoselectivity.[90] Alcohol **486** was converted into δ-lactone **487** in five steps and 60% yield. The C_1-C_2 fragment was introduced using benzyl acetate. The C_3 stereochemistry was established by acidic equilibration. The synthesis of the C_1-C_9 fragment **478** was completed in 20 steps and 6% overall yield from **481**.

Scheme 106[a]



[a] (a) BH_3·THF, H_2O_2, NaOH; (b) *n*-BuLi, $(MeO)_2P(O)CH(Me)CO_2Me$, THF, −78 °C; (c) DIBAL, Tol, −80 °C; (d) CSA, *i*-PrOH; (e) DDQ, $CH_2Cl_2-H_2O$-*i*-PrOH; (f) $Rh-Al_2O_3$, H_2, Et_2O; (g) $LiCH_2CO_2Bn$; (h) H^+, H_2O; (i) SO_3Py, DMSO, Et_3N; (j) H_2, 10% Pd/C. (Reprinted with permission from refs 88a and 88c. Copyright 1992 and 1996 Elsevier Sciences Ltd.)

Scheme 107[a]



[a] (a) NaH, DMSO/THF, 0 °C; (b) Me_2CuLi, Et_2O/THF, −78 °C; (c) EtMgBr, THF, −78 °C. (Reprinted with permission from ref 88a. Copyright 1992 Elsevier Sciences Ltd.)

2. Synthesis of the C_{16}–C_{23} Fragment

Horner−Emmons reaction of phosponate **488**, derived from D-mannitol, and D-glyceraldehyde acetonide **186** provided enone **489** in 75% isolated yield (Scheme 107). Chelate-controlled Michael reaction of Me_2CuLi to **489** afforded **490** as a 6.3:1 mixture of C_{18} methyl epimers. The (*R*)-selectivity of the 1,4-addition was rationalized by chelation of the cuprate with the C_{17} oxygen of the acetonide. Subsequent Cram-chelate addition of EtMgBr to **490** provided **491** as a single isomer in 86% isolated yield from enone **489**. Five-step conversion of **491** into **480** completed the synthesis of the C_{16}−C_{23} fragment in eight steps and 50% overall yield from **488**.

3. Fragment Coupling–The Aldol Reaction

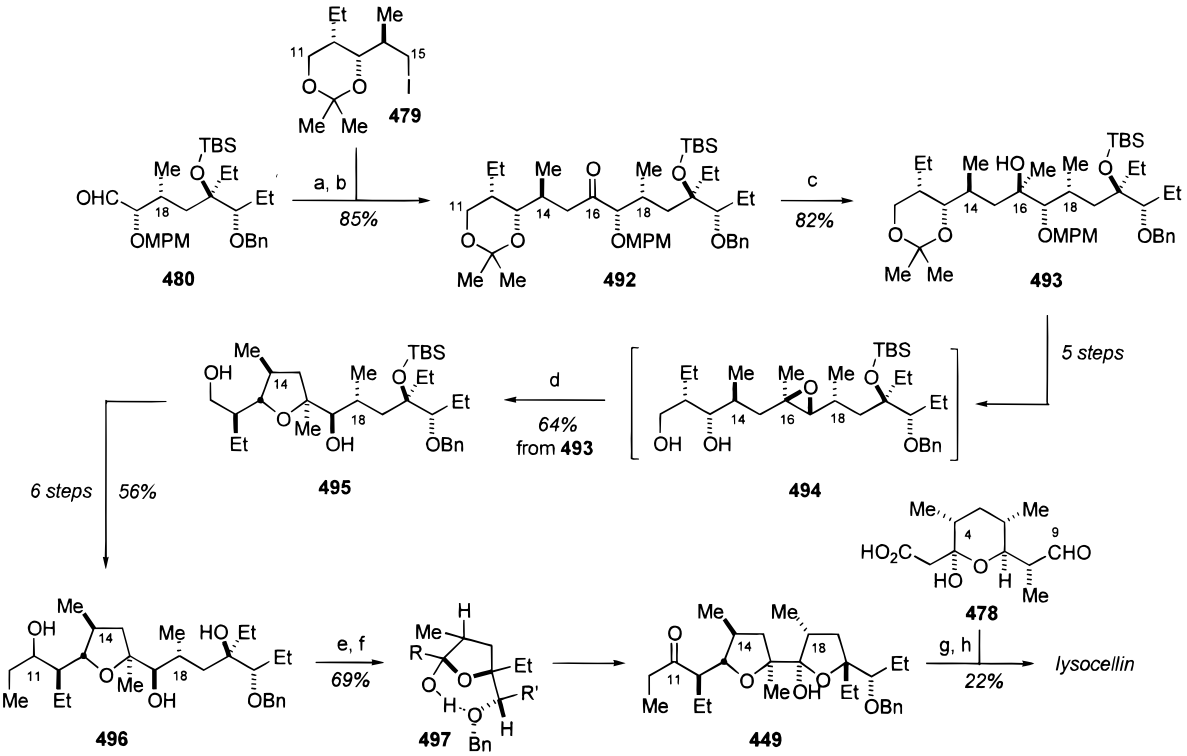
Coupling of the lithium salt of the C_{11}−C_{15} fragment **479**, derived from D-glucose, with aldehyde **480** provided a 1:1 mixture of C_{16} alcohols that were oxidized to ketone **492** in 85% yield (Scheme 108). Chelate-controlled addition of MeMgBr to the C_{16} ketone provided a single isomer of alcohol **493** in 82% yield. Removal of protecting groups, mesylation of the C_{17} alcohol, and acid-catalyzed tetrahydrofuran formation of the intermediate epoxide **494** afforded the B-ring tetrahydrofuran **495** in 64% overall yield.

Conversion of **495** into alcohol **496** and oxidation with PCC afforded a 1:1 mixture of C_{17} γ-lactols that were successfully equilibrated under acidic conditions to provide **449** as the sole product in 69% yield. The success of the acid-catalyzed isomerization was due to the thermodynamic stabilization of **449** by internal hydrogen bonding between the C_{17} lactol and the C_{21} benzylic hydroxyl group, as illustrated in **497**. Removal of the C_{21} benzyl, formation of the zinc enolate, and condensation with **478** afforded lysocellin in 22% yield.[91]

Y. 1992, Tetronomycin (Yoshii)

Yoshii reported the first total synthesis of tetronomycin in 1992[92] and the closely related tetronosin in

Scheme 108[a]



[a] (a) *t*-BuLi, Et_2O, −78 °C; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (c) MeMgI, Et_2O, −78 °C; (d) CSA, CH_2Cl_2, 0 °C; (e) PCC, 3 Å Molecular sieves, CH_2Cl_2; (f) 1 N H_2SO_4, THF; (g) Ra/Ni, H_2, EtOH; (h) LDA, $ZnCl_2$, THF. (Reprinted with permission from ref 88b. Copyright 1992 Elsevier Sciences Ltd.)

Scheme 109

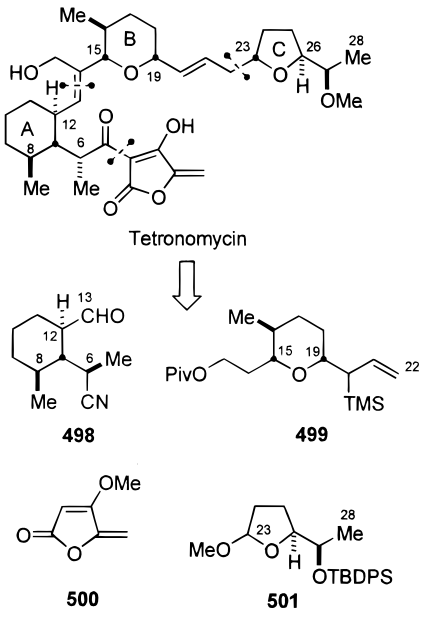


Table 26. Stereochemical Inventory for Yoshii's Synthesis of Tetronomycin

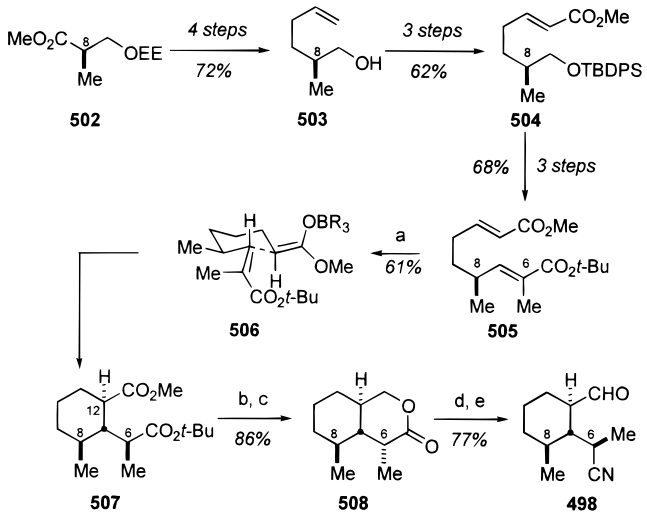
carbon	method	reaction/source
C_6	thermodynamic	equilibration
C_7	cyclic stereocontrol	intramolecular Michael
C_8	chiral pool	(*R*)-3-hydroxy-2-methylpropionate
C_{12}	cyclic stereocontrol	intramolecular Michael
C_{15}	A-1,3	Sharpless AE
C_{16}	chiral pool	(*R*)-3-hydroxy-2-methylpropionate
C_{19}	cyclic stereocontrol	alkoxymercuration
C_{23}	thermodynamic	Lewis acid alkylation
C_{26}	chiral pool	L-rhamnal acetate
C_{27}	chiral pool	L-rhamnal acetate

1993.[93] Both compounds contain a cyclohexyl and acyl tetronic acid moiety not found in other ionophores. For tetronomycin, disconnection of the $C_{13}-C_{14}$ olefin and the $C_{22}-C_{23}$ bond revealed the C_6-C_{13}, $C_{14}-C_{22}$, and $C_{23}-C_{28}$ fragments **498**, **499**, and **501**, respectively (Scheme 109). The C_4-C_5 bond was disconnected by an aldol reaction to afford the sensitive tetronic acid portion **500**. The stereochemical inventory for Yoshii's synthesis of tetronomycin is summarized in Table 26.

1. Synthesis of the C_5–C_{13} Fragment

The nonadienoate **505**, derived from (*R*)-3-hydroxy-2-methylpropionate **(502)**, was selectively reduced with L-selectride to afford the cyclohexane diester **507** in 61% yield (Scheme 110). Hydride addition occurred at the less hindered methyl ester, generating the *Z*-enolate **506**. Internal Michael addition of the C_{12} enolate to the C_7 α,β-unsaturated ester proceeded via the chairlike transition state **506** to generate **507**. The reaction afforded the desired C_8-C_7 *trans*/C_7-C_{12} *trans* stereochemistry but gave the undesired stereochemistry at C_6. Lactonization with *t*-BuOK, followed by in-situ equilibration of the C_6 stereocenter, provided **508** in 86% yield. Ring opening of the lactone with Me_2AlNH_2 followed by oxidation completed the synthesis of the C_5-C_{13} fragment in 15 steps and 12% overall yield.[94]

Scheme 110[a]



[a] (a) Li(*s*-Bu)$_3$BH, THF; (b) Red-Al; (c) *t*-BuOK, THF; (d) Me_2AlNH_2, PhMe; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2. (Reprinted with permission from ref 100. Copyright 1993 Elsevier Sciences Ltd.)

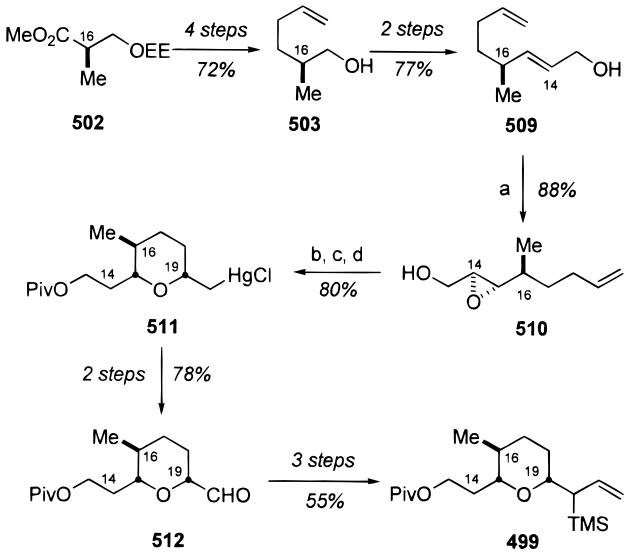
2. Synthesis of the C_{14}–C_{22} Fragment

Sharpless asymmetric epoxidation of olefin **509**, also derived from (*R*)-3-hydroxy-2-methylpropionate **(502)**, established the C_{15} stereochemistry in 88% yield (Scheme 111). Internal alkoxymercuration of **510** with $Hg(OAc)_2$ followed by NaCl treatment afforded the desired 2,6-*cis*-tetrahydropyran **511** in 80% yield along with 18% of the minor *trans* isomer. Oxidation of the intermediate C_{20} organomercurial provided aldehyde **512** in 78% yield. Addition of vinyl Grignard and S_N1' addition of TMSCu completed the synthesis of the $C_{14}-C_{22}$ fragment in 15 steps and 17% overall yield.[95]

3. Synthesis of the C_{23}–C_{28} Fragment

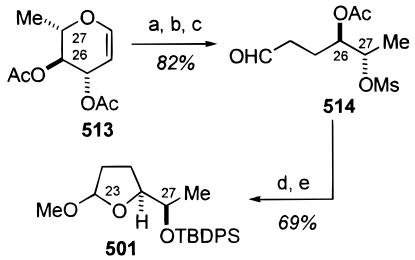
The six-carbon $C_{23}-C_{28}$ fragment was derived from L-rhamnal diacetate **513** by inversion of the C_4 and

Scheme 111[a]



[a] (a) (+)-Diisopropyl-(L)-tartrate, Ti(O-*i*-Pr)$_4$, *t*-BuOOH; (b) Red-Al; (c) Me_3CCOCl; (d) $Hg(OAc)_2$, NaCl.

Scheme 112[a]



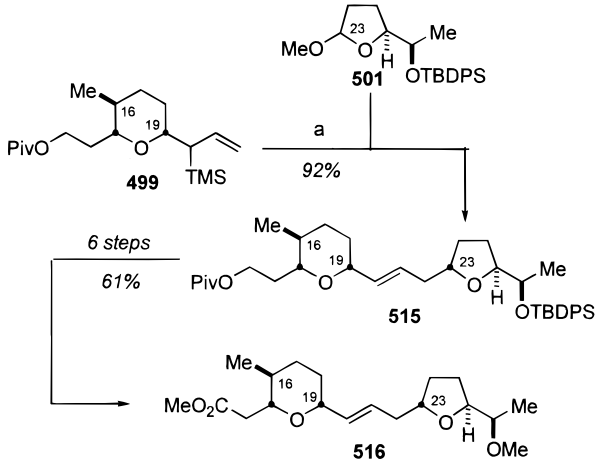
[a] (a) H_2SO_4, H_2O, $HgSO_4$; (b) MsCl, CH_2Cl_2, DMAP (cat); (c) H_2, Pd/C; (d) NaOMe, MeOH; (e) TBDPSCl, DMF, imidazole.

C_5 carbons corresponding to C_{26} and C_{27} (Scheme 112). Perkin hydrolysis of **513** followed by mesylation and hydrogenation provided **514** in 82% yield. Methoxide-induced epoxide formation followed by silyl protection of the C_{27} alcohol provided the tetrahydrofuran subunit **501** as an anomeric mixture in 69% yield.[96,97]

4. Fragment Coupling

Fragment **499** was coupled with tetrahydrofuran **501** in the presence of $BF_3{\cdot}Et_2O$ to provide exclusively *E*-olefin **515** in 92% yield as a 95:5 mixture of C_{23} epimers. The desired *trans* tetrahydrofuran was expected based on axial attack of the allyl group to the C_{23} oxonium ion.[98] Adjustment of the oxidation state at C_{13} and methylation of C_{27} completed the synthesis of the $C_{14}-C_{28}$ fragment **516** in seven steps and 50% overall yield (Scheme 113).[99]

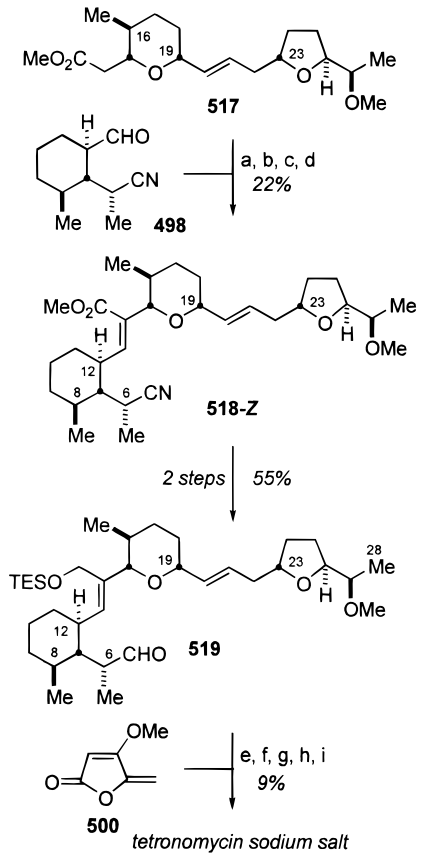
Scheme 113[a]



[a] (a) $BF_3{\cdot}OEt_2$.

Treatment of the lithium enolate of **517** with aldehyde **498** provided a quantitative mixture of β-hydroxyester diastereomers that was eliminated with DBU to afford the desired α,β-unsaturated ester in 91% yield as a 95:5 ratio of *E*:*Z* isomers (Scheme 114). Isomerization with a low-pressure Hg lamp provided a 58:42 ratio of *E*:*Z*-olefins from which the desired *Z*-ester **518** was isolated in 22% yield from **517**. Reduction of the ester and nitrile groups of **518** followed by protection afforded **519** in 55% yield. Aldol reaction of the lithium anion of tetronic acid **500** with **519**, oxidation of the resulting C_5 alcohol, and removal of the protecting groups completed the synthesis of tetronomycin.

Scheme 114[a]



[a] (a) LDA, THF, 100 °C; (b) MsCl, DMAP; (c) DBU; (d) Hg-lamp, acetone; (e) LDA, DMPU, THF, −100 °C; (f) PCC, CH_2Cl_2; (g) HF, MeCN, H_2O; (h) LiCl, DMSO; (i) $NaHCO_3$.

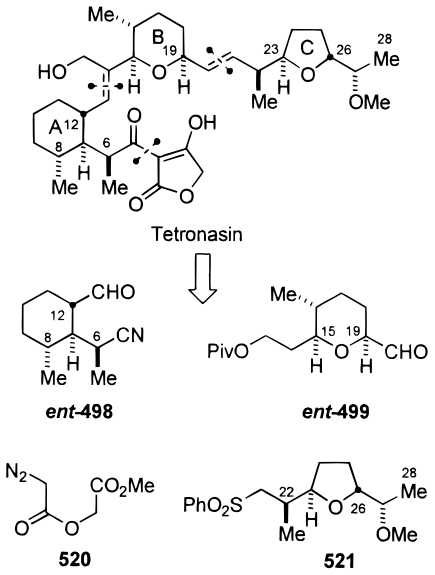
Z. 1993, Tetronosin (Yoshii)

The first total synthesis of tetronosin was reported by Yoshii in 1993.[100] The structure of tetronosin is closely related to tetronomycin, except that the absolute stereochemistry at every stereogenic center has the opposite configuration, an additional methyl substituent is present at the C_{22} carbon, and the α-acyl tetronic acid is unsubstituted in the γ-position. Yoshii's retrosynthetic approach to tetronosin was similar to tetronomycin affording four fragments *ent*-**498**, *ent*-**499**, **520**, and **521**. The syntheses of the *ent*-**498** and *ent*-**499** were identical to that employed in the synthesis of tetronomycin. However, a different strategy was employed to prepare the $C_{14}-C_{28}$ fragment and incorporate the γ-unsubstituted α-acyltetronic acid moiety (Scheme 115).

1. Synthesis of the C_{14}–C_{28} Fragment

Reaction of hexanal derivative **522**, derived from L-rhamnal acetate **513**, with the Roush crotylborane **523** provided the anti:syn homoallylic alcohol **524**. Treatment of **524** with TBAF deprotected the C_{27} alcohol and afforded the 2,5-*trans*-tetrahydrofuran **525** in 78% yield (Scheme 116). Formation of sulfone **526** and Julia olefination with *ent*-**499** afforded an *E*-olefin, which was deprotected, oxidized, and esterified to afford the $C_{14}-C_{28}$ fragment **527** in 18 steps and 6% overall yield.

Scheme 115



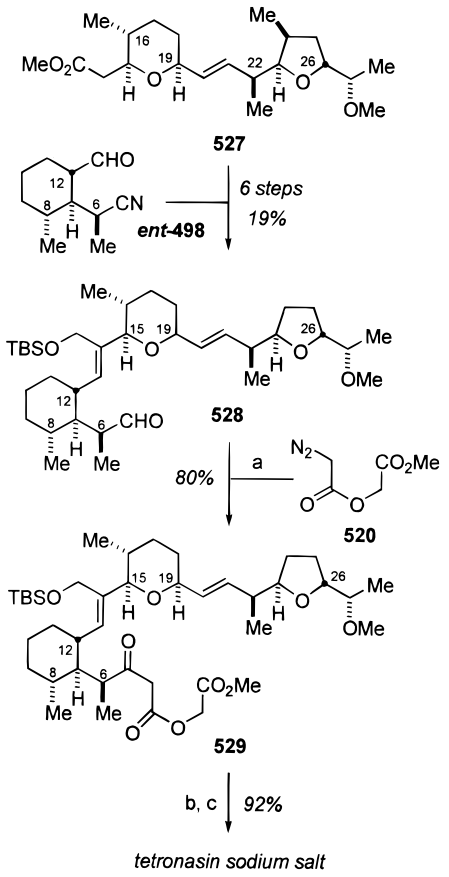
2. Fragment Coupling

Coupling of *ent*-**498** with ester **527** using conditions similar to those employed by Yoshii in his synthesis of tetronomycin afforded aldehyde **528** in 19% yield (Scheme 117). Reaction of aldehyde **528** with methyl (diazoacetoxy)acetate in the presence of $ZrCl_4$ generated β-keto ester **529** in 80% yield. Interestingly, other Lewis acids were ineffective in this transformation. Internal Dieckmann cyclization of **529** was effected upon treatment with TBAF to afford the sodium salt of tetronasin in 92% yield.

AA. 1993, Monensin A (Ireland)

Ireland reported the third total synthesis of monensin A using the ester−enolate Claisen reaction to couple the key fragments (Scheme 118).[101] Ester−enolate Claisen disconnection of the $C_{12}-C_{13}$ bond afforded the C_1-C_{12} and $C_{13}-C_{26}$ fragments **530** and **531**. Further disconnection of both of these fragments, again using the ester−enolate Claisen reaction, gave fragments **532**, **533**, and **534**. The stereochemical inventory for Ireland's synthesis of monensin A is summarized in Table 27.

Scheme 117[a]

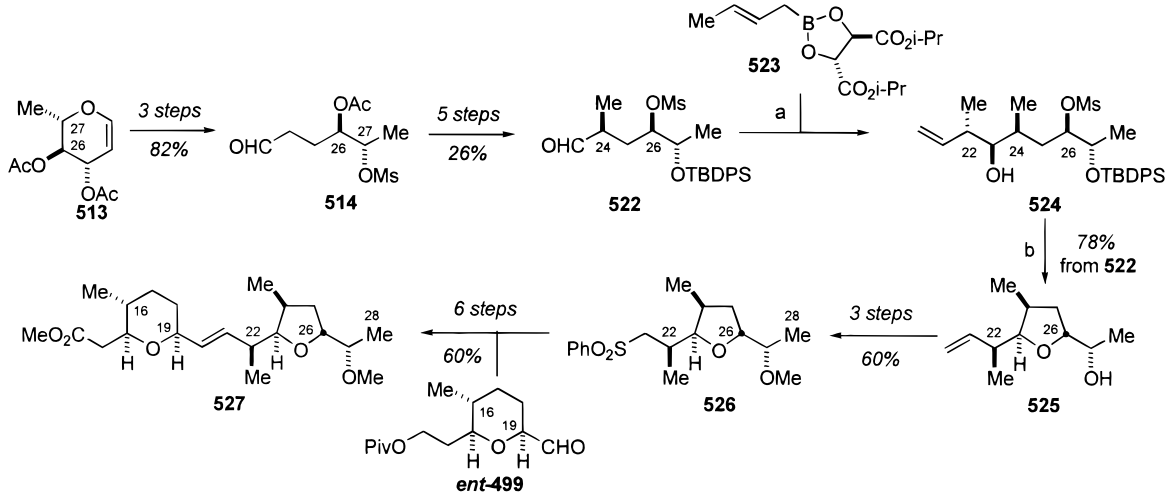


[a] (a) $ZrCl_4$, CH_2Cl_2; (b) TBAF, THF; (c) HF, MeCN, $NaHCO_3$. (Reprinted with permission from ref 100. Copyright 1993 Elsevier Sciences Ltd.)

1. Synthesis of the C_1–C_{12} Fragment

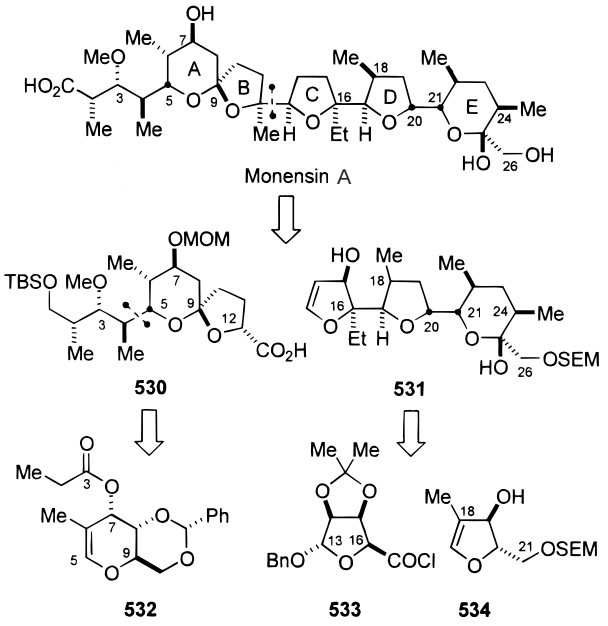
Ester−enolate Claisen reaction of glycal ester **532**, derived from D-mannose, followed by reduction with $LiAlH_4$, provided alcohol **535** in 87% yield (Scheme 119). Swern oxidation of the C_3 alcohol, crotylboration with (+)-Ipc_2B(*cis*-2-butene), and C_3 methylation

Scheme 116[a]



[a] (a) PhMe, −75 °C; (b) TBAF, THF. (Reprinted with permission from ref 100. Copyright 1993 Elsevier Sciences Ltd.)

Scheme 118

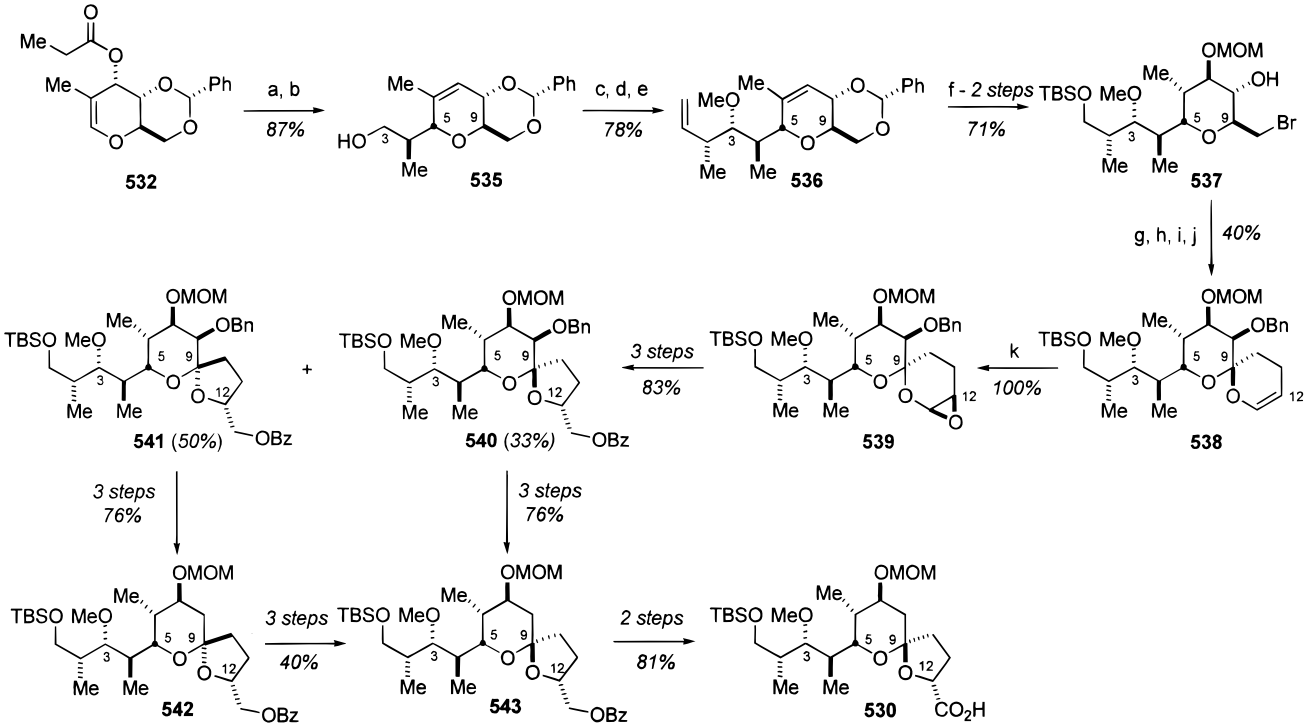


afforded **536** in 78% yield and set the desired *S*,*R* stereochemistry at C_2 and C_3. Hydroboration of the C_6-C_7 olefin occurred in high stereoselectivity (10:1) and 91% yield from the β-face to introduce the C_6 and C_7 stereocenters. Protection of the C_7 alcohol and bromination of the C_{10} hydroxyl provided **537** in 71% overall yield from **536**. Oxidation of the C_8 hydroxyl and hetero-Diels–Alder reaction of the resulting ketone with acrolein afforded a 1:1 mixture of C_9 spiroketal epimers. Reduction of the C_8 ketone, followed by benzylation, afforded **538** in 40% overall yield from **537**. Formation of **538** indicated that the hetero-Diels–Alder condensation had occurred from the top (β) face of the intermediate methylenetetrahydropyran and that **538** was the anomerically favored alcohol. Epoxidation of **538** with dimethyldioxirane afforded **539** as a single epoxide in quantitative yield. Treatment of **539** with mild acid followed by formation of the benzoate ester yielded spiroketals **540**:**541** in 83% yield. Deoxygenation of the C_8 hydroxyl of **540** afforded spiroketal **543**, containing the desired stereochemistry at C_9 for monensin A in 76% yield. Spiroketal **543** was also prepared in 30% yield from **541** by deoxygenation followed by epimerization. Oxidation of the C_{12} hydroxymethyl to carboxylic acid **530** completed the synthesis of the C_1-C_{12} fragment in 24 steps and 4% overall yield.

Table 27. Stereochemical Inventory for Ireland's Synthesis of Monensin A

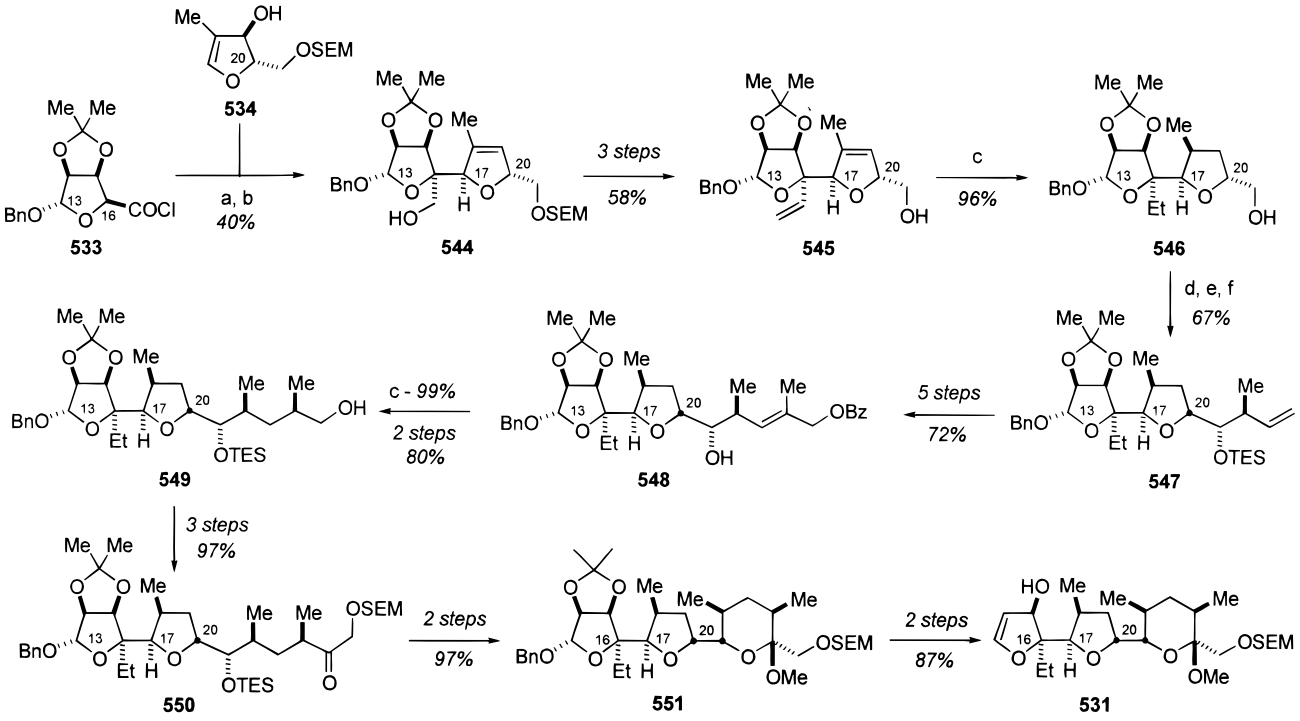
carbon	method	reaction/source
C_2	Cram-chelate	chiral crotyl borane
C_3	Cram-chelate	chiral crotyl borane
C_4	cyclic stereocontrol	ester–enolate Claisen
C_5	cyclic stereocontrol	ester–enolate Claisen
C_6	cyclic stereocontrol	hydroboration
C_7	cyclic stereocontrol	hydroboration
C_9	thermodynamic	equilibration
C_{12}	cyclic stereocontrol	epoxidation
C_{13}	cyclic stereocontrol	ester–enolate Claisen
C_{16}	cyclic stereocontrol	ester–enolate Claisen
C_{17}	cyclic stereocontrol	ester–enolate Claisen
C_{18}	cyclic stereocontrol	hydrogenation
C_{20}	chiral pool	L-arabinose
C_{21}	Cram-chelate	chiral crotyl borane
C_{22}	Cram-chelate	chiral crotyl borane
C_{24}	A-1,3	hydrogenation
C_{25}	thermodynamic	equilibration

Scheme 119[a]



[a] (a) LiHMDS, TBSCl, HMPA, PhH; (b) $LiAlH_4$; (c) $(COCl)_2$, DMSO, Et_3N; (d) (+)Ipc_2B(*cis*-2-butene), H_2O_2, NaOH; (e) MeI, NaH; (f) BH_3, THF, NaOAc, H_2O; (g) Dess–Martin periodinane; (h) CH_2CHCHO, Et_3N; (i) $NaBH_4$; (j) BnBr, NaH, THF; (k) dimethyldioxirane, acetone, 0 °C.

Scheme 120[a]



[a] (a) TMSCl, HMPA, LDA; (b) $LiAlH_4$; (c) [Rh(COD)DIPHOS-4]BF_4, 640 psi, H_2; (d) Dess−Martine oxidation; (e) (−)-Ipc_2B(*trans*-2-butene), H_2O_2, NaOH; (f) TESOTf, lutidine.

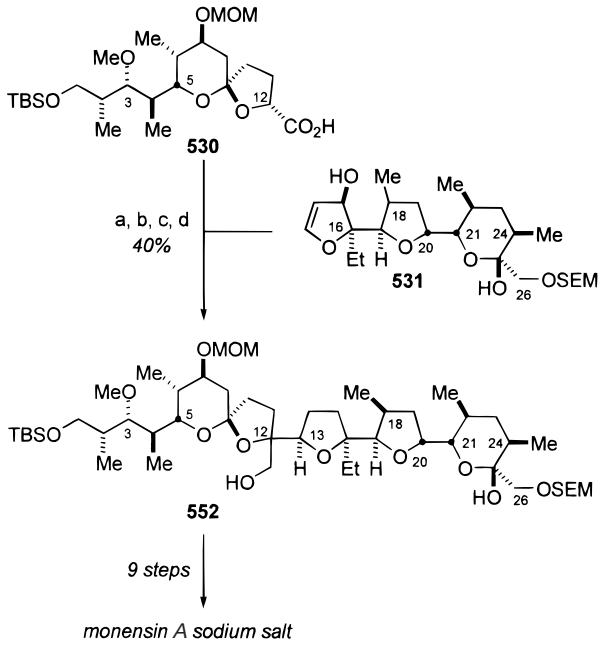
2. Synthesis of the C_{13}–C_{26} Fragment

Ester−enolate Claisen rearrangement of the intermediate ester prepared from alcohol **534**, derived from L-arabinose, with acid chloride **533**, derived from D-mannose, afforded the C/D-ring fragment as a 1:1 mixture of C_{16} epimers that were separated, after reduction with $LiAlH_4$, to afford **544** in 40% yield (Scheme 120). Conversion of the C_{16} hydroxylmethyl into the C_{16} vinyl derivative **545** was completed in three steps and 58% overall yield. Reduction of the terminal olefin and the C_{18}−C_{19} double bond with [Rh(COD)DIPHOS-4]BF_4 provided the directed hydrogenation product **546** in 96% yield and >95:5 selectivity and set the C_{18} stereochemistry. Oxidation of **546** to the corresponding aldehyde, crotylation with (−)-Ipc_2B(*trans*-2-butene), and protection of the C_{19} alcohol afforded alkene **547** in 67% yield. Dihydroxylation and oxidative cleavage of the terminal olefin provided the corresponding aldehyde, which was subjected to Wittig olefination, ester reduction, and benzoylation to afford **548** in 72% yield. A second directed hydrogenation introduced the C_{24} methyl as a single diastereomer in 99% yield. Protecting-group manipulation provided **549** in 80% yield. One-carbon homologation at C_{25} afforded the SEM-protected derivative **550** in 97% yield. Deprotection of the C_{21} hydroxyl, E-ring formation in the presence of trimethylorthoacetate, and elimination of the C_{13} and C_{14} hydroxyls completed the synthesis of the C_{13}−C_{26} fragment **531** in 24 steps and 7% overall yield.

3. Fragment Coupling—Ester–Enolate Claisen

Esterification of the C_{13}−C_{26} fragment **531** with the C_1−C_{12} fragment **530** followed by ester−enolate Claisen rearrangement and reduction afforded **552** as a 2:1 mixture of C_{12} hydroxymethyl epimers in 40% combined yield. The minor isomer contained the desired C_{12} stereochemistry. Deoxygenation of the C_{12} hydroxymethyl followed by oxidation of C_1 and removal of protecting groups completed the synthesis of the monensin A sodium salt (Scheme 121).

Scheme 121[a]

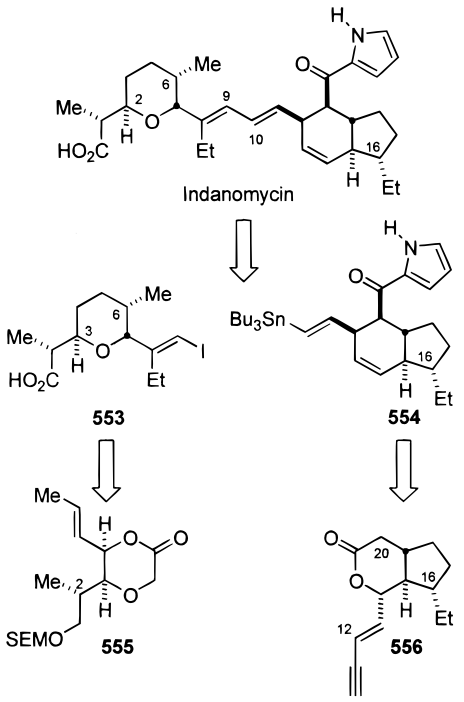


[a] (a) DCC, DMAP; (b) TMSCl, HMPA, LDA; (c) W-2 Raney Ni, H_2; (d) $LiAlH_4$.

AB. 1994, Indanomycin (Burke)

In contrast to the reported syntheses of indanomycin by Nicolaou, Ley, Roush, and Boeckman,

Scheme 122



Burke's retrosynthetic approach involved disconnection of the C_9-C_{10} bond by application of a palladium-catalyzed cross-coupling reaction to afford vinyl iodide **553** and vinyl stannane **554** (Scheme 122).[102] The degree of functional-group complexity in each of the subunits provided a challenging test to the tolerence of the Stille methodology.[103] Furthermore, final coupling of the molecule in this fashion eliminated the need for protecting groups or postcoupling manipulations. Disconnection of tetrahydropyran **553** yielded **555** by application of the dioxanone-to-dihydropyran version of the Claisen rearrangement.[104] A synthesis of tetrahydroindan **554** was envisioned from **556** by application of a retro-hetero-Diels–Alder/intramolecular Diels–Alder ("mock-Claisen") reaction. The stereochemical inventory for Burke's synthesis of indanomycin is summarized in Table 28.

1. Synthesis of the C_1–C_9 Fragment

Chelate-controlled addition of lithium divinylcuprate to aldehyde **557**, also employed by Boeckman

Table 28. Stereochemical Inventory for Burke's Synthesis of Indanomycin

carbon	control element	reaction/source
C_2	chiral pool	methyl-(*R*)-(+)-hydroxy-2-methyl propionate
C_3	Cram-chelate	organocuprate addn
C_6	cyclic stereocontrol	ester–enolate Claisen
C_7	cyclic stereocontrol	ester–enolate Claisen
C_{12}	cyclic stereocontrol	Diels–Alder
C_{15}	cyclic stereocontrol	Diels–Alder
C_{16}	cyclic stereocontrol	organocuprate addn
C_{19}	cyclic stereocontrol	Diels–Alder
C_{20}	cyclic stereocontrol	Diels–Alder

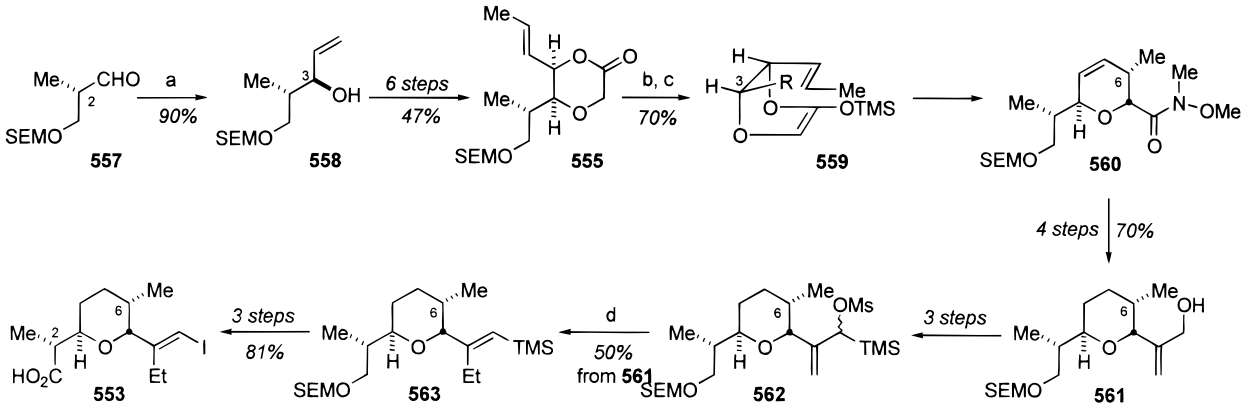
in his synthesis of the C_1-C_{10} fragment, afforded allylic alcohol **558** in 90% yield (Scheme 123). This reaction established the C_2-C_3 *threo* relationship of indanomycin. Conversion of **558** into dioxolane **555** was achieved in six steps and 47% overall yield. Claisen rearrangement of the silyl ketene acetal derived from **555** proceeded through conformation **559**. The product carboxylic acid was converted into Weinreb amide **560** in 70% overall yield.

The iodide was generated by a novel procedure through the intermediacy of the [α-(mesyloxy)allyl]-silane **562**. Treatment of **562** with MeMgBr and catalytic CuCN afforded a 3.8:1 mixture of *E*:*Z*-vinyl silanes by S_N2' displacement. The desired *E*-isomer was isolated in 50% yield. The minor *Z*-vinylsilane was converted by a three-step procedure into an 8:1 mixture of *E*:*Z* isomers in 64% yield. Treatment of **563** with *N*-iodosuccinimide afforded the vinyl iodide with complete retention of configuration. Cleavage of the SEM ether followed by Jones oxidation afforded carboxylic acid **553** in 81% yield.[105]

2. Synthesis of the C_{10}–C_{21} Fragment

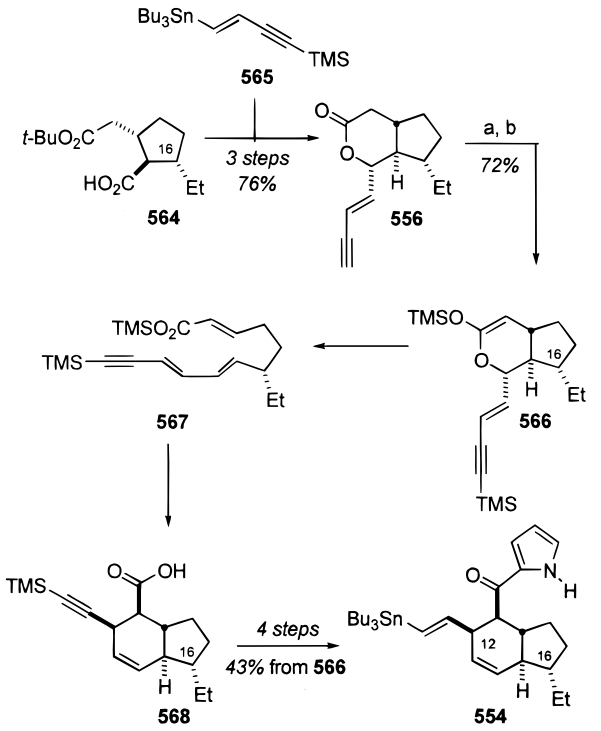
An enantioselective synthesis of the $C_{10}-C_{21}$ fragment was developed from the *trans*,*anti*-trisubstitued cyclopentane **564** prepared using Noyori's three-component coupling procedure.[106] Palladium-catalyzed acylation of vinylstannane **565** with the acid chloride derived from **564** followed by ketone reduction and lactonization afforded enynone **556** in 76% yield (Scheme 124). Although Burke initially envisioned an ester–enolate Claisen rearrangment for synthesis of this fragment, the geometric constraints

Scheme 123[a]



[a] (a) Lithium divinylcuprate; (b) LiHMDS, TMSCl/Et_3N, THF, −78 to 23 °C; (c) PhMe, reflux 4 h; HCl (aq) Et_2O; (d) MeMgBr, CuCN (cat), THF, −78 to −40 °C.

Scheme 124[a]



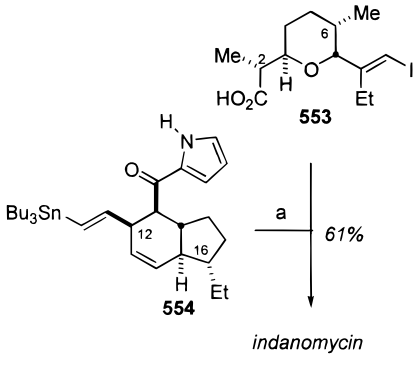
[a] (a) LiHMDS, $TMSCl/Et_3N$, −100 to 23 °C, 40 min; (b) HCl (aq), Et_2O.

imposed by the *trans* fusion on the five-membered array rendered the transition state inaccessible. Instead, thermolysis of **566** afforded carboxylic acid **568** by a retro-hetero-Diels−Alder reaction to **567** followed by Diels−Alder reaction. Carboxylic acid **568** was not isolated but converted directly into the corresponding ketopyrrole using the procedure of Mukiayama, as previously described. Alkyne desilylation and formation of the *E*-vinylstannane[107] afforded **554** in 43% overall yield from **566**.

3. Fragment Coupling—The Stille Reaction

Stille coupling of the C_1-C_9 and $C_{10}-C_{21}$ fragments **553** and **554** afforded indanomycin in 61% yield (Scheme 125). The choice of catalyst proved critical: although use of $(CH_3CN)_2PdCl_2$ led to extensive homocoupling of the vinyl stannane, reductive dimerization was supressed when freshly prepared $(Ph_3P)_4$-Pd was employed. The success of the coupling in the presence of the free carboxylic acid and the acyl

Scheme 125[a]



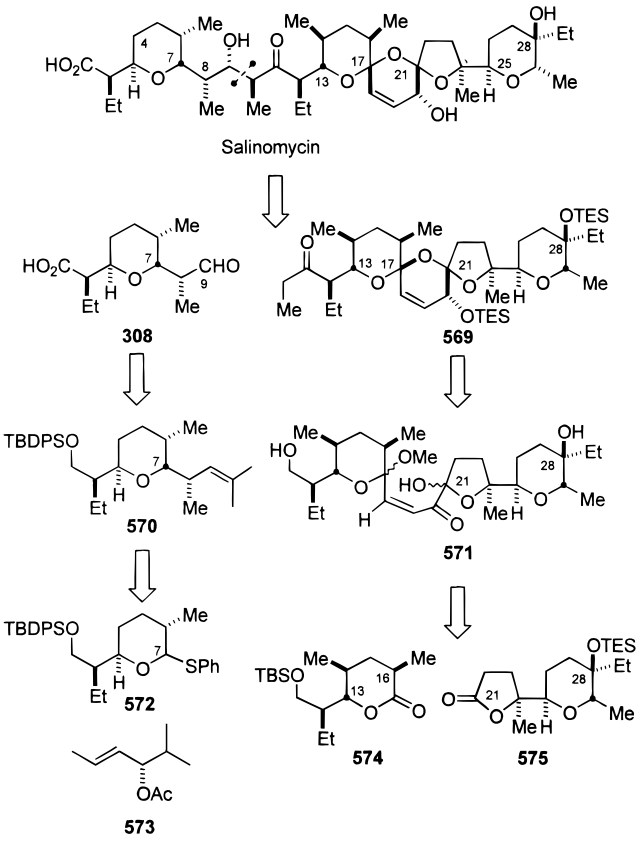
[a] (a) $Pd(Ph_3)_4$, DMF, 25 °C.

pyrrole groups indicates the power of this methodology in the total synthesis of complex natural products.

AC. 1994, Salinomycin (Kocienski)

In analogy with the work of Kishi, Horita, and Yonemitsu, Kocienski's approach to salinomycin involved aldol disconnection of the C_9-C_{10} bond to yield the C_1-C_9 and $C_{10}-C_{30}$ fragments **308** and **569** (Scheme 126).[108] In contrast to the previous ap-

Scheme 126



proaches to prepare **308**, Kocienski envisioned that the C_6-C_8 stereotriad of the C_1-C_9 fragment could be derived from allyl derivative **570** by application of the S_E2' reaction on an α-alkoxyalkylmetal species derived from **572** with a η^3-allyl cationic complex derived from **573**. Disconnection of the C_{17} acetal of **569** afforded allenol ether **571**, which was further disconnected at the $C_{20}-C_{21}$ and $C_{17}-C_{18}$ bonds to reveal the $C_{11}-C_{17}$ and $C_{21}-C_{30}$ lactones **574** and **575**.[109,110,111] The stereochemical inventory for Kocienski's synthesis of salinomycin is summarized in Table 29.

1. Synthesis of the C_1–C_9 Fragment

Sharpless asymmetric epoxidation of allylic alcohol **576** afforded the corresponding oxirane in 78% yield and 94% ee and introduced the C_2 and C_3 stereocenters (Scheme 127). Copper-catalyzed opening of the oxirane with EtMgBr afforded a 3:1 ratio of regioisomeric diols. Removal of the 1,2-diol by periodate cleavage, protection of the 1,3-diol, and ozonolysis of the alkene afforded ketone **577** in 35% yield

Table 29. Stereochemical Inventory for Kocienski's Synthesis of Salinomycin

carbon	method	reaction/source
C_2	A-1,3	Sharpless AE
C_3	A-1,3	Sharpless AE
C_6	thermodynamic	THP formation
C_7	radical anomeric effect	lithium 4,4′-di-*tert*-butylbiphenylide
C_8	chiral pool	η^3-allyl Mo complex
C_9	Cram addn	aldol/Mg enolate
C_{10}	Cram addn	aldol/Mg enolate
C_{12}	A-1,3	aldol/oxazolidinethione
C_{13}	A-1,3	aldol/oxazolidinethione
C_{14}	resolution	α-methylbenzylamine
C_{16}	resolution	α-methylbenzylamine
C_{17}	thermodynamic	equilibration
C_{20}	Cram-chelate	hydride/Mitsunobu
C_{21}	thermodynamic	equilibration
C_{24}	$KMnO_4$ oxidative cyclization	(2*S*)-bornane-10,2-sultam
C_{25}	$KMnO_4$ oxidative cyclization	(2*S*)-bornane-10,2-sultam
C_{28}	$KMnO_4$ oxidative cyclization	(2*S*)-bornane-10,2-sultam
C_{29}	$KMnO_4$ oxidative cyclization	(2*S*)-bornane-10,2-sultam

from **576**. Condensation of **577** with phosphonate **578** gave ketenethioacetal **579** in 76% yield. Hydrolysis of the benzoate esters followed by acid-catalyzed cyclization of the resulting diol afforded, after protection of the C_1 alcohol, spirocyclic dithioorthoester **580** in 73% yield. This sequence established the C_6 methyl stereocenter as a 12:1 mixture of diastereomers. Hydrolysis of the dithiane, reduction of the resulting lactone, and treatment of the intermediate lactols with thiophenol under BF_3 catalysis afforded a 3:1 mixture of phenylthioacetals **572** in 69% yield. In analogy with work of Boeckman in the synthesis of indanomycin, reductive lithiation of **572** with lithium 4,4′-di-*tert*-butylbiphenylide gave only the desired axial oxanyllithium, which was converted into the corresponding cuprate **581**. Alkylation of **581** with the η^3-allyl cationic complex **582**, prepared in three steps and 60% yield from (*S*)-allylic acetate **573** (94% ee),[112] afforded, after oxidative destruction of the molybendum species and C_1 deprotection, olefin **583** in 40% yield and high facial and regioselectivity. Oxidation of the C_1 alcohol and ozonolysis of the alkene completed the synthesis of the C_1-C_9 fragment **308** in 20 steps and 3% overall yield from **576**.

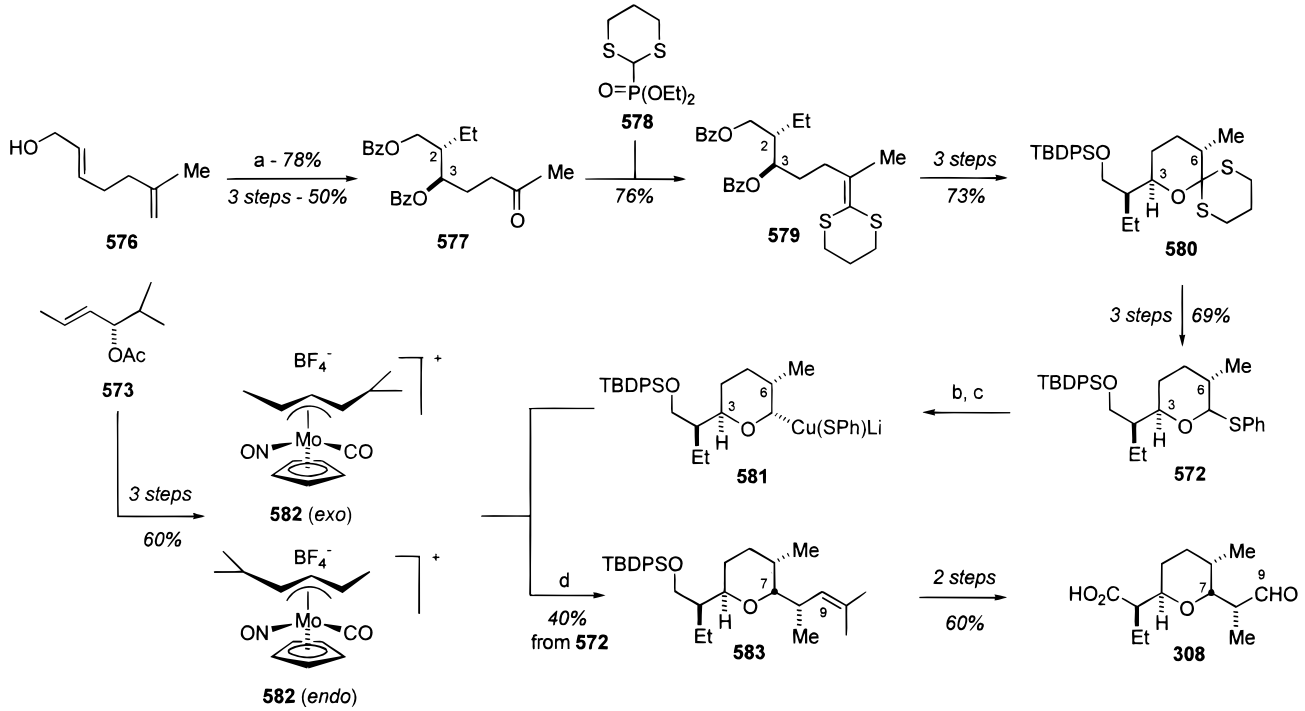
2. Synthesis of the C_{11}–C_{17} Fragment

Methanolysis of 2,4-dimethylpentanedioic anhydride **(584)** afforded a racemic mixture of 2,4-dimethylpentanedioic acid monomethyl esters that were resolved with α-methylbenzylamine to afford the $C_{13}-C_{17}$ fragment **585** in 41% yield (Scheme 128). Reduction of the carboxylic acid provided alcohol **586** in 97% yield. Conversion of **586** into aldehyde **587** was completed in five steps and 58% yield. Aldol reaction of **587** with *N*-butanoyl oxazolidinethione **588** catalyzed by $Sn(OTf)_2$, using conditions developed by Nagao[113] afforded aldol adduct **589** in 91% yield. Reductive removal of the auxiliary, followed by lactone formation, completed the synthesis of the $C_{11}-C_{17}$ fragment **574** in 12 steps and 15% overall yield.[114]

3. Synthesis of the C_{21}–C_{30} Fragment

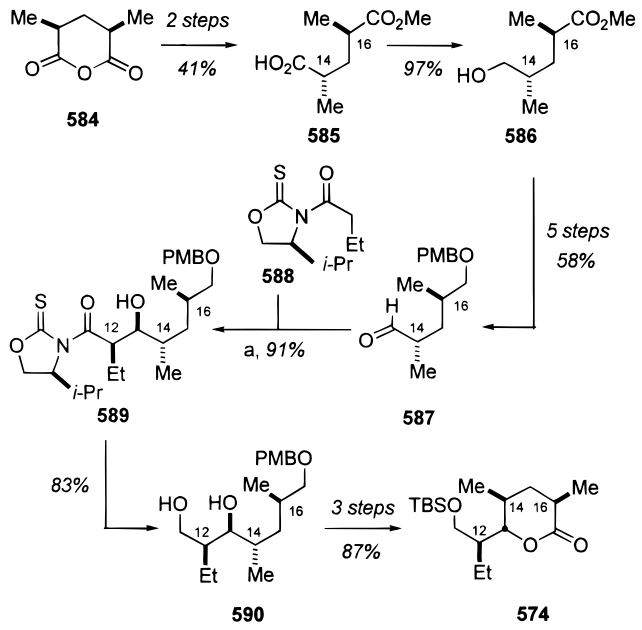
Kocienski exploited known methodology for the synthesis of tetrahydrofurans from 1,5-dienes for his synthesis of the $C_{21}-C_{30}$ fragment of salinomycin.[115,116] Acylation of Oppolzer's (2*S*)-bornane-10,2-sultam **(592)**[117] with the acid chloride derived from **591** afforded the chiral diene **593** in 65% yield. Oxidative cyclization of **593** afforded the desired tetrahydrofuran **594** in 54% yield as a 6:1 mixture of diastereomers. Treatment of **594** with excess ozone

Scheme 127[a]



[a] (−)-Diisopropyltartrate, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −25 °C; (b) LiDBB, THF, −80 °C; (c) CuBr·SMe_2, −80 °C; (d) O_3, CH_2Cl_2, rt.

Scheme 128[a]



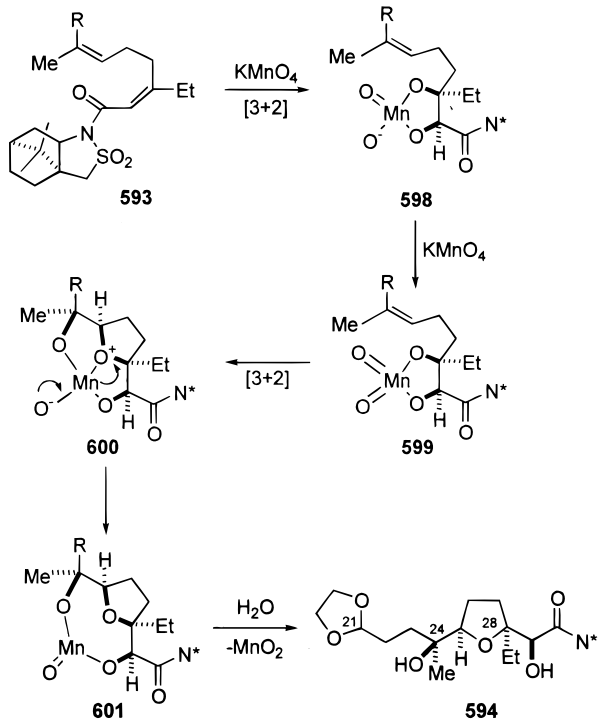
[a] (a) $Sn(OTf)_2$, *N*-Et-piperidine, CH_2Cl_2, −50 °C.

afforded the intermediate hydroxyesters, which were cyclized directly using *p*-TsOH to give lactone **595** in 68% yield, Scheme 129).

The stereochemistry obtained in the oxidative cyclization reaction was rationalized by a reaction sequence that first involved a diastereoselective [3+2]-cycloaddition of permanganate to the electron-deficient enoyl double bond to form the cyclic Mn^{V} diester **598**. Manganate ester **598** underwent rapid oxidation by permanganate to the Mn^{VI} diester **599**. A second intramolecular cycloaddition on the remaining trisubstituted alkene followed by hydrolysis of the Mn^{IV} diester **601** afforded the observed product (Scheme 130).[118,119]

Reductive removal of the sultam and formation of the tosylate of the primary alcohol allowed for separation of the diastereomeric lactones. Reductive removal of the tosylate afforded **596** in 70% yield. Formation of the C_{29} mesylate followed by silver carbonate promoted solvolytic ring expansion afforded the desired lactone **575** by capture of the oxiranium ion intermediate **597** by path *a*. Starting lactone **596** derived from solvolysis via path *b* was also recovered. Protection of the C_{28} alcohol completed the synthesis of the C_{21}−C_{30} fragment in 22 steps and 2% overall yield.

Scheme 130[a]

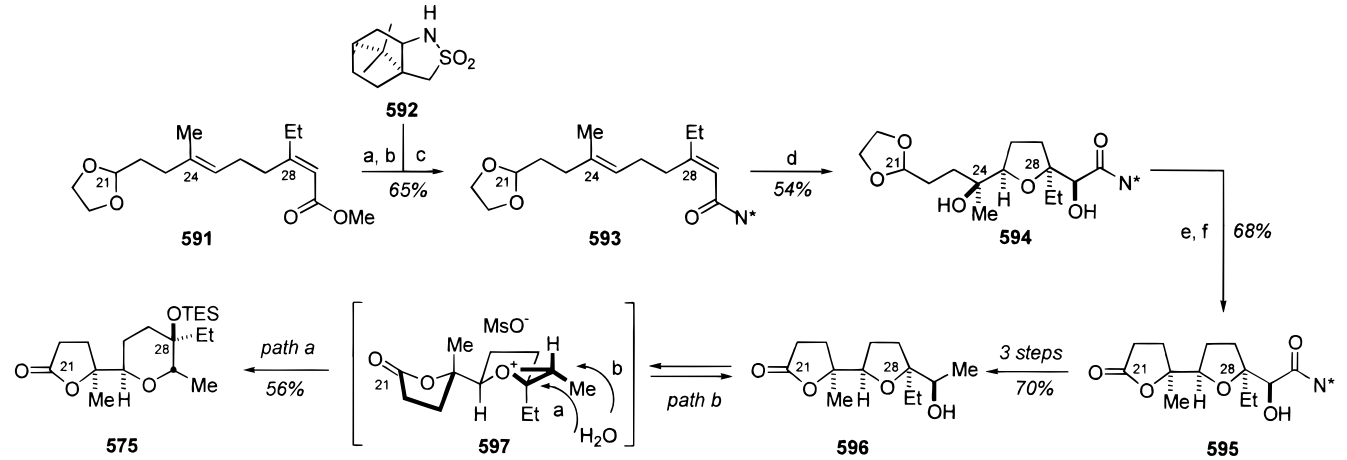


[a] Reprinted with permission from ref 110a. Copyright 1998 Royal Society of Chemistry.

4. Synthesis of the C_{11}–C_{30} Fragment

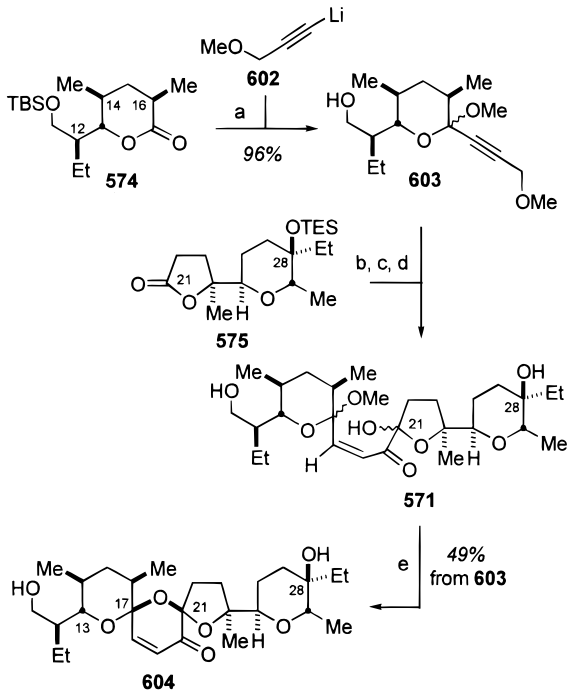
Addition of the lithium derivative of 1-methoxyprop-2-yne **602** to lactone **574** followed by treatment of the crude hemiacetal adduct with $BF_3{\cdot}OEt_2$ in MeOH afforded alkyne **603** as a single diastereomer in 96% yield (Scheme 131). Prototropic rearrangement of **603**, followed by metalation with *n*-BuLi and addition of lactone **575** afforded, after acidic hydrolysis, *cis*-enone **571**. Treatment of **571** directly with HF

Scheme 129[a]



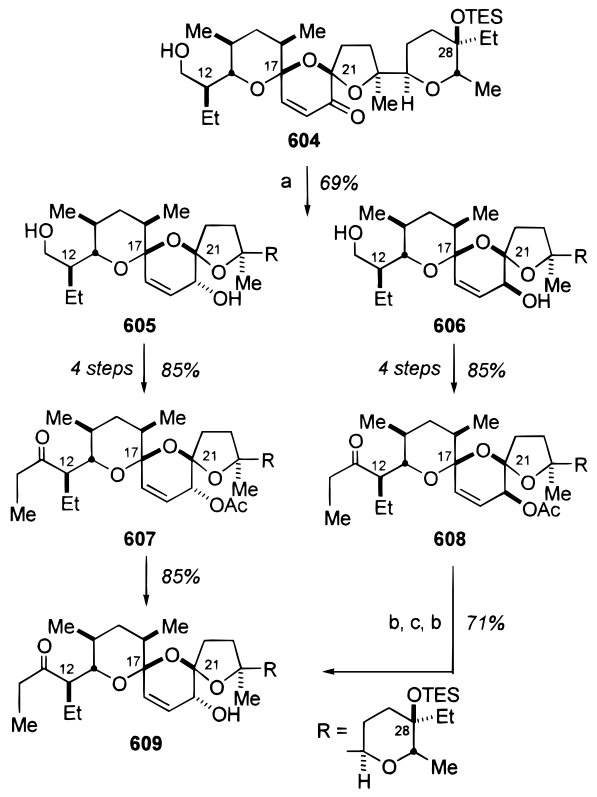
[a] (a) NaOH, MeOH; (b) $(COCl)_2$; (c) *n*-BuLi, (d) $KMnO_4$, pH 6 acetate buffer, acetone-HOAc−H_2O, −35 °C; (e) O_3, EtOAc, −80 °C; (f) *p*-TsOH, CH_2Cl_2, rt. (Reprinted with permission from ref 110. Copyright 1998 Royal Society of Chemistry.)

Scheme 131[a]



[a] (a) $BF_3{\cdot}OEt_2$; (b) *t*-BuOK, 18-crown-6, pentane, rt; (c) *n*-BuLi, Et_2O, −80 to −30 °C; (d) H_2SO_4, THF−H_2O, rt; (e) HF, I_2, MeCN−H_2O, rt. (Reprinted with permission from ref 110a. Copyright 1998 Royal Society of Chemistry.)

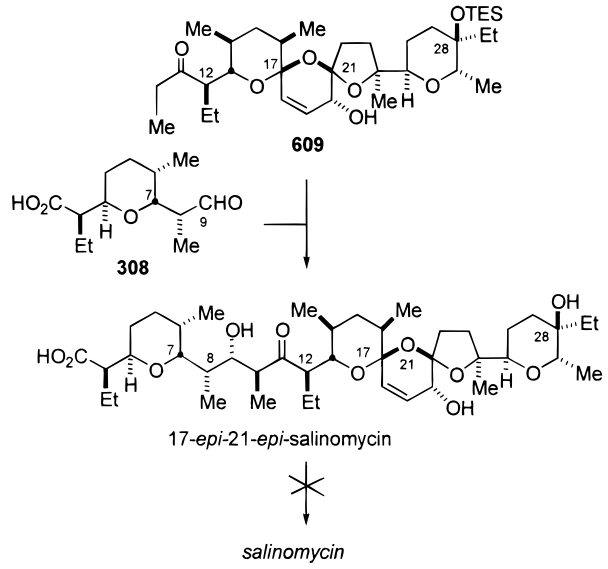
Scheme 132[a]



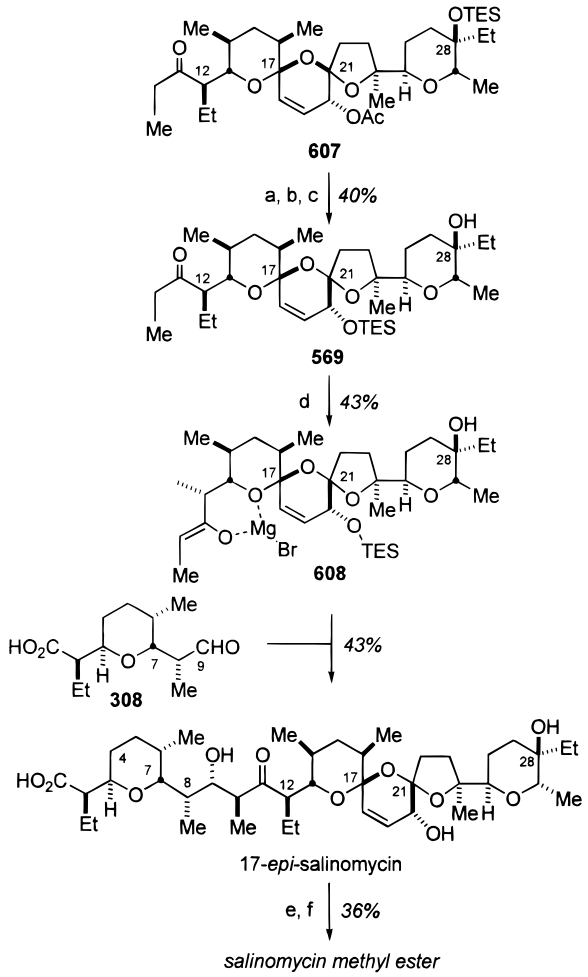
[a] (a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$; (b) K_2CO_3, MeOH; (c) *p*-$NO_2C_6H_4CO_2H$, Ph_3P, DEAD, PhH. (Reprinted with permission from ref 110a. Copyright 1998 Royal Society of Chemistry.)

in aqueous acetonitrile afforded dispiroacetal **604**. Unreacted starting material was recycled through this reaction four times, affording **604** in 49% overall yield from **603**. The C_{11}−C_{30} dispiroacetal, **604**, containing the undesired stereochemistry at C_{17} and C_{21} for salinomycin was thus obtained in four steps and 39% overall yield from **574**.

Scheme 133



Scheme 134[a]



[a] (a) CSA, CH_2Cl_2, pyr; (b) K_2CO_3, MeOH; (c) TESOTf, 2,6-lutidine, CH_2Cl_2; (d) $(C_6H_{11})_2MgBr$, THF, −65 °C; (e) Trifluoroacetic acid, mol sieves, CH_2Cl_2; (f) CH_2N_2, Et_2O. (Reprinted with permission from ref 110a. Copyright 1998 Royal Society of Chemistry.)

Reduction of the C_{21} ketone **604** with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ afforded an inseparable mixture of two allylic alcohols **605** and **606** in 69% yield and 1:7 diastereoselectivity. The major diastereomer **606** contained the undesired stereochemistry at C_{20} (Scheme 132). The minor isomer **605** was efficiently converted into **607** in 85% yield by a four-step sequence involving C_{20} acylation, C_{11} oxidation, and reaction with EtMgBr followed by reoxidation at C_{11}. Deacylation of **607** afforded **609** containing the desired stereochemistry at C_{20} but the wrong stereochemisty at C_{17} and C_{21} for salinomycin. Using a similar sequence of reactions the undesired diastereomer **606** was converted into **608**. Inversion of the C_{20} stereocenter of **608** using the Mitsunobu reaction also afforded **609** in 60% yield from **606** and completed the synthesis of the $C_{11}-C_{30}$ fragment in 13 steps and 30% overall yield from **604**.

5. Fragment Coupling—The Aldol Reaction

Initial attempts to induce acid-catalyzed rearrangement of the C_{17} and C_{21} stereocenters of 17-*epi*-21-*epi*-salinomycin derived from aldol reaction of **308** with ketone **609** were unsuccessful (Scheme 133). The optimal approach to complete the synthesis of salinomycin involved epimerization of the C_{21} stereocenters prior to the aldol coupling reaction (Scheme 134). Thus, treatment of **607** with CSA epimerized C_{21} and afforded, after protecting-group manipulation, dispiroacetal **569** in 40% yield as a 1:9 mixture of C_{17} diastereomers. Formation of the magnesium enolate **608** and aldol reaction with aldehyde **308** afforded, after removal of the TES protecting groups, a single major *anti*-adduct of 17-*epi*-salinomycin in 43% yield. Treatment of the crude product with trifluoroacetic acid in CH_2Cl_2 facilitated epimerization at the C_{17} stereocenter and completed the synthesis of salinomycin in 36% yield from 17-*epi*-salinomycin.

AD. 1995, Lonomyin A (Evans)

Lonomycin A contains an array of 23 stereogenic stereocenters and a latent β-keto acid moiety masked as an internal hemiketal. A total synthesis of lonomycin A was reported by Evans in 1995.[120] In direct analogy to the synthesis of monensin A, opening of the B/C spiroketal revealed a β-hydroxy ketone **609** that was sectioned at $C_{11}-C_{12}$ by an aldol disconnection dividing the molecule into two fragments **610** and **611** (Scheme 135). Opening of the ring A-lactol generated the C_1-C_{11} synthon **612**. Further disconnection of the C_4-C_5 and C_8-C_9 bonds indicated that this fragment could be prepared by two successive aldol reactions of β-keto imide **614** with methacrolein **615**. New methodology to perform this chemistry was successfully developed by Evans.

The epoxide cascade reaction, developed by Still[121] and Schrieber,[122] was employed to generate the $C_{12}-$

Scheme 135

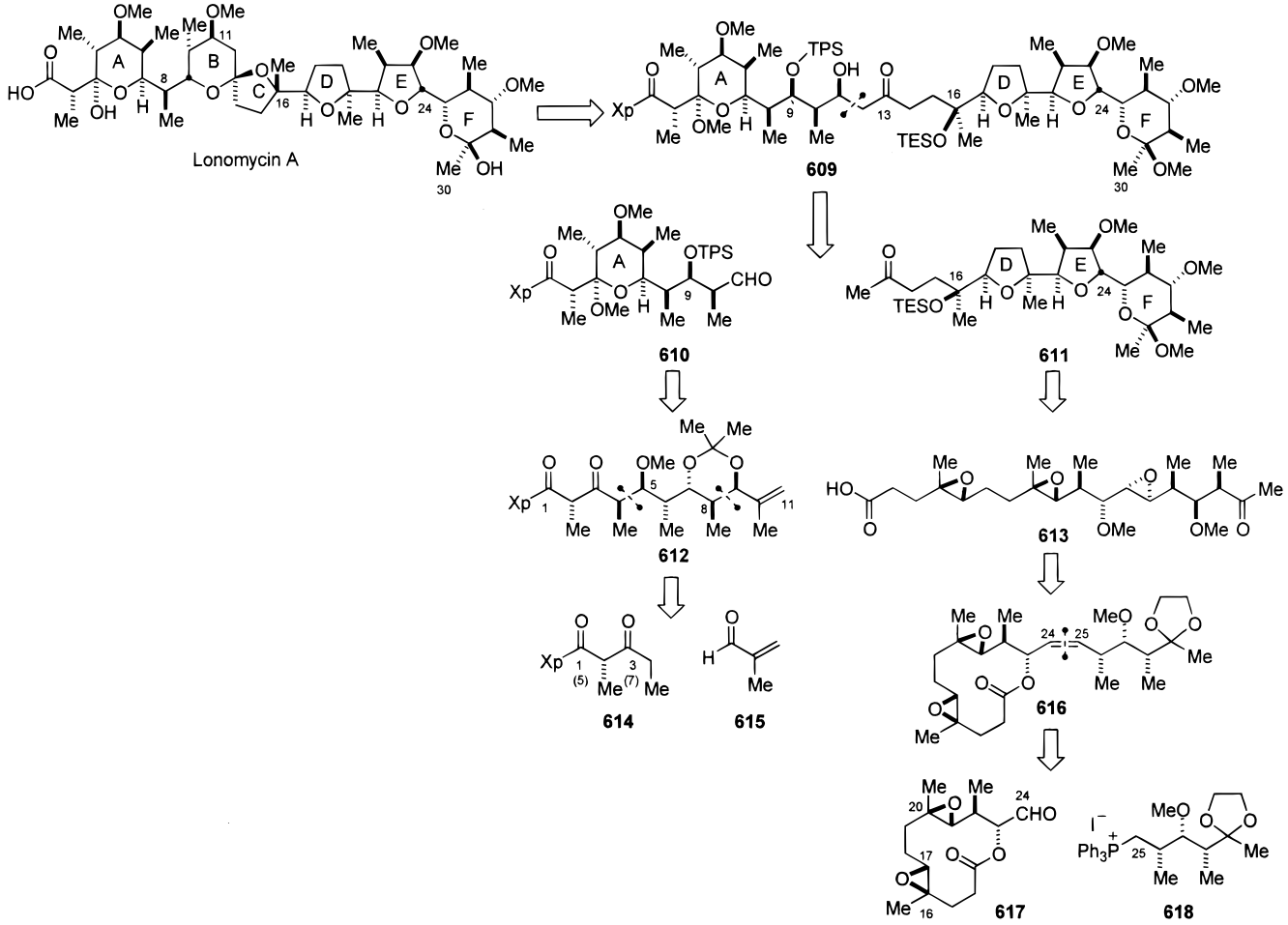


Table 30. Stereochemical Inventory for Evan's Synthesis of Lonomycin A

carbon	control element	reaction/source
C_2	A-1,3	alkylation/oxazolidinone
C_3	thermodynamic	THF formation
C_4	A-1,3	$Sn(OTf)_2$ aldol/β-keto imide
C_5	A-1,3	$Sn(OTf)_2$ aldol/β-keto imide
C_6	A-1,3	alkylation/oxazolidinone
C_7	directed reaction	hydride reduction
C_8	A-1,3	$Sn(OTf)_2$ aldol/β-keto imide
C_9	A-1,3	$Sn(OTf)_2$ aldol/β-keto imide
C_{10}	A-1,2	hydroboration
C_{11}	Cram addn	organolithium
C_{13}	thermodynamic	equilibration
C_{16}	macrocyclic stereocontrol	epoxidation
C_{17}	macrocyclic stereocontrol	epoxidation
C_{20}	macrocyclic stereocontrol	epoxidation
C_{21}	macrocyclic stereocontrol	epoxidation
C_{22}	A-1,3	boron aldol/oxazolidinone
C_{23}	A-1,3	boron aldol/oxazolidinone
C_{24}	A-1,3	epoxidation
C_{25}	Cram-chelate	hydride reduction
C_{26}	A-1,3	alkylation/oxazolidinone
C_{27}	Cram-chelate	hydride reduction
C_{28}	A-1,3	$TiCl_4$ acylation/β-keto imide
C_{29}	thermodynamic	equilibration

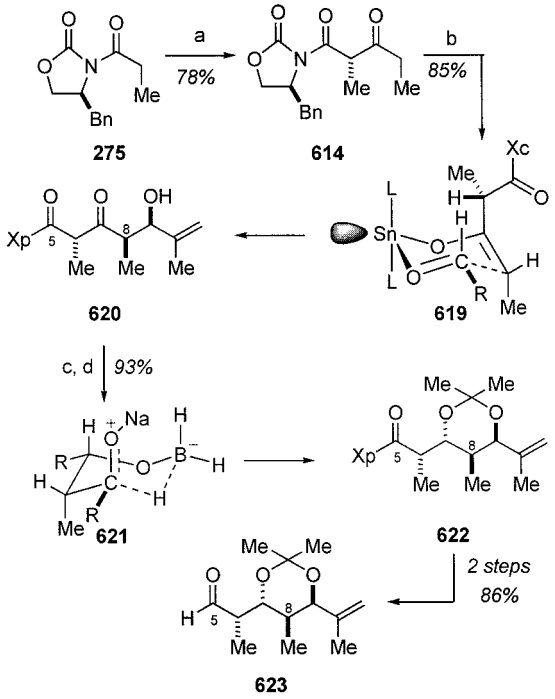
C_{30} fragment **611** from **616**. Disconnection of the $C_{24}-C_{25}$ olefin by a Wittig reaction afforded lactone **617** and phosphonium salt **618**. The 12-membered lactone **617** was chosen as the synthetic target, based on Schreiber's results with a similar 12-membered lactone to prepare the C_9-C_{23} fragment of monensin B. Although the decision to employ the $C_{24}-C_{25}$ *Z*-olefin required inversion of the C_{25} oxygen substituent, it provided a strong facial bias to secure the stereochemical course of the epoxidation reaction. The stereochemical inventory for Evan's synthesis of lonomycin A is summarized in Table 30.

1. Synthesis of the C_1–C_{11} Fragment[123]

Evans extended the chiral imide enolate chemistry previously developed in the synthesis of X-206 to β-ketoimides. Thus, treatment of the magnesium enolate of **275** with propionyl chloride afforded β-ketoimide **614** in 78% yield and 20:1 diastereoselectivity (Scheme 136). The C_2 methyl stereocenter of **614** is stable to enolization due to A-1,3 conformational effects as previously described (Scheme 66). Treatment of **614** with $Sn(OTf)_2$ afforded the stereochemically homogeneous *Z*-enolate **619**. Aldol reaction of **619** with methacrolein **615** afforded aldol adduct **620** in 95:5 selectivity and 85% yield. Reduction of **620** with $NaBH_4$ proceeded with internal hydride delivery via the intermediate alkoxyborohydride **621** to afford, after acetonide formation, **622** in 93% yield. Reductive removal of the auxiliary followed by oxidation provided **623** in 86% yield and completed the synthesis of the C_5-C_{11} fragment in 53% overall yield.

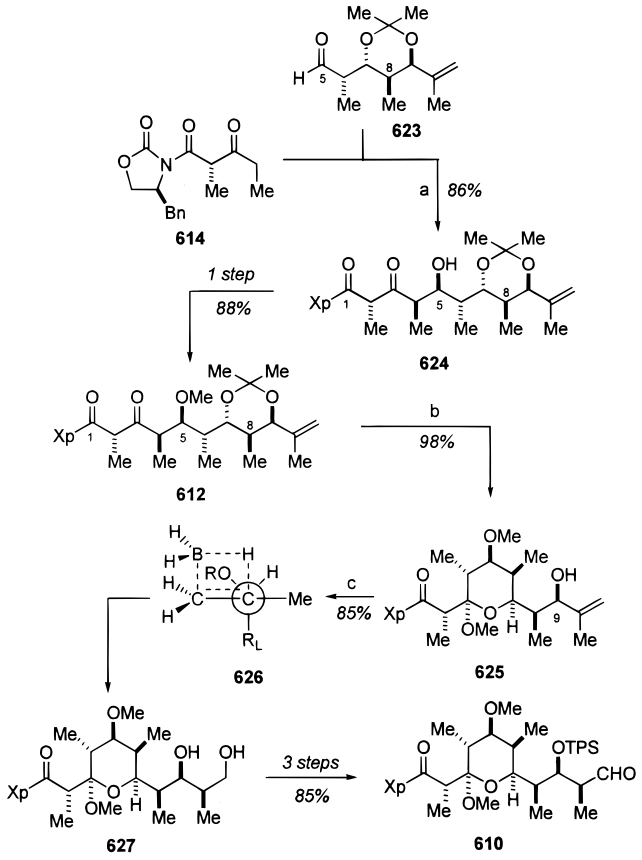
A second β-keto-imide aldol reaction of **614** and C_5-C_{11} aldehyde **623** using $Sn(OTf)_2$ also proceeded with >95:5 selectivity and afforded the *anti*-Cram adduct **624** in 86% yield (Scheme 137). Due to the ease of epimerization of the C_2 stereocenter, the oxazolidinone protected A-ring analog of lonomycin A was employed. This added significant stability to

Scheme 136[a]



[a] (a) LDA, $MgBr_2$, EtCOCl; (b) $Sn(OTf)_2$, methacrolein, Et_3N; (c) $NaBH_4$, HOAc; (d) 2,2-dimethoxypropane, Dowex 50, CH_2Cl_2.

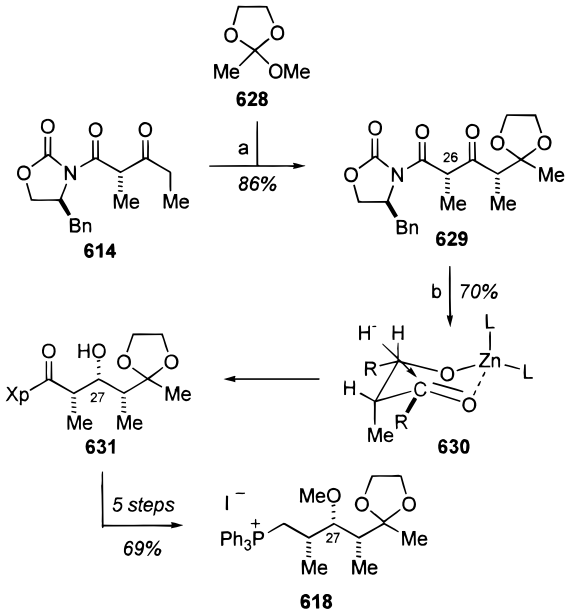
Scheme 137[a]



[a] (a) $Sn(OTf)_2$, Et_3N; (b) Dowex 50, MeOH, CH_2Cl_2, $CH(OMe)_3$; (c) $BH_3{\cdot}Me_2S$, THF.

the epimerization-prone C_2 center since deprotonation of this center is disfavored due to destabilizing A-1,3 interactions. Methylation of the C_5 hydroxyl afforded **612** in 88% yield. Removal of the acetonide

Scheme 138[a]



[a] (a) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2; (b) $Zn(BH_4)_2$, CH_2Cl_2, −20 °C.

resulted in formation of the A-ring tetrahydropyran, which was methylated to afford **625** in 98% yield. Again, the power of the imide methodology is evident by its ability to generate six of the nine stereogenic centers of the C_1-C_{11} fragment.

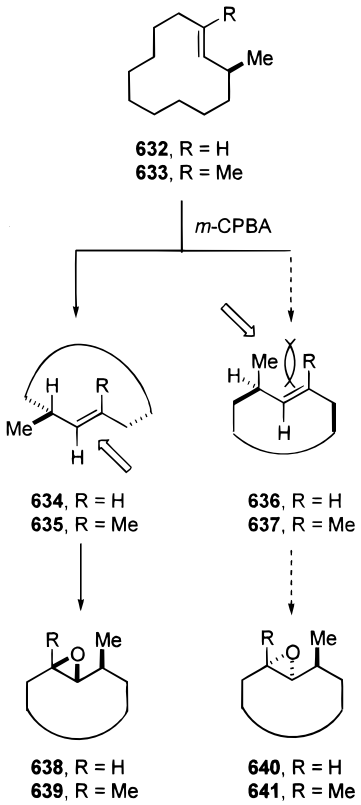
Diastereoselective hydroboration of **625** with BH_3·Me_2S afforded **627** in 85% yield and 92:8 stereoselectivity. The reaction proceeded through transition state **626** where the destabilizing A-1,2 interactions between the allylic OR substituent and $=CH_2$ are minimized. Bis-silylation of **627**, monodeprotection, and oxidation of the primary alcohol with Dess−Martin periodinane completed the synthesis of the C_1-C_{11} fragment **610** in 12 steps and 36% overall yield.

2. Synthesis of the C_{12}–C_{30} Fragment

The key step in the synthesis of the $C_{25}-C_{30}$ polypropionate subunit involved orthoester acylation of the titanium enolate derived from the β-keto imide **614** (Scheme 138). Thus, reaction of **614** with orthoester **628** afforded **629** in 86% yield and 93:7 selectivity. Chelate-controlled reduction of **629** with $Zn(BH_4)_2$ involved external hydride delivery and proceeded through transition state **630** to afford **631** as a single diastereomer in 70% yield. Methylation of the C_{27} alcohol and formation of the phosphonium salt **618** completed the synthesis of the $C_{25}-C_{30}$ fragment in seven steps and 42% overall yield.

Evans employed the epoxide cascade reaction, pioneered by Still and Schreiber, for his synthesis of the $C_{13}-C_{24}$ fragment. In this approach the challenge is to set the absolute stereochemistry of the epoxides in the absence of directing groups, such as an allylic alcohol. This goal is achieved by incorporation of the diene or triene into a macrocycle, where the selectivity of the epoxidation reaction is controlled by the conformation of the macrocycle. This approach is largely based on the observation of Vedejs that

Scheme 139

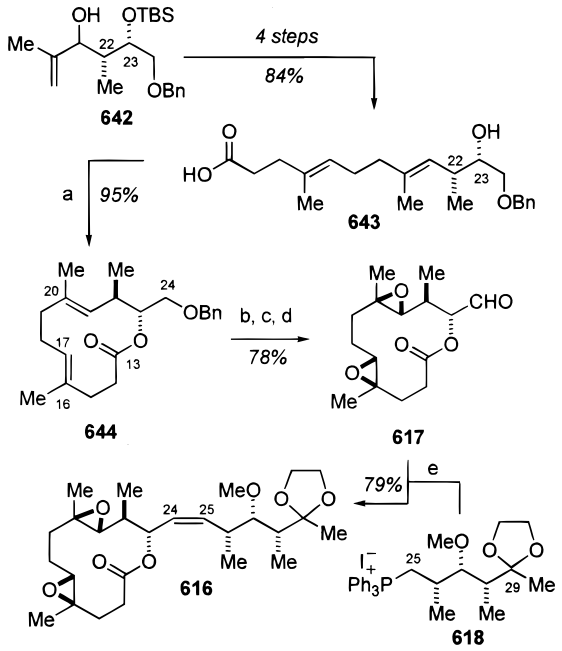


epoxidation of medium-ring macrocycles with an allylic alkyl group, such as a methyl, provides products from peripheral epoxidation.[124] Furthermore, the preferred conformation of *E*-macrocyclic olefins should be that shown in **634** and **635** where allylic 1,3 interactions are minimized.[125] Indeed, epoxidation of **632** with *m*-CPBA provided a 6:1 mixture of epoxide diastereomers **638**:**640** (Scheme 139). As expected, higher diastereoselectivity was achieved upon epoxidation of the *E*-trisubstituted olefin **633** with *m*-CPBA, which afforded a >20:1 mixture of epoxide diastereomers **639**:**641**.

In the $C_{13}-C_{24}$ subunit **644**, the *E*-trisubstituted double bonds were introduced by two Claisen rearrangements from **643**, prepared using a diastereoselective imide aldol reaction to establish the C_{22} and C_{23} stereocenters (Scheme 140). Macrolactonization under Mitsunobu conditions afforded the 12-membered lactone **644** in 95% yield. Epoxidation of **644** with *m*-CPBA afforded a 9:1 mixture of bisepoxide isomers. Debenzylation followed by oxidation afforded aldehyde **617** in 78% yield. The $C_{20}-C_{21}$ olefin was epoxidized with excellent stereocontrol (97:3), due to the well-defined conformational bias imposed by the macrocycle and by an A-1,3 strain control element due to the C_{22} methyl. However, the $C_{16}-C_{17}$ olefin epoxidized with lower selectivity, affording a 9:1 mixture of diastereomeric epoxides due to conformational flexibility in the region of the $C_{16}-C_{17}$ double bond. Wittig coupling of **617** and **618** afforded *Z*-olefin **616** in 79% yield.

Lactone hydrolysis of **616** afforded hydroxy acid **645**. Treatment of **645** with acid initiated the polyepoxide cascade reaction to afford lactone **646** as the only detectable product in 85% yield (Scheme 141).

Scheme 140[a]



[a] (a) DIAD, Ph_3P, PhMe, −10 °C; (b) *m*-CPBA, CH_2Cl_2, −78 to 0 °C; (c) Pd/C, H_2 (300 psi), EtOAc; (d) Dess−Martin periodinane, pyridine, CH_2Cl_2, 0 °C; (e) LiHMDS, THF, −78 to 0 °C.

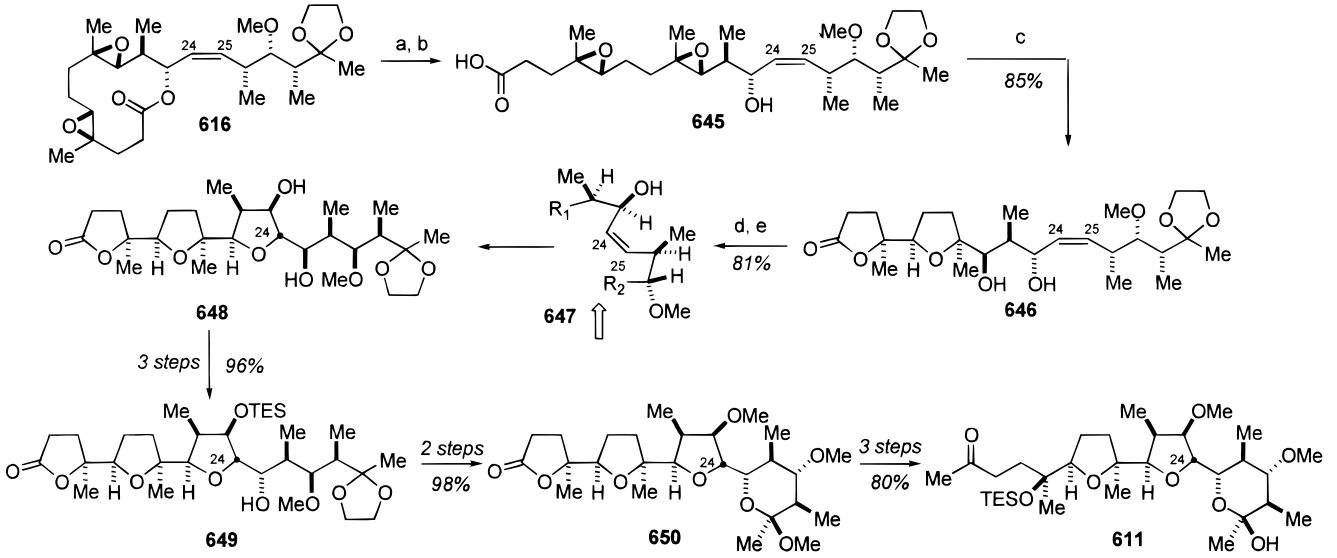
Diastereoselective hydroxyl-directed epoxidation of the C_{24}−C_{25} olefin was accomplished using buffered magnesium monoperoxyphthalate (MMPP). The π-facial selectivity of the epoxidation was governed by A-1,3 strain, where the allylic stereocenters at C_{23} and C_{26} shield the top face of the olefin leaving the bottom face open for epoxidation as illustrated in **647**. Subsequent treatment of the labile epoxide with acetic acid induced the hydroxy-mediated heterocyclization to diol **648** in 81% yield for the two steps. The overall diastereoselectivity of 98% for the merged oxidation and cyclization steps reflects the good level of stereocontrol in the epoxidation reaction.

Protection of the C_{23} alcohol, conversion of the C_{25} alcohol to the ketone, followed by a chelate-controlled reduction with $Zn(BH_4)_2$ provided the inverted alcohol **649** in quantitative yield. The stereochemical outcome was rationalized by reduction via a five-membered chelate formed between the ketone carbonyl and the E-ring tetrahydrofuran oxygen, since based on chelate ring size the alternative six-membered chelate between the C_{25} ketone and the C_{27} methoxyl was less favored.[126] Assemblage of the F-ring lactol was accomplished by transketalization with PPTS in MeOH with concomitant removal of the C_{23} silyl protecting group. The E-ring hydroxyl group was then methylated and the C_{12}−C_{30} subunit completed by formation of the methyl ketone **611**.

3. Fragment Coupling—The Aldol Reaction

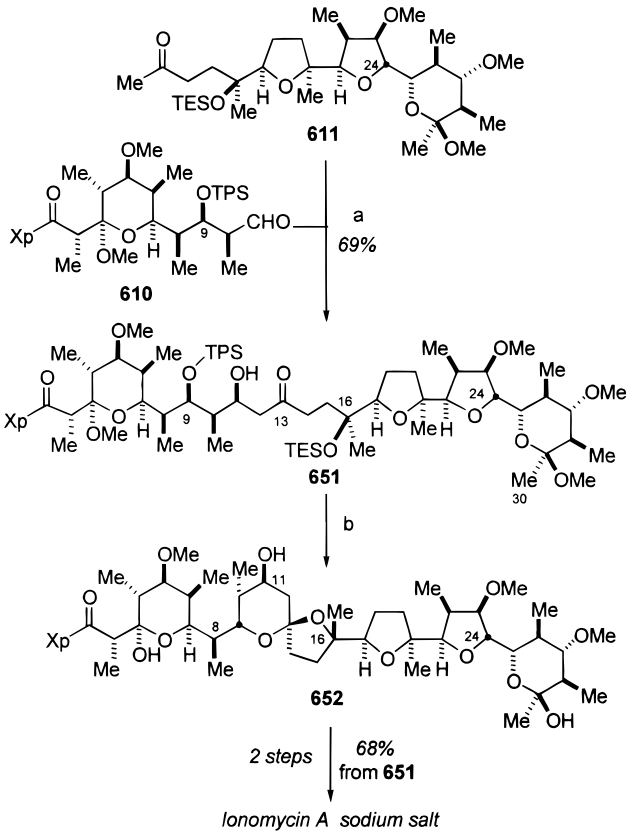
The C_9 protecting group had a significant effect on the diastereoselectivity of the aldol reaction. Small silyl protecting groups, TMS and TES, displayed only modest Cram selectivity, ranging from 2:1 to 4:1, respectively. Using the *tert*-butyldimethylsilyl group the diastereoselectivity of the reaction dramatically increased to 92:8; however, upon desilylation elimination of the A-ring lactol as well as epimerization of the C_2 stereocenter was observed. For this reason the triphenylsilyl protecting group, which provided steric bulk for a selective reaction and acid lability for deprotection under mild conditions, was employed. Thus, reaction of aldehyde **610** and ketone **611** afforded aldol adduct **651** in 69% yield, along with 29% recovered ketone **611** (Scheme 142). Treatment of **651** with aqueous HF in MeCN initiated three reactions involving removal of the silicon protecting groups, spiroketalization to a single spiroketal diastereomer and hydrolysis of the C_3 and C_{29} lactol methyl ethers to afford **652**. Methylation of the B-ring C_{11} hydroxyl, hydrolysis of the C_1 oxazolidinone and formation of the sodium salt provided lonomycin A.

Scheme 141[a]



[a] (a) KOH, 3:1 MeOH:H_2O, 23 °C; (b) HOAc; (c) 4 Å mol sieves, CH_2Cl_2; (d) MMPP, 4 Å mol sieves, CH_2Cl_2, 0 °C; (e) HOAc, CH_2Cl_2, 23 °C.

Scheme 142[a]



[a] (a) LDA, THF, −78 °C; (b) 5:86:9 48% aq HF/MeCN/H_2O, 0 °C.

III. Concluding Remarks

Clearly, the past 20 years of research on the synthesis of polyether ionophore antibiotics has provided a valuable set of tools to construct these molecules in an efficient and enantioselective fashion. The early work of Kishi and Still, who applied the fundamentals of A-1,3 interactions and Cram and *anti*-Cram addition reactions, provided a foundation for the elegant syntheses described in this review. In the pursuit of the total synthesis of polyether ionophores, valuable general methodology has been developed: the chiral imide alkylation and aldol reactions developed by Evans, the chiral crotyl borane chemistry developed by Roush, Ireland's ester−enolate chemistry, Hanessian's chiral replication strategy, and the development of directed reactions such as epoxidation, reduction, and hydroboration.[127] The power of these methods is demonstrated in their continued application to the synthesis of other complex natural products.

While many of the problems associated with the synthesis of polyether ionophore antibiotics have been resolved, it is anticipated that future work may reside in developing more efficient and predictable methods for fragment coupling. In the syntheses described in this review, the principal methods employed to couple the fragments included Julia olefination, the Wittig reaction, the aldol reaction, and the ester−enolate Claisen rearrangement. In most cases these coupling reactions provided the lowest selectivity in synthesis. For example, the aldol reaction can still be considered somewhat unpredictable. While the selectivity in the coupling of fragment **610** with **611** in the synthesis of lonomycin A provided a 95:5 ratio of products, similar coupling reactions employed in the synthesis of ferensmycin B, 4:1 (Evans), monensin A, 1:1−3:1 (Still and Kishi), and lasalocid A, 3:1 (Ireland and Kishi), had considerably lower selectivity. In addition, although the stereochemical outcome of the aldol reaction can be predicted based on the Felkin-Anh paradigm, it cannot be extrapolated from simpler substrates. The development of new methods to efficiently couple polypropionate fragments in high yields with good stereochemical control would provide an excellent complement to the methods for polypropionate synthesis outlined in this review.

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