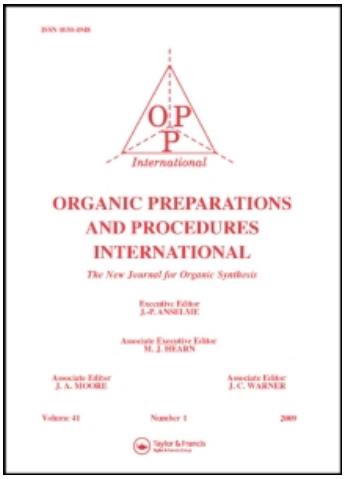

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NATURALLY OCCURRING β-LACTONES: OCCURRENCE, SYNTHESES AND PROPERTIES. A REVIEW

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NATURALLY OCCURRING β-LACTONES: OCCURRENCE, SYNTHESES AND PROPERTIES. A REVIEW

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INTRODUCTION

A convulsant natural product known as anisatin was isolated[1] over forty years ago from the Japanese star anise *Illicium anisatum*, yet it was not until 1965 that it was characterized[2] as a naturally occurring β-lactone. With few exceptions, it was only in the 1980s that all of the currently known natural β-lactones were identified and investigated for their interesting biological properties. This is probably due to the enhanced reactivity of β-lactones and their tendency to open by attack of nucleophiles at the β-position (C-4 of the oxetanone) as well as at the carbonyl. However, milder isolation methods and more comprehensive biological assays will no doubt add new members to this class of microbial and plant products. Because of their potential as medicinal agents or biochemical tools, many eminent chemists have reported syntheses of these secondary metabolites and their analogs within the last decade.

The current review focuses on the various classes of natural β-lactones, their occurrence, biological properties, and total syntheses; the preparation of some analogs of these compounds is also discussed. Particular emphasis is on the formation of the β-lactone moiety and stereocontrol in the synthetic method. The reader is also referred to recent literature[3] describing methodology for the preparation of β-lactones and their reactivity with various reagents, both in a general comprehensive review[3a] as well as in more specialized articles.[3b,c] The authors apologize for any inadvertent omissions or errors.

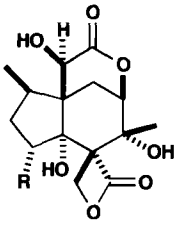
I. TERPENOID β-LACTONES

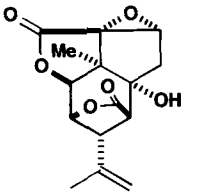
A number of terpenoid natural products, consisting of multiples of C_5 (isoprene) units, contain a β-lactone ring. Examples isolated thus far include sesquiterpenes (C_{15}), diterpenes (C_{20}), and triterpenes (C_{30}). Each of these groups is discussed separately below.

1. Sesquiterpenes

The most extensively studied sesquiterpenoid β-lactones are anisatin (**1**),[2] neoanisatin (**2**),[4] and closely related compounds isolated from plants of the *Illicium* species. They are among the more powerful poisons of plant origin (anisatin, mouse LD_{50} 1mg/kg) and possess a potent convulsant activity comparable to that observed with the structurally related natural product, picrotoxinin (**3**),[5] the physiologically active component of picrotoxin. Picrotoxinin (**3**) is believed to cause a specific blockade of inhibitory synaptic transmission mediated by γ-aminobutyric acid (GABA).[6] The binding of GABA to a post-synaptic receptor triggers the release of chloride ions through a nearby ion channel.

Picrotoxinin and anisatin are believed to display non-competitive GABA antagonism by binding to a specific yet distinct receptor causing the constriction of this ion channel.[7] Dysfunctions of GABA synapses may be involved in diseases such as epilepsy and Huntington's Disease; consequently, much research has focused on understanding the mechanism of these convulsant principles.

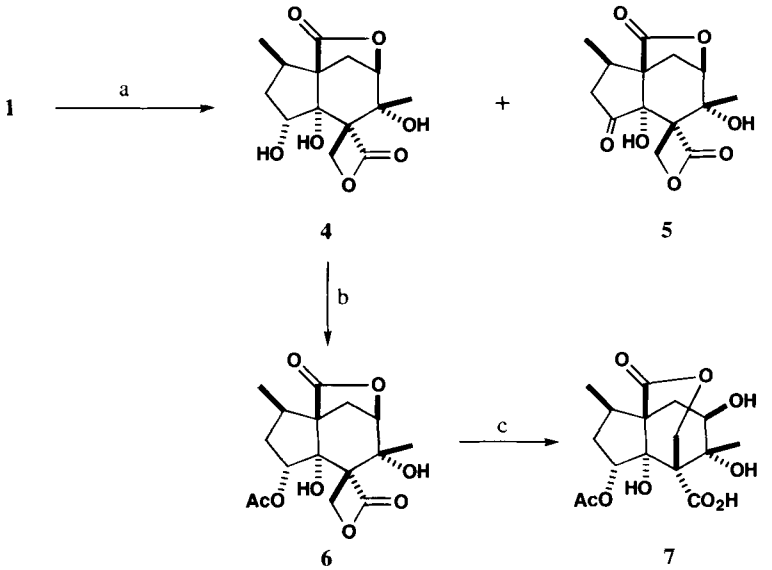




1 anisatin (R = OH)
2 neoanisatin (R = H)

3

The spiro β-lactone present in the polyoxygenated tetracyclic structure exhibits diminished reactivity with reagents that would normally be expected to cause ring opening, probably due to steric hindrance that prevents the approach of nucleophilic species.[8] This relative lack of reactivity was first noticed during structure determination studies. Since anisatin degradation often led to the formation of poorly defined derivatives, initial structural elucidation targeted noranisatin (**4**), an oxidation product of anisatin which affords easily characterizable derivatives. Thus, potassium permanganate oxidation of anisatin yields noranisatin (**4**) and noranisatinone (**5**) (Scheme 1). Anisatin is stable to various acids (e.g. HCl, conc. H_2SO_4, *p*-TsOH, BF_3-Et_2O), even at elevated temperatures. However, treatment of noranisatin monoacetate (**6**) with potassium bicarbonate produces noranisatinic acid (**7**), presumably



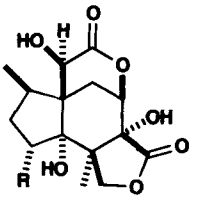
a) $KMnO_4$, AcOH b) Ac_2O, pyr. c) $KHCO_3$

Scheme 1

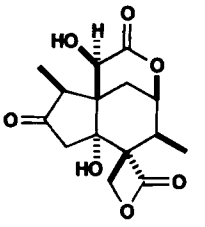
due to initial hydrolysis of the γ-lactone, which thereby increases the flexibility of the molecule, reduces steric hindrance, and allows cleavage of the β-lactone with subsequent intramolecular lactonization to **7**.

Several investigations[8,9] to determine the relative stereochemistry of anisatin employed chemical, spectral and X-ray crystallographic techniques, but the absolute stereochemistry was not defined until Niwa's stereospecific total synthesis[10] (see below) allowed comparison of synthetic material and the natural product. In this review all structures are drawn based on this absolute stereochemistry, but in other anisatin-related publications, the opposite enantiomer is commonly drawn.

Related sesquiterpene lactones occur in Chinese *Illicium* plants, such as majucin (**8**) and neomajucin (**9**) from *Illicium majus*.[11] It is interesting to note that structures which contain a γ-lactone instead of a β-lactone display either no toxicity (e.g. majucin (**8**)), or extremely weak picrotoxin-like activity, as in the case of neomajucin (**9**) (mouse LD_{50} 10mg/kg). More recently, other neurotoxic anisatin-related β-lactones have been isolated from this plant, including 2-oxo-6-dehydroxyneoanisatin (**10**),[12] 2α-hydroxyneoanisatin (**11**),[13] 1-hydroxyneoanisatin (**12**),[14] 1-hydroxy-6-dehydroxyneoanisatin (**13**),[14] and 3,4-dehydroxy-2-oxoneoanisatin (**14**).[14] A related species, *Illicium*



8 R = OH
9 R = H



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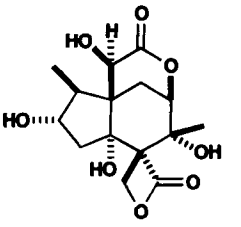

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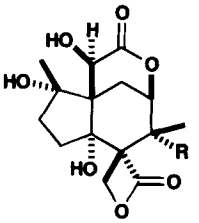
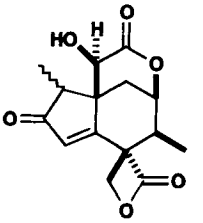


12 R = OH
13 R = H



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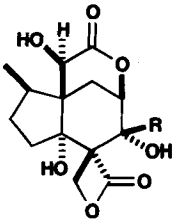
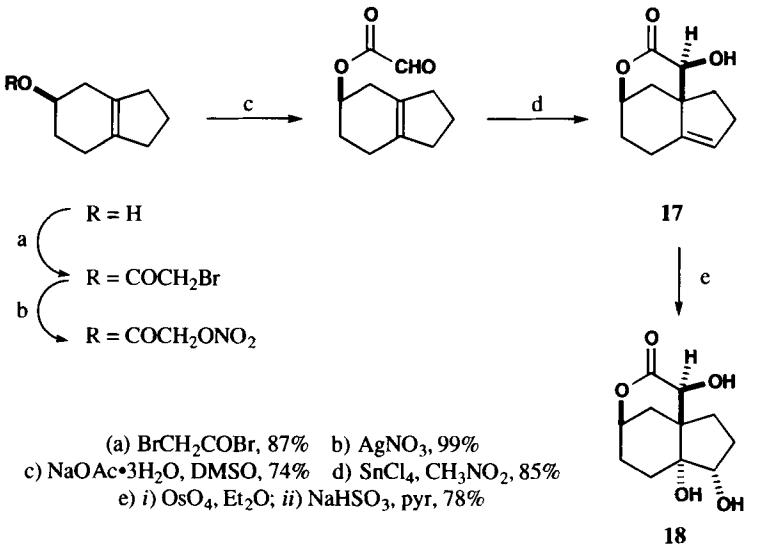


15 R = CH_2OCH_3
16 R = CO_2CH_3

verum, produces veranisatins A (**15**) and B (**16**).[15] Interestingly, *I. verum* has been used as a spice, and is employed in traditional Oriental medicine as an analgesic and treatment for stomach disease.

The unique structure and biological properties of anisatin have prompted many synthetic studies,[16-19] but only one stereocontrolled total synthesis[10] of (-)-anisatin (**1**) has been published thus far. In a model study reported in 1982 by Lindner *et al.*,[16] construction of the α-hydroxy δ-lactone ring used a highly stereoselective intramolecular ene reaction. This process determines the relative stereochemistry of three of the chiral centers in anisatin and concomitantly forms the bridgehead

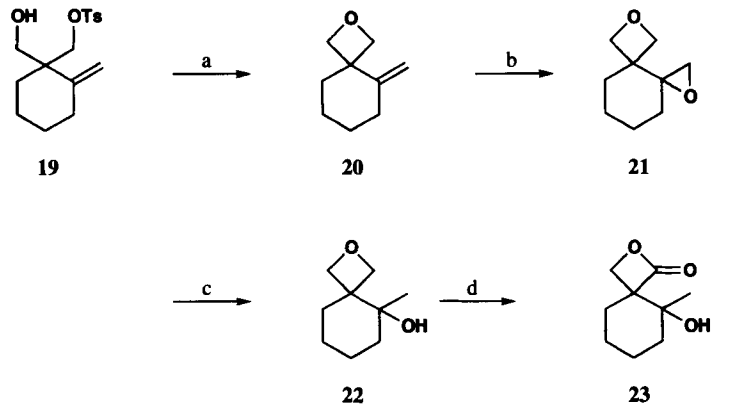
quaternary carbon center of the tricyclic ring system (Scheme 2). The resulting α-hydroxy lactone **17** is the sole regio- and stereoisomer obtained. A subsequent *cis*-dihydroxylation sets the final two stereocenters in the anisatin model **18**.



Scheme 2

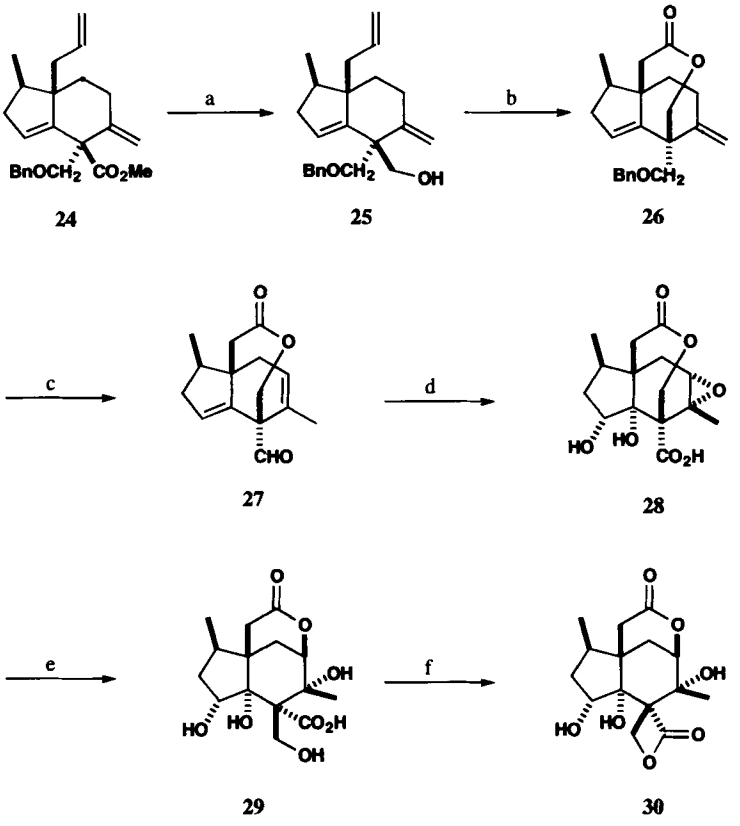
β-Lactone formation in an anisatin model study by Yoshikoshi and coworkers utilized an interesting oxidation process, although no stereoselectivity was observed.[17] Thus treatment of **19** with sodium hydride generates the oxetane **20**, which reacts with MCPBA to give epoxide **21**. Regioselective ring opening of the epoxide **21** with super hydride affords the tertiary alcohol **22**. Oxidation of this oxetane with ruthenium tetraoxide forms the β-lactone **23** as an inseparable 1:1 mixture of diastereoisomers (Scheme 3).

A stereoselective total synthesis of (±)-8-deoxyanisatin (**30**) was achieved by Kende and coworkers (Scheme 4).[19] A key feature of their approach is the blocking of the β-face of the developing molecular skeleton, thereby facilitating stereoselective *cis*-dihydroxylation and epoxidation reactions on the α-face. Reduction of the ester **24** by $LiAlH_4$ gives alcohol **25**, which upon Lemieux-von Rudloff oxidation and mild lactonization affords the ε-lactone **26**. Isomerization of the exocyclic double bond and oxidation of the benzyl ether to the aldehyde **27**, sets the stage for the stereoselective *cis*-dihydroxylation and epoxidation, which upon subsequent sodium chlorite oxidation gives **28**, whose structure is confirmed X-ray crystallographic analysis. Treatment with lithium hydroxide, followed by mild acidification produces the δ-lactone **29**; its formation probably proceeds by participation of the bridging carboxyl in a diaxial opening of the epoxide. Due to steric constraints, the freshly exposed primary hydroxyl group can then lactonize only with the remaining carboxylic acid group. Treatment of **29** with phenylsulfonyl chloride activates this carboxyl for cyclization which gives the desired β-lactone, racemic 8-deoxyanisatin (**30**).[20]



a) NaH, THF, 95% b) MCPBA, CH_2Cl_2, 73%
c) $LiBHEt_3$, THF, 95% d) RuO_4, CH_2Cl_2, 25%

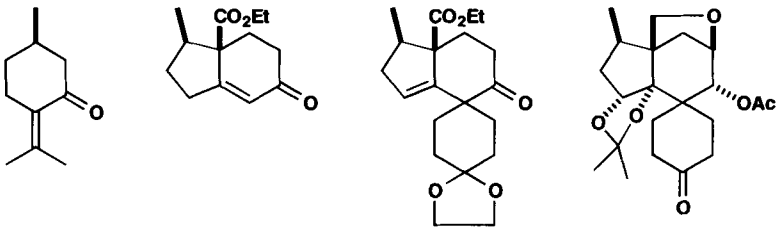
Scheme 3



(a) $LiAlH_4$; (b) i) KIO_4, K_2CO_3, $KMnO_4$, *t*-BuOH; ii) *p*-TsOH, C_6H_6, reflux, 33%;
(c) i) CH_3SO_3H (cat.), 75%; ii) BBr_3, -78°; iii) PDC, 70%; (d) i) OsO_4, pyr., 37%;
ii) CF_3CO_3H, 0°, 100%; iii) $NaClO_2$, 76%; (e)15% LiOH, MeOH, 68%;
(f) $PhSO_2Cl$, pyr., CH_2Cl_2, 0°, 90%.

Scheme 4

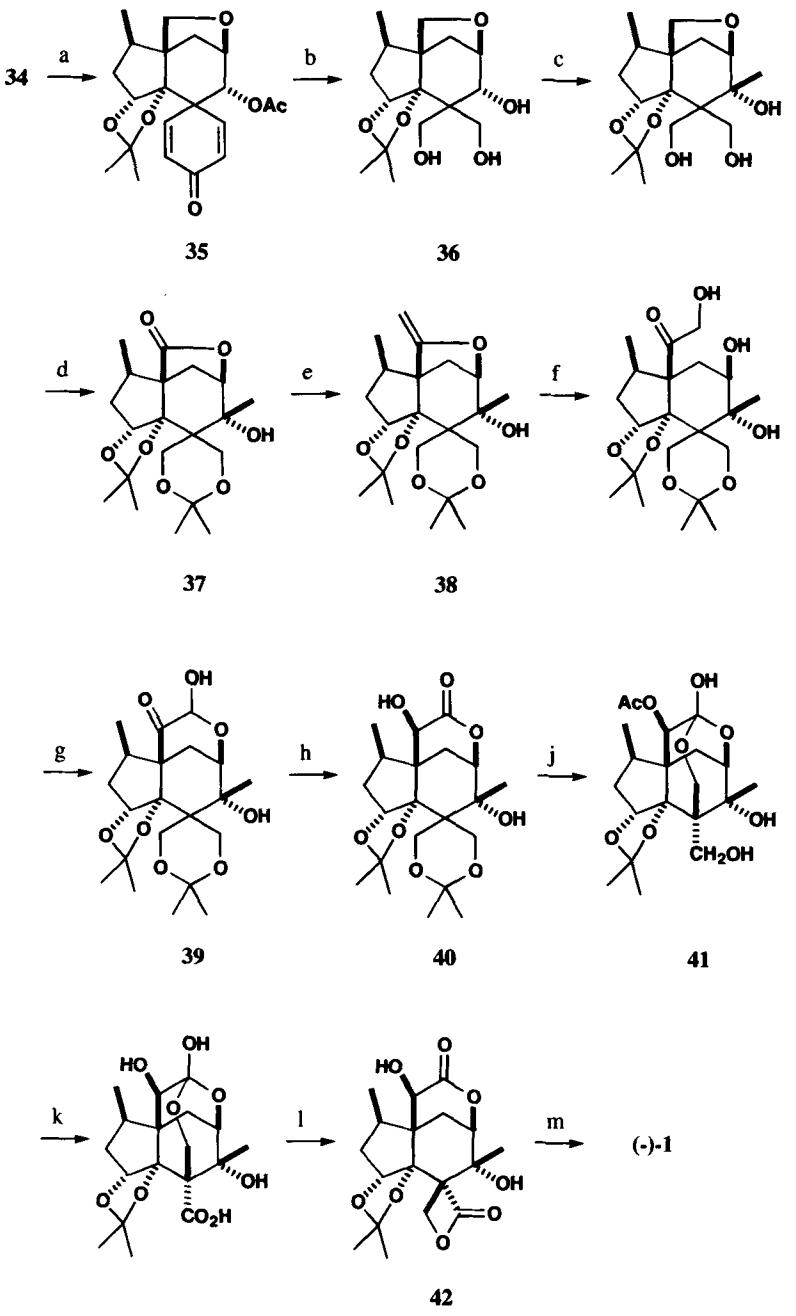
Niwa's stereocontrolled synthesis of natural (-)-anisatin, reported in 1990, confirms the absolute stereochemistry as shown in **1**, which is enantiomeric to that depicted in earlier publications describing this compound.[10] This synthesis generally has high yielding steps and begins with the bicyclic enone **32** (prepared from (R)-(+)-pulegone (**31**)) which is converted to a spiro enone (**33**) that contains much of the framework of **1**. A ten step sequence involving *cis*-hydroxylation, generation of an olefin, reduction of the ester, epoxidation, and a diaxial opening of the epoxide reminiscent of Kende's synthesis of **8**, and deprotection of the spiroketal leads to the cyclic ether **34** (ca. 42%



31 **32** **33** **34**

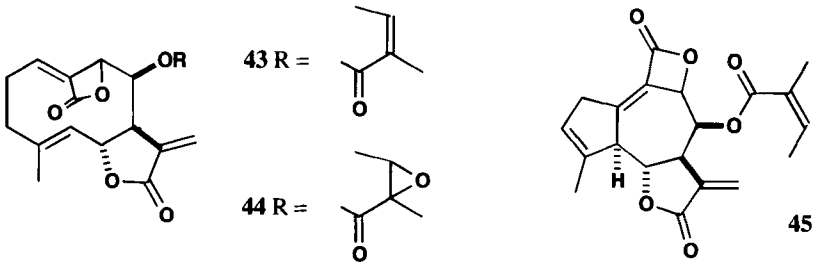
overall). The resulting cyclohexanone ring is then converted into the cross-conjugated dienone **35** by a modification of the Barton method (85% yield) (Scheme 5). The double bonds are then individually cleaved by a three step procedure: osmium tetraoxide hydroxylation, oxidative diol cleavage, and reduction of the resulting aldehyde to give the triol **36** (characterized as its diacetate, overall 36% yield). The next stages of the synthesis involve the stereoselective introduction of a methyl group by oxidation of the secondary hydroxyl, treatment of the ketone with CH_3MgI, and the protection of the two primary hydroxyl groups as an acetonide. The α-hydroxy δ-lactone moiety is then constructed. A ruthenium trichloride-sodium periodate oxidation gives the γ-lactone **37** (87%) which is converted into the enol ether **38** by treatment with methyllithium and subsequent dehydration (98%). The latter compound is then oxidized sequentially with osmium tetraoxide and SO_3.Py-DMSO-Et_3N to furnish the keto hemiacetal **39** (96%) as a single diastereomer which readily isomerizes to the desired α-hydroxy δ-lactone **40** on silica gel. Acetylation and selective acetonide deprotection affords the ortho ester **41**; the primary hydroxyl group is then oxidized to the acid. This allows formation of the β-lactone **42** (91%) by treatment with phenylsulfonyl chloride. Final deprotection gives (-)-anisatin (**1**).

The only other known sesquiterpene lactones unrelated to anisatin are the grazielolides **43** and **44**, and guaiagrazielolide **45**, isolated from the South American Compositae, *Grazielia intermedia*.[21] In compounds **43** and **44**, the IR band observed at 1825 cm^{-1} is indicative of an unusually strained β-lactone, whereas the corresponding band in **45** is at 1835 cm^{-1}, which is more typical for this type of functionality. The high melting point of **45** (111°) suggests that the β-lactone is thermally quite stable. Bohlmann, who isolated these natural products, has reported the synthesis of the model compound **51**, related to **45** (Scheme 6).[22] Treatment of the hexahydroazulenone **46** with basic methanolic hydrogen peroxide gives the epoxide **47**. A Wittig reaction of **47** with methoxymethylene

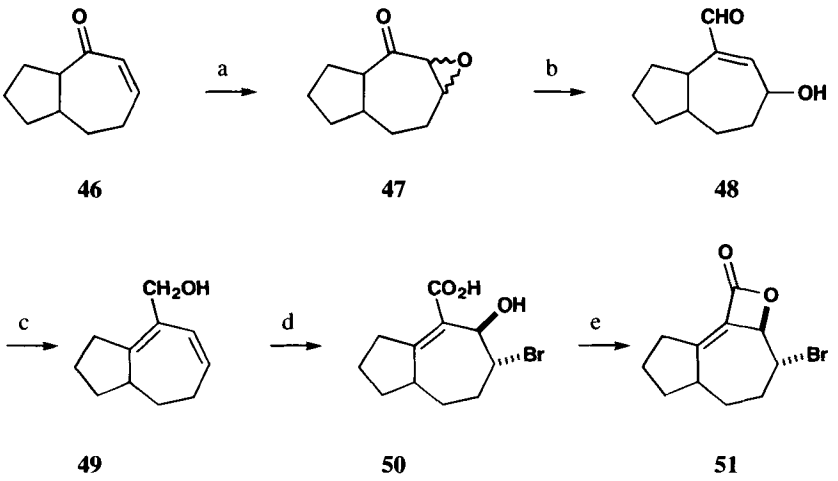


(a) $(PhSe)_2$, m-$IC_6H_4CO_3H$, pyr.; (b) i) OsO_4; ii) $Pb(OAc)_4$; iii) $LiAlH(OtBu)_3$; iv) OsO_4; v) $Pb(OAc)_4$; vi) $LiAlH_4$; (c) i) Ac_2O, pyr.; ii) PCC; iii) CH_3MgI; (d) i) $CH_2{=}C(OCH_3)CH_3$, CSA; ii) $RuCl_3$, $NaIO_4$; (e) i) CH_3Li; ii) CSA; (f) OsO_4; (g) SO_3.pyr.; (h) silica gel; (j) i) Ac_2O, DMAP; ii) AcOH, H_2O; (k) i) PDC; ii) $KMnO_4$; iii) K_2CO_3; (l) $PhSO_2Cl$; (m) 2M HCl.

Scheme 5



triphenylphosphorane and ammonium chloride work up leads to the direct isolation of aldehyde **48**. Subsequent reduction to the alcohol, and dehydration with PPTS gives the diene **49**. Two step oxidation of the primary hydroxyl group generates the corresponding acid. The bromohydrin **50**, formed by treatment with NBS in wet DMSO, readily cyclizes to the model compound **51** upon treatment with phenylsulfonyl chloride in pyridine.

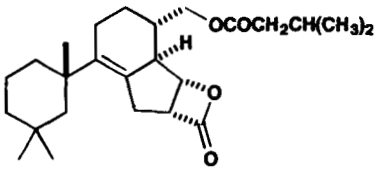


(a) H_2O_2, MeOH, 6N NaOH, 87%; (b) i) $MeOCH{=}PPh_3$; ii) NH_4Cl, 57%; (c) i) $NaBH_4$, *i*-PrOH, 70%; ii) PPTS, 44%; (d) i) MnO_2; ii) $NaClO_2$, 57%; iii) NBS, DMSO, H_2O, 33%; (e) $PhSO_2Cl$, pyr., 27%.

Scheme 6

2. Diterpenes

Only one diterpene β-lactone, spongiolactone (**52**) from the Mediterranean sponge *Spongionella gracilis*, has been isolated.[23] The relative stereochemistry was determined by nOe data, but to date no biological activity or syntheses have been reported.



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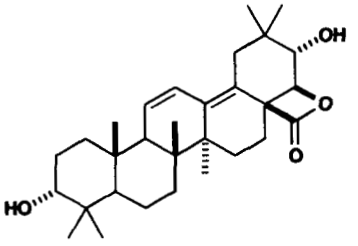
3. Triterpenes

An oleanane-type triterpene papyriogenin G (**53**) was isolated from the leaves of *Tetrapanax papyriferum* and its structure was determined by an X-ray study.[24] It has a very high melting point (188-190°), which indicates that the β-lactone moiety (ν_{max} 1828 cm^{-1}) has good thermal stability. Lupeolactone (**54**), a hypolipidermic substance, is a lupeane-type triterpene β-lactone isolated from



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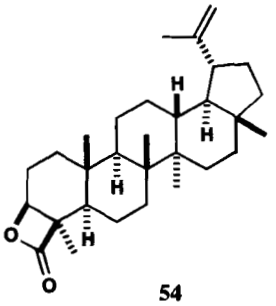

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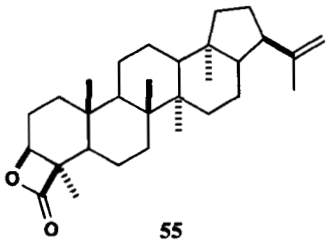


55

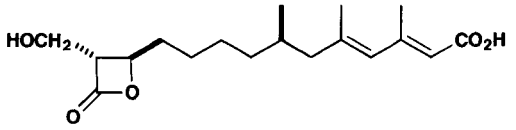
Antidesma pentandrum Merr. during pharmacological screening.[25] Its structure is based on spectroscopic and X-ray crystallographic analyses. Upon oral administration, lupeolactone significantly lowers serum cholesterol levels both in normal rats and in rats made hypercholesterolemic beforehand by a high fat diet.

Moretenolactone (**55**) is a β-lactone hopanoid from *Ficus insipida* and bears a close structural resemblance to lupeolactone and moretenol.[26] *Ficus insipida* Willdenow occurs from Central America to Argentina, where its latex, leaves and unripe fruits are used by the natives in the treatment of worm diseases, although the actual biological properties of moretenolactone itself were not reported. No total syntheses of these triterpene β-lactones have been published.

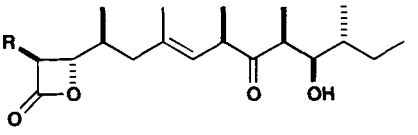
II. FATTY ACID AND POLYKETIDE-LIKE β-LACTONES

The members of this group of compounds generally exhibit lipase or esterase activity and some inhibit cholesterol formation *in vivo*. Hence some of these β-lactones or their analogs have considerable medicinal potential. Biosynthetically, they originate via the fatty acid or polyketide pathway, and all naturally-occurring derivatives reported thus far possess a trans relationship of substituents on the β-lactone ring.

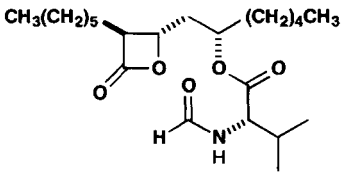
The first member of this group to be characterized was the carboxylic acid Antibiotic 1233A (**56**),[27] but the absolute stereochemistry was not determined until recently using chemical degradation and NMR spectroscopy.[28] It was originally obtained from a *Cephalosporium* species, as the first β-lactone produced by a fungus. Subsequently, **56** was independently isolated from *Scopulariopsis* sp. as F-244[29] and from *Fusarium* sp. as the Merck compound L-659,699.[30] Its antimicrobial activity[31b] is related to its potent specific inhibition of 3-hydroxy-3-methylglutaryl coenzyme A synthase (HMG-CoA synthase), an enzyme essential for construction of mevalonate during the early stages of cholesterol biosynthesis.[29-31] The inhibition is irreversible *in vitro*,[31c] but can easily be reversed in cultured



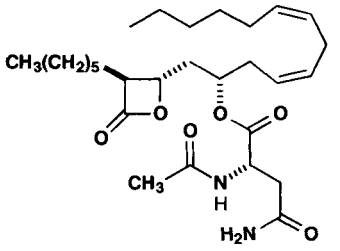
56 Antibiotic 1233A



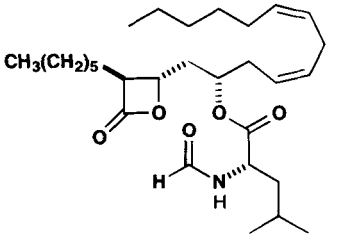
57 Ebelactone A (R = CH_3)
58 Ebelactone B (R = CH_3CH_2)



59 Valilactone



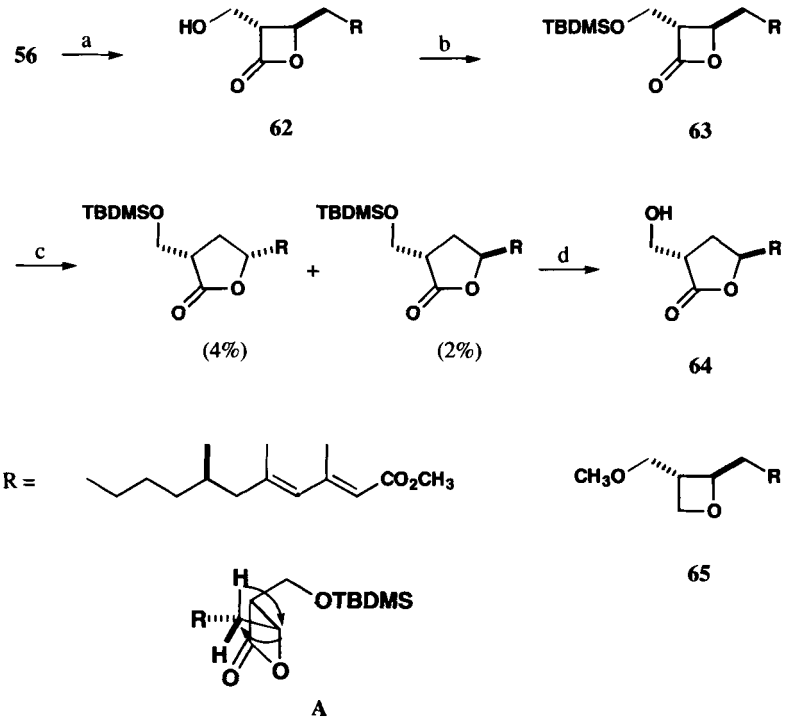
60 Esterastin



61 Lipstatin

cells and animals[31c] and shows an IC_{50} value of less than 0.27 μM, with the actual value depending on the analytical method. Several natural and synthetic fatty acids and their analogs are known to affect cholesterol biosynthesis. Although 1233A resembles a fatty acid, derivatives prepared either by chemical modification or synthesis demonstrate that both the β-lactone and the hydroxymethyl moiety are essential for inhibitory activity against HMG-CoA synthase.[29,30,31c] It seems likely that a cysteine thiol group in the enzyme active site attacks the β-lactone carbonyl group to form an enzyme bound thioester.[31c,e,f]

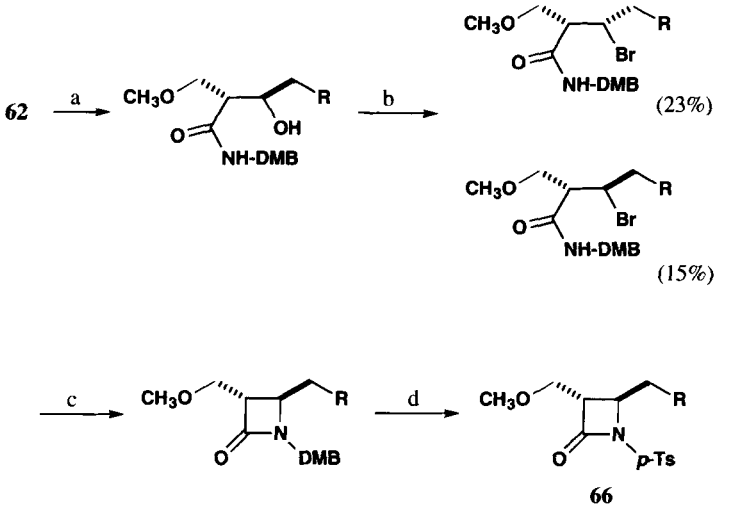
Several analogs have been obtained directly from **56**.[32] For example, the γ-lactone analog **64** is available by a concerted dyotropic rearrangement[33] of **63** (via the transition state **A**) followed by deprotection (Scheme 7). Neither **64** nor the oxetane analog **65** inhibit HMG-CoA synthase, but the N-tosyl azetidinone **66**, prepared as shown in Scheme 8, does show inhibition with an IC_{50} value of 3.6 μM.



(a) CH_2N_2, 96%; (b) TBDMSCl, Imidazole, 71%; (c) $MgBr_2.OEt_2$, 7%; (d) Bu_4NF, THF, AcOH, 53%.

Scheme 7

The first total synthesis of **56** was reported in 1989 by a Merck group (Scheme 9).[34] (R)-(+)-Pulegone (**31**) is first converted in several steps to the aldehyde **67** to form the basis of the side chain. The key step of the subsequent synthesis is a highly diastereoselective aldol condensation with a chiral

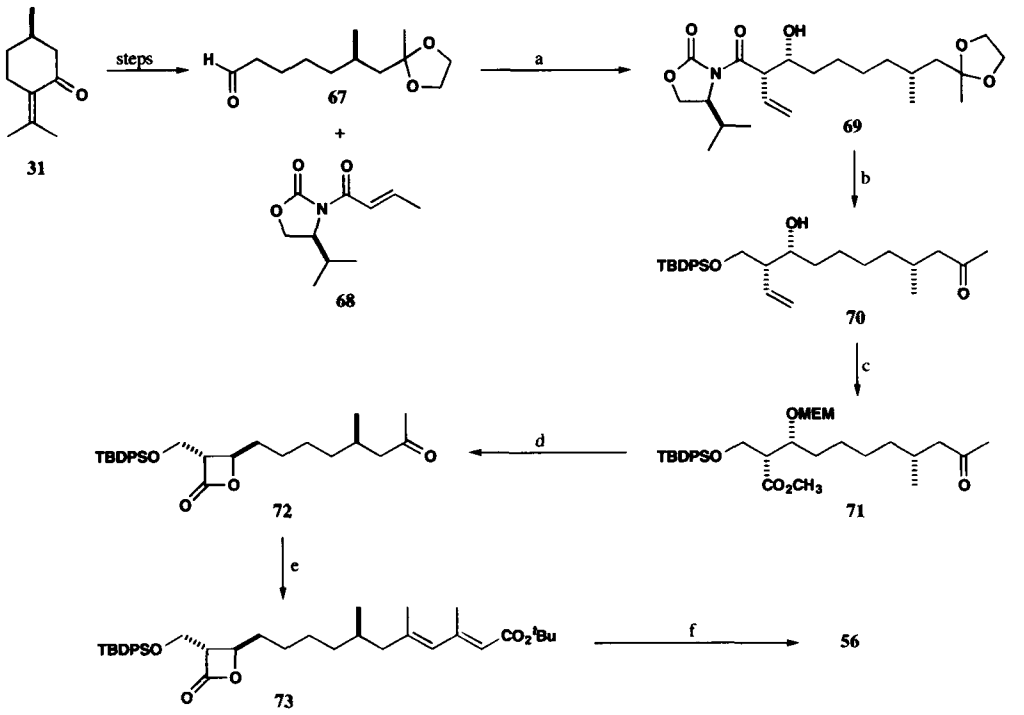


(a) i) Ag_2O, CH_3I, 66%; ii) 2,4-dimethoxybenzylamine, 50%; (b) i) MsCl, pyr., 85%; ii) NaBr, DMF, 38%; (c) KOH, Bu_4NBr, 53%; (d) i) $(NH_4)_2Ce(NO_3)_6$, 65%; ii) TsCl.

Scheme 8

crotonate imide **68**, to form **69** and introduce the stereogenic centers of the β-lactone with 94% diastereomeric excess. Reductive removal of the chiral auxiliary by formation of the dibutylboryl aldolate, followed by $LiAlH_4$ reduction and oxidative workup affords an alcohol, which is then protected as a silyl ether after the the ketal is cleaved, to yield the ketone **70**. The secondary hydroxyl group is protected, the olefin is cleaved by ozonolysis, and the resulting aldehyde is oxidized to the acid, which after treatment with diazomethane gives the methyl ester **71**. The MEM group is removed with zinc bromide, the ester is saponified, and cyclization to the β-lactone **72** is achieved with phenylsulfonyl chloride. Comparison with a sample of **72** prepared by degradation of the natural product **56** confirms the stereochemistry. Elaboration of the side chain employs a Reformatsky reaction followed by dehydration with thionyl chloride to afford **73**. Final deprotection to **56** proceeds with hydrofluoric acid.

A different approach by Mori and Takahashi[35] involves the addition of the sulfone anion derived from **74** with the magnesio epoxide derived from **75** as the key carbon-carbon bond forming step to generate **76**. Desulfurization and diol protection leads to the acetal **77**. Completion of the side chain construction using a Horner-Wittig reaction, and simple protection/deprotection and oxidation procedures then afford the hydroxy acid **78**. Cyclization to the β-lactone as above, and removal of the trityl group yield **56**.

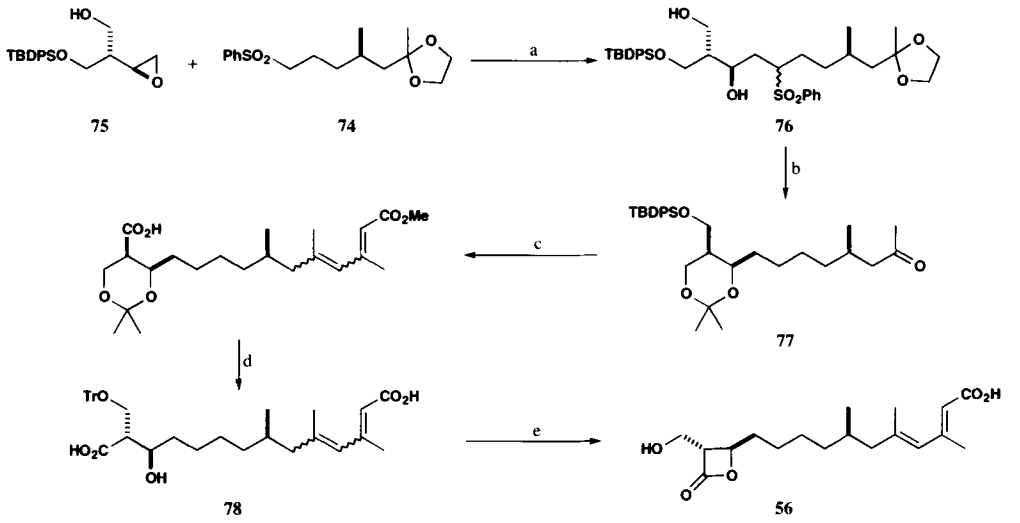


(a) Bu_2BOTf, Et_3N, then add 67, 66%; (b) i) Bu_3B, AcOH; ii) $LiBH_4$; iii) H_2O_2; iv) TBDPSCl; v) HCl, 38%; (c) i) MEMCl; ii) O_3, Me_2S; iii) PDC, DMF; iv) CH_2N_2, 43%; (d) i) $ZnBr_2$; ii) NaOH; iii) $PhSO_2Cl$, py, 35%; (e) i) $BrCH_2C(CH_3)=CHCO_2tBu$, Zn, THF; ii) $SOCl_2$, py, 30%; (f) HF, 76%.

Scheme 9

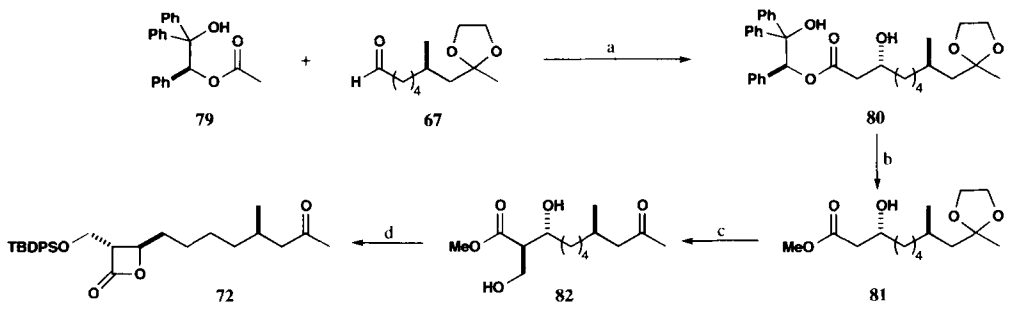
A concise and highly diastereoselective preparation of the intermediate **72** used in the Merck synthesis above has recently been reported by researchers at Sandoz (Scheme 11).[36] Thus the asymmetric aldol condensation of the aldehyde **67** and Braun's chiral acetate **79** produces **80** in 80% yield. Removal of the chiral auxiliary by methanolysis affords **81** with >99% diastereoselection. Alkylation of the β-hydroxy lithium dianion of **81** with benzyl chloromethyl ether provides a 98:2 (*anti:syn*) diastereoselection, albeit in low yield. Simultaneous hydrogenation of the benzyl group and unexpectedly facile cleavage of the cyclic ketal by palladium/carbon in methanol quantitatively furnishes **82**. Protection of the primary alcohol as its silyl ether prior to saponification of the ester and cyclization using the standard conditions of phenylsulfonyl chloride in pyridine gives the desired intermediate **72**.

A total synthesis by a Roche group demonstrates an efficient stereoselective preparation of the diene portion of **56** (Scheme 12).[37] The intermediate aldehyde **83** is converted to the homologated acetylene **84** using diethyl (diazomethyl)phosphonate. Treatment with trimethylaluminum and zirconocene dichloride, followed by iodine, produces the diol iodide **85** stereospecifically. A small amount of the iodide bearing an intact acetonide group is also obtained, but this is readily cleaved by the use of dimethylaluminum chloride. Coupling of this vinylic iodide **85** with *tert*-butyl crotonate



(a) i) 75, EtMgBr, THF/HMPA, then ii) 74, BuLi, THF/HMPA, 79%; (b) i) Na/Hg, EtOH, 96%; ii) $Me_2C(OMe)_2$, PPTS, 95%; (c) i) KH, THF, $(MeO)_2P(O)CH_2C(CH_3)=CHCO_2Me$, 78%; ii) Bu_4NF, THF, 75%; iii) DMSO, $(COCl)_2$, Et_3N; iv) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 95%; (d) i) Amberlyst-15, MeOH, quant.; ii) TrCl, pyr., 85%; iii) LiOH, THF/H_2O, quant.; (e) i) $PhSO_2Cl$, pyr., 26%; ii) AcOH, 71%.

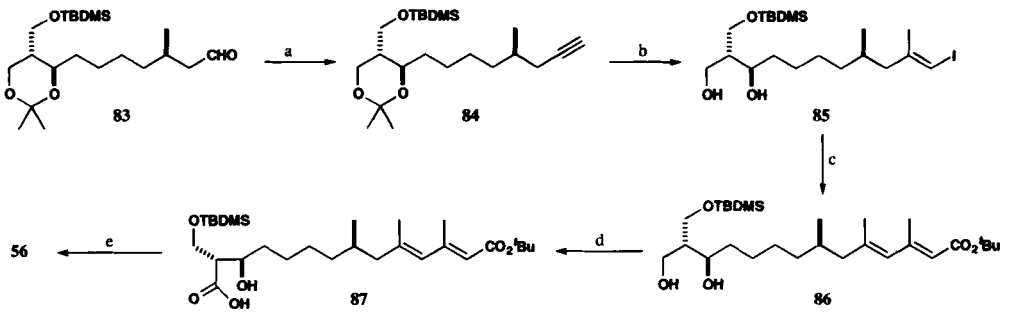
Scheme 10



(a) LiHMDS, THF, 80%; (b) K_2CO_3, MeOH, 90%; (c) i) $BnOCH_2Cl$, LDA, THF, 35%; ii) H_2, Pd/C, 100%; (d) i) TBDPSCl, 78%; ii) NaOH; iii) $PhSO_2Cl$, pyr., 40%.

Scheme 11

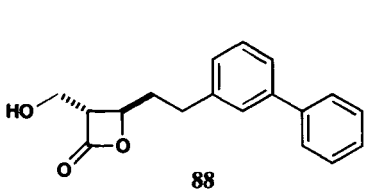
under modified Heck conditions using a palladium catalyst and potassium carbonate in dichloromethane under phase transfer conditions yields the desired *E,E* olefin **86**, with only a few percent of the *Z,E* isomer. The solvent choice is critical for success in this reaction. Oxidation of the diol with the *N*-oxammonium chloride derived from TEMPO, followed by sodium chlorite, gives the hydroxy acid **87** which readily cyclizes under standard conditions to the β-lactone. Deprotection yields **56**. The preparation of the aldehyde **83** in the above synthesis proved to be somewhat tortuous; an improved convergent synthesis of this material has recently been described.[38]



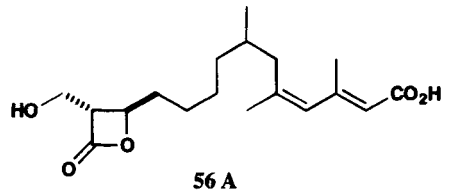
(a) $(EtO)_2P(O)CHN_2$, 70%; (b) Me_3Al, Cp_2ZrCl_2, I_2, 63%; (c) $Pd(OAc)_2$, *t*-Butyl crotonate, 65%; (d) i) TEMPO-Cl; ii) $NaClO_2$, 79%; (e) i) $PhSO_2Cl$, pyr., 70%; ii) HF, 78%.

Scheme 12

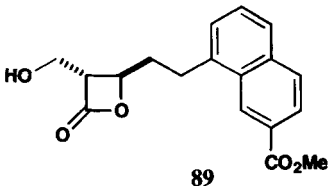
Some recent studies describe the preparation of analogs such as **88** and **89**.[39] These compounds are designed to mimic the hypothetically folded side chain of 1233A as exemplified by conformers A and B. In a few cases, the inhibition of HMG-CoA synthase is comparable to that shown by 1233A itself, suggesting that the folded structure appears to play an important role in the interaction of 1233A with the target enzyme. The total syntheses are straightforward and produce optically inactive compounds.



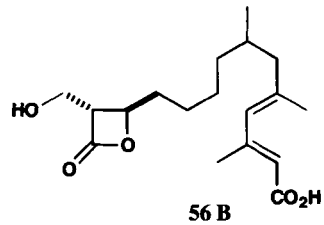
88



56 A



89

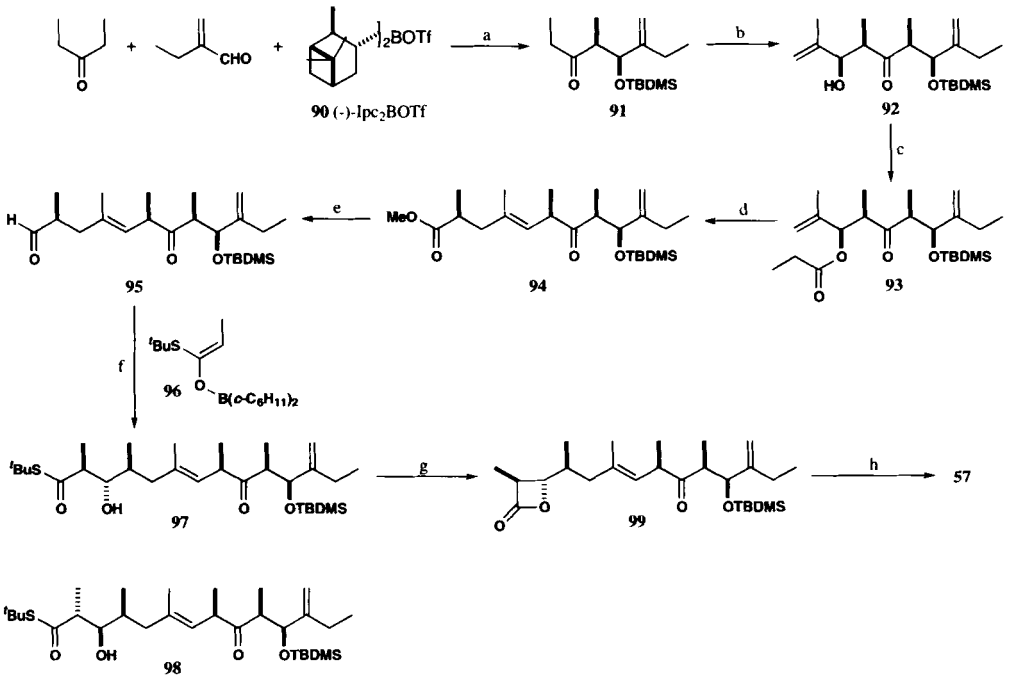


56 B

Ebelactones A (**57**) and B (**58**) were isolated in 1980 from culture filtrates related to *Streptomyces aburaviensis* during a screening program for esterase inhibitors.[40,41] Biosynthetic studies using ^{13}C NMR spectroscopy and incorporation of ^{13}C-labeled compounds suggest a polyketide pathway. Ebelactone A is derived from one acetate unit and six propionate units, whereas ebelactone B originates from one acetate, one butyrate and five propionate units.[42] Ebelactones inhibit esterases, lipases, N-formyl-methionine aminopeptidases, and carboxypeptidases from various sources, and cause enhanced immune responses.[40,43] They also inhibit acylpeptide hydrolase[44] and cutinases[45] produced by

fungal plant pathogens. All fungal cutinases have been identified as serine hydrolases akin to esterases and lipases; consequently the ebelactones may have potential as plant protection agents.

A concise synthesis of ebelactone A, which includes two highly diastereoselective (>95%) aldol condensations and an Ireland ester enolate Claisen rearrangement, has been reported by Paterson and coworkers (Scheme 13).[46] An aldol condensation between diethyl ketone and 2-ethylacrolein, mediated by the chiral boron reagent **90** used to generate the boron enolate, produces the *syn*-aldol adduct **91** (86% ee, 98% ds). The diastereoselectivity of a subsequent *syn*-aldol condensation between **91** and methacrolein is then controlled by the substrate to yield **92** (95% ds) in 95% yield. Generation of the propionate ester **93** precedes the Ireland-Claisen rearrangement to **94**, which is obtained in 83% yield with >95% diastereoselectivity. The methyl ester is reduced to the aldehyde **95** before an *anti*-aldol reaction with the borinate **96** which furnishes the desired **97** together with the unwanted adduct **98** in a 55:45 ratio. Thioester hydrolysis followed by lactonization under the usual conditions yields the β-lactone **99**. The hydroxyl group is deprotected, and Rh(I) catalyzed hydrogenation gives ebelactone A (**57**) as the major product.



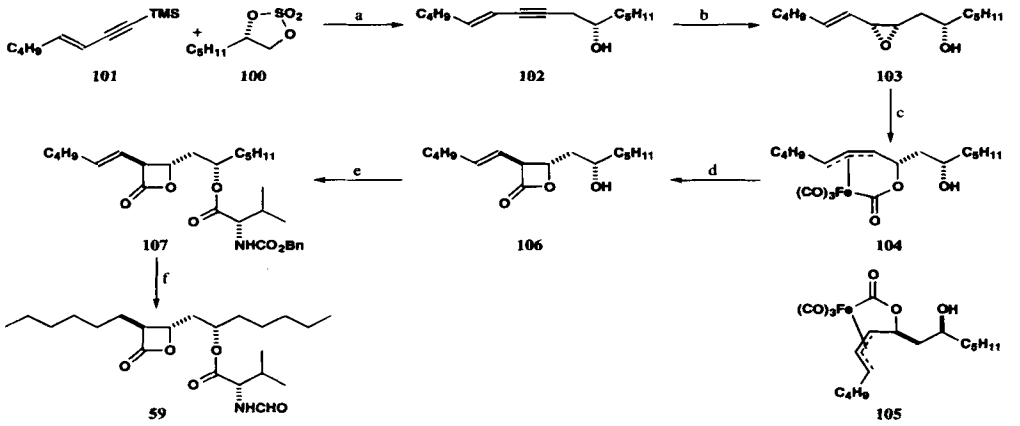
90 (-)-Ipc$_2$BOTf; 91; 92; 93; 94; 95; 96; 97; 98; 99

(a) i) *i*-Pr$_2$NEt; ii) TBSOTf; (b) 9-BBNOTf, Et$_3$N, 2-methylacrolein, 95%; (c) (EtCO)$_2$O, DMAP, Et$_3$N, 94%; (d) i)TMSCl, Et$_3$N, LDA, THF, then HCl; ii) CH_2N_2, 83%; (e) DIBAL, 80%; (f) -78° to -4°, 16 hrs, then H_2O_2, 77%; (g) i) H_2O_2, LiOH then Na_2SO_3, 99%; ii) $PhSO_2Cl$, pyr., 87%; (h) i) HF, 100%; ii) H_2, $(Ph_3P)_3RhCl$, 70%.

Scheme 13

Valilactone (**59**) was isolated from soil actinomycetes species closely related to *Streptomyces albolongus*. It shows esterase and lipase inhibitory activity comparable to that of the ebelac-

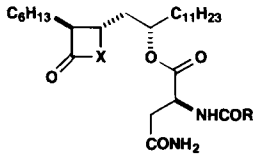
tones, but it has no effect on immune responses.[47] A total synthesis of valilactone, employing an interesting ceric ammonium nitrate oxidation of a π-allyltricarbonyliron lactone complex to form the β-lactone ring, has been reported by Ley and coworkers (Scheme 14).[48] The cyclic sulfate **100** is prepared by treatment of (*S*)-heptane-1,2-diol with thionyl chloride, followed by oxidation with ruthenium trichloride/sodium periodate. Reaction of this with the anion derived from the trimethylsilylacetylene **101** affords the alcohol **102** after acidic work up. The acetylene is then reduced stereoselectively using Zn/Cu/Ag to the *Z*-olefin, which is epoxidized, again with high stereoselectivity (>30:1), to generate the desired isomer **103**. Reaction of **103** with diiron nonacarbonyl gives an 80% yield of the separable *exo* and *endo* complexes **104** and **105** in a ratio of 4:1. Oxidation of the complex **104** with ceric ammonium nitrate produces the desired β-lactone **106** in 26% yield. Coupling of the alcohol functionality with *N*-Cbz-L-valine gives **107**, which is catalytically hydrogenated to simultaneously reduce the side chain and remove the benzyl group. The product is immediately formylated to give valilactone (**59**).



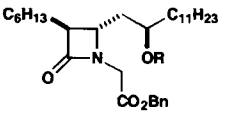
(a) i) **101**, MeLi, then **100**; ii) 20% H_2SO_4, 63%; (b) i) Zn(Cu/Ag), MeOH/H_2O, 90%; ii) $VO(acac)_2$, *t*BuOOH, 73%; (c) $Fe_2(CO)_9$, 80%; (d) CAN, EtOH, 26%; (e) *N*-Cbz-L-valine, DCC, then DMAP, 56%; (f) H_2, Pd/C, then AcOCHO, 62%.

Scheme 14

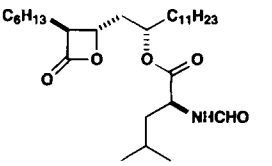
Esterastin (**60**), isolated from *Streptomyces lavendulae*, also exhibits very potent esterase and lipase inhibitory activity.[49-51] However, unlike ebelactone and valilactone, it suppresses immune responses. Studies on its inhibition of lysosomal acid lipase are potentially useful in elucidating the role of this enzyme in the pathogenesis of lysosomal lipid storage problems such as Wolman's disease, cholesterol ester storage disease, and atherosclerosis.[51] No total synthesis of esterastin (**60**) has been reported, but its tetrahydro-derivative has been described with a total synthesis of tetrahydrolipstatin (**113**), as discussed below. The stereoselective syntheses of some tetrahydroesterastin-β-lactam analogs **108-112** have also been completed.[52] These were prepared because tetrahydroesterastin (**128**) is inactive as a lipase inhibitor *in vivo* and a more hydrolytically stable β-lactam ring may overcome this problem. However, no biological results have yet been reported.



128 X = O, R = Me tetrahydroesterastin
108 X = NH, R = H



109 R = L-*N*-formylleucyl
110 R = L-*N*-Cbz-asparagyl
111 R = L-*N*-formyl(phenylalanyl)
112 R = *N*-formylglycyl



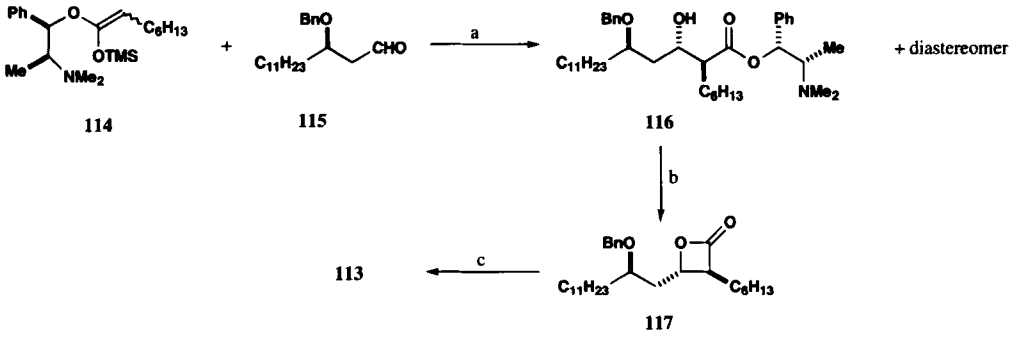
113 tetrahydrolipstatin

Lipstatin (**61**) and its derivative tetrahydrolipstatin (**113**), prepared by catalytic hydrogenation, are probably the most widely studied of all biologically significant β-lactones. Interest in these compounds stems from their ability to potently and specifically inhibit pancreatic lipase from several sources, including man. This inhibition thereby reduces fat absorption and lowers plasma cholesterol levels.[53] Tetrahydrolipstatin (Orlistat®) is now in clinical trials as a treatment for obesity and hypercholesterolemia.[54,55]

Lipstatin was first isolated from *Streptomyces toxytricini* in 1987 by researchers at Roche, and its effective inhibition of pancreatic lipase was demonstrated.[56] Elucidation of its structure by spectroscopic and chemical methods revealed its close resemblance to esterastin, and showed that it has an *N*-formyl-L-leucine side chain instead of the *N*-acetyl-L-asparagine in esterastin.[57,58] The β-lactone unit and the *N*-formyl-leucine side chain of lipstatin are essential for the lipase inhibition.[56] Studies on tetrahydrolipstatin indicate the irreversible formation of a covalent intermediate with a serine residue at the active site of the enzyme. The compound has significant specificity since several other hydrolases tested were at least a thousand times less potently inhibited.[59-61]

Several different approaches to the total synthesis of tetrahydrolipstatin have been reported; some of these will be discussed below. The first syntheses of tetrahydrolipstatin (**113**) were non-stereoselective and involved separation of mixtures of diastereoisomers.[58] However a subsequent stereoselective procedure from the same laboratory generated **113** via a titanium tetrachloride mediated condensation of the ketene silyl acetal derivative **114** of (-)-*N*-methylephedrine with the aldehyde **115** (Scheme 15).[62] This condensation yields only two hydroxy esters in a 3:1 ratio, the major one, **116**, having the desired (2*S*, 3*S*) configuration. Saponification of the ester and lactonization of the resulting hydroxy acid affords **117**. Deprotection and coupling with (*S*)-*N*-formylleucine with inversion of configuration under Mitsunobu conditions yields tetrahydrolipstatin (**113**).

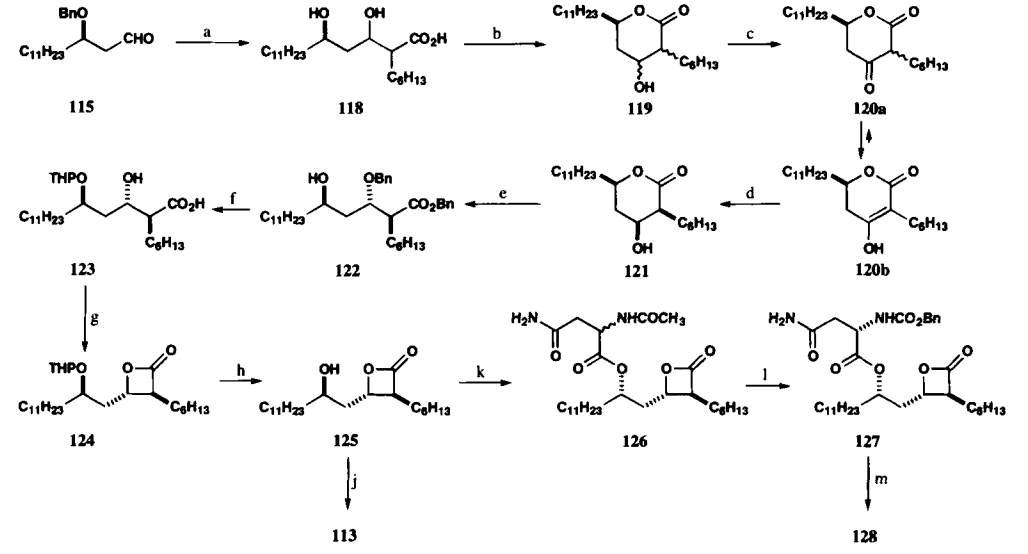
The β-keto δ-lactone **120** has been successfully employed as an intermediate in stereoselective tetrahydrolipstatin synthesis (Scheme 16).[63] The readily prepared aldehyde **115** used in the previous synthesis is condensed with the anion of lithium octanoate to yield, after deprotection, the hydroxy acid **118** as a mixture of diastereomers. Cyclization to the β-hydroxy δ-lactone **119** followed by oxidation gives the β-keto δ-lactone **120a**, present as its enol form **120b** in solution. Hydrogenation on the least hindered face of the molecule then furnishes the β-hydroxy δ-lactone **121** as a single



(a) $TiCl_4$, 40%; (b) i) KOH/MeOH, 64%; ii) $PhSO_2Cl$, pyr., 61%; (c) i) H_2, Pd/C, 70%; ii) (S)-N-formylleucine, Ph_3P, DEAD, 77%.

Scheme 15

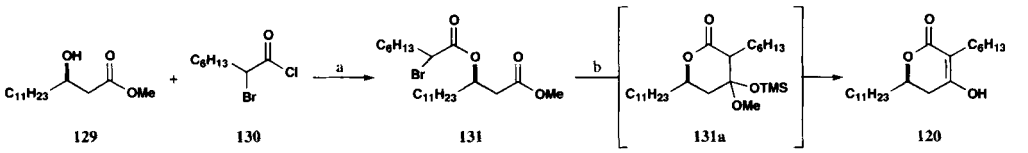
isomer. Alcohol protection and ring opening of **121** using KOH gives a carboxylate salt which is trapped as its benzyl ester **122**. Protection of the alcohol and hydrogenation generates the hydroxy acid **123**. Cyclization to the β-lactone **124** followed by deprotection produces **125**, which can be coupled as above to yield tetrahydrolipstatin. However, epimerization at the α-position of the amino acid occurs during a similar coupling with *N*-acetylasparagine in an attempt to produce tetrahydroesterastin (**128**). This is resolved by hydrolysis of the ester **126** and coupling of the now inverted alcohol with a mixed anhydride prepared from pivaloyl chloride and (*S*)-*N*-*Z*-asparagine to form **127**. Hydrogenolysis and acetylation then gives pure tetrahydroesterastin (**128**).



(a) i) Octanoic acid, LDA; ii) H_2, Pd/C; (b) TsOH; (c) Jones' reagent; (d) H_2, PtO_2, 84%; (e) i) Benzyl trichloroacetimidate, CF_3SO_3H, 73%; ii) KOH; iii) BnBr, THF/HMPA, 60%; (f) i) Dihydropyran, TsOH, 73%; ii) H_2, Pd/C; (g) $PhSO_2Cl$, pyr., 55%; (h) PPTS, EtOH, 88%; (j) (*S*)-*N*-formylleucine, PPh_3, DEAD, 80%; (k) (*S*)-*N*-acetyl-asparagine, PPh_3, DEAD, 38%; (l) i) 0.02N NaOH, 63%; ii) (*S*)-*N*-Cbz-asparagine, pivaloyl chloride, Et_3N, 33%; (m) i) H_2, Pd/C; ii) CH_3COCl, Et_3N, 98%.

Scheme 16

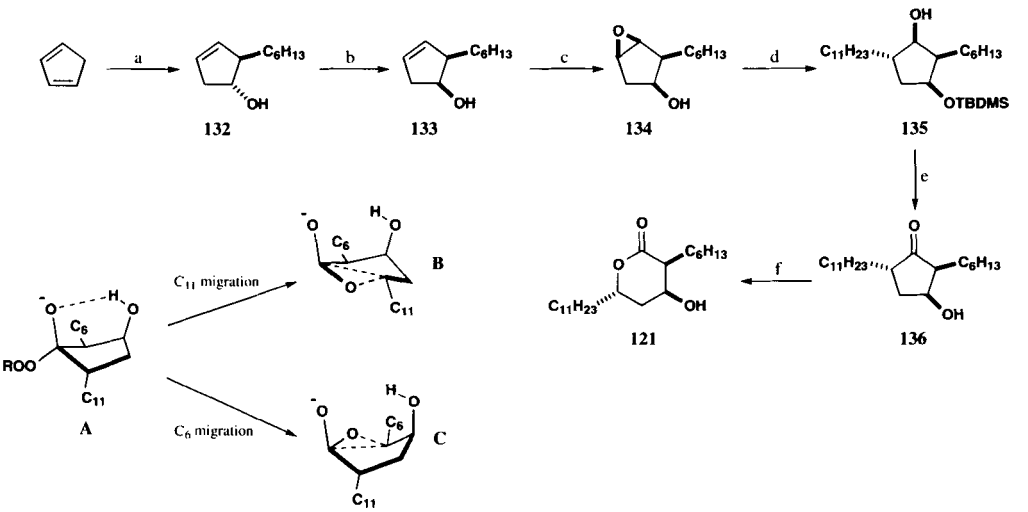
An improved preparation of the intermediate **120** has recently been reported (Scheme 17).[64] Treatment of methyl (*R*)-3-hydroxytetradecanoate (**129**) with 2-bromooctanoyl chloride (**130**) in pyridine provides bromodiester **131**. This compound could also be prepared by treatment of 2-bromooctanoic acid with **129** in the presence of DCC/DMAP. Cyclization of **131** using zinc in a mixture of ether/trimethylsilyl chloride (1:4) at reflux gives the lactone **120** in 70% yield. The trimethylsilyl chloride may both activate the zinc and form an intermediate silyl-protected ketal **131a**, thus peventing quenching of the zinc enolate by the product **120**. This product is then generated by the workup.



(a) Pyr., 87%; (b) Zn, TMSCl, Et_2O, reflux, 70%.

Scheme 17

A highly efficient synthesis of the intermediate β-hydroxy δ-lactone **121** was described by Uskokovic and coworkers.[65] Cyclopentadiene is first alkylated with hexyl iodide and then subjected to asymmetric hydroboration with (+)-diisopinocampheylborane to give, after oxidative work up, the cyclopentenol **132** with 96% e.e. (Scheme 18). Mitsunobu inversion followed by hydrolysis of the resulting benzoate generates the *cis*-cyclopentenol **133**. The hydroxyl group, in the correct absolute configuration for tetrahydrolipstatin, is a critical directing element for the introduction of the remaining structural features. The hydroxyl-directed epoxidation generates the all *cis*-epoxide **134**,

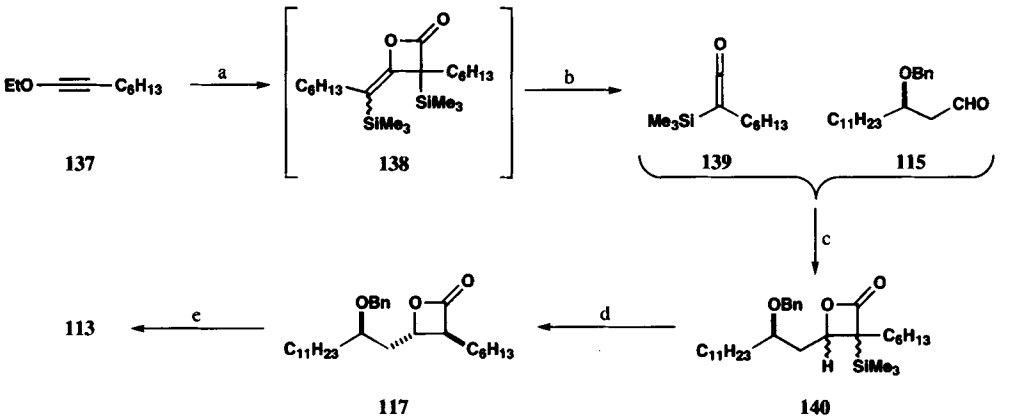


(a) i) Na, $C_6H_{13}I$; ii) $(+)\text{-}(IPC)_2BH$, 57%; (b) i) $PhCO_2H$, DEAD, Ph_3P, 72%; ii) KOH/MeOH, 62%; (c) MCPBA, 73%; (d) i) TBDMSCl, 83%; ii) $(C_{11}H_{23})_2Cu(CN)Li_2$, 68%; (e) i) $(COCl)_2$, DMSO, Et_3N, 89%; ii) HF, 71%; (f) MCPBA, 60%.

Scheme 18

which after silylation, undergoes a regioselective epoxide opening with the cuprate derived from undecanyllithium to give **135**. Oxidation to the ketone under Swern conditions and HF desilylation produces **136**. A regioselective Baeyer-Villiger oxidation yields a single δ-lactone **121** having the desired *SSS* stereochemistry. The surprising regioselectivity of the reaction can be rationalized by the more favorable chair-like transition state **B** compared to the possibility of a twist-boat-like transition state **C**. The sole generation of oxyanion **A** is favored due to stabilization through hydrogen bonding of the free hydroxyl proton to the negatively charged oxygen. The intermediate **121** was subsequently converted to tetrahydrolipstatin (**113**) by a process similar to that previously described.

A different approach to β-lactone formation was taken by Pons and Kocienski[66] who employed a Lewis acid-catalyzed [2+2] cycloaddition of *n*-hexyltrimethylsilyl ketene (**139**) to (*R*)-3-(benzyloxy)tetradecanal (**115**) (Scheme 19). The ketene is prepared by treatment of 1-ethoxy-1-octyne (**137**) with trimethylsilyl iodide to give the intermediate **138** as a diastereomeric mixture of products that are not isolated. The stable ketene **139** is then formed by thermolysis under high vacuum. In the presence of boron trifluoride etherate, **139** and **115** react to generate the β-lactones **140** as a diastereomeric mixture. Desilylation and chromatographic separation shows that the desired β-lactone **117** is the major component (55-61%). Hydrogenolysis of the benzyl protecting group and Mitsunobu esterification with (*S*)-*N*-formylleucine gives (-)-tetrahydrolipstatin (**113**).

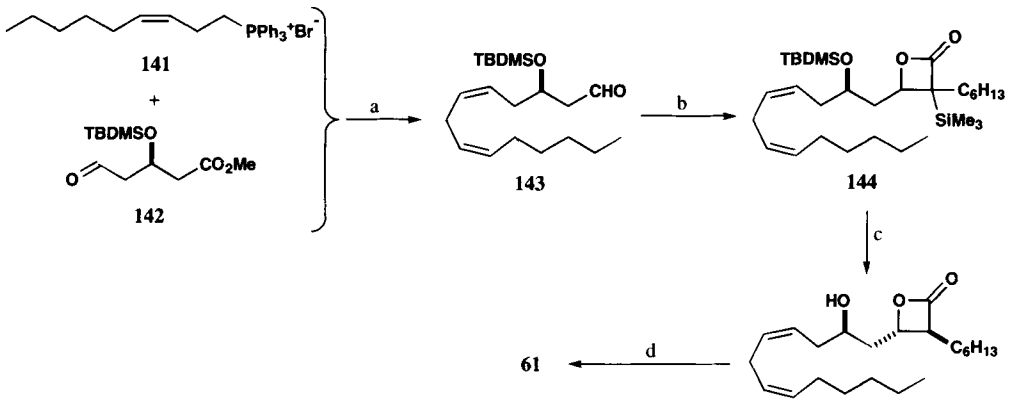


(a) TMSI, 70°, 44h; (b) 80°/0.5 mm Hg, 50% from **137**; (c) $BF_3.OEt_2$, 83%; (d) i) TBAF, 84%; ii) SiO_2 chromatography, 55%; (d) i) H_2, Pd/C, 88%; ii) (*S*)-*N*-formylleucine, Ph_3P, DEAD, 73%.

Scheme 19

This group used the same approach to complete the first reported synthesis of lipstatin (**61**).[67] The *Z,Z*-diene aldehyde **143** is first prepared by a Wittig reaction of the phosphonium bromide salt **141** with the aldehyde **142**, followed by DIBAH reduction (Scheme 20). Reaction of **143** with the previously prepared silyl ketene **139** in the presence of ethyldichloroaluminum gives the β-lactone **144**, again as a mixture of diastereoisomers. However, the major compound (70%) is the desired isomer for the completion of the synthesis in a manner identical to that in Scheme 19, thereby

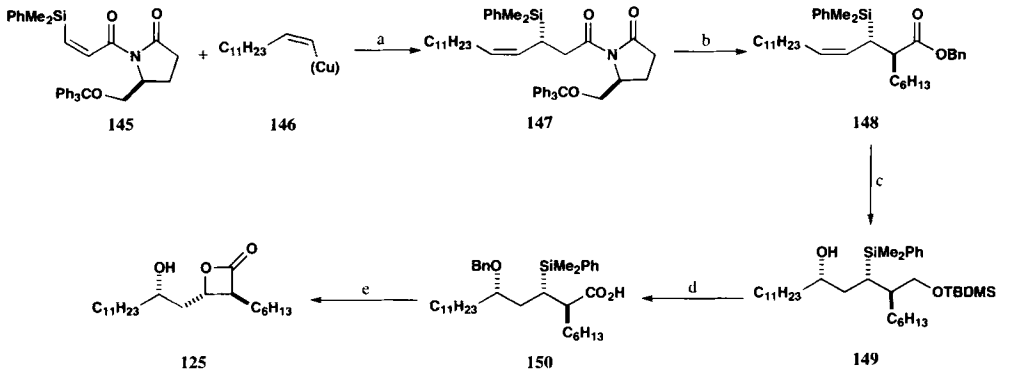
showing that favorable 1,3-asymmetric induction had occurred in the [2+2] cycloaddition.



(a) i) $NaN(SiMe_3)_2$, 86%; ii) DIBAH, 93%; (b) **139**, $EtAlCl_2$, 81%; (c) i) HF, 70%; ii) TBAF, 70%; (d) (*S*)-*N*-formylleucine, PPh_3, DEAD, 50%.

Scheme 20

Fleming and coworkers[68] took advantage of the high degree of stereocontrol observed in the alkylations of β-silylenolates and in hydroborations of allylsilanes to effect a total synthesis of tetrahydrolipstatin (**113**). An asymmetric Michael reaction between the *Z*-silylacryloyl derivative **145** (prepared from Koga's chiral auxiliary) and the *Z*-vinylcuprate **146** in the presence of magnesium bromide to chelate the carbonyl oxygens, gives the allylsilane **147** with 90% d.e. (Scheme 21). Removal of the auxiliary generates the benzyl ester; this is then followed by a stereoselective alkylation with *n*-hexyl iodide to give **148**. Reduction of the benzyl ester and silyl protection of the resulting alcohol, precedes hydroboration-oxidation of the allylsilane, which produces the C-5 alcohol **149** with

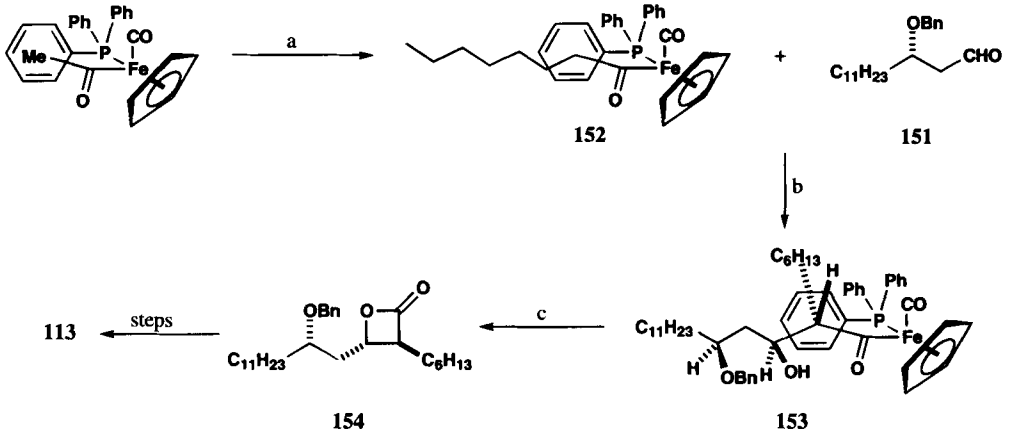


(a) $MgBr_2$, THF, 94%; (b) i) BnOLi, 93%; ii) LDA, then n-$C_6H_{13}I$, 85%; (c) i) $LiAlH_4$; ii) NH_4Cl; iii) TBDMSCl, imidazole, 91%; iv) 9-BBN, 24h, reflux, then NaOH, H_2O_2, 68%; (d) i) $BnOC(=NH)CCl_3$, CF_3SO_3H, 91%; ii) TBAF; iii) PDC, DMF; iv) CrO_3, Me_2CO, H_2O, H_2SO_4, 61%; (e) i) $Hg(OAc)_2$, AcOOH, AcOH; ii) $PhSO_2Cl$, pyr; iii) H_2, Pd/C, 70%.

Scheme 21

excellent *anti-syn* selectivity (>95:5). After standard modification to afford **150**, the silyl group is converted, with complete retention of configuration, to a hydroxyl moiety with mercuric acetate and peroxyacetic acid. The β-lactone is then readily formed by usual treatment with phenylsulfonyl chloride. Hydrogenation of the benzyl ether affords **125**, a common intermediate (see above) in the preparation of tetrahydrolipstatin, in good yield.

The enantiomer **151** of the aldehyde **115** featured in a high-yielding stereoselective aldol reaction, in a synthesis of tetrahydrolipstatin (**113**) devised by Davies and colleagues (Scheme 22).[69] This interesting approach utilizes condensation with the (*S*)-iron octanoyl complex **152**.[69] The weak inherent stereochemical bias present within **151** is for ester enolates to attack the *si*-face of the aldehyde and generate the undesired (*R*) stereochemistry at the new stereogenic centre. However, the powerful stereocontrol exerted by the iron chiral auxiliary $[(C_5H_5)Fe(CO)(PPh_3)]$ during aldol reactions is sufficient to overwhelm this tendency. Hence, deprotonation of **152** followed by transmetallation with chlorodiethylaluminum and addition of the aldehyde **151** generates the desired (*S,S,S,S*)-aldol product **153** (less than 5% of other diastereomers). Oxidative decomplexation gives directly the β-lactone **154** in 57% yield, which after hydrogenation of the benzyl ether, is readily converted to **113** by previously described methodology.

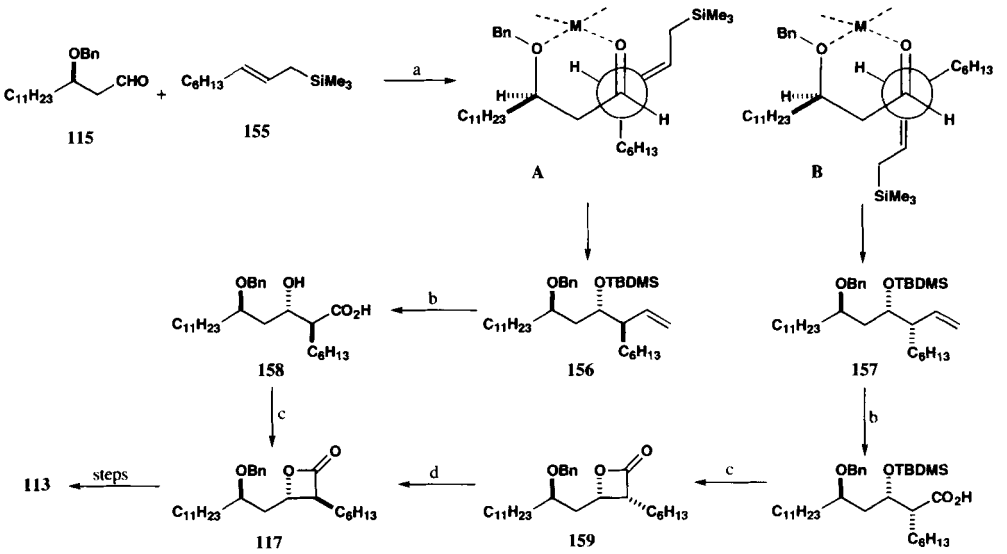


(a) i) BuLi, -78°; ii) $C_6H_{13}I$, 97%; (b) i) BuLi, -78°; ii) Et_2AlCl; iii) **151**, -98°, 92%; (c) Br_2, -78°, 57%.

Scheme 22

Recent syntheses of tetrahydrolipstatin were reported by Hanessian and coworkers.[70] In the first example, a Lewis acid-mediated condensation between the aldehyde **115** and the 2-alkenylsilane **155** proceeds with modest stereoselectivity to furnish mainly the *anti* isomer **156** via the more favored transition state **A** (Scheme 23). A moderate amount of the *syn* isomer **157** is also produced via transition state **B**. However, if this material is also carried through the synthesis to the β-lactone **159**, the stereochemistry at C-2 can be inverted simply by deprotonation and subsequent acidification to afford the desired β-lactone **117**. The terminal olefin of **156** is cleaved by ozonolysis and oxidized to the acid **158** by sodium chlorite; the hydroxyl group is protected as a silyl ether during this process. Cycliza-

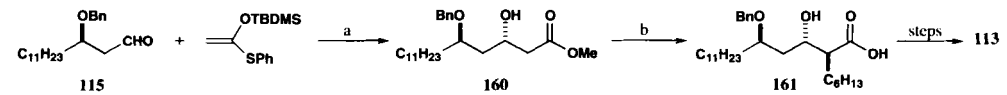
tion of the hydroxy acid using phenylsulfonyl chloride generates the β-lactone **117**, which is then converted uneventfully to tetrahydrolipstatin (**113**). From the aldehyde **115**, the overall yield of **113** is 24% over eight steps without recycling the unwanted isomer, or 33% with recycling.



(a) i) $TiCl_4$, Cp_2TiCl_2, CH_2Cl_2, -78°; ii) TBSCl, imidazole, 79%; (b) i) O_3, then Me_2S; ii) $NaClO_2$, $NaH_2PO_4.H_2O$, *t*BuOH, $CH_3CH{=}C(CH_3)_2$, H_2O; iii) HF, 72%; (c) $PhSO_2Cl$, pyr., ~89%; (d) LDA, THF, -78°, then AcOH, ~41%.

Scheme 23

The second synthesis by Hanessian also employed aldehyde **115** as the starting material, although it was prepared in this case by an improved procedure using allyl diisopinocampheylborane for the asymmetric allylation of lauraldehyde, which is followed by ozonolysis (Scheme 24). Treatment of **115** with the *O*-tert-butyldimethylsilyl ketene acetal derived from phenylthioacetate in the



(a) i) $TiCl_4$; ii) CF_3SO_3Ag, MeOH/CH_2Cl_2, 77%; (b) i) LDA, $C_6H_{13}I$; ii) KOH, MeOH, 85%.

Scheme 24

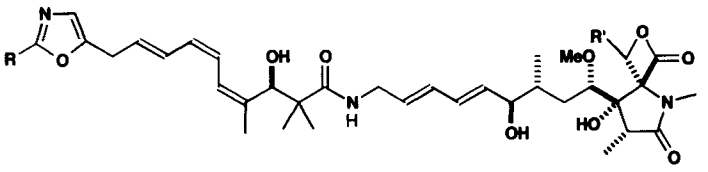
presence of titanium tetrachloride leads to the corresponding β-hydroxy derivative with greater than 21:1 selectivity in favor of the desired diastereomer. [Reaction of **115** with the *O*-tert-butyldimethylsilyl ketene acetal of methyl acetate gives a much poorer selectivity (~3:1), presumably because the desired transition state is more favored in the presence of a phenylthio group compared to a methoxy group.] Treatment of the phenyl thioester with methanol in the presence of silver triflate produces the methyl ester **160**. A stereoselective n-hexylation of the dianion of **160** (40:1 selectivity), followed by saponification of the methyl ester generates the hydroxy acid **161**. Completion of the synthesis employs previously described procedures. The overall yield of the synthesis is 38% over seven steps from **115**.

III. α-AMINO-β-LACTONES

Natural products incorporating an α-amino-β-lactone moiety can be roughly categorized into two groups: the polyene antibiotics which contain a spiro-fused β-lactone ring and a simpler family having an isolated α-amino-β-lactone moiety. Most members of these families were only discovered within the last decade and consequently relatively few syntheses are reported in the literature.

1. Spiro-fused β-Lactone Antibiotics

Resistaphylin, from *Streptomyces antibioticus*, was isolated in 1971 and shown to possess marked inhibitory activity against Gram-positive bacteria.[71] The presence of a triene moiety and a β-lactone was detected, but it was not until the structure of oxazolomycin (**162**) from a *Streptomyces* sp. was elucidated in 1985 that comparison suggested the two compounds are identical.[72] Oxazolomycin (**162**) contains a unique combination of a spiro-fused β-lactone, a γ-lactam moiety, and a long aliphatic chain bearing a triene and an oxazole. It displays activity against P-388 leukemia and inhibits crown gall tumor formation on various dicotyledonous plants,[73] due to antibacterial activity against *Agrobacterium tumefaciens*. Subsequently, the structurally-related curromycins A (**163**) and B (**164**) were identified from *Streptomyces hygroscopicus*.[74]



162 Oxazolomycin (R = H, R' = H)
163 Curromycin A (R = CH_3, R' = CH_3OCH_2)
164 Curromycin B (R = CH_3, R' = CH_3)

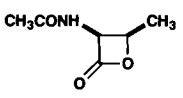
The triene β-lactone antibiotic IM8443T was isolated independently and shown to be identical with curromycin B.[75] A more recent report isolated the 'triedimycins' from *Streptomyces melanosporofaciens*, although it now appears that these are identical to the curromycins.[76] The curromycins have similar antibacterial and antitumor properties to oxazolomycin, although their antimicrobial spectrum is slightly narrower. They also inhibit human immunodeficiency virus (HIV) replication in both acute and chronic infections.[77]

A recent study shows that oxazolomycin (**162**) is an effective protonophore at pH <7.0, but conveys both protons and monovalent cations, such as potassium, through an artificial lipid membrane at pH>7.5. These ionophoric properties may be linked with its antibacterial, antiviral, and cytotoxic activities.[78] The biosynthesis of oxazolomycin has also been investigated,[79] but no total synthesis has been published. However, Kende and coworkers have synthesized a natural analog without a β-lactone, neooxazolomycin.[80]

2. Monocyclic α-Amino-β-lactones

In 1982, during a screening process for β-lactam antibiotics, *N*-acylated α-amino-β-lactone antibiotics which possess monocyclic β-lactone rings were isolated from bacterial cultures.[81] The first

such compound to be characterized was SQ 26,517 (**165**) from *Bacillus* sp. which displays quite weak antimicrobial activity. Its very simple structure resembles the monobactam class of β-lactam antibiotics exemplified by **166**.



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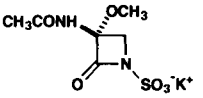

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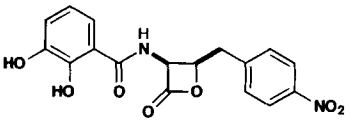
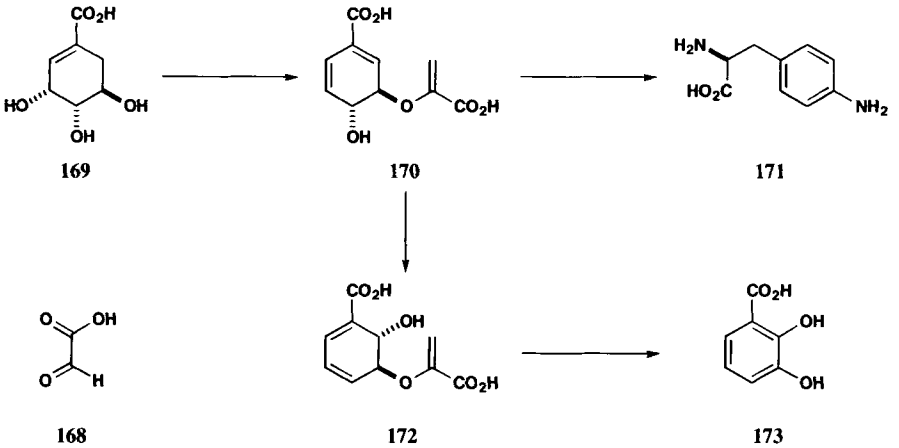


167

Some time later, in 1984, the novel β-lactone obafluorin (**167**) was isolated from *Pseudomonas fluorescens*.[82] Obafluorin shows weak antibacterial activity against a range of bacteria, but with minimum inhibitory concentrations of greater than 100 μg/mL. However, it is the first non-β-lactam antibiotic to demonstrate a high degree of susceptibility to hydrolysis by β-lactamase enzymes. Its structure contains two substituents which potentially influence its biological activity, a 2,3-dihydroxybenzamido (catecholamido) function and a *p*-nitrobenzyl function in a *cis* relationship on the β-lactone ring.[83] Although little is known about the mode of action of these antibacterial compounds, it is interesting to note that the stereochemistry on the β-lactone ring is the same as that of the corresponding penicillins and cephalosporins. Biosynthetic studies suggest that obafluorin is derived from glyoxylate (**168**, from glycine), L-*p*-aminophenylalanine (**171**) and a catechol moiety (**173**), the two latter components probably arising from shikimic acid (**169**) via chorismate (**170**) and isochorismate (**172**) (Scheme 25).[84]



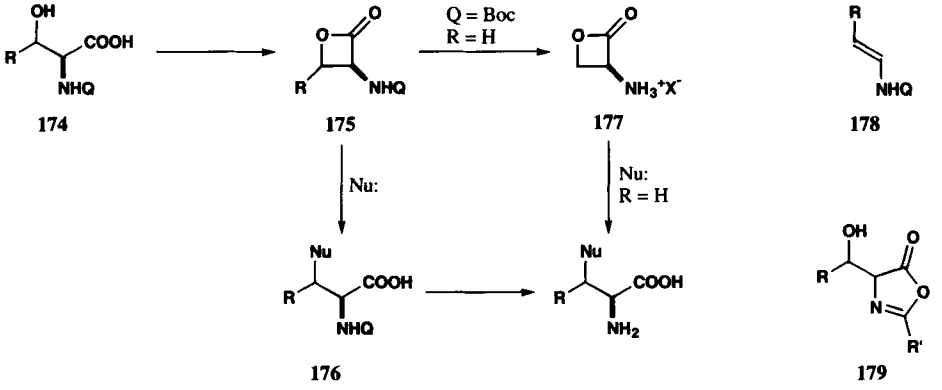
169 **170** **171**

168 **172** **173**

Scheme 25

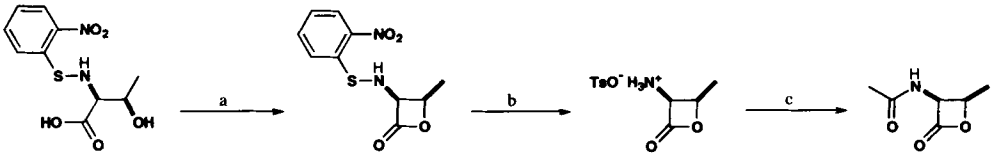
Formation of *N*-acylated α-amino-β-lactones **175** with no substituent at C-4 of the oxetanone ring (R = H) proceeds readily by hydroxyl group activation of the corresponding serine derivative **174** under Mitsunobu conditions at low temperature (Scheme 26).[85] These β-lactones have considerable synthetic utility since they can react with various carbon or heteroatom nucleophiles to produce novel amino acids and derivatives **176** with no loss of stereochemical integrity.[85] If the

protecting group (Q) is *tert*-butyloxycarbonyl (Boc), then treatment with non-nucleophilic acids such as TsOH provides salts such as **177** that react similarly with various nucleophiles to allow direct access to sensitive unprotected α-amino acids.[85d]



Scheme 26

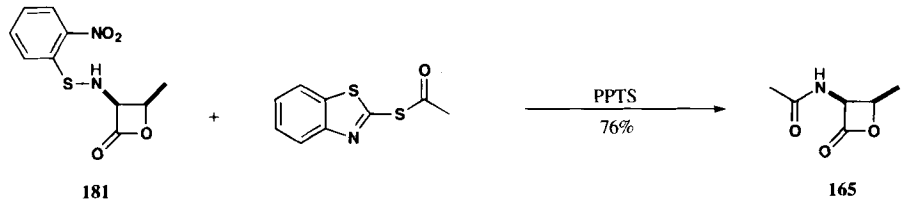
However, Mitsunobu cyclization conditions cannot be applied to β-hydroxy amino acid derivatives bearing a β alkyl substituent because rapid stereospecific decarboxylative elimination (e.g. to **178**) intervenes.[86] This problem can be circumvented by a carboxyl group activation process, but acceptable yields are obtained only if the protecting group is incapable of forming azlactones **179**.[86] The *o*-nitrophenylsulfenyl[87] group fulfills this criterion and was used successfully in a synthesis of SQ 26,517 (**165**) (Scheme 27).[88] Thus treatment of *N*-[(*o*-nitrophenyl)sulfenyl]-L-threonine (**180**) with 4-bromobenzenesulfonyl chloride in pyridine at low temperature generates the corresponding β-lactone **181** via carboxyl group activation. The 4-bromobenzenesulfonyl chloride gives better yields of β-lactone products than the reagent commonly used in such procedures, benzenesulfonyl chloride. The *N*-protecting group is removed by treatment with *p*-thiocresol in the presence of *p*-toluenesulfonic acid to generate **182**. Such salts are moderately stable under neutral or mildly acidic conditions, but are destroyed instantly by dilute aqueous base. Treatment of **182** with acetyl chloride and pyridine affords the antibiotic SQ 26,517 (**165**) with no detectable epimerization.



(a) $BrC_6H_4SO_2Cl$, pyr., 56%; (b) MeC_6H_4SH, TsOH, 75%; (c) CH_3COCl, pyr, 84%.

Scheme 27

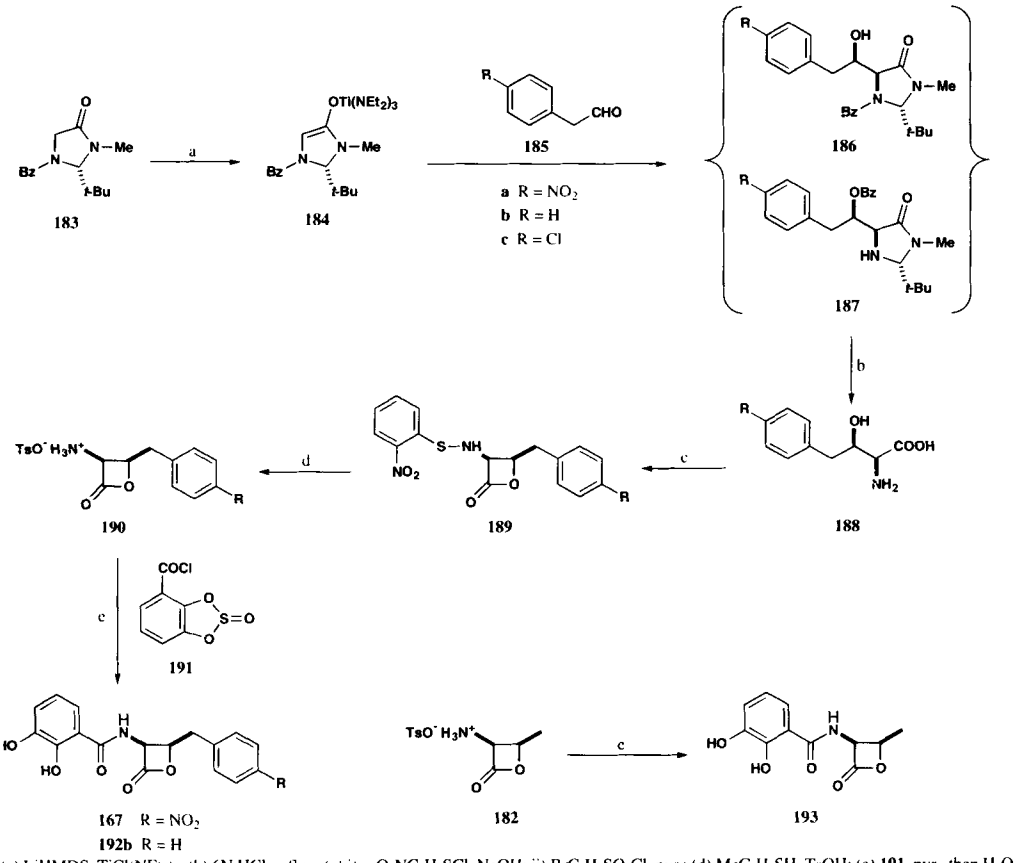
An alternative method utilizing transacylation was successful for synthesis of SQ 26,517 (**165**). Thus, treatment of the protected β-lactone **181** with 2-acetylmercaptobenzothiazole in the presence of pyridinium *p*-toluenesulfonate (PPTS) produces **165** directly (Scheme 28).[89]



181 165

Scheme 28

The versatile procedure outlined in Scheme 27 has been extrapolated to a total synthesis of (+)-obafluorin (**167**) and analogs designed to probe the influence of the substituted aromatic rings on biological activity and stability.[90] Although obafluorin is considerably more antimicrobially active than **165**, it is also much more sensitive and decomposes relatively rapidly upon standing in aqueous solution. A key problem in the construction of this deceptively simple molecule is use of a sufficiently mild protection-deprotection procedure for the catechol functionality in the presence of the β-lactone ring. Treatment of the Seebach imidazolidinone **183** with LiHMDS followed by *in situ* addition of chloro[tris(diethylamino)]titanium generates the titanium enolate **184** (Scheme 29). This enhances



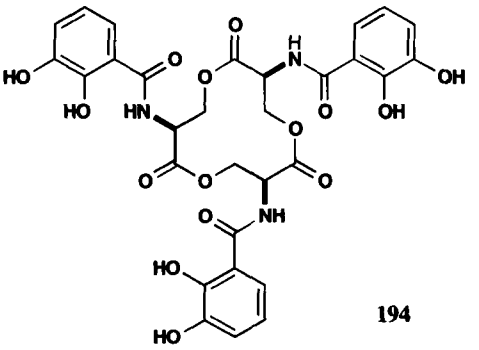
183 184 186 187 188 189 190 167 R = NO_2 192b R = H 182 193

(a) LiHMDS, $TiCl(NEt_2)_3$; (b) 6N HCl, reflux; (c) i) *o*-$O_2NC_6H_4SCl$, NaOH; ii) $BrC_6H_4SO_2Cl$, pyr.; (d) MeC_6H_4SH, TsOH; (e) **191**, pyr., then H_2O.

Scheme 29

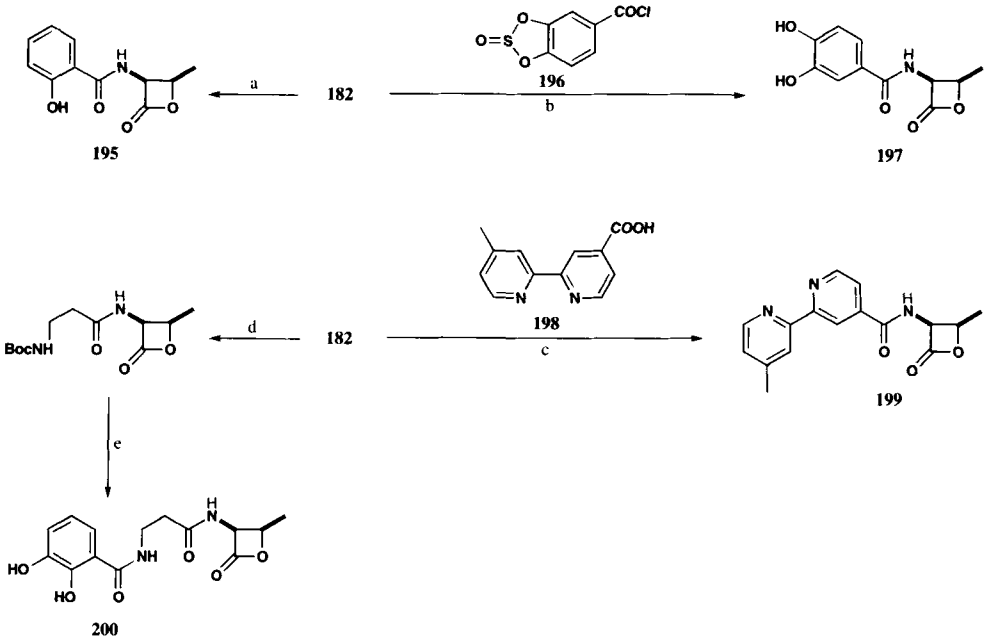
threo vs *erythro* diastereoselectivity in the ensuing aldol condensations with the aldehydes **185a-c**, producing solely the *threo* aldol product (within detection limits) as a mixture of rearranged adducts **186a-c** and **187a-c**. Acidic hydrolysis of the mixture of **186/187** gives the *threo* β-hydroxy α-amino acids **188a-c**, which can be protected on nitrogen with the *o*-nitrophenylsulfenyl group, cyclized to the β-lactones **189a-c**, and deprotected as described above to furnish the tosylate salts **190a-c**. The acid chloride **191** has both phenolic hydroxyl groups protected as a cyclic sulfite that hydrolyzes very readily upon exposure to water. Thus, reaction of the salt **190a** with **191**, followed by aqueous work-up produces (+)-obafluorin (**167**). Similarly, **190b**, **190c** and **182** can be individually acylated to generate the obafluorin analogs **192b**, **192c** and **193**. In biological assays, the latter three analogs display mild antibacterial activity (MIC ≥ 125μg/mL) against some bacterial strains, comparable to obafluorin itself. The acylation with **191** overcomes potential problems of catechol deprotection faced in an earlier synthesis of racemic *O,O'*-diacetylobafluorin by Rao *et al.* wherein racemic **189** was transacylated with 2-(*O,O'*-diacetylbenzoyl)mercaptobenzothiazole in the presence of pyridinium *p*-toluene-sulfonate (PPTS).[89]

The 2,3-dihydroxybenzoyl substituent present in (+)-obafluorin (**167**) enhances the aqueous solubility and is also a powerful iron-chelating moiety which occurs as a key structural feature in the siderophore, enterobactin (**194**). It seemed that both of these factors could contribute to antibacterial activity since transport of the antibiotic into the cell may be enhanced through iron chelation. To probe the key structural features which influence



194

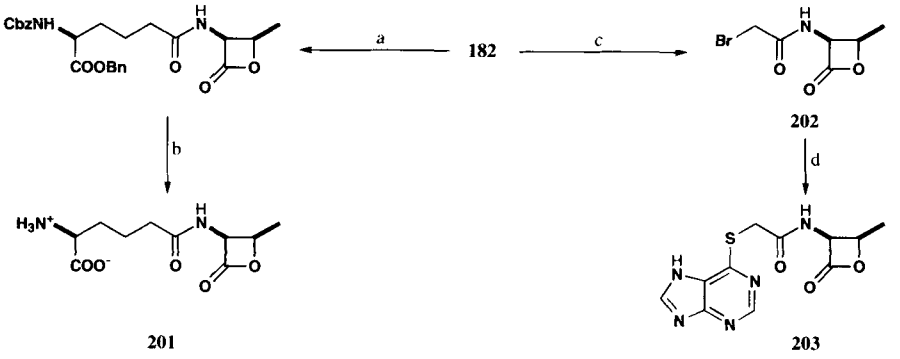
biological activity and cause the lack of stability relative to other β-lactones, a series of analogs shown in Schemes 30 and 31 were prepared.[90] Compounds **195** and **197** are accessible from the tosylate salt **182** analogously to **193** above, using salicyloyl chloride and the cyclic sulfite acid chloride **196**, respectively. Direct coupling with the bipyridyl carboxylic acid **198** affords the derivative **199**. The bipyridyl group is a potent metal chelator that has been coupled to peptides and used as a labeling device in biological systems. Compound **200** maintains structural elements of the parent obafluorin, but separates the *N*-(2,3-dihydroxybenzoyl) moiety from the β-lactone ring with a β-alanine unit in an attempt to reduce interactions which could lead to decomposition. Consideration



(a) *o*-HOC_6H_4COCl, pyr., then H_2O, 45%; (b) **196**, pyr., then H_2O, 46%; (c) **198**, $(EtO)_2POCN$, Et_3N, 61%; (d) *N*-Boc-β-alanine, EtOCOCl, pyr., 65%; (e) i) CF_3CO_2H, TsOH, 99%; ii) **191**, pyr, then H_2O, 68%.

Scheme 30

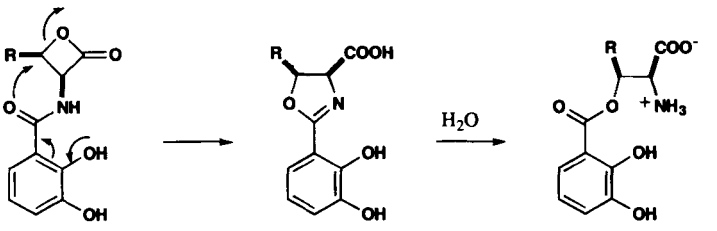
of β-lactam antibiotic structures suggests that certain N-acyl groups such as those in **201** and **203** could enhance aqueous solubility and transport. Thus, condensation of **182** with the mixed anhydride formed between *N*-Cbz-α-aminoadipic acid, α-benzyl ester and ethyl chloroformate, followed by hydrogenolysis, affords the derivative **201** (Scheme 31). Acylation of **182** with bromoacetyl chloride produces **202**, which undergoes a nucleophilic displacement of bromine with 6-thiopurine to give **203**. Examination of the antimicrobial



(a) *N*-Cbz-L-α-aminoadipic acid α-benzyl ester, EtOCOCl, Et_3N; (b) H_2, Pd/C, 54% overall; (c) $BrCH_2COCl$, pyr., 95%; (d) 6-thiopurine, Et_3N, 68%.

Scheme 31

activity of these and other analogs shows that compounds **199**, **202**, and **203** have antibacterial potency comparable to the parent obafluorin (**167**). The enhanced tendency of obafluorin (**167**) and other catechol-containing N-acyl-α-amino-β-lactones to decompose is primarily due to the dihydroxybenzoyl moiety, which catalyzes hydrolysis of the β-lactone ring in the presence of trace impurities. Once these are removed by careful HPLC purification, slow decomposition proceeds by intramolecular attack of the amide oxygen on C-4 of the oxetanone **204** to generate an intermediate oxazoline **205** that hydrolyzes to an O-acyl derivative **206** (Scheme 32).[90]

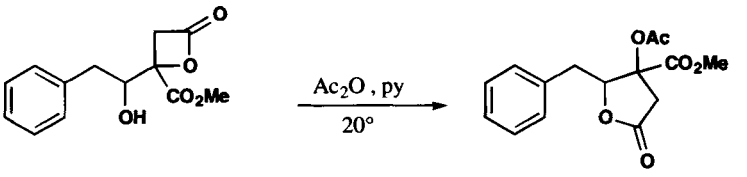


204 205 206

Scheme 32

IV. OTHER β-LACTONES

Since β-lactone moieties can be quite sensitive to nucleophiles and may be destroyed *in vivo* or during isolation procedures, it is highly likely that careful work will discover additional naturally-occurring examples in the future. Papulinone (**207**) is one of three weakly phytotoxic metabolites of *Pseudomonas syringae* pv *papulans*, the causative agent of blister spot disease in apple and pear trees (Scheme 33).[91] An interesting process observed during structural studies is the transformation of

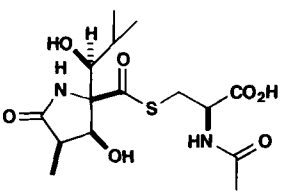


207 208

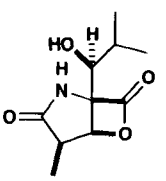
Scheme 33

papulinone (**207**) into γ-lactone **208** upon treatment with acetic anhydride in pyridine at room temperature (75% yield). The authors propose intramolecular attack by the free hydroxyl of **207** on the β-lactone carbonyl, but the process may involve initial ring opening followed by relactonization to the less strained five membered ring.

Lactacystin (**209**) was isolated by Omura and coworkers from a *Streptomyces* species and is the first neurotrophic factor to be obtained from a microbial source.[92] Although **209** is not a β-lactone, a synthetic derivative *clasto*-lactacystin β-lactone (**210**) is also active, suggesting that these compounds may act by acylation of target molecules in the cell to induce morphological changes in

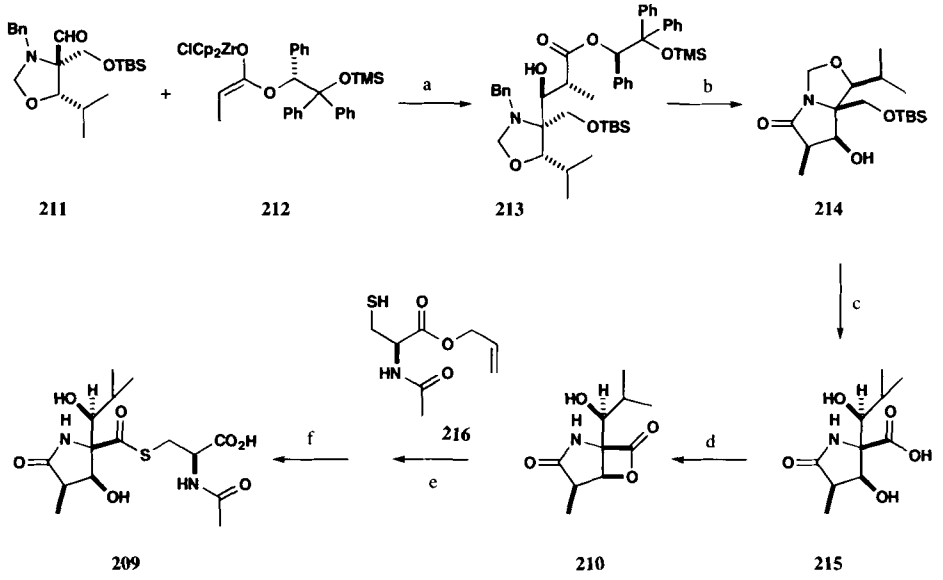


209



210

nerve cells such as neurite outgrowth.[93] The possible natural occurrence of **210** remains to be verified, but it is a key intermediate in the final stage of the synthesis of lactacystin (**209**) by Corey and coworkers (Scheme 34).[94]



(a) THF, -20°, 80%; (b) i) H_2, Pd/C; ii) CH_2N_2; iii) MeOH, 64%; (c) i) HF/MeCN; ii) Swern; iii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene 23°, 62%; (d) BOP-Cl, Et_3N, 95% (e) **216**, Et_3N, 90%, (f) $Pd(Ph_3P)_4$, HCO_2H, Et_3N, THF, 23°, 84%.

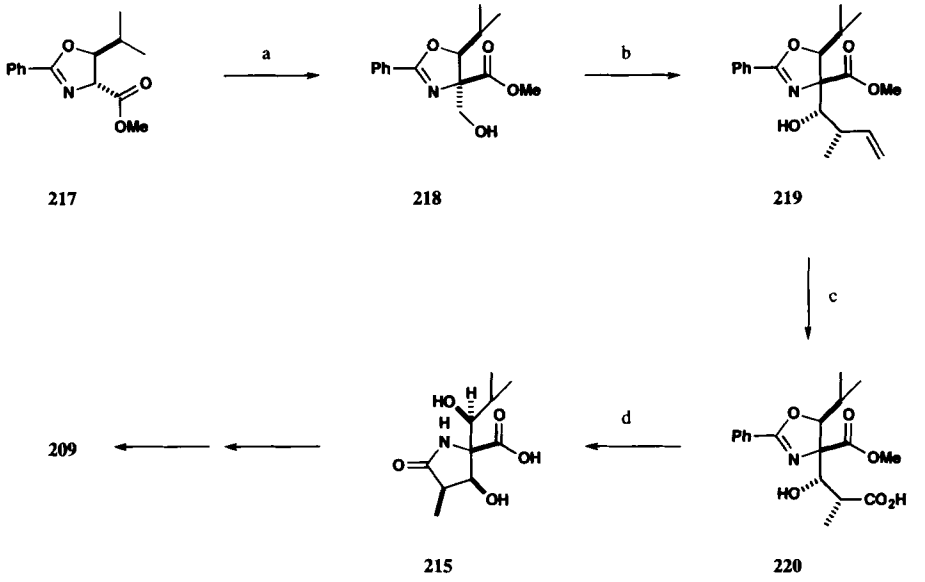
Scheme 34

The same last steps are also used in total syntheses reported by two other groups.[95,96] The tendency of **210** to form upon activation of the carboxyl group of the corresponding ring-opened hydroxy acid **215**,[94c] and the utilization of L-cysteine in the biosynthesis of lactacystin (**209**)[97] suggest that the β-lactone (**210**) may occur naturally and possibly even be involved in the mechanism of neurotrophic action.

The Corey syntheses[94] manufacture chiral oxazolidine **211** as a key intermediate which undergoes aldol condensation in the improved procedure[94c] with the zirconium enolate of propionate ester **212** to give **213**. Hydrogenolysis of the N-benzyl and ester groups, methyl ester formation, and

cyclization by heating in methanol gives **214**, a key intermediate in both syntheses. Removal of the silyl group and oxidation of the resulting primary hydroxyl produces a physiologically inactive[93] hydroxy acid **215** which upon activation with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) generates the key neurotrophic[93] *clasto*-lactacystin β-lactone (**210**). Treatment with the allyl ester of N-acetylcysteine (**216**) affords lactacystin allyl ester, which is deprotected to produce lactacystin (**209**).

A second synthesis of **209** by Omura, Smith, and coworkers[95] begins with aldol condensation of formaldehyde with chiral oxazoline **217**, conversion of the resulting primary alcohol **218** to an aldehyde, and extension of the side chain using an *E*-crotyl diisopinocampheylborane (crotyl-Ipc_2B) to give **219** (Scheme 35). Oxidation generates the side chain carboxyl of **220**, which upon transfer



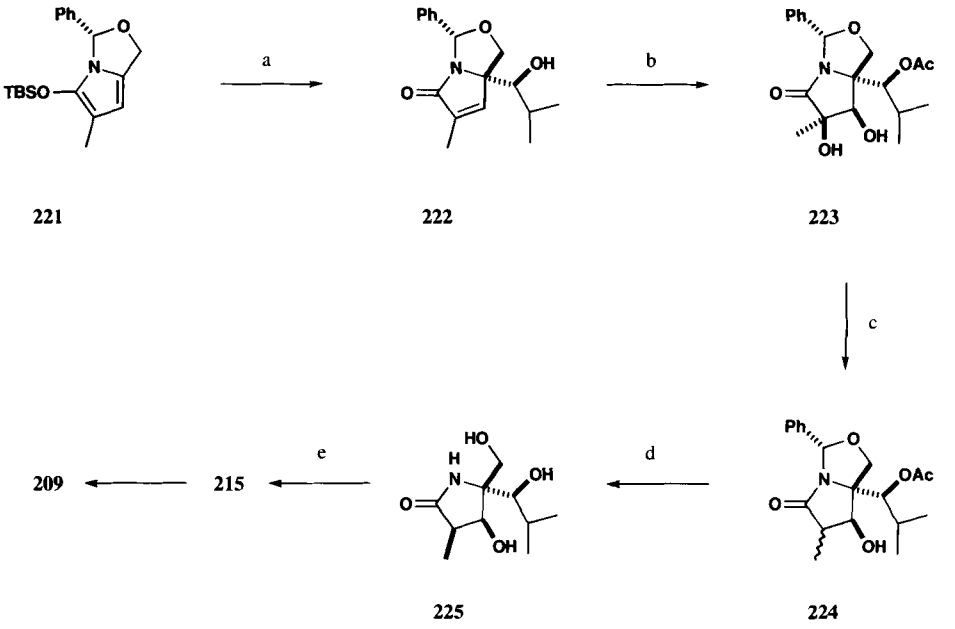
(a) i) LiHMDS, HCHO, 85%; (b) i) Moffatt [O]; ii) crotyl-Ipc_2B, 70%; (c) i) O_3, Me_2S; ii) $NaClO_2$, NaH_2PO_4, 56%; (d) i) Pd, HCO_2NH_4; ii) 0.1 N NaOH, 82%.

Scheme 35

hydrogenation and ester hydrolysis gives the newly cyclized lactam **215**. The rest of the synthesis uses the Corey procedure,[94c] but the intermediate β-lactone **210** which forms upon the BOP-Cl activation of the carboxyl is not isolated. Overall, the process from **217** to **215** proceeds in 27% yield over 7 steps. Corey's improved synthesis converts **211** to **215** in comparable yield (32%) in fewer steps, but **217** is more readily accessible from commercial materials than **211**.

In a recent synthesis of lactacystin (**209**), Baldwin and coworkers use a Lewis acid catalyzed aldol reaction to attach isobutyraldehyde to the siloxypyrrole **221** to form **222** (Scheme 36).[96] Protection of the hydroxyl as an acetate, oxidation to diol **223**, and reductive removal of the hydroxyl α to the carbonyl gives **224**. Hydrolysis of the acetate with base-catalyzed isomerization of the methyl to the more stable epimer (7:1 ratio) followed by hydrogenolysis produces the triol **225**. At this point a series

of selective protection-deprotection procedures are necessary to permit selective oxidation of the primary alcohol to the carboxylic group of hydroxy acid **215**. The overall yield from **221** to **215** is about 24 %. The final conversion to **209** again employs Corey's procedure without isolation of the intermediate β-lactone.[94c]



(a) iPrCHO, $SnCl_4$, -78°, 55%; (b) i) Ac_2O, pyr., 99%; ii) OsO_4, N-Me-morpholine N-oxide, 2 cycles, 87%; (c) *i) Thiocarbonyldiimidazole; ii)* Bu_3SnH, *AIBN, toluene reflux, 85%;* (d) *i)* 2N NaOH, MeOH; ii) H_2, Pd/C, HCl, MeOH, 82%; (e) i) Et_3SiCl, pyr; ii) Ac_2O; iii) 40% HF, MeCN; iv) Jones reagent; v) 0.2N NaOH, 74%.

Scheme 36

V. CONCLUSION

In summary, a number of β-lactones have been isolated from higher plants and microorganisms. They and their derivatives often have interesting biological properties, and at least in the case of tetrahydrolipstatin, considerable potential as drugs. Depending on the substitution pattern, β-lactones can act as good electrophiles both at the carbonyl (i.e. as acylating agents) and at the β-carbon (i.e. as alkylating agents) for nucleophilic groups commonly found in receptors or enzyme active sites. It is likely that additional natural examples will be discovered and synthetic derivatives will be developed for this purpose in the near future.

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