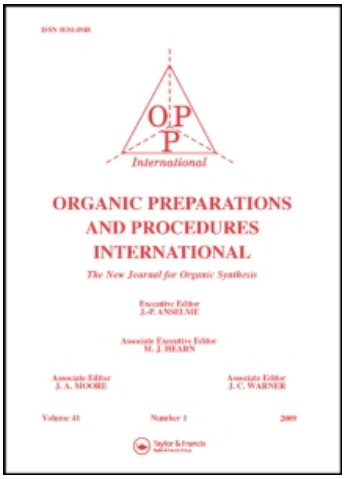

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Kinder Jr, Frederick R.(2002) 'SYNTHETIC APPROACHES TOWARD THE BENGAMIDE FAMILY OF ANTITUMOR MARINE NATURAL PRODUCTS. A REVIEW', Organic Preparations and Procedures International, 34: 6, 559 — 583
To link to this Article: DOI: 10.1080/00304940209355783
URL: http://dx.doi.org/10.1080/00304940209355783

ORGANIC PREPARATIONS AND PROCEDURES INT., 34 (6), 559-583 (2002)

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INTRODUCTION

1. Discovery

The bengamide class of sponge-derived natural products has been studied for over 15 years.[1-4] Bengamides contain unusual structural elements consisting of fused ketide and amino acid biosynthetic moieties that together impart antiparasitic, antimicrobial, and cytotoxic activity. In 1986, Crews and coworkers disclosed the first examples of this class, bengamides A and B, as an easily separable mixture from a small sponge collection, subsequently identified as *Jaspis* cf. *coriacea* (family Coppatiidae, Order Choristida). The absolute stereochemistry of each of the six chiral sites in bengamides A and B was established from extensive spectroscopic studies and confirmed by total syntheses.

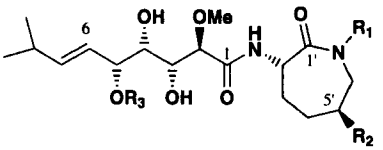
2. Antitumor Activity Profile

The bengamides are potent antiproliferative agents against both transformed and non-transformed cells.[5] Bengamide B was evaluated in the NCI 60 cell line screening panel and found to have a unique profile compared to that of standard anti-tumor agents. Fluorescence-activated cell sorter (FACS) analyses of transformed and non-transformed cells treated with bengamides revealed arrest at both G1 and G2/M phases of the cell cycle.[6] Additional experiments including Western blot analysis of key cell cycle regulators and FACS analysis of synchronized cells suggested that the G1 arrest occurs at the G1/S restriction point. Interestingly, cells that are arrested in the G2/M phase of the cell cycle do not seem to be inhibited during nuclear division but rather during cytokinesis. The intracellular target of the bengamides is under investigation.

The bengamides may be categorized into two structural classes: 1) hydroxylysine-derived (*e.g.*, bengamides A, B, and Z) and 2) lysine-derived (*e.g.*, bengamides E, F, and P). The structures and antiproliferative activities (MDA-MB-435 breast carcinoma, IC_{50} values) of six representative

bengamides are given in Table 1.[1] Hydroxylysine-derived bengamides that bear a myristate ester (bengamides A and B) are *ca.* 1000-fold more potent than non-myristate-containing bengamide Z and all of the lysine-derived bengamides. Bengamide P is 1000-5000-fold less potent than bengamides A and B despite the presence of a myristate ester on the allylic hydroxy position. Thus, from this limited structure activity relationship (SAR) data it appears that the presence of a lipophilic ester on the caprolactam is essential for *in vitro* potency and that lactam *N*-substitution by a methyl group has no effect on *in vitro* potency.

Table 1. Structures and MDA-MB-435 Human Breast Carcinoma in vitro Activity of Selected Bengamides.



Bengamide	R_1	R_2	R_3	IC_{50} (μM)[a]
A(**1**)	H	$O_2C(CH_2)_{12}CH_3$	H	0.001 ± 0.0006
B(**2**)	Me	$O_2C(CH_2)_{12}CH_3$	H	0.0024 ± 0.0008
E(**3**)	H	H	H	3.3 ± 1.2
F(**4**)	Me	H	H	2.9 ± 2.9
P(**5**)	H	H	$O_2C(CH_2)_{12}CH_3$	1.2 ± 7.9
Z(**6**)	Me	OH	H	2.9 ± 1.5

a) IC_{50} values are the concentrations corresponding to 50% growth inhibition.

Sufficient amounts of bengamides B, E, and Z were isolated from a supply of crude sponge extract to test against MDA-MB-435 breast carcinoma cells grown as xenografts in nude mice.[7] Bengamide B was the most potent of the three: 70% tumor growth inhibition with minimal body weight loss at a dose of 20 mg/kg administered intravenously every second day for a total of 8 doses. However, the differences in potency were small compared to the potency differences observed in the MDA-MB-435 *in vitro* assay. The poor water solubility of bengamide B limited intravenous administration to the maximum 20 mg/kg dose. Future biological profiling of bengamides depends on a reliable source of gram amounts of these compounds. Harvesting bengamide-producing sponges or finding a bengamide-producing organism that could be grown in culture is most likely not feasible. This has led to a great deal of interest in producing suitable amounts of these compounds by total synthesis. In addition, a feasible synthesis would make the synthesis of analogues possible. Indeed, analogues have been prepared with superior antitumor activity and better solubility than bengamide B. All of the published bengamide syntheses are reviewed herein.

I. GENERAL ASPECTS

1. General Bengamide Retrosynthetic Analyses

Every reported bengamide synthesis utilizes an amide coupling reaction between a protected polyhydroxylated side-chain intermediate and a cyclolysine intermediate. The resulting amide produced is then usually converted to the desired bengamide after the removal of one or more protecting groups. The most interesting molecular transformations within these reported syntheses reside in the variety of methods employed in the preparation of the two amide coupling partners. The polyhydroxylated side chain intermediates have been prepared from both L- and D-glucose,[8,9] L-quebrachitol,[10] (*R*)-glyceraldehyde,[11] α-D-glucoheptonic γ-lactone,[12,13] and D-tartaric acid.[14] For the synthesis of bengamide E, cyclolysine is commercially available. In order to synthesize bengamides A and B, the substituted cyclolysine intermediate was synthesized. These intermediates have been prepared from (*S*)-butanetriol,[8] L-quebrachitol,[15] L-glutamic acid,[16] and (5*R*)-5-hydroxy-L-lysine.[13] A general bengamide retrosynthesis is shown in *Fig. 1*.

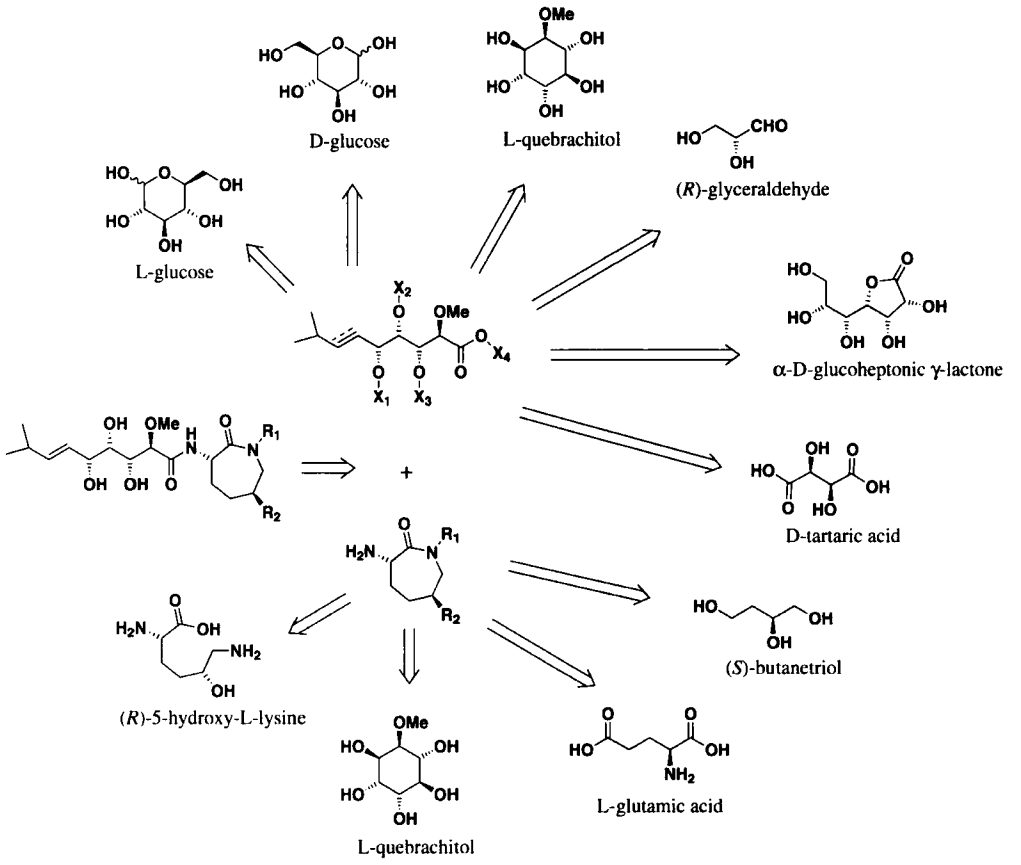
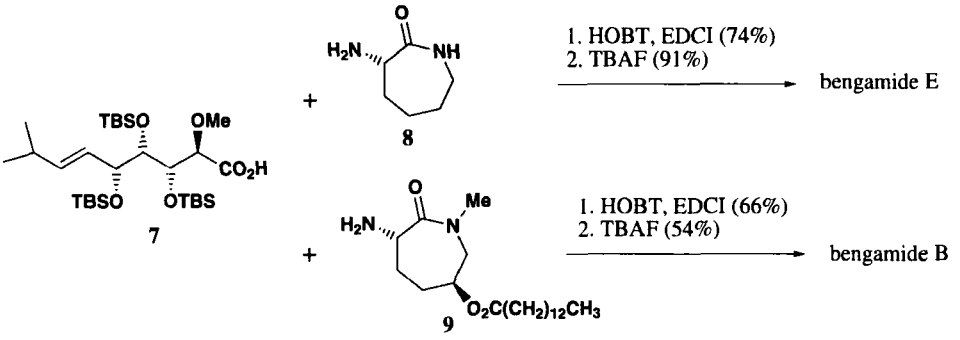


Fig 1

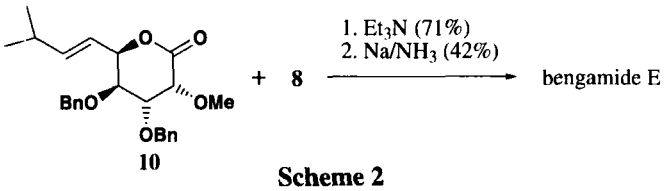
2. Amide Coupling and Subsequent Reactions

Broka and Ehrler reported the amide coupling of carboxylic acid **7** with either cyclolysines **8** or **9** to provide bengamides E or B, respectively (*Scheme 1*).[8] The coupling reactions were conducted in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI)/1-hydroxybenzotriazole (HOBT). The natural products were generated by the removal of three *t*-butyldimethylsilyl (TBS) groups with tetrabutylammonium fluoride (TBAF) treatment.



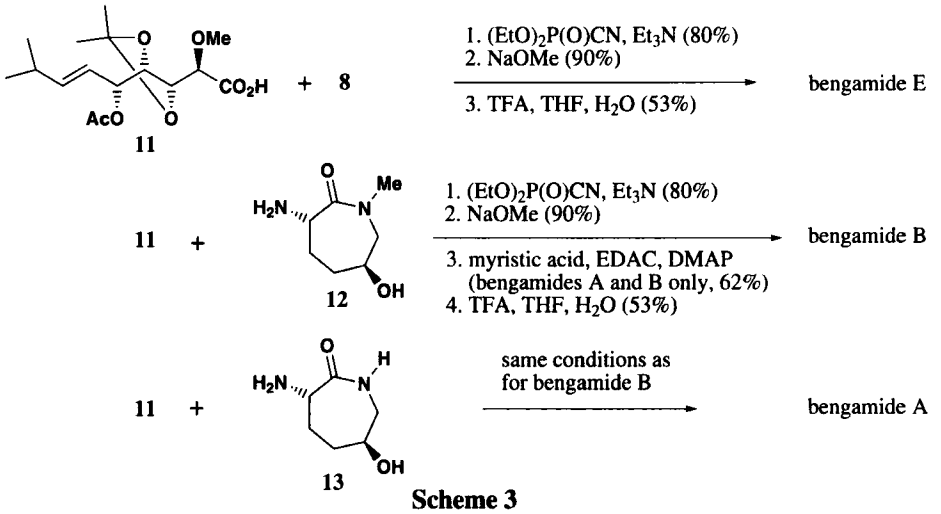
Scheme 1

The bengamide E synthesis reported by Ohrui and co-workers required Et_3N-mediated coupling of lactone **10** and **8** (*Scheme 2*).[9] Dissolving metal reduction of the amide



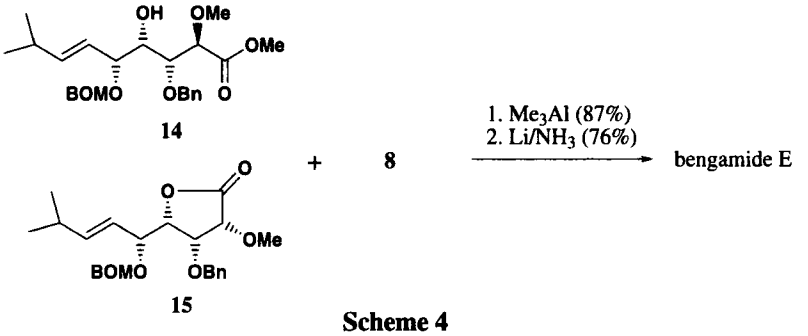
Scheme 2

product provided bengamide E. Ogawa and co-workers have described the syntheses of bengamides A, B, and E (*Scheme 3*).[10, 15, 16] The cyclitol-derived carboxylic acid intermediate **11** was coupled with the appropriate cyclolysine intermediates (**8**, **12**, or **13**) using Shiori's protocol.[17] The allylic acetate was then cleaved with NaOMe. In the case of bengamides A and B, the free caprolactam hydroxyl group was esterified. Finally, trifluoroacetic acid (TFA)-promoted hydrolysis of the acetonide provided the corresponding bengamide.



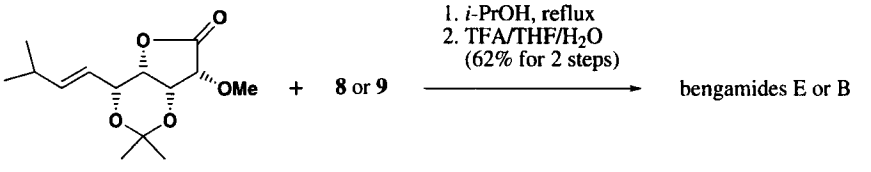
Scheme 3

Marshall and Luke utilized the Weinreb coupling protocol to join the ester/lactone mixture **14** and **15** with the bis(dimethylaluminum) adduct prepared *in situ* from **8** and Me_3Al (Scheme 4).[11,18] Both the benzyloxymethyl (BOM) and benzyl ethers were removed with Li dissolved in NH_3.



Scheme 4

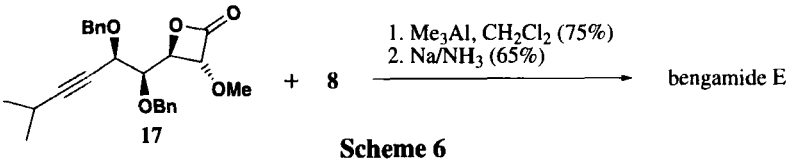
The Oncology Medicinal Chemistry Group at Novartis Pharmaceuticals Corporation reported that lactone intermediate **16** and either caprolactam **8** or **9** could be efficiently coupled simply by heating the two intermediates in *i*-PrOH at reflux (*Scheme 5*).[13] The reaction proceeded without



Scheme 5

competing amine attack on the acyclic ester moiety of **9**. TFA-mediated acetonide hydrolysis similar to the method reported by Ogawa and coworkers (see *Scheme 3*) provided bengamides B and E. The Novartis group produced over 1 gram of bengamide B using this route.

Mukai and coworkers reported the synthesis of bengamide E from alkyne **17** and cyclolysine **8** (Scheme 6).[14,19] The amide coupling was achieved using the Weinreb protocol that Marshall employed in his bengamide E synthesis (*Scheme 4*). The final step in this synthesis is unique with respect to the other syntheses described in this review in that not only does the Birch reduction



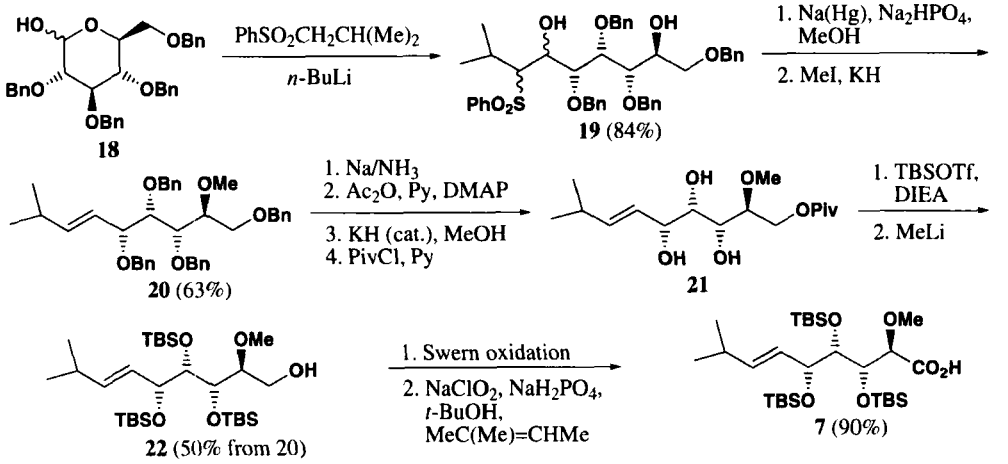
Scheme 6

remove a benzyl ether, it also generated the *E*-alkene from the corresponding alkyne. Unlike the amide coupling and subsequent reactions described in this section, the protected polyhydroxylated ester and cyclolysine intermediates used for the amide coupling were prepared using entirely different synthetic pathways. Section III reviews syntheses reported for the preparation of the protected polyhydroxylated ester intermediates. Section IV reviews the preparation of the hydroxycyclolysine intermediates used in the preparation of bengamides A and B.

II. SYNTHESIS OF PROTECTED POLYHYDROXYLATED BENGAMIDE SIDE-CHAIN INTERMEDIATES

1. Synthesis from L-*Glucose*

L-Glucose contains the same four contiguous stereocenters found on the polyhydroxlated side chain of all bengamides. The conversion of L-glucose to carboxylic acid **7** used in the synthesis of bengamides B and E was described by Broka and Luke (*Scheme 7*).[8] Commercially available L-glucose was converted to the tetrabenzyl ether **18** in two steps.[20] **18** was treated with isobutylsulfone

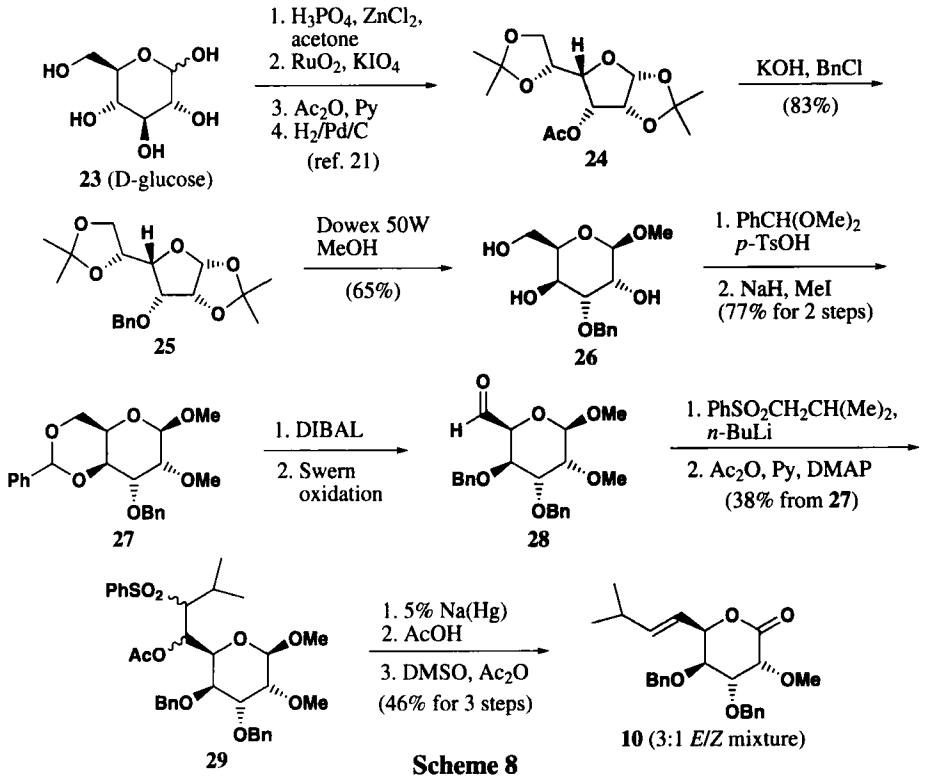


Scheme 7

lithium salt to give a mixture of 1,2-hydroxysulfonyl diastereomers **19**. The *E*-alkene was generated following treatment of **19** with 6% Na(Hg). The remaining free hydroxy group was methylated with MeI/KH to give the methyl ether **20**. Dissolving metal reductive hydrolysis of the benzyl groups, peracetylation for purification purposes, acetate hydrolysis, and pivalate protection of the primary hydroxy group gave intermediate **21**. The remaining three hydroxy groups were protected as TBS ethers. The pivalate was then hydrolyzed liberating the primary alcohol **22**. Two-step oxidation of **22** afforded the carboxylic acid intermediate **7**.

2. *Synthesis from D-Glucose*

Although D-glucose is far less expensive than L-glucose, the number of transformations required to convert it to a useful bengamide synthesis intermediate reduces its attractiveness as a starting material. Ohrui and coworkers reported the conversion of D-glucose to lactone intermediate **10** in *1992 (Scheme 8)*.[9] D-Glucose (**23**) was converted to D-gulofuranose **24** using literature procedures.[21] Simultaneous acetate hydrolysis and *O*-benzylation with KOH/BnCl afforded benzyl ether **25**.



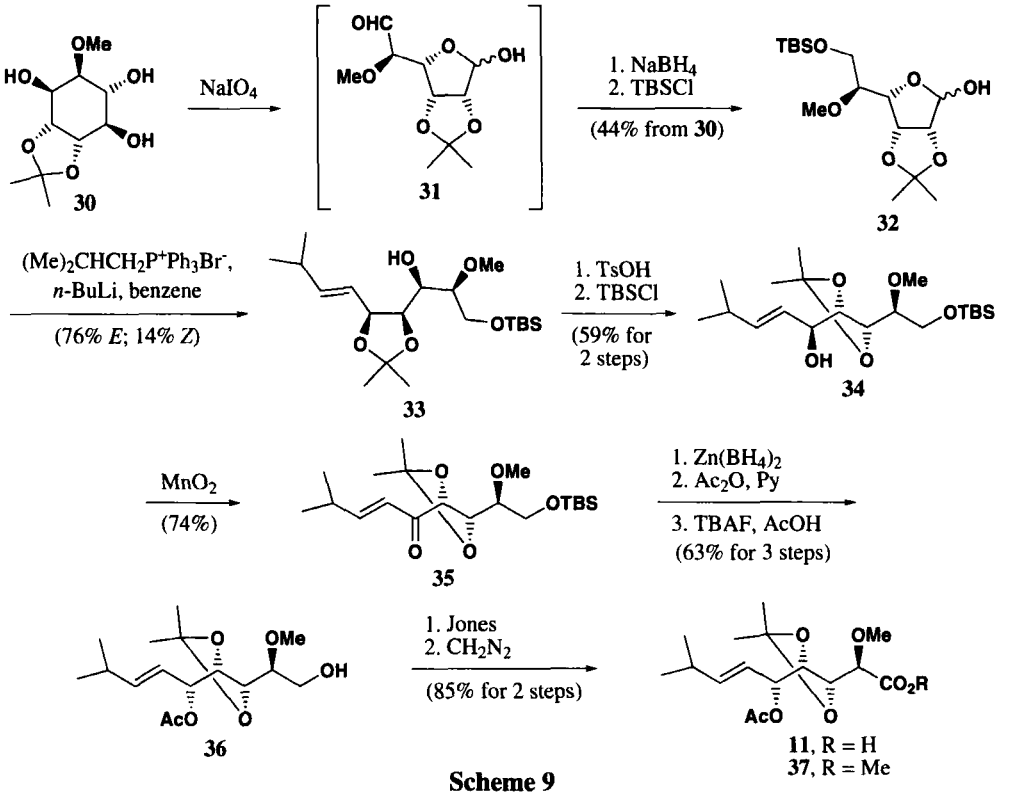
Scheme 8

Treatment of **25** with Dowex 50W in MeOH provided pyranoside **26** plus two other isomeric products. The benzylidene acetal was generated by treating **26** with benzaldehyde dimethyl acetal with cat. *p*-toluenesulfonic acid (TsOH). The remaining free hydroxy group was then methylated to give ether **27**. Reductive cleavage of the acetal with diisobutylaluminum hydride (DIBAL) and subsequent

Swern oxidation provided aldehyde **28**. Julia olefination on the aldehyde generated a 3:1 mixture of *E* and *Z* alkenes, respectively. Acid hydrolysis of the glycosidic linkage followed by DMSO-Ac_2O oxidation afforded lactone intermediate **10**. The mixture of alkene isomers could only be separated after the amide coupling step (see *Scheme 2*).

3. *Synthesis from L-Quebrachitol*

Ogawa and coworkers reported the first synthesis of bengamide E in 1991.[10] The cyclitol, quebrachitol, was selected as the starting material for the preparation of the carboxylic acid intermediate **11** (*Scheme 9*). Acetonide **30**, prepared in one step from quebrachitol, underwent oxidative



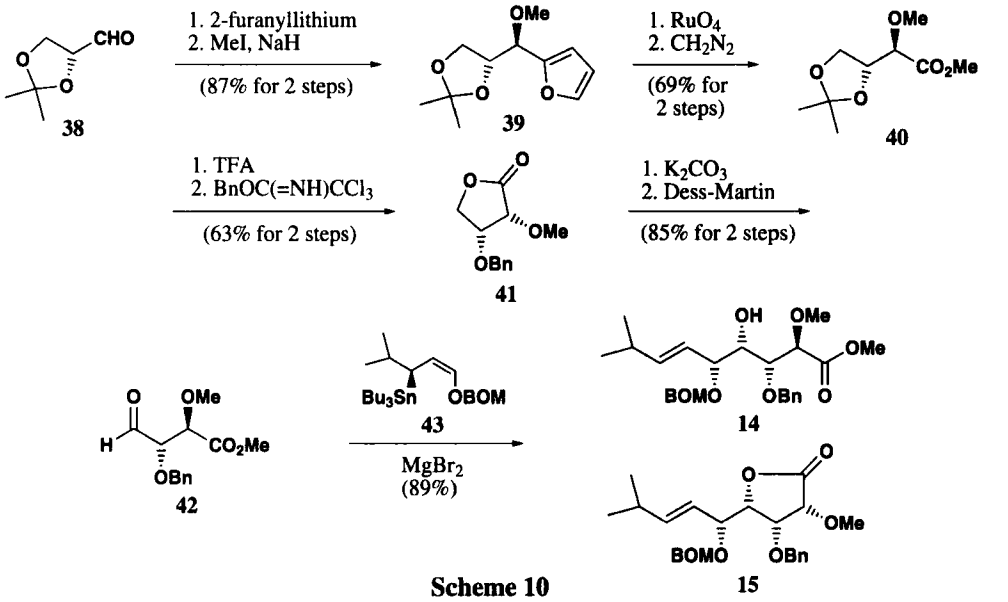
Scheme 9

cleavage to give furanose **31**. Treatment of **31** with $NaBH_4$ followed by TBSCl provided TBS ether **32**. Wittig olefination of **32** gave the desired *E*-alkene as the major product. This is the only reported example among the reported bengamide syntheses where a Wittig olefination reaction was used successfully to install the 6,7-*E*-alkene. The next transformation was the inversion of the allylic hydroxy group. This was accomplished by TsOH-induced migration of the acetonide to give allylic alcohol **34**. After unsuccessful attempts using the Mitsunobu reaction, **34** was oxidized with MnO_2 to ketone **35**. $Zn(BH_4)_2$ reduction provided the desired 5-*R*-hydroxy group (natural product configuration) as the major product. Approximately 10% of the 5-*S*-hydroxy compound was also formed. The allylic hydroxy group was then acetylated and the TBS ether cleaved with TBAF to provide primary

alcohol **36**. Jones oxidation provided the carboxylic intermediate **11**. Subsequent methylation with diazomethane gave methyl ester **37**. This compound was then further converted to one of the bengamide degradation products reported by Crews and coworkers for structure identification purposes.[3]

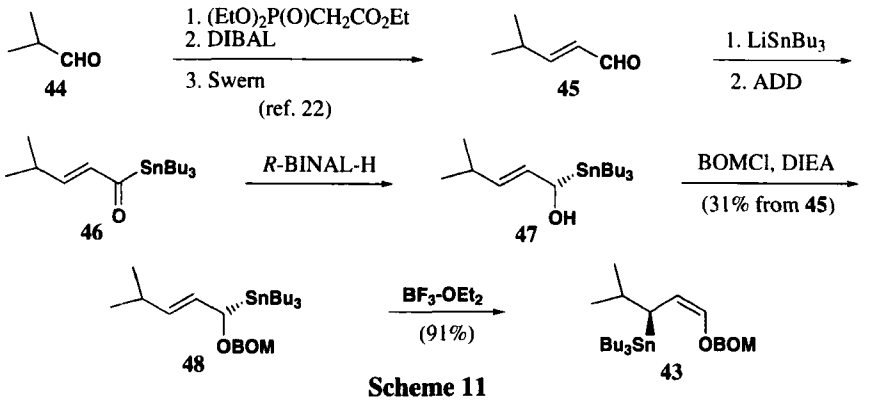
4. Synthesis from (R)-Glyceraldehyde

Most of the reported bengamide syntheses utilize a natural compound with four contiguous stereocenters. One of the few exceptions to this is the bengamide E synthesis described by Marshall and Luke in 1993.[11] Their convergent synthesis of the mixture of ester and lactone intermediates **14** and **15**, respectively, begins with (*R*)-glyceraldehyde acetonide **38**. Stereoselective addition of lithiated furan followed by *O*-methylation provided methyl ether **39**. RuO_4-mediated oxidative hydrolysis gave the carboxylic acid that was subsequently methylated with diazomethane. Methyl ester **40** was converted to furanone **41** by TFA-promoted acetonide hydrolysis and subsequent benzylation. Aldehyde **42** was produced by methanolysis of **41** with K_2CO_3, then oxidation of the resulting alcohol with Dess-Martin reagent. Exposure of aldehyde **42** to intermediate **43** in the presence of $MgBr_2$ led to a nearly 1:1 mixture consisting of ester **14** and lactone **15**.



Scheme 10

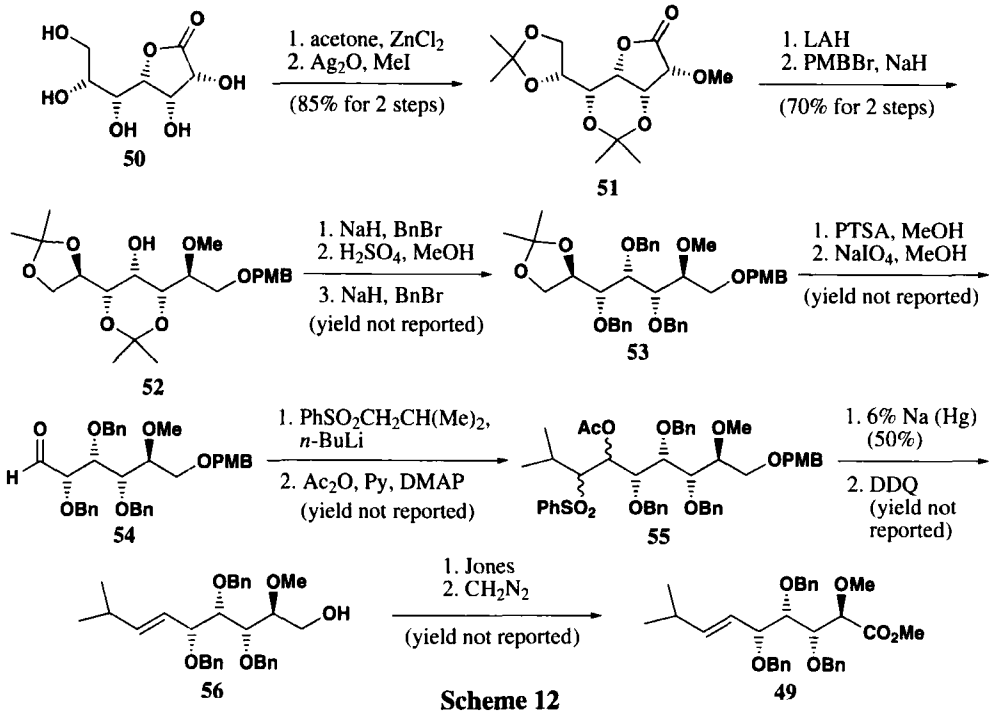
The preparation of chiral allyl stannane **43** is outlined in *Scheme 11*.[11] Isobutyraldehyde (**44**) was converted to *E*-enal **45** in three steps.[22] Treatment of **45** with tributylstannyllithium provided the corresponding hydroxystannane that was subsequently oxidized with azodicarbonyldipiperidine (ADD) to provide acylstannane **46**. Stereoselective reduction of **46** was accomplished with (*R*)-binaphthol lithium aluminum hydride ((*R*)-BINAL-H) to give (*S*)-hydroxystannane **47**. Treatment of **47** with BOMCl, followed by BF_3-promoted isomerization produced (*S*)-allyl stannane **43**.



Scheme 11

5. Synthesis from α-D-Glucoheptonic γ-Lactone

Interestingly, one of the first bengamide syntheses and the latest published bengamide synthesis both use α-D-glucoheptonic-γ-lactone (**50**) as a starting material. In 1991, Gurjar and Srinivas reported the synthesis of the bengamide polyhydroxlated side chain intermediate **49** from this reagent (*Scheme 12*).[12] Although the total synthesis of a bengamide was not reported by the authors, it is clear from the other syntheses included in this review that the synthesis of bengamide E from **49** is

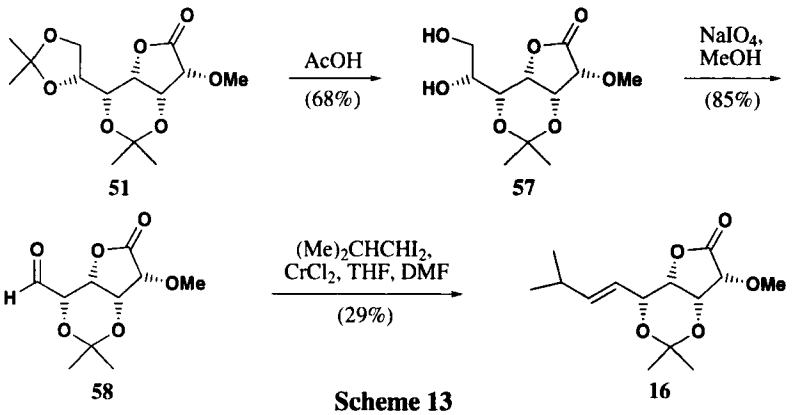


Scheme 12

certainly feasible. **50** was treated with acetone in the presence of acid to give a bis(acetonide) intermediate.[23] The remaining free hydroxy group was methylated with MeI in the presence of Ag_2O to give

methyl ether **51**. LAH reduction of **51** provided the corresponding diol. The primary alcohol was selectively protected as the *p*-methoxybenzyl (PMB) ether **52** using PMBBr and NaH. The remaining hydroxy group was protected as the benzyl ether. Treatment with 0.8% H_2SO_4 gave rise to a 3:1 mixture of 5-ring and 6-ring monoacetonides, respectively. After chromatographic separation, the two free hydroxy groups on the 5-ring monoacetonide were protected as benzyl ethers to provide intermediate **53**. Treatment of **53** with TsOH gave the corresponding vicinal diol. Oxidative cleavage with $NaIO_4$ produced aldehyde **54**. The aldehyde was converted to the desired *E*-alkene (via acetoxysulfone **55**) using the Julia olefination protocol as described in other bengamide syntheses in this review. DDQ-mediated PMB cleavage of this intermediate produced primary alcohol **56**. Coversion of **56** to ester **49** was achieved using the Jones oxidation protocol. The resulting carboxylic acid was then converted to the methyl ester using diazomethane.

Novartis published total syntheses of bengamides B and E in 2001.[13] Like Gurjar and coworkers ten years earlier, the Novartis synthesis began with α-D-glucoheptonic γ-lactone (**50**). Similar conversion of **50** to **51** was achieved by treatment of an acetone solution of **50** with catalytic I_2.[24] The reaction also produced ~10% of another bis(acetonide) that could be removed through crystallization. Methylation of the remaining unprotected hydroxyl group using Ag_2O with methyl iodide provided methyl ether **51**. The key step in the transformation of **51** to the advanced intermediate **16** was the selective removal of the 1,2-acetonide in the presence of the 1,3-acetonide. This was accomplished by the treatment of bis(acetonide) **51** with acetic acid. The desired vicinal diol **57** was produced.[25] Every step up to this point did not require chromatographic purification. Oxidative cleavage of the diol with $NaIO_4$ produced aldehyde **58**. This aldehyde was prone to hydration and required repeated rotary evaporation with $CHCl_3$ or toluene to remove all traces of water. Aldehyde **58** was then olefinated with the low valent organochromium species generated *in situ* from 1,1-diodoisobutane (prepared in two steps from isobutyraldehyde [26]) and $Cr(II)Cl_2$ to produce a nearly 3:1 mixture of *E* and *Z* isomers in 39% yield.[27] The desired *E* isomer, **16**, was isolated in 29% yield using preparative normal phase HPLC. None of aldehyde **58** was recoverable from the reaction mixture. Alternative olefination attempts including the Wittig reaction and the S. Julia olefination produced <10% of the olefin **16**.[28,29] This five step sequence to produce lactone **16** is the shortest published route to the protected polyhydroxylated bengamide side chain intermediate.

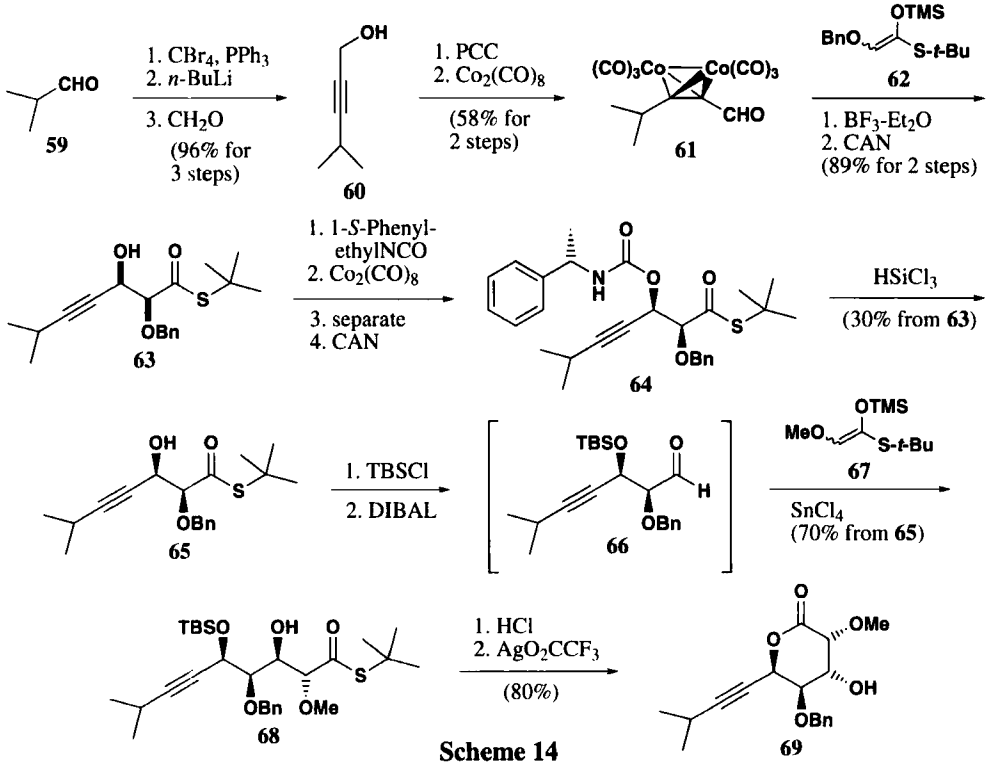


51 57 58 16

Scheme 13

6. Synthesis from D-Tartaric Acid

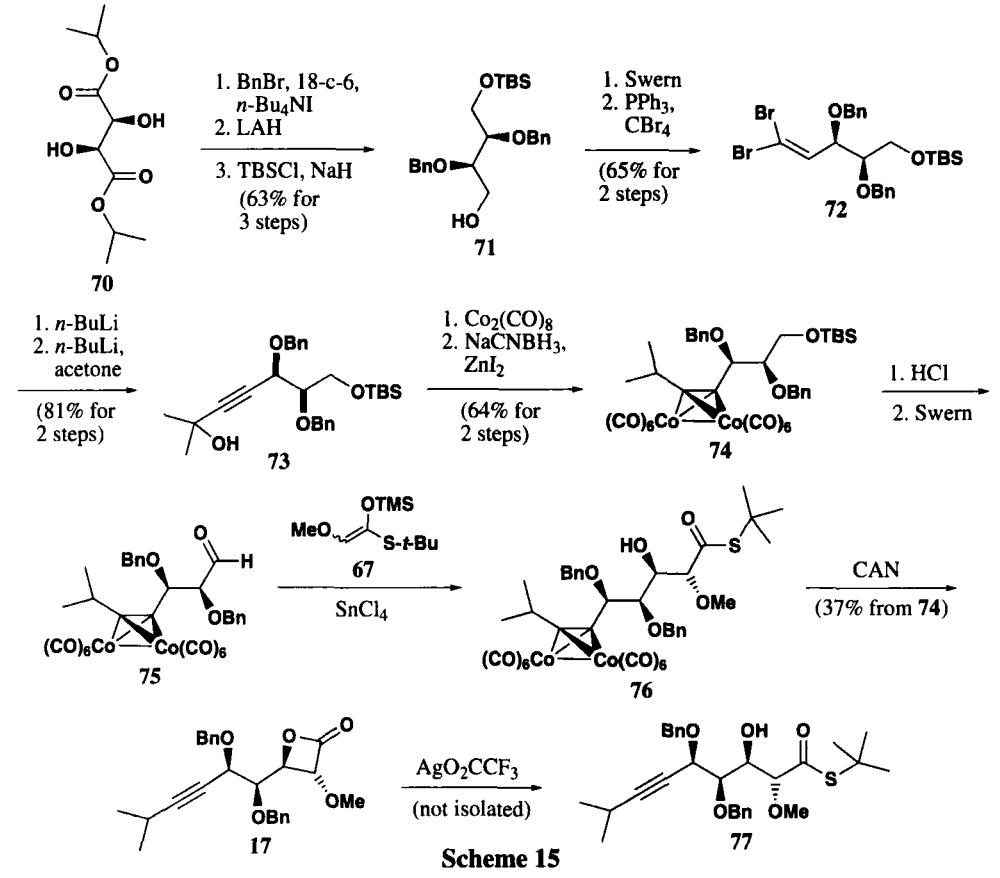
Mukai and coworkers have published two syntheses of bengamide E. The first approach utilizes two aldol reactions to establish the four contiguous chiral centers in the polyhydroxylated bengamide side chain.[19] Unfortunately, this first method required optical resolution after the first aldol reaction. The second bengamide E synthesis utilized diisopropyl D-tartrate as starting material which eliminated the resolution step.[14] The first of the two syntheses is outlined in Scheme 14. Isobutyraldehyde (**59**) was transformed to propargyl alcohol **60** in three steps using published procedures.[30] PCC oxidation and subsequent exposure to $Co_2(CO)_8$ provided cobalt complex **61**. The *O,S*-acetal **62** was prepared from the corresponding thioester as reported by Gennari.[31] Treatment of aldehyde **61** with **62** in the presence of BF_3-OEt_2 produced the (±)-*syn*-aldol condensation product **63** as the major product (95:5, *syn*:*anti*). Previous studies have determined that analogous aldol reactions with alkynes favor formation of *anti*-aldol condensation products.[32,33,34] In order to isolate the desired (-)-enantiomer of **63**, an optical resolution was required. The authors chose 1-*S*-phenylethylisocyanate as the resolving reagent as reported by Pirkle.[35,36,37] Although the secondary alcohols were easily carbamoylated, chromatographic separation proved difficult. It was fortunate that the corresponding hexacarbonyl alkyne complexes were easily separable and, once reconstituted with ceric ammonium nitrate (CAN), the desired enantiomer was produced. **65** was then converted to the silyl ether and subsequently reduced to aldehyde **66**. The second aldol reaction was conducted with aldehyde **66** and *O,S*-acetal **67** in the presence of $SnCl_4$ following the Gennari protocol to provide the desired *anti*-aldol condensation



Scheme 14

product (92:8, *anti*:*syn*).[28] The stereoselectivity of this condensation was explained by a chelation-control transition state model. Removal of the TBS group with HCl followed by lactonization provided polyhydroxylated bengamide side-chain intermediate **68** used in the first of Mukai's two reported bengamide E syntheses.

Diisopropyl-D-tartrate (**70**) was used as starting material in Mukai and coworkers' second bengamide side chain synthesis (*Scheme 15*). TBS ether **71** was prepared from **70** in three steps (dibenzylation, reduction, and monosilylation). Swern oxidation of the free hydroxy group followed by Corey – Fuchs dibromo olefination provided divinyl bromide **72**. The bengamide side chain isopropyl group was installed in two steps by treatment of **72** with *n*-BuLi to give the terminal alkyne.



Scheme 15

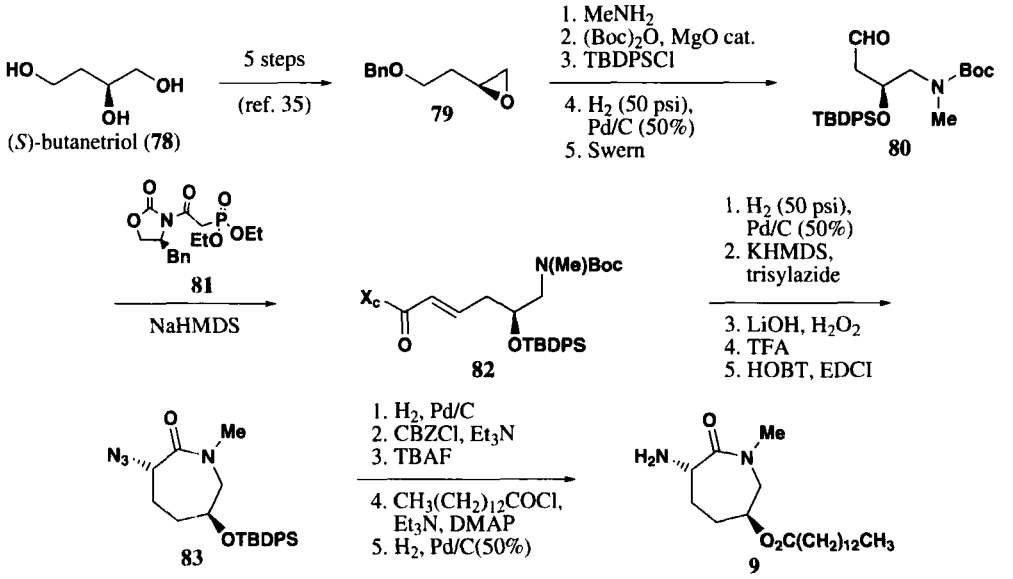
Lithiation of the isolated alkyne with *n*-BuLi follwed by addition of acetone provided tertiary alcohol **73**. The authors were unable to convert **72** to **73** in one pot. Deoxygenation of the propargyl hydroxy group also proved problematic. The problem was solved by converting the alkyne to the dicobalthexacarbonyl complex. Treatment of the complexed propargyl alcohol with $NaCNBH_3/ZnI_2$ provided isopropyl intermediate **74**. The authors also discovered that the *anti*-selective Gennari aldol condensation proceeds with far better selectivity when the alkyne is complexed with dicobalt hexacar-

bonyl than with the alkyne itself. Thus, **74** was converted to aldehyde **75**. Condensation of **75** with *O,S*-acetal **67** in the presence of $SnCl_4$ provided *anti*-aldol condensation product **76**. The *syn*-aldol product was not detectable. Finally, removal of the cobalt complex with CAN and subsequent AgO_2CCF_3-promoted lactonization provided β-lactone **17**. The instability of **17** necessitated its immediate use in the next step (*see Scheme 6*) without isolation.

III. SYNTHESIS OF HYDROXYCYCLOLYSINE INTERMEDIATES

1. Synthesis from (S)-Butanetriol

The bengamide B synthesis reported by Broka and Ehrler utilizes cyclolysine **9** which was prepared in 21 steps starting from (*S*)-butanetriol (**78**).[8] **78** was converted to the known epoxide **79** following a literature procedure.[38] Treatment with methylamine in a sealed tube at 120 °C followed by *tert*-butoxycarbonyl (*t*-BOC) protection provided the corresponding protected methylamine. The resulting free hydroxy group was protected as the *tert*-butyldiphenylsilyl (TBDPS) ether. The primary benzyl ether on the molecule was then hydrogenolyzed. Swern oxidation of the resulting primary alcohol provided aldehyde **80**. Phosphonate **81** was prepared from the corresponding bromoacetyloxazolidinone and triethylphosphite.[39] Horner-Emmons olefination of **80** with **81** provided the *E*-unsaturated acyloxazolidinone **82**. Hydrogenation of the alkene, followed by an asymmetric azidation reaction provided the corresponding chiral α-azidoacyloxazolidinone. The chiral auxiliary group was cleaved with $LiOH/H_2O_2$. The *t*-BOC group was then cleaved with TFA. The resulting aminocaproic acid intermediate was cyclized using a standard peptide coupling protocol to give caprolactam **83**.



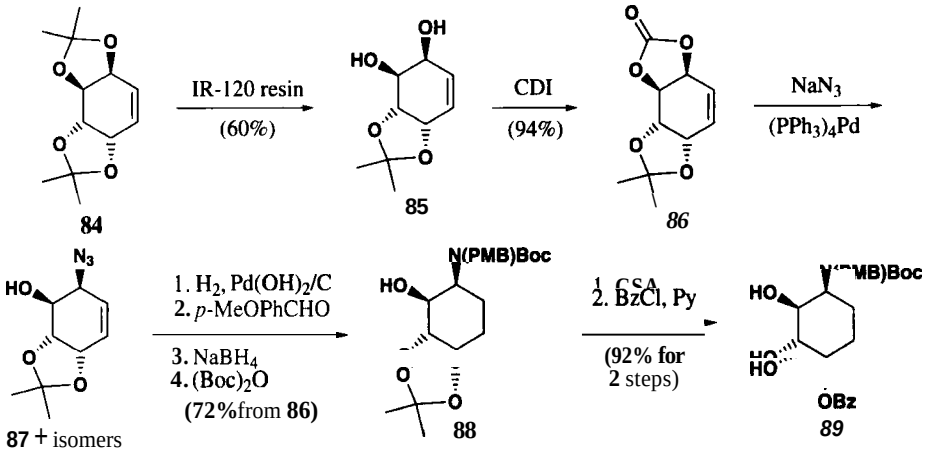
Scheme 16

Hydrogenation of **83** produced the corresponding amine that was subsequently protected as a benzylcarbamate. The TBDPS group was then removed with TBAF and the resulting free hydroxy group

was myristoylated. Finally, removal of the carbobenzyloxy (CBZ) group provided cyclolysine intermediate 9.

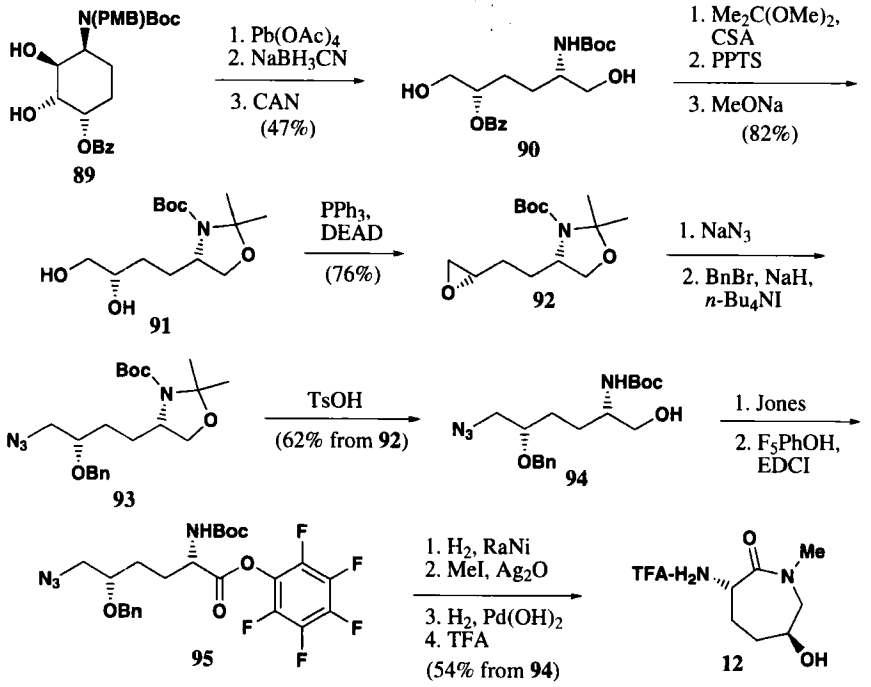
2. *Synthesis from L-Quebrachitol*

The stereoselective conversion of L-quebrachitol to bengamide B cyclolysine precursor 12 was reported by Chida and coworkers in 1994 (Schemes *17a* and *b*).[15] L-Quebrachitol was converted



Scheme 17a

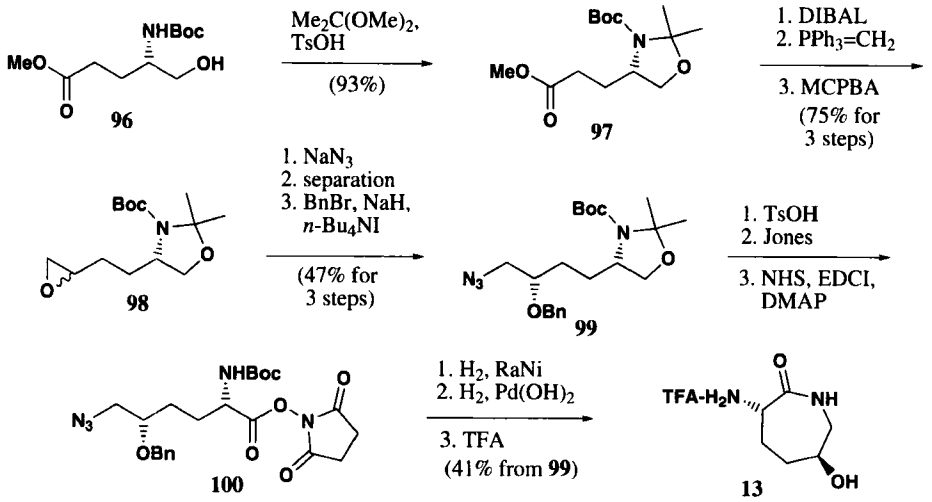
to bis(acetonide) 84 in three steps using a previously reported literature synthesis.[40] Treatment of 84 with mild acid resulted in partial hydrolysis to give monoacetonide 85. The allylic alcohol was converted to allylic azide 87 with retention of configuration via the cyclic carbonate 86 and subsequent palladium-mediated acyl displacement. In addition to 87, two other azide isomers were formed that were removed chromatographically at a later stage in the synthesis (intermediate 88). Hydrogenolysis afforded the corresponding amine. The amine was then doubly protected with a PMB group and a t-BOC group. Camphorsulfonic acid (CSA)-promoted acetonide hydrolysis of 88 followed by monobenzoylation provided intermediate 89. The remainder of the synthesis of 12 is outlined in Scheme 17b. Monobenzoate 89 was oxidatively cleaved with $Pb(OAc)_4$ followed by reduction with $NaBH_3CN$ to give the corresponding acyclic diol. CAN-mediated removal of the *N*-PMB group provided carbamate 90. Exposure of 90 to 2,2-dimethoxypropane in the presence of acid followed by benzoate hydrolysis with methoxide generated vicinal diol 91. The diol was converted to the corresponding epoxide 92 using Mitsunobu conditions. Azide attack on the epoxide was followed by protection of the resulting free hydroxy group as the benzyl ether 93. The other hydroxy group was then liberated using TsOH to give 94. Jones oxidation followed by esterification with pentafluorophenol provided the activated ester 95. Lactamization was induced with the hydrogenolysis of the azide of 95 to the corresponding amine. The caprolactam amide nitrogen was then methylated. Cyclolysine 12 was produced by hydrogenolysis of the benzyl ether to give the corresponding secondary alcohol followed by t-BOC removal with TFA.



Scheme 17b

3. Synthesis from L-Glutamic Acid

Only one synthesis of bengamide A has been published to date. Ogawa and coworkers reported the preparation of cyclolysine intermediate **13** and its subsequent conversion to bengamide A (*Scheme 18*).[16] L-Glutamic acid was converted to *t*-BOC -protected aminoalcohol **96** in four steps as



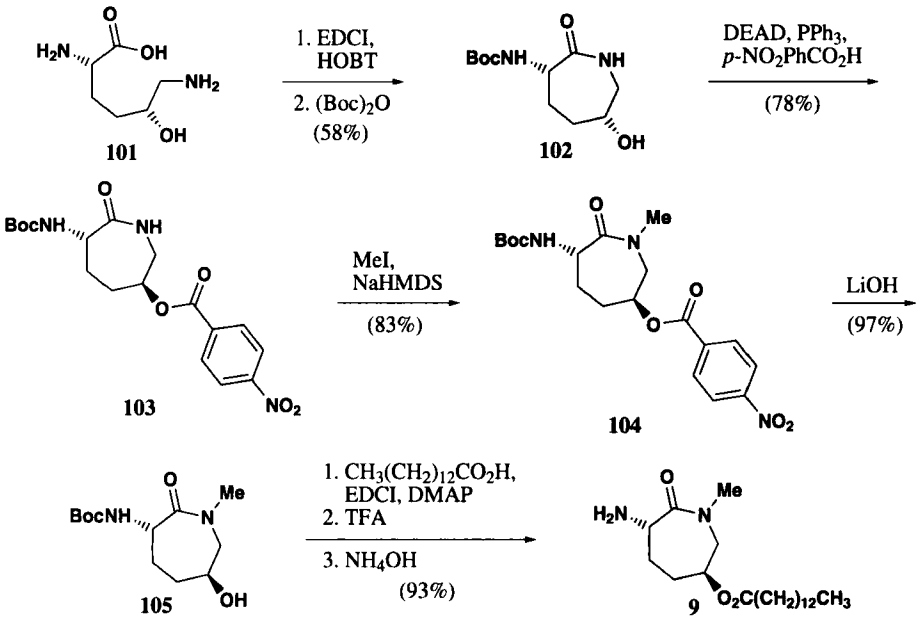
Scheme 18

reported in the literature previously.[41] Treatment of **96** with 2,2-dimethoxypropane and TsOH gave the *N,O*-acetonide **97**. DIBAL reduction of **97**, Wittig olefination, and MCPBA oxidation gave

epoxide **98** as a mixture of diastereomers. Azide attack provided a mixture of azidoalcohols that were separated by chromatography. The newly formed hydroxy group was benzylated to give benzyl ether **99**. Acid-promoted hydrolysis of the acetonide generated the corresponding primary alcohol. Jones oxidation and subsequent carboxylic acid activation provided *N*-hydroxysuccinate ester **100**. Treatment of **100** with H_2/RaNi converted the azide to the corresponding amine which underwent lactamization. Hydrogenolysis of this intermediate removed the benzyl protecting group. TFA-promoted *t*-BOC removal produced the bengamide A cyclolysine intermediate **13**.

4. Synthesis from (5R)-5-Hydroxy-L-Lysine

Hydroxylysine **101** contains all the functionality required to prepare bengamides that bear a caprolactam oxygen substituent. The Novartis group reported the conversion of **101** to bengamide B via cyclolysine intermediate **9** (*Scheme 19*).[13] Cyclization of (5*R*)-5-hydroxy-L-lysine (**101**) followed by *N*- *t*-BOC carbamoylation of the free amine was performed in one pot using standard peptide



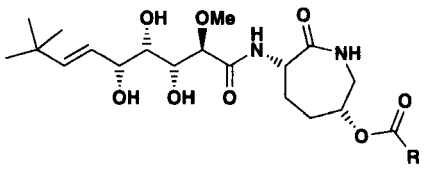
Scheme 19

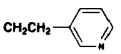
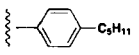
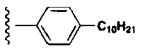
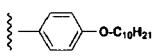
synthesis conditions to produce caprolactam **102**. The secondary alcohol was inverted using Mitsunobu conditions to give *p*-NO_2-benzoate **103** in the desired (*S*)- configuration. Selective methylation of the lactam nitrogen with MeI/NaHMDS produced lactam intermediate **104**. LiOH-promoted ester hydrolysis of **104** generated the corresponding alcohol **105**. Esterification of **105** with myristic acid in the presence of EDCI and 4-(dimethylamino)pyridine (DMAP) produced the corresponding myristate ester. Treatment of this intermediate with TFA removed the *t*-BOC protecting group. Neutralization (NH_4OH) of the crude TFA salt and chromatographic purification gave the amine **9** in 93% yield.

IV. SYNTHESIS OF BENGAMIDE B ANALOGUES

The Oncology Medicinal Chemistry Group at Novartis was interested in the discovery of bengamide analogues with improved antitumor efficacy and solubility.[7] Bengamide B was not a candidate for further preclinical development because of limited supply (*via* sponge extraction or total synthesis) and poor water solubility (0.002 mg/mL at pH 6.8). Although an improved total synthesis of bengamide B was recently developed in our laboratories, the synthesis still requires 14 steps and suffers from a low yield olefination reaction (see **Section II.5**). The design and synthesis of bengamide B analogues was initiated as a means to address the synthetic feasibility and water solubility issues. The first hurdle was to prepare analogues using shorter and higher yielding synthetic routes with *in vivo* efficacy equal to or greater than that of bengamide B. Three modifications to the structure of bengamide B were made: 1) removal of the lactam *N*-methyl group (*i.e.*, bengamide A) 2) replacement of the *i*-Pr alkene substituent by a *t*-Bu group, and 3) inversion of the caprolactam ester-bearing hydroxy group. Analogue **106** bears these three modifications (*Table 2*). Once it was established that these structural changes were well tolerated, a focused SAR study based on substitution of the myristate group with less lipophilic ester moieties was performed (*Table 2*).

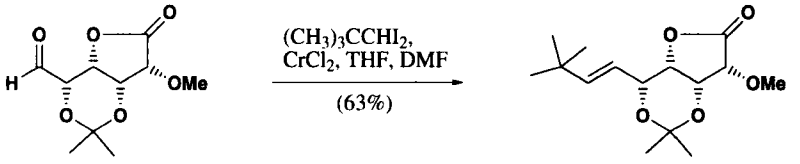
Table 2.



Compound	R	Compound	R
106	$(CH_2)_{12}CH_3$		
107	*c*-pentyl	**114**	
108	*c*-hexyl	**115**	
109	*c*-heptyl	**116**	
110	CH_2-c-hexyl	**117**	
111	CH_2PH	**118**	
113	*trans*-CH=CHPh	**119**	

The synthesis of each analogue utilizes lactone **120** and a substituted cyclolysine intermediate which are joined via an amide coupling reaction. The synthesis of lactone **120** uses the same

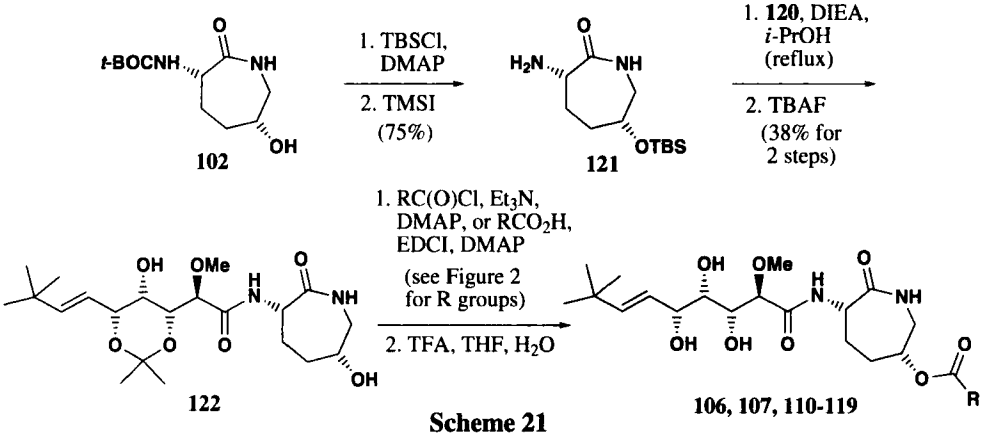
route used to prepare **16** in Scheme 13. Aldehyde **58** was olefinated with the low valent organochromium species generated *in situ* from 1,1-diiodoneopentane (prepared in two steps from pivaldehyde) and $Cr(II)Cl_2$ to produce the desired *E*- olefin in 63% yield after flash column chromatography. A small, variable amount (up to 10%) of the *Z*- olefin was also produced during the reaction. The yield and selectivity of this reaction was significantly improved compared to the analogous reaction with 1,1-diiodoisobutane used to prepare bengamides **B** and E (39% yield of a 3:1 mixture of *E*- to *Z*- isomers).



58 **120**

Scheme 20

Bengamide analogues **106, 107, 110 - 119** were prepared using the synthetic route outlined *in Scheme 21*. **102** (see *Scheme 19*) was protected as the corresponding TBS ether using TBSCl and DMAP. Treatment with TMSI removed the *t*-BOC protecting group to give the amine **121**. Amine **121** was coupled with lactone **120** in a minimal amount of *i*-propanol and diisopropylethylamine (DIEA) stirred at reflux. The resulting amide was treated with TBAF to remove the TBS protecting group to give alcohol **122**. Esterification of **122** with either an acid chloride (using Et_3N and DMAP) or a carboxylic acid in the presence of EDCI and DMAP produced the acetonide-protected analogues **123**. Hydrolysis of the acetonide using $TFA/H_2O/THF$ furnished the desired target compound. This synthesis permits stockpiling of the late intermediate **122** so that analogues can be quickly assembled in 2 steps.



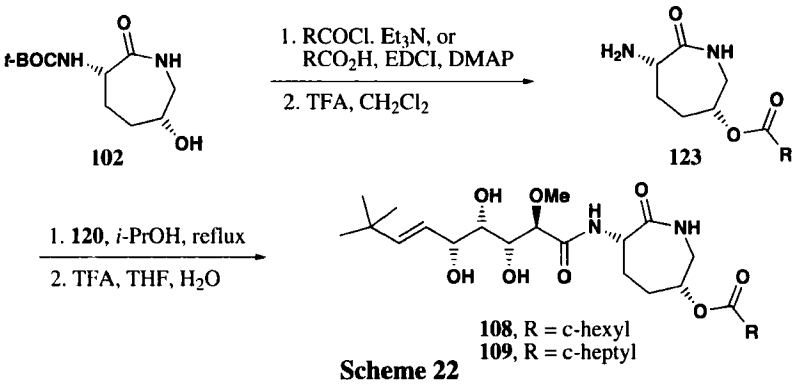
102 **121**

122 **106, 107, 110-119**

Scheme 21

An alternative synthesis that eliminates the TBS protection/deprotection steps was used in the syntheses of analogues **108** and **109** (*Scheme 22*). Rather than protect the caprolactam hydroxy

group as a TBS ether, intermediate **102** was acylated directly, then treated with TFA to remove the *t*-BOC protecting group to give ester **123**. The aminocaprolactam was coupled with lactone **120**, then treated with TFA, as before, to give the desired analogues. It was also found that the amide coupling step proceeded in higher yield without DIEA.



Scheme 22

The first bengamide analogues prepared were intended to improve synthetic feasibility through incorporation of minor structural changes. The first modification was simple replacement of the *i*-Pr group alkene substituent with a *t*-Bu group. The substitution of *i*-Pr with *t*-Bu in the Takai-Utimoto olefination reaction improved the yield and selectivity dramatically.[27] Since the presence of the caprolactam *N*-methyl group did not affect the anti-tumor activity between closely related bengamides, it was expected that this change could be made freely on all bengamide analogues. Syntheses of the hydroxylysine-derived bengamides (A, B, and Z) required that the 5'-OH group, originating from commercially available (5*R*)-5-hydroxy-L-lysine, needed to be inverted. (5*S*)-5-hydroxy-L-lysine was not readily available. In order to test whether the *S*-configuration at the 5'-hydroxy position was essential for anti-tumor activity, compound **106** was prepared. **106** was one of the most potent bengamide B analogues tested in this series *in vitro* and halted the tumor's growth (~0% T/C) *in vivo* at the same dose that bengamide B produced a 31% T/C value.[7] By significantly increasing the yield in the olefination step (*Scheme 20*) and eliminating the lactam *N*-methylation and Mitsunobu inversion steps, compound **106** is synthetically more feasible than bengamide B; however, water solubility of **106** was as low as that of bengamide B.

The second hurdle was to prepare equally or more efficacious bengamide B analogues with improved water solubility. The myristate ester of bengamide B clearly increased *in vitro* and *in vivo* potency compared to bengamides F and Z, but also decreased water solubility. Further, inversion of the lactam 5'-position was tolerated both *in vitro* and *in vivo*, suggesting that bengamide analogues could tolerate diverse structures at this position. Thus, a series of analogues were made to test the hypothesis that replacement of the long alkyl myristate chain with less lipophilic groups at the bengamide lactam 5'-position would create analogues that had enhanced water solubility, but similar growth inhibitory activity relative to bengamide B. Alkyl and aryl ester substituents were selected

based on differences in lipophilicity, size, and shape (see *Table* 2). Over 2/3 of the analogues in Figure 2 inhibited *in vivo* tumor growth as well or better than bengamide B at the same dose with no loss in body weight. **108** and **112** were found to have comparable activity to bengamide B *in vitro*, and superior activity *in vivo*. Consequently, these analogues were selected for further preclinical development.[7]

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(Received October 4, 2001; in final form January 28, 2002)