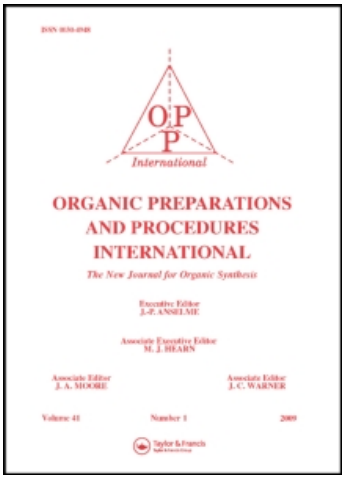

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TOTAL SYNTHESES OF PANCRATISTATIN. A REVIEW

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INTRODUCTION AND BIOMEDICAL SIGNIFICANCE

The medicinal value of Amaryllidaceae plant extracts has been recognized for a long time. It dates back to at least the fourth century B.C., when physician Hippocrates of Cos used oil from the daffodil *Narciclasus poeticus L.* for the treatment of uterine cancer.[1] From the currently known 860 – 1100 species of plants belonging to the Amaryllidaceae family, at least 30 species have been used in ancient folk medicine to treat cancer. In more recent times, more than 100 structurally diverse alkaloids, possessing a wide spectrum of activities have been isolated from the Amaryllidaceae species.[2] Lycorine *(Fig. 1)*, shown to possess antitumor and

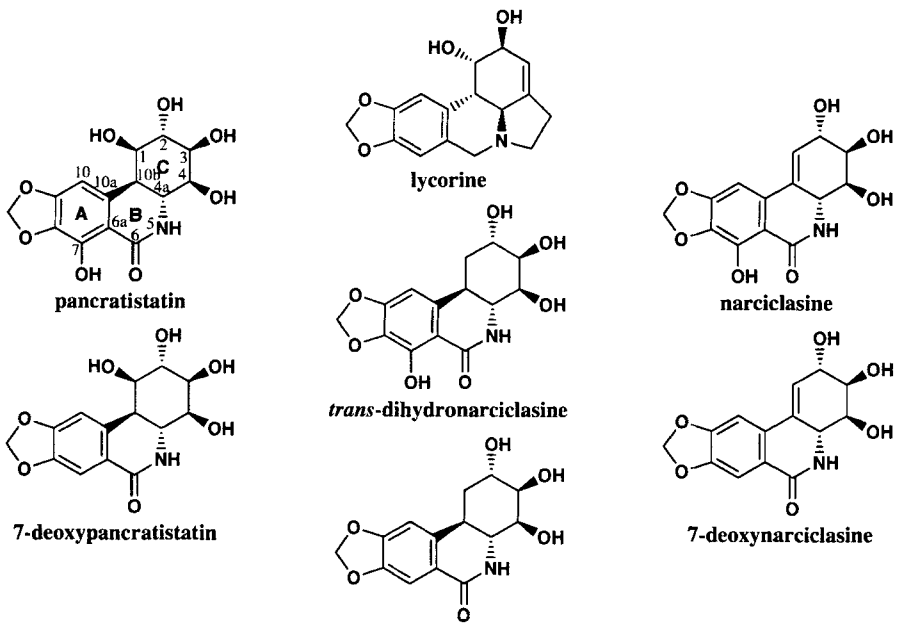


Fig 1

antiviral activities,[3] was the first member of the family isolated in 1877.[4] Later, the phenanthridones narciclasine and 7-deoxynarciclasine (lycoricidine) attracted considerable interest due to their antineoplastic properties, including activity against Ehrlich carcinoma.[5,6] The latter natural products have been proposed to inhibit the growth of eukaryotic cells by disrupting protein biosynthesis.[7-9] Additional members of the Amaryllidaceae anticancer constituents include *trans*-dihydronarciclasine and 7-deoxy-*trans*-dihydronarciclasine, which were first synthetically prepared by hydrogenation of the double bond in their corresponding congeners[10] and then isolated from natural sources.[11,12]

The most promising spectrum of biological activities, however, resides with the isocarbostyril (+)-pancratistatin, isolated by Pettit and coworkers in 1984 from the bulbs of Hawaiian *Hymenocallis littoralis* (originally *Pancratium littorale*) in a low yield of 0.028%.[13,14] Additional sources of this natural product were found later and include *Haemanthus Kalbreyeri* (India),[15] *Hymenocallis Pedalis* (Seychelles), *Hymenocallis speciosa* (Singapore) and *Hymenocallis sonoranensis* (Mexico).[16] Also, frozen extracts of the Texas grasshopper *Brachystola magna* from 1967, which were only analyzed recently, were found to have 0.041% pancratistatin.[17] The structure of pancratistatin was determined by NMR spectral analysis and confirmed by the determination of an X-ray crystal structure of pancratistatin monomethyl ether.[13] The X-ray structure of the natural product itself was obtained later.[17] Similarly to narciclasine/7-deoxynarciclasine pair, pancratistatin was found to have its naturally occurring 7-deoxy congener, isolated by Ghosal and coworkers in 1989 from *Haemanthus Kalbreyeri*.[15]

The interest in pancratistatin stems from its strong *in vitro* cancer cell growth inhibitory activities against the US National Cancer Institute (NCI) panel of cancer cell lines, showing a highly characteristic differential cytotoxicity profile with a pronounced activity towards the melanoma panel of cell lines as well as a number of *in vivo* experimental cancer systems.[12,14] Powerful antiviral[18] and antiparasitic[19] activities of pancratistatin constitute a related area of promise. Importantly, it has been noted that pancratistatin and 7-deoxypancratistatin are the only known agents (other than an interferon inducer) to show a significant chemotherapeutic efficacy in a Japanese encephalitis virus-infected mouse model.[18] Based on its structural similarity to narciclasine, pancratistatin has been surmised to exert its antitumor effect through the disruption of protein biosynthesis.[7-9] Notwithstanding, some recent intriguing data have indicated the involvement of an antiangiogenesis/vascular targeting mechanism for *in vivo* neoplastic disease.[20,21] Additional promising data were recently reported by Pandey and coworkers, who investigated the effects of pancratistatin on normal and cancer cells, providing evidence supporting selective toxicity of this isocarbostyril to cancer cells.[22-24] In contrast, such chemotherapeutic drugs as paclitaxel and etoposide show toxicity to both cell types. The authors speculate that pancratistatin may take advantage of the differences between mitochondria in cancerous and non-cancerous cells to selectively induce apoptosis in the former cell types. These experiments bode well for the clinical development of this anticancer agent.[19,20,25,26]

Because of the structural complexity of the natural product, several research groups have synthesized and evaluated for anticancer activity numerous simplified pancratistatin analogues. Unfortunately, so far such efforts have not resulted in compounds with medicinal potential comparable to that of the natural product itself. All three rings, A, B and C (*Fig. 1*) have been targeted for modifications. Removal of the oxygen substituents on ring A leads to significant reduction of potency. 7-Deoxypancratistatin is about 10-fold less potent,[27] while analogue **1** (*Fig. 2*) with a single alkoxy group, prepared by Hudlicky and coworkers,[28] is 100-fold less cytotoxic than pancratistatin. The interesting bioisosteric replacement of the methylenedioxybenzene ring with the indole moiety as in compound **2**, also prepared by Hudlicky and coworkers, leads to essentially complete loss of *in vitro* anticancer activity.[29,30]

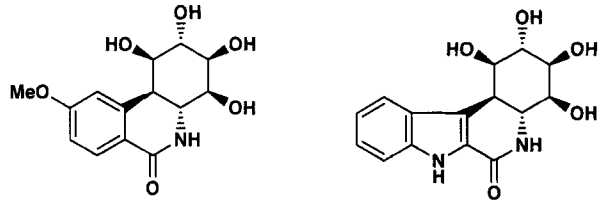


Fig 2

Numerous analogues have been prepared to evaluate the criticality of the *trans* B-C ring junction stereochemistry and the integrity of ring B itself for the anticancer activity of pancratistatin. Compound **3** lacking the C10a-C10b bond[31] and **4**, a lactone analogue of narciclasine synthesized by Chapleur and his coworkers,[32] did not show any significant anticancer activity *(Fig. 3)*. C10b-(S)-epimers of 7-deoxypancratistatin[33] and pancratistatin[34] (**5** and **7**) as well as the analogue possessing the C10b-(*R*)-hydroxyl (**6**)[35] exhibited significantly reduced potencies or were completely inactive. From the above data it can be concluded that the *R*-stereochemistry of the C10a-C10b bond of pancratistatin is crucial for activity.

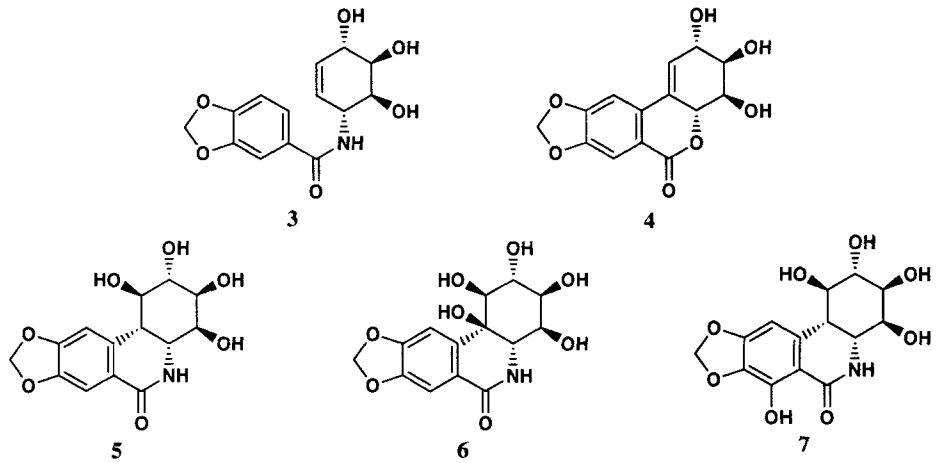


Fig 3

Recently, Kornienko and coworkers[36] synthesized ring B opened analogues **8a-e**, **9a-e** and **10a-e**, which possess this essential C10a-C10b bond with the correct stereochemistry (*Fig. 4*). Unfortunately, none of the analogues showed any significant anticancer activity.

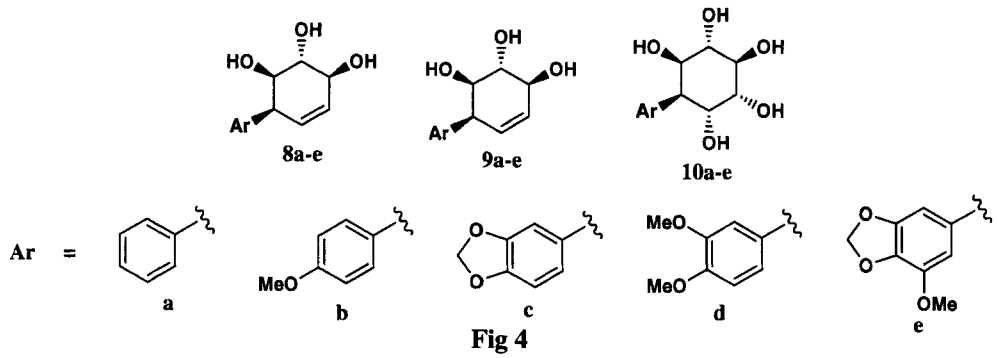


Fig 4

Finally, synthetic work aimed at simplification of ring C by various investigators produced several deoxygenated analogues (*Fig. 5*). Compounds **11**, **12** and **13** were prepared by McNulty and coworkers,[37,38] while diol **14** was reported by Hudlicky and coworkers.[39] **11** and **12** were found inactive, **13** is on average 2-3 orders of magnitude less potent than pancratistatin in the NCI 60 cell line screen, while **14** only showed low micromolar growth-inhibitory potency against the murine P388 cell line but was completely inactive against a panel of human cancer cell lines.

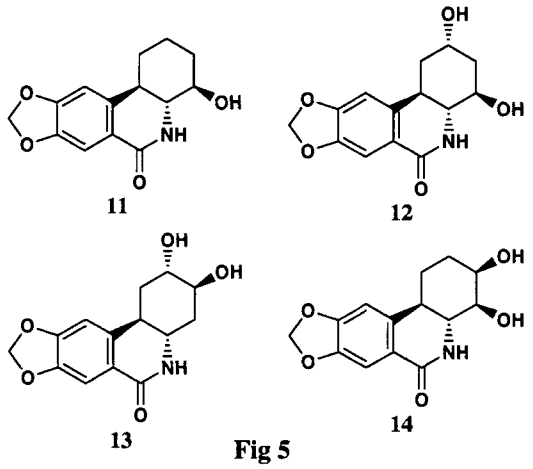


Fig 5

The lack of promising activity associated with the above-mentioned structurally simplified analogues underscores the importance of all elements of complexity present in the structure of pancratistatin. This makes the development of a practical chemical synthesis of the natural isocarbostyril an important research direction, which has been pursued by several dozen groups worldwide. Several excellent reviews discussing the synthetic work in the area of

Amaryllidaceae anticancer constituents have appeared.[2,3,4,40,41,42] The purpose of this review is a detailed description and comparative evaluation of the nine total syntheses of pancratistatin reported to date.

While pancratistatin is not a large molecule, it has a number of elements of complexity. Perhaps, the combination of these two factors is what makes this target a formidable challenge. The small overall structure harbors six stereogenic centers, all of which are located on ring C. The pentasubstituted aromatic ring A requires a regiocontrolled introduction of the aromatic substituents, such that the groups installed first dictate the positioning of the subsequent aromatic derivatization. Furthermore, the lactam ring B is highly strained, because the *trans* fusion with ring C distorts the planarity created by the four atoms in the sp^2-hybridization state (C10a, C6a, C6 and C5). While with larger molecules different individual segments can be worked on independently, the high density of structural complexity in pancratistatin requires a thoroughly designed synthetic plan, in which each step must be scrutinized in the context of the entire molecule rather than its small portion.

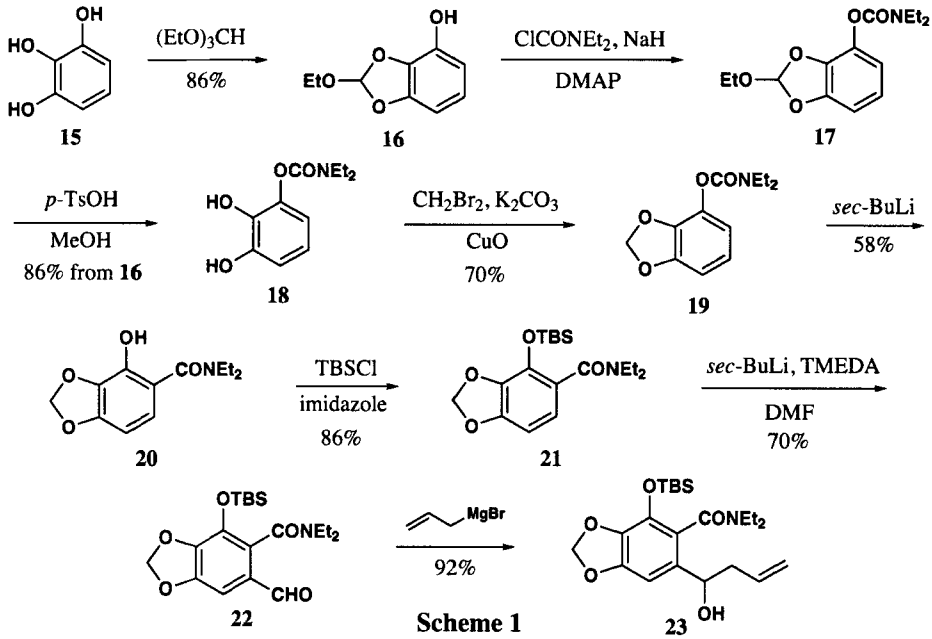
Nine strategies have resulted in completed synthetic pathways to pancratistatin. The description of each synthesis will be split into two sections. The first one, entitled "synthetic sequence and tactical nuances," will detail the entire pathway along with various problems encountered by investigators and their corresponding solutions. The second section, entitled "evaluation of the strategy," will summarize and evaluate how the structural complexity issues were resolved. Of these, we will focus on (a) choice of the starting material, (b) strategy for achieving the asymmetric synthesis if only (+)-enantiomer of the natural product was prepared, (c) installation of stereocenters in the stereo-congested ring C, (d) strategy for closure of ring B, containing the strained lactam moiety, and (d) regioselective introduction of the substituents in the pentasubstituted aromatic ring A.

I. FIRST SYNTHESIS OF (±)-PANCRATISTATIN BY DANISHEFSKY'S GROUP (1989)

1. Synthetic Sequence and Tactical Nuances

Danishefsky and Lee accomplished the first total synthesis of racemic pancratistatin in 1989, starting from readily available pyrogallol (**15**, *Scheme 1*).[43] The major features of the synthetic design involve the Diels-Alder reaction to construct ring C and the Overman rearrangement to introduce the nitrogen with the correct stereochemistry in lactam ring B.

Reaction of **15** with triethylorthoformate gave orthoester **16**, whose carbamoylation was achieved with diethylcarbamoyl chloride *(Scheme 1)*. Subsequent methanolysis of **17** and installation of the methylenedioxy moiety by treatment of the intermediate diol **18** with methylene bromide in the presence of potassium carbonate and copper (II) oxide afforded selectively protected trioxybenzene **19**. The carbonyl group of the carbamate functionality then served as a handle for directed lithiation of the adjacent free *ortho*-position in **19** with *sec*-butyl lithium to

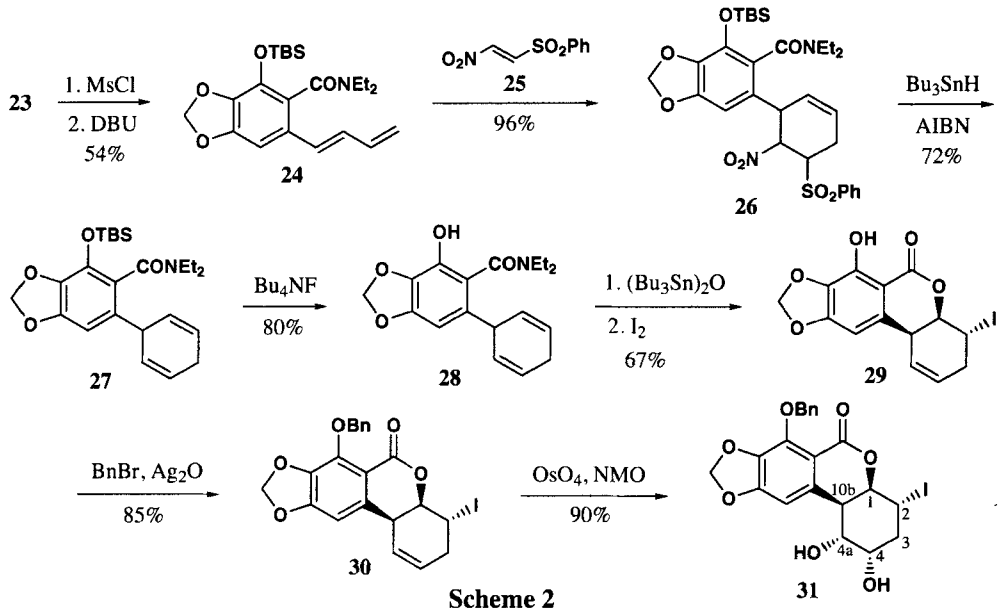


Scheme 1

generate an intermediate aryl lithium species, which underwent the Snieckus rearrangement[44] to yield tetra-substituted aromatic compound **20**. The phenolic hydroxyl was protected using TBS group and second metalation with *sec*-butyl lithium followed by addition of DMF gave penta-substituted aromatic aldehyde **22** in 70% yield. Thus, the selective protection of **15** and the sequential lithiation strategy allowed for the introduction of all substituents in the aromatic ring with complete regiocontrol.

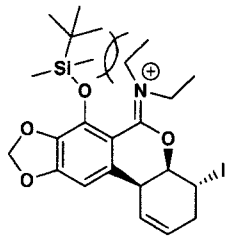
To prepare the required diene **24** for the Diels-Alder cycloaddition, aldehyde **22** was treated with allylmagnesium bromide and the resulting alcohol group was converted to the mesylate ester (*Scheme 2*). Elimination of the mesylate to install the double bond was achieved by treatment with DBU to form the desired diene **24**. The Diels-Alder reaction of diene **24** with β-nitrovinyl sulfone **25**, a known acetylenic dienophile equivalent,[45,46] proceeded in 96% yield to give cycloadduct **26**. Radical elimination of the nitro and the benzenesulfonyl groups was accomplished by treatment of **26** with AIBN/Bu_3SnH. In preparation for iodolactonization the TBS ether was removed using Bu_4NF to give phenol **28**. Removal of the silyl group was necessary, since halolactonization under various conditions was not successful due to the increased repulsive forces between the large OTBS group and the hypothetical intermediate diethyl imminium ion as shown in **32** *(Fig. 6)*.

Still, iodolactonization of **28** was not successful. Here it was reasoned that the amidic carbonyl in **28** was not nucleophilic enough to accomplish the ring opening of the iodonium ion. Stannylation of the phenolic hydroxyl increased the nucleophilicity of the carbonyl oxygen[47] and the lactonization proceeded in 67% yield in the presence of I_2 in THF to form **29**.



Scheme 2

This transformation allowed the investigators to introduce the *cis*-C10b-C1 relationship. The phenolic OH was now protected as a benzyl ether to give **30** in 85% yield. Efforts towards



32

Fig 6

elimination of HI to install the C2-C3 double bond by treating with a base resulted in the formation of the fully aromatic ring C in **34** *(Fig. 7)*.

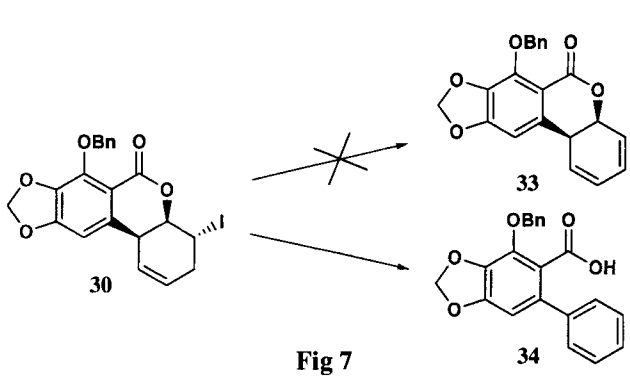
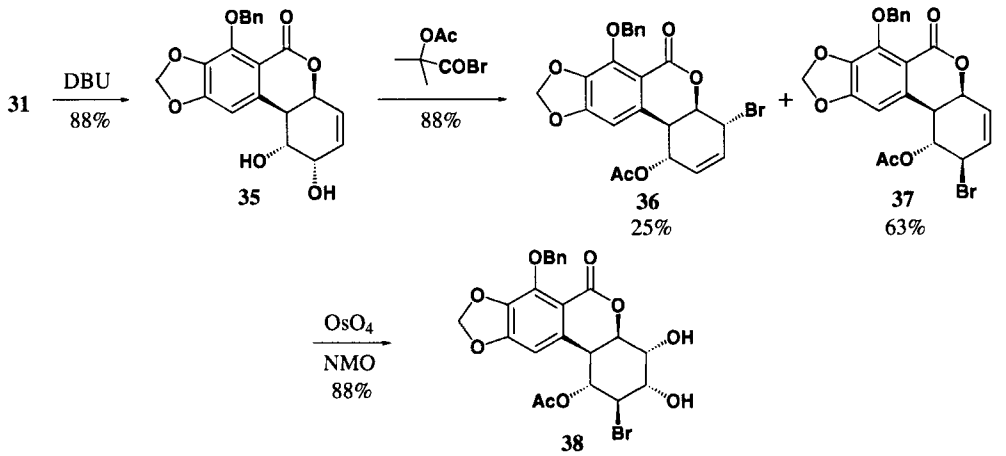


Fig 7

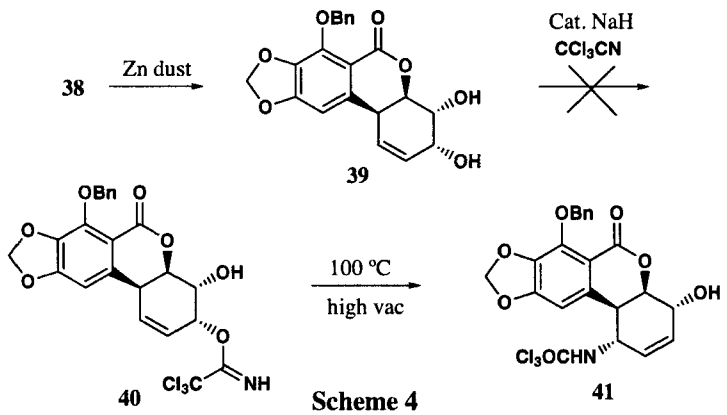
To solve the aromatization problem, the double bond was dihydroxylated using catalytic OsO_4 and NMO to give **31** as a single stereoisomer in 90% yield. This transformation led to trouble-free elimination of HI when **31** was treated with DBU to give **35** (*Scheme 3*).



Scheme 3

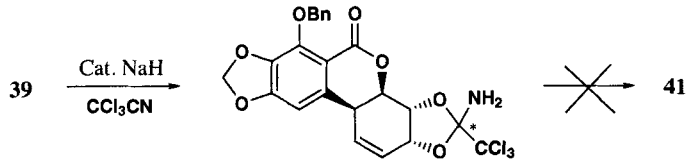
Before introducing the C2-C3 *cis* functionality, the investigators prepared for the regiospecific reductive elimination of the C4a and C4 heteroatoms by converting the *cis*-C4a-C4 diol into *trans*-bromoacetate by treatment of **35** with 2-acetoxy-*iso*-butyryl bromide.[48,49] This reaction resulted in formation of **37** in 63% yield along with 25% yield of the allylic isomer **36**. Dihydroxylation of **37** with OsO_4/NMO proceeded selectively from the less hindered α face due to the presence of the C1- and C4-substituents blocking the β face to give **38**.

To introduce the C4a-α-amino moiety, the researchers relied on the Overman rearrangement[50] that could be accomplished by the reductive removal of the *trans* bromoacetate, conversion of the allylic hydroxyl to imidate followed by suprafacial [3,3]-sigmatropic rearrangement to give the desired compound **41** *(Scheme 4)*.



Scheme 4

However, the reaction of **39** with trichloroacetonitrile led to the formation of the cyclic orthoamide as a mixture of two diastereomers **42** and **43** which did not undergo the Overman rearrangement (*Scheme 5*).



42, 43

Scheme 5

To overcome the formation of the orthoamide, the C2 hydroxyl had to be blocked. This was achieved by the reaction of **38** with *bis*(di-*n*-butyltin)oxide and further treatment of the resultant stannylene with *p*-methoxybenzyl bromide to give **44** in 84% yield.

The C2 hydroxyl group was now protected as benzyl ether and the PMB protection was removed by the treatment of **45** with DDQ to give **46** *(Scheme 6)*. Upon treatment with Zn dust acetoxy bromide **46** formed the desired C2-protected allylic alcohol **47**. Reaction of **47** with NaH and trichloroacetonitrile gave **48** in 74% yield and, as expected, **48** under thermal conditions underwent suprafacial [3,3]-sigmatropic reaction to give **49** in 56% yield. Dihydroxylation of **49** to install the C3-C4 hydroxyl functional groups proceeded from the β face due to the presence of the C2 and C4a α-functionality. This concluded the installation of all six stereocenters in ring C. Under basic conditions the lactone ring was opened to form the intermediate amino acid **51** that in the presence of DCC cyclized to form the *trans* fused lactam **52** in 82% yield. Deprotection of the benzyl ether gave racemic pancratistatin with an overall yield of 0.13% over 27 steps.

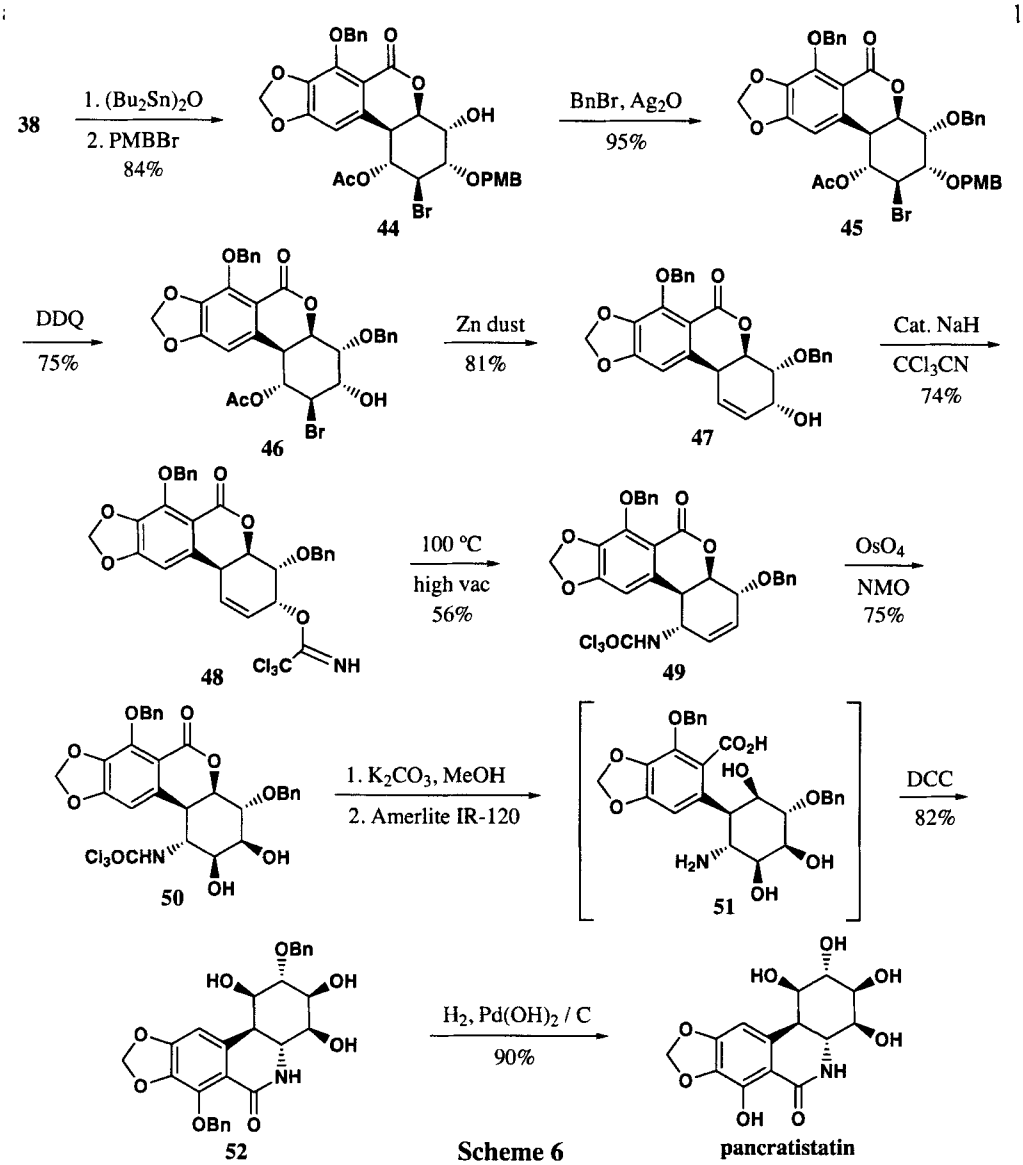
2. Evaluation of the Strategy

a) Starting Material. The synthetic effort started with inexpensive achiral pyrogallol (**15**, *Scheme 7*), which incorporates three oxygen-bearing centers found in ring A of pancratistatin.

b) Asymmetric Strategy. Racemic target natural product was synthesized.

c) Installation of Stereocenters. Ring C was formed by the Diels–Alder reaction and iodolactonization of the diene **27** allowed the introduction of the C10b-C1 *cis* geometry in pancratistatin. Various problems encountered at this stage were resolved by deprotection of the bulky silyl group and stannylating the phenolic hydroxyl to improve the nucleophilicity necessary to open the iodonium ion ring to form the lactone **29**. The key step resulting in installation of the C4a-nitrogen functionality involved the [3,3]-sigmatropic rearrangement of imidate **48**. This suprafacial transformation gave the *trans* C10b-C4a relationship. Finally β-orientation of the C4a and C2 substituents in **37** guided the dihydroxylation of the double bond from the less hindered α-face to introduce the C3-C4 *cis* hydroxyl groups.

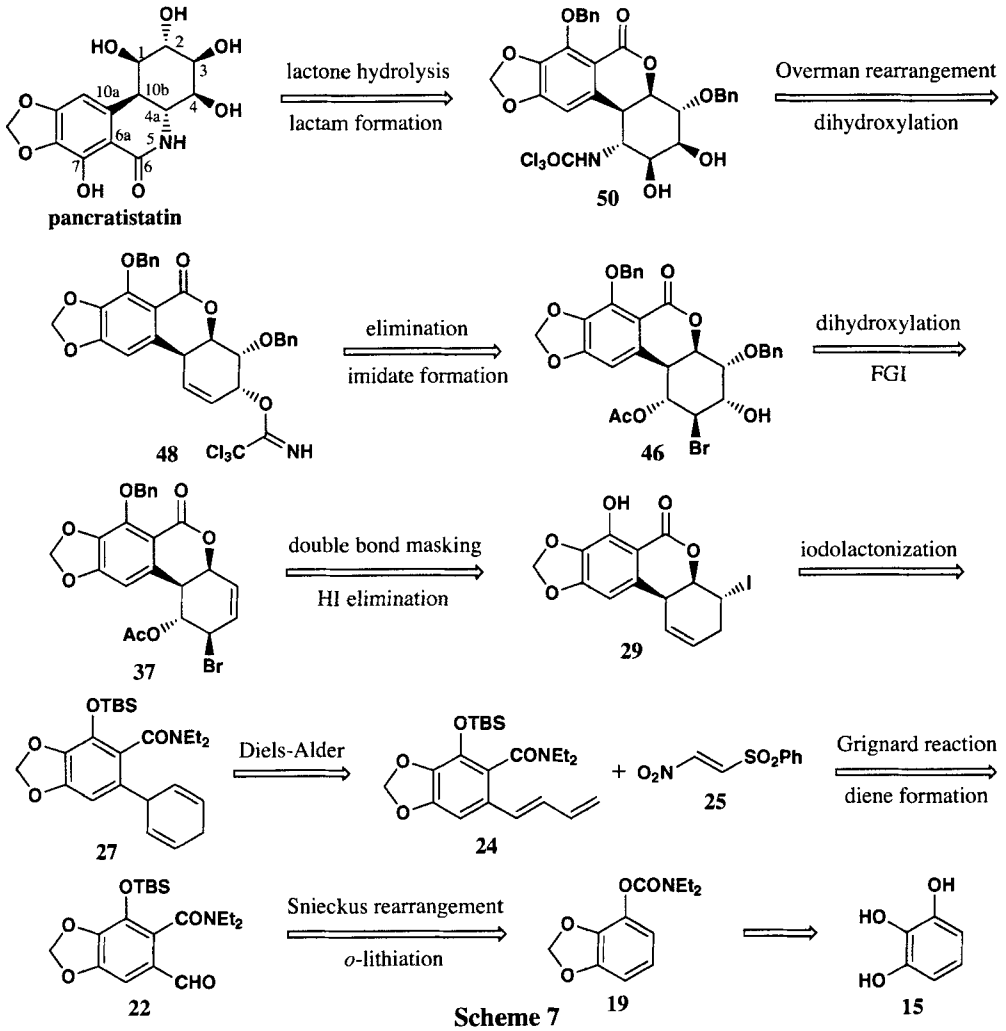
d) Lactam Formation. The C6 carbonyl of pancratistatin was introduced early in the synthesis



Scheme 6

was engaged as a lactone with the C1 hydroxyl. Hydrolysis of the lactone after installing the C4a amino group with the right stereochemistry allowed for the formation of the *trans* lactam in the presence of the coupling reagent DCC.

e) Regioselective Introduction of the Substituents on the Aromatic Ring. The starting material pyrogallol has three hydroxyl groups, two of which were selectively protected as methylene-dioxy moiety and the third one was carbamoylated. Snieckus rearrangement of **19** installed the C6 carbonyl and another metalation reaction of **21** led to the introduction of the aldehyde group that was transformed into C10a-C10b bond later in the synthesis.



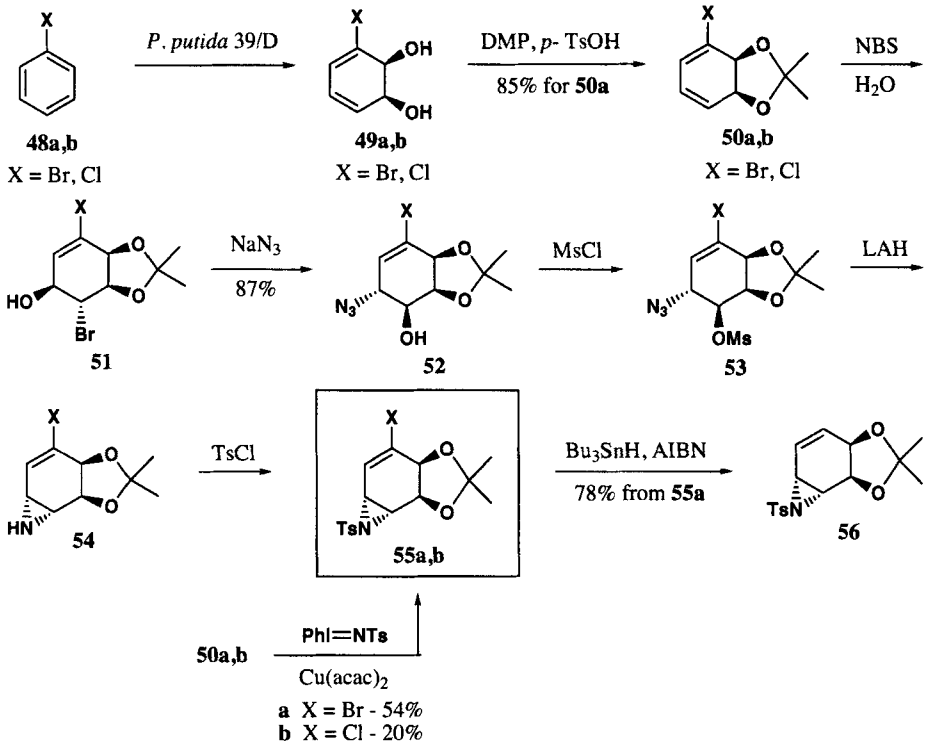
Scheme 7

II. CHEMOENZYMATIC SYNTHESIS OF (+)-PANCRATISTATIN BY HUDLICKY'S GROUP (1995)

1. Synthetic Sequence and Tactical Nuances

Hudlicky's group successfully employed a *trans* aziridine ring opening process with a higher order cuprate reagent to achieve the first asymmetric synthesis of (+)-pancratistatin.[51,52]

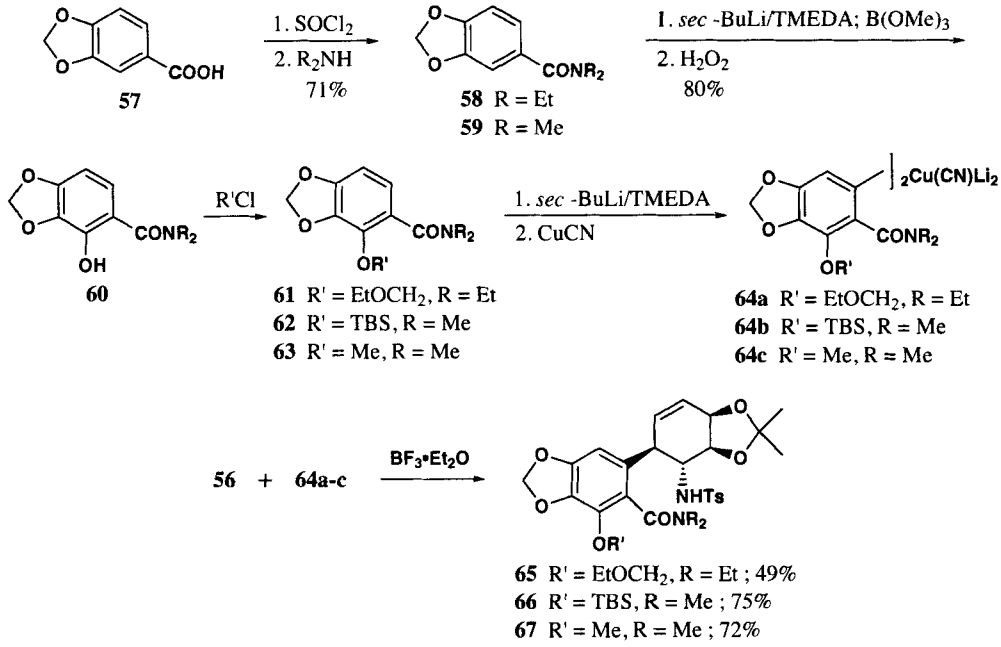
The synthesis commenced (*Scheme 8*) from bromobenzene or chlorobenzene and their oxidation to enantiomerically pure diols **49a,b**, by the whole cell fermentation with *Pseudomonas putida* 39/D1.[53] These were protected as their respective acetonides to form **50a,b**. To reach the desired aziridines **55a,b**, two independent paths were pursued. One involved treatment of **50a,b** with NBS followed by aqueous work-up, which gave bromohydrins **51**. The latter were reacted with sodium azide to afford hydroxy azides **52**, possibly via the intermediacy of the



Scheme 8

β-epoxides. Subsequent mesylation and azide reduction was accompanied by aziridine formation to give **54**. These were tosylated to give tosyl aziridines **55a,b**. A much shorter route involved the direct treatment of **50a,b** with Yamada's iodonium ylide[54] to give α-aziridines **55a,b** in 54% and 20% yields respectively. Bromide **55a**, which was obtained in significantly higher yield than the corresponding chloride **55b**, was further dehalogenated to furnish vinylaziridine **56** in good yield.

The aromatic ring A of pancratistatin was synthesized using piperonic acid (**57**, *Scheme 9*) as a starting material. Treatment of **57** with thionyl chloride followed by diethyl or dimethyl amines gave amides **58**, **59**. The phenolic OH at C7 of pancratistatin was installed by *o*-lithiation of the amides using *sec*-BuLi/TMEDA and quenching with trimethylborate followed by oxidation with hydrogen peroxide. The resulting phenols **60** were protected as ethers **61**, **62** and **63**. Second lithiation at the other *ortho* position of the amide directing groups and transmetalation using CuCN gave the higher order cuprates **64a-c**. The researchers investigated the nucleophilic ring opening of vinylaziridines under various conditions[55,56,57] and found that lithium dimethylcyanocuprate gave *syn*-1,4-addition product, while lithium diphenylcyanocuprate resulted in formation of *anti*-1,2-addition product. With these encouraging results obtained with higher order cuprates, the reactions of **64a-c** with aziridine **56** were performed. As expected the *anti*-



57

58 R = Et
59 R = Me

60

61 R' = $EtOCH_2$, R = Et
62 R' = TBS, R = Me
63 R' = Me, R = Me

64a R' = $EtOCH_2$, R = Et
64b R' = TBS, R = Me
64c R' = Me, R = Me

65 R' = $EtOCH_2$, R = Et ; 49%
66 R' = TBS, R = Me ; 75%
67 R' = Me, R = Me ; 72%

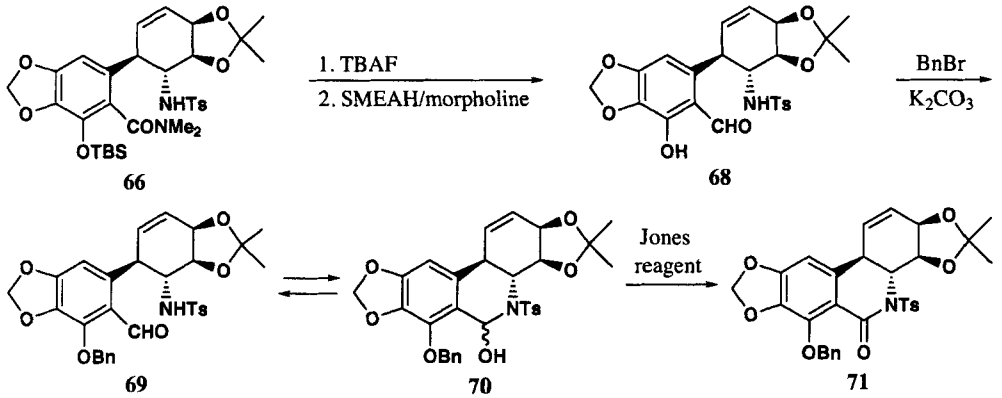
Scheme 9

1,2-addition products **65**, **66** and **67** were obtained in 49%, 75% and 72% yields, and this accomplished the construction of the carbon skeleton of pancratistatin.

Various routes were explored to achieve the cyclization to form ring B. Transamidation using *sec*-BuLi at -15 °C utilized earlier by Heathcock and coworkers[58] for the synthesis of pancratistatin models failed to induce cyclization in **65**, possibly due to the allylic and benzylic nature of the C10b hydrogen, and therefore, its enhanced acidity. Efforts to convert the benzamide group into a more versatile group that could facilitate cyclization failed, since the benzamide was resistant to various hydrolysis and reduction conditions, possibly due to the presence of the bulky *ortho* substituents.

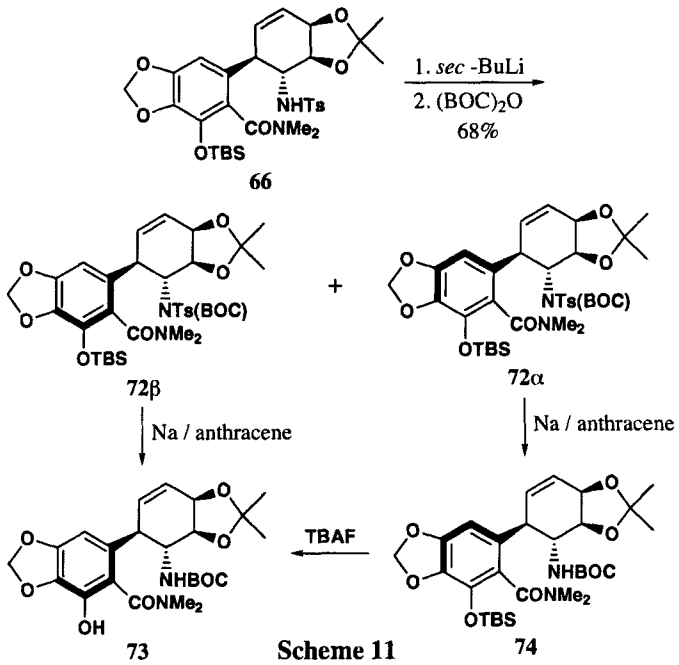
After extensive experimentation the investigators focused on TBS-protected benzamide **66** to complete the synthesis of pancratistatin. Removal of the silyl protection using TBAF (*Scheme 10*) and reduction of the benzamide to the corresponding aldehyde using sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) gave aldehyde **68**. Protection of the phenolic hydroxyl as benzyl ether gave **69**, which existed as a mixture with hemiaminal **70**. Oxidation of this mixture with Jones reagent gave **71**. Various attempts to remove the tosyl-protecting group under a number of reductive conditions led to disappointing results reforming hemiacetal **70**. It was reasoned that the lactam ring in **71** is highly strained forcing the sp^2 carbonyl to form a tetrahedral intermediate, and therefore, removal of the tosyl group at an earlier stage was imperative.

At this stage it was also observed that compounds **65** and **66** existed as α and β atropisomers. Boc protection of **66** formed a mixture of atropisomers **72α** and **72β** in 68% yield



Scheme 10

(*Scheme 11*). The α isomer in which the carbonyl oxygen participates in hydrogen bonding with the sulfonamide NH showed much reduced reactivity due to steric congestion as can be seen in *Fig. 8*.



Scheme 11

Treatment of the mixture of **72** with Na/anthracene led to the formation of desilylated β-atropoisomer **73** and α-isomer **74** in 82% combined yield. α-Isomer **74** was isolated and desilylated using TBAF to give **73** as a single compound.

Reduction of benzamide **73** using SMEAH/morpholine then gave aldehyde **75** (*Scheme 12*). The latter was protected as benzyl ether and oxidized with sodium chlorite to give acid **77**.

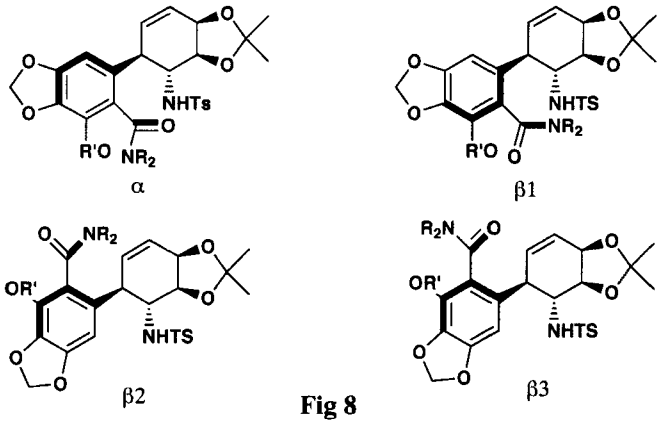
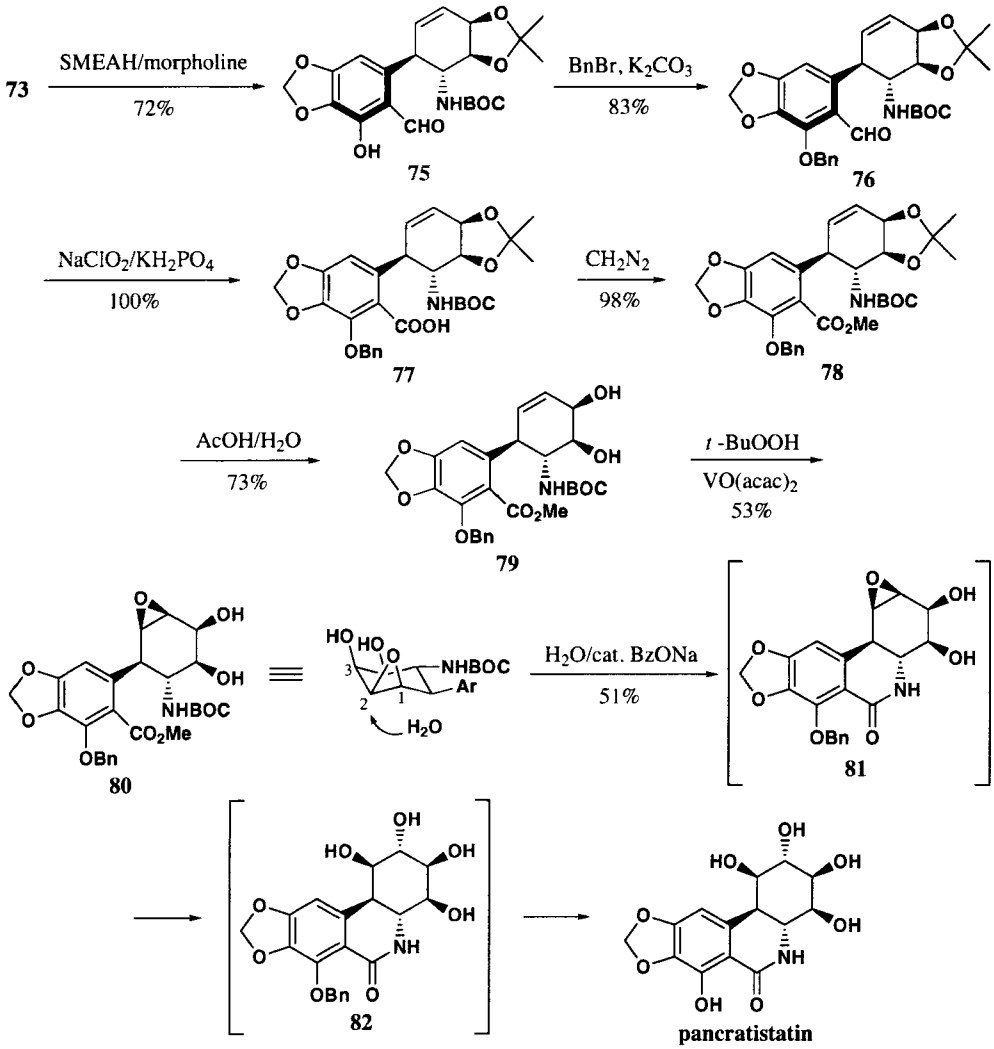


Fig 8

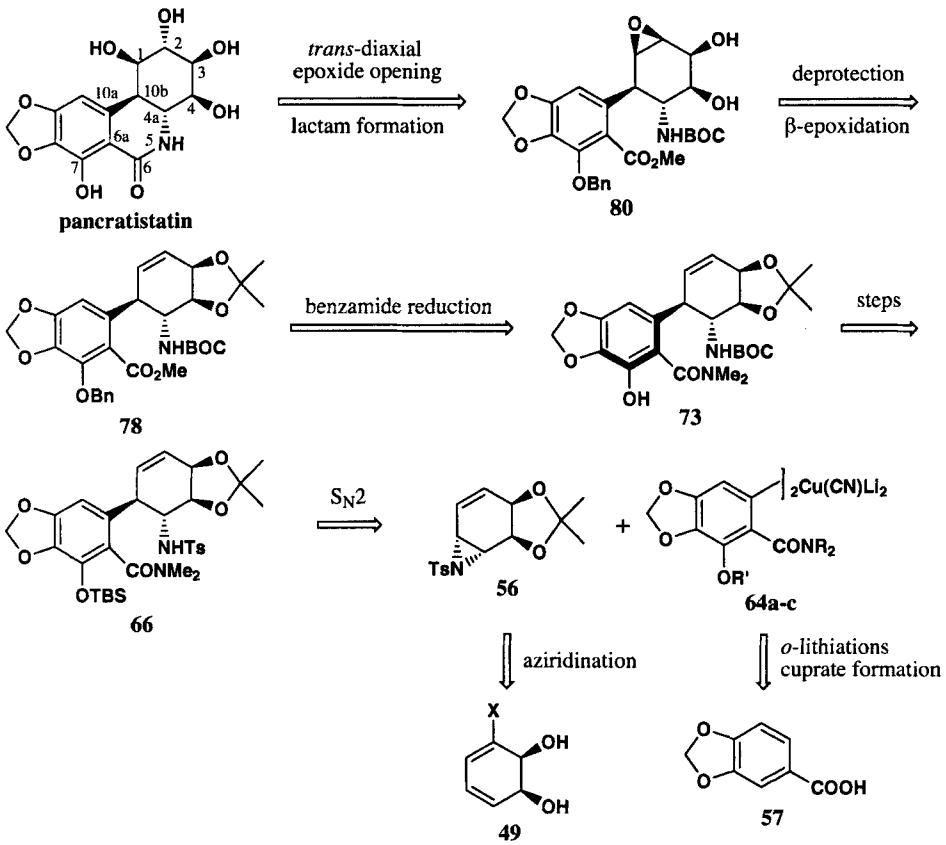


Scheme 12

Subsequent methylation using diazomethane afforded metyl ester **78** in quantitative yield. The presence of the bulky Boc protecting group, however, disfavored cyclization of the acid or the ester under various conditions. The removal of the Boc protecting group to form the primary amine using trifluoroacetic acid led to the desired cyclization, but also resulted in migration of the olefin to the conjugated C10b-C1 position. To avoid further complications, the acetonide group was cleaved and epoxidation of diol **79** using *t*-BuOOH/VO(acac)$_2$ formed β-epoxide **80** as a single compound. Finally, refluxing **80** in water in the presence of catalytic sodium benzoate resulted in a number of desired transformations. These conditions led to the cleavage of the Boc group, cyclization to form the lactam as well as trans-diaxial opening of the epoxide at C2 position to give pancratistatin in 51% yield for this transformation. Overall, the target natural product was reached in 14 steps and 2 % yield starting from bromobenzene.

2. Evaluation of the Strategy

a) Starting Material. The synthesis began with the microbial oxidation of readily available halobenzenes to give compounds **49**, which have two hydroxyl groups found in pancratistatin already



Scheme 13

present. In addition, the two double bonds differ in reactivity patterns making selective transformations possible.

b) Asymmetric Strategy. Toluene dioxygenase enzyme-mediated enantiospecific dihydroxylation of halobenzenes formed the basis for the introduction of asymmetry in the molecule. Easily accomplished in one step, enzymatic oxidation of aromatic groups efficiently introduced C3-C4 *cis* hydroxyl groups, which control the stereochemical outcome of the crucial aziridination reaction.

c) Installation of Stereocenters. C3-C4 stereocenters are already present in diol **49**. Protecting the *cis* diol with isopropylidene moiety imparted steric blocking of the β-face of the diol forcing aziridination from the less hindered α-face. Regiocontrolled S_N2 opening of the aziridine led to the inversion at C10b, allowing the construction of C10a-C10b bond in the right configuration. Allylic alcohol-directed epoxidation gave β-epoxide **80**, whose trans-diaxial opening by H_2O resulted in the incorporation of C1-C2 hydroxyls with the required stereochemistry.

d) Lactam Formation. Though the authors envisioned the lactamization process at a much earlier stage of the synthesis, the failure to achieve the desired ring closure by *trans*-amidation and the facility of formation of the sp^3 hybridized hemiacetal **70** made the researchers redesign their strategy. In addition, the attempted cyclization by attack of the primary amine onto the methyl ester, led to the migration of the olefin to form the more stable conjugated system. However, epoxidation of the olefin and opening of the epoxide with H_2O/cat.BzONa facilitated lactamization without the accompanying olefin migration, and along with the concomitant epoxide opening provided an excellent solution to the earlier setbacks in the synthesis.

e) Regioselective Introduction of the Substituents on the Aromatic Ring. The arylcuprate required for the opening of the aziridine was synthesized from piperonic acid. Two sequential *ortho*-lithiation reactions of amides **58** and **59** accomplished the regioselective installation of the C7 hydroxy group of pancratistatin and gave rise to the formation of the necessary copper-carbon bond.

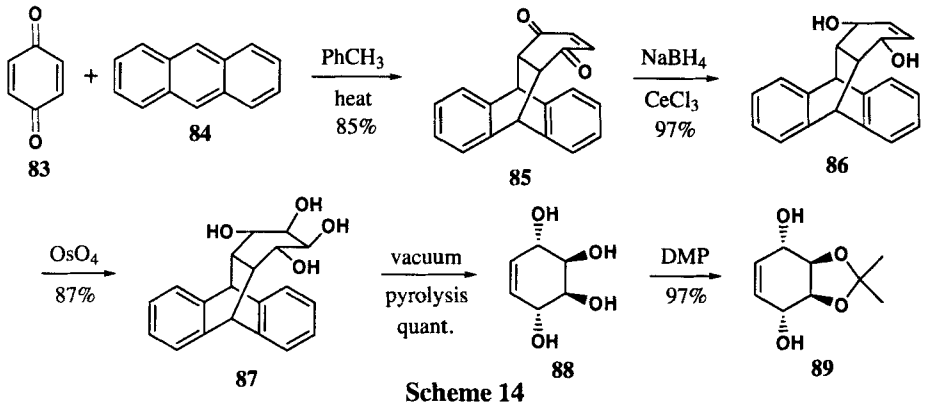
III. DESYMMETRIZATION ROUTE TO (+)-PANCRATISTATIN BY TROST'S GROUP (1995)

1. Synthetic Sequence and Tactical Nuances

Trost and coworkers described an asymmetric synthesis of (+)-pancratistatin[59] utilizing a palladium-catalyzed desymmetrization methodology developed by this group earlier.[60] The starting material of the synthesis was benzoquinone, which was converted to key conduritol derivative **89** following a known five-step procedure in 69% overall yield (*Scheme 14*).[61]

Diol **89** was treated with *n*-BuLi and methylchloroformate to form symmetric dicarbonate **90** (*Scheme 15*), which was subjected to a desymmetrization process in the presence of the palladium complex derived from the chiral ligand **A** (*Fig. 9*) and $TMSN_3$ as a source of azide nucleophile.

Azide **91** was obtained in >95% ee and 82% yield. The earlier mechanistic studies of Trost and coworkers revealed that ionization is the enantiodetermining step in the catalytic cycle



Scheme 14

of this highly selective process.[60] In addition, these investigators previously proposed a mnemonic rule[62] to predict the favored pathway for the enantioselective ionization, and the stereochemical outcome of the transformation **90** → **91** is fully consistent with these studies. Thus, the absolute sense of chirality for the amide ligand **A** can be reduced to representation **B**, highlighting the positioning of the large (L) and small (S) substituents on the bis-phosphine skeleton (*Fig. 9*). The energy difference of the two diastereomeric transition states, one leading to the

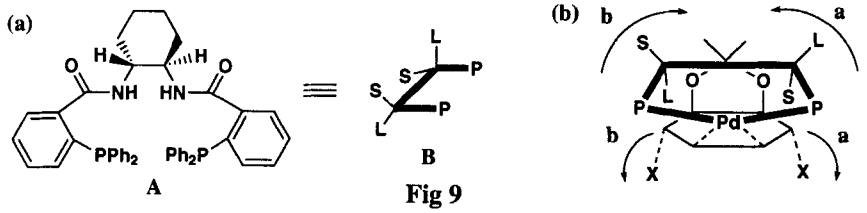
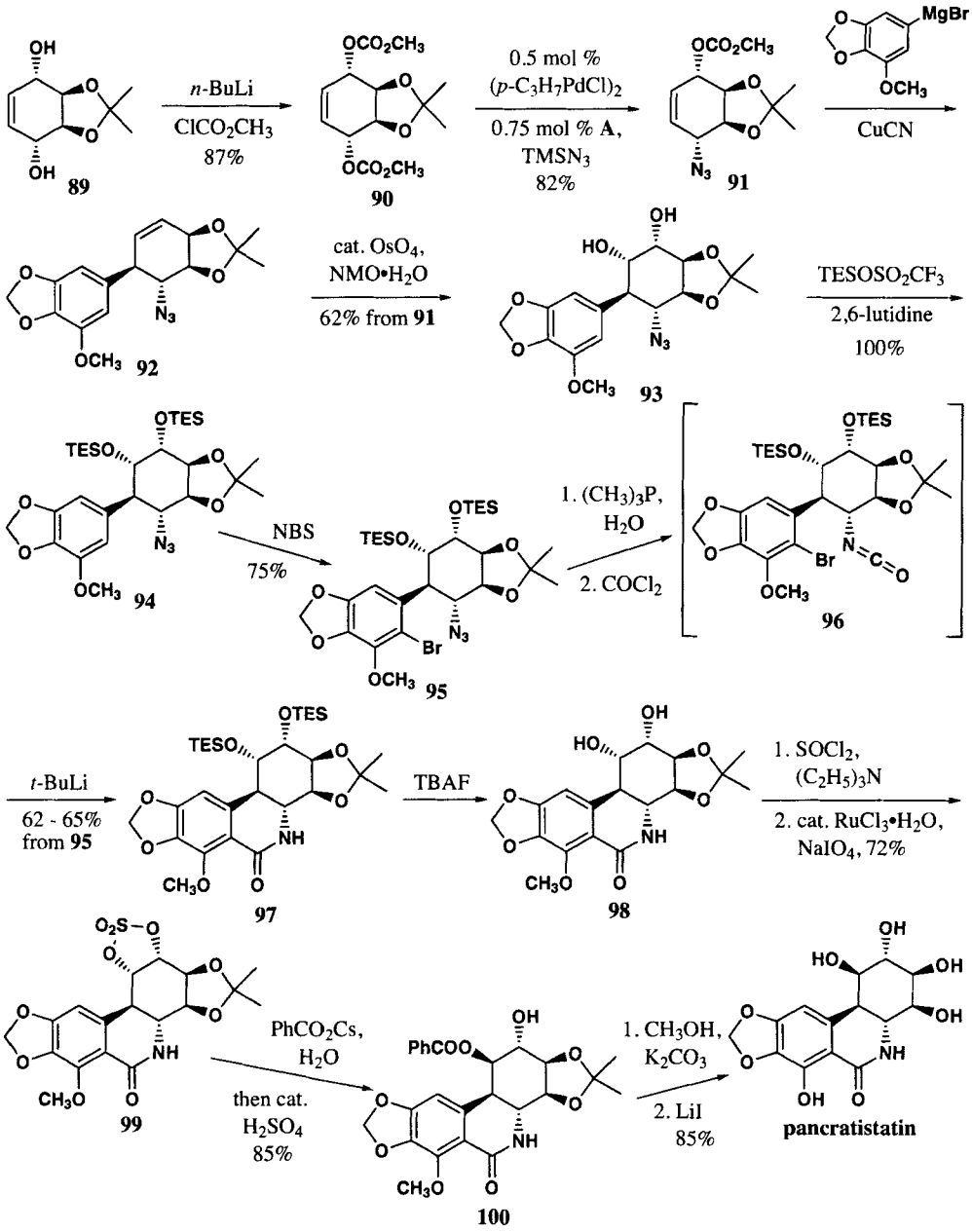


Fig 9

departure of the *pro-S* carbonate (path "a" in *Figure 9*) and the other that of the *pro-R* carbonate (path "b"), is controlled by the steric interaction of the substituents L and S with the rest of the cyclohexene ring, as the palladium complex turns counter-clockwise (a) or clockwise (b) respectively. The steric clash of the substituent L with the acetonide moiety virtually prevents the type "b" rotation and, consequently, the ionization of the *pro-R* carbonate.

With the key intermediate **91** in hand, regio- and diastereocontrolled S_N2' introduction of the aryl moiety was achieved by reaction of the requisite Grignard reagent with **91** in the presence of CuCN. Dihydroxylation of the resulting olefin **92** from the sterically more accessible α-face gave diol **93**, whose protection as bis-triethylsilyl ether proceeded quantitatively. The next crucial step in the synthesis was an intramolecular cyclization of the isocyanate, derived from the azido group in **94**, to form the lactam ring of pancratistatin. However, all efforts to induce such cyclization failed, leading to mixtures of products that appeared to have lost the acetonide protection. The investigators suspected that the ether oxygen of acetonide is more nucleophilic compared to the aromatic ring. Therefore, an alternate route involving the



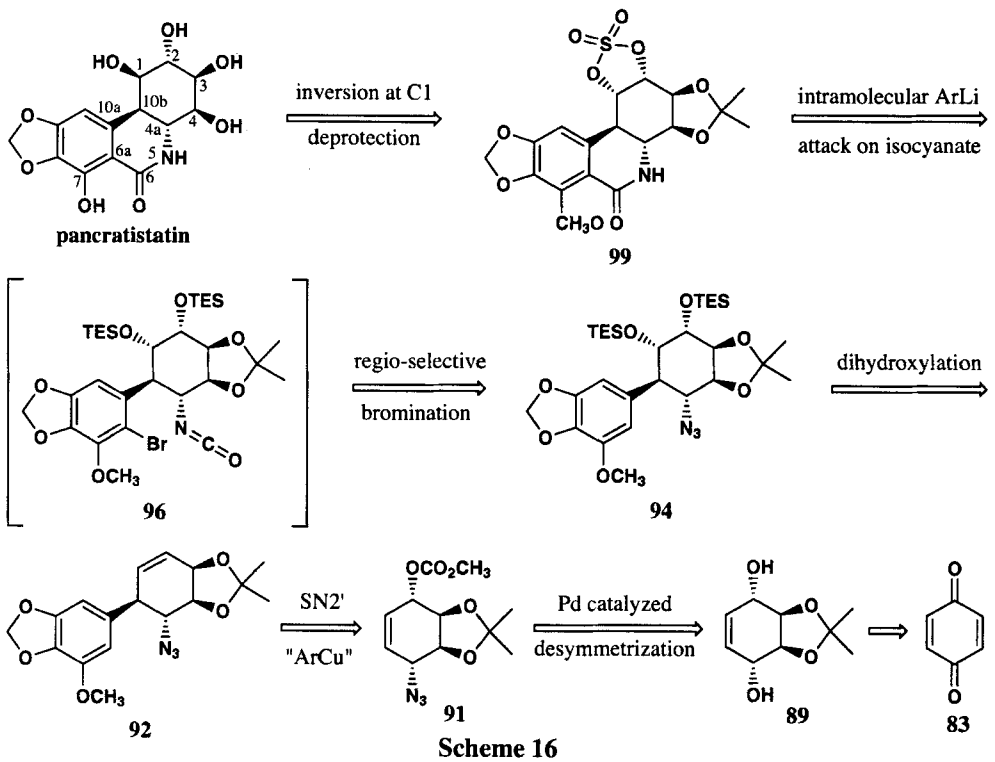
Scheme 15

conversion of the π-nucleophilic aromatic ring to a more powerful σ-nucleophilic species was undertaken. Thus, bromination of **94** *ortho*[63] to the methoxy group using NBS gave **95** in 75% yield. Isocyanate **96** was prepared from **95** using trimethyphosphine-mediated azide reduction and treatment with phosgene, and without purification **96** was reacted with *t*-BuLi. The lithium-bromine exchange was faster than the nucleophilic addition of *t*-BuLi to isocyanate and the

lithiated species immediately underwent intramolecular cyclization to form the desired lactam **97**. To achieve the right stereochemistry at the C1 position of pancratistatin, the silyl groups were removed and the resultant diol **98** was converted to cyclic sulfate **99**. It was hoped that the S_N2 opening with an oxygen-based nucleophile would occur at C1 position to avoid the steric interaction with the isopropylidene group. Indeed, nucleophilic ring opening of **99** using cesium benzoate occurred as predicted to give a benzoate, whose subsequent treatment with dilute sulfuric acid resulted in simultaneous cleavage of the alkyl sulfate and acetonide moieties to give **100** in 85% overall yield. Finally, methanolysis of the benzoate ester and cleavage of the methyl ether with lithium iodide yielded pancratistatin in 85% yield over the last two steps. The synthesis proceeded in 19 steps and 8% overall yield from benzoquinone.

2. Evaluation of the Strategy

a) Starting Material. Although the synthesis began with a complex conduritol derivative **89**, containing four stereocenters, the meso-symmetry of the latter allowed for its concise five-step preparation from benzophenone using a protocol reported previously by Rutledge and coworkers.[61]



Scheme 16

b) Asymmetric Strategy. The critical stereochemical design element of the pathway involved a palladium-catalyzed desymmetrization of conduritol **89**. The advantage of this process over a conventional kinetic resolution approach is undoubtedly the possibility of conversion of the

entire meso starting material to just one enantiomer of azide **91**. The investigators reported the enantiomeric excess value of > 95% for this transformation. Together with the high yield of 83% this approach rendered the asymmetric strategy an extremely efficient approach for the synthesis of pancratistatin in single enantiomeric form.

c) Installation of Stereocenters. In azide **91** the C3, C4 and C4a stereocenters are already in place. The regio- and diastereocontrolled allylic substitution of the C2-carbonate with an aryl-copper reagent resulted in formation of the C10b stereocenter with the correct configuration in **92**. The β-orientation of the C3 and C10b substituents allowed for facile installation of the two oxygen-bearing stereocenters at C1 and C2 from the α-face of the double bond. Finally, steric shielding of the C2 carbon by the acetonide moiety resulted in efficient stereochemistry inversion at C1 exclusively using ring opening of cyclic sulfate in **99** with benzoate ion.

d) Lactam Formation. The direct attack by the π-nucleophilc aromatic ring onto the isocyanate group failed, possibly due to the presence of a nearby oxygen at C4 and the subsequent deprotection of the acetonide moiety. However, conversion of the π-nucleophilic aromatic ring to a σ-nucleophilic one provided a nice solution to this problem, although it led to the necessity of prior bromination of the aromatic ring *ortho* to the methoxy group.

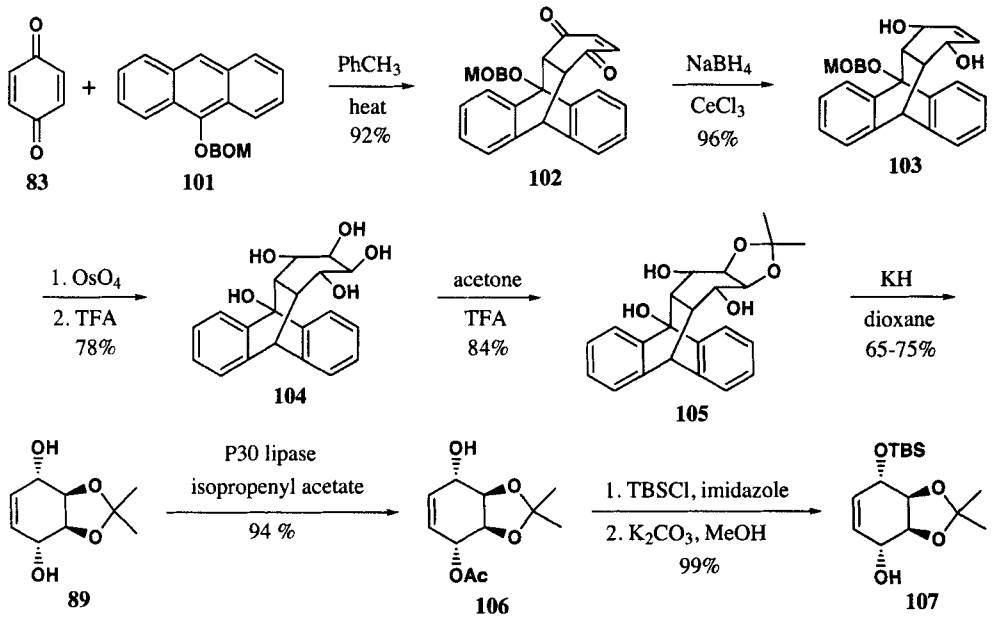
e) Regioselective Introduction of the Substituents on the Aromatic Ring. The aromatic bromide necessary for the preparation of the cuprate had been described in the literature before,[64,65] and therefore, azide **92** already had four out of five substituents correctly positioned on the aromatic ring. The problem of regioselectivity of the introduction the fifth substituent was solved by highly selective bromination at position C6a. A strong *para*-directing aptitude of the methylenedioxy group, compared to the alkoxy one, had been previously observed by other investigators[66-69] and this phenomenon is most likely due to a better overlap of the lone pair of electrons on oxygen atoms of the methylenedioxy group with the p-orbitals of the benzene ring.

IV. FORMAL SYNTHESIS OF (+)-PANCRATISTATIN BY HASELTINE'S GROUP (1997)

1. Synthetic Sequence and Tactical Nuances

In 1997 Haseltine and coworkers reported a total synthesis of (+)-pancratistatin,[70] which led to an intermediate in the Danishefsky's pathway. Thus, the synthetic sequence constitutes a formal synthesis of (+)-pancratistatin. Ring C of pancratistatin was constructed using the retro-Diels-Alder reaction of acetonide **105**, following the strategy developed by Knapp and coworkers *(Scheme 17)*.[71] In contrast to the thermally induced retro Diels-Ader reaction (*Scheme 14*), this original procedure utilized the "Evans Accelerating Effect" of the alkoxide brought about by treatment of alcohol **105** with potassium hydride. Desymmetrization using P30 lipase with isopropenyl acetate, silylation of the free hydroxyl and deacetylation afforded **107** in 93% yield over three steps.

The aromatic portion of pancratistatin was prepared from piperonol **108** (*Scheme 18*). The original plan involved the introduction of the C7 phenolic hydroxyl at an early stage

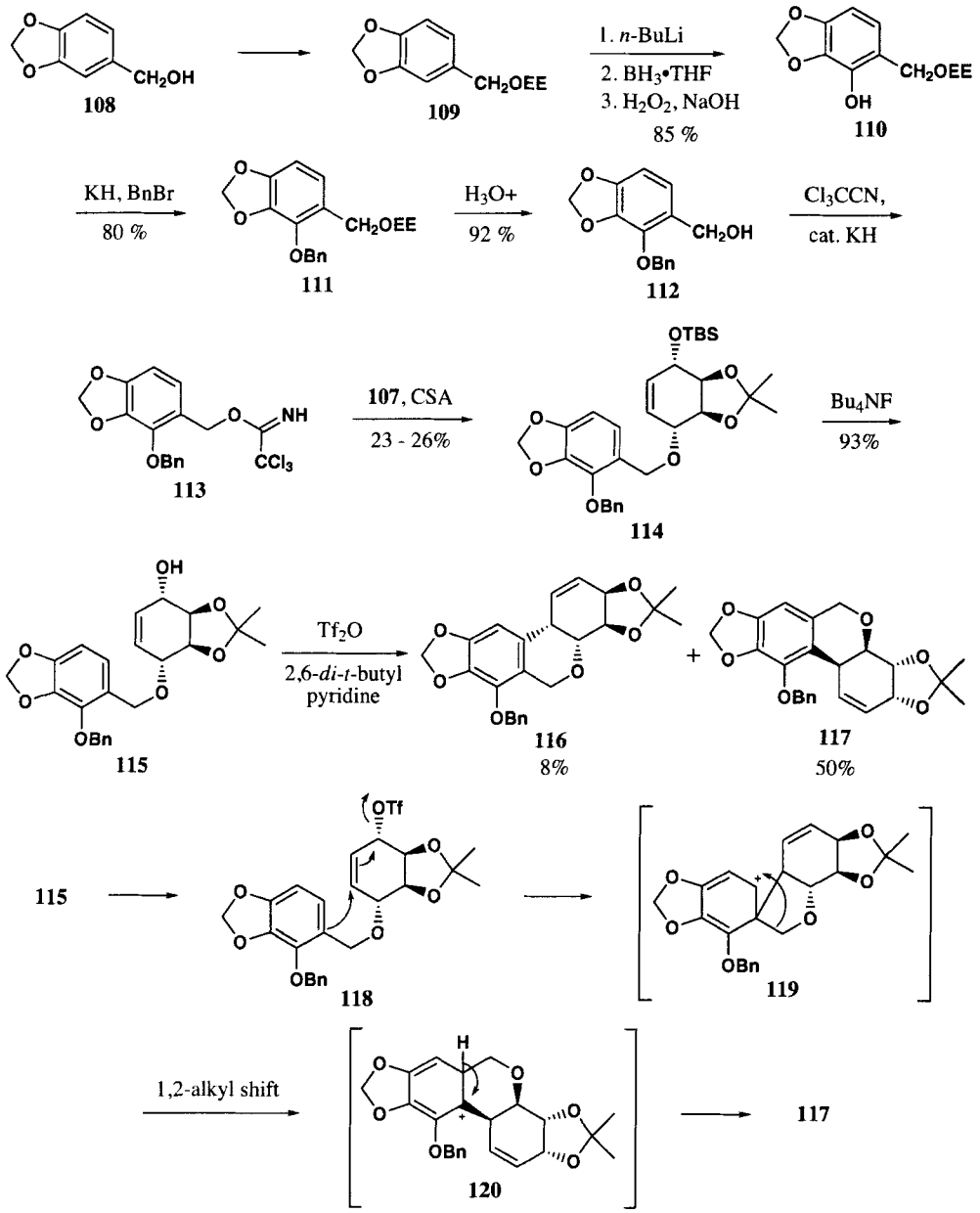


Scheme 17

by *o*-lithiation of the ethoxyethyl-protected piperonol and treatment with BH_3•THF to generate an intermediate arylborohydride, which was then oxidized with H_2O_2. The hydroxyl group in **110** was protected as benzyl ether and the ethoxyethyl protection was removed to give **112**.

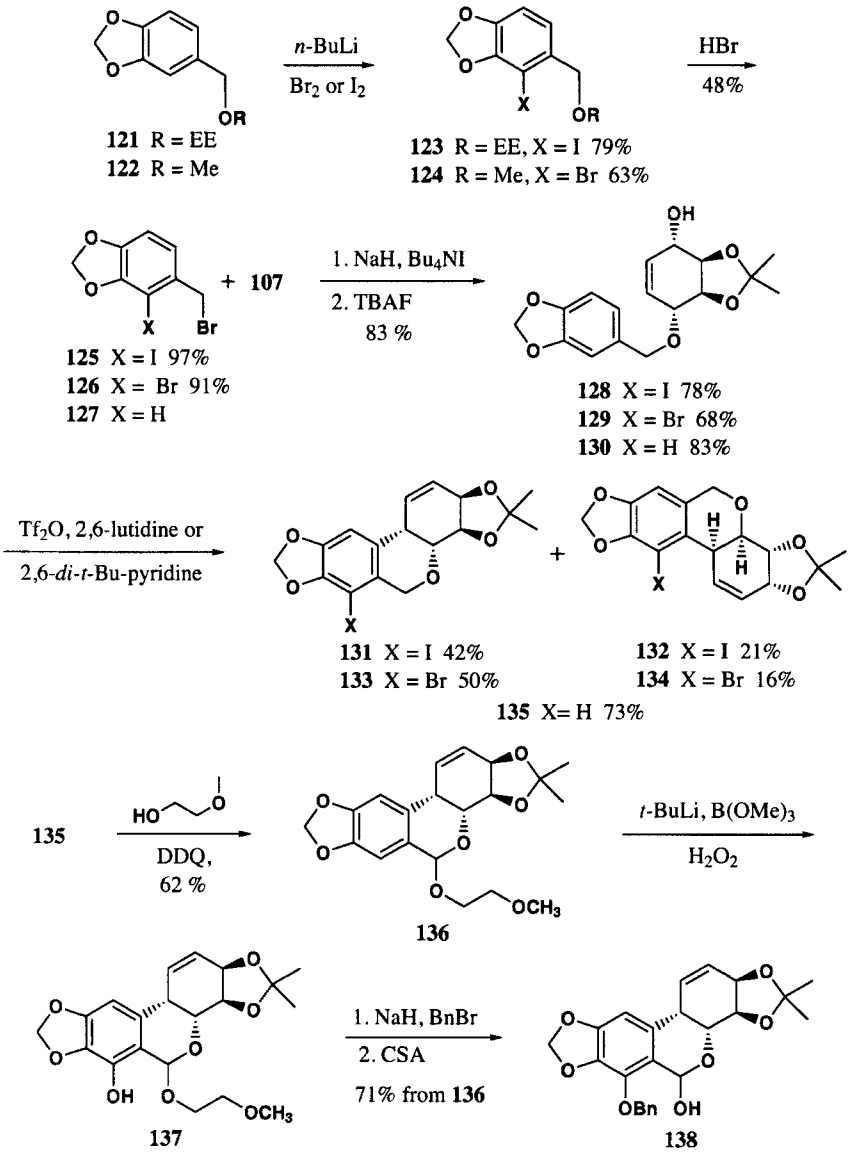
Trichloroacetimidate methodology was subsequently used to join the piperonol unit **112** with the conduritol derivative **107** to give **114**, which was desilylated with TBAF. Intramolecular electrophilic aromatic substitution was envisioned for the construction of the C10b-C10a bond. Such process was brought about by conversion of the allylic alcohol to the corresponding triflate ester using triflic anhydride and 2,6-*di-tert*-butylpyridine. The desired cyclized product **116** was obtained only in low 8% yield, together with 50% of the rearrangement product **117**. The formation of **117** was explained by the S_N2' attack on the olefin at position C6a of the aromatic ring (*ipso* to the tether) with the subsequent 1,2-shift of the alkoxymethyl group and deprotonation to reestablish the aromatic system. Furthermore, resonance activation of the C6a position by the presence of the benzyloxy group at C7 was thought to be responsible for this undesired process.

The investigators reasoned that to avoid the resonance activation of the C6a position, the C7 oxygen functionality would have to be installed later in the synthesis. Because a halogen at C7 could be converted into a hydroxyl at a later stage, halogenation of metalated **121** and **122** was carried out to give **123** and **124**. Upon treatment with HBr **123**, **124** and a non-halogenated precursor gave piperonyl bromides **125-127** (*Scheme 19*). Williamson ether formation of **125-127** with conduritol **107** proceeded in much better yields compared to the earlier imidate strategy to furnish coupled products **128-130**. Cyclization induced by treatment with Tf_2O gave the



Scheme 18

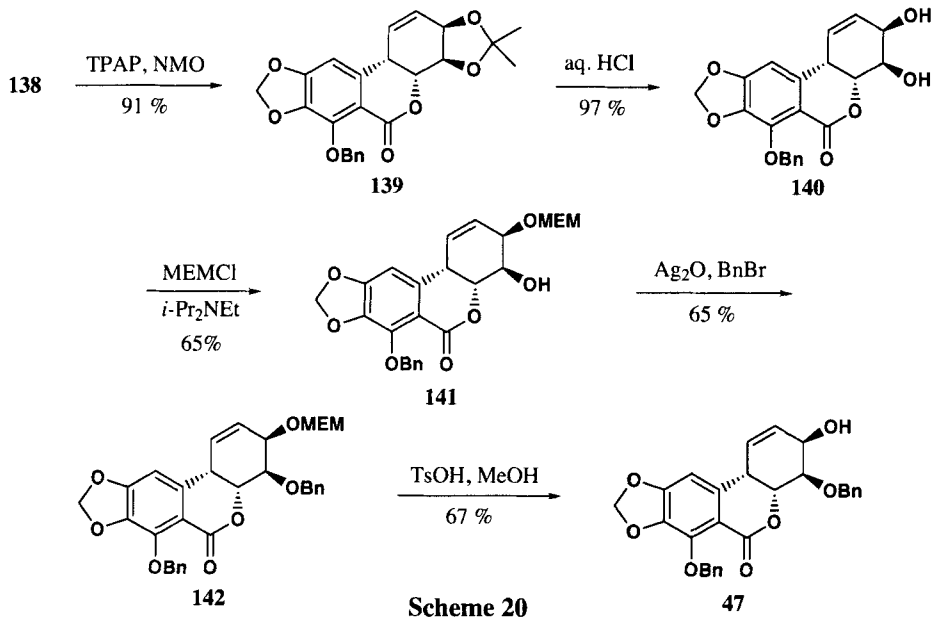
desired pentacyclic compounds along with the rearrangement products **132** and **134**. Importantly, compound **130**, lacking any substituent at the C7 aromatic position, cleanly gave the desired cyclization product **135** in 73% yield without any accompanying rearrangement. To introduce the C7 hydroxyl in **135** the researchers followed the same strategy that led to **110** from **109**. Previous work by Xu and co-workers[72] showed that isochromane structures such as **135** could be



Scheme 19

regioselectively coupled with alcohols in the presence of DDQ. This process is facilitated by the presence of alkoxy substituents in the *para* position. Thus, coupling of methoxyethanol with **135** in the presence of DDQ gave rise to diastereomerically pure acetal **136**. Lithiation guided by the alkoxy appendage was selective for the C7 position and the intermediate aryl lithium species was oxygenated in the usual manner. The hydroxyl group was then protected as its benzyl ether and the alkoxy linkage was cleaved to give **138** in 71% yield.

Since **138** is very similar to Danishefsky's compound **47**[43] now the focus was to achieve the conversion of **138** to **47** *(Scheme 20)*. Oxidation of lactol **138** to lactone **139** was



Scheme 20

followed by acetonide hydrolysis. Protection of the allylic hydroxyl as a methoxyethoxymethyl ether allowed for the benzyl protection of the second hydroxyl. Finally, removal of the MEM group afforded **47** in overall 25% yield from **138**. Formal synthesis of pancratistatin was achieved.

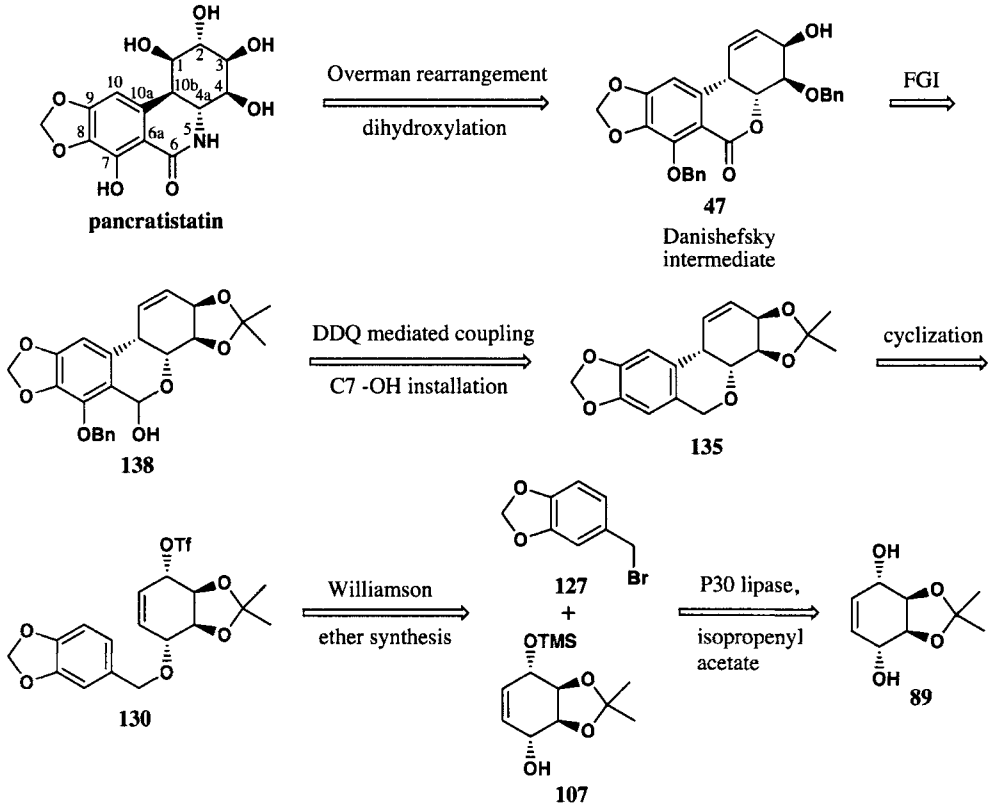
2. Evaluation of the Strategy

a) Starting material. The synthesis utilized acetonide **105** that was made in four steps from benzoquinone using the procedure developed by Knapp and coworkers.[71] The retro Diels-Alder of **105** afforded protected conduritol **89** in 65-75% yield, which is the same starting material utilized by Trost and coworkers in their synthesis of (+)-pancratistatin.

b) Asymmetric Strategy. Enzymatic acetylation[73] using P30 lipase and isopropenyl acetate led to desymmetrization of meso diol **89** to form enantiopure acetate **106** in high 94% yield.

c) Installation of Stereocenters. An intramolecular electrophilc aromatic S_N2' substitution process was used to introduce the aromatic group. Unlike Trost's synthesis,[62] in which the acetonide cis diol was equivalent to the C3-C4 hydroxyls in pancratistatin, in the Haseltine's synthesis the conduritol unit was modified to obtain Danishefsky's late stage intermediate **47** in which the acetonide oxygens correspond to the C2-C3 groups in pancratistatin. *Syn*-specific Overman rearrangement of the acetimidate, formed with the unprotected C3 hydroxyl group in **47**, resulted in the introduction of the C4a nitrogen.

d) Lactam Formation. This would be similar to the Danishefsky's synthesis, namely hydrolysis of the lactone to give the intermediate amino acid followed by cyclization in the presence of DCC to form the *trans*-lactam.



Scheme 21

e) Regioselective Introduction of the Substituents on the Aromatic Ring. Aromatic ring made from piperonol already has the methylenedioxy moiety and the C6a bond. The investigators planned to introduce the C7 hydroxyl before the intramolecular coupling of the rings A and C portions. However, the failure to achieve the desired cyclization to form the C10a-C10b bond forced the C7 installation at a later stage in the synthesis. The direct *o*-lithiation of **135** was not successful, which prompted the researchers to introduce the ethoxymethoxy tether, which resolved the problem efficiently.

V. SYNTHESIS OF (+)-PANCRATISTATIN BY MAGNUS' GROUP BASED ON β-AZIDONATION (1998)

1. Synthetic Sequence and Tactical Nuances

The synthesis of pancratistatin by Magnus and Sebhat[74,75] is based on utilization of the β-azidonation reaction using hypervalent iodine and trimethylsilyl azide developed in this group earlier.[76] The synthesis began with the bromination of *o*-vanillin **143** with Br_2/AcOH to give **144,** which was oxidized with H_2O_2/NaOH to form diol **145** *(Scheme 22)*. Methylenation of diol **145** using $BrCH_2Cl$ in the presence of potassium carbonate yielded aryl bromide **146** in an overall yield of 65% from **144.**

Lithiation of aryl bromide **146** followed by the addition to ketone **147** gave tertiary alcohol **148** in 85% yield. The latter was dehydrated using $POCl_3$ and DBU in pyridine and the resulting double bond was hydrogenated. Removal of the acetal-protecting group by acid hydrolysis generated ketone **151** in good yield. Asymmetric lithium enolate formation was achieved by the treatment of **151** with lithium (+)-bis(α-methylbenzyl)amide in the presence of LiCl. The enolate was trapped with TIPSOTf to give silyl enol ether **152** in ≥ 85% enantiomeric excess. Earlier mechanistic studies by this group showed that silyl enol ethers in the presence of $(PhIO)_n/TMSN_3$ undergo hydride abstraction at the more stabilized β carbon to form positively charged intermediate **162**, rather than the removal of the hydride to afford the non-stabilized intermediate **163** *(Fig. 10)*.[76]

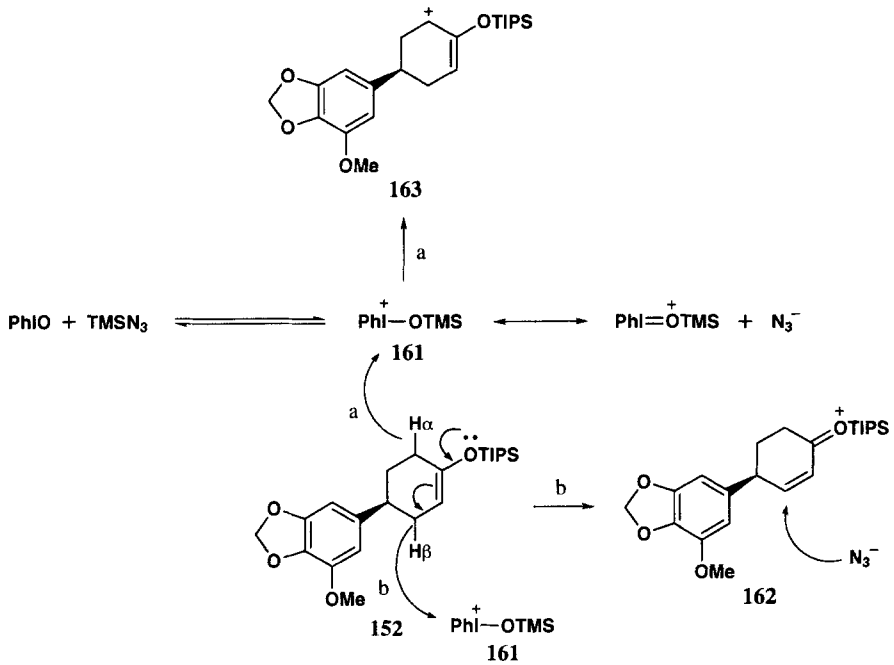
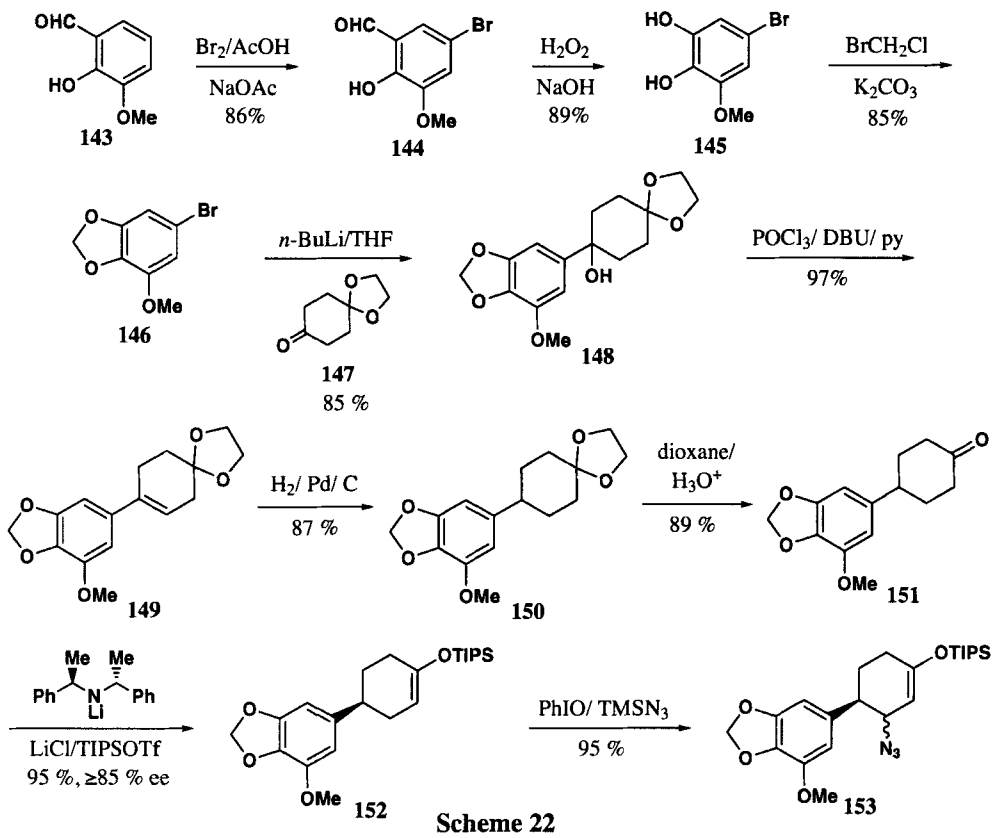


Fig 10

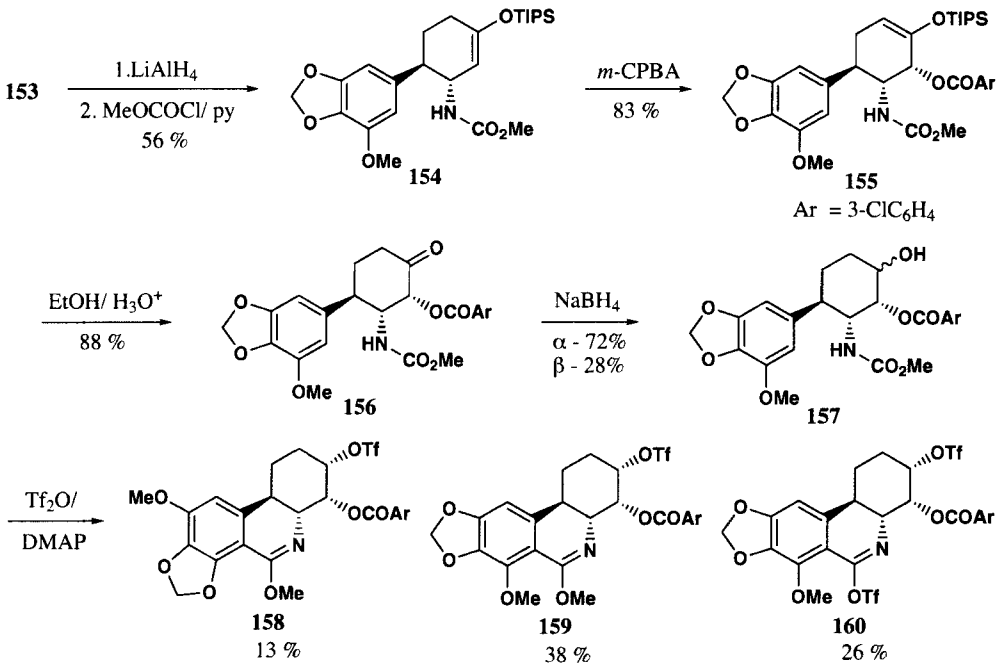
The β-azidation process indeed proceeded selectively to produce *cis* and *trans* diastereomers **153** in a 1:3.5 ratio *(Scheme 22)*. The mixture of inseparable diastereomers was reduced using $LiAlH_4$ and the resulting amino group was protected as a carbamate using methyl chloroformate in pyridine to afford a separable mixture of epimers, from which pure *trans* isomer **154** was isolated in 56% yield *(Scheme 23)*. Unfortunately, trialkylsilyl enol ether **154** in the presence of *m*CPBA preferentially underwent axial epoxidation and after a series of intermediate reactions gave **155**, which had the wrong stereochemistry at C4. This was confirmed by reducing the keto group in **156** using $NaBH_4$ to give two isomers α:β in 72 and 28 % yields. The major diastereomer upon the Bischler-Napieralski cyclization formed three products **158**, **159** and **160**. X-ray crystal structure of **159** unambiguously established the incorrect stereochemistry at both C3 and C4 positions.



Scheme 22

To obtain the correct configuration at C4, the axial –OCOAr group in **156** was epimerized to the more stable equatorial position by treatment of **156** with *t*-BuOK/HMPA to give **164** in 91% yield (*Scheme 24*).

Further functionalization of the C ring of pancratistatin was continued by formation of TMS enol ether **165**, which was converted to α:β-unsaturated ketone **167** by treatment with $PhSeOCOCF_3$ and oxidation of the resultant selenide **166** with H_2O_2 in pyridine to afford **167** in 85% yield from **164** *(Scheme 24)*. Epoxidation of **167** under mild alkaline conditions and L-selectride reduction of the carbonyl formed **169** as a single diastereomer. Acetylation of **169** and regioselective opening of the epoxide ring by the C1 axial attack of sodium benzoate gave an intermediate alcohol, which was protected as acetate to give **171**. Modified Bishler-Napieralski conditions using Tf_2O/DMAP[77] induced lactam formation to give **173** along with its regioisomer **172** (7:1) in 60 % total yield as an inseparable mixture. Removal of the phenolic methyl ether with BBr_3 allowed for the separation of the regioisomers and gave exclusively **174**, since **172** did not react. Lastly, deprotection of the acetate esters with NaOMe in MeOH afforded (+)-pancratistatin in an overall yield of 1.2% over the 22 step synthesis.



Scheme 23

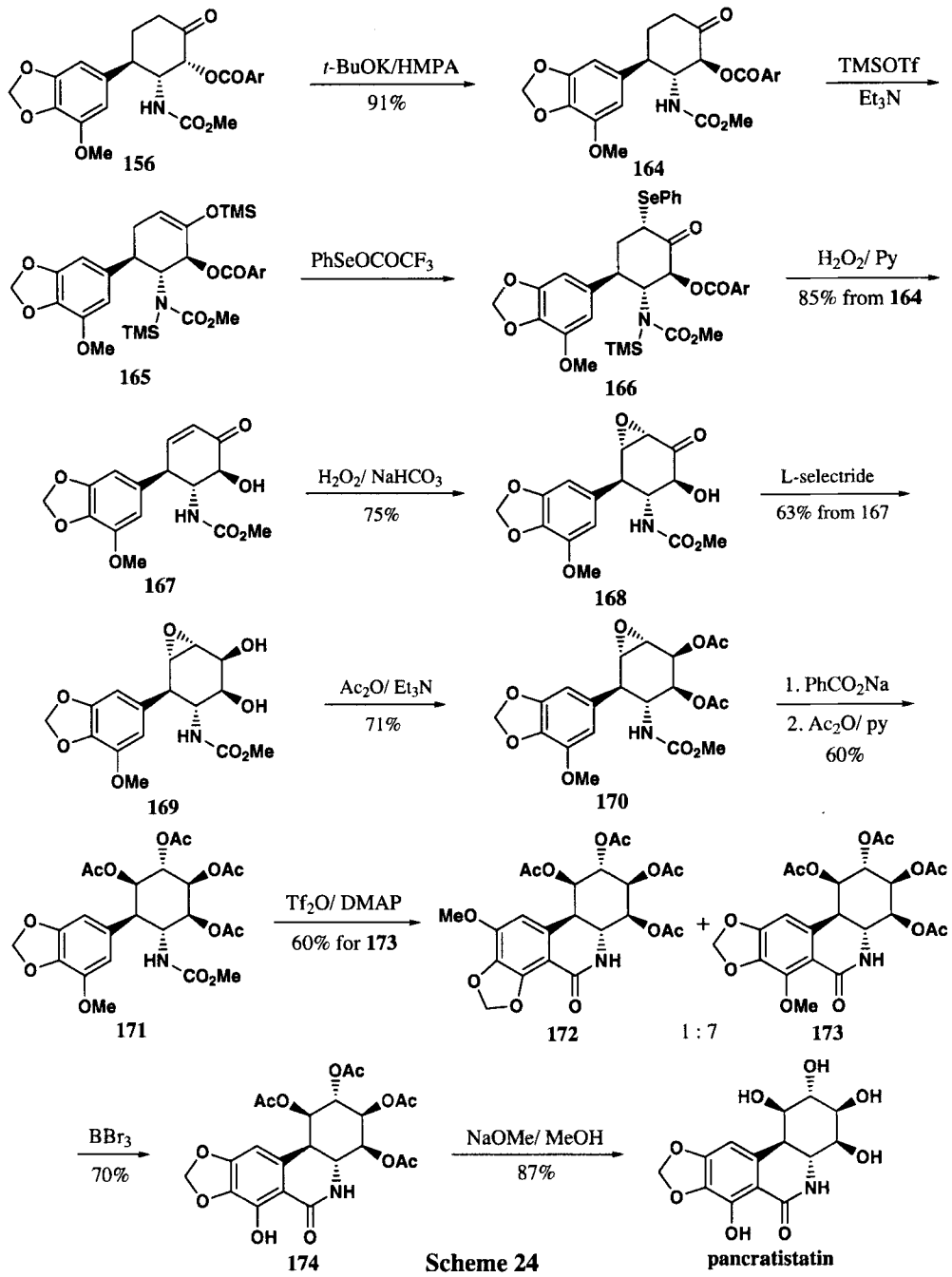
2. Evaluation of the Strategy

a) Starting Material. The synthesis started with the known arylbromide **146**, possessing three oxygen substituents found in the target molecule. **146** was synthesized in three steps from inexpensive *o*-vanillin.

b) Asymmetric Strategy. Enantioselective enolate formation with lithium (+)-bis(α-methylbenzyl)amide using ketone **151** and subsequent trapping with TIPSCl gave silyl enol ether **152** in more than 85% enantiomeric excess. The β-azidonation process affording azides **153** secured the required absolute stereochemistry.

c) Installation of Stereocenters. After obtaining the required C10b stereochemistry using asymmetric deprotonation with a chiral lithium base, the researchers performed epoxidation of silyl enol ether **153**, which proceeded in the axial manner to give the unwanted configuration of the C4 stereocenter. Equilibration with a strong base brought about epimerization at C4, which can be explained on the basis of the preference for the bulky ester moiety to occupy the equatorial position as opposed to the axial one in **156**. Epoxidation of C1, C2 double bond from the α-face to give **168**, followed by selective reduction of the C3 keto group from the α-face and trans-diaxial S_N2 ring opening of the epoxide with benzoate ion at C1 led to the installation of all stereocenters in ring C of pancratistatin.

d) Lactam Formation. Regioselective Bischler-Napieralski process resulted in ring B closure by affording a 7:1 inseparable mixture of C6a and C10 cyclization products. However, only the



156 164 165 166 167 168 169 170 171 172 173 174

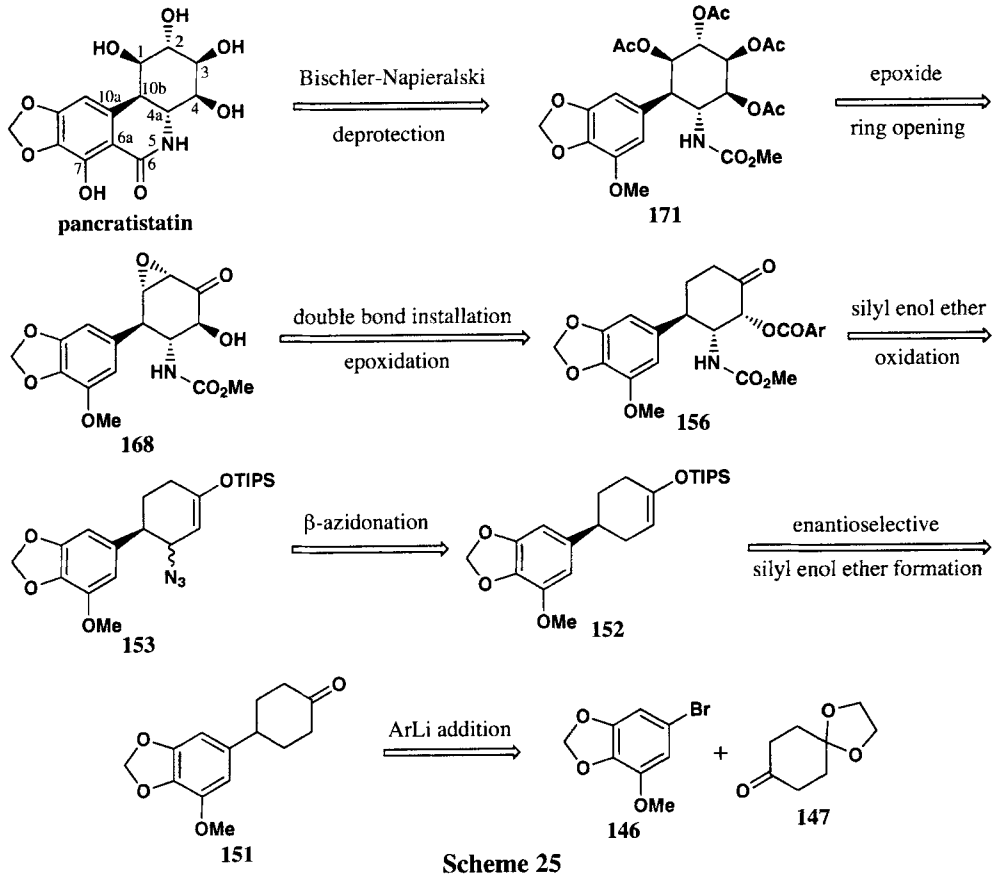
Scheme 24

pancratistatin

desired C6a compound underwent the deprotection of the phenolic methyl ether with BBr_3, in a process involving a possible assistance of the neighboring amidic carbonyl.

e) Regioselective Introduction of the Substituents on the Aromatic Ring. Arylbromide **146**, synthesized using a literature procedure possessed three oxygens in place and the bromine

substituent at the pancratistatin position C10a leading to facile creation of the C10a-C10b bond by lithium-halogen exchange and the addition of the resulting aryllithium to ketone **151**.



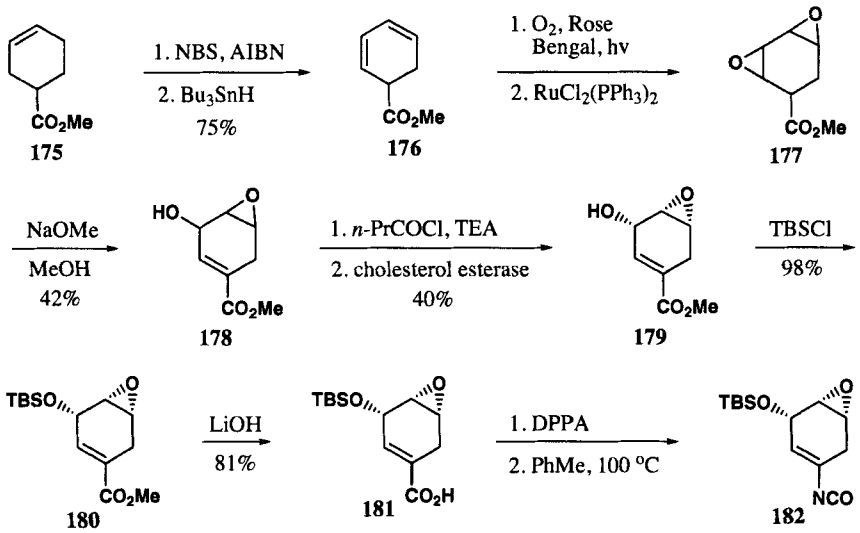
Scheme 25

VI. ARYL ENAMIDE PHOTOCYCLIZATION APPROACH TO (+)-PANCRATISTATIN BY RIGBY'S GROUP (2000)

1. Synthetic Sequence and Tactical Nuances

In 2000, Rigby and coworkers reported a new synthetic route using a hydrogen bond controlled aryl enamide photocyclization approach[78] to synthesize both (+)-pancratistain and its natural congener (+)-narciclasine from a common intermediate.[79]

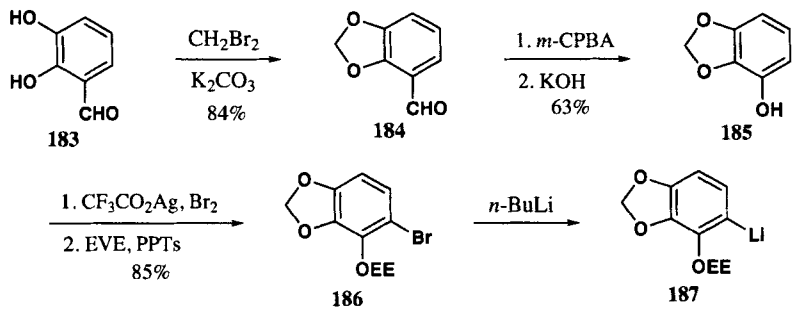
A key intermediate isocyanate **182** was synthesized using a previously published procedure[80] from acid **181** starting from commercially available ester **175**. Upon treatment with NBS and Bu_3SnH, **175** formed diene **176** in 75% yield *(Scheme 26)*. Oxidation to generate diepoxide **177** followed by treatment with sodium methoxide resulted in racemic *syn*-epoxy alcohol **178** in 42% yield. Enzymatic resolution of the esterified alcohol **178** using cholesterol esterase gave enantiomerically pure *syn*-epoxy alcohol **179** with > 93% enantiomeric excess and 40% yield.



Scheme 26

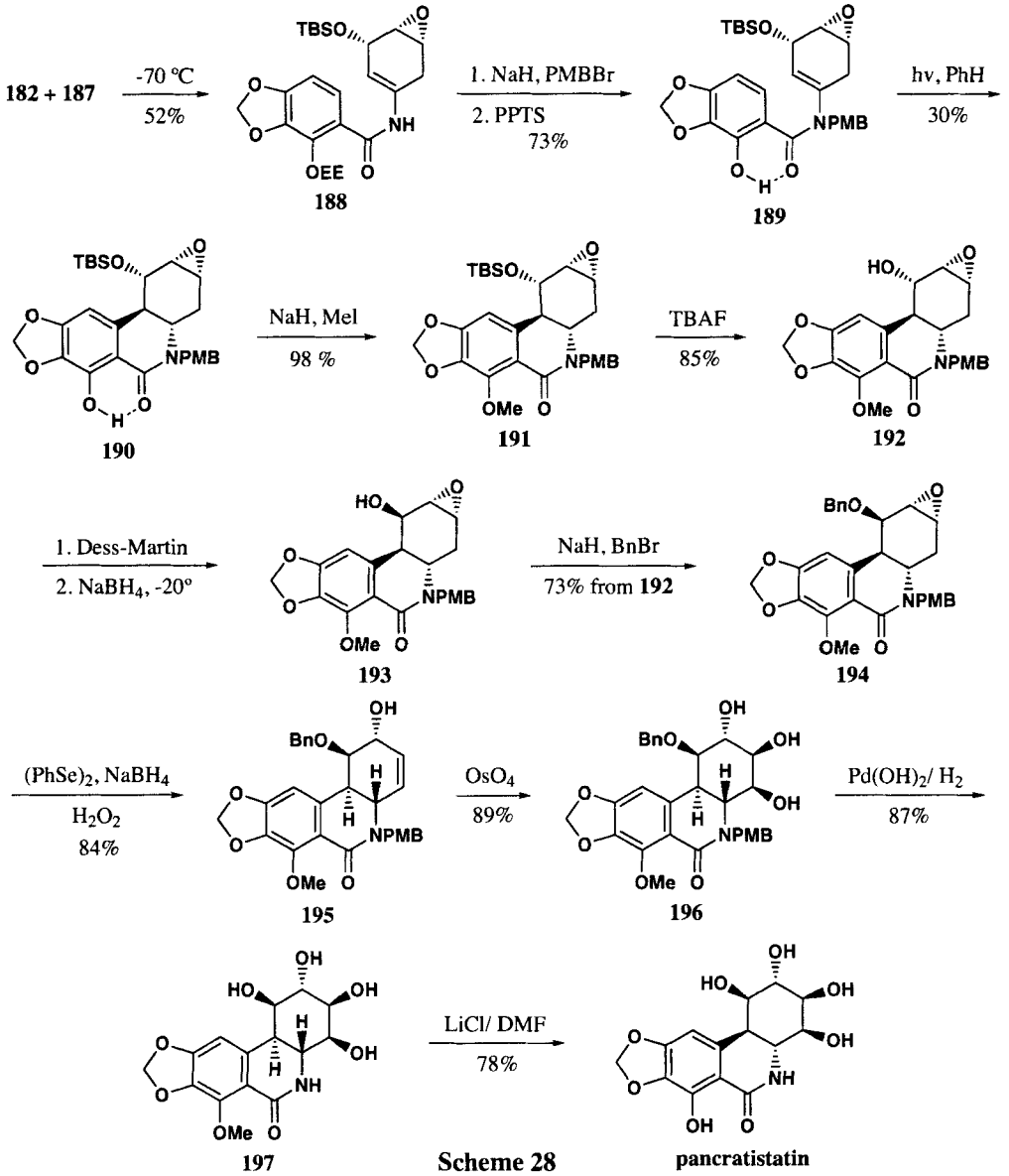
Silyl protection of the free hydroxyl and saponification gave *syn*-epoxy acid **181**. Finally, the Curtius rearrangement of an acyl azide derived from carboxylic acid **181** gave isocyanate **182**.

The aromatic portion of pancratistatin was prepared in three steps from 2,3-dihydroxybenzaldehyde *(***183**, *Scheme 27)*. Protection of the diol using CH_2Br_2 and potassium carbonate followed by oxidation of the aldehyde group under Bayer-Villiger conditions led to phenol **185** in 63% yield. Bromination in the presence of silver trifluoroacetate was selective *ortho* to the hydroxyl group, which was then protected as ethoxyethyl ether for subsequent lithiation.



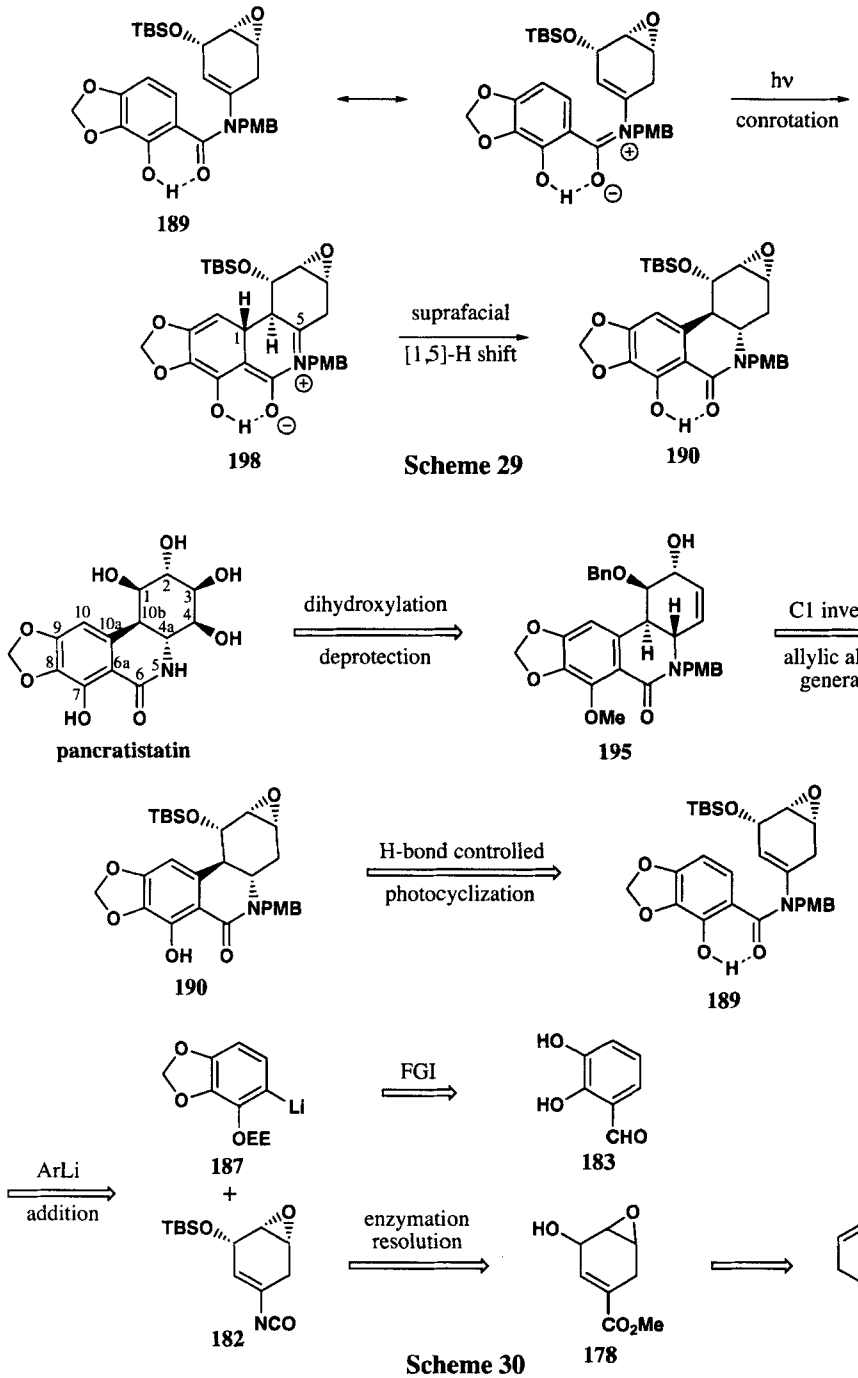
Scheme 27

Lithiated arylbromide **187** was then reacted with isocyanate **182** to give enamide **188** in 52% yield *(Scheme 28)*. Protection of the NH of the amide group as PMB ether and removal of the ethoxyethyl protection formed **189,** the desired precursor for the key photocyclization reaction. Removal of the ethoxyethyl group was necessary to allow for H-bonding between the amide carbonyl and the phenolic hydroxyl. The investigators reasoned that this would restrict rotation about the aryl-amide bond and increase the desired rotamer population of the secondary amide.



Scheme 28

In the event, irradiation of **189** at 254 nm in benzene brought about the desired cyclization giving the *trans* fused B-C ring junction in a modest yield of 30%. While the bulky TBS ether at C1 provided the necessary stereocontrol at the C10b position, the *trans* B-C ring fusion in the product **190** is most likely the result of stereospecific requirements of the two concerted processes involved (*Scheme 29*). **189** should undergo conrotatory 6π electrocyclic ring closure due to photoexcitation to give intermediate **198**. This is followed by the suprafacial [1,5]-hydrogen shift, which restores the aromatic system and results in the observed *trans* fusion.



With A and B rings in place, the focus was turned to functionalizing the C ring. Inversion of the alcohol stereochemistry at C1 required removal of the silyl group and protection of the phenolic hydroxyl to give **192** in 83% yield over two steps *(Scheme 28)*. Alcohol **192** failed

to undergo inversion under the Mitsunobu conditions, and therefore, the investigators opted for oxidation of the hydroxyl followed by the ketone reduction from the α-face to give the desired stereochemistry at C1 in **193**. The procedure involving oxidation using the mild Dess-Martin reagent with the immediate *in situ* reduction with $NaBH_4$ at -20 °C was critical for the success of this transformation to avoid the epimerization at C10b, which would form the less strained *cis* fused ring.[80] The C1 hydroxyl was protected as benzyl ether and allylic alcohol **195** was made in 84% yield by opening the epoxide with *in situ* generated phenyl selenide followed by elimination of the selenoxide. Stereoselective *cis*-dihydroxylation of the olefin to install the C3-C4 diol and deprotection of benzyl and N-*p*-methoxybenzyl groups by hydrogenolysis gave **197** in 78% yield over two steps. Similar to the synthesis by Trost's group, removal of the C7 methyl group was accomplished by refluxing **197** with LiCl in DMF to give pancratistatin in 78% yield. Overall Rigby and coworkers completed the synthesis of pancratistatin in 23 steps with an overall yield of 0.35%.

2. Evaluation of the Strategy

a) Starting Material. The synthetic design involved the use of enantiomerically pure vinyl isocyanate **182**, which was a key intermediate in Berchtold's synthesis of (-)-chorismic acid.[81-83] **182** was prepared from rather inexpensive commercially available ester **175**.

b) Asymmetric Strategy. Enzymatic resolution of racemic epoxy ester **178** with cholesterol esterase gave enantiomerically pure material. An important drawback of the strategy is the fact that kinetic resolution was performed on an intermediate obtained in five steps, thus resulting in significant loss of the material.[84]

c) Installation of Stereocenters. The key vinyl isocyanate already has three stereocenters in place. Although the stereochemistry at C1 was opposite at this stage in the synthesis, it was critical for the installation of C10b and C4a chiral centers through the aryl enamide cyclization. Inversion of C1 stereochemistry was achieved by oxidation and immediate *in situ* reduction of the carbonyl to avoid epimerization of the *trans* lactam. Opening of the epoxide with phenyl selenide and elimination of the intermediate selenoxide formed allylic alcohol **195** with the desired C2 geometry. Final functionalization of the C ring was achieved by simple dihydroxylation using OsO_4 to install the C3-C4 hydroxyl groups at the β-face of **195**. Nitrogen functionality at C4a was introduced by Curtius rearrangement of the acid **181** to form isocyanate **182**.

d) Lactam Formation. The C1 silyloxy group-guided conrotatory electrocyclic ring closure of the enamide, and this accomplished the lactam formation. Steric shielding of the bottom face in enamide **189** by the bulky OTBS favored cyclization to give the correct *trans* diastereomer.

e) Regioselective Introduction of the Substituents on the Aromatic Ring. Diol of 2,3-dihydroxybenzaldehyde **183** was protected using dibromomethane and potassium carbonate to form the C9-C10 methylenedioxy ring of pancratistatin. The aldehyde functionality was converted to phenolic hydroxyl, which controlled the regioselective bromination of **185** *ortho* to the OH group and *para* to one of the oxygens of the methylenedioxy moiety. Halogen metal transfer with *n*-

BuLi allowed coupling of **187** with **182** to form the C6-C6a bond. Lastly, photocyclization formed the crucial C10a-C10b bond.

VII. RELAY SYNTHESIS OF (+)-PANCRATISTATIN FROM ITS NATURAL CONGENER (+)-NARCICLASINE BY PETTIT'S GROUP (2001)

1. Synthetic Sequence and Tactical Nuances

Pettit and coworkers developed a new route to pancratistatin[85] using its more naturally abundant congener narciclasine as the starting material. The synthesis commenced with the protection of the C3,C4-vicinal diol as an acetonide in 97% yield *(Scheme 31)*. The C2 and C7 hydroxyl groups were acetylated with acetic anhydride in pyridine to give **200** along with minor quantities of monoacetylated compound **201**. Epoxidation of **200** using *m*CPBA formed the desired α-diastereomer **202** in 55% yield. Hydrogenolysis of the epoxide in the presence of 10% Pd/C followed by reaction with methanolic potassium carbonate formed four products **203-206**, which were separated by column chromatography and characterized.

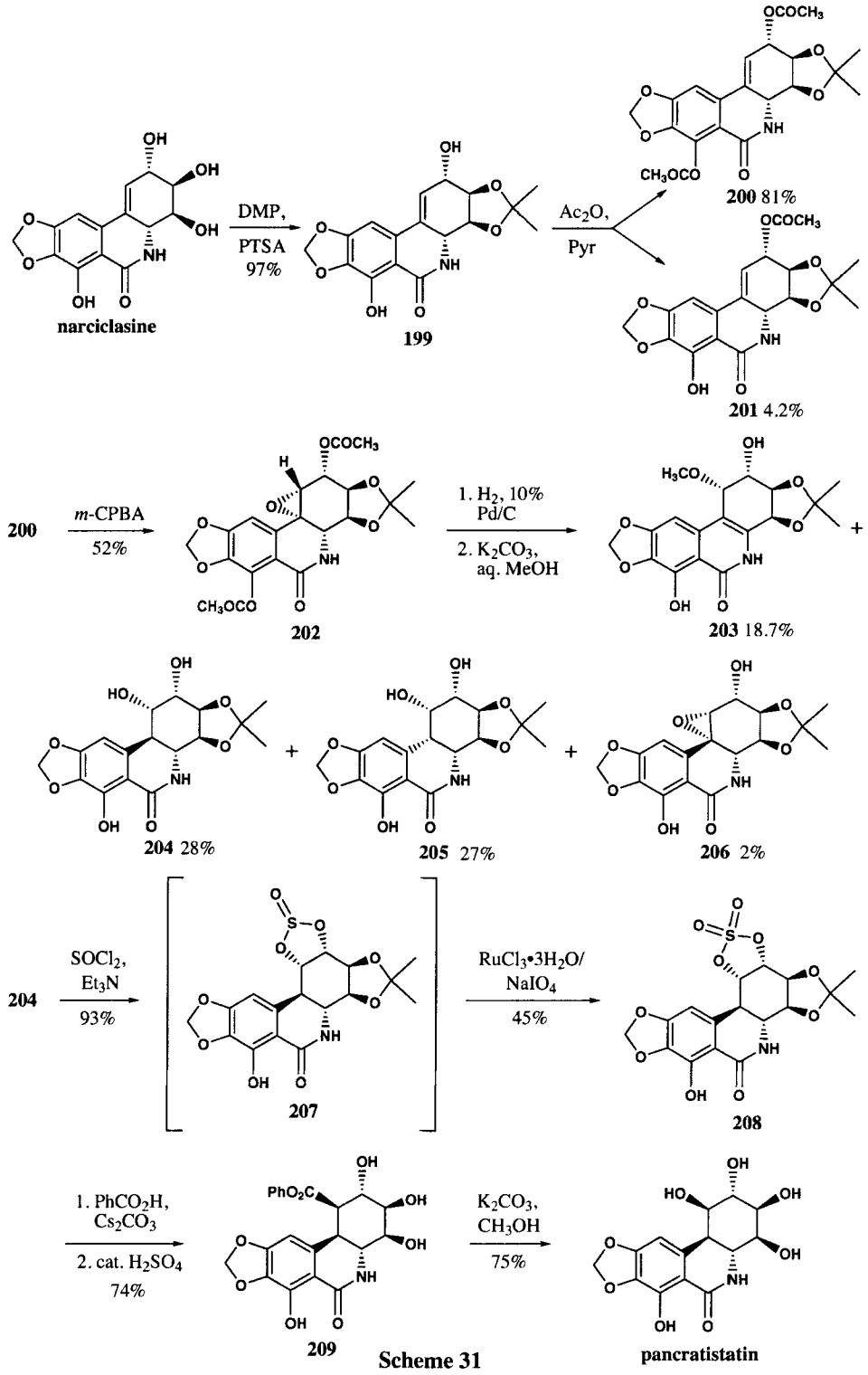
Diol **204** was the only compound out of the mixture with the correct stereochemistry of the aromatic group at C10b. It was obtained with an overall yield of 15% starting from narciclasine. However, the configuration at the C1 position required inversion. To this end **204** was treated with thionyl chloride to form cyclic sulfite **207**, which was further oxidized to cyclic sulfate **208** in 47% yield using catalytic $RuCl_3 \cdot 3H_2O$ and 3.5 equivalents of $NaIO_4$. The nucleophilic attack of $PhCO_2Cs$ on the cyclic sulfate proceeded at the C1 carbon. This was followed by acid hydrolysis of the alkyl sulfate, which concomitantly cleaved the isopropylidene protecting group to give benzoate **209** in 74% yield. Removal of the benzoate ester group using K_2CO_3 in MeOH gave (+)-pancratistatin with an overall yield of 3.6 % in 10 steps starting from narciclasine.

2. Evaluation of the Strategy

a) Starting Material. Narciclasine is a close structural analogue of pancratistatin. The only difference is the presence in narciclasine of the C1-C10b double bond, and therefore, reduced structural complexity due to the absence of C1 and C10b stereocenters. Although narciclasine can be obtained more easily than pancratistatin using isolation from plant sources, its availability is still rather limited. One could envision the ideal relay synthesis of pancratistatin from narciclasine in one step by a regio- and stereoselective hydration of the C1-C10b double bond.

b) Asymmetric Strategy. No strategy was required.

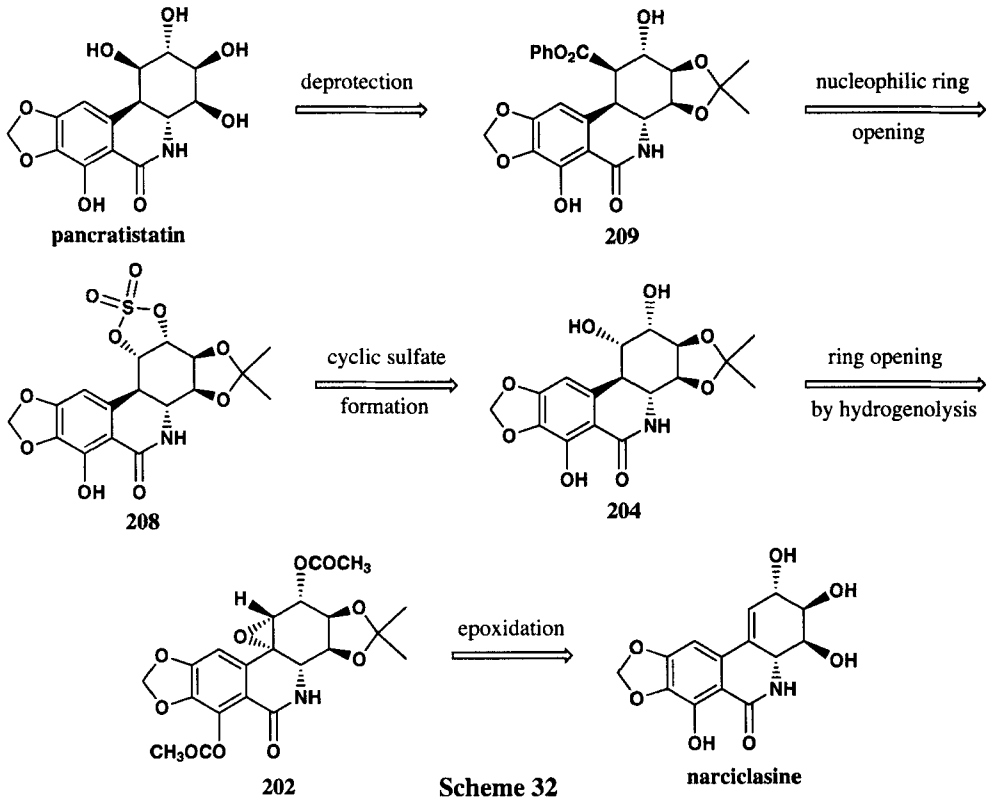
c) Installation of Stereocenters. Narciclasine possesses four stereocenters, which are also found in pancratistatin. To install the remaining two stereocenters at C1 and C10b, Pettit and coworkers performed epoxidation that occurred from the α-face of the double bond giving **202** due to the steric shielding of the top face by the C3,C4-acetonide ring. Hydrogenolysis was not selective resulting in a mixture of compounds. Only one of the four products had the right configuration at C10b. Nucleophilic ring opening of the cyclic sulfate by cesium benzoate in **208** gave the desired stereochemistry at C1.



Scheme 31

d) Lactam Formation. None was required.

e) Regioselective Introduction of the Substituents on the AromaticRing. None was required.



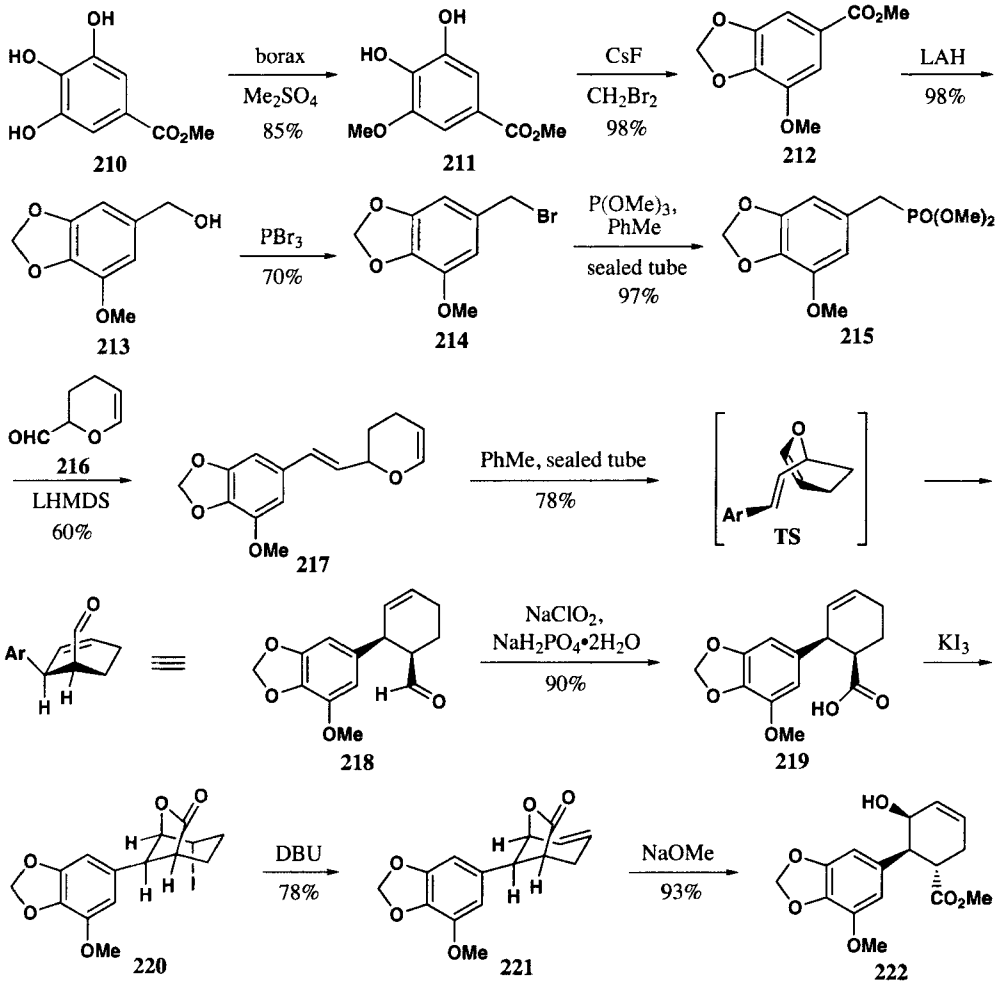
Scheme 32

VIII. [3,3]-SIGMATROPIC REARRANGEMENT APPROACH TO (+)-PANCRATISTATIN BY KIM'S GROUP (2002)

1. Synthetic Sequence and Tactical Nuances

Kim and coworkers accomplished a synthesis of (±)-pancratistatin[86,87] utilizing the Claisen rearrangement as a key step.

The synthesis began with bromide **214** prepared from methyl gallate using previously published methods *(Scheme 33).*[88] Initially bromide **214** was converted to a phosphonium ylide and reacted with acrolein dimer **216** resulting in the formation of a minor product *trans*-olefin **217** along with the major *cis*-olefin **223** in 1:4.6 ratio in the presence of KOH and catalytic 18-crown-6 in 85% yield. Based on earlier studies by Büchi,[89] the investigators proposed that the Claisen rearrangement of the *Z*-olefin **223** would proceed through a boat-like transition state to afford *trans*-aldehyde **224** with the correct C4a-C10b *trans* geometry *(Fig. 11).* However, the *Z*-olefin was reluctant to undergo rearrangement even at 250 °C while the *E*-olefin under similar conditions yielded the *cis*-disubstituted cyclohexane **218**. The high-energy transition state involving unfavorable steric interaction between the aromatic group and the hydrogen atom on



Scheme 33

the dihydropyran ring was thought to be responsible for the lack of reactivity of the *Z*-olefin.

Aldehyde **218** was therefore chosen for further functionalization of ring C. The reaction of Horner-Wadsworth-Emmons ylide **215** with aldehyde **216** gave *E*-olefin **217** exclusively *(Scheme 33)*. To functionalize the C ring aldehyde **218** was oxidized to acid **219** in 90% yield using $NaClO_2$. Iodolactionization of **219** using KI_3 gave intermediate iodo compound **220**, which after treatment with DBU formed unsaturated lactone **221**. Reflux of **221** in methanol not only led to lactone ring opening to install C1-C10b *cis* relationship, but also resulted in epimerization at C4a to give ester **222** with three of the six stereocenters in pancratistatin assembled.

In an attempt to synthesize enantiopure (+)-pancratistatin, aryl bromide **146** was coupled with a chiral building block *(R)*-**225**[90] and the resulting alcohol was esterified with 5-hexenoic acid **227** to yield (+)-**228**. The latter underwent [3,3]-sigmatropic rearrangement when treated with LDA and TBSCl forming a mixture of **230** and **231** in 77% yield *(Scheme 34)*. Ring closing metathesis using Grubbs' ruthenium catalyst afforded a mixture of cyclohexenes **219** and

232. Iodolactonization of the mixture gave (+)-**221** along with unreacted **232** that could be separated at this stage. However, the investigators encountered problems with scaling up the synthesis of (+)-**221**, and therefore, the synthesis was completed using racemic ester **222**.

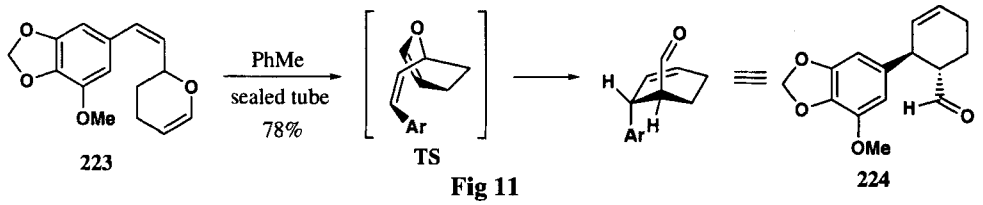
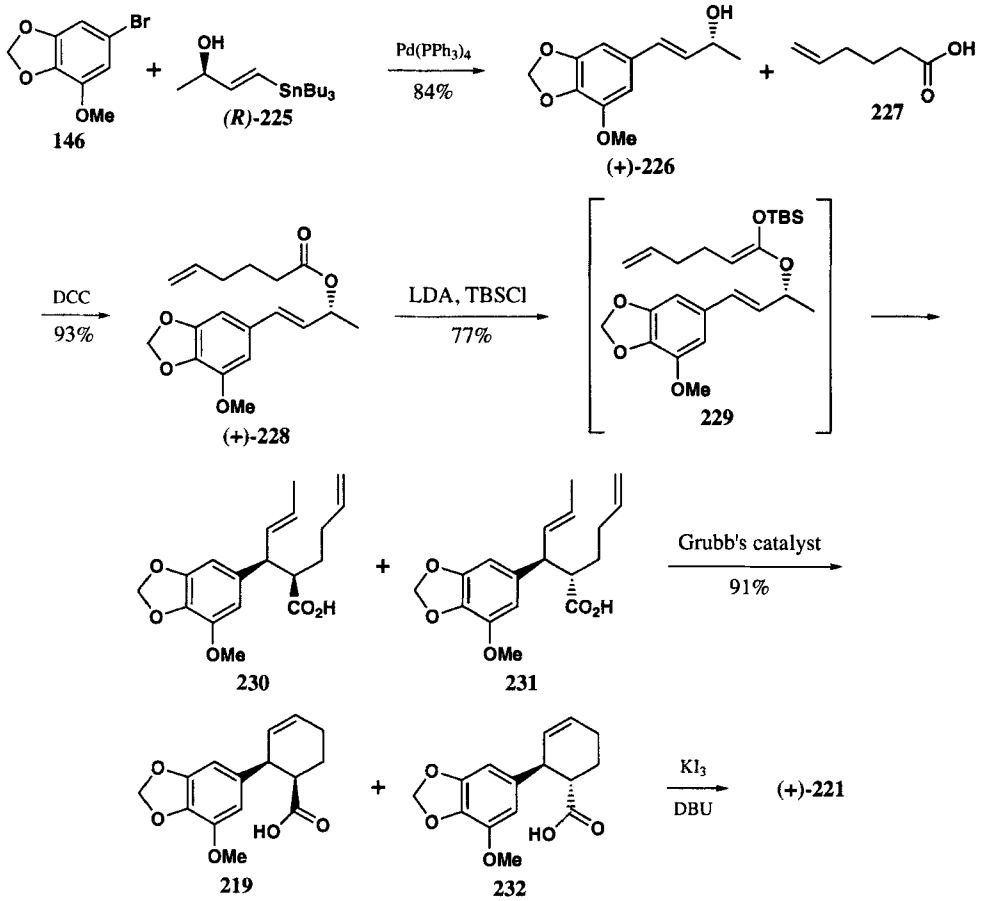


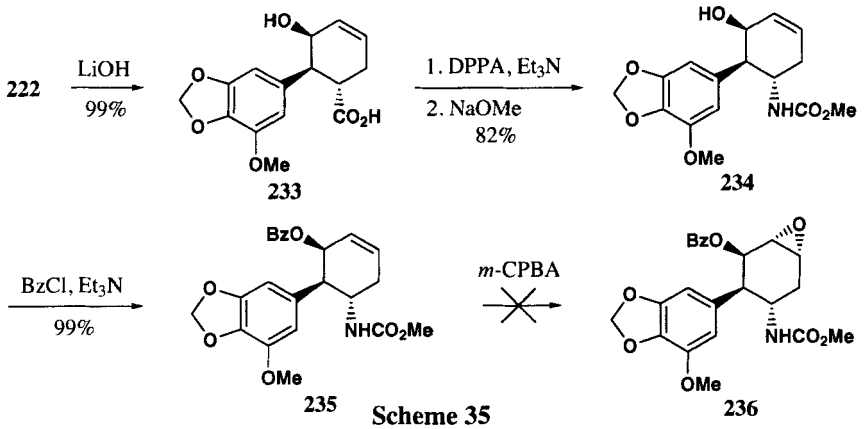
Fig 11

Hydrolysis of the ester **222** using 1N LiOH furnished acid **233** in 99% yield (*Scheme 35*). Reaction of diphenyphosphoryl azide with **233** formed the intermediate isocyanate by way of the Curtius rearrangement, which gave carbamate **234** after treatment with NaOMe in 82%

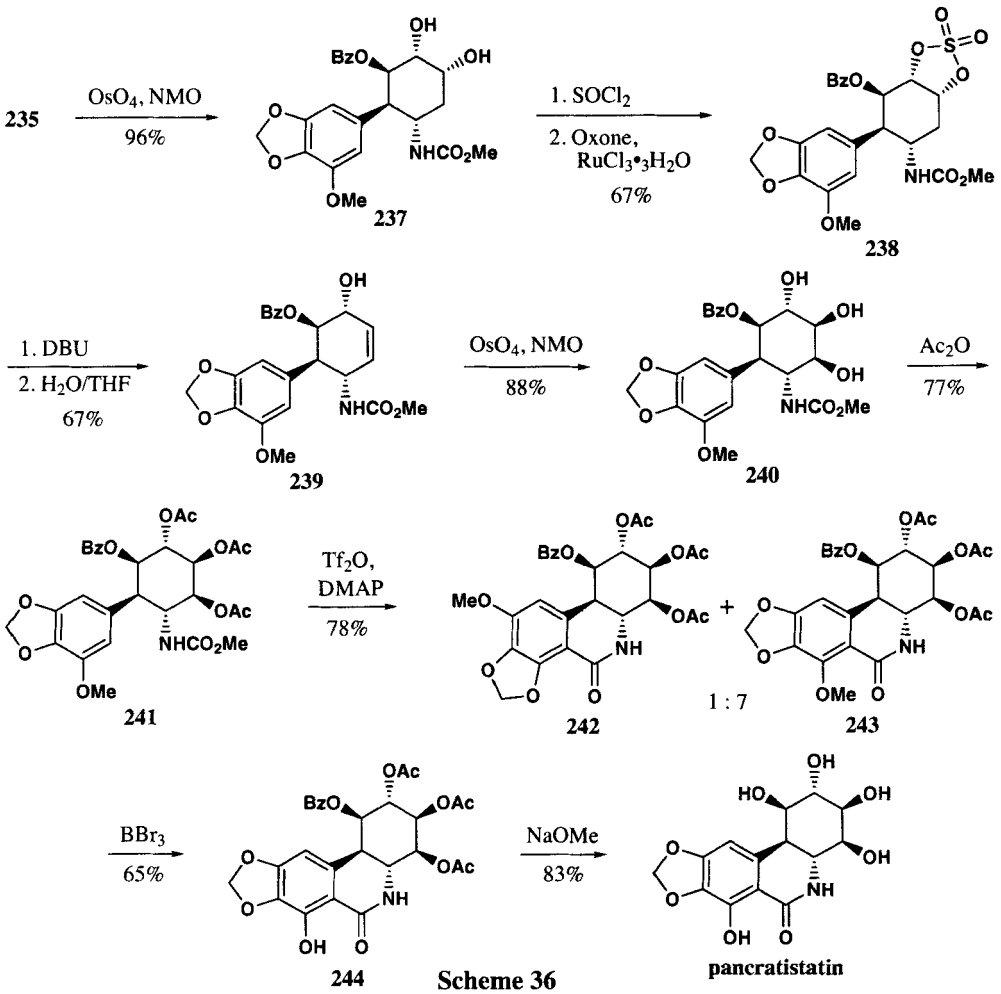


Scheme 34

yield. Epoxidation of **235** under various conditions was not successful. The investigators opted for dihydroxylation, which proceeded from the less hindered α-face to afford **237** (*Scheme 36*).



Scheme 35

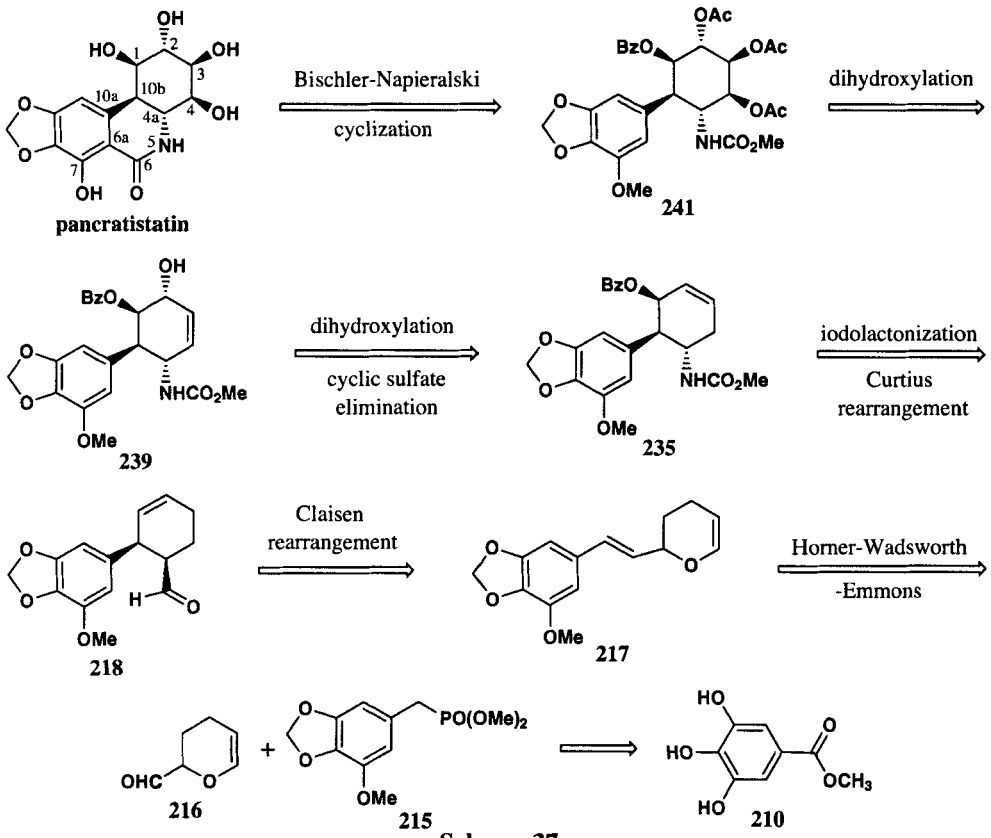


Scheme 36

Converting diol **237** to cyclic sulfate **238** and reacting the latter with DBU followed by acidic workup led to the installation of the C3-C4 double bond *(Scheme 36)*. As was the case in the previous syntheses of pancratistatin, dihydroxylation occurred from β-face to afford **240** which has fully functionalized C and A rings. Similar to Magnus's synthesis, acetyl protection of the hydroxyl groups followed by Bischler-Napieralski cyclization using Tf_2O/DMAP accomplished the lactam formation and two regioisomers **243** and **242** were formed in 7:1 ratio. Removal of the phenolic methyl group allowed for facile separation of the two regioisomers. Final deprotection with sodium methoxide gave pancratistatin in 3.6% overall yield over 16 steps.

2. Evaluation of the Strategy

Starting Material. The synthesis began with the Horner-Wadsworth-Emmons process of phosphonate **215** made in five steps from methyl gallate **210** and acrolein dimer **216**. Phosphonate

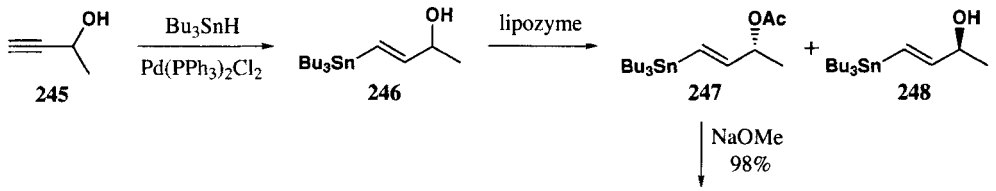


Scheme 37

215 has all three oxygens installed in proper positions.

a) Asymmetric Strategy. The investigators initially started with the synthesis of racemic

pancratistatin. After having worked out the Claisen rearrangement and iodolactonization processes they attempted an asymmetric synthesis using aryl bromide **146** and *(R)*-**225**. Enantiopure *(R)*-**225** had been previously prepared by the same investigators utilizing enzymatic resolution of racemic γ-hydroxy vinylstannane **246** in > 99% ee *(Scheme 38)*.[90] However, the problems with purification of the mixture of **230** and **231** and scale-up of the synthesis forced the investigators to pursue the synthesis of (±)-pancratistatin.



Scheme 38

b) Installation of Stereocenters. [3,3]-sigmatropic rearrangement of the *E*-olefin **217** installed the aromatic ring at C10b and the aldehyde group at C4a *cis* to each other. The C1 hydroxyl was efficiently introduced by iodolactonization of the acid **219** to form bicyclic lactone **221**, which after methanolysis formed **222** with C1, C10b and C4a stereocenters installed in the desired configuration. After the disappointment with epoxidation of **235**, the investigators found success by dihydroxylation and cyclic sulfate elimination reactions to introduce the C2 hydroxyl. Simple dihydroxylation of the **239** completed the functionalization of ring C of pancratistatin.

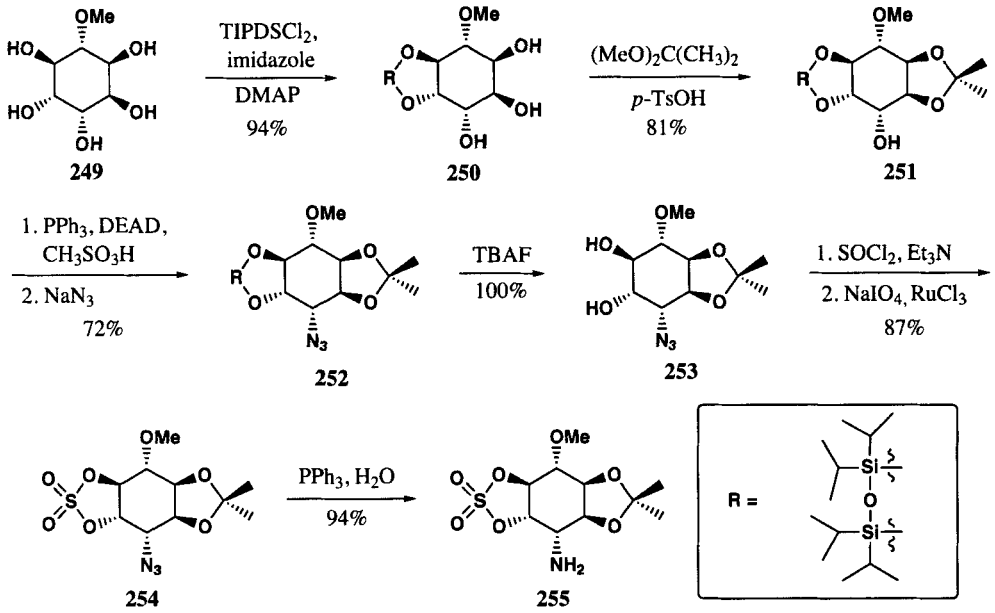
c) Lactam Formation. Curtius rearrangement of the azide formed by the reaction of acid **233** with DPPA gave the intermediate isocyanate, which upon treatment with sodium methoxide afforded carbamate **235**. Lactamization was accomplished by the Bischler-Napieralski process at a much later stage in the synthesis similar to the precedent of Magnus. Lactam **243** was formed along with its regioisomer **242** in 7:1 selectivity.

d) Regioselective Introduction of the Substituents on the Aromatic Ring. Methyl gallate already has three oxygen groups as hydroxyl functionality. Two of them were protected as a methylenedioxy ring and the remaining alcohol was protected as methyl ether.

IX. SHORTEST SYNTHESIS OF (+)-PANCRATISTATIN BY LI'S GROUP (2006)

1. Synthetic Sequence and Tactical Nuances

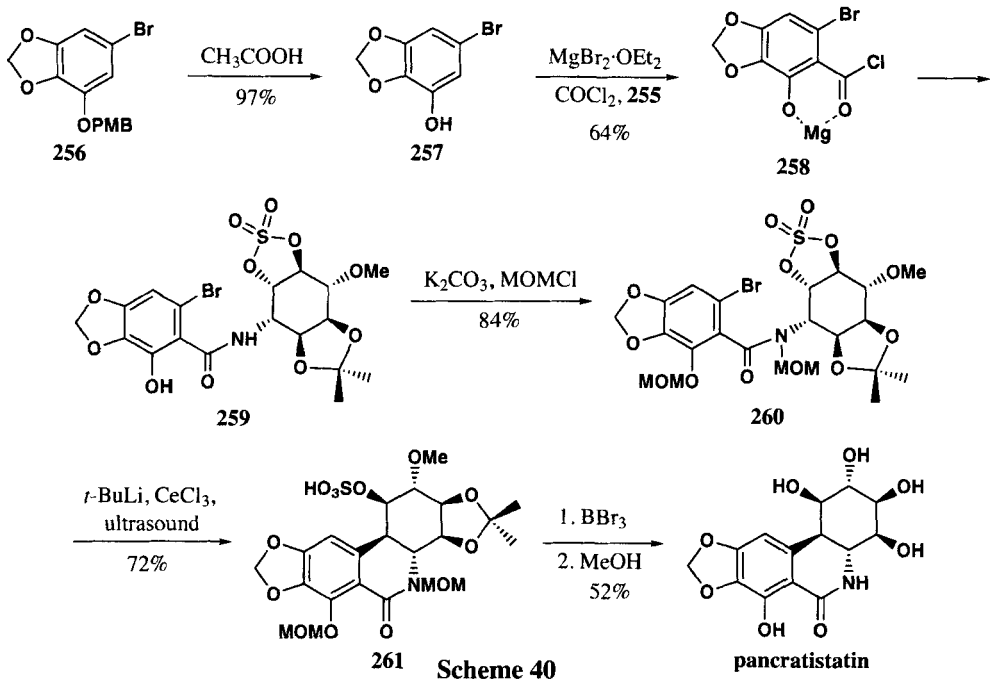
The starting material for Li's synthesis[91] of pancratistatin was pinitol **249**, which is expensive but has the right stereochemistry at five out of the six carbons present in the cyclitol portion of pancratistatin *(Scheme 39)*. Compound **251** was prepared in two steps from pinitol by selective protection of the *trans* and *cis* hydroxy functionality using the bulky TIPDS and acetonide protecting groups. It is noteworthy that TIPDS is a selective protecting group for trans diols.[94] The configuration of the only remaining hydroxyl was inverted using the Mitsunobu reaction with methyl sulfonate as nucleophile, followed by the S_N2 substitution of the sulfonate



Scheme 39

with azide ion to install the C4a nitrogen center in pancratistatin, utilizing the procedure by Aher and Pore.[93] The silyl group was then removed and the diol functionality in **253** was converted to the cyclic sulfate to give **254**. The Staudinger reduction process for converting the azide to free amine generated the crucial intermediate **255** that would undergo a coupling reaction in a later part of the synthesis.

Ring A part of pancratistatin was introduced using the intermediate **256**, which was synthesized according to the previously known method *(Scheme 40)*.[94] Removal of the PMB protection and phosgene mediated coupling with amine **255**, yielded amide **259**, in which the phenolic hydroxyl was protected as MOM ether to give **260** *(Scheme 41)*. The crucial reaction of this synthesis involved the intramolecular ring opening of the cyclic sulfate at the C10b carbon. Nucleophilic ring opening using aryllithium and arylmagnesium species led to various side reactions due to the basic nature of these reagents. However, the low basicity and high nucleophilicity of the arylcerium reagents compared to the aryllithium or arylmagnesium ones makes it a softer nucleophile and ideal for intramolecular ring opening reactions.[95] There had been no previous precedence of organocerium reagents being used for such reactions. Using organocerium methodology, compound **261** was obtained in 72% yield from **260**. Removing all the protecting groups using BBr_3 and methanol completed the synthesis of pancratistatin. This sequence represents the shortest synthesis of (+)-pancratistatin so far involving only 13 steps and proceeding in 9% overall yield from (+)-pinitol.



Scheme 40

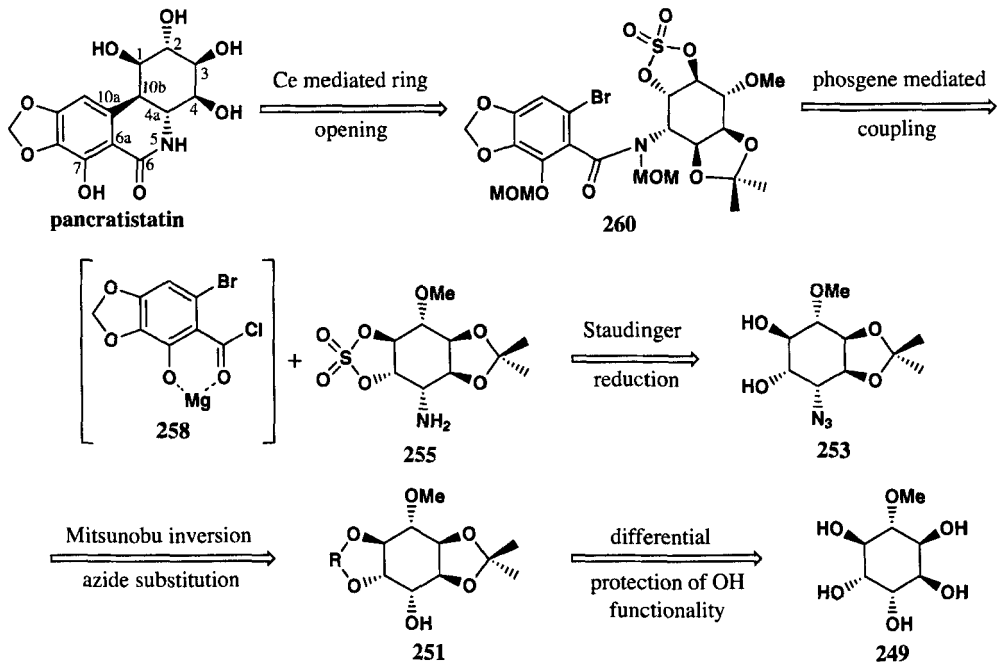
2. *Evaluation of the Strategy*

a) Starting Material. One of the synthetic challenges presented by pancratistatin is the presence of six stereocenters on ring C. Li's synthesis of pancratistatin utilized (+)-pinitol as the starting material. Although relatively expensive, it has four stereocenters already present in pancratistatin.

b) Asymmetric Strategy. The investigators approached the synthesis starting with optically pure (+)-pinitol. Unlike the previous syntheses of pancratistatin (except Pettit's synthesis), where the researchers started with achiral starting materials and introduced asymmetry by enzymatic or chemical desymmetrization, Li and his coworkers approached the synthesis of (+)-pancratistatin utilizing a chiral pool starting material (+)-pinitol.

c) Installation of Stereocenters. (+)-Pinitol has the correct stereochemistry at C1, C2, C3, C4 carbons and opposite geometry at C4a and C10b positions. Mitsunobu inversion of C4a followed by azide substitution successfully installed the C4a nitrogen present in pancratistatin. To attain inversion of C10b, the investigators functionalized the *trans* C1 and C4a diol as a cyclic sulfate. Nucleophilic ring opening using arylcerium allowed for the coupling of the aromatic and the cyclitol portions of pancratistatin with the inversion of configuration at C10b.

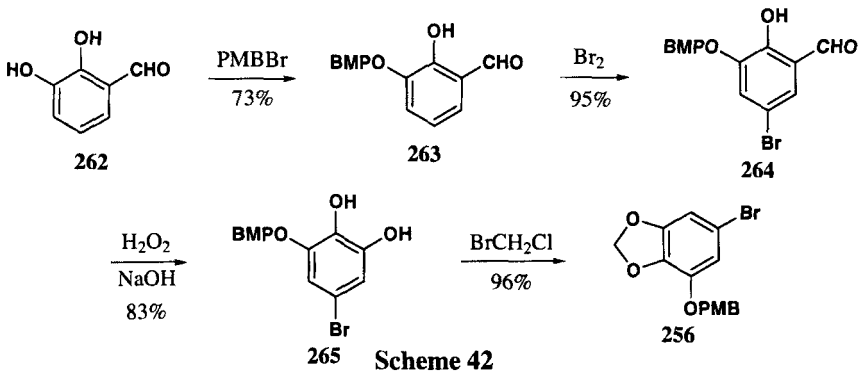
d) Lactam Formation. Phosgene mediated coupling of the amine **255** and the presumed intermediate acid chloride **258** afforded the crucial amide **259**. It was envisioned that generation of the carbanion in **260** by halogen metal exchange would cause nucleophilic ring opening of the cyclic sulfate closing the B ring of pancratistatin. The investigators could not accomplish this step with



Scheme 41

traditional reagents such as ArLi and ArMg, which are strong bases and led to a complex mixture of products. The authors developed a new methodology using organocerium, a softer nucleophile, for the desired ring opening to obtain **261** in 72% yield.

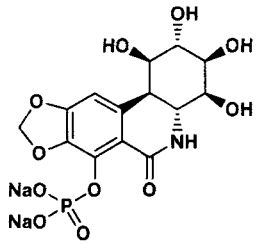
e) Regioselective Introduction of the Substituents on the Aromatic Ring. Aromatic ring A was synthesized from 2,3-dihydroxybenzaldehyde following the procedure developed by Coleman and Gurrala *(Scheme 42)*.[94] Formation of the presumed acid chloride **258** occurred *ortho* to the phenolic hydroxyl and *para* to an oxygen of the methylenedioxy moiety.



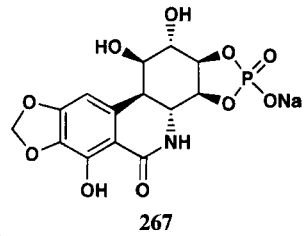
Scheme 42

X. CONCLUSION

The above discussion of the successful strategies, resulting in completed syntheses of the promising medicinal agent (+)-pancratistatin, illustrates the challenge of developing a practical scalable pathway suitable for preparation of multigram quantities of this natural product. Pancratistatin has been in preclinical development for over 20 years with two major hurdles towards its advancement to clinical trials, namely its poor aqueous solubility (53 μg/mL) and lack of availability from natural sources. The first problem has been addressed in a variety of ways including the addition of DMSO or complex formation with nicotinamide to enhance the aqueous solubility.[96] In addition, the use of a 40% aqueous solution of hydroxypropyl-β-cyclodextrin (HPCD) solubilizes pancratistatin up to 1.2 mg/mL.[97] The best solution was, however, offered by Pettit's group with the preparation of phosphate prodrugs **266** and **267** (*Fig. 12*), which were designed to undergo non-specific dephosphorylation in biological systems with the release of pancratistatin.[25,26] These prodrugs have already shown efficacy in experimental *in vivo* cancer systems and their clinical development is anticipated.[20,21] Both **266** and **267**, however, are prepared from the natural product itself and the availability of pancratistatin has become an even more pressing necessity.



266



267

Fig 12

The nine successful synthetic pathways to pancratistatin are summarized in *Table*. Apart from a short 10-step relay synthesis of (+)-pancratistatin from its natural congener (+)-narciclasine, only two other synthetic sequences involve less than 15 steps. This number has been suggested by Hudlicky,[98] and it serves as a good standard for evaluation of practicality of synthetic endeavors. The synthesis of Hudlicky, albeit short, is rather low yielding and very arduous. A number of important issues have to be resolved before the synthesis can be scaled-up. The shortest synthesis so far is the most recent report from Li's group. It proceeds in 13 steps and good 9% overall yield. The main drawback is the expense of the starting material, (+)-pinitol. The practicality, however, should also be assessed on the basis of the number of chromatographic purifications. The investigators are encouraged to combine sequential steps, so that crude material is utilized as often as possible, as well as replace chromatography with recrystallization whenever possible. On the basis of this criterion, none of the reported

syntheses stands out. The publications from Trost's and Li's groups, however, are in a communication format and full procedures have not been disclosed. Therefore, no evaluation can be done until full articles appear.

Table

Year	Author	# of Steps[a]	Yield[a] %	Starting Material	Price per 10 grams	# of Column Purifications
1989	Danishefsky	27	0.16	pyrogallol	$3.71	27
1995	Hudlicky	14	2	bromobenzene	$1	13
1995	Trost	20	8	benzoquinone	$31	NA[b]
1997	Haseltine	24	0.97	benzoquinone	$31	16
1998	Magnus	22	1.2	*o*-vanillin	$6	17
2000	Rigby	23	0.35	methylcyclohex-3-enecarboxylate	$18	17
2001	Pettit	10	3.6	narciclasine	NA[c]	3
2002	Kim	21	4	methyl gallate	$12	15
2006	Li	13	9	(+)-pinitol	$1,027	NA[b]

a) Number of steps and overall yield from commercially available starting material for the longest linear sequence. One-pot procedures are counted as one step. If the utilized starting material is not commercially available, but had been reported previously by other investigators, the number of steps and yields were taken from the cited sources. *b)* Procedures are unavailable. c) Isolated from plant sources.

Finally, the investigators are encouraged to continue optimizing their synthetic routes in search for practicality and scalability. The challenge of pancratistatin clearly requires multigenerational synthetic effort to facilitate its long-awaited advancement to human clinical trials.

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ABBREVIATIONS

Ac, acetyl; AIBN, azobisisobutyronitrile; Bn, benzyl; BOC, *t*-butoxycarbonyl; CSA, camphorsulfonic acid; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, N,N'-dicyclohexylcarbodiimide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMP, Dess-Martin periodinane; DPPA, diphenylphosphorylazide; LDA, lithium diisopropylamine; *m*CPBA, *m*-chloroperbenzoic acid; MsCl, methanesulfonyl chloride; NBS, *N*-bromosuccinimide; NMO, N-methylmorpholine-N-oxide; PMB, *p*-methoxybenzyl; TBAF, tetra-*n*-butylammonium fluoride; TBSCl, *t*-butyldimethylsilyl chloride; Tf_2O, triflic anhydride; $TIPDSCl_2$, 1,1,3,3-tetraisopropyl-1,3-dichlorosiloxane; TIPS, triisopropylsilyl; TMEDA, tetramethylethylenediamine; TMS, trimethylsilyl; TsCl, *p*-toluenesulfonyl chloride

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