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Synthesis of Amaryllidaceae Constituents – An Update

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Abstract: Recent progress in the synthesis of major constituents of the Amaryllidaceae family is reviewed. Total syntheses of pancratistatin, narciclasine, and their 7-deoxy- derivatives, 7-deoxypancratistatin and lycoricidine, respectively, are covered in detail. Also included are preparations of truncated derivatives and unnatural mimics of pancratistatin. The literature coverage begins with the publication of the last major review in 1996 and is complete through the fall of 2004.

Key words: total synthesis, Amaryllidaceae constituents (alkaloids), unnatural and truncated derivatives

1 Introduction

The hydroxylated phenanthridones[1] of the Amaryllidaceae group (Figure 1) have a rich and old history. The plant species in which they originate have been known for their medicinal and also toxic value since ancient Greece.[2] Lycorine (**1**) was first studied for its antitumor activity in 1958.[3] With narciclasine (**3**) identified as a promising antineoplastic agent in 1975[4–8] and pancratistatin (**2**) in 1984,[9] these compounds have been the focus of clinical studies since. While little is known about the mode of action of these compounds, except for limited studies performed with narciclasine,[4,5] there has been quite a bit of activity in SAR with pancratistatin in order to identify the pharmacophore as well as to provide a more bioavailable derivative or potential prodrug.[10,11] In addition to its antitumor activity, pancratistatin also displays a reasonable antiviral profile,[12] most likely because of its aminoinositol moiety, which would effectively serve to act as an inhibitor of common glucosidases.

No less intense has been the activity in the synthetic community. Amaryllidaceae constituents offer an opportunity for stereocontrolled synthesis and many groups responded to this challenge with regard to all major natural products in this group.

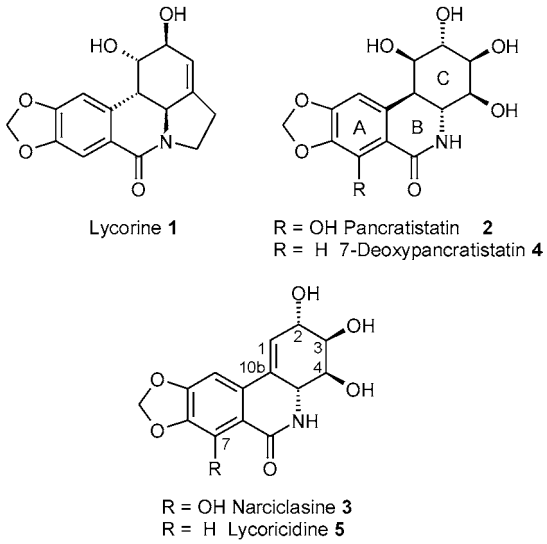

Figure 1 Major compounds of the Amaryllidaceae group

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Milestone accomplishments include the first total synthesis of lycorine by Tsuda et al.,[13] the first synthesis of racemic pancratistatin by Danishefsky in 1989,[14] and the first asymmetric synthesis of this compound by Hudlicky in 1995.[15] Since the last major review written on this subject by Polt in 1996,[16] many total syntheses of these compounds and their unnatural or truncated derivatives have been reported. An abbreviated summary of all total syntheses in this area published to date is shown in Table 1. This review constitutes an update of the major developments in this area for the period 1996 to 2004.

2 Total Syntheses

Key transformations in the syntheses of Amaryllidaceae constituents or unnatural derivatives are shown in blue within the schemes.

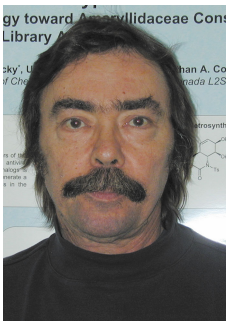
2.1 Pancratistatin

2.1.1 Haseltine (1997)

In 1997 Haseltine and coworkers published a formal synthesis of pancratistatin.[28] The synthetic strategy is based

Biographical Sketches

Uwe Rinner was born in 1975 in Leoben, Austria. He grew up in Knittelfeld and went to high school in Seckau where he was educated with emphasis on Latin and Ancient Greek. In 1994 he graduated from high school and moved to Graz where he attended the Technical University to study chemistry. During his undergraduate career he worked under the guidance of Professor Herfried Griengl in the area of cyanohydrine synthesis and with Professor Tomas Hudlicky toward the synthesis of 7-deoxypancratistatin in Gainesville, Florida. He received his Diplom Ingenieur (MSc) degree in 2000 and moved to Gainesville, Florida to pursue graduate studies in the field of total synthesis of Amaryllidaceae constituents under the direction of Professor Tomas Hudlicky. In 2003, he received his PhD degree and moved as post-doctoral fellow with Professor Hudlicky to Brock University, Canada, where he stayed until May, 2004. Currently, he is working under the guidance of Professor Johann Mulzer at the University of Vienna in the area of terpene synthesis.



Tomas Hudlicky was born in 1949 in Prague, Czechoslovakia, where he received his elementary and middle school education. He was denied access to higher forms of education beyond grade 9 and worked for a number of years in odd jobs around the city as well as a process chemist apprentice in pharmaceutical industry. In 1968 he emigrated to the U.S. with his family and continued his educational experience by attending Blacksburg High School, dropping out in the spring of 1969. Accepted as a probational student at Virginia tech in the fall of that year he graduated with a BSc in chemistry in 1973 and pursued graduate studies at Rice University under the direction of Professor Ernest Wenkert in indole alkaloid total synthesis. Following his PhD in 1977, he spent a year as a postdoctoral fellow with Professor Wolfgang Oppolzer at the university of Geneva working on the synthesis of isocomene. In 1978 he joined the faculty at Illinois Institute of Technology to start his independent career in the field of general methods of synthesis for triquinane sesquiterpenes and other natural products containing five-membered rings. The development of [4+1] and [3+2] annulation methodologies dates to this period of time. In 1982 he moved back to his alma mater, Virginia Tech where he rose to the rank of Professor in 1988. One year later at the 20-year reunion of his High School class of ’69 he was awarded his High School Diploma. The next phase of his research involved the use of prokaryotic enzymes in generating useful chiral metabolites for asymmetric synthesis. In 1995 he moved to the University of Florida and in 2003 he accepted a position at Brock University as Canada Research Chair Professor of Chemistry and Biocatalysis.

His current research interests include the development of enantioselective synthetic methods, biocatalysis, total synthesis of morphine and amaryllidaceae alkaloids, isolation and use of metabolites derived by enzymatic dihydroxylation of aromatics, design of inositol-containing oligomers, and organic electrochemistry. His hobbies include skiing, martial arts, music, and hockey and he enjoys all of these with his 14-year old son Jason.

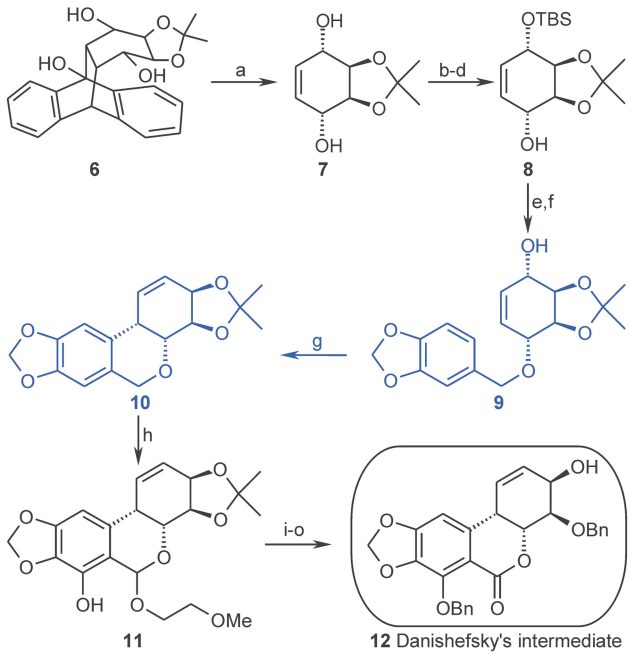
Table 1 Summary of Total Syntheses of Pancratistatin, 7-Deoxypancratistatin, Narciclasine, and Lycoricidine[a]

Year	Natural product	Author	Number of steps (*)[b]
1975	Lycoricidine	Ohta	19[17]
1982	Lycoricidine	Paulsen	13[18,19]
1982	7-Deoxypancratistatin	Paulsen	17*,[18,19]
1987	Lycoricidine	Schubert	17[20]
1989	Pancratistatin	Danishefsky	26[14]
1991	Lycoricidine	Chida	24[21]
1992	Lycoricidine	Hudlicky	9[22]
1995	Pancratistatin	Hudlicky	14[15]
1995	Pancratistatin	Trost	15[23]
1995	7-Deoxypancratistatin	Hudlicky	13[24]
1995	7-Deoxypancratistatin	Keck	21[25]
1995	7-Deoxypancratistatin	Chida	15*,[26]
1996	7-Deoxypancratistatin	Hudlicky	11[27]
1997	**Pancratistatin**	**Haseltine**	**15 (Danishefsky's intermediate)**[28]
1997	**Narciclasine**	**Rigby**	**22**[29]
1998	**Pancratistatin**	**Magnus**	**19**[30]
1998	**7-Deoxypancratistatin**	**Keck**	**13**[31]
1999	**Narciclasine**	**Hudlicky**	**12**[32]
1999	**Narciclasine**	**Keck**	**12**[33]
1999	**Lycoricidine**	**Keck**	**9**[33]
2000	**Pancratistatin**	**Rigby**	**22**[34]
2000	**7-Deoxypancratistatin**	**Plumet**	**19**[35]
2001	**Pancratistatin**	**Pettit**	**10**[36]
2002	**Pancratistatin**	**Kim**	**16**[37]
2002	**Narciclasine**	**Yan**	**12***,[38]
2002	**Lycoricidine**	**Yan**	**12***,[39]

[a] Entries in bold face indicate syntheses discussed in this review.
[b] An asterisk indicates an estimate in cases where exact step count could not be made from published reports.

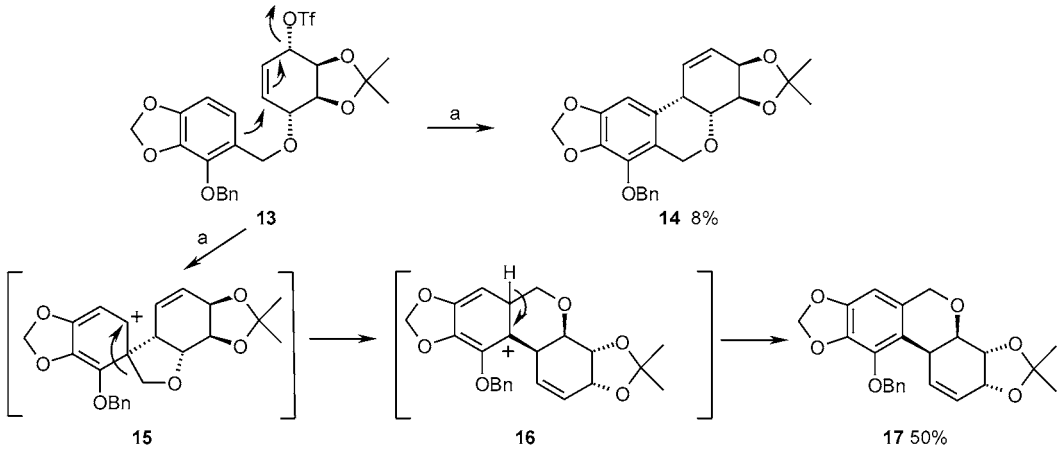
on the coupling of conduritol A with a piperonol derivative and subsequent Lewis acid-mediated ring-closure. Further functionalization of this material was projected to intersect a known intermediate in Danishefsky's synthesis.[14]

The synthesis of the acetonide of conduritol A (**7**) was carried out on multigram scale from anthrone and benzoquinone following a protocol developed by Knapp (Scheme 1).[40] Desymmetrization of conduritol A with lipase, followed by TBS protection of the remaining hydroxyl functionality and cleavage of the acetate afforded alcohol **8** in high overall yield. Initially, a tetra-substituted derivative of piperonol was used to establish the ether linkage between the conduritol and the aromatic moieties, but this approach had to be abandoned when the major product in the ring-closure reaction was identified to be **17** instead of the expected ether **14**. The reaction is believed to proceed through an initial attack of the highly activated *ipso*-position to the tethering element, followed by a 1,2-shift of the alkoxymethyl substituents to furnish pentacycle **17** (Scheme 2).



Scheme 1 *Reaction conditions*: (a) KH, dioxane, reflux, 65–75%; (b) P30 lipase, isopropenylacetate, 94%; (c) TBSCl, imidazole; (d) K_2CO_3, MeOH, 99% (over 2 steps); (e) NaH, piperonyl bromide, *n*-Bu_4NI, THF; (f) TBAF, THF, 83% (over 2 steps); (g) Tf_2O, 2,6-lutidine, CH_2Cl_2, 73%; (h) DDQ, 2-methoxyethanol, CH_2Cl_2, 62%; (i) *t*-BuLi, DME, then $B(OCH_3)_3$, then HOAc–H_2O_2; (j) NaH, BnBr, *n*-Bu_4NI, THF; (k) CSA, THF, H_2O, 71% (over 3 steps); (l) TPAP, NMO, CH_2Cl_2, 91%; (m) HCl (aq), THF, 97%; (n) MEMCl, *i*-Pr_2NEt, CH_2Cl_2, 65%; (o) *p*-TsOH, MeOH, H_2O, 67%.

Benzylation of the conduritol derivative **8** using piperonyl bromide followed by cleavage of the silyl ether afforded alcohol **9** (Scheme 1), which was used successfully to establish the B-ring of the natural product in a reaction with triflic anhydride and 2,6-di-*tert*-butylpyridine. Oxidation of the benzylic position with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and methoxyethanol was followed by the introduction of the phenolic hydroxyl functionality. Hydrolysis of the acetal and tetrapropylammonium perruthenate–4-methyl-morpholine *N*-oxide (TPAP–NMO) oxidation to the lactone with subsequent cleavage of the

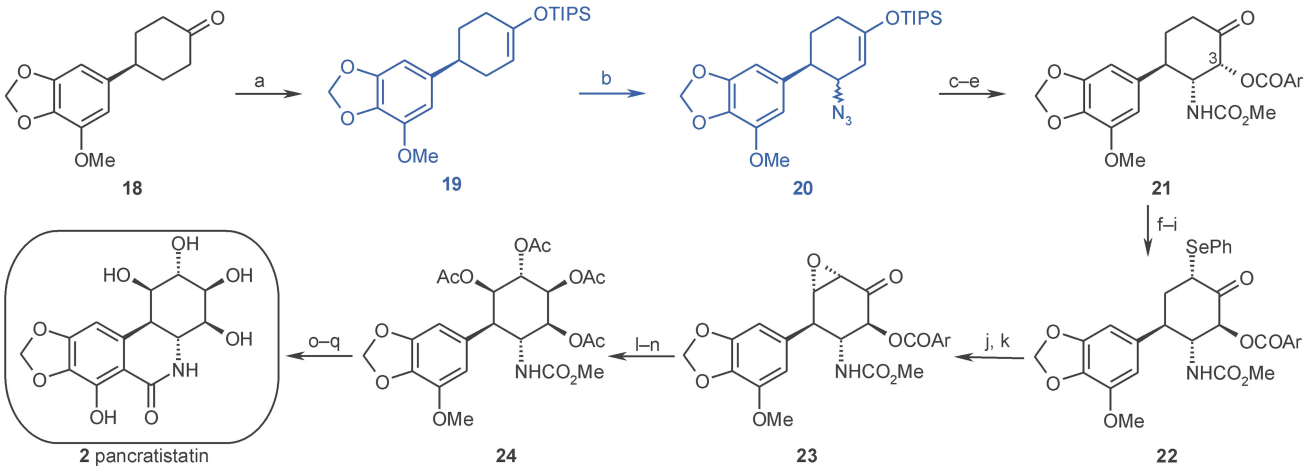


Scheme 2 *Reaction conditions*: (a) Tf_2O, 2,6-di-*t*-butylpyridine, CH_2Cl_2, 0 °C to r.t.

acetonide afforded the corresponding lactone diol. This material was transformed into intermediate **12** by protection of the allylic hydroxyl group with MEM chloride followed by benzylation of the remaining hydroxyl functionality and subsequent cleavage of the MEM group. As alcohol **12** is an advanced intermediate in Danishefsky's synthesis of pancratistatin, this constituted a formal synthesis of the natural product.

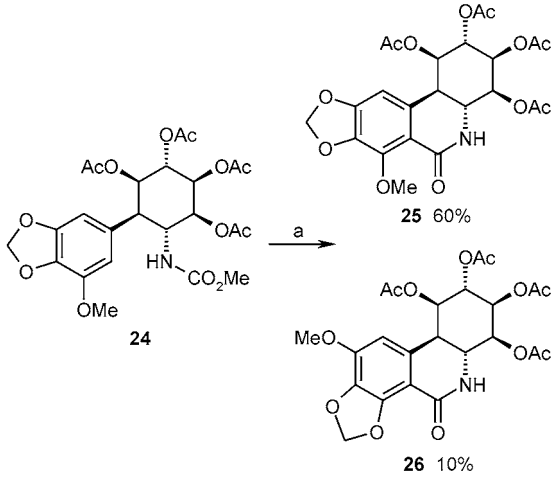
2.1.2 Magnus (1998)

Magnus and Sebhat presented a total synthesis of pancratistatin[30] based on β-azido triisopropylsilyl enol ether functionalization.[41] Treatment of prochiral arylcyclohexanone **18** with lithium (+)-bis(methylbenzyl)amide followed by triisopropylsilyl triflate (TIPSOTf) afforded chiral TIPS ether **19** with an ee of 85% (Scheme 3). Treatment of this material with $(PhIO)_n$–$TMSN_3$ in methylene chloride at –15 °C yielded azide **20** in excellent 95% yield as an inseparable mixture of *trans*- and *cis*-diasteromers in a 3.5:1 ratio. Reduction of the azide in **20** with $LiAlH_4$ in diethyl ether followed by the installation of the carbamate moiety afforded a mixture of diasteromers, which was successfully separated by crystallization. When the major *trans*-isomer was allowed to react with *m*-CPBA in methylene chloride in the presence of imidazole, benzoate **21** was isolated in excellent yield after mild acid hydrolysis of the TIPS ether. Inversion of the stereocenter at C-3 on treatment of ketone **21** with *t*-BuOK–HMPA proceeded smoothly in 91% yield. Subsequently, the material was reacted withTMSOTf–Et_3N to afford the bis-TMS adduct and exposed to $PhSeOCOCF_3$ yielding selenide **22**, which was oxidized. Following the selenoxide elimination the enone was treated with H_2O_2 under mildly basic conditions to afford epoxide **23**. Reduction of the ketone functionality in **23** with L-Selectride in THF, opening of the epoxide and treatment of the intermediate diol with acetic anhydride afforded peracetylated carbamate **24**, which



Scheme 3 *Reaction conditions*: (a) (+)-bis(α-methylbenzyl)amine, *n*-BuLi, THF, –78 °C, then LiCl, TIPSOTf, THF, 95%; (b) $(PhIO)_n$, $TMSN_3$, CH_2Cl_2, –15 °C, 95%; (c) $LiAlH_4$, Et_2O; (d) MeOCOCl, pyridine, CH_2Cl_2, 56% (over 2 steps); (e) *m*-CPBA, imidazole, CH_2Cl_2, 83%; (f) EtOH, HCl, H_2O, 88%; (g) *t*-BuOK, HMPA, 91%; (h) TMSOTf, Et_3N, CH_2Cl_2; (i) $AgCO_2CF_3$, PhSeCl, CH_2Cl_2; (j) H_2O_2, pyridine, CH_2Cl_2, 85% (over 3 steps); (k) $NaHCO_3$, H_2O_2, THF, MeOH, H_2O; (l) L-Selectride, THF, 63% (over 2 steps); (m) $C_6H_5CO_2Na$, H_2O, 100 °C; (n) Ac_2O, pyridine, 60% (over 2 steps); (o) Tf_2O, DMAP, CH_2Cl_2, 60%; (p) BBr_3, CH_2Cl_2, –78 °C, 73%; (q) MeONa, THF, 87%.

was allowed to react under Banwell's modified Bischler–Napieralski conditions[42] to yield the phenanthridone skeleton in 60% yield. In Magnus' synthesis, the Bischler–Napieralski reaction was not regiospecific and produced 10% of the corresponding regiosisomer **26** resulting from electrophilic substitution *ortho* to the methylenedioxy functionality (Scheme 4). The presence of the acetoxy functionality at C-1 in **24** improved the ratio of regioisomers. Derivatives of **24** lacking the acetoxy functionality at C-1 gave mixtures of corresponding lactams in a ratio of 3:1. Exposure of the inseparable mixture of regioisomers to BBr_3 afforded cleavage of the methyl group on the phenol at C-7 and the resulting material was treated with $NaOCH_3$. Pancratistatin was obtained in an overall yield of 1.2% from arylcyclohexanone **18**.



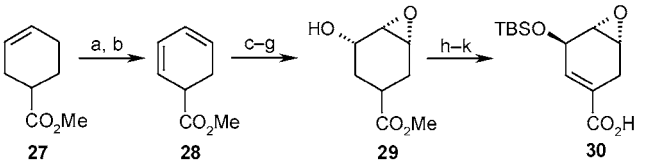
Scheme 4 *Reaction conditions*: (a) Tf_2O, DMAP.

2.1.3 Rigby (2000)

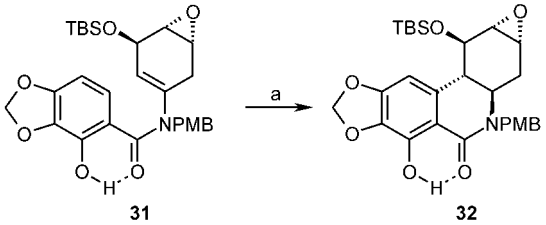
The key step in Rigby's synthesis of pancratistatin[34] is a hydrogen bond-controlled aryl enamide photcyclization reaction to generate advanced intermediate **36**. Aryl enamide **35** was synthesized by addition of a metalated arene to a protected vinyl isocyanate. Further functionalization of the C-ring and deprotection would complete the synthesis.

This approach was also successfully used in the synthesis of narciclasine[29] – outlined in Section 2.3 of this review. Epoxy acid **30**, a key-intermediate in Berchtold's synthesis of (–)-chorismic acid,[43–45] was found to be the ideal material for a precursor to the C-ring of the natural compound (Scheme 5). Following Berchtold's protocol, epoxy acid **30** was prepared in 11 steps and in an overall yield of 8–9% from commercially available ester **27**.

Initial photocyclization studies were carried out with substrate **31**, derived from epoxy acid **30**. However, the presence of the β-silyloxy group lead to the incorrectly *trans*-fused tetracycle **32** (Scheme 6). This outcome required a slight change in the synthetic strategy and further studies were carried out using *syn*-epoxy alcohol **33** with the correct stereochemistry. Protection of the hydroxyl functionality in acid **33** and formation of the isocyanate by a Curtius rearrangement to **34** was followed by coupling with the aromatic portion of the Amaryllidaceae constituent. Protection of the amide nitrogen and deprotection of the phenolic hydroxyl functionality and subsequent irradiation of the material afforded phenanthridone **36** with the correct *trans* relationship. This material, the last common intermediate in Rigby's synthesis of pancratistatin and narciclasine (Section 2.3), was treated with sodium hydride and methyl iodide to alkylate the phenolic hydroxyl group. The correction of the stereochemistry at C-1 of the natural product was carried out by cleavage of the silyl group, followed by Dess–Martin oxidation of the hydroxyl functionality, reduction of the ketone with $NaBH_4$ and subsequent benzylation of the now inverted hydroxyl group at C-1 with benzyl bromide to generate epoxide **37**. Treatment of this material with $(PhSe)_2$, $NaBH_4$, and H_2O_2 afforded allylic alcohol **38**, which was transformed into pancratistatin by dihydroxylation of the double bond with OsO_4 in *t*-BuOH, followed by deprotection of the hydroxyl groups and the amide nitrogen. The natural product was obtained in 22 steps from ester **27** (Scheme 7).



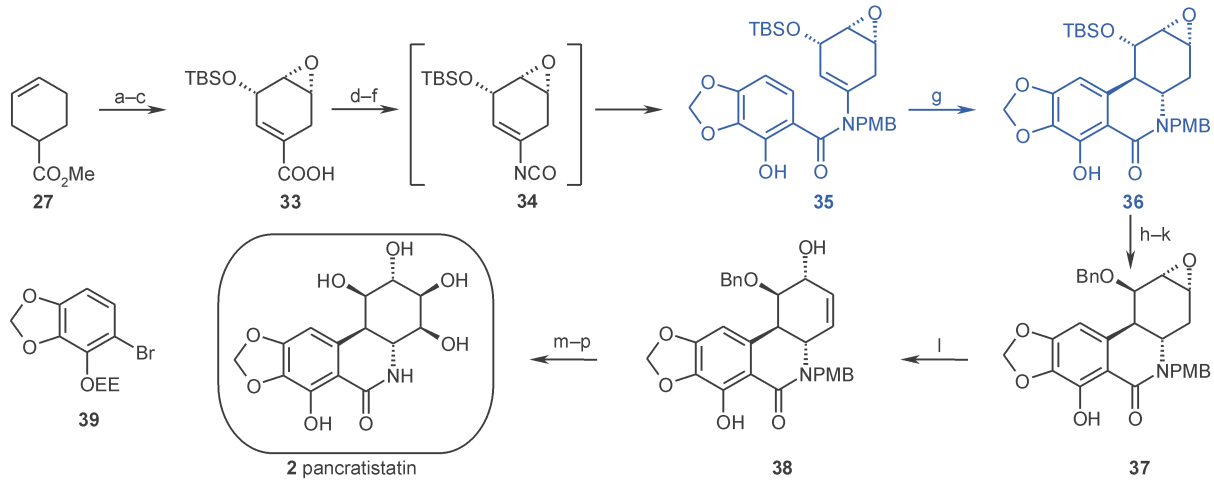
Scheme 5 *Reaction conditions*: (a) NBS, AIBN; (b) Bu_3SnH, 75% (over 2 steps); (c) O_2, Rose Bengal, hν, (d) $RuCl_2(PPh_3)_2$; (e) MeONa, MeOH, 42% (over 3 steps); (f) *n*-PrCOCl, Et_3N; (g) cholesterol esterase, 40% (over 2 steps); (h) DIAD, PPh_3, HOAc; (i) MeONa; (j) TBSCl, imidazole; (k) LiOH, 66% (over 4 steps).



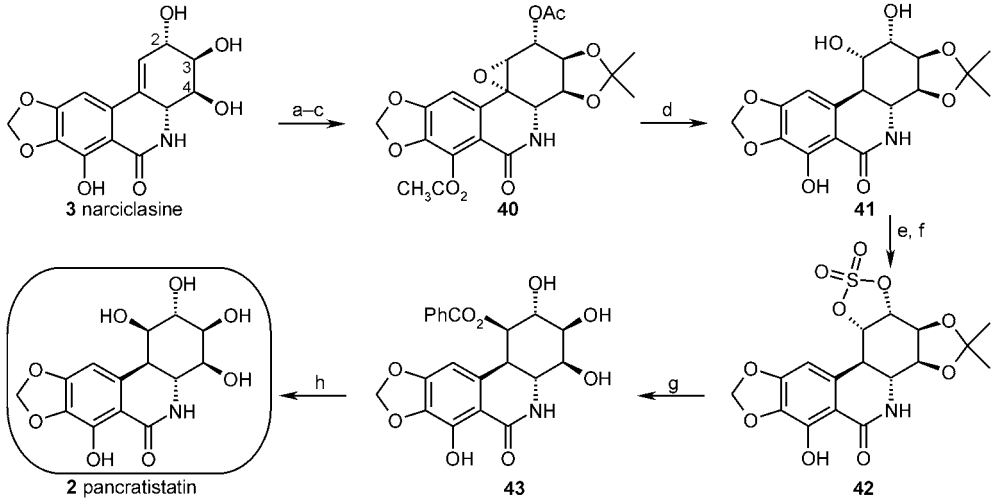
Scheme 6 *Reaction conditions*: (a) hν, C_6H_6, 50%.

2.1.4 Pettit (2001)

Because of the higher availability of narciclasine in the plant extracts (18–200 mg/kg wet plant material),[46] Pettit and coworkers developed a synthesis of pancratistatin from the more easily obtained Amaryllidaceae constituent narciclasine.[36] Acetylation of the 3,4-acetonide of narciclasine at C-3 and C-7 was followed by oxidation of the olefin to afford epoxide **40** (Scheme 8). Hydrogenation of this material in the presence of 10% palladium on carbon and subsequent saponification yielded in a mixture of four compounds, one of them, the desired diol **41**, in 28% yield. Treatment of diol **41** with thionyl chloride and



Scheme 7 *Reaction conditions*: (a) steps (a)–(g) see Scheme 5; (b) TBSCl, imidazole, 98%; (c) LiOH, 81%; (d) DPPA, $C_6H_5CH_3$, 110 °C, then **39**, *n*-BuLi, THF, –70 °C, 52%; (e) NaH, PMBBr; (f) PPTS, 73%; (over 2 steps); (g) hν, C_6H_6, 30%; (h) NaH, MeI, 98%; (i) TBAF, 85%; (j) Dess–Martin, CH_2Cl_2; (k) $NaBH_4$, –20 °C; (l) NaH, BnBr, 73% (over 3 steps); (m) $(PhSe)_2$, $NaBH_4$, H_2O_2, reflux, 84%; (n) OsO_4, *t*-BuOH, 89%; (o) $Pd(OH)_2/H_2$, 87%; (p) LiCl, DMF, 78%.



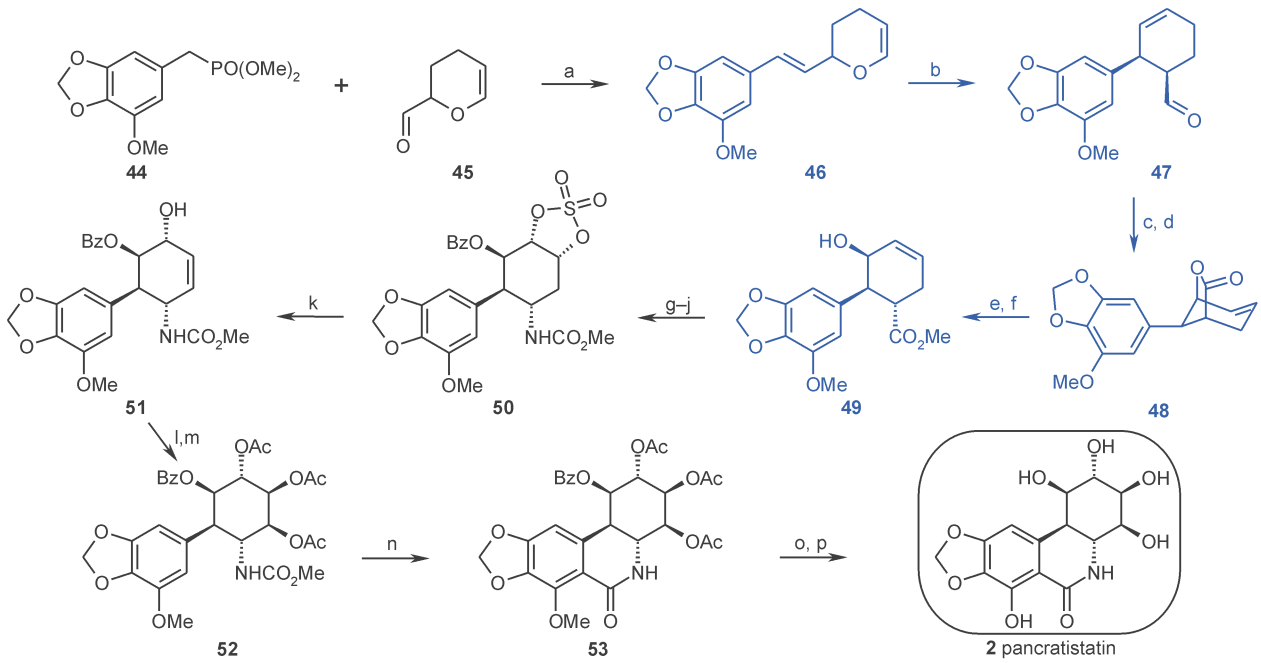
Scheme 8 *Reaction conditions*: (a) DMF, DMP, *p*-TSOH, 97%; (b) Ac_2O, pyridine, 81%; (c) *m*-CPBA, phosphate puffer, CH_2Cl_2, H_2O, 52%; (d) i) H_2, Pd/C 10%; ii) K_2CO_3, MeOH, H_2O, 28%; (e) $SOCl_2$, Et_3N, THF; (f) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, MeCN, CCl_4, H_2O, 47% (over 2 steps); (g) i) $PhCO_2H$, $CsCO_3$, DMF; ii) THF, H_2O, H_2SO_4, 74%; (h) K_2CO_3, MeOH, 75%.

oxidation of the epimeric cyclic sulfites with sodium periodate and a catalytic amount of ruthenium trichloride afforded cyclic sulfate **42** in 47% yield from alcohol **41**. Nucleophilic opening of the cyclic sulfate with cesium benzoate followed by hydrolysis of the alkyl sulfate with simultaneous cleavage of the acetonide using a catalytic amount of sulfuric acid allowed the isolation of benzoate **43**. Deprotection of the benzyl group at C-1 yielded in pancratistatin in 10 steps and an overall yield of 3.6% from narciclasine.

2.1.5 Kim (2002)

Kim's approach toward racemic pancratistatin features a Claisen rearrangement of dihydropyran derivative **46** as the key step (Scheme 9).[37] Cyclohexene derivative **47** was further functionalized to the fully hydroxylated material **52**, which was used to establish the phenanthridone through Bischler–Napieralski ring-closure reaction.

Reaction of commercially available acrolein dimer **45** with phosphonate **44** (obtained in a five-step sequence from methyl gallate)[47] under Horner–Wadsworth–Emmons conditions afforded the desired *trans*-olefin **46** in 60% yield (92% based on recovered starting material, see Scheme 9). Heating of this material in a sealed tube to 250 °C allowed the isolation of the *cis*-disubstituted cyclohexene **47** in 78% yield as a single isomer from the Claisen rearrangement. Oxidation of the aldehyde functionality in **47** was followed by iodolactonization and treatment of the iodolactone with DBU to form bicyclic lactone **48**. Methanolysis of the lactone in **48** at reflux afforded methyl ester **49** with epimerization at C-4a



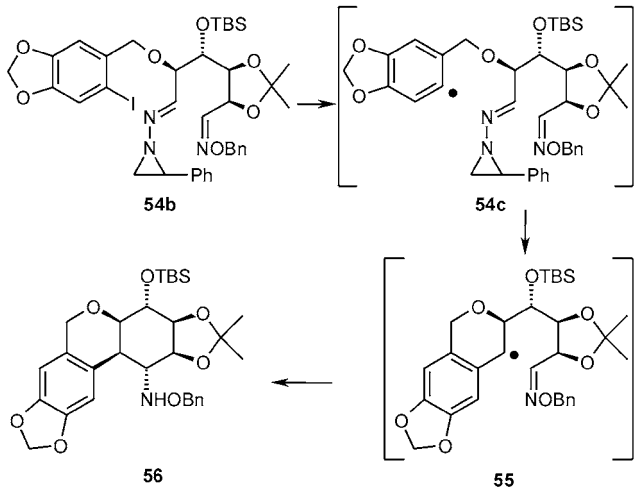
Scheme 9 *Reaction conditions*: (a) LHMDS, THF, 0 °C, 22 h, 60% (92% based on recovered starting material); (b) $C_6H_5CH_3$, sealed tube, 250 °C, 78%; (c) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, THF, *t*-BuOH, H_2O, 90%; (d) i) KI_3, $NaHCO_3$ (aq), CH_2Cl_2; ii) DBU, C_6H_6, reflux, 78%; (e) MeONa, MeOH, reflux, 93%; (f) LiOH, THF, 99%; (g) i) DPPA, Et_3N, $C_6H_5CH_3$, reflux; ii) MeONa, MeOH, 82%; (h) BzCl, Et_3N, DMAP, CH_2Cl_2, 99%; (i) OsO_4, NMO, THF–H_2O, 96%; (j) i) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C; ii) oxone, $RuCl_3{\cdot}3H_2O$, EtOAc, MeCN, THF, 83%; (k) DBU, $C_6H_5CH_3$, reflux, then H_2SO_4, H_2O, THF, 67%; (l) OsO_4, NMO, THF, H_2O, 88%; (m) Ac_2O, DMAP, pyridine, CH_2Cl_2, 77%; (n) Tf_2O, DMAP, CH_2Cl_2, 0 °C, 78%; (o) BBr_3, CH_2Cl_2, –78 °C to 0 °C, 65%; (p) MeONa, MeOH, THF, 83%.

(pancratistatin numbering). Saponification of the methyl ester was followed by a modified Curtius rearrangement with diphenylphosphoryl azide in refluxing toluene and treatment of the resulting isocyanate with NaOMe–MeOH to afford the corresponding carbamate in good yield. Benzylation of the free hydroxyl functionality was followed by dihydroxylation of the double bond with OsO_4 and installation of the cyclic sulfate **50** via the formation of a cyclic sulfite and further oxidation of the sulfur atom with oxone and $RuCl_3{\cdot}H_2O$. The formation of the allylic alcohol **51** was effected by reaction of sulfate **50** with DBU in refluxing toluene followed by acidic work up and used in a dihydroxylation with OsO_4 to afford the corresponding triol. Peracetylation with acetic anhydride gave carbamate **52**, which upon treatment with triflic anhydride and DMAP in CH_2Cl_2 yielded phenanthridone **53**.[42] The ring-closure reaction also provided the corresponding regioisomer in a ratio of 7:1 in favor of **53** as an inseparable mixture. This finding is in perfect agreement with the results obtained by Magnus and Sebhat in their synthesis of the natural product.[30] Cleavage of the anisole functionality with BBr_3 and removal of the benzoate and acetate groups concluded this synthesis.

2.2 7-Deoxypancratistatin

2.2.1 Keck (1998)

In 1995 Keck and coworkers reported their first total synthesis of 7-deoxypancratistatin by a radical cyclization approach.[25] In that particular synthesis a benzylic radical intermediate was generated and cyclized onto the O-protected oxime. Except for the differences in the oxidation state and the nature of protecting groups the key intermediate in the synthesis of 1995 resembled compound **55** (Scheme 10). A second-generation total synthesis of this Amaryllidaceae constituent was published in 1998 and featured a radical cascade strategy depicted in Scheme 10.[31]



Scheme 10

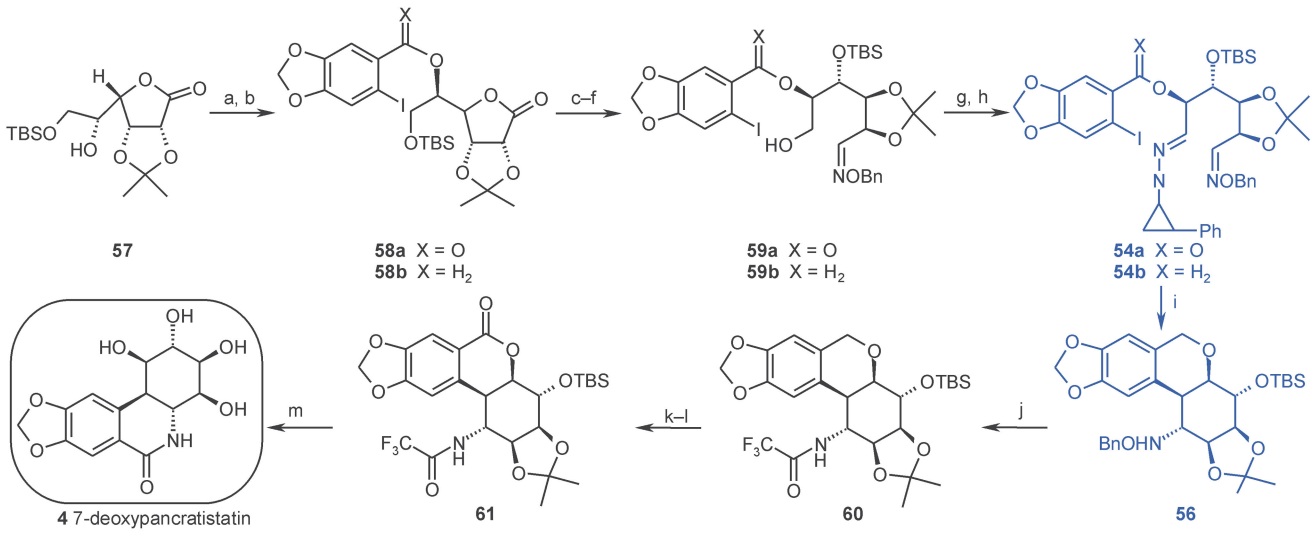
The key step in the latter synthesis is an application of a radical cascade as developed by Kim and coworkers.[48,49] Such a 6-*exo*-trig cyclization, i.e., **54c** to **55**, occurs with the loss of nitrogen and styrene, driven by the energy release in the aza-cyclopropylcarbinyl rearrangement (Scheme 10) and generated a similar radical intermediate **55** as in Keck's first total synthesis of the natural product. Radical **55** then successfully underwent the cyclization reaction to yield the desired material as a single diastereomer.

The first attempt began by esterification of lactone **57**, accessible in five steps from glucose,[50] with piperonylic acid; however, this approach was abandoned because of problems with the radical ring-closure. Probable reasons for the failure of the ester series, i. e., the closure of **54a**, may have been in the preferred s-*trans*-configuration of the ester rather than the s-*cis*-configuration that would favor the radical cyclization. A slightly modified synthesis was designed with an ether linkage instead of the ester functionality, as shown in Scheme 11 with the series **58b**, **59b**, and **54b**. Conversion of iodopiperonol to the corresponding trichloroacetamide by treatment with NaH and Cl_3CCN followed by alkylation with alcohol **57** afforded ether **58b** in 75% yield. The lactone was reduced to the lactol with L-Selectride, and the aldehyde was transformed into an *O*-benzyloxime. Silylation of the secondary alcohol and selective desilylation of the primary hydroxyl functionality with HF–pyridine gave alcohol **59b** which was oxidized (TPAP, NMO) and treated with 1-amino-2-phenylaziridine to form the precursor for the key radical cyclization step, namely **54b**. The cyclization was carried out in benzene at 80 °C with Ph_3SnH and AIBN and afforded **56** in excellent 78% yield. Trifluoroacetamide **60**, generated by cleavage of the N-O bond with SmI_2 and quenching of the reaction with TFAA, was oxidized to lactone **61** with PCC in CH_2Cl_2. Simultaneous cleavage of the silyl protecting group and the acetonide afforded the corresponding lactone triol, which upon treatment with K_2CO_3 in methanol afforded the natural product via the lactone–lactam rearrangement. The second-generation synthesis of the natural product with an overall yield of 7% and 13 linear steps from 6-iodopiperonol constituted a clear improvement over Keck's first synthesis of this natural product, which required a total of 21 steps.

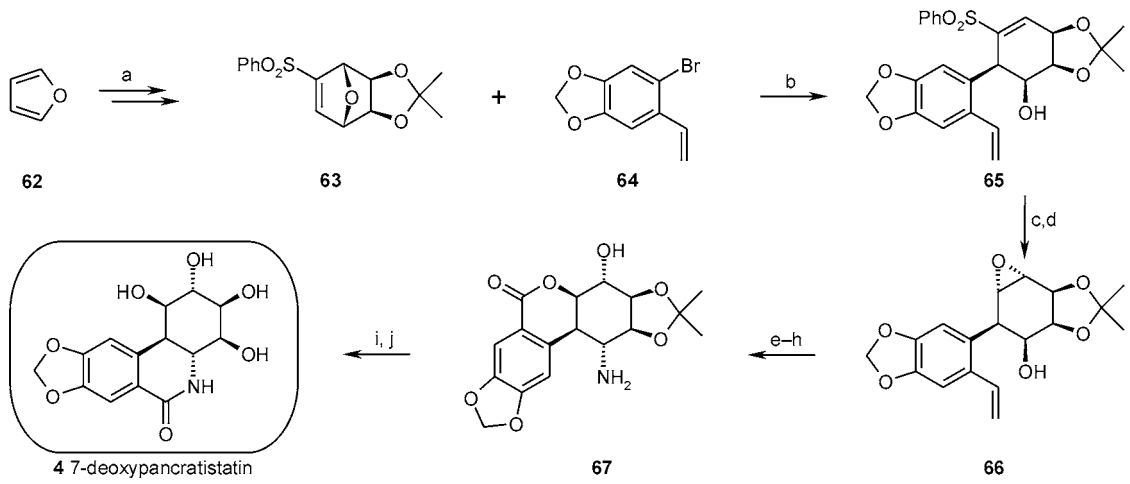
2.2.2 Plumet (2000)

Plumet's strategy for the total synthesis of 7-deoxypancratistatin[35] is based on the ring-opening of vinyl sulfone **63**, accessible from furan in 10 steps and 26% overall yield,[51] with the metalated species of aromatic substrate **64** (Scheme 12). This ring-opening would afford the correct configuration at C-10b of the natural product. Correction of the stereochemistry of the hydroxyl group at C-4b obtained in the ring-opening reaction, would be required. The *trans*-diol at C-1 and C-2 would be generated by opening of an oxirane ring. The phenanthridone skeleton finally would be generated by a lactone–lactam rearrangement.

The opening of vinyl sulfone **63** with aryl bromide **64** was carried out successfully to afford the desired alcohol **65** in excellent yield. Treatment of this material with *t*-BuOOLi resulted in the formation of the corresponding epoxide as a single isomer. Reductive cleavage of the sulfone with sodium amalgam afforded epoxy alcohol **66**. Conversion of the alcohol to an azide, oxidation of the aryl olefin and intramolecular opening of the epoxide afforded, after reduction of the azido group, lactone **67**. Cleavage of the acetonide functionality and lactone–lactam rearrangement completed this synthesis of 7-deoxypancratistatin in 19 steps from furan and an overall yield of 8%.



Scheme 11 *Reaction conditions*: (a) 6-iodopiperonol, NaH, Cl_3CCN, 0 °C; (b) TfOH, THF, 0 °C, 75% (over 2 steps); (c) L-Selectride, CH_2Cl_2, –78 °C; (d) $BnONH_2$·HCl, pyridine, 96% (over 2 steps); (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (f) HF–pyrdidine, THF, 84% (over 2 steps); (g) TPAP, NMO, 4 Å MS; (h) 1-amino-2-phenyl-aziridine, EtOH, 0 °C, 83% (over 2 steps); (i) Ph_3SnH, AIBN, C_6H_6, reflux, 78%; (j) SmI_2, then TFAA, 88%; (k) PCC, CH_2Cl_2, 83%; (l) BF_3·OEt_2; (m) K_2CO_3, MeOH, 88% (over 2 steps). Reaction conditions and yields for reactions (c)–(h) correspond to the ether series.

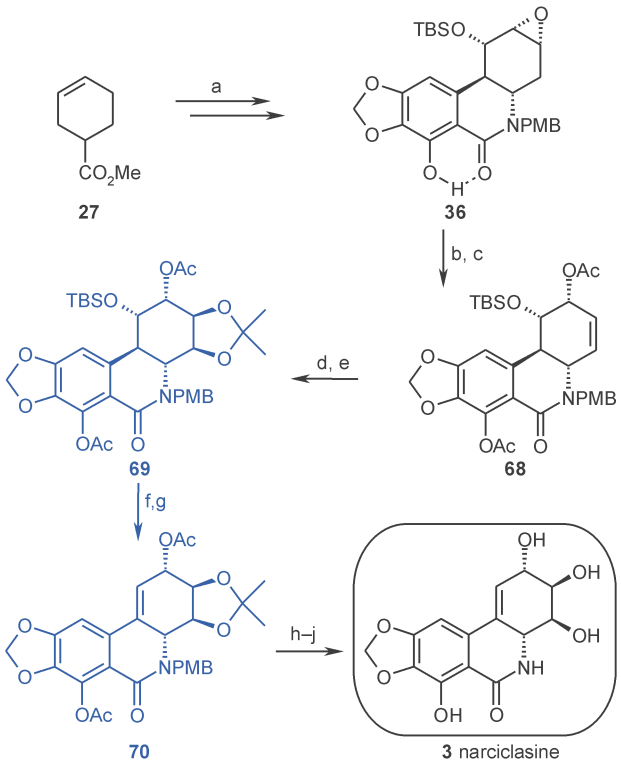


Scheme 12 *Reaction conditions*: (a) 10 steps, for experimental procedure see ref.[40]; (b) BuLi, THF, $C_6H_5CH_3$, –78 °C, 96%; (c) *t*-BuOOH, BuLi, THF, –78 °C, 84%; (d) Na-Hg, MeOH, THF, –23 °C, 81%; (e) Tf_2O, pyridine, CH_2Cl_2, 0 °C; (f) Bu_4NN_3, benzene, 82% (over 2 steps); (g) $NaIO_4$, $RuCl_3$, MeCN, CCl_4, H_2O, 79%; (h) H_2 40 psi, Pd/C 10%, MeOH, 88%; (i) CF_3COOH, 0 °C; (j) K_2CO_3, MeOH, 82% (over 2 steps).

2.3 Narciclasine

2.3.1 Rigby (1997)

In addition to pancratistatin (see Section 2.1),[34] Rigby's photocyclization approach also yielded the synthesis of narciclasine.[29] The initial synthetic strategy is described in Section 2.1.



Scheme 13 *Reaction conditions*: (a) see Scheme 7; (b) $(PhSe)_2$, $NaBH_4$, oxidation; (c) NaH, AcCl, 48% (over 2 steps); (d) OsO_4, TMNO, *t*-BuOH; (e) TsOH, 2,2-DMP, 76% (over 2 steps); (f) F^-, THF; (g) Burgess reagent, 64% (over 2 steps); (h) K_2CO_3, MeOH; (i) *n*-BuLi, THF, O_2; (j) TsOH, 37% (over 3 steps).

Commercially available ester **27** was thus converted into phenanthridone **36** with a photocyclization as the key step as described in Section 2.1. Epoxide **36** was treated with diphenyldiselenide–$NaBH_4$, followed by H_2O_2 to install the double bond between C-3 and C-4 (Scheme 13). The free hydroxyl functionality was acylated to afford tetracycle **68**, which was dihydroxylated and converted to acetonide **69**. Cleavage of the silyl ether at C-1 and dehydration of the alcohol with Burgess reagent in refluxing benzene gave alkene **70**. Cleavage of the protecting groups provided the natural product in 22 steps and 0.3% overall yield.

2.3.2 Hudlicky (1999)

Our synthesis of narciclasine[32] is based on the utilization of cyclohexadiene diol **72** (Scheme 14) derived by the whole-cell fermentation of 1,3-dibromobenzene with recombinant *Escherichia coli* JM109 (pDTG601A) according to a well established procedure.[52,53] Other key steps in this synthesis are the Suzuki coupling of Diels–Alder adduct **73** with boronic acid **77** and the Bischler–Napieralski ring-closure reaction (Scheme 14).

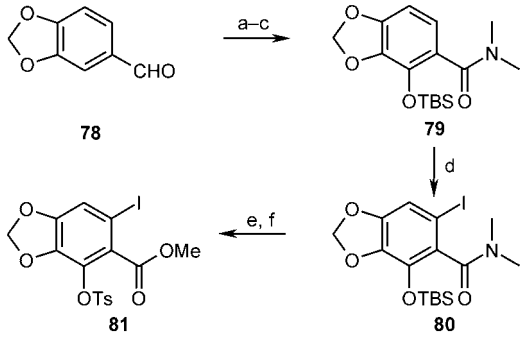
Biooxidation of 1,3-dibromobenzene with *E. coli* JM109 (pDTG601A) afforded diol **72**, the starting material for this approach, with an ee of >99%. Because of the symmetry inherent in *m*-dibromobenzene only one enantiomer is possible as a result of the biooxidation. Cyclohexadiene diol **72** was allowed to react with 2,2-DMP to give the corresponding acetonide. Without further purification this material was used in a hetero-Diels–Alder reaction to generate oxazine **73** in an overall yield of 70% (Scheme 14). Suzuki coupling of bromide **73** with boronic acid **77** afforded the desired coupled product which was treated with *tris*-trimethylsilylsilane to form α,β-unsaturated ketone **74** in moderate yield. Alternatively, ketone **74** was also obtained in a one-pot procedure from oxazine **73** by Suzuki coupling followed by reduction with $Mo(CO)_6$ in

a refluxing mixture of acetonitrile and water without the isolation of intermediates. Reduction of the ketone in **74** with $NaBH_4$ was followed by inversion of the stereochemistry at C-2 under Mitsunobu conditions as reported by Chida. In this way benzoate **75** with the correct narciclasine stereochemistry was obtained. Cleavage of the acetonide and acetylation of the free hydroxyl functionalities with acetic anhydride and pyridine was required for successful Bischler–Napieralski ring-closure (modified conditions as reported by Banwell)[42] and phenanthridone **76** was isolated in 40% yield. Cleavage of the protecting groups and the phenolic methyl group with LiCl afforded the natural product in 12 steps from 1,3-dibromobenzene.

2.3.3 Keck (1999)

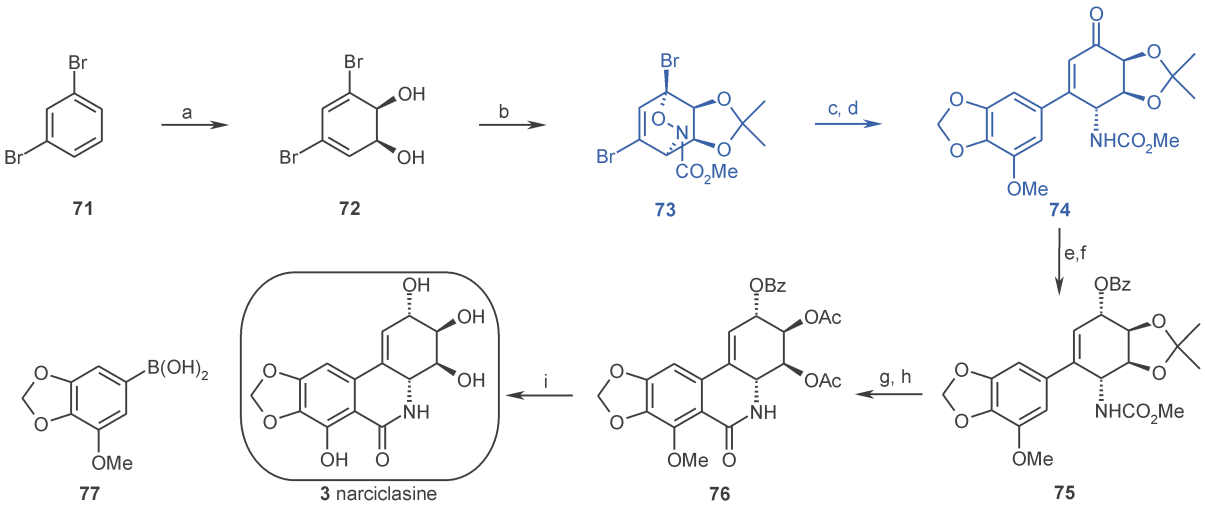
In 1996 Keck reported the total synthesis of *ent*-lycoricidine (see Section 3).[54] The strategy in that particular synthesis was based upon a thiyl-initiated radical ring-closure of a disubstituted acetylene derivative, constructed by a coupling reaction of a suitable aromatic substrate and a mono-substituted alkyne. D-Gulonolactone was chosen as an ideal precursor for the C-ring of the natural product with three of the four stereocenters set correctly. The synthesis of narciclasine[33] (as well as the synthesis of natural lycoricidine, Section 2.4) are modifications of the strategy developed for the preparation of *ent*-lycoricidine.

The synthetic strategy required coupling of an aryl substrate with the acetylene compound derived from D-gulonolactone. The synthesis of this aromatic coupling partner is shown in Scheme 15. Piperonal (**78**) was converted to the corresponding *N*,*N*-dimethylamide following a procedure of Gilman.[55] *ortho*-Lithiation of this material and treatment with trimethyl borate afforded amide **79** after oxidative work up with H_2O_2 and silylation of the resulting phenol with TBSCl and imidazole. Directed metallation protocol was utilized for iodination to **80**. Conversion of this material to the corresponding methyl ester was attempted by reduction of the amide to the aldehyde and subsequent Corey–Gilman–Ganem oxidation but this procedure failed. The ester was therefore prepared by treatment of amide **80** with trimethyloxonium tetrafluoroborate and tosylation of the phenolic hydroxyl group.



Scheme 15 *Reaction conditions*: (a) MnO_2, NaCN, Me_2NH, *i*-PrOH, 95%; (b) i) *n*-BuLi, TMEDA, –104 °C, $B(OMe)_3$, THF; ii) HOAc, H_2O_2, 78%; (c) TBSCl, imidazole, 95%; (d) *n*-BuLi, TMEDA, –104 °C, Et_2O, I_2, 72%; (e) Me_3OBF_4, Na_2HPO_4, MeCN, 91%; (f) TsCl, pyridine, 86%.

D-Gulonolactone was converted to the 2,3-acetonide **82** in a two-step procedure.[56] As mentioned earlier, this material contains the correct stereochemistry for all three hydroxyl groups of narciclasine as well as lycoricidine. Oxidative cleavage of the diol with $NaIO_4$ was followed by Corey–Fuchs reaction, and dibromide **83** was isolated in 80% yield over two steps (Scheme 16). Subsequently, the lactone was reduced to the corresponding lactol with L-Selectride and directly converted to the *O*-benzyl amine **84**. Exposure of this material to BuLi in Et_2O at low temperature gave the alkyne derivative, which was used in a



Scheme 14 *Reaction conditions*: (a) *E. coli* JM109 (pDTG601A), 4 g/L; (b) i) DMP, acetone, TsOH, r.t.; ii) $NHCO_2Me$, $NaIO_4$, r.t., 70%; (c) borate 77, $Pd(PPh_3)_4$, aq Na_2CO_3, PhH, reflux, 30%; (d) TTMSS, AIBN, PhH, reflux, 80%; (e) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 80%; (f) BzOH, Bu_3P, DEAD, THF, r.t., 65%; (g) i) Dowex 50X8-100, MeOH, r.t.; ii) Ac_2O, pyridine, DMAP, r.t., 70%; (h) Tf_2O, DMAP, CH_2Cl_2, 0 °C, 40%; (i) i) Amberlyst A21, MeOH; ii) LiCl, DMF, 120 °C, 20%.

Pd-catalyzed coupling reaction with aromatic substrate **81** to provide **85**, the required precursor for the key cyclization step. The radical cyclization step was carried out with thiophenol in toluene under irradiation and allowed for isolation of the desired product **86** in 88% yield. Cleavage of the tosyl group in **86** with SmI_2 and methylation of the phenolic hydroxyl functionality was followed by Me_3Al-catalyzed cyclization to the phenanthridone skeleton in 72% yield. Reductive removal of the thioether with SmI_2 and treatment of the obtained material with TFA afforded narciclasine in twelve steps from acetonide **82**.

2.3.4 Yan (2002)

Elango and Yan presented a total synthesis of narciclasine[38] with stereocontrolled epoxide formation and $SnCl_4$-catalyzed arene-epoxide coupling as the key step following a strategy developed by us in the synthesis of *epi*-7-deoxypancratistatin.[57] Epoxide **93** (Scheme 17) was synthesized starting from the corresponding *cis*-cyclohexadiene diol derived from whole-cell oxidation of benzene with *Pseudomonas putida* 39/D. Benzylic oxidation of **94**, formation of the double bond in the C-ring, and cleavage of the protecting groups completed the synthesis.

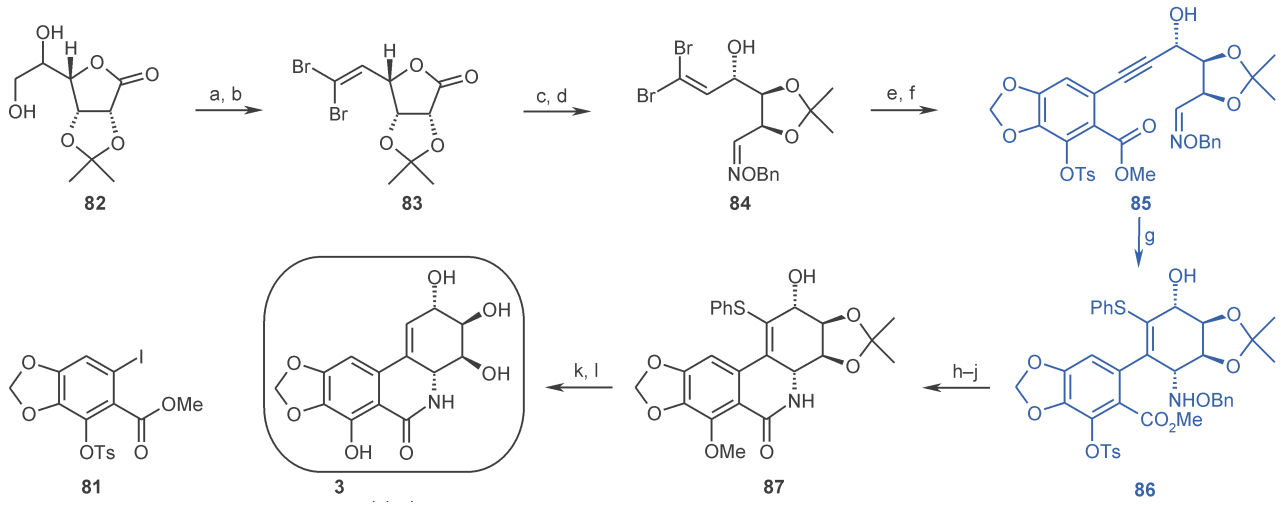
Protected *cis*-cyclohexadiene diol **88**, derived from whole-cell fermentation of benzene with *P. putida* 39/D was allowed to react with chiral chloronitroso derivative **96** to afford bicyclic oxazine hydrochloride **89** with ee <99% (Scheme 17). Reduction of the N-O bond with Al-Hg under conditions first described by Keck[58] afforded amino alcohol **90** in 85% over two steps. Protection of the amino and hydroxyl functionalities was followed by epoxidation of the olefin via treatment of bromohydrines **91** and **92** with base. Alkylation of the nitrogen with aromatic substrate **97** gave arene-epoxide **93** in high overall yield. The arene-epoxide coupling, the key step in this sequence, was successfully carried out in the presence of $SnCl_4$ as Lewis acid in CH_2Cl_2 at room temperature and the reaction was quenched with acetic anhydride to give **94** directly in 93% overall yield. Similar cyclization attempts with substrates with a methoxy group at C-7 (pancratistatin numbering) gave the desired coupled material in low yield and poor selectivity of inter- and intramolecular coupling reactions. Cleavage of the nosyl group from the nitrogen in **94** with mercaptoacetic acid in the presence of LiOH and treatment of the resulting amine with $(BOC)_2O$ afforded phenanthridone **95** after oxidation of the benzylic position with $NaIO_4$ and $RuCl_3$. Exposure of imide **95** to DBU at elevated temperature followed by treatment of the resulting olefin with formic acid and LAH gave narciclasine in 12 steps and 19% overall yield.

2.4 Lycoricidine

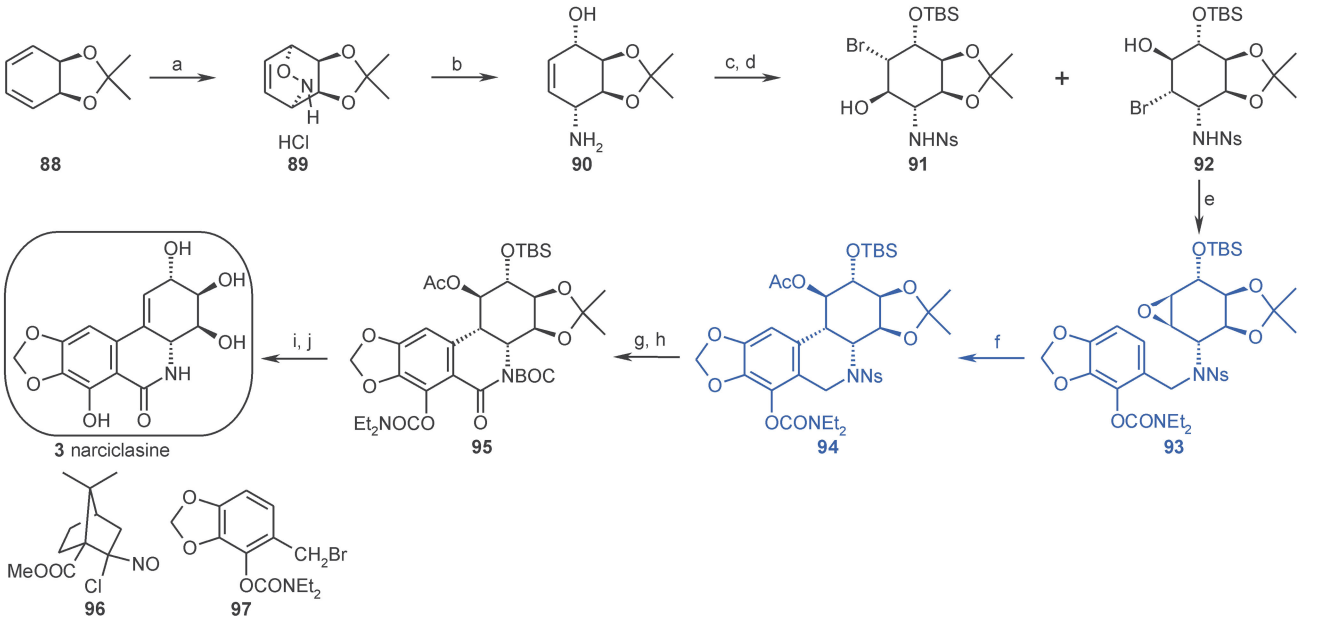
2.4.1 Keck (1999)

Keck's 1999 synthesis of lycoricidine is an improvement over his synthesis of *ent*-lycoricidine, published three years earlier (Section 3). It is similar in concept to his synthesis of narciclasine (Section 2.3).[33] The key step is a radical cyclization of disubstituted alkyne **98** derived from D-gulonolactone and the required aromatic substrate in a six-step procedure (Scheme 18). The synthesis takes advantage of the stereochemistry of gulonolactone, which resembles the stereochemistry of the target molecule.

Dibromide **84** (the synthesis of this material from D-gulonolactone is described in Section 2.3) was reacted with BuLi to afford the corresponding alkyne and used in a Pd-catalyzed coupling reaction with aromatic substrate **100** to provide the disubstituted alkyne **98**. Irradiation of this material in toluene in the presence of thiophenol cleanly led to the desired ring-closure and thioether **99** was isolated in 90% yield. SmI_2-mediated reduction of the N-O bond and

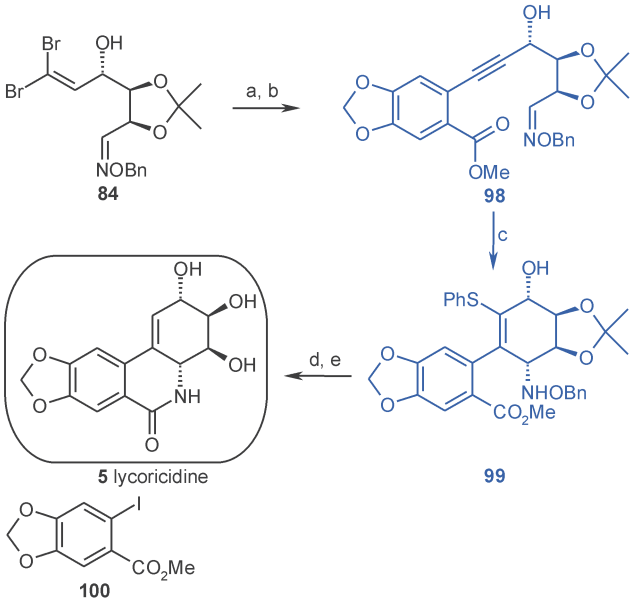


Scheme 16 *Reaction conditions*: (a) $NaIO_4$, CH_2Cl_2; (b) CBr_4, PPh_3, Et_3N, 80% (over 2 steps); (c) L-Selectride, Et_2O, –78 °C; (d) $HCl{\cdot}H_2NOBn$, pyridine, 90% (over 2 steps); (e) *n*-BuLi, Et_2O, –90 °C, 93%; (f) $Pd(OAc)_2$, PPh_3, CuI, Et_3N, **81**, THF, 89%; (g) PhSH, hν, toluene, 27 °C, 88%; (h) SmI_2, THF, H_2O, 0 °C, 94%; (i) MeI, K_2CO_3, DMF, 96%; (j) Me_3Al, THF, –15 °C to 65 °C, 72%; (k) SmI_2, MeOH, THF, 0 °C, 87%; (l) TFA, 0 °C, 89%.



Scheme 17 *Reaction conditions*: (a) **96**, CH_2Cl_2, 0 °C, 12 h; (b) Al-Hg, MeCN, 85% (over 2 steps); (c) i) Et_3N, NsCl, MeCN, r.t.; ii) DBU, TBSCl, 78%; (d) NBS, H_2O, r.t., 93%; (e) **97**, K_2CO_3, MeCN, 60 °C, 4 h, 88%; (f) CH_2Cl_2, $SnCl_4$, r.t., 20 min, K_2CO_3, DMAP, pyridine, Ac_2O, 98%; (g) $HSCH_2COOH$, DMF, LiOH, r.t., 78; (h) i) $(BOC)_2O$, MeCN; ii) H_2O, $RuCl_3$, $NaIO_4$, r.t., 67%; (i) DBU, C_6H_6, 70 °C, 96%; (j) i) HCOOH, THF, 60 °C; ii) LAH, THF, 65%.

cleavage of the sulfide was followed by cleavage of the acetonide with TFA to complete this synthesis of narciclasine in nine linear steps and an overall yield of 44%. This synthesis of the natural product is a greatly improved version of the synthesis of its enantiomer (see next section). Keck was able to reduce the number of steps from 14 to 9 and increase the yield from 11% to 44%.



Scheme 18 *Reaction conditions*: (a) *n*-BuLi, Et_2O, –90 °C, 93%; (b) $Pd(OAc)_2$, PPh_3, CuI, Et_3N, **100**, THF, 95%; (c) PhSH, hν, toluene, 27 °C, 90%; (d) SmI_2, THF, 86%; (e) TFA, 90%.

2.4.2 Yan (2002)

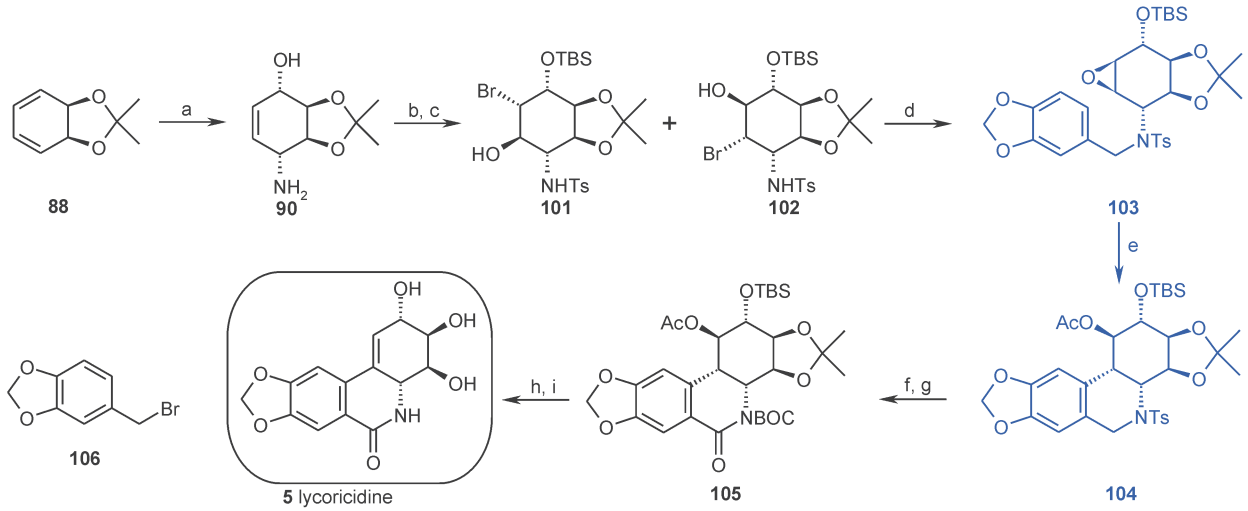
Yan's synthesis of lycoricidine[39] is based on the application of $SnCl_4$-catalyzed arene-epoxide coupling in close analogy to his synthesis of narciclasine, outlined in Section 2.3.[38]

Enantiomerically pure amino alcohol **90** was derived from acetonide **88** as described in section 2.3 (Scheme 19). Protection of the amino and hydroxyl functionalities was followed by the epoxide formation via treatment of a mixture of bromohydrines **101** and **102** with base. Subsequent alkylation of the resulting material gave epoxy-arene **103**. $SnCl_4$-mediated arene-epoxide coupling and acetylation afforded tetracycle **104** in 93% isolated yield. Cleavage of the tosyl group under reductive photolytic conditions followed by installation of a carbamate gave imide **105** after oxidation of the benzylic position with $NaIO_4$ and $RuCl_3$. Reaction of acetate **105** with DBU at elevated temperature and subsequent cleavage of the protecting groups gave lycoricidine (**5**) in an overall yield of 13%.

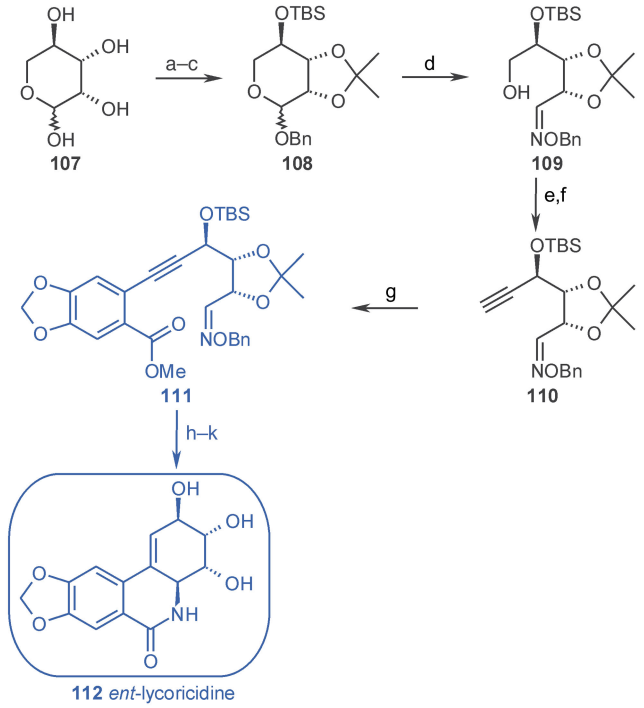
3 Unnatural and Truncated Derivatives

3.1 *ent*-Lycorocicidine (Keck, 1996)

Keck and Wager published a synthesis of *ent*-lycoricidine based on a radical cyclization as the key step.[54] This approach also provided the naturally occurring enantiomer and was later improved (see Section 2.4).



Scheme 19 *Reaction conditions*: (a) see Scheme 17; (b) i) TsCl, Et_3N, MeCN; ii) TBSCl, DBU, r.t., 78%; (c) NBS, H_2O, acetone, r.t., 98%; (d) **106**, NaOH (aq), Bu_4NHSO_4, CH_2Cl_2, r.t., 91%; (e) i) 20 mol% $SnCl_4$, CH_2Cl_2, r.t.; ii) Ac_2O, K_2CO_3, DMAP, pyridine, 93%; (f) hν, EtOH, $NaBH_4$, r.t., 45%; (g) i) $(BOC)_2O$, MeCN; ii) H_2O, $RuCl_3$, CCl_4, $NaIO_4$, r.t., 50%; (h) DBU, C_6H_6, 70 °C, 97%; (i) HCOOH, THF, 60 °C, 98%.

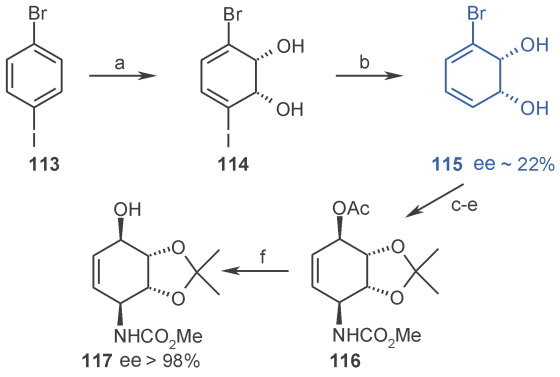


Scheme 20 *Reaction conditions*: (a) BnOH, *p*-TsOH, 81%; (b) DMP, acetone, *p*-TsOH, 90%; (c) TBSCl, imidazole, 95%; (d) i) Li, NH_3; ii) $BnONH_2$·HCl, pyridine, 93% (over 2 steps); (e) i) TPAP, NMO, 4 Å MS; ii) CBr_4, PPh_3, Et_3N, 55% (over 2 steps); (f) *n*-BuLi, 91%; (g) HF–pyridine, 88%; (h) MnO_2, NaCN, HOAc, MeOH, 81%; (i) PhSH, $C_6H_5CH_3$, 27 °C, hν, 91%; (j) SmI_2, THF, 76%; (k) TFA, 77%.

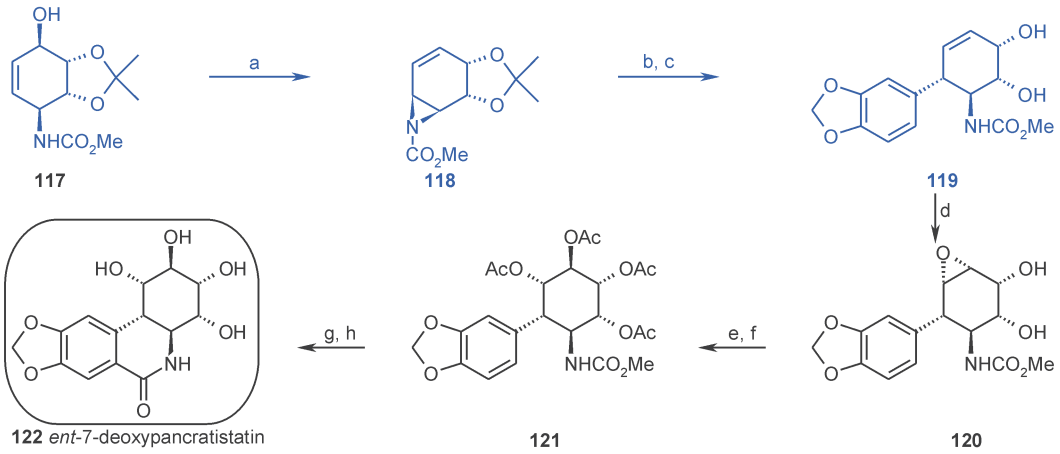
O-Benzyl-3,4-isopropylidenlyxopyranoside (**108**) was synthesized from D-lyxose.[59] After silylation, the sugar derivative was reduced with lithium in liquid ammonia and converted to oxime **109**. Oxidation of the primary alcohol was followed by a Corey–Fuchs sequence to give alkyne **110** which was used in a Sonagashira coupling with bromopiperonal to afford the key intermediate **111** after oxidation of the aldehyde moiety to a methyl ester. The C-ring of the natural product was established in the key radical cyclization step with thiophenol. Reductive cleavage of the N-O bond and the removal of the thiophenol group were accomplished with SmI_2. Formation of the lactam and deprotection of the acetonide completed the synthesis of *ent*-lycoricidine **112** (Scheme 20).

3.2 *ent*-7-Deoxypancratistatin (Hudlicky, 1999)

Interest in gaining further information about the biological activity of pancratistatin and related Amaryllidaceae constituents motivated us to synthesize *ent*-7-deoxypancratistatin.[60] Key steps in this synthesis are the formation of aziridine **118** from an enzymatically derived *cis*-cyclohexadiene diol and the opening of the aziridine in **118** with a higher order cyanocuprate to form advanced intermediate **119** (Scheme 22).



Scheme 21 *Reaction conditions*: (a) *E. coli* JM109 (pDTG601); (b) Bu_3SnH, AIBN, THF; (c) DMP, *p*-TsOH, then $HONHCO_2Me$, $NaIO_4$, H_2O, MeOH; (d) Al(Hg), THF, H_2O; (e) Ac_2O, pyridine; (f) PPL lipase, pH 7.



Scheme 22 *Reaction conditions*: (a) PPh_3, DEAD, THF, 60%; (b) (3,4-methylenedioxy)bromobenzene, *n*-BuLi, CuCN, $BF_3{\cdot}OEt_2$, –78 °C, 20–40%; (c) Dowex-50W, MeOH, 95%; (d) $VO(acac)_2$, *t*-BuOOH, C_6H_6, 70 °C, 67%; (e) BzONa, H_2O, 100 °C, 80%; (f) Ac_2O, pyridine, 82%; (g) Tf_2O, DMAP, CH_2Cl_2, 0 °C, 61%; (h) K_2CO_3, MeOH, 72%.

The synthesis of the *ent*-7-deoxypancratistatin was carried out in analogy to our synthesis of the natural product. The required enantiomer of the enzymatically accessible bromodiol **115** was obtained by whole-cell oxidation of *p*-iodobromo benzene with recombinant *E. coli* JM109 (pDTG601) expressing toluene dioxygenase and subsequent selective cleavage of the iodide in diol **114** under radical conditions (Scheme 21). The synthesis of enantiomeric diol **114** was reported by Boyd and coworkers[61] and relies on the directing effect of the larger substituent in the enzymatic oxidation with *P. putida* UV4. After removal of the iodide the undesired enantiomer was consumed in a second fermentation with a nonblocked strain of *P. putida*. The disadvantage of this protocol is that a considerable amount of chiral material has to be destroyed in order to obtain the desired target in high ee. We transformed the scalemic bromodiol **115** into conduramine derivative **116** by a nitroso-Diels–Alder cycloaddition–reduction sequence[62] and employed a lipase resolution following a protocol developed by Johnson.[63] Protected aminoalcohol **117** was obtained in enantiomerically pure form (ee > 98%, Scheme 21).

The *ent*-conduramine (**117**) was subjected to a modified Mitsunobu protocol developed by Olivo[64] to afford vinyl aziridine **118** in >60% yield. Addition of this material to the corresponding cuprate generated from (3,4-methylenedioxy)bromobenzene resulted in the isolation of diol **119** after cleavage of the acetonide functionality. Vanadium oxide-catalyzed epoxidation, followed by opening of the oxirane ring and treatment of the tetrol with acetic anhydride and pyridine afforded peracetylated material **121**. The closure of the B-ring was carried out by exposing carbamate **121** to modified Bischler–Napieralski conditions as reported by Banwell and coworkers.[42] Cleavage of the acetyl groups under basic conditions gave the enantiomer of the natural product, **122** in 14 steps from *p*-iodobromobenzene and an overall yield of approximately 1%.

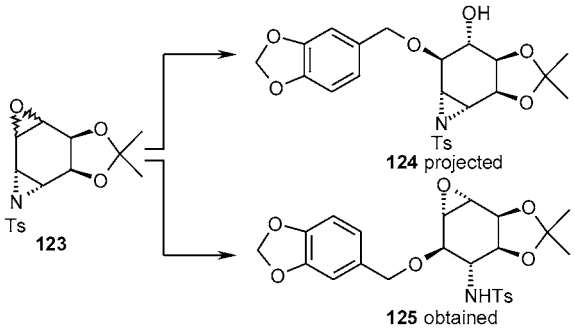
When screened in biological activity studies, *ent*-7-deoxypancratistatin (**122**) was found to be active against several cancer cell lines, although the activity was one order of magnitude less than that of the natural enantiomer.

3.3 Positional Isomer of 7-Deoxypancratistatin (Hudlicky, 2000)

During an attempt to improve on an earlier synthesis of 7-deoxypancratistatin, we investigated the possibility of a selective opening of epoxides over aziridines with oxygen nucleophiles. This effort, however, led to the formation of epoxide **125** rather than aziridine **124** in the key step of the synthesis (Scheme 23) and a positional isomer of 7-deoxypancratistatin was synthesized.[65]

Whole-cell oxidation of bromobenzene with recombinant *E. coli* JM109 (pDTG601) according to a well established procedure[66,67] gave cyclohexadiene diol **126**. Protection of the diol as the acetonide was followed by aziridination with Yamamoto's reagent[68] according to Evans' and Jacobsen's protocol[69,70] to furnish vinyl aziridine **127** after dehalogenation under radical conditions with *n*-Bu_3SnH and AIBN. Epoxidaton of the remaining double bond with *m*-CPBA in refluxing dichloro ethane gave an inseparable mixture of epoxides **123** (α:β = 2.6:1) Treatment of this material with the potassium salt of piperonol produced epoxide **125** rather than the expected aziridine **124**. Difficulties in precise stereochemical and regiochemical assignments with this material and further intermediates resulted in incorrect assignments. The error was only identified at the end of the synthesis after isolation of the tetraacetate and its comparison with that obtained from natural 7-deoxypancratistatin.

Benzylation of tosylamide **125** and subsequent treatment of the benzylated epoxide with Me_2AlCl at –25 °C in CH_2Cl_2 afforded pentacycle **128** in 77% yield. Oxidation of the benzylic position with DDQ in the presence of 2-methoxyethanol resulted in acetal **129**. Reaction with $(BOC)_2O$, followed by reductive detosylation gave acetal



Scheme 23

130. Deprotection of the acetal and PCC oxidation of the lactol to the corresponding lactone was followed by thermolysis of the carbamate and cleavage of the acetonide afforded triol **131**. Hydrolysis of this material with potassium carbonate proceeded in 44% yield to the more stable *trans*-fused lactone, which was treated with acetic anhydride. Hydrogenation of the obtained intermediate and acetylation afforded tetraacetate **132** (Scheme 24).

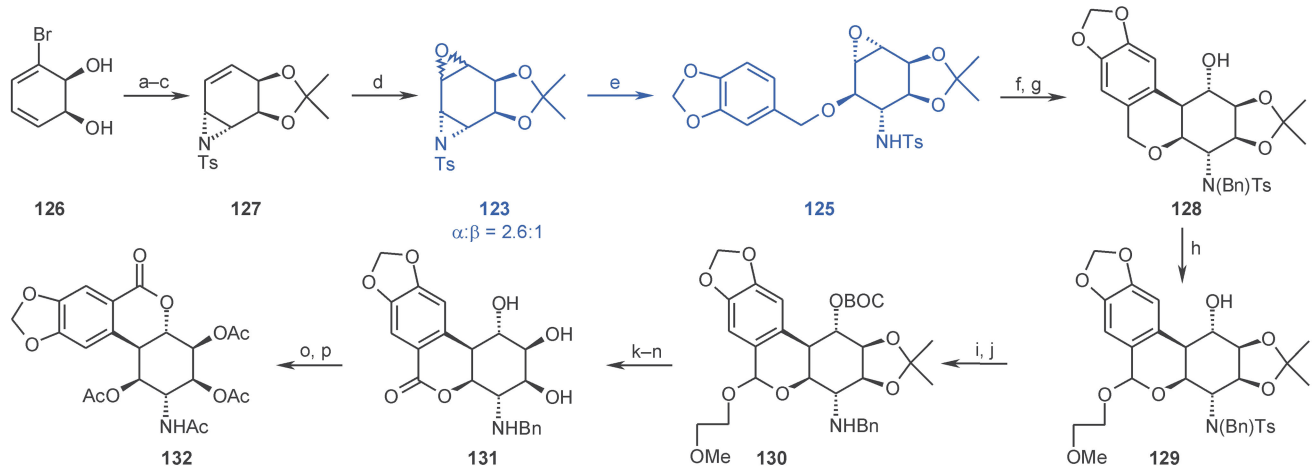
The synthesis of this positional isomer resulted from the unexpected preference for the opening of the aziridine over the epoxide and the subsequent erroneous assignment of the resulting product by spectroscopic methods.

3.4 *epi*-7-Deoxypancratistatin (Hudlicky, 2001)

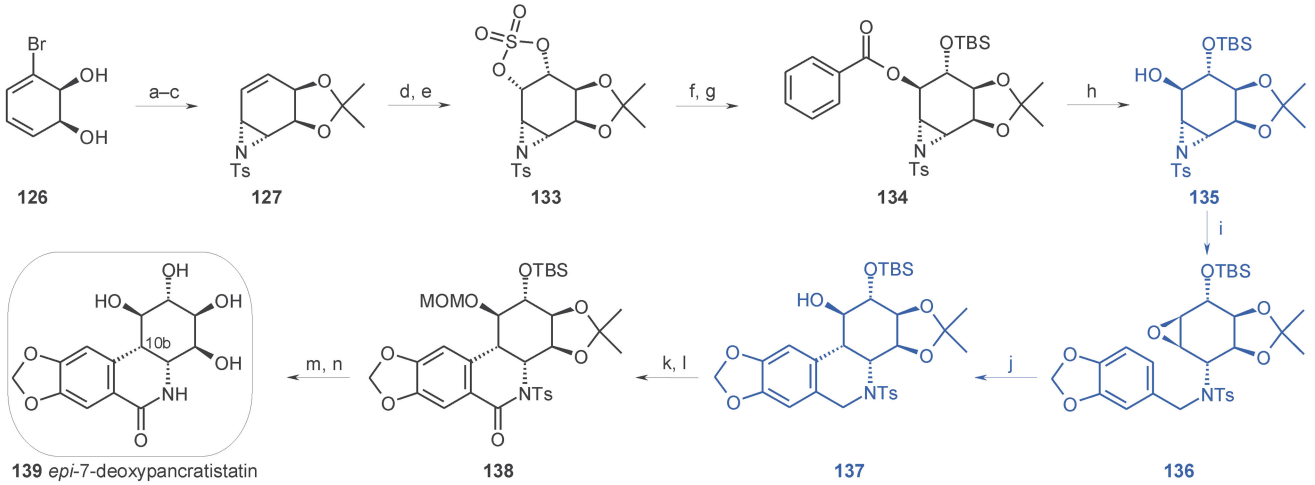
The inability to open an epoxide selectively over an aziridine as discussed above ultimately led to the synthesis of cyclic sulfate **133**.[57] Opening of the cyclic sulfate in **133** was expected to proceed in preference to the opening of the aziridine. Intramolecular opening of the aziridine, followed by oxidation of the benzylic position, lactone–lactam rearrangement and final deprotection lead to the epimer of the natural product.

Dihydroxylation of vinyl aziridine **127**, accessible in three steps from biocatalytically derived bromodiol **126**, with $NaIO_4$ and a catalytic amount of $RuCl_3{\cdot}H_2O$, was followed by conversion of the diol into cyclic sulfate **133** with sulfuryl chloride and triethyl amine. Exposure of this compound to ammonium salts of benzoic acid derivatives and subsequent treatment with a catalytic amount of sulfuric acid[71] resulted in the selective opening of the cyclic sulfate over the aziridine; the free hydroxyl was protected as its TBS ether. All attempts towards intramolecular aziridine opening with ester **134** and corresponding piperonyl derivatives failed and a slight change in the synthetic strategy was necessary. Hydrolysis of the benzoate and alkylation of **135** with piperonyl bromide, however, furnished amino oxirane **136** through an aza-Payne rearrangement.

Intramolecular opening of the epoxide in **136** would lead to the phenanthridone skeleton of the target molecule, however, the stereochemistry at the ring junction at C-10b would be opposite of the natural product. Although it was clear that this approach would not result in the natural product, we decided to complete the synthesis in order to gain additional information about structural requirements of Amaryllidaceae constituents for biological activity. Epoxide **136** underwent smooth cyclization with Me_2AlCl as Lewis acid and tetracycle **137** was isolated in 68% yield. Protection of the hydroxyl group in **137** as MOM ether and subsequent oxidation of the benzylic position with $NaIO_4$ and a catalytic amount of $RuCl_3{\cdot}H_2O$ afforded phenanthridone **138**. Reductive detosylation (Na/naphthalene) and final hydrolysis furnished 10b-*epi*-7-deoxypancratistatin **139** in an overall yield of approximately 4% and 12 steps from bromobenzene (Scheme 25).



Scheme 24 *Reaction conditions*: (a) DMP, *p*-TSA (cat.), acetone, r.t.; (b) PhINTs, $Cu(acac)_2$, MeCN, r.t., 63% (over 2 steps); (c) Bu_3SnH, AIBN, THF, reflux, 78%; (d) *m*-CPBA, $C_2H_4Cl_2$, reflux, 80%; (e) potassium piperonoxide, 18-crown-6, DME, r.t.; (f) i) NaH, THF; ii) BnBr, Bu_4NI, r.t., 71% (over 2 steps); (g) Me_2AlCl, CH_2Cl_2, –25 °C, 77%; (h) DDQ, 2-methoxyethanol, CH_2Cl_2, r.t., 78%; (i) NaH, $(BOC)_2O$, THF, reflux; (j) Na/naphthalene, DME, –50 °C, 85% (over 2 steps); (k) CSA, THF, H_2O, r.t.; (l) PCC, CH_2Cl_2, r.t., 72% (over 2 steps); (m) $C_6H_5CO_2Na$, MeOH–H_2O, reflux; (n) *p*-TsOH, MeOH, 84% (over 2 steps); (o) K_2CO_3, MeOH, 44%; (p) Ac_2O, DMAP, pyridine, 61%; (q) i) H_2, $Pd(OH)_2$, MeOH; ii) Ac_2O, DMAP, pyridine, 55% (over 2 steps).



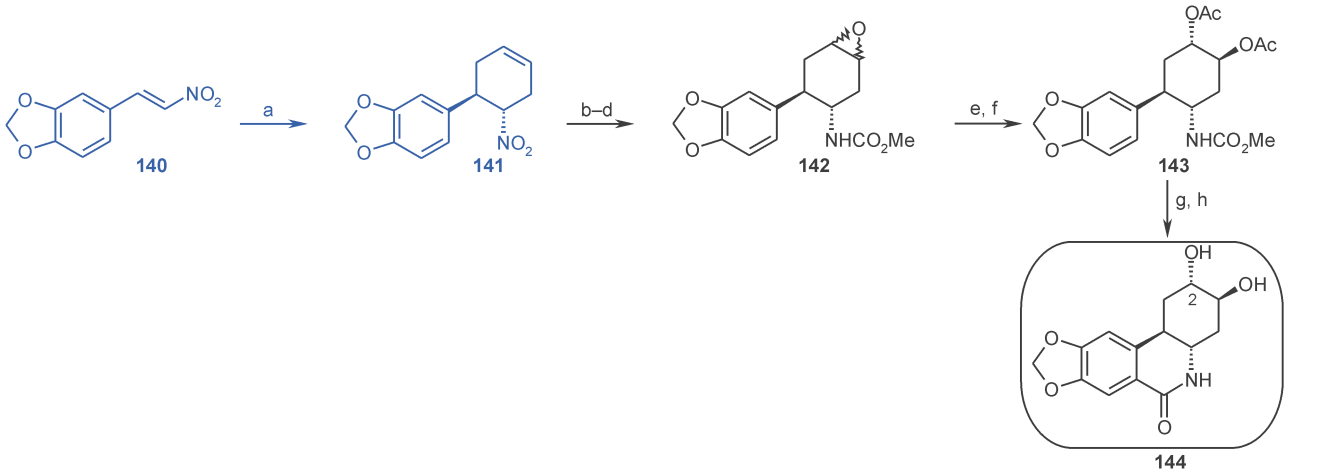
Scheme 25 *Reaction conditions*: (a) DMP, *p*-TSA (cat.), acetone, r.t.; (b) PhINTs, $Cu(acac)_2$, MeCN, r.t., 63% (over 2 steps); (c) Bu_3SnH, AIBN, THF, reflux, 78%; (d) $RuCl_3{\cdot}H_2O$, $NaIO_4$, EtOAc, H_2O, 15 s, 85%; (e) SO_2Cl_2, Et_3N, CH_2Cl_2, 93%; (f) i) DMF; ii) THF, H_2O, H_2SO_4, 90%; (g) TBSCl, imidazole, DMF, r.t.; (h) MeONa, THF, r.t., 63% (over 2 steps); (i) i) *t*-BuLi, THF, –30 °C; ii) piperonyl bromide, NBu_4I, 68%; (j) Me_2AlCl, CH_2Cl_2, –30 °C, 68%; (k) MOMCl, Hünig's base, r.t., 97%; (l) $RuCl_3{\cdot}H_2O$, $NaIO_4$, MeCN, CCl_4, H_2O, r.t., 50%; (m) Na/naphthalene, DME, –50 °C, 75%, (n) HCl–MeOH, r.t., 68%.

3.5 Deoxygenated Derivative of 7-Deoxypancratistatin (McNulty, 2001)

Based on limited structure–activity studies of Amaryllidaceae constituents, McNulty and Pettit suggested that deoxygenated derivative **144** might possess the minimum requirement for biological activity.[72] As the key step in the synthesis, the C-ring of the target molecule was elaborated through Diels–Alder reaction of nitroalkene **140** (Scheme 26). Further functionalization of the C-ring and Bischler–Napieralski ring-closure reaction completed the synthesis.

Reaction of nitroalkene **140** with butadiene at increased temperature afforded cyclohexene **141**. Reduction of the nitro group with aluminum amalgam followed by protection of the immediate amine as the methoxy carbonyl derivative gave epoxide **142** after reaction with *m*-CPBA. Epoxide opening with aqueous sodium benzoate at reflux and treatment of the diol with acetic anhydride furnished diacetate **143**, the precursor for the ring-closure reaction which afforded the phenanthridone skeleton in 10% yield, and the synthesis was completed by cleavage of the acetate groups.

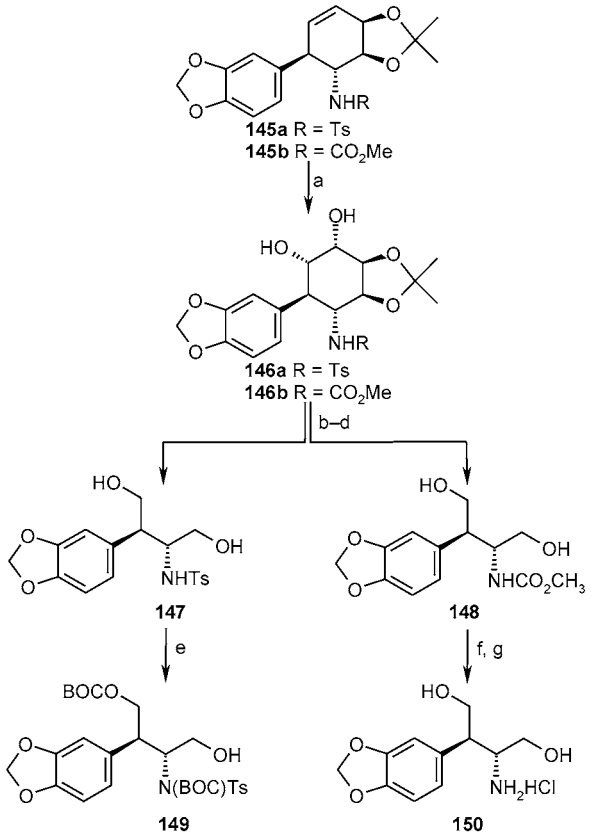
Phenanthridone **144** showed some activity against several human cancer cell lines. Although the deoxygenated material was 2-3 orders of magnitude less potent than pancratistatin, inhibition of some of the cell lines was indicated. The hydroxyl group at C-2 seems to play an important function in the active binding of the Amaryllidaceae constituent.



Scheme 26 *Reaction conditions*: (a) butadiene sulfone, PhMe, 127 °C, $ZnCl_2$, 12 h, 85%; (b) Al/Hg, THF–H_2O, 22 °C, 12 h; (c) $ClCO_2Me$, (1.5 equiv), CH_2Cl_2, Et_3N, 0 °C, 5 h, 96%; (d) *m*-CPBA (3.0 equiv), CH_2Cl_2 0 °C, 5 h, 93%; (e) $PhCO_2Na$, H_2O, 100 °C, 12 h; (f) Ac_2O, pyridine, 0 °C, 12 h, 55–62% (over 2 steps); (g) Tf_2O (5.0 equiv), DMAP (3.0 equiv), CH_2Cl_2, 0–15 °C, 15 min; then 2 M HCl (aq), dioxane, 20 °C, 18 h; then Ac_2O, pyridine, 0 °C, 6 h, 85%; (h) MeONa (2.1 equiv), THF–MeOH (1:3), 0–18 °C, 12 h, 96%.

3.6 Truncated Derivatives of 7-Deoxypancratistatin (Hudlicky, 2002)

We have also provided truncated derivatives of 7-deoxypancratistatin for biological activity studies.[73] The compounds were synthesized as indicated in Scheme 27 with the coupling of a higher order cyanocuprate with a vinyl aziridine as the key step.



Scheme 27 *Reaction conditions*: (a) $RuCl_3 \cdot H_2O$, $NaIO_4$, EtOAc, MeCN, R = Ts: 75%, R = CO_2CH_3: 69%; (b) TFA, THF, H_2O; (c) $NaIO_4$, acetone, H_2O; (d) $NaBH_4$, MeOH, 0 °C, R = Ts: 60% (over 3 steps), R = CO_2CH_3: 45% (over 3 steps); (e) NaH, $(BOC)_2O$, THF, 85%; (f) KOH, MeOH; (g) HCl, MeOH, 0 °C, 82% (over 2 steps).

Coupling of the higher order cyanocuprate derived from 4-bromo-(1,2-methylenedioxy)benzene with vinyl aziridines gave functionalized cyclohexenes **145a** and **145b**, respectively. Dihydroxylation of the double bond with $NaIO_4$ and a catalytic amount of $RuCl_3 \cdot H_2O$ afforded diols **146a** and **146b**. Deprotection of the acetonide and oxidative degradation of the intermediate tetrols with $NaIO_4$ followed by the reduction of the resulting dialdehydes gave diols **147** and **148** in 60% and 45% yield, respectively. Attempts to detosylate diol **147** failed and the material was converted to bis-BOC derivative **149** with excess base and $(BOC)_2O$, however, all detosylation attempts with carbamate **149** failed as well. Deprotection of carbamate **148** under basic conditions afforded the free amine, which was isolated as hydrochloride **150**.

When tested against a minipanel of six human cancer cell lines and murine P388 lymphocytic leukemia, only tosylamide **149** displayed inhibition activity, although several orders of magnitude lower than pancratistatin. Results of these studies are summarized in Table 2, Section 4.

3.7 Deoxygenated Derivative of 7-Deoxypancratistatin (Hudlicky, 2004)

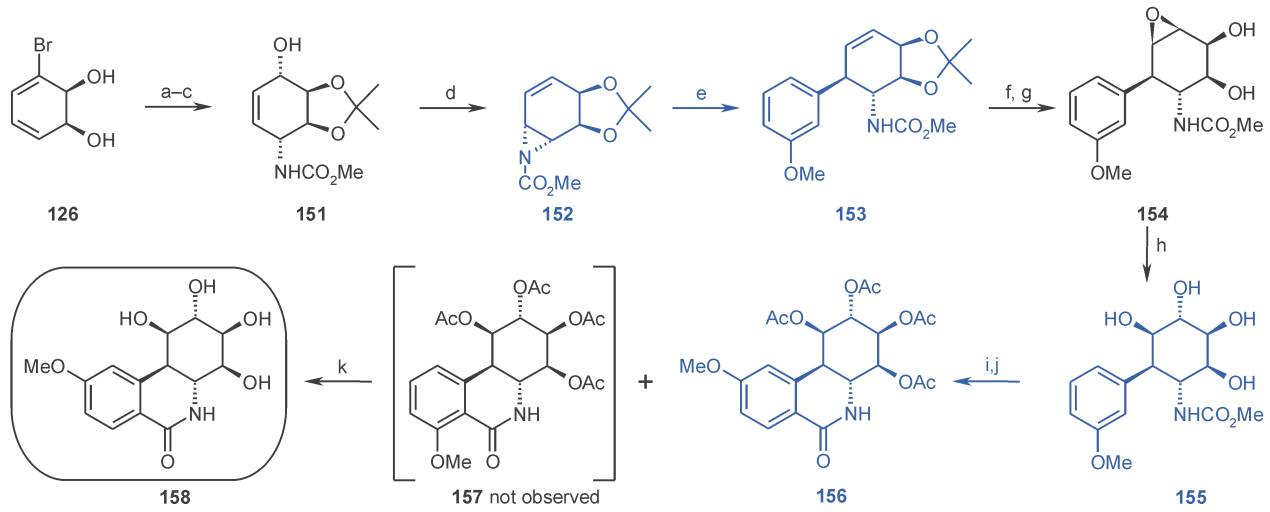
Detailed studies about structural requirements for biological activity of pancratistatin are not available. We intended to synthesize derivatives of Amaryllidaceae constituents lacking the methylene dioxy functionality. The strategy is based on earlier work in this area with an intermolecular aziridine opening and Bischler–Napieralski ring-closure reaction as key steps.[74]

Cyclohexadiene diol **126**, derived from whole-cell oxidation of bromobenzene with recombinant *E. coli* JM109 (pDTG601) expressing toluene dioxygenase was protected as its acetonide and used in a regio- and stereoselective hetero-Diels–Alder reaction to afford aminoalcohol **151** after reductive cleavage of the N–O bond. Exposure of aminoalcohol **151** to Ph_3P and DEAD gave aziridine **152** which was allowed to react with the lithio derivative of 3-bromo anisol to furnish carbamate **153** in moderate to good yield. Cleavage of the acetonide followed by directed epoxidation gave epoxy-diol **154**. Opening of the epoxide in refluxing water with a catalytic amount of sodium benzoate[75] and exposure of the intermediate tetrol to acetic acid afforded peracetate **156**, precursor for the Bischler–Napieralski ring-closure (modified conditions as reported by Banwell).[42] The cyclization reaction was expected to yield in a mixture of both possible products, **156** and **157**, and both products were intended to be transformed to the corresponding derivatives of pancratistatin. However, only phenanthridone **156** was isolated from the reaction mixture (Scheme 28). Cleavage of the acetate groups yielded in the final product with a methoxy group at C-9 instead of a full methylenedioxy functionality.

When screened against a minipanel of human cancer cell lines, phenanthridone **158** was found to be active against several cell lines, although 10 to 100-fold less active than the natural product. This result suggests that the intact methylenedioxy functionality is essential for significant biological activity in this class of natural compounds.

Speculations by McNulty and Pettit about the minimum pharmacophore of the natural product[72] motivated us to prepare phenanthridone **159**.[74] The synthesis was carried out in analogy to previous syntheses of pancratistatin. The key step in the synthesis was the opening of the aziridine in **127** with a higher order cyanocuprate. Installation of a carbamate followed by a modified Bischler–Napieralski ring-closure reaction completed the synthesis of the deoxygenated derivative of the natural product.

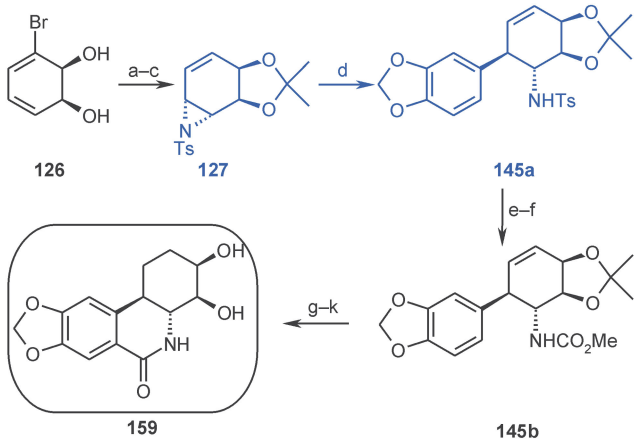
Protection of the hydroxyl groups of enzymatically derived cyclohexadiene diol followed by aziridination and debromination gave aziridine **127**, which was used in a nucleophilic aziridine opening with a higher order cyanocuprate to afford tosylamide **145a**. Substitution of the



Scheme 28 *Reaction conditions*: (a) DMP, *p*-TSA (cat.), acetone, r.t.; (b) CH_3ONHOH; $NaIO_4$, MeOH, H_2O, r.t., 60%; (c) Al(Hg), THF, H_2O, r.t., 68%; (d) Ph_3P, DEAD, THF, r.t., 61%; (e) i) 3-bromoanisol, *n*-BuLi, THF, –78 °C; ii) CuCN, 2 h; iii) $BF_3{\cdot}OEt_2$, –78 °C to r.t., 50%; (f) HOAc, THF, H_2O, 60 °C, 76%; (g) *t*-BuOOH, $VO(acac)_2$, C_6H_6, 60 °C, 22%; (h) NaOBz, H_2O, reflux, 54%; (i) Ac_2O, pyridine, 88%; (j) i) DMAP, Tf_2O, CH_2Cl_2, 4 °C; ii) THF, HCl (2 M), 76%; (k) MeONa, THF, r.t., 85%.

tosyl group with a carbamate functionality by reaction of tosylamide **145a** with dimethyl pyrocarbamate and reductive detosylation was followed by cleavage of the acetonide with acidic ion exchange resin and subsequent treatment of the intermediate with acetic anhydride. The closure of the B-ring was accomplished under modified Bischler–Napieralski conditions following a protocol developed by Banwell.[42] Cleavage of the acetate groups completed the synthesis of the deoxygenated derivative **159** (Scheme 29).

When tested against several human cancer cell lines, slight activity was detected (see Section 4 for test results). However, the activity of the deoxygenated material was found to be 100-fold lower than the activity of 7-deoxypancratistatin. Results obtained in this study helped to further define the minimum pharmacophore of Amaryllidaceae constituents.



Scheme 29 *Reaction conditions*: (a) DMP, *p*-TSA (cat.), acetone, r.t.; (b) PhINTs, $Cu(acac)_2$, MeCN, r.t., 63% (over 2 steps); (c) Bu_3SnH, AIBN, THF, reflux, 78%; (d) i) 4-bromo-1,2-(methylenedioxy)benzene, BuLi, ii) CuCN; iii) $BF_3{\cdot}OEt_2$, 16%; (e) BuLi, THF, dimethyl pyrocarbonate, 73%; (f) Na/naphthalene, DME, –60 °C, 73%; (g) H^+, MeOH, 87%; (h) Ac_2O, pyridine, 98%; (i) H_2, Pd/C, EtOH, 95%; (j) Tf_2O, DMAP, CH_2Cl_2, 4 °C, 50%; (k) MeONa, MeOH, 70%.

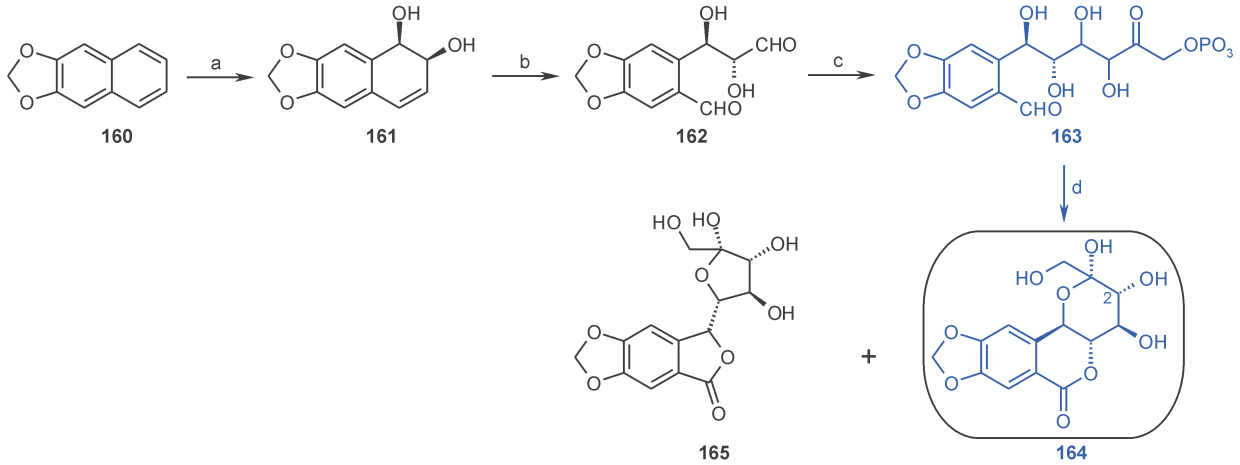
3.8 Carbohydrate Analog of 7-Deoxypancratistatin (Fessner, 2004)

Recently, Fessner and coworkers prepared a derivative of pancratistatin with a carbohydrate unit as C-ring instead of the inositol moiety with a lactone in the B-ring instead of the lactam (Scheme 30).[76] The carbohydrate unit was established enzymatically by an aldolase reaction. The reaction partner for this transformation originated from a biooxidation of the naphthalene derivative **160** with a mutant strain of *E. coli* expressing naphthalene dioxygenase.

Biotransformation of dioxole **160** with a mutant strain of *E. coli* gave diol **161** which underwent ozonolysis to dialdehyde **162**. Conversion of aldehyde **162** with dihydroxyacetone phosphate and rhamnulose-1-phosphate aldolase afforded aldole adduct **163** which was converted to the desired carbohydrate derivative of pancratistatin **164** and the furanoid **165** (1:1) in a reaction catalyzed by acid phosphatase (Scheme 30).

The biological activity study of this carbohydrate analog of pancratistatin has not been reported by Fessner. These tests might give interesting results concerning the structural requirements with respect to the lactone and lactam functionality in the B-ring and also about the stereochemical requirements of the hydroxyl functionality at C-2 of the natural product since the reported analog shows opposite stereochemistry at this position (Scheme 30).

Recently, Chapleur and coworkers published the synthesis of lactone analogs of narciclasine and lycoricidine.[77] The lactone analogs of both natural products were subjected to biological activity studies against cancer cell lines



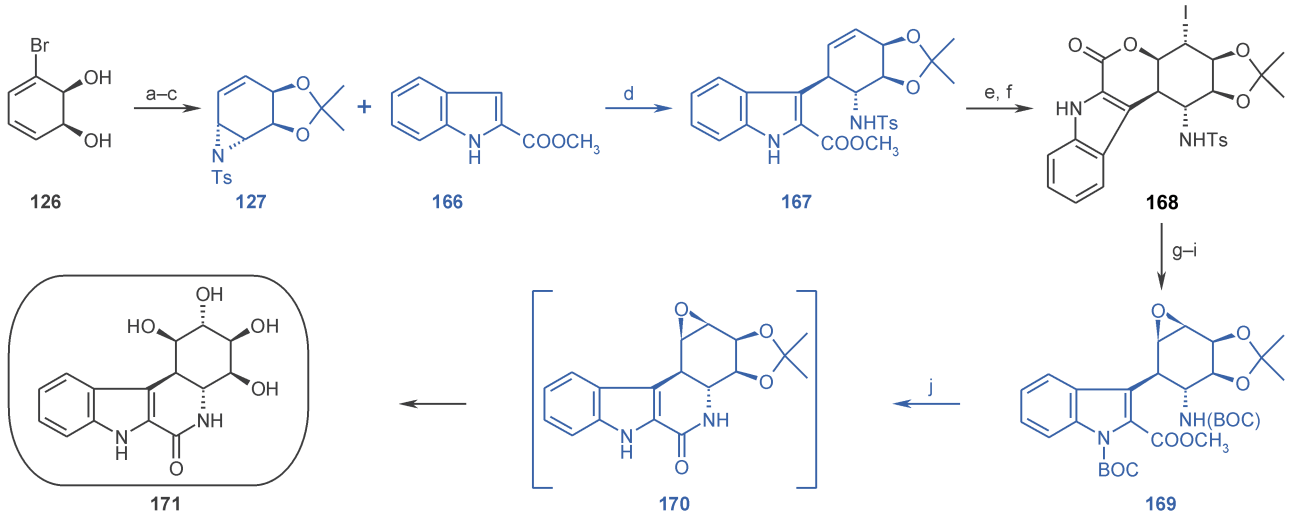
Scheme 30 *Reaction conditions*: (a) *P. putida* G7 or *E. coli*; (b) O_3, –78 °C, MeOH, then Me_2S, r.t.; (c) rhamnulose-1-phosphate aldolase, dihydroxyacetone phosphate, pH 7.0, r.t., 2 d; (d) acid phosphatase, pH 5.9, 3 d, then Br_2, $BaCO_3$, product ratio of **164**:**165** = 1:1, 10% (over 3 steps).

but were found to be completely inactive. Obviously, the amide present in Amaryllidaceae alkaloids is of significant importance for antitumor activity.

3.9 β-Carboline-1-one Analog of Pancratistatin (Hudlicky, 2004)

Electronic, structural, and electrostatic similarities between pancratistatin and the corresponding β-carboline-1-one (**171**, Scheme 31) motivated us to synthesize this compound for biological activity studies.[78] Key steps in this synthesis are the nucleophilic opening of a vinyl aziridine with the methyl ester of indole-2-carboxylic acid, the functionlization of the C-ring by means of iodolactonization and the final internal amidation of the methyl ester.

Vinylaziridine **127** was prepared from enzymatically derived bromodiol by protection of the diol as acetonide, aziridination with Yamamoto's reagent and cleavage of the bromide under radical conditions was absorbed on dry silica gel with indole-2carboxylic acid methylester (**166**) and heated to 70 °C for 48 hours to afford tosylamide **167** in good yield. Direct oxidation of the remaining double bond was not possible because of the indole moiety; therefore the ester in **167** was hydrolyzed with lithium hydroxide followed by iodolactonization of the intermediate acid to furnish the corresponding iodolactone **168**. Hydrolysis of the ester with $LiOCH_3$ and installation of BOC groups at the indole nitrogen and the tosylamide was necessary before the reductive cleavage of the tosyl group with Na/naphthalene could be accomplished successfully to give carbamate **169**. The final transformation to β-carboline-1-one analog **171** was accomplished in water at 170 °C with silica as the acidic catalyst. Thermolytic cleavage of the BOC groups via a retro-ene reaction, opening of the epoxide, and internal amidation took place in this remark-



Scheme 31 *Reaction conditions*: (a) DMP, *p*-TSA (cat.), acetone, r.t.; (b) PhINTs, $Cu(acac)_2$, MeCN, r.t., 63% (over 2 steps); (c) Bu_3SnH, AIBN, THF, reflux, 78%; (d) silica gel, 70 °C, 48 h, 68%; (e) LiOH, H_2O, 95%; (f) I_2, $NaHCO_3$, THF, 71%; (g) LiOMe, MeOH, 85%; (h) $(BOC)_2O$, 40 °C, 88%; (i) Na/naphphalene, DME, –50 °C; (j) silica gel, H_2O, 170 °C, 16 h, 31%.

able one-pot procedure, and the target molecule was isolated in a total of nine steps (Scheme 31). Although the final compound proved to be inactive against several human cancer cell lines, some of the synthetic intermediates showed slight activity and may give rise to further biological activity studies.

4 Conclusion

Several derivatives of Amaryllidaceae constituents and synthetic intermediates described in this review have been screened in biological activity studies against murine P388 lymphocytic leukemia and a minipanel of six major human cancer cell lines. These test results are summarized in Table 2.

It is clear from the results of biological screening that none of the unnatural derivatives rival the potency of either pancratistatin or narciclasine. Nevertheless, continuing preparation of new compounds that resemble the structural motifs of the natural products represents an endeavor with the potential for discovery as well as the eventual deciphering of the mode of action for these compounds. In addition, creative new approaches to the synthesis of Amaryllidaceae constituents continue to appear despite the fact that fifteen years elapsed since the first synthesis of pancratistatin and that lycoricidine was synthesized almost thirty years ago. Several groups continue a multi-generational effort in synthesis of these compounds to this date and it seems almost certain that an efficient and practical synthesis (<8 steps) will eventually materialize. Amaryllidaceae constituents represent ideal targets on which synthetic design may be practiced in an aesthetic manner. There is no doubt that the activity in this field will continue at the interface of biology (activity screening) and chemistry (synthetic design). The potential for discovery in both disciplines is enormous and valuable results will surely be forthcoming.

Table 2 Murine P388 Lymphocytic Leukemia and Human Cancer Cell Line Evaluations for Amaryllidaceae Constituents and Synthetic Intermediates

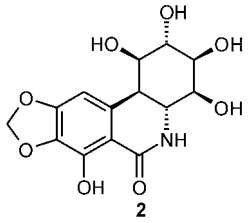
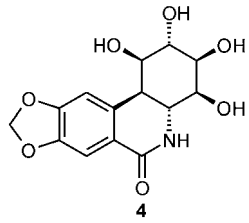
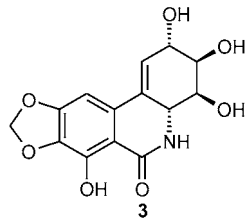
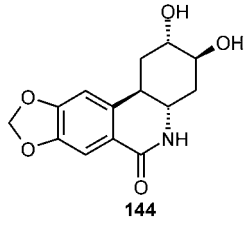
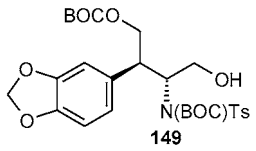
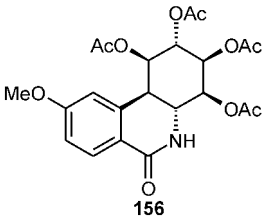
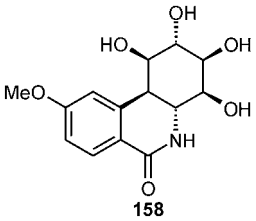
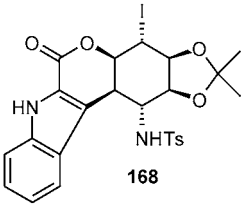
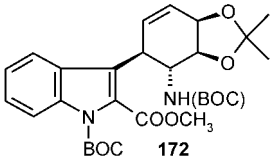
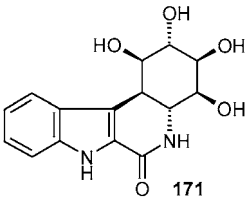
	Cancer cell lines[a]						
Compound	P388	BXPC-3	MCF-7	SF-268	NCI-H460	KM20L2	DU-145
 **2**	0.039[79]	0.028	0.032	0.017	0.048	0.062	0.016
 **4**	0.44[79]	–	–	–	0.29	0.22	–
 **3**	0.0012[79]	0.026	0.019	0.021	0.032	0.021	0.011
 **144**	0.45[72]	–	–	–	0.65	–	–

Table 2 Murine P388 Lymphocytic Leukemia and Human Cancer Cell Line Evaluations for Amaryllidaceae Constituents and Synthetic Intermediates (continued)

	Cancer cell lines[a]						
Compound	P388	BXPC-3	MCF-7	SF-268	NCI-H460	KM20L2	DU-145
 **149**	–[73]	5.3	–	–	8.5	–	–
 **156**	2.1[74]	–	4.6	–	–	–	6.7
 **158**	4.3[74]	4.9	4.4	3.3	2.8	3.6	2.6
 **168**	11.7[78]	1.9	4.3	–	–	–	–
 **172**	11.8[78]	8.6	10.5	–	–	–	–
 **171**	18.3[78]	–	–	–	–	–	–

[a] Cancer type: P388 (murine lymphocytic leukemia); human lines BXPC-3 (pancreas adenocarcinoma), MCF-7 (breast adenocarcinoma), SF-268 (CNS glioblastoma), NCI-H460 (lung large cell), KM20L2 (colon adenocarcinoma), DU-145 (prostate carcinoma); data reported as GI_{50} in μg/mL.

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publications and simply refer to these compounds as 'constituents'.
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