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Synthesis of Amaryllidaceae Constituents and Unnatural Derivatives

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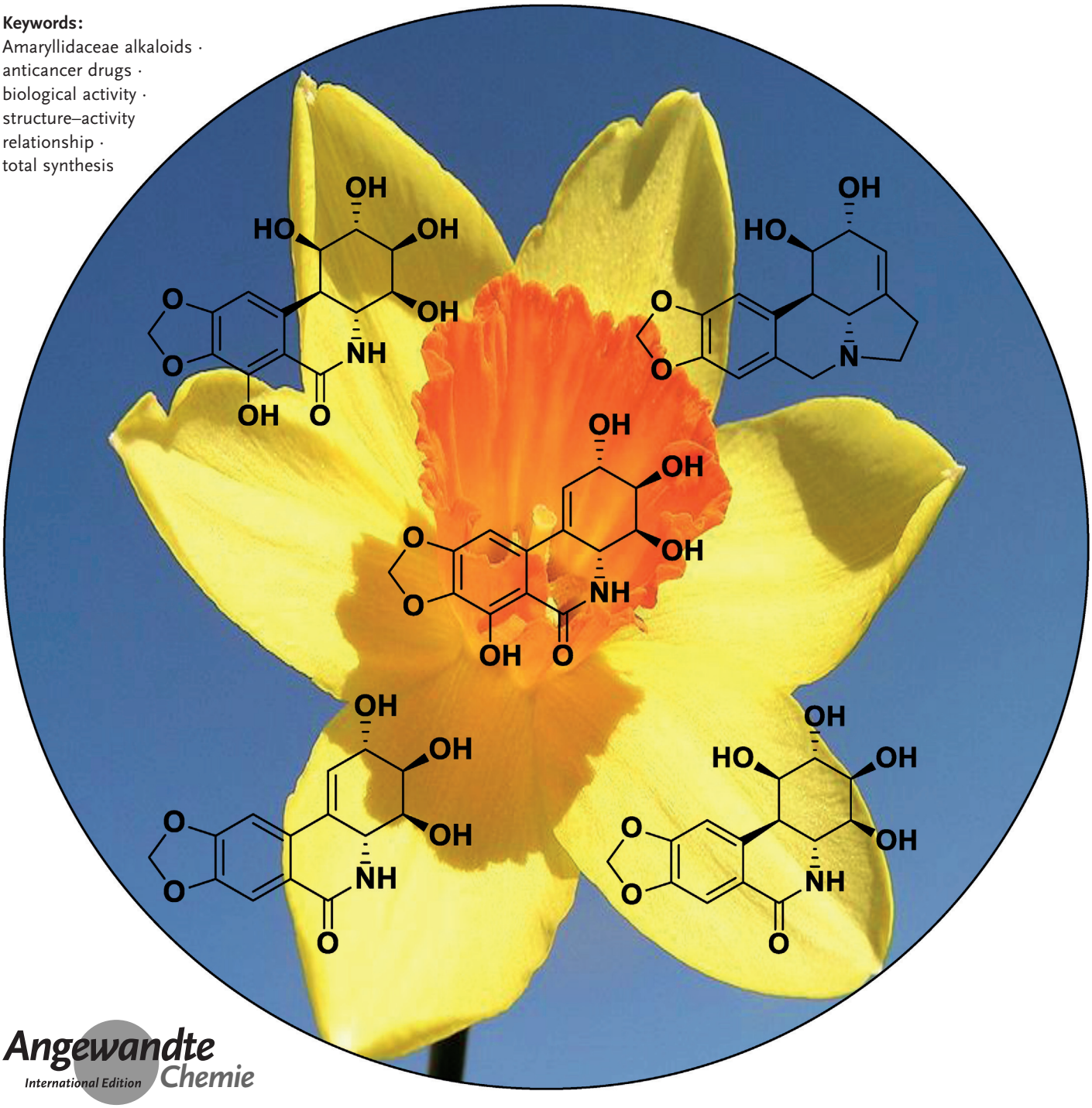
Amaryllidaceae alkaloids · anticancer drugs · biological activity · structure–activity relationship · total synthesis



This update covers the syntheses of Amaryllidaceae alkaloids since the publication of the last major review in 2008. A short summary of past syntheses and their step count is provided for the major constituents; pancratistatin, 7-deoxypancratistatin, narciclasine, lycoricidine, lycorine, and for other natural constituents, as well as for unnatural derivatives. Discussion of biological activities is provided for unnatural derivatives. Future prospects and further developments in this area are covered at the end of the review. The literature is covered to the end of August 2015.

"*Wherever the art of medicine is loved, there is also a love of humanity.*
Hippocrates (460–357 BC)"

From the Contents

1. Introduction

The Amaryllidaceae alkaloids are a large group of biogenetically related compounds, over 300 of which have been identified.[1,2] Many of these compounds are known to be produced exclusively by plants of the Amaryllidaceae family, which are found primarily in tropical regions.[2] Plant extracts from this family have a long history of use as traditional remedies, having been used by the ancient Greeks for the treatment of cancer, as well as by African, Asian, and Polynesian communities for the treatment of various ailments.[3,4a,b] The isocarbostyrils (**1**–**4**, Figure 1) are major components of Amaryllidaceae extracts, and are well known to have potent anti-cancer activity.[3,4a,b] The anti-proliferative activity of these compounds has been attributed to their interaction with a variety of cellular targets such as the mitochondria and the 60S ribosomal subunit. Such interactions are thought to result in inhibition of protein biosynthesis, and specific interactions with the mitochondria of cancer cells can result in apoptosis.[4b,5] The related compound lycorine (**5**, Figure 1), the first Amaryllidaceae alkaloid isolated in 1877,[6] is also known to possess anti-proliferative properties.[2,3,4a,5] The biological activity of these compounds, as well as their challenging structural features, have sparked significant interest among biologists and chemists alike. Because of the continuing interest in these compounds, this update will focus on their synthesis, as well as the preparation of unnatural analogues that are being produced as a means of probing bioactivity through the accurate identification of the pharmacophore.

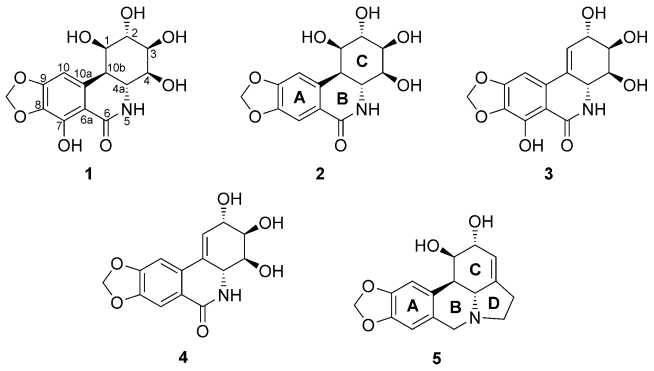


Figure 1. Major Amaryllidaceae constituents: (+)-pancratistatin (**1**), (+)-7-deoxypancratistatin (**2**), (+)-narciclasine (**3**), (+)-lycoricidine (**4**), and (+)-lycorine (**5**).

Amaryllidaceae alkaloids present significant challenges to synthetic chemists, who have responded by producing many efficient and creative approaches toward these compounds. The syntheses have been the subject of many reviews,[4] the most recent published by Kornienko in 2008.[4b] Excellent reviews on the biological activity of Amaryllidaceae alkaloids are also available.[2,3e,4a,b,5] Tables 1–6 summarize the accomplishments in total synthesis of the major Amaryllidaceae constituents. The syntheses published after 2008, as well as syntheses of unnatural Amaryllidaceae analogues, are covered in detail in this update.

2. Total Syntheses of the Major Amaryllidaceae Constituents – An Update

The importance of the biological activity of Amaryllidaceae alkaloids has been well established, and the key issue that remains is the efficient means of supplying these compounds in large quantities. In particular, the anti-tumor isocarbostyrils have a relatively low natural abundance, making their isolation from plant sources an impractical solution to the supply problem.[4b] One potential solution,

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tissue culture cloning of *Hymenocallis littoralis* bulbs by Pettit, afforded gram quantities of pancratistatin and lycoricidine.[7] Many synthetic chemists have attempted to develop practical routes for the production of these compounds as is clear from the number of entries in Tables 1–6. Further improvements in synthetic methodology utilized for the production of Amaryllidaceae alkaloids could ultimately lead to a practical means of supplying these medicinally relevant compounds.

At the beginning of each section a tabular survey of the past syntheses is provided. The author, the year of publication, the step count, and the optical series are provided. Note that epimers, *ent*-constituents, and racemates are included in the respective sections. Other Amaryllidaceae alkaloids as well as unnatural or truncated derivatives are covered in subsequent sections.

Table 1: Summary of total and formal syntheses of pancratistatin.

Author	Year	Number of steps	Optical series	Reference
Danishefsky	1989	26	(±)	[10]
Hudlicky	1995	14	(+)	[11]
Trost	1995	15	(+)	[12]
Haseltine	1997	15[a]	(+)	[13]
Magnus	1998	19	(+)	[14]
Rigby	2000	22	(+)	[15]
Pettit	2001	10[b]	(+)	[16]
Kim	2002	16	(±)	[17]
Li	2006	13	(+)	[18]
Madsen	2009	18	(+)	[19]
Cho	2011	16	(±)	[20]
Alonso	2012	14	(+)	[21]
Sato	2013	18	(+)	[22]
Cho	2013	13	(±)-1-*epi*	[23]

[a] Denotes a formal synthesis. [b] Semi-synthesis from narciclasine.

2.1. Pancratistatin

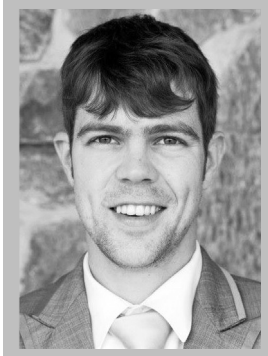
Pancratistatin was isolated in 1984 by Pettit who also elucidated its structure.[8] Later, it was shown that pancratistatin's activity against cancer cell lines exceeded that of the related compound lycoricidine,[3e,9] and this finding made pancratistatin an attractive and popular synthetic target. The first racemic synthesis was accomplished by Danishefsky in 1989[10] and the first asymmetric synthesis was reported by Hudlicky in 1995.[11] Since then a total of twelve syntheses have been reported and these are summarized in Table 1. The latest five syntheses published since 2008 are discussed in detail.

2.1.1. Madsen (2009) – (+)-Pancratistatin (1)

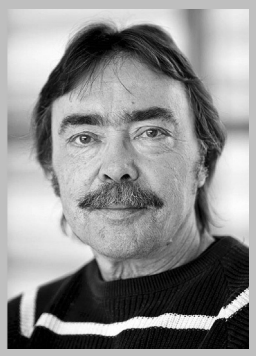
This total synthesis of dextrorotatory pancratistatin[19] employs the same overall strategy as that used by the author in the synthesis of (+)-7-deoxypancratistatin in 2006.[24] This is a convergent synthesis involving the coupling of the aromatic fragment **7** with furanoside **8** (Scheme 1). The

Mukund Ghavre was born in 1982 in Pune, India. He studied chemistry at the University of Pune (M.Sc. 2006) and then worked as an R&D chemist at Emcure Pharmaceuticals. In 2008 he joined Nicholas Gathergood's research group at Dublin City University to pursue his doctoral research in biodegradable ionic liquids (Ph.D. 2012). Currently, he is working as a postdoctoral researcher with Milan Pour at Charles University. He has also worked with Professor Tomas Hudlicky during his tenure as a visiting researcher at Brock University (Canada) in 2014.

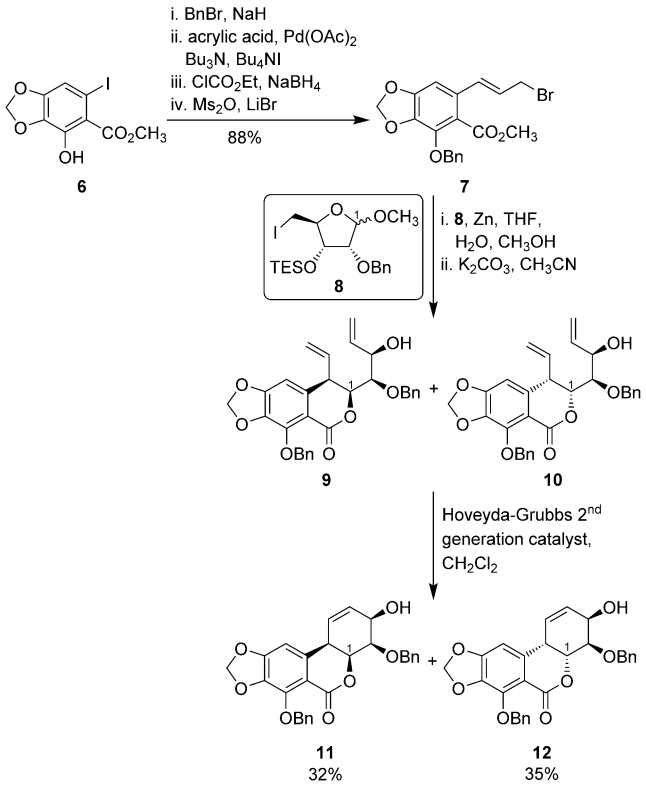
Milan Pour was born in 1966 in Hradec Králové in former Czechoslovakia. Following undergraduate studies at Charles University and the Czechoslovak Academy of Sciences in Prague (M.Sc. 1989), he completed his Ph.D. in chemistry (1994) under the supervision of Lew Mander at the Australian National University in Canberra. After a postdoctorate with E.-I. Negishi at Purdue University (USA), he accepted an academic position at the School of Pharmacy, Charles University, where he has served to date as a Lecturer (1996), Associate Professor (1999) and Full Professor of Organic Chemistry (2007).



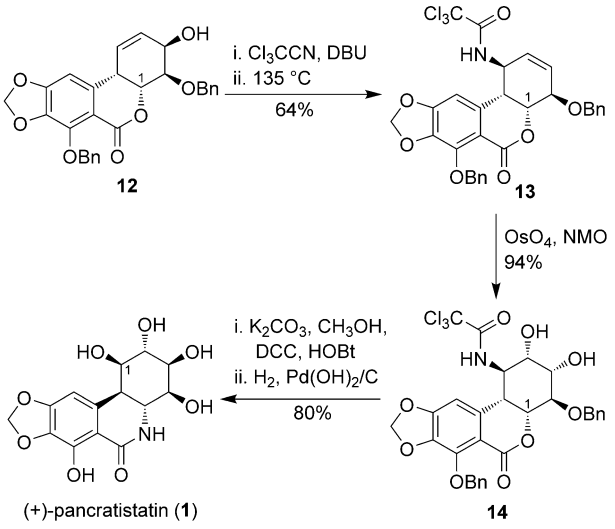
Jordan Froese was born in Hamilton, Ontario (Canada) in 1988. He studied biology and chemistry at the University of Toronto (B.Sc. 2010). After receiving his B.Ed. from Brock University in 2011, he joined Tomas Hudlicky's group at Brock University to pursue his graduate education in Chemical Biotechnology and is currently completing his PhD. His research interests include biocatalysis, fermentation technology, and natural product synthesis.



Tomas Hudlicky was born in 1949 in Prague, Czechoslovakia and immigrated to the USA in 1968. He received his BS in 1973 from Virginia Tech and his Ph.D. in 1977 at Rice University under the direction of Ernest Wenkert. After a year at the University of Geneva with Wolfgang Oppolzer, he joined the faculty at the Illinois Institute of Technology in 1978. He returned to Virginia Tech in 1982 and rose to the rank of professor in 1988. In 1995, he moved to the University of Florida in Gainesville. Since 2003 he has been at Brock University, where he currently holds Canada Research Chair professorship.



Scheme 1. Synthesis of lactone **12** by Madsen.[19]



Scheme 2. Synthesis of (+)-pancratistatin (**1**) by Madsen.[19]

inexpensive and readily available starting material, piperonal, was subjected to a sequence of six reactions to provide ester **6** in 70% yield.[24] The phenolic functionality in **6** was protected as its benzyl ether while the allylic bromide moiety was introduced by a sequence of reactions involving Heck coupling[25] with acrylic acid, conversion of carboxylic acid to its anhydride, reduction of the anhydride to an alcohol, and finally, displacement of the allylic mesylate with LiBr to produce ester **7**. The authors stated that the Heck coupling proceeded only in moderate yields in the presence of triphenylphosphine; when the coupling was carried out under phosphine-free conditions near quantitative yields were achieved.

Furanoside **8** was synthesized from D-xylose according to a published protocol in seven steps and in 42% overall yield.[24] An intermediate aldehyde was formed when furanoside **8** was treated with activated Zn under sonication at 40–45 °C. At the same time compound **7** was being added to this reaction mixture, which promoted the formation of allylzinc bromide. The reaction of allylzinc bromide with aldehyde afforded an inseparable mixture of alcohols **9** and **10** in 1.1:1 ratio. This mixture of alcohols **9** and **10** was treated with potassium carbonate in acetonitrile to effect lactonization. The lactones were also found to be inseparable by column chromatography, therefore the subsequent intramolecular metathesis was carried out with the mixture to obtain olefin **11** and its diastereomer **12** in 32% and 35% yield, respectively. Lactone **12** is similar to an intermediate used by Danishefsky in the first synthesis of racemic pancratistatin.[10]

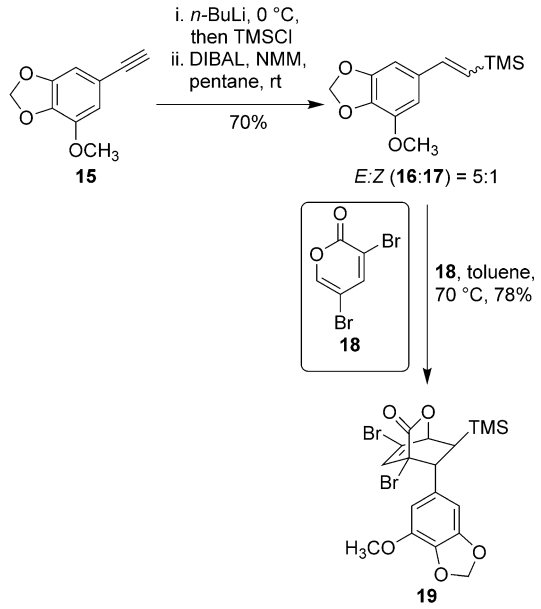
The alcohol in lactone **12** was converted to the corresponding imidate with trichloroacetonitrile/1,8-diazabicycloundec-7-ene (DBU),[*] and the subsequent Overman rearrangement[26] provided the corresponding allylic amine **13**, protected as trichloroacetamide (Scheme 2). This compound was subjected to Upjohn dihydroxylation[27] to obtain the corresponding *cis*-diol **14**. Treatment of diol **14** with potassium carbonate in methanol accomplished the hydrolysis of the lactone and trichloroacetamide moieties, with concomitant amide formation in the presence of dicyclohexyl carbodiimide (DCC)/hydroxybenzotriazole (HOBt). Finally, the removal of the benzyl group was accomplished by hydrogenolysis with Pearlman's catalyst to yield (+)-pancratistatin (**1**). The synthesis was accomplished in 18 steps with 7.1% overall yield.

2.1.2. *Cho (2011) – (±)-Pancratistatin (1)*

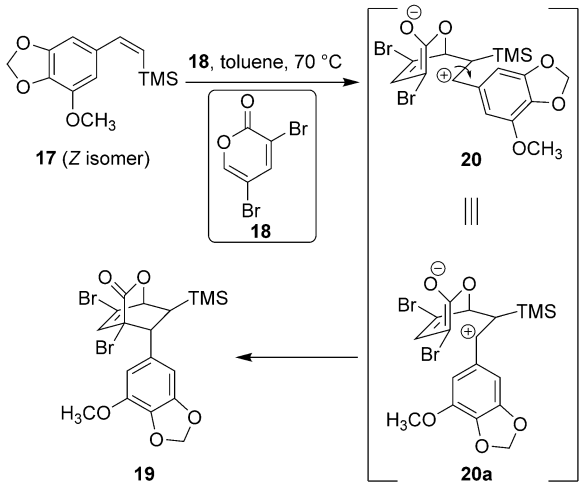
In 2011, Cho and co-workers published a synthesis of racemic pancratistatin[20] by a strategy that utilized a Diels–Alder cycloaddition[28] to construct the C ring. As shown in Scheme 3, the synthesis began with silylation of alkyne **15** and hydroalumination of the resulting trimethylsilylalkyne to obtain a mixture of *E*:*Z* isomers of the β-styrenes **16** and **17** in a 5:1 ratio, respectively. It was found that the *E*:*Z* ratio was highly solvent-dependent.

The mixture of *E*:*Z* isomers was heated with **18** (prepared in three steps from 2-pyrone),[29] leading to the Diels–Alder cycloadduct **19**, obtained as the only product in 78% yield (Scheme 4). The stereochemistry of the TMS and aryl functionalities in **19** was determined to be *anti* to each other. This observation indicated that the cycloaddition of *Z* isomer may have proceeded in a stepwise manner so as to produce **19** with the observed stereochemistry. The authors proposed that the electron rich dienophile **17** may have

[*] A glossary of abbreviations can be found at the end of the review.



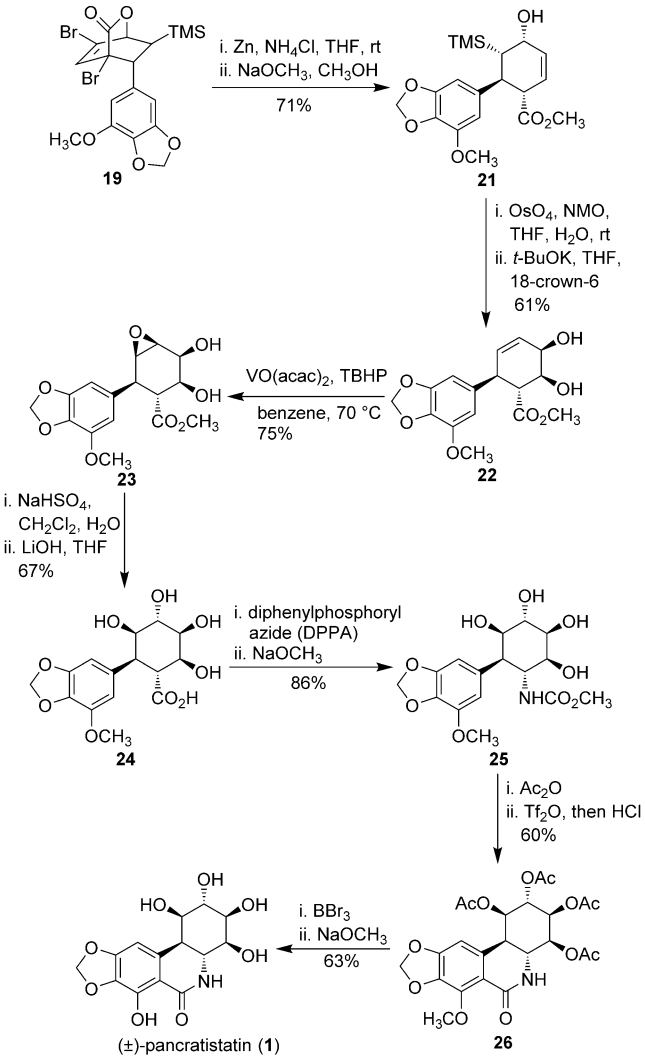
Scheme 3. Synthesis of cycloadduct **19** by Cho.[20]



Scheme 4. Formation of cycloadduct **19** from *Z*-dienophile **17**.[20]

initiated the reaction by attacking the C-6 of the pyrone **18**, creating a benzylic cation **20**. Thermodynamically favored transition state **20a**, would then undergo further cyclization leading to cycloadduct **19**, in which the TMS and aryl functionalities have the *anti* relationship. Thus the *trans* or *cis* stereochemistry of the dienophile (**16** or **17**) was found to be unimportant as far as formation of **19** was concerned. The proposed mechanism of the formation of cycloadduct **19** from *cis* dienophile **17** is shown (Scheme 4).

Debromination of **19** was followed by opening of the lactone with sodium methoxide in methanol to afford the β,γ unsaturated ester **21** (Scheme 5). Upjohn hydroxylation of **21** and subsequent Peterson elimination of the C-1 TMS group with potassium *tert*-butoxide in tetrahydrofuran (THF) gave access to alkene **22**. Allylic epoxidation of **22** afforded epoxide **23**, whose *trans*-diaxial opening with sodium bisulfate in methylene chloride/water provided the correct *trans* relationship of C-1/C-2 diol. The saponification of the



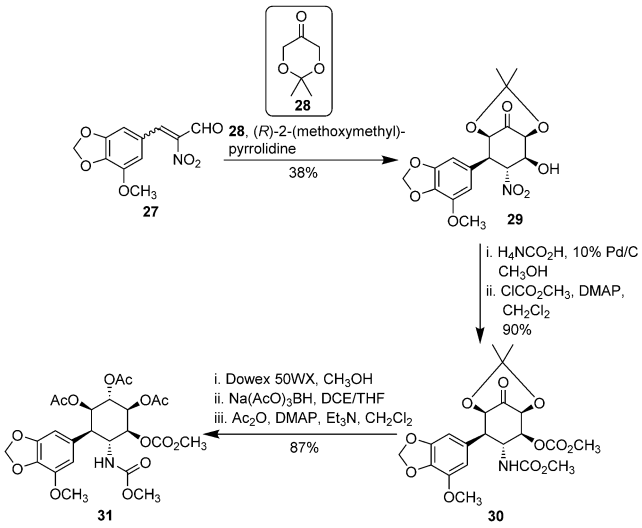
Scheme 5. Synthesis of (±)-pancratistatin (**1**) by Cho.[20]

methyl ester furnished carboxylic acid **24** and its Curtius rearrangement,[30] effected with diphenylphosphoryl azide (DPPA), followed by treatment with sodium methoxide afforded the corresponding methyl carbamate **25**.

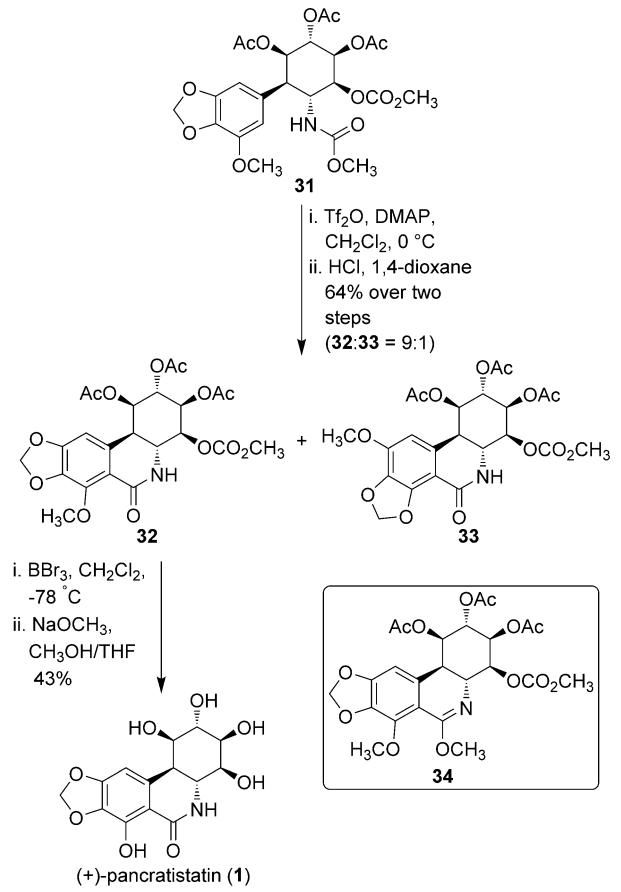
The hydroxy groups in compound **25** were acetylated to obtain Magnus's intermediate.[14a] In order to construct ring B, the Magnus's intermediate was subjected to Banwell modification of the Bischler–Napieralski reaction[31] with trifluoromethanesulfonic anhydride (Tf_2O), to provide phenanthridone **26**. This cyclization produced a mixture of two inseparable regioisomers in a 7:1 ratio, favouring the required isomer **26**, as described previously by Magnus.[14a] Finally, deprotection of the methyl ether in **26** and removal of the acetates furnished (±)-pancratistatin **1** in 3.9% overall yield in 16 linear steps from alkyne **15**.

2.1.3. *Alonso (2012) – (+)-Pancratistatin (1)*

In this short synthesis of (+)-pancratistatin (**1**) by Alonso,[21] an enantioselective annulation via one-pot Michael addition[32] and aldol reaction[33] was used as a key sequence. The starting material **27** (Scheme 6), was prepared



Scheme 6. Synthesis of carbamate **31** by Alonso.[21]



Scheme 7. Synthesis of (+)-pancratistatin (**1**) by Alonso.[21]

in five steps from the commercially available vanillin and 2-nitroethanol according to a published procedure.[34]

Ketone **28** was converted to a chiral enamine with (*R*)-2-(methoxymethyl)-pyrrolidine and reacted with enal **27** in sequential Michael addition and aldol reactions to construct the C ring. The nitro functionality in compound **29** was reduced to an amine by transfer hydrogenation, followed by O- and N-acylation with ethyl chloroformate/4-dimethylaminopyridine (DMAP) to obtain ketone **30**. In the next sequence of reactions, the acetonide functionality in **30** was deprotected, the ketone reduced to an alcohol and the resulting triol was protected as triacetate to yield carbamate **31**.

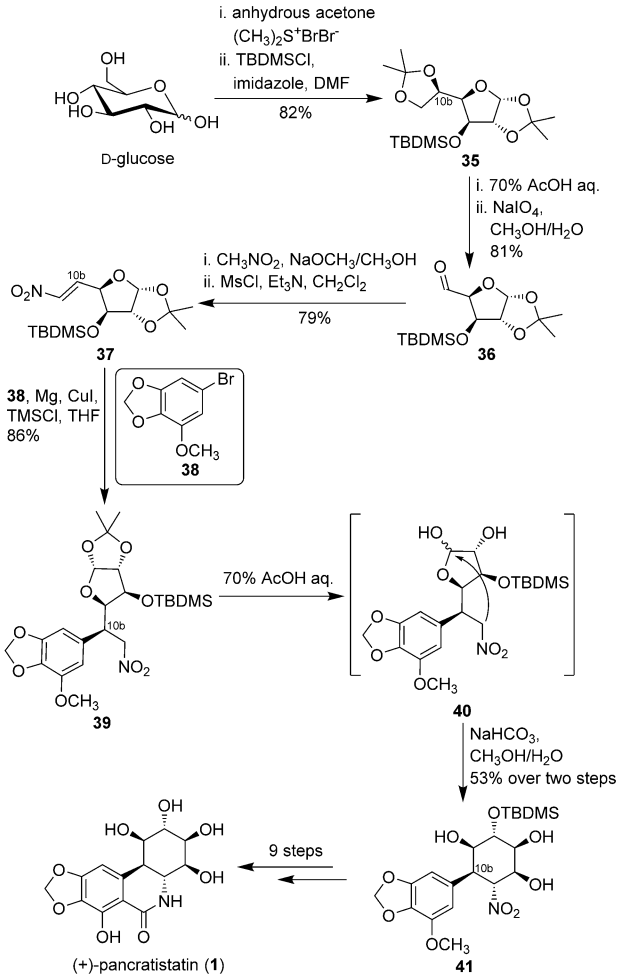
Thereafter, Alonso used a similar strategy as that of Cho[20] in order to construct the B ring with improved regioselectivity (Scheme 7). After treatment of carbamate **31** with Tf_2O/DMAP and subsequent hydrolysis of the iminoethers, the resulting phenanthridones were isolated as a 9:1 mixture of regioisomers (**32** and **33**). Formation of **32** from **31** proceeds through iminoether **34**. Removal of protecting groups afforded dextrorotatory pancratistatin (**1**) in 43% yield over two steps. The cleavage of the C-7 methyl ether by BBr_3 was the lowest yielding step (50%) in this synthesis.

2.1.4. *Sato (2013) – (+)-Pancratistatin (1)*

A chiral pool strategy was utilized in the total synthesis of (+)-pancratistatin (**1**) reported by Sato and co-workers in 2013.[22] The key steps involved the construction of the ring C from D-glucose and the coupling of ring A with fragment **37** by Michael addition.

D-Glucose was converted to protected D-glucofuranose **35** after treatment with dry acetone and bromodimethylsulfonium bromide, followed by silyl protection according to published procedures (Scheme 8).[35] Selective deprotection of the exocyclic acetonide in compound **35** gave access to a diol, which was oxidatively cleaved to afford aldehyde **36**. The Henry reaction[36] of aldehyde **36** with nitromethane, mesylation of the resulting alcohol, and the elimination of the mesylate under basic conditions produced nitroolefin **37**. The authors exploited the Michael acceptor capacity of compound **37** in its reaction with the aryl cuprate generated from **38** with Mg/CuI/TMSCl in THF. Only one enantiomer (Michael adduct **39**) was formed in this step. Model reactions suggested that replacement of the *tert*-butyldimethylsilyl (TBDMS) functionality with methyl group gave rise to a mixture of isomers, hence the role of the TBDMS functionality was significant in the stereoselectivity of the reaction. In the subsequent steps, the acetonide in **39** was deprotected, the furanose ring in **40** was opened under alkaline conditions, and simultaneously closed by a Henry reaction to afford D-*muco*-inositol derivative **41**.

Although the cyclization via the Henry reaction could have theoretically yielded up to four isomers, only one stereoisomer was formed. The authors attributed this selectivity to the stable, six-membered transition state, TS-1 (Figure 2). TS-1 is stabilized by intramolecular hydrogen bonding, the equatorial orientation of the bulky aryl and nitro groups, and the parallel π-orbital alignment of the C=O bond of aldehyde and the C=N bond of nitronate. Finally, (+)-pancratistatin (**1**) was synthesized from compound **41** in nine steps, similar to those used by Cho[20] and Alonso.[21] This synthesis was accomplished in 18 steps from D-glucose with 8.5% overall yield.



Scheme 8. Synthesis of (+)-pancratistatin (**1**) by Sato.[22]

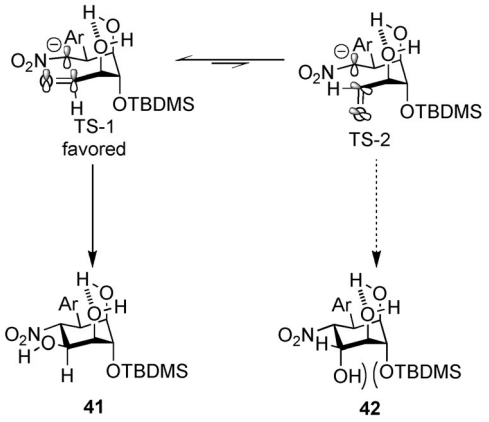
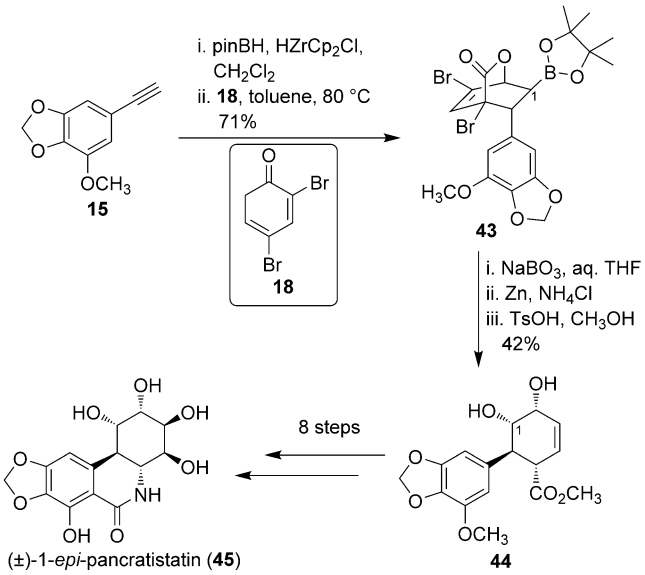


Figure 2. Favored transition state for the formation of compound **41**.[22]

2.1.5. *Cho (2013) – (±)-1-epi-Pancratistatin (45)*

In 2013, Cho[23] reported the total synthesis of (±)-1-*epi*-pancratistatin (**45**) along a similar path that he used in his published synthesis of (±)-pancratistatin (**1**).[20] The major difference is the incorporation of a boronate ester at the terminus of alkyne **15** (Scheme 9), as opposed to the previously used silyl group (Scheme 3). Hydroboration of **15** in presence of zirconium catalyst followed by Diels–Alder reaction with diene **18** furnished *endo*-bicyclolactone **43**.



Scheme 9. Synthesis of (±)-1-*epi*-pancratistatin **45** by Cho.[23]

Oxidation of organoborane **43** with sodium perborate afforded the desired alcohol in 81% yield. The organoborane was used in order to obtain the α-configuration of the C-1 hydroxy with retention of configuration after oxidation. Debromination was followed by methanolysis of the lactone functionality to afford ester **44**. Hereafter, the synthesis followed the same route as that previously published.[20] (±)-1-*epi*-pancratistatin (**45**) was synthesized from ester **44** in 8 steps. The synthesis of **44** was completed in five steps from alkyne **15** in 30% overall yield.

In this section, three total syntheses of dextrorotatory pancratistatin (**1**), and one total synthesis of racemic pancratistatin (**1**) were discussed. Out of these four syntheses, Alonso's reported in 2012, was the shortest, comprising 14 steps and accomplished in 8.2% overall yield.[21] For the synthesis of (+)-pancratistatin (**1**), Alonso[21] and Sato[22] both employed classical reactions, such as the aldol reaction, and Michael addition, while Cho[20] utilized Diels–Alder chemistry in his synthesis to achieve the required stereochemistry. Sato and co-workers[22] adopted the chirality from D-glucose and elaborated it further to build the natural product **1**, thus fulfilling the 7th principle of Green Chemistry (i.e. use of renewable feedstocks).[37] In Madsen's synthesis[19] of (+)-pancratistatin (**1**), ring closing metathesis (RCM)[38] was exploited to construct ring C, which could lead to a higher cost. Also covered was the synthesis of racemic C-1-*epi*-pancratistatin (**45**) by Cho and co-workers,[23] which applied a similar strategy for the preparation of **45** as that used for (±)-pancratistatin (**1**). In next section, recent syntheses of 7-deoxypancratistatin (**2**), a closely related alkaloid, are discussed.

2.2. 7-Deoxypancratistatin

7-Deoxypancratistatin was first isolated from the resting bulbs of *Haemanthus kalbreyeri* in 1989.[39] It was an intermediate in the total synthesis of (+)-lycoricidine published by Paulsen in 1983.[40] Hence, this publication can be called as the first "unofficial" total synthesis of 7-deoxypancratistatin. Although the biological activity of 7-deoxypancratistatin is 10 times lower[41] than that of pancratistatin, its synthesis serves as a suitable model for the exploration of efficient, shorter approaches to Amaryllidaceae class of alkaloids. In all, 16 total and formal syntheses have been reported to date and these are summarized in Table 2. The four most recent syntheses will be discussed in this section.

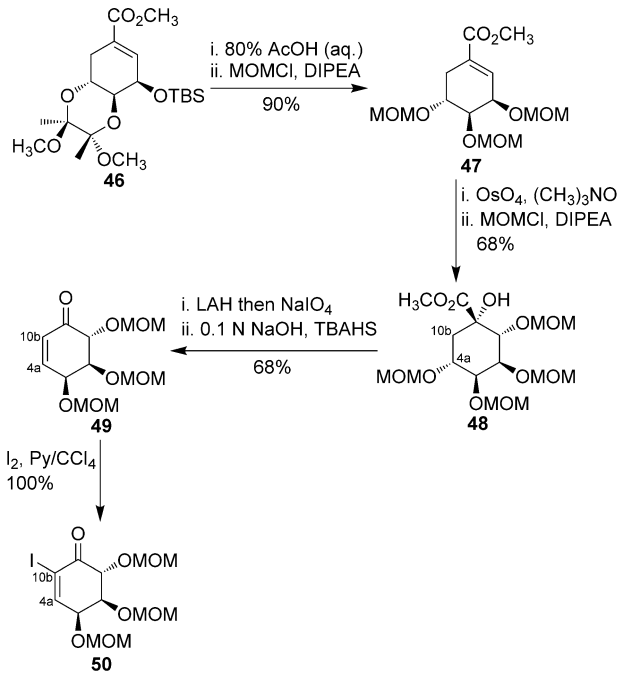
Table 2: Summary of total and formal syntheses of 7-deoxypancratistatin.

Author	Year	Number of steps	Optical series	Reference
Paulsen	1983	17[a]	(+)	[40]
Hudlicky	1995	13	(+)	[42]
Keck	1995	22	(+)	[43]
Chida	1995	15[a]	(+)	[44]
Hudlicky	1996	11	(+)	[45]
Keck	1998	13	(+)	[46]
Hudlicky	1999	14	(−)	[47]
Plumet	2000	19	(+)	[48]
Hudlicky	2002	12	(+)-10b-*epi*	[49]
Madsen	2006	13	(+)	[24]
Padwa	2006	23	(±)	[50]
Pandey	2008	16	(+)-1,10b-di-*epi*	[51]
Hudlicky	2010	18[b]	(+)	[52]
DeShong	2012	4[b]	(±)	[53]
Alonso	2012	10	(±)	[54]
Alonso	2012	10 11	(±)-2-*epi*, (±)-2,4-di-*epi*	[54]

[a] Indicates an estimate in cases where exact step count could not be determined from published reports. [b] Denotes a formal synthesis.

2.2.1. Pandey (2008) – (+)-1,10b-Di-epi-7-deoxypancratistatin (56)

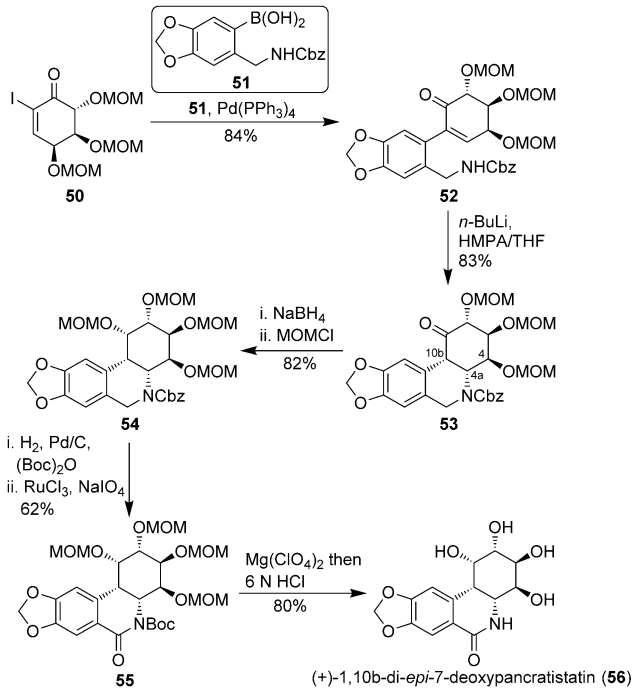
In a different strategy from others that have been reported for the synthesis of pancratistatin derivatives, Pandey and coworkers[51] decided to assemble ring B via an intramolecular aza-Michael addition of an amine (from the side chain of ring A) to an α,β unsaturated ketone in ring C (structure **52**). Chirality was adopted from the readily available cyclitol, (−)-D-quinic acid, which was converted to the protected triol **46** in a sequence of reactions according to Whitehead's protocol.[55] The triol was deprotected and then reprotected as methoxymethyl (MOM) ethers, to allow for all of these protecting groups to be cleaved in the last stage of synthesis (Scheme 10). Acrylate **47** was subjected to osmylation and the resultant diol was selectively protected to obtain ester **48**. In the following step, ester **48** was reduced to the corresponding alcohol and the exocyclic diol was oxidatively cleaved with sodium metaperiodate. The resulting ketone was treated with



Scheme 10. Preparation of ketone **50** by Pandey.[51]

sodium hydroxide and a catalytic amount of tetrabutylammonium hydrogen sulfate to introduce the α,β double bond via elimination of the MOM group at C-4a (pancratistatin numbering) to obtain enone **49**. The α-iodination was achieved according to Johnson's method[56] and provided the vinyl iodide **50** in 68% yield over three steps.

The vinyl iodide **50** was subjected to Suzuki cross-coupling with boronic acid **51** (prepared from piperonyl amine in two steps) to obtain enone **52** (Scheme 11). The fact that ring A and C were in place at this stage provided the opportunity for the formation of ring B through the aza-Michael addition. The key intramolecular aza-Michael addition was carried out with *n*-BuLi/hexamethyl-phosphoramide (HMPA) in THF, leading to a *cis* fusion between rings B and C (C-10b-*cis*-C-4a). The authors claim that all efforts to invert the stereochemistry at C-10b were unsuccessful suggesting that the *cis* junction, in this case, was thermodynamically most stable. The resulting ketone **53** was reduced and subsequently protected as its corresponding MOM ether to afford phenanthridine **54**. In the endgame of this particular synthesis, the carboxybenzyl (Cbz) group at N-5 was replaced with *tert*-butyloxycarbonyl (Boc) carbamate and the subsequent benzylic oxidation furnished phenanthridone **55**. Finally, the Boc group was removed by treatment with magnesium perchlorate and the MOM ethers were cleaved providing 10b-*epi*-7-deoxypancratistatin (**56**). The original target, 7-deoxypancratistatin (**2**), was not attained because the stability of the *cis* fusion between rings B and C precluded epimerization. The epimer, 1,10b-*epi*-7-deoxypancratistatin (**56**) was synthesized in 16 steps from **46** with 11.8% overall yield.

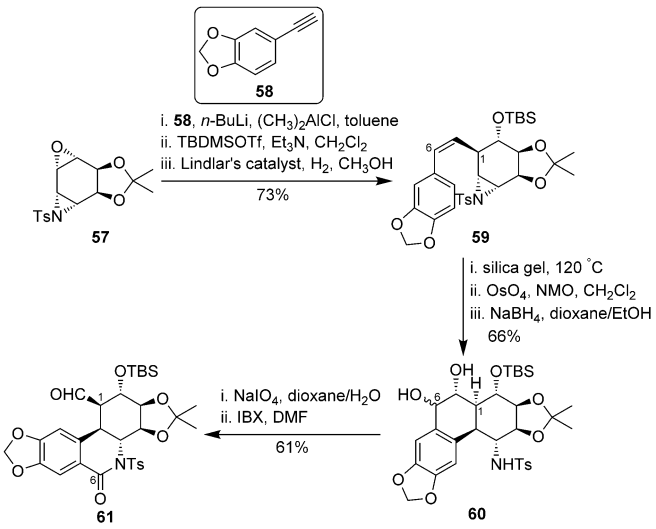


Scheme 11. Synthesis of (+)-1,10b-di-*epi*-7-deoxypancratistatin (**56**) by Pandey.[51]

2.2.2. *Hudlicky (2010) – (+)-7-Deoxypancratistatin (2)*

The efforts of the Hudlicky group aimed at the synthesis of 7-deoxypancratistatin derivatives,[42,45,47,49] continued with the next generation synthesis of (+)-7-deoxypancratistatin (**2**), published in 2010.[52] In this formal synthesis of (+)-7-deoxypancratistatin, compound **57** was synthesized according to the previously reported procedure starting with the diene diol derived enzymatically from bromobenzene (see compound **74**, Scheme 16).[57]

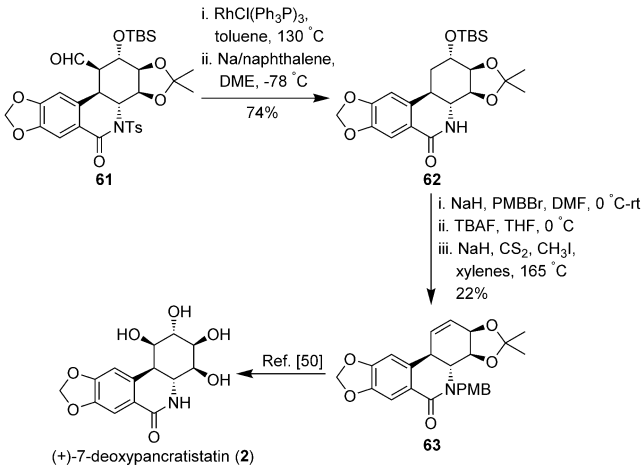
Epoxy aziridine **57** was reacted with an organoaluminium compound derived from **58**/*n*-BuLi/dimethylaluminium chloride in toluene at −50 to −20 °C (Scheme 12). The nucleophile opened the epoxide from the more accessible site in a *trans* diaxial fashion and the resulting alcohol was immediately protected as its silyl ether. This compound was then subjected to partial reduction with Lindlar's catalyst[58] to afford *cis*-alkene **59**. Adsorption of **59** on activated silica gel followed by heating at 120 °C (solid phase) facilitated the intramolecular cyclization,[59] with the aziridine being opened in a *trans*-diaxial manner. The olefin was subsequently subjected to osmylation conditions to produce a mixture of diol and overoxidized keto-alcohol; the crude mixture was reduced completely to diol **60** and cleaved oxidatively with sodium metaperiodate. One of the aldehyde functionalities spontaneously cyclized with the tosylamine functionality to construct the phenanthridol core. The aminal was then oxidized to phenanthridone **61** with 2-iodoxybenzoic acid (IBX). This synthesis was designed to produce the C-1 aldehyde that could eventually serve as a source of unnatural derivatives (see Section 3.16). The C-1 space constitutes the only part of the pancratistatin pharmacophore



Scheme 12. Synthesis of phenanthridone **61** from aziridine **57** by Hudlicky.[52]

where changes in structure or functionality may be made without detrimental effects on biological activity.[60]

The original aim of this particular strategy was the synthesis of aldehyde **61** and its conversion to 7-deoxypancratistatin (**2**) was of secondary importance. It did not proceed without problems, as evidenced by the number of quite arduous transformations required to convert **61** to 7-deoxypancratistatin (**2**) (Scheme 13). In the final sequence of the



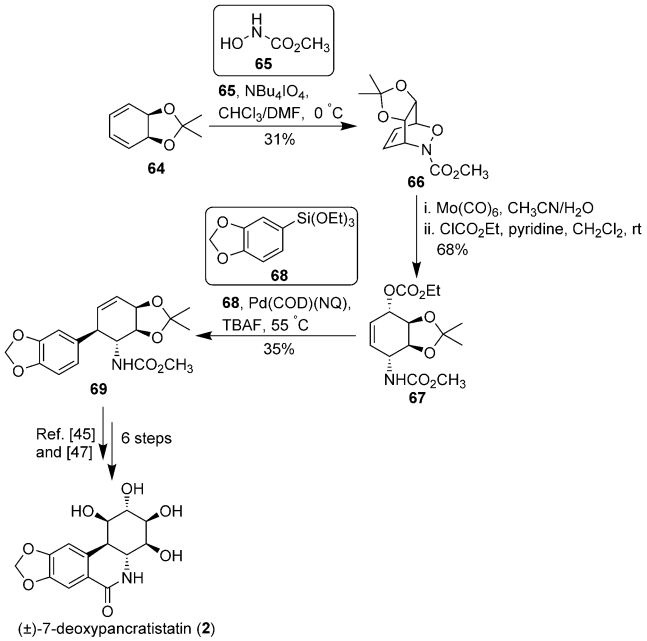
Scheme 13. Synthesis of (+)-7-deoxypancratistatin (**2**) from aldehyde **61** by Hudlicky.[52]

synthesis, aldehyde **61** was subjected to Wilkinson decarbonylation[61] followed by reduction of the tosyl amide with sodium/naphthalene to obtain phenanthridone **62** (Scheme 13). The amide nitrogen was then reprotected as its corresponding PMB ether, and the TBDMS ether was cleaved with TBAF. In the following step, Chugaev elimination[62] of an alcohol at C-2 provided olefin **63** in 22 % yield over three steps. Compound **63** is a known intermediate in

Padwa's synthesis of 7-deoxypancratistatin[50] and its attainment formalized the synthesis of 7-deoxypancratistatin (Padwa prepared **2** in 7 steps from **63**).

2.2.3. DeShong (2012) – (±)-7-Deoxypancratistatin (2)

In the synthesis of (+)-pancratistatin by Trost,[12] rings A and C were coupled by Tsuji–Trost reaction[63] using aryl cuprates as nucleophiles. In 2012, DeShong[53] employed the same strategy and explored the performance of aryl siloxanes, as opposed to aryl cuprates, as nucleophiles. In this formal synthesis of (±)-7-deoxypancratistatin (**2**), oxazine **66** was synthesized from diene **64** by a hetero Diels–Alder cycloaddition with a nitroso dienophile prepared from **65** (Scheme 14). Cleavage of the N–O bond in bicyclic compound **66** followed by N- and O-protection produced allylic carbonate **67**.

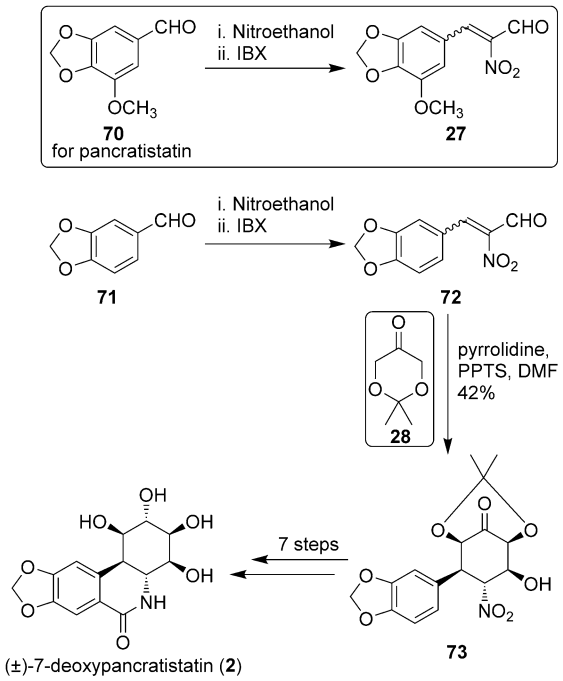


Scheme 14. Formal synthesis of (±)-7-deoxypancratistatin (**2**) by DeShong.[53]

The palladium-catalyzed Tsuji–Trost reaction of allylic carbonate **67** and aryl siloxane **68**[64] gave access to olefin **69**. The authors observed that the Pd-catalyst, bearing bulky π-donor ligands [e.g., 1,5-cyclooctadiene (COD) and 1,4-naphthoquinone (NQ)] promoted the product formation while the Pd-catalysts with σ-bonding ligands (e.g. phosphines) were found to be inactive. The preparation of **69** completed the fomal synthesis of 7-deoxypancratistatin (**2**), reported by Hudlicky.[45,47] It should be noted that the change in the nature of the nucleophile (siloxane instead of cuprate) did not lead to significant improvements, in fact, the yields in the case of siloxane were lower for the Tsuji–Trost reaction.

2.2.4. Alonso (2012) – (±)-7-Deoxypancratistatin (2)

This strategy for the total synthesis of (±)-7-deoxypancratistatin (**2**) is similar to that used for (+)-pancratistatin (**1**) and reported by the same group.[21] The major difference is the use of precursor **72** instead of **27** (Scheme 15).



Scheme 15. Preparation of precursor **73** in the synthesis of (±)-7-deoxypancratistatin (**2**) by Alonso.[54]

Piperonal **71** was reacted with 2-nitroethanol in a Henry reaction to obtain the corresponding allylic alcohol, which was oxidized to **72** with IBX. Aldehyde **72** was then reacted with **28** in the presence of pyrrolidine to obtain acetonide **73**. The subsequent part of synthesis proceeded in an identical manner to that which was previously shown (Scheme 6 and 7). The synthesis was accomplished in 10 steps with 2.8% overall yield.

To sum up this section, two syntheses of racemic 7-deoxypancratistatin (**2**) and a synthesis of dextrorotatory 7-deoxypancratistatin (**2**) were discussed. In Hudlicky's[52] formal synthesis of (+)-7-deoxypancratistatin (**2**), the chirality was achieved by the enzyme-catalyzed enantioselective dihydroxylation followed primarily by classical reactions, including the Lemieux–Johnson oxidation,[65] and Wilkinson decarbonylation. DeShong[53] attempted the Tsuji–Trost reaction of allylic carbonate **67** and aryl siloxane **68**, for the connection of ring A with ring C, however this strategy resulted in low yields, which is the primary reason for the low overall yield (7.4%) of this formal synthesis. Alonso[54] utilized the aldol reaction and Michael addition for the synthesis of (±)-7-deoxypancratistatin (**2**), as he also had used in his synthesis of (+)-pancratistatin (**1**). Pandey's synthesis[51] of (+)-1,10b-di-*epi*-7-deoxypancratistatin (**56**) was also reviewed. The initial plan was to synthesize (+)-7-deoxypan-

cratistatin, which was not realized since epimerization at C-10b was unsuccessful. The synthesis (+)-1,10b-di-*epi*-7-deoxypancratistatin (**56**) was reported in 16 linear steps, with chirality adopted from (−)-D-quinic acid. In the next section the syntheses of narciclasine (**3**), one of the most active anticancer compounds in the Amaryllidaceae family, are discussed.

2.3. Narciclasine

Narciclasine was isolated in 1967 by Ceriotti and was shown to have potent antimitotic activity.[66] A structure was proposed in 1968 by Ceriotti and Piozzi,[67] and was finally confirmed in 1972.[68] Despite the recognition of narciclasine's bioactivity, the interest of the synthetic community did not materialize for several decades. The first total synthesis was not reported until 1997, when Rigby prepared (+)-narciclasine.[69] A summary of the six subsequent total syntheses reported is shown in Table 3, with Banwell's synthesis of (−)-narciclasine discussed in detail.[70]

2.3.1. Banwell (2008) – (−)-Narciclasine (3)

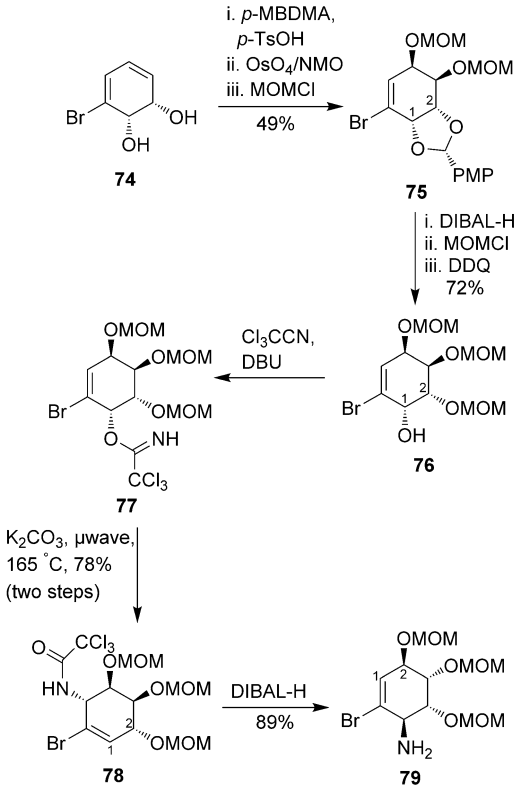
A total synthesis of (−)-narciclasine, the enantiomer of natural narciclasine, was reported by Banwell in 2008.[70] A convergent strategy was employed, with the key transformation being the Suzuki–Miyaura cross-coupling of the aromatic (A-ring) and aminocyclitol (C-ring) fragments, with the concomitant amide bond formation furnishing the B-ring. As previously reported in Banwell's 2007 synthesis of (−)-lycoricidine (**4**), aminocyclitol fragment **79** was assembled from the *cis*-diol **74**,[74] produced by the enzymatic dihydroxylation of bromobenzene (Scheme 16).[57] The diene-diol **74** was converted to its corresponding *p*-methoxybenzylidene acetal (PMP-acetal), which was subsequently subjected to Upjohn dihydroxylation and MOM protection of the resulting diol to afford compound **75**. Regioselective cleavage of the PMP-acetal with diisobutylaluminium hydride (DIBAL-H) provided the C-2 alcohol which was subsequently protected as MOM ether. The resultant PMB ether (at C-1) was oxidatively deprotected with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and the resulting alcohol was treated with trichloroacetonitrile to afford acetimidate **77**. The heating of acetimidate **77** under microwave irradiation resulted in the production of amide **78**, constituting one of the few examples of microwave-promoted Overman rearrangement. Cleavage of the amide functionality afforded aminoconduritol **79**, the desired C-ring fragment.

The aromatic fragment was made via a directed *ortho*-metalation strategy, based largely on the report by Keck in the synthesis of (+)-narciclasine.[72] Accordingly, piperonal (**71**) was subjected to amidation conditions introduced by Gilman,[75] installing the diethylamide functionality as the directing group for the *o*-metalation (Scheme 17). Treatment of **80** with *sec*-BuLi, trimethyl borate and hydrogen peroxide/acetic acid afforded the corresponding phenol with complete regioselectivity. The phenol was subsequently protected to produce silyl ether **81**. A second directed *o*-metalation

Table 3: Summary of total syntheses of narciclasine.

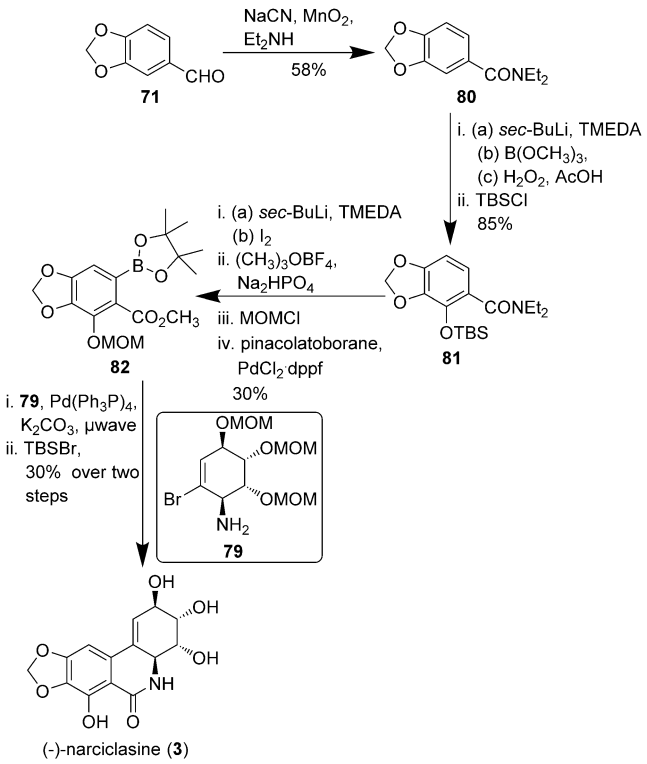
Author	Year	Number of steps	Optical series	Reference
Rigby	1997	22	(+)	[69]
Hudlicky	1999	12	(+)	[71]
Keck	1999	12	(+)	[72]
Rigby	2000	24	(+)	[15]
Yan	2002	12[a]	(+)	[73]
Banwell	2008	11	(−)	[70]

[a] Indicates an estimate in cases where exact step count could not be determined from published reports.



Scheme 16. Synthesis of the C-ring fragment **79** by Banwell.[70]

protocol afforded the corresponding aryl iodide, which was then treated with trimethyloxonium tetrafluoroborate and sodium phosphate to effect the methanolysis of the amide residue and the deprotection of the silyl ether. The free phenol was then protected as its MOM ether, before being subjected to a Miyaura borylation reaction to afford compound **82**. The highest yields for the final borylation step (54%) were obtained using conditions introduced by Tønder.[76] The key step in this synthesis involved the coupling of aminocyclitol fragment **79** with the aryl fragment **82**. To this end, a toluene solution of compounds **79** and **82** was treated with palladium, aqueous potassium carbonate, and tetra-*n*-butylammonium bromide as a phase-transfer catalyst. Under these conditions the Suzuki–Miyaura coupling and amide bond formation were accomplished in a concomitant fashion and led to the production of the tetra-MOM protected



Scheme 17. Synthesis of (−)-narciclasine (**3**) by Banwell.[70]

derivative of (−)-narciclasine. A final deprotection with *tert*-butyldimethylsilyl bromide (TBSBr) afforded (−)-narciclasine (**3**), completing the synthesis in a total of 11 steps and an overall yield of 7%.

It is evident from Table 3 that narciclasine has not received the level of attention from the synthetic community that other Amaryllidaceae alkaloids have garnered. In spite of this fact, the published syntheses of this alkaloid represent some of the most efficient and creative means of assembling the isocarbostyril skeleton. Of particular note are the 12-step syntheses of (+)-narciclasine (**3**) reported by Hudlicky[71] and Keck.[72] The synthesis of (−)-narciclasine (**3**) by Banwell[70] further improved the efficiency of generating the isocarbostyril skeleton by making excellent use of a tandem Suzuki–Miyaura coupling/amidation reaction to construct the target compound in just eleven steps. The following section will focus on lycoricidine, a target for synthetic chemists for over forty years.

2.4. Lycoricidine

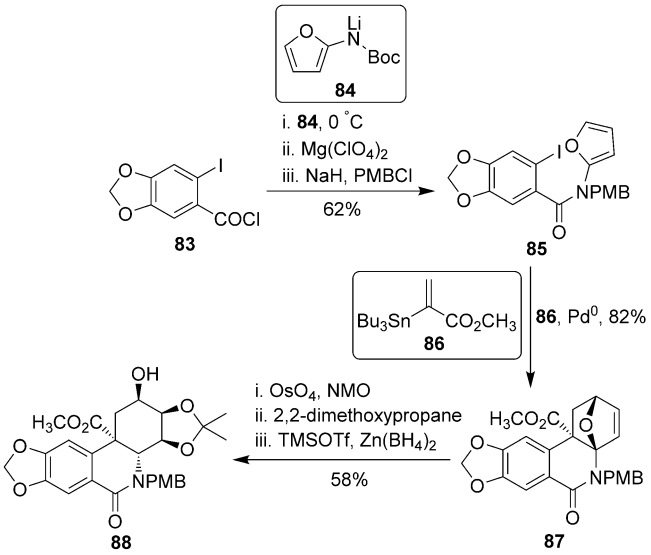
Lycoricidine was first isolated from the bulbs of *Lycoris radiata* in 1968.[77] Although, its biological activity is lower than that of narciclasine and pancratistatin,[3e] it is a close analogue of these Amaryllidaceae constituents, and it has served as an attractive target for years. Twelve total syntheses have been reported to date and these are summarized in Table 4. The three most recent syntheses will be discussed in this section.

Table 4: Summary of total and formal syntheses of lycoricidine.

Author	Year	Number of steps	Optical series	Reference
Ohta	1975	19	(±)	[78]
Paulsen	1982	13	(±)	[40]
Schubert	1987	17	(±)	[79]
Ogawa	1991	24	(+)	[80]
Hudlicky	1992	9	(+)	[81]
Martin	1993	11	(±)	[82]
Keck	1996	14	(−)	[83]
Keck	1999	9	(+)	[72]
Yan	2002	15	(+)	[84]
Padwa	2007	13	(±)	[50b]
Banwell	2007	11	(−)	[74]
Yadav	2010	14	(+)	[85]
Panda	2015	20	(+)-3-*epi*	[86]

2.4.1. *Padwa (2007) – (±)-Lycoricidine (4)*

A synthesis of racemic lycoricidine was reported by Padwa in 2007.[50b] The strategy of this synthesis was based upon a Stille coupling/Diels–Alder sequence to produce key intermediate **87**. In order to construct the precursor for this key transformation, amide **85** was synthesized in a sequence of reactions involving the coupling of acid chloride **83** with Boc-protected lithium carbamate **84**, removal of the Boc protecting group with magnesium perchlorate, and reprotection with *p*-methoxybenzyl chloride (PMBCl) (Scheme 18).

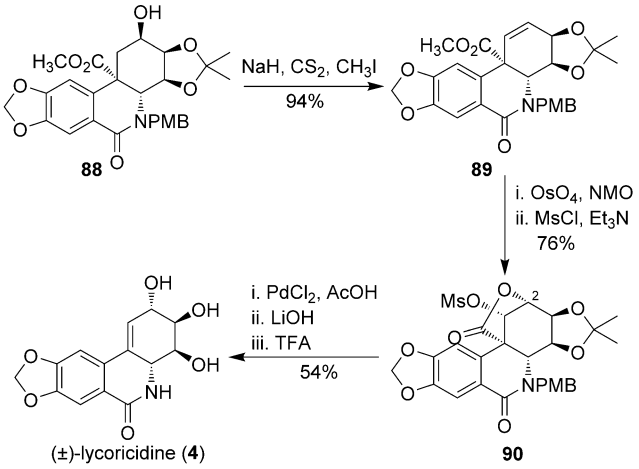


Scheme 18. Synthesis of alcohol **88** by Padwa.[50b]

A key step in this synthesis was the construction of the phenanthridone core through the Stille coupling of amide **85** and organostannane **86**, which was followed by a spontaneous Diels–Alder reaction to afford phenanthridone **87**. Upjohn dihydroxylation provided exclusively the exo diol, which was subsequently protected as an acetonide. The oxabicyclo ring was opened with trimethylsilyl trifluoromethanesulfonate

(TMSOTf) under reductive condition to obtain phenanthridone **88**.

With compound **88** in hand, inversion of configuration of the hydroxy group at C-2 and introduction of the π bond between C1–C10b were required in order to obtain the target molecule (Scheme 19). The hydroxy group at C-2 was



Scheme 19. Synthesis of (±)-lycoricidine (**4**) from alcohol **88** by Padwa.[50b]

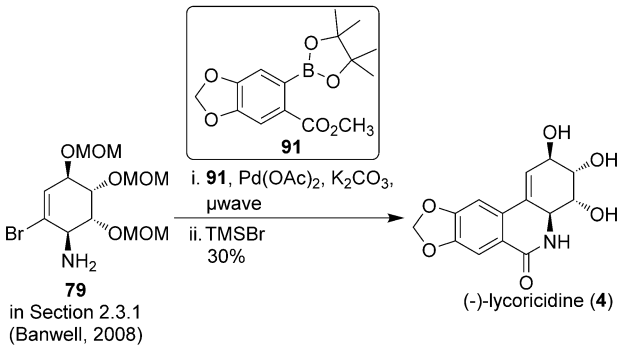
removed by Chugaev elimination (sodium hydride/carbon disulfide/methyl iodide) to obtain olefin **89**, and the double bond in **89** was dihydroxylated under Upjohn conditions. Spontaneous γ-lactonization and mesylation of the free hydroxy at C-1 afforded compound **90**. Removal of the PMB protecting group was followed by treatment with lithium hydroxide, effecting a hydrolysis/decarboxylation/elimination sequence.[87] Finally, deprotection of the acetonide was performed providing access to (±)-lycoricidine (**4**). This synthesis was completed in 13 steps with 11.4% overall yield.

2.4.2. *Banwell (2007) – (−)-Lycoricidine (4)*

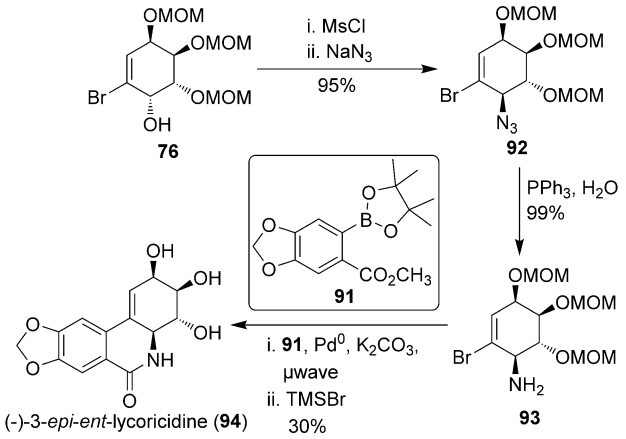
Banwell reported a short synthesis of (−)-lycoricidine, the enantiomer of the natural product, in 11 steps with 12.6% overall yield.[74] The synthesis leading to intermediate **79** has been discussed in Section 2.3.1, where Banwell's synthesis of (−)-narciclasine (**3**) was described (Scheme 16).[70]

The endgame of this synthesis utilized the Suzuki–Miyaura coupling of the vinyl bromide **79** and boronate ester **91**, resulting in the construction of the phenanthridone skeleton (Scheme 20). Finally, removal of the MOM groups furnished (−)-lycoricidine (**4**).

In the same paper Banwell also described the preparation of (−)-3-*epi*-*ent*-lycoricidine (**94**). The alcohol **76** (an intermediate in Banwell's synthesis of narciclasine, see Scheme 16)[70] was converted to azide **92**, which was followed by reduction under Staudinger conditions[88] (Scheme 21). Amine **93** was reacted with boronate ester **89** under microwave-assisted Suzuki–Miyaura conditions to form the phenanthridone framework, which was then treated with TMSBr



Scheme 20. Synthesis of (−)-lycoricidine (**4**) by Banwell.[74]



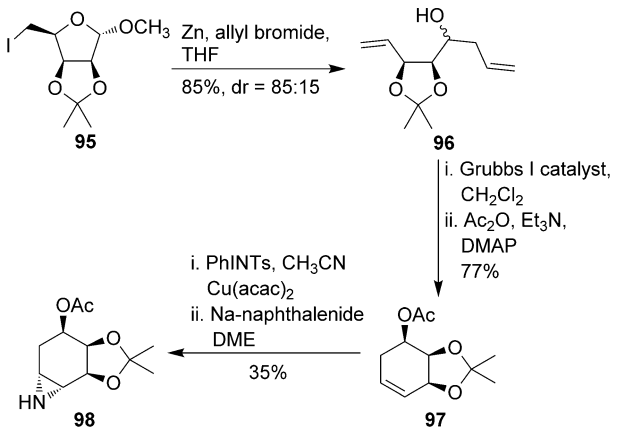
Scheme 21. Synthesis of (−)-3-*epi*-*ent*-lycoricidine (**94**) by Banwell.[74]

to cleave the MOM groups producing (−)-3-*epi*-*ent*-lycoricidine (**94**). Compound **94** was evaluated for its biological activity against 13 cancer cell lines with (+)-narciclasine (**3**) as a control. (−)-3-*epi*-*ent*-lycoricidine (**94**) was shown to be one or two orders of magnitude less cytotoxic than the control, and therefore was regarded as inactive.[89]

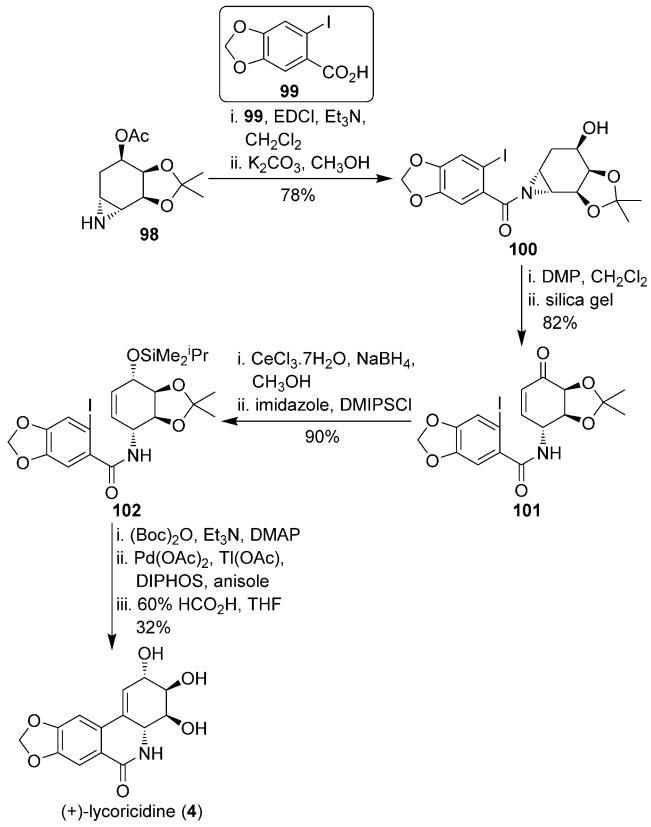
2.4.3. *Yadav (2010) – (+)-Lycoricidine (4)*

In a recent total synthesis of (+)-lycoricidine (**4**), Yadav employed a chiral pool strategy.[85] Furan **95** was obtained from D-(+)-mannose in a sequence of reactions according to a previously published protocols.[90] In the key step, furan **95** was treated with zinc/allyl bromide to afford diene **96** (Scheme 22). An intramolecular metathesis was carried out to obtain a homoallylic alcohol which was then acetylated to obtain cyclohexene **97**. Copper(II)-catalyzed aziridination of **97** with *N*-tosyliminobenzyliodinane[52,91] and removal of the tosyl group furnished compound **98**.

Amide formation with carboxylic acid **99** according to Steglich protocol[92] followed by hydrolysis of the acetate functionality afforded compound **100** (Scheme 23). Oxidation of the resulting secondary alcohol with Dess–Martin periodinane (DMP), followed by treatment with silica gel, provided enone **101**. Luche reduction[93] of enone **101** and subsequent



Scheme 22. Synthesis of aziridine **98** by Yadav.[85]

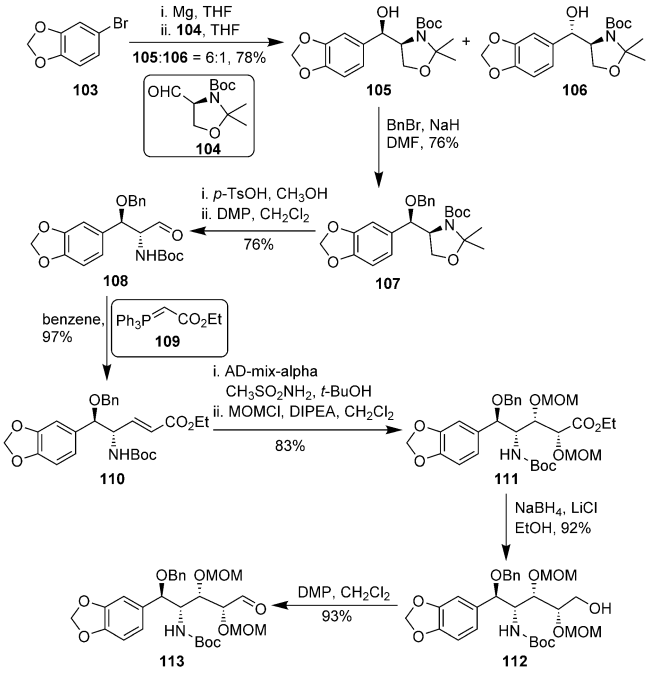


Scheme 23. Synthesis of (+)-lycoricidine (**4**) by Yadav.[85]

protection of the resulting alcohol with dimethylisopropylsilyl chloride (DMIPSCl) afforded a diastereomeric mixture of products in a 60:40 ratio, favoring the undesired isomer. The mixture was separated to isolate the required isomer **102**, and the undesired isomer was deprotected and oxidized to afford **101**. This procedure was repeated in order to obtain additional amounts of **102**. In the final stage of the synthesis, the phenanthridone skeleton was constructed according to the intramolecular Heck reaction strategy of Hudlicky[81] and Ogawa.[80a] The amide nitrogen was protected to avoid any potential interference during the coupling step. The protected amide was then subjected to the Heck reaction conditions with palladium acetate/thallium acetate/1,2-bis(diphenylphosphino)ethane (DIPHOS)/anisole. The cyclization furnished the required phenanthridone scaffold. Finally, the Boc protecting group was removed to obtain (+)-lycoricidine (**4**). This synthesis was accomplished in 14 steps and in 4.2% overall yield.

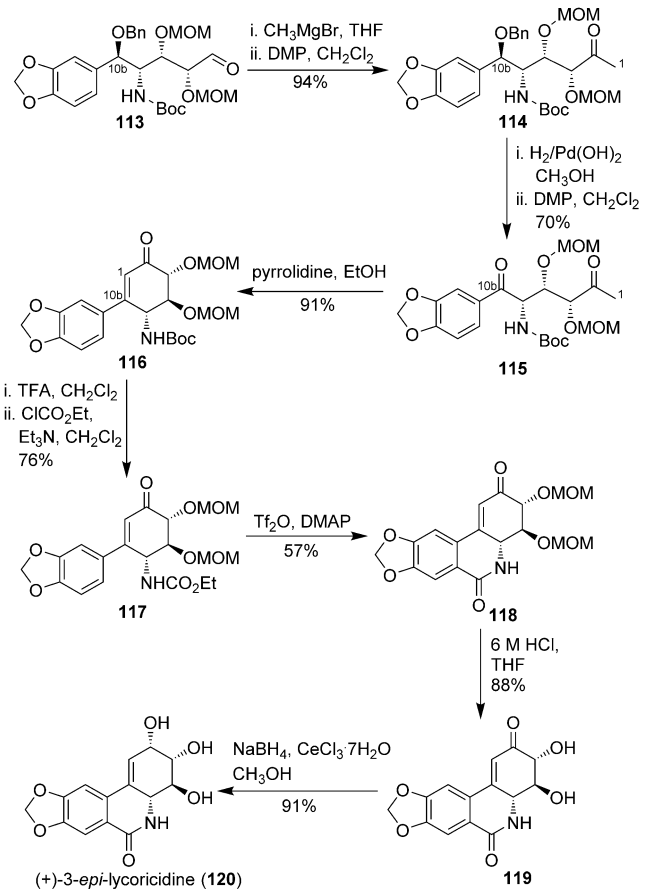
2.4.4. *Panda (2015) – (+)-3-epi-Lycoricidine (120)*

Recently, Panda synthesized the C-3 epimer of (+)-lycoricidine.[86] For this synthesis, the authors designed a new strategy to construct ring C via cyclization involving an intramolecular aldol reaction at a late stage of the synthesis. The synthesis commenced by reacting a Grignard reagent prepared from aryl bromide **103** with Garner aldehyde (**104**) (Scheme 24). The reaction provided a mixture of diastereomers **105** and **106** in a 6:1 ratio, respectively.



Scheme 24. Synthesis of aldehyde **113** by Panda.[86]

Benzylic alcohol **105** was separated from the mixture and protected with benzyl bromide (BnBr)/NaH. The cleavage of oxazolidine ring in **107** was effected with *p*-TsOH and the resulting primary alcohol was oxidized with DMP to obtain aldehyde **108**. Horner–Wadsworth–Emmons olefination of aldehyde **108** with reagent **109** yielded ester **110** in excellent yield (97%). In the following step, the olefin in **110** was subjected to Sharpless asymmetric dihydroxylation conditions using AD-mix-α and the resulting alcohols were protected as their corresponding MOM ethers to obtain compound **111**. The ester functionality in **111** was reduced with $NaBH_4$/LiCl to afford alcohol **112**, which was subsequently oxidized with DMP to furnish aldehyde **113**.



Scheme 25. Synthesis of (+)-3-*epi*-lycoricidine (**120**) from aldehyde **113** by Panda.[86]

The next step in the synthesis involved the reaction of aldehyde **113** with methylmagnesium bromide and subsequent oxidation of the resulting alcohol with DMP to ketone **114** (Scheme 25). The benzyl ether at C-10b was removed by hydrogenation over Pearlman's catalyst and the ensuing free alcohol was oxidized with DMP to furnish diketone **115**. At this point, all of the necessary fragments, containing the correct stereochemistry, were tethered to ring A. The intramolecular aldol reaction of **116**, promoted by pyrrolidine, led to the construction of ring C. For this transformation, a number of bases were screened, in particular, LDA, KHMDS, and DIPEA, however, all of these resulted in a mixture of several products. In order to form the phenanthridone skeleton, it was necessary to change the protecting group at N-5. Thus, removal of the Boc group in **116** was effected with TFA and the resulting free amine was protected with ethylchloroformate/Et_3N to provide enone **117**. A Banwell-modified Bischler–Napieralski reaction[31] of **117** gave rise to phenanthridone core **118**. Finally, cleavage of the MOM ethers with 6 M hydrochloric acid followed by Luche reduction of enone **119** provided (+)-3-*epi*-lycoricidine (**120**). The synthesis was accomplished in 20 linear steps with 7% overall yield.

Three lycoricidine (**4**) syntheses were discussed in this section, as well as a recent synthesis of its C-3 epimer **114**. Padwa[50b] utilized a Stille cross-coupling/Diels–Alder sequence in his synthesis of racemic lycoricidine (**4**). In the case of Banwell's synthesis[74] of (−)-lycoricidine (**4**), Suzuki cross-coupling was employed to to connect ring A and ring C. Yadav[85] synthesized (+)-lycoricidine (**4**) starting with D-(+)-mannose. He applied ring closing metathesis, Yamada–Jacobsen–Evans aziridination, Heck cross-coupling, and Luche reduction in his synthesis. Panda utilized an intramolecular aldol reaction to furnish ring C and a Banwell modified Bischler–Napieralski reaction[31] to establish ring B. In the next section, the first member of Amaryllidaceae family to be discovered, lycorine (**5**), is discussed.

2.5. Lycorine

Lycorine (**5**) is an alkaloid found in several plants of the Amaryllidaceae family.[94] Additionally, it is the only alkaloid among the compounds (**1**–**5**) discussed in this review that conforms to the strict definition of an alkaloid (i.e., a compound containing a basic nitrogen).[95] Lycorine was first isolated in 1877 from *Narcissus pseudonarcissus*.[6] Since its isolation, it has been recognized as a potent emetic;[94] studies have shown that lycorine inhibits protein and DNA synthesis in murine cells and in vivo growth of a murine transplantable ascite tumor.[94,96] Lycorine (**5**) serves as a powerfull inhibitor of growth and cell division in plants, algae, and yeasts[97] and also has antiviral activity.[5b,98] However, it was shown that lycorine (**5**) is approximately 100 times less potent at inhibiting cancer cell proliferation than narciclasine (**3**).[99] A number of total and formal syntheses of (±)-lycorine, have been published, as shown in Table 5. However, only one protocol describes an enantioselective total synthesis of the natural enantiomer, (+)-lycorine.[100]

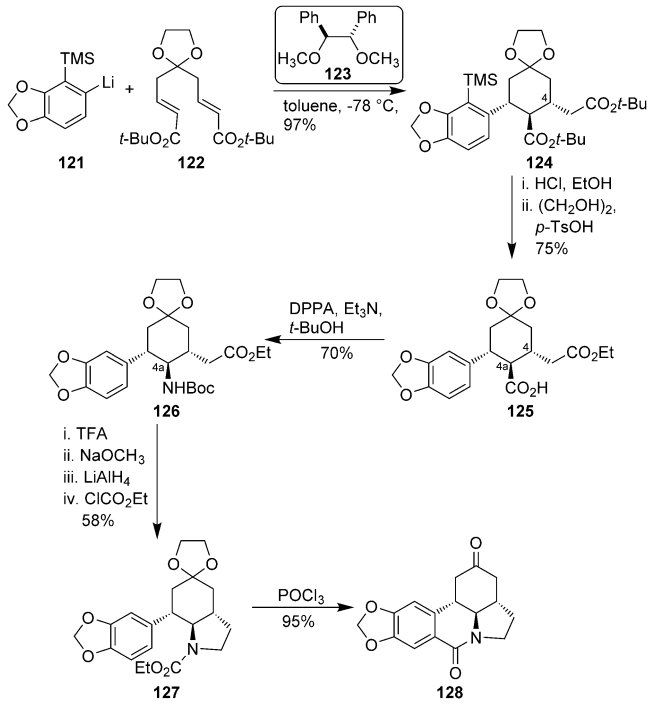
Table 5: Summary of total and formal syntheses of lycorine.

Author	Year	Number of steps	Optical series	Reference
Tsuda	1975	11	(−)	[101]
Torssell	1978	16	(±)	[102]
Umezawa	1979	21[a]	(±)	[103]
Martin	1981	6[a]	(±)	[104]
Umezawa	1984	13[a]	(±)	[105]
Boeckman	1988	13	(±)	[106]
Hoshino	1991	16	(±)	[107]
Schultz	1993	13	(+)-1-deoxy	[108]
Hoshino	1996	20	(±)	[109]
Schultz	1996	14	(+)	[100]
Tomioka	2009	18	(−)	[110]
Tomioka	2009	17	(−)-2-*epi*	[110]
Shao	2014	17[a]	(+)	[111]
Cho	2014	17	(±)	[112]
Cho	2014	18	(±)-1,2-diacetoxy	[112]

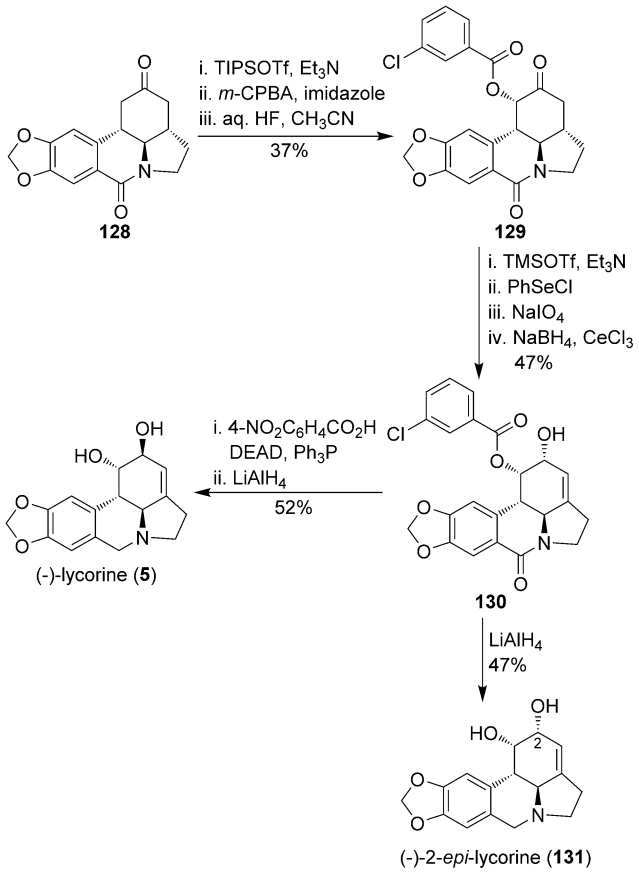
[a] Denotes a formal synthesis.

2.5.1. Tomioka (2009) – (−)-Lycorine (5)

In Tomioka's synthesis[110] the cyclohexanone core of lycorine was constructed by a Michael addition cascade of



Scheme 26. Synthesis of isoquinolinone **128** by Tomioka.[110]



Scheme 27. Synthesis of (−)-lycorine (**5**) and (−)-2-*epi*-lycorine (**131**) from isoquinolinone **128** by Tomioka.[110]

aryl lithium **121** and di-ester **122** in the presence of chiral ligand **123** (Scheme 26). The presence of a TMS group on the aromatic ring of **121** led to a significant improvement in the enantiomeric excess of the product, cyclohexane **124**. Removal of the TMS group and transesterification was followed by reketalization to provide acid **125**. Curtius rearrangement of the carboxylic acid at C-4a with DPPA/triethyl amine/*tert*-butanol afforded carbamate **126**.

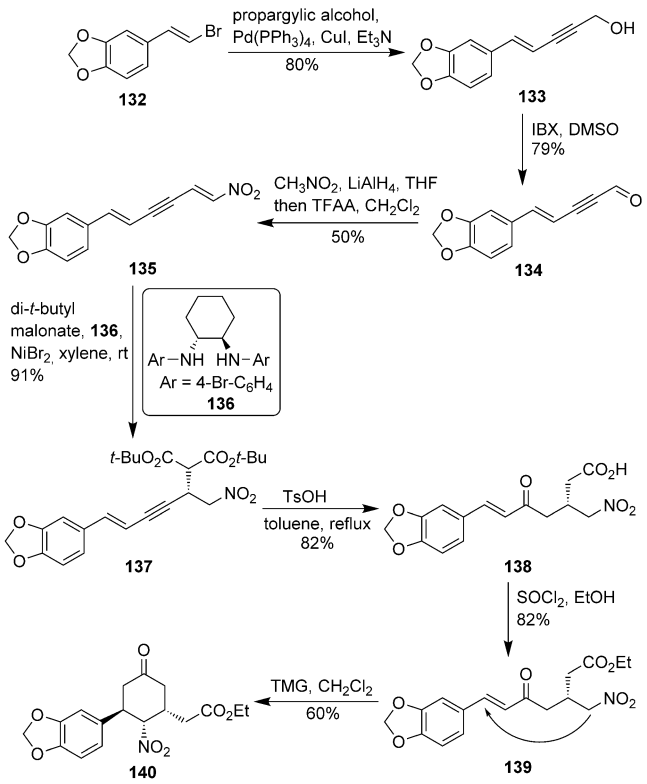
Deprotection of the Boc group permitted the construction of ring D under alkaline conditions. Reduction of this cyclic amide to an amine was followed by in situ acylation with ethyl chloroformate, giving access to **127**. Compound **127** was then subjected to a Bischler–Napieralski reaction[113] with phosphorous oxychloride to construct the isoquinolinone scaffold **128**.

The oxidation of the silyl enolate of ketone **128** at C-1 was achieved following Magnus's procedure[14a] with *m*-chloroperbenzoic acid (*m*-CPBA)/imidazole to obtain ketone **129** (Scheme 27). Phenylselenylation of the TMS enolate of **129** followed by oxidation with sodium periodate and subsequent Luche reduction produced allylic alcohol **130**. The stereochemistry of the C-2 hydroxy was inverted by the Mitsunobu reaction[114] of the allylic alcohol **130**. Finally, reduction of the resultant diester furnished (−)-lycorine (**5**). The synthesis of (−)-lycorine (**5**) was completed in 18 steps from aryl lithium **121** with 2.5% overall yield. The authors have also synthesized (−)-2-*epi*-lycorine (**131**) by reducing **130** (Scheme 27).

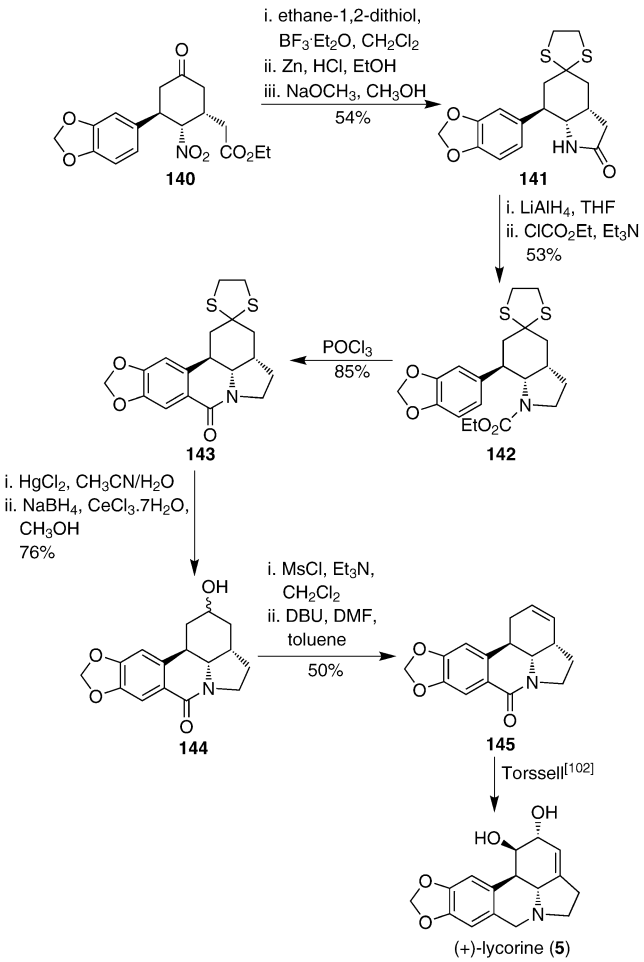
2.5.2. Shao (2014) – (+)-Lycorine (5)

In a recent article, Shao reported a formal synthesis of (+)-lycorine (**5**).[111] The authors utilized a strategy in which two Michael additions (intermolecular and intramolecular, respectively) occurred to construct the substituted cyclohexanone **140**. Sonogashira coupling[115] of compound **132** with propargylic alcohol afforded alcohol **133**, which was subsequently oxidized to aldehyde **134** (Scheme 28). Henry reaction of the aldehyde **134** with nitromethane using 0.1 equivalents of $LiAlH_4$ as a base was followed by elimination to produce dienyne **135**. Exclusive stereoselectivity in favor of the *E* isomer was observed. Michael addition of dienyne **135** and di-*tert*-butyl malonate in the presence of chiral diamine **136** afforded the corresponding diester **137** with 93% enantiomeric excess. It is noteworthy that neither 1,6- nor 1,8-conjugate additions were observed. Hydrolysis and subsequent decarboxylation of the diester were achieved by the treatment of **137** with *p*-toluenesulfonic acid (*p*-TsOH) to obtain **138**. This was followed by Fisher–Speier esterification of the carboxylic acid **138**, and intramolecular Michael addition of compound **139** in presence of tetramethylguanidine (TMG) to furnish cyclohexanone **140** in a diastereomeric ratio 6:1, favoring the desired isomer.

Cyclohexanone **140** was protected with ethane-1,2-dithiol to afford the corresponding thioketal. The nitro functionality was then reduced to an amine and subsequent treatment with sodium methoxide in methanol gave access to cyclized product **141** (Scheme 29). Reduction of the amide followed by acylation of the amine afforded carbamate **142**. Carbamate



Scheme 28. Synthesis of ketone **140** by Shao.[111]



Scheme 29. Formal synthesis of (+)-lycorine (**5**) by Shao.[111]

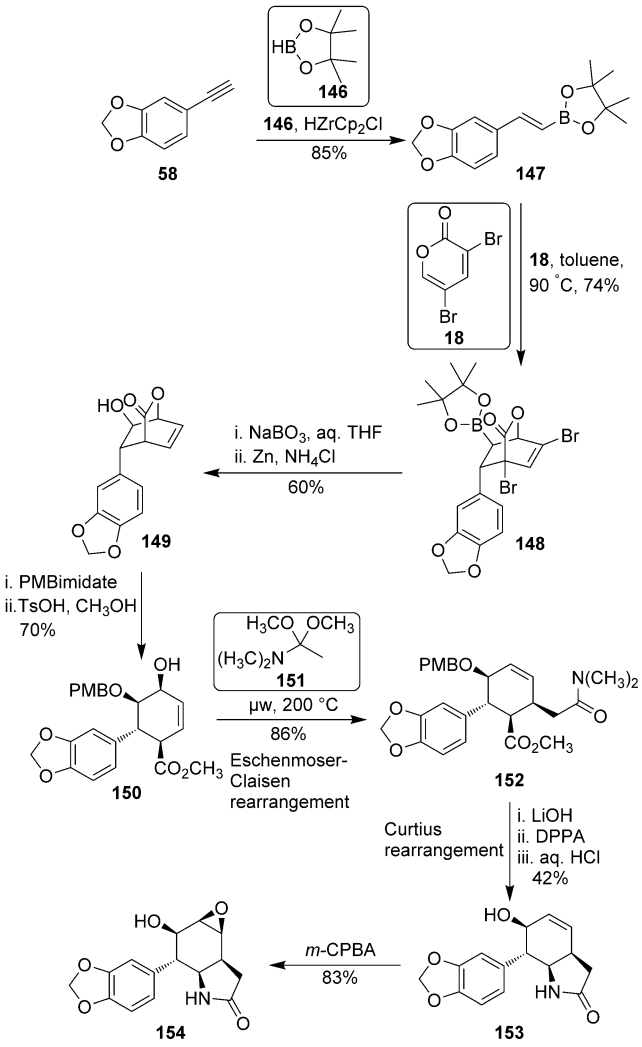
142 was then subjected to a Bischler–Napieralski reaction to provide **143**, completing the construction of ring B. Deprotection of the thioketal, and reduction of the resulting ketone afforded the corresponding alcohol **144**. Mesylation of the alcohol with methanesulfonyl chloride (MsCl)/Et_3N and subsequent elimination produced amide **145**, with complete regioselectivity. Compound **145** is a known intermediate (also known as Torssell's intermediate) in the racemic synthesis of lycorine reported by Torssell.[102] An additional five-step sequence was required to synthesize lycorine from **145**. Thus, Shao and co-workers completed the formal synthesis of (+)-lycorine (**5**) in 17 steps from the vinylic bromide **132** with 1.1% overall yield.

2.5.3. *Cho (2014) – (±)-Lycorine (5)*

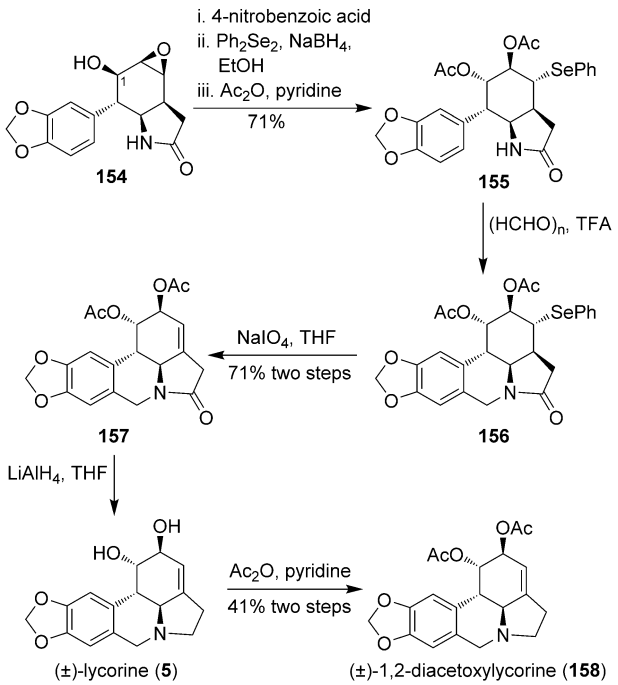
Cho's synthesis of racemic lycorine[112] is very different from those reported by others, namely Tomioka[110] and Shao.[111] Cho employed the Diels–Alder strategy, that he also used in the synthesis of (±)-1-*epi*-pancratistatin, for the construction of ring C.[23] Alkyne **58**, used previously in Hudlicky's synthesis of 7-deoxypancratistatin (**2**),[52] was subjected to a hydroboration reaction with **146** to obtain organoborane **147**. Diels–Alder cycloaddition of **147** with diene **18** proceeded exclusively to provide the *endo* product **148** (Scheme 30). Oxidation of the boronate group with sodium perborate, followed by reductive debromination, afforded bicyclic lactone **149**. Protection of the hydroxy moiety as its PMB ether and methanolysis of the lactone furnished ester **150**.

In the key step of the synthesis, the side chain required for ring D was introduced by means of the Eschenmoser–Claisen rearrangement of the allylic alcohol in **150**. Saponification of the methyl ester, subsequent Curtius rearrangement with diphenylphosphoryl azide, and acidic hydrolysis of the amide resulted in the establishment of ring D (lactam **153**). Epoxidation of the allylic alcohol occurred in the *syn* fashion producing epoxide **154**.

The inversion of the C-1 hydroxy of epoxide **154** was accomplished by a Mitsunobu reaction with 4-nitrobenzoic acid. The presence of a bulky benzoate functionality on the α-face of the ring facilitated selective opening of epoxide via C-3 attack of phenylselenolate (Scheme 31). During this reaction, the 4-nitrobenzoyl group was concomitantly cleaved and the resulting unstable diol was immediately converted into diacetate **155**. In the endgame of the synthesis, the authors adapted the route developed by Sato to build ring B prior to the introduction of the double bond between C-3 and C-3a.[116] Subjecting diacetate **155** to a Pictet–Spengler reaction[117] led to a smooth construction of ring B. Subsequent selenoxide elimination generated the C3–C3a double bond (compound **157**). The amide functionality in **157** was reduced with $LiAlH_4$ to obtain (±)-lycorine (**5**). However, because of the low solubility of lycorine **(5)** in organic solvents, it was subsequently converted to 1,2-diacetoxy-



Scheme 30. Synthesis of epoxide **154** by Cho.[23,112]



Scheme 31. Synthesis of (±)-lycorine (**5**) and (±)-1,2-diacetoxylycorine (**158**) from epoxide **154** by Cho.[112]

lycorine (**158**) for structural confirmation. The synthesis was accomplished in 18 steps from alkyne **58** in 1.6% overall yield.

In summary, three total syntheses of (−)-lycorine (**5**) and one synthesis of (−)-2-*epi*-lycorine (**131**) were reviewed in this section. Tomioka,[110] employed a consecutive Michael addition strategy in the synthesis of (−)-lycorine (**5**). The Curtius rearrangement, Bischler–Napieralski reaction, and Mitsunobu reaction were also utilised in their strategy. This group also prepared (−)-2-*epi*-lycorine (**131**) by using the same strategy. Shao's synthetic design[111] of (−)-lycorine (**5**) also involved two Michael additions, first intermolecular and then intramolecular, for the construction of ring C. Chiral ligand **136** was used for asymmetric induction. Sonogashira cross-coupling, Bischler–Napieralski reaction and Luche reduction were also utilised, however, the use of $HgCl_2$ for deprotection of dithiolane **143**, can be noted as a potential limitation of this synthesis. Cho[112] employed a Diels–Alder reaction, Eschenmoser–Claisen rearrangement, and Curtius rearrangement in the synthesis of (±)-lycorine (**5**), although, he derivatized lycorine (**5**) immediately to (±)-1,2-diacetoxylycorine (**158**) for characterization. In the next section, recent syntheses of *trans*-dihydrolycoricidine (**159**) will be discussed.

2.6. (+)-trans-Dihydrolycoricidine

This natural derivative of lycoricidine was first isolated in 1993,[118] and its first enantioselective total synthesis was reported in 1996.[44] A synthesis of racemic *trans*-dihydrolycoricidine was published in 2009,[119] however, the key strategy employed was similar to Seebach's synthesis of (±)-1-desoxy-2-lycorinone[120] and McNulty's synthesis of (±)-2,3-deoxy-*trans*-dihydrolycoricidine (Table 6).[121]

Table 6: Summary of total and formal syntheses of *trans*-dihydrolycoricidine.

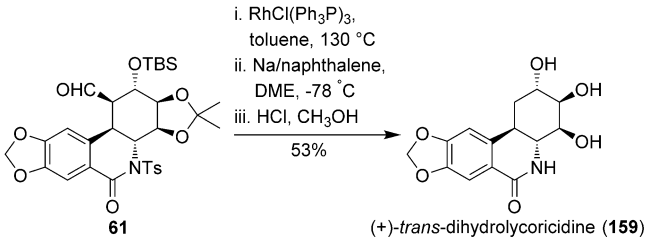
Author	Year	Number of steps	Optical series	Reference
Tsuda	1978	16	(±)	[122]
Chida	1996	24	(+)	[44]
Iwabuchi	2005	24	(+)	[123]
Kádas	2009	12	(±)	[119]
Kádas	2009	12	(−)	[124]
Hudlicky	2010	15	(+)	[52]
Morken	2011	17	(+)	[125]
McNulty	2014	9	(+)	[126]

2.6.1. Hudlicky (2010) – (+)-trans-Dihydrolycoricidine (159)

Hudlicky published the total synthesis of (+)-*trans*-dihydrolycoricidine (**159**) in 15 steps,[52] out of which the

first twelve steps (up to aldehyde **61**) have been discussed in Section 2.2.2 on 7-deoxypancratistatin (**2**) (Scheme 12).

In the last part of synthesis, Wilkinson decarbonylation of aldehyde **61** with $RhCl(Ph_3P)_3$/toluene, removal of the tosyl group with sodium/naphthalene, and subsequent removal of the protecting groups (acetonide and TBS) under acidic condition gave access to *trans*-(+)-dihydrolycoricidine (**159**) (Scheme 32). This synthesis was completed in a total of 15 steps from diol **74**,[57] and in an overall yield of 11.4%.

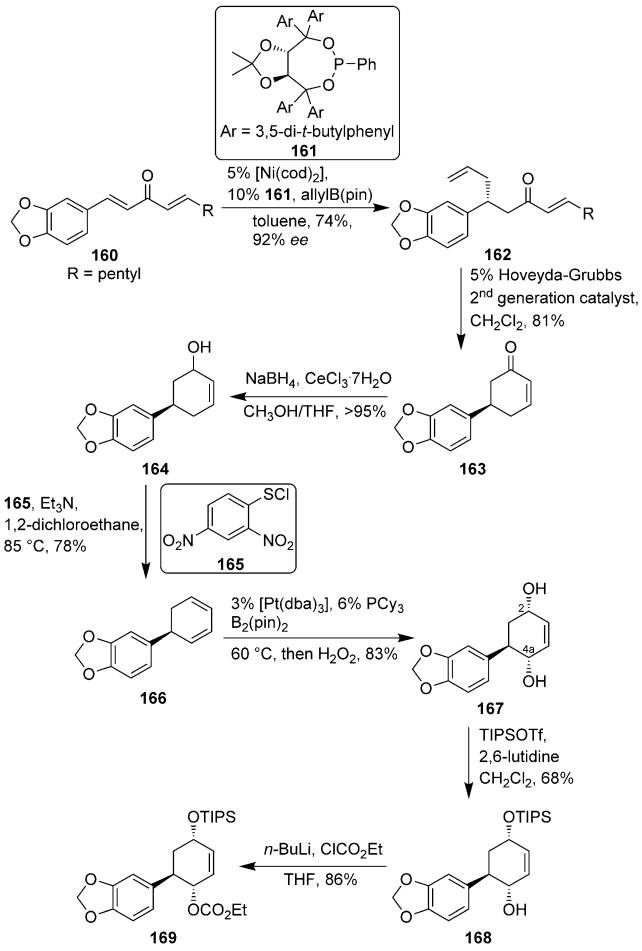


Scheme 32. Synthesis of (+)-*trans*-dihydrolycoricidine (**159**) by Hudlicky.[52]

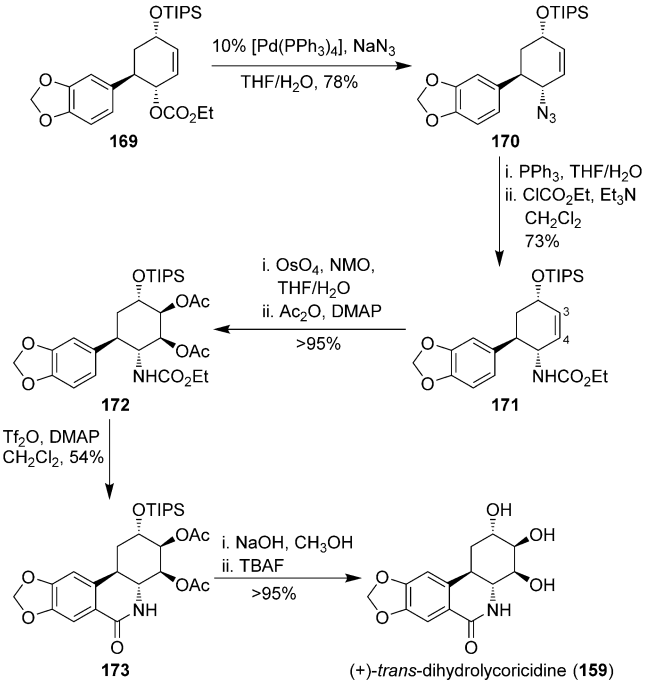
2.6.2. *Morken (2011) – (+)-trans-Dihydrolycoricidine (159)*

In the last decade, the Morken group developed a platinum-catalyzed enantioselective 1,4-diboration of 1,3-dienes as a method for 1,4-dioxygenation of these substrates.[127] Morken employed the same strategy in his total synthesis of (+)-*trans*-dihydrolycoricidine (**159**),[125] to introduce stereochemistry at C-2 and C-4a. The synthesis commenced with the enantioselective conjugate allylation of dialkylidene ketone **160** with allylboronic acid pinacol ester [allylB(pin)] catalyzed by **161**/$Ni(COD)_2$ to furnish diene **162** in 92% enantiomeric excess (Scheme 33). Ring-closing metathesis of diene **162** employing Hoveyda–Grubbs 2nd generation catalyst[128] provided enone **163**, which upon subsequent Luche reduction gave rise to allylic alcohol **164** in excellent yield (>95%). Treatment of **164** with 2,4-dinitrobenzenesulfenyl chloride (**165**) effected an allylic transposition and a subsequent sulfoxide elimination afforded diene **166**. The platinum-catalyzed enantioselective 1,4-diboration and oxidation of diene **166** occured with excellent diastereoselectivity (20:1, favoring the desired isomer). As anticipated by the authors, protection of the C-2 alcohol in diol **167** with (triisopropylsilyl trifluoromethanesulfonate) TIPSOTf/2,6-lutidine was found to be regioselective, producing allylic alcohol **168**. The authors predicted that protection of the C-4a hydroxy would be slow because of the steric hindrance by the neighboring aryl moiety, hence silylation of the C-2 hydroxy would dominate. In the next step, the C-4a alcohol in **168** was protected as its ethylcarbonate **169**.

In order to incorporate an amino group at the C-4a position, allylic carbonate **169** was subjected to a Tsuji–Trost reaction employing sodium azide as a nucleophile to afford allylic azide **170** (Scheme 34). Azide **170** was reduced by Staudinger reaction[129] and subsequently protected as its ethylcarbamate **171**. Osmylation of the C3–C4 olefin and



Scheme 33. Synthesis of carbonate **169** by Morken.[125]



Scheme 34. Synthesis of (+)-*trans*-dihydrolycoricidine (**159**) from carbonate **169** by Morken.[125]

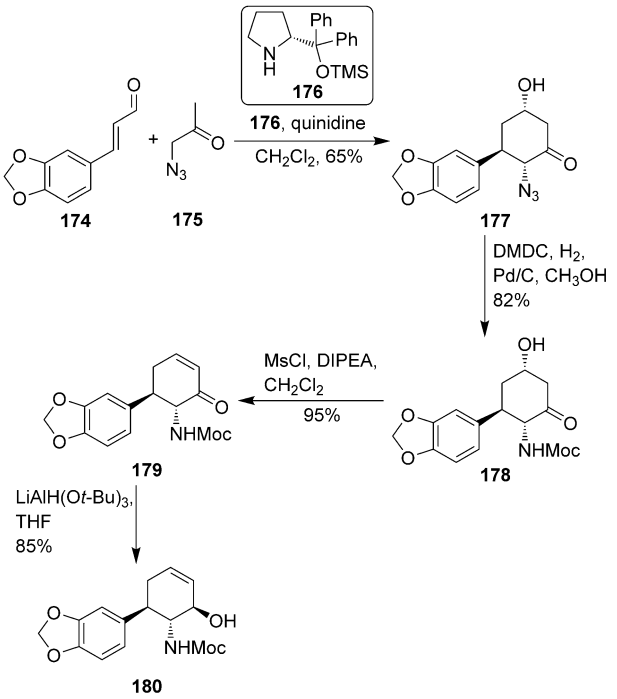
protection of the resulting diol as the corresponding diacetate provided carbamate **172** in excellent yield (> 95 %).

The endgame of the synthesis involved the use of the Banwell-modified Bischler–Napieralski reaction[31] of carbamate **172** to construct ring C, and thus the phenanthridone core, producing compound **173**. Finally, removal of the protecting groups afforded (+)-*trans*-dihydrolycoricidine (**159**) in 17 linear steps from ketone **160** in 6 % overall yield.

2.6.3. McNulty (2014) – (+)-trans-Dihydrolycoricidine (159)

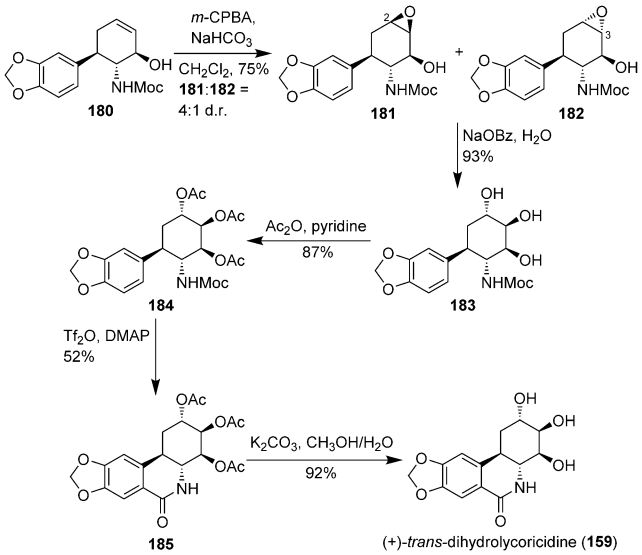
The total synthesis of this isomer of *trans*-dihydrolycoricidine has previously been published by four different groups.[44,52,123,125] In 2014, McNulty and his group published the fifth synthesis of this isomer by a sequence of Michael and aldol reactions employed to construct ring C. The enantioselectivity was achieved by the use of proline-based organocatalyst **176**.[126]

Aldehyde **174** underwent sequential Michael addition and aldol reactions with ketone **175**, catalyzed by quinidine and the proline-based catalyst **176** (10 mol %), providing ketone **177** with > 98 % enantiomeric excess (Scheme 35). The azide



Scheme 35. Synthesis of allylic alcohol **180** from aldehyde **174** by McNulty.[126]

functionality in **177** was reduced by hydrogenolysis in the presence of dimethyl dicarbonate (DMDC), leading to the corresponding methoxycarbonyl (Moc) carbamate **178**. The C-2 alcohol was activated with mesyl chloride and subsequently eliminated with Hünig's base to obtain enone **179**. Chemoselective reduction of enone **179** with lithium tri-*tert*-butoxyaluminium hydride gave access to allylic alcohol **180**.



Scheme 36. Synthesis of (+)-*trans*-dihydrolycoricidine (**159**) from **180** by McNulty.[126]

Diastereoselective epoxidation of **180** produced a mixture of **181** (β-epoxide) and **182** (α-epoxide) in a 4:1 ratio, respectively (Scheme 36). The mixture of **181** and **182**, when treated with aqueous sodium benzoate, produced triol **183** through a *trans*-diaxial opening of either epoxide in an example of "redundant" operation.[130] The opening of the epoxide functionality took place at C-2 of **181** or C-3 of **182**. The triol **183** was protected as triacetate **184** prior to the Banwell-modified Bischler–Napieralski reaction.[31] The cyclization established ring B in phenanthridone **185** in > 98 % enantiomeric excess. Finally, removal of the acetate protecting groups under alkaline condition afforded (+)-*trans*-dihydrolycoricidine (**159**). This synthesis was accomplished in a total of only 9 steps and in 12.5 % overall yield.

In this section, three syntheses of (+)-*trans*-dihydrolycoricidine (**159**) were discussed. Hudlicky's[52] synthesis of (+)-*trans*-dihydrolycoricidine (**159**) involved decarbonylation of the C-1 aldyhyde in **61**, whereas, Morken[125] utilized Hoveyda–Grubbs RCM, diboration/oxidation, Tsuji–Trost reaction and Banwell-modified Bischler–Napieralski reaction. It was McNulty who produced the shortest synthesis of (+)-*trans*-dihydrolycoricidine (**159**), completing the synthesis in just 9 steps.[126] The McNulty group used an aldol reaction, a Michael addition, and a Banwell-modified Bischler–Napieralski reaction in their synthesis. The chiral induction was achieved with proline-based organocatalyst **176** during the aldol reaction. In the following section, syntheses of *trans*-dihydronarciclasine (**192**) are discussed.

2.7. (+)-trans-Dihydronarciclasine (192)

trans-Dihydronarciclasine was first isolated from *Zephyranthes candida* by Pettit in 1990.[131] This compound was previously generated by hydrogenation of narciclasine,[132] but was not known to be a product of biosynthesis before 1990. It

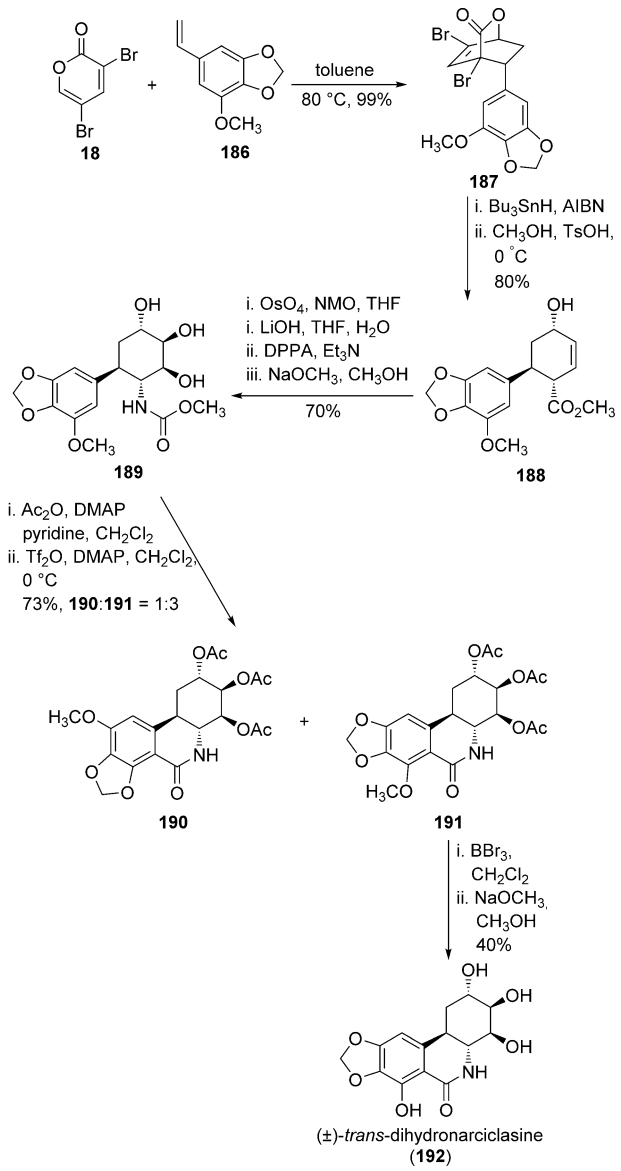
is of particular interest as its potency against human cancer cell lines has been shown to be 2 to 16 times greater than that of pancratistatin.[133] The first synthesis of *trans*-dihydronarciclasine was reported by Cho in 2007.[134] This synthesis, as well as three other reported syntheses of this compound, will be discussed in detail (Table 7).

Table 7: Summary of total and formal syntheses of *trans*-dihydronarciclasine.

Author	Year	Number of steps	Optical series	Reference
Cho	2007	11	(±)	[134]
Cho	2008	11	(±)	[134b]
Studer	2008	17	(+)	[135]
Kim	2012	14	(+)	[136]
Tomioka	2012	18	(+)	[137]

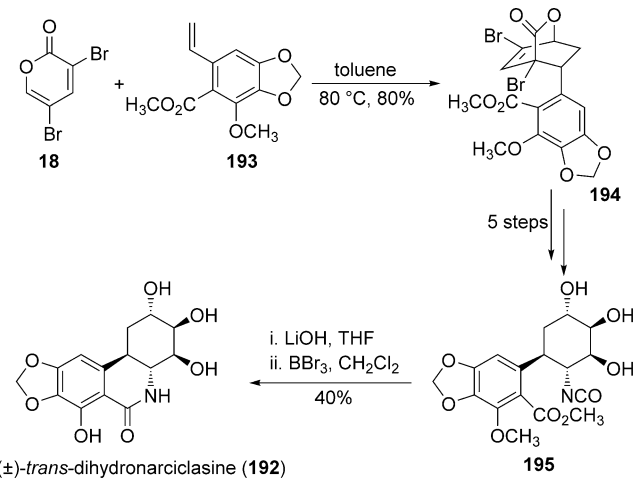
2.7.1. *Cho (2007) – (±)-trans-Dihydronarciclasine (192)*

The strategy employed by Cho was based on the early stage Diels–Alder cyclization of diene **18** and dienophile **186**[134] (Scheme 37). This approach is similar to the one employed by this group in the synthesis of (±)-pancratistatin (**1**)[20] and (±)-lycorine (**5**).[112] Dienophile **186** was prepared in multi-gram quantities from 5-bromovanillin according to published procedures,[138] and was subjected to the key Diels–Alder cyclization with dibromo-2-pyrone (**18**). This cycloaddition smoothly afforded the bicyclic lactone **187** in a 98:2 ratio of the *endo* and *exo* diastereomers, respectively (Scheme 37). The desired *endo* product **187** was easily purified from this mixture. Compound **187** was then subjected to debromination conditions, followed by methanolysis under acidic conditions to afford compound **188**. Acidic methanolysis conditions were employed because both hydrolysis and methanolysis under basic conditions were shown to cause olefin isomerization to the α,β-unsaturated carboxylic acid or ester. In order to avoid the isomerization in the subsequent ester hydrolysis, the hydrolysis was preceded by Upjohn dihydroxylation, which took place exclusively on the less hindered β-face. The initial synthetic plan called for the protection of allylic alcohol **188** prior to Upjohn dihydroxylation and ester hydrolysis. This plan had to be altered, however, because steric encumberance caused by the protecting group prevented the subsequent hydrolysis of the ester moiety. In light of this observation, the allylic alcohol was subjected to Upjohn dihydroxylation and subsequent ester hydrolysis without the use of protecting groups. This procedure allowed for the smooth production of carbamate **189** via a Curtius rearragement and treatment with sodium methoxide. Carbamate **189** was then protected as its corresponding peracetate, followed by a Banwell-modified Bischler–Napieralski cyclization,[31] which afforded a mixture of cyclized products **190** and **191** in a 1:3 ratio respectively. This mixture was subjected to O-demethylation, which did not affect compound **190**, permitting the separation of this byproduct. Deprotection of the acetate protecting groups afforded (±)-*trans*-dihydronarciclasine (**192**) in a total of 11 steps, and in an overall yield of 15.8%.



Scheme 37. Synthesis of (±)-*trans*-dihydronarciclasine (**192**) by Cho.[134]

In order to improve the overall efficiency of this initial synthesis, the Banwell-modified Bischler–Napieralski reaction,[31] which afforded an inseparable mixture of products (**190** and **191**), was targeted for possible improvement. To this end, an improved synthesis published in 2008[134b] utilized a dienophile starting material with an ester moiety already installed as in **193** (Scheme 38). The synthesis was carried out as before to produce isocyanate **195**. Isocyanate **195** was treated with lithium hydroxide to effect the hydrolysis of the isocyanate moiety and the lactamization in a concomittant fashion, eliminating the regioselectivity issue observed in the previous generation synthesis. A final demethylation step afforded (±)-*trans*-dihydronarciclasine (**192**) in 8 steps from dienophile **193**, or 15 steps including the production of



Scheme 38. Improved synthesis of (±)-*trans*-dihydronarciclasine (**192**) by Cho.[134b]

dienophile **193** from bromobenzaldehyde. The overall yield of the synthesis was improved to 21% from dienophile **193**.

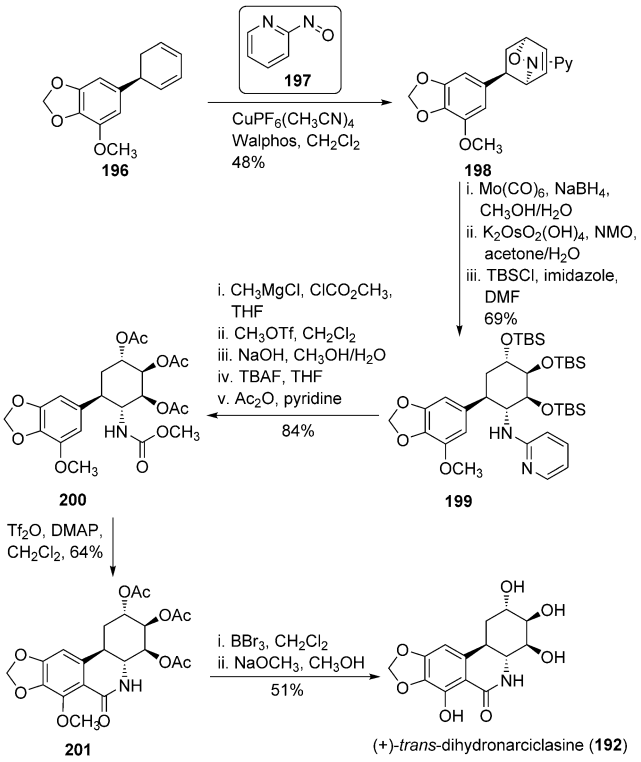
2.7.2. *Studer (2008) – (+)-trans-Dihydronarciclasine (192)*

Similar to the synthesis published by Cho in 2007,[134] the strategy employed in this synthesis is based upon an early stage Diels–Alder reaction to construct the core of *trans*-dihydronarciclasine.[135] However, this synthesis utilizes an enantioselective hetero-Diels–Alder reaction developed by Studer,[139] to synthesize *trans*-dihydronarciclasine in an enantiopure form for the first time. The key nitroso Diels–Alder reaction was found to provide the highest levels of enantioselectivity (>99% *ee*) when dienophile **196** (synthesized over 5 steps from *o*-vanillin)[14,135] was used as the substrate with 2-nitrosopyridine (**197**) (Scheme 39). The resulting cycloadduct **198** was then subjected to reductive N–O bond cleavage, followed by a diastereoselective dihydroxylation and persilylation to afford compound **199**. Carbamoylation of the secondary amine in **199** was followed by cleavage of the pyridyl moiety through quaternization and basic hydrolysis. Removal of the silyl protecting groups and acetylation of the resulting hydroxy moieties afforded triacetate **200**. In order to effect the final cyclization to create the B ring of *trans*-dihydronarciclasine, a Banwell-modified Bischler–Napieralski reaction[31] was utilized, as previously demonstrated by Cho.[134a] This reaction proceeded with good regioselectivity, providing compound **201** in 64% yield.

O-Demethylation and removal of the acetate protecting groups afforded the target compound, (+)-*trans*-dihydronarciclasine (**192**). The synthesis was completed in a total of 17 steps from *o*-vanillin in an overall yield of 5.6%.

2.7.3. *Kim (2012) – (+)-trans-Dihydronarciclasine (192)*

In this synthesis the author makes excellent use of a Boc-protected amino functionality to direct the stereochemistry of the key Ireland–Claisen rearrangement.[136] This functionality also serves to generate an isocyanate intermediate in an



Scheme 39. Synthesis of (+)-*trans*-dihydronarciclasine (**192**) by Studer.[135]

electrophilic aromatic substitution reaction, used to furnish ring B. This B-ring cyclization proceeded with greater regioselectivity than similar closures used in the previous syntheses.[134–136] The substrate for the key Ireland–Claisen rearrangement was generated by the reaction of allylic alcohol **202**, previously utilized in Kim's synthesis of pancratistatin,[17b] with *N*-Boc glycine to afford amino acid ester **203** (Scheme 40). The excellent stereoselectivity of the Ireland–Claisen rearragement resulted from the chair-like transition state (Figure 3), the formation of which was influenced by the sterically imposing Boc protecting group. Esterification of the rearranged product afforded aminoester **204**.

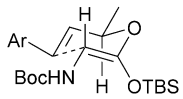
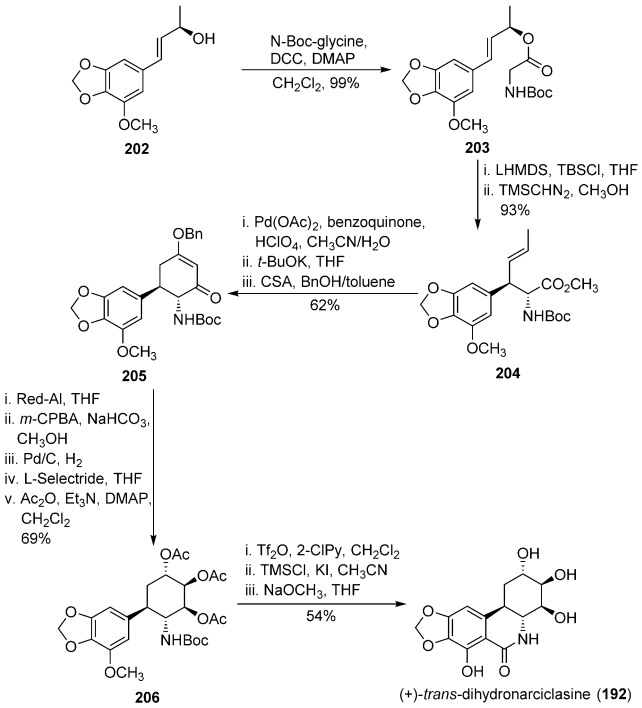
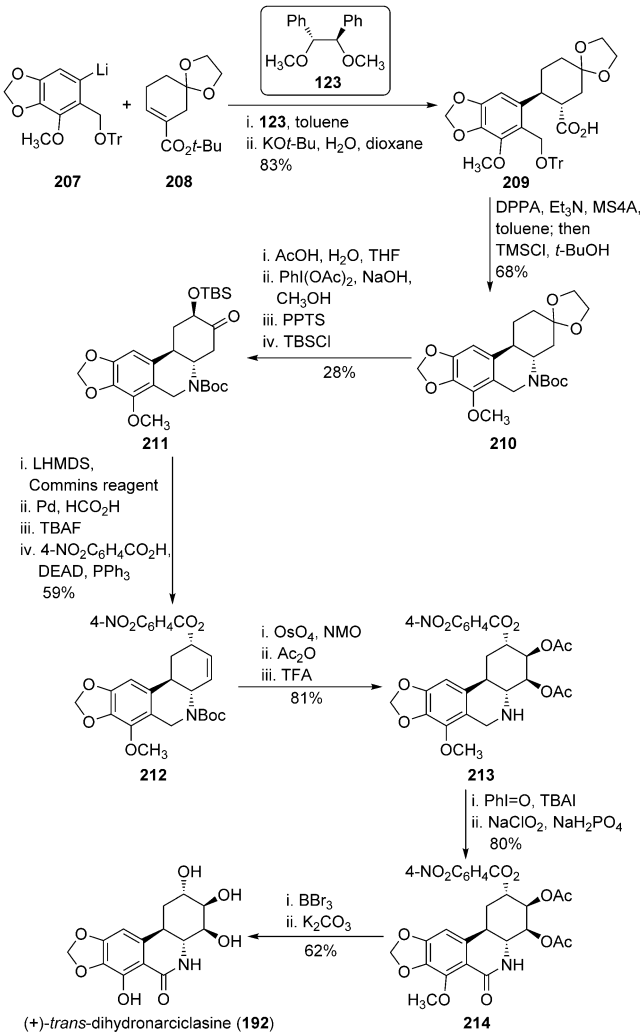


Figure 3. Chair-like transition state of the key Ireland–Claisen rearrangement.[136]

The C-ring was constructed through oxidation of the internal olefin, followed by Dieckmann condensation and benzylation of the enolized 1,3-diketone to afford compound **205**. Stereoselective reduction of the carbonyl moiety, followed by a domino epoxidation-methanolysis procedure afforded the desired ketal, which was converted to the corresponding ketone under mild hydrogenation conditions. Selective reduction of the ketone, followed by protection of the resulting triol as the corresponding triacetate provided compound **206**. As has previously been discussed, the Banwell-modified Bischler–Napieralski reaction,[31] which was used by both Cho and Studer to construct the B-ring of *trans*-dihydronarciclasine, can suffer from regioselectivity issues.[134,135] In an attempt to circumvent this problem, Kim took advantage of



Scheme 40. Synthesis of (+)-*trans*-dihydronarciclasine (**192**) by Kim.[136]



Scheme 41. Synthesis of (+)-*trans*-dihydronarciclasine (**192**) by Tomioka.[137]

the *N*-Boc functionality to generate an isocyanate intermediate, as opposed to the imino-triflate intermediate of the Banwell-modified Bischler–Napieralski reaction.[31] The attack of the aromatic ring on the isocyanate intermediate was shown to proceed with much higher levels of regioselectivity than previously observed.[134,135] Careful study of the isocyanate generation and electrophilic aromatic substitution identified the optimal conditions for this transformation, leading to the efficient construction of the B-ring. O-Demethylation and removal of the acetate protecting groups afforded (+)-*trans*-dihydronarciclasine (**192**) in a total of 14 steps from allylic alcohol **202**, in an overall yield of 16%.

2.7.4. *Tomioka (2012) – (+)-trans-Dihydronarciclasine (192)*

As discussed in Section 2.5.1, Tomioka previously utilized a Michael addition cascade as a key transformation in his 2009 synthesis of (−)-lycorine (**5**) (Scheme 26 and 27).[110] A similar strategy was employed in the synthesis of (+)-*trans*-dihydronarciclasine, wherein chiral ligand **123** was utilized to control the stereochemistry in the key asymmetric Michael addition.[137] This transformation facilitated the coupling of the A-ring fragment **207** and C-ring fragment **208** (Scheme 41). The coupled product was shown to be produced in a ratio of 95:5, *cis*:*trans*. Epimerization to the desired *trans* configuration was accomplished with concurrent ester hydrolysis to afford key intermediate **209**. Conversion of the carboxylic acid moiety to the corresponding isocyanate was accomplished through a Curtius rearrangement. The rearrangement was followed by conversion of the intermediate isocyanate to the corresponding *tert*-butyl carbamate and this conversion unexpectedly proceeded with concomitant cyclization to the protected amine **210**. The authors propose that the cyclization occurs because of the loss of the trityloxy group to form a benzylic carbocation under acidic conditions. Hydrolysis of the acetal moiety was followed by the stereo- and regioselective introduction of a hydroxy group with iodobenzene diacetate that can be rationalized through the reaction pathway (Figure 4). As shown in Figure 4, this transformation occurred with the formation of a dimethyl ketal which was subse-

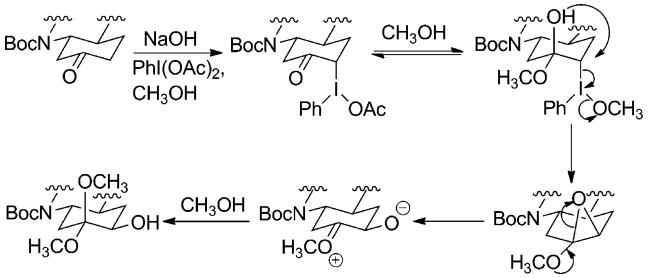


Figure 4. Stereoselective introduction of the hydroxy moiety.[137]

quently hydrolyzed before protection of the hydroxy moiety, affording α-siloxy ketone **211**.

Ketone **211** was regioselectively converted to the corresponding vinyl triflate, which was then subjected to hydrogenolysis to effect the removal of the triflyloxy group. Deprotection of the silyl ether was followed by treatment with modified Mitsunobu reaction conditions[140] to invert the stereochemistry of the secondary alcohol, affording 4-nitrobenzoate **212**. Diastereoselective dihydroxylation was followed by acetylation and deprotection of the Boc group to afford diacetate **213**. Benzylic oxidation of diacetate **213** was performed over two steps, by conversion to the corresponding imine followed by imine oxidation with sodium chlorite to afford lactam **214**. O-Demethylation and removal of the acyl groups afforded (+)-*trans*-dihydronarciclasine (**192**) in a total of 18 steps and an overall yield of 3.4%.

Of the four syntheses of *trans*-dihydronarciclasine (**192**) discussed in this section, both Cho and Studer used strategies based on Diels–Alder cycloadditions to generate the key intermediates.[134,135] Kim employed a key Ireland–Claisen rearrangement to set the C-4a/C-10b stereochemistry in an enantioselective synthesis[136] while Tomioka utilized an asymmetric Michael addition to set the stereochemistry at these positions.[137] Cho, Studer and Kim all took advantage of an electrophilic aromatic substitution reaction to construct ring B,[134–136] while Tomioka profited from an unexpected cyclization through a benzylic carbocation to furnish this ring.[137] Continued efforts towards the efficient production of *trans*-dihydronarciclasine (**192**) remain important because of the potent biological activity of this compound.[133] The following section will continue this theme, as many of the unnatural Amaryllidaceae analogues which will be discussed have been produced with the explicit goal of studying the biological activity and structure–activity relationships of these compounds.

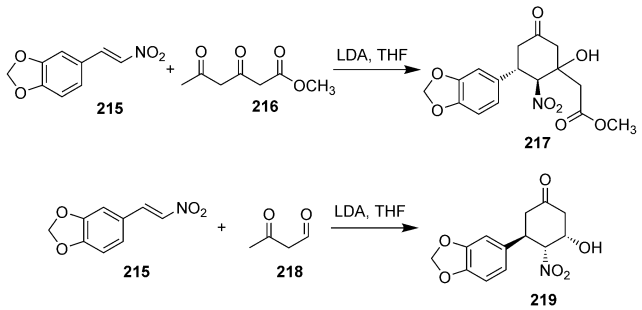
3. Unnatural Analogues of Amaryllidaceae Alkaloids

The earliest unnatural analogues of Amaryllidaceae alklaloids were produced through semi-synthesis in order to accurately determine the structure of the natural compounds, and to probe their structure–activity relationships.[67,132] Although the importance of this seminal work by Piozzi,[67] Mondon,[132] Pettit,[133,141] and others cannot be overstated, it will not be covered in detail as the focus of this section is on total synthesis of new analogues. However, it is important to briefly mention this work as it has been essential to the preliminary understanding the structure activity relationships of these compounds.

Early work by Mondon demonstrated the importance of the *trans* C-4a/C-10b ring juntion for biological activity.[132] This was confirmed when Pettit first reported the inhibition concentrations [for example, *trans*-dihydronarciclasine (0.0126 μM) versus *cis*-dihydronarciclasine (3.8 μM) mean panel growth inhibition (GI_{50}) values] for these Amaryllidaceae alkaloids against a panel of cancer cell lines.[118] This data also confirmed the importance of the C-7 hydroxy group for biological activity.[118] Later work by Pettit also demonstrated the importance of the C-2, C-3 and C-4 alcohols,[141c] as well as their stereochemistry.[142] Although few of the unnatural Amaryllidaceae analogues that have been produced have approached the level of biological activity observed in their parent compounds, work by Pettit identified a C-1 benzoate analogue of (+)-pancratistatin (**1**) that displayed biological activity levels exceeding those of the parent compound.[16] This finding demonstrated that substitution at C-1 is not only tolerated, but has the potential to improve the bioactivity of designed Amaryllidaceae analogues.[16] The total syntheses of unnatural Amaryllidaceae analogues discussed in this section have been aimed at advancing the understanding of the structure–activity relationships of the parent compounds, at increasing the poor aqueous solubility of these compounds, and at obtaining biological activity levels greater than those of the parent compounds. In all of these cases, the work performed by synthetic chemists has been guided by the semi-synthesis work of Pettit and others. In all, 28 syntheses of unnatural Amaryllidaceae analogues have been reported; of these 22 are discussed in this section, Table 8. The remaining six syntheses were covered in our previous review in 2005.[4e]

3.1. Seebach (1982) – (±)-1-Desoxy-2-lycorinone (221) and C-Ring Analogue of trans-Dihydrolycoricidine 224

Seebach reported the synthesis of ester **217** and ketone **219** from 1-methylenedioxyphenyl-2-nitroethene (**215**) in 1975,[164] and later used these compounds in the production of unnatural Amaryllidaceae analogues (Scheme 42).[120]



Scheme 42. Synthesis of ester **217** and ketone **219** by Seebach.[164]

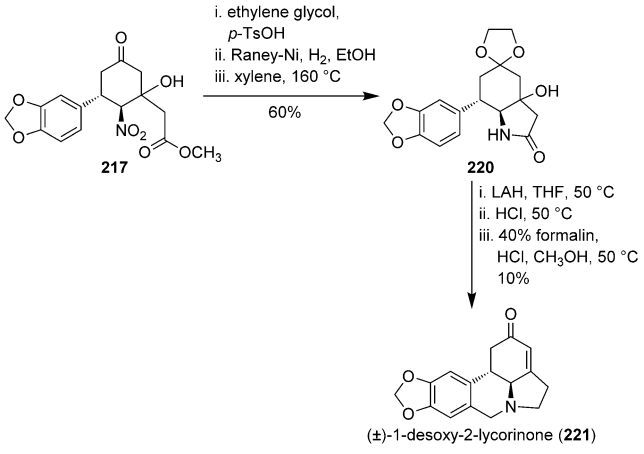
The synthesis of (±)-1-desoxy-2-lycorinone (**221**) from ester **217** began with acetal protection of the ketone moiety in ester **217** (Scheme 43).[120] Acetal protection was followed by reduction of the nitro functionality to the corresponding amine and subsequent heating in xylene afforded lactam **220**. Lactam in **220** was reduced to the corresponding amine, and then subjected to a number of conditions for Pictet–Spengler cyclization, all of which failed. This issue was addressed by effecting acetal hydrolysis and dehydration to the corresponding enone before performing a Pictet–Spengler reaction with formaldehyde to afford (±)-1-desoxy-2-lycorinone (**221**).

Ketone **219** was utilized in the synthesis of a C-ring analogue of *trans*-dihydrolycoricidine **224** (Scheme 44).[120] Similar to the synthesis of (±)-1-desoxy-2-lycorinone (**221**),

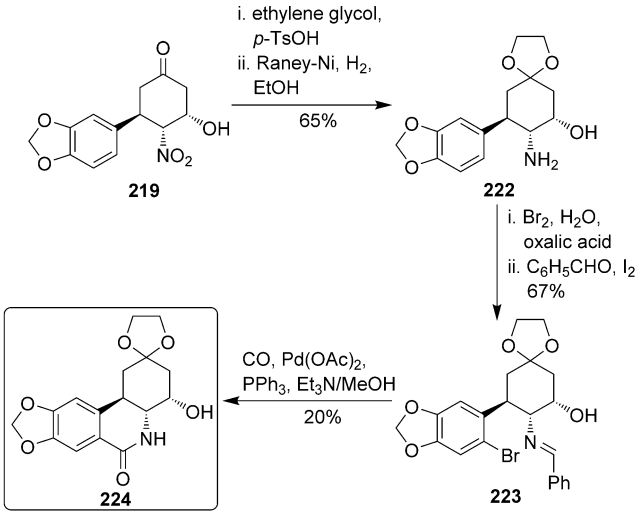
Table 8: Summary of total syntheses of unnatural Amaryllidaceae analogues.

Author	Target	Year	Reference
Seebach	(±)-1-desoxy-2-lycorinone	1982	[120]
Chapleur	*seco*-structural analogues (+)-narciclasine/lycoricidine	1993	[143]
Banwell	C-ring analogues pancratistatin and lycoricidine	1994	[31a]
McNulty	C-ring analogue (±)-dihydrolycoricidine	1998	[121]
Hudlicky[a]	positional isomer 7-deoxypancratistatin	2000	[144]
McNulty[a]	C-ring analogue (+)-dihydrolycoricidine	2001	[145]
Hudlicky[a]	positional isomer and truncated derivatives 7-deoxypancratistatin	2002	[71b]
Fessner[a]	B/C-ring analogues pancratistatin	2003	[146]
Hudlicky[a]	A/C-ring analogues (+)-pancratistatin	2004	[147]
Chapleur	B-ring lactone analogues 7-methoxynarciclasine and lycoricidine	2004	[148]
Hudlicky[a]	β-carbolin-1-one A-ring analogue (+)-pancratistatin	2004	[59,149]
McNulty	(±)-3-deoxydihydrolycoricidine	2005	[150]
Hudlicky	A/B ring deoxygenated analogues (+)-pancratistatin	2005	[41,151]
Kornienko	truncated A/C-ring analogues lacking B-ring	2006	[152]
DeShong	(±)-3,4,7-trideoxypancratistatin	2006	[153]
Alonso	(±)-7-deoxy-2-*epi*-pancratistatin tetraacetate	2006	[154]
Afarinkia	A-ring analogue of (±)-3,4-di*epi*-*trans*-dihydrolycoricidine	2007	[155]
Banwell	C-ring analogues (−)-lycoricidine	2007	[74,89]
Hudlicky	7-deoxypancratistatin-1-carboxaldehyde and carboxylic acid	2008	[60]
McNulty	*seco*-pancratistatin structural analogues	2008	[156]
Kornienko	C-ring analogues (+)-pancratistatin	2009	[157]
Marion	C-1 analogues (+)-pancratistatin	2009	[158]
Hudlicky	C-1 homologues (+)-7-deoxypancratistatin	2010	[52]
Hudlicky	C-1 homologues (+)-pancratistatin	2011	[159]
Gonzalez	A-ring analogues (+)-pancratistatin	2011	[160]
Alonso	(±)-7,9-dideoxypancratistatin	2013	[161]
Hudlicky	7-aza-nornarciclasine and corresponding *N*-oxide	2014	[162]
Hudlicky	10-aza-narciclasine	2015	[163]

[a] The syntheses of these derivatives were covered in the review published in *Synlett*, 2005.[4e]



Scheme 43. Synthesis of (±)-1-desoxy-2-lycorinone (**221**) from ester **217** by Seebach.[120]



Scheme 44. Synthesis of C-ring analogue of *trans*-dihydrolycoricidine **224** from ketone **219** by Seebach.[120]

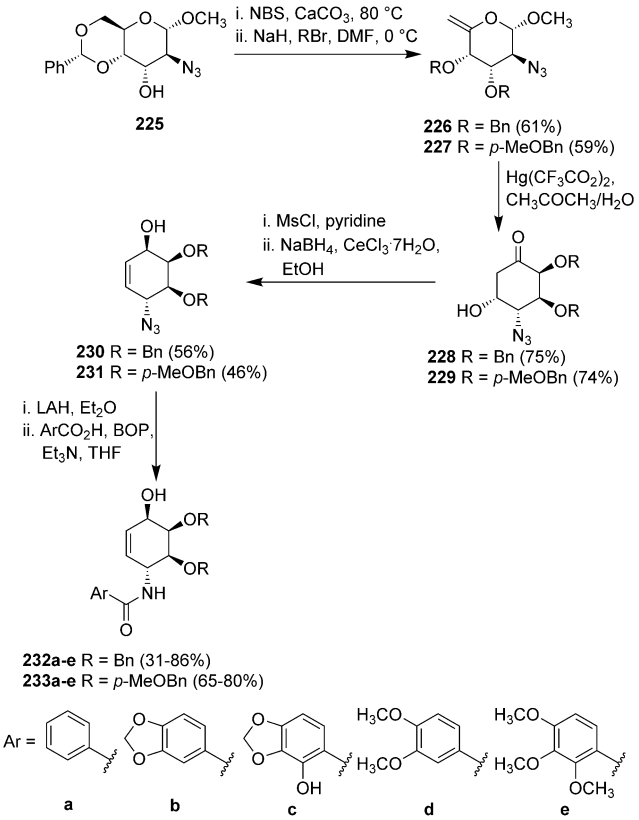
ketal protection of ketone **219** was followed by reduction of the nitro functionality to afford amino-alcohol **222**. Amino-alcohol **222** failed to undergo cyclization under Bischler–Napieralski or Pictet–Spengler conditions, which led the authors to pursue a carbonylation to construct the B-ring. To prepare the substrate for carbonylation, amino-alcohol **222** was subjected to bromination, followed by treatment with benzaldehyde to afford imine **223**. The carbonylation of imine **223** afforded the desired C-ring analogue of *trans*-dihydrolycoricidine **224**.

No biological activity data were reported for (±)-1-desoxy-2-lycorinone (**221**) or C-ring analogue of *trans*-dihydrolycoricidine **224**.

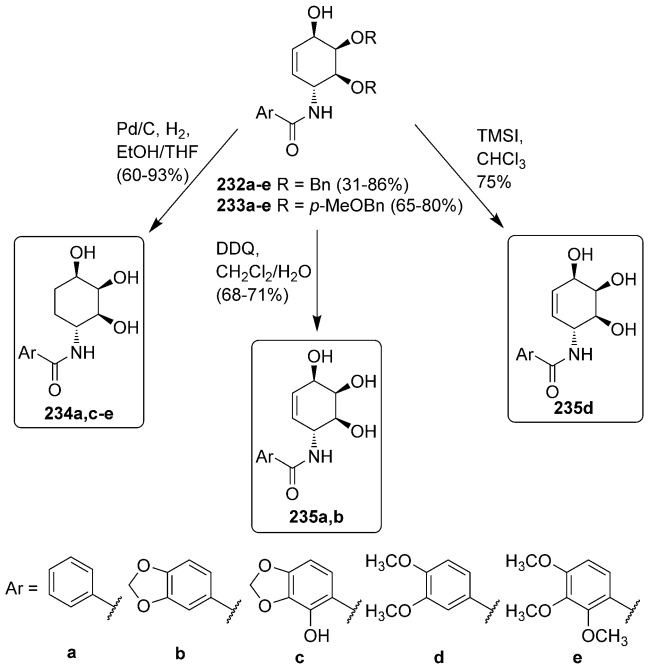
3.2. Chapleur (1993) – seco-Structural Analogues (+)-Narciclasine/Lycoricidine (234, 235, 240 and 241)

In order to investigate the effect of various A-ring substituents and the changes in the B-ring fusion on the biological activity of Amaryllidaceae analogues, a series of *seco*-structural analogues of (+)-narciclasine/lycoricidine were designed by Chapleur.[143] The synthesis of these compounds was based on the use of a known sugar derivative as the starting material, and utilized a Ferrier carbocyclization as a key transformation.[165] The benzylidene ring of the known sugar derivative, azide **225**,[166] was opened with *N*-bromosuccinimide (NBS) (Scheme 45), and followed by (dimethylamino)phosphonium hexafluorophosphate (BOP) as an activating agent. This procedure was used to produce amides **232a–e** and **233a–e**, each obtained in high yield with the exception of **232c** (31%).

Amides **232a,c–e** were subjected to hydrogenation conditions to afford the desired *seco*-analogues **234a,c–e** (Scheme 46). Amide **232d** was also subjected to deprotection with iodotrimethylsilane to afford *seco*-analogue **235d**. Oxidative removal of the *p*-methoxybenzyl groups was employed to produce *seco*-analogues **235a** and **235b** from **233a** and **233b**, respectively. Analogue **235c** could not be synthesized in this way, likely because of over-oxidation of the desired product.



Scheme 45. Synthesis of protected amides **232a–e**, and **233a–e** from azide **225** by Chapleur.[143]

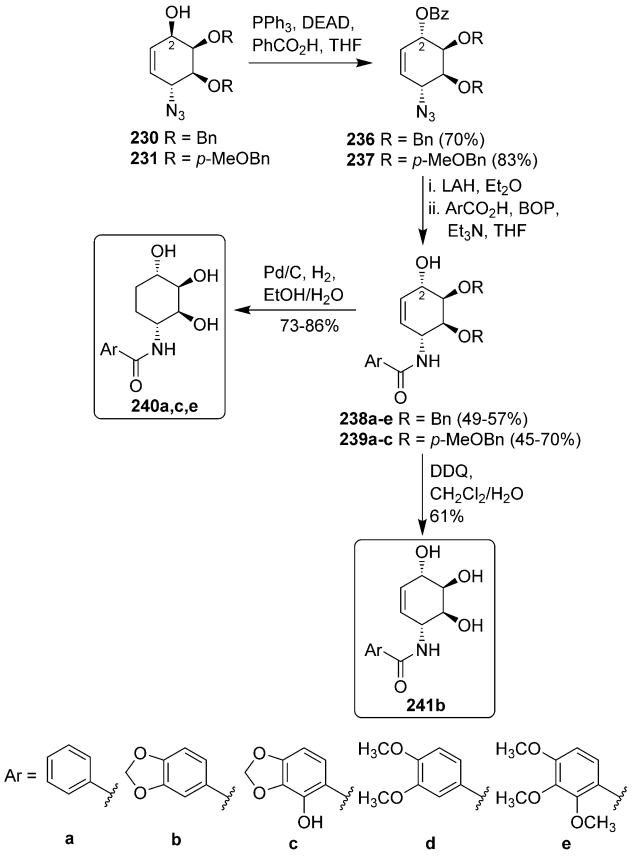


Scheme 46. Synthesis of *seco*-structural analogues of (+)-narciclasine/lycoricidine **234a,c–e**, and **235a,b,d** from amide **232a–e** and **233a–e** by Chapleur.[143]

debenzoylation, and treatment with benzyl bromide and sodium hydride to effect the protection and dehydrobromination in one step, affording compound **226**. Compound **227** was prepared in an identical manner. Compounds **226** and **227** were then separately subjected to a variety of conditions for the Ferrier carbocyclization,[165] the most successful of which is shown (Scheme 45). This key transformation led to the production of ketones **228** and **229**, which were subsequently subjected to elimination to the corresponding enones followed by reduction to the allylic alcohols **230** and **231**. Reduction of the azide functionality in **230** and **231** to the corresponding amine was followed by selective N-acylation with various aromatic acids using benzotriazolyl-*N*-oxytris-

The methodology discussed above was successfully applied to the synthesis of a library of *seco*-analogues **234a,c–e**, and **235a,b**, however, the stereochemistry of these analogues at C-2 is opposite to that of the natural compounds. In order to address this issue, allylic alcohols **230** and **231** were subjected to Mitsunobu reactions with benzoic acid to afford esters **236** and **237** (Scheme 47). Reduction of both the ester and azide functionalities was followed by N-acylation to produce amides **238a–e** and **239a–c**. The previously discussed deprotection/hydrogenation conditions were applied to produce the desired *seco*-analogues **240a,c,e** from amides **238a,c,e** and *seco*-analogue **241b** from amide **239b**. Similar to previous results, attempts to isolate *seco*-analogue **241c** through oxidative deprotection of **239c** led to over-oxidation of the desired product.

The biological activity of *seco*-analogues **234a,c–e**, **235a,b,d**, **240a,c,e** and **241b** were all tested against leukemia



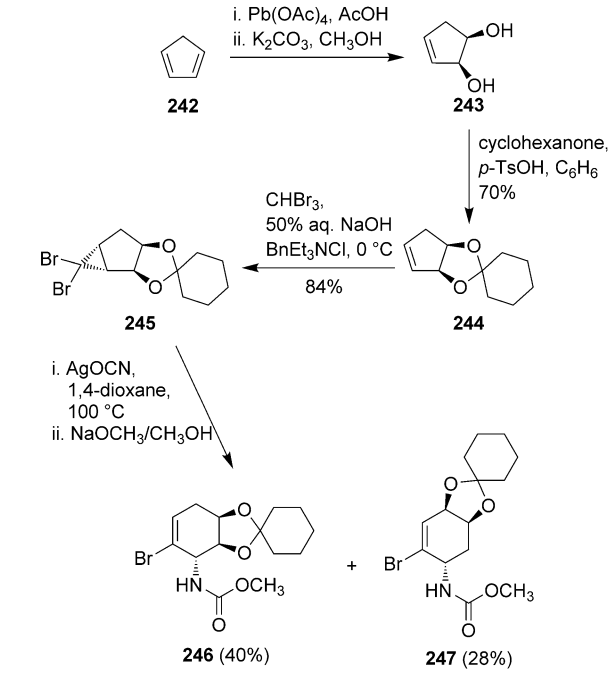
Scheme 47. Synthesis of *seco*-structural analogues of (+)-narciclasine/lycoricidine **240a,c,e**, and **241b** from allylic alcohols **230** and **231** by Chapleur.[143]

strain L1210. Unfortunately, all of the compounds were shown to be inactive.

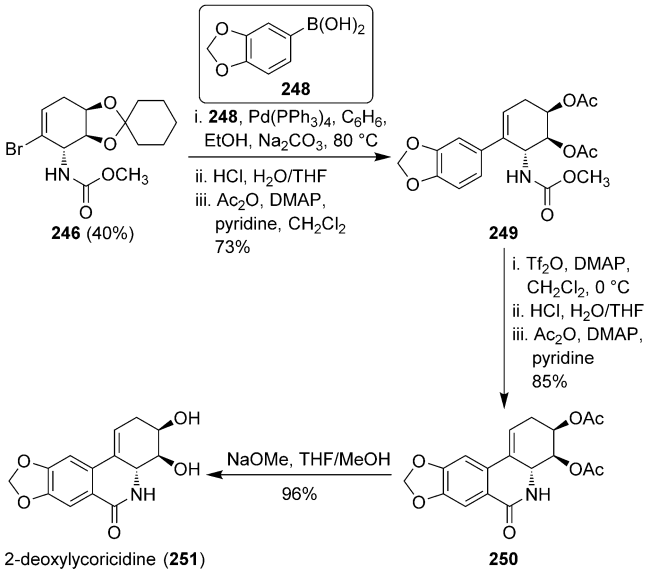
3.3. Banwell (1994) – 2-Deoxylycoricidine (251) and 4,7-Dideoxypancratistatin (254)

In an effort to develop a means of accessing the core structure of Amaryllidaceae alkaloids from readily available starting materials, Banwell reported the synthesis of C-ring analogues of 7-deoxypancratistatin (**2**) and lycoricidine (**4**) from cyclopentadiene (**242**).[31a] In the initial stages of the synthesis, cyclopentadiene (**242**) was subjected to dihydroxylation with $Pb(OAc)_4$, and the resulting diol **243** was protected as the ketal **244** (Scheme 48). The addition of dibromocarbene to ketal **244** was accomplished under Makosza conditions to afford dibromide **245**.[167] In the key step, silver isocyanate was used to promote an electrocyclic ring opening of dibromide **245** to produce a regioisomeric mixture of allylic isocyanates. The crude mixture was treated with sodium methoxide, which allowed for the isolation of carbamates **246** and **247**.

Carbamate **246** was then subjected to Suzuki cross-coupling with boronic acid **248** and this was followed by hydrolysis of the ketal and reprotection to the corresponding diacetate **249** (Scheme 49). In order to effect B-ring cyclization, modified conditions for the Bischler–Napieralski reaction were employed (Scheme 49). After acidic hydrolysis of the resulting imidates and reacetylation phenanthridone **250** was obtained in good yield (85%). As is evident by their appearance throughout this review, the success of these modified conditions for the Bischler–Napieralski reaction led to the application of these conditions in many syntheses of natural and unnatural Amaryllidaceae alkaloids.[20–23,31a,54,86,125,126,134a,135,136] Hydrolysis of the acetate protecting groups afforded 2-deoxylycoricidine (**251**).

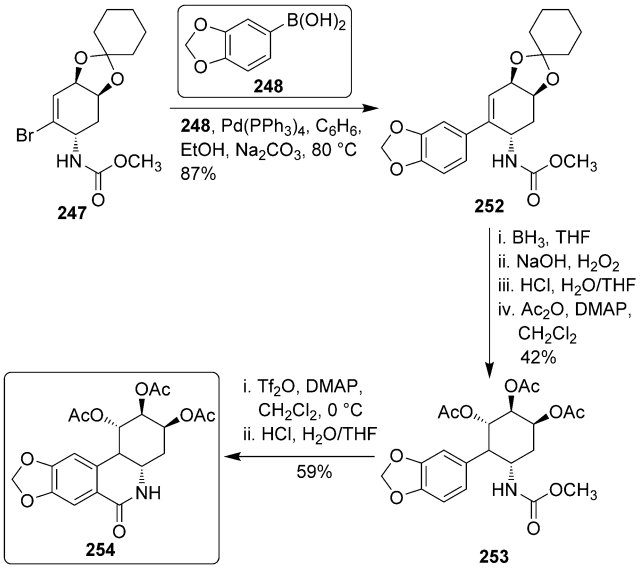


Scheme 48. Synthesis of vinylic bromides **246** and **247** by Banwell.[31a]



Scheme 49. Synthesis of 2-deoxylycoricidine (**251**) from **246** by Banwell.[31a]

Having produced carbamate **247** as a minor product in the key electrocyclic ring opening discussed above, Banwell utilized this compound as a precursor in the production of an analogue of 4,7-dideoxypancratistatin **254**.[31a] Similar to the strategy used in the synthesis of 2-deoxylycoricidine (**251**), carbamate **247** was subjected to Suzuki cross-coupling with boronic acid **248** to afford compound **252** (Scheme 50).



Scheme 50. Synthesis of 4,7-dideoxypancratistatin analogue **254** from carbamate **247** by Banwell.[31a]

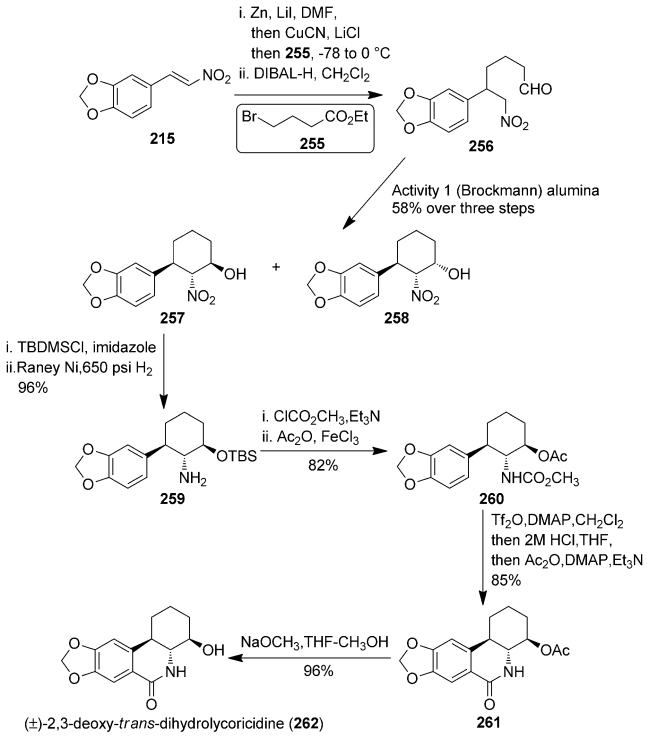
Hydroboration/oxidation of **252** was accomplished with complete stereoselectivity, and the product was subjected to ketal deprotection and acetylation of the resultant triol to produce triacetate **253**. The triacetate **253** was then subjected to the Banwell modification of Bischler–Napieralski cyclization,[31] leading to the isolation of the desired 4,7-dideoxypancratistatin analogue **254**.

No biological activity data was reported for 2-deoxylycoricidine (**251**) or 4,7-dideoxypancratistatin analogue **254**.

3.4. McNulty (1998) – (±)-2,3-Deoxy-trans-dihydrolycoricidine (262)

In this synthesis, alumina-promoted 6-*exo*-*trig* intramolecular nitroaldol cyclization was employed as a key transformation.[121] The strategy resembles that utilized by Seebach in the synthesis of (±)-1-desoxy-2-lycorinone (**221**).[120,164] A copper-zinc reagent derived from ethyl 4-bromobutyrate (**255**) underwent Michael addition to nitroalkene **215** followed by partial reduction of the ester with DIBAL-H to provide aldehyde **256** (Scheme 51). In the key step, aldehyde **256** was treated with basic alumina to promote intramolecular nitroaldol cyclization.

Two diastereoisomers, **257** and **258** were isolated in the ratio 95:5 respectively, with **257** being the desired isomer. The hydroxyl in **257** was protected as its corresponding TBS ether and the nitro group was reduced by hydrogenation over

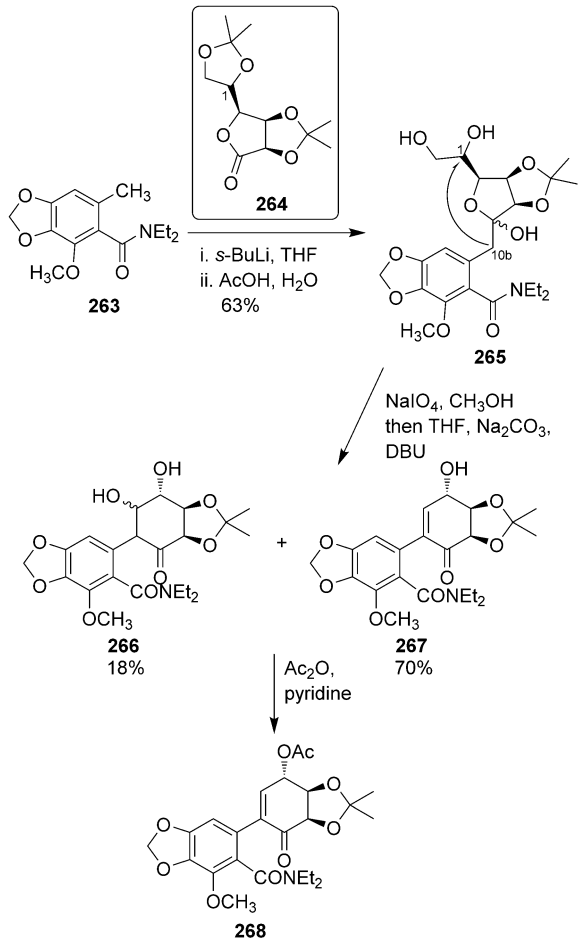


Scheme 51. (±)-2,3-deoxy-trans-dihydrolycoricidine (**262**) by McNulty.[121]

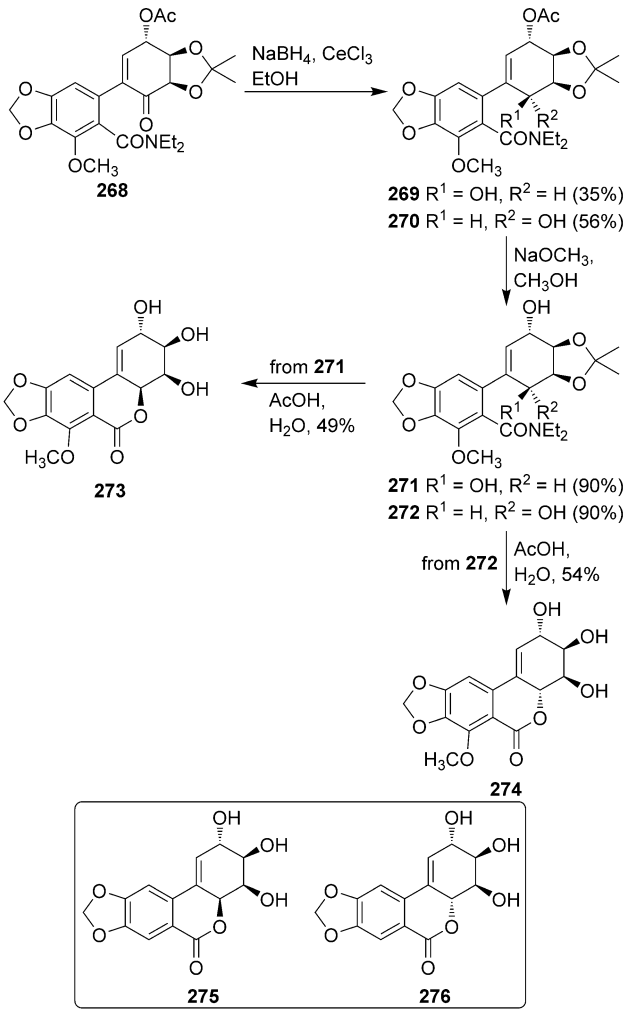
Raney nickel to produce amine **259**. Amine **259** was acylated to its methyl carbamate and the TBS protected alcohol was transprotected to its acetate ester to obtain compound **260**. The transprotection was required because the construction of ring B could not be achieved with substrates containing a TBS ether. Carbamate **260** was then subjected to Banwell modification of Bischler–Napieralski cyclization[31] followed by cleavage of the acetate functionality to produce (±)-2,3-dideoxy-*trans*-dihydrolycoricidine (**262**). Thus the synthesis gave access to a C-ring modified derivative of *trans*-dihydrolycoricidine. (±)-2,3-Dideoxy-*trans*-dihydrolycoricidine (**262**) was later tested against a P-388 leukemia cell line, and demonstrated low levels of inhibition (ED_{50} = 40.1 μg mL^{-1}).[145]

3.5. Chapleur (2004) – B-Ring Lactone Analogues of 7-Methoxynarciclasine and Lycoricidine (273–276)

In 2004, Chapleur and co-workers synthesized lactone analogues of 7-methoxynarciclasine and lycoricidine and evaluated their antitumor activities.[148] The primary motive of this work was the investigation of the necessity for the amide linkage in the ring B of active compounds. In order to achieve the desired stereochemistry, D-gulonolactone (**264**) was chosen as a starting material. The condensation of the lithium anion derived from **263** with D-gulonolactone (**264**), followed by acetonide deprotection gave access to lactol **265** (Scheme 52). Malaprade oxidation[168] of a free diol promoted the Knoevenagel-type cyclization[169] (between C-1 and C-10b) to produce a mixture of compounds **266** (β-hydroxy-



Scheme 52. Synthesis of ester **268** from **263** by Chapleur.[148]



Scheme 53. B-ring lactone analogues of 7-methoxynarciclasine and lycoricidine (**273**–**276**) by Chapleur.[148]

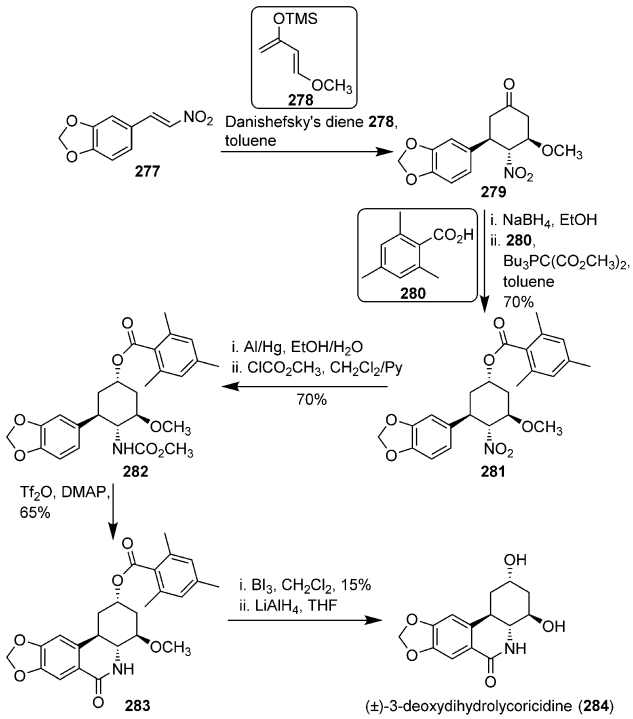
ketone) and **267**. The mixture was treated with acetic anhydride/pyridine in order to convert **266** into **267** and subsequently protect the C-2 hydroxy as its acetate ester **268**.

In the following step, the Luche reduction of the enone functionality in compound **268** provided two diastereomers **269** (C4a-β-OH) and **270** (C4a-α-OH) in 35% and 56% yields respectively (Scheme 53). Both **269** and **270** were separately subjected to acetate cleavage with sodium methoxide in methanol. The resulting alcohols **271** and **272** were treated with acetic acid at reflux, promoting lactone formation and acetonide deprotection. Lactone derivatives of 7-methoxynarciclasine, **273** and **274** were obtained in 49% and 54% yields respectively. By using the same strategy, the authors had also synthesized lactone derivatives of lycoricidine, that is, **275** and **276** (Scheme 53). When all four lactones (**273**–**276**) were screened as antitumor agents against L1210 cell lines, no significant biological activity was observed, confirming the need for the amide and especially for the enolized β-ketoamide moiety found in the most active C-7 hydroxy derivatives.

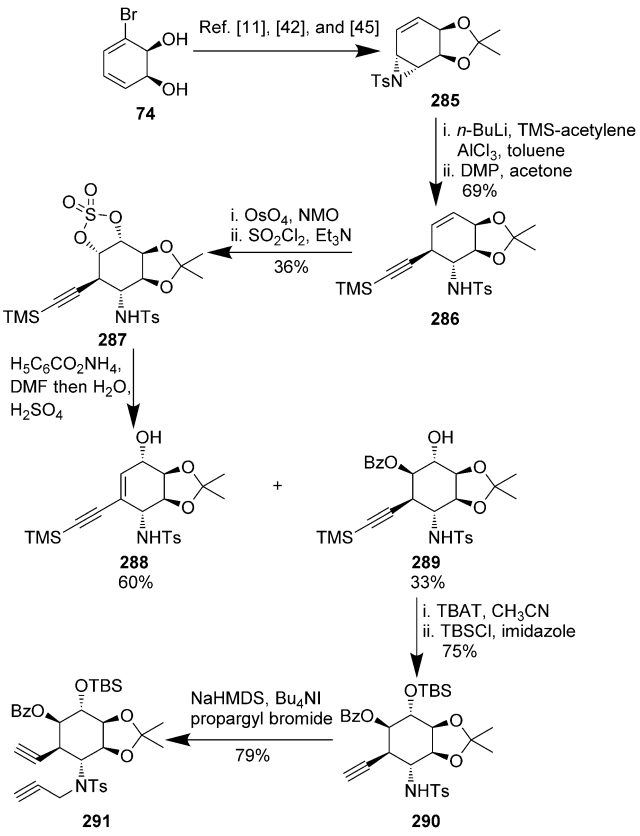
3.6. McNulty (2005) – (±)-3-Deoxydihydrolycoricidine (284)

The synthesis of this unnatural derivative of lycoricidine, reported by McNulty,[150] begins with the Diels–Alder reaction of **277** with Danishefsky's diene (**278**) to obtain the *exo* adduct **279** with high selectivity (96:4) (Scheme 54). Reduction of the C-2 ketone followed by inversion of the stereochemistry of the C-2 hydroxy by Mitsunobu reaction with carboxylic acid **280** produced ester **281**.

Reduction of the nitro functionality in **281** with aluminium amalgam followed by protection of the amine provided carbamate **282**. Ring B construction was accomplished when carbamate **282** was treated with Tf_2O/DMAP (lactam **283**). Deprotection of the methyl ether and subsequent reduction of the ester gave access to (±)-3-deoxydihydrolycoricidine (**284**). The synthesis was completed with 4.8% overall yield. (±)-3-Deoxydihydrolycoricidine (**284**) was tested against both breast MCF-7 and leukemia Jurkat cancer cell lines but was found to be inactive at the test concentration 10 μM.[150]



Scheme 54. Synthesis of (±)-3-deoxydihydrolycoricidine (**284**) by McNulty.[150]

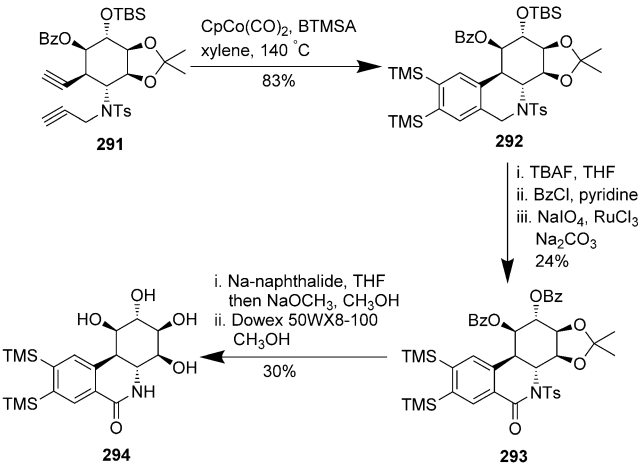


Scheme 55. Synthesis of diyne **291** from **74** by Hudlicky.[151]

3.7. Hudlicky (2005) – A/B Ring Deoxygenated Analogues of (+)-Pancratistatin (294)

The method published by Hudlicky[151] allows for the synthesis of pancratistatin analogues with a deoxygenated aromatic core. The authors claim that pancratistatin analogues having a number of substitution patterns on their respective aromatic rings can be prepared by this protocol. The strategy involves cyclotrimerisation of substituted acetylenes. Diol **74**[57] was converted to aziridine **285** by a sequence of reactions according to a published method[170] (Scheme 55). Opening of the aziridine ring from the more accessible site by the anion of trimethylsilylacetylene gave access to cyclohexene derivative **286**. Upjohn dihydroxylation of an olefin in **286** followed by protection of the resulting diol as its cyclic sulfate provided compound **287**. Treatment of **287** with ammonium benzoate resulted in a mixture of **288** and **289** in 60% and 33% yield respectively. Upon detailed study of this reaction, the authors concluded that the formation of **288** occures by *anti* elimination of the intermediate sulfate anion derived from ester **289**. The removal of the TMS group in **289** was effected by tetrabutylammonium triphenyldifluorosilicate (TBAT) and the resultant alcohol was protected as its TBS ether **290**. The tosylamide in **290** was alkylated with propargyl bromide to obtain diyne **291**.

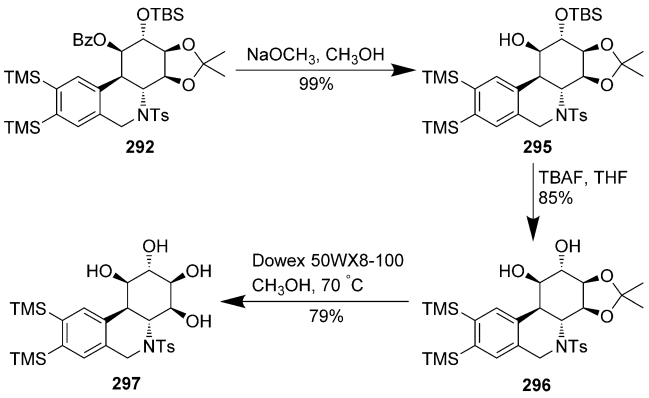
In the key step, cyclotrimerisation of diyne **291** with bistrimethylsilylacetylene (BTMSA) catalyzed by $CpCo(CO)_2$ afforded tetracyle **292** in 83% yield (Scheme 56). Transprotection of the C-2 TBS ether as a benzoate ester and oxidation of benzylic carbon C-6 with sodium metaperiodate/ruthenium trichloride provided phenanthridone **293**. Finally,



Scheme 56. Synthesis of bisTMS analogue **294** from diyne **291** by Hudlicky.[151]

removal of protecting groups gave access to target compound **294**.

In a divergent synthesis, the benzoate ester in the intermediate **292** was cleaved by sodium methoxide to obtain alcohol **295** (Scheme 57). In a subsequent reaction the TBS group was removed by treatment with TBAF to obtain diol **296**. Finally, deprotection of the acetonide resulted in tosylamide **297**.

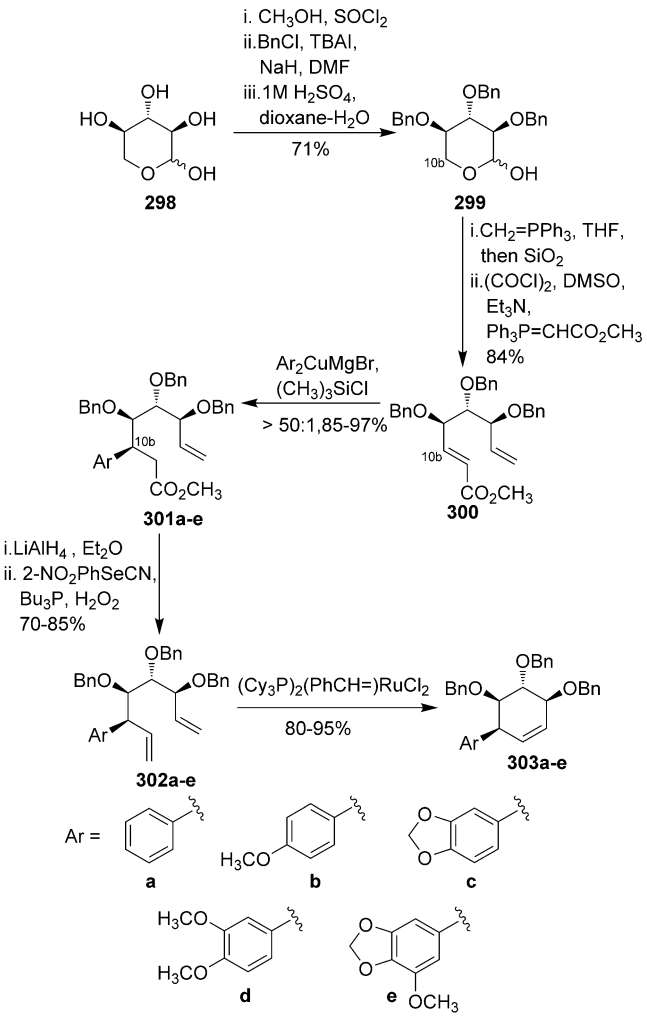


Scheme 57. Synthesis of intermediates **295**, **296** and **297** by Hudlicky.[151]

Compounds **292**, and **294–297** were evaluated for their biological activity against a panel of murine P388 lymphocytic leukemia and six other human cancer cell lines (pancreas BXPC, breast MCF-7, CNS SF-268, lung NCI-H460, colon KM20L2, and prostate DU-145) with 7-deoxypancratistatin (**2**) and narciclasine (**3**) being the control.[41] Compound **294** was found to be inactive while tosylamide **292** exhibited $>10\ \mu g\,mL^{-1}$ as GI_{50} (50% growth inhibition) value for all cell lines. Somewhat surprisingly, intermediates **295** [GI_{50} in $\mu g\,mL^{-1}$; pancreas (3.6), breast (2.2), CNS (3.8), lung (4.7), colon (3.1), and prostate (3.1)], **296** [GI_{50} in $\mu g\,mL^{-1}$; leukemia (3.0), pancreas (1.7), breast (1.5), CNS (1.6), lung (1.7), colon (1.6), and prostate (1.6)], and **297** [GI_{50} in $\mu g\,mL^{-1}$; leukemia (3.3), pancreas (1.7), breast (1.7), CNS (1.6), lung (1.7), colon (1.4), and prostate (1.8)] displayed better activities than expected. These values indicate that **295**, **296** and **297** are approximately 8-fold less active than 7-deoxypancratistatin (**2**) [GI_{50} in $\mu g\,mL^{-1}$; leukemia (0.44), lung (0.29), and colon (0.22)].

3.8. Kornienko (2006) – Truncated A/C Ring Analogues Lacking Ring B (304a–e, 305a–e and 307a–e)

Kornienko synthesized aromatic analogues of conduritol F, L-*chiro*-inositol, and dihydroconduritol F in order to synthesize simplified derivatives of pancratistatin and related compounds.[152] The importance of the intact phenanthridone core in the anticancer activity of pancratistatin-type compounds was also to be evaluated. Tri-*O*-benzyl-D-xylopyranose (**299**) was prepared from D-xylose (**298**) by a sequence of reactions (Scheme 58). Wittig reaction[171] with hemiacetal in **299**, Swern oxidation[172] of the resulting primary alcohol at C-10b and its in situ two-carbon Wittig reaction afforded ester **300**. Diastereoselective Michael addition of magnesiumdiarylcuprate bromide to the α,β-unsaturated ester provided compounds **301a–e** with >50:1 selectivity favoring the desired isomer. Reduction of the ester to alcohol and subsequent Grieco elimination[173] gave access to isolated diene **302a–e**. Ring closing metathesis of **302a-e** catalyzed by Grubbs's 1st generation catalyst[174] produced cyclohexene derivatives **303a–e**.

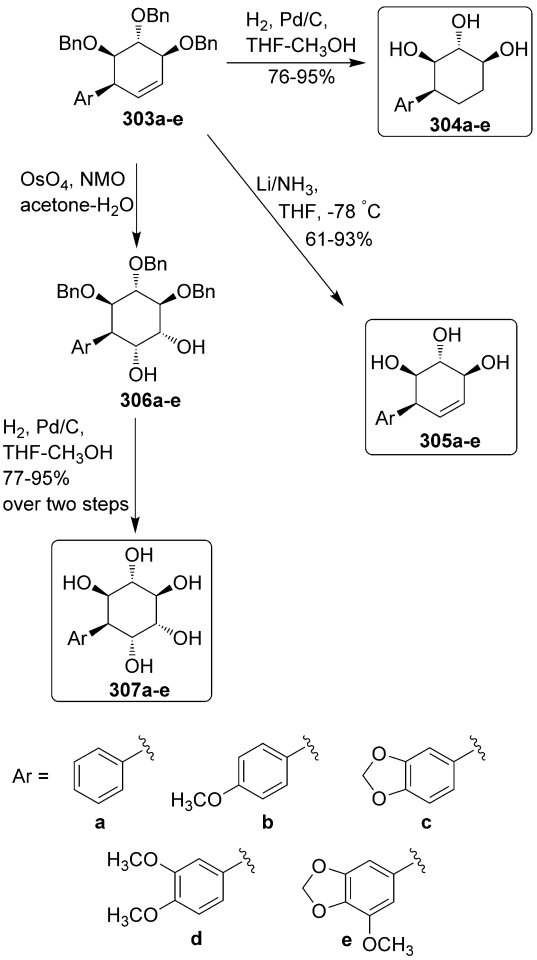


Scheme 58. Synthesis of cyclohexene derivatives **303a–e** by Kornienko.[152]

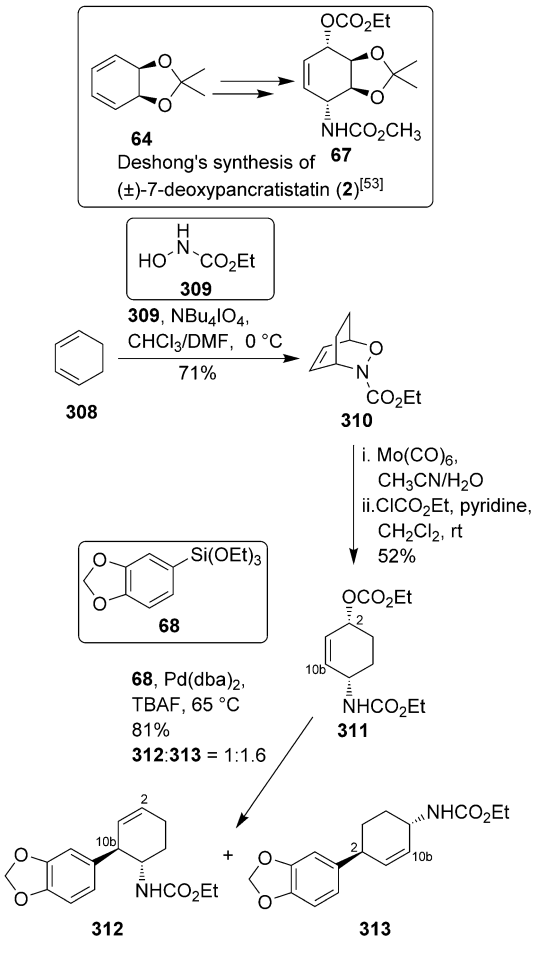
The reduction of the olefin in **303a–e** and debenzylation under the same conditions provided aromatic analogues of dihydroconduritol F **304a–e** (Scheme 59). In a separate reaction, cleavage of the benzyl ethers in **303a–e** with Li/NH_3 gave access to aromatic analogues of conduritol F **305a–e**. Another sequence involved Upjohn dihydroxylation of the olefin functionality in **303a–e** followed by reductive cleavage of benzyl ethers to afford aromatic analogues of L-*chiro*-inositol **307a–e**. All of the synthesized derivatives **304a–e**, **305a–e** and **307a–e** were found to be inactive up to 300 μM concentration when screened for cytotoxic, apoptosis inducing, and growth inhibitory properties with the use of Jurkat and HeLa cell lines as models for human T-cell leukemia and adenocarcinoma, respectively. The observed results again suggested that the intact phenanthridone core is necessary for the anticancer activity of these type of compounds.

3.9. DeShong (2006) – (±)-3,4,7-Trideoxypancratistatin (315)

After an unsuccessful attempt at the synthesis of (±)-7-deoxypancratistatin (**2**), DeShong developed a synthesis of



Scheme 59. Truncated A/C ring analogues lacking ring B (**304a–e**, **305a–e** and **307a–e**) by Kornienko.[152]

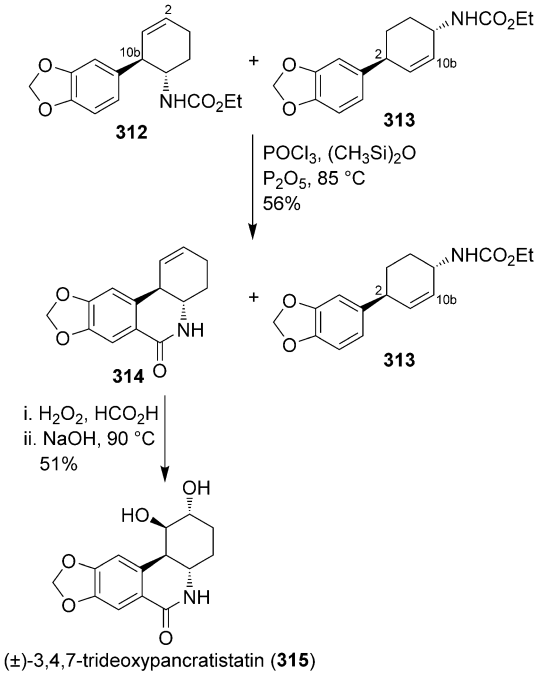


Scheme 60. Synthesis of ethyl carbamate **312** by DeShong.[153]

(±)-3,4,7-trideoxypancratistatin (**315**),[153] prior to the successful synthesis of (±)-7-deoxypancratistatin (**2**) published in 2012.[53] The basic strategy of the synthesis remains the same as discussed in Section 2.2.3 (DeShong, 2012). Diene **308** was used as a starting material, as opposed to **64**, as the Tsuji–Trost reaction could not be effected with the precursor **67** (prepared from **64**) (Scheme 14 and 60). This was the reason that the original approach to (±)-7-deoxypancratistatin (**2**) was not fruitful in 2006.

Carbonate **311** was prepared by hetero-Diels–Alder reaction between **308** and **309** followed by subsequent cleavage of the bicyclo adduct **310** (Scheme 60). Tsuji–Trost reaction of **311** with the electron rich aryl siloxane **68** produced a mixture of regioisomers in the ratio of 1:1.6 (**312**:**313**) favoring the undesired isomer. The authors claimed that the regioselectivity favoring **313** was expected based on the results reported by Szabó.[175]

The regioisomeric mixture of **312** and **313** was subsequently subjected to Bischler–Napieralski cyclization with P_2O_5, $POCl_3/(CH_3Si)_2O$ to produce phenanthridone **314** (Scheme 61). As anticipated, only carbamate **312** underwent the cyclization with complete regioselectivity, in analogy to the results reported by Magnus.[14a] In order to introduce the



Scheme 61. Synthesis of (±)-3,4,7-trideoxypancratistatin (**315**) from **312** by DeShong.[153]

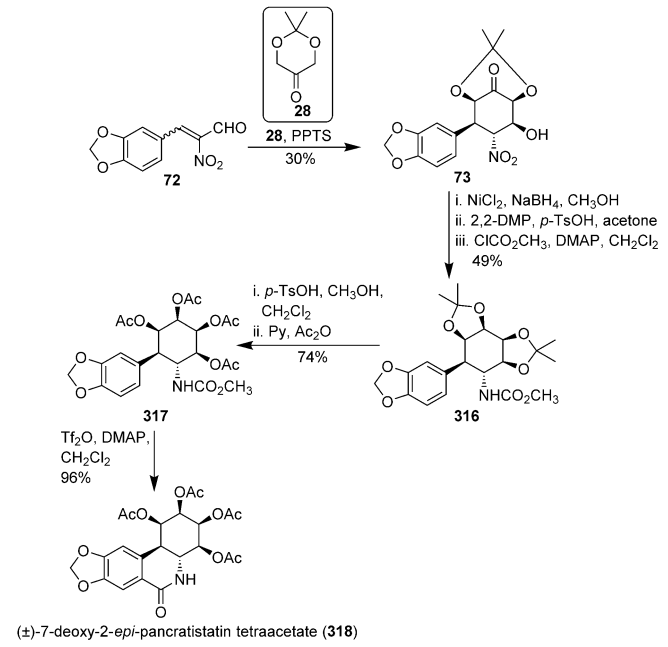
trans C-1 and C-2 diol functionality, a one pot epoxidation and hydrolysis sequence was chosen. A number of epoxidation methods were explored, most of which were low-yielding.

Finally, epoxidation with H_2O_2/formic acid, and subsequent hydrolysis produced (±)-3,4,7-trideoxypancratistatin (**315**) in reasonable yield (51%). Following the unsuccessful synthesis of (±)-7-deoxypancratistatin (**2**) and after extensive research, DeShong and co-workers were able to couple the precursor **67** with siloxane **68** using Pd(COD)(NQ) and tetrabutylammonium fluoride (TBAF).[53] No biological activity data was reported for (±)-3,4,7-trideoxypancratistatin (**315**).[153]

3.10. Alonso (2006) – (±)-7-Deoxy-2-epi-pancratistatin Tetraacetate (318)

This synthesis of (±)-7-deoxy-2-*epi*-pancratistatin tetraacetate (**318**) constituted an initial attempt by the Alonso group to construct ring C via one pot Michael addition and aldol reaction sequence.[154] This strategy was later implemented in the synthesis of (+)-pancratistatin (**1**)[21] (Scheme 6), and (±)-7-deoxypancratistatin (**2**) (Scheme 15).[54]

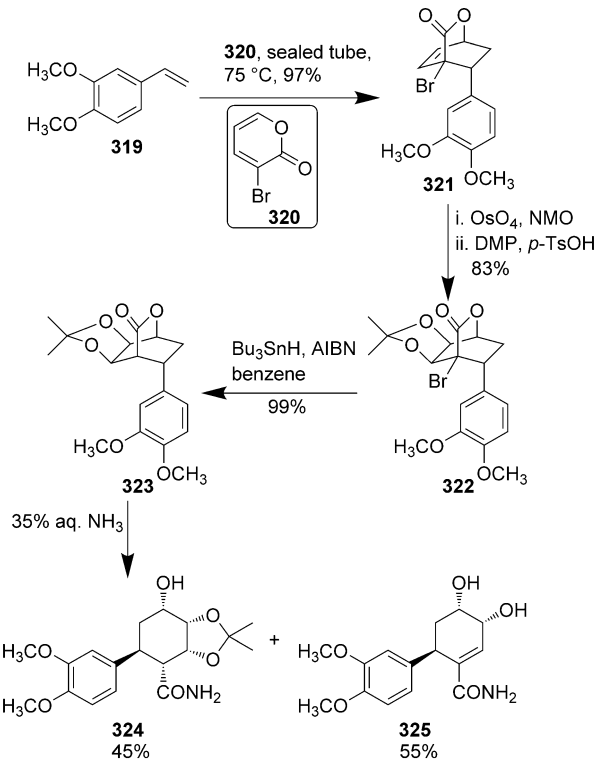
The α-nitroenal **72** and ketone **28** underwent sequential Michael addition and aldol reaction under acidic conditions to produce nitrocyclitol **73** (Scheme 62). The simultaneous reduction of the nitro and ketone functionalities with $NiCl_2$ and $NaBH_4$ proceeded with complete stereocontrol. Protection of the resultant tetrol as two 1,2-acetonides and the amine moiety as a methyl carbamate gave access to compound **316**. At the end of the synthesis, both acetonides were cleaved under acidic condition and the resultant tetrol reprotected as the corresponding peracetate **317**. Finally, Banwell-modified Bischler–Napieralski cyclization[31] provided (±)-7-deoxy-2-*epi*-pancratistatin tetraacetate (**318**) with 96% yield. No biological activity data was reported for (±)-7-deoxy-2-*epi*-pancratistatin tetraacetate (**318**).[154]



Scheme 62. Synthesis of (±)-7-deoxy-2-*epi*-pancratistatin tetraacetate (**318**) by Alonso.[154]

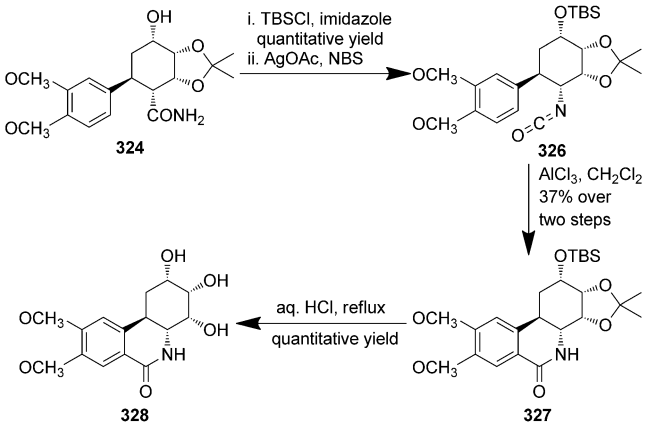
3.11. Afarinkia (2007) – A-Ring Analogue of (±)-3,4-Di-epi-trans-dihydrolycoricidine (328)

In 2007 Afarinkia published the synthesis of an A-ring analogue of (±)-3,4-di-*epi*-*trans*-dihydrolycoricidine (**328**).[155] The authors employed a Diels–Alder reaction to connect ring A with ring C. It is noteworthy that a similar strategy was applied by Cho for the synthesis of (+)-*trans*-dihydronarciclasine (**192**) in early 2007.[134] The key step involved the Diels–Alder reaction of **319** and **320** to provide bicyclic compound **321** (Scheme 63). Upjohn dihydroxylation of **321** followed by protection of the diol gave acetonide **322**. Debromination of **322** with Bu_3SnH/AIBN smoothly furnished lactone **323**. Opening of the lactone functionality was carried out with 35% aqeous ammonia to obtain amides **324** and **325** in 45% and 55% yield respectively.



Scheme 63. Synthesis of amide **324** by Afarinkia.[155]

The alcohol functionality in compound **324** was protected as the corresponding TBS ether and the resulting compound was subjected to Hofmann rearrangement[176] with silver acetate to obtain isocyanate **326** (Scheme 64). Treatment of **326** with Lewis acid ($AlCl_3$) constructed the phenanthridone skeleton and gave access to compound **327**. Cleavage of the



Scheme 64. Synthesis of A-ring analogue of (±)-3,4-di*epi-trans*-dihydrolycoricidine (**328**) by Afarinkia.[155] Note that NBS was missing from the reagents provided in reference [155] but was the required reagent in the original literature cited.

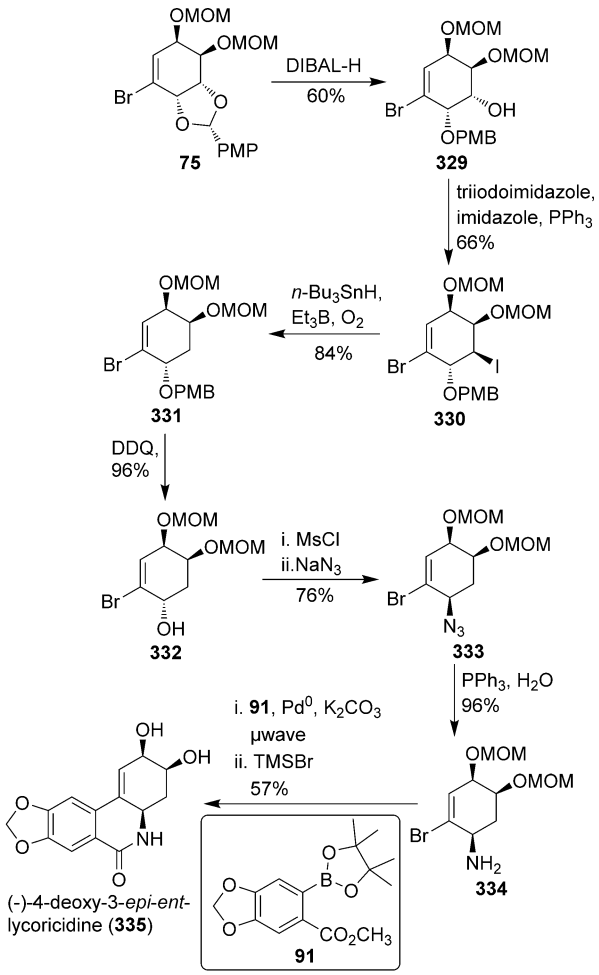
TBS ether and acetonide under acidic conditions provided A-ring analogue of (±)-3,4-di-*epi-trans*-dihydrolycoricidine (**328**). No biological activity data were reported.

3.12. Banwell (2007) – C-Ring Analogues of (−)-Lycoricidine (335, 337)

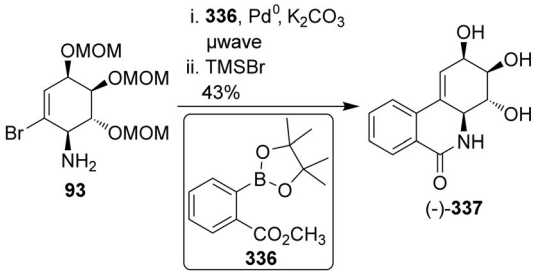
As a part of their continuing interest in providing a short syntheses of lycoricidine congeners, the Banwell group published a preparation of two derivatives of lycoricidine.[74,89] The key step involved a Suzuki coupling[177] of a ring A boronate ester **91** with a ring C vinylic bromide **334** followed by Bischler–Napieralski cyclization to construct the B ring. In order to produce the desired vinylic bromide **334**, the benzylidene protecting group in **75** was reductively cleaved to obtain alcohol **329** (Scheme 65). Conversion of the alcohol functionality in **329** to an iodide was performed according to a published procedure using triiodoimidazole/PPh_3/imidazole.[178]

Selective dehalogenation of **330** was achieved with the treatment of *n*-$Bu_3SnH/Et_3B/O_2$ producing vinylic bromide **331**. The resulting PMB ether in **331** was subjected to oxidative cleavage to afford alcohol **332**. Activation of the alcohol functionality as a mesylate followed by displacement with NaN_3 gave rise to azide **333**. The Staudinger reduction of the azide functionality in **333** provided amine **334**. Finally, the vinylic bromide **334** and boronate ester **91** were subjected to microwave-assisted Suzuki–Miyaura cross-coupling that led to the construction of the phenanthridone core. Although the sequence of reactions is not clear, the authors proposed that the cross-coupling precedes the lactamization step. Removal of the MOM protecting groups with TMSBr gave access to the target molecule, (−)-4-deoxy-3-*epi-ent*-lycoricidine (**335**).

In order to synthesize the 8,9-dideoxy derivative of (−)-3-*epi-ent*-lycoricidine (**337**), amine **93** was subjected to Suzuki coupling with boronate ester **336** (Scheme 66). After the removal of the MOM protecting groups, phenanthridone **337** was obtained. Congeners **335**, and **337** were evaluated for



Scheme 65. Synthesis of (−)-4-deoxy-3-*epi-ent*-lycoricidine (**335**) by Banwell.[74]

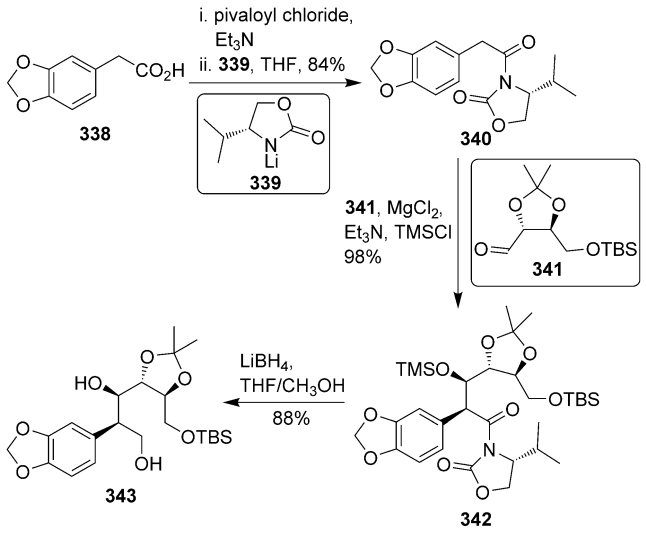


Scheme 66. Synthesis of **337** by Banwell.[74,89]

their biological activity against 13 cancer cell lines [skin A-375, skin A-431, colon HCT-15, myelogenous leukemia K-562, MDA MB-231, breast A-549, ovarian teratocarcinoma PA-1, bladder carcinoma HT-1376, lung HTB-178, uterine sarcoma MES-SA, liver hepatocellular carcinoma HepG2, breast MCF-7, prostate DU-145] with (+)-narciclasine (**3**) as a control. Both compounds were shown to be one or two orders of magnitude less cytotoxic than the control, and therefore were regarded as inactive.[89]

3.13. McNulty (2008) – seco-Pancratistatin Structural Analogues (348, 349)

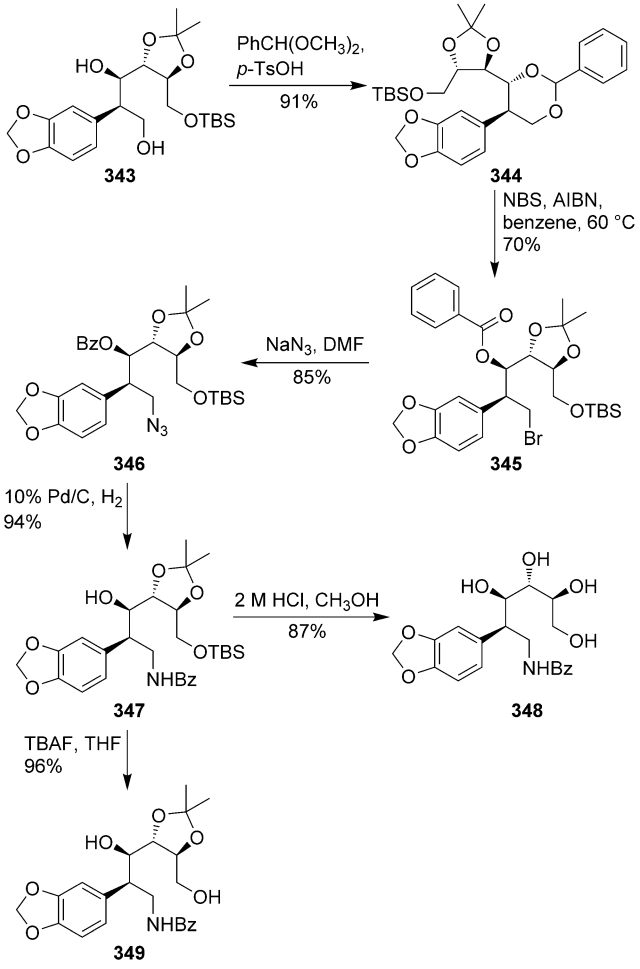
A number of derivatives of the pancratistatin family have been synthesized in order to identify the best candidate as a pharmaceutical lead compound. The C-1 benzoate is the most potent anticancer derivative of pancratistatin known to date (murine leukemia cell line, $ED_{50} = 0.0017\ \mu g\,mL^{-1}$).[16] With consideration of pharmacophoric elements that are required for potent anticancer activity, McNulty[156a] decided to synthesize *seco*-derivatives and evaluate their biological activity. The synthesis commences with the activation of 3,4-methylenedioxyphenylacetic acid (**338**) by conversion to a mixed anhydride using pivaloyl chloride (Scheme 67). The mixed anhydride was quenched with the lithium salt of (*R*)-(+)-oxazolidinone (**339**) to produce imide **340**.



Scheme 67. Synthesis of diol **343** from acid **338** by McNulty.[156a]

An Evans aldol reaction[179] of **340** was then carried out with L-threose-derived aldehyde **341** to afford the *anti*-adduct **342** as the major diastereomer. This is the key step in the synthesis as it connects ring A (aromatic moiety) with a truncated ring C. More importantly, it sets the required stereochemistry at C-10b and C-1. Treatment of **342** with lithium borohydride cleaved the oxazolidinone auxilliary and TMS group simultaneously to afford diol **343**.

1,3-Diol **343** was smoothly transformed into benzylidene **344** with benzaldehyde dimethyl acetal (Scheme 68). Protection of the diol functionality as a bezylidene acetal helped to assign the absolute stereochemistry of the molecule through a single crystal X-ray. Furthermore, the cleavage of benzylidene **344** with NBS and AIBN discriminated between the primary and secondary alcohols and allowed for the selective bromination of the primary alcohol to produce **345**. Displacement of the bromide in **345** with azide and subsequent hydrogenolysis of the resultant azide **346** gave access to alcohol **347**. *O*,*N*-Benzoyl intramolecular migration was observed, as anticipated based on previous work by the same group.[121] Removal of the acetonide and TBS functionalities in **347** under acidic conditions provided tetrahydroxybenzamide **348**. In a parallel route, the TBS functionality in **347** was cleaved with TBAF to obtain dihydroxybenzamide **349**. These truncated derivatives, **348** and **349**, were tested for anticancer activity against human breast carcinoma (MCF-7) cell line, however, neither of these exhibited any activity at the test concentrations, $30\ \mu g\,mL^{-1}$ (median effective dose, ED_{50} value).

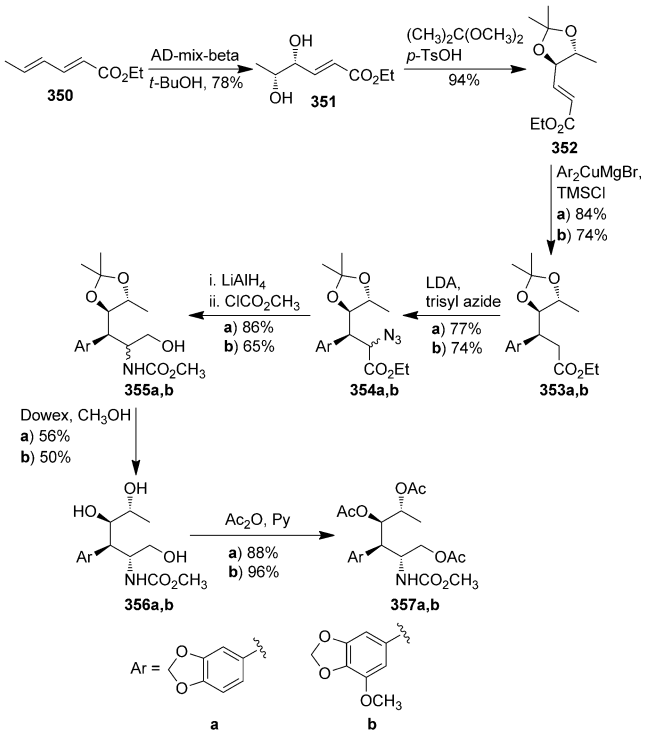


Scheme 68. Synthesis of *seco*-pancratistatin structural analogues **348** and **349** by McNulty.[156a]

3.14. Kornienko (2009) – C-Ring Analogues of (+)-Pancratistatin (360a, 360b, 361a)

Because of the formidable synthetic challenges imposed by the molecules of the pancratistatin type, and a desire to understand the core pharmacophore of these compounds, a number of attempts have been reported to simpler truncated derivatives for biological activity evaluation.[120,143,147] Neverthless, none of these derivatives exhibited anticancer activities comparable to (+)-narciclasine (**3**), (+)-pancratistatin (**1**), or (+)-7-deoxypancratistatin (**2**). In fact, simplification of the structures by reducing the number

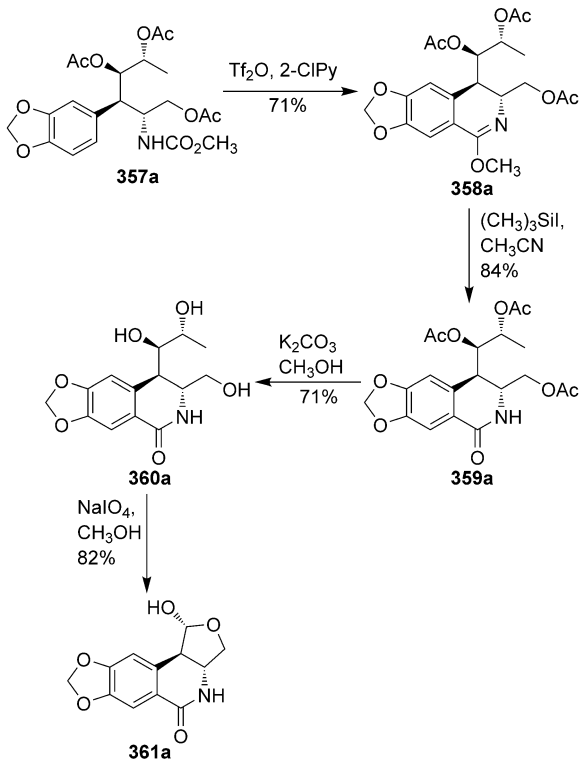
of oxygens on ring C was shown to reduce the activity of these analogues significantly.[120,147] Hence, Kornienko decided to synthesize truncated derivatives in which at least three hydroxy groups are maintained on ring C while modifying the carbon scaffold.[157] Commercially available sorbate ester **350** was dihydroxylated with AD-mix-β to obtain diol **351** as a single enantiomer (Scheme 69). Protection of the diol



Scheme 69. Synthesis of Bischler–Napieralski precursors **357a** and **357b** by Kornienko.[157]

functionality as its acetonide produced **352**. Michael addition of aryl cuprates (both **a** and **b**) to the α,β unsaturated ester **352** proceeded with exclusive *anti*-selectivity (*anti*:*syn*, >50:1) to yield esters **353**. Both esters **353a** and **353b** were separately subjected to azidation by treatment with LDA/trisyl azide. This resulted in *syn* selectivity in both cases with 2.5:1 (*syn*:*anti*) for **354a** and 2:1 (*syn*:*anti*) for **354b**. Simultaneous reduction of the azide and ester functionalities in the epimeric mixtures **354a** and **354b** was followed by their conversion to a similar mixture of carbamates **355a** and **355b**. The acetonide functionalities in both the mixtures **355a** and **355b** were cleaved and the crude products were purified to isolate major epimers **356a** and **356b** in moderate yields (56% and 50% respectively). Protection of triols **356a** and **356b** as their corresponding peracetates produced precursors **357a** and **357b**.

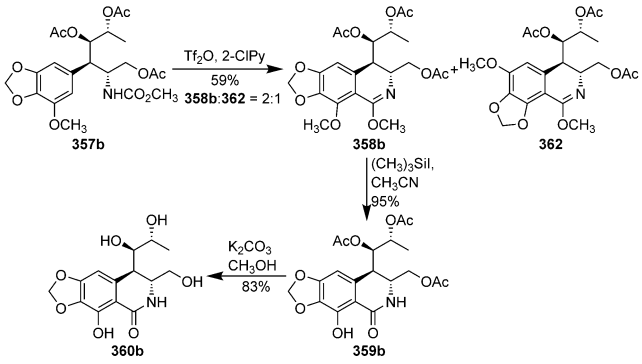
In carbamate **357a**, ring B was constructed by the Banwell modification of Bischler–Napieralski cyclization (Scheme 70).[31] Imidate **358a** was the only regioisomer obtained. The methyl ether functionality in **358a** was cleaved by TMSI affording amide **359a**. The acetate protecting groups were removed under basic conditions to provide triol **360a**,



Scheme 70. Synthesis of C-ring analogues (+)-7-deoxypancratistatin (**360a**, **361a**) by Kornienko.[157]

one of the targeted truncated derivatives. The diol functionality in **360a** was oxidatively cleaved to produce an aldehyde functionality, which spontaneously cyclized, affording the single anomeric lactol **361a**.

Unlike in the case of **357a**, the Banwell modification of Bischler–Napieralski cyclization of **357b** was not exclusively regioselective (Scheme 71). The products of this reaction, regioisomers **358b** and **362**, were isolated in the ratio 2:1, respectively. Simultaneous cleavage of both methyl ether functionalities in **358b** was effected with TMSI to afford acetate **359b** in excellent yield (95%). Finally, removal of the acetate protecting groups under basic conditions produced another truncated derivative of pancratistatin **360b**.



Scheme 71. Synthesis of C-ring analogue (+)-pancratistatin (**360b**) by Kornienko.[157]

Derivatives **360a**, **360b** and **361a** were evaluated for antiproliferative activity using HeLa and MCF-7/AZ human cancer cell lines.[157] Compounds **360a** and **360b** were found to be virtually inactive. The lactol **361a** displayed the highest potency (HeLa = 59% and MCF-7/AZ = 48% cell viability) at 330 μM among the synthesized compounds, although, it was much lower in comparison with the control (+)-narciclasine (**3**) (HeLa = 6% and MCF-7/AZ = 8% cell viability).

3.15. Marion (2009) – C-1 Analogues of (+)-Pancratistatin (266–271 and Other Compounds)

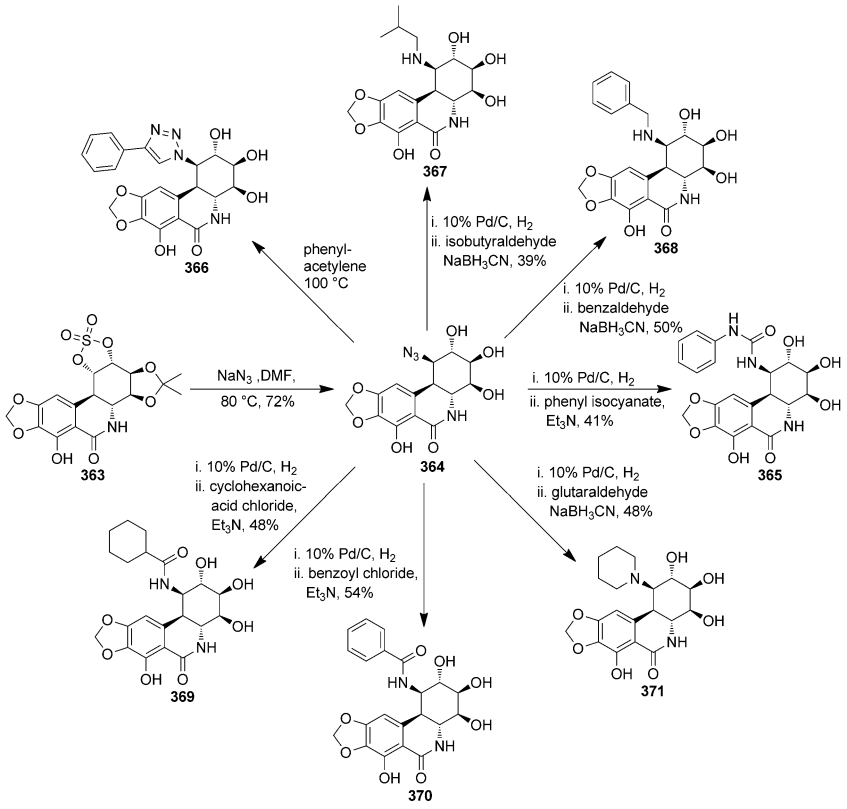
Although, (+)-narciclasine (**3**) and its hydrated derivative (+)-pancratistatin (**1**) are among the most potent molecules from Amaryllidaceae family which have shown anticancer activity, they often suffer from lower solubility in aqeous solvents or pharmaceutically acceptable media. In 2009, Marion[158] synthesized C-1 aza-derivatives of pancratistatin in order to improve the solubility while maintaining or enhancing their biological activity. The derivatives were made by divergent synthesis, primarily from azide **364** (Scheme 72). The azide functionality was introduced at C-1, simply by S_N2 reaction of NaN_3 with the cyclic sulfate **363**, which happens to be an intermediate in Pettit's synthesis of (+)-pancratistatin (**1**).[16] Thereafter, **364** was converted to 35 derivatives, out of which several representative examples are depicted (Scheme 72). The azide functionality in **364** was reduced by hydrogenolysis and resulting amine was reacted with phenyl isocyanate to obtain compound **365** whereas cycloaddition between phenyl acetylene and **364** produced triazole derivative **366**.

The most frequently utilized strategy involved the reduction of the azide functionality followed by derivatization of the amine either by acylation or by reductive amination with an aldehyde. Compounds **367**, **368** and **371** were prepared by reductive amination with corresponding aldehydes using sodium cyanoborohydride while amides **369** and **370** were synthesized by acylation. The authors evaluated the biological activity of all 35 C-1-aza derivatives. Compound **370** exhibited the most potent activity against A549 (lung) and HCT 116 (colon) cell lines with IC_{50} values of 8.7 nM and 4.7 nM respectively. In addition, the activity of benzamide **370** was five-fold higher than that of (+)-narciclasine (**3**). This is in direct correlation with the results obtained by Pettit[16] wherein a benzoyl ester functionality at C-1 was shown to also increase the biological activity over the parent compound, (+)-pancratistatin (**1**). Additionally, the solubility of **370** was found to be twice that of (+)-narciclasine (**3**) in a pH 7.2 buffer.

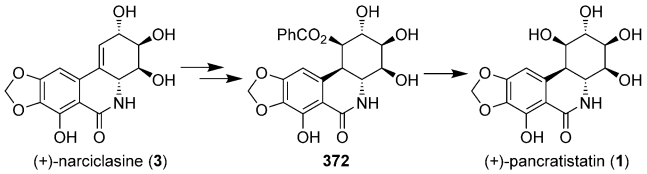
3.16. Hudlicky (2010) – C-1 Homologues of (+)-7-Deoxypancratistatin (374, 375, 377 and 378)

Attempts by the Hudlicky group to identify analogues of the natural Amaryllidaceae constituents that possess greater solubility and bioavailability, while maintaining or improving their bioactivity, have led to the production of a variety of these analogues.[52,60,71b,147,149,151,159,162,163] In 2010, this research program was expanded to include the production of C-1 homologues of (+)-7-deoxypancratistatin **374, 375, 377** and **378** (Scheme 74 and 75).[52] This work was guided by the identification of benzoate **372** (Scheme 73), by Pettit.[16] This compound was made in the course of a semi-synthesis of (+)-pancratistatin (**1**) and was shown to possess potent bioactivity against a variety of cancer cell lines, particularly the murine leukemia cell line ($ED_{50} = 0.0017\ \mu g\,mL^{-1}$). This level of activity is greater than that of both pancratistatin (**1**) ($ED_{50} = 0.032\ \mu g\,mL^{-1}$) and narciclasine (**3**) ($ED_{50} = 0.0044\ \mu g\,mL^{-1}$).[16] This work identified the C-1 space as a desirable, and likely the only, area for derivatization in designed Amaryllidaceae analogues.[16]

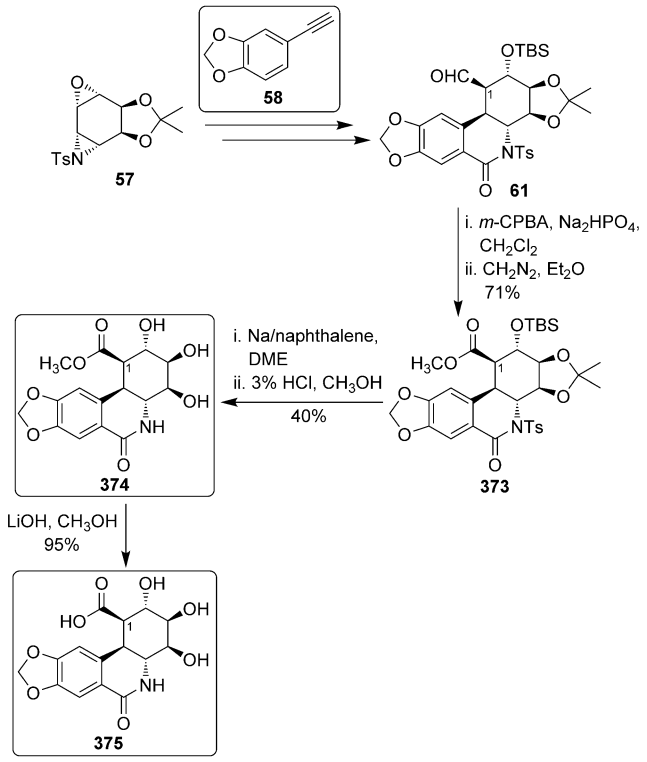
The synthesis of C-1 analogues of (+)-7-deoxypancratistatin was based upon the strategy that was used in the production of the natural compound by Hudlicky.[52] As has previously been discussed (see Section 2.2.2, Scheme 12), the coupling of aziridine **57** with the aryl acetylene **58** followed by a series of



Scheme 72. Synthesis of C-1 analogues (+)-pancratistatin (**1**) by Marion.[158]



Scheme 73. Production of compound **372** by Pettit in the course of the semi-synthesis of (+)-pancratistatin (**1**).[16]

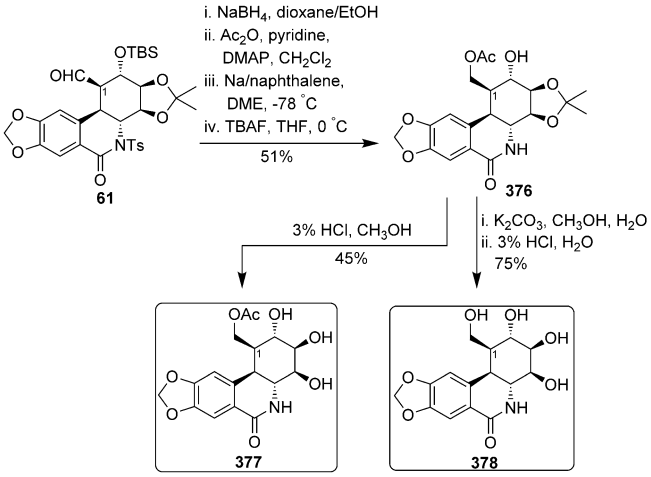


Scheme 74. Production of C-1 acid and ester analogues of (+)-7-deoxypancratistatin **374** and **375** by Hudlicky.[52]

transformations led to aldehyde **61** (Scheme 74), utilized as the common intermediate for the approach to several C-1 analogues of (+)-7-deoxypancratistatin.[52] In order to access the C-1 acid and methyl ester analogues, aldehyde **61** was subjected to oxidation with buffered *m*-CPBA followed by diazomethane esterification to afford ester **373**. Full deprotection afforded the desired C-1 ester analogue **374**. Hydrolysis of the ester moiety under mild conditions gave the corresponding C-1 acid analogue **375**.

Aldehyde **61** was also utilized in the production of C-1 hydroxymethylene and acetoxymethylene analogues **377** and **378** (Scheme 75). Borohydride reduction of aldehyde **61** was followed by acetylation and deprotection of the tosyl and silyl protecting groups to provide acetate **376**. Exhaustive hydrolysis of acetate **376** afforded the desired hydroxymethylene analogue **378**, while acid-catalyzed acetonide deprotection led to the desired acetoxymethylene analogue **377**.

Analogues **374**, **375**, **377** and **378** were evaluated for antitumour activities, and it was shown that the ester analogue

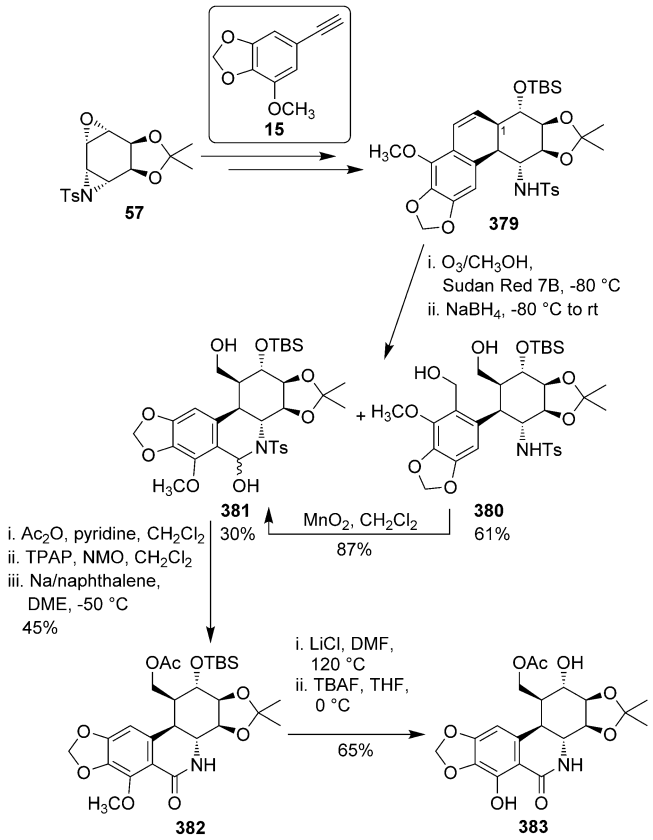


Scheme 75. Production of C-1 acetoxymethylene and hydroxymethylene analogues of (+)-7-deoxypancratistatin **377** and **378** by Hudlicky.[52]

374 and the acid analogue **375** were inactive. The acetoxymethylene and hydroxymethylene analogues **377** and **378** however, did demonstrate useful levels of biological activity when tested against a panel of six cancer cell lines (pancreas BxPC-3, breast MCF-7, lung-NSC NCI-H460, prostate DU-145, leukemia Jurkat, neuroblastoma Shsy5y) [for **377**, ED_{50} in $\mu g\,mL^{-1}$ pancreas (0.11), breast (0.29), lung (0.11), prostate (0.37), leukemia (0.183), neuroblastoma (0.183) and for **378**, ED_{50} in $\mu g\,mL^{-1}$, pancreas (0.19), breast (0.65), lung (0.09), prostate (0.26), leukemia (1.615), neuroblastoma (1.615)], although the potency was less than that of (+)-pancratistatin (**1**) or (+)-narciclasine (**3**).[52] The potencies of analogues **377** and **378** were equal to or greater than that of natural (+)-7-deoxypancratistatin (**2**), supporting the beneficial effect of C-1 derivatization.[52]

3.17. Hudlicky (2011) – C-1 Homologues of (+)-Pancratistatin (384–386)

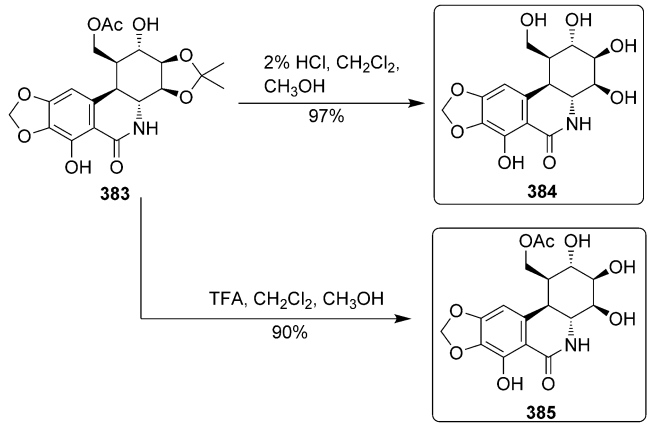
Because the C-1 analogues of 7-deoxypancratistatin were found to be moderately active, it appeared logical to proceed to the corresponding compounds containing the C-7 hydroxy group. The recognized importance of the C-7 hydroxy functionality in maintaining the biological activity of Amaryllidaceae alkaloids[52] led the Hudlicky group to the design of C-1 analogues of pancratistatin.[159] The production of C-1 analogues of pancratistatin was based upon a similar strategy to that used in the synthesis of C-1 analogues of 7-deoxypancratistatin and (+)-7-deoxypancratistin (**2**).[52,159] Coupling of the aryl acetylene fragment **15** (now containing the C-7 methoxy group) with aziridine **57**, followed by a series of previously discussed transformations afforded olefin **379** (Scheme 76). Olefin **379** was subjected to oxidative cleavage, and recyclization to produce hemiaminal **381**, possessing the complete skeleton of the natural product. The alcohol in **381** was then acetylated followed by an oxidation of the hemiaminal and reductive detosylation to afford amide **382**. The common intermediate for the synthesis of C-1 analogues of



Scheme 76. Synthesis of alcohol **383**, a common intermediate for the production of C-1 analogues of pancratistatin by Hudlicky.[159]

pancratistatin, alcohol **383**, was then produced from amide **382** through demethylation using a modification of Trost's procedure[12] and removal of the silyl protecting group.

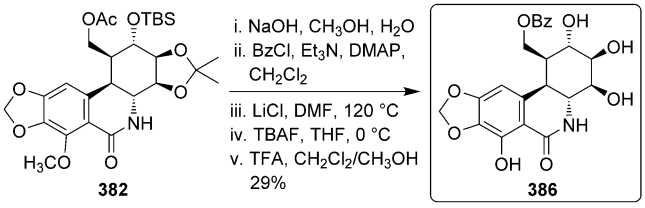
Alcohol **383** was converted to the C-1 hydroxymethylene analogue of pancratistatin **384** by partial deprotection with HCl and methanol and to the C-1 acetoxymethylene analogue **385** by partial deprotection with trifluoroacetic acid (TFA) (Scheme 77).



Scheme 77. Synthesis of C-1 hydroxymethylene and acetoxymethylene analogues of pancratistatin **384** and **385** by Hudlicky.[159]

Analogues **384** and **385** were tested alongside C-1 analogues of 7-deoxypancratistatin **377** and **378** for their anti-proliferative properties against a panel of four cancer cell lines (pancreatic CRL-1687/BXPC-3, prostate HTB-81/DU-145, lung HTB-177/NCI-H460, and breast HTB-22/MCF-7). As expected, the C-1 analogues of pancratistatin demonstrated higher levels of potency than their 7-deoxy counterparts [for **384**, pancreatic (0.22 μM), prostate (0.09 μM), lung (0.09 μM) and breast (0.24 μM) cancer cell lines; for **385**, pancreatic (0.07 μM), prostate (0.06 μM), lung (0.07 μM) and breast (0.52 μM) cancer cell lines (values are denoted for half maximal inhibitory concentration, IC_{50})], confirming again the importance of the C-7 hydroxy moiety for anti-cancer activity.[159] The C-1 acetoxymethylene derivative **385** exhibited the highest levels of potency against pancreatic (0.07 μM), lung (0.07 μM) and prostate (0.06 μM) cancer cell lines, with activity levels approaching that of (+)-narciclasine (**3**) [IC_{50} values, pancreatic (0.05 μM), lung (0.04 μM), prostate (0.05 μM), and breast (0.04 μM) cancer cell lines]. This finding is in accordance with Pettit's observation that a hydrophobic substituent at the C-1 position does not decrease the potency of the compound, and may in fact increase activity.[16]

The C-1 acetoxymethylene derivative of pancratistatin **385** was identified as the most potent unnatural Amaryllidaceae analogue produced to this point by the Hudlicky group and this work was extended in 2012 to include the production of the C-1 benzoate analogue **386**.[159b] This compound was identified as a potential target because of its similarity to compound **372** (Scheme 73), which was shown to possess greater potency against cancer cell lines than both (+)-pancratistatin (**1**) and (+)-narciclasine (**3**).[16] The C-1 benzoate analogue **386** was synthesized through a route similar to the one utilized for the production of the C-1 acetoxymethylene and hydroxymethylene analogues (Scheme 78). The fully protected intermediate, acetate **382**, was subjected to basic hydrolysis, followed by benzoylation and a series of deprotection steps to afford the C-1 benzoxymethylene analogue of pancratistatin **386**.



Scheme 78. Synthesis of C-1 benzoxymethylene analogue of pancratistatin **386** by Hudlicky.[159b]

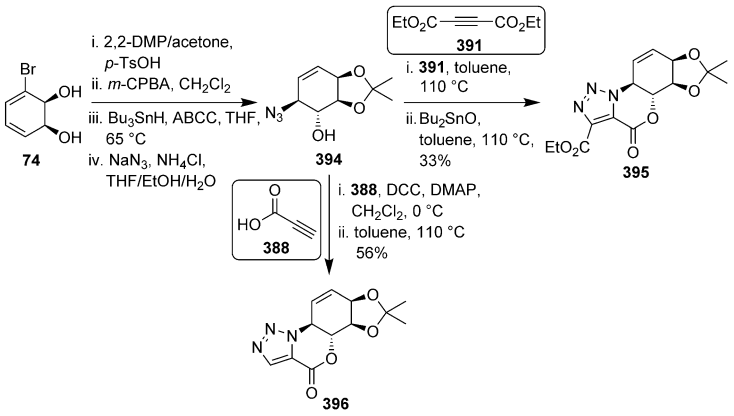
The C-1 benzoxymethylene analogue of pancratistatin **386** was subsequently tested for anti-proliferative activity and exhibited the greatest anti-cancer activity of all the unnatural analogs tested [IC_{50} for **386** for pancreatic BXPC-3 (0.01 μM), prostate DU-145 (0.01 μM), lung NCI-H460 (0.03 μM) and breast MCF-7 (0.08 μM) cancer cell lines], with potency three to five times greater than (+)-narciclasine (**3**) [IC_{50} for pancreatic BXPC-3 (0.05 μM), prostate DU-145 (0.03 μM),

lung NCI-H460 (0.05 μM) and breast MCF-7 (0.06 μM) cancer cell lines] against pancreatic and prostate cancer cell lines.[159b] This result further demonstrates the potentially beneficial effect of C-1 substitution in unnatural Amaryllidaceae analogues.

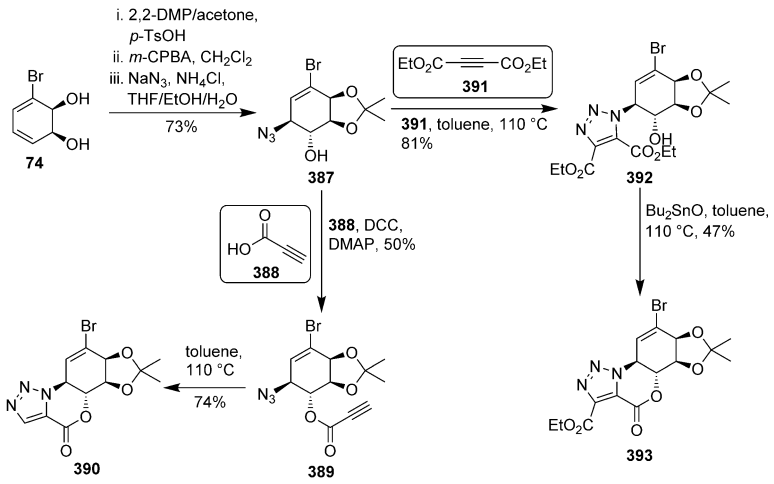
3.18. Gonzalez (2011) – A-Ring Analogues of (+)-Pancratistatin (395, 396)

Having previously worked on triazole synthesis through Huisgen cycloaddition[180] chemistry,[181] Gonzalez designed the unnatural pancratistatin/7-deoxypancratistatin analogues **395** and **396** based upon the idea that the aromatic triazole functionality could act as a surrogate for the aromatic A-ring, with the ester moiety of analogue **395** acting as a mimic for the C-7 hydroxy functionality of pancratistatin (possibly by hydrolysis to the corresponding acid).[160] Although the triazole functionality is aromatic, the differences between the A-ring of analogues **395** and **396** and the A-ring of the natural compounds are significant and it is difficult to see how the functionality of these designed analogues would effectively mimic those of the natural compounds. Similar to the syntheses by Hudlicky[11,42,45,47,49,52,60,71,81,144,147,149,151,159,162,163] and Banwell,[31a,70,74,89] the approach to analogues **395** and **396** utilized the enzymatic metabolite of bromobenzene, diol **74**, as the starting material.[57] Two routes were envisioned for the production of analogues **395** and **396**, in both of which azide **387** was used as a common intermediate. Diol **74** was protected as its corresponding acetonide before being subjected to epoxidation and the opening of the epoxide with sodium azide (Scheme 79). An intramolecular cycloaddition strategy was employed to construct the vinylic bromide **390**, involving the esterification of alcohol **387** with propiolic acid (**388**) followed by heating of the resultant ester **389** in toluene to afford **390**. In order to synthesize the vinylic bromide **393**, an intermolecular cycloaddition of azide **387** and diethylacetylenedicarboxylate (**391**) was employed to produce triazole **392**. B-ring cyclization required an intramolecular transesterification of triazole **392**, which was accomplished through the formation of a stannyl derivative, known to increase the nucleophilicity of the relevant oxygen,[182] smoothly affording brominated analogue **393**.

With the brominated analogues **390** and **393** in hand, the completion of the desired analogues **395** and **396** required only debromination. Unfortunately, all attempts of the debromination of **390** and **393**, as well as azide **387**, failed. To resolve this issue, an early stage debromination was employed (Scheme 80). The use of a new common intermediate, olefin **394**, allowed for the synthesis of the desired analogues **395** and **396**. Analogues **395** and **396** were not deprotected to the corresponding diols, nor were any biological activity data reported for these compounds.



Scheme 80. Synthesis of pancratistatin analogue **395** and 7-deoxypancratistatin analogue **396** by Gonzalez.[160]

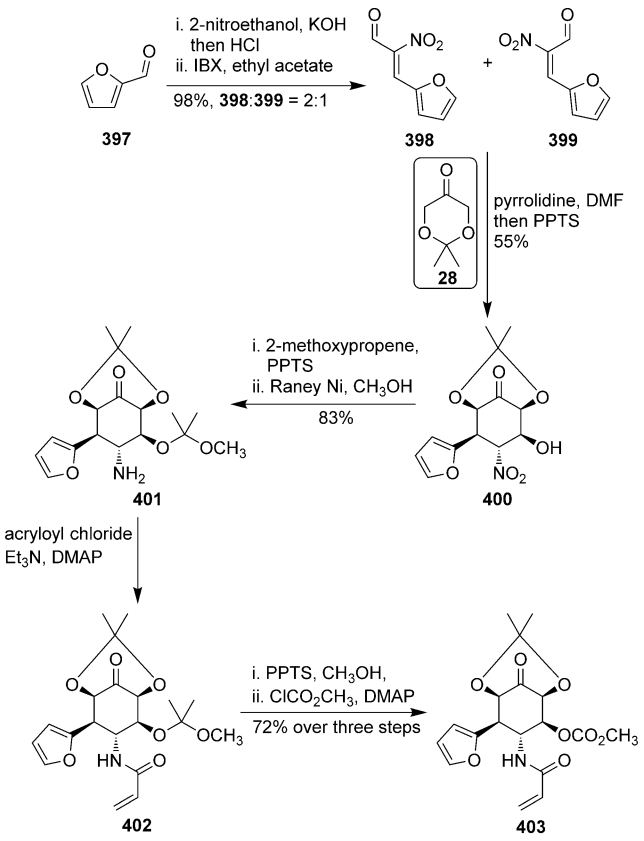


Scheme 79. Synthesis of brominated Amaryllidaceae analogues **390** and **393** by Gonzalez.[160]

3.19. Alonso (2013) – (±)-7,9-Dideoxypancratistatin (407)

Earlier in this section, a number of syntheses were discussed that were focused on truncation or modification of ring C functionalities, in an attempt to enhance the activity of natural isomers. Unfortunately, none of these approaches produced promising results, exception being the C-1 analogues prepared by Pettit[16] and Hudlicky.[159] The function of ring A in the pharmacophore has not been as well studied. In 2004, Hudlicky and co-workers synthesized A-ring modified 7,8-dideoxypancratistatin analogues.[147] It was found that this modification has reduced the anticancer activity of 7,8-dideoxypancratistatin by ten-fold as compared to (+)-7-deoxypancratistatin (**2**). [IC_{50} values in $\mu g\,mL^{-1}$, murine P388 (4.3), pancreas

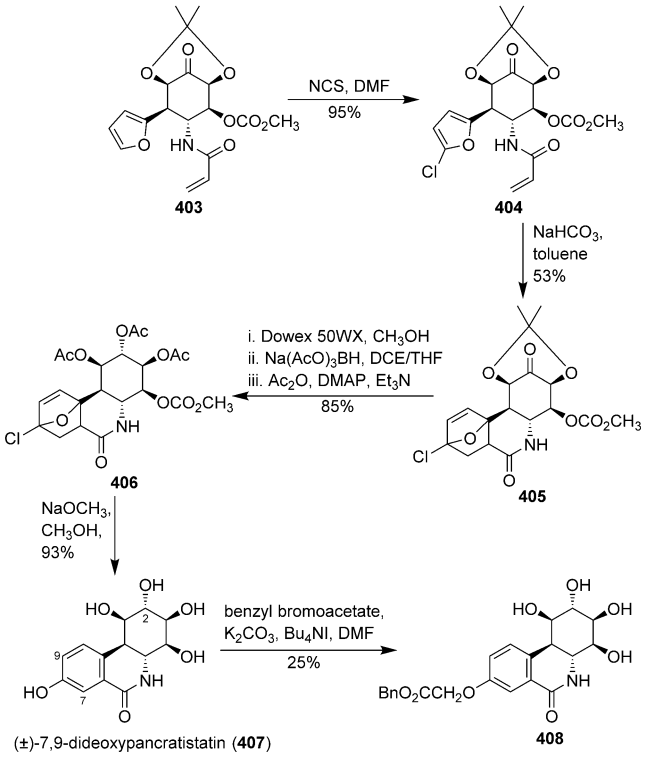
BXPC-3 (4.9), breast MCF-7 (4.4), CNS SF-268 (3.3), lung NCI-H460 (2.8), colon KM20 L2 (3.6), prostate DU-145 (2.6)]. Furthermore, in order to investigate the importance of the C-9 oxygen in the biological activity of 7-deoxypancratistatin (**2**), Alonso[161] prepared (±)-7,9-dideoxypancratistatin (**407**). The authors employed a Diels–Alder/aromatization sequence to form the 7,9-dideoxy aromatic core. The synthesis began with a Henry reaction of furfural (**397**) with 2-nitroethanol followed by oxidation with IBX to obtain a mixture of geometrical isomers **398** and **399** in the ratio 2:1 respectively (Scheme 81). The *cis*- and *trans*-mixture of



Scheme 81. Synthesis of carbonate **403** by Alonso.[161]

aldehydes **398** and **399** was treated with ketone **28** in the presence of pyrrolidine to isolate the desired ketone **400**. It is believed that compound **28** undergoes sequential Michael addition and aldol reactions with aldehyde **398**. The alcohol functionality in **400** was protected as a mixed ketal with 2-methoxypropene, and the nitro group was reduced with Raney nickel to afford amine **401**. Treatment of **401** with acryloyl chloride/Et_3N/DMAP gave access to amide **402**. The mixed ketal in compound **402** was cleaved under acidic conditions and the ensuing alcohol was protected as its methyl carbonate **403**.

In the next stage of synthesis, carbonate **403** was treated with *N*-chlorosuccinimide (NCS) in dimethyl formamide (DMF) ensuring chlorination at the α-carbon of the furan ring to obtain the chlorofuran **404** (Scheme 82). In the

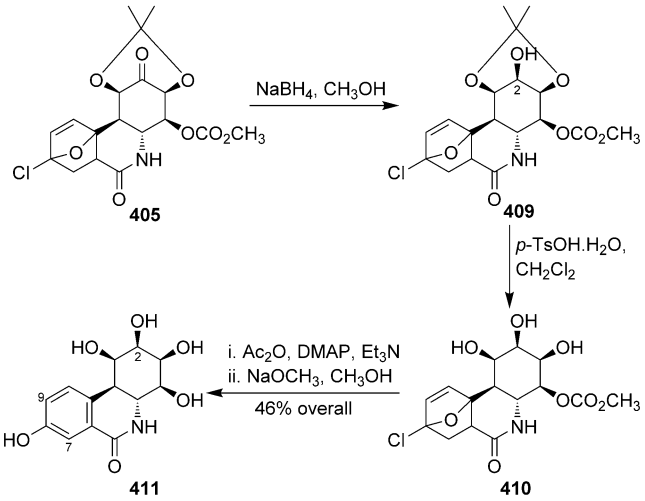


Scheme 82. Synthesis of (±)-7,9-dideoxypancratistatin (**407**) from carbonate **403** by Alonso.[161]

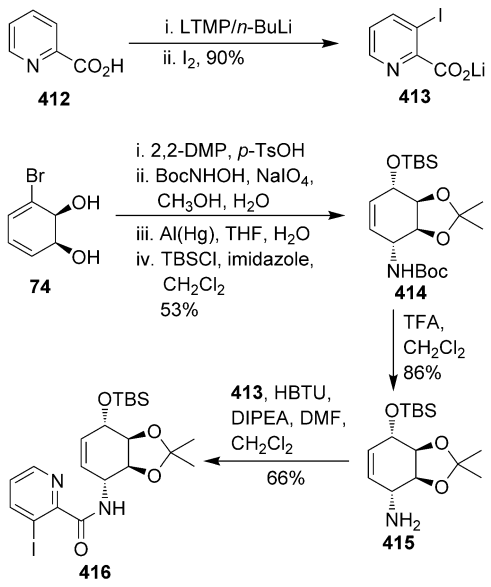
following step, a Diels–Alder reaction of the acryl amide **404** under basic conditions gave phenanthridone **405**. A three-step sequence applied to **405** involved the cleavage of the acetonide, reduction of the ketone, and acetylation of the resulting triol to furnish phenanthridone **406** in 85% yield. Finally, aromatization of ring A, and cleavage of the alcohol protecting groups in one step, were achieved by the treatment of **406** with $NaOCH_3$ in methanol furnishing (±)-7,9-dideoxypancratistatin (**407**). The phenolic functionality in (±)-7,9-dideoxypancratistatin (**407**) was later protected with benzyl bromoacetate/K_2CO_3 to yield compound **408**.

The C-2 epimer of (±)-7,9-dideoxypancratistatin (**407**) was also prepared for evaluation of the biological activity. The ketone functionality in phenanthridone **405** was reduced with sodium borohydride to afford β-alcohol **409** (Scheme 83). Treatment of compound **409** with *p*-TsOH removed the acetonide protecting group, producing triol **410**. The protection of the triol as the corresponding peracetate, and subsequent aromatization/deprotection provided (±)-2-*epi*-7,9-dideoxypancratistatin (**411**) in 46% overall yield.

When compounds **407**, **408** and **411** were tested for antiproliferative activity against a lung NCI-H460 cancer cell line, it was found that the removal of the C-9 hydroxy group resulted in a significant loss in biological activity ($IC_{50} > 30\ \mu g\,mL^{-1}$ for **407**, **408** and **411**) with respect to 7-deoxypancratistatin (**2**) ($IC_{50} = 1.57\ \mu g\,mL^{-1}$).[161] Interestingly, the benzyl acetate analogue **408** exhibited the greatest level of growth inhibition among the analogues tested (7% GI at 100 μM against a lung NCI-H460 cancer cell line).



Scheme 83. Synthesis of (±)-2-*epi*-7,9-dideoxypancratistatin (**411**) by Alonso.[161]



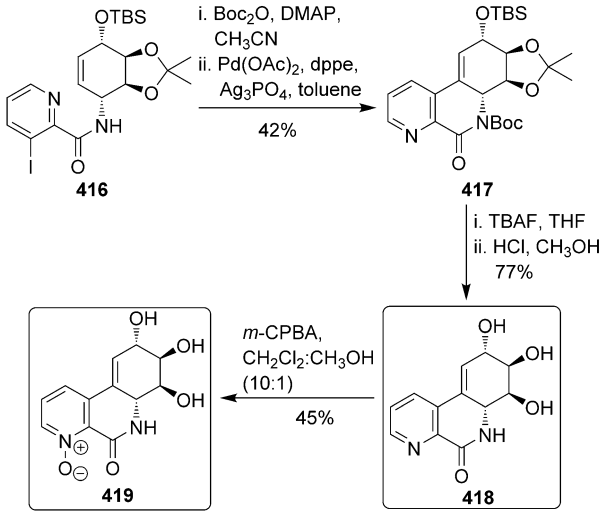
Scheme 84. Synthesis of amide **416** by Hudlicky.[162]

3.20. Hudlicky (2014) – 7-Aza-Nornarciclasine and the Corresponding N-Oxide (418, 419)

Most of the research effort aimed at unnatural analogues of Amaryllidaceae constituents has been directed towards the analogues of pancratistatin (**1**) and 7-deoxypancratistatin (**2**), as is evident from Table 8. Very few modifications of the functionality on the aromatic ring A have been reported.[41,59,147,149,151,162] None report modifications of the ring itself. Having established the importance of the C-7 hydroxy functionality for anti-cancer activity,[52,159] 7-aza-nornarciclasine analogues **418** and **419** were designed, based upon the hypothesis that the *N*-oxide moiety in compound **419** could mimic the donor-acceptor functionality of the 7-hydroxy phenanthridone moiety of natural narciclasine (**3**).[162] The strategy that was utilized in the synthesis of these analogues was based upon the coupling of conduramine **415** with the aromatic fragment **413**, followed by a Heck coupling to establish the B-ring, in a manner similar to the one applied in the synthesis of lycoricidine (**4**).[81]

The aromatic coupling partner **413** was synthesized by the directed *ortho*-metalation of picolinic acid (**412**) (Scheme 84). The free iodopicolinic acid was produced but was shown to be unstable, therefore the lithium salt **413** was utilized as the coupling partner. The C-ring conduramine **415**, previously used in the Hudlicky synthesis of (+)-lycoricidine (**4**) with minor differences in the protecting groups,[81] was prepared as a coupling partner. The enzymatic metabolite **74** was utilized as a starting material[57] and was subjected to acetonide protection followed by a hetero-Diels–Alder reaction. Reduction of the N–O bond and silyl protection of the free alcohol afforded the required conduramine. The key amide coupling of aromatic fragment **413** with the protected conduramine **414** failed, however after removal of the Boc protecting group the amide coupling of **413** and conduramine **415** was successful, affording the key intermediate amide **416**.

All of the previous approaches to the narciclasine skeleton that utilize a Heck coupling had required a protected



Scheme 85. Production of 7-aza-nornarciclasine (**418**) and its corresponding *N*-oxide (**419**) by Hudlicky.[162]

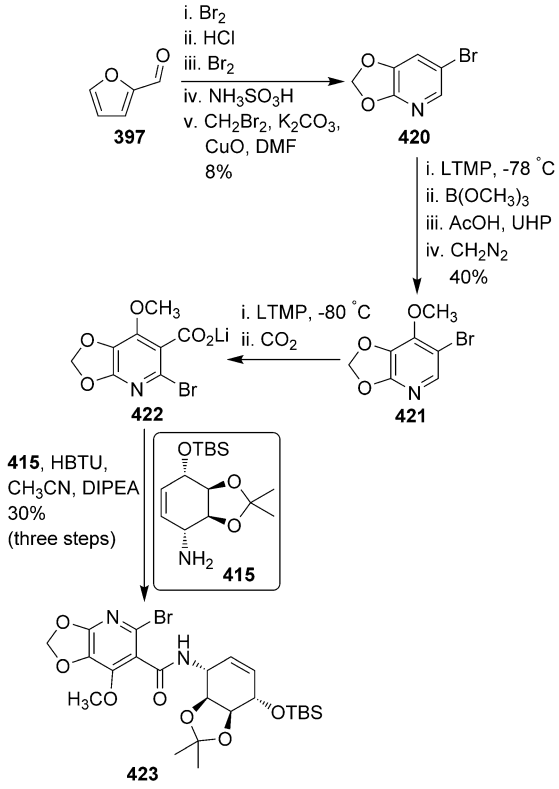
amine,[81,82,85,183] and therefore the secondary amide nitrogen of amide **416** was protected prior to the key Heck coupling step. Several conditions for the Heck reaction were screened and the desired product **417** was obtained only under the conditions shown (Scheme 85). With the coupled product **417** in hand, full deprotection afforded 7-aza-nornarciclasine (**418**). 7-Aza-nornarciclasine (**418**) was then oxidized to its corresponding *N*-oxide (**419**), and both compounds were submitted for biological testing.

Neither 7-aza-nornarciclasine (**418**) nor its *N*-oxide **419** were shown to possess any significant anti-cancer properties when tested against cervical HeLa and breast MCF7 cancer cell lines [**418** was found to be non-inhibitory for both cell lines while **419** showed $IC_{50} > 100\ \mu M$ for both cell lines; narciclasine IC_{50} MCF7 ($0.04\ \mu M$)]. The loss of biological

activity relative to natural (+)-narciclasine (**3**) can likely be attributed to the inability of the *N*-oxide to adequately mimic the 7-hydroxy functionality unit of the donor-acceptor pair inherent in the enolized β-ketoamide, and may also be the result of the lack of the methylene dioxy functionality in these compounds.

3.21. Hudlicky (2015) – 10-Aza-Narciclasine (424)

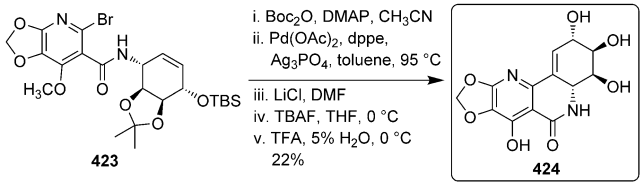
Having determined that the *N*-oxide moiety of compound **419** did not adequately mimic the donor-acceptor functionality of the C-7 hydroxy group,[162] 10-aza-narciclasine (**424**) was designed to retain the C-7 hydroxy group as well as the methylenedioxy functionality of the natural compound.[163] The strategy employed in the synthesis of 10-aza-narciclasine (**424**) was similar to that which was used in the production of 7-aza-nornarciclasine analogues and involved the coupling of the aromatic A-ring fragment **422** with conduramine **415**, followed by a Heck reaction to construct the B-ring (Scheme 86).[162,163] The synthesis of the aromatic A-ring



Scheme 86. Synthesis of amide **423** by Hudlicky.[163]

fragment **422** however, followed a significantly different pathway than that previously utilized. This process involved the production of 2,3-methylenedioxy-5-bromopyridine (**420**) from furfural (**397**) in a five step sequence by a known procedure[184] (Scheme 86). Despite the fact that the overall yield of this process was low, its simplicity allowed for the gram-scale production of 2,3-methylenedioxy-5-bromopyridine (**420**). 2,3-Methylenedioxy-5-bromopyridine (**420**) was then subjected to an *ortho*-metallation/borylation/oxidation sequence, which was followed by diazomethane methylation to afford compound **421**, the desired precursor for the key "halogen dance" reaction. The halogen dance reaction[185] proceeded smoothly with slow reverse addition of lithium tetramethylpiperidide (LTMP) at low temperature followed by methanol quench. A second deprotonation and quench with carbon dioxide was initially used to install the carboxylate functionality, however these two steps were later combined to efficiently produce nicotinic acid derivative **422**, the desired A-ring fragment. With the desired A-ring fragment in hand, nicotinic acid derivative **422** was subjected to coupling with the known conduramine **415** to afford amide **423**.

With the amide **423** in hand, the synthesis of 10-aza-narciclasine (**424**) proceeded in a similar manner to the previously discussed preparation of 7-aza-nornarciclasine (**418**).[162] This process involved Boc-protection of the amide nitrogen, followed by Heck coupling and full deprotection to afford the desired compound, 10-aza-narciclasine (**424**) (Scheme 87).



Scheme 87. Production of 10-aza-narciclasine (**424**) by Hudlicky.[163]

10-Aza-narciclasine (**424**) was tested against a panel of three cancer cell lines (human mammary carcinoma HCC1954, human T-cell leukemia Jurkat, and pancreatic carcinoma PANC-1), and was shown to have comparable activity ($EC_{50} = 193.7$ nM) to narciclasine ($EC_{50} = 173.2$ nM) against a HCC1954 cancer cell line. Whilst **424** was found to be 2 and 6 times less active than narciclasine for Jurkat and PANC-1 cell lines respectively [half maximal effective concentration (EC_{50}) for **424** Jurkat (82.9 nM), PANC-1 (1644 nM) and for narciclasine Jurkat (36.9 nM), PANC-1 (271.9 nM)] (Figure 5).

4. Future Prospects

A total of 22 unnatural derivatives of Amaryllidaceae constituents were discussed in Section 3. Modifications of natural products and studies of the biological activity profiles of the new derivatives provide key information that will prove beneficial in order to prepare new unnatural derivatives with improved anticancer activities. Shown in Figure 6 are regions of the pancratistatin pharmacophore that are essential or variable and subject to functional modifications. Similar limitations are also valid for narciclasine although much

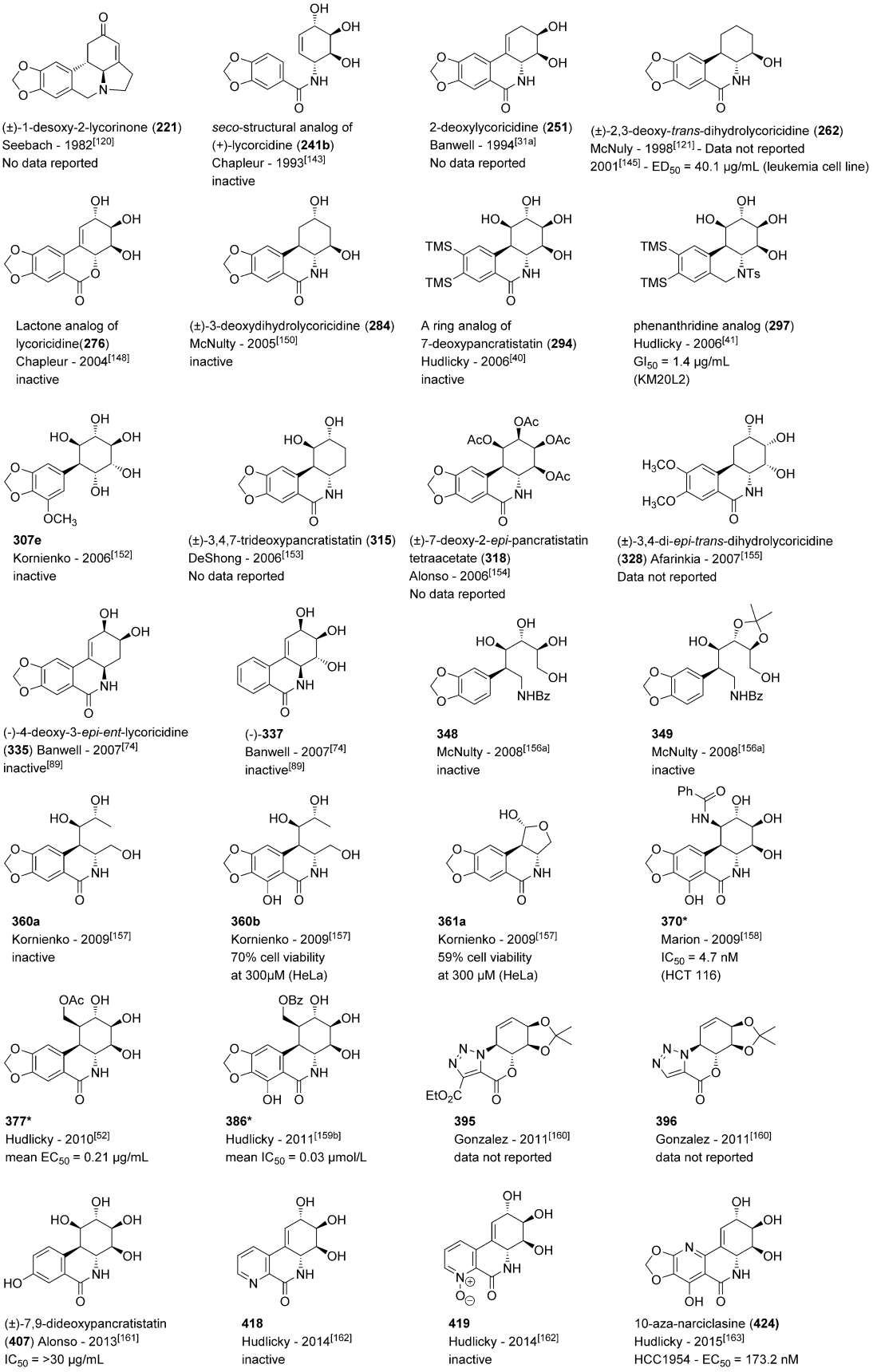


Figure 5. Summary of unnatural Amaryllidaceae analogues discussed in Section 3. * Analogue with the most potent biological activity selected as a representative example from a library of analogues produced.

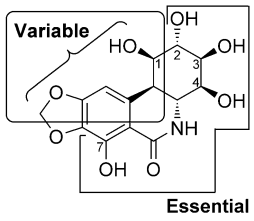


Figure 6. Essential and variable regions of (+)-pancratistatin (**1**) for structural modification.

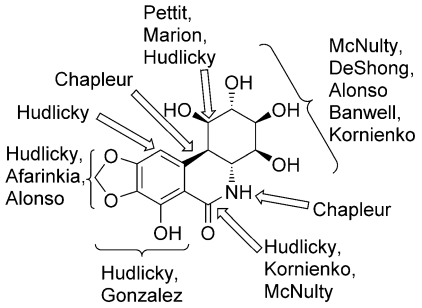


Figure 7. Pictorial representation of structural modifications of pancratistatin.

fewer modifications have been explored for this natural product as compared to pancratistatin.

The various sites of pancratistatin that have been modified are shown in Figure 7, along with the authors who had reported these structural changes as part of the search for more bioavailable derivatives.

Chapleur's compounds **241b**[143] and **276**[148] clearly indicated that the absence of C10a-C10b linkage or the replacement of N-5 with oxygen diminished the anticancer activity (Figure 5 and 7). It is necessary to mention that the investigation by Kiss[3a] and Mondon[132] has already confirmed the importance of *trans* C-4a/C-10b junction in the anticancer activity. Kornienko[152] prepared derivatives without an amide functionality (**307e**) and those compounds were found to be inactive. Additionally, McNulty's[156a] truncated B and C ring derivatives (**348**, **349**) and Kornienko's[157] truncated C ring derivatives (**360a**, **360b**, and **361a**) were also found to be inactive. These observations affirm that the intact phenanthridone core with *trans* B/C ring junction are both essential. The absence of C-2 and C-3 hydroxyls (**262**),[121] C-3 hydroxyl (**284**),[150] and C-4 hydroxyl (**335**)[74] resulted in partial or total loss of biological activity. Such observations were also reported by Kiss.[186] This suggests the necessity of free hydroxy groups on ring C and their natural configuration.

As mentioned earlier in this review, limited studies were carried out on modifications of the A ring. The C-8 and C-9 bis-silylated derivative (**294**)[40] was found to be inactive, whereas its phenanthridine analog (**297**)[41] displayed somewhat encouraging results. The absence of either C-8 oxygen[147] or C-9 oxygen (**407**)[161] or both (**337**)[74] phenolic oxygens caused complete loss of activity. The 7-aza-nornarciclasine derivatives (**418**, and **419**), which also lack the C-8, and C-9 oxygens were found to be inactive; however, the diminished activity could be attributed to the absence of the C-7 phenolic group. Marion's C-1 benzamide (**370**),[158] Pettit's C-1 benzoate (**372**)[16] as well as Hudlicky's C-1 homologue derivatives (**377**),[52] (**386**),[159b] and 10-aza-narciclasine (**424**)[163] showed better or equal anticancer activity when compared to the activities of the natural isomers.

Thus a set of suggestions may be formulated below that indicates the essential parts of the compound and provides a guide to future structural modifications that would be allowed without detriment to activity (Figure 6).

1. An intact phenanthridone skeleton with *trans* B/C junction is required.
2. All C-rings hydroxyls (C-2, C-3, and C-4) are necessary (unprotected) in their natural stereochemical configuration.
3. Unsubstituted N-5 of the phenanthridone and C-7 hydroxyl are essential.
4. The C-1 substitution is the "sweet spot" where structural modifications are possible. New compounds having C-1 heteroatoms (O, N, S, halides) bearing different functional groups (carbonate, carbamates, thioesters) may be prepared and would be expected to retain activity.
5. Additionally, compounds with a substituted phenyl ring at C-1, such as benzamide (**370**), and benzoate (**372**) may be prepared and retain activity.
6. The nitro group might also be incorporated at C-1 or in the ring A (probably at C-10).
7. The methylenedioxy functionality at C-8 and C-9 appears to be essential. Only limited studies of this region are available hence more structural modifications may be required.
8. When designing future structural modifications the solubility issues must be considered, and functionalities that improve the solubility in water should be chosen. Large lipophilic groups at C-1 have been shown not to retard activities.

In conclusion, it appears that functional manipulations in the C-1 domain of pancratistatin will be ones most likely to yield further beneficial improvements in activity and/or solubility of new derivatives.

5. Summary

It is clear from the content of this review that the total synthesis of Amaryllidaceae alkaloids, both natural and unnatural, remains a very active field of research. This research continues to be driven by the potent biological activity of these compounds, and their potential as pharmaceutical agents.[3,4a,b] Along with many impotant studies based on the semi-synthesis of Amaryllidaceae alkaloids,[67,132,133,141] the total synthesis of unnatural analogues has provided critical understanding of the structure activity relationships of these compounds and as well has led to new analogues with greater levels of biological activity.[158,159] In recent years, the

total syntheses of natural Amaryllidaceae alkaloids have also taken significant steps towards the practical production of these compounds as is evident, for example, from McNulty's nine step synthesis of (+)-*trans*-dihydrolycoricidine.[126] The efforts in total synthesis have also led to important discoveries with general and lasting chemical applications. These include the modification of the Bischler–Napieralski reaction reported by Banwell,[31] and the use of enzymatic dihydroxylations and hetero-Diels–Alder cycloadditions in the chemoenzymatic syntheses of aminocyclitols,[187] the subunits of Amaryllidaceae alkaloids.

The future developments in this area must address improvements in the practical and general means of producing the natural products and their derivatives on large scale in order to permit focused studies of their mode of action. Adjustments in the current synthetic protocols will be required in order to prepare the compounds in sufficient amount (hundreds of grams) for pharmacokinetic and toxicity studies. Perhaps the advances in flow chemistry (to our knowledge not yet applied in this area) would help in solving the supply problem. From the summary of productive modifications of the pharmacophore it would appear that the C-1 space offers the best opportunity in the search of more bioavailable and active derivatives. Given the continuing activity in this field it is reasonable to expect further advances.

Glossary

acac	acetyl acetonate
AIBN	2,2′-azobisisobutyronitrile
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOP	benzotriazolyl-*N*-oxytris(dimethylamino)-phosphonium hexafluorophosphate
BTMSA	bistrimethylsilylacetylene
Bz	benzoyl
Cbz	carbobenzyloxy
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
dba	dibenzylideneacetone
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DIPHOS	1,2-bis(diphenylphosphino)ethane
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMIPSCl	dimethylidopropylsilyl chloride
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
dppf	1,1′-bis(diphenylphosphino)ferrocen
EDCl	*N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide
HBTU	*O*-(benzotriazol-1-yl)tetramethyluronium hexafluorophosphate
HMPA	hexamethyl-phosphoramide
IBX	2-iodoxybenzoic acid
LAH	lithiumaluminium hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m-CPBA	*m*-chloroperbenzoic acid
Ms	mesyl
Moc	methoxycarbonyl
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NQ	1,4-naphthoquinone
PMB	*p*-methoxybenzyl
PMP	*p*-methoxybenzylidene
PPTS	pyridinium tosylate
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBAHS	tetrabutylammonium hydrogen sulfate
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDMS	*tert*-butyldimethylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TFA	trifluoroacteic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TMG	*N,N,N′,N′*-tetramethylguanidine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate

Note Added in Proof

Since the submission of this review the following publications on this topic have appeared: "Catalytic Enantioselective Nitroso Diels-Alder Reaction": B. Maji, H. Yamamoto, *J. Am. Chem. Soc.* **2015**, *137*, 15957; "Design, Synthesis and Structure-Activity Relationship Optimization of Lycorine Derivatives for HCV Inhibition": D. Chen, J. Cai, J. Cheng, C. Jing, J. Yin, J. Jiang, Z. Peng, X. Hao, *Sci. Rep.* **2015**, *5*, 14972, 1; Review: "Apoptosis-Inducing Effects of Amaryllidaceae Alkaloids": J. J. Nair, J. van Staden, J. Bastida, *Curr. Med. Chem.* **2016**, *23*, 161; Review: "Isocarbostyril alkaloids and their derivatives as promising antitumor agents": N. Chen, *Guangzhou Huagong* **2015**, *43*, 7 [in Chinese].

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