TRANSFORMATIONS OF ISOCARBOSTYRILS FOR THE SYNTHESIS OF ISOQUINOLINE ALKALOIDS AND THE RELATED ANALOGUES

by

YIJUN HUANG

Bachelor of Science, 2003
Nanjing University
Nanjing, China

Master of Science, 2006
Nanjing University
Nanjing, China

Submitted to the Graduate Faculty of the
College of Science and Engineering
Texas Christian University
in partial fulfillment of the requirements
for the degree of

Master of Science

August, 2008

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my research advisor, Professor David E. Minter. None of this work would have been possible without his support and guidance. His admirable personality and impressive knowledge give me a deep impression. I also wish to thank my colleagues in Dr. Minter's group, Lixin, Zhiguo and Rene. I really appreciate them for many nice help during the past two years. Second, I'd like to thank Dr. Dzyuba and Dr. Coffer for serving as my thesis committee. I am also very grateful to the faculty, staff, and students in TCU chemistry community. More importantly, their help and friendship make my two years in TCU a great memory. Finally, I appreciate all the help from my family members and friends. I extremely acknowledge my mom for her everlasting support to me. I am especially grateful to my wife, Hong, for her love and encouragement in my life.

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF SCHEMES (Cont.)

LIST OF FIGURES

1. INTRODUCTION

1.1 The Isoquinoline Alkaloids

Alkaloids are members of a group of natural products which are nitrogen-containing organic compounds.[1] Alkaloids are found in a large variety of organisms, including plants, animals, fungi, and bacteria. The chemical classification of alkaloids is based on their carbon-nitrogen skeletons.[2] Examples of well-known alkaloids (Figure 1.1) are morphine (isoquinoline group), nicotine (pyrrolidine group), quinine (quinoline group), ephedrine (phenethylamine group), and caffeine (purine group).[3] Although the widespread use of plants containing alkaloids of medicinal value dates back many centuries, the applications of alkaloids as isolated and characterized compounds started a new era of drug discovery beginning in the 19th century.[4] Many alkaloids of great therapeutic value have been discovered.[5] Since obtaining alkaloids from the natural sources in bulk quantities is very difficult, chemical synthesis provides a powerful means for solving supply problems in clinical trails and marketing. Therefore, the syntheses of alkaloids and their analogues has became one of the most active research areas in modern organic chemistry.[6]

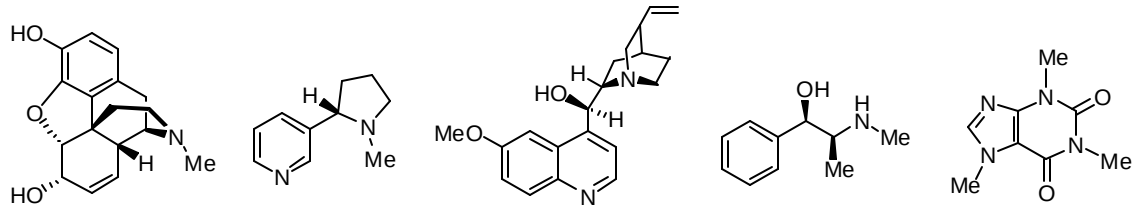


Figure 1.1 Examples of well-known alkaloids

Isoquinoline, also known as benzo[c]pyridine or 2-benzanine, consists of a benzene ring fused to a pyridine ring (Figure 1.2). It was first isolated by Hoogewerf and van

Dorp in 1885 as a constituent of coal tar.[7] It was also found in the plants *Cistanche salsa* (Orobanchaceae), *Nicotiana tabacum cv* (Solanaceae), *Papaver somniferum* (Papaveraceae), and *Spigelia anthelmia* (Loganiaceae).[8] Isoquinoline is an important structural backbone in alkaloid natural products with the total number of isoquinoline alkaloids known today amounting to *ca.* 1,200.[9] Alkaloids containing the isoquinoline ring as such or as part of a more complex ring system are not only numerous but also widely distributed.[10] Several classes of isoquinolines may occur together in plant families rich in alkaloids.

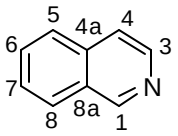


Figure 1.2 Numbering system of isoquinoline

Many isoquinoline alkaloids are of pharmacological importance exhibiting a variety of antimalarial, anti-HIV, antitumor, antimicrobial, and antibacterial activities.[11] Other than the direct application of alkaloids in practical medicine, they are also valuable as lead compounds for activity studies. During the 20th century, numerous medicinal drugs containing the isoquinoline ring system were developed. Isoquinoline derivatives of current pharmacological interest are shown in Figure 1.3. The frequent occurrence of the isoquinoline ring system in alkaloids and physiologically active compounds has led to a considerable interest in the synthesis of isoquinoline derivatives.[12]

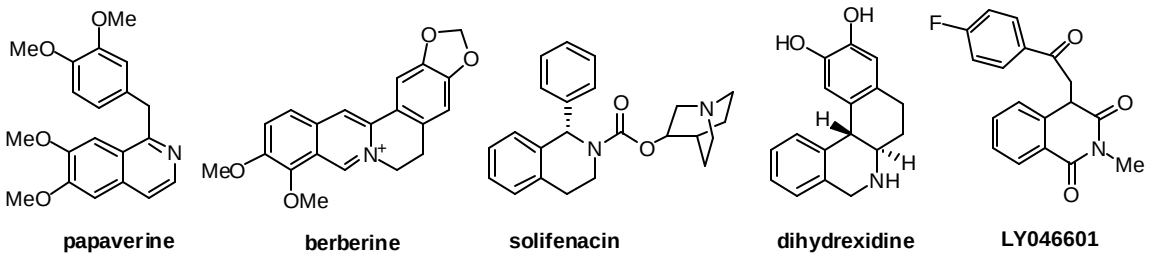


Figure 1.3 Pharmaceutical compounds containing the isoquinoline nucleus

The isoquinoline ring can be constructed by several classical methods, such as the Pictet-Spengler reaction (formation of C_1-N_2 bond), the Bischler-Napieralski reaction (formation of C_1-C_{8a} bond), the Pictet-Gams reaction (formation of C_1-C_{8a} bond), and the Pomeranz-Fritsch reaction (formation of C_4-C_{4a} bond).[13] However, the use of isoquinolines themselves as starting materials for synthesizing alkaloids and their analogues could also be advantageous. The parent molecule isoquinoline is commercially available and simple substituted isoquinolines are readily synthesized. The use of substituted isoquinolines as synthons in alkaloid synthesis is an approach that has not been adequately developed. The projects in this thesis are aimed at preparing isoquinoline synthons for the construction of alkaloid skeletons.

1.2 Current Interest in 1,3,4(2*H*)-Isoquinolinetriones

During the past two years, investigations of the 1,3,4(2*H*)-isoquinolinetrione skeleton (Figure 1.4) have attracted much research interest. Phthalonimide (R = H, Figure 1.4) is a lead-like hit identified from the high throughput screening of a library containing 22,800 organic compounds with diverse chemical structures. It was found to inhibit the enzyme caspase-3 with an IC_{50} of 0.15 μM.[14] 1,3,4(2*H*)-Isoquinolinetrione derivatives have a variety of biological activities and are synthetic precursors for several types of naturally occurring alkaloids.

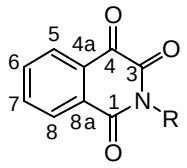


Figure 1.4 The 1,3,4(2*H*)-isoquinolinetrione skeleton

The synthetic isoquinolinetrione derivative **1** is highly potent in inhibiting caspase-1 activity in an irreversible and slow-binding manner. This broad-spectrum inhibitor may

provide a novel therapeutic approach to the treatment of certain inflammatory diseases.[15] The semicarbazide derivative **2** prepared from phthalonimide shows good binding affinity toward oxytocin receptors (K_i = 1.6 nM) and a high selectivity toward vasopressin receptors (K_i = 730 nM).[16] Amino substituted derivatives of **3** have been found to be active as herbicides due to their efficient redox mediation of photosystem I.[17a] Compound **4a** appears to have the free-radical properties that could enhance the generation of superoxide radicals in plants.[17b] The herbicidal activity of the (*E*)-*O*-methyl oxime **5** was found to be greater than that of the parent trione **3**.[18]

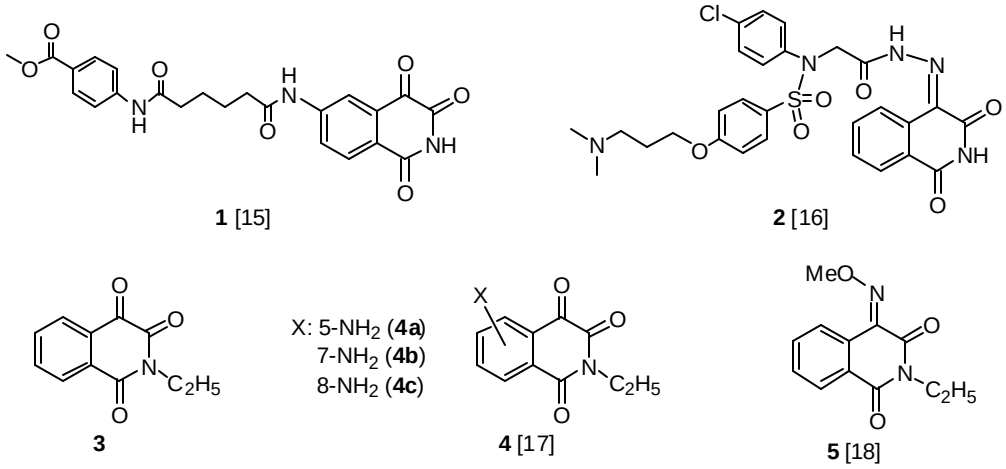
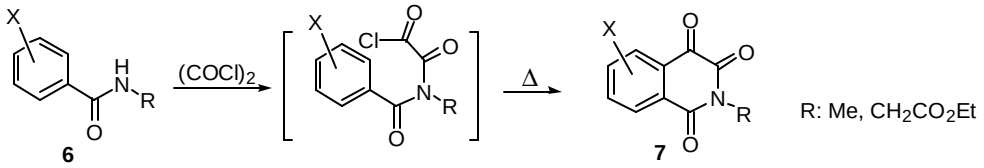


Figure 1.5 1,3,4(2*H*)-Isoquinolinetrione derivatives of biological interest

1.2.1 Preparation of 1,3,4(2*H*)-Isoquinolinetriones

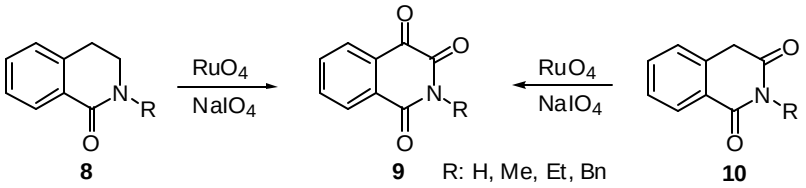
Isoquinolinetriones have become increasingly interesting not only because they have shown promising biological activity but also because they are potential precursors to synthetic alkaloids. Some isoquinolinetriones can be prepared from the corresponding secondary benzamides, as shown in Scheme 1.1. The reactions of appropriate benzamides **6** and oxalyl chloride lead to *N*-aroyloxamoyl chlorides. These isolable intermediates undergo cyclization upon heating to give **7** when the group X is an activating group such as an alkoxy substituent.[19]

Scheme 1.1 Isoquinolinetriones from benzamides and oxalyl chloride



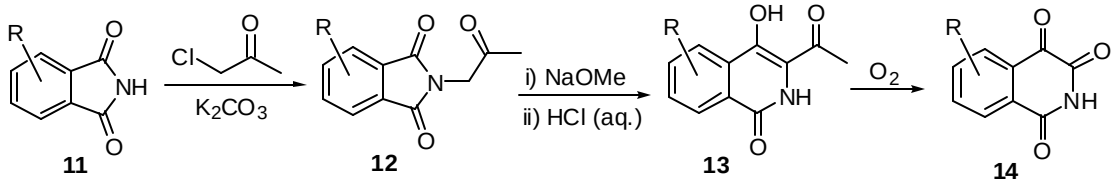
1,3,4(2*H*)-Isoquinolinetriones **9** can also be obtained by oxidations of 3,4-dihydro-isoquinolin-1(2*H*)-ones **8** and homophthalimides **10** (Scheme 1.2). These oxidations proceed in high yields by using a catalytic amount of ruthenium tetroxide with an excess of sodium periodate in an EtOAc/H_2O two-phase system.[20] In the case of *N*-alkyl derivatives having two oxidation sites adjacent to the nitrogen atom, the regioselective endocyclic oxidation was observed.

Scheme 1.2 Isoquinolinetriones from the RuO_4-$NaIO_4$ oxidation system



Phthalimides can be transformed into isoquinolinetriones through the steps shown in Scheme 1.3.[21] Phthalimides **11** are easily alkylated with chloroacetone and ring expanded in the presence of excess sodium methoxide to give 4-hydroxyisocarbostyrils **13**. The isoquinolinetriones **14** are be obtained from **13** in a suitable solvent using air to effect an oxidative deacylation.

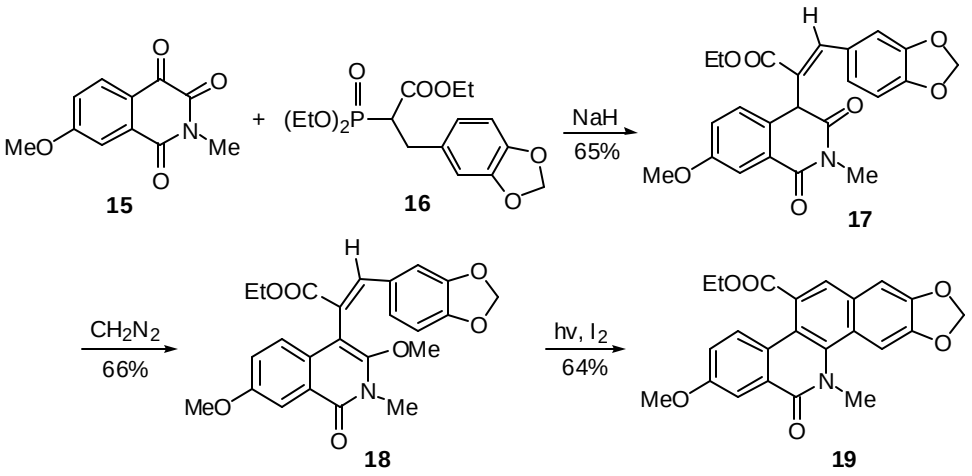
Scheme 1.3 Synthetic route of isoquinolinetrione from phthalimide



1.2.2 Synthesis of Alkaloids via 1,3,4(2*H*)-Isoquinolinetrione Precursors

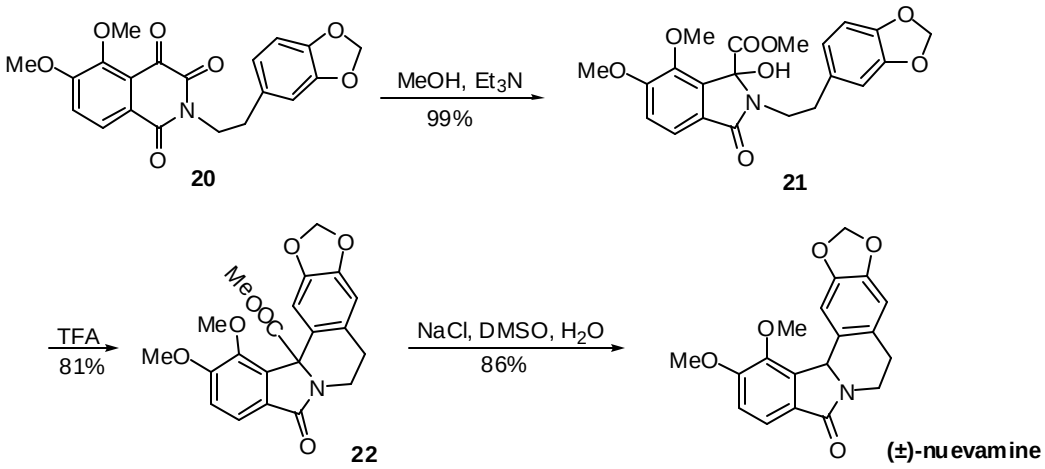
The *N*-methylisoquinolinetrione **15** has been used in the concise synthesis of the phenanthridinone alkaloid **19** as shown in Scheme 1.4.[22] The reaction of **15** with the phosphonate **16** yields a 4-functionalized isoquinoline derivative **17**. Methylation with diazomethane followed by oxidative photocyclization affords the benzo[c]phenanthridone **19**. Isoquinolinetrione plays an important role as the key intermediate in this convenient synthetic route.

Scheme 1.4 Synthesis of phenanthridine alkaloids from isoquinolinetrione



A facile synthesis of the natural product (±)-nuevamine has been described using the *N*-homopiperonyl-1,3,4-isoquinolinetrione **20** as a key intermediate.[23] The base-catalyzed alcoholysis of **20** using triethylamine and methanol led to a completely regioselective ring contraction process affording the lactamol **21** in quantitative yield. An acid-catalyzed intramolecular cyclization of **21** gave **22**. As expected, the decarboxylation of the angular carbomethoxy function gave the alkaloid (±)-nuevamine (Scheme 1.5).

Scheme 1.5 Synthesis of (±)-nuevamine



1.3 Synthesis of Galanthan Skeleton via [4+2] Cycloaddition Approach

Lycorine-type alkaloids characterized by a pyrrolo[d,e]phenanthridine skeleton **23** (galanthan tetracyclic system) represent an important subclass in *Amaryllidaceae* alkaloids.[24] These compounds including lycorine (**24**) possess potent biological activities such as antiviral, antineoplastic, and insect antifeedant activity as well as plant growth inhibition and disruption of protein synthesis.[25] Therefore, considerable effort has been devoted to the development of efficient synthetic approaches to these alkaloids and the galanthan backbone.

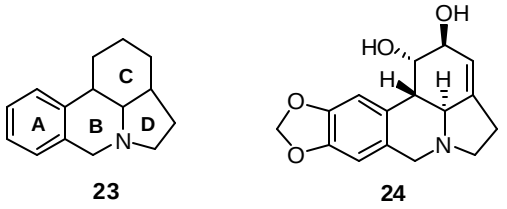
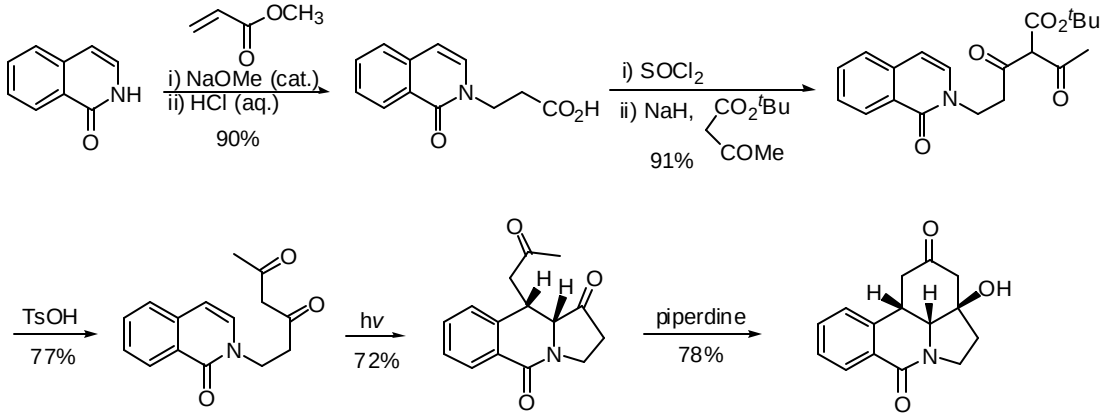


Figure 1.6 Skeleton of lycorine-type alkaloids

Our group's research interests focus on the development of synthetic methodology for the total syntheses of *Amaryllidaceae* alkaloids and their precursors starting from an isoquinoline nucleus. An approach to the galanthan skeleton based on the intramolecular

de Mayo reaction has been developed recently (Scheme 1.6).[26] Since the Diels-Alder reaction has proven to be a key step in the synthesis of many tri- and tetracyclic natural products,[27] an approach to the galanthan skeleton based on the [4+2] cycloaddition is also worthy of attention.

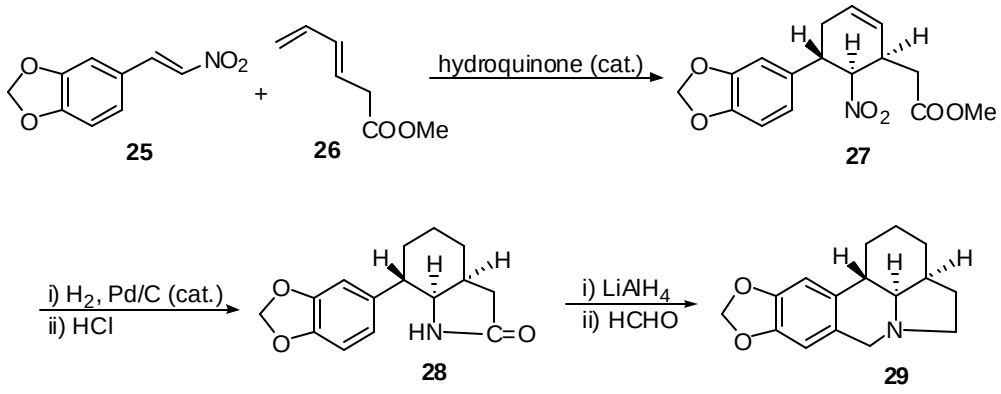
Scheme 1.6 Photochemical approach to the galanthan ring system



1.3.1 Intermolecular Approach

The most common procedures for the synthesis of **23** involve the formation of the B-ring at a late stage. Strategies for preparing the tetracyclic ring system are of the general types A=>C=>B=>D and A=>C=>D=>B.[24] For example, the intermolecular Diels-Alder reaction has been used to construct *a*-lycorane in a stereospecific manner (Scheme 1.7).[28]

Scheme 1.7 Stereoselective synthesis of *d, l-a*-lycorane

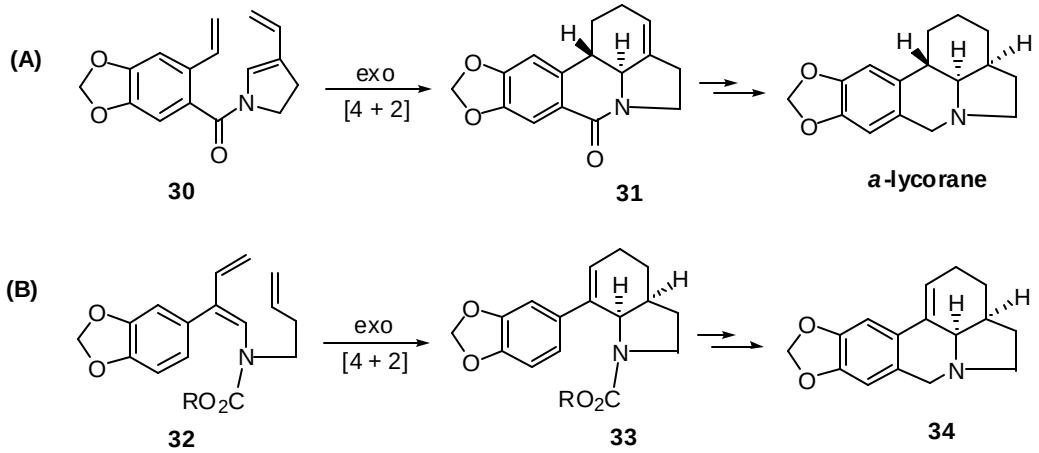


The cycloaddition of 3,4-methylenedioxy-ß-nitrostyrene (**25**) and methyl hexa-3,5-dienoate (**26**) gave a moderate yield of the adduct **27** as a single diastereomer: (i) the *trans* geometry of the ß-nitrostyrene was preserved; (ii) the adduct has the nitro group *cis* to the diene substituent in a 1,2-relationship. The subsequent catalytic hydrogenation was accompanied by a spontaneous ring closure to give the lactam **28**. The reduction of **28** to the amine with lithium aluminum hydride and final closure of the B-ring using a Pictet-Spengler reaction completed the synthesis of **29**.

1.3.2 Intramolecular Approach

The intramolecular Diels-Alder reaction has played a key role in the synthesis of the galanthan skeleton in the lycorine family. The advantage is that this strategy can close two rings at the same time. Stork's group constructed a connection between the A and D rings via an amide link.[29] The triene **30** cyclized in 51% yield to give only the *trans*-fused isomer **31** (Scheme 1.8A). In this case, the constraints imposed by the planarity of the amide system were such that only the exo transition state could be reasonably expected.

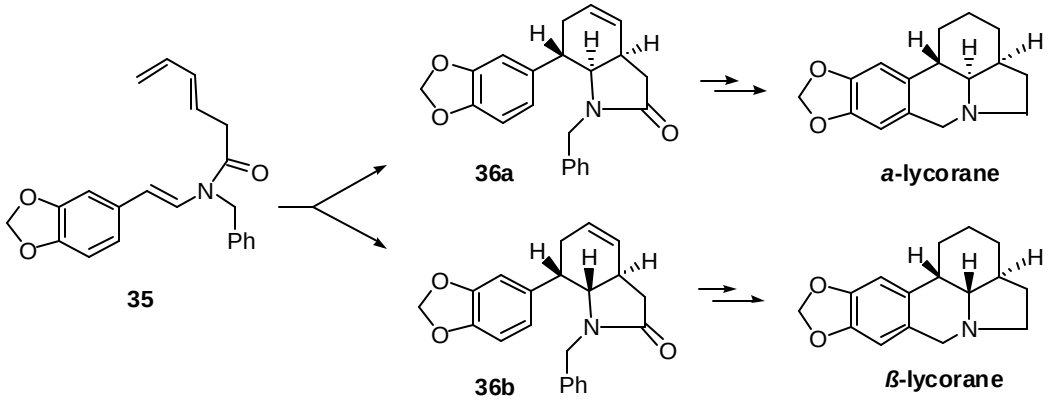
Scheme 1.8 Stereoselective synthesis of galanthan ring system



Magnus's group developed another stereospecific approach by using an alternative triene **32** (Scheme 1.8B).[30] The stereochemical outcome of the cyclization reaction was controlled by the geometry of the diene. The conversion of **33** into (±)-1,12b-didehydro-lycorane (**34**) to used to verify the *cis*-stereochemistry of the CD-ring fusion.

More interesting, Martin's group developed the intramolecular [4+2] cycloaddition as a general strategy for synthesizing lycoranes (Scheme 1.9).[31] The aryl-substituted enamido diene **35** was produced by thermal, cheletropic extrusion of sulfur dioxide from its dihydrothiophene dioxide precusor. The mixture of *cis*- and *trans*-hydroindoles **36a** and **36b** in a ratio of 1 to 1.5, respectively, was obtained in 45-50% yield. The structures were convincingly established by their eventual conversion to *a*-lycorane and *ß*-lycorane, respectively.

Scheme 1.9 Martin's approach to galanthan ring system



2. RESULTS AND DISCUSSION

2.1 Synthesis of the Alkaloid 1,3,4(2*H*)-Isoquinolinetrione and Its Analogues

2.1.1 Synthesis of *N*-Methyl-1,3,4(2*H*)-isoquinolintriones

Recently, 6,7-dimethoxy-*N*-methyl-1,3,4(2*H*)-isoquinolintrione (Figure 2.1) was isolated from the roots of *Menispermum dauricum* (Menispermacese).[32] This plant is known in Chinese medicine as Bei-Dou-Gen, which is used for treating sore throats, colitis, dysentery, and rheumatic arthralgia. Following column chromatography on silica gel and Sephadex LH-20, 28 mg of the alkaloid was separated from 5.0 kg of *M. dauricum* roots. To date, no biological studies have been conducted on this compound.

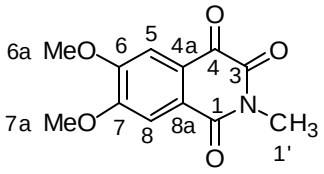
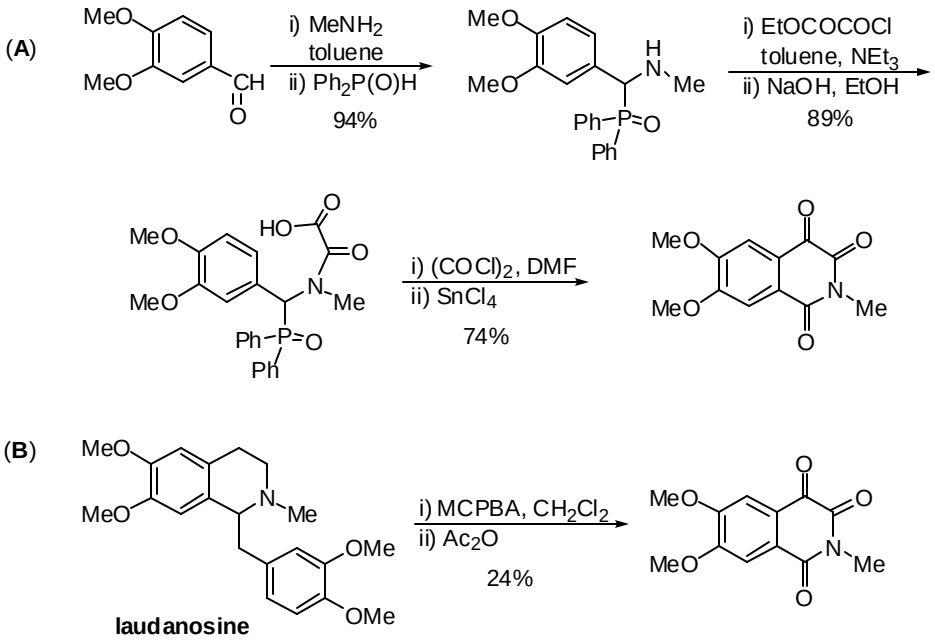


Figure 2.1 1,3,4(2*H*)-Isoquinolinetrione in *Menispermum dauricum*

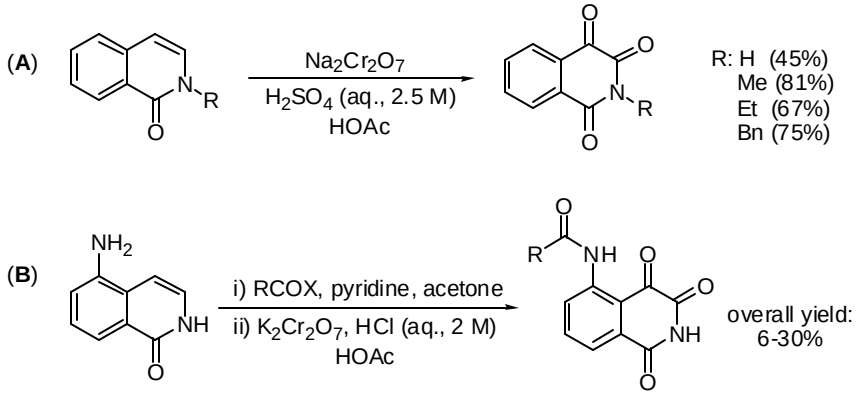
There are two examples of known methods to synthesize **42b**, as shown in Scheme 2.1. Method A starts with veratraldehyde and produces **42b** in an overall yield of 62%.[33] In the last step, Friedel-Crafts ring closure and oxidation of the phosphorylated oxalamic acid occur spontaneously. Method B involves the oxidation and Polonovski reaction of (±)-laudanosine. Laudanosine, when treated with *m*-chloroperbenzoic acid (MCPBA) followed by acetic anhydride, yields **42b** in an overall yield of 24%.[34] However, there is still ample room to develop a practical method for the synthesis of alkaloid **42b** and its analogues.

Scheme 2.1 Known methods for the synthesis of 42b



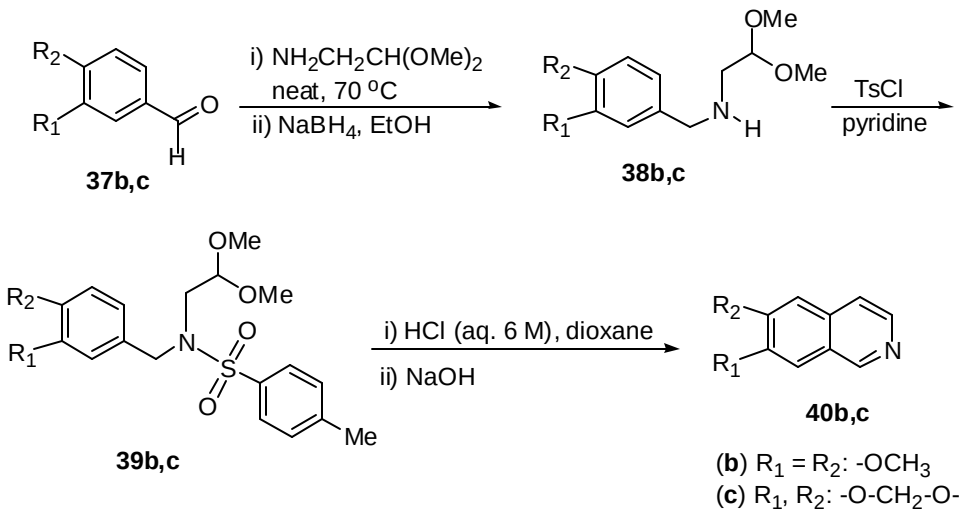
Meanwhile, the direct oxidation of isocarbostyrils to 1,3,4(2*H*)-isoquinolinetriones attracted our attention (Scheme 2.2). It is known that isocarbostyrils can be oxidized by sodium dichromate or potassium dichromate.[14, 35] The real oxidizing agent, chromic acid, is generated *in situ* by treatment of sodium or potassium dichromate with aqueous acid. The active oxidant under these conditions is probably the bichromate ion ($HCrO_4^-$), but a detailed mechanism for this transformation has not been elucidated.[36]

Scheme 2.2 Oxidation of isocarbostyrils



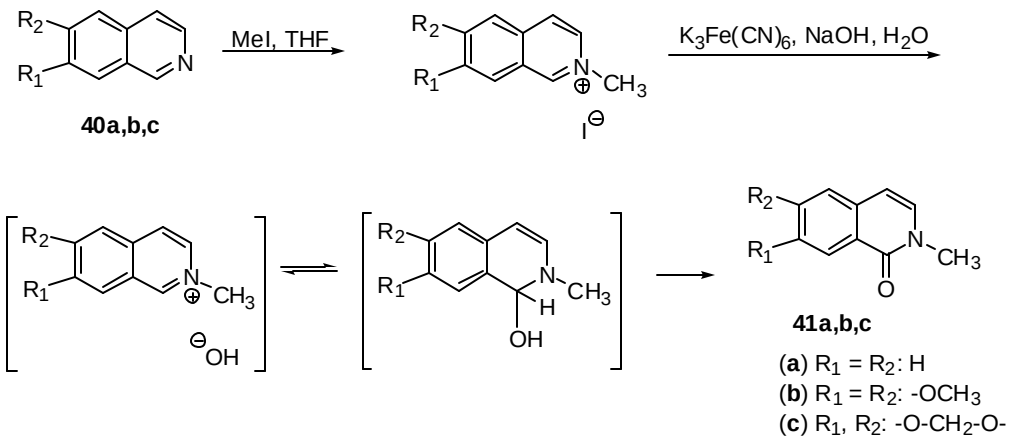
Inspired by this methodology, we set out to synthesize the target alkaloid **42b** and its analogues starting from isocarbostyrils since our group has successfully developed the preparation of isocarbostyrils from the corresponding isoquinolines.[37] The precursor 6,7-disubstituted isoquinolines, backebergine (**40b**) and papraline (**40c**), occur commonly in natural alkaloids.[8] Both **40b** and **40c** were synthesized following Birch's procedure in overall yields of 79% and 87%, respectively, from the corresponding substituted benzaldehydes **37b** and **37c** (Scheme 2.3).[38] The tosylation of **38b** and **38c** gave the corresponding tosylates **39b** and **39c**, which affords the isoquinolines directly.

Scheme 2.3 Synthesis of 6,7-substituted isoquinolines



Both doryphornine methyl ether (**41b**) and doryanine (**41c**) are widely distributed in several families of plants and available in large amounts.[8] There are numerous ways to synthesize this type of isocarbostyril derivative.[39] We prepared *N*-methylisocarbostyrils **41a-c** using the standard ferricyanide oxidation of the corresponding isoquinoline salts, which could be obtained in nearly quantitative yields from isoquinolines (Scheme 2.4).[40] These salts were dissolved in water and oxidized using potassium ferricyanide under alkaline conditions. *N*-Methylisocarbostyrils **41a-c** were be prepared in overall yields ranging from 69 to 92% from the corresponding isoquinolines **40a-c**.

Scheme 2.4 Synthesis of *N*-methylisocarbostyrils



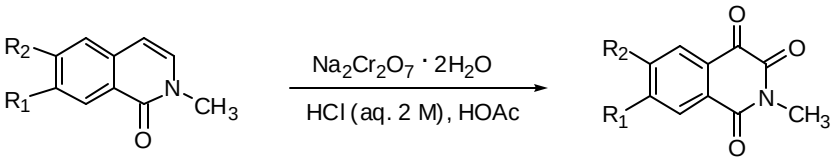
40a,b,c

41a,b,c

(**a**) $R_1 = R_2$: H
(**b**) $R_1 = R_2$: -OCH_3
(**c**) R_1, R_2: -O-CH_2-O-

We found that isoquinolinetriones **42** can be produced in excellent yields from the oxidation of the isocarbostyril precursors **41** (Scheme 2.5). Acetic acid served as the most suitable solvent to make a homogeneous reaction system. The starting materials **41a-c** were consumed completely after stirring overnight at room temperature in the oxidizing medium. *N*-Methyl-1,3,4(2*H*)-isoquinolintriones **42a-c** were isolated in yields of 82-90% from the corresponding *N*-methylisocarbostyrils **41a-c**.

Scheme 2.5 Synthesis of *N*-methylphthalonimides



41a,b,c

42a,b,c

(**a**) $R_1 = R_2$: H
(**b**) $R_1 = R_2$: -OCH_3
(**c**) R_1, R_2: -O-CH_2-O-

The structures of **42a-c** were supported by NMR data including HMQC and HMBC spectra to confirm all proton and carbon assignments (as shown in the experimental section, pp 36-40). The HMBC spectra of **42b-c** allowed for unambiguous assignments of all three carbonyl carbons and all six aromatic carbons using 3-bond

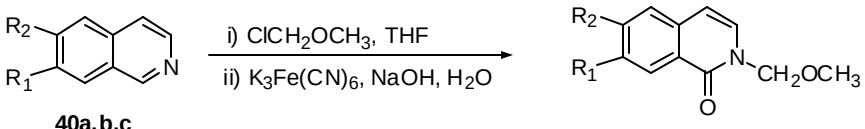
connectivity peaks. Our methoxy methyl carbon and proton assignments determined in d_6-DMSO solvent are both reversed from the literature assignments determined in a mixture of $CDCl_3$ and CD_3OD (1:1).[32]

2.1.2 Synthesis of Phthalonimides

Encouraged by this result, we turned our attention to the synthesis of phthalonimide derivatives using the same strategy. The interest in these compounds based on current investigations of their biological activities increases the significance of developing a practical method for synthesizing phthalonimides.[14] Therefore, we continued our quest to synthesize phthalonimides starting from known isoquinolines through the intermediacy of isocarbostyrils in keeping with our general design philosophy.

Isocarbostyrils **44** were prepared in three steps from the isoquinolines **40**.[37] In the beginning, *N*-methoxymethyl (MOM) substituted isocarbostyrils **43** were synthesized in high yield from isoquinolines **40** (Scheme 2.6). An excess amount of methoxymethyl chloride was used, and the residual was removed *in vacuo*. *N*-MOM-isocarbostyrils **43a-c** were obtained in overall yields ranging from 70 to 95% and could be used in the next step without further purification.

Scheme 2.6 Synthesis of *N*-MOM-isocarbostyrils



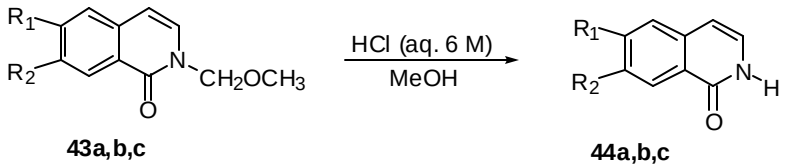
40a,b,c **43a,b,c**

(**a**) $R_1 = R_2$: H
(**b**) $R_1 = R_2$: -OCH_3
(**c**) R_1, R_2: -O-CH_2-O-

The third step of the sequence involved deprotection of the amide nitrogen with 6 M aqueous HCl in methanol (Scheme 2.7). Isocarbostyrils **44a-c** were obtained in yields of

74-88% after refluxing for a suitable time as determined by TLC monitoring to follow the disappearance of the starting materials. Although the use of methanol as a co-solvent prevented the decomposition of the products to some extent, **44b** proved particularly labile with by-products appearing after only 8 hours of reflux.

Scheme 2.7 Synthesis of isocarbostyrils

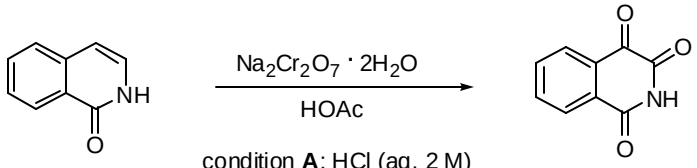


43a,b,c **44a,b,c**

(**a**) $R_1 = R_2$: H
(**b**) $R_1 = R_2$: -OCH_3
(**c**) R_1, R_2: -O-CH_2-O-

As a model study, the first attempt to synthesize the phthalonimide **45a** involved the direct oxidation of isocarbostyril (**44a)** (Scheme 2.8). The reaction mixture was stirred for two days at room temperature. However, only a 17% yield of **45a** could be isolated by chromatography under condition A (sodium dichromate in 2M HCl). Under condition B (sodium dichromate in 3 M H_2SO_4), a 34% yield of **45a** was obtained in agreement with a reported result.[35] Compared to *N*-methylisocarbostyril, isocarbostyril (**44a**) appeared to be much less active under the same condition for this oxidation process.

Scheme 2.8 Direct oxidation of isocarbostyril



44a

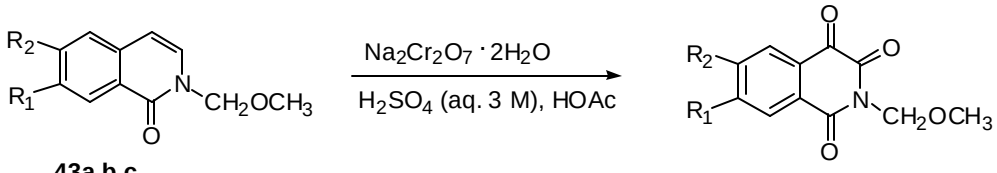
condition **A**: HCl (aq. 2 M)
condition **B**: H_2SO_4 (aq. 3 M)

45a

Therefore, the reaction sequence was revised by reversing the last two steps. We used the *N*-MOM substituted isocarbostyrils **43** as the substrates for the oxidation process and

removed the protecting group in the last reaction. Following the same procedure as for the synthesis of **42b**, the oxidation of **43b** was investigated first under condition A (sodium dichromate in 2 M HCl). The starting material was almost completely consumed after 18 hours to give **46b** and a small amount of the deprotected product **45b**, which could be detected by ^{1}H NMR spectra. Surprisingly, the oxidation of **46b** was complete after only 15 minutes under condition B (sodium dichromate in 3M H_2SO_4), and the deprotected product **45b** was not detected unless the reaction was stirred for a much longer time. As shown in Scheme 2.9, the *N*-MOM substituted isoquinolintriones **46a-c** can be prepared easily in yields of 72-82% from **43a-c** under condition B. Apparently, an alkyl substituent on nitrogen, whether it be methyl or MOM, is necessary for high yields in this oxidation reaction.

Scheme 2.9 Synthesis of *N*-MOM-phthalonimides

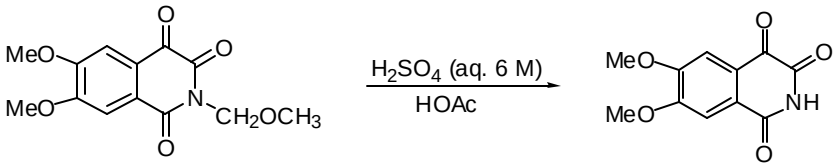


43a,b,c → **46a,b,c**

(**a**) $R_1 = R_2$: H
(**b**) $R_1 = R_2$: -OCH_3
(**c**) R_1, R_2: -O-CH_2-O-

The last step involved the removal of the MOM group in **46a-c**. The procedure used for the deprotection of **43** (6 M HCl in methanol) resulted only in the recovery of the starting materials. The reaction of **46** under harsher conditions in concentrated HCl and methanol gave a mixture of decomposition products. An alternate procedure[41] using a mixture of 6 M sulfuric acid and acetic acid to remove the MOM group was successful for converting **46b** into **45b**. However, both **46a** and **46c** decomposed when refluxed with 6 M H_2SO_4 and acetic acid. As shown in Scheme 2.10, **45b** was obtained in 85% yield after refluxing for 15 hours. The reaction time was critical since **45b** also decomposed when the reflux period was extended to 24 hours.

Scheme 2.10 Deprotection of *N*-MOM-phthalonimides

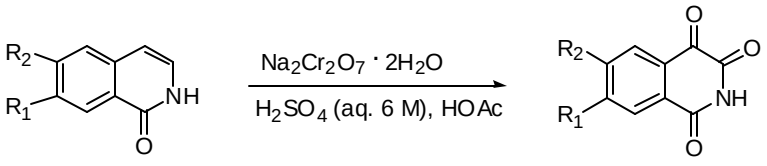


46b **45b**

We also attempted other methods for the removal of the MOM group in **46a** and **46c**. Both boron tribromide and boron trichloride in dichloromethane[42] at -78 ºC failed due to extensive decomposition. The treatment of **46c** with 3 M H_2SO_4 in trifluoroacetic acid at reflux gave a small amount of **45c** after 24 hours, but extensive decomposition ensued after that time.

Since **45b** was relatively stable in the mixture of 6M H_2SO_4 in acetic acid even at reflux for short reaction times, we examined the direct oxidation of isocarbostyrils using sodium dichromate in 6M H_2SO_4 and acetic acid at overly extended reaction times at room temperature. Recall that condition B resulted in only a 34% conversion after 2 days at room temperature of **44a** to **45a**. However, as shown in Scheme 2.11, **45a** was obtained in 80% yield without decomposition after stirring for 3 days at room temperature. Both **45b** and **45c** were synthesized following the same procedure in yields of 68% and 27%, respectively. For a reason that is not obvious, **44c** appeared to be much less soluble in the mixture of 6 M H_2SO_4 and acetic acid; and this is probably the cause of the poor yield.

Scheme 2.11 Synthesis of phthalonimides

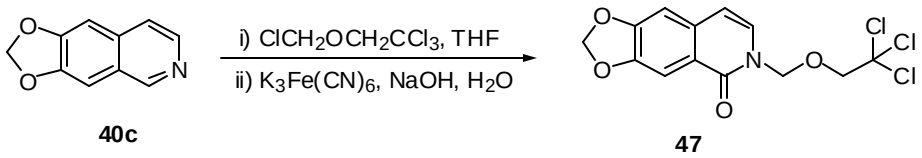


44a,b,c **45a,b,c**

(**a**) $R_1 = R_2$: H
(**b**) $R_1 = R_2$: -OCH_3
(**c**) R_1, R_2: -O-CH_2-O-

Since **45c** is produced only in low yield by direct oxidation of **44c** and cannot be prepared by removal of the MOM group of **46c**, a strategy using a different protecting group was devised. The 2,2,2-trichloroethoxymethyl (TceOM) group, was used to replace the MOM group on nitrogen. Although 2,2,2-trichloroethyl chloromethyl ether is not commercially available, it can be prepared from 2,2,2-trichloroethanol, paraformaldehyde and gaseous hydrogen chloride.[43] The *N*-TceOM substituted isocarbostyril **47** was obtained in an overall yield of 62% from **40c** (Scheme 2.11).[37]

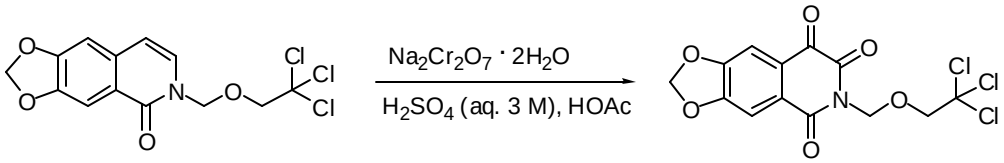
Scheme 2.12 Synthesis of *N*-TceOM-isocarbostyril



40c **47**

Following the procedure for the synthesis of **46**, the oxidation of **47** to **48** was also unsatisfactory under condition A (sodium dichromate in 2M HCl) because of the deprotection of the product. It proceeded in 87% yield after stirring for 1 hour under condition B (sodium dichromate in 3M H_2SO_4), as shown in Scheme 2.13.

Scheme 2.13 Synthesis of *N*-TceOM-phthalonimide

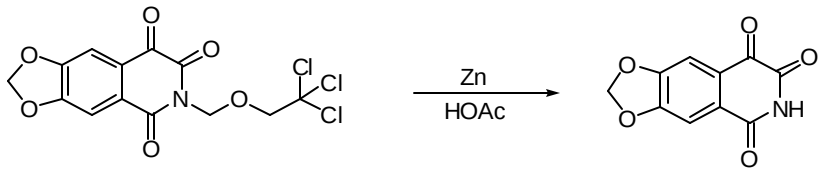


47 **48**

In the final step, the TceOM group in **48** was successfully removed by reductive cleavage with activated zinc dust in glacial acetic acid at reflux for 15 hours. As indicated in Scheme 2.14, **45c** was isolated by column chromatography in 64% yield. The use of potassium acetate as an additive gave a mixture of decomposition products,[44] and adding

methanol or dichloromethane as a co-solvent also failed to increase the yield. Similar to the case of **46c**, the deprotection of **48** using a mixture of 3M H_2SO_4 and acetic acid was also unsuccessful.

Scheme 2.14 Deprotection of *N*-TceOM-phthalonimide



48 **45c**

In conclusion, we have demonstrated a practical method of synthesis for *N*-methyl phthalonimides. Two new methods for synthesizing substituted phthalonimides from the corresponding isocarbostyrils have also been developed. Phthalonimide derivatives were obtained by the oxidation of isocarbostyrils protected with MOM and TceOM groups. The direct oxidation of isocarbostyrils under different conditions was also investigated. These new methods as well as the phthalonimide derivatives themselves could be applied to the syntheses of alkaloids or other bioactive targets in the future.

2.2 Synthesis of the Galanthan Skeleton via the [4+2] Cycloaddition Approach

According to frontier molecular orbital theory, the Diels-Alder reaction is controlled by the suprafacial *in phase* interaction of the highest occupied molecular orbital (HOMO) of one component and the lowest unoccupied molecular orbital (LUMO) of the other.[45] The closer these orbitals are in energy, the lower the transition state energy of the reaction (Figure 2.2). Normal electron-demand Diels-Alder reactions are accelerated by electron-donating substituents on the diene and by electron-withdrawing substituents on the dienophile, while inverse electron-demand Diels-Alder reactions are influenced by electronic effects in the opposite direction.

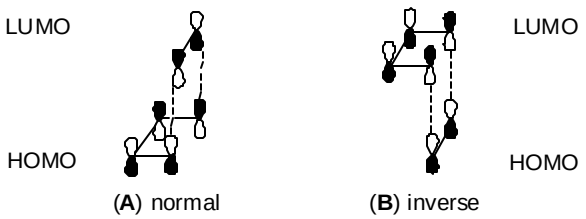
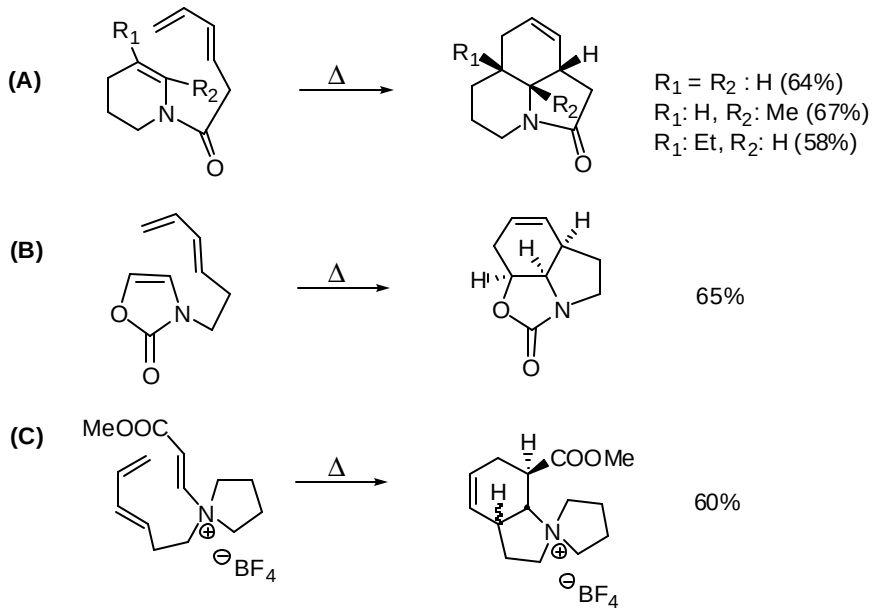


Figure 2.2 Symmetry-allowed [4+2] cycloadditions

The most fascinating feature of this intramolecular [4+2] cycloaddition is its ability to form two rings in a single step. Such [4+2] cycloadditions using unactivated dienes and enamides as dienophiles have been developed (Scheme 2.15). Example A illustrates the intramolecular Diels-Alder approach to hydroquinolines as a general method to prepare alkaloid backbone structures.[46] Reaction B demonstrates the use of an *N*-substituted oxazolone as a dienophile in an intramolecular Diels-Alder process.[47] Example C verifies the use of alkenylammonium salts in an intramolecular Diels-Alder reaction.[48]

Scheme 2.15 Intramolecular [4+2] cycloaddition of enamides



Due to the aromaticity of both rings in isoquinoline, the most common strategies for the construction of the tetracyclic galanthan skeleton involve the cyclization of ring B at a

late stage of the synthesis[24] as opposed to using isoquinoline itself as a primary starting material. However, the retrosynthetic analysis shown in Figure 2.3 illustrates a possible [4+2] cycloaddition approach starting from an isocarbostyril. Compared to isoquinoline, the B-ring of isocarbostyril is only weakly aromatic. Thus, the C=C double bond of the enamide becomes a potential dienophile for a [4+2] cycloaddition.

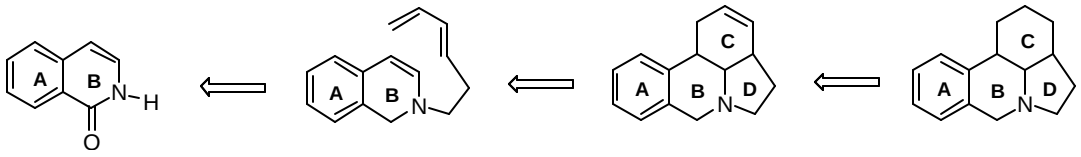
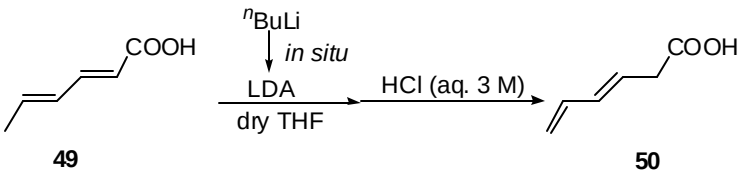


Figure 2.3 Retrosynthetic analysis of Galanthan Skeleton

2.2.1 Synthesis of Dienes

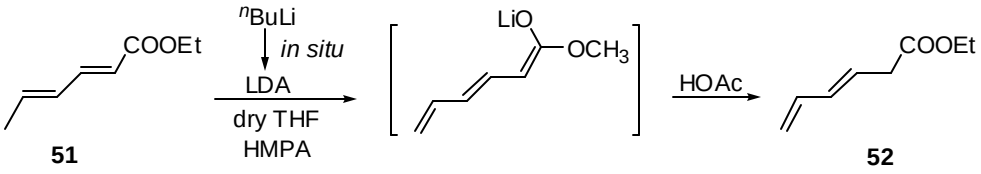
Since the hexadiene tether on nitrogen plays a critical role in our strategy, we began this project by synthesizing a series of diene synthons derived from commercially available sorbic acid (**49**) and ethyl sorbate (**51**). As shown in Scheme 2.16, 3,5-hexadienoic acid (**50**) was obtained from the deconjugation of **49** in nearly quantitative conversion.[49] Lithium diisopropylamide (LDA) was generated *in situ* by deprotonation of diisopropylamine with *n*-butyllithium at -78 ºC. The reaction of LDA with **49** produces the conjugated dianion which undergoes kinetic protonation at C-2 using 3 M HCl. The product can be isolated in 95% yield and requires storage at low temperature in a refrigerator.

Scheme 2.16 Deconjugation of sorbic acid



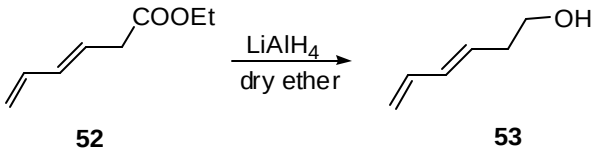
Similarly, the deprotonation of ethyl sorbate (**51**) using the complex of LDA and hexamethylphosphoramide (HMPA) at -78 ^{o}C followed by kinetic protonation of the intermediate trienolate with aqueous acetic acid afforded the deconjugated ester **52** in 89% yield (Scheme 2.17).[50] Unlike the dianion of **49**, which forms easily with LDA alone, the enolate from **51** requires the addition of HMPA.[51] Luckily, HMPA can be completely removed by partitioning the reaction mixture between hexane and an aqueous phase.

Scheme 2.17 Deconjugation of sorbic ester



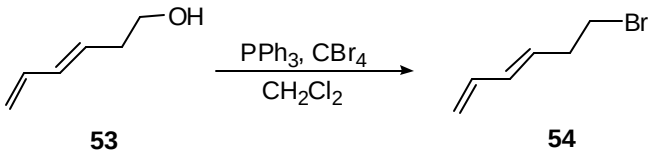
The reduction of an acid derivative is a key method for preparing primary alcohols. The reduction of **52** with lithium aluminum hydride provided the alcohol **53** in 90% yield (Scheme 2.18).[52]

Scheme 2.18 Synthesis of 3,5-hexadien-1-ol



Anticipating the need for hexadienyl alkylating agents, we developed the methods for converting alcohol **53** into the corresponding bromide, tolylate, and iodide under mild conditions. An adaptation of the bromination procedure using carbon tetrabromide and triphenylphosphine allowed the synthesis of **54** in 64% yield (Scheme 2.19).[53] The by-product triphenylphosphine oxide precipitate was removed and the product was obtained by further purification via dry-column flash chromatography.

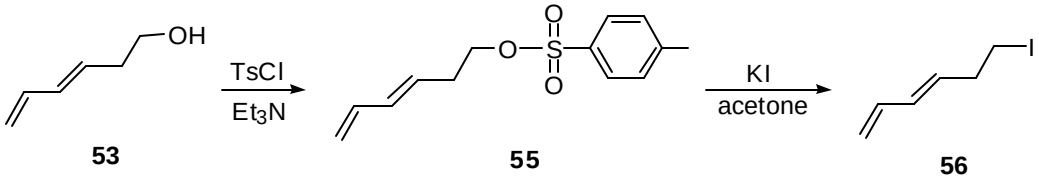
Scheme 2.19 Bromination of 3,5-hexadien-1-ol



53 **54**

Conversion of **53** to the iodide **56** involves two functional group transformations (Scheme 2.20).[54] The hydroxyl group is first converted to the tosylate using tosyl chloride and triethylamine instead of pyridine. Triethylamine can be removed by washing the aqueous layer with dilute HCl during the work-up process. The crude tosylate **55** can be obtained in 84% yield and used without further purification. The iodide **56** is then synthesized from the tosylate in 72% yield using the Finkelstein reaction with KI. The intermediate tosylate **55** is also a viable alkylating agent.

Scheme 2.20 Synthesis of iodo-3,5-hexadiene



53 **55** **56**

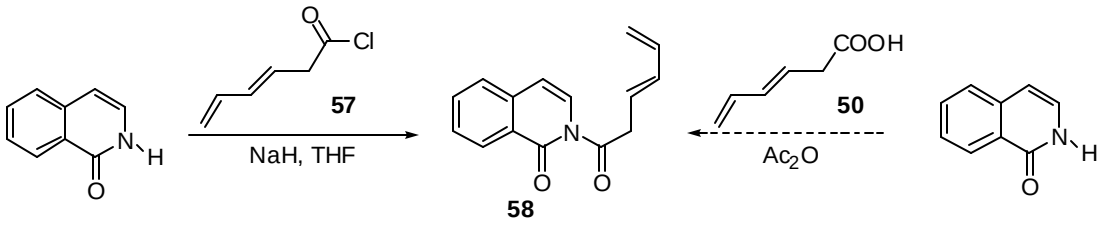
Since all of the dienes (**50**, **52-56**) could be prepared from sorbic acid or sorbic ester in multi-gram quantities, we were able to stockpile these important building blocks for attaching the diene tether to nitrogen in the isocarbostyril unit. The next step involved synthesizing precursors for the intramolecular Diels-Alder cycloaddition study.

2.2.2 Synthesis of Diels-Alder Precursors and Dienophiles

In our group's previous work, we attempted to introduce the diene tether into the isoquinoline nucleus using an acylation reaction with isocarbostyril.[36] However, the yield

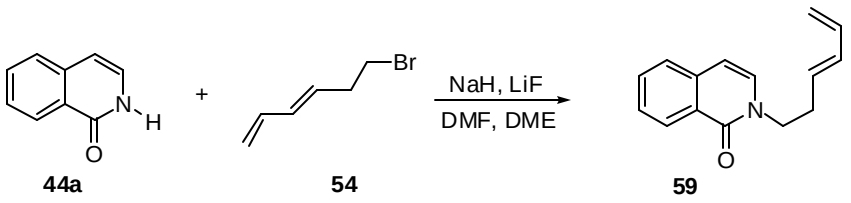
of **58** was not satisfactory (Scheme 2.21). We also attempted a one-pot *N*-acylation using sorbic acid with acetic anhydride acting as both an activating and a dehydrating agent.[55] Unfortunately, only *N*-acetylisocarbostyril rather than **58** was produced.

Scheme 2.21 *N*-Acylation of isocarbostyril



Then we tried to carry out *N*-alkylations of the isocarbostyril ring nitrogen using the electrophilic agents **54-56**; and in fact, 6-bromo-1,3-hexadiene (**54**) proved to be suitable for this reaction. In order to improve the solubility of **44a** in the reaction mixture, DMF was chosen as the solvent and sodium hydride served as the base. Under these conditions, only a 9% yield of **59** was isolated by chromatography. Using a published procedure for the high yield alkylation of **44c** with 4-bromo-1-butene and LiBr[56] improved the yield to only 18% (Scheme 2.22). This yield is even lower than Winslow's five-step method from isoquinoline, and is not a competitive way to synthesize **59**.[57]

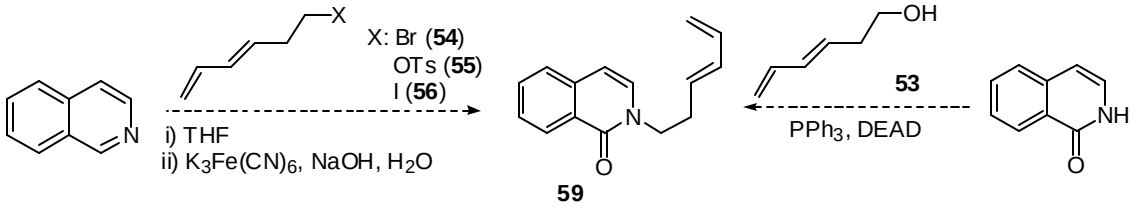
Scheme 2.22 *N*-Alkylation of isocarbostyril



We also attempted two alternative methods to synthesize **59** (Scheme 2.23). The ferricyanide oxidation of the corresponding isoquinoline salt could be an effective way. However, the reactions of isoquinoline with **54**-**56** in dry THF at room temperature were

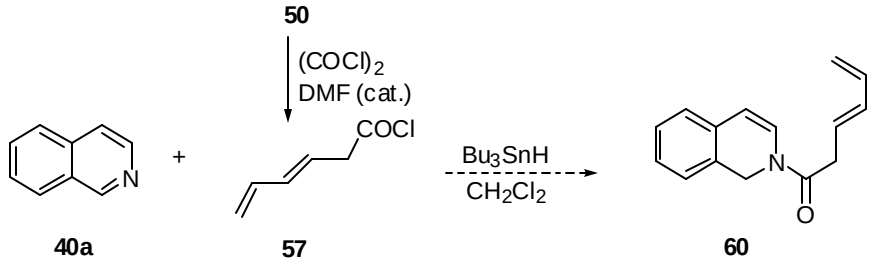
extremely slow. A trace amount of the quaternary salt was detected by TLC after heating for a short time at reflux, but continued refluxing caused extensive decomposition. A modification using the Grignard reagent prepared from **56** also failed.[58] On the other hand, a new approach to *N*-alkylated isocarbostyrils using the Mitsunobu reaction has been reported,[59] but our experiments show that **53** is not a suitable substrate for this reaction.

Scheme 2.23 Attempted synthesis of 59



Considering the difficulty of finding a short, efficient synthesis of **59** coupled with the fact that our group's preliminary work[37,57] on the [4+2] cycloadditions of both **58** and **59** was not successful, we abandoned the development of *N*-substituted isocarbostyrils for this project in favor of an *N*-substituted 1,2-dihydroisoquinoline such as **60** in Scheme 2.24.

Scheme 2.24 Attempted synthesis of 60

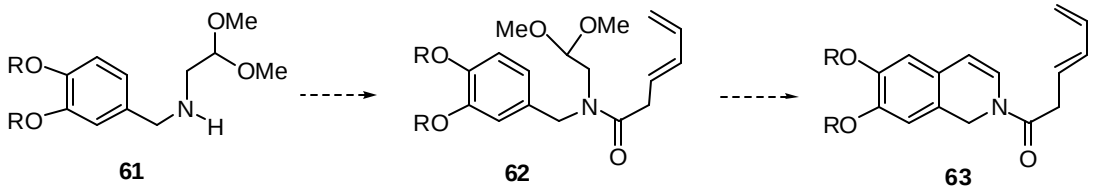


In looking for alternatives to **58** and **59**, the amide **60** was a logical choice since it is electronically similar to **35**, which Martin used in his lycorane syntheses.[31] An attempt to prepare this compound using known methodology is shown in Scheme 2.24.[60] The acid

chloride **57** was prepared *in situ* by the treatment of **50** with oxalyl chloride in methylene chloride and catalytic DMF. An attempt to prepare and reduce the *N*-acylisoquinolinium salt with tributyltin hydride did not produce the desired product.

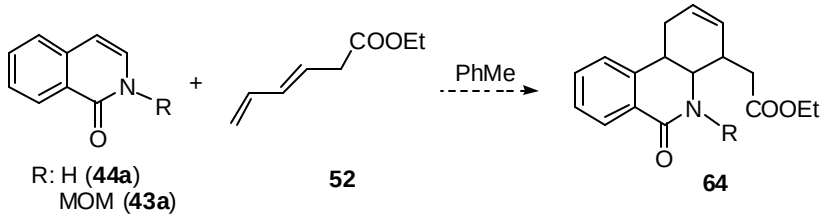
Another approach to a similar diene **63** is potentially available from a modification of the synthesis of **40b** (Scheme 2.3). As shown in Scheme 2.25, the intermediate **62** could be obtained by the treatment of amine **61** with the acid chloride **57** in the pyridine or triethylamine. The cyclization of **62** under acidic conditions could be effected by the addition of Lewis acids.[61] Although time did not permit an investigation of this plan, it provides a starting point for future study.

Scheme 2.25 Proposed Diels-Alder precursor



In addition to these precursors for the intramolecular Diels-Alder reaction, we also attempted to develop the intermolecular [4+2] cycloaddition of isocarbostyril ring. In the literature, only a few examples of such reactions have been developed.[62]

Scheme 2.26 Attempted Diels-Alder reaction of isocarbostyrils

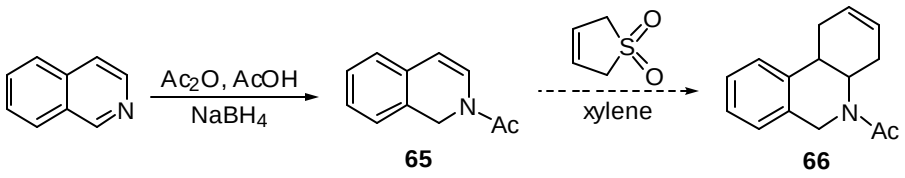


We tried to use the isocarbostyrils **44a** and **43a** as the dienophiles for **52** (Scheme 2.26). However, no detectable amount of the cyclization products (such as **64**) was

produced after refluxing in anhydrous toluene for 15-24 hours. Attempts to catalyze the reaction with Lewis acids such as titanium tetrachloride, aluminum trichloride and boron trifloride diethyl etherate also failed. In another model reaction, no cycloadduct was formed by heating butadiene sulfone with *N*-methylisocarbostyril (**41b**).

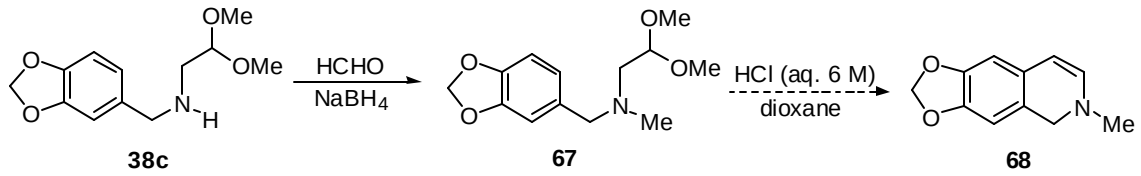
Since isocarbostyrils appeared not to be useful, we investigated the possibility that 1,2-dihydroisoquinoline derivatives could be potential dienophiles for the intermolecular Diels-Alder reaction. Based on its synthetic availability from isoquinoline, *N*-acetyl-1,2-dihydroisoquinoline (**65**) was synthesized according to a known procedure (Scheme 2.27).[63] However, **66** was not formed when **65** and butadiene sulfone were heated in refluxing *m*-xylene for 48 hours.

Scheme 2.27 Synthesis of *N*-acyl-1,2-dihydroisoquinoline



One last attempt to carry out an intermolecular Diels-Alder reaction involved using components for an inverse electron-demand process. For this, it appeared that the *N*-methyl-1,2-dihydroisoquinoline derivatives might be sufficiently electron-rich to serve as the dienophile. In fact, the alkaloid **68** (Scheme 2.28), which was isolated from the leaves of *Doryphora sassafras* in 1965,[64] had already been characterized. We tried to synthesize **68** from the readily available amine intermediate **38c**. The methyl group was introduced by a reductive amination.[65] However, the cyclization of **67** under the same conditions used previously for the preparation of isoquinolines (Scheme 2.3) or by using aluminum trichloride in THF[61] was not successful. In retrospect, **68** could probably have been made much more easily by the reduction of the corresponding *N*-methyliso-quinolinium iodide salt.

Scheme 2.28 Attempted synthesis of 68



In conclusion, we have successfully synthesized six dienes for potential use in the development of a [4+2] cycloaddition approach to the galanthan ring system. These precursors and dienophiles are based on dihydroisoquinoline and isocarbostyril nuclei. As such, this work provides the basis for future investigations.

2.3 Summary

The 1,3,4(2*H*)-isoquinolinetrione alkaloid **42b** and its analogues were synthesized in two steps with good overall yields (62-80%) starting from readily available isoquinolines. The methods for the synthesis of phthalonimide and its derivatives were developed from the corresponding isocarbostyrils, which could be easily prepared from isoquinolines according to the general philosophy of our group's approach to this research .

In addition, we have synthesized six dienes for potential use in the development of a [4+2] cycloaddition approach to the galanthan tetracyclic ring system. These precursors and dienophiles are based on and derived from isoquinolines and isocarbostyrils.

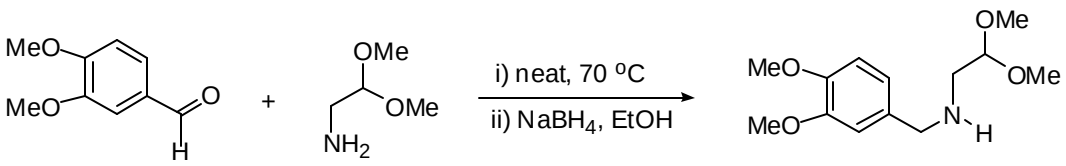
3. EXPERIMENTAL SECTION

3.1 General Procedures

All reagents were obtained from commercial sources and used as purchased without further purification unless otherwise indicated. Tetrahydrofuran (THF) was dried and distilled from calcium hydride and subsequently from sodium and benzophenone under nitrogen atmosphere. Dichloromethane (CH_2Cl_2) was dried and distilled from calcium hydride prior to use. Isoquinoline was distilled *in vacuo* and stored under nitrogen. The technical grade of methoxymethyl chloride from Sigma-Aldrich was sufficient for direct usage. Chloromethyl 2,2,2-trichloroethyl ether was prepared using an extension of the Boeckman protocol for benzyl chloromethyl ether and stored over anhydrous calcium chloride in a refrigerator.[43] Column chromatography was performed using silica gel (60 Å, 230-400 mesh). Thin layer chromatography (TLC) was performed using silica gel plastic plates visualized by irradiation with UV light. All reactions involving air- and/or moisture-sensitive reagents were carried out under nitrogen atmosphere. Solvents were removed using a Buchi R110 rotary evaporator under the reduced pressure. A mechanical pump was used to remove the residual solvents at room temperature and 0.1 torr.

^{1}H NMR and ^{13}C NMR spectra were recorded with either a Varian Mercury^{PLUS} 300 NMR spectrometer (operating at 300.05 MHz for ^{1}H NMR and 75.45 MHz for ^{13}C NMR) or a Varian Inova 400 NMR spectrometer (operating at 399.97 MHz for ^{1}H NMR and 100.58 MHz for ^{13}C NMR). Chemical shifts are reported in ppm (d) using $CDCl_3$ or d_6-DMSO as solvent, and tetramethylsilane (TMS) as internal standard. Observed coupling constants (*J*) are reported in Hertz (Hz), and the multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m). Melting points were determined using a Mel-Temp II capillary melting point apparatus made by Laboratory Devices and are uncorrected. Elemental analyses of new compounds were provided by Atlantic Microlab.

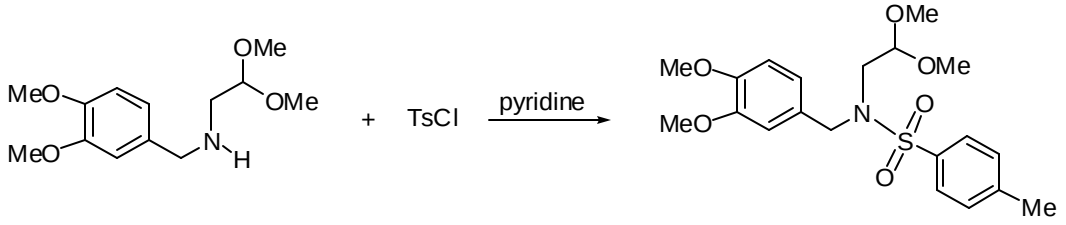
3.2 Synthesis of Isoquinolines



***N*-(2,2-Dimethoxyethyl)-3,4-dimethoxybenzylamine (38b).** A mixture containing 24.9 g (150 mmol) of 3,4-dimethoxybenzaldehyde and 20 mL (19.3 g, 184 mmol) of aminoacetaldehyde dimethyl acetal was heated under nitrogen at 70 °C for 4.5 hours in a 250-mL round-bottomed flask with condenser. The crude product was cooled and used without further purification. A solution of the imine in 175 mL of 95% ethanol was cooled to 0 °C, and sodium borohydride (5.0 g, 130 mmol) was added in small portions over 30 minutes. After complete addition, the yellow solution was allowed to stir at room temperature under nitrogen for 18 hours. The reaction was quenched by addition of 175 mL of water. After hydrogen evolution ceased (approx. 1 hour), the reaction mixture was transferred to a 1 L separatory funnel containing 375 mL of water. The product was extracted with dicholoromethane (4 x 125 mL), dried over sodium sulfate, and rotary evaporated. After removal of residual solvent using a mechanical pump, 36.4 g (95.1 % over 2 steps) of yellow oil was obtained. The crude sample was spectrally pure by NMR analysis and used for the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 2.75 (2H, d, *J* = 5.6 Hz), 3.38 (6H, s), 3.76 (2H, s), 3.87 (3H, s), 3.89 (3H, s), 4.49 (1H, t, *J* = 5.6 Hz), 6.83 (2H, m), 6.88 (1H, m).

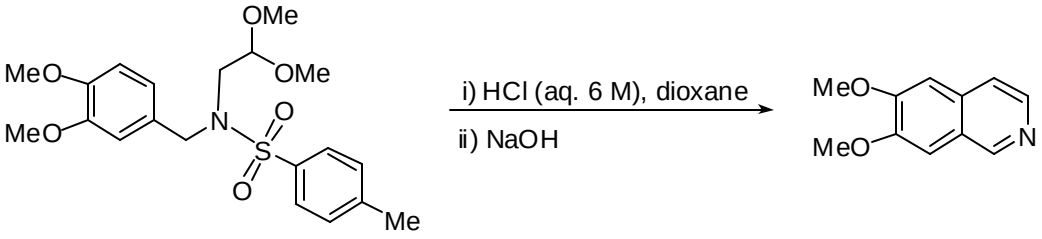
^{13}C NMR (75 MHz, $CDCl_3$): 50.7, 53.9, 54.2, 56.1, 56.2, 104.1, 111.2, 111.6, 120.5, 133.0, 148.3, 149.2.



***N*-(2,2-Dimethoxyethyl)-*N*-[(3,4-dimethoxyphenyl)methyl]-4-toluene sulfonamide (39b).** A solution of crude **38b** (36.4 g, 142.7 mmol) in 150 mL of dry pyridine was cooled to 0 ^{o}C, and tosyl chloride (37.6 g, 197 mmol) was added all at once after which the water-ice bath was removed. After stirring for 48 hours at room temperature, the reaction mixture was poured into 500 mL of water. Saturated sodium bicarbonate solution was added at 0 ^{o}C with rapid stirring until the evolution of CO_2 ceased and the solution tested alkaline to litmus. The reaction mixture was transferred to a 1 L separatory funnel and extracted with dichloromethane (5 x 100 mL). The combined extracts were washed repeatedly with 1 M HCl until the spot for pyridine disappeared in the TLC analysis. The organic layer was washed with brine, dried over sodium sulfate, rotary evaporated, and then pumped. The crude product (57.4 g of brown oil, 98%) was spectrally pure by NMR analysis and suitable for use in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 2.43 (3H, s), 3.21 (2H, d, *J* = 5.3 Hz), 3.26 (6H, s), 3.75 (3H, s), 3.85 (3H, s), 4.36 (1H, t, *J* = 5.3 Hz), 4.41 (2H, s), 6.67 (1H, s), 6.74 (2H, m), 7.31 (2H, d, *J* = 8.5 Hz), 7.74 (2H, d, *J* = 8.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): 21.7, 48.6, 52.5, 54.9, 55.9, 56.1, 104.2, 111.0, 111.6, 121.4, 127.4, 128.7, 129.9, 138.0, 143.5, 148.8, 149.3.

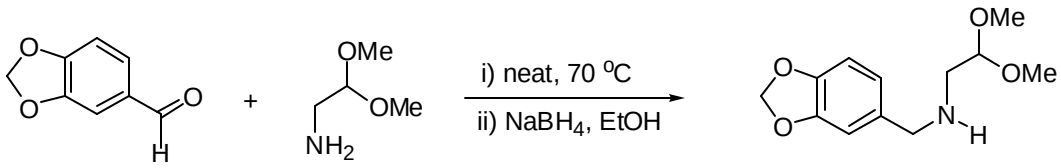


6,7-Dimethoxyisoquinoline (40b). The crude tosylamide **39b** (57.4 g, 140.3 mmol) was dissolved in 600 mL of dioxane and 110 mL of 6 M HCl. The resulting mixture was heated at reflux under nitrogen in the dark overnight. The solution was concentrated using a simple distillation to remove most of the dioxane. The residue was cooled and poured into 500 mL of water. The resulting solution was washed with ether (4 x 300 mL) and

then made alkaline by the addition of 250 mL of 10% NaOH. The product was extracted with ether (3 x 200 mL) and dichloromethane (3 x 200 mL). The combined extracts were washed with brine, dried over sodium sulfate, and rotary evaporated. The brown oil was pumped on a vacuum line overnight to give 22.5 g (85%) of pale yellow solid, m.p. 80-82 ^{o}C. The sample was spectrally pure by NMR analysis and ready to use without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 4.04 (6H, s), 7.07 (1H, s), 7.21 (1H, s), 7.51 (1H, d, *J* = 5.6 Hz), 8.40 (1H, d, *J* = 5.6 Hz), 9.05 (1H, s).

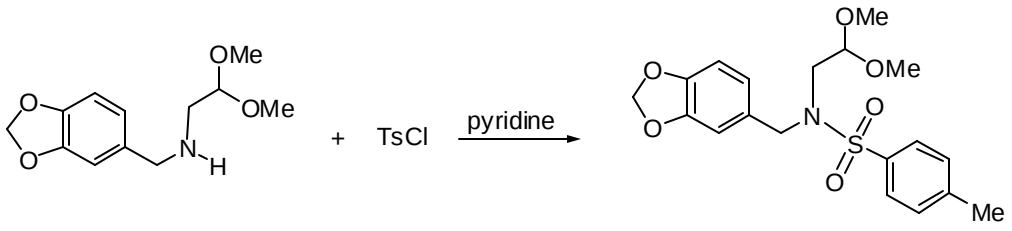
^{13}C NMR (75 MHz, $CDCl_3$): 56.28, 56.33, 104.8, 105.5, 119.4, 125.0, 132.8, 142.3, 150.2, 150.5, 153.2.



***N*-(2,2-Dimethoxyethyl)-3,4-methylenedioxybenzylamine (38c).** A mixture containing 22.5 g (150 mmol) of 3,4-methylenedioxybenzaldehyde and 20 mL (19.3 g, 184 mmol) of aminoacetaldehyde dimethyl acetal was heated under nitrogen at 70 ^{o}C for 4.5 hours in a 250-mL round-bottomed flask with condenser. The crude product was cooled and used without further purification. A solution of the imine in 175 mL of 95% ethanol was cooled to 0 ^{o}C and sodium borohydride (5.0 g, 130 mmol) was added in small portions over 30 minutes. After complete addition, the yellow solution was allowed to stir under nitrogen at room temperature for 18 hours. The reaction was quenched by addition of 175 mL of water. After hydrogen evolution ceased (approx. 1 hour), the reaction mixture was transferred to a 1 L separatory funnel containing 375 mL of water. The product was extracted with dichloromethane (4 x 125 mL), dried over sodium sulfate, and rotary evaporated. After removal of residual solvent using a mechanical pump, 34.8 g (97% over 2 steps) of yellow oil was obtained. The sample was spectrally pure by NMR analysis and used for the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 2.72 (2H, d, *J* = 5.6 Hz), 3.37 (6H, s), 3.71 (2H, s), 4.48 (1H, t, *J* = 5.6 Hz), 5.93 (2H, s), 6.75 (2H, m), 6.83 (1H, s).

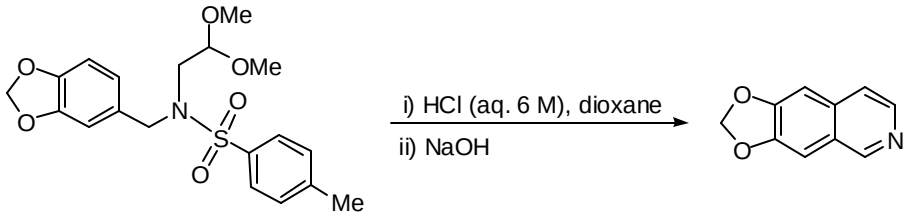
^{13}C NMR (75 MHz, $CDCl_3$): 50.5, 53.9, 54.2, 101.1, 104.1, 108.3, 108.9, 121.5, 134.3, 146.7, 147.9.



***N*-(3,4-Methylenedioxybenzyl)-*N*-(2,2-dimethoxyethyl)-4-toluene sulfonamide (39c).** A solution of crude **38c** (17.4 g, 72.8 mmol) in 75 mL of dry pyridine was cooled to 0 ^{o}C, and tosyl chloride (18.8 g, 98.5 mmol) was added all at once after which the water-ice bath was removed. After stirring for 48 hours at room temperature, the reaction mixture was poured into 250 mL of water. Saturated sodium bicarbonate solution was added at 0 ^{o}C with rapid stirring until the evolution of CO_2 ceased and the solution tested alkaline to litmus. The reaction mixture was transferred to a 500 mL separatory funnel and extracted with dichloromethane (5 x 50 mL). The combined extract was washed repeatedly with 1 M HCl until the spot for pyridine disappeared in the TLC analysis. The organic layer was washed with brine, dried over sodium sulfate, rotary evaporated, and then pumped. The crude product (28.05 g of brown solid, 98%; m.p. 58-60 ^{o}C) was spectrally pure by NMR analysis and suitable for use in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 2.44 (3H, s), 3.21 (2H, d, *J* = 5.3 Hz), 3.26 (6H, s), 4.33-4.36 (3H, m), 5.93 (2H, s), 6.68-6.72 (3H, m), 7.31 (2H, d, *J* = 8.5 Hz), 7.73 (2H, d, *J* = 8.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): 21.8, 48.6, 52.5, 54.9, 101.3, 104.1, 108.2, 109.2, 122.3, 127.4, 129.9, 130.1, 137.8, 143.6, 147.4, 148.1.

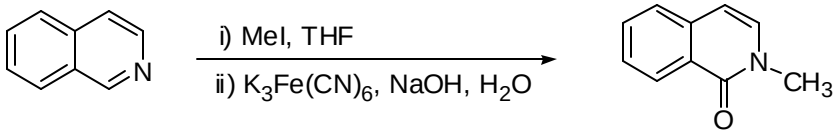


6,7-Methylenedioxyisoquinoline (40c). The crude tosylamide **39c** (28.05 g, 71.4 mmol) was dissolved in 300 mL of dioxane and 55 mL of 6 M HCl. The resulting mixture was heated at reflux under nitrogen in the dark overnight. The solution was concentrated using a simple distillation to remove most of dioxane. The residue was cooled and poured into 250 mL of water. The resulting solution was washed with ether (4 x 150 mL) and made alkaline by the addition of 125 mL of 10% NaOH. The aqueous phase was then extracted with ether (3 x 100 mL) and dichloromethane (3 x 100 mL). The combined extracts were washed with brine, dried over sodium sulfate, and rotary evaporated. The tan oil was pumped on a vacuum line overnight to give 11.3 g (92%) of off-white solid, m.p. 119-120 ^{o}C. The sample was spectrally pure by NMR analysis and ready to use without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 6.11 (2H, s), 7.08 (1H, s), 7.20 (1H, s), 7.49 (1H, d, *J* = 5.6 Hz), 8.38 (1H, d, *J* = 5.6 Hz), 9.00 (1H, s).

^{13}C NMR (75 MHz, $CDCl_3$): 101.7, 102.4, 103.1, 120.1, 126.0, 134.2, 142.3, 148.4, 150.3, 150.9.

3.3 Synthesis of *N*-Methylisoquinolinetriones

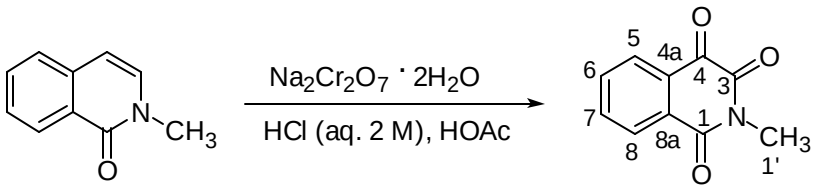


***N*-Methylisocarbostyril (41a).** A solution of isoquinoline (2.95 mL, 3.24 g, 25.1 mmol) and methyl iodide (3.13 mL, 7.13 g. 50.3 mmol) in 50 mL of dry THF was stirred overnight in a round-bottomed flask under dry nitrogen. The reaction was kept in the dark,

and a large amount of yellow solid was formed. The product was isolated by filtration, washed with dry ether, and then dissolved in 50 mL of distilled water in a 250-mL three necked round-bottomed flask. The mixture was cooled with an ice-water bath as solution A (4.7 g of NaOH in 25 mL of water) and half of solution B (16.35 g $K_3Fe(CN)_6$ in 50 mL of water) were added simultaneously while maintaining the temperature below 20 ^oC. After the remainder of solution B was added, the ice-water bath was removed and the reaction mixture was opened to the atmosphere and stirred overnight. The product was extracted with dicholoromethane (3 x 100 mL). The combined extracts were washed with brine and then dried over magnesium sulfate. After removal of the residual solvent by rotary evaporation and mechanical pumping, 2.73 g (69% over 2 steps) of yellow oil was obtained. The sample is spectrally pure by NMR analysis and used in the next step without further purification.[40b]

^{1}H NMR (300 MHz, $CDCl_3$): 3.58 (3H, s), 6.45 (1H, d, *J* = 7.3 Hz), 7.03 (1H, d, *J* = 7.3 Hz), 7.43-7.49 (2H, m), 7.60 (1H, m), 8.42 (1H, m).

^{13}C NMR (75 MHz, $CDCl_3$): 37.2, 106.1, 126.1, 126.3, 127.0, 127.8, 132.2, 132.6, 137.3, 162.8.

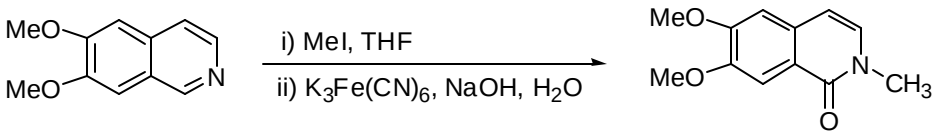


***N*-Methyl-1,3,4(2*H*)-isoquinolinetrione (42a).** A 50-mL round-bottom flask was charged with a magnetically stirred solution of **41a** (0.16 g, 1.0 mmol) in 6 mL of acetic acid. A solution of sodium dichromate dihydrate (0.89 g, 3.0 mmol) in 6 mL of 2 M HCl was added dropwise at such a rate that the reaction temperature did not exceed 30 ^oC. The mixture was opened to the atmosphere and stirred overnight. The product was extracted with ethyl acetate (3 x 30 mL). The combined extracts were first neutralized by the addition of solid sodium bicarbonate, then washed with brine and dried over magnesium

sulfate. After removal of the residual solvents by rotary evaporation and mechanical pumping, 0.17 g (90%) of yellow solid was obtained. An analytical sample obtained by recrystallization from dichloromethane had a melting point of 180-182 °C (lit.:[40b] m.p. 186.5-188.0 °C, recrystalized from ethanol).

^{1}H NMR (400 MHz, $CDCl_3$): 3.48 (3H, s, H-1'), 7.85 (1H, ddd, *J* = 7.7, 7.5, 1.3 Hz, H-6), 7.93 (1H, ddd, *J* = 7.8, 7.5, 1.4 Hz, H-7), 8.22 (1H, ddd, *J* = 7.7, 1.4, 0.5 Hz, H-5), 8.35 (1H, ddd, *J* = 7.8, 1.3, 0.5 Hz, H-8).

^{13}C NMR (100 MHz, $CDCl_3$): 27.6 (C-1'), 127.8 (C-5), 129.9 (C-8a), 129.8 (C-8), 130.7 (C-4a), 134.5 (C-6), 136.1 (C-7), 157.3 (C-3), 162.4 (C-1), 174.5 (C-4).

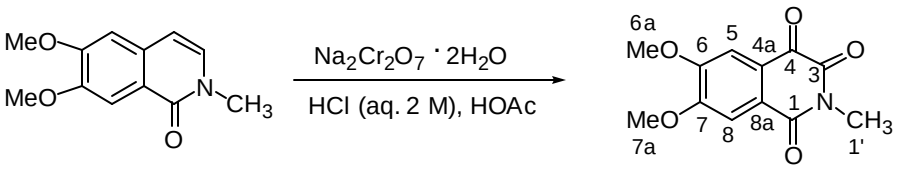


Doryphornine methyl ether (41b). A solution of **40b** (0.95 g, 5.0 mmol) and methyl iodide (0.63 mL, 1.43 g, 10.1 mmol) in 10 mL of dry THF was stirred overnight in a round-bottomed flask under dry nitrogen. The reaction was kept in the dark, and a large amount of yellow solid was formed. The crude product was isolated by filtration and washed by dry ether. The dry salt (1.65 g, 5.0 mmol) was dissolved in 10 mL of distilled water in a 50-mL three necked round-bottomed flask. The mixture was cooled in an ice-water bath as solution A (0.94 g of NaOH in 5 mL of water) and half of solution B (3.27 g $K_3Fe(CN)_6$ in 10 mL of water) were added simultaneously while maintaining the temperature below 20 °C. After the remainder of solution B was added, the ice-water bath was removed. The reaction mixture was opened to the atmosphere and stirred overnight. The product was extracted with dichloromethane (3 x 30 mL). The combined extracts were washed with brine and then dried over magnesium sulfate. After removal of the residual solvents by rotary evaporation and mechanical pumping, 1.00 g (91.3% over two steps) of an off-white solid was obtained. This material was suitable for use in the next step without further purification. An analytical sample was obtained by recrystallization

from dichloromethane and hexanes, m.p. 108-109 °C. The physical and spectroscopic data were in agreement with the literature values.[66]

^{1}H NMR (300 MHz, $CDCl_3$): 3.60 (3H, s), 3.98 (3H, s), 4.01 (3H, s), 6.40 (1H, d, *J* = 7.3 Hz), 6.86 (1H, s), 7.00 (1H, d, *J* = 7.3 Hz), 7.80 (1H, s).

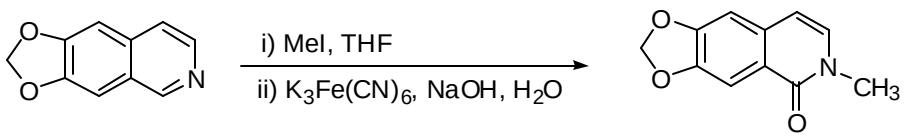
^{13}C NMR (75 MHz, $CDCl_3$): 37.3, 56.2, 56.4, 105.6, 106.1, 107.7, 120.3, 131.3, 132.8, 149.4, 153.4, 162.1.



6,7-Dimethoxy-2-methylisoquinoline-1,3,4(2*H*)-trione (42b). A round-bottom flask was charged with a magnetically stirred solution of **41b** (0.22 g, 1.0 mmol) in 6 mL of acetic acid. A solution of sodium dichromate dehydrate (0.89 g, 3.0 mmol) in 6 mL of 2 M HCl was added dropwise at such a rate that the reaction temperature did not exceed 30 °C. The mixture was opened to the atmosphere and stirred overnight. The product was extracted with dichloromethane (3 x 30 mL). The combined extracts were neutralized by addition of solid sodium bicarbonate, then washed with brine and dried over magnesium sulfate. After removal of residual solvents by rotary evaporation and mechanical pumping, 0.22 g (88.3%) of yellow solid was obtained. An analytical sample recrystallized from dichloromethane melted at 262-263 °C (lit.:[67] m.p. 256-257 °C).

^{1}H NMR (400 MHz, DMSO): 3.24 (3H, s, H-1'), 3.95 (3H, s, H-6a), 3.98 (3H, s, H-7a), 7.48 (1H, s, H-5), 7.60 (1H, s, H-8).

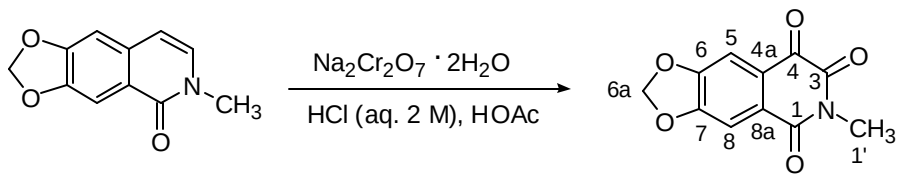
^{13}C NMR (100 MHz, DMSO): 26.7 (C-1'), 56.3 (C-7a), 56.2 (C-6a), 107.7 (C-5), 109.8 (C-8), 124.4 (C-8a), 125.3 (C-4a), 152.9 (C-6), 154.3 (C-7), 157.6 (C-3), 162.3 (C-1), 173.1 (C-4).



Doryanine (41c). A solution of **40c** (0.87 g, 5.0 mmol) and methyl iodide (0.63 mL, 1.44 g, 10.1 mmol) in 10 mL of dry THF was stirred overnight in a round-bottomed flask under dry nitrogen. The reaction was kept in the dark, and a large amount of yellow solid was formed. The crude product was isolated by filtration and washed with dry ether. The dry salt (1.57 g, 4.98 mmol) was dissolved in 10 mL of distilled water in a 50-mL three necked round-bottomed flask. The mixture was cooled in an ice-water bath as solution A (0.94 g of NaOH in 5 mL of water) and half of solution B (3.27 g $K_3Fe(CN)_6$ in 10 mL of water) were added simultaneously while maintaining the temperature below 20 ^oC. After the remainder of solution B was added, the ice-water bath was removed. The reaction mixture was opened to the atmosphere and stirred overnight. The product was extracted with dichloromethane (3 x 30 mL). The combined extracts were washed with brine and then dried over magnesium sulfate. After removal of the residual solvents by rotary evaporation and mechanical pumping, 0.93 g (91.6% over two steps) of yellowish solid, m.p. 157-159 ^oC, was obtained. The sample was spectrally pure by NMR analysis and used in the next step without further purification. The physical and spectroscopic data were in agreement with the literature values.[66]

^{1}H NMR (300 MHz, $CDCl_3$): 3.58 (3H, s), 6.06 (2H, s), 6.36 (1H, d, *J* = 7.3 Hz), 6.84 (1H, s), 6.98 (1H, d, *J* = 7.3 Hz), 7.77 (1H, s).

^{13}C NMR (75 MHz, $CDCl_3$): 37.3, 101.9, 103.9, 105.8, 106.0, 121.9, 131.5, 134.6, 148.1, 151.9, 162.1.

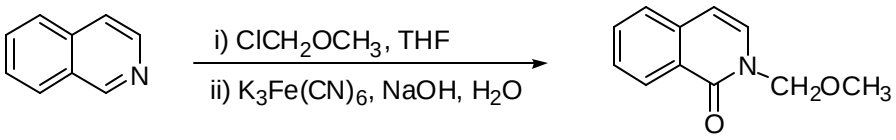


6,7-Methylenedioxy-2-methylisoquinoline-1,3,4(2*H*)-trione (42c). A round-bottom flask was charged with a magnetically stirred solution of **41c** (0.20g, 0.99 mmol) in 6 mL of acetic acid. A solution of sodium dichromate dihydrate (0.89 g, 3.0 mmol) in 6 mL of 2 M HCl was added dropwise at such a rate that the reaction temperature did not exceed 30 ^{o}C. The mixture was opened to the atmosphere and stirred overnight. The product was extracted with dichloromethane (3 x 30 mL). The combined extracts were neutralized by addition of solid sodium bicarbonate, then washed with brine and dried over magnesium sulfate. Removal of the residual solvents by rotary evaporation and mechanical pumping gave 0.19 g (82.3%) of yellow solid. An analytical sample obtained by recrystallization from dichloromethane had a melting point of 216-217 ^{o}C (lit.:[19] m.p. 232 °C, recryst. from chloroform).

^{1}H NMR (400 MHz, DMSO): 3.23 (3H, s, H-1'), 6.31 (2H, s, H-6a), 7.46 (1H, s, H-5), 7.57 (1H, s, H-8).

^{13}C NMR (100 MHz, DMSO): 26.9 (C-1'), 103.6 (C-6a), 105.2 (C-5), 107.4 (C-8), 126.9 (C-8a), 127.9 (C-4a), 152.2 (C-6), 153.3 (C-7), 157.4 (C-3), 162.1(C-1), 172.8 (C-4).

3.4 Synthesis of Isocarbostyrils

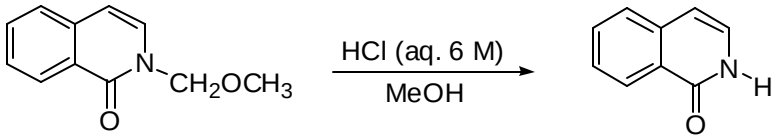


***N*-(Methoxymethyl)isocarbostyril (43a).** A solution of isoquinoline (4.6 mL, 5.0 g, 39.0 mmol) and methoxymethyl chloride (4.5 mL, 4.8 g, 59.6 mmol) in 100 mL of dry THF in a round-bottomed flask was stirred overnight under dry nitrogen. A large amount of white solid was formed. The solvent was removed by rotary evaporation and the dry salt was dissolved in 50 mL of distilled water in a three necked round-bottomed flask. The mixture was cooled in an ice bath as solution A (4.7 g of NaOH in 7 mL of water)

and half of solution B (16 g $K_3Fe(CN)_6$ in 40 mL of water) were added simultaneously while maintaining the temperature below 20 °C. After the remainder of solution B was added, the ice bath was removed. The reaction mixture was opened to the atmosphere and stirred overnight. The product was extracted with dicholoromethane (3 x 50 mL). The combined extracts were washed with 50 mL of 1M HCl, 50 mL of brine, and then dried over magnesium sulfate. After removal of the residual solvents by rotary evaporation and mechanical pumping, 5.06 g (68.7% over 2 steps) of brown oil was obtained. The sample was spectrally pure by NMR analysis and used without further purification in the next step.

^{1}H NMR (300 MHz, $CDCl_3$): 3.41 (3H, s), 5.41 (2H, s), 6.54 (1H, dd, *J* = 7.5, 0.6 Hz, H-4), 7.18 (1H, d, *J* = 7.5 Hz), 7.52 (2H, m, H-5, H-7), 7.66 (1H, ddd, *J* = 8.0, 7.0, 1.4 Hz, H-6), 8.44 (1H, dddd, *J* = 8.0, 1.4, 0.8, 0.6 Hz, H-8).

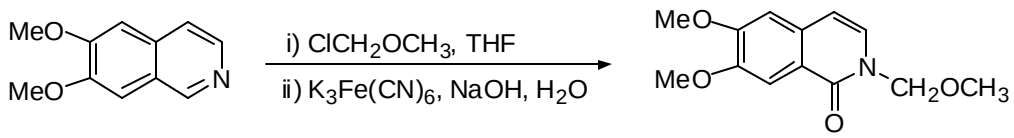
^{13}C NMR (75 MHz, $CDCl_3$): 57.0, 78.2, 106.8 (C-4), 126.3 (C-5), 126.4 (C-8a), 127.3 (C-7), 128.4 (C-8), 130.3 (C-3), 132.9 (C-6), 137.3 (C-4a), 163.0 (C-1).



Isocarbostyril (44a). A solution of **43a** (5.06 g, 26.8 mmol) in 45 mL of 6M HCl and 6 mL of methanol was heated at reflux overnight. After cooling the mixture to room temperature and neutralizing the acid with saturated sodium bicarbonate solution, 3.31 g (85%) of white solid was isolated by filtration, m.p. 201-202 °C (lit.:[68] m.p. 203-205 °C, recryst. from benzene). This material was suitable for use in the next step without further purification, although it could be recrystallized from chloroform.

^{1}H NMR (300 MHz, $CDCl_3$): 6.59 (1H, d, *J* = 7.3 Hz, H-4), 7.20 (1H, d, *J* = 7.0 Hz, H-3), 7.54 (2H, m), 7.69 (1H, m, H-6), 8.43 (1H, m, H-8), 11.5 (1H, br. s, NH).

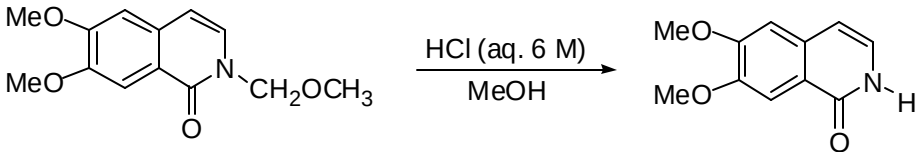
^{13}C NMR (75 MHz, $CDCl_3$): 107.0 (C-4), 126.3, 126.5, 127.0, 127.5, 127.9, 132.9 (C-6), 138.4 (C-4a), 164.7 (C-1).



***N*-Methoxymethyl-6,7-dimethoxyisocarbostyril (43b).** A solution containing 6,7-dimethoxyisoquinoline (3.81 g, 20.2 mmol) and methoxymethyl chloride (2.0 mL, 2.1 g, 26.1 mmol) in 50 mL of dry THF in a round-bottomed flask was stirred overnight under dry nitrogen. A large amount of yellowish precipitate was formed. The solvent was removed by rotary evaporation and the dry salt was dissolved in 50 mL of distilled water in a three necked round-bottomed flask. The mixture was cooled in an ice-water bath as solution A (3.8 g of NaOH in 5 mL of water) and half of solution B (13.2 g $K_3Fe(CN)_6$ in 20 mL of water) were added simultaneously while maintaining the temperature below 20 ^oC. After the remainder of solution B was added, the ice-water bath was removed. The reaction mixture was opened to the atmosphere and stirred overnight. The product was extracted with dicholoromethane (3 x 30 mL). The combined extracts were washed with 30 mL of 1M HCl, 50 mL of brine, and then dried over magnesium sulfate. After removal of the residual solvents by rotary evaporation and mechanical pumping, 4.78 g (95.0% over two steps) of off-white solid was obtained. The sample was spectrally pure by NMR analysis and used in the next step without further purification, m.p. 88-89 ^oC.

^{1}H NMR (300 MHz, $CDCl_3$): 3.40 (3H, s), 4.00 (3H, s), 4.01 (3H, s), 5.41 (2H, s), 6.46 (1H, d, *J* = 7.4 Hz, H-4), 6.88 (1H, s, H-5), 7.11 (1H, d, *J* = 7.4 Hz, H-3), 7.82 (1H, s, H-8).

^{13}C NMR (75 MHz, $CDCl_3$): 56.3, 56.4, 57.0, 78.3, 106.4 (C-4, C-5), 108.3 (C-8), 120.1 (C-8a), 129.1 (C-3), 132.8 (C-4a), 149.5 (C-7), 153.8 (C-6), 162.3 (C-1).

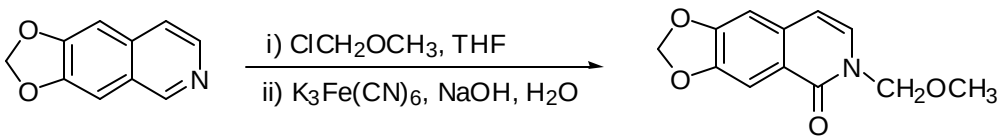


6,7-Dimethoxyisocarbostyril (44b). A solution of **43b** (0.125 g, 0.50 mmol) in 5 mL

of 6M HCl and 2 mL of methanol was heated at 70 °C for 6 hours. After cooling the mixture to room temperature, 10 mL of water was added. The product was extracted with ethyl acetate (3 x 20 mL). The combined extracts were neutralized by the addition of solid sodium bicarbonate, washed with brine, and then dried over magnesium sulfate. After removal of residual solvents by rotary evaporation and mechanical pumping, 0.90 g (87.8%) of white solid was obtained. An analytical sample obtained by recrystallization from a mixture of ethyl acetate and hexanes had a melting point of 226-228 °C (lit.:[69] m.p. 233-234 °C, recryst. from benzene).

^{1}H NMR (300 MHz, $CDCl_3$): 4.01 (3H, s), 4.03 (3H, s), 6.51 (1H, d, *J* = 7.0 Hz, H-4), 6.93 (1H, s, H-5), 7.15 (1H, d, *J* = 7.0 Hz, H-3), 7.79 (1H, s, H-8), 11.80 (1H, br. s, NH).

^{13}C NMR (75 MHz, $CDCl_3$): 56.3, 56.4, 106.42 (C-5), 106.45 (C-4), 107.1 (C-8), 120.1 (C-8a), 126.7 (C-3), 134.1 (C-4a), 149.5 (C-7), 153.9 (C-6), 163.9 (C-1).

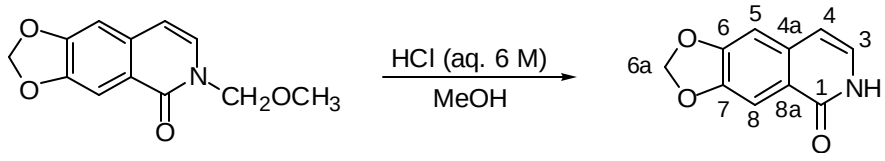


***N*-Methoxymethyl-6,7-methylenedioxyisocarbostyril (43c).** A solution containing 6,7- methylenedioxyisoquinoline (3.03 g, 17.5 mmol) and methoxymethyl chloride (2 mL, 2.1 g, 26.1 mmol) in 25 mL of dry THF in a round-bottomed flask was stirred overnight under dry nitrogen. A large amount of yellow precipitate was formed. The solvent was removed by rotary evaporation and the dry salt was dissolved in 6 mL of distilled water in a three necked round-bottomed flask. The mixture was cooled in an ice-water bath as solution A (3.35 g of NaOH in 5 mL of water) and half of solution B (15 g $K_3Fe(CN)_6$ in 50 mL of water) were added simultaneously while maintaining the temperature below 20 °C. After the remainder of solution B was added, the ice-water bath was removed. The reaction mixture was opened to the atmosphere and stirred overnight. The product was extracted with dichloromethane (3 x 50 mL). The combined extracts were washed with 50 mL of 1M HCl, 50 mL of brine, and then dried over magnesium sulfate. After removal of

the residual solvents by rotary evaporation and mechanical pumping, 3.57 g (87.5% over two steps) of yellow solid was obtained. The sample was spectrally pure by NMR analysis and used in the next step without further purification, m.p. 111-112 °C.

^{1}H NMR (300 MHz, $CDCl_3$): 3.39 (3H, s), 5.38 (2H, s), 6.08 (2H, s), 6.41 (1H, d, *J* = 7.4 Hz, H-4), 6.86 (1H, s, H-5), 7.08 (1H, d, *J* = 7.4 Hz. H-3), 7.78 (1H, s, H-8).

^{13}C NMR (75 MHz, $CDCl_3$): 57.0, 78.3, 102.0, 104.2 (C-5), 106.3 (C-8), 106.7 (C-4), 121.8 (C-8a), 129.2 (C-3), 134.6 (C-4a), 148.2 (C-7), 152.3 (C-6), 162.1 (C-1).

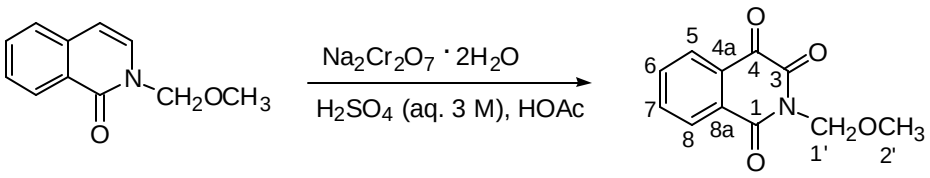


6,7-Methylenedioxyisocarbostyril (44c). A solution of **43c** (1.0 g, 4.3 mmol) in 10 mL of 6M HCl and 2 mL of methanol was heated at reflux for 12 hours. The product crystallized as needles upon cooling the reaction mixture to room temperature. Vacuum filtration afforded 0.6 g (73.8%) of yellowish solid, m.p. 270-271 °C (lit.:[56] m.p. 283-284 °C, recryst. from ethanol). This material was suitable for use in the next step without further purification, although it could be recrystallized from chloroform.

^{1}H NMR (400 MHz, $CDCl_3$): 6.07 (2H, s, H-6a), 6.42 (1H, d, *J* = 7.3 Hz, H-4), 6.88 (1H, s, H-5), 7.02 (1H, d, *J* = 7.3 Hz, H-3), 7.74 (1H, s, H-8), 10.25 (1H, br. s, NH).

^{13}C NMR (100 MHz, $CDCl_3$): 101.9 (H-6a), 104.1 (H-5), 105.2 (H-8), 106.7 (H-4), 121.7 (H-8a), 126.2 (H-3), 135.6 (H-4a), 148.0 (H-7), 152.3 (H-6), 162.9 (H-1).

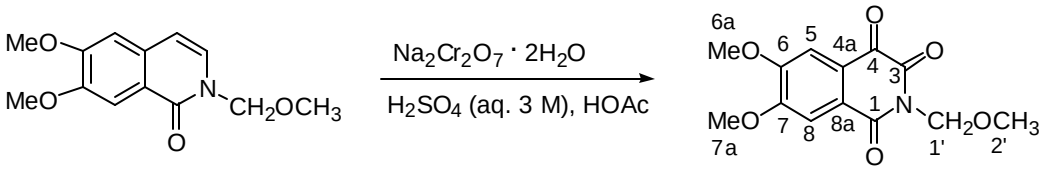
3.5 Synthesis of Phthalonimide Derivatives



***N*-Methoxymethyl-1,3,4(2*H*)-isoquinolinetrione (46a).** A round-bottomed flask was charged with a magnetically stirred solution of **43a** (0.19 g, 1.0 mmol) in 5 mL of acetic acid and cooled in an ice/water bath. A solution of sodium dichromate dihydrate (0.89 g, 3.0 mmol) in 5 mL of 3 M H_2SO_4 was added dropwise at such a rate that the reaction temperature did not exceed 30 ^oC. The mixture was opened to the atmosphere and stirred for 15 mins. Then 10 mL of water was added and the product was extracted with ethyl acetate (3 x 20 mL). The combined extracts were neutralized by addition of solid sodium bicarbonate, washed with brine, and then dried over magnesium sulfate. After removal of the residual solvents by rotary evaporation and mechanical pumping, 0.18 g (82.2%) of yellow solid was obtained. This material was suitable for use in the next step without further purification. An analytically pure sample was obtained by recrystallization from a mixture of ethyl acetate and hexanes, m.p. 127-128 ^oC. Elemental analysis: Anal. Calcd. for $C_{11}H_9NO_4 \cdot 0.2H_2O$: C, 59.30; H, 4.09. Found: C, 59.36; H, 4.04.

^{1}H NMR (400 MHz, $CDCl_3$): 3.48 (3H, s, H-2'), 5.50 (2H, s, H-1'), 7.89 (1H, ddd, J = 7.7, 7.7, 1.4 Hz, H-6), 7.96 (1H, ddd, J = 7.8, 7.7, 1.4 Hz, H-7), 8.24 (1H, ddd, J = 7.7, 1.4, 0.5 Hz, H-5), 8.38 (1H, ddd, J = 7.8, 1.4, 0.5 Hz, H-8).

^{13}C NMR (100 MHz, $CDCl_3$): 58.2 (C-2'), 71.9 (C-1'), 127.9 (C-5), 129.5 (C-8a), 130.1 (C-8), 131.0 (C-4a), 134.8 (C-6), 136.3 (C-7), 157.0 (C-3), 162.2 (C-1), 174.5 (C-4).

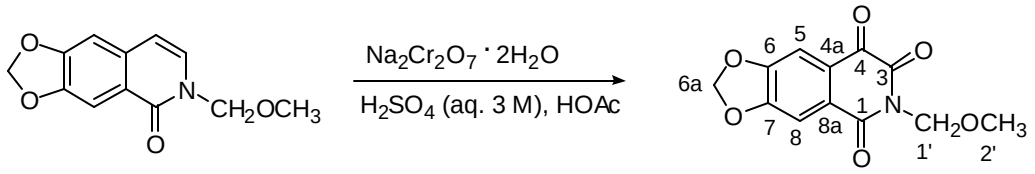


6,7-Dimethoxy-2-methoxymethylisoquinoline-1,3,4(2*H*)-trione (46b). A round-bottomed flask was charged with a magnetically stirred solution of **43b** (0.50 g, 2.0 mmol) in 10 mL of acetic acid and cooled in an ice/water bath. A solution of sodium dichromate dihydrate (1.78 g, 6.0 mmol) in 10 mL of 3 M H_2SO_4 was added dropwise at such a rate that the reaction temperature did not exceed 30 ^oC. The mixture was opened to the

atmosphere and stirred for 15 mins. Then 20 mL of water was added and the product was extracted with ethyl acetate (3 x 40 mL). The combined extracts were neutralized by the addition of solid sodium bicarbonate, washed with brine, and then dried over magnesium sulfate. After removal of the residual solvents by rotary evaporation and mechanical pumping, 0.42 g (75.3%) of yellow solid was obtained. This material was suitable for use in the next step without further purification. An analytically pure sample, m.p. 194-195 ^{o}C, was obtained by recrystallization from a mixture of dichloromethane and hexanes. Elemental analysis: Anal. Calcd. for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.69. Found: C, 55.67; H, 4.73.

^{1}H NMR (400 MHz, $CDCl_3$): 3.48 (3H, s, H-2'), 4.05 (3H, s, H-6a), 4.09 (3H, s, H-7a), 5.49 (2H, s, H-1'), 7.60 (1H, s, H-5), 7.74 (1H, s, H-8).

^{13}C NMR (100 MHz, $CDCl_3$): 56.8 (C-6a), 56.9 (C-7a), 58.1 (C-2'), 71.7 (C-1'), 108.4 (C-5), 110.7 (C-8), 124.5 (C-8a), 125.7 (C-4a), 154.2 (C-6), 155.8 (C-7), 157.4 (C-3), 162.2 (C-1), 173.3 (C-4).

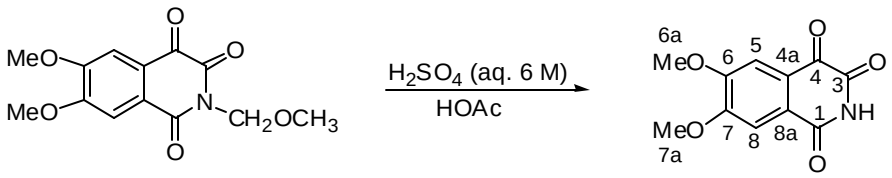


6,7-Methylenedioxy-2-methoxymethylisoquinoline-1,3,4(2*H*)-trione (46c). A round-bottomed flask charged with a magnetically stirred solution of **43c** (0.23 g, 0.99 mmol) in 5 mL of acetic acid was cooled in an ice/water bath. A solution of sodium dichromate dehydrate (0.89 g, 3.0 mmol) in 5 mL of 3 M H_2SO_4 was added dropwise at such a rate that the reaction temperature did not exceed 30 ^{o}C. The mixture was opened to the atmosphere and stirred for 15 mins. Then 10 mL of water was added and the product was extracted with ethyl acetate (3 x 20 mL). The combined extracts were neutralized by addition of solid sodium bicarbonate, washed with brine, and then dried over magnesium sulfate. After removal of residual solvents by rotary evaporation and mechanical pumping,

0.19 g (73.1%) of yellow solid was obtained, m.p. 186-187 °C. Elemental analysis: Anal. Calcd. for $C_{12}H_9NO_6$: C, 54.76; H, 3.45. Found: C, 54.30; H, 3.45.

^{1}H NMR (400 MHz, $CDCl_3$): 3.48 (3H, s, H-2'), 5.47 (2H, s, H-1'), 6.24 (2H, s, H-6a), 7.56 (1H, s, H-5), 7.71 (1H, s, H-8).

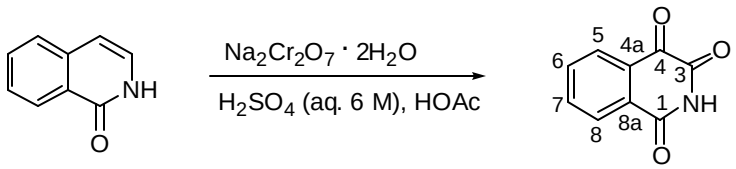
^{13}C NMR (100 MHz, $CDCl_3$): 58.2 (C-2'), 71.9 (C-1'), 103.5 (C-6a), 106.4 (C-5), 108.9 (C-8), 127.0 (C-8a), 128.0 (C-4a), 153.2 (C-6), 154.6 (C-7), 157.0 (C-3), 161.6 (C-1), 172.9 (C-4).



6,7-Dimethoxy-1,3,4(2*H*)-isoquinolinetrione (45b). A reaction mixture containing 0.14 g (0.50 mmol) of **46b**, 5 mL of acetic acid, and 10 mL of 6 M H_2SO_4 was heated at reflux for 15 hours. After cooling the mixture to room temperature, 10 mL of water was added. The product was extracted with ethyl acetate (3 x 20 mL). The combined extracts were neutralized by the addition of solid sodium bicarbonate, washed with brine, and then dried over magnesium sulfate. After removal of residual solvents by rotary evaporation and mechanical pumping, 0.10 g (85.1%) of yellow solid was obtained. An analytically pure sample was obtained by recrystallization from ethyl acetate, m.p. 258-260 °C (lit.:[70] m.p. 269-275 °C).

^{1}H NMR (400 MHz, $CDCl_3$): 4.06 (3H, s, H-6a), 4.09 (3H, s, H-7a), 7.63 (1H, s, H-5), 7.68 (1H, s, H-8), 8.56 (1H, br. s, NH).

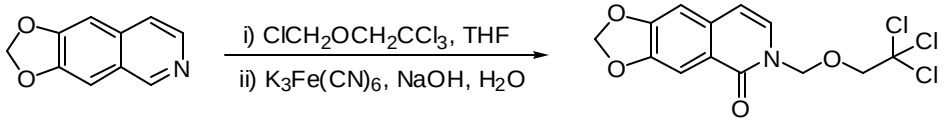
^{13}C NMR (100 MHz, $CDCl_3$): 56.8 (C-6a), 56.9 (C-7a), 108.9 (C-5), 110.2 (C-8), 124.0 (C-8a), 126.1 (C-4a), 154.3 (C-6), 155.8 (C-7), 156.3 (C-3), 161.5 (C-1), 173.9 (C-4).



1,3,4(2*H*)-Isoquinolinetrione (45a). A round-bottom flask charged with a magnetically stirred solution of **43a** (0.145 g, 1.00 mmol) in 5 mL of acetic acid was cooled in an ice/water bath. A solution of sodium dichromate dihydrate (0.89 g, 3.0 mmol) in 5 mL of 6 M H_2SO_4 was added dropwise at such a rate that the reaction temperature did not exceed 30 ^oC. The mixture was opened to the atmosphere and stirred for 3 days. Then 10 mL of water was added and the product was extracted with ethyl acetate (3 x 20 mL). The combined extracts were neutralized by the addition of solid sodium bicarbonate, washed with brine, and then dried over magnesium sulfate. After removal of the residual solvents by rotary evaporation and mechanical pumping, 0.140 g (80.0%) of yellowish solid was obtained. An analytical sample was obtained by recrystallization from ethyl acetate, m.p. 220-221 ^oC (lit.:[35] m.p. 221-223 °C).

^{1}H NMR (400 MHz, DMSO): 7.88 (1H, ddd, *J* = 7.6, 7.4, 1.4 Hz, H-6), 7.93 (1H, ddd, *J* = 7.4, 7.4, 1.7 Hz, H-7), 8.06 (1H, ddd, *J* = 7.6, 1.7, 0.7 Hz, H-5), 8.13 (1H, ddd, *J* = 7.4, 1.4, 0.7 Hz, H-8), 11.98 (1H, br.s, NH).

^{13}C NMR (100 MHz, DMSO): 126.6 (C-5), 128.0 (C-8), 129.7 (C-8a), 132.2 (C-4a), 133.9 (C-6), 134.8 (C-7), 157.4 (C-3), 163.1 (C-1), 175.4 (C-4).

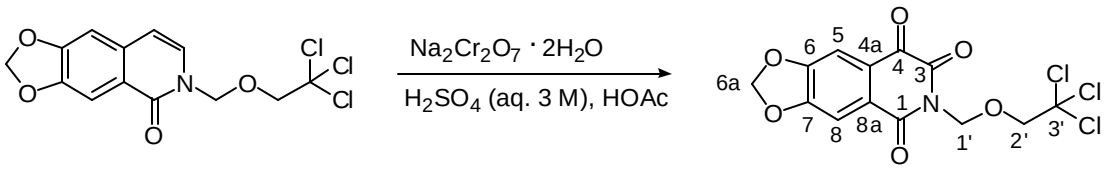


***N*-(2,2,2-Trichloroethoxymethyl)-6,7-methylenedioxyisocarbostyril (47).** A solution of 6,7-methylenedioxyisoquinoline (1.40 g, 8.1 mmol) and 2,2,2-trichloroethoxymethyl chloride (1.6 g 8.1 mmol) in 10 mL of dry THF in a round-bottomed flask was stirred under dry nitrogen for 72 hours. A large amount of precipitate was formed, and the solvent was removed by rotary evaporation. The dry salt was transferred to a three necked round-bottomed flask and dissolved in 7 mL of distilled water. The mixture was cooled

with an ice-water bath as solution A (0.54 g of NaOH in 6 mL of water) and half of solution B (4.87 g $K_3Fe(CN)_6$ in 25 mL of water) were added simultaneously while maintaining the temperature below 20 °C. After the remainder of solution B was added, the ice-water bath was removed. The reaction mixture was opened to the atmosphere and stirred overnight, after which the product was extracted with ethyl acetate (3 x 25 mL). The combined extracts were washed with 25 mL of 1M HCl, 25 mL of brine, and then dried over magnesium sulfate. After removal of the residual solvents, the product was recrystallized from a mixture of ethyl acetate and hexanes to give 1.75 g (61.8% over two steps) of yellow solid, m.p. 169-170 °C.

^{1}H NMR (300 MHz, $CDCl_3$): 3.39 (3H, s), 5.38 (2H, s), 6.08 (2H, s), 6.41 (1H, d, *J* = 7.3 Hz), 6.86 (1H, s), 7.08 (1H, d, *J* = 7.3 Hz), 7.78 (1H, s).

^{13}C NMR (75 MHz, $CDCl_3$): 57.0, 78.3, 102.0, 104.2, 106.3, 106.7, 121.8, 129.2, 134.6, 148.2, 152.3, 162.1.

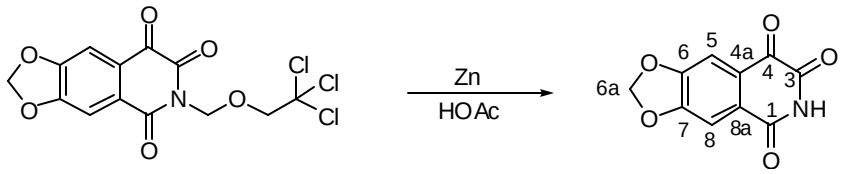


6,7-Methylenedioxy-2-(2,2,2-trichloroethoxymethyl)isoquinoline-1,3,4(2*H*)-trione (48). A round-bottom flask charged with a magnetically stirred solution of **47** (0.35 g, 1.0 mmol) in 5 mL of acetic acid was cooled in an ice-water bath. A solution of sodium dichromate dihydrate (0.89 g, 3.0 mmol) in 5 mL of 3 M H_2SO_4 was added dropwise at such a rate that the reaction temperature did not exceed 30 °C. The mixture was opened to the atmosphere and stirred for 1 hour. Then 10 mL of water was added and the product was extracted with dichloromethane (3 x 20 mL). The combined extracts were neutralized by the addition of solid sodium bicarbonate, washed with brine, and then dried over magnesium sulfate. After the removal of residual solvents by rotary evaporation and mechanical pumping, 0.33 g (86.9%) of yellow powder was obtained. Although this material was suitable for use in the next step without further purification, an analytical

sample was obtained by recrystallization from a mixture of ethyl acetate and hexanes, m.p. 156-158 ^{o}C. Elemental analysis: Anal. Calcd. for $C_{13}H_8NO_6Cl_3$: C, 41.03; H, 2.12. Found: C, 42.23; H, 2.17.

^{1}H NMR (400 MHz, $CDCl_3$): 4.39 (2H, s, H-2'), 5.78 (2H, s, H-1'), 6.25 (2H, s, H-6a), 7.58 (1H, s, H-5), 7.72 (1H, s, H-8).

^{13}C NMR (100 MHz, $CDCl_3$): 72.0 (C-1'), 83.5 (C-2'), 96.7 (C-3'), 103.6 (C-6a), 106.6 (C-5), 109.0 (C-8), 126.7 (C-8a), 128.1 (C-4a), 153.4 (C-6), 154.7 (C-7), 156.8 (C-3), 161.4 (C-1), 172.6 (C-4).

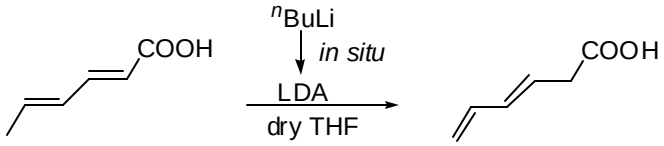


6,7-Methylenedioxy-1,3,4(2*H*)-isoquinolinetrione (45c). To a solution of **48** (0.19 g, 0.50 mmol) in 5 mL of acetic acid was added 0.2 g of freshly activated zinc dust (Zinc dust was washed with aqueous 2% hydrochloric acid, then ether, and dried *in vacuo*). The mixture was stirred and heated at reflux for 15 hours and then cooled to room temperature. The reaction mixture was diluted with 10 mL of water and the product was extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with water and brine, then dried over magnesium sulfate. Removal of the solvent at reduced pressure followed by flash silica gel chromatography (hexanes/ethyl acetate, 3:1) gave 0.070 g (64.2%) of **45c** as a yellow solid, m.p. 268-269 ^{o}C. Elemental analysis: Anal. Calcd. for $C_{10}H_5NO_5$: C, 54.81; H, 2.30. Found: C, 54.22; H, 2.44.

^{1}H NMR (400 MHz, DMSO): 6.31 (2H, s, H-6a), 7.46 (1H, s, H-5), 7.52 (1H, s, H-8), 11.93 (1H, br.s, NH).

^{13}C NMR (100 MHz, DMSO): 103.4 (C-6a), 105.3 (C-5), 106.8 (C-8), 126.8 (C-8a), 128.8 (C-4a), 152.1 (C-6), 153.1 (C-7), 157.2 (C-3), 162.4 (C-1), 173.9 (C-4).

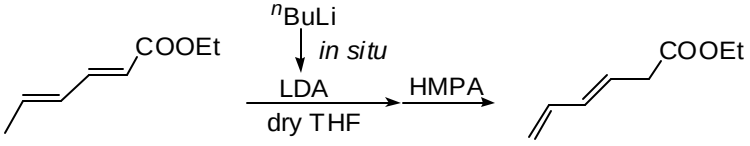
3.6 Synthesis of Dienes



3,5-Hexadienoic acid (50). To a solution of diisopropylamine (7.0 mL, 5.04 g, 50.0 mmol) in 30 mL of anhydrous THF, 20.0 mL (50.0 mmol) of *n*-butyllithium (2.5 M in hexanes) was added dropwise at -78 °C under dry nitrogen. After stirring for 2 hours, a solution of sorbic acid (2.50 g, 22.3 mmol) in 10 mL of anhydrous THF was added dropwise to the LDA at -78 °C . A white precipitate formed immediately and the light green/yellow solution gradually turned orange. After the addition was complete, the reaction mixture was stirred at room temperature overnight and then quenched with 3 M HCl to pH ~ 5. (Caution: the flask was fitted with a reflux condenser and cooled in the ice-water bath during this process). The organic layer was separated, and the aqueous layer was extracted with ether (3 x 50 mL). The combined extracts were dried over magnesium sulfate. The solvent was removed by rotary evaporation under reduced pressure to give 2.38 g (95.2%) of yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$): 3.17 (2H, d, *J* = 7.3 Hz), 5.08 (1H, d, *J* = 10.0 Hz), 5.13 (1H, d, *J* = 17.0 Hz), 5.77 (1H, m), 6.15 (1H, m), 6.30 (1H, m), 11.40 (1H, br. s)

^{13}C NMR (75 MHz, $CDCl_3$): 37.8, 117.6, 124.8, 135.1, 136.4, 178.4.

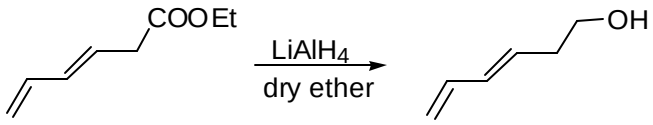


Ethyl 3,5-hexadienoate (52). To a stirred solution of diisopropylamine (10.0 mL, 7.22 g, 71.4 mmol) in 50 mL of anhydrous THF, 32 mL (80 mmol) of *n*-butyllithium (2.5 M in hexanes) was added dropwise at -78 °C under dry nitrogen. After 2 hours, 16 mL of hexamethyl phosphoramide (HMPA) was added and the reaction mixture was stirred for

an additional 20 min. Then a solution of ethyl sorbate (5.6 g, 40 mmol) in 20 mL of anhydrous THF was added dropwise to the cold solution. After the addition was complete, the reaction mixture was stirred at -78 ^{o}C for 2 hours. The resulting dark red solution was poured into a rapidly stirred mixture of ice-water (80 mL) and acetic acid (16 mL). The resulting solution was extracted with hexanes (3 x 50 mL), and the combined extracts were washed with saturated sodium bicarbonate, brine and then dried over magnesium sulfate. The solvent was removed by rotary evaporation under reduced pressure to give 4.98 g (88.9%) of yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$): 1.26 (3H, t, *J* = 7.3 Hz), 3.11 (2H, d, *J* = 7.3 Hz), 4.15 (2H, q, *J* = 7.3 Hz), 5.06 (1H, d, *J* = 10.0 Hz), 5.16 (1H, d, *J* = 17.0 Hz), 5.79 (1H, m), 6.14 (1H, m), 6.34 (1H, m).

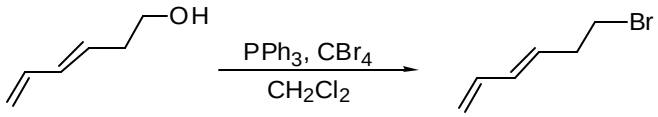
^{13}C NMR (75 MHz, $CDCl_3$): 14.4, 38.3, 61.0, 117.2, 126.0, 134.5, 136.6, 171.8.



3,5-Hexadien-1-ol (53). A solution of **52** (4.98 g, 35.6 mmol) in 30 mL of anhydrous ether was added slowly to a well-stirred solution of lithium aluminum hydride (25 mL of 2.0 M solution in THF diluted with 40 mL of anhydrous ether, 50 mmol). (Caution: the flask was fitted with a reflux condenser and cooled in an ice-water bath during this process). The reaction was allowed to stir at room temperature overnight followed by quenching with sequential additions of water (2 mL), 2 M NaOH (2 mL), and water (6 mL). The mixture was filtered and the filtrate was washed with brine and dried over magnesium sulfate. The solvent was removed by rotary evaporation under vacuum to give 3.14 g (90.0%) of yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$): 2.36 (2H, q, *J* = 6.7 Hz), 3.68 (2H, m), 5.02 (1H, d, *J* = 10.0 Hz), 5.14 (1H, d, *J* = 17.0 Hz), 5.68 (1H, m), 6.16 (1H, m), 6.32 (1H, m).

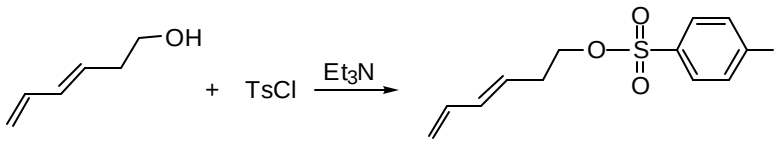
^{13}C NMR (75 MHz, $CDCl_3$): 36.2, 62.1, 116.3, 130.8, 134.1, 137.0.



6-Bromo-1,3-hexadiene (54). A three-necked flask was cooled in an ice-water bath and charged with 4.03 g (12.1 mmol) of carbon tetrabromide, 1.08 g (11.0 mmol) of **53**, and 50 mL of dry CH_2Cl_2. To this solution, 3.17 g (12.1 mmol) of triphenylphosphine was added, and the reaction mixture was stirred at 5 ^oC for 1 hour. After most of the solvent was removed by rotary evaporation, the mixture was diluted with 60 mL of hexanes and stirred for an additional 1 hour. The triphenylphosphine oxide precipitate was filtered and washed with 20 mL of hexanes. The combined filtrates were vacuum filtered through a two-inch plug of silica gel packed in a sintered glass funnel. The silica gel was washed with an additional 50 mL of hexanes and the combined filtrates were concentrated by rotary evaporation to give 1.13 g (63.8%) of colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): 2.65 (2H, q, *J* = 5.9 Hz), 3.40 (2H, t, *J* = 7.0 Hz), 5.06 (1H, d, *J* = 10.3 Hz), 5.17 (1H, d, *J* = 17.9 Hz), 5.67 (1H, m), 6.14 (1H, m), 6.30 (1H, m).

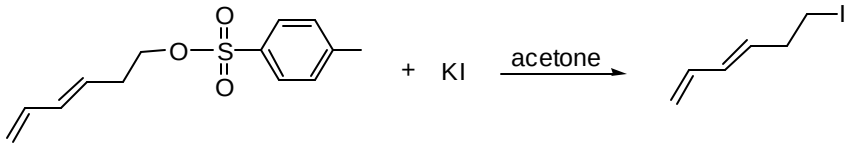
^{13}C NMR (75 MHz, $CDCl_3$): 32.3, 36.1, 116.9, 131.0, 133.8, 136.8.



1-Hexa-3,5-dienyl-*p*-toluenesulfonate (55). A three-necked flask was cooled in an ice-water bath and charged with 5.04 g of **53** (51.4 mmol) and 25 mL of triethylamine. Tosyl chloride (10.8 g, 56.7 mmol) was added to the solution over 30 min. The mixture was allowed to stir overnight at room temperature, then poured into water, and extracted with ether (4 x 50 mL). The ether extracts were washed repeatedly with 1M HCl to remove the triethylamine, then brine, and finally dried over magnesium sulfate. After the solvent was evaporated under reduced pressure, 10.9 g (84.5%) of yellowish oil was obtained.

^{1}H NMR (300 MHz, $CDCl_3$): 2.39-2.45 (5H, m), 4.06 (2H, t, *J* = 6.7 Hz), 5.03 (1H, d, *J* = 10.0 Hz), 5.11 (1H, d, *J* = 16.7 Hz), 5.51 (1H, m), 6.09 (1H, m), 6.23 (1H, m), 7.35 (2H, d, *J* = 8.2 Hz), 7.79 (2H, d, *J* = 8.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): 21.9, 32.2, 69.7, 116.9, 128.13, 128.17, 130.1, 133.3, 134.4, 136.7, 145.0.

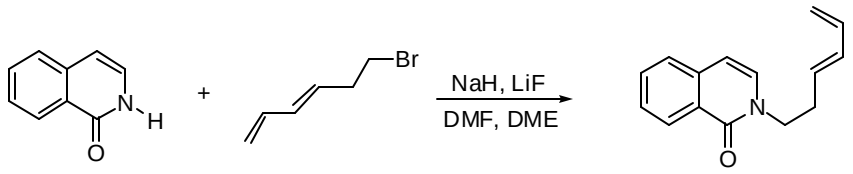


1-Iodo-3,5-hexadiene (56). A suspension of **55** (10.9 g, 43.3 mmol) and potassium iodide (14.3 g, 86.1 mmol) in 50 ml of dry acetone was heated under reflux for 6 hours. After most of the acetone was removed by rotary evaporation, the residue was poured into water and extracted with hexanes (3 x 50 mL). The combined extracts were washed with water and dried over sodium sulfate. Removal of the solvent by rotary evaporation gave 6.45 g (71.7%) of yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): 2.67 (2H, q, *J* = 7.3 Hz), 3.18 (2H, t, *J* = 7.3 Hz), 5.08 (1H, d, *J* = 9.7 Hz), 5.17 (1H, d, *J* = 16.7 Hz), 5.64 (1H, m), 6.14 (1H, m), 6.33 (1H, m).

^{13}C NMR (75 MHz, $CDCl_3$): 4.97, 36.8, 116.9, 132.8, 133.4, 136.8.

3.7 Synthesis of Diels-Alder Precusors

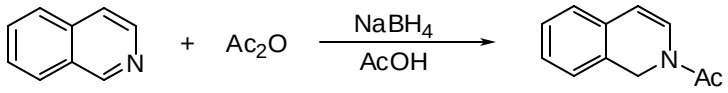


***N*-(3,5-Hexadienyl)isocarbostyril (59).** To a suspension of NaH (0.075 g, 3.1 mmol, rinsed three times with hexanes to remove mineral oil from a 60% dispersion) in DMF (1 mL) and DME (4 mL) was added a solution of isocarbostyril (0.29 g, 2.0 mmol) in DME (10 mL) at 0 °C. After 10 min, LiF (0.104 g, 4.00 mmol) was added; and after an

additional 15 minutes of stirring, **54** (0.48 g, 3.0 mmol) in DME (2 mL) was added dropwise. The resulting mixture was stirred at room temperature overnight and then quenched with ice water. The mixture was extracted with ethyl acetate (3 x 15 mL); the combined extracts were washed successively with water and brine, then dried over sodium sulfate. Removal of the solvent under reduced pressure followed by flash silica gel chromatography (hexanes/ethyl acetate, 2:1) gave 0.080 g of **59** (17.8%) as a yellow solid, m.p. 64-65 ^{o}C.

^{1}H NMR (300 MHz, $CDCl_3$): 2.58 (2H, q, *J* = 7.2 Hz), 4.05 (2H, t, *J* = 7.2 Hz), 5.00 (1H, d, *J* = 10.0 Hz), 5.10 (1H, d, *J* = 17.0 Hz), 5.69 (1H, m), 6.10 (1H, m), 6.29 (1H, m), 6.48 (1H, d, *J* = 7.0 Hz), 7.02 (1H, d, *J* = 7.3 Hz), 7.50 (2H, m), 7.62 (1H, m), 8.43 (1H, m).

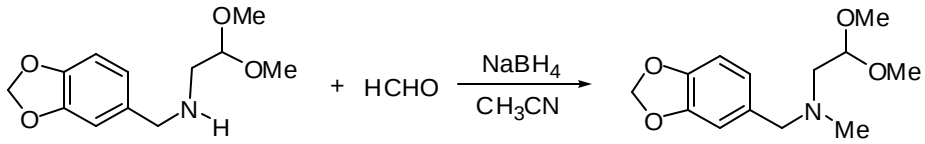
^{13}C NMR (75 MHz, $CDCl_3$): 32.5, 49.5, 106.2, 116.5, 126.1, 126.5, 127.0, 128.0, 130.2, 132.0, 132.3, 134.1, 136.9, 137.3, 162.3.



***N*-Acyl-1,2-dihydroisoquinoline (65).** Sodium borohydride (1.55 g, 40.0 mmol) was gradually added to a mixture of isoquinoline (1.18 mL, 1.29 g, 10.0 mmol), acetic acid (10 mL) and acetic anhydride (5 mL) over a period of 30 minutes with ice-water bath cooling. The mixture was allowed to stir at room temperature overnight. The reduction mixture was diluted with water, basified with sodium bicarbonate and extracted with ether (3 x 30 mL). The extracts were washed with 1M HCl and brine and dried over magnesium sulfate. After the solvent was removed by rotary evaporation, 1.42 g (82.1%) of colorless oil was obtained. An analytical sample was obtained by flash silica gel chromatography (hexanes/ethyl acetate, 1:1), and NMR data of the major product are consistent with the literature.[63]

^{1}H NMR (300 MHz, $CDCl_3$): 2.22 (3H, s), 4.95 (2H, s), 5.83 (1H, d, *J* = 7.6 Hz), 6.65 (1H, d, *J* = 7.9 Hz), 7.02-7.19 (4H, m).

^{13}C NMR (75 MHz, $CDCl_3$): 21.3, 44.3, 109.7, 124.7, 126.0, 126.1, 127.4, 127.7, 129.5, 130.5, 168.5.



***N*-Methyl-*N*-(2,2-dimethoxyethyl)-3,4-dimethoxybenzylamine (68).** To a solution of the amine **38c** (0.72 g, 3.0 mmol) in acetonitrile (10 ml) were added aqueous CH_2O (0.45 g of paraformaldehyde in 1 mL of water) and AcOH (4 ml) at room temperature. The mixture was stirred for 20 min followed by addition of $NaBH_4$ (0.3 g, 7.8 mmol). After stirring overnight, acetonitrile was removed *in vacuo*, and the residue was treated with 2 M NaOH (3 ml). The aqueous phase was extracted with ethyl acetate (3 x 30 mL), and the combined extracts were dried over anhydrous magnesium sulfate. The solution was evaporated *in vacuo*, and 0.53 g (69.8%) of yellowish oil was obtained. The sample was spectrally pure and ready to use without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 2.28 (3H, s), 2.54 (2H, d, J = 5.3 Hz), 3.33 (6H, s), 3.48 (2H, s), 4.52 (1H, t, J = 5.3 Hz), 5.93 (2H, s), 6.74 (2H, m), 6.86 (1H, s).

^{13}C NMR (75 MHz, $CDCl_3$): 43.2, 53.4, 58.2, 62.8, 101.1, 103.0, 108.0, 109.8, 122.5, 132.7, 146.8, 147.8.

REFERENCES

1. Bentley, K. W. The Alkaloids. Chemistry of Natural Products, Vol. 1; Interscience Publishers: New York, **1957**, pp 1-9.

2. Robinson, T. The Biochemistry of Alkaloids, 2nd Ed.; Springer: New York, **1981**, pp 1-11.

3. Pelletier, S. W. Chemistry of the Alkaloids. Van Nostrand Reinhold: New York, **1970**, pp 1-10.

4. Cordell, G A. Introduction to Alkaloids: A Biogenetic Approach. Wiley: New York, **1981**, pp 1-2.

5. Hesse, M. Alkaloids: Nature's Curse or Blessing. Wiley: New York, **2002**, pp 283-312.

6. Cordell, G. A. The Alkaloids: Chemistry and Biology, Vol. 50; Academic Press: San Diego, **1998**, pp 377-414.

7. Hoogewerf, S.; van Dorp, W. A. *Rec. Trav. Chim. Pays-Bas* **1885**, *4*, 125.

8. Shulgin, A. T.; Perry, W. E. The Simple Plant Isoquinolines. Transform Press: Berkeley, **2002**.

9. Grethe, G. Isoquinolines. Chemistry of Heterocyclic Compounds, Vol. 38; Wiley: New York, **1981**.

10. Kametani, T. The Chemistry of the Isoquinoline Alkaloids. Hirokawa Publishing Company: Tokyo, **1969**.

11. Shamma, M. The Isoquinoline Alkaloids: Chemistry and Pharmacology. Academic Press: New York, **1972**.

12. Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

13. Li, J. J. Name Reactions, 3rd Expanded Ed.; Springer: New York, **2006**.

14. Chen, Y.-H.; Zhang, Y.-H.; Zhang, H.-J.; Liu, D.-Z.; Gu, M.; Li, J.-Y.; Wu, F.; Zhu, X.-Z.; Li, J.; Nan, F.-J. *J. Med. Chem.* **2006,** *49*, 1613.

15. Ma, X.-Q.; Zhang, H-J.; Zhang, Y-H.; Chen, Y.-H.; Wu, F.; Du, J.-Q.; Yu, H.-P.;

Zhou, Z.-L.; Li, J.-Y.; Nan, F.-J.; Li, J. *Biochem. Cell Biol.* **2007**, *85*, 56.

16. Quattropani, A. Dorbais, J.; Covini, D.; Pittet, P.-A.; Colovray, V.; Thomas, R. J.; Coxhead, R.; Halazy, S.; Scheer, A.; Missotten, M.; et. al. *J. Med. Chem.* **2005,** *48,* 7882.

17. (a) Mitchell. G.; Clarke, E. D.; Ridley, S. M.; Greenhow, D. T.; Gillen, K. J.; Vohra, S. K.; Wardman, P. *Pest Manag. Sci.* **1995**, *44*, 49; (b) Mitchell, G; Clarke, E. D.; Ridley, S. M.; Bartlett, D. W.; Gillen, K. J.; Vohra, S. K.; Greenhow, D. T.; Ormrod, J. C.; Wardman, P. *Pest Manag. Sci.* **2000**, *56*, 120.

18. Mitchell, G; Clarke, E. D.; Ridley, S. M.; Bartlett, D. W.; Gillen, K. J.; Vohra, S. K.; Greenhow, D. T. *Pest Manag. Sci.* **2000**, *56*, 127.

19. Vekemans, J.; Hoornaert, G. *Tetrahedron* **1980**, *36*, 943.

20. Yoshifuji, S.; Arakawa, Y. *Chem. Pharm. Bull.* **1989**, *37*, 3380.

21. Nan, F.; Li, J.; Chen, Y.; Zhang, Y.; Gu, M.; Zhang, H. U.S. Pat. Appl. Publ. 2006/ 0135557 A1.

22. Pollers-Wieers, C.; Veremans, J.; Toppet, S.; Hoornaert, G. *Tetrahedron* **1981**, *37*, 4321.

23. Wakchaure, P. B.; Easwar, S.; Puranik, V. G.; Argade, N. P. *Tetrahedron* **2008**, *64*, 1786.

24. Brossi, A. The Alkaloids, Vol. 30. Academic Press: New York, **1987**, pp 251-376.

25. Pettit, G. R.; Gaddamidi, V.; Goswami, A.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 796.

26. Minter, D. E.; Winslow, C. D. *J. Org. Chem.* **2004**, *69*, 1603.

27. Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005,** *105*, 4779.

28. Hill, R. K.; Joule, J. A.; Loeffler, L. J. *J. Am. Chem. Soc.* **1962**, *84*, 4951.

29. Stork, G.; Morgans Jr., D. J. *J. Am. Chem. Soc.* **1979**, *101*, 7110.

30. Hwang, G.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1983**, 693.

31. Martin, S. F.; Tu, C.-y.; Kimura, M.; Simonsen, S. H. *J. Org. Chem.* **1982**, *47*, 3634.

32. Zhang, X.; Ye, W.; Zhao, S.; Che, C.-T. *Phytochemistry* **2004**, *65*, 929.

33. Hoarau, C.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2001**, 2559.

34. Rajaraman, R.; Rajalakshmi, S.; Chinnasamy, P. *Indian J. Chem. (B: Org. Chem. Med. Chem.)* **1986**, *25B*, 517.

35. Muchowski, J. M. *Can. J. Chem*. **1969**, *47*, 657.

36. Lee, D. G.; Spitzer, U. A. *Can. J. Chem*. **1971**, *49*, 2763.

37. Han, J. New Methods for the Synthesis of Isocarbostyrils (Thesis). Texas Christian University, **2004**.

38. Birch, A. J.; Jackson, A. H.; Shannnon, P. V. R.; Varma, P. S. P. *Tetrahedron Lett.* **1972**, 4789.

39. Glushkov, V. A.; Shklyaev, Yu. V. *Chemistry of Heterocyclic Compounds* **2001**, *37*, 663.

40. (a) Cava, M. P.; Buck, K. T. *Tetrahedron* **1969**, *25*, 2795. (b) Henry, R. A.; Heller, C. A.; Moore, D. W. *J. Org. Chem.* **1975**, *40*, 1760.

41. Kurita, J.; Yamanaka, T.; Tsuchiya, T. *Heterocycles* **1991**, *32*, 2089.

42. Li, M.; Wu, A.; Zhou, P. *Tetrahedron Lett.* **2006**, *47*, 3707.

43. Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K., Jr.; Medwid, J. B. *Org. Syn. Coll. Vol. VI* **1988**, 101.

44. Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4069.

45. Fringuelli, F.; Taticchi, A. The Diels-Alder Reaction: Selected Practical Methods. Wiley: New York, **2002**; pp 1-25.

46. Martin, S. F.; Desai, S. R.; Phillips, G. W.; Miller, A. C. *J. Am. Chem. Soc.* **1980**, *102*, 3294.

47. Fearnley, S. P.; Market, E. *Chem. Commun.* **2002**, 438.

48. Jung, M. E.; Buszek, K. R. *J . Org. Chem.* **1985**, *50*, 5440.

49. Martin, S. F.; Tu, C.-Y.; Chou, T.-S. *J. Am. Chem. Soc.* **1980**, *102*, 5274.

50. Stevens, R. V.; Cherpeck, R. E.; Harrison, B. L.; Lai, J.; Lapalme, R. *J. Am. Chem. Soc.* **1976**, *98*, 6317.

51. Pfeffer, P. E.; Silbert, L. S. *J. Org. Chem.* **1971**, *36*, 3290.

52. Miller, C. A.; Batey, R. A. *Org. Lett.* **2004**, *6*, 699.

53. Calzada, J. G.; Hooz, J. *Org. Syn. Coll. Vol. VI* **1988**, 634.

54. Howden, M. E. H.; Maercker, A.; Burdon, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 1732.

55. Dusemund, J. *Arch. der Pharm.* **1977**, *310*, 846.

56. Osornio, Y. M.; Miranda, L. D. *Rev. Soc. Quim. Mex*. **2004**, *48*, 288.

57. Winslow, C. D. A Methods Development Approach towards the Galanthan Skeleton Starting with Isoquinoline (Dissertation). Texas Christian University, **2000**.

58. Vaccher, C.; Berthelot, P.; Devergnies, M.; Debaert, M.; Bonte, J.-P.; Viel, C. *J. Heterocycl. Chem.* **1989**, *26*, 811.

59. Ferrer, S.; Naughton, D. P.; Parveen, I.; Threadgill, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 335.

60. (a) Yamaguchi, R.; Hamasaki, T.; Utimoto, K. *Chem. Lett.* **1988**, 913. (b) Yamaguchi, R.; Otsuji, A.; Utimoto, K. *J. Am. Chem. Soc.* **1988**, *110*, 2186.

61. Perchonock, C. D.; Lantos, I.; Finkelstein, J. A.; Holden, K. G. *J. Org. Chem.* **1980**, *45*, 1950.

62. (a) Hoshino, M.; Watanabe, K.; Ohtake, Y.; Sato, T.; Matsuzaki, H.; Fujita, R. *Heterocycles* Published online, March 14, 2008. (b) Fujita, R.; Wakayanagi, S.; Wakamatsu, H.; Matsuzaki, H. *Chem. Pharm. Bull.* **2006**, *54*, 209.

63. Katayama, H.; Ohkoshi, M.; Yasue, M. *Chem. Pharm. Bull.* **1980**, *28*, 2226.

64. Gharbo, S. A.; Beal, J. L.; Schlessinger, R. H.; Cava, M. P.; Svoboda, G. H. *Lloydia* **1965**, *28*, 237.

65. Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 8940.

66. Krane, B. D.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 377.

67. Carmody, M. P.; Sainsbury, M.; Newton, R. F. *J. Chem. Soc. Perkin I* **1980**, 2013.

68. Takaki, K.; Okamura, A.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1978**, *43*, 402.

69. Chatterjea, J. N.; Jha, H. C.; Banerjee, B. K. *J. Indian Chem. Soc.* **1966**, *43*, 633.

70. Ahl, A.; Reichstein, T. *Helv. Chim. Acta* **1944**, *27*, 366.

VITA

Personal	Yijun Huang
Background	Jiangsu Province, China, March 15, 1981
	Son of Caizhong Huang and Yunxian Zuo
	Married Hong Zhang, December 27, 2007
Education	Bachelor of Science, Chemistry, Nanjing University
	Nanjing, China, 2003
	Master of Science, Organic Chemistry, Nanjing University
	Nanjing, China, 2006
	Master of Science, Chemistry, Texas Christian University
	Fort Worth, Texas, 2008
Experience	Teaching Assistant, Nanjing University
	Feb 2004 - Jun 2004
	Teaching Assistant, Texas Christian University
	Aug 2006 - Dec 2007
Professional Membership	Chinese Chemical Society

ABSTRACT

TRANSFORMATIONS OF ISOCARBOSTYRILS FOR THE SYNTHESIS OF ISOQUINOLINE ALKALOIDS AND THE RELATED ANALOGUES

by Yijun Huang, M.S., 2008

Department of Chemistry

Texas Christian University

Thesis Advisor: David E. Minter, Professor of Chemistry

A practical method for the synthesis of an isoquinoline alkaloid 6,7-dimethoxy-2-methylisoquinoline-1,3,4(2*H*)-trione and its analogues has been demonstrated. Two new methods for synthesizing substituted phthalonimides from the corresponding isocarbostyrils have been developed. Phthalonimide derivatives were obtained by the oxidation of isocarbostyrils protected with methoxymethyl and ß,ß,ß-trichloroethoxy-methyl groups. The direct oxidation of isocarbostyrils under different conditions was also investigated.

In addition, six dienes for potential use in the development of a [4+2] cycloaddition approach to galanthan tetracyclic ring system have been synthesized. These precursors and dienophiles are based on and drived from isoquinolines and isocarbostyrils.