

# HETEROCYCLES AND NATURAL PRODUCTS SYNTHESIS THROUGH OXIDATIVE DEAROMATIZATION

DOI: <http://dx.medra.org/10.17374/targets.2017.20.33>

Gaëtan Maertens and Sylvain Canesi

Laboratory of Methodology and Natural Product Synthesis, University of Quebec at Montreal,  
Downtown Branch, P.O. Box 8888, QC H3C 3P8-Montreal, Canada  
(e-mail: [canesi.sylvain@uqam.ca](mailto:canesi.sylvain@uqam.ca))

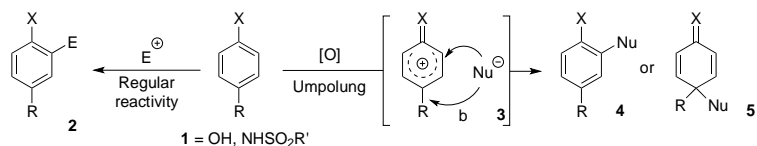
**Abstract.** This chapter first summarizes our work on heterocycle synthesis by oxidative dearomatization of phenol or aniline derivatives with hypervalent iodine reagents. The process creates electrophilic agents that function as 1,3-dipoles in formal cycloadditions with furan, electron-rich alkenes, allylsilanes, and even unactivated benzene derivatives. In a second part, total syntheses of Amaryllidaceae, Aspidosperma, Erythrina and Strychnos alkaloids that highlight the above methodology are described.

## Contents

1. Introduction
  2. Oxidative cycloadditions with substituted phenols and sulfonamides
    - 2.1. Formal oxidative cycloadditions between substituted phenols and furan
    - 2.2. Reactions between substituted phenols and electron-rich alkenes
    - 2.3. Reactions between substituted phenols and allylsilanes
    - 2.4. Reactions between substituted phenols and unactivated benzene derivatives
    - 2.5. Formal oxidative cycloadditions with *N*-aryl sulfonamides
  3. Heterocyclic natural product synthesis from functionalized dienones
    - 3.1. Amaryllidaceae alkaloids: synthesis of mesembrine and dihydro-*O*-methylsceletenone
    - 3.2. Amaryllidaceae alkaloids: synthesis of sceletenone and *O*-methylsceletenone
    - 3.3. Lycorine alkaloids: asymmetric synthesis of (–)-fortucine
    - 3.4. Aspidosperma alkaloids: synthesis of aspidospermidine
    - 3.5. Aspidosperma alkaloids: synthesis of acetylaspidalbidine
    - 3.6. Erythrina alkaloids: synthesis of erysotramidine
    - 3.7. Strychnos alkaloids: synthesis of isostrychnine
    - 3.8. Strychnos alkaloids: asymmetric synthesis of (–)-strychnopivotine
  4. Conclusions
- Acknowledgments  
References

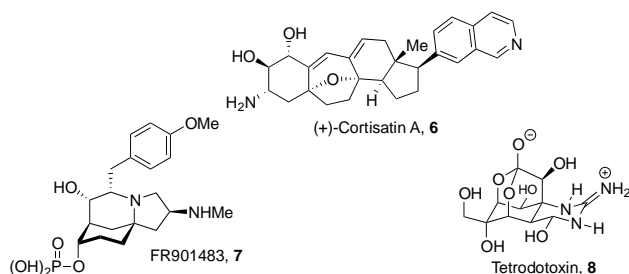
## 1. Introduction

Oxidative dearomatization, also termed “aromatic ring umpolung”, transforms simple, inexpensive aromatics into more functionalized and reactive compounds. Indeed, electron-rich aromatics, such as phenols and anilines, usually react as nucleophiles (Scheme 1). However, suitable oxidative activation enables their conversion into electrophilic species **3**.



**Scheme 1.** Illustration of the “aromatic ring umpolung” concept.

This process may occur through a Single-Electron Transfer (SET) mechanism. Electrophile **3** can then be captured with an appropriate nucleophile. In a bimolecular process, the regioselectivity of this step depends on the nature of the nucleophile. As demonstrated by Kita,<sup>1</sup> heteronucleophiles tend to react at the site with the larger LUMO coefficient (pathway b), thus leading to a prochiral dienone **5**. In contrast, steric interactions guide carbon nucleophiles to the less hindered position (pathway a), leading to a substituted aromatic product **4**. Oxidative dearomatization processes can be triggered by hypervalent iodine reagents, such as (diacetoxyiodo)benzene (DIB) or bis(trifluoroacetoxy)iodobenzene (PIFA), and are often performed in protic polar solvents like hexafluoropropan-2-ol (HFIP) or trifluoroethanol (TFE) to stabilize the phenoxonium ion, as demonstrated by Kita and coworkers.<sup>1</sup> In the past decades, this synthetic tool has aroused interest of the scientific community<sup>2</sup> and has played a substantial role in the total synthesis of heterocyclic natural compounds, as highlighted in different reviews.<sup>3</sup> For example, the synthesis of the main core of (+)-cortistatin A<sup>4</sup> **6**, the total synthesis of FR901483<sup>5</sup> **7** and a recent formal synthesis of tetrodotoxin<sup>6</sup> **8** are based on an oxidative dearomatization as key step (Figure 1).

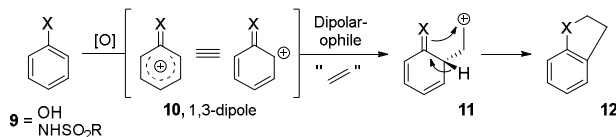


**Figure 1.** Representative examples of structures synthesized through oxidative dearomatization.

This chapter first describes our work on the synthesis of heterocycles through oxidative cycloadditions with phenols or sulfonamide substrates. Subsequently, our syntheses of *Amaryllidaceae*, *Aspidosperma*, *Erythrina* and *Strychnos* alkaloids based on oxidative dearomatization strategies are reviewed.

## 2. Oxidative cycloadditions with substituted phenols and sulfonamides

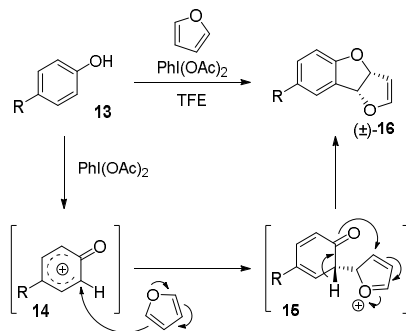
Electrophilic ions **10**, arising through oxidative activation of electron-rich aromatics with hypervalent iodine reagents, can be considered as 1,3-dipoles thanks to the presence of both a cationic charge and a nucleophilic heteroatom (Scheme 2). Indeed, they can combine with a dipolarophile through a formal cycloaddition pathway to produce 1,2-dihydrobenzofurans (**12**, X = O) or indolines (**12**, X = NR) via an intermediate such as **11**. The overall process may be described as a formal oxidative cycloaddition, several examples of which are illustrated in the next section.



**Scheme 2.** Formal oxidative cycloaddition concept.

### 2.1. Formal oxidative cycloadditions between substituted phenols and furan

In 2007, we demonstrated that *para*-substituted phenols **13** are transformed into tricyclic structures **16** by reaction with DIB and furan in TFE (Scheme 3).<sup>7</sup> Mechanistically, attack of furan on intermediate **14**, termed a phenoxonium ion, generates oxonium species **15**. The carbonyl oxygen subsequently adds to the activated unsaturation, and the process is concluded by rearomatization of the dienone moiety. A formal [2+3] cycloaddition has thus occurred. Substituent R can be alkyl, ester, protected amine and even a trimethylsilyl group. In all cases, the transformation proceeds in good yields.

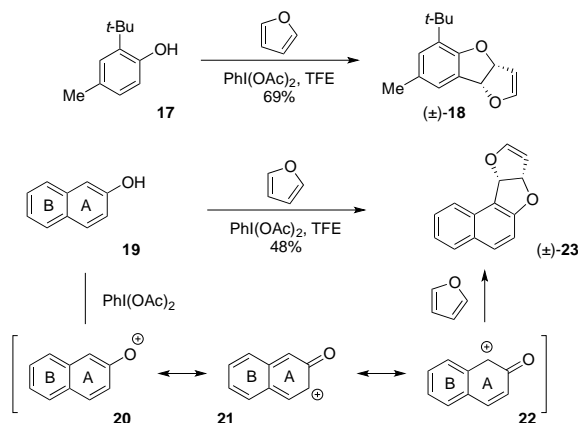


**6 examples**  
38-61 % yield  
R = Alkyls, OMe, CH<sub>2</sub>CO<sub>2</sub>Me, (CH<sub>2</sub>)<sub>2</sub>NHTs, SiMe<sub>3</sub>

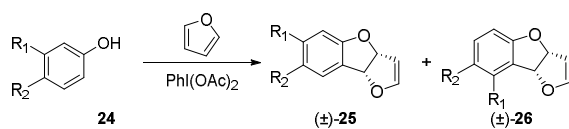
**Scheme 3.** Oxidative cycloaddition between *para*-substituted phenols and furan.

The process can be extended to 2,4-disubstituted phenols and to 2-naphthol (Scheme 4). The regioselectivity observed in the latter case may be due to the phenoxonium species reacting preferentially as mesomer **22**, which is favored relative to **21** because it retains an aromatic B ring. A significant loss of regioselectivity is observed if the phenolic substrate is *meta*-substituted. For instance, a 1:1 mixture of regioisomers **25a** and **26a** (41%) was recovered from the reaction of **24a** with DIB in the presence of furan (Scheme 5). Marginally improved regioselectivity was observed with *meta*-ethyl phenol **24b** (3:2 in favor of **25b**). However, the same reaction of 3-methoxyphenol **27** was appreciably regioselective for **29** (6:1).

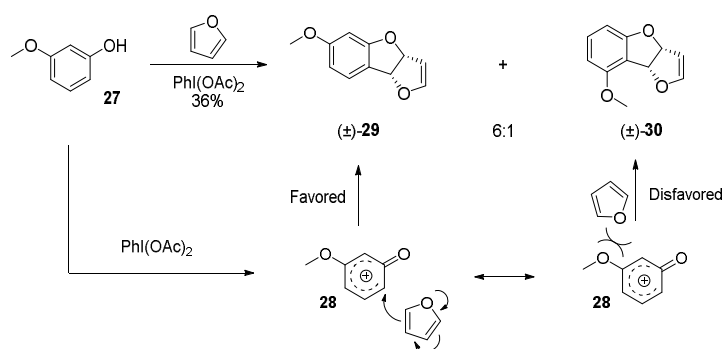
Perhaps, and unlike the ethyl group of **24b**, the lone pairs of the oxygen atom of the MeO group induce electronic repulsions that disfavor approach of the furan to the neighboring position. Regiocontrol may be re-established by blocking one of the phenolic *ortho*-positions with a suitable group. For example, oxidative activation of *ortho*-TMS phenol **31** in the presence of furan gave **32** as the sole regioisomer (Scheme 6). Product **32** is a key intermediate in our total synthesis of (±)-panacene.<sup>8</sup> Thus, desilylation with TBAF and CsF led to **33**, oxymercuration-demercuration of which produced hemi-ketal **34**.



**Scheme 4.** Cycloadditions between 2,4-disubstituted phenols or 2-naphthol and furan.



**24a** :  $R_1 = R_2 = \text{Me}$ , 41% yield, 1:1 **25a/26a**  
**24b** :  $R_1 = \text{Et}$ ,  $R_2 = \text{H}$ , 46% yield, 3:2 **25b/26b**

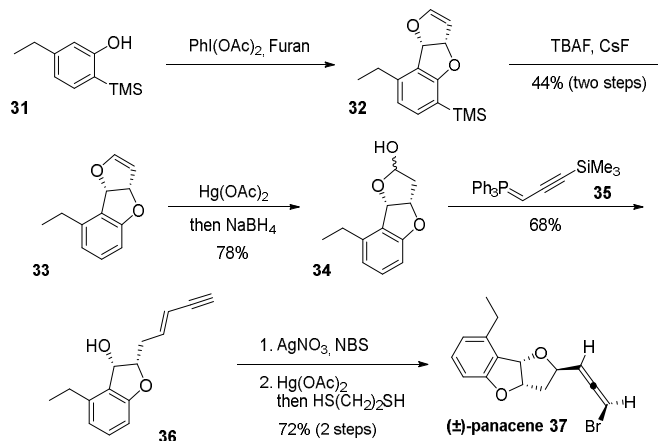


**Scheme 5.** Cycloaddition between 3-substituted phenols and furan.

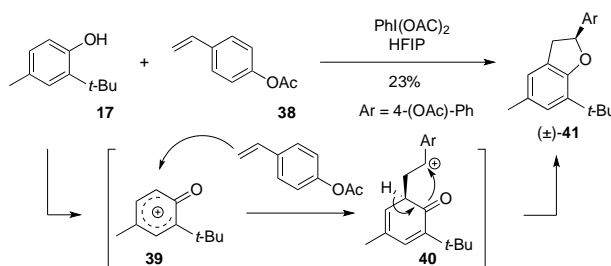
Wittig reaction of **34** with ylide **35** delivered the (*E*)-isomer of **36**. Finally, bromination of the alkyne followed by mercury(II)-promoted cyloetherification produced panacene **37** (Scheme 6).

## 2.2. Reactions between substituted phenols and electron-rich alkenes

Certain electron-rich alkenes react with phenoxonium ions in a similar manner. To illustrate, DIB-mediated reaction of phenol **17** with 4-acetoxystyrene **38** leads to dihydrobenzofuran **41** (Scheme 7).<sup>8b</sup> This is in agreement with previous reports by Swenton and coworkers.<sup>9</sup> The process embodies a formal [2+3] cycloaddition beginning with the attack of the styrene on phenoxonium ion **39**. Cation **40** is then trapped by the carbonyl oxygen and a final aromatization yields **41**.

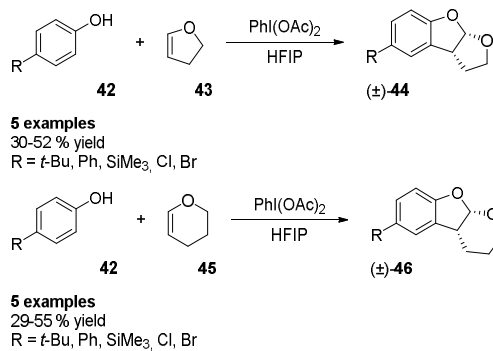


**Scheme 6.** Synthesis of panacene through oxidative formal [2+3] cycloaddition.



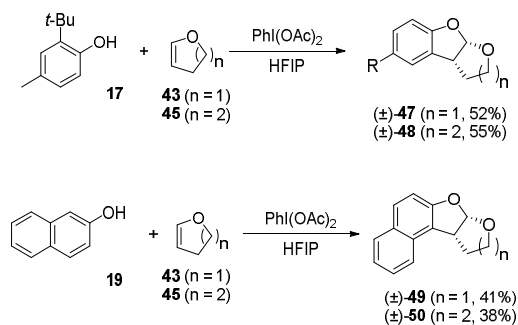
**Scheme 7.** Reaction between phenol **17** and 4-acetoxystryrene **38**.

Cyclic vinyl ethers also participate in this cycloaddition process (Scheme 8). Reaction between *para*-substituted phenols **42** and dihydrofuran in the presence of DIB afforded dihydrobenzofurans **44**, while the use of dihydropyran resulted in formation of tricycles **46**. Phenolic substituents R that can be useful for further functionalization, like a TMS group or halogens, are well tolerated.



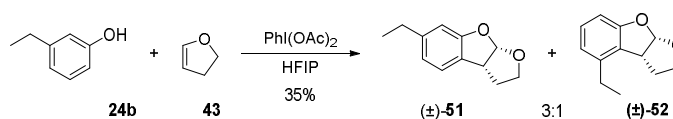
**Scheme 8.** Reaction between *para*-substituted phenols and cyclic vinyl ether.

As in the case of furan (Scheme 5), the cycloaddition process can be extended to 2,4-disubstituted phenols and 2-naphthol, leading to tricycles **47** and **48** and tetracycles **49** and **50**, respectively (Scheme 9).



**Scheme 9.** Reaction between 2,4-disubstituted phenols or 2-naphthol with cyclic enol ethers.

Oxidative cycloaddition of 3-ethylphenol **24b** to dihydrofuran (Scheme 10) occurred with higher regioselectivity compared to the same reaction of furan (Scheme 5) and produced a 3:1 mixture of regioisomers **51** and **52** in 35% yield.



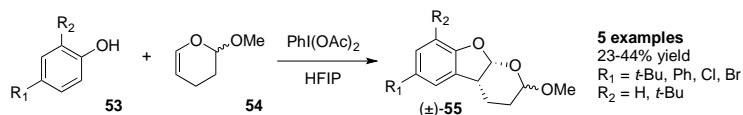
**Scheme 10.** Influence of the *meta* substitution on the regioselectivity.

Improved selectivity is attributable to a different orientation of the nucleophile during addition to the phenoxonium ion. Furan reacts from its position 2, so that steric interactions experienced during attack at either C-2 or C-6 of the phenoxonium ion are very similar, resulting in poor/no regioselectivity. Dihydrofuran reacts from its position 3, and approach to C-2 of the phenoxonium ion engenders significantly greater steric interactions than attack at C-6. The latter pathway is thus favored. Finally, tetrahydrofurobenzofurans **55** emerge in moderate yields (23-44%) upon reaction of variously substituted phenols **53** with ketal **54** under similar conditions (Scheme 11).

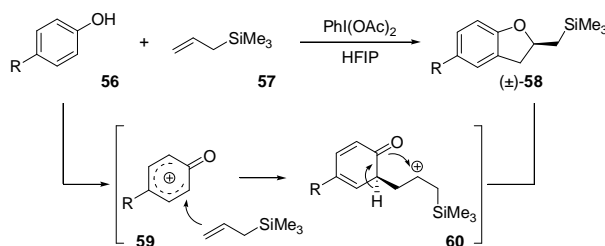
### 2.3. Reactions between substituted phenols and allylsilanes

Allylsilanes are also suitable components of formal oxidative [2+3] cycloadditions (Scheme 12).<sup>10,8b</sup> The use of a polar, protic, non-nucleophilic solvent is required to stabilize the positive charge in **60** and prevent desilylation. Diverse substituents R are well tolerated, including halogens, which allow further functionalization of products **58** through palladium chemistry.

However, a significant decrease in yields is observed when R incorporates a benzylic hydrogen (Scheme 13). This may be ascribed to competing deprotonation of reactive intermediate **63**, leading to quinoid species **64**, which then can give rise to complex mixtures of byproducts or polymers.

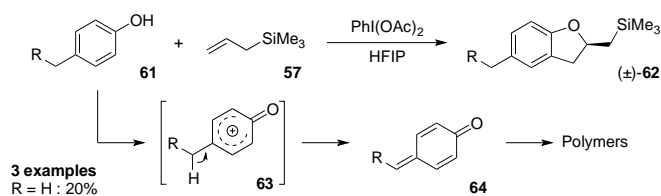


**Scheme 11.** Reaction between substituted phenols **53** and ketal **54**.



**7 examples**  
40-58% yield  
R = *t*-Bu, I, Br, Cl, OMe, OPh, SiMe<sub>3</sub>

**Scheme 12.** Reaction between *para*-substituted phenols and allyltrimethylsilane.



**3 examples**  
R = H : 20%  
R = CH<sub>2</sub>OH : 21%  
R = CH<sub>2</sub>NHTs : 35%

**Scheme 13.** Limitation of the reaction between *para*-substituted phenols and allyltrimethylsilane.

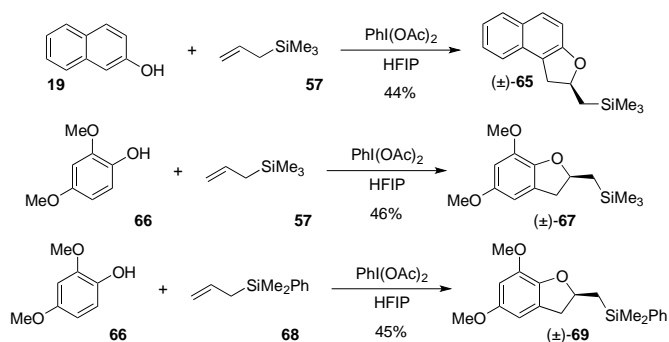
The same reaction of 2-naphthol and 2,4-dimethoxy phenol affords **65** and **67** in 44% and 46% yields respectively (Scheme 14). More complex allylsilanes such as **68** may be employed in lieu of **57**.

#### 2.4. Reactions between substituted phenols and unactivated benzene derivatives

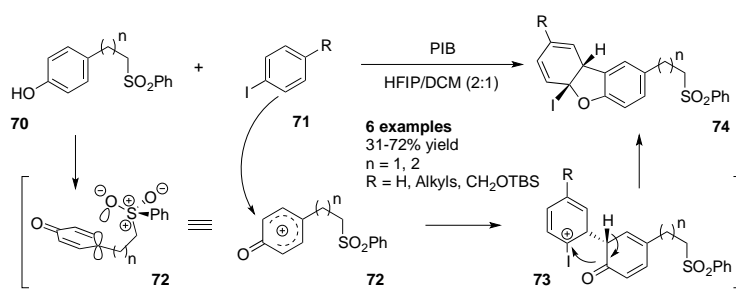
Formal oxidative [2+3] cycloadditions can be carried out even with unactivated benzene derivatives.<sup>11</sup> For instance, oxidative activation of sulfonyl phenol **70** with bis-(pivaloyloxy)iodobenzene (PIB) in a 2:1 mixture of HFIP/DCM, and in the presence of iodoaryls **71** incorporating diverse substituents R, results in formation of dihydrobenzofurans **74** in generally good yield (Scheme 15).

The proposed mechanism envisions stabilization of ion **72** by an intramolecular n(O)-π\* interaction, which extends the lifetime of **72**, enabling subsequent reactions. In the absence of this interaction, the phenoxonium ion would suffer benzylic deprotonation (Scheme 13).

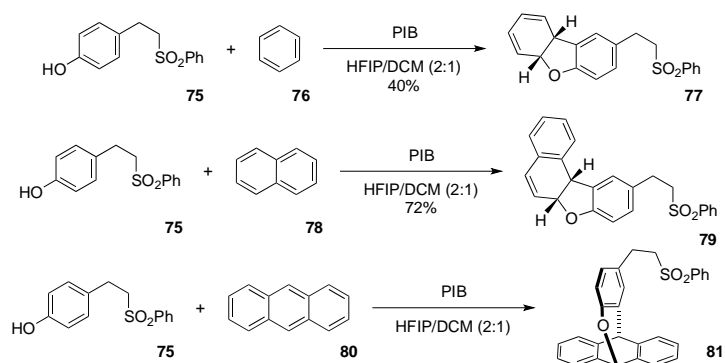
Attack of the iodoarene on **72**, interception of Wheland intermediate **73** by the carbonyl oxygen, and aromatization yield the product. Even plain benzene participates in the reaction, leading to tricycle **77** in 40% yield (Scheme 16). Naphthalene reacts more efficiently (72% yield), and anthracene combines with **75** to give heterocycle **81** in 58% yield.



**Scheme 14.** Reaction between 2-naphthol or 2,4-dimethoxyphenol and allylsilane.



**Scheme 15.** Cycloaddition between phenols **70** and iodoaryls **71**.



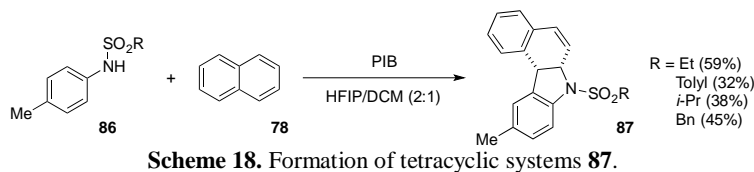
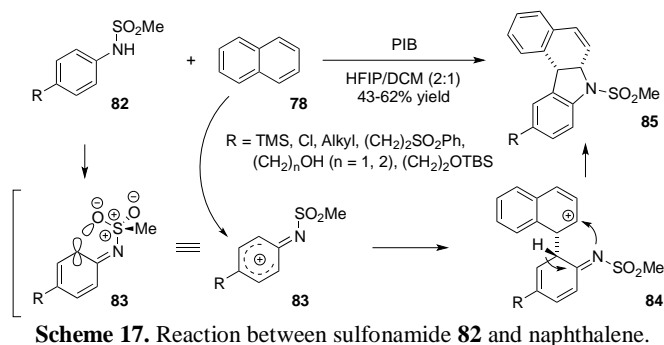
**Scheme 16.** Cycloaddition between phenol **75** and benzene or naphthalene.

### 2.5. Formal oxidative cycloadditions with *N*-aryl sulfonamides

The transformations described above are not limited to phenolic substrates. Indeed, hypervalent iodine reagents oxidize *N*-aryl sulfonamides to electrophilic species that also act as dipoles in cycloaddition processes. For instance, sulfonamides **82** advance to tetracyclic indole derivatives **85** upon reaction with naphthalene in the presence of PIB (Scheme 17).<sup>11a</sup> Again, stabilization of **83** by the sulfonyl group seems to be important to avoid benzylic deprotonation and prolong the lifetime of the cation. Good yields are achieved when R is chlorine, TMS, alkyl, or a free or protected hydroxyalkyl group. On a final note, the nature of the sulfonyl moiety appears to influence the outcome of the reaction through steric effects (Scheme

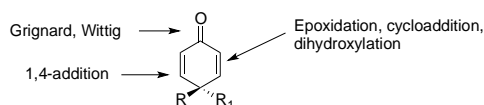


18). Thus, an ethylsulfonamide reacts as efficiently as a methylsulfonamide (59% vs 61), but yields drop with progressively bulkier sulfonyl groups.



### 3. Heterocyclic natural product synthesis from functionalized dienones

Functionalized cyclohexadienones are versatile educts in heterocyclic natural product synthesis. The simultaneous presence of electrophilic unsaturation and carbonyl subunits permits further elaboration to a diverse array of derivatives through carbonyl 1,2- and 1,4-addition, Wittig olefination, cycloaddition, epoxidation, dihydroxylation, etc. (Figure 2). In this section, we review some syntheses of *Amaryllidaceae*, *Aspidosperma*, *Erythrina*, and *Strychnos* alkaloids recently achieved in our group, and based upon phenolic oxidative dearomatization strategies that produce cyclohexadienones.

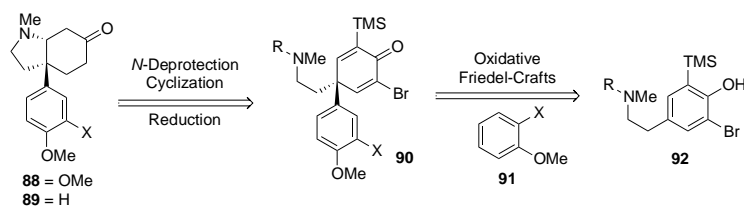


#### 3.1. *Amaryllidaceae* alkaloids: synthesis of mesembrine and dihydro-O-methylsceletenone

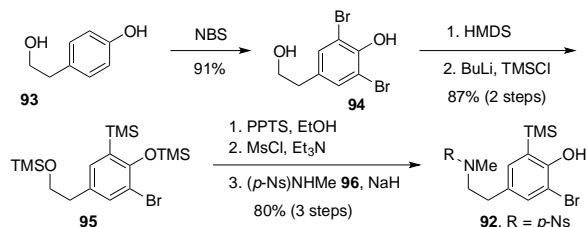
In 2008, we reported a total synthesis of mesembrine<sup>12,13</sup> **88** and dihydro-O-methylsceletenone **89**, two *Amaryllidaceae* alkaloids respectively found in *Sceletium tortuosum*<sup>14</sup> and *A. cordifolia*.<sup>15</sup> These compounds are very active serotonin reuptake inhibitors, even at low doses. Our retrosynthetic strategy (Scheme 19)<sup>16</sup> envisions pyrrolidine ring formation via *N*-deprotection-cyclization of dienone **90**, which is available from phenol **92** via an oxidative Friedel-Crafts reaction.

Compound **92** was prepared starting with dibromination and *O*-silylation of commercial **93**, followed by halogen-metal exchange and silylation of the intermediate organometallic (Scheme 20). The primary

alcohol in **95** was selectively de-protected and the corresponding mesylate was displaced with the sodium salt of sulfonamide **96**, resulting in formation of the desired phenol.

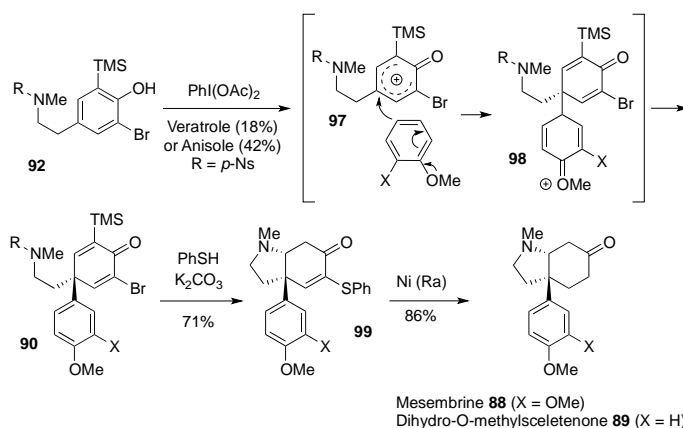


**Scheme 19.** Retrosynthesis of mesembrine and dihydro-O-methylsceletenone.



**Scheme 20.** Synthesis of phenol **92**.

Oxidative activation of **92** with DIB in the presence of veratrole or anisole returned products **90** in 18% and 42% yield, respectively, arguably through an oxidative Friedel-Crafts reaction evolving from phenoxonium ion **97** (Scheme 21).<sup>16</sup>



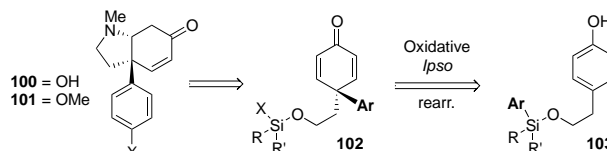
**Scheme 21.** Formation of **90** through an oxidative Friedel-Crafts reaction.

The moderate yield of this step constitute a weakness, a general solution to which was subsequently devised as outlined in the following section. The synthesis thus continued with treatment of **90** with thiophenol and  $K_2CO_3$ . This induced a cascade of events (Fukuyama deprotection<sup>17</sup> of the amine, Michael-retro-Michael processes, nucleophilic substitution of bromide, desilylation) that resulted in formation of **99**

in 71% yield. A final Raney Nickel reduction of **99** completed the total synthesis of mesembrine **88** and dihydro-O-methylsceletenone **89**.

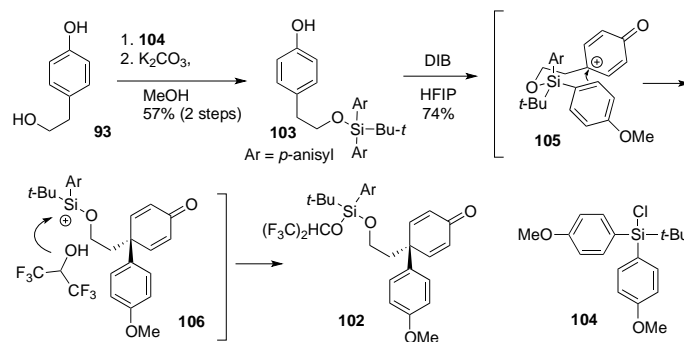
### 3.2. Amaryllidaceae alkaloids: synthesis of sceletenone and O-methylsceletenone

An efficient avenue to dienones of the type **90** becomes possible via intramolecular aryl group transfer from a suitably placed silyl protecting group to the phenoxonium ion arising upon oxidative activation of a phenol. We describe this process as an oxidative *ipso* rearrangement (cf. **103**→**102**, Scheme 22).<sup>18</sup> The technique illustrates the use of *functional protecting groups*,<sup>19</sup> and it forms the centerpiece of our total synthesis of O-methylsceletenone **101** and sceletenone **100**, natural products isolated from *A. cordifolia* and *Sceletium strictum*,<sup>20</sup> respectively.



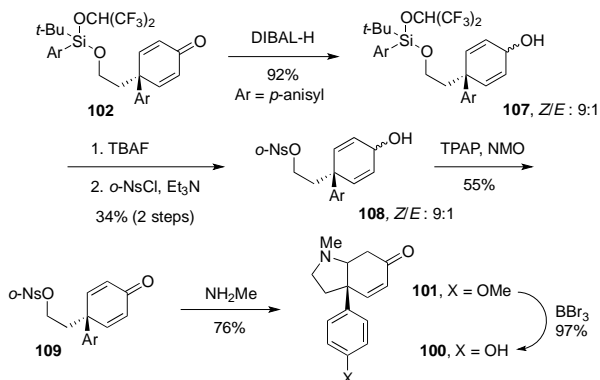
**Scheme 22.** Sceletenone and O-methylsceletenone: dienone **102** via oxidative *ipso* rearrangement.

This effort started with bis-silylation of commercial **93** with di(4-methoxyphenyl)tert-butylchlorosilane **104**<sup>18</sup> and selective deprotection of the phenol under basic conditions (Scheme 23). Reaction of the resulting **103** with DIB in hexafluoroisopropanol provided dienone **102** in 74% yield: a significant improvement over the past (cf. Scheme 21). This transformation probably involves aryl transfer from the silyl group to phenoxonium ion **105**<sup>18</sup> via a chair-like transition and solvolysis of silyl cation **106**.



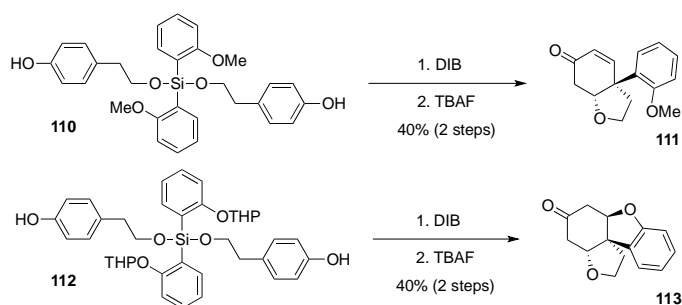
**Scheme 23.** Synthesis of dienone **102** by an oxidative *ipso*-rearrangement.

The carbonyl group in **102** was now reduced (DIBAL-H) to a 9:1 mixture of *Z*:*E* alcohols **107** (Scheme 24). Reduction was necessary to avoid oxo-Michael cyclization during the subsequent TBAF deprotection of the hydroxyl group. This produced a diol that reacted selectively with bulky 2-nitrobenzenesulfonyl chloride to yield sulfonate **108**, which upon Ley-Griffith<sup>21</sup> oxidation provided dienone **109**. Treatment of **109** with methylamine promoted a tandem S<sub>N</sub>2-aza-Michael process that furnished O-methylsceletenone **101**, easily converted into sceletone **100** with BBr<sub>3</sub>.



**Scheme 24.** Completion of the synthesis of O-methylsceletenone **101** and sceletenone **100**.

Oxidative *ipso* rearrangements are a method of choice for the synthesis of certain oxygen heterocycles. To illustrate (Scheme 25), phenol **110** advanced to **111** upon DIB oxidation and TBAF deprotection (40% over two steps). Tetracyclic structure **113** was produced under similar conditions from **112**.

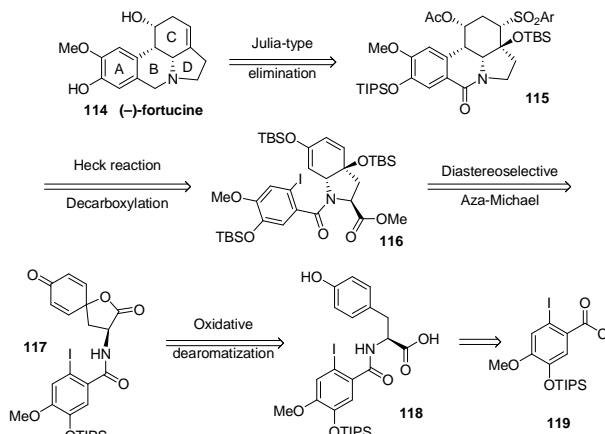


**Scheme 25.** Formation of **111** and **113** through oxidative *ipso* rearrangement.

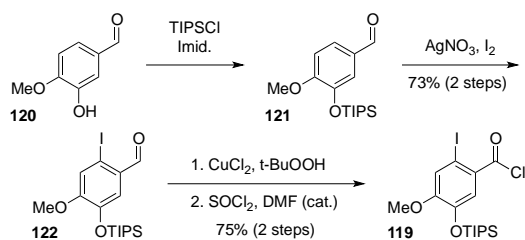
### 3.3. Lycorine alkaloids: asymmetric synthesis of (–)-fortucine

Lycorine alkaloids<sup>22</sup> are a subgroup of *Amaryllidaceae* alkaloids that possess interesting antiviral and antitumor activities.<sup>23</sup> A representative lycorine alkaloid is fortucine **114**, found in the fortune variety of narcissus<sup>24</sup> and based on a pyrrolo[d,e]phenantridine skeleton with a *cis*-B/C ring junction. The first synthesis of (±)-fortucine was achieved by Zard and coworkers in 2008.<sup>25</sup> Our enantiocontrolled route to **114** (Scheme 26) envisions Julia-type elimination of sulfone **115** to produce the required C=C bond and installation of the B ring by an intramolecular Heck reaction of enol-ether **116**. The carbomethoxy group in **116** serves only as an element of stereocontrol during Michael cyclization of **117** and would be removed at an appropriate stage. Substance **117** is available by oxidative dearomatization of **118**, recognized at the product of *N*-acylation of natural tyrosine with acid chloride **119**.

Fragment **119** was prepared starting with TIPS protection of isovanillin **120** and iodination of **121** using I<sub>2</sub> and AgNO<sub>3</sub> (Scheme 27), followed by oxidation of the aldehyde in the presence of CuCl<sub>2</sub> and *t*-BuOOH and DMF-catalyzed chlorination.<sup>26</sup>



**Scheme 26.** Retrosynthesis of (-)-fortucine.

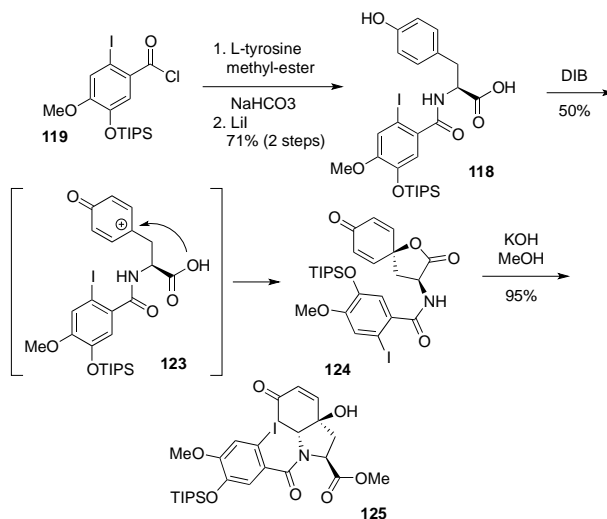
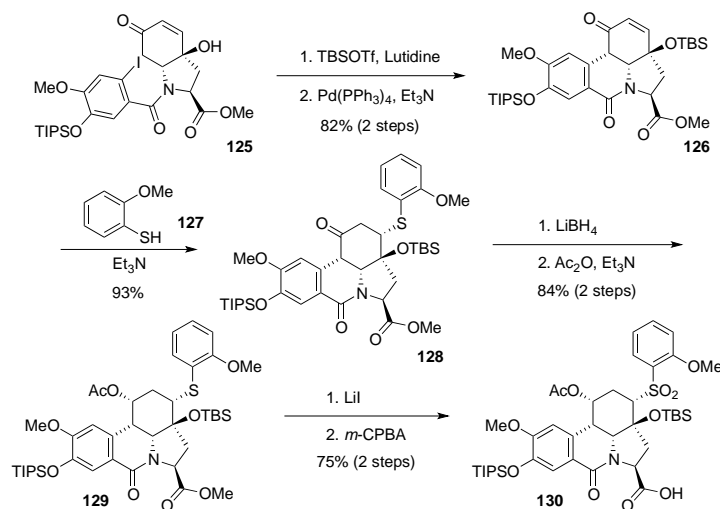


**Scheme 27.** Synthesis of acyl chloride **119**.

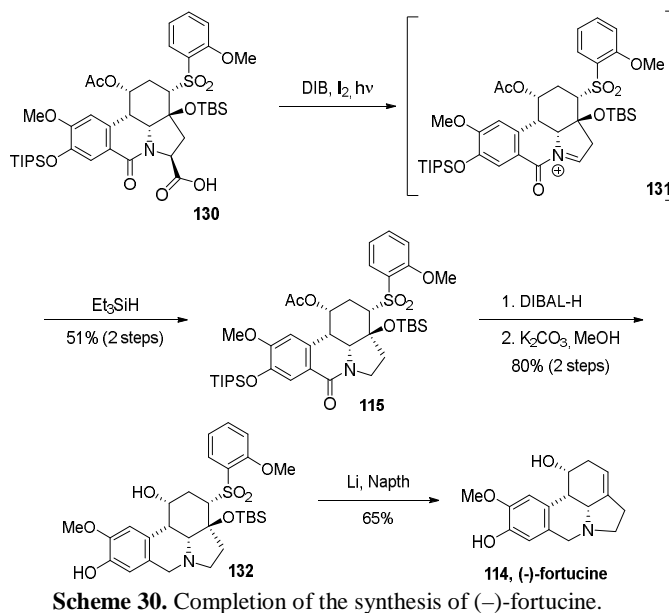
Schotten-Baumann acylation of L-tyrosine methyl ester with **119** and ester cleavage under Krapcho-like conditions<sup>28</sup> provided phenol **117**, which upon treatment with DIB cyclized to spirolactone **124** (Scheme 28). Reaction of **124** with methanolic KOH induced trans-esterification of the lactone and diastereoselective conjugate addition of the amido group to the dienone, producing bicyclic structure **125** in 95% yield. The stereochemical course of this transformation is governed by the chiral center of tyrosine.<sup>28</sup> A critical desymmetrization of the dienone is thus achieved, enabling access to an enantioenriched end product.

Enone **125** was then transformed into an enol ether, and the B ring of fortucine was closed by a stereoselective Heck reaction (Scheme 29). Thioether **128** resulted upon 1,4-addition of thiophenol **127** to **126** into (93% yield). The ketone was selectively reduced to the  $\alpha$ -alcohol, which was immediately acetylated prior to cleavage of the methyl ester under Krapcho-like conditions.<sup>27</sup> Finally, the thioether was oxidized to sulfone **130**.

The carboxylic acid subunit was excised at this juncture. This was accomplished by oxidative decarboxylation of **130** with DIB and iodine, followed by *in situ* reduction of iminium ion **131** with triethylsilane<sup>29</sup> (Scheme 30). Treatment of the resultant **115** with DIBAL followed by methanolic  $\text{K}_2\text{CO}_3$  produced **132**, which upon reaction of **132** with Li/Naph<sup>30</sup> was converted into fully synthetic, enantiopure fortucine. However, the synthetic compound was found to be levorotatory, whereas the natural product is dextrorotatory.

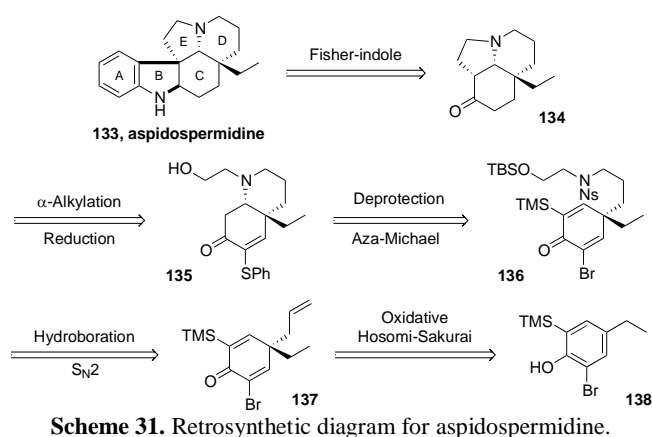
Scheme 28. Desymmetrization of dienone **124**.Scheme 29. Synthesis of acid **130**.

Single-crystal X-ray diffractometry and circular dichroism spectroscopy confirmed that synthetic (–)-fortucine is indeed structure **114** and that this configuration corresponds to the enantiomer of the natural alkaloid. The absolute configuration of the latter had been assigned as **114** without experimental evidence, probably by analogy with other lycorine alkaloids. The present effort thus served also to correct the absolute configuration of the natural product.



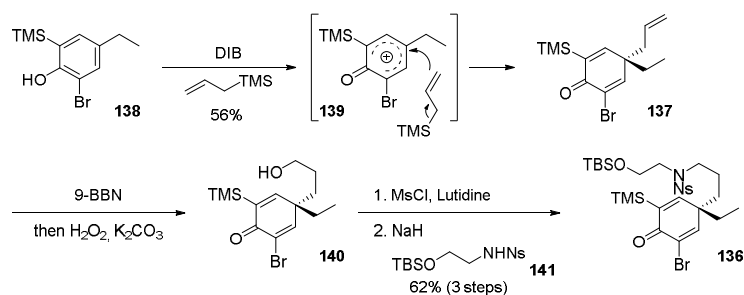
### 3.4. *Aspidosperma* alkaloids: synthesis of aspidospermidine

Aspidospermidine **133** (Scheme 31), a representative *Aspidosperma* alkaloid, was isolated in 1961 by Bienmann and coworkers from the bark of the *Aspidosperma quebracho-blanco* tree.<sup>31</sup>



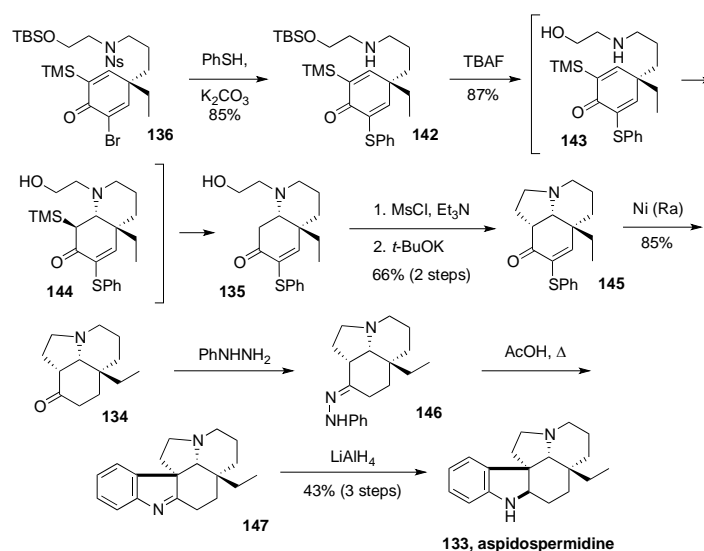
The first synthesis of ( $\pm$ )-**133** was reported by Stork and Dolfini in 1963,<sup>32</sup> and it has been followed by several others.<sup>33</sup> In 2009, we described a total synthesis that rests on the creation of the quaternary carbon via an oxidative Hosomi-Sakurai reaction of phenol **138**.<sup>34</sup> The resultant **137** would be advanced to **135** in preparation for closure of the E ring via intramolecular enolate alkylation and Fisher indole synthesis with ketone **134**. Oxidative Hosomi-Sakurai reaction of **138** produced dienone **137** (56% yield),<sup>35</sup> hydroboration-

oxidation of which afforded alcohol **140** (Scheme 32). Activation of the latter as a mesylate and reaction with the anion of sulfonamide **141** then returned **136**.



**Scheme 32.** Synthesis of dienone **136**.

Release of the sulfonamide under Fukuyama conditions<sup>17</sup> yielded amine **142** (Scheme 33), which upon exposure to TBAF was converted into **135** in 87% yield, presumably through the same sequence of events alluded-to earlier (cf. Scheme 21). Compound **135** was then processed to **144** by mesylation followed by reaction with *t*-BuOK and Raney Nickel reduction of intermediate **145**. In accord with Stork and Dolfini,<sup>32</sup> **144** underwent Fischer indole reaction to afford imine **147**, which upon reduction with LiAlH<sub>4</sub> provided aspido-spermidine (Scheme 34).



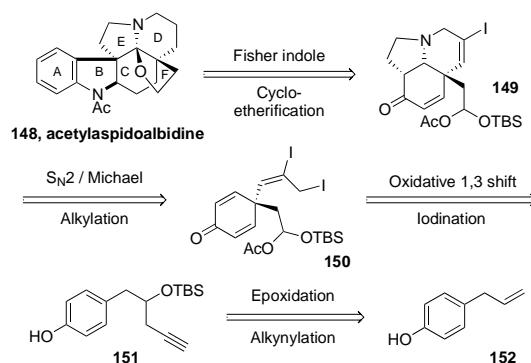
**Scheme 33.** Synthesis of aspido-spermidine.

### 3.5. *Aspidosperma* alkaloids: synthesis of acetylaspidalbidine

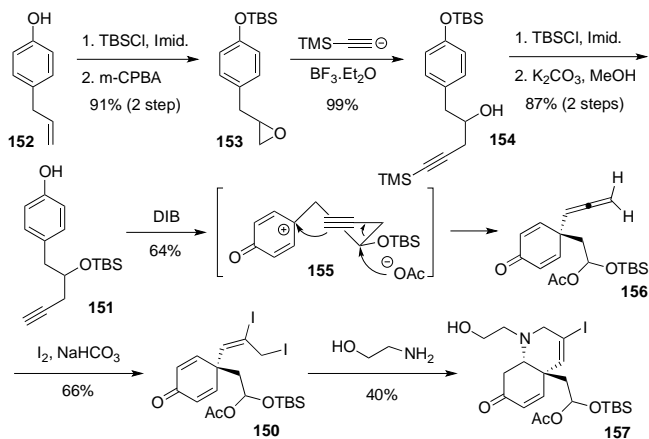
Acetylaspidalbidine **148** (Scheme 34) is an *Aspidosperma* alkaloid that is structurally similar to aspido-spermidine but it contains an additional tetrahydrofuran ring. The compound was first isolated from



the Venezuelan trees species *Aspidosperma fendleri woodson* and *Aspidosperma rhombeosignatum markgraf*.<sup>36</sup> In 2012 we disclosed a new synthesis of **148**<sup>37</sup> that relies on yet another transformation devised in our laboratories: an oxidative 1,3-transposition of acetylenic phenols such as **151**. The latter was efficiently made from commercial **152**, and upon oxidative activation with DIB it was converted into allene **156** in 64% yield, presumably through the mechanism outlined in Scheme 35.<sup>37</sup> Iodination of the allene ( $I_2$ ,  $NaHCO_3$ ) returned *E*-iodoalkene **150**, which combined with ethanolamine to produce **157**.



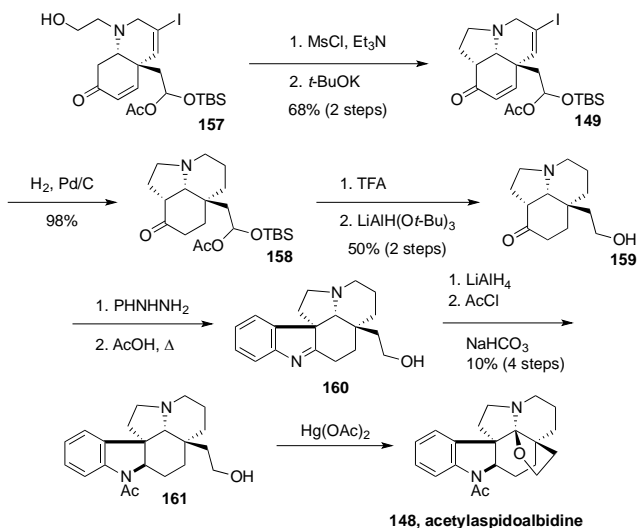
**Scheme 34.** Retrosynthetic analysis of acetylaspidalbidine.



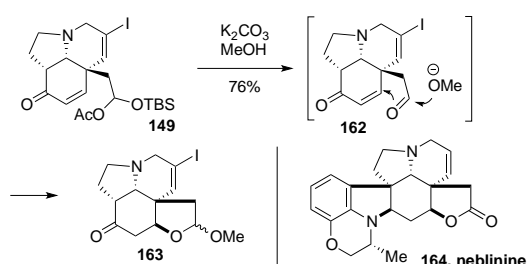
**Scheme 35.** Synthesis of bicyclic intermediate **157**.

As seen in Scheme 36, the latter was advanced to ketoalcohol **160**, which upon Fischer reaction afforded pentacyclic intermediate **160**. The imine was reduced with  $LiAlH_4$  and the amine was selectively acetylated under Schotten-Bauman conditions, setting the stage for a final cycloetherification of **161** by the method of Ban and coworkers [ $Hg(OAc)_2$ ].<sup>36b-d</sup> Acetylaspidalbidine **148** thus emerged in 64% yield.

It is worthy of note that enone **149** can be transformed into the tetracyclic core of neblinine **164**,<sup>38</sup> another *Aspidosperma* alkaloid. Indeed, treatment of **149** with methanolic  $K_2CO_3$  liberated aldehyde **162**, which immediately underwent tandem hemiacetalization-1,4-cyclization to **163** (76% yield, Scheme 37).



**Scheme 36.** Completion of the synthesis of acetylaspidobidine.

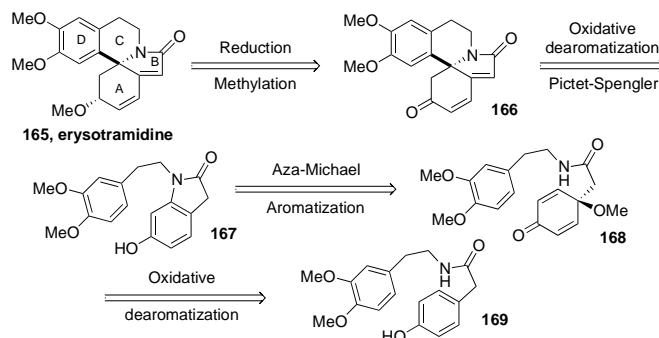


**Scheme 37.** Synthesis of the tetracyclic core of neblinine.

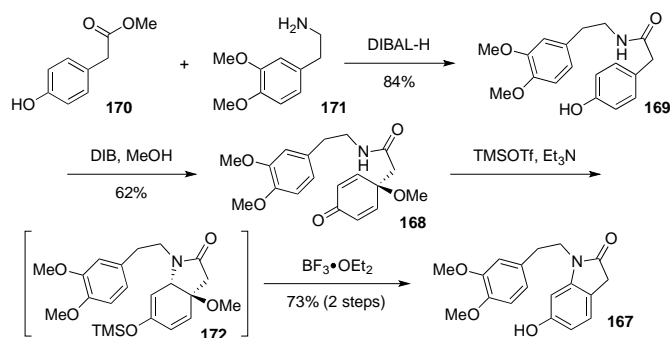
### 3.6. *Erythrina* alkaloids: synthesis of erysotramidine

Dienones arising through the above transformations undergo 1,4-addition to give products that may be re-aromatized to valuable intermediates, thus expanding the horizon of oxidative dearomatization chemistry. This is apparent from our synthesis of erysotramidine<sup>39</sup> **165**, an aromatic *Erythrina* alkaloid displaying an interesting tetracyclic azaspiranic structure (Scheme 40).<sup>40</sup> *Erythrina* alkaloids are found in various tropical plants and exhibit curare-like-, hypotensive, sedative or anticonvulsive properties.<sup>41</sup> They have aroused much interest of the chemical community, as demonstrated by the numerous syntheses that have been described.<sup>42,43</sup> Our strategy for **165** (Scheme 38)<sup>44</sup> rests on tandem oxidative dearomatization-Pictet-Spengler-like reaction of **168**, which results from **169** via an aza-Michael-aromatization sequence.

Compound **169**, prepared by the union of **170** and **171**, reacted with DIB in methanol to give dienone **168** in 62% yield (Scheme 39). The action of TMSOTf and Et<sub>3</sub>N on **168** provided enol ether **172** via a tandem aza-Michael/enol silylation process. *In situ* treatment of **172** with BF<sub>3</sub>•OEt<sub>2</sub> promoted rearomatization to phenol **167** (73% over two steps).



**Scheme 38.** Approach to erysotramidine via oxidative dearomatization–rearomatization.



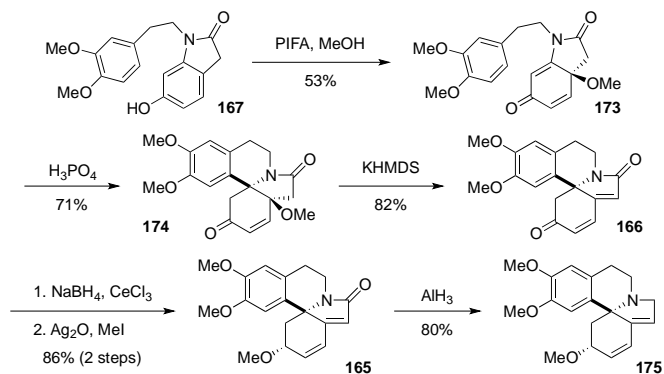
**Scheme 39.** Synthesis of the phenol **167**.

A second oxidative dearomatization of **167** with PIFA in methanol, followed by Pictet-Spengler-like cyclization of **173** with phosphoric acid,<sup>45</sup> delivered **174**, which upon exposure to KHMDS underwent elimination of methanol to **166** (Scheme 40). Finally, stereoselective Luche reduction<sup>46,47</sup> and methylation of the resultant alcohol with Ag<sub>2</sub>O and MeI afforded erysotramidine in 86% yield over two steps. Erysotrine **176**, another *Erythrina* alkaloid, can be obtained by reduction of erysotramidine with AlH<sub>3</sub>, as first demonstrated by Tsuda and coworkers.<sup>42</sup>

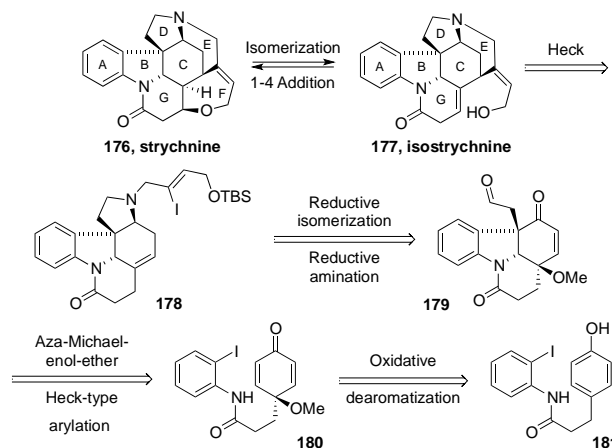
### 3.7. *Strychnos* alkaloids: synthesis of isostrychnine

*Strychnos* alkaloids, exemplified by strychnine **176** and its isomer isostrychnine **177** (Scheme 41) are also within the scope of oxidative dearomatization chemistry. Strychnine itself was isolated by Pelletier and Caventou in 1818 from the seeds of the tree *Strychnos nux-vomica*<sup>48</sup> and was first synthesized by Woodward and coworkers in 1954.<sup>49</sup>

To date, more than 20 formal or total syntheses of **176** have been reported, reflecting the great interest that this compound has aroused in the scientific community.<sup>50</sup> Strychnine can be obtained from isostrychnine through an isomerization/oxa-Michael process that occurs in methanolic KOH.<sup>50</sup> A synthesis of isostrychnine thus constitutes a formal synthesis of strychnine. In 2015, we reported a new synthesis of isostrychnine<sup>51</sup> based on the retrosynthetic logic of Scheme 41.



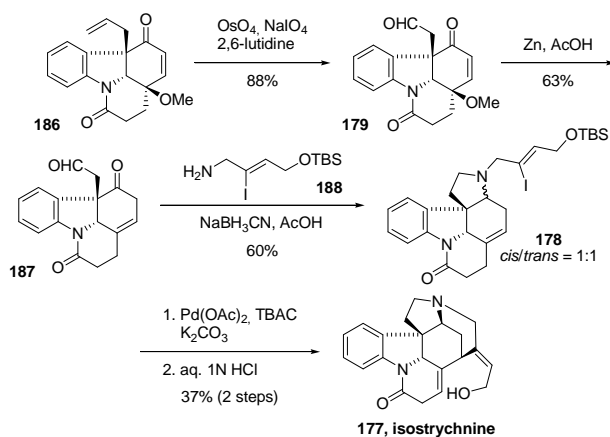
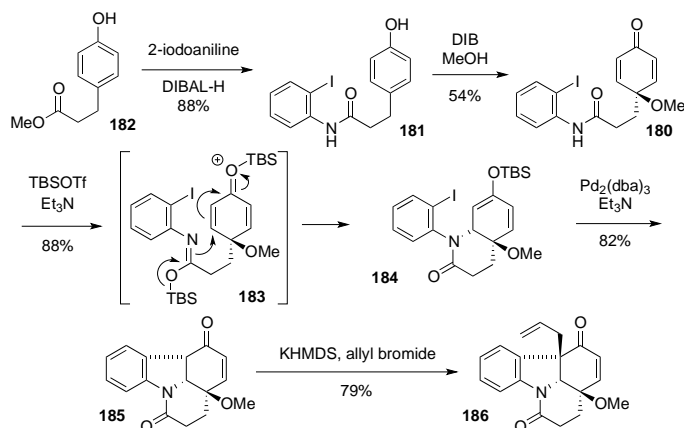
**Scheme 40.** Completion of the synthesis of erysotramidine.



**Scheme 41.** Retrosynthesis of isostrychnine.

Ring E would be closed by intramolecular Heck reaction of **178**, which is available from **179** by tandem reductive isomerization/double reductive amination. Compound **179** may be reached from dienone **180** by sequential aza-Michael cyclization/silyl enol ether formation/intramolecular Heck reaction/alkylation. In turn, **180** is the product of oxidative dearomatization of phenol **181**. The actual synthesis (Scheme 42) commenced with Weinreb amidation<sup>52</sup> of **182** with 2-iodoaniline and oxidative dearomatization of **181** with DIB in methanol. Cyclization/silyl ether formation of **180** triggered by TBSOTf and triethylamine returned **184**, which underwent Heck-type cyclization to **185** in 88% yield. Diastereoselective allylation of the enolate of **185** introduced the requisite quaternary carbon center and afforded **186**. This substance was elaborated to isostrychnine as seen in Scheme 43. Lemieux-Johnson oxidation<sup>53</sup> to aldehyde **179** and Wipf-type reductive isomerization<sup>28</sup> thereof returned deconjugated ketone **187**. Surprisingly, a subsequent double reductive amination of **187** with amine **188** was completely non-stereoselective, providing **178** as a 1:1 mixture of *cis* and *trans* isomers (separable by silica gel flash chromatography).

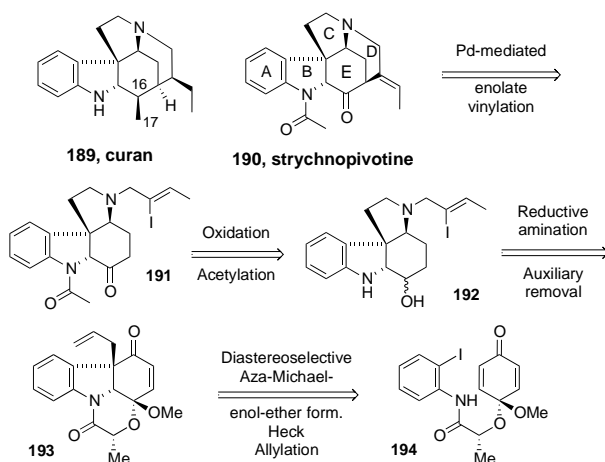
This problem was corrected at later time (*vide infra*). We note that *cis*-**178** is an intermediate in the Rawal formal synthesis of strychnine.<sup>50d</sup> Our own synthesis was completed by intramolecular Heck reaction of *cis*-**178** and alcohol deprotection under acidic conditions. Strychnine can be obtained from isostrychnine through an isomerization/oxa-Michael process mediated by potassium hydroxide in methanol.



### 3.8. *Strychnos* alkaloids: asymmetric synthesis of (-)-strychnopivotine

The search for an enantiocontrolled route to *Strychnos* alkaloids led to a solution that forms the centerpiece of our total synthesis of (-)-strychnopivotine<sup>54</sup> **190** (Scheme 44), a pentacyclic *Strychnos* alkaloid<sup>55</sup> structurally related to curan **189**. Strychnopivotine was isolated from the root bark of *Strychnos variabilis* by the group of Angenot in 1980,<sup>56</sup> and differs from curan substances in that an oxygen atom replaces the missing C<sub>17</sub> carbon. Moreover, it is one of the few *Strychnos* alkaloids that exhibit an N-acyl indoline moiety. Its absolute configuration was uncertain due to the lack of X-ray structural data. Only one total synthesis of (±)-strychnopivotine has yet been recorded,<sup>57</sup> although synthetic studies toward its CDE

subunit have been described.<sup>58</sup> Our approach to (–)-**190** rests upon a diastereoselective cyclization of dienone **194** controlled by the chirality of a lactic acid moiety, functioning now both as a chiral auxiliary and as a linker of dienone and iodoaniline segments. As before, Heck-type formation of the B ring and allylation of the resultant ketone would secure **193**, which can be elaborated to **191** substantially by the method of Scheme 43. The target alkaloid would be reached by Pd-mediated cyclization of **191**.

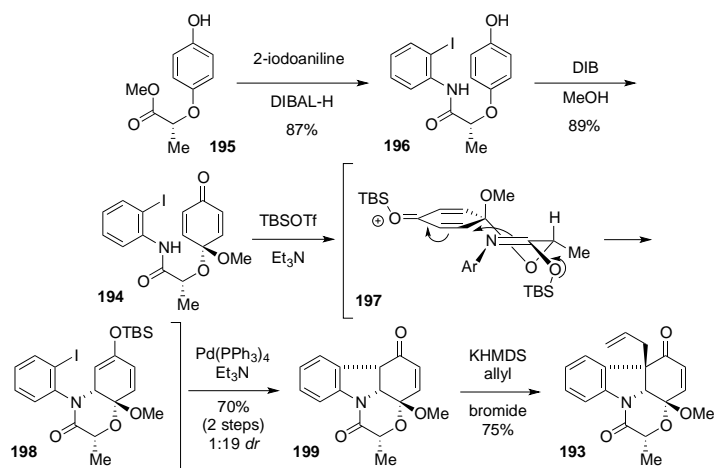


**Scheme 44.** Retrosynthetic analysis of strychnopivotine.

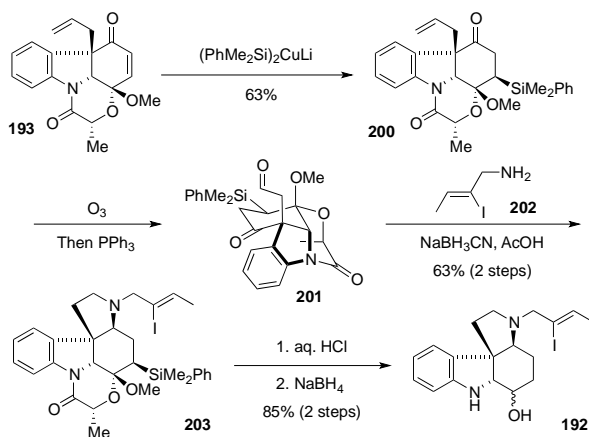
Amide **196** was prepared as shown in Scheme 47 and oxidized to dienone **194** with DIB in methanol. Exposure of the latter to TBSOTf and triethylamine induced diastereoselective cyclization to silyl enol ether **198**, which upon Heck-type cyclization delivered tetracyclic intermediate **199** in 70% yield over the two steps. The <sup>1</sup>H NMR spectrum of **199** suggested the presence of a very minor diastomeric product (ca. 1:19 ratio; limit of 300 MHz NMR spectroscopy), probably arising through cyclization of **194** toward the other double bond of the dienone. The aza-Michael step had thus taken place with an excellent diastereoselectivity consistent with an equatorial preference for the methyl group during cyclization (cf. **197**). Ketone **199** again underwent efficient allylation to **193**, the absolute configuration of which was confirmed by single crystal X-ray diffractometry (Scheme 45).

It will be recalled that the double reductive amination employed earlier for the construction of ring C of isostrychnine was non-diastereoselective (Scheme 43). The present effort provided an opportunity to correct that problem, and an effective remedy emerged as follows. It was envisaged that the temporary introduction of a bulky, removable group on the cyclohexanone moiety might lock the six-membered ring in a conformation that would promote the desired diastereoselectivity during reductive amination. A silicon-based group seemed a good choice. Accordingly, reaction of enone **193** with Fleming's cuprate<sup>59</sup> returned compound **200** as a single isomer (300 MHz <sup>1</sup>H NMR; Scheme 46). Ketoaldehyde **201**, arising from onolysis of **200**, combined with amine **202** in the presence of NaBH<sub>3</sub>CN and acetic acid to afford a single diastereomer (300 MHz <sup>1</sup>H NMR) of pentacycle **203** with the required *cis*-C-E ring junction: the silyl group had performed admirably well as an element of stereocontrol. Acid hydrolysis of the ketal took place with concomitant desilylation, and subsequent NaBH<sub>4</sub> reduction returned a mixture of epimeric of alcohols **192**,

which had conveniently lost the lactic acid segment, perhaps due to the presence of sodium methoxide in the reaction medium.



**Scheme 45.** Synthesis of tetracycle **193**.



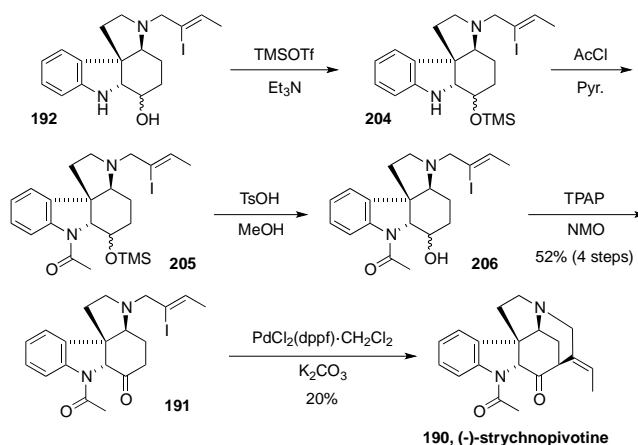
**Scheme 46.** Synthesis of alcohols **192**.

The first asymmetric synthesis of of (–)-strychnopivotine was completed (Scheme 47) by elaboration of **192** to **191** and cyclization of the latter catalyzed by  $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$  in the presence of  $\text{K}_2\text{CO}_3$ .<sup>60</sup> Circular dichroism of synthetic material, combined with the X-Ray structure of **193**, confirmed the absolute configuration of the natural compound as **191**, as initially proposed by Angenot and coworkers.

#### 4. Conclusions

In conclusion, we have illustrated several methodologies involving oxidative formal [2+3] cycloadditions developed by our group. We have also summarized our different syntheses of *Amaryllidacea*,

*Aspidosperma*, *Erythrina* and *Strychnos* alkaloids through oxidative dearomatization of phenols. These results highlight the importance of hypervalent iodine reagents and the utility of the “aromatic ring umpolung” in the construction of complex and functionalized heterocycles.



**Scheme 47.** Completion of the synthesis of (-)-strychnopivotine.

### Acknowledgments

We thank Prof. Marco Ciufolini for his kind invitation to prepare this chapter as well as for his corrections and precious advices. We are very grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Foundation for Innovation (CFI), and the provincial government of Quebec (FQRNT and CCVC) for financial support in this research.

### References

- (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797. (c) Dohi, T.; Takenaga, N.; Nakae, T.; Toyoda, Y.; Yamasaki, M.; Shiro, M.; Fujioka, H.; Maruyama, A.; Kita, Y. *J. Am. Chem. Soc.* **2013**, *135*, 4558. (d) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775
- For reviews or books, see: (a) Wirth, T., Ed. *Hypervalent Iodine Chemistry: Modern Developments in Organic Synthesis. Top. Curr. Chem.* **2003**, *224*. (b) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, *24*, 3759. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. For publications, see: (a) Liang, H.; Ciufolini, M. A. *Chem. Eur. J.* **2010**, *16*, 13262. (b) Vanderlaan, D. G.; Schwartz, M. A. *J. Org. Chem.* **1985**, *50*, 743. (c) Lewis, N.; Wallbank, P. *Synthesis* **1987**, 1103. (d) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135. (e) Swenton, J. S.; Callinan, A.; Chen, Y.; Rohde, J. J.; Kearns, M. L.; Morrow, G. W. *J. Org. Chem.* **1996**, *61*, 1267. (f) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E. M. *Tetrahedron Lett.* **1998**, *39*, 4667. (g) Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1*, 1651. (h) Braun, N. A.; Bray, J.; Ousmer, M.; Peters, K.; Peters, E. M.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397. (i) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 4593. (j) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4336. (k) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. A. *Tetrahedron* **2001**, *57*, 319. (l) Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. *Tetrahedron Lett.* **2002**, *43*, 5193. (m) Quideau, S.; Pouységu, L.;



- Deffieux, D. *Curr. Org. Chem.* **2004**, *8*, 113. (n) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175. (o) Honda, T.; Shigehisa, H. *Org. Lett.* **2006**, *8*, 657. (p) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 3942; *Angew. Chem.* **2007**, *119*, 4016. (q) Silva, L. F. Jr.; Siqueira, F. A.; Pedrozo, E. C.; Vieira, F. Y. M.; Doriguette, A. C. *Org. Lett.* **2007**, *9*, 1433. (r) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, 467. (s) Liang, H.; Ciufolini, M. A. *J. Org. Chem.* **2008**, *73*, 4299. (t) Giroux, M. A.; Guérard, K. C.; Beaulieu, M. A.; Sabot, C.; Canesi, S. *Eur. J. Org. Chem.* **2009**, 3871. (u) Peuchmaur, M.; Saidani, N.; Botté, C.; Maréchal, E.; Vial, H.; Wong, Y. S. *J. Med. Chem.* **2008**, *51*, 4870. (v) Mendelsohn, B. A.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 4736. (w) Jen, T.; Mendelsohn, B. A.; Ciufolini, M. A. *J. Org. Chem.* **2011**, *76*, 728. (x) Traoré, M.; Ahmed-Ali, S.; Peuchmaur, M.; Wong, Y. S. *J. Org. Chem.* **2011**, *76*, 1409.
3. (a) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (b) Silva, L. F.; Olofsson, B. *Nat. Prod. Rep.* **2011**, *28*, 1722.
4. (a) Dai, M.; Danishefsky, S. J. *Heterocycles* **2009**, *77*, 157. (b) Dai, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6610. (c) Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6650. (d) Liu, L.; Gao, Y.; Che, C.; Wu, N.; Wang, D. Z.; Li, C.-C.; Yang, Z. *Chem. Commun.* **2009**, 662. (e) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. *J. Org. Lett.* **2009**, *11*, 5394.
5. Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534.
6. Xu, S.; Ciufolini, M. A. *Org. Lett.* **2015**, *17*, 2424.
7. Bérard, D.; Jean, A.; Canesi, S. *Tetrahedron Lett.* **2007**, *48*, 8238.
8. (a) Sabot, C.; Bérard, D.; Canesi, S. *Org. Lett.* **2008**, *10*, 4629. (b) Bérard, D.; Giroux, M.-A.; Racicot, L.; Sabot, C.; Canesi, S. *Tetrahedron* **2008**, *64*, 7537.
9. (a) Wang, S.; Gates, B. D.; Swenton, J. S. *J. Org. Chem.* **1991**, *56*, 1979–1981; (b) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 7537.
10. Bérard, D.; Racicot, L.; Sabot, C.; Canesi, S. *Synlett* **2008**, *7*, 1076.
11. (a) Jacquemot, G.; Ménard, M.-A.; L'Homme, C.; Canesi, S. *Chem. Sci.* **2013**, *4*, 1287. For a catalytic version of this process see (b) Ito, M. Kubo, H.; Itani, I.; Morimoto, K.; Dohi, T.; Kita, Y. *J. Am. Chem. Soc.*, **2013**, *135*, 14078.
12. For synthesis of (-)-mesembrine, see: (a) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711. (b) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143. (c) Ogasawara, K.; Kamikudo, T. *Chem. Commun.* **1998**, 783. (d) Ogasawara, K.; Yamada, O. *Tetrahedron Lett.* **1998**, *39*, 7747. (e) Langlois, Y.; Dalko, P. I.; Brun, V. *Tetrahedron Lett.* **1998**, *39*, 8979. (f) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. (g) Mori, M.; Kuroda, S.; Zhang, C.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263. (h) Yoshimitsu, T.; Ogasawara, K. *Heterocycles* **1996**, *42*, 135. (i) Nemoto, H.; Tanabe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6785. (j) Nemoto, H.; Tanabe, T.; Fukumoto, K. *Tetrahedron Lett.* **1994**, *35*, 6499. (k) Takano, S.; Samizu, K.; Ogasawara, K. *Chem. Lett.* **1990**, 1239. (l) Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479. (m) Strauss, H. F.; Wiechers, A. *Tetrahedron Lett.* **1979**, *20*, 4495. (n) Arns, S.; Lebrun, M. E.; Grise, C. M.; Deniss, I.; Barriault, L. *J. Org. Chem.* **2007**, *72*, 9314. For synthesis of (+)-mesembrine, see: (o) Paul, T.; Malachowski, W. P.; Lee, J. *Org. Lett.* **2006**, *8*, 4007. (p) Kosugi, H.; Miura, Y.; Kanna, H.; Uda, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1409. (q) Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1992**, *33*, 6999. (r) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776. (s) Yamada, S.-I. *Tetrahedron Lett.* **1971**, *16*, 1133.
13. For racemic synthesis of mesembrine, see: (a) Chavan, S. P.; Khobragade, D. A.; Pathak, A. B.; Kalkote, U. R. *Tetrahedron Lett.* **2004**, *45*, 5263. (b) Kulkarni, M. G.; Rasne, R. M.; Davawala, S. I.; Doke, A. K. *Tetrahedron Lett.* **2002**, *43*, 2297. (c) Rigby, J. H.; Dong, W. *Org. Lett.* **2000**, *2*, 1673. (d)

- Rajagopalan, P. *Tetrahedron Lett.* **1997**, *38*, 1893. (e) Michael, J. P.; Howard, A. S.; Katz, R. B.; Zwane, M. I. *Tetrahedron Lett.* **1992**, *33*, 6023. (f) Bauermeister, S.; Gouws, I. D.; Strauss, H. F.; Venter, E. M. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 561. (g) Parkinson, C. J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1055. (h) Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831. (i) Livinghouse, T.; Hackett, S. *J. Org. Chem.* **1986**, *51*, 1629. (j) Gramain, J.-C.; Remuson, R. *Tetrahedron Lett.* **1985**, *26*, 4083. (k) Sanchez, I. H.; de Jesus Soria, J.; Larraza, M. I.; Flores, H. J. *Tetrahedron Lett.* **1983**, *24*, 551. (l) Jeffs, P. W.; Redfearn, R.; Wolfram, J. *J. Org. Chem.* **1983**, *48*, 3861. (m) Pinnick, H. W.; Kochlar, K. S. *Tetrahedron Lett.* **1983**, *24*, 4785. (n) Keck, G. E.; Webb, R. R. *J. Org. Chem.* **1982**, *47*, 1302. (o) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391. (p) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2579. (q) Stevens, R. V.; Lesko, P. M.; Lapalme, R. *J. Org. Chem.* **1975**, *40*, 3495. (r) Keely, S. L.; Tahk, F. C. *J. Am. Chem. Soc.* **1968**, *90*, 5584. (s) Rodriguez, H. R.; Shamma, M. *Tetrahedron* **1968**, *24*, 6583. (t) Stevens, R. V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5580. (u) Kugita, H.; Oh-ishi, T. *Tetrahedron Lett.* **1968**, *9*, 5445. (v) Curphey, T. J.; Kim, H. L. *Tetrahedron Lett.* **1968**, *9*, 1441. (w) Rodriguez, H. R.; Shamma, M. *Tetrahedron Lett.* **1965**, *6*, 4847.
14. Popelak, A.; Haack, E.; Lettenbauer, G.; Spingler, H. *Naturwissenschaften* **1960**, *47*, 156. (b) Smith, E.; Hosansky, N.; Shamma, M.; Moss, J. B. *Chem. Ind.* **1961**, 402.
15. Sanchez, I. H.; Larraza, M. I.; Flores, H. J.; Rojas, I.; Alcalá, R. *Synth. Commun.* **1983**, *13*, 35.
16. Guérard, K. C.; Sabot, C.; Racicot, L.; Canesi, S. *J. Org. Chem.* **2009**, *74*, 2039.
17. For a review, see: Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 105.
18. Jacquemot, G.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 7588.
19. Coulibali, S.; Godou, T.; Canesi, S.; *Org. Lett.* **2016**, *18*, 4348.
20. (a) Jeffs, W.; Capps, T. M.; Johnson, D. B.; Karle, J. M.; Martin, N. H.; Rauckman, B. *J. Org. Chem.* **1974**, *39*, 2703. (b) Sanchez, I. H.; Larraza, M. I.; Flores, H. J.; Rojas, I.; Alcalá, R. *Synth. Commun.* **1983**, *13*, 35. (c) Jeffs, P. W.; Karle, J. M.; Martin, N. H. *Phytochemistry* **1978**, *17*, 719. (d) Gaffney, C. D. Dissertation, University of Johannesburg, **2008**.
21. (a) Griffith, W. P.; Ley, S. L.; Whitcombe, G. P.; White, A. D. *Chem. Commun.* **1987**, 1625. (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
22. Dalton, D. R. in *The Alkaloids: The Fundamental Chemistry, A Biogenetic Approach*; in *Studies in Organic Chemistry*, Ed. Gassman, P. G., Ed; Marcel Dekker, New-York, **1979**, Vol. 7, 57.
23. (a) S. F. Martin, in *The Alkaloids*, Brossi, A., Ed.; Academic Press, New York, **1987**, Vol. 30, 251. (b) Ghosal, S.; Saini, K. S.; Razdan, S. *Phytochemistry* **1985**, *24*, 2141. (c) Mineshita, T.; Yamaguchi, K.; Takeda, K.; Kotera, K. *Ann. Rep. Shionogi Res. Lab.* **1956**, *6*, 119. (d) Chattopadhyay, U.; Chaudhuri, L.; Das, S.; Kumar, Y.; Ghosal, S. *Pharmazie* **1984**, *39*, 855. (e) De Leo, P.; Dalessandro, G.; De Santis, A.; Arrigoni, O. *Plant Cell Physiol.* **1973**, *14*, 487.
24. (a) Gorbunova, G. M.; Sheichenko, V. I.; Tolkachev, O. N. *Khim. Prir. Soedin.* **1984**, 800. (b) Tokhtabaeva, G. M.; Sheichenko, G. M.; Yartseva, I. V.; Tolkachev, O. N. *Khim. Prir. Soedin.* **1987**, *23*, 727.
25. (a) Biechy, A.; Hachisu, S.; Quiclet-Sire, B.; Ricard, L.; Zard, S. Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 1436; *Angew. Chem.* **2008**, *120*, 1458. (b) Biechy, A.; Hachisu, S.; Quiclet-Sire, B.; Ricard, L.; Zard, S. Z. *Tetrahedron* **2009**, *65*, 6730.
26. Eilingsfeld, H.; Seefelder, M.; Weidinger, H. *Angew. Chem.* **1960**, *72*, 836.
27. Fisher, J. W.; Trinkle, K. L. *Tetrahedron Lett.* **1994**, *35*, 2505.

28. (a) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5457. (b) Wipf, P.; Kim, Y.; Goldstein, D. *J. Am. Chem. Soc.* **1995**, *117*, 11106. (c) Wipf, P.; Li, W. *J. Org. Chem.* **1999**, *64*, 4576. (d) Wipf, P.; Mareska, D. A. *Tetrahedron Lett.* **2000**, *41*, 4723. (e) Methot, J. L.; Wipf, P. *Org. Lett.* **2000**, *2*, 4213.
29. (a) Boto, A.; Hernandez, R.; Suarez, E. *J. Org. Chem.* **2000**, *65*, 4930. (b) Boto, A.; Hernandez, R.; Leon, Y.; Suarez, E. *J. Org. Chem.* **2001**, *66*, 7796.
30. Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833.
31. Biemann, K.; Friedmann-Spiteller, M.; Spiteller, G. *Tetrahedron Lett.* **1961**, *2*, 485. (b) Biemann, K.; Spiteller-Friedmann, M.; Spiteller, G. *J. Am. Chem. Soc.* **1963**, *85*, 631.
32. Stork G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872.
33. (a) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995. (b) Toczko, M. A.; Heathcock, C. A. *J. Org. Chem.* **2000**, *65*, 2642; (c) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628. (d) Marino, J. P.; Rubio, M. B.; Cao, G.; de Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398. (e) Fukuda, Y.; Shindo, M.; Shishido, K. *Org. Lett.* **2003**, *5*, 749. (f) Gnecco, D.; Vazquez, E.; Galindo, A.; Teran, J. L.; Orea, L.; Bernes, S.; Enriquez, R. G. *ARKIVOC* **2003**, 185. (g) Tanino, H.; Fukuishi, K.; Ushiyama, M.; Okada, K. *Tetrahedron* **2004**, *60*, 3273. (h) Banwell, M. G. D.; Lupton, W. *Org. Biomol. Chem.* **2005**, *3*, 213. (i) Banwell, M. G.; Lupton, D. W.; Willis, A. C. *Aust. J. Chem.* **2005**, *58*, 722. (j) Iyengar, R.; Schildknecht, K.; Morton, M.; Aubé, J. *J. Org. Chem.* **2005**, *70*, 10645. (k) Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831. (l) Pearsona, W. H.; Aponick, A. *Org. Lett.*, **2006**, *8*, 1661. (m) Coldham, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 6159. (n) Callier-Dublanchet, A. C.; Cassayre, J.; Gagosz, F.; Quiclet-Sire, B.; Sharp, L. A.; Zard, S. Z. *Tetrahedron* **2008**, *64*, 4803. (o) Ishikawa, T.; Kudo, K.; Kuroyabu, K.; Uchida, S.; Kudoh, T.; Saito, S. *J. Org. Chem.* **2008**, *73*, 7498. (p) Suzuki, M.; Kawamoto, Y.; Sakai, T.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2009**, *11*, 653. (q) Burrell, A. J. M.; Coldham, I.; Watson, L.; Oram, N.; Pilgram, C. D.; Martin, N. G. *J. Org. Chem.* **2009**, *74*, 2290.
34. Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941.
35. Sabot, C.; Commare, B.; Duceppe, M. A.; Nahi, S.; Guérard, K. C.; Canesi, S. *Synlett* **2008**, 3226.
36. (a) Hesse, M. *Indolalkaloide in Tabellen-Ergänzungswerk*; Springer-Verlag: Berlin, **1968**, 77. (b) Ban, Y.; Ohnuma, T.; Seki, K.; Oishi, T. *Tetrahedron Lett.* **1975**, *16*, 727. (c) Honma, Y.; Ohnuma, T.; Ban, Y. *Heterocycles* **1976**, *5*, 47. (d) Yoshido, K.; Sakuma, Y.; Ban, Y. *Heterocycles* **1987**, *25*, 47. (e) Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598. (f) Campbell, E. L.; Zuhl, A. M.; Liu, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3009. (g) Brown, K. S.; Budzikiewicz, H.; Djerassi, C. *Tetrahedron Lett.* **1963**, *4*, 1731. (h) Walser, A.; Djerassi, C. *Helv. Chim. Acta* **1965**, *48*, 391.
37. Guérard, K. C.; Guérinot, A.; Bouchard-Aubin, C.; Ménard, M.-A.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 2121.
38. Brown, K. S.; Djerassi, C. *J. Am. Chem. Soc.* **1964**, *86*, 2451.
39. (a) Ito, K.; Furukawa, H.; Haruna, M. *Yakugaku Zasshi* **1973**, *93*, 1611. (b) Mantle, P. G.; Laws, I.; Widdowson, D. A. *Phytochemistry* **1984**, *23*, 1336.
40. Tsuda, Y.; Sano, T. in *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, **1996**; Vol. 48, 249.
41. (a) Boekelheide, V. in *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, **1960**; Vol. 7, 201. (b) Hill, R. K. in *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, **1967**; Vol. 9, 483. (c) Dyke, S. F.; Quessy, S. N. in *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic Press: New York, **1981**; Vol. 18, 1. (d) Chawala, A. S.; Jackson, A. H. *Nat. Prod. Rep.* **1984**, *1*, 371.

42. (a) Joo, J. M.; David, R. A.; Yuan, Y.; Lee, C. *Org. Lett.* **2010**, *12*, 5704. (b) Tuan, L. A.; Kim, G. *Bull. Korean Chem. Soc.* **2010**, *31*, 1800. (c) Liang, J.; Chen, J.; Liu, J.; Li, L.; Zhang, H. *Chem. Commun.* **2010**, *46*, 3666. (d) Onoda, T.; Takikawa, Y.; Fujimoto, T.; Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2009**, 1041. (e) Yoshida, Y.; Mohri, K.; Isobe, K.; Itoh, T.; Yamamoto, K. *J. Org. Chem.* **2009**, *74*, 6010. (f) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Chem. Asian J.* **2007**, *2*, 1127. (g) Shimizu, K.; Takimoto, M.; Sato, Y.; Mori, M. *J. Organomet. Chem.* **2006**, *691*, 5466. (h) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143. (i) Kim, G.; Kim, J. H.; Lee, K. Y. *J. Org. Chem.* **2006**, *71*, 2185. (j) Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, 619. (k) Fukumoto, H.; Esumi, T.; Ishihara, J.; Hatakeyama, S. *Tetrahedron Lett.* **2003**, *44*, 8047. (l) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2323. (m) Kalaitzakis, D.; Montagnon, T.; Antonatou, E.; Vassilikogiannakis, G. *Org. Lett.* **2013**, *15*, 3714. (n) Isobe, K.; Mohri, K.; Takeda, N.; Suzuki, K.; Hosoi, S.; Tsuda, Y. *Chem. Pharm. Bull.* **1994**, *42*, 197. (o) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Chem. Pharm. Bull.* **1993**, *41*, 2087. (p) Tsuda, Y.; Hosoi, S.; Sano, T.; Suzuki, H.; Toda, J. *Heterocycles* **1993**, *36*, 655. (q) Isobe, K.; Mohri, K.; Suzuki, K.; Haruna, M.; Ito, K.; Hosoi, S.; Tsuda, Y. *Chem. Pharm. Bull.* **1991**, *32*, 1195. (r) Tsuda, Y.; Hosoi, S.; Nakai, A.; Sakai, Y.; Abe, T.; Ishi, Y.; Kiuchi, F.; Sano, T. *Chem. Pharm. Bull.* **1991**, *39*, 1365. (s) Sano, T.; Toda, J.; Kashiwaba, N.; Ohshima, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 479. (t) Ito, K.; Suzuki, F.; Haruna, M. *J. J. Chem. Soc., Chem. Commun.* **1978**, 733. (u) Andreev, I. A.; Ratmanova, N. K.; Novoselov, A. M.; Belov, D. S.; Seregina, I. F.; Kurkin, A. V. *Chem. Eur. J.* **2016**, *22*, 7262. (v) Paladino, M.; Zaifman, J.; Ciufolini, M. A.; *Org. Lett.* **2015**, *17*, 3422. (w) Mostowicz, D.; Dygas, M.; Kaluza, Z.; *J. Org. Chem.* **2015**, *80*, 1957. (x) Kalaitzakis, D.; Montagnon, T.; Antonatou, E.; Vassilikogiannakis, G.; *Org. Lett.* **2013**, *15*, 3714.
43. (a) Ogawa, S.; Iida, N.; Tokunaga, E.; Shiro, M.; Shibata, N. *Chem. Eur. J.* **2010**, *16*, 7090. (b) Juma, B.; Adeel, M.; Villinger, A.; Reinke, H.; Spannenberg, A.; Fischer, C.; Langer, P. *Adv. Synth. Catal.* **2009**, *351*, 1073. (c) Tietze, L. F.; Tolle, N.; Kratzert, D.; Stalke, D. *Org. Lett.* **2009**, *11*, 5230. (d) Zhang, F.; Simpkins, N. S.; Blake, A. *J. Org. Biomol. Chem.* **2009**, *7*, 1963. (e) Padwa, A.; Wang, Q. *J. Org. Chem.* **2006**, *71*, 7391. (f) Wang, Q.; Padwa, A. *Org. Lett.* **2006**, *8*, 601. (g) Gao, S.; Tu, Y. Q.; Hu, X.; Wang, S.; Hua, R.; Jiang, Y.; Zhao, Y.; Fan, X.; Zhang, S. *Org. Lett.* **2006**, *8*, 2373. (h) El Bialy, S. A. A.; Braun, H.; Tietze, L. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 5391. (i) Padwa, A.; Lee, H. I.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2004**, *69*, 8209. (j) Lee, H. I.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *Org. Lett.* **2003**, *5*, 5067. (k) Chikaoka, S.; Toyao, A.; Ogasawara, M.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2003**, *68*, 312. (l) Padwa, A.; Hennig, R.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1998**, *63*, 1144. (m) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Heterocycles* **1992**, *33*, 497. (n) Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8975. (o) Tsuda, Y.; Hosoi, S.; Nakai, A.; Ohshima, T.; Sakai, Y.; Kiuchi, F. *Chem. Commun.* **1984**, 1216. (p) Sano, T.; Toda, J. *Heterocycles* **1982**, *18*, 229. (q) Mondon, A.; Nestler, H. *J. Chem. Ber.* **1979**, *112*, 1329. (r) Haruna, M.; Ito, K. *Chem. Commun.* **1976**, 345. (s) Mondon, A.; Nestler, H. *J. Angew. Chem. Int. Ed.* **1964**, *3*, 588; *Angew. Chem.* **1964**, *76*, 651.
44. L'Homme, C.; Ménard, M. A.; Canesi, S. *J. Org. Chem.* **2014**, *79*, 8481.
45. Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.
46. (a) Luche, J. L.; *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J. L.; Rodriguez-Hahn, L.; Crabbé, P.; *J. Chem. Soc., Chem. Commun.* **1978**, 601. (c) Gemal, A. L.; Luche, J. L.; *J. Am. Chem. Soc.* **1981**, *103*, 5454.

47. For some other recent examples in synthesis, see: (a) Nicolaou, K. C.; Totokotsopoulos, S.; Giguère, D.; Sun, Y.-P.; Sarlah, D.; *J. Am. Chem. Soc.*, **2011**, *133*, 8150. (b) Ding, M.; Tong, X.; Li, D.; Liang, K.; Zhou, A.; Zuo, Z.; Xia, C.; *Tetrahedron Lett.* **2015**, *56*, 5460. (c) Wipf, P.; Spencer, S.; *J. Am. Chem. Soc.* **2005**, *127*, 225. (d) Wipf, P.; Rector, S. R.; Takahashi, H.; *J. Am. Chem. Soc.* **2002**, *124*, 14848. (e) Bru, C.; Thal, C.; Guillou, C.; *Org. Lett.* **2003**, *5*, 1845. (f) Pandey, G.; Gupta, N. R.; Pimpalpal, T. M.; *Org. Lett.* **2009**, *11*, 2547. (g) Bru, C.; Guillou, C.; *Tetrahedron* **2006**, *62*, 9043. (h) Pandey, G.; Gupta, N. R.; Gadre, S. R.; *Eur. J. Org. Chem.* **2011**, 740.
48. (a) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1818**, *8*, 323. (b) Pelletier, P. J.; Caventou, J. B. *Ann. Chim. Phys.* **1819**, *10*, 142.
49. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749.
50. (a) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403. (b) Knight, S. D.; Overman, L. E.; Pairedeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293. (c) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490. (d) Rawal, V. H.; Iwasa, S.; *J. Org. Chem.* **1994**, *59*, 2685. (e) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9427. (f) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidrú, E.; Bosch, J. *Angew. Chem. Int. Ed.* **1999**, *38*, 395; *Angew. Chem.* **1999**, *111*, 408. (g) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003. (h) Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479. (i) Nakanishi, M.; Mori, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 1934; *Angew. Chem.* **2002**, *114*, 2014. (j) Bodwell, G. J.; Li, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3261; *Angew. Chem.* **2002**, *114*, 3395. (k) Ohshima, T.; Xu, Y.; Takita, R.; Shimuzu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546. (l) Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 10246. (m) Zhang, H.; Boonsombat, J.; Padwa, A. *Org. Lett.* **2007**, *9*, 279. (n) Sirasani, G.; Paul, T.; Dougherty, W. Jr.; Kassel, S.; Andrade, R. B. *J. Org. Chem.* **2010**, *75*, 3529. (o) Beemelmans, C.; Reissig, H. U. *Angew. Chem. Int. Ed.* **2010**, *49*, 8021; *Angew. Chem.* **2010**, *122*, 8195. (p) Martin, D. B. C.; Vanderwal, C. D. *Chem. Sci.* **2011**, *2*, 649. (q) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183. (r) Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455. (s) Mori, M. *Heterocycles* **2010**, *81*, 259. (t) Furst, L.; Stephenson, C. R. *Nat. Chem. Biol.* **2011**, *7*, 582. (u) Beemelmans, C.; Reissig, H. U. *Chem. Soc. Rev.* **2011**, *40*, 2199. (v) Martin, D. B. C.; Nguyen, L. Q. C.; Vanderwal, D. *J. Org. Chem.* **2012**, *77*, 17. (w) Cannon, J. S.; Overman, L. E. *Angew. Chem. Int. Ed.* **2012**, *51*, 4288; *Angew. Chem.* **2012**, *124*, 4362.
51. Jacquemot, G.; Maertens, G.; Canesi, S. *Chem. Eur. J.* **2015**, *21*, 7713.
52. Huang, P. Q.; Zheng, X.; Deng, X.-M.; *Tetrahedron Lett.* **2001**, *42*, 9039.
53. Pappo, R.; Allen, D. S. Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
54. Maertens, G.; Canesi, S. *Chem. Eur. J.* **2016**, *22*, 7090.
55. (a) Bosch, J.; Bonjoch, J.; Amat, M. in *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, **1996**, Vol. 48, 75. (b) Sapi, J.; Massiot, G. in *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; in *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; Wiley: New York, **1994**, Supp. to Vol. 25, part 4, 279.
56. Tits, M.; Tavernier, D.; Angenot, L. *Phytochemistry* **1980**, *19*, 1531.
57. Boonsombat, J.; Zhang, H.; Chughtai, M.; Hartung, J.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 3539.
58. (a) Teuber, H. J.; Tsaklakidis, C.; Bats, J. W. *Liebigs Ann.* **1992**, *5*, 461. (b) Solé, D.; Urbaneja, X.; Cordero-Vargas, A.; Bonjoch, J. *Tetrahedron* **2007**, *63*, 10177.
59. Ager, D. J.; Fleming, I.; Patel, S. K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520.

60. Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wroblewski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368.