HETEROCYCLES AND NATURAL PRODUCTS SYNTHESIS THROUGH OXIDATIVE DEAROMATIZATION

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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.

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1. Introduction

Oxidative dearomatization, also termed “aromatic ring umpolung”, transforms simple, inexpensive aromatics into more functionalyzed 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.
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,\(^1\) heteronucleophiles tend to react at the site with the larger LUMO coefficient (pathway b), thus leading to a prochiral diene 5. In contrast, steric interactions guide carbon nucleophiles to the less hindered position (pathway a), leading to a substituted aromatic product 4. Oxidative dearamatization 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.\(^1\) In the past decades, this synthetic tool has aroused interest of the scientific community\(^2\) and has played a substantial role in the total synthesis of heterocyclic natural compounds, as highlighted in different reviews.\(^3\) For example, the synthesis of the main core of (+)-cortistatin A\(^4\) 6, the total synthesis of FR901483\(^5\) 7 and a recent formal synthesis of tetrodotoxin\(^6\) 8 are based on an oxidative dearamatization as key step (Figure 1).

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

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 dearamatization 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.
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). 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.

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. 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.

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-acetoxy styrene 38 leads to dihydrobenzofuran 41 (Scheme 7). This is in agreement with previous reports by Swenton and coworkers. 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 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 teracycles 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). 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.

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

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.\(^{11}\) 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.
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 indoline derivatives 85 upon reaction with naphthalene in the presence of PIB (Scheme 17).\textsuperscript{11a} 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.

Scheme 17. Reaction between sulfonamide 82 and naphthalene.

Scheme 18. Formation of tetracyclic systems 87.

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.

Figure 2. Synthetic potential of cyclohexadienones.

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

In 2008, we reported a total synthesis of mesembrine 12,13 and dihydro-O-methylsceletenone 89, two Amaryllidaceae alkaloids respectively found in Sceletium tortuosum 14 and A. cordifolia.15 These compounds are very active serotonin reuptake inhibitors, even at low doses. Our retrosynthetic strategy (Scheme 19)16 envisions pyrrolidine ring formation via N-deprotection-cyclization of diene 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-blocked and the corresponding mesylate was displaced with the sodium salt of sulfonamide 96, resulting in formation of the desired phenol.


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 phenoxyion ion 97 (Scheme 21).16

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 K₂CO₃. This induced a cascade of events (Fukuyama deprotection17 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).

The technique illustrates the use of *functional protecting groups,* 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,* respectively.

![Scheme 22. Sceletenone and O-methylsceletenone: dienone 102 via oxidative *ipso* rearrangement.](image)

This effort started with bis-silylation of commercial 93 with di(4-methoxphenyl)tert-butylichrolosilane 104 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 via a chair-like transition and solvolysis of silyl cation 106.

![Scheme 23. Synthesis of dienone 102 by an oxidative *ipso*-rearrangement.](image)

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-nitrobenzensulfonyl chloride to yield sulfonate 108, which upon Ley-Griffith oxidation provided dienone 109. Treatment of 109 with methylene promoted a tandem SN2-aza-Michael process that furnished O-methylsceletenone 101, easily converted into sceletone 100 with BBr3.
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 are a subgroup of Amaryllidaceae alkaloids that possess interesting antiviral and antitumor activities. A representative lycorine alkaloid is fortucine 114, found in the fortune variety of narcissus and based on a pyrrolo[de]phenantridine skeleton with a cis-B/C ring junction. The first synthesis of (±)-fortucine was achieved by Zard and coworkers in 2008. 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 I₂ and AgNO₃ (Scheme 27), followed by oxidation of the aldehyde in the presence of CuCl₂ and t-BuOOH and DMF-catalyzed chlorination.
Schotten-Baumann acylation of L-tyrosine methyl ester with 119 and ester cleavage under Krapcho-like conditions 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 diene, producing bicyclic structure 125 in 95% yield. The stereochemical course of this transformation is governed by the chiral center of tyrosine. 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 α-alcohol, which was immediately acetylated prior to cleavage of the methyl ester under Krapcho-like conditions. 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 (Scheme 30). Treatment of the resultant 115 with DIBAL followed by methanolic K$_2$CO$_3$ produced 132, which upon reaction of 132 with Li/Napth was converted into fully synthetic, enantiopure fortucine. However, the synthetic compound was found to be levorotatory, whereas the natural product is dextrorotatory.
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.\(^3\)

The first synthesis of (±)-133 was reported by Stork and Dolfini in 1963,\(^3\) and it has been followed by several others.\(^3\) 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.\(^4\) 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 diene 137 (56% yield),\(^3\) 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 diene 136.

Release of the sulfonamide under Fukuyama conditions 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 134 by mesylation followed by reaction with t-BuOK and Raney Nickel reduction of intermediate 145. In accord with Stork and Dolfini, 134 underwent Fischer indole reaction to afford imine 147, which upon reduction with LiAlH₄ provided aspidospermidine (Scheme 34).

Scheme 33. Synthesis of aspidospermidine.

3.5. Aspidosperma alkaloids: synthesis of acetylaspidodoidalbidine

Acetylaspidoidalbidine 148 (Scheme 34) is an Aspidosperma alkaloid that is structurally similar to aspidospermidine but it contains an additional tetrahydrofuran ring. The compound was first isolated from
the Venezuelan trees species *Aspidosperma fendleri* woodson and *Aspidosperma rhombeosignatum* markgraf. In 2012 we disclosed a new synthesis of 148 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. Iodination of the allene (I2, NaHCO\textsubscript{3}) returned E-iodoalkene 150, which combined with ethanolamine to produce 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\textsubscript{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 \[\text{Hg(OAc)}\textsubscript{2}\]. Acetylaspidoalbidine 148 thus emerged in 64\% yield.

It is worthy of note that enone 149 can be transformed into the tetracyclic core of neblinine 164, another *Aspidosperma* alkaloid. Indeed, treatment of 149 with methanolic K\textsubscript{2}CO\textsubscript{3} liberated aldehyde 162, which immediately underwent tandem hemiacetalization-1,4-cyclization to 163 (76\% yield, Scheme 37).
3.6. Erythrina alkaloids: synthesis of erysotramidine

Dienones arising through the above transformations undergo of 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\textsuperscript{39} 165, an aromatic Erythrina alkaloid displaying an interesting tetracyclic azaspiranic structure (Scheme 40).\textsuperscript{40} Erythrina alkaloids are found in various tropical plants and exhibit curare-like, hypotensive, sedative or anticonvulsive properties.\textsuperscript{41} They have aroused much interest of the chemical community, as demonstrated by the numerous syntheses that have been described.\textsuperscript{42,43} Our strategy for 165 (Scheme 38)\textsuperscript{44} 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 diene 168 in 62% yield (Scheme 39). The action of TMSOTf and Et\textsubscript{3}N on 168 provided enol ether 172 via a tandem aza-Michael/enol silylation process. In situ treatment of 172 with BF\textsubscript{3}•OEt\textsubscript{2} promoted rearomatization to phenol 167 (73% over two steps).
A second oxidative dearomatization of 167 with PIFA in methanol, followed by Pictet-Spengler-like cyclization of 173 with phosphoric acid\(^{45}\) delivered 174, which upon exposure to KHMDS underwent elimination of methanol to 166 (Scheme 40). Finally, stereoselective Luche reduction\(^{46,47}\) and methylation of the resultant alcohol with Ag\(_2\)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\(_3\), as first demonstrated by Tsuda and coworkers.\(^{42}\)

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\(^{48}\) and was first synthesized by Woodward and coworkers in 1954.\(^{49}\)

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.\(^{50}\) Strychnine can be obtained from isostrychnine through an isomerization/oxa-Michael process that occurs in methanolic KOH.\(^{50}\) A synthesis of isostrychnine thus constitutes a formal synthesis of strychnine. In 2015, we reported a new synthesis of isostrychnine\(^{51}\) 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 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 of 185 to aldehyde 179 and Wipf-type reductive isomerization thereof returned deconjugated ketone 187. Surprisingly, a subsequent double reductive amination of 187 with amine 188 was completely nonstereoselective, 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. 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.

![Scheme 42. Formation of tetracyclic core 186.](image)

![Scheme 43. Completion of the synthesis of isostrychnine.](image)

### 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\(^4\) 190 (Scheme 44), a pentacyclic *Strychnos* alkaloid\(^5\) structurally related to curan 189. Strychnopivotine was isolated from the root bark of *Strychnos variabilis* by the group of Angenot in 1980,\(^6\) and differs from curan substances in that an oxygen atom replaces the missing C\(_{17}\) 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,\(^7\) although synthetic studies toward its CDE
Our approach to (−)-190 rests upon a diastereoselective cyclization of diene 194 controlled by the chirality of a lactic acid moiety, functioning now both as a chiral auxiliary and as a linker of diene 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.

Amide 196 was prepared as shown in Scheme 47 and oxidized to diene 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 1H NMR spectrum of 199 suggested the presence of a very minor diastereomeric product (ca. 1:19 ratio; limit of 300 MHz NMR spectroscopy), probably arising through cyclization of 194 toward the other double bond of the diene. 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 cuprate30 returned compound 200 as a single isomer (300 MHz 1H NMR; Scheme 46). Ketoaldehyde 201, arising from onolysis of 200, combined with amine 202 in the presence of NaBH4:CN and acetic acid to afford a single diastereomer (300 MHz 1H NMR) of pentacyle 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 NaBH4 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.](image)

![Scheme 46. Synthesis of alcohols 192.](image)

The first asymmetric synthesis of of (–)-strychnopivotine was completed (Scheme 47) by elaboration of 192 to 191 and cyclization of the latter catalyzed by PdCl2(dppf)•CH2Cl2 in the presence of K2CO3. 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.

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