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'Aromatic ring umpolung', a rapid access to the main core of several natural products

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This paper is dedicated to Pr. Marco Ciufolini on the occasion of his birthday and for all his noteworthy contributions in the area of total synthesis

ABSTRACT

Treatment of various substituted phenols in the presence of (diacetoxyiodo)benzene promotes the formation of a phenoxenium ion, a very electrophilic species able to react with various nucleophiles leading rapidly to a plethora of different cores present in natural products via several novel oxidative processes. This strategy fits within the concept of 'aromatic ring umpolung'; in this paper a personal account by our laboratory on this thematic is described.

1. Introduction

The umpolung concept or polarity inversion of functional groups is a well known concept, very used in organic transformation that allows extending chemical possibilities to produce important structures rapidly. This concept has been first introduced by Corey and Seebach.[1] An extension of this concept to the aromatic chemistry would provide new strategic opportunities in synthetic chemistry, by extension of several well known reactions in aliphatic chemistry to the aromatic chemistry. To accomplish such transpositions, the well known electrophilic substitution of aromatic compounds has to be considered. Indeed, during this important transformation, electron rich nucleus, such as phenol or aniline derivatives normally react as a nucleophile; suitable oxidative activation can convert it into a reactive electrophilic intermediate **3**, which may be intercepted with appropriate nucleophiles (Fig. 1).

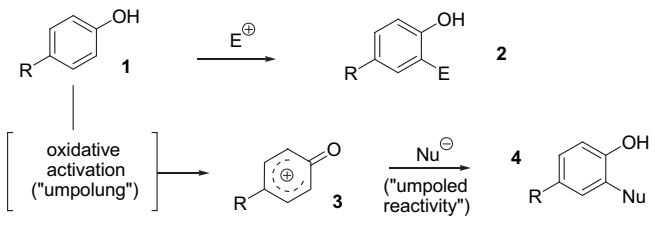

Figure 1.

If one considers the behavior of the species **3**, this reversal of reactivity may thus be thought of as involving 'aromatic ring umpolung'. If several oxidising agent may be used as demonstrated first by Kita,[2] a hypervalent iodine reagent,[3] such as (diacetoxyiodo) benzene (DIB), was found to be the reagent of choice to promote rapidly the formation of the phenoxenium ion **3**. Such hypervalent iodine complexes are very used in synthesis[4,5] due to their versatility. Indeed, they are considered as environmentally benign and inexpensive reagents able to substitute heavy metal agents. This process is best performed in perfluorinated alcohols, such as trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP). On the basis of this concept, two reactions may be in competition: aromatic substitution (pathway a) versus oxidative addition (pathway b), Figure 2.

Figure 2.

In bimolecular processes, it has been demonstrated that the regioselectivity depends on the nucleophiles involved. Indeed, with heteronucleophiles the pathway b, leading to a dienone core, is observed, resulting from the attack of the unhindered heteroatom on the stronger contributor mesomer form to the overall delocalized system, the tertiary carbocation. However, with more hindered carbon-based nucleophiles, the pathway a is preferred, leading to a more substituted aromatic compound **4**. Following the behavior of the nucleophile used, radically different cores are

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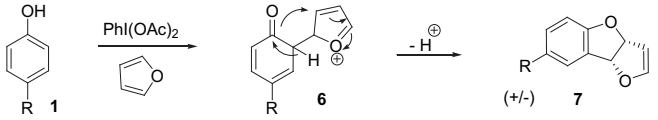
obtained. This observation demonstrates the importance of the species **3** in chemical synthesis. It should be noted that such intermediate is usually involved in the biosynthesis of several natural products,[6] demonstrating that the aromatic ring umpolung chemistry is an important concept. This paper is described as a personal account of our laboratory focusing on the capture of such intermediates with carbon-based nucleophiles, leading to the formation of new C–C bonds and the direct application of these methodologies as key steps in the total synthesis of several natural products.

2. Formal cycloaddition with furan

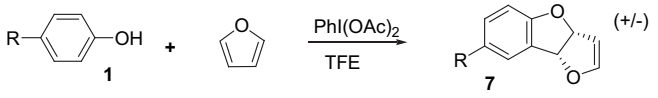
Interestingly, the use of furan, a weak aromatic system, in presence of the species **3**, leads to tricyclic compounds **7** resulting from a formal oxidative [2+3] cycloaddition process[7] (Scheme 1). The reaction, in this case, is best carried out in TFE as solvent instead of HFIP, which has been observed to be too acidic for the very unusual dihydrofurobenzofuran core **7** produced.[8] The selectivity observed results from the attack of the nucleophilic position 2 of the furan moiety in *ortho* position of the electrophilic species. The Wheland like intermediate **6** generated is subsequently trapped by the oxygen atom to afford compound **7**, Scheme 1.



Scheme 1.

In this process, one aromatic system reacts as a nucleophile and the other one as an electrophile. Only unactivated sp^2 carbon interactions occur between the *ortho* position of compound **1** and position 2 of furan. Most probably secondary π staking interactions are present during the transition state. To verify the scope of this novel reaction, various substituted phenols were converted to **7** in 38–61% yield. A summary of representative experiments with *para*-substituted phenols appears in Table 1.

Table 1
[2+3] cycloaddition process with furan



Entry	R	Yield (%)
a	*t*-Bu	61
b	Me	38
c	OMe	41
d	CH_2COOMe	52
e	CH_2CH_2NHTs	47
f	$SiMe_3$	59

The ring system **7** produced by this oxidative cycloaddition process leads to a main tricyclic core present in some natural products, such as panacene[9] **8** and psorofebrin **9**, an antileukemic xanthone,[10] Figure 3.

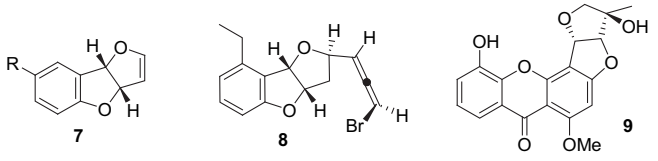
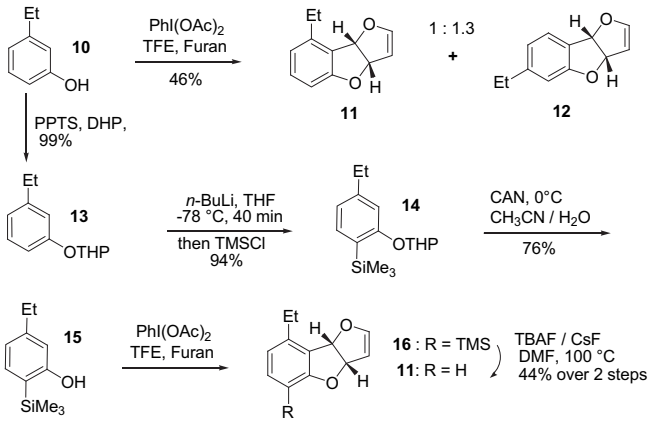


Figure 3.

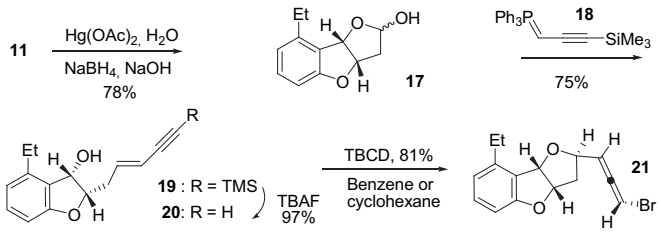
As a first application of this methodology, a total synthesis of panacene has been rapidly accomplished.[11] This compound was isolated in 1977 by Meinwald and co-workers from *Aplysia brasiliana*,[9a] a sea hare indigenous to the gulf coast of Florida. Panacene has shark antifeedant properties, and it is thus believed to protect the sea hare from predatory fish. The unusual architecture of **8** has elicited substantial interest in the synthetic arena. This has led to total syntheses of the racemate, and of the natural (–)-form. Our approach starts with inexpensive 3-ethyl phenol **10**. This material may be directly converted into a mixture (1:1.3) of **11** and **12** in 46% yield using the oxidative cycloaddition process in presence of furan. Despite the fact that these compounds are separable at the next step, a more selective route evolves from derivative **15**, which is readily accessed from **10** in three steps. The TMS group blocks position 6 of the phenol and forces the subsequent oxidative annulation sequence to occur exclusively at position 2. Thus, the core of panacene is assembled in a single step. It is worthy of note that the silyl substituent survives the DIB oxidation step largely unscathed. Indeed, the desired cycloadduct **16** was accompanied by only a small amount (~5%) of **11** and **12**, which clearly arise through partial loss of the TMS group during the reaction. Without separation, this crude mixture was treated with TBAF and CsF in DMF to induce desilylation, Scheme 2.



Scheme 2.

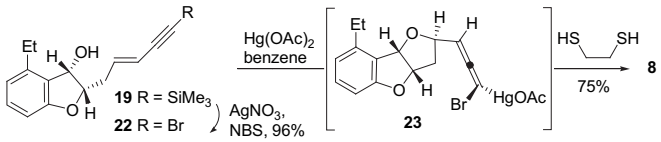
To complete the synthesis of panacene, an oxymercuration reaction carried out on key compound **11**, followed by treatment with sodium borohydride, affords **17**. To illustrate the synthetic potential of the oxidative annulation process, it should be noted that compound **17**, easily obtained directly in two steps from 3-ethyl phenol **10**, is an advanced intermediate previously synthesized in nine steps during the unique asymmetric total synthesis of (–)-panacene.[9e] To achieve the diastereoselective total synthesis, a ring opening/ring closing strategy has been used. Indeed, compound **17** is treated with the corresponding Wittig reagent **18** to yield **19** with a great selectivity (9:1) in favor of the trans isomer, easily separable by flash chromatography. Deprotection of the TMS group with TBAF affords **20** and a treatment of this latter in presence of TBCD (tetrabromo-cyclohexadienone)[12] in apolar solvents, such as benzene or cyclohexane leads to a high diastereoselective synthesis of the unnatural epipanacene **21** Scheme 3.

The diastereoselectivity observed has been obtained by a treatment of the free enyne **20** with a brominating agent in an apolar solvent. To invert the selectivity observed, we have envisaged to introduce first the bromine on the enyne segment and to treat it with a protonating agent. The selectivity observed in such solvent could be explained by an intramolecular hydrogen bond between the hydroxyl group and the *cyclo*-ether favoring one conformer during the transition state. The TMS group on compound **19** was



Scheme 3.

substituted by treatment with silver nitrate and NBS to yield **22**. The latter, treated by mercury acetate in benzene, leads to the corresponding mercuric compound **23**, which was demercurated in situ, with retention of allene configuration, upon contact with ethanedithiol leading to a fully stereoselective synthesis of (±)-panacene **8**, Scheme 4.



Scheme 4.

Using this novel oxidative [2+3] cycloaddition process, a concise and fully diastereoselective synthesis of panacene was accomplished. One may thus reach panacene in an unprecedented five steps from inexpensive 3-ethyl phenol. Finally, a novel highly stereoselective oxymercuration-demercuration process has been devised for the construction of the bromoallene segment of panacene. This concise synthesis demonstrates the potential of 'aromatic ring umpolung' as a powerful tool for the development of novel methodologies and its application to the rapid synthesis of natural product.

3. Oxidative addition of carbon-based nucleophiles

Normally, carbon-based nucleophiles react at the *ortho* position on the electrophile species **3** (pathway a). However, it has been demonstrated, during the total synthesis of panacene, that some protecting groups could block these positions and force the nucleophile to interact at the desired position in a bimolecular mode. This process would allow controlling the oxidative addition versus the aromatic substitution that would open up novel opportunities in the field of chemical synthesis. Indeed, aromatic compounds have several insaturations, but due to their stability, few transformations are allowed. However, a mild desaromatising process, including a C–C bond formation, would produce rapidly a highly functionalized core containing a quaternary carbon center and a prochiral dienone system. The use of the remaining insaturations generated could lead to the concise syntheses of several natural products, Figure 4.

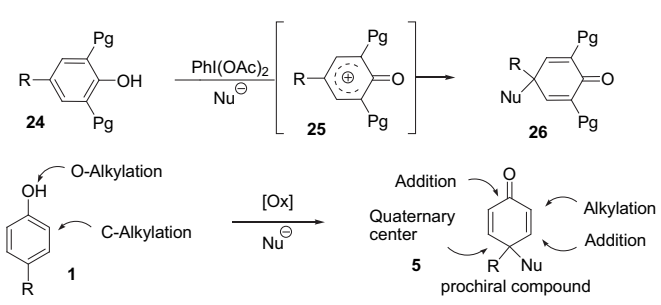
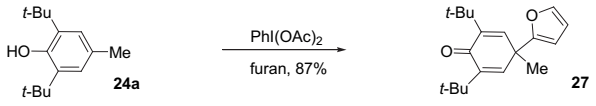


Figure 4.

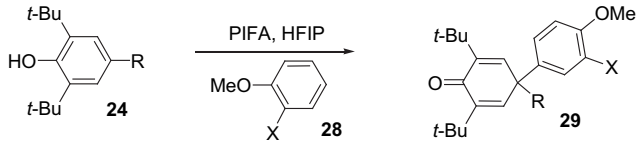
In order to add different carbon-based nucleophiles on the desired *para* position, the *ortho* positions have been blocked with a bulky *tert*-butyl group. In addition, a unique example of such an outstanding transformation has been demonstrated by the transformation of 4-methyl-2,6-di-*tert*-butylphenol into 4-methyl-4-phenylcyclohexa-2,5-dienone upon treatment with chlorodiphenyl-λ^3-iodane (Ph_2ICl) by Quideau and Ozanne-Beaudenon.[4c] With polysubstituted phenols **24a**, the oxidation process in presence of furan leads in high yield to the desired dienones **27**, via an oxidative Friedel–Crafts process,[13] Scheme 5.



Scheme 5.

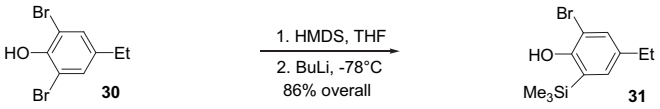
Moreover, this reaction may be extended to anisole derivatives, a quite electron rich system sufficiently nucleophilic to react with species **25** in good yield. To avoid a potential addition of acetic acid released during the process, DIB has been substituted by phenyliodine bis-trifluoracetate (PIFA). Indeed, the trifluoroacetic acid generated during this process is a stronger acid but a weaker nucleophile than acetic acid. A summary of representative experiments with *para*-substituted phenols appears in Table 2.

Table 2
Oxidative addition with di-*tert*-butylphenols



Entry	R	X	Yield (%)
a	Me	H	80
b	Me	Br	82
c	Et	H	70
d	Bu	H	73
e	Me	OMe	64

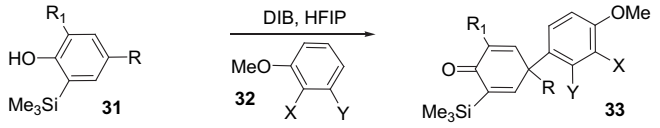
If polysubstituted phenols such as alkyl-di-*tert*-butyl-phenols are useful for exploring the scope of such reaction, they are actually of low potential as starting materials for the total synthesis of natural products. Consequently, in order to move away from *tert*-butyl groups, we have investigated easily removable protecting groups capable of blocking selected positions on the aromatic ring. The choice of directing groups has to achieve two possible results: a steric effect similar to that of a *tert*-butyl, e.g., trimethysilyl; or an inductive effect such as that induced by an electronegative halide. An interesting choice would be the halides, which can be efficiently introduced onto an aromatic ring and are convenient handles to generate C–C bonds by means of palladium chemistry. This synthetic strategy could be useful for the total synthesis of a number of natural products. Unfortunately, oxidation of 2-6-di-bromo cresol led to inextricable by-products. A plausible explanation is that the two electron-withdrawing atoms provide excessive destabilisation of the generated electrophilic species **25**, which rapidly decomposes. In order to avoid this pitfall, we studied the combination of a halide and a TMS group as substituents. In this case, the umpoled intermediate is sufficiently stable to afford the desired compounds. These compounds are easily obtained from the corresponding di-bromophenols by a retro-brook reaction on the corresponding *O*-TMS-dibromo-phenol,[14] as demonstrated with compound **30**, Scheme 6.



Scheme 6.

However, such protected phenols are not compatible with an oxidant like PIFA, probably due to the high acidity generated in the medium, and in such cases, DIB has to be used despite the presence of a small amount of a by-product resulting from the addition of acetic acid on the electrophilic species (~15%). In order to evaluate the scope of this reaction, different moderately nucleophilic functionalities were introduced on the side chain and different substituted anisoles were used. Numerous spectator functionalities, such as alcohols, sulfonamides, and alkenes are compatible with the reaction conditions. A summary of representative experiments appears in Table 3.

Table 3
Oxidative addition with anisole derivatives



Entry	R	R_1	X	Y	Yield (%)
a	$CH_2CH_2OTBDPS$	Br	H	H	37
b	$CH_2CH_2OTBDPS$	Ci	H	H	38
c	$CH_2CH_2OTBDPS$	Ci	H	Br	52
d	CH_2CH_3	Br	H	H	43
e	$CH_2CH{=}CH_2$	Br	H	H	42
f	CH_2CH_2OMs	Br	H	Br	41
g	CH_2CH_2NMeNs	Br	I	H	44
h	CH_2CH_3	Br	OMe	H	37

Despite the modest yields observed with such protecting groups, it should be noted that the starting material used is easily obtained and leads, in only one step, to a highly functionalised core containing a quaternary carbon center connected to three sp^2 carbons; the formation of such a structure using usual chemistry could be more problematic. In addition, the skeletons afforded are present in numerous natural products, such as the family of *Amaryllidaceae* alkaloids,[15] Figure 5.

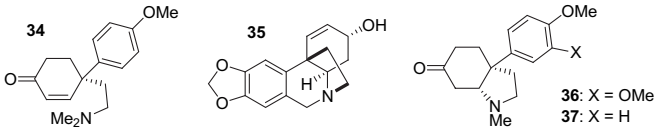
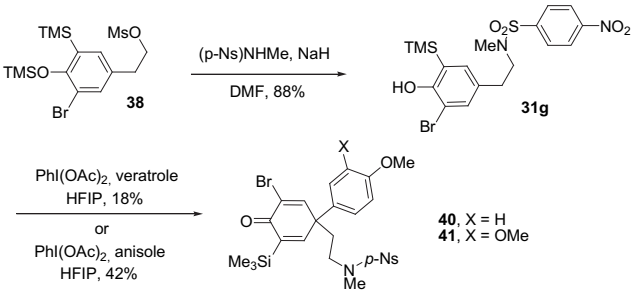


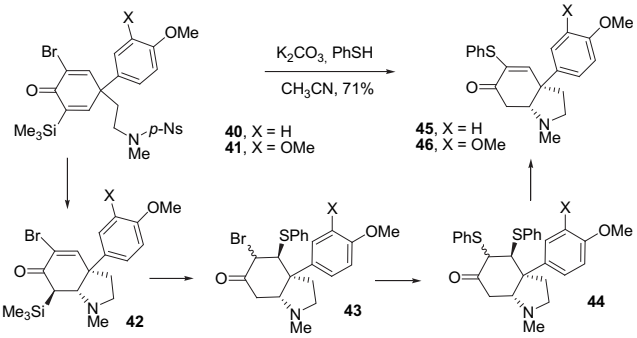
Figure 5.

As a first illustration of the potential of this method, total syntheses of molecules belonging to this family has been accomplished, such as mesembrine **36**,[16] isolated from *Sceletium tortuosum* and the 4,5-dihydro-4′-*O*-methylsceletenone **37**,[17] a simpler natural derivative isolated from *a. cordifolia*. These alkaloids have been shown to be very potent serotonin reuptake inhibitors. Compound **38** was easily obtained from the available 2-(4-hydroxyphenyl)ethanol using conventional chemistry.[13] In order to introduce the necessary nitrogen moiety, an S_N2 reaction was performed between **38** and the corresponding anion of *N*-methyl-*para*-nosylamide in 88% yield; Compound **31g**, when treated with anisole or veratrole in oxidative conditions, led to the corresponding dienone **40** and **41** in modest to low yield, Scheme 7.



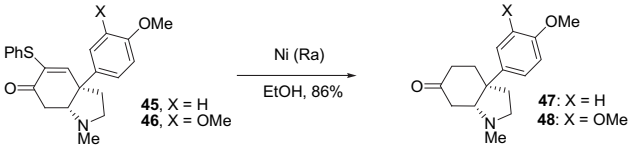
Scheme 7.

From these key compounds the main bicyclic core of these natural products were efficiently accomplished via a treatment of compounds **40** or **41** with K_2CO_3 and thiophenol (Fukuyama's conditions). This novel transformation, occurring in good yield (71% yield), takes place via six successive distinct steps: (1) a nucleophilic aromatic substitution (S_NAr) deprotection leads to the corresponding free amine; (2) the free amine reacts via a Michael process to afford the bicyclic compound **42**; (3) desylilation followed by (4) addition of thiophenol leads to compound **43**; (5) substitution of the bromide by an S_N2 process occurs to generate **44**; (6) a final retro-Michael reaction produces **45** (X=H) or **46** (X=OMe). This method may be assimilated to a Fukuyama and Michael-retro-Michael tandem process, Scheme 8.



Scheme 8.

Total syntheses of mesembrine and 4,5-dihydro-4′-*O*-methylsceletenone were completed by treatment of compounds **45** and **46** with Raney Nickel in ethanol to reduce the alkene and remove the thio-ether, forming the desired natural product in 86% yield, Scheme 9.

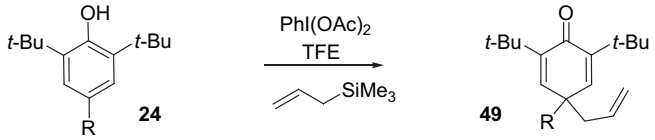


Scheme 9.

This bimolecular oxidative process occurring to the C–C bond formation has been extended to allylsilanes. In this purpose, different 4-alkyl-2-6-di-*tert*-butyl phenols **24** were successfully oxidised leading to an oxidative variant of the famous Hosomi/Sakurai allylation.[18] This approach has already been efficiently used in an intramolecular process as a key step in the synthesis of platensimycin by Nicolaou[19] and co-workers. Moreover, a first approach to this reaction was developed by Quideau and co-workers in aprotic solvents with PIFA, which has provided some noteworthy examples of oxidative allylation on substituted 1-naphthol.[5c] By generalizing this reaction to different aromatic

compounds in a bimolecular process, we would introduce novel opportunities in the field of chemical synthesis. A summary of representative experiments appears in Table 4.

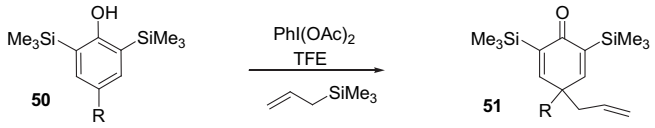
Table 4
Oxidative addition with allylsilane



Entry	R	Yield (%)
a	Me	84
b	*n*-Pen	79
c	*i*-Pr	74
d	CH_2CH_2OH	71
e	$CH_2OTBDMS$	81
f	CH_2CH_2NHTs	61
g	CH_2CO_2Me	70

Different removable protecting groups have been tried, such as a trimethylsilyl group, a motif quite similar to *tert*-butyl with the advantage of being easily removed. Consequently, different di-TMS-phenols **50** have been treated under the oxidative conditions. A summary of representative experiments appears in Table 5.

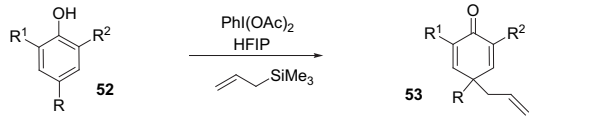
Table 5
Oxidative addition with di-TMS-phenols



Entry	R	Yield (%)
a	Me	52
b	Et	46
c	*i*-Pr	34
d	Ph	37
e	CH_2CH_2OH	41

Unfortunately, yields observed with TMS groups are lower than yields observed with *tert*-butyl groups. While the oxidation of di-bromo-phenols is not efficient, a combination of halogen and *tert*-butyl or trimethylsilyl groups affords the desired core **53** in useful yields, Table 6.

Table 6
Oxidative addition with mixed protecting groups



Entry	R	R_1	R_2	Yield (%)
a	Me	Cl	*t*-Bu	65
b	Me	Br	*t*-Bu	51
c	Me	I	*t*-Bu	45
d	*i*-Pr	Br	*t*-Bu	42
e	Me	Br	TMS	53
f	Et	Br	TMS	56
g	*n*-Bu	Br	TMS	52

As a first application of this oxidative allylation, a total synthesis of aspidospermidine has been accomplished.[20] The complex architecture and biological activities of this product[21] have elicited substantial interest in the synthetic arena. The usual strategy used to produce this compound is generally based on the formation of a key intermediate **56**, first described by Stork and Dolfini.[22] Since then, many other syntheses or formal syntheses have been reported, Figure 6.

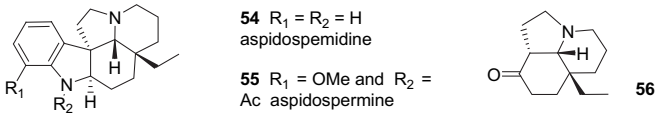
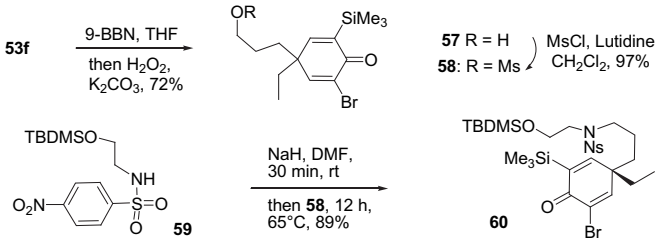


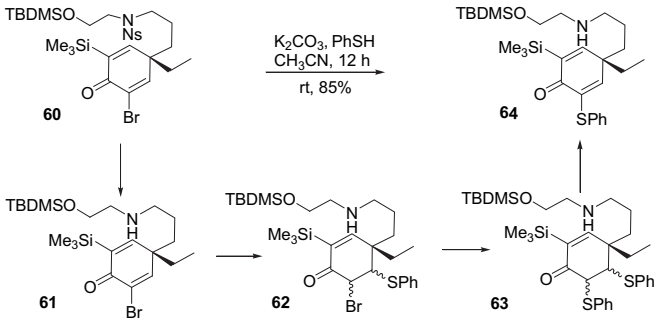
Figure 6.

This synthesis is based on the synthesis of compound **53f**, obtained via the oxidative Hosomi-Sakurai process in 56% yield, then a hydroboration reaction, producing alcohol **57** in 72% yield. The latter is activated with mesyl chloride to generate compound **58** in 97% yield. At this point the nitrogen moiety is efficiently introduced by a S_N2 reaction between **58** and the corresponding anion of **59** to afford the sulfonamide **60** in 89% yield, Scheme 10.



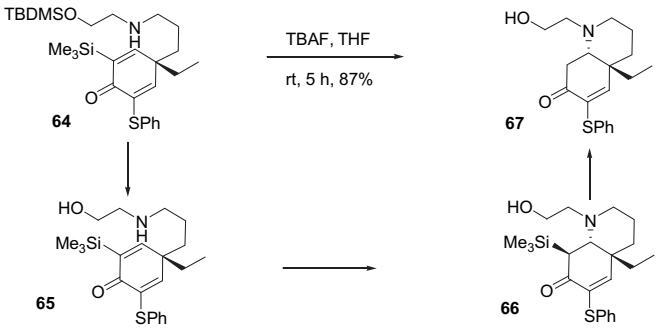
Scheme 10.

This product contains protected secondary amine and alcohol that represent a good precursor of the main tricyclic core of aspidospermidine. Indeed, the elaboration of the main tricyclic core has been produced using the Fukuyama and Michael tandem process, developed previously for the synthesis of mesembrine. This transformation, occurring in 85% yield, takes place via four successive distinct steps: (1) nucleophilic aromatic substitution (S_NAr) deprotection leads to the corresponding free amine **61**; (2) addition of thiophenol leads to compound **62**; (3) substitution of the bromide by an S_N2 process generates **63**; and (4) a final retro-Michael reaction produces **64**, Scheme 11.



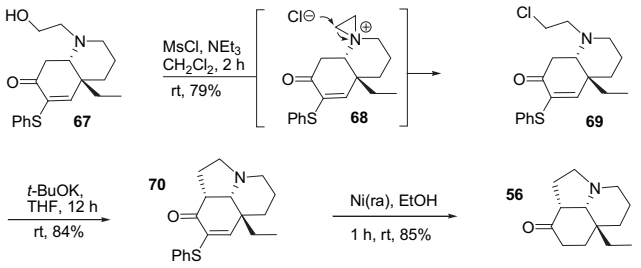
Scheme 11.

At this point, we were surprised not to observe the addition of the free amine on the dienone, but a treatment of compound **64** with TBAF produces the free alcohol and bicyclic ring **67** in 87% yield. Once again, different transformations occurred in the same pot: (1) desilylation of the TBDMS moiety produces **65**; (2) the free amine reacts via a Michael process to afford the bicyclic compound **66**; (3) desilylation of the TMS group occurs to produce **67**. The cyclisation occurring at this point could be explained if we consider that the free alcohol generated first is able to protonate the enolate resulting from the 1–4 addition and could move the reaction equilibrium in favor of the bicyclic core, Scheme 12.



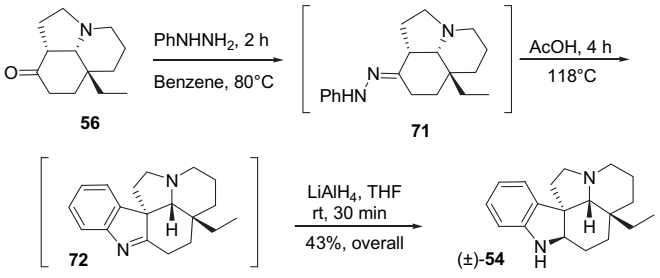
Scheme 12.

The action of mesyl chloride on compound **67** results in the formation of the corresponding chloride **69** in 79% yield, probably via the formation of the intermediate aziridinium **68**. Treatment of **69** with a base, such as potassium *tert*-butoxide leads to the desired tricyclic compound **70** in 84% yield. At this point, treatment of **70** with Raney Nickel in ethanol produces **56** in 85% yield. This sequence of reactions, including a Fukuyama and Michael tandem process, offers an efficient access to key intermediate **56**, known as formal synthesis of aspidospermine, aspidospermidine and quebrachamine,[21m] Scheme 13.



Scheme 13.

To complete the total synthesis, the known tricycle **56**,[22] is converted to aspidospermidine via a Fischer indole synthesis. Indeed, treatment of compound **56** with phenyl hydrazine at reflux leads to the hydrazone **71**, which is converted to imine **72** in acetic acid. The latter is reduced in the same pot by $LiAlH_4$ to produce the aspidospermidine, **54**, in 43% yield overall, Scheme 14.



Scheme 14.

4. Oxidative transposition, a rapid access to highly functionalized cores

Transpositions are very important processes in chemical transformations; indeed such rearrangements allow modifying, by a spectacular avenue, simple structures into a variety of more complex motifs. The most known transpositions are the Wagner/Meerwein reaction, the pinacolic transformation and the Namyotkin rearrangement.[23] If one considers the behavior of the electrophilic species **3** generated during the umpolung activation, it seems reasonable to extend such transpositions known in aliphatic chemistry to the aromatic chemistry via an oxidative process,[24] Figure 7.

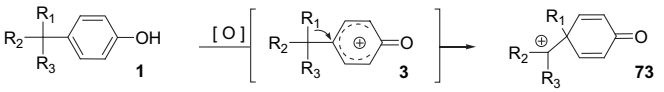
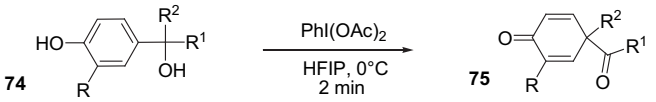


Figure 7.

In this purpose, corresponding phenol **74** has been synthesised to produce, via a kind of oxidative pinacolic transposition, skeletons, such as **75**. This novel process occurs in an intramolecular way that does not require the blocking of *ortho* positions with appropriated protecting groups. Compound **74** is easily obtained in high yield by addition of an excess of allyl Grignard on the corresponding 4-hydroxyphenones. To exemplify this transformation, phenols containing different alkyl and aryl groups have been oxidised. A summary of representative experiments appears in Table 7.

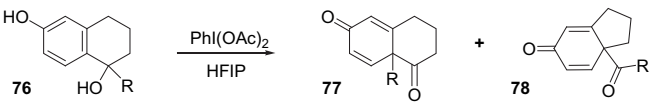
Table 7
Oxidative transposition process



Entry	R	R_1	R_2	Yield (%)
a	H	Me	$CH_2CH{=}CH_2$	62
b	H	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	67
c	Me	Me	$CH_2CH{=}CH_2$	63
d	H	Me	Ph	51
e	Me	Me	Ph	34
f	H	Me	$CH{=}CH_2$	34
g	H	*n*-Bu	*n*-Bu	41
h	H	Me	*n*-Bu	35

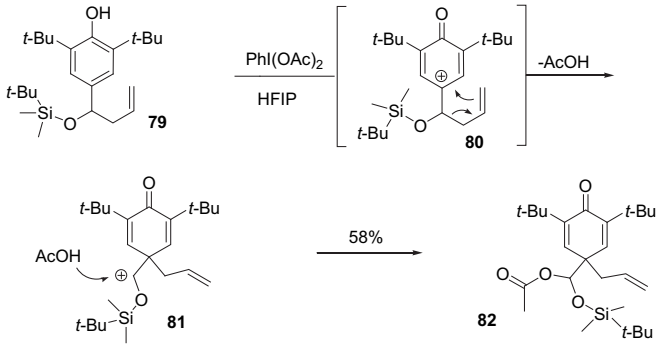
As expected, during the oxidation of compound **74h** the migration of the *n*-butyl group is very predominant; only a small amount of methyl migration is observed (~5%). This oxidative process seems to occur as a regular rearrangement applicable to a large scope of aryl, allyl, and alkyl groups. Indeed, the same rules as the ones applying to a conventional Wagner/Meerwein transposition are observed. This process seems less effective with alkyl groups (entries **74g** and **74h**) probably due to the migration of a sigma bond by comparison with substituents having a Π-bond, such as allyl or aryl groups (entries **74a**, **74b**, and **74c**). In this case, the migration could be envisaged via a concerted mechanism or via an areniun ion (entries **74d** and **74e**). It should be stressed that this process produces, in one step, highly functionalised cores. Indeed, compounds, such as **75d**, **75e**, and **75f** have a quaternary carbon center connected to four sp^2 carbons, the formation of such architecture using conventional chemistry could be problematic. The skeleton generated should have different applications in total synthesis, due to the numerous natural products containing such core, such as the *Amaryllidaceae* alkaloids family.[25] In addition, this transposition has been extended to bicyclic phenols such as tetralone **76**, Table 8.

Table 8
Contraction versus migration



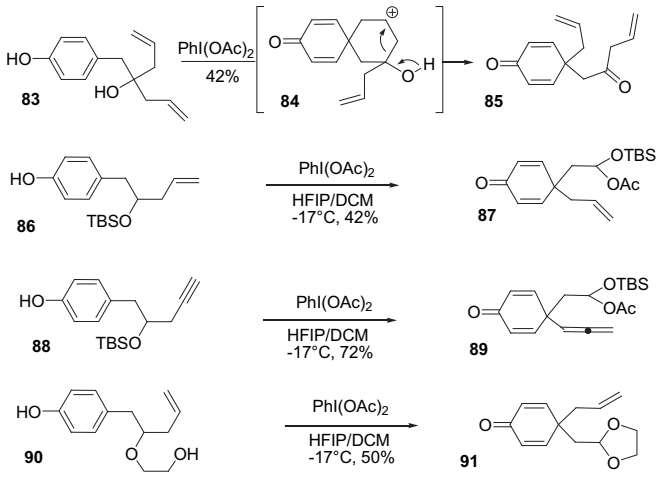
Entry	R	Yield (%) **77**	Yield (%) **78**
a	$CH_2{-}CH{=}CH_2$	43	—
b	Ph	54	—
c	Me	—	53

As envisaged, with good migrating groups such allyl and aryl, the formation of dienone **77** is observed in reasonable yield. In the case **76c** (R=Me), a ring contraction[26] occurs in 53% yield. These results, leading rapidly to an interesting bicyclic system, demonstrate the large potential of this novel transformation and its potential application in synthesis. In addition, a noteworthy transformation is observed by oxidation of the protected alcohol **79** leading to the acetal **82** in 58% yield. Indeed, the allyl C–C bond fragmentation would lead to the intermediate **81** that would be trapped by the acetic acid released during the reaction to afford **82**. This transformation is similar to an oxidative pinacol/acetalisation tandem process. Compound **82** is a dienone system having a quaternary carbon center connected to two different carbonyl precursors, Scheme 15.



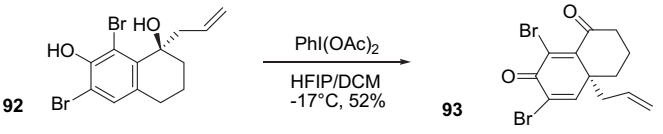
Scheme 15.

In presence of a substituent such as allyl or propargyl groups, due to a potential concerted mechanism involving a species, such as **84**, this oxidative rearrangement process can be extended to an unprecedented 1,3-allyl shift. This transformation could be assimilated to an unreported homo-Wagner/Merweein process. The transposition/acetalisation process described previously has been extended to produce an acetal functionality. Scheme 16.



Scheme 16.

Oxidation of compound **88** produces the desired allenic moiety with a noteworthy global yield of 72%. This process seems to occur more efficiently with a propargylic group than an allylic group. This aspect could be rationalized by the linear geometry of the sp. carbon center that would be more oriented to interact with the phenoxenium ion generated. In addition, we have also been interested in trapping the corresponding oxonium generated on the side chain with an intramolecular nucleophile that does not need the presence of acetic acid in the medium. The oxidation of compound **90** leads to the acetal **91**, in 50% yield. An interesting aspect of this reaction is the spectacular rearrangement observed during the umpolung activation. Indeed, a simple phenol containing an ether functionality is redesigned in only one step into a highly elaborated core containing several functionalities present on almost each carbon. Moreover, this transposition can be accomplished on a bicyclic phenol **92** to yield the dienone **93**, Scheme 17.



Scheme 17.

The introduction of bromines in *ortho* position is necessary to force the allylic group during the oxidative process to react only in *para* position. Moreover, we suppose that the migration of the allylic group should occur stereospecifically with a retention of configuration, due to the concertness of the mechanism involved. In addition, the bicyclic compound **93**, represents a bicyclic intermediate of the main core **94** of platensimycin **95**, a selective FabF inhibitor,[27] Figure 8.

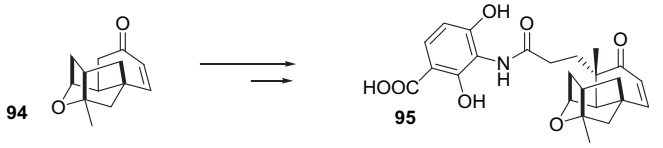
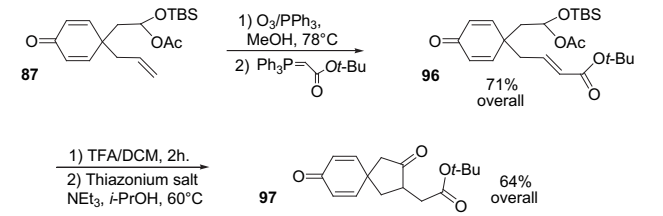


Figure 8.

Furthermore, compound **87** can lead to the spiro-bicyclic system of platensimycin **95**. Indeed, an ozonolysis on **87** followed by a Wittig reaction lead to compound **96** in 71% yield and a treatment of this latter with TFA and in Stetter's conditions[28] produce the desired bicyclic core **97** in 64% yield, Scheme 18.



Scheme 18.

5. Conclusion

In conclusion, several novel methodologies have been developed on the basis of a common phenoxenium ion mediated by noteworthy and environmentally benign hypervalent iodine reagents. Indeed, following the substituents present on the phenol and the nucleophiles introduced in the medium, intriguing oxidative reactions have been performed such as a [2+3] cycloaddition process, an aromatic electrophilic substitution extension, an efficient allylation transformation and unprecedented skeleton transpositions. All these transformations expand novel strategic opportunities in the chemical synthesis that has already allowed rapid accesses to several total syntheses of natural products such as panacene, mesembrine and its natural analogous, aspidospermine and two advanced intermediates of the main core of platensimycin. An important aspect of this umpolung strategy is the ability to transform quickly an inexpensive and simple phenol into a highly

functionalized core containing a prochiral dienone, and a quaternary carbon center connected to several sp^2 carbons. All these methodologies using an electron rich aromatic reversal of reactivity may thus be thought of as involving 'aromatic ring umpolung'; this intriguing concept opens up novel chemical strategies. New results in ongoing investigations and development for asymmetric syntheses in this field will be disclosed in due course.

6. Experimental protocols

6.1. General

Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ at 300 MHz for ^1H and 75 MHz or 150 MHz for ^{13}C. Chemical shift (δ) are in parts per million, and coupling constants (J) are in hertz. Multiplicities are reported as: 's' (singlet), 'd' (doublet), 'dd' (doublet of doublets), 't' (triplet), 'q' (quartet), 'm' (multiplet), 'c' (complex), 'br' broad. All reactions were monitored by TLC. Reagents and solvents were commercial products and were used as received, including trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP).

*6.1.1. Compound (**96**).* To a stirred solution of **87** (20 mg, 0.057 mmol) in MeOH (10 mL) at −78 °C, ozone was passed through for 15 s. (lightly blue). The solution was then purged with argon for 10 min and warmed to room temperature. PPh_3 (0.19 mg, 0.06 mmol) was added and the reaction mixture was stirred for 10 min. The solution was concentrated under vacuum and the residue was dissolved in dry THF (1 mL), the corresponding Wittig reagent was introduced (32 mg, 0.085 mmol, 1.5 equiv) and the reaction was stirred for 3 h. and concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane/ethyl acetate, 3/1) to give **96** (18 mg, 0.04 mmol, 71%) as a pale yellow oil: ^1H NMR (600 MHz, $CDCl_3$) δ=6.83 (dd, 1H, J=10.4, 3.3), 6.78 (dd, 1H, J=10.4, 3.3), 6.55 (dt, 1H, J=15.4, 7.7), 6.32 (dd, 1H, J=10.4, 2.2), 5.80 (t, 1H, J=5), 5.73 (t, 1H, J=15.4), 2.41 (d, 2H, J=7.7), 2.14 (dd, 1H, J=13.7, 4.4), 2.04 (dd, 1H, J=13.7, 4.4), 1.96 (s, 3H), 1.44 (s, 9H), 0.85 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); HRMS: calcd for $C_{24}H_{38}O_6SiNa$ $(MNa)^+$: 473.2330; found: 473.2333.

*6.1.2. Compound (**97**).* To a stirred solution of **96** (6 mg, 0.0133 mmol) in CH_2Cl_2 (0.6 mL) was added TFA (0.029 mmol, 2.2 equiv) dissolved in CH_2Cl_2 (0.1 mL). The solution was stirred for 2 h, then dropwise added on a warm (60 °C) mixture of isopropanol (0.6 mL), NEt_3 (0.1 mL, 0.067 mmol, 2.2 equiv), and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride (7 mg, 0.0266 mmol). The solution was stirred for further 2 h and directly filtrated on a small pad of silica gel (washed with ethyl acetate/hexane, 1/1) and the solution was concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane/ethyl acetate, 1/1) to give **98** (2.5 mg, 0.009 mmol, 64%) as a pale yellow oil: ^1H NMR (600 MHz, $CDCl_3$) δ=6.97 (d, 1H, J=9.4), 6.86 (d, 1H, J=9.4), 6.34 (d, 1H, J=9.4), 6.30 (d, 1H, J=9.4), 2.77 (m, 1H), 2.69 (d, 1H, J=18.2), 2.67 (m, 2H), 2.43 (d, 1H, J=18.2), 2.23 (t, 1H, J=8.2), 2.15 (t, 1H, J=12.3), 1.45 (s, 9H); HRMS: calcd for $C_{16}H_{20}O_4Na$ $(MNa)^+$: 299.1254; found: 299.1257.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.03.096. These data include MOL files and InChIKeys of the most important compounds described in this article.

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