JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

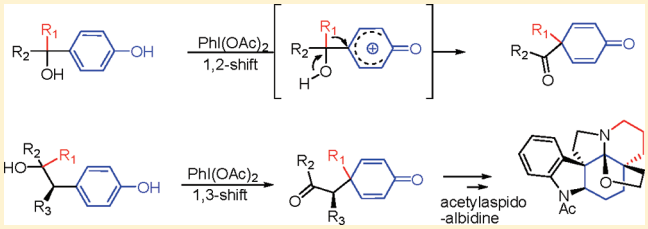
Oxidative 1,2- and 1,3-Alkyl Shift Processes: Developments and Applications in Synthesis

Kimiaka C. Guérard, Amandine Guérinot, Cloé Bouchard-Aubin, Marc-André Ménard, Mathieu Lepage, Marc André Beaulieu, and Sylvain Canesi*

Laboratoire de Méthodologie et Synthèse de Produits Naturels, Université du Québec à Montréal, C.P. 8888, Succ. Centre-Ville, Montréal, H3C 3P8 Quebec, Canada

Supporting Information

ABSTRACT: Oxidative 1,2- and 1,3- alkyl shifts mediated by a hypervalent iodine reagent were performed on simple and inexpensive phenol derivatives. These transpositions enable rapid redesign of the main aromatic skeleton to generate good yields of highly functionalized scaffolds containing a prochiral dienone system, a quaternary carbon center connected to as many as four sp^2 centers, and a carbonyl functionality or precursor. An efficient enantioselective version of this process resulting in the formation of a challenging quaternary carbon center is also described. The products represent the central cores of several natural products having important bioactivities. As an illustration of the potential of this method, we describe the rapid synthesis of several functionalized polycyclic systems as well as a formal synthesis of acetylaspidoalbidine, a hexacyclic alkaloid belonging to the *Aspidosperma* family.



INTRODUCTION

The sigmatropic rearrangement is one of the most impressive transformations in organic synthesis. Processes of this type permit rapid reconfiguration of simple skeletons into complex architectures via 1,2-substituent shifts such as the Wagner–Meerwein, pinacolic, and semipinacolic transpositions. Despite being first described more than a century ago, these cationic molecular transpositions[1] still represent an appealing and efficient route to complex molecular structures. The transformations are generally performed on aliphatic substrates, and an extension to aromatic scaffolds would open up several applications in chemical synthesis. Our interest in oxidative dearomatization of phenols[2] mediated by hypervalent iodine reagents[3−5] led us to question whether an analogous process could be initiated by oxidative activation. While electron-rich aromatic systems normally react as nucleophiles, oxidative activation converts them into highly electrophilic species, which may then be intercepted with appropriate nucleophiles. If one considers the behavior of the intermediate **2**, this reversal of reactivity may be thought of as involving "aromatic ring umpolung",[2,3d] an aromatic version of the umpolung concept,[6] providing new strategic opportunities in synthesis by extending several well-known aliphatic reactions to aromatic chemistry. Such phenol dearomatization processes are generally mediated by hypervalent iodine reagents such as iodobenzene diacetate (DIB, an environmentally benign reagent), are well documented in the literature, and have elicited substantial interest in the synthetic arena. An indication of how the formation of the corresponding phenoxonium ion **2** may be efficiently achieved and sufficiently stabilized for nucleophilic trapping is apparent in the work of Kita,[7] who reported that such transformations are best performed in solvents such as hexafluoroisopropyl alcohol (HFIP).[8] An extension of the process to aromatic derivatives would facilitate rapid redesign of simple and inexpensive cores, such as phenols, into more complex spirodienone architectures. In addition, this method is capable of transforming stable aromatic ring structures into reactive dienone cores for use as highly functionalized intermediates. Oxidative extensions of cationic sigmatropic rearrangements via a 1,2-shift process or an unprecedented 1,3 shift extension mediated by a concerted mechanism involving a π-bond in a chairlike transition state (contained in the substituent R_3) would provide a rapid and esthetically appealing route to complex structures, Figure 1.

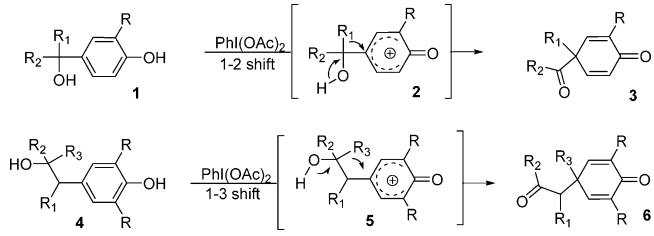


Figure 1. Presumed course of oxidative 1,2- and 1,3-alkyl shifts.

Architectures generated by these methods are often present in several natural products containing a quaternary carbon center in a functionalized cyclohexanone subunit or its derivative. Some examples include hamayne **7**, a pentacyclic core belonging to the Amaryllidaceae alkaloids,[9] jiadifenin **8**, a

Received: January 22, 2012
Published: February 14, 2012

 © 2012 American Chemical Society dx.doi.org/10.1021/jo300169k | J. Org. Chem. 2012, 77, 2121–2133

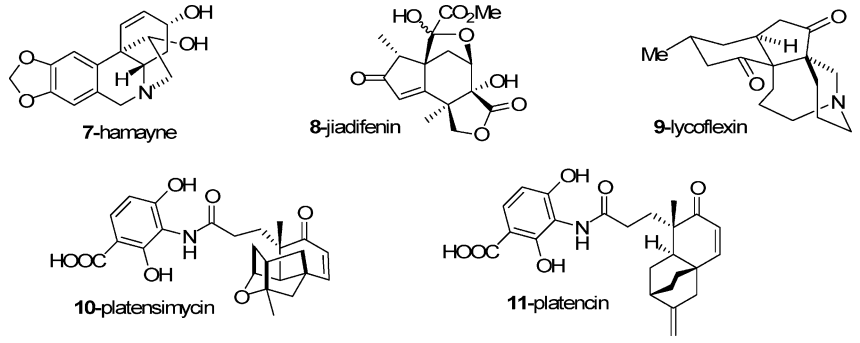
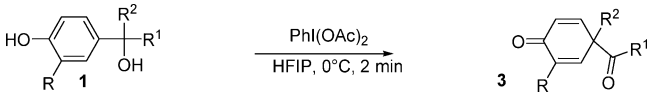


Figure 2. Natural products containing a quaternary carbon center.

Table 1. Oxidative 1,2-Alkyl Shift 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	CH_2OTBS	$CH_2CH{=}CH_2$	33
e	H	Me	$CH_2C(Me){=}CH_2$	37
f	H	Me	$CH{=}CH_2$	34
g	H	Me	Ph	51
h	H	Et	Ph	35
i	Me	Me	Ph	34
j	H	*n*-Bu	*n*-Bu	41
k	H	Me	*n*-Bu	35

novel majucin-type prezizaane isolated from the *Illicium jiadifengpi* species of China,[10] lycoflexine **9**, an alkaloid belonging to the lycopodium family,[11] and (−)-platensimycin **10** and (−)-platencin **11**, two exciting experimental antibiotics acting as FabF inhibitors[12] (Figure 2).

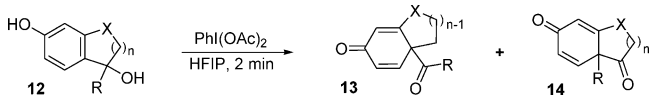
In this paper, we present an extension of our previous oxidative alkyl shift processes[2f] to a large range of phenol derivatives as well as an efficient enantioselective version of this method. In addition, the formation of several advanced polycyclic cores and a formal synthesis of acetylaspidoalbidine (an alkaloid belonging to the *Aspidosperma* family) are described.

RESULTS AND DISCUSSION

We decided to initially test the feasibility of oxidative 1,2-alkyl shifts on phenol derivatives by oxidizing various benzylic alcohol systems **1** readily obtained from various alkyl-Grignard reagent additions to 4-hydroxyphenyl ketones. Oxidation of these compounds promotes the desired rearrangement leading to the products **3** in 33−67% yield. Several functional groups were investigated including allyl segments, which are known to be good migrating group, as well as vinyl, phenyl, and simple alkyl groups. A summary of representative experiments appears in Table 1.

An important aspect of this strategy is the ability to quickly transform an inexpensive and simple phenol into a highly functionalized core containing a prochiral dienone in the form of a quaternary carbon center connected to several sp^2 carbons.[13] The reaction occurs in useful yields in the presence of allyl groups (up to 67%) and is less efficient with vinyl, phenyl, or alkyl groups. The migration of aryl groups to enable the formation of compounds **3g−i** represents a synthetic challenge due to the complexity of generating a quaternary carbon center connected to four sp^2 centers in a single step. This most probably occurs via the formation of an arenium intermediate. It should be noted that a similar subunit is present in several natural products such as hamayne and vindoline (Figures 2 and 3). As expected in a normal pinacol process involving a 1,2-alkyl shift, migration of the more electron-rich group predominates as well exemplified by entry **3k**, for which only a small amount of methyl migration is observed (∼5%). In addition, the rearrangement may be extended to bicyclic phenols **12**, Table 2.

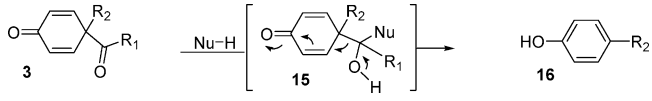
Table 2. Bicyclic System Contraction versus Migration



entry	X	R	*n*	yield **13** (%)	yield **14** (%)
a	CH_2	$CH_2CH{=}CH_2$	2		43
b	CH_2	Ph	2		54
c	O	$CH_2CH{=}CH_2$	1		43
d	CH_2	Me	2	53	

Another interesting example of this oxidative process is the ring contraction observed in the tetralone derivative **12d**, leading to **13d** in 53% yield. The process appears to occur as a normal sigmatropic rearrangement and the rules applying to conventional Wagner−Meerwein transpositions are observed. One limitation results from the formation of phenol **16** as a side product through a retro-Claisen process following nucleophilic attack of species present in the medium (acetate, etc.) on compound **3**. Formation of this byproduct is increased if a withdrawing substituent is present on the lateral chain (entry **1d**), which increases the electrophilicity of the ketone involved in the retro-Claisen pathway if the reaction is not rapidly stopped (Scheme 1).

Scheme 1. Oxidative Ring Contraction and Retro-Claisen Process

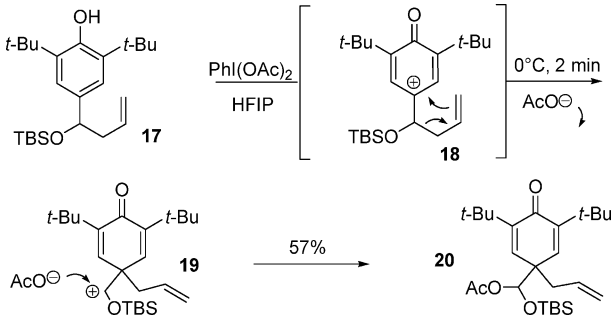


Protection of the alcohol moiety enabling the alkyl shift leads to a corresponding acetal functionality **20** as an aldehyde precursor in 57% yield. The formation of this compound results from a direct attack by acetate ion released during the oxidative process on oxonium species **19**; the relative stability of this carbocation enables it to react in a bimolecular mode with an

dx.doi.org/10.1021/jo300169k | J. Org. Chem. 2012, 77, 2121−2133

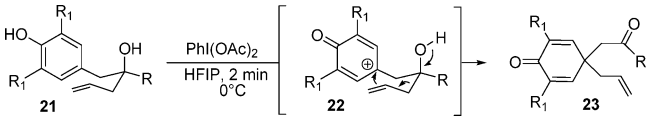
external nucleophile despite the presence of a neighboring silicon ether functionality, which could be explained by the presence of HFIP as a non-nucleophilic and highly polar solvent. This transformation appears to proceed through an oxidative semipinacol/acetalization tandem process with the formation of an intriguing and surprisingly stable acetal functionality. It should be stressed that the formation of this acetal occurs only with a protected secondary alcohol functionality, and no corresponding ketal moiety has been observed with protected tertiary alcohol derivatives, which would lead directly to a ketone (Scheme 2).

Scheme 2. Oxidative Pinacol-Acetalization Tandem Process



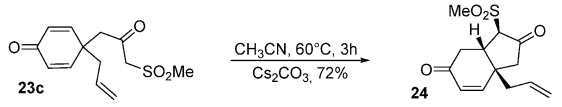
In order to explore the potential of this process, we envisaged trapping the resulting phenoxonium ion with an intramolecular homoallyl segment to produce a dienone core such as **23**. This unprecedented 1,3-allyl shift would be mediated by a concerted mechanism involving a π-bond in a chairlike transition state **22** to produce the corresponding dienone **23**. This novel extension opens new avenues in chemical synthesis and may be extended to several phenols **21**. A summary of representative experiments appears in Table 3.

Table 3. Oxidative 1,3-Allyl Shift Process



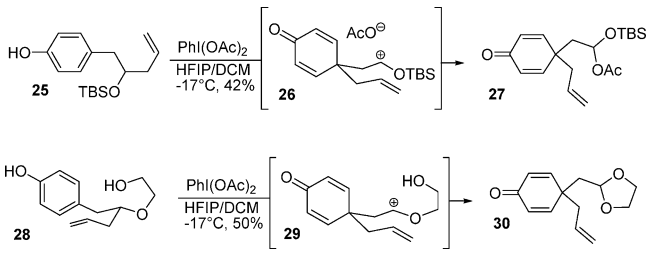
entry	R_1	R	Yield (%)
a	H	CH_2-CH=CH_2	**42**
b	Br	CH_2-CH=CH_2	**61**
c	H	CH_2-SO_2Me	**44**
d	H	H	**25 (54)***

* crude



As a rapid application of such a functionalized core, subsequent treatment of **23c** with Cs_2CO_3 led to a single diastereomer of the bicyclic core **24** in 72% yield. It appears that oxidation of a free secondary alcohol such as **21d** leads to aldehyde **23d** in low (25%) yield, despite the fact that the crude yields estimated from NMR results were reasonable. This is because aldehyde **23d** is not very stable, particularly on silica gel, and yields were reduced during purification. The instability is due to rapid Michael addition of the aldehyde to the dienone moiety, resulting in formation of a hemiacetal in a manner similar to the transformation described in Scheme 12. The problem may be solved by using a protected alcohol to promote the 1,3-shift process as outlined in Scheme 2. Under such conditions the stable acetal functionality **27** is formed, avoiding further transformation of the aldehyde functionality. In addition, this tandem oxidative transposition–acetalization process may be accomplished in an intramolecular mode with alcohol **28**, producing the acetal system **30** in 50% yield in one step via a cascade transformation involving species **29**. This tandem process permits the rapid formation of a polyfunctionalized compact core containing a dienone structure, a quaternary carbon center, and two different aldehyde precursors on each lateral chain (Scheme 3).

Scheme 3. Oxidative Transposition–Acetalization Tandem Process



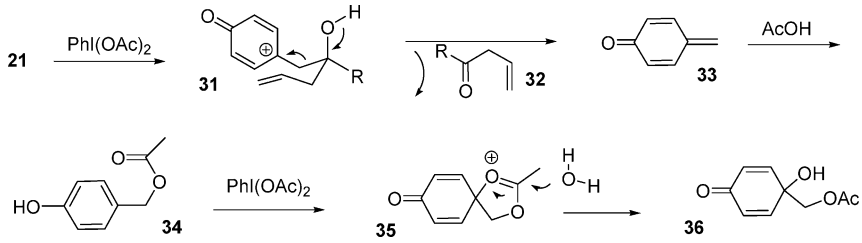
One limitation observed during this 1,3-shift process is the formation of the side product dienone system **36**, apparently via oxidative Grob fragmentation[14] from a direct sigmatropic carbon–carbon bond cleavage on species **31** leading to methide quinone **33**, which is able to react with acetic acid released in the medium during the umpolung activation in a 1,6 Michael addition to produce phenol **34**. A subsequent overoxidation of **34** with DIB leads to the side product **36**, probably with the assistance of the acetate **35** (Scheme 4).

The presence of an electron-rich substituent in the benzylic position increases formation of methide quinone species (such as **33**), limiting the scope of this process when an allyl group is used as a 1,3-migrating agent. As an example, oxidation of compound **37** leads to the formation of two tricyclic systems, one (pathway a) following π-bond attack of the allyl group leading to the desired compound **39** and followed by Michael addition to the hemiketal functionality leading to the tricyclic system **41**. A second route (pathway b) proceeds via direct σ C–C bond cleavage from an apparent oxidative Grob process to produce the phenol **40** after 1,6-Michael addition with acetic acid released from a methide quinone species. Overoxidation with DIB leads to the *o*-acetate system **42** resulting from attack by the primary alcohol present on the lateral chain. Compounds **41** and **42** have been obtained in 29% and 23% yield, respectively (Scheme 5).

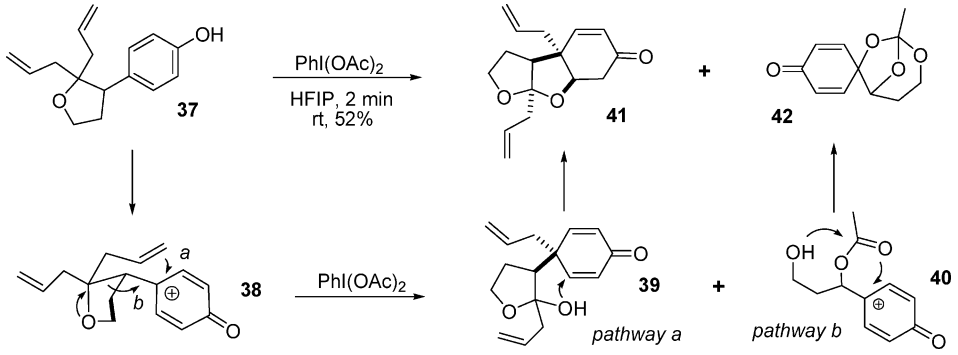
This process may also be applied to tetralone derivatives containing the required homoallylic segment in the *meta* position. However, in this case, the *ortho* positions must be blocked with bromine atoms to force reaction of the allyl group exclusively at the *para* position during oxidation. The migration is otherwise mainly observed at the less hindered *ortho* position, producing the substituted phenol **48** in 57% yield, Scheme 6. The regioselectivity observed with bromine atoms may be explained by considering that the first intermediate is a highly delocalized carbonium ion, which can be represented by the resonance structure **44**. We believe that **44** rather than the *ortho* mesomer **47** is the dominant resonance form because of the presence of the electron-withdrawing bromine atoms. Consequently, the reaction primarily occurs at the *para* position

dx.doi.org/10.1021/jo300169k | J. Org. Chem. 2012, 77, 2121–2133

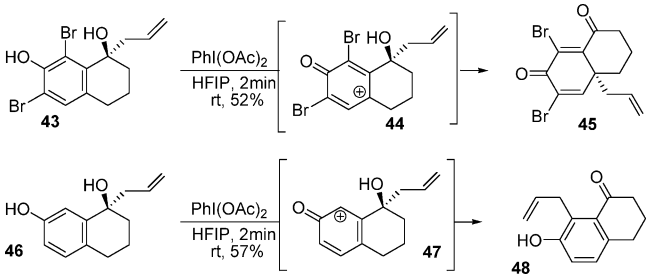
Scheme 4. Oxidative Grob Fragmentation as a Side Reaction



Scheme 5. 1,3-Allyl Shift versus Grob Fragmentation



Scheme 6. *Ortho* versus *Para* Attack

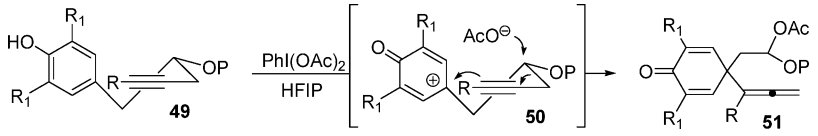


when bromine atoms shield the *ortho* positions through stereoelectronic effects. The presence of a nucleophilic π-bond in the *meta* position is in accordance with the results observed when the transformation occurs through a bimolecular pathway, and the same behavior was observed in the case of external nucleophiles acting on phenoxonium species. Indeed, small nucleophiles such as alcohols react at the *para* position, while stereoelectronically stabilized carbonium species[7] **44** and more hindered carbon-based nucleophiles react at the more accessible *ortho* position **47**.[2g] An added advantage is that the bromine atoms could subsequently be used to introduce other substituents through transition-metal chemistry (Scheme 6).

The oxidative 1,3-shift process is not restricted to allyl groups and may be efficiently extended to alkynes to produce allenyl systems such as **51**. This aspect could be rationalized by the linear geometry of the two *sp* carbon centers mediating a half chair transition state **50**, leading to **51** in good yield. In this case, the side product **36** resulting from Grob fragmentation was present in small amounts or not observed at all. Several 1,3-alkyne promoters have been investigated, leading to the isolated acetal **51** (Table 4).

The 1,3-alkyne shift process may also be extended to tertiary alcohols such as **52** to furnish diallenic systems **53**. The additional allenyl Michael acceptor moiety present in **53** results from rapid isomerization of the remaining alkyne that has not intercepted the phenoxonium ion **50**. Consequently, the yields listed in Table 5 represent a tandem 1,3-alkyne shift-isomerization process. Migration of a single alkyne moiety occurs more efficiently than allyl group migration (Tables 4 and 5 versus Table 3), probably due to a favorable half-chair transition state resulting from the less hindered geometry of the linear alkyne moiety. This leads, in one step, to a polysubstituted and highly functionalized core **53** containing a large number of unsaturation sites. Furthermore, even when a substituted electron donor group is present in the benzylic position, the undesired competitive Grob fragmentation occurs only minimally (Scheme 5)

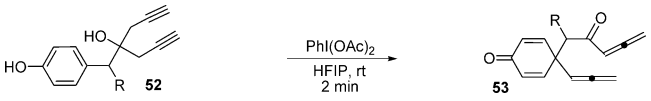
Table 4. Oxidative 1,3-Alkyne Shift Process



entry	R_1	P	R	yield (%)
a	H	TBDMS	H	64
b	Br	TBDMS	H	76
c	H	TIPS	H	61
d	Br	TIPS	H	70
e	H	TBDMS	$SiMe_3$	55

dx.doi.org/10.1021/jo300169k | J. Org. Chem. 2012, 77, 2121−2133

Table 5. Diallenic Ketone System Formation

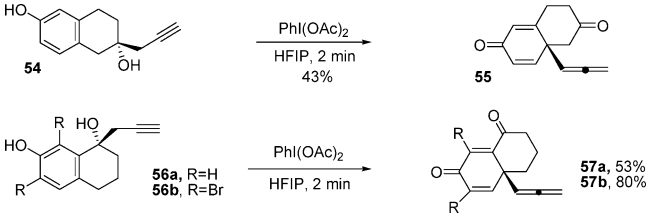


entry	R	yield (%)
a	H	60
b	Me	45
c	$CH_2CH{=}CH_2$	46
d	$CH_2C{\equiv}CH$	52

and the 1,3-alkyl shift process proceeds through one transition state such as **50** remains the main pathway (entries **53b–d**, Table 5).

This method is also compatible with bicyclic phenols **54** and **56**, yielding the desired dienones **55** and **57**. It should be noted that in the case of compound **56** and in contrast to the allyl version **46** (Scheme 6), a free phenol **56a** may be directly oxidized to produce the dienone **57a** without bromine atom protection of the *ortho* positions. Indeed, due to the linear and unhindered geometry of free alkynes, which are some of the smallest carbon-based nucleophiles, direct addition of the alkyne moiety at the stereoelectronically favored *para* position is observed in 53% yield. However, in accordance with observations of the more hindered sp^2 allyl group in Scheme 6, this process is more efficient with the dibromo tetralone derivative **56b**, which leads to **57b** in 80% yield and avoids competitive pathways. An important aspect enabling this transformation is the favored axial position of the migrating substituent (allyl or propargyl moiety), which is required to minimize 1,2 allylic strain with the aryl moiety during the transition state and provide favorable π overlap with the phenoxonium ion generated during the umpolung activation. This leads to formation of a quaternary carbon center with retention of configuration from the alcohol stereocenter (Scheme 7).

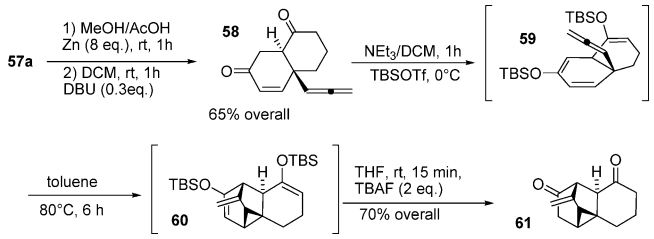
Scheme 7. Tetralone Derivatives



Interestingly, compound **57a** may be rapidly elaborated into a functionalized polycyclic system through an intramolecular Diels–Alder process. Selective reduction of the dienone **57a** with zinc leads to an epimeric mixture of compound **58**, which is rapidly transformed into the most stable *trans* isomer in the presence of DBU. Treatment of **58** with TBS-triflate generates intermediate **59** which is slowly transformed into the tetracyclic core **60**; treatment with TBAF furnishes the ketones **61** in 70% yield, Scheme 8.

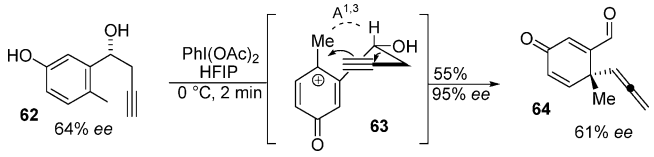
Based on a hypothetical half-chair transition state, an enantioselective route enabling the formation of quaternary carbon centers was developed beginning with the enantioenriched alcohol **62** (64% ee), which may be obtained using a chiral and user-friendly organoindium reagent.[15] The enantiomeric excess of **62** obtained from this practical asymmetric pathway has not been optimized but was sufficient to demonstrate the stereoselectivity of the 1,3-shift process. Oxidation of phenol **62** leads

Scheme 8. Rapid Tetracyclic System Elaboration



to the aldehyde **64** in 55% yield and a very good 95% corrected ee if we consider the optical purities of the starting material (64%) and the final compound (61%). This could be explained by the required minimal 1,3-allylic strain interactions between the methyl group and the hydroxyl during the open transition state **63**. In addition, the presence of protic HFIP increases the *A* value of the hydroxyl group (hydrogen bonds), favoring the required equatorial position. The ee could be probably improved by protecting the secondary alcohol moiety with a bulky protecting group or reaction at lower temperature to stabilize the required transition state. These observations demonstrate the stereoselectivity of this process and its potential applications in asymmetric synthesis (Scheme 9).

Scheme 9. Enantioselective Route



An initial application of oxidative shift transposition is the synthesis of the tricyclic core **72**, which is a potential intermediate for a plethora of natural products belonging to the *Aspidosperma* family, including acetylaspidoalbidine **80**[16] isolated from the Venezuelan tree species *Aspidosperma fendleri woodson* and *Aspidosperma rhombeosignatum markgraf*, neblinine **81**,[17a] vindoline **82**,[17b] aspydophytine **83**,[18] a heptacyclic compound isolated from *Aspidosperma neblinae monachino*, and beninine **84**,[19] isolated from *Callichilia barteri* isolated from *Catharanthus roseus*. We employed the formal synthesis of acetylaspidoalbidine as an example of this process in the production of complex natural products such as those illustrated in Figure 3.

The *Aspidosperma* family is one of the most abundant indole alkaloid families, containing more than 250 compounds from several sources, many of which have important biological activities. The core of these compounds is the pentacyclic subunit named aspidospermidine.[19] The synthesis of aspidospermine has elicited substantial interest in the field of natural products chemistry since the first and brilliant synthesis developed by Stork and co-workers,[20,21] who employed a Fischer indole strategy. The oxidative 1,3-shift transposition described in this paper provides an expeditious route to the various functionalities present in several complex structures in the *Aspidosperma* family. The tricyclic system **72** is a compact polyfunctionalized scaffold containing a masked aldehyde functionality, an enone, and an iodoalkene subunit. These groups are well positioned to produce several congeners of this important alkaloid family. The key tricyclic system **72** can be readily and efficiently obtained from an inexpensive phenol and can be further transformed into

dx.doi.org/10.1021/jo300169k | J. Org. Chem. 2012, 77, 2121–2133

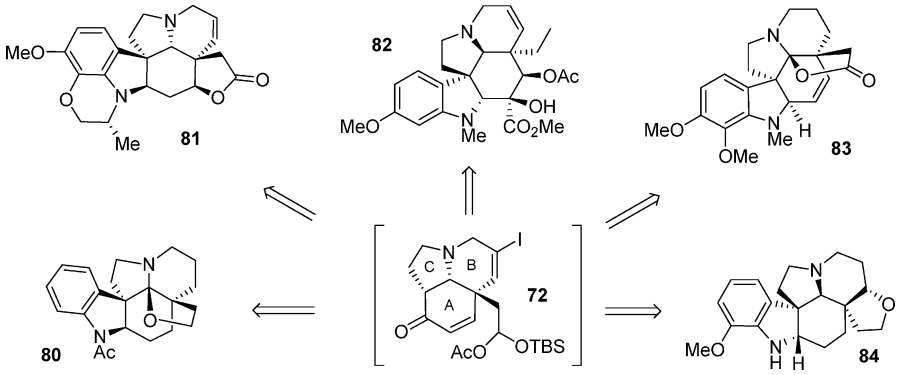


Figure 3. Members of the *Aspidosperma* alkaloid family.

acetylaspidoalbidine **80** using conventional methodologies. The global retrosynthetic pathway is presented in Figure 4.

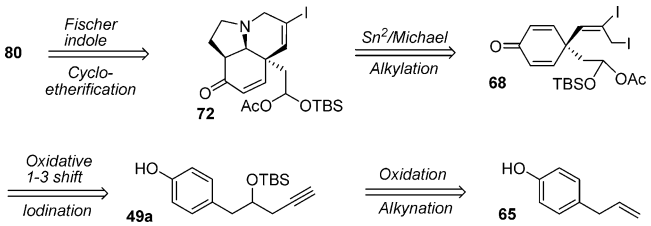
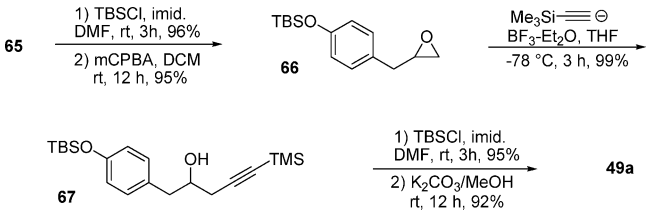


Figure 4. Retrosynthetic pathway to acetylaspidoalbidine.

The required phenol **49a** may be easily obtained by protection of 4-allylphenol **65** with TBS-Cl, followed by epoxidation with *m*-CPBA to afford compound **66** in 91% yield in two steps. At this stage, the resulting epoxide is activated using $BF_3{\cdot}OEt_2$ and captured by the anion of (TMS)-acetylene, quantitatively producing compound **67**. Protection of the secondary alcohol with TBS-Cl followed by selective deprotection of the phenol functionality under basic conditions leads to the required phenol **49a** in 87% overall yield (Scheme 10).

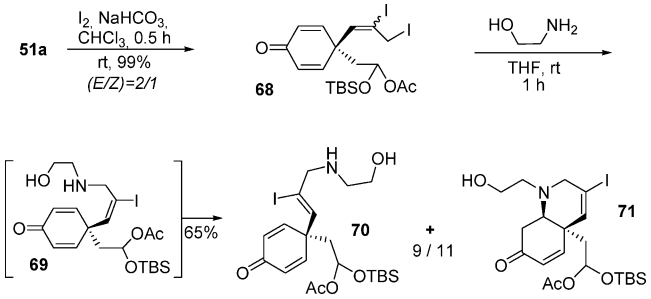
Scheme 10. Formation of the Phenolic Precursor 49a



The dienone system **51a** resulting from the oxidative shift process (Table 4) represents an advanced intermediate. Mild treatment of this allene with iodine resulted in a (*Z*/*E*) mixture of the iodo substrate **68** in favor of the desired diastereoisomer. Subsequent treatment with ethanolamine leads, via a S_N2-Michael tandem process, to bicyclic core **71** as well as the undesired (*Z*)-secondary amine **70**, depending on the former configuration of the diiodo adduct **68** in 65% yield and in an 11/9 ratio in favor of the desired compound **71** (Scheme 11).

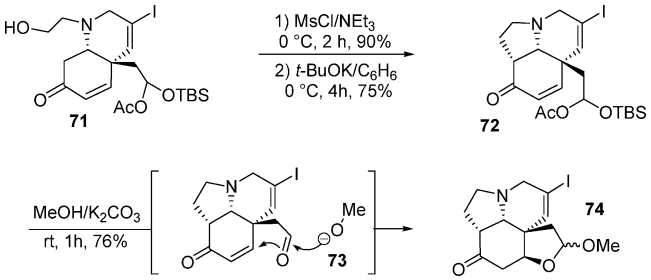
The S_N2-Michael tandem process is a concise route to the bicyclic system **71**; we suspect that the preorganization of the *cis*-double bond increases the feasibility of the *6-exo-trig* Michael process leading to **71**. Further activation of the hydroxyl group with mesyl chloride and treatment with potassium *tert*-butoxide led to the tricyclic core **72** in 70% yield over two steps. At this

Scheme 11. Concise Approach to the Tricyclic Core of Aspidosperma Compounds



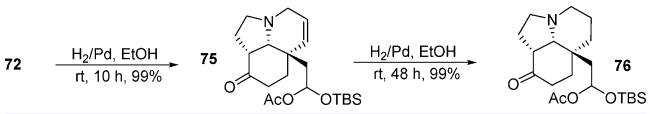
stage, the tetracyclic main core of neblinine **81** may be generated through a trans-acetalization process by treatment of **72** with methanol and potassium carbonate, proceeding through formation of the intermediate **73** (Scheme 12).

Scheme 12. Formation of the Main Tetracyclic Core of Neblinine



Treatment of compound **72** with hydrogen over Pd/C selectively reduced the iodo segment and the enone functionality, quantitatively producing the ketone **75** (Scheme 13). At this

Scheme 13. Selective Hydrogenation



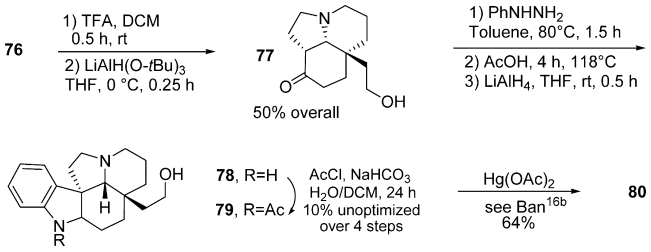
stage, we were pleased to observe an unexpected and efficient selective reduction of the enone segment. It should be noted that the remaining alkene moiety is present in several important alkaloids possessing antitumor activity and belonging to the same family, including vindoline and beninine. This method appears to be an attractive approach to a wide array of alkaloids

dx.doi.org/10.1021/jo300169k | *J. Org. Chem.* 2012, 77, 2121−2133

having a double bond at this position. The remaining double bond may be hydrogenated by extending the reaction over two days to produce the saturated tricyclic core **76** in excellent yield from compound **72**. Compounds **75** and **76** may be incorporated into the synthesis of several alkaloids belonging to the *Aspidosperma* family, as depicted in Figure 3.

In order to rapidly demonstrate the synthetic applications of this process, we focused on the hexacyclic core of acetylaspidoalbidine **80**, a fendleridine natural derivative.[16] These compounds have elicited substantial interest, and a number of elegant syntheses have already been described by groups such as Ban, Overman, and Boger.[16] The mixed acetal moiety of **76** was hydrolyzed in the presence of TFA and selectively reduced using a hindered hydride to produce alcohol **77**. The pentacyclic skeleton was constructed using a Fischer indole process followed by treatment with $LiAlH_4$. This strategy led to a mixture of the indoline core **78** and an undesired indole (depending on the position of the enamine triggering the Claisen process), in a 2:1 ratio favoring the desired **78**. A Schotten−Bauman protocol selectively produced the known *N*-acetyl compound **79** in an unoptimized 10% yield over four steps from compound **77**. Similar transformations are well described in the literature and the present work describes only a single application to demonstrate the potential of the oxidative 1,3-alkyl shift process. Compound **79** has been employed as the final precursor of acetylaspidoalbidine and may be transformed in one step into acetylaspidoalbidine **80** by treatment with $Hg(OAc)_2$ as first demonstrated by Ban et al.[16b] and later described by Overman and co-workers.[16e] This final intermediate leading to the hexacyclic natural product has been obtained in 11 steps from the key dienone system **51a** (Scheme 14).

Scheme 14. Formal Synthesis of Acetylaspidoalbidine



CONCLUSION

We have developed an unprecedented synthetic method based on oxidative 1,2- and 1,3-alkyl shift processes. This method enables the stereoselective formation of polyfunctionalized and polysubstituted compounds containing a quaternary carbon center, a dienone system, and several other functionalities from simple and inexpensive phenol derivatives in good yield. An efficient enantiospecific version of this process enabling the formation of a quaternary carbon center was also demonstrated. The resulting structures are present in numerous natural products possessing important biological activities. A rapid approach to several polycyclic systems, including the main tricyclic or tetracyclic systems of alkaloids belonging to the *Aspidosperma* family and a new formal synthesis of acetylaspidoalbidine were described. The results demonstrate the potential of these oxidative transposition processes as well as the utility of the "aromatic ring umpolung" concept.

EXPERIMENTAL SECTION

Unless otherwise indicated, ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts are reported in ppm on the δ scale. Multiplicities are described as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quartet), quin (quintuplet), m (multiplet), and further qualified as app (apparent), br (broad). Coupling constants, *J*, are reported in Hz. IR spectra (cm^{-1}) were recorded from thin films. Mass spectra (*m*/*e*) were measured in the electrospray (ESI) mode.

General Procedure for Oxidation of Phenols into Corresponding Dienones. *Method A: General Procedure for the Oxidative (1,2-Alkyl Shift Process).* To a stirred solution of phenol (0.1 mmol) in HFIP (0.5 mL) at 0 °C was added DIB (38 mg, 0.11 mmol, 1.1 equiv) dissolved in HFIP (0.2 mL). The solution was stirred for a further 1 min and then quenched by addition of acetone (0.2 mL, the blue-green color disappears). The solution was directly filtrated on a small pad of silica gel (washed with ethyl acetate) and then concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane/ethyl acetate) to afford the corresponding dienone. *Note: as soon as cold HFIP is introduced, the DIB solution has to be added quickly. Indeed, some tertiary alcohol compounds are not very stable in these acidic conditions and are transformed into an alkene via an E_1 reaction.*

Method B: General Procedure for the Oxidative 1,3-Alkyl Shift Process. To a stirred solution of phenol (0.1 mmol) in HFIP (0.6 mL) at 0 °C was added DIB (38 mg, 0.11 mmol, 1.1 equiv) dissolved in HFIP (0.2 mL) over 10 s. The solution was stirred for further 2 min and then quenched by an addition of acetone (0.2 mL, the blue-green color disappears). The solution was directly filtrated on a small pad of silica gel (washed with ethyl acetate) and then concentrated under reduced pressure. The crude product was purified by chromatography (*n*-hexane/ethyl acetate) to afford the corresponding dienone.

*4-Acetyl-4-allylcyclohexa-2,5-dienone (**3a**).* Pale yellow oil: 0.062 mmol, 10.9 mg, 62% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.18 (d, 2H, *J* = 8.4 Hz), 7.00 (d, 2H, *J* = 8.4 Hz), 5.93 (m, 1H), 5.08 (d, 1H, *J* = 8.0 Hz), 5.07 (d, 1H, *J* = 17.1 Hz), 3.37 (d, 2H, *J* = 6.7 Hz), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.8, 149.1, 137.8, 137.3, 129.7, 121.6, 116.2, 39.7, 21.3. IR ν (cm^{-1}) 2913, 1752, 1199; HRMS calcd for $C_{11}H_{13}O_2$ $(M + H)^+$ 177.0910, found 177.0908.

*4-Allyl-4-(but-3-enoyl)cyclohexa-2,5-dienone (**3b**:* Pale yellow oil: 0.067 mmol, 13.5 mg, 67% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.18 (d, 2H, *J* = 8.4 Hz), 7.00 (d, 2H, *J* = 8.4 Hz), 6.03 (m, 1H), 5.95, (m, 1H), 5.28 (d, 1H, *J* = 18.2 Hz), 5.25 (d, 1H, *J* = 11.7 Hz), 5.09 (d, 1H, *J* = 8.2 Hz), 5.07 (d, 1H, *J* = 17.7 Hz), 3.37 (d, 2H, *J* = 6.5 Hz), 3.33 (d, 2H, *J* = 7.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 170.0, 148.9, 137.6, 137.0, 129.6, 129.4, 121.3, 119.1, 116.0, 39.5, 39.1; IR ν (cm^{-1}) 2915, 1754, 1641, 1505, 1201; HRMS calcd for $C_{13}H_{15}O_2$ $(M + H)^+$ 203.1067, found 203.1063.

*4-Acetyl-4-allyl-2-methylcyclohexa-2,5-dienone (**3c**).* Pale yellow oil: 0.063 mmol, 12.0 mg, 63% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.05 (s, 1H), 7.02 (d, 1H, *J* = 7.9 Hz), 6.92 (d, 1H, *J* = 7.9 Hz), 5.95 (m, 1H), 5.10 (d, 1H, *J* = 9.4 Hz), 5.80 (d, 1H, *J* = 17.1 Hz), 3.34 (d, 2H, *J* = 6.7 Hz), 2.31 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.3, 147.5, 137.7, 137.2, 131.2, 129.8, 126.9, 121.6, 115.8, 39.5, 20.7, 16.1; IR ν (cm^{-1}) 2911, 1752, 1646, 1503, 1205; HRMS calcd for $C_{12}H_{15}O_2$ $(M + H)^+$ 191.1067, found 191.1062.

*4-Allyl-4-(2-((tert-butyldimethylsilyl)oxy)acetyl)cyclohexa-2,5-dienone (**3d**).* Pale yellow oil: 0.033 mmol, 10.2 mg, 33% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.95 (d, 2H, *J* = 7.7 Hz), 7.05 (d, 2H, *J* = 7.7 Hz), 6.08 (m, 1H), 5.44 (s, 2H), 5. 02 (m, 2H), 3.73 (d, 2H, *J* = 6.7 Hz), 0.88 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 161.3, 131.4, 130.4, 118.4, 115.5, 87.5, 43.2, 25.7, 25.5, 17.8, −5.0; IR ν (cm^{-1}) 2929, 1725, 1679, 1508, 1255; HRMS calcd for $C_{17}H_{27}O_3Si$ $(M + H)^+$ 307.1724, found 307.1725.

*4-Acetyl-4-(2-methylallyl)cyclohexa-2,5-dienone (**3e**).* Pale yellow oil: 0.037 mmol, 7.0 mg, 37% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.18 (d, 2H, *J* = 7.9 Hz), 7.00 (d, 2H, *J* = 7.9 Hz), 5.82 (s, 1H), 4.73 (s, 1H), 3.31 (s, 2H), 2.28 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (150 MHz,

dx.doi.org/10.1021/jo300169k | J. Org. Chem. 2012, 77, 2121−2133

$CDCl_3$) δ = 169.5, 148.9, 144.7, 137.2, 129.7, 121.2, 112.1, 43.9, 22.0, 21.1; IR ν (cm^{-1}) 1755; HRMS calcd for $C_{12}H_{15}O_2$ $(M + H)^+$ 191.1067, found 191.1066.

*4-Acetyl-4-vinylcyclohexa-2,5-dienone (**3f**).* Pale yellow oil: 0.034 mmol, 5.5 mg, 34% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.42 (d, 2H, J = 8.2 Hz), 7.05 (d, 2H, J = 8.2 Hz), 6.70 (dd, 1H, J = 17.0; 10.4 Hz), 5.70 (d, 1H, J = 17.0 Hz), 5.52 (d, 1H, J = 10.4 Hz), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.4, 150.1, 135.8, 135.3, 127.1, 121.5, 114.0, 21.1; IR ν (cm^{-1}) 1647; HRMS calcd for $C_{10}H_{10}O_2Na$ $(M + Na)^+$ 185.0573, found 185.0571.

*1-Acetyl[1,1′-biphenyl]-4(1H)-one (**3g**).* Pale yellow oil: 0.051 mmol, 10.8 mg, 51% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.57 (d, 2H, J = 8.2 Hz), 7.55 (d, 2H, J = 8.2 Hz), 7.42 (t, 2H, J = 8.2 Hz), 7.14 (d, 2H, J = 8.2 Hz), 2.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.5, 150.0, 140.3, 138.9, 128.7, 128.1, 127.3, 127.1, 121.8, 21.1; IR ν (cm^{-1}) 1760, 1645, 1506, 1202; HRMS calcd for $C_{14}H_{12}O_2Na$ $(M + Na)^+$ 235.0730, found 235.0734.

*1-Propionyl[1,1′-biphenyl]-4(1H)-one (**3h**).* Pale yellow oil: 0.035 mmol, 7.9 mg, 35% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.59 (d, 2H, J = 8.2 Hz), 7.57 (d, 2H, J = 8.2 Hz), 7.44 (t, 2H, J = 8.2 Hz), 7.35 (t, 1H, J = 8.2 Hz), 7.16 (d, 2H, J = 8.2 Hz), 2.62 (q, 2H, J = 7.6 Hz), 1.29 (t, 3H, J = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 173.0, 150.1, 140.3, 138.8, 128.7, 127.2, 127.0, 121.7, 27.7, 9.0; IR ν (cm^{-1}) 1764, 1642; HRMS calcd for $C_{15}H_{15}O_2$ $(M + H)^+$ 227.1067, found 227,1066.

*1-Acetyl-3-methyl[1,1′-biphenyl]-4(1H)-one (**3i**).* Pale yellow oil: 0.034 mmol, 7.7 mg, 34% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.54 (d, 2H, J = 8.2 Hz), 7.41 (m, 4H), 7.32 (t, 1H, J = 8.2 Hz), 7.07 (d, 1H, J = 8.2 Hz), 2.33 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.2, 148.8, 140.5, 139.2, 130.2, 129.9, 128.7, 127.1, 125.7, 122.1, 20.8, 16.3; IR ν (cm^{-1}) 2923, 1760, 1641, 1505, 1202; HRMS calcd for $C_{15}H_{15}O_2$ $(M + H)^+$ 227.1067, found 227.1062.

*4-Butyl-4-pentanoylcyclohexa-2,5-dienone (**3j**).* Pale yellow oil: 0.041 mmol, 9.6 mg, 41% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.16 (d, 2H, J = 8.2 Hz), 6.97 (d, 2H, J = 8.2 Hz), 2.59 (t, 2H, J = 7.6 Hz), 2.54 (t, 2H, J = 7.6 Hz), 1.74 (q, 2H, J = 7.6 Hz), 1.59 (q, 2H, J = 7.6 Hz), 1.44 (s, 2H, J = 7.6 Hz), 1.35 (sext, 2H, J = 7.6 Hz), 0.97 (t, 3H, J = 7.6 Hz), 0.92 (t, 3H, J = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 172.4, 148.6, 140.2, 129.2, 121.1, 35.0, 34.1, 33.5, 27.0, 22.2, 13.9, 13.7; HRMS calcd for $C_{15}H_{23}O_2$ $(M + H)^+$ 235.1693, found 235.1695.

*4-Acetyl-4-butylcyclohexa-2,5-dienone (**3k**).* Pale yellow oil: 0.035 mmol, 6.8 mg, 35% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.17 (d, 2H, J = 8.2 Hz), 6.98 (d, 2H, J = 8.2 Hz), 2.60 (t, 2H, J = 7.6 Hz), 2.29 (s, 3H), 1.59 (q, 2H, J = 7.6 Hz), 1.35 (sext, 2H, J = 7.6 Hz), 0.92 (t, 3H, J = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 169.6, 148.5, 140.4, 129.2, 121.1, 35.0, 33.5, 22.2, 21.1, 13.9; HRMS calcd for $C_{12}H_{16}O_2Na$ $(M + Na)^+$ 215.1043, found 215.1041.

*7-Acetyl-2,3-dihydro-1H-inden-5(7H)-one (**13d**).* Pale yellow oil: 0.053 mmol, 9.3 mg, 53% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.76 (d, 1H, J = 10.0 Hz), 6.72 (d, 1H, J = 10.0 Hz), 6.58 (s, 1H), 2.51 (t, 2H, J = 7.6 Hz), 2.42 (t, 2H, J = 7.6 Hz), 2.15 (s, 3H), 1.79 (q, 2H, J = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 207.7, 187.5, 187.3, 148.7, 136.7, 136.3, 132.6, 42.6, 29.9, 28.3, 21.6; IR ν (cm^{-1}) 2923, 1711, 1655, 1597, 1354, 1290, 904; HRMS calcd for $C_{11}H_{13}O_2$ $(M + H)^+$ 177.0910, found 177.0909.

*8-Allyl-3,4-dihydronaphthalene-1,6(2H,8H)-dione (**14a**).* Pale yellow oil: 0.043 mmol, 8.7 mg, 43% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.76 (d, 1H, J = 10.0 Hz), 6.71 (d, 1H, J = 10.0 Hz), 6.58 (s, 1H), 5.90 (m, 1H), 5.19 (d, 1H, J = 10.0 Hz), 5.15 (d, 1H, J = 17.0 Hz), 3.17 (d, 2H, J = 7.0 Hz), 2.52 (t, 2H, J = 7.6 Hz), 2.41 (t, 2H, J = 7.6 Hz), 1.80 (q, 2H, J = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 207.6, 187.5, 187.3, 148.7, 136.7, 136.3, 132.6, 130.3, 119.0, 47.8, 41.2, 28.3, 21.5; IR ν (cm^{-1}) 2911, 1710, 1650, 1285, 1194; HRMS calcd for $C_{13}H_{15}O_2$ $(M + H)^+$ 203.1067, found 203.1064.

*8-Phenyl-3,4-dihydronaphthalene-1,6(2H,8H)-dione (**14b**).* Pale yellow oil: 0.054 mmol, 12.8 mg, 54% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.94 (d, 2H, J = 8.2 Hz), 7.57 (t, 1H, J = 8.2 Hz), 7.47 (t, 2H, J = 8.2 Hz), 6.77 (d, 1H, J = 10.0 Hz), 6.72 (d, 1H, J = 10.0 Hz), 6.62 (s, 1H), 3.06 (t, 2H, J = 7.6 Hz), 2.52 (t, 2H, J = 7.6 Hz), 1.98 (q, 2H, J = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 199.1, 187.6, 187.3, 148.8, 136.7, 136.3, 133.1, 132.6, 128.6, 127.9, 37.6, 28.5, 22.0; HRMS calcd for $C_{16}H_{15}O_2$ $(M + H)^+$ 239.1067, found 239.1057.

*3-Allylbenzofuran-3,6(2H,3H)-dione (**14c**).* Pale yellow oil: 0.043 mmol, 8.2 mg, 43% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.54 (d, 1H, J = 10.0 Hz), 6.49 (d, 1H, J = 10.0 Hz), 5.86 (s, 1H), 5.84 (m, 1H), 5.27 (d, 1H, J = 17.0 Hz), 5.26 (d, 1H, J = 10.4 Hz), 4.50 (d, 1H, J = 11.0 Hz), 4.30 (d, 1H, J = 11.0 Hz), 2.78 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 186.9, 171.8, 137.2, 131.7, 130.1, 120.2, 105.4, 74.7, 72.5, 32.2; HRMS calcd for $C_{11}H_{10}O_3Na$ $(M + Na)^+$ 213.0522, found 213.0528.

*(1-Allyl-3,5-di-tert-butyl-4-oxocyclohexa-2,5-dien-1-yl)((tert-butyldimethylsilyl)oxy)methyl Acetate (**20**).* Pale yellow oil: 0.057 mmol, 25.5 mg, 57% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 6.50 (d, 1H, J = 2.7 Hz), 6.46 (d, 1H, J = 2.7 Hz), 6.05 (s, 1H), 5.42 (m, 1H), 4.96 (m, 2H), 2.41 (m, 2H), 1.96 (s, 3H), 1.22 (s, 9H), 1.19 (s, 9H), 0.89 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 187.2, 170.0, 149.9, 149.8, 140.2, 140.1, 132.5, 130.5, 118.7, 94.1, 49.3, 39.3, 35.3, 29.8, 25.9, 21.4, 18.2, −4.2, −4.9; IR ν (cm^{-1}) 2932, 2861, 1746, 1661, 1644, 1471, 1365, 1238, 1153, 839; HRMS (ESI) calcd for $C_{26}H_{44}O_4SiNa$ $(M + Na)^+$ 471.2901, found 471.2905

*4-Allyl-4-(2-oxopent-4-en-1-yl)cyclohexa-2,5-dienone (**23a**).* Pale yellow oil: 0.042 mmol, 9.1 mg, 42% yield; ^1H NMR (MHz, $CDCl_3$) δ = 6.94 (d, 2H, J = 10.0 Hz), 6.29 (d, 2H, J = 10.0 Hz), 5.84 (m, 1H), 5.56 (m,1H), 5.20 (d, 1H, J = 11.7 Hz), 5.12 (d, 1H, J = 17.0 Hz), 5.09 (d, 1H, J = 11.7 Hz), 5.06 (d, 1H, J = 17 Hz), 3.12 (d, 2H, J = 7.4 Hz), 2.71 (s, 2H), 2.47 (d, 2H, J = 7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 204.8, 185.8, 152.3, 131.6, 129.6, 119.7, 119.5, 48.8, 48.6, 43.3, 42.0; IR ν (cm^{-1}) 2920, 1760, 1215, 1189; HRMS calcd for $C_{14}H_{16}O_2Na$ $(M + Na)^+$ 239.1043, found 239.1040.

*4-Allyl-2,6-dibromo-4-(2-oxopent-4-en-1-yl)cyclohexa-2,5-dienone (**23b**).* Pale yellow oil: 0.042 mmol, 9.1 mg, 42% yield; ^1H NMR (MHz, $CDCl_3$) δ = 6.94 (d, 2H, J = 10.0 Hz), 6.29 (d, 2H, J = 10.0 Hz), 5.84 (m, 1H), 5.56 (m,1H), 5.20 (d, 1H, J = 11.7 Hz), 5.12 (d, 1H, J = 17.0 Hz), 5.09 (d, 1H, J = 11.7 Hz), 5.06 (d, 1H, J = 17 Hz), 3.12 (d, 2H, J = 7.4 Hz), 2.71 (s, 2H), 2.47 (d, 2H, J = 7.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 204.8, 185.8, 152.3, 131.6, 129.6, 119.7, 119.5, 48.8, 48.6, 43.3, 42.0; IR ν (cm^{-1}) 2920, 1760, 1215, 1189; HRMS calcd for $C_{14}H_{16}O_2Na$ $(M + Na)^+$ 239.1043, found 239.1040.

*4-Allyl-4-(3-(methylsulfonyl)-2-oxopropyl)cyclohexa-2,5-dienone (**23c**).* Pale yellow oil: 0.061 mmol, 22.8 mg, 61% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.43 (s, 2H), 5.84 (m, 1H), 5.56 (m, 1H), 5.24 (d, 1H, J = 10.0 Hz), 5.17 (d, 1H, J = 15.8 Hz), 5.16 (d, 1H, J = 10.0 Hz), 5.11 (d, 1H, J = 15.8 Hz), 3.14 (d, 2H, J = 7.0 Hz), 2.77 (s, 2H), 2.53 (d, 2H, J = 7.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.1, 172.8, 152.8, 130.8, 129.5, 122.7, 121.2, 120.2, 49.3, 48.7, 47.6, 41.4; HRMS (ESI) calcd for $C_{14}H_{15}O_2Br_2$ $(M + H)^+$ 374.9412, found 374.9407.

*2-(1-Allyl-4-oxocyclohexa-2,5-dien-1-yl)acetaldehyde (**23d**).* Pale yellow oil: 0.025 mmol, 4.4 mg, 25% yield; ^1H NMR (600 MHz, $CDCl_3$) δ 9.51 (t, J = 2.1 Hz, 1H), 6.90 (d, J = 10.1 Hz, 2H), 6.37 (d, J = 10.1 Hz, 2H), 5.59 (m, 1H), 5.11 (c, 2H), 2.66 (d, J = 2.1 Hz, 2H), 2.44 (d, J = 7.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.8, 185.4, 151.5, 130.9, 130.4, 120.2, 50.0, 43.1, 43.0; IR (cm^{-1}) 2918, 2849, 1723, 1664, 1625, 1404; HRMS calcd for $C_{11}H_{12}O_2Na$ $(M + Na)^+$ 199.0730, found 199.0736.

*7-Allyl-3-(methylsulfonyl)-3,4-dihydro-1H-indene-2,5(3H,7H)-dione (**24**).* Pale yellow oil: 8.5 mg, 72% yield; ^1H NMR (600 MHz, $CDCl_3$) δ 6.52 (d, J = 10.0 Hz, 1H), 6.09 (d, J = 10.0 Hz, 1H), 5.83 (sext, J = 7.8 Hz, 1H), 5.26 (d, J = 9.4 Hz, 1H), 5.24 (d, J = 16.4 Hz, 1H), 3.42 (d, J = 9.4 Hz, 1H), 3.40 (m, 1H), 3.10 (s, 3H), 2.90 (s, 2H), 2.73 (d, J = 17.0 Hz, 1H), 2.61 (dd, J = 13.4, 7.6 Hz, 1H), 2.52 (dd, J = 13.4, 7.6 Hz, 1H), 2.48 (d, J = 17.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.6, 195.4, 167.3, 152.0, 131.3, 130.4, 120.8, 71.0, 51.1, 42.4, 41.8, 40.6, 39.0, 37.4; HRMS (ESI) calcd for $C_{13}H_{17}O_4S$ $(M + H)^+$ 269. 0842, found 269.0845.

*2-(1-Allyl-4-oxocyclohexa-2,5-dien-1-yl)-1-((tert-butyldimethylsilyl)-oxy)ethyl Acetate (**27**).* Pale yellow oil: 0.042 mmol, 14.7 mg, 42% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 6.80 (m, 2H), 6.27 (m, 2H), 5.78 (t, J = 5.1 Hz, 1H), 5.53 (m, 1H), 5.02 (c, 2H), 2.29 (d, J = 7.4 Hz, 2H), 2.13 (dd, J = 14.1, 4.8 Hz, 1H), 2.02 (c, 1H), 1.94 (s, 3H), 0.83 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 186.1, 169.5, 153.5, 153.4, 131.3, 129.5, 129.3, 119.6, 90.9, 46.1, 44.6, 43.5, 25.5, 21.3, 17.7, −4.5, −5.1; IR ν (cm^{-1}) 2956, 1738, 1667, 1626, 1256; HRMS (ESI) calcd for $C_{19}H_{30}NaO_4Si$ $(M + Na)^+$ 373.1806, found 373.1805.

*4-((1,3-Dioxolan-2-yl)methyl)-4-allylcyclohexa-2,5-dienone (**30**).* Pale yellow oil: 0.05 mmol, 11 mg, 50% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, J = 10.2 Hz, 2H), 6.31 (d, J = 10.2 Hz, 2H), 5.57 (m, 1H), 5.05 (m, 2H), 4.65 (t, J = 4.5 Hz, 1H), 3.81 (c, 4H), 2.35 (d, J = 7.3 Hz, 2H), 2.05 (d, J = 4.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.4, 153.7, 131.5, 129.3, 119.4, 101.7, 64.8, 44.1, 43.3, 42.9; IR ν (cm^{-1}) 2921, 2886, 1661, 1622, 1406, 1138; HRMS (ESI) calcd for $C_{13}H_{17}O_3$ $(M + H)^+$ 221.1172, found 221.1173.

*(1-Hydroxy-4-oxocyclohexa-2,5-dienyl)methyl Acetate (**36**).* ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (d, J = 10.2 Hz, 2H), 6.27 (d, J = 10.2 Hz, 2H), 4.19 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 170.6, 147.2, 129.7, 68.6, 68.1, 20.6; HRMS (ESI) calcd for $C_9H_{10}O_4Na$ $(M + Na)^+$ 205.0471, found 205.0474.

*3b,8a-Diallyl-3,3a,3b,7,7a,8a-hexahydrofuro[2,3-b]benzofuran-6(2H)-one (**41**).* Pale yellow oil: 0.029 mmol, 7.5 mg, 29% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.54 (d, 1H, J = 10.0 Hz), 6.03 (d, 1H, J = 10.0 Hz), 5.85 (m, 1H), 5.64 (m, 1H), 5.10 (m, 4H), 4.28 (s, 1H), 4.15 (q, 2H, J = 7.6 Hz), 4.11 (q, 2H, J = 7.6 Hz), 2.72 (dd, 1H, J = 8.8, 5.3 Hz), 2.20 (s, 2H), 2.57 (dd, 1H, J = 14.1, 5.3 Hz), 2.28 (dd, 1H, J = 14.1, 7.6 Hz), 2.24−1.98 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.5, 146.8, 133.4, 128.3, 119.0, 118.5, 87.4, 83.4, 75.5, 71.6, 57.8, 44.0, 38.6, 38.2, 28.8; HRMS (ESI) calcd for $C_{16}H_{21}O_3$ $(M + H)^+$ 261.1485, found 261.1481.

*1-Methyl-2,7,8-trioxaspiro[bicyclo[3.2.1]octane-6,1′-cyclohexa-[2,5]dien]-4′-one (**42**).* Pale yellow oil: 0.023 mmol, 5.6 mg, 23% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.18 (d, 1H, J = 10.0 Hz), 6.40 (d, 1H, J = 10.0 Hz), 6.22 (d, 1H, J = 10.0 Hz), 4.33 (m, 1H), 4.28 (dd, 1H, J = 11.7, 8.2 Hz), 2.40 (m, 2H), 1.69 (s, 3H), 1.64 (dd, 1H, J = 14.6, 4.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.5, 148.6, 141.4, 132.6, 128.1, 121.0, 79.8, 77.7, 58.7, 25.5, 23.3; HRMS (ESI) calcd for $C_{11}H_{12}NaO_4$ $(M + Na)^+$ 231.0628, found 231.0630.

*4-Allyl-6,8-dibromo-2,3,4,4a-tetrahydronaphthalene-1,7-dione (**45**).* Pale yellow oil: 0.05 mmol, 18.7 mg, 52% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.24 (s, 1H), 5.45 (m, 1H), 5.13 (d, 1H, J = 10.4 Hz), 5.07 (d, 1H, J = 17.0 Hz), 2.74 (dm, 1H, J = 13.7 Hz), 2.51 (dd, 1H, J = 12.6; 7.2 Hz), 2.43 (t, 2H, J = 7.2 Hz), 2.29 (dd, 1H, J = 12.6; 7.2 Hz), 2.15 (m, 3H), 1.89 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 200.5, 173.7, 172.8, 153.1, 129.3, 122.0, 121.2, 117.8, 53.7, 42.6, 38.8, 35.5, 20.2; IR ν (cm^{-1}) 2922, 1716, 1673, 1200; HRMS calcd for $C_{13}H_{13}Br_2O_2$ $(M + H)^+$ 360.9262, found 360.9259.

*8-Allyl-7-hydroxy-3,4-dihydronaphthalen-1(2H)-one (**48**).* Pale yellow oil: 0.057 mmol, 11.5 mg, 57% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.05 (d, 1H, J = 8.2 Hz), 6.97 (d, 1H, J = 8.2 Hz), 5.12 (m, 3H), 3.89 (d, 1H, J = 6.0 Hz), 2.88 (t, 2H, J = 6.1 Hz), 2.63 (d, 2H, J = 6.1 Hz), 2.061 (q, 2H, J = 6.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 200.6, 153.7, 138.3, 136.6, 132.0, 127.8, 126.6, 120.7, 115.3, 40.8, 31.0, 30.3, 23.1; HRMS calcd for $C_{13}H_{15}O_2$ $(M + H)^+$ 203.1067, found 203.1071.

*1-((tert-Butyldimethylsilyl)oxy)-2-(4-oxo-1-(propa-1,2-dien-1-yl)-cyclohexa-2,5-dien-1-yl)ethyl Acetate (**51a**).* Pale yellow oil (this transformation has been done on 1.80 mmol): 1.15 mmol, 0.4 g, 64% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.88 (dd, 1H, J = 10.0; 3.0 Hz), 6.80 (dd, 1H, J = 10.0; 3.0 Hz), 6.26 (dd, 1H, J = 10.0; 3.0 Hz), 6.24 (dd, 1H, J = 10.0; 3.0 Hz), 5.90 (t, 1H, J = 5.3 Hz), 5.00 (t, 1H, J = 7.0 Hz), 4.92 (d, 2H, J = 7.0 Hz), 2.21 (dd, 1H, J = 14.1, 4.8 Hz), 2.11 (dd, 1H, J = 14.1, 4.8 Hz), 1.98 (s, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 185.6, 169.5, 152.1, 128.3, 93.1, 90.7, 79.5, 45.6, 42.3, 25.5, 21.3, 17.7, −4.5, −5.1; IR ν (cm^{-1}) 2955, 1664, 1256; HRMS (ESI) calcd for $C_{19}H_{28}NaO_4Si$ $(M + Na)^+$ 371.1649, found 371.1650.

*1-((tert-Butyldimethylsilyl)oxy)-2-(3,5-dibromo-4-oxo-1-(propa-1,2-dien-1-yl)cyclohexa-2,5-dien-1-yl)ethyl Acetate (**51b**).* Pale yellow: 0.076 mmol, 38 mg, 76% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.37 (d, 1H, J = 3.0 Hz), 7.25 (d, 1H, J = 3.0 Hz), 5.96 (t, 1H, J = 4.7 Hz), 5.00 (m, 3H), 2.26 (dd, 1H, J = 14.1, 4.1 Hz), 2.17 (dd, 1H, J = 14.1, 4.1 Hz), 2.02 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.3, 172.5, 169.6, 152.5, 152.4, 121.1, 120.8, 91.4, 90.4, 80.6, 47.8, 45.1, 25.6, 21.2, 17.7, −4.6, −5.0, HRMS (ESI) calcd for $C_{19}H_{26}O_4Br_2SiNa$ $(M + Na)^+$ 528.9838, found 528.9835.

*2-(4-Oxo-1-(propa-1,2-dien-1-yl)cyclohexa-2,5-dien-1-yl)-1-((triisopropylsilyl)oxy)ethyl Acetate (**51c**).* Pale yellow: 0.061 mmol, 23.8 mg, 61% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.91 (dd, 1H, J = 10.0; 3.1 Hz), 6.81 (dd, 2H, J = 10.0; 3.1 Hz), 6.26 (d, 1H, J = 10.0 Hz), 6.24 (d, 1H, J = 10.0 Hz), 6.03 (t, 1H, J = 4.7 Hz), 5.02 (t, 1H, J = 6.0 Hz), 4.92 (d, 2H, J = 6.0 Hz), 2.26 (d, 1H, J = 14.6, 5.3 Hz), 2.14 (dd, 1H, J = 14.6, 5.3 Hz), 1.97 (s, 3H), 1.04 (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.4, 185.7, 169.5, 152.1, 128.3, 128.0, 93.1, 91.1, 79.5, 46.0, 42.2, 21.3, 17.6, 17.8, 12.2; HRMS (ESI) calcd for $C_{22}H_{34}O_4SiNa$ $(M + Na)^+$ 413.2119, found 413.2117.

*2-(3,5-Dibromo-4-oxo-1-(propa-1,2-dien-1-yl)cyclohexa-2,5-dien-1-yl)-1-((triisopropylsilyl)oxy)ethyl Acetate (**51d**).* Pale yellow oil (this transformation has been done on 0.05 mmol): 0.035 mmol, 19.1 mg, 70% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 7.38 (d, 1H, J = 3.0 Hz), 7.24 (d, 1H, J = 3.0 Hz), 6.08 (t, 1H, J = 4.6 Hz), 5.00 (m, 3H), 2.32 (dd, 1H, J = 14.4, 4.4 Hz), 2.23 (dd, 1H, J = 14.4, 4.4 Hz), 2.03 1.04 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 172.4, 169.6, 152.4, 152.3, 121.2, 120.8, 91.6, 90.8, 80.6, 47.8, 45.4, 21.2, 17.8, 17.7, 12.2; HRMS (ESI) calcd for $C_{22}H_{32}O_4SiNaBr_2$ $(M + Na)^+$ 571.0308, found 571.0312.

*1-((tert-Butyldimethylsilyl)oxy)-2-(4-oxo-1-(1-(trimethylsilyl)-propa-1,2-dien-1-yl)cyclohexa-2,5-dien-1-yl)ethyl Acetate (**51e**).* Pale yellow oil: 0.055 mmol, 23.1 mg, 55% yield; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.88 (dd, 1H, J = 10.0, 3.0 Hz), 6.81 (dd, 1H, J = 10.0, 3.0 Hz), 6.28 (d, 1H, J = 10.0 Hz), 6.26 (d, 1H, J = 10.0 Hz), 5.90 (t, 1H, J = 5.3 Hz), 5.79 (t, 1H, J = 5.3 Hz), 4.62 (s, 2H), 2.33 (dd, 1H, J = 14.1, 4.8 Hz), 2.23 (dd, 1H, J = 14.1, 4.8 Hz), 1.96 (s, 3H), 0.85 (s, 9H), 0.07 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.9, 169.5, 153.7, 153.6, 128.7, 128.3, 97.7, 90.6, 73.4, 46.5, 44.6, 25.5, 21.3, 17.7, 0.5, −4.5, −5.0; HRMS (ESI) calcd for $C_{22}H_{36}O_4Si_2Na$ $(M + Na)^+$ 443.2044, found 443.2040.

*4-(2-Oxopenta-3,4-dien-1-yl)-4-(propa-1,2-dien-1-yl)cyclohexa-2,5-dienone (**53a**).* Pale yellow oil: 0.06 mmol, 12.7 mg, 60% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 6.96 (d, 1H, J = 10.0 Hz), 6.26 (d, 1H, J = 10.0 Hz), 5.76 (t, 1H, J = 6.4 Hz), 5.29 (d, 2H, J = 6.4 Hz), 5.21 (t, 1H, J = 6.4 Hz), 4.91 (d, 2H, J = 6.4 Hz), 2.98 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.0, 207.3, 195.8, 185.5, 151.3, 128.3, 97.5, 92.1, 79.3, 46.1, 42.4; HRMS (ESI) calcd for $C_{14}H_{13}O_2$ $(M + H)^+$ 213.0910, found 213.0904.

*4-(3-Oxohexa-4,5-dien-2-yl)-4-(propa-1,2-dien-1-yl)cyclohexa-2,5-dienone (**53b**).* Pale yellow oil: 0.045 mmol, 10.2 mg, 45% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.23 (dd, 1H, J = 10.2, 2.9 Hz), 6.75 (dd, 1H, J = 10.0, 2.9 Hz), 6.34 (dd, 1H, J = 10.0, 2.9 Hz), 6.30 (dd, 1H, J = 10.0, 2.9 Hz), 5.82 (t, 1H, J = 6.4 Hz), 5.32 (d, 2H, J = 6.4 Hz), 4.87 (dd, 1H, J = 11.2, 6.8 Hz), 4.82 (dd, 1H, J = 11.2, 6.8 Hz), 3.48 (q, 1H, J = 7.2 Hz), 1.02 (q, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.0, 207.4, 200.8, 185.7, 150.7, 150.0, 129.6, 129.3, 97.7, 91.2, 80.1, 78.8, 47.9, 46.2, 13.5; HRMS (ESI) calcd for $C_{15}H_{15}O_2$ $(M + H)^+$ 227.1067, found 227.1070.

*4-(5-Oxoocta-1,6,7-trien-4-yl)-4-(propa-1,2-dien-1-yl)cyclohexa-2,5-dienone (**53c**).* Pale yellow oil: 0.046 mmol, 11.6 mg, 46% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.12 (dd, 1H, J = 10.6, 3.4 Hz), 6.78 (dd, 1H, J = 10.6, 3.4 Hz), 6.33 (d, 2H, J = 10.2 Hz), 5.88 (t, 1H, J = 6.6 Hz), 5.58 (m, 1H), 5.33 (d, 2H, J = 6.4 Hz), 5.18 (t, 1H, J = 6.6 Hz), 4.98 (d, 1H, J = 16.8 Hz), 4.97 (d, 1H, J = 10.3 Hz), 4.89 (dd, 1H, J = 11.2, 6.8 Hz), 4.84 (dd, 1H, J = 11.2, 6.8 Hz), 3.50 (dd, 1H, J = 11.3, 3.1 Hz), 2.31 (m, 1H), 2.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.0, 207.3, 199.9, 185.5, 150.2, 149.6, 134.2, 129.5, 129.6, 117.5, 99.6, 91.1, 80.3, 78.9, 52.9, 45.9, 33.0; HRMS (ESI) calcd for $C_{17}H_{17}O_2$ $(M + H)^+$ 253.1223, found 253.1218.

*4-(5-Oxoocta-6,7-dien-1-yn-4-yl)-4-(propa-1,2-dien-1-yl)-cyclohexa-2,5-dienone (**53d**).* Pale yellow oil: 0.052 mmol, 12.9 mg, 52% yield; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.08 (dd, 1H, J = 10.6, 3.4 Hz), 6.75 (dd, 1H, J = 10.6, 3.4 Hz), 6.33 (d, 2H, J = 10.2 Hz), 5.97 (t, 1H, J = 6.6 Hz), 5.42 (dd, 1H, 11.2, 6.8 Hz), 5.36 (dd, 1H, 11.2, 6.8 Hz), 5.18 (t, 1H, J = 6.6 Hz), 4.90 (dd, 1H, J = 11.2, 6.8 Hz),

dx.doi.org/10.1021/jo300169k | J. Org. Chem. 2012, 77, 2121−2133

4.86 (dd, 1H, J = 11.2, 6.8 Hz), 3.68 (dd, 1H, J = 11.3, 3.1 Hz), 2.44 (ddd, 1H, J = 16.5, 11.1, 2.6 Hz), 2.22 (dt, 1H, J = 16.5, 2.6 Hz), 1.95 (t, 1H, J = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.3, 207.3, 198.8, 185.2, 149.5, 148.6, 129.9, 129.8, 99.5, 90.8, 80.6, 79.2, 70.5, 51.9, 45.5, 18.2; HRMS (ESI) calcd for $C_{17}H_{15}O_2$ $(M + H)^+$ 251.1067, found 251.1061.

*8-(Propa-1,2-dien-1-yl)-1,3,4,8-tetrahydronaphthalene-2,6-dione (**55**).* Pale yellow oil: 0.043 mmol, 8.6 mg, 43% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.66 (d, 1H, J = 10.0 Hz), 6.33 (d, 1H, J = 1.8 Hz), 6.26 (dd, 1H, J = 10.0, 1.8 Hz,), 5.03 (m, 2H), 4.87 (td, 1H, J = 6.6, 1.0 Hz), 2.97 (tdd, 1H, J = 13.5, 7.6, 1.7 Hz), 2.83 (dd, 1H, J = 14.7, 2.3 Hz), 2.72 (dd, 1H, J = 14.3, 7.2 Hz), 2.63 (ddt, 1H, J = 14.3, 6.3, 2.3 Hz), 2.45 (m, 1H), 2.36 (d, 1H, J = 14.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 205.3, 185.9, 159.6, 151.1, 127.2, 126.7, 92.6, 81.0, 48.2, 44.4, 39.7, 30.9; HRMS (ESI) calcd for $C_{13}H_{13}O_2$ $(M + H)^+$ 201.0910, found 201.0917.

*4-(Propa-1,2-dien-1-yl)-2,3,4,4-tetrahydronaphthalene-1,7-dione (**57a**).* Pale yellow oil: 0.053 mmol, 10.6 mg, 53% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.79 (d, 1H, J = 10.0 Hz), 6.49 (d, 1H, J = 1.8 Hz), 6.24 (dd, 1H, J = 10.0, 1.8 Hz,), 5.01 (t, 1H, J = 6.8 Hz), 4.87 (dd, 1H, J = 11.7, 7.0 Hz), 4.82 (dd, 1H, J = 11.7, 7.0 Hz), 2.43−1.95 (m, 4H), 1.85 (td, 1H, J = 14.2, 5.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 200.5, 186.1, 156.3, 152.1, 126.9, 91.4, 79.5, 46.1, 40.3, 34.2, 19.1; HRMS (ESI) calcd for $C_{13}H_{13}O_2$ $(M + H)^+$ 201.0910, found 201.0907.

*6,8-Dibromo-4-(propa-1,2-dien-1-yl)-2,3,4,4-tetrahydronaphthalene-1,7-dione (**57b**).* Pale yellow oil: 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.26 (s, 1H), 4.97 (m, 3H), 2.72 (d, 1H, J = 15.6 Hz), 2.46 (m, 1H), 2.30−1.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 199.1, 172.7, 155.5, 152.0, 120.3, 118.3, 88.6, 80.6, 52.8, 42.5, 36.3, 20.3; HRMS (ESI) calcd for $C_{13}H_{11}O_2Br_2$ $(M + H)^+$ 358.9099, found 358.9101.

*trans-4a-(Propa-1,2-dien-1-yl)-2,3,4,4a,8,8a-hexahydronaphthalene-1,7-dione (**58**).* Compound **57a** (10.5 mg, 0.052 mmol) was dissolved in MeOH (4 mL), and activated Zn (10.0 equiv) was added followed by glacial acetic acid (5.0 equiv) at 0 °C. The resulting mixture was stirred until no starting material was detected by TLC (∼1 h). The mixture was directly filtered through a short pad of silica with a mixture (1:1, ethyl acetate−hexane), and the filtrate was concentrated under reduced pressure. The obtained residue was dissolved in DCM (2.5 mL), and DBU (0.02 mmol) was added at 0 °C. The resulting mixture was stirred during 1 h, and then a saturated solution of NH_4Cl was added (4 mL) as well as ethyl acetate (8 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 4 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated under vacuo. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc 7/3) to give 6.8 mg (65%) of a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.38 (d, 1H, J = 10.2 Hz), 5.95 (d, 1H, J = 10.2 Hz), 5.26 (t, 1H, J = 6.6 Hz), 4.87 (d, 1H, J = 6.6 Hz), 3.40 (m, 1H), 2.86 (m, 2H), 2.60−2.27 (m, 4H), 2.07−1.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 207.1, 196.9, 150.9, 130.3, 95.7, 78.8, 53.4, 44.8, 40.4, 37.0, 34.6, 29.6, 22.4; HRMS (ESI) calcd for $C_{13}H_{15}O_2$ $(M + H)^+$ 203.1067, found 203.1072.

*9-Methylenehexahydro-1,4-methanocyclopropa[d]naphthalene-3,5(1H,6H)-dione (**61**).* To a solution of **58** (6.7 mg, 0.033 mmol) in dry CH_2Cl_2 (1.5 mL) at 0 °C were added triethylamine (5 equiv) and *tert*-butyldimetyl triflate (2.4 equiv) dropwise. The solution was stirred for 1 h, the mixture was directly filtered through a short pad of silica with a mixture of ethyl acetate−hexane (15:85), and the filtrate was concentrated under reduced pressure. The crude product was dissolved in toluene (5 mL) and stirred at 80 °C during 6 h, and the solvent was evaporated under vacuo. At this stage, the corresponding dienol−ether **60** could be purified by chromatography (1:9, ethyl acetate−hexane) or used as obtained for further transformation. The crude mixture was dissolved in THF (2 mL), and TBAF (0.1 mmol, 3 equiv) was added at 0 °C. The solution was stirred for 1 h, the mixture was directly filtered through a short pad of silica with a mixture (15:85, ethyl acetate−hexane), and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc: 3/1) to give 4.7 mg (70% from **58**) of a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.98 (s, 1H), 4.96 (s, 1H), 3.67 (s, 1H), 2.62 (s, 1H), 2.60 (dd, 2H, J = 6.1, 3.5 Hz), 2.53 (m, 2H), 2.43−2.30 (m, 2H), 2.10 (m, 1H), 1.87 (d, 1H, J = 7.6 Hz), 1.80 (m, 1H), 1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 206.0, 144.0, 108.2, 57.8, 52.4, 41.2, 34.4, 33.5, 28.5, 27.9, 24.8, 19.5; HRMS (ESI) calcd for $C_{13}H_{15}O_2$ $(M + H)^+$ 203.1067, found 203.1069.

*6-Methyl-3-oxo-6-(propa-1,2-dienyl)cyclohexa-1,4-dienecarbaldehyde (**64**).* Pale yellow oil: 0.055 mmol, 9.6 mg, 55% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.71 (s, 1H), 6.88 (d, 1H, J = 10.0 Hz), 6.82 (d, 1H, J = 1.8 Hz), 6.32 (dd, 1H, J = 10.0, 1.8 Hz), 5.40 (t, 1H, J = 6.6 Hz), 4.89 (dd, 1H, J = 11.2, 6.6 Hz), 4.81 (dd, 1H, J = 11.2, 6.6 Hz), 1.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 192.9, 186.3, 156.0, 155.7, 140.1, 126.6, 92.7, 78.7, 40.7, 23.9; HRMS (ESI) calcd for $C_{11}H_{11}O_2$ $(M + H)^+$ 175.0754, found 175.0748.

*tert-Butyldimethyl(4-(oxiran-2-ylmethyl)phenoxy)silane (**66**).* To a solution of 4-allylphenol (2.9 g, 21.6 mmol, 1 equiv) in DMF (20 mL) at 0 °C were added imidazole (2.9 g, 43.2 mmol, 2 equiv) and TBSCl (3.9 g, 26.0 mmol, 1.2 equiv). The reaction mixture was allowed to warm to room temperature, and after 15 min, a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc 100/0 to 90/10) to give 5.16 g (96%) of the desired product as an oil. **4-(Allylphenoxy)(*tert*-butyl)dimethylsilane:** IR ν (cm^{-1}) 3384, 2946, 1511, 1264; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, 2H, J = 8.2 Hz), 6.76 (d, 2H, J = 8.2 Hz), 5.95 (m, 1H), 5.09 (d, 1H, J = 15.8 Hz), 5.07 (d, 1H, J = 10.4 Hz), 3.32 (d, 2H, J = 6.6 Hz), 0.98 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.8, 137.8, 132.6, 129.4, 119.9, 115.3, 39.4, 25.6, 18.1, −4.4; HRMS (ESI) calcd for $C_{15}H_{25}OSi$ $(M + H)^+$ 249.1669, found 249.1666. To a solution of the alkene (1.019 g, 4.11 mmol, 1 equiv) in CH_2Cl_2 (12 mL) at 0 °C was added *m*-CPBA (70% in water, 1.3 g, 5.34 mmol, 1.3 equiv). The reaction mixture was allowed to warm to room temperature, and after 9 h, a saturated aqueous solution of $NaHCO_3$ was added. The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated under vacuo. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc 100/0 to 95/5) to give the corresponding epoxide (936 mg, 86%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, 2H, J = 8.4 Hz), 6.79 (d, 2H, J = 8.4 Hz), 5.95 (m, 1H), 3.12 (m, 1H), 2.86 (dd, 1H, J = 14.6, 5.5 Hz), 2.78 (t, 2H, J = 5.0 Hz), 2.75 (dd, 1H, J = 14.6, 5.5 Hz), 2.53 (dd, 1H, J = 2.6, 5.0 Hz), 0.99 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 129.8, 129.7, 120.0, 52.5, 46.7, 37.8, 25.6, 18.1, −4.4; HRMS (ESI) calcd for $C_{15}H_{25}O_2Si$ $(M + H)^+$ 265.1618, found 265.1626.

*1-(4-((tert-Butyldimethylsilyl)oxy)phenyl)-5-(trimethylsilyl)pent-4-yn-2-ol (**67**).* To a solution of trimethylsilylacetylene (4.0 mL, 28.1 mmol, 2.1 equiv) in dry THF (80 mL) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 10.2 mL, 25.5 mmol, 1.9 equiv). After 30 min at −78 °C, a solution of the previous epoxide (3.54 g, 13.4 mmol, 1 equiv) in dry THF (10 mL) and $BF_3{\cdot}Et_2O$ (2.0 mL, 16.1 mmol, 1.2 equiv) were successively added. The resulting mixture was stirred at −78 °C for 30 min, and a saturated aqueous solution of NH_4Cl was added (50 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc 100/0 to 9/1) to yield 6 (4.84 g, quant) as a pale yellow oil: IR ν (cm^{-1}) 3350, 2942, 1509, 1254; ^{1}H (300 MHz, $CDCl_3$) δ 7.08 (d, 2H, J = 8.4 Hz), 6.78 (d, 2H, J = 8.4 Hz), 3.92 (m, 1H), 2.84 (dd, 1H, J = 13.7, 5.8 Hz), 2.75 (dd, 1H, J = 13.7, 5.8 Hz), 2.44 (dd, 1H, J = 16.8, 5.8 Hz), 2.37 (dd, 1H, J = 16.8, 5.8 Hz), 1.99 (br, 1H), 0.98 (s, 9H), 0.19 (s, 6H), 0.17 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.3, 130.3(*2), 120.0, 103.1, 87.8, 70.9, 41.6, 27.7, 25.6, 18.1, 0.0, −4.4; HRMS (ESI) calcd for $C_{20}H_{34}O_2Si_2Na$ $(M + Na)^+$ 385.1990, found 385.1994.

*tert-Butyl(4-(2-((tert-butyldimethylsilyl)oxy)-5-(trimethylsilyl)-pent-4-yn-1-yl)phenoxy)dimethylsilane (**68**).* To a solution of

6 (4.88 g, 13.49 mmol, 1 equiv) in DMF (20 mL) at 0 °C were successively added imidazole (2.7 g, 40.39 mmol, 3 equiv) and TBSCl (3.0 g, 20.24 mmol, 1.5 equiv). The resulting mixture was allowed to reach room temperature and stirred overnight. A saturated aqueous solution of $NaHCO_3$ (20 mL) and water (50 mL) was added. The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layers were combined and dried over Na_2SO_4. The solvents were evaporated in vacuum, and the crude product was purified by flash chromatography on silica gel (hexanes/EtOAc:100/0 to 9/1) to afford the desired product (5.8 g, 90%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, 2H, J = 8.2 Hz), 6.79 (d, 2H, J = 8.2 Hz), 3.95 (p, 1H, J = 6.1 Hz), 2.92 (dd, 1H, J = 13.5, 4.8 Hz), 2.70 (dd, 1H, J = 13.5, 7.1 Hz), 2.37 (d, 2H, J = 6.1 Hz), 1.02 (s, 9H), 0.88 (s, 9H), 0.22 (s, 6H), 0.21 (s, 9H), 0.02 (s, 3H), −0.15 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 131.4, 130.7, 119.7, 104.6, 86.5, 72.7, 42.5, 28.5, 25.8, 25.7, 18.2, 18.0, 0.0, −4.4, −4.7, −4.9; HRMS (ESI) calcd for $C_{26}H_{49}O_2Si_3$ $(M + H)^+$ 477.3035, found 477.3030.

*4-(2-((tert-Butyldimethylsilyl)oxy)pent-4-yn-1-yl)phenol (**49a**).* To a solution of the alkyne **49a** (5.8 g, 12.18 mmol, 1 equiv) in MeOH (100 mL) was added K_2CO_3 (3.3 g, 23.91 mmol, 2 equiv). The resulting mixture was stirred overnight at room temperature, and water was added (50 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 60 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under vacuo. The resulting crude product was purified by flash chromatography on silica gel (hexanes/EtOAc 9/1 to 7/3) and **49** was isolated as an oil (4.10 g, quant): IR ν (cm^{-1}) 3384, 2946, 1511, 1264; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, 2H, J = 8.2 Hz), 6.76 (d, 2H, J = 8.2 Hz), 3.93 (p, 1H, J = 5.3 Hz), 2.91 (dd, 1H, J = 14.1, 8.3 Hz), 2.70 (dd, 1H, J = 13.5, 7.0 Hz), 2.30 (m, 2H), 2.05 (t, 1H, J = 2.3 Hz), 0.86 (s, 9H), 0.00 (s, 3H), −0.15 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9, 130.9, 130.6, 115.0, 81.6, 72.3, 70.3, 42.0, 26.8, 25.7, 18.0, −4.8, −5.0; HRMS (ESI) calcd for $C_{17}H_{27}O_2Si$ $(M + H)^+$ 291.1775, found 291.1772.

*(Z)-1-((tert-Butyldimethylsilyl)oxy)-2-(1-(3-((2-hydroxyethyl)-amino)-2-iodoprop-1-en-1-yl)-4-oxocyclohexa-2,5-dien-1-yl)ethyl Acetate (**70**) and 1-((tert-Butyldimethylsilyl)oxy)-2-(1-(2-hydroxyethyl)-3-iodo-7-oxo-1,2,4a,7,8,8a-hexahydroquinolin-4a-yl)ethyl Acetate (**71**).* To a solution of **51a** (342 mg, 0.982 mmol, 1 equiv) in $CHCl_3$ (20 mL) were successively added $NaHCO_3$ (1.2 g, 14.285 mmol, 15 equiv) and iodine (499 mg, 3.929 mmol, 2 equiv). The resulting suspension was vigorously stirred at room temperature, and after 1 h, the mixture was directly purified by flash chromatography on silica gel (hexanes/EtOAc 100/0 and then 50/50) to afford 600 mg of **68** (quant) as a 2/1 mixture of *cis* and *trans* diastereomers (see the ^{1}H NMR spectrum for ratio determination). This mixture of two diastereomers was used without any further purification in the next step, and to a stirred solution (600 mg, 0.982 mmol, 1 equiv) in dry THF (40 mL) was added 1,2-aminoethanol (1.25 mL, 20.249 mmol, 20 equiv). The reaction mixture was stirred at room temperature for 1 h and then directly filtered over silica gel (CH_2Cl_2/MeOH/Et_3N 90/10/1). The solvents were removed in vacuo, and the residue was purified by flash chromatography on silica gel (hexanes/EtOAc 9/1 to 6/4 and then CH_2Cl_2/MeOH 100/5 to 9/1) to yield **70** (157 mg) and **71** (178 mg) in 64% yield overall from compound **51a**. **(*Z*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-(1-(3-((2-hydroxyethyl)amino)-2-iodoprop-1-en-1-yl)-4-oxocyclohexa-2,5-dien-1-yl)ethyl acetate (70)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (dt, J = 10.5, 3.3 Hz, 1H), 6.78 (dt, J = 10.5, 3.3 Hz, 1H), 6.36 (d, J = 10.1 Hz, 2H), 6.26 (s, 1H), 5.94 (t, J = 4.9 Hz, 1H), 3.68−3.56 (m, 2H), 3.46 (s, 1H), 2.63 (t_{app}, J = 6.0 Hz, 3H), 2.28 (dd, J = 14.0, 4.5 Hz, 1H), 2.18−2.10 (m, 2H), 2.14 (s, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 186.1, 169.8, 149.8, 149.3, 133.1, 130.5, 130.3, 90.7, 62.5, 61.2, 49.0, 48.1, 45.2, 25.8 (3C), 21.6, 18.0, −4.2, −4.8; HRMS (ESI) calcd for $C_{21}H_{35}INO_5Si$ $(M + H)^+$ 536.1324, found 536.1314.

*1-((tert-Butyldimethylsilyl)oxy)-2-(1-(2-hydroxyethyl)-3-iodo-7-oxo-1,2,4a,7,8,8a-hexahydroquinolin-4a-yl)ethyl acetate (**71**):* IR ν (cm^{-1}) 3487, 2933, 2851, 1733, 1682, 1471, 1379, 1256, 1148; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (d, J = 10.2 Hz, 1H), 6.12 (t, J = 5.0 Hz, 1H), 6.02 (s, 1H), 5.88 (d, J = 10.1 Hz, 1H), 3.69−3.53 (m, 2H), 3.48 (d, J = 17.4 Hz, 1H), 3.35 (dd, J = 11.4, 5.4 Hz, 1H), 3.01 (d, J = 17.3 Hz, 1H), 2.77−2.33 (m, 5H), 2.00 (s, 3H), 1.90 (dd, J = 14.2, 6.1 Hz, 1H), 0.81 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 170.5, 152.7, 135.5, 128.2, 92.1, 91.7, 77.5, 59.0, 58.7, 57.5, 56.4, 46.1, 45.3, 33.0, 25.9 (3C), 21.7, 17.9, −4.4, −4.8; HRMS (ESI) calcd for $C_{21}H_{35}INO_5Si$ $(M + H)^+$ 536.1324, found 536.1311.

*1-((tert-Butyldimethylsilyl)oxy)-2-(3-iodo-1-(2-((methylsulfonyl)-oxy)ethyl)-7-oxo-1,2,4a,7,8,8a-hexahydroquinolin-4a-yl)ethyl Acetate (**72**).* To a solution of **71** (218 mg, 0.407 mmol, 1 equiv) in CH_2Cl_2 (4 mL) at 0 °C were added Et_3N (200 μL, 1.42 mmol, 3.5 equiv) and MsCl (56 μL, 0.710 mmol, 1.7 equiv). The reaction mixture was allowed to warm to room temperature and after 2 h stirring, it was directly purified by flash chromatography on silica gel (hexanes/EtOAc: 8/2 to 5/5) to give 224 mg (90%) of the corresponding mesylate compound **1-((*tert*-butyldimethylsilyl)oxy)-2-(3-iodo-1-(2-((methylsulfonyl)oxy)ethyl)-7-oxo-1,2,4a,7,8,8a-hexahydroquinolin-4a-yl)-ethyl acetate** as an oil: IR ν (cm^{-1}) 2933, 2851, 1733, 1682, 1553, 1466, 1353, 1251, 1169; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, J = 10.2 Hz, 1H), 6.15−6.04 (m, 2H), 5.94 (d, J = 10.2 Hz, 1H), 4.29 (t, J = 5.2 Hz, 2H), 3.50 (d, J = 10.2 Hz, 1H), 3.38 (dd, J = 12.4, 4.4 Hz, 1H), 3.20 (d, J = 17.2 Hz, 1H), 3.04 (s, 3H), 2.97−2.77 (m, 2H), 2.62−2.29 (m, 3H), 2.18−1.97 (m, 1H), 1.97 (s, 3H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 198.6, 170.0, 152.0, 135.7, 128.4, 91.7, 91.5, 67.5, 58.7, 58.0, 46.1, 45.1, 37.7, 33.4, 31.8, 25.9 (3C), 21.8, 18.0, 4.2, 4.7; HRMS (ESI) calcd for $C_{22}H_{37}INO_7SSi$ $(M + H)^+$ 614.1099, found 614.1082. To a solution of the mesylate (82 mg, 0.133 mmol, 1 equiv) in dry toluene (1.5 mL) at 0 °C was added *t*-BuOK (32 mg, 0.306 mmol, 2.3 equiv). The resulting mixture was allowed to reach room temperature, and after 4 h, brine (1 mL) was added. The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 1 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc:9/1 to 7/3) to give 52 mg of **72** (75%): IR ν (cm^{-1}) 2943, 2912, 1733, 1671, 1246, 1143; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (m, 2H), 6.18 (t, J = 6.0 Hz, 1H), 5.93 (d, J = 10.2 Hz, 1H), 3.69 (d, J = 16.0 Hz, 1H), 3.16 (m, 1H), 3.01 (d, J = 16.5 Hz, 1H), 2.91−2.78 (m, 2H), 2.42−2.28 (m, 1H), 2.26−2.13 (m, 1H), 2.12−1.99 (m, 2H), 2.07 (s, 3H), 1.88 (dd, J = 14.4, 5.7 Hz, 1H), 0.90 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 199.0, 149.8, 138.2, 125.4, 91.0, 64.4, 63.0, 52.2, 46.0, 45.0, 44.0, 26.0 (3C), 25.2, 21.8, 18.1, 4.1, 4.7; HRMS (ESI) calcd for $C_{21}H_{33}INO_4Si$ $(M + H)^+$ 518.1218, found 518.1207.

*6-(2-Hydroxyethyl)-31,4,6a,7,8,9a-hexahydro-1H-pyrrolo[3,2,1-ij]quinolin-9(2H)-one (**75** Derivative).* To a solution of **72** (99 mg, 0.191 mmol, 1 equiv) in EtOAc (100 μL) and EtOH (5 mL) was added Pd/C (10%, 81 mg, 0.076 mmol, 0.4 equiv). The reaction mixture was stirred at room temperature under an H_2 atmosphere, and after 10 h, it was filtered through a pad of Celite (EtOAc). The solvents were evaporated to give **75** (80 mg, quant) which was used in the following step without any further purification. To a stirred solution of the compound **75** (80 mg, 0.191 mmol, 1 equiv) in CH_2Cl_2 (1.5 mL) at 0 °C was added TFA (50 μL, 0.650 mmol, 3.4 equiv). After 15 min at 0 °C and 10 min at room temperature, a saturated aqueous solution of $NaHCO_3$ (1 mL) was added. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 1 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was dissolved in dry THF (1.5 mL), and $LiAlH(O\text{-}t\text{-}Bu)_3$ (1 M in THF, 180 μL, 0.180 mmol, 0.94 equiv) was added at 0 °C. The resulting mixture was stirred at 0 °C for 15 min and quenched by addition of a saturated aqueous solution of NH_4Cl (1 mL). The phases were separated, and a saturated aqueous solution of $NaHCO_3$ (1 mL) was added to the aqueous layer. The aqueous phase was extracted with EtOAc (3 × 1 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 100/0 to 85/15), and an oil was obtained (32 mg, 76% from **72**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (dt, J = 10.1, 3.0 Hz, 1H), 5.53 (dt, J = 10.1, 2.2 Hz, 1H), 3.88−3.70 (m, 2H), 3.23−3.13(m, 1H), 3.10 (dd, J = 9.2, 2.4 Hz, 1H), 2.88−2.74 (m, 3H), 2.57−2.22 (m, 5H), 2.04−1.69 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 131.6, 124.7, 68.6, 59.1, 53.8, 50.3, 48.3, 46.1, 40.3, 37.7, 36.5,

dx.doi.org/10.1021/jo300169k | J. Org. Chem. 2012, 77, 2121−2133

33.4, 21.1, 8.8; HRMS (ESI) calcd for $C_{13}H_{20}NO_2$ $(M + H)^+$ 222.1489, found 222.1488.

*1-((tert-Butyldimethylsilyl)oxy)-2-(9-oxodecahydro-1H-pyrrolo-[3,2,1-ij]quinolin-6a-yl)ethyl Acetate (**76**).* To a solution of **75** (78 mg, 0.151 mmol, 1 equiv) in EtOAc (100 μL) and EtOH (5 mL) was added by portions Pd/C (10%, 190 mg, 0.181 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature under an H_2 atmosphere, and after 2 days, it was filtered through a pad of Celite (EtOAc). The solvents were evaporated to give **76** (59 mg, quant) which was used in the following step without any further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (t, *J* = 5.1 Hz, 1H), 3.12−2.99 (m, 2H), 2.74−2.53 (m, 2H), 2.51−2.22 (m, 4H), 2.04 (s, 3H), 1.94−1.29 (m, 10H), 0.91 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 170.1, 91.6, 73.1, 53.2, 53.0, 48.3, 44.6, 37.0, 34.6, 34.2, 27.7, 25.9*3, 21.8, 21.4, 21.3, 18.1, −4.1, −4.7; HRMS (ESI) calcd for $C_{21}H_{38}NO_4Si$ $(M + H)^+$ 396.2565, found 396.2570.

*6-(2-Hydroxyethyl)octahydro-1H-pyrrolo[3,2,1-ij]quinolin-9(2H)-one (**77**).* To a stirred solution of the compound **76** (53 mg, 0.134 mmol, 1 equiv) in CH_2Cl_2 (1 mL) at 0 °C was added TFA (35 μL, 0.456 mmol, 3.4 equiv). After 15 min at 0 °C and 10 min at room temperature, a saturated aqueous solution of $NaHCO_3$ (1 mL) was added. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 1 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was dissolved in dry THF (1 mL), and LiAlH(O-*t*-Bu)$_3$ (1 M in THF, 120 μL, 0.120 mmol, 0.90 equiv) was added at 0 °C. The resulting mixture was stirred at 0 °C for 15 min and quenched by addition of a saturated aqueous solution of NH_4Cl (1 mL). The phases were separated, and a saturated aqueous solution of $NaHCO_3$ (1 mL) was added to the aqueous layer. The aqueous phase was extracted with EtOAc (3 × 1 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH: 100/0 to 85/15) to yield **77** (15 mg, 50%) as an oil: ^{1}H (300 MHz, $CDCl_3$) δ 3.52 (t, *J* = 7.4 Hz, 2H), 3.06 (m, 3H), 2.74 (t, J = 6.2 Hz, 1H), 2.54 (dd, *J* = 15.3, 5.1 Hz, 1H), 2.54 (dd, *J* = 15.3, 5.1 Hz, 1H), 2.43 (dd, *J* = 15.3, 5.1 Hz, 1H), 2.36 (m, 3H), 2.2−1.84 (m, 5H), 1.83−1.56 (m, 3H), 1.50 (m, 1H), 1.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 77.5, 73.4, 59.1, 53.8, 53.3, 48.5, 40.5, 37.1, 34.8, 34.1, 27.7, 21.5; HRMS (ESI) calcd for $C_{13}H_{22}NO_2$ $(M + H)^+$ 224.1645, found 224.1651.

*3-(2-Hydroxyethyl)-2,3,3a,4,5,5a,11,12-octahydro-1H-indolizino-[8,1-cd]carbazol-6(3a-1H)-yl)ethanone (**79**).* To a solution of ketone **77** (8 mg, 0.036 mmol, 1 equiv) in dry toluene (1 mL) was added phenylhydrazine (6 μL, 0.054 mmol, 1.5 equiv), and the resulting mixture was heated at 80 °C for 1 h 30. The mixture was then cooled to room temperature, and the solvent was evaporated. The crude was dissolved in dry toluene and solvent evaporated under reduced pressure to remove residual water. The mixture was redissolved in dry acetic acid (1 mL) and was heated under reflux. After 4 h, the mixture was cooled to room temperature, the solvent was evaporated, and the mixture was dissolved in THF (1 mL). $LiAlH_4$ (14 mg, 0.360 mmol, 10 equiv) was added at 0 °C, and the mixture was stirred at room temperature for 30 min. The mixture was cooled to 0 °C, water (100 μL) was added, and the suspension was filtered through Celite and washed with EtOAc. The resulting crude mixture was filtered over silica gel (triethylamine/MeOH/CH_2Cl_2, 1/5/95) to give **78** together with some inseparable impurities such as the unwanted indole byproduct). This mixture was dissolved in a 1/1 mixture of CH_2Cl_2 and 2 M $NaHCO_3$ (1.6 mL). AcCl (25 μL, 0.360 mmol, 10 equiv) and the resulting solution were vigorously stirred at room temperature for 24 h. The phases were separated, the aqueous layer was extracted with EtOAc (3 × 1 mL), the combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated in vacuo. The crude product was purified by preparative TLC (AcOEt/Et_3N 100/5) to give 1.2 mg (∼10%) of **79** identical to the literature;[16e] see Overman's formal synthesis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.7 Hz, 1H), 7.2 (d+t, *J* = 7.7 Hz, 2H), 4.07 (dd, *J* = 11.3, 6.3 Hz, 1H), 3.60 (m, 2H), 3.13 (td, *J* = 9.0, 3.2 Hz, 1H), 3.06 (d, *J* = 12.4 Hz, 1H), 2.38 (d, *J* = 13.2 Hz, 1H), 2.26 (m+s, 4H), 2.16 (s, 1H), 2.20−1.88 (m, 4H), 1.84−1.462 (m, 6H), 1.35−1.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 141.6, 138.1, 128.0, 124.6, 122.5, 118.6, 70.5, 68.1, 58.6, 53.9, 53.1, 52.6, 40.6, 39.7, 35.5, 35.3, 26.1, 24.4, 23.4, 21.7. HRMS (ESI) calcd for $C_{21}H_{29}N_2O_2$ $(M + H)^+$ 341.2224, found 341.2225.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: canesi.sylvain@uqam.ca.

■ ACKNOWLEDGMENTS

We thank Dr. Alexandre Arnold (UQAM) for his help with ^{19}F NMR. We are very grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada Foundation for Innovation (CFI), the provincial government of Quebec (FQRNT and CCVC), and Boehringer Ingelheim (Canada) Ltd. for financial support of this research. K.C.G. and M.A.B. acknowledge the NSERC Vanier CGS and the NSERC CGS-D programs, respectively.

■ REFERENCES

(1) (a) Fittig, R. *Justus Liebigs Ann. Chem.* **1860**, *114*, 54. (b) Wagner, G. *J. Russ. Chem. Soc.* **1899**, *31*, 690. (c) Meerwein, H. *Justus Liebigs Ann. Chem.* **1914**, *405*, 129. (d) Nametkin, S. S. *Ann.* **1923**, *432*, 207. (e) Olah, G. A. *Acc. Chem. Res.* **1976**, *9*, 41. (f) Hanson, J. R. *Comp. Org. Synth.* **1991**, *3*, 705.

(2) (a) Bérard, D.; Giroux, M. A.; Racicot, L.; Sabot, C.; Canesi, S. *Tetrahedron* **2008**, 7537. (b) Sabot, C.; Bérard, D.; Canesi, S. *Org. Lett.* **2008**, *10*, 4629. (c) Sabot, C.; Commare, B.; Nahi, S.; Duceppe, M. A.; Guérard, K. C.; Canesi, S. *Synlett* **2008**, 3226. (d) Guérard, K. C.; Sabot, C.; Racicot, L.; Canesi, S. *J. Org. Chem.* **2009**, *74*, 2039. (e) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941. (f) Guérard, K. C.; Chapelle, C.; Giroux, M. A.; Sabot, C.; Beaulieu, M. A.; Achache, N.; Canesi, S. *Org. Lett.* **2009**, *11*, 4756. (g) Guérard, K. C.; Sabot, C.; Beaulieu, M. A.; Giroux, M. A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893. (h) Andrez, J. A.; Giroux, M. A.; Lucien, J.; Canesi, S. *Org. Lett.* **2010**, *12*, 4368. (i) Beaulieu, M. A.; Sabot, C.; Achache, N.; Guérard, K. C.; Canesi, S. *Chem.—Eur. J.* **2010**, *16*, 11224. (j) Desjardins, S.; Andrez, J. A.; Canesi, S. *Org. Lett.* **2011**, *13*, 3406. (k) Beaulieu, M. A.; Guérard, K. C.; Maertens, G.; Sabot, C.; Canesi, S. *J. Org. Chem.* **2011**, *76*, 9460.

(3) (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. (d) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (e) Liang, H.; Ciufolini, M. A. *Chem.—Eur. J.* **2010**, *16*, 13262.

(4) (a) Vanderlaan, D. G.; Schwartz, M. A. *J. Org. Chem.* **1985**, *50*, 743. (b) Lewis, N.; Wallbank, P. *Synthesis* **1987**, 1103. (c) Gates, B. D.; Dalidowicz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135. (d) Swenton, J. S.; Callinan, A.; Chen, Y.; Rohde, J. J.; Kearns, M. L.; Morrow, G. W. *J. Org. Chem.* **1996**, *61*, 1267. (e) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E. M. *Tetrahedron Lett.* **1998**, *39*, 4667. (f) Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1*, 1651. (g) Braun, N. A.; Bray, J.; Ousmer, M.; Peters, K.; Peters, E. M.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397. (h) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593. (i) Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534. (j) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. A. *Tetrahedron* **2001**, *57*, 319.

(k) Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. *Tetrahedron Lett.* **2002**, *43*, 5193. (l) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336. (m) Quideau, S.; Pouységu, L.; Deffieux, D. *Current 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.* **2007**, *119*, 4016. (q) Silva, L. F. Jr.; Siqueira, F. A.; Pedrozo, E. C.; Vieira, F. Y. M.; Doriguetto, 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.; Saıdani, 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.

(5) (a) Pelter, A.; Drake, R. A. *Tetrahedron Lett.* **1988**, *29*, 4181. (b) Quideau, S.; Looney, M. A.; Pouységu, L. *J. Org. Chem.* **1998**, *63*, 9597. (c) Ozanne-Beaudenon, A.; Quideau, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7065. (d) Ciufolini, M. A.; Canesi, S.; Ousmer, M.; Braun, N. A. *Tetrahedron* **2006**, *62*, 5318. (e) Bérard, D.; Jean, A.; Canesi, S. *Tetrahedron Lett.* **2007**, *48*, 8238. (f) Jean, A.; Cantat, J.; Bérard, D.; Bouchu, D.; Canesi, S. *Org. Lett.* **2007**, *9*, 2553. (g) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A. M.; Miqueu, K.; Sotiropoulos, J. M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3552. (h) Bérard, D.; Racicot, L.; Sabot, C.; Canesi, S. *Synlett* **2008**, 1076. (i) Pouységu, L.; Marguerit, M.; Gagnepain, J.; Lyvinec, G.; Eatherton, A. J.; Quideau, S. *Org. Lett.* **2008**, *10*, 5211. (j) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539. (k) Quideau, S.; Lyvinec, G.; Marguerit, Bathany, K.; Ozanne-Beaudenon, A.; Bufeteau, T.; Cavagnat, D.; Chenede, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605. (l) Liang, H.; Ciufolini., M. A. *Org. Lett.* **2010**, *12*, 1760. (m) Traoré, M.; Ahmed-Ali, S.; Peuchmaur, M.; Wong, Y. S. *Tetrahedron* **2010**, *66*, 5863. (n) Liang, H.; Ciufolini, M. A. *Tetrahedron* **2010**, *66*, 5884. (o) Pouységu, L.; Sylla, T.; Garnier, T.; L. B. Rojas, L. B.; Charris, J.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 5908. (p) Dylan Turner, C.; Ciufolini, M. A. *ARKIVOC* **2011**, *1*, 410. (q) Chau, J.; Ciufolini, M. A. *Marine Drugs* **2011**, *9*, 2016. (r) Liang, H; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11849.

(6) (a) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231. (b) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239.

(7) (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (c) Kita, Y.; Takada, T.; Gyoten, M.; Tohma, H.; Zenk, M. H.; Eichhorn, J. *J. Org. Chem.* **1996**, *61*, 5854. (d) Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. *Chem. Commun.* **1996**, 1481. (e) Takada, T.; Arisawa, M.; Gyoten, M.; Hamada, R.; Tohma, H.; Kita, Y. *J. Org. Chem.* **1998**, *63*, 7698. (f) Arisawa, M.; Utsumi, S.; Nakajima, M.; Ramesh, N. G.; Tohma, H.; Kita, Y. *Chem. Commun.* **1999**, 469. (g) Akai, S.; Kawashita, N.; Morita, N.; Nakamura, Y.; Iio, K.; Kita, Y. *Heterocycles* **2002**, *58*, 75. (h) Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787. (i) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (j) Dohi, T.; Ito, M.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Tetrahedron* **2009**, *65*, 10797. (k) Fujioka, H.; Komatsu, H.; Nakamura, T.; Miyoshi, A.; Hata, K.; Ganesh, J.; Murai, K.; Kita, Y. *Chem. Commun.* **2010**, *46*, 4133. (l) Dohi, T.; Kato, D.; Hyodo, R.; Yamashita, D.; Shiro, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 3784.

(8) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

(9) Ochi, M.; Otsuki, K.; Nagao, K. *Bull. Chem. Soc. Jpn.* **1976**, 3363.

(10) Yokoyama, R.; Huang, J.-M.; Yang, C. S.; Fukuyama, Y. *J. Nat. Prod.* **2002**, *65*, 527.

(11) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752.

(12) Wang, J.; et al. *Nature* **2006**, *441*, 358.

(13) (a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, 2005. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (c) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (d) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (e) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (f) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5448.

(14) Grob, C. A.; Baumann, W. *Helv. Chim. Acta* **1955**, *38*, 594.

(15) Hirayama, L. C.; Dunham, K. K.; Singaram, B. *Tetrahedron Lett.* **2006**, *47*, 5173 The enantiomeric excess of compound **62** was calculated by NMR using a coupling with (*S*)-*O*-acetylmandelic acid. The enantiomeric excess of compound **64** was obtained by a selective reduction of the aldehyde moiety of **64** with $LiAl(O\text{-}t\text{-}Bu)_3H$, followed by a coupling with (*S*)-Mosher acid in the presence of DCC, of the resulting primary alcohol.

(16) (a) Hesse, M. *Indolalkaloide in Tabellen-Erganzungswerk*; Springer-Verlag: Berlin, 1968; p 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.

(17) (a) Brown, K. S.; Djerassi, C. *J. Am. Chem. Soc.* **1964**, *86*, 2451. (b) Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, *84*, 1058.

(18) (a) Yates, P.; MacLachlan, F. N.; Rae, I. D.; Rosenberger, M.; Szabo, A. G.; Willis, C. R.; Cava, M. P.; Behforouz, M.; Lakshmikantham, M. V.; Zeiger, W. *J. Am. Chem. Soc.* **1973**, *95*, 7842. (b) Rogers, E. F.; Snyder, H. R.; Fischer, R. F. *J. Am. Chem. Soc.* **1952**, *74*, 1987. (c) Snyder, H. R.; Fischer, R. F.; Walker, J. F.; Els, H. E.; Nussberger, G. A. *J. Am. Chem. Soc.* **1954**, *76*, 2819. (d) Synder, H. R.; Strohmayer, H. F.; Mooney, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 3708.

(19) (a) Gorman, A. A.; Agwada, V.; Hesse, M.; Renner, U.; Schmid, H. *Helv. Chim. Acta* **1966**, *49*, 2072. (b) Agwada, V.; Gorman, A. A.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 1939. (c) Agwada, V.; Patel, M. B.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1970**, *53*, 1567. (d) Kunesch, N.; Rolland, Y.; Poisson, J.; Majumder, P. L.; Majumder, R.; Chatterjee, A.; Agwada, V. C.; Naranjo, J.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1977**, *60*, 2854.

(20) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872.

(21) Pearson, A. J.; Rees, D. C. *J. Am. Chem. Soc.* **1982**, *104*, 1118.