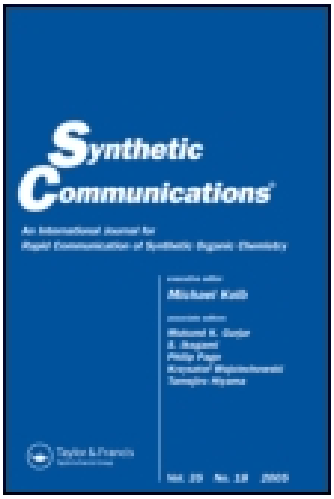


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Alternative Mild Route to the Synthesis of 4-Methylenecyclohex-2-enone, a Key Moiety of the Anticancer Compounds Ottelione A and B

Elena Lestini [a], Keith Robertson [a], Cormac D. Murphy [a] & Francesca Paradisi [a]

[a] University College Dublin, Dublin, Ireland

Accepted author version posted online: 07 Dec 2011.Published online: 27 Feb 2012.

To cite this article: Elena Lestini, Keith Robertson, Cormac D. Murphy & Francesca Paradisi (2012) Alternative Mild Route to the Synthesis of 4-Methylenecyclohex-2-enone, a Key Moiety of the Anticancer Compounds Ottelione A and B, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:12, 1864-1876, DOI: 10.1080/00397911.2011.607936

To link to this article: http://dx.doi.org/10.1080/00397911.2011.607936

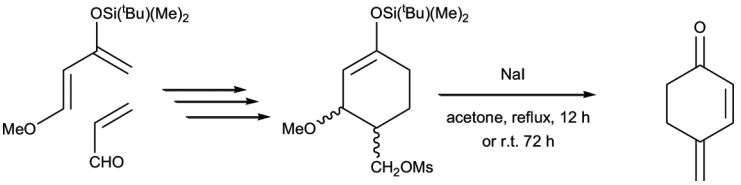
Synthetic Communications®, 42: 1864–1876, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.607936

ALTERNATIVE MILD ROUTE TO THE SYNTHESIS OF 4-METHYLENECYCLOHEX-2-ENONE, A KEY MOIETY OF THE ANTICANCER COMPOUNDS OTTELIONE A AND B

Elena Lestini, Keith Robertson, Cormac D. Murphy, and Francesca Paradisi
University College Dublin, Dublin, Ireland

GRAPHICAL ABSTRACT



Abstract

INTRODUCTION

In recent years, the discovery of the powerful anticancer and antitubercular properties of otteliones A and B, originally extracted from the freshwater plant *Ottelia alismoides*, have aroused great interest in the total synthesis of otteliones and their analogs.[1–4] Alternative mild synthetic strategies to the preparation of the key dienone, 4-methylenecyclohex-2-enone **6**, become an important task, because otteliones embed this rare electrophilic dienone in their bicyclic hydrindane skeleton (Fig. 1).

The cytotoxicity of this class of compounds is strongly related to the presence of the dienone functionality. Indeed, the aromatic analogs of ottelione, in which the embedded dienone functionality is not present, display significantly lower biological activity than that of the otteliones.[3b,3c] Although biological activity has not been assessed so far for the 4-methylenecyclohex-2-enone **6**, it has been reported that ottelione A inhibits tubulin polymerization.[3c]

Received July 12, 2011.
Address correspondence to Francesca Paradisi, University College Dublin, Dublin 4, Ireland. E-mail: francesca.paradisi@ucd.ie

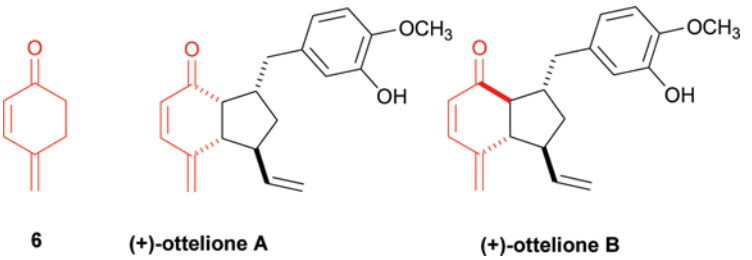


Figure 1. Representative 4-methylenecyclohex-2-enone embedded structure in ottelione A and B. (Figure is provided in color online.)

It is proposed that the disruption of the microtubule dynamics results from the specific binding of the 4-methylenecyclohex-2-enone functionality embedded in otteliones to the sulfhydryl groups of the cysteine residues in tubulin.[3b] The mechanism is believed to be similar to that of the cytotoxic molecule T138067 and of the alkaloids colchicine, vincristine, and vinbrastine.[5] The antitumor activity of the otteliones has stimulated interest in the synthesis of dienones such as **6**.

Thus far, however, few synthetic procedures are available in the literature.[6] The first approach reported relies on the Birch reduction of 4-methoxybenzyl alcohol followed by deoxygenation of the reduced products, affording **6** in yields of around 40%.[6a] The most recent approach employs a Diels–Alder adduct from the Diels–Alder reaction between Danishefsky's diene and methyl acrylate followed by acidic hydrolysis of the β-methoxy silyl enol ether adducts to ketones in *p*-toluene sulfonic acid. The compounds are converted to the final product by a stepwise procedure that employs ketalization with ethylene glycol, reduction of the ester adduct with diisobutylaluminium hydride (DIBALH), and final ketal deprotection with pyridinium *p*-toluenesulfonate in acetone. Following such a procedure, dienone **6** was obtained in 65–75% overall yield.[6b] 4-Methylenecyclohex-2-enone analogs may also be obtained via cross coupling of Baylis–Hillman acetates and aliphatic 1,3-diketones in ethanol and in the presence of K_2CO_3 with yields up to 70%.[6c] A bicyclic core intermediate for the synthesis of (+)-ottelione A was also synthesized using an enantioselective Diels–Alder strategy that in principle allows the preparation of a variety of chiral 4-methylenecyclohex-2-enone derivatives.[6d]

Extended structures of 4-methylenecyclohex-2-enone were also obtained by flash-vacuum pyrolysis of ketone spiro[5.6]dodeca-l,4,9-trien-3-one. However, in the latter case the synthesis of 4-methylenecyclohex-2-enone analogs is carried out under quite harsh conditions, which can promote unwanted tautomerization.[6e]

Not only is 4-methylenecyclohex-2-enone **6** a target product for potential biological activity when used on its own or when embedded in otteliones, but it is also a valuable starting material in the synthesis of several natural antifungal and antibiotic products such as chlorotetaine, bacilysin, and anticapsin.[7]

In this article, we describe an alternative synthesis of **6** using methanesulfonate **4a** and sodium iodide in acetone. Methanesulfonate adduct **4a** was obtained from Diels–Alder cycloaddition between the commercially available Danishefky's diene *trans*-4-methoxy-3-buten-2-one (**1a**) and acrolein under mild conditions.[8]

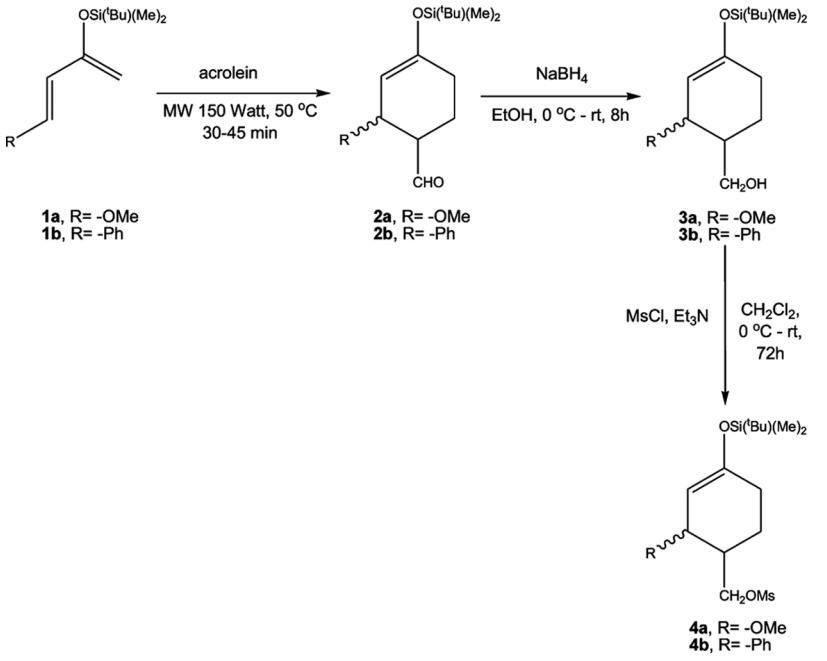
DISCUSSION

The Diels–Alder reaction in principle allows access to a range of methanesulfonate adducts that we envisage could be converted through this synthetic procedure to their 4-methylenecyclohex-2-enone analogs, which may exhibit biological activity similar to that of the otteliones.

Our approach to the synthesis of 4-methylenecyclohex-2-enone **6** employs milder conditions than those previously reported in literature and allows **6** to be obtained in yields up to 70% from commercially available materials (Scheme 1).[6]

The *tert*-butyldimethylsilyl analog of Danishefsky's diene **1a** chosen as this compound is highly reactive to cycloaddition reactions but is more stable to hydrolysis than the classic Danishefsky diene, owing to the presence of the more robust *tert*-butyldimethylsilyl protecting group. However, the *tert*-butyl silyl group can still be easily cleaved by a variety of selective conditions.[8f,9] Because the stereoselectivity of the cycloaddition was not relevant to the synthesis of 4-methylenecyclohex-2-enone **6**, the reaction of cycloaddition was carried out in the absence of conventional Lewis acids such as $ZnCl_2$ or $AlCl_3$ to minimise decomposition of **1a**.

Cycloaddition was performed under solvent-free conditions and irradiated by microwave (150 W) at 50 °C for 30 min (Scheme 1). Acrolein was used in excess to *trans*-3-(*tert*-butyldimethylsiloxy)-1-methoxy-1,3-butadiene **1a**, acting both as reagent and solvent. Under such conditions, no decomposition of diene **1a** was observed and aldehyde **2a** was obtained in almost quantitative yield. Side products due to the polymerization of acrolein were detected, but they were easily separated



Scheme 1. Stepwise synthesis of mesylate intermediates **4a** and **4b** from Danishefsky diene **1a** and **1b**, respectively.

from aldehyde **2a** by filtration, as they precipitate in diethyl ether. It is noteworthy to mention that the amount of acrolein seems critical to the cycloaddition reaction. Indeed, when acrolein was used in equimolar ratio to diene **1a**, considerable amounts of undesired products due to cycloaddition between *trans*-4-methoxy-3-buten-2-one, arising from deprotection of **1a**, and acrolein or 1,3-diene **1a** were detected. Thus, lower amounts of acrolein seem to favor the formation of side products over cross-cycloaddition of acrolein to 1,3-diene **1a**. It is likely that the polymerization process of acrolein, taking place under microwave irradiation, leads to depletion of free dienophile available for the reaction of cycloaddition with 1,3-diene **1a**, thus lowering the yield of **2a** to 50%.

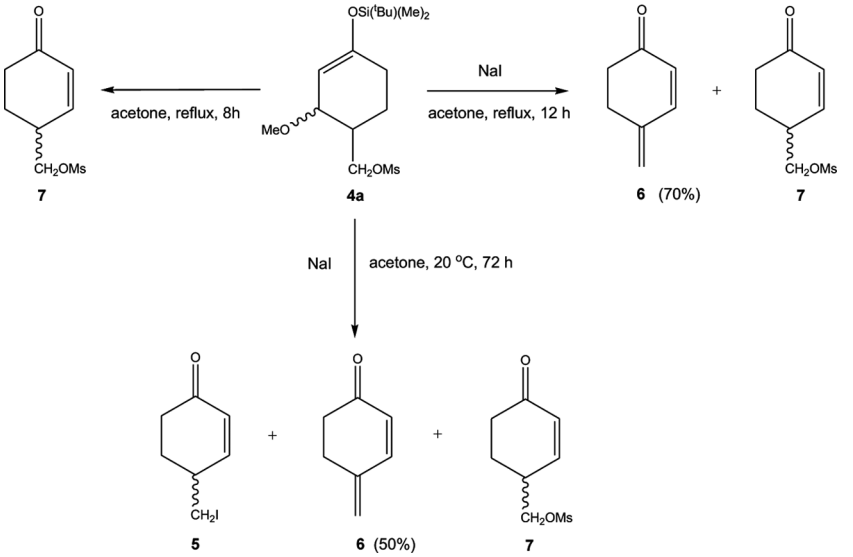
Cycloaddition of acrolein and 1,3-diene **1a** showed moderate stereoselectivity; the ratio of *syn* and *anti* diasteroisomers was evaluated to be 69:31 by NMR spectroscopy. Aldehyde **2a** was reduced with $NaBH_4$ in methanol to yield the corresponding alcohol **3a** as a racemic mixture of *syn* and *anti* diastereoisomers in almost quantitative yield.[10] However, the yield varied depending on the amount of sodium borohydride used. The best yield was obtained when sodium borohydride was used in slight molar excess to aldehyde **2a**.

Alcohol **3a** was easily converted to mesylate **4a** in the presence of triethylamine and mesyl chloride (Scheme 1). Dry conditions were employed to avoid acid-catalyzed deprotection of *tert*-butyldimethylsilyl group and elimination of methanol from alcohol **3a**. The formation of methanesulfonic acid was avoided by employing activated molecular sieves in situ. Under such conditions, mesylate **4a** was obtained in practically quantitative yield and was used directly in the next step of the reaction.

The use of strong bases such as sodium methoxide or 1,8-diazabicyclo[5.4.0.]-undec-7-ene (DBU) was unnecessary to promote formation of the methylene functionality (as in the synthesis of glucose derivatives bearing the methylene moiety).[11] When NaI was employed, formation of the methylene group along with desilanization of the silyl enol ether functionality and elimination of the β-methoxy silil enol ether in **4a** occurred, leading to the formation of the target product **6**. To investigate the possible role of sodium iodide in the formation of **6**, mesylate **4a** was refluxed in acetone in the absence of sodium iodide (Scheme 2). The reaction led to practically quantitative formation of ketone **7** (due to desilanization of the silyl enol ether and elimination of β-methoxy silyl enol ether), but to only traces of ketone **6**. This result strongly suggests that the reaction leading to the formation of ketone **6** and employing Finkelstein conditions[12] still needs a better leaving group and proceeds through formation of a halide intermediate such as **5**. The iodide intermediate **5** was isolated in traces when the reaction between **4a** and sodium iodide was carried out at 20 °C. However, it was found that such an intermediate readily undergoes elimination of hydrogen iodide under our experimental conditions. Subsequent elimination of hydrogen iodide from this intermediate might range from a concerted mechanism to a stepwise sequence, involving cationic intermediates and leading to the formation of the methylene functional group in **6**.

The latter findings underline the importance of sodium iodide in the formation of ketone **6** from mesylate **4a**. Indeed, simply refluxing **6** in acetone leads only to the formation of ketone **7** (Scheme 2).

However, the embedded β-methoxy silyl enol ether moiety in **4a** also appears to play an important role in the formation of ketone **6**. To investigate the role of this

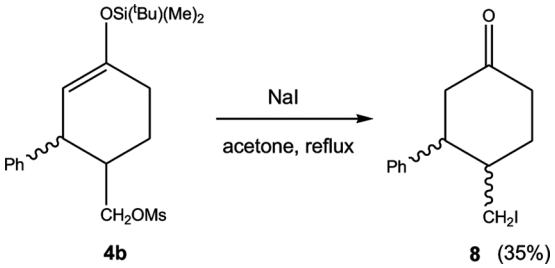


Scheme 2. Synthesis of 4-methylenecyclohex-2-enone **6**, mesylate **7**, and iodide **5** from mesylate **4a** under different experimental conditions.

group, a model mesylate **4b**, bearing a β-phenyl silyl enol ether group, neither heat nor acid labile was prepared following the same synthetic strategy employed for mesylate **4a** (Scheme 2) and reacted with sodium iodide under similar experimental conditions (Scheme 3).

It is noteworthy to compare the results obtained from the exchange reaction between sodium iodide and mesylate **4a** in acetone with those of model mesylate **4b**. When **4b** was exchanged with sodium iodide in acetone, intermediate **8** was isolated in 35% yield but no products bearing the methylene functional group in the γ-position to the carbonyl group were detected (Scheme 3) as in the case of mesylate **4a** (Scheme 2).

This result, along with the finding that ketone **6** was also formed in significant yield (50%) when **4a** was reacted with sodium iodide in acetone at 20 °C over 3 days (Scheme 2), indicates that the formation of a highly conjugated ketone such as **6**



Scheme 3. Reaction of exchange between model mesylate **4b** and sodium iodide.

might be regarded as the overall driving force for the process of dehydroiodination of intermediate **5** (Scheme 2).

In summary, an alternative four-step procedure for the synthesis of 4-methylenecyclohex-2-enone **6** was developed employing relatively mild conditions of reaction, leading to formation of ketone **6** in relatively good yields. The results underline the importance of both sodium iodide and of the embedded β-methoxy silyl enol ether functionality in **4a** in the formation of the target product 4-methylenecyclohex-2-enone **6**.

Finally, we believe that this procedure could effectively be employed in the synthesis of biologically active ottelione-type molecules. Further studies on the optimization of experimental conditions of the last step of synthetic scheme and on the application of this reaction to the synthesis of ottelione-type compounds are currently in progress.

EXPERIMENTAL

Synthesis of (E)-*tert*-Butyldimethyl(4-phenylbut-1,3-dien-2-yloxy)silane (1b)

(*E*)-4-Phenylbut-3-en-2-one (6 mmol, 0.61 mL) was added to a solution of dry triethyl amine (15 mmol, 2.1 mL) in dry diethyl ether (20 mL) in the presence of activated molecular sieves under a nitrogen atmosphere. The stirred mixture was cooled to 0 °C and *tert*-butyldimethylsilyl triflate (TBDMSTf, 6.3 mmol, 1.45 ml) was added dropwise. Once addition of TBDMSTf was complete, the mixture was allowed to warm to room temperature and stirred overnight. The reaction was worked up by filtration to remove the molecular sieves and washed successively with saturated sodium bicarbonate solution (20 mL), deionized water (20 mL), and brine (20 mL). The organic phase was collected and dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure to afford a pale yellow oil in 87% yield. The product was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$ δ/ppm 7.41 (d, $J = 7.3$ Hz, 2H, *ArH*), 7.32 (t, $J = 7.5$ Hz, 2H, *ArH*), 7.23 (t, $J = 7.4$ Hz, 1H, *ArH*), 6.86 (d, $J = 15.7$ Hz, 1H, *Ar-CH=CH*), 6.58 (d, $J = 15.7$ Hz, 1H, *Ar-CH=CH*), 4.45 (s, 1H, *C=CHH*), 4.42 (s, 1H, *C=CHH*), 1.03 [bs, 9H, *SiC(CH$_3$)$_3$*], 0.23 [bs, 6H, *Si(CH$_3$)$_2$*]. ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 155.3 (*CO*), 136.9, 129.3, 128.6, 127.6, 126.8, 126.6, 96.7 (*C=CHH*), 25.9 [*SiC(CH$_3$)$_3$*], 18.4 [*SiC(CH$_3$)$_3$*], −4.6 [*Si(CH$_3$)$_2$*]. HR-MS: *m/z* calcd for $C_{16}H_{25}OSi$ $(M + H)^+$: 261.1675; found: 261.1675.

Synthesis of 4-(*tert*-Butyldimethylsilyloxy)-2-methoxycyclohex-3-enecarbaldehyde (2a)

A mixture of diene **1a** (0.32 g, 1.5 mmol) and acrolein (0.17 mL, 0.25 mmol) was irradiated for 30 min at 50 °C by microwave (150 W). The reaction was worked up by addition of diethyl ether to precipitate the insoluble acrolein polymers, filtration, and removal of the solvent under reduced pressure. No further purification was necessary. Product **2a** was obtained as a colorless oil in 89% yield as a mixture of the *syn* and *anti* diastereomers. The ^{1}H NMR spectrum of aldehyde **2a** reveals the

presence of two distinct diastereomers. More specifically, the integrals of the well-resolved pair of diastereotopic protons corresponding to the *O=CH* protons at 9.78 ppm and 9.74 ppm display a 69:31 ratio.

Major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 9.78 (s, 1H, *O=CH*), 5.18 (d, $J = 5.1$ Hz, 1H, *OC=CH*), 4.26 (t, $J = 4.4$ Hz, 1H, *CHOCH$_3$*), 3.31 (s, 3H, *OCH$_3$*,), 2.41 (dt, $J = 10.4$, 3.4 Hz, 1H, *O=CHCH*), 2.14–1.87 (m, 4H, overlap with minor diastereomer), 0.91 [9H, bs, *SiC(CH$_3$)$_3$*), 0.17 (bs, 3H, *CH$_3$SiCH$_3$*), 0.16 (bs, 3H, *CH$_3$SiCH$_3$*). ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 203.2 (*O=CH*), 156.3 (*OC=CH*), 102.0 (*OC=CH*), 73.3 (*CHOCH3*), 55.8 (*OCH$_3$*), 50.5 (*O=CHCH*), 28.9 (*SiOCCH$_2$CH$_2$*), 25.6 [*SiC(CH$_3$)$_3$*], 19.4 (*SiOCCH$_2$CH$_2$*), 18.0 [*SiC(CH$_3$)$_3$*], −4.4 (*CH$_3$SiCH$_3$*), −4.5 (*CH$_3$SiCH$_3$*).

Main resonances of minor diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 9.74 (d, J = 0.9 Hz, 1H, *O=CH*), 5.05 (dt, $J = 3.8$, 1.2 Hz, 1H, *OC=CH*), 4.24–4.20 (m, 1H, *CHOCH$_3$*), 3.35 (s, 3H, *OCH$_3$*), 2.59–2.54 (m, 1H, *O=CHCH*), 2.14–1.87 (m, 4H, overlap with major diastereomer), 0.91 [s, 9H, *SiC(CH$_3$)$_3$*], 0.15 (s, 3H, *CH$_3$SiCH$_3$*), 0.14 (s, 3H, *CH$_3$SiCH$_3$*). ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 202.7 (*O=CH*), 152.6 (*OC=CH*), 102.5 (*OCCH=C*), 74.2 (*CHOCH$_3$*), 55.6 (*OCH$_3$*), 50.5 (*O=CHCH*), 28.0 (*SiOCCH$_2$CH$_2$*), 25.6 [*SiC(CH$_3$)$_3$*], 19.5 (*SiOCCH$_2$CH$_2$*), 18.1 [*SiC(CH$_3$)$_3$*], −4.4 (*CH$_3$SiCH$_3$*), −4.5 (*CH$_3$SiCH$_3$*). HR-MS: *m/z* $C_{14}H_{26}O_3Si$ $(M)^+$: 270.1651; found: 270.1650.

Synthesis of 4-(*tert*-Butyldimethylsilyloxy)-2-phenylcyclohex-3-enecarbaldehyde (2b)

A mixture of diene **1b** (5 mmol, 1.3 g) and acrolein (0.84 mL, 12.5 mmol) was irradiated for 45 min at 50 °C by microwave (150 W). The reaction was worked up by addition of diethyl ether to precipitate the insoluble acrolein polymers and filtered, and the solvent was removed under reduced pressure. No further purification was necessary. Product **2b** was obtained as a colorless oil in 87% yield as a mixture of the *syn* and *anti* diastereomers in 60:40 ratio. However, it was possible to isolate, for characterization purposes, the major diastereomer but, this was never achieved for the minor diastereomer, which remained partially contaminated by the other one.

Main resonances of major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) (δ/ppm): 9.63 (d, $J = 1.2$ Hz, 1H, *O=CH*), 7.28–7.22 (m, 2H, *ArH*), 7.20–7.14 (m, 3H, *ArH*), 4.86–4.81 (m, 1H, *OC=CH*), 3.83–3.77 (t, $J = 4.8$ Hz, 1H, *MeOCH*), 2.45–2.38 (m, 1H), 2.19–2.07 (m, 2H), 1.90–1.86 (m, 1H), 1.83–1.77 (m, 1H), 0.88 [bs, 9H, *SiC*]*CH$_3$)$_3$*,), 0.11 (s, 3H, *CH$_3$SiCH$_3$*), 0.09 (s, 3H, *CH$_3$SiCH$_3$*). ^{13}CNMR (126 MHz, $CDCl_3$) δ/ppm: 204.4 (*O=CH*), 152.4 (*OC=CH*), 141.0 (*Ar*), 129.0 (*Ar*), 128.3 (*Ar*), 126.7 (*Ar*), 105.7 (*OCCH=C*), 50.5, 41.4, 27.9 (*SiOCCH$_2$CH$_2$*), 25.6 [*SiC(CH$_3$)$_3$*, overlap with minor], 19.5 (*SiOCCH$_2$CH$_2$*), 18.0 [*SiC(CH$_3$)$_3$*], −4.3 (*CH$_3$SiCH$_3$*), −4.4 (*CH$_3$SiCH$_3$*).

Main resonances from minor diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 9.46 (d, $J = 1.8$ Hz, 1H, *O=CH*), 7.30–7.16 (5H, *ArH*, overlap with minor diastereomer), 5.02 (dt, 4.5, 1.3 Hz, 1H, *OC=CH*), 4.03 (t, $J = 5.0$ Hz, 1H, *MeOCH*), 2.70–2.64 (m, 1H), 2.26–2.10 (m, 2H, overlap with major diastereomer), 2.01–1.80

(m, 2H, overlap with major diastereomer), 0.93 [bs, 9H, $SiC(C\underline{H}_3)_3$], 0.16 (s, 3H, $CH_3SiC\underline{H}_3$), 0.16 (s, 3H, $C\underline{H}_3SiCH_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 203.6 ($O{=}\underline{C}H$), 151.6 ($O\underline{C}{=}CH$), 144.3 (*Ar*), 128.5 (*Ar*), 128.1 (*Ar*), 126.7 (*Ar*), 106.7 ($OC{=}\underline{C}H$), 53.7, 41.2, 27.9 ($SiOC\underline{C}H_2CH_2$), 25.6 [$SiC(\underline{C}H_3)_3$], 21.0 ($SiOCCH_2\underline{C}H_2$), 18.0 [$Si\underline{C}(CH_3)_3$], −4.4 ($CH_3Si\underline{C}H_3$), −4.4 ($\underline{C}H_3SiCH_3$). HR-MS: m/z calcd $C_{19}H_{28}O_2SiNa$ $(M+Na)^+$: 339.1756; found 339.1770.

Synthesis of (4-(*tert*-Butyldimethylsilyloxy)-2-methoxycyclohex-3-enyl)methanol (3a)

Aldehyde **2a** (2.8 mmol, 0.76 g) was dissolved in ethanol (30 mL) and cooled to 0 °C. Sodium borohydride (1.5 mmol, 57 mg) was added portionwise, and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of ammonium chloride (~100 mg) and stirred for an additional 5 min. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane and washed successively with saturated sodium bicarbonate solution (20 mL), deionised water (20 mL), and brine (20 mL). The organic layer was dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure. The viscous, orange oil was then purified on alumina using 5% ethyl acetate in cyclohexane running to pure ethyl acetate. The product **3a** as mixture of diastereoisomes (69:31 ^{1}H NMR ratio) was obtained as a colorless oil in 84% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 5.14 (d, $J=5.1$, 1H, $OC{=}C\underline{H}$), 3.95 (t, $J=4.4$ Hz, 1H, $MeOC\underline{H}$), 3.82–3.77 (m, 1H, $HOC\underline{H}H$), 3.74–3.68 (m, 1H, $HOCH\underline{H}$), 3.34 (s, 3H, $OC\underline{H}_3$), 2.66 (m, 1H), 2.12–2.08 (m, 1H), 1.95–1.85 (m, 1H), 1.78–1.70 (m, 1H), 1.60–1.55 (m, 1H, overlap with water), 0.93 [bs, 9H, $SiC(C\underline{H}_3)_3$], 0.17 (bs, 3H, $CH_3SiC\underline{H}_3$), 0.16 (bs, 3H, $C\underline{H}_3SiCH_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 156.2 ($O\underline{C}CH$), 102.4 ($OC{=}\underline{C}H$), 76.9 ($\underline{C}HOCH_3$), 65.4 ($\underline{C}H_2OH$), 55.6 ($CHO\underline{C}H_3$), 39.8 ($\underline{C}HCH_2OH$), 29.9 ($SiOC\underline{C}H_2CH_2$), 25.6 [$SiC(\underline{C}H_3)_3$], 20.8 ($SiOCCH_2\underline{C}H_2$), 18.0 [$Si\underline{C}(CH_3]_3$), −4.4 ($CH_3Si\underline{C}H_3$), −4.4 ($\underline{C}H_3SiCH_3$).

Main resonances of minor diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 4.97 (t, $J=2.0$ Hz, 1H, $OCC\underline{H}{=}C$), 3.93–3.89 (m, 1H, $CH_3OC\underline{H}$), 3.71–3.54 (m, 2H), 3.33 (s, 3H, $OC\underline{H}_3$), 2.57–2.51 (m, 1H), 2.20–2.08 (m 1H), 2.01–1.96 (m, 1H), 1.87–1.79 (m, 1H), 1.46–1.36 (m, 1H), 0.92 [bs, 9H, $SiC(C\underline{H}_3)_3$], 016 (bs, 6H, $C\underline{H}_3SiC\underline{H}_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 155.2 ($OC{=}CH$), 103.1 ($OC{=}\underline{C}H$), 80.0 ($\underline{C}HOCH_3$), 66.8 ($\underline{C}H_2OH$), 54.5 ($CHO\underline{C}H_3$), 40.3 ($\underline{C}HCH_2OH$), 29.0 ($SiOC\underline{C}H_2CH_2$), 25.6 [$SiC(\underline{C}H_3)_3$], 22.9 ($SiOCCH_2\underline{C}H_2$), 18.0 [$Si\underline{C}(CH_3]_3$), −4.3 ($CH_3Si\underline{C}H_3$), −4.5 ($\underline{C}H_3SiCH_3$). HR-MS: m/z calcd. for $C_{19}H_{30}O_2Si$ $(M+H)^+$: 295.1705; found: 295.1707.

Synthesis of (4-(*tert*-Butyldimethylsilyloxy)-2-phenylcyclohex-3-enyl)methanol (3b)

Aldehyde **2b** (2.9 mmol, 0.92 g) was dissolved in ethanol (30 mL) and cooled to 0 °C. Sodium borohydride (1.5 mmol, 57 mg) was added portionwise to the stirred

solution, and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of ammonium chloride (~100 mg) and stirred for an additional 5 min. The solvent was removed under reduced pressure, and the residue was dissolved in dichloromethane and washed successively with saturated sodium bicarbonate solution (20 mL), deionized water (20 mL), and brine (20 mL). The organic layer was dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure. The viscous, orange oil was then purified on silica using 10% ethyl acetate in cyclohexane running to pure ethyl acetate. Product **3b** was recovered as a colorless oil in 82% yield. The well-resolved pair of diastereotopic protons corresponding to the $OC{=}C\underline{H}$ protons at 4.98 ppm and 4.81–4.79 ppm display a 60:40 ratio.

Main resonances of minor diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 7.32–7.26 ($Ar\underline{H}$, m, 3H, overlap with major diastereomer), 7.24–7.19 (m, 2H, $Ar\underline{H}$, overlap with major diastereomer), 4.81–4.79 (m, 1H, $OC{=}C\underline{H}$), 3.62–3.56 (m, 1H), 3.45–3.38 (m, 1H), 3.32–3.17 (m, 1H, overrun with major diastereomer), 2.33–2.06 (m, 3H, overlap with major diastereomer), 1.99–1.96 (m, 1H), 1.71–1.57 (m, 1H, overlap with major diastereomer), 0.93 [s, 9H, $SiC(C\underline{H}_3)_3$], 0.16 (s, 3H, $CH_3SiC\underline{H}_3$), 0.14 (s, 3H, $C\underline{H}_3SiCH_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 151.2 ($O\underline{C}{=}CH$), 145.8, 128.3, 128.2, 126.3, 108.0 ($OC\underline{C}H{=}C$), 65.1, 44.1, 43.9, 29.2 ($SiOC\underline{C}H_2CH_2$), 25.7 [$SiC(\underline{C}H_3)_3$], 25.0 ($SiOCCH_2\underline{C}H_2$), 18.0 [$Si\underline{C}(CH_3)_3$], −4.3 ($CH_3Si\underline{C}H_3$), −4.4 ($\underline{C}H_3SiCH_3$). HR-MS: m/z calcd for $C_{14}H_{28}O_3Si$ $(M+Na)^+$: 319.2088; found 319.2078.

Synthesis of (4-(*tert*-Butyldimethylsilyloxy)-2-methoxycyclohex-3-enyl)methyl Methanesulfonate (4a)

Alcohol **3a** (1.6 mmol, 0.44 g) was dissolved in dry dichloromethane (10 mL) under a nitrogen atmosphere, utilizing activated molecular sieves, and cooled to 0 °C. Dry triethyl amine (2 mmol, 0.28 mL) was added to the solution, and mesyl chloride (1.8 mmol, 0.14 mL) was added dropwise. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature and stirred for a further 72 h. The mixture was filtered to remove molecular sieves, washed with deionized water (15 mL) and brine (15 mL), dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give a pale yellow oil in 88% yield. The product was used immediately without further purification due to decomposition. An attempt to purify the product for analysis using alumina and 5% ethyl acetate in cyclohexane running to pure ethyl acetate as an eluant was partially successful. Purification gave the major diastereomer with some minor contamination.

Major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 5.07 (d, $J = 5.3$ Hz, 1H, $OC{=}C\underline{H}$), 4.27 (dd, $J = 9.6$, 7.6 Hz, 1H, $SOC\underline{H}H$), 4.07 (dd, $J = 9.6$, 7.2 Hz, 1H, $SOCH\underline{H}$), 3.76 (t, $J = 4.5$ Hz, 1H, $CH_3OC\underline{H}$), 3.23 (s, 3H, $OC\underline{H}$), 2.93 (bs, 3H $SC\underline{H}_3$), 2.06–1.92 (m, 3H), 1.72–1.53 (m, 2H), 0.85 [bs, 9H, $SiC(C\underline{H}_3)_3$], 0.10 (bs, 3H, $C\underline{H}_3SiCH_3$), 0.09 (bs, 3H, $CH_3SiC\underline{H}_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 155.7 ($O\underline{C}CH{=}C$), 102.1 ($OC\underline{C}H{=}C$), 72.5, 71.3, 55.5 ($O\underline{C}H_3$), 38.1, 36.8, 29.2 ($SiOC\underline{C}H_2CH_2$), 25.5 [$SiC(\underline{C}H_3)_3$], 20.1 ($SiOCCH_2\underline{C}H_2$),

17.9 [$SiC(CH_3)_3$], −4.5 (CH_3SiCH_3), −4.6 (CH_3SiCH_3). HR-MS: m/z calcd. for $C_{15}H_{30}O_5SSiNa$ $(M+Na)^+$: 373,1481; found 373.1498.

Synthesis of (4-(*tert*-Butyldimethylsilyloxy)-2-phenylcyclohex-3-enyl)methyl Methanesulfonate (4b)

Alcohol **3b** (1.2 mmol, 0.38 g) was dissolved in dry dichloromethane (10 mL) under a nitrogen atmosphere, utilizing activated molecular sieves, and cooled to 0 °C. Dry triethyl amine (2 mmol, 0.28 mL) was added to the solution, and mesyl chloride (1.3 mmol, 0.1 mL) was added dropwise. The reaction mixture was stirred for 5 min, allowed to warm to room temperature, and stirred for a further 72 h. The mixture was filtered to remove molecular sieves, washed with deionized water (15 mL) and brine (15 mL), dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The product was obtained as a pale yellow oil in 85% yield. The product was used immediately without further purification to avoid decomposition. The well-resolved pair of diastereotopic protons corresponding to the $OC=CH$ protons at 4.96 ppm and 4.81–4.78 ppm display a 60:40 ratio.

Major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 7.34–7.28 (m, 2H, ArH, overlap with minor diastereomer), 7.26–7.19 (m, 3H, ArH, overlap with minor diastereomer), 4.96 (d, $J = 5.0$ Hz, 1H, $OCCH=C$), 3.78–3.73 (m, 2H, $SOCH_2$), 3.71 (t, $J = 5.3$ Hz, 1H, $SOCH_2CH$), 2.92 (s, 3H, SCH_3), 2.36–2.18 (m, 4H), 1.70–1.63 (m, 1H, overlap with minor diastereomer), 0.94 [s, 9H, $SiC(CH_3)_3$), 0.17 (bs, 3H], 0.17 (bs, 3H). ^{13}CNMR (126 MHz, $CDCl_3$) δ/ppm: 151.7 ($OCCH=C$), 140.8 (Ar), 129.4 (Ar), 128.2 (Ar), 126.9 (Ar), 106.0 ($OCCH=C$), 71.7 ($SOCH_2$), 41.6, 37.5, 37.2, 28.6 ($SiOCCH_2CH_2$), 25.7 [$SiC(CH_3)_3$], 20.8 ($SiOCCH_2CH_2$), 18.0 [$SiC(CH_3)_3$], −4.3 (CH_3SiCH_3), −4.4 (CH_3SiCH_3).

Minor diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 7.34–7.28 (ArH, m, 2H, overlap with minor diastereomer), 7.26–7.19 (ArH, m, 3H, overlap with minor diastereomer), 4.81–4.78 ($OCCH=C$, m, 1H), 4.13–4.08 ($SOCHH$, m, 1H), 4.06–4.00 ($SOCHH$, m, 1H), 3.34–3.27 (S$OCH2CH$, m, 1H), 2.89 (SCH_3, s, 3H), 2.16–2.09 (m, 1H), 2.02–1.95 (m, 1H), 1.94–1.87 (m, 1H), 1.70–1.63 (m, 1H, overlap with major diastereomer), 0.93 [$SiC(CH_3)_3$, s, 9H], 0.16 (bs, 3H, CH_3SiCH_3), 0.14 (bs, 3H, CH_3SiCH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 151.1 ($OCCH=C$), 144.5 (Ar), 128.6 (Ar), 128.1 (Ar), 126.7 (Ar), 107.1 ($OCCH=C$), 71.6 ($SOCH_2$), 43.3, 41.3, 37.1, 28.8 ($SiOCCH_2CH_2$), 25.6 ($SiC(CH_3)_3$), 24.7 ($SiOCCH_2CH_2$), 18.0 ($SiC(CH_3)_3$), −4.3 (CH_3SiCH_3), −4.4 (CH_3SiCH_3). HR-MS: m/z calcd. for $C_{20}H_{33}O_4SSi$ $(M+H)^+$: 397.1869; found: 397.1880.

Synthesis of 4-Methylenecyclohex-2-enone (6) and (4-Oxocyclohex-2-enyl)methylmethanesulfonate (7)

Methanesulfonate **4a** (1.07 mmol, 0.37 g) was added to a solution of sodium iodide (2 mmol, 0.13 g) in acetone (15 ml). The reaction was refluxed under stirring for 12 h. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (20 ml). The resulting solution was washed with water (15 mL)

and brine (15 mL). The organic phase was collected, dried with magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The products **6** and **7** were purified on silica gel using 30% ethyl acetate in cyclohexane as an eluant. Product **6** was obtained as a colorless oil in 70% yield; **7** was obtained as an off-white, waxy solid as a minor side product.

Compound 6. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm 7.09 (d, $J = 9.9$ Hz, 1H, *O=CCH=CH*), 5.96 (d, $J = 9.9$ Hz, 1H, *O=CCH=CH*), 5.34 (s, 1H, *C=CHH*), 5.29 (s, 1H, *C=CHH*), 2.76 (t, $J = 7.2$ Hz, 2H, *O=CCH$_2$*), 2.53 (t, 7.3 Hz, 2H, *O=CCH$_2$CH$_2$*). ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 199.0 (*C=O*), 147.3 (*O=CCH=CH*), 140.6 (*CH$_2$=C*), 128.1 (*O=CCH=CH*), 119.3 (*CH$_2$=C*), 37.1 (*O=CCH2*), 29.2 (*O=CCH$_2$CH$_2$*). HR-MS: *m/z* calcd. for C_7H_8O $(M)^+$; 108.0575, found: 108.0573.

Compound 7. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 6.87–6.83 (m, 1H, *O=CCH=CH*), 6.11 (1H, dd, $J = 10.2$ Hz, 2.3 Hz, *O=CCH=CH*), 4.28–4.13 (2H, m, *CH$_2$OS*), 3.05 (3H, s, *SCH$_3$*), 2.93–2.86 (1H, m, *O=CCHH*), 2.47–2.37 (1H, m, *O=CCHH*), 2.47–2.37 (1H, m, *SOCH$_2$CH*), 2.23–2.15 (1H, m, *O=CCH$_2$CHH*), 1.92–1.85 (1H, m, *O=CCH$_2$CHH*). ^{13}C NMR (500 MHz, $CDCl_3$) δ/ppm: 198.2 (*C=O*), 147.8 (*O=CCH=CH*), 131.3 (*O=CCH=CH*), 70.4 (*CH$_2$OS*), 37.6, 36.2, 36.2, 25.3 (*O=CCH$_2$CH$_2$*). HR-MS: *m/z* calcd. for $C_8H_{12}OSNa$ $(M + Na)^+$: 227.0354; found: 227.0348.

Synthesis of (4-Oxocyclohex-2-enyl)methylmethanesulfonate (7)

Methanesulfonate **4a** (1.5 mmol, 0.53 g) was dissolved in acetone (20 mL) and refluxed for 8 h. The reaction was worked up and purified as described for **6** and **7**. Product **7** was obtained as an off-white waxy solid in 76% yield.

4-(Iodomethyl)-3-phenylcyclohexanone (8)

The synthetic procedure employed for **6** and **7** was utilized to produce **8**, using methanesulfonate **4b** as a starting material. The product was purified on silica gel, eluant 10% ethyl acetate in cyclohexane. Compound **8** was recovered as a white solid in 35% yield. No optimization was attempted. A mixture of diastereomers was obtained in 70:30 ratio. The major diastereomer was obtained as a pure sample for analysis; it was not possible to obtain the minor diastereomer as a pure sample and the NMR of a mixture is given.

Major. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 7.35–7.26 (m, 3H, *ArH*), 7.14 (d, $J = 7.0$ Hz, 2H, ArH), 3.63 (q, $J = 5.8$ Hz, 1H, *HC-Ar*), 3.07–2.94 (m, 2H, *CH$_2$I*), 2.75–2.63 (m, 2H, *O=CCH$_2$CH-Ar*), 2.57–2.42 (m, 3H), 2.10–1.93 (m, 2H, *O=CCH$_2$CH$_2$*). ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 210.6 (*C=O*), 140.0 (*Ar*), 128.6 (*Ar*), 128.2 (*Ar*), 127.2 (*Ar*), 44.7, 44.2, 42.7, 38.6 (*O=CCH$_2$CH$_2$*), 27.7 (*O=CCH$_2$CH$_2$*), 8.1 (*CH$_2$I*).

Minor. ^{1}H NMR (500 MHz, $CDCl_3$) δ/ppm: 7.37–7.26 (m, 3H, *ArH*, overlap with major diastereomer), 7.26–7.23 (m, 1H, *ArH*, overlap with major diasteromer), 7.15–7.13 (m, 1H, *ArH*), 3.20–3.15 (m, 1H, *HC-Ar*), 2.86–2.78 (m, 2H, *CH$_2$I*),

2.76–2.42 (m, 4H, overlap with major diastereomer), 2.32–2.24 (m, 1H), 1.93–1.83 (m, 1H), 1.81–1.69 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ/ppm: 209.4, 141.8, 129.1, 127.3, 127.2, 49.0, 48.2, 41.9, 40.5, 32.4, 26.9, 12.9 HR-MS: m/z calcd. for $C_{13}H_{15}IO$ $(M)^+$: 314.0168; found: 314.0172.

ACKNOWLEDGMENTS

This work was supported by HEA PRTLI cycles 3 and 4. The authors thank Michael Carroll for his contribution to the project.

REFERENCES

1. (a) Ayyad, S.-E. N.; Judd, A. S.; Shier, W. T.; Hoye, T. R. *J. Org. Chem.* **1998**, *63*, 8102–8106; (b) Lewis, H. J. PhD dissertation, University of Minnesota, Minneapolis, 2005.
2. Li, H.; Qu, X.; Shi, Y.; Guo, L.; Yuan, Z. *Zhongguo Zhongyao Zazhi (Chin. J. Chin. Mater. Med.)* **1995**, *20*, 115–116, 128.
3. (a) Cook, C. D. K.; Symoens, J.-J.; Urmi-König, K. *Aquatic Botany* **1984**, *18*, 263–274; (b) Leboul, J.; Provost, J. French patent WO96/00205, 1996; *Chem. Abstr.* **1996**, *124*, 242296; (c) Combeau, C.; Provost, J.; Lancelin, F.; Tournoux, Y.; Prod'-homme, F.; Herman, F.; Lavelle, F.; Leboul, J.; Vuilhorgne, M. *Mol. Pharmacol.* **2000**, *57*, 553–563; (d) Mehta, G.; Islam, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2396–2398.
4. (a) Mehta, G.; Islam, K. *Tetrahedron Lett.* **2003**, *44*, 6733–6736; (b) Araki, H.; Inoue, M.; Katoh, T. *Org. Lett.* **2003**, *5*, 3903–3906; (c) Clive, D. L. J.; Liu, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 3738–3740; (d) Araki, H.; Inoue, M.; Suzuki, T.; Yamori, T.; Kohno, M.; Watanabe, K.; Abe, H.; Katoh, T. *Chem. Eur. J.* **2007**, *13*, 9866–9881; (e) Clive, D. L. J.; Liu, D. *J. Org. Chem.* **2008**, *73*, 3078–3087; (f) Chen, H.-C.; Chen, Y.-K.; Sha, C.-K. *Org. Lett.* **2010**, *12*, 1377–1379.
5. Beckers, T.; Mahboobi, S. *Drugs of the Future* **2003**, *28*, 767–785.
6. (a) Birch, A. *J. Proc. R. Soc. N. S. W.* **1949**, *83*, 245–250; (b) Jung, M. E.; Rayle, H. L. *Synth. Commun.* **1994**, *24*, 197–203; (c) Chamakh, A.; Amri, H. *Tetrahedron Lett.* **1998**, *39*, 375–378; (d) Lee, M. Y.; Kim, K. H.; Jiang, S.; Jung, Y. H.; Sim, J. Y.; Hwang, G.-S.; Ryu, D. H. *Tetrahedron Lett.* **2008**, *49*, 1965–1967; (e) Murray, D. F.; Baum, M. W.; Jones, Jr., M.; *J. Org. Chem.* **1986**, *51*, 1–7.
7. (a) Richards, R. W.; Rodwell, J. L.; Schmalzl, K. J. *J. Chem. Soc., Chem. Commun.* **1977**, 849–850; (b) Laguzza, B. C.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 1483; (c) Souchet, M.; Baillarge, M.; LeGoffic, F. *Tetrahedron Lett.* **1988**, *29*, 191–193; (d) Wild, H.; Born, L. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1685–1687; (e) Baldwin, J. E.; Adlington, R. M.; Mitchell, M. B. *J. Chem. Soc., Chem. Commun.* **1993**, 1332–1335; (f) Wild, H. *J. Org. Chem.* **1994**, *59*, 2748–2761.
8. (a) Zhang, Y.; Danishefsky, S. *J. Am. Chem. Soc.* **2010**, *132*, 9567–9569; (b) Massa, A.; De Sio, V.; Villano, R.; Acocella, M. R.; Palombi, L.; Giusi, S.; Peduto, A.; Filosa, R.; De Capraris, P.; Scettri, A. *Synthesis* **2009**, *4*, 643–649; (c) Spino, C.; Crawford, J.; Cui, Y.; Gugelchuck, M. *J. Chem. Soc., Perkin Trans.* **1998**, *2*, 1499–1506; (d) Quirante, J.; Vila, X.; Bonjoch, J. *Synthesis* **2001**, *13*, 1971–1973; (e) Danishefsky, S.; Kitara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996–7000; (f) Danishefsky, S.; Kitara, T. *J. Org. Chem.*, **1975**, *40*, 538–539.
9. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1991; (b) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo

Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843–2859; (c) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.
10. Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746–1756.
11. (a) Lei, P.-S.; Duchaussoy, P.; Sizun, P.; Mallet, J.-M.; Petitou, M.; Sinay, P. *Bioorg. Med. Chem.* **1998**, *6*, 1337–1346; (b) Sato, K.-I.; Kubo, N.; Takada, R.; Aqeel, A.; Hashimoto, H.; Yoshimura, J. *Chem. Lett.* **1988**, *17*, 1703–1704; (c) Gallagher, T. F.; Horton, D. *Carbohydr. Res.* **1983**, *116*, 227–237; (d) Sakairi, N.; Kuzuhara, H. *Tetrahedron Lett.* **1982**, *23*, 5327–5330.
12. Finckelstein, H. *Ber.* **1910**, *43*, 1528–1532.