Tetrahedron 65 (2009) 3261–3269

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Consecutive sigmatropic rearrangements in the enantioselective total synthesis of (−)-joubertinamine and (−)-mesembrine

Elizabeth A. Ilardi, Michael J. Isaacman, Ying-chuan Qin, Sommer A. Shelly, Armen Zakarian *

Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106-9510, USA

ARTICLE INFO

Article history:
Received 15 September 2008
Received in revised form 14 October 2008
Accepted 16 October 2008
Available online 1 November 2008

Keywords:
Sigmatropic rearrangements
Sceletium alkaloids
Mesembrine
Joubertinamine

ABSTRACT

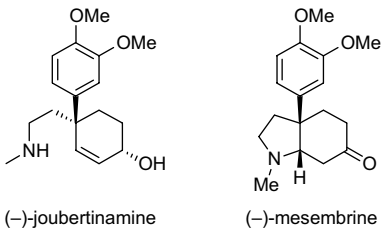
Joubertinamine and mesembrine are two related alkaloids isolated from *Sceletium* plants. From the perspective of chemical synthesis, the major challenge posed by joubertinamine and mesembrine is undoubtedly the construction of the benzylic quaternary stereogenic center. We became intrigued by the prospect of applying successive sigmatropic rearrangements to build the key structural features of these alkaloids in enantioselective manner. In this article, we detail our results in this area, which include the enantioselective total synthesis of (−)-joubertinamine and (−)-mesembrine.

1. Introduction

Beneficial properties of plants of the *Sceletium* family have been known for centuries to populations of the southern regions of Africa, including the Khoikhoi and Sans peoples.[1a] Dried leaves of *Sceletium* plants have been used widely in shamanic practices to elevate mood and to alleviate anxiety and tension, and by shepherds as appetite suppressants during long journeys in arid areas. These intriguing biological properties have been associated with the presence of alkaloids like mesembrine and joubertinamine (Fig. 1), which are found in *Sceletium* plants in significant concentrations. Mesembrine has been recently shown to be a potent serotonin uptake inhibitor.[1]

Joubertinamine can be converted to mesembrine in one step by oxidation with activated manganese(II) oxide through the intermediacy of the corresponding enone, which undergoes a spontaneous Michael cyclization to mesembrine.[3f] Although more than a dozen of syntheses of mesembrine have been reported,[2] some enantioselective, only a few are amenable for the synthesis of joubertinamine,[3] and no enantioselective synthesis of joubertinamine has been described.

From the perspective of chemical synthesis, the major challenge posed by joubertinamine and mesembrine is undoubtedly the construction of the benzyllic quaternary stereogenic center. In the case of mesembrine, several strategies have been employed for its enantioselective formation. These include chiral auxiliary-based stereoselective alkylation,[2f,m] tandem [4+2]/[3+2] cycloaddition of a nitroalkene,[2g] tandem epoxidation–ring expansion of cyclopropylidene alcohols,[2j] [2+2]-cycloaddition of vinyl sulfoxides,[2l] enantioselective Birch–Cope sequence,[2a] palladium catalyzed allylic substitution followed by zirconium mediated cyclization,[2h] asymmetric dihydroxylation of a 1-aryl-1-cyclohexene,[2e,i] opening of aryl-substituted epoxides with Grignard reagents,[2b] an intramolecular cycloaddition of azomethine ylides,[2k] and a direct formation and allylation of enamines.[3g] We became intrigued by the prospect of applying successive sigmatropic rearrangements to build the key structural features of these alkaloids in enantioselective manner. In this article, we detail our results in this area, which include the enantioselective total synthesis of both (−)-joubertinamine and (−)-mesembrine.



(−)-joubertinamine (−)-mesembrine

Figure 1.

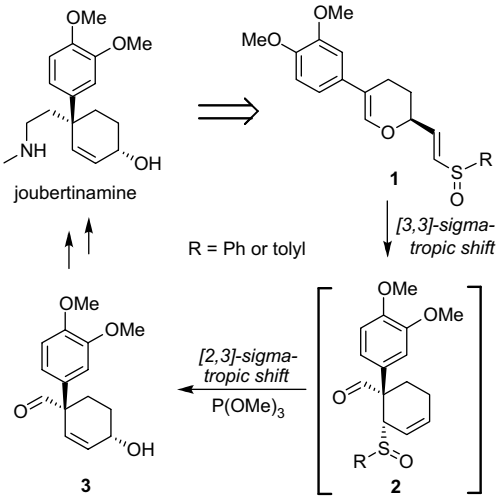
* Corresponding author. Tel.: +1 805 893 3717; fax: +1 805 893 4120.
E-mail address: zakarian@chem.ucsb.edu (A. Zakarian).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.10.048

2. Results and discussion

2.1. General synthesis plan

Our analysis of the cyclohexenol substructure of joubertinamine led us to consider a tandem [3,3]/[2,3]-sigmatropic reorganization of sulfinylvinyl dihydropyran **1** (Scheme 1). Under the conditions required for the initial Claisen rearrangement of **1**, the resulting allylic sulfoxide (**2**) is expected to undergo a Mislow–Evans rearrangement to cyclohexenol **3** with complete diastereocontrol.



Scheme 1. General outline of the synthesis plan.

The basis for this key element of our synthesis plan was provided by our earlier work directed at the synthesis of a marine natural product (+)-pinnatoxin A.[4] We developed a similar process, efficiently converting a more complex sulfinylvinyl dihydropyran (**4**) to cyclohexenol **5** in high yield (Scheme 2).[5] A tight, highly organized transition structure required for the Claisen rearrangement of vinyl dihydropyrans ensured complete diastereoselectivity during the formation of the quaternary stereocenter and the tertiary alcohol.[6]

In comparison with the known example, the differences in the planned transformation of **1** to **3** include (a) a lack of substitution at positions 2 and 6 of the dihydropyran ring system and (b) an electron-rich aromatic substituent in the place of β-branched alkyl group at position 3. In order to determine the effect of the changes on the tandem rearrangement, we set out to prepare vinyl sulfoxide **1** and its diastereomer in enantiopure form.

2.2. The synthesis of sulfoxides of the structure 1 and attempted tandem rearrangement

Our first approach to **1** is illustrated in Scheme 3. It relied on the Sharpless asymmetric dihydroxylation to introduce the stereocenter in compound **1**.[7] Alkylation of ester **6** with 1-iodo-3-butene followed by the Sharpless asymmetric dihydroxylation delivered a mixture of diastereomers **8**, which, as we established later, corresponded to an unoptimized ee of about 55%. Lactonization to **9** occurred in 83% yield.

Rather than optimizing the dihydroxylation reaction, we modified our strategy as shown in Scheme 4. Known iodide **11** was prepared in two steps and in 88% overall yield from commercially available (*S*)-1,2,4-butanetriol,[8] and used to alkylate the zinc-ate enolate generated from ester **10**. Using Noyori's protocol, ester **12** was formed in 96% yield.[9] The yield with the corresponding lithium enolate was ~50%. Subsequent removal of the acetonide and lactonization occurred upon exposure of ethyl ester **12** to a mixture of THF and 2 M hydrochloric acid.

Silylation of the lactone delivered **13** in 87% overall yield. Reduction of the lactone to lactol and dehydration (MsCl, Et_3N) afforded dihydropyran **14**. The sulfinylvinyl substituent was appended in four steps after desilylation. Thus, oxidation to the aldehyde, addition of the lithiated (*S*)-methyl *p*-tolyl sulfoxide, silylation, and elimination upon treatment with LDA provided **16**. The diastereomer at the sulfinyl center (**17**) was prepared analogously employing (*R*)-methyl *p*-tolyl sulfoxide in 49% overall yield from **15**.

The tandem Claisen–Mislow–Evans rearrangements of **16** and **17** were attempted next. We have discovered that, in contrast to **4**, these substrates do not undergo the rearrangement at temperatures up to 150 °C (Scheme 5). Only the starting material was recovered. At higher temperatures, decomposition was observed.

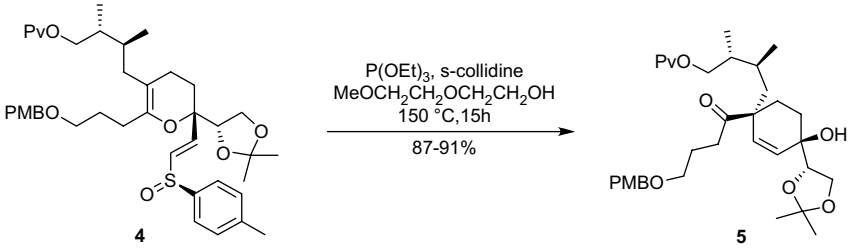
Presently, the reasons for the difference in reactivity comparing to sulfoxide **4** are unclear, and after extensive attempts to improve the outcome of the tandem rearrangement we opted to modify our approach.

2.3. Consecutive sigmatropic rearrangements using vinyl sulfides

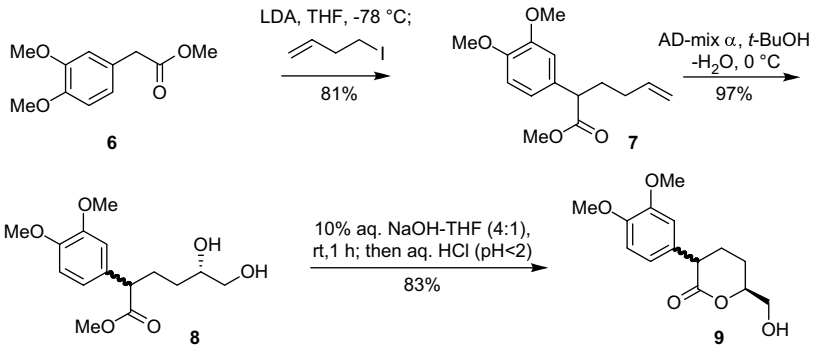
We next explored the Claisen rearrangement of vinyl sulfides related to sulfoxides **16** and **17**. The substrates were prepared using a Wittig olefination as illustrated in Scheme 6.

The Wittig reaction produced a mixture of *E*- and *Z*-isomer, and, as can be seen in Table 1, the *Z*-isomer is the major product under all conditions we employed. In a polar solvent (THF–DMPU) with a weakly coordinating counterion (KHMDS), a 70:30 inseparable mixture of *Z*- and *E*-vinyl sulfides **18** was obtained in 95% yield over two steps. Without DMPU as an additive, the *Z*/*E*-selectivity was increased to 82%. In a non-polar solvent (toluene) with a more coordinating counterion (NaHMDS), 78% of the *Z*-isomer was formed along with 22% of the *E*-isomer. Thus, our brief survey of the reaction conditions revealed that there appears to be only a slight effect of the nature of solvent or base on the stereoselectivity of the olefination without any discernable pattern.

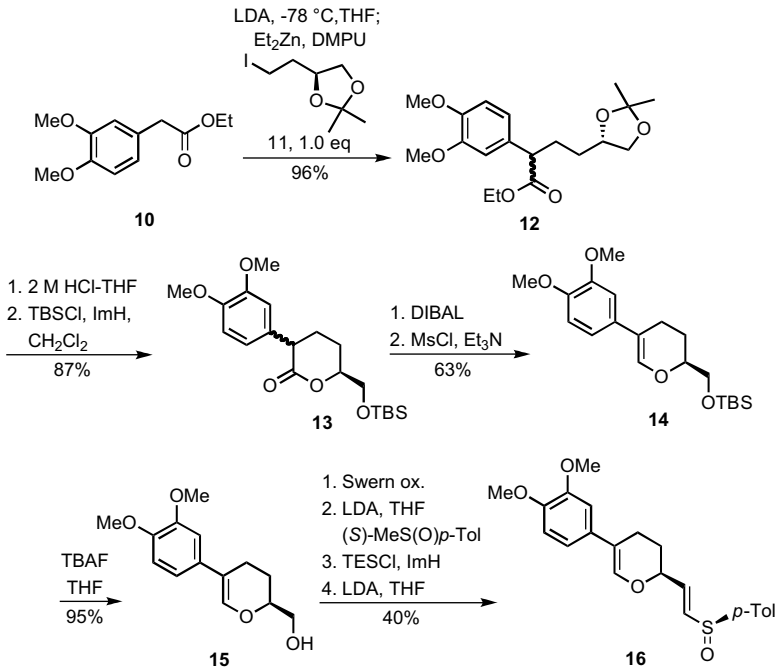
Production of ***Z*-18** as the major isomer in the olefination reaction was a significant setback, because the *Z* double bond



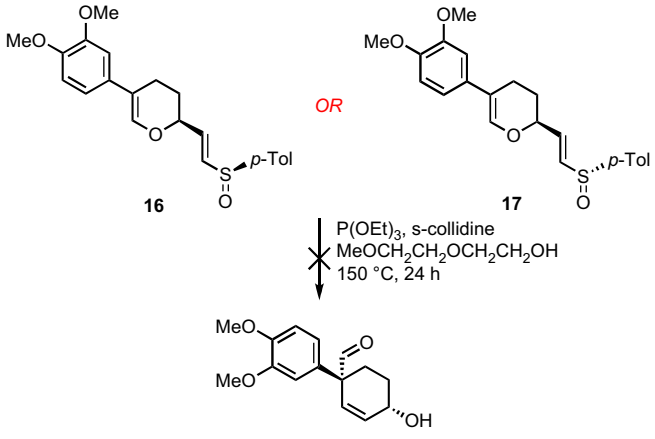
Scheme 2. An example of the tandem Claisen–Mislow–Evans rearrangement.



Scheme 3.



Scheme 4.

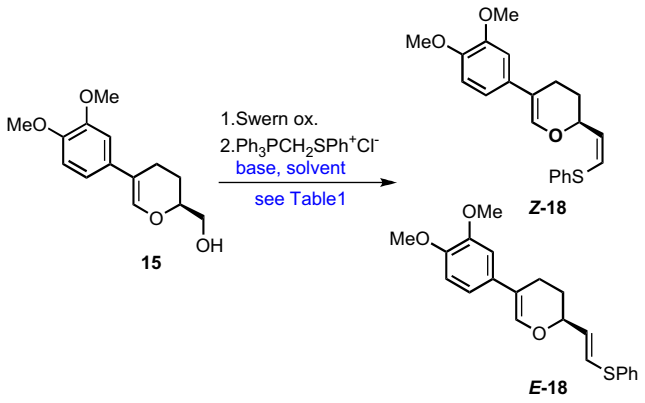


Scheme 5.

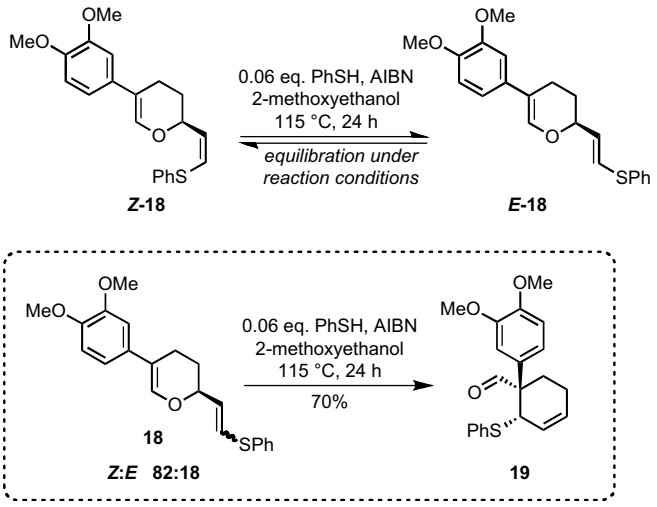
geometry would be translated into the undesired configuration of the allylic sulfide upon the Claisen rearrangement. Although, based on the seminal studies by Büchi more than three decades ago,[6] we could expect that the *Z*-isomer would not undergo the [3,3]-sigmatropic rearrangement, resulting in the selective formation of only the desired diastereomer (**19**) (Scheme 7), the overall yield would be low. Indeed, when a mixture of *E*-**18** and *Z*-**18** was heated at 120 °C for 24 h, a smooth rearrangement of only *E*-**18** was observed, giving the desired diastereomer and recovering the unreacted *Z*-sulfide.

The lack of reactivity of *Z*-**18** also suggested a solution: if under certain reaction conditions suitable for the [3,3]-sigmatropic shift the olefins could undergo *E*/*Z*-isomerization, then only the rearrangement of *E*-**18** would take place, converting all material to the desired diastereomer of the product (**19**).

It is known that *E*- and *Z*-alkene can efficiently interconvert under radical conditions in the presence of a catalytic amount of thiophenol and a radical initiator (2,2′-azaisobutyronitrile, AIBN) at elevated temperatures, presumably through a radical addition–elimination mechanism.[10] These reaction condition appeared to be



Scheme 6.



Scheme 8.

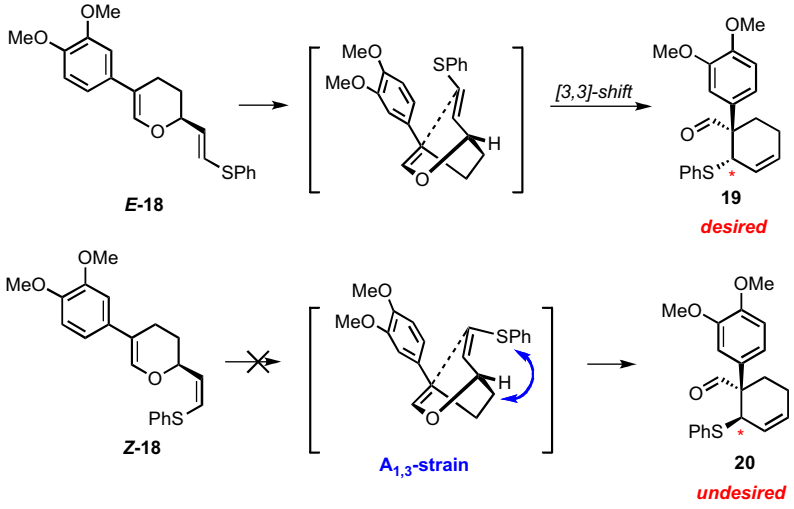
Table 1
Stereoselectivity of the Wittig olefination shown in Scheme 6

Entry	Base	Solvent, temperature, time	Ratio *Z*/*E*	Yield over two steps (%)
1	KHMDS	THF, 20 °C, 1 h	82:18	92
2	KHMDS	THF–DMPU [3:1], 20 °C, 1 h	70:30	95
3	NaHMDS	Toluene, 20 °C, 2 h	78:22	93

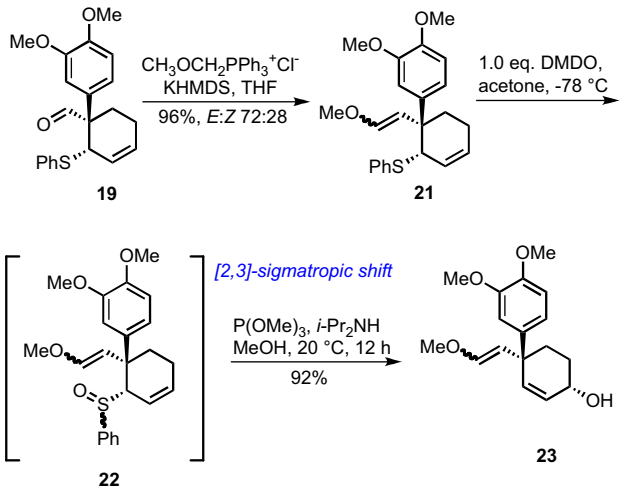
ideally suitable for our purposes because no interference of the isomerization with the sigmatropic transposition would be expected, thus allowing for a dynamic kinetic separation process. Indeed, we were delighted to find out that exposure of an 82:18 mixture of the *Z*/*E*-vinyl sulfides **18** to a catalytic amount of thiophenol in the presence of AIBN at 115 °C for 24 h resulted in the formation of **19** in 70% yield, and no diastereomer could be isolated. When the reaction was terminated after about 2 h and the starting material was isolated, the ratio of the alkenes ranged from 2:1 to 1:1, favoring the *E*-sulfide, which initially was the minor stereoisomer (18%). This observation supports our hypothesis that the rearrangement proceeds through olefin isomerization followed by selective rearrangement of the *trans*-vinylsulfide only (Scheme 8).

The difference in reactivity between sulfoxides **16** and **17** and sulfides **18** is quite remarkable. The striking rate acceleration in [3,3]-sigmatropic rearrangements of 1,5-unsaturated systems bearing a sulfide substituent at the 6-position has been well established. Studies by the groups of Paquette and Houk report a three order of magnitude rate enhancement in the anionic oxy-Cope rearrangements for phenylsulfido-substituted substrates compared to the parent unsubstituted analogs.[11] Although a mild decelerating effect of electron-withdrawing substituents at position 6 on [3,3]-sigmatropic shifts is known,[12] the low reactivity of **16** and **17** is still surprising, especially compared to that of **4**. Consequently, it is possible that there is a notable effect of the electron-rich aryl substituent at the 3 position of the dihydropyran, either steric or electronic. This hypothesis will be tested in our subsequent studies.

Having prepared the desired allylic sulfide **19**, we were well positioned to investigate the second sigmatropic rearrangement. This operation required oxidation of the phenyl sulfide to the corresponding sulfoxide. In order to anticipate the aldehyde homologation, which will be required subsequently, and to eliminate potential complications during the oxidation that might be due to the presence of the aldehyde functional group, a Wittig olefination with triphenyl(methoxymethyl)phosphorane was carried out first (Scheme 9). Methoxyalkenes **21** were isolated in 96% yield as a 3:1 mixture of *E*- and *Z*-isomer. At this stage, a clean oxidation of sulfide **21** was achieved upon a brief exposure to dimethyldioxirane at −78 °C. The diastereomeric mixture of the allylic sulfoxides was



Scheme 7.

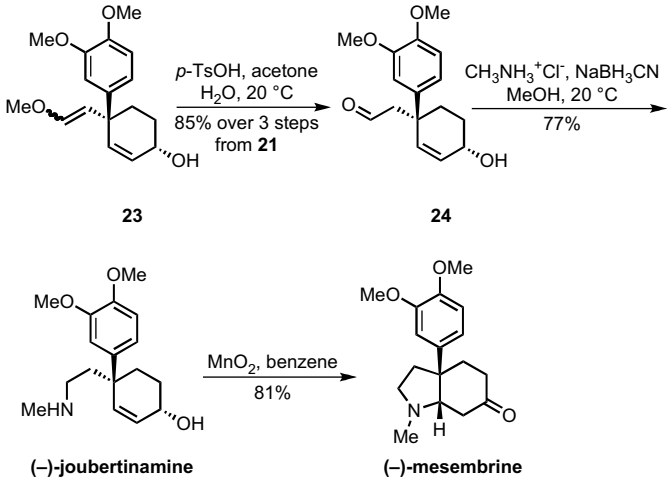


Scheme 9.

subjected to the Mislow–Evans rearrangement without purification.[13] The [2,3]-sigmatropic transposition occurred smoothly at ambient temperature, providing the desired allylic alcohol in 92% overall yield. Di-*iso*-propylamine was used as a buffer to prevent complications associated with partial hydrolysis of the methyl alkenyl ether, which was observed when no basic additive was used.

2.4. Completion of the total synthesis of (−)-joubertinamine and (−)-mesembrine

The enantioselective total synthesis of (−)-joubertinamine was completed in two steps from methyl alkenyl ether **23**. Hydrolysis of the ether in aqueous acetone in the presence of *p*-toluenesulfonic acid afforded aldehyde **24**. The last three steps, that is, oxidation of the sulfide to sulfoxide with DMDO, the Mislow–Evans rearrangement, and the hydrolysis of **23** were conveniently carried out in one-pot in 85% overall yield, simply replacing the solvent by evaporation and dissolution of the residue after each step. Aldehyde **24** was converted to the natural alkaloid by reductive amination with methylammonium chloride and sodium cyanoborohydride (Scheme 10). This reductive amination is similar to that employed recently by Cho and Tam in the synthesis of racemic joubertinamine.[3a] Finally, oxidation with manganese oxide produced (−)-mesembrine in 81% yield.



Scheme 10.

3. Conclusions

The synthesis of (−)-joubertinamine described in this article proceeds in 13 steps from ethyl (3,4-dimethoxyphenyl)acetate (14 steps from (*S*)-1,2,4-butanetriol) and in 20% overall yield. In turn, (−)-mesembrine is reached in 14 steps and 16% overall yield. The key transformations in the synthesis are the consecutive sigmatropic rearrangements. Thus, a Claisen rearrangement of a 2-(phenylthio)vinyl dihydropyrans **18** is followed by the Mislow–Evans rearrangement after oxidation of the intermediate allylic sulfide. The originally designed tandem sequence of these two reactions was not successful due to low reactivity of the corresponding sulfoxides. Further studies to gain a better mechanistic understanding on the sigmatropic process are underway in our laboratory.

4. Experimental section

4.1. General information

All non-aqueous reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware. Tetrahydrofuran (THF) and ether (Et_2O) were distilled from sodium–benzophenone under an atmosphere of argon. Dichloromethane, di-*iso*-propylamine, pyridine, triethylamine, and chlorotrimethylsilane were distilled from calcium hydride in a continuous still under and atmosphere of argon. Chlorotriethylsilane (TESCl) and di-*iso*-propylethylamine (Hunig's Base) were distilled from calcium hydride under an inert atmosphere of dry argon and stored over calcium hydride. Reaction temperatures were controlled by IKA ETS-D4 fuzzy thermo couples. Room temperature reactions were carried out between 20 and 24 °C. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F_{254} (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, and iodine staining. Flash column chromatography was preformed using 40–63 μm silica gel (Merck, Geduran, no. 11567-1) as the stationary phase. Proton magnetic resonance spectra were recorded at 300, 400, and 500 MHz on Varian Mercury, Varian Unity Inova, and Varian VXR spectrometers, respectively. Carbon magnetic resonance spectra were recorded at 75 and 125 MHz on Varian Mercury and Varian VXR spectrometers, respectively. All chemical shifts were reported in δ units relative to tetramethylsilane. Optical rotations were measured on a Jasco P-2000 polarimeter. High resolution mass spectral data were obtained by the Mass Spectrometry laboratory at Florida State University or at the University of California, Santa Barbara. Optical rotations were measured on a Jasco DIP-2000 polarimeter with a sodium lamp.

4.2. Experimental procedures

4.2.1. *Methyl 2-(3,4-dimethoxyphenyl)hex-5-enoate (**7**)*

Methyl (3,4-dimethoxyphenyl)acetate **6**[14] and 1-iodo-3-butene[15] were prepared according to literature protocols. *n*-Butyllithium (2.46 M in hexane, 44.0 mmol, 17.9 mL) was added to a solution of di-*iso*-propylamine (6.7 mL, 48.4 mmol) in 80 mL of dry THF dropwise at −78 °C, and the mixture was stirred for 30 min. A solution of ester **6** (4.60 g, 22.0 mol) in 10 mL of THF was added and the reaction mixture was stirred at −78 °C for 20 min. A solution of 1-iodo-3-butene (6.0 g, 33.0 mmol) in 5 mL of THF was added to the resulting mixture and the solution was stirred at −78 °C for 1 h and then at 0 °C for 1 h. Saturated ammonium chloride (40 mL) was added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (10%

EtOAc–hexanes) to give pure ester **7** (4.69 g, 17.8 mmol, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.89–6.74 (m, 3H), 5.78 (dddd, J=17.0, 10.5, 6.5, 6.5 Hz, 1H), 5.02 (m, 1H), 4.97 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.66 (s, 3H), 3.51 (t, J=7.57 Hz, 1H), 2.22–2.07 (m, 1H), 2.06–1.92 (m, 2H), 1.92–1.76 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 174.5, 148.9, 148.2, 137.5, 131.3, 120.1, 115.3, 111.1, 110.9, 55.9, 55.8, 51.9, 50.2, 32.5, 31.4. HRMS (ESI$^+$) calcd for $C_{15}H_{20}NaO_4$ $(MNa)^+$ 287.1266, found 287.1259.

4.2.2. Methyl 2-(3,4-dimethoxyphenyl)-5,6-dihydroxyhexanoate (*8*)

Ester **7** (3.96 g, 15.0 mmol) was added to a solution of 21.0 g of AD-mix α (Aldrich) in water (80 mL) and *tert*-butanol (80 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 8 h. The reaction was quenched with 50 mL of 2 M Na_2SO_3 and the resulting mixture was stirred at room temperature for 1 h. The mixture was extracted with ethyl acetate (3×100 mL), and the organic layers were combined and washed with brine. The organic phase was dried over sodium sulfate and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (30% EtOAc–CH_2Cl_2) to give pure product diol **8** as a mixture of diastereomers (4.10 g, 14.6 mmol, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.91–6.63 (m, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.67 (m, 1H), 3.66 (s, 3H), 3.50 (m, 1H), 3.42 (m, 1H), 2.38–1.61 (m, 3H), 1.39 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 173.4, 172.3, 149.3, 148.1, 131.8, 130.5, 121.8, 114.7, 74.7, 70.5, 56.2, 50.3, 30.6, 26.3. HRMS (ESI$^+$) calcd for $C_{15}H_{22}NaO_6$ $(M+Na)^+$ 321.1311, found 321.1314.

4.2.3. (S)-3-(3,4-Dimethoxyphenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-2-one (*9*)

A 10% aqueous solution of sodium hydroxide (10 mL) was added to a solution of diol **8** (3.98 g, 13.4 mmol) in 40 mL of dry THF at 0 °C, and the mixture was stirred vigorously at room temperature for 1 h. The reaction mixture was carefully acidified to pH <5 with 6 N HCl and then to pH <2 with 1 N HCl. The resulting mixture was transferred to a separatory funnel and extracted with dichloromethane (12×30 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The residue was dried under high vacuum overnight and purified by flash column chromatography (silica, 30% ethyl acetate–hexanes) to give pure lactone **9** as a mixture of diastereomers (2.95 g, 11.1 mmol, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.79 (m, 3H), 4.58 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.71 (m, 1H), 3.59 (m, 1H), 2.32 (m, 1H), 2.16 (m, 2H), 1.96 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 173.8, 172.7, 149.2, 148.4, 131.6, 130.8, 120.6, 120.3, 111.7, 111.5, 111.3, 82.3, 79.8, 65.0, 64.7, 56.0, 48.0, 45.2, 28.6, 26.4, 24.5, 22.2. FTIR (CH_2Cl_2), ν(cm^{-1}): 3790, 3437, 3060, 2936, 1726, 1593, 1517, 1259, 1145, 1026. HRMS (ESI$^+$) calcd for $C_{14}H_{18}NaO_5$ $(MNa)^+$ 289.1062, found 289.1052.

4.2.4. (S)-Ethyl 2-(3,4-dimethoxyphenyl)-4-(2,2-dimethyl-1,3-dioxolan-4-yl)butanoate (*12*)

Iodide **11** was prepared according to a literature procedure.[16] *n*-Butyllithium (2.38 M in hexane, 7.1 mL, 16.9 mmol) was added to a solution of di-*iso*-propylamine (2.6 mL, 18.6 mmol) in 21 mL of dry THF dropwise at −78 °C and the mixture was stirred at −78 °C for 30 min. A solution of ester **10** (3.14 g, 14.00 mol) in dry THF (5 mL total with rinses) was added to the reaction mixture and the reaction mixture was stirred for 10 min at −78 °C. Diethylzinc (1.9 mL, 18.5 mmol) was added to the resulting light yellow solution, followed by DMPU (15 mL) and a solution of (*S*)-4-(2-iodoethyl)-2,2-dimethyl-1,3-dioxolane **11** (3.60 g, 14.0 mmol) in THF (5 mL total with rinses), and the mixture was stirred for 1 h at −78 °C and then slowly warmed to −25 °C for 4.5 h. The mixture was warmed to room temperature and carefully quenched with saturated ammonium chloride (4 mL), and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (silica, 35% ethyl acetate–hexanes) to give pure ester **12** (4.75 g, 13.48 mmol, 96%) as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.85–6.75 (m, 3H), 4.18–3.96 (m, 4H), 3.86 (s, 3H), 3.85 (s, 3H), 3.50–3.42 (m, 2H), 2.21–2.12 (m, 0.5H), 2.06–1.97 (m, 0.5H), 1.93–1.84 (m, 0.5H), 1.79–1.70 (m, 0.5H), 1.61–1.45 (m, 2H), 1.38 (s, 1.5H), 1.36 (m, 1.5H), 1.32 (s, 3H), 1.20 (t, J=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 174.1, 149.1, 148.4, 131.5, 120.3, 111.2, 110.9, 110.8, 109.0, 75.91, 75.86, 69.55, 69.45, 60.9, 56.0, 51.3, 51.2, 31.8, 31.6, 29.9, 27.1, 25.85, 25.84, 14.3. FTIR (CH_2Cl_2), ν(cm^{-1}): 3437, 2984, 2936, 2871, 1727, 1591, 1515, 1261, 1155, 1030. HRMS (ESI$^+$) calcd for $C_{18}H_{26}NaO_6$ $(MNa)^+$ 361.1612, found 361.1627.

4.2.5. (S)-6-((tert-Butyldimethylsilyloxy)methyl)-3-(3,4-dimethoxyphenyl)tetrahydro-2H-pyran-2-one (*13*)

An aqueous solution of hydrochloric acid (2 M, 85 mL) was added to a solution of ester **12** (4.27 g, 12.12 mmol) in 85 mL of dry THF at 0 °C, and the mixture was stirred vigorously at room temperature for 1 h. Brine (250 mL) was added and the aqueous layer was extracted with ethyl acetate (150 mL, then 3×50 mL). The combined organic layers were dried over sodium sulfate and concentrated. The residue was dissolved in 20 mL of ethyl acetate and stirred with 4.5 g of silica for 1.5 h at room temperature. The solution was filtered using 80 mL of ethyl acetate and concentrated.

The crude product was dissolved in dichloromethane (25 mL), and imidazole (2.45 g, 36.0 mmol) and *tert*-butylchlorodimethylsilane (2.17 g, 14.4 mmol) were added. The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with 100 mL of dichloromethane and transferred to a separatory funnel. The organic phase was washed with 1 M HCl, brine, saturated sodium bicarbonate, dried over sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (silica, 35% ethyl acetate–hexanes) to give pure **13** (4.00 g, 10.51 mmol, 87% for two steps) as a mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.97–6.64 (m, 3H), 4.50–4.42 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.84–3.71 (m, 2H), 3.58 (dd, J=12.0, 8.0 Hz, 0.5H), 2.27–2.16 (m, 1H), 2.14–1.86 (m, 3H), 0.89 (two s, 9H), 0.08 (two s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 173.2, 172.3, 149.1, 148.3, 132.0, 131.3, 120.5, 120.3, 111.8, 111.5, 111.4, 111.2, 81.3, 79.4, 65.4, 65.1, 56.0, 48.1, 45.5, 28.6, 26.5, 26.0, 25.1, 22.8, 18.46, 18.43, −5.2, −5.3. HRMS (ESI$^+$) calcd for $C_{20}H_{32}NaO_5Si_1$ $(MNa)^+$ 403.1911, found 403.1917.

4.2.6. (S)-tert-Butyl((5-(3,4-dimethoxyphenyl)-3,4-dihydro-2H-pyran-2-yl)methoxy)dimethylsilane (*14*)

To a solution of lactone **13** (3.795 g, 9.97 mmol) in dry dichloromethane (85 mL) was added DIBAL (1 M in toluene, 20 mL, 20 mmol) dropwise for 20 min at −78 °C. The reaction mixture was stirred at −78 °C for additional 30 min, quenched with saturated Rochelle's salt (80 mL), and stirred for 3 h at room temperature. The resulting mixture was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The crude product was dissolved in dichloromethane (50 mL), and triethylamine (5.4 mL, 38.7 mmol) followed by methanesulfonyl chloride (1.0 mL, 12.9 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 10 min. The resulting mixture was diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, water, and brine, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (silica, 13% ethyl acetate–hexanes) to give 2.408 g (6.61 mmol, 63%) of the

dihydropyran **14**. $[\alpha]_D^{20}$ +127.6 (*c* 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.83 (s, 1H), 6.82 (m, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.81 (dd, *J*d1=10.6 Hz, *J*d2=5.3 Hz, 1H), 3.70 (dd, *J*=10.6, 5.5 Hz, 1H), 2.42 (m, 2H), 2.13–1.97 (m, 1H), 1.85–1.72 (m, 1H), 0.92 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 148.8, 147.5, 140.7, 132.6, 116.5, 112.6, 111.3, 107.9, 75.4, 65.4, 55.9, 55.8, 25.9, 24.1, 22.3, 18.4, −5.3. FTIR (CH_2Cl_2), ν(cm^{-1}): 3489, 3060, 2928, 2856, 1726, 1639, 1517, 1465, 1251, 1163, 1029. HRMS (ESI^+) calcd for $C_{20}H_{32}NaO_4Si$ $(MNa)^+$ 387.1960, found 387.1967.

4.2.7. (S)-(5-(3,4-Dimethoxyphenyl)-3,4-dihydro-2H-pyran-2-yl)methanol (**15**)

Tetra-*n*-butylammonium fluoride (2.1 g, 6.7 mmol) was added to a solution of dihydropyran **14** (0.830 g, 2.28 mmol) in dry THF (12 mL). The reaction mixture was stirred for 1 h at room temperature and quenched with saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (silica, 1% triethylamine in 75% ethyl acetate–hexanes) to give 0.544 g (2.17 mmol, 95%) of the dihydropyran **15**. $[\alpha]_D^{20}$ +185.4 (*c* 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.84 (m, 3H), 6.83 (s, 1H), 4.02 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.78 (m, 1H), 3.72 (m, 1H), 2.46 (m, 2H), 2.07–1.78 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 148.7, 147.5, 140.3, 132.1, 116.5, 112.9, 111.2, 107.8, 75.3, 65.1, 55.8, 55.7, 23.6, 22.4. FTIR (CH_2Cl_2), ν(cm^{-1}): 3498, 2998, 2932, 2838, 1638, 1518, 1250, 1142, 1026. HRMS (ESI^+) calcd for $C_{14}H_{18}NaO_4Si_1$ $(MNa)^+$ 273.1107, found 273.1103.

4.2.8. (S)-5-(3,4-Dimethoxyphenyl)-2-((E)-2-((S)-p-tolylsulfinyl)vinyl)-3,4-dihydro-2H-pyran (**16**)

A solution of dimethyl sulfoxide (0.12 mL, 1.7 mmol) in dichloromethane (0.5 mL) was added to a solution of oxalyl chloride (73 μL, 0.86 mmol) in 1 mL of dichloromethane at −78 °C. The mixture was stirred for 15 min and then a solution of alcohol **15** (0.10 g, 0.40 mmol) in dichloromethane (1.0 mL total with rinses) was added dropwise. After stirring for 20 min at −78 °C, triethylamine (0.36 mL, 2.6 mmol) was added dropwise, and, after 5 min, the reaction mixture was stirred at 0 °C for 15 min. HCl (3 M, 2.6 mL) was added and the mixture was extracted with dichloromethane. The organic layers were washed with water and saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, and concentrated. The crude aldehyde was used directly in the next step.

n-Butyllithium (2.45 M in hexanes, 0.25 mL, 0.61 mmol) was added to a solution of di-*iso*-propylamine (91 μL, 0.65 mmol) in THF (0.75 mL) and the mixture was stirred for 20 min at −20 °C. (*S*)-Methyl *p*-tolyl sulfoxide (0.100 g, 0.65 mmol) was added and then stirring was continued for 20 min at −20 °C. The solution was cooled to −78 °C and a solution of the aldehyde from the previous step (~0.40 mmol) in THF (1.2 mL total with rinses) was added dropwise. After 30 min, the cooling bath was removed and a solution of saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography (silica, 100% ethyl acetate containing 0.1% triethylamine) to provide 0.115 g (0.286 mmol, 72% over two steps) of the addition product as a mixture of diastereomers.

Chlorotriethylsilane (0.14 mL, 0.83 mmol) was added to a solution of the above product (0.115 g, 0.286 mmol) and imidazole (0.17 g, 2.5 mmol) in dichloromethane (1.7 mL). After stirring for 20 min at room temperature, the reaction mixture was diluted with dichloromethane and washed with 1 M hydrochloric acid, water, and saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate, concentrated, and dried in vacuum. The crude product was used in the next step without further purification.

n-Butyllithium (2.45 M in hexanes, 0.40 mL, 1.00 mmol) was added to a solution of di-*iso*-propylamine (0.16 mL, 1.14 mmol) in THF (2.0 mL) and the mixture was stirred for 20 min at −78 °C. A solution of the sulfoxides obtained in the previous step in THF (1.5 mL total with rinses) was added dropwise. After stirring for 15 min, the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride and the resultant mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (50–80% ethyl acetate–hexanes) to afford the desired vinyl sulfoxide **16** (61 mg, 0.159 mmol, 55% over two steps). $[\alpha]_D^{20}$ +247.8 (*c* 4.2, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.50 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=8.5 Hz, 2H), 6.81–6.77 (m, 4H), 6.63 (dd, *J*=15.0, 4.0 Hz, 1H), 6.51 (dd, *J*=15.0, 2.0 Hz, 1H), 4.61–4.58 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.49–2.36 (m, 5H), 2.19–2.14 (m, 1H), 1.89–1.81 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.0, 147.8, 142.0, 140.4, 139.9, 135.8, 135.3, 132.1, 130.3, 125.0, 116.8, 113.4, 111.4, 108.0, 73.4, 56.1, 56.0, 29.8, 27.4, 22.3, 21.6. FTIR (CH_2Cl_2), ν(cm^{-1}): 3662, 2925, 2852, 1639, 1517, 1249, 1045. HRMS (ESI^+) calcd for $C_{22}H_{24}NaO_4S$ $(M+Na)^+$ 407.1293, found 407.1295.

4.2.9. (S)-5-(3,4-Dimethoxyphenyl)-2-((E)-2-((R)-p-tolylsulfinyl)vinyl)-3,4-dihydro-2H-pyran (**17**)

Sulfoxide **17** was prepared by a four-step reaction sequence described above for **16**, starting from 0.100 g (0.40 mmol) of alcohol **15**, which furnished 75 mg (0.165 mmol, 49% over four steps) of the final product. $[\alpha]_D^{20}$ +10.1 (*c* 4.9, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.49 (d, *J*=8.0 Hz, 2H), 7.26 (d, *J*=8.0 Hz, 2H), 6.80–6.74 (m, 4H), 6.59 (dd, *J*1=15.0 Hz, *J*2=3.5 Hz, 1H), 6.51 (dd, *J*=15.0, 1.5 Hz, 1H), 4.66–4.62 (m, 1H), 3.86 (s, 6H), 2.59–2.35 (m, 5H), 2.19–2.13 (m, 1H), 1.88–1.80 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.0, 147.8, 142.1, 140.4, 139.9, 135.8, 135.2, 132.2, 130.3, 125.2, 115.9, 113.4, 111.3, 108.0, 73.3, 56.1, 56.0, 29.9, 27.4, 22.4, 21.6. FTIR (CH_2Cl_2), ν(cm^{-1}): 3661, 3050, 2924, 2851, 1639, 1518, 1464, 1249, 1141, 1046, 1027. HRMS (ESI^+) calcd for $C_{22}H_{24}O_4S$ $(M+Na)^+$ 407.1295, found 407.1293.

4.2.10. (S)-5-(3,4-Dimethoxyphenyl)-2-(2-(phenylthio)vinyl)-3,4-dihydro-2H-pyrans (Z-**18** and E-**18**)

Dimethylsulfoxide (0.47 mL, 6.62 mmol) was added to a solution of oxalyl chloride (0.28 mL, 3.31 mmol) in CH_2Cl_2 (12 mL) dropwise at −78 °C. The mixture was stirred at −78 °C for 15 min, and a solution of alcohol **15** (0.53 g, 2.12 mmol) in CH_2Cl_2 (4 mL total with rinses) was added dropwise. The resulting mixture was stirred for 25 min at −78 °C and then triethylamine (1.40 mL, 10 mmol) was added after 5 min, the reaction mixture was warmed to 0 °C, and stirred for 15 min. The resulting mixture was diluted with dichloromethane, washed with 1 M HCl, water, and brine, dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The residue (0.578 g) was used in the next step without further purification.

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 8.5 mL, 4.25 mmol) was added to a suspension of (phenylthiomethyl)-triphenylphosphonium chloride (1.80 g, 4.28 mmol) in THF (20 mL) dropwise at 0 °C and the mixture was stirred at 0 °C for 1 h. A solution of the aldehyde (0.578 g, 2.12 mmol) in THF (5 mL total with rinses) was added to the above yellow solution and the resulting mixture was stirred for 2 h at 0 °C, and quenched with saturated aqueous ammonium chloride. The aqueous layer was separated and extracted with ethyl acetate (30 mL×3), and the combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (silica, 20% ethyl acetate–hexanes) to give vinyl sufides **18** (0.691 g, 1.95 mmol,

92%) as a mixture of *E*- and *Z*-isomer (18:82). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39–7.37 (m, 2H), 7.34–7.31 (m, 3H), 7.27–7.25 (m, 1H), 6.87 (s, 1H), 6.86–6.82 (m, 3H), 6.53 (dd, *J*=16.0, 1.0 Hz, 1H, *E*-isomer), 6.43 (dd, *J*=9.5, 1.5 Hz, 1H, *Z*-isomer), 5.95–5.92 (m, 1H), 4.88–4.85 (m, 1H, *Z*-isomer), 4.49–4.46 (m, 1H, *E*-isomer), 3.90 (s, 3H, *Z*-isomer), 3.89 (s, 3H, *E*-isomer), 3.87 (s, 3H, *E*- and *Z*-isomer), 2.56–2.42 (m, 2H), 2.13–2.07 (m, 1H), 1.98–1.83 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.0, 147.7, 140.7, 140.5, 135.5, 132.6, 131.1, 130.8, 130.1, 129.6, 129.3, 127.2, 127.1, 126.9, 126.0, 116.8, 113.03, 113.00, 111.4, 108.0, 74.8, 72.4, 56.1, 56.0, 28.0, 27.5, 22.54, 22.48.

4.2.11. (1R,2S)-1-(3,4-Dimethoxyphenyl)-2-(phenylthio)cyclohex-3-enecarbaldehyde (**19**)

A mixture of *Z*-**18** and *E*-**18** (82:18, 50 mg, 0.141 mmol) was dissolved in 2.5 mL of 2-methoxyethanol freshly distilled from calcium hydride. The solution was degassed by applying vacuum at room temperature until bubbling was observed and then backfilling with argon after about 10 s. This process was repeated twice. The reaction flask was charged with thiophenol (0.8 μL, 7.8 μmol, 6 mol %) and AIBN (~1 mg), and the flask was sealed and heated at 115 °C for 24 h. After cooling to room temperature, the reaction mixture was concentrated on a rotary evaporator and the residue was purified by column chromatography to afford the requisite allylic sulfide **19** (35 mg, 0.987 mmol, 70%). $[\alpha]_D^{23}$ +378.7 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.32 (s, 1H), 7.49–7.46 (m, 2H), 7.32–7.24 (m, 3H), 6.82–6.78 (m, 2H), 6.68 (d, *J*=2.0 Hz, 1H), 6.12–6.08 (m, 1H), 5.76–5.73 (m, 1H), 4.30 (d, *J*=4.5 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.24–2.19 (m, 1H), 2.10–2.01 (m, 2H), 1.59–1.52 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 198.0, 149.2, 148.6, 135.4, 133.0, 130.0, 129.1, 129.4, 128.1, 126.1, 120.6, 111.2, 111.0, 58.5, 56.2, 56.0, 48.8, 25.2, 22.8. HRMS (ESI$^+$) calcd for $C_{21}H_{22}NaO_3S$ (M+Na)$^+$ 377.1189, found 377.1187.

4.2.12. ((1S,6S)-6-(3,4-Dimethoxyphenyl)-6-(2-methoxyvinyl)cyclohex-2-enyl)(phenyl)sulfane (**21**)

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 2.80 mL, 1.40 mmol) was added to a suspension of (methoxymethyl)-triphenylphosphonium chloride (0.480 g, 1.40 mmol) in THF (10 mL) dropwise at 0 °C and the mixture was stirred at 0 °C for 1 h. A solution of aldehyde **19** (0.250 g, 0.705 mmol) in THF (2 mL) was added to the above mixture, the resulting mixture was stirred for 2 h at room temperature, and then quenched with saturated ammonium chloride. The aqueous layer was separated and extracted with ethyl acetate (2×10 mL), and the combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (silica, 20% ethyl acetate–hexanes) to give **21** (*E*/*Z*=72:28, 0.258 g, 0.674 mmol, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.37 (m, 2H), 7.24–7.11 (m, 3H), 7.08–6.86 (m, 1H), 6.92 (s, 1H), 6.84–6.72 (m, 1H), 6.16 (d, *J*=13.0 Hz, 1H, *E*-isomer), 6.97 (m, 1H), 5.83 (d, *J*=7.7 Hz, 1H, Z-isomer), 5.63 (m, 1H), 4.83 (d, *J*=13.0 Hz, 1H, *E*-isomer), 4.57 (d, *J*=6.8 Hz, 1H, *Z*-isomer), 4.26 (m, 1H, *E*-isomer), 4.08 (m, 1H, *Z*-isomer), 3.85 (s, 3H), 3.83 (s, 3H), 3.42 (s, 3H, *Z*-isomer), 3.21 (s, 3H, *E*-isomer), 2.48 (m, 1H, *Z*-isomer), 2.27–1.81 (m, 3H), 1.70 (m, 1H, *E*-isomer). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.3, 148.2, 147.7, 147.6, 147.4, 147.2, 140.7, 138.8, 137.9, 137.8, 132.0, 131.0, 129.7, 129.3, 128.9, 128.8, 127.6, 127.0, 126.6, 126.4, 119.5, 119.1, 116.8, 111.6, 111.3, 111.2, 110.32, 110.26, 72.5, 59.9, 56.1, 56.0, 55.9, 55.5, 54.0, 46.5, 45.7, 32.9, 30.4, 27.5, 24.2, 23.3, 22.6. HRMS (ESI$^+$) calcd for $C_{23}H_{26}NaO_3S$ (M+Na)$^+$ 405.1487, found 405.1487.

4.2.13. (1S,4S)-4-(3,4-Dimethoxyphenyl)-4-(2-methoxyvinyl)cyclohex-2-enol (**23**)

A solution of freshly titrated dimethyldioxirane in acetone (0.073 M, 4.7 mL, 0.34 mmol) was added to a solution of vinyl methyl ethers **21** (0.130 g, 0.340 mmol) in acetone (2.0 mL) dropwise at −78 °C. After 5 min, two more portions of the DMDO solution (0.33 mL each) were added in 5 min intervals, until TLC indicated completion. The resulting mixture was warmed to room temperature, concentrated on a rotary evaporator, and dried under vacuum. The crude sulfoxide was used without further purification. HRMS (ESI$^+$) calcd for $C_{23}H_{26}NaO_4S$ (MNa)$^+$ 421.1450, found 421.1450.

The above crude product was dissolved in methanol (5.7 mL). Di-*iso*-propylamine (0.24 mL, 1.71 mmol) and trimethylphosphite (0.20 mL, 1.70 mmol) were added. The resulting mixture was stirred at room temperature for 25 h and then concentrated on a rotary evaporator. The residue was dried in vacuum and used in the next step without purification. Partial data for **23** after column chromatography (silica, 60% ethyl acetate–hexanes) (*E*/*Z*=3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.86 (m, 1H), 6.32 (d, *J*=12.9 Hz, 1H, *E*-isomer), 6.07 (d, *J*=10.0 Hz, 1H, *Z*-isomer), 5.97–5.85 (m, 1H), 5.79 (d, *J*=10.1 Hz, 1H), 4.98 (d, *J*=12.9 Hz, 1H, *E*-isomer), 4.54 (d, *J*=6.8 Hz, 1H), 4.27 (m, 1H, *E*-isomer), 4.25 (m, 1H, *Z*-isomer), 3.88 (s, 3H), 3.86 (s, 3H), 3.55 (s, 3H, *E*-isomer), 3.51 (s, 3H, *Z*-isomer), 2.25 (m, 1H, *Z*-isomer), 2.00–1.67 (m, 4H, *E*-isomer), 2.00–1.67 (m, 3H, *Z*-isomer).

4.2.14. 2-((1R,4S)-1-(3,4-Dimethoxyphenyl)-4-hydroxycyclohex-2-enyl)acetaldehyde (**24**)

p-Toluenesulfonic acid monohydrate (0.150 g, 0.789 mmol) was added to a solution of *E*/*Z*-vinyl ethers **23** from the previous reaction in 15 mL of acetone–water (15:1) at room temperature. After stirring at room temperature for 28 h, the reaction mixture was neutralized with solid sodium bicarbonate (0.4 g) to pH ~7 and concentrated. The residue was extracted with ethyl acetate (25 mL) and the organic layer was washed with water. The aqueous layer was extracted with ethyl acetate (3×10 mL), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (silica, 50%, 75, 90% ethyl acetate–hexanes) to give aldehyde **24** (80 mg, 0.290 mmol, 85% over three steps). $[\alpha]_D^{21}$ −106.2 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.58 (t, *J*=2.6 Hz, 1H), 6.84–6.79 (m, 3H), 6.10–6.06 (m, 2H), 4.18 (br s, 1H), 3.86 (m, 3H), 3.85 (m, 3H), 2.86 (dd, *J*=15.0, 2.6 Hz, 1H), 2.75 (dd, *J*=15.0, 2.6 Hz, 1H), 2.02 (ddd, *J*=14.0, 8.0, 4.5 Hz, 1H), 1.93 (br s, 1H), 1.87 (ddd, *J*=14.0, 6.0, 4.0 Hz, 1H), 1.71–1.64 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 202.6, 149.0, 147.8, 137.3, 135.0, 131.1, 119.0, 111.1, 110.0, 64.0, 56.1, 56.0, 54.5, 41.4, 33.1, 28.1. HRMS (ESI$^+$) calcd for $C_{16}H_{20}NaO_4$ (M+Na)$^+$ 299.1258, found 299.1259.

4.2.15. (−)-Joubertinamine

Methylamine hydrochloride (85 mg, 1.26 mmol) and sodium cyanoborohydride (76 mg, 1.21 mmol) were added to a solution of aldehyde **24** (50 mg, 0.180 mmol) in methanol (3.6 mL) at room temperature under argon. The resulting mixture was stirred at room temperature for 4 h and then quenched with 15 mL of 3 M aqueous sodium hydroxide. Chloroform (15 mL) was added, and the layers were separated, and the aqueous layer was extracted with chloroform (3×5 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (alumina [basic, activity I, particle size 0.063–0.200 mm], 2% triethylamine in 50% ethyl acetate–methanol) to give (−)-joubertinamine (42 mg, 0.144 mmol, 77%). $[\alpha]_D^{22}$ −77.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.81–6.76 (m, 3H), 6.01 (s, 2H), 4.13 (br t, *J*=4.5 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 2.53 (ddd, *J*=11.0, 10.0, 5.5 Hz, 1H), 2.40 (ddd, *J*=11.0, 9.5, 5.5 Hz, 1H), 2.36 (s, 3H), 1.99 (m, 1H) 1.92 (m, 2H), 1.78 (m, 1H), 1.63 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 148.7, 147.2, 139.0, 136.1, 130.0,

118.8, 110.7, 110.0, 64.2, 55.9, 55.8, 47.8, 41.8, 41.7, 36.4, 32.7, 28.4. FTIR (CH_2Cl_2), ν(cm^{-1}): 3660, 3309, 2933, 2853, 1588, 1516, 1464, 1259, 1146, 1027. HRMS (ESI^+) calcd for $C_{17}H_{26}NO_3$ $(M+H)^+$ 292.1888, found 292.1913.

4.2.16. (−)-Mesembrine

Activated manganese(IV) dioxide (Aldrich, 0.215 g, 2.47 mmol) was added to a solution of (−)-joubertinamine (18 mg, 0.062 mmol) in benzene (5 mL) and the mixture was stirred at room temperature for 24 h. The resulting suspension was filtered through a thin pad of aluminum oxide, washed thoroughly with methanol, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography (alumina [basic, activity I, particle size 0.063–0.200 mm], 100% ethyl acetate) to give (−)-mesembrine (14.5 mg, 0.050 mmol, 81%). $[\alpha]_D^{20}$ −61.6 (*c* 0.20, MeOH). ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 6.90 (m, 3H), 3.90 (s, 3H), 3.88 (s, 3H), 3.16 (m, 1H), 2.96 (t, *J*=3.2 Hz, 1H), 2.61 (d, *J*=3.4 Hz, 1H), 2.44 (m, 1H), 2.33 (s, 3H), 2.24–2.06 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 212.4, 149.1, 147.6, 140.3, 117.9, 111.1, 110.0, 70.4, 56.0, 55.9, 54.9, 47.5, 40.6, 40.1, 38.9, 36.2, 35.3. HRMS (ESI^+) calcd for $C_{17}H_{24}NO_3$ $(M+H)^+$ 290.1751, found 290.1756.

Acknowledgements

We are grateful to the NSF (CAREER, CHE-0836757) and the Department of Chemistry and Biochemistry, University of California, Santa Barbara, for financial support of this work. Partial funding was also provided by the ACS Petroleum Research Fund (43838-G1).

References and notes

1. (a) Smith, M. T.; Crouch, N.; Gericke, N.; Hirst, M. *J. Ethnopharmacol.* **1996**, *50*, 119–130; (b) Gericke, N. P.; VanWyk, B.-E. PCT Int. Appl., WO 9746234 CAN 128: 80030, 1997.
2. (a) Paul, T.; Malachowski, W. P.; Lee, J. *Org. Lett.* **2006**, *8*, 4007–4010; (b) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711–7714; (c) Chavan, S. P.; Khobragade, D. A.; Pathak, A. B.; Kalkote, U. R. *Tetrahedron Lett.* **2004**, *45*, 5263–5265; (d) Rigby, J. H.; Dong, W. *Org. Lett.* **2000**, *2*, 1673–1675; (e) Ogasawara, K.; Yamada, O. *Tetrahedron Lett.* **1998**, *39*, 7747–7750; (f) Langlois, Y.; Dalko, P. I.; Brun, V. *Tetrahedron Lett.* **1998**, *39* 8979–8982; (g) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675–1686; (h) Mori, M.; Kuroda, S.; Zhang, C.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263–3270; (i) Yoshimitsu, T.; Ogasawara, K. *Heterocycles* **1996**, *42*, 135–140; (j) Nemoto, H.; Tanabe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6785–6790; (k) Takano, S.; Samizu, K.; Ogasawara, K. *Chem. Lett.* **1990**, 1239–1242; (l) Kosugi, H.; Miura, Y.; Kanna, H.; Uda, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1409–1412; (m) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776–7778.
3. (a) Tam, N. T.; Cho, C.-G. *Org. Lett.* **2007**, *9*, 3391–3392; (b) Hoshino, O.; Ishizaki, M.; Sawaki, S.; Yuasa, M.; Umezawa. *Chem. Pharm. Bull.* **1988**, *36*, 3373–3380; (c) Jeffs, P. W.; Redfearn, R.; Wolfram, J. *J. Org. Chem.* **1983**, *48*, 3861–3863; (d) Sánchez, I. H.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *Tetrahedron Lett.* **1983**, *24*, 551–554; (e) Psotta, K.; Wiechers, A. *Tetrahedron* **1979**, *35*, 255–257; (f) Psotta, K.; Strelow, F.; Wiechers, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1063–1065; For synthesis of *O*-methyljoubertiamine and mesembrine, see: (g) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391–3396.
4. (a) Stivala, C.; Zakarian, A. *J. Am. Chem. Soc.* **2008**, *130*, 3774–3776; (b) Lu, C.-D.; Zakarian, A. *Org. Lett.* **2007**, *9*, 3161–3163; (c) Stivala, C. E.; Zakarian, A. *Tetrahedron Lett.* **2007**, *48*, 6845–6848.
5. (a) Pelc, M. J.; Zakarian, A. *Org. Lett.* **2005**, *7*, 1629–1631; (b) Pelc, M. J.; Zakarian, A. *Tetrahedron Lett.* **2006**, *47*, 7519–7523.
6. Büchi, G.; Powell, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 3126–3133.
7. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
8. (a) Taber, D. F.; Xu, M.; Hartnett, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 13121–13126; (b) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 295–304.
9. Noyori, R.; Morita, Y.; Suzuki, M. *J. Org. Chem.* **1989**, *54*, 1785–1787.
10. For a recent example, see: O'Doherty, G. A.; Harris, J. M. *Tetrahedron* **2001**, *57*, 5161–5171.
11. (a) Paquette, L. A.; Reddy, Y. R.; Haeffner, F.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 740–741; (b) Paquette, L. A.; Reddy, Y. R.; Vayner, G.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 10788–10794.
12. A review: Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219–225.
13. (a) Evans, D. A.; Andrews, G. C. *J. Am. Chem. Soc.* **1972**, *94*, 3672–3674; (b) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147–155.
14. Gardiner, J. M.; Bryce, M. R. *J. Org. Chem.* **1990**, *55*, 1261–1266.
15. Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263–8266.
16. Allingham, M. T.; Howard-Jones, A.; Murphy, P. J.; Thomas, D. A.; Caulkett, P. R. *Tetrahedron Lett.* **2003**, *44*, 8677–8680.