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Diastereoselective Construction of Quaternary Carbons Directed via Macrocyclic Ring Conformation: Formal Synthesis of (−)-Mesembrine

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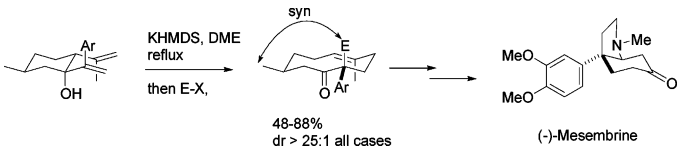

In this article, we report a highly diastereoselective new method for the generation of quaternary carbon centers through an anionic oxy-Cope/alkylation sequence where the diastereoselectivity is induced by the conformation of a macrocyclic tetrasubstituted enolate. The use of our methodology culminated in the formal total synthesis of (−)-mesembrine (**34**) in 11 steps from known starting materials.

Introduction

The task of constructing quaternary carbon centers has been and still is one of the most challenging problems faced in organic chemistry, particularly when it is necessary to synthesize these centers with high enantio- or diastereoselectivity. Quaternary carbon centers are prevalent throughout most classes of natural products and pharmaceutical agents; hence, it is to be expected that there are numerous ingenious methods that have been developed to selectively access this structural motif.[1] Despite these advances, the solution to this far-reaching problem has not been completely resolved.

One time-honored method used for the construction of quaternary centers is the alkylation of a tetrasubstituted enolate. Classically, the selectivity of this reaction can be achieved through the use of a chiral auxiliary or some other structural feature of the molecule that shields one face of the enolate from electrophilic attack, allowing the production of one diastereomer. Metal catalysis using chiral ligands has also been used to promote the diastereoselective addition of electrophiles to tetrasubstituted enolates.[1g]

During the course of our investigations into cascading pericyclic reactions, we became interested in how the conformation of the macrocyclic intermediates in these processes dictated the stereochemical outcome of the reactions.[2] Keeping true to this theme, we wondered whether or not macrocyclic conformation could be used to control the diastereoselectivity in other types of reactions, for example, the alkylation of tetrasubstituted enolates.

We thought that, if we could generate a chiral tetrasubstituted enolate embedded in a macrocycle that was conformationally constrained, we would be able to stereoselectively construct quaternary carbon centers upon the addition of various electrophiles.[3,4] To obtain high selectivity in this process, several criteria must be met. First, it is of paramount importance to control the geometry of the tetrasubstituted enolate. To this end,

(1) For recent reviews, see: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (b) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (c) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis;* Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (d) Ramon, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149. (e) Douglas, C. J.; Overmann, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (f) Barriault, L.; Denissova, I. *Tetrahedron* **2003**, *59*, 10105. (g) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (h) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (i) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *110*, 402.

(2) (a) Gauvreau, D.; Barriault, L. *J. Org. Chem.* **2005**, *70*, 1382. (b) Sauer, E. L. O.; Barriault, L. *J. Am. Chem. Soc.* **2004**, *126*, 8569. (c) Sauer, E. L. O.; Hooper, J.; Woo, T.; Barriault, L. *J. Am. Chem. Soc.* **2007**, *129*, 2112.

(3) Pioneering work of Still demonstrated that the conformation of medium and large macrocycles affords an effective vehicle in which the asymmetric synthesis of stereogenic centers can be achieved. See: (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (b) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186. (c) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493. (d) Still, W. *Curr. Trends Org. Synth., Proc. Int. Conf. 4th* **1983**, 233. (e) Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625. (f) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148. (g) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105.

(4) von Zezschwitz, P.; Voight, K.; Noltemeyer, M.; de Meijere, A. *Synthesis* **2000**, 1327.

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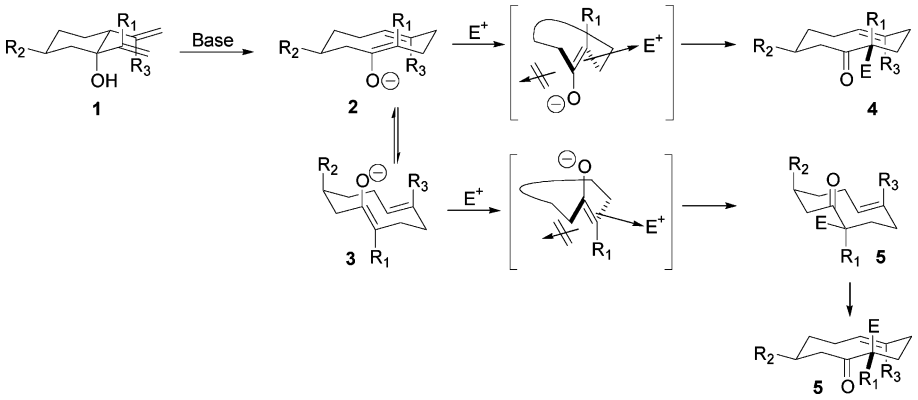
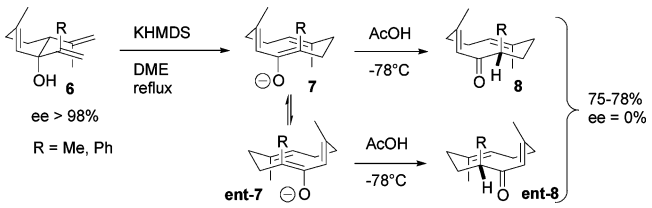
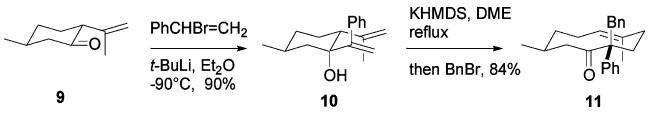
SCHEME 1



SCHEME 2



SCHEME 3



the anionic oxy-Cope rearrangement[5] was our method of choice to selectively generate the desired tetrasubstituted enolates. For instance, the anionic rearrangement of *trans*-1,2-divinylcyclohexanol **1** should afford, via a chairlike transition state, the corresponding *E*-enolate **2** (with respect to the macrocyclic ring) (Scheme 1).

Second, the peripheral addition of the electrophile must occur exclusively on one face of the enolate. Despite the fact that the macrocyclic backbone blocks the internal enolate face, the effectiveness of the chirality transfer in this process relies upon the preferential conformation of the macrocycle during the alkylation. Recently, we reported that the anionic oxy-Cope reaction of enantiomerically pure **6** (ee > 98%) gave, after protonation, the corresponding 10-membered ring **8** in its racemic form (Scheme 2).[2a] This suggests that the rotation barrier of the enolate moiety (i.e., the ring inversion of **7** → *ent*-**7**) might be a low-energy process that occurs before the protonation.

Assuming that the process is under thermodynamic control, one might suggest that a remote control element ($R_2 \neq H$) on framework **1** will favor enolate **2** over **3**. As a result, one might expect that, after the addition of the electrophile, the formation of ketone **4** should be preferred over **5**. In this article, we report a highly diastereoselective method for the construction of quaternary carbon centers using macrocyclic conformation as the control element and its application to the synthesis of (−)-mesembrine.

Results and Discussion

Our investigation began with isopulegone **9**, which is readily prepared in chiral or racemic form from commercially available citronellal (Scheme 3).[6] Alkylation with α-lithiostyrene gave 1,2-divinylcyclohexanol **10** in 90% yield as the major product.[7] The latter was then subjected to optimized anionic oxy-Cope rearrangement conditions to produce in situ the corresponding enolate that was trapped with benzyl bromide to afford macrocycle **11** in 84% yield as the sole diastereomer. The relative stereochemistry of macrocycle **11** was confirmed by X-ray crystallography.[8]

The formation of quaternary carbon centers using this methodology was extended to other electrophiles (Table 1). The use of allyl and propargyl halides gave the corresponding 10-membered ring macrocycles **13**−**15** in 72, 60, and 80% yields, respectively, as single diastereomers (entries 1−3). C-Alkylation with MOMCl provided macrocycle **16** in 71% yield (entry 4). The addition of a less reactive electrophile such as ethyl iodide resulted in diminished yields, as evident in the formation of **17** in 48% yield (entry 5).[9] The addition of the Davis oxaziridine resulted in the diastereoselective synthesis of the tertiary α-hydroxyketone **18** in 88% yield (entry 6).

Much to our surprise, a closer inspection of the alkylation products revealed that we unambiguously obtained the opposite diastereoselectivity than what was predicted, with electrophilic addition occurring syn with the distal methyl group. On the basis of the reaction mechanism depicted in Scheme 1, products resulting from an addition of the electrophile anti to the methyl were anticipated. To explain this, one can imagine that after the anionic oxy-Cope rearrangement, enolate **20** undergoes a rapid equilibration between conformers through a stepwise ring inversion (**20** → **21** → **22**) where the alkylation step takes place exclusively on the higher-energy ground-state conformer **22** to give ketone **23** (Scheme 4). This scenario is, however, not

(5) For a review, see: (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. For selected examples of anionic oxy-Cope of 1,2-divinylcyclohexanol, see: (b) Marvell, E. N.; Whalley, W. *Tetrahedron Lett.* **1970**, 509. (c) Macdonald, T. L.; Natalie, K. J., Jr.; Prasad, G.; Sawyer, J. S. *J. Org. Chem.* **1986**, *51*, 1124. (d) Kuwahara, S.; Mori, K. *Heterocycles* **1989**, *28*, 167. (e) Hauptmann, H.; Miihlbauer, G.; Walker, N. P. C. *Tetrahedron Lett.* **1986**, *27*, 1315. (f) Kuwahara, S.; Mori, K. *Tetrahedron* **1990**, *46*, 8075. (g) Kuroda, C.; Hirota, H.; Takahashi, T. *Chem. Lett.* **1982**, 249. (h) Kuroda, C.; Nakamura, T.; Hirota, H.; Enomoto, E.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 146. (i) Clive, D. L. J.; Russell, C. G.; Suri, S. C. *J. Org. Chem.* **1982**, *47*, 1632

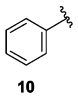
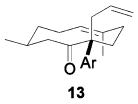
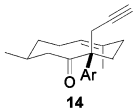
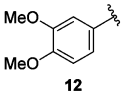
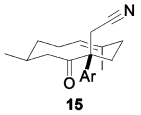
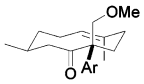
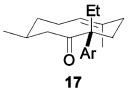
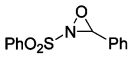
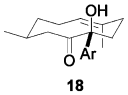
(6) Corey, E. J.; Ensley, H. E.; Suggs, J. W. *J. Org. Chem.* **1976**, *41*, 380.

(7) The relative configuration of **10** was established without ambiguity by COSY and NOESY experiments. See the Supporting Information.

(8) For an ORTEP view of **11**, see the Supporting Information.

(9) Other electrophiles such as aldehydes and α,β-unsaturated aldehydes or ketones were found to be unreactive under these reaction conditions.

TABLE 1. Scope of the Anionic oxy-Cope/Enolate Trapping Sequence

Entry	Ar	R-X	Product	Yield (%)[a]
1	 **10**		 **13**	72
2	 **10**		 **14**	60[b]
3	 **12**		 **15**	80
4	 **10**		 **16**	71
5	 **10**	Et—I	 **17**	48
6	 **10**		 **18**	88

[a] In all cases, only one diastereomer was observed (dr > 25:1). This was established by ^{1}H NMR of the crude reaction mixture. [b] This product was characterized by derivatization to the acid-catalyzed transannular ene reaction adduct due to extreme line broadening of the signals in the NMR spectra of the macrocycle. NOESY analysis of the ene reaction product further confirmed the relative stereochemistry of the newly generated quaternary center (see Supporting Information).

consistent with a thermodynamic process. Alternatively, one can suggest that the unexpected selectivity could be the result of the electrophile addition on the *Z*-enolate **25**. The latter can be generated via two distinct pathways: (1) directly from the anionic oxy-Cope reaction of **19** passing through a boatlike transition state or (2) from an isomerization of the *E* enolate **20**.

To gain more insight in the reaction mechanism, a thermal oxy-Cope was performed on the silylenol ether **26** (Scheme 5). After being heated at 220 °C in degassed toluene for 1 h using microwaves, the corresponding *E*-enol ether **27** was isolated in 15% yield as the sole isomer along with **26** (75%).[10] This is in agreement with previous findings where we demonstrated that swiveling tetrasubstituted enols in a 10-membered ring is not possible.[2b,c] This rules out the first pathway and strongly suggests that, under basic conditions, a thermodynamically more stable enolate is obtained via a complete isomerization of the *E*-enolate **20**. This is supported by the fact that the anionic rearrangement of **10** under standard conditions followed by an enolate trapping with TMSCl gave exclusively the *Z*-silyl enol ether in 80% yield. This isomerization may be possible through several manifolds including, but not limited to, a carbanion inversion (**29** → **30**) if the enolate exists with the majority of the charge residing on the enolate carbon as opposed to the oxygen (Scheme 6). One might also consider a rotation of the C1−C2 bond (**29** → **25**) in lieu of carbanion inversion as the pathway to obtain **25**.

This approach represents an interesting and conceptually unique entry for the asymmetric construction of quaternary centers. We then decided to test our methodology in the arena of total synthesis, which would also serve to further confirm the absolute stereoselectivity of the process. One can imagine dividing macrocycle **23** (R = Ar) in half to liberate the α,α′-disubstituted aryl acetic acid derivative **31** (Scheme 7). This subunit of the macrocycle is a ubiquitous structural motif and can serve as a building block for the enantioselective synthesis of natural and non-natural products. For example, the carbon skeleton of **31** is found embedded (in blue) in the carbon frameworks of medicinally important compounds such as galanthamine **32**,[11] morphine **33**,[12] mesembrine **34**,[13] and a phosphorodiesterase-4 inhibitor named Ariflo **35**.[14]

We selected natural (−)-mesembrine (**34**) as a synthetic target to quickly validate our quaternary carbon center forming process. (−)-Mesembrine **34** is an alkaloid isolated from the plant *Sceletium tortuosum*, which has been used by the indigenous population of the Kalahari Desert for its stimulant properties. Recently, Gericke and VanWyk reported that (−)-mesembrine displays nanomolar inhibition of serotonin reuptake.[15] A continuing interest in this natural product arises not from an intriguing biological activity but from the fact that it is a relatively simple structure that contains a quaternary carbon center, essentially making it a test piece for methodologies that are used to generate quaternary centers.[16,17]

Our efforts began by exposing (−)-isopulegone **9** to the lithium anion of **36**,[18] providing **37** in 59% yield along with a 26% recovery of the starting ketone **9** (Scheme 8). As expected, the anionic oxy-Cope/alkylation sequence worked nicely, affording **38** as a single isomer (dr > 25:1). Having successfully constructed the required quaternary center found in (−)-mesembrine (**34**), we were ready to complete the synthesis. Formation of the α-hydroxyketone of **38** followed by reduction

(10) The oxy-Cope reaction of **26** proved to be a reversible process. In fact, submission of **27** to the reaction condition gave back the same ratio of **26** and **27**.

(11) For a recent review of the synthesis and pharmacology of galanthamine, see: Marco-Contelles, J.; Carreiras, M. D.; Rodriguez, C.; Villarroya, M.; Garcia, A. G. *Chem. Rev.* **2006**, *106*, 116.

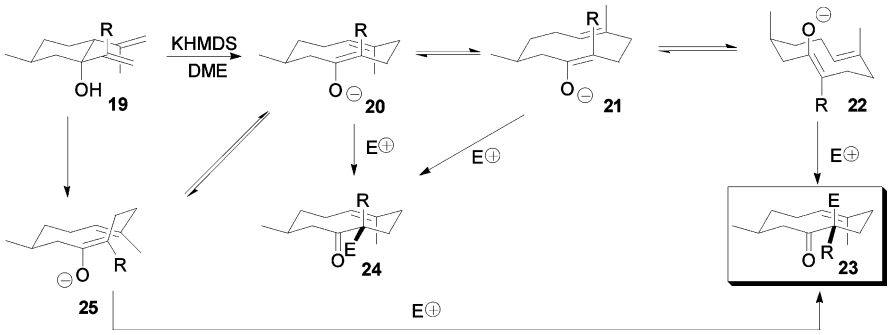
(12) For a review on morphine synthesis, see: (a) Zezula, J.; Hudlicky, T. *Synlett* **2005**, 388. For more recent syntheses, see: (b) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Org. Lett.* **2006**, *8*, 5311. (c) Parker, K. A.; Fokas, D. *J. Org. Chem.* **2006**, *71*, 449. (d) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785.

(13) For isolation and structure elucidation, see: (a) Popelak, A.; Haack, E.; Lettenbauer, G.; Spingler, H. *Naturwissenschaften* **1960**, *47*, 156. (b) Smith, E.; Hosansky, N.; Shamma, M.; Moss, J. B. *Chem. Ind.* **1961**, 402.

(14) Christensen, S. B.; Guider, A.; Forster, C. J.; Gleason, J. G.; Bender, P. E.; Karpinski, J. M.; DeWolf, W. E., Jr.; Barnette, M. S.; Underwood, D. C.; Griswold, D. E.; Cieslinski, L. B.; Burman, M.; Bochnowicz, S.; Osborn, R. R.; Manning, C. D.; Grous, M.; Hillegas, L. M.; Bartus, J. O.; Ryan, M. D.; Eggleston, D. S.; Haltiwanger, R. C.; Torphy, T. J. *J. Med. Chem.* **1998**, *41*, 821.

(15) Gericke, N. P.; VanWyk, B.-E. PCT Int. Appl., WO 9746234 CAN 128:80030, 1997.

SCHEME 4



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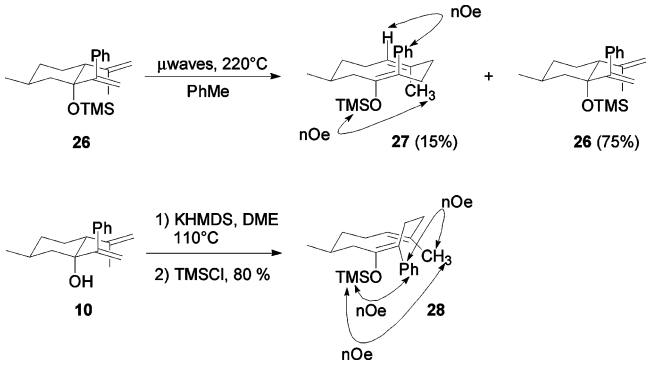

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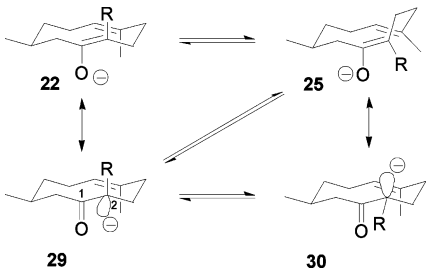
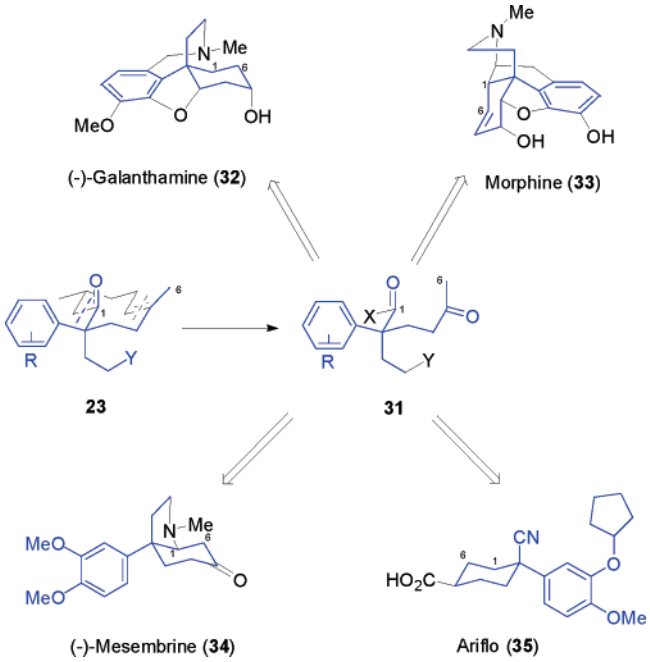


SCHEME 7



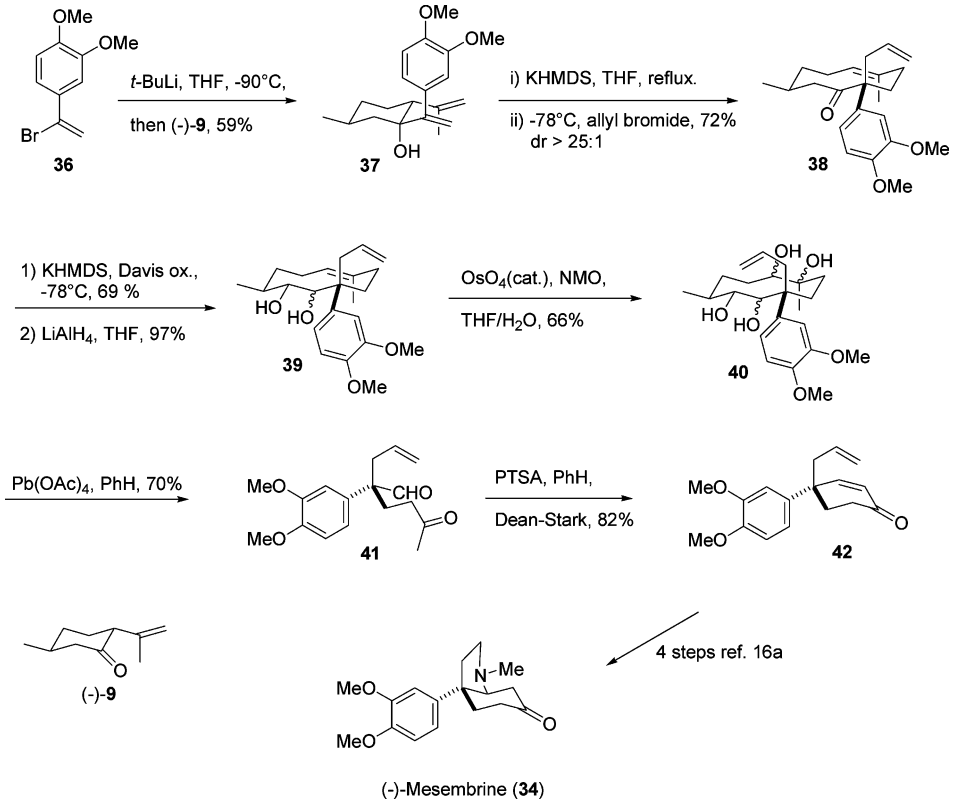
of the ketone with $LiAlH_4$ to give diol **39** proceeded smoothly. Chemoselective dihydroxylation of the more electron-rich double bond of **39** followed by cleavage of the bis-diol **40** by treatment with $Pb(OAc)_4$ afforded **41** in 70% yield, which was perfectly situated to undergo an intramolecular acid-catalyzed aldol condensation, ultimately yielding cyclohexenone **42** in 82% yield. At this point, the generation of cyclohexenone **42** constitutes a formal total synthesis of (−)-mesembrine (**34**).

Cyclohexanone **42** has identical spectra and optical rotation to the same material generated by Taber and He in their 2005 synthesis of (−)-mesembrine,[16a] which is available from **42** in four steps according to those protocols. Thus, we have developed

(16) For synthesis of (−)-mesembrine, see: (a) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711. (b) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143. (c) Ogasawara, K.; Kamikudo, T. *Chem. Commun.* **1998**, 783. (d) Ogasawara, K.; Yamada, O. *Tetrahedron Lett.* **1998**, *39*, 7747. (e) Langlois, Y.; Dalko, P. I.; Brun, V. *Tetrahedron Lett.* **1998**, *39*, 8979. (f) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. (g) Mori, M.; Kuroda, S.; Zhang, C.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263. (h) Yoshimitsu, T.; Ogasawara, K. *Heterocycles* **1996**, *42*, 135. (i) Nemoto, H.; Tanabe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6785. (j) Nemoto, H.; Tanabe, T.; Fukumoto, K. *Tetrahedron Lett.* **1994**, *35*, 6499. (k) Takano, S.; Samizu, K.; Ogasawara, K. *Chem. Lett.* **1990**, 1239. (l) Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479. (m) Strauss, H. F.; Wiechers, A. *Tetrahedron Lett.* **1979**, 4495. For synthesis of (+)-mesembrine, see: (n) Paul, T.; Malachowski, W. P.; Lee, J. *Org. Lett.* **2006**, *8*, 4007. (o) Kosugi, H.; Miura, Y.; Kanna, H.; Uda, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1409. (p) Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1992**, *33*, 6999. (q) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776. (r) Yamada, S.-I. *Tetrahedron Lett.* **1971**, *16*, 1133.

(17) For racemic synthesis of mesembrine, see: (a) Chavan, S. P.; Khobragade, D. A.; Pathak, A. B.; Kalkote, U. R. *Tetrahedron Lett.* **2004**, *45*, 5263. (b) Kulkarni, M. G.; Rasne, R. M.; Davawala, S. I.; Doke, A. K. *Tetrahedron Lett.* **2002**, *43*, 2297. (c) Rigby, J. H.; Dong, W. *Org. Lett.* **2000**, *2*, 1673. (d) Rajagopalan, P. *Tetrahedron Lett.* **1997**, *38*, 1893. (e) Michael, J. P.; Howard, A. S.; Katz, R. B.; Zwane, M. I. *Tetrahedron Lett.* **1992**, *33*, 6023. (f) Bauermeister, S.; Gouws, I. D.; Strauss, H. F.; Venter, E. M. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 561. (g) Parkinson, C. J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1055. (h) Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831. (i) Livinghouse, T.; Hackett, S. *J. Org. Chem.* **1986**, *51*, 1629. (j) Gramain, J.-C.; Remuson, R. *Tetrahedron Lett.* **1985**, *26*, 4083. (k) Sanchez, I. H.; de Jesus Soria, J.; Larraza, M. I.; Flores, H. J. *Tetrahedron Lett.* **1983**, *24*, 551. (l) Jeffs, P. W.; Redfearn, R.; Wolfram, J. *J. Org. Chem.* **1983**, *48*, 3861. (m) Pinnick, H. W.; Kochlar, K. S. *Tetrahedron Lett.* **1983**, *24*, 4785. (n) Keck, G. E.; Webb, R. R. *J. Org. Chem.* **1982**, *47*, 1302. (o) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391. (p) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2579. (q) Stevens, R. V.; Lesko, P. M.; Lapalme, R. *J. Org. Chem.* **1975**, *40*, 3495. (r) Keely, S. L.; Tahk, F. C. *J. Am. Chem. Soc.* **1968**, *90*, 5584. (s) Rodriguez, H. R.; Shamma, M. *Tetrahedron* **1968**, 6583. (t) Stevens, R. V.; Wentland, M. P. *J. Am. Chem. Soc.* **1968**, *90*, 5580. (u) Kugita, H.; Oh-ishi, T. *Tetrahedron Lett.* **1968**, 5445. (v) Curphey, T. J.; Kim, H. L. *Tetrahedron Lett.* **1968**, 1441. (w) Rodriguez, H. R.; Shamma, M. *Tetrahedron Lett.* **1965**, 4847.

SCHEME 8



a novel route to (−)-mesembrine (**34**) in 11 steps from readily available (−)-isopugelone **9**. While this is not the shortest synthesis to date, it illustrates how our conceptually unique entry to the quaternary carbon motif can be applied to the total synthesis of natural products.

Conclusion

In conclusion, we have developed a novel method for the diastereoselective generation of quaternary carbon centers through an anionic oxy-Cope/alkylation sequence where the diastereoselectivity is directed by the conformation of the macrocycle generated in the anionic oxy-Cope step of the reaction. We discovered that a facile isomerization of the E-tetrasubstituted enolate through a carbanion inversion or carbonyl rotation occurred to give the thermodynamically more stable *Z*-enolate. While the isomerization mechanism is not completely understood, we can reliably generate chiral carbon centers in a high diastereoselectivity with the use of an appropriate optically pure starting material. The use of our methodology culminated in the formal total synthesis of (−)-mesembrine (**34**) in 11 steps from known starting materials. Currently, DFT calculations on this isomerization mechanism will be performed, and the results will be reported in due course.

Experimental Section

10. (±)-(1*R*,2*R*,5*S*)-5-Methyl-1-(1-phenylvinyl)-2-(prop-1-en-2-yl)cyclohexanol. To a solution of α-bromostyrene (0.34 mL g, 2.64 mmol) in Et_2O (10 mL) cooled to −90 °C was added *t*-BuLi (1.70 M, 2.50 mL, 4.21 mmol), and the resulting solution was stirred at −90 °C for 35 min. To this mixture was added a solution of ketone **9** (100.0 mg, 0.66 mmol) in Et_2O (2 mL) by cold cannulation, and the resulting solution was stirred at −90 °C for 0.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (40 mL) followed by warming to room temperature. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% EtOAc/hex) afforded **10** (152.1 mg, 0.594 mmol, 90%) as a yellow oil. ^{1}H NMR (C_6D_6, 300 MHz): δ 7.35−7.32 (m, 2H), 7.17−7.05 (m, 3H), 5.34 (d, J = 1.6 Hz, 1H), 5.03 (d, J = 1.6 Hz, 1H), 4.93−4.91 (m, 2H), 2.25 (dd, J = 12.9 Hz, J = 3.5 Hz, 1H), 1.93 (dddd, J = 12.6 Hz, J = 12.6 Hz, J = 12.6 Hz, J = 3.1 Hz, 1H), 1.84 (s, 3H), 1.86−1.69 (m, 1H), 1.64−1.44 (m, 3H), 1.32−1.23 (m, 2H), 0.80−0.66 (m, 1H), 0.76 (d, J = 6.6 Hz, 3H). ^{13}C NMR (C_6D_6, 75 MHz): δ 157.4 (C_{QUAT}), 148.4 (C_{QUAT}), 142.4 (C_{QUAT}), 129.3 (CH), 129.3 (CH), 127.6 (CH), 127.6 (CH), 127.3 (CH), 114.3 (CH_2), 113.5 (CH_2), 76.8 (C_{QUAT}), 51.5 (CH), 49.4 (CH_2), 35.1 (CH_2), 28.8 (CH_2), 27.8 (CH), 23.9 (CH_3), 22.5 (CH_3). IR (neat): ν_{max} 3561 (b), 3476 (b), 3079 (w), 2984 (s), 2924 (s), 2867 (w), 2843 (w), 1636 (m), 1597 (w), 1571 (w), 1491 (m), 1454 (w), 1441 (m). HRMS (EI): calcd for $C_{18}H_{24}O$, 256.1827; found, 256.1831.

General Procedure for the Anionic oxy-Cope Reaction/Enolate Trapping Sequence. Alcohol **10** (1 equiv) was dissolved in benzene (0.1 M) and concentrated under reduced pressure three times to remove water and then dried under high vacuum for 1 h. The compound was then dissolved in DME (0.1 M), and to this was added a solution of KHMDS (2−3 equiv) in DME (0.4 M). The resulting mixture was heated at reflux for 15 min, after which it was cooled to room temperature and then −78 °C. To the cooled solution was then added the electrophile (2 equiv), and the mixture was stirred at −78 °C for 30 min. The reaction was quenched by the addition of water followed by warming to room temperature. The layers were separated, and the aqueous phase was extracted with Et_2O (3×). The organic layers were combined, dried over

(18) Vinyl bromide **36** was easily prepared from commercially available 3,4-dimethoxybenzaldehyde in three steps. See: (a) Rosiak, A.; Christoffers, J. *Synlett* **2006**, 1434. (b) Rosiak, A.; Wolfgang, F.; Christoffers, J. *Eur. J. Org. Chem.* **2006**, *17*, 4044.

$MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography.

11. (±)-(*E*,2*S*,9*S*)-2-Benzyl-5,9-dimethyl-2-phenylcyclodec-5-enone 11. Follow general procedure: alcohol **10** (236.5 mg, 0.919 mmol), KHMDS (367.0 mg, 1.84 mmol), and benzyl bromide (distilled twice over CaH_2, 0.22 mL, 1.84 mmol). Flash chromatography (2% EtOAc/hex) afforded **11** (266.1 mg, 0.772 mmol, 84%) as light brown crystals. This compound was then recrystallized from a mixture of hexanes and CH_2Cl_2, affording white crystals that were used for X-ray diffraction analysis. Mp: 141−144 °C. ^{1}H NMR (C_6D_6, 300 MHz): δ 7.08−6.95 (m, 8H), 6.70−6.69 (m, 2H), 5.27 (d, J = 9.2 Hz, 1H), 3.51−3.42 (m, 1H), 3.28 (d, J = 13.2 Hz, 1H), 3.08 (dd, J = 7.7 Hz, J = 17.9 Hz, 1H), 2.77−2.68 (m, 1H), 2.58−2.50 (m, 1H), 2.35−2.30 (m, 1H), 2.25−2.12 (m, 1H), 1.97−2.12 (m, 2H), 1.74 (d, J = 12.5 Hz, 1H), 1.63 (d, J = 15.5 Hz, 1H), 1.56 (s, 3H), 1.24−1.09 (m, 2H), 0.88 (d, J = 7.1 Hz, 3H). ^{13}C NMR (C_6D_6, 75 MHz): δ 210.0 (C_{QUAT}), 137.9 (C_{QUAT}), 137.2 (C_{QUAT}), 130.5 (CH), 128.8 (CH), 128.3 (CH), 127.8 (CH), 127.2 (CH), 126.3 (CH), 58.1 (C_{QUAT}), 49.5 (CH_2), 39.3 (CH_2), 37.6 (CH_2), 36.2 (CH_2), 32.5 (CH_2), 27.9 (CH_3), 27.7 (CH_2), 24.7 (CH_3), 23.9 (CH), 15.5 (CH). IR (neat): ν_{max} 3058 (w), 3028 (w), 3028 (m), 2951 (br), 2915 (s), 2865 (s), 1696 (s), 1600 (w), 1496 (m), 1445 (m), 1409 (w), 1358 (w). HRMS (EI): calcd for $C_{25}H_{30}O$, 346.2297; no M^+ observed.

13. (±)-(*E*,2*S*,9*S*)-2-Allyl-5,9-dimethyl-2-phenylcyclodec-5-enone. Follow general procedure: alcohol **10** (75.0 mg, 0.293 mmol), KHMDS (175.0 mg, 0.878 mmol), allyl bromide (distilled twice over CaH_2, 0.05 mL, 0.585 mmol) in DME. Flash chromatography (5% EtOAc/hex) afforded **13** (62.2 mg, 0.210 mmol, 72%) as a colorless oil. ^{1}H NMR (d_6-acetone, 500 MHz): δ 7.35 (d, J = 7.8 Hz, 2H), 7.28 (dd, J = 7.8, 7.8 Hz, 2H), 7.16 (dd, J = 7.8, 7.8 Hz, 1H), 5.49 (d, J = 10.0 Hz, 1H), 5.30−5.25 (m, 1H), 5.17 (d, J = 17.1 Hz, 1H), 4.93 (d, J = 10.0 Hz, 1H), 3.30 (dd, J = 17.8, 7.8 Hz, 1H), 3.25−3.17 (m, 2H), 2.86−2.82 (m, 2H), 2.40 (dd, J = 12.7, 12.7 Hz, 1H), 2.17−2.04 (m, 4H), 1.95 (dd, J = 24.2, 14.2 Hz, 1H), 1.71 (d, J = 13.7 Hz, 1H), 1.47 (s, 3H), 1.34 (dd, J = 12.9, 10.7 Hz, 1H), 0.94 (d, J = 7.1 Hz, 3H). ^{13}C NMR (d_6-acetone, 125 MHz): δ 210.2 (C_{QUAT}), 146.3 (C_{QUAT}), 138.4 (CH), 135.4 (CH), 129.6 (CH), 128.2 (CH), 127.5 (CH), 118.5 (CH_2), 57.2 (C_{QUAT}), 49.3 (CH_2), 38.7 (CH_2), 38.6 (CH_2), 36.5 (CH2), 34.8 (CH_2), 29.1 (CH_3), 28.7 (CH_2), 25.8 (CH_3), 16.9 (CH). IR (neat): ν_{max} 3058 (w), 2951 (m), 2913 (m), 2865 (m), 1696 (s), 1637 (w), 1594 (w), 1497 (w), 1444 (m), 1410 (w), 1379 (w), 1359 (w), 1168 (w), 1133 (m), 1093 (m), 1027 (w), 1003 (w), 912 (m), 862 (w), 699 (s). HRMS (EI): calcd for $C_{21}H_{28}O$, 296.2140; found, 296.2112.

14. (±)-(*E*,2*S*,9*S*)-5,9-Dimethyl-2-phenyl-2-(prop-2-ynyl)cyclodec-5-enone. Follow general procedure: alcohol **10** (72.0 mg, 0.280 mmol), KHMDS (168.0 mg, 0.842 mmol), propargyl bromide (0.06 mL, 0.541 mmol). Flash chromatography (5% EtOAc/hex) afforded **14** (49.8 mg, 0.169 mmol, 60%) as a colorless oil. Proton and carbon spectra not interpreted because of severe line broadening. Any heating resulted in decomposition of the material. IR (neat): ν_{max} 3295 (m), 3095 (w), 3060 (w), 3021 (w), 2952 (m), 2927 (m), 2863 (m), 2115 (w), 1696 (s), 1598 (w), 1579 (w), 1498 (m), 1444 (s), 1413 (w), 1382 (w), 1363 (m), 1316 (w), 1301 (w), 1247 (w), 1197 (w), 1127 (m), 1081 (w), 1050 (w), 954 (w), 696 (s). HRMS (EI): calcd for $C_{21}H_{26}O$, 294.1983; found, 294.1929.

Protocol for Ene Reaction and Characterization: 14ene. (±)-(4*S*,4a*R*,6*S*,8a*R*)-Decahydro-6-methyl-1-methylene-4-phenyl-4-(prop-2-ynyl)naphthalen-4a-ol. To a solution of **14** (24.9 mg, 0.0846 mmol) in $CHCl_3$ (4 mL) was added PTSA (1.6 mg, 0.00842 mmol), and the mixture was stirred at room temperature for 19 h. The reaction was then quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% EtOAc/hex) afforded **14ene** (19.1 mg, 0.0649 mmol, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49 (dd, J = 8.5, 1.0 Hz, 2H), 7.37 (dd, J = 8.5, 7.7 Hz, 2H), 7.29−7.26 (m, 1H), 4.98 (d, J = 1.5 Hz, 1H), 4.75 (d, J = 1.2 Hz, 1H), 3.15 (dd, J_{ab} = 17.1 Hz, J = 2.2 Hz, 1H), 3.07 (ddd, J_{ab} = 17.1 Hz, J = 2.4, 2.2 Hz, 1H), 2.61−2.55 (m, 1H), 2.48−2.38 (m, 2H), 2.27−2.25 (m, 1H), 2.10−2.06 (m, 1H), 1.83 (dd, J = 2.7, 2.7 Hz, 1H), 1.75−1.61 (m, 4H), 1.22 (bs, 1H), 1.17−1.14 (m, 1H), 1.08−1.03 (m, 1H), 0.92−0.84 (m, 1H), 0.77 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.3 (C_{QUAT}), 140.7 (C_{QUAT}), 129.4 (CH), 127.8 (CH), 126.8 (CH), 109.0 (CH_2), 81.7 (C_{QUAT}), 76.0 (C_{QUAT}), 71.0 (CH), 50.1 (C_{QUAT}), 44.1 (CH), 41.0 (CH_2), 34.4 (CH_2), 32.2 (CH_2), 31.2 (CH_2), 27.5 (CH), 25.1 (CH_2), 22.5 (CH_3), 21.7 (CH_2). IR (neat): ν_{max} 3565 (b), 3307 (m), 3091 (w), 3060 (w), 3017 (w), 2948 (s), 2926 (s), 2866 (m), 2115 (w), 1640 (w), 1598 (w), 1517 (w), 1498 (m), 1444 (m), 1409 (w), 1343 (w), 1312 (w), 1285 (w), 1262 (w), 1235 (w), 1185 (w), 1162 (m), 1131 (w), 1096 (w), 1069 (w), 1023 (w), 942 (w), 891 (m), 811 (w), 772 (w), 749 (w), 698 (s). HRMS (EI): calcd for $C_{21}H_{26}O$, 294.1984; found, 294.1977.

15. (±)-2-((*E*,1*S*,8*S*)-1-(3,4-Dimethoxyphenyl)-4,8-dimethyl-1-oxocyclodec-4-enyl)acetonitrile. Follow general procedure: alcohol **12** (235.1 mg, 0.743 mmol), KHMDS (444.6 mg, 2.23 mmol), and bromoacetonitrile (0.10 mL, 1.50 mmol). Flash chromatography (5% EtOAc/hex) afforded **15** (219.9 mg, 0.594 mmol, 80%) as a yellow oil. ^{1}H NMR (d_6-DMSO, 500 MHz): δ 6.92−6.91 (m, 2H), 6.89−6.87 (m, 1H), 5.51 (d, J = 8.7 Hz, 1H), 3.85 (d, J_{ab} = 16.7 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.63 (d, J_{ab} = 17.1 Hz, 1H), 2.93 (dd, J = 18.1, 8.0 Hz, 1H), 2.86 (dd, J = 13.1, 13.1 Hz, 1H), 2.29 (dd, J = 13.1, 13.1 Hz, 1H), 2.08−1.91 (m, 6H), 1.65−1.62 (m, 1H), 1.39 (s, 3H), 1.27−1.20 (m, 1H), 0.89 (d, J = 7.0 Hz, 3H). ^{13}C NMR (d_6-DMSO, 125 MHz): δ 206.0 (C_{QUAT}), 148.4 (C_{QUAT}), 147.9 (C_{QUAT}), 136.2 (C_{QUAT}), 134.9 (C_{QUAT}), 127.0 (CH), 118.7 (CH), 118.6 (C_{QUAT}), 111.5 (CH), 110.6 (CH), 55.7 (CH_3), 55.4 (CH_3), 53.8 (C_{QUAT}), 47.2 (CH_2), 36.5 (CH_2), 35.7 (CH_2), 34.6 (CH_2), 27.4 (CH), 26.9 (CH_2), 24.4 (CH_3), 22.7 (CH_2), 15.8 (CH_3). IR (neat): ν_{max} 2956 (m), 2874 (m), 2854 (w), 2252 (w), 1696 (s), 1602 (w), 1583 (w), 1518 (s), 1457 (m), 1442 (m), 1414 (w), 1359 (w), 1320 (w), 1260 (s), 1230 (m), 1183 (w), 1144 (m), 1129 (m), 1050 (m), 1023 (s), 937 (w), 925 (w), 870 (w), 823 (w), 800 (w), 757 (w). HRMS (EI): calcd for $C_{22}H_{29}NO_3$, 355.2147; found, 355.2138.

16. (±)-(*E*,2*S*,9*S*)-2-Methoxymethyl-5,9-dimethyl-2-phenylcyclodec-5-enone. Follow general procedure: alcohol **10** (99.4 mg, 0.388 mmol), KHMDS (232.0 mg, 1.16 mmol), and chloromethyl methyl ether (0.06 mL, 0.790 mmol). Flash chromatography (5% EtOAc/hex) afforded **16** (82.7 mg, 0.275 mmol, 71%) as a yellow solid. The solid was recrystallized from a mixture of hexanes and CH_2Cl_2, affording white crystals that were used for X-ray diffraction analysis. Mp: 100−101 °C. ^{1}H NMR (C_6D_6, 300 MHz): δ 7.44−7.42 (m, 2H), 7.31−7.10 (m, 2H), 7.06−7.01 (m, 1H), 5.18 (d, J = 10.5 Hz, 1H), 3.93 (s, 2H), 3.03 (s, 3H), 2.92−2.84 (m, 1H), 2.62−2.53 (m, 1H), 2.32−2.27 (m, 2H), 2.17−2.13 (m, 2H), 1.96−1.83 (m, 2H), 1.83−1.77 (m, 1H), 1.61 (s, 3H), 1.61−1.55 (m, 1H), 1.02−0.97 (m, 1H), 0.77 (d, J = 6.6 Hz, 3H). ^{13}C NMR (C_6D_6, 75 MHz): δ 206.6 (C_{QUAT}), 143.9 (C_{QUAT}), 138.4 (C_{QUAT}), 128.4 (CH), 127.4 (CH), 127.0 (CH), 126.6 (CH), 73.2 (CH_2), 59.1 (CH_3), 58.0 (C_{QUAT}), 49.5 (CH_2), 38.4 (CH_2), 36.5 (CH_2), 36.0 (CH_2), 28.0 (CH_2), 27.8 (CH_3), 25.2 (CH_3), 16.5 (CH). IR (neat): ν_{max} 2951 (s), 2919 (br), 2870 (s), 2811 (w), 1696 (s), 1559 (w), 1492 (m), 1455 (m), 1443 (m), 1409 (w), 1376 (w), 1355 (w). HRMS (EI): calcd for $C_{20}H_{28}O_2$, 300.2089; found, 300.2086.

17. (±)-(*E*,2*R*,9*S*)-2-Ethyl-5,9-dimethyl-2-phenylcyclodec-5-enone. Follow general procedure: alcohol **10** (157 mg, 0.61 mmol), KHMDS (245 mg, 1.22 mmol), and freshly distilled iodoethane (0.059 mL, 0.733 mmol). The product was isolated by flash chromatography (5% EtOAc/hex) to give **17** (83 mg, 48%) as a yellow oil. ^{1}H NMR (C_6D_6, 300 MHz): δ 7.23−7.20 (m, 2H), 7.14−7.11 (m, 2H), 7.05−7.01 (m, 1H), 5.11 (d, J = 9.5 Hz, 1H), 2.98−2.85 (m, 2H), 2.27−1.81 (m, 7H), 1.72 (d, J = 17 Hz, 2H), 1.61 (s, 3H), 1.40−1.00 (m, 1H), 0.98−0.94 (m, 1H), 0.78 (d, J = 7.1 Hz, 3H), 0.57 (t, J = 7.32 Hz, 3H). ^{13}C NMR (C_6D_6, 75

MHz): δ 208.8 (C_{QUAT}), 144.7 (C_{QUAT}), 137.7 (C_{QUAT}), 128.4 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 127.0 (CH), 126.4 (CH), 57.0 (C_{QUAT}), 47.8 (CH_2), 38.2 (CH_2), 35.8 (CH_2), 33.0 (CH_2), 28.0 (CH), 37.9 (CH_2), 25.2 (CH_3), 25.2 (CH_2), 16.5 (CH_3), 8.2 (CH_3). IR (neat): ν_{max} 3085 (w), 3024 (w), 2952 (s), 2929 (s), 2867 (m), 1954 (w), 1866 (w), 1801 (w), 1696 (s), 1598 (w), 1498 (w), 1445 (m). HRMS (EI): degradation observed, no M^+ detected.

18. (±)-(*E*,2*S*,9*S*)-2-Hydroxy-5,9-dimethyl-2-phenylcyclodec-5-enone. Follow general procedure: alcohol **10** (74.4 mg, 0.290 mmol), KHMDS (173.4 mg, 0.869 mmol), and a solution of the Davis oxaziridine (151.7 mg, 0.581 mmol) in DME. Flash chromatography (5% EtOAc/hex) afforded **18** (69.8 mg, 0.256 mmol, 88%) as a white solid. Mp: 110−111 °C. ^{1}H NMR (C_6D_6, 500 MHz): δ 7.60 (d, *J* = 7.9 Hz, 2H), 7.18−7.15 (m, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 5.37 (d, *J* = 9.8 Hz, 1H), 3.47 (dd, *J* = 17.5, 9.2 Hz, 1H), 3.06 (ddd, *J* = 13.8, 13.8, 3.5 Hz, 1H), 2.32 (ddd, *J* = 13.2, 13.2, 3.2 Hz, 1H), 2.18−2.08 (m, 2H), 1.97−1.94 (m, 1H), 1.70−1.66 (m, 1H), 1.62 (s, 3H), 1.56−1.50 (m, 3H), 1.35 (ddd, *J* = 13.9, 3.4, 3.4 Hz, 1H), 1.13−1.06 (m, 1H), 0.69 (d, *J* = 72 Hz, 3H). ^{13}C NMR (C_6D_6, 125 MHz): δ 208.9 (C_{QUAT}), 145.3 (C_{QUAT}), 137.1 (C_{QUAT}), 128.8 (CH), 128.7 (CH), 127.8 (CH), 125.9 (CH), 82.7 (C_{QUAT}), 43.8 (CH_2), 41.6 (CH_2), 38.5 (CH_2), 35.6 (CH_2), 28.5 (CH), 28.2 (CH_2), 25.3 (CH_3), 16.7 (CH_3). IR (neat): ν_{max} 3472 (b), 2951 (s), 2914 (s), 2866 (m), 1692 (s), 1598 (w), 1491 (m), 1445 (m), 1415 (m), 1382 (m), 1355 (m), 1324 (m), 1309 (w), 1288 (w), 1199 (m), 1161 (w), 1123 (w), 1072 (m), 1054 (m), 1033 (m), 996 (w), 968 (w), 864 (w), 840 (w), 753 (m), 689 (s), 631 (m). HRMS (EI): calcd for $C_{18}H_{24}O_2$, 372.1776; found, 372.1789. Also found $M^+ - H_2O$ at 354.1706; actual 354.1671.

26. (±)-((1*R*,2*R*,5*S*)-5-Methyl-1-(1-phenylvinyl)-2-(prop-1-en-2-yl)cyclohexyloxy)trimethylsilane. A stirring solution of **10** (103.0 mg, 0.402 mmol) in THF (5 mL) was treated with KHMDS (320.8 mg, 1.61 mmol) and then TMSCl (0.20 mL, 1.58 mmol). After being stirred at room temperature for 5 min, the reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The product was isolated by flash chromatography (hexanes), affording **26** (126.7 mg, 0.386 mmol, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30−7.19 (m, 5H), 5.38 (d, *J* = 2.0, 1H), 4.98 (d, *J* = 2.0 Hz, 1H), 4.82−4.81 (m, 1H), 4.78 (d, *J* = 2.5 Hz, 1H), 2.12 (dd, *J* = 12.3, 3.3 Hz, 1H), 1.91 (dddd, *J* = 7.5, 7.5, 7.5, 3.6 Hz, 1H), 1.82−1.65 (m, 3H), 1.79 (s, 3H), 1.47 (dddd, *J* = 12.9, 3.3, 3.3, 3.3 Hz, 1H), 1.09 (dd, *J* = 13.9, 12.3 Hz, 1H), 0.92−0.81 (m, 1H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.17 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.0 (C_{QUAT}), 148.6 (C_{QUAT}), 143.1 (C_{QUAT}), 128.9 (CH), 127.7 (CH), 126.7 (CH), 116.1 (CH_2), 113.2, (CH_2), 82.2 (C_{QUAT}), 53.4 (CH), 46.5 (CH_2), 34.9 (CH_2), 28.5 (CH_2), 27.9 (CH), 22.2 (CH_3), 22.1 (CH_3), 2.3 (CH_3). IR (neat): ν_{max} 3078 (w), 3029 (w), 3017 (w), 2951 (s), 2926 (s), 2867 (m), 1598 (w), 1491 (w), 1455 (w), 1442 (w), 1372 (w), 1250 (s), 1229 (w), 1189 (w), 1150 (m), 1118 (m), 1096 (m), 1052 (s), 1028 (w), 1014 (w), 985 (w), 962 (w), 929 (w), 916 (m), 837 (s), 771 (w), 701 (s). HRMS (EI): calcd for $C_{21}H_{32}OSi$, 328.2222; found, 328.2228.

27. (±)-((*S*,1*E*,5*E*)-5,9-Dimethyl-2-phenylcyclodeca-1,5-dienyloxy)trimethylsilane. A solution of **26** (126.7 mg, 0.386 mmol) in toluene (14 mL) was transferred to a microwave cell, and the solution was degassed with argon for 15 min. This solution was then subjected to microwave irradiation (20 min heat ramp to 220 °C followed by 1 h at 220 °C). After cooling to room temperature, the solution was concentrated and the products were isolated by flash chromatography (hexanes), affording returned **26** (95.4 mg, 0.290 mmol, 75%) as a colorless oil and **27** (19.3 mg, 0.0587 mmol, 15%) as a colorless oil. ^{1}H NMR (C_6D_6, 500 MHz): δ 7.48 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.32 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 4.98 (d, *J* = 9.2 Hz, 1H), 3.00 (ddd, *J* = 12.8, 12.8, 5.0 Hz, 1H), 2.53 (dd, *J* = 14.3, 10.7 Hz, 1H), 2.48 (ddd, *J* = 12.7, 4.9, 4.9 Hz, 1H), 2.35−2.15 (m, 5H), 2.00−1.93 (m, 1H), 1.90 (s, 3H), 1.60 (dd, *J* = 14.5, 6.5 Hz, 1H), 1.09−0.98 (m, 1H), 0.90 (d, *J* = 7.1 Hz, 3H), 0.25 (s, 9H). ^{13}C NMR (d_6-acetone, 100 MHz): δ 151.0 (C_{QUAT}), 143.7 (C_{QUAT}), 130.5 (C_{QUAT}), 129.8 (CH), 129.6 (CH), 128.9 (CH), 126.6 (CH), 120.4 (C_{QUAT}), 44.1 (CH_2), 40.5 (CH_2), 39.9 (CH_2), 33.7 (CH), 32.8 (CH_2), 29.5 (CH_2), 26.3 (CH_3), 18.4 (CH_3), 0.84 (CH_3). IR (neat): ν_{max} 3083 (w), 3052 (w), 3033 (w), 3021 (w), 2953 (s), 2925 (s), 2871 (m), 1491 (w), 1441 (w), 1370 (w), 1289 (w), 1260 (m), 1251 (w), 1209 (w), 1139 (w), 1112 (w), 1060 (m), 1031 (w), 1010 (w), 977 (w), 953 (m), 896 (m), 880 (m), 842 (s), 757 (m), 734 (w), 699 (m), 664 (m). HRMS (EI): calcd for $C_{21}H_{32}OSi$, 328.2222; found, 328.2223.

28. (±)-((*S*,1*Z*,5*E*)-5,9-Dimethyl-2-phenylcyclodeca-1,5-dienyloxy)trimethylsilane. Alcohol **10** (86.1 mg, 0.336 mmol) was dissolved in benzene (10 mL) and concentrated under reduced pressure three times to remove water and then dried under high vacuum for 1 h. The compound was then dissolved in DME (4 mL), and to this was added a solution of KHMDS (201.0 mg, 1.01 mmol) in DME (2 mL). The resulting mixture was heated at reflux for 15 min, after which it was cooled to room temperature and then −78 °C. To the cooled solution was then added freshly distilled TMSCl (0.09 mL, 0.709 mmol), and the mixture was stirred at −78 °C for 15 min. The reaction was quenched by the addition of water (10 mL) followed by warming to room temperature. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes) afforded **28** (88.3 mg, 0.269 mmol, 80%) as a colorless oil. ^{1}H NMR (C_6D_6, 500 MHz): δ 7.40 (d, *J* = 7.2 Hz, 2H), 7.21 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.07 (dd, *J* = 7.5, 7.5 Hz, 1H), 5.32 (dd, *J* = 10.5, 4.6 Hz, 1H), 2.39−2.20 (m, 4H), 2.06−1.96 (m, 3H), 1.91−1.81 (m, 3H, 1.53−1.50 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), −0.13 (s, 9H). ^{13}C NMR (d_6-acetone, 100 MHz): δ 149.9 (C_{QUAT}), 142.6 (C_{QUAT}), 131.2 (CH), 129.6 (CH), 129.2 (C_{QUAT}), 128.2 (CH), 126.3 (CH), 119.2 (C_{QUAT}), 38.7 (CH_2), 37.0 (CH_2), 33.0 (CH_2), 30.8 (CH_2), 30.6 (CH), 23.5 (CH_2), 21.0 (CH_3), 17.1 (CH_3), −0.3 (CH_3). IR (neat): ν_{max} 3078 (m), 3056 (m), 3025 (m), 2953 (s), 2919 (s), 2871 (m), 2854 (s), 2824 (m), 1599 (m), 1492 (m), 1455 (m), 1443 (m), 1385 (w), 1363 (w), 1336 (w), 1291 (m), 1250 (s), 1200 (s), 1100 (s), 1061 (s), 1030 (w), 1000 (w), 963 (m), 938 (s), 906 (m), 880 (m), 842 (s), 774 (m), 757 (m), 699 (s), 665 (w). HRMS (EI): calcd for $C_{21}H_{32}OSi$, 328.2222; found, 328.2212.

37. (+)-(1*R*,2*R*,5*S*)-1-[1-(3,4-Dimethoxyphenyl)-vinyl]-2-isopropenyl-5-methylcyclohexanol. To a solution of vinyl bromide **36** (1.42 g, 5.83 mmol) in THF (30 mL) cooled to −90 °C was added *t*-BuLi (1.70 M, 6.86 mL, 11.66 mmol), and the resulting solution was stirred at −90 °C for 35 min. To this mixture was added a solution of ketone **(−)-9** (0.444 g, 2.91 mmol) in THF (10 mL) by cold cannulation, and the resulting solution was stirred at −90 °C for 0.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (40 mL) followed by warming to room temperature. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% EtOAc/hex) afforded **37** (0.544 g, 1.72 mmol, 59%) as a colorless oil. Starting ketone **9** (0.115 g, 0.758 mmol, 26% recovery) was also isolated from the flash. ^{1}H NMR (d_6-acetone, 500 MHz): δ 6.94−6.84 (m, 2H), 6.78 (dd, *J* = 8.3, 2.0 Hz, 1H), 5.48 (d, *J* = 2.2 Hz, 1H), 4.90 (d, *J* = 2.4 Hz, 1H), 4.88−4.87 (m, 1H), 4.79−4.78 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.21 (s, 1H), 2.54 (dd, *J* = 12.6, 3.5 Hz, 1H), 1.99 (ddd, *J* = 12.9, 3.7, 3.7 Hz, 1H), 1.96−1.89 (m, 1H), 1.79 (s, 3H), 1.72−1.65 (m, 2H), 1.48−1.43 (m, 1H), 1.36 (ddd, *J* = 13.4, 12.3, 12.3 Hz, 1H), 0.96−0.87 (m, 1H), 0.82 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (d_6-acetone, 125 MHz): δ 158.6 (C_{QUAT}), 150.0 (C_{QUAT}), 149.7 (C_{QUAT}), 149.6 (C_{QUAT}), 136.3 (C_{QUAT}), 122.5 (CH), 114.7 (CH), 114.5 (CH_2), 113.8 (CH_2), 112.3 (CH), 78.0 (C_{QUAT}), 56.5 (CH_3), 56.4 (CH_3), 52.7 (CH), 49.8 (CH_2), 36.2 (CH_2), 29.7 (CH_2), 28.7 (CH), 23.5 (CH_3), 23.1 (CH_3). IR (neat): ν_{max} 3531 (b), 3072 (m), 3003 (m),

2947 (s), 2866 (m), 2839 (m), 1632 (m), 1601 (m), 1578 (m), 1511 (s), 1461 (s), 1449 (s), 1407 (m), 1374 (m), 1319 (m), 1289 (w), 1248 (s), 1219 (m), 1175 (m), 1140 (s), 1101 (w), 1028 (s), 976 (w), 902 (m). HRMS (EI): calcd for $C_{20}H_{28}O_3$, 316.2038; found, 316.2058. $[\alpha]^{22}_D$ +34.1°, *c* 19.1 mg/mL.

38. (+)-(*E*,2*S*,9*S*)-2-Allyl-2-(3,4-dimethoxyphenyl)-5,9-dimethylcyclodec-5-enone. Alcohol **37** (149.9 mg, 0.474 mmol) was dissolved in benzene (10 mL) and concentrated under reduced pressure three times to remove water and then dried under high vacuum for 1 h. The compound was then dissolved in DME (10 mL), and to this was added a solution of KHMDS (283.5 mg, 1.42 mmol) in DME (5 mL). The resulting mixture was heated at reflux for 15 min, after which it was cooled to room temperature and then −78 °C. To the cooled solution was then added allyl bromide (distilled twice over CaH_2, 0.08 mL, 0.924 mmol), and the mixture was stirred at −78 °C for 30 min. The reaction was quenched by the addition of water (15 mL) followed by warming to room temperature. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% EtOAc/hex) afforded **38** (143.5 mg, 0.403 mmol, 72%) as a colorless oil. ^{1}H NMR (d_6-acetone, 500 MHz): δ 6.92 (s, 1H), 6.90−6.83 (m, 2H), 5.45 (d, J = 10.3 Hz, 1H), 5.37−5.30 (m, 1H), 5.18 (d, J = 17.1 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.25 (dd, J = 17.8, 7.8 Hz, 1H), 3.18 (d, J = 6.4 Hz, 2H), 2.85−2.79 (m, 1H), 2.37 (t, J = 12.5 Hz, 1H), 2.17−2.07 (m, 2H), 1.99−1.94 (m, 2H), 1.89 (dd, J = 17.8, 13.2 Hz, 2H), 1.70 (d, J = 13.9 Hz, 1H), 1.45 (s, 3H), 1.36−1.27 (m, 1H), 0.93 (d, J = 7.1 Hz 3H). ^{13}C NMR (d_6-acetone, 125 MHz): δ 210.0 (C_{QUAT}), 150.4 (C_{QUAT}), 149.4 (C_{QUAT}), 138.6 (C_{QUAT}), 138.4 (C_{QUAT}), 135.7 (CH), 128.0 (CH), 120.2 (CH), 118.2 (CH_2), 112.9 (CH), 112.5 (CH), 56.7 (CH_3), 56.6 (C_{QUAT}), 56.5 (CH_3), 48.9 (CH_2), 38.8 (CH_2), 38.4 (CH_2), 36.5 (CH_2), 35.0 (CH_2), 29.1 (CH), 28.7 (CH_2), 25.6 (CH_3), 16.9 (CH_3). IR (neat): ν_{max} 3077 (w), 3951 (s), 2933 (s), 2846 (m), 1694 (s), 1638 (w), 1602 (w), 1587 (w), 1517 (s), 1463 (m), 1442 (m), 1408 (m), 1375 (w), 1356 (w), 1323 (w), 1261 (s), 1235 (m), 1179 (w), 1149 (s), 1129 (w), 1028 (s), 1003 (w), 913 (w). HRMS (EI): calcd for $C_{23}H_{32}O_3$, 356.2351; found, 356.2352. $[\alpha]^{22}_D$ +61.5°, *c* 24.0 mg/mL.

39. (−)-(*E*,1*R*,3*S*,10*S*)-3-Allyl-(3,4-dimethoxyphenyl)-6,10-dimethylcyclodec-6-ene-1,2-diol. To a solution of KHMDS (428.6 mg, 2.19 mmol) in THF (5 mL) cooled to −78 °C was added a solution of ketone **38** (153.2 mg, 0.430 mmol) in THF (3 mL). The resulting mixture was stirred at −78 °C for 0.5 h, after which the Davis oxaziridine (134.7 mg, 0.515 mmol) was added as a solution in THF (3 mL), followed by another 0.5 h of stirring at −78 °C. The reaction was quenched by the addition of H_2O (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated, and the product was isolated by flash chromatography (30% EtOAc/hex) to afford **38int** (110.5 mg, 0.297 mmol, 69%) as a white solid. Mp: 148−149 °C. ^{1}H NMR (d_6-DMSO, 500 MHz, 373 K): δ 7.24 (d, J = 1.7 Hz, 1H), 7.01 (dd, J = 8.4, 1.4 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 5.40−5.32 (m, 1H), 5.11 (d, J = 17.1 Hz, 1H), 6.00 (bs, 1H), 5.53 (d, J = 6.7 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 4.31 (d, J = 8.0 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.41−3.37 (m, 1H), 3.16 (dd, J = 14.8, 8.1 Hz, 1H), 2.64−2.59 (m, 1H), 2.36−2.30 (m, 1H), 2.09−2.05 (m, 1H), 1.98−1.88 (m, 5H), 1.46 (s, 3H), 1.34−1.30 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H). ^{13}C NMR: Carbon spectrum unavailable; severe line broadening at room temperature, rapid decomposition upon heating. IR (neat): ν_{max} 3492 (b), 3410 (b), 3070 (w), 2960 (m), 2929 (m), 2862 (m), 1696 (m), 1637 (w), 1590 (w), 1518 (s), 1461 (s), 1453 (m), 1410 (w), 1379 (w), 1328 (w), 1260 (s), 1234 (m), 1199 (w), 1183 (w), 1153 (m), 1109 (w), 1025 (m), 964 (w), 952 (w), 906 (m), 878 (m), 831 (w), 804 (m), 702 (w). HRMS (EI): calcd for $C_{23}H_{32}O_4$, 372.2301; found, 372.2299. $[\alpha]^{22}_D$ +20.7°, *c* 35.3 mg/mL.

A solution of **38int** (30.3 mg, 0.0813 mmol) in THF (3 mL) cooled to 0 °C was treated with $LiAlH_4$ (15.4 mg, 0.406 mmol), and the resulting mixture was stirred for 0.5 h. The reaction was quenched by the addition of 1 M sodium tartrate (5 mL) followed by 2 h of vigorous stirring. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated, and the product was isolated by flash chromatography (50% EtOAc/hex) to afford **39** (30.8 mg, 0.0789 mmol, 97%) as a white solid. Mp: 136−137 °C. ^{1}H NMR (C_6D_6, 500 MHz): δ 7.05 (s, 1H), 6.92 (dd, J = 8.3, 1.8 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 5.62−5.55 (m, 1H), 5.27 (d, J = 9.9 Hz, 1H), 5.19 (d, J = 17.1 Hz, 1H), 4.99 (d, J = 10.2 Hz, 1H), 4.41 (d, J = 4.3 Hz, 1H), 3.53 (s, 1H), 3.44 (s, 6H), 2.98 (dd, J = 15.1, 4.2 Hz, 1H), 2.82 (dd, J = 15.0, 8.5 Hz, 1H), 2.65 (dd, J = 13.5, 13.5 Hz, 1H), 2.47 (dd, J = 13.1, 13.1 Hz, 1H), 2.40−2.28 (m, 2H), 2.05 (d, J = 11.8 Hz, 1H), 1.99−1.91 (m, 1H), 1.86 (s, 1H), 1.76 (dd, J = 14.3, 7.4 Hz, 1H), 1.56−1.48 (m, 1H), 1.38−1.31 (m, 1H), 1.18 (s, 3H), 1.04−0.98 (m, 1H), 0.92 (d, J = 7.0 Hz, 3H). ^{13}C NMR (C_6D_6, 125 MHz): δ 150.3 (C_{QUAT}), 148.9 (C_{QUAT}), 142.5 (C_{QUAT}), 136.7 (C_{QUAT}), 135.6 (CH), 128.7 (CH), 120.2 (CH), 117.6 (CH_2), 112.7 (CH), 112.2 (CH), 84.5 (CH), 75.2 (CH), 56.2 (CH_3), 56.0 (CH_3), 50.5 (C_{QUAT}), 37.2 (CH_2), 36.7 (CH_2), 34.9 (CH_2), 32.9 (CH), 29.5 (CH_2), 28.2 (CH_2), 16.8 (CH_3), 15.8 (CH_3). IR (neat): ν_{max} 3524 (b), 3070 (w), 2964 (s), 2929 (s), 2858 (s), 2835 (m), 1637 (w), 1606 (w), 1586 (w), 1512 (s), 1461 (m), 1442 (m), 1406 (m), 1379 (w), 1324 (w), 1262 (s), 1230 (m), 1152 (m), 1121 (w), 1074 (w), 1027 (w), 999 (w), 956 (w), 913 (w), 878 (w), 808 (w), 772 (w), 694 (w), 557 (w). HRMS (EI): calcd for $C_{23}H_{34}O_4$, 374.2457; found, 374.2446. $[\alpha]^{22}_D$ −5.1°, *c* 24.0 mg/mL.

40. (5*S*,6*R*,8*S*)-8-Allyl-8-(3,4-dimethoxyphenyl)-1,5-dimethylcyclodecane-1,2,6,7-tetraol. A solution of **39** (61.9 mg, 0.165 mmol) in THF/H_2O (5:1, 15 mL) was treated with NMO (17.4 mg, 0.149 mmol) and OsO_4 (4% in H_2O, 0.11 mL, 0.0173 mmol) and stirred for 3 h at room temperature. The reaction was quenched by the addition of saturated aqueous Na_2SO_3 (20 mL) followed by stirring for a further 0.5 h. The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 25 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (EtOAc) afforded **40** (44.5 mg, 0.109 mmol, 66%) as a yellow oil. This product rapidly decomposed, and it was used directly without further purification or characterization in the next step of the sequence.

41. (−)-(*S*)-2-Allyl-2-(3,4-dimethoxyphenyl)-5-oxohexanal. A solution of **40** (16.8 mg, 0.0411 mmol) in benzene (5 mL) was treated with $Pb(OAc)_4$ (109.4 mg, 0.247 mmol), and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (50% EtOAc/hex) afforded **41** (8.4 mg, 0.0289 mmol, 70%) as a colorless oil. ^{1}H NMR (C_6D_6, 400 MHz): δ 9.37 (s, 1H), 6.68 (d, J = 2.2 Hz, 1H), 6.63 (dd, J = 8.3, 2.3 Hz, 1H), 6.53 (d, J = 8.3 Hz, 1H), 5.57−5.48 (m, 1H), 4.97−4.91 (m, 2H), 3.37 (s, 3H), 3.36 (s, 3H), 2.61−2.50 (m, 2H), 2.36−2.29 (m, 1H), 2.25−2.18 (m, 1H), 2.07−1.88 (m, 2H), 1.54 (s, 3H). ^{13}C NMR (C_6D_6, 100 MHz): δ 205.5 (C_{QUAT}), 200.9 (CH), 150.6 (C_{QUAT}), 149.7 (C_{QUAT}), 133.4 (CH), 130.8 (C_{QUAT}), 120.2 (CH), 118.5 (CH_2), 112.4 (CH), 111.8 (CH), 56.0 (C_{QUAT}), 55.6 (CH_3), 55.2 (CH_3), 37.8 (CH_3), 37.7 (CH_2), 29.4 (CH_3), 26.2 (CH_2). IR (neat): ν_{max} 3075 (w), 2998 (w), 2963 (w), 2940 (m), 2917 (w), 2836 (w), 2709 (w), 1716 (s), 1652 (w), 1563 (w), 1519 (s), 1486 (w), 1417 (m), 1363 (m), 1332 (w), 1259 (s), 1239 (m), 1212 (w), 1150 (m), 1085 (w), 1025 (s), 919 (w), 880 (w), 857 (w), 807 (w). HRMS (EI): calcd for $C_{17}H_{22}O_4$, 290.1518; found, 290.1503. $[\alpha]^{22}_D$ −8.1°, *c* 12.2 mg/mL.

42. (−)-(*R*)-4-Allyl-4-(3,4-dimethoxyphenyl)cyclohex-2-enone. A solution of **41** (10.5 mg, 0.0362 mmol) in benzene (5 mL) was treated with PTSA (0.7 mg, 0.00368 mmol). The flask containing

the mixture was fitted with a Dean−Stark trap and reflux condenser, and the mixture was heated at reflux for 1.5 h. The reaction was then cooled to room temperature and then diluted with EtOAc (15 mL) and H_2O (15 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (50% EtOAc/hex) afforded **42** (8.1 mg, 0.0297 mmol, 82%) as a colorless oil. ^{1}H NMR (C_6D_6, 500 MHz): δ 7.06 (d, J = 10.3 Hz, 1H), 6.84−6.81 (m, 3H), 6.17 (dd, J = 10.2, 0.5 Hz, 1H), 5.60−5.51 (m, 1H), 5.13−5.07 (m, 2H), 3.87 (s, 6H), 2.70 (ddd, J = 5.9, 1.4, 1.4 Hz, 1H), 2.49 (dd, J = 13.4, 8.5 Hz, 1H), 2.37−2.20 (m, 4H). ^{13}C NMR (C_6D_6, 125 MHz): δ 199.7 (C_{QUAT}), 155.3 (CH), 149.2 (C_{QUAT}), 148.1 (C_{QUAT}), 135.4 (C_{QUAT}), 133.6 (CH), 129.6 (CH), 119.5 (CH), 119.0 (CH_2), 111.1 (CH), 110.2 (CH), 65.1 (CH_3), 56.0 (CH_3), 46.4 (CH_2), 43.6 (C_{QUAT}), 36.2 (CH_2), 34.6 (CH_2). IR (neat): ν_{max} 3071 (w), 3002 (w), 2933 (m), 2840 (w), 1683 (s), 1633 (w), 1606 (w), 1582 (w), 1555 (w), 1521 (s), 1459 (m), 1413 (m), 1382 (m), 1251 (s), 1239 (s), 1117 (m), 1147 (m), 1120 (m), 1085 (w), 1027 (m), 988 (w), 919 (w), 888 (w), 846 (w), 807 (w), 792 (w), 765 (w). HRMS (EI): calcd for $C_{17}H_{20}O_3$, 272.1412; found, 272.1432. $[\alpha]^{22}_D$ −104.6°, *c* 8.1 mg/mL.

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Supporting Information Available: Spectral data for compounds **10**, **11**, **13**−**18**, **27**, **28**, **37**−**42** (^{1}H and ^{13}C NMR, IR, HRMS) and CIF files. ORTEP view of **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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