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Stereoselective synthesis of exocyclic allenes by double hydride reduction of 3-alkynyl-2-cycloalkenones

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Dedicated to Professor Gary H. Posner

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ABSTRACT

Exocyclic allene natural products and pharmaceutical agents are rare but interesting compounds: Fucoxanthin, grasshopper ketone, and analogues of prostacyclins, cephalosporins, antithrombic agents and sterol biosynthesis inhibitors are representative. Syntheses of exocyclic allenes commonly rely on extended conjugate additions to e.g., alk-2-en-4-ynones, *syn* S_N2'-like additions to alkynyl oxiranes, and substitution reactions such as electrophilic substitutions of propargylic silanes. We report that the reaction of 3-alkynyl-2-cycloalkenones with 2 equiv of various hydridoaluminates but not hydridoborates proceeds via diastereoselective 1,4-reduction of a vinylogously propargylic intermediate alcoholate to provide exocyclic allenes as major products. Isomeric 3-alkynylcycloalkanols also are observed.

1. Introduction

Allenes are the simplest of the cumulene hydrocarbon class. They are rare in nature, with under 200 allene-containing natural products having been identified.[1,2] Historically, unambiguous structural assignment of a natural product as containing an allene sometimes has been challenging,[3,4] so that structural revisions are not uncommon. As a consequence the class has gained a reputation as being not only rare but perhaps exotic. Nonetheless, with a rigid, all-carbon core of orthogonal π bonds imposing a 90° twist and therefore potential axial chirality, this deceptively simple functional group has found interesting applications in organic synthesis.[5]

One allene subclass, the exocyclic allenes, is relatively widely represented among allene-containing natural products. It is a subunit of the most common carotenoid, the anti-obesity agent fucoxanthin,[6] as well as other carotenoids, including mimulaxanthin,[7] neoxanthin,[8] paracentrone,[9] and peridinin.[10] Consequently, exocyclic allenes are routinely exploited as subunits in convergent syntheses of allene-containing carotenoids[10,11] and carotenoid metabolites or degradation products, including grasshopper ketone[12] and an allenic epoxycyclohexane isolated from *Eutypa lata*.[13] Exocyclic allene analogues of prostacyclins,[14] penams, and cephems[15] also have been prepared and investigated for unique pharmacological activities. Useful as intermediates in the synthesis of nonallene-containing natural products,[16] exocyclic allenes themselves have been the objects of conjugation, strain, and isomerization studies.[17]

Syntheses of exocyclic allenes[18] rely on a small set of strategies. Most popular are additions, including nucleophilic extended conjugate additions to alk-2-en-4-ynones and alk-2-en-4-ynonates,[19] *syn* S_N2'-like alkylations and reductions of alkynyl oxiranes,[11d,12b] and rhodium(II)-catalyzed reaction of carbenoids with propargylic alcohols.[20] Substitution strategies also are known and include electrophilic substitution reactions of propargylic silanes,[16d,g,,21] Wittig reactions of ketenes,[22] Petasis reaction of hydroxyketones,[23] cross-coupling reactions of allenic zirconium complexes and aryl halides[24] and recently, titanium-catalyzed Barbier-type cyclization of propargylic halides.[25] A titanium based cyclization method produces exocyclic bis-allenes.[26]

While preparing 3-alkynyl-2-methylcyclohexenols from the corresponding ketones as intermediates in the synthesis of 1-alkynyl-6-methylbicyclo[4.1.0]alkan-5-ones for study of ring-expanding extended conjugate additions leading to 4-(ethenylidene)-2-methylcycloheptanones (e.g., Eq. 1) we noted a surprising solvent effect: When excess lithium aluminum hydride (LAH) was used in diethyl ether, the anticipated alcohol resulted; however, a small quantity of an allenyl alcohol, easily identified by its intense IR absorption at 1940 cm^{-1}, often was observed.

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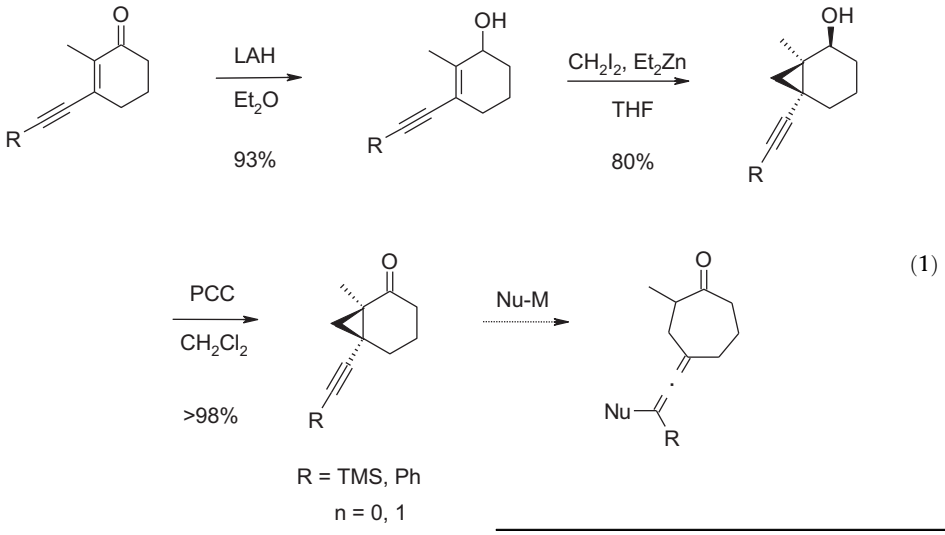
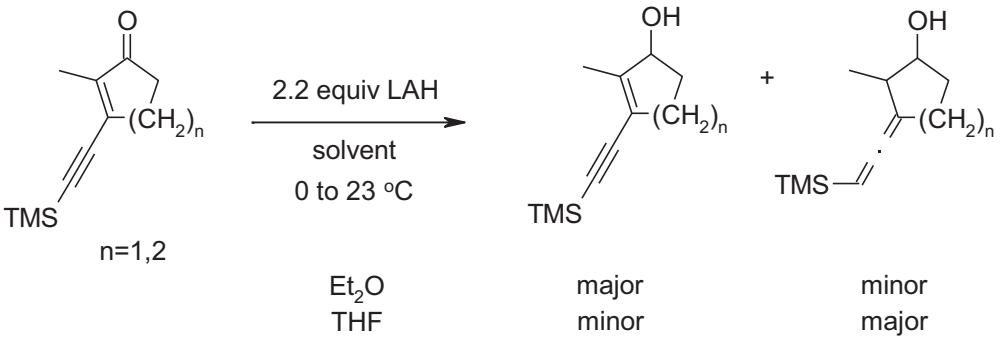


(1)

In tetrahydrofuran (THF) this allenyl alcohol, a product of double hydride reduction, was observed to be the major product. An isomeric alkynyl cycloalkanol also formed (Eq. 2). To the best of our knowledge, this double hydride reduction is a new strategy for access to exocyclic allenes. We report here optimization, stereochemical, and mechanistic studies of this exocyclic allene-forming reaction.

solvents clearly indicated that double hydride reduction was favored in more coordinating solvents (Table 1). Structural studies of the solvation of aluminum hydride reagents[28] have determined that, in contrast to LAH in diethyl ether, benzene or 1,4-dioxane, LAH in THF exists as a monomeric solvent-separated ion pair, providing enhanced nucleophilicity. Similar significant solvent



(2)

2. Results and discussion

To discover the scope and nature of this double hydride reduction, the influence of the identities of solvent, hydride donor, and substrate were investigated.

2.1. Solvent identity

Using 2-methyl-3- trimethylsilylethynyl-2-cyclopentenone[27] (**1a**) as substrate, a series of LAH reductions in commonly used

influences are observed in addition reactions of alkylaluminum reagents to expoxides and carbonyl compounds[29] and aluminum hydride reductions of *N*-benzyl-4-ethoxycarbonylpiperidine[30] and various tosylates and halides,[28c,31] suggesting that this enhanced nucleophilicity is required for successful addition of the second hydride to **1a**.

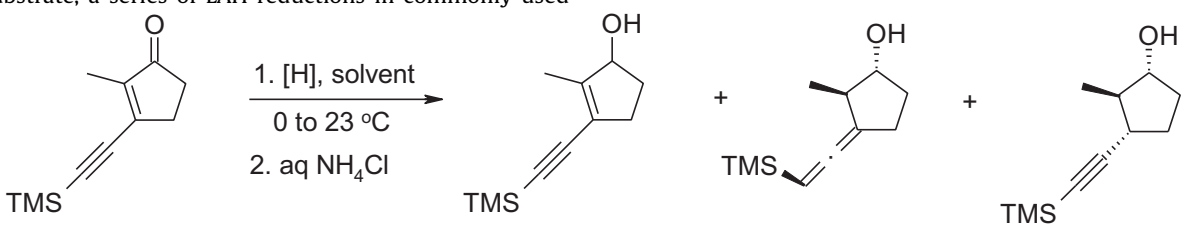


Table 1
Solvent, hydride and stoichiometry effects

Hydride donor [H]	Solvent	mol equiv [H]	Yield, %[a]	**2a**	**3a**	**4a**
LAH	Diethyl ether	2.2	92	45	29	18
LAH	Benzene	2.3	78 (57[b])	78		
LAH	1,4-Dioxane	2.2	89	13	45	31
LAH	THF	0.55	98	45	29	18
LAH	THF	1.1	98	8	51	31
LAH	THF	2.2	96		65	31
LAH+$NaOCH_3$[c]	Diethyl ether	2.2	96	96		
$NaAlH_2(OCH_2CH_2OCH_3)_2$	THF	2.2	96		79	19
$LiAlH(t\text{-}OC_4H_9)(iC_4H_9)_2$	THF	2.2	96	96		
$LiAlH(t\text{-}OC_4H_9)_3$	THF	2.1	98	98		
$(iC_4H_9)_2AlH$	THF	2.2	99	99		
$NaBH_4$	THF	2.4	86	[d]		
$Li(iC_4H_9)_3BH$	THF	2.2	[e]			

[a] GC yield.
[b] Isolated yield after chromatography.
[c] 2:1 LAH: $NaOCH_3$.
[d] 3-Ethynyl-2-methyl-2-cyclopentenol.
[e] 2-Methyl-3-(3-methylpentynyl)-2-cyclopentenone.

2.2. Hydride donor and stoichiometry

Using THF as the solvent, the preferred stoichiometry of the reaction for allene formation was determined. Varying the molar ratio of LAH to **1a** while maintaining a theoretical 10 mol % excess of the hydride, a minimum of 2 mol equivalents of LAH were required; the reaction was complete upon warming to room temperature over 2 h.

To determine if other hydride donor reagents would be effective in this double addition reaction, some readily available LAH and sodium borohydride analogues were employed. Sodium borohydride provided exclusive carbonyl reduction with concomitant desilylation to provide 3-ethynyl-2-methyl-2-cyclopentenol as the only product. On the other hand, treatment of **1a** with lithium tri-*sec*-butylborohydride (L-Selectride), otherwise known to produce cyclopentenols from cyclopentenones,[32] resulted in substitution of the trimethylsilyl moiety for a *sec*-butyl group. Of the LAH analogues, only sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al)[33] was effective in forming the allene, with a ca. 20% enhancement in allene production compared to LAH. Other mild, sterically congested hydroaluminates[34,35] and diisobutylaluminum hydride only reduced the carbonyl, as did sodium methoxide-modified LAH.[36]

2.3. Substrate identity

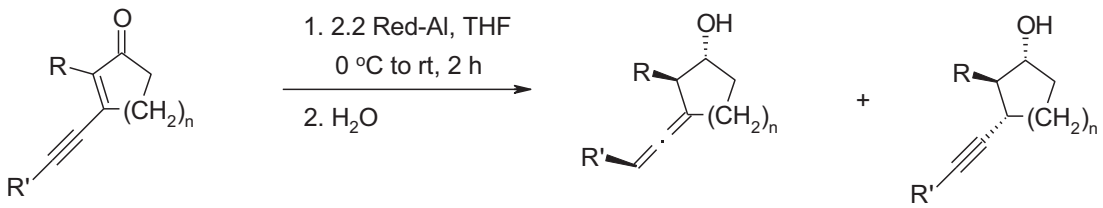
A range of starting cycloalkenones demonstrated that allenes form as major products regardless of ring size, substitution at the 2-position of the cycloalkeneone, or identity of the alkynyl substituent (Table 2). A 3-phenylethynyl substituent (**1d**–**f**) clearly favored allene formation relative to the isomeric alkynyl cycloalkanol when compared to a 3-trimethylsilylethynyl substituent (**1a**–**c**). Isolated yields of a single diastereoisomer of the allene products ranged from 54 to 96%.

2.4. Stereochemistry

A study of the stereochemical outcome of the reaction first determined that reduction products **4a**–**c** predominantly (79 to ≥98%) formed with all-*trans*, (1*R**,2*R**,3*S**) and (1*R**,3*S**) relative configurations. For example, the relative configuration of major diastereoisomer (1*R**,2*R**,3*S**)-**4a**, isolated chromatographically from the reaction of **1a** with 2.2 mol equiv of LAH in THF, was determined by NOE spectroscopy: Similar enhancements of the C1 and C3 methine hydrogen NMR signals were observed when the methyl group was irradiated, and enhancements of the methyl and C3 methine hydrogen signals were observed when the C1 methine hydrogen was irradiated (Fig. 1).

The assignment of the relative configuration of **3** was more challenging. While NOE spectroscopy readily assigned a relative (1*R**,2*R**) configuration for the C1 and C2 carbons with a strong enhancement of the C1 methine hydrogen upon irradiation of the methyl group of **3a** or **3e**, the greater distances between the allene hydrogen and any substituents of the ring made further use of the technique moot. Long-range coupling constants have been used to assign allene configurations[16g] by employing a Karplus-like dihedral angle versus $|^5J|$ relationship.[37] In the case at hand, analyses of the five-bond coupling networks of the allene hydrogens of **3a** and **3e** (Table 3) were ambiguous: Allene hydrogen-C2 and C4 pseudoaxial hydrogen dihedrals of about 150° (an anti-like relationship) and about 35° (a syn-like relationship) determined from a geometry-optimized AM1 model

Table 2
Allene formation versus substrate identity



1 **3** **4**

1	R	R′	*n*	Yield 3, %	Yield 4, %
a	CH_3	TMS	1	69	15
b	CH_3	TMS	2	64	14
c	H	TMS	2	54[a]	5[a]
d	CH_3	Ph	1	54[a]	0
e	CH_3	Ph	2	96[b]	0
f	H	Ph	2	56[a]	0

[a] Isolated yield after chromatography.
[b] Isolated yield after recrystallization.

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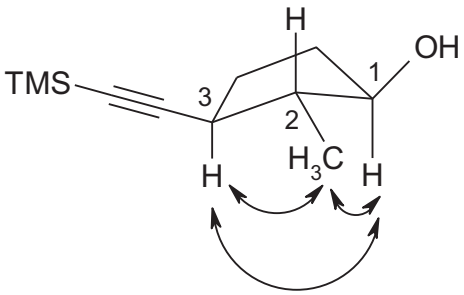
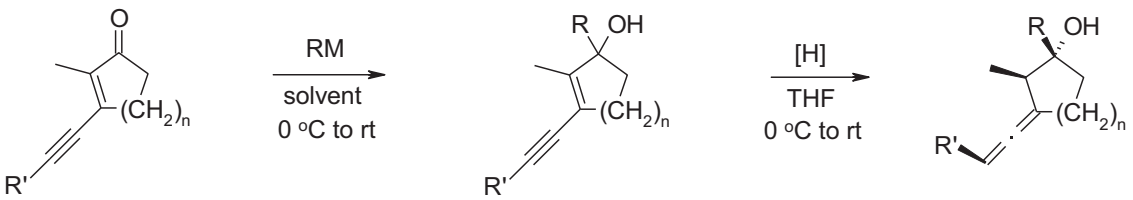


Fig. 1. NOE contacts for (1*R**,2*R**,2*S**)-**4a**.

of **2** formed from addition of LAH to **1** to be a requisite intermediate for subsequent formation of **3**. Indeed, when **1a** was treated with LAH in benzene and the corresponding allylic alcohol isolated, then treated with 2 mol equiv of LAH in THF, the same yield of allene was observed as that produced from direct treatment of **1a** with 2.2 mol equiv of LAH in THF. Similarly, when **2g** formed by addition of methyllithium to **1e** was treated with excess Red-Al, allene was produced in excellent yield (Eq. 3).



(3)

	RM	solvent		[H]	
1a n = 1, R' = TMS	LAH	benzene	68% **2a**, n = 1, R = H, R' = TMS	LAH	66% **3a**, n = 1, R = H. R' = TMS
1e n = 2, R' = Ph	MeLi	THF	67% **2g**, n = 2, R = Me, R' = Ph	Red-Al	99% **3g**, n = 2, R = Me. R' = Ph

of **3a** predict the same coupling constant magnitudes. Regardless, these predicted coupling constants were not in agreement with those observed. Consequently, single-crystal X-ray diffraction of **3e**, which was easily recrystallized from aqueous ethanol, unambiguously established its (1*R**,2*R**,*S**) relative configuration (Fig. 2).

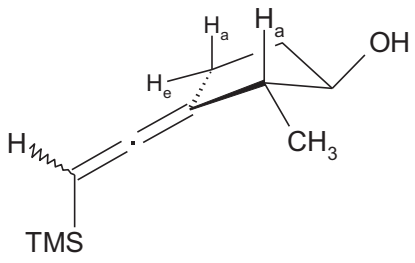
2.5. Mechanistic studies

To formulate a hypothesis for the mechanism of the reaction, it was first noted from studying its stoichiometry that production of allylic alcohol **2** decreased as the amount of LAH used increased. This suggested that the reaction was stepwise, with the aluminate

Deuterium labeling studies further detailed the sequence of double hydride addition. When **1e** was reacted with lithium aluminum deuteride and the reaction quenched with aqueous ammonium chloride, (1*R**,2*R**,*S**)-**3e** (Eq. 4) was isolated with deuterium specifically incorporated in the C1 and C2 positions. Complementary labeling of **1e** using LAH followed by quenching with D_2O (Eq. 5) provided (1*R**,2*R**,*S**)-**3e** with deuterium specifically incorporated in its alcohol and allene moieties.

Taken together, the data suggest a tandem reaction. Using a 2-methyl-3-alkynyl-2-cyclohexenone as an example starting material (Fig. 3), equatorial aluminum hydride carbonyl reduction[38] results in a vinylogous propargylic alanate, **5**. Because the addition of the hydride is anti with respect to the first, intramolecular addition[39] of hydride to C2, perhaps facilitated by a second equivalent of aluminum hydride reagent, results in net *syn*-1,4-hydroalumination[40] to provide the observed allenyl alcohols after

Table 3
Measured versus predicted $|^5J|$ values for **3a**



3a

$\|^5J\|$	Measured, Hz	(1*R**,2*R**,*R**) predicted, Hz	(1*R**,2*R**,*S**) predicted, Hz
($H-H_{2a}$)	5.3	1.7	1.9
($H-H_{4a}$)	0.6	2.0	1.9
($H-H_{4e}$)	10.8	1.8	1.9

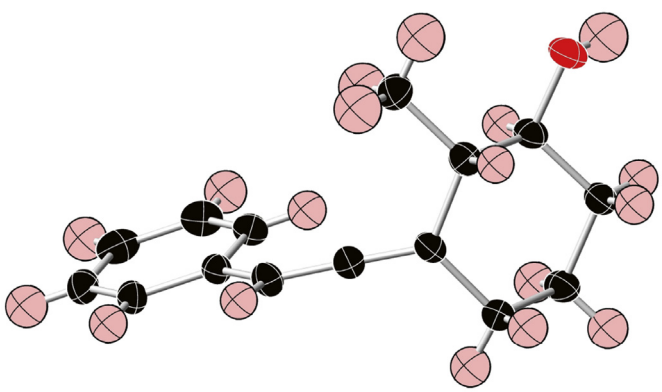


Fig. 2. Single-crystal X-ray structure of (1*R**,2*R**,*S**)-**3e**, 50% thermal ellipsoids.

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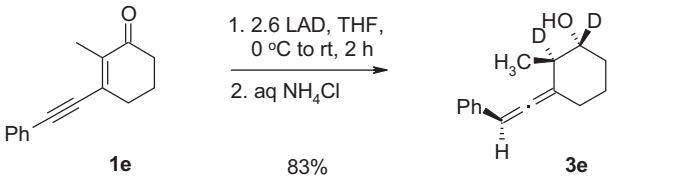
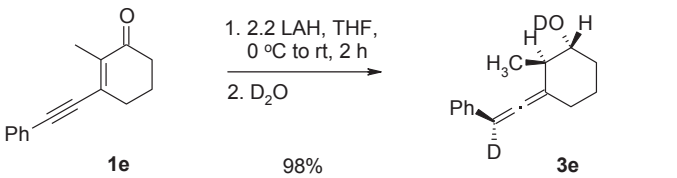
aqueous workup. 1,2-Hydroalumination of propargylic alcohols,[41] vinylogous propargylic alcohols,[42] and propargylic amines[43] is well-known; generally, hydroalumination of propargylic alcohols exhibit *anti*-stereoselectivity, providing thermodynamically more stable (*E*)-alkenes.[39,43,44] Similarly, equilibration[45] of the intermediate **6** to propargylic alanate **7** would lead to **4**, as observed when **1a**–**c** are reduced.



(4)



(5)

3. Conclusion

3-Trimethylsilylethenylidinecycloalkanols and 3-phenylethenylidinecycloalkanols can be prepared in 54–96% isolated yields in 2 h from the corresponding alkynylcyclolalkenones using 2 mol equiv of Red-Al in THF. The reaction proceeds in a tandem manner, and is highly diastereoselective: Aluminum hydride carbonyl reduction gives a vinylogous propargylic alanate, which in turn undergoes intramolecular *syn*-1,4-hydroalumination to provide the observed products after aqueous workup. Direct and indirect alkylation strategies that may afford entry into syntheses of allene-containing carotenoid analogues are under investigation and will be reported in due course.

4. Experimental section

4.1. General methods

Diethyl ether, THF, 1,4-dioxane and benzene from Fisher Scientific (Pittsburgh, PA) were dried using sodium-benzophenone and stored over 4 Å molecular sieves. Trimethylsilylethyne, phenylethyne and *tert*-butyldimethylsilyl chloride were from Oakwood Products (West Columbia, SC). All other solvents were from Fisher Scientific and used as received. Lithium aluminum hydride, lithium *tert*-butoxydiisobutylaluminum hydride, lithium tri-*tert*-butoxyaluminum hydride, sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), sodium borohydride and lithium tri-*sec*-butylborohydride were purchased from Acros Organics. Thin layer chromatography was performed on precoated silica gel F_{254} glass plates from Analtech (Newark, DE) with visualization by UV light, phosphomolybdic acid spray, or iodine vapor. Flash column chromatography was performed using 32–63 μm silica gel and medium pressure column chromatography used LiChroprep Si 60 size A and B columns. Melting points are uncorrected. Infrared spectra were obtained using a single-bounce ZnSe ATR accessory; absorptions are reported in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded at 300 or 400 MHz and ^{13}C NMR spectra at 75 or 100 MHz; chemical shifts (δ) are reported in parts per million (ppm) relative to TMS. GC/MSD data were obtained using a 30 m AT-5 capillary column and the temperature program 120 °C, 3 min; 10 °C/min to 240 °C; 240 °C, 3 min, or using a 30 m ZB-5 capillary column and the temperature program 60 °C, 3 min; 10 °C/min to 230 °C; 230 °C, 3 min. MALDI-TOF mass spectra were obtained in reflector positive mode with 2,5-dihydroxybenzoic acid as the matrix and ESI-TOF mass spectra were obtained in reflector positive mode by infusion in 0.1% trifluoroacetic acid/acetonitrile.

4.2. 2-Methyl-3-(trimethylsilylethynyl)-2-cyclopentenone (1a)[27]

Ethylmagnesium bromide (32.7 mL, 32.7 mmol, 1.0 M in THF) was added to an argon-purged, oven-dried 250 mL round bottom flask equipped with magnetic stirring bar, constant pressure addition funnel and an argon inlet. Stirring was begun and the flask was cooled to 0 °C in an ice water bath. Trimethylsilylethyne (3.53 g, 36.0 mmol) in THF (35 mL) was added dropwise over 30 min, after which time the ice water bath was removed and the flask allowed to warm to room temperature. Cooling to −78 °C was followed by dropwise addition of 3-isobutoxy-2-methyl-2-cyclopentenone[46] (5.00 g, 29.7 mmol) in THF (65 mL) over 30 min. The cold bath was left to exhaust itself as the reaction slowly warmed to room temperature overnight.

The reaction was quenched by the addition of water (10 mL), followed by K_2CO_3 (1 g) with rapid stirring. Dilution with diethyl ether (200 mL) was followed by transfer to a separatory funnel and washing with water (50 mL). The organic layer subsequently was washed with aqueous saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation gave an amber liquid (8.78 g) which was taken up in diethyl ether (30 mL), then stirred rapidly with 1 M HCl (10 mL) for 3 h. Dilution with diethyl ether (40 mL) and transfer to a separatory funnel was followed by washing with aqueous saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation gave an orange liquid (4.92 g) that was purified by flash chromatography (9:1 hexane:diethyl ether) to give the *title compound* **1a** (3.25 g, 57%), which solidified upon standing: R_f (9:1 hexane:diethyl ether) 0.29; bp 50 °C (0.75 mmHg); mp 34–36 °C; ν_{max} 2960, 2144, 1704, 1615, 885, 846 cm^{-1}; δ_H ($CDCl_3$) 2.62–2.56 (m, 2H), 2.39–2.34 (m, 2H), 1.81 (t, J=2.2 Hz, 3H), 0.21 (s, 9H); δ_C ($CDCl_3$) 209.2, 149.8, 145.8, 112.2, 100.3, 34.1, 30.1, 9.9, −0.1; t_R 15.8 min, *m/z* (EI) 192 (40, M^+), 177 (100).

A sample of **1a** (36.8 mg, 0.19 mmol) was dissolved in 95% ethanol (1.5 mL) and 2,4-dinitophenylhydrazine reagent[47] (2.00 mL, 0.28 mmol, 0.14 M) added. A precipitate formed almost immediately. After stirring for 15 min at room temperature, the reaction was cooled in an ice water bath, then vacuum filtered. Air drying gave the crude product (79.6 mg) as an orange solid. Recrystallization from hot 95% ethanol gave fine orange needles (61.9 mg, 87%) of the 2,4-dinitrophenyl hydrazone of **1a**: R_f (11:1 hexane:ethyl acetate) 0.58; mp 215–216 °C; ν_{max} 3286, 3113, 2657,

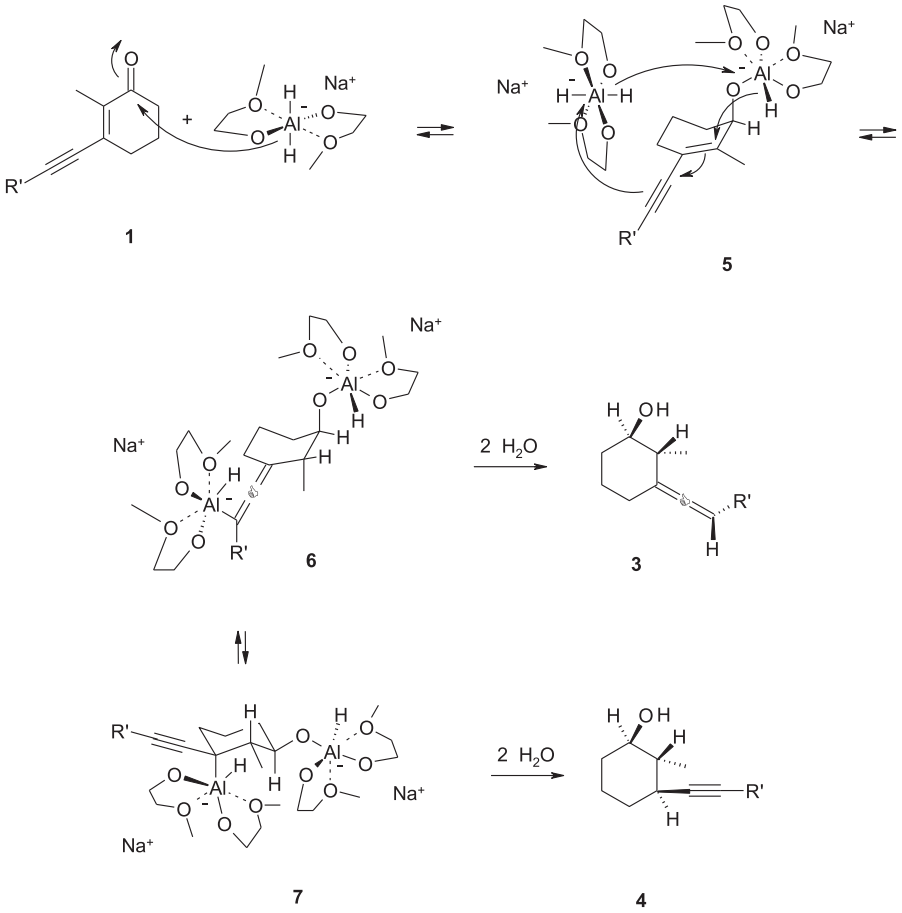


Fig. 3. Mechanistic proposal for tandem 1,2-, 1,4-hydride reduction.

2143, 1594, 1308, 835 cm^{-1}; δ_H ($CDCl_3$) 10.94 (s, 1H), 9.13 (d, J=2.5 Hz, 1H), 8.32 (dd, J=9.5, 2.5 Hz, 1H), 8.00 (d, J=9.5 Hz, 1H), 2.84–2.76 (m, 2H), 2.76–2.70 (m, 2H), 2.06 (t, J=1.9 Hz, 3H) 0.28 (s, 9H); δ_C ($CDCl_3$) 183.0, 166.2, 145.0, 144.8, 138.1, 136.1, 130.2, 123.8, 116.7, 108.0, 100.8, 32.9, 25.5, 11.2, 0.1; HRMS (MALDI): MH^+, found 373.1361. $[C_{17}H_{21}N_4O_4Si]^+$ requires 373.1332.

4.3. 2-Methyl-3-(trimethylsilylethynyl)-2-cyclohexenone (1b)[27]

Ethylmagnesium bromide (33.1 mL, 33.1 mmol, 1.0 M in THF) was added to an argon-purged, oven-dried 250 mL round bottom flask equipped with magnetic stirring bar, constant pressure addition funnel and an argon inlet. Stirring was begun and the flask was cooled to 0 °C in an ice water bath. Trimethylsilylethyne (3.58 g, 36.4 mmol) in THF (35 mL) was added dropwise over 30 min, after which time the ice water bath was removed and the flask allowed to warm to room temperature. Cooling to −78 °C was followed by dropwise addition of 3-isobutoxy-2-methyl-2-cyclohexenone[48] (5.00 g, 30.1 mmol) in THF (65 mL) over 30 min. The cold bath was left to exhaust itself as the reaction slowly warmed to room temperature overnight.

The reaction was quenched by the addition of water (10 mL), followed by K_2CO_3 (1 g) with rapid stirring. Dilution with diethyl ether (200 mL) was followed by transfer to a separatory funnel and washing with water (50 mL). The organic layer subsequently was washed with aqueous saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation gave a clear yellow liquid (9.08 g) which was taken up in diethyl ether (30 mL), then stirred rapidly with 1 M HCl (10 mL) for 3 h. Dilution with diethyl ether (40 mL) and transfer to a separatory funnel was followed by washing with aqueous saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation provided a clear yellow liquid (7.53 g) which was purified by kugelrohr distillation (85–90 °C, 2 mmHg) to give the *title compound* **1b** (4.26 g, 69%) as a clear, colorless liquid: ν_{max} 2956, 2139, 1669, 1595, 838 cm^{-1}; δ_H ($CDCl_3$) 2.53–2.43 (m, 4H), 2.05–1.95 (m, 2H), 1.99 (t, J=1.9 Hz, 3H), 0.3 (s, 9H); δ_C ($CDCl_3$) 198.8, 140.1, 137.3, 109.4, 103.6, 38.1, 31.1, 22.8, 14.2, −0.1; t_R 13.6 min, m/z (EI) 206 (32, M^{+A}), 191 (100), 187 (9), 163 (18).

A sample of **1b** (44.9 mg, 0.22 mmol was dissolved in 95% ethanol (1.5 mL) and dinitophenylhydrazine reagent[47] (2.00 mL, 0.28 mmol, 0.14 M) added. A precipitate formed almost immediately. After stirring for 15 min at room temperature, the reaction was cooled in an ice water bath, then vacuum filtered. Air drying gave the crude product (74.9 mg) as an orange solid. Recrystallization from hot 95% ethanol gave fine red-orange needles (65.7 mg, 77%) of the 2,4-dinitrophenyl hydrazone of **1b**: R_f (12:1 hexane:diethyl ether) 0.43; mp 210–212 °C; ν_{max} 3314, 3101, 2956, 2132, 1616, 1591, 13,301, 838 cm^{-1}; δ_H ($CDCl_3$) 11.3 (s, 1H), 9.14 (d, J=2.6 Hz, 1H), 8.37 (dd, J=9.5, 2.6 Hz, 1H), 8.02 (d, J=9.5 Hz, 1H) 2.58 (t, J=6.7 Hz, 2H), 2.46–2.39 (m, 2H), 2.23 (t, J=1.6 Hz, 3H), 1.94 (p, J=6.3 Hz, 2H) 0.24 (s, 9H); δ_C ($CDCl_3$) 153.6, 145.0, 138.8, 138.4, 130.3, 129.9, 127.5, 123.7, 116.9, 105.5, 50.1, 30.0, 24.5, 21.2, 15.9, 0.2; HRMS (MALDI): MH^+, 387.1476. $[C_{18}H_{23}N_4O_4Si]^+$ requires 387.1489.

4.4. 3-(Trimethylsilylethynyl)-2-cyclohexenone (1c)[19c]

Ethylmagnesium bromide (65.0 mL, 65.0 mmol, 1.0 M in THF) was added to an argon-purged, oven-dried 250 mL round bottom flask equipped with magnetic stirring bar, constant pressure addition

funnel and an argon inlet. Stirring was begun and the flask was cooled to 0 °C in an ice water bath. Trimethylsilylethyne (7.06 g, 71.9 mmol) in THF (65 mL) was added dropwise over 30 min, after which time the ice water bath was removed and the flask allowed to warm to room temperature. Cooling to −78 °C was followed by dropwise addition of 3-isobutoxy-2-cyclohexenone[49] (10.00 g, 59.4 mmol) in THF (130 mL) over 30 min. The cold bath was left to exhaust itself as the reaction slowly warmed to room temperature overnight.

The reaction was quenched by the addition of water (20 mL), followed by K_2CO_3 (1 g) with rapid stirring. Dilution with diethyl ether (200 mL) was followed by transfer to a separatory funnel and washing with water (100 mL). The organic layer subsequently was washed with aqueous saturated $NaHCO_3$ (40 mL), water (40 mL), and brine (40 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation gave a clear yellow liquid (18.04 g) which was taken up in diethyl ether (60 mL), then stirred rapidly with 1 M HCl (20 mL) for 2.5 h. Dilution with diethyl ether (40 mL) and transfer to a separatory funnel was followed by washing with aqueous saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation provided a clear, yellow liquid (12.85 g) which was purified by fractional distillation to give the *title compound* **1c** (9.01 g, 79%) as a nearly colorless liquid which solidified upon standing: bp 67–68 °C (0.8 mmHg) [lit.[19c] 50–55 °C (0.1 mmHg)]; mp 34–35 °C.

A sample of **1c** (38.3 mg, 0.20 mmol) was dissolved in 95% ethanol (1.5 mL) and 2,4-dinitophenylhydrazine reagent[47] (2.00 mL, 0.28 mmol, 0.14 M) added. A precipitate formed almost immediately. After stirring for 15 min at room temperature, the reaction was cooled in an ice water bath, then vacuum filtered. Air drying gave the crude product (73.5 mg) as an orange solid. Recrystallization from hot 95% ethanol/ethyl acetate gave fine orange needles (60.0 mg, 81%) of the 2,4-dinitrophenyl hydrazone **1c** as a mixture of diasteromers: R_f (10:1 hexane:ethyl acetate) 0.47 and 0.41; mp 173–189 °C; ν_{max} 3301, 3110, 2954, 2142, 1616, 1592,1369, 1331, 843 cm^{-1}; δ_H ($CDCl_3$) 11.48 and 11.32 (s, 1H), 9.16 (d, J=2.6 Hz, 1H), 8.35 and 8.33 (ddd, J=9.6, 2.6, 0.6 Hz, 1H) 8.02 and 7.99 (d, J=9.5 Hz, 1H), 6.82 and 6.69 (t, J=1.7 Hz, 1H), 2.60 and 2.59 (t,=10.2 and 6.7 Hz, 2H), 2.49 and 2.43 (td, J=6.0, 1.6 Hz, 2H), 2.00 (p, J=6.4 Hz, 2H), 0.28 and 0.26 (s, 9H); δ_C major isomer ($CDCl_3$) 153.4, 144.8, 138.5, 132.9, 130.8, 130.3, 123.7, 116.9, 105.4, 101.2, 29.5, 23.7, 21.2, 6.3; HRMS (MALDI): MH^+, 373.1358. $[C_{17}H_{21}N_4O_4Si]^+$ requires 373.1332.

4.5. 2-Methyl-3-(phenylethynyl)-2-cyclopentenone (1d)[48]

Ethylmagnesium bromide (20.6 mL, 24.3 mmol, 1.2 M in THF) was added to an argon-purged, oven-dried 250 mL round bottom flask equipped with magnetic stirring bar, constant pressure addition funnel and an argon inlet. The addition funnel was washed with additional THF (5 mL). Stirring was begun and the flask was cooled to 0 °C in an ice water bath. Phenylethyne (2.43 g, 23.8 mmol) in THF (27 mL) was added dropwise over 30 min, after which time the ice water bath was removed and the flask allowed to warm to room temperature. Cooling to −78 °C was followed by dropwise addition of 3-isobutoxy-2-methyl-2-cyclopentenone[46] (3.33 g, 19.8 mmol) in THF (27 mL) over 30 min. The cold bath was left to exhaust itself as the reaction slowly warmed to room temperature overnight.

The reaction was quenched by the addition of water (10 mL), followed by K_2CO_3 (1 g) with rapid stirring. Transfer to a separatory funnel was followed by extraction with diethyl ether (50 mL) four times. The pooled organic extracts were washed with water (20 mL) twice. The organic layer subsequently was washed with aqueous saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation gave the crude product, which was taken up in THF (20 mL), then stirred rapidly with 1 M HCl (20 mL) for 2 h. Dilution with diethyl ether (50 mL) and transfer to a separatory funnel was followed by washing with aqueous saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation gave a yellow liquid (4.75 g) which was purified by flash chromatography (4:1 petroleum ether:diethyl ether) to give the *title compound* **1d** (2.78 g, 72%) as an off-white solid: mp 70.5–71.5 °C (lit.[49] mp 85–87 °C); ν_{max} 3061, 2918, 2193, 1683, 1611, 763, 690 cm^{-1}; δ_H ($CDCl_3$) 7.60–7.52 (m, 2H), 7.46–7.34 (m, 3H), 2.76 (apparent octet, J=2.3 Hz, 2H), 2.52–2.45 (m, 2H), 1.96 (t, 2.1 Hz, 3H); δ_C ($CDCl_3$) 209.2, 150.2, 144.8, 132.1, 129.7, 128.7, 122.3, 105.7, 85.2, 34.2, 30.2, 10.0; t_R 18.9 min, m/z (EI) 196 (100, M^+), 181 (15), 167 (68), 153 (55), 139 (56).

A sample of **1d** (35.9 mg, 0.18 mmol) was dissolved in 95% ethanol (1.5 mL) and 2,4-dinitophenylhydrazine reagent[47] (2.00 mL, 0.28 mmol, 0.14 M) added. A precipitate formed almost immediately. After stirring for 15 min at room temperature, the reaction was cooled in an ice water bath, then vacuum filtered. Air drying gave the crude product (65.8 mg) as a red solid. Recrystallization from hot 95% ethanol/ethyl acetate gave red prisms (45.7 mg, 67%) of the 2,4-dinitrophenyl hydrazone of **1d**: R_f (10:1 hexane:ethyl acetate) 0.50; mp 240.0–241.0 °C; ν_{max} 3298, 3113, 2923, 1616, 1592, 1514, 1334, 1312 cm^{-1}; δ_H ($CDCl_3$) 11.01 (s, 1H), 9.17 (d, J=2.5 Hz, 1H), 8.35 (dd, J=9.5, 2.5 Hz, 1H), 8.04 (d, J=9.7 Hz, 1H), 7.59–7.53 (m, 2H), 7.46–7.33 (m, 3H), 2.99–2.89 (m, 2H), 2.89–2.76 (m, 2H), 2.17 (t, J=1.8 Hz, 3H); δ_C ($CDCl_3$) 166.3, 145.0, 143.8, 138.0, 136.3, 132.0, 130.2, 129.4, 129.3, 128.8, 123.9, 122.8, 116.7, 101.9, 85.7, 33.0, 25.6, 11.3; HRMS (MALDI): MH^+, 377.1246. $[C_{20}H_{17}N_4O_4]^+$ requires 377.1250.

4.6. 2-Methyl-3-(phenylethynyl)-2-cyclohexenone (1e)

Ethylmagnesium bromide (20.0 mL, 23.6 mmol, 1.2 M in THF) was added to an argon-purged, oven-dried 250 mL round bottom flask equipped with magnetic stirring bar, constant pressure addition funnel and an argon inlet. The addition funnel was washed with additional THF (5 mL). Stirring was begun and the flask was cooled to 0 °C in an ice water bath. Phenylethyne (2.46 g, 24.1 mmol) in THF (28 mL) was added dropwise over 30 min, after which time the ice water bath was removed and the flask allowed to warm to room temperature. Cooling to −78 °C was followed by dropwise addition of 3-isobutoxy-2-methyl-2-cyclohexenone[50] (3.64 g, 20.0 mmol) in THF (28 mL) over 30 min. The cold bath was left to exhaust itself as the reaction slowly warmed to room temperature overnight.

The reaction was quenched by the addition of water (10 mL), followed by K_2CO_3 (1 g) with rapid stirring. Transfer to a separatory funnel was followed by extraction with diethyl ether (50 mL) four times. The pooled organic extracts were washed with water (20 mL) twice. The organic layer subsequently was washed with aqueous saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation gave the crude product, which was taken up in THF (20 mL), then stirred rapidly with 1 M HCl (20 mL) for 2 h. Dilution with diethyl ether (50 mL) and transfer to a separatory funnel was followed by washing with aqueous saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation gave a yellow liquid (6.14 g), which solidified upon standing. Recrystallization from hot petroleum ether gave the *title compound* **1e** (2.85 g, 68%): mp 62–63 °C; ν_{max} 2945, 2197, 1647,768, 694 cm^{-1}; δ_H ($CDCl_3$) 7.57–7.47 (m, 2H), 7.44–7.34 (m, 3H), 2.61 (t of q, J=1.8, 6.0 Hz, 2H), 2.51 (t, J=6.5 Hz, 2H), 2.08 (t, J=3.6 Hz, 3H), 2.60 (p, J=6.6 Hz, 2H); δ_C ($CDCl_3$) 198.5, 139.3, 137.6, 131.9, 129.4, 128.7, 122.8, 103.2, 88.5, 38.2, 31.3, 23.0, 14.2; t_R 15.1 min, m/z (EI) 210 (100, M^+), 182 (38), 167 (45), 154 (53),

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139 (30); HRMS (MALDI): MH^+, 211.1108. $[C_{15}H_{15}O]^+$ requires 211.1123.

A sample of **1e** (31.7 mg, 0.15 mmol) was dissolved in 95% ethanol (1.5 mL) and added dropwise with stirring to 2,4-dinitophenylhydrazine reagent[47] (2.00 mL, 0.28 mmol, 0.14 M). A precipitate formed almost immediately. After stirring for 15 min at room temperature, the reaction was cooled in an ice water bath, then vacuum filtered. Air drying gave the crude product (90.6 mg) as an orange powder. Recrystallization from hot ethyl acetate gave small dark red prisms (41.0 mg, 70%) of the 2,4-dinitrophenyl hydrazone **1e**: R_f (11:1 hexane:ethyl acetate) 0.44; mp 215–217 °C; ν_{max} 3304, 3113, 2947, 1613, 1589, 1309 cm^{-1}; δ_H ($CDCl_3$) 11.35 (s, 1H), 9.17 (d, J=2.5 Hz, 1H), 8.36 (dd, J=2.5, 9.5 Hz, 1H), 8.06 (d, J=9.5 Hz, 1H), 7.57–7.48 (m, 2H), 7.43–7.34 (m, 3H), 2.65 (t, J=6.6 Hz, 2H), 2.55 (td, J=1.4, 6.1 Hz, 2H), 2.34 (t, J=1.5 Hz, 3H), 2.02 (apparent p, J=6.4 Hz, 2H); δ_C ($CDCl_3$) 153.7, 145.0, 138.4, 137.8, 131.8, 130.3, 129.9, 129.0, 128.7, 127.8, 123.8, 123.3, 117.0, 100.0, 89.9, 30.2, 24.6, 21.3, 16.0; HRMS (MALDI): MNa^+, 413.1241. $[C_{21}H_{18}N_4O_4Na]^+$ requires 413.1226.

4.7. 3-(Phenylethynyl)-2-cyclohexenone (1f)[48]

Butylmagnesium bromide (16.0 mL, 23.5 mmol, 1.5 M in THF) was added to an argon-purged, oven-dried 250 mL round bottom flask equipped with magnetic stirring bar, constant pressure addition funnel and an argon inlet. The addition funnel was washed with additional THF (16 mL). Stirring was begun and the flask was cooled to 0 °C in an ice water bath. Phenylethyne (2.46 g, 24.1 mmol) in THF (28 mL) was added dropwise over 30 min, after which time the ice water bath was removed and the flask allowed to warm to room temperature. Cooling to −78 °C was followed by dropwise addition of 3-isobutoxy-2-cyclohexenone[49] (3.37 g, 20.0 mmol) in THF (28 mL) over 30 min. The cold bath was left to exhaust itself as the reaction slowly warmed to room temperature overnight.

The reaction was quenched by the addition of water (10 mL), followed by K_2CO_3 (1 g) with rapid stirring. Transfer to a separatory funnel was followed by extraction with diethyl ether (50 mL) four times. The pooled organic extracts were washed with water (20 mL) twice. The organic layer subsequently was washed with aqueous saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation gave the crude product, which was taken up in THF (20 mL), then stirred rapidly with 1 M HCl (20 mL) for 2 h. Dilution with diethyl ether (50 mL) and transfer to a separatory funnel was followed by washing with aqueous saturated $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$), filtration and concentration by rotary evaporation provided a yellow liquid (4.18 g) which was purified by kugelrohr distillation to give the *title compound* **1f** (3.46 g, 88%): bp 110 °C (0.1 mmHg); mp 37–40 °C (lit.[48] mp 90–92 °C); ν_{max} 3078, 2948, 2194, 1663, 1599, 761, 690 cm^{-1}; δ_H ($CDCl_3$) 7.55–7.45 (m, 2H) 7.45–7.30 (m, 3H), 6.31 (t, J=1.8 Hz, 1H), 2.56 (t of d, J=5.9, 1.8 Hz, 2H), 2.44 (t, J=7.2 Hz, 2H), 2.06 (p, J=7.2 Hz, 2H); δ_C ($CDCl_3$) 198.7, 143.5, 132.6, 132.2, 129.7, 128.7, 122.3, 99.9, 88.7, 37.6, 30.8, 22.9; t_R 16.8 min, m/z (EI) 196 (100, M^+), 168 (70), 139 (89).

A sample of **1f** (35.8 mg, 0.18 mmol) was dissolved in 95% ethanol (1.5 mL) and added dropwise with stirring to 2,4-dinitophenylhydrazine reagent[47] (2.00 mL, 0.28 mmol, 0.14 M). A precipitate formed almost immediately. After stirring for 15 min at room temperature, the reaction was cooled in an ice water bath, then vacuum filtered. Air drying gave the crude product (68.8 mg) as a red solid. Recrystallization from hot ethyl acetate gave red crystals (53.9 mg, 80%) of the 2,4-dinitrophenyl hydrazone of **1f** as a 1:1 mixture of diasteromers: R_f (11:1 hexane:ethyl acetate) 0.32 and 0.27; mp 225–228 °C; ν_{max} 3304, 3114, 2946, 1612, 1586, 1331, 1305 cm^{-1}; δ_H ($CDCl_3$) 11.53 and 11.35 (two s, 1H), 9.17 (d, J=2.5 Hz, 1H), 8.44–8.30 (m, 1H), 8.03 (t, J=9.7 Hz, 1H), 7.63–7.48 (m, 2H), 7.48–7.36 (m, 3H), 6.88 and 6.75 (two t, J=1.8 and 1.5 Hz, 1H), 2.77–2.49 (m, 4H), 2.15–1.96 (m, 2H); δ_C ($CDCl_3$) 153.6, 152.3, 145.1, 144.8, 138.5, 138.1, 137.0, 132.2, 132.0, 131.9, 131.1, 130.3, 130.2, 129.6, 129.4, 129.1, 128.8, 128.7, 123.8, 123.7, 122.9, 122.3, 119.7, 116.9, 116.6, 97.9, 95.7, 90.2, 89.9, 31.7, 31.2, 29.7, 23.8, 22.6, 21.3; HRMS (MALDI): MH^+, 377.1218. $[C_{20}H_{17}N_4O_4]^+$ requires 377.1250.

4.8. Lithium aluminum hydride reduction of 1a in THF: (1*R**,2*R**,*S**)-2-methyl-3-(trimethylsilylethenylidene)cyclopentanol [(1*R**,2*R**,*S**)-3a] and (1*R**,2*R**,3*S**)-2-methyl-3-(trimethylsilylethynyl)cyclopentanol [(1*R**,2*R**,3*S**)-4a]

A solution of **1a** (39.4 mg, 0.20 mmol) in THF (2.3 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun as the reaction was cooled to 0 °C. A solution of lithium aluminum hydride (430 μL, 0.43 mmol, 1 M in THF) was added dropwise, then the cold bath removed. The resultant solution was stirred at room temperature for 2 h. The reaction subsequently was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (6 drops) added. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a colorless oil (37.9 mg).

Purification of a sample of the crude product (69.9 mg) by medium pressure liquid chromatography (2 mL/min, 4:1 hexane:diethyl ether) gave two fractions. Fraction one was concentrated by rotary evaporation to give a colorless oil (29.5 mg, 42%) consisting of a 92:8 mixture of isomeric alcohols. The major diastereomer was identified as the *title compound* (1*R**,2*R**,*S**)-**3a**: R_f (4:1 hexane:diethyl ether) 0.21; ν_{max} 3337, 2946, 1940, 1242, 1067, 1042, 856, 836 cm^{-1}; δ_H ($CDCl_3$) 5.04 (ddd, J=10.8, 5.3, 0.6 Hz, 1H), 3.76 (dd, J=12.9, 6.7 Hz, 1H), 2.57–2.43 (m, 1H), 2.40–2.22 (two m, 2 H), 1.97–1.84 (m, 1H), 1.54 (s, 1H), 1.58–1.45 (m, 1H), 1.11 (d, J=6.7 Hz, 3H), 0.10 (s, 9H); δ_C ($CDCl_3$) 205.5 (C), 99.0 (C), 86.2 (CH), 80.1 (CH), 45.5 (CH), 33.4 (CH_2), 26.2 (CH_2), 17.1 (CH_3), -0.5 (CH_3); t_R 15.5 min, m/z (EI) 196 (48, M^+), 163 (23), 105 (31), 91 (83), 75 (95), 73 (100). Minor isomer: t_R 14.6 min, m/z (EI) 196 (42, M^+), 165 (20), 105 (28), 91 (78), 75 (99), 73 (100); HRMS (MALDI): MH^+, 197.1334. $[C_{11}H_{21}OSi]^+$ requires 197.1362. Fraction two was concentrated by rotary evaporation to give of a colorless oil (10.7 mg, 15%) consisting of a 93:7 mixture of isomeric alcohols. The major isomer was identified as the *title compound* (1*R**,2*R**,3*S**)-**4a**: R_f (4:1 hexane:diethyl ether) 0.17; ν_{max} 3327, 2956, 2162, 1453, 1248, 846, 760 cm^{-1}; δ_H ($CDCl_3$) 3.97 (dd, J=10.4, 4.7 Hz, 1H), 3.02 (dd, J=14.5, 7.2 Hz, 1H), 2.20–2.03 (m, 1H), 2.02–1.89 (m, 1H), 1.99–1.90 (m, 1H), 1.83–1.68 (m, 1H), 1.62–1.58 (m, 1H), 1.05 (d, J=7.0 Hz, 3H), 0.14 (s, 9H); δ_C ($CDCl_3$) 107.0 (C), 86.8 (C), 79.3 (CH), 46.0 (CH), 34.1 (CH), 32.9 (CH_2), 29.7 (CH_2), 14.3 (CH_3), 0.5 (CH_3); t_R 14.9 min, m/z (EI) 196 (0.4, M^+), 195 (1), 181 (62), 165 (51), 163 (59), 152 (31), 91 (30), 75 (100), 73 (64); HRMS (MALDI): MH^+-H_2O, 179.1212. $[C_{11}H_{19}Si]^+$ requires 179.1256. Minor isomer: t_R 14.6 min, m/z (EI) 196 (0.6, M^+), 195 (0.7), 181 (24), 163 (58), 75 (100), 73 (23).

4.9. Lithium aluminum hydride reduction of 1a in benzene: 2-methyl-3-(trimethylsilylethynyl)-2-cyclopentenol (2a)

Lithium aluminum hydride (19.8 mg, 0.52 mmol) and benzene (1.0 mL) were added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun and the suspension cooled to 0 °C. A solution of **1a** (29.8 mg, 0.16 mmol) in benzene (1.0 mL) was added dropwise. Once the addition was complete, the cold bath was removed and reaction the stirred at room temperature for 2 h. The reaction subsequently was diluted with diethyl ether (20 mL), then

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aqueous saturated ammonium chloride (6 drops) added. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a crude product (25.8 mg) as a colorless oil.

A sample of crude product (141.9 mg) was purified by preparative thin layer chromatography (4:1 hexane:diethyl ether) to give the *title compound* **2a** (96.2 mg, 68%) as a white solid: R_f (4:1 hexane:diethyl ether) 0.24; mp 63–64 °C; ν_{max} 3188, 2962, 2859, 2144, 841 cm^{-1}; δ_H ($CDCl_3$) 4.64 (br q, J=5.9 Hz, 1H), 2.63–2.48 (m, 1H), 2.43–2.24 (m, 2H), 1.91 (p, J=1.1 Hz, 3H), 1.75–1.61 (m, 1H), 1.60–1.41 (m, 1H), 0.22 (s, 9H); δ_C ($CDCl_3$) 149.5, 121.5, 101.8, 99.6, 80.3, 33.7, 33.2, 13.4, 0.3; t_R 16.0 min, *m/z* (EI) 194 (37, M^+), 179 (100), 161 (66), 121 (82).

A sample of purified **2a** (22.1 mg, 0.12 mol) and DMF (1.0 mL) were added to a dry 25 mL round bottom flask equipped with a magnetic stirring bar. *tert*-Butyldimethylsilyl chloride (27.0 mg, 0.18 mmol) and imidazole (20.0 mg, 0.29 mmol) were added sequentially and the reaction stoppered and stirred overnight at room temperature. Dilution with diethyl ether (50 mL) was followed by washing with water (25 mL) five times. The ether solution then was dried (Na_2SO_4), filtered and concentrated by rotary evaporation to provide a colorless oil (38.4 mg). Purification of this oil by preparative thin layer chromatography (hexane) gave 3-(*tert*-butyldimethylsilyloxy)-2-methyl-1-(trimethylsilylethynyl)cyclopentene (27.9 mg, 75%): R_f (hexane) 0.20; ν_{max} 2957, 2858, 2144, 1250, 1066, 842 cm^{-1}; δ_H ($CDCl_3$) 4.68 (t, J=4.7 Hz, 1H), 2.59–2.47 (m, 1H), 2.38–2.28 (m, 1H), 2.28–2.16 (m, 1H), 1.89–1.80 (m, 3H), 1.72–1.52 (m, 1H), 0.92 (s, 9H), 0.22 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); δ_C ($CDCl_3$) 150.3, 119.7, 102.1, 98.5, 80.0, 33.4, 25.8, 18.2, 13.3, 0.1, -4.5, -4.8; t_R 16.8 min, *m/z* (EI) 308 (9, M^+), 293 (9), 177 (10), 161 (27), 147 (100), 97 (12), 75 (33); HRMS (MALDI): MH^+, 309.2099. $[C_{17}H_{33}OSi_2]^+$ requires 309.2070.

4.10. Lithium aluminum hydride reduction of 2a in THF: (1*R**,2*R**,*S**)-3a and (1*R**,2*R**,3*S**)-4a

A solution of **2a** (21.5 mg, 0.11 mmol) and THF (2.0 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun and the flask cooled to 0 °C. A solution of lithium aluminum hydride (245 μL, 0.24 mmol, 1 M in THF) was added dropwise, then the cold bath removed. The resultant solution was stirred at room temperature for 2 h. The reaction subsequently was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (5 drops) added. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a colorless oil (25.6 mg). GC/MSD analysis determined the ratio of **3a**:**4a** to be 66:34. (1*R**,2*R**,*S**)-**3a** was the major (91:9) double reduction allene product and (1*R**,2*R**,3*S**)-**4a** was the major (90:10) alkyne double reduction product.

4.11. Sodium bis(2-methoxyethoxy)aluminum hydride reduction of 1a in THF: 2a, (1*R**,2*R**,*S**)-3a and (1*R**,2*R**,3*S**)-4a

A solution of **1a** (42.5 mg, 0.22 mmol) in THF (2.0 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun and the solution cooled to 0 °C. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (280 μL, 0.98 mmol. 3.5 M in toluene) was added dropwise. Once the addition was complete, the cold bath was removed and the reaction was stirred at room temperature for 2 h. After recooling to 0 °C, the reaction was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (15 drops) added. The cold bath was removed and the flask warmed to room temperature. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a pale yellow oil (47.3 mg). GC/MSD analysis determined the ratio of **3a**:**4a**:**2a** to be 68:18:14. (1*R**,2*R**,*S**)-**3a** was the major (96:4) double reduction allene product and (1*R**,2*R**,3*S**)-**4a** was the major (79:21) alkyne double reduction product.

4.12. Sodium bis(2-methoxyethoxy)aluminum hydride reduction of 1b in THF: (1*R**,2*R**,*S**)-2-methyl-3-(trimethylsilylethenylidene)cyclohexanol [(1*R**,2*R**,*S**)-3b] and 2-methyl-3-(trimethylsilylethynyl)cyclohexanol [(1*R**,2*R**,3*S**)-4b]

A solution of **1b** (61.2 mg, 0.30 mmol) in THF (4.0 mL) was added to an argon-purge, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun and the solution cooled to 0 °C. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (190 μL, 0.66 mmol, 3.5 M in toluene) was added dropwise. Once the addition was complete, the cold bath was removed and the reaction was stirred at room temperature for 2 h. After recooling to 0 °C the reaction was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (10 drops) added. The cold bath was removed and the flask warmed to room temperature. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a pale yellow oil (66.4 mg). GC/MSD analysis determined the ratio of 2-methyl-3-(trimethylsilylethenylidene)cyclohexanol (**3b**):2-methyl-3-(trimethylsilylethynyl)cyclohexanol (**4b**) to be 74:26. The *title compound* (1*R**,2*R**,*S**)-**3b** was the major (86:14) double reduction allene product and the *title compound* (1*R**,2*R**,3*S**)-**4b** was the major (83:17) alkyne double reduction product.

Purification of the crude product by medium pressure liquid chromatography (1.3 mL/min, 4:1 hexane:diethyl ether) gave (1*R**,2*R**,*S**)-**3b** (32.0 mg, 51%) as a colorless oil: R_f (4:1 hexane:diethyl ether) 0.25; ν_{max} 3351, 2955, 2928, 2857, 1941, 1246, 839 cm^{-1}; δ_H ($CDCl_3$) 4.99 (t, J=4.8 Hz, 1H), 3.24 (apparent heptet, J=4.8 Hz, 1H), 2.25 (dt, J=3.4, 14.2 Hz, 1H), 2.81–1.82 (m, 4H), 1.48–1.25 (m, 3 H), 1.11 (d, J=6.6 Hz, 3H), 0.11 (s, 9H); δ_C ($CDCl_3$) 206.6, 98.5, 83.9, 76.6, 41.3, 35.3, 31.0, 25.6, 15.6, -0.6; t_R 13.2 min, *m/z* (EI) 210 (42, M^+), 192 (27), 177 (44), 149 (9), 119 (23), 105 (42), 91 (37), 75 (83), 73 (100); HRMS (MALDI): MH^+-H_2O, 193.1449. $[C_{12}H_{21}Si]^+$ requires 193.1413. It was not possible to isolate a chromatographically pure fraction of isomeric, slightly more polar (1*R**,2*R**,3*S**)-**4b**.

4.13. Lithium aluminum hydride reduction of 1b in THF: (*R**,2*R**,*S**)-3b and (1*R**,2*R**,3*S**)-4b

A solution of **1b** (40.7 mg, 0.20 mmol) in THF (2.0 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun and the flask was cooled to 0 °C. A solution of lithium aluminum hydride (435 μL, 0.43 mmol, 1 M in THF) was added dropwise. Once the addition was complete, the cold bath was removed and the stirred at room temperature for 2 h. After recooling to 0 °C the reaction was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (7 drops) added. The cold bath was removed and the flask warmed to room temperature. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a clear, colorless oil (40.0 mg). GC/MSD analysis determined the ratio of **3b**:**4b** to be 74:26. (*R**,2*R**,*S**)-**3b** was the major (89:11) double reduction allene product and (1*R**,2*R**,3*S**)-**4b** was the major (88:12) alkyne double reduction product.

4.14. Lithium aluminum hydride reduction of 1c in THF: (1*R**,*S**)-3-(trimethylsilylethenylidene)cyclohexanol [(1*R**,*S**)-3c] and (1*R**,3*S**)-3-(trimethylsilylethynyl)cyclohexanol [(1*R**,3*S**)-4c]

A solution of **1c** (61.0 mg, 0.32 mmol) in THF (4.0 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet.

Stirring was begun and the flask was cooled to 0 °C. A solution of lithium aluminum hydride (700 μL, 0.70 mmol, 1.0 M in THF) was added dropwise. Once the addition was complete, the cold bath was removed and the reaction stirred at room temperature for 2 h. After recooling to 0 °C the reaction was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (15 drops) added. The cold bath was removed and the flask warmed to room temperature. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a clear, colorless oil (72.2 mg). GC/MSD analysis determined the ratio of 3-(trimethylsilylethenylidene)cyclohexanol (**3c**):3-(trimethylsilylethynyl) cyclohexanol (**4c**) to be 80:20. The *title compound* (1*R**,*S**)-**3c** was the major (69:31) double reduction allene product and only one diastereoisomer of the alkyne double reduction product, ostensibly the *title compound* (1*R**,3*S**)-**4c**, was observed.

Purification of the crude product by medium pressure liquid chromatography (1.5 mL/min, 4:1 hexane:diethyl ether) gave (1*R**,*S**)-**3c** (6.4 mg, 10%) as a clear, colorless oil: R_f (4:1 hexane:diethyl ether) 0.25; ν_{max} 3324, 2934, 1947, 1247, 1052, 840 cm^{-1}; δ_H ($CDCl_3$) 4.90–4.84 (m, 1H), 3.83–3.72 (m, 1H), 2.50 (m, 1H), 2.20–1.69 (m, 5H), 1.52–1.34 (m, 2H), 1.29 (s, 1H), 0.11 (s, 9H); δ_C ($CDCl_3$) 206.8, 91.7, 81.9, 70.0, 39.7, 34.9, 30.0, 24.4, -0.6; t_R 12.3 min, *m/z* (EI) 196 (42, M^+), 178 (29), 163 (64), 105 (27), 91 (80), 73 (100); HRMS (MALDI): MH^+, 197.1367. $[C_{11}H_{21}OSi]^+$ requires 197.1362. A second, more polar fraction returned (1*R**,3*S**)-**4c** (6.2 mg, 10%) as a clear, colorless oil: R_f (4:1 hexane:diethyl ether) 0.14; ν_{max} 3188, 2930, 2165, 841 cm^{-1}; δ_H ($CDCl_3$) 4.06 (s, 1H), 2.94–2.85 (m, 1H), 1.98–1.86 (m, 1H), 1.86–1.76 (m, 1H), 1.73–1.55 (m, 5H), 1.48–1.26 (m, 2H), 0.17 (s, 9H); δ_C ($CDCl_3$) 110.7, 67.0, 39.8, 34.5, 31.3, 27.0, 20.5, 14.4, 0.5; t_R 12.1 min, *m/z* (EI) 196 (5, M^+), 181 (19), 178 (24), 163 (79), 151 (52), 75 (100); HRMS (ESI): MH^+, 197.1320. $[C_{11}H_{21}OSi]^+$ requires 197.1362.

4.15. Sodium bis(2-methoxyethoxy)aluminum hydride reduction of 1c in THF: (1*R**,*S**)-3c and (1*R**,3*S**)-4c

A solution of **1c** (58.4 mg, 0.30 mmol) in THF (3.0 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun and the solution cooled to 0 °C. A solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (190 μL, 0.67 mmol, 3.5 M in toluene) was added dropwise. Once the addition was complete, the cold bath was removed and the reaction was stirred at room temperature for 2 h. After recooling to 0 °C the reaction was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (11 drops) added. The cold bath was removed and the flask warmed to room temperature. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a clear, colorless oil (59.2 mg) which was purified by preparative thin layer chromatography (2:1 hexane:diethyl ether) to yield two fractions. Fraction 1: (1*R**,*S**)-**3c**, clear, colorless oil (31.6 mg, 54%); R_f (2:1 hexane:diethyl ether) 0.32. Fraction 2: (1*R**,3*S**)-**4c**, clear, colorless oil (2.8 mg, 5%); R_f (2:1 hexane:diethyl ether) 0.20.

4.16. Sodium bis(2-methoxyethoxy)aluminum hydride reduction of 1d in THF: (1*R**,2*R**,*S**)-2-methyl-3-(phenylethenylidene)cyclopentanol [(1*R**,2*R**,*S**)-3d]

A solution of **1d** (38.2 mg, 0.19 mmol) in THF (2.0 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun and the solution cooled to 0 °C. A solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (122 μL, 0.43 mmol, 3.5 M in toluene) was added dropwise. Once the addition was complete, the cold bath was removed and the reaction was stirred at room temperature for 2 h. After recooling to 0 °C the reaction was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (7 drops) added. The cold bath was removed and the flask warmed to room temperature. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a yellow oil (42.9 mg) which was purified by preparative thin layer chromatography (4:1 hexane:diethyl ether) to yield of the *title compound* (1*R**,2*R**,*S**)-**3d** (20.6 mg, 54%) as a clear, colorless oil: R_f (4:1 hexane:diethyl ether) 0.40; ν_{max} 3354, 3030, 2960, 2928, 2870, 1951, 1598, 1455, 1073, 1047, 693 cm^{-1}; δ_H ($CDCl_3$) 7.37–7.29 (m, 4H), 7.26–7.16 (m, 1H), 6.22 (q, *J*=4.2 Hz, 1H), 3.92 (q, *J*=6.4 Hz, 1H), 2.84–2.46 m, 3H, 2.22–2.04 (m, 1H), 1.82–1.59 (m, 2H), 1.22 (d, *J*=7.0 Hz, 3H); δ_C ($CDCl_3$) 199.7, 135.8, 128.8, 126.9, 126.7, 111.0, 97.3, 80.0, 47.4, 33.4, 26.7, 17.4; t_R 19.2 min, *m/z* (EI) 200 (76, M^+), 167 (46), 156 (60), 141 (100), 128 (56), 115 (41), 102 (17), 91 (27); HRMS (MALDI): MH^+, 201.1309. $[C_{14}H_{17}O]^+$ requires 201.1280.

4.17. Sodium bis(2-methoxyethoxy)aluminum hydride reduction of 1e in THF: (1*R**,2*R**,*S**)-2-methyl-3-(phenylethenylidene)cyclohexanol [(1*R**,2*R**,*S**)-3e]

A solution of **1e** (34.0 mg, 0.16 mmol) in THF (2.0 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun and the solution cooled to 0 °C. A solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (105 μL, 0.37 mmol, 3.5 M in toluene) was added dropwise. Once the addition was complete, the cold bath was removed and the reaction was stirred at room temperature for 2 h. After recooling to 0 °C the reaction was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (7 drops) added. The cold bath was removed and the flask warmed to room temperature. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a white solid (39.3 mg), which was dissolved in warm hexane (2.0 mL). Slow cooling to −18 °C and isolation of the solid that formed by vacuum filtration gave the *title compound* (1*R**,2*R**,*S**)-**3e** (33.3 mg, 96%) as a white solid: R_f (3:1 hexane:diethyl ether) 0.30; mp 112–114 °C; ν_{max} IR 3454, 2981, 2952, 2924, 2861, 1952, 1453, 1061, 1031, 1014, 827, 748, 694 cm^{-1}; δ_H ($CDCl_3$) 7.37–7.27 (m, 4H), 7.26–7.16 (m, 1H), 6.20 (t, *J*=3.7 Hz, 1H), 3.43 (apparent heptet, *J*=4.6 Hz, 1H) 2.42 (dtd, *J*=1.5, 3.6, 12.5 Hz, 1H), 2.21–1.90 (m, 4H), 1.71 (d, *J*=4.7 Hz, 1H), 1.67–1.41 (m, 2H), 1.18 (d, *J*=6.7 Hz, 3H); δ_C ($CDCl_3$) 201.0, 136.0, 128.8, 126.8, 126.6, 110.2, 95.5, 76.9, 43.0, 35.1, 31.5, 25.7, 15.4; t_R 20.1 min, *m/z* (EI) 214 (100, M^+), 181 (59), 167 (23), 155 (38), 143 (87), 129 (67), 115 (49), 91 (60); HRMS (MALDI): MH^+-H_2O, 197.1334. $[C_{15}H_{17}]^+$ requires 197.1330.

4.18. Lithium aluminum deuteride reduction of 1e in THF: (1*R**,2*R**,*S**)-(1,2-$^2H_2$)-2-methyl-3-(phenylethenylidene) cyclohexanol

Lithium aluminum deuteride (16.7 mg, 0.39 mmol) and THF (1.0 mL) were added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum, and argon inlet. Stirring was begun and the suspension cooled to 0 °C. A solution of **1e** (31.8 mg, 0.15 mmol) in THF (1.0 mL) was added dropwise. Once the addition was complete, the cold bath was removed and the stirred at room temperature for 2 h. After recooling to 0 °C the reaction was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (10 drops) added. The cold bath was removed and the flask warmed to room temperature. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give the crude *title compound* (27.0 mg) as an oil which solidified upon standing. ^1H NMR and GC/MSD analyses indicated ≥96% deuterium incorporation at

positions 1 and 2: δ_H ($CDCl_3$) 7.39–7.27 (m, 4H), 7.26–7.16 (m, 1H), 6.20 (d, *J*=3.6 Hz, 1H), 2.42 (dtd, *J*=1.4, 3.7, 14.2 Hz, 1H), 2.21–1.78 (m, 3H), 1.75–1.40 (m, 3H), 1.17 (s, 3H); t_R 20.1 min, *m/z* (EI) 216 (100, M^+), 183 (52), 168 (21), 156 (33), 144 (81), 129 (64), 115 (27), 91 (39).

4.19. Lithium aluminum hydride reduction of 1e in THF with deuterium oxide quenching: (1*R**,2*R**,*S**)-2-methyl-3-(2-^{2}H-2-phenylethenylidene)cyclohexan(^{2}H)ol

A solution of **1e** (25.7 mg, 0.12 mmol) in THF (2.0 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun and the flask was cooled to 0 °C. A solution of lithium aluminum hydride (270 μL, 0.27 mmol, 1.0 M in THF) was added dropwise. Once the addition was complete, the cold bath was removed and the stirred at room temperature for 2 h. After recooling to 0 °C the reaction was diluted with diethyl ether (20 mL), then deuterium oxide (0.5 mL) added dropwise. A few 4 Å molecular sieves were added and the resulting mixture stirred at room temperature for 10 min. Vacuum filtration was followed by washing the sieves and precipitate with dry diethyl ether. The filtrate and washings were combined and concentrated by rotary evaporation to give the crude *title compound* (30.4 mg) with regioselective 93% incorporation of deuterium at position 2 of the ethenylidene substituent and 21% incorporation of deuterium at the hydroxy substituent as determined by ^{1}H NMR and GC/MSD analyses: δ_H ($CDCl_3$) 7.43–7.26 (m, 4H), 7.26–7.16 (m, 1H), 3.42 (td, *J*=4.1, 9.6 Hz, 1H), 2.42 (dtd, *J*=1.6, 3.7, 13.3 Hz, 1H), 2.21–1.81 (m, 3H), 1.80–1.40 (m, 3H), 1.18 (d *J*=6.7 Hz, 3H); t_R 20.1 min, *m/z* (EI) 216 (45, M^+), 215 (100), 182 (58), 168 (27), 156 (37), 144 (87), 130 (68), 129 (69), 116 (41), 92 (48).

4.20. Sodium bis(2-methoxyethoxy)aluminum hydride reduction of 1f in THF: 3-(phenylethenylidene)cyclohexanol (3f)

A solution of **1f** (56.2 mg, 0.29 mmol) in THF (3.0 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun and the solution cooled to 0 °C. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (180 μL, 0.63 mmol, 3.5 M in toluene) was added dropwise. Once the addition was complete, the cold bath was removed and the reaction was stirred at room temperature for 2 h. After recooling to 0 °C the reaction was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (10 drops) added. The cold bath was removed and the flask warmed to room temperature. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a clear oil (59.5 mg), which was purified by preparative thin layer chromatography (2:1 hexane:diethyl ether) to give a mixture of diasteromers of the *title compound* **3f** (32.0 mg, 56%) as a colorless oil: R_f (2:1 hexane:diethyl ether) 0.31; ν_{max} 3346, 3030, 2934, 2890, 2857, 1954, 1598, 1051, 745, 693 cm^{-1}; δ_H ($CDCl_3$) 7.38–7.27 (m, 4H), 7.26–7.17 (m, 1H), 6.13–6.05 (m, 1H), 4.00–3.88 (m, 1H), 2.63 (t of m, *J*=12.9 Hz, 1H), 2.38–2.06 (m, 3H), 2.06–1.87 (m, 2H), 1.72 (s, 1H), 1.71–1.45 (m, 2H); major isomer δ_C ($CDCl_3$) 201.4, 135.7, 128.8, 126.9, 126.8, 103.4, 93.3, 70.2, 40.1, 34.6, 30.7, 24.4; t_R 19.8 min, *m/z* (EI) 200 (100, M^+), 181 (23), 167 (48), 154 (34), 141 (64), 129 (82), 115 (36), 102, (18), 91, (37), 77 (15); HRMS (MALDI): MH^+, 201.1297. $[C_{14}H_{17}O]^+$ requires 201.1280.

4.21. 1,2-Dimethyl-3-(phenylethynyl)-2-cyclohexenol (2g)

THF (2.0 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun as the flask was cooled to 0 °C. A solution of methyllithium (400 μL, 0.64 mmol, 1.6 M in diethyl ether) of was added, followed by dropwise addition of a solution of **1e** (60.1 mg, 0.29 mmol) in THF (4.0 mL). Once the addition was complete, the reaction was stirred at 0 °C for 1.5 h, then the cold bath removed and the reaction warmed to room temperature over 1.5 h. Quenching with aqueous saturated NH_4Cl (0.3 mL) and water (0.3 mL) was followed by dilution with diethyl ether (20 mL), drying through $MgSO_4$, and concentration by rotary evaporation. A yellow oil (84.1 mg) resulted and was purified by preparative thin layer chromatography (3:1 hexane:diethyl ether) to give the *title compound* **2g** (44.0 mg, 67%) as a colorless oil: R_f (3:1 hexane:diethyl ether) 0.29; ν_{max} 3375, 3055, 2971, 2936, 2866, 1596, 755, 734, 690 cm^{-1}; δ_H ($CDCl_3$) 7.50–7.43 (m, 2H), 7.39–7.30 (m, 3H), 2.39–2.20 (m, 2H), 2.09 (t, *J*=2.0 Hz, 3H), 1.87–1.69 (m, 4H), (1.57 br s, 1H), 1.38 (s, 3H); δ_C ($CDCl_3$) 145.1, 131.6, 128.5, 128.2, 124.0, 117.7, 93.0, 89.9, 70.8, 39.3, 30.8, 27.4, 19.8, 16.1; t_R 19.4 min, *m/z* (EI) 226 (16, M^+), 211 (100). The total ion chromatogram indicated a propensity for the product to thermally dehydrate: t_R 18.1 min, *m/z* (EI) 208 (100, M^+), 193 (23), 178 (52), 165 (19), 115 (16).

4.22. (1*R**,2*R**,*S*$_a$*)-1,2-Dimethyl-3-(phenylethenylidene)cyclohexanol [(1*R**,2*R**,*S**)-3g]

A solution of **2g** (44.0 mg, 0.19 mmol) in THF (3.0 mL) was added to an argon-purged, oven-dried 25 mL round bottom flask equipped with magnetic stirring bar, serum septum and argon inlet. Stirring was begun and the solution cooled to 0 °C. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (125 μL, 0.43 mmol, 3.5 M in toluene) was added dropwise. Once the addition was complete, the cold bath was removed and the reaction left to stir at room temperature for 2 h. After recooling to 0 °C the reaction was diluted with diethyl ether (20 mL), then aqueous saturated ammonium chloride (10 drops) added. The cold bath was removed and the flask warmed to room temperature. Filtration through anhydrous $MgSO_4$ was followed by concentration by rotary evaporation to give a colorless oil (51.8 mg). Preparative thin layer chromatography (2:1 hexane:diethyl ether) gave the *title compound* (1*R**,2*R**,*S**)-**3g** (32.5 mg, 75%) as a colorless oil: R_f (2:1 hexane:diethyl ether) 0.36; ν_{max} 3308, 2967, 2929, 2862, 1948, 1598, 1119, 981, 690 cm^{-1}; δ_H ($CDCl_3$) 7.37–7.30 (m, 5H), 7.25–7.16 (m, 1H), 6.19 (td, *J*=1.0, 3.2 Hz, 1H), 2.46–2.35 (m, 1H), 2.32–2.21 (m, 1H), 2.21–2.08 (m, 1H), 1.92–1.80 (m, 1H) 1.75–1.54 (m, 3H), 1,27 (s, 3H), 1.12 (d, *J*=6.9 Hz, 3H); δ_C ($CDCl_3$) 201.1, 136.1, 128.8, 126.7, 126.7, 109.6, 95.2, 73.7, 45.9, 40.5, 30.4, 24.4, 22.2, 13.0; t_R 18.6 min, *m/z* (EI) 228 (22, M^+), 210 (6), 195 (15), 185 (8), 170 (25), 155 (51), 143 (100), 129 (46), 115 (35), 91 (38) 71 (23); HRMS (MALDI): MH^+-H_2O, 211.1480. $[C_{16}H_{19}]^+$ requires 211.1487.

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Supplementary data

Supplementary data related to this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.07.058. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1476506. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: despoit@ccdc.cam.ac.uk.

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