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Strategies and Tactics for Site Specific Deuterium Incorporation at Each Available Carbon Atom of α -Pinene

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Abstract

The development of several unique strategies and tactics for the synthesis of α -pinene isotopologues that has culminated in access to all eight possible isomers with deuterium incorporated selectively at each available carbon atom is described. Access to this library of isotopologues provides new tools to more fully investigate the atmospheric autoxidation of α -pinene, a complex process that plays a major role in the formation of secondary organic aerosol in the Earth's atmosphere.

Graphical Abstract

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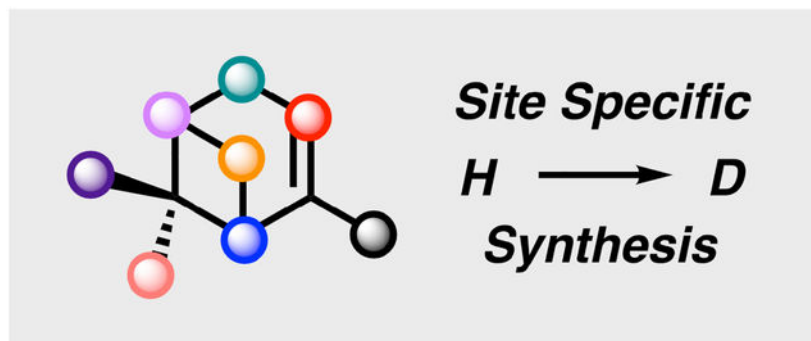
Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.4c01702>.

Synthetic procedures and characterization data for new compounds (PDF)

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/acs.joc.4c01702>

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INTRODUCTION

α -pinene (**1**), a chiral bicyclic monoterpene, is the most abundant terpenoid found in nature.¹ Named for the conifer pine trees whose oils contain it in concentrations as high as 80%, α -pinene (**1**) plays important roles in plant and animal biological processes, as well as chemical synthesis, where it has found widespread use as an inexpensive chiral building block.^{2,3} Beyond its terrestrial importance, α -pinene (**1**) plays a major role in the Earth's climate system due to its high volatility and rapid reactivity toward atmospheric oxidants driven by its electron-rich alkene, abundant C–H bonds and strained cyclobutane ring (Figure 1A).^{4–7} Emitted from the Earth's Boreal forests in quantities of 32 Tg/year (from a total of ~95 Tg/year monoterpene),¹ α -pinene (**1**) undergoes gas-phase oxidation in the troposphere with ozone to generate the unstable Criegee intermediate **2** (Figure 1B), which decomposes rapidly through a series of H atom abstractions and hydroperoxyl radical intermediates formed by oxygen addition to produce a complex mixture of highly oxidized molecules (also known as HOMs).^{8–10} These HOMs are significantly less volatile and more polar than α -pinene, leading to a condensation from the gas-phase to the aqueous-phase and the formation of secondary organic aerosol (SOA) which ultimately influences the global climate system through the nucleation of clouds.⁶

Numerous studies have probed the formation of HOMs in ambient conditions or under controlled conditions within atmospheric chambers, providing initial key insights into the oxidation kinetics and possible structures of intermediates through the use of mass spectrometric techniques.^{6,7,10–16} Remarkably, α -pinene undergoes gas-phase autoxidation to produce highly oxidized monomers incorporating up to 11 oxygen atoms within 300 ms reaction time,⁹ while longer times lead to formation of dimers possessing upward of 18 oxygens.^{7,10,17} The structural identity of these species and mechanisms for their formation have been the subject of speculation on the basis of a combination of mass spectrometric data and computational investigations (Figure 1C). For example, breakdown of Criegee intermediate **2** followed by 1,4-H atom abstraction, loss of HO• and subsequent reaction with dioxygen leads to detected species with a molecular formula C₁₀H₁₅O₄, whose open-shell structure could be one or all of the possible isomers **3**, **4** or **5**.^{14,18} Similarly, incorporation of additional oxygen atoms leads to a dominant signal with the molecular formula C₁₀H₁₅O₈, whose structure has been suggested as the ring-opened peroxy radical **6** and/or intact cyclobutane **8**,^{9,19} while structures such as peroxides **7** and **9** have been

proposed for higher weight dimeric ion peaks formed from these respective monomer species.^{19,20} Despite the importance of α -pinene-derived HOMs there remains limited experimental evidence to validate the positions of C–H abstraction, hampering definitive structural identification of proposed compounds (i.e., **3–9**, for example) and limiting a comprehensive elucidation of the complex oxidation pathways.

Motivated by these and other questions, we have explored the role that synthetic organic chemistry can play in providing new insights into atmospheric chemistry.²¹ This work targeted stable and isolatable compounds, such as isoprene-derived epoxides^{22–24} and organosulfates,^{25,26} α -pinene-derived ester and aldol dimers,²⁷ and caryophyllene-derived aldehydes.^{28,29} We considered the synthesis of complex peroxide dimers such as **7** and **9** to be impractical due to their presumed instability and possible hazardous decomposition, yet were drawn to the puzzle of α -pinene autoxidation pathways and the structure of HOMs. Consequently, we initiated an effort to prepare deuterated isotopologues of α -pinene for use in studies aimed at providing new insights into HOM formation mechanisms, structure and properties (Figure 2). The rationale for stable isotope incorporation was driven by the planned use of HRMS to distinguish between oxidized intermediates, thereby providing valuable information into the site of C–H abstraction. Some preliminary results from early efforts have been reported,^{11,18,30,31} in part due to the ease with which α -pinene-10,10,10-*d*₃ (**11**) could be accessed (see Scheme 1).³² This work has, however, been limited by a lack of access to the full suite of site-selectively deuterated isotopologues in order to generate a comprehensive data set. In this full report focused only on synthesis, we now reveal the fruition of our goal to prepare the eight possible isotopologues of α -pinene with deuterium substitution at each possible individual carbon atom (Figure 2).³³

At the outset it was important for us to clearly define the required parameters for deuterium incorporation within α -pinene such that the products obtained would be useful for future autoxidation investigations,¹¹ namely 100% site selectivity and complete deuterium incorporation as defined by the limits of ¹H NMR spectroscopy signal-to-noise (i.e., ~ 20:1). Samples existing as mixtures of regioisomeric isotopologues would be problematic in a study focused on determining the specific site of oxidation. α -Pinene possesses eight hydrogen bearing carbon atoms in distinct environments and it was tempting to conjecture that an approach utilizing direct C–H functionalization of α -pinene itself might provide access to the eight required targets. Given the inherent challenges of such an undirected C–H functionalization strategy,³⁴ however, we did not view such an approach as currently feasible or practical and therefore opted to pursue an approach with its foundations in synthetic design and functional group manipulation (Figure 2). Broadly speaking, our work employs two distinct approaches; a top-down strategy wherein the bicyclo[3.1.1]heptyl ring system is already present within the starting material [i.e., nopinone (**10**) or verbenone (**14**)] and a bottom-up strategy that forges the crucial bicyclic framework from monocyclic precursors [i.e., Hagemann's ester (**18**) or carvone (**20**)]. Incorporation of deuterium atoms was accomplished from suitably disposed precursors either by addition of CD₃Li, H–D exchange with D₂O or by exhaustive reduction using LiAlD₄. Each of these methods, when conducted on the appropriately designed synthetic intermediate, would fulfill the parameters for deuterium incorporation we had defined at the outset (see above). While the focus of this

report is on the diverse array of synthetic strategies and tactics employed to access these new compounds, we envision that this access will open exciting avenues for discovery in the field of atmospheric science in the near future.

RESULTS AND DISCUSSION

When we initiated our research project, only limited prior effort had been directed toward the synthesis of deuterium labeled α -pinene isotopologues. In 1974, Shaffer and Pesaro had reported a synthesis of α -pinene-9,9,9- d_3 (**13**) as a precursor to verbenone-9,9,9- d_3 as part of an effort to investigate the photochemical isomerization of verbenone.³⁵ Borden and co-workers reported a related route to **13** in 1980 as part of studies investigating the rearrangement of bicyclooctadienes.³⁶ In 1980, Skattebøl and Stenstrom reported a synthesis of α -pinene-10,10,10- d_3 (**11**) in order to probe the biosynthetic origins of insect pheromones.³⁷ Beyond these two isotopologues, access to the other isotopologues was unknown in the literature thereby providing us with significant intellectual motivation to devise novel and efficient approaches for site selective deuteration of all possible carbon atoms within α -pinene. Because we desired access to α -pinene-10,10,10- d_3 (**11**) for some planned environmental chamber and spectroscopic studies, we first considered Skattebøl and Stenstrøm's reported route which proceeded by the addition of CD_3MgI to nopinone (**10**) followed by dehydration of alcohol **22** using "thoroughly purified sulfonyl chloride in pyridine" to afford **11** in 37% yield from **10** (Scheme 1).³⁷ They reported that 2% of a β -pinene derivative along with 2% of an unidentified impurity was present within the distilled product, so while this route may have proven serviceable, we sought an alternative method. To avoid the formation of the unwanted β -pinene isomer, our new route involved initial formation of enol triflate **24** using Comin's reagent (**23**),³⁸ which underwent a smooth, regiospecific coupling with the cuprate derived from CD_3Li to afford α -pinene-10,10,10- d_3 (**11**) in 57% yield from nopinone (**10**).³² This strategy was then adapted to access α -pinene-3- d (**12**) by first carrying out an exhaustive hydrogen–deuterium exchange at C3 of nopinone (**10**) under basic conditions, followed by formation of 3- d -enol triflate **25**. Subsequent methyl cuprate coupling delivered the desired isotopologue **12** in 27% over the three steps from nopinone (**10**).

Nopinone (**10**) also served as the starting material for our previously reported synthesis of α -pinene-9,9,9- d_3 (**13**),³² which was inspired by the earlier work of Shaffer and Pesaro,³⁵ as well as Borden and co-workers.³⁶ Briefly, caged ether **26** could be generated in reasonable yields by the stereoselective addition of methyl lithium to **10** followed by a Suárez-type oxidative etherification.³⁹ Fragmentation of the cyclic ether within **26** using acetic anhydride reinstalled the trisubstituted alkene, leading to an intermediate primary acetate that was converted to alcohol **27** upon exposure to $LiAlH_4$. Oxidation with wet pyridinium dichromate proceeded with low conversions, giving a 1:1 ratio of the corresponding aldehyde and carboxylic acid. However, a cycle of two consecutive purifications and resubmissions to the oxidation conditions allowed the desired acid **28** to be obtained in an overall yield of 65%. Lastly, the desired α -pinene-9,9,9- d_3 (**13**) isotopologue could be produced in three steps by a sequence of iterative reductions with $LiAlD_4$.

Verbenone (**14**) served as a suitable starting material for three additional isotopologues: α -pinene-4,4- d_2 (**15**), α -pinene-7,7- d_2 (**16**) and α -pinene-1- d (**17**). Reduction of verbenone (**14**) with lithium aluminum deuteride following the procedure by Valterová and co-workers generated deuterated verbenol **31**,⁴⁰ which was then treated with thionyl chloride to yield a 3:5:1 mixture of unstable diastomeric allyl chlorides (major isomer **32** shown) with a crude yield of approximately 80% (Scheme 2). The allylic chlorides proved highly unstable and the mixture was treated directly with LiAlD₄ without purification to afford two reduced products in a ratio 3:1 favoring the desired S_N2 product (**15**) over the undesired minor product, **33** (stereochemistry not determined), derived from a competing S_N2' pathway. Separation of these two hydrocarbons could be accomplished by careful chromatography using AgNO₃-impregnated silica gel⁴¹ to ultimately allow isolation of pure α -pinene-4,4- d_2 (**15**) in 13% yield. It is also worth highlighting at this point that the isolation of α -pinene derivatives using chromatographic methods can be particularly challenging due to their relative volatility (the very property that makes α -pinene atmospherically relevant!); care must be taken to use low boiling eluents, such as pentane and ether, and to remove these solvents with care under moderate levels of reduced pressure so as to not also vaporize the precious α -pinene species.

The photochemical isomerization of verbenone (**14**) to chrysanthenone (**34**) has been studied extensively,^{42,43} and we hoped to exploit this rearrangement to access α -pinene-7,7- d_2 (**16**) and α -pinene-1- d (**17**). Using an improved protocol for the isomerization that uses narrow spectrum 350 nm UV bulbs rather than the traditional Hg-lamp (Scheme 3), we were able to access chrysanthenone (**34**) in 67% yield in order to explore the exhaustive reductive deuteration of the C7 carbonyl group.⁴⁴ We initially explored formation of tosylate **36** via alcohol **35**, but (unsurprisingly) this species proved recalcitrant to reduction with LiAlD₄ due to a combination of steric and strain effects that preclude S_N2 displacement. We turned next to carbonyl deletion methods utilizing hydrazones, but initially had no success, which at the juncture led us to devise a completely different approach involving total synthesis (see later in Scheme 4). However, returning to this problem sometime later led to the successful implementation of a modified version of the Cram conditions for the Wolff–Kishner reduction⁴⁵ whereby treatment of the corresponding preformed hydrazone derived from ketone **34** with potassium *tert*-butoxide in DMSO- d_6 generated the desired product, α -pinene-7,7- d_2 (**16**), in 13% isolated yield. While the yield of this process was not high, the route is short and deuterium incorporation was complete within the limits of ¹H NMR spectroscopic detection.

Photochemical isomerization of the verbenone scaffold also proved useful to access the C1 bridgehead isotopologue α -pinene-1- d (**17**, Scheme 3). Hydrogenation of verbenone (**14**)⁴⁶ followed by treatment with NaOD in D₂O provided ketone **37** in 64% yield, which was converted to verbenone-1- d (**38**) through a Saegusa–Ito oxidation.⁴⁷ Exposure of **38** to 350 nm UV light then provided ketone **39** in 49% yield with the deuterium atom now situated at the required bridgehead location. The modified Cram conditions for the Wolff–Kishner reduction we had devised earlier then allowed direct access to α -pinene-1- d (**17**) in 21% yield.

As alluded to earlier, frustrations that grew from a strategy whereby the α -pinene skeleton was manipulated to allow for deuterium atom incorporation led us to investigate an alternative total synthesis strategy. We reasoned that such a de novo approach would allow more flexibility in the tactics used to install the required deuterium atoms. We first targeted α -pinene-7,7- d_2 (**16**) since this was the compound that had initially stymied our α -pinene skeleton-based efforts (Scheme 4). This strategy, which we initially reported in 2019,⁴⁸ was based upon the pioneering total synthesis of α -pinene by Fallis and Thomas reported in 1973.^{49,50} Thus, reduction of Hagemann's ester (**18**) using LiAlD₄ afforded diol **40**, which was converted to enone **41** by treatment with DDQ. Protection and conjugate methylation generated ketone **42** which set the stage for the key cyclobutene ring-forming step that served as a lynch-pin in the Fallis and Thomas synthesis. An initial aldol condensation with benzaldehyde was carried out to yield enone **43**; a process that ensures regioselective formation of the desired cyclobutane (i.e., **44**) upon exposure to NaH. Removal of the benzyldiene blocking group through a retro-aldol process in the presence of γ -aminobutyric acid (GABA) gave rise to nopinone isotopologue **45**. Completion of the synthesis of α -pinene-7,7- d_2 (**16**) then proceeded via triflate **46** in a method akin to the synthesis of α -pinene-10,10,10- d_3 (**11**, see Scheme 1).

This earlier route established the viability of the total synthesis approach to deuterium labeled α -pinene isotopologues and was used to prepare deuterium labeled secondary organic material for a series of surface specific spectroscopic investigations.⁴⁸ However, in comparison to the route that delivers **16** from verbenone (**14**, see Scheme 3) it is less efficient and also provides the product as a racemate. On the other hand, we considered the total synthesis strategy to be a superior platform for the preparation of the remaining bridgehead isomer, namely α -pinene-5- d (**19**, Scheme 5).

Treatment of Hagemann's ester (**18**) with NaH followed by an acidic quench with deuterated sulfuric acid in D₂O led to formation of doubly deuterated Hagemann's ester analog **47**. A reduction, oxidation and protection sequence then provided enone **48** which underwent smooth conjugate methylation to yield ketone **49** in 83% yield. Aldol condensation with benzaldehyde using sodium hydroxide also effected cleavage of the acetate group and removal of the unwanted C1 deuterium atom; tosylation of the liberated hydroxy group afforded enone **50**. As before, formation of the cyclobutane ring proceeded effectively and in good yield to deliver enone **51**. Unfortunately, however, the strongly basic conditions required to remove the benzyldiene group led to significant (40–50%) loss of deuterium at C5 during formation of ketone **52**. Suppression of this loss could be accomplished by using DMSO- d_6 as the solvent, but this also led to additional unselective deuteration at C3 and C4.⁴⁸ Deuteration at C4 under these conditions likely proceeded via formation of the extended benzylic anion, a potential pathway for isomerization of the exocyclic enone within **51** to the corresponding endocyclic isomer, which in turn could enhance the acidity of the C5 bridgehead position to allow a basic exchange. A control experiment exposing nopinone (**10**) to the DMSO- d_6 conditions did not afford any deuteration at the C5 bridgehead, providing evidence against an exchange mechanism directly involving nopinone (**10**). Regardless, the basic conditions of the retro-aldol approach would not be viable to access the desired compound with only C5 deuterated, and as such we needed to devise

an alternative end-game for converting enone **51** into α -pinene-5-*d* (**19**). Ultimately, this goal was accomplished by an initial cerium chloride-promoted 1,2-addition of MeLi to the ketone of **51** to form tertiary alcohol **53**,⁵¹ which underwent subsequent ozonolysis to generate α -ketol **54**. Ketone reduction with sodium borohydride was unselective, whereas diastereoselective reduction could be accomplished effectively using DIBAL, producing diol **55** as a single stereoisomer in 76% yield. Selective formation of the syn-diol was critical and allowed final installation of the requisite alkene by means of a Corey–Winter olefination via thiocarbonate **56**,⁵² ultimately allowing isolation of α -pinene-5-*d* (**19**) in 24% yield from diol **55**.

The final analog required to complete our goal of providing access to all possible α -pinenes with site specific deuterium incorporation at each available carbon atom was α -pinene-8,8,8-*d*₃ (**21**), which has the exomethyl group substituted. While the diastereomeric endomethyl group (i.e., C9) could be deuterated by taking advantage of an intramolecular oxidation (see Scheme 1), it was not obvious that functionalization of C8 could be accomplished in a related manner. We were drawn, however, to the known hydroxy pinene derivatives, **57** and **58**, produced by the reductive cyclization of epoxycarvone (Scheme 6).^{53–55} Epoxidation of carvone (**20**) followed by treatment with Cp₂TiCl₂ produces a 2:3 mixture of the diastereomeric diols **57** and **58**. In this case, diol **58**, which could be isolated in 38% yield, possesses hydroxylation at the desired C8 carbon, but would require removal of the unwanted bridgehead hydroxy group. Protection of the less hindered C8 hydroxy group as its TBDPS ether afforded tertiary alcohol **59**, which served as a suitable substrate to explore deoxygenation conditions to form ether **60**. Ultimately, after extensive exploration and optimization,⁵⁶ it was found that initial quantitative formation of the *N*-phthalimidoyl oxalate allowed for a Ru(bpy)₃(PF₆)₂ photocatalyzed-reduction to deliver the requisite hydrocarbon (i.e., **60**) in 15% isolated yield.^{57,58} While low yielding, this protocol provided sufficient material throughput to allow synthesis of the desired deuterium labeled α -pinene to proceed. Consequently, carboxylic acid **61** was produced in 40% yield following TBDPS removal and oxidation of the free alcohol using wet PDC.

Reduction with LiAlD₄ generated alcohol **62**, which was converted to α -pinene-8,8,8-*d*₃ (**21**) by an additional LiAlD₄ reductive displacement of the corresponding tosylate.

CONCLUSION

Synthetic approaches providing access to the eight possible isotopologues of α -pinene possessing site specific deuterium substitution at each of the available carbon atoms have been developed. Two distinct strategies were realized; one that used starting materials already possessing the bicyclo[3.1.1]heptyl ring system present within α -pinene (i.e., nopinone and verbenone), and the other requiring formation of the cyclobutane ring from cyclohexyl precursors (i.e., Hagemann's ester and carvone). The completion of each individual α -pinene target relied upon effective means for quantitative deuterium incorporation and utilized a careful combination of classic and contemporary chemical transformations. For example, synthesis of the C5 bridgehead isotopologue **19** used the venerable Corey–Winter olefination to avoid deuterium loss, while access to the C8 endomethyl species **21** deployed a modern photocatalytic deoxygenation to remove an

unwanted tertiary hydroxy group. A novel modification of the Cram conditions for the Wolff–Kishner reduction of ketones was also developed to allow carbonyl deletion with concomitant incorporation of deuterium atoms. While the focus of our efforts was on analogues with single carbon atoms deuterated, it is conceivable that a combination of the various protocols developed would allow preparation of additional α -pinene isotopologues with two or more carbon atoms selectively labeled should such species be desired. Current attention is now focused on using the eight isotopologues reported here in atmospheric studies to probe the intricate details of α -pinene autoxidation, the results of which will be reported in due course.

EXPERIMENTAL PROCEDURES

General Experimental.

All experiments were conducted under a nitrogen atmosphere in flame-dried glassware. All reagents were used as purchased. Reaction solvents were purchased as anhydrous or purified by either a solvent purification column or distillation. Starting materials and reagents were purchased from Sigma-Aldrich, Thermo Fisher Scientific, or TCI and used without further purification unless otherwise noted. Diisopropylamine and pyridine were distilled over CaH_2 prior to use. Purifications of products were performed by flash column chromatography using silica gel (230–400 mesh) as a stationary phase. Silver nitrate-impregnated silica gel was purchased from Sigma-Aldrich (10 wt % loading, 230 mesh) and used directly from the bottle. Blue light irradiation was conducted with two Kessil A160WE Tuna Blue lamps with brightness at maximum and wavelength at minimum (deepest blue), placed two inches distance from either side of the reaction vessel. The reaction vessel used was a Chemglass Life Sciences 75 mL Heavy Wall Pressure Vessel. Analytical thin-layer chromatography technique was performed on silica gel precoated glass-backed plates, and the reactions were examined by UV-light (254 nm) irradiation or staining with potassium permanganate stain or *p*-anisaldehyde stain. A Bruker Avance III 400, 500, or 600 MHz instrument was used to record ^1H and ^{13}C NMR spectra of all compounds. NMR data are reported as brs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Signals are detailed in ppm and coupling constants in Hz. High-resolution mass spectra were recorded with a time-of-flight (TOF) mass analyzer Bruker Impact-II Mass Spectrometer. A Bruker Tensor 37 FTIR spectrometer was used to obtain infrared spectra of compounds and data were reported in cm^{-1} . All melting points are uncorrected. The syntheses of α -pinene-9,9,9- d_3 (**11**), α -pinene-10,10,10- d_3 (**13**) and α -pinene-6,6- d_2 (**16**) were carried out according to our previously published procedures.^{32,48}

Synthetic Procedures and Compound Data.

(1R)-6,6-Dimethylbicyclo[3.1.1]heptan-2-one-3,3- d_2 (S1).—To a solution of (1R)-nopinone (**10**) (2.10 g, 15 mmol, 1 equiv) in DMSO- d_6 (40 mL) was added 40 wt % NaOD in D_2O (7 mL). The reaction mixture was heated to 90 °C for 3 h, then cooled to room temperature and diluted with D_2O (40 mL) and Et_2O (40 mL). The organic phase was collected and the aqueous layer extracted with Et_2O (3 × 40 mL). Combined organics were dried with MgSO_4 , filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel using 15–20% Et_2O in pentane as the eluent afforded the title

compound (1.83 g, 87%) as a light yellow oil. ^1H NMR (500 MHz, CDCl_3) δ : 2.58–2.47 (m, 2H), 2.26–2.19 (m, 1H), 2.07–1.98 (m, 1H), 1.96–1.89 (m, 1H), 1.57 (d, $J = 10.3$ Hz, 1H), 1.32 (s, 3H), 0.84 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 215.1, 58.0, 41.2, 40.4, 32.0 (m, 1C), 25.9, 25.3, 22.1, 21.2. FT-IR (neat): 2930, 2874, 1715, 1459. 1370, 1268, 1159, 1053 cm^{-1} . HRMS (APCI): exact mass calcd for $\text{C}_9\text{H}_{13}\text{D}_2\text{O}$ $[\text{M} + \text{H}]^+$, 141.1243. Found 141.1242.

(1R)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl-3-d Trifluoromethanesulfonate

(25).—To a solution of diisopropylamine (0.9 mL, 6.42 mmol, 1.5 equiv) in THF (12 mL) at -78 °C was added *n*-butyllithium (2.5 mL, 6.42 mmol, 2.5 M in hexanes, 1 equiv). After 15 min, (1*R*)-6,6-dimethylbicyclo[3.1.1]heptan-2-one-3,3-*d*₂ (**S1**) (600 mg, 4.28 mmol, 1 equiv) in THF (10 mL) was added dropwise into the solution of LDA and stirred for 40 min. At this time, a solution of Comins' reagent (3.36 g, 8.56 mmol, 2 equiv) in THF (8 mL) was added over a period of 15 min. The resulting mixture was warmed to 0 °C and stirred for 2 h. The reaction mixture was diluted with D_2O (50 mL) and Et_2O (25 mL) and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with Et_2O (3×30 mL). The combined organics were dried with MgSO_4 . Concentration under reduced pressure and flash column chromatography on silica gel in 0–3% Et_2O in pentane as the eluent afforded the title compound (790 mg, 68% yield) as a clear oil. ^1H NMR (500 MHz, CDCl_3): 2.56 (dt, $J = 9.1, 5.7$ Hz, 1H), 2.41–2.25 (m, 3H), 2.17–2.12 (m, 1H), 1.38 (d, $J = 9.2$ Hz, 1H), 1.35 (s, 3H), 0.93 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 155.0, 118.5 (q, 1C, $J = 321$ Hz), 111.2 (m, 1C), 46.3, 40.1, 39.7, 31.7, 28.1, 25.5, 25.5, 20.8. FT-IR (neat): 2940, 2841, 1653, 1418, 1202, 1138, 1058 cm^{-1} . HRMS (APCI): APCI, exact mass calcd for $\text{C}_{10}\text{H}_{12}\text{F}_3\text{O}_3\text{S}$ $[\text{M} - \text{D}]^-$, 269.0645. Found 269.0640.

(1S)2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene-3-d (12).—Methyl lithium bromide complex (3.9 mL, 5.86 mmol, 1.5 M in Et_2O , 3.5 equiv) was added to a slurry of CuI (0.80 g, 4.18 mmol, 2.5 equiv) in THF (8 mL) at -5 °C. After stirring for 15 min, a room temperature solution of (1*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl-3-*d* trifluoromethanesulfonate (**25**) (0.45 g, 1.67 mmol, 1 equiv) in THF (7 mL) was added dropwise. The reaction mixture turned dark red and was allowed to warm to room temperature overnight after which the mixture was cooled to 0 °C, then quenched with dropwise addition of H_2O until bubbling subsided. The mixture was diluted with H_2O (50 mL) and extracted with pentane (3×30 mL). Combined organics were dried with Na_2SO_4 and filtered. Concentration under reduced pressure and flash column chromatography on silica gel in 100% pentane as the eluent afforded the title compound (105 mg, 46% yield, >20:1 deuterium incorporation) as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 2.33 (dt, $J = 8.5, 5.6$ Hz, 1H), 2.28–2.11 (m, 2H), 2.11–2.03 (m, 1H), 1.93 (t, $J = 5.6$ Hz, 1H), 1.66 (t, $J = 2.2$ Hz, 3H), 1.27 (s, 3H), 1.15 (d, $J = 8.5$ Hz, 1H), 0.84 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) 144.4, 115.7 (m, 1C), 47.0, 47.0, 40.7, 38.0, 31.5, 31.1, 26.4, 22.9, 20.8. FT-IR (neat): 2986, 2917, 2834, 1469, 1436, 1380, 1365, 1207, 1099, 1061 cm^{-1} . HRMS (APCI): exact mass calcd for $\text{C}_{10}\text{H}_{16}\text{D}$ $[\text{M} + \text{H}]^+$, 138.1388. Found 138.1388.

2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene-4,4-*d*₂ (15).—To a solution of 4,6,6-trimethylbicyclo [3.1.1]hept-3-en-2-*d*-2-ol (**31**)⁴⁰ (1.9 g, 12.4 mmol, 1 equiv) in Et_2O (45

mL) was added SOCl₂ (0.94 mL, 13 mmol 1.05 equiv). The reaction mixture was stirred at room temperature for 1 h, then quenched with saturated sodium bicarbonate. The organic phase was collected and the aqueous layer extracted with Et₂O (3 × 40 mL). Combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated carefully under reduced pressure. The crude allyl chloride was dissolved in 3 mL Et₂O and added dropwise to a suspension of LiAlD₄ (352 mg, 8.4 mmol, 0.7 equiv) in Et₂O (12 mL) at -50 °C. The reaction mixture was slowly warmed to room temperature over 4 h, then diluted with 10 mL pentane and quenched with dropwise addition of H₂O (0.5 mL), followed by 15% NaOH in H₂O (0.5 mL), then H₂O (1 mL). The resulting suspension was filtered through Celite and the filtrate dried with Na₂SO₄ then concentrated. The product was purified via flash column chromatography on silica gel in 100% pentane as the eluent followed by flash column chromatography on silver nitrate-impregnated silica gel with 1.5% Et₂O in pentane as the eluent. Careful concentration of fractions yielded the title compound (227 mg, 13% over 2 steps, >20:1 deuterium incorporation) as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ: 5.18 (s, 1H), 2.33 (ddd, *J* = 8.5, 5.8, 5.3 Hz, 1H), 2.26 (t, *J* = 5.6 Hz, 1H), 1.93 (td, *J* = 5.6 Hz, 1.5 Hz, 1H), 1.66 (d, *J* = 1.7 Hz, 3H), 1.27 (s, 3H), 1.15 (d, *J* = 8.5 Hz, 1H), 0.83 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ: 144.7, 116.0, 47.1, 40.6, 38.1, 31.5, 30.9–30.4 (m), 26.4, 23.1, 20.9. FT-IR (neat): 2985, 2915, 2868, 2724, 1469, 1440, 1346, 1259, 1133, 1102 cm⁻¹. HRMS (EI): exact mass calcd for C₁₀H₁₄D₂ [M]⁺, 138.1372. Found 138.1371.

4,6,6-Trimethylbicyclo[3.1.1]heptan-2-one-3,3-d₂ (37).—4,6,6-

Trimethylbicyclo[3.1.1]heptan-2-one (**S2**)⁴⁶ (5.0 g, 33 mmol, 1 equiv) was dissolved in THF (100 mL). To the solution was added 33 mL 40 wt % NaOD in D₂O and the reaction was stirred at reflux overnight. The reaction mixture was cooled to room temperature, diluted with D₂O (50 mL) and Et₂O (100 mL). The organic layer was separated and the aqueous layer extracted with pentane (3 × 100 mL). Combined organic layers were dried with MgSO₄, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel with 20% Et₂O in pentane as the eluent to yield the title compound (4.0 g, 80%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ: 2.64–2.52 (m, 2H), 2.36 (q, *J* = 7.5 Hz, 1H), 2.11–2.14 (m, 1H), 1.43–1.37 (m, 1H), 1.34 (s, 3H), 1.16 (d, *J* = 7.5 Hz, 3H), 1.00 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ: 214.7, 58.2, 47.5, 41.0–40.5 (m), 40.4, 31.0, 28.5, 27.1, 24.7, 21.1. FT-IR (neat): 2976, 2953, 2916, 2876, 1703, 1471, 1456, 1370, 1244, 1201, 1153, 1047, 974, 731 cm⁻¹. HRMS (ESI): exact mass calcd for C₁₀H₁₅D₂O [M + H]⁺, 155.1399. Found 155.1401.

4,6,6-Trimethylbicyclo[3.1.1]hept-3-en-2-one-3-d (38).—Diisopropylamine (2.2 mL, 15.6 mmol, 1.3 equiv) was dissolved in anhydrous THF (65 mL). The mixture was cooled to -78 °C and 2.5 M *n*-BuLi in hexanes (6.6 mL, 16.6 mmol, 1.35 equiv) was added dropwise. The solution was stirred for 15 min, then a solution of 4,6,6-trimethylbicyclo[3.1.1]heptan-2-one-3,3-d₂ (**37**) (1.85 g, 12 mmol, 1 equiv) in THF (27 mL) was added dropwise via cannula. The resulting mixture was stirred for 30 min at -78 °C, then TMSCl (2.1 mL, 16.8 mmol, 1.4 equiv) was added dropwise. The reaction was stirred for 30 min at -78 °C then slowly warmed up to 0 °C and stirred at 0 °C for 1 h. The reaction was then quenched slowly with pH 7 buffer and extracted with pentane (3 × 100 mL). Combined organic layers were

dried with MgSO₄, filtered, and concentrated carefully. The crude material was dissolved in acetonitrile (120 mL) and palladium acetate (2.88 g, 12.8 mmol, 1.07 equiv) was added to the solution. The reaction mixture was stirred overnight at room temperature, then filtered through a silica gel column with 10% EtOAc in hexanes as the eluent to remove palladium residue. The product was concentrated and repurified with flash column chromatography on silica gel with 10% EtOAc in hexanes as the eluent to yield the title compound (950 mg, 52% over 2 steps) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ: 2.80 (d, *J* = 9.1 Hz, 1H), 2.64 (t, *J* = 5.9 Hz, 1H), 2.41 (t, *J* = 5.8 Hz, 1H), 2.08 (d, *J* = 9.1 Hz, 1H), 2.01 (s, 3H), 1.50 (s, 3H), 1.01 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ: 204.0, 170.1, 121.0 (t, *J* = 25 Hz), 57.7, 54.1, 49.7, 40.9, 26.6, 23.6, 22.1. FT-IR (neat): 2941, 2872, 2850, 1669, 1605, 1469, 1371, 1281, 1108, 979 cm⁻¹. HRMS (ESI): exact mass calcd for C₁₀H₁₄DO [M + H]⁺, 152.1180. Found 152.1175.

2,7,7-Trimethylbicyclo[3.1.1]hept-2-en-6-one-1-d (39).—4,6,6-

Trimethylbicyclo[3.1.1]hept-3-en-2-one-3-*d* (**38**) (500 mg, 3.3 mmol) was dissolved in cyclohexane (50 mL). The solution was irradiated in a quartz vessel in a Rayonet RPR-100 photoreactor with 350 nm ultraviolet bulbs for 5.5 h, then concentrated and the crude product purified with flash column chromatography on silica gel with 3% EtOAc in hexanes as the eluent to yield the title compound (244 mg, 49%) as a pale yellow oil. ¹H NMR (500 MHz, CDCl₃) δ: 5.39–5.30 (m, 1H), 2.67–2.59 (m, 2H), 2.57–2.53 (m, 1H), 1.70 (q, *J* = 2.0 Hz, 3H), 1.21 (s, 3H), 1.18 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ: 206.56, 138.64, 118.62, 77.33, 77.10, 76.85, 67.46 (t, *J* = 25 Hz), 62.67, 33.04, 29.79, 27.30, 22.99, 14.76. FT-IR (neat): 2953, 2858, 1826, 1750, 1653, 1589, 1468, 1447, 1369, 1287, 1222, 1080 cm⁻¹. HRMS (ESI): exact mass calcd for C₁₀H₁₄DONa [M + Na]⁺, 174.0994. Found 174.0994.

2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene-1-d (17).—2,7,7-

Trimethylbicyclo[3.1.1]hept-2-en-6-one-1-*d* (**17**) (168 mg, 1.1 mmol, 1 equiv) was dissolved in absolute EtOH (3 mL). To the solution was added anhydrous hydrazine (0.14 mL, 4.4 mmol, 4 equiv) and glacial acetic acid (63 μL, 1.1 mmol, 1 equiv). The reaction mixture was refluxed for 3 h, then cooled to room temperature and concentrated. The residue was diluted with Et₂O (10 mL), washed with 1:1 2 M NaOH/brine (1 mL) once, then brine (3 mL) 3 times. The ether layer was dried with Na₂SO₄, and concentrated. The crude hydrazone was dissolved in DMSO (1 mL) and added slowly dropwise to a stirred solution of KO^tBu (187 mg, 1.7 mmol, 1.5 equiv) in DMSO (3 mL). The dark red reaction mixture was stirred at room temperature overnight, then poured into ice water (4 mL), acidified with 2 M HCl, and extracted with pentane (3 × 5 mL). Combined organic layers were dried with Na₂SO₄, filtered, and concentrated carefully. The crude product was purified with flash column chromatography on silica gel with 100% pentane as the eluent to yield the title compound (31 mg, 21%, >20:1 deuterium incorporation) as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ: 5.24–5.10 (m, 1H), 2.37–2.29 (m, 1H), 2.29–2.11 (m, 2H), 2.09–2.04 (m, 1H), 1.66 (q, *J* = 2.1 Hz, 3H), 1.26 (s, 3H), 1.14 (d, *J* = 8.4 Hz, 1H), 0.84 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ: 144.6, 116.1, 46.7 (t, *J* = 21 Hz), 40.8, 37.9, 31.4, 31.4, 26.4, 23.0, 20.9. FT-IR (neat): 3024, 2986, 2914, 2835, 1468, 1446, 1380, 1365, 1260, 1215, 1095 cm⁻¹. HRMS (EI): exact mass calcd for C₁₀H₁₅D [M]⁺, 137.1309. Found 137.1308.

2,7,7-Trimethylbicyclo[3.1.1]hept-2-en-6-one (34).—Verbenone (1.0 g, 6.7 mmol) was dissolved in cyclohexane (100 mL). The solution was irradiated in a quartz vessel in a Rayonet RPR-100 photoreactor with 350 nm ultraviolet bulbs for 5 h, then concentrated and the crude product purified with flash column chromatography on silica gel with 3% EtOAc in hexanes as the eluent to yield the title compound (515 mg, 51%) as a clear oil. The spectral data were consistent with those reported in the literature.⁴⁴

2,7,7-Trimethylbicyclo[3.1.1]hept-2-en-6-d-6-ol (35).—LiAlD₄ (6.66 mL, 6.66 mmol, 1.0 M in Et₂O) was added to a solution of 2,7,7-trimethylbicyclo[3.1.1]hept-2-en-6-one (34) (1.0 g, 6.66 mmol) in Et₂O (15 mL) at 0 °C under N₂. After stirring for 3 h, the reaction was carefully quenched with saturated Na₂SO₄, until bubbling subsided. The reaction was warmed to room temperature and stirred for 30 min and filtered over Celite. Concentration under reduced pressure and flash column chromatography on silica gel using 10% Et₂O in pentanes as the eluent afforded the title compound (712 mg, 4.6 mmol, 70% yield) as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ: 5.20 (dd, *J* = 2.7, 1H, 1.4 Hz), 2.26–2.24 (m, 2H), 1.98 (s, 2H), 1.87 (t, 1H, *J* = 2.7 Hz), 1.66 (q, 3H, *J* = 1.9 Hz), 1.56 (s, 3H), 0.90 (s, 3H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ: 142.5, 117.6, 78.3 (t, *J* = 25 Hz), 53.4, 46.7, 37.1, 32.0, 27.3, 23.0, 22.7. FT-IR (film): 3293, 2922, 1201, 1072, 779 cm⁻¹. LRMS (EI): calcd for C₁₀H₁₅DO [M]⁺, 153.1. Found 153.1.

2,7,7-Trimethylbicyclo[3.1.1]hept-2-en-6-yl-6-d 4-Methylbenzenesulfonate (36).—*p*-Toluensulfonyl chloride (2.97 g, 15.6 mmol) was added to a stirred solution of 2,7,7-trimethylbicyclo[3.1.1]hept-2-en-6-*d*-6-ol (35) (600 mg, 3.9 mmol) in pyridine (18 mL) at 0 °C. After 12 h, the reaction was diluted with a sat. NH₄Cl solution (50 mL), dichloromethane (50 mL), and transferred to a separatory funnel. The organic phase was collected and the aqueous layer extracted with dichloromethane (2 × 50 mL). Combined organics were washed with brine (75 mL) and dried with Na₂SO₄. Concentration under reduced pressure and flash column chromatography on silica gel using 10% EtOAc in hexanes as the eluent afforded the title compound (1.04 g, 3.38 mmol, 87% yield) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ: 7.79 (d, 2H, *J* = 8.3 Hz), 7.34 (dd, 2H, *J* = 8.6, 0.6 Hz), 5.21 (td, 1H, *J* = 2.8, 1.5 Hz), 2.45 (s, 3H), 2.25 (dq, 2H, *J* = 7.1, 2.4 Hz), 2.15–2.13 (m, 1H), 1.99 (dd, 1H, *J* = 7.2, 1.2 Hz), 1.57 (q, 3H, *J* = 1.9 Hz), 1.42 (s, 3H), 0.85 (s, 3H). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ: 144.6, 141.3, 134.3, 129.8, 127.9, 118.2, 85.9 (t, *J* = 25 Hz), 51.4, 45.6, 37.5, 31.8, 26.5, 22.4, 21.7. FT-IR (film): 2929, 1363, 1171, 930 cm⁻¹. LRMS (ESI): calcd for C₁₇H₂₁DO₃S [M + Na]⁺, 330.1. Found 330.1.

2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene-7,7-d₂ (16).—2,7,7-Trimethylbicyclo[3.1.1]hept-2-en-6-one (34) (450 mg, 3 mmol, 1 equiv) was dissolved in absolute EtOH (7 mL). To the solution was added anhydrous hydrazine (0.51 mL, 12 mmol, 4 equiv) and glacial acetic acid (0.17 mL, 3 mmol, 1 equiv). The reaction mixture was refluxed for 3 h, then cooled to room temperature and concentrated. The residue was diluted with Et₂O (30 mL), washed with 1:1 2 M NaOH/brine (9 mL) once, then brine (9 mL) 3 times. The ether layer was dried with Na₂SO₄, and concentrated. The crude hydrazone was dissolved in DMSO (3 mL) and added slowly dropwise to a stirred solution of KOtBu (504 mg, 4.5 mmol, 1.5 equiv) in DMSO (3 mL). The dark red reaction mixture was stirred

at room temperature overnight, then poured into ice water (12 mL), acidified with 2 M HCl, and extracted with pentane (3 × 15 mL). Combined organic layers were dried with Na₂SO₄, filtered, and concentrated carefully. The crude product was purified with flash column chromatography on silica gel with 100% pentane as the eluent to yield the title compound (55 mg, 13%, >20:1 deuterium incorporation) as a clear oil. The spectral data were consistent with those reported in the literature.⁴⁸

(E)-(5-Benzylidene-2,2-dimethyl-4-oxocyclohexyl-1-d)methyl 4-

Methylbenzenesulfonate (50).—(2,2-Dimethyl-4-oxocyclohexyl-1,3-*d*₂)methyl acetate (**49**)⁴⁸ (300 mg, 1.5 mmol, 1 equiv) was dissolved in absolute EtOH (4 mL). Benzaldehyde (0.35 mL, 3.3 mmol, 2.2 equiv) was then added, followed by a 10% solution of NaOH in H₂O (0.75 mL, 1.88 mmol, 1.25 equiv). The reaction mixture was stirred at room temperature overnight, then concentrated. The residue was dissolved in Et₂O and diluted with H₂O. The organic layer was separated, and the aqueous layer extracted with Et₂O. The combined organic layers were washed with brine, dried with magnesium sulfate, filtered, and concentrated. The crude material was then dissolved in DCM (8 mL). To the solution was added TsCl (0.43 g, 2.25 mmol, 1.5 equiv) followed by triethylamine (0.42 mL, 3 mmol, 2 equiv). The reaction mixture was stirred overnight until TLC showed complete consumption of starting material, then diluted with H₂O. The organic phase was collected and the aqueous phase extracted with DCM. The combined organic layers were washed with a solution of 1:4 1 M HCl/H₂O, then washed with brine and dried with sodium sulfate, filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel with 25–30% EtOAc in hexanes as the eluent to yield the title compound (365 mg, 60% over 2 steps) as a white solid. Melting point: 118–123 °C. ¹H NMR (500 MHz, CDCl₃) δ: 7.77–7.71 (m, 2H), 7.51 (t, *J* = 2.4 Hz, 1H), 7.44–7.35 (m, 5H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.28 (d, *J* = 9.8 Hz, 1H), 3.98 (d, *J* = 9.8 Hz, 1H), 3.07 (dd, *J* = 17.0, 1.8 Hz, 1H), 2.55 (dd, *J* = 16.9, 2.8 Hz, 1H), 2.44 (s, 3H), 2.39–2.25 (m, 2H), 1.03 (s, 3H), 0.95 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ: 200.2, 145.0, 136.6, 135.2, 133.2, 132.9, 130.7, 130.0, 123.0, 129.1, 128.6, 127.9, 127.9, 70.8, 54.5, 42.5 (t, *J* = 20 Hz), 33.6, 29.0, 28.6, 22.1, 21.7. FT-IR (solid): 2961, 2888, 1677, 1603, 1492, 1445, 1354, 1306, 1262, 1174, 955 cm⁻¹. HRMS (ESI): exact mass calcd for C₂₃H₂₅D₀₄SNa [M + Na]⁺, 422.1507. Found 422.1509.

3-((E) Benzylidene)-6,6-dimethylbicyclo[3.1.1]heptan-2-one-5-d (51).—To

a solution of (*E*)-(5-benzylidene-2,2-dimethyl-4-oxocyclohexyl-1-*d*)methyl 4-methylbenzenesulfonate (**50**) (365 mg, 0.85 mmol, 1 equiv) in DME (6 mL) was added NaH (68 mg, 1.7 mmol, 2 equiv). The reaction mixture was heated to 80 °C for 1.5 h until TLC showed complete consumption of starting material, then cooled to room temperature and concentrated. The residue was diluted with Et₂O and H₂O. The organic layer was collected and the aqueous layer extracted with Et₂O. Combined organic layers were washed with brine, dried with magnesium sulfate, filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel with 5% EtOAc in hexanes as the eluent to yield the title compound (112 mg, 58%) as a white solid. Melting point: 68–71 °C. ¹H NMR (500 MHz, CDCl₃) δ: 7.71 (t, *J* = 2.6 Hz, 1H), 7.63–7.56 (m, 2H), 7.45–7.38 (m, 2H), 7.39–7.32 (m, 1H), 2.98 (t, *J* = 2.3 Hz, 2H), 2.71 (d, *J* = 5.6 Hz, 1H), 2.62 (ddd,

$J = 10.6, 5.7, 1.4$ Hz, 1H), 1.50 (d, $J = 10.5$ Hz, 1H), 1.39 (s, 3H), 0.93 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 203.7, 135.8, 132.7, 130.9, 129.0, 128.7, 56.0, 40.9, 39.3, 38.9 (t, $J = 21$ Hz), 27.4, 26.3, 21.8. FT-IR (solid): 2953, 2868, 1686, 1609, 1573, 1490, 1385, 1283, 1204, 1119 cm^{-1} . HRMS (ESI): exact mass calcd for $\text{C}_{16}\text{H}_{18}\text{DO}$ $[\text{M} + \text{H}]^+$, 228.1493. Found 228.1492.

3-((E)-Benzylidene)-2,6,6-trimethylbicyclo[3.1.1]hepton-5-d-2-ol (53).—

Anhydrous CeCl_3 (4.01 g, 16.25 mmol, 2.5 equiv) was suspended in THF (110 mL) and the mixture stirred vigorously at room temperature for 1 h, then cooled to -78 °C. 1.5 M MeLi·LiBr in diethyl ether solution (10.8 mL, 16.25 mmol, 2.5 equiv) was added dropwise and the bright yellow solution was stirred at -78 °C for 1 h, after which a solution of 3-((E)-benzylidene)-6,6-dimethylbicyclo-[3.1.1]heptan-2-one-5-*d* (**51**) in THF (20 mL) was added dropwise. The reaction was stirred at -78 °C for 1 h until TLC showed complete consumption of starting material, then warmed to 0 °C and quenched with saturated ammonium chloride solution. The organic layer was separated and the aqueous layer extracted with EtOAc. Combined organic layers were washed with brine, dried with Na_2SO_4 , filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel with 8–10% EtOAc in hexanes as the eluent to yield the title compound (1.34 g, 85%) as a thick off-white oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.43–7.37 (m, 2H), 7.38–7.32 (m, 2H), 7.25–7.19 (m, 1H), 6.85 (t, $J = 2.6$ Hz, 1H), 2.92 (dt, $J = 17.4, 2.4$ Hz, 1H), 2.81 (dd, $J = 17.4, 2.9$ Hz, 1H), 2.42 (ddd, $J = 10.5, 6.5, 2.6$ Hz, 1H), 2.02–1.97 (m, 2H), 1.48 (s, 3H), 1.28 (s, 3H), 1.14 (d, $J = 10.6$ Hz, 1H), 1.05 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 145.7, 137.9, 129.1, 128.3, 127.4, 126.6, 78.4, 52.9, 39.2 (t, $J = 23$ Hz), 38.3, 34.1, 30.6, 30.5, 27.1, 22.6. FT-IR (neat): 2916, 2463, 2175, 1598, 1492, 1472, 1445, 1367, 1332, 1060 cm^{-1} . HRMS (ESI): exact mass calcd for $\text{C}_{17}\text{H}_{21}\text{DNaO}$ $[\text{M} + \text{Na}]^+$, 266.1626. Found 266.1619.

2-Hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one-5-d (54).—3-((E)-

Benzylidene)-2,6,6-trimethylbicyclo [3.1.1]heptan-5-*d*-2-ol (**53**) (1.3 g, 5.34 mmol, 1 equiv) was dissolved in DCM (60 mL) and cooled to -78 °C. Ozone was bubbled through the solution for 30 min until the surface of the reaction mixture appeared visibly blue. The reaction mixture was then flushed with oxygen for 30 min followed by the addition of dimethylsulfide (4.19 mL, 56.6 mmol, 10.6 equiv). The reaction mixture was allowed to warm up to room temperature overnight, then concentrated and the residue purified with flash column chromatography on silica gel with 8–10% EtOAc in hexanes as the eluent to yield the title compound (435 mg, 48%) as a white crystalline solid. Melting point: 48–53 °C. ^1H NMR (500 MHz, CDCl_3) δ : 2.71 (dd, $J = 19.0, 3.4$ Hz, 1H), 2.67–2.59 (m, 2H), 2.52 (d, $J = 19.0$ Hz, 1H), 2.16 (d, $J = 6.5$ Hz, 1H), 1.34 (s, 3H), 1.31 (d, $J = 11.3$ Hz, 1H), 1.29 (s, 3H), 0.96 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 216.9, 79.1, 49.9, 43.1, 38.8 (t, $J = 23$ Hz), 38.4, 31.0, 27.0, 25.9, 22.7. FT-IR (solid): 3430, 2977, 2914, 1710, 1460, 1405, 1383, 1368, 1315, 1289, 1260, 1244, 1156, 1133, 1070 cm^{-1} . HRMS (ESI): exact mass calcd for $\text{C}_{10}\text{H}_{15}\text{DO}_2$ $[\text{M}]^+$, 169.1208. Found 169.1208.

2,6,6-Trimethylbicyclo[3.1.1]heptane-5-d-2,3-diol (55).—A solution of 3-((E)-benzylidene)-2,6,6-trimethylbicyclo [3.1.1]heptan-5-*d*-2-ol (**54**) (202 mg, 1.2 mmol, 1

equiv) in THF (5 mL) was cooled to 0 °C. Twenty-five wt % DIBAL solution in toluene (2.0 mL, 3 mmol, 2.5 equiv) was added dropwise and the reaction mixture stirred for 2 h until TLC showed complete consumption of starting material, then diluted with H₂O and EtOAc. The mixture was stirred then saturated Rochelle's salt solution added until the layers cleanly separated. The organic layer was collected and the aqueous layer extracted with EtOAc. Combined organic layers were dried with Na₂SO₄, filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel with 30% EtOAc in hexanes as the eluent to yield the title compound (171 mg, 84%) as a white solid. Melting point: 38–42 °C. ¹H NMR (500 MHz, CDCl₃) δ: 3.87 (dt, *J* = 9.5, 6.9 Hz, 1H), 2.50–2.46 (m, 1H), 2.38 (dd, *J* = 13.8, 9.5 Hz, 1H), 2.26–2.18 (m, 1H), 2.15–2.09 (m, 1H), 2.04 (d, *J* = 6.2 Hz, 1H), 1.74 (ddd, *J* = 13.8, 7.0, 1.8 Hz, 1H), 1.23 (s, 3H), 1.23 (s, 3H), 1.14 (d, *J* = 10.6 Hz, 1H), 1.06 (s, 3H). FT-IR (solid): 3415, 3298, 3005, 2982, 2954, 2911, 2867, 1455, 1383, 1330, 1291, 1263, 1227, 1168, 1145, 1058 cm⁻¹. ¹³C{¹H} NMR (126 MHz, CDCl₃) δ: 75.2, 52.4, 39.8 (t, *J* = 23 Hz), 38.9, 34.9, 29.5, 27.5, 26.5, 23.1. HRMS (CI): exact mass calcd for C₁₀H₂₃DNO₂ [M + NH₄]⁺, 189.1708. Found 189.1702.

2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene-5-d (19).—A solution of 2,6,6-trimethylbicyclo[3.1.1]heptane-5-*d*-2,3-diol (**55**) (70 mg, 0.41 mmol, 1 equiv) was dissolved in DCM (5 mL) and cooled to 0 °C. DMAP (751 mg, 6.15 mmol, 15 equiv) was added followed by thiophosgene (242 mg, 2.05 mmol, 5 equiv). The reaction mixture was warmed to room temperature and stirred for 2 h. Silica gel was added to the reaction mixture and stirred until the mixture turned light yellow. Solvent was removed, and the silica gel loaded onto a silica gel plug and eluted with 20% EtOAc in hexanes. The solvent was concentrated and the thiocarbonate dissolved in triethyl phosphite (15 mL) in a sealed tube. The reaction mixture was heated under reflux for 4 days, then loaded directly onto a silica gel column and eluted with pentane. Fractions were carefully concentrated and this process was repeated to remove residual triethyl phosphite. Concentration of fractions from the second column yielded the title compound (28, 24% over 2 steps, >20:1 deuterium incorporation) as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ: 5.21–5.16 (m, 1H), 2.33 (dd, *J* = 8.5, 5.4 Hz, 1H), 2.12–2.34 (m, 2H), 1.93 (d, *J* = 5.4 Hz, 1H), 1.66 (q, *J* = 2.0 Hz, 3H), 1.26 (s, 3H), 1.14 (d, *J* = 8.5 Hz, 1H), 0.83 (s, 3H). ¹³C{¹H} NMR (126 MHz, CDCl₃) δ: 144.7, 116.1, 47.1, 40.4 (t, *J* = 21 Hz), 37.9, 31.4, 31.2, 26.4, 23.1, 20.9. FT-IR (neat): 3025, 2985, 2922, 2834, 1468, 1435, 1379, 1364, 1249, 1200, 1145 cm⁻¹. HRMS (EI): exact mass calcd for C₁₀H₁₅D [M]⁺, Found 137.1309.

(1*S*,6*R*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,6-dimethylbicyclo[3.1.1]hept-2-en-1-ol (59).—To a solution of (1*S*,6*R*)-6-(hydroxymethyl)-2,6-dimethylbicyclo[3.1.1]hept-2-en-1-ol (**58**)⁵⁵ (336 mg, 2 mmol, 1 equiv) in DCM (20 mL) was added imidazole (409 mg, 6 mmol, 3 equiv) followed by TBDPSCI (0.68 mL, 2.6 mmol, 0.3 equiv). The reaction mixture was stirred at room temperature for 1.5 h until TLC showed complete consumption of starting material, then quenched with water (20 mL). The organic layer was separated and the aqueous layer extracted with DCM (4 × 40 mL). Combined organic layers were dried with Na₂SO₄ filtered, and concentrated. The crude product was purified with flash column chromatography

on silica gel with 2.5% EtOAc in hexanes as the eluent to yield the title compound (670 mg, 83%) as a viscous white oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.70 (ddt, $J = 6.7, 5.0, 1.5$ Hz, 4H), 7.48–7.37 (m, 6H), 5.19 (tq, $J = 3.3, 1.7$ Hz, 1H), 4.27 (d, $J = 10.3$ Hz, 1H), 3.72 (d, $J = 10.4$ Hz, 1H), 2.33 (dd, $J = 8.6, 7.0$ Hz, 1H), 2.11 (dq, $J = 17.5, 2.6$ Hz, 1H), 2.02 (dq, $J = 17.6, 2.6$ Hz, 1H), 1.87 (dq, $J = 7.5, 2.7$ Hz, 1H), 1.80 (q, $J = 2.1$ Hz, 3H), 1.66 (s, 1H), 1.08 (s, 9H), 1.04 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 147.3, 135.9, 135.7, 132.9, 132.6, 129.99, 129.97, 128.0, 127.9, 116.8, 78.7, 71.1, 46.9, 40.7, 31.3, 30.5, 26.9, 19.3, 17.5, 14.9. FT-IR (thin film): 3504, 2930, 2881, 2857, 1427, 1222, 1153, 1111, 1064, 997, 882 cm^{-1} . HRMS (EI): exact mass calc'd for $\text{C}_{26}\text{H}_{34}\text{O}_2\text{Si}$ $[\text{M}]^+$, 406.2323. Found 406.2325.

(1S,6R)-6-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,6-dimethylbicyclo[3.1.1]hept-2-en-1-yl (1,3-dioxoisindolin-2-yl)

oxalate (S4).—A round-bottom flask was charged with (1S,6R)-6-(((tert-butyldiphenylsilyl)oxy)methyl)-2,6-dimethylbicyclo [3.1.1] hept-2-en-1-ol (**59**) (488 mg, 1.2 mmol, 1 equiv), DMAP (14.6 mg, 0.12 mmol, 0.1 equiv) and triethylamine (0.42 mL, 3 mmol, 2.5 equiv). A solution of 1,3-dioxoisindolin-2-yl 2-chloro-2-oxoacetate (**S3**)⁵⁸ (2.4 mmol, 2 equiv) in THF (40 mL) was added via cannula and the mixture stirred for 1.5 h. The reaction mixture was concentrated and the residue dissolved in DCM (16 mL) and poured into 800 mL hexanes. The resulting solid was filtered through a rigorously dried glass frit with a thin layer of Celite. The filtrate was concentrated to yield the title compound as a foamy white solid (747 mg, quant, yield). ^1H NMR (500 MHz, CDCl_3) δ : 7.91 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.82 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.69–7.65 (m, 4H), 7.42–7.36 (m, 6H), 5.40 (m, 1H), 3.98 (d, $J = 10.4$ Hz, 1H), 3.84 (d, $J = 10.3$ Hz, 1H), 2.60–2.51 (m, 2H), 2.33–2.21 (m, 1H), 2.16–2.05 (m, 2H), 1.71 (q, $J = 2.1$ Hz, 3H), 1.15 (s, 3H), 1.07 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 160.8, 153.9, 153.6, 141.6, 135.8, 135.1, 133.7, 133.6, 12.987, 129.7, 128.8, 127.8, 127.8, 124.3, 120.1, 88.7, 66.9, 49.2, 38.8, 32.4, 30.7, 27.0, 19.5, 17.4, 14.9. FT-IR (thin film) 2953, 2927, 2866, 2855, 1825, 1792, 1746, 1476, 1360, 1287, 1080, 835 cm^{-1} . Attempts to acquire HRMS data were unsuccessful under a variety of ionization conditions, likely due to the sensitivity of the *N*-phthalimidoyl oxalate functional group.

(1R,6S)-tert-Butyl((2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl)-methoxy)diphenylsilane (60).—A 75 mL

sealed vessel was charged with (1R,6S)-6-(((tert-butyldiphenylsilyl)oxy)methyl)-2,6-dimethylbicyclo [3.1.1]hept-2-en-1-yl (1,3-dioxoisindolin-2-yl) oxalate (**S3**) (1.5 g, 2.4 mmol, 1 equiv), $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ (104 mg, 0.12 mmol, 0.05 equiv), Hantzsch ester (912 mg, 3.6 mmol, 1.5 equiv), a magnetic stir bar, and nitrogen-sparged toluene (24 mL). The heterogeneous reaction was placed into a preheated oil bath (110 °C) in the center of two Tuna Blue Kessil lamps and allowed to stir at 110 °C for 18 h. The reaction was filtered through a pad of silica gel, washed with CH_2Cl_2 (120 mL), and the filtrate was concentrated. The crude product was purified with flash column chromatography on silica gel with 0–1% EtOAc in hexanes as the eluent to yield the title compound (109 mg, 12%) as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.72–7.66 (m, 4H), 7.44–7.37 (m, 6H), 5.24 (m, 1H), 3.81 (d, $J = 9.9$ Hz, 1H), 3.76 (d, $J = 10.0$ Hz, 1H), 2.31–2.02 (m, 5H), 1.66 (q, $J = 1.9$ Hz, 3H), 1.14 (d, $J = 8.7$ Hz, 1H), 1.07 (s, 9H), 0.99 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 144.1, 135.8, 134.2, 129.6, 127.7, 116.8, 70.0, 44.1, 43.0, 36.5, 31.7, 31.3,

27.0, 23.0, 19.6, 16.4. FT-IR (neat): 2955, 2927, 2855, 1427, 1362, 1111, 1073, 822, 799, 701 cm^{-1} . HRMS (EI): exact mass calc'd for $\text{C}_{26}\text{H}_{34}\text{OSi} [\text{M}]^+$, 390.2373. Found 390.2375.

((1*R*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)methanol (S5).—To a solution of ((1*R*,6*S*)-*tert*-butyl(2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl)methoxy)diphenylsilane (**60**) (440 mg, 1.13 mmol, 1 equiv) in THF (3 mL) was added 1 M TBAF solution in THF (6.8 mL, 6.8 mmol, 6 equiv) dropwise. The reaction was stirred overnight, then cooled to 0 °C and slowly quenched with saturated NH_4Cl . The mixture was extracted with EtOAc and combined organic layers were washed with brine, dried with Na_2SO_4 , filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel with 20% EtOAc in hexanes as the eluent to yield the title compound (151 mg, 88%) as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 5.25 (dq, $J = 3.0, 1.5$ Hz, 1H), 3.82 (d, $J = 10.9$ Hz, 1H), 3.77 (d, $J = 10.9$ Hz, 1H), 2.37–2.26 (m, 2H), 2.26–2.10 (m, 2H), 2.07 (td, $J = 5.7, 1.5$ Hz, 1H), 1.68 (q, $J = 2.1$ Hz, 3H), 1.24 (d, $J = 8.8$ Hz, 1H), 0.93 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 143.9, 116.9, 69.5, 43.6, 42.7, 36.4, 31.6, 30.9, 23.0, 15.9. FT-IR (thin film): 3345, 2919, 2850, 1710, 1445, 1375, 1083, 1023, 788 cm^{-1} . HRMS (EI): exact mass calc'd for $\text{C}_{10}\text{H}_{16}\text{O}^+ [\text{M}]^+$, 152.1196, found 152.1201.

((1*R*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-ene-6-carboxylic Acid (61).—To a solution of ((1*R*,6*S*)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl)methanol (**S5**) (151 mg, 1 mmol, 1 equiv) in DMF (4.5 mL) at 0 °C was added PDC (1.5 g, 4 mmol, 4 equiv). The reaction mixture was stirred for 18 h followed by the addition of DMF (1.5 mL) and PDC (0.94 g, 2.5 mmol, 2.5 equiv). After stirring for another 18 h until TLC showed complete consumption of starting material, the reaction mixture was poured in 20 mL water and diluted with EtOAc (20 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 \times 20 mL). Combined organic layers were washed with 20% LiCl solution (2 \times 5 mL), dried with Na_2SO_4 , filtered, and concentrated. The crude product was purified with flash column chromatography on silica gel with 100% DCM as the eluent to yield the title compound (75 mg, 45%) as a white solid. Melting point: 49–52 °C. ^1H NMR (500 MHz, CDCl_3) δ : 5.30 (m, 1H), 2.77 (m, 1H), 2.63 (t, $J = 5.8$ Hz, 1H), 2.34 (m, 1H), 2.22–2.08 (m, 2H), 1.72 (q, $J = 2.0$ Hz, 3H), 1.27 (d, $J = 8.9$ Hz, 1H), 1.13 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 185.7, 142.0, 117.0, 48.9, 45.0, 39.0, 31.8, 30.1, 22.9, 16.2. FT-IR (solid): 3025, 2958, 2925, 2853, 2640, 1693, 1452, 1434, 1367, 1282, 1160, 1064 cm^{-1} . HRMS (ESI): exact mass calc'd for $\text{C}_{10}\text{H}_{13}\text{O}_2 [\text{M} - \text{H}]^-$, 165.0916. Found 165.0916.

((1*R*,6*S*)-2,6-Dimethylbicyclo[3.1.1]hept-2-en-6-yl)methan- d_2 -ol (62).—To a solution of (1*R*,6*S*)-2,6-dimethylbicyclo[3.1.1]hept-2-ene-6-carboxylic acid (**61**) (75 mg, 0.45 mmol, 1 equiv) in THF (3 mL) was added 2.5 M *n*-BuLi in hexanes (0.18 mL, 0.45 mmol, 1 equiv). The solution was stirred for 1 min and LiAlD_4 (18.9 mg, 0.45 mmol, 1 equiv) was added to the mixture and the mixture was heated under reflux for 3 h until TLC showed complete consumption of starting material. The reaction mixture was cooled to room temperature and then cooled to 0 °C and it was quenched with saturated NH_4Cl (2 mL) and H_2O (2 mL), then poured into H_2O (3 mL) and Et_2O (3 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (4 \times 4 mL). Combined organic layers were washed with brine, dried with Na_2SO_4 , filtered, and concentrated. The crude

product was purified with flash column chromatography on silica gel with 10% EtOAc in hexanes as the eluent to yield the title compound (68 mg, 98%) as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ : 5.25 (s, 1H), 2.35–2.24 (m, 2H), 2.25–2.11 (m, 2H), 2.07 (m, 1H), 1.68 (q, $J = 2.0$ Hz, 3H), 1.24 (d, $J = 8.8$ Hz, 1H), 0.93 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 143.9, 116.9, 68.7 (t, $J = 21$ Hz), 43.4, 42.7, 36.4, 31.6, 30.8, 23.0, 15.8. FT-IR (neat): 3336, 3023, 2983, 2953, 2918, 2205, 2089, 1445, 1217, 1073, 906, 789 cm^{-1} . HRMS (ESI): exact mass calcd for $\text{C}_{10}\text{H}_{14}\text{D}_2\text{O}$ $[\text{M} + \text{H}]^+$, 155.1400. Found 155.1406.

((1R,6S)-2,6-Dimethylbicyclo[3.1.7]hept-2-en-6-yl)methyl- d_2 4-Methylbenzenesulfonate (S6).—To a solution of ((1R,6S)-2,6-

dimethylbicyclo[3.1.1]hept-2-en-6-yl)methan- d_2 -ol (**62**) (68 mg, 0.44 mmol, 1 equiv) in pyridine (2 mL) at 0 °C was added TsCl (336 mg, 1.76 mmol, 4 equiv). The reaction mixture was stirred at room temperature overnight until TLC showed complete consumption of starting material, then quenched with 4 mL saturated NH_4Cl solution and diluted with DCM (4 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 \times 4 mL). Combined organic layers were washed with brine, dried with Na_2SO_4 , and concentrated. The crude product was purified with flash column chromatography on silica gel with 15% EtOAc in hexanes as the eluent to yield the title compound (94 mg, 69%) as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ : 7.86–7.77 (d, $J = 8.3$ Hz, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 5.24 (m, 1H), 2.45 (s, 3H), 2.31–2.00 (m, 5H), 1.64 (q, $J = 2.0$ Hz, 3H), 1.20 (d, $J = 9.1$ Hz, 1H), 0.85 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 144.7, 143.0, 133.3, 129.9, 128.0, 117.1, 76.7–76.1 (m), 42.5, 41.9, 36.5, 31.3, 30.5, 22.8, 21.7, 15.9. FT-IR (neat): 3026, 2956, 2925, 2886, 2836, 1598, 1435, 1401, 1359, 1189, 1178, 1099, 1066, 948, 812 cm^{-1} . HRMS (ESI): exact mass calcd for $\text{C}_{17}\text{H}_{20}\text{D}_2\text{O}_3\text{SNa}$ $[\text{M} + \text{Na}]^+$, 331.1298. Found 331.1307.

(1R,6S)-2,6-Dimethyl-6-(methyl- d_3)bicyclo[3.1.1]hept-2-ene (21).—To a solution of ((1R,6S)-2,6-dimethylbicyclo[3.1.1]hept-2-en-6-yl)methyl- d_2 4-methylbenzenesulfonate (**S6**) (94 mg, 0.305 mmol, 1 equiv) in Et_2O (2 mL) was added LiAlD_4 (19.2 mg, 0.458 mmol, 1.5 equiv) over 5 min. The reaction mixture was stirred for 1 h and incomplete by TLC. Another 10 mg LiAlD_4 (0.24 mmol, 0.8 equiv) was added and the reaction mixture stirred for another 1 h. The reaction mixture was then directly loaded onto a column of Florisil packed with pentane, and eluted with pentane. Careful concentration of fractions yielded the title compound as a clear oil (24 mg, 58%, >20:1 deuterium incorporation). ^1H NMR (500 MHz, CDCl_3) δ : 5.17–5.20 (m, 1H), 2.33 (dt, $J = 8.5, 5.6$ Hz, 1H), 2.28–2.11 (m, 2H), 2.07 (td, $J = 2.9, 1.3$ Hz, 1H), 1.93 (td, $J = 5.6, 1.5$ Hz, 1H), 1.66 (q, $J = 2.1$ Hz, 3H), 1.15 (d, $J = 8.5$ Hz, 1H), 0.83 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 144.6, 116.1, 47.1, 40.8, 37.8, 31.5, 31.3, 25.8–25.2 (m), 23.1, 20.8. FT-IR (neat): 3025, 2964, 2918, 2860, 2834, 1435, 1261, 1195, 1122, 985 cm^{-1} . HRMS (EI): exact mass calcd for $\text{C}_{10}\text{H}_{13}\text{D}$, $[\text{M}]^+$, 139.1435. Found 139.1431.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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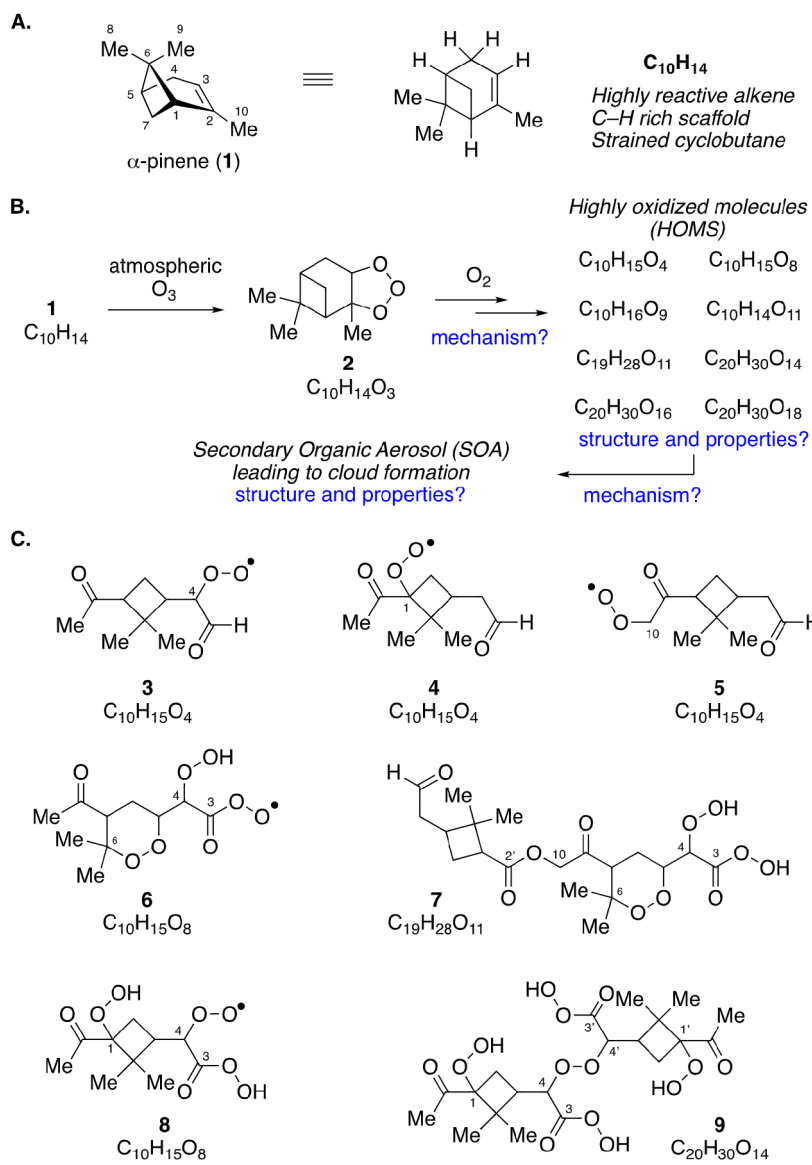


Figure 1. Structure of α -pinene (A), oxidation pathways leading to SOA formation (B) and proposed structures of selected HOMs (C).

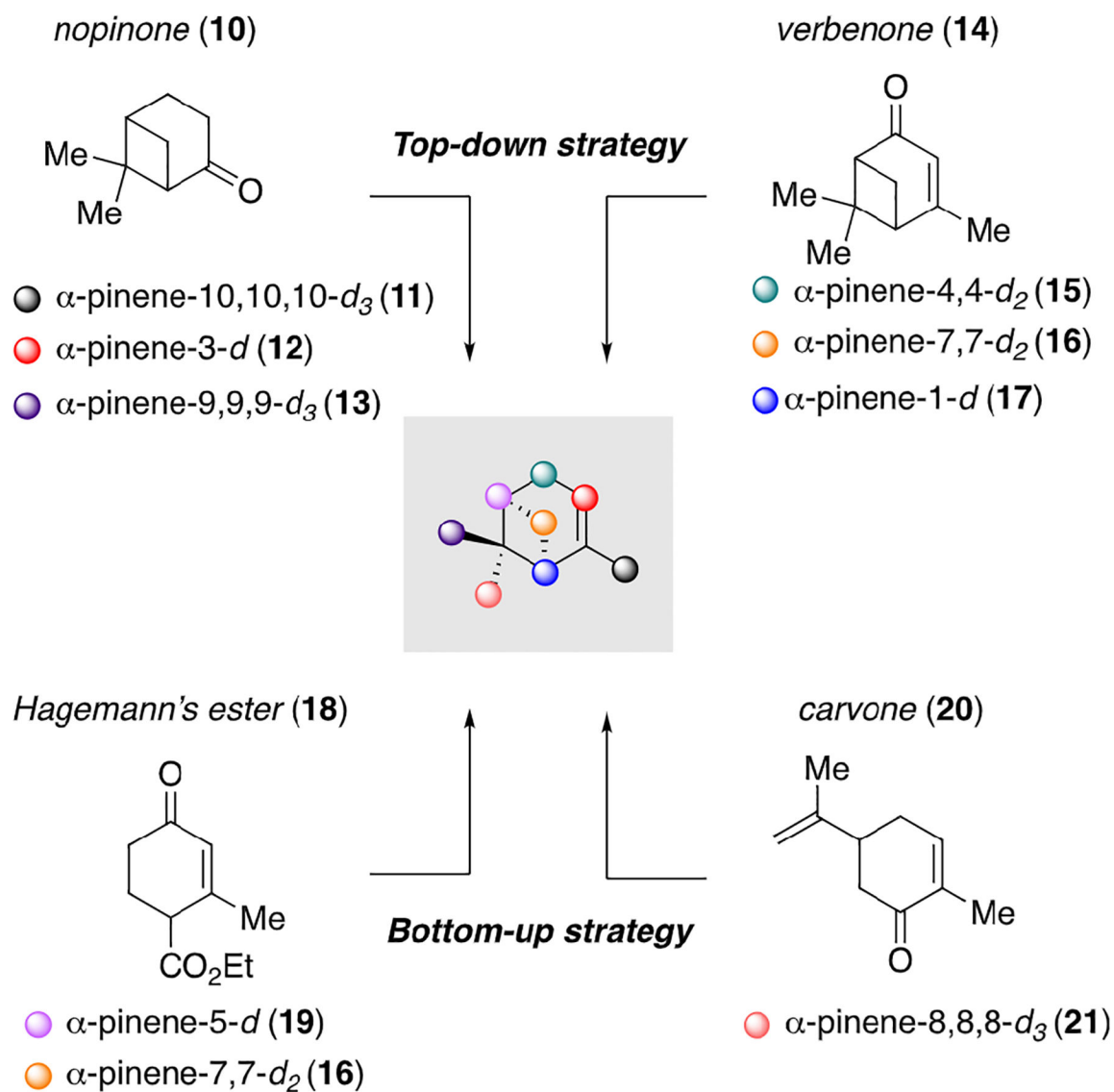
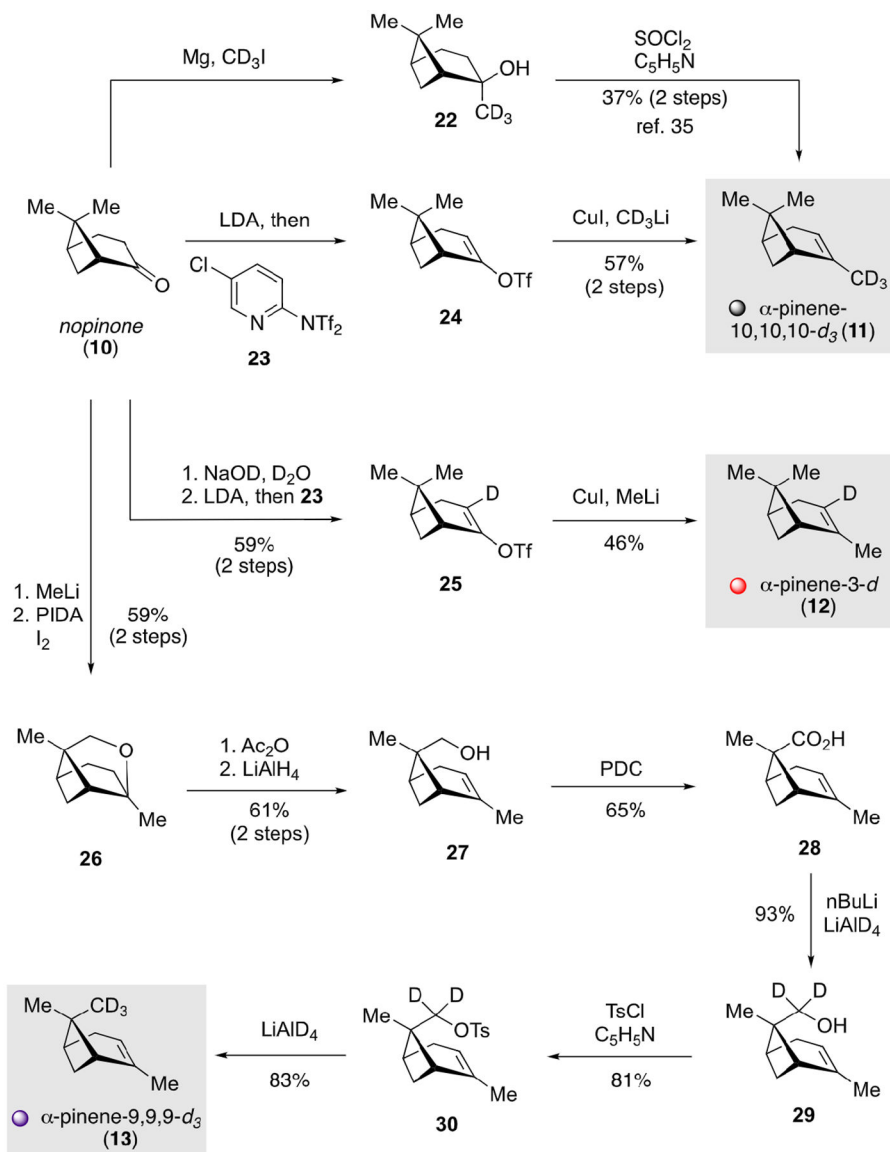
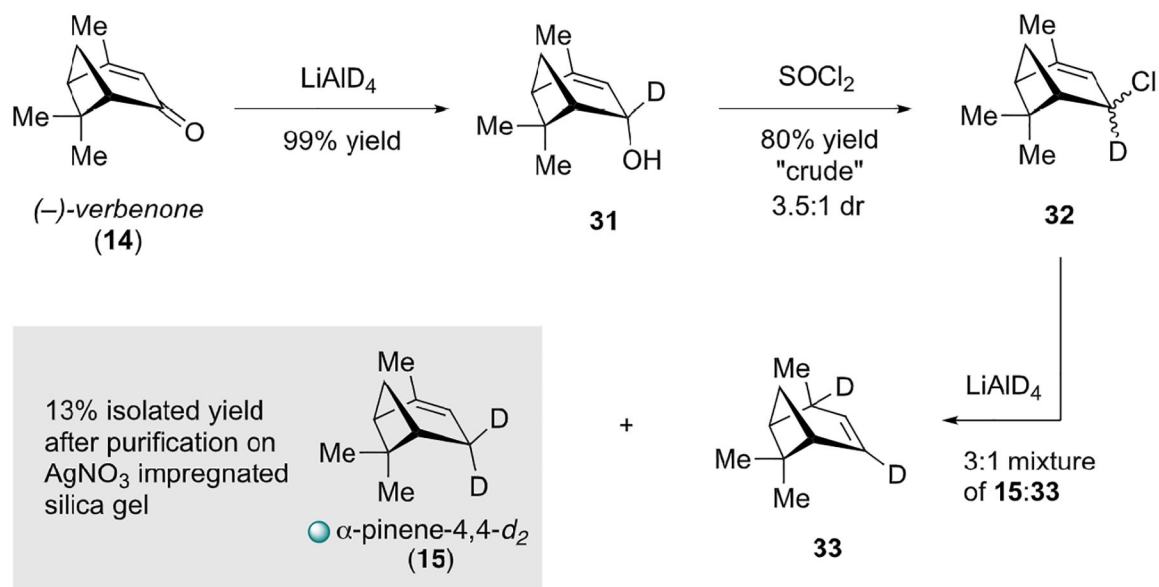


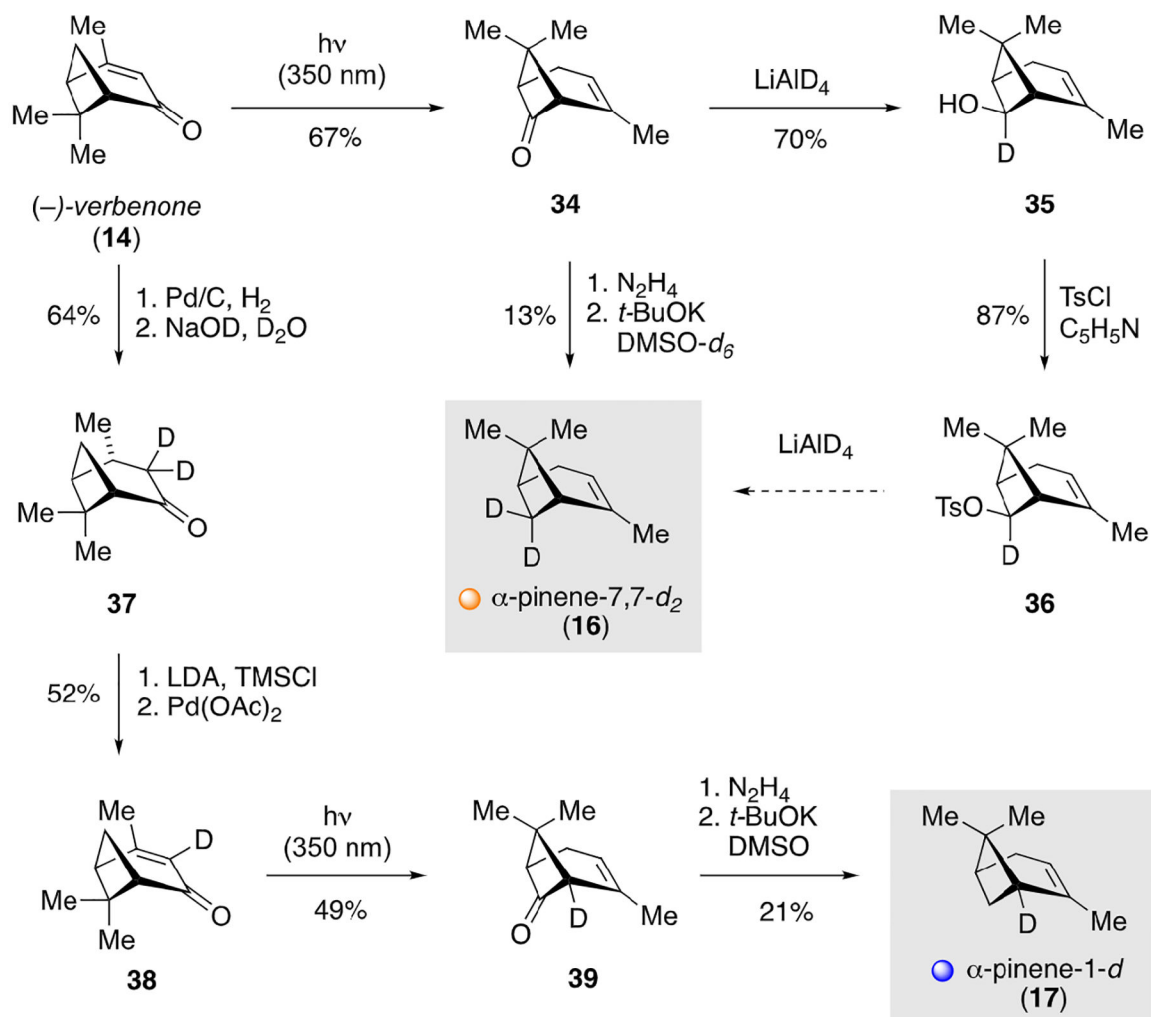
Figure 2. Overview of synthetic strategies utilized to access site specifically deuterated α -pinene isotopologues and the structures of the eight compounds prepared with each possible single carbon atom labeled



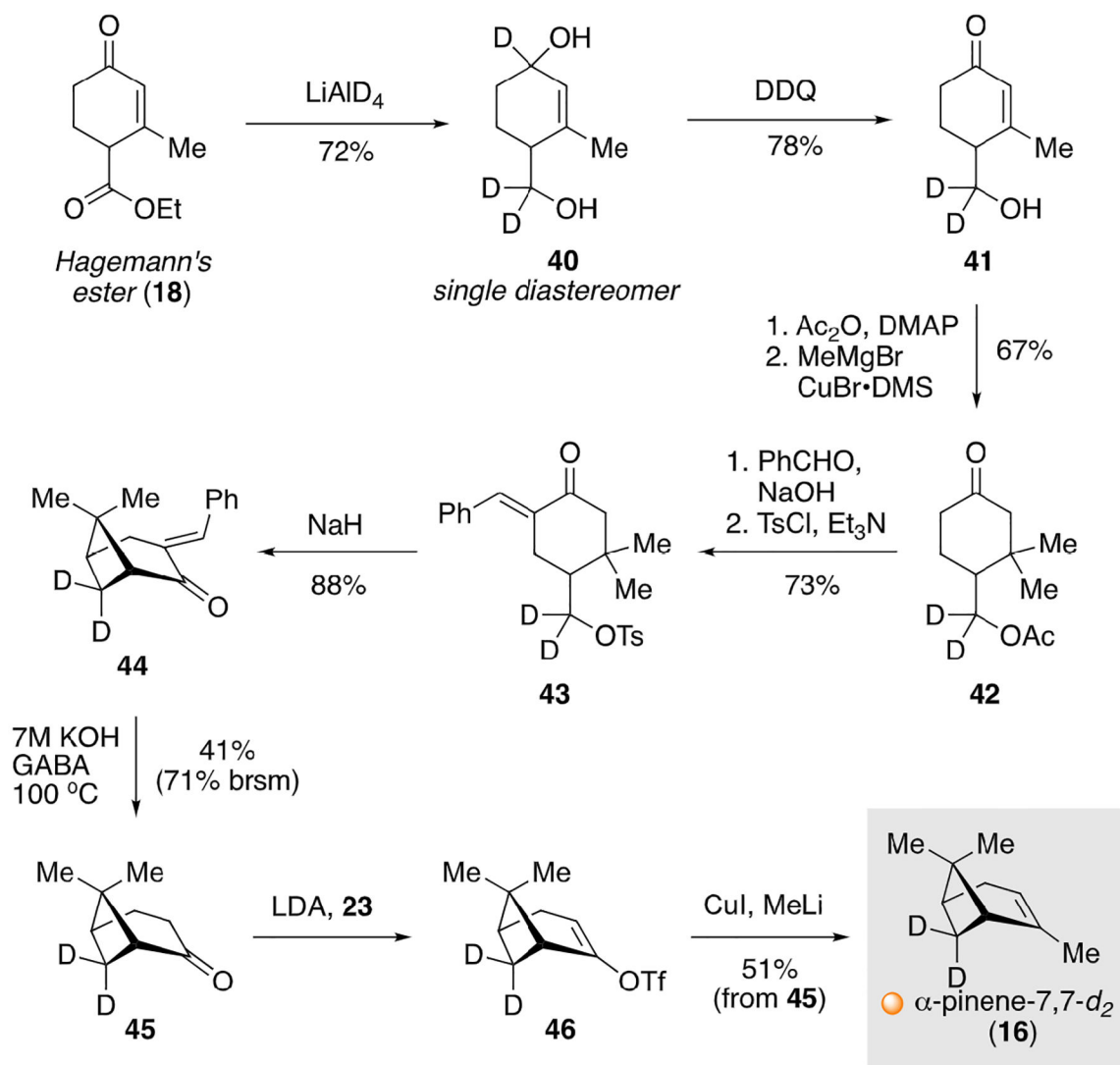
Scheme 1.
Synthesis of α -pinene Isotopologues With Site Specific Deuterium Incorporation at C10, C3 and C9



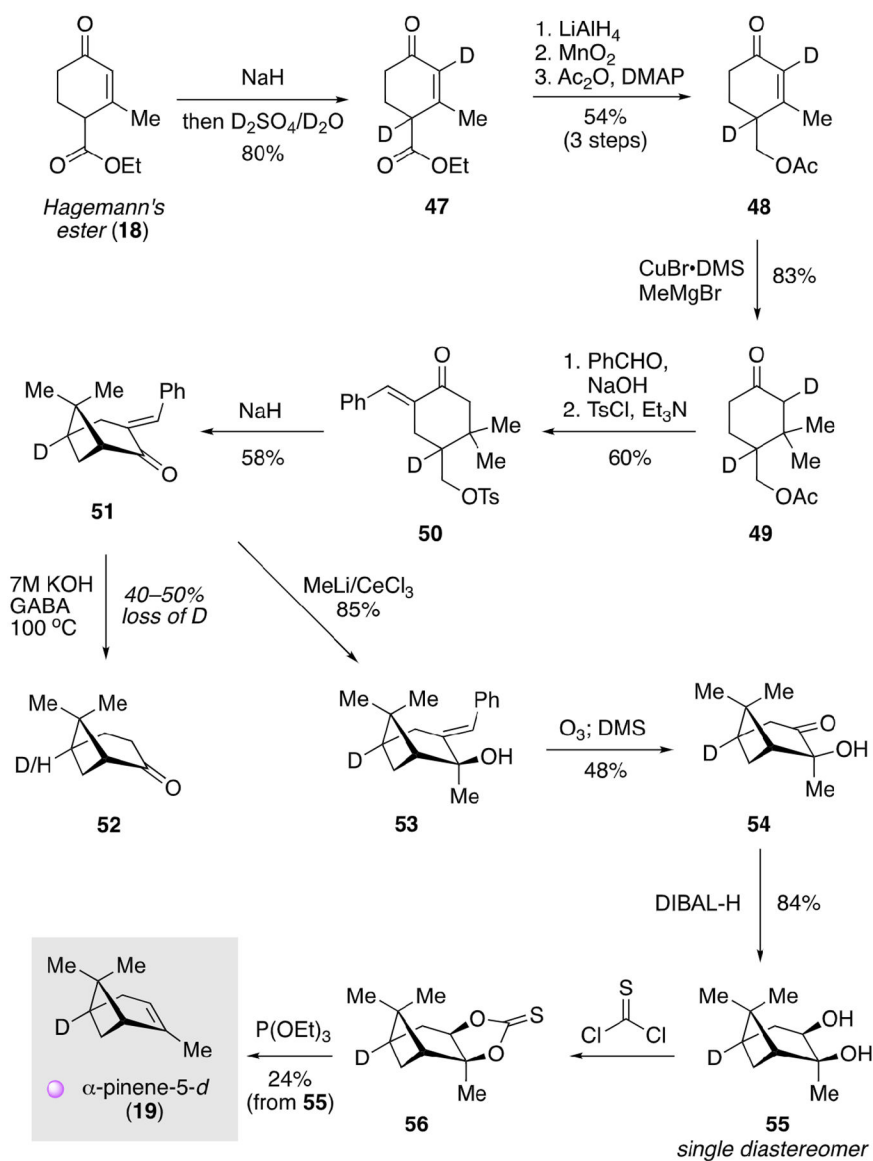
Scheme 2.
Synthesis of the α -pinene Isotopologue With Site Specific Deuterium Incorporation at C4



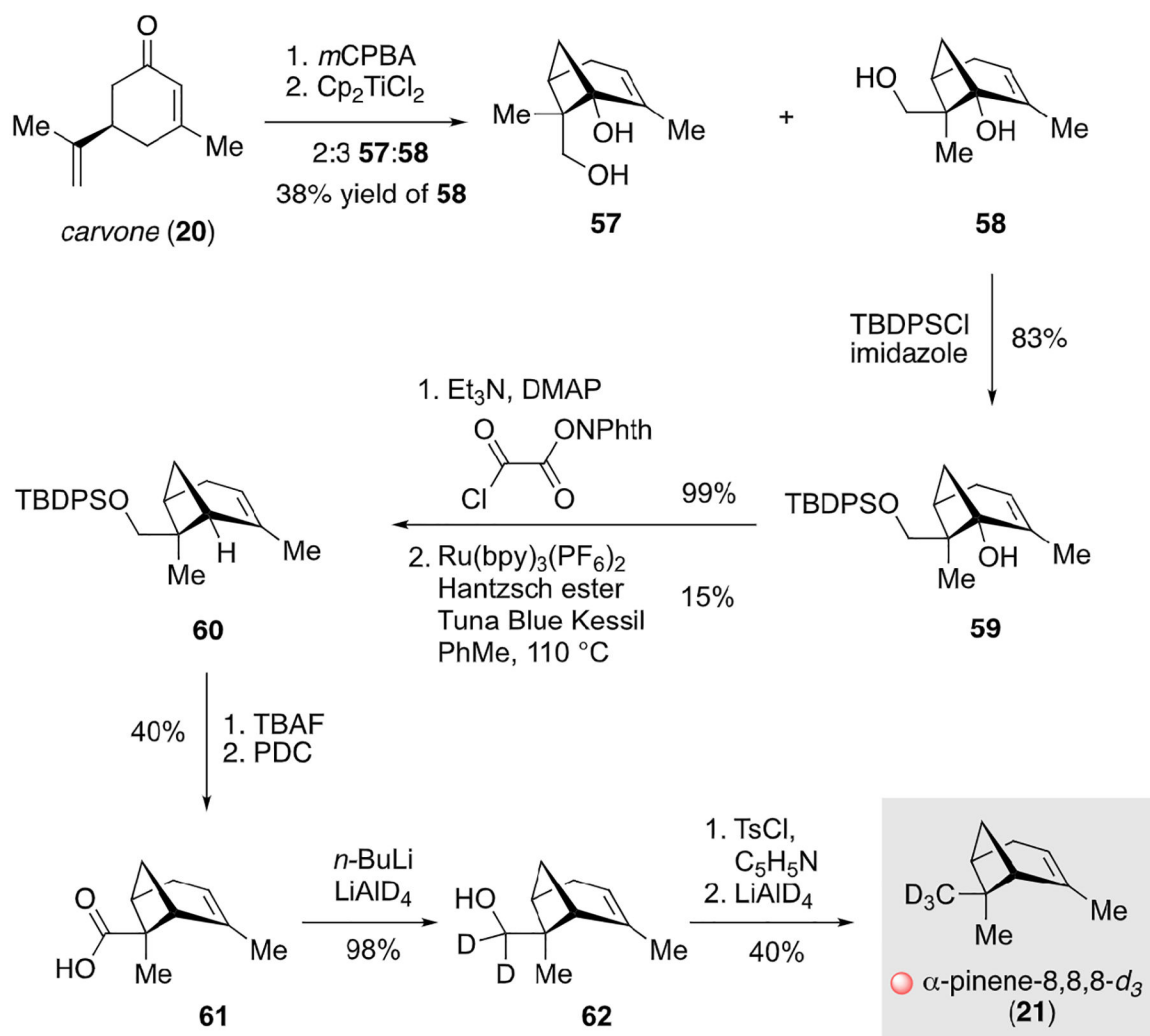
Scheme 3.
Synthesis of α -pinene Isotopologues With Site Specific Deuterium Incorporation at C7 and C1



Scheme 4.
Synthesis of the α -pinene Isotopologue With Site Specific Deuterium Incorporation at C7



Scheme 5.
 Synthesis of the α -pinene Isotopologue With Site Specific Deuterium Incorporation at C5



Scheme 6.
 Synthesis of the α -pinene Isotopologue With Site Specific Deuterium Incorporation at C8