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Graphical Abstract

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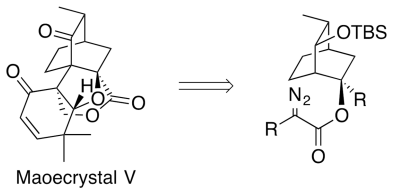

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Stereoelectronic Factors in Bridgehead C-H Bond Insertion: Studies Toward the Total Synthesis of Maoecrystal V

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ABSTRACT

A strategy for the total synthesis of maoecrystal V is presented. The key interior vicinal quaternary carbon centers will be formed via sequential bridgehead C-H bond insertion and enolate functionalization. Studies herein validate the C-H bond insertion as feasable in model studies, though there are significant effects on the selectivity for the bridghead position from neighboring groups. Both inductive electron withrawing elements and sterics play a role in deactivating that position, with the former having a greater effect. Forming the second quaternary carbon is possible via enolate acylation and alkylation. Lastly, an approach to synthesize the cyclohexenone ring of maoecrystal V is described.

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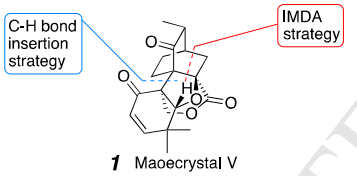
1. Introduction

The diterpenoid natural product maoecrystal V (**1**, Figure 1), which was isolated from the leaves of the Chinese medicinal herb *Isodon eriocalyx*,[1] is an inviting synthetic target for many reasons.[2] Rather than exhibiting broad cytotoxicity, a selective lethality for the gynecological cancer HeLa cell line – with no effect for K562, A549, BGC-823, and CNE lines – was disclosed concurrently with its molecular structure (Figure 1).[1] The architecture of maoecrystal V is remarkable in its own right. Whereas other members of the maoecrystal family contain a bicyclo[3.2.1]octane core, maoecrystal V uniquely contains a bicyclo[2.2.2]octane ring. This core is further functionalized at the bridgehead position to present the challenge of vicinal all-carbon quaternary centers, followed by an ethereal stereocenter bookended by yet another quaternary carbon. The degree of oxidation presents multiple potentially problematic eliminations and skeletal rearrangements for total synthesis efforts. Nevertheless, multiple reports have been made of synthetic strategies[3,4] for maoecrystal V, including four disclosures of its total synthesis.[5] The successful total syntheses of maoecrystal V (**1**) have mainly relied on an intramolecular Diels-Alder (IMDA) reaction, which forms the bicyclo[2.2.2]octane core and the vicinal quaternary centers, though one report performs this transformation intermolecularly.[6,Error! Bookmark not defined.e] We see value in an alternative synthetic strategy that forms the central bond of maoecrystal V through a bridgehead C-H bond insertion, allowing for a retrosynthetic bifurcation of the molecule at the C-C bond between the quaternary carbons (see 1, Figure 1). This strategy offers high levels of convergency as well as the potential for new synthetic lessons learned and access to alternative maoecrystal V analogs than the IMDA approach.[7]



	A549	BGC-823	CNE	K562	HeLa
1	796 mM	44.5 mM	> 800 mM	195 mM	60 nM
cis-platin	5.37 μM	830 nM	7.7 μM	1.3 μM	3.3 μM

Figure 1: Maoecrystal V and Strategic Disconnections

2. Background

2.1. A Bridgehead C-H Bond Functionalization Strategy

Our proposed C-H bond insertion strategy leads to the retrosynthetic analysis in Figure 2. This sequence is predicated on the late-stage introduction of the cyclohexenone ring after the synthesis of bridged bicycle **2**. Bis-lactone **2** would be formed via a transition metal catalyzed carbene C-H bond insertion at the bridgehead position, followed by alkylation and ester formation. Consequently, a diazoester such as **3** was proposed to be suitable for the construction of maoecrystal V's core and would be accessible from the bridged bicyclic Diels-Alder reaction product **4**.

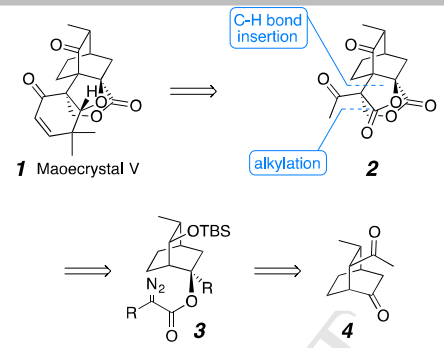


Figure 2. Proposed Retrosynthesis.

2.2. Examples of Bridgehead C-H Bond Insertion by Carbenes

There are few reports in the literature that correspond to our proposed bridgehead C-H bond insertion. Sonowane and co-workers showed a very selective insertion into a bridgehead methine from **5**, generating a five membered ring (see **6**, Figure 3).[8] The products with 4- or 6-membered rings that would be formed by insertion into other nearby C-H bonds were not observed. In more recent work, Lee and co-workers reported a very selective insertion by a vinylidene carbene into the more electron rich methine (product **8**), with no methylene insertion being observed.[9] These findings support the feasibility of the strategy in Figure 2.

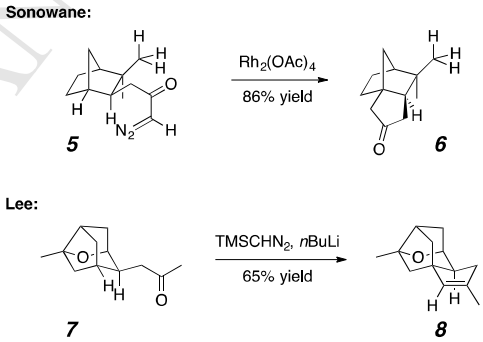


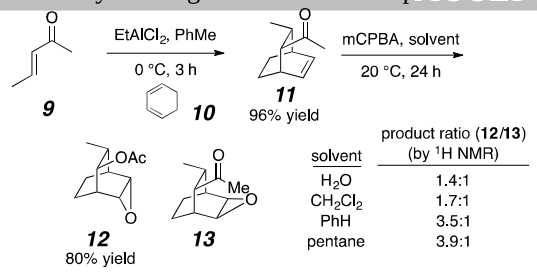
Figure 3. Examples of Insertion in Bridgehead C-H Bonds.

3. Results/Discussion

3.1. Routes to a Key Ketone Synthetic Intermediate

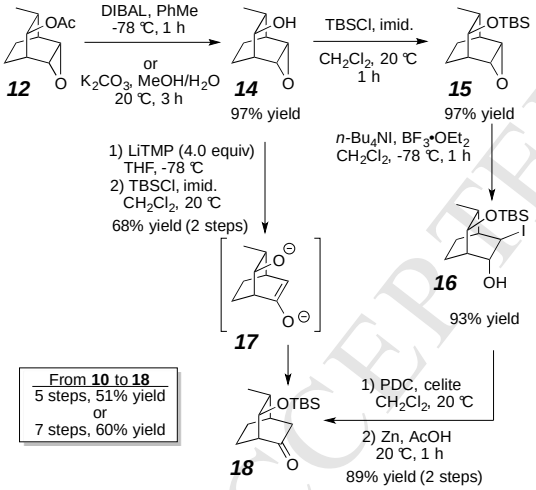
We began the synthesis of maoecrystal V with an intermolecular Diels-Alder reaction between 3-penten-2-one (**9**) and 1,3-cyclohexadiene (**10**, Scheme 1). The cyclization generated the endo product **11** and introduced the methyl group with the correct stereochemistry. Next, the bicyclo[2.2.2]octene **11** was subjected to Baeyer-Villiger oxidation. As anticipated, epoxidation competed with the Bayer-Villiger oxidation, generating the doubly oxidized epoxyester **12** and epoxyketone **13**. A change of oxidants to H_2O_2, magnesium monoperoxyphthalate, tBuOOH, $(TMSO)_2$, or urea hydroperoxide in combination with different additives (acid or base) and different solvents did not provide selectivity for the Baeyer-Villiger reaction. We realized that ester **12** could be readily transformed into the ketone **18** (Scheme 2). Using pure mCPBA as an oxidant and benzene or pentane as a reaction solvent led to the highest ratio of **12**:**13** and 75-85% isolated yields.

Scheme 1. Baeyer-Villiger Oxidation and Epoxidation.



Next, the acetate group in **12** was removed in preparation for installation of a strategic TBS ether. We then evaluated two pathways to access synthetic intermediate **18** (Scheme 2). The longer route uses a nucleophilic epoxide opening with iodide, oxidation of the secondary alcohol in **16** to the α-iodo ketone, and then the reductive halide removal to generate **18** with 80% overall yield from **14** (60% overall yield from **10**). On the other hand, when compound **14** is treated with 4 equivalents of the strong base TMPLi, the initially formed alkoxide directs the base for deprotonation of the closest epoxide hydrogen, which generates the enolate **17** upon epoxide opening via elimination. After the protonation of the enolate in the aqueous workup and then etherification, the desired ketone **18** was isolated as a single isomer. It is important to note that LDA, a weaker base, does not promote the rearrangement, and solvents like Et_2O and PhMe are not suitable due to the poor solubility of the deprotonated species. If less than 4 equivalents of TMPLi base are used, the reaction does not go to completion and starting material is recovered. An overall 68% yield can be obtained for the shorter route from **14** to **18** (51% overall from **10**).

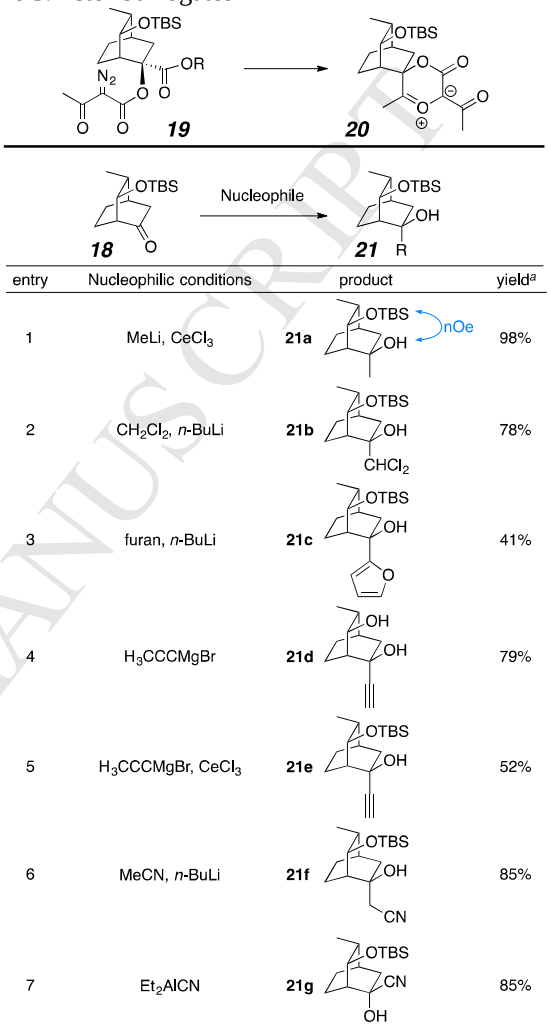
Scheme 2. Epoxide Rearrangement.



3.2. Ester Synthetic Equivalents

With this bridged bicyclic ketone in our hands, we prepared for the key C-C bond formation through C-H bond insertion. It is known that carbenoids generate dipoles like **20** in the presence of carbonyls (Scheme 3).[10] That transformation would be unproductive in this strategy. In order to avoid the formation of dipole **20**, the R group in compound **21** must be unreactive towards the in-situ generated metal carbene during the C-H bond insertion step, but should be easily transformed into a carboxylate group. We started to examine the addition of different nucleophiles to the ketone **18**. As expected, the large silyl group generally prevented nucleophile addition from the β-face, which led to the desired stereoisomer as confirmed by a clear nOe signal between the silyl group and hydroxyl. Cyanohydrine **21g** was an exception. The opposite stereoisomer was formed when ketone **18** was reacted with Nagata's reagent (Et_2AlCN) as evidenced by the disappearance of the nOe observed for the other products. The cyanide addition under these reaction conditions is known to be a reversible process,[11] and thus the formation of a thermodynamic product is observed. Trauner et al. observed similar stereoselectivity when reacting a ketone with cyanide in their studies.[4c]

Scheme 3. Ester Surrogates



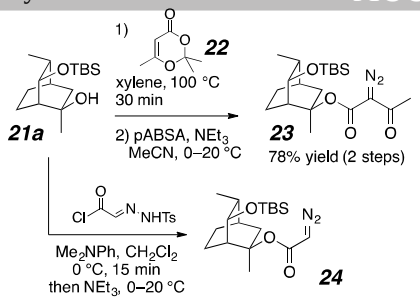
[a] Isolated yields.

All attempts to add a trichloromethyl anion to ketone **18** were unsuccessful. Interestingly, the in situ generated dichloromethyl anion cleanly added to ketone **18** to generate product **21b**. Cleavage of the silyl protecting group was encountered with propynylmagnesium bromide. Switching to the less basic organocerium reagent[12] allowed the isolation of the desired product **21e** in acceptable yield. The tertiary alcohol **21a** was chosen as a model substrate for the initial C-H bond insertion trials.

3.3. Diazoester Formation

Pyrolysis of dioxinone **22** takes place above 100 °C providing acetylketene, which in the presence of alcohol **21a** generated a β-ketoester as a mixture of keto-, enol-tautomers (Scheme 4).[13] Reacting that β-ketoester with the diazo-transfer reagent pABSA formed diazo-acetoacetate **23**.[14] A diazo-acetate group was introduced using the protocol reported by House and Blankley.[15]

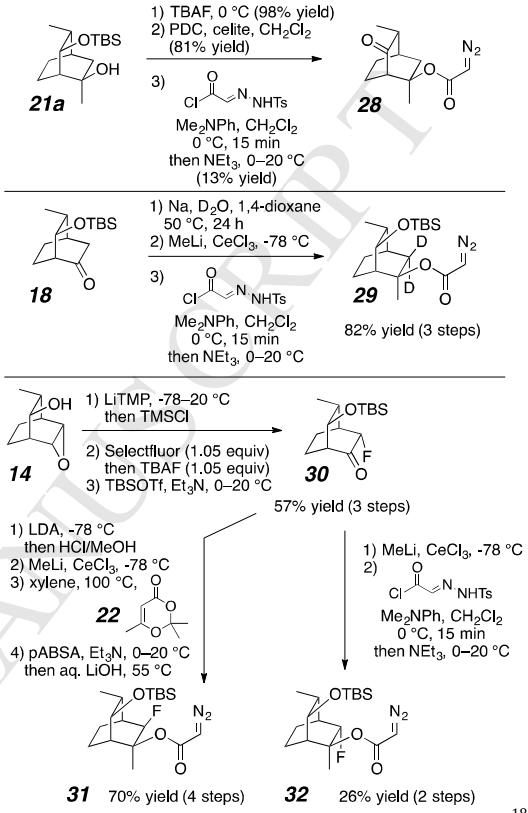
Scheme 4. Syntheses of Diazoesters.



3.5. Alternative Diazoesters

To further test the influence of the large TBS group on C-H bond insertion, we attempted to synthesize a diazo-acetate with a smaller group at the ether position. Thus, after deprotection and oxidation of the resulting secondary alcohol, followed by a similar sequence to that in Scheme 5, the ketodiazo-acetate **28** was obtained (Scheme 6).

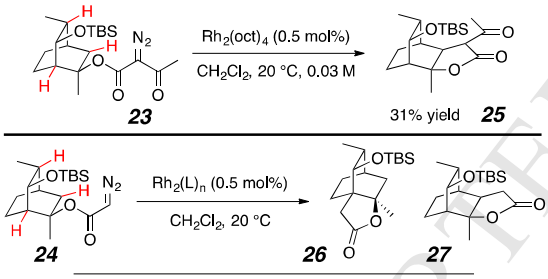
Scheme 6. Alternative Diazoesters



3.4. Initial C-H Bond Insertion Results

Diazoesters **23** and **24** each have two tertiary and one secondary C-H bonds (highlighted in red in Scheme 5) that would be accessible to the carbene. Relative rates of C-H insertion reactions are usually based on an interplay of bond electronics, which favor tertiary C-H bond insertion, and sterics, which favor methylene insertion.[16] Methyl groups are typically unreactive. Bridgehead insertion would also generate a five-atom ring, which is generally preferred. Based on Sonowane's work in which the bridgehead tertiary C-H bond was the most reactive for insertion, methylene insertion products like **25** and **27** were predicted to be disfavored. Since the methine on the alkyl bridge is syn-periplanar to the large silyl ether, insertion at that site was also expected to be slow. On the other hand, there was a possibility that the inductive electron withdrawing effect of the silyl ether oxygen might deactivate the two methines for C-H bond insertion, which could allow methylene insertion to become competitive.

Scheme 5. C-H insertion results



entry	catalyst	concentration	yield **26**	yield **27**
1	$Rh_2(oct)_4$	0.03 M	8%	24%
2	$Rh_2(esp)_2$	0.01 M	25%	32%
3	$Rh_2(esp)_2$	0.005 M	26%	35%

The C-H bond insertion study began with substrate **23**. Unfortunately, when it was subjected to catalytic amounts of $Rh_2(oct)_4$, none of the desired methine C-H insertion product was observed. A variety of other conditions were examined, but no bridgehead insertion was seen. Either the intermediate carbene was more sensitive towards the steric hindrance provided by large silyl group or the methine C-H bond was less activated than the methylene C-H bond due to the inductive electron withdrawing effect of the ether oxygen on the bridge. If it were the former, a smaller and more reactive diazo-acetate group might change the selectivity, favoring methine over methylene C-H bond insertion. While the smaller diazo-acetate **24** did produce the methine insertion product **26**, it was in a low yield and the major product was still derived from methylene insertion. Again, a variety of catalysts and reaction conditions were examined, with the most productive listed in Scheme 5. Importantly, $Rh_2(esp)_2$ proved to be a more effective catalyst for the C-H insertion, which reflects results seen in our carbene cascade reactions.[17]

A strategic use of a deuterium kinetic isotope effect[18] in the total synthesis of the Welwitindolinones has been reported by Garg.[19] A similar use of deuterium as a blocking group for the methylene carbon in **29** could be envisioned to eventually provide deuteromaoecrystal V by biasing insertion for the methine position. NaOD in D_2O[20] deuterated the ketone **18** better than other exchange conditions (KOtBu/D_2O; TBD/$CDCl_3$[21]), leading to 99% substitution. Diazoester **29** was then synthesized.

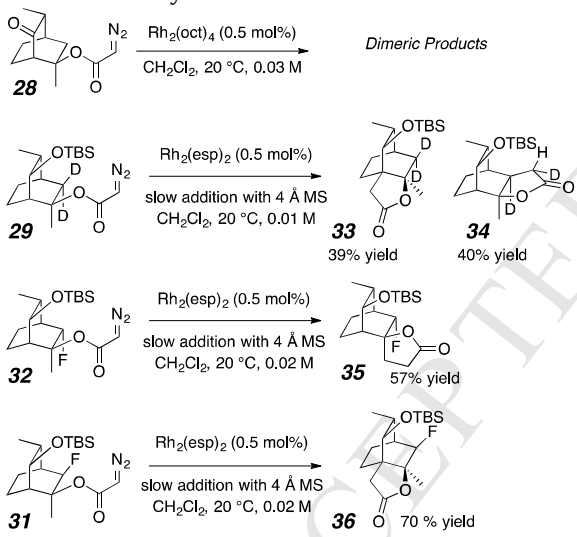
Next, we proposed to use different groups at the methylene competing for C-H bond insertion to deactivate that position and probe the stereoelectronic effects controlling the selectivity. The deactivation could arise from steric blocking, electronic deactivation, or both. The α-iodo from oxidation of ketone **16** (Scheme 2) was not suitable for the formation of the corresponding α-iodo diazo-acetates as it was readily converted into a cerium enolate when treated with organocerium reagents,[12]. Thus, a smaller, less reactive, and more electron withdrawing halogen – fluorine – was chosen to be introduced to the methylene adjacent to the diazoacetate (see **32**, Scheme 6) as a test compound. Attempted fluorination of ketone **18** with selectfluor produced a mixture of products. To eliminate the side reactions, we started with the epoxide **14**. After the deprotonation/rearrangement with , both the alkoxide and enolate were protected as TMS ethers. Then the silyl enol ether was subjected to fluorination. Next, the secondary alcohol was protected with a TBS group, which gave **30** in 57% overall yield. The milder TBSCl/imidazole conditions did not work for this particular substrate. Due to steric hindrance around the ketone **30**, a mixture of products was produced in the reaction with methyl

cerium. Still, enough material was obtained to carry on diazoester formation, and diazoacetate **32** was isolated in 26% yield from ketone **30**. To see if the selectivity for C-H insertion would change with cis-fluorodiazo-acetate **31,** the opposite diazoacetate diastereomer was obtained through an initial epimerization. A direct diazoacetate transfer reaction did not work well, so a stepwise alternative was employed. Indeed, when the diazo-acetoacetate produced from reaction with pyrone **22** and then pABSA was heated in aqueous base solution, deacetylation took place, giving product **31** in 86-91% yield for that step.

3.6. C-H Bond Insertion Selectivity for Alternative Esters

The ketodiazoester **28** was tested for selectivity in the C-H bond insertion reaction (Scheme 7). Normally, the inductive electron withdrawing effect of a carbonyl group would be expected to deactivate α-C-H bonds for insertion reactions. However, in this case there would be insufficient orbital overlap between the bridgehead methine C-H bond and the π-system of the carbonyl group for resonance-based or hyperconjugative charge delocalization, though some inductive effects would likely remain. Certainly, the steric blocking of the bridgehead position would be lessened relative to the silyl ether, allowing for distinguishing between the effects. When carbonyl compound **28** was treated with $Rh_2(oct)_4$, however a mixture of products was formed, with homodimerization being by far the most dominant. No clean C-H bond insertion product could be isolated, indicating that a hindered environment around the carbene prevented many side reactions.

Scheme 7. Reactivity of Diazoesters.



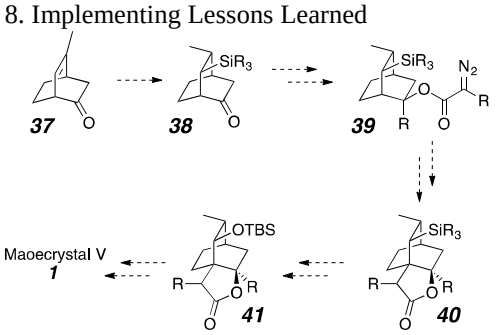
The deuterated diazo-acetate **29** was also reacted with $Rh_2(esp)_2$. The desired methine insertion product **33** was isolated in 39% yield. The rates of insertion into the methine C-H and methylene C-D bonds were almost equal, which represents a slight shift in selectivity toward methine insertion relative to the non-deuterated substrate. Thus, a very small deuterium isotope effect was observed. Previously, Adams saw a minimal isotope effect in a competition study for the formation of bridged bicycles.[22] Practically speaking, therefore, using kinetic isotope effects to control carbene C-H bond insertion selectivity does not appear as viable as for controlling nitrene C-H bond insertion. On the other hand, this result shows that the pathways to form **33** and **34** are very close in energy, and so eliminating the electronic or steric deactivation for bridgehead insertion should lead to **33** as the major insertion product.

We next looked at fluorinated diazoesters **32** and **31**. The C-H bond at the fluorinated carbon in the diazoacetates was expected to be deactivated towards insertion due to the strong electron withdrawing nature of the halogen. To our surprise, when diazoester **32** was reacted with catalytic amounts of $Rh_2(esp)_2$, insertion into the C-H bond of the *methyl* group produced the major product **35**. Only trace amounts of the bridgehead C-H bond insertion product were observed, and no methylene C-H bond insertion occurred as was hypothesized. It is not initially apparent why the syn-periplanar fluoride activates the methyl C-H bond for insertion, but it may be due to its proximity in space. In contrast, the diastereomeric α-fluoro diazoacetate **31** gave the lactone **36** when reacted with catalytic amounts of $Rh_2(esp)_2$. Not surprisingly, the C-H bond insertion was very selective for the bridgehead position, and **36** was isolated in 70% yield.

The desire to achieve selective C-H insertion in a complex system led to new, interesting, and valuable results. The inductive electron-withdrawing effects of a β-ether, along with the steric bulk of the TBS group, disfavored C-H bond insertion at the bridgehead position relative to the unfunctionalized substrates of Sonowane. Additionally, corroboration was obtained that intramolecular C-H bond insertion shows only a small deuterium isotope effect. Lastly, a syn-periplanar fluoride activated a methyl group for C-H bond insertion through as yet unidentified means. The lactones **33** and **36** have also allowed the exploration of key late-stage transformations for the total synthesis of Maoecrystal V as explained below in sections 3.7 and 3.8.

From the insights gained in these experiments, we propose that a slight modification to the original strategy will overcome the selectivity problems encountered with these substrates (Scheme 8). The known bicyclo[2.2.2]octane **37**[23] will serve as a substrate for hydrosilylation,[24] which will provide **38** as a silyl analog of ketone **18**, as long as the hydrosilylation occurs on the less hindered olefin face. Using the transformations described above, diazoester **39** will be prepared. With the silyl group on the bridge, the inductively electron withdrawing β-oxygen has been exchanged for a neutral or even electron donating group, and so the C-H bond insertion at the bridgehead position will again be favored. After the insertion product **40** is obtained, the silyl ether may be restored to the bridge via a Tamao-Fleming oxidation, and the original route is thus intercepted. We anticipate that this may even be a more rapid synthesis of **41** relative to the original route.

Scheme 8. Implementing Lessons Learned

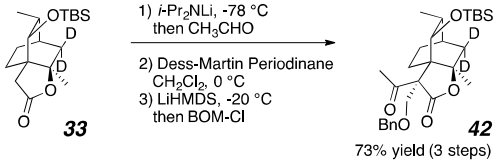


3.7. Vicinal Quaternary Carbon Construction

Since we had advanced lactone intermediates in hand, post-C-H bond insertion transformations were examined. First, we attempted to test the influence of the large silyl group on diastereoselectivity around the fused γ-lactone in **33** (Scheme 9). To install the second of the vicinal quaternary carbon centers, the

lactone **33** was deprotonated with LDA, and the resulting enolate was reacted with acetaldehyde. The alcohol was isolated in 96% yield. Next, that secondary alcohol was oxidized with Dess-Martin periodinane (90% yield), and then deprotonation and exposure to BOM-Cl formed the quaternary carbon in **42** with diastereoselectivity again dictated by the TBS ether. Unfortunately, all attempts to use formaldehyde as an electrophile failed. Having established a method to install the second of the vicinal quaternary carbons, a preliminary approach to form the cyclohexenone ring was examined.

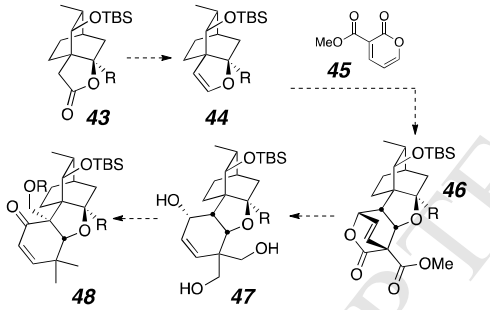
Scheme 9. Vicinal Quaternary Center Formation.



3.8. Approach to Cyclohexenone Construction

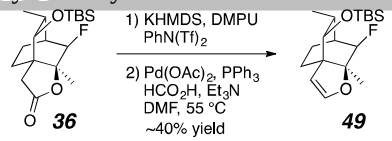
Similar cyclohexene ring systems to those in compound **46** (Scheme 10) can be accessed through Diels-Alder reactions.[25] Dihydrofuran **44** would act as a dienophile in an inverse electron demand Diels-Alder reaction, and 3-carbomethoxy-2-pyrone (**45**) would be used as a diene for the formation of doubly-bridged polycycle **46**. This would also allow accessing the gem-dimethyl group in the cyclohexenone ring of **48** through sequential reduction. Weaker Lewis acids would be used, like $Yb(OTf)_3$ or $Eu(hfc)_3$[26] in order to prevent decarboxylation, which takes place in the presence of strong Lewis acids.[27]

Scheme 10. Dimethylcyclohexenone via Diels-Alder Reaction.



Vinyl ethers can be accessed by a variety of methods. Lactone **36** was successfully transformed to dihydrofuran **49** through hydrometallation of the vinyl triflate (Scheme 11). Formation of the vinyl triflate was very clean as shown by ^{1}H NMR spectroscopy of the crude material. However, its isolation was problematic due to its instability. Thus, crude material was directly subjected to the next step. Only the conditions shown in Scheme 11 produced the vinyl ether **49**, which was obtained in ~40% yield based on the crude NMR. Its isolation from the crude mixture was very difficult due to a similar R_F value to that of the triflate. The product was unstable during chromatographic purification as well. Other hydride sources, like Et_3SiH or Bu_3SnH, were ineffective. No reaction was observed in toluene or THF, and a Pd^0 catalyst ($Pd(PPh_3)_4$) was ineffective as well. Preliminary investigations into the Diels-Alder cycloaddition using **45** and similar pyrones have not yet born fruit due to the sensitivity of **49**, but they remain ongoing with other electron deficient dienes. Vinyl ether **49** is still expected to be a productive motif for cyclohexanone construction.

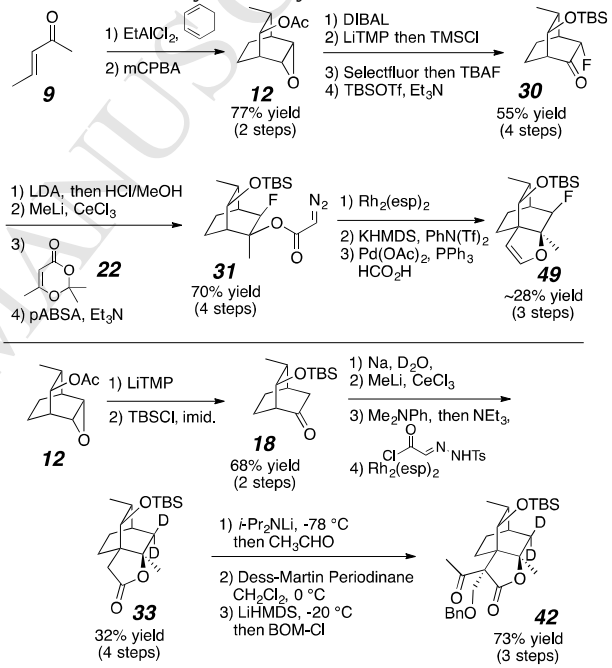
Scheme 11. Cyclic Vinyl Ether Formation.



4. Conclusion

Despite multiple obstacles, advanced intermediates for the core structure of Maoecrystal V have been synthesized without the use of an IMDA reaction to form the vicinal quaternary carbons. The effects of substituents on C-H bond insertions have been defined for neighboring ethers, fluorides (including a rare activation of a methyl group by a locked syn-periplanar fluoride), and deuteration. The introduction of a fluoride into the molecule also allowed us to build model systems for late stage transformations. The dihydrofuran **49** was synthesized in 13 steps with ~8% overall yield, and lactone 42 containing the key vicinal quaternary carbons was accessed in 11 reactions in 12% overall yield (Scheme 12).

Scheme 12. Summary of the Synthetic Work



5. Experimental section

5.1. General Considerations

All reactions were carried out in flame- or oven-dried glassware. THF, toluene and CH_2Cl_2 were purged with argon and dried over activated alumina columns. Flash chromatography was performed on 60 Å silica gel (Sorbent Technologies). Analytical thin layer chromatography was performed on EMD silica gel/TLC plates with fluorescent indicator 254 nm. The ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using residual solvent peak as an internal reference ($CDCl_3$: 7.25 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR; DMSO-d_6: 2.50 ppm for ^{1}H NMR and 39.51 ppm for ^{13}C NMR; benzene-d_6: 7.16 ppm for ^{1}H NMR). Hexafluorobenzene (δ = -164.9 ppm) was employed as an internal standard in ^{19}F NMR spectra. For ^{13}C NMR, multiplicities were distinguished using DEPT experiments: methyl and methine carbons appear positive (up); methylene carbons appear negative. IR spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. HRMS analyses

were performed under contract by UT Austin's mass spectrometric facility via positive mode ESI method and US10252005 instrument. Commercially available compounds were purchased from Aldrich Chemical Co., Acros Organics, Alfa Aesar, or TCI America and were used without further purification. Note that all designations of *R* or *S* stereochemistry is to denote diastereomeric relationships and that all compounds are racemic.

1.4.2. Syntheses of Compounds

*1-((1S,4R,7S,8R)-8-Methylbicyclo[2.2.2]oct-2-en-7-yl)ethanone (**28**).*

A flame-dried one liter round-bottom flask was charged with 1,4-cyclohexadiene (**26**) (9.8 mL, 0.10 mol) and penten-2-one (**27**) (10.0 mL, 0.10 mol, 70% purity). Anhydrous PhMe (0.20 L, 0.5M) was added and the flask was cooled in an ice/water bath. $EtAlCl_2$ (113 mL, 0.11 mol) was then added, the reaction mixture was stirred at 0 °C for 3 hours. Afterward, 1N HCl solution was added slowly to the reaction mixture, until the evolution of gas had ceased. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. Acetone was added to the residue, the white precipitate formed was removed by filtration through a small plug of Celite® and rinsed with acetone. Solvent was removed via rotary evaporation. The obtained yellow oil was subjected to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41-6.33 (m, 1H), 6.10-6.03 (m, 1H), 2.81- 2.73 (m, 1H), 2.29-2.22 (m, 1H), 2.10 (s, 3H), 2.03 (dd, *J* = 6.4 Hz, 1.8 Hz, 1H), 1.91-1.81 (m, 1H), 1.79-1.69 (m, 1H), 1.56-1.46 (m, 1H), 1.34-1.24 (m, 1H), 1.12-1.01 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 1H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 210.0, 136.9, 130.6, 60.6, 36.0, 33.8, 32.9, 28.4, 26.2, 20.0, 18.2.

A one liter round-bottom flask was charged with the crude material from the previous reaction. Reagent grade pentane (0.5 L, 0.2M) was added, followed by purified mCPBA (37.0 g, 0.30 mol). The order of the addition is important! The reaction mixture was stirred at room temperature for 48 hours. To the reaction mixture saturated $NaHCO_3$ solution was added slowly, until the benzoic acid dissolved. The mixture was extracted with EtOAc (3x), the organic phases were combined and washed with saturated $Na_2S_2O_3$ solution and brine, then dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The residue was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. 7-Methyl-3-oxatricyclo[3.2.2.0^{2,4}]non-6-yl acetate (**29**) was obtained as a clear oil (12.5 g, 88%) with the corresponding spectroscopic data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (t, *J* = 3.4 Hz, 1H), 3.33 (t, *J* = 4.6 Hz, 1H), 3.24 (t, *J* = 4.6 Hz, 1H), 2.33-2.29 (m, 1H), 2.04 (s, 3H), 2.01-1.97 (m, 1H), 177-1.64 (m, 2H), 1.52-1.44 (m, 1H), 1.33-1.24 (m, 1H), 1.19- 1.10 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 170.8, 80.9, 54.0, 50.4, 37.0, 34.6, 33.4, 21.5, 21.0, 18.0, 16.5. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{11}H_{16}O_3$, 197.1178; found 197.1183. R_f: 0.41 in 20% EtOAc/hexanes. 1-(7-Methyl-3-oxatricyclo[3.2.2.0^{2,4}]non-6-yl)ethanone (**30**) was obtained as a clear oil, with the corresponding spectroscopic data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (t, *J* = 4.6 Hz, 1H), 3.18 (t, *J* = 4.6 Hz, 1H), 2.73-2.69 (m, 1H), 2.29-2.22 (m, 1H), 2.16 (s, 3H), 2.02-1.97 (m, 1H), 1.80-1.72 (m, 1H), 1.67-1.58 (m, 1H), 1.54-1.50 (m, 1H), 1.49-1.42 (m, 1H), 1.40-1.31 (m, 1H), 1.07 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 209.2, 58.3, 53.2, 51.0, 33.6, 30.5, 29.9, 27.0, 21.7, 21.1, 16.6. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{11}H_{16}O_2$, 181.1229; found 181.1237. R_f: 0.20 in 20% EtOAc/hexanes. 1D nOe analysis revealed the stereochemistry of epoxide in **30**.

*7-Methyl-3-oxatricyclo[3.2.2.0^{2,4}]nonan-6-ol (**31**).*

A round-bottom flask was charged with **31** (2.00 g, 0.01 mol). Reagent grade MeOH (51 mL, 0.2M), water (22 mL, 0.45M) and K_2CO_3 (4.20 g, 0.03 mol) were added. The reaction mixture was stirred at room temperature overnight. MeOH was removed via rotary evaporation. To the residue 1N HCl solution (100 mL) was added, the product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered through short silica gel plug and rinsed with Et_2O. Solvent was removed via rotary evaporation to yield clean product as a white solid (1.53 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53-3.47 (m, 1H), 3.36-3.29 (m, 1H), 2.25-2.18 (m, 1H), 2.00-1.93 (m, 1H), 1.72 (d, *J* = 3.2 Hz, 1H), 1.71-1.59 (m, 2H), 1.50-1.39 (m, 1H), 1.27-1.18 (m, 1H), 1.13-0.99 (m, 1H), 1.11 (d, *J* = 7.3Hz, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 79.4, 54.4, 50.8, 39.8, 36.4, 34.8, 21.4 (CH_2), 18.1, 16.5 (CH_2). HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_9H_{13}O_2$, 154.0994; found 154.0990. R_f: 0.29 in 50% EtOAc/hexanes.

*tert-Butyldimethyl({7-methyl-3-oxatricyclo[3.2.2.0^{2,4}]nonan-6-yl}oxy)silane (**32**).*

A round-bottom flask was charged with **31** (1.25 g, 8.1 mmol). Anhydrous CH_2Cl_2 (32 mL, 0.25M) was added, followed by the addition of imidazole (1.93 g, 28.3 mmol) and TBSCl (3.05 g, 20.2 mmol). The reaction mixture was stirred overnight at room temperature. CH_2Cl_2 was removed via rotary evaporation. To the residue 5% EtOAc in hexanes solution was added, the mixture was filtered through short silica gel plug and rinsed with 5% EtOAc in hexanes solution. Solvent was removed via rotary evaporation to yield clean product as a colorless oil (2.15 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.39 (t, *J* = 2.9 Hz, 1H), 3.30 (t, *J* = 4.6 Hz, 1H), 3.26 (t, *J* = 4.6 Hz, 1H), 2.14-2.09 (m, 1H), 1.95-1.90 (m, 1H), 1.70-1.58 (m, 2H), 1.47-1.38 (m, 1H), 1.25-1.17 (m, 1H), 1.07-0.97 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 79.7, 54.3, 51.4, 40.1, 36.7, 34.7, 25.9, 21.3, 18.1, 16.5, -4.5. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{15}H_{28}O_2Si$, 269.1937; found 269.1927. R_f: 0.69 in 20% EtOAc/hexanes.

*(1S,2R,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-iodo-5-methylbicyclo-[2.2.2]octan-2-ol (**33a**).*

A flame-dried round-bottom flask was charged with **32** (2.15 g, 8.00 mmol) and Bu_4NI (3.85 g, 10.4 mmol). Anhydrous CH_2Cl_2 (80.0 mL, 0.1M) was added and the flask was cooled to -78 °C in a dry ice/acetone bath. $BF_3 \cdot OEt_2$ (1.3 mL, 10.4 mmol) was then added dropwise, the reaction mixture was stirred at -78 °C for 30 minutes, then allowed to warm to room temperature. CH_2Cl_2 was removed via rotary evaporation. To the residue saturated NH_4Cl solution was added, product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The obtained yellow oil was subjected to the next step without further purification. To obtain an analytical sample, the residue was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (2.54 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75- 4.66 (m, 1H), 4.10 (dd, *J* = 5.0 Hz and 1.8 Hz, 1H), 3.15 (dd, *J* = 5.5 Hz and 2.3 Hz, 1H), 2.30-2.21 (m, 1H), 1.84-1.74 (m, 1H), 1.59-1.55 (m, 1H), 1.55-1.50 (m, 1H), 1.48 (s, 1H), 1.31-1.16 (m, 2H), 1.06 (s, 9H), 1.09-0.92 (m, 1H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.14 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (125.76

MHz, benzene-d_6) δ 78.0, 77.1, 44.5, 44.2, 43.2, 38.8, 26.4, 21.3, 18.5, 18.1, 16.2, -4.1. R_f: 0.14 in 5% EtOAc/hexanes.

*(1S,2R,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-bromo-5-methyl- bicyclo[2.2.2]octan-2-ol (**33b**).*

A flame-dried round-bottom flask was charged with **32** (0.51 g, 1.90 mmol) and Bu_4NBr (0.80 g, 2.49 mmol). Anhydrous CH_2Cl_2 (19.0 mL, 0.1M) was added and the flask was cooled to -78 °C in a dry ice/acetone bath. $BF_3 \cdot OEt_2$ (0.3 mL, 2.49 mmol) was then added dropwise. The reaction mixture was stirred at -78 °C for 30 minutes, then allowed to warm to room temperature. CH_2Cl_2 was removed via rotary evaporation. To the residue saturated NH_4Cl solution was added, and product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The obtained yellow oil was subjected to the next step without further purification. To obtain an analytical sample, the residue was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.45 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50-4.43 (m, 1H), 4.00 (dd, *J* = 5.0 Hz and 1.8 Hz, 1H), 3.27 (dd, *J* = 5.5 Hz and 2.3 Hz, 1H), 2.06-1.96 (m, 1H), 1.93 (s, 1H), 1.84-1.73 (m, 1H), 1.69-1.56 (m, 3H), 1.53-1.43 (m, 1H), 1.29-1.19 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H). R_f: 0.26 in 10% EtOAc/hexanes.

*(1S,2R,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-chloro-5-methyl-bicyclo[2.2.2]octan-2-ol (**33c**).*

A flame-dried round-bottom flask was charged with **32** (100 mg, 0.37 mmol) and Bu_4NCl (207 mg, 0.74 mmol). Anhydrous CH_2Cl_2 (3.7 mL, 0.1M) was added and the flask was cooled to -78 °C in a dry ice/acetone bath. $BF_3 \cdot OEt_2$ (0.4 mL, 1.11 mmol) was then added dropwise, the reaction mixture was stirred at -78 °C for 30 minutes, and then it was allowed to warm to room temperature. CH_2Cl_2 was removed via rotary evaporation. To the residue saturated NH_4Cl solution was added, and the product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The obtained yellow oil was subjected to the next step without further purification. To obtain an analytical sample, the residue was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (48 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33-4.28 (m, 1H), 3.85 (dd, *J* = 4.6 Hz and 1.7 Hz, 1H), 3.28 (dd, *J* = 5.7 Hz and 2.3 Hz, 1H), 2.02-1.91 (m, 2H), 1.81-1.72 (m, 1H), 1.69-1.66 (m, 1H), 1.66-1.54 (m, 2H), 1.47-1.38 (m, 1H), 1.29-1.20 (m, 1H), 1.02 (d, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 77.3, 75.0, 69.6, 43.4, 42.0, 35.3, 25.9, 20.1, 18.1, 17.4, 16.5, -4.5.

*(1R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-5-methylbicyclo[2.2.2]octan-2-one (**35**).*

Method A: A round-bottom flask was charged with **33a** (0.45 g, 1.29 mmol). Anhydrous CH_2Cl_2 (13 mL, 0.1M) was added, followed by the addition of Celite® (1.45 g) and PDC (1.45 g, 3.80 mmol). The reaction mixture was stirred overnight at room temperature. The heterogeneous solution was filtered through short silica gel plug and rinsed with CH_2Cl_2. After the removal of solvent via rotary evaporation and drying under high vacuum for few hours, product solidified. Product as a light yellow solid was collected in 94% yield and used in the next reaction (0.42 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (d, J = 2.9 Hz, 2H), 3.45-3.40 (m, 1H), 2.39 (q, J = 2.9 Hz, 1H), 2.35-2.27 (m, 1H), 2.11-2.06 (m, 1H), 1.99-1.91 (m, 1H), 1.79-1.70 (m, 1H), 1.70-1.61 (m, 1H), 1.61-1.52 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 207.3, 52.7, 51.4, 42.3, 37.1, 25.7, 19.6, 19.0, 18.3, 17.9, -4.6. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{15}H_{28}O_2Si$, 349.1021; found 349.1031. R_f: 0.22 in 5% EtOAc/hexanes.

A round-bottom flask was charged with the product of the previous reaction (3.62 g, 9.2 mmol). Glacial AcOH (50.0 mL, 0.18M) and Zn dust (1.71 g, 26.1 mmol) were added. The solution was stirred at room temperature and monitored by TLC. After completion, the reaction mixture was filtered through the short plug of Celite® and rinsed with CH_2Cl_2. To the ice cold solution of filtrate, saturated $NaHCO_3$ solution was added slowly dropwise, until the pH paper indicated a neutral media. The mixture was extracted with CH_2Cl_2 (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (2.42 g, 98%).

Method B: A flame-dried round-bottom flask was charged with TMPH (4.6 mL, 27.2 mmol) under an argon atmosphere. Anhydrous THF (25.0 mL, 0.26 M) was added, and the flask was cooled to - 78 °C in a dry ice/acetone bath. 2.5 M *n*BuLi solution (10.4 mL, 25.9 mmol) was then added. After 15 minutes at -78 °C alcohol **31** (1.00 g, 6.48 mmol), dissolved in 7.0 mL of anhydrous THF (0.9M), was added dropwise to the base solution. The reaction mixture was allowed to warm to room temperature and stir for 2 more hours. After completion, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude (1R,4R,5R,6S)-6-Hydroxy-5-methylbicyclo[2.2.2]octan-2-one was purified by column chromatography on silica gel using 50% EtOAc in hexanes as an eluent. The rearranged ketone was obtained as a viscous oil (0.64 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (t, *J* = 3.7 Hz, 1H), 2.99 (bs, 1H), 2.38- 2.33 (m, 1H), 2.30-2.16 (m, 2H), 1.95-1.89 (m, 1H), 1.81-1.61 (m, 4H), 1.43-1.33 (m, 1H), 1.15 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 216.6, 51.5, 45.6, 41.5, 33.7, 20.1, 18.8, 18.2. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_9H_{13}O_2$, 154.0994; found 154.0993. R_f: 0.20 in 50% EtOAc/hexanes.

A round-bottom flask was charged with the ketone of the previous reaction (0.64 g, 4.15 mmol). Anhydrous CH_2Cl_2 (21 mL, 0.2M) was added, followed by the addition of imidazole (0.56 g, 8.30 mmol) and TBSCl (0.94 g, 6.22 mmol). The reaction mixture was stirred overnight at room temperature. CH_2Cl_2 was removed via rotary evaporation. To the residue 5% EtOAc in hexanes solution was added, the mixture was filtered through the short silica gel plug and rinsed with 5% EtOAc in hexanes solution. Solvent was removed via rotary evaporation to yield clean **35** as a colorless oil (1.02 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (t, *J* = 3.2 Hz, 1H), 2.31-2.14 (m, 3H), 1.96-1.91 (m, 1H), 1.80-1.56 (m, 4H), 1.40-1.30 (m, 1H), 1.11 (d, *J* = 7.3 Hz, 1H), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 214.8, 51.6, 45.6 (CH_2), 42.6, 33.7, 25.8, 20.1, 18.9 (CH_2), 18.5, 18.0 (CH_2), -4.6. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{15}H_{28}O_2Si$, 269.1937; found 269.1932. R_f: 0.34 in 10% EtOAc/hexanes.

*(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2,5-dimethylbicyclo-[2.2.2]octan-2-ol (**38a**).*

Anhydrous $CeCl_3$ was obtained by dehydrating $CeCl_3 \cdot 7H_2O$) (5.41 g, 14.5 mmol) under high vacuum at 165 °C for 2 hours.

After 2 hours the flask was allowed to cool to room temperature and then filled with inert gas. To the $CeCl_3$ anhydrous THF (100.0 mL) was added and the suspension was stirred for 2 hours at room temperature. 1.6M MeLi solution (9.1 mL, 14.5 mmol) was added to the above solution at -78 °C. After 30 minutes ketone **35** (1.95 g, 7.26 mmol) dissolved in anhydrous THF (21.0 mL) was added slowly. After 1 hour at -78 °C, the reaction mixture was quenched with saturated NH_4Cl solution and allowed to warm to room temperature. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil, which, when stored at low temperatures, solidified (2.00 g, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (s, 1H), 3.50-3.46 (m, 1H), 1.80-1.55 (m, 5H), 1.52-1.48 (m, 1H), 1.47-1.39 (m, 1H), 1.26-1.18 (m, 1H), 1.22 (s, 3H), 1.16-1.07 (m, 1H), 1.01 (d, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 80.8, 71.2, 47.0, 42.9, 41.6, 32.4, 30.0, 25.9, 20.9, 18.9, 17.9, -4.5. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{16}H_{32}O_2Si$, 285.2250; found 285.2243. R_f: 0.48 in 10% EtOAc/hexanes.

*6-[(tert-Butyldimethylsilyl)oxy]-2-(dichloromethyl)-5-methyl(3,3-D_2) bicyclo[2.2.2]octan-2-ol (**38b**).*

A flame-dried round-bottom flask was charged with anhydrous CH_2Cl_2 (35.0 µl, 0.55 mmol) and anhydrous THF (0.75 mL, 0.5M) under an argon atmosphere. The flask was cooled to -78 °C in a dry ice/acetone bath. 2.5M *n*BuLi solution (0.18 mL, 0.44 mmol) was then added. After 15 minutes at -78 °C alcohol **35** (100 mg, 0.37 mmol) dissolved in 1.0 mL of anhydrous THF was added dropwise to the above solution. After 1 hour at -78 °C, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (131.0 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (s, 1H), 5.44 (s, 1H), 3.47-3.42 (m, 1H), 2.08- 2.03 (m, 1H), 1.90-1.83 (m, 1H), 1.61-1.57 (m, 1H), 1.54-1.39 (m, 2H), 1.39-1.30 (m, 1H), 1.17-1.08 (m, 1H), 1.04 (d, *J* = 7.4 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 80.3, 80.0, 77.4 (CH_0), 76.2 (CH_0), 40.3, 39.3, 31.9, 25.8, 19.8 (CH_2), 18.2, 17.9 (CH_2), -4.5. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{16}H_{28}D_2O_2SiCl_2$, 355.1596; found 355.1592. R_f: 0.66 in 20% EtOAc/hexanes.

*(1R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2-iodo-5-methylbicyclo- [2.2.2]octane-2-carbaldehyde (**39**).*

A flame-dried round-bottom flask, covered by aluminum foil, was charged with 1.0M LiHMDS solution (0.59 mL, 0.59 mmol), anhydrous THF (1.60 mL, 0.11 M) and anhydrous Et_2O (1.00 mL, 0.19 M) under an argon atmosphere. The flask was cooled to -78 °C in a dry ice/acetone bath. CH_2I_2 (54.0 µl, 0.67 mmol) dissolved in anhydrous THF (0.40 mL) was then added. After 20 minutes ketone **35** (50.0 mg, 0.19 mmol), dissolved in 0.80 mL of anhydrous THF, was added dropwise to the above solution. After 20 minutes at -78 °C, saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 2.5% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (56.0 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 3.44 (t, *J* = 3.7 Hz, 1H), 2.97 (dt, J =15.6 HZ and 2.8 Hz, 1H), 2.18 (dd, *J* = 15.6 Hz and 3.2 Hz, 1H), 2.15-2.05 (m, 2H), 1.76-1.52 (m, 3H), 1.46-1.39 (m, 1H), 1.38-1.29 (m, 1H), 0.96 (d, *J* = 7.3 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 189.2, 77.6, 62.7, 45.4, 41.0, 38.4, 31.4, 25.9, 24.2, 18.9, 18.3, 18.0, -4.4, -4.4. R_f: 0.43 in 5% EtOAc/hexanes.

*(1R,2R,4R,5R,6S)-2-(Furan-2-yl)-5-methylbicyclo[2.2.2]octane-2,6-diol (**38c**).*

A flame-dried round-bottom flask was charged with furan (80 µl, 1.08 mmol) under an argon atmosphere. Anhydrous Et_2O (3.0 mL) was added, and the flask was cooled to 0 °C in an ice/water bath. 2.5M *n*BuLi solution (0.3 mL, 0.72 mmol) was then added. After 30 minutes at 0 °C ketone **35** (96 mg, 0.36 mmol), dissolved in 3.0 mL of anhydrous Et_2O, was added dropwise to the above solution. The reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a light yellow solid (50.0 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.35 (m, 1H), 6.31-6.27 (m, 2H), 5.50 (s, 1H), 3.55 (dd, *J* = 4.6 Hz and 2.3 Hz, 1H), 2.39 (dd, *J* = 14.3 Hz and 2.9 Hz, 1H), 2.14 (q, *J* = 2.9 Hz, 1H), 1.99 (dt, *J* = 14.3 Hz and 2.9 Hz, 1H), 1.93-1.86 (m, 1H), 1.64-1.60 (m, 1H), 1.46-1.38 (m, 1H), 1.27-1.13 (m, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). R_f: 0.51 in 20% EtOAc/hexanes.

*(1R,2R,4R,5R,6S)-5-Methyl-2-(prop-1-ynyl)bicyclo[2.2.2]octane-2,6-diol (**38d**).*

A flame-dried round-bottom flask was charged with ketone **35** (200.0 mg, 0.74 mmol) under an argon atmosphere. Anhydrous THF (3.7 mL) was added, and the flask was cooled to -78 °C in a dry ice/aceone bath. 0.5M propynyl magnesium bromide solution (4.5 mL, 2.23 mmol) was then added. After 30 minutes the reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 50% EtOAc in hexanes as an eluent. The product was obtained as a white solid (114.0 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (bs, 2H), 3.27 (dd, *J* = 5.7 Hz and 1.7 Hz, 1H), 2.09-2.02 (m, 1H), 2.00-1.96 (m, 1H), 1.94-1.88 (m, 1H), 1.82 (s, 3H), 1.78- 1.63 (m, 2H), 1.51-1.36 (m, 2H), 1.25-1.14 (m, 1H), 1.05 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (125.77 MHz, $CDCl_3$) δ 84.3, 79.0, 78.3, 70.7, 46.7, 43.3, 41.4, 31.7, 21.5, 18.3, 17.9, 3.7. R_f: 0.09 in 20% EtOAc/hexanes.

*(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-5-methyl-2-(prop-1- ynyl)bicyclo[2.2.2]octan-2-ol (**38e**).*

Anhydrous $CeCl_3$ was obtained by dehydrating $CeCl_3 \cdot 7\ H_2O$ (0.83 g, 2.23 mmol) under high vacuum at 165 °C for 2 hours. After 2 hours the flask was allowed to cool to room temperature and then filled with inert gas. To the $CeCl_3$ anhydrous THF (11.0 mL) was added and the suspension was stirred for 2 hours at room temperature. 0.5M propynyl magnesium bromide solution (4.5 mL, 2.23 mmol) was added to the above solution at 0 °C. After 30 minutes ketone **35** (0.30 g, 1.12 mmol) dissolved in anhydrous THF (8.0 mL) was added slowly. After 2.5 hours at 0 °C, the reaction mixture was quenched with saturated NH_4Cl

solution. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product **38e** was obtained as a white solid (0.18 g, 52%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 (s, 1H), 3.51-3.46 (m, 1H), 2.15 (dd, *J* = 14.3 Hz and 2.9 Hz, 1H), 1.92-1.81 (m, 2H), 1.83 (s, 3H), 1.76-1.69 (m, 1H), 1.53-1.49 (m, 1H), 1.47-1.39 (m, 1H), 1.35-1.21 (m, 2H), 1.02 (d, *J* = 7.4 Hz, 3H),0.88 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 84.5, 79.6, 77.9, 69.3, 48.1, 42.8, 41.1, 31.6, 25.9, 21.2, 18.7, 17.8, 17.7, 3.9, -4.5, -4.6. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{18}H_{32}O_2Si$, 309.2250; found 309.2239. R_f: 0.63 in 20% EtOAc/hexanes. Product **38d** was isolated in 12% yield (26.8 mg).

*2-{6-[(tert-Butyldimethylsilyl)oxy]-2-hydroxy-5-methyl(3,3-D_2) bicyclo[2.2.2]octan-2-yl}acetonitrile (**38f**).*

A flame-dried round-bottom flask was charged with 2.5M *n*BuLi solution (0.35 mL, 0.89 mmol) under an argon atmosphere. Anhydrous THF (4.0 mL) was added, and the flask was cooled to -78 °C in a dry ice/acetone bath. MeCN (0.19 mL, 3.70 mmol) was then added. After 20 minutes at -78 °C ketone **35** (200 mg, 0.74 mmol), dissolved in 3.0 mL of anhydrous THF, was added dropwise to the above solution. After 1 hour at -78 °C, saturated NH_4Cl solution was added and reaction mixture was allowed to warm to room temperature. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (195.5 mg, 85%). 21.5 mg of starting material **35** was recovered (11%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (s, 1H), 3.52-3.49 (m, 1H), 2.59 (d, *J* = 16.0 Hz, 1H), 2.43 (dd, *J* = 16.0 Hz and 1.2 Hz, 1H), 1.91-1.86 (m, 1H), 1.83- 1.75 (m, 1H), 1.58-1.54 (m, 1H), 1.54-1.44 (m, 2H), 1.42-1.33 (m, 1H), 1.15-1.07 (m, 1H), 1.04 (d, *J* = 7.4 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 117.9, 79.9, 71.4 (CH_0), 41.1, 40.2, 31.6, 31.3 (CH_2), 25.8, 20.5 (CH_2), 18.5, 17.9 (CH_0), 17.8 (CH_0), -4.5, -4.6. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{17}H_{29}D_2NO_2Si$, 312.2328; found 312.2329. R_f: 0.37in 20% EtOAc/hexanes.

*(1R,2S,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2-hydroxy-5-methyl- bicyclo[2.2.2]octane-2-carbonitrile (**38g**).*

A flame-dried round-bottom flask was charged with ketone **35** (0.24 g, 0.88 mmol) under an argon atmosphere. Anhydrous PhMe (5.0 mL) was added, and the flask was cooled to 0 °C in an ice/water bath. 1.0M Et_2AlCN solution (1.3 mL, 1.32 mmol) was then added. After 30 minutes the reaction mixture was diluted with EtOAc and saturated Rochelle's solution was added. After stirring at room temperature for 30 minutes, the layers were separated, aqueous layer was extracted with EtOAc (2x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (237 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.47 (t, *J* = 3.4 Hz, 1H), 2.35 (dt, *J* = 14.3 Hz and 2.3 Hz, 1H), 2.28 (s, 1H), 2.06-2.01 (m, 1H), 1.96-1.88 (m, 1H), 1.79 (dd, *J* = 14.3 Hz and 3.4 Hz, 1H), 1.68-1.61 (m, 1H), 1.60- 1.55 (m, 1H), 1.54-1.45 (m, 1H), 1.39-1.31 (m, 1H), 1.25-1.16 (m, 1H), 1.04 (d, *J* = 7.4 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 123.9, 76.3, 65.4, 43.6, 43.4, 41.5, 31.0, 26.0, 18.6, 18.3, 17.7, 17.7, -4.3, -4.6. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{16}H_{29}NO_2Si$, 296.2046; found 296.2046. R_f: 0.48 in 20% EtOAc/hexanes.

*(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2,5-dimethylbicyclo[2.2.2]octan-2- yl 2-diazo-3-oxobutanoate (**41**).*

A flame-dried round-bottom flask was charged with tertiary alcohol **38a** (85.0 mg, 0.30 mmol) and dioxinone **40** (0.16 mL, 1.20 mmol) under an argon atmosphere. Xylene (60 µl, 5.0M) was added, and the flask was placed in a preheated (100 °C) oil bath. After 30 minutes the reaction mixture was allowed to cool to room temperature. Afterwards, the crude reaction mixture was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (86 mg, 81%). ^{1}H NMR spectrum revealed that the initial product consists of a 1:0.2 mixture of keto/enol tautomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.26 (s, 1H, minor), 4.89 (s, 1H, minor), 3.37 (d, *J* = 14.9 Hz, 1H, major), 3.37-3.33 (m, 2H, minor), 3.23 (d, *J* = 14.9 Hz, 1H, major), 2.45-2.42 (m, 1H, minor), 2.42-2.38 (m, 1H, major), 2.25 (s, 3H, major), 2.06-1.96 (m, major/minor), 1.85 (s, 3H, minor), 1.78-1.69 (m, major/minor), 1.60 (s, 3H, minor), 1.60 (s, 3H, major), 0.53-1.36 (m, major/minor), 1.18-1.10 (m, major/minor), 1.00 (d, *J* = 6.9 Hz, 3H, major), 1.00-0.97 (d, 3H, minor), 0.88 (s, 9H, major), 0.85 (s, 9H, minor), 0.04 (s, 3H, major), 0.03 (s, 3H, major), 0.01 (s, 3H, minor), -0.01 (s, 3H, minor). R_f: 0.57 in 20% EtOAc/hexanes.

A flame-dried round-bottom flask was charged with the β-ketoester from above (86 mg, 0.23 mmol) under an argon atmosphere. MeCN (0.60 mL, 0.4M) was added and the flask was cooled to 0 °C in an ice/water bath. (0.10 mL, 0.69 mmol) followed by pABSA (62 mg, 0.25 mmol) were then added. After 10 minutes the reaction mixture was allowed to warm to room temperature and stir overnight. MeCN was removed via rotary evaporation. To the residue DI water was added, the product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (85 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (dd, *J* = 7.3 Hz and 1.8 Hz, 1H), 2.53-2.47 (m, 1H), 2.41 (s, 3H), 1.96-1.88 (m, 1H), 1.69 (s, 3H), 1.67-1.58 (m, 1H), 1.54-1.41 (m, 5H), 1.21-1.11 (m, 1H), 1.01 (d, *J* = 7.3 Hz, 3H), 0.83 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 191.1, 160.8, 84.8, 79.5, 44.8, 40.4, 40.0, 32.7, 28.2, 26.5, 26.2, 22.4, 19.0, 18.6, 18.1, -4.0, -4.8. R_f: 0.48 in 5% EtOAc/hexanes. FTIR (neat, cm^{-1}): 2927, 2136, 1713, 1644, 1362, 1140, 1082, 1004.

General procedure A for diazo-acetate synthesis:

A flame-dried round-bottom flask was charged with tertiary alcohol (1.0 eq) under an argon atmosphere. Anhydrous CH_2Cl_2 (0.17 M) was added, and the flask was cooled to 0 °C. Glyoxylic acid chloride *p*-toluenesulfonylhydrazone (2.0 eq) was added in one portion followed by *N,N*-dimethyl aniline (1.8 eq). The reaction mixture was stirred for 15 minutes before adding triethylamine (5.0 eq) and was stirred for 10 more minutes at 0 °C. The reaction was concentrated under reduced pressure. A concentrated citric acid solution and an EtOAc/hexanes mixture were added to the residue. The layers were separated, and the aqueous layer was extracted two times with the EtOAc/hexanes mixture. The combined organic phases were washed with concentrated citric acid solution and brine, dried over $MgSO_4$,

filtered through a short silica gel plug, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel.

*(1R,2R,4R,5R,6S)-6-(tert-Butyldimethylsilyloxy)-2,5-dimethyl-bicyclo[2.2.2]octan-2-yl 2-diazoacetate (**42**).*

42 was synthesized from tertiary alcohol **38a** (0.22 g, 0.77 mmol) following general procedure A. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (0.22 g, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (s, 1H), 3.34 (dd, *J* = 6.9 Hz and 1.7 Hz, 1H), 2.47-2.42 (m, 1H), 1.73-1.66 (m, 1H), 1.62 (s, 3H), 1.52-1.35 (m, 4H), 1.17-1.10 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 187.9, 135.6, 83.2, 79.5, 47.3, 40.8, 39.8, 32.6, 26.2, 26.1, 22.5, 21.8, 19.1, 18.5, 18.1, -4.0, -4.8. R_f: 0.54 in 20% EtOAc/hexanes. FTIR (neat, cm^{-1}): 2952, 2102, 1693, 1472, 1342, 1140, 1090.

*(1S,2R,4R,5R)-2,5-Dimethyl-6-oxobicyclo[2.2.2]octan-2-yl 2-diazo-acetate (**46**).*

A flame-dried round-bottom flask was charged with TBS-ether **38a** (0.47 g, 1.65 mmol) under an argon atmosphere. Anhydrous THF (2.20 mL) was added and the flask was cooled to 0 °C in an ice/water bath. Then TBAF (1.96 mL, 1.98 mmol) was added dropwise. The reaction mixture was warmed to room temperature. After 10 minutes, TLC analysis showed no starting material. Saturated $NaHCO_3$ solution was added, the mixture was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude alcohol product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. (1R,2R,4R,5R,6S)-2,5-Dimethylbicyclo[2.2.2]octane-2,6-diol was obtained as a white solid (0.27 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35- 3.26 (m, 2H), 2.68 (s, 1H), 1.77-1.66 (m, 3H), 1.65-1.59 (m, 1H), 1.56-1.41 (m, 3H), 1.40- 1.30 (m, 1H), 1.29 (s, 3H), 1.16-1.05 (m, 1H), 1.07 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 79.5, 73.5, 46.2, 43.0, 41.6, 32.5, 30.5, 21.4, 18.6, 18.1. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{10}H_{18}O_2$, 171.1385; found 171.1387. R_f: 0.14 in 40% EtOAc/hexanes.

A round-bottom flask was charged with the diol from the previous reaction (0.29 g, 1.73 mmol). Anhydrous CH_2Cl_2 (17 mL, 0.1M) was added, followed by the addition of Celite® (1.3 g) and PDC (1.3 g, 3.46 mmol). The reaction mixture was stirred overnight at room temperature. Heterogeneous solution was filtered through a short plug of Celite® and rinsed with CH_2Cl_2. After the removal of solvent via rotary evaporation, the crude product was purified by column chromatography on silica gel using 40% EtOAc in hexanes as an eluent. (1S,3R,4R,6R)-6-Hydroxy-3,6-dimethylbicyclo[2.2.2]octan-2-one was obtained as a white solid (0.24 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43-2.35 (m, 1H), 2.19-2.15 (m, 1H), 2.01-1.96 (m, 1H), 1.90-1.83 (m, 1H), 1.82 (s, 1H), 1.79- 1.64 (m, 4H), 1.43-1.33 (m, 1H), 1.37 (s, 3H), 1.11 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 218.4, 72.1, 55.9, 45.0, 44.0, 34.7, 28.9, 20.6, 19.3, 13.3. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{10}H_{16}O_2$, 169.1229; found 169.1229. R_f: 0.48 in 40% EtOAc/hexanes.

(1S,2R,4R,5R)-2,5-Dimethyl-6-oxobicyclo[2.2.2]octan-2-yl 2-diazo-acetate (**46**) was synthesized from the tertiary alcohol above (90 mg, 0.53 mmol) following general procedure A. 20% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 1% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (40 mg, 32% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (bs, 1H), 2.65-2.60 (m, 1H), 2.36-2.29 (m, 1H), 2.29-2.22 (m, 1H), 2.00-1.95 (m, 1H), 1.89-1.77 (m, 2H), 1.76-1.66 (m, 2H), 1.68 (s, 3H), 1.46-1.38 (m, 1H), 1.12 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 216.3, ~165, 83.8, 52.9, 47.1, 45.2, 42.3, 34.5, 24.2, 19.7, 19.1, 13.4. R_f: 0.17 in 20% EtOAc/hexanes. FTIR (neat, cm^{-1}): 2933, 2105, 1721, 1682, 1366, 1180.

*6-[(tert-Butyldimethylsilyl)oxy]-2,5-dimethyl(3,3-D_2) bicyclo[2.2.2] octan-2-yl 2-diazoacetate (**47**).*

To a stirred solution of 2.2 mL 1,4-dioxane (0.6M) and 3.8 mL D_2O (0.7M) under an inert atmosphere was added Na metal (73 mg, 3.17 mmol) in small pieces. After the Na had reacted, ketone **35** (0.71 g, 2.64 mmol) dissolved in 2.0 mL of 1,4-dioxane was added and the resulting solution was heated at 50 °C for 24 hours. The reaction mixture was cooled to room temperature, saturated NH_4Cl solution was added. The reaction mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (717 mg, 99%). 99% Substitution of hydrogen to deuterium was obtained after analyzing the ^{1}H NMR spectrum of clean 6-[(tert-Butyldimethylsilyl)oxy]-5-methyl(3,3-D_2)bicyclo[2.2.2]octan-2-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55-3.50 m, 1H), 2.31- 2.27 (m, 1H), 1.95-1.90 (m, 1H), 1.79-1.67 (m, 3H), 1.66-1.57 (m, 1H), 1.40-1.31 (m, 1H), 1.11 (d, *J* = 7.4 Hz, 3H), 0.83 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 215.0, 51.6, 42.5, 33.6, 33.5, 25.8, 20.1, 18.9, 18.5, 18.0, -4.6. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{15}H_{26}D_2O_2Si$, 271.2062; found 271.2065. R_f: 0.66 in 20% EtOAc/hexanes.

Anhydrous $CeCl_3$ was obtained by dehydrating $CeCl_3 \cdot 7H_2O$ (4.52 g, 12.1 mmol) under high vacuum at 165 °C for 2 hours. After 2 hours the flask was allowed to cool to room temperature and then filled with inert gas. To the $CeCl_3$ anhydrous THF (60.0 mL) was added and the suspension was stirred for 2 hours at room temperature. 1.6M MeLi solution (7.6 mL, 12.1 mmol) was added to the above solution at -78 °C. After 30 minutes the ketone synthesized above (1.64 g, 6.06 mmol) dissolved in anhydrous THF (16.0 mL) was added slowly. After 1 hour at -78 °C, the reaction mixture was quenched with saturated NH_4Cl solution and allowed to warm to room temperature. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. 6-[(tert-Butyldimethylsilyl)oxy]-2,5-dimethyl(3,3-D_2)bicyclo[2.2.2]octan- 2-ol was obtained as a colorless oil, which, when stored at low temperatures, solidified (1.71 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (s, 1H), 3.49- 3.45 (m, 1H), 1.76-1.69 (m, 5H), 1.62-1.54 (m, 2H), 1.50-1.46 (m, 1H), 1.46-1.38 (m, 1H), 1.26-1.18 (m, 1H), 1.21 (s, 3H), 1.15-1.07 (m, 1H), 1.01 (d, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 80.8, 71.0, ~48, 42.9, 41.6, 32.2, 30.0, 25.9, 20.9, 18.9, 17.9, 17.8, -4.5. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{16}H_{30}D_2O_2Si$, 287.2375; found 287.2375. R_f: 0.66 in 20% EtOAc/hexanes.

Diazo-acetate **47** was synthesized from the tertiary alcohol (1.00 g, 0.49 mmol) following general procedure A. 10% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica

gel using 5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (1.06 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (s, 1H), 3.34 (dd, *J* = 6.9 Hz and 1.4 Hz, 1H), 2.48-2.42 (m, 1H), 1.74- 1.64 (m, 1H), 1.62 (s, 3H), 1.53-1.36 (m, 4H), 1.18-1.08 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100.53 MHz, $CDCl_3$) δ ~165, 83.2, 79.5, 47.4, 40.7, 39.8, 32.5, 26.2, 26.1, 22.5, 19.1, 18.5, 18.1, -4.0, -4.8. R_f: 0.34 in 10% EtOAc/hexanes. FTIR (neat, cm^{-1}): 2949, 2929, 2103, 1711, 1366, 1112, 858.

*(1R,3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-5-methyl- bicyclo[2.2.2]octan-2-one (**48**).*

Step I: A flame-dried round-bottom flask was charged with TMPH (9.27 mL, 54.5 mmol) under an argon atmosphere. Anhydrous THF (33.0 mL) was added, and the flask was cooled to -78 °C in a dry ice/acetone bath. 2.5M *n*BuLi solution (20.8 g, 51.9 mmol) was then added. After 15 minutes at -78 °C alcohol **31** (2.00 g, 13.0 mmol), dissolved in 10.0 mL of anhydrous THF, was added dropwise to the base solution. The reaction mixture was allowed to warm to room temperature and stir for 1 hours. Afterwards, TMSCl (7.08 mL, 55.7 mmol) was added to the above solution at -78 C and warmed to room temperature. After being stirred for 1 hour at room temperature, cold saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with cold saturated $NaHCO_3$ solution, brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude (1R,3S,4S,5R,6S)-3-Fluoro-6-hydroxy-5-methylbicyclo[2.2.2]octan-2-one. Crude product was subjected to the next step without any further purification.

Step II: A flame-dried round-bottom flask was charged with Selectfluor (7.6 g, 21.4 mmol) under an argon atmosphere. Anhydrous DMF (25.0 mL) was added, and the flask was cooled to 0 °C in an ice/ H_2O bath. Crude product from the previous reaction was dissolved in 14 mL of anhydrous DMF and added to the above solution via cannula. After the addition reaction mixture was stirred 0 °C for 30 minutes. 1.0M TBAF solution (21.0 mL, 19.5 mmol) then was added. The reaction mixture was allowed to warm to room temperature, saturated NaCl solution was added. The mixture was extracted with Et_2O (5x), and the organic phases were combined and dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 40% EtOAc in hexanes as an eluent. The product was obtained as a white foam (1.99 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74-4.53 (m, 1H), 3.72-3.61 (m, 1H), 2.57-2.47 (m, 1H), 2.33-2.24 (m, 1H), 2.21 (s, 1H), 1.96-1.79 (m, 2H), 1.79-1.59 (m, 3H), 1.23 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ (210.4, 210.3), (92.3, 90.4), 75.2, 50.9, (39.7, 39.5), (39.1, 39.0), 21.2, 18.5, 12.4. R_f: 0.51 in 40% EtOAc/hexanes.

A round-bottom flask was charged with the alcohol from above (1.62 g, 9.41 mmol). Anhydrous CH_2Cl_2 (19.0 mL, 0.5M) was added, and the flask was cooled to 0 °C in an ice/ H_2O bath. NEt_3 (1.97 mL, 14.1 mmol), followed by TBSOTf (2.38 mL, 10.3 mmol) were added. The reaction mixture was allowed to warm to room temperature and stir for 20 minutes. Solvent was removed via rotary evaporation. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product **48** was obtained as a colorless oil (2.53 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76-4.61 (m, 1H), 3.54 (d, *J* = 4.0 Hz, 1H), 2.49-2.43 (m, 1H), 2.31-2.23 (m, 1H), 1.99-1.91 (m, 1H), 1.87-1.77 (m, 1H), 1.75-1.58 (m, 3H), 1.18 (d, *J* = 7.4 Hz, 3H), 0.82 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ (209.9, 209.8), (92.6, 91.1), 75.2, 50.9, (40.8, 40.7), (39.8, 39.7), 25.7, 21.1, (18.4, 17.9), 12.7, -4.7. ^{19}F NMR (470.62 MHz, $CDCl_3$) δ -189.19 (dt, *J* = 52.0 Hz and 6.5 Hz, 1F). HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{15}H_{27}O_2FSi$, 287.1843; found 287.1850. R_f: 0.60 in 20% EtOAc/hexanes.

(1R,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-5-methylbicyclo[2.2.2]octan-2-one (the diastereomer at the C-F bond of **48**) was also obtained as a white solid (89 mg, 21% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56 (dd, J = 48.7 Hz and 2.9 Hz, 1H), 3.52 (dd, J = 5.2 Hz and 2.3 Hz, 1H), 2.30 (quintet, J = 2.9 Hz, 1H), 2.14-2.08 (m, 1H), 2.08-2.01 (m, 1H), 1.95-1.85 (m, 1H), 1.75-1.63 (m, 2H), 1.59-1.51 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 208.2, 208.1, 92.3, 90.7, 78.9, 51.0, 39.3-39.2, 36.2, 25.7, 19.0, 18.0, 17.2, 16.4, -4.4. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{15}H_{27}O_2FSi$, 287.1843; found 287.1841. R_f: 0.29 in 10% EtOAc/hexanes.

*(1R,2S,3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-2,5- dimethylbicyclo[2.2.2]octan-2-yl 2-diazoacetate (**50**)*

Anhydrous $CeCl_3$ was obtained by dehydrating $CeCl_3 \cdot 7H_2O$ (1.14 g, 3.02 mmol) under high vacuum at 165 °C for 2 hours. After 2 hours the flask was allowed to cool to room temperature and then filled with inert gas. To the $CeCl_3$ anhydrous THF (20.0 mL) was added and the suspension was stirred for 2 hours at room temperature. 1.6M MeLi solution (1.9 mL, 3.02 mmol) was added to the above solution at -78 °C. After 30 minutes ketone **48** (0.43 g, 1.51 mmol) dissolved in anhydrous THF (5.0 mL) was added slowly. After 1 hour at -78 °C, the reaction mixture was quenched with saturated NH_4Cl solution and allowed to warm to room temperature. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified twice by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. (1R,2R,3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-2,5-dimethylbicyclo-[2.2.2]octan-2-ol was obtained as a colorless oil (182 mg, 38% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40-4.25 (m, 1H), 3.35 (dd, *J* = 5.2 Hz and 2.3 Hz, 1H), 2.57 (d, *J* = 10.9 Hz, 1H), 2.02-1.93 (m, 1H), 1.78-1.72 (m, 1H), 1.65-1.56 (m, 2H), 1.58-1.46 (m, 1H), 1.42 (d, *J* = 1.7 Hz, 3H), 1.37-1.28 (m, 1H), 1.19-1.10 (m, 1H), 1.05 (d, *J* = 8.0 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 97.0, 95.2, 77.9, 69.3, 69.2, 44.6, 39.2, 39.1, 37.5, 37.4, 30.9, 25.9, 25.7, 19.5, 18.0, 17.8, 11.9, 11.8, -4.2, -4.7. ^{19}F NMR (470.62 MHz, $CDCl_3$) δ -197.10 (d, *J* = 52.0 Hz, 1F). HRMS-ESI *m/z*: [M+Na], calculated for $C_{16}H_{31}FO_2Si$, 325.19700; found 325.19760. R_f: 0.46 in 10% EtOAc/hexanes.

The diazoester was synthesized from the tertiary alcohol from above (70 mg, 0.23 mmol) following general procedure A. 20% EtOAc/hexanes mixture was used to extract the product. The crude product was purified by column chromatography on silica gel using 1% EtOAc in CH_2Cl_2 as an eluent, then purified one more time using 2.5% EtOAc in hexanes as an eluent. The product was obtained as a yellow oil (86 g, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (s, 1H), 4.63-4.49 (m, 1H), 3.35 (dd, *J* = 6.3 Hz and 2.3 Hz, 1H), 2.10-2.04 (m, 1H), 1.84-1.73 (m, 2H), 1.80 (d, *J* = 1.7 Hz, 3H), 1.66-1.57 (m, 1H), 1.57-1.49 (m, 1H), 1.39- 1.29 (m, 1H), 1.27-1.15 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ ~165, 95.1, 93.2, 80.6, 80.5, 77.4, 46.8, 43.2, 38.1, 38.0, 37.5, 37.3, 26.4, 25.9, 25.8, 19.6, 18.0, 17.5, 12.3, 12.3, -4.3, -4.7. R_f: 0.28 in 10% EtOAc/hexanes. FTIR (neat, cm^{-1}): 2930, 2106, 1709, 1642, 1366, 1226.

*(1R,2S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-2,5-dimethylbicyclo-[2.2.2]octan-2-yl 2-diazoacetate (**49**).*

A flame-dried round-bottom flask was charged with ketone (1R,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-5-methylbicyclo[2.2.2]octan-2-one (0.30 g, 1.05 mmol) under an argon atmosphere. Anhydrous THF (12.0 mL) was added, and the flask was cooled to -78 °C in a dry ice/acetone bath. 1.6M MeLi solution (1.30 mL, 2.10 mmol) was then added. The reaction mixture was warmed to room temperature and stirred for 2 hours before saturated NH_4Cl solution was added. The mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered through short silica gel plug and concentrated to yield crude product. Crude (1R,2S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-2,5-dimethylbicyclo-[2.2.2]octan-2-ol was subjected to the next step without any further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (s, 1H), 4.22 (dd, *J* = 51.0 Hz and 3.4 Hz, 1H), 3.46 (t, *J* = 3.4 Hz, 1H), 2.18-2.11 (m, 1H), 1.85-1.79 (m, 1H), 1.66-1.62 (m, 1H), 1.61-1.48 (m, 2H), 1.26 (s, 3H), 1.28-1.13 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 96.0, 94.4, 79.8, 70.7, 70.6, 43.0, 37.7, 37.5, 33.4, 28.6, 25.8, 20.2, 18.0, 17.9, 15.9, 15.8, -4.5, -4.6. ^{19}F NMR (470.62 MHz, $CDCl_3$) δ -197.21 (d, *J* = 50.9 Hz, 1F). *m/z*: $[M+Na]^+$, calculated for $C_{16}H_{31}FO_2Si$, 325.1970; found 325.1976. R_f: 0.51 in 20% EtOAc/hexanes.

A flame-dried round-bottom flask was charged with the tertiary alcohol (1.05 mmol) from the previous reaction and dioxinone **40** (0.22 mL, 1.58 mmol) under an argon atmosphere. Xylene (0.21 mL, 5.0M) was added, and the flask was placed in a preheated (100 °C) oil bath. After 30 minutes the reaction mixture was allowed to cool to room temperature. Afterwards, the crude reaction mixture was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. 6-[(tert-Butyldimethylsilyl)oxy]-3-fluoro-2,5-dimethylbicyclo[2.2.2]octan-2-yl-3-oxobutanoate was obtained as a white solid (349 mg, 86%) that was directly used in the next reaction. R_f: 0.51 in 20% EtOAc/hexanes.

A flame-dried round-bottom flask was charged with the β-ketoester (1.00 g, 2.59 mmol) under an argon atmosphere. Anhydrous MeCN (26.0 mL, 0.1M) was added and the flask was cooled to 0 °C in an ice/water bath. NEt_3 (0.54 mL, 3.88 mmol) followed by pABSA (0.68 g, 2.85 mmol) were then added. After 10 minutes the reaction mixture was allowed to warm to room temperature and stir for 1 hour (monitored by TLC). After 1 hour LiOH (1.09 g, 25.9 mmol) and water (3.5 mL, 0.7M) were added to the above solution. The reaction mixture was heated at 55 °C for 24 hours (monitored by TLC). After completion, the reaction mixture was cooled to room temperature before adding saturated NH_4Cl solution. The product was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 5% EtOAc in hexanes as an eluent. The product **49** was obtained as a yellow oil (0.82 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (bs, 1H), 4.16 (dd, *J* = 49.0 Hz and 1.8 Hz, 1H), 3.35-3.29 (m, 1H), 2.56-2.50 (m, 1H), 2.17-2.08 (m, 1H), 1.72 (s, 3H), 1.70-1.53 (m, 2H), 1.43-1.34 (m, 2H), 1.30-1.20 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ ~165, 97.5, 95.6, 80.1, 80.0, 78.8, 47.7, 41.3, 38.7, 38.5, 33.3, 26.2, 25.7, 24.3, 21.6, 18.5, 17.3, 17.1, -4.8. R_f: 0.31 in 5% EtOAc/hexanes. FTIR (neat, cm^{-1}): 2955, 2928, 2104, 1695, 1369, 1241.

*(2R)-5-Acetyl-9-[(tert-butyldimethylsilyl)oxy]-2,8-dimethyl-3-oxatricyclo[5.2.2.0^{2,6}]undecan- 4-one (**43**).*

A flame dried round-bottom flask was charged with diazo-acetate **41** (100.0 mg, 0.25 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (9.0 mL, 0.03M) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(oct)_4$ (1.0 mg, 0.5 mol%) in one portion. After 20 minutes, TLC analysis showed no starting material. The reaction was concentrated under reduced pressure and the residue was purified by flash column chromatography using 5% EtOAc in hexanes as an eluent. The product was obtained as a white solid (28.9 mg, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.54 (s, 1H, major), 3.65 (d, *J* = 4.0 Hz, 1H, minor), 3.34 (dd, *J* = 5.2 Hz and 2.3 Hz, 1H, minor), 3.31 (dd, *J* = 5.2 Hz and 2.3 Hz, 1H, major), 2.70 (t, *J* = 3.4 Hz, 1H, minor), 2.60 (d, *J* = 2.3 Hz, 1H, major), 2.45 (s, 3H, minor), 1.92 (s, 3H, major), 1.84 (q, *J* = 2.9 Hz, 1H, minor), 1.83-1.80 (m, 1H, major), 1.71-1.51 (m, major/minor), 1.44-1.35 (m, major/minor), 1.39 (s, 3H, minor), 1.38 (s, 3H, major), 1.34-1.21 (m, major/minor), 1.02 (d, *J* = 6.9 Hz, 3H, minor), 0.96 (d, *J* = 6.9 Hz, 3H, major), 0.89 (s, 9H, minor), 0.88 (s, 9H, major), 0.04 (s, 3H, minor), 0.03 (s, 3H, major), 0.02 (s, 3H, minor), 0.00 (s, 3H, major). ^{13}C NMR (100.25 MHz, $CDCl_3$) δ 200.8, 175.6, 171.3, 168.4, 99.7, 85.9, 85.4, 78.3, 77.9, 59.9, 48.0, 44.6, 41.7, 41.6, 37.1, 36.8, 36.4, 36.0, 29.5, 27.7, 27.3, 25.8, 25.8, 21.9, 21.7, 19.0, 18.8, 18.7, 18.6, 18.0, -4.3, -4.3, -4.6, -4.7. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{20}H_{32}O_5Si$, 381.2097; found 381.2098. R_f: 0.68 in 20% EtOAc/hexanes.

*(2R)-9-[(tert-Butyldimethylsilyl)oxy]-2,8-dimethyl-3-oxatricyclo [5.2.2.02,6]undecan-4-one (**45**).*

A flame dried round-bottom flask was charged with diazo-acetate **42** (163.0 mg, 0.46 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (15.4 mL, 0.03M) was added. The reaction mixture was vigorously stirred at room temperature while adding $Rh_2(oct)_4$ (1.8 mg, 0.5 mol%) in one portion. After 20 minutes, TLC analysis showed no starting material. The reaction was concentrated under reduced pressure and the residue was purified by flash column chromatography using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (36.0 mg, 24% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.32 (dd, *J* = 5.7 Hz and 2.3 Hz, 1H), 2.79 (dd, *J* = 18.9 Hz and 10.9 Hz, 1H), 2.39 (dd, *J* = 18.9 Hz and 2.9 Hz, 1H), 2.10 (dt, *J* = 10.9 Hz and 2.9 Hz, 1H), 1.84-1.81 (m, 1H), 1.70-1.51 (m, 3H), 1.47-1.36 (m, 2H), 1.40 (s, 3H), 1.28-1.19 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 176.7, 86.4, 78.0, 43.6, 42.0, 37.3, 35.3, 32.9, 27.5, 25.8, 22.0, 19.3, 18.5, 18.0, -4.6. *m/z*: $[M+H]^+$, calculated for $C_{18}H_{32}O_3Si$, 325.2199; found 325.2206. R_f: 0.23 in 20% EtOAc/hexanes.

*(5R)-9-[(tert-Butyldimethylsilyl)oxy]-5,8-dimethyl-4-oxatricyclo [5.2.2.0^{1,5}]undecan-3-one (**44**).*

From the above reaction, product **44** was obtained as a white solid (12.5 mg, 8% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29-2.25 (m, 1H), 2.26 (dd, *J* = 109.4 Hz and 16.9 Hz, 2H), 2.04 (d, *J* = 13.3 Hz, 1H), 1.90 (dd, *J* = 13.3 Hz and 5.0 Hz, 1H), 1.83-1.69 (m, 2H), 1.68-1.50 (m, 4H), 1.40 (s, 3H), 1.34- 1.21 (m, 1H), 1.03 (d, *J* = 7.3 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 176.6, 84.7, 82.6, 44.4, 44.3, 39.3, 37.6, 32.1, 27.9, 25.9, 23.8, 19.4, 19.0, 17.8, -4.0, -4.8. R_f: 0.31 in 20% EtOAc/hexanes.

*(5R)-9-[(tert-Butyldimethylsilyl)oxy]-5,8-dimethyl(6,6-D$_2$)-4-oxatricyclo [5.2.2.0^{1,5}]undecan-3-one (**52**).*

A round-bottom flask charged with 4 Å molecular sieves (~3g/mmol) was flame-dried under high vacuum. The flask was allowed to cool to room temperature then it was purged with an argon atmosphere. $Rh_2(esp)_2$ (3.2 mg, 0.5 mol%) was added followed by anhydrous CH_2Cl_2 (36.0 mL, 0.02M). Diazo-acetate **47** (0.25 g, 0.72 mmol) dissolved in anhydrous CH_2Cl_2 (8.0 mL, 0.1M) was added dropwise slowly (20 mL/h) via syringe pump. After the addition, the TLC analysis showed no starting material. The reaction was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a white solid (94 mg, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.30-3.25 (m, 1H), 2.25 (dd, *J* = 109.4 Hz and 16.5 Hz, 2H), 1.82-1.69 (m, 2H), 1.67-1.47 (m, 3H), 1.40 (s, 3H), 1.34-1.22 (m, 1H), 1.03 (d, *J* = 7.3 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 176.6, 84.6, 82.6, 44.3, 44.2, 37.6, 31.9, 27.8, 25.9, 23.8, 19.4, 18.9, 17.8, -4.0. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{18}H_{30}D_2O_3Si$, 327.2325; found 327.2323. R_f: 0.28 in 20% EtOAc/hexanes.

*(2S,5S,6R)-9-[(tert-Butyldimethylsilyl)oxy]-2,8-dimethyl(5,6-D_2)-3- oxatricyclo[5.2.2.0^{2,6}]undecan-4-one (**53**).*

From the above reaction, product **53** was obtained as a white solid (94 mg, 39% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.31 (dd, *J* = 5.7 Hz and 2.3 Hz, 1H), 2.39-2.33 (m, 1H), 1.84-1.79 (m, 1H), 1.69-1.49 (m, 3H), 1.49-1.34 (m, 2H), 1.39 (s, 3H), 1.26-1.18 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 176.6, 86.3, 78.0, 41.9, 37.1, 35.3, 27.4, 25.8, 22.0, 19.2, 18.5, 18.0, -4.3. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{18}H_{30}D_2O_3Si$, 327.2325; found 327.2336. R_f: 0.23 in 20% EtOAc/hexanes.

From the above reaction, product 8-[(tert-Butyldimethylsilyl)oxy]-3,7-dimethyl(2,2-D_2)-4-oxatricyclo [5.4.0.0^{3,9}]undecan-5-one was also obtained as a white solid (19 mg, 8% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (s, 1H), 2.54 (dd, *J* = 32.5 Hz and 17.9 Hz, 2H), 1.76-1.72 (m, 1H), 1.68-1.52 (m, 3H), 1.46-1.30 (m, 2H), 1.35 (s, 3H), 0.99 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 173.6, 80.8, 78.1, 44.1, 43.6, 38.2, 36.5, 26.8, 25.8, 25.7, 24.6, 22.3, 21.1, 18.1, -4.4. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{18}H_{30}D_2O_3Si$, 327.2325; found 327.2325. R_f: 0.20 in 20% EtOAc/hexanes.

*(1R,2S,3S,4S,5R,6S)-6-(tert-Butyldimethylsilyloxy)-3-fluoro-5-methyl-3'H-spiro[bicyclo[2.2.2]octane-2,2'-furan]-5'(4'H)-one (**54**).*

A round- bottom flask charged with 4 Å molecular sieves (~3g/mmol) was flame-dried under high vacuum. The flask was allowed to cool to room temperature then it was purged with an argon atmosphere. $Rh_2(esp)_2$ (0.5 mg, 0.5 mol%) was added followed by anhydrous CH_2Cl_2 (7.0 mL, 0.02M). Diazo-acetate **50** (51.0 mg, 0.14 mmol) dissolved in anhydrous CH_2Cl_2 (1.4 mL, 0.1M) was added dropwise slowly (10 mL/h) via syringe pump. After the addition, the TLC analysis showed no starting material. The reaction was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. The product was obtained as a colorless oil (26 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59-4.40 (m, 1H), 3.40 (t, *J* = 3.2 Hz, 1H), 2.70-2.57 (m, 1H), 2.49-2.38 (m, 1H), 2.37-2.21 (m, 2H), 2.07-1.97 (m, 1H), 1.93-1.81 (m, 2H), 1.81-1.69 (m, 1H), 1.63-1.52 (m, 1H), 1.43-1.32 (m, 1H), 1.20-1.10 (m, 1H), 1.08 (d, *J* = 7.3 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 176.8, (95.8, 93.8), (83.9, 83.7), 76.8, 43.6, (40.9, 40.8), 37.9, (37.1, 37.0), 28.5, 26.0, 19.0, 18.3, 18.0, 11.6, -4.4, -4.6. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{18}H_{31}O_3FSi$, 343.2105; found 343.2106. R_f: 0.14 in 5% EtOAc/hexanes.

*(5S)-9-[(tert-Butyldimethylsilyl)oxy]-6-fluoro-5,8-dimethyl-4-oxatricyclo [5.2.2.01,5]undecan-3-one (**55**).*

A round-bottom flask charged with 4 Å molecular sieves (~3g/mmol) was flame-dried under high vacuum. The flask was allowed to cool to room temperature then it was purged with an argon atmosphere. $Rh_2(esp)_2$ (13.8 mg, 0.6 mol%) was added followed by anhydrous CH_2Cl_2 (160 mL, 0.017M). Diazo-acetate **49** (0.99 g, 2.67 mmol) dissolved in anhydrous CH_2Cl_2 (24 mL, 0.11M) was added dropwise slowly (45 mL/h) via syringe pump. After the addition, the TLC analysis showed no starting material. The reaction was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. The product was obtained as a white solid (0.64 g, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (dd, *J* = 52.1 Hz and 5.2 Hz, 1H), 3.26 (d, *J* = 1.7 Hz, 1H), 2.40 (d, *J* = 16.6 Hz, 1H), 2.19 (d, *J* = 16.6 Hz, 1H), 2.32-2.24 (m, 1H), 2.12-2.06 (m, 1H), 1.80-1.70 (m, 1H), 1.61-1.53 (m, 1H), 1.4-1.28 (m, 2H), 1.38 (d, *J* = 2.3 Hz, 3H), 1.06 (d, *J* = 7.4 Hz, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 175.6, (91.9, 90.3), (81.2, 81.0), 53.6, 44.4, 37.3, (37.1, 36.9), (33.8, 33.8), (26.5, 26.5), 25.8, 23.3, 18.5, 18.0, 17.0, -4.0, -4.7. ^{19}F NMR (470.62 MHz, $CDCl_3$) δ –197.97 (d, *J* = 52.0 Hz). HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{18}H_{31}O_3SiF$, 343.2105; found 343.2113. R_f: 0.14 in 20% EtOAc/hexanes.

(5R)-9-Hydroxy-5,8-dimethyl(6,6-$^2H_2$)-4-oxatricyclo[5.2.2.0^{1,5}]undecan-3-one.

A flame-dried round-bottom flask was charged with TBS-ether **52** (35.2 mg, 0.11 mmol) under an argon atmosphere. Anhydrous THF (1.10 mL, 0.1M) was added and the flask was cooled to 0 °C in an ice/water bath. Then TBAF (0.13 mL, 0.13 mmol) was added dropwise. The reaction mixture was warmed to room temperature. After 10 minutes, TLC analysis showed no starting material. Saturated $NaHCO_3$ solution was added, the mixture was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 30% to 40% EtOAc in hexanes as an eluent. The product was obtained as a white solid (22 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (d, *J* = 2.8 Hz, 1H), 2.60 (d, *J* = 16.9 Hz, 1H), 2.24-2.15 (m, 1H), 2.15 (d, *J* = 16.9 Hz, 1H), 1.78-1.66 (m, 2H), 1.60-1.54 (m, 1H), 1.44-1.33 (m, 1H), 1.27 (s, 3H), 1.15 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100.52 MHz, $CDCl_3$) δ 178.0, 90.3, 73.6, 45.4, 36.4, 35.3, 32.9, 28.2, 26.2, 20.8, 18.1. R_f: 0.23 in 50% EtOAc/hexanes.

*(2S,5R)-2-Acetyl-2-[(benzyloxy)methyl]-9-[(tert-butyldimethylsilyl)oxy]-5,8-dimethyl(6,6-2H2)-4-oxatricyclo[5.2.2.0^{1,5}]undecan-3-one (**63a**).*

A flame-dried round-bottom flask was charged with iPr_2NH (0.33 mL, 2.35 mmol) under an argon atmosphere. Anhydrous THF (3.6 mL) was added, and the flask was cooled to 0 °C. 2.5M *n*BuLi solution (0.90 mL, 2.24 mmol) was added, and the reaction mixture was stirred for 15 minutes at 0 °C. Lactone **52** (183.0 mg, 0.56 mmol) dissolved in 2.0 mL of anhydrous THF was added dropwise to the above solution at -78 °C and stirred for 30 minutes. Acetaldehyde (0.16 mL, 2.80 mmol) was then added and the reaction mixture was allowed to warm to room temperature. After completion, saturated NH_4Cl solution was added. The reaction mixture was extracted with Et_2O (3x), and the organic phases were combined and washed with brine, dried

over anhydrous $MgSO_4$, filtered and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 30% EtOAc in hexanes as an eluent. (2S,5R)-9-[(tert-Butyldimethylsilyl)oxy]-2-[(1S)-1-hydroxyethyl]-5,8-dimethyl(6,6-D_2)-4-oxatricyclo[5.2.2.01,5]undecan-3-one was obtained as a white solid (0.20 g, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17-4.09 (m, 1H), 3.90 (s, 1H), 3.20 (s, 1H), 2.18 (d, *J* = 9.7 Hz, 1H), 1.86-1.78 (m, 1H), 1.78-1.73 (m, 1H), 1.73-1.63 (m, 2H), 1.56-1.46 (m, 1H), 1.48 (s, 3H), 1.27 (d, *J* = 5.7 Hz, 3H), 1.28-1.20 (m, 1H), 1.04 (d, *J* = 7.4 Hz, 3H), 0.86 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 179.5, 85.5, 84.3, 66.6, 54.4, 46.1, 43.8, 31.2, 30.2, 25.8, 23.9, 22.0, 19.3, 18.9, 17.8, -3.9. R_f: 0.14 in 20% EtOAc/hexanes.

A flame-dried round-bottom flask was charged with the alcohol from the previous reaction (0.24 g, 0.65 mmol) under an argon atmosphere. Anhydrous CH_2Cl_2 (12.0 mL, 0.05M) was added and the flask was cooled to 0 °C in an ice/water bath, then Dess Martin Periodinane (0.33 g, 0.78 mmol) was added. The reaction mixture was warmed to room temperature. After 3 hours, TLC analysis showed no starting material. Saturated $NaHCO_3$/Na_2SO_3 (1:1) solution was added, the mixture was extracted with CH_2Cl_2 (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 10% EtOAc in hexanes as an eluent. (2Z,5R)-9-[(tert-Butyldimethylsilyl)oxy]-2-(1-hydroxyethylidene)-5,8-dimethyl(6,6-D_2)-4-oxatricyclo[5.2.2.0^{1,5}]undecan-3-one was obtained as a white solid (195 mg, 82%). A mixture of keto and enol tautomers (3.5:3.0 ratio) was observed in ^{1}H NMR spectrum after isolation. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (s), 4.25 (s), 3.36-3.16 (m), 2.49 (s), 2.32 (s), 2.08-1.98 (m), 1.92 (s), 1.84-1.43 (m), 1.41 (s), 4.39 (s), 1.37 (s), 1.06 (d, *J* = 7.3 Hz), 1.05 (d, *J* = 7.3 Hz), 1.04 (d, *J* = 7.3 Hz), 0.87 (s), 0.83 (s), 0.10 (s), 0.07 (s), 0.07 (s), 0.02 (s), -0.11 (s), -0.12 (s). R_f: 0.37 in 20% EtOAc/hexanes.

A flame-dried round- bottom flask was charged with the acetoacetate (30 mg, 0.08 mmol) under an argon atmosphere. Anhydrous THF (1.0 mL, 0.08M) was added and the flask was cooled to -10 °C and 1.0M LiHMDS solution (0.10 mL, 0.10 mmol) was added. After 1 hour BOMCl (17 µl, 0.12 mmol) was added. The reaction mixture was allowed to warm to room temperature and stir overnight. Saturated NH_4Cl solution was added, the mixture was extracted with Et_2O (3x). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product. The crude product was purified by column chromatography on silica gel using 20% EtOAc in hexanes as an eluent. The product **63a** was obtained as a white solid (34 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.23 (m, 5H), 5.20 (dd, *J* = 63.2 Hz and 7.3 Hz, 2H), 4.73 (dd, *J* = 33.4 Hz and 11.9 Hz, 2H), 3.39-3.36 (m, 1H), 2.07 (s, 3H), 1.84-1.71 (m, 3H), 1.68-1.48 (m, 3H), 1.31 (s, 3H), 1.05 (d, *J* = 7.3 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), -0.05 (s, 3H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 169.3, 159.5, 137.4, 128.6, 128.2, 128.0, 113.4, 92.3, 81.2, 81.0, 70.7, 48.6, 44.3, 31.5, 29.3, 26.0, 25.8, 24.7, 19.5, 19.1, 17.8, 16.4. HRMS-CI *m/z*: $[M+H]^+$, calculated for $C_{28}H_{40}D_2O_5Si$, 489.3005; found 489.3005. R_f: 0.20 in 20% EtOAc/hexanes.

*tert-Butyl({[(5S)-6-fluoro-5,8-dimethyl-4-oxatricyclo[5.2.2.0^{1,5}]undec-2-en-9-yl]oxy})dimethylsilane (**70**).*

A flame-dried round-bottom flask was charged with lactone **55** (30.0 mg, 0.09 mmol), $PhN(Tf)_2$ (37.0 mg, 0.11 mmol) under an argon atmosphere. Anhydrous THF (0.9 mL, 0.1M) was added and the flask was cooled to -78 °C in a dry ice/acetone bath. DMPU (11.0 µl, 0.09 mmol) followed by 1.0M KHMDS (0.11 mL, 0.12 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 1 hours. Afterwards, solvent was removed via rotary evaporation. To the crude product Et_2O was added and the mixture was filtered through short plug of Celite®. After the removal of solvent via rotary evaporation a light yellow oil was obtained. The crude (5S)-9-[(tert-Butyldimethylsilyl)oxy]-6-fluoro-5,8-dimethyl-4-oxatricyclo[5.2.2.0^{1,5}] undec-2-en-3-yl trifluoromethanesulfonate was used directly in the next step without any further purifications. R_f: 0.43 in 10% EtOAc/hexanes.

A flame-dried round-bottom flask was charged with the crude vinyl triflate (30.0 mg, 0.09 mmol), deoxygenated DMF (1.80 mL, 0.05M), NEt_3 (0.14 mL, 1.08 mmol), PPh_3 (18.4 mg, 0.08 mmol), $Pd(OAc)_2$ (8.0 mg, 0.04 mmol), and 98% formic acid (26.0 µl, 0.72 mmol) under an argon atmosphere. The reaction mixture was heated at 55 °C for 10 minutes. The mixture turned black during the first few minutes. When cooled to room temperature, the product was extracted with hexanes (3x). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered through the pad of Celite®, and concentrated to yield the crude product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, *J* = 2.8 Hz, 1H), 4.72 (dd, *J* = 52.7 Hz and 5.5 Hz, 1H), 4.58 (d, *J* = 2.8 Hz, 1H), 2.92 (s, 1H), 2.31- 2.21 (m, 1H), 2.07-1.99 (m, 1H), 1.75-1.59 (m, 2H), 1.50-1.38 (m, 1H), 1.33 (s, 3H), 1.27- 1.14 (m, 1H), 1.04 (s, 3H), 0.86 (s, 9H), 0.02 (s, 3H), -0.05 (s, 3H). R_f: 0.48 in 10% EtOAc/hexanes.

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