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$Pb(OAc)_4$ mediated transannular oxidative ring cleavage

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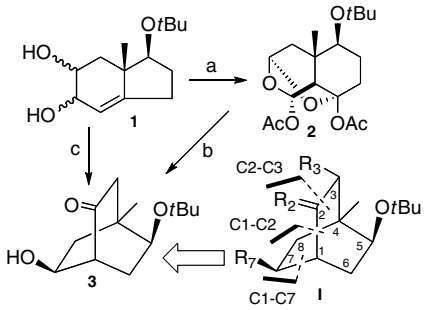
Abstract—$Pb(OAc)_4$ oxidation of homoallylic alcohols at room temperature leads to the formation of a variety of fragmentation products, whose formation requires spatial proximity of the alcohol and the olefin moieties.

1. Introduction

The potential interest of $Pb(OAc)_4$ in organic chemistry lies in its ability to bring about various reactions under mild conditions and its low cost.[1] Apart from the widely used oxidative cleavage (C–C bond cleavage),[2] decarboxylations,[3] acetoxylation,[4] and formation of cyclic ethers (C–O bond formation),[5] $Pb(OAc)_4$ is also used in C–C bond formation,[6] aziridination (C–N bond formation),[7] and various other transformations.[8] We have previously reported that $Pb(OAc)_4$ in a variety of solvents initiated a domino reaction[9] influenced by the stoichiometry,[10] the solvent,[11] or the substitution pattern.[12] At the outset, interest in this work arose out of a need to perform a practical synthesis of a conveniently functionalized taxoid C-ring precursor.[13] Thus, the unsaturated bicyclic vic. diols **1** were converted, via a domino sequence, into ring-expanded cycloalkane **2**, which was used as a C-ring precursor in taxoid total synthesis.[14] On the other hand, the bicyclic aldol framework **3**, which could also be used as more elaborate taxoid C-ring precursor was prepared from **2** or directly from **1**, in one pot, using a consecutive domino reaction (Scheme 1).[15]

In the course of these studies, we found that starting from the key intermediate **3** and using the appropriate sequencing of the steps, the reaction conditions can be tailored to fit a particular type of transformation. The probe used is a bicyclo[2.2.2]octane framework of general type **I**, having a variable substitution pattern at the positions C2 (R2), C3 (R3), and C7 (R7), accessed from **3** using published procedures.[16] Of special interest for our ongoing synthetic endeavors are the C1–C7 and C1–C2 cleavage products with the highest possible regioselectivity.



Scheme 1. Reagents and conditions: (a) 2.4 equiv $Pb(OAc)_4$, PhMe, 25 °C; (b) K_2CO_3, MeOH, H_2O, 25 °C; (c) 2.4 equiv $Pb(OAc)_4$, PhMe then K_2CO_3, MeOH, H_2O, 25 °C, one pot.

It has been shown long ago, that introduction of remote double bonds into alcohols oxidized with $Pb(OAc)_4$ gives the opportunity for neighboring group participation,[17] and a radical mechanism was claimed, based on the early explorations of Rao et al., reporting on the lead tetraacetate mediated fragmentation of pulegol (possessing a homoallylic olefin segment) upon heating in benzene.[18] In their work dealing with new coupling processes upon treatment of ω-functionalized carboxylic acids with various lead tetracarboxylates, Moloney et al. proposed a mechanistic rationale based on the formation of a π-allyl type $Pb^{(IV)}$ species **II** (Fig. 1) as an intermediate.[6c] More recently, Preite et al.[19] reported the reaction of homoallylic alcohols

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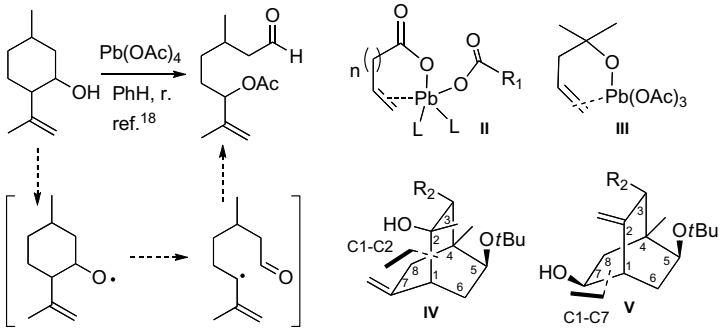
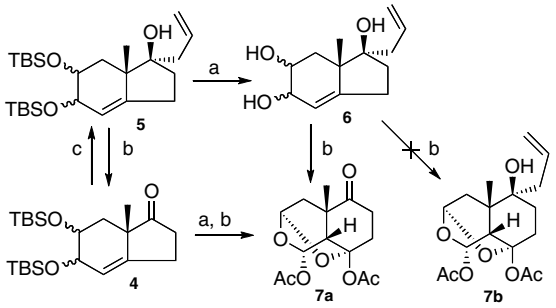


Figure 1. Proposed mechanistic rationale for the interaction of an olefin (p base) with $Pb(OAc)_4$ (a Lewis acid).

with $Pb(OAc)_4$ in refluxing benzene, ending with atom loss; these results were suggestive of the involvement of an organolead intermediate **III** similar to the one proposed by Moloney et al.[20]

A hint as to the potential use of this type of rearrangement arose from previous work in our laboratory upon attempted domino transformation of substrate **6** (Scheme 2). Prepared from hydrindenone **4** in two steps (AllylMgBr, THF, −78 °C, 1 h, 88% then TBAF, 60 °C, 1 h, 80%), the unsaturated diol **6** was subjected to our standard domino conditions [2.4 equiv $Pb(OAc)_4$, PhMe, 25 °C, 15 h] aimed at the corresponding ring-expanded domino product **7b**. Instead, the loss of the allylic fragment was observed with concomitant oxidation of the hydroxyl moiety. Although free-hydroxyl bearing carbinols exhibited good reactivity in reactions with $Pb(OAc)_4$, domino substrate **6** gave rearranged ketone **7a** in 71% isolated yield. The latter could also be accessed from **4** via a fluoride induced deprotection and subsequent treatment with $Pb(OAc)_4$ in toluene at room temperature. The same phenomenon was also detected upon treatment of the bis-TBS-protected unsaturated diol **5**, which, unable to undergo an oxidative cleavage induced domino transformation, under the standard conditions (2 equiv of the oxidant in AcOH or PhMe or else, at 25 °C), afforded **4**.

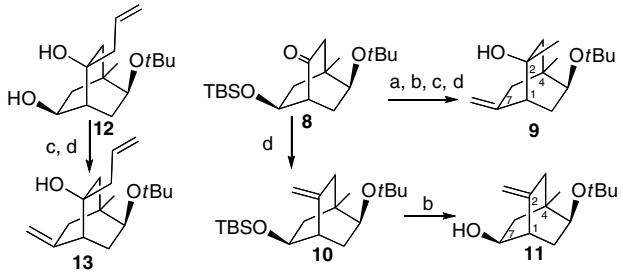


Scheme 2. Reagents and conditions: (a) TBAF, 60 °C, 1 h; (b) 2.4 equiv $Pb(OAc)_4$, PhMe, 25 °C, 15 h; (c) AllylMgBr, THF, −78 °C, 1 h.

The observed fragmentation pathway for the conversion of homoallylic alcohols **5** to **4** and **6** to **7a** is precedented[18] and similar to the one described by Preite et al.,[19] who reported the reaction of homoallylic alcohols with $Pb(OAc)_4$ in refluxing benzene, which was accompanied with atom loss. These preliminary results encouraged us to investigate various substrates and reaction conditions, in an attempt to study the scope and selectivity of the process. Since elaborated six-membered rings are present in a large variety of biologically important natural products, establishing the relative configuration of a quaternary carbon still remains a major synthetic challenge. To that end, a synthetic route had to be examined for suitable intermediates that might allow the desired inversion or retention of the relative configuration at quaternary centers, with the unsaturated diol **1** (Scheme 1) taken as reference. The purpose of this work is to put forward routes, allowing for a substrate controlled transannular ring opening and hence a modular construction of functionalized cyclohexanes, starting from the variously substituted bridged-bicyclic frameworks of type **IV** and **V** as portrayed in Figure 1. We now report the fast, room temperature reaction of $Pb(OAc)_4$ with bicyclic homoallylic alcohols leading to transannular ring opening.

2. Results and discussion

Methods for the synthesis of **8**, **12** (Scheme 3), **14** (Scheme 4), **34** and **36** (Scheme 8) are described in previous papers.[15,16]



Scheme 3. Reagents and conditions: (a) MeLi, THF, −78 °C; (b) TBAF, 60 °C, 1 h; (c) DMP, py, CH_2Cl_2, 25 °C, 2.5 h; (d) $MeP^+Ph_3Br^-$, *t*-BuOK, THF, 25 °C, 6 h.

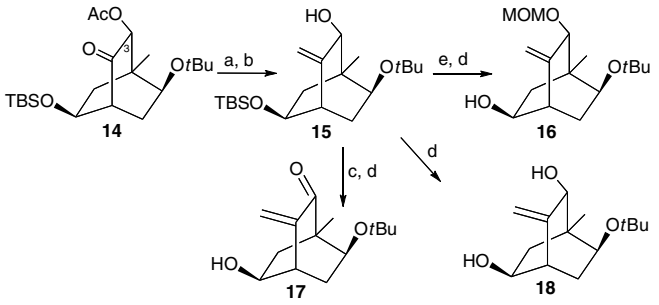
2.1. Elaboration of the substrates

The necessary test reactants, homoallylic alcohols **9** and **11**, were prepared uneventfully, in their enantiomerically pure form, from the known key intermediate **8**, the two-directional transformation of which was accomplished by func-

tional group interconversion. Thus, by using known procedures and by partially reversing the order of the reactions, both target products can be synthesized efficiently (Scheme 3). Wittig olefination ($MeP^{+}Ph_3Br^{-}$, *t*-BuOK, THF, 25 °C, 6 h, 90%) and subsequent fluoride deprotection (TBAF, 60 °C, 1 h, 90%) cleanly afforded **11**. The second target homoallylic alcohol **9** was obtained via a four-step sequence starting with methyl carbinol formation (MeLi, THF, −78 °C) followed by desilylation as above, subsequent Dess–Martin oxidation (DMP, py, CH_2Cl_2, 25 °C, 2.5 h, 60% three steps) and finally a Wittig olefination as above (75%).

The known compound **12**[16] was converted into the bis-homoallylic alcohol substrate **13** by a Dess–Martin oxidation (DMP, py, CH_2Cl_2, 25 °C, 2.5 h, 82%) and a subsequent Wittig olefination ($MeP^{+}Ph_3Br^{-}$, *t*-BuOK, THF, 25 °C, 6 h, 75%). With a satisfactory domino approach to the synthesis of both homo-allylic carbinol types **9** and **11** in hand, attention was directed to the C3 oxygenated substrates, to examine the effect of substitution at C3. The substrates were prepared as shown in Scheme 4. The known C3-acetoxy derivative **14**[16] served as a common intermediate for the synthesis of substrates **15**–**18**. Starting from **14**, the target allylic alcohol derivative **15** was prepared straightforwardly by a Wittig olefination ($MeP^{+}Ph_3Br^{-}$, *t*-BuOK, THF, 25 °C, 6 h, 86%) followed by a mild base treatment (K_2CO_3, MeOH–H_2O (10:1), 25 °C, 72 h, 95%).[21] Upon Dess–Martin oxidation of **15** (DMP, py, CH_2Cl_2, 25 °C, 1.5 h, 79%) and subsequent desilylation (TBAF, DMF, 2 h at 60 °C, 85%), the desired C3-oxo homoallylic alcohol **17** was obtained in good overall yield.

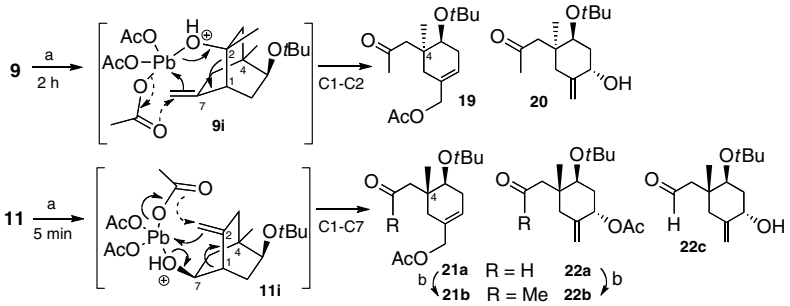
The required mono-protected allylic–homoallylic carbinol **16** was prepared by a two-step route starting with **15**, via a MOM-protection (MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 25 °C, 3 h, 88%) and subsequent desilylation (TBAF, 60 °C, 1 h, 80%) (Scheme 4). The target free allylic–homoallylic alcohol **18** was prepared from **15** by fluoride deprotection under the same conditions than for **17**, in 95% isolated yield.



Scheme 4. Reagents and conditions: (a) $MeP^{+}Ph_3Br^{-}$, *t*-BuOK, THF, 25 °C, 6 h; (b) K_2CO_3, MeOH–H_2O (10:1), 25 °C, 72 h; (c) DMP, py, CH_2Cl_2, 25 °C, 1.5 h; (d) TBAF, 60 °C, 1 h; (e) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 25 °C, 3 h.

2.2. Selective C1–C7/C1–C2 cleavage

It was anticipated that the TBS-protected domino product, bicyclic aldol **8**, could be further elaborated to either **9** or **11** (Scheme 3) and hence through transannular ring opening maneuvers, into **19/20** and **21/22**, respectively (Scheme 5). C1–C2 ring opening on **9** would afford reversal at C4 quaternary center (compared to **1**) while applying the same conditions to **11** would ensure retention at C4 via a C1–C7 ring opening, thus enabling a straightforward preparation of taxoid C-ring segments. The bicyclic rings in **9** and **11** hold the hydroxyl groups at C2 and C7, respectively, and the newly formed olefin in a favorable orientation for interaction. The process was initiated by the exposure of homoallylic alcohol **11** to $Pb(OAc)_4$ successively in acetone, toluene, acetic acid, dichloromethane or acetonitrile at 25 °C resulting, in all cases, in quantitative conversion of the bicyclic framework into the ring-opened **21/22**. After screening several temperatures in one of the above cited solvents, as well as mixed solvent systems such as acetone–AcOH, 1:1, we found that all these solvents, at room temperature, afforded similar product distribution and in comparable isolated yields, although in slightly different ratios. Selected typical reaction conditions involve the use of 2 M equiv of $Pb(OAc)_4$ in AcOH at room temperature and stirring under an inert atmosphere, until TLC control indicated consumption of the starting material (from 5 min to 6 h, depending on the substrate investigated). Transannular oxidative ring cleavage on homoallylic alcohol **11** under these conditions afforded, after only 5 min, **21a** (41%) along with **22a** (20%) and its free-hydroxyl derivative **22c** (18%). Performing the reaction in acetonitrile at 25 °C with 2 equiv of $Pb(OAc)_4$ led to the formation of **21a**, **22a** and **22c** in 78% combined isolated yield, after nearly an hour of stirring. This reaction was performed at a variety



Scheme 5. Reagents and conditions: (a) $Pb(OAc)_4$, AcOH, 25 °C; (b) (i) Me_3Al (2 M in hexane), CH_2Cl_2, 0 °C, 20 min, (ii) DMP, py, CH_2Cl_2, 25 °C, 30 min.

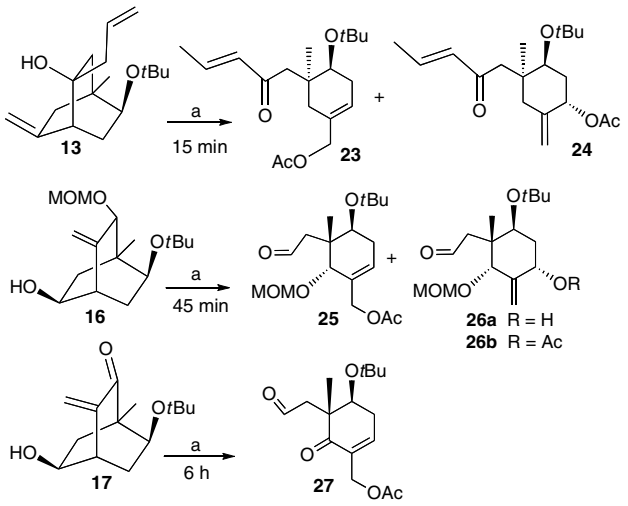
of temperatures from 0 °C to 60 °C with negligible differences in the product ratio, while large amounts of starting material were recovered at 0 °C and extensive degradation at 60 °C.

The initially obtained aldehydes **21a** and **22a** were treated with Me_3Al (2 M in hexane, CH_2Cl_2, 0 °C, 20 min, 78% and 74%, respectively) and subsequently with Dess–Martin periodinane (DMP, py, CH_2Cl_2, 25 °C, 30 min) to afford **21b** (80%) and **22b** (79%). As with **11**, different reaction conditions were used to optimize the yields of individual products from **9**. Treatment of the former with 2 equiv of $Pb(OAc)_4$ for 45 min afforded 45% of **19** and 25% of **20**, along with recovered starting material **9** (10%). A prolonged reaction time (2 h at room temperature) gave a two-component mixture **19** (53%) and **20** (40%), which was stable and easily separable. Presumably, the transition state required for production of the transannularly cleaved products **21**, **22** can be attained with much less steric strain than the one for **19** and **20**.

A speculative mechanism, inspired by Moloney's π-allyl type Pb(IV) species **II** (Fig. 1), already adapted to the homoallylic carbinol **III**, involves an initial ligand exchange followed by an electrophilic plumbation (the olefin acting as a π-base), and a subsequent skeletal rearrangement accompanying the C–C bond cleavage as illustrated in Scheme 5. The overall stereochemical outcome was such that it could be accommodated via homoallylic alcohol containing substrates, in which the olefin and the hydroxyl group are disposed in a *cis* fashion, affording an intermediate generalized as **9i** or **11i**. The results support that the reaction involves the formation of a π-allyl type $Pb^{(IV)}$ species **III** (Fig. 1) followed by ring opening and acyl anion addition leading to **19** and **21a**. This transformation, in addition to creating a reversal at quaternary center (**19** vs **21b** and **20** vs **22b**) provides a useful functional handle for further manipulation.

To evaluate the scope of the process we set out to apply the method to some more complex bicyclic frameworks, including bis-homoallylic alcohol **13**, the mono-protected alcohol **16**, and enone **17**. We pursued this study at room temperature in AcOH using 2 equiv of $Pb(OAc)_4$, and found that the reaction was complete (all starting material consumed) in 15 min for **13**, 45 min for **16**, while it required 6 h for **17** (Scheme 5). The regiochemical issue, when two homoallylic alcohols are in competition, such as **13**, was resolved unambiguously upon subjection of the latter to the standard conditions. The starting material **13** was consumed after only 15 min, while the initially formed allylketones were converted into the corresponding crotylketones **23** and **24**, following an in situ olefin migration (by stirring for an additional 1 h before work up or even by standing in the NMR tube in the presence of $CDCl_3$). Under these conditions reproducibly good yields of **23** (42%) and **24** (25%) were readily obtained. Evidence that olefinic products **23** and **24** have the *E*-geometry came from the coupling constants and spatial proximity measurements. NOE difference spectra showed strong enhancements between the vinylic methyl group and the relevant vinylic proton in both cases.

The homoallylic alcohol **16** when subjected to the fragmentation conditions (AcOH, 25 °C, 45 min) afforded 57% isolated yield of pure **25** along with 36% of an inseparable mixture of **26a** and its acetylated derivative **26b**, which were not characterized as pure. Inserting a carbonyl into the bicyclic ring system α-to the olefin at the C3 position, caused a large rate retarding effect and modified the reaction outcome affording a single compound. Thus, under the typical procedure ($Pb(OAc)_4$, AcOH, 25 °C, 6 h), **27** was produced in 66% isolated yield, to the exclusion of its corresponding exocyclic olefin, along with recovered **17** (13%, Scheme 6). Steric energy for **27** was calculated (MM3) to be 29.8 kcal/mol while that for its corresponding exocyclic olefin containing isomer was considerably higher (35.5 kcal/mol). Satisfactory yields were achieved in Schemes 5 and 6, with 66–75% combined yields for the transannular cleavage. The results obtained using **13**, **16**, and **17** as substrates were very similar to those obtained with **9** and **11** again suggesting a reaction pathway as depicted in Scheme 5.



Scheme 6. Reagents and conditions: (a) $Pb(OAc)_4$, AcOH, 25 °C (15 min to 6 h).

It was reasoned that if **25/26** resulted from **16** by treatment with $Pb(OAc)_4$ (Scheme 6), then **32/33** should be accessible by the reaction of $Pb(OAc)_4$ with the allylic–homoallylic template **18**. Treatment of the latter with 2 equiv of $Pb(OAc)_4$ for 45 min at room temperature in AcOH, gave four rearrangement products, **28** (13%), **29** (14%), **30** (60%), and **31** (13%), which were stable and isolable, although **29**, **30**, and **31** were characterized as anomeric mixtures. The structure of **28** was assigned by extensive spectroscopic investigations (HMBC, NOESY) and further supported by X-ray crystallographic analysis (Fig. 2). Apparently the cyclic acetal **28**, was formed spontaneously from its parent dihydroxy-aldehyde upon subjection of **18** to the reaction conditions. In assigning the structure for this product only one possible orientation of the hydroxyl groups (both α) at C3, C5, could be conceived (taxoid numbering).

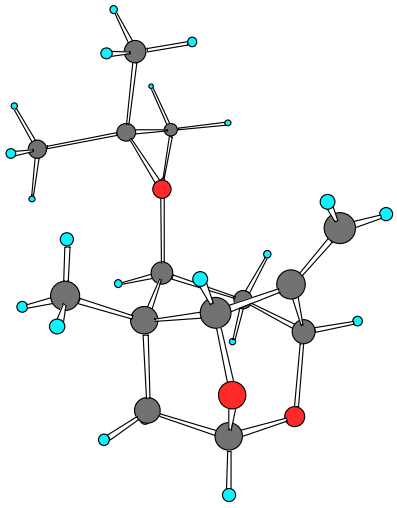
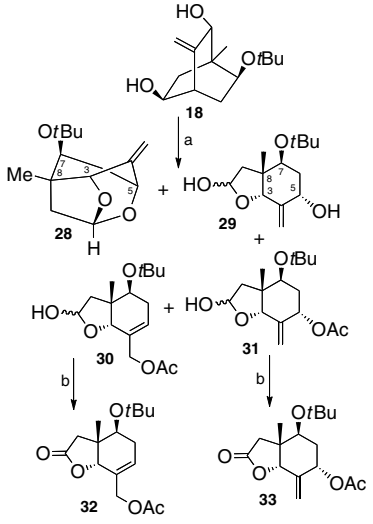


Figure 2. X-ray structure of **28** (Chem3D output).

In order to simplify the isolation of the products, the number of compounds can be produced by treatment of the anomeric mixtures **30** and **31** with PCC. Thus, upon oxidation (PCC, CH_2Cl_2, 25 °C, 1 h) lactol **30** furnished **32** (71%) and **31** afforded **33** (66%), which were fully characterized.[22] As a result we have a precursor for the taxoid C-ring moiety, compound **33**, which contains three out of four stereogenic centers (C5, C7, and C8) with the correct relative and absolute stereochemistry. It, therefore, becomes unnecessary to block the secondary hydroxyl function at C3 temporarily, unless its further use in intramolecular lactone formation (Scheme 7) is undesired. Moreover, it is expected that the allyl acetate **32** could be transformed in a separate step to the exocyclic olefin containing isomer **33**, or to even more elaborate C-ring precursors using osmylation or Sharpless epoxidation.



Scheme 7. Reagents and conditions: (a) $Pb(OAc)_4$, AcOH, 25 °C, 45 min; (b) PCC, CH_2Cl_2, 25 °C, 1 h.

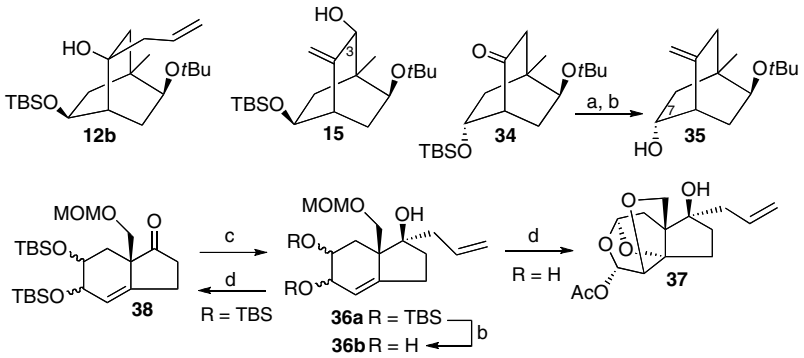
Finally, in order to obtain supporting evidence for the proposed mechanism, we examined substrates **12b**, **15**, **35**, **36a**, and **36b** (Scheme 8). Homoallylic alcohol **12b**, when subjected to transannular cleavage conditions, gave after 1 h at room temperature in acetic acid, starting material **12b** along with the bicyclic ketone **8** in a 4:1 ratio, while extended stirring (15 h) afforded **8** quantitatively. The allylically positioned hydroxyl group (C3) on **15** remains a spectator insofar as the transannular oxidative ring cleavage is concerned, since allylic alcohol **15**, subjected to the standard conditions, [2 equiv of $Pb(OAc)_4$, in AcOH, at 25 °C, for more than 1 h] remained intact. Homoallylic alcohol **35**, prepared straightforwardly from the known **34**[15] via a two-step sequence (Wittig olefination followed by a fluoride deprotection, 78% combined yield) and subjected to transannular oxidative ring opening conditions (2 equiv, 25 °C, 1 h) was recovered intact. Thus, while the homoallylic alcohol **11** upon treatment with the oxidant (2 equiv, 5 min, 25 °C) led to the C1–C7 bond cleavage affording cyclohexane derivatives **21** and **22** (Scheme 5), the homoallylic alcohol **35** with an inverted C7 hydroxyl configuration remained unchanged, even under prolonged reaction time (Scheme 8). The fact that the α-hydroxyl containing bicyclic framework **35** was unreactive upon subjection to the reaction conditions suggests that alcohol stereochemistry is a critical factor. An example of a stereoselective cleavage was described by Preite et al. who also found that the corresponding *anti*-isomer exhibited virtually no reactivity.[19]

Upon treatment with $Pb(OAc)_4$ (2 equiv, 25 °C, 1 h) the homoallylic alcohol **36a** gave back the hydrindenone **38**, from which it originated, in 81% isolated yield. Interestingly, when treated in toluene with 2.4 equiv of $Pb(OAc)_4$ at room temperature for 12 h, its free-diol derivative **36b**, led to the domino product **37**[12] in 72% isolated yield, without re-forming the carbonyl. On the other hand **37**, itself stayed inert under the standard conditions (2 equiv $Pb(OAc)_4$, AcOH, 1 h), and even after prolonged reaction times.

In summary we have described a simple method for the ring cleavage of bicyclo[2.2.2]homoallylic alcohols toward endocyclic cyclohexenes and their in situ allylic rearrangement to partially form exocyclic cyclohexanes. Complete dependence on topology (**15**) and stereochemistry (**35**) of the hydroxy group versus the olefinic moiety was observed. The apparent region- and stereocontrol in product distribution, is supportive of the mechanistic reasoning advanced in Scheme 5. The results obtained using type **9** and **11** as substrates were very similar to those obtained with all additional structures investigated in this paper suggesting a reaction pathway as depicted in Scheme 5.

3. Conclusion

The bridged-bicyclic aldol **3**, which is available in quantity from fused-bicyclic diol **1**, can be readily elaborated to the variously substituted cyclohexanes (Schemes 5–7), by $Pb(OAc)_4$ mediated transannular cleavage of the related homoallylic alcohols at room temperature. It was found that the overall result can be strongly influenced by subtle variations of the substrate; the reaction conditions for this



Scheme 8. Reagents and conditions: (a) $MeP^{+}Ph_3Br^{-}$, *t*-BuOK, THF, 25 °C; (b) TBAF, 60 °C, 1 h; (c) AllylMgBr, THF, −78 °C; (d) $Pb(OAc)_4$, AcOH, 25 °C.

transformation are mild and tolerate various solvents but also various substituents. Consistently good combined yields (70–80%) were observed for a range of homoallylic alcohols. For maximum efficiency, control of the regiochemical outcome (*endo*/*exo* double bond in **19**/**20**, **21**/**22**, and **25**/**26**) of the process must be improved. Equally, an efficient method for the *endo*/*exo* double bond interconversion will be necessary if this synthetic route is to meet program objectives. Both of these problems are currently under investigation and results will be reported in due course.

4. Experimental

4.1. General

General experimental details were as previously described. NMR spectra were run in $CDCl_3$ and specific rotations were measured in chloroform. Experimental evidence favoring the structures investigated came from a comprehensive range of ^{1}H and ^{13}C NMR data (1 and 2D experiments) and corroborated by spatial proximity studies using mainly the 1D NOEDIFF technique.[23] For all compounds investigated, multiplicities of ^{13}C resonances were assigned by the SEFT technique.[24] Electron spray mass spectra were obtained in instances where electron impact and chemical ionization failed to produce molecular ions. Mass spectra acquired in the positive ion mode under electron spray ionization (ES^{+}) using a mobile phase of methanol, will be abbreviated as ESIMS (MeOH). HR will be added for the high resolution mass measurements (HRESIMS). 'Usual work up' means washing of the organic layer with brine, drying over anhydrous magnesium sulfate, and evaporating in vacuo with a rotary evaporator at aspirator pressure. Commercial $Pb(OAc)_4$ was used without purification. The acetic acid content of the latter (introduced in excess of 0.2 equiv) was mostly removed under vacuum in the reaction vessel. Optical rotations were measured in $CHCl_3$.

4.2. General procedures

4.2.1. General procedure for the lead tetraacetate mediated oxidative cleavage. To a flame dried flask containing 1.0 mmol of substrate homoallylic alcohol and 2.0 mmol of $Pb(OAc)_4$, evacuated and flashed with argon, were added 5 mL of dry acetic acid at room temperature. After consumption of starting material (TLC monitoring, from 5 min to 6 h), the reaction mixture was diluted with ethyl acetate, washed with aqueous saturated $NaHCO_3$, worked up as usual, and chromatographed on SiO_2 column chromatography.

4.2.2. General procedure for fluoride deprotection. To a magnetically stirred solution of TBS-protected alcohol (1.0 mmol) was added tetrabutylammonium fluoride (2.0 mmol). The reaction was stirred at 60 °C until TLC monitoring showed no starting material left (usually ca. 1 h). After dilution with EtOAc, usual work up and chromatography on SiO_2 gave the expected compound.

4.2.3. General procedure for oxidation with Dess–Martin's periodinane. To a stirred solution of alcohol (1 mmol) in 15 mL of dry methylene chloride and 2 mL of dry pyridine 3 equiv of Dess–Martin periodinane reagent were added and the reaction mixture was stirred at room temperature until TLC analysis indicated that the reaction was complete (ca. 1–3 h). The mixture was diluted with methylene chloride, washed with a saturated aqueous solution of sodium bicarbonate, then sodium thiosulfate solution, worked up as usual, and chromatographed on SiO_2 (eluent heptane–EtOAc) to give the desired ketone.

4.2.4. General procedure for Wittig methylenation. A solution of potassium *tert*-butoxide (5.6 mmol) in 6 mL of dry THF was stirred under argon at room temperature as methyltriphenylphosphonium bromide (6 mmol) was added. The resulting bright yellow solution was stirred for 1 h, cooled to 0 °C before the ketone (1 mmol) was added in dry THF (6 mL). The ice bath was removed and the solution stirred at room temperature while the reaction progress was monitored by TLC. After TLC analysis indicated consumption of the starting ketone, the reaction mixture was diluted with heptane and worked up as usual. Rapid filtration on silica gel with heptane–EtOAc as eluent afforded the desired compound.

4.3. Preparation and oxidative cleavage of unsaturated diols 6

To a solution of hydrindenone **4** (200 mg, 0.48 mmol) in dry THF (3 mL) was added allylmagnesium bromide (1.0 M in ether, 1.9 mL, 1.92 mmol), at −78 °C, and the mixture stirred for 1 h under argon. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl at 0 °C. This was then extracted with EtOAc, washed with saturated aqueous $NaHCO_3$, worked up as usual, and chromatographed on silica gel (heptane–EtOAc, 95:5) to give the expected compound **5** (190 mg, 88%).

4.3.1. (1*R*,5*S*,6*R*,7a*S*)-1-Allyl-5,6-bis(*tert*-butyldimethylsilyloxy)-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-ol 5. Colorless oil; $[\alpha]_D^{20} = -96$ (*c* 1.5, $CHCl_3$); IR (film): $\nu = 3365, 1639, 1471, 1462, 1407, 1386, 1360, 1251, 1101, 1071, 1030, 1005, 880, 869, 834, 773\ cm^{-1}$; ^1H NMR (300 MHz): $\delta = 0.09$ (s, 3H), 0.10 (s, 6H), 0.11 (s, 3H), 0.90 (s, 9H), 0.91 (s, 9H), 1.19 (s, 3H), 1.70 (m, 3H), 2.08 (m, 3H), 2.26 (dd, $J = 6.5$, 13.1 Hz, 1H), 2.42 (m, 2H), 3.92 (ddd, $J = 3.6$, 6.8, 11.0 Hz, 1H), 4.07 (m, 1H), 5.09 (d, $J = 2.2$, 1H), 5.15 (b, 1H), 5.19 (d, $J = 2.2$ Hz, 1H), 5.91 (m, 1H); ^{13}C NMR (75 MHz): $\delta = -4.5, -4.4, -3.9, -3.8$, 18.0, 18.2, 21.2, 24.8, 26.0 (3C), 26.8 (3C), 32.6, 37.3, 40.6, 49.1, 73.1, 75.4, 81.3, 119.0, 122.2, 134.4, 146.8; ESIMS (MeOH): 475.3 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{25}H_{48}O_3Si_2Na$ *m*/*z* 475.3040, found: 475.3050; Anal. Calcd for $C_{25}H_{48}O_3Si_2$ (452.31): C, 66.31; H, 10.68. Found: C, 66.16; H, 10.91.

Fluoride deprotection was carried out on **5** (190 mg, 0.42 mmol) using the general procedure (1 h, 60 °C) to give after chromatography (SiO_2, heptane–EtOAc, 2:1) **6** (75 mg, 80%).

4.3.2. (1*R*,5*S*,6*R*,7a*S*)-1-Allyl-7a-methyl-2,3,5,6,7,7a-hexahydro-1*H*-indene-1,5,6-triol 6. Colorless oil; $[\alpha]_D^{20} = -78$ (*c* 1.2, MeOH); IR (film): $\nu = 3336, 1638, 1435, 1373, 1308, 1270, 1185, 1114, 1034, 1007, 911\ cm^{-1}$; ^1H NMR (300 MHz): $\delta = 1.19$ (s, 3H), 1.66 (m, 3H), 1.96 (m, 3H), 2.37 (m, 4H), 3.32 (t, $J = 3.2$ Hz, 1H), 3.88 (m, 2H), 5.05 (m, 2H), 5.20 (dd, $J = 3.1$, 4.3 Hz, 1H), 5.93 (m, 1H); ^{13}C NMR (75 MHz): $\delta = 22.3$, 25.6, 32.3, 37.5, 42.2, 50.8, 73.3, 75.8, 82.5, 118.0, 122.0, 136.5, 150.0; ESIMS (MeOH): 247.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{13}H_{20}O_3Na$ *m*/*z* 247.1310, found: 247.1301.

Placed in a flame dried flask, **6** (70 mg, 0.31 mmol) and $Pb(OAc)_4$ (329 mg, 0.74 mmol) were vacuumed, flashed with argon and cooled to 0 °C. Toluene (2 mL) was added, the ice bath removed soon after, and the mixture was stirred at room temperature while TLC monitored. The reaction mixture was diluted with Et_2O and filtered through Celite. The filtrate was concentrated and purified by SiO_2 flash column chromatography (heptane–EtOAc, 3:1 as eluent) affording **7a** (65.6 mg, 71%).

4.3.3. (1*R*,3*R*,7*S*,8*R*,9*S*)-Acetic acid-9-acetoxy-7-methyl-6-oxo-2,10-dioxa-tricyclo[5.3.1.0^{3,8}]undec-3-yl ester 7a. Colorless oil; $[\alpha]_D^{20} = +17$ (*c* 1.3, $CHCl_3$); IR (film): $\nu = 2941, 1731, 1715, 1450, 1368, 1325, 1219, 1170, 1105, 1083, 1062, 1019, 996\ cm^{-1}$; ^1H NMR (500 MHz): $\delta = 1.47$ (s, 3H), 1.93 (d, $J = 14.2$ Hz, 1H), 2.11 (s, 3H), 2.12 (s, 3H), 2.30 (dd, $J = 3.3$, 14.2 Hz, 1H), 2.51 (m, 1H), 2.61 (dd, $J = 12.9$, 4.2 Hz, 1H), 2.66 (m, 1H), 2.73 (dd, $J = 5.3$, 13.0 Hz, 1H), 3.03 (dd, $J = 0.9$, 3.0 Hz, 1H), 5.40 (d, $J = 3.3$ Hz, 1H), 6.40 (d, $J = 3.0$ Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 21.3$, 22.0, 22.8, 32.0, 34.5, 40.0, 41.5, 42.3, 90.0, 93.1, 102.9, 169.1, 169.4, 211.1; ESIMS (MeOH): 321.1 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{14}H_{18}O_7Na$ *m*/*z* 321.0950, found 321.0947.

4.4. Preparation of target molecules 9, 11, 13, and their transannular oxidative ring cleavage

4.4.1. Homoallylic alcohol 9. The target homoallylic alcohol **9** was synthesized from **8** by the addition of methyllithium[16] on followed by desilylation (TBAF, 60 °C, 1 h) and oxidation of the resulting alcohol (485 mg, 2.0 mmol) with a Dess–Martin periodinane (2.54 g, 6.0 mmol) in dry pyridine (1.6 mL) using the general procedure affording after SiO_2 chromatography (heptane–EtOAc, 2:1) the corresponding ketone (280 mg, 60%).

4.4.1.1. (1*R*,4*R*,5*S*,7*S*)-5-*tert*-Butoxy-7-hydroxy-4,7-dimethylbicyclo[2.2.2]octan-2-one. Colorless oil; $[\alpha]_D^{20} = +52$ (*c* 0.6, $CHCl_3$); IR (film): $\nu = 3426, 2972, 2933, 1737, 1719, 1457, 1389, 1369, 1230, 1204, 1190, 1131, 1071\ cm^{-1}$; ^1H NMR (500 MHz): $\delta = 0.93$ (s, 3H), 1.14 (s, 9H), 1.31 (d, $J = 14.4$ Hz, 1H), 1.41 (s, 3H), 1.56 (s, 1H), 1.66 (ddd, $J = 2.0$, 2.9, 14.8 Hz, 1H), 1.91 (dd, $J = 2.8$, 18.8 Hz, 1H), 2.07 (m, 1H), 2.12 (dd, $J = 2.9$, 14.2 Hz, 1H), 2.17 (t, $J = 2.9$ Hz, 1H), 2.24 (t, $J = 18.8$ Hz, 1H), 3.30 (ddd, $J = 1.5$, 3.5, 8.9 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 23.5$, 28.5, 28.7 (3C), 33.5, 37.6, 42.5, 46.9, 56.6, 69.7, 72.3, 73.3, 213.9; ESIMS (MeOH): 263.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{14}H_{24}O_3Na$ *m*/*z* 263.1623, found: 263.1607; Anal. Calcd for $C_{14}H_{24}O_3$ (240.17): C, 69.96; H, 10.07. Found: C, 69.26; H, 10.15.

Wittig methylenation of the ketone thus obtained (270 mg, 1.12 mmol) in dry THF (6 mL) with potassium *tert*-butoxide (700 mg, 6.25 mmol) and methyltriphenylphosphonium bromide (2.40 g, 6.75 mmol) using the general procedure afforded after SiO_2 chromatography (heptane–EtOAc, 8:2) **9** (200 mg, 75%).

4.4.1.2. (1*S*,4*S*,5*S*,7*S*)-5-*tert*-Butoxy-4,7-dimethyl-2-methylenebicyclo[2.2.2]octan-7-ol 9. Colorless oil; $[\alpha]_D^{20} = +72$ (*c* 1.0, $CHCl_3$); IR (film): $\nu = 3453, 2972, 2925, 1649, 1461, 1437, 1387, 1363, 1244, 1189, 1067, 989, 897, 880\ cm^{-1}$; ^1H NMR (500 MHz): $\delta = 0.79$ (s, 3H), 1.04 (d, $J = 14.5$ Hz, 1H), 1.10 (s, 9H), 1.33 (s, 3H), 1.66 (td, $J = 2.6$, 14.2 Hz, 1H), 1.90 (m, 2H), 1.96 (m, 3H), 2.09 (td, $J = 1.9$, 17.4 Hz, 1H), 3.15 (ddd, $J = 1.5$, 2.6, 9.0 Hz, 1H), 4.79 (dd, $J = 1.9$, 3.9 Hz, 1H), 4.84 (dd, $J = 1.9$, 3.9 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 24.0$, 27.1, 28.6 (3C), 35.5, 36.4, 39.4, 44.8, 49.6, 70.5 (2C), 72.7, 109.3, 147.6; ESIMS (MeOH): 261.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{15}H_{26}O_2Na$ *m*/*z* 261.1830, found: 261.1849.

Transannular oxidative ring cleavage of **9** (40 mg, 0.16 mmol) was achieved using the general procedure (45 min, AcOH, 25 °C) to afford **19** (21.3 mg, 45%) and **20** (10.2 mg, 25%) after SiO_2 flash column chromatography (heptane–EtOAc, 9:1). Yields were higher (**19**, 53% and **20**, 40%) while no starting material was recovered upon prolonged stirring (2 h at room temperature).

4.4.1.3. ((4*S*,5*S*)-4-*tert*-Butoxy-5-methyl-5-(2-oxopropyl)cyclohex-1-enyl)methyl acetate 19. Colorless oil; $[\alpha]_D^{20} = +46$ (*c* 1.6, $CHCl_3$); IR (film): $\nu = 2971$, 1740, 1710, 1457, 1362, 1192, 1072, 1023, 959, 895, 842 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.07$ (s, 3H), 1.15 (s, 9H), 1.81 (dd, $J = 2.5$, 17.1 Hz, 1H), 2.06 (s, 3H), 2.07 (m, 1H), 2.14 (s, 3H), 2.28 and 2.61 (ABquartet, $J = 14.7$ Hz, 2H), 2.30 (m, 2H), 3.45 (dd, $J = 5.6$, 7.5 Hz, 1H), 4.42 (d, $J = 12.4$ Hz, 2H), 5.60 (m, 1H); ^{13}C NMR (125 MHz): $\delta = 20.9$, 24.1, 29.0 (3C), 31.9, 32.7, 36.7, 36.8, 45.8, 68.0, 72.7, 73.3, 123.5, 131.3, 170.9, 209.6; ESIMS (MeOH): 319.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{17}H_{28}O_4Na$ *m*/*z* 319.1885, found: 319.1890; Anal. Calcd for $C_{17}H_{28}O_4$ (296.19): C, 68.89; H, 9.52. Found: C, 68.17; H, 9.49.

4.4.1.4. 1-((1*S*,2*S*,4*S*)-2-*tert*-Butoxy-4-hydroxy-1-methyl-5-methylenecyclohexyl)propan-2-one 20. Colorless oil; $[\alpha]_D^{20} = -7$ (*c* 0.9, $CHCl_3$); IR (film): $\nu = 3424$, 2971, 1708, 1654, 1456, 1364, 1233, 1191, 1090, 1058, 1023, 898 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.01$ (s, 3H), 1.21 (s, 9H), 1.75 (d, $J = 13.4$ Hz, 1H), 1.90 (m, 2H), 2.11 (s, 3H), 2.34 and 2.65 (ABquartet, $J = 16.6$ Hz, 2H), 2.62 (d, $J = 13.4$ Hz, 1H), 3.71 (t, $J = 4.0$ Hz, 1H), 3.85 (s, 1H), 4.09 (dd, $J = 4.7$, 9.3 Hz, 1H), 4.76 (s, 1H), 4.96 (s, 1H); ^{13}C NMR (125 MHz): $\delta = 22.1$, 28.8 (3C), 32.2, 35.8, 38.9, 39.4, 49.3, 72.0, 74.0, 74.7, 110.1, 147.1, 208.7; ESIMS (MEOH): 277.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{15}H_{26}O_3Na$ *m*/*z* 277.1779, found: 277.1781.

4.4.2. Homoallylic alcohol 11. Wittig methylenation of **8** (500 mg, 1.46 mmol) in dry THF (10 mL) with potassium *tert*-butoxide (918 mg, 8.18 mmol) and methyltriphenylphosphonium bromide (3.13 g, 8.76 mmol) using the general procedure gave after SiO_2 chromatography (heptane–EtOAc, 8:2) **10** (448 mg, 90%).

4.4.2.1. (1*R*,4*R*,5*S*,7*S*)-(5-*tert*-Butoxy-4-methyl-2-methylenebicyclo[2.2.2]octan-7-yloxy)(*tert*-butyl)dimethylsilane 10. Colorless oil; $[\alpha]_D^{20} = +49$ (*c* 0.6, $CHCl_3$); IR (film): $\nu = 2928$, 2856, 1654, 1462, 1387, 1362, 1255, 1201, 1059, 1005, 936, 907, 870, 835, 802, 773, 695 cm^{-1}; ^1H NMR (500 MHz): $\delta = 0.01$ (s, 6H), 0.79 (s, 3H), 0.86 (s, 9H), 1.11 (s, 9H), 1.20 (dd, $J = 3.4$, 14.0 Hz, 1H), 1.48 (td, $J = 3.4$, 13.8 Hz, 1H), 1.68 (ddd, $J = 3.0$, 9.1, 14.0 Hz, 1H), 1.84 (dd, $J = 1.6$, 16.8 Hz, 1H), 1.92 (ddd, $J = 2.8$, 9.0, 13.8 Hz, 1H), 2.08 (dd, $J = 2.8$, 5.8 Hz, 1H), 2.53 (dd, $J = 2.3$, 16.8 Hz, 1H), 3.18 (ddd, $J = 1.6$, 3.2, 9.0 Hz, 1H), 3.82 (td, $J = 3.4$, 9.1 Hz, 1H), 4.70 (dd, $J = 2.3$, 4.2 Hz, 2H); ^{13}C NMR (125 MHz): $\delta = -4.7$, -4.5, 18.1, 24.2, 25.8 (3C), 28.7 (3C), 33.4, 35.2, 37.7, 44.0, 44.7, 69.6, 70.6, 72.6, 107.4, 146.9; ESIMS (MeOH): 361.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{20}H_{38}O_2SiNa$ *m*/*z* 361.2539, found: 361.2564; Anal. Calcd for $C_{20}H_{38}O_2Si$ (338.26): C, 70.94; H, 11.31. Found: C, 70.93; H, 11.23.

Fluoride deprotection of **10** (448 mg, 1.32 mmol) using the general procedure (1 h, 60 °C) afforded after SiO_2 chromatography (heptane–EtOAc, 2:1) the target homoallylic alcohol **11** (287 mg, 90%).

4.4.2.2. (1*R*,2*S*,4*R*,5*S*)-5-*tert*-Butoxy-4-methyl-7-methylenebicyclo[2.2.2]octan-2-ol 11. Colorless oil; $[\alpha]_D^{20} = +48$ (*c* 0.9, $CHCl_3$); IR (film): $\nu = 3293$, 2971, 2919, 1651, 1450, 1434, 1384, 1359, 1309, 1232, 1192, 1094, 1048, 1008, 887, 878, 742, 742, 694 cm^{-1}; ^1H NMR (500 MHz): $\delta = 0.80$ (s, 3H), 1.11 (s, 9H), 1.14 (m, 1H), 1.58 (td, $J = 3.3$, 14.0 Hz, 1H), 1.72 (s, 1H), 1.80 (m, 2H), 1.99 (ddd, $J = 2.9$, 9.2, 13.9 Hz, 1H), 2.17 (dd, $J = 2.9$, 6.0 Hz, 1H), 2.60 (ddd, $J = 2.6$, 5.3, 17.2 Hz, 1H), 3.20 (ddd, $J = 1.6$, 3.3, 9.2 Hz, 1H), 3.81 (td, $J = 3.3$, 9.2 Hz, 1H), 4.84 (dd, $J = 1.3$, 3.2 Hz, 2H); ^{13}C NMR (125 MHz): $\delta = 24.1$, 28.7 (3C), 34.2, 35.1, 36.9, 43.8, 44.4, 68.3, 70.2, 72.7, 109.6, 146.2; ESIMS (MeOH): 247.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{14}H_{24}O_2Na$ *m*/*z* 247.1674, found: 247.1686; Anal. Calcd for $C_{14}H_{24}O_2$ (224.17): C, 74.95; H, 10.78. Found: C, 75.37; H, 10.14.

Transannular oxidative ring cleavage of **11** (90 mg, 0.41 mmol) was achieved using the general procedure to afford after 5 min of stirring, **21a** (46.2 mg, 41%), **22a** (22 mg, 20%), and **22c** (17.2 mg, 18%) after SiO_2 flash column chromatography (heptane–EtOAc, 9:1).

4.4.2.3. ((4*S*,5*R*)-4-*tert*-Butoxy-5-methyl-5-(2-oxoethyl)-cyclohex-1-enyl)methyl ethanoate 21a. Colorless oil; $[\alpha]_D^{20} = +55$ (*c* 1.3, $CHCl_3$); IR (film): $\nu = 2975$, 2928, 1740, 1714, 1465, 1433, 1364, 1230, 1192 1074, 1024, 961 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.10$ (s, 3H), 1.15 (s, 9H), 1.94 (d, $J = 17.3$ Hz, 1H), 2.06 (s, 3H), 2.09 (m, 2H), 2.17 (dd, $J = 1.7$, 15.5 Hz, 1H), 2.36 (dd, $J = 8.4$, 14.2 Hz, 1H), 2.41 (dd, $J = 3.7$, 15.5 Hz, 1H), 3.50 (dd, $J = 5.6$, 8.3 Hz, 1H), 4.39 and 4.43 (ABquartet, $J = 12.3$ Hz, 2H), 5.60 (m, 1H), 9.85 (m, 1H); ^{13}C NMR (125 MHz): $\delta = 17.9$, 20.9, 28.9 (3C), 31.8, 36.8, 39.2, 54.3, 68.0, 72.0, 73.9, 123.9, 130.5, 170.7, 203.2; ESIMS (MeOH): 305.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{16}H_{26}O_4Na$ *m*/*z* 305.1729, found: 305.1722.

4.4.2.4. (1*S*,4*R*,5*S*)-5-*tert*-Butoxy-4-methyl-2-methylene-4-(2-oxoethyl)cyclohexyl ethanoate 22a. Colorless oil; $[\alpha]_D^{20} = +30$ (*c* 1.5, $CHCl_3$); IR (film): $\nu = 2973$, 1737, 1718, 1653, 1365, 1237, 1191, 1070 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.06$ (s, 3H), 1.18 (s, 9H), 1.88 (dddd, $J = 3.6$, 7.3, 12.4, 13.9 Hz, 1H), 2.07 (s, 3H), 2.24 (m, 4H), 2.46 (dd, $J = 3.4$, 15.3 Hz, 1H), 3.70 (dd, $J = 3.6$, 8.2 Hz, 1H), 4.84 (s, 1H), 4.99 (s, 1H), 5.43 (t, $J = 5.0$ Hz, 1H), 9.86 (dd, $J = 2.2$, 3.4 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 19.2$, 21.2, 28.8 (3C), 35.3, 39.6, 42.0, 53.2, 71.5, 73.2, 73.9, 112.6, 141.8, 169.9, 202.8; ESIMS (MeOH): 305.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{16}H_{26}O_4Na$ *m*/*z* 305.1729, found: 305.1700.

4.4.2.5. 2-((1*R*,2*S*,4*S*)-2-*tert*-Butoxy-4-hydroxy-1-methyl-5-methylenecyclohexyl)ethanal 22c. Colorless oil; $[\alpha]_D^{20} = +46$ (*c* 1.8, $CHCl_3$); IR (film): $\nu = 3409$, 2973, 2359, 1715, 1654, 1469, 1389, 1364, 1230, 1191, 1069, 1024, 899 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.04$ (s, 3H), 1.18 (s, 9H), 1.83

(m, 3H), 1.60 and 2.32 (ABquartet, $J = 13.5$ Hz, 2H), 2.16 and 2.43 (ABquartet, $J = 15.3$ Hz, 2H), 3.76 (dd, $J = 3.9$, 7.6 Hz, 1H), 4.37 (t, $J = 5.2$ Hz, 1H), 4.77 (s, 1H), 4.97 (s, 1H), 9.85 (t, $J = 2.8$ Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 19.4$, 28.9 (3C), 38.0, 39.8, 41.5, 53.2, 71.0, 71.4, 73.9, 110.2, 147.0, 203.1; ESIMS (MeOH): 263.1 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{14}H_{24}O_3Na$ m/z 263.1623, found: 263.1607.

Aldehydes **21a** and **22a** (140 mg, 0.49 mmol scale each) were dissolved in dry CH_2Cl_2 (5 mL), chilled to 0 °C, treated dropwise with Me_3Al (2.0 M in hexane, 5 mL) and stirring was continued, at 0 °C, for 20 min. The reaction mixtures were diluted with CH_2Cl_2, and quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was back-extracted with CH_2Cl_2. The extracts were worked up as usual and chromatographed on silica gel (heptane–EtOAc, 4:1) to give the corresponding methyl carbinols as a mixture of diastereomers (122 mg, 78% for **21a** and 116 mg, 74% for **22a**).

The methyl carbinols thus obtained (116 mg, 0.388 mmol scale each) in dry CH_2Cl_2 (4 mL) and pyridine (0.3 mL) were oxidized with Dess–Martin periodinane (516.5 mg, 1.16 mmol) at room temperature for 30 min. The reaction mixtures were then diluted with CH_2Cl_2, quenched with a saturated aqueous solution of sodium bicarbonate, usual work up and chromatography (heptane–EtOAc, 4:1) to afford **21b** (94 mg, 80%) and **22b** (91 mg, 79%).

4.4.2.6. ((4*S*,5*R*)-4-*tert*-Butoxy-5-methyl-5-(2-oxopropyl)cyclohex-1-enyl)methylacetate 21b. Colorless oil; $[\alpha]_D^{20} = +38$ (c 1.1, $CHCl_3$); IR (film): $\nu = 2974$, 2934, 1740, 1716, 1362, 1229, 1195, 1069, 1022, 957, 772 cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 0.96$ (s, 3H) 1.15 (s, 9H), 2.02 (m, 1H), 2.05 (s, 3H), 2.11 (s, 3H), 2.15 (m, 2H), 2.29 (m, 1H), 2.35 and 2.58 (ABquartet, $J = 16.2$ Hz, 2H), 3.66 (dd, $J = 5.5$, 7.2 Hz, 1H), 4.41 (s, 2H), 5.56 (s, 1H); ^{13}C NMR (125 MHz): $\delta = 19.0$, 21.0, 29.1 (3C), 31.8, 32.4, 36.5, 36.7, 51.7, 57.2, 70.7, 73.2, 123.2, 131.2, 170.9, 208.9; ESIMS (MeOH): 319.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{17}H_{28}O_4Na$ m/z 319.1885, found: 319.1872; Anal. Calcd for $C_{17}H_{28}O_4$ (296.19): C, 68.89; H, 9.52. Found: C, 69.47; H, 9.53.

4.4.2.7. (1*S*,4*R*,5*S*)-5-*tert*-Butoxy-4-methyl-2-methylene-4-(2-oxopropyl)cyclohexyl acetate 22b. Colorless oil; $[\alpha]_D^{20} = +82$ (c 0.7, $CHCl_3$); IR (film): $\nu = 2974$, 2933, 1739, 1716, 1364, 1239, 1064, 1027, 901, 772 cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 0.97$ (s, 3H), 1.18 (s, 9H), 1.77 (ddd, $J = 3.2$, 8.1, 13.6 Hz, 1H), 1.89 (ddd, $J = 4.6$, 6.6, 13.5 Hz, 1H), 2.09 (s, 3H), 2.12 (s, 3H), 2.19 (d, $J = 13.5$ Hz, 1H), 3.34 (d, $J = 9.3$ Hz, 1H), 2.36 and 2.55 (ABquartet, $J = 16.2$ Hz, 2H), 3.90 (dd, $J = 3.1$, 6.7 Hz, 1H), 4.78 (s, 1H), 4.89 (s, 1H), 5.46 (dd, $J = 4.6$, 7.9 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 20.6$, 21.3, 28.9 (3C), 32.5, 35.6, 39.5, 41.3, 50.9, 68.4, 70.7, 73.6, 110.1, 143.2, 170.1, 208.6; ESIMS (MeOH): 319.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{17}H_{28}O_4Na$ m/z 319.1885, found: 319.1871; Anal. Calcd for $C_{17}H_{28}O_4$ (296.19): C, 68.89; H, 9.52. Found: C, 68.12; H, 9.67.

4.4.3. Preparation of bis-homoallylic alcohol 13 and its transannular oxidative ring cleavage. Dess–Martin oxidation of the known diol **12**[16] (260 mg, 0.97 mmol) was carried out with DMP (1.23 g, 2.91 mmol) in pyridine (0.75 mL) for 2.5 h using the general procedure to give, after chromatography, (heptane–EtOAc, 1:1) the corresponding ketone (210 mg, 82%).

4.4.3.1. (1*R*,4*R*,5*S*,7*S*)-7-Allyl-5-*tert*-butoxy-7-hydroxy-4-methylbicyclo[2.2.2]octan-2-one. White solid; mp: 88–89 °C (heptane); $[\alpha]_D^{20} = +66$ (c 1.0, $CHCl_3$); IR (film): $\nu = 3444$, 3073, 2973, 2930, 2360, 2340, 1718, 1639, 1451, 1389, 1364, 1202, 1191, 1126, 1071, 1042, 1023, 1000, 973, 913 cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 0.93$ (s, 3H), 1.15 (s, 9H), 1.26 (dd, $J = 1.4$, 14.2 Hz, 1H), 1.68 (t, d, $J = 3.0$, 14.9 Hz, 1H), 1.85 (s, 1H), 1.93 (dd, $J = 2.8$, 18.8 Hz, 1H), 2.05 (ddd, $J = 3.5$, 9.1, 14.9 Hz, 1H), 2.13 (dd, $J = 2.8$, 14.2 Hz, 1H), 2.25 (m, 2H), 2.46 (m, 2H), 3.32 (ddd, $J = 1.8$, 3.6, 9.2 Hz, 1H), 5.19 (ddd, $J = 1.5$, 3.4, 9.0 Hz, 1H), 5.23 (dd, $J = 2.2$, 10.2, Hz, 1H), 5.84 (tdd, $J = 7.5$, 10.2, 17.5 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 23.5$, 28.7 (3C), 32.8, 37.3, 41.7, 44.1, 47.3, 53.9, 69.6, 73.0, 73.3, 120.4, 132.4, 213.5; ESIMS (MeOH): 289.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{16}H_{26}O_3Na$ m/z 289.1780, found: 289.1791; Anal. Calcd for $C_{16}H_{26}O_3$ (266.18): C, 72.14; H, 9.84. Found: C, 72.25; H, 9.82.

Wittig methylenation of the ketone thus obtained (210 mg, 0.78 mmol) in dry THF (2 mL) with potassium *tert*-butoxide (489 mg, 4.36 mmol) and methyltriphenylphosphonium bromide (1.67 g, 4.68 mmol) using the general procedure gave after SiO_2 chromatography (heptane–EtOAc, 8:2) **13** (154 mg, 75%).

4.4.3.2. (1*S*,4*S*,5*S*,7*S*)-7-Allyl-5-*tert*-butoxy-4-methyl-2-methylenebicyclo[2.2.2]octan-7-ol 13. Colorless oil; $[\alpha]_D^{20} = +79$ (c 1.0, $CHCl_3$); IR (film): $\nu = 3559$, 3070, 2972, 2924, 1640, 1451, 1432, 1388, 1363, 1249, 1229, 1186, 1170, 1058, 1023, 1000, 962, 908, 887 cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 0.83$ (s, 3H), 1.01 (dd, $J = 1.5$, 14.2 Hz, 1H), 1.14 (s, 9H), 1.69 (td, $J = 2.7$, 14.3 Hz, 1H), 1.91 (ddd, $J = 3.2$, 9.2, 14.3 Hz, 1H), 2.02 (m, 3H), 2.10 (t, $J = 3.0$ Hz, 1H), 2.16 (td, $J = 2.1$, 17.3 Hz, 1H), 2.49 (tdd, $J = 1.3$, 5.1, 7.7 Hz, 2H), 3.21 (ddd, $J = 1.6$, 2.7, 9.0 Hz, 1H), 4.82 (dd, $J = 2.0$, 4.0 Hz, 1H), 4.85 (dd, $J = 2.1$, 4.2 Hz, 1H), 5.12 (t, $J = 1.2$ Hz, 1H), 5.15 (m, 1H), 5.95 (tdd, $J = 7.3$, 11.2, 16.2 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 24.0$, 28.8 (3C), 35.3, 35.8, 39.7, 43.7, 43.8, 47.1, 70.4, 71.8, 72.8, 109.2, 117.7, 134.5, 147.5; ESIMS (MeOH): 287.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{17}H_{28}O_2Na$ m/z 287.1987, found: 287.1980.

Oxidative cleavage of **13** (200 mg, 0.75 mmol) was achieved using the general procedures to afford **23** (85 mg, 42%) and **24** (45 mg, 25%) after SiO_2 flash column chromatography (heptane–EtOAc, 4:1 as eluent).

Transannular oxidative ring cleavage of **13** (200 mg, 0.75 mmol) was achieved using the general procedure to afford after 15 min stirring **23** (85 mg, 42%) and **24** (45 mg, 25%) after SiO_2 flash column chromatography (heptane–EtOAc, 4:1).

4.4.3.3. ((4*S*,5*S*)-4-*tert*-Butoxy-5-methyl-5-((*E*)-2-oxopent-3-enyl)cyclohex-1-enyl)methylethanoate 23. Colorless oil; $[\alpha]_D^{20} = +46$ (*c* 0.3, $CHCl_3$); IR (film): $\nu = 2971$, 2925, 1740, 1687, 1661, 1628, 1456, 1438, 1387, 1366, 1227, 1192, 1071, 1023, 969, 895 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.02$ (s, 3H), 1.17 (s, 9H), 1.78 (d, $J = 17.0$ Hz, 1H), 1.87 (dd, $J = 2.1$, 6.8 Hz, 3H), 2.06 (s, 3H), 2.12 (m, 1H), 2.30 (d, $J = 17.0$ Hz, 1H), 2.34 (m, 1H), 2.42 and 2.68 (ABquartet, $J = 14.0$ Hz, 2H), 3.45 (dd, $J = 5.3$, 7.4 Hz, 1H), 4.40 and 4.45 (ABquartet, $J = 13.7$ Hz, 2H), 5.60 (s, 1H), 6.10 (qd, $J = 1.7$, 15.6 Hz, 1H), 6.78 (qd, $J = 6.7$, 15.7 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 18.1$, 20.9, 24.2, 29.0 (3C), 31.9, 36.4, 36.9, 42.0, 68.0, 72.8, 73.2, 123.2, 131.3, 133.9, 141.7, 170.9, 201.1; ESIMS (MeOH): 345.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{19}H_{30}O_4Na$ *m*/*z* 345.2042; found: 345.2023.

4.4.3.4. (1*S*,4*S*,5*S*)-5-*tert*-Butoxy-4-methyl-2-methylene-4-((*E*)-2-oxopent-3-enyl)cyclohexyl ethanoate 24. Colorless oil; $[\alpha]_D^{20} = +19$ (*c* 0.4, $CHCl_3$); IR (film): $\nu = 2976$, 2930, 2360, 2330, 1738, 1695, 1659, 1439, 1367, 1238, 1194, 1059, 1026, 969, 897, 773, 669 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.03$ (s, 3H), 1.18 (s, 9H), 1.77 (m, 1H), 1.87 (dd, $J = 1.5$, 6.8 Hz, 3H), 1.94 (m, 1H), 1.99 and 2.51 (ABquartet, $J = 13.5$ Hz, 2H), 2.08 (s, 3H), 2.43 and 2.66 (ABquartet, $J = 15.3$ Hz, 2H), 3.71 (dd, $J = 7.0$, 14.0 Hz, 1H), 4.80 (s, 1H), 4.91 (s, 1H), 5.47 (dd, $J = 4.5$, 8.0 Hz, 1H), 6.08 (dd, $J = 1.5$, 15.6 Hz, 1H), 6.78 (qd, $J = 6.8$, 15.6 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 18.0$, 21.2, 23.0, 28.9 (3C), 35.3, 39.7, 41.0, 44.4, 72.6, 72.9, 73.6, 110.4, 133.6, 141.5, 143.0, 170.0, 200.4; ESIMS (MeOH): 345.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{19}H_{30}O_4Na$ *m*/*z* 345.2042; found: 345.2020; Anal. Calcd for $C_{19}H_{30}O_4$ (322.21): C, 70.83; H, 10.30. Found: C, 69.71; H, 10.14.

4.5. Preparation of target molecules 16, 17, 18, and their transannular oxidative ring cleavage

4.5.1. Homoallylic alcohol 16. Wittig methylenation of **14** (1.9 g, 4.7 mmol) in dry THF (10 mL) with potassium *tert*-butoxide (2.9 g, 26.3 mmol) and methyltriphenylphosphonium bromide (10.0 g, 28.2 mmol) using the general procedure (6 h) gave after SiO_2 chromatography (heptane–EtOAc, 8:2) the C3-acetoxy olefin (1.6 g, 86%).

4.5.1.1. (1*R*,2*S*,4*R*,5*S*,7*S*)-2-*tert*-Butoxy-5-(*tert*-butyldimethylsilyloxy)-1-methyl-8-methylenebicyclo[2.2.2]octan-7-yl ethanoate. Colorless oil; $[\alpha]_D^{20} = +83$ (*c* 1.5, $CHCl_3$); IR (film): $\nu = 2957$, 2928, 2856, 1737, 1462, 1366, 1245, 1102, 1062, 1008, 836 cm^{-1}; ^1H NMR (500 MHz): $\delta = 0.00$ (s, 3H), 0.01 (s, 3H), 0.80 (s, 3H), 0.85 (s, 9H), 1.11 (s, 9H), 1.48 (m, 2H), 1.63 (ddd, $J = 0.7$, 3.9, 14.2 Hz, 1H), 1.92 (ddd, $J = 2.9$, 9.2, 13.8 Hz, 1H), 2.15 (q, $J = 3.0$ Hz, 1H), 2.07 (s, 3H), 3.30 (dd, $J = 3.5$, 9.2 Hz, 1H), 3.80 (ddd, $J = 3.0$, 3.9, 9.1 Hz, 1H), 4.93 (dd, $J = 1.3$, 2.5 Hz, 1H), 5.01 (t, $J = 1.5$ Hz, 1H), 5.65 (dd, $J = 1.8$, 3.7 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = -4.6$, −4.5, 18.0, 20.1, 21.2, 25.7 (3C), 28.6 (3C), 36.9, 37.8, 38.2, 44.7, 69.1, 70.9, 72.0, 73.0, 112.8, 146.0, 171.4; ESIMS (MeOH): 419.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{22}H_{40}O_4NaSi$ *m*/*z* 419.2594, found: 419.2550; Anal. Calcd for $C_{22}H_{40}O_4Si$ (396.26): C, 66.62; H, 10.16. Found: C, 66.52; H, 10.23.

To a stirred solution of the C3-acetoxy olefin (380 mg, 0.95 mmol) in methanol (10 mL) and water (1 mL), was added potassium carbonate (1322 mg, 9.58 mmol). The resulting mixture was stirred at room temperature for 3 days. After removing the solvents without heating and dilution with EtOAc, usual work up and chromatography on silica gel (heptane–EtOAc, 9:1) afforded the allylic alcohol **15** (322 mg, 95%).

4.5.1.2. (1*S*,2*S*,4*R*,5*S*,7*R*)-2-*tert*-Butoxy-5-(*tert*-butyldimethylsilyloxy)-1-methyl-8-methylenebicyclo[2.2.2]octan-7-ol 15. White solid; mp: 50–51 °C (heptane); $[\alpha]_D^{20} = -16$ (*c* 1.3, $CHCl_3$); IR (film): $\nu = 3514$, 2954, 2927, 2856, 1462, 1388, 1363, 1250, 1201, 1098, 1053, 997, 948, 897, 878, 836, 775 cm^{-1}; ^1H NMR (500 MHz): $\delta = 0.03$ (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 0.98 (s, 3H), 1.10 (s, 9H), 1.48 (m, 1H), 1.52 (m, 2H), 1.80 (ddd, $J = 1.9$, 8.4, 13.9 Hz, 1H), 2.32 (s, 1H), 2.37 (d, $J = 10.2$ Hz, 1H), 3.28 (d, $J = 8.3$ Hz, 1H), 3.86 (ddd, $J = 1.2$, 4.2, 8.1 Hz, 1H), 4.06 (d, $J = 10.0$ Hz, 1H), 4.98 (s, 1H), 5.20 (s, 1H); ^{13}C NMR (125 MHz): $\delta = -4.9$, −4.7, 18.0, 20.7, 25.8 (3C), 28.6 (3C), 36.6, 37.0, 38.9, 43.5, 69.1, 71.0, 71.8, 72.9, 113.2, 150.5; ESIMS (MeOH): 377.2 ($[M+Na]^+$, 100); HRESIMS: calcd for $C_{20}H_{38}O_3NaSi$ *m*/*z* 377.2488, found: 377.2489; Anal. Calcd for $C_{20}H_{38}O_3Si$ (354.25): C, 68.10; H, 10.92. Found: C, 68.24; H, 11.21.

To an ice-cold solution of allylic alcohol **15** (540 mg, 1.52 mmol) in 6.5 mL of dry CH_2Cl_2, under argon, were added chloromethyl methylether (269.7 mg, 3.35 mmol) and diisopropylethylamine (490 mg, 3.8 mmol). The reaction mixture was allowed to warm and stirred at room temperature for 3 h while TLC-monitored. Quenched with water, extracted with CH_2Cl_2, washed with diluted 1 M HCl, a saturated aqueous solution of $NaHCO_3$, the crude, after the usual work up and silica gel chromatography (heptane–EtOAc, 9:1) gave the corresponding MOM-protected product (531 mg, 88%).

4.5.1.3. ((1*R*,3*R*,4*R*,5*S*,7*S*)-5-*tert*-Butoxy-3-(methoxymethoxy)-4-methyl-2-methylenebicyclo[2.2.2]octan-7-yloxy)-(*tert*-butyl)dimethylsilane. Colorless oil; $[\alpha]_D^{20} = +23$ (*c* 1.6, $CHCl_3$); IR (film): $\nu = 2955$, 2927, 2856, 2360, 1462, 1364, 1251, 1100, 1060, 1045, 835, 773, 668 cm^{-1}; ^1H NMR (500 MHz): $\delta = 0.01$ (s, 6H), 0.85 (s, 9H), 0.90 (s, 3H), 1.11 (s, 9H) 1.39 (ddd, $J = 1.7$, 9.2, 14.1 Hz, 1H), 1.46 (td, $J = 3.6$, 13.7 Hz, 1H), 1.65 (dd, $J = 4.2$, 14.1 Hz, 1H), 1.91 (ddd, $J = 2.9$, 9.2, 13.6 Hz, 1H), 2.15 (q, $J = 2.9$ Hz, 1H), 3.28 (dd, $J = 3.6$, 9.2 Hz, 1H), 3.43 (s, 3H), 3.76 (ddd, $J = 2.8$, 4.2, 9.2 Hz, 1H), 4.23 (d, $J = 1.8$ Hz, 1H), 4.69 and 4.79 (ABquartet, $J = 6.8$ Hz, 2H), 5.0 (t, $J = 1.8$ Hz, 1H), 5.12 (t, $J = 1.8$ Hz, 1H); ^{13}C NMR (125 MHz): $\delta = -4.6$, −4.5, 18.1, 20.5, 25.8 (3C), 28.7 (3C), 37.4, 37.8, 39.7, 45.2, 55.9, 69.7, 71.2, 72.9, 76.9, 96.9, 112.4, 147.5; ESIMS (MeOH): 421.2 ($[M+Na]^+$, 100); HRESIMS calcd for $C_{22}H_{42}O_4NaSi$ *m*/*z* 421.2750; found: 421.2721.

Fluoride deprotection was carried out on the silyl ether thus obtained (449 mg, 1.12 mmol) using the general procedure (1 h, 60 °C) to give, after chromatography (heptane–EtOAc, 2:1), the desired homoallylic alcohol **16** (255 mg, 80%).

4.5.1.4. (1*R*,2*S*,4*R*,5*S*,8*R*)-5-*tert*-Butoxy-8-(methoxymethoxy)-4-methyl-7-methylenebyciclo[2,2,2]octan-2-ol 16. White solid; mp: 62–63°C (heptane); $[\alpha]_D^{20} = +11$ (*c* 0.9, $CHCl_3$); IR (film): $\nu = 3473$, 2973, 1458, 1389, 1364, 1194, 1143, 1098, 1039, 926, 754 cm^{-1}; ^1H NMR (500 MHz): $\delta = 0.98$ (s, 3H), 1.10 (s, 9H), 1.57 (m, 3H), 1.86 (ddd, $J = 2.1$, 8.6, 12.8 Hz, 1H), 2.37 (d, $J = 12.8$ Hz, 1H), 2.44 (s, 1H), 3.27 (dd, $J = 1.7$, 8.5 Hz, 1H), 3.41 (s, 3H), 3.76 (s, 1H), 4.18 (dd, $J = 1.4$, 3.1 Hz, 1H), 4.68 and 4.84 (ABquartet, $J = 6.7$ Hz, 2H), 5.18 (dd, $J = 1.4$, 7.6 Hz, 2H); ^{13}C NMR (125 MHz): $\delta = 21.0$, 28.6 (3C), 37.4, 37.3, 38.9, 43.7, 56.0, 68.2, 71.6, 73.1, 76.7, 95.8, 115.4, 146.6; ESIMS (MeOH): 307.2 ([M+Na]$^+$, 100); HRESIMS (MeOH) calcd for $C_{16}H_{28}O_4Na$ *m*/*z* 307.1885; found: 307.1896.

Transannular oxidative ring cleavage of **16** (110 mg, 0.38 mmol) was achieved using the general procedure (45 min, AcOH, 25 °C) affording after SiO_2 flash column chromatography (heptane–EtOAc, 4:1) pure**25** (74 mg, 57%) along with an inseparable mixture of **26a** and **26b** (45 mg, 36%).

4.5.1.5. ((4*S*,5*R*,6*S*)-4-*tert*-Butoxy-6-(methoxymethoxy)-5-methyl-5-(2-oxoethyl)cyclohex-1-enyl)methyl ethanoate 25. Colorless oil; $[\alpha]_D^{20} = +55$ (*c* 1.3, $CHCl_3$); IR (film): $\nu = 2973$, 2925, 1738, 1713, 1463, 1364, 1227, 1193, 1146, 1073, 1021, 919, 754 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.05$ (s, 3H), 1.16 (s, 9H), 2.05 (s, 3H), 2.08 (m, 1H), 2.37 (d, $J = 16.2$ Hz, 1H), 2.46 (td, $J = 5.5$, 18.5 Hz, 1H), 2.56 (dd, $J = 3.8$, 16.2 Hz, 1H), 3.34 (s, 3H), 3.75 (s, 1H), 3.86 (dd, $J = 5.5$, 8.6 Hz, 1H), 4.57 (m, 2H), 4.62 (s, 2H), 5.77 (d, $J = 2.9$ Hz, 1H), 9.89 (dd, $J = 1.3$, 3.8 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 16.2$, 20.9, 28.9 (3C), 32.7, 41.9, 50.0, 56.0, 65.8, 68.3, 74.2, 81.7, 98.4, 128.9, 131.5, 170.7, 203.2; ESIMS (MeOH): 365.2 ([M+Na]$^+$, 100); HRESIMS calcd for $C_{18}H_{30}O_6Na$ *m*/*z* 365.1940; found: 365.1929; Anal. Calcd for $C_{18}H_{30}O_6$ (342.2): C, 63.14; H, 8.83. Found: C, 63.13; H, 9.03.

4.5.2. Homoallylic alcohol 17. Dess–Martin oxidation of **15** (250 mg, 0.89 mmol) was carried out with DMP (1.13 g, 2.67 mmol) in pyridine (0.75 mL) for 1.5 h using the general procedure, to give after chromatography (heptane–EtOAc, 1:1), the corresponding enone (195 mg, 79%).

4.5.2.1. (1*R*,2*S*,4*R*,5*S*)-2-*tert*-Butoxy-5-(*tert*-butyldimethylsilyloxy)-1-methyl-8-methylenebicyclo[2.2.2]octan-7-one. White solid; mp: 76–77 °C (heptane); $[\alpha]_D^{20} = -12$ (*c* 0.8, $CHCl_3$); IR (film): $\nu = 2959$, 2338, 2360, 1732, 1715, 1637, 1363, 1250, 1100, 1066, 1030, 775, 668 cm^{-1}; ^1H NMR (500 MHz): $\delta = 0.00$ (s, 3H), 0.01 (s, 3H), 0.82 (s, 9H), 1.02 (s, 3H), 1.09 (s, 9H), 1.43 (ddd, $J = 1.0$, 2.8, 14.6 Hz, 1H), 1.69 (ddd, $J = 2.5$, 4.3, 14.1 Hz, 1H), 2.00 (dd, $J = 8.9$, 14.6 Hz, 1H), 2.08 (ddd, $J = 2.2$, 8.6, 13.9 Hz, 1H), 2.62 (d, $J = 2.6$ Hz, 1H), 3.52 (dd, $J = 2.3$, 8.6 Hz, 1H), 4.94 (td, $J = 2.8$, 8.6 Hz, 1H), 5.13 (d, $J = 1.5$ Hz, 1H), 6.07 (d, $J = 1.5$ Hz, 1H); ^{13}C NMR (125 MHz): $\delta = -4.8$, −4.6, 17.4, 18.0, 25.7 (3C), 28.6 (3C), 36.9, 41.7, 44.5, 48.2, 68.4, 72.4, 76.4, 119.3, 143.1, 201.5; ESIMS (MeOH): 375.2 ([M+Na]$^+$, 100); HRESIMS calcd for $C_{20}H_{36}O_3NaSi$ *m*/*z* 375.2340; found: 375.2331.

Fluoride deprotection was carried out on TBS-protected enone thus obtained (180 mg, 0.64 mmol) using the general procedure (2 h, 60 °C) to give after SiO_2 chromatography (heptane–EtOAc, 2:1) the homoallylic alcohol **17** (90 mg, 85%).

4.5.2.2. (1*R*,2*S*,4*R*,5*S*)-2-*tert*-Butoxy-5-hydroxy-1-methyl-8-methylenebicyclo[2.2.2]octan-7-one 17. White solid; mp: 137–138 °C (heptane); $[\alpha]_D^{20} = +5$ (*c* 0.5, $CHCl_3$); IR (film): $\nu = 3315$, 2925, 2969, 2358, 1714, 1640, 1362, 1096, 1024 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.04$ (s, 3H), 1.10 (s, 9H), 1.43 (ddd, $J = 0.9$, 2.8, 15.2 Hz, 1H), 1.53 (d, $J = 6.8$ Hz, 1H), 1.76 (ddd, $J = 2.5$, 4.0, 14.2 Hz, 1H), 2.12 (m, 2H), 2.77 (dd, $J = 3.8$, 6.1 Hz, 1H), 3.55 (ddd, $J = 1.0$, 2.3, 6.2 Hz, 1H), 4.01 (m, 1H), 5.25 (d, $J = 1.58$ Hz, 1H), 6.18 (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 17.2$, 28.5 (3C), 36.8, 41.1, 44.1, 48.3, 67.8, 72.1, 73.7, 120.7, 142.1, 201.0; ESIMS (MeOH): 261.1 ([M+Na]$^+$, 100); HRESIMS: calcd for $C_{14}H_{22}O_3Na$ *m*/*z* 261.1467, found: 261.1468; Anal. Calcd for $C_{14}H_{22}O_3 \times 0.15\ H_2O$ (238.32): C, 69.77; H, 9.33. Found: C, 69.73; H 9.23.

Transannular oxidative ring cleavage of **17** (95 mg, 0.54 mmol) was achieved using the general procedure (6 h, AcOH, 25 °C) to afford **27** (105 mg, 66%) and the recovered starting material **17** (16 mg, 13%) after SiO_2 flash column chromatography (heptane–EtOAc, 9:1).

4.5.2.3. ((4*S*,5*R*)-4-*tert*-Butoxy-5-methyl-6-oxo-5-(2-oxoethyl)cyclohex-1-enyl)methyl ethanoate 27. Colorless oil; $[\alpha]_D^{20} = +15$ (*c* 1.1, $CHCl_3$); IR (film): $\nu = 2974$, 2933, 1743, 1720, 1671, 1458, 1366, 1228, 1192, 1072, 1023, 965, 885 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.12$ (s, 3H), 1.14 (s, 9H), 2.06 (s, 3H), 2.46 (dddd, $J = 2.1$, 4.4, 9.5, 18.9 Hz, 1H), 2.67 (td, $J = 5.8$, 18.9 Hz, 1H), 2.76 and 2.80 (ABquartet, $J = 17.9$ Hz, 2H), 4.07 (dd, $J = 5.3$, 9.5 Hz, 1H), 4.73 (s, 2H), 6.81 (tdd, $J = 1.3$, 2.5, 6.4 Hz, 1H), 9.72 (s, 1H); ^{13}C NMR (125 MHz): $\delta = 16.8$, 20.9, 28.9 (3C), 32.3, 47.9, 49.9, 61.3, 69.8, 74.3, 132.9, 144.2, 170.7, 200.6, 201.0; ESIMS (MeOH): 319.1 ([M+Na]$^+$, 100); HRESIMS: calcd for $C_{16}H_{24}O_5Na$ *m*/*z* 319.1521, found: 319.1517.

4.5.3. Allylic–homoallylic diol 18. Fluoride deprotection was carried out on TBS-protected allylic alcohol **15** (425 mg, 1.20 mmol) using the general procedure (1 h, 60 °C) to give after chromatography (SiO_2, heptane–EtOAc, 1:1) **18** (270 mg, 95%).

4.5.3.1. (1*R*,2*S*,4*S*,5*S*,8*R*)-5-*tert*-Butoxy-4-methyl-7-methylenebicyclo[2,2,2]octane-2,8-diol 18. White solid; mp: 107–108 °C (heptane); $[\alpha]_D^{20} = +10$ (*c* 0.7, $CHCl_3$); IR (film): $\nu = 3303$, 2971, 2929, 1389, 1362, 1203, 1095, 1057, 997, 900, 742, 996 cm^{-1}; ^1H NMR (500 MHz): $\delta = 0.90$

(s, 3H), 1.04 (s, 9H), 1.47 (m, 2H), 1.50 (m, 1H), 1.84 (ddd, $J = 2.4$, 8.9, 13.8 Hz, 1H), 2.08 (br s, 2H), 2.30 (dd, $J = 3.6$, 6.1 Hz, 1H), 3.25 (dd, $J = 2.4$, 8.8 Hz, 1H), 3.76 (td, $J = 3.6$, 7.6 Hz, 1H), 4.19 (s, 1H), 5.04 (s, 1H), 5.2 (s, 1H); ^{13}C NMR (125 MHz): $\delta = 19.4$, 27.7 (3C), 35.5, 35.6, 37.9, 42.9, 67.3, 69.5, 70.4, 72.1, 112.6, 149.1; ESIMS (MeOH): 263.2 ([M+Na]$^+$, 100); HRESIMS: calcd for $C_{14}H_{24}O_3Na$ m/z 263.1623 found: 263.1613.

Transannular oxidative ring cleavage of **18** (100 mg, 0.41 mmol) was achieved using the general procedure (45 min, AcOH, 25 °C) to afford **28** (12 mg, 13%), **29** (anomeric mixture, 13.2 mg, 14%), **30** (anomeric mixture, 12.6 mg, 13%), and **31** (anomeric mixture, 69 mg, 60%) after SiO_2 flash column chromatography (heptane–EtOAc, 4:1). Compounds **30** and **31** were characterized as pure lactones **32** and **33**, respectively (see below).

4.5.3.2. (1*S*,3*S*,4*S*,6*R*,8*R*)-4-*tert*-Butoxy-3-methyl-7-methylene-9,10-dioxa-tricyclo[4.3.1.0^{3,8}]decane 28. White solid; mp: 54–55 °C (heptane); $[\alpha]_D^{20} = -27$ (c 0.5, $CHCl_3$); IR (film): $\nu = 2974$, 2868, 1457, 1362, 1231, 1136, 1076, 974, 896, 761 cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 1.11$ (s, 9H), 1.30 (s, 3H), 1.79 (dd, $J = 3.8$, 12.8 Hz, 1H), 1.97 (dd, $J = 6.2$, 15.4 Hz, 1H), 2.09 (d, $J = 12.8$ Hz, 1H), 2.52 (dd, $J = 6.2$, 15.4 Hz, 1H), 3.74 (d, $J = 6.1$ Hz, 1H), 4.25 (d, $J = 6.2$ Hz, 1H), 4.41 (d, $J = 6.1$ Hz, 1H), 4.81 (s, 1H), 4.86 (s, 1H), 5.43 (d, $J = 3.8$ Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 25.1$, 27.5 (3C), 41.1, 44.5, 45.6, 69.5, 72.2, 72.4, 84.5, 98.9, 104.5, 143.5; ESIMS (MeOH): 261.1 ([M+Na]$^+$, 20); HRESIMS: calcd for $C_{14}H_{22}O_3Na$ m/z 261.1467, found: 261.1447; Anal. Calcd for $C_{14}H_{22}O_3$ (238.32): C, 70.56; H, 9.30. Found: C, 69.93; H, 9.31.

X-ray data for **28**: CCDC deposited number: CCDC 620079. A needle of $0.30 \times 0.125 \times 0.125$ mm was used for data collection. Empirical formula $C_{14}H_{22}O_3$, $M = 238.32$, $T = 293$ K. Orthorhombic system, space group $P2_12_12_1$, $Z = 4$, $a = 6.386(4)$, $b = 10.977(6)$, $c = 19.482(12)$ Å, $V = 1365.7$ Å^3, $d_{calc} = 1.159$ g cm^{-3}, $F(000) = 520$, $\mu = 0.080$ mm^{-1}, λ(Mo Kα) = 0.71073 Å. A total of 4496 intensity data was measured with a Nonius Kappa-CCD diffractometer up to $\theta = 20.89°$, reduced to 1427 orthorhombic unique reflections.[1] The structure was solved with program SHELXS86.[2] Refinement of 167 parameters on F^2, using program SHELXL97,[3] leaded to $R_1(F) = 0.0623$, calculated with the 1173 observed reflections having $I \geqslant 2\sigma(I)$ and $wR_2(F^2) = 0.1112$ considering all the 1427 data. Goodness of fit = 1.054. Residual electronic density between −0.11 and 0.11 e Å^3.

4.5.4. PCC oxidation of lactols 30 and 31. To a stirred solution of lactol **30** (anomeric mixture, 35 mg, 0.11 mmol), in dry CH_2Cl_2 (1.3 mL), were added 92 mg of Celite and PCC (126 mg, 0.58 mmol). The reaction mixture was stirred at room temperature for 1 h, Et_2O was added, the suspension was applied to Celite column, eluting with further diethyl ether. The solution was concentrated and the residue was purified by silica gel flash chromatography (heptane–EtOAc, 4:1) to give the corresponding lactone **32** (23.3 mg, 71%).

4.5.4.1. ((3a*R*,4*S*,7a*S*)-4-*tert*-Butoxy-3a-methyl-2-oxo-2,3,3a,4,5,7a-hexahydrobenzofuran-7-yl)methyl ethanoate 32. Colorless oil; $[\alpha]_D^{20} = -40$ (c 1.2, $CHCl_3$); IR (film): $\nu = 2974$, 2941, 1782, 1742, 1459, 1364, 1224, 1195, 1153, 1077, 1024, 944, 753, 667 cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 1.08$ (s, 3H), 1.19 (s, 9H), 2.08 (s, 3H), 2.17 (dd, $J = 9.7$, 18.3 Hz, 1H), 2.42 (td, $J = 5.3$, 18.3 Hz, 1H), 2.30 and 2.80 (ABquartet, $J = 17.4$ Hz, 2H), 3.50 (dd, $J = 5.3$, 9.5 Hz, 1H), 4.48 (s, 1H), 4.55 and 4.68 (AB quartet, $J = 12.8$ Hz, 2H), 5.97 (d, $J = 5.6$ Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 16.1$, 21.0, 29.0 (3C), 31.1, 41.2, 42.7, 65.4, 67.2, 74.1, 82.9, 128.3, 131.2, 170.6, 175.6; ESIMS (MeOH + CH_2Cl_2): 319.1 ([M+Na]$^+$, 100); HRESIMS: calcd for $C_{16}H_{24}O_5Na$ m/z 319.1521, found: 319.1509; Anal. Calcd for $C_{16}H_{24}O_5$ (296.16): C, 64.84; H, 8.16. Found: C, 64.24; H, 8.25.

To a stirred solution of lactol **31** (anomeric mixture, 21 mg, 0.07 mmol), in dry CH_2Cl_2 (0.7 mL), were added 55 mg of Celite and PCC (75.4 mg, 0.35 mmol). The reaction mixture was stirred at room temperature for 1 h, and Et_2O added. The suspension was applied to a Celite column, eluting with further diethyl ether. The solution was concentrated and the residue was purified by silica gel flash chromatography (heptane–EtOAc, 2:1) to give the corresponding lactone **33** (13.6 mg, 66%).

4.5.4.2. (3a*R*,4*S*,6*S*,7a*S*)-4-*tert*-Butoxy-3a-methyl-7-methylene-2-oxooctahydrobenzofuran-6-yl-ethanoate 33. Colorless oil; $[\alpha]_D^{20} = -32$ (c 0.5, $CHCl_3$); IR (film): $\nu = 2972$, 2936, 1782, 1738, 1367; 1234; 1189, 1023, 1011, 947, 938 cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 1.11$ (s, 3H), 1.21 (s, 9H), 1.85 (m, 1H), 2.02 (ddd, $J = 3.4$, 5.2, 14.1 Hz, 1H), 2.07 (s, 3H), 2.22 and 2.70 (AB quartet, $J = 17.0$ Hz, 2H), 3.85 (dd, $J = 3.4$, 9.9 Hz, 1H), 4.55 (s, 1H), 5.42 (s, 1H), 5.48 (s, 1H), 5.53 (dd, $J = 3.2$, 5.2 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = 17.2$, 21.2, 29.0 (3C), 34.8, 41.5, 45.3, 66.6, 71.7, 74.3, 87.6, 122.1, 137.5, 170.2, 175.7; ESIMS (MeOH + CH_2Cl_2): 319.1 ([M+Na]$^+$, 100); HRESIMS calcd for $C_{16}H_{24}O_5Na$ m/z 319.1521 found: 319.1526; Anal. Calcd for $C_{16}H_{24}O_5$ (296.16): C, 64.84; H, 8.16. Found: C, 65.11; H, 8.15.

4.6. Preparation of homoallylic alcohol 35

Wittig methylenation was carried out on known **34**[15] (160 mg, 0.47 mmol) in dry THF (4 mL) with potassium *tert*-butoxide (295 mg, 2.63 mmol) and methyltriphenylphosphonium bromide (1008 mg, 2.82 mmol) using the general procedure to give, after SiO_2 chromatography (heptane–EtOAc, 4:1), the desired TBS-protected olefin (142 mg, 90%).

4.6.1. ((1*R*,4*R*,5*S*,7*R*)-5-*tert*-Butoxy-4-methyl-2-methylene-bicyclo[2.2.2]octan-7-yloxy)(*tert*-butyl)dimethylsilane. Colorless oil; $[\alpha]_D^{20} = +12$ (c 1.2, $CHCl_3$); IR (film): $\nu = 2970$, 2950, 2928, 2856, 1362, 1063, 1042, 869, 833, 774 cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 0.04$ (s, 3H), 0.05 (s, 3H), 0.83 (s, 3H), 0.91 (s, 9H), 1.10 (t, $J = 2.8$ Hz, 1H), 1.15 (s, 9H), 1.31 (dddd, $J = 1.1$, 2.6, 3.7, 12.3 Hz, 1H), 1.62 (ddd, $J = 1.8$, 3.6, 16.6 Hz, 1H), 1.75 (dd, $J = 8.9$, 14.1 Hz, 1H), 2.18 (dd, $J = 3.2$, 6.4 Hz, 1H), 2.42 (ddd,

$J = 3.2$, 9.8, 12.9 Hz, 1H), 2.51 (ddd, $J = 2.7$, 5.4, 16.6 Hz, 1H), 3.39 (ddd, $J = 1.6$, 3.6, 9.1 Hz, 1H), 3.77 (ddd, $J = 2.6$, 5.2, 6.2 Hz, 1H), 4.66 (dd, $J = 2.0$, 4.1 Hz, 1H), 4.81 (dd, $J = 2.2$, 4.4 Hz, 1H); ^{13}C NMR (125 MHz): $\delta = -4.8$, -4.7, 18.1, 24.1, 25.9 (3C), 28.8 (3C), 33.4, 34.5, 35.5, 44.7, 45.2, 69.3, 70.9, 72.5, 106.5, 149.9; ESIMS (MeOH): 361.2 ([M+Na]$^+$, 100); HRESIMS: calcd for $C_{20}H_{38}O_2SiNa$ m/z 361.2539, found: 361.2564; Anal. Calcd for $C_{20}H_{38}O_2Si$ (338.26): C, 70.94; H, 9.45. Found: C, 71.56; H, 10.55.

Fluoride deprotection was carried out on the TBS-protected intermediate thus obtained (120 mg, 0.35 mmol) using the general procedure (1 h, 60 °C) to give, after SiO_2 chromatography (heptane–EtOAc, 1:1), **35** (68 mg, 86%).

4.6.2. (1*R*,2*R*,4*R*,5*S*)-5-*tert*-Butoxy-4-methyl-7-methylenebicyclo[2.2.2]octan-2-ol 35. Colorless oil; $[\alpha]_D^{20} = +42$ (c 1.1, $CHCl_3$); IR (film): $\nu = 3340$, 2972, 2927, 1462, 1387, 1362, 1305, 1252, 1227, 1192, 1167, 1131, 1091, 1068, 1049, 1022, 988, 874, 754 cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 0.75$ (s, 3H), 0.99 (t, $J = 2.9$ Hz, 1H), 1.04 (s, 9H), 1.27 (dddd, $J = 1.2$, 2.5, 5.1, 13.7 Hz, 1H), 1.53 (ddd, $J = 1.7$, 3.6, 17.5 Hz, 1H), 1.67 (br s, 1H), 1.73 (dd, $J = 9.3$, 14.4 Hz, 1H), 2.16 (dd, $J = 3.2$, 6.2 Hz, 1H), 2.23 (ddd, $J = 3.2$, 9.4, 13.5 Hz, 1H), 2.42 (ddd, $J = 2.9$, 5.6, 17.5 Hz, 1H), 3.29 (ddd, $J = 1.6$, 3.6, 9.1 Hz, 1H), 3.82 (tdd, $J = 1.1$, 3.6, 9.3 Hz, 1H), 4.57 (dd, $J = 2.0$, 4.1 Hz, 1H), 4.71 (dd, $J = 2.2$, 4.4 Hz, 1H); ^{13}C NMR (75 MHz): $\delta = 24.0$, 28.8 (3C), 33.2, 34.1, 35.3, 43.8, 44.5, 68.9, 70.8, 72.7, 106.9, 149.1; ESIMS (MeOH): 247.2 ([M+Na]$^+$, 100); HRESIMS: calcd for $C_{14}H_{24}O_2Na$ m/z 247.1674 found: 247.1673; Anal. Calcd for $C_{14}H_{24}O_2$ (224.17): C, 74.95; H, 10.78. Found: C, 75.26; H 10.57.

4.7. Preparation and oxidative cleavage of diol 36b

Proceeding as above, treatment of **38** (100 mg, 0.2 mmol) with allylmagnesium bromide (1.0 M in ether, 0.8 mL, 0.8 mmol) in dry THF (5 mL) for 1 h, furnished, after chromatography (SiO_2, heptane–EtOAc, 95:5), **36a** (98 mg, 90%).

4.7.1. (1*R*,5*R*,6*R*,7a*S*)-1-Allyl-5,6-bis(*tert*-butyldimethylsilyloxy)-7a-((methoxymethoxy)methyl)-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-ol 36a. Characterized as a diastereomeric mixture, colorless oil; IR (film): $\nu = 3351$, 1638, 1435, 1373, 1300, 1270, 1181, 1110, 1030, 1005, 880, 860, 834, 773 cm^{-1}; ESIMS (MeOH): 535.3 ([M+Na]$^+$, 100); HRESIMS: calcd for $C_{27}H_{52}O_5Si_2Na$ m/z 535.3251, found 535.3210; Anal. Calcd for $C_{27}H_{52}O_5Si_2$ (512.34): C, 63.23; H, 10.22, Found: C, 62,98; H, 9.95.

Fluoride deprotection of **36a** (90 mg, 0.17 mmol) using the general procedure (1 h, 60 °C) afforded after chromatography (heptane–EtOAc, 2:1), **36b** (42 mg, 87%).

4.7.2. (1*R*,5*R*,6*R*,7a*S*)-1-Allyl-7a-((methoxymethoxy)-methyl)-2,3,5,6,7,7a-hexahydro-1*H*-indene-1,5,6-triol 36b. Characterized as a diastereomeric mixture, colorless oil; IR (film): $\nu = 3332$, 3318, 1430, 1353, 1300, 1260, 1111, 1014, 997, 910 cm^{-1}; ESIMS (MeOH): 307.1 ([M+Na]$^+$, 100); HRESIMS: calcd for $C_{15}H_{24}O_5Na$ m/z 307.1521, found 307.1517; Anal. Calcd for $C_{15}H_{24}O_5$ (284.16): C, 63.36; H, 8.51. Found: C, 63.10; H, 8.13.

Placed in a flame dried flask, **36b** (40 mg, 0.14 mmol) and $Pb(OAc)_4$ (149 mg, 0.34 mmol) were vacuumed, flashed with argon and cooled to 0 °C. 2 mL of toluene were added, and the ice bath removed soon after; the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with Et_2O and filtered through Celite. The filtrate was concentrated and purified by SiO_2 flash column chromatography (heptane–EtOAc, 1:1 as eluent) to afford **37** (29.8 mg, 72%).

4.8. Domino product 37

Colorless oil; $[\alpha]_D^{20} = -30$ (c 0.7, $CHCl_3$); IR (film): $\nu = 3491$, 2961, 2884, 2360, 2334, 1738, 1367, 1243, 1131, 1088, 980, 939, 924, 785 cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 1.75$ (dd, $J = 2.7$, 12.2 Hz, 1H), 1.90 (m, 1H), 1.95 (dd, $J = 6.5$, 12.3, Hz, 1H), 2.01 (ddd, $J = 5.7$, 11.2, 17.2 Hz, 2H), 2.09 (d, $J = 2.9$ Hz, 1H), 2.12 (s, 3H), 2.33 (dq, $J = 7.5$, 14.2 Hz, 2H), 3.81 (d, $J = 9.1$ Hz, 1H), 4.12 (s, 1H), 4.52 (d, $J = 9.1$ Hz, 1H), 5.10 (qd, $J = 1.7$, 17.0, 1H), 5.14 (dd, $J = 2.0$, 10.2 Hz, 1H), 5.73 (d, $J = 2.8$ Hz, 1H), 5.77 (m, 1H), 5.92 (s, 1H); ^{13}C NMR (125 MHz): $\delta = 21.3$, 31.0, 40.2, 41.8, 42.8, 63.5, 75.4, 80.1, 80.9, 93.2, 102.0, 102.1, 119.9, 132.9, 169.8; ESIMS (MeOH): 319.1 ([M+Na]$^+$, 100); HRESIMS: calcd for $C_{15}H_{20}O_6Na$ m/z 319.1158; found 319.1160; Anal. Calcd for $C_{15}H_{20}O_6$ (296.12): C, 60.80; H, 6.80. Found: C, 59.48; H, 6.64.

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