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Variations of solvent and substitution pattern in $Pb(OAc)_4$ mediated domino reactions

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Abstract—The effect of solvent on oxidative cleavage of the Hajos–Parrish ketone derived hydrindene–diols **1**, and Wieland–Miescher ketone derived octaline–diols **2** with $Pb(OAc)_4$ is presented. Various solvents were screened and compared for these domino reactions. Changing the solvent influenced the reaction rate, product distribution, and chemical yield in the octalin–diol series, while no-effect was detected in the lower homologue hydrindene–diol series. The use of a cheap, readily available chiral carboxylic acid, such as (*S*)-2-acetoxypropionic acid gave diastereomeric mixtures when performed in the racemic series, offering the potential of a chemical resolution. The influence of the substitution pattern on the substrate was also investigated on variously substituted derivatives of **1**. Diols **38** failed to give any detectable amount of IMDA type ring closure, leading only to dialdehyde **39**. For the compounds studied, alkyl or carboxyalkyl substituents on the olefin **41** and **44** led to incomplete cascade transformation due to steric interference caused by the alkyl or acyl groups. The oxidative cleavage of unsaturated diols **46** and **48** derived from monocyclic precursors, used as templates to determine whether any unsaturated 1,2-diol could be regarded as a substrate, is also described.

1. Introduction

Unsaturated bicyclic diol system **1** (**2**) has proven to be a versatile archetype for domino[1] transformations initiated by $Pb(OAc)_4$-mediated oxidative cleavage.[2] The effectiveness of this methodology with regard to the synthesis of biologically active natural products was demonstrated by the large-scale preparation of a conveniently functionalized taxoid C-ring precursor,[3] which in turn was elaborated into the highly oxygenated taxoid ABC tricyclic system.[4] The oxidative cleavage of selected unsaturated bicyclic 1,2-diols, derived from steroidal diols[5] and carvone based octalin–diols[6] proved advantageous for the synthesis of elaborated six- and seven-membered ring compounds. A less toxic version of this process, using only 1 equiv of $Pb(OAc)_4$, was the two-reagent consecutive[7] hetero-domino reaction initiated by iodobenzene diacetate (oxidative/pericyclic transformation), and completed by $Pb(OAc)_4$ (ring expansion) all in one pot.[8] Exploring the solvent effect on the above mentioned transformations, we examined a number of solvents compatible with the reagent used, namely acetonitrile, benzene, trifluorotoluene, toluene, anisole, 1,2-dichlorobenzene, acetone, methylene chloride, chloroform, DME, DMF, THF, acetic acid, and (*S*)-2-acetoxypropionic acid. While focusing on the mechanistic rationale of these interesting domino reactions we briefly examined the scope and limitations of the process through a series of selected examples.

To explain the formation of the products, a series of transformations in a row was proposed (Scheme 1) involving the oxidative cleavage leading to internally linked hetero-diene–hetero-dienophiles **3** or **4**, subsequent IMDA furnishing the half-cascade intermediates **5** or **6**, and finally an oxyplumbation/deplumbation/ring expansion sequence (**i**, **ii**, **iii**) giving rise to either **7**, whose structure was secured by X-ray analysis or **8**. The particularly significant role, which $Pb(OAc)_4$ plays, as a multipurpose reagent, at all stages of these one-pot multistage transformations deserves attention. The use of other oxidants invariably resulted in either an interrupted domino process or simple allylic oxidation.[9]

The structural changes occurring during the conversion of **1** to **7** and **2** to **8** have been corroborated by a computational study where the thermodynamic features for the proposed mechanistic rationale supported the

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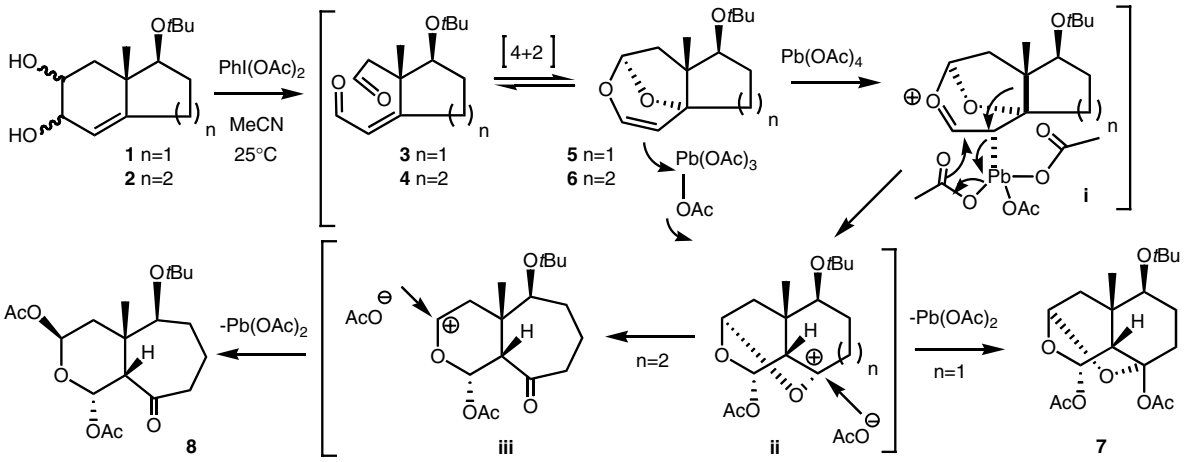


Scheme 1. Proposed mechanism for the consecutive hetero-domino reactions of **1** and **2** via oxidative cleavage/intramolecular 4 + 2 cycloaddition/oxyplumbation/ring expansion.

experimental findings.[10] Herein we report examples showing the scope and limitations, including the question of ring size, nature of the substituents on the bicyclic framework, and the more general question of whether other than bicyclic or steroidal unsaturated 1,2-diols will undergo similar domino reactions.

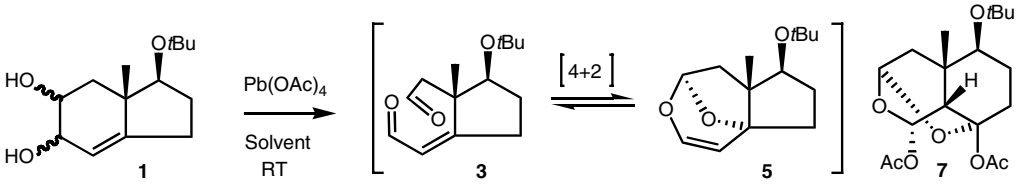
2. Results and discussion

The ready availability of the above cited unsaturated diols, and various derivatives, in their enantiomerically pure forms (both antipodes) provided incentive for analysis of the scope of this domino process. To gain insight into the mechanistic course, it was essential to this study that a series of other solvents and substrates be employed. The Hajos–Parrish and Wieland–Miescher ketones derived unsaturated diol systems, **1** and **2**, respectively, were chosen to start this study because they offered optimum opportunities to examine the process, as the resulting domino products are fully characterized. We first examined a number of solvents, compatible with the reagent used. Then, we focused our attention on a brief scope and limitation study, varying several reaction parameters such as the substitution pattern and the nature of the unsaturated diol.

2.1. The solvent

To examine the solvent effect, we studied the $Pb(OAc)_4$ mediated domino transformations in a dozen solvents (Tables 1 and 2). The choice of solvent resulted partly from a literature survey but equally importantly from consideration of how the cleavage reaction would incorporate into the subsequent process (Scheme 1, mechanistic rationale).

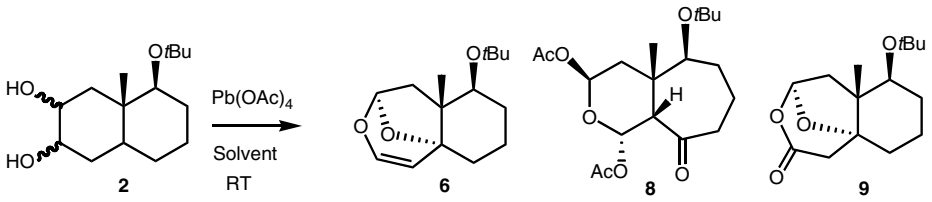
Table 1. Product distribution on oxidation of vicinal unsaturated diols in the hydrindene–diol series using various solvents



Entry	Solvent	% Yield of **3** + **5**	% Yield of **7**
1	MeCN	—	82
2	AcOH	—	88
3	Acetone	—	85
4	Benzene	—	97
5	Toluene	—	85
6	Trifluorotoluene	—	92
7	Anisole	—	97
8	1,2-Dichlorobenzene	—	89
9	$CHCl_3$	—	86
10	CH_2Cl_2	—	84
11	THF	**3** ⇌ **5** only	—
12	DMF	**3** ⇌ **5** only	—
13	DME	—	78

Conditions: 2.4 equiv of $Pb(OAc)_4$, solvent (5 mL/mmol) at room temperature for 20 h.

Table 2. Product distribution on oxidation of vicinal unsaturated diols in the octaline–diol series using various solvents



2 6 8 9

Entry	Solvent	Time (h)	Yield (%)		
			6	**8**	**9**
1	MeCN	48	25	60	<5
2	AcOH	15	5	68	11
3	Acetone	45	64	9	5
4	Benzene	78	63	24	12
5	Toluene	78	68	10	—
6	Trifluorotoluene	78	68	12	—
7	Anisol	29	57	11	5
8	1,2-Dichlorobenzene	50	66	12	22
9	$CHCl_3$	50	40	30	10
10	CH_2Cl_2	45	30	31	10
11	THF	48	98	—	—
12	DMF	24	40	—	—
13	DME	48	55	3	—

Conditions: 2.4 equiv of $Pb(OAc)_4$, solvent (5 mL/mmol) at room temperature.

2.1.1. Solvent variations in the Hajos–Parrish series. In the hydrindene–diol series **1**, the initially formed cyclic ene–acetal **5** (the half-cascade intermediate) was not isolable in most cases but observed by NMR (in equilibrium with the ring opened dialdehyde **3**). The equilibrium mixture underwent oxymetalation and subsequent ring opening upon addition of a second equivalent of $Pb(OAc)_4$, to give the ring-enlarged compound **7**. It is yet unclear whether oxyplumbation/ring-expansion/acetoxylation occur simultaneously[11] through the postulated intermediate **i** (with intramolecular assistance to ring expansion) or in a stepwise manner via **ii** (Scheme 1).

Changing the solvent in the hydrindene–diol series showed only marginal effects on the reaction rate and chemical yield, while in two solvents (entries 11 and 12) the process was interrupted in the half-cascade stage. For the solvents listed in entries 1–10 (Table 1), the half-cascade intermediate **5** was obtained in equilibrium with its open counterpart **3** if only 1 equiv of $Pb(OAc)_4$ was employed. Upon addition of one more equivalent, even after long-time conservation of the equilibrium mixture in solution, the process was completed with the formation of **7**. As can be seen from Table 1, this domino reaction works well not only in acetonitrile (82% yield, 95% average yield per transformation) but also in many other solvents. The optimal conditions employed 2.4 equiv of commercial $Pb(OAc)_4$ (used as supplied commercially, contains acetic acid in ca. 5–10%), room temperature stirring in various solvents. High isolated yields (>82%) of full-cascade product **7** are obtained in entries 1–10 at room temperature with reaction times of 12–15 h, whatever the solvent is. With optimum conditions established, the oxidative cleavage of unsaturated 1,2-diols **1** was examined and results are given in Table 1. The reaction works very well in benzene (97%), toluene (85%), TFT (92%), CH_2Cl_2 (84%), anisol (97%), chloroform (86%), acetone (85%), but less so in THF or DMF. Utilization of an excess of $Pb(OAc)_4$ was beneficial to the process. The use of as much as 5 equiv of the oxidant rather than the theoretical 2 equiv did not increase the yield, although shortened significantly the reaction time (the reaction was completed in less than 5 h). The solvent profile study in hydrindene–diol series revealed that a wide range of solvents can be employed with no evidence of significant alteration in the product composition.

2.1.2. Solvent variations in the Wieland–Miescher series. The effect of solvent was then investigated in the reaction of **2** (octalin–diol series) with $Pb(OAc)_4$. The choice of solvent was found to be important in these series where reaction rates varied depending upon the nature of the solvent used. A brief study of the reaction conditions with $Pb(OAc)_4$ established that, acetic acid is the most effective solvent. Unsurprisingly, we have a faster cascade in acetic acid than in benzene. While most of the domino reactions took approximately 50 h to complete in MeCN, PhH, PhMe, $CHCl_3$, CH_2Cl_2 it only required 15 h to **2** to be converted into ring-expanded **8**, cyclic ene–acetal **6**, and the corresponding lactone **9**. The ring-expanded fused bicycle **8**, where a seven-membered ring is fused to an α,α′-functionalized tetrahydropyran ring, was not always the major component of the reaction crude although the half-cascade intermediate **6** can be cleanly recycled to yield slightly higher yields of **8**, compared to the yields obtained via the unsaturated diols **2**. Changing to DME, DMF, or THF as solvent was ineffective in promoting the ring expansion step of the domino process. The reaction sequence can be monitored by TLC with all intermediates possessing distinct R_f values. The results of solvent effect on the yields, reaction time and on product distribution in the octaline–diol series are summarized in Table 2.

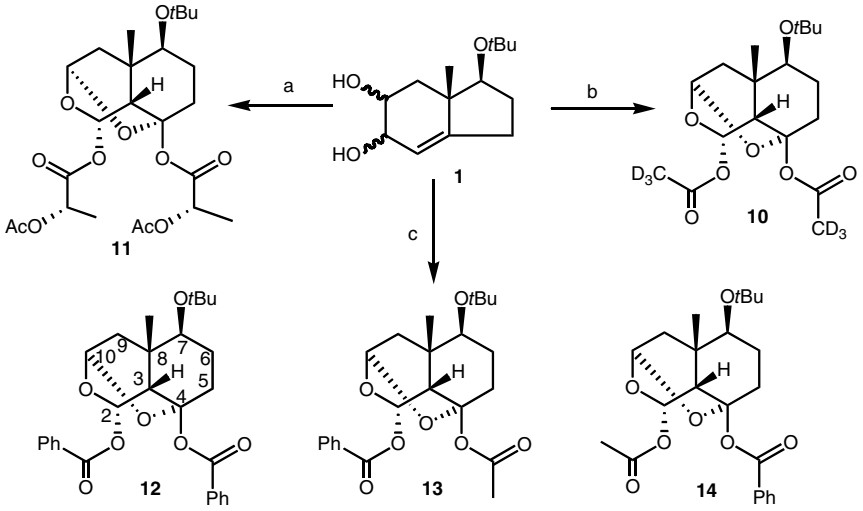
In these series, the rate increases dramatically with carboxylic solvents (vide infra) and also with increased amounts of the oxidant. The best isolated yields of ring-enlarged product **8** are obtained in carboxylic solvents at room temperature with reaction times of 12–15 h. When the reaction was attempted at reflux, extensive degradation was observed.

2.1.3. Other carboxylic species used as solvent or co-solvent. We elected to use a solid achiral carboxylic acid, namely benzoic acid, to investigate (and compare to) practical aspects of ligand exchange and a chiral-liquid carboxylic acid to study the feasibility of a domino process allowing for resolution. Previously[12] we reported preliminary details on the applicability of $Pb(OAc)_4$ mediated hetero-domino transformations in chiral solvents, compatible with the reagent. Lead(IV) acetate undergoes a rapid ligand exchange with carboxylic acids and several lead(IV) carboxylates can be easily prepared by metathesis of the acetate with the corresponding acid.[13] The synthesis, characterization, and reactivity of a number of lead(IV) carboxylates have been reported by Moloney et al. These authors found that replacement of the acetate ligands of $Pb(OAc)_4$ by other carboxylic functions gives the corresponding lead tetracarboxylates, which resist hydrolysis better than $Pb(OAc)_4$.[14] In their elegant studies concerning the effect of ligands on the structure and reactivity of lead(IV) compounds, they provided a wealth of information, which is of capital importance for the understanding of the chemistry involving lead tetracarboxylates.[15]

(*S*)-2-Acetoxypropionic acid was found to be an optimal solvent for this process as it is liquid, it boils much higher than acetic acid and it is easy to prepare on a large scale from commercially available inexpensive lactic acid. We found that enantiomerically pure **1** underwent domino transformations when treated with 2.4 equiv of $Pb(OAc)_4$ in (*S*)-2-acetoxypropionic acid[16] under reduced pressure, in less than 10 h at room temperature, to give **11** in 87% isolated yield. Taking into account the high level of molecular complexity attained in a one-pot transformation, the yield is remarkably high (the only loss appeared to be due to the work-up conditions). The way we proceeded is different from the one used in the literature. Our purpose was to test the synthetic viability of just mixing selected carboxylic acids with $Pb(OAc)_4$ and the unsaturated diols, without caring about completion of the ligand exchange or the easy ligand equilibration. Conditions allowing for lead tetrabenzoate formation were chosen because the latter is a widely known reagent,[17] while the tetralactate was targeted for a domino process offering potential for resolution. Deuterium labeled acetic acid, the use of which led to the exclusive formation of CD_3-labeled compounds such as **10**, could help in mechanistic rationale.

Under Rubottom's conditions, **12** can be obtained cleanly, while just mixing the unsaturated diol **1** (1 equiv) with $Pb(OAc)_4$ (2.4 equiv), and benzoic acid (36 equiv) in dichloromethane (co-solvent) and stirring under argon at room temperature, **12** remains by far the major component (65% isolated yield) of a mixture containing also **13** (16%) and **7** (6%), which are easily separable by flash chromatography, while the C-2 OAc/C-4 OBz analog **14** present in small amounts (ca. 3%) could not be obtained pure. The connectivity in the NMR spectrum was confirmed by ^1H–^1H COSY, HMQC, and HMBC experiments. For **13**, the broad proton singlet at δ 6.60 correlated to the methine carbon resonating at δ 92.5 and was assigned H-2. This proton signal showed ^1H–^1H COSY coupling to the broad singlet at δ 3.21, which correlated to the methine carbon at δ 37.6 and was assigned H-3. Long-range hetero-nuclear coupling observed in the HMBC spectrum confirmed the location of the OBz substituent at C-2 and the acetoxy substituent at C-4. Thus, proton H-2 showed diagnostic ^{3}J-HMBC correlations to the C-4 quaternary carbon at δ 105.1 and to the benzoate carbonyl carbon at δ 166.0. Stereochemical assignments for **13** were based on our previous observations (Scheme 2).[18]

As part of the efforts to arrive at the optimal set of reaction parameters and choice of appropriate precursors,



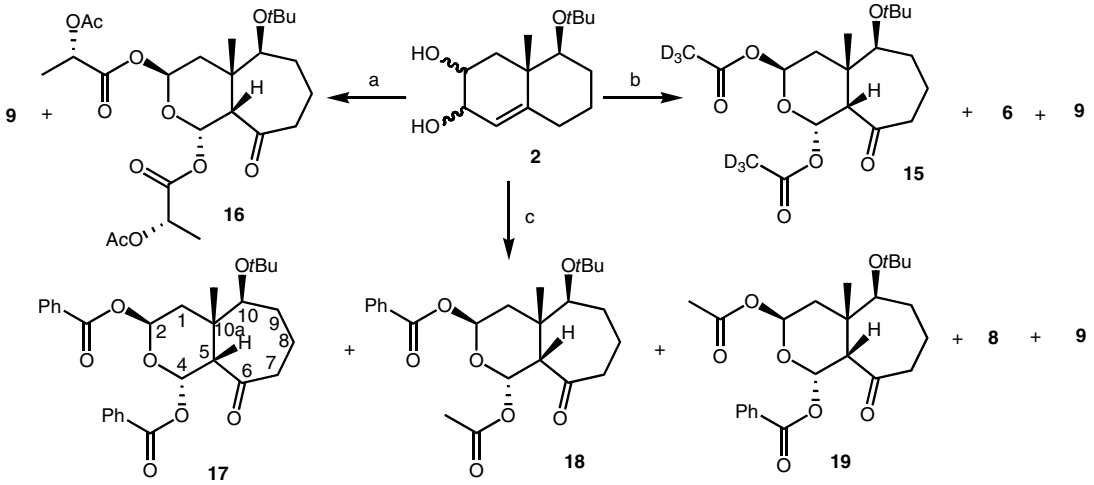
Scheme 2. Reagents and conditions: (a) $Pb(OAc)_4$, (*S*)-2-acetoxypropionic acid, 25 °C; (b) $Pb(OAc)_4$, CD_3COOD, 25 °C; (c) $PhCO_2H$-DCM, 25 °C.

we undertook a spectroscopic study to monitor the formation of chiral lead tetracarboxylates. However, our efforts to fully characterize $Pb(OCOCH(OAc)CH_3)_4$, remained fruitless as we did not succeed in getting molecular ions whatever the ionization technique used (EI, CI, FAB, ESI spectra). Instead, we repeatedly obtained ions corresponding to *m/z* $Pb(OCOCH(OAc)CH_3)_3$ as the highest lead containing mass fragment, indicating either that complete metathesis did not occur (in that case we should be dealing with the M–OAc peak), or impossibility of getting molecular ion. In some cases, as for example, in the progression of transient organolead intermediate **i** (Scheme 1), mechanisms may be drawn formally involving either in situ metathesis or direct carboxylate attack from the solvent and considerable work may be needed to establish the correct mechanism.

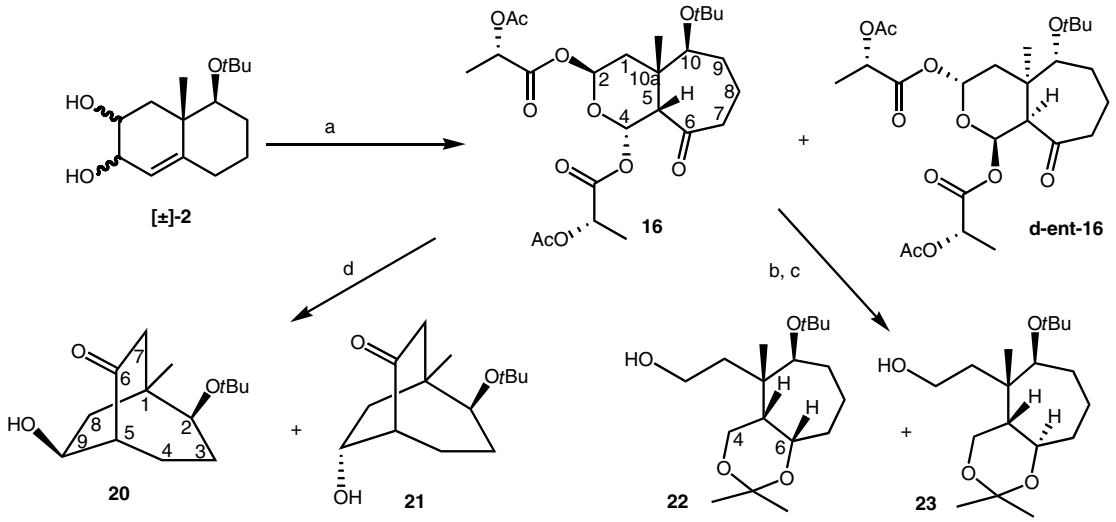
We next carried out the ligand exchange experiments using benzoic acid as well as (*S*)-2-acetoxypropionic acid in the octalin–diol series. Under Rubottom's conditions, **17** can be obtained cleanly upon treatment with freshly prepared $Pb(OBz)_4$, along with half-cascade **6** and lactone **9**. Proceeding as in hydrindene–diol series, simply mixing the unsaturated diol **2** (1 equiv) with $Pb(OAc)_4$ (2.4 equiv), but diminishing the amount of benzoic acid (10 equiv), in dichloromethane (co-solvent), **17** is no more the major component (8% isolated yield) of the crude reaction mixture. The latter contains **18** (15%) and **19** (9%), which are easily separable by flash chromatography, along with **8** (12%) and **9** (28%). The results clearly show that simply mixing the ingredients when using a nonliquid carboxylic acid, which clearly needs a co-solvent, could not be a method of choice for such endeavors. In common with the above products, the gross structures of **18** and **19**, as well as the stereochemistry, was proven in the following manner. Firstly, ^1H–^1H, ^1H–^{13}C correlation spectra allowed a definite assignment of the respective resonances due to the α,α′-functionalized tetrahydropyran part of the molecule. The structure of **18** was apparent from long-range hetero-nuclear coupling observed in the HMBC spectrum between H-2 and the carbonyl carbon at δ 164.7 of OBz, which confirmed the location of this substituent at C-2. The identification of the H-2 proton (δ 6.67) was secured from a COSY experiment from the coupling of H-2 with H-1. Complementary long-range hetero-nuclear couplings between H-4 proton (δ 6.46) and OAc-carbonyl carbon at δ 168.9, as well as H-4/C-6 carbonyl carbon at δ 209.0 confirmed the regiochemical assignment for **18** locating the OBz group at C-2 and OAc group at C-4, as depicted in Scheme 3. Experimental evidence favoring the structure of **19** came again from diagnostic long-range hetero-nuclear couplings observed in the HMBC spectrum. H-2 (δ 6.48) and H-4 (δ 6.60) display ^{3}J-HMBC correlation to the carbonyl carbons resonating at δ 164.6 and 169.4, assigned to the carbonyls of OAc and OBz groups, respectively. The proton doublet H-4 also displayed a ^{3}J-HMBC correlation to the C-6 carbonyl group at δ 209.3. Further evidence for the location of the acetate carbonyl group was obtained from the ^{2}J-HMBC correlation with the methyl protons resonating at δ 2.14.

In the enantiomerically pure octalin–diol series, proceeding as in the lower homologue, bis-lactyloxy acetal **16** and lactone **9** were obtained in 70% and 11% yields, respectively. It was interesting to observe that the use of (*S*)-2-acetoxypropionic acid as solvent gave rise to a dramatic acceleration in these series, furnishing a high isolated yield of **16** after less than 3 h stirring at room temperature. It should be reminded that using acetonitrile, toluene or benzene as solvent the corresponding bis-acetoxy acetal **8** required 50 h of stirring at room temperature for completion.

When performed in the racemic series, the use of a chiral carboxylic acid as solvent gives diastereomeric mixtures, offering the possibility for a resolution. By far the most promising application of these domino reactions would have been the rapid synthesis of complex chiral molecules using inexpensive chiral solvents. It was then of interest to investigate the applicability of this approach for the synthesis of chiral nonracemic cycloheptane derivatives using in situ generated chiral lead



Scheme 3. Reagents and conditions: (a) $Pb(OAc)_4$–(*S*)-2-acetoxypropionic acid, 25 °C; (b) $Pb(OAc)_4$–CD_3CO_2D, MeCN, 25 °C; (c) $Pb(OAc)_4$–$PhCO_2H$–CH_2Cl_2, 25 °C.



Scheme 4. Reagents and conditions: (a) $Pb(OAc)_4$, (*S*)-2-acetoxypropionic acid, 25 °C; (b) $LiAlH_4$, THF, reflux; (c) acetone, H^+; (d) K_2CO_3, MeOH–H_2O, 25 °C.

carboxylates, in a chiral carboxylate rich medium. This would be of great synthetic use, especially for the Wieland–Miescher ketone derived diols of type **2**, as the enantiomeric excess obtained via the proline-catalyzed Robinson annulation remains modest (ca. 63%) and tedious recrystallization processes are required for further enrichment.[19]

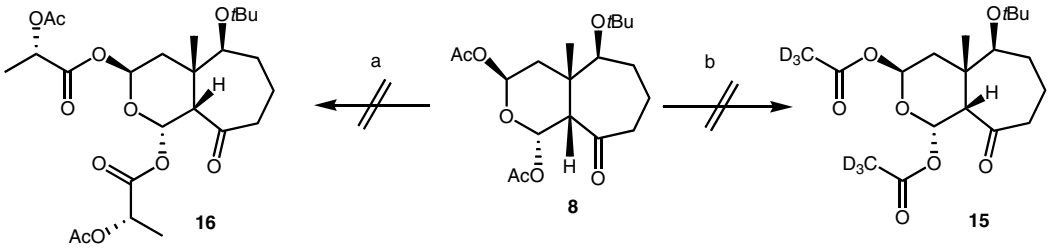
Upon treatment with 2.4 equiv of $Pb(OAc)_4$ in (*S*)-2-acetoxypropionic acid and proceeding as above, racemic diol **2** gave, following chromatographic separation, **16** (36%) and **d-ent-16** (34%) in 70% combined isolated yield, along with lactone **9** (8%, Scheme 4). Reduction of **16** with $LiAlH_4$ in THF afforded the diastereomeric mixture of the corresponding, enantiomerically pure, cycloheptane–triols (1:1 ratio, 91% isolated yield). Selective protection of the C-4, C-6 hydroxy groups (anhydrous acetone, cat. *p*TsOH, in CH_2Cl_2) afforded *cis*-fused acetonide **22** along with the *trans*-fused isomer **23** (85% combined yield). The bicyclo[3.2.2]nonane aldol derivatives **20** and **21** were easily obtained in one step from the *cis*-fused bicyclic derivative **16**, by dissolving the latter in methanol–water (8:1) and stirring the reaction mixture in the presence of K_2CO_3 (nearly 1:1 ratio, 87% yield).

(*S*)-2-Acetoxypropionic acid proved compatible with the domino transformations; the process offers the possibility for a resolution, via chromatographic separation or recrystallization, when performed in the racemic series. So far, these promising results have a shortcoming: only very few cases proved synthetically interesting, allowing for diastereomeric separation via recrystallization. In most cases investigated, chromatographic separation is required, and this can be often tedious.

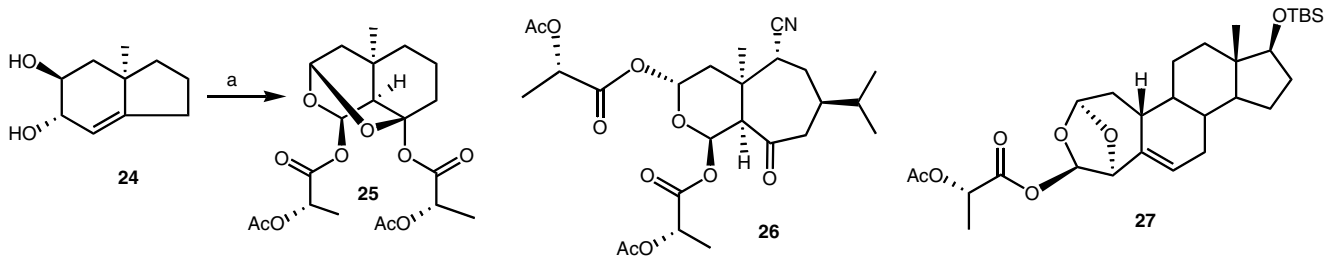
An exchange mechanism that does involve transesterification on stirring **7** or **8** with deuterated acetic acid or with (*S*)-2-acetoxypropionic acid in the presence of $Pb(OAc)_4$ as Lewis acid is ruled out by experiments performed on **8**. The latter was stirred in excess CD_3CO_2D and in (*S*)-2-acetoxypropionic acid at room temperature for 24 h after which the starting material was recovered intact. This clearly eliminates exchange processes during the domino reaction, as neither **15** nor **16** are observed after prolonged treatment (several days) (Scheme 5).

A similar one-pot sequence was successfully employed for the conversion of **24** into the 7-nor taxoid C-ring precursor **25** in 67% isolated yield, but also for the conversion of carvone derived and steroidal unsaturated diols into **26**[6] and **27**,[20] respectively (Scheme 6).

It should be noted however, that using O-acetyl mandelic acid in various solvents failed to produce a comparable yield of the corresponding ring-expanded intermediate, the reaction being sluggish. This observation is in agreement with the statement that the nature



Scheme 5. Reagents and conditions: (a) (*S*)-2-acetoxypropionic acid, $Pb(OAc)_4$, 25 °C, 24 h; (b) CD_3CO_2D, $Pb(OAc)_4$, 25 °C, 24 h.



Scheme 6. Reagents and conditions: (a) (*S*)-2-acetoxypropionic acid, $Pb(OAc)_4$, 25 °C, 24 h.

of ligand could influence the reactivity of the lead carboxylate.

2.1.4. On the diverging behavior in the Hajos–Parrish and Wieland–Miescher ketone series: ring size effects. The size of the ring annulated to the ene–diol portion proved to be an important structural change as it can be seen that the five-membered ring system in the Hajos–Parrish series allows for the fastest and cleanest domino transformations. In brief, neither side product nor a solvent effect was detected when started from hydrindene–diols **1**. In octalin–diol **2** series, on the other hand, much slower reaction, solvent dependence, and side product formation (lactone) was observed. For the hydrindene series, which are of particular interest in taxoid construction, and six-membered ring manufacture in general, only a single product was observed by high-field NMR control of the reaction crude. A simple filtration through a pad of silica gel can be used in these series, while in the higher homologue, the octaline–diol series, a flash chromatography is required for product separation. The influence of ring size in cyclization reactions has been frequently addressed, and we briefly considered its impact on the results presented below. In this regard, we found that there was significant change in product distribution when **1** and **2** were subjected to the $Pb(OAc)_4$-mediated domino process, the ring size affecting the reaction outcome.[21] Side product formation and solvent induced rate increase in the octaline–diol series is partially due to the fused-ring size effect. By visualizing the Chem3D output of the lowest energy conformers (PM3), portrayed in Figure 1 (arbitrary numbering), the effect of ring size in orbital alignment, is obvious. That is smaller ring (Pb–C4–C5–C9 = −179°) in **i**, provides better orbital alignment than larger ring (Pb–C4–C5–C10 = −147°) in **ii**. This can help in rationalizing, in part, the diverging behavior of the organolead intermediates.[10]

Ring expansion requires alignment of C4–Pb bond with the C9–C-5 and C10–C5 bond in transient organolead intermediates **i** and **ii**, respectively (Fig. 1). Increasing the size of the B-ring moiety, significantly decreases the rate of the domino transformations and allows for the production of a side product, the lactone, which is totally absent in the lower homologue series.

2.2. The substitution pattern

2.2.1. Allylic substitution. Practical syntheses of enantiopure taxoid subunits, which possess oxygenation at sites appropriate for further elaboration into various members of the major taxoid families continue to provide challenges to the synthetic chemist. We had

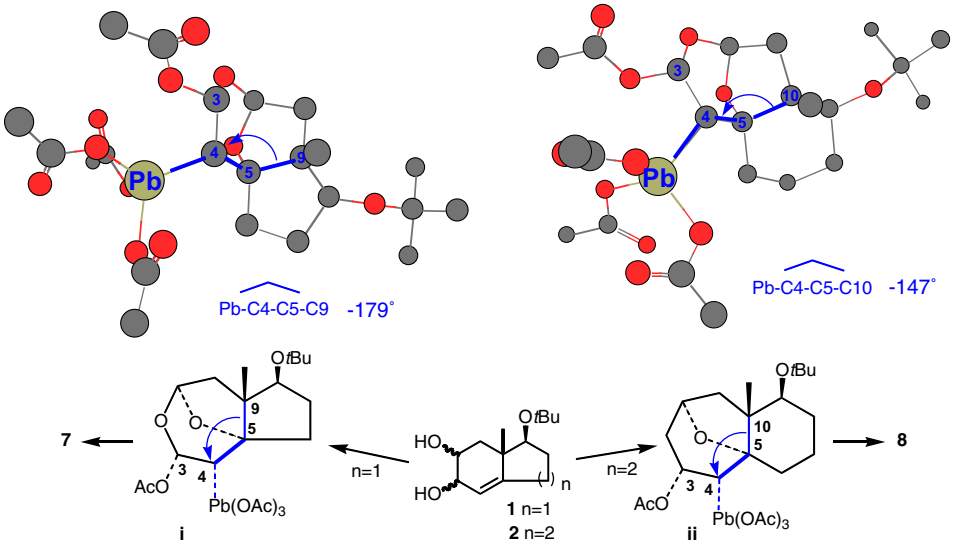


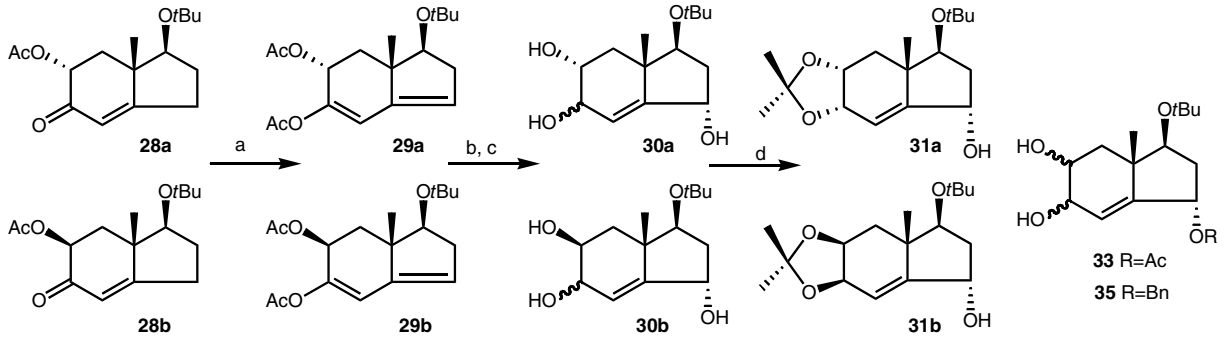
Figure 1. The effectiveness of orbital overlap depends on the initial alignment of relevant bonds (shown in bold blue color). Hydrindene–diol derived transient organolead intermediate **i** can more easily attain the required transition state, than **ii**.

developed an attractive approach that relies on an A+C fragment coupling.[3,4] The route followed, a four-step preparation of homochiral taxoid ABC diterpene framework, represents one of the most straightforward routes to these compounds, is operationally simple and serves to further validate the synthetic utility of our domino reaction. A second generation of substrates, in the Hajos–Parrish diol derived series, should contain a protected α-hydroxy functionality at C-5. These molecules were targeted for an improved taxoid A+C approach, as we hypothesized that an additional functionalization sequence could be inserted prior to the beginning of the linear synthesis, and this hypothesis was tested by preparing C5α-OR **33** and **35**. The hoped for complex hetero-cycles **34** and **36** could prove a challenging synthetic aim due to the presence of the C5α-OH group, necessary for esterification,[22] thus avoiding post-coupling operations. As a consequence, we decided to synthesize these allylic benzyl ethers or acetate esters. The substrates **28a** and **28b** used in this investigation were prepared according to our earlier work.[23] To synthesize the necessary test reactants, we generated the allylic alcohols **30** from the corresponding enone **28** by way of the intermediate dienol acetate species **29** as depicted in Scheme 7.[24]

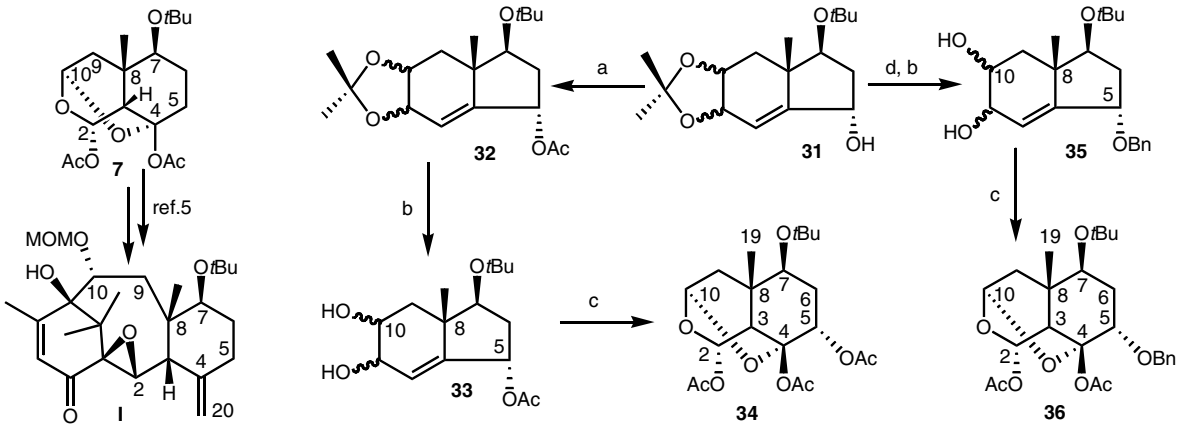
Dienol-acetates were then treated with methyltrioxorhenium (MTO) as catalyst and aqueous hydrogen peroxide as terminal oxidant to give exclusively the C5α-OH epimer (taxoid numbering), and in ca. 60% yield along with recovered starting material (ca. 36%). Complete reduction of the acetoxy–hydroxy enones with $LiAlH_4$ in Et_2O at 0 °C, afforded triols **30**. Diols **33** and **35** were prepared by selective acetonide formation and installation of the appropriate protective group. Finally, removal of the acetonide protection set the stage for the crucial domino reaction. Through a series of experiments on **33** and **35**, the influence of the substitution at C5α-position was investigated. Neither the optimal procedure (room temperature stirring under argon in any of the solvents depicted in Table 1) nor harsh conditions (prolonged reaction time, more equiv of the reagent) delivered the desired ring-expanded target molecule **34** or **36**. In an attempt to force the formation of the ring-expanded, full-cascade intermediate **36**, diol **35** was heated straightforwardly in a preheated oil bath at 100 °C. Although the aforementioned reaction did provide some of the desired ring-expanded product (21% isolated yield), it is far too inefficient to be synthetically useful as the desired compound is accompanied by a substantial loss of weight. The choice of diol **35** (and/or **33**) was dictated by the importance of compounds like **36** (a fully functionalized enantiopure taxoid C-ring unit) in taxane synthesis. If the yields of this domino reaction were improved, it would offer an attractive step-efficient approach to a fully functional taxoid ABC-diterpene framework. Regrettably, this reaction could not be driven to complete conversion without significant degradation of the desired product. Allylic α-hydroxy compound **33** did undergo cascade transformations proceeding as above (preheated oil bath at 100 °C); however the yield (26% of **34**) was substantially reduced relative to 85% yield obtained upon reaction of $Pb(OAc)_4$ and diol **1**. Clearly, despite the high oxygenation degree of **34/35** their synthetic utility is compromised by the significant yield lowering and the dirty nature of the reaction crude, due in part to high temperatures required for the domino transformation to occur (Scheme 8).

For comparison purposes we have also investigated the chemistry of the closely related diols **38** where the allylic functionality has been switched from the C-5α to the C-5β-position. The precursor of the β-OH containing substrate **37a** was obtained by means of a microbial transformation, using *Rhizopus arrhizus* ATCC 11145.[23] The fungus acts as a nearly quantitative oxidizing reagent (>95% isolated yields, large-scale preparations), albeit with poor stereoselectivity (5α-OH:5β-OH, 88:12), and therefore a chromatographic separation is needed. The C-5β hydroxy group was protected as its *t*Bu-ether upon treatment with isobutylene, in the presence of boron trifluoride etherate and phosphoric acid before lithium aluminum hydride reduction, as above.

All efforts to induce the C-5, C-7 bis-O*t*Bu substituted unsaturated diol **38** to undergo a domino transformation (oxidative/pericyclic) failed to generate even a trace of the required cycloadduct **40**, necessary to complete the process (even after prolonged heating, 90–100 °C, for 72 h). These results indicate that cyclic ene–acetal **40** is not formed or, if it is formed, unlike its C5α–OBn and C5α–OAc counterparts, is unreactive toward electrophilic attack of the olefin by the metal. On the other hand, we do know that in these series, except for



Scheme 7. Reagents and conditions: (a) Ac_2O, Py, DMAP, 100 °C; (b) MTO, 30% H_2O_2, Py, CH_2Cl_2, 25 °C; (c) $LiAlH_4$, Et_2O, 0 °C; (d) acetone, *p*TsOH, 25 °C.



Scheme 8. Reagents and conditions: (a) Ac_2O, Py, DMAP, CH_2Cl_2, 0 °C; (b) 12% HCl–THF, 25 °C; (c) $Pb(OAc)_4$, MeCN, 100 °C; (d) BnBr, NaH–DMF.

a few exceptions, the equilibrium mixture persists and upon longer reaction times at high temperatures *Z*/*E* isomerization and decomposition occurs to a considerable extent. Insofar as a mechanistic rationale is concerned, the results obtained are consistent with the sequence of events proposed in Scheme 1. For an organolead derived from **5α–OBn** the conformation required for formation of the C4–Pb bond eclipses the C6α–OBn substitution as portrayed in Figure 2 (Chem3D output). One possible reason for the failure of diol **38** to give the desired ring-expanded product may be due to its crowded β-face on the five-membered ring resulting in a slow cycloaddition step toward **40**, thus allowing for enal isomerization, which in turn prevents the 4+2 step (Schemes 9).

For **38**, intra-molecular Diels–Alder type ring closure to form the tricyclic enol ether **40** should have a considerably higher energy transition state, than ring closure toward **5α–OBn** with an α-substituent at C-5 (taxoid numbering).

2.2.2. Substitution at the double bond. Alongside the work just described we were also pushing forward a vinylically substituted model system as depicted in Scheme 10. To evaluate the part of electronic versus

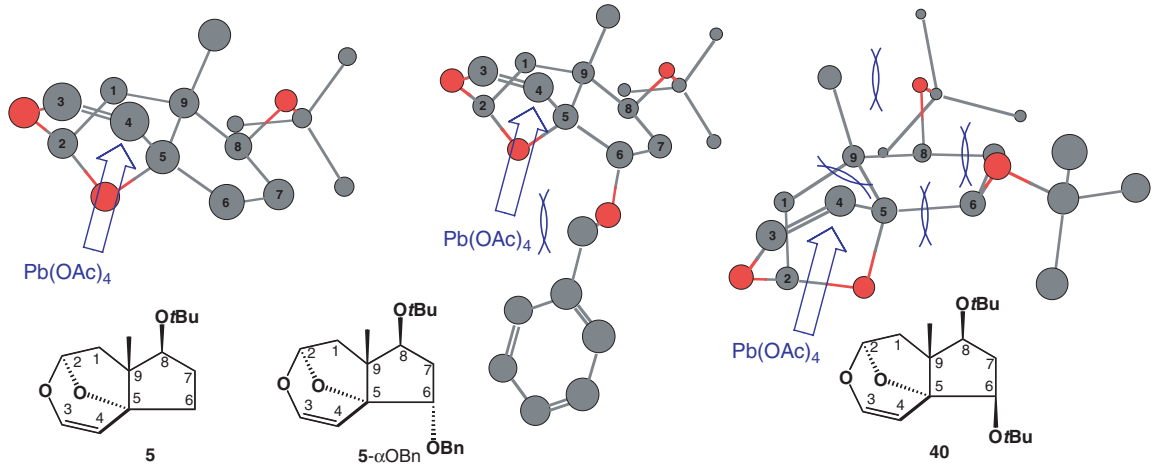
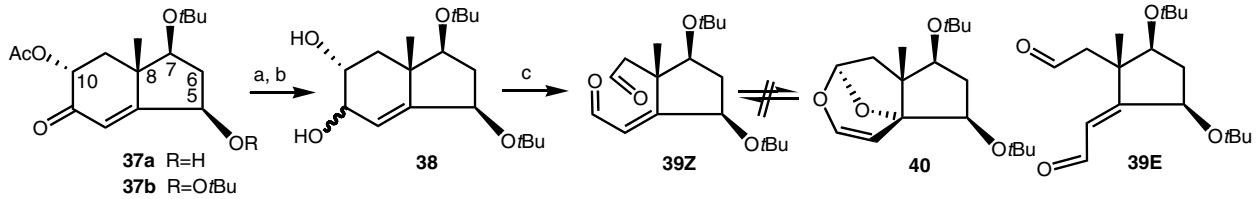
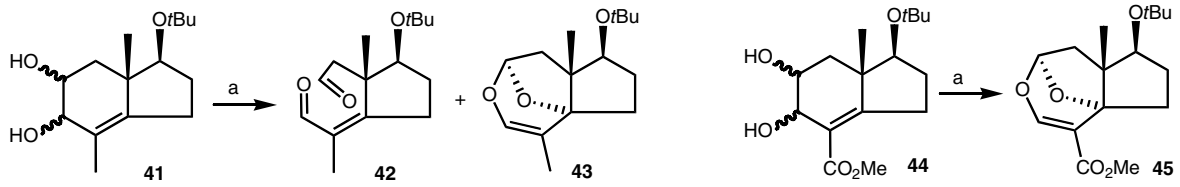


Figure 2. Rationalizing the encountered difficulties and the complete interruption of the domino process: lowest energy conformers of **5**, **5α–OBn**, and **40**.



Scheme 9. Reagents and conditions: (a) isobutylene, $BF_3{\cdot}Et_2O$, H_3PO_4, P_2O_5, −78 °C; (b) $LiAlH_4$–Et_2O, 0 °C; (c) $Pb(OAc)_4$, MeCN, 100 °C.



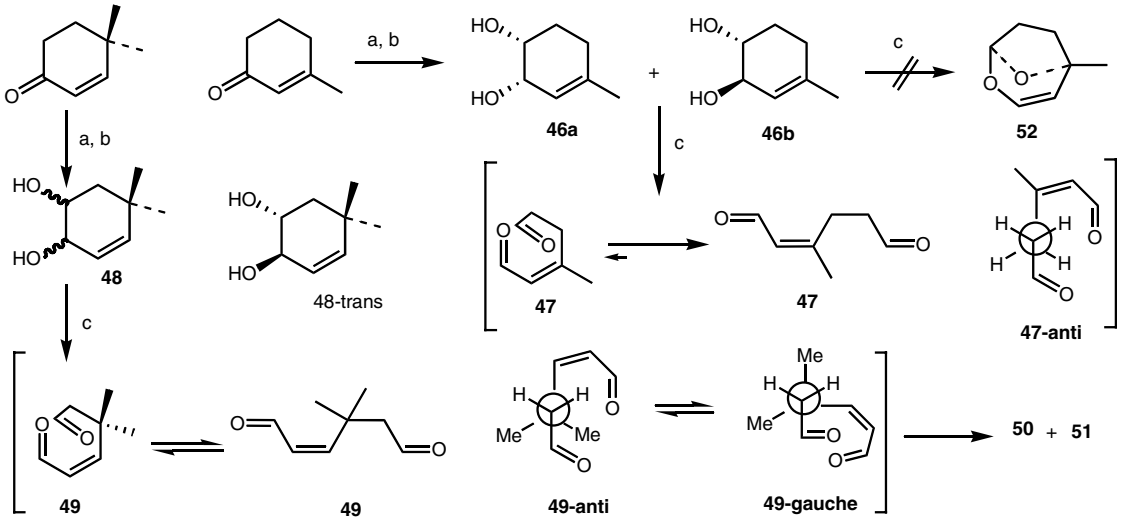
Scheme 10. Reagents and conditions: (a) $Pb(OAc)_4$, MeCN, −25 to 25 °C.

steric factors we elected to examine two additional cases, the methyl and carbomethoxy substituted derivatives, **41** and **44**, containing a donor and an acceptor substituent, respectively, on the olefin, which could have an adverse effect on the process. The requisite diols were prepared from their corresponding acetoxy enones, intermediates in our previous work,[23] by lithium aluminum hydride reduction in ether at 0 °C. When the carbomethoxy substituted **44** was subjected to domino conditions with $Pb(OAc)_4$ an 89% conversion to the Diels–Alder adduct **45** was observed. The failure of the latter to yield the corresponding 'full-cascade' ring-enlarged product when exposed to an excess reagent is postulated to be a combination of the steric and the electron-withdrawing effects of the carbomethoxy group.

When a donor substituent was situated on the olefin, the process again stopped half the way through, on the cyclic ene–acetal stage. Treatment of **41** with 2 equiv of $Pb(OAc)_4$ in MeCN at −25 °C to rt afforded, after chromatography, **42** (72%) and **43** (15%), both unstable on standing. When operating at reflux temperatures and prolonged reaction time, workup provided extensive decomposition products, which could not be characterized. The results indicate that when a methyl group is present as opposed to a carbomethoxy group, the oxidative/pericyclic transformation still proceeds smoothly. The initially formed cycloadduct **43** was isolable and thus characterized by NMR, although decomposed through its opened form **42** on standing. Both **42** and **43** were unstable, while **45** was stable (resonance stabilized) and could be stored for long periods of time. It appeared that donation of electron density to the olefinic linkage was not important, and this suggested that the donor properties of the substituent were less significant then its steric contribution. Both diols, **41** and **44**, failed to give any trace of ring-enlarged product when treated with $Pb(OAc)_4$ in any of the solvents figuring in Table 1, including acetic acid or (*S*)-2-acetoxypropionic acid.

2.3. Pushing the limits: monocyclic ene–diols

To answer the question whether any unsaturated diol can be regarded as a substrate, we decided to perform further experiments and carry out a proper study. To this aim, we reduced the complexity of the requisite template, the unsaturated-1,2 diol, to a simple cyclohexene–diol of type **46**[25] and **48**. Their synthesis began with the corresponding, commercially available, enones and used the acetoxylation ($Pb(OAc)_4$, PhH, reflux)-reduction ($LiAlH_4$, Et_2O, 0 °C) protocol.[26] The limits of the $Pb(OAc)_4$-mediated domino transformations are illustrated with these two examples. In the first case, monocyclic unsaturated diol **46**, only the dialdehyde **47** derived from a simple oxidative cleavage is obtained. Upon treatment with $Pb(OAc)_4$, monocyclic unsaturated diol **46** failed to yield any cyclic ene–acetal (such as **52**, Scheme 11). Instead, **46** furnished only the dialdehyde **47**, which remained essentially unchanged even after 60 h at 75 °C in acetic acid or acetonitrile. All efforts to induce **46** to undergo a full-cascade transformation under a variety of conditions, several solvents, excess of the reagent, and elevated temperatures, failed to generate even a trace of **52** and hence the correspond-



Scheme 11. Reagents and conditions: (a) $Pb(OAc)_4$, PhH, 90 °C, 4 days; (b) $LiAlH_4$–Et_2O, 0 °C; (c) 2.4 equiv $Pb(OAc)_4$, MeCN, −30 to 25 °C.

ing ring-expanded intermediate. In the second case, monocyclic unsaturated diol **48**, containing the *gem*-dimethyl group[27] in the connecting chain, higher population of reactive *syn* rotamers due to methyl substituents on the chain connecting the hetero-diene to the hetero-dienophile, enabled the transformation.[28] The system also possesses ring strain to act as a driving force and full domino transformation occurs to give **50** and **51** in 62% combined yield. No intermediate bicyclic enol ether was isolated, although characterized by NMR. In the absence of a *gem*-dimethyl group the domino reaction does not proceed and this could be attributed to the conformational freedom of the acyclic chain of the resulting dialdehyde product **47** and its reluctance to adopt the required conformation for further reaction.

For the unsaturated ene–diol **48**, the cycloaddition is indeed facilitated by the increased population of the reactive conformer since the anti-form could be essentially iso-energetic to the gauche form, therefore the crucial cyclization to the half-cascade intermediate does occur. The higher population of reactive syn rotamers can be verified graphically via Newman projections portrayed in Scheme 11. The one-pot conversion of **48** to **50** and **51** is best explained by the 3D representation shown in Figure 3.

Domino reactions of **48** conducted in CD_3CO_2D also proceeded smoothly with the deuterium labeled dioxa-bicyclo[2.2.2]octane derivatives **50-d$_6$** and **51-d$_6$**, obtained in 66% isolated yield. The ESI mass spectrum of **50-d$_6$** exhibited a molecular ion at *m*/*z* 287 (M+Na) and *m*/*z* 303 (M+K) consistent with the molecular formula $C_{12}H_{12}D_6O_6$.

The C-3 (C-5) stereochemistry of **50** followed from NOE experiments where irradiation of methyl (δ 1.30) led to enhancements of the H-3 (H-5) (δ 6.43), H-4 (δ 2.12), and H-7 (δ 1.78) signals. Hence these sets of protons must lie on the same face of the molecule confirming the location and the stereochemistry of the 3 α-(5α)-acetoxy group. The minor isomer was assigned as **51** on the basis of diagnostic NOEs for the protons attached to C-3 and C-5 observed upon irradiation of the *gem*-methyl-a and *gem*-methyl-b group signal, respectively. Thus, transannular enhancements were observed between H-3 (δ 6.49) and methyl-a for which the chemical shift was unequivocally established at δ 1.23 on the minor dioxa-bicyclo[2.2.2]octane derivative **51**. Failure to observe an enhancement at the C-5 H (δ 6.53) on irradiation of the C-8 methyl-b (δ 1.40) group provides evidence that they are on opposite faces of the molecule, an observation in agreement with NMR data, where in the ^{1}H and ^{13}C NMR spectra, resonances for all protons and carbons were observed due to the lack of symmetry.

A plausible mechanistic pathway to rationalize these observations is shown in Scheme 12 and Figure 3. The initially formed half-cascade intermediate **i**, the transition structures **ii** and **iii**, as well as the final products **50** and **51** were optimized using the semi-empirical PM3 method (Chem3D drawings, Fig. 3).

As a consequence of the control originating from the geminal methyl group on cyclic ene–acetal **i**, the transient organolead intermediate **ii** has the C6–C5 bond in a *trans* coplanar arrangement to the C4–Pb bond. The resulting geometry gives ring-expansion leading to cation **iii**. Transition state representations illustrating the relationship of these two factors (steric **i** → **ii**, **iii** → **50**, **51** and stereoelectronic **ii** → **iii**) are depicted in Figure 3. Thus, we assume that the *gem*-dimethyl group will first favor an entire α-face attack of the metal on **i**, creating the geometry, which favors ring

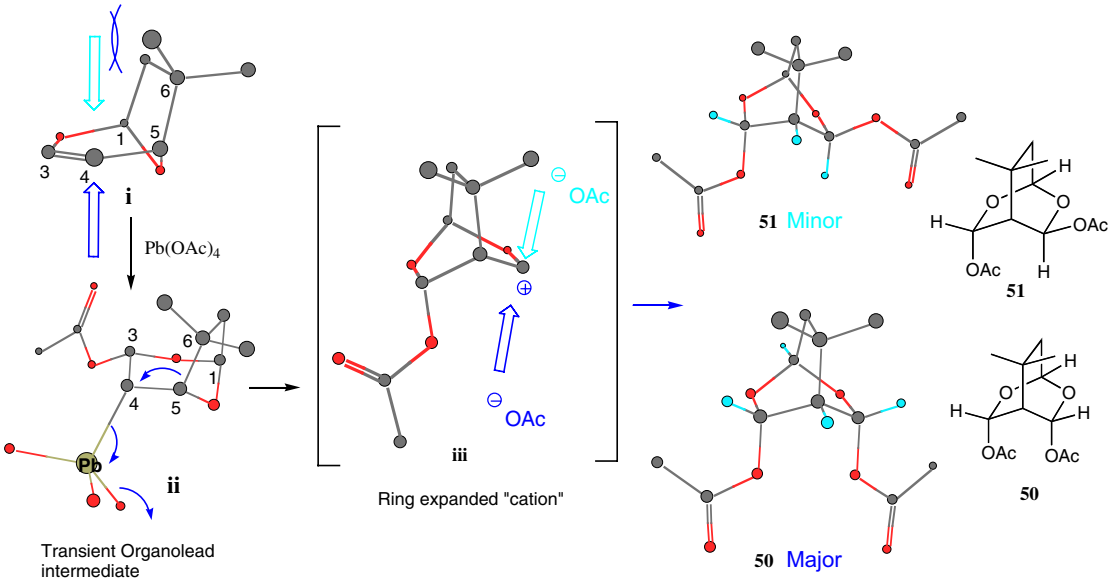
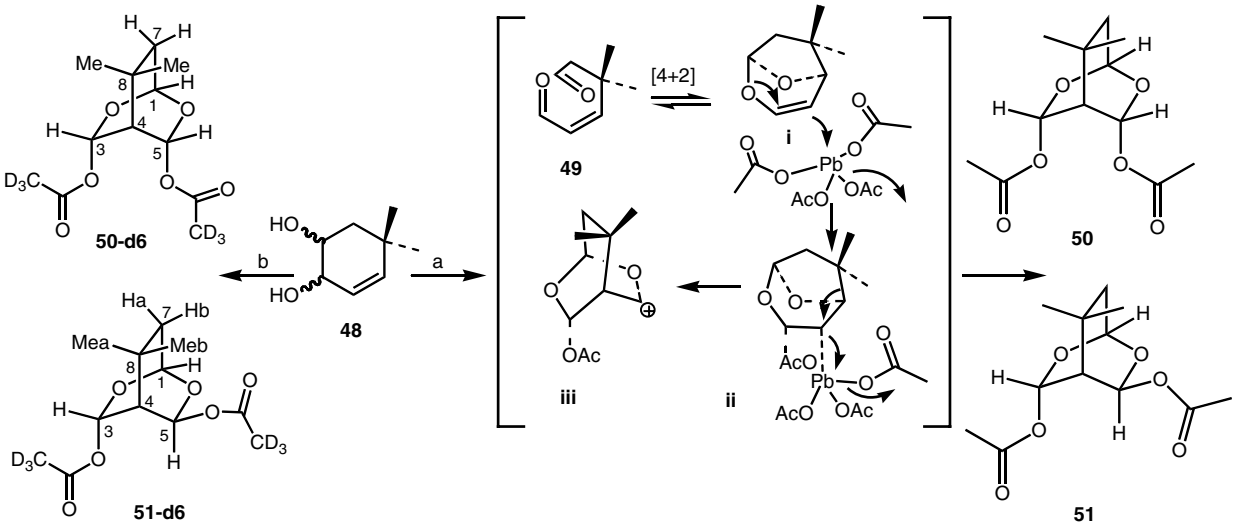


Figure 3. Stereodrawing depicting the source of control for domino transformations starting from diol **48**; possible transition state structures for the likely intermediates **ii** and **iii**.



Scheme 12. Reagents and conditions: (a) 2.4 equiv $Pb(OAc)_4$, MeCN, −30 to 25 °C; (b) 2.4 equiv $Pb(OAc)_4$, CD_3CO_2D, −30 to 25 °C.

expansion, then will ensure a net preference for an α-face attack on cation **iii**.

3. Conclusion

A solvent profile study revealed that a wide range of solvents can be employed. It was demonstrated that changing the solvent influenced the domino reaction rate, product distribution and chemical yield in the Wieland–Miescher series while no appreciable change was observed in the Hajos–Parrish series. The use of acetic acid as solvent, in the octalin–diol series shortens the time required for the ring-expanded compound from 50 h to ca. 15 h. An even more important acceleration was observed when (*S*)-2-acetoxypropionic acid was used (ca. 3 h). The domino reaction is sensitive to alterations made to the substitution pattern. The process successfully accommodated both hydrindene and octaline–diol bicyclic ring systems, **1** and **2**, respectively, while attempts with allylically or vinylically substituted templates met with partial or total failure. This study revealed an important limitation to the method: any unsaturated diol cannot be regarded as a substrate.

4. Experimental

4.1. General

General experimental details were as previously described.[8] NMR spectra were run in $CDCl_3$ and specific rotations were measured in chloroform, unless otherwise noted. ^1H (600/800 MHz) and ^{13}C NMR (150/200 MHz) experiments were carried out on a Bruker Avance DRX-600/800 spectrometer, equipped with triple resonance H/C/N probehead and a three-axis pulsed field gradient module. Gradients were used for the coherence transfer pathway selection in HMBC and HMQC experiments. In the latter, broadband decoupling was performed by using GARP sequence. Experimental evidence favoring the structures investigated came from a comprehensive range of ^1H and ^{13}C NMR data (1 and 2D experiments) and corroborated by spatial proximity studies using mainly the 1D NOEDIFF technique.[29] For all compounds investigated, multiplicities of ^{13}C resonances were assigned by the SEFT technique.[30] 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). '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 acetoxylation of bicyclic enones with $Pb(OAc)_4$. A dry three-necked flask, equipped with a Dean–Stark apparatus was charged with **1** or **2** (12.76 mmol) and $Pb(OAc)_4$ (22.62 g, 51.02 mmol, 4 equiv) put under vacuum, flushed with argon before dry benzene (80 mL) was added and the reaction mixture was heated at 90 °C (oil bath temperature should not exceed 100 °C) for 3 days. After cooling a large volume of ether was added, and the reaction mixture stirred for an additional hour, filtered, and the filtrate washed with brine and water, dried on $MgSO_4$, concentrated, and purified by chromatography on silica with heptane–EtOAc 5:1 as eluent afforded 95% of the desired bicyclic acetoxy enones as a nearly 1:1 epimeric mixture.

4.2.2. General procedure for reduction of acetoxyenones. To a magnetically stirred suspension of $LiAlH_4$ (8.0 mmol, 2.0 equiv) in 50 mL of anhydrous Et_2O, cooled to nearly 0 °C, was added dropwise a solution of the acetoxyenone (4.0 mmol, 1.0 equiv) in anhy-

drous ether (50 mL). After stirring at this temperature for 30–40 min (TLC monitoring) the mixture was diluted with wet Et_2O and treated with a small amount of 6 N NaOH solution (for each 1 g of $LiAlH_4$: 1 mL of water, 1 mL of 6 N NaOH, and 3 mL more water were added). The organic layer was worked up as usual to give, after silica gel chromatography (eluent: heptane–EtOAc), >95% of the desired diols.

4.2.3. General procedure for domino transformations in the hydrindene–diol series. A dry flask was charged with unsaturated diols **1** (603 mg, 2.42 mmol, diastereomeric mixture) and $Pb(OAc)_4$ (2.57 g, 5.80 mmol, 2.4 equiv) put under vacuum, flushed with argon, and cooled to 0 °C. Solvent (10 mL) was added, the cooling bath removed soon after and the reaction mixture was stirred for 19 h at room temperature (TLC monitoring). Upon completion, the reaction mixture was diluted with Et_2O or EtOAc, filtered through a path of Celite and silica gel, and flash chromatographed using heptane as eluent, to remove most of the solvent, then heptane–Et_2O, 1:1 as eluent to afford pure **7**.

4.2.4. General procedure for domino transformations in the octaline–diol series. A dry flask was charged with unsaturated diols **2** (1.0 mmol) and $Pb(OAc)_4$ (2.4 mmol, 2.4 equiv) vacuumed, flushed with argon, and cooled to 0 °C. Acetic acid (5 mL) was added, the cooling bath removed soon after, and the reaction mixture was stirred for 17 h at room temperature. The mixture was diluted with EtOAc and washed carefully with satd $NaHCO_3$ solution till neutral pH and brine. The organic layer was concentrated under reduced pressure, dried over $MgSO_4$, and purified through flash chromatography using heptane–EtOAc as eluent affording the ring-expanded intermediate **8** as the major component of a mixture of three compounds. The half-cascade **6**, which can be recycled, and the lactone derivative **9**.

For other solvents, see reaction time in Table 2.

4.3. Solvent variations in the Hajos–Parrish series

4.3.1. Domino reactions in labeled solvent: Trideuterium-acetic acid (6*S*)-*tert*-butoxy-(7*S*)-methyl-3-trideuterium-acetoxy-2,10-dioxa-tricyclo[5.3.1.0]undec-(9*S*)-yl ester 10. CD_3COOD (2.5 mL) was added to an evacuated argon flashed mixture of **1** (85 mg, 0.35 mmol, 1 equiv) and $Pb(OAc)_4$ (471 mg, 1.06 mmol, 3 equiv) under argon. The reaction mixture was stirred for 18 h at room temperature (TLC monitoring), then diluted with EtOAc, washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Crude product was chromatographed on silica gel (heptane–EtOAc 3:1 to 1:1) to give 109 mg (85%) of **10**: mp: 142 °C (heptane–ether), $[\alpha]_D^{20} = -14$ (*c* 1.10, $CHCl_3$), IR (film): 2975, 1737, 1464, 1446, 1372, 1322, 1308, 1277, 1250, 1229, 1187, 1171, 1142, 1126, 1099, 1078, 1044, 1025, 977, 962, 911, 850, 831 cm^{-1}. ^1H NMR (250 MHz): 1.21 (9H, s), 1.29 (3H, s), 1.62–1.77 (2H, m), 1.64 (1H, dd, $J = 1.6$, 14.3), 1.77 (1H, dd, $J = 2.6$, 14.3), 1.89 (1H, ddt, $J = 2.3$, 4.8, 14.6), 2.7 (1H, td, $J = 5.0$, 13.0), 3.14 (1H, d, $J = 1.2$), 3.29 (1H, t, $J = 2.5$), 5.32 (1H, dd, $J = 1.5$, 2.4), 6.42 (1H, d, $J = 1.3$). ^{13}C NMR (75 MHz): 21.0 (2C, $J = 19.5$), 25.3, 25.6, 28.3, 28.7 (3C), 36.0, 36.5, 39.5, 72.5, 73.4, 90.6, 92.5, 104.1, 169.1, 169.5. CIMS: 380 ($[M+NH_4]^+$, 47), 317 (18), 300 (100), 297 (23), 52 (41). Anal. Calcd for $C_{18}H_{22}D_6O_7$: C, 59.65; H, 6.11. Found: C, 59.84; H, 5.83.

4.3.2. Domino reactions in chiral solvent

4.3.2.1. (2′*S*)-Acetoxy-propionic acid 3-[(2′*S*)-acetoxy-propionyloxy]-(6*S*)-*tert*-butoxy-(7*S*)-methyl-2,10-dioxa-tricyclo[5.3.1.0]undec-(9*S*)-yl ester 11. (*S*)-2-Acetoxy-propionic acid (8 mL), $Pb(OAc)_4$ (1374 mg, 3.10 mmol), and diol **1** (240 mg, 1.0 mmol) were stirred under vacuum at 25 °C for 18 h (TLC monitoring). Upon completion, the reaction mixture was diluted with Et_2O, washed with water and 15% NaOH, dried over $MgSO_4$, and chromatographed on silica gel (heptane–EtOAc 2:1) gave 436 mg (87%) of **11**: $[\alpha]_D^{20} = -35$ (*c* 1.76, $CHCl_3$). IR (film): 2973, 1750, 1461, 1370, 1236, 1144, 1103, 989 cm^{-1}. ^1H NMR (600 MHz): 1.20 (9H, s), 1.30 (3H, s), 1.54 (3H, d, $J = 7.0$), 1.56 (3H, d, $J = 8.0$), 1.61 (1H, dd, $J = 1.2$, 14.2), 1.68–1.73 (1H, m), 1.75 (1H, dd, $J = 2.6$, 14.2), 1.86–1.93 (1H, m), 2.13 (3H, s), 2.14 (3H, s), 2.16–2.25 (2H, m), 2.69 (1H, s), 3.28 (1H, t, $J = 2.4$), 5.06 (1H, q, $J = 7.1$), 5.12 (1H, q, $J = 7.1$), 5.31 (1H, br s), 6.5 (1H, s). ^{13}C NMR (75 MHz): 16.7, 20.6, 20.7, 25.3, 25.8, 27.8, 28.9 (3C), 36.4, 38.5, 39.7, 68.7, 69.0, 72.6, 73.7, 77.2, 91.8, 92.7, 104.8, 168.4, 170.2, 170.3 (2C). ESIMS (MeOH): 539 ($[MK]^+$, 20), 523 ($[MNa]^+$, 100).

4.3.2.2. (2′*S*)-Acetoxy-propionic acid 9-[(2′*S*)-acetoxy-propionyloxy]-(7*R*)-methyl-2,10-dioxa-tricyclo[5.3.1.0]undec-(3*S*)-yl ester 25. (*S*)-2-Acetoxypropionic acid (10 mL) was added to a mixture of hydrindene–diol **24** (270 mg, 1.60 mmol) and $Pb(OAc)_4$ (1.78 g, 4.01 mmol). The reaction mixture was stirred under vacuum overnight. Dilution with ether and washing with 6 N NaOH solution and brine afforded, after column chromatography using heptane–EtOAc 3:1, 67% of **25**: $[\alpha]_D^{20} = +6$ (*c* 1.41, $CHCl_3$). IR (film): 2942, 1744, 1451, 1373, 1309, 1237, 1177, 1130, 1093, 1068, 1049, 1027, 976, 841 cm^{-1}. ^1H NMR (300 MHz): 1.29 (3H, s), 1.31–1.69 (4H, m), 1.46 (3H, d, $J = 7.0$), 1.55 (3H, d, $J = 7.0$), 1.65 (1H, d, $J = 11.9$), 1.73 (1H, d, $J = 11.9$), 1.83 (1H, dd, $J = 2.7$, 14.0), 1.89–1.98 (1H, m), 2.13 (3H, s), 2.14 (3H, s), 2.55 (1H, s), 5.11 (1H, q, $J = 7.1$), 5.29 (1H, q, $J = 7.1$), 5.30–5.33 (1H, m), 6.40 (1H, s). ^{13}C NMR (75 MHz): 16.8, 17.1, 18.9, 20.5, 20.7, 27.9, 32.0, 33.3, 38.1, 39.6, 42.6, 68.6, 68.8, 91.4, 92.2, 105.1, 169.1, 169.9, 170.3, 170.8. ESIMS (MeOH): 467 ($[MK]^+$, 70), 451 ($[MNa]^+$, 100).

4.3.3. Domino reactions in the presence of benzoic acid in DCM. Dichloromethane (30 mL) was added to a stirring mixture of **1** (340 mg, 1.42 mmol, 1.0 equiv), LTA (1.884 g, 4.25 mmol, 3.0 equiv), and benzoic acid (6300 mg, 51.55 mmol, 36.3 equiv) under argon. The reaction mixture was stirred for 26 h at room temperature (controlled by TLC monitoring), then diluted with DCM, washed with water, brine and $NaHCO_3$, dried

over $MgSO_4$, and concentrated. The reaction crude was chromatographed on silica gel (heptane–EtOAc 3:1 to 1:1) to give 27 mg (6%) of **7**, 437 mg (65%) of **12**, and 93 mg (16%) of **13**.

4.3.3.1. Benzoic acid (9*S*)-benzoyloxy-(6*S*)-*tert*-butoxy-(7*S*)-methyl-2,10-dioxa-tricyclo[5.3.1.0]undec-(3*R*)-yl ester 12. Mp: 195 °C (heptane–ether), $[\alpha]_D^{20} = -14$ (*c* 1.02, $CHCl_3$), IR (film): 3067, 2972, 2664, 2547, 1720, 1692, 1602, 1586, 1452, 1368, 1323, 1295, 1234, 1228, 1222, 1189, 1144, 1110, 1091, 1071, 1047, 1025, 973, 919, 711 cm^{-1}. ^1H NMR (600 MHz): 1.25 (9H, s), 1.41 (3H, s), 1.75–1.83 (3H, m), 1.87 (1H, dd, $J = 2.7$, 14.1), 2.00 (1H, ddt, $J = 2.2$, 4.8, 13.8), 2.90 (1H, dt, $J = 4.8$, 13.3), 3.36 (1H, t, $J = 2.5$), 3.50 (1H, s), 5.45 (1H, t, $J = 1.6$), 6.70 (1H, d, $J = 0.9$), 6.89 (2H, t, $J = 7.7$), 7.28 (3H, m), 7.46 (1H, t, $J = 7.4$), 7.60 (2H, d, $J = 7.7$), 7.99 (2H, d, $J = 7.7$). ^{13}C NMR (150 MHz): 25.2, 25.5, 28.2, 28.6 (3C), 36.2, 37.2, 39.6, 72.5, 73.2, 91.8, 92.4, 104.9, 127.3, 127.8, 128.1, 128.6, 129.2, 129.5, 129.7, 130.9, 132.4, 133.3, 164.6, 165.7, 169.7, 171.2. CIMS: 498 ($[M+NH_4]^+$, 41), 359 (100). Anal. Calcd for $C_{28}H_{32}O_7$: C, 69.98; H, 6.71. Found: C, 70.11; H, 6.71.

4.3.3.2. Benzoic acid (3*R*)-acetoxy-(6*S*)-*tert*-butoxy-(7*S*)-methyl-2,10-dioxa-tricyclo[5.3.1.0]undec-(9*S*)-yl ester 13. Mp: 173–175 °C (heptane–ether), $[\alpha]_D^{20} = -13$ (*c* 0.80, $CHCl_3$), IR (film): 2979, 1729, 1695, 1460, 1370, 1325, 1286, 1185, 1090, 1028, 910, 730 cm^{-1}. ^1H NMR (600 MHz): 1.22 (9H, s), 1.37 (3H, s), 1.66–1.95 (5H, m), 1.91 (3H, s), 2.59 (1H, dt, $J = 4.6$, 13.1, H-5), 3.21 (1H, br s, H-3), 3.32 (1H, t, $J = 2.4$), 5.39 (1H, t, $J = 1.9$, H-10), 6.60 (1H, br s, H-2), 7.48 (2H, t, $J = 7.7$), 7.62 (1H, m), 8.13 (2H, dd, $J = 1.3$, 8.3). ^{13}C NMR (150 MHz): 22.8, 25.4, 25.8, 28.2, 28.8 (3C), 36.2, 37.6, 39.7, 72.7, 73.5, 92.5, 92.7, 104.2, 128.2, 128.3, 129.7, 129.8, 130.0, 133.6, 166.0, 169.5. CIMS: 436 ($[M+NH_4]^+$, 100), 359 (54), 297 (38), 254 (17), 105 (46). Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.77; H, 7.09.

4.4. Solvent variations in the Wieland–Miescher series

4.4.1. Domino reactions in labeled solvent. CD_3COOD (5 mL) was added to mixture of **2** (241 mg, 0.95 mmol, 1 equiv) and $Pb(OAc)_4$ (1.05 g, 2.37 mmol, 2.5 equiv) under argon. The reaction mixture was stirred for 15 h at room temperature (TLC monitoring), then diluted with EtOAc, washed with $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated. Crude product was chromatographed on silica gel (heptane–EtOAc 4:1 to 1:1) to give 12 mg (5%) of **6**, 27.5 mg (11%) of **9**, and 241 mg (68%) of **15**.

4.4.1.1. (5*S*)-*tert*-Butoxy-(6*R*)-methyl-9,12-dioxa-tricyclo[6.3.1.0]dodecan-10-one 9. $[\alpha]_D^{20} = +13$ (*c* 1.38, $CHCl_3$). IR (film): 2980, 2938, 2875, 1757, 1462, 1370, 1223, 1068, 1019, 991, 962, 941, 878, 843 cm^{-1}. ^1H NMR (600 MHz): 1.09 (3H, s), 1.19 (9H, s), 1.15–1.8 (3H, m), 1.32 (1H, ddd, $J = 6.0$ 12.1, 16.6), 1.45 (1H, dd, $J = 15.1$, 18.1), 1.79 (1H, d, $J = 15.1$), 1.88 (1H, br d, $J = 15.1$), 2.48 (1H, d, $J = 18.8$), 2.63 (1H, dd, $J = 5.8$, 15.1), 2.76 (1H, d, $J = 18.8$), 3.28 (1H, dd, $J = 3.5$, 11.4), 5.81 (1H, d, $J = 5.8$). ^{13}C NMR (62.5 MHz): 14.5, 19.4, 29.0, 29.2 (3C), 31.2, 40.3, 47.4, 47.8, 73.3, 74.3, 85.8, 100.9, 168.3. CIMS: 269 ($[MH]^+$, 95), 195 (100), 177 (27), 57 (83). HRCIMS: calcd for $C_{15}H_{24}O_4$ *m/z* 269.1753, found 269.1739.

4.4.1.2. Trideuterium-acetic acid (5*S*)-*tert*-butoxy-(4a*S*)-methyl-9-oxo-3-trideuteriumacetoxy-decahydro-cyclohepta[*c*]pyran-(1*S*)-yl ester 15. Mp: 140 °C (heptane–ether), $[\alpha]_D^{20} = -64$ (*c* 0.92, $CHCl_3$), IR (film): 2973, 2931, 1757, 1714, 1461, 1398, 1363, 1342, 1236, 1173, 1110, 1068, 997, 955, 913, 737 cm^{-1}. ^1H NMR (300 MHz): 1.15 (9H, s), 1.65 (3H, s), 1.50–2.14 (6H, m), 2.42–2.55 (2H, m), 2.93 (1H, d, $J = 3.3$), 3.06 (1H, d, $J = 8.7$), 6.34 (1H, d, $J = 3.4$), 6.39 (1H, dd, $J = 2.0$, 3.7). ^{13}C NMR (75 MHz): 19.7 (2C, $J = 40.2$), 20.3, 22.4, 28.5 (3C), 30.4, 35.0, 37.2, 45.2, 53.6, 73.5, 79.2, 88.2, 91.9, 168.5, 168.7, 208.6. CIMS: 394 ($[M+NH_4]^+$, 100), 331 (18), 314 (36), 118 (13), 105 (27), 88 (27). Anal. Calcd for $C_{19}H_{24}D_6O_7$: C, 60.62; H, 6.43. Found: C, 60.89; H, 6.18.

4.4.2. Domino reactions in the presence of benzoic acid in DCM. Dichloromethane (4 mL) was added to a mixture of **2** (305 mg, 1.21 mmol, 1.0 equiv), LTA (1073 mg, 2.42 mmol, 2.0 equiv), and benzoic acid (1476 mg, 12 mmol, 10 equiv) under argon. The reaction mixture was stirred for 61 h at room temperature (TLC monitoring), then diluted with EtOAc, washed with water and $NaHCO_3$, dried over $MgSO_4$, and concentrated. Crude product was chromatographed on silica gel (toluene–ether 15:1 to 4:1) to give 20 mg (12%) of compound **8**, 92 mg (28%) of lactone **9**, 45 mg (8%) of compound **17**, 47 mg (9%) of compound **19**, 75 mg (15%) of compound **7**.

4.4.2.1. Benzoic acid (5*S*)-*tert*-butoxy-(4a*S*)-methyl-9-oxo-3-benzyloxy-decahydro-cyclohepta[*c*]pyran-(1*S*)-yl ester 17. Mp: 166–168 °C (heptane–ether), $[\alpha]_D^{20} = -21$ (*c* 1.50, $CHCl_3$), IR (film): 2980, 1727, 1606, 1453, 1267, 1174, 1114, 1086, 1064, 950, 911, 736, 649 cm^{-1}. ^1H NMR (600 MHz): 1.17 (9H, s), 1.48 (3H, s), 1.60–2.10 (6H, m), 2.45–2.60 (2H, m), 3.11 (1H, d, $J = 9.0$), 3.16 (1H, d, $J = 3.6$), 6.72 (1H, d, $J = 3.4$), 6.75 (1H, t, $J = 4.1$), 7.42 (2H, t, $J = 7.5$), 7.48 (2H, t, $J = 7.5$), 7.56 (1H, t, $J = 7.5$), 7.59 (1H, t, $J = 7.5$), 7.97 (2H, d, $J = 8.3$), 8.09 (2H, d, $J = 8.3$). ^{13}C NMR (150 MHz): 20.7, 22.9, 28.7 (3C), 30.6, 35.4, 37.6, 45.6, 53.7, 73.9, 80.0, 89.1, 93.3, 128.4 (4C), 128.9 (2C), 129.7 (2C), 129.8 (2C), 133.2, 133.5, 164.4, 164.7, 209.0. CIMS: 512 ($[M+NH_4]^+$, 100), 450 (40), 390 (78), 373 (86). Anal. Calcd for $C_{29}H_{34}O_7$: C, 70.43; H, 6.93. Found: C, 69.92; H, 6.89.

4.4.2.2. Benzoic acid (3*S*)-acetoxy-(5*S*)-*tert*-butoxy-(4a*S*)-methyl-9-oxo-decahydro-cyclohepta[*c*]pyran-(1*S*)-yl ester 19. Mp: 175–177 °C (heptane–ether), $[\alpha]_D^{20} = -47$ (*c* 1.25, $CHCl_3$), IR (film): 2981, 2942, 1729, 1449, 1366, 1265, 1231, 1176, 1108, 1086, 1069, 985, 946, 712 cm^{-1}. ^1H NMR (600 MHz): 1.14 (9H, s), 1.36 (3H, s), 1.55 (1H, dd, $J = 9.2$, 14.0, H-1), 1.65 (1H, m), 1.76 (1H, td, $J = 4.3$, 15.2), 1.85 (1H, d, $J = 14.0$, H-1), 1.96 (1H,

dd, $J = 4.3$, 14.0), 2.04 (1H, m), 2.14 (3H, s), 2.49 (1H, m), 2.51 (1H, dd, $J = 6.50$, 10.6), 3.08 (1H, d, $J = 3.5$, H-5), 3.08 (1H, d, $J = 10.1$, H-10), 6.48 (1H, dd, $J = 1.7$, 4.1, H-2), 6.60 (1H, d, $J = 3.5$, H-4), 7.42 (1H, t, $J = 7.8$), 7.48 (1H, t, $J = 7.8$), 7.59 (1H, dt, $J = 7.8$, 8.0), 7.98 (1H, d, $J = 8.0$), 8.12 (1H, d, $J = 8.0$). ^{13}C NMR (150 MHz): 20.6, 21.2, 22.8, 28.8 (3C), 30.7, 35.3, 37.7, 45.5, 54.0, 73.9, 79.8, 89.1, 92.6, 128.4 (2C), 129.0, 129.8, 130.1, 133.5, 164.6, 169.4, 209.3. CIMS: 450 ($[M+NH_4]^+$, 100), 390 (8), 373 (19), 328 (98), 311 (31), 105 (53). Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.58; H 7.41.

4.4.2.3. Benzoic acid (1*S*)-acetoxy-(5*S*)-*tert*-butoxy-(4a*S*)-methyl-9-oxo-decahydro-cyclohepta[*c*]pyran-(3*S*)-yl ester 18. $[\alpha]_D^{20} = -49$ (*c* 0.75, $CHCl_3$), IR (film): 2977, 2936, 1757, 1722, 1606, 1455, 1396, 1367, 1269, 1228, 1187, 1170, 1112, 1089, 1065, 1048, 1025, 996, 943, 711 cm^{-1}. ^{1}H NMR (600 MHz): 1.15 (9H, s), 1.42 (3H, s), 1.55–2.11 (6H, m), 2.08 (3H, s), 2.40–2.60 (2H, m), 3.01 (1H, d, $J = 3.4$, H-5), 3.07 (1H, d, $J = 8.9$, H-10), 6.46 (1H, d, $J = 3.4$, H-4), 6.67 (1H, dd, $J = 1.8$, 4.1, H-2), 7.44–7.49 (2H, m), 7.56–7.63 (1H, m), 8.04–8.11 (2H, m). ^{13}C NMR (150 MHz) 20.9 (2C), 22.8, 28.8 (3C), 30.7, 35.4, 37.5, 45.5, 53.7, 73.9, 79.8, 88.6, 93.1, 128.4 (2C), 128.9, 129.7 (2C), 133.2, 164.7, 168.9, 209.0. CIMS: 450 ($[M+NH_4]^+$, 75), 390 (100), 373 (26), 328 (27), 311 (27), 105 (19).

4.4.3. Domino reactions in chiral solvent. A dry flask was charged with 700 mg (2.92 mmol) of (±)-**2** and 2.7 g (6.1 mmol) of $Pb(OAc)_4$, vacuumed, flushed with argon and then again vacuumed for 1 h. (*S*)-2-Acetoxy-propionic acid (10 mL) was then added at room temperature and stirring continued for 30 min under argon and an additional 30 min under reduced pressure (ca. 4 mmHg). The reaction mixture was then diluted with ether (200 mL), washed with water (3 × 20 mL), 6 N NaOH (3 × 10 mL), and water again (2 × 20 mL). The organic layer was dried over magnesium sulfate and the solvent evaporated under reduced pressure. The residue was purified on silica gel (toluene–ether 4:1) to yield 536 mg of **16** (36%), 506 mg of **d-ent-16** (34%) along with 62 mg of lactone **9** (8%).

4.4.3.1. (2′*S*)-Acetoxy-propionic acid (1*S*)-[(2′*S*)-acetoxy-propionyloxy]-(5*S*)-*tert*-butoxy-(4a*S*)-methyl-9-oxo-deca hydro-cyclohepta[*c*]pyran-(3*S*)-yl ester 16. $[\alpha]_D^{20} = -80$ (*c* 1.70, $CHCl_3$). IR (film): 2982, 2943, 1746, 1456, 1371, 1345, 1312, 1246, 1187, 1127, 1101, 1062, 1049, 989, 943, 910, 737 cm^{-1}. ^{1}H NMR (600 MHz): 1.14 (9H, s, *t*Bu), 1.30 (3H, s, Me-10a), 1.48 (3H, d, $J = 7.2$), 1.55 (3H, d, $J = 6.7$), 1.62 (1H, m, H-8α), 1.72 (1H, dt, $J = 4.3$, 14.9, H-9α), 1.84 (1H, dd, $J = 1.4$, 14.8, H-1β), 1.88 (1H, dd, $J = 4.2$, 14.8, H-1α), 1.93 (1H, m, H-8β), 2.00 (1H, dq, $J = 2.6$, 14.9, H-9β), 2.08 (3H, s, *Me*CO), 2.11 (3H, s, *Me*CO), 2.42 (1H, m, H-7), 2.54 (1H, m, H-7′), 2.93 (1H, d, $J = 3.4$, H-5), 2.95 (1H, d, $J = 8.9$, H-10), 4.92 (1H, q, $J = 7.2$), 5.08 (1H, q, $J = 7.2$), 6.30 (1H, d, $J = 3.4$, H-4), 6.47 (1H, dd, $J = 1.4$, 3.8, H-2). Diagnostic NOEs: {Me-10a}: H-4, H-1βeq, H-5, H-9βax; {H-4}: H-5, Me-10a; {H-10}: H1αax, H-8α; {H-5}: H-4, H7β, H-9β, Me-10a; {H-9β}: Me-10a, H-5, H-9α (NOE *gem*). ^{13}C NMR (75 MHz): 16.4 (*Me*CH), 16.7 (*Me*CH), 20.1 (Me-10a), 20.5 (*C*H$_3$CO), 20.6 (*C*H$_3$CO), 22.9 (C-8), 28.7 (*t*Bu), 30.5 (C-9), 35.0 (C-1), 37.6 (Cq-10a), 45.5 (C-7), 53.2 (C-5), 68.3 (C*H), 68.4 (C*H), 73.9 (Cq–*t*Bu), 80.0 (C-10), 88.8 (C-4), 93.1 (C-2), 168.8 (2×C, Me*C*O), 170.2 (Me*C*O), 170.4 (Me*C*O), 208.7 (C-6). ESIMS (MeOH): 537 ($[MNa]^+$, 100), 553 ($[MK]^+$, 12), 1051 ($[2MNa]^+$, 20).

4.4.3.2. (2′*S*)-Acetoxy-propionic acid (1*R*)-[(2′*S*)-acetoxy-propionyloxy]-(5*R*)-*tert*-butoxy-(4a*R*)-methyl-9-oxo-deca hydro-cyclohepta[*c*]pyran-(3*R*)-yl ester d-ent-16. $[\alpha]_D^{20} = -4$ (*c* 1.20, $CHCl_3$). IR (film): 2975, 2941, 1747, 1716, 1583, 1455, 1372, 1344, 1303, 1237, 1189, 1174, 1127, 1097, 1049, 994, 941, 736 cm^{-1}. ^{1}H NMR (600 MHz): 1.13 (9H, s), 1.21–2.59 (9H, m), 1.29 (3H, s), 1.49 (3H, d, $J = 6.9$), 1.53 (3H, d, $J = 6.9$), 2.09 (3H, s), 2.13 (3H, s), 2.96 (1H, t, $J = 3.4$), 5.07 (1H, q, $J = 6.9$), 5.18 (1H, q, $J = 6.9$), 6.33 (1H, d, $J = 3.2$), 6.47 (1H, br s). ^{13}C NMR (75 MHz): 16.7, 16.8, 20.5 (3C), 23.1, 28.8 (3C), 30.5, 35.1, 37.4, 45.6, 53.1, 68.5 (2C), 74.0, 80.2, 89.2, 93.7, 168.6, 168.9, 170.1, 170.5, 208.7. CIMS: 532 ($[M+NH_4]^+$, 97), 460 (47), 400 (100), 383 (6).

4.5. One pot fused to bridged ring system interchange: preparation of bicyclo[3.2.2]nonane derivatives 20 and 21

To a stirred solution of **16** (1.0 g, 2.7 mmol) in a mixture of methanol (40 mL) and water (5 mL), was added potassium carbonate (2.1 g, 15 mmol). The resulting mixture was stirred at room temperature for 15 h, diluted with water, and extracted with methylene chloride. Following usual work up the residue was purified by flash chromatography on silica gel affording 550 mg (2.29 mmol, 85%) of a diastereomeric mixture of **20** and **21** in a nearly 1:1 ratio. Elution with ethyl acetate–heptane–methanol (1:1:0.01) allowed separation; higher eluting isomer (2*S*)-*tert*-butoxy-(9*R*)-α-hydroxy-(1*S*)-methyl-bicyclo[3.2.2]nonane-6-one **21**: $[\alpha]_D^{20} = +70$ (*c* 1.12, $CHCl_3$). IR (film): 3422, 2971, 2934, 2871, 1705, 1458, 1387, 1364, 1189, 1057, 1024, 991 cm^{-1}. ^{1}H NMR (400 MHz): 1.02 (3H, s, Me-1), 1.15 (9H, s, *t*Bu), 1.45 (1H, m, H-3αax), 1.55–1.75 (2H, m, H-4), 1.66 (1H, dd, $J = 3.9$, 14.7, H8α), 1.68 (1H, d, $J = 18.7$, H-7β), 1.93 (1H, m, H-4), 2.06 (1H, dd, $J = 9.5$, 14.7, H-8β), 2.07 (1H, m, H-4), 2.60 (1H, m, H-5), 2.63 (1H, dd, $J = 2.6$, 18.7, H-7α), 3.44 (1H, t, $J = 5.7$, H-2), 4.20 (1H, ddd, $J = 3.9$, 6.7, 9.5, H-9). Diagnostic NOEs: {Me-1}: H-8β, H-7α, H-7β, H-2; {H-9}: H-5, H8β; {H-2}: H-8α; {H-5}: H-9, H-4, 4′; {H-8α}: H-2. ^{13}C NMR (75 MHz): 19.8 (CH$_2$), 29.1 (*t*Bu), 29.3 (Me-1), 30.4 (CH$_2$), 37.6 (Cq-1), 41.6 (C-8), 45.2 (C-7), 54.1 (C-5), 66.6 (C-9), 73.2 (Cq–*t*Bu), 77.6 (C-2), 214.6 (C-6). EIMS: 240 ($M^{+\cdot}$, 89), 184 (100), 166 (34), 57 (89). HREIMS: calcd for $C_{14}H_{24}O_3$: *m*/*z* 240.1725, found: 240.1729.

Lower eluting isomer (2*S*)-*tert*-butoxy-(9*S*)-β-hydroxy-(1*S*)-methyl-bicyclo[3.2.2]nonane-6-one **20**: mp 76–78 °C (ether–heptane). $[\alpha]_D^{20} = +92$ (*c* 1.10, $CHCl_3$). IR (film): 3422, 2957, 2871, 1705, 1458, 1392, 1361, 1235,

1192, 1108, 1060, 1024, 991, 895 cm^{-1}. ^1H NMR (400 MHz): 1.03 (3H, s, Me-1), 1.14 (9H, s, *t*Bu), 1.57 (1H, dd, $J = 15.5$, 1.5, H-8β), 1.52–1.62 (3H, m, H-4, 3), 1.75 (2H, m, H-3, 4), 1.97 (1H, d, $J = 18.7$, H-7β), 2.20 (1H, ddd, $J = 2.4$, 7.9, 15.5, H-8α), 2.57 (1H, ddd, $J = 3.1$, 4.7, 4.8, H-5), 2.72 (1H, dd, $J = 2.7$, 18.7, H-7α), 3.39 (1H, dd, $J = 4.2$, 5.1, H-2), 4.26 (1H, ddd, $J = 1.5$, 3.1, 8.0, H-9). Diagnostic NOEs: {Me-1}: H-8β, H-7α, H-7β, H-2; {H-9}: H8α; {H-2}: H-8α; {H-5}: H-4, 4′; {H-8α}: H-2, H-9. ^{13}C NMR (75 MHz): 21.7 (CH_2), 29.1 (*t*Bu), 29.6 (Me-1), 30.5 (CH_2), 36.9 (Cq-1), 41.8 (C-8), 45.1 (C-7), 54.5 (C-5), 69.2 (C-9), 73.1 (Cq–*t*Bu), 76.6 (C-2), 215.5 (C-6). EIMS: 240 ($M^{+\cdot}$, 18), 184 (30), 166 (64), 57 (100). HREIMS: calcd for $C_{14}H_{24}O_3$: *m*/*z* 240.1725, found: 240.1716.

4.6. Reduction of 16 and selective acetonide formation

To a stirred suspension of 500 mg (13.18 mmol, 7.8 equiv) of $LiAlH_4$ in THF (10.0 mL) a solution of 500 mg (1.35 mmol) of **16** in THF (10.0 mL) was added at room temperature. The reaction mixture was then refluxed for 30 min, cooled, quenched with 0.5 mL of water, 0.50 mL of 15% NaOH, 1.5 mL of water, and stirring was continued at room temperature for an additional 1 h. Filtration and concentration under reduced pressure gave a mixture of triols. The latter without purification, was dissolved in acetone (1.0 mL) and methylene chloride (10.0 mL) and 20 mg of *p*TsOH was added. The mixture was stirred at room temperature for 1 h, filtered through aluminum oxide with ethyl acetate, and concentrated under reduced pressure. Rapid filtration on silica gel with a mixture of ethyl acetate–heptane (1:1) gave **22** and **23** (386 mg, 91%) as a diastereomeric mixture in 1:1 ratio. The lower eluting isomer **22** (*cis* acetonide) was precipitated from hexane at room temperature. Pure sample of the higher eluting isomer was obtained by silica gel flash chromatography (elution with methylene chloride–methanol, 98:2). Data for higher eluting isomer 2-[(6*S*)-*tert*-butoxy-2,2,5-trimethyl-octahydro-cyclohepta[1,3]dioxin-(5*S*)-yl]-ethanol **23** (*trans* acetonide): $[\alpha]_D^{20} = +30$ (*c* 1.17, $CHCl_3$), IR (film): 3440, 2976, 2940, 2873, 1462, 1380, 1364, 1268, 1256, 1228, 1190, 1168, 1118, 1085, 1054, 1019, 874, 738 cm^{-1}. ^1H NMR (800 MHz): 0.94 (3H, s), 1.18 (9H, s), 1.35 (3H, s), 1.40 (3H, s), 1.46–1.52 (1H, m), 1.58–1.64 (2H, m), 1.72 (1H, td, $J = 7.5$, 14.0), 1.75–1.89 (5H, m), 2.02 (1H, ddd, $J = 5.6$, 7.8, 9.9), 3.36 (1H, dd, $J = 1.2$, 5.3), 3.73 (2H, dd, $J = 7.9$, 9.7), 3.74 (1H, dd, $J = 5.6$, 7.6), 3.78 (1H, dd, $J = 5.6$, 11.7), 3.84 (1H, ddd, $J = 4.7$, 7.1, 11.7). ^{13}C NMR (200 MHz): 19.8, 21.0, 23.4, 27.9, 29.1 (3C), 29.4, 35.8, 37.4, 40.7, 45.6, 59.5, 60.5, 70.1, 73.4, 76.8, 98.2. EIMS: 314 ($M^{+\cdot}$, 2), 299 (20), 285 (3), 256 (10), 57 (100). HREIMS: calcd for $C_{18}H_{34}O_4$ *m*/*z* 314.2457, found 314.2462. Lower eluting isomer 2-[(6*S*)-*tert*-butoxy-2,2,5-trimethyl-octahydro-cyclohepta[1,3]dioxin-(5*S*)-yl]-ethanol **22** (*cis* acetonide): mp 135–137 °C (hexane), $[\alpha]_D^{20} = +33$ (*c* 0.86, $CHCl_3$), IR ($CHCl_3$): 3440, 2978, 2938, 2882, 1467, 1388, 1366, 1227, 1191, 1099, 1080, 1041, 1024, 983 cm^{-1}. ^1H NMR (800 MHz): 0.98 (3H, s), 1.15 (9H, s), 1.36 (3H, s), 1.37 (3H, s), 1.44–1.49 (1H, m), 1.58–1.71 (3H, m), 1.87–1.91 (1H, m), 2.05 (1H, ddd, $J = 6.1$, 9.4, 14.4), 2.11 (1H, ddd, $J = 5.6$, 9.6, 15.0), 2.15 (1H, td, $J = 7.9$, 14.1), 2.29 (1H, q, $J = 5.5$), 3.47 (1H, dd, $J = 1.7$, 4.8), 3.70 (1H, td, $J = 6.1$, 10.0), 3.79 (1H, dd, $J = 5.4$, 10.2), 3.80 (1H, dd, $J = 6.1$, 11.7), 3.86 (1H, dd, $J = 6.3$, 11.9), 4.19 (1H, ddd, $J = 5.5$, 9.5, 15.0). ^{13}C NMR (200 MHz) 16.8, 21.3, 25.2, 26.3, 29.1 (3C), 33.2, 34.6, 38.3, 38.9, 42.9, 59.4, 61.5, 71.5, 73.0, 76.1, 99.2. EIMS: *m*/*z* 314 ($M^{+\cdot}$, 0.5), 299 (1), 256 (3), 225 (18), 89 (80), 57 (100). Anal: calcd for $C_{18}H_{34}O_4$: C 68.75, H 10.90. Found: C 68.86, H 10.91.

4.7. Preparation and domino reactions of the allylically substituted substrates 33, 35, 37a

Starting from the known C-2β acetoxy enone **28a**, obtained as described in Ref. 23, the required C-6 hydroxylated derivative **30a** was synthesized in four straightforward steps as follows. To a magnetically stirred solution of acetoxy enone **28a** (3.145 g, 7.82 mmol) and DMAP (521 mg, 4.26 mmol) in pyridine (12 mL), acetic anhydride (12 mL, 108 mmol) was added at 0 °C. The reaction mixture was allowed to reach room temperature, then heated at 100 °C for 27 h after what solvent was removed under reduced pressure. Usual work-up gave after silica gel chromatography (using heptane–EtOAc, 8:1 to 3:1 as eluent) 2.39 g (69%) of the desired dienol acetate **29a** along with unreacted starting material (21%).

4.7.1. 5-(Acetoxy)-(1*S*)-*tert*-butoxy-(7a*S*)-methyl-2,6,7,7a-tetrahydro-1*H*-inden-(6*R*)-yl acetate 29a. $[\alpha]_D^{20} = +20$ (*c* 2.42, $CHCl_3$). IR (film): 2975, 2359, 2347, 1759, 1739, 1366, 1239, 1197, 1124, 1087, 1016, 665 cm^{-1}. ^1H NMR (300 MHz): 1.07 (3H, s), 1.17 (9H, s), 1.53 (1H, t, $J = 10.8$), 2.07 (3H, s), 2.11 (3H, s), 2.24 (1H, dd, $J = 6.5$, 11.7), 2.41 (2H, m), 3.84 (1H, t, $J = 7.9$), 5.44 (1H, t, $J = 3.0$), 5.81 (1H, t, $J = 7.5$), 6.02 (1H, d, $J = 1.7$). ^{13}C NMR (75 MHz): 16.5, 20.7, 21.0, 28.6 (3C), 39.0, 39.8, 46.1, 67.8, 72.7, 79.8, 115.1, 122.4, 142.2, 146.2, 168.6, 170.3. TOFESIMS 361 ($[MK]^+$, 100), 345 ($[MNa]^+$, 12).

Starting from **28b** and proceeding as above dienol acetate **29b** was obtained along with recovered starting material.

4.7.2. 5-(Acetoxy)-(1*S*)-*tert*-butoxy-(7a*S*)-methyl-2,6,7,7a-tetrahydro-1*H*-inden-(6*S*)-yl acetate 29b. $[\alpha]_D^{20} = -88$ (*c* 3.09, $CHCl_3$). IR (film): 2973, 2952, 2359, 2349, 1759, 1739, 1366, 1239, 1197, 1122, 1087, 1014, 668 cm^{-1}. ^1H NMR (300 MHz): 1.10 (3H, s), 1.17 (9H, s), 1.80 (1H, dd, $J = 5.4$, 14.6), 2.08 (3H, s), 2.14 (3H, s), 2.40–2.50 (3H, m), 3.78 (1H, t, $J = 8.3$), 5.53 (1H, t, $J = 5.5$), 5.55 (1H, t, $J = 5.4$), 6.14 (1H, s). ^{13}C NMR (75 MHz): 17.2, 20.8, 21.1, 28.6 (3C), 38.8, 39.5, 43.5, 67.1, 72.7, 81.0, 116.8, 123.9, 142.7, 145.6, 169.1, 170.4. TOFESIMS 361 ($[MK]^+$, 100). 345 ($[MNa]^+$, 18). HRESIMS: calcd for $C_{18}H_{26}O_5Na$ *m*/*z* 345.1678, found 345.1674.

Installation of the C-6 hydroxy group was then carried out using methyltrioxorhenium developed by the Herrmann group.[31] To a stirred solution of dienol acetate

29a (1.82 g, 4.09 mmol) in 4.0 mL of CH_2Cl_2, pyridine (0.04 mL, 0.49 mmol), 30% H_2O_2 (0.63 mL, 6.14 mmol), and $MeReO_3$ (5.0 mg, 0.02 mmol) were added and the reaction mixture stirred under argon at room temperature for 26 h. Upon dilution with CH_2Cl_2, and washings with $Na_2S_2O_3$ and brine, the organic layers were dried, concentrated, and chromatographed (SiO_2, heptane–EtOAc, 6:1 to 1:1) to afford 1.21 g (71% yield) of the corresponding 5α-OH derivative as a single epimer, at this position. The allylic α- and β-hydroxy substituent bearing acetoxy enones were described in our earlier publications.[23] Using *m*CPBA as the oxidant (834 mg, 2.9 mmol) in 16 mL of dioxane/phosphate buffer pH = 8 (1:1) at 0 °C, **29a** (468 mg, 1.45 mmol) was oxidized in 70% isolated yield. Standard $LiAlH_4$ reduction using the general procedure afforded the corresponding triol, which was selectively protected as its acetonide (acetone, methylene chloride, *p*TsOH) without purification. Acetonide formation allowed for the isolation of **31a** for characterization purposes.

4.7.3. (7*S*)-*tert*-Butoxy-2,2,7a-trimethyl-5,6,7,7a,8,8a-hexahydro-3a*H*-indeno[5,6-*d*][1,3]dioxol-(5*S*)-ol 31a. $[\alpha]_D^{20} = +92$ (*c* 0.74, $CHCl_3$). IR ($CHCl_3$): 3400, 2975, 2940, 1720, 1452, 1360, 1190, 1090, 1025, 889, 870, 756 cm^{-1}. ^1H NMR (300 MHz): 0.88 (3H, s), 1.16 (9H, s), 1.40 (3H, s), 1.48 (3H, s), 1.87–2.18 (5H, m), 3.71 (1H, t, *J* = 8.7), 4.41 (1H, dt, *J* = 5.7, 11.4), 4.60 (1H, m), 4.67 (1H, br s), 5.91 (1H, dd, *J* = 2.0, 3.2). ^{13}C NMR (75 MHz): 18.0, 25.4, 28.1, 28.6 (3C), 39.4, 42.0, 45.5, 69.3, 71.2, 72.8, 73.0, 77.8, 108.9, 116.7, 156.4.

Starting from **28b** and proceeding as above, **31b** was obtained pure for characterization.

4.7.4. (7*S*)-*tert*-Butoxy-2,2,7a-trimethyl-5,6,7,7a,8,8a-hexahydro-3a*H*-indeno[5,6-*d*][1,3]dioxol-(5*S*)-ol 31b. $[\alpha]_D^{20} = +70$ (*c* 0.90, $CHCl_3$). IR ($CHCl_3$): 3450, 2975, 2940, 1750, 1450, 1380, 1360, 1252, 1200, 1146, 1105, 1040, 990, 904, 848 cm^{-1}. ^1H NMR (300 MHz): 1.12 (3H, s), 1.15 (9H, s), 1.36 (3H, s), 1.44 (3H, s), 1.54 (1H, dd, *J* = 3.4, 14.7), 1.83 (1H, m), 2.08 (1H, m), 2.28 (1H, dd, *J* = 2.3, 14.7), 3.62 (1H, t, *J* = 8.7), 4.47 (1H, dt, *J* = 2.8, 6.0), 4.64 (1H, m), 4.69 (1H, m), 5.74 (1H, dd, *J* = 1.8, 3.6). ^{13}C NMR (75 MHz): 19.1, 25.2, 27.5, 28.6 (3C), 38.6, 41.3, 42.4, 69.5, 72.4, 72.5, 72.9, 79.1, 108.5, 117.8, 153.2.

4.8. Benzylation

Sodium hydride (60% w/w in mineral oil; 53.00 mg, 1.33 mmol) was washed twice with dry hexane under argon atmosphere and the remainder of the hexane removed via syringe and the flask put under vacuum then filled with argon. *N*,*N*-Dimethylformamide (3.0 mL) and isopropylidene–alcohol **31a** (195 mg, 0.66 mmol) were added. After stirring for 0.5 h the reaction mixture was cooled to 0 °C, BnBr (0.125 g, 0.73 mmol) and *N*,*N*-dimethylformamide (1.0 mL) were added, and the mixture was stirred for 20 h. Water and ether were added, the two phases separated and the organic phase was worked-up as usual. Chromatography of the residue (hexane–EtOAc, 1:1) gave the desired benzyl-protected product (252 mg, 99%). ^1H NMR (300 MHz): 0.85 (3H, s), 1.14 (9H, s), 1.25 (1H, m), 1.37 (3H, s), 1.46 (3H, s), 1.85–2.12 (3H, m), 3.71 (1H, t, *J* = 8.7), 4.40 (2H, m), 4.49 (ABq, *J* = 11.9), 4.55 (1H, m), 6.00 (1H, dd, *J* = 2.2, 3.2), 7.31–7.35 (5H, m). ^{13}C NMR (75 MHz): 17.9, 25.3, 28.0, 28.5 (3C), 38.1, 39.2, 45.1, 71.1, 71.3, 72.9, 75.5, 78.2, 108.7, 117.7, 127.5, 127.6 (2C), 128.3 (2C), 137.3, 138.4, 152.4.

4.9. Acetonide cleavage

The isopropylidene-benzyl alcohol (112 mg, 0.29 mmol) thus obtained was stirred at room temperature in 4 mL 12% HCl–THF (1:1) while TLC monitored. Quenched with a saturated $NaHCO_3$ solution, evaporated to dryness, and extracted in CH_2Cl_2 the reaction crude was worked-up as usual to give quantitatively the unsaturated diols **35** as an undefined diastereomeric mixture (characterized as such). **35**: ^1H NMR (300 MHz): 0.91 (3H, s), 1.14 (9H, s), 1.40 (1H, m), 1.76 (1H, m), 1.90–2.06 (2H, m), 3.67 (1H, t, *J* = 8.8), 3.75 (2H, br s), 4.09 (1H, m), 4.42 (2H, m), 4.53 (2H, ABq, *J* = 11.9), 5.92 (1H, br s), 7.20–7.40 (5H, m). ^{13}C NMR (75 MHz): 18.5, 28.6 (3C), 38.1, 38.6, 45.9, 65.6, 67.4, 71.6, 72.9, 75.7, 78.1, 119.8, 127.6 (3C), 128.4 (2C), 138.1, 151.5.

4.10. Oxidative cleavage

A dry flask was charged with unsaturated diols **35** (45 mg, 0.13 mmol, diastereomeric mixture) and $Pb(OAc)_4$ (173 mg, 0.39 mmol, 3 equiv) put under vacuum, flushed with argon, dry MeCN (5 mL) was added, and the reaction mixture was immediately immersed into a preheated oil bath (oil bath temperature 100 °C). Following 24 h stirring at this temperature the reaction was stopped by dilution with hepatane–ether, 1:1 and filtration through a pad of silica gel. Flash chromatography afforded 12 mg of **36** (21%) along with dialdehyde mixture (10 mg, 22%) and 6 mg of the corresponding unstable half-cascade.

4.10.1. Acetic acid (9*S*)-acetoxy-(4*S*)-benzyloxy-(6*S*)-*tert*-butoxy-(7*S*)-methyl-2,10-dioxa-tricyclo[5.3.1.0]-undec-(3*S*)-yl ester 36. $[\alpha]_D^{20} = +3$ (*c* 0.74, $CHCl_3$). IR ($CHCl_3$): 3065, 3032, 2976, 2938, 2875, 1740, 1680, 1456, 1370, 1248, 1235, 1216, 1197, 1067, 1028, 996, 737, 705 cm^{-1}. ^1H NMR (400 MHz): 1.23 (9H, s), 1.25 (3H, s), 1.65 (1H, dd, *J* = 1.5, 14.2, H-9β); 1.74 (1H, dd, *J* = 2.6, 14.2, H-9α), 1.86 (1H, ddd, *J* = 2.3, 11.2, 13.8, H-6ax), 1.96 (1H, ddd, *J* = 3.2, 5.2, 13.8, H-6eq), 2.10 (3H, s, *Me*C=O), 2.13 (3H, s, *Me*C=O), 3.17 (1H, d, *J* = 1.2, H-3), 3.33 (1H, t, *J* = 2.7, H-7), 4.56 (2H, ABq, *J* = 11.9, OCH_2Bn), 4.57 (1H, dd, *J* = 5.2, 11.2, H-5), 5.34 (1H, dd, *J* = 1.5, 2.5, H-10), 6.38 (1H, d, *J* = 1.2, H-2), 7.3 (5H, m). Diagnostic NOEs: {H-2}: H-3, H-9β, Me-19; {H-10}: H-9α, H-9α; {H-5}: H-3, H-6eq; {H-3}: H-2, H-5, Me-19; {Me-19}: H-2, H-7, H-3, H-9b. ^{13}C NMR (75 MHz): 21.2 (*Me*C=O), 22.4 (*Me*C=O), 25.4 (Me-19), 28.7 (3C), 32.5 (C-6), 35.9 (C-8), 36.4 (C-3), 39.5 (C-9),

72.6 (O*C*H$_2$Bn), 72.7 (C-5), 73.6 (C-7), 73.8 (Cq–O*t*Bu), 90.6 (C-2), 92.3 (C-10), 103.7 (C-4), 127.7, 128.2 (2C), 128.3 (2C), 137.9 (*C*q-Ph), 169.7 (2C, Me*C*=O). ESIMS (MeOH): 501 ([MK]$^+$, 28), 485 ([MNa]$^+$, 100), 947 ([2MNa]$^+$, 14).

4.11. Acetylation

Acetic anhydride (0.1 mL, 1.24 mmol) was added to a stirring mixture of isopropylidene alcohol **31** (125 mg, 0.41 mmol) and DMAP (catalytic) in dry CH_2Cl_2 (5.0 mL) and pyridine (0.1 mL) under argon at 0 °C. The reaction mixture was stirred for 1 h 30 min at 0 °C (TLC monitoring), diluted with dichloromethane, washed with saturated sodium bicarbonate then 1 N hydrochloric acid, and worked-up as usual to give, after silica gel flash column chromatography (eluent: heptane–EtOAc 8:1), 112 mg (92%) of the corresponding acetate **32** as a diastereomeric mixture, which was used as such for the next step.

Isopropylidene acetate **32** (105 mg, 0.31 mmol) were dissolved in 6 mL of a 1:1 mixture of 12% HCl–THF at room temperature. The reaction was complete at nearly 1 h; quenched with a saturated solution of $NaHCO_3$ and the residue evaporated to dryness, diluted with water and extracted in CH_2Cl_2. Usual work-up gave a 92% yield of the expected unsaturated 1,2-diols **33** as a diastereomeric mixture (all characteristic peaks present). **33**: IR (film): 3400, 2973, 2936, 1741, 1364, 1243, 1196, 1098, 1056, 1039 cm^{-1}. ^{1}H NMR (300 MHz): 0.99 (3H, s), 1.13 (18H, s), 1.15 (3H, s), 1.60–2.30 (m), 2.08 (3H, s), 2.09 (3H, s), 3.02 (m), 3.59 (1H, t, J = 7.9), 3.69 (1H, t, J = 8.8), 3.92 (m), 4.19 (m), 5.54 (m). ^{13}C NMR (75 MHz): 18.3 (Me), 20.8 (Me), 21.0 (Me), 28.5 (*t*Bu), 37.3 (CH$_2$), 38.2 (CH$_2$), 38.9 (CH$_2$), 39.4 (CH$_2$), 43.3 (Cq), 46.0 (Cq), 65.4 (CHO), 67.2 (CHO), 67.6 (CHO), 67.7 (CHO), 71.3 (CHO), 71.4 (CHO), 72.9 (Cq–*t*Bu), 73.0 (Cq–*t*Bu), 76.4 (CHO), 77.7 (CHO), 118.5 (=CH), 119.6 (=CH), 147.7 (=Cq), 148.9 (=Cq), 170.7 (Me*C*O), 170.9 (Me*C*O).

4.12. Oxidative cleavage

A dry flask was charged with unsaturated diols **33** (47 mg, 0.16 mmol, diastereomeric mixture) and $Pb(OAc)_4$ (210 mg, 0.47 mmol, 3 equiv) vacuumed, flushed with argon, dry MeCN (5 mL) was added and the reaction mixture was immediately immersed into a preheated oil bath (oil bath temperature 100 °C). Following 24 h stirring at this temperature the reaction was stopped by dilution with hepatane–ether, 1:1 and filtration through a pad of silica gel. Flash chromatography afforded 18 mg of **34** (26%) along with the corresponding dialdehyde mixture (8 mg) and 5 mg of half-cascade, both unstable.

4.12.1. Acetic acid (4*S*,9*S*)-diacetoxy-(6*S*)-*tert*-butoxy-(7*S*)-methyl-2,10-dioxa-tricyclo[5.3.1.0]undec-(3*S*)-yl ester 34. $[\alpha]_D^{20} = -21$ (c 0.77, $CHCl_3$). IR ($CHCl_3$): 2974, 1751, 1748, 1369, 1267, 1250, 1232, 1216, 1198, 1150, 1140, 1094, 1070, 1047, 1021, 991, 971, 952, 937 cm^{-1}. ^{1}H NMR (600 MHz): 1.24 (9H, s), 1.30 (3H, s), 1.71 (1H, dd, J = 1.2, 14.4, H-9β); 1.80 (1H, dd, J = 2.6, 14.3, H-9α), 1.95 (1H, ddd, J = 2.2, 11.6, 13.7, H-6ax), 2.12 (1H, m, H-6eq), 2.08 (3H, s, *Me*C=O), 2.09 (3H, s, *Me*C=O), 2.10 (3H, s, *Me*C=O), 3.44 (1H, t, J = 2.7, H-7), 3.45 (1H, d, J = 1.1, H-3), 5.37 (1H, d, J = 1.8, H-10), 5.86 (1H, dd, J = 5.3, 11.4, H-5), 6.40 (1H, d, J = 1.2, H-2). ^{13}C NMR (75 MHz): 20.9 (*Me*C=O), 21.2 (*Me*C=O), 22.1 (*Me*C=O), 25.4 (Me-19), 28.7 (3C), 31.6 (C-6), 35.9 (Cq-8), 36.1 (C-3), 39.5 (C-9), 68.6 (C-5), 73.2 (C-7), 74.4 (Cq–O*t*Bu), 90.3 (C-2), 92.4 (C-10), 102.1 (Cq-4), 169.6 (Me*C*=O), 169.7 (Me*C*=O), 170.0 (Me*C*=O). ESIMS (MeOH): 453 ([MK]$^+$, 42), 437 ([MNa]$^+$, 100), 851 ([2MNa]$^+$, 8). HRESIMS calcd for $C_{20}H_{30}O_9Na$: 437.1787, found: 437.1782.

4.13. Preparation of 37b, the precursor of 5b-O*t*Bu substituted diol 38

Starting from the O–*t*Bu-protected hydrindenone derivative **37a** and proceeding as described in Ref. 23 the C-5, C-7 bis-O*t*Bu-protected acetoxyenone **37b** was obtained pure after a silica gel flash chromatography (eluent heptane–EtOAc, 4:1) and was further reduced with lithium aluminum hydride in ether at 0 °C to afford the desired unsaturated diol 38 as a diastereomeric mixture in 90% combined yield.

4.13.1. (1*R*,3*S*)-Di-*tert*-butoxy-(3a*S*)-methyl-6-oxo-2,3,3a,4,5,6-hexahydro-1*H*-inden-(5*R*)-yl acetate 37b. $[\alpha]_D^{20} = +18$ (c 0.92, $CHCl_3$). IR ($CHCl_3$): 2982, 2930, 2356, 2337, 1750, 1689, 1463, 1367, 1237, 1192, 1138, 1095, 1067, 887 cm^{-1}. ^{1}H NMR (300 MHz): 1.17 (9H, s), 1.20 (9H, s), 1.36 (3H, s), 1.85 (2H, m), 2.17 (3H, s), 2.30 (2H, m), 3.45 (1H, dd, J = 7.3, 10.3), 4.29 (1H, t, J = 7.7), 5.61 (1H, dd, J = 5.4, 13.4), 5.95 (1H, s). ^{13}C NMR (75 MHz): 16.5, 20.7, 28.5 (6C), 40.9, 41.7, 45.4, 69.1, 70.9, 73.0, 74.1, 76.7, 123.7, 169.9, 173.7, 194.2. EIMS: *m*/*z* 352 (M$^+$, 5), 296 (100), 279 (3), 254 (5), 223 (13), 193 (20), 57 (60).

4.14. Domino reactions of vinylically substituted substrates 41, 44

The synthesis of **41** started from the corresponding acetoxyenone, a known intermediate. To a stirred solution of **41** (170 mg, 0.7 μmol) in MeCN (3 mL) was added $Pb(OAc)_4$ (890 mg, 2.0 mmol, 3 equiv) at −25 °C. The mixture was stirred at room temperature for 1 h, (TLC monitoring) till no evolution of the **42:43** ratio observed. The residue was purified by flash chromatography on silica gel. Elution with heptane–ethyl acetate (10:1) afforded 27 mg (15%) of **43** (unstable) along with 128 mg (72%) of dialdehyde **42** (also unstable on standing).

4.14.1. (2*Z*)-2-[(3*S*)-*tert*-Butoxy-2-methyl-(2*S*)-(2-oxoethyl)cyclopentylidene]propanal 42. $[\alpha]_D^{20} = +56$ (c 1.03, $CHCl_3$). IR (film) 2972, 2940, 2870, 1635, 1364, 1213, 1202, 1138, 1095, 1070, 1024, 987 cm^{-1}. ^{1}H NMR (300 MHz): 1.19 (9H, s), 1.25 (3H, s), 1.71 (3H, s), 1.90–2.10 (2H, m), 2.40–2.70 (2H, m), 2.98 (2H, m), 3.98 (1H, dd, J = 6.0, 10.2), 9.69 (1H, s), 10.18 (1H, s).

^{13}C NMR (75 MHz): 11.8, 22.9, 28.5 (3C), 28.6, 29.3, 47.3, 53.4, 73.5, 77.5, 130.5, 167.2, 189.5, 200.2. EIMS: *m/z* 252 ($M^{+\cdot}$, 8), 251 (34), 237 (21), 209 (18), 197 (48), 196 (98), 195 (55), 179 (31), 178 (100), 167 (97), 154 (65), 153 (57), 151 (47), 150 (100), 123 (89), 109 (82), 106 (95), 98 (81), 90 (92). HREIMS calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1708.

4.14.2. (4*S*)-*tert*-Butoxy-5,10-dimethyl-8,11-dioxatricyclo[5.3.1.0^{1,5}]undec-9-ene 43. $[\alpha]_D^{20} = +44$ (*c* 1.0, $CHCl_3$). IR (film) 2971, 2931, 2884, 1802, 1717, 1654, 1621, 1458, 1415, 1387, 1364, 1281, 1189, 1110, 1074, 900 cm^{-1}. ^{1}H NMR (200 MHz): 1.04 (3H, s), 1.14 (9H, s), 1.00–2.20 (4H, m), 1.55 (3H, br s), 1.91 (1H, d, *J* = 14.0), 2.31 (1H, dd, *J* = 5.1, 14.0), 3.90 (1H, t, *J* = 8.2), 5.61 (1H, d, *J* = 5.1), 6.04 (1H, br s). ^{13}C NMR (50 MHz): 13.8, 15.7, 24.8, 28.8 (3C), 32.6, 47.8, 53.5, 72.5, 78.9, 93.9, 100.7, 112.2, 135.3. EIMS: *m/z* 252 ($M^{+\cdot}$, 9), 219 (39), 167 (45), 149 (100), 57 (50).

Diol **44** was obtained in 69% yield from its corresponding acetoxy enone by a Luche reduction ($NaBH_4$–$CeCl_3$, 0 °C, 30 min) and used as a crude diastereomeric mixture for the next operation. Oxidative cleavage using the general procedure afforded (**4*S***)-*tert*-butoxy-5-methyl-8,11-dioxa-tricyclo[5.3.1.0^{0,0}]undec-9-ene-10-carboxylic acid methyl ester **45**.

$[\alpha]_D^{20} = +75$ (*c* 1.01, $CHCl_3$). IR (film): 3021, 2976, 2953, 2360, 1701, 1604, 1438, 1216, 1186, 1146, 1103, 1071, 1026 cm^{-1}. ^{1}H NMR (250 MHz): 1.04 (3H, s), 1.15 (9H, s), 1.60–1.90 (2H, m), 1.90 (1H, d, *J* = 14.3), 2.00–2.20 (1H, m), 2.37 (1H, dd, *J* = 5.0, 14.3), 2.85–3.05 (1H, m), 3.68 (3H, s), 3.85 (1H, t, *J* = 8.0), 5.72 (1H, d, *J* = 5.0), 7.44 (1H, s); ^{13}C NMR (62.5 MHz): 13.9, 25.2, 28.8 (3C), 33.0, 48.2, 50.9, 62.9, 72.5, 78.7, 93.7, 102.2, 110.0, 153.2, 165.5. EIMS: *m/z* 296 ($M^{+\cdot}$, 14), 196 (77), 154 (99), 57 (100). HREIMS: calcd for $C_{16}H_{24}O_5$ *m/z* 296.1624, found 296.1629.

The tricyclic enol ether intermediate, unlike most other vinylically substituted analogs, is stable and easily isolable.

4.15. Preparation and domino reactions of racemic unsaturated diols 46 and 48

The general procedure for acetoxylation with $Pb(OAc)_4$ and subsequent $LiAlH_4$ reduction of the corresponding enones was used for the large-scale synthesis of the requisite unsaturated diols **46** and **48** in 82% and 95% combined yields, respectively. Given the fact that $Pb(OAc)_4$ mediated domino transformations are insensitive to diol stereochemistry, the starting diols [±]-**46** and [±]-**48** were used as diastereomeric mixtures. However, we separated the racemic *cis* and *trans* diols for characterization purposes.

4.15.1. Faster eluting *cis*-4-methylcyclohex-3-ene-1,2-diol-46α. IR (film): 3391, 2913, 1667, 1432, 1377, 1262, 1218, 1155, 1119, 1071, 1049, 995, 961, 902, 848 cm^{-1}. ^{1}H NMR (300 MHz): 1.69 (3H, s), 1.73–2.19 (4H, m), 3.26–3.58 (2H, m), 3.67–3.82 (1H, m), 4.06 (1H, br s), 5.44 (1H, br s). ^{13}C NMR (75 MHz): 23.2, 25.7, 28.5, 66.7, 68.7, 121.6, 139.3. EIMS: 128 ($[M]^+$, 16), 84 (100), 83 (51). HREIMS: calcd for $C_7H_{12}O_2$ *m/z* 128.0837, found 128.0831.

4.15.2. Slower eluting *trans*-4-methylcyclohex-3-ene-1,2-diol-(±)-46β. Mp: 58–60 °C (heptane–ether). IR (film): 3435, 2914, 1673, 1651, 1434, 1377, 1264, 1227, 1155, 1062, 1029, 1007, 970, 937, 905, 875, 807 cm^{-1}. ^{1}H NMR (300 MHz): 1.67 (3H, s), 1.63–2.20 (4H, m), 3.51–3.61 (1H, m), 3.96–4.31 (2H, m), 4.05 (1H, br s), 5.27 (1H, br s). ^{13}C NMR (75 MHz): 22.7, 28.7, 29.6, 73.5 (2C), 123.1, 136.9. EIMS: 128 ($[M]^+$, 10), 84 (100), 83 (55). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.54; H, 9.38.

4.16. Oxidative cleavage of unsaturated diols 46

A dry flask was charged with unsaturated diol **46** (90 mg, 0.70 mmol) and $Pb(OAc)_4$ (342 mg, 0.77 mmol, 1.1 equiv) vacuumed, flushed with argon, and cooled to −25 °C. Acetonitrile (3.5 mL) was then added and the reaction mixture was stirred at −30 °C for 15 min. Direct column chromatography with heptane first to remove the acetonitrile and then with heptane–EtOAc 1:1 afforded 72 mg, 81% of the dialdehyde **47**. (2*Z*)-3-Methylhex-2-enedial 47: IR (film): 2978, 2835, 2734, 1722, 1668, 1644, 1444, 1402, 1324, 1261, 1211, 1170, 1117, 1059, 1023, 847, 734 cm^{-1}. ^{1}H NMR (300 MHz): 1.99 (3H, d, *J* = 1.4), 2.74 (2H, dt, *J* = 0.9, 7.4), 2.91 (2H, t, *J* = 7.4), 5.91 (1H, d, *J* = 7.7), 9.83 (1H, t, *J* = 0.9), 9.98 (1H, d, *J* = 7.7). ^{13}C NMR (75 MHz): 24.5, 24.7, 42.0, 128.6, 161.2, 190.3, 199.9. ESIMS (MeOH): 127 ($[MH]^+$, 100).

4.17. Preparation and oxidative cleavage of unsaturated diols 48

Starting from the commercially available 4,4-dimethylcyclohex-2-enenone and proceeding as above the requisite diol was obtained in 95% combined yield.

4.17.1. (±)-*trans* 5,5-Dimethylcyclohex-3-ene-1,2-diol 48. Mp: 56–58 °C (heptane–ether). IR (film): 3418, 2956, 2920, 2864, 1651, 1645, 1633, 1469, 1455, 1361, 1257, 1058, 946, 876 cm^{-1}. ^{1}H NMR (300 MHz): 1.03 (3H, s), 1.05 (3H, s), 1.49 (1H, t, *J* = 12.7), 1.74 (1H, dd, *J* = 3.2, 12.7), 3.44–3.87 (2H, m), 3.72 (1H, ddd, *J* = 3.2, 7.8, 12.7), 4.04 (1H, d, *J* = 7.8), 5.38 (1H, d, *J* = 10.6), 5.42 (1H, d, *J* = 10.6). ^{13}C NMR (75 MHz): 28.8, 31.0, 34.9, 43.2, 71.7, 74.3, 125.5, 139.0. EIMS: 142 ($[M]^+$, 0.03), 124 (1.5), 109 (1), 98 (100), 86 (20), 83 (10), 55 (10), 41 (10). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C 67.24; H, 10.12.

A dry flask was charged with starting diols (±)-**48**–*trans* (123 mg, 0.87 mmol) and $Pb(OAc)_4$ (960 mg, 2.16 mmol, 2.5 equiv), vacuumed, and flushed with argon several times. Dry acetic acid (3 mL) was then added and the reaction mixture was stirred at room temperature for 5 h, at which point TLC indicated complete consumption of starting diols. Dilution with ether followed by washing with saturated aqueous $NaHCO_3$, till neutral

pH, and brine, drying over $MgSO_4$, and concentration under reduced pressure afforded 139 mg (62%) of a mixture of **50** and **51**. A careful silica gel flash column chromatography, eluent heptane–EtOAc, 3:1, allowed separation and hence identification of pure **50**: IR (film): 2968, 1735, 1369, 1223, 1178, 1127, 1050, 962, 872 cm^{-1}. ^1H NMR (300 MHz): 1.30 (6H, s), 1.77–1.79 (2H, m), 2.12 (1H, dd, $J = 0.9, 3.2$), 2.14 (6H, s), 4.98 (1H, t, $J = 2.1$), 6.43 (2H, d, $J = 1.7$). ^{13}C NMR (75 MHz): 21.2 (2C), 28.4 (2C), 29.0, 41.7, 41.8, 91.9 (2C), 92.9, 169.8 (2C). ESIMS: 297 ($[MK]^+$, 5), 281 ($[MNa]^+$, 100), 539 ($[2MNa]^+$, 18). **51** was contaminated with some **50** thus, it was better characterized in its deuterium labeled form, as pure **51-d_6**.

Proceeding as above, **48** (152 mg, 1.07 mmol), and $Pb(OAc)_4$ (1185 mg, 2.67 mmol, 2.5 equiv) were stirred at room temperature in a large excess of deuterated acetic acid (10 mL) for 22.5 h. The large excess of labeled acetic acid (high-quality standards of the commercial solvent sold in sealed tubes for NMR studies was used) is to ensure metathesis of the acetate by the labeled carboxylate, while the extra stirring time is to remove as much as possible the left-over nonlabeled acetoxy group, by exchange (and hence to measure the extent of exchange). Work-up and flash chromatography using heptane–EtOAc 3:1 as eluent afforded 169 mg (60%) of **50-d_6** and 18 mg (6%) of **51-d_6**. The unlabeled **50** is present as could be seen from proton, contribution from the unlabeled counterpart at 2.15 (*Me*CO), from carbon, at 21.2 (*Me*CO) and Electron Spray Ionization Mass spectra, $C_{12}H_{18}O_6$ at *m/z* 281 ($[MNa]^+$, 12), 297 ($[MK]^+$, 5).

4.17.2. 5-(Trideuteriumacetoxy)-8,8-dimethyl-2,6-dioxabicyclo[2.2.2]oct-3-yl trideuteriumacetate 50-d_6. IR (film): 2966, 2875, 1725, 1638, 1447, 1368, 1278, 1229, 1178, 1127, 1047, 999, 944 cm^{-1}. ^1H NMR (600 MHz): 1.30 (6H, s, Me-*gem*), 1.78 (2H, d, $J = 2.0$, H-7), 2.12 (1H, t, $J = 1.5$, H-4), 5.27 (1H, t, $J = 2.0$, H-1), 6.43 (2H, d, $J = 1.5$, H-3, H-5). ^{13}C NMR (150 MHz): 20.5 (*C*D_3), 28.4 (Me-*gem*), 29.0 (Cq-8), 41.7 (C-4), 41.8 (C-7), 91.9 (C-3, C-5), 93.0 (C-1), 169.9 (Me*C*O). ESIMS: 303 ($[MK]^+$, 12), 287 ($[MNa]^+$, 100).

51-d_6: ^1H NMR (600 MHz): 1.23 (3H, s, Me-a), 1.40 (3H, s, Me-b), 1.81 (1H, dd, $J = 3.0, 13.7$, H-7a), 1.87 (1H, t, $J = 13.7$, H-7b), 2.08–2.24 (1H, m, H-4), 5.31 (1H, br s, H-1), 6.49 (1H, d, $J = 2.9$, H-3), 6.53 (1H, d, $J = 2.9$, H-5). ^{13}C NMR (150 MHz): 20.5 and 20.7 (*C*D_3), 28.0, 30.6 (Me-b), 30.7 (Me-a), 41.3 (C-7), 41.6 (C-4), 91.2 (C-5), 91.6 (C-3), 93.9 (C-1), 169.5 (Me*C*O), 170.2 (Me*C*O). ESIMS: 287 ($[MNa]^+$, 100).

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