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The Domino Chemistry Approach to Molecular Complexity: Competing Domino Processes Modulated by the Substitution Pattern

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Abstract: Oxidative cleavage with lead tetraacetate results in the synthesis of different oxygen heterocycles starting from the same unsaturated 1,2-diol of type **I** by tuning of the substitution pattern at the angular position. When this compound bears a functional substituent, such as an alkoxy, ester, alkenyl, or simply a hydrogen, more than one reaction pathway are in competition. The process allows for the selective formation of three different complex ring systems, by the appropriate choice of the angular substituent, leading to either a ring-expanded type **1**, ring-retained type **2**, or domino products **3**.

Keywords: cyclic oxoniums · domino reactions · lead tetraacetate · ring expansion

Introduction

Processes wherein numerous carbon–carbon bond making/breakings occur in a single synthetic operation are considered as cost-effective. We have previously noted that the $[Pb(OAc)_4]$-mediated domino[1] reactions on steroidal unsaturated 1,2-diols could be modulated by the substitution pattern of the substrate, which led to the preparation of several modified steroids upon variations at the angular position (C10, steroid numbering).[2] Selective formation of ring-retained domino products with the 19-nor testosterone-derived substrates raised the question as to whether a synthetically significant modular construction of either ring-expanded type **1**, alternative domino products of type **2**, or **3**[3] was possible by altering the angular substitution. We thus directed our efforts towards the preparation of a simple system, the unsaturated bicyclic diol of type **I**, containing a variable substitution pattern at the angular position, to probe the modular aspect of the reaction. Domino reactions with type **I** substrates which harbor alkyl, hydrogen, alkoxy, or ester groups all proceed smoothly to the half-cascade level **II**, afterwards they diverge.[4] Products of type **1**, **2**, or **3**, determined by the substitution pattern of the angular position, are obtained (Scheme 1). At the outset, a common sequence of an "oxidative/pericyclic" process, in which the reagent acts as an oxidant,[5] operates (**I** to **II**).[6] For some substrates the hetero-domino process is continued by an "oxyplumbation/ring expansion" sequence (path i), while for other substrates the whole hetero-domino process becomes "oxidative/pericyclic/cationic" in which an oxonium intermediate **IV** is involved (path ii). For substrates lacking the angular substitution (R = H), the reaction course is directed towards either pathway i or iii, which gives mixed results affording almost equal amounts of **3** via **V** and a type **1** derivative via **III**.

The structural diversity offered by the modulable domino sequence derives from the number of permutations possible for attachment of the various functional groups to the hydrindene diol framework. Two out of the three possible structures, **1** and **2**, could be obtained as single products, in high yields, by simply tuning the nature of the angular substituent (ether, ester, alkyl, alkenyl linkage). To arrive at the optimal set of reaction parameters for the selection of suitable precursors and to monitor the formation of either target compound (path i, ii, or iii), we embarked on a substituent effect study focusing on several goals. One was that of investigating whether glycal-type half-cascade intermediates **II**,

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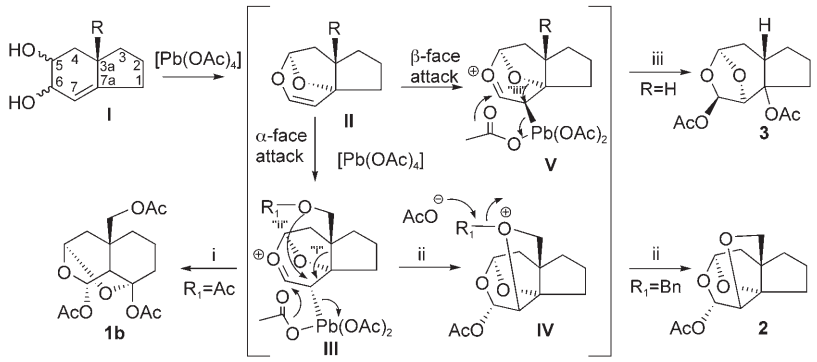
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author and contains procedures for the synthesis and spectral characterization for all compounds including X-ray data for **2**, **29**, and **31**.



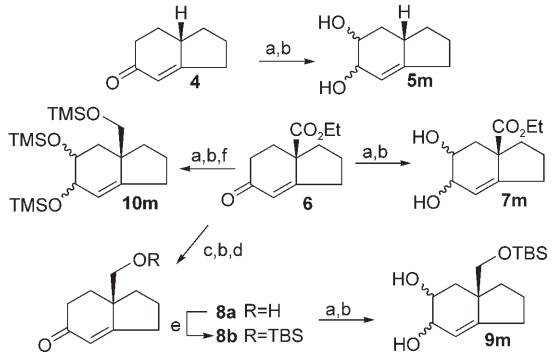
Scheme 1.

which bear potential neighboring group participants on their resident functionalities, might serve as effective intermediates in the formation of complex heterocycles. The participation of the methyl, benzyl, methoxymethyl, *tert*-butyldimethylsilyl, trimethylsilyl group oxygen allowed an instructive comparison of the relative nucleophilicities in the corresponding functional groups. In this paper we provide insight into the feasibility of the process in the presence of a variety of functional groups, and the substituent's influence in the path-selection of the $[Pb(OAc)_4]$-mediated domino reaction. Notable advantages of this particular sequence are the very rapid increase in molecular complexity and its modular character allowing selective access to either complex molecule as portrayed in Scheme 1.

Results and Discussion

Synthesis of the required templates: As our primary concern was the assessment of new designs for generating molecular complexity, it was not essential to operate with optically homogeneous templates.[7] While we preferred to commence our exploratory phase with racemic **I**, the ready availability of its 3a*R* enantiomer[8] could prove to be of great value toward the ultimate goal of synthesizing optically homogeneous spiranic compounds and fused tetrahydrofuranes. In a search for various routes to elaborate the key intermediates, aiming at practicality and better yields, we investigated several protocols for efficient construction of the target unsaturated 1,2-diols. Needless to say that the routes followed may be interchanged or even completely modified to arrive at the same result. The domino precursors **4** and **6** were prepared from the corresponding commercially available cyclic ketones and MVK by using the Robinson annulation under conditions developed by Stork and Dauben.[9] Unsaturated diols **5m** and **7m**[10] were prepared in multigram quantities by a straightforward two-step route using the regular method from the appropriate enones,[11] as outlined in Scheme 2. The first step involved acetoxylation ($[Pb(OAc)_4]$, PhH, 90 °C) of the bicyclic enone, followed by lithium aluminum hydride-mediated diol formation ($LiAlH_4$, Et_2O, −20 °C, chemoselective at this temperature). The stereochemistry at the secondary hydroxyl groups is not important as it is destroyed in the generation of the 4+2 template **II** (Scheme 1). The synthesis of the first target substrates is described in Scheme 2.

In light of the tendency of diol **7** to undergo intramolecular lactonization, a different strategy was applied to synthesize the TBS-protected bicyclic unsaturated diol **9m**. This goal was realized by an inversion in

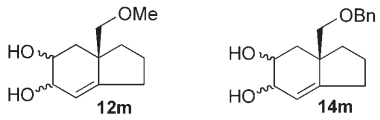


Scheme 2. a) $[Pb(OAc)_4]$, PhH, reflux, 90 °C, 3 d; b) $LiAlH_4$, Et_2O, −20 to 0 °C; c) ethylene glycol, *p*TsOH, Dean–Stark, 2.5 h; d) 2 N HCl/THF 1:1, 25 °C, 3 h; e) TBSCl, DMF/imidazole, 0 to 25 °C, 16 h; f) TMSOTf, collidine, PhMe, 25 °C. Ts = tosyl; Tf = triflate.

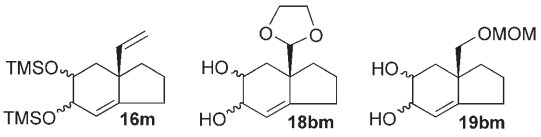
the synthetic sequence in which the ester group elaboration preceded the acetoxylation–reduction as above. Conversion of **6** into the target **9** was realized in six efficient steps. The known enone-ester **6** was treated with ethylene glycol, in the presence of *p*TsOH (2.5 h reflux, Dean–Stark trap), to provide the corresponding ketal (81 %), which was reduced to the alcohol ($LiAlH_4$, Et_2O, 0 to 25 °C, 30 min), deketalized (2 N HCl/THF 1:1, RT, 3 h, 93 %) to **8a**, and finally protected as its *tert*-butyl dimethylsilylether (TBSCl, DMF/imidazole, 0 to 25 °C, 16 h, 93 %) **8b**. The required unsaturated diol **9m** was then obtained as a diastereomeric mixture in two steps by lead tetraacetate-mediated acetoxylation ($[Pb(OAc)_4]$ PhH, reflux, 90 °C, 90 %) and reduction of the intermediate acetoxyenone ($LiAlH_4$, Et_2O, 0 °C, 30 min, 87 %) as above. Separation of the α- and β-acetoxyenone intermediates was difficult, and furthermore useless for the next operations. Yet another route towards the target is the straightforward synthesis of tristrimethylsilyl-protected derivative **10m**, again circumventing the lactone issue. The latter was cleanly obtained by over-reduction ($LiAlH_4$, Et_2O, 0 to 25 °C) and per-silylation (TMSOTf, collidine, PhMe, 25 °C).

The unsaturated diol **7m**, possessing a carboethoxy group at the angular position, served as a key intermediate for the construction of nearly all domino templates by a sequence

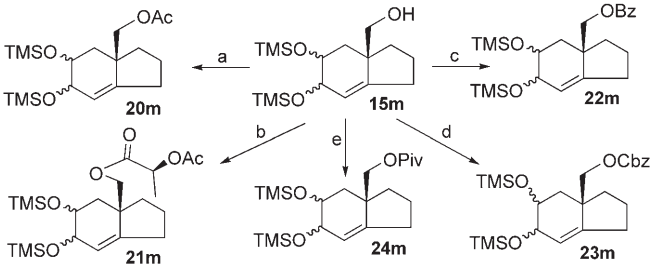
of functional-group interconversions. The identity of the angular substituent should, according to the proposed mechanism, exert a significant effect on the course and hence might drastically alter the outcome of the domino reaction. Thus, the substrates **12m** and **14m** were prepared first.



At the outset, we hypothesized that with provision of an appropriate protective group at the primary alcohol, reactivity could have been switched towards/away the ring-expansion process. This idea has been tested on the additional selected substrates **16m**, **18bm**, and **19bm** synthesized from



7m and **20**–**24** prepared straightforwardly from **15m** (itself derived from **7m**, Scheme 3).



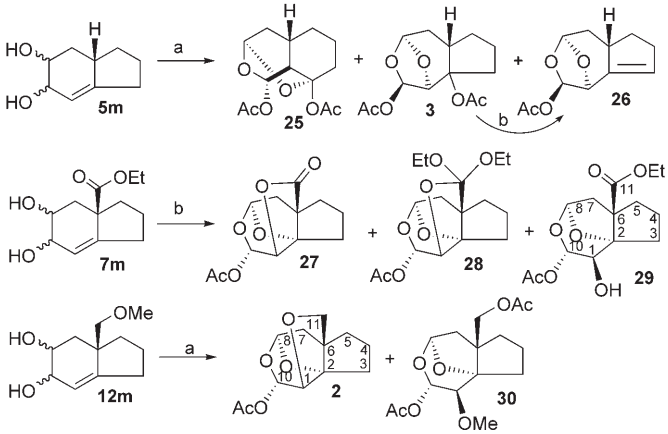
Scheme 3. a) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 to 25 °C; b) (*S*)-2-acetoxypropionyl chloride, Et_3N, DMAP, CH_2Cl_2, 25 °C; c) BzCl, Et_3N, CH_2Cl_2, 0 to 25 °C; d) benzylchloroformate, DMAP, py, CH_2Cl_2, 0 °C; e) pivalyl chloride, Et_3N, DMAP, CH_2Cl_2, 25 °C. DMAP = 4-dimethylaminopyridine.

The details for the preparation of the target unsaturated diols **12m**, **14m**, **16m**, **18bm**, and **19bm** is described in the Supporting Information. It should be pointed out that all domino reactions are performed on crude diastereomeric mixtures and various amounts of the stereopure compounds were separated by using the eluent indicated in the Experimental Section for characterization purposes.

The preparation of domino precursors **20**–**24**, with **21** being a conveniently functionalized variant to be used as a template offering possibilities for resolution, is summarized in Scheme 3. Starting from **15m**, the requisite templates **20** (Ac_2O, py, DMAP, 0 °C, 86 %), **22** (BzCl, CH_2Cl_2, NEt_3 0 °C, 12 h, 85 %), **23** (benzyl chloroformate, CH_2Cl_2, py, DMAP, 3 d, 0 °C, 43 %, 92 % based on recovered starting material) and **24** (pivaloyl chloride, CH_2Cl_2, Et_3N, DMAP, 25 °C, 20 h, 95 %) were prepared uneventfully. On the other hand, diastereomeric derivatization with (*S*)-2-acetoxypropionyl chloride in the presence of triethylamine and DMAP in dry CH_2Cl_2 at 0 °C, under inert atmosphere, afforded the corresponding esters **21** (99 %) as a mixture of diastereomers which were used as such in the domino process. Although the oxidative cleavage can be run directly on the bis(TMS)-protected diols, without prior deprotection, the corresponding free unsaturated diols were obtained in two cases for comparison purposes (domino yields). Thus, removal of the trimethylsilyl protective group from **21m** and **23m** ($n$$Bu_4NF$-THF) afforded the corresponding unsaturated diols in approximately 95 % yield.

Domino reactions

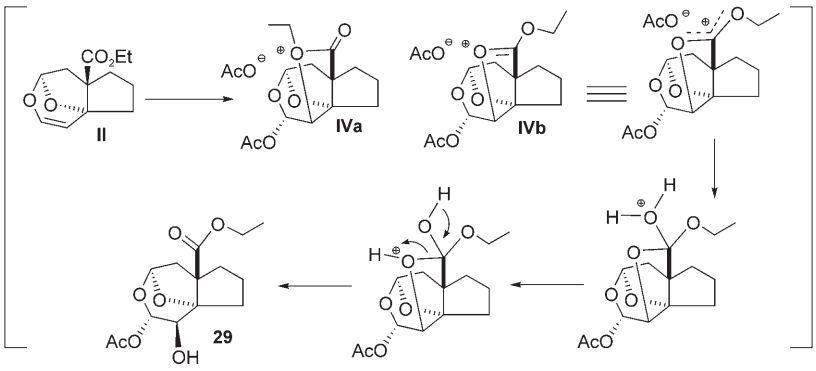
Preliminary screening experiments: With a reliable access to domino precursors established and with a representative range of templates in hand we were now in a position to explore the factors that govern the path selectivity in the domino protocol. Reactions were run in PhMe or AcOH, at room temperature or at 60 °C, and were generally complete within less than 15 h under these conditions.[12] When diol **5m** was treated with $[Pb(OAc)_4]$ (2.4 equiv), a domino reaction ensued from which a moderate yield of ring-expanded product **25** (27 %) was isolated, along with ring-retained domino products **3** (13 %) and **26** (17 %). These data suggested that two reaction pathways were operating in this domino process; one pathway (α-face attack, Scheme 1) producing the ring-expanded product **25** and another pathway (β-face attack) producing the ring-retained intermediate **3** and hence **26**, with concomitant loss of an acetic acid unit (Scheme 4). As a result, replacing the methyl group at the angular position by a hydrogen caused the path selectivity to drop to a nearly 1:1 ratio **25**/**26**+**3**, as the half-cascade product **II** (Scheme 1) evolved also in a new direction (path iii) due to the lack of an angular methyl group. Clearly, the



Scheme 4. a) $[Pb(OAc)_4]$, PhMe, 25 °C; b) $[Pb(OAc)_4]$ PhMe (or EtOAc or AcOH), 60 °C.

absence of the methyl group at the angular position affects the reaction conditions in such a way that β-face attack becomes competitive with the α-face attack.

The angularly functionalized carboxylic ester unsaturated diol **7m** behaves rather curiously, with formation of an ortho-ester **28** among the final products, all derived from the same path (ii, Scheme 1). The reason for this is not apparent at this time and further work must be done before this point can be clarified. Thus, when diol **7m** underwent oxidative cleavage with $[Pb(OAc)_4]$ in AcOH, a 30% yield of the lactone intermediate **27** was obtained along with the ortho-ester derivative **28** (12%) and the hydroxyacetal **29** (20%). The reaction has also been carried out in benzene, toluene, ethyl acetate, deuterium-labeled ethyl acetate, and deuterium-labeled acetic acid at room temperature or 60°C. The only observed, albeit insignificant, variation was at the product distribution level, while conversion to domino products remained poor. The structure of **29** was determined through extensive NMR spectroscopic experiments. Furthermore, a single crystal of the latter was grown in heptane, and an X-ray diffraction study corroborated its structure depicted in Figure 1.



Scheme 5. Possible intermediates for vicinal unsaturated diols containing carboethoxy-angular substitution.

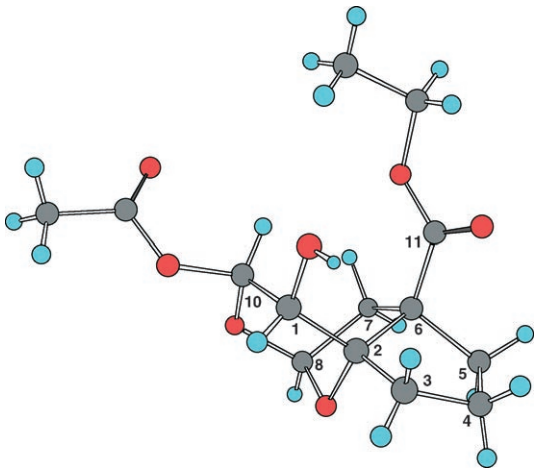


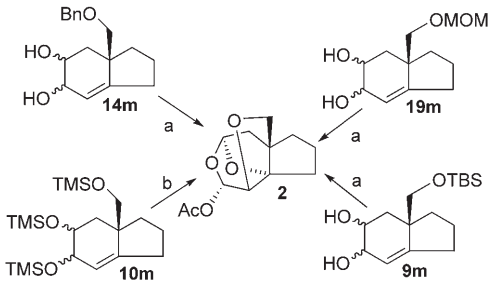
Figure 1. Perspective drawing of the X-ray structure of **29** (Chem 3D output from X-ray coordinates; gray, carbon; red, oxygen, cyan, hydrogen; arbitrarily numbered).

Formation of **27** could be rationalized by postulating a participation of the ester functionality as neighboring group by nucleophilic attack of the alkoxy group; displacement of lead triacetate should lead to a cyclic acyldialkyloxonium ion **IVa** (Scheme 5). Correspondingly, nucleophilic attack of the carbonyl should lead to lactonium ion **IVb**, which could then evolve to the orthoester **28** (provided that an "ethoxy" source is available) while hydroxy ester **29** could occur either directly from **II** (R = CO_2Et) or **IVb** admitting water addition/transprotonation/ring opening.[13]

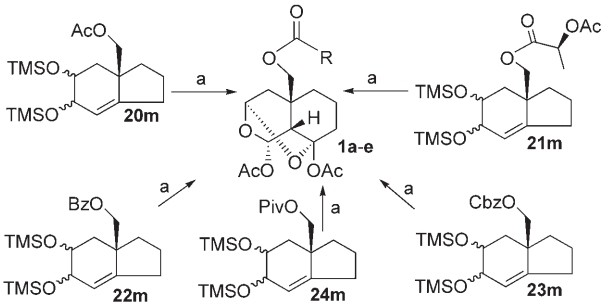
Finally, treatment of **12m** with $[Pb(OAc)_4]$ 2.4 equiv, in dry PhMe, 25°C, overnight stirring) led to a mixture of two domino products, **2** (36%) and **30** (49%), both arising from the oxonium path (ii, Scheme 1).

These experiments clearly lack practical synthetic utility as more than one product is formed, poor yields are obtained, and chromatographic separations are needed, which is in marked contrast to the trend involving the corresponding unsaturated diols, containing any alkyl group at the angular position. Although not encouraging in terms of the ultimate objective of selectively producing ring-expanded or -retained frameworks, in a modular way, they provided a hint that the nature of the angular substituent may indeed provide complexity through the agency of oxonium ions, which compete with the ring-expansion step of the domino process. Yet, these reactions are quite attractive and show much promise in generating complexity, even though an important issue must be addressed if this methodology is to become synthetically useful: establishing a regioselective profile of the oxyplumbation/deplumbation sequence, when various angular substituents are employed. This issue has been addressed in some detail and a variant of this domino reaction was brought to practice in which the cyclic system and the angular substituent are tethered by spacers of various nature.

The influence of the nature of the angular substituent: As changing the angular substituent was found to dramatically alter the course of the domino reaction, the following trials were designed to set in opposition an ether-linked substituent against an ester-linked one. Orienting experiments exemplified by the conversion of selected unsaturated diols (diastereomeric mixtures) into the complex ring-retained/-expanded heterocycles, showing that the distribution can be altered through the presence of an ether or ester linkage are outlined in Schemes 6 and 7, respectively. Alkoxy-substituted diols **9**, **10**, **14**, and **19** undergo domino transformation solely with retention of the cyclopentane skeleton (Scheme 6). Conversely, an O-ester substituent at the angu-



Scheme 6. a) $[Pb(OAc)_4]$ (2.4 equiv), PhMe, 25 °C, 22 h or 60 °C, 3 h; b) $[Pb(OAc)_4]$ (2.4 equiv), AcOH, 25 °C, 15 h.



Scheme 7. a) $[Pb(OAc)_4]$ (2.4 equiv), AcOH, 25 °C, 15 h. **1a**: R = Me; **1b**: R = MeCH(OAc); **1c**: R = Ph; **1d**: R = OBn; **1e**: R = *t*Bu.

lar position reverses the tendency to ring expansion as illustrated by the exclusive conversion of **20**–**24** into **1a**–**e** (Scheme 7).

The only product isolated from the reaction of unsaturated diols **9m**, **10m**, **14m**, and **19m** with $[Pb(OAc)_4]$ was **2**, which was stable and easily isolable. In three runs with all unsaturated diol frameworks the domino yield was uniformly good (81–99 %). The process gave no detectable quantities of ring-expanded structures of type **1**; cyclic tertiary oxonium formation proved much faster than ring-expansion. Thus, the ring-retained, fused-tatrahydrofurane **2** was obtained exclusively as a pure crystalline substance from the $[Pb(OAc)_4]$-mediated domino reaction of **14m** bearing a benzyl group as well as from **9m**, **10m**, and **19m** bearing a *tert*-butyldimethylsilyl, trimethylsilyl, and methoxymethyl substituant at the angular alkoxy position, respectively (Scheme 6). Noteworthy features of this domino protocol include simultaneous formation of two additional rings while stereochemical control is realized through destruction–reconstruction of the hydroxy-bearing stereocenters (stereocleaning). The structure of the fused-bridged ring system **2**, with a quaternary atom common to all four rings, was unambiguously established by X-ray crystallographic analysis (Figure 2).

Whilst no special effort was taken to optimize these reactions, the yields range from good to excellent. Varying experimental conditions, such as solvent and temperature, did not affect the product distribution. However, lowering the temperature of the reaction resulted in a slower rate along with a slight decrease in yield. On the other hand, these results were unchanged by substituting for toluene the more

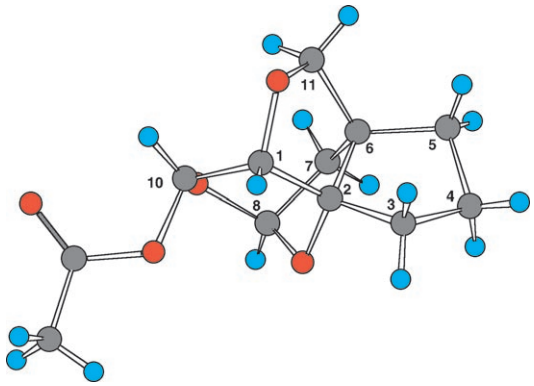
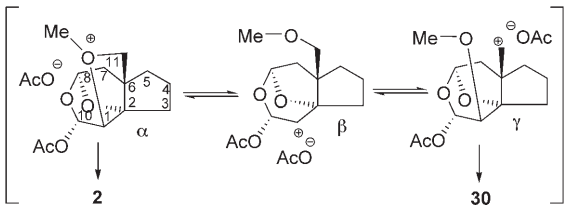


Figure 2. Perspective drawing of the X-ray structure of **2** (Chem 3D output from X-ray coordinates; gray, carbon; red, oxygen, cyan, hydrogen; arbitrarily numbered).

polar solvent, acetic acid, or a number of other solvents (MeCN, EtOAc, CH_2Cl_2 etc) and indicate that the domino process is operative over a wide range of solvents and temperatures (0 to 60 °C). Accordingly, exposure of **14m** to $[Pb(OAc)_4]$ at room temperature for 10–12 h, furnished a 78 % yield of **2**. Further extension of the reaction time to 22 h resulted in clean conversion only to **2** (99 % isolated yield). When the reaction temperature was raised to 60 °C, a 3 h TLC control indicated that starting material was no longer present in the mixture, which now constituted exclusively of **2** (92 % isolated yield).

A divergence in behavior of methyl and benzyl-tethered unsaturated diols **12m** and **14m**, respectively, was observed upon subjecting them to standard domino conditions. Although the transient entities produced by each of these ethers are similar, the pathway with which the corresponding cyclic tertiary oxonium[14] collapses depends upon its degree of stabilization. Thus, while methoxonium has the opportunity to collapse either to the tetracyclic system **2** or the tricyclic system **30**, benzyloxonium has the opportunity only of collapsing to the tetracyclic system **2**. The reaction course, in both cases, implies that the formation of the cyclic oxonium intermediate has taken precedence over the migration of the C2–C6 bond. A rationale for these results based on the proposed mechanism (Scheme 1) is outlined in Scheme 8.

The reactive cyclic trialkyloxonium ion **α**, first formed, undergoes cleavage under the action of a nucleophile (the reagent's AcO^-). At equilibrium, O-methyltetrahydrofuranium ion **α** should be accompanied by **β** and **γ**. Acetate attack



Scheme 8. Possible paths of *O*-methyltetrahydrofuranium ion collapse showing the routes to **2** and **30**.

on the transient O-methyltetrahydrofuranium ion results in considerably more methylene–oxygen than methyl–oxygen cleavage, leading predominantly to **30** (49%) versus **2** (36%). The analogous intermediates should also exist in the case of benzyl ether, but the corresponding tetrahydrofuranium ion gives exclusively Bn–O cleavage.

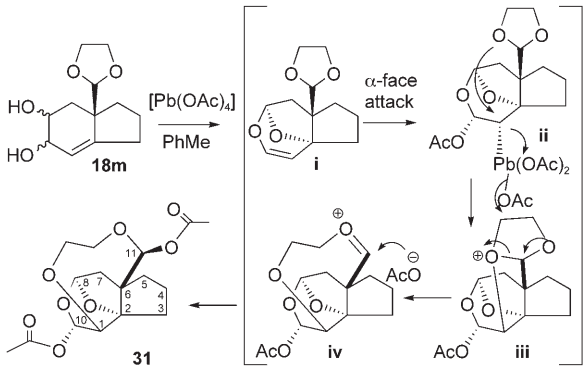
Starting from ester-linked substrates **20**–**24**, the experiments undertaken with $[Pb(OAc)_4]$ uniformly gave rise to ring-expanded bisacetoxyacetals **1a**–**e** as the only detectable products, potentially valuable precursors for spirocycles (Scheme 7). When performed in AcOH, the oxidative cleavage could be carried out directly on the bis(TMS)-protected diol.[15] Thus, rather than performing typical glycol fission with free diols, we performed the domino transformations directly on TMS-protected diols **20m**, **21m**, **22m**, **23m**, and **24m**. This led exclusively to ring-expanded products **1a**–**e** (**a**: R = Me, **b**: R = MeCH(OAc), **c**: R = Ph, **d**: R = OBn, **e**: R = *t*Bu) starting from the silyl-protected diols, though the yields are lower (approximately 10–15%) compared to those obtained from the free diols in the two cases investigated (diols obtained from **21m** and **23m**).

It is noteworthy that there was no sign of the alternative regioisomer, arising from the oxonium path, in any of the reactions shown in Scheme 7 or any byproduct observed.

Finally, we examined the possibility of acetal participation, for elucidation of the mechanism and for a direct comparison with the structurally related unsaturated diols studied previously. To this aim, treatment of unsaturated diols **18m** with $[Pb(OAc)_4]$ in an analogous manner (25°C, 6 h; 60°C, 3 h 30 min) cleanly afforded the complex oxygen heterocycle **31** (79 and 90% isolated yield, respectively). Isolation of the latter demonstrates the complexity of the structures that can be obtained in a single synthetic operation by using our domino methodology. The resulting polycyclic system represents an efficient method for generating multiple contiguous stereocenters on polyfunctional fused/bridged systems. Starting from only one stereodefined center in the starting material **18m**, the quaternary center at the ring junction and the hydroxyl containing stereocenters present in all possible configurations, a total of five stereocenters could be formed in one reaction vessel in a totally stereocontrolled manner. The one-pot conversion of **18m** to **31** could be rationalized by the reactions shown in Scheme 9. An initial five-membered oxonium ring **iii**, which then collapses to the eight-membered ring complex heterocycle can be formulated to explain the domino transformation of **18m**.

Interestingly, the complex ring-retained product **31** was formed as the sole product;[16] its structural assignment which rests firmly on spectroscopic grounds, with HMBC and 1D NOE difference studies proving particularly informative, was further corroborated by single-crystal X-ray analysis (Figure 3).

The results obtained for $[Pb(OAc)_4]$-induced domino transformations show that there is a dual pathway to high molecular complexity with a strong dependence on the nature of the angular substituent in the starting unsaturated



Scheme 9. Proposed mechanism for the lead tetraacetate-mediated domino transformation of **18m** to **31** by means of oxidative/pericyclic (**18m** to **i**), oxyplumbation (**i** to **ii**), deplumbation (**ii** to **iii**), and finally acetoxylation (**iii** to **iv**). Acetal-assisted deplumbation completely dominates the ring-expansion process.

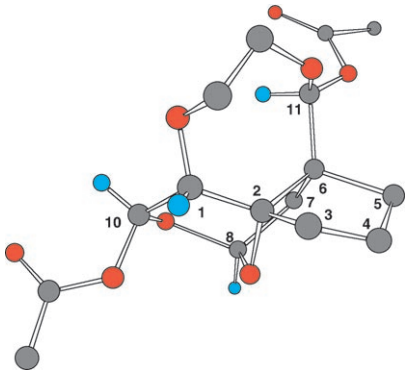
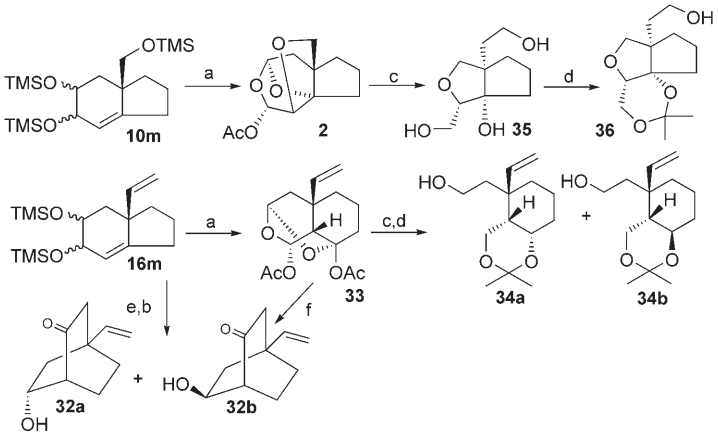


Figure 3. Perspective drawing of the X-ray structure of **31** (Chem 3D output from X-ray coordinates; gray, carbon; red, oxygen, cyan, hydrogen; arbitrarily numbered).

diol. The ether-linked derivatives undergo facile cyclization (the oxonium path ii) at room temperature, while the ester derivatives and the alkyl, olefin, or any other than angular hydrogen-containing compounds appear to go exclusively through the ring-expansion path i. Consequently, the angular substitution has the advantage of providing a convenient handle for further modification through the use of the heteroatom as a reactive center for straightforward access to variably elaborated targets. Thus far, the obtained product ratios show a clear bias toward either ring expansion or the oxonium path, depending on the identity of the angular substituent, which has an important role in the reaction outcome.

The modular domino process offers a platform structure for evaluating possibilities for the synthesis of either ring-expanded (**32**, **33**, **34**) or ring-retained (**2**, **35**, **36**) frameworks from bicyclic unsaturated diols differing only in the angular substitution. Thus, unsaturated diols **10m** and **16m** prepared by a straightforward three and six-step route, respectively, from the known carboethoxy-bicyclic enone **6**, afforded good yields of **2** and **33**, (69 and 75%, respectively), when subjected to $[Pb(OAc)_4]$-mediated oxidative cleavage in

AcOH at room temperature. Conversion of **2** to **36** was accomplished by reduction with excess $LiAlH_4$ in THF at 25 °C to the bis(angularly)-substituted fused tetrahydrofurane **35** (75 %, as a single product) and subsequent selective acetonide formation (acetone, *p*TsOH, 25 °C, 69 %). In an analogous manner **33** was converted to **34a** and **34b** ($LiAlH_4$, THF, reflux, 72 %, then acetone, *p*TsOH, 25 °C, 24 h, 96 %, 1:8 epimeric mixture). Subjected to a mild base treatment (K_2CO_3/MeOH/H_2O, 25 °C) **33** afforded bicyclic aldols **32a** and **32b** (90 % yield, 1:8 ratio) by a ring-system interchange. Finally, a consecutive hetero-domino transformation ([$Pb(OAc)_4$], PhMe, then K_2CO_3/MeOH/H_2O, 25 °C)[6] starting from **16m** afforded cleanly **32**, albeit in lower yield (50 % combined yield, 1:8 ratio). The one-pot path-selective conversion of unsaturated diols **10m** and **16m** into the complex frameworks **2**, **32**, and **33** is outlined in Scheme 10.



Scheme 10. a) [$Pb(OAc)_4$] (2.4 equiv), AcOH, 25 °C; b) [$Pb(OAc)_4$] (2.4 equiv), PhMe then K_2CO_3/MeOH, H_2O, 25 °C; c) $LiAlH_4$, THF, reflux; d) acetone, *p*TsOH, MS 4 Å, 25 °C; e) nBu_4NF/THF, 25 °C; f) K_2CO_3/MeOH, H_2O, 25 °C.

In summary, selection of a suitable functional groups at the angular position is crucial for the efficient execution of such synthetic strategies. The effectiveness of the process is further improved when the resulting complex molecule, such as **34**, is poised to undergo spirocyclization.

Conclusion

The angularly alkoxy-substituted derivatives show an interesting variation from the previously established pattern of behavior,[17] with the isolation of ring-retained domino products. Thus far, the obtained product ratios show a clear bias toward either ring expansion (path i) or oxonium collapse (path ii, Scheme 1) depending on the identity of the angular substituent, which has an important role in the reaction outcome. This work did have an important benefit, as it resulted in the synthesis of various complex structures starting from the same unsaturated diol by tuning of the substitution pattern. The key step (metal addition on the olefin) is responsible for the course of the domino process and reaction conditions can be tailored to fit a particular type of transformation. To the best of our knowledge, the related competing domino process has not been studied previously. The transformations described in this paper broaden the scope of the methodology, and greatly expands on the previously communicated results. On the basis of the work reported here and earlier, its our belief that lead tetraacetate is overall the most effective reagent yet reported for carrying out diol cleavage reactions while generating complexity.[18] Identifying new insights to ultimately achieve high molecular complexity in a modular fashion will remain as a future endeavor as considerable refinement of this process may be anticipated.

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