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Microwave-Accelerated Competing Domino Processes: A Tether-Controlled Dual Pathway into High Molecular Complexity

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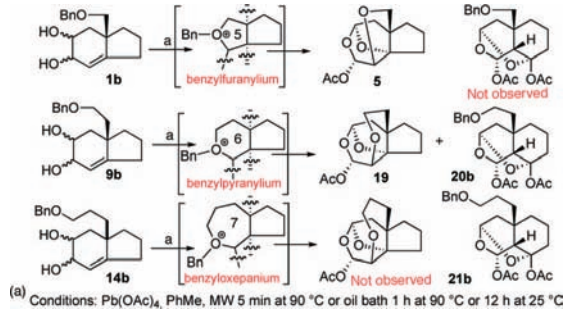
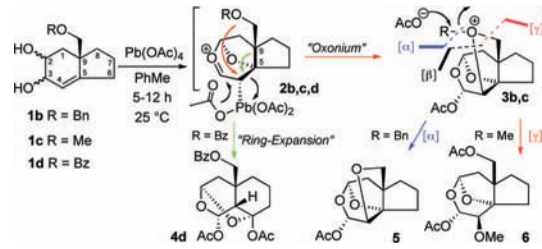
ABSTRACT



Bicyclic unsaturated diols undergo a path selective modular domino transformation upon subjection to $Pb(OAc)_4$, the reaction being biased to the nature of the angular substituent. The magnitude of the linking chain and the nature of the angular substituent determine the reaction course. Methylene ether linkage acts as an autoremovable directing group (ring-retained domino product 5), whereas a propylene linkage switches the path toward the ring-expanded type 21 domino product. Reaction times were substantially reduced using microwave irradiation.

Recently, we reported that type **1** bicyclic unsaturated vicinal diols react efficiently with $Pb(OAc)_4$ to afford rearranged oxygenated heterocycles **4**−**6**, possessing additional rings and numerous stereogenic centers, in high yields.[1] These domino reactions[2] have been shown to rely on four separate steps taking place within a single reaction vessel: an oxidative cleavage, a [4 + 2] cycloaddition, and an oxyplumbation-deplumbation all occurring sequentially in an efficient manner. Remarkably, we could direct the reactivity along two distinctly different pathways by the simple choice of the R group at the angular position (Scheme 1). For example, subjection of **1d** (ester linkage) to $Pb(OAc)_4$ produced solely the ring expanded tricyclic domino product **4d**. In striking contrast to this result, treatment of substrate **1b** (ether linkage) with $Pb(OAc)_4$ led to the ring-retained tetracyclic domino product **5**, whereas **1c** furnished a mixture of **5** and **6**.

Scheme 1. Alternate Pathways by Tuning the Angular Substituent[a]



[a]Colored arrows indicate the dominant reaction course.

A partial explanation for the dominant reaction pathway and product distribution may be found in the relative rates of type-**3** oxonium formation from the type-**2** transient organolead intermediate.[3] Compound **1b** easily forms the

(1) Safir, I.; Castellote, I.; Porcel, S.; Kaoudi, T.; Birlirakis, N.; Toupet, L.; Arseniyadis, S. *Chem.−Eur. J.* **2006**, *12*, 7337–7344.

(2) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131–163. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (c) *Domino Reactions In Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K. M., Eds.; Wiley-VCH: Weinheim, Germany, 2006; ISBN: 3-527-29060-5.

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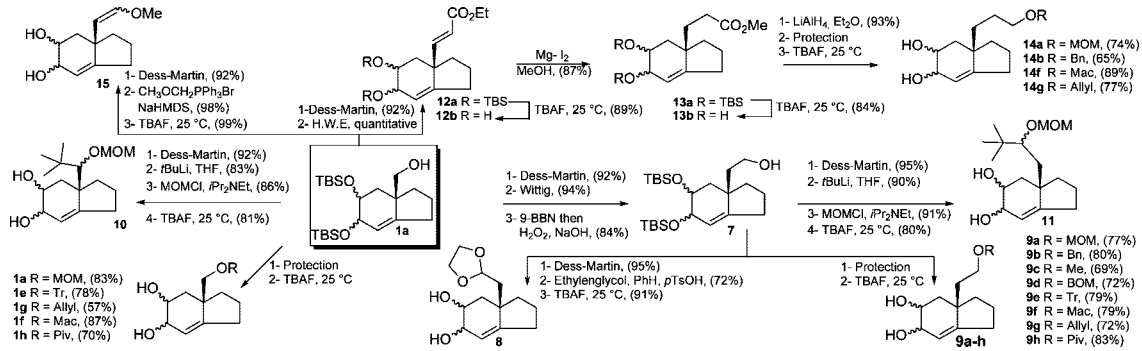
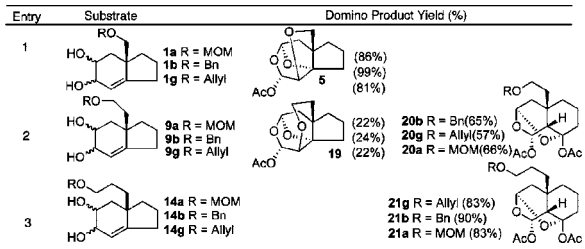
Scheme 2. Preparation of Domino Substrates from Common Precursor **1a**



oxonium ion **3b**. As a consequence, it has much less opportunity to undergo a strain-relieving ring expansion and instead follows the course of benzyloxonium collapse. In the case involving an ether linkage, the ring expansion path is less likely and the reaction proceeds via an intermediate oxonium **3** unless additional steric bulk and chain lengthening is introduced (Table 1). The ester linkage, however, always

Table 1. Tuning the Length of the Connecting Chain[a]



[a] Conditions: b(OAc)4 in PhMe, MW, 5 min at 90 °C or 1 h oil bath at 90 °C or 12−15 h at 25 °C.

gives rise to ring expansion. This switch in reactivity related to the presence of an ester or an alkoxy linkage encouraged us to continue probing this class of domino reactions in an effort to define the origins of orienting factors and to develop a prognostic model for general use. The first question raised was whether a path-selective modular construction of either type **4** or **5** domino product was possible by altering the length and the nature of the linking chain (the tether length between the heteroatom and the bicyclic diol). Indeed, as the length of the linking chain increases, a greater tendency to ring expansion might be anticipated. On the other hand, use of bulky protecting groups or substituents could be utilized to discourage oxonium formation and thus promote the ring expansion process that otherwise does not occur in the case of ether linkage. If so, the problem of competitive pathways could be reduced to the simpler task of preparing appropriately substituted higher analogues of alkoxy-angular substituents. Such selectivity-tuning should be of considerable use in synthesis. With **1a** in hand,[4] variations of the alkoxy substituent at the angular position that should retard oxonium formation and thus favor ring expansion were sought initially. To this aim, trityl protected substrate-diol **1e** and *t*Bu-substituted **10**/**11** were prepared uneventfully. To widen the scope of both the ether and the ester linkage (in addition to those published in our previous work), the primary hydroxyl group at the angular position was protected with an allyl and a methoxyacetyl (Mac) group (Scheme 2). The common precursor **1a** was next subjected to one- and two-carbon homologation. The one-carbon homologated alcohol **7** was prepared by a Dess-Martin oxidation, followed by a Wittig olefination of the resulting aldehyde, which was then taken to the target via a hydroboration-oxidation sequence. The ethylene-tethered **7** was converted into a series of variously substituted diols, by the appropriate protection (ether/ester linkage; we chose **9a**−**h** as representative targets) using standard literature procedures. Whereas the angular acetal containing diol **8** was prepared from **7** via the corresponding aldehyde, following protection of the angular carbonyl as an acetal, the *t*Bu-substituted substrate diols **10** and **11** were obtained by *t*BuLi addition on the corresponding aldehydes and subsequent MOM protection. The two-carbon homologated templates containing alkenyl, ester, and ether functionality were prepared next (Scheme 2). Alkoxymethylenation of the aldehyde obtained from **1a** afforded the required enol ether-diol **15** as a mixture of *E*/*Z* isomers. The two-carbon homologated targets could also be synthesized from **1a**, by converting the same aldehyde as previously into the unsaturated ester derivative **12a** in nearly quantitative yield. Selective reduction of the acrylate moiety in **12a** was achieved using the Mg/MeOH reduction.[5] $LiAlH_4$ reduction of the saturated ester thus obtained afforded the corresponding alcohol, which upon treatment with the appropriate

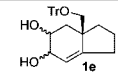
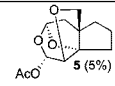
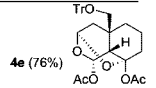
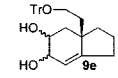
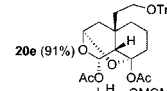
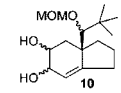
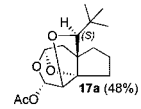
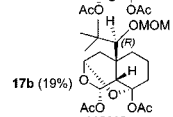
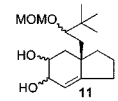
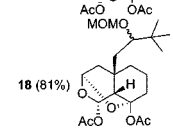
(3) Articles dealing with specific aspects of organolead chemistry: (a) Criegee, R. In *Oxidation In Organic Chemistry*; Wiberg, K. B., Ed.; Academic Press; New York, 1965; Part *A*, p 277−366. (b) Rubottom, G. M. In *Oxidation In Organic Chemistry*; Trahanovsky, W. H., Ed.; Academic Press: London, 1982; Vol. D, Chapter 1. (c) Moloney, M. G. *Main Group Metal Chem.* **2001**, *24*, 653–660. (d) Moloney, M.; Nettleton, E.; Smithies, K. *Tetrahedron Lett.* **2002**, *43*, 907–909.

(4) Obtained in quantity in our previous work, **1a** served as common intermediate for the synthesis of all but two (**16a**, **16b**) domino precursors in this study.

protecting group furnished substrate-diols **14a**,**b**,**f**, and **g**. The more elaborated substrate diols **16a** and **16b** were synthesized uneventfully according to published procedures.[6] In all cases investigated the requisite free-diols were obtained by a fluoride promoted deprotection of the bis-*tert*-butyldimethylsilyl ether protecting group. Substrate-diols possessing chain lengths exceeding three carbon atoms were not evaluated as the use of longer than 3-carbon chains should result in further increase in entropic cost.[7] We studied the domino reaction with the substrates thus obtained, at 90 °C under microwave irradiation[8] for 5 min, and observed a dramatic rate acceleration compared to transformations at 25 °C. However, under conventional heating rate differences decreased considerably (oil bath temperature 90 °C requires only 1 h). Because no significant differences in yields and product distribution were observed under all-three procedures, the yields given in the text, as well as in the Supporting Information, are average values (three runs per method). All the reagents were added at the same time and the mixture in PhMe was either irradiated for 5 min, heated in an oil bath at 90 °C for 1 h or simply stirred at room temperature for 12−15 h (TLC monitoring). Replacing toluene with other solvents (AcOH, MeCN) did not lead to an increase of reaction rate, nor improvement in yield, using any of the three conditions. At the outset, we wanted to test the influence of the tether length (methylene/ethylene/propylene-tethered substrates). Thus, the steric hindrance of the ether protecting group was kept constant, so that it does not interfere with the pathway followed.

To this aim, the methoxymethyl (MOM), benzyl, and allyl protected homologues **1a**,**b**,**g**, **9a**,**b**,**g**, and **14a**,**b**,**g**, respectively, were subjected to the domino conditions. Whereas **1a**,**b**,**g** afforded ring-retained **5** as the only product, the higher homologues **9a**,**b**,**g** showed a different product distribution with the ring-expanded products **20a**,**b**,**g** (57−66%) being isolated as the major products versus 22−24% of **19**. This difference is likely to be due to an entropy effect since the dominant reaction pathway after generation of the transient organolead intermediate is via C5−C9 bond migration[9] while cyclic oxonium formation is less prevalent. Thus, moving the alkoxy substituent one carbon farther in **9a**,**b**,**g** (ethylene-tethered substrates) by homologation of the linking chain (tether length effect) disfavored oxonium formation[10] while the potential for migrating was still maintained. Complete mutation of the path then occurs in the next higher homologues **14a**,**b**,**g**, which yield exclusively **21a**,**b**,**g** (83−90% isolated yields), resulting from a ring expansion[11] as contrasted with the formation of significant amounts of ring-retained **19** from **9**. Ester-tethered substrates always proceed in a totally selective manner toward a ring-expanded domino product (entries 1, 4 in Table 3 and previous work[2]). The experiments portrayed in Table 2 show that the tendency of the organolead

Table 2. Influence of the Steric Bulk at the Angular Position Combined to the Length of the Linking Chain[a]

Entry	Substrate	Domino Product Yield (%)	
1	 **1e**	 **5** (5%)	 **4e** (76%)
2	 **9e**		 **20e** (91%)
3	 **10**	 **17a** (48%)	 **17b** (19%)
4	 **11**		 **18** (81%)

[a] Conditions: Pb(OAc)4 in PhMe, MW, 5 min at 90 °C or 1 h oil bath at 90 °C or 12−15 h at 25 °C.

intermediate, bearing an alkoxy-angular substituent, to rearrange with ring expansion is directly related to the cyclic oxonium's ring size (furylium, pyranylium, oxepanium), that is the length of the linking chain. To address the question of path selectivity, when the cyclic system and the angular substituent are tethered by spacers of bulky nature and various lengths, competition experiments involving the domino substrates **1e**/**9e** and **10**/**11** were conducted.

The ethylene tethered **9e** and **11** were expected to combine the two advantages, steric hindrance and entropic factor, favoring ring-expansion. Evidently in this case, the steric factors imposed by the additional aromatic groups (benzyl versus trityl) or the bulky *t*Bu, combined to the entropy factor (methylene versus ethylene linkage) are sufficient to completely eliminate the oxygen participation.

An increase in the size of the alkyl group on the angular ether substituent from benzyl **1b**[12] to trityl **1e** led to a decrease in the yield of oxonium-path favoring ring-expansion (Table 2). The latter, bearing a bulky trityl group at the angular position, undergoes predominant ring-expansion to give a 1:15 mixture of ring-retained **5** (5%) and ring-

(5) For the original procedure (reduction of acrylonitriles) see: (a) Profitt, J. A.; Watt, D. S.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 127–128. Adapted to a,*β*,-unsaturated esters by: (b) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G *Tetrahedron Lett.* **1987**, *28*, 5287–5290.

(6) (a) Corbu, A.; Gauron, G.; Castro, J. M.; Dakir, M.; Arseniyadis, S. *Org. Lett.* **2007**, *9*, 4745–4748. (b) Adler, M. E.; Yumagulova, S. A.; Torosyan, S. A.; Miftakhov, M. S. *Russ. J. Org. Chem.* **1994**, *30*, 1006–1007. (c) Hanselmann, R.; Benn, M. *Synth. Commun.* **1996**, *26*, 945–961.

(7) The entropic requirement to form an eight-membered cyclic oxonium intermediate renders the ring-retained path unlikely (ca. millionfold drop in reactivity from 5 to 8-membered ring formation). For entropic and enthalpic factors during the formation of medium-sized rings, see: Illuminati, G.; Mandolini, L *Acc. Chem. Res.* **1981**, *14*, 95–101.

(8) (a) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005. (b) Kappe, C. O.; Dallinger, D. *Drug Discovery* **2006**, *5*, 51–63.

(9) Stereoelectronic control: PM3 calculated dihedral angle of 178° for a nearly ideal orbital alignment.

(10) Formation of the 6-membered oxonium ion is slower than that of the 5-membered one (ca. two powers of ten drop in reactivity per added methylene, see ref 7).

(11) The entropic requirement to form a seven-membered cyclic oxonium intermediate renders the ring-retained (oxonium) path unlikely.

(12) The benzyl group in **1b** can assume a disposition antiperiplanar to the carbon-metal bond. This gives rise to a type **2b** cyclic tertiary oxonium formation via $Pb(OAc)_3$ displacement, which completely dominates the ring expansion path.

expanded **4e** (76%) in 81% combined yield. For comparison, the less bulky benzyl ether **1b** gave a single product **5** in 99% yield.[2] In comparison, oxidative cleavage of diols **9a**,**b**,**g** favor ring expansion for entropic reasons but less selectively because of the absence of the beneficial steric hindrance. We then proceeded to examine the path-discriminating ability of the highly strained (those containing a *t*Butyl group) angular alkoxy substituted substrate diol **10** and its higher homologue **11**. We found that the oxonium pathway was disadvantaged in one of the two epimers of **10** where the stereocenter at the angular position is of (*R*)-configuration. Thus, substrate-diol **10** reacted via an oxonium path for the (*S*)- and via a ring-expansion path for its (*R*)-counterpart, furnishing a 48% isolated yield of **17a** (X-ray structure, Figure 1) and 19% of **17b**. The path appears to be simply

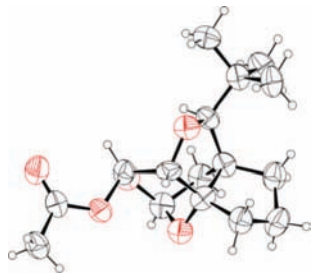
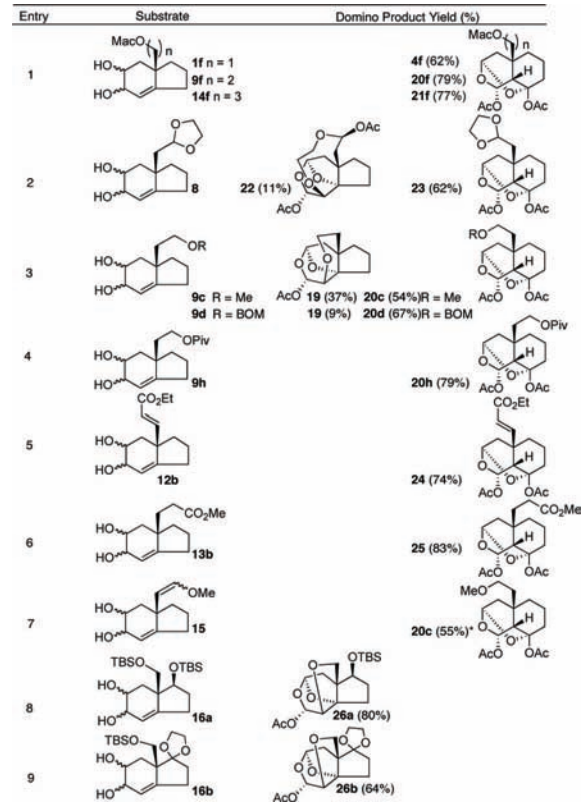


Figure 1. ORTEP drawing of **17a**.

entropy-dependent for the ethylene-tethered substrate-diol **11**, leading exclusively into ring-expanded domino product **18** (81% yield, 1:1 epimeric mixture). As shown in Table 2, the oxonium pathway is severely compromised as the steric hindrance of the ether protective group as well as the tether length and bulk increase. Obviously, the size of the tether at the angular position has a controlling influence on the path selectivity; entropic restrictions imposed by the length of the tether combined to steric bulk of the angular substituent determine the path of the reaction. The part of entropy factor is clearly illustrated by comparison among the product distributions in domino reactions with diols **1a**,**b**,**g**/**9a**,**b**,**g**/**14a**,**b**,**g**, whereas the combined effect of steric/entropic influence is well illustrated with the reactivity pattern of diols **1e**/**9e** and **10**/**11**.

Orienting experiments exemplified by the conversion of the selected unsaturated diols into the complex ring-retained and ring-expanded domino products are outlined in Table 3. Hence, substrate-diol **8** reacted predominantly via a ring-expansion path (entry 2, Table 3) while all ester (entries 1, 4, 6) alkyl and alkenyl (entries 5, 7) substituted diols reacted exclusively via a ring-expansion path. The highly elaborated substrate-diols **16a** and **16b** (entries 8, 9, Table 3) reacted, as expected, exclusively via the oxonium path, providing ring-retained domino products **26a** and **26b** in 80 and 64% yield respectively. Further to our earlier report,[2] we have investigated domino behavior of 24 additional diols. In the context of this work, the dual-path observed when the angular substituent is an ether group is notably more interesting, and indeed a distinct

Table 3. $Pb(OAc)_4$-Mediated Domino Reactions: More Orienting Experiments[a]



[a] Conditions: Pb(OAc)4 in PhMe, MW, 5 min at 90 °C or 1 h oil bath at 90 °C or 12−15 h at 25 °C. *Reduction with H2−Pd/C in PhMe followed the domino process.

trend of reversed path-selectivity as the linking chain is increased in size from methylene to ethylene can be distinguished. In summary, we can reliably control the orientation of the domino process using the steric/stereoelectronic/entropic triade as a means of gaining path selectivity. The differences in product distribution are ascribed to different types of reactivity of the transient organolead intermediates (**2b**,**c**,**d** and **3b**,**c**, Scheme 1), the reaction being biased to the nature of substitution at the angular position.

Ether linkage is a prerequisite for the oxonium path. The distribution can be altered through shortening of the tether chain, which increases the effectiveness of the oxonium path, or lengthening of the tether amplifying its bulkiness, which increases the effectiveness of the ring-expansion path. Insofar as the use of microwave assisted domino chemistry is concerned, though there is no specific nonthermal microwave effect, the very fast reaction rate (less than five minutes) will certainly allow working in water containing solvents (tests with 1:1 AcOH-H_2O proved extremely promising).

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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