ORGANIC LETTERS

2009
Vol. 11, No. 16
3610−3613

Competing Domino Processes: Path-Discriminating Ability of Epoxide Stereochemistry at the Angular Position

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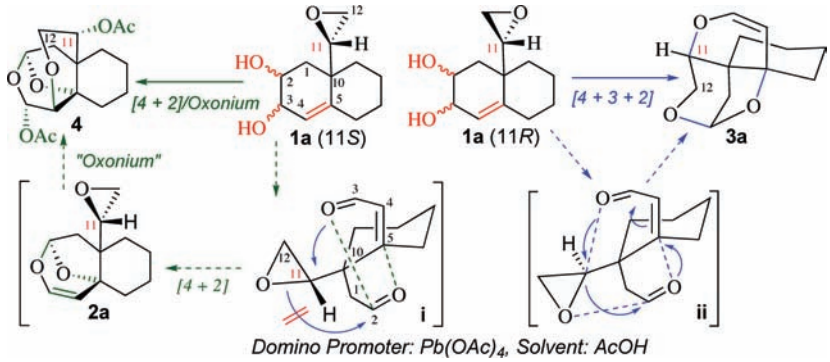
Received June 15, 2009

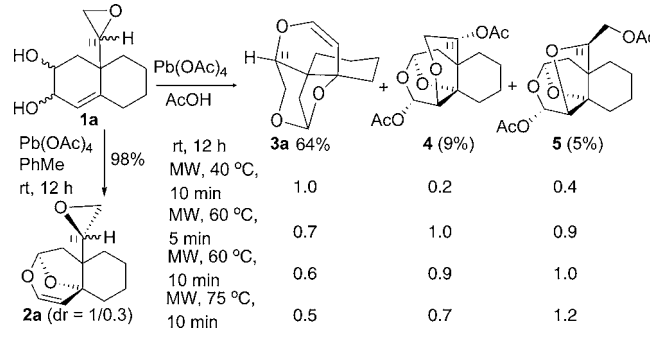
ABSTRACT



Structurally different products can be reached selectively from unsaturated vicinal bicyclic diols, which differ only by the epoxide configuration at the angular position. It is possible to modify the regiochemical outcome of the domino process in such a way as to create a different pathway, [4 + 2] versus [4 + 3 + 2], and control product distribution by using the configuration bias. No previous example of a domino variant of the [4 + 3 + 2] process appears to have been documented.

The development of modular domino reactions remains an attractive challenge.[1] Recently, it was reported from this laboratory that the oxidative cleavage of bicyclic unsaturated diols bearing an olefin or a ketone at the angular position results in the formation of a tricyclic ene-acetal via a [4 + 2] or a tetracyclic bis-acetal via a [4 + 2 + 2] pathway depending on the substitution pattern.[2] In anticipation that substitution at the angular position by epoxy, rather than carbonyl groups, might also favor the extended Michael path, a series of type **1** substrate-diols were synthesized and their reactivity pattern explored. Herein, we describe the regiochemical course of these domino reactions based on the path-

Scheme 1



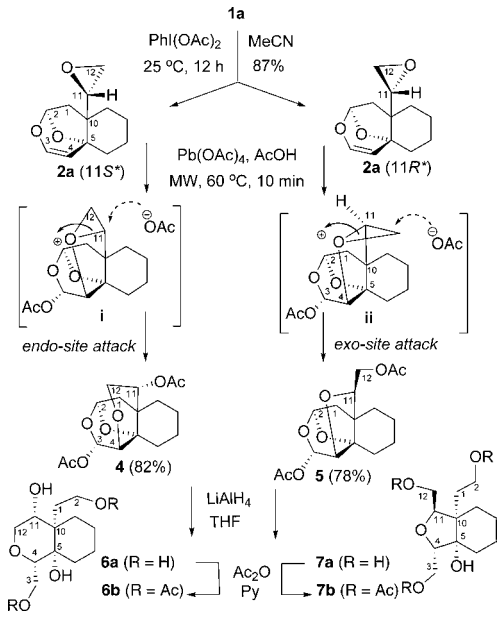
(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (b) *Domino Reactions In Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K. M., Eds.; Wiley-VCH: Weinheim, Germany, 2006; ISBN 3-527-29060-5.

(2) Elkhayat, Z.; Safir, I.; Retailleau, P.; Arseniyadis, S. *Org. Lett.* **2007**, *9*, 4841–4844. The first example of an intramolecular [4 + 2 + 2] cycloaddition was reported by Lautens et al.: Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, C. *J. Am. Chem. Soc.* **1995**, *117*, 6863–6879.

10.1021/ol9013377 CCC: $40.75
Published on Web 07/24/2009

discriminating ability of oxirane configuration at C11. Our first experiments along these lines were concerned with domino reactions portrayed in Schemes 1 and 2, and in these

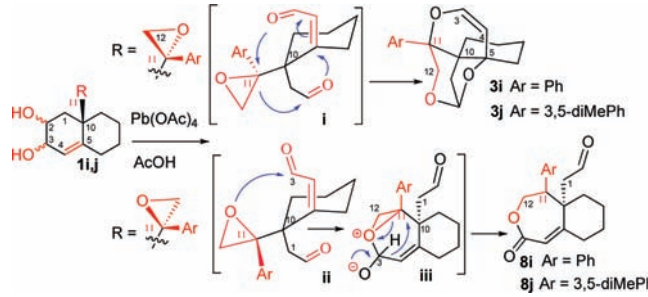
Scheme 2



undertakings we observed the conversion of an angularly substituted octalin diol **1a** to a tetracyclic acetal **3a**, a fused-oxan **4**, and a fused-oxolan **5** in various ratios (Scheme 1).

Thus, upon $Pb(OAc)_4$-mediated oxidative cleavage[3] of the unsaturated diol **1a** the dihydropyrane-bridged tetracyclic acetal **3a** was isolated in 64% yield along with **4** (9%) and **5** (5%), products of the serial [4 + 2]/oxonium path.[4] The latter was favored by conventional and microwave[5] heating, since the percentage of **3a** decreases with increasing temperature. The mechanism proposed for this $Pb(OAc)_4$[6] mediated domino reaction consists of the following key steps: (1) oxidative cleavage generating an intramolecularly linked two-component hetero-π system in conjuction with an epoxide, a potential [$m + n + o$] motive,[7] and (2) depending on the C11 configuration this evolves through a hetero[4 + 3 + 2] cycloaddition, an extended Michael path, to form a type-**3** complex heterocycle, or through a hetero[4 + 2] path, to form a type-**2** half-cascade intermediate, which in turn undergoes an intramolecular oxonium formation, followed by oxonium collapse with acetate attack at either C11 or at C12 to furnish the final domino products **4** or **5** (graphical abstract and Scheme 3). Inasmuch as it seemed possible that

Scheme 3



the configurational inversion might be of use in deducing a mechanism, we chose to carry out C11 epimer separation at the half-cascade level **2**. This was reached by using either $PhI(OAc)_2$ or $Pb(OAc)_4$ as the domino promoter.[8] Reaction of each individual epimeric epoxide **2a**(11*S**) and **2a**(11*R**) with $Pb(OAc)_4$ in AcOH at room temperature proceeded in a path-selective manner to give an acetoxylated fused-tetrahydropyran **4** and an acetoxylated fused-tetrahydrofuran **5**, respectively. As shown in Scheme 2, **2a**(11*S**) reacts with $Pb(OAc)_4$ acting as a Lewis acid to afford a transient organolead intermediate that is attacked by the tethered epoxide generating bicyclic epoxonium ion **i**, which reacts with acetate nucleophile at C11 to give **4** as a single product. In an analogous manner, **2a**(11*R**) gives **5**. Upon reductive treatment of **4**, the tetrahydropyran-fused bicyclic framework **6a** (better characterized as the corresponding bis-acetate **6b**) is obtained. Under the same conditions, the epimeric **2a**(11*R**) afforded the fully functional tetrahydrofuran-fused bicyclic framework **7a** (better characterized as the corresponding tris-acetate **7b**). Repeatedly, diastereomerically pure

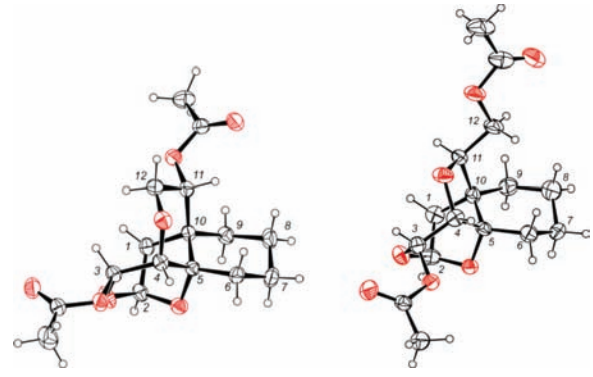


Figure 1. ORTEP view of the molecular structures of **4** and **5**.

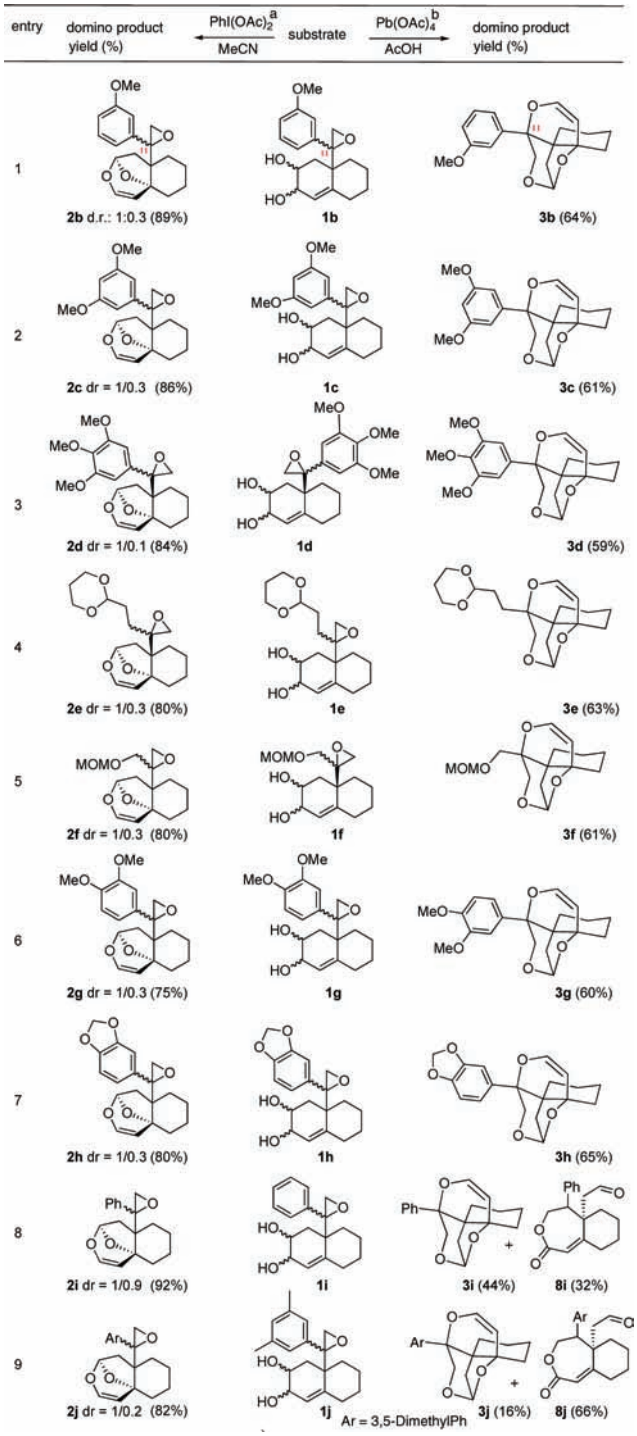
(3) For recent examples, see: (a) Ozturk, C.; Topal, K.; Avijente, V.; Tuzun, N.; Sanchez, E.; Arseniyadis, S. *J. Org. Chem.* **2005**, *70*, 7080–7086. (b) Safir, I.; Castellote, I.; Porcel, S.; Kaoudi, T.; Birlirakis, N.; Toupet, L.; Arseniyadis, S. *Chem.—Eur. J.* **2006**, *12*, 7337–7344. (c) Elkhayat, Z.; Safir, I.; Castellote, I.; Retailleau, P.; Arseniyadis, S. *Org. Lett.* **2008**, *10*, 2219–2222. (d) Elkhayat, Z.; Safir, I.; Aquino, M.; Perez, M.; Gandara, Z.; Retailleau, P.; Arseniyadis, S. *Eur. J. Org. Chem.* **2009**, 2687–2694.

(4) For an intermolecular serial process see: Wender, P. A.; Gamber, G. G.; Scanio, M. J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 3895–3897.

(5) For reviews on the use of microwaves in organic synthesis see: (a) de la Hoz, A.; Diaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659–3673. (b) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005. (c) Kappe, C. O.; Dallinger, D. *Drug Discovery* **2006**, *5*, 51–63.

(6) For articles dealing with specific aspects of organolead chemistry see: (a) Criegee, R. In *Oxidation In Organic Chemistry*; Wiberg, K. B., Ed.; Academic Press: New York, 1965; Part A, pp 277−366. (b) Rubottom, G. M. In *Oxidation In Organic Chemistry*; Trahanovsky, W. H., Ed.; Academic Press: London, UK, 1982; Vol. D, Chapter 1. (c) Moloney, M. G. *Main Group Metal Chem.* **2001**, *24*, 653–660.

Table 1. Variation of the C11 Substituent and the Domino Promoter: Hetero[4 + 2]/Hetero[4 + 3 + 2] Cycloaddition



[a] Reactions conducted with 1.2 mmol of $PhI(OAc)_2$ and 1.0 mmol of substrate-diol in MeCN (5 mL), 12 h at 25 °C. [b] Reactions conducted with 2.4 mmol of $Pb(OAc)_4$ and 1.0 mmol of substrate-diol in AcOH (5 mL) at 25 °C for 12−15 h or MW irradiation at 60 °C, 10 min.

epoxides (11*S**)-**2a** and (11*R**)-**2a** provided the topologically complex tetracyclic compounds **4** and **5** (X-ray structures: Figure 1), with *endo* and *exo* selectivity,[9] respectively, under exclusive regiochemical control and in good yields. *Endo*-selectivity could be attributed to the minimization of the ring strain in formation of the tetracyclic intermediate **4** and the unfavorable *syn*-pentane interaction between the entering nucleophile and C1−C10−C11−C12. On the other hand, the domino reaction on (11*R**)-**2a** shows preference for THF over THP formation because of both steric and stereoelectronic preference for *exo*-attack on the bicyclic epoxonium ion relative to *endo*-mode addition. Experimental facts show that each of the two bicyclic epoxonium ions formed, **i** and **ii**, react cleanly at a different carbon on the three-membered ring.

Therefore, the combination of reagent (or solvent)-based modulation and path-discriminating ability of epoxide's stereochemistry at C11 in the domino reaction of epoxydiols **1a** allows for selective preparation of either highly functionalized type-**6** cis-fused oxans or fully functionalized type-**7** cis-fused oxolans. To determine the generality of this hetero[4 + 3 + 2] process, diols **1b**−**j** (entries 1−9, Table 1) were prepared from the known aldehyde[2] and subjected to the standard domino conditions.

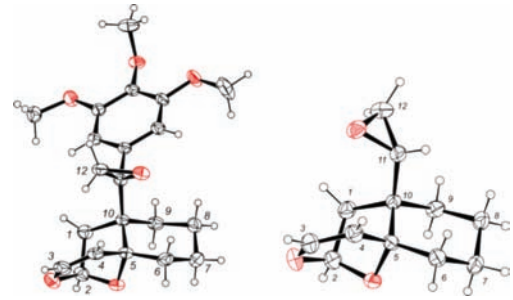


Figure 2. ORTEP view of the molecular structure of **2d** (major diastereoisomer) and **2a** (minor diastereoisomer).

Mechanistic probes for distinguishing the domino pathways have included interrupted domino experiments, which detect the rearrangement that can occur only via the [4 + 2] pathway. Control of the regiochemical outcome of the domino process could be achieved either by changing the domino promoter from $Pb(OAc)_4$ into $PhI(OAc)_2$ or simply changing the solvent from AcOH to PhMe. The percentage of each epimeric epoxide **2a**−**j** was determined by ^{1}H NMR analysis of reaction mixtures as the H3−H4 proton doublets of the isomers were sufficiently separated for integration. The identity of each component of the epimeric mixture was

(7) For [*m* + *n* + *o*] cycloadditions, see: (a) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876–2877. (b) Wegner, H. A.; de Meijere, A.; Wender, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 6530–6531. (c) Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc.* **2006**, 5354–5355, and references cited therein.

(8) During our previous investigations,[3d] it was observed that substrate-diols show a dual behavior, depending on the the domino promoter $Pb(OAc)_4$/ $PhI(OAc)_2$ or the solvent used (PhMe or AcOH).

(9) For *endo*, *exo mode* discussion, see: (a) Fujiwara, K.; Murai, A. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 2129–2146. (b) Valentine, J. C.; McDonald, F. E. *Synlett* **2006**, 1816–1828. (c) Kumar, V. S.; Wan, S.; Aubele, D. L.; Floreancig, P. E. *Tetrahedron: Asymmetry* **2005**, *16*, 3570–3578. For a computational study on bicyclic epoxonium ions, see: (d) Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915–7923.

determined by measuring spatial proximity effects (NOESY) and corroborated by X-ray analysis of the crystalline half-cascade products **2a** and **2d** (Figure 2).[10]

The domino outcome of the reactions of **1b**−**j** agreed with the ratio determined in all but one case (entry 3, Table 1). This prompted us to carry out additional experiments to check the configurational stability of the epoxide component under domino conditions. To this end, bis-TBS protected epoxy-diols **1a**−**j** were stirred in AcOH, at 25 °C for 12−15 h, in the presence of the domino promoter.

All substrates were recovered intact, except **1d**-bis-TBS, which repeatedly gave an inseparable mixture of diastereomeric aldehydes, where epoxy functionality was missing. This could explain the 59% isolated yield (which raises to 80% when run under microwave irradiation), taking into account that the C11 configuration of the major component (10:1, X-ray, Figure 2) is the one not allowing for a hetero[4 + 3 + 2] process.

By replacing the hydrogen at C11 by an alkyl or aryl group, no byproducts could be clearly identified, except for entries 8 and 9, the only isolated domino product being the one deriving from a hetero[4 + 3 + 2] path. However, the mass balance of the reaction was low (ca. 60%), suggesting that decomposition of the domino product from the epimeric counterpart was occurring during workup or column chromatography. X-ray analysis of **3b** (Figure 3) confirmed the

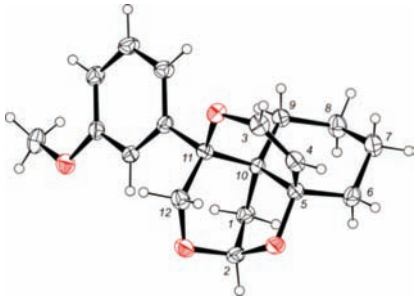


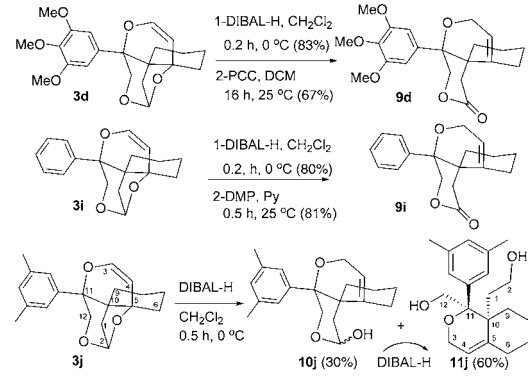
Figure 3. ORTEP view of the molecular structure of **3b**.

structures of all type-**3** complex molecules synthesized throughout this investigation, by analogy. It should be pointed out that substituting $Pb(OAc)_4$ by $PhI(OAc)_2$ failed to produce any type-**3** domino product in either solvent at room temperature or under microwave heating.[11]

Domino probes **1i** and **1j** with a phenyl and 3,5-dimethylphenyl group at C11, respectively (entries 8 and 9, Table 1), provided a mixture of two separable products **3i**(**3j**) and **8i**(**8j**). The path-discriminating ability of the angular epoxide's stereochemistry in these domino reactions with $Pb(OAc)_4$ is rationalized in Scheme 3.

Insofar as formation of the hetero[4 + 3 + 2] adducts **3i** and **3j** is concerned, in the C11(*R**) configuration the epoxide unit is so oriented that SN_2-like attack by the neighboring enol, coupled with epoxide ring-opening oxacyclization, is favorable and ensures an expanded Michael process ending in **3i** (**3j**). In the C11(*S**) configuration, the epoxide-oxygen's free doublet bonds with C3 thus creating the appropriate environment, which promotes a ring-expanding rearrangement. The new domino product, a seven-membered-ring lactone **8i** (**8j**) formed in this reaction, most likely arises through the intermediacy of an intramolecular hydride shift (cyclic epoxonium **iii**), the overall process being an oxidoreduction.[12] In summary, the above results could be rationalized in terms of the orientation control offered by the stereogenic center at C11 through the intermediates **i**/**ii**. As a concluding remark on the advantage of this modular domino approach, the type-**3** [4 + 3 + 2] adducts could then be efficiently converted into type-**9** tricyclic lactones by a two-step sequence or type-**11j** fused-DHP, simply by extending the DIBAL reduction time, as outlined in Scheme 4.

Scheme 4



A great increase in molecular complexity has been realized by bringing together two in situ generated components with a preexisting third one (the angular epoxide). The principal domino product proved to be of type **3** (except entry 9). 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, otherwise difficult to obtain.[13]

Acknowledgment. Financial support from the Centre National de la Recherche Scientifique, fellowship awards from Institut de Chimie des Substances Naturelles (France), and discussion with Professor Henry Rzepa (Imperial College, London, UK) are gratefully acknowledged.

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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(10) We systematically elucidated the structures of the resulting domino products by extended high-field NMR studies, and corroborated by several single-crystal X-ray diffraction analyses and molecular mechanics calculations.

(11) We examined the effect of substituting $PhI(OAc)_2$ by $PhI(OCOCF_3)_2$, but nothing useful was achieved.

(12) Swain, C. G.; Powell, A. L.; Sheppard, W. A.; Morgan, C. H. *J. Am. Chem. Soc.* **1979**, *101*, 3576–3583.

(13) From a more general point of view, the results obtained raise the question of "how the C11 stereochemistry can be controlled so as to control the formation of one type of product over another", as one of the referees has kindly remarked.