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Exploring Modular Domino Reactions: Competing Processes Based on the Nature of the Angular Substituent

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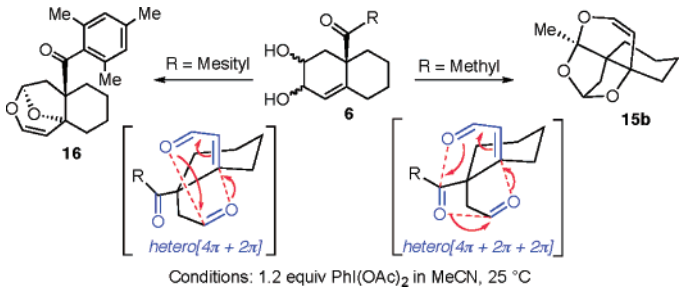
ABSTRACT



The octaline diol system 6 was found to undergo an interesting set of reactions upon treatment with $PhI(OAc)_2$, leading, in a single synthetic operation, to complex oxygen heterocycles. Experimental evidence supports an intramolecular hetero[4 + 2 + 2] adduct that has heretofore never been observed, which completely dominates the hetero[4 + 2] path in several cases. The domino protocol can be biased one way or another depending on both the nature of the π-system and the length of the methylene spacer at the angular position.

A domino methodology,[1] based on $Pb(OAc)_4$-mediated oxidative cleavage, has been developed within our group, by good fortune more than through deliberate effort, which has proven valuable for the construction of complex oxygen heterocycles.[2] The major obstacle, which could have precluded extension of the above process has been the lack of reagents able to replace the multi-task lead tetraacetate in generating the same degree of molecular complexity.[3] Accordingly, we oriented part of this research to the synthesis and reactivity of the hetero[$4\pi + 2\pi$] domino products, the so-called "half-cascade" intermediates,[4] for which lead tetraacetate could effectively be replaced by iodobenzene diacetate in the oxidative/pericyclic part of the domino process.[5] During the course of this study, a new rearrangement in the resulting intramolecularly linked heterodiene/heterodienophile framework was uncovered. The basis of this investigation is the unsuspected course of the $PhI(OAc)_2$-mediated domino reactions[6] of unsaturated *vic*-diols of type **6** allowing the production of a tetracyclic bisacetal of type **15** in a single operation. The first example of an intra-

(1) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131−163. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (c) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304−322. (d) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vogtle, F., Eds.; Wiley-VCH: Weinheim, Germany, 2000; pp 39−64. (e) *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) The probe used is an unsaturated bicyclic 1,2-diol having a variable substitution pattern. Advantages are the very rapid increase in molecular complexity and its modular character. (a) Finet, L.; Candela Lena, J. I.; Kaoudi, T.; Birlirakis, N.; Arseniyadis, S. *Chem.—Eur. J.* **2003**, *9*, 3813−3820. (b) Safir, I.; Castellote, I.; Porcel, S.; Kaoudi, T.; Birlirakis, N.; Toupet, L.; Arseniyadis, S. *Chem.—Eur. J.* **2006**, *12*, 7337−7344.

(3) Candela Lena, J. I.; Sánchez Fernández, E.; Ramani, A.; Birlirakis, N.; Barrero, A. F.; Arseniyadis, S. *Eur. J. Org. Chem.* **2005**, 683−700.

(4) (a) Chanu, A.; Safir, I.; Basak, R.; Chiaroni, A.; Arseniyadis, S. *Org. Lett.* **2007**, *9*, 1351−1354. (b) Chanu, A.; Safir, I.; Basak, R.; Chiaroni, A.; Arseniyadis, S. *Eur. J. Org. Chem.* **2007**, 4305−4312.

(5) First observed by Criegee, $PhI(OAc)_2$ cleaves *vic*-diols in AcOH at 50−80°C with a rate constant about 1/100 that of $Pb(OAc)_4$: Criegee, R.; Beucker, H. *Ann. Chem.* **1939**, *541*, 218−238.

(6) Hypervalent iodine reagents frequently imitate the transformations mediated by Hg^{2+}, Tl^{3+}, Pb^{4+}, and Pd^{2+} but without the toxic and environmental issues: (a) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431−447. (b) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179−1255. (c) Ladziata, U.; Zhdankin, V. *ARKIVOC* **2006**, *ix*, 26−58.

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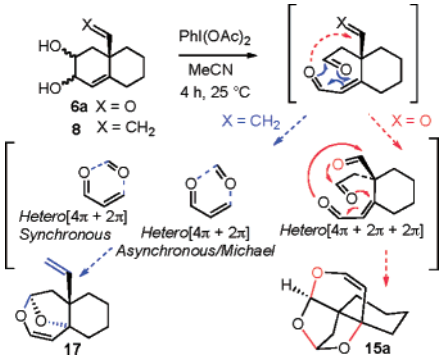
molecular [4 + 2 + 2] cycloaddition was reported by Lautens et al.[7] The concerted eight-electron process took 20 h at room temperature and required 8% of cobalt catalyst, $Co(acac)_2$, 8% of dppe, and 32% of Et_2AlCl. The intermolecular version of transition-metal-catalyzed [4 + 2 + 2] discovered earlier by Carbonaro et al. used also a three-component system, $CoCl_2/Et_2AlCl$/dppe.[8] More recently, Snyder et al. reported a cobalt-catalyzed [4 + 2 + 2] cycloaddition of homoconjugated dienes (benzobarrelene) using $Co(acac)_2$/DPPE/Et_2AlCl (1/1.5/10) in considerably higher yields (24−48 h, 50 °C, 80% yield).[9] Herein, we disclose exploratory studies on the $PhI(OAc)_2$-mediated oxidative cleavage of bicyclic unsaturated diols[10] bearing a ketone or an olefin at the angular position aimed to divert the reaction course from the [4 + 2] pathway. Initial attempts were centered on the aldehyde **6a** and its corresponding olefin **8** (Scheme 1).

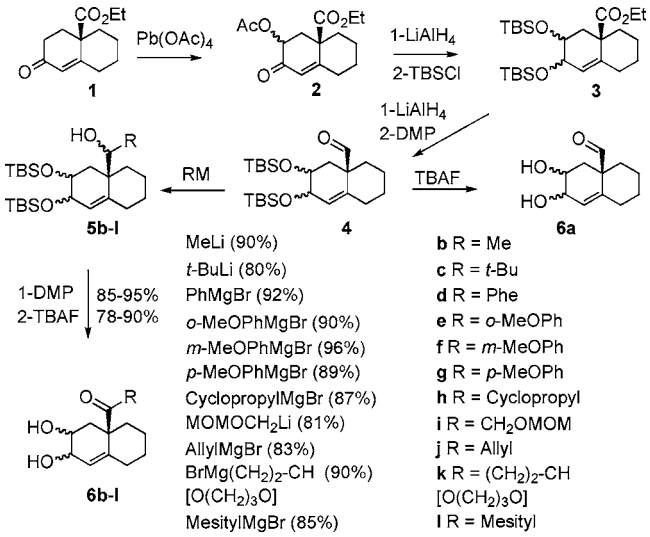
Scheme 1. Possible Pathways Following Oxidative Cleavage



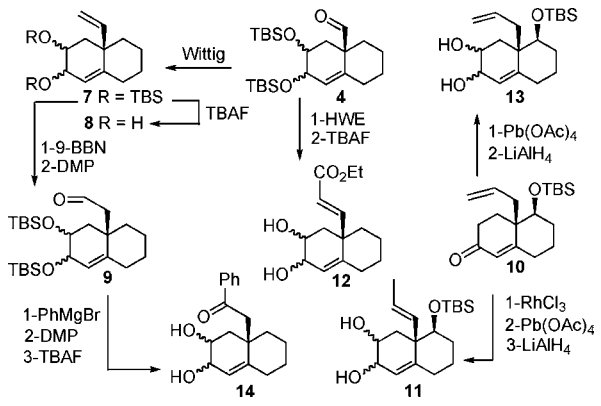
The former, upon subjection to $PhI(OAc)_2$ in MeCN, afforded after 4 h stirring at room temperature a new adduct, to which structure **15a** was assigned. As portrayed in Scheme 1, the carbonyl present at the angular position reacted with the in situ delivered 4π and 2π species to generate a highly complex oxygen heterocycle, the bisacetal **15a**. Although the isolated yield was very low (13%), the result was remarkable since this one-pot conversion requires an oxidative cleavage of a C−C bond, three new C−O bond formations, three new asymmetric centers controlled, and three new rings formed. To the best of our knowledge, this type of hetero[4 + 2 + 2]cycloaddition has never been observed before. On the other hand, replacing the carbonyl by a methylene group and treatment with $PhI(OAc)_2$ as above afforded **17** as a single domino product. Its structure was secured by extensive 1D and 2D ^1H and ^{13}C NMR analyses. The proposed mechanism portrayed in Scheme 1 consists of the following key steps: (1) oxidative cleavage generating an intramolecularly linked 4π + 2π + 2π system, (2) formation of either a tricyclic ene-acetal **17** or a tetracyclic bisacetal **15a** depending upon the substitution pattern. As yet, we do not have a definitive proof that the step following the oxidative cleavage of **8** is a concerted (synchronous/asynchronous)[11] or stepwise (largely asynchronous/Michael-type addition) reaction nor we can exclude the possibility for a concerted eight-electron process rather than an extended intramolecular Michael-type addition en route to **15a**.

The uniqueness of this transformation led us to pursue this study, varying the substitution pattern at the angular position of the bicyclic framework. The structural range of unsaturated 1,2-diols surveyed is represented by formulas **6**−**14** (Schemes 2 and 3). These compounds were either prepared from **1** by literature methods or were available from **10**, used in our previous studies.[3] The Robinson annulation product **1**, obtained in large scale and good yield using Jung's modification,[12] was acetoxylated ($Pb(OAc)_4$, PhH, 3 days), affording the required acetoxy enones **2** as an epimeric mixture (73%). Selective reduction ($LiAlH_4$, Et_2O, −20 °C,

Scheme 2. Preparation of Type **6** Domino Substrates



Scheme 3. Preparation of the Domino Substrates **8**−**14**



(7) (a) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, C. *J. Am. Chem. Soc.* **1995**, *117*, 6863−6879. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92.

(8) Carbonaro, A.; Cambrisi, F.; Dall'Asta, G. *J. Org. Chem.* **1971**, *36*, 1443−1445.

(9) Kiattansakul, R.; Snyder, J. K. *Tetrahedron Lett.* **1999**, *40*, 1079−1082.

(10) Candela Lena, J. I.; Altınel, E.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron Lett.* **2002**, *43*, 1409−1412.

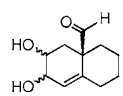
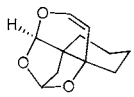
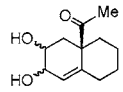
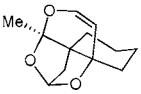
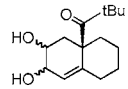
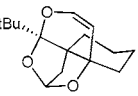
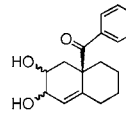
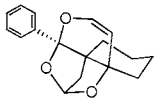
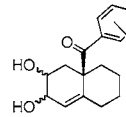
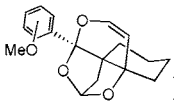
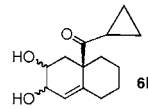
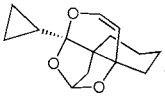
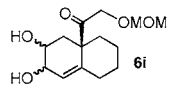
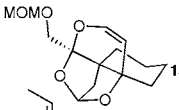
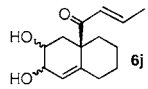
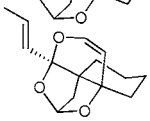
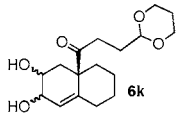
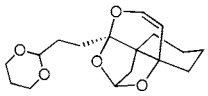
30 min) followed by TBS protection of the resulting diol (TBSCl, DMF, imidazole, 25 °C, 12 h) afforded the TBS ester **3** (87%). The latter was reduced to the corresponding alcohol ($LiAlH_4$, Et_2O, 0 °C, 30 min, 84%), which in turn was converted to the target **4**, by a Dess−Martin oxidation (DMP, py, CH_2Cl_2, 1 h, 25 °C, 90%).

The aldehyde **4**, thus obtained, served as key intermediate for the construction of all but two domino templates (namely, **11** and **13**, Scheme 3). Grignard or organolithium addition at below zero temperatures provided the intermediate carbinols **5b**−**l** (80−96%). Dess−Martin oxidation (DMP, py, CH_2Cl_2, 1 h, 25 °C, 85−95%), followed by a desilylation (TBAF, 60 °C, 1 h, 78−90%), completed the synthesis of substrate diols **6b**−**l** (Scheme 2). The preparation of domino precursors **8** and **11**−**14** is summarized in Scheme 3. Starting from the common intermediate **4**, a Wittig olefination ($MeP^+Ph_3Br^-$, *t*BuOK, THF, 12 h, 25 °C) afforded **7** (97%), which in turn furnished **8** upon desilylation (TBAF, 82%) and also the homologated ketone **14**, through hydroboration (9-BBN, 0 °C), oxidation (DMP, 95%), Grignard addition (PhMgBr, 89%), oxidation of the resulting carbinol (DMP, 92%), and desilylation (TBAF, 89%). Conjugated ester **12** was obtained straightforwardly from **4** via a HWE olefination [$(EtO)_2P(O)CH_2CO_2Et$, NaHMDS, THF, 25 °C, 14 h, 85%] and a subsequent desilylation (TBAF, 86%). The remaining targets, **11** and **13**, were synthesized from **10** in three- and two-step sequences, respectively.[13] Acetoxylation of the latter as above followed by reduction ($LiAlH_4$, Et_2O, 0 °C) furnished the homologated olefin **13**, albeit in low yields, while olefin migration ($RhCl_3$, *i*-PrOH, reflux, 68%),[14] followed by the same two-reaction sequence as for **13**, afforded the last target **11** (57%, two steps).

With the substrate diols in hand, the scope of the methodology in terms of substrate structure was investigated. The key results are summarized in Tables 1 and 2 for the [4 + 2 + 2] and [4 + 2] paths, respectively. First, in the **6a**−**k** series, each diol was reacted with 1.2 equiv of $PhI(OAc)_2$ in MeCN or 1.4 equiv of $Pb(OAc)_4$ in PhMe at 25 °C, as indicated in Table 1, and the corresponding [4 + 2 + 2] adducts **15a**−**k** were isolated as the sole products and characterized. The tetracyclic bisacetal **15b**, whose structure was secured by X-ray analysis (Figure 1) was isolated in 51% yield upon $PhI(OAc)_2$-mediated oxidative cleavage (56% using lead tetraacetate) of the substrate diol **6b**. The structural range of unsaturated *vic*-diols first surveyed is represented by formulas **6a**−**k**.

Diols bearing various groups (alkyl, cycloalkyl, alkenyl, acetal, aryl) efficiently undergo this domino process to generate moderate to good yields of the corresponding complex oxygen heterocycle (Table 1, entries 1−11). The

Table 1. $PhI(OAc)_2$- and $Pb(OAc)_4$-Mediated Domino Reactions: Variation of the Ketone Component in a Hetero[4π + 2π + 2π] Cycloaddition

entry	substrate	domino product	yield (%) A[a] (B)[b]
1	 **6a**	 **15a**	13
2	 **6b**	 **15b**	51 (56)
3	 **6c**	 **15c**	68 (60)
4	 **6d**	 **15d**	61 (60)
5	 **6e** (*o*-MeO)	 **15e** (*o*-MeO)	67[c] (60)
6	**6f** (*m*-MeO)	**15f** (*m*-MeO)	68 (68)
7	**6g** (*p*-MeO)	**15g** (*p*-MeO)	63 (63)
8	 **6h**	 **15h**	57 (54)
9	 **6i**	 **15i**	60 (62)
10	 **6j**	 **15j**	64 (63)
11	 **6k**	 **15k**	58 (57)

[a] Method A: The substrate (1 mmol) and $PhI(OAc)_2$ (1.2 mmol) in MeCN (5 mL) were stirred at room temperature for 4 h (TLC monitoring). [b] Method B: The substrate (1 mmol) and $Pb(OAc)_4$ (1.4 mmol) in 5 mL of toluene were stirred at room temperature for 4 h (TLC monitoring). [c] Very unstable, decomposes on standing.

mass losses observed in these reactions could be explained by the fact that the domino products appear to be sensitive to the chromatographic conditions used.[15]

The structures of the 10 additional hetero[4 + 2 + 2] type **15** products were assigned by correlation to **15b**, whose structure was established through X-ray crystallography.

The $PhI(OAc)_2$- and $Pb(OAc)_4$-mediated domino reactions affording [4 + 2 + 2] adducts were found to differ from the known intra- and intermolecular [4 + 2 + 2] cycloadditions in several ways. The latter required a three-component catalytic system. In contrast, the former proceed smoothly

(11) For a discussion of pericyclic reaction transition states, see: Houk, K. N.; Gonzales, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81−90.

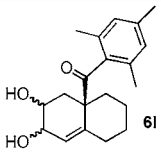
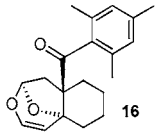
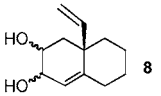
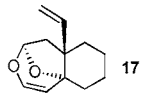
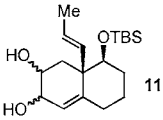
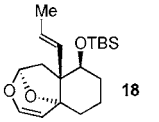
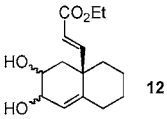
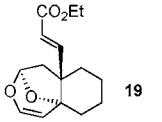
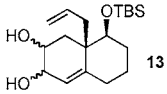
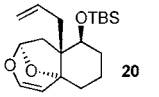
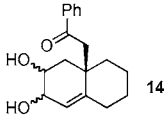
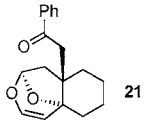
(12) Best preparation of the common intermediate **1**: (a) Jung, M. E.; Piizzi, G. *Org. Lett.* **2003**, *5*, 137−140. (b) Jung, M. E.; Piizzi, G. *J. Org. Chem.* **2003**, *68*, 2572−2582.

(13) It should be pointed out that all domino reactions are performed on crude diastereomeric mixtures; we only show the stereopure target diols for characterization purposes, by separating various amounts of stereopure compounds using the eluent indicated in the experimental part.

(14) Hanselmann, R.; Benn, M. *Synth. Commun.* **1996**, *26*, 945−961.

(15) To test this hypothesis, 20 mg of **15b** was dissolved in 1:1 heptane/EtOAc containing 2 g of silica gel, stirred for 20 min. Only 17 mg of **15b** was recovered after filtration, even after washing the silica with 5% MeOH in $CHCl_3$.

Table 2. Iodobenzene Diacetate or Lead Tetraacetate-Mediated Domino Reactions: Intramolecular Hetero[$4\pi + 2\pi$] Cycloaddition

entry	substrate	domino product	yield (%) A[a] (B)[b]
1	 **6l**	 **16**	77 81)
2	 **8**	 **17**	62 (84)
3	 **11**	 **18**	61 (79)
4	 **12**	 **19**	62 (80)
5	 **13**	 **20**	63 (_)
6	 **14**	 **21**	73 (78)

[a] Method A: The substrate (1 mmol) and $PhI(OAc)_2$ (1.2 mmol) in MeCN (5 mL) were stirred at room temperature for 4 h (TLC monitoring). [b] Method B: The substrate (1 mmol) and $Pb(OAc)_4$ (1.4 mmol) in 5 mL of toluene were stirred at room temperature for 4 h (TLC monitoring).

without any additive, and it is considerably faster at room temperature.

Replacement of the phenyl or the *o*-, *m*-, *p*-methoxyphenyl (entries 4−7, Table 1) with a mesityl group (entry 1, Table 2) led exclusively to a [4 + 2] product **16**. To further clarify this process, we have examined a few additional cases (entries 2−6, Table 2). As illustrated in Table 2, a complete switch in reactivity was observed via tuning of the angular substituent. Replacing the carbonyl by an olefin (entries 2−4) or placing a methylene spacer (entries 5 and 6) and finally increasing the bulk around the angular ketone is crucial for the execution of a [4 + 2] path-selective process. Entry 3 indicates that, when a methyl group is present as opposed to a carbomethoxy group, the oxidative cleavage and the subsequent intramolecular [4 + 2] cycloaddition (oxidative/pericyclic domino process) still proceed in the same direction.

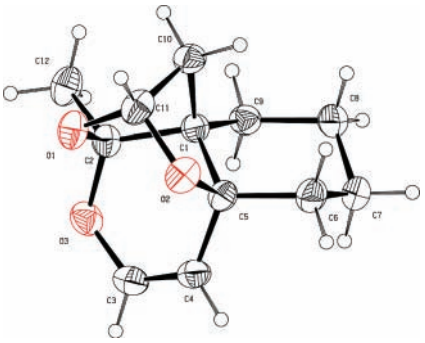


Figure 1. ORTEP view of the molecular structure of **15b**.

As in Table 1, each reaction was also examined for $Pb(OAc)_4$-mediated oxidative cleavage and yields are comparable. While no special efforts were taken to optimize these reactions, the yields range from good to high.[16] They display an important functional group tolerance while they are compatible with a wide range of solvents. Examination of a variety of substrates (Tables 1 and 2) indicates that $PhI(OAc)_2$ is at least as effective as $Pb(OAc)_4$.

In summary, the results described herein show that, by placing either a carbonyl or an olefin at the angular position, two different paths can be put in competition. The general course of these modular domino reactions can be represented by Scheme 1. Structurally different products of type **15** or **17** can be reached selectively, in spite of the similarities in the starting compounds which differ only by the nature of X (O or CH_2) at the angular position (Scheme 1).

The exact scope of the skeletal rearrangement described above remains to be elucidated. Further study of this reaction process is currently underway, with emphasis on efforts to create more complexity and to better control the product distribution.

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

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(16) The only loss in yield appeared to be due to the work-up conditions; ^1H and ^{13}C NMR of the crude material showed no resonances other than those due to the expected products **16**−**2l**.