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Diverging Pathways to Topologically Complex Polycyclic Bis-acetals and Their Ring System Interchange

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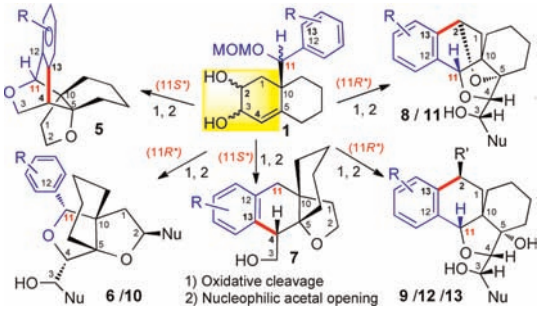
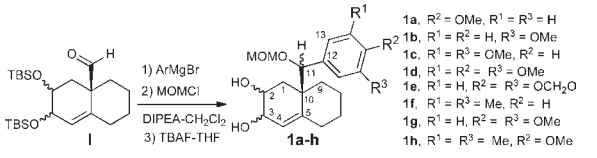
ABSTRACT



Carbinol-tethered octalin-diols (1), which differ only by the C11 configuration at the angular position, were transformed selectively to three types of structurally unrelated original scaffolds such as unsymmetrical octahydroanthracenes (5/7), furofuranes (6), or spirans (8/9) *via* a two-step protocol. The 11*S configuration ensures a C13−C4 Friedel−Crafts type C−C bonding (through an unprecedented oxidative cleavage-triggered domino process) while the 11*R** configuration allows for a C13−C2 Marson-type Friedel−Crafts C−C bonding (through a nucleophilic acetal opening).**

We recently described the path-discriminating ability of ether, ester, acetal, ketone, and epoxide substituents at the angular position in the $Pb(OAc)_4$ mediated domino[1] reactions in the hydrindene- and octalin-diol series.[2] This resulted in efficient ways for the construction of manifold frames in a few steps by a planned combination of reactive groups, showing that the process was sensitive to the substitution pattern at C11. The ability to alter the domino path at will has enabled selective access to original polycyclic scaffolds bearing fascinating architectures and have brought about an interest in their further elaboration.

Scheme 1



Herein, we report tuning of this chemistry to accommodate type-**1** carbinol-tethered octalin-diols, and subsequent Lewis acid mediated opening of the resulting polycyclic acetals based on selective trapping of the in situ formed oxocarbenium.[3] The probe of the present study, represented

(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) (a) Safir, I.; Castellote, I.; Porcel, S.; Kaoudi, T.; Birlirakis, N.; Toupet, L.; Arseniyadis, S. *Chem.—Eur. J.* **2006**, *12*, 7337–7344. (b) Elkhayat, Z.; Safir, I.; Castellote, I.; Retailleau, P.; Arseniyadis, S. *Org. Lett.* **2008**, *10*, 2219–2222. (c) Elkhayat, Z.; Safir, I.; Retailleau, P.; Arseniyadis, S. *Org. Lett.* **2007**, *9*, 4841–4844. (d) Aquino, M.; Safir, I.; Elkhayat, Z.; Gandara, Z.; Perez, M.; Retailleau, P.; Arseniyadis, S. *Org. Lett.* **2009**, *11*, 3610–3613.

(3) Marson, C. M.; Campbell, J.; Hursthouse, M. B.; Abdul Malik, K. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1122–1124.

(4) All reactions were performed on a racemic series; only one antipode is represented. The diol stereochemistry had no effect on the reaction as demonstrated by control experiments where substrates with *cis* diols performed identically to substrates with *trans* diols.

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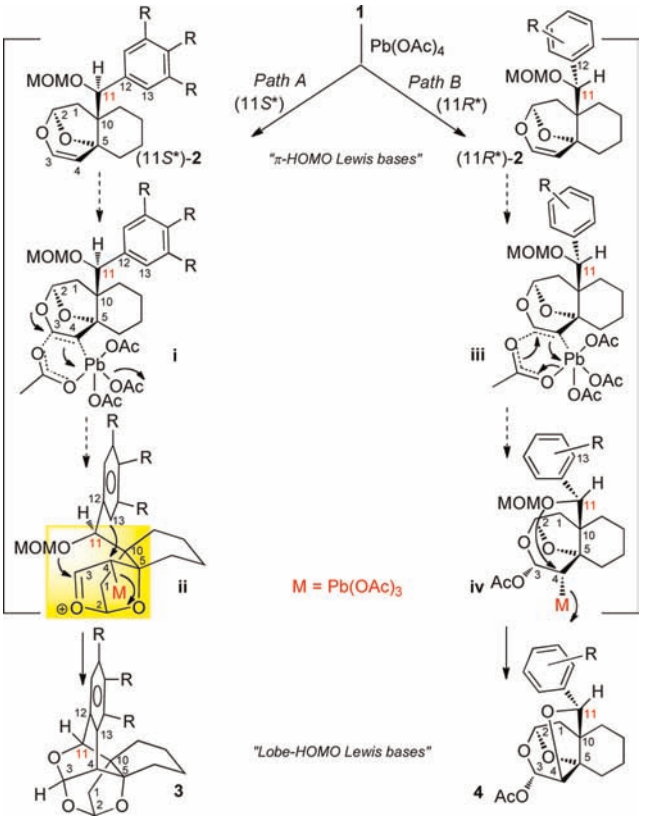
by **1**[4] (Scheme 1), is readily prepared by procedures described earlier, in which the aromatic moieties were chosen for their favorable electronic content. The known aldehyde **I**,[2] was the starting point for the synthesis of the requisite domino precursors, prepared by a three-step procedure: addition of a Grignard reagent to **I** followed by MOM protection[5] of the resulting carbinol and desilylation.

Scheme 2. Tether-Controlled Reactivity in Competing Domino Processes: C11 Configuration Sets the Final Destination, Path A (**3**) versus Path B (**4**) Domino Products



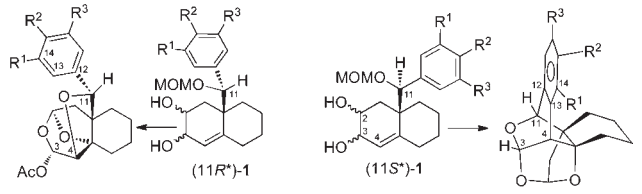
We hypothesized that attaching an electron donor bearing an aromatic group at C11 would enhance the tendency of C13 to undergo a Friedel–Crafts type C–C bonding in the (C11*S**) series, provided that the transient organolead intermediate **ii** (Scheme 2) is able to fulfill the orbital alignment requirements and complies with the requisite proximity of the C4–C13 carbon centers. On the other hand, the (C11*R**) series, which contain structural features that restrict attainment of the normal transition states for the type-A domino path, would show a clear bias toward type-B path domino products **4**. The fulfillment of the objectives displayed in Scheme 2 requires either that we are able to synthesize the C-11 epimerically pure domino probes of type **1** or **2** in some reasonable way or that the domino products **3** and **4**, obtained in the mixture depending upon the original C11*R**/*S** ratio, are easily separable.[6]

(5) Tris-TMS (C2,3,11) or C11Bn-protected type-**1** substrate diols can also be used as domino probes.

We thus studied the behavior of methoxy and methyl derivatives **1a**–**h** obtained epimerically pure, under microwave (MW) assisted[7] domino conditions.[8] Each underwent a remarkable skeletal rearrangement to give **3a**–**h** and **4a**–**h** respectively, as the result of oxidative cleavage followed by consecutive cyclizations (Table 1). Interrupted domino experiments, which detect the rearrangement that occurs *via* the hetero[$4\pi + 2\pi$] cycloaddition (**2**, isolable and stable), were also realized as mechanistic probes for distinguishing the domino pathways. Thus, using PhI(OAc)$_2$[9] as the domino promoter in MeCN at rt, epimerically pure (C11*S**)-**2c**,**d**,**e**,**f**,**h** and (C11*R**)-**2c**,**d**,**e**,**f**,**h** were cleanly obtained and characterized. Each one, independently, was then subjected to domino conditions with Pb(OAc)$_4$ in AcOH under microwave heating (90 °C, 5 min) to afford, as anticipated, the corresponding **3** and **4** domino products respectively.

The results are consistent with an anchimerically assisted arene π-nucleophile mediated deplumbation (**i**→**ii**→**3**, path A) or heteroatom-promoted deplumbation (**iii**→**iv**→**4**, path B) and can be accounted for by writing a series of interconversions with the final bonding occurring through

Table 1. The (11*R**/*S**) Configuration Is Responsible for the Modular Aspect of This Domino Process[a]



entry	domino product (yield %)	substrate diol	entry	substrate diol	domino product (yield %)
1	**4a** (78%)	(11*R**)-**1a**	9	(11*S**)-**1a**	**3a** (55%)
2	**4b** (82%)	(11*R**)-**1b**	10	(11*S**)-**1b**	**3b** (58%)
3	**4c** (79%)	(11*R**)-**1c**	11	(11*S**)-**1c**	**3c** (54%)
4	**4d** (81%)	(11*R**)-**1d**	12	(11*S**)-**1d**	**3d** (56%)
5	**4e** (56%)	(11*R**)-**1e**	13	(11*S**)-**1e**	**3e** (42%)
6	**4f** (75%)	(11*R**)-**1f**	14	(11*S**)-**1f**	**3f** (51%)
7	**4g** (79%)	(11*R**)-**1g**	15	(11*S**)-**1g**	**3g** (45%)
8	**4h** (80%)	(11*R**)-**1h**	16	(11*S**)-**1h**	**3h** (49%)

[a] Reactions conducted with (2.4 mmol) of Pb(OAc)$_4$ and (1.0 mmol) of substrate-diol in AcOH (5 mL) under MW irradiation at 90 °C, 5 min.

(6) We have at present been able to generate the stereochemically pure C11-carbinols by direct chromatographic separation of the starting diastereomeric mixtures (only C11 configuration matters, as C2, C3 configurations are programmed to be destroyed) or by conversion to the half-cascade mixture (C11*R**,*S**)-**2**, using PhI(OAc)$_2$ as the domino promoter, and chromatographic separation.

(7) 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, 2005. 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) Moloney, M. G. *Main Group Metal Chem.* **2001**, *24*, 653–660 and references cited therein.

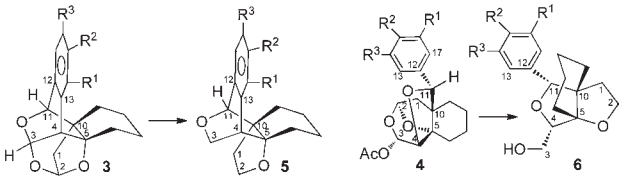
(8) (a) Finet, L.; Candela Lena, J. I.; Kaoudi, T.; Birlirakis, N.; Arseniyadis, S. *Chem.—Eur. J.* **2003**, *9*, 3813–3820. (b) Candela Lena, J. I.; Sánchez Fernández, E.; Ramani, A.; Birlirakis, N.; Barrero, A. F.; Arseniyadis, S. *Eur. J. Org. Chem.* **2005**, 683–700.

(9) For a review on hypervalent iodine chemistry, see: Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358.

either **ii** or **iv** respectively (Scheme 2). As anticipated, the C11 configuration controls the orientation of the domino path *via* dissimilar neighboring-group participation and provides an efficient means for gaining access to multiply fused ring systems otherwise accessible only through lengthy alternate pathways.

Having disclosed the potential of this modular domino sequence, we turned our focus toward the reductive/alkylative opening of the path A and B derived polycyclic acetals. This led to new and attractive molecules providing, incidentally, several examples of a Marson type Friedel–Crafts cycloalkylation.[10] Inspired by earlier contributions, we chose a hard Lewis acid ($TiCl_4$) mediated breakdown for diversification of the bis-acetal moiety of **3** and **4** (both lobe-HOMO-Lewis bases, hence "hard") with triethylsilylhydride and allyltrimethylsilane as carbocation traps.[11] Efforts to expand the skeletal diversity of topologically complex polycyclic bis-acetals upon Lewis acid mediated reductive acetal opening of **3** and **4** (using an acetal/Et_3SiH/$TiCl_4$ ratio of 1:4:1) afforded an unsymmetrical octahydroanthracene (*u*8H-A) core **5**, to which are appended two oxa-bridge units, and a cyclohexane bridged furofurane backbone **6** respectively (Table 2).

Table 2. Reductive Acetal Opening of Path A and B Domino Products[a]

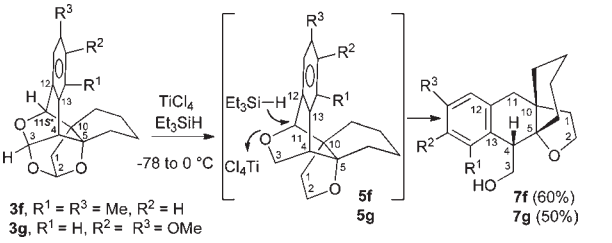


entry	domino product	reduced product (yield %)	entry	domino product	reduced product (yield %)
1	**3b**, $R^1 = R^2 = H$, $R^3 = OMe$	**5b** (70%)	7	**4b**	**6b** (88%)
2	**3c**, $R^1 = R^3 = OMe$, $R^2 = H$	**5c** (56%)	8	**4c**	**6c** (60%)
3	**3d**, $R^1 = R^2 = R^3 = OMe$	**5d** (77%)	9	**4d**	**6d** (63%)
4	**3f**, $R^1 = R^3 = Me$, $R^2 = H$	**5f** (77%)	10	**4f**	**6f** (87%)
5	**3g**, $R^1 = H$, $R^2 = R^3 = OMe$	**5g**[b]	11	**4g**	**6g** (61%)
6	**3h**, $R^1 = R^3 = Me$, $R^2 = OMe$	**5h** (81%)	12	**4h**	**6h** (95%)

[a] Conditions: 1 equiv of Lewis acid/4 equiv of Et_3SiH in CH_2Cl_2 at −78 °C for 20 min, then diluted with cold *t*BuOMe and quenched with brine. [b] Characterized in mixture with **7g** (see Scheme 3).

The combined results of a reductive acetal opening generating original scaffolds with distinct molecular frameworks bearing stereochemical and functional group diversity are displayed in Table 2. Starting from path A derived polycyclic bis-acetals **3b**–**h**, a smooth reaction took place in the presence of $TiCl_4$ and Et_3SiH in CH_2Cl_2 at −78 °C to give **5b**–**h** in 56–81% isolated yields. In parallel, path B derived tetracyclic acetoxy-bis-acetals **4b**–**h** reacted rapidly under the same conditions to give **6b**–**h**, in 53–95% yields along with unreacted bis-acetals (up to 10%). In addition, nucleophilic acetal opening of type-**3** (path A) domino products could be achieved by treatment with Lewis acid/Et_3SiH under conditions favoring sequential acetal and then ether opening (50 mM in acetal, at −78 °C, using an acetal:Et_3SiH:$TiCl_4$ ratio of 1:8:2) leading to more simplified, still heavily functionalized, type-**7** *u*8H-A frameworks in good yield (Scheme 3). The latter conditions allow for direct access from **3** as well as from **5** to **7**.

Scheme 3. [a]



[a] Conditions favoring sequential acetal then ether opening: (Acetal/Et_3SiH/$TiCl_4$ ratio of 1:8:2).

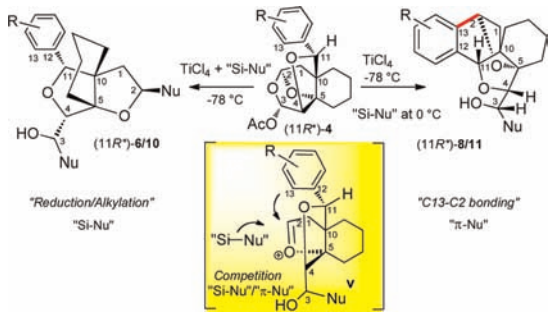
The oxocarbenium ions, plausible intermediates during the reductive acetal opening, are susceptible to nucleophilic attack from the silicon-containing nucleophile present in the reaction mixture. Yet, the effectiveness of the process could be further improved since the transient oxocarbenium ions of type **v** in the C11*R** series (Scheme 4) are poised to undergo a competitive Marson type cyclization. If the arene group attached to the C-11 position is capable of giving anchimeric assistance (because of the electronic content of the aromatic nucleus and spatial proximity), competition between π- and silicon-containing nucleophiles would set the path for the final oxocarbenium trapping. A mechanistic estimate accounting for orientational issues derived from substrate-controlled selectivity and competition between appropriately positioned arene π- and silicon-containing nucleophiles is portrayed in Scheme 4. It could thus be possible to steer the reaction in the desired direction by the appropriate choice of the experimental conditions such as the choice of concentration, temperature, and order of reaction component addition, since depending on how the titanium(IV) chloride mediated acetal opening reaction is performed and quenched, two different products could arise. Indeed, operating at higher concentration and quenching at −78 °C could favor a type **6**/**10** furofurane derivative, whereas if the reaction is warmed to 0 °C before quenching with a silicon-containing nucleophile, a type **8**/**11**spirane could be obtained.

Two protocols were probed; the first series of experiments were performed at a 50 mM concentration (50 μmol of acetal in 1 mL of CH_2Cl_2), by rapid addition of reaction components (Et_3SiH or allylTMS and $TiCl_4$) in CH_2Cl_2

(10) For an elegant use of Marson type intramolecular Friedel–Crafts alkylation, see: (a) Martinez Solorio, D.; Jennings, M. P. *J. Org. Chem.* **2007**, *72*, 6621–6623. (b) Martinez-Solorio, D.; Jennings, M. P. *Org. Lett.* **2009**, *11*, 189–192.

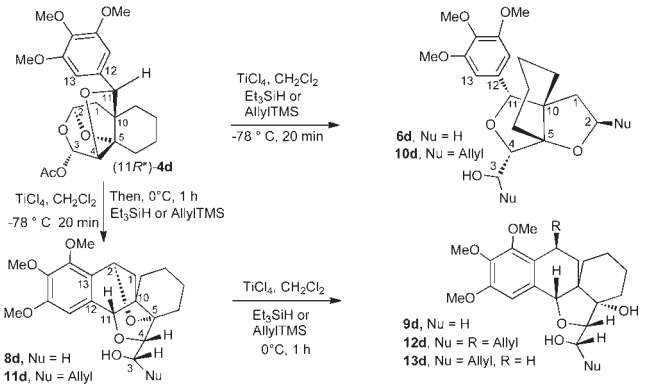
(11) The nucleophilic propensities of such silanes toward Lewis acid activated electrophilic centers have been amply demonstrated. (a) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595–4612. (b) Gomez, A. M.; Uriel, C.; Jarosz, S.; Valverde, S.; Lopez, J. C. *Eur. J. Org. Chem.* **2003**, 4830–4837. (c) Gómez, A. M.; Uriel, C.; Valverde, S.; Jarosz, S.; López, J. C. *Tetrahedron Lett.* **2002**, *43*, 8935–8940.

Scheme 4. Possible Reaction Paths for Nucleophilic Acetal Opening Based on a Rational Prediction of the Fate of the Transient Oxocarbenium Ion **v** (R = OMe, Me; Nu = H, allyl)



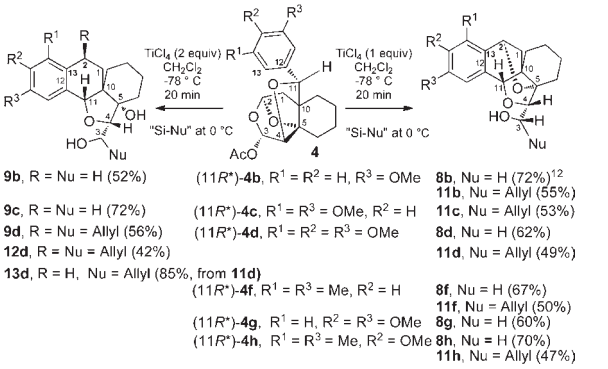
at −78 °C and stirring at this temperature before workup. For the second series of experiments, designed to favor an internal nucleophile, we opted for sequential addition of the reagents, at 5 mM (50 μmol of acetal in 10 mL of CH_2Cl_2), starting with the Lewis acid at −78 °C and raising the reaction temperature to 0 °C before addition of the silicon-containing nucleophile.

Scheme 5. Selective Access towards Either Furofuranes **6**/**10** or Spirans **8/11** (Acetal/"Si-Nu"/$TiCl_4$ ratio of 1:4:1)



The obtained product distributions show a clear bias toward either **6** /**10** or **8**/**11** depending on the temperature, concentration, and sequencing of the reagents, which had an important role in the reaction outcome. The Scheme 5 conclusions appear to hold true for the nucleophilic acetal opening of path B type domino products (11*R**)-**4b,c,f,g,h**, as good yields of the corresponding pentacyclic spiran derivatives **8/11** and the tetracycles **9/12**/**13** were selectively produced using conditions favoring an aryl nucleophile vs a silicon nucleophile for the oxocarbenium trapping (Scheme 6).

Scheme 6. Selective Access to Either **8**/**11** or **9/12** Based on Reaction Conditions[12]



Substrate-diol **1a** appears to represent the lower limit of arene reactivity required to observe cycloalkylation, since nonactivated arenes (possessing no electron-donor groups) or those possessing them in an inappropriate position failed to give path A type domino products. The structural assignment to the path A (**3**) and B (**4**) domino products, as well as the nucleophilic acetal opening products *u*8H-A (**5**/**7**), furofuranes (**6**/**10**), and Marson-type products (**8**/**11**), rests firmly on spectroscopic grounds with HMBC studies proving particularly informative. X-ray crystallography on (C11*R**)-**2c**, (C11*S**)-**2e**, (C11*R**)-**2f**, **3b**, **3c**, **3e**, (C11*R**)-**4d**, (C11*R**)-**4e**, **5b**, **6f**, **8d**, **8h**, and **11b** further corroborated the resulting structures (see Supporting Information).

In summary, the electron-rich ligating aromatic group appended to the octalin diol moiety makes the oriented intramolecular trapping of the *in situ* formed oxocarbenium possible. By using the *R** or *S** configuration at C11 and by choosing the appropriate reaction conditions one could tune the selectivity accordingly. The work presented here emphasizes the potential for altering the domino outcome through the judicious choice of substrate design and reaction parameters.

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

The authors declare no competing financial interest.

(12) When the path B type domino product presents two sites (both activated) for the C−C bonding as in **4b**, the less hindered prevails (**8b** versus **14b**):