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Tandem glycol cleavage—intramolecular 4+2 cycloadditions mediated by $Mn(OAc)_3$

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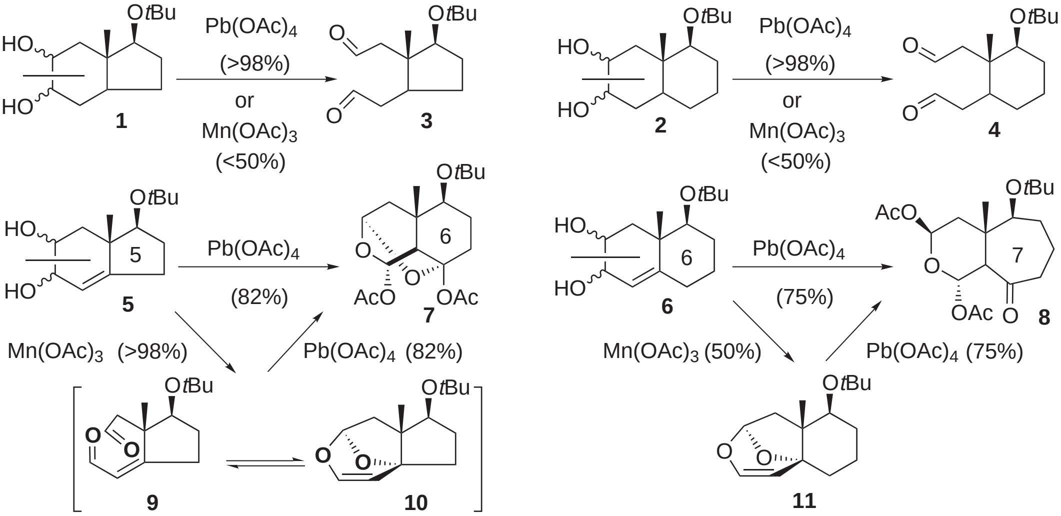
Abstract—The $Mn(OAc)_3$ mediated oxidative cleavage of **1** and **2** proceeded as expected, while molecular diversity was generated upon cleavage of their unsaturated counterparts **5** and **6** via a tandem glycol cleavage/4+2 process. Minor products of the reaction were identified as the α-dicarbonyl derivative (i.e. **25**) and the corresponding cross-conjugated hydroxy dienone (i.e. **26**). The process tolerates a variety of substitution patterns and protecting groups. A brief comparison with the $Pb(OAc)_4$ initiated cascade transformations is presented. © 2001 Elsevier Science Ltd. All rights reserved.

While treatment of hydrindane or decalin diols, **1** and **2**, respectively, with $Pb(OAc)_4$ produced the dialdehydes **3** and **4** resulting from a glycol fission, inserting an olefin into the ring system changed totally the reaction outcome. Thus, treatment of the unsaturated counterparts, diols **5**[1] and **6**,[2] with 2 equiv. of $Pb(OAc)_4$ in MeCN (but also in AcOH, PhH, CH_2Cl_2, $CHCl_3$, acetone, TFT and other solvents) initiated an unprecedented sequence of events involving glycol fission, intramolecular 4+2 cycloaddition, oxymetallation and ring-enlargement in a row, affording high molecular diversity (**7**, **8**). This serendipitous discovery led to the development of a new ring-expansion methodology and served for the elaboration of heavily substituted six- and seven-membered rings from simple and well known building blocks in a limited number of synthetic opera-



Scheme 1. The potential of an olefin to create 'reagent-dependent' molecular diversity; embedding a double bond into the bicyclic ring system (**5**, **6**), adjacent to the vicinal diol part, completely modified the reaction outcome.

Keywords: glycol cleavage; tandem reactions; manganic acetate; lead tetraacetate; bis-hetero IMDA.

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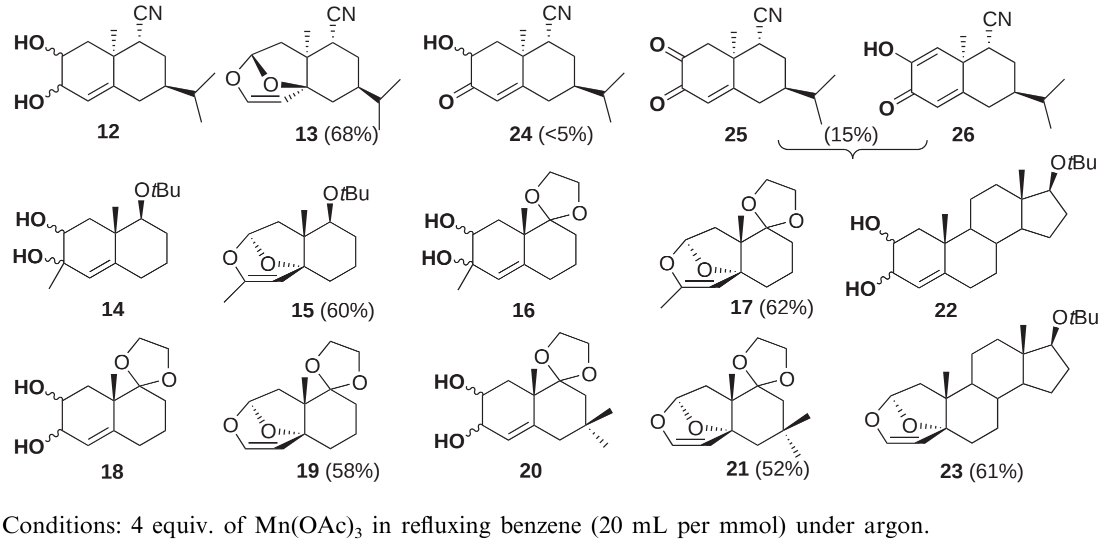
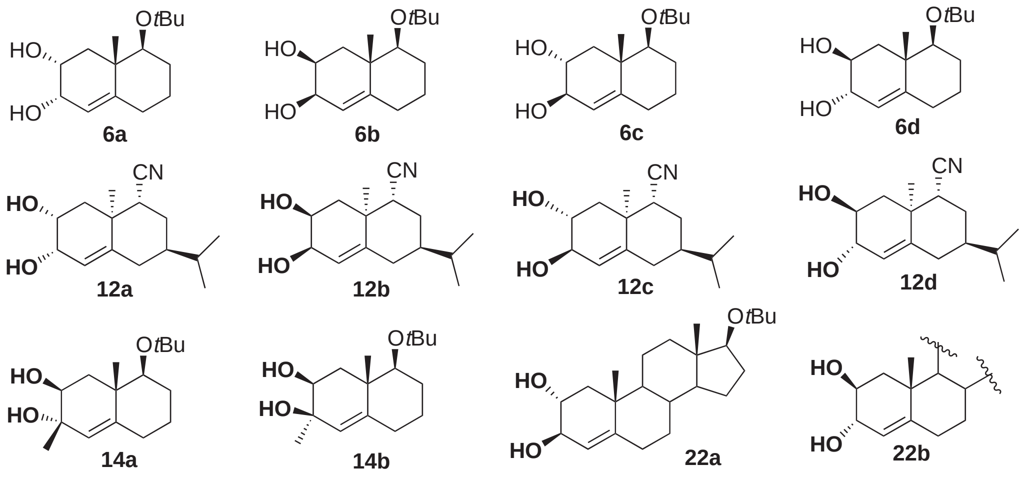
tions.[3] A series of experiments were then addressed to better understand the factors involved in these cascade transformations such as the influence of solvent[4] and substitution pattern.[5] To gain insight into the mechanistic course and eventually extend the scope of the process, it was essential to this study that some other oxidants in various solvents were employed. To this aim, the effect of the oxidant was examined using a number of known reagents employed in glycol cleavage. We describe here our findings on a one-pot conversion of several unsaturated 1,2-diols into cyclic ene-acetals by treatment with manganic acetate.[6]

The requisite diols were prepared by the standard method from the appropriate α-acetoxy enones which upon lithium aluminium hydride reduction led to a range of unsaturated diols,[7] while Raney-Ni reduction (THF, 0°C, 1 h)[8] followed by LAH reduction afforded their saturated counterparts. Subjection of the saturated diols **1** and **2** to $Pb(OAc)_4$ (1 equiv., in MeCN, −20°C, 10 min) or $Mn(OAc)_3$ (4 equiv., in MeCN, reflux, 4 h) mediated oxidative cleavage furnished, as expected, glycol fission products **3** and **4**, respectively. Yields are near quantitative using $Pb(OAc)_4$, while they stay well under 50% using $Mn(OAc)_3$ as oxidant. In the hydrindene series, **5**, treatment with either 1 equiv. of $Pb(OAc)_4$ or 5–6 equiv. of $Mn(OAc)_3$ led to the tricyclic enol ether **10** (which was not isolable) in equilibrium with the ring-opened dialdehyde **9**. The equilibrium mixture was very stable in solution for several weeks and readily underwent oxyplumbation-ring expansion upon addition of 1 more equiv. of $Pb(OAc)_4$ to give the full-cascade product **7** in 82% yield. A similar behaviour was observed with decalin diols **2** and their unsaturated counterparts **6**; however, the half-cascade product **11**, obtained using either oxidant (though in much higher yields using lead tetraacetate as the oxidant) is easily isolable and can be stored for long periods. Treatment of diol **6** with 1 equiv. of $Pb(OAc)_4$ for 1 h at room temperature gave tricyclic enol ether (or cyclic ene-acetal) **11** in 95% yield. When $Mn(OAc)_3$ in MeCN was used instead of $Pb(OAc)_4$, the half-cascade product **11** was obtained in ca. 50% isolated yield; however, conversion required 4 equiv. and 4 h heating at reflux temperature. The most noteworthy difference between the two oxidants relies on the fact that $Mn(OAc)_3$ failed to effect the 'full cascade' (no trace of **7** or **8**). The ability of Pb^{4+} to perform different tasks, acting as an oxidizing agent (glycol fission) and as a Lewis acid (attacking the electron rich olefin) secured the ring-expanded intermediates **7** and **8**. As portrayed in Scheme 1, only $Pb(OAc)_4$ can effect the ring expansion, transformations of **10** to **7** and **11** to **8**; $Mn(OAc)_3$ can effect the two first transformations up to half-cascade (cleavage/4+2) but the process is interrupted at this level. Various solvents were examined; replacing acetonitrile with benzene led to a decrease of side reactions and improved the yields. The use of as much as 6 equiv. of $Mn(OAc)_3$ did not increase the yield, although it shortened significantly the reaction time. The use of fewer than 4 equiv. of $Mn(OAc)_3$ gave a slower and less clean reaction; allylic oxidation and products resulting thereof become more important using 2 or 3 equiv. of the oxidant. To assess the scope of this one-pot transformation, a number of unsaturated 1,2-diols were subjected to reaction with 4 equiv. $Mn(OAc)_3$ in dry and degassed benzene at reflux under an argon atmosphere. Reactions were generally complete within less than 4 h under these conditions. The bicyclic unsaturated diol **12** was prepared from (*R*)-carvone and the *gem*-dimethyl substituted octaline diol **20** from dimedone using the Robinson annelation methodology. Compounds **16**, **18** and **20** were obtained via selective ketal protection of the corresponding enone, followed by acetoxylation ($Pb(OAc)_4$) and reduction ($LiAlH_4$ in Et_2O); for the synthesis of **16** and **14**, MeLi addition preceded the LAH reduction. The preparation of the requisite steroidal diol **22** was achieved straightforwardly from 17-O*t*Bu-protected testosterone.[9] The structures of these compounds were assigned by NMR techniques and by analogy to our earlier work; the results we obtained starting with diastereomeric mixtures are exhibited in Scheme 2 (yields are given in parentheses). In every case studied, the allylic oxidation product leading to the corresponding acyloin and hence to the diketone was observed; only **24**, **25** and **26** are depicted in Scheme 2. The process accommodates those



Scheme 2. Conditions: 4 equiv. of $Mn(OAc)_3$ in refluxing benzene (20 mL per mmol) under argon.



Scheme 3. Some of the diastereomerically pure unsaturated diols examined.

unsaturated diols possessing a tertiary–secondary diol system (**14**, **16**) and is compatible with substrates having various protecting groups and functionalities such as ketal, *tert*-butyl ether, cyano, *gem*-dimethyl, isopropyl and eventually many others. Thus, in the case of **12** the $Mn(OAc)_3$ mediated reaction furnished the tricyclic enol ether **13** together with the allylic oxidation product **24** and the keto-enol form **26** of the corresponding diketone **25** in variable yields (ca. 15%).

The tertiary–secondary unsaturated diols **14** and **16**, as well as the ketal protected **18** and **20** furnished cleanly **15**, **17**, **19** and **21**. Starting from steroidal unsaturated diol **22**, the other products formed alongside **23** were assigned as the allylic oxidation product (type **24** acyloin) and the corresponding (type **25**) ene-dione, sometimes exclusively in its (type **26**) keto-enol form. To explore the influence of 1,2-diol stereochemistry on product distribution and reaction rate, studies were conducted on a series of diastereomerically pure diols (Scheme 3). Starting with the pure *cis* and *trans* variants from **6**, **12**, **14** and **22** and proceeding as above, the corresponding half-cascade intermediates (**11**, **13**, **15** and **23**) were produced as the major component of a chromatographically separable mixture of three products. Yields and ratios are comparable to those obtained above starting from a mixture of diols. This clearly shows that the cleavage process is not depending upon diol stereochemistry. The rather low isolated yields (ca. 60%, despite a clean TLC) observed with manganic acetate mediated tandem transformations could be attributed to the use of excess (up to 4 molar equiv.) and to the quality of the reagent.[10]

For comparison purposes, we have also carried out a study of the oxidative cleavage of diols **5**, **6**, **12**, **20** and **22** with several other oxidants. Among the oxidants screened, $NaIO_4$, $NaBiO_3$, Ph_3BiCO_3, Dess–Martin periodinane cause cleavage on vicinal diols, while using TPAP-NMO, PDC, PCC, or $Pd(OAc)_2$, allylic oxidation is essentially quantitative (no cleavage is detected). None of these oxidants produced the ring expanded product (type **7** or **8**) regularly obtained from $Pb(OAc)_4$ mediated cascade transformations; the latter ensures the highest molecular diversity, the mildest conditions and the highest yields. In conclusion, the $Mn(OAc)_3$ mediated transformations differ from those mediated by $Pb(OAc)_4$ in several fundamental respects such as the degree of generated molecular diversity, the reaction rate, the temperature and the yields.

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10. In a typical experiment, a dry flask was charged with 1 mmol of diol and 4 mmol of Mn(OAc)$_3$, vacuumed and flushed with argon several times; 20 mL of sodium dried and degassed benzene was then added and the resulting mixture was stirred at reflux, with removal of water using a Dean–Stark trap, until TLC monitoring showed no starting material left (ca. 4 h). The cooled mixture was diluted with EtOAc, filtered on Celite, washed with 1N HCl, saturated aq. NaHCO$_3$ and brine. The organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. Yields refer to spectroscopically and chromatographically (silica gel, heptane–ethyl acetate, 4:1 as eluent) homogeneous materials. Complete IR, mass, elemental analysis, ^{1}H and ^{13}C NMR data were obtained for each compound synthesized; optical rotations were measured in chloroform. Selected data: **6a**: mp: 101–103°C (heptane–Et$_2$O); $[\alpha]_D$ +149 (*c* 0.6). **6b**: $[\alpha]_D$ +87 (*c* 1.1). **6c**: mp: 99–101°C (heptane–Et$_2$O); $[\alpha]_D$ +45 (*c* 1.3). **6d**: mp: 133–134°C (heptane–Et$_2$O); $[\alpha]_D$ +15 (*c* 0.9). **13**: $[\alpha]_D$ −11 (*c* 1.8). **14a**: $[\alpha]_D$ −12 (*c* 2.1). **14b**: mp: 100–102°C (heptane–EtOAc); $[\alpha]_D$ −21 (*c* 2.3). **15**: $[\alpha]_D$ −7 (*c* 2.2). **19**: mp: 60–62°C (heptane–Et$_2$O–EtOAc). **26**: $[\alpha]_D$ −44 (*c* 1.1).