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Iodobenzene diacetate-mediated hetero-domino transformations

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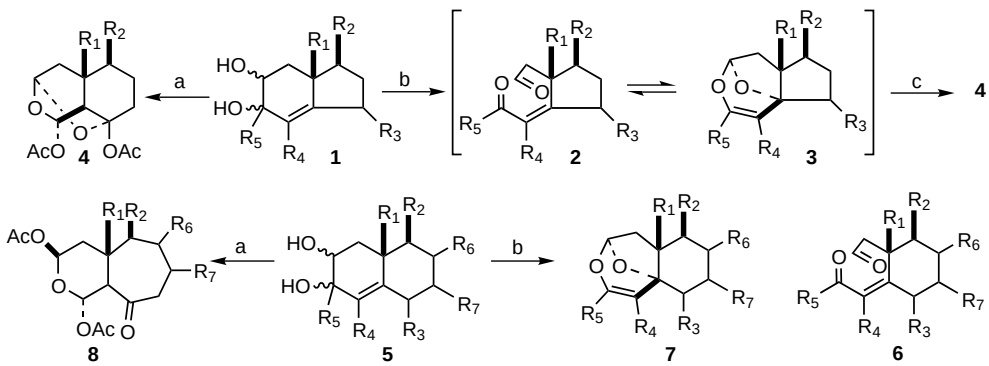
Abstract—Treatment of a series of unsaturated diols with iodobenzene diacetate ($PhI(OAc)_2$), in various solvents gave cyclic ene-acetals by a sequential oxidative cleavage-intramolecular [4+2] cycloaddition. The reaction is easy to perform, can be scaled up safely and occurs efficiently irrespective of the diol stereochemistry. © 2002 Elsevier Science Ltd. All rights reserved.

Elaborated six- and seven-membered ring systems cover the backbone of several biologically important natural compounds. In our early studies dealing with the $Pb(OAc)_4$-mediated glycol fission reaction of bicyclic unsaturated diols of type **1** and **5**, the ring expanded products of type **4** and **8** were generated in a single synthetic operation.[1] Crucial to the success of the process was the substitution pattern around the olefin; allylic (R_3, R_5) and vinylic (R_4) substitution interrupted the transformation at the half-cascade level (cyclic ene-acetals of type **3** and **7**), while R_1, R_2, R_6, R_7 could be alkyl, alkenyl, alkoxy, free carbonyl, ketal or others.

More recently, we reported that the synthesis of cyclic ene-acetals (the so called 'half-cascade' intermediates) of type **7** can occur in good yield on simple room temperature treatment of unsaturated diols with Dess–Martin periodinane in toluene[2] or $Mn(OAc)_3$ in refluxing benzene.[3] We now report an extension of this reaction in the rearrangement of a series of unsaturated diols of type **1** and **5** with $PhI(OAc)_2$,[4] a hypervalent iodine (III) reagent,[5] as a practical method for the synthesis of elaborated ring systems. The $PhI(OAc)_2$-mediated oxidation of 1,2-diols is a clean method for the cleavage of glycols.[6] In the absence of an olefin, the source of diversity, fission of 1,2-glycols forms the corresponding dicarbonyl compounds according to a mechanism similar to that proposed for $Pb(OAc)_4$ cleavage. In an effort to probe its ability to generate diversity, substrates of type **1** and **5** were subjected to $PhI(OAc)_2$-mediated sequential transformation conditions. Therefore, a set of substrates was investigated and the results obtained are exhibited in Schemes 2 and 3 (all isomers could be isolated diastereomerically pure). The required α-acetoxy enones were prepared by the regular method from the appropriate enones.[7] For the synthesis of the (*R*)-(−)-carvone derived unsaturated bicyclic diols, a slightly modified de Groot procedure was employed.[8] The domino transformations



Scheme 1. (a) 2 equiv. $Pb(OAc)_4$, MeCN, rt; (b) 1.2 equiv. $PhI(OAc)_2$, MeCN, rt; (c) 1 equiv. $Pb(OAc)_4$, MeCN, rt.

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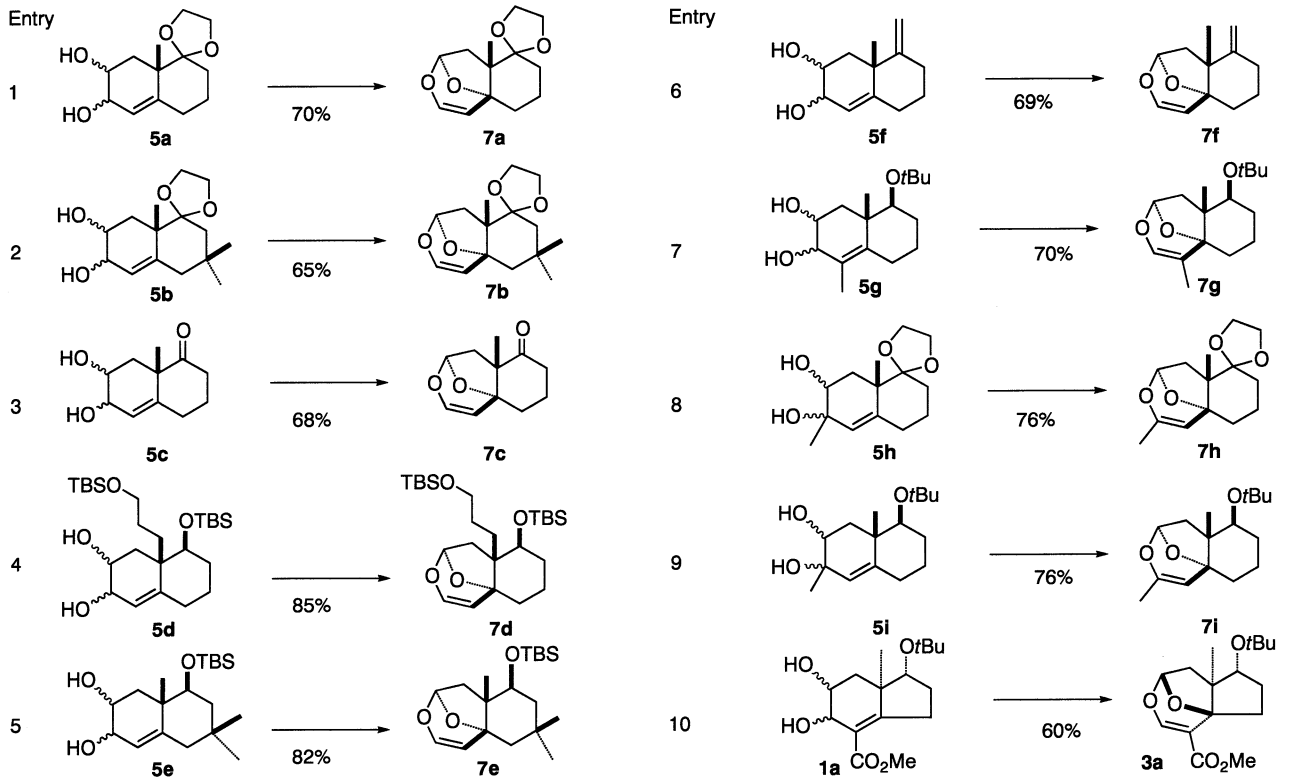


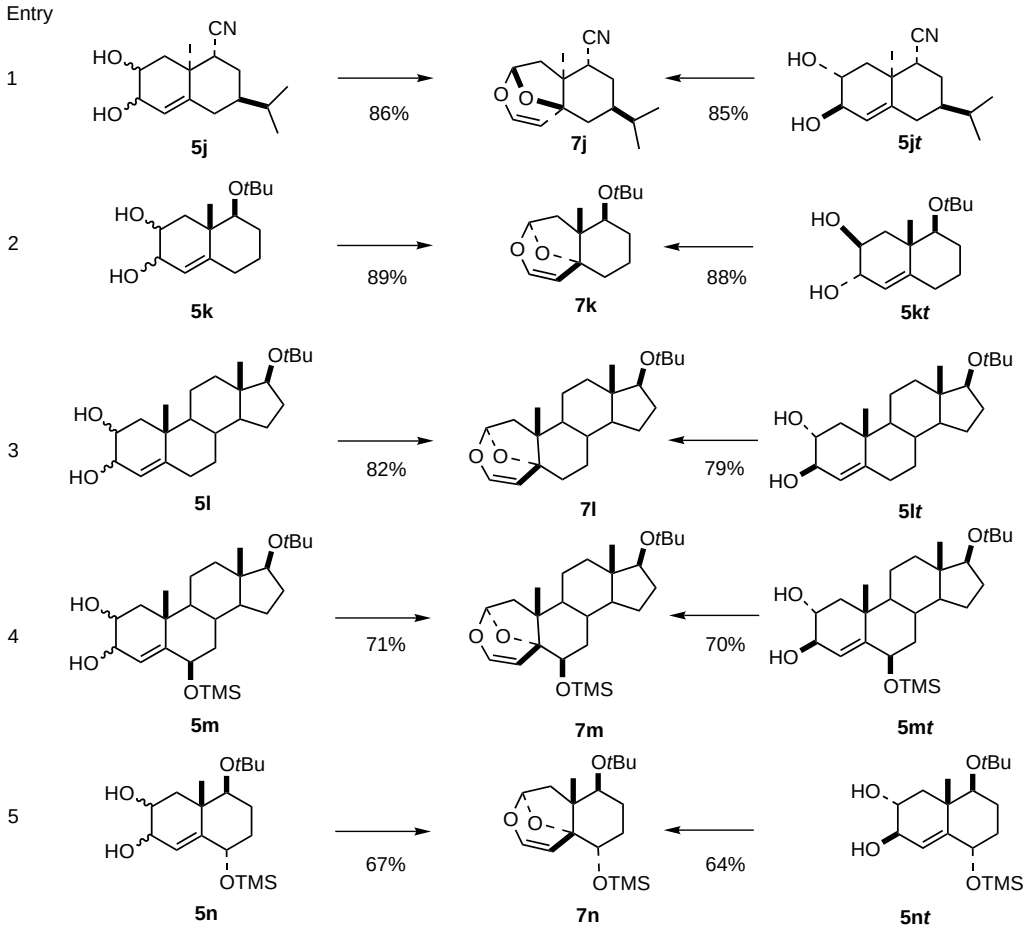
Scheme 2. *Reagents and conditions*: 1.2 equiv. of $PhI(OAc)_2$, in acetonitrile, 15–24 h at room temperature.

carried out on diastereomeric mixtures proceeded in 60–89% isolated yields. Taking into account the level of molecular complexity attained in a one-pot transformation, yields are quite high. The optimized procedure involved addition of iodobenzene diacetate (1.2 equiv.) to a solution of the unsaturated diol (4 mmol) in acetonitrile (40 mL), and stirring, under inert atmosphere, at room temperature for ca. 24 h. Following TLC control indicating half-cascade formation, cyclic ene-acetals were isolated after workup and chromatography. Domino transformations starting from diols **5** (entries 1–10), uniformly gave rise to the type-**7** 'half-cascade' intermediates, as the only detectable products (Scheme 2). Thus, in the case of **5d** (entry 4), the $PhI(OAc)_2$-mediated reaction furnished the half-cascade intermediate **7d** in an 85% isolated yield. On the other hand, the equilibrium mixture obtained from diols **1** (Scheme 1), readily underwent oxyplumbation-ring expansion upon addition of 1 equiv. of $Pb(OAc)_4$ into the reaction vessel, to give the full-cascade products **4** in remarkably high yields (ca. 82%). Thus, treatment of **1**, **5** with iodobenzene diacetate yielded cleanly the half-cascade intermediates **3**, **7** via the intermediate dialdehydes of type **2**, and **6**. Cyclic ene-acetals of type **3** can only be characterized as an equilibrium mixture by NMR techniques, although a few exceptions existed (entry 10). In the higher homologue, octaline diol series, all the half-cascade products **7** are isolable and stable, and some interesting chemistry can be done providing access to bicyclic or steroidal lactones.[9]

The effect of solvent was briefly investigated in the reaction of unsaturated diols **5** with $PhI(OAc)_2$. To this end, we examined the possibility of replacing acetonitrile with other solvents, compatible with the reagent, in the hope of improving the yield and the rate of the one-pot multistage transformations. Cleavage with $PhI(OAc)_2$, in methylene chloride, acetonitrile, benzene, or toluene occurred efficiently at room temperature. For example, starting from carvone derived diols **5j** solvent variation gave the following results: in MeCN an 86% yield of **7j** was obtained after chromatography, while yields decreased in PhMe (75%), PhH (69%), trifluorotoluene (65%), dichloromethane (57%), and AcOH (53%). As a consequence of the above results, the best reaction conditions involve use of dry acetonitrile at room temperature.

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 (entries 1–5, Scheme 3). The $PhI(OAc)_2$ oxidation on diastereomerically pure *trans*-diols, **5j–n** (entries 1–5, Scheme 3), derived from (*R*)-(−)-carvone (**5j**), Wieland–Miescher ketone (**5k**, **5n**) and testosterone (**5l**, **5m**) followed an identical cursus to that when diols were used as a diastereomeric mixture, as portrayed in Scheme 3. This is also valid for all the unsaturated diols investigated in this study (entries 1–10, Scheme 2).

An examination of these examples reveals that the process is insensitive to the substitution pattern and gives good yields in all cases investigated. The results with $PhI(OAc)_2$, $Pb(OAc)_4$, and $Mn(OAc)_3$ indicate that in contrast to other cleavage reagents, such as Dess–Martin periodinane (DMP) or Ph_3BiCO_3, these



Scheme 3. *Reagents and conditions*: 1.2 equiv. of $PhI(OAc)_2$, in acetonitrile, 15–24 h at room temperature.

three oxidants do not show stereochemical preference. Furthermore, the process is compatible with numerous functionalities, and can accommodate those unsaturated diols possessing a tertiary–secondary diol system. The effect of solvent, temperature, stoichiometry, and reaction time has been studied on diols of type **1**, with the hope of completing the cascade towards **4**. Prolonged room temperature stirring in the presence of a threefold excess of iodobenzene diacetate did not produce a trace of the type **4** ring expanded products, even after a 3-day reflux in acetonitrile, benzene or toluene. However, heating at reflux in acetic acid gave ring-expanded products, albeit in very low yields. Hence, starting from **1b** (R_1 = Me, R_2 = O*t*Bu, $R_3 = R_4 = R_5$ = H), the domino transformations (oxidative–pericyclic) proceeded without incident except for the fact that to complete the cascade, the process must be carried out in acetic acid at reflux using a threefold excess of the reagent, as opposed to the mild room temperature stirring with 2 equiv. of $Pb(OAc)_4$.

In conclusion, we have demonstrated that domino reactions mediated by $PhI(OAc)_2$ constitute a synthetically useful procedure not involving harsh conditions that preclude the presence of sensitive functional groups. According to Tietze's classification,[10] the process is a hetero-domino reaction (oxidative–pericyclic) where olefin is the *sine qua non* for the generation of such a high diversity[11] while $Pb(OAc)_4$ remains the reagent that affords the highest degree of diversity. Thus far, $PhI(OAc)_2$ is the only oxidant other than $Pb(OAc)_4$ that can effect the ring expansion, even though the yields are not exceeding 20% and the reaction is sluggish. In all cases investigated, structures and stereochemistry of products are assigned by comprehensive spectral data; optical rotations were measured in chloroform and NMR spectra in $CDCl_3$.[12]

Acknowledgements

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12. Procedure: A dry flask was charged with 1.09 g (4.37 mmol) of unsaturated diol **5j**, obtained from (*R*)-(−)-carvone and 1.690 g (5.25 mmol) of $PhI(OAc)_2$ vacuumed, flushed with argon and cooled to 0°C. Acetonitrile (45 mL) was then added and the cooling bath removed soon after. It should be pointed out that, when the reactions were run without 2special precautions such as solvent degassing, reagent preparations (drying), and vacuum-flushing yields were comparable. The mixture was stirred at room temperature for 24 h (TLC-monitoring), diluted with dichloromethane, washed with a saturated aqueous solution of $NaHCO_3$, water, and brine, dried and concentrated. The residue was chromatographed on Silica Gel using heptane–ethyl acetate (1:1) as eluent to yield 894 mg (86%) of pure **7j**: $[\alpha]_D$ −11 (*c* 1.84). IR (film): 2958, 2869, 2236, 1633, 1449, 1432, 1388, 1367, 1211, 1185, 1139, 1090, 1073, 1056, 964, 932, 832, 793, 723 cm^{-1}. ^1H NMR (800 MHz): 0.88 (3H, d, $J=6.6$), 0.97 (3H, d, $J=6.5$), 1.34 (3H, s), 1.30–1.40 (1H, m), 1.43 (1H, dd, $J=6.0$, 15.6), 1.72 (1H, dt, $J=4.8$, 13.3), 1.92–1.99 (1H, m), 2.03 (1H, qd, $J=2.6$, 14.2), 2.16 (1H, dd, $J=1.1$, 14.4), 2.21 (1H, td, $J=2.1$, 15.6), 2.28 (1H, dd, $J=5.8$, 14.4), 2.82 (1H, dd, $J=2.9$, 13.3), 4.74 (1H, d, $J=6.1$), 5.62 (1H, d, $J=5.6$), 6.23 (1H, d, $J=6.1$). ^{13}C NMR (75 MHz): 14.7, 21.5 (2C), 26.8, 27.3, 29.5, 32.5, 38.4, 48.4, 51.0, 82.0, 98.0, 109.0, 121.3, 139.9. EIMS (DCM–MeOH): 248 ($[MH]^+$, 10), 247 (17), 246 (100). Starting from [±]-**5d** (410 mg, 0.9 mmol) and $PhI(OAc)_2$ reagent (330 mg, 1.0 mmol, 1.2 equiv.) in dry acetonitrile (15 mL) 350 mg (88%) of [±]-**7d** was obtained after 17 h stirring at room temperature. [±]-**7d**: IR (film): 2929, 2856, 1630, 1471, 1388, 1256, 1095, 934, 835 cm^{-1}. ^1H NMR (300 MHz): 0.05 (12H, s), 0.88 (9H, s), 0.90 (9H, s), 1.13–1.96 (10H, m), 2.08 (1H, d, $J=14.2$), 2.30 (1H, dd, $J=5.7$, 14.2), 3.49–3.59 (2H, m), 3.64 (1H, dd, $J=4.0$, 11.4)), 4.78 (1H, d, $J=6.1$), 5.64 (1H, d, $J=5.5$), 6.17 (1H, d, $J=6.1$). ^{13}C NMR (75 MHz): −5.2 (2C), −4.8, −4.0, 18.0, 18.3, 19.8, 24.1, 26.0 (6C), 29.3, 30.6, 31.6, 44.7, 58.4, 64.22, 76.6, 84.8, 99.5, 109.9, 139.4. EIMS: 507 ($[M+K]^+$, 18), 491 ($[M+Na]^+$, 100). Starting from **1a** (optically homogeneous, anti-steroid series) and proceeding as above, silica-gel flash chromatography (eluent heptane–EtOAc, 6:1) afforded 60% of **3a**: $[\alpha]_D$ −75° (*c* 1.01); IR (film) 3021, 2976, 2953, 2360, 1701, 1604, 1438, 1216, 1186, 1146, 1103, 1071, 1026 cm^{-1}, ^1H NMR (250 MHz): 1.04 (3H, s), 1.15 (9H, s), 1.60–1.90 (2H, m), 1.90 (1H, d, $J=14.3$), 2.00–2.20 (1H, m), 2.37 (1H, dd, $J=5.0$, 14.3), 2.85–3.05 (1H, m), 3.68 (3H, s), 3.85 (1H, t, $J=8.0$), 5.72 (1H, d, $J=5.0$), 7.44 (1H, s); ^{13}C NMR (62.5 MHz): 13.9, 25.2, 28.8 (3C), 33.0, 48.2, 50.9, 62.9, 72.5, 78.7, 93.7, 102.2, 110.0, 153.2, 165.5. EIMS: *m*/*z* 296 (M^+, 14), 196 (77), 154 (99), 57 (100).