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Lead Tetraacetate Mediated "One-Pot" Multistage Transformations On Selected Unsaturated 1,2-Diols: The Wieland-Miescher Series

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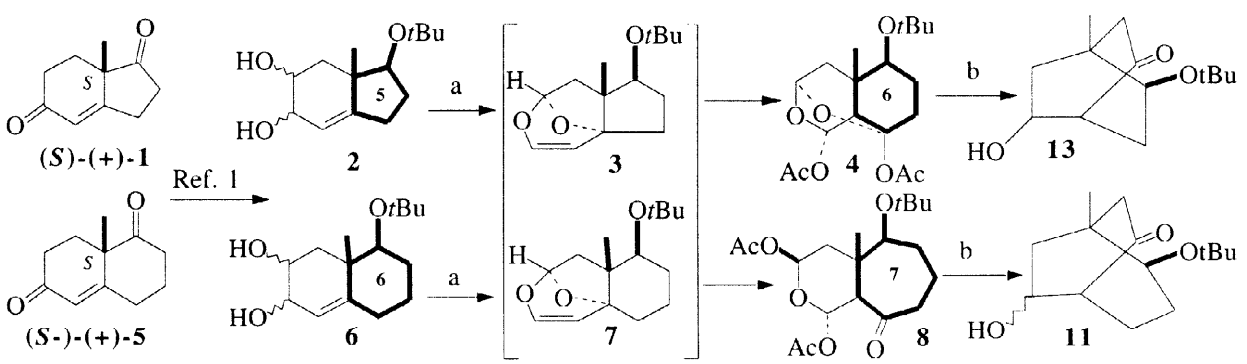
Abstract: *Starting with the unsaturated diol **6**, a rapid entry into fused bicyclic derivative **8** and hence to the bridged ring system **11** (both one-pot processes) is achieved.*

We have recently reported a new ring expansion/rearrangement approach based on the oxidative cleavage of unsaturated 1,2-diols **2**, derived from the Hajos-Parrish ketone **1**, providing convenient access to taxoid C-ring building blocks. Whith this method, cyclohexane derivatives as complex as **4** could be assembled in a single step, while the bicyclo[2.2.2]octane derivative **13** needed only two steps from **2**.[1] Following these successful undertakings work in our laboratory has focused on the design and application of one-pot multistage transformation chemistry.[2] We next investigated the unsaturated 1,2-diols **6** derived from Wieland-Miescher ketone **5**, the higher homologue of **1**. During the course of this work we discovered a new single reagent, one-pot cascade type reaction sequence and devised an efficient route to functionalized cycloheptanone[3] derivative **8**,



Scheme 1: a) $Pb(OAc)_4$, CH_3CN, rt, 15 h for **4**, 48 h for **8** b) K_2CO_3-MeOH-H_2O, rt, 16 h.

fused with an α,α'-disubstituted tetrahydropyran unit (which may be regarded as a bis-acetoxy-acetal). Subsequent room temperature basic treatment of **8** afforded cleanly the bicyclo[3.2.2]nonane aldol framework **11**.[4] There is considerable precedent in the literature for cleaving glycols [5] such as the Malaprade reaction (periodic acid cleavage) or the Rigby oxidation (glycol fission with sodium bismuthate) and others. Among them, the Criegee lead tetraacetate mediated glycol cleavage is the most commonly used 1,2-diol cleavage

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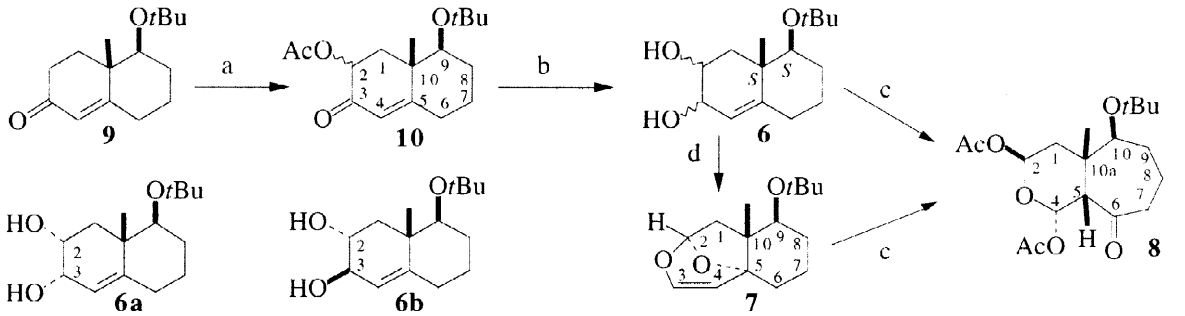
reaction because of the ability of the reagent to cleave both *cis* and *trans* diols and its compatibility with protic as well as aprotic solvents; its mechanistic aspects have been thoroughly studied and reported in several review articles and books.[6] We report herein the full experimental details for a short and efficient preparation of synthetically interesting fused and bridged bicyclic compounds in their optically pure form, obtained from diol **6**. The expediency of the overall transformations leading to a new ring expansion methodology as well as to a fused-to -bridged ring system interchange is illustrated in Scheme 1.

Results and discussions

The lead tetraacetate as a multi-job reagent: ring expansion-functional redistribution

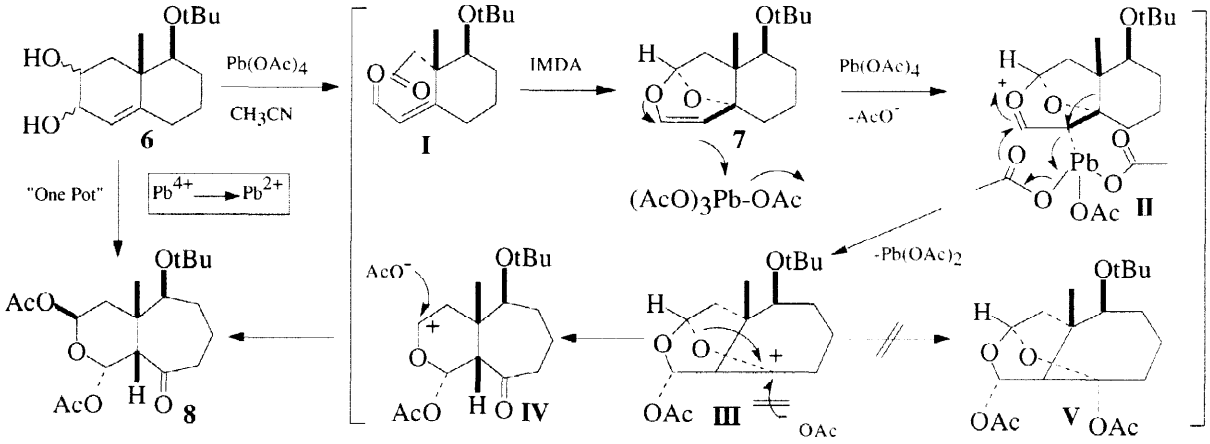
The starting diols **6** were efficiently synthesized on a large scale in high yield and excellent optical purity using the chemistry we developed in our earlier work, where easy access to the enantiopure diols **6** was achieved by the lipase catalyzed enzymatic hydrolysis of the 2-acetoxylated derivatives **10**.[7]



Scheme 2 a) $Pb(OAc)_4$, PhH, reflux, 4 days. b) $LiAlH_4$, Et_2O, 0°C to rt. c) 2.2 equiv. $Pb(OAc)_4$, CH_3CN, rt, 48 h. d) 1.1 equiv. $Pb(OAc)_4$, CH_3CN, -40°C to rt, 1 h. Numbering throughout the text is arbitrary.

Thus, the required acetoxyenone **10** was prepared in a straightforward manner from **9** (itself prepared as racemic) following our previously published procedure, resolved *via* a lipase catalyzed hydrolysis (*H.L.E.*) and subsequently converted to the corresponding epimeric mixture of diols **6**, upon reduction (either $LiAlH_4$ in ether or L-selectride in THF). The epimeric mixture of unsaturated diols **6** (separated only for characterization) thus obtained needed neither purification nor separation of the diastereomers and could be used as such. Following reduction of **10** to **6**, the stage was set for examining the capability of this unsaturated diol to undergo one-pot sequential transformations. Subjection of the latter to $Pb(OAc)_4$ (2.2 equiv.) in CH_3CN (*ca* 5 mL per mmol for small scale experiments, less when scaling up) afforded upon room temperature stirring (48 h) good isolated yields of **8** (60%) along with **7** (25%). The reaction sequence can be monitored by TLC with all intermediates possessing distinct R_f values. Five minutes after addition of the oxidant, two new higher R_f spots appear on the TLC: a UV active spot (dialdehyde **I**) together with a second, higher R_f, non UV active one (tricyclic enol ether **7**) while the starting diols disappear. The dialdehyde initially formed was entirely transformed to the higher R_f non UV active spot, the tricyclic enol ether **7**, upon less than 1 h room temperature stirring or simply on standing in an NMR tube (control aliquot). Two more days at room temperature stirring then gave rise to a lower R_f spot than **I** and **7** corresponding to **8**. Reactions were generally complete within less than 5 min for the oxidative cleavage leading to the dialdehyde **I**, less than 2 h for the bis-hetero-IMDA cycloaddition leading to the isolable **7** and required 48 h for the complete sequence, the "full cascade", leading to the ring expanded fused bicycle **8** where a seven-membered ring is fused to an α, α'-functionalized tetrahydropyran ring. Increasing the reaction temperature (until reflux) resulted in a decrease in chemical yield compared with reactions run at room

temperature. Acting as for the Hajos-Parrish series, control experiments (^{1}H-NMR on aliquots) have been carried out to ascertain whether **7** might be an intermediate in the formation of ring enlarged product **8**. With the hope that **7** could have been more stable than **3** (and hence isolable), we tried the oxidative cleavage using only one equivalent of lead tetraacetate and stopped the reaction immediately after the first transformation (10 minutes at -40°C) by diluting with ether and subsequently by filtrating the reaction mixture through a column containing silica gel. In doing so we discovered that the first forming dialdehyde **I** is rapidly and entirely evolving towards the tricyclic enol ether **7** on standing and that 10 min at -40°C were enough to ensure a quantitative formation of the latter (the intramolecular Diels-Alder adduct). The overall $Pb(OAc)_4$ mediated transformation starting either from the unsaturated diol **6**, or from the isolable tricyclic enol ether intermediate **7** in one-pot, was a ring expansion/functional redistribution leading to a tetrasubstituted seven-membered ring containing [6+7]-fused ring system **8**.



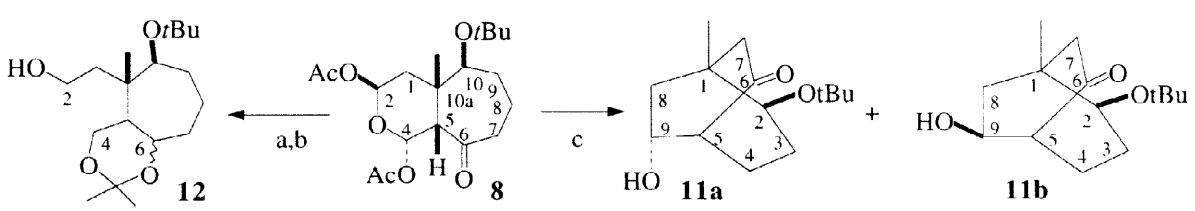
Scheme 3: A mechanistic rationale for the one-pot multistage transformations in the octaline-diol series.

As illustrated in Scheme 2, transformations from **9** to **8** (all but the reduction operation, **10** to **6**) are carried through with the aid of a single reagent: lead tetraacetate. The latter serves as the acetoxylating reagent on **9**, affording the requisite α-acetoxy enone **10**, as an oxidant, allowing glycol cleavage on **6**, as a Lewis acid catalyzing the intramolecular [4+2] cycloaddition of the internally linked heterodiene-heterodienophile **I**, as a Lewis acid again, promoting the ring expansion *via* the organolead intermediate **II** and finishes the sequence just as it started: as an acetoxylating reagent. Although mechanistic studies concerning the precise mechanistic details have not been conducted at the present time there is ample evidence to support the operation of each transformation proposed in Scheme 3 and no compelling reasons to discount any. The process is initiated by the oxidative cleavage (first transformation) leading to **I**. The following transformation affording **7** is an intramolecular hetero-Diels-Alder [4+2] cycloaddition where both diene and dienophile components contain a heteroatom.[8] The isolable and stable tricyclic enol ether intermediate **7** then suffers an electrophilic attack from the metal leading to a carbon-lead bond formation in a way entirely analogous to the chemistry of thalium, mercury and lead elegantly developed by McKillop, Larock and Rubottom respectively[9] and it is reasonable to conclude that an organolead compound **II** is formed as intermediate. The latter first undergoes a ring opening to generate the ring-expanded bridghead cation **III** which in turn undergoes successive skeletal rearrangement to **IV** and a subsequent acetate ion attack to afford the final product **8**. The transformation which gives rise to a ring expansion is by far the most important of the cascade as it contains the stage including the driving force

operation; it is based on the ease with which Pb^{4+} undergoes reduction to Pb^{2+} and constitutes the most useful aspect of organolead chemistry.[10] Up until the formation of the bridgehead cation **III** (the ring expansion stage), the same mechanistic course operates as in the Hajos-Parrish series (see ref. 1). From this point on, we observe an alternative evolution: the bridgehead cation **III** first undergoes skeletal rearrangement into **IV** and subsequent acetate ion attack, leading to the final ring enlarged compound **8** whereas in the Hajos-Parrish series, direct acetate ion attack on the bridgehead cation (lower homologue of **III**) leads to a strain-free six-membered ring, containing a bridgehead acetate, as the only isolated product. The driving force for the diverging behaviour of the bridghead cations obtained in the end of the third transformation in the Hajos-Parrish and Wieland-Miescher (hydrinden-diol and octaline-diol respectively) series, explaining the preferential formation of the cycloheptanone derivative **8**, could be attributed to the generation of a resonance stabilized cation **III**, a putative anti-Bredt structure only possible in the Wieland-Miescher series. The latter could then evolve in two ways to yield a ring-expanded product: either by direct attack of the acetate ion yielding **V** containing an sp^3 center in the seven membered ring (severe eclipsing and transanular interactions) or by rearranging first into cation **IV** and subsequent acetoxy ion attack. The fact that direct acetate ion attack on **III** leading to **V** is not observed experimentally can be explained on the grounds of thermodynamic stability of the product; the pathway from **III** to **IV** then **8**, rather than to **V**, corresponds to a transformation of a tetrahedral ring atom into a trigonal one in a seven membered ring which means less internal strain for the molecule.[11]

The configurations at the newly formed asymmetric centers at C-2 and C-4 in bis-acetoxy acetal **8** are assigned to be as depicted in Scheme 3.[12] For stereoelectronic reasons, at least one of the acetoxy groups (the one at C-2) prefers to adopt an axial arrangement to benefit from the anomeric effect with the ring oxygen. Thus, the stereochemical arrangement at C-2 might have been controlled both by the cavity of the [7+6] *cis*-fused bicyclic ring system and the anomerically more favorable, axially oriented carbon-oxygen bond disposition, while the one at C-4 should have been controlled by the intramolecular acetate anion delivery. This could well be explained on the basis of the proposed mechanistic pathway (Scheme 3) where the sense of acetate ion attack leading into intermediate **II**, is likely to be governed by steric factors, (electrophilic attack of the metal is only possible from the face opposite to the angular methyl group thus insuring the facial selectivity).

The construction of the functionalized seven-membered ring segment **12** was then undertaken. Reduction of **8** with $LiAlH_4$ in THF (room temperature, then reflux for 30 min) afforded the diastereomeric mixture of the corresponding cycloheptane-triols.



Scheme 4 a) $LiAlH_4$, THF, rt. b) methylene chloride, acetone, TsOH, rt. c) K_2CO_3-MeOH-H_2O, rt, 16 h

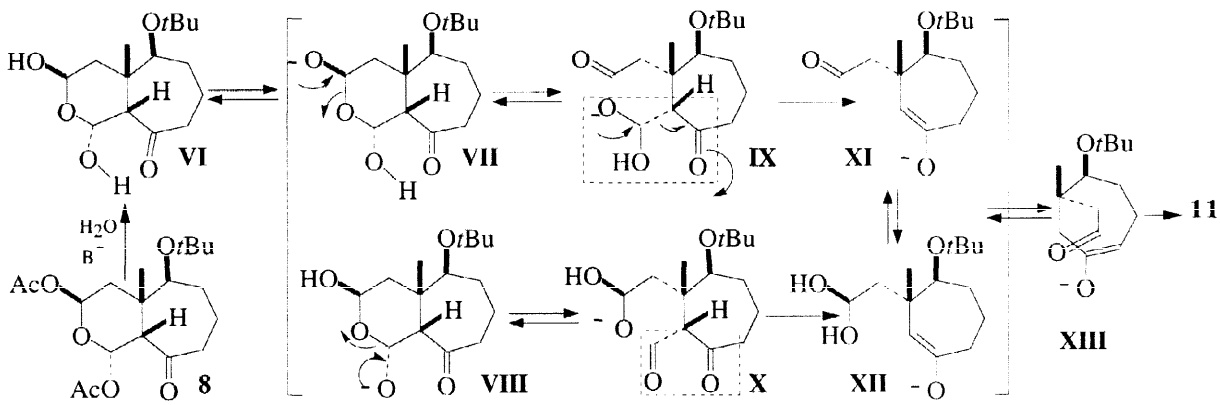
For the preparation of a synthetically useful 1,2,3,4-tetrasubstituted cycloheptanone derivative of type **12**, selective differential blocking of the C-4, C-6 hydroxyl groups could have been achieved in various ways, some of them (such as benzylideneacetals, stannylene derivatives, cyclic ketene acetals) offering additional chemoselectivity and thus step efficiency.[13] In a preliminary experiment, selective protection of the C-4, C-6 hydroxy groups as the acetonide was best accomplished by treating the resulting triol in methylene chloride with

anhydrous acetone and a catalytic amount of *p*TsOH under argon, at room temperature.

The crude mixture of acetonides thus obtained (77%, 1:1 ratio) was first recrystallized from hexanes, precipitating most of the lower eluting isomer **12b** and then separated on silica gel using methylene chloride-methanol (98:2) as eluent. Following transformation of the free primary hydroxyl group at C-2, a chemoselective functionalization of the secondary hydroxyl group of **12** at C-6 using literature procedures should provide an easy access to polysubstituted cycoheptane derivatives.

Fused to bridged ring system interchange:

The formation of the bicyclo[3.2.2]nonane unit **11** from the starting diol **6** involves the elaboration of the *cis*-fused bicyclic derivative **8** obtained in one-pot as described above, followed by a basic treatment. Thus, the bridged system **11**, was easily obtained in one step from **8**, by dissolving the latter in methanol-water (8:1) and stirring the reaction mixture in the presence of K_2CO_3 at room temperature. When the base treatment was stopped after an overnight stirring at room temperature, a diastereomeric mixture (in a nearly 1:1 ratio) of bicyclic aldols **11** was obtained in 85% yield (Scheme 4). From the fused ring system **8** to the bicyclo[3.2.2]nonane aldol derivatives **11**, again a one-pot sequential transformation protocol operates; overall we have a single-step "fused to bridged ring system interchange" ensuring functional diversity and enantiomeric purity. The three functional groups (free hydroxyl, *t*Bu-protected hydroxyl and carbonyl) on each ring offer easy chemodifferentiation for further selective transformations. The mechanistic pathways proposed for the one-pot formation of the bicyclo[3.2.2]nonane aldol derivative **11** from the fused [6+7]-ring system **8** presented in Scheme 5, involve a retro-Claisen and an intramolecular aldol reaction.



Scheme 5: Proposed mechanism for the one-pot "fused to bridged" ring system interchange.

The process begins with acetate hydrolysis of **8** to transient cyclic hemihydrate intermediate **VI** and most probably evolves towards the anionic forms **VII-VIII**. Although ionization first to **VII** (by abstraction of the more acidic proton due to hydrogen bonding) before ring opening seems favored we have no evidence to confirm the exact pathway. However, we can reasonably admit that the starting bis-acetoxy acetal **8** is immediately converted to the anionic species **VII-VIII** in aqueous base. Once formed, the latter then undergo ring opening with subsequent formation of 1,3-dicarbonyl intermediates **IX**, or **X** (structural subunits for the retro-Claisen transform, as shown in the boxed portions) which suffer a retro-Claisen deacylation to deliver **XI**, or **XII**. Finally an enolate isomerization to **XIII** sets up the intramolecular aldol reaction, which in turn ends the fused to bridge ring system interchange *via* an aldol process. In the presence of water and base species **VII-XII**

could well be in equilibrium leading to the same aldol precursor **XIII**. The anticipated stereochemistries of these highly oxygenated ring systems were verified by high field NMR techniques. Assignment of all protons and carbons was straightforward using ^{1}H-^{1}H, ^{1}H-^{13}C correlation spectroscopy. Most of the proton signals are well separated from each other thus allowing n.O.e. measurements. A series of n.O.e. difference experiments (diagnostic n.O.e.'s, see experimental part) allowed us to establish the relative configurations at the newly created centers C-5, C-9.

Conclusion:

The $Pb(OAc)_4$ mediated one pot multistage transformations of unsaturated vicinal diols, have resulted in the development of a new ring expansion methodology and hold considerable potential for the synthesis of a series of complex molecules. The studies presented above combine multiple bond-forming and bond-breaking sequences into a one pot reaction; only one workup is needed from the unsaturated diols **6** to the ring-enlarged compound **8**, just as from **2** to **4**. The starting diols can be readily assembled and constitute attractive precursors for highly elaborated cyclohexanes, cycloheptanes, a number of fused and bridged bicyclic systems and finally taxoid building blocks. While no special efforts were taken to optimize these reactions, the yields range from good to excellent. Further studies on the mechanistic details and synthetic potential of these sequential transformations are in progress.

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Experimental section:

General experimental details were as previously described (ref 1). Experimental evidence favouring the structures **7**, **8**, **11a** and **11b** came from a comprehensive range of ^{1}H and ^{13}C-NMR data (1D and 2D experiments) and corroborated by spatial proximity (n.O.e) studies. "Usual work up" means washing of the organic layer with brine, drying on anhydrous $MgSO_4$, and evaporating *in vacuo* with a rotary evaporator at aspirator pressure. The optically pure compounds were prepared starting from racemic material resolved according to our lipase catalyzed resolution technique.[7]

Preparation of the unsaturated diol 6 from 10 as a diastereomeric mixture: a) reduction with $LiAlH_4$: to a suspension of $LiAlH_4$ (1.52 g, 40 mmol) in 40 mL of anhydrous ether, cooled at 0°C, was added dropwise a solution of acetoxyenone **10** (2.94 g, 10 mmol, epimeric mixture, 58:42 ratio) obtained according to ref. 7, in 25 mL anhydrous ether. The reaction mixture was stirred at room temperature for 30 min at which point no starting material remained (TLC monitoring), diluted with wet ether and treated with a small amount of 15% aq.NaOH solution. The organic layer was worked up as usual to give 2.46 g (9.68 mmol, 97%) of the desired diols after filtration on silica gel (ethyl acetate-heptane, 1:1) as an epimeric mixture.

b) reduction with L-Selectride: to a stirred solution of **10** (980 mg, 3.33 mmol) in THF (10 mL) at -70°C was added 1M solution of L-selectride (20.0 mL, 20 mmol, 2.0 eq.). The mixture was stirred at room temperature for 1h, hydrolyzed with 15% NaOH in water (70 mL) and 30%-H_2O_2 (70 mL) and stirred at room temperature for 1 h, diluted with water, and extracted with methylene chloride. The combined extracts were worked up as usual to yield the Wieland-Miescher diol **6** as an epimeric mixture in 95% combined yield.

Starting from the 2-α-acetoxyenone (2*R*, 9*S*, 10*S*)-(+)-**10**, (294 mg, 1 mmol) in 5 ml of dry ether, treatment with an excess of lithium aluminum hydride (4 mmol) at 0°C for 1 h 50 min afforded after work up as above a mixture of two diols **6a** and **6b** in a nearly 1:5 ratio which were flash chromatographed on silica gel using

heptane-ethyl acetate, 1:1.5 as eluent. The higher eluting diastereoisomer **6a** (17%, minor) and the lower eluting one **6b** (83%, major) were then characterized. (2*R*, 3*S*, 9*S*, 10*S*)-(+)-**6a**: **m.p.**: 101-103°C (heptane-ether). $[\alpha]_D$ +149 (*c* 0.6). **IR** (film): 3302, 2971, 2941, 2910, 2870, 1656, 1466, 1437, 1390, 1375, 1362, 1255, 1191, 1071, 1043, 1027, 1010, 981, 854 cm^{-1}. **^{1}H-NMR** (300 MHz):1.07 (3H, s, Me), 1.18 (9H, s, tBu), 1.20-2.30 (8H, m), 3.13 (1H, dd, *J*=4.0, 11.0), 3.81 (1H, ddd, *J*=3.8, 7.7, 12.6), 4.04 (1H, dd, *J*=3.8, 5.4), 5.50 (1H, dd, *J*=1.7, 5.4). **^{13}C-NMR** (75 MHz): 17.8 (Me), 23.7 (CH_2), 29.1 (tBu), 30.3 (CH_2), 31.2 (CH_2), 38.7 (CH_2), 42.7 (Cq-10), 66.2 (CHO), 67.4 (CHO), 73.2 (Cq-tBu), 78.1 (C- 9), 120.2 (C-4), 148.9 (C-5).

(2*R*, 3*R*, 9*S*, 10*S*)-(+)-**6b**: **m.p.**: 99-101°C (heptane-ether). $[\alpha]_D$ +46 (*c* 1.3). **IR** (film): 3381, 2974, 2941, 2879, 1657, 1467, 1440, 1390, 1372, 1363, 1200, 1191, 1043, 1022, 965, 917, 882, 848 cm^{-1}. **^{1}H-NMR** (400 MHz): 1.07 (3H, s, Me), 1.15 (9H, s, tBu), 1.22 (1H, m), 1.38 (1H, t, *J*=12.7, H-1αax), 1.55 (1H, m, H-6βax), 1.68-1.71 (2H, m), 1.95-2.14 (2H, m), 2.00 (1H, dd, *J*=3.4, 12.7, H-1βeq), 3.04 (1H, dd, *J*=4.0, 11.0, H-9), 3.64 (1H, ddd, *J*=3.4, 7.6, 12.4, H-2βax), 3.99 (1H, br. d, *J*=7.6, H-3αax), 5.16 (1H, br s, H-4). **Diagnostic n.O.e.'s**: {Me-10}: H-2βax; **^{13}C-NMR** (75 MHz): 18.5 (CH_3), 24.1 (CH_2), 29.2 (tBu), 30.4 (CH_2), 30.9 (CH_2), 42.8 (Cq-10), 43.1 (CH_2), 71.3 (CHO), 73.1 (Cq-tBu), 74.3 (CHO), 78.4(C-9), 122.3 (C-4), 145.1 (C-5). **EIMS**: 254 ($M^{+\cdot}$, 1), 236 (M-H_2O, 2), 196 (8), 180 (34), 57 (100).

Preparation of the tricyclic enol ether 7, the interrupted cascade: A dry flask was charged with 830 mg (3.27 mmol) of the Wieland-Miescher diol **6**, obtained from (*S*)-(+)-**5** (steroid series) and 2.90 g (6.54 mmol) of $Pb(OAc)_4$ vacuumed, flushed with argon and cooled to -25°C. Acetonitrile (20 mL) was then added at -25°C, the cooling bath removed soon after. Five minutes upon start up a UV-active spot appears which gradually collapses to a higher non UV-active spot. The mixture was stirred at room temperature for 1-2 h (TLC-monitoring), diluted with heptane, and filtered through silica gel using heptane-ether (1:1) as an eluent to yield 768 mg (93%) of pure **7**: **m.p.** 46-48°C (pentane). $[\alpha]_D$ -13 (*c* 1.01). **IR** (film): 2969, 2938, 2869, 1725, 1638, 1456, 1362, 1281, 1206, 1131, 1069, 1019, 994, 938 cm^{-1}. **^{1}H-NMR** (400 MHz): 1.07 (3 H, s, Me-10), 1.18 (9 H, s, tBu), 1.31 (1 H, m, H-8βax.), 1.35 (1 H, m, H-7αeq.), 1.55 (1 H, m, H-6αeq.), 1.61 (1 H, m, H-6βax.), 1.70 (1 H, ddt, *J*= 1.7, 3.3, 12.9, H-8αeq.), 1.86 (1 H, dd, *J*=1.2, 14.3, H-1βeq.), 1.91 (1 H, d quintet, *J*=1.7, 14.5, H-7βeq.), 2.44 (1 H, dd, *J*=5.8, 14.3, H-1αax.), 3.37 (1 H, dd, *J*=3.6, 11.4, H-9), 4.75 (1 H, d, *J*= 6.1, H-4), 5.63 (1 H, d, *J*= 5.8, H-2), 6.18 (1 H, d, *J*= 6.1, H-3). **Diagnostic n.O.e.'s**: {Me-10}: H-4, H-1b, H-8βax; {H-1α}: H-2, H-9; {H-9}: H-8αeq, H-1α; {H-4}: H-3, Me-10. **^{13}C-NMR** (75 MHz): 12.5 (Me-10), 19.8 (C-6), 28.9 (C-7), 29.3 (tBu), 29.7 (C-8), 46.7 (C-1), 55.4 (Cq-10), 72.8 (Cq-tBu), 73.5 (C-9), 84.5 (C-5), 99.4 (C-2), 110.0 (C-4), 135.5 (C-3). **EIMS**: m/z 252 ($M^{+\cdot}$, 26), 196 (50), 195 (30), 57 (100). **HREIMS** calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1709. **Anal**: calcd. for $C_{15}H_{24}O_3$ C 71.38, H 9.59, found C 71.34, H 9.59.

One pot ring expansion starting from 7 leading to 8 : 2.52 g (10 mmol) of **7** were treated as above with 8.86 g (20 mmol) of $Pb(OAc)_4$ in acetonitrile (80 mL). 48 h later the reaction was stopped and gave unreacted **7** (25%) and the ring enlarged compound **8** (60%).

One pot ring expansion from 6 to 8; the whole cascade: Proceeding as above 2.54 g (10 mmol) of **6**, and 8.86 g (20 mmol) of $Pb(OAc)_4$ in acetonitrile (80 mL) were stirred at room temperature for 50 h. TLC monitoring shows rapid disappearance of the starting diols, appearance of the dialdehyde **16** and right after the bis-hetero-IMDA adduct **7**. The ring expansion process leading to **8** is time demanding and its completion takes over two days stirring at room temperature, while the oxidative cleavage and the IMDA are considerably faster, never more than two hours for these first two transformations. Two out of four transformations leading to

isolable compounds such as dialdehyde **I** (Scheme 3, oxidative cleavage) and tricyclic enol ether **7** (bis-hetero intramolecular Diels-Alder cycloaddition) can be stepwisely stopped and the resulting compounds characterized by IR and NMR spectra. Nevertheless dialdehyde **I** (^{1}H-NMR: 9.7 and 10.1 ppm; ^{13}C-NMR: 192.2 and 200.6 ppm) rapidly undergoes intramolecular Diels-Alder cyclization towards **7** and hence it was characterized as a mixture with **7**.

The residue was purified on silica gel (heptane-ethyl acetate 2:1) to yield 60% of **8** along with 25% of **7** which can be easily separated and recycled. **8**: **m.p.** 135-6°C (pentane). $[\alpha]_D$ -39 (*c* 1.29). **IR:** ($CHCl_3$): 3022, 2978, 2936, 1752, 1716, 1391, 1366, 1230, 1217, 1189, 1173, 1109, 1071, 1049, 1021, 994, 947, 926 cm^{-1}. **^{1}H-NMR** (400 MHz): 1.15 (9H,s, tBu), 1.31 (3H,s, Me-10a), 1.62 (1H, m, H-8α), 1.75 (1H, m, H-9α), 1.78 (1H, dd, *J*=2.1, 14.6, H-1β), 1.92 (1H, dd, *J*= 4.3, 14.6, H-1α), 1.93 (1H, m, H-8β), 2.00 (1H, dq, *J*= 2.6, 12.1, H-9β), 2.08 and 2.11 (6H, s, OAc), 2.41-2.54 (2H, m, *J*= 7.1, 11.6, H-7,7'), 2.93 (1H, d, *J*= 3.4, H-5), 3.05 (1H, d, *J*= 8.9, H-10), 6.34 (1H, d, *J*= 3.4, H-4), 6.40 (1H, dd, *J*= 2.1, 4.2, H-2). **Diagnostic n.O.e.'s**: {Me-10a}: H-4, H-1βeq., H-5, H-9βax; {H-4}: H-5, Me-10a;{H-10}: H1αax, H-8α; {H-5}: H-4, H7β, H-9β, Me-10a; {H-9β}: Me-10a, H-5, H-9α (n.O.e.gem). **^{13}C-NMR** (75 MHz): 20.5 (Me-10a), 20.8 and 21.0 ($\underline{C}H_3CO$), 22.5 (C-8), 28.7 (tBu), 30.6 (C-9), 35.2 (C-1), 37.4 (Cq-10a), 45.3 (C-7), 53.8 (C-5), 73.7 (Cq-tBu), 79.4 (C-10), 88.4 (C-4), 92.1 (C-2), 168.7 and 168.9 ($O\underline{C}OCH_3$), 208.8 (C-6). **CIMS**: 311 [(M+H)-AcOH] (99), 195 (70). **HRCIMS**: calcd. for $C_{17}H_{27}O_5$: *m/z* 311.1858 found: 311.1860; calcd. for $C_{11}H_{15}O_3$: *m/z* 195.1021 found: 195.1029. **Anal**: calcd. for $C_{19}H_{30}O_7$ C 61.59, H 8.17, found C 61.32, H 8.08.

One pot fused to bridged ring system interchange: preparation of bicyclo[3.2.2]nonane derivatives 11. To a stirred solution of **8** (1.0 g, 2.7 mmol) in a mixture of methanol (40 mL) and water (5 mL), was added potassium carbonate (2.1 g, 15 mmol). The resulting mixture was stirred at room temperature for 15 h, diluted with water, and extracted with methylene chloride. Following usual work up the residue was purified by flash chromatography on silica gel affording 550 mg (2.29 mmol, 85%) of a diastereomeric mixture of **11** in a nearly 1:1 ratio. Elution with ethyl acetate-heptane-methanol (1:1:0.01) allowed separation; higher eluting isomer (1*S*, 2*S*, 5*R*, 9*R*)-2-*tert*-butoxy-9α-hydroxy-1-methyl-bicyclo[3.2.2]nonane-6-one **11a**: $[\alpha]_D$ +70 (*c* 1.12). **IR** (film): 3422, 2971, 2934, 2871, 1705, 1458, 1387, 1364, 1189, 1057, 1024, 991 cm^{-1}. **^{1}H-NMR** (400 MHz): 1.02 (3H, s, Me-1), 1.15 (9H, s, tBu), 1.45 (1H, m, H-3αax), 1.55-1.75 (1H, m, H-4), 1.66 (1H, dd, *J*=3.9, 14.7, H8α), 1.68 (1H, d, *J*=18.7, H-7β), 1.93 (1H, m, H-4), 2.06 (1H, dd, *J*=9.5, 14.7, H-8β), 2.07 (1H, m, H-4), 2.60 (1H, m, H-5), 2.63 (1H, dd, *J*=2.6, 18.7, H-7α), 3.44 (1H, t, *J*=5.7, H-2), 4.20(1H, ddd, *J*=3.9, 6.7, 9.5, H-9). **Diagnostic n.O.e.'s**: {Me-1}: H-8β, H-7α, H-7β, H-2; {H-9}: H-5, H8β; {H-2}: H-8α; {H-5}: H-9, H-4, 4'; {H-8α}: H-2. **^{13}C-NMR** (75MHz): 19.8 (CH_2), 29.1 (tBu), 29.3 (Me-1), 30.4 (CH_2), 37.6 (Cq-1), 41.6 (C-8), 45.2 (C-7), 54.1 (C-5), 66.6 (C-9), 73.2 (Cq-tBu), 77.6 (C-2), 214.6 (C-6). **EIMS**: 240 ($M^{+\cdot}$, 89), 184 (100), 166 (34), 57 (89). **HREIMS**: calcd. for $C_{14}H_{24}O_3$: m/z 240.1725, found: 240.1729.

Lower eluting isomer (1*S*, 2*S*, 5*R*, 9*S*)-2-*tert*-butoxy-9β-hydroxy-1-methyl-bicyclo[3.2.2]nonane-6-one **11b**: **m.p.** 76-78°C (ether-heptane). $[\alpha]_D$ +92 (*c* 1.1). **IR** (film): 3422, 2957, 2871, 1705, 1458, 1392, 1361, 1235, 1192, 1108, 1060, 1024, 991, 895 cm^{-1}. **^{1}H-NMR** (400 MHz): 1.03 (3H, s, Me-1), 1.14 (9H, s, tBu), 1.57 (1H, dd, *J*=15.5, 1.5, H-8β), 1.52-1.62 (2H, m, H-4, 3), 1.75 (2H, m, H-3, 4), 1.97 (1H, d, *J*=18.7, H-7β), 2.20 (1H, ddd, *J*=2.4, 7.9, 15.5, H-8α), 2.57 (1H, ddd, *J*=3.1, 4.7, 4.8, H-5), 2.72 (1H, dd, *J*=2.7, 18.7, H-7α), 3.39 (1H, dd, *J*=4.2, 5.1, H-2), 4.26 (1H, ddd, *J*=1.5, 3.1, 8.0, H-9). **Diagnostic n.O.e.'s**: {Me-1}: H-8β, H-7α, H-7β, H-2; {H-9}: H8α; {H-2}: H-8α; {H-5}: H-4, 4'; {H-8α}: H-2, H-9. **^{13}C-NMR**

(75MHz): 21.7 (CH_2), 29.1 (tBu), 29.6 (Me-1), 30.5 (CH_2), 36.9 (Cq-1), 41.8 (C-8), 45.1 (C-7), 54.5 (C-5), 69.2 (C-9), 73.1 (Cq-tBu), 76.6 (C-2), 215.5 (C-6). **EIMS**: 240 ($M^{+\cdot}$, 18), 184 (30), 166 (64), 57 (100). **HREIMS**: calcd. for $C_{14}H_{24}O_3$: m/z 240.1725, found: 240.1716.

Reduction of 8 and selective acetonide formation: To a stirred suspension of 500 mg (13.175 mmol, 7.8 eq.) of $LiAlH_4$ in tetrahydrofuran (10.0 mL) a solution of 500 mg (1.350 mmol) of racemic **8** in tetrahydrofuran (10.0 mL) was added at room temperature. The reaction mixture was then refluxed for 30 min, cooled, quenched with 0.5 mL of water, 0.50 mL of 15% NaOH, 1.5 mL of water, and stirring was continued at room temperature for an additional 1 h. Filtration and concentration under reduced pressure gave a mixture of triols. The latter without purification, was dissolved in acetone (1.0 mL) and methylene chloride (10.0 mL) and 20 mg of pTsOH was added. The mixture was stirred at room temperature for 1 h, filtered through aluminium oxide with ethyl acetate, and concentrated under reduced pressure. Rapid filtration on silica gel with a mixture of ethyl acetate-heptane (1:1) gave **12** (327 mg, 77%) as a diastereomeric mixture in 1:1 ratio. The lower eluting isomer **12b** was precipitated from hexane at room temperature. Pure sample of the higher eluting isomer was obtained by silica gel flash chromatography (elution with methylene chloride-methanol, 98:2). Data for higher eluting isomer **12a: IR** (film): 3440, 2976, 2940, 2873, 1462, 1380, 1364, 1268, 1256, 1228, 1190, 1168, 1118, 1085, 1054, 1019, 874, 738 cm^{-1}. **^{1}H NMR** (250 MHz): 0.94 (s, 3 H, Me), 1.18 (s, 9 H, t-Bu), 1.35 and 1.40 (6 H, s, Me of acetonide), 1.10 - 2.10 (9 H,m, CH and CH_2), 3.37 (1 H, dd, J = 1.3, 6.3, C<u>H</u>-O-tBu), 3.67-3.90 (5 H, m, CHO and CH_2O). **^{13}C NMR** (75 MHz): 21.0, 23.4, 27.9 (Me), 29.1 (tBu), 19.8, 29.4, 35.8, 37.4, (CH_2), 40.7 (Cq), 73.4 (Cq-tBu), 45.6 (CH), 59.5 and 60.5 (CH_2O), 70.1 and 76.8 (CHO), 98.2 (C_q of acetonide). **EIMS**: 314 ($M^{+\cdot}$, 2), 299 (20), 285 (3), 256 (10), 57 (100). **HREIMS**: calc. for $C_{18}H_{34}O_4$ m/z 314.2457, found 314.2462. Lower eluting isomer **12b**: **mp** 124-125°C (hexane). **IR** ($CHCl_3$) 3440, 2978, 2938, 2882, 1467, 1388, 1366, 1227, 1191, 1099, 1080, 1041, 1024, 983 cm^{-1}. **^{1}H NMR** (250 MHz) 0.98 (3 H, s, Me), 1.15 (9 H, s, t-Bu), 1.37 (6 H, s, Me of acetonide), 1.10-2.35 (9 H, m, CH and CH_2), 3.47 (bd, 1 H, J = 5.3 Hz, C<u>H</u>-OtBu), 3.60-4.25 (m, 5 H, CHO and CH_2O). **^{13}C NMR** (50 MHz) 21.3, 25.2, 26.3 (Me), 29.1 (t-Bu), 16.8, 33.2, 34.6, and 38.3 (CH_2), 42.9 (C_q), 73.0 (<u>C</u>q-tBu), 38.9 (CH), 59.4 and 61.5 (CH_2O), 71.5 and 76.1 (CHO), 99.2 (<u>C</u>q of acetonide). **EIMS**: m/z 314 ($M^{+\cdot}$, 0.5), 299 (1), 256 (3), 225 (18), 89 (80), 57 (100). **Anal**: Calc. for $C_{18}H_{34}O_4$ C 68.75, H 10.90. Found: C 68.86, H 10.91.

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