An Efficient One-Pot Approach to Bridged Bicyclic Ring-Systems through Consecutive Hetero-Domino Transformations: A Mechanistic Rationale and Further Rearrangements

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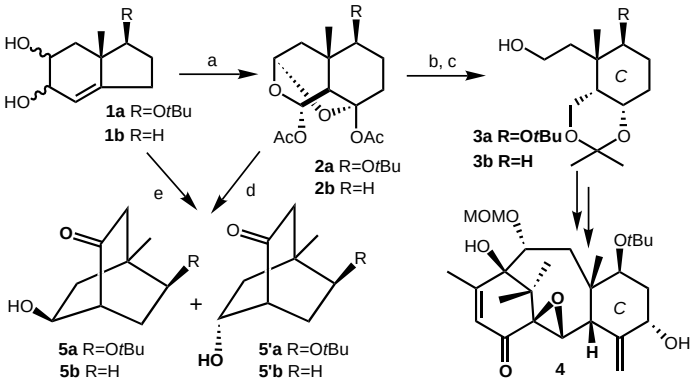
Abstract: This article describes the design of olefin-generated/reagent-modulated consecutive hetero-domino reactions of 1,2-unsaturated bicyclic diols, which are potentially of great use, initiated by $PhI(OAc)_2$, continued by $[Pb(OAc)_4]$, and completed by use of a mild base (K_2CO_3). Inversion of a quaternary center has been achieved through a three-reaction sequence: a domino transformation followed by an *m*-CPBA-mediated Baeyer–Villiger oxidation and subsequent reductive lactone ring opening.

Keywords: Baeyer–Villiger oxidation · configuration inversion · domino reactions · ring expansion · ring-system interchange

Introduction

The importance of domino reactions[1] as a tool to attain high diversity is well established. Earlier accounts from this laboratory dealt with development of a ring-expansion methodology for accessing optically homogeneous and conveniently functionalized six and seven-membered rings by $[Pb(OAc)_4]$-mediated hetero-domino reactions.[2] These studies established the feasibility of incorporating most of the essential features of a taxoid C-ring precursor **2** in a "one-pot" fashion; precursor **2** was then transformed into the isopropylidene alcohol **3**, which was subsequently taken into the highly functionalized taxoid diterpene skeleton **4** (Scheme 1).[3] On the other hand, mild base treatment of ring-expanded intermediates **2** led to the bicyclo[2.2.2]octane derivatives **5** in high yields. The bridged bicyclic aldol frameworks **5a**, which offer chemoselectivity owing to the threefold oxygenation pattern, are of high synthetic value. Obtained both efficiently and in high yield, they might serve either as a chiral platform for the construction of asymmetric catalysts from cheap achiral catalysts,[4] or be used as building blocks for further selective transformations.

Recent studies in our laboratories focusing on rendering our chemistry environmentally friendly revealed that several other oxidants could perform, at least partially, domino transformations and, most importantly, that they could be used in combination with $[Pb(OAc)_4]$. This insight prompted us to investigate consecutive domino reactions, which are especially attractive because of their operational simplicity; the need to use only half the amount of $[Pb(OAc)_4]$ compared to the initial domino reactions and reduced workup. We highlight herein a mechanistic rationale that accounts for the "one-pot" transformation of **1** to **5**, which can be carried out in two distinct ways by the sequential use of either one oxidant and one base (routes a and d, Scheme 1), or two oxidants and one base (route b Scheme 2), as well as secondary reactions of the bicyclic framework **5** thus obtained.



Scheme 1. a) 2.4 equiv $[Pb(OAc)_4]$, PhMe, 25 °C (85% for **2a**, 80% for **2b**); b) $LiAlH_4$, Et_2O, 0 °C; c) acetone, *p*-TosH, 25 °C, 80% 2 steps; d) K_2CO_3/MeOH, H_2O, 25 °C (92% for **2a**, 90% for **2b**); e) 2.4 equiv $[Pb(OAc)_4]$, PhMe, then K_2CO_3/MeOH, H_2O, 25 °C, (68% for **5a** and **5′a**, 10:1; 61% for **5b** and **5′b**, 8:1).

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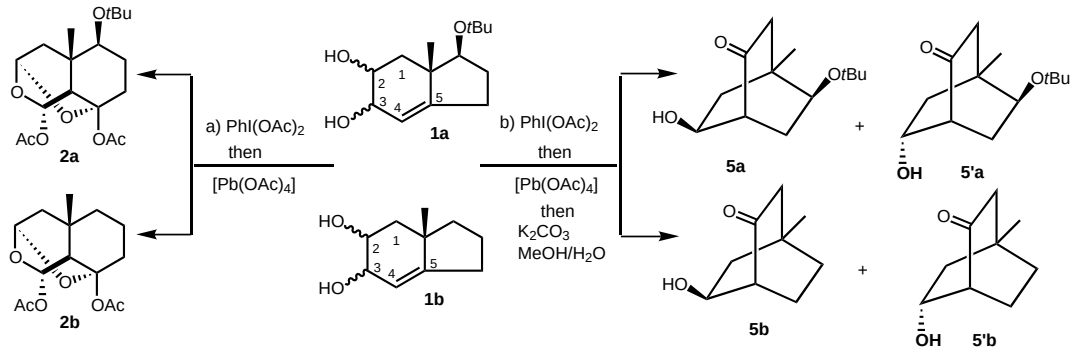


Scheme 2. a) 1.2 equiv $PhI(OAc)_2$, 24 h, then 1.2 equiv $[Pb(OAc)_4]$, PhMe, 15 h, 25 °C (80% for **2a**, 78.5% for **2b**); b) 1.2 equiv $PhI(OAc)_2$, 24 h, then 1.2 equiv $[Pb(OAc)_4]$, PhMe, 15 h, then K_2CO_3/MeOH, H_2O, 25 °C (55% for **5a**, 51% for **5b**).

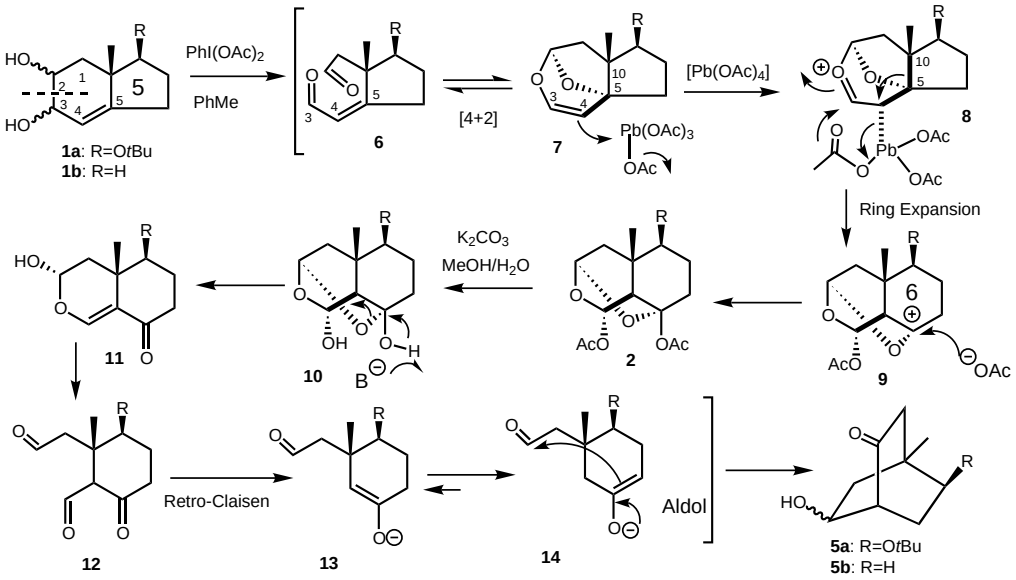
Results and Discussion

Since diol cleavage and the subsequent bis(hetero) intramolecular Diels–Alder (IMDA) reaction is achievable in various solvents (MeCN, AcOH, PhH, PhMe, CH_2Cl_2, $CHCl_3$, acetone, trifluorotoluene, anisole, and others) with a variety of oxidants other than $[Pb(OAc)_4]$, such as Dess–Martin periodinane,[5] $[Mn(OAc)_3]$,[6] Ph_3BiCO_3, and $PhI(OAc)_2$,[7] it creates the opportunity for the design and execution of consecutive domino transformations. Therefore, we focused our efforts in order to achieve the highest diversity from an unsaturated 1,2-diol by carefully tuning reaction conditions, such as timing of reagent addition, functional compatibility, and choice of solvent. Firstly, we envisioned that a short sequence from unsaturated diols **1** to bicyclic[2.2.2]aldols **5** could be put into practice. This would consist of a one-pot "ring expansion/fused to bridged-ring-system interchange", which would render isolation of the ring-expanded intermediates prior to the ring-system interchange unnecessary. The question was whether we could go from the fused bicyclic diol **1** to the bridged bicyclic aldol **5** in one-pot. To our pleasure, we found that the sequential use of $[Pb(OAc)_4]$ and potassium carbonate on a variety of unsaturated bicyclic diols (only two of them, **1a** and **1b**, are selected for this paper) resulted in formation of the anticipated bicyclic aldols in yields that were comparable or superior to that of the stepwise variant. Only one workup procedure was needed and no by-products were detected (route e Scheme 1). However, these time-resolved transformations, which can be modulated by reagent,[5, 6] solvent,[8] and substitution pattern,[9] only partially satisfy Tietze's requirements ("*the first stereogenic center must be introduced catalytically, the process must be elegant, efficient and non-polluting*"), because of the need to use a twofold excess of the toxic $[Pb(OAc)_4]$.[10]

Therefore, we focused our attention on employing an alternative reagent in place of the inexpensive but relatively toxic $[Pb(OAc)_4]$. To accomplish this task, we clearly needed an oxidant that would be able to perform both the oxidative cleavage and the ensuing intramolecular bis(hetero) Diels–Alder cycloaddition. This was best achieved by the use of $PhI(OAc)_2$, which offsets, in part, the disadvantage of $Pb(OAc)_4$-induced toxicity in these domino reactions (Scheme 2).[7] In practice the reactions were slower but clean. Control experiments in which $[Pb(OAc)_4]$ as the co-oxidant was omitted from the reaction afforded only the first two transformations, even when a threefold excess of the reagent (iodobenzene diacetate) was used with prolonged reaction times at room temperature. A procedure is thus available to cleanly effect an unprecedented sequence of events, while partially attenuating the problem of toxicity (Scheme 2).

This finding makes available a new process, namely, the three-reagent consecutive domino reaction, which is initiated by iodobenzene diacetate (oxidative/pericyclic transformation), continued by lead tetraacetate (oxyplumbation/ring expansion), and completed by a mild base that consists of solid K_2CO_3 in MeOH/H_2O (ring-system interchange). Nevertheless, the overall yields are lower (around 50%, unoptimized) and the reaction is slower than when lead tetraacetate is used as the oxidant (route e, Scheme 1). The examples shown in Scheme 2 provide an illustration of the high diversity generated by consecutive reactions. The transformation of **1** to **2** (route a) with $PhI(OAc)_2$ and $[Pb(OAc)_4]$ can be effected in acetonitrile, benzene, toluene, acetic acid, or (*S*)-*O*-acetyllactic acid, while conversion of **1** to **5** (route b) is best achieved in toluene or acetonitrile. The reaction can be followed by TLC, with all intermediates possessing R_f values substantially different from one another. The mechanistic pathway involved in the one-pot transformation of **1** to **5** is portrayed in Scheme 3.

A prerequisite for the domino process to occur is the presence of an unsaturated α-position with respect to the 1,2-diol system,[11] as olefins possess a high potential for being involved in diverse chemistry due to their free energy content.[12] Moreover, $[Pb(OAc)_4]$ has a high oxidation potential and is a good electrophile. Consequently, $[Pb(OAc)_4]$ can act as a multi-task reagent that behaves both as the oxidant and as the Lewis-acid promoter in the same reaction; the first equivalent of $[Pb(OAc)_4]$ is used for the oxidative cleavage, while the second equivalent is used in the oxyplumbation, which promotes ring expansion. Finally, $PhI(OAc)_2$ can efficiently replace $[Pb(OAc)_4]$ for the first two transformations, whereas, the latter is essential for effecting the ring expansion at room temperature. With regard to the proposed mechanism, exposure of the unsaturated diols **1** to $PhI(OAc)_2$ results in glycol fission/intramolecular [4+2] cycloaddition to give the cyclic ene–acetal **7**

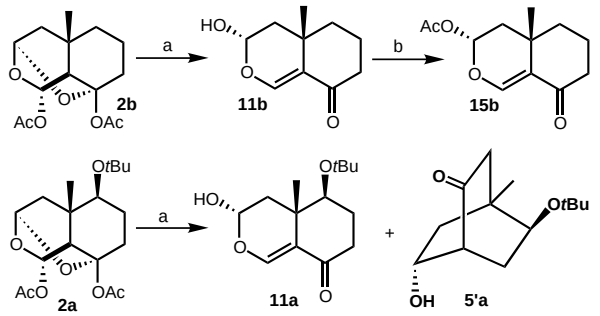


Scheme 3. A mechanistic rationale for the consecutive hetero-domino transformations.

in which the olefin at C4–C5 has been transferred α to the oxygen atom at C3 and, thus, facilitates the metal attack to afford the transient organolead intermediate **8**. The strain associated with the ring system and the geometry in **8** (ring expansion requires alignment of C–Pb bond with the C10–C5 bond) then favors a ring expansion, with concomitant loss of a $Pb(OAc)_2$ unit, and acylation. Saponification of the resulting bis(acetoxy) bis(acetal) **2** then initiates sequential transformations to afford **5**. The process begins with acetate hydrolysis of **2** to give the transient cyclic hemihydrate intermediate **10**. Once formed, **10** undergoes ring opening with subsequent dehydration to afford **11** en route to the 1,3-dicarbonyl species **12**. Aldehyde **12** then deacylates through a retro-Claisen process to generate the intramolecularly linked aldol precursor **13**. Finally, an enolate isomerization to **14** followed by an intramolecular aldol reaction ends the fused to bridge ring-system interchange.

Undertaking experiments where we could isolate and characterize intermediates, as portrayed in Scheme 4, we investigated the mechanism of the transformation of **2** to **12**.

Starting from **2b**, careful monitoring of the reaction by TLC and NMR spectroscopy (aliquots) revealed a rapid initial hydrolysis followed by a slower transformation requiring approximately 20 min at 0 °C. Alcohols **11** were identified as the first occurring intermediates and provided insight into the hydrolysis mechanism. Compound **11b** was fully characterized as its corresponding acetylated counterpart **15b**, but **11a** (from **2a**) was slightly contaminated with the minor bicyclic aldol product **5′a** (Scheme 4).

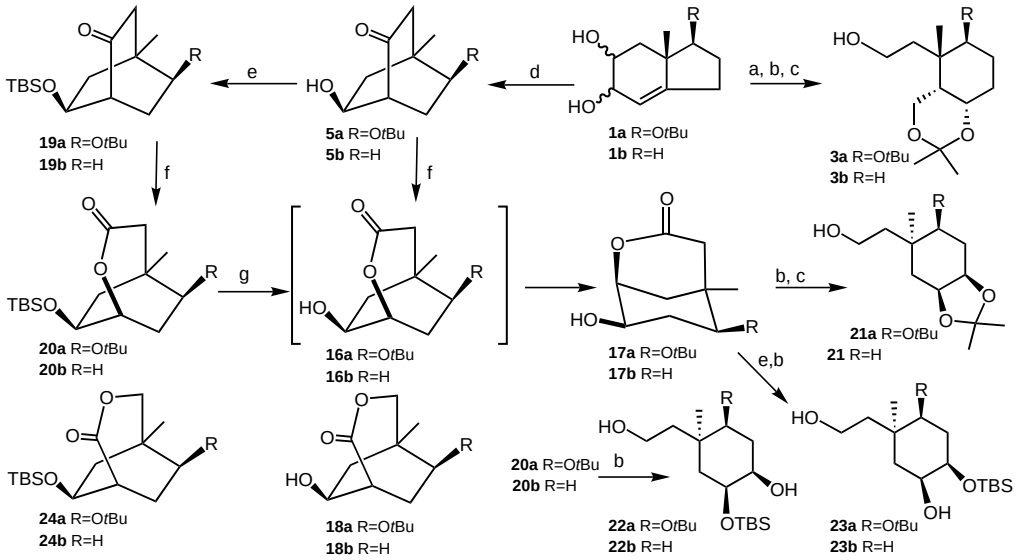


Scheme 4. a) K_2CO_3/MeOH, H_2O, 0 °C, 20 min, 81 %; b) Ac_2O, py, DMAP, 0 °C, 30 min, 85 %.

Following the mechanistic rationale, we briefly examined the viability of utilizing the ensuing products as substrates for further elaboration in an effort to invert the configuration at the quaternary center. The purpose of this exploration was to render operational a modular construction of cyclohexanes of type **3** or **21**, starting from the optically pure hydrindene diol **1** (Scheme 5).

Six-membered rings containing quaternary centers are valuable building blocks as they are found to be structural units in numerous biologically active natural products, such as taxoids,[13] clerodanes,[14] galbanic acid,[15] phomactin,[16] disydiolide,[17] fuscol,[18] and many others. Thus, with the aim of preparing heavily functionalized cyclohexane derivatives, we carried out Baeyer–Villiger oxidations of bicyclic aldols **5a** and **5b**, obtained in one step through consecutive domino transformations. As depicted in Scheme 5, oxidation of bicyclic aldols **5** and subsequent lactone ring opening would provide 1,2,4,5-tetrasubstituted cyclohexanes of type **21a**, **22a**, or **23a** (and the corresponding 1,2,4-trisubstituted **21b**, **22b**, **23b**) with an inverted configuration at the quaternary center. Given the fact that the nature of the peroxy acid used may influence the results obtained,[19] the Baeyer–Villiger oxidations were all carried out with excess *m*-chloroperbenzoic acid in methylene chloride at room temperature and in the presence of sodium bicarbonate. The structures of the resultant lactones **17**, **18**, **20**, and **24** were consistent with NMR data.

Baeyer–Villiger oxidation of the bicyclic aldol **5a** gives largely the bridgehead-migrated lactone[20] 2-oxa-bicyclo-[3.2.2]nonane-3-one (**16a**), which then undergoes transesterification to give the sterically less crowded 2-oxa-



Scheme 5. a) 2.4 equiv $[Pb(OAc)_4]$, PhMe, 25 °C; b) $LiAlH_4$, Et_2O, 0 °C; c) acetone, *p*-TosH, 25 °C; d) 1.2 equiv $PhI(OAc)_2$, 24 h, then 1.2 equiv $[Pb(OAc)_4]$, PhMe, 15 h, then K_2CO_3/MeOH, H_2O, 25 °C; e) TBSCl, imidazole, DMF, 0 °C; f) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 25 °C; g) TBAF, THF, 0 °C.

bicyclo[3.3.1]nonane-3-one (**17a**), along with its methylene migrated counterpart, 3-oxa-bicyclo[3.2.2]nonane-2-one (**18a**), in 66% isolated yield and 94:6 ratio. The distinction between the bridgehead- and methylene-migrated compounds **17** and **18**, respectively, is readily made on the basis of ^1H NMR spectroscopy. In particular, the geminally coupled protons attached to C4 appear at higher field for **17**-type lactones relative to those of type **18**. Under the same conditions, bicyclic aldol **5b** gave a mixture of isomeric lactones in 71% yield and 95:5 ratio. The isomers were separated by chromatography and the major product was identified as lactone **17b**. Based on literature, we anticipated that in **19** methylene-group migration would be favored over bridgehead migration due to the presence of the bulky protective group (and absence of hydrogen bonding with the free hydroxyl). Indeed, methylene-group migration was clearly preferred when the free hydroxyl group in **5a** was TBS-protected; Baeyer–Villiger oxidation of **19a** thus furnished lactones **20a** and **24a** in a 30:70 ratio and 56% yield, along with 43% recovered starting material. Under similar conditions, **19b** gave lactone **24b** in higher yield and with greater selectivity (73% isolated yield, 92% based on recovered starting material, 9:1 preference for methylene migration). The major lactones **17** could be converted either into **21**, which contain the inverted quaternary carbon configuration and can be obtained by direct reduction using lithium aluminium hydride (diethyl ether, 0 °C, 45 min) and subsequent selective acetonide formation (dry acetone, cat. *p*-TosOH, 4 Å MS, 25 °C, 80%), or into **23** by firstly protecting the alcohol as the TBS-ether (TBSCl, imidazole, DMF, 0 °C to 25 °C, 4.5 h, 100%) prior to reduction as described above. On the other hand, the TBS-protected 2-oxa-bicyclo[3.2.2]nonane-3-one (**20**), obtained as the minor component of the regioisomeric lactone mixture **20** and **24**, leads to the isomeric **22** if reduced prior to TBS deprotection, while upon fluoride-initiated deprotection the initially formed lactone **16** undergoes translactonization to afford **17** (both **a** and **b**). Overall, the approach represents an interesting application of $[Pb(OAc)_4]$-mediated one-pot multistage transformation methodology that provides functionalized and optically pure cyclohexanes of type **21**–**23**. Furthermore, these contain inverted configurations at the quaternary center, which nicely complements the synthesis of type **3** cyclohexanes whereby the configuration at the quaternary center is retained.

Conclusion

With the mechanistically challenging and synthetically useful formation of bicyclic aldols **5** from hydrindene diol derivatives **1**, a simple procedure for creating diversity in one synthetic operation has been developed. In all cases high molecular complexity was achieved and chemo-differentiation was secured. Scaled-up versions of these reactions (100 mmol of unsaturated diol) succeeded routinely. The present study, the consecutive hetero-domino transformation, which is effected in a single reaction vessel and, furthermore, allows the configuration at the quaternary center to be inverted, demonstrates the effectiveness of a new variant of this ring expansion–rearrangement strategy within the context of a synthetically useful oxidative cleavage (mediated by $PhI(OAc)_2$), ring expansion (mediated by $[Pb(OAc)_4]$), and ring-system interchange (mediated by K_2CO_3 in MeOH/H_2O). Several extensions of this chemistry are currently being investigated.

Experimental Section

General: Solvents and reagents used in this work were purified according to standard literature techniques and stored under argon. Experiments that required an inert atmosphere were carried out under dry argon in a flame-

dried glass system. Flash chromatography was run on silica gel (Merck 60, 230—400 mesh) with the solvent mixture indicated. Thin-layer chromatography was performed on commercial silica-gel plates that were developed by immersion into 5% phosphomolybdic acid in 95% ethanol. "Usual workup" means washing the organic layer with brine, drying over anhydrous $MgSO_4$, and evaporating in vacuo with a rotary evaporator at aspirator pressure. NMR spectra were run in $CDCl_3$ and specific rotations were measured in chloroform at 20 °C, unless otherwise noted. Experimental evidence favoring the structures investigated came from a comprehensive range of ^1H and ^{13}C NMR data (400/300/250 and 100/75/69.5 MHz respectively, 1D and 2D experiments) and were corroborated by spatial proximity (nOe) studies by using mainly the 1D NOEDIFF technique.[21] ^1H (800 MHz) and ^{13}C NMR (200 MHz) experiments were carried out on a Bruker Avance DRX-800 spectrometer equipped with triple resonance H/C/N probeheads and a three-axis pulsed field gradient module. Gradients were used for the coherence transfer pathway selection in HMBC and HMQC experiments. In the latter, broadband decoupling was performed by using adiabatic WURST-40 pulses. For all compounds investigated, multiplicities of ^{13}C resonances were assigned by the SEFT technique.[22] Electron-spray mass spectra were obtained in instances in which electron impact and chemical ionization failed to produce molecular ions. Mass spectra acquired in the positive ion mode under electron-spray ionization (ES^+) by using a mobile phase of methanol are abbreviated as ESIMS (MeOH).

The required unsaturated diols were prepared, in their optically pure form, by following published procedures.[23] Commercial $PhI(OAc)_2$ and $[Pb(OAc)_4]$ were used without purification. The acetic acid content of the latter (introduced in excess of 0.2 equiv) was mostly removed under vacuum in the reaction vessel.

Typical procedure for two-reagent (two oxidants) domino reactions (route a Scheme 2): $PhI(OAc)_2$ (1.932 g, 6 mmol) was added to a solution of the selected unsaturated diol **1** (5 mmol) in anhydrous toluene (50 mL) under an inert atmosphere . Stirring was maintained under argon for 24 h, at which point, $[Pb(OAc)_4]$ (2.660 g, 6 mmol) was added. After stirring at room temperature for an additional 15 h, the reaction mixture was diluted with methylene chloride, and washed with saturated sodium bicarbonate, water, and brine. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Silica-gel flash chromatography (eluent: heptane/EtOAc 3:1) afforded compounds **2a** (80% from **1a**) and **2b** (78.5% from **1b**), which have been fully characterized in our previous publications.[2]

Typical procedure for two-reagent (oxidant and base) domino reactions (route e Scheme 1): A dry flask was charged with unsaturated diol **1a** (white solid, 5 mmol) and $[Pb(OAc)_4]$ (5.316 g, 12 mmol), placed under vacuum, flushed with argon, and placed under vacuumed again for 1 h. Dry toluene (10 mL) was then added at −20 °C and stirring was continued for 30 min at this temperature, then for an additional 15 h at room temperature. After TLC indicated formation of **2a**, K_2CO_3 (4.83 g, 35 mmol) in $MeOH/H_2O$ (60 mL, 8:1) was added, and the reaction mixture was stirred for 12 h at room temperature. Methanol was removed under reduced pressure, the reaction mixture was diluted with methylene chloride and washed with brine, the organic layer was dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The residue was purified on silica gel (eluent: heptane/EtOAc 2:1) to give a 68% combined yield of **5a** and **5′a** (10:1). Since the starting diols **1b** are liquid, they were added with the solvent after removing the acetic acid content of lead tetraacetate. Proceeding as for **1a**, the process afforded a 61% combined yield of **5b** and **5′b** (8:1).

Typical procedure for three-reagent (two oxidants and one base) domino reactions (route b Scheme 2): The procedure for route a (same scale) was repeated for the sequential addition of $PhI(OAc)_2$ and $[Pb(OAc)_4]$. Formation of the ring-expanded intermediate **2** was monitored by TLC. K_2CO_3 (4.83 g, 35 mmol) in $MeOH/H_2O$ (60 mL, 8:1) was added and the reaction stirred overnight at room temperature. Workup as above afforded a 55% combined yield of **5a** and **5′a** (from **1a**) and 50% combined yield of **5b** and **5′b** (from **1b**). The epimeric aldols were separated by silica-gel flash chromatography (eluent: heptane/EtOAc 2:1)?

5-*tert*-Butoxy-7-β-hydroxy-4-methylbicyclo[2.2.2]octan-2-one (5a): M.p. 94–95 °C (pentane); $[\alpha]_D^{20} = +55$ ($c = 1.3$ in chloroform); IR ($CHCl_3$): $\tilde{\nu} = 3418$, 3018, 2977, 2929, 2872, 1710, 1391, 1365, 1216, 1196, 1088, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (s, 3H), 1.18 (s, 9H), 1.44 (ddd, $J = 0.9$, 2.4, 14.7 Hz, 1H), 1.69 (ddd, $J = 2.4$, 3.4, 14.5 Hz, 1H), 1.91 (dd, $J = 1.5$, 16.3 Hz, 1H), 1.91 (ddd, $J = 3.0$, 8.9, 14.7 Hz, 1H), 2.06 (ddd, $J = 2.6$, 8.4, 14.6 Hz, 1H), 2.41 (m, 1H), 2.58 (dd, $J = 2.6$, 16.2 Hz, 1H), 3.32 (ddd, $J = 1.6$, 2.3, 8.4 Hz, 1H), 4.16 ppm (ddd, $J = 1.7$, 3.6, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.5$, 28.6 (3C), 34.5, 36.6, 41.3, 44.0, 51.3, 68.7, 69.6, 73.2, 209.2 ppm; EIMS: *m*/*z* (%): 226 (15) $[M]^+$, 170 (44) $[M-56]^+$, 57 (100); HREIMS: *m*/*z* calcd for $C_{13}H_{22}O_3$: 226.1569; found: 226.1570; elemental analysis calcd (%) for $C_{13}H_{22}O_3$: C 68.99, H 9.80; found: C 68.90, H 9.81.

5-*tert*-Butoxy-7-α-hydroxy-4-methylbicyclo[2.2.2]octan-2-one (5′a): M.p. 93–94 °C (pentane); $[\alpha]_D^{20} = +54$ ($c = 1.0$ in chloroform); IR (film): $\tilde{\nu} =$ 3440, 2973, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.94$ (s, 3H), 1.13 (s, 9H), 1.30 (dt, $J = 3.2$, 14.6 Hz, 1H), 1.50 (d, $J = 14.3$ Hz, 1H), 1.61 (dd, $J = 1.0$, 19.1 Hz, 1H), 1.94 (dd, $J = 9.5$, 14.6 Hz, 1H), 2.38 (q, $J = 2.8$ Hz, 1H), 2.49 (dd, $J = 3.2$, 19.1 Hz, 1H), 2.60 (ddd, $J = 2.8$, 8.8, 14.3 Hz, 1H), 3.5 (ddd, $J = 1.4$, 2.7, 7.3 Hz, 1H), 4.07 (dt, $J = 3.0$, 9.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.5$, 28.8 (3C), 31.0, 37.2, 42.6, 43.5, 52.4, 65.3, 70.0, 73.3, 216 HZ; HRESIMS (MeOH): *m*/*z* calcd for $C_{13}H_{22}O_3Na$: 249.1467; found: 249.1489; elemental analysis calcd (%) for $C_{13}H_{22}O_3$: C 68.99, H 9.80; found: C 68.85, H 9.83.

6-β-Hydroxy-4-methylbicyclo[2.2.2]octan-2-one (5b): M.p. 92–93 °C (heptane/diethyl ether); $[\alpha]_D^{20} = -11$ ($c = 1.0$ in chloroform); IR (film): $\tilde{\nu} = 3444$, 2942, 2926, 2869, 1705, 1448, 1399, 1299, 1207, 1105, 1073, 1019, 976, 782 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.99$ (s, 3H), 1.29–1.47 (m, 3H), 1.65–1.82 (m, 2H), 1.91–2.23 (m, 3H), 2.45 (dd, $J = 3.5$, 6.7 Hz, 1H), 3.41 (br s, 1H), 4.24 ppm (ddd, $J = 2.3$, 4.1, 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.3$, 26.3, 30.8, 32.7, 42.9, 50.2, 50.4, 68.9, 216.3 ppm; CIMS: *m*/*z* (%): 155 (20) $[M+1]^+$, 137 (100), 94 (29), 93 (30), 71 (28), 69 (10); elemental analysis calcd for $C_9H_{14}O_2$: C 70.10, H 9.15; found: C 70.29, H 9.21.

6-α-Hydroxy-4-methylbicyclo[2.2.2]octan-2-one (5′b): $[\alpha]_D^{20} = -3$ ($c = 1.0$ in chloroform); IR (film): $\tilde{\nu} = 3420$, 2951, 2926, 2869, 1715, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.00$ (s, 3H), 1.24–1.52 (m, 2H), 1.57–1.74 (m, 2H), 1.93 (dd, $J = 2.0$, 18.9 Hz, 1H), 1.95 (m, 1H), 2.03 (dd, $J = 3.0$, 18.9 Hz, 1H), 2.27 (m, 1H), 2.43 (m, 1H), 4.22 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.7$, 26.3, 31.6, 32.8, 43.7, 49.6, 51.2, 65.8, 216.3 ppm; ESIMS (MeOH): *m*/*z* (%): 155 (16) $[M+H]^+$, 177 (100) $[M+Na]^+$, 193 (31) $[M+H]^+$; HRESIMS (MeOH): *m*/*z* calcd for $C_9H_{14}O_2Na$: 177.0891; found: 177.0881.

Procedure for 15b: Potassium carbonate (216.7 mg, 1.57 mmol, 5.5 equiv) was added to a stirred solution of **2b** (81 mg, 0.28 mmol) in MeOH/water (9 mL, 8:1) cooled at 0 °C. After stirring the resulting suspension at 0 °C for 20 min, the solvents were removed under reduced pressure (without heating), the residue was diluted with EtOAc and washed with brine, and the organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography on silica gel (eluent: heptane/EtOAc 1:1) afforded **11b** (42 mg, 81%). Acetic anhydride (0.5 mL) was added to a stirred mixture of **11b** (42 mg, 0.23 mmol) and DMAP (cat.) in pyridine (1 mL) at 0 °C under argon. After 30 min, the mixture was diluted with EtOAc and washed with dilute hydrochloric acid, saturated sodium bicarbonate, water and brine. The organic layer was dried over $MgSO_4$, the solvent was evaporated under reduced pressure, and the residue was chromatographed (SiO_2, heptane/EtOAc 1:1) to give the corresponding acetate **15b** (44 mg, 85%). M.p. 75–76 °C (heptane/diethyl ether); IR (film): $\tilde{\nu} = 2952$, 1761, 1678, 1595, 1457, 1368, 1322, 1284, 1212, 1194, 1166, 1144, 1118, 1087, 1036, 952, 932, 899, 841, 820 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.16$ (s, 3H), 1.48 (dt, $J = 4.2$, 13.0 Hz, 1H), 1.59–2.55 (m, 6H), 2.11 (s, 3H), 2.25 (dd, $J = 7.7$, 11.4 Hz, 1H), 6.27 (dd, $J = 3.1$, 10.7 Hz, 1H), 7.12 ppm (s, 1H); ^{13}C NMR (69.5 MHz, $CDCl_3$): $\delta = 18.0$, 20.8, 26.8, 32.5, 36.9, 38.8, 40.1, 90.6, 120.2, 148.5, 169.1, 198.8 ppm; ESIMS (MeOH): *m*/*z* (%): 263 (55) $[M+K]^+$, 247 (100) $[M+Na]^+$; elemental analysis calcd (%) for $C_{12}H_{16}O_4$: C 64.27, H 7.19; found: C 64.21, H, 7.23.

Typical procedure for TBS-protection of the bicyclic aldols 5 and bicyclic lactones 17: *tert*-Butyldimethylsilyl chloride (4.93 g, 32.7 mmol, 2 equiv) was added to a solution of imidazole (4.46 g, 65.5 mmol, 4 equiv) and the bicyclic aldol **5a** (3.70 g, 16.4 mmol) in DMF (40 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 4.5 h (TLC monitoring). After cooling again to 0 °C, the reaction mixture was extracted with methylene chloride, washed with 1N HCl and sat. $NaHCO_3$

solution, and worked up in the usual manner, and the residue was purified by chromatography (eluent: heptane/EtOAc 20:1) to give **19a** (5.67 g, 100%).

5-*tert*-Butoxy-7-(*tert*-butyldimethylsilanyloxy)-4-methylbicyclo[2.2.2]octan-2-one (19a): M.p. 70–71 °C (heptane/diethyl ether); $[\alpha]_D^{20} = +41$ ($c = 1.09$ in chloroform); IR (film): $\tilde{\nu} = 2929, 2857, 1728, 1462, 1387, 1372, 1361, 1256, 1168, 1095, 1052, 996, 837, 776\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 0.02 (s, 6H), 0.84 (s, 9H), 0.94 (s, 3H), 1.12 (s, 9H), 1.42 (d, $J = 14.5$ Hz, 1H), 1.64 (ddd, $J = 2.2$, 3.7, 5.9 Hz, 1H), 1.85 (ddd, $J = 2.9$, 8.5, 14.5 Hz, 1H), 1.88 (d, $J = 18.0$ Hz, 1H), 2.02 (ddd, $J = 2.5$, 8.5, 11.0 Hz, 1H), 2.33 (m, 1H), 2.51 (dd, $J = 2.9$, 18.0 Hz, 1H), 3.27 (br d, $J = 8.4$ Hz, 1H), 4.04 ppm (ddd, $J = 1.8$, 4.1, 5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.9$ (2C), 17.9, 23.7, 25.7 (3C), 28.6 (3C), 34.5, 36.6, 42.9, 43.8, 51.1, 69.1, 69.9, 73.2, 214.0 ppm; HRESIMS (MeOH): *m/z* calcd for $C_{19}H_{36}O_3NaSi$: 363.2331; found: 363.2333; elemental analysis calcd (%) for $C_{19}H_{36}O_3Si$: C 67.01, H 10.65; found: C 67.03, H, 10.52.

6-(*tert*-Butyldimethylsilanyloxy)-4-methylbicyclo[2.2.2]octan-2-one (19b): Starting from **5b** (R = H) and following the procedure described above, the TBS-protected bicyclic aldol **19b** was obtained in 81% yield after chromatography (eluent: heptane/EtOAc 20:1). $[\alpha]_D^{20} = -3$ ($c = 1.48$ in chloroform); IR (film): $\tilde{\nu} = 2952, 2858, 1732, 1471, 1257\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.03$ (s, 6H), 0.84 (s, 9H), 0.99 (s, 3H), 1.33 (m, 2H), 1.41 (d, $J = 13.7$ Hz, 1H), 1.58–1.80 (m, 2H), 1.88–1.96 (m, 1H), 1.97 (d, $J = 18.3$ Hz, 1H), 2.18 (d, $J = 18.3$ Hz, 1H), 2.36 (m, 1H), 4.12 ppm (ddd, $J = 1.6$, 4.1, 5.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.0$, -4.9, 17.8, 20.4, 25.6 (3C), 26.5, 31.1, 32.7, 44.5, 50.2, 50.3, 69.4, 214.3 ppm; ESIMS (MeOH): *m/z* (%): 269.2 (6) $[M+H]^+$, 291.1 (100) $[M+Na]^+$, 307.0 (21) $[M+K]^+$; elemental analysis calcd (%) for $C_{15}H_{28}O_2Si$: C 67.11, H 10.51; found: C 66.92, H 10.51.

6-*tert*-Butoxy-8-(*tert*-butyldimethylsilanyloxy)-5-methyl-2-oxabicyclo-[3.3.1]nonan-3-one (17a-OTBS): Starting from **17a** and following the procedure described above, **17a-OTBS** was obtained in 89% yield after chromatography (eluent: heptane/EtOAc 10:1). M.p. 142–143 °C (heptane); $[\alpha]_D^{20} = +65$ ($c = 1.08$ in chloroform); IR (film): $\tilde{\nu} = 2957, 2928, 2857, 1715, 1390\ cm^{-1}$; ^1H NMR (800 MHz, $CDCl_3$): $\delta = 0.05$ (2 × s, 6H), 0.87 (s, 9H), 0.95 (s, 3H), 1.15 (s, 9H), 1.45 (m, 2H), 1.85 (dd, $J = 4.6$, 14.4 Hz, 1H), 1.94 (dd, $J = 0.7$, 19.0 Hz, 1H), 2.02 (dtd, $J = 1.2$, 5.0, 14.0 Hz, 1H), 2.96 (dd, $J = 2.3$, 19.0 Hz, 1H), 3.19 (dd, $J = 4.9$, 11.3 Hz, 1H), 3.68 (ddd, $J = 2.4$, 5.0, 11.8 Hz, 1H), 4.46 ppm (br s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = -4.5$, 18.1, 25.7 (3C), 27.1, 28.9 (3C), 33.9, 34.4, 36.9, 71.2, 72.4, 73.6, 78.2, 171 ppm; ESIMS (MeOH): *m/z* (%): 378.8 (100) $[M+Na]^+$, 394.8 (21) $[M+K]^+$; elemental analysis calcd (%) for $C_{19}H_{36}O_4Si$: C 64.00, H 10.18; found: C 63.91, H 10.21.

8-(*tert*-Butyldimethylsilanyloxy)-5-methyl-2-oxabicyclo[3.3.1]nonan-3-one (17b-OTBS): Starting from **17b** and following the procedure described above, **17b-OTBS** was obtained in 91% yield after chromatography (eluent: heptane/EtOAc 20:1). M.p. 92 °C (heptane); $[\alpha]_D^{20} = +62$ ($c = 0.8$ in chloroform); IR (film): $\tilde{\nu} = 2952, 2854, 1722, 1463, 1217, 776\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.05$ (s, 6H), 0.89 (s, 9H), 1.00 (s, 3H), 1.39–1.60 (m, 4H), 1.77 (m, 1H), 1.85 (m, 1H), 2.32 (dd, $J = 1.0$, 18.6 Hz, 1H), 2.41 (dd, $J = 2.0$, 18.6 Hz, 1H), 3.67 (m, 1H), 4.55 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.75$, -4.59, 18.0, 25.7 (3C), 27.0, 29.5, 29.6, 36.5, 37.0, 42.8, 72.1, 79.4, 171.4 ppm; ESIMS (MeOH): *m/z* (%): 285.3 (40) $[M+H]^+$, 307.2 (100) $[M+Na]^+$, 323.2 (25) $[M+K]^+$; elemental analysis calcd (%) for $C_{15}H_{28}O_3Si \cdot 0.1\,CH_2Cl_2$: C 61.91, H 9.70; found: C 61.83, H 9.95.

Typical procedure for Baeyer–Villiger oxidation: Sodium hydrogen carbonate (5.3 mmol) and *m*-chloroperbenzoic acid (13.3 mmol) was added to the appropriate bicyclic aldol (4.4 mmol) in methylene chloride (14 mL) at 0 °C. The mixture was stirred at room temperature for approximately 17 h (TLC monitoring). The crude reaction mixture was diluted with methylene chloride and filtered through a plug of Celite. The excess peracid was decomposed by washing with aqueous 10% sodium sulfite. Finally, the organic phase was washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated under reduced pressure.

Starting from **5a** and following the procedure described above, **17a** and **18a** were obtained in 66% combined yield and 94:6 ratio after silica gel chromatography (eluent: heptane/EtOAc 1.5:1).

6-*tert*-Butoxy-8-hydroxy-5-methyl-2-oxabicyclo[3.3.1]nonan-3-one (17a): M.p. 170–172 °C (heptane); $[\alpha]_D^{20} = +81$ ($c = 0.8$ in chloroform); IR (film): $\tilde{\nu} = 3406, 2975, 2878, 1704, 1390\ cm^{-1}$; ^1H NMR (800 MHz, $CDCl_3$): $\delta = 0.98$ (s, 3H), 1.18 (s, 9H), 1.33 (dt, $J = 11.7$, 13.8 Hz, 1H), 1.52 (dt, $J = 2.2$, 14.5 Hz, 1H), 1.94 (dd, $J = 4.6$, 14.5 Hz, 1H), 2.00 (d, $J = 19.0$ Hz, 1H), 2.27 (ddt, $J = 1.5$, 5.0, 13.8 Hz, 1H), 2.99 (dd, $J = 2.2$, 19.0 Hz, 1H), 3.23 (dd, $J =$ 5.0, 11.2 Hz, 1H), 3.67 (ddd, $J = 2.1$, 5.1, 12.0 Hz, 1H), 4.63 ppm (br s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 27.1$, 29.0 (3C), 34.0, 34.3, 36.8, 36.9, 70.6, 72.3, 73.8, 78.4, 172 ppm; ESIMS (MeOH): *m/z* (%): 242.8 (25) $[M+H]^+$, 264.9 (100) $[M+Na]^+$, 280.9 (46) $[M+K]^+$; elemental analysis calcd (%) for $C_{13}H_{22}O_4$: C 64.44, H 9.15; found: C 64.09, H 9.12.

6-*tert*-Butoxy-8-hydroxy-5-methyl-3-oxabicyclo[3.2.2]nonan-2-one (18a): M.p. 94–95 °C (heptane); $[\alpha]_D^{20} = +62$ ($c = 1.20$ in chloroform); IR (film): $\tilde{\nu} = 3420, 2974, 2932, 1716, 1192, 1062\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (s, 3H), 1.16 (s, 9H), 1.70 (br s, 1H), 1.77 (dd, $J = 5.5$, 14.7 Hz, 1H), 1.90 (ddd, $J = 1.3$, 5.6, 15.2 Hz, 1H), 2.04 (ddd, $J = 1.4$, 8.9, 14.7 Hz, 1H), 2.17 (ddd, $J = 7.7$, 8.7, 15.2 Hz, 1H), 3.03 (m, 1H), 3.43 (dd, $J = 5.6$, 7.7 Hz, 1H), 3.72 (dd, $J = 0.95$, 11.8 Hz, 1H), 4.10 (dt, $J = 5.5$, 8.7 Hz, 1H), 4.35 ppm (dd, $J = 1.4$, 11.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.5$, 28.8 (3C), 32.2, 39.2, 40.5, 49.2, 66.2, 69.1, 73,6, 73.7, 174 ppm; ESIMS (MeOH): *m/z* (%): 243.1 (3) $[M+H]^+$, 265.2 (100) $[M+Na]^+$, 281.2 (18) $[M+K]^+$; HRESIMS: *m/z* calcd for $C_{13}H_{22}O_4Na$: 265.1416; found: 265.1425; elemental analysis calcd (%) for $C_{13}H_{22}O_4 \cdot 0.25\,CH_2Cl_2$: C 60.39, H 8.61; found: C 60.24, H 8.45.

Starting from **5b** and following the procedure described above, **17b** and **18b** were obtained in 71% combined yield and 95:5 ratio after silica gel chromatography (eluent: heptane/EtOAc 2:1), along with some unreacted starting material.

8-Hydroxy-5-methyl-2-oxabicyclo[3.3.1]nonan-3-one (17b): M.p. 134 °C (heptane); $[\alpha]_D^{20} = +68$ ($c = 0.8$ in chloroform); IR (film): $\tilde{\nu} = 3426, 2950, 2865, 1702, 1225\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.01$ (s, 3H), 1.40–1.57 (m, 3H), 1.60 (dt, $J = 1.8$, 14.1 Hz, 1H), 1.90 (ddd, $J = 3.0$, 4.6, 14.1 Hz, 1H), 1.99 (m, 1H), 2.34 (d, $J = 18.6$ Hz, 1H), 2.44 (dd, $J = 1.8$, 18.6 Hz, 1H), 3.24 (br s, OH), 3.66 (m, 1H), 4.71 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.8$, 29.4, 29.7, 36.2, 36.9, 42.8, 71.1, 79.7, 171.9 ppm; ESIMS (MeOH): *m/z* (%): 171.0 (12) $[M+H]^+$, 192.8 (100) $[M+Na]^+$, 208.8 (30) $[M+K]^+$, 362.8 (75) $[2M+Na]^+$, 378.7 (2) $[2M+K]^+$; elemental analysis calcd (%) for $C_9H_{14}O_3$: C 63.51, H 8.29; found: C 63.48, H 8.51.

8-Hydroxy-5-methyl-3-oxabicyclo[3.2.2]nonan-2-one (18b): M.p. 94–95 °C (diethyl ether); $[\alpha]_D^{20} = -13$ ($c = 0.6$ in chloroform); IR (film): $\tilde{\nu} = 3429, 2926, 2870, 1723, 1454, 1079\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (s, 3H), 1.40–1.54 (m, 1H), 1.61–1.80 (m, 3H), 1.92–2.07 (m, 2H), 3.15 (td, $J = 2.2$, 5.6 Hz, 1H), 3.93 (dd, $J = 1.9$, 11.6 Hz, 1H), 4.09 (dd, $J = 1.9$, 11.6 Hz, 1H), 4.18 ppm (ddd, 3.9, 6.1, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.5$, 26.7, 29.8, 34.4, 41.5, 48.3, 67.1, 79.3 (C4), 174.8 ppm (C2); ESIMS (MeOH): *m/z* (%): 171.2 (27) $[M+H]^+$, 193.1 (68) $[M+Na]^+$, 209.0 (42) $[M+K]^+$, 363.2 (100) $[2M+Na]^+$, 379.1 (16) $[2M+K]^+$; elemental analysis calcd (%) for $C_9H_{14}O_3 \cdot 0.15\,H_2O$: C 62.52, H 8.34; found: C 63.51, H 8.29.

Starting from **19a** and following the procedure described above, **20a** and **24a** were obtained in 56% combined yield and 30:70 ratio, along with unreacted starting material (43%).

6-*tert*-Butoxy-8-(*tert*-butyldimethylsilanyloxy)-5-methyl-2-oxabicyclo-[3.2.2]nonan-3-one (20a): M.p. 109–110 °C (diethyl ether/heptane); $[\alpha]_D^{20} = +9$ ($c = 1.0$ in chloroform); IR (film): $\tilde{\nu} = 2928, 2856, 1715, 1082\ cm^{-1}$; ^1H NMR: (800 MHz, $CDCl_3$): $\delta = 0.08$ (2s, 6H), 0.88 (s, 9H), 0.91 (s, 3H), 1.17 (s, 9H), 1.63 (dd, $J = 4.2$, 14.6 Hz, 1H), 1.85 (ddd, $J = 2.6$, 8.6, 14.6 Hz, 1H), 2.11 (m, 2H), 2.45 (dd, $J = 1.3$, 18.3 Hz, 1H), 3.01 (dd, $J =$ 2.6, 18.3 Hz, 1H), 3.43 (ddd, $J = 1.0$, 5.1, 7.4 Hz, 1H), 3.97 (ddd, $J = 4.2$, 4.3, 8.6 Hz, 1H), 4.28 ppm (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = -4.8$ (2C), 18.0, 25.7 (3C), 27.9, 28.8 (3C), 34.7, 36.8, 42.8, 43.7, 67.6, 70.2, 73.6, 77.2, 172.9 ppm; ESIMS (MeOH): *m/z* (%): 357.2 (54) $[M+H]^+$, 379.1 (100) $[M+Na]^+$, 395.1 (19) $[M+K]^+$; elemental analysis calcd (%) for $C_{19}H_{36}O_4Si$: C 64.00, H 10.18; found: C 63.97, H 10.22.

6-*tert*-Butoxy-8-(*tert*-butyldimethylsilanyloxy)-5-methyl-3-oxabicyclo-[3.2.2]nonan-2-one (24a): M.p. 88–89 °C (heptane); $[\alpha]_D^{20} = +36$ ($c = 1.1$ in chloroform); IR (film): $\tilde{\nu} = 2934, 1715, 1070\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.06$ (s, 6H), 0.88 (s, 12H), 1.16 (s, 9H), 1.70 (dd, $J = 4.2$, 14.6 Hz, 1H), 1.87 (m, 2H), 2.06 (m, 1H), 2.95 (m, 1H), 3.41 (dd, $J = 4.6$, 8.3 Hz, 1H), 3.74 (d, $J = 11.6$ Hz, 1H), 4.00 (m, 1H), 4.35 ppm (dd, $J = 1.7$, 11.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -4.8$, -4.9, 18.0, 24.5, 25.7 (3C), 28.8 (3C), 32.3, 39.2, 42.3, 49.0, 66.7, 69.6, 73.4, 73.5, 174 ppm; ESIMS

(MeOH): *m/z* (%): 357.2 (47) $[M+H]^+$, 379.1 (12) $[M+Na]^+$, 395.0 (5) $[M+K]^+$; elemental analysis calcd (%) for $C_{19}H_{36}O_4Si$: C 64.00, H 10.18; found: C 64.33, H 10.15.

Starting from **19b** and following the procedure described above, **20b** and **24b** were obtained in 73% combined yield and 10:90 ratio after chromatography (eluent: heptane/EtOAc 20:1), along with unreacted starting material (20%).

8-(*tert*-Butyldimethylsilanyloxy)-5-methyl-2-oxabicyclo[3.2.2]nonan-3-one (20b): $[\alpha]_D^{20} = -33$ ($c = 0.5$ in chloroform); IR (film): $\tilde{\nu} = 3406$, 2938, 2864, 1713, 1235, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.08$ (s, 6H), 0.89 (s, 9H), 0.95 (s, 3H), 1.43–1.70 (m, 3H), 1.76 (m, 1H), 1.87 (ddd, $J = 2.7$, 8.1, 14.2 Hz, 1H), 2.20 (m, 1H), 2.59 (dd, $J = 2.7$, 18.5 Hz, 1H), 2.80 (dd, $J = 2.5$, 18.5 Hz, 1H), 4.05 (m, 1H), 4.37 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.0$, -4.9, 18.0, 25.0, 25.7 (3C), 29.9, 30.4, 30.7, 43.4, 49.8, 68.3, 76.5, 173.0 ppm; ESIMS (MeOH): *m/z* (%): 285.2 (13) $[M+H]^+$, 307.2 (100) $[M+Na]^+$, 323.1 (45) $[M+K]^+$; HRMS (MALDI-TOF): *m/z* calcd for $C_{15}H_{28}O_3Si$: 285.18860; found: 285.18979; elemental analysis calcd (%) for $C_{15}H_{28}O_3Si$: C 63.33, H 9.92; found: C 61.25, H 9.71.

8-(*tert*-Butyldimethylsilanyloxy)-5-methyl-3-oxabicyclo[3.2.2]nonan-2-one (24b): $[\alpha]_D^{20} = -29$ ($c = 1.1$ in chloroform); IR (film): $\tilde{\nu} = 2951$, 2929, 2853, 1723, 1464, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.08$ (s, 6H), 0.88 (s, 9H), 0.93 (s, 3H), 1.39–2.03 (m, 6H), 3.12 (m, 1H), 3.82 (dd, $J = 2.3$, 11.4 Hz, 1H), 4.09 (dd, $J = 1.6$, 7.3 Hz, 1H), 4.16 ppm (d, $J = 11.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.0$, -4.9, 17.9, 20.5, 25.7 (3C), 26.8, 29.2, 33.8, 43.3, 48.8, 67.6, 78.6, 174.3 ppm; ESIMS (MeOH): *m/z* (%): 285.2 (14) $[M+H]^+$, 307.2 (100) $[M+Na]^+$, 323.1 (47) $[M+K]^+$; elemental analysis calcd (%) for $C_{15}H_{28}O_3Si$: C 63.33, H 9.92; found: C 63.25, H 9.91.

Experimental procedure for TBS-deprotection of bicyclic lactones: Tetrabutylammonium fluoride (1M in tetrahydrofuran; 1.7 mL, 1.7 mmol) was added to a magnetically stirred solution of **20** (1.1 mmol) in dry THF (10 mL) at $-75\,^\circ C$. The reaction mixture was allowed to warm from $-75\,^\circ C$ to $-30\,^\circ C$ over 2.25 h (TLC monitoring). Ethyl acetate was then added and, following extraction, the crude mixture was worked up as usual. The residue was purified by chromatography (SiO_2, eluent: heptane/EtOAc 3:1) to give the corresponding lactone alcohols **16**, which subsequently underwent transesterification to give **17** (91%) directly.

Experimental procedure for reduction with lithium aluminium hydride: Lithium aluminium hydride (1.0 mmol) was added to a magnetically stirred solution of bicyclic lactone (1 mmol) in dry Et_2O (5 mL) at $0\,^\circ C$ under argon, and stirring was continued for 45 min at $0\,^\circ C$. The reaction mixture was then diluted with technical-grade Et_2O, H_2O was added, and the reaction mixture was worked up as usual after extraction. In all cases investigated some TBS-deprotection, which led to the corresponding triols, was observed. The latter were easily converted to the corresponding isopropylidene acetals **21**.

4-*tert*-Butoxy-2-(*tert*-butyl-dimethylsilanyloxy)-5-(2-hydroxy-ethyl)-5-methyl-cyclohexanol (23a): M.p. 68–69 °C (heptane); $[\alpha]_D^{20} = +4.9$ ($c = 1.1$ in chloroform); IR (film): $\tilde{\nu} = 3400$, 2956, 2930, 2858, 1658, 1462, 1362, 1061 cm^{-1}; ^1H NMR (800 MHz, [D$_6$]DMSO): $\delta = -0.08$ (s, 6H), 0.79 (s, 3H), 0.82 (s, 9H), 1.02 (dd, $J = 2.2$, 14.9 Hz, 1H), 1.09 (s, 9H), 1.48 (dt, $J = 4.0$, 12.0 Hz, 1H), 1.53 (ddd, $J = 5.8$, 9.0, 13.8 Hz, 1H), 1.67 (dd, $J = 3.0$, 14.9 Hz, 1H), 1.79 (dd, $J = 7.0$, 13.7 Hz, 1H), 1.83 (dt, $J = 11.5$, 12.0 Hz, 1H), 3.12 (dd, $J = 3.5$, 11.5 Hz, 1H), 3.44 (m, 2H), 3.58 (m, 2H), 3.94 (d, $J = 2.0$ Hz, 1H; C1-OH), 4.17 ppm (t, $J = 5.0$ Hz, 1H; CH_2-OH); ^{13}C NMR (200 MHz, [D$_6$]DMSO): $\delta = -4.7$ (2C), 17.9, 25.7 (3C), 27.1, 28.7 (3C), 34.2, 35.5, 36.0, 38.4, 57.8, 68.3, 71.5, 72.7, 75.3; ESIMS (MeOH): *m/z* (%): 360.9 (32) $[M+H]^+$, 382.8 (71) $[M+Na]^+$, 398.8 (20) $[M+K]^+$, 721.2 (13) $[2M+H]^+$, 743.3 (54) $[2M+Na]^+$, 759.2 (7) $[2M+K]^+$; elemental analysis calcd (%) for $C_{19}H_{40}O_4Si$: C 63.28, H 11.18; found: C 63.11, H 11.11.

5-*tert*-Butoxy-2-(*tert*-butyldimethylsilanyloxy)-4-(2-hydroxyethyl)-4-methylcyclohexanol (22a): $[\alpha]_D^{20} = +41$ ($c = 0.2$ in chloroform); IR (film): $\tilde{\nu} = 3407$, 2929, 2857, 1726, 1390, 1064, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.10$ (s, 6H), 0.93 (s, 9H), 0.97 (s, 3H), 1.25 (s, 9H), 1.35 (m, 2H), 1.72 (dd, $J = 4.6$, 14.5 Hz, 1H), 1.85 (dt, $J = 2.7$, 12.7 Hz, 1H), 2.03 (dt, $J = 9.8$, 12.7 Hz, 1H), 2.37 (m, 1H), 3.23 (dd, $J = 2.9$, 9.8 Hz, 1H), 3.48–3.62 (m, 2H), 3.68 (br t, 1H), 3.88 ppm (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -6.0$, -5.2, 17.2, 24.2, 24.9 (3C), 27.6 (3C), 28.7, 33.4, 37.0, 39.7, 57.8, 69.3, 70.0, 74.2, 74.3 ppm; ESIMS (MeOH): *m/z* (%): 361.5 (100) $[M+H]^+$; HRESIMS: *m/z* calcd for $C_{19}H_{40}O_4SiNa$: 383.25936; found: 383.25964.

2-(*tert*-Butyldimethylsilanyloxy)-5-(2-hydroxyethyl)-5-methylcyclohexanol (23b): $[\alpha]_D^{20} = -10$ ($c = 0.9$ in chloroform); IR (film): $\tilde{\nu} = 3379$, 2930, 2856, 1254, 1078, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.08$ (s, 6H), 0.91 (s, 9H), 0.92 (s, 3H), 1.12 (m, 1H), 1.34 (dd, $J = 3.7$, 13.5 Hz, 1H), 1.42–1.53 (m, 2H), 1.57 (dt, $J = 3.3$, 9.6 Hz, 1H), 1.69–1.87 (m, 3H), 3.63–3.80 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.9$, -5.5, 17.1, 24.6, 24.7 (3C), 26.0, 31.5, 32.3, 38.8, 44.2, 58.1, 68.4, 70.2 ppm; ESIMS (MeOH): *m/z* (%): 289.3 (100) $[M+H]^+$, 311.3 (61) $[M+Na]^+$, 327.3 (10) $[M+K]^+$; elemental analysis calcd (%) for $C_{15}H_{32}O_3Si$: C 62.45, H 11.18; found: C 62.27, H 11.11.

Experimental procedure for reduction with lithium aluminium hydride and selective acetonide formation: Lithium aluminium hydride (1.0 mmol) was added to a magnetically stirred solution of bicyclic lactone (1 mmol) in dry Et_2O (5 mL) at $0\,^\circ C$ under argon, and stirring was continued for 45 min at $0\,^\circ C$. The reaction mixture was then diluted with technical-grade Et_2O, H_2O was added, and the reaction mixture was worked up as usual after extraction. The resulting crude triol was dissolved in dry acetone (10 mL), and a catalytic amount of *p*-TosOH was added at $0\,^\circ C$. The mixture was stirred under argon at room temperature for 24 h in the presence of 4 Å molecular sieves. The reaction mixture was filtered through a plug of basic alumina, the acetone evaporated under reduced pressure, and the residue was extracted with EtOAc. Usual workup gave, after chromatography, the desired isopropylidene alcohols **21**.

2-(6-*tert*-Butoxy-2,2,5-trimethylhexahydrobenzo[1,3]dioxol-5-yl)ethanol (21a): (eluent: heptane/EtOAc 5:1, 80%, two steps): $[\alpha]_D^{20} = +53$ ($c = 0.7$ in chloroform); IR (film): $\tilde{\nu} = 3430$, 2977, 2932, 1462, 1367, 1219, 1077, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.00$ (s, 3H), 1.23 (s, 9H), 1.32 (s, 3H), 1.36 (ddd, $J = 1.9$, 5.3, 15.6 Hz, 1H), 1.55 (s, 3H), 1.55 (dd, $J = 4.1$, 15.6 Hz, 1H), 1.97 (m, 2H), 2.06 (dd, $J = 1.6$, 15.6 Hz, 1H), 2.50 (ddd, $J = 3.0$, 10.3, 15.6 Hz, 1H), 3.16 (dd, $J = 6.2$, 9.5 Hz, 1H), 3.55 (m, 1H), 3.71 (m, 1H), 4.12 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 26.1$, 26.2, 28.5, 28.6 (3C), 34.6, 36.9, 39.1, 40.3, 58.8, 73.1, 73.8, 74.8, 75.0, 108.5 ppm; ESIMS (MeOH): *m/z* (%): 309.2 (100) $[M+Na]^+$; HRESIMS: *m/z* calcd for $C_{16}H_{30}O_4Na$: 309.2042; found: 309.2029; elemental analysis calcd (%) for $C_{16}H_{30}O_4$: C 67.10, H 10.56; found: C 67.08, H 10.76.

2-(2,2,5-Trimethylhexahydro-benzo[1,3]dioxol-5-yl)ethanol (21b): Following the procedure described above, isopropylidene alcohol **21b** was obtained in 80% combined yield (eluent: heptane/EtOAc 5:1). $[\alpha]_D^{20} = -10$ ($c = 0.6$ in chloroform); IR (film): $\tilde{\nu} = 3429$, 2933, 1379, 1216, 1053, 856 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (s, 3H), 1.16 (dddd, $J = 1.2$, 4.5, 6.5, 13.5 Hz, 1H), 1.33 (s, 3H), 1.49 (m, 1H), 1.51 (s, 3H), 1.59 (dd, $J = 7.0$, 13.7 Hz, 1H), 1.62 (d, $J = 6.7$ Hz, 1H), 1.67 (dd, $J = 7.0$, 13.7 Hz, 1H), 1.76–1.92 (m, 2H), 3.73 (t, $J = 7.0$ Hz, 2H), 4.12–4.22 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 24.1$, 24.9, 26.0, 28.3, 32.0, 32.1, 38.7, 45.5, 59.1, 73.0, 73.2, 107.7 ppm; ESIMS (MeOH): *m/z* (%): 237.1 (100) $[M+Na]^+$; HRESIMS: *m/z* calcd for $C_{12}H_{22}O_3Na$: 237.1467; found: 237.1483; elemental analysis calcd (%) for $C_{12}H_{22}O_3 \cdot 0.1\,H_2O$: C 66.61, H 10.35; found: C 66.61, H 10.38.

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[1] Tietze proposed the following definition: "a domino reaction is a process involving two or more bond-forming transformations (usually C–C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step." a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163; c) L. F. Tietze, A. Modi, *Med. Res. Rev.* **2000**, *20*, 304–322.

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