Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 2277–2290

TETRAHEDRON: *ASYMMETRY*

Lead tetraacetate mediated domino reactions on (*R*)-(−)-carvone-derived bicyclic unsaturated 1,2-diols and further rearrangements

Elena M. Sanchez Fernandez,[a] José I. Candela Lena,[a] Ertan Altinel,[a] Nicolas Birlirakis,[a] Alejandro F. Barrero[b] and Siméon Arseniyadis[a,*]

[a]*Institut de Chimie des Substances Naturelles, CNRS, F-91198 Gif-sur-Yvette, France*
[b]*Universidad de Granada, Avda. Fuentenueva s/n, 18071, Granada, Spain*

Received 14 May 2003; accepted 13 June 2003

Abstract—Carvone derived octaline diols **1** and **2** were subjected to $Pb(OAc)_4$-mediated glycol fission conditions. The isolable 'half-cascade' intermediate **3** was subjected to ozonolysis in methylene chloride, and subsequent basic treatment, providing bis-angularly substituted bicyclic lactone **5** via an intramolecular Cannizzaro type oxidoreduction. The ring expanded products **4** and **6** subjected to basic treatment afforded bicyclic aldols **8** and **7**, respectively, via a fused-to-bridged ring system interchange. The methods described here represent efficient approaches to a variety of conveniently functionalized chiral backbones offering chemoselectivity. The mechanistic pathways involved in both the oxidative cleavage induced domino transformations and in the base-induced ring-system interchange reactions are discussed.

1. Introduction

Organolead compounds are widely used in organic synthesis; among their numerous applications are glycol fission, decarboxylation, and cyclic ether formation.[1] Of key importance in such reactions are functional group and solvent compatibility, and ample investigations have been carried out to shed light on factors that affect these outcomes. Lead tetraacetate cleaves 1,2-diols regardless of stereochemistry (*cis*, *trans*) and olefins (π-bases) react with $Pb(OAc)_4$ which behaves as an electrophile. However, most studies in this area have been carried out on saturated substrates, and relatively little attention has been paid to unsaturated glycols. There are scattered examples on Pb(IV) initiated ring expansions, by electrophilic attack of the reagent to the C5–C6 olefin of some selected steroids, for example one reported by Bowers et al.[2] in the early 1960s, during their efforts to synthesize fluorinated steroids from pregnenolone. The main objective of this investigation was the controlled addition of fluorine to olefins, as the addition of fluorine to carbon–carbon double bonds was troublesome. In their investigation using lead tetrafluoride, prepared in situ from lead tetraacetate and anhydrous hydrogen fluoride, the authors noticed that using longer reaction times or higher temperatures a new product was obtained in low yield which appears to be formed as the result of a molecular rearrangement. Later, Levisalles et al.[3] re-investigated the $Pb(OAc)_4$–HF on pregnenolone and cholesterol identifying the A-homo-B-nor steroid, first observed but not characterized by Bowers. Several years ago, it was reported from this laboratory that $Pb(OAc)_4$ addition to bicyclic unsaturated 1,2-diols initiated a domino[4] process resulting in a ring-expansion. This reagent appears especially suited to the one-pot multistage transformation sequence because of its high oxidation potential and its ability to perform different tasks, acting as an oxidizer and as a Lewis acid in the same reaction vessel. Generally, we have used the easily available Hajos–Parrish, Wieland–Miescher ketone derived hydrindene and octaline–diols as well as steroidal-1,2-diol templates as the starting materials in such rearrangements.[5] We were particularly interested in examining the reactions of carvone derived unsaturated bicyclic diols **1** with lead tetraacetate, as these are readily available in enantiomerically pure form and large scale using the synthetic procedure developed by

* Corresponding author. Tel./fax: +33-1-69.82.30.29; e-mail: simeon.arseniyadis@icsn.cnrs-gif.fr

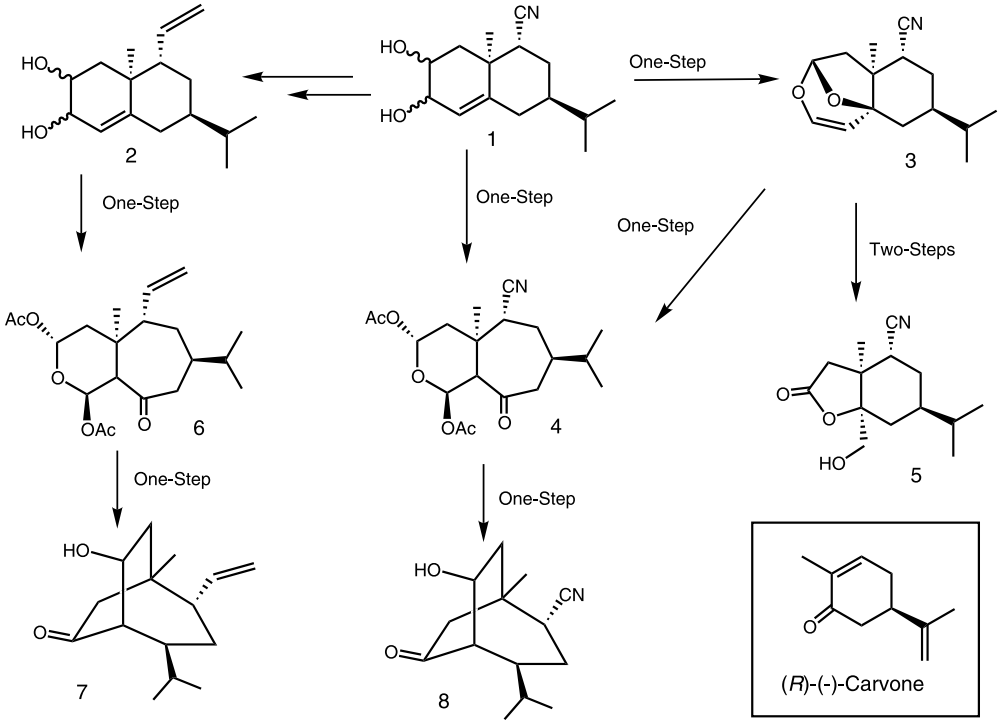
0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0957-4166(03)00480-4

de Groot.[6] With both the reagent and the unsaturated diols readily available, the reactions could be carried out on a large array of substrates leading to interesting intermediates. In particular, we envisaged their use as precursors to highly functionalized seven-membered ring containing fused **4**, **6** and bridged **7**, **8** structures. Herein we report a series of diversity generating domino transformations for the synthesis of stereodefined ring systems, representative examples of which are portrayed in Scheme 1.

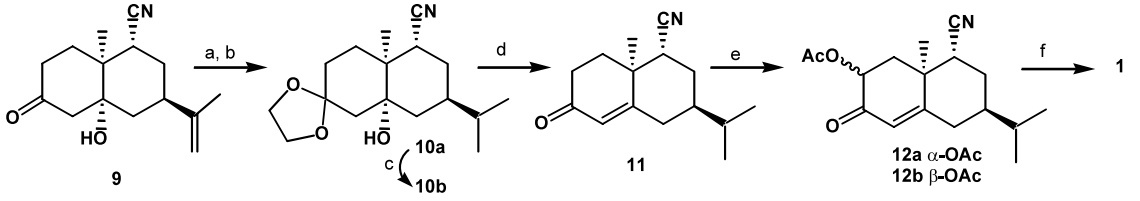
2. Results and discussion

The synthesis of the required unsaturated diols **1** started with bicyclic aldol **9**, itself prepared from commercially available and inexpensive (*R*)-(−)-carvone in a straightforward manner using the de Groot procedure. Conversion of **9** to the key enone intermediate **11** was then realized in the following manner. Ketal protection of **9** (ethylene glycol, *p*-TosOH, 4 Å MS, 25°C, 92%)[7] followed by reduction of the double bond (H_2–Pd/C, heptane–toluene, 2:1, 25°C) afforded protected aldol **10a** (95% isolated yield). Subsequent ketal deprotection (1:1 THF–6%HCl, 25°C, 4.5 h, 96% of **10b**) and dehydration (*p*-TosOH, toluene, reflux, 1 h, 87%) furnished the requisite bicyclic enone **11**. The acetoxyenone **12** was then obtained from **11** following our previously published procedure employing lead tetraacetate to install the acetoxy functionality [$Pb(OAc)_4$, PhH, reflux, 4 days, 96%] and uneventfully converted to the corresponding diastereomeric mixture of diols **1**, upon reduction ($LiAlH_4$ in ether, 0°C, 98%). The overall yield for this five-step sequence, conveniently executed on a 100-g scale, was 70% (Scheme 2).

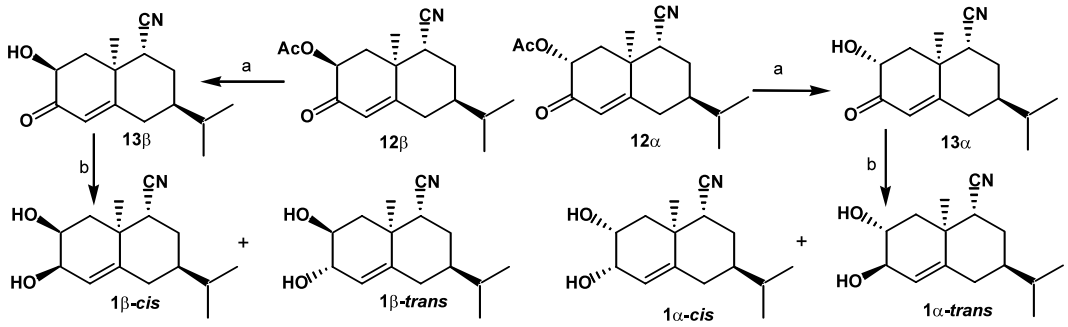
The diastereomeric mixture of unsaturated diols **1** (separated only for characterization vide infra) thus obtained needed neither purification nor separation of the diastereomers and could be used as such. However, to fully characterize all possible stereoisomers, and also to explore the influence of 1,2-diol stereochemistry on product distribution and reaction rate, diastereomerically pure diols **1** were obtained through a *Horse Liver Esterase*-mediated mild saponification (to avoid known complications using basic hydrolysis)[8] followed by a hydride reduction as portrayed in Scheme 3.



Scheme 1.



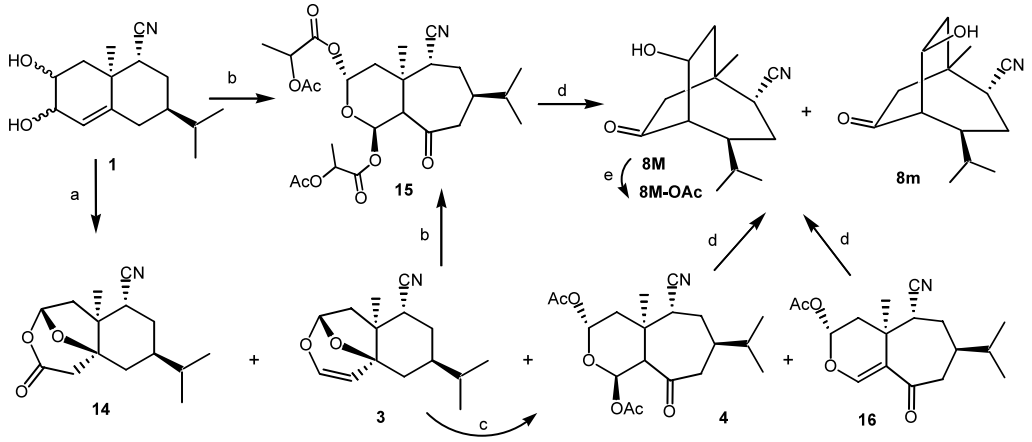
Scheme 2. *Reagents and conditions*: (a) $HO(CH_2)_2OH$, *p*-TosOH; (b) H_2, Pd–C, heptane–PhMe, 2:1, 25°C; (c) 1:1 6% HCl–THF, 25°C, 4.5 h; (d) *p*-TosOH, PhMe, reflux; (e) $Pb(OAc)_4$, PhH, reflux, 4 days; (f) $LiAlH_4$, Et_2O, 0°C, 30 min.



Scheme 3. *Reagents and conditions*: (a) *HLE*, pH 7, 25°C; (b) $LiAlH_4$, Et_2O, 0°C, 30 min.

The $Pb(OAc)_4$ oxidation on diastereomerically pure *cis* (*cis*-**1α**, *cis*-**1β**) and *trans* (*trans*-**1α**, *trans*-**1β**) diols, derived from (*R*)-(−)-carvone followed an identical course to that when diols were used as a diastereomeric mixture indicating, as expected, that the process is insensitive to the diol stereochemistry and gives similar yields in all cases investigated. Thus, subjection of **1** to $Pb(OAc)_4$ (2.4 equiv.) in CH_3CN (ca. 5 mL per mmol for small scale experiments, less when scaling up) afforded, upon room temperature stirring (48 h), unexceptional isolated yields of **4** together with its deacetoxylated analogue **16** and lactone **14** (42% combined yield) along with the half-cascade intermediate **3** (42%). The origin of lactone **14** presumably results from the open form of the half cascade intermediate **3**. Prolonged reaction times under the above conditions, 2.4 equiv. of $Pb(OAc)_4/CH_3CN$/room temperature for 5 days, afforded a 42% isolated yield of the tricyclic enol ether (cyclic enol acetal, 'half-cascade' product) **3** along with the tricyclic lactone **14** (30%) as well as 20% of **4** accompanied by small amounts of **16** (Scheme 4, all products are separable by chromatography).

In an effort to both improve the yield and reaction rate and to elucidate a reaction mechanism, we examined the possibility of replacing acetonitrile with other solvents. Accordingly, we examined a number of solvents, compatible with the reagent and found that reaction rates and yields vary dramatically depending upon the nature of the solvent used. In toluene, the reaction was clean but afforded mainly half-cascade product **3** (90% isolated yield) even after prolonged reaction times (64 h) at room temperature, together with a very small amount of lactone **14** (less than 2%). Using benzene as solvent furnished only **3** (85% isolated yield) after 3 days at room temperature, but upon refluxing the reaction mixture for an additional 21 h the product distribution changed significantly. Half-cascade product **3** was present as only 11% in the reaction mixture thus obtained, along with a considerable amount of lactone **14** (50%) and a 20% isolated yield of the hoped for fused bicyclic compound **4** together with its deacetoxylated derivative **16**. Thus, the $Pb(OAc)_4$-mediated oxidative cleavage of diols **1** in solvents such as benzene, toluene, but also trifluorotoluene, methylene chloride or THF at room temperature gave only half-cascade product **3** while failed to produce detectable amounts of the corresponding ring expanded intermediate **4**, indicating that the nature of solvent influences the reactivity of the lead carboxylate. On the other hand, starting from the isolable and stable **3**, upon subjection to 1.2 equiv. of the oxidant, similar results were furnished. Given these observations the original optimal conditions (2.4 equiv. of $Pb(OAc)_4$ in MeCN) were modified to incorporate acetic acid rather than MeCN. When carvone derived cyano-unsaturated diol **1** was treated



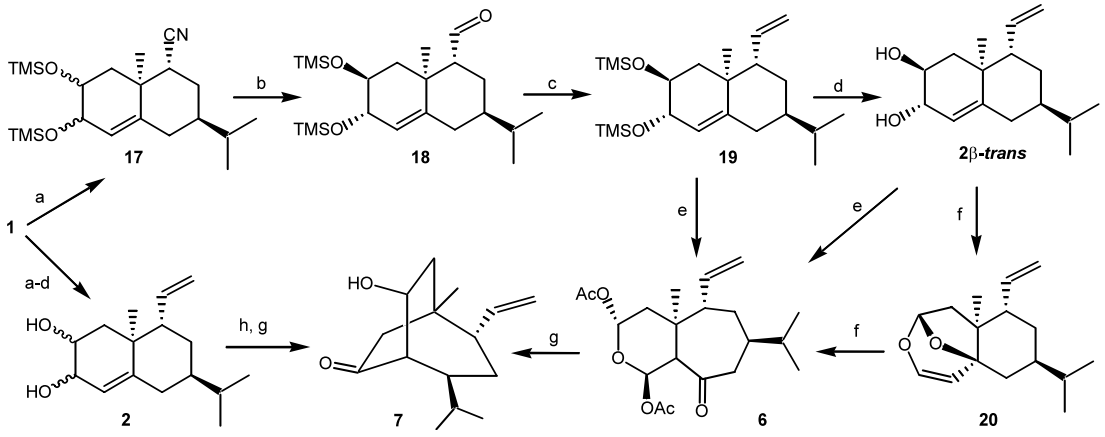
Scheme 4. *Reagents and conditions*: (a) 2.4 equiv. $Pb(OAc)_4$, AcOH, 19 h, 25°C (28% for **3**, 44% for **4**, 24% for **14**); (b) 2.4 equiv. $Pb(OAc)_4$, (*S*)-2-acetoxypropionic acid, 25°C, 15 h; (c) 1.2 equiv. $Pb(OAc)_4$, AcOH, 25°C, 19 h; (d) K_2CO_3–MeOH, H_2O, 25°C (92% for **8M**, 1% for **8m**); (e) Ac_2O, pyridine–DMAP, 0°C, 1 h 30 min.

with $Pb(OAc)_4$ in acetic acid (19 h, 25°C) followed by hydrolytic treatment, four compounds were produced. The hoped for ring-enlarged fused heterocycle **4**, isolated after workup and chromatography in a satisfactory 44% yield, was produced as the major component of a chromatographically separable mixture of four rearrangement products. Minor products of the reaction were identified as the lactone **14** (24%) and the half-cascade product **3** (28%) which can be directly converted to **4** by resubjection to lead tetraacetate oxidation. Variable amounts of the deacetoxylated derivative **16** were also detected and characterized, though upon basic hydrolysis the latter is converted to the same bicyclic aldols **8**. There is a substantial rise in yield as well as a rate acceleration in acetic acid, in agreement with the proposed mechanism (vide infra). This observation may suggest that the carboxyl rich environment increases the rate of acetate delivery providing faster full-cascade products and in higher isolated yields. When (*S*)-2-acetoxypropionic acid (*O*-acetyl lactic acid) was used as solvent the corresponding ring expanded heterocycle **15** was obtained in 30% isolated yield, along with its analogues resulting from mixed acyl transfers and the type **16** deacetoxylated derivative. When **1** was exposed to $Pb(OAc)_4$ oxidative cleavage conditions using half the amount needed of the oxidant (1.2 equiv.) in either MeCN, benzene, toluene, methylene chloride, trifluorotoluene or acetic acid, the expected heterocycle, the cyclic ene-acetal **3**, was isolated in 85% yield. Mild base treatment of bis-acetoxy acetal **4** (K_2CO_3, MeOH–H_2O, 0°C to room temperature, 29 h) led to the bicyclo[3.2.2]nonane framework **8M** (94%) along with trace amounts of the epimeric bicyclic aldol **8m**. The major bicyclic aldol **8M** was easily protected as its acetate (Ac_2O, pyridine, DMAP, 0°C, 93%) for further elaboration. The bridged-bicyclic frame thus formed offers chemoselectivity and constitutes a 'Fused to Bridged Ring System Interchange' through one-pot sequential transformations.

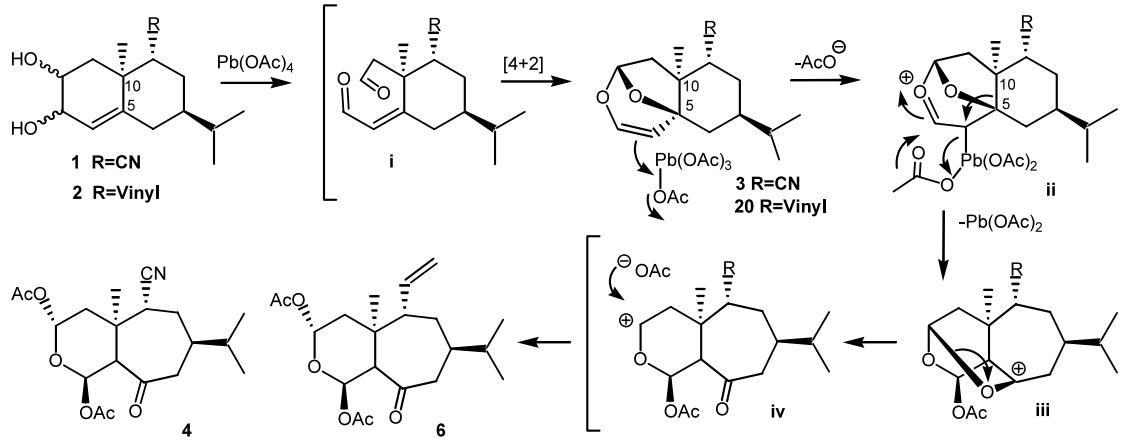
The rather modest yields in ring-expanded fused bicyclic product **4**, prompted us to examine the possibility of replacing the cyano group by an alkene. Although the reaction of alkenes with lead tetraacetate is well known and can lead to a number of products, e.g. esters of 1,2-glycols or allylic alcohols, at relatively high temperatures (80–90°C)[9] oxidation of the alkenes is less serious at lower temperatures. In the hope of improving the yield of the one-pot multistage transformations, the target diols **2** were then synthesized straightforwardly starting from **1** (or from *trans*-**1β**, leading to stereopure **18** and **19**, only for characterization purposes) in a four-step sequence. TMS-protection (TMSOTf, collidine, PhMe, 0°C, 1 h 15 min, 84%), followed by DIBAL reduction (DIBAL-H, PhMe, −78°C, 6 h 30 min, 89%) and subsequent Wittig olefination ($MePPh_3Br$, *t*-BuOK, PhMe, 13 h, 25°C) afforded the bis-TMS protected alkylidene diol **19** which was further deprotected (TBAF, THF, 25°C, 2 h, 92%), even though this was proved unnecessary.[10] Subjection of 8-vinyl-unsaturated 1,2-diol **2** to $Pb(OAc)_4$-mediated cleavage in acetic acid (25°C, 8 h) followed by hydrolytic treatment afforded the expected ring-enlarged compound **6** in 82% isolated yield. ^1H and ^{13}C NMR spectra of the crude material showed no resonances other than those due to bis-acetoxy bis-acetal **6**. The unwanted side products (of type **14**, **16**), and the half-cascade intermediate (of type **3**) were not detected in the lead tetraacetate mediated domino reaction of **2**. The stable tricyclic enol ether **20** was prepared in a 'one-pot' reaction sequence involving oxidative cleavage of 1,2-unsaturated diol **2** under conditions of the 'interrupted cascade' (1.2 equiv. of $Pb(OAc)_4$, MeCN, 25°C) in 88% yield. Subsequent treatment of the latter with an extra 1.2 equiv. of $Pb(OAc)_4$ in acetic acid, smoothly produced **6** in 82% isolated yield. Mild base treatment of the latter (K_2CO_3, MeOH–H_2O, 25°C) furnished the bicyclo[3.2.2]aldol product **7** as a single diastereoisomer in 80% isolated yield. The assigned structure of **7** is consistent with the analytical results, including 2D NMR techniques. Starting from unsaturated diols **2**, treatment with 2.4 equiv. of $Pb(OAc)_4$ using (*S*)-*O*-acetyl lactic acid as solvent slightly accelerated the domino process. Subsequent hydrolytic workup followed by a mild base treatment without isolation of the *O*-acetyl lactic analogue of **6**,[11] afforded higher isolated yields of **7** (80% two steps). This combination showed a marked improvement over the previously examined cleavage conditions (even using acetic acid as solvent) given the fact that no separation of mixed acetals and deacetoxy derivatives of type **16** is needed before the fused to bridged ring-system interchange operation (Scheme 5, 'h, g' from **2** to **7**).

In this domino process, the first two transformations (oxidative/pericyclic) leading to the half cascade intermediates **3** and **20** proceed with an 85% isolated yield (an average 92% yield per transformation) while the full-cascade which includes two more transformations (oxyplumbation/ring expansion) proceed in a much better yield when R = vinyl (**6**, 82%, 95% average yield per transformation, and most importantly: no side products at all)[12] while yields are modest when R = CN (**4**, 44% isolated yield, 81.5% average yield per transformation). The reaction sequence can be monitored by TLC with all intermediates possessing distinct R_f values. Reactions were generally complete within less than 10 min for the glycol fission leading to the dialdehyde **i** (Scheme 6), less than 5 h for the bis-hetero-IMDA cycloaddition leading to the isolable **3** (or **20**) and required 6-48 h (depending on the solvent used) for the complete sequence, the 'full cascade', leading to the ring expanded fused bicycle **4** (or **6**) where a seven-membered ring is fused to an α,α′-functionalized tetrahydropyran ring. Such a ring system, a bis-acetoxy bis-acetal, is found in spongiane diterpenes[13] and its analogous bis-ethoxy acetal in the antifeedant (−)-specionin.[14] A mechanistic rationale for the skeletal reorganization of **1** to **4** (or **2** to **6**) in the presence of Pb^{4+} is offered in Scheme 6.

With regard to the reaction mechanism, the process starts with the well known cleavage of 1,2-diols by Pb^{4+}, discovered by Criegee.[15] The oxidative cleavage and the ensuing bis-hetero IMDA generates the postu-



Scheme 5. *Reagents and conditions*: (a) TMSOTf, collidine, PhMe, 0°C, (85%); (b) DIBAL-H, PhMe, −78°C, (89%); (c) $MePPh_3Br$, *t*-BuOK, PhMe, 25°C (90%); (d) TBAF, THF, 25°C (92%); (e) 2.4 equiv. $Pb(OAc)_4$, AcOH, 25°C, 8 h (82%); (f) 1.2 equiv. $Pb(OAc)_4$, MeCN, 25°C (88%); (g) K_2CO_3–MeOH, H_2O, 25°C (80%); (h) 2.4 equiv. $Pb(OAc)_4$, (*S*)-2-acetoxypropionic acid, 25°C, 15 h.



Scheme 6.

lated bridgehead carbocation **iii**. This key intermediate first rearranges to **iv**, releasing internal strain, then reacts with the acyl group to furnish the corresponding bis-acetoxy bis-acetal **4** (**6**) thus ending the process by forming a tetrahedral carbon on a six-membered ring and a trigonal one in a seven-membered ring.[16] During the ring expansion process the stereochemistry of the transient organolead intermediate **ii** is important, as ring expansion requires C5–C10/C–lead bond alignment. The observed solvent effect on the rate of domino transformations can be rationalized by examining the proposed mechanism of the reaction sequence. A number of mechanistically interesting issues is embedded in these synthetically useful transformations. The process can be interrupted at will either by stoichiometry or by the choice of the solvent used; that is using 1.2 equiv. of $Pb(OAc)_4$ the process stops half the way through ('half cascade' products **3**, **20**) in any solvent cited above, while using 2.4 equiv. of $Pb(OAc)_4$ the process goes to completion (products **4**, **6**, the so-called 'full cascade') in acetonitrile, acetic acid or (*S*)-2-acetoxypropionic acid. Upon treatment of the bicyclic unsaturated diol with only 1.2 equiv. of $Pb(OAc)_4$ in any of the above mentioned solvents, the tricyclic enol ether intermediate **3** can be easily isolated and stored without any special care. Some interesting chemistry can be done using the interrupted cascade **3** whose formation allows for the subsequent ozonolysis and hence the convenient preparation of bis-angularly substituted bicyclic lactone **5**.[17]

Following the two first hetero-domino transformations (oxidative-pericyclic), the alkylidene double bond was cleaved ozonolytically. Introduction of ozone into a solution of **3** in dry methylene chloride at −78°C, followed by Me_2S reductive workup, delivered the isomerically pure formylacetal-aldehyde **21** in 67% yield. The latter, a white crystalline compound stable to long-term storage at or below room temperature, underwent a Cannizzaro type oxido-reduction which proceeds under very mild conditions (K_2CO_3–MeOH, H_2O, 10 h, room temperature) allowing for the construction of lactone **5** (73%). A mechanistic framework that accounts for this intramolecular Cannizzaro reaction is as follows: saponification of the starting formyl acetal **21** occurs in the presence of base to give the corre-

sponding lactolate which undergoes a subsequent intramolecular hydride transfer (IHT) leading to the bicyclic lactone **5**. The site-selective disproportionation of the Cannizzaro oxido-reduction is consistent with direct hydride shift on the lactol–aldehyde **i** (Scheme 7), leading to the bicyclic lactone **5**. On the other hand, when ozonolysis of **3** was carried out in methanol (10 mL per mmol), at −78°C, a diastereomeric mixture of methyl furanosides **22** and **23** was obtained following reductive treatment with excess Me_2S, in 72% combined yield (Scheme 7). The diastereomers were separated by flash chromatography, using heptane–ethyl acetate 8:1, as eluent to afford a 5.8% for the minor, less polar, α-methoxy isomer **23** and 66.2% for the more polar, major isomer **22**.

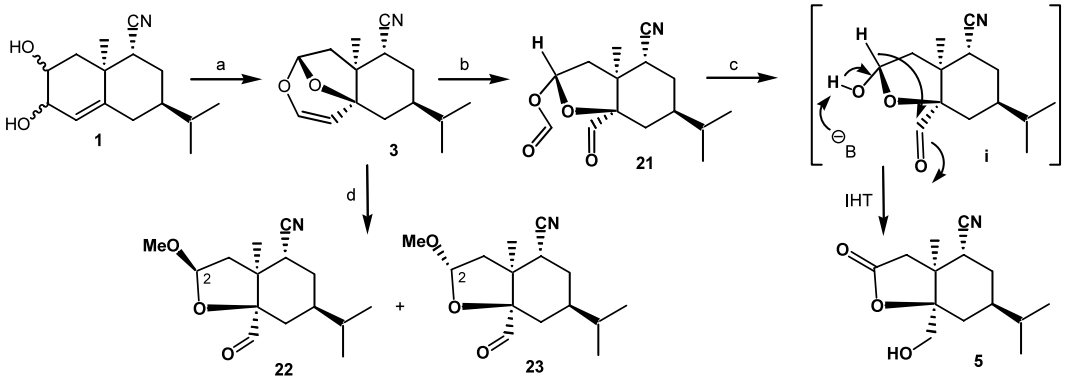
The proposed assigned structures of **22** and **23** are consistent with the analytical results, including 2D NMR techniques. The α/β-orientation of the C-2 methoxy group was established by NOE difference experiments performed on both furanosides (**22** and **23**). As a consequence of the 1,3-*syn* relationships involving the angular methyl group and H-2, double irradiation of the signals associated to the α-oriented H-2 and angular methyl group of **22** displays significant enhancements to the protons resident on the α-face of the molecule, (interactions not observed in **23** where the methoxy group is α-oriented).

The ring-expanded compounds **4** and **6** were readily transformed to the bicyclo[3.2.2]ring system via a mild base treatment. From the fused ring system **4** or **6** to the bridged derivatives **7**, **8**, again a one-pot sequential transformation protocol operates; overall we have a single-step 'fused to bridged ring system interchange' ensuring functional diversity. The three functional groups (free hydroxyl, cyano/allyl and carbonyl) on each ring offer easy chemodifferentiation for further selective transformations. The mechanism of the one-pot formation of the bicyclic aldols **8** and **7** from the fused [6+7]-ring systems **4** and **6**, involving a retro-Claisen (**ii** to **iii** Scheme 8) and an intramolecular aldol reaction (**iv** to **7** or **8**) can be explained by the pathway outlined in Scheme 8.

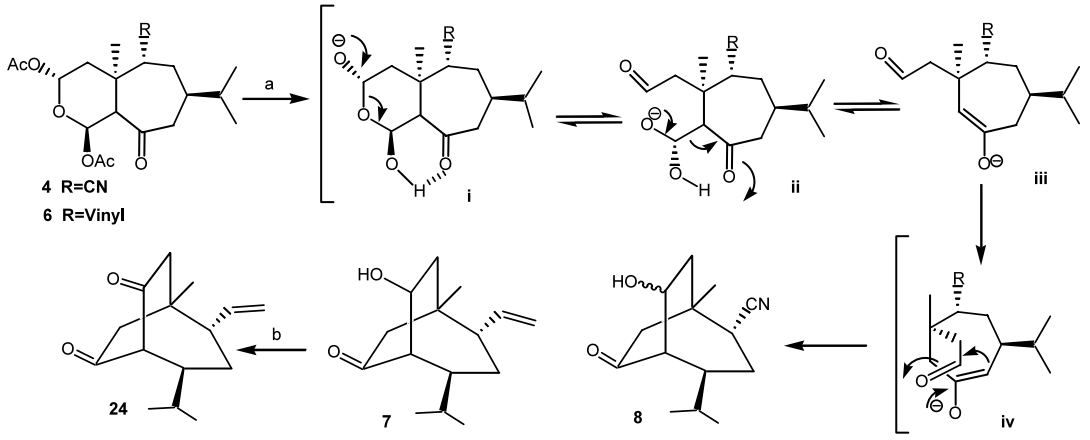
Dess–Martin oxidation of bicyclic aldol **7** (periodinane, pyridine, in methylene chloride 1 h 30 min at 25°C) furnished the 1,3-dicarbonyl species **24**, useful for the preparation of various chiral ligands,[18] in 84% isolated yield.

3. Conclusion

We have demonstrated that elaborated seven-membered ring containing compounds can be prepared in



Scheme 7. *Reagents and conditions*: (a) 1.2 equiv. $Pb(OAc)_4$, PhMe, 25°C, 5 h; (b) O_3/CH_2Cl_2, −78°C, then Me_2S, −78°C to 25°C, 30 min; (c) K_2CO_3–MeOH, H_2O, 25°C; (d) O_3/MeOH, −78°C, Me_2S, −78°C to 25°C, 30 min.



Scheme 8. *Reagents and conditions*: (a) K_2CO_3–MeOH, H_2O, 25°C; (b) Dess–Martin periodinane, CH_2Cl_2, Py, 25°C.

good yields using our one-pot multistage transformation protocol. The reaction successfully accommodates cyano, allyl and isopropyl substituents and its modular nature has been illustrated with unsaturated diols **1** and **2** to provide **3**/**4** or **6**/**20**, respectively, and compound **3** to release bis-angularly substituted bicyclic lactone **5** or methylfuranosides **23**, **24**. The effect of solvent and substitution, on the yields, reaction time and on product distribution has been studied. The best yields (82%) of full cascade products are obtained in acetic acid at room temperature with reaction times of 8 h starting from the vinyl substituted carvone derived bicyclic unsaturated diol **2** (best substrate). On the basis of the results reported here, it is our belief that $Pb(OAc)_4$ is an effective reagent for generating diversity while carrying out diol cleavage reactions. Alternatively the domino sequence could also be activated at room temperature by utilizing the less toxic iodobenzene diacetate[19] as the oxidative cleavage/[4+2] promoter and continued by lead tetraacetate (oxyplumbation/ring expansion) with the whole process performed in sequence.[20] These rearrangements are of interest in view of the synthesis of a number of heavily substituted seven-membered ring systems.

4. Experimental

4.1. General

Solvents and reagents used in this work were purified according to standard literature techniques and stored under argon. Experiments, which required an inert atmosphere were carried out under dry argon in a flame dried glass system. Flash chromatographies were 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 in 5% phosphomolybdic acid in 95% ethanol. '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. 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 (300–250 and 75–69.5 MHz, respectively, 1D and 2D experiments) and corroborated by spatial proximity (NOE) studies 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 modules. 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 where electron impact and chemical ionization failed to produce molecular ions. Mass spectra acquired in the positive ion mode under electron spray ionization (ES^+) using a mobile phase of methanol, will be abbreviated as ESIMS (MeOH), and the corresponding high-resolution mass spectra as HRESIMS. Commercial $Pb(OAc)_4$ was 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.

4.2. Preparation of the key intermediates, the unsaturated 1,2-diols 1 and 2

4.2.1. (8′a*R*)-Hydroxy-(7′*R*)-isopropyl-(4′a*S*)-methyl-octahydrospiro[[1,3]dioxolane - 2,2′ - naphthalene] - (5′*R*)-carbonitrile 10a. Commercially available (*R*)-(−)-carvone was converted into **9** on a 100.0 g scale according to published procedures.[6] Compound **9** was further hydrogenated in a Parr hydrogenator at 15 psi and rt, by first placing palladium (10% w/w) on activated carbon (215 mg) in the flask, followed by **9** (2.15 g, 7.42 mmol) dissolved in 2:1 heptane–toluene (anhydrous) (60 mL). The mixture was allowed to react for 15 h (disappearance of **9** as indicated by TLC). The catalyst was removed by filtration on Celite and rinsed with ethyl acetate. Removal of the solvent of the filtrate gave a solid which was purified by SiO_2 flash chromatography (eluent: heptane–EtOAc, 2:1) to give the 2.04 g, 95%, of the isopropyl derivative **10a**: mp: 130–132°C (heptane–ether). $[\alpha]_D^{20} = +36$ (*c* 2.32, $CHCl_3$). IR (film): 3495, 2958, 2875, 2236, 1466, 1432, 1387, 1367, 1315, 1093, 992, 822 cm^{-1}. ^1H NMR (300 MHz): 0.91 (3H, dd, $J = 3.0, 6.4$), 0.92 (3H, dd, $J = 3.0, 6.4$), 1.32 (3H, d, $J = 3.2$), 1.02–2.29 (11H, m), 1.63 (1H, d, $J = 14.2$), 1.94 (1H, t, $J = 13.6$), 2.58 (1H, bs), 3.84–4.03 (4H, m). ^{13}C NMR (75 MHz): 19.8 (3C), 27.5, 30.6, 31.2, 31.6, 35.2, 37.2, 37.5, 38.9, 45.3, 63.8, 64.5, 73.6, 108.4, 122.3. EIMS: 293 ($[M]^+$, 1), 250 (25), 99 (100), 86 (36), 43 (40). Anal. calcd for $C_{17}H_{27}NO_3$ C, 69.59; H, 9.28; found: C, 69.31; H, 9.29.

4.2.2. (4a*R*)-Hydroxy-(3*R*)-isopropyl-(8a*S*)-methyl-6-oxo-decahydronaphthalene-(1*R*)-carbonitrile 10b. A solution of **10a** (4.30 g, 14.66 mmol) in 1:1 THF–6%HCl (150 mL) was stirred at rt for 4.5 h, while TLC monitored. The reaction mixture was diluted with EtOAc, quenched with solid sodium bicarbonate, concentrated under reduced pressure, diluted with water, and extracted with EtOAc. Following usual work up the residue was purified by silica gel flash chromatography. Elution with heptane–ethyl acetate (1:2) afforded 3.50 g (96%) of **10b**: mp: 128–130°C (heptane–ether). $[\alpha]_D^{20} = +40$ (*c* 0.96, $CHCl_3$). IR (film): 3400, 2961, 2106, 1648, 1476, 1408, 1315, 1269, 1238, 1125, 1043, 1015 cm^{-1}. ^1H NMR (250 MHz): 0.89 (3H, d, $J = 6.8$), 0.90 (3H, d, $J = 6.8$), 1.21–2.12 (8H, m), 1.54 (3H, s), 2.21 (1H, s), 2.24–2.39 (2H, m), 2.44–2.64 (1H, m), 2.70 (1H, dd, $J = 2.2, 5.0$), 2.82 (1H, d, $J = 14.1$). ^{13}C NMR (62.5 MHz): 19.5 (2C), 19.9, 27.5, 31.8 (2C), 35.0, 36.9, 37.0, 37.8, 38.9, 53.4, 75.0, 121.9, 207.8. EIMS: 249 ($[M]^+$, 0.3), 206 (3), 179 (10), 55 (25), 43 (100). Anal. calcd for $C_{15}H_{23}NO_2$ C, 72.25; H, 9.30; found: C, 72.12; H, 9.22.

4.2.3. (3*R*)-Isopropyl-(8a*S*)-methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalene-(1*R*)-carbonitrile 11. A three-necked flask, equipped with a Dean–Stark apparatus was charged with bicyclic aldol **10b** (1.51 g, 6.05 mmol) in toluene (40 mL), under argon and heated at 100°C. *p*-TsOH (15 mg, 0.079 mmol, 0.013 equiv.) was added and the reaction mixture was stirred at this temperature for 1 h. After cooling to 25°C, dilution with heptane, and washing with satd $NaHCO_3$ sol. and brine, filtration on silica using heptane–EtOAc 1:1 as eluent afforded 1.21 g (87%) of enone **11**: mp: 118–120°C (heptane–ether). $[\alpha]_D^{20} = -183$ (*c* 2.0, $CHCl_3$). IR (film): 2961, 2896, 2233, 1670, 1618, 1463, 1435, 1387, 1366, 1273, 1231, 1187, 1163, 1008, 870, 774 cm^{-1}. ^1H NMR (300 MHz): 0.92 (6H, d, $J=6.4$), 1.33–1.64 (2H, m), 1.44 (3H, s), 1.90 (1H, dt, $J=5.3$, 13.7), 2.03 (1H, dd, $J=4.1$, 14.1), 2.08–2.24 (2H, m), 2.33–2.58 (4H, m), 2.64 (1H, dd, $J=4.3$, 12.8), 5.79 (1H, s). ^{13}C NMR (75 MHz): 18.9, 20.4, 20.7, 26.5, 28.1, 33.6, 34.5, 36.2, 36.9, 37.4, 40.2, 119.8, 127.3, 163.5, 197.5. EIMS: 231 ($[M]^+$, 9), 189 (26), 188 (20), 147 (55), 146 (50), 91 (40), 43 (75), 41 (100). Anal. calcd for $C_{15}H_{21}NO$ C, 77.88; H, 9.15; found: C, 77.83; H, 9.09.

4.2.4. Procedure for acetoxylation with LTA, acetoxy cyano octalone 12. A dry three-necked flask, equipped with a Dean–Stark apparatus was charged with **11** (2.95 g, 12.76 mmol) and $Pb(OAc)_4$ (22.62 g, 51.02 mmol, 4 equiv.) vacuumed, flushed with argon before dry benzene (80 mL) was added and the reaction mixture was heated at 90°C (oil bath temperature should not exceed 100°C) for 3 days. After cooling a large volume of ether was added, and the reaction mixture stirred for an additional hour, filtered, and the filtrate washed with brine and water, dried on $MgSO_4$, concentrated and purified by chromatography on silica with heptane–EtOAc 5:1 as eluent afforded 3.50 g (95%) of a nearly 1:1 mixture of **12α** and **12β**.

4.2.4.1. Acetic acid (8*R*)-cyano-(6*R*)-isopropyl-(8a*S*)-methyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-(2*R*)-yl ester 12α. $[\alpha]_D^{20} = -8$ (*c* 1.76, $CHCl_3$). IR (film): 2964, 2874, 2238, 1748, 1690, 1623, 1462, 1436, 1377, 1226, 1121, 1100, 1062, 1003, 890, 872, 736 cm^{-1}. ^1H NMR (300 MHz): 0.83 (3H, d, $J=6.4$), 0.86 (3H, d, $J=6.4$), 1.14–1.46 (1H, m), 1.41 (3H, s), 1.51–1.65 (1H, m), 1.96–2.21 (3H, m), 2.10 (3H, s), 2.27 (1H, dd, $J=5.6$, 14.4), 2.37 (1H, td, $J=2.1$, 13.6), 2.54 (1H, ddd, $J=1.6$, 5.4, 13.5), 2.89 (1H, dd, $J=4.4$, 12.6), 5.24 (1H, dd, $J=5.6$, 11.7), 5.79 (1H, d, $J=1.5$). ^{13}C NMR (75 MHz): 20.6 (2C), 20.7, 23.6, 25.9, 27.9, 34.0, 34.6, 38.8, 39.2, 41.5, 69.6, 119.4, 124.6, 163.0, 169.9, 192.0. EIMS: 289 ($[M]^+$, 0.2), 247 (2), 203 (20), 96 (29), 70 (24), 49 (33), 43 (100).

4.2.4.2. Acetic acid (8*R*)-cyano-(6*R*)-isopropyl-(8a*S*)-methyl-3-oxo-1,2,3,5,6,7,8,8a-octahydronaphthalen-(2*S*)-yl ester 12β. Mp: 134–136°C (heptane–ether). $[\alpha]_D^{20} = -176$ (*c* 3.26, $CHCl_3$). IR (film): 2964, 2874, 2238, 1749, 1690, 1623, 1461, 1377, 1226, 1121, 1100, 1061, 1003, 890, 872, 736 cm^{-1}. ^1H NMR (300 MHz): 0.85 (6H, d, $J=6.5$), 1.24–1.57 (2H, m), 1.51 (3H, s), 1.89–2.13 (3H, m), 2.11 (3H, s), 2.36 (1H, dd, $J=5.3$, 12.5), 2.41 (2H, bd, $J=3.8$), 2.54 (1H, dd, $J=4.1$, 12.9), 5.42 (1H, dd, $J=5.3$, 14.0), 5.77 (1H, t, $J=1.1$). ^{13}C NMR (75 MHz): 19.6, 20.3, 20.6 (2C), 26.4, 27.5, 34.0, 37.1, 39.1, 40.1, 41.5, 70.0, 119.0, 125.4, 163.2, 169.8, 192.2. EIMS: 289 ($[M]^+$, 0.2), 247 (2), 203 (20), 96 (20), 70 (12), 49 (23), 43 (100). Anal. calcd for $C_{17}H_{23}NO_3$ C, 70.56; H, 8.01; found: C, 70.36; H, 8.02.

4.2.5. Procedure for *HLE*-catalyzed hydrolysis of the acetates

4.2.5.1. (7*R*)-Hydroxy-(3*R*)-isopropyl-(8a*S*)-methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalene-(1*R*)-carbonitrile 13α. To a mixture of acetate **12α** (261 mg, 0.90 mmol) in toluene (1 mL) and 20 mM phosphate buffer (pH 7, 65 mL), commercially available horse liver esterase (*HLE*, 250 mg, acetone powder) was added and the reaction mixture was stirred at rt while TLC monitored. The reaction was diluted with EtOAc, and filtered on Celite. The extracts were washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Chromatography on silica gel with heptane–EtOAc 4:1 as eluent afforded **13α**: $[\alpha]_D^{20} = +29$ (*c* 1.61, $CHCl_3$). IR (film): 3472, 2964, 2872, 2237, 1688, 1623, 1462, 1389, 1275, 1219, 1125, 1099, 1074, 1010, 862, 755 cm^{-1}. ^1H NMR (300 MHz): 0.87 (3H, d, $J=5.9$), 0.89 (3H, d, $J=6.1$), 1.18–1.44 (1H, m), 1.41 (3H, s), 1.55–1.67 (1H, m), 1.80 (1H, t, $J=13.8$), 2.03–2.23 (2H, m), 2.41 (1H, bd, $J=13.2$), 2.51 (1H, dd, $J=6.0$, 14.2), 2.60 (1H, dd, $J=5.4$, 13.2), 2.98 (1H, dd, $J=4.8$, 12.3), 3.54 (1H, bs), 4.16 (1H, dd, $J=6.0$, 13.2), 5.87 (1H, s). ^{13}C NMR (75 MHz): 20.6 (2C), 23.9, 25.7, 27.9, 33.8, 34.0, 39.4, 40.7, 41.7, 68.4, 119.5, 122.9, 164.3, 198.3. EIMS: 247 ($[M]^+$, 2), 203 (100), 160 (28), 43 (47).

Proceeding as above, **12β** (182 mg, 0.63 mmol) was dissolved in toluene (1 mL) and 20 mM phosphate buffer (pH 7 buffer, 50 mL), horse liver esterase (*HLE*, 150 mg, acetone powder) was added and the reaction mixture was stirred at rt for 24 h.

4.2.5.2. (7*S*)-Hydroxy-(3*R*)-isopropyl-(8a*S*)-methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalene-(1*R*)-carbonitrile 13β. $[\alpha]_D^{20} = -204$ (*c* 2.02, $CHCl_3$). IR (film): 3473, 2964, 2873, 2238, 1682, 1621, 1461, 1436, 1389, 1369, 1273, 1224, 1115, 1099, 1068, 851 cm^{-1}. ^1H NMR (300 MHz): 0.92 (3H, d, $J=6.6$), 0.92 (3H, d, $J=6.2$), 1.32–1.38 (1H, m), 1.52–1.54 (1H, m), 1.56 (3H, s), 1.76 (1H, t, $J=13.2$), 2.01–2.22 (2H, m), 2.49 (2H, bd, $J=3.9$), 2.58 (1H, dd, $J=5.4$, 12.6), 2.65 (1H, dd, $J=4.3$, 12.7), 3.57 (1H, bs), 4.33 (1H, dd, $J=5.7$, 13.7), 5.90 (1H, s). ^{13}C NMR (75 MHz): 19.7, 20.4, 20.7, 26.5, 27.7, 34.5, 37.3, 39.1, 40.4, 44.2, 69.0, 119.2, 124.1, 165.4, 198.5. EIMS: 247 ($[M]^+$, 3), 203 (100), 201 (40), 160 (30), 43 (26).

4.2.6. Reduction of acetoxy-enones. To a magnetically stirred suspension of $LiAlH_4$ (315 mg, 8.30 mmol, 2 equiv.) in 50 mL of anhydrous Et_2O, cooled to nearly 0°C, was added dropwise a solution of acetoxyenone **12a** (1.20 g, 4.15 mmol, 1 equiv.) in anhydrous ether (50

mL). After stirring at this temperature for 30–40 min (TLC monitoring) the mixture was diluted with wet Et_2O and treated with a small amount of 6N NaOH solution (for each 1 g of $LiAlH_4$ 1 mL of water, 1 mL of 6N NaOH and 3 mL more water were added). The organic layer was worked up as usual to give, after silica gel chromatography (ethyl acetate–heptane, 4:1), 98% of the desired diols *cis*-**1α**/*trans*-**1α** in a 6.4:1 ratio.

4.2.6.1. (6*S*,7*R*)-Dihydroxy-(3*R*)-isopropyl-(8a*S*)-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene-(1*R*)-carbonitrile *cis*-1α. $[\alpha]_D^{20}=+15$ (*c* 2.94, $CHCl_3$). IR (film): 3367, 2958, 2234, 1655, 1460, 1388, 1367, 1281, 1235, 1115, 1088, 1060, 962, 880, 756 cm^{-1}. ^1H NMR (300 MHz): 0.88 (3H, d, $J=6.0$), 0.89 (3H, d, $J=5.7$), 1.38–1.50 (2H, m), 1.38 (3H, s), 1.73 (1H, dd, $J=3.2$, 14.0), 1.94–2.11 (3H, m), 2.19 (1H, bd, $J=13.8$), 2.38 (1H, dd, $J=3.6$, 14.1), 2.58 (1H, dd, $J=4.9$, 11.8), 3.53 (2H, s), 3.82–3.91 (1H, m), 4.12 (1H, bs), 5.45 (1H, d, $J=4.2$). ^{13}C NMR (75 MHz): 20.4, 20.6, 22.1, 25.0, 27.7, 32.8, 35.9, 37.5, 38.6, 40.6, 66.4, 66.5, 120.5, 123.0, 141.5. EIMS: 249 ([M]$^+$, 0.01), 55 (85), 53 (55), 43 (42), 42 (100).

4.2.6.2. (6*R*,7*R*)-Dihydroxy-(3*R*)-isopropyl-(8a*S*)-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene-(1*R*)-carbonitrile *trans*-1α. $[\alpha]_D^{20}=-58$ (*c* 1.29, $CHCl_3$). IR (film): 3399, 2960, 2870, 2236, 1663, 1460, 1387, 1367, 1239, 1118, 1063, 1017, 923, 883, 755 cm^{-1}. ^1H NMR (300 MHz): 0.90 (3H, d, $J=6.5$), 0.91 (3H, d, $J=6.3$), 1.16–1.83 (2H, m), 1.32 (3H, s), 1.99 (1H, dt, $J=4.5$, 14.1), 2.10 (1H, dd, $J=3.9$, 14.2), 2.21 (1H, bd, $J=$ 13.7), 2.34–2.43 (1H, m), 2.79 (1H, dd, $J=4.1$, 12.7), 3.50–3.62 (1H, m), 3.99–4.14 (3H, m), 5.32 (1H, s). ^{13}C NMR (75 MHz): 20.6, 20.9, 23.1, 25.0, 28.1, 32.2, 34.9, 38.9, 40.5, 41.2, 70.1, 73.0, 120.7, 125.3, 138.7. EIMS: 249 ([M]$^+$, 0. 1), 107 (2), 55 (25), 43 (100), 41 (97).

To a magnetically stirred suspension of $LiAlH_4$ (178 mg, 9.38 mmol, 2 equiv.) in 40 mL of anhydrous Et_2O, cooled to nearly 0°C, was added dropwise a solution of acetoxyenone **13β** (1.16 g, 4.69 mmol, 1 equiv.) in anhydrous ether (50 mL). Proceeding as above, a nearly quantitative yield of diols *cis*-**1β**/*trans*-**1β** in a nearly 1:1 ratio was obtained.

4.2.6.3. (6*R*,7*S*)-Dihydroxy-(3*R*)-isopropyl-(8a*S*)-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene-(1*R*)-carbonitrile *cis*-1β. $[\alpha]_D^{20}=-182$ (*c* 1.22, $CHCl_3$). IR (film): 3385, 3273, 2951, 2938, 2870, 2234, 1660, 1461, 1422, 1388, 1369, 1284, 1236, 1148, 1095, 1046, 983, 860 cm^{-1}. ^1H NMR (300 MHz): 0.89 (3H, d, $J=6.4$), 0.91 (3H, d, $J=6.2$), 1.23–2.36 (9H, m), 1.32 (3H, s), 1.98 (1H, dd, $J=4.1$, 13.1), 2.65 (1H, dd, $J=4.1$, 13.1), 3.84–3.95 (1H, m), 4.06–4.13 (1H, m), 5.53 (1H, dd, $J=1.7$, 5.0). ^{13}C NMR (75 MHz, DMSO-d_6): 20.8 (2C), 21.4, 26.2, 28.7, 33.9, 37.9, 39.4, 40.4, 42.0, 67.1, 67.6, 121.8, 125.0, 142.9. EIMS: 249 ([M]$^+$, 0.01), 91 (15), 79 (20), 77 (22), 55 (100), 53 (40), 43 (25), 42 (75). Anal. calcd for $C_{15}H_{23}NO_2$ C, 72.25; H, 9.30; found: C, 72.01; H, 9.19.

4.2.6.4. (6*S*,7*S*)-Dihydroxy-(3*R*)-isopropyl-(8a*S*)-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene-(1*R*)-carbonitrile *trans*-1β. Mp: 114–116°C (heptane–ether). $[\alpha]_D^{20}=+77$ (*c* 1.16, $CHCl_3$). IR (film): 3386, 3273, 2951, 2938, 2870, 2234, 1660, 1461, 1422, 1388, 1369, 1284, 1236, 1148, 1095, 1046, 983, 860 cm^{-1}. ^1H NMR (300 MHz): 0.90 (3H, d, $J=6.2$), 0.91 (3H, d, $J=6.1$), 1.37 (3H, s), 1.38–1.51 (1H, m), 1.53 (1H, t, $J=12.4$), 1.61–1.65 (2H, m), 1.94 (1H, dd, $J=3.9$, 14.2), 1.98 (1H, dd, $J=3.9$, 13.2), 2.03–2.09 (1H, m), 2.12 (1H, dd, $J=3.6$, 12.7), 2.23–2.28 (2H, m), 2.49 (1H, dd, $J=3.9$, 13.0), 3.70–3.81 (1H, m), 4.04–4.12 (1H, m), 5.30 (1H, bs). ^{13}C NMR (75 MHz): 20.4, 20.8 (2C), 25.4, 27.6, 32.7, 37.3, 38.7, 40.4, 43.7, 70.1, 73.6, 120.3, 125.2, 139.1. EIMS: 249 ([M]$^+$, 23), 232 (10), 162 (15), 121 (25), 107 (40), 91 (40), 79 (35), 77 (32), 55 (55), 43 (92), 41 (100). Anal. calcd for $C_{15}H_{23}NO_2$ C, 72.25; H, 9.30; found: C, 71.98; H, 9.49.

4.2.7. Functional group interconversion: preparation of the vinyl octaline diol 2. To a stirred solution of **1** (1.52 g, 6.09 mmol) in dry toluene (40 mL) and collidine (3.69 g, 30.45 mmol), chilled at 0°C, TMSOTf (4.06 g, 18.27 mmol) was added under argon. The mixture was stirred at 0°C for 1 h 15 min (TLC monitoring). Upon disappearance of the starting material, dilution with heptane and usual workup afforded 2.03 g of **17** (84%) which was taken as such for the next step.

4.2.7.1. 3-Isopropyl-8a-methyl-6,7-bis-(trimethylsilanyloxy)-1,2,3,4,6,7,8,8a-octahydro-naphthalene-1-carbaldehyde 18. Diisobutylaluminium hydride (1 M in heptane, 56.80 mL, 56.80 mmol) was added slowly to the nitrile **17** (2. 00 g, 5.08 mmol) in toluene (27 mL) at −78°C, under argon. The reaction was stirred for 6 h 30 min at this temperature, then diluted with heptane and after water addition (a few drops) extracted in ethyl acetate and washed with brine. The organic layer was concentrated under reduced pressure and SiO_2 flash chromatography of the residue (eluent heptane:EtOAc, 1:1) gave the title compound (1.79 g, 89% yield). **18**: $[\alpha]_D^{20}=-2.5$ (*c* 1.25, $CHCl_3$). IR (film): 2957, 2898, 2870, 1720, 1460, 1388, 1367, 1250, 1107, 1090, 1060, 948, 895, 870, 843, 746, 685 cm^{-1}. ^1H NMR (300 MHz): 0.14 (9H, s), 0.16 (9H, s), 0.85 (3H, d, $J=6.4$), 0.90 (3H, d, $J=6.4$), 1.22 (3H, s), 1.40 (1H, m), 1.50 (1H, m), 1.63–1.95 (3H, m), 1.81 (1H, d, $J=12.8$), 1.97 (2H, dd, $J=3.5$, 12.8), 2.19 (2H, bs), 3.72 (1H, ddd, $J=3.8$, 7.4, 11.4), 4.06 (1H, d, $J=7.4$), 5.07 (1H, bs), 9.79 (1H, d, $J=1.3$). ^{13}C NMR (75 MHz): 0.18 (6C), 20.5, 20.9, 23.6, 25.7, 29.5, 33.6, 39.2, 40.4, 45.1, 55.7, 70.2, 73.9, 125.0, 140.9, 203.7. ESIMS: 435 ([MK]$^+$, 46), 419 ([MNa]$^+$, 100).

4.2.8. Wittig methylenation and desilylation. A solution of potassium *tert*-butoxide (3.03 g, 25.68 mmol) in 30 mL of dry toluene was stirred under argon at rt as methyltriphenylphosphonium bromide (3.12 g, 8.57 mmol) was added. The resulting bright yellow solution was stirred for 1 h, cooled to 0°C before aldehyde **18** (1.70 g, 4.28 mmol) was added in dry toluene (30 mL). The ice bath was removed and the solution was stirred

at rt while the reaction progress was monitored by TLC. After 6 h stirring the reaction mixture was diluted with heptane and worked up as usual. Rapid filtration on silica gel with heptane–EtOAc as eluent afforded a 90% mixture of bis-TMS protected **19**, mono-TMS-protected as well as completely deprotected *trans*-**2β**. Fluoride deprotection on the reaction crude was carried out with TBAF (4 equiv.) in dry THF (5 mL per mmol) at rt for 2 h. Ethyl acetate was then added and the mixture was washed with brine, dried on $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (SiO_2, heptane–EtOAc, 1:1) to give the diol **2** (92%). It should be pointed out that some self deprotection on standing was also observed.

4.2.8.1. (6*R*)-Isopropyl-(8a*S*)-methyl-(8*S*)-vinyl-1,2,3,5,6,7,8,8a-octahydronaphthalene-(2*S*, 3*S*)-diol *trans*-2β. Mp: 85–87°C. $[\alpha]_D^{20}=-12$ (*c* 0.90, $CHCl_3$). IR (film): 3370, 3074, 2937, 2867, 1636, 1460, 1417, 1383, 1265, 1223, 1144, 1088, 1056, 1017, 960, 913, 890, 840, 738, 704, 669 cm^{-1}. ^1H NMR (300 MHz): 0.78 (3H, d, $J=6.4$), 0.82 (3H, d, $J=6.4$), 1.01 (3H, s), 1.24 (1H, m), 1.36 (1H, t, $J=12.7$), 1.47–1.60 (3H, m), 1.76 (1H, dd, $J=3.6$, 12.7), 1.92 (1H, q, $J=8.4$), 2.20 (2H, bs), 2.53 (2H, bs), 3.61 (1H, ddd, $J=3.6$, 7.8, 12.7), 3.98 (1H, d, $J=7.8$), 4.94 (1H, d, $J=16.0$), 4.95 (1H, d, $J=11.4$), 5.10 (1H, d, $J=1.1$), 5.63 (1H, ddd, $J=8.4$, 11.4, 16.0). ^{13}C NMR (75 MHz):19.6, 20.7, 21.2, 26.0, 29.4, 33.9, 39.9, 41.4, 44.0, 48.2, 71.2, 74.4, 115.5, 122.5, 138.6, 144.0. ESIMS (MeOH): 273 ([MNa]$^+$, 100).

4.3. Domino transformations

4.3.1. The interrupted cascade. Placed in a flame dried flask, solid **1** (249 mg, 1.0 mmol) and $Pb(OAc)_4$ (532 mg, 1.2 mmol) were vacuumed and flashed with argon, cooled to −20°C and 5 mL of acetonitrile were added the ice bath removed soon after and the mixture was stirred at rt. TLC control upon 1 h rt stirring indicated total consumption of the starting diol and appearance of two new higher R_f spots, a UV-active higher spot corresponding to the intermediate dialdehyde together with a second, still higher R_f non UV active one, the half-cascade product **3**. The mixture was stirred at rt for 4 h, diluted with acetonitrile, filtered through Celite, the filtrate concentrated and purified by silica gel chromatography using ethyl acetate–heptane, 1:3 as eluent to afford 217 mg (88%) of **3**. Similar results were obtained running the domino reaction in toluene, trifluorotoluene, benzene, dichloromethane or acetic acid.

4.3.1.1. (3*R*)-Isopropyl-(6*S*)-methyl-9,12-dioxa-tricyclo[6.3.1.0]dodec-10-ene-(5*R*)-carbonitrile 3. $[\alpha]_D^{20}=-11$ (*c* 1.84, $CHCl_3$). 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), 1.96 (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 (200 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. ESIMS (DCM–MeOH): 248 ([MH]$^+$, 10), 247 (17), 246 (100).

4.3.1.2. Preparation of the tricyclic enol ether 20. A dry flask was charged with diol **2** (250 mg, 1 mmol) and $Pb(OAc)_4$ (532 mg, 1.2 mmol, 1.2 equiv.) vacuumed, flushed with argon and cooled to nearly 0°C. Acetonitrile (5 mL) was added, the ice bath removed soon after and the mixture was stirred at rt for 5 h, diluted with acetonitrile, filtered through Celite, the filtrate concentrated and purified by silica gel chromatography using ethyl acetate–heptane, 1:5 as eluent to give **20** (218 mg, 88%).

4.3.1.3. (3*R*)-Isopropyl-(6*S*)-methyl-(5*S*)-vinyl-9,12-dioxa-tricyclo[6.3.1.$0^{0.0}$]dodec-10-ene 20. $[\alpha]_D^{20}=+25$ (*c* 1.25, $CHCl_3$). IR (film): 3070, 2965, 2866, 1633, 1447, 1430, 1385, 1339, 1274, 1211, 1185, 1139, 1084, 1047, 998, 957, 942, 911, 888, 831, 793, 722 cm^{-1}. ^1H NMR (300 MHz): 0.77 (3H, d, $J=6.7$), 0.89 (3H, d, $J=6.5$), 0.97 (3H, s), 1.16–1.30 (2H, m), 1.31–1.41 (2H, m), 1.58 (1H, dq, $J=2.7$, 14.0), 1.75 (1H, d, $J=14.0$), 2.00 (1H, octet), 2.11 (1H, m), 2.22 (1H, dd, $J=5.8$, 14.0), 4.69 (1H, d, $J=6.1$), 4.95 (2H, m) 5.51 (1H, d, $J=5.8$), 5.60 (1H, ddd, $J=8.2$, 10.9, 16.5), 6.12 (1H, d, $J=6.1$). ^{13}C NMR (75 MHz): 13.8, 21.6, 22.0, 28.1, 28.3, 30.9, 39.3, 41.8, 47.1, 52.5, 83.76, 98.9, 110.7, 115.4, 139.1, 139.6. ESIMS (MeOH): 271[MNa]$^+$, 100). Anal. calcd for $C_{16}H_{24}O_2$ C, 77.38; H, 9.74; found: C, 77.32; H, 9.76.

4.3.2. The full-cascade. A dry flask was charged with unsaturated diols **1** (603 mg, 2.42 mmol, diastereomeric mixture) and $Pb(OAc)_4$ (2.57 g, 5.80 mmol, 2.4 equiv.) vacuumed, flushed with argon and cooled to 0°C. Acetic acid (10 mL) was added, the cooling bath removed soon after and the reaction mixture was stirred for 19 h at rt. The mixture was diluted with EtOAc and washed carefully with satd $NaHCO_3$ solution till neutral pH and brine. The organic layer was concentrated under reduced pressure, dried over $MgSO_4$ and purified through flash chromatography using heptane–EtOAc 1:1 as eluent afforded 166.4 mg (28%) of **3**, 513 mg (24%) of lactone **14** and 390 mg (44%) of **4**. **16** was obtained and characterized from another run in acetonitrile.

4.3.2.1. (3*R*)-Isopropyl-(6*S*)-methyl-10-oxo-9,12-dioxa-tricyclo[6.3.1.0]dodecane-(5*R*)-carbonitrile 14. $[\alpha]_D^{20}=-19$ (*c* 0.92, $CHCl_3$). IR (film): 2961, 2869, 2238, 1751, 1460, 1376, 1218, 961, 938, 845, 733 cm^{-1}. ^1H NMR (300 MHz): 0.90 (3H, d, $J=6.7$), 0.95 (3H, d, $J=6.6$), 1.33–1.49 (1H, m), 1.38 (3H, s), 1.63 (1H, dd, $J=5.2$, 15.2), 1.71–1.86 (2H, m), 1.90–2.02 (2H, m), 2.19 (1H, d, $J=14.8$), 2.40 (1H, dd, $J=5.1$, 14.8), 2.58 (1H, d, $J=18.4$), 2.77 (1H, dd, $J=4.4$, 12.3), 2.80 (1H, d, $J=18.4$), 5.82 (1H, d, $J=5.2$). ^{13}C NMR (75 MHz): 18.5, 20.4, 20.8, 26.6, 29.2, 33.3, 34.9, 36.6, 41.0, 43.6, 49.1, 84.1, 100.2, 120.6, 166.6. EIMS: 263 ([M]$^+$, 3), 177 (30), 175 (40), 132 (21), 43 (100).

4.3.2.2. Acetic acid (1*R*)-acetoxy-(5*R*)-cyano-(7*R*)-isopropyl-(4a*S*)-methyl-9-oxo-decahydrocyclohepta[*c*]

pyran-(3*R*)-yl ester 4. $[\alpha]_D^{20}=+79$ (*c* 1.57, $CHCl_3$). IR (film): 2961, 2927, 2237, 1756, 1717, 1579, 1465, 1371, 1227, 1184, 1148, 1089, 1047, 1000, 949, 924, 874, 755 cm^{-1}. ^1H NMR (800 MHz): 0.94 (3H, d, $J=6.7$), 0.96 (3H, d, $J=6.7$), 1.56 (3H, s), 1.59 (1H, m), 1.90 (1H, dd, $J=2.9$, 14.8), 1.93 (1H, m), 1.96 (1H, m), 2.02 (1H, dd, $J=4.2$, 14.8), 2.08 (3H, s), 2.13 (3H, s), 2.18 (1H, m), 2.41 (1H, dd, $J=10.9$, 15.9), 2.54 (1H, dd, $J=4.1$, 15.9), 2.76 (1H, dd, $J=3.2$, 11.3), 3.10 (1H, d, $J=3.6$), 6.32 (1H, d, $J=3.6$), 6.38 (1H, dd, $J=2.9$, 4.2). ^{13}C NMR (200 MHz): 19.4, 19.6, 20.9, 23.4, 29.7, 31.8, 35.7, 36.0, 38.2, 39.2, 45.1, 53.7, 87.2, 90.5, 109.6, 119.3, 168.6, 168.7, 205.8. EIMS: 365 ($[M]^+$, 6), 364 ($[M-1]^+$, 26), 246 (27), 164 (35), 95 (50), 43 (100). ESIMS (MeOH): 404 ($[MK]^+$, 20), 388 ($[MNa]^+$, 50). HRES-IMS (MeOH) calcd. for $C_{19}H_{27}NO_6Na$ 388.1736; found 388.1739.

4.3.2.3. Acetic acid (5*R*)-cyano-(7*R*)-isopropyl-(4a*S*)-methyl-9-oxo-3,4,4a,5,6,7,8,9-octahydrocyclohepta[*c*]-pyran-(3*R*)-yl ester 16. Mp: 110–112°C (heptane–ether). $[\alpha]_D^{20}=+12$ (*c* 1.61, $CHCl_3$). IR (film): 2961, 2236, 1760, 1673, 1578, 1462, 1390, 1370, 1295, 1247, 1210, 1196, 1139, 1093, 1050, 989, 967, 953, 933, 878, 834, 799, 753, 725 cm^{-1}. ^1H NMR (800 MHz): 0.94 (6H, d, $J=6.5$), 1.51 (1H, m), 1.53 (3H, s), 1.63 (1H, m), 2.14 (3H, s), 2.19 (1H, dd, $J=3.5$, 14.6), 2.20 (1H, dd, $J=5.2$, 14.6), 2.25 (1H, ddd, $J=3.6$, 12.7, 15.1), 2.39 (1H, ddd, $J=1.9$, 3.0, 15.1), 2.71 (1H, dd, $J=2.8$, 15.5), 2.85 (1H, dd, $J=3.0$, 12.7), 2.88 (1H, ddd, $J=1.7$, 6.1, 15.5), 6.34 (1H, dd, $J=3.5$, 5.2), 7.41 (1H, s). ^{13}C NMR (75 MHz): 20.5, 20.8 (2C), 21.5, 27.3, 32.4, 33.1, 38.9, 39.1, 40.0, 47.1, 88.9, 120.1 (2C), 152.1, 168.9, 198.7. EIMS: 305 ($[M]^+$, 2.5), 202 (22), 150 (15), 43 (100). Anal. calcd for $C_{17}H_{23}NO_4$ C, 66.86; H, 7.59; found: C, 66.98; H, 7.67.

4.3.2.4. Acetic acid (3*R*)-acetoxy-(7*R*)-isopropyl-(4a*S*)-methyl-9-oxo-(5*S*)-vinyl-decahydrocyclohepta[*c*]-pyran-(1*R*)-yl ester 6. A dry flask was charged with **2β**-*trans* (169 mg, 0.67 mmol) and $Pb(OAc)_4$ (945 mg, 2.02 mmol), vacuumed, flushed with argon and cooled to 0°C. Acetic acid (6.8 mL) was added and the reaction mixture was stirred at rt for 8 h (TLC monitoring). Following disappearance of the starting material the reaction mixture was diluted with ether and washed carefully with an aqueous saturated $NaHCO_3$ solution and brine till neutral pH. Flash chromatography using heptane–EtOAc 1:1 as eluent afforded 202 mg (82%) of **6** as the only product. $[\alpha]_D^{20}=+93$ (*c* 1.04, $CHCl_3$). IR (film): 3074, 2959, 2873, 1756, 1716, 1637, 1464, 1431, 1369, 1228, 1184, 1119, 1084, 997, 920, 873, 790 cm^{-1}. ^1H NMR (300 MHz): 0.84 (3H, d, $J=6.7$), 0.85 (3H, d, $J=6.7$), 1.24 (3H, s), 1.30 (1H, m), 1.32 (1H, m), 1.55 (1H, d, $J=14.9$), 1.69 (1H, dd, $J=4.1$, 14.9), 1.79–1.97 (3H, m), 2.01 (3H, s), 2.02 (3H, s), 2.22 (1H, dd, $J=11.3$, 17.2), 2.40 (1H, dd, $J=4.1$, 17.0), 3.13 (1H, d, $J=3.4$), 4.93 (1H, d, $J=17.2$), 4.98 (1H, d, $J=10.2$), 5.56 (1H, ddd, $J=8.9$, 10.2, 17.2), 6.22 (1H, d, $J=3.4$), 6.26 (1H, dd, $J=1.7$, 3.9). ^{13}C NMR (75 MHz): 19.6, 19.8, 20.9, 21.1 (2C), 32.4, 32.7, 35.8, 36.6, 38.6, 46.1, 50.4, 53.5, 87.2, 92.3, 117.1, 137.4, 169.0 (2C), 208.2. ESIMS (MeOH): 405 ($[MK]^+$, 100), 389 ($[MNa]^+$, 96).

4.3.2.5. Using (*S*)-*O*-acetyllactic acid as solvent. A dry flask was charged with 249 mg (1 mmol) of solid **1** and 1.33 g (3 mmol) of $Pb(OAc)_4$, vacuumed, flushed with argon and then again vacuumed for 1 h. (*S*)-2-Acetoxypropionic acid (10 mL) was added at rt and the reaction mixture was stirred for 14 h under argon. It was then diluted with ether (200 mL), washed with water (3×20 mL), 6N NaOH (3×10 mL) and water again (2×20 mL). The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified on silica gel (heptane–EtOAc, 4:1) to yield 183 mg of **15** (36%), along with lactone **14**, and mixed-cascades which need no separation for the next step (mild base induced ring system interchange).

4.3.2.6. (2′*S*)-Acetoxy-propionic acid (1*R*)-[(2′*S*)-acetoxy-propionyloxy]-(5*R*)-cyano-(7*R*)-isopropyl-(4a*S*)-methyl-9-oxo-decahydrocyclohepta[*c*]pyran-(3*R*)-yl ester 15. $[\alpha]_D^{20}=+18$ (*c* 0.93, $CHCl_3$). IR (film): 2961, 2238, 1746, 1455, 1372, 1304, 1236, 1096, 1050, 1007, 940, 901, 836, 754 cm^{-1}. ^1H NMR (300 MHz): 0.95 (6H, d, $J=6.7$), 1.49 (3H, s), 1.53 (3H, s), 1.57 (3H, s), 1.82–2.34 (6H, m), 2.51–2.59 (3H, m), 2.09 (3H, s), 2.13 (3H, s), 3.20 (1H, d, $J=3.4$), 4.99 (1H, q, $J=7.1$), 5.16 (1H, q, $J=7.1$), 6.30 (1H, d, $J=3.4$), 6.42 (1H, bs). ^{13}C NMR (75 MHz): 16.4, 16.7, 19.3, 19.6, 20.4, 20.5, 22.8, 29.6, 31.8, 35.5, 35.6, 38.1, 39.8, 45.2, 52.3, 68.3, 68.6, 88.1, 92.0, 119.1, 168.4, 168.5, 170.0, 170.6, 205.8. ESIMS (MeOH): 548 ($[MK]^+$, 19), 532 ($[MNa]^+$, 52).

4.4. One-pot fused to bridged ring system interchange

4.4.1. Preparation of bicyclo[3.2.2]nonane derivatives 8. To a stirred solution of **4** (349.4 mg, 0.956 mmol) in a 8:1 mixture of methanol (40 mL) and water (5 mL), chilled at 0°C was added potassium carbonate (727 mg, 5.26 mmol, 5.5 equiv.). The resulting mixture was stirred at rt for 29 h. After removing the solvents without heating, dilution with EtOAc and washing with brine till neutral pH, the organic layers were dried over magnesium sulfate, concentrated under reduced pressure and the residue was purified by flash chromatography (heptane–EtOAc 1:1) affording 212 mg (94%) of **8M** and 2.5 mg (1.0%) of **8m**. Several runs were needed to obtain more of **8m**, which could not be completely purified and thus the given a value should be used only as indicative.

4.4.1.1. (6*R*)-Hydroxy-(4*S*)-isopropyl-(1*R*)-methyl-9-oxo-bicyclo[3.2.2]nonane-(2*R*)-carbonitrile 8M. Mp: 122–124°C (heptane–ether). $[\alpha]_D^{20}=-70$ (*c* 1.10, $CHCl_3$). IR (film): 3402, 2952, 2874, 2233, 1712, 1468, 1392, 1374, 1291, 1240, 1161, 1024, 960 cm^{-1}. ^1H NMR (800 MHz): 0.96 (3H, d, $J=6.7$), 0.98 (3H, d, $J=6.7$), 1.21 (3H, s), 1.56 (1H, ddd, $J=3.9$, 6.1, 13.3), 1.68 (1H, dd, $J=2.2$, 15.4), 1.73 (2H, ddd, $J=5.6$, 9.5, 13.3), 1.89 (1H, td, $J=3.3$, 14.6), 2.11–2.15 (1H, m), 2.26 (1H, ddd, $J=3.3$, 8.7, 15.2), 2.29 (1H, dd, $J=1.3$, 19.4), 2.56

(1H, s), 2.81 (1H, m), 2.82 (1H, dd, $J=3.3$, 19.4), 4.39 (1H, td, $J=2.2$, 8.7). ^{13}C NMR (200 MHz): 20.1 (2C), 29.6, 30.2, 32.8, 35.0, 40.2 (2C), 42.0, 47.0, 57.2, 66.0, 119.9, 211.6. EIMS 235 ([M]$^+$, 5), 220 (15), 192 (18), 176 (26), 79 (31), 69 (62), 55 (93), 53 (74), 41 (100). Anal. calcd for $C_{14}H_{21}NO_2$ C, 71.46; H, 8.99; found: C, 71.08; H, 9.14.

4.4.1.2. (6*S*)-Hydroxy-(4*S*)-isopropyl-(1*R*)-methyl-9-oxo-bicyclo[3.2.2]nonane-(2*R*)-carbonitrile 8m. $[\alpha]_D^{20}=-10$ (*c* 0.98, $CHCl_3$). IR (film): 3403, 2952, 2874, 2233, 1712, 1468, 1392, 1374, 1291, 1240, 1161, 1024, 960, 756 cm^{-1}. ^{1}H NMR (800 MHz): 0.94 (3H, d, $J=6.7$), 1.03 (3H, d, $J=6.6$), 1.20 (3H, s), 1.49 (1H, ddd, $J=3.7$, 8.6, 13.2), 1.64 (1H, bs), 1.78 (1H, td, $J=4.4$, 15.1), 1.83–1.88 (1H, m), 2.00 (1H, d, $J=19.45$), 2.02 (1H, td, $J=2.9$, 14.5), 2.16 (1H, dd, $J=10.8$, 15.1), 2.37 (1H, ddd, $J=5.9$, 13.4, 14.5), 2.82 (1H, dd, $J=3.4$, 19.45), 2.86 (1H, d, $J=5.4$), 2.91 (1H, td, $J=2.0$, 5.8), 4.37 (1H, ddd, $J=5.0$, 10.6, 14.4). ^{13}C NMR (200 MHz): 21.1, 21.6, 29.5, 30.3, 32.8, 35.4, 41.4, 41.9, 44.1, 46.9, 55.4, 66.8, 120.3, 211.1. EIMS 235 ([M]$^+$, 10), 220 (35), 192 (32), 176 (55), 55 (32), 53 (26), 43 (82), 41 (100).

4.4.1.3. Acetylation of the major bicyclic aldol. Acetic anhydride (3.52 mL) was added to a stirring mixture of bicyclic aldol **8M** (207 mg, 0.88 mmol) and DMAP (cat.) in pyridine (5.3 mL) at 0°C under argon. After 1 h 30 min, the mixture was diluted with DCM and washed with dilute hydrochloric acid, saturated sodium bicarbonate, water, brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2, heptane–EtOAc, 1:1) to give 227.5 mg (93%) of **8M-OAc**.

4.4.1.4. Acetic acid-(2*R*)-cyano-(4*S*)-isopropyl-(1*R*)-methyl-9-oxo-bicyclo[3.2.2]non-(6*S*)-yl ester 8M-OAc. Mp: 94–95°C. $[\alpha]_D^{20}=-36$ (*c* 1.20, $CHCl_3$). IR (film): 2960, 2236, 1739, 1651, 1558, 1459, 1372, 1242, 1162, 1118, 1024, 965, 736, 605 cm^{-1}. ^{1}H NMR (300 MHz): 0.91 (3H, d, $J=7.3$), 0.94 (3H, d, $J=7.1$), 1.16 (3H, s), 1.47–1.77 (4H, m), 1.88 (1H, m), 1.94 (3H, s), 2.18 (1H, d, $J=19.0$), 2.29 (1H, dd, $J=3.4$, 9.2), 2.53 (1H, bs), 2.78 (1H, m), 2.83 (1H, dd, $J=3.4$, 19.0), 5.32 (1H, td, $J=2.2$, 9.1). ^{13}C NMR (75 MHz): 19.9 (2C), 21.1, 29.7, 30.1, 32.7, 35.0, 39.7, 40.2, 40.5, 47.2, 53.5, 68.7, 119.5, 169.8, 209.0. ESIMS (MeOH): 316 ([MK]$^+$, 25), 300 ([MNa]$^+$, 100). Anal. calcd for $C_{16}H_{23}NO_3$ C, 69.29; H, 8.36; N, 5.05, found: C, 69.01; H, 8.14; N, 4.94.

4.4.2. Preparation of the bicyclic aldol (9*R*)-hydroxy-(4*S*)-isopropyl-(1*R*)-methyl-(2*S*)-vinyl-bicyclo[3.2.2]-nonan-6-one, 7. To a stirred solution of **6** (132 mg, 0.36 mmol) in a 8:1 mixture of methanol (16 mL) and water (2 mL), chilled at 0°C was added potassium carbonate (276 mg, 1.99 mmol). The resulting mixture was stirred at rt for 19 h (TLC monitoring). Proceeding as above, SiO_2 flash column chromatography (heptane–EtOAc, 1:1) afforded 80% yield of a bicyclic diol **7**. Mp: 85–86°C. $[\alpha]_D^{20}=-90$ (*c* 0.80, $CHCl_3$). IR (film): 3427, 2959, 2873, 1705, 1462, 1389, 1265, 1216, 1161, 1114, 1030, 1001, 966, 920, 876 cm^{-1}. ^{1}H NMR (300 MHz): 0.86 (3H, d, $J=6.7$), 0.91 (3H, d, $J=6.7$), 0.94 (3H, s), 1.37 (1H, m), 1.37 (1H, m), 1.46–1.63 (5H, m), 2.04 (1H, d, $J=19.0$), 2.23 (1H, m), 2.29 (1H, dd, $J=3.1$, 19.0), 2.47 (1H, bs), 4.33 (1H, d, $J=8.0$), 4.93 (1H, d, $J=16.9$), 4.98 (1H, d, $J=10.3$), 5.66 (1H, ddd, $J=9.1$, 10.3, 16.9). ^{13}C NMR (75 MHz): 20.4, 20.8, 29.6, 31.7, 33.0, 35.0, 40.2, 44.1, 46.6, 50.4, 57.8, 66.4, 116.4, 137.5, 214.7. ESIMS (MeOH): 275 ([MK]$^+$, 2), 259 ([MNa]$^+$, 100). Anal. calcd for $C_{15}H_{24}O_2$ (0.1 equiv. of H_2O) C, 75.65; H, 10.24; found: C, 75.36; H, 10.12.

4.4.2.1. Oxidation of 7 with Dess–Martin's periodinane. To a solution of the above bicyclic aldol (66 mg, 0.28 mmol) in dry methylene chloride (7 mL) and pyridine (0.9 mL) were added 356 mg (0.84 mmol) of periodinane and stirring continued at rt for 1 h 30 min. The reaction was then diluted with methylene chloride quenched with a saturated aqueous solution of sodium bicarbonate and washed with brine. Usual work up and chromatography (heptane–EtOAc, 2:1) afforded 55 mg (84%) of the desired 1,3-dicarbonyl species.

4.4.2.2. (4*S*)-Isopropyl-(1*R*)-methyl-(2*S*)-vinyl-bicyclo[3.2.2]nonane-6,9-dione 24. $[\alpha]_D^{20}=-55$ (*c* 1.47, $CHCl_3$). IR (film): 2961, 2930, 2876, 1728, 1703, 1460, 1414, 1393, 1372, 1268, 1242, 1205, 1179, 1107, 1016, 922, 737 cm^{-1}. ^{1}H NMR (300 MHz): 0.84 (3H, d, $J=6.4$), 0.89 (3H, d, $J=6.4$), 1.05 (3H, s), 1.48–1.75 (4H, m), 1.94 (1H, d, $J=19.3$), 2.20 (1H, d, $J=19.3$), 2.36 (1H, m), 2.51 (1H, dd, $J=3.4$, 19.4), 2.62 (1H, dd, $J=3.4$, 19.3), 3.19 (1H, s), 5.03 (1H, d, $J=16.9$), 5.10 (1H, d, $J=10.4$), 5.78 (1H, ddd, $J=8.8$, 10.4, 16.9). ^{13}C NMR (75 MHz): 19.5, 20.0, 28.7, 31.4, 33.0, 34.5, 43.5, 47.1, 49.6, 51.2, 68.9, 117.4, 136.4, 207.2 (2C). ESIMS (MeOH): 257 ([MNa]$^+$,100). Anal. calcd for $C_{15}H_{22}O_2$ C, 76.88; H, 9.46; found: C, 76.79; H, 9.48.

4.5. Ozonolysis of 3 in CH_2Cl_2 and MeOH; Cannizzaro type base-catalyzed oxidoreduction of 21; preparation of the bicyclic lactone 5 and methylfuranosides 22–23

4.5.1. Ozonolysis of 3 in CH_2Cl_2. Ozone was passed into a stirred solution of **3** (228 mg, 0.92 mmol) in 12 mL of methylene chloride and 0.3 mL of pyridine at −78°C until blue color persisted, stirred for an additional 5 min at this temperature after what 1 mL of Me_2S were added dropwise. The mixture was allowed to reach rt within approximately 30 min, concentrated under reduced pressure without heating, and purified through silica gel using heptane–ethyl acetate 3:1 as eluent, to give 173 mg (67%) of formyl-aldehyde **21**.

4.5.1.1. Formic acid (4*R*)-cyano-(7a*R*)-formyl-(6*R*)-isopropyl-(3a*S*)-methyl-octahydrobenzofuran-(2*R*)-yl ester 21. Mp: 94–96°C (heptane–ether). $[\alpha]_D^{20}=+38$ (*c* 1.22, $CHCl_3$). IR (film): 2954, 2936, 2875, 2846, 2243, 1725, 1460, 1449, 1372, 1317, 1240, 1166, 1133, 1107, 1075, 1037, 1010, 947, 869, 842 cm^{-1}. ^{1}H NMR (800 MHz): 0.90 (3H, d, $J=6.6$), 0.91 (3H, d, $J=6.6$), 1.41 (3H, s), 1.44 (1H, dd, $J=9.1$, 14.8), 1.66 (1H, octet,

$J=6.6$), 1.68–1.73 (1H, m), 1.79 (1H, ddd, $J=4.4$, 7.4, 14.0), 1.89 (1H, dddd, $J=0.9$, 5.2, 9.9, 14.0), 1.96 (1H, ddd, $J=0.8$, 4.4, 14.7), 2.01 (1H, dd, $J=3.0$, 14.4), 2.64 (1H, dd, $J=6.3$, 14.4), 2.88 (1H, dd, $J=4.4$, 9.0), 6.51 (1H, ddd, $J=0.9$, 3.0, 6.3), 8.11 (1H, s), 9.81 (1H, s). ^{13}C NMR (200 MHz): 19.0, 19.9, 20.0, 26.9, 30.2, 30.3, 34.5, 35.8, 44.2, 44.8, 90.7, 96.2, 119.8, 159.7, 201.0. ESIMS (MeOH): 318 ([MK]$^+$, 15), 302 ([MNa]$^+$, 100). Anal. calcd for $C_{15}H_{21}NO_4$ C, 64.50; H, 7.58; found: C, 64.59; H, 7.66.

4.5.2. Cannizzaro type oxidoreduction: preparation of bis-angularly substituted bicyclic lactone 5. Formylacetal-aldehyde **21** (123 mg, 0.44 mmol) was dissolved in a 10:1 mixture of methanol (5 mL) and water (0.5 mL), and of potassium carbonate (609 mg, 4.41 mmol, 10 equiv.) was added at 0°C under argon. The mixture was stirred at rt for 15 h. Methanol was removed first under reduced pressure without heating. Water was added and the crude reaction mixture was acidified with 1N HCl until pH 2, extracted in EtOAc and washed with brine. Following usual work up the residue was purified by flash chromatography on silica gel (eluent: heptane–EtOAc 2:1) to afford 81 mg (73%) of bicyclic lactone **5**.

4.5.2.1. (7a*R*)-Hydroxymethyl-(6*R*)-isopropyl-(3a*S*)-methyl-2-oxo-octahydrobenzofuran-(4*R*)-carbonitrile 5. $[\alpha]_D^{20}=-59$ (*c* 0.85, $CHCl_3$). IR (film): 3436, 2959, 2238, 1769, 1643, 1469, 1357, 1391, 1226, 1037, 937 cm^{-1}. ^{1}H NMR (800 MHz): 0.90 (3H, d, $J=6.8$), 0.92 (3H, d, $J=6.8$), 1.36 (1H, dd, $J=11.7$, 14.5), 1.41 (3H, s), 1.47–1.53 (1H, m), 1.60 (1H, octet, $J=6.8$), 1.75 (1H, ddd, $J=5.5$, 9.8, 14.1), 1.93 (1H, dddd, $J=1.5$, 5.4, 7.7, 13.0), 2.12 (1H, dd, $J=2.5$, 14.5), 2.58 (1H, d, $J=17.5$), 2.73 (1H, d, $J=17.5$), 2.90 (1H, dd, $J=5.5$, 7.7), 3.77 (1H, d, $J=12.6$), 3.87 (1H, d, $J=12.6$). ^{13}C NMR (200 MHz): 19.1, 19.4, 19.8, 27.2, 31.0, 31.4, 34.3, 35.7, 42.1, 42.3, 64.5, 88.5, 120.2, 174.5. ESIMS (MeOH): 290 ([MK]$^+$, 30), 274 ([MNa]$^+$, 100).

4.5.3. Ozonolysis of 3 in MeOH. Ozone was passed into a stirred solution of 217 mg (0.88 mmol) of **3** in methanol (15 mL) at −78°C until purple–blue color persisted. Me_2S (ca. 5 mL) was added. The reaction mixture was allowed to reach rt within an hour, concentrated under reduced pressure, and the residue was flash chromatographed on silica gel. Elution with heptane–EtOAc (8:1) afforded 13.5 mg (5.8%) of **23** (H-2α) and 154 mg (66.2%) of **22** (H-2β) in 72% combined yield and ca. 1:11.5 ratio.

4.5.3.1. (7a*R*)-Formyl-(6*R*)-isopropyl-(2*S*)-methoxy-(3a*S*)-methyl-octahydrobenzofuran-(4*R*)-carbonitrile 23 (faster eluting minor diastereoisomer). $[\alpha]_D^{20}=+25$ (*c* 0.20, $CHCl_3$). IR (film): 2924, 2238, 1731, 1463, 1455, 1385, 1261, 1210, 1102, 1035, 970, 801 cm^{-1}. ^{1}H NMR (300 MHz): 0.81 (3H, d, $J=6.5$), 0.85 (3H, d, $J=6.5$), 1.27 (3H, s), 1.38–1.90 (7H, m), 2.39 (1H, dd, $J=2.0$, 13.8), 2.72 (1H, t, $J=7.5$), 3.38 (3H, s), 5.10 (1H, dd, $J=3.4$, 5.7), 9.74 (1H, s). ^{13}C NMR (75 MHz): 18.1, 20.3, 20.4, 26.9, 29.0, 29, 9, 34.4, 36.0, 44.9, 46.3, 55.9, 89.5, 104.3, 120.4, 202.9. ESIMS (MeOH): 304 ([MK]$^+$, 18), 288 ([MNa]$^+$, 100).

4.5.3.2. (7a*R*)-Formyl-(6*R*)-isopropyl-(2*R*)-methoxy-(3a*S*)-methyl-octahydrobenzofuran-(4*R*)-carbonitrile 22 (slower eluting major diastereoisomer). $[\alpha]_D^{20}=-95$ (*c* 0.32, $CHCl_3$). IR (film): 2959, 2237, 1735, 1466, 1388, 1208, 1108, 1031, 912 cm^{-1}. ^{1}H NMR (800 MHz): 0.92 (3H, d, $J=6.2$), 0.95 (3H, d, $J=6.2$), 1.29 (3H, s), 1.64 (1H, dd, $J=9.1$, 14.4), 1.70 (1H, m), 1.72 (1H, m), 1.84 (1H, ddd, $J=5.0$, 7.6, 13.8), 1.89 (1H, ddd, $J=4.4$, 8.7, 13.8), 2.00 (1H, dd, $J=3.2$, 14.4), 2.03 (1H, dd, $J=6.1$, 13.8), 2.25 (1H, dd, $J=2.5$, 13.8), 3.40 (1H, dd, $J=4.9$, 8.9), 3.42 (3H, s), 5.25 (1H, dd, $J=2.5$, 6.1), 9.64 (1H, s). ^{13}C NMR (200 MHz): 19.5, 20.0 (2C), 27.1, 30.2, 30.6, 33.5, 36.3, 43.7, 45.0, 55.9, 88.8, 104.7, 120.5, 201.0. ESIMS (MeOH): 304 ([MK]$^+$, 25), 288 ([MNa]$^+$, 100).

Acknowledgements

The authors thank the European Commission for a Research Training Grant to J. I. Candela Lena, ICSN-CNRS for a scholarship to E. Sanchez Fernandez and Professor Jean-Yves Lallemand for his kind interest and constant encouragement.

References

1. Criegee, R., In *Oxidation in Organic Chemistry*, Part A; Wiberg, K. B., Ed.; Academic Press: New York, 1965; p. 277.
2. Bowers, A.; Holton, P. G.; Denot, E.; Loza, M. C.; Urquiza, R. *J. Am. Chem. Soc.* **1962**, *84*, 1050–1053.
3. Levisalles, J.; Molimard, J. *Bull. Soc. Chim. Fr.* **1971**, 2037.
4. (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131–163; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (c) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304–322.
5. (a) Arseniyadis, S.; Yashunsky, D. V.; Pereira de Freitas, R.; Muñoz-Dorado, M.; Potier, P.; Toupet, L. *Tetrahedron* **1996**, *52*, 12443–12458; (b) Arseniyadis, S.; Brondi Alves, R.; Pereira de Freitas, R.; Muñoz-Dorado, M.; Yashunsky, D. V.; Potier, P.; Toupet, L. *Heterocycles* **1997**, *46*, 727; (c) Candela Lena, J. I.; Martín Hernando, J. I.; Rico Ferreira, M.; Altinel, E.; Arseniyadis, S. *Synlett* **2001**, 597–600.
6. Swartz, H. J.; Verstegen-Haaksma, A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10083–10094. (*R*)-(−)-carvone, a readily available monoterpene, is widely used as building block in the synthesis of natural products. Ho, T.-L., *Enantioselective Synthesis of Natural Products from Chiral Terpenes*, John-Wiley: Chichester, 1992.
7. Ciceri, P.; Demnitz, J. *Tetrahedron Lett.* **1997**, *38*, 389–390.
8. Arseniyadis, S.; Rodriguez, R.; Brondi, R.; Spanevello, R.; Ouazzani, J.; Ourisson, G. In *Microbial Reagents in Organic Synthesis*; Servi, S., Ed., NATO ASI Series C; Kluwer Academic: Dordrecht, 1992; Vol. 381, pp. 313–321.
9. Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc. B* **1967**, 771–779; *idem* **1968**, 994–1005.

10. Indeed, the domino transformations in acetic acid can be carried out directly on the bis-TMS protected diols **19**. On the other hand, during several runs, substantial deprotection of the TMS groups was observed during Wittig olefination.
11. The reason for not isolating the bis-lactyl analogue of **6** is that mixed acetals are present and their chromatographic separation (which is useless for further elaboration) is tedious.
12. Although as much as seven bond making-braking processes take place in one synthetic operation, the average yield is calculated based on only four transformations (oxidative/pericyclic/oxyplumbation/ring expansion).
13. (a) Cimino, G.; Morrone, R.; Sodano, G. *Tetrahedron Lett*. **1982**, *23*, 4139–4142; (b) Gonzales Sierra, M.; Mischne, M. P.; Ruveda, E. A. *Synth. Commun*. **1985**, *15*, 727–735.
14. Van der Eyken, E.; Janssens, A.; Vandewalle, M. *Tetrahedron Lett*. **1987**, *28*, 3519–3520.
15. (a) Criegee, R. *Ber*. **1931**, *64*, 260; (b) Criegee, R. *Angew. Chem*. **1958**, *70*, 173.
16. Unaleroglu, C.; Aviyente, V.; Arseniyadis, S. *J. Org. Chem*. **2002**, *67*, 2447–2452.
17. We applied this chemistry to 'half-cascade' intermediates obtained from unsaturated bicyclic diols in the octaline–diol series as well as from steroidal diols: (a) Arseniyadis, S.; Quilez del Moral, J.; Brondi Alves, R.; Potier, P.; Toupet, L. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2871–2878; (b) Rico Ferreira, M.; Martín Hernando, J. I.; Candela Lena, J. I.; Quílez del Moral, J.; Arseniyadis, S. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1527–1537.
18. A number of possibilities exist for an efficient use of these chiral templates: Sarvary, I.; Almqvist, F.; Frejd, T. L. *Chem. Eur. J*. **2001**, *7*, 2158–2166.
19. The $PhI(OAc)_2$ mediated oxidation of 1,2-diols, known long ago, is a clean method for the cleavage of glycols: Criegee, R.; Beucker, H. *Ann. Chem*. **1939**, *541*, 218.
20. (a) Candela Lena, J. I.; Altinel, E.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron Lett*. **2002**, *43*, 1049–1412; (b) Finet, L.; Candela Lena, J. I.; Kaoudi, T.; Birlirakis, N.; Arseniyadis, S. *Chem. Eur. J*. **2003**, in press.
21. Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc*. **1980**, *102*, 5703–5711.
22. LeCocq, C.; Lallemand, J-Y. *J. Chem. Soc., Chem. Commun*. **1981**, 150–152.