Mild Protocols for Generating Molecular Complexity: A Comparative Study of Hetero-Domino Reactions Based on the Oxidant and the Substitution Pattern

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A bicyclic unsaturated 1,2-diol framework was found to undergo an interesting set of domino reactions on treatment with oxidants. One-pot syntheses of seven-membered-ring-containing frameworks were achieved by a $Pb(OAc)_4$-mediated domino process, while with other oxidants investigated, such as $Mn(OAc)_3$, Dess–Martin periodinane, $PhI(OAc)_2$, $Ph_3Bi(CO)_3$, $NaIO_4$, and $NaBiO_3$, the domino process was interrupted halfway through. Finally, tetrapropylammonium perruthenate (TPAP-NMO), $Pd(OAc)_2$, pyridinium dichromate (PDC), and pyridinium chlorochromate (PCC) gave only allylic oxidation and further diketone formation without any of the bond cleavage that is necessary to initiate the domino process. The substrates were chosen to test the limits of reactivity of various unsaturated 1,2-diol derivatives and to provide guidelines for their use in constructing complex synthetic targets. In this article we provide details of the reaction conditions, preparation of the starting materials and characterization of the products, along with new, unpublished results. Information is assembled to facilitate comparison between the various oxidants, solvents and substitution patterns.

Introduction

Domino reactions continue to be a topic of substantial interest and intensive exploration.[1] Their usefulness in synthesis stems from their ability to maximize molecular complexity while minimizing waste. This has significantly broadened their applicability for multi-step syntheses of natural compounds. The reaction of lead tetraacetate with olefins, as well as the glycol fission reaction, were originally investigated by Criegee[2] and subsequently studied by several other chemists. There is considerable precedent in the literature for cleaving glycols, such as the Malaprade reaction (periodic acid cleavage) or the Rigby oxidation (glycol fission with sodium bismuthate), and others.[3] The presence of an adjacent olefin considerably increases the range of products accessible.[4] Unsaturated 1,2-diols undergo glycol fission upon treatment with $Pb(OAc)_4$, which initiates a domino process under very mild conditions. In our efforts to generate high molecular complexity in a one-pot reaction we examined the unsaturated bicyclic diol system **I** (Scheme 1), which is a versatile template for the domino transformations during lead tetraacetate mediated oxidative cleavage in the synthesis of highly elaborated cyclic systems containing six- or seven-membered rings.[5] We have already ?shown in several publications that the reaction of $Pb(OAc)_4$?with a series of ene-diols can lead to a cascade of reactions that provides an entry into a variety of molecular architectures. The direct fragmentation of octaline diols provides access to a range of functionalized cycloheptanes,[6] as well as bicyclo[3.2.2]nonanes. The domino sequence can be controlled by changing the stoichiometry: using only one equivalent of the reagent generates the isolable, and stable, cyclic ene-acetal **III**, the so-called "half-cascade" intermediate, while two equivalents lead to the ring-expanded product **II** (Scheme 1). These rearrangements are of interest in view of the synthesis of a number of bis-angularly substituted bicyclic lactones **V**, as well as heavily substituted bridged and fused seven-membered-ring-containing systems such as **IV** and **VI**. Tricyclic lactones of type **VII** are the only byproducts obtained so far. The octalone-derived unsaturated diol system **I** was chosen to initiate this study because it presents optimum opportunities to examine the processes as the "half-cascade" intermediate **III** is isolable and stable in this series.

The mechanistic pathways involved in both the oxidative-cleavage-induced domino transformations and in the base-induced ring-system interchange reactions have been discussed in previous papers.[7] An overview of the mechanism deduced from earlier studies is portrayed in Scheme 1 to assist the reader's understanding. The domino process is shown to proceed by a cleavage/[4+2] cycloaddition/oxyplumbation/deplumbation/ring-expansion sequence, all the steps of which are initiated by a multi-task reagent: lead tetraacetate.

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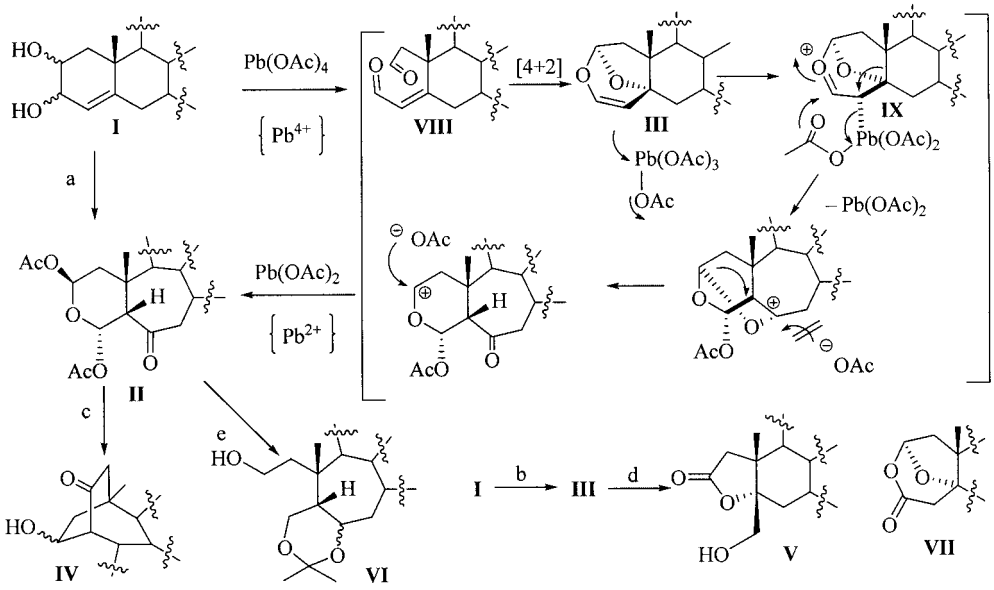


Scheme 1. Reagents and conditions: (a) 2.4 equiv. $Pb(OAc)_4$, MeCN, 0 °C to room temp.; (b) 1.2 equiv. $Pb(OAc)_4$, MeCN, 0 °C to room temp.; (c) K_2CO_3/MeOH/H_2O, room temp.; (d) O_3, CH_2Cl_2 at –78 °C, then K_2CO_3/MeOH/H_2O, room temp.; (e) $LiAlH_4$, THF, reflux then H^+-acetone room temp.

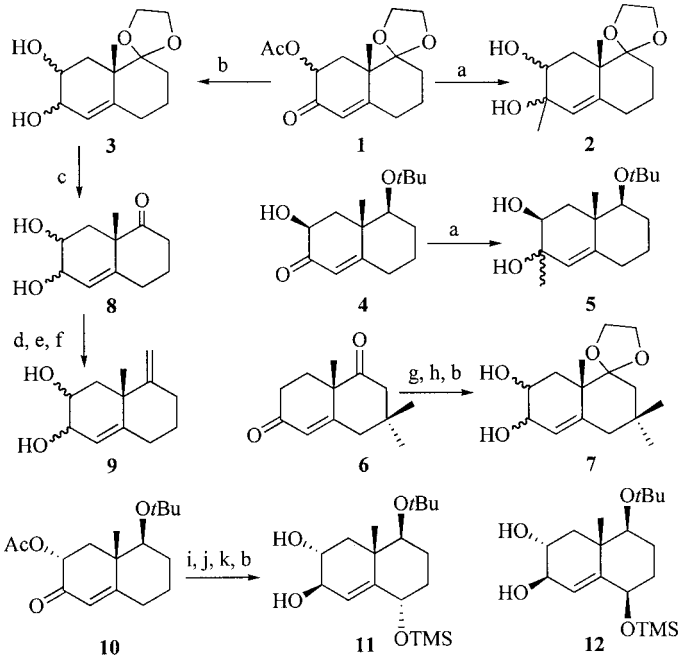
To extend the scope of the process, it was essential to this study that some other oxidants, less toxic than lead tetraacetate, were studied in various solvents. To this aim, the effect of the oxidant was examined using a number of known reagents employed in glycol cleavage. This paper describes the synthesis of several variously substituted 2,3-dihydroxy-4-ene bicyclic frameworks, and the rearrangements that these systems undergo when treated with an oxidant.

Preparation of Substrates

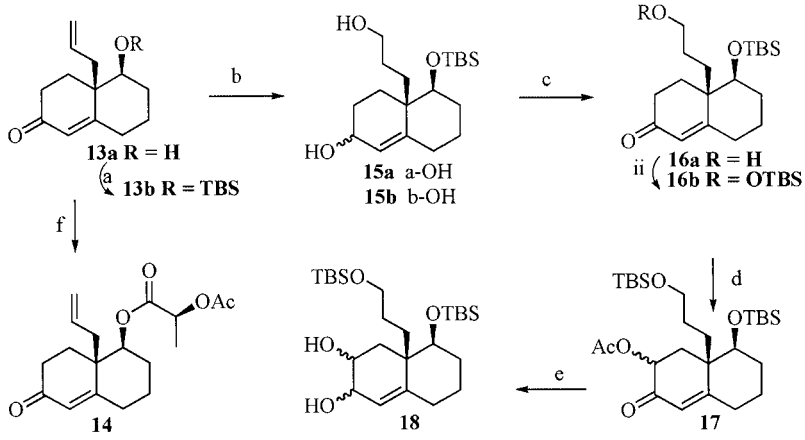
We thus embarked on the synthesis of a set of substrates for investigating the effect of stoichiometry, oxidant, substitution pattern, solvent, temperature, and reaction time. Diols of type **2**, **3**, **5**, **7**, **8**, **9**, **11**, **12** (Scheme 2), and **18** (Scheme 3) were studied in order to optimize the conditions. On the whole, for the preparation of the bicyclic unsaturated 1,2-diols − the required domino substrates − the well-known Robinson annulation procedure was used,[8] starting from the appropriate cyclic ketone and methyl vinyl ketone. The required diols were prepared, in a straightforward manner, from the bicyclic enones thus obtained following our previously published procedure.[9] To prepare acetoxy-enones (such as **1** Scheme 2), $Pb(OAc)_4$ and the corresponding enones were heated in benzene at reflux, under Dean–Stark conditions for water removal. Acetoxylated compounds were isolated in good yields (70–90% yield) along with unreacted starting material. The diols were then obtained by reduction with lithium aluminum hydride in diethyl ether at 0 °C. Exploratory studies focused on the synthesis of diols **2**, **3**, **5**, **7**, **8**, **9**, **11**, and **12**. The unsaturated diols **2** and **5**, which possess a tertiary-secondary diol system, were obtained from the acetoxy-enone **1** and acyloin **4**, respectively (intermediates in our earlier studies).[9] Thus, acetoxy-enone **1** was converted into the unsaturated diol **2** by a simple low temperature treatment with methyllithium (THF, –78 °C); similarly, **4** gave the unsaturated diol **5**. The next target, the unsaturated bicyclic diol **7**, was synthesized in a three-step sequence from **6**, which, in turn, was prepared from commercially available dimedone on a large scale using the Heathcock procedure.[10]

Previously described methods were used to prepare octaline-diol **3**, its free-ketone counterpart **8** and hence the *exo*-methylene derivative **9** from the well known Wieland–Miescher ketone.[11] The four-step process from **3** was effected in 78% overall yield (Scheme 2). The allylically substituted substrates **11**, **12**, and **26** (Table 1) were generated from the corresponding acetoxy-enones by way of the intermediate dienol acetate species, using known procedures.[12] The dienol acetates, obtained by heating of the acetoxy-enones in pyridine in the presence of acetic anhydride and 4-(dimethylamino)pyridine (DMAP), were then epoxidized with methyltrioxorhenium (MTO) as catalyst and aqueous hydrogen peroxide as terminal oxidant.[13]

As the effectiveness of the process could be further improved if the resulting complex heterocycle is poised to undergo spirocyclization, we came to favor octaline-diol **18**, obtained by an asymmetric Robinson annulation,[14] as a subgoal of the synthesis of spirocycles. This intermediate would provide a platform structure for evaluating possibilities for the construction of the spirocyclic frameworks found in many natural products. The elaboration of the target octaline diol **18** began with the known bicyclic enone alcohol **13a**,[15] which was converted into the bis-OTBS protected acetoxy-enone **17** in four steps by the sequence shown in Scheme 3. TBS protection of the secondary hydroxyl group (TBSCl, DMF/imidazole, 0 °C, 24 h) followed by hydroboration (BH_3·Me_2S, H_2O_2/NaOH, EtOH, 8 h),



Scheme 2. Reagents and conditions: (a) MeLi, THF, –78 °C (86–90%); (b) $LiAlH_4/Et_2O$, 0 °C (99%); (c) 10% HCl/THF, 1:1, 4 °C, 12 h (99%); (d) TBSCl, DMF/imidazole, 0 °C, 2 h (87%); (e) PPh_3MeBr, *t*BuOK, PhMe, room temp., 4 h (94%); (f) TBAF/THF, 60 °C, 4 h (96%); (g) ethylene glycol, *p*-TosH, room temp. (95%); (h) 4 equiv. $Pb(OAc)_4$, benzene, 90 °C, 4 d (85%); (i) Ac_2O, Py, 4-DMAP, 80–100 °C (90%). (j) MTO, 30% H_2O_2, Py, CH_2Cl_2, room temp.(70%); (k) TMSOTf, collidine, PhMe, –40 °C (95%)



Scheme 3. Reagents and conditions: (a) TBSCl, DMF/imidazole, 0 °C, 24 h (89%). (b) $BH_3 \cdot Me_2S$, H_2O_2/NaOH, EtOH, 8 h (78%). (c) i. PCC, 3,5-DMP, 0 °C (62%), ii. TBSCl, DMF/imidazole, 0 °C, 1.5 h (91%); (d) $Pb(OAc)_4$, PhH, reflux, 4 d (90%); (e) $LiAlH_4/Et_2O$, 0 °C, 30 min (99%); (f) (*S*)-2-acetoxypropionyl chloride, DMAP, CH_2Cl_2, 0 °C, 30 min.

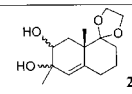
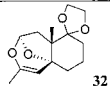
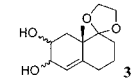
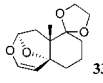
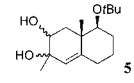
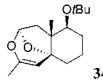
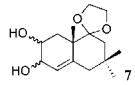
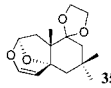
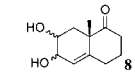
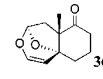
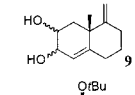
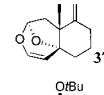
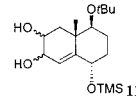
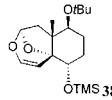
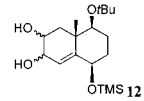
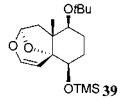
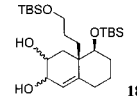
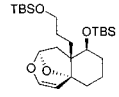
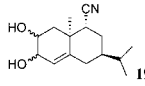
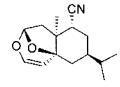
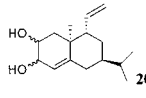
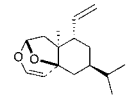
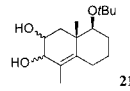
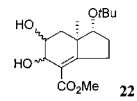
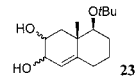
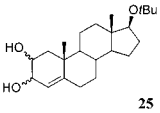
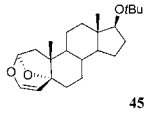
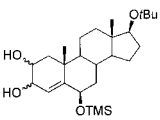
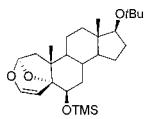
selective allylic oxidation (3,5-DMP, PCC, 0 °C), and TBS protection of the primary hydroxyl group as above. Conversion to the requisite diol was then accomplished by reduction with $LiAlH_4$.

For the synthesis of the (*R*)-(–)-carvone derived unsaturated bicyclic diols **19** and **20** (Table 1) a slightly modified de Groot procedure was employed.[16] Unsaturated diols **21**–**26** (Table 1) and their $Pb(OAc)_4$-mediated domino products, described in our previous work, were also examined in order to more fully document the functional-group compatibility of this domino process.

The Oxidant

It is clear that the $Pb(OAc)_4$-induced domino reaction is an effective one, but the use of two equivalents of $Pb(OAc)_4$ is a potentially hazardous process due to the toxicity of this oxidant. To satisfy Tietze's requirements,[17] various oxidants known to be efficient glycol fission reagents[18] were screened and compared for these domino reactions.[19] Accordingly, we undertook a systematic study with four oxidants (Table 1); studies with triphenylbismuth carbonate, which produces triphenylbismuth as a byproduct that is

Table 1. Reagents and conditions: 1) 1.2 equiv. of $PhI(OAc)_2$, in acetonitrile, 15–24 h at room temp.; 2) 4 equiv. of $Mn(OAc)_3$ in refluxing PhH; 3) 2 equiv. of Dess–Martin periodinane in dry PhMe, room temp. to 72 °C; 4) 1.5 equiv. of $Pb(OAc)_4$ in dry PhMe at room temp.

Entry	Substrate	Product	Oxidant (% yield)			
			IBD	$Mn(OAc)_3$	DMP	LTA
1	 2	 32	76	62	67	79
2	 3	 33	70	58	51	78
3	 5	 34	76	60	76	82
4	 7	 35	65	52	42	70
5	 8	 36	68	–	40	70
6	 9	 37	69	–	69	80
7	 11	 38	67	–	69	85
8	 12	 39	70	–	65	89
9	 18	 40	85	49	65	88
10	 19	 41	86	68	47	85
11	 20	 42	83	–	42	88
12	 21	 43	70	59	46	89
13	 22	 44	60	59	46	89
14	 23	 27	89	54	76	95
15	 25	 45	82	61	72	98
16	 26	 46	71	–	70	82

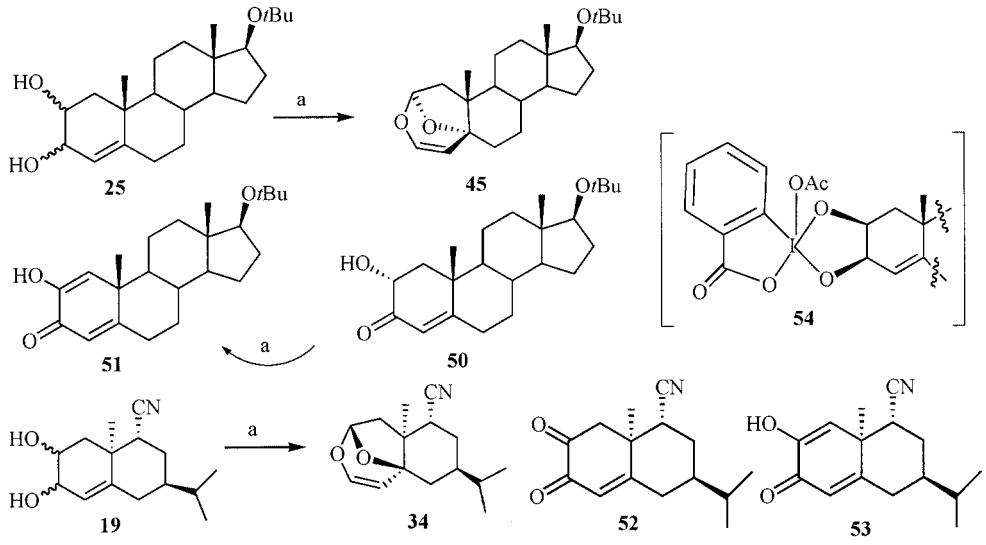
sometimes difficult to remove chromatographically, and sodium bismuthate, which is much less efficient, are not included in the table. A series of experiments were addressed to assess the factors involved in these domino transformations. The variables examined include: a) treatment of each one of the four possible diastereomers (two with a *cis*- and two with a *trans*-1,2-diol relationship) with the oxidant separately and as a diastereomeric mixture, b) a temperature range from room temperature to 85 °C, c) various solvents (MeCN, CH_2Cl_2, AcOH, $CHCl_3$, C_6H_6, toluene, trifluorotoluene, DMSO/toluene), and d) tuning of the stoichiometry.

Table 1 illustrates a wide range of substrates that undergo an efficient glycol fission/intramolecular bis-hetero Diels–Alder process when treated with iodobenzene diacetate (IBD), manganese(III) acetate, Dess–Martin periodinane (DMP), or lead tetraacetate (LTA); they all give good to excellent yields.

The product distribution for the oxidation of vicinal unsaturated diols with DMP as oxidant under various conditions was examined first.[20] Glycol cleavage using Dess–Martin periodinane was reported several years ago by Grieco et al.[21] Recently, Frigerio and Santagostino have reported that *o*-iodoxybenzoic acid (IBX) in DMSO is capable of oxidizing primary and secondary alcohols to aldehydes and ketones, and also 1,2-diols to either 1,2-dicarbonyl compounds or acyloins, without any oxidative cleavage of the glycol bond.[22] Recent work from Nicolaou et al. has shown that IBX is effective in converting saturated alcohols to α,β-unsaturated carbonyl systems[23] and in mediating processes for amino sugar construction,[24] and that IBX and DMP promote molecular diversity when treated with anilides and related compounds.[25]

Starting from a diastereomeric mixture of steroidal unsaturated 1,2-diol **25** in acetonitrile, the reaction with three equivalents of DMP was sluggish and only 15% of the corresponding cyclic ene-acetal **45** was obtained after stirring at ambient temperature for 20 h. The byproduct in this reaction was acyloin **50**, which arises as a consequence of allylic oxidation and which is further transformed to the ene-dione exclusively in its keto-enol form **51** (Scheme 4). with CH_2Cl_2 as solvent, in the presence of pyridine and a threefold excess of DMP, the half-cascade intermediate **45** was obtained in 40% isolated yield after stirring at room temperature for four hours. Better yields and faster rates were obtained in benzene or toluene (20 mL $mmol^{-1}$). In the optimized conditions, the experiments undertaken with two equivalents of DMP, in dry toluene (20 mL $mmol^{-1}$) from room temperature to 72 °C in about one hour uniformly gave rise to the type-**45** "half-cascade" intermediates, type-**50** acyloins, and type-**51** cross-conjugated hydroxydienones as the only detectable products (Scheme 4). The glycol fission is stereochemistry dependent; nevertheless, it constitutes a useful method for glycol fission and offers molecular complexity.

Running the reaction with only one equivalent of DMP repeatedly afforded a greater than 50% yield of tricyclic enol ether **45** along with the corresponding acyloin and the



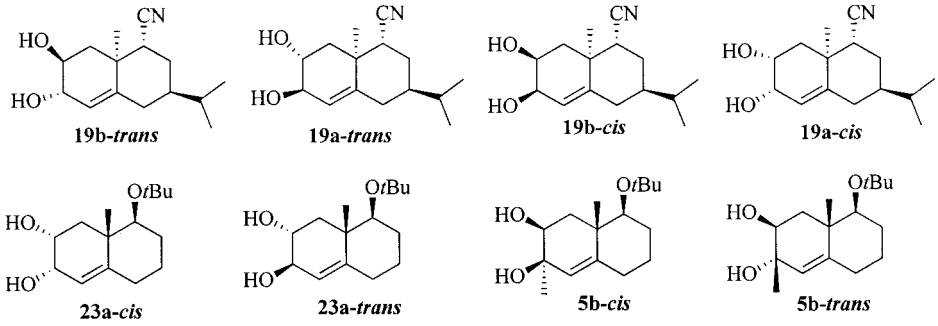
Scheme 4. Reagents and conditions: (a) 2 equiv. Dess–Martin periodinane in dry PhMe, room temp. to 72 °C

resulting cross-conjugated 2-hydroxydienone **51** (approx. 20% combined yield), thus corroborating a cyclic complex formation, such as **54** (Scheme 4), similar to the periodic acid mechanism proposed by Buist and Bunton.[26] Analogous results were obtained starting from the diastereomeric mixture **19**, the byproduct being the keto-enol form (**53**) of the diketone **52**, along with a small amount (<5%) of the allylic oxidation product as above.

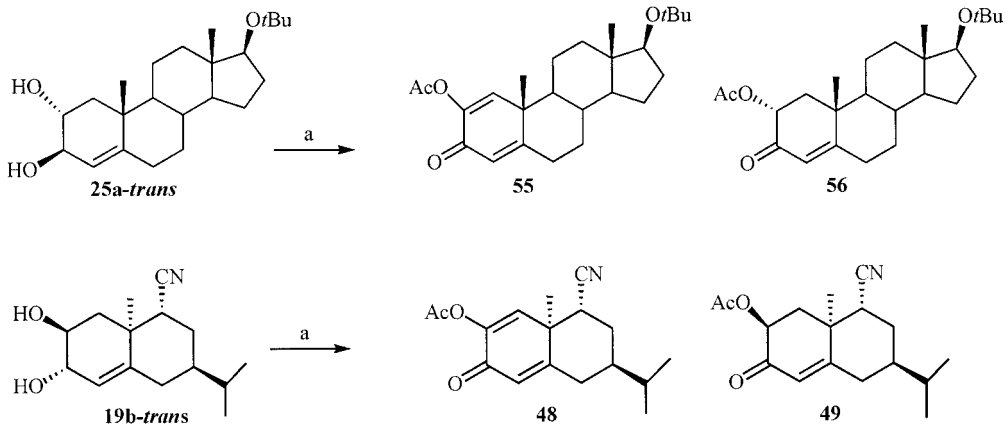
The domino transformations carried out on diastereomeric mixtures (all isomers present in various ratios, not always determined) proceeded in 42–76% isolated yields. To explore the influence of the 1,2-diol stereochemistry on product distribution and reaction rate, (*R*)-(–)-carvone derived diastereomerically pure diols **19**, as well as diols **5** and **23** derived from the Wieland–Miescher ketone and testosterone (**25**), were prepared and subjected separately to the Dess–Martin periodinane mediated oxidative cleavage. Some of the diastereomerically pure unsaturated 1,2-diols examined are portrayed in Scheme 5.

The reactivity pattern of four vicinal 1,2-diols **19** (**19β-*trans***, **19α-*trans***, **19β-*cis***, and **19α-*cis***), as well as **5**, **23**, and **25** was examined. The *trans* isomers **23α-*trans*** and **25α-*trans*** are completely resistant to both the glycol splitting reagents DMP and $Ph_3Bi(CO)_3$, while $Pb(OAc)_4$, $Mn(OAc)_3$, and $PhI(OAc)_2$ give glycol fission regardless of the stereochemistry of the starting diols. Unsaturated diols **19**, with a *cis*-1,2-OH relationship, afforded **41** (72%) cleanly, while the *trans* 1,2-diol **19β-*trans*** gave only allylic oxidation, which further evolved towards the hydroxydienone **53** (the keto-enol form of the corresponding diketone **52**), with no glycol fission (Scheme 6). The DMP oxidation of diastereomerically pure diols **5β-*trans*** and **5β-*cis*** followed an identical course as for the carvone derived analogs.

To obtain stable derivatives in the keto-enol form, the 2-acetoxy cross-conjugated dienone **55** was prepared from the steroidal diol **25α-*trans***. This could be achieved either stepwise or in one pot by adding Ac_2O/pyridine to the reaction mixture once formation of the enedione **52** was complete (TLC monitoring). Yields of enol-acetates generated by either the direct or two-step approach are comparable. When used as a diastereomeric mixture, **25** gave 72% of **45** along with 15% of the 2-hydroxy cross-conjugated dienone **51**. The 2-acetoxy cross-conjugated dienone **48** was also prepared straightforwardly, by a route similar to that employed for the synthesis of **55**, from the corresponding diol **19β-*trans***. This method is valid for all the unsaturated diols investigated in this study. The process tolerates a variety of substitution patterns and protecting groups (entries



Scheme 5. Some of the diastereomerically pure unsaturated 1,2-diols examined



Scheme 6. Reagents and conditions: (a) Dess–Martin periodinane (2 equiv.), dry PhMe, room temp. to 72 °C, ca. 1 h, then cool to 0 °C, Ac_2O/py, DMAP

1–16, Table 1). More interestingly, the oxidative-pericyclic hetero-domino reaction was successfully employed for the conversion of the tertiary-secondary unsaturated diols **2** and **5** to **32** and **34** in 67% and 76% yield, respectively, that is, the bis-hetero-intramolecular-Diels–Alder stage of the domino reaction, with a ketone component, carried out on a diastereomeric mixtures of the starting diols, works in high yields and offers stereo-cleaning and room for further selective transformations of the highly functionalized, rigid tricyclic framework. Even though such hetero-Diels–Alder cycloadditions are rare due to steric and electronic reasons,[27] intramolecular versions form part of an elegant multicomponent domino sequence developed by Tietze et al.[28] The process accommodates free carbonyl **8**, ketal protective groups (**2**, **3**, and **7**), **a** cyano group (**19**), an ester group (**22**), and an exocyclic double bond (**9**, **20**, Table 1). The mechanism of cleavage by DMP is consistent with a cyclic five-membered ring intermediate such as **54** (Scheme 4). Support for this proposal comes from the fact that the *cis* isomers of the bicyclic unsaturated diols are more reactive than the *trans* isomers: **19α-*cis*** and **19β-*cis*** undergo oxidative cleavage, while their **25α-*trans*** and **19β-*trans*** counterparts, which cannot form a cyclic intermediate, are inert towards cleavage (Scheme 6).

The $Mn(OAc)_3$-mediated[29] oxidative cleavage of unsaturated diols (Table 1) again generated molecular diversity along with the α-dicarbonyl derivatives and the corresponding cross-conjugated hydroxydienones as byproducts, in about 10–15% yield. Studies conducted on a series of diastereomerically pure diols showed that the yields and ratios are similar to those obtained starting from a diastereomeric mixture of diols. This clearly shows that the cleavage process is not dependent on the diol stereochemistry. The choice of solvent was found to be important in these transformations: replacing acetonitrile with benzene led to a decrease of the amount of side products and improved yields. When unsaturated diols were treated with four equivalents of $Mn(OAc)_3$ in dry and degassed benzene at reflux under argon, the reactions were generally complete within less than four hours. The rather low isolated yields (ca. 60%, despite a clean TLC) observed with manganese(III) acetate mediated tandem transformations can be attributed to the use of an excess of reagent and its purity.[30]

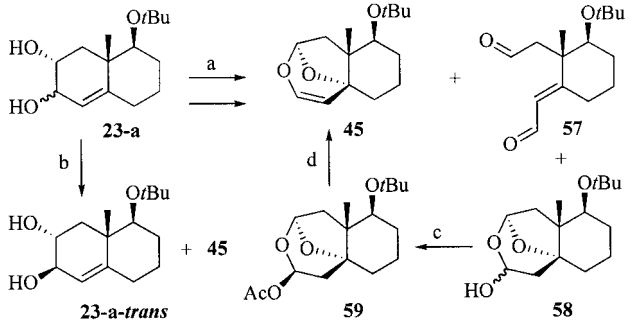
The process tolerates a variety of substitution patterns and protecting groups. The tertiary-secondary unsaturated diols **2**, **5**, as well as the ketal-protected **7** and the bis-TBS-protected **18** furnished **32**, **34**, **35**, and **40**, respectively, cleanly. Starting from steroidal unsaturated diol **25**, the other products formed alongside **45** were assigned as the allylic oxidation product **50** and the corresponding ene-dione, sometimes exclusively in its keto-enol form **51**. In all cases investigated the $Mn(OAc)_3$-mediated reaction furnished the cyclic ene-acetals (half-cascade intermediates) together with the allylic oxidation product and the keto-enol form of the corresponding diketone in variable yields (ca. 15%) that were not dependent upon the composition of the starting diastereomeric mixture.

The next oxidant studied was iodobenzene diacetate. Even though we did not find precedent for manganese(III) acetate mediated glycol cleavage in the literature, the $PhI(OAc)_2$-mediated oxidation of 1,2-diols has been known for a long time as a clean method for the cleavage of glycols.[31] Treatment of a series of unsaturated diols with iodobenzene diacetate ($PhI[OAc]_2$), in dichloromethane, acetonitrile, benzene, or toluene, at room temperature, gave cyclic ene-acetals by a sequential oxidative cleavage-intramolecular [4+2] cycloaddition.[32] Starting from carvone-derived diols **19** (entry 10), variation of the solvents gave the following results: in MeCN an 86% yield of **41** was obtained after chromatography, while yields were lower in toluene (75%), benzene (69%), trifluorotoluene (65%), dichloromethane (57%), and AcOH (53%). As a consequence of the above results, the optimized procedure involves use of dry acetonitrile and stirring, under an inert atmosphere, at room temperature for about 24 h. As with the two previous oxidants [DMP and $Mn(OAc)_3$], the process tolerates a variety of substitution patterns and protecting groups. The reaction is easy to perform, can be scaled up safely, and occurs efficiently irrespective of the diol stereochemistry. Domino transformations carried out on diastereomeric mixtures of

all the unsaturated 1,2-diols investigated (entries 1–16), uniformly gave rise to the "half-cascade" intermediates **32**–**46**, as the only detectable products in 60–89% yields (Table 1). Taking into account the level of molecular complexity attained in a one-pot transformation, the yields are quite high.

Finally, in the closing stage of this comparative study, the oxidative cleavage of unsaturated diols **23** with bismuth reagents was also evaluated in the hope of finding mechanistic similarities between Pb^{4+} and Bi^{5+}, two $5d^{10}$ oxidants. Watt et al. have investigated cleavage of unsaturated α-ketols using sodium periodate, sodium bismuthate, manganese dioxide, and lead tetraacetate, and found sodium periodate to be the best reagent.[33] Considerably lower yields of type-**45** "half-cascades" were obtained in the reaction of diol **23α**, derived from the Wieland–Miescher ketone, (and various diols from Table 1) and Ph_3BiCO_3, while a new compound was also obtained when sodium bismuthate was used as the oxidant.

Thus, using the procedure of Watt, **23α** was treated with $NaBiO_3$ in 50% aqueous AcOH at room temperature for 19 h (Scheme 7) to afford 15% of the half-cascade **45**, 5% of dialdehyde **57**, 28% of starting material **23**, and 44% of **58** (anomeric mixture). The latter was acetylated to the corresponding acetate **59** nearly quantitatively for characterization (pyridine, Ac_2O and a catalytic amount of DMAP, room temperature stirring while TLC monitoring; the stereochemistry of the major acetate is as depicted).



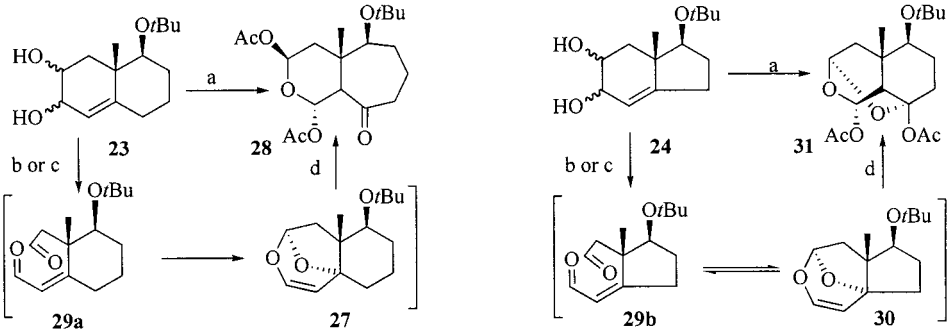
Scheme 7. Reagents and conditions: a) $NaBiO_3$, AcOH(H_2O, room temp., 19 h; b) Ac_2O, Py, DMAP, room temp., 3 h; c) 50 °C, 2 Torr, 5 h.

Oxidation of diol **23** with $NaIO_4$ leads to the dialdehyde **57**, along with about 20–30% of tricyclic enol ether **45**. Allowing this reaction mixture to stand gave no more **45**, even after addition of further oxidant. Instead, a geometrical isomerization of the initially formed dialdehyde was observed. This result probably indicates that, in the lead tetraacetate mediated domino transformations, a catalytic action exists in the cyclization process, with the Pb^{4+} playing the role of a Lewis acid to catalyze the intramolecular bis-hetero [4+2] cycloaddition after previously acting as an oxidizer.

The last three oxidants we tried were PDC, PCC, and a mixture of tetra-*N*-propylammonium perruthenate and *N*-methylmorpholine *N*-oxide (TPAP-NMO). It is known that chromium-based reagents lead to a cleavage of vicinal diols,[34] but in our hands PDC or PCC failed to produce any glycol fission, as did a mixture of tetra-*N*-propylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO), which has been used by Wiberg et al. for glycol fission in their studies on bridged spiropentanes.[35]

Thus, after a detailed examination of various oxidants and substrates, $Pb(OAc)_4$ was found to be the only oxidant capable of completing the present domino reaction to give the ring-expanded products of type **II**; the others stopped at the halfway domino system, the cyclic ene-acetals of type **III** (Scheme 1). From a synthetic point of view it would, of course, be more environmentally friendly to be able to at least effect a consecutive domino transformation using two oxidants of different toxicity. We therefore examined the combined use of other oxidants and discovered that a combination of manganese(III) acetate and $Pb(OAc)_4$ or iodobenzene diacetate and $Pb(OAc)_4$ proved to be as effective as $Pb(OAc)_4$ alone. Scheme 8, which illustrates the notion of incorporating a (supposedly) less-toxic oxidant, such as $Mn(OAc)_3$ or $PhI(OAc)_2$, that is capable of carrying out the first two hetero-domino transformations, details our first attempts at reducing this concept to practice.

The reaction was carried out in a single reaction vessel and the best yields were obtained using acetonitrile as solvent for the octaline-diol series, while toluene was equally efficient for the hydrindene-diol series. The equilibrium mixture of **29b** and **30**, obtained from diols **24** upon treatment with either $Mn(OAc)_3$ or $PhI(OAc)_2$, readily under-



Scheme 8. Reagents and conditions: (a) 2.4 equiv. of $Pb(OAc)_4$ in dry MeCN, –20 °C to room temp.; (b) 1.2 equiv. of $PhI(OAc)_2$ in acetonitrile, 15–24 h at room temp.; (c) 4 equiv. of $Mn(OAc)_3$ in refluxing MeCN; (d) 1.2 equiv. of $Pb(OAc)_4$ in dry MeCN at room temp.

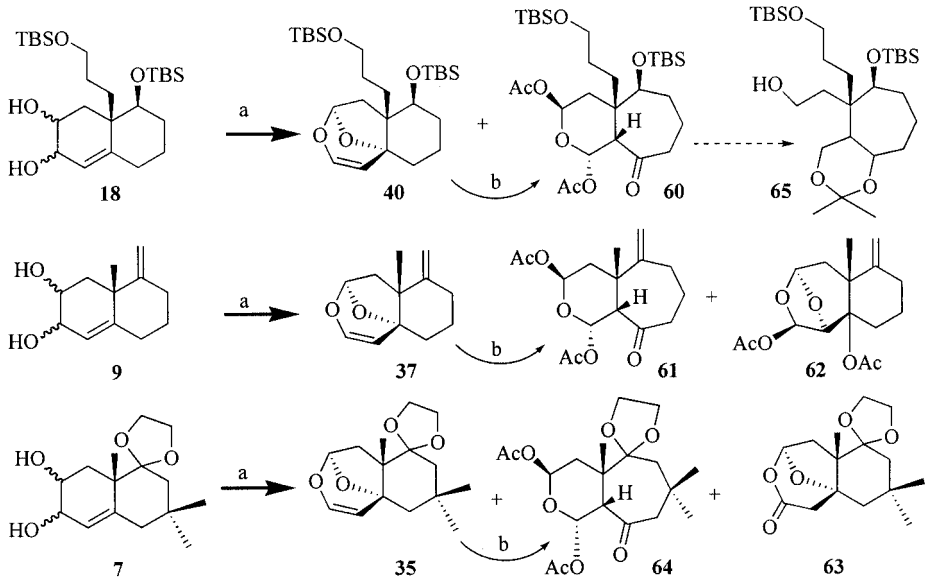
went oxyplumbation-ring expansion upon addition of one equivalent of $Pb(OAc)_4$ to the reaction vessel to give the full-cascade product **31** in remarkably high yield (ca. 82%). The cyclic ene-acetal **30** in the hydrindene-diol series could only be characterized as an equilibrium mixture with its dialdehyde counterpart **29b** by NMR techniques, although a few exceptions exist (entry 13, Table 1). In the higher homologue, octaline-diol series, all the half-cascade products are isolable and stable, and some interesting chemistry can be done to give access to bicyclic or steroidal lactones.[36] Thus, treatment of octaline-diols **23** with either manganese(III) acetate or iodobenzene diacetate yielded the half-cascade intermediates **27** cleanly (54 and 89% yield, respectively, compared to a 95% yield obtained with lead tetraacetate), which was converted into the ring-expanded intermediate **28** upon subsequent addition (one pot) of $Pb(OAc)_4$. Based on the above results, a hetero-domino reaction initiated by iodobenzene diacetate, Dess–Martin periodinane, or $Mn(OAc)_3$ (oxidative/pericyclic), and another one upon addition of lead tetraacetate (oxidative/cationic), can be performed sequentially to afford high molecular complexity after a ring expansion. According to Tietze's classification, the process is a consecutive hetero-domino reaction where the olefin is the sine qua non for the generation of diversity, while $Pb(OAc)_4$ remains the reagent that affords the highest degree of diversity. In the absence of the latter the process is interrupted halfway through and the resulting products of type **27** or **30** are called "half-cascade" products in our earlier publications. Prolonged stirring at room temperature in the presence of a threefold excess of iodobenzene diacetate did not produce any traces of the type-**28** or -**31** ring-expanded products, even after refluxing for three days in acetonitrile, benzene, or toluene. However, heating at reflux in acetic acid gave ring-expanded products in the hydrindene-diol series, albeit in very low yields (ca. 20%). The one-pot preparation of the ring-expanded molecule **31** was accomplished on a large scale (10–20 g) by a controlled iodobenzene diacetate oxidative cleavage of the unsaturated diols **24** and subsequent lead tetraacetate mediated ring enlargement.

The Substitution Pattern

$Pb(OAc)_4$-mediated cleavage in acetic acid, followed by hydrolytic treatment, was successfully used in our previous studies to form seven-membered-ring carbocycles.[5] The process generally afforded three compounds, among which the ring-expanded type-**II** (Scheme 1) derivatives were the major products of the reaction. Minor products were identified as the type-**VII** lactone and the type-**III** half-cascade derivatives, which could be re-subjected to the domino conditions to afford more type-**II** products. The choice of solvent was found to be crucial in these transformations: $Pb(OAc)_4$ gave the ring-expanded derivatives in yields of 45–82% from the diols if acetic acid was used as solvent, and a similar yield was obtained with acetonitrile as solvent, although the required reaction time for the domino process to complete was much higher (15 h versus 48 h respectively). Toluene, benzene, and trifluorotoluene gave mainly half-cascade products, even after prolonged treatment. The dramatic reduction in reaction time when using carboxylic acids as solvent is noteworthy. The observed solvent effect on the rate of cascade transformations can be rationalized by examining the proposed mechanism of this reaction sequence.[7]

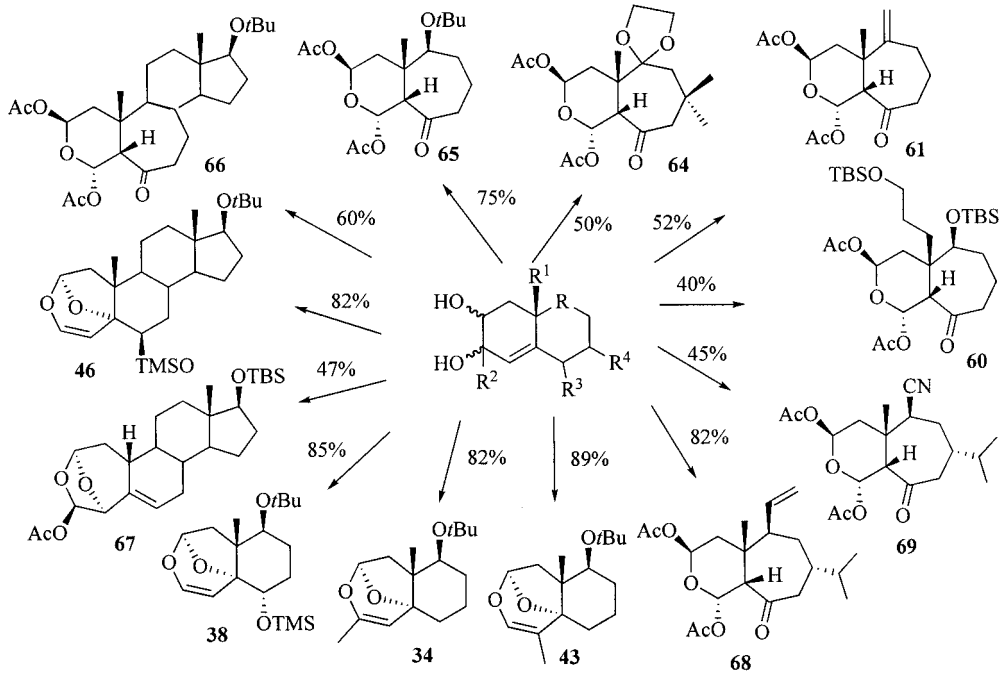
The question of whether a change in substitution pattern can alter the reaction course of the domino transformation has already been the concern of our preliminary communications. As we reported, the pathway of such $Pb(OAc)_4$-mediated domino reactions depends crucially on the substrate's substitution pattern[37] and the solvent.[38] An interesting feature of the domino reaction is that it can be effected on angularly alkoxy-substituted unsaturated diol systems such as **18**. Thus, we chose to examine an allyl group in the angular position, since this group might be transformed later into a variety of functional groups via **65**, which is obtainable by a reductive treatment followed by a selective acetonide formation according to our published procedures. This intermediate would provide a platform structure for evaluating possibilities for stereocontrolled spirocycle construction. The angularly functionalized alkoxy octaline-diol **18** underwent clean hetero-domino transformations, modulable by stoichiometry, to afford either cyclic ene-acetal **40** or the spirocyclic precursor **60** in good yields upon treatment with 1.2 or 2.4 equiv. of lead tetraacetate, respectively (Scheme 9). The half-cascade intermediate **40** can be recycled, as pre-formation of **40** under the 1.2 equiv. conditions and further treatment with lead tetraacetate led to an efficient domino transformation to deliver **60**. In the case of diols **9**, the alternative rearrangement pathway[36] leading to **61** (52%) competes to a minor, although significant, extent with the normal mode of rearrangement involving ring expansion, to produce the rearranged species **62** (6%). This was the first case of a domino reaction with a β-face attack of the metal and was a worrisome outcome until we realized that is almost surely due to the absence of the O*t*Bu substituent which pushes the angular methyl group closer to the olefin (competing C5–C10 and 1,2-oxygen migrations). Pre-formation of half-cascade **37** (80% yield) upon treatment with one equivalent of $Pb(OAc)_4$ also led to an efficient domino transformation (oxidative/cationic) to deliver **61** in 55% yield. In both cases, the ring-enlarged compound **61** was produced as the major component of a chromatographically separable mixture of two rearrangement products. Taking into account the level of molecular complexity attained in an one-pot transformation, the yields are quite good to high.

Treatment of diols **7** with lead tetraacetate in acetic acid, at room temperature, cleanly afforded the corresponding ring-expanded intermediate **64** in 50% isolated yield along with the cyclic ene-acetal **35** (6%), which could be resubjected to the domino conditions to give more of the ring-expanded product. The other product formed alongside **35** and **64** was assigned as the lactone **63** (20%).



Scheme 9. Reagents and conditions: (a) 2.4 equiv. $Pb(OAc)_4$, AcOH, room temp., 17 h; (b) 1.2 equiv. $Pb(OAc)_4$, AcOH, room temp., 17 h

The presence of allylic or vinylic substituents (entries 1, 3, 7, 8, 12, 13, and 16) is a chief factor controlling the competition between "half" and "full cascade", while the distribution is not altered by the presence of either an electron-donating or -withdrawing group (entries 12 and 13). Thus, substitution at the allylic position and at the olefin resulted in the interruption of the domino process at the half-cascade levels (**32**, **34**, **38**, **39**, **43**, **44**, and **46** in Table 1) even after addition of excess lead tetraacetate and prolonged stirring or heating. In all these cases, upon addition of extra oxidant [up to three more equivalents of $Pb(OAc)_4$] the second half of the domino process was sluggish and mainly the half-cascade intermediates could be recovered from the reaction mixture even after prolonged reaction time (up to three days) and heating. From these results, it is highly likely that completion of the domino process (oxyplumbation-ring expansion) is affected by the steric accessibility of the electron-rich olefin resulting from the [4+2] cycloaddition. Since both donors or acceptors lead to the same reaction outcome, electronic factors can be ruled out. Formation of **60**, **61**, and **64** shows that the process accommodates primary-secondary TBS protective groups, an olefin, and a ketal-protective group, respectively (Scheme 10).[39]



Scheme 10. Reagents and conditions: 2.4 equiv. $Pb(OAc)_4$ in AcOH at room temp.

As shown in Scheme 10, oxidative cleavage furnished good yields of ring-expanded "full-cascade" intermediates in cases where $R^2 = R^3 = H$, $R_1 \neq H$, and R, R^4 = a plethora of functional or protecting groups (**60**, **61**, **64**, **65**, **66**, **68**, and **69**), while the process was completely interrupted at the half-cascade stage in the presence of allylic or vinylic substituents (e.g. **34**, **38**, **43**, and **46**). The main results of this and previous work, assembled in Scheme 10, demonstrate a marked substituent effect.

Conclusions

We have investigated the feasibility of our domino process with a number of other oxidants, the majority of which are known to promote glycol fission. The key observations are simply summarized as follows: among the oxidants screened, Dess–Martin periodinane, $Mn(OAc)_3$, $PhI(OAc)_2$, $NaIO_4$, $NaBiO_3$, and Ph_3BiCO_3 cause cleavage of vicinal diols, while TPAP-NMO, PDC, PCC, or $Pd(OAc)_2$ give allylic oxidation essentially quantitatively and no cleavage is detected. The $Mn(OAc)_3$-, DMP-, and $PhI(OAc)_2$-mediated transformations differ from those mediated by $Pb(OAc)_4$ in several fundamental respects, such as the degree of molecular diversity generated, the reaction rate, the temperature, the yields, and finally the side products. While no side-product formation was observed with lead tetraacetate and iodobenzene diacetate, manganese(III) acetate (irrespective of the diol stereochemistry) and Dess–Martin periodinane (depending on the stereochemistry of starting diols) gave rise to allylic oxidation and subsequent re-oxidation toward the corresponding diketone, and hence to the cross-conjugated analog, albeit in low yields. The most noteworthy difference between the oxidants used in this investigation is the fact that $Mn(OAc)_3$, Dess–Martin's periodinane, $PhI(OAc)_2$, $Ph_3Bi(CO)_3$, $NaIO_4$, and $NaBiO_3$ failed to effect the "full cascade" leading to the ring-expanded products normally obtained from $Pb(OAc)_4$-mediated domino transformations. Attempts to replace $Pb(OAc)_4$ entirely with other, less-toxic oxidants, especially $PhI(OAc)_2$, failed under the same mild conditions. On the other hand, $Pb(OAc)_4$ and $PhI(OAc)_2$ both effect the cleavage in a variety of solvents at room temperature irrespective of the stereochemistry of the hydroxyl groups.

None of the alternative conditions proved superior to $Pb(OAc)_4$, which ensures the mildest conditions, the highest yields, and the highest molecular diversity due to its ability to perform different tasks − it acts as an oxidizing agent and as a Lewis acid − during the same reaction. Of the other oxidants investigated, those based on hypervalent iodine proved the most satisfactory.[40] The domino reaction is very sensitive to the substitution pattern of the byciclic framework; we have demonstrated that allylic and vinylic substitution interrupts the process at the half-cascade level.

Experimental Section

General: All 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 in 5% phosphomolybdic acid in 95% ethanol. "Usual workup" means washing of the organic layer with brine, drying with 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 spectroscopic data (400, 300, 250 and 100, 75, 69.5 MHz respectively, 1D and 2D experiments) and corroborated by spatial proximity (n.O.e) studies using mainly the 1D NOEDIFF technique.[41] ^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.[42] 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, are abbreviated as ESIMS (MeOH). HR is added for the high-resolution mass measurements (HRESIMS).

The required unsaturated diols were prepared straightforwardly, in their optically pure form, following published procedures.[23] Commercial $Mn(OAc)_3$, $PhI(OAc)_2$, 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. The assignment of the stereochemistry of the ring system was made on the basis of diagnostic NOEs of the various structural isomers. The relative stereochemistry was deduced from the magnitudes of vicinal coupling constants and corroborated by 1D difference NOE experiments.

General Procedure for the Acetoxylation with LTA to Form Acetoxy Octalones: A dry three-necked flask, equipped with a Dean–Stark apparatus, was charged with the octalone (12.0 mmol) and $Pb(OAc)_4$ (48.0 mmol, 4.0 equiv.). It was then evacuated and 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 three days. After cooling, a large volume of diethyl ether was added and the reaction mixture stirred for an additional hour, filtered, and the filtrate washed with brine and water, dried with $MgSO_4$, concentrated, and purified by chromatography on silica with heptane/EtOAc (5:1) as eluent to afford 70–90% of a nearly 1:1 mixture of the desired acetoxy enones.

General Procedure for the Reduction of Acetoxy Enones: A solution of the acetoxy enone (4.0 mmol, 1.0 equiv.) in anhydrous diethyl ether (50 mL) was added dropwise to a magnetically stirred suspension of $LiAlH_4$ (8.0 mmol, 2.0 equiv.) in 50 mL of anhydrous Et_2O, cooled to nearly 0 °C. 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 6 N NaOH solution (for each gram of $LiAlH_4$ 1 mL of water, 1 mL of 6 N NaOH, and 3 mL more of water were added). The organic layer was worked up as usual to give, after silica gel chromatography (eluent: heptane/EtOAc), yields of more than 95% of the desired diols.

Domino Transformations: The yields given in Table 1 refer to spectroscopically and chromatographically (silica gel) homogeneous materials.

General Experimental Procedure for the Lead Tetraacetate Mediated Oxidative Cleavage. Modulation by Stoichiometry: The solid unsaturated diol (1.0 mmol) and $Pb(OAc)_4$ (1.2 mmol) were placed in a flame-dried flask, which was evacuated and then flushed with argon. The flask was then cooled to –20 °C and 5 mL of acetonitrile was added. The ice bath was removed soon afterwards and the mixture was stirred at room temperature whilst monitoring by TLC. After TLC analysis indicated consumption of the starting diol and conversion of the intermediate dialdehyde into the cyclic ene-acetal (ca. 12 h), the reaction mixture was diluted with acetonitrile, filtered through Celite, and the filtrate concentrated and purified by silica gel chromatography using heptane/EtOAc as eluent to afford the desired half-cascade intermediate in high yields. Similar results were obtained running the domino reaction in toluene, trifluorotoluene, benzene, dichloromethane, or acetic acid. No side products were produced.

General Experimental Procedure for Oxidation with $Mn(OAc)_3$: A dry flask was charged with 1.0 mmol of diol and 4.0 mmol of $Mn(OAc)_3$, then evacuated and flushed with argon several times. Sodium-dried, degassed benzene (20 mL) was then added and the resulting mixture was stirred at reflux, whilst removing water with a Dean–Stark trap, until TLC monitoring showed no remaining starting material (ca. 4 h). The cooled mixture was diluted with EtOAc, filtered through Celite, and washed with 1 N HCl, saturated aq. $NaHCO_3$, and brine. The organic layers were dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by silica gel flash column chromatography (eluent: heptane/EtOAc). Regardless of the diol stereochemistry, 2-hydroxy cross-conjugated dienones were observed as side products.

General Experimental Procedure for Oxidation with DMP: A dry flask was charged with the starting diol (1.0 mmol) and DMP (2.0 mmol, 2.0 equiv.), then evacuated and flushed with argon several times. Sodium-dried toluene (20 mL) was then added and the reaction mixture was gently heated to 72 °C (oil bath temperature) in about 20 min, and stirred at this temperature for 30–60 min, at which point TLC indicated complete consumption of the starting diol. After cooling, dilution with EtOAc, washing with a saturated aqueous solution of sodium hydrogen carbonate and brine, drying over $MgSO_4$, and concentration under reduced pressure gave crude product which was purified on silica gel by flash column chromatography (eluent: heptane/EtOAc). Depending on the diol stereochemistry, 2-hydroxy cross-conjugated dienones were observed as side products.

General Experimental Procedure for Oxidation with $PhI(OAc)_2$: A dry flask was charged with 1.0 mmol of unsaturated diol and 1.2 mmol of $PhI(OAc)_2$, then evacuated, flushed with argon several times, and cooled to 0 °C. Acetonitrile (10 mL) was then added and the cooling bath removed soon after. It should be pointed out that when the reactions were run without special precautions, such as solvent degassing, drying of the reagent, and vacuum-flushing cycles, the yields were comparable. The mixture was stirred at room temperature for 24 h (TLC monitoring), then diluted with dichloromethane, washed with a saturated aqueous solution of $NaHCO_3$, water, and brine, and then dried and concentrated. The residue was chromatographed on silica gel using heptane/EtOAc as eluent. No side products were produced.

General Experimental Procedure for the Full-Cascade: A dry flask was charged with unsaturated diol (1.0 mmol) and $Pb(OAc)_4$ (2.4 mmol), then evacuated, flushed with argon several times, and cooled to 0 °C. Acetic acid (5 mL) was added, the cooling bath removed soon after, and the reaction mixture stirred for 17 h at room temperature. The mixture was diluted with EtOAc and washed carefully with sat. $NaHCO_3$ solution to neutral pH, and then washed again with brine. The organic layer was concentrated under reduced pressure, dried with $MgSO_4$, and purified by flash chromatography using heptane/EtOAc as eluent to afford the ring-expanded intermediate as the major component of a mixture of three compounds, which also contains the half-cascade product, which can be recycled, and a lactone derivative.

Preparation of Acetoxy Enones 1: The acetoxylation was performed according to the general procedure for the acetoxylation of octalones on a 12 mmol (26.64 g) scale to afford the α- and β-acetates (30.24 g, 90%) in a nearly 1:1 ratio. An analytical sample was purified on SiO_2 by flash chromatography (eluent: EtOAc/heptane, 1:1).

1α-OAc: IR (film): $\tilde{\nu}$ = 2951, 2878, 1751, 1695, 1669, 1620, 1446, 1376, 1334, 1223, 1158, 1116, 1073, 1052, 1020, 949, 916, 874 cm^{-1}. ^1H NMR (300 MHz): δ = 1.47 (s, 3 H), 1.53–1.94 (m, 4 H), 1.88 (dd, J = 5.6, 12.4 Hz, 1 H), 2.15 (s, 3 H), 2.21–2.46 (m, 2 H), 2.37 (t, J = 13.3 Hz, 1 H), 3.80–4.09 (m, 4 H), 5.42 (dd, J = 5.6, 14.3 Hz, 1 H), 5.79 (d, J = 1.8 Hz, 1 H) ppm. Diagnostic NOEs: {Me-10}: H-2, H-1β eq.; {H-2}: Me-10. ^{13}C NMR (75 MHz): δ = 20.5, 20.6, 21.1, 28.9, 30.7, 32.2, 46.6, 64.6, 65.1, 71.1, 111.3, 123.2, 167.2, 169.7, 192.8 ppm. ESIMS (MeOH): m/z (%) = 319 (25) $[MK]^+$, 303 (100) $[MNa]^+$, 281 (6) $[MH]^+$. $C_{15}H_{20}O_5$ (280.13): calcd. C 64.27, H 7.19; found C 64.16, H 7.22.

1β-OAc: IR (film): $\tilde{\nu}$ = 2953, 2876, 1750, 1695, 1669, 1620, 1334, 1225, 1154, 1118, 1075, 1052, 1020, 916, 871 cm^{-1}. ^1H NMR (300 MHz): δ = 1.32 (s, 3 H), 1.50–1.74 (m, 1 H), 1.62 (t, J = 13.5 Hz, 1 H), 1.79–1.92 (m, 3 H), 2.15 (s, 3 H), 2.22 (m, 1 H), 2.47 (dd, J = 2.5, 12.3 Hz, 1 H), 2.55 (dd, J = 6.6, 13.8 Hz, 1 H), 3.90–4.20 (m, 4 H), 5.78 (dd, J = 6.6, 12.9 Hz, 1 H), 5.85 (d, J = 1.6 Hz, 1 H) ppm. Diagnostic NOEs: {Me-10}: H-1β axial (inverted half-chair) ppm. ^{13}C NMR (75 MHz): δ = 20.6, 23.3, 26.0, 30.1, 31.2, 34.3, 46.6, 64.5, 65.3, 71.6, 113.5, 122.5, 166.5, 169.7, 193.8 ppm. ESIMS (MeOH): m/z (%) = 319 (33) $[MK]^+$, 303 (100) $[MNa]^+$, 281 (4) $[MH]^+$. $C_{15}H_{20}O_5$ (280.13): calcd. C 64.27, H 7.19; found C 64.02, H 7.30.

Preparation of Tertiary-Secondary Alcohols 2 and 5 and Their Oxidative Cleavage: The tertiary-secondary alcohol **2b-*cis*** was prepared straightforwardly. THF (10 mL) and MeLi (1.5 M, 37 mL, 55.7 mmol, 12 equiv.) were added dropwise to a stirred solution of the acetoxy enone **1β-OAc** (1.30 g, 4.64 mmol) cooled to –78 °C under argon. The reaction mixture was stirred at –78 °C for 30 minutes, quenched with sat. NH_4Cl solution, diluted with EtOAc, and worked up as usual. Silica gel flash column chromatography with heptane/EtOAc (3:1) as eluent afforded 1.06 g (90%) of the desired diol.

2b-*cis*: M.p. 144–145 °C (hexane/EtOAc). IR (film): $\tilde{\nu}$ = 3401, 2937, 2885, 1664, 1461, 1440, 1370, 1342, 1181, 1117, 1093, 1077, 1062, 938, 872, 859 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 6 H), 1.19 (dd, J = 10.4, 14.3 Hz, 1 H), 1.41 (m, 1 H), 1.55–1.80 (m, 3 H), 1.97 (m, 1 H), 2.16 (dd, J = 4.6, 14.2 Hz, 1 H), 2.26 (m, 1 H), 2.35 (br. s, 2 H), 3.86–4.04 (m, 4 H), 3.95 (dd, J = 4.6, 10.5 Hz, 1 H), 5.37 (d, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 21.6, 23.5, 25.8, 30.0, 30.2, 35.4, 45.0, 64.5, 65.0, 72.5, 73.6, 113.3, 128.5, 141.5 ppm. ESIMS (MeOH): m/z (%) = 277 (100) $[MNa]^+$. $C_{14}H_{22}O_4$ (254.15): calcd. C 66.12, H 8.72; found C 66.31, H 8.87.

While the initial ^1H and ^{13}C NMR characterization of **2b-*cis*** was done with $CDCl_3$ as solvent, the assignment of the stereostructure for **2b-*cis*** was made in C_6D_6 as tentative assignment of the C2/C3-

diol stereochemistry by analogy to the O*t*Bu counterpart **5** did not allow an unambiguous assignment for the configurations at C-2 and C-3 to be made. In both solvents the ring protons resonate as distinct multiplets, whereas the two methyl groups resonate as overlapping singlets at δ = 1.20 ppm in $CDCl_3$ and undergo a solvent shift in C_6D_6 such that they appear as singlets at δ = 1.31 and 1.40 ppm, which can be assigned to the C-10 and C-3 methyl groups, respectively.

^{1}H NMR (300 MHz, C_6D_6): δ = 1.31 (s, 3 H), 1.40 (s, 3 H), 1.46 (dd, *J* = 10.4, 14.3 Hz, 1 H), 1.92 (m, 1 H), 1.50–1.76 (m, 4 H), 2.06–2.2 (m, 4 H), 2.47 (dd, *J* = 4.6, 14.3 Hz, 1 H), 3.44–3.67 (m, 4 H), 5.53 (d, *J* = 1.4 Hz, 1 H) ppm. Diagnostic NOEs: {Me-3}: H-4; {Me-10}: H-1β; {H-2}: H-1β; {H-1β}: H1; {H-4}: Me-3, H-6 eq. ^{13}C NMR (75 MHz, C_6D_6): δ = 22.5, 24.0, 25.9, 30.4, 30.9, 35.7, 45.2, 64.7, 65.0, 72.2, 74.2, 114.0, 129.0, 142.0 ppm.

Oxidative cleavage of **2** was achieved following the general procedures (see Table 1 for yields) to afford **32** [silica gel flash column chromatography with heptane/EtOAc (7:1) as eluent].

32: M.p. 114–115 °C (heptane/diethyl ether). IR (film): $\tilde{\nu}$ = 2951, 1667, 1438, 1381, 1258, 1170, 1141, 1110, 1068, 1050, 1032, 996, 953, 936, 918, 892 cm^{-1}. ^{1}H NMR (300 MHz): δ = 1.26 (s, 3 H), 1.28–2.03 (m, 7 H), 1.72 (s, 3 H), 2.48 (dd, *J* = 5.8, 13.7 Hz, 1 H), 3.84–3.91 (m, 2 H), 3.96–4.05 (m, 2 H), 4.57 (s, 1 H), 5.60 (d, *J* = 5.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 17.3, 18.4, 19.0, 28.7 (2C), 43.4, 57.2, 63.1, 65.3, 83.8, 99.6, 105.0, 111.2, 147.0 ppm. ESIMS: *m*/*z* (%) = 252 (0.5) [M]$^+$, 99 (50), 55 (30), 43 (100). $C_{14}H_{20}O_4$ (252.13): calcd. C 66.65, H 7.99; found C 66.95, H 8.18.

A dry flask was charged with hydroxy enone **1β-OH** (400 mg, 1.6 mmol), evacuated, flushed with argon, and then cooled to –78 °C. THF (10 mL) was added and the reaction mixture was stirred at this temperature for 5 min, after which time a 1.5 M solution of MeLi (4.5 mL, 6.8 mmol, 4.3 equiv.) was added dropwise. The resulting mixture was stirred at –78 °C for 30 min, then quenched with a saturated solution of NH_4Cl, diluted with EtOAc, and worked up as usual. Flash chromatography (eluent: heptane/EtOAc, 3:1) afforded 365 mg (86%) of a mixture of **5-*cis*** and **5-*trans*** in a nearly 1:1 ratio.

5β-*cis*: M.p. 100–102 °C (heptane/EtOAc). $[\alpha]_D^{20}$ = –21 (*c* = 2.25, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3401, 2973, 1659, 1469, 1362, 1231, 1190, 1070, 1050, 1018, 967, 894, 858 cm^{-1}. ^{1}H NMR (300 MHz): δ = 1.10 (s, 3 H), 1.21 (s, 9 H), 1.31 (s, 3 H), 1.42 (dd, *J* = 11.6, 13.8 Hz, 1 H), 1.45–1.95 (m, 7 H), 2.12 (dd, *J* = 3.6, 13.8 Hz, 1 H), 2.21 (dd, *J* = 4.6, 13.8 Hz, 1 H), 3.20 (dd, *J* = 4.6, 10.9 Hz, 1 H), 3.52 (dd, *J* = 3.6, 11.6 Hz, 1 H), 5.31 (s, 1 H) ppm. Diagnostic NOEs: {Me-3}: H-2, H-4; {H-2}: H-9; {H-9}: H-2. ^{13}C NMR (75 MHz): δ = 20.8, 25.6, 26.6, 29.0 (3C), 30.6, 31.1, 36.9, 42.7, 69.4, 71.0, 73.3, 74.1, 125.1, 147.9 ppm. ESIMS: *m*/*z* (%) = 268 (0.1) [M]$^+$, 194 (40), 161 (24), 57 (100). $C_{16}H_{28}O_3$ (268.20): calcd. C 71.60, H 10.52; found C 71.89, H 10.53.

5β-*trans*: $[\alpha]_D^{20}$ = –12 (*c* = 2.05, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3401, 2974, 2935, 1651, 1469, 1388, 1363, 1246, 1188, 1068, 1017, 937, 894, 845 cm^{-1}. ^{1}H NMR (300 MHz): δ = 1.00 (s, 3 H), 1.21 (s, 9 H), 1.24 (s, 3 H), 1.50–2.00 (m, 6 H), 2.15 (bdt, *J* = 4.1, 12.9 Hz, 1 H), 2.27 (dd, *J* = 4.1, 13.9 Hz, 1 H), 2.75–3.00 (m, 2 H), 3.23 (dd, *J* = 4.6, 10.7 Hz, 1 H), 3.78 (dd, *J* = 4.1, 12.9 Hz, 1 H), 5.25 (s, 1 H) ppm. Diagnostic NOEs: {Me-3}: H-1β, H-4; {H-2}: H-9; {H-9}: H-2. ^{13}C NMR (75 MHz): δ = 21.1, 22.0, 25.6, 29.0 (3C), 30.7, 30.8, 37.2, 43.0, 72.7, 73.3, 73.7, 73.9, 126.9, 144.0 ppm. HRESIMS calcd. for $C_{16}H_{28}NaO_3$: *m*/*z* = 291.1936; found 291.1941.

Oxidative cleavage of **5** was achieved following the general procedures (see Table 1 for yields) to afford **34** [silica gel flash column chromatography with heptane/EtOAc (8:1) as eluent].

34: $[\alpha]_D^{20}$ = –7 (*c* = 2.24, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2972, 2940, 2870, 1671, 1464, 1448, 1383, 1365, 1296, 1253, 1193, 1141, 1066, 1016, 943, 875, 788 cm^{-1}. ^{1}H NMR (300 MHz): δ = 1.04 (s, 3 H), 1.18 (s, 9 H), 1.25–1.80 (m, 7 H), 1.71 (s, 3 H), 2.40 (dd, *J* = 5.9, 14.2 Hz, 1 H), 3.37 (dd, *J* = 3.5, 11.5 Hz, 1 H), 4.51 (s, 1 H), 5.61 (d, *J* = 5.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 12.7, 18.9, 19.8, 29.0, 29.2 (3C), 29.7, 46.6, 55.2, 72.8, 73.5, 84.3, 99.0, 104.5, 146.6 ppm. ESIMS (MeOH): *m*/*z* (%) = 305 (35) [MK]$^+$, , 289 (55) [MNa]$^+$, 267 (28) [MH]$^+$. HRESIMS calcd. for $C_{16}H_{26}NaO_3$: *m*/*z* = 289.1779; found 289.1772.

Preparation and Oxidative Cleavage of 7: The *gem*-dimethyl substrate **7** prepared using the Heathcock procedure was acetoxylated and then reduced to the diol following the general procedures above. Oxidative cleavage of **7** was achieved using the general procedures (see Table 1 for yields) to afford **35** [silica gel flash column chromatography with heptane/EtOAc (8:1) as eluent].

35: IR (film): $\tilde{\nu}$ = 2951, 2897, 1628, 1459, 1437, 1387, 1279, 1212, 1200, 1131, 1081, 1054, 1034, 949, 915, 860, 824, 725 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.95 (s, 3 H), 1.20 (s, 3 H), 1.25 (d, *J* = 1.8 Hz, 3 H), 1.30 (d, *J* = 15.3 Hz, 1 H), 1.39 (d, *J* = 14.0 Hz, 1 H), 1.52 (d, *J* = 14.0 Hz, 1 H), 1.79 (d, *J* = 13.8 Hz, 1 H), 1.86 (d, *J* = 15.3 Hz, 1 H), 2.52 (ddd, *J* = 1.6, 5.8, 13.8 Hz, 1 H), 3.76–3.90 (m, 2 H), 3.93–4.07 (m, 2 H), 4.75 (dd, *J* = 1.8, 6.1 Hz, 1 H), 5.57 (d, *J* = 5.8 Hz, 1 H), 6.18 (dd, *J* = 1.6, 6.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 17.4, 27.5, 31.1, 34.6, 40.2, 40.9, 43.2, 56.5, 62.8, 65.0, 85.0, 99.6, 110.8, 111.5, 139.7 ppm. ESIMS: *m*/*z* (%) = 266 (0.04) [M]$^+$, 237 (0.03), 223 (0.20), 127 (22), 56 (30), 55 (36), 53 (26), 45 (34), 43 (54), 41 (100). ESIMS (MeOH): *m*/*z* (%) = 289 (100) [MNa]$^+$. HRESIMS calcd. for $C_{15}H_{22}NaO_4$: *m*/*z* = 289.1416; found 289.1410.

Oxidative cleavage of **7** (268 mg, 1.0 mmol) with 2.4 equiv. of lead tetraacetate in acetic acid at room temperature for 22 h gave, after silica gel flash column chromatography with heptane/EtOAc (4:1) as eluent, **35** (15.6 mg, 6%) along with lactone **63** (56.4 mg, 20%) and the ring-expanded full-cascade intermediate **64** (192.0 mg, 50%).

63: IR (film): $\tilde{\nu}$ = 2951, 1751, 1375, 1333, 1287, 1256, 1221, 1207, 1129, 1073, 1044, 1000, 957 cm^{-1}. ^{1}H NMR (300 MHz): δ = 1.04 (s, 3 H), 1.13 (s, 3 H), 1.14 (s, 3 H), 1.43 (d, *J* = 13.9 Hz, 1 H), 1.57–1.67 (m, 3 H), 2.02 (d, *J* = 14.6 Hz, 1 H), 2.53 (d, *J* = 18.0 Hz, 1 H), 2.64 (dd, *J* = 4.6, 14.6 Hz, 1 H), 2.72 (d, *J* = 18.0 Hz, 1 H), 3.80–4.10 (m, 4 H), 5.82 (d, *J* = 4.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 19.0 (2C), 29.9, 32.9, 38.9, 41.8, 42.3, 45.8, 48.2, 64.1, 64.9, 87.3, 102.1, 112.2, 167.8 ppm. ESIMS: *m*/*z* (%) = 282 (0.5) [M]$^+$, 127 (46), 86 (10), 69 (12), 55 (33), 43 (100). ESIMS (MeOH): *m*/*z* (%) = 305 (100) [MNa]$^+$. HRESIMS calcd. for $C_{15}H_{22}NaO_5$: *m*/*z* 305.1365; found 305.1362.

64: IR (film): $\tilde{\nu}$ = 2956, 2894, 1755, 1704, 1673, 1583, 1369, 1211, 1159, 1139, 1069, 988 cm^{-1}. ^{1}H NMR (300 MHz): δ = 1.06 (s, 3 H), 1.07 (s, 3 H), 1.40 (s, 3 H), 1.69 (d, *J* = 15.5 Hz, 2 H), 1.89 (d, *J* = 15.5 Hz, 1 H), 2.06 (s, 3 H), 2.12 (s, 3 H), 2.43 (d, *J* = 11.1 Hz, 1 H), 2.46 (dd, *J* = 4.6, 15.5 Hz, 1 H), 2.62 (d, *J* = 11.1 Hz, 1 H), 2.81 (d, *J* = 3.9 Hz, 1 H), 3.78–4.16 (m, 4 H), 6.38 (d, *J* = 3.9 Hz, 1 H), 6.44 (d, *J* = 4.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 20.9, 21.1, 23.6, 31.6, 31.7, 32.2, 41.5, 43.9, 54.8, 56.3, 64.9, 65.1, 88.2, 92.0, 113.4, 168.9, 169.1, 205.7 ppm. ESIMS: *m*/*z* (%) = 384 (0.1) [M]$^+$, 324 (0.10), 127 (55), 86 (50), 55 (45), 43 (100). ESIMS (MeOH): *m*/*z* (%) = 407 (100) [MNa]$^+$. HRESIMS calcd. for $C_{19}H_{28}NaO_8$: *m*/*z* = 407.1682; found 407.1697.

Preparation of Unsaturated Diols 3, 8, and 9 and Their Oxidative Cleavage: Diol **3** was obtained by reduction of acetoxy enone **1** using the general procedure for the reduction of acetoxy enones.

Oxidative cleavage of **3** was achieved following the general procedures (see Table 1 for yields) to afford **33** [silica gel flash column chromatography with heptane/EtOAc (4:1) as eluent].
33: M.p. 60–62 °C (heptane/diethyl ether/EtOAc). IR (film): $\tilde{\nu}$ = 3066, 2952, 2882, 1627, 1460, 1440, 1375, 1286, 1212, 1127, 1071, 1047, 946, 818, 727 cm^{-1}. ^1H NMR (500 MHz): δ = 1.28 (s, 3 H), 1.30–1.72 (m, 5 H), 1.80 (d, J = 13.7 Hz, 1 H), 2.00 (br. d, J = 16.0 Hz, 1 H), 2.51 (dd, J = 5.8, 13.7 Hz, 1 H), 3.88 (t, J = 6.4 Hz, 2 H), 4.00 (t, J = 6.4 Hz, 2 H), 4.81 (d, J = 6.0 Hz, 1 H), 5.59 (d, J = 5.8 Hz, 1 H), 6.19 (d, J = 6.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 16.9, 18.2, 28.4, 28.6, 43.3, 57.2, 63.0, 65.2, 83.8, 99.8, 110.3, 111.0, 139.6 ppm. ESIMS: m/z (%) = 238 (7) $[M]^+$, 237 (9), 149 (40), 137 (51), 122 (53), 121 (87), 119 (92), 109 (100), 107 (96), 106 (70), 91 (73). $C_{13}H_{18}O_4$ (238.12): calcd. C 65.53, H 7.61; found C 65.54, H 7.67.

Ketal deprotection of **3** (1.20 g, 5.0 mmol) in 20 mL of 10% HCl/THF (1:1) at 0 °C for 12 h afforded, after stirring at room temperature overnight, the free keto octaline diol **8** (970.2 mg, 99%), which was subjected to oxidative cleavage following the general procedures (see Table 1 for yields) to afford **36** [silica gel flash column chromatography with heptane/EtOAc (4:1) as eluent].
36: IR (film): $\tilde{\nu}$ = 2957, 2877, 1710, 1632, 1458, 1442, 1393, 1363, 1312, 1279, 1260, 1214, 1135, 1101, 1061, 1002, 965, 913, 833, 771 cm^{-1}. ^1H NMR (300 MHz): δ = 1.31 (s, 3 H), 1.76–2.40 (m, 4 H), 1.86 (d, J = 14.1 Hz, 1 H), 2.01 (td, J = 1.2, 13.2 Hz, 1 H), 2.49 (dt, J = 6.2, 13.2 Hz, 1 H), 3.32 (ddd, J = 0.7, 5.9, 14.1 Hz, 1 H), 4.91 (dd, J = 0.7, 6.1 Hz, 1 H), 5.56 (d, J = 5.9 Hz, 1 H), 6.25 (dd, J = 0.9, 6.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 18.0, 20.2, 28.5, 37.1, 43.0, 64.1, 84.8, 98.7, 107.6, 140.3, 212.9 ppm. CIMS: m/z (%) = 195 (52) $[M + H]^+$, 149 (80), 137 (100), 95 (32). HRCIMS calcd. for $C_{11}H_{15}O_3$: m/z = 195.1021; found 195.1023.

Functional-Group Interconversion

Preparation of the Octaline Diol 9. TBS-Protection: *tert*-Butyldimethylsilyl chloride (10.34 g, 68.6 mmol) was added to a solution of imidazole (9.35 g, 137.3 mmol) and the alcohol (4.49 g, 22.9 mmol) in DMF (73 mL) at room temperature (TLC monitoring). The reaction mixture was stirred for 36 h then diluted with hexane, washed with brine, and dried with $MgSO_4$. Concentration under reduced pressure and flash chromatography (heptane/EtOAc, 9:1) of the residue gave the title compound (8.41 g, 87% yield) as a white solid.

Wittig Methylenation and Desilylation: A dry flask was charged with methyltriphenylphosphonium bromide (2.81 g, 7.9 mmol), *t*BuOK (2.79 g, 23.6 mmol), and a stir bar under argon. Dry PhMe (56 mL) was added from a syringe, and the suspension was stirred for 1 h at room temperature. The reaction mixture was cooled to 0 °C, and a solution of the ketone (2.20 g, 5.2 mmol) in PhMe (56 mL) was added over a few seconds. The ice bath was removed and the reaction mixture was stirred at room temperature under argon (TLC monitoring). After dilution with EtOAc, water (56 mL) was added slowly, and the product was extracted with EtOAc, the organic phase was worked up as usual. Chromatography on silica gel eluting with heptane/EtOAc (10:1) gave **9-bis-(OTBS)** (2.06 g, 94%) along with unreacted starting material. An analytical sample was characterized.

9-Bis(OTBS): IR (film): $\tilde{\nu}$ = 3086, 2931, 2857, 1636, 1462, 1388, 1361, 1253, 1211, 1093, 1062, 1006, 938, 883, 836, 775, 742, 671 cm^{-1}. ^1H NMR (300 MHz): δ = 0.11 (s, 6 H), 0.12 (s, 6 H), 0.93 (s, 9 H), 0.94 (s, 9 H), 1.30 (s, 3 H), 1.71–2.52 (m, 8 H), 3.84 (ddd, J = 3.2, 7.3, 11.1 Hz, 1 H), 4.05 (d, J = 7.3 Hz, 1 H), 4.64 (br. s, 1 H), 4.68 (br. s, 1 H), 5.07 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = –4.7, –4.6, –3.9, –3.7, 18.1, 18.4, 26.2 (6 C), 26.8, 28.4, 29.7, 31.9, 32.7, 42.9, 72.3, 75.1, 106.1, 123.5, 143.8, 156.2 ppm. ESIMS (MeOH): m/z (%) = 461 (17) $[MK]^+$, 445 (100) $[MNa]^+$. HRESIMS calcd. for $C_{24}H_{46}O_2NaSi_2$: m/z = 445.29339; found 445.29342.

TBS Deprotection: Tetrabutylammonium fluoride (1 M in THF; 1.9 mL, 1.9 mmol) was added to the bis-TBS protected alcohol (200 mg, 0.47 mmol) under argon, and the reaction mixture immediately heated to 60 °C (oil bath) for 4 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc, and washed with brine till neutral. Usual work up and SiO_2 flash chromatography (heptane/EtOAc, 1:2) of the residue gave **9** (87.6 mg, 96% yield). A major component of a diastereomeric mixture (relative stereochemistry of hydroxyl group bearing carbons unassigned) after chromatography is described.
9: IR (film): $\tilde{\nu}$ = 3352, 2925, 1636, 1461, 1376, 1056, 893 cm^{-1}. ^1H NMR (300 MHz): δ = 1.31 (s, 3 H), 1.33–2.56 (m, 10 H), 3.84 (m, 1 H), 4.01 (dd, J = 2.0, 7.9 Hz, 1 H), 4.68 (br. s, 1 H), 4.71 (br. s, 1 H), 5.18 (d, J = 1.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 28.4, 29.7, 31.8, 32.7, 39.4, 41.2, 71.7, 74.4, 106.5, 121.2, 145.5, 153.1 ppm. ESIMS: m/z (%) = 233 (8) $[MK]^+$, 217 (100) $[MNa]^+$. HRESIMS calcd. for $C_{12}H_{18}NaO_2$: m/z = 217.1204; found 217.1203.

Oxidative cleavage of **9** was achieved following the general procedures (see Table 1 for yields) to afford **37** [Silica gel flash column chromatography with heptane/EtOAc (1:1) as eluent].
37: IR (film): $\tilde{\nu}$ = 2936, 2868, 1630, 1452, 1391, 1370, 1214, 1135 1104, 1068, 1043, 1007, 993, 924, 876, 830, 724 cm^{-1}. ^1H NMR (300 MHz): δ = 1.20 (s, 3 H), 1.37–1.72 (m, 3 H), 1.98 (d, J = 13.7 Hz, 1 H), 2.01–2.30 (m, 3 H), 2.82 (dd, J = 5.3, 13.7 Hz, 1 H), 4.70 (br. s, 1 H), 4.76 (d, J = 5.3 Hz, 1 H), 4.79 (br. s, 1 H), 5.51 (d, J = 5.3 Hz, 1 H), 6.15 (d, J = 5.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 20.9, 21.3, 29.7, 32.1, 45.7, 55.9, 82.7, 98.6, 108.3, 109.4, 139.4, 152.5 ppm. ESIMS: m/z (%) = 231(5) $[MK]^+$, 215 (100) $[MNa]^+$. HRESIMS calcd. for $C_{12}H_{16}NaO_2$: m/z = 215.1048; found 215.1043.

Oxidative cleavage of **9** (194 mg, 1 mmol) using 2.4 equiv. of lead tetraacetate in 5 mL of acetic acid at room temperature for 21 h gave **61** (161.2 mg, 52%), along with the alternative full-cascade intermediate **62** (18.6 mg, 6%), after silica gel flash column chromatography with heptane/EtOAc (2:1) as eluent.
61: IR (film): $\tilde{\nu}$ = 2938, 2864, 1753, 1717, 1451, 1438, 1371, 1346, 1229, 1173, 1114, 1064, 990, 944, 917, 731 cm^{-1}. ^1H NMR (300 MHz): δ = 1.09–1.54 (m, 2 H), 1.37 (s, 3 H), 1.81 (d, J = 14.5 Hz, 1 H), 2.01 (s, 3 H), 2.04 (s, 3 H), 2.23–2.53 (m, 5 H), 3.16 (d, J = 3.0 Hz, 1 H), 4.72 (br. s, 1 H), 4.82 (br. s, 1 H), 6.26 (d, J = 3.0 Hz, 1 H), 6.38 (br. d, J = 3.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 20.9, 21.2, 28.1 (2C), 31.0, 32.9, 37.4, 45.5, 53.1, 88.1, 92.8, 111.8, 155.9, 168.9, 169.0, 207.8 ppm. ESIMS (MeOH): m/z (%) = 349 (40) $[MK]^+$, 333 (100) $[MNa]^+$. HRESIMS calcd. for $C_{16}H_{22}NaO_6$: m/z = 333.1314; found 333.1314.

62: IR (film): $\tilde{\nu}$ = 3054, 2928, 2856, 1742, 1461, 1372, 1265, 1155, 1004, 938, 896, 738, 705 cm^{-1}. ^1H NMR (500 MHz): δ = 1.34–1.47 (m, 1 H), 1.48 (s, 3 H), 1.51–1.71 (m, 2 H), 2.13 (s, 3 H), 2.17 (s, 3 H), 2.19 (m, 1 H), 2.26 (m, 1 H), 2.32 (m, 1 H), 2.47 (d, J = 14.4 Hz, 1 H), 2.95 (dd, J = 6.4, 14.4 Hz, 1 H), 4.84 (s, 1 H), 4.89 (s, 1 H), 4.99 (s, 1 H), 5.44 (d, J = 6.2 Hz, 1 H), 5.85 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 20.9 (2C), 21.2, 23.5, 27.5, 32.9, 43.2, 47.4, 69.9, 85.2, 92.3, 98.3, 109.5, 154.5, 168.7, 170.0 ppm. ESIMS (MeOH): m/z (%) = 349 (40) $[MK]^+$, 333 (100) $[MNa]^+$. HRESIMS calcd. for $C_{16}H_{22}O_6Na$: m/z = 333.1314; found 333.1312.

Angularly Functionalized Substrates

Preparation of the Octaline Diol 18. Determination of the Optical Purity of 13a: Prepared according to Hanselmann and Benn,[14] scalemic (first obtained in ca. 80% *ee*) **13a** (199 mg, 0.96 mmol) was dissolved in dry CH_2Cl_2 (20 mL) at 0 °C. NEt_3 (976 mg, 9.6 mmol), DMAP (236 mg, 1.9 mmol), and, 10 min later, (*S*)-2-acetoxypropionyl chloride, (725 mg, 4.8 mmol) were then added at 0 °C. After 25 min at this temperature (TLC monitoring) the reaction mixture was quenched with a saturated solution of aqueous $NaHCO_3$. Extraction with CH_2Cl_2, washing with 1 N aq. HCl, $NaHCO_3$, water, and brine, and finally drying with $MgSO_4$ afforded a crude residue which was purified on silica gel (heptane/EtOAc, 3:1) to yield a mixture of lactates **14** (285 mg, 93%). Integration of the ^{1}H NMR spectrum at 800 MHz gives an acceptable optical purity (90% *ee*). ^{1}H NMR (800 MHz): δ = 1.50 (m, 1 H), 1.527 (d, *J* = 7.1 Hz, 3 H), 1.786 (ddd, *J* = 5.4, 11.3, 14.1 Hz, 1 H), 1.865 (m, 1 H), 1.940–2.050 (m, 2 H), 2.102 (dt, *J* = 6.0, 14.2 Hz, 1 H), 2.15 (s, 3 H), 2.257 (m, 1 H), 2.359 (m, 1 H), 2.403 (dd, *J* = 8.1, 14.5 Hz, 1 H), 2.460 (dd, *J* = 5.5, 11.3 Hz, 1 H), 2.477 (dd, *J* = 5.5, 11.3 Hz, 1 H), 2.677 (dd, *J* = 6.7, 14.5 Hz, 1 H), 4.842 (dd, *J* = 4.7, 11.8 Hz, 1 H), 5.066 (q, *J* = 7.1 Hz, 1 H), 5.084 (d, *J* = 10.0 Hz, 1 H), 5.143 (d, *J* = 16.9 Hz, 1 H), 5.776 (dddd, *J* = 6.7, 8.1, 10.0, 16.9 Hz, 1 H), 5.925 (d, *J* = 1.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 16.8, 20.4, 23.4, 26.4, 30.1, 31.8, 33.7, 36.6, 43.5, 68.5, 79.4, 118.1, 127.1, 133.6, 163.8, 169.9, 170.1, 198.5 ppm. TOFESIMS: *m*/*z* (%) = 663 (18) $[2MNa]^+$, 343 (100) $[MNa]^+$. HRESIMS calcd. for $C_{18}H_{24}NaO_5$: *m*/*z* = 343.1521; found 343.1531.

TBS Protection: *tert*-Butyldimethylsilyl chloride (4.834 g, 32.0 mmol) was added to a solution of imidazole (4.36 g, 64.1 mmol) and the alcohol (3.30 g, 16.0 mmol) in DMF (25 mL) at 0 °C (TLC monitoring). After 6 h, one more equivalent of *tert*-butyldimethylsilyl chloride (2.42 g) was added. The reaction mixture was stirred for 36 h then diluted with CH_2Cl_2, washed with 1 N HCl, sat. $NaHCO_3$, and brine, and dried with $MgSO_4$. Concentration under reduced pressure and flash chromatography (heptane/AcOEt, 9:1) of the residue gave 4.30 g (84%) of **13b**. $[\alpha]_D^{20}$ = +77 (*c* = 1.19, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3412, 3076, 2953, 2856, 2357, 1686, 1683, 1674, 1661, 1651, 1634, 1622, 1615, 1471, 1463, 1455, 1435, 1389, 1360, 1330, 1252, 1221, 1193, 1098, 1005, 911, 867, 835, 814, 773, 667 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.06 (s, 6 H), 0.91 (s, 9 H), 1.24–1.47 (m, 2 H), 1.73–1.96 (m, 4 H), 2.12–2.59 (m, 6 H), 3.53 (t, *J* = 7.6 Hz, 1 H), 5.02 (t, *J* = 10.0 Hz, 1 H), 5.09 (d, *J* = 16.9 Hz, 1 H), 5.82 (m, 1 H), 5.86 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = –5.1, –4.1, 17.9, 23.7, 25.7 (3C), 30.6, 31.6, 32.3, 34.3, 36.3, 45.4, 78.5, 117.2, 126.5, 135.1, 166.4, 199.5 ppm. ESIMS: *m*/*z* (%) = 320 (0.5) $[M]^+$, 222 (76), 221 (46), 171 (22), 143 (13), 129 (21), 115 (13), 91 (20), 75 (99), 73 (100), 59 (21), 45 (13), 41 (33). HRESIMS calcd. for $C_{19}H_{32}NaO_2Si$: *m*/*z* = 343.2069; found 343.2075.

Hydroboration-oxidation was carried out using standard literature techniques. Hydroboration was achieved by dropwise addition of $BH_3{\cdot}Me_2S$ (7.3 mL, 14.7 mmol) to **13b** (3.14 g, 9.8 mmol) in heptane (48 mL) under argon at 0 °C. Following the addition of the hydride the cooling bath was removed and the solution stirred for 2.5 h. EtOH (48 mL) was then added followed by careful addition of 3 N NaOH (5 L, 14.7 mmol). After cooling to 0 °C in an ice-water bath, hydrogen peroxide (30% aqueous solution; 5 mL, 1.50 g, 44 mmol) was added at such a rate that the reaction mixture warmed to 25–35 °C. Immediately afterwards the cooling bath was removed and the mixture heated at reflux for 1.5 h. Extraction with EtOAc and usual work up followed by silica gel flash column chromatography with heptane/EtOAc (1:1) as eluent afforded 2.59 g (78%) of **15α-OH** and **15β-OH**.

15β-OH: $[\alpha]_D^{20}$ = +46 (*c* = 1.3, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3338, 2935, 2858, 2709, 2240, 1660, 1471, 1462, 1449, 1407, 1388, 1361, 1251, 1197, 1087, 1006, 976, 914, 836, 773, 734, 668, 644 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.01 (s, 6 H), 0.85 (s, 9 H) 1.12–2.46 (m, 15 H), 3.49–3.61 (m, 4 H), 4.09 (m, 1 H), 5.48 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = –5.02, –4.07, 25.4, 25.8 (3C), 26.2, 26.7, 27.2, 28.9, 30.7, 31.6, 44.1, 53.4, 63.6, 66.9, 75.8, 127.5, 143.6 ppm. ESIMS: *m*/*z* (%) = 379 (5) $[MK]^+$, 363 (100) $[MNa]^+$. HRESIMS calcd. for $C_{19}H_{36}NaO_3Si$: *m*/*z* = 363.2331; found 363.2339.

15α-OH: $[\alpha]_D^{20}$ = +6 (*c* = 1.3, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3338, 2935, 2857, 1659, 1471, 1462, 1388, 1361, 1254, 1194, 1094, 1070, 1005, 957, 931, 914, 889, 866, 834, 814, 773, 734, 666, 645 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.00 (s, 6 H), 0.86 (s, 9 H), 1.09–2.15 (m, 14 H), 2.96 (br. s, 2 H), 3.34 (dd, *J* = 5.4, 9.8 Hz, 1 H), 3.44–3.65 (m, 2 H), 4.05(m, 1 H), 5.55 (d, *J* = 3.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = –4.9, –4.1, 18.0, 25.2, 25.8 (3 C), 26.8, 27.4, 28.0, 28.5, 31.0, 31.6, 44.0, 63.6, 65.5, 77.5, 125.8, 145.1 ppm. ESIMS: *m*/*z* (%) = 379 (12) $[MK]^+$, 363 (100) $[MNa]^+$. HRESIMS calcd. for $C_{19}H_{36}NaO_3Si$: *m*/*z* = 363.2331; found 363.2330.

Selective allylic oxidation was achieved by adding 3,5-DMP (631 mg, 6.6 mmol) and PCC (1.28 g, 6.0 mmol) to a stirred a solution of **15α,β** (1.02 g, 3.0 mmol) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred at 0 °C for 40 min, then diluted with CH_2Cl_2 and worked up as usual. Silica gel flash column chromatography with heptane/EtOAc (1:4) as eluent afforded the desired enone **16a** (0.63 g, 62%), along with some enone aldehyde, which could be easily recycled.

16a: $[\alpha]_D^{20}$ = +52 (*c* = 1.14, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3420, 2937, 2859, 1660, 1558, 1495, 1457, 1255, 1099, 832, 774 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.01 (s, 6 H), 0.85 (s, 9 H), 1.04–2.29 (m, 12 H), 2.10–2.43 (m, 3 H), 3.46–3.65 (m, 3 H), 5.81 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = –5.0 (2 C), 17.9, 24.0, 25.7 (3 C), 27.7, 27.9, 30.4 (2 C), 32.4, 34.2, 45.2, 63.1, 78.1, 126.1, 168.1, 199.7 ppm. ESIMS: *m*/*z* (%) = 377 (17) $[MK]^+$, 361 (100) $[MNa]^+$, 339 (98) $[MH]^+$. HRESIMS calcd. for $C_{19}H_{34}NaO_3Si$: *m*/*z* = 361.2174; found 361.2179.

TBS Protection: Proceeding as above, *tert*-butyldimethylsilyl chloride (1.03 g, 6.8 mmol) was added to a solution of imidazole (931 mg, 13.7 mmol) and the alcohol (1.16 g, 3.4 mmol) in DMF (25 mL) at 0 °C (TLC monitoring). The reaction mixture was stirred at 0 °C for 1 h 35 min then diluted with CH_2Cl_2, washed with 1 N HCl, sat $NaHCO_3$, and worked up as usual. SiO_2 flash chromatography (heptane/AcOEt, 5:1) of the residue gave 1.41 g (91%) of **16b**. $[\alpha]_D^{20}$ = +43 (*c* = 1.66 $CHCl_3$). IR (film): $\tilde{\nu}$ = 2929, 1684, 1653, 1472, 1361, 1256, 1191, 1102, 1003, 940, 831, 774, 668 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.03 (s, 6 H), 0.04 (s, 6 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 1.16–2.40 (m, 14 H), 3.50–3.64 (m, 3 H), 5.85 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = –5.0 (2C), –4.0 (2C), 17.2 (2C), 24.1, 25.1 (6C), 27.9 (2C), 30.5, 32.4, 34.4, 45.3, 63.4, 68.4, 78.1, 126.3, 167.8, 199.6 ppm. ESIMS: *m*/*z* (%) = 491 (8) $[MK]^+$, 475 (24) $[MNa]^+$, 453 (100) $[MH]^+$. HRESIMS calcd. for $C_{25}H_{48}NaO_3Si_2$: *m*/*z* = 475.3039; found 475.3032.

Acetoxylation, performed on a 12 mmol (5.42 g) scale according to the general procedure, afforded the α- and β-acetates **17** {4.41 g, 72%; IR (film): $\tilde{\nu}$ = 2932, 2858, 1750, 1698, 1623, 1470, 1369, 1254, 1191, 1108, 1006, 940, 836 cm^{-1}. ESIMS: *m*/*z* (%) = 549 (22) $[MK]^+$, 533 (100) $[MNa]^+$} which were used as such in the subsequent reduction to the diol **18** (4.06 g, 99%), using the general procedure for acetoxy enone reduction.

18: IR (film): $\tilde{\nu}$ = 3390, 2926, 2856, 1738, 1469, 1362, 1254, 1093, 957, 912, 872, 836 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.05 (s, 12 H), 0.90 (s, 18 H), 1.30–2.18 (m, 13 H), 3.47 (dd, *J* = 5.6, 9.9 Hz, 1 H),

3.57 (m, 3 H), 3.94 (m, 1 H), 4.08 (m, 1 H), 5.58 (d, J = 3.8 Hz, 1 H) ppm. ^{13}C NMR (300 MHz): δ = –5.3 (2 C), –4.8, –4.0, 18.3 (2 C), 24.3, 25.9 (6 C), 27.9, 28.3, 30.8, 31.2, 37.0, 45.8, 63.8, 66.5, 68.0, 80.7, 122.1, 147.0 ppm. ESIMS (MeOH): m/z (%) = 509 (5) $[MK]^+$, 493 (27) $[MNa]^+$. HRESIMS calcd. for $C_{25}H_{50}NaO_4Si_2$: m/z = 493.3145; found 493.3149.

Oxidative cleavage of **18** was achieved using the general procedures (see Table 1 for yields) to afford **40** [silica gel flash column chromatography with heptane/diethyl ether (1:1) as eluent]. $[\alpha]_D^{20}$ = +9 (c = 2.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2929, 2856, 1630, 1471, 1388, 1256, 1095, 934, 835 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.05 (s, 12 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 1.13–1.96 (m, 10 H), 2.08 (d, J = 14.2 Hz, 1 H), 2.30 (dd, J = 5.7, 14.2 Hz, 1 H), 3.49–3.59 (m, 2 H), 3.64 (dd, J = 4.0, 11.4 Hz, 1 H), 4.78 (d, J = 6.1 Hz, 1 H), 5.64 (d, J = 5.5 Hz, 1 H), 6.17 (d, J = 6.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = –5.2 (2 C), –4.8, –4.0, 18.0, 18.3, 19.8, 24.1, 26.0 (6 C), 29.3, 30.6, 31.6, 44.7, 58.4, 64.22, 76.6, 84.8, 99.5, 109.9, 139.4 ppm. ESIMS: m/z (%) = 507 (18) $[M + K]^+$, 491 (100) $[M + Na]^+$. HRESIMS calcd. for $C_{25}H_{48}NaO_4Si_2$: m/z = 491.2989; found 491.2991.

Oxidative cleavage of **18** (0.94 g, 2 mmol) with 2.4 equiv. of lead tetraacetate in acetic acid (10 mL) at room temperature for 19 h gave **60** (609 mg, 52%), along with the half-cascade intermediate **40** (205 mg, 22%), after silica gel flash column chromatography with heptane/EtOAc (5:1) as eluent.

60: $[\alpha]_D^{20}$ = –4 (c = 1.59, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2930, 2858, 1765, 1692, 1472, 1368, 1257, 1074, 949, 835, 774 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.05 (s, 12 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 1.22–2.02 (m, 7 H), 2.07 (s, 3 H), 2.08 (s, 3 H), 2.30 (dd, J = 2.6, 13.9 Hz, 1 H), 2.49–2.59 (m, 2 H), 2.81 (d, J = 3.8 Hz, 1 H), 3.50–3.70 (m, 3 H), 3.91 (s, 1 H), 4.26 (dd, J = 4.5, 8.8 Hz, 1 H), 6.27 (dd, J = 2.6, 7.2 Hz, 1 H), 6.43 (d, J = 3.8 Hz, 1 H) ppm. ^{13}C NMR: (75 MHz): δ = –5.3, –5.2 (2 C), –4.0, 18.1, 18.2, 20.3, 20.9 (2 C), 25.9 (6 C), 27.3, 31.9, 33.6, 33.8, 40.8, 44.5, 56.3, 63.4, 75.3, 88.8, 91.7, 168.3, 168.9, 208.6 ppm. ESIMS: m/z (%) = 625 (32) $[MK]^+$, 609 (100) $[MNa]^+$. HRESIMS calcd. for $C_{29}H_{54}NaO_8Si_2$: m/z = 609.32548; found 609.32541.

Oxidative Cleavage of 21: Obtained as a diastereomeric mixture from an intermediate used in our previous work, unsaturated diol **21** was subjected to oxidative cleavage, using the general procedures (see Table 1 for yields), without prior diastereomeric separation. Silica gel flash column chromatography with heptane/EtOAc (4:1) as eluent afforded **43**. IR (film): $\tilde{\nu}$ = 3024, 2971, 2944, 2864, 1656, 1457, 1450, 1390, 1364, 1224, 1145, 1111, 1085, 1025, 1005, 972, 965, 925, 753 cm^{-1}. ^{1}H NMR (300 MHz): δ = 1.05 (s, 3 H), 1.19 (s, 9 H), 1.20–1.40 (m, 2 H), 1.54 (d, J = 1.5 Hz, 3 H), 1.55–1.80 (m, 4 H), 1.82 (d, J = 14.2 Hz, 1 H), 2.43 (dd, J = 5.7, 14.2 Hz, 1 H), 3.35 (dd, J = 3.6, 11.6 Hz, 1 H), 5.61 (d, J = 5.7 Hz, 1 H), 6.01 (d, J = 1.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 12.8, 15.4, 19.6, 26.5, 29.3 (3C), 30.0, 46.7, 55.9, 72.8, 73.7, 86.1, 98.8, 115.1, 134.8 ppm. ESIMS: m/z (%) = 266 (100) $[M]^+$, 211 (6), 210 (30), 209 (19), 166 (95), 57 (98). HREIMS calcd. for $C_{16}H_{26}O_3$: m/z = 266.18818; found 266.1882.

Diol **22** was obtained in 69% yield from its corresponding acetoxy enone[9] by a Luche reduction ($NaBH_4/CeCl_3$, 0 °C, 30 min) and used as a crude diastereomeric mixture for the next operation. This unsaturated diol, belonging to the hydrindene diol series, was incorporated into this study because the tricyclic enol ether intermediate is stable and easily isolable.

Oxidative Cleavage of 22: Oxidative cleavage using the general procedures (see Table 1 for yields) afforded **44**. $[\alpha]_D^{20}$ = –75 (c = 1.01, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3021, 2976, 2953, 2360, 1701, 1604, 1438, 1216, 1186, 1146, 1103, 1071, 1026 cm^{-1}. ^{1}H NMR (250 MHz): δ = 1.04 (s, 3 H), 1.15 (s, 9 H), 1.60–1.90 (m, 2 H), 1.90 (d, J = 14.3 Hz, 1 H), 2.00–2.20 (m, 1 H), 2.37 (dd, J = 5.0, 14.3 Hz, 1 H), 2.85–3.05 (m, 1 H), 3.68 (s, 3 H), 3.85 (t, J = 8.0 Hz, 1 H), 5.72 (d, J = 5.0 Hz, 1 H), 7.44 (s, 1 H) ppm. ^{13}C NMR (62.5 MHz): δ = 13.9, 25.2, 28.8 (3C), 33.0, 48.2, 50.9, 62.9, 72.5, 78.7, 93.7, 102.2, 110.0, 153.2, 165.5 ppm. ESIMS: m/z (%) = 296 (14) $[M^+]$, 196 (77), 154 (99), 57 (100). HREIMS calcd. for $C_{16}H_{24}O_5$: m/z = 296.1624; found 296.1629.

Preparation and Domino Reactions of the Allyl-Substituted Substrates 11 and 12: The procedures used for the synthesis of **26**[13e] was repeated and allyl-functionalized bicyclic unsaturated diols **11** and **12** were synthesized from **10** by way of the intermediate dienol acetate species. Installation of the allylic hydroxy group was then carried out by treatment with methyltrioxorhenium and its protection was performed without separation of the major and minor isomers with TMSOTf (trimethylsilyl trifluoromethanesulfonate) in the presence of collidine. The required unsaturated diols **11** and **12** were then prepared using the general procedure for reduction of acetoxy enones. Silica gel flash column chromatography with heptane/EtOAc (1:1) as eluent afforded pure **11** (slower eluting) and **12** (faster eluting).

11: M.p. 179–181 °C (heptane/diethyl ether). IR (film): $\tilde{\nu}$ = 3371, 2975, 1454, 1389, 1365, 1254, 1190, 1076, 1045, 998, 921, 890, 841 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.13 (s, 9 H), 1.12 (s, 3 H), 1.17 (s, 9 H), 1.20–1.34 (m, 3 H), 1.42 (t, J = 12.7 Hz, 1 H), 1.55–1.92 (m, 3 H), 1.99 (dd, J = 3.4, 12.7 Hz, 1 H), 3.10 (dd, J = 4.3, 11.2 Hz, 1 H), 3.62–3.72 (m, 1 H), 4.04–4.15 (m, 2 H), 5.58 (s, 1 H) ppm. Diagnostic NOEs: {Me-10}: H-2, H-6, H-1eq; {H-2}: H-1 eq., Me-10; {H-6 + H-3}: Me-10. ^{13}C NMR (75 MHz): δ = –0.02 (3 C), 19.4, 28.6, 29.2 (3 C), 33.8, 43.2, 43.9, 68.7, 71.6, 73.2, 74.8, 78.0, 120.0, 146.3 ppm. TOFESIMS: m/z (%) = 365 (100) $[MNa]^+$. HRESIMS calcd. for $C_{18}H_{34}O_4Si$: m/z = 365.2124; found 365.2124. $C_{18}H_{34}O_4Si$ (342.22): calcd. C 63.11, H 10.00; found C 63.10, H 10.19.

12: M.p. 131–133 °C (heptane/diethyl ether). IR (film): $\tilde{\nu}$ = 3369, 2973, 1458, 1387, 1362, 1250, 1191, 1074, 1041, 999, 966, 923, 891, 840 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.06 (s, 9 H), 1.17 (s, 9 H), 1.26 (s, 3 H), 1.35 (t, J = 12.9 Hz, 1 H), 1.43 (m, 1 H), 1.53 (br. dd, J = 3.2, 13.1 Hz, 1 H), 1.72 (br. dd, J = 2.8, 13.6 Hz, 1 H), 1.93 (dd, J = 3.2, 12.6 Hz, 1 H), 1.97 (m, 1 H), 2.80 (br. s, 2 H), 3.05 (dd, J = 3.8, 11.4 Hz, 1 H), 3.74 (ddd, J = 3.5, 8.1, 11.6 Hz, 1 H), 3.99 (d, J = 7.8 Hz, 1 H), 4.08 (t, J = 3.3 Hz, 1 H), 5.33 (s, 1 H) ppm. Diagnostic NOEs: {Me-10}: H-2, H-1 eq.; {H-2}: Me-10. ^{13}C NMR (75 MHz): δ = 0.3 (3 C), 20.6, 24.9, 29.2 (3 C), 32.7, 42.7, 44.6, 71.4, 72.3, 73.0, 74.5, 78.8, 126.2, 145.8 ppm. ESIMS: m/z (%) = 342 (0.6) $[M]^+$, 268 (12), 230 (10), 229 (45), 228 (25), 211 (66), 210 (30), 193 (25), 75 (20), 73 (24), 57 (100), 41 (42). $C_{18}H_{34}O_4Si$ (342.22): calcd. C 63.11, H 10.00; found C 63.03, H 10.21.

Oxidative cleavage of **11** was achieved using the general procedures (see Table 1 for yields) to afford **38** [silica gel flash column chromatography with heptane/diethyl ether (8:1) as eluent]. IR (film): $\tilde{\nu}$ = 2967, 2872, 1639, 1463, 1389, 1377, 1363, 1250, 1212, 1197, 1144, 1126, 1090, 1070, 1049, 1033, 994, 967, 933, 919, 869, 840 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.14 (s, 9 H), 1.09 (s, 3 H), 1.17 (s, 9 H), 1.34–1.51 (m, 1 H), 1.60–1.92 (m, 3 H), 1.86 (dd, J = 1.0, 14.2 Hz, 1 H), 2.40 (dd, J = 5.9, 14.2 Hz, 1 H), 3.39 (dd, J = 3.8, 11.6 Hz, 1 H), 3.59 (dd, J = 5.1, 11.6 Hz, 1 H), 4.77 (d, J = 6.4 Hz, 1 H), 5.65 (d, J = 5.6 Hz, 1 H), 6.24 (d, J = 6.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 0.5 (3 C), 12.6, 28.8, 28.9, 29.2 (3 C), 46.8, 57.7, 71.3, 72.8, 73.1, 86.0, 99.4, 108.4, 140.3 ppm. ESIMS: m/z (%) = 340 (0.3) $[M]^+$, 238 (15), 194 (19), 175 (19), 151 (21), 150 (45), 137 (25), 95 (46), 73 (68), 57 (100), 41 (47). TOFESIMS: m/z (%) = 363

(100) [MNa]$^+$; 703 (96) [2M + Na]$^+$. HRESIMS (MeOH) calcd. for $C_{18}H_{32}NaO_4Si$: *m*/*z* = 363.1967; found 363.1968.

Oxidative cleavage of **12** was achieved using the general procedures (see Table 1 for yields) to afford **39** [silica gel flash column chromatography with heptane/diethyl ether (8:1) as eluent]. IR (film): $\tilde{\nu}$ = 2972, 2923, 1631, 1461, 1387, 1378, 1362, 1251, 1197, 1135, 1111, 1081, 1067, 1040, 947, 843 cm^{-1}. ^{1}H NMR (400 MHz): δ = 0.09 (s, 9 H), 1.17 (s, 3 H), 1.20 (s, 9 H), 1.47 (m, 1 H), 1.58 (m, 1 H), 1.80 (d, *J* = 14.2 Hz, 1 H), 1.75–1.83 (m, 2 H), 2.43 (dd, *J* = 14.2, 5.8 Hz, 1 H), 3.34 (dd, *J* = 11.0, 3.7 Hz, 1 H), 3.90 (t, *J* = 2.4 Hz, 1 H), 5.22 (d, *J* = 6.2 Hz, 1 H), 5.58 (d, *J* = 5.7 Hz, 1 H), 6.22 (d, *J* = 6.2 Hz, 1 H) ppm. Diagnostic NOEs: {Me-10}: H-1β; {H-1α}: H-1β, H-9; {H-9}: H-1α, H-7α; {H-6}: H-4, H-7α, H-7β. ^{13}C NMR (75 MHz): δ = 0.3 (3 C), 13.1, 24.2, 28.6, 29.3 (3 C), 29.8, 47.3, 68.7, 73.0, 73.7, 84.7, 99.6, 108.0, 139.6. TOFESIMS: *m*/*z* (%) = 363 (100) [MNa]$^+$; 703 (88) [2M + Na]$^+$. HRESIMS (MeOH) calcd. for $C_{18}H_{32}NaO_4Si$: *m*/*z* = 363.1967; found 363.1966.

Identification of the Side Products Obtained by Mn(OAc)$_3$- and Dess–Martin Periodinane-Mediated Oxidative Cleavage: The former oxidant produced side products regardless of the substrate's stereochemistry, while the latter produced them as the only new products starting from the *trans* diols, although not at all starting from *cis*-diols. We will first describe the stepwise preparation of 2-hydroxy cross-conjugated dienone **51**, which exists exclusively in its keto-enol form, and its subsequent acetylation into **55**, and then the one-pot procedure leading directly to the 2-acetoxy cross-conjugated derivatives.

Using the general procedure for the Dess–Martin periodinane-mediated oxidative cleavage, ***25α-trans*** (664 mg, 2 mmol) afforded **51** (465 mg, 71%) and the allylic oxidation product, the acyloin **50** (99 mg, 15%), after silica gel flash column chromatography on silica gel with heptane/EtOAc (7:1) as eluent.[13e,19]

51: M.p. 146–147 °C (hexane/diethyl ether). $[\alpha]_D^{20}$ = +3 (*c* = 0.98, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3379, 2972, 2937, 2851, 1644, 1428, 1360, 1304, 1251, 1227, 1194, 1074, 884 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.78 (s, 3 H), 1.12 (s, 9 H), 1.24 (s, 3 H), 0.81–2.02 (m, 13 H), 2.35–2.53 (m, 2 H), 3.35 (t, *J* = 7.8 Hz, 1 H), 6.17 (s, 1 H), 6.33 (s, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 11.5, 19.6, 22.8, 23.8, 28.6 (3C), 31.0, 32.7, 33.4, 35.2, 36.7, 42.6, 44.0, 49.9, 53.8, 72.1, 80.3, 120.9, 124.5, 146.0, 173.0, 181.4 ppm. ESIMS: *m*/*z* (%) = 358 (6) [M]$^+$, 302 (8), 147 (20), 137 (60), 57 (100). $C_{23}H_{34}O_3$ (358.25): calcd. C 77.05, H 9.56; found C 76.61, H 9.61.

The 2-hydroxy cross-conjugated dienone **51** (143 mg, 0.6 mmol, 1 equiv.) was further acetylated with Ac_2O (2.70 g, 26.5 mmol, 2.5 mL) in the presence of DMAP (143 mg, 1.12 mmol, 2 equiv.), in pyridine (2.93 g, 37.1 mmol, 3.0 mL) under argon at 0°C. Following stirring for 55 min, dilution with EtOAc and usual work up furnished **55** (201.6 mg, 84%) after silica gel flash column chromatography with heptane/EtOAc (6:1) as eluent,.

Experimental Procedure for the "One-Pot" Formation of 2-Acetoxy-1,4-dien-3-one: Proceeding as above, ***25α-trans*** (362 mg, 1.0 mmol) and DMP (852 mg, 2.0 mmol) in sodium-dried toluene (20 mL) were gently heated to 72 °C over 20 min and then stirred at this temperature for 30 min (TLC monitoring). After cooling the yellow suspension to 0 °C DMAP (242 mg, 1.6 mmol), pyridine (6 mL), and Ac_2O (4 mL) were added and the reaction mixture was stirred at 0 °C for 2 h. Dilution with diethyl ether, washing with 1 N HCl and saturated aq. $NaHCO_3$ solution, and usual work up gave **55** (344 mg, 86%) after silica gel flash column chromatography (eluent: heptane/EtOAc, 4:1). M.p. 177–178 °C (heptane/diethyl ether). $[\alpha]_D^{20}$ = +22 (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2971, 2936, 2851, 1769, 1675, 1653, 1458, 1362, 1205, 1153, 1074, 871, 755 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.78 (s, 3 H), 1.12 (s, 9 H), 1.30 (s, 3 H), 0.79–2.57 (m, 15 H), 2.26 (s, 3 H), 3.35 (t, *J* = 7.8 Hz, 1 H), 6.11 (s, 1 H), 6.73 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 11.5, 19.0, 20.4, 22.5, 23.8, 28.5 (3C), 30.9, 32.2, 33.0, 35.1, 36.6, 42.5, 44.6, 49.8, 52.7, 72.1, 80.3, 123.2, 141.3, 144.2, 168.4, 169.2, 179.0 ppm. ESIMS: *m*/*z* (%) = 400 (1) [M]$^+$, 137 (25), 57 (100). $C_{25}H_{36}O_4$ (400.26): calcd. C 74.96, H 9.06; found C 74.89, H 9.14.

The above procedure was repeated with ***19β-trans*** (249 mg, 1.0 mmol) to give **48** (241 mg, 84%) after silica gel flash column chromatography with heptane/EtOAc (6:1) as eluent. M.p. 155–157 °C (heptane/diethyl ether). $[\alpha]_D^{20}$ = –78 (*c* = 1.01, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2964, 2894, 2235, 1767, 1678, 1659, 1617, 1462, 1440, 1371, 1206, 1148, 896 cm^{-1}. ^{1}H NMR (300 MHz): δ = 0.83 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.4 Hz, 3 H), 1.22–1.39 (m, 1 H), 1.47 (3 , 3 H), 1.57–1.68 (m, 1 H), 2.02 (dt, *J* = 4.4, 13.3 Hz, 1 H), 2.11–2.21 (m, 1 H), 2.23 (s, 3 H), 2.53 (d, *J* = 3.8 Hz, 2 H), 2.64 (dd, *J* = 4.0, 13.1 Hz, 1 H), 6.13 (s, 1 H), 6.36 (s, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 20.3 (2C), 20.5, 20.7, 25.5, 27.1, 33.6, 34.5, 41.0, 41.8, 118.9, 126.8, 138.1, 145.1, 160.5, 168.1, 178.1 ppm. ESIMS (MeOH): *m*/*z* (%) = 326 (72) [MK]$^+$, 310 (83) [MNa]$^+$, 288 (100) [MH]$^+$. $C_{17}H_{21}NO_3$ (287.15): calcd. C 71.06, H 7.37; found C 70.99, H 7.51.

Oxidative Cleavage of 23a with Sodium Bismuthate: Using the procedure of Watt,[33] $NaBiO_3$ (1.231 g, 4.39 mmol) was added to **23-α** (535 mg, 2.1 mmol) in 21 mL of 50% aqueous AcOH. The mixture was stirred at room temperature for 19 h, diluted with EtOAc, and worked up as usual. The product was chromatographed on silica gel with heptane/EtOAc (1:1) as eluent to afford half-cascade **45** (79.4 mg, 15%), dialdehyde **57** (26.5 mg, 5%), starting material **23-α** (149.8 mg, 28%), and **58** (249 mg, 44%; anomeric mixture). The latter was acetylated for characterization. A mixture containing **58** (210 mg, 0.78 mmol), 2.5 mL of pyridine, 2.5 mL of Ac_2O, and a catalytic amount of DMAP was stirred at room temperature whilst monitoring by TLC. The corresponding acetate **59** (241 mg) was obtained in nearly quantitative yield after silica gel flash chromatography (eluent: heptane/EtOAc, 4:1). The stereochemistry of the major acetate is as depicted in Scheme 7). IR (film): $\tilde{\nu}$ = 2969, 2931, 2864, 1752, 1365, 1246, 1232, 1164, 1150, 1052, 1036, 941, 875 cm^{-1}. ^{1}H NMR (600 MHz): δ = 1.10 (s, 3 H), 1.18 (s, 9 H), 1.29 (m, 1 H), 1.36 (dd, *J* = 5.5, 14.3 Hz, 1 H), 1.51 (m, 1 H), 1.56 (dt, *J* = 3.6, 13.4 Hz, 1 H), 1.66 (dd, *J* = 9.4, 13.6 Hz, 1 H), 1.72 (m, 1 H), 1.84 (m, 1 H), 1.87 (d, *J* = 15.0 Hz, 1 H), 1.91 (dd, *J* = 4.3, 13.6 Hz, 1 H), 2.09 (s, 3 H), 2.38 (dd, *J* = 6.3, 15.0 Hz, 1 H), 3.25 (dd, *J* = 3.5, 11.6 Hz, 1 H), 5.47 (d, *J* = 6.3 Hz, 1 H), 6.16 (dd, *J* = 4.3, 9.3 Hz, 1 H) ppm. ^{13}C NMR (150 MHz): δ = 12.7, 19.6, 21.1, 29.4 (3C), 29.6, 32.0, 39.1, 43.8, 46.7, 73.1, 75.9, 85.2, 88.2, 98.7, 169.5 ppm. ESIMS: *m*/*z* (%) = 312 (16) [M]$^+$, 253 (8), 252 (10), 197 (16), 196 (54), 195 (18), 179 (26), 178 (52), 150 (100), 59 (46). HREIMS calcd. for $C_{17}H_{28}O_5$: *m*/*z* = 312.1937; found 312.1941.

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