Studies towards Trichodimerol: Novel Cascade Reactions and Polycyclic Frameworks

K. C. Nicolaou,* Rolf Jautelat, Georgios Vassilikogiannakis, Phil S. Baran, and Klaus B. Simonsen[a]

Dedicated to Dr. Manfred Jautelat on the occasion of his 60th birthday

Abstract: Trichodimerol (**1**) is a synthetically attractive natural product because of its potential medical use against septic shock and its striking molecular architecture. We report herein the possible biosynthetic pathway for its formation from the hexaketide sorbicillin (**3**) and our preliminary results towards the total synthesis of trichodimerol (**1**) and its congener demethyltrichodimerol (**2**). These studies provided a way to synthesize β-ketal ketones by a novel variation of the Mukaiyama Aldol reaction, afforded new insight into the mild and regioselective formation of silyl enol ethers, and allowed the preparation of the advanced intermediate **38**. Furthermore, a number of unprecedented cascade reactions were discovered furnishing novel polycyclic, highly oxygenated compounds from simple starting materials.

Keywords: aldol reactions · biosynthesis · cascade reactions · natural products · silyl enol ether

Introduction

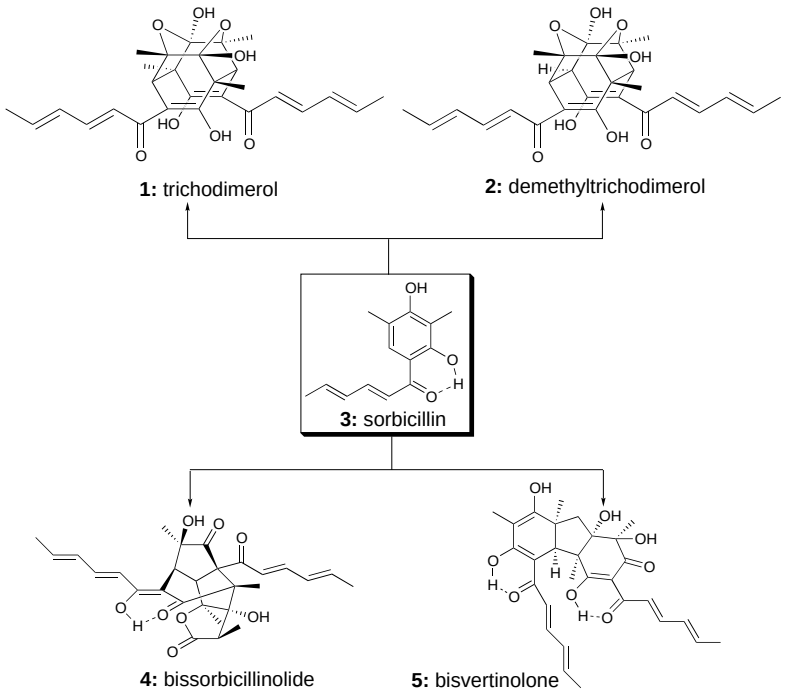
Trichodimerol (**1**),[1] demethyltrichodimerol (**2**),[1d)] bissorbicillinolide (**4**),[2] and bisvertinolone(**5**)[3] (Scheme 1) are members of a growing family of natural products isolated from different fungi.[1–4] The unifying feature of these related dodecaketides resides in their mechanistically related biosynthetic pathways involving the oxidatively initiated dimerization of the natural hexaketide sorbicillin (**3**)[5] (vide infra). Since there is no name available to summarize this class of natural products, we would like to put forth the name bisorbicillinoids.

The bisorbicillinoids are appealing synthetic targets because of their complex molecular architecture and interesting biological properties. Antioxidant properties were reported for **1**, **2**, and **4** and several other bisorbicillinoids,[1d, 2] while bisvertinolone (**5**) proved to be the first β-1,6-glucan biosynthesis inhibitor,[6] making it a potential fungicide.

The most intriguing biological activity was reported for trichodimerol (**1**), originally isolated from a fungus of the genus *Trichoderma* in 1992 by Ayers and co-workers.[1a)] In 1996, a team from Bristol-Myers Squibb demonstrated trichodimerol's ability to inhibit in vitro the lipo polysaccharide (LPS)-induced production of tumor necrosis factor α (TNF-α) in human monocytes and, therefore, to have potential use for the treatment of septic shock.[1b, 7] Septic shock is responsible for the death of about 200 000 people in the western hemisphere annually.[8] Since there is no effective treatment yet available for this condition,[8] a synthetic program which targeted this novel molecule, eventually allowing us to probe facets of its chemical biology through designed analogues, was deemed important. Trichodimerol's novel, cagelike and topologically symmetrical structure provides a particularly challenging synthetic target by virtue of the wealth of chirality (eight stereogenic centers) embedded in its core and the high degree of connectivity (six quatenary centers) displayed in the pentacyclotetradecadiene core skeleton. The underlying hope of our synthetic endeavor was to charter a synthetic pathway which would be efficient enough to generate a library of designed analogues for biological screening. In addition, we planned to develop novel synthetic tactics and strategies as well as to investigate and utilize new reactions. Here, we present an account of a variety of interesting and, in some cases, astonishing discoveries resulting from our initial investigations in this field.

[a] Prof. Dr. K. C. Nicolaou, Dr. R. Jautelat, Dr. G. Vassilikogiannakis, P. S. Baran, Dr. K. B. Simonsen
Department of Chemistry and The Skraggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037 (USA)
and
Department of Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, CA 92093 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu

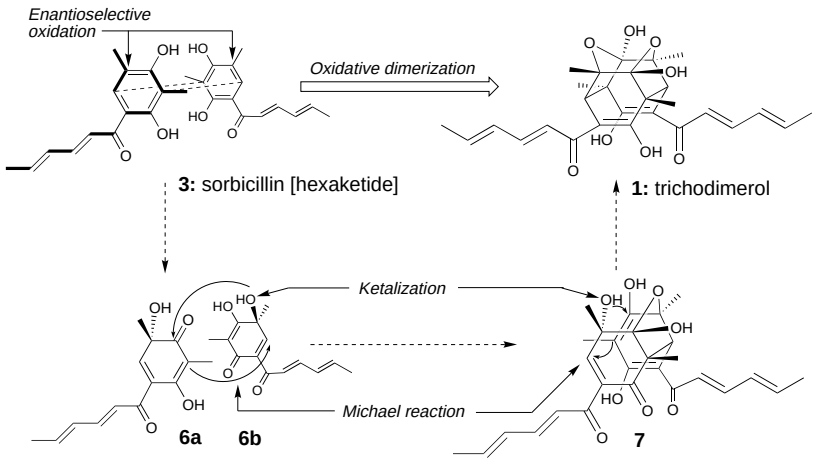
  0947-6539/99/0512-3651 $ 17.50+.50/0



Scheme 1. Structures of sorbicillin (**3**) and selected bisorbicillinoids.

There has been no clear pathway proposed thus far for the biosynthesis of trichodimerol (**1**)—only the oxidation product **6a** was suggested as a potential intermediate (Scheme 2).[1c)] Here, we propose a detailed mechanism for the formation of trichodimerol (**1**) from sorbicillin (**3**) by an oxidation–Michael-ketalization cascade as depicted in Scheme 2.

Our retrosynthetic analysis was formulated on the guiding principles of the proposed biosynthesis (vide supra). Thus, we planned to establish the core structure **9** by a biomimetic intramolecular double Michael addition from the all-*syn* tricyclic diendione **11** as depicted retrosynthetically in Scheme 3. Alternatively, this key step might also be carried out in a photochemical way by a [4+4] electrocyclization of the related tetraene **10** to afford **8**, a reaction performed successfully by Sikrishna and co-workers in the all-carbon case (Scheme 3).[9] These key bond-forming events required the synthesis of the central tricyclic all-*syn* precursor **11**, which could conceivably be derived from the fusion of a novel electron-rich ketene acetal of type **13** with two electrophilic units of the general type **12** (Scheme 3). Although this sequence takes full advantage of the inherent C_2-symmetry of the trichodimerol cage, we were aware that at certain stages of the synthesis we might be able to desymmetrize the system in order to gain access to demethyltrichodimerol (**2**) and novel analogues.



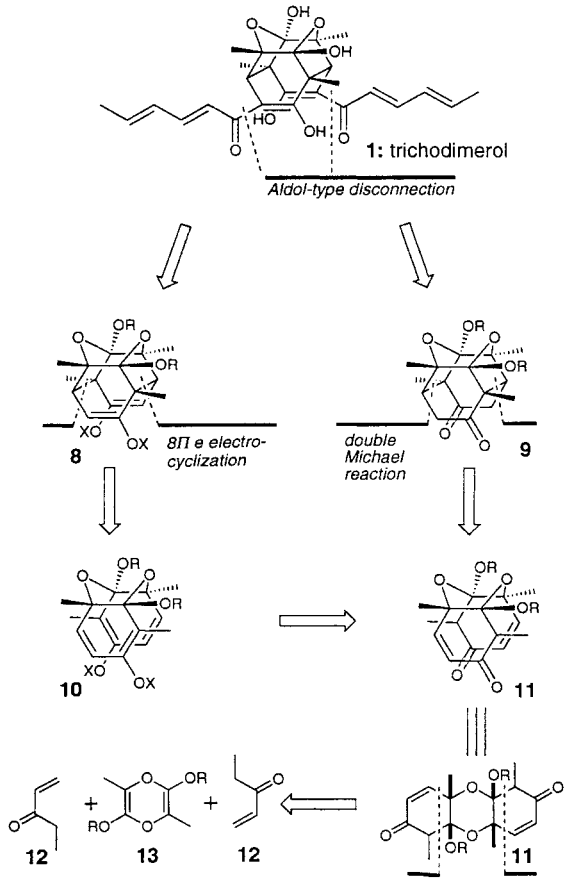
Scheme 2. Proposed biosynthetic pathway from sorbicillin (**3**) to trichodimerol (**1**).

Results and Discussion

The requisite novel bisketene acetal **13** was synthesized in a straightforward manner. Treatment of commercially available racemic lactide **14** with LDA/TMSCl (for abbreviations of reagents and groups, see legends in Schemes) at $-100\,^{\circ}C$ afforded the thermally unstable[10] bisketene acetal **13** in essentially quantitative yield and about 95% purity (Scheme 4). Experimental fine-tuning proved to be essential for this transformation since we also discovered that lactide **14** gave rise to the novel tricyclic lactone **15** in fair yield (41%) under different basic conditions (Scheme 4). The structure of crystalline lactone **15** was confirmed by X-ray crystallographic analysis (see Figure 1 for ORTEP structure). This transformation is likely to proceed through an anionic cascade commencing with an intramolecular lactide contraction[11] to form lactone **16** followed by consecutive Claisen and Adol reactions to finally afford **15** (Scheme 4).

A wide variety of possibilities appeared to be logical for the required transformation of ketene acetal **13** into tricyclic precursors of type **10** or **11** (Scheme 3). We first explored an approach which could directly furnish the 8π system **10** in essentially one pot by using an inverse-electron-demand double Diels–Alder reaction[12] (with concomitant CO_2 extrusion) cascade as retrosynthetically depicted in Scheme 5. Un-

0947-6539/99/0512-3652 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 12



Scheme 3. Retrosynthetic analysis of trichodimerol (**1**).

fortunately, all attempts so far to react bisketene acetal **13** under various conditions (e.g. Lewis acid catalyzed,[13] pressure 13 kbar[14]) with pyrone **18**[15] and with more electron-deficient pyrones like **19**,[16] **20**,[17] and **21**[18] did not lead to the expected Diels–Alder adduct **17**.

We, therefore, set out to access tricycle **11** via ketene acetal **13** in a more stepwise approach related to the Robinson annulation as retrosynthetically depicted in Scheme 6. Thus,

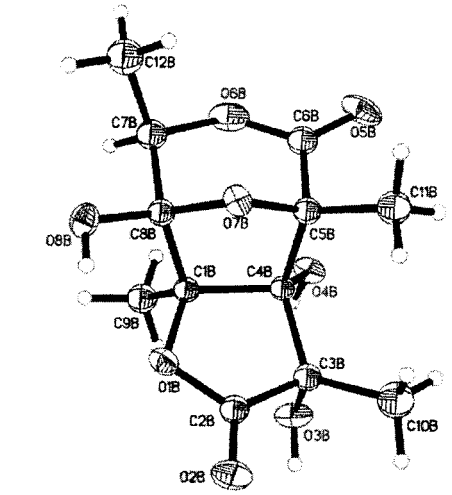
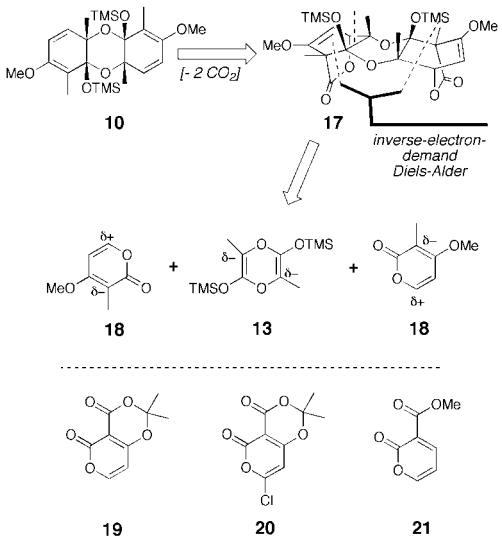
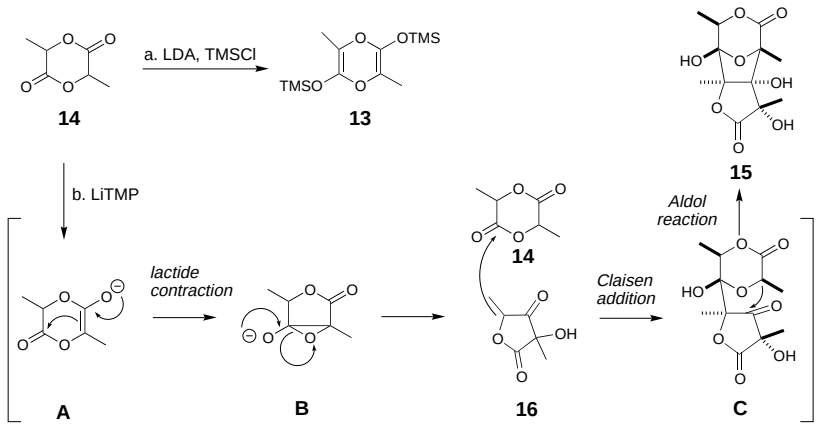


Figure 1. ORTEP drawing of tricyclic lactone **15**.



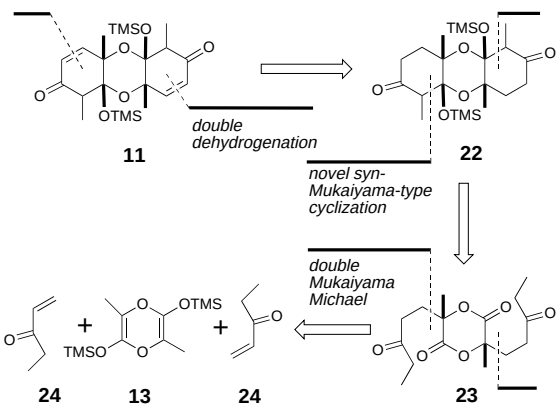
Scheme 5. Retrosynthetic analysis of key intermediate **10** based on Diels–Alder chemistry.



Scheme 4. Reaction of lactide **14** under basic conditions. a) 2.2 equiv of LDA, 2.3 equiv of TMSCl, THF, $-110 \rightarrow 10\,^{\circ}C$, "quantitative"; b) 2.2 equiv of LiTMP, THF, $-78\,^{\circ}C$, 4 h, 41 %. LDA = lithium diisopropylamide, LiTMP = lithium 2,2,6,6-tetramethylpiperidyl, TMSCl = trimethylsilyl chloride.

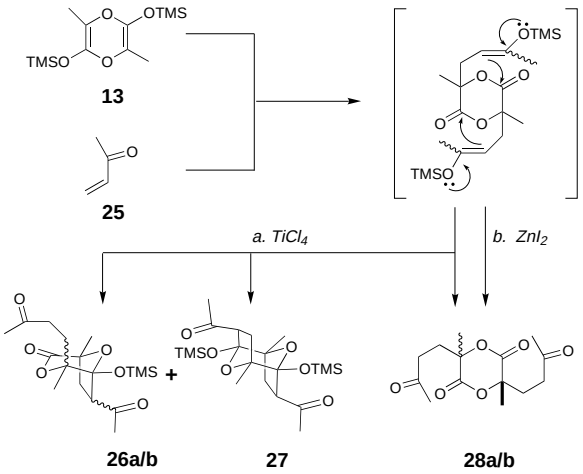
in a retrosynthetic sense, tricycle **11** could be derived from the bisketal **22** by a double dehydrogenation reaction. Arrival at the bisketal **22** would require the development of a novel Mukaiyama-type cyclization (vide infra) to close the second and third rings from the requisite diketodilactone **23**. Realization of this strategy would rely on the utilization of ketene acetal **13** in an unprecedented double Mukaiyama Michael reaction to construct diketodilactone **23**.

To avoid stereochemical complications in the cyclization steps



Scheme 6. Retrosynthetic analysis of key intermediate **11** based on Mukaiyama-type chemistry.

we initiated our investigations with methyl vinyl ketone (**25**) as electrophile. Indeed, bisketene acetal **13** reacted with methyl vinyl ketone (**25**) under mild Lewis acidic conditions (ZnI_2)[19] in a double Mukaiyama – Michael reaction to give an inseparable 1:1 mixture of *cis*- and *trans*-diketodilactones **28a/b** (Scheme 7) in good overall yield (60%, from lactide **14**). Interestingly, when we employed the originally reported



Scheme 7. Bis-Mukaiyama-Michael reactions of bisketene acetal **13**. a) 2.0 equiv of $TiCl_4$, CH_2Cl_2, $-78\,^{\circ}C$, 3 h, 9% **26a**, 5% **26b**, 5% **27**, and 7% **28a/b**; b) 0.13 equiv of ZnI_2, CH_2Cl_2, $0\,^{\circ}C$, 4 h, then + aqueous HF, acetone, 1 h, $25\,^{\circ}C$, 60% from **14**.

conditions for the union of ketene acetals with methyl vinyl ketone (**25**)[20] we isolated the tri- and tetracyclic ketals **26a/b** (two diastereomers, stereochemistry not assigned) and **27** as products resulting from the Mukaiyama cascade reaction sequence depicted in Scheme 7. The structure of tetracyclic ketal **27** was unambiguously confirmed by X-ray crystallographic analysis (see Figure 2 for ORTEP structure).

The intermolecular reaction of ketene acetals with lactones to form the corresponding β-ketal esters was pioneered by Mukaiyama et al.[21] and later applied to intramolecular cases by others.[22] Understandably, there exist no reports on a similar reaction employing the less reactive silyl enol ethers[23]

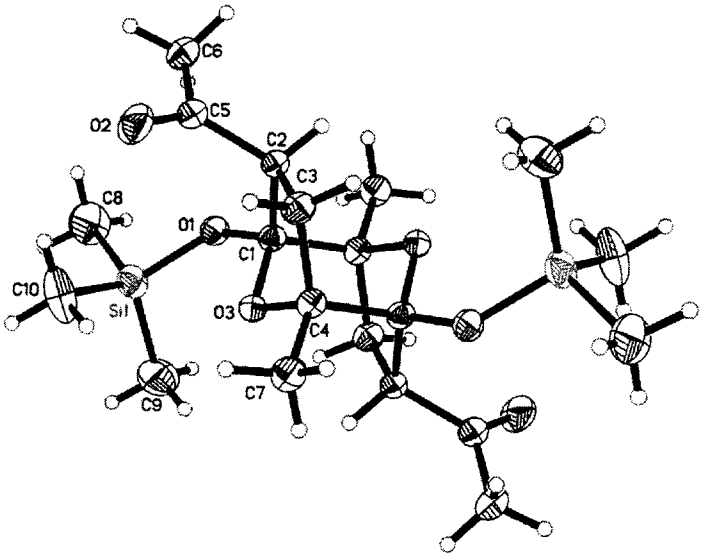
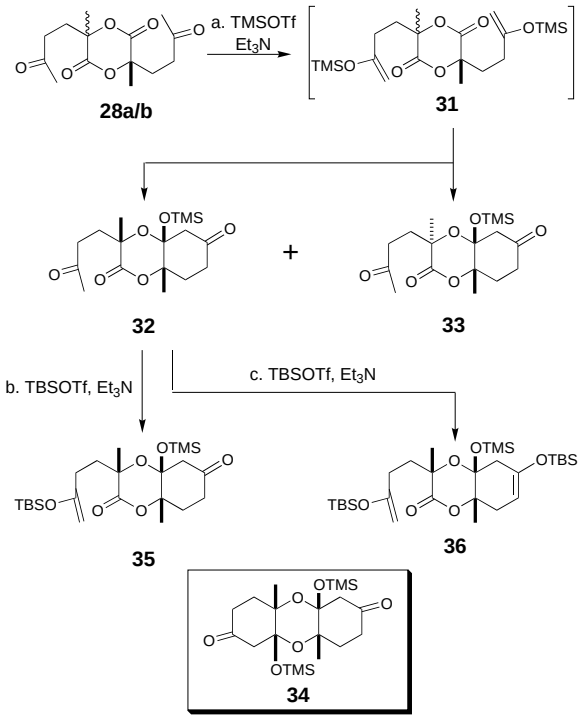


Figure 2. ORTEP drawing of tricyclic ketal **27**.

as nucleophiles. However, we reasoned that carrying out this transformation in an intramolecular fashion should allow us to overcome this hurdle.[24] Indeed, treatment of diketo dilactones **28a/b** with TMSOTf/Et_3N[25] accomplished the initial formation of the terminal silyl enol ethers (observation by NMR spectroscopy) followed by a slow monocyclization (Scheme 8). Ketal ketones **32** and **33** were obtained in 29 and



Scheme 8. Novel Mukaiyama-type cyclization of **28a/b.** a) 2.3 equiv of Et_3N, 2.5 equiv of TMSOTf, CH_2Cl_2, $-78 \rightarrow -10\,^{\circ}C$, 7 h, 29% **32** and 31% **33**; b) 1.3 equiv of Et_3N, 1.1 equiv of TBSOTf, CH_2Cl_2, $-78\,^{\circ}C$, 4 h, 90%; c) 4.0 equiv of Et_3N, 3.0 equiv of TBSOTf, CH_2Cl_2, $-78 \rightarrow 10\,^{\circ}C$, 5 h, 86%. TMSOTf = trimethylsilyl trifluoromethanesulfonate, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

0947-6539/99/0512-3654 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 12

31 % yields, respectively, and the structure of ketal ketone **33** was unambiguously proven by X-ray crystallographic analysis (Figure 3).

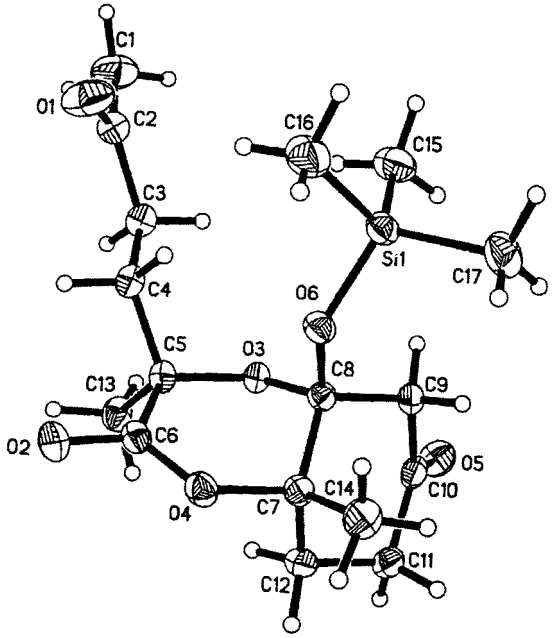


Figure 3. ORTEP drawing of *trans*-ketal ketone **33**.

Several points regarding this critical C–C bond-forming maneuver to afford **32** and **33** (Scheme 8) are worth mentioning. First, as from the inspection of molecular models, cyclization occurs in a *syn*-mode. More importantly, this reaction represents an efficient desymmetrization of the C_2-symmetric precursor (**28a**). As alluded to earlier, this type of symmetry disruption holds potential for the total synthesis of the unsymmetrical demethyltrichodimerol (**3**) and designed analogues. Also noteworthy is the observed stability of the TMS-protected ketal moiety. In parallel experiments, we found this compound to be extraordinarily stable towards base-induced β-elimination,[26] elevated temperatures, and even conditions suited for standard $(CH_3)_3Si{-}O$ cleavage.[27] Presumably, this unique and essential stability is due to the strong attractive nonbonded OSi···O interactions within the R-O-C-O-Si system.[28] Finally, the high regioselectivity observed in the formation of the terminal silyl enol ethers with trialkylsilyl triflates/Et_3N at low temperatures (see formation of **31**, **35**, and **36**) from the methyl alkyl ketone moieties should be noted, as these results contrast with reports in which dismal regioselectivities predominated with related unsymmetrically substituted ketones at higher temperatures.[29] An explanation for this observation might be that the formation of the silyl enol ether is very sensitive to the steric environment. Indeed, while the formation of a terminal silyl enol ether such as in **35** proceeded at $-78\,^{\circ}C$ within 4 h, generation of the more highly substituted enol ether function in **36** required warming to $10\,^{\circ}C$. All of these silyl enol ether preparations proceeded in excellent yield under simplest reaction and workup conditions.

All attempts to access the projected tricyclic bisketal **34** starting from diketo dilactones **28a/b**, ketal ketone **32** or the corresponding TBS-enol ethers **35** and **36** failed under a variety of conditions (e.g. Lewis acid catalyzed,[30] basic[31] and/or thermal conditions). We believe that the 1,3-pseudo diaxial interactions depicted in structure **35** (Figure 4) are the primary cause for the missing second ring closure. A similar explanation was offered by Mukaiyama and co-workers in structurally related cases where ketene acetals failed to react with lactones.[30]

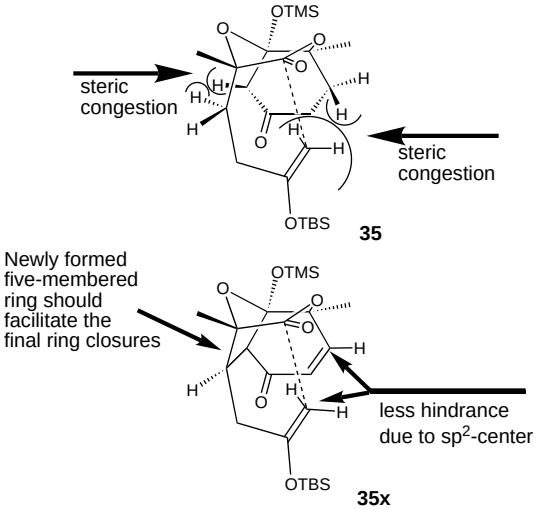
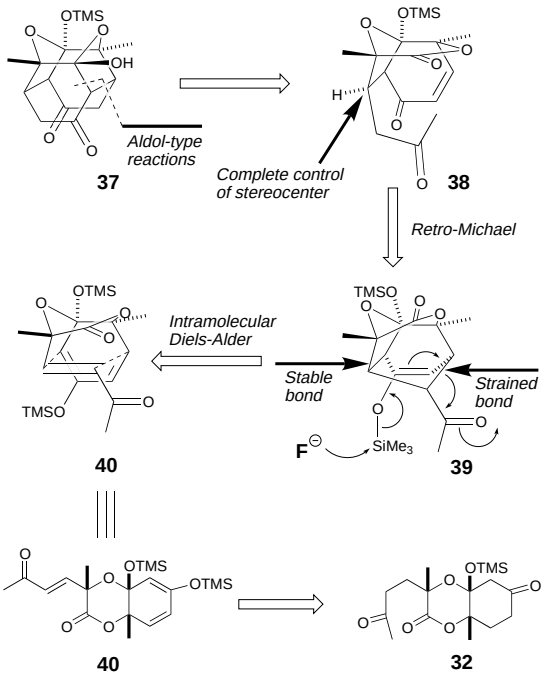


Figure 4. Possible explanation for the failure to cyclize **35** and design of a new substrate **35x**.

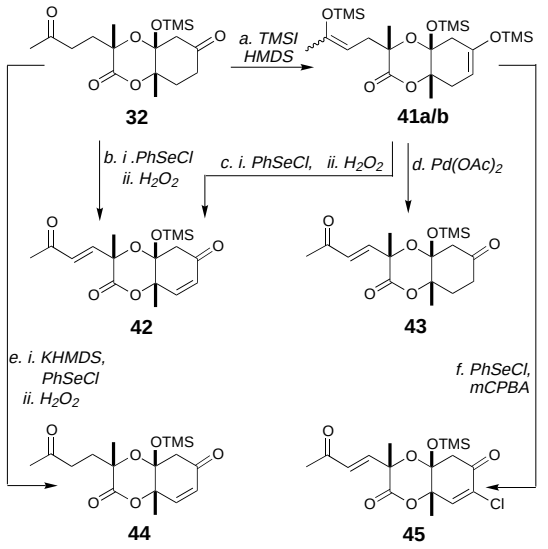
Undeterred by this seemingly detrimental outcome, we reasoned that the reduction of these pseudo-*trans*-annular repulsions should allow the generation of the coveted fourth quaternary center on the central dioxane ring. Thus, an enol ether of type **35x** (Figure 4) should allow this critical bond formation owing to two major structural changes: First, the newly formed tetrahydrofuran ring should properly position the side chain for the cyclization event, and, second, it was reasoned that the introduction of a double bond into the cyclohexanone moiety would relieve some of the steric repulsions described earlier (Figure 4).

On the basis of these considerations, we designed a partially altered approach to the trichodimerol core skeleton as depicted retrosynthetically in Scheme 9. Thus, the core skeleton **37** was expected to arise from two sequential aldol-type reactions of tricyclic lactone **38**. Lactone **38** could arise from Diels–Alder adduct **39** by a retro-Michael reaction opening the strained bond indicated in Scheme 9. Realization that **39** could be assembled by using a stereocontrolled intramolecular Diels–Alder reaction led to the bicyclic trienone **40**. The synthesis of a model trichodimerol skeleton **37** could, therefore, be traced back to the readily available ketal ketone **32** (Scheme 9).

The investigations aimed at the Diels–Alder product **39** began with the bis-dehydrogenation of ketal ketone **32** into the diendione **42** (Scheme 10). Utilization of the Sharpless protocol (i. PhSeCl, ii. H_2O_2)[32] allowed the straightforward synthesis of diendione **42**, but only in poor yield due to the strong acidic conditions involved. Therefore, a two-step procedure was adopted which proved to be superior.[33] The ketal ketone **32** was first converted into a mixture of the



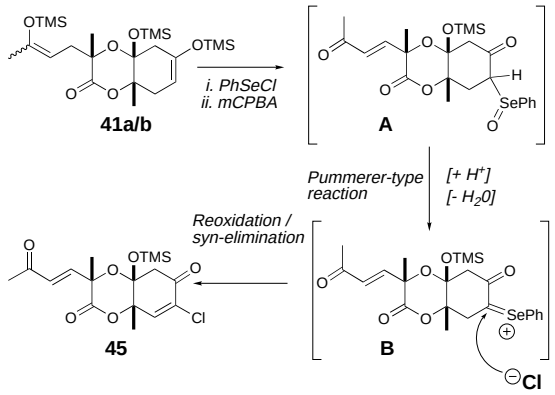
Scheme 9. Retrosynthetic analysis of the trichodimerol core system **37**.



Scheme 10. Conversion of ketal ketone **32** to unsaturated systems **42**–**45**. a) 3.0 equiv of HMDS, 0.5 equiv of TMSI, CH_2Cl_2, $-20 \rightarrow 25\,^{\circ}C$, 4 h, quantitative; b) i. 2.3 equiv of PhSeCl, EtOAc, 4 h; ii. excess of H_2O_2, EtOAc/THF 1:1, 30 min, 30%; c) i. 2.2 equiv of PhSeCl, THF, $-78\,^{\circ}C$, 3 h; ii. 7.0 equiv of H_2O_2, THF, 50 °C, 50 min, 70%; d) 2.0 equiv of $Pd(OAc)_2$, 3.0 equiv of Et_3N, MeCN, 50 min, 46%; e) i. 1.0 equiv of LiHMDS, THF, $-78 \rightarrow -50 \rightarrow -100\,^{\circ}C$, 2 h, then +1.0 equiv of PhSeCl; ii. excess of H_2O_2, THF, 1 h, 47% based on recovered starting material; f) 2.3 equiv of PhSeCl, THF, $-78 \rightarrow -50\,^{\circ}C$, 1 h, then +5.0 equiv of *m*CPBA, $-50 \rightarrow 0\,^{\circ}C$, 1 h, 34%. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, TMSI = trimethylsilyl iodide, LiHMDS = lithium hexamethylsilazide, *m*CPBA = 3-chloroperbenzoic acid.

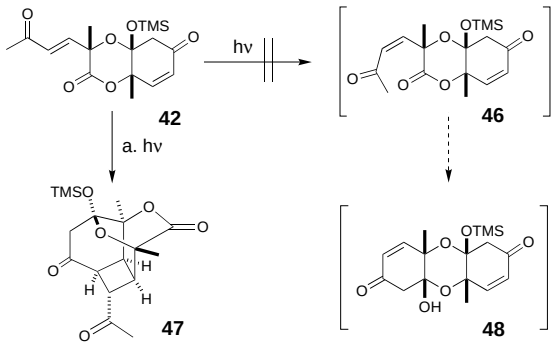
thermodynamic trimethylsilyl enol ethers **41a/b**.[34] We found the use of only catalytic amounts of TMSI in the presence of an excess of HMDS to be a substantial improvement over the published procedure.[35] Electrophilic addition of PhSeCl then transformed the silyl enol ethers **41a/b** into a diastereomeric mixture of the corresponding α-seleno ketones (not shown) which smoothly furnished the desired diendione **42** in 70% overall yield from ketal ketone **32** upon oxidative treatment (H_2O_2).

During the course of these studies, we also discovered ways to synthesize the mono-unsaturated endiones **43** and **44** in a selective manner, but only with moderate yields (unoptimized) (see Scheme 10).[36] Finally, in one instance, we observed the formation of novel product chloro diendione **45** from a one-pot reaction of silyl enol ethers **41a/b** with PhSeCl at $-78\,^{\circ}C$, followed by oxidation with *m*CPBA and warming to 0 °C (Scheme 10). A mechanistic rationale for the formation of **45** traversing through a Pummerer-type intermediate[37] is depicted in Scheme 11.



Scheme 11. Proposed mechanism for the formation of **45** from **41a/b**.

With the diendione **42** in hand, we first attempted a shortcut to the central tricyclic diendione type structure **11** (Scheme 3) by irradiating **42** under a variety of conditions in an attempt to isomerize the *trans* double bond of **42**.[38] Such an isomerization could conceivably set the stage for an irreversible collapse of the pendant enone onto the lactone to yield tricycle **48** as projected in Scheme 12. Instead, irradiation of diendione **42** gave rise to the novel cyclobutane **47** as the result of an intramolecular [2+2] cycloaddition reaction (Scheme 12).[39]



Scheme 12. Formation of cyclobutane **47** via an intramolecular [2+2] cycloaddition. a) *hν*, benzene, 30 min, quantitative.

We expected the construction of the requisite trienone **40** as the precursor of the intramolecular Diels–Alder reaction to be an easy task from diendione **42** (Scheme 13). However, despite our efforts employing a broad variety of well-

0947-6539/99/0512-3656 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 12

established reagent combinations (e.g. LDA/TMSCl, LiNH*n*-Bu/TMSCl, KHMDS/TMSCl, KH/TMSCl, TMSOTf/Et_3N, TMSI/HMDS, and others), a successful conversion of the diendione **42** into the recalcitrant tetraene **51** eluded us. Instead, we came upon the serendipitous isolation of novel polycyclic frameworks. Thus, the tricyclic iodoenolether **50** arose in moderate yield from **42** presumably by a cascade involving transformation of the acyclic enone into the 4π system followed by double vinylogous "transannular" addition of TMSI to the cyclic enone moiety as depicted in Scheme 13.[40] On the other hand, treatment of diendione **42** under strongly basic conditions led to the formation of tetracyclic lactone **53** as the sole product in 37% yield. We presume that the latter tranformation proceeds by a translactonization–Michael addition cascade (Scheme 13). Since we suspected that this reaction was initiated by a nucleophilic cleavage of the O–Si bond, we examined other conditions and indeed could synthesize this unusual tetracycle (**53**) in 89% yield by treatment of **42** with catalytic amounts of LiHMDS in THF/*t*BuOH at low temperature. The structure of the tetracyclic lactone **53** was confirmed by X-ray crystallographic analysis (see ORTEP drawing, Figure 5).

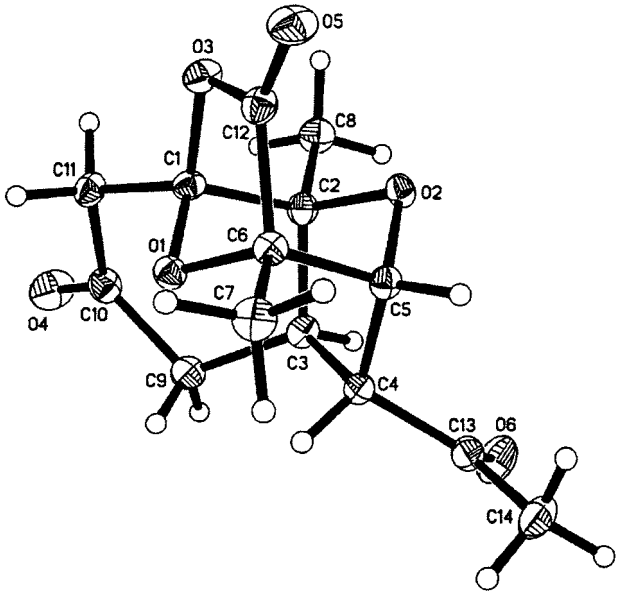
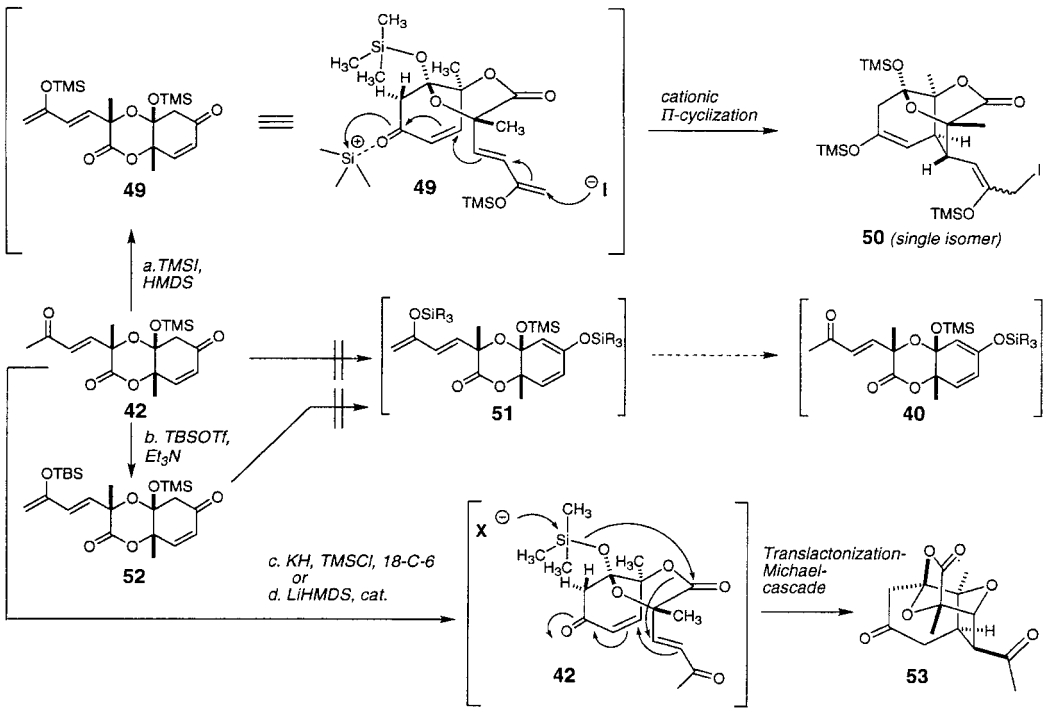


Figure 5. ORTEP drawing of spiroketal **53**.

Thwarted in our attempts to access trienone **40**, we searched for reasons to explain the difficulty of what essentially amounted to removing one methylene proton adjacent to a cycloenone moiety. Based on the inspection of molecular models founded on computational studies and X-ray crystallographic data from the related structures **33** and **45**, it appeared that the methylene protons adjacent to the keto group in the cycloenone moiety are extremely shielded—on the one side by the inherent concave folding of the molecule and on the other side by the TMS group, which is quasi-stationary due to a strong nonbonding OSi···O interaction (vide supra), as depicted in Figure 6.[41]

Earlier studies (vide supra) had given us critical information regarding the unusual stability of these compounds. In a bold decision, we reasoned that simply heating diendione **42** at high enough temperature may provide the necessary energy to effect an in situ tautomerization of the enone moiety,[42] generating the desired Diels–Alder precursor which would be poised for the critical intramolecular cycloaddition (Scheme 14). In the event, we were delighted to observe the



Scheme 13. Synthetic investigations towards trienone **40**. a) 5.0 equiv of HMDS, 2.2 equiv of TMSI, CH_2Cl_2, $-20 \rightarrow 25\,^{\circ}C$, 8 h, 55%; b) 1.3 equiv of Et_3N, 1.1 equiv of TBSOTf, CH_2Cl_2, $-78\,^{\circ}C$, 4 h, 94%; c) 4.0 equiv of KH, 2.3 equiv of TMSCl, [18]crown-6 (trace), DME, $0 \rightarrow 50\,^{\circ}C$, 6 h, 37%; d) 0.3 equiv of LiHMDS, THF/*tert*-butyl alcohol 10:1, $-78 \rightarrow 0\,^{\circ}C$, 3 h, 89%. DME = dimethoxyethane, LiHMDS = lithium hexamethydisilazide.

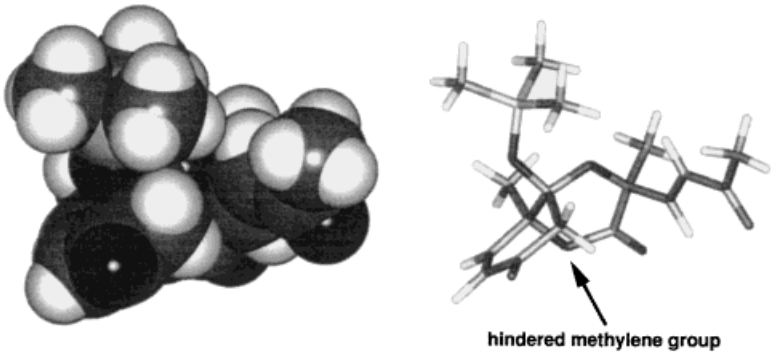
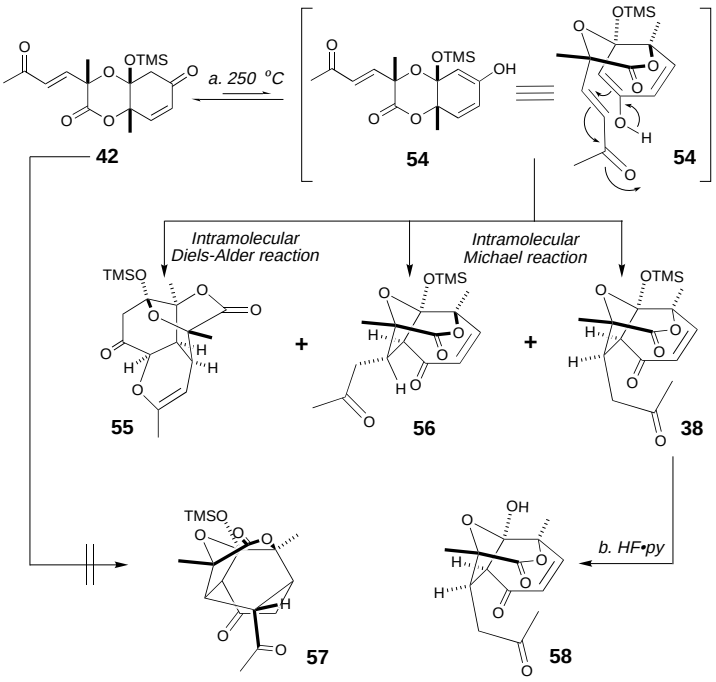


Figure 6. Computer-generated minimum-energy structure of diendione **42** depicting the strong steric shielding of the methylene protons next to the cyclic enone moiety. Carbon = gray, hydrogen = white, oxygen = black, silicon = gray-white. Molecular dynamics and minimization calculations (CV Force Field) were performed on an SGI Indigo-2 workstation using the program Insight II (Biosym Technologies Inc., San Diego, CA, USA). The picture was created with AVS software (AVS Inc., Waltham, MA, USA) and locally developed modules running on a DEC Alpha 3000/500 with a Kubota Pacific Denali graphics card.



Scheme 14. Thermal intramolecular Michael reaction of diendione **42**. a) hydroquinone (trace), toluene, 250 °C, 50 min, 23 % **38**, 34 % **56** and **55** (trace); b) HF · py, MeCN, 0 → 25 °C, 91 %.

formation of the two diastereomeric tricyclic lactones **38** (23 %) and **56** (34 %) upon heating a solution of diendione **42** in benzene in a pressure vial at 250 °C.[43] Although the expected intramolecular Diels – Alder product **57** (Scheme 14) was not formed, this was of no consequence, since the next step would have involved the conversion of **57** to **38**. The stereochemistry of tricycles **38** and **56** was secured upon observation of key NOE enhancements and finally proven by the X-ray crystallographic analysis of the deprotected lactone **58** (see Scheme 14 and Figure 7 for ORTEP structure). The excitement of forming the coveted lactone **38**, however, was somewhat tempered by the soon to come realization of the capricious nature of this rare reaction. For instance, the reaction needed to be performed nearly neat in a small amount of solvent, so that the actual reaction temperature at the bottom of the vial approached the temperature of the oil bath (250 °C). But running the reaction completely neat led to rapid and complete decomposition. More "mild" conditions (e.g. 200 °C in triisopropylbenzene) increased the selectivity towards the undesired lactone **56** (50 % yield). A number of solvents (e.g. DME, DMSO, MeCN, toluene, mesitylene, chlorobenzene, triisopropylbenzene) and different reaction conditions (e.g. neutral, basic (pyridine, Et_3N) and

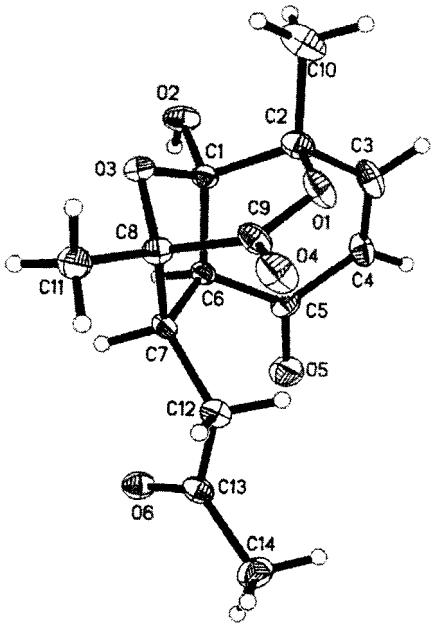


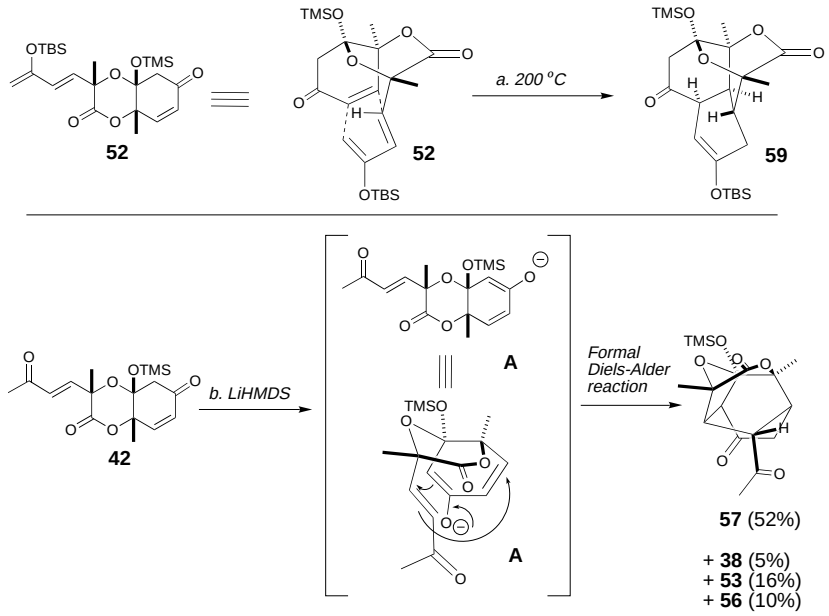
Figure 7. ORTEP drawing of tricyclic hemiketal **58**.

acidic (PPTS)) were investigated, but showed no improvement for accessing lactone **38**.

Since we placed high confidence on lactone **38** as a key synthon in our journey to trichodimerol (**1**), we required a more efficient protocol for its procurement. Because the thermal conditions had succeeded in forcing the fleeting tautomerization of the cycloenone moiety of **42**, we undertook another attempt towards a Diels – Alder adduct of type **39**/**57** by subjecting the readily available trienone **52** lacking the Michael acceptor system in the side chain to the thermal conditions. But not surprisingly, trienone **52** led to the electronically matched, but substantially strained, Diels – Alder adduct **59** resulting from the attack of the diene moiety onto the electron-poor cycloenone, followed by a consecutive double bond migration (Scheme 15).[44]

Because Michael reactions are normally performed at relatively low temperatures under basic conditions, we inves-

  0947-6539/99/0512-3658 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 12



Scheme 15. Successful Diels–Alder reaction of diendione **42**. a) toluene, 200 °C, 2 h, 32%; b) 0.3 equiv of LiHMDS, THF, −78 →0 °C, 3 h, 52% **57** and 5% **38** and 16% **53** and 10% **56**.

tigated such conditions to access either lactone **38** by a direct Michael addition (see Scheme 14), or the formal Diels–Alder adduct **57** by two consecutive Michael additions from substrate **42**.[45] Indeed, under the auspices of base at reduced temperature (i.e. LiHMDS cat., THF, −78 to 0 °C), we have been able to isolate the formal Diels–Alder adduct **57** as the main product formed from diendione **42** (Scheme 15). Though the structure of **57** was unambiguously assigned by NMR spectroscopy, we submitted this crystalline substance to X-ray crystallographic analysis, which gave final proof for the formation of this novel and rather strained molecule (see ORTEP drawing, Figure 8).

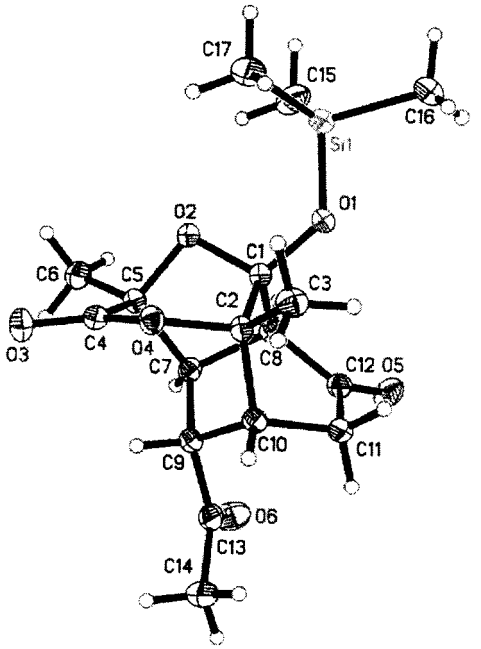


Figure 8. ORTEP drawing of Diels–Alder adduct **57**.

Conclusion

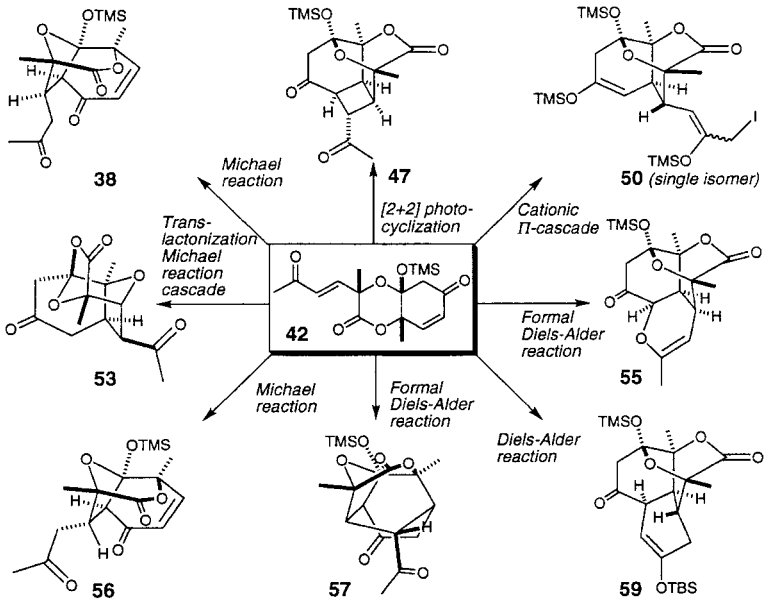
Our adventurous journey into the chemistry of bisorbicillinoids has resulted in a number of new and interesting discoveries. Namely, the reactive bisketene acetal **13** as a versatile building block, the extension of the borders of known Mukaiyama-type chemistry by intramolecular formation of β-ketal ketones, and new insight into the mild and regioselective formation of silyl enol ethers laid the foundations for the synthesis of tricyclic lactone **38** as an advanced intermediate in our synthetic endevor towards trichodimerol (**1**) and demethyltrichodimerol (**2**). Last, but not least, the serendipitous construction of a number of novel polycyclic, highly oxygenated compounds, which were efficiently assembled from simple starting materials using unprecedented cascade sequences, arose from our studies. Scheme 16 summarizes these novel reactions and molecular frameworks. In retrospect, these novel polycycles owe their formation to the close positioning of functionalities with complementary reactivity. Thus the described chemistry should add further information to the pool of knowledge regarding the synthesis of congested molecules of unique functional group interposition. Finally, the intelligence harvested during this stage of the program will serve as a strong foundation towards the total synthesis of trichodimerol (**1**) and its classmates.

Experimental Section

General techniques: All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (ether) and methylene chloride (CH_2Cl_2) were obtained by passing commercially available predried, oxygen-free formulations[46] through activated alumina columns.

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Irradiation experiments were performed with a Hannovia 450-W medium-pressure mercury lamp. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an acidic mixture of phosphomolybdic acid/cerium sulfate,[47] and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50, or 1 mm E. Merck silica gel plates (60F-254).

NMR spectra were recorded on Bruker DRX-600, DRX-500 or AMX-500 instruments and calibrated by using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. DEPT spectra are quoted as CH_3, CH_2, CH, and C. Assigned protons and carbons are cited with position numbers (e.g. Pos 3)

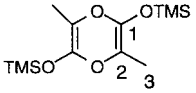


Scheme 16. Summary of novel structures derived from diendione **42**.

as shown in the appending structures. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer and are presented as: s (strong), m (medium), w (weak) and br. (broad). Electrospray ionization mass spectrometry (ESIMS) experiments were performed on an API 100 Perkin Elmer SCIEX single quadrupole mass spectrometer at 4000V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions with nitrobenzyl alcohol (NBA) as the matrix. Melting points (m.p) are uncorrected and were recorded on a Thomas-Hoover Unimelt capillary melting point apparatus.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC-123396 (**15**), CCDC-123392 (**27**), CCDC-123395 (**33**), CCDC-123393 (**53**), CCDC-123391 (**57**) and CCDC-123394 (**58**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

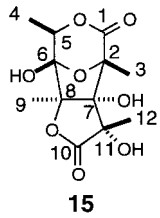
Ketene acetal 13: *n*BuLi (48 mL, 1.6 M solution in hexanes, 77 mmol, 2.2 equiv) was added slowly to a solution of dry diisopropylamine (10.9 mL, 84 mmol, 2.4 equiv) in THF (250 mL, 0.1 M) at 0 °C. After 60 min the solution was cooled to −110 °C (cooling bath temperature) and TMSCl



13

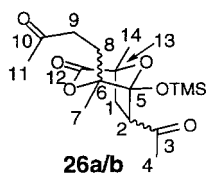
(10.2 mL, 80.5 mmol, 2.3 equiv) was added within 5 min, directly followed by slow addition (within 10 min) of a solution of lactide **14** (5.0 g, 35 mmol, 1.0 equiv) in THF (25 mL). The solution was kept at −110 °C for a further 40 min and then warmed slowly to 10 °C over 3 h. The solvent was removed in vacuum (water bath 15 °C) to afford a white slurry (ca. 10 mL). The white solid (LiCl) was removed by a fast filtration (celite 545 [Fisher Scientific]; dry ether [40 mL]) and the resulting solution was concentrated under vacuum (water bath 15 °C) to afford ketene acetal **13** (10.2 g, ≡10.2 mL, quantitative yield, purity ≈95% (NMR spectroscopy), liquid contains about 2% wt ether) as a clear, slightly yellow liquid. All workup procedures were performed under argon. IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2960 w (C−H), 1767 s (C=C), 1254 s (C−O), 1099 s, 848 s; ^{1}H NMR (500 MHz, $CDCl_3$, all signals ×2): δ = 1.66 (s, 3H, Pos 3), 0.21 (s, 9H, Si(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.2 (Pos 1), 114.5 (Pos 2), 12.4 (Pos 3), 0.0 (Si(CH_3)$_3$).

Tricyclic lactone 15: *n*BuLi (9.5 mL, 1.6 M solution in hexanes, 15.2 mmol, 2.2 equiv) was added slowly to a 0 °C cold solution of dry 2,2,6,6-tetramethylpiperidine (2.8 mL, 16.6 mmol, 2.4 equiv) in THF (50 mL). The solution was stirred for another 30 min and then cooled to −78 °C whereupon lactide **14** (1.0 g, 6.9 mmol, 1.0 equiv) was added in two portions while the solution turned intensively yellow-orange. After

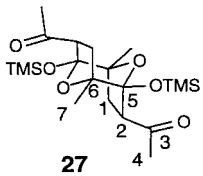


15

120 min a −78 °C cold solution of formaldehyde (excess) in THF (150 mL) was added slowly.[48] After another 120 min the reaction was stopped by addition of saturated NH_4Cl (30 mL) and warmed to room temperature. Ether (100 mL) and water (20 mL) were added. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (silica gel, hexanes:ethyl acetate 1:1) to afford tricyclic lactone **15** (411 mg, 1.43 mmol, 41%) as a white crystalline solid. M.p. 233 °C (decomp; after recrystallization from CH_2Cl_2); R_f = 0.23 (silica gel, hexanes:ethyl acetate 1:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 3409 s br. (O−H), 2958 w (C−H), 1782 s (C=O, γ-lactone), 1754 s (C=O, δ-lactone), 1362 s, 1281 m, 1181 s, 1121 s, 1075 s; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.55 (q, $^3J_{5,4}$ = 7.5 Hz, 1H, Pos 5), 2.10-1.85 (s br, 3H, OH), 1.57 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.48 (d, $^3J_{4,5}$ = 7.5 Hz, 3H, Pos 4); ^{13}C NMR (125 MHz, $CDCl_3$:CD_3OD 4:1): δ = 174.0, 167.4 (Pos 1 + Pos 10), 99.6 (Pos 6), 91.9, 83.4, 82.7, 74.6, 18.7, 18.0, 15.6, 15.2; HRMS: calcd for $C_{12}H_{16}O_8$ [M+Na$^+$] 311.0743, found 311.0750.



26a/b



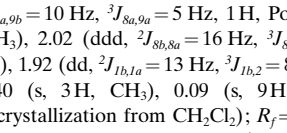
27

Tricyclic ketals 26a/b and tetracyclic ketal 27: Freshly destilled methyl vinyl ketone (**25**) (0.12 mL, 1.4 mmol, 2.0 equiv) was added to a solution of ketene acetal **13** (0.2 mL, 0.7 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at −78 °C. After 15 min $TiCl_4$ (1.4 mL, 1.0 M solution in CH_2Cl_2, 1.4 mmol, 2 equiv) was added slowly dropwise. The reaction mixture was stirred for 3 h at −78 °C and then quenched by addition of saturated $NaHCO_3$ (3 mL). After the mixture was allowed to warm to room temperature, more CH_2Cl_2 (20 mL) was added, and the two-phase slurry was filtered (Celite 545, CH_2Cl_2). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by gradient flash chromatography (silica gel, hexanes:ethyl acetate 2:1 →1:1) to afford tetracyclic lactone **27** (14 mg, 0.033 mmol, 5%) as a white crystalline solid and trcyclic lactones **26a** (23 mg, 0.065 mmol, 9%) and **26b** (12 mg, 0.034 mmol, 5%) as colorless oils, accompanied by diketo dilactones **28a/b** (14 mg, 0.049 mmol, 7%; vide infra). **26a**: R_f = 0.47 (silica gel, hexanes:ethyl acetate 1:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2961 w (C−H), 1750 s (C=O, lactone), 1716 s (C=O, ketone), 1254 s, 1184 m, 1141 s, 1097 s, 872 s, 848 s; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.73 (t, $^3J_{2,1a,1b}$ = 8.5 Hz, 1H, Pos 2), 2.73 (ddd, $^2J_{9a,9b}$ = 18 Hz, $^3J_{9a,8b}$ = 9.5 Hz, $^3J_{9a,8a}$ = 5.5 Hz, 1H, Pos 9a), 2.60 (dd, $^2J_{1a,1b}$ = 13 Hz, $^3J_{1a,2}$ = 8.5 Hz, 1H, Pos 1a), 2.55 (ddd, $^2J_{9b,9a}$ = 18 Hz, $^3J_{9b,8a}$ = 10 Hz, $^3J_{9b,8b}$ = 5.5 Hz, 1H, Pos 9b), 2.42 (ddd, $^2J_{8a,8b}$ = 19 Hz, $^3J_{8a,9b}$ = 10 Hz, $^3J_{8a,9a}$ = 5.5 Hz, 1H, Pos 8a), 2.24 (s, 3H, CH_3), 2.17 (s, 3H, CH_3), 1.95 (dd, $^2J_{1b,1a}$ = 13 Hz, $^3J_{1b,2}$ = 8.5 Hz, 1H, Pos 1b), 1.86 (ddd, $^2J_{8b,8a}$ = 19 Hz, $^3J_{8b,9a}$ = 9.5 Hz, $^3J_{8b,9b}$ = 5.5 Hz, 1H, Pos 8b), 1.58 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 0.12 (s, 9H, Si(CH_3)$_3$); assignment of ^{1}H NMR signals was aided by H,H-COSY; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.6, 204.0 (Pos 3 + Pos 10), 170.2 (Pos 12), 106.8 (Pos 5), 88.9, 81.6 (Pos 6 + Pos 13), 53.0 (Pos 2), 37.5 br. (2 carbons), 31.2, 30.1, 28.4, 19.8, 19.6, 1.8; HRMS: calcd for $C_{17}H_{28}O_6Si$

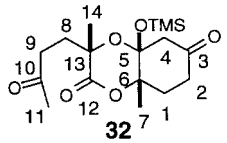
0947-6539/99/0512-3660 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 12

[M+Na$^+$] 379.1553, found 379.1564. **26b:** R_f = 0.53 (silica gel, hexanes:ethyl acetate 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.81 (t, $^3J_{2,1a,1b}$ = 8.5 Hz, 1H, Pos 2), 2.80 (ddd, $^2J_{9a,9b}$ = 18 Hz, $^3J_{9a,8b}$ = 10.5 Hz, $^3J_{9a,8a}$ = 5 Hz, 1H, Pos 9a), 2.61 (ddd, $^2J_{9b,9a}$ = 18 Hz, $^3J_{9b,8a}$ = 10 Hz, $^3J_{9b,8b}$ = 5.5 Hz, 1H, Pos 9b), 2.59 (dd, $^2J_{1a,1b}$ = 13 Hz, $^3J_{1a,2}$ = 8.5 Hz, 1H, Pos 1a), 2.30 (ddd, $^2J_{8a,8b}$ = 16 Hz, $^3J_{8a,9b}$ = 10 Hz, $^3J_{8a,9a}$ = 5 Hz, 1H, Pos 8a), 2.26 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.02 (ddd, $^2J_{8b,8a}$ = 16 Hz, $^3J_{8b,9a}$ = 10.5 Hz, $^3J_{8b,9b}$ = 5.5 Hz, 1H, Pos 8b), 1.92 (dd, $^2J_{1b,1a}$ = 13 Hz, $^3J_{1b,2}$ = 8.5 Hz, 1H, Pos 1b), 1.56 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 0.09 (s, 9H, $Si(CH_3)_3$); **27:** M.p. 201 °C (after recrystallization from CH_2Cl_2); R_f = 0.57 (silica gel, hexanes:ethyl acetate 5:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2959 w (C–H), 1714 s (C=O, ketone), 1251 s, 1174 m, 1121 m, 1066 s, 1002 s, 844 s, 737 s, 704 s; ^{1}H NMR (500 MHz, $CDCl_3$, all signals × 2): δ = 3.52 (dd, $^3J_{2,1b}$ = 9 Hz, $^3J_{2,1a}$ = 5.5 Hz, 1H, Pos 2), 2.21 (dd, $^2J_{1a,1b}$ = 12.5 Hz, $^3J_{1a,2}$ = 5.5 Hz, 1H, Pos 1a), 2.17 (s, 3H, CH_3), 1.96 (dd, $^2J_{1b,1a}$ = 12.5 Hz, $^3J_{1b,2}$ = 9 Hz, 1H, Pos 1b), 1.34 (s, 3H, Pos 7), 0.07 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.8 (Pos 3), 109.6 (Pos 5), 85.3 (Pos 6), 54.7 (Pos 2), 33.2, 31.2, 18.8, 1.9; HRMS: calcd for $C_{20}H_{36}O_6Si_2$ [M+Na$^+$] 451.1948, found 451.1935.

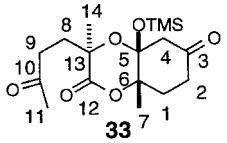
Diketo dilactones 28a/b: Anhydrous ZnI_2 (140 mg, 0.125 mmol, 0.13 equiv) was added to a solution of freshly distilled methyl vinyl ketone (**25**) (0.7 mL, 8.6 mmol, 2.4 equiv) and ketene acetal **13** (1.0 mL, 3.5 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at 0 °C under vigorous stirring. The suspension was stirred for another 4 h at 0 °C and then acetone (15 mL) and aqueous HF (0.2 mL, 48% wt solution in water, 13 mmol, 3.8 equiv) were added at room temperature. After further stirring (2 h), CH_2Cl_2 (150 mL) and water (10 mL) were added. The organic layer was washed with saturated $NaHCO_3$ (2 × 25 mL), brine (25 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (silica gel, hexanes:ethyl acetate 3:2) to afford diketo dilactones **28a/b** (596 mg, 2.10 mmol, 60% over two steps from lactide **14**; ≈1:1 mixture of epimers) as a white crystalline solid.[49] R_f = 0.23 (silica gel, hexanes:ethyl acetate 1:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2926 w (C–H), 1742 s (C=O, lactone), 1721 s (C=O, ketone), 1188 m, 1108 m; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.64-2.50 (m, 4H, CH_2), 2.39–2.26 (m, 2H, CH_2), 2.22–2.17 (m, 2H, CH_2), 2.17 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.68 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.1, 206.0, 167.43, 167.40, 83.1 br. (2 carbons), 37.5, 37.2, 34.0 br. (2 carbons), 29.9, 29.8, 26.5, 25.9; HRMS: calcd for $C_{14}H_{20}O_6$ [M+Na$^+$] 307.1158, found 307.1168.



28a/b



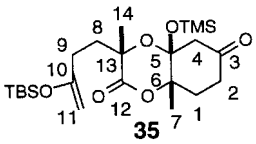
32



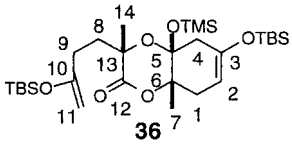
33

Ketal ketones 32 and 33: Dry triethylamine (0.56 mL, 4.04 mmol, 2.3 equiv) was added to a solution of diketo dilactones **28a/b** (500 mg, 1.76 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL, 0.3 M) at −78 °C. Then TMSOTf (0.88 mL, 4.85 mmol, 2.8 equiv) was added dropwise over 20 min. The clear solution was stirred for a further 30 min at −78 °C and then the reaction temperature was slowly raised to −10 °C over 2 h. After an additional 5 h at −10 °C the reaction mixture was quickly warmed to room temperature and saturated $NaHCO_3$ (10 mL) was added under vigorous stirring. After 15 min, ether (50 mL) was added. The organic layer was washed with saturated NH_4Cl (10 mL), the combined aqueous layers were extracted with ether (2 × 10 mL), and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated to afford a mostly crystalline, yellow solid (585 mg). The crude material was pulverized and then added to refluxing ether (80 mL; incomplete dissolution). The suspension was partially concentrated (→35 mL) and kept at 0 °C for 12 h. Filtration afforded *anti*-ketal ketone **33** (195 mg, 0.547 mmol, 31%) as colorless, crystalline solid and 355 mg of a yellow oil after concentration of the mother liquor. The residue was purified by flash chromatography (silica gel, hexanes:ethyl acetate 2:1) to afford *syn*-ketal ketone **32** (182 mg, 0.511 mmol, 29%) as a white crystalline solid. **32**: M.p. 101 °C (after recrystallization from ethyl acetate); R_f=0.36 (silica gel, hexanes:ethyl acetate 1:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2959 w (C–H), 1728 s br. (C=O), 1256 m, 1150 m, 1087 s, 847 s; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.81 (dd, $^2J_{4a,4b}$ = 14 Hz, $^4J_{4a,2a}$ = 2 Hz, 1H, Pos 4a), 2.65 (d, $^2J_{4b,4a}$ = 14 Hz, 1H, Pos 4b), 2.56 (t, $^3J_{9a,9b,8a,8b}$ = 7.5 Hz, 2H, Pos 9a + Pos 9b), 2.49 (d br, $^2J_{2a,2b}$ = 15.5 Hz, 1H, Pos 2a), 2.34 (ddd, $^2J_{2b,2a}$ = 15.5 Hz, $^3J_{2b,1a}$ = 12.5 Hz, $^3J_{2b,1b}$ = 7 Hz, 1H, Pos 2b), 2.13 (s, 3H, Pos 11) and 2.22–2.07 (m, additional 3H, Pos 1a + Pos 8a + Pos 8b), 2.02 (dtr, $^2J_{1b,1a}$ = 14.5 Hz, $^3J_{1b,2a,2b}$ = 7 Hz, 1H, Pos 1b), 1.56 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 0.20 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.1/203.4 (Pos 3 + Pos 10), 171.7 (Pos 12), 97.3 (Pos 5), 84.4/76.0 (Pos 6 + Pos 13), 50.4 (Pos 4), 37.5, 37.1, 34.2, 33.6, 30.1, 26.3, 21.6, 1.9; HRMS: calcd for $C_{17}H_{28}O_6Si$ [M + Na$^+$] 379.1553, found 379.1565. **33:** M.p. 155 °C (after recrystallization from CH_2Cl_2); R_f = 0.43 (silica gel, hexanes:ethyl acetate 1:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2962 w (C–H), 1726 s br. (C=O), 1257 m, 1150 m, 1088 s, 847 s; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.83 (dd, $^2J_{4a,4b}$ = 14 Hz, $^4J_{4a,2a}$ = 2 Hz, 1H, Pos 4a), 2.68 (ddd, $^2J_{9a,9b}$ = 18 Hz, $^3J_{9a,8b}$ = 10.5 Hz, $^3J_{9a,8a}$ = 6 Hz, 1H, Pos 9a), 2.60 (d, $^2J_{4b,4a}$ = 14 Hz, 1H, Pos 4b), 2.58 (ddd, $^2J_{9b,9a}$ = 18 Hz, $^3J_{9b,8a}$ = 10 Hz, $^3J_{9b,8b}$ = 4.5 Hz, 1H, Pos 9b), 2.49 (dddd, $^2J_{2a,2b}$ = 15 Hz, $^3J_{2a,1b}$ = 6.5 Hz, $^3J_{2a,1a}$ = 6 Hz, $^4J_{2a,4a}$ = 2 Hz, 1H, Pos 2a), 2.32 (ddd, $^2J_{2b,2a}$ = 15 Hz, $^3J_{2b,1a}$ = 9 Hz, $^3J_{2b,1b}$ = 6.5 Hz, 1H, Pos 2b), 2.24 (ddd, $^2J_{8a,8b}$ = 14.5 Hz, $^3J_{8a,9b}$ = 10 Hz, $^3J_{8a,9a}$ = 6 Hz, 1H, Pos 8a), 2.15 (ddd, $^2J_{8b,8a}$ = 14.5 Hz, $^3J_{8b,9a}$ = 10.5 Hz, $^3J_{8b,9b}$ = 4.5 Hz, 1H, Pos 8b), 2.14 (s, 3H, Pos 11), 2.11 (ddd, $^2J_{1a,1b}$ = 14 Hz, $^3J_{1a,2b}$ = 9 Hz, $^3J_{1a,2a}$ = 6 Hz, 1H, Pos 1a), 2.04 (dt, $^2J_{1b,1a}$ = 14 Hz, $^3J_{1b,2a,2b}$ = 6 Hz, 1H, Pos 1b), 1.55 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 0.17 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.1, 203.9 (Pos 3 + Pos 10), 171.9 (Pos 12), 97.8 (Pos 5), 84.1 / 76.6 (Pos 6 + Pos 13), 50.3 (Pos 4), 37.4, 37.2, 34.2, 33.4, 30.1, 25.5, 21.6, 1.8; HRMS: calcd for $C_{17}H_{28}O_6Si$ [M+Na$^+$] 379.1553, found 379.1566.

TBS-enol ether 35: Dry triethylamine (200 µL, 1.43 mmol, 1.6 equiv) was added to a solution of *syn*-ketal ketone **32** (320 mg, 0.90 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) at −78 °C. TBSOTf (228 µL, 1.00 mmol, 1.1 equiv) was then added dropwise over 20 min. The clear solution was stirred for a further 4 h at −78 °C and then the reaction was quenched by addition of saturated $NaHCO_3$ (4 mL). Further CH_2Cl_2 (30 mL) was added and the temperature was raised to room temperature. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by rapid flash chromatography (silica gel, hexanes:ethyl acetate 3:1) to afford TBS-enol ether **35** (381 mg, 0.81 mmol, 90%) as a colorless oil. R_f = 0.50 (silica gel, hexanes:ethyl acetate 2:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2957 m (C–H), 2928 w (C–H), 2858 w (C–H), 1732 s br. (C=O), 1254 m, 1150 m, 1087 s, 843 s; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.02 (s, 1H, Pos 11a), 4.00 (s, 1H, Pos 11b), 2.85 (dd, $^2J_{4a,4b}$ = 14 Hz, $^4J_{4a,2a}$ = 1.5 Hz, 1H, Pos 4a), 2.63 (d, $^2J_{4b,4a}$ = 14 Hz, 1H, Pos 4b), 2.50–2.46 (m, 1H, CH_2), 2.36-2.30 (m, 1H, CH_2), 2.19–1.97 (m, 6H, all CH_2), 1.56 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 9H, $Si(CH_3)_3$), 0.13 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 203.6 (Pos 3), 172.2 (Pos 12), 158.4 (Pos 10), 97.5 (Pos 5), 90.1 (Pos 11), 84.1, 77.0 (one carbon hidden in $CDCl_3$ signals, Pos 6 + Pos 13), 53.4, 50.4, 38.5, 37.4, 33.5, 30.5, 30.3, 25.7, 21.7, 18.0, 1.8, −4.8; HRMS: calcd for $C_{23}H_{42}O_6Si_2$ [M+Na$^+$] 493.2418, found 493.2404.



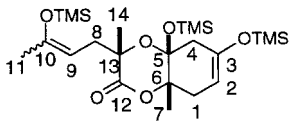
35



36

TBS-enol ether 36: Dry triethylamine (182 µL, 1.31 mmol, 4 equiv) was added to a solution of *syn*-ketal ketone **32** (117 mg, 0.328 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL, 0.1 M) at −78 °C. TBSOTf (226 µL, 0.985 mmol, 3 equiv) was then added dropwise over 20 min. The clear solution was stirred for further 20 min at −78 °C and then the reaction temperature was slowly raised to 10 °C over 4 h. The reaction was quenched by addition of saturated $NaHCO_3$ (2 mL) and then further CH_2Cl_2 (20 mL) was added. The organic layer was dried ($MgSO_4$) and concentrated to afford an orange emulsion. This was purified by rapid flash chromatography (silica gel, hexanes:ether 10:1) to afford TBS-enol ether **36** (165 mg, 0.282 mmol, 86%) as a colorless oil. R_f = 0.58 (silica gel, hexanes:ethyl acetate 5:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2956 m (C–H), 2930 m (C–H), 2858 m (C–H),

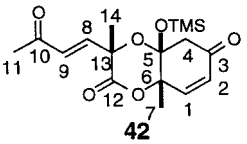
1746 s (C=O, lactone), 1682 m (C=C), 1362 m, 1254 s, 1207 s, 1151 s, 1110 s, 1058 s, 896 s, 841 s, 780 s; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 4.68$ (d br, $^3J_{2,1a} = 6$ Hz, 1H, Pos 2), 4.00 (s, 1H, Pos 11a), 3.98 (s, 1H, Pos 11b), 2.52–2.45 (m, 3H, all CH_2), 2.33–2.27 (m, 1H, CH_2), 2.17–2.13 (m, 2H, both CH_2), 1.94–1.88 (m, 1H, CH_2), 1.53 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.21 (s, 9H, $Si(CH_3)_3$), 0.13 (s, 3H, $Si(CH_3)$), 0.13 (s, 6H, 2 × $Si(CH_3)$), 0.12 (s, 3H, $Si(CH_3)$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 173.0$ (Pos 12), 158.4, 1.46.0 (Pos 3 + Pos 10), 100.2 (Pos 2), 95.8 (Pos 5), 89.7 (Pos 11), 83.7, 76.1 (Pos 6 + Pos 13), 41.7, 39.1, 36.4, 30.5, 26.7, 25.7, 25.6, 22.5, 18.0 br. (2x carbon), 2.1, −4.4, −4.5, −4.76, −4.79; HRMS: calcd for $C_{29}H_{56}O_6Si_3$ [M+Na$^+$] 607.3282, found 607.3292.



41a/b

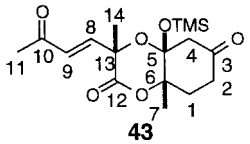
Silyl enol ethers 41a/b: Dry hexamethyldisilazane (2.40 mL, 11.36 mmol, 3 equiv) was added to a solution of *syn*-ketal ketone **32** (1.35 g, 3.79 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) at −20 °C. Then TMSI (0.27 mL, 1.90 mmol, 0.5 equiv) was added slowly dropwise over 10 min. The solution was then stirred for additional 4 h at room temperature. The reaction was quenched by addition of saturated $NaHCO_3$ (20 mL) and then further CH_2Cl_2 (200 mL) was added. The organic layer was dried ($MgSO_4$) and concentrated in high vacuum to afford silyl enol ethers **41a/b** (1.90 g, 3.79 mmol, quantitative; ca. 2:1 mixture of geometrical isomers, double bond stereochemistry not assigned) as a colorless oil. $R_f = 0.57$ (silica gel, hexanes:ether 2:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2958 m (C–H), 1742 s (C=O, lactone), 1682 m (C=C), 1253 s, 1204 m, 1150 m, 1107 m, 1059 m, 900 s, 845 s; ^{1}H NMR (500 MHz, C_6D_6): $\delta = 5.03$ (t, $^3J_{9,8a,8b} = 8$ Hz, 0.3H, Pos 9-B), 4.86 (t, $^3J_{9,8a,8b} = 8$ Hz, 0.7H, Pos 9-A), 4.67–4.62 (m, 1H, Pos 2), 2.97–2.59 (m, 5H, all CH_2), 2.23–2.17 (m, 1H, CH_2), 1.84 (s, 2H, CH_3-A), 1.80 (s, 1H, CH_3-B), 1.75 (s, 1H, CH_3-B), 1.73 (s, 2H, CH_3-A), 1.38 (s, 2H, CH_3-A), 1.37 (s, 2H, CH_3-B), 0.25 (s, 3H, $Si(CH_3)_3$-B), 0.18 (s, 12H, $Si(CH_3)_3$-A), 0.18 (s, 3H, $Si(CH_3)_3$-B), 0.11 (s, 3H, $Si(CH_3)_3$-B), 0.10 (s, 6H, $Si(CH_3)_3$-A); ^{13}C NMR (125 MHz, $CDCl_3$): diastereomer A: $\delta = 173.1$ (Pos 12), 149.2, 145.8 (Pos 3 + Pos 10), 101.5, 100.4 (Pos 2 + Pos 9), 95.7 (Pos 5), 83.6, 76.9 (Pos 6 + Pos 13), 41.7, 37.4, 36.4, 27.1, 22.7, 22.5, 2.1, 0.7, 0.1; diastereomer B: $\delta = 173.2$ (Pos 12), 151.0, 145.9 (Pos 3 + Pos 10), 101.6, 99.7 (Pos 2 + Pos 9), 95.7 (Pos 5), 83.7, 77.2 (Pos 6 + Pos 13), 41.9, 39.5, 36.6, 27.2, 22.4, 18.0, 2.1, 0.3, 0.2; HRMS: calcd for $C_{23}H_{44}O_6Si_3$ [M+Na$^+$] 523.2343, found 523.2350.

Diendione 42: A solution of phenylselenenyl chloride (2.29 g, 11.95 mmol, 2.2 equiv) in THF (10 mL) was added slowly over 50 min to a solution of silyl enol ethers **41a/b** (2.72 g, 5.43 mmol, 1.0 equiv) in THF (50 mL) at −78 °C. After two more hours, the reaction was quenched at −78 °C by adding saturated $NaHCO_3$ (40 mL) under vigorous stirring. Ether (100 mL) was added and the slurry was warmed to room temperature. The aqueous layer was extracted with ether (2 × 50 mL); the combined organic layers were washed with saturated $NaHCO_3$ (40 mL), saturated NH_4Cl (40 mL), and brine (40 mL), dried ($MgSO_4$), and concentrated to afford a yellow oil (4.1 g). The crude material was then dissolved in warm THF (320 mL, $T_{solution} = 50$ °C) and aqueous H_2O_2 (3.7 mL, 30 % wt solution in water, 36.3 mmol, ≈7 equiv) was added. After 50 min at 50 °C the solution was partially concentrated in vacuum (→100 mL). CH_2Cl_2 (400 mL) was added and the organic layer was washed with saturated $NaHCO_3$ (2×50 mL), saturated NH_4Cl (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, hexanes:ether 1:2) to afford diendione **42** (1.336 g, 3.79 mmol, 70 %) as a white crystalline solid. M.p. 136 °C (after recrystallization from CH_2Cl_2); $R_f = 0.27$ (silica gel, hexanes:ethyl acetate 2:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2959 w (C–H), 1750 s (C=O, lactone), 1690 s (C=O, enone), 1628 w (C=C, enone), 1255 s, 1123 s, 1085 s, 1044 m, 915 m, 848 s; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.73$ (d, $^3J_{1,2} = 10$ Hz, 1H, Pos 1), 6.55 (d, $^3J_{8,9} = 16$ Hz, 1H, Pos 8), 6.06 (d, $^3J_{9,8} = 16$ Hz, 1H, Pos 9), 5.97 (d, $^3J_{2,1} = 10$ Hz, 1H, Pos 2), 3.05 (d, $^2J_{4a,4b} = 16$ Hz, 1H, Pos 4a), 2.80 (d, $^2J_{4b,4a} = 16$ Hz, 1H, Pos 4b), 2.19 (s, 3H, Pos 11), 1.66 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 0.26 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 197.3$, 193.9 (Pos 3 + Pos 10), 168.1 (Pos 12), 149.1, 144.8 (Pos 1 + Pos 8), 129.9, 127.5 (Pos 2 + Pos 9), 96.5 (Pos 5), 84.1, 76.4 (Pos 6 + Pos 13), 48.0 (Pos 4), 28.5, 27.8, 23.8, 1.8; HRMS: calcd for $C_{17}H_{24}O_6Si$ ([M H$^+$]) 353.1420, found 353.1414.



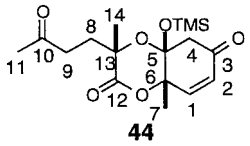
42

Endione 43: A suspension of $Pd(OAc)_2$ (8.7 mg, 0.038 mmol, 2 equiv) and silyl enol ethers **41a/b** (9.7 mg, 0.019 mmol, 1.0 equiv) in MeCN (0.3 mL) was stirred vigorously for 50 min. Then the suspension was concentrated and purified by flash chromatography (silica gel, hexanes: ethyl acetate 2:1) to afford endione **43** (3.1 mg, 0.0087 mmol, 46 %) as a white crystalline solid. M.p. 148 °C (after recrystallization from CH_2Cl_2:ether 1:1); $R_f = 0.22$ (silica gel, hexanes:ethyl acetate 2:1); IR (thin film): $\tilde{\nu}_{max} = 2960$ w (C–H), 1738 s (C=O, lactone), 1716 s (C=O, ketone), 1682 s (C=O, enone), 1627 m (C=C), 1303 s, 1255 s, 1123 s, 1087 s, 848 s; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.85$ (d, $^3J_{8,9} = 16$ Hz, 1H, Pos 8), 6.27 (d, $^3J_{9,8} = 16$ Hz, 1H, Pos 9), 2.84 (dd, $^2J_{4a,4b} = 16$ Hz, $^4J_{4a,2a} = 2$ Hz, 1H, Pos 4a), 2.63 (dd, $^2J_{4b,4a} = 16$ Hz, $^4J_{4b,2b} = 1$ Hz, 1H, Pos 4b), 2.49 (dtd, $^2J_{2a,2b} = 15.5$ Hz, $^3J_{2a,1a,1b} = 6$ Hz, $^4J_{2a,4a} = 2$ Hz, 1H, Pos 2a), 2.34 (dtd, $^2J_{2b,2a} = 15.5$ Hz, $^3J_{2b,1a,1b} = 6$ Hz, $^4J_{2b,4b} = 1$ Hz, 1H, Pos 2b), 2.26 (s, 3H, Pos 11), 2.03 (t, $^3J_{1a,2a,2b} = 6$ Hz, 1H, Pos 1a), 2.02 (t, $^3J_{1b,2a,2b} = 6$ Hz, 1H, Pos 1b), 1.69 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 0.24 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 203.9$ (Pos 3), 197.4 (Pos 10), 168.5 (Pos 12), 146.7 (Pos 8), 129.4 (Pos 9), 97.8 (Pos 5), 84.3, 77.2 (Pos 6 + Pos 13), 50.3 (Pos 4), 37.1, 33.1, 29.2, 27.9, 21.5, 1.8; HRMS: calcd for $C_{17}H_{26}O_6Si$ [M+Na$^+$] 377.1396, found 377.1384.



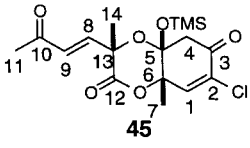
43

Endione 44: LiHMDS (84 μL, 1.0 M solution in THF, 0.084 mmol, 1 equiv) was added dropwise within 5 min to a solution of ketal ketone **32** (30.0 mg, 0.084 mmol, 1.0 equiv) in THF (0.6 mL) at −78 °C. The temperature was slowly raised to −40 °C and kept at this temperature for 1 h. Then the reaction mixture was cooled to −100 °C and a solution of phenylselenenyl chloride (16.1 mg, 0.084 mmol, 1 equiv) in THF (0.6 mL) was added dropwise. The reaction was quenched by adding saturated $NaHCO_3$ (2 mL) under vigorous stirring and then CH_2Cl_2 (8 mL) was added. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, hexanes: ethyl acetate 2:1) to afford the corresponding selenoketones (11.0 mg, mixture of diastereomers; not shown) as a white solid and recoverd ketal ketone **32** (14.9 mg). The selenoketones were dissolved in THF (1 mL) and aqueous H_2O_2 (2 drops, ≈15 μL, 30 % wt solution in water, ≈0.15 mmol, excess) was added. After 1 h water (3 mL) and CH_2Cl_2 (8 mL) was added and the organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, hexanes: ethyl acetate 2:1) to afford endione **44** (7.2 mg, 0.020 mmol, 24 %, 47 % based on recoverd starting material) as a white crystalline solid. $R_f = 0.28$ (silica gel, hexanes:ethyl acetate 2:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2960 w (C–H), 1746 s (C=O, lactone), 1716 s (C=O, ketone), 1692 s (C=O, enone), 1257 s, 1162 m, 1124 s, 1084 s, 1055 m, 922 s, 848 s; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.87$ (d, $^3J_{1,2} = 10$ Hz, 1H, Pos 1), 6.01 (dd, $^3J_{2,1} = 10$ Hz, $^4J_{2,4a} = 1$ Hz, 1H, Pos 2), 2.97 (dd, $^2J_{4a,4b} = 16$ Hz, $^4J_{4a,2} = 1$ Hz, 1H, Pos 4a), 2.77 (d, $^2J_{4b,4a} = 16$ Hz, 1H, Pos 4b), 2.48 (ddd, $^2J_{9a,9b} = 18$ Hz, $^3J_{9a,8a} = 9.5$ Hz, $^3J_{9a,8b} = 6.5$ Hz, 1H, Pos 9a), 2.35 (ddd, $^2J_{9b,9a} = 18$ Hz, $^3J_{9b,8b} = 9$ Hz, $^3J_{9b,8a} = 6.5$ Hz, 1H, Pos 9b), 2.10 (s, 3H, Pos 11), 1.94-1.89 (m, 2H, Pos 8a + Pos 8b), 1.60 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 0.26 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 206.9$ (Pos 10), 194.3 (Pos 3), 170.9 (Pos 12), 149.5 (Pos 1), 127.3 (Pos 2), 96.2 (Pos 5), 83.9, 75.8 (Pos 6 + Pos 13), 48.3 (Pos 4), 37.7, 34.1, 30.0, 26.6, 23.8, 1.8.



44

Chloro diendione 45: A solution of phenylselenenyl chloride (13.2 mg, 0.069 mmol, 2.3 equiv) in THF (0.25 mL) was added slowly (within 15 min) to a solution of silyl enol ethers **41a/b** (14.8 mg, 0.030 mmol,

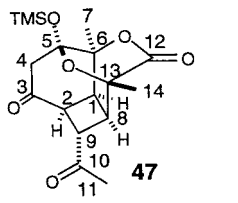


45

0947-6539/99/0512-3662 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 12

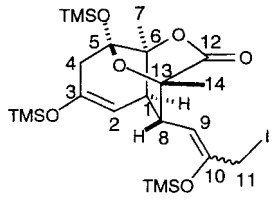
≡2 equiv) in THF (0.3 mL) at −78 °C. The temperature was slowly raised to −50 °C over 1 h. Then *m*CPBA (50 mg, 57–86 % wt, ≈0.15 mmol, ≈5 equiv) was added in one batch and the temperature was raised within the next 1 h to 0 °C. The reaction was quenched at 0 °C by adding saturated $NaHCO_3$ (2 mL) under vigorous stirring and then CH_2Cl_2 (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (2 × 1 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, hexanes: ether 1:1) to afford chloro diendione **45** (3.9 mg, 0.010 mmol, 34 %) as a colorless crystalline solid. M.p. 140 °C (after recrystallization from CH_2Cl_2); R_f = 0.26 (silica gel, hexanes:ether 2:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2959 w (C–H), 1754 s (C=O, lactone), 1711 s (C=O, chloro enone), 1682 m (C=O, enone), 1628 w (C=C), 1311 m, 1256 s, 1096 s, 1046 m, 880 s, 848 s; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.90 (s, 1H, Pos 1) 6.57 (d, $^3J_{8,9}$ = 16 Hz, 1H, Pos 8), 6.04 (d, $^3J_{9,8}$ = 16 Hz, 1H, Pos 9), 3.25 (d, $^2J_{4a,4b}$ = 16 Hz, 1H, Pos 4a), 2.91 (d, $^2J_{4b,4a}$ = 16 Hz, 1H, Pos 4b), 2.22 (s, 3H, Pos 11), 1.66 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 0.28 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 197.7 (Pos 10), 187.0 (Pos 3), 168.4 (Pos 12), 145.3/144.8 (Pos 1 + Pos 8), 132.9 (Pos 2), 130.4 (Pos 9), 97.1 (Pos 5), 85.3/77.6 (Pos 6 + Pos 13), 48.4 (Pos 4), 29.4, 29.2, 24.5, 2.6; HRMS: calcd for $C_{17}H_{23}O_6SiCl$ ([*M* H^+]) 387.1031, found 387.1024.

[2 + 2] Adduct 47b: A degassed solution of diendione **42** (10.0 mg, 0.028 mmol) in [D_6]benzene (0.4 mL) in an NMR tube was irradiated for 30 min with a mercury medium-pressure lamp (see General techniques section). The solution was concentrated to afford [2 + 2] adduct **47** (10.0 mg, 0.028 mmol, quantitative) as a colorless crystalline solid. M.p. 97 °C (after recrystallization from CH_2Cl_2); R_f = 0.37 (silica gel, hexanes:ethyl acetate 2:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2959 w (C–H), 1760 s (C=O, lactone), 1715 s (C=O, ketone), 1307 m, 1252 s, 1152 s, 1085 s, 886 s, 845 s; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.35 (dd, $^3J_{2,1}$ = 9 Hz, $^3J_{2,9}$ = 5 Hz, 1H, Pos 2), 3.28 (dd, $^3J_{9,2}$ = 5 Hz, $^3J_{9,8}$ = 4 Hz, 1H, Pos 9), 3.13 (d, $^2J_{4a,4b}$ = 19 Hz, 1H, Pos 4a), 2.87 (dd, $^3J_{1,8}$ = 9.5 Hz, $^3J_{1,2}$ = 9 Hz, 1H, Pos 1), 2.72 (d, $^2J_{4b,4a}$ = 19 Hz, 1H, Pos 4b), 2.70 (dd, $^3J_{8,1}$ = 9.5 Hz, $^3J_{8,9}$ = 4 Hz, 1H, Pos 8), 2.21 (s, 3H, Pos 11), 1.45 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 0.16 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, C_6D_6): δ = 204.2, 202.3 (Pos 3 + Pos 10), 169.8 (Pos 12), 98.8 (Pos 5), 80.5, 74.1 (Pos 6 + Pos 13), 51.1, 45.3, 43.0, 40.5, 35.1, 26.2, 18.2, 16.1, 1.6; HRMS: calcd for $C_{17}H_{24}O_6Si$ [*M* + Na^+] 353.1420, found 353.1424.



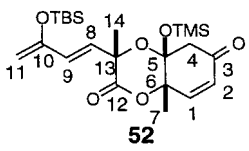
47

Iodo lactone 50: Hexamethyldisilazane (30 μL, 0.14 mmol, 5 equiv) and then trimethylsilyl iodide (9 μL, 0.063 mmol, 2.2 equiv) were added to a solution of diendione **42** (10.0 mg, 0.028 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL) at −20 °C. After 10 min the reaction mixture was warmed to room temperature and stirred for 8 h. Then the solution was directly subjected to flash chromatography (silica gel, hexanes: ether 5:1) to afford iodo lactone **50** (9.6 mg, 0.015 mmol, 55 %) as a colorless glass. R_f = 0.52 (silica gel, hexanes:ether 4:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2958 w (C–H), 1770 s (C=O, lactone), 1667 w (C=C, enol ether), 1651 w (C=C, enol ether), 1366 m, 1253 s, 1140 s, 1087 m, 1037 m, 900 m, 845 s; ^{1}H NMR (500 MHz, C_6D_6): δ = 5.03 (dd, $^3J_{2,1}$ = 7 Hz, $^4J_{2,4b}$ = 1.9 Hz, 1H, Pos 2), 4.61 (d, $^3J_{9,8}$ = 10.5 Hz, 1H, Pos 9), 3.31 (d, $^2J_{11a,11b}$ = 10.5 Hz, 1H, Pos 11a), 3.25 (d, $^2J_{11b,11a}$ = 10.5 Hz, 1H, Pos 11b), 2.96 (dd, $^3J_{8,9}$ = 10.5 Hz, $^3J_{8,1}$ = 2.2 Hz, 1H, Pos 8), 2.78 (d, $^2J_{4a,4b}$ = 18 Hz, 1H, Pos 4a), 2.43 (dd, $^2J_{4b,4a}$ = 18 Hz, $^4J_{4b,2}$ = 1.9 Hz, 1H, Pos 4b), 2.13 (dd, $^3J_{1,2}$ = 7 Hz, $^3J_{1,8}$ = 2.2 Hz, 1H, Pos 1), 1.60 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 0.25 (s, 9H, $Si(CH_3)_3$), 0.18 (s, 9H, $Si(CH_3)_3$), 0.15 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, C_6D_6): δ = 170.3 (Pos 12), 149.9 / 147.7 (Pos 3 + Pos 10), 110.2 (Pos 9), 106.4 (Pos 2), 98.1 (Pos 5), 81.1, 74.1 (Pos 6 + Pos 13), 48.4 (Pos 8), 43.8, 43.2 (Pos 1 + Pos 4), 18.8, 18.7 (Pos 7 + Pos 14), 6.7 (Pos 11), 1.6, 0.5, 0.1; Assignment of ^{1}H and ^{13}C NMR signals were aided by HMQC; MS-FAB: *m/z* (%): 625 ([*M*+H^+], 18), 757 [*M*+Cs^+], 100); HRMS: calcd for $C_{23}H_{41}O_6Si_3I$ [*M*+Cs^+] 757.0310, found 757.0333.



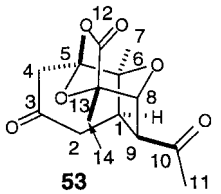
50, *single isomer*

TBS-enol ether 52: An identical procedure as the one used for the preparation of TBS-enol ether **35** (vide supra) afforded from diendione **42** (115 mg, 0.326 mmol) the TBS-enol ether **52** (143 mg, 0.306 mmol, 94 %) as a colorless oil. R_f = 0.50 (silica gel, hexanes:ethyl acetate 2:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2958 m (C–H), 2859 m, (C–H), 1754 s (C=O, lactone), 1694 s (C=O, enone), 1594 m (C=C, diene), 1315 s, 1256 s, 1123 s, 1086 s, 916 s, 845 s, 783 s; ^{1}H NMR (600 MHz, C_6D_6): δ = 6.29 (d, ^3J = 15 Hz, 1H, CH), 6.25 (d, ^3J = 15 Hz, 1H, CH), 6.07 (d, $^3J_{1,2}$ = 10 Hz, 1H, Pos 1), 5.75 (d, $^3J_{2,1}$ = 10 Hz, 1H, Pos 2), 4.35 (s, 1H, Pos 11a), 4.30 (s, 1H, Pos 11b), 2.96 (d, $^2J_{4a,4b}$ = 16 Hz, 1H, Pos 4a), 2.35 (d, $^2J_{4b,4a}$ = 16 Hz, 1H, Pos 4b), 1.81 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 0.97 (s, 9H, $SiC(CH_3)_3$) 0.10 (s, 3H, $Si(CH_3)$), 0.09 (s, 3H, $Si(CH_3)$), −0.06 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (150 MHz, C_6D_6): δ = 193.8 (Pos 3), 169.0 (Pos 12), 154.9 (Pos 10), 149.6 (Pos 1), 132.0, 129.8, 127.9 (Pos 2 + Pos 8 + Pos 9), 98.2, 97.3 (Pos 5 + Pos 11), 83.8, 77.6 (Pos 6 + Pos 13), 49.1 (Pos 4), 29.7, 26.4, 24.1, 18.9, 2.0, −4.2 br; HRMS: calcd for $C_{23}H_{38}O_6Si_2$ ([*M*+H^+]) 467.2285, found 467.2290.

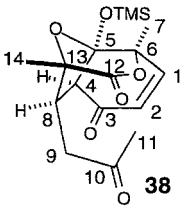


52

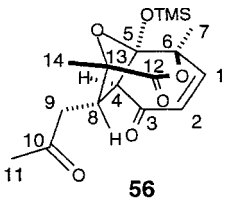
Spiroketal 53: LiHMDS (9 μL, 1.0 M solution in THF, 0.009 mmol, 0.3 equiv) was added dropwise to a solution of diendione **43** (10.0 mg, 0.028 mmol, 1.0 equiv) in THF (0.3 mL) and *t*BuOH (0.03 mL) at −78 °C. Then the reaction temperature was raised to 5 °C over 3 h, while a white suspension was formed. The reaction was quenched by addition of saturated NH_4Cl (1 mL) followed by CH_2Cl_2 (6 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (silica gel, hexanes: ethyl acetate 1:1) to afford spiroketal **53** (7.1 mg, 0.025 mmol, 89 %) as a colorless crystalline solid. M.p. 223 °C (decomp; after recrystallization from CH_2Cl_2/MeOH); R_f = 0.28 (silica gel, hexanes:ethyl acetate 1:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2927 w (C–H), 1804 s (C=O, lactone), 1711 s (C=O, ketones), 1279 m, 1150 s, 1017 s; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.37 (s, 1H, Pos 8), 3.15 (d, $^3J_{9,1}$ = 4.5 Hz, 1H, Pos 9), 2.94 (dd, $^2J_{2a,2b}$ = 17.5 Hz, $^3J_{2a,1}$ = 4.5 Hz, 1H, Pos 2a), 2.92 (d, $^2J_{4a,4b}$ = 17.5 Hz, 1H, Pos 4a), 2.89 (dd, $^2J_{2b,2a}$ = 17.5 Hz, $^3J_{2b,1}$ = 9.5 Hz, 1H, Pos 2b), 2.77 (d, $^2J_{4b,4a}$ = 17.5 Hz, 1H, Pos 4b), 2.76 (dt, $^3J_{1,2b}$ = 9.5 Hz, $^3J_{1,2a,9}$ = 4.5 Hz, 1H, Pos 1), 2.25 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.34 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.0, 202.3 (Pos 3 + Pos 10), 171.3 (Pos 12), 105.5 (Pos 5), 83.1, 82.4 (Pos 6 + Pos 13), 80.8 (Pos 8), 63.5, 44.4, 42.4, 41.3, 29.7, 28.1, 15.4; ESIMS ($C_{14}H_{16}O_6$ – ex. mass 280.0947): *m/z* (%): negative 342 [*M*+Cl^-], 93, 279 ([*M* − H], 28).



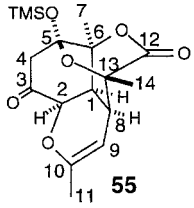
53



38



56



55

Tricyclic lactones 38 and 56 and enol ether 55:[50] A solution of diendione **42** (6.1 mg, 0.017 mmol) and hydroquinone (trace) in toluene (0.6 mL) in a sealed tube was submerged into a hot oil bath (250 °C) for 50 min. The solution was concentrated and purified by PTLC (0.25 mm plate, hexanes:ethyl acetate 1:1) to afford concave lactone **38** (1.4 mg, 0.004 mmol, 23 %) as a colorless oil and convex lactone **56** (2.1 mg, 0.006 mmol, 34 %) as a colorless crystalline solid. Performing this reaction on larger scale (≈40 mg) allowed for the isolation of enol ether **55** in trace quantities (≈4 % yield). **38:** R_f = 0.42 (silica gel, hexanes:ethyl acetate 2:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2958 w (C–H), 1754 s (C=O, lactone), 1722 s (C=O, ketone), 1681 s (C=O, enone), 1253 s, 1174 s, 1083 s, 871 s, 848 s; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.75 (d, $^3J_{1,2}$ = 10 Hz, 1H, Pos 1), 6.15 (d, $^3J_{2,1}$ = 10 Hz, 1H, Pos 2), 3.27 (ddd, $^3J_{8,4}$ = 13.5 Hz, $^3J_{8,9a}$ = 9 Hz, $^3J_{8,9b}$ = 5 Hz, 1H, Pos 8), 3.17 (d, $^3J_{4,8}$ = 13.5 Hz, 1H, Pos 4), 2.28 (dd, $^2J_{9a,9b}$ = 18 Hz, $^3J_{9a,8}$ = 9 Hz, 1H, Pos 9a), 2.14 (dd, $^2J_{9b,9a}$ = 18 Hz, $^3J_{9b,8}$ = 5 Hz, 1H, Pos 9b), 2.12 (s,

3H, Pos 11), 1.72 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 0.20 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 204.5$ (Pos 10), 197.0 (Pos 3), 167.9 (Pos 12), 147.4 (Pos 1), 131.3 (Pos 2), 102.8 (Pos 5), 83.8, 80.9 (Pos 6 + Pos 13), 55.9 (Pos 4), 41.5, 40.0, 30.6, 21.5, 20.0, 1.4; HRMS: calcd for $C_{17}H_{24}O_6Si$ ($[M+H^+]$) 353.1420, found 353.1424. **56:** M.p. 124 °C (after recrystallization from CH_2Cl_2); $R_f = 0.33$ (silica gel, hexanes:ethyl acetate 2:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2958 w (C–H), 1760 s (C=O, lactone), 1715 s (C=O, ketone), 1682 s (C=O, enone), 1254 s, 1174 s, 1126 s, 1083 s, 878 s, 848 s; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.71$ (d, $^3J_{1,2} = 10$ Hz, 1H, Pos 1), 6.12 (d, $^3J_{2,1} = 10$ Hz, 1H, Pos 2), 2.85 (dd, $^2J_{9a,9b} = 16$ Hz, $^3J_{9a,8} = 8.5$ Hz, 1H, Pos 9a), 2.78 (ddd, $^3J_{8,4} = 10.5$ Hz, $^3J_{8,9a} = 8.5$ Hz, $^3J_{8,9b} = 5.5$ Hz, 1H, Pos 8), 2.65 (d, $^3J_{4,8} = 10.5$ Hz, 1H, Pos 4), 2.63 (dd, $^2J_{9b,9a} = 16$ Hz, $^3J_{9b,8} = 5.5$ Hz, 1H, Pos 9b), 2.21 (s, 3H, Pos 11), 1.60 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 0.20 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 204.9$ (Pos 10), 196.3 (Pos 3), 168.5 (Pos 12), 146.9 (Pos 1), 128.9 (Pos 2), 102.0 (Pos 5), 81.5, 80.2 (Pos 6 + Pos 13), 60.2 (Pos 4), 45.8, 41.8, 29.8, 21.9, 16.5, 1.5; HRMS: calcd for $C_{17}H_{24}O_6Si$ ($[M+H^+]$) 353.1420, found 353.1424. **55**: $R_f = 0.32$ (silica gel, hexanes:ethyl acetate 3:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2959 w (C–H), 1770 s (C=O, lactone), 1732 s (C=O, ketone), 1687 m (C=C, enol ether), 1253 s, 1157 s, 1111 s, 884 s, 846 s, 738 s; ^1H NMR (600 MHz, $CDCl_3$): $\delta =$ 4.56 (d, $^3J_{2,1} = 7.5$ Hz, 1H, Pos 2), 4.55 – 4.54 (m, 1H, Pos 9), 3.09 (dd, $^3J_{1,8} =$ 10 Hz, $^3J_{1,2} = 7.5$ Hz, 1H, Pos 1), 2.87 (d, $^2J_{4a,4b} = 16$ Hz, 1H, Pos 4a), 2.63 (d, $^2J_{4b,4a} = 16$ Hz, 1H, Pos 4b), 2.32 (dm, $^3J_{8,1} = 10$ Hz, 1H, Pos 8), 1.92 (dd, $^4J_{11,9} = 1.0$ Hz, $^5J_{11,8} = 0.8$ Hz, 3H, Pos 11), 1.72 (s, 3H, Pos 7), 1.38 (s, 3H, Pos 14), 0.12 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (150 MHz, $CDCl_3$, DEPT): $\delta =$ 201.0 (C, Pos 3), 172.6 (C, Pos 12), 156.9 (C, Pos 10), 99.4 (C, Pos 5), 93.8 (CH, Pos 9), 82.2 (C), 77.6 (CH, Pos 2), 74.4 (C), 49.7 (CH_2, Pos 4), 40.8 (CH), 37.6 (CH), 21.1 (CH_3), 19.6 (CH_3), 16.9 (CH_3), 2.4 (CH_3); HRMS: calcd for $C_{17}H_{24}O_6Si$ $[M + Na^+]$ 375.1240, found 375.1250; nOe experiments (in $CDCl_3$): $\delta =$ irradiation of 4.56 (Pos 2 + Pos 9) effects 3.09 (1.8%, Pos 1), 2.63 (0.7%, Pos 4b), 1.72 (1.5%, Pos 7) via Pos 2 and 2.32 (0.8%, Pos 8), 1.92 (1.2%, Pos 11), 1.38 (1.3%, Pos 14) via Pos 9, irradiation of 3.09 (Pos 1) effects 4.56 (2.4%, d, Pos 2), 2.32 (2.5%, Pos 8), 1.72 (1.7%, Pos 7).

Diels – Alder adduct 57: LiHMDS (14 µL, 1.0 M solution in THF, 0.014 mmol, 0.3 equiv) was added dropwise to a solution of diendione **42** (17.0 mg, 0.048 mmol, 1.0 equiv) in THF (0.4 mL) at −78 °C. The reaction temperature was then slowly raised to 0 °C over 3 h and kept at 0 °C for a further 90 min. The reaction was quenched by addition of saturated NH_4Cl (1 mL) followed by CH_2Cl_2 (6 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by gradient flash chromatography (silica gel, hexanes:ethyl acetate 3:1 → 2:1 → 1:1) to afford Diels – Alder adduct **57** (8.8 mg, 0.025 mmol, 52%) as a white, crystalline solid along with concave lactone **38** (0.9 mg, 0.0025 mmol, 5%), spiroketal **53** (2.1 mg, 0.0075 mmol, 16%) and convex lactone **56** (1.7 mg, 0.0048 mmol, 5%). **57**: M.p. 205 °C (after recrystallization from ethyl acetate); $R_f = 0.42$ (silica gel, hexanes:ethyl acetate 1:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2958 w (C–H), 1756 s (C=O, lactone), 1732 s br. (C=O, ketones), 1250 m, 1151 s, 1091 m, 881 s, 844 s; ^1H NMR (500 MHz, $CDCl_3$): 2.93 (d, $^3J_{4,8} = 6.5$ Hz, 1H, Pos 4), 2.81 (s br, 2H, Pos 1 + Pos 9), 2.72 (d, $^3J_{8,4} = 6.5$ Hz, 1H, Pos 8), 2.27 (d br, $^2J_{2a,2b} =$ 19.5 Hz, 1H, Pos 2a), 2.16 (s, 3H, Pos 11), 2.10 (dd, $^2J_{2b,2a} = 19.5$ Hz, $^3J_{2b,1} =$ 3.5 Hz, 1H, Pos 2b), 1.52 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 0.17 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 205.8$, 204.2 (Pos 3 + Pos 10), 171.5 (Pos 12), 103.9 (Pos 5), 86.7, 82.3 (Pos 6 + Pos 13), 58.2, 50.0, 42.1, 41.2, 37.1, 28.6, 20.2, 19.8, 1.3; HRMS: calcd for $C_{17}H_{24}O_6Si$ $[M+Na^+]$ 375.1240, found 375.1250.

Hemiketal 58: HF · pyridine (2 drops ≅ 15 µL, ≅ 10 mg HF, excess) was added to a solution of tricyclic lactone **38** (4.7 mg, 0.013 mmol) in anhydrous MeCN at 0 °C. The reaction mixture was warmed to 25 °C over 3 h. Then the reaction was stopped by addition of saturated $NaHCO_3$ (0.5 mL) and CH_2Cl_2 (5 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by (short!) flash chromatography (silica gel, hexanes:ethyl acetate 1:1) to afford hemiketal **58** (3.4 mg, 0.012 mmol, 91%) as a colorless crystalline solid. M.p. 172 °C (after recrystallization from CH_2Cl_2); $R_f = 0.30$ (silica gel, hexanes:ethyl acetate 1:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 3400 w br. (O–H), 2919 w (C–H), 1746 s (C=O, lactone), 1713 s (C=O, ketone), 1667 s (C=O, enone), 1632 m (C=C), 1453 s, 1358 m, 1314 m, 1171 s, 1073 s; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 6.80$ (d, $^3J_{1,2} = 10$ Hz, 1H, Pos 1), 6.17 (d, $^3J_{2,1} =$ 10 Hz, 1H, Pos 2), 4.09 (s, 1H, OH, variable—depending on concentration), 3.30 (ddd, $^3J_{8,4} = 13$ Hz, $^3J_{8,9a} = 9$ Hz, $^3J_{8,9b} = 4$ Hz, 1H, Pos 8), 3.27 (d, $^3J_{4,8} = 13$ Hz, 1H, Pos 4), 2.28 (dd, $^2J_{9a,9b} = 18$ Hz, $^3J_{9a,8} = 9$ Hz, 1H, Pos 9a), 2.19 (dd, $^2J_{9b,9a} = 18$ Hz, $^3J_{9b,8} = 4$ Hz, 1H, Pos 9b), 2.14 (s, 3H, Pos 11), 1.75 (s, 3H, CH_3), 1.55 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 206.3$ (Pos 10), 197.4 (Pos 3), 168.8 (Pos 12), 148.0 (Pos 1), 132.1 (Pos 2), 102.1 (Pos 5), 84.5, 81.0 (Pos 6 + Pos 13), 56.0 (Pos 4), 42.9, 40.9, 31.5, 21.9, 20.7; ESIMS ($C_{14}H_{16}O_6$: ex. mass 280.0947): *m/z* (%): positive 303 $[M+Na^+]$, 22, negative 279 ($[M-H]$, 68).

Diels – Alder adduct 59: A solution of TBS-enol ether **52** (20.0 mg, 0.043 mmol) in toluene (2.0 mL) in a sealed tube was submerged into a hot oil bath (200 °C) for 2 h. Afterwards the solution was concentrated and the residue was purified by flash chromatography (silica gel, hexanes: ethyl acetate 10:1) to afford Diels – Alder adduct **59** (6.3 mg, 0.013 mmol, 32%) as a colorless crystalline solid. $R_f =$ 0.55 (silica gel, hexanes:ethyl acetate 2:1); IR (thin film): $\tilde{\nu}_{max}$ (cm^{-1}) = 2958 m (C–H), 2929 m (C–H), 2857 w (C–H), 1775 s (C=O, lactone), 1715 s (C=O, ketone), 1625 w (C=C), 1251 s, 1180 m, 1160 m, 1137 m, 1081 s, 862 s, 842 s; ^1H NMR (600 MHz, C_6D_6): $\delta = 5.17$ (dd, $^3J_{11,2} = 6$ Hz, $^4J_{11,9b} = 1.5$ Hz, 1H, Pos 11), 2.91 (dd, $^2J_{4a,4b} = 18.5$ Hz, $^4J_{4a,2} = 0.7$ Hz, 1H, Pos 4a), 2.40 (d, $^2J_{4b,4a} = 18.5$ Hz, 1H, Pos 4b), 2.33 (s br, 1H, Pos 2), 1.82 (dd, $^2J_{9a,9b} = 15$ Hz, $^3J_{9a,8} = 3.5$ Hz, 1H, Pos 9a), 1.64 (ddd, $^2J_{9b,9a} = 15$ Hz, $^3J_{9b,8} = 10$ Hz, $^4J_{9b,11} =$ 1.5 Hz, 1H, Pos 9b), 1.55 (dt, $^3J_{8,1,9b} = 10$ Hz, $^3J_{8,9a} = 3.5$ Hz, 1H, Pos 8), 1.32 (dd, $^3J_{1,8} = 10$ Hz, $^3J_{1,2} = 3.5$ Hz, 1H, Pos 1), 1.14 (s, 3H, Pos 7), 1.11 (s, 3H, Pos 14), 0.94 (s, 9H, $SiC(CH_3)_3$) 0.16 (s, 9H, $Si(CH_3)_3$), 0.12 (s, 3H, $Si(CH_3)$), 0.09 (s, 3H, $Si(CH_3)$)); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 206.2$ (Pos 3), 171.2 (Pos 12), 153.9 (Pos 10), 103.4 (Pos 11), 99.1 (Pos 5), 82.1, 75.5 (Pos 6 + Pos 13), 54.9, 48.6, 47.8, 45.6, 33.9, 31.6, 25.5, 22.6, 14.1, 1.6, −4.5, −4.7; HRMS: calcd for $C_{23}H_{38}O_6Si_2$ ($[M+H^+]$) 467.2285, found 467.2281; NOE experiments (in C_6D_6): $\delta =$ irradiation of 5.17 (Pos 11) effects 2.33 (2.3%, Pos 2), 0.94 (0.5%, $SiC(CH_3)_3$), 0.12 (0.7%, $Si(CH_3)$), 0.09 (0.6%, $Si(CH_3)$), irradiation of 2.33 (Pos 2) effects 5.17 (2.2%, Pos 11), 1.32 (1.6%, Pos 1), 1.14 (2.4%, Pos 7), irradiation of 1.32 (Pos 2) effects 2.33 (1.4%, Pos 2), 1.64 (1.4%, Pos 9b), 1.14 (1.1%, Pos 7).

Acknowledgements

We thank Dr. R. Chadha, Dr. G. Suizdak, and Dr. D. H. Huang for X-ray crystallographic, mass spectrometric, and NMR assistance, respectively. This work was financially supported by the National Institutes of Health, USA, The Skaggs Institute for Chemical Biology, postdoctoral fellowships from the Humboldt Foundation (Feoder Lynen Scholarship to R. J.), and Alfred Benzon Foundation (to K. B. S.), a predoctoral fellowship from the National Science Foundation (to P. S. B.), and grants from Pfizer, Schering-Plough, Hoffmann La Roche, Merck, Abbott Laboratories, Boehringer Ingleheim, Glaxo, and DuPont.

[1] Trichodimerol (**1**) has been isolated independently from four different sources: a) R. Andrade, W. A. Ayer, P. P. Mebe, *Can. J. Chem.* **1992**, *70*, 2526 – 2535; b) G. A. Warr, J. A. Veitch, A. W. Walsh, G. A. Hesler, D. M. Pirnik, J. E. Leet, P.-F. M. Lin, I. A. Medina, K. D. McBrien, S. Forenza, J. M. Clark, K. S. Lam, *J. Antibiotics* **1996**, *49*, 234 – 240; c) O. Shirota, V. Pathak, C. F. Hossain, S. Sekita, K. Takatori, M. Satake, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2961 – 2964; d) N. Abe, T. Murata, A. Hirota, *Biosci. Biotechnol. Biochem.* **1998**, *62*, 661 – 666.

[2] N. Abe, T. Murata, A. Hirota, *Biosci. Biotechnol. Biochem.* **1998**, *62*, 2120 – 2126.

  0947-6539/99/0512-3664 $ 17.50+.50/0 *Chem. Eur. J.* **1999**, *5*, No. 12

[3] L. S. Trifonov, H. Hilpert, P. Floersheim, A. S. Dreiding, D. M. Rast, R. Skrivanova, L. Hoesch, *Tetrahedron* **1986**, *42*, 3157–3179.
[4] a) R. Anrade, W. A. Ayer, L. S. Trifonov, *Can. J. Chem.* **1996**, *74*, 371–379; b) L. S. Trifonov, J. H. Bieri, R. Prewo, A. S. Dreiding, L. Hoesch, D. M. Rast, *Tetrahedron* **1983**, *39*, 4243–4256, and references therein.
[5] a) D. J. Cram, M. Tishler, *J. Am. Chem. Soc.* **1948**, *70*, 4238–4239; b) D. J. Cram, *J. Am. Chem. Soc.* **1948**, *70*, 4240–4243.
[6] M. Kontani, Y. Sakagami, S. Marumo, *Tetrahedron Lett.* **1994**, *35*, 2577–2580.
[7] C. E. Mazzucco, G. Warr, *J. Leukocyte Biol.* **1996**, *60*, 271–277.
[8] a) A. Beihuzen, I. Vermes, C. Haanen, *Adv. Clin. Chem.* **1999**, *33*, 55–131; b) P. Periti, T. Mazzei, *J. Chemother.* **1998**, *10*, 427–448; c) B. Klosterhalfen, R. S. Bhardwaj, *Gen. Pharmacol.* **1998**, *31*, 25–32; d) J. R. Prous, T. Wroblewski, J. Castaner, *Drugs Future* **1998**, *23*, 123–132; e) J. S. Downey, J. Han, *Frontiers in Bioscience* **1998**, *3*, 468–476; f) further general information available on the internet: http://www.usatoday.com/life/health/lhs383.htm.
[9] A. Srikrishna, G. Sunderbabu, *J. Org. Chem.* **1987**, *52*, 5037–5039.
[10] For a related case of a thermally unstable ketene acetal, see: S. H. Montgomery, M. C. Pirrung, C. H. Heathcock, *Carbohydrate Res.* **1990**, *202*, 13–32.
[11] U. Schoellkopf, W. Hartwig, *Angew. Chem.* **1979**, *91*, 329–330; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 310–311. R. J. thanks Dr. W. Hartwig, Bayer AG, Germany, for helpful discussions.
[12] For a similar stereochemical outcome in a bis-Diels Alder reaction (all-*syn*), see: D. M. Bratby; G. I. Fray, *J. Chem. Soc. Perkin Trans. 1* **1972**, 195–199.
[13] a) D. L. Boger, M. D. Mullican, *J. Org. Chem.* **1984**, *49*, 4033–4044; b) I. E. Markó, G. R. Evans, P. Seres, I. Chellé, Z. Janousek, *Pure Appl. Chem*. **1996**, *68*, 113–122.
[14] a) V. Prapansiri, E. R. Thornton, *Tetrahedron Lett.* **1991**, *27*, 3147–3150; b) E. Winterfeldt, *Chem. Rev.* **1993**, *93*, 827–843.
[15] F. Effenberger, T. Ziegler, K.-H. Schönwälder, T. Kesmarsky, B. Bauer, *Chem. Ber.* **1986**, *119*, 3394–3404.
[16] V. Kvita, H. Sauter, *Helv. Chim. Acta* **1990**, *73*, 883–889.
[17] S. J. Davis, J. A. Elvidge, *J. Chem. Soc.* **1952**, 4109–4114.
[18] Purchased from Aldrich Chemical Co.
[19] A. Quendo, G. Rousseau, *Synth. Commun.* **1989**, 1551–1559.
[20] C. Gennari, L. Colombo, G. Bertolini, G. Schimperana, *J. Org. Chem.* **1987**, *52*, 2754–2760.
[21] T. Mukaiyama, K. Homma, H. Takenoshita, *Chem. Lett.* **1988**, 1725–1728.
[22] H. Faltz, J. Bohrisch, W. Wohlauf, M. Pätzel, P. G. Jones, J. Liebscher, *Tetrahedron* **1996**, *52*, 9035–9046.
[23] H. Mayr, M. Patz, *Angew. Chem.* **1994**, *106*, 990; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938–957.
[24] A. Eschenmoser, *Quart. Rev. Chem. Soc.* **1970**, *24*, 366–415.
[25] G. Simchen, W. Korber, *Synthesis* **1976**, 259–261.
[26] a) D. H. Hua, M. J. Coulter, I. Bajedo, *Tetrahedron Lett.* **1987**, *28*, 5465; b) K. Weiniges, H. Iatridou, H.-G. Stammler, J. Weiss, *Angew. Chem.* **1989**, *101*, 485–486; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 447–448.
[27] Ketal ketone **32** proved inert to mildly acidic deprotection conditions (e. g. acetone/H_2O/AcOH).
[28] P. Aped, Y. Apeloig, A. Ellencweig, B. Fuchs, I. Goldberg, M. Karni, E. Tartakovsky, *J. Am. Chem. Soc.* **1987**, *109*, 1486–1495.
[29] a) H. Emde, A. Götz, K. Hofmann, G. Simchen, *Liebigs Ann. Chem.* **1981**, 1634–1657; b) L. N. Mander, S. P. Sethi, *Tetrahedron Lett.* **1984**, *25*, 5953–5956.
[30] K. Homma, T. Mukaiyama, *Chem. Lett.* **1990**, 161–164.
[31] J. Ishihara, R. Nonaka, Y. Terasawa, K. Tadano, S. Ogawa, *Tetrahedron: Asymmetry* **1994**, *5*, 2217–2232.
[32] K. B. Sharpless, R. F. Lauer, A. Y. Teranishi, *J. Am. Chem. Soc.* **1973**, *95*, 6137–6139.
[33] F. J. Sardina, M. H. Howard, A. M. P. Koskinen, H. Rapoport, *J. Org. Chem.* **1989**, *54*, 4654–4660.
[34] R. D. Miller, D. R. McKean, *Synthesis* **1979**, 730–732.
[35] The catalytic system TMSI/HMDS has been used before for the TMS-protection of anilins, see: A. B. Smith III, M. Visnick, J. N. Haseltine, P. A. Sprengeler, *Tetrahedron* **1986**, *42*, 2957–2969.
[36] **43**: Obtained from silyl enol ethers **41a/b** under Saegusa conditions ($Pd(OAc)_2/Et_3N$, see Y. Ito, T. Hirato, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011–1013). Seagusa et al also observed partial silyl enol ether hydrolysis. In our case, the difference in steric environment apparently favors the dehydrosilylation of the more accessible side chain silyl enol ether while the more hindered cyclic enol ether undergoes acid-catalyzed hydrolysis. **44:** Obtained from ketal ketone **32** by deprotonation with one equivalent of base (LiHMDS) under thermodynamic conditions, followed by quenching of the resulting enolate with the powerful electrophile PhSeCl. In this case the cyclic enolate is obviously the thermodynamically most stable species.
[37] H. J. Reich, J. M. Renga, I. L. Reich, *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.
[38] P. E. Sonnet, *Tetrahedron* **1980**, *36*, 557–604.
[39] a) D. I. Schuster, G. Lem, N. A. Kaprinidis, *Chem. Rev.* **1993**, *93*, 3–22; b) P. Margaretha, K. Grohmann, *Helv. Chim. Acta* **1982**, *65*, 556–557; c) M. T. Crimmins, S. W. Marsacarella, L. D. Bredon, *Tetrahedron Lett.* **1985**, *26*, 997–1000.
[40] The direct 1,4-addition of TMSI to enone systems was previously reported: a) R. D. Miller, D. R. McKean, *Tetrahedron Lett.* **1979**, 2305–2308; b) G. L. Larson, R. Klesse, *J. Org. Chem.* **1985**, *50*, 3627–3627.
[41] Attempts to remove the TMS protecting group by standard, fluoride-mediated procedures (e. g. HF·py, TBAF) resulted either in the decomposition of the starting material or in numerous polar products.
[42] a) J. M Conia, M. Bortilussi, R. Bloch, *Tetrahedron Lett.* **1973**, *27*, 2499–2502; b) E. Brenner, *Acta. Chem. Scand.* **1956**, *19*, 268.
[43] During detailed studies we also isolated enol ether **55** as a byproduct (≈4%) from this reaction.
[44] The Brønsted acid catalyzed thermal isomerization of silyl enol ethers was previously reported, see: A. Deyine, G. Dujardin, M. Mammeri, J.-M. Poirier, *Synth. Commun.* **1998**, *28*, 1817–1821, and references therein. In our case, the flask walls are apparently acidic enough at the high temperatures used to cause isomerization.
[45] M. Ihara, M. Katogi, K. Fukumoto, T. Kametani, *J. Chem. Soc. Perkin Trans. 1* **1988**, 2963–2970.
[46] Dry, degased THF was purchased form Aldrich Chemical Co., while dry, degassed CH_2Cl_2, toluene and ether were obtained from Fischer Scientific.
[47] Standard solution contains: water (94 mL), H_2SO_4, concentrated (6 mL), $Ce(SO_4)_2 \cdot (H_2O)_n$ (1.0 g) and phosphomolybdic acid (1.5 g).
[48] The procedure presented here was originally expected to provide hydroxymethylation of lactide **14**. See also: B. M. Trost, A. S. Tasker, G. Rüther, A. Brandes, *J. Am. Chem. Soc.* **1991**, *113*, 670–672.
[49] Alternatively, on a large scale, diketo dilactones **28a/b** could be purified by trituration in warm ether.
[50] **Caution**: This reaction proved very scale-dependent and sensitive!

Received: May 28, 1999 [F1816]