2-Acetonyl-2,4-di(hydroxy)tetrahydropyrans versus γ-Pyrones: A Chemodivergent Issue for the Condensation of Acetylacetone Dianion Equivalents with α,β-Disubstituted β-Hydroxyaldehydes Leading to Potential New Synthons for Spiroketals

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Abstract: In order to develop a new route to ketal or spiroketal subunits present in numerous natural products, condensation of acetylacetone bis(silyl) enol ether 2-Si or acetylacetone lithium dianion 2-Li with various anti α,β-disubstituted β-hydroxy aldehydes 11 was studied. It has been shown that under Lewis acid-promoted Mukaiyama conditions it is possible to realize such condensation reactions without formation of the well-known Danishefsky γ-pyrones 8. The required 2-acetonyl-2,4-dihydroxytetrahydropyrans 1 for further synthetic purposes were prepared in good to high yields from the intermediate acyclic aldol adduct 7. Particularly crucial are i) the deprotection conditions of the O-silyl protected acyclic intermediate 7 with tetrabutylammonium fluoride in dimethylformamide and ii) the subsequent montmorillonite K10-promoted protection of the hemiketal 1 hydroxy group. The parameters governing the stereoselectivity of the initial condensation reaction have been studied. Under apparent Felkin or anti-Felkin/Cram-chelate conditions, syn,anti-adducts are obtained with high selectivity from acetylacetone bis(silyl) enol ether 2-Si. Partial modulation of the stereoselectivity can be achieved through condensation of the acetylacetone lithium dianion 2-Li with aldehydes bearing bulky O-silyl protecting groups which allows a preferential access to the anti,anti triads.

Key words: silyl enols ethers, dianions, aldol reactions, cyclizations, chemoselectivity, diasteroselectivity, spiro compounds

Spiroketals are widespread structural subunits of numerous biologically active compounds of various sources, as exemplified in the Figure, and a great deal of work has been devoted to their synthesis during the last two decades, as testified by several reviews.3 Several years ago, we initiated efforts for developing new synthetic routes to naturally occurring substances that include such spiroketal substructures, and a total synthesis of the aglycone of 22,23-dihydroavermectin B1b, one of the components of commercial antiparasitic agent ivermectin has been accomplished.4 Current efforts are still devoted to the synthesis of the other members of the avermectin-milbemycin family5 as well as versatile intermediates for the synthesis of other hemiketal or spiroketal containing metabolites, such as bafilomycins, for example.6 This paper deals with the preparation and use of the key methyl ketone 1 which is a useful synthon for the synthesis of various natural products possessing spiroketal moiety.

For the synthesis of the spiroketal subunit of 22,23-dihydroavermectin B1b, we had previously developed a strategy involving a sequential double condensation at both ends of an acetylacetone unit as shown in Scheme 1. First alkylation of the lithium dianion 2-Li with bromide 3 led, after citric acid workup, to the ketal 4, which was readily transformed into the sulfonyl building block 5 through a subsequent aldol reaction.

A common structural feature of the spiroketal subunits of many natural products is the presence of hydroxy groups at the β or β'-positions of the central spirocenter (see Figure). By analogy with the above acetylacetone alkylation-aldolization sequence leading to the spiroketal 5 via the hemiketal intermediate 4, it could be anticipated that a double aldolization sequence at both ends of a pentane-2,4-dione central building block would lead to the required hydroxylated spiroketals.

Cyclic hemiketals of general structure 1-α or 1-β, occurring from either an anti or syn stereoselectivity of the al-
dolization condensation step respectively, would be synthesized by condensation of acetylacetone dianion equivalents $2-\text{Li}$ or $2-\text{Si}$ with aldehydes of general structure $6$, that possess the appropriate structural features required for the elaboration of most of the target complex spiroketal subunits (Scheme 2).

As a corollary of the elected strategy, we are now confronted with the new challenge of generating a supplementary stereogenic center in a stereoselective manner, a goal generally achieved through the use of stereocontrolled condensation of silyl enol ether nucleophiles as $2-\text{Si}$ with conveniently protected $\beta$-hydroxy aldehydes $6$ under Mukaiyama Lewis acid-promoted conditions. However, two major problems are anticipated:

The first point of importance is to avoid the formation of $\gamma$-pyrones of type $8$ usually expected from Danishefsky’s well known hetero-Diels chemistry. The condensation of bis(silyl) enol ethers of 1,3-dicarbonyl nucleophiles with aldehydes has received much interest since the pioneering work of Danishefsky with 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene $8$ (Danishefsky’s diene). Although less considered in term of synthetic applications, 2,4-bis(silyloxy)penta-1,3-diene ($2-\text{Si}$), initially first studied by Chan et al., also represents an interesting diene which was shown to exhibit high reactivity and stereoselectivity in cycloaddition reactions with aldehydes such as $6$ where $\text{PG} = \text{Bn}$, leading to the corresponding $\gamma$-dihydropyranone $8$. These reactions between activated bis(oxo)diienes and aldehydes have been shown, depending on the substrates and the reaction conditions, to proceed via either a 4+2 cycloaddition reaction, also called hetero-Diels reaction or a Mukaiyama aldol condensa-
tion followed, during the workup procedure, by an acid-promoted cyclization of the intermediate aldol 7 leading to 8.13 This cyclization step leads to the most thermodynamically stable γ-pyrone adducts among other possible cyclic products. Therefore, careful kinetic control appeared to be required to synthesize hemiketals 1 instead of 8. A factor also anticipated to be important is the subsequent stability of the tetrahydropyran nucleus. Fortunately most of the natural products bearing spiroketals subunits exhibit major to exclusive all-equatorial dispositions, a structural feature probably reflecting the requisite bias to ensure the stability of the final metabolite.

The stereochemical control of the aldol reaction in relation to the target molecule is the second crucial problem to solve to develop such a synthetic route to hydroxylated spiroketalts. It is important to point out that, except for the anomic effect directed groups orientation,14 the most stabilizing all-trans equatorial disposition of the tetrahydropyran nucleus substituents of 1-β formally comes from syn,anti-aldol type triads (required for bafilomycin A1, for example) whereas anti,anti triads that are known to be among the most difficult to elaborate, would lead to the intermediate 1-α required for avermectins series.2,15 Therefore, before testing the reaction conditions allowing formation of hemiketal 1 instead of γ-pyrene 8, it was decided to undertake a preliminary study on the condensation reaction of acetalacetone dianion equivalents 2 with aldehydes 6, specially under Mukaiyama aldol conditions using 2-Si.

Stereocontrolled Mukaiyama condensation of acetalacetone dianion equivalents: To our knowledge, the only available data concerning the stereocchemical course of Lewis acid-promoted condensations of acetalacetone bis(silyl) enol ether with aldehydes bearing stereogenic centers is the Danishefsky’s precedent on the condensation of bis(silyloxy)penta-1,3-diene (2-Si) with α-alkoxy or α-methyl-β-alkoxy aldehydes. Thus, it was shown that the reaction of α-methyl β-benzyloxypropionaldehyde (9) with 2-Si in the presence of MgBr2 led, after trifluoroacetic acid workup, to the anti-Felkin γ-dihydropyranone anti-10 expected from chelation control, in a 90:10 anti/syn ratio (Scheme 3).16

Parallel experiments from these authors were carried out with a dioxydiene analog of 2-Si (1-methoxy-2-methyl-3-[trimethylsilyloxy]penta-1,3-diene) in presence of BF3·OEt2 and showed a 5:1 Felkin preference in favor of the syn-adduct corresponding to syn-10. This reversal of the selectivity is in full agreement with the 8:1 syn/anti selectivities observed for the condensation of tert-butyline-thylketone silyl enol ether with 9 under non-chelation BF3·OEt2 promoted conditions.17

On the other hand, numerous studies have been published on the condensation reaction of methyl ketone enol ethers with diversely substituted aldehydes including α,β-disubstituted β-hydroxy aldehydes 11,18 If these results have been successfully applied to the total syntheses of complex natural products,19 only one synthetic example involves, to our knowledge, the direct condensation of a β-keto ester bis(enol ether) with a complex aldehyde, precursor of lepicidin.20

Condensation of enol ether 2-Si with anti-aldehydes 11: The present study has been carried out using anti-2,4-dimethyl-β-alkoxypentanal 11 corresponding to a realistic model or even to the genuine precursors for most of the depicted spiroketalts in the Figure.21 In a first set of experiments, bis[(trimethylsilyl)oxy]penta-2,3-diene (2-Si)22 was condensed with 11 bearing either O-TBS or O-TES protecting groups to give adducts 12 or 13 respectively, in good yields (Scheme 4). In all reactions, careful non-acidic workup afforded a crude product containing almost exclusively acyclic aldols adducts which were shown to exist mostly under the enol tautomeric form (see experimental section). Of diagnostic values were the 1H NMR signals corresponding to the enol form at 6–7 ppm together with a CH1 AB quartet at 2–3 ppm corresponding to the keto form (enol/keto >90:10). All attempts to purify or separate the condensation adducts by chromatography revealed particularly difficult because partial uncontrolled cyclization and/or elimination occurred, even when deactivated silica gel was used (this was particularly verified in the case of 13). In practice, the unambiguous identification of the Felkin/anti-Felkin stereoadducts configuration has been done after transformation into the corresponding hemiketals 22-α or 22-β (see below).

As expected, typical non-chelating conditions (entries 2,3) led to the Felkin/anti-Felkin stereoisomers syn-12 or syn-13 respectively. In a second set of reactions, chelation conditions were carried out with aldehyde 11(O-Bn). The same syn topological selectivity as above was observed and apparent Felkin adducts syn-14 were obtained almost exclusively (entries 4,5,7). Particularly, the conditions previously used by Danishefsky to synthesize anti-10 from the β-unsubstituted aldehyde 9 led, in the present case, to a 82:18 syn/anti ratio in favor of the Felkin product (entry 4).

Therefore, in the case of anti-aldehydes 11, all conditions tested provided almost exclusively syn,anti-adducts. Under Felkin non-chelating conditions, this efficient 1,3-anti stereoiduction, due to reinforced α,β effects of the substituents, is in full agreement with the same mutually reinforced α,β effects observed with simple methylketone silyl enol ethers. These results complement a similar study
realized by Evans et al. in the case of condensation of methyl ketones enolates. Examination of the influence of the methyl ketone substituents size on the final diastereomeric ratio shows that the selectivity obtained with acetylaceton is close to the one obtained with isopropyl methyl ketone.

However, in contrast with the results observed for aldehyde 9, no inversion of the selectivity was observed in the case of aldehydes 11 when the same apparent chelating conditions were used. In the case of Cram-chelate conditions, the opposite results obtained between aldehyde 9 and 11 are in agreement with a precedent reported for the condensation of 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1,3-diene with a syn β-trisopropoxyaldehyde analogous to 15 during the total synthesis of Lepicidin A by Evans et al.26

**Scheme 4**

As a conclusion, the anti,anti triad necessary for the synthesis of 1-α building blocks is not accessible through this approach, a result in agreement with those obtained with silyl enol ethers of simple ketones.

**Condensation of enol ether 2-Si with syn-aldehyde 15:** Complementary experiments were carried out with the corresponding syn-aldehyde 15(O-TBS) under non-chelate conditions (Scheme 5).

Although TiCl₄ gave the best stereoselectivity, these conditions only led to low conversion levels. However, when BF₃·Et₂O has been used as Lewis acid, good yields of condensation products 16 have been obtained. Direct transformation of the crude products into the corresponding γ-pyranones 17 allowed unambiguous stereochemical assignments. As expected from syn-aldehydes, a Felkin type control has been observed and the syn,syn adduct 16 leading to 17 has been obtained predominantly. This result is in agreement with a precedent reported for the condensation 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1,3-diene with a syn β-trisopropoxyaldehyde analogous to 15 during the total synthesis of Lepicidin A by Evans et al.26

**Scheme 5**

Condensation of lithium dianion 2-Li with 11: In order to complement the preceding studies, parallel experiments have been carried out with the lithium dianion of acetylaceton 2-Li which was condensed with anti-aldehydes 11 bearing various protecting groups.27 The results, summarized in Scheme 6, showed interesting stereochemical trends depending on the silyl protecting group: an inversion from a Felkin to a anti-Felkin selectivity was observed when changing from the trimethylsilyl (72:28 syn/anti) to the trisopropylsilyl group (62:38 anti/syn).
Although modest, these levels of selectivity may reveal useful for synthetic applications, especially when anti-Felkin (or Cram-cyclic type) adducts, unobtainable through the preceding Mukaiyama Lewis-acid promoted conditions, are required. Interestingly, the 57:43 syn/anti-selectivity observed for 12 is similar to a result obtained for condensation of the lithium anion of a methylethoxypyrone with the same anti-aldehyde.23 However, the trends observed here are opposite to those observed for condensation of a methylketone lithium enolate with several differently protected syn α-methyl-β-hydroxy aldehydes during a synthesis of lonomycin A. 28 Contrary to our current results, there was, in the Evans case, an improvement of the Felkin syn diastereocntrol when increasing the bulkiness of the silyl protecting group. Although not fully understood, the syn or anti configuration of the starting α-methyl-β-hydroxy aldehydes appears to be essential for the observed tendency. Interestingly for synthetic applications, the syn,syn diastereoisomer can be easily purified by chromatography after the subsequent cyclization step.

Cyclization experiments: Having in hand the expected acyclic syn,anti or syn,syn precursors required for the synthesis of the target spirotetra Ketals, we next turned to the study of the deprotection-cyclization reactions. Despite the obvious risk of transformation of the acyclic aldol adducts into the undesirable corresponding γ-pyrones 8 as pointed out before, we initially tried to find convenient mild acidic conditions to yield the required hemiketals 1. For these studies, it has been decided to start from the 57:43 mixture of syn/anti-diastereoisomers 12 obtained after condensation of 2-Li with 11(O-TBS). The results of these preliminary assays are summarized in Scheme 7.

Citic acid, which proved very efficient in the case of 4 used for the synthesis of 22,23-dihydroavermectin B1b (see Scheme 1), was disappointing and led to a mixture of γ-pyranones 17 and 18. When treated with 10% aqueous HCl in methanol, 12 yielded a more complex mixture of cyclic products 17,19 and 20 in a 4.3:2.4:1 ratio. The major unwanted γ-pyrone 17 was accompanied by two interesting minor compounds which have been isolated: i) the 8-membered diene derivative 19, and ii) perhaps more promising for our purpose, the cyclic methyl ketone 20 which could occur from a dehydration reaction of an expected intermediate of type 1. Further treatment of methoxypyrone 18 with p-toluenesulfonic acid led to 17 which, under prolonged reaction times, was transformed into diene 19.29

We next considered fluoride-promoted desilylation reactions. Here again, most of the tested conditions proved unsuccessful (Scheme 8). The tetrabutylammonium fluoride (TBAF) promoted reactions in THF afforded only degradation products. Probably due to its high basicity, cesium fluoride in DMF led to β-elimination product 21 with no trace of the desilylated adduct whereas more acidic lithium tetrafluoroborate conditions led to formation of 17. However, we were delighted to see that short treatment of 12 with an excess of tetrabutylammonium fluoride in DMF at 55 °C led to the quasi-exclusive formation of the two desired diastereomeric hemiketals 22-α and 22-β (29% and 45% isolated yield respectively) with only a minor formation of elimination product 21(O-TBS).30 At this level, these two cyclic epimers proved stable and easily separable by flash-chromatography and the configuration assignment of their secondary hydroxy group was achieved by routine 'H NMR analysis as depicted.

One crucial point to get a clean reaction is short reaction time. All attempts to reduce the number of tetrabutylammonium fluoride equivalents were unsatisfactory. Obviously, the ease of removal of the protecting group would be a crucial factor for the subsequent one-pot deprotection-cyclization step while mild conditions would probably avoid further isomerizsation-degradation reactions. This has been verified when the pure Mukaiyama aldol adduct syn-13 bearing a O-TES protective group.
was submitted to the preceding deprotection-cyclization conditions. As expected, milder reaction conditions have been required to carry out this reaction which allowed formation of 22-β in a nearly quantitative yield when tetrabutylammonium fluoride in DMF at only –15 °C in presence of 6 equivalents of TBAF was used (Scheme 9).

Hemiketal protection: At this stage the main goal of the designed synthetic strategy was reached. The second part of the synthetic route towards spiroketals involves condensation reactions at the other end of the acetylacetone central building block through formation of an intermediate methylketone enolate derived from 1. Therefore, it appeared necessary to protect the hemiketalic OH groups of 22-α and 22-β. Here again some difficulties were anticipated since acidic conditions could lead to partial or total isomerization of these hemiketal intermediates into the corresponding thermodynamically favored γ-pyrones.

The first protection reactions were carried out with hemiketal 22-α bearing an axial secondary hydroxyl group. Here again, as shown in Scheme 10, citric acid conditions furnished unsatisfactory results, leading to a mixture of cyclic ketone 23-α and of the corresponding γ-pyrene adduct anti-24. Heterogeneous conditions with montmorillonite K10 as a mild acid were more efficient, particularly when short reaction times were used. Finally the best results were obtained with montmorillonite K10 in nitromethane, which allowed isolation of methylketal 23-α in 87% yield together with only trace amounts of the corresponding unwanted anti-24 γ-pyrone.

Hemiketal 22-β bearing the most stable equatorial secondary hydroxyl group was next submitted to the same...
Protecting conditions and the expected methylketal 23-β was obtained in 96% yield together with only traces of syn-24.

**Conclusions:** The possibility of developing condensation reactions of dianion equivalents of acetaldehyde with β-hydroxy aldehydes in a direction different than the well-known γ-pyrone classical route has been demonstrated. If syn isomers corresponding to apparent Felkin adducts can be efficiently prepared with high stereoselectivity, the access to the corresponding anti adducts were more problematic. However, partial tuning of the stereoselectivity can be achieved through condensation of the lithium dianion 2-Li with aldehydes bearing well-chosen protecting groups. Alternatively, Mitsunobu inversion of the secondary hydroxyl group of syn adducts can be envisioned to achieve this goal. As summarized in Scheme 11, this new approach allowed synthesis of both methylketals 23-α or 23-β in three steps from anti-aldehydes 11 and the required acetaldehyde dianion equivalent.

![Scheme 11](image)

The overall yield obtained in the case of 23-β is very good with an excellent stereocontrol for 4 stereogenic centers whereas, the yield of 23-α encompassing the unfavorable anti,anti stereotriad is more modest. Application of these building blocks to total syntheses of complex bioactive compounds, particularly avermectin series 2 (from Elaiophylin A 1 (from Elaeophylin A 1) or Bafilomycin A 1 (from Bafilomycin A 1)) is under current investigation and will be published in due course.

Melting points (mp) were determined on a Reichert apparatus and are uncorrected. 1H NMR spectra were recorded on Bruker WP 200 (200 MHz), AC 250 (250 MHz) or AM 400 (400 MHz) instruments. Unless otherwise stated, spectra are recorded in CDCl 3 . The chemical shifts are expressed in parts per million (ppm) generally referred to residual CHCl 3 (7.27 ppm). Data are reported as follows: multiplicities as s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintuplet), sext (sexuplet), sept (septuplet), oct (octuplet) and m (multiplet); coupling constants (J in Hertz, Hz); integrations and assignments. H,H-COSY and H,H-NOESY experiments were routinely carried out to ascertain H-H connectivities and configuration assignments, respectively. 13C NMR spectra were recorded on the same instruments at 50.3 MHz, 63 MHz or 100.6 MHz, respectively. The chemical shifts are expressed in parts per million (ppm). C(H)n multiplicities were evaluated using J-modulated spin-echo technique (J-mod) experiments. When necessary, 13C spectra were assigned with the aid of HETCOR experiments. IR spectra were obtained either on Perkin-Elmer 599 model or Perkin-Elmer FT 1600 instruments using either thin films on NaCl plates or NaCl cell (in the specified solvent) and are reported in terms of frequency of absorption (cm⁻¹). Microanalyses were performed by the Laboratoire d’analyses de l’Université Pierre et Marie Curie, Université Paris VI, 75005, Paris or by the Service de Microanalyse, Institut de Chimie des Substances Naturelles, C.N.R.S., F-91198, Gif sur Yvette. Mass spectra (MS) were obtained either on Nermag R10-10B or Hewlett-Packard HP 5989B spectrometers via direct introduction [chemical ionization with ammonia (CI, NH₃)] or electronic impact (EI)]. Occasionally, a Hewlett-Packard HP 5890 chromatograph was used for GC/MS coupling analysis. Mass spectral data are reported as m/z.

TLC was performed on precoated plates of silica gel 60F 254 (Merck, Art. 7735, 5549 or 5554). Silica gel Merck 60 40–63 μm (Art. 9385) was used for flash chromatography. Gas liquid chromatography was performed on a Girdel 30 gas chromatograph using a wide bore capillary column (BPS, SGE, 12 m × 0.52 mm). Medium pressure chromatography (MPLC) was carried out with a Büchi MPLC equipment, the columns being coated with Merck Lichroprep Si 60 silica gels (generally MERCK Lichroprep Art. 13905 (40–63 μm) or Art. 9336 (12–25 μm). All air and/or water sensitive reactions were carried out under N₂ or argon with anhydrous, freshly distilled solvents using standard syringe-cannula/ septa techniques. All corresponding glassware was oven dried (110 °C) and/or carefully dried in line with a flameless heat gun. Usual workup includes at least 3 extractions with the indicated solvent. The combined organic phases are then washed with H₂O unless otherwise stated, dried (MgSO₄) and evaporated in vacuo using a rotatory evaporator.

[2R*,3S*]-3-(tert-Butyldimethylsilyloxy)-2,4-dimethylpentanal 11 (O-TBS)

To a –78 °C cooled solution of crotyl N,N-diisopropylcarbamate (35 g, 176 mmol) and TEMEDA (29 mL, 193 mmol, 1.1 equiv) in Et₂O (500 mL), was added dropwise a 1.6 M solution of BuLi (120 mL, 193 mmol, 1.1 equiv). After 15 min, freshly distilled titanium isopropoxide (230 mL, 772 mmol, 4 equiv) was added dropwise. The resulting clear red solution was stirred for 30 min, then isobutyraldehyde (17.5 mL, 193 mmol, 1.1 equiv) was added. After stirring for 30 min at –78 °C, the reaction mixture was allowed to warm to r.t. and treated with 2 M aq HCl (40 mL). H₂O (300 mL) was added and after decantation, the aqueous phase was re-extracted with Et₂O. Usual treatment of the combined organic phases including washing with H₂O (300 mL) and brine (300 mL) led to a crude extract which was separated by flash chromatography (EtOAc/pentane) to give pure (1Z)-[2R*,3S*]-4-hydroxy-3,5-dimethylhex-1-enyl N,N-diisopropylcarbamate (45% yield) as a colorless oil.
duct (11.5 g, 42.4 mmol) in CH$_2$Cl$_2$ (100 mL) was added dropwise to a solution of the preceding intermediate crude homoaldol adduct (3 g, 11 mmol) and Et$_3$N (3.8 mL, 27.5 mmol, 2.5 equiv) in CH$_2$Cl$_2$ (20 mL). After 5 min, the reaction mixture was allowed to warm to r.t. and poured into H$_2$O (100 mL). Usual extraction with Et$_2$O (washing twice with H$_2$O and twice with brine) followed by brine, dried (MgSO$_4$), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (Et$_2$O-petroleum ether, 0:100 to 50:50) gave 1.14 g (69%) of a 93:7 mixture of pure silylated aldehyde 11-(O-TBS) as a colorless oil.

IR (film): 2958, 2910, 2880, 2732, 1727, 1462, 1241, 1096, 1055, 1010 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 0.60$ [g, 6 H, $J = 7.9$ Hz, (CH$_3$)$_2$Si], 0.90 [9 H, (CH$_3$)$_3$Si], 0.92 [2 d, $J = 6.9$ Hz, 6 H, (CH$_3$)$_2$CH$_2$], 1.11 [d, $J = 7.1$ Hz, 3 H, CH$_3$-2], 1.85 (m, 1 H, H-4), 2.54 (m, 1 H, H-2), 3.68 (dd, $J = 4.8$, 4.2 Hz, 1 H, H-3), 9.8 (d, $J = 2.5$ Hz, 1 H, C-1).

13C NMR (100 MHz, CDCl$_3$): $\delta = -4.4$, -41.5 [(CH$_3$)$_2$Si], 11.9, 18.2, 18.7 (CH$_2$-2, CH$_3$-1), 25.6 [(CH$_3$)$_2$Si], 25.9 [(CH$_3$)$_3$Si], 32.8 (C-4), 49.8 (C-2), 79.1 (C-3), 205.0 (C-1).

All data are in agreement with reported values.33

Condensation Reactions ( Typical Examples)

Condensation Reaction Between 2,4-Bis(silyloxy)pentanal 11-(O-TES) and anti-Aldehyde 11-(O-TES)

To a solution of the freshly prepared aldehyde 11-(O-TES) (1.18 g, 4.84 mmol) in CH$_2$Cl$_2$ (20 mL) were successively added dropwise freshly distilled BF$_3$-OEt$_2$ (896 $\mu$L, 7.22 mmol, 1.5 equiv) and bis(silyloxy)diene 2-Si (1.77 g, 2.0 mL, 7.26 mmol, 1.5 equiv) at $-78^\circ$C over 10 min. The mixture was stirred for 20 min, treated with sat. aq NaHCO$_3$ solution (10 mL), warmed to r.t., and diluted with Et$_3$O. After decantation and separation, the aqueous layer was extracted with Et$_2$O (3 x 50 mL). The combined organic layers were washed with H$_2$O, brine, dried (Na$_2$SO$_4$) and concentrated in vacuo. Purification by flash chromatography on silica gel (Et$_2$O-petroleum ether, 0:100 to 50:50) gave 1.14 g (69%) of a 93:7 mixture of syn,anti- and anti,anti-adducts 13 as well as 53 mg (5%) of the corresponding cyclohexim (vide infra for characterization).
Condensation Reaction Between the Lithium Dianion of Acetylace tone 2-Li and 11-(O-TES) To a mixture of diisopropylamine (4.7 mL, 33.7 mmol, 2.2 equiv) in THF (36 mL) at –78 °C was added a solution of 1.5 M BuLi in hexanes (21.0 mL, 31.0 mmol, 2.1 equiv). The resulting LDA solution (ca. 0.55 M) was warmed to 0 °C for 1 h and then a solution of acetylace tone (1.7 mL, 16.8 mmol, 1.1 equiv) in THF (10 mL) was added dropwise via cannula. The mixture was stirred for 20 min, cooled to –78 °C and treated dropwise via cannula with a solution of the freshly prepared aldehyde (3.73 g, 15.3 mmol) in THF (5 mL). The resulting mixture was stirred for 30 min at –78 °C, treated with sat. aq NH₄Cl solution (20 mL), warmed to r.t. and distilled with Et₂O (200 mL). After decantation and separation, the aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated in vacuo to give a 67:33 mixture of syn,anti- and anti,anti-diastereoisomers.

Purification by flash chromatography on silica gel (EtOAc/pentane, 0:100 to 30:70) gave in the order of elution anti-13 (150 mg, 3%), an unseparated mixture of both isomers (1.95 g, 37%) and syn-13 (470 mg, 9%) as colorless oils (49% overall yield).

**13C NMR (50.3 MHz, CDCl₃):** δ (ppm) = 54. [CH(CH₃)₂Si], 69 [(CH₂CH₂)Si], 146 (CH-7), 179, 20.7 [(CH₂CH₂)Si], 24.4 (C-1), 32.8 (C-9), 41.8 (C-7), 43.2 (C-5), 70.7 (C-6), 81.7 (C-8), 100.9 (C-3), 116.6 (C-2), 194.3, 189.9 (C≡O).

**MS (DI, CI, NH₃):** m/z = 362 (M + H⁺), 345 (MH⁺), 327, 308, 275, 261, 245, 213, 195, 187, 153, 132 (100%), 118, 96.

**1H NMR (250 MHz, CDCl₃):** δ (ppm) = 6.8, 6.7 (CH(CH₂)₃Si), 8.05 [2 d, J = 6.3 Hz, CH(CH₂)₂Si], 9.05 [d, J = 6.3 Hz, CH(CH₂)₂Si], 10.25 [d, J = 6.3 Hz, CH(CH₂)₂Si], 17.7 [CH₃CH₂Si], 30.7 (C-7, C-9), 43.2 (C-5), 70.7 (C-6), 81.7 (C-8), 100.9 (C-3), 116.6 (C-2), 194.3, 189.9 (C≡O).

**IR (film):** 3448, 2960, 2877, 1718, 1618, 1458, 1419, 1302, 1239, 1054, 1006, 833, 800, 737 cm⁻¹.

**Potential New Synthons for Spiroketals**

1H NMR (250 MHz, CDCl₃): δ (enol form) = 0.10, 0.12 [2 s, 6 H, (CH₃)₂Si], 0.89, 0.90 [2 d, J = 7.3 Hz, 6 H, (CH₃)₂Si], 0.95 [s, 9 H, (CH₃)₃CSi], 0.94 (d, J = 6.7 Hz, 3 H, CH₃-7), 1.83 (m, 2 H, H-7, H-9), 2.06 (s, 3 H, CH₃-1), 2.29 (dd, J = 14.8, 9.5 Hz, 1 H, H-5a), 2.60 (dd, J = 14.8, 2.6 Hz, 1 H, H-5b), 2.38 (t, J = 4.8 Hz, 1 H, H-8), 3.59 (br s, 1 H, D₂O exchangeable, HOCH₆), 4.05 (br t, 1 H, H-6), 5.59 (s, 1 H, H-3), 12.91 (br s, 1 H, D₂O exchangeable, HO-enol).

**13C NMR (CDCl₃):** δ (enol form) = 4.26, –4.0 [15.2 (CH₃)₂Si], 15.2 (CH₂CH₂), 18.0 [CH₂CH₂Si], 18.2 [(CH₂)₂Si], 19.4 [CH₂CH₂], 24.5 (C-1), 26.0 [(CH₂)₃Si], 33.0, 41.7 (C-7, C-9), 43.7 (C-5), 70.6 (C-6), 81.2 (C-8), 101.1 (C-3), 190.1, 194.1 (C-21, C-22).

**MS (Cl, NH₃):** m/z = 345 (MH⁺), 327, 287, 245.

**Condensation Reaction Between the Lithium Dianion of Acetylace tone 2-Li and anti Aldehyde 11-(O-TBS) Acetylace tone (1.15 mL, 11.2 mmol) was added dropwise under N₂ at 0–5 °C (ice/water bath) to a preformed 1.08 M solution of LDA in THF (20.9 mL, 22.5 mmol). After stirring at this temperature for 20 min, the reaction mixture was cooled to –78 °C before slow addition of a solution of the aldehyde (2.5 g, 10.2 mmol) in THF (5 mL). The resulting mixture was stirred for 20 min at –78 °C, added with a sat. aq NH₄Cl solution (10 mL) and allowed to warm to r.t. before supplementary addition of a sat. aq NH₄Cl solu tion (100 mL). Usual workup with Et₂O including successive washing with H₂O (100 mL) and brine (100 mL) afforded 3.36 g of crude product, which was purified by flash chromatography to give the homooldalolod product 12 (2.48 g, 70%) as a 57:43 mixture of syn/anti-diastereoisomers.

For analytical purposes, the two diastereoisomers were separated by silica gel column chromatography (EtOAc/pentane, 1.9). Starting from 1.13 g of the aldehyde product, the products obtained were in order of elution, 260 mg of the pure anti,anti-isomer, 470 mg of unseparated products and 180 mg of the syn,anti-isomer (80% overall recovery).
filtered, and concentrated in vacuo. Purification by flash-chromatography on silica gel (30:70 EtO$_2$-petroleum ether) afforded the aldol 16 as a 84:16 mixture of syn- and anti-diastereomers as a colorless oil (85.2 mg, 85%). The diastereomeric ratio was determined after conversion of the unpurified product to the corresponding pyrones (vide infra) followed by GC analysis (DELSI DL-200 chromatograph, SGE BP5 capillary column, 190 °C, 0.7 bar, $t_{\text{R}30}$ 15.78 min, $t_{\text{R}24}$ 16.13 min).

(6R*,7S*,8S*)-8-tert-Butyldimethylsiloxy)-6-hydroxy-7,9-dimethylene-2,4-dione (syn-16)

1H NMR (400 MHz, CDCl$_3$): δ (3:1 mixture of regiomer enols) = 0.04–0.12 [m, 6 H, Si(CH$_3$)$_2$], 0.83–1.00 [m, 18 H, Si(CH$_3$)$_2$], 1.65–1.80 (m, 1 H, H-5), 2.0 (l, 3 H, H$_3$-3), 2.53 (s, 3 H, CH$_3$-2), 2.62 (m, 1 H, H-3), 2.45 (l, 3 H, H$_3$-2), 7.18 (m, 1 H, H-2), 7.36 (m, 1 H, H-2'), 7.46 (m, 1 H, H-2'), 7.56 (m, 1 H, H-2'), 7.66 (m, 1 H, H-2').

IR (film): 2960, 2930, 2860, 1620, 1580, 1270, 1050 cm$^{-1}$.

White solid; mp 90–91 °C.

IR (film): 2960, 2930, 2860, 1620, 1580, 1270, 1050 cm$^{-1}$.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

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White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.

White solid; mp 90–91 °C.
B. Via Fluoride Treatment

CsF/DMF: A solution of the above aldols mixture 12 (10 mg, 0.03 mmol) in DMF (2 mL) was treated at r.t. with CsF (0.18 mmol, 28 mg). The reaction mixture was stirred at 60 °C for 30 min, then added to water (2 mL). Usual workup with Et2O (washing with brine) gave a crude product which was shown to be the elimination adduct 21 (O-TBS).

(5E,7E,8Z)-8-(3-tert-Butyldimethylsilyloxy)-7,9-dimethylene-5-ene-2,4-dione (21-O-TBS)

Colorless oil.

1H NMR (250 MHz, CDCl3): δ = 0.05, 0.06 [2 d, J = 6.7 Hz, 6 H, (CH3)2Si], 0.86, 0.88 [2 d, J = 7.1 Hz, 6 H, CH(CH3)2], 0.92 [s, 9 H, (CH3)2Si], 1.08 (d, J = 6.9 Hz, 3 H, CH–H–7), 1.71 (m, 1 H, H–9), 2.25 (s, 3 H, CH–H–1), 2.50 (m, 1 H, H–2), 3.38 (dd, J = 5.3, 3.5 Hz, 1 H, H–6), 6.02 (dd, J = 16.0, 1.0 Hz, 1 H, H–5), 6.92 (dd, J = 16.0, 8.3 Hz, 1 H, H–6).

LiBF4/McCN: A solution of the above aldols mixture 12 (10 mg, 0.03 mmol) in MeCN (2 mL) was reacted at r.t. with LiBF4 (14 mg, 0.15 mmol, 5 equiv). After 30 min, usual workup led to the isolation of dihydropyranone 17 as a ca. 1:1 mixture of diastereoisomers.

TBAF/DMSO: A solution of the above aldols mixture 12 (1.05 g, 3.05 mmol) in DMSO (50 mL) was added in one portion to TBAF trihydrate (5.8 g, 18.3 mmol, 6 equiv). The resulting solution was carefully added to H2O (5.0 mL) and diluted with Et2O (25 mL). The combined organic extracts were washed with H2O, brine (150 mL) and H2O (50 mL). After decantation and separation, the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic phases were treated as usual (washing with brine, 20%) to give a crude dark-brown residue, which was diluted with EtOAc (20 mL) and filtered through a silica gel pad (EtOAc–pentane, 80:20). The filtrate was concentrated to afford a pale yellow viscous oil (10 mg, 0.03 mmol) in MeCN (2 mL) and filtered through a silica gel pad (EtOAc–pentane, 80:20). The filtrate was concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc–petroleum ether, 20:80) gave total yield for the desilylation-cyclization step: 74%.

(5E,7E,8Z)-7,9-Dimethyl-8-hydropyrene-5,6-dione (21-OH)

Colorless oil.

1H NMR (250 MHz, CDCl3): δ (enol form) = 0.94, 0.95 [2 d, J = 6.7 Hz, 6 H, CH(CH3)2], 1.10 (d, J = 6.8 Hz, 3 H, CH–H–7), 1.74 (oct, J = 6.7 Hz, 1 H, H–9), 2.13 (s, 3 H, H–1), 2.54 (ddq, J = 8.6, 6.8, 5.8, 1.0 Hz, 1 H, H–7), 3.21 (t, J = 5.8 Hz, 1 H, H–8), 5.53 (s, 1 H, H–3), 5.91 (dd, J = 15.6, 1.0 Hz, 1 H, H–5), 6.86 (dd, J = 15.6, 8.6 Hz, 1 H, H–6).

(2R*,4R*,5S*,6R*)-2-Acetonyl-2,4-dihydroxy-6-isopropyl-5-methyltetrahydropyran (22-a)

White solid; mp 58–59 °C (EtO–pentane).

IR (CHCl3): 3600–3300, 2980, 2940, 2880, 1700, 1430, 1170, 1030 cm–1.

1H NMR (250 MHz, CDCl3): δ = 5.8 (CH–H–23), 6.7 (CH–H–22), 6.9 (CH–H–21), 7.1 (CH–H–17), 7.3 (CH–H–16), 7.5 (CH–H–12), 7.6 (CH–H–15), 7.7 (CH–H–13), 7.8 (CH–H–14), 7.9 (CH–H–11), 8.0 (CH–H–10), 8.1 (CH–H–9), 8.4 (CH–H–8), 8.7 (CH–H–7), 8.8 (CH–H–6), 8.9 (CH–H–5), 9.0 (CH–H–4), 9.1 (CH–H–3), 9.2 (CH–H–2), 9.3 (CH–H–1), 2.24 (s, 3 H, CH3CO), 2.54, 2.82 (2 d, J = 14.7 Hz, 2 H, COCH3), 3.42 (d, J = 9.0 Hz, 1 H, D2O exchangeable, HOCH–4), 3.71 (dd, J = 11.2, 2.2 Hz, 1 H, H–6), 3.84 (dddd, J = 9.0, 3.0, 2.9, 2.6 Hz, 1 H, H–4), 5.32 (d, J = 2 Hz, 1 H, D2O exchangeable, HOCH–2).

13C NMR (CDCl3): δ = 13.60 (CH–H–4), 14.00, 20.2 [CH(CH3)2], 27.7 [CH(CH3)2], 32.6 (CH3CO), 35.9 (C–5), 40.1 (C–3), 52.4 (COCH3), 70.3 (C–4), 72.6 (C–6), 97.1 (C–2), 209.5 (C=O).

MS (ClNH3): m/z = 248 (MH+ + 17), 230 (M–), 213, 195, 136.

Deprotection-Cyclization of syn-13 Adducts Obtained from Condensation of anti-Aldehyde 11(O-TES)

Deprotection with TBAF in THF: To a solution of pure syn-13 (740 mg, 2.15 mmol) in THF (10 mL) at −15 °C was added 1 M commercial solution of TBAF in THF (8.6 mL, 8.6 mmol, 4.0 equiv). The mixture was allowed to warm to 20 °C and stirred for 90 min, then H2O (10 mL) was added and the organic layer was separated. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine, dried (MgSO4), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc–petroleum ether, 20:80 to 100:0) gave the hemiketal 22-β as a single isomer (401 mg, 81%).

Deprotection with TBAF in DMF: To a stirred solution of pure syn-13 (103 mg, 0.30 mmol) in DMF (40 mL), was added TBAF (568 mg, 1.80 mmol, 6.0 equiv) in one portion at −15 °C and the mixture was stirred for 30 min at this temperature. The resulting red solution was carefully added to H2O (5.0 mL) and diluted with EtO (100 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with H2O, brine, dried (MgSO4), filtered and concentrated in vacuo without heating. Purification by flash chromatography on silica gel (EtOAc–petroleum ether, 50:50 to 100:0) afforded the pure hemiketal 22-β (65.3 mg, 95%).

Deprotection with HP-pyridine (excess of pyridine): To a stirred solution of syn-13 (104 mg, 0.30 mmol) in THF (2.0 mL), was added dropwise a mixture of HP-pyridine in excess of pyridine (1.5 mL, 5.27 mmol, 8.6 equiv) at −15 °C. The resulting mixture was allowed to warm to 20 °C and stirred overnight, then diluted with EtOAc (25 mL) and quenched with sat. aq NH4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with H2O, brine, dried (MgSO4), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc–petroleum ether, 50:50 to 100:0) gave the pure hemiketal 22-β (55.0 mg, 73%).
Optimized Condensation-Deprotection-Cyclization Procedure for the Preparation of 22-f from and 11(O-TES) and 2-Si

According to the preliminary reaction conditions described above for the condensation of 11(O-TES) and 2-Si, 2.80 g of crude syn-13 was obtained as a 93:7 syn/anti diastereomeric mixture from freshly prepared aldehyde 11(O-TES) (1.84 g, 7.5 mmol) and bis(silyloxy)dienone 2-Si (3.1 mL, 2.75 g, 11.25 mmol, 1.5 equiv). To a stirred solution of the freshly isolated crude syn-13 (2.8 g, ca. 7.5 mmol) in DMF (40 mL) was added TBAF (8.0 g, 25.5 mmol, 3.4 equiv) in one portion at –78 °C and the mixture was allowed to warm to 0 °C over 30 min. The resulting red solution was slowly added to H₂O (20 mL) and sat. aq NH₄Cl solution (20 mL) at 0 °C and then diluted with Et₂O (200 mL). The organic layers were separated and the aqueous phase was extracted with (EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated in vacuo without heating. Purification by flash chromatography on silica gel (Et₂O–petroleum ether, 10:90 to 50:50) was obtained as a 93:7 syn/anti mixture.

If the same reaction mixture as above was stirred for 2 h, dihydropyranone anti-24 (70 mg, 34%).

Methylketal 23-α

Citric acid/MeOH: Hemiketal 22-α (205 mg, 0.9 mmol) was added in one portion at r.t. to a suspension of 4 Å molecular sieves (500 mg) in a 0.33 M solution of citric acid in MeOH (10 mL). After stirring for 7 h, the reaction mixture was quenched by the addition of sat. aq NaHCO₃ solution (50 mL) and extracted with EtOAc as usual to give, after silica gel flash chromatography (EtOAc–pentane fractions from 10:90 to 50:50), in order of elution, the expected methyl ketal 23-α (60 mg, 27%) and dihydropyranone anti-24 (70 mg, 34%).

(2R*,4R*,5S*,6R*)-2-Acetonyl-4-hydroxy-6-isopropyl-2-methoxy-5-methylhexan-2-yn-4-one (23-α)

Colorless oil.

IR (film): 3600–3400, 2980–2880, 1710, 1650, 1600, 1400, 1300, 1000 cm⁻¹.

1H NMR (250 MHz, CDCl₃, 11(H-HOSY and HETCOR experiments): δ = 0.84 [d, J = 6.9 Hz, 3 H, CH(CH₃)₂], 0.9 [d, J = 6.9 Hz, 3 H, CH₂-5], 1.07 [d, J = 6.9 Hz, 3 H, CH(CH₃)₂], 1.51 (dqd, J = 10.7, 6.9, 4.0 Hz, 1 H, H-5), 1.89 [sept, J = 6.9, 2.3 Hz, 1 H, CH₂-3], 1.90 [dd, J = 14.3, 3.5 Hz, 1 H, H₂-3], 2.02 (dd, J = 14.3, 2.9 Hz, 1 H, H-5), 2.33 (s, 3 H, CH₃CO), 2.49, 2.96 (2 d, J = 14.7 Hz, 2 H, COCH₂), 3.27 (s, 3 H, CH₃CO), 3.45 [dd, J = 10.7, 2.5 Hz, 1 H, H-6], 3.49 (d, J = 9.6 Hz, D₂O exchangeable, HOCH₂), 3.75 (sdd, J = 9.6, 4.0, 3.5, 2.9 Hz, 1 H, H-4).

13C NMR (CDCl₃): δ = 13.6 (CH₃-5), 14.0, 20.3 [CH(CH₃)₂], 27.9 [CH₂-3], 32.1 (CH₂CO), 35.7 (C-5), 38.6 (C-3), 47.5 (CH₃O), 49.6 (COCH₂), 69.5 (C-4), 73.5 (C-6), 99.9 (C-2), 205.9 (C=O).


(2R*,4R*,5S*,6R*)-2-(1,3-Dimethyl-2-hydroxybutyl)-6-methyl-2,3-dihydropyran-4-one (anti-24)

Colorless oil.

IR (CHCl₃): 3600–3400, 2950, 2920, 2880, 1700, 1650, 1600, 1400, 990, 900 cm⁻¹.

1H NMR (250 MHz, CDCl₃, 11(H-HOSY and HETCOR experiments): δ = 0.85 [d, J = 6.8 Hz, 3 H, CH(CH₃)₂], 0.94 (d, J = 6.6 Hz, 3 H, CH₂-5), 1.05 [d, J = 6.8 Hz, 3 H, CH₂(CH₃)₂], 1.33 (ddq, J = 10.3, 10.0, 6.6 Hz, 1 H, H-5), 1.55 (dd, J = 12.8, 11.1 Hz, 1 H, H₂-3), 1.61 [dd, J = 5.2 Hz, 1 H, HOCCH₂-4], 1.93 [sept, J = 6.8 Hz, 2.2 Hz, 1 H, CH₂(CH₃)₂], 2.11 [dd, J = 12.8, 4.8 Hz, 1 H, H₂-3], 2.24 (s, 3 H, CH₂CO), 2.49, 2.96 (2 d, J = 12.8 Hz, 2 H, COCH₂), 3.15 (dd, J = 10.3, 2.2 Hz, 1 H, H-6), 3.20 (s, 3 H, CH₃O), 3.63 (sdd, J = 11.1, 10.0, 5.2, 4.8 Hz, 1 H, H-4).

13C NMR (CDCl₃): δ = 12.0 (CH₂-24), 14.1, 20.3 [CH(CH₃)₂], 27.9 [CH₂-3], 31.9 (CH₂CO), 40.1 (C-5), 42.2 (C-3), 47.6 (CH₂O), 49.9 (COCH₂), 69.7 (C-4), 77.6 (C-6), 99.0 (C-2), 205.5 (C=O).

MS (CI, NH₃): m/z = 230, 213, 195, 187, 169, 151, 137, 115. 

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(26) See Ref. 20. This condensation reaction, performed in the presence of TiCl2(OPr-i)2, led to an excellent Felkin syn-selectivity (>95:5).


(29) For recent synthetic efforts on eight-membered heterocycles, see: Crimmins, M. T.; Choy, A. L. J. Am. Chem. Soc. 1999, 121, 5653; and references cited therein.


