Natural Product-Guided Synthesis of a Spiroacetal Collection Reveals Modulators of Tubulin Cytoskeleton Integrity

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The spiro[5.5]ketal moiety forms the underlying structural skeleton of numerous biologically active natural products. Since simplified but characteristic spiroketals derived from the parent natural products retain biological activity, the spiro[5.5]ketal unit can be regarded as a biologically prevalidated framework for the development of natural product-derived compound collections. We report an enantioselective synthesis of spiro[5.5]ketals on solid support. The reaction sequence employs asymmetric boron enolate aldol reactions with the enolate bound to the polymer or in solution as the key enantiodifferentiating step. It proceeds in up to 12 steps on solid support, makes the desired spiroketals available in high overall yields and with high stereoselectivities and is amenable to structural variation of the products. The small spiroketal collection synthesized contains phosphatase inhibitors and compounds that modulate the formation of the tubulin cytoskeleton in human cancer cells without directly targeting microtubules.

Introduction

The solid-phase synthesis of collections of compound with predetermined profiles of properties has evolved to become one of the crucial enabling techniques in post-genomic chemical biology and medicinal chemistry research. Paramount to success in this area is that the underlying chemical structures of the compound libraries are meaningful to nature. Ideally they should be biologically prevalidated[1] and/or embody so-called privileged structures: structures that enable the library members to bind to several different proteins.[2]

The precondition of biological validation is fulfilled by biologically active natural products that can be regarded as evolutionarily selected ligands for structurally conserved yet genetically mobile protein domains.[1] This insight points to the synthesis of natural product-derived compound libraries as promising starting points for initiation of research in chemical biology as well as in the development of hits and leads in medicinal chemistry programs. This requires the availability of efficient and practical solid-phase synthesis methods and multi-step synthesis sequences (typically >10 linear steps) that will provide access to frameworks of biologically promising natural products and will proceed with degrees of efficiency and selectivity comparable to those of competing solution-phase techniques. To date this goal has been achieved in only a few cases.[1,3,4]

Spiroketals are found in abundance, generally across the insect kingdom, and are known for their pheromonal activities.[5] In particular, the importance of the spiro[5.5]ketal has been increasing due to its rigid molecular framework and its occurrence as a fragment in various complex natural products displaying a wide range of biological activities. Examples include the extraordinarily potent tubulin polymerization-inhibiting spongistatins,[6] the protein phosphatase inhibitors okadaic acid,[7] tautomycin,[8] and the HIV-1 protease inhibitors integramycin.[9] Many groups have already started investigations into the roles of spiroketal fragments in their parent molecules. Interestingly, structurally simplified but characteristic spiroketals derived from the parent natural products retain biological activity (Figure 1).[10–12] The spiroketal motifs present in okadaic acid and tautomycin are enantiomers, and the stereochemistry of the spiroketal moieties could be the major determining factor for the affinity characteristics of okadaic acid and tautomycin towards the PP1 and PP2 phosphatases.[13] The above findings validate the choice of the spiro[5.5]ketal as an underlying structural framework for the development of promising natural product-derived compound collections. The useful-

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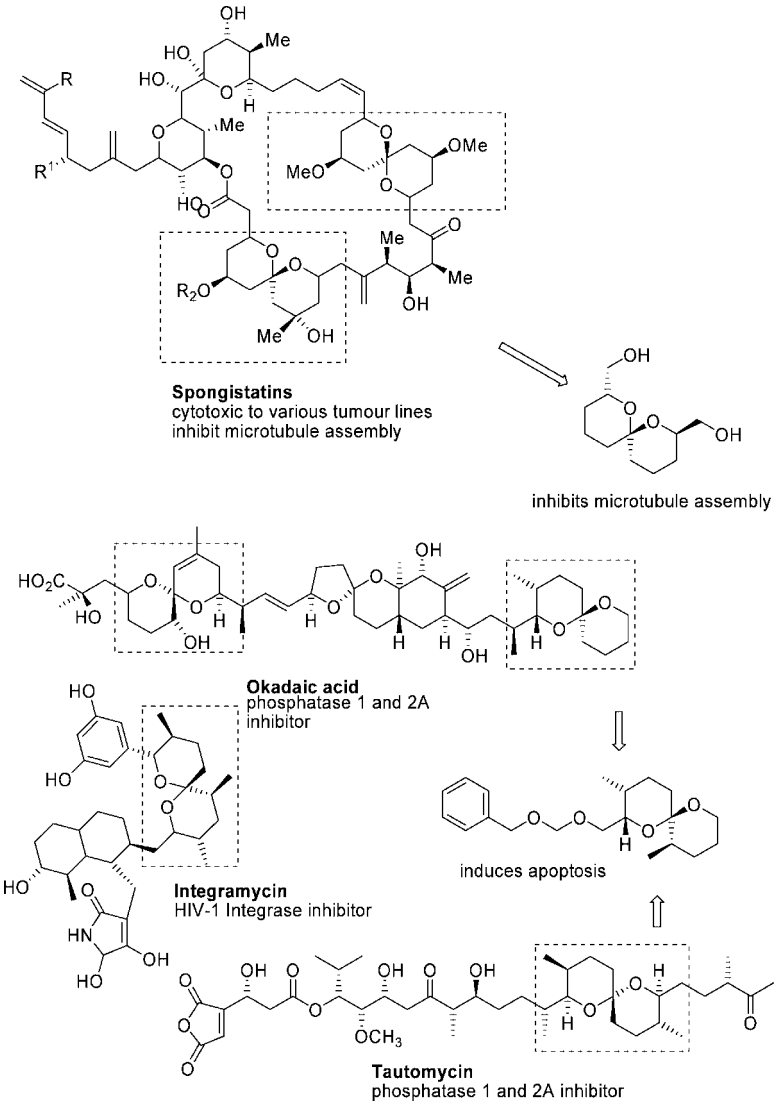


Figure 1. Biologically active natural products with spiroketal substructure and structurally simplified yet biologically active analogues embodying the spiroketal substructure.

ness of spiroketals in combinatorial chemistry[10] and a method for their synthesis on solid support have already been reported by Ley and co-workers.[14]

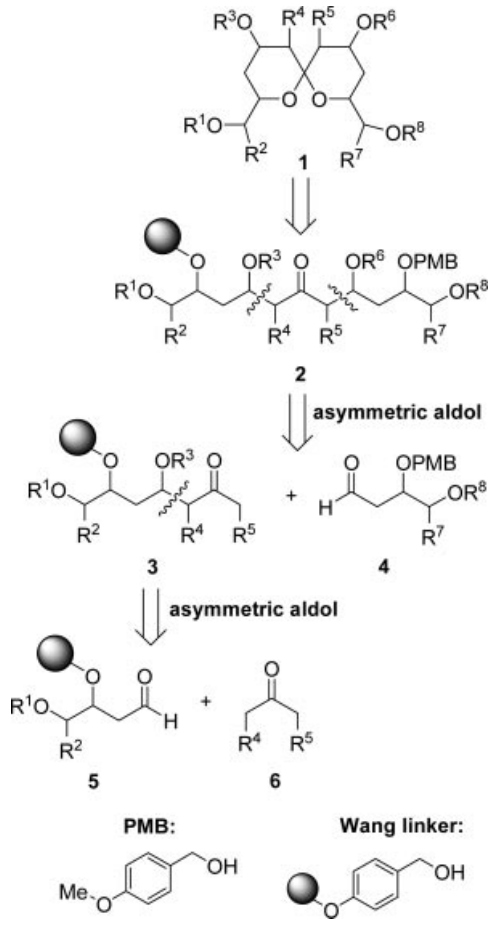
Here we describe in detail the development of an asymmetric synthesis of spiro[5.5]ketals on solid support through the use of stereoselective boron-mediated aldol reactions as key stereodefining transformations.[15]

Results and Discussion

In planning the synthesis we chose as targets compounds of the general structure **1** (Scheme 1), since they incorporate up to eight sites of possible diversification, thereby opening up opportunities to synthesize a fairly diverse compound library.

Spiroketal **1** was retrosynthetically traced back to aldol adduct **2**. One of the hydroxy groups required for acetal formation was chosen for attachment to the solid support, while the other alcohol would have to be protected by an appropriate blocking function orthogonally stable to the other protecting groups employed. We envisioned that, if this protecting group were chosen such that it were of the same chemical type as the anchor to the solid support, final release from the polymeric carrier should be accompanied by cleavage of the blocking function. Also, under appropriate conditions spontaneous ketalization might be induced, giving rise to the desired spiroketals **1**. We expected that these preconditions should be fulfilled by the *p*-methoxybenzyl (PMB) group and its analogue incorporated into the Wang linker for syntheses on solid supports (Scheme 1).

We reasoned that the immobilized aldol intermediate **2** might be formed through an asymmetric aldol reaction be-



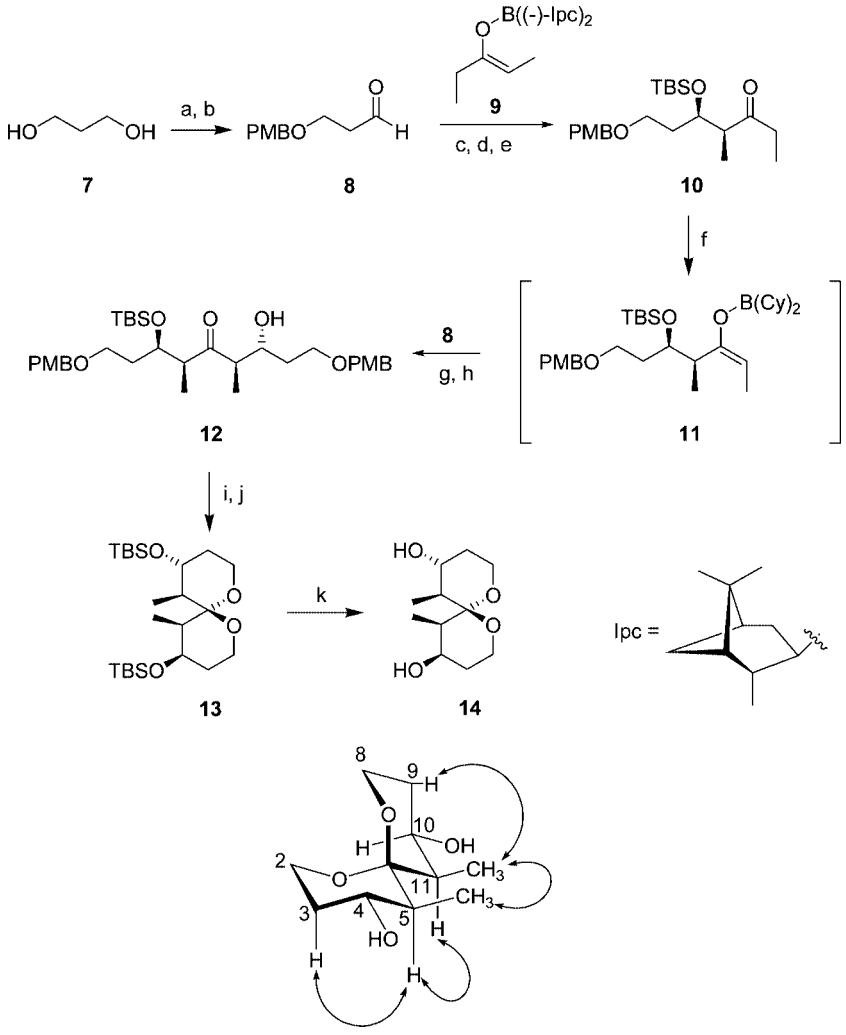
Scheme 1. Retrosynthetic analysis of the spiro[5.5]ketal structure.

tween an enolate generated from polymer-bound ketone **3** and aldehyde **4**. Similarly, the immobilized ketone **3** was traced back to the polymer-linked aldehyde **5** and ketone **6**, which would again be subjected to an asymmetric aldol reaction. This strategy requires the application of asymmetric aldol reactions employing both polymer-bound[16] and soluble chiral enolates.[17] A few examples of stereoselective aldol reactions with soluble and polymer-bound chiral enolates have been described, but the use of polymer-bound chiral enolates in aldol reactions has not yet been explored.

The feasibility of the strategy was first investigated in solution (Scheme 2). To this end, *p*-methoxybenzyl-protected aldehyde **8** was synthesized in two steps from commercially available propane-1,3-diol (**7**) and treated with (*Z*)-diisopinocampheyl borinate **9**,[18] generated from (–)-Ipc_2BOTf and pentan-3-one. Further oxidative workup with 30% aq. H_2O_2 in MeOH/pH 7 buffer solution afforded the *syn*-aldol adduct with very high stereoselectivity (*de* > 98%, *ee* > 91%). The aldol OH group was then protected as a *tert*-butyldimethyl silyl ether to give **10** in 69% yield in two steps. The (*E*) enolate **11** was then generated by treatment of **10** with dicyclohexylboron chloride by established methods.[19] It was subjected to a further aldol reaction with aldehyde **8**. Oxidative workup yielded *anti*-aldol adduct **12** (*de* >97%). The absolute configuration of aldol adduct **12** was assigned on the basis of the assumption that the reaction proceeds analogously to the stereochemical course observed for related cases.[20] The alcohol was again masked as a TBS ether, with an overall yield of 89% for two steps. Simultaneous oxidative cleavage of both PMB protecting groups proceeded smoothly on treatment with DDQ for 3 h and was followed – as hoped – by spontaneous formation of spiroketal **13**, which was obtained as a single isomer in 88% yield.

Furthermore, to ascertain the structure of compound **13** it was deprotected by treatment with TBAF to yield spiroketal **14** in 81% yield. This compound's analytical data were compared with those recorded for closely related compounds,[21] and additional NOE-spectroscopic investigations also confirmed the stereochemical course of the overall reaction sequence. Clear NOE signal enhancements were detected between the two methyl groups and between the two protons at C-5 and C-11, respectively indicating close proximity (Scheme 2). In addition, an NOE enhancement was detected between the methyl group at C-11 and the proton at H-9, but not between the methyl group at C-5 and the proton at H-2, so the methyl group at C-5 is in the equatorial position whereas the methyl group at C-11 is in the axial orientation. This conclusion is further supported by the observation of a fairly high melting point and by the fact that the signal of the hydroxy protons in the ^1H NMR spectrum appears at δ = 1.75–1.52 (D_2O exchange), which has been shown to be diagnostic of equatorial hydroxy protons in related systems.[21]

After development of this reaction sequence we investigated whether it could be successfully transferred to the solid support. To this end, Merrifield resin modified with the Wang linker **15** (loading 1.2 mmol g^{-1}) was activated as trichloroacetimidate **16** (Scheme 3),[22] and this was then subjected to nucleophilic displacement by mono-TBS-protected propanediol **17**. This two-step sequence was conveniently monitored by FT-IR spectroscopy. After cleavage of the TBS group the primary alcohol was oxidized to the corresponding aldehyde **19** by use of IBX as oxidant. At this stage, resin loading was determined to be 0.75 mmol g^{-1} by application of a method developed earlier by us, based on formation of the corresponding dinitrophenylhydrazone.[4] At this stage we wanted to attempt the *anti*-aldol reactions with the enolate generated in solution phase, in order subsequently to construct the spiroketal. Preformed (*E*)-enolate **11** derived from **10** in solution phase as described above was allowed to react with aldehyde-bound Wang resin at 0 °C in diethyl ether. Oxidative workup with H_2O_2 in a pH 7 buffer/MeOH/DMF mixture at 0 °C yielded *anti*-aldol **20** (detected by IR; strong absorption at 3504 cm^{-1} and 1714 cm^{-1}). Notably, raising the temperature during oxidative workup resulted in partial cleavage from the resin. After oxidative workup to cleave the B–O bond, **20** was treated with DDQ in a CH_2Cl_2/buffer (pH 7) mixture to afford spiroketal **21** along with unidentified mixtures. Since the separation of **21** from anisaldehyde was difficult the resin-bound intermediate **20** was protected as a TBS ether to yield the corresponding immobilized aldol product (monitored by FT-IR spectroscopy). Treatment of



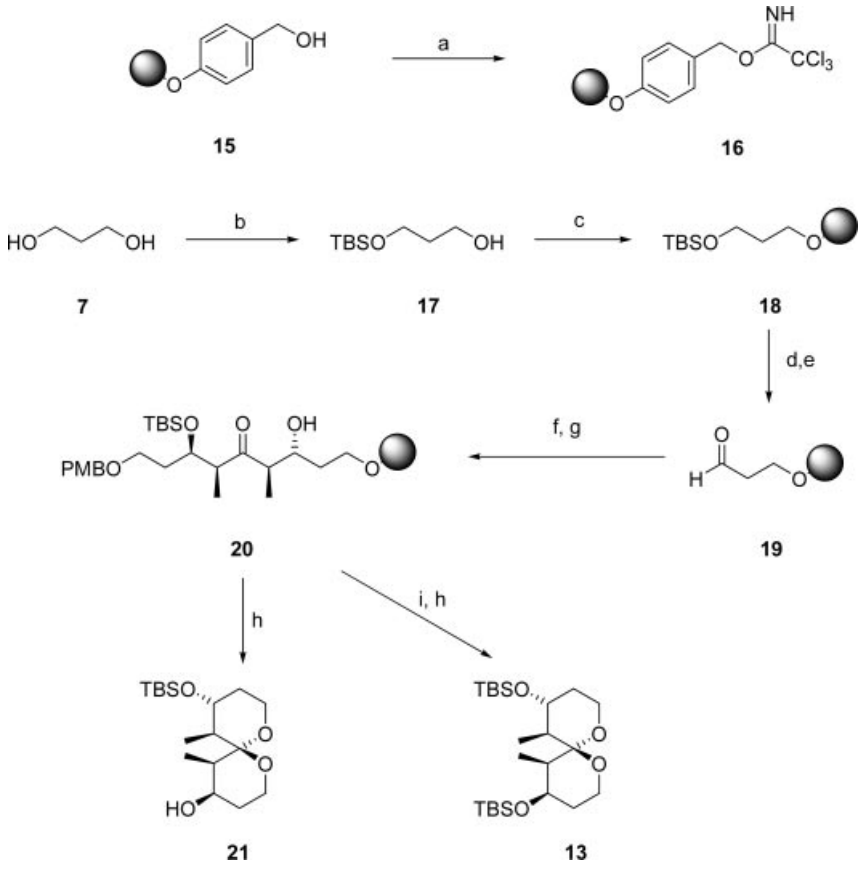
Scheme 2. Solution-phase synthesis of spiroketals **13** and **14**. a) NaH (1.5 equiv.), $CH_3OC_6H_4CH_2Cl$ (1.1 equiv.), DMF, 0 °C to room temp., 24 h, 63%. b) $COCl_2$ (1.5 equiv.), DMSO (2.5 equiv.), Et_3N (4 equiv.), CH_2Cl_2, –78° to 0 °C, 2 h, 93%. c) Pentan-3-one (1 equiv.), (–)-Ipc_2BOTf (1.2 equiv.), *i*Pr_2NEt (1.5 equiv.), CH_2Cl_2, –78° to –30 °C, 20 h. d) 30% aq. H_2O_2/MeOH/pH 7 buffer (1.5:5:1), 0 °C to room temp., 2 h, 69%. e) TBSCl (1.3 equiv.), imidazole (2.1 equiv.), DMF, room temp., 24 h, 91%. f) Dicyclohexylboron chloride (1.3 equiv.), Et_3N (1.5 equiv.), Et_2O, 0 °C, 4 h. g) Compound **8** (1.4 equiv.), Et_2O, –78° to –30 °C, 24 h. h) 30% aq. H_2O_2, MeOH, pH 7 buffer (1.5:5:1), 0 °C to room temp., 2 h, 89%. i) TBSCl (1.3 equiv.), imidazole (2.5 equiv.), DMF, room temp., 24 h 92%. j) DDQ (2.8 equiv.), CH_2Cl_2, pH 7 buffer, 0 °C to room temp., 3 h, 88%. k) TBAF (3 equiv.), THF, room temp., 48 h 81%.

this intermediate with DDQ in a CH_2Cl_2/buffer (pH 7) mixture resulted in simultaneous cleavage of the PMB ether, release from the Wang resin and spiroketalization. After purification by filtration through a short silica gel column, spiroketal **13** was obtained (42% overall yields in 7 steps) as a single stereoisomer as determined by HPLC and ^1H/^{13}C NMR spectroscopy. Comparison of the spectroscopic data and the specific rotation, together with NOE spectroscopic investigation, showed it to be identical to the spiroketal synthesized in solution as described above.

We next attempted to perform all transformations on solid support by the same strategy as in solution-phase synthesis (Scheme 4). The polymer-bound aldehyde **19** (0.75 mmol g^{-1}) was treated at –78 °C with the preformed (*Z*)-enolate **9** in dichloromethane for 1.5 h. After the reaction mixture had been stored at –27 °C for 16 h, the resin was filtered and the whole process was repeated once. After oxidative workup to cleave the B–O bond, the secondary alcohol was protected as TBS ether to yield immobilized aldol product **22** (monitored by FT-IR spectroscopy).

For the crucial second aldol reaction on the solid support, employing a polymer-bound chiral boron enolate, ketone resin **22** was swollen in diethyl ether and a solution of dicyclohexylboron chloride and triethylamine in diethyl ether was then added to the resin at 0 °C. After 6 h the resin was washed and the procedure was repeated once again. It was expected that, analogously with enolate formation in solution (see above and Ref.[15]), (*E*)-dicyclohexylboron enolate **23** would be formed on the solid support.

Boron enolate resin **23** was then treated at –78 °C with aldehyde **8** and, after oxidative workup as described above, the secondary alcohol **24** (strong absorptions at 3504 cm^{-1}



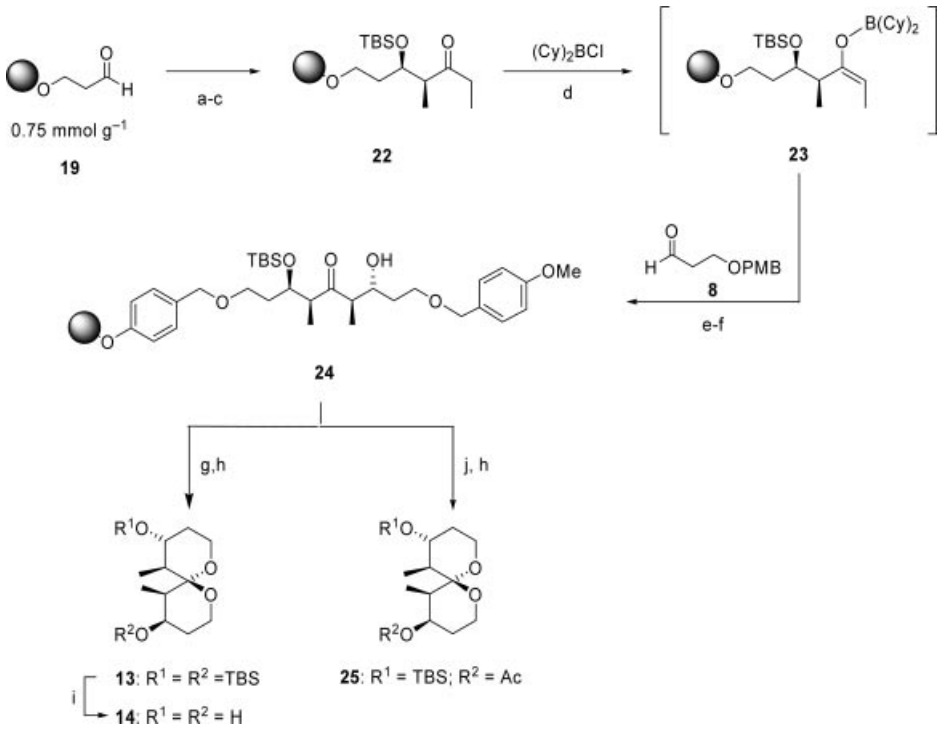
Scheme 3. *anti*-Aldol reaction on solid phase with boron enolate in solution phase. a) Cl_3CCN (8 equiv.), DBU (3 mol-%), CH_2Cl_2, 0 °C, 40 min. b) TBSCl (1.2 equiv.), imidazole (2.0 equiv.), DMF, room temp., 24 h. c) Compound **16**, $BF_3{\cdot}Et_2O$ (3 mol-%), cyclohexane, CH_2Cl_2, room temp., 15 min. d) TBAF (8 equiv.), THF, room temp., 14 h. e) IBX (8 equiv.), DMSO, room temp., 36 h. f) **11** (6 equiv.), Et_2O, –78° to –27 °C 20 h (two cycles). g) 30% aq. H_2O_2/MeOH/DMF/pH 7 buffer (1.5:4:4:1, 0 °C, 3 h. h) DDQ (10 equiv.), CH_2Cl_2/pH 7 buffer (20:1), 0 °C to room temp. 6 h. i) TBSCl (10 equiv.), DMAP (1 mol-%), imidazole (10 equiv.), DMF/CH_2Cl_2 (1:1), room temp., 24 h (two cycles).

and 1714 cm^{-1} in the IR spectrum) was liberated (Scheme 4). The intermediate **24** was then protected with a TBS group, and subsequent treatment with DDQ in a CH_2Cl_2/buffer (pH 7) mixture resulted in simultaneous cleavage of the PMB ether, release from the Wang resin and spiroketalization to give **13**. The compound was found to be identical to that synthesized in solution phase as described above and in Scheme 3.

The spiroketal was obtained in a 12-step solid-phase synthesis in an overall yield of 16%, which corresponds to an average yield of 86% yield for each step. This compares very favourably with the overall yield of 27% recorded for the 10-step solution synthesis described above. The fact that the configurations of the spiroketals obtained both from the solid-phase and from the solution-phase syntheses are identical confirmed that both aldol reactions on the polymeric support proceed completely analogously to the corresponding asymmetric transformations in solution. In addition, the finding that the desired product was obtained with very high stereoselectivity convincingly demonstrates that the degree of stereodifferentiation is also very comparable in both cases. To extend the scope of the synthesis the alcohol-bound resin **24** was protected with an acetyl group by treatment with acetic anhydride in THF in the presence of pyridine and DMAP. Oxidative cleavage with DDQ gave spiroketal **25** in 14% overall yield.

In order to demonstrate that the reaction sequence shown in Scheme 4 is amenable to the synthesis of compound collections, seven further building blocks were synthesized and subjected to solid-phase aldol chemistry. All protected *β*-hydroxyaldehydes were available in a few simple transformations from chiral pool compounds or by applying enantioselective allylations to aldehydes with subsequent alcohol protection and oxidative cleavage of the double bond (Scheme 5).[23] The spiroketals **38** to **53** were obtained by the established route in overall yields ranging from 5 to 13% (Scheme 6).

To gain further insight into the stereoselectivity of the asymmetric boron-mediated aldol reactions on solid support, we investigated whether the principle of double diastereodifferentiation was also operative in this case. Therefore, both enantiomers of chiral aldehyde **27** were used on the solid support. After treatment with DDQ, spiroketalization gave compounds **38**, **39** and **40** as single isomers,

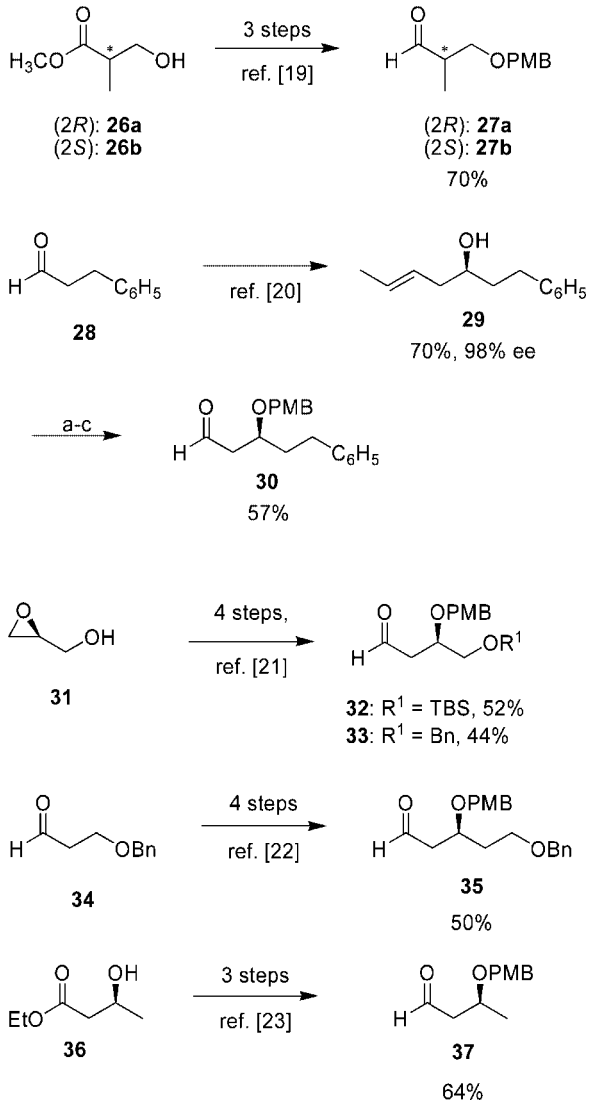


Scheme 4. Synthesis of spiroketals through *syn* and *anti* aldol reactions on solid support. a) Pentan-3-one (6 equiv.), (–)-Ipc$_2$BOTf (6.1 equiv.), *i*Pr$_2$NEt (7 equiv.), CH_2Cl_2, –78° to 0 °C, 20 h; filter and wash (two cycles). b) 30% aq. H_2O_2/MeOH/DMF/pH 7 buffer (1.5:4:4:1, 0 °C room temp., 4 h. c) TBSCl (10 equiv.), DMAP (1 mol-%), imidazole (10 equiv.), DMF/CH_2Cl_2 (1:1), room temp., 24 h (two cycles). d) Dicyclohexylboron chloride (8 equiv.), Et_3N (9 equiv.), Et_2O, 0 °C, 24 h, filter and wash (two cycles). e) Compound **8** (10 equiv.), Et_2O, –78° to 20 °C, 26 h (2 cycles). f) 30% aq. H_2O_2/MeOH/DMF/pH 7 buffer (1.5:4:4:1), 0 °C, 4 h. g) TBSCl (10 equiv.), DMAP (1 mol-%), imidazole (10 equiv.), DMF/CH_2Cl_2 (1:1), room temp., 24 h (two cycles). h) DDQ (10 equiv.), CH_2Cl_2/pH 7 buffer (20:1), 0 °C to room temp., 6 h. i) TBAF (3 equiv.), THF, room temp., 48 h, 81%. j) Ac_2O (30 equiv.), pyridine (30 equiv.), DMAP (cat.), THF, room temp., 20 h.

whereas **41** and **42** were isolated along with two minor inseparable isomers (detected by GC-MS) (Scheme 6). Thus, in aldol reactions of the chiral enolate **23** with the two enantiomeric aldehydes **27a** and **27b**, the *anti*-aldol adduct is formed as the major product. Consistently with related findings,[24] the combination of **23** and **27b** represents the *matched case* and the combination of **23** and **27a** the *mismatched case*. Spiroketals **43** to **53** were obtained as single isomers.

Furthermore, decoration of the spiroketal skeleton with stereogenic centres was achieved through the use of the corresponding substituted resin-bound aldol intermediates. To this end, two additional aldol intermediates were prepared on solid support (Scheme 7) through *syn*-aldol reactions between resin-bound *β*-hydroxy aldehydes and pentan-3-one. The secondary alcohol obtained after the stereoselective ring-opening of *O*-benzyl-(*S*)-glycidol by vinyl Grignard reagent was attached to Wang resin via the resin trichloroacetimidate under acid catalysis conditions, followed by ozonolysis to give aldehyde **54** with a loading of 0.45 mmol g^{-1} (see Supporting Information). This aldehyde was used for a *syn*-aldol reaction with pentan-3-one with subsequent TBS protection of the formed alcohol to yield intermediate **55**. Commercially available ethyl (*S*)-3-hydroxybutyrate (**36**) was directly attached to Wang resin with subsequent reduction to the alcohol by DIBAH. The alcohol was oxidized with IBX to give the aldehyde **56** with a loading of 0.7 mmol g^{-1}. A *syn*-aldol reaction of this aldehyde with pentan-3-one, followed by TBS protection of the alcohol, yielded intermediate **57**.

The resin-bound aldol intermediates **55** and **57** were employed to synthesize further spiroketal molecules. When resin-bound intermediate **55** was used in the corresponding sequence (i.e., an *anti*-aldol reaction with protected *β*-hydroxy aldehyde **27b**, acylation of the alcohol, simultaneous deprotection of the PMB group and cleavage from the resin), a mixture of products was obtained. Along with other impurities, spiroketal isomers were formed in low yield. This is notable, since the aldehyde **27b** had yielded spiroketals in good yields in the reaction sequence described above (Scheme 6). In the reaction sequence involving **55**, however, at least four spiroketal isomers were formed (in a ratio of 55:35:8:2, determined by GC). The major isomer **58** could be purified after TBS group deprotection, and the minor isomer **59**, which was found to be the 10-epimer of the major product, could be isolated by preparative HPLC. The structure of the minor product **59** was determined from NMR spectroscopic data and NOE experiments. In the spiroketal **59**, the proton at C-10 appears relatively upfield (at 4.64 ppm) relative to where it usually appears in the case



Scheme 5. Synthesis of building blocks **27a**, **27b**, **30**, **32**, **33**, **35** and **37**. a) $CH_3OC_6H_4CH_2OC(=NH)CCl_3$ (1.5 equiv.), $BF_3{\cdot}Et_2O$ (cat.), pentane/CH_2Cl_2 (5:1), 0 °C to room temp., 16 h, 75%. b) OsO_4 (0.01 equiv.), *N*-methylmorpholine oxide (1.1 equiv.), *t*BuOH/H_2O (2:1), 0 °C to room temp., 6 h, 94%. c) $NaIO_4$ (2.5 equiv.), CH_2Cl_2/H_2O (1:1), 0 °C to room temp., 6 h, 93%.

of the major isomers (≈ 5.02–5.20 ppm), suggesting that it occupies an equatorial position. Furthermore, the coupling constant value of 8.4 Hz for this proton clearly indicates the absence of a diaxial arrangement. The latter observation was further strengthened by the absence of any NOE signal between protons at C10, C2 and C8. Moreover, the NOE signal enhancement between methyl protons of the acetyl group and the proton at C-8 confirms this conformation (Scheme 8).

The low stereoselectivity recorded above may reflect a mismatch in at least one of the aldol reactions. Similarly, when *β*-hydroxyaldehyde **8**, which does not possess an additional stereogenic centre, was used in the second aldol reaction, as many as four spiroketals were again observed after the reaction sequence. This result suggests that both the aldol reactions in this sequence might have been mismatches, resulting in isomer formation. The next sequence was therefore tested with resin-bound aldol intermediate **57**, starting with an *anti*-aldol reaction with aldehyde **27b**. After the reaction sequence we were, to our delight, able to observe only two isomers of spiroketals (in a ratio of 5:1), which could be purified by HPLC. As the aldol reactions in this sequence appear to be the matching cases, further spiroketals were synthesized by this sequence through variation of the *β*-hydroxy aldehydes for the *anti*-aldol reaction (Scheme 8). In most cases the major product was accompanied by varying amounts of its 10-epimer. The major product could be easily separated by HPLC, and 16 highly substituted spiroketals were added to the collection by this reaction sequence (Scheme 8).

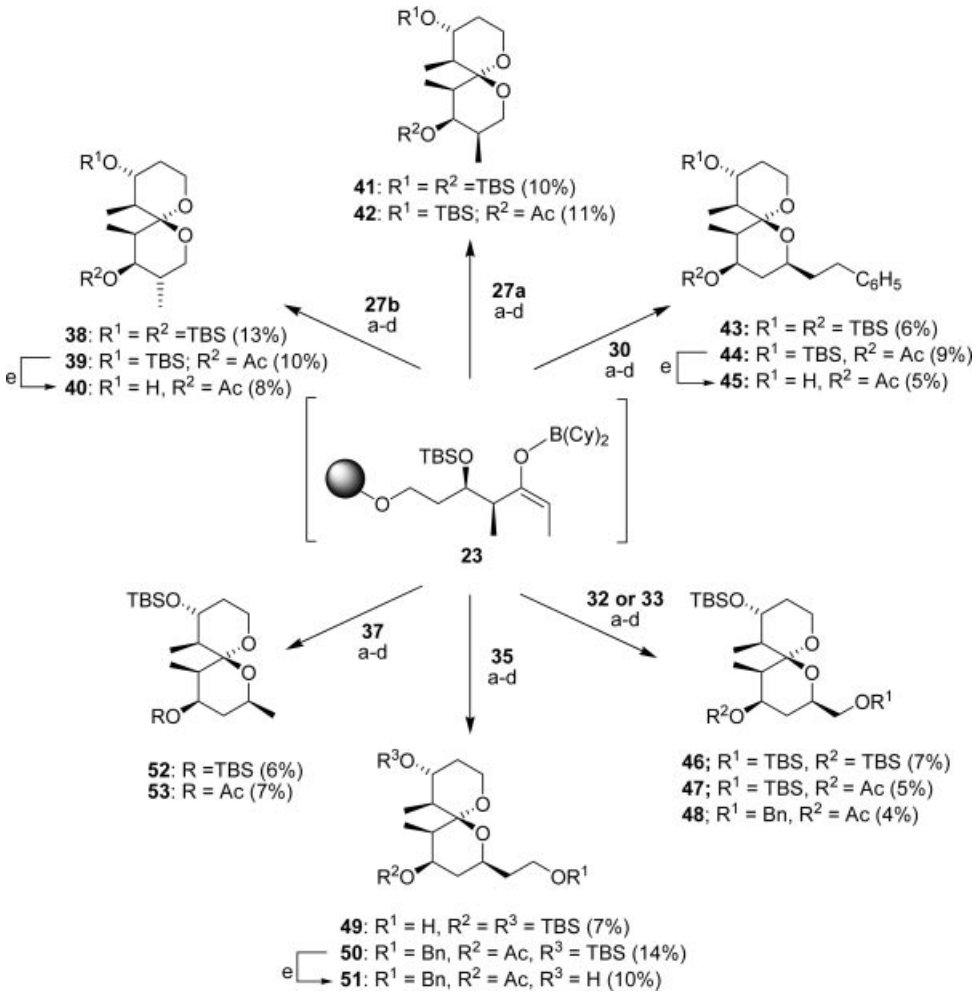
In order to determine whether the synthesized spiroketals displayed biological activity associated with some of the activities characteristic of naturally occurring spiroacetals (see above) they were tested in different assays. In particular, we investigated whether the spiroacetal collection contained phosphatase inhibitors and modulators of microtubule formation.

The protein tyrosine phosphatase PTP1b, the dual specificity phosphatase VHR and Cdc25a and the serine-threonine phosphatase PP1 were chosen as representative enzymes. PTP1B is a key negative regulator of insulin receptor activity and PTP1B-inhibitors are expected to enhance insulin sensitivity and act as effective therapeutic treatments for Type II diabetes, insulin resistance and obesity. The vaccinia virus VH1-related phosphatase VHR is a physiological regulator of extracellular regulated kinases of the MAP (mitogen-activated protein) kinase family and influences signalling through the MAP kinase pathway. Cdc25a is involved in cell cycle regulation and PP1 influences various biological processes. Great attention has been paid to the development of inhibitors of these phosphatases for biological studies and drug development.[25]

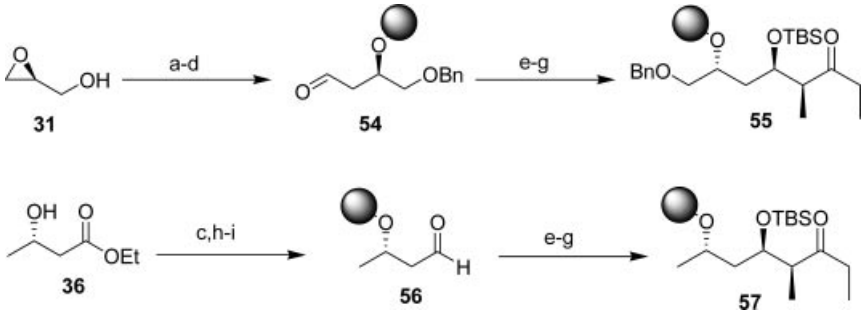
The results of the assays are shown in Table 1. Spiroacetal **39** inhibits VHR with an IC_{50} value in the low micromolar range and weakly inhibits PTP1b. Compound **42** turned out to be a moderate inhibitor of VHR, and compounds **50** and **53** proved to be moderate inhibitors of PTP1b and VHR. None of the synthesized spiroacetals inhibited Cdc25a or PP1.

Comparison between spiroacetals **39** and **42** shows that the configurations of the stereocenters embedded in the spiroacetal rings markedly influence phosphatase inhibition. The observation that analogues **38**, **40** and **41** (Scheme 6) are not active modulators indicates that the variation of the substituents attached to the basic skeleton of the molecules appears to be of similar importance.

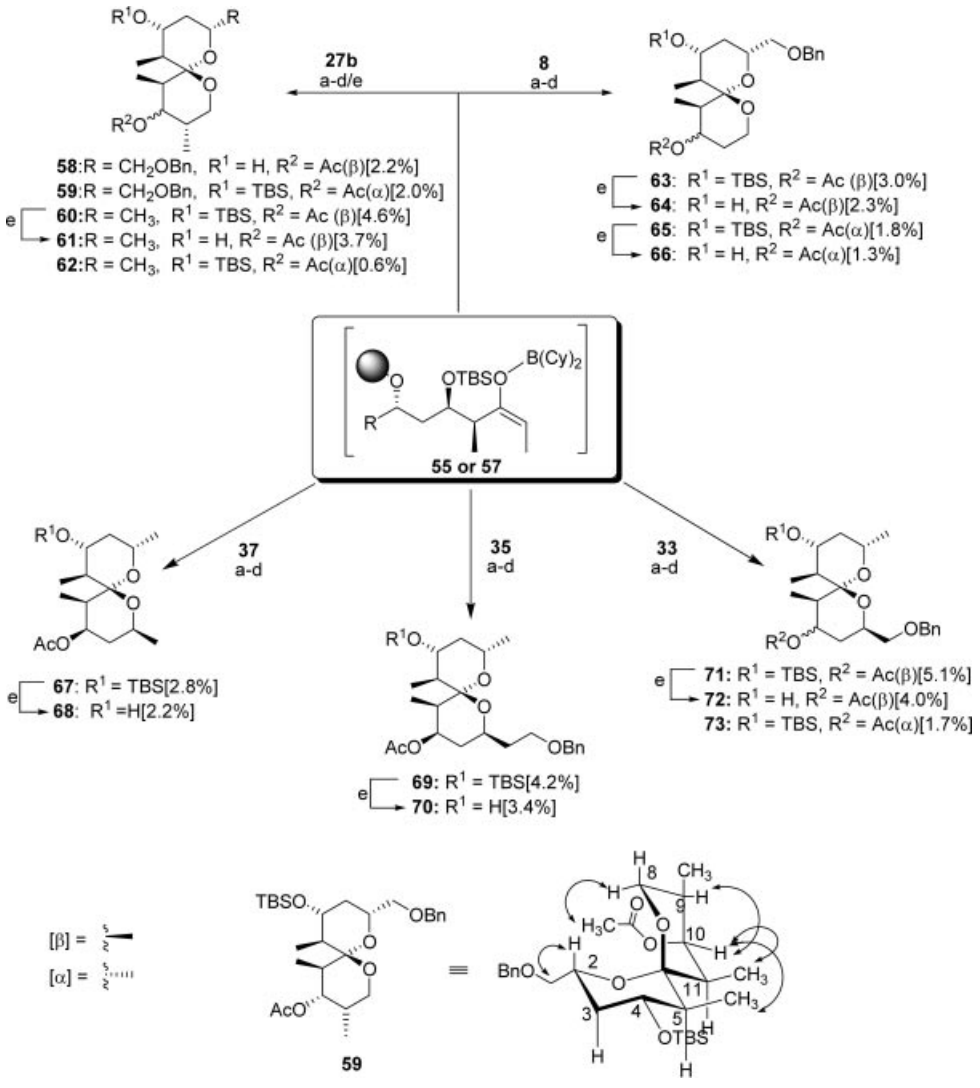
In order to determine whether some of the spiroacetals described above would affect microtubule formation, their influence on the tubulin and the actin cytoskeletons of the human breast carcinoma cell line MDA-MB-231 was investigated.



Scheme 6. Solid-phase synthesis of spiroketals **38**–**53**. a) Aldehyde (10 equiv.), Et_2O, –78° to 20 °C, 26 h (2 cycles). b) 30% aq. H_2O_2/MeOH/DMF/pH 7 buffer (1.5:4:4:1), 0 °C 4 h. c) TBSCl (10 equiv.), DMAP (1 mol-%), imidazole (10 equiv.), DMF/CH_2Cl_2 (1:1), room temp., 24 h (two cycles) or Ac_2O (30 equiv.), pyridine (30 equiv.), DMAP (cat.), THF, room temp., 20 h. d) DDQ (10 equiv.), CH_2Cl_2/pH 7 buffer (20:1), 0 °C to room temp., 6 h. e) TBAF (5 equiv.), THF, room temp., 24 h; overall yields are given in parentheses.



Scheme 7. Synthesis of aldol intermediates **55** and **57** on solid support. a) NaH (1.2 equiv.), DMF, benzyl bromide (1.25 equiv.), 0 °C to room temp., overnight. b) Vinylmagnesium bromide (1.3 equiv.), CuI (10 mol-%), –30 °C. c) Compound **16**, $BF_3{\cdot}Et_2O$ (3 mol-%), cyclohexane, CH_2Cl_2, room temp., 15 min. d) O_3, CH_2Cl_2, –78 °C, PPh_3, –78 °C to room temp., overnight. e) Pentan-3-one (6 equiv.), (–)-Ipc_2BOTf (6.1 equiv.), iPr_2NEt (7 equiv.), CH_2Cl_2, –78° to 0 °C, 20 h; filter and wash (two cycles). f) 30% aq. H_2O_2/MeOH/DMF/pH 7 buffer (1.5:4:4:1, 0 °C room temp., 4 h. g) TBSCl (10 equiv.), DMAP (1 mol-%), imidazole (10 equiv.), DMF/CH_2Cl_2 (1:1), room temp., 24 h (two cycles). h) DIBAH (5.0 equiv.), THF, 5 h. i) IBX (8 equiv.), DMSO, room temp., 36 h (see Supporting Information).



Scheme 8. Solid-phase synthesis of spiroketals **58**–**73**: a) Aldehyde (10 equiv.), Et_2O, –78° to 20 °C, 26 h (2 cycles). b) 30% aq. H_2O_2/MeOH/DMF/pH 7 buffer (1.5:4:4:1), 0 °C 4 h. c) Ac_2O (30 equiv.), pyridine (30 equiv.), DMAP (cat.), THF, room temp., 20 h. d) DDQ (10 equiv.), CH_2Cl_2/pH 7 buffer (20:1), 0 °C to room temp., 6 h. e) TBAF (3 equiv.), THF, room temp., 24 h; overall isolated yields are given in parentheses.

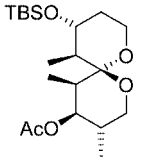
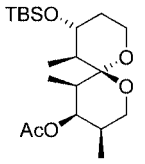
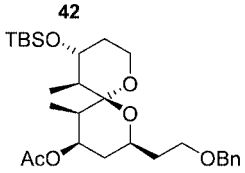
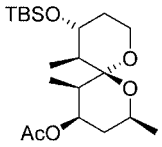
Figure 2 shows that untreated cells displayed intact tubulin and actin networks. Upon addition of spiroacetals **39** and **42**, the microscopically visible tubulin structure was affected. Cells treated with 5 μM **39** displayed irregular and folded tubulin cytoskeletons, whereas the tubulin fibres in cells treated with 5 μM **42** were rather incomplete. The compounds had no effect on the actin structure or on the overall cell morphology. Lower concentrations of **39** or **42** and all other tested compounds had no effect.

Uckun et al.[11] recently reported that a model spiroacetal derived from spongistatin 1 prevents microtubule formation in cells. This conclusion was subsequently questioned by Smith III. et al.[26]

In order to determine whether the microscopically visible effect of compounds **39** and **42** (Figure 2) was due to direct targeting of microtubules by these spiroacetals we polymerized fluorescently labelled microtubules in vitro in the presence of compounds **39**, **42** or DMSO as a solvent control. Microscopic analyses revealed that neither compound significantly affected microtubule polymerization in vitro at concentrations as high as 200 μM (Figure 3). To confirm that our in vitro microtubule polymerization assay is sensitive to microtubule-depolymerizing molecules we included nocodazole as a positive control. As shown in Figure 3, nocodazole inhibited microtubule polymerization in vitro almost completely at concentrations as low as 100 nM. Taken together, these data suggest that the compounds **39** and **42** affect the organization of the microtubule cytoskeleton in cells by a mechanism other than direct targeting of microtubules.

It has not escaped our attention that the influence on microtubule integrity is paralleled by phosphatase-in-

Table 1. IC_{50} values of phosphatase inhibitors.

Entry	Structure	IC_{50} [μM][a]			
		PTP1b	**VHR**	**Cdc25a**	**PP1**
1	 **39**	39 ± 12	6 ± 4	> 100	> 100
2	 **42**	> 100	31 ± 17	> 100	> 100
3	 **50**	56 ± 13	37 ± 21	> 100	> 100
4	 **53**	36 ± 5	24 ± 9	> 100	> 100

[a] All IC_{50} values were calculated from at least three independent determinations. IC_{50}: concentration required for 50% inhibition.

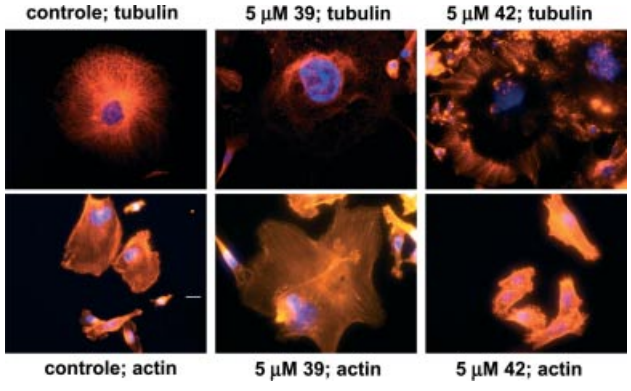


Figure 2. Effects of spiroketals on tubulin skeleton in MDA-MB-231 breast tumour cells; DNA immmunostained (blue). Upper row: tubulin immunostained (orange). Lower row: actin immunostained (yellow). Left column: control cells show intact tubulin and actin networks. Middle column: cells treated with compound **39** at 5 μM final concentration show an irregular and folded tubulin network and an intact actin network. Right column: cells treated with compound **42** at 5 μm final concentration show incomplete tubulin fibres and an intact actin network.

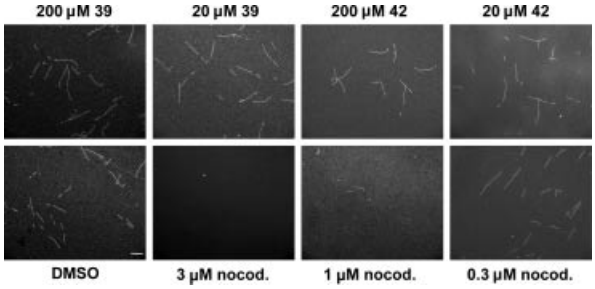


Figure 3. Compound **39** and **42** do not significantly affect microtubule polymerization in vitro. Microscope images of fluorescently labelled microtubules polymerized in vitro in the presence of the indicated concentrations of compounds or DMSO as a solvent control (scale bar: 10 mm).

hibiting activity in the cases of both **39** and **42**. While this observation alone does not prove a link between the two phenomena it suggests avenues for subsequent research aimed at identifying the cellular targets of these compounds responsible for the influence on the tubulin cytoskeleton.

Conclusions

In conclusion, we have developed an efficient solid-phase synthesis of spiro[5.5]ketals. It proceeds on a polymeric carrier in up to 12 steps, makes the desired spiroketals available in high overall yields and with high stereoselectivities, and is amenable to structural variation of the products. We have demonstrated that demanding transformations in solution-phase synthesis can be adapted to solid-support conditions for library synthesis, generating a small collection of spiro[5.5]ketals. This sequence should allow the development of structurally diverse spiroketal libraries and other related compound libraries as new tools and reagents for chemical biology and medicinal chemistry research.

Research along this line is particularly strongly motivated and justified by the finding that the small collection of spiroketals described here is enriched in bioactivity. Analogously with the activities described for some of the natural product guides, it contains phosphatase inhibitors and modulators affecting the tubulin cytoskeletons of breast cancer cells.

Experimental Section

General: ^{1}H NMR and ^{13}C spectra were recorded on a Varian Mercury 600 or a Bruker DRX 500 spectrometer. GC-MS (EI) were measured on a Hewlett–Packard 6890 series gas chromatograph connected to a Hewlett–Packard 5973 series mass spectrometer; column: H&W 19091σ-102 HP-5MS capillary: 25.0 m × 201 μm × 0.33 μm nominal. LC-MS was performed on a Hewlett–Packard 1100 series connected to a Finnigan LCQ ESI-Spectrometer; column: VP 50/10 Nucleosil C18PPN-column (Macherey–Nagel); gradient: 90:10 (v/v) H_2O/acetonitrile (0.1% formic acid) to 10:90 (v/v) in 30 min, flow 1.00 mL min^{-1}. Preparative HPLC was conducted with an Agilent 1100 series; column: VP 125/21 NUCLEODUR C18 Gravity, 5 μ (Macherey–Nagel); gradient: 60:40 (v/v) H_2O/acetonitrile (no acid!) to 100% acetonitrile in 29 min, flow 10 mL min^{-1}. High-resolution mass spectra (HR-MS) were measured on a Finnigan MAT 8200 spectrometer. IR spectra were measured on a Bruker Vector 22 spectrometer with an A527 diffuse reflectance head from Spectra Tech. UV spectra were measured on a Perkin–Elmer Cary 50 spectrometer. HPLC was measured on Hewlett–Packard 1100 HPLC. The optical rotation was determined with a Perkin–Elmer 241 polarimeter. Chiral GC was measured on an Agilent Technologies 6890N; column: Lipodex-E (25 m, 0.025 mm); 85 °C isotherm. Wang resin (1.1 mmol g^{-1}, 1% DVB, 100–200 mesh) was purchased from Novabiochem. All reactions were performed under argon with freshly distilled and dried solvents. All solvents were distilled by standard procedures. Unless otherwise noted, reagents were obtained from Aldrich, Acros, Fluka, Lancaster and Strem and were used without further purification.

Procedure for Boron-Mediated Aldol Reactions on Wang Resin

Generation of Enolate 11 in Solution and *anti*-Aldol Reaction with Resin-Bound Aldehyde 19: Triethylamine (1.56 mL, 11.25 mmol) was added at 0 °C to a solution of dicyclohexylboron chloride (9.60 mL of 1 M in hexane, 9.60 mmol) in diethyl ether (10 mL). The reaction mixture was stirred for 1 h at the same temperature. A solution of TBS-protected aldol **10** (3 g, 7.50 mmol) in diethyl ether (5 mL) was then added by cannula and the mixture was stirred for 4 h at the same temperature. After the system had been cooled to –78 °C, the enolate solution was transferred by cannula to the Wang resin-bound aldehyde (1.66 g, 1.25 mmol), swollen in CH_2Cl_2 (10 mL) at –78 °C. It was stirred for another 1.5 h at –78 °C, and the reaction mixture was then stored for 18 h at –27 °C. The solution was filtered and the resin was washed with CH_2Cl_2 and dried under vacuum for 5 h. A second aldol reaction cycle under the same reaction conditions was carried out. After the solution from the second cycle had been filtered, the resin was washed with CH_2Cl_2, pH 7 buffer (phosphate), DMF and MeOH. It was then swollen in a mixture of MeOH (12 mL), DMF (12 mL) and pH 7 buffer (phosphate, 3 mL). After the system had been cooled to 0 °C, aq. H_2O_2 (30%, 4.5 mL) was added, and the mixture was kept shaking for another 8 h at the same temperature. The solution was filtered and the resin was washed with H_2O, pH 7 buffer, THF/H_2O, THF, CH_2Cl_2 and MeOH, and was then dried under vacuum for 5 h to afford yellowish resin **20**. IR (SiC): $\tilde{\nu}_{max}$ = 3506, 3059, 2930, 1720, 1604, 1450 cm^{-1}.

Generation of Enolate 9 in Solution and Reaction with Wang Resin-Bound Aldehyde 19 (19 to 22 in Scheme 4): Diisopropylethylamine (1.73 mL, 10.5 mmol) was added at –78 °C to a solution of (–)-Ipc_2BOTf (3.96 g, 9.15 mmol) in CH_2Cl_2 (20 mL). After the reaction mixture had been stirred for 30 min, a solution of pentan-3-one (952 μL, 9.0 mmol) in CH_2Cl_2 was added at the same temperature. After 4 h, the solution was carefully transferred by cannula to the aldehyde bound to Wang resin **19** (2 g, 1.5 mmol), swollen in CH_2Cl_2 (10 mL) at –78 °C. The reaction mixture was stirred for another 1.5 h at –78 °C and was then stored for 18 h at –27 °C. The solution was filtered and the resin was washed with CH_2Cl_2 and dried under vacuum for 5 h. A second aldol reaction cycle was carried out under the same reaction conditions . After the solution from the second cycle had been filtered, the resin was washed with CH_2Cl_2, pH 7 buffer (phosphate), DMF and MeOH and was then swollen in a mixture of MeOH (4 mL), DMF (4 mL) and pH 7 buffer (phosphate, 1 mL). After the system had been cooled to 0 °C, aq. H_2O_2 (30%, 1.5 mL) was added, and the mixture was kept shaking for another 8 h at the same temperature. The solution was filtered and the resin **22** was washed with H_2O, pH 7 buffer, THF/H_2O, THF, CH_2Cl_2 and MeOH, and was then dried under vacuum for 5 h. IR (SiC): $\tilde{\nu}_{max}$ = 3504, 3062, 2928, 1714, 1604, 1585, 1453 cm^{-1}.

Generation of Enolate 23 on Solid Support and Reaction with Aldehyde 8: The intermediate resin **22** (1.5 g, 1.15 mmol) was swollen in diethyl ether (8 mL) and cooled to 0 °C. Triethylamine (1.44 mL, 10.35 mmol) was added at 0 °C to a flask containing dicyclohexylboron chloride (9 mL, 9.0 mmol) in diethyl ether (3 mL). After the mixture had been stirred for 1 h it was transferred to the resin by cannula at 0 °C. The shaking was continued for 10 h and the solution was removed (by syringe) while the resin was still kept at 0 °C. The resin was washed with cold diethyl ether (3 × 15 mL) by syringe. Fresh diethyl ether (10 mL) was added and the above process was repeated again but with a shorter reaction time (4 h). The solution was removed carefully by syringe and was washed with cold diethyl ether (4 × 15 mL). Throughout the process the resin was kept at 0 °C. Fresh cold diethyl ether (10 mL) was again added and the mixture was then cooled to –78 °C. A solution of aldehyde **8** (2.13 g) in diethyl ether (5 mL) was added by cannula and the mixture was shaken for 2 h at –78 °C before storage at –27 °C for 24 h. After the mixture had been washed with diethyl ether and dried under vacuum, a second cycle of the process, under the same reaction conditions but with half the equivalent of the reagents, was carried out on this resin sample swollen in diethyl ether. It was then swollen in a mixture of MeOH (5 mL), DMF (5 mL) and pH 7

buffer (phosphate, 1.7 mL). After the system had been cooled to 0 °C, aq. H_2O_2 (30%, 2 mL) was added, and it was kept shaking for another 6 h. The solution was filtered and the resin was washed with H_2O, pH 7 buffer, THF/H_2O, THF, CH_2Cl_2 and MeOH, and was then dried under vacuum for 5 h. IR (SiC): $\tilde{\nu}_{max}$ = 3510, 3059, 2926, 1713, 1575, 1442 cm^{-1}.

A similar reaction procedure was followed for all other *anti*-aldol reactions of the ketones **22**, **55** and **57** (Scheme 6 and 8) with *β*-hydroxy aldehydes.

General Procedure for the Protection of Secondary Alcohols with a *tert*-Butyldimethylsilyloxy Group on Solid Support: The resin-bound secondary alcohol (1 g) was swollen at room temperature in a mixture of CH_2Cl_2 (10 mL) and DMF (10 mL). After addition of TBSCl (1.13 g, 7.5 mmol), DMAP (5 mg, 0.075 mmol) and imidazole (0.51 g, 7.5 mmol), the resin was shaken for 24 h. The resin was filtered and a second cycle was performed with half the equivalents of the reagents in order to complete the reaction (monitored by FT-IR until the bands at 3504 cm^{-1} and 3062 cm^{-1} had completely disappeared). The resin was washed with CH_2Cl_2, DMF, THF/H_2O, THF and CH_2Cl_2 and dried under vacuum for 5 h.

General Procedure for the Protection of a Secondary Alcohol with an Acetyl Group on Solid Support: The resin-bound secondary alcohol (1 g) was swollen at room temperature in THF (10 mL). After the addition of pyridine (3.3 mL, 22.5 mmol), DMAP (5 mg, 0.075 mmol) and acetic anhydride (1.53 g, 22.5 mmol), the resin was shaken for 24 h. The resin was filtered (monitored by FT-IR until the bands at 3504 cm^{-1} and 3062 cm^{-1} had completely disappeared, with the appearance of sharp peak at 1725 to 1730 cm^{-1}). The resin was washed in turn with THF, THF/H_2O, THF and CH_2Cl_2 and was dried under vacuum for 5 h.

General Procedure for Spiroketalization and Cleavage from the Solid Support: The intermediate resin (200 mg) was swollen in a mixture of CH_2Cl_2 (10 mL) and pH 7 buffer (phosphate, 0.5 mL), and recrystallized DDQ (425 mg, 7.5 mmol) was added at 0 °C. Shaking was continued for 1 h at 0 °C followed by 6 h at room temperature. The solution was filtered and the resin was washed repeatedly with CH_2Cl_2 and aqueous $NaHCO_3$ (aq. sat.). The combined organic solution was washed with brine (8 mL). It was then dried with $MgSO_4$ and the solvents were evaporated in vacuo to yield a mixture of spiroketal with 4-methoxybenzaldehyde, detected by GC-MS [HP-MS (0.33 μm, 25 m × 0.2 mm ID), t_R = 13.45 min]. The pure single spiroketal was obtained by silica gel column chromatography.

General Procedure for the Removal of a TBS Group on a Spiroketal: TBAF (0.017 mL, 0.017 mmol, 1 M solution in THF, 5 equiv.) was added at 0 °C to a stirred solution of the TBS-protected spiroketal (0.0033 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 24 h. Saturated NH_4Cl solution (3 ml) was added, and it was extracted with ethyl acetate, washed with water and dried with $MgSO_4$ and concentrated to afford crude hydroxy spiroketal. This was purified by silica gel column chromatography with ethyl acetate/cyclohexane (0.5:10) as eluent.

Spiroketal (–)-25: Yield: 12.5 mg (from 200 mg resin), 14.0%. R_f = 0.21 (silica gel, ethyl acetate/cyclohexane 0.1:10). $[\alpha]_D^{20}$ = +114.5 ($CHCl_3$, c = 0.39). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.00 (dd, ^3J = 11.2, ^3J = 4.6 Hz, 1 H), 3.64–3.60 (m, 1 H), 3.51–3.26 (m, 3 H), 3.44–3.30 (m, 1 H), 2.35–2.28 (m, 1 H), 2.00 (s, 3 H), 1.91–1.84 (m, 2 H), 1.69–1.51 (m, 1 H), 1.62–1.53 (m, 1 H), 1.49–1.45 (m, 1 H), 1.15 (d, ^3J = 6.6 Hz, 3 H), 0.99 (d, ^3J = 7.0 Hz, 3 H), 0.91 (s, 9 H), 0.25 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.64, 102.44, 75.47, 72.53, 65.08, 58.16, 43.83, 40.12, 33.21, 29.53, 25.93, 21.23, 18.13, 13.72, 13.34, 10.67, –4.08, –4.54 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2838, 1732, 1143, 1127 cm^{-1}. GC-MS (*m*/*z*,%) 372 $[M]^+$ (5), 352 $[M - 15]^+$ (10).

Spiroketal (+)-38: Yield: 14.2 mg (from 200 mg resin), 13.0%. R_f = 0.26 (silica gel, cyclohexane). $[\alpha]_D^{20}$ = +109.5 ($CHCl_3$, c = 0.49). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30 (dt, ^3J = 11.3, ^3J = 4.7 Hz, 1 H), 3.68–3.59 (m, 4 H), 3.51–3.49 (m, 1 H), 2.20–2.15 (m, 1 H), 1.79–1.50 (m, 4 H), 1.20 (d, ^3J = 6.1, 3 H), 1.13 (d, ^3J = 6.7 Hz, 3 H), 1.03 (d, ^3J = 6.8 Hz, 3 H), 0.87 (s, 9 H), 0.89 (s, 9 H), 0.53 (s, 3 H), 0.04 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.59, 72.61, 66.90, 59.35, 58.00, 44.40, 43.47, 35.53, 29.58, 26.17, 26.12, 18.34, 18.24, 18.07, 14.07, 9.61, –3.80, –4.33, –4.40, –4.42 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2880, 1156, 1132 cm^{-1}. GC-MS (*m*/*z*,%) 458 $[M]^+$ (3), 401 $[M - 57]^+$ (16). HR-MS (EI) (70 eV): calcd. for $C_{24}H_{50}O_4Si_2$ 458.3248; found 458.3243.

Spiroketal (+)-39: Yield: 9.1 mg (from 200 mg resin), 10.0%. R_f = 0.26 (silica gel, ethyl acetate/cyclohexane 0.1:10). $[\alpha]_D^{20}$ = +104.5 ($CHCl_3$, c = 0.69). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.08 (dd, ^3J = 11.12, ^3J = 4.8 Hz, 1 H), 3.74–3.67 (m, 1 H), 3.61–3.46 (m, 3 H), 3.34–3.29 (m, 1 H), 2.45–2.38 (m, 1 H), 2.02 (s, 3 H), 1.95–1.89 (m, 1 H), 1.77–1.71 (m, 1 H), 1.64–1.57 (m, 1 H), 1.51–1.42 (m, 1 H), 1.06 (d, ^3J = 6.6 Hz, 3 H), 0.99 (d, ^3J = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.77 (d, ^3J = 6.6 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.55, 102.54, 75.57, 72.54, 65.09, 58.17, 43.82, 40.10, 33.23, 29.52, 25.96, 21.28, 18.13, 13.73, 13.38, 10.69, –4.09, –4.59 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2878, 1729, 1143, 1127 cm^{-1}. GC-MS (*m*/*z*,%) 386 $[M]^+$ (9). HR-MS (EI) (70 eV): calcd. for $C_{20}H_{38}O_5Si$ 386.2489; found 386.2471.

Spiroketal (+)-40: Yield: 5.0 mg, 8.0%. R_f = 0.4 (silica gel, cyclohexane/EtOAc 10:0.3). $[\alpha]_D^{20}$ = +105 ($CHCl_3$, c = 0.21). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.11 (dd, ^3J = 11.1, ^3J = 5.08 Hz, 1 H), 3.73–3.70 (m, 1 H), 3.60–3.50 (m, 3 H), 3.32–3.26 (m, 1 H), 2.30–2.26 (m, 1 H), 2.24 (s, 3 H), 1.99–1.84 (m, 2 H), 1.59 (br., 3 H), 1.16 (d, ^3J = 6.4 Hz, 3 H), 1.01 (d, ^3J = 7.2 Hz, 3 H), 0.78 (d, ^3J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.59, 102.32, 75.53, 71.88, 65.15, 57.93, 45.15, 41.66, 33.47, 29.45, 21.30, 13.70, 13.32, 10.61 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3430, 1731, 1153, 1132 cm^{-1}. GC-MS (*m*/*z*,%) 272 $[M]^+$ (7), 254 $[M - 18]^+$ (15). HR-MS (EI) (70 eV): calcd. for $C_{14}H_{24}O_5$ 272.1624; found 272.1649.

Spiroketal (+)-41: Yield: 10.9 mg (from 200 mg resin), 10.0%. R_f = 0.26 (silica gel, cyclohexane). $[\alpha]_D^{20}$ = +86.5 ($CHCl_3$, c = 0.42). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.20 (t, ^3J = 4.4 Hz, 1 H), 3.67–3.59 (m, 2 H), 3.55–3.46 (m, 2 H), 3.27–3.21 (m, 1 H), 2.23–2.19 (m, 1 H), 1.79–1.62 (m, 4 H), 1.05 (d, ^3J = 6.6 Hz, 3 H), 1.01 (d, ^3J = 7.2 Hz, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.77 (d, ^3J = 6.4 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.93, 72.98, 72.62, 65.49, 57.93, 43.97, 43.17, 33.22, 32.06, 26.04, 26.03, 18.26, 18.16, 14.03, 13.87, 10.11, –4.10, –4.13, –4.52, –4.65 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2891, 1166, 1152 cm^{-1}. GC-MS (*m*/*z*,%) 458 $[M]^+$ (3), 401 $[M - 57]^+$ (16). HR-MS (EI) (70 eV): calcd. for $C_{24}H_{50}O_4Si_2$ 458.3248; found 458.3263.

Spiroketal (+)-42: Yield: 10.0 mg (from 200 mg resin), 11.0%. R_f = 0.26 (silica gel, ethyl acetate/cyclohexane 0.1:10). $[\alpha]_D^{20}$ = +98.5 ($CHCl_3$, c = 0.25). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.29 (t, ^3J = 5.2 Hz, 1 H), 3.89 (dd, ^3J = 11.3, ^3J = 5.1 Hz, 1 H), 3.65–3.54 (m, 3 H), 3.35 (dd, ^3J = 11.4, ^3J = 2.8 Hz, 1 H), 2.19–2.16 (m, 1 H), 2.08 (s, 3 H), 1.72–1.71 (m, 1 H), 1.61–1.58 (m, 3 H), 1.10 (d, ^3J = 6.6 Hz, 3 H), 1.07 (d, ^3J = 7.6 Hz, 3 H), 1.02 (d, ^3J = 7.2 Hz, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.83, 102.63, 72.40, 71.64, 63.42, 58.62, 44.33, 42.67, 34.75, 32.02, 26.00, 21.28, 18.17, 14.82, 13.62, 13.34, –3.19, –4.54 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2880, 1726, 1155, 1122 cm^{-1}. GC-MS

(*m*/*z*,%) 386 [*M*]$^+$ (3). HR-MS (EI) (70 eV): calcd. for $C_{20}H_{38}O_5Si$ 386.2489; found 386.2463.

Spiroketal (+)-43: Yield: 7.8 mg (from 200 mg resin), 6.0%. R_f = 0.32 (silica gel, ethyl acetate/cyclohexane 0.2:10). $[\alpha]_D^{20}$ = +114.5 ($CHCl_3$, *c* = 0.23). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.40 (m, 5 H), 4.29 (dt, ^3J = 11.4, ^3J = 4.8 Hz, 1 H), 3.67–3.52 (m, 4 H), 2.67–2.52 (m, 2 H), 2.14–2.02 (m, 1 H), 1.81–1.73 (m, 1 H), 1.71–1.63 (m, 2 H), 1.52–1.30 (m, 4 H), 1.04 (d, ^3J = 6.7 Hz, 3 H), 0.98 (d, ^3J = 6.8 Hz, 3 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 9 H). IR (KBr): $\tilde{\nu}_{max}$ = 2933, 1260, 1245 cm^{-1}. HR-MS (EI) (70 eV): calcd. for $C_{31}H_{56}O_4Si_2$ 548.3371; found 548.3725.

Spiroketal (+)-44: Yield: 10.2 mg (from 200 mg resin), 9.0%. R_f = 0.2 (silica gel, ethyl acetate/cyclohexane 0.1:10). $[\alpha]_D^{20}$ = +121.5 ($CHCl_3$, *c* = 0.35). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.25 (m, 2 H), 7.19–7.17 (m, 3 H), 5.04 (dt, ^3J = 11.9, ^3J = 4.7 Hz, 1 H), 4.44–4.38 (m, 1 H), 3.84–3.77 (m, 2 H), 3.53–3.50 (m, 1 H), 2.74–2.60 (m, 1 H), 2.33–2.25 (m, 1 H), 2.03 (s, 3 H), 1.83–1.73 (m, 2 H), 1.62–1.53 (m, 1 H), 1.38 (dd, ^2J = 12.8, ^3J = 2.4 Hz, 1 H), 1.07 (d, ^3J = 7.4 Hz, 3 H), 1.02–0.99 (m, 1 H), 0.93 (d, ^3J = 6.6 Hz, 3 H), 0.91 (s, 9 H), 0.89 (d, ^3J = 5.6 Hz, 3 H), 0.64 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.20, 142.43, 128.45, 128.33, 125.80, 100.49, 72.01, 69.92, 69.20, 60.47, 56.71, 38.37, 37.40, 34.60, 31.55, 30.49, 28.74, 21.40, 21.15, 18.70, 15.51, 14.31, 6.41, –4.48, –4.67 ppm. GC-MS (*m*/*z*,%) 476 [*M*]$^+$ (6), 419 [*M* – 57]$^+$ (10). HR-MS (EI) (70 eV): calcd. for $C_{27}H_{44}O_5Si$ 476.2958; found 476.2972.

Spiroketal (+)-45: Yield: 4.2 mg, 5.0%. R_f = 0.41 (silica gel, ethyl acetate/cyclohexane 1.5:10). $[\alpha]_D^{20}$ = +118.5 ($CHCl_3$, *c* = 0.22). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.27 (m, 2 H), 7.20–7.15 (m, 3 H), 5.01 (dt, ^3J = 11.7, ^3J = 4.5 Hz, 1 H), 4.30–4.23 (m, 1 H), 3.99–3.92 (m, 1 H), 3.70 (dd, ^3J = 11.7, ^3J = 5.6 Hz, 1 H), 2.85–2.77 (m, 1 H), 2.70–2.62 (m, 1 H), 2.47 (dt, ^2J = 14.1, ^3J = 6.8 Hz, 1 H), 2.32–2.58 (m, 1 H), 2.06 (s, 3 H), 2.05–1.93 (m, 3 H), 1.89–1.80 (m, 1 H), 1.77–1.61 (m, 3 H), 1.49 (d, ^2J = 14.0 Hz, 1 H), 1.06 (d, ^3J = 7.0 Hz, 3 H), 0.92 (d, ^3J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.20, 141.20, 128.29, 128.03, 125.83, 102.30, 70.72, 70.24, 68.82, 55.99, 38.04, 36.70, 33.10, 31.39, 30.17, 26.93, 21.04, 14.19, 5.85 ppm. GC-MS (*m*/*z*,%) 362 [*M*]$^+$ (10), 303 [*M* – 59]$^+$ (8). HR-MS (EI) (70 eV): calcd. for $C_{21}H_{30}O_5$ 362.2093; found 362.2078.

Spiroketal (+)-46: Yield: 9.8 mg (from 200 mg resin), 7.0%. R_f = 0.30 (silica gel, ethyl acetate/cyclohexane 0.1/20). $[\alpha]_D^{20}$ = +119 ($CHCl_3$, *c* = 0.54). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (dt, ^3J = 11.3, ^3J = 4.9 Hz, 1 H), 3.61–3.58 (m, 4 H), 3.51–3.48 (m, 2 H), 2.03–2.02 (m, 1 H), 1.81–1.73 (m, 1 H), 1.52–1.26 (m, 4 H), 1.03 (d, ^3J = 6.6 Hz, 3 H), 0.92 (d, ^3J = 6.7 Hz, 3 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.07 (s, 6 H), 0.05 (s, 3 H), 0.04 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.72, 72.58, 69.59, 67.19, 66.63, 57.87, 44.77, 43.35, 36.04, 33.92, 31.39, 26.15, 26.02, 18.44, 18.22, 18.15, 13.81, 9.48, –4.03, –4.40, –4.56, –4.61, –5.07, –5.16 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2930, 1260, 1245 cm^{-1}. GC-MS (*m*/*z*,%) 588 [*M*]$^+$ (0.5), 531 [*M* – 57]$^+$ (14). HR-MS (EI) (70 eV): calcd. for $C_{30}H_{64}O_5Si_3$ 588.4062; found 588.4069.

Spiroketal (+)-47: Yield: 6.0 mg (from 200 mg resin), 5.0%. R_f = 0.30 (silica gel, ethyl acetate/cyclohexane 0.1:10). $[\alpha]_D^{20}$ = +114 ($CHCl_3$, *c* = 0.3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.94 (dt, ^3J = 11.2, ^3J = 4.5 Hz, 1 H), 4.31–4.38 (m, 1 H), 3.82–3.75 (m, 1 H), 3.62–3.45 (m, 4 H), 2.31–2.2.20 (m, 2 H), 2.14–1.10 (m, 1 H), 2.03 (s, 2 H), 1.94–1.82 (m, 1 H), 1.81–1.72 (m, 1 H), 1.69–1.51 (m, 1 H), 1.36 (dd, ^2J = 13.7, ^3J = 2.1 Hz, 1 H), 1.04 (d, ^3J = 7.2 Hz, 3 H), 0.90 (d, ^3J = 6.8 Hz, 3 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.06 (s, 6 H), 0.04 (s, 6 H) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2941, 1730, 1223, 1215 cm^{-1}. GC-MS (*m*/*z*,%) 516 [*M*]$^+$ (7), 459 [*M* – 57]$^+$ (10). HR-MS (EI) (70 eV): calcd. for $C_{26}H_{52}O_6Si_2$ 516.3302; found 516.3339.

Spiroketal (+)-48: Yield: 4.7 mg (from 200 mg resin), 4.0%. R_f = 0.30 (silica gel, ethyl acetate/cyclohexane 0.3:10). $[\alpha]_D^{20}$ = +94 ($CHCl_3$, *c* = 0.3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H), 4.99 (dt, ^3J = 11.7, ^3J = 4.9 Hz, 1 H), 4.48 (s, 2 H), 4.39–4.33 (m, 1 H), 3.81–3.79 (m, 1 H), 3.62–3.48 (m, 3 H), 2.31–2.2.20 (m, 2 H), 2.15–1.12 (m, 1 H), 2.03 (s, 3 H), 1.94–1.82 (m, 2 H), 1.81–1.72 (m, 1 H), 1.69–1.51 (m, 1 H), 1.36 (dd, ^2J = 13.7, ^3J = 2.1 Hz, 1 H), 1.04 (d, ^3J = 7.2 Hz, 3 H), 0.90 (d, ^3J = 6.8 Hz, 3 H), 0.87 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, $CDCl_3$): δ = 170.67, 138.68, 128.46, 127.78, 127.61, 100.48, 73.13, 71.90, 69.88, 67.55, 67.11, 56.74, 37.36, 36.31, 34.54, 30.55, 28.70, 26.30, 21.44, 18.66, 15.47, 6.40, –4.55, –4.59 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2961, 1727, 1238, 1210 cm^{-1}. GC-MS (*m*/*z*,%) 492 [*M*]$^+$ (4), 407 [*M* – 85]$^+$ (10). HR-MS (EI) (70 eV): calcd. for $C_{26}H_{52}O_6Si_2$ 492.2907; found 492.2928.

Spiroketal (+)-49: Yield: 8.0 mg (from 200 mg resin), 7.0%. R_f = 0.35 (silica gel, ethyl acetate/cyclohexane 1.5:10). $[\alpha]_D^{20}$ = +52 ($CHCl_3$, *c* = 0.15). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.28 (dt, ^3J = 11.3, ^3J = 5.0 Hz, 1 H), 4.00–3.90 (m, 1 H), 3.79–3.77 (m, 2 H), 3.73–3.68 (m, 1 H), 3.62–3.51 (m, 2 H), 2.68 (br., 1 H), 2.21–2.17 (m, 1 H), 1.85–1.67 (m, 4 H), 1.53–1.38 (m, 3 H), 1.04 (d, ^3J = 6.6 Hz, 3 H), 0.97 (d, ^3J = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, $CDCl_3$): δ = 102.91, 72.75, 69.36, 66.59, 61.77, 58.22, 51.60, 43.44, 42.27, 37.60, 35.14, 32.79, 32.56, 25.99, 25.97, 18.19, 18.13, 14.03, 9.34, –4.19, –4.45, –4.60, 4.71 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2965, 1251, 1233 cm^{-1}. GC-MS (*m*/*z*,%) 488 [*M*]$^+$ (6), 492 [*M* – 129]$^+$ (35). HR-MS (EI) (70 eV): calcd. for $C_{25}H_{52}O_5Si_2$ 488.3353; found 488.3327.

Spiroketal (+)-50: Yield: 17.0 mg (from 200 mg resin), 14.0%. R_f = 0.30 (silica gel, ethyl acetate/cyclohexane 0.2:10). $[\alpha]_D^{20}$ = +83 ($CHCl_3$, *c* = 0.3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 5 H), 5.02 (dt, ^3J = 11.7, ^3J = 4.5 Hz, 1 H), 4.59–4.40 (m, 2 H), 4.37–4.33 (m, 1 H), 3.90–3.81 (m, 1 H), 3.80–3.79 (m, 1 H), 3.62 (dd, ^3J = 9.3, ^3J = 3.5 Hz, 1 H), 3.50–3.46 (m, 2 H), 2.29–2.20 (m, 2 H), 2.03 (s, 3 H), 1.81–1.70 (m, 4 H), 1.31 (br., ^2J = 13.68 Hz, 1 H), 1.03 (d, ^3J = 7.2 Hz, 3 H), 0.90 (d, ^3J = 6.64 Hz, 3 H), 0.85 (s, 9 H), 0.012 (s, 3 H), 0.0005 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, $CDCl_3$): δ = 170.66, 138.57, 128.44, 127.85, 127.64, 100.67, 73.76, 73.15, 71.72, 69.82, 68.77, 56.77, 37.42, 34.19, 28.45, 28.20, 26.14, 21.43, 18.45, 15.24, 6.28, –4.68, –4.77 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 2961, 1727, 1238, 1210 cm^{-1}. GC-MS (*m*/*z*,%) 506 [*M*]$^+$ (6), 492 [*M* – 99]$^+$ (10). HR-MS (EI) (70 eV): calcd. for $C_{28}H_{46}O_6Si$ 506.3064; found 506.3046.

Spiroketal (+)-51: Yield: 5.5 mg (from 10 mg of **50**), 10.0%. R_f = 0.23 (silica gel, ethyl acetate/cyclohexane 1.0:1.0). $[\alpha]_D^{20}$ = +103.8 ($CHCl_3$, *c* = 0.3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.24 (m, 5 H), 5.02 (dt, ^3J = 11.6, ^3J = 4.8 Hz, 1 H), 4.57 (s, 2 H), 4.29 (dt, ^3J = 12.0, ^3J = 2.8 Hz, 1 H), 4.17–4.09 (m, 2 H), 3.75 (br., 1 H), 3.66 (dd, ^3J = 11.6, ^2J = 5.6 Hz, 1 H), 3.53 (dd, ^2J = 9.8, ^3J = 8.0 Hz, 1 H), 3.45 (dd, ^2J = 9.8, ^3J = 2.8 Hz, 1 H), 2.53–2.47 (m, 1 H), 2.31–2.27 (m, 1 H), 2.07–1.98 [m, with a singlet at 2.03 (3 H), 4 H], 1.59–1.46 (m, 5 H), 1.04 (d, ^3J = 7.2 Hz, 3 H), 0.89 (d, ^3J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, $CDCl_3$): 170.43, 138.08, 128.56, 127.80, 127.78, 127.62, 102.27, 73.48, 73.06, 71.07, 69.97, 69.22, 56.59, 36.99, 33.31, 27.37, 26.75, 24.28, 21.33, 16.64, 14.57, 6.18 ppm. GC-MS (*m*/*z*,%) 392 [*M*]$^+$ (5), 375 (5), 146 (58), 91 (100). HR-MS (EI) (70 eV): calcd. for $C_{22}H_{32}O_6$ 392.2198; found 392.2173.

Spiroketal (+)-52: Yield: 6.5 mg (from 200 mg resin), 6.0%. R_f = 0.30 (silica gel, ethyl acetate/cyclohexane 0.2:10). $[\alpha]_D^{20}$ = +64

($CHCl_3$, c = 0.15). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.25 (dt, ^3J = 12.12, ^3J = 4.8 Hz, 1 H), 3.82–3.63 (m, 3 H), 3.54–3.49 (m, 1 H), 2.20–2.17 (m, 1 H), 1.83–1.79 (m, 1 H), 1.72–1.65 (m, 1 H), 1.46–1.25 (m, 3 H), 1.13 (d, ^3J = 6.24 Hz, 3 H), 1.03 (d, ^3J = 6.64, 3 H), 0.95 (d, ^3J = 7.04, 3 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 9 H) ppm. GC-MS (m/z,%) 458 $[M]^+$ (6), 401 $[M - 57]^+$ (19). HR-MS (EI) (70 eV): calcd. for $C_{24}H_{50}O_4Si_2$ 458.3248; found 458.3225.

Spiroketal (+)-53: Yield: 6.5 mg (from 200 mg resin), 7.0%. R_f = 0.39 (silica gel, ethyl acetate/cyclohexane 1:10). $[\alpha]_D^{20}$ = +79 ($CHCl_3$, c = 0.20). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.96 (dt, ^3J = 12.12, ^3J = 4.8 Hz, 1 H), 4.40–4.34 (m, 1 H), 3.58–3.45 (m, 3 H), 2.30–2.25 (m, 1 H), 2.22–2.18 (m, 1 H), 2.12–1.97 (m, 1 H), 2.00 (s, 3 H), 1.95–1.85 (m, 1 H), 1.62–1.58 (m, 1 H), 1.51–1.42 (m, 1 H), 1.20 (d, ^3J = 6.0 Hz, 3 H), 1.00 (d, ^3J = 7.4 Hz, 3 H), 0.85 (d, ^3J = 5.9 Hz, 3 H), 0.84 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.69, 100.47, 71.73, 69.92, 65.52, 56.70, 37.17, 34.23, 32.74, 28.48, 26.10, 22.07, 21.43, 18.43, 15.33, 6.30, –4.68, –4.76 ppm. GC-MS (m/z,%) 386 $[M]^+$ (12), 301 $[M - 85]^+$ (15). HR-MS (EI) (70 eV): calcd. for $C_{20}H_{38}O_5Si$ 386.2489; found 386.2465.

Spiroketal (–)-58: Yield: 8.2 mg (from 800 mg resin), 2.2%. R_f = 0.18 (silica gel, ethyl acetate/cyclohexane 3:10). $[\alpha]_D^{20}$ = –7.2 ($CHCl_3$, c = 0.25). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 5 H), 5.23 (dd, ^3J = 11.2 and 5.2 Hz, 1 H), 4.61 (br. s, 2 H), 3.77–3.70 (m, 1 H), 3.60–3.48 (m, 4 H), 3.33 (appt, ^3J = 11.2, ^2J = 11.6 Hz, 1 H), 2.21 (dd, ^3J = 7.2, ^3J = 5.2 Hz, 1 H), 2.06 (s, 3 H), 1.96–1.89 (m, 2 H), 1.51–1.31 (m, 3 H), 1.17 (d, ^3J = 6.4 Hz, 3 H), 1.02 (d, ^3J = 7.2 Hz, 3 H), 0.72 (d, ^3J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.24, 138.72, 128.56, 127.65, 127.65, 102.56, 75.62, 73.73, 73.39, 72.11, 67.19, 65.18, 45.46, 42.35, 36.08, 29.56, 21.35, 13.80, 13.35, 10.58 ppm. GC-MS (m/z,%) 392 $[M]^+$ (0.1), 251 (17), 139 (21), 91 (100). HRMS-FAB (70 eV) calcd. for $C_{22}H_{32}O_6$ 392.2199; found 415.2087 $[M + Na]^+$.

Spiroketal (+)-59: Yield: 9.7 mg (from 800 mg resin), 2.0%. R_f = 0.63 (silica gel, ethyl acetate/cyclohexane 3:10). $[\alpha]_D^{20}$ = +19 ($CHCl_3$, c = 0.43). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.22 (m, 5 H), 4.64 (dd, ^3J = 8.4 and 4.0 Hz, 1 H), 4.58 (br s, 2 H), 3.95–3.88 (m, 2 H), 3.67 (dt, ^3J = 9.2 and 5.6 Hz, 1 H), 3.57 (dd, ^2J = 9.6, ^3J = 5.6 Hz, 1 H), 3.44 (dd, ^2J = 10.0, ^3J = 5.6 Hz, 1 H), 3.29 (dd, ^2J = 12.0, ^3J = 7.8 Hz, 1 H), 2.27–2.22 (m, 1 H), 2.05–2.03 (m, 1 H), 2.00 (s, 3 H), 1.94–1.86 (m, 2 H), 1.74–1.66 (m, 1 H), 1.07 (d, ^3J = 7.2 Hz, 3 H), 0.98 (d, ^3J = 6.8 Hz, 3 H), 0.87 (d, ^3J = 6.8 Hz, 3 H), 0.85 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.03, 138.71, 128.48, 127.82, 127.67, 102.78, 76.30, 74.77, 73.54, 72.06, 70.70, 64.80, 42.74, 35.99, 35.01, 30.36, 25.96, 21.26, 18.10, 15.06, 14.52, 9.83, –4.13, –4.55 ppm. GC-MS (m/z,%) 506 $[M]^+$ (0.1), 389 $[M - 117]^+$ (14), 115 (21), 91 (100). HR-MS (FAB, 70 eV) calcd. for $C_{28}H_{46}O_6Si$ 506.3064; found 529.2986 $[M + Na]^+$.

Spiroketal (–)-60: Yield: 22.0 mg (from 800 mg resin), 4.6%. R_f = 0.55 (silica gel, ethyl acetate/cyclohexane 1:10). $[\alpha]_D^{20}$ = –9.0 ($CHCl_3$, c = 1.0). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.14 (dd, ^3J = 11.2 and 5.2 Hz, 1 H), 3.58–3.46 (m, 3 H), 3.15 (appt, ^3J = 11.6 and 11.2 Hz, 1 H), 2.13 (dd, ^3J = 7.2 and 5.2 Hz, 1 H), 2.02 (s, 3 H), 1.95–1.86 (m, 1 H), 1.75–1.69 (m, 1 H), 1.45–1.36 (m, 2 H), 1.14 (d, ^3J = 6.8 Hz, 3 H), 1.08 (d, ^3J = 6.4 Hz, 3 H), 0.99 (d, ^3J = 6.4 Hz, 3 H), 0.85 (s, 9 H), 0.75 (d, ^3J = 6.4 Hz, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.30, 102.61, 75.63, 72.97, 64.77, 63.05, 45.01, 42.24, 29.58, 26.85, 25.80, 21.32, 21.17, 17.99, 13.92, 13.33, 10.70, –3.56, –4.31 ppm. GC-MS (m/z,%) 400 $[M]^+$ (0.1), 382 (0.5), 283 (14), 127 (100). HR-MS (FAB, 70 eV) calcd. for $C_{21}H_{40}O_5Si$ 400.2645; found 401.2699 $[M + H]^+$.

Spiroketal (–)-61: Yield: 7.0 mg (from 12 mg of **60**), 3.7%. R_f = 0.35 (silica gel, ethyl acetate/cyclohexane 3:10). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.10 (dd, ^3J = 11.2 and 4.8 Hz, 1 H), 3.61–3.44 (m, 3 H), 3.13 (t, ^3J = 11.2 Hz, 1 H), 2.28 (dd, ^3J = 7.6 and 7.2 Hz, 1 H), 2.12 (dd, ^3J = 7.2 and 5.2 Hz, 1 H), 1.99 (s, 3 H), 1.91–1.80 (m, 3 H), 1.13 (d, ^3J = 6.4 Hz, 3 H), 1.11 (d, ^3J = 6.4 Hz, 3 H), 0.95 (d, ^3J = 7.6 Hz, 3 H), 0.71 (d, ^3J = 6.4 Hz, 3 H) ppm. GC-MS (m/z,%) 268 $[M - 18]^+$ (0.1), 209 (4), 127 (100). HR-MS (FAB, 70 eV) calcd. for $C_{15}H_{26}O_5$ 286.178; found 227.1663 $[M - OAc]^+$.

Spiroketal (+)-62: Yield: 2.8 mg (from 800 mg resin), 0.6%. R_f = 0.48 (silica gel, ethyl acetate/cyclohexane 1:10). $[\alpha]_D^{20}$ = +20 ($CHCl_3$, c = 0.10). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.65 (dd, ^3J = 7.6 and 4.0 Hz, 1 H), 4.01 (dd, ^2J = 12.0, ^3J = 5.2 Hz, 1 H), 3.90–3.77 (m, 1 H), 3.63 (dt, ^3J = 10.4 and 6.4 Hz, 1 H), 3.28 (dd, ^3J = 12.0 and 6.4 Hz, 1 H), 2.24 (dq, ^3J = 7.2 and 4.0 Hz, 1 H), 2.03 (s, 3 H), 1.93–1.86 (m, 2 H), 1.75 (dq, ^3J = 6.0 and 6.4 Hz, 1 H), 1.61 (dd, ^3J = 12.0 and 11.6 Hz, 1 H), 1.14 (d, ^3J = 6.0 Hz, 3 H), 1.04 (d, ^3J = 7.2 Hz, 3 H), 0.97 (d, ^3J = 7.2 Hz, 3 H), 0.90 (d, ^3J = 6.8 Hz, 3 H), 0.83 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.30, 102.61, 75.63, 72.97, 64.77, 63.05, 45.01, 42.24, 29.58, 26.85, 25.80, 21.32, 21.17, 17.99, 13.92, 13.33, 10.70, –3.56, –4.31 ppm. GC-MS (m/z,%) 400 $[M]^+$ (0.1), 382 (0.5), 283 (14), 127 (100). HR-MS (FAB, 70 eV) calcd. for $C_{21}H_{40}O_5Si$ 400.2645; found 401.2709 $[M + H]^+$.

Spiroketal (+)-63: Yield: 10.0 mg (from 610 mg resin), 3.0%. R_f = 0.37 (silica gel, ethyl acetate/cyclohexane 1:10). $[\alpha]_D^{20}$ = +10 ($CHCl_3$, c = 0.25). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 5 H), 5.49 (dd, ^3J = 12.0 and 4.8 Hz, 1 H), 4.64 (s, 2 H), 3.86–3.43 (m, 6 H), 2.18–2.11 (m, 1 H), 1.92 (s, 3 H), 1.83–1.71 (m, 2 H), 1.49–1.42 (m, 1 H), 1.37–1.28 (m, 3 H), 1.10 (d, ^3J = 6.4 Hz, 3 H), 0.95 (d, ^3J = 6.8 Hz, 3 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H) ppm. GC-MS (m/z,%) 492 $[M]^+$ (0.8), 375 $[M - 117]^+$ (13), 91 (100). HR-MS (EI) (70 eV): calcd. for $C_{27}H_{44}O_6Si$ 492.2907; found 493.2986 $[M + H]^+$.

Spiroketal (–)-64: Yield: 5.9 mg (from 10 mg of **63**), 2.3%. R_f = 0.31 (silica gel, ethyl acetate/cyclohexane 3:10). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 5 H), 5.48 (dd, ^3J = 11.6 and 4.8 Hz, 1 H), 4.60 (s, 2 H), 3.73–3.64 (m, 2 H), 3.58–3.47 (m, 4 H), 2.22–2.13 (m, 1 H), 1.99 (s, 3 H), 1.97–1.91 (m, 1 H), 1.75 (dd, ^2J = 12.0, ^3J = 5.6 Hz, 1 H), 1.67–1.61 (m, 2 H), 1.41 (br., 1 H), 1.39–1.31 (m, 1 H), 1.17 (d, ^3J = 6.8 Hz, 3 H), 1.05 (d, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.39, 137.29, 128.40, 127.51, 127.47, 102.21, 73.49, 73.01, 71.87, 70.11, 66.83, 58.84, 45.46, 42.09, 35.84, 31.11, 21.35, 13.62, 11.13 ppm. GC-MS (m/z,%) 378 $[M]^+$ (1.0), 319 (5), 173 (19), 91 (100).

Spiroketal (–)-65 (as a mixture of 65/63 in a ratio of 86:14): Yield: 6.4 mg (from 610 mg resin), 1.8%. R_f = 0.54 (silica gel, ethyl acetate/cyclohexane 1:10). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.21 (m, 5 H), 4.99 (dd, ^3J = 8.8 and 5.2 Hz, 1 H), 4.57 (dd, ^2J = 12.0 Hz, 2 H), 4.12–4.06 (m, 1 H), 4.02–3.96 (m, 1 H), 3.74 (ddd, ^3J = 10.0, 7.6 and 5.6 Hz, 1 H), 3.60 [m, 2 H (with a ddd, ^2J = 9.6, ^3J = 5.6 Hz, 1 H)], 3.44 (dd, ^2J = 9.6, ^3J = 5.6 Hz, 1 H), 2.20–2.13 (m, 1 H), 1.98 (s, 3 H), 1.97–1.91 (m, 3 H), 1.87 (appt, ^3J = 7.6 and 7.2 Hz, 1 H), 1.77–1.73 (m, 2 H), 1.06 (d, ^3J = 7.2 Hz, 3 H), 1.03 (d, ^3J = 7.2 Hz, 3 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.01, 138.49, 128.34, 127.66, 127.55, 102.19, 77.20, 74.46, 73.39, 71.41, 71.08, 70.82, 45.63, 37.73, 36.22, 27.95, 25.81, 21.16, 17.97, 13.85, 11.88, –4.35,

–3.84 ppm. GC-MS (*m*/*z*,%) 492 $[M]^+$ (0.1), 375 $[M - 117]^+$ (9), 287 (8), 115 (18), 91 (100).

Spiroketal (–)-66: Yield: 3.6 mg, 1.3%. R_f = 0.31 (silica gel, ethyl acetate/cyclohexane 3:10). $[\alpha]_D^{20}$ = –12 ($CHCl_3$, *c* = 0.6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 5 H), 4.98 (dd, ^3J = 6.8 and 3.6 Hz, 1 H), 4.57 (s, 2 H), 3.84–3.77 (m, 1 H), 3.69 (dt, ^3J = 10.8 and 4.8 Hz, 1 H), 3.55 (dd, ^2J = 10.4, ^3J = 5.6 Hz, 1 H), 3.44 (dd, ^2J = 11.2, ^3J = 4.4 Hz, 1 H), 3.40 (dd, ^2J = 11.2, ^3J = 5.2 Hz, 1 H), 1.98–1.91 (m, 1 H), 1.87 (s, 3 H), 1.82–1.75 (m, 1 H), 1.65–1.61 (m, 1 H), 1.52–1.48 (m, 3 H), 1.29–1.18 (m, 2 H), 0.98 (d, ^3J = 6.8 Hz, 3 H), 0.87 (d, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.18, 138.68, 128.37, 127.55, 127.46, 101.21, 73.54, 70.09, 69.50, 67.50, 54.82, 53.40, 42.87, 37.41, 36.09, 30.20, 21.20, 11.98, 11.42 ppm. GC-MS (*m*/*z*,%) 378 $[M]^+$ (1.0), 319 (5), 173 (19), 91 (100).

Spiroketal (–)-67: Yield: 20.0 mg (from 1.5 g resin), 2.8%. R_f = 0.60 (silica gel, ethyl acetate/cyclohexane 1:10). $[\alpha]_D^{20}$ = –34.1 ($CHCl_3$, *c* = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.42 (dd, ^3J = 11.8 and 4.8 Hz, 1 H), 3.70–3.63 (m, 1 H), 3.55–3.45 (m, 2 H), 2.04 (dd, ^3J = 7.0 and 5.8 Hz, 1 H), 2.00 (s, 3 H), 1.76–1.67 (m, 2 H), 1.42–1.19 (m, 3 H), 1.14 (d, ^3J = 6.0 Hz, 3 H), 1.12 (d, ^3J = 6.0 Hz, 3 H), 1.09 (d, ^3J = 6.4 Hz, 3 H), 1.00 (d, ^3J = 6.44 Hz, 3 H), 0.86 (s, 9 H), –0.05 (s, 3 H), –0.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.32, 102.40, 72.97, 70.69, 63.86, 62.84, 45.25, 42.38, 41.51, 32.86, 25.86, 21.39, 21.33 (2 Cs), 18.00, 13.86, 10.34, –3.83, –4.62 ppm. GC-MS (*m*/*z*,%) 400 $[M]^+$ (0.1), 382 (0.5), 341 (4), 269 (14), 127 (100), HR-MS (FAB, 70 eV) $C_{21}H_{40}O_5Si$ 400.2645; found 401.2703 $[M + H]^+$.

Spiroketal (–)-68: Yield: 5.7 mg (from 10 mg of **67**), 2.2%. R_f = 0.30 (silica gel, ethyl acetate/cyclohexane 3:10). $[\alpha]_D^{20}$ = –31 ($CHCl_3$, *c* = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.42 (dd, ^3J = 11.8 and 4.9 Hz, 1 H), 3.72–3.64 (m, 1 H), 3.59–3.51 (m, 2 H), 2.09 (dq, ^3J = 7.2 and 5.2 Hz, 1 H), 2.01 (s, 3 H), 1.88 (dq, ^3J = 7.2 and 4.9 Hz, 1 H), 1.72–1.67 (m, 1 H), 1.43–1.32 (m, 3 H), 1.24 (br., 1 H), 1.17 (d, ^3J = 7.2 Hz, 3 H), 1.15 (d, ^3J = 7.2 Hz, 3 H), 1.14 (d, ^3J = 6.6 Hz, 3 H), 1.01 (d, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.31, 102.12, 72.12, 70.56, 64.05, 63.00, 45.24, 41.47, 41.40, 32.75, 21.37, 21.34, 21.28, 13.45, 10.18 ppm. GC-MS (*m*/*z*,%) 268 $[M - H_2O]^+$ (0.1), 209 (4), 127 (100). HR-MS (FAB, 70 eV) calcd. for $C_{15}H_{26}O_5$ 286,178; found 227.1022 $[M - OAc]^+$.

Spiroketal (–)-69: Yield: 22.4 mg (from 750 mg resin), 4.2%. R_f = 0.41 (silica gel, ethyl acetate/cyclohexane 1:10). $[\alpha]_D^{20}$ = –48 ($CHCl_3$, *c* = 0.6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.27 (m, 5 H), 5.46 (dt, ^3J = 12.0 and 4.8 Hz, 1 H), 4.45 (q, ^2J = 12.0 Hz, 2 H), 3.79–3.70 (m, 1 H), 3.62–3.43 (m, 4 H), 2.10–2.00 (m, 1 H), 1.99 (s, 3 H), 1.80–1.72 (m, 2 H), 1.69–1.63 (m, 2 H), 1.43–1.37 (m, 2 H), 1.20 (app q, ^3J = 12.4 and 11.2 Hz, 1 H), 1.07 (d, ^3J = 6.4 Hz, 3 H), 1.06 (d, ^3J = 6.0 Hz, 3 H), 0.98 (d, ^3J = 7.2 Hz, 3 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.28, 138.41, 130.13, 128.35, 127.62, 102.18, 73.11, 73.06, 70.61, 66.61, 64.31, 62.99, 53.40, 45.33, 42.33, 41.66, 35.77, 31.26, 25.87, 21.27, 18.02, 13.82, 10.34, –3.82, –4.63. MS-FAB (*m*/*z*,%) 521 $[M + 1]^+$ (1.1), 520 $[M]^+$ (0.7), 461 (21), 389 (14), 145 (21), 91 (100). HR-MS (FAB, 70 eV) calcd. for $C_{29}H_{48}O_6Si$ 520.3220; found 461.3073 $[M - OAc]^+$.

Spiroketal (–)-70: Yield: 9.2 mg (from 15 mg of **69**), 3.4%. R_f = 0.30 (silica gel, ethyl acetate/cyclohexane 3:10). $[\alpha]_D^{20}$ = –15 ($CHCl_3$, *c* = 0.8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 5 H), 5.43 (dt, ^3J = 11.8 and 4.8 Hz, 1 H), 4.45 (app q, ^2J = 11.7 and 11.4 Hz, 2 H), 3.81–3.73 (m, 1 H), 3.64–3.42 (m, 4 H), 2.10 (dq, ^3J = 7.0 and 5.6 Hz, 1 H), 2.00 (s, 3 H), 1.85–1.62 (m, 5 H), 1.49–1.36 (m, 3 H), 1.15 (d, ^3J = 6.4 Hz, 3 H), 1.09 (d, ^3J = 6.2 Hz, 3 H), 0.99 (d, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.22, 138.36, 128.34, 127.67, 127.56, 101.88, 73.11, 72.23, 70.49, 66.47, 64.44, 63.10, 45.31, 41.59, 41.43, 35.76, 31.22, 29.69, 21.28, 13.45, 10.17 ppm. GC-MS (*m*/*z*,%) 389 $[M + 1 - H_2O]^+$ (3), 307 (4), 207 (4), 145 (9), 91 (100).

Spiroketal (–)-71: Yield: 25 mg (from 800 mg resin), 5.1%. R_f = 0.40 (silica gel, ethyl acetate/cyclohexane 1:10). $[\alpha]_D^{20}$ = –33 ($CHCl_3$, *c* = 1.0). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.31 (m, 5 H), 5.46 (dt, ^3J = 11.2 and 5.2 Hz, 1 H), 4.61 (d, ^2J = 12.4 Hz, 1 H), 4.57 (d, ^2J = 12.4 Hz, 1 H), 3.82–3.76 (m, 1 H), 3.59–3.45 (m, 4 H), 2.09 (dq, ^3J = 7.2 and 5.6 Hz, 1 H), 2.00 (s, 3 H), 1–75–1.70 (m, 2 H), 1.48–1.40 (m, 2 H), 1.24 (q, ^2J = 11.2 Hz, 1 H), 1.13 (d, ^3J = 6.0 Hz, 3 H), 1.11 (d, ^3J = 6.4 Hz, 3 H), 1.01 (d, ^3J = 7.2 Hz, 3 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.23, 138.66, 128.35, 127.46, 127.29, 102.53, 73.36, 73.05, 72.96, 70.37, 67.92, 63.15, 45.21, 42.30, 41.77, 27.65, 25.86, 21.34 (2 Cs), 18.00, 13.92, 10.32, –3.83, –4.64 ppm. MS-FAB (*m*/*z*,%) 507 $[M + 1]^+$ (3), 506 $[M]^+$ (1), 447 (50), 145 (15), 91 (100). HR-MS (FAB, 70 eV) calcd. for $C_{28}H_{46}O_6Si$ 506.3064; found 507.3147 $[M + H]^+$.

Spiroketal (–)-72: Yield: 9.0 mg (from 15 mg of **71**), 4.0%. R_f = 0.35 (silica gel, ethyl acetate/cyclohexane 3:10). $[\alpha]_D^{20}$ = –43 ($CHCl_3$, *c* = 0.9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.31 (m, 5 H), 5.46 (dt, ^3J = 11.8 and 5.0 Hz, 1 H), 4.59 (q, ^2J = 12.3 Hz, 2 H), 3.83–3.76 (m, 1 H), 3.65–3.57 (m, 3 H), 3.53 (dd, ^2J = 10.5, ^3J = 5.8 Hz, 1 H), 3.46 (dd, ^2J = 10.5, ^3J = 4.1 Hz, 1 H), 2.12 (dq, ^3J = 7.0 and 5.2 Hz, 1 H), 2.01 (s, 3 H), 1.89 (dq, ^3J = 7.2 and 2.1 Hz, 1 H) 1.77–1.70 (m, 1 H), 1.29–1.21 (m, 2 H), 1.20 (d, ^3J = 6.2 Hz, 3 H), 1.17 (d, ^3J = 6.2 Hz, 3 H), 1.02 (d, ^3J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.22, 138.56, 128.35, 127.49, 127.33, 102.24, 73.42, 73.02, 72.13, 70.25, 68.03, 63.26, 53.40, 45.17, 41.68, 41.43, 27.58, 21.34, 13.54, 10.15 ppm. GC-MS (*m*/*z*,%) 372 $[M - H_2O]^+$ (0.1), 281 (32), 207 (100), 115 (27), 91 (42). HR-MS (FAB, 70 eV) calcd. for $C_{22}H_{32}O_6$ 392.2199; found 393.2275 $[M + H]^+$.

Spiroketal (–)-73: Yield: 8.2 mg (from 800 mg resin), 1.7%. R_f = 0.60 (silica gel, ethyl acetate/cyclohexane 3:10). $[\alpha]_D^{20}$ = –22.4 ($CHCl_3$, *c* = 0.5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.31 (m, 5 H), 5.06 (dd, ^3J = 6.8 and 3.2 Hz, 1 H), 4.59 (s, 2 H), 4.00–3.96 (m, 1 H), 3.79–3.71 (m, 2 H), 3.50–3.40 (m, 2 H), 2.01 (s, 3 H), 1.93 (dq, ^3J = 6.8 and 3.6 Hz, 1 H), 1.81–1.70 (m, 2 H), 1.57–1.53 (m, 1 H), 1.24–1.17 (m, 2 H), 1.12 (d, ^3J = 6.0 Hz, 3 H), 0.94 (d, ^3J = 6.8 Hz, 3 H), 0.90 (d, ^3J = 6.8 Hz, 3 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.20, 138.66, 128.35, 127.46, 127.28, 102.55, 73.41, 73.17, 7058, 70.45, 63.73, 63.18, 43.25, 42.65, 36.14, 32.57, 25.88, 21.55, 21.15, 18.06, 11.72, 11.62, –4.01, –4.63 ppm. GC-MS (*m*/*z*,%) 506 $[M]^+$ (4.0), 407 (15), 207 (100), 91 (86). HR-MS (FAB, 70 eV) calcd. for $C_{28}H_{46}O_6Si$ 506.3064; found 507.3149 $[M + H]^+$.

Supporting Information (for details see footnote on the first page of this article): Spectroscopic and analytical data, selected experimental procedures and procedure for different enzymatic assays are available.

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