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# Solid-Phase Synthesis of [5.5]-Spiroketals

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Dedicated to Professor Chi-Huey Wong on the occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

**Abstract:** An efficient and reliable multi-step synthesis of 251 natural product-like [5.5]-spiroketals on solid supports has been developed. As central key step, a double intramolecular hetero-Michael (DIHMA) reaction to alkynones was applied. The sequence allows for introduction of numerous substituents on the scaffold and for variation of stereochemistry. [5.5]-Spiroketals bearing an additional ketone were obtained in high overall yields. Further diversification was achieved by reduction of the ketone and reductive amination using polymer-supported borohydride, Grignard reaction and conversion to oxime derivatives in the solution phase.

**Keywords:** asymmetric synthesis; chemical biology; natural products; solid-phase synthesis; spiroketals

## Introduction

Biologically active small molecules have proven to be valuable tools for the study of biological phenomena. For the synthesis of such molecules in the format of compound collections with a high degree of substituent variation on a given scaffold,[1] in particular, diversity-oriented synthesis (DOS)[2] and biology-oriented synthesis (BIOS)[3] of natural product-derived and -inspired compound collections were recently introduced as hypothesis-generating approaches. BIOS refers to natural products as evolutionary selected starting points for compound collection synthesis. Due to their biosynthetic origin and their manifold interactions with proteins when exerting their functions, the characteristic structural scaffolds of natural products can be regarded as biologically prevalidated starting points in structure space for compound collection development.

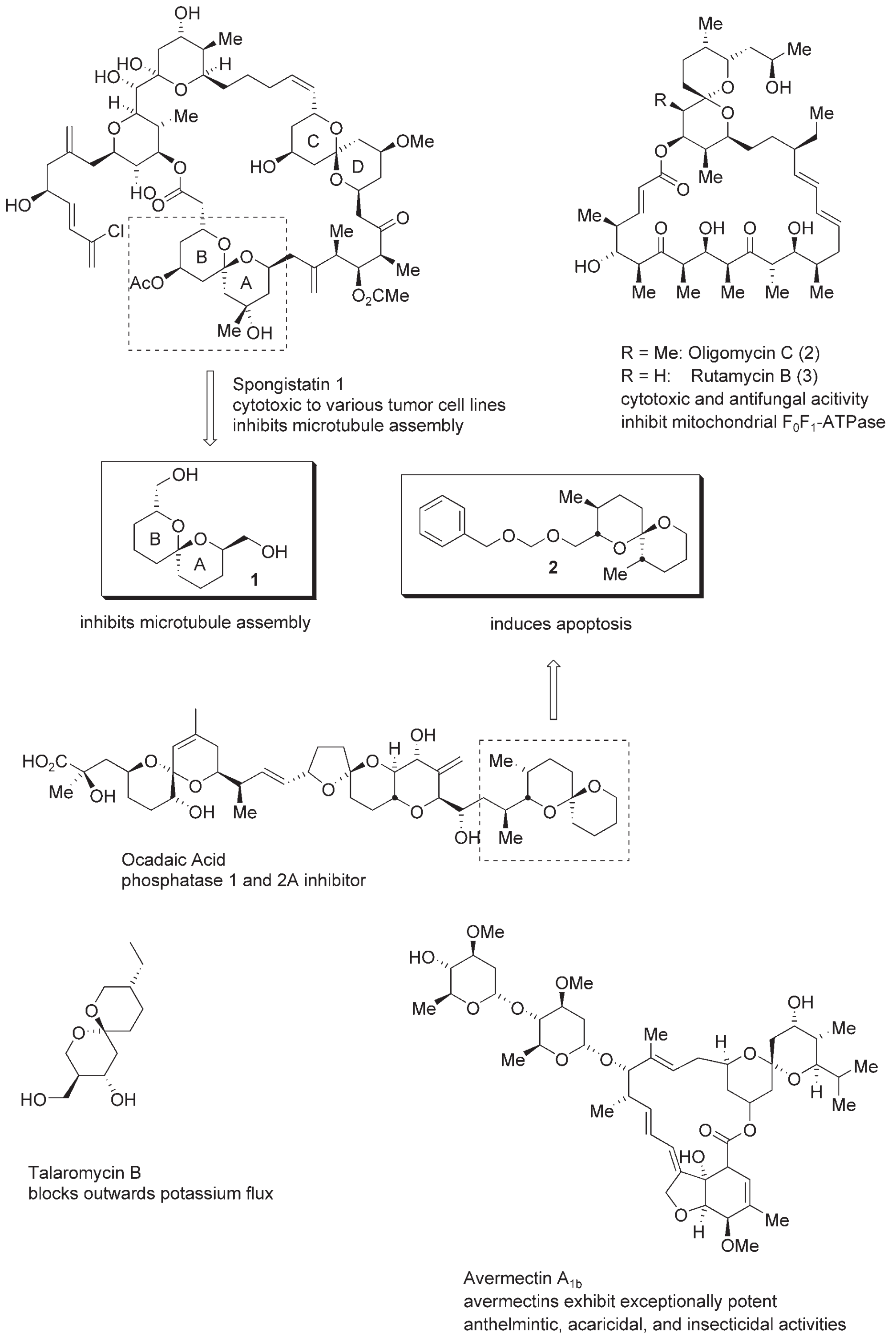
For the synthesis of natural product-inspired and -derived compound collections solid-phase organic synthesis is a viable technology. Immobilization of the substrate on a polymeric carrier enables efficient and straightforward removal of all surplus reagents required in the multi-step sequences typical for the synthesis of such compound collections and thereby facilitates purification of the desired compounds.

Thus, we[3,4] and others[1,5] have used this approach for the synthesis of different natural product-derived and -inspired compound collections in more than 10 steps on the polymeric carrier.

In the context of employing natural product-inspired compound collections in chemical biology, we became interested in the synthesis and biological evaluation of natural product-derived molecules which contain a spiroketal as scaffolding unit.

The spiroketal unit is a widespread substructure in many biologically active natural products, including steroidal saponins, polyether ionophores, macrolide antibiotics, insect pheromones, and toxic metabolites from algae and fungi.[6–8]

Examples are the extraordinarily potent tubulin polymerisation inhibiting spongistatins,[9] the protein phosphatase inhibitors okadaic acid[10] and tautomycin[11] and the HIV-1 protease inhibitor integramycin.[12] Interestingly, structurally simplified but characteristic spiroketals **1** and **2** derived from the parent natural products retain biological activity (Figure 1).[13] The spiroketal motifs present in okadaic acid and tautomycin have an enantiomeric relationship and the stereochemistry of the spiroketal moieties could be a determining factor for the affinity characteristics of okadaic acid and tautomycin to the PP1 and PP2A phosphatases.[14] These findings validate the choice of the [5.5]-spiroketal as underlying structural framework for the development of promising natural product-derived compound collections. The usefulness of spiroketals in combinatorial chemistry[15]



Spongistatin 1
cytotoxic to various tumor cell lines
inhibits microtubule assembly

R = Me: Oligomycin C (2)
R = H: Rutamycin B (3)
cytotoxic and antifungal acitivity
inhibit mitochondrial $F_0F_1$-ATPase

inhibits microtubule assembly

induces apoptosis

Ocadaic Acid
phosphatase 1 and 2A inhibitor

Talaromycin B
blocks outwards potassium flux

Avermectin $A_{1b}$
avermectins exhibit exceptionally potent anthelmintic, acaricidal, and insecticidal activities

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

and methods for their synthesis on solid supports have been reported earlier by us[4f,g] and the groups of Ley and Paterson.[16]

Herein we describe in detail the development of an asymmetric synthesis of [5.5]-spiroketals on a solid support by using readily accessible and enantiomerically pure building blocks and employing a double-hetero-Michael addition as key transformation.

## Results and Discussion

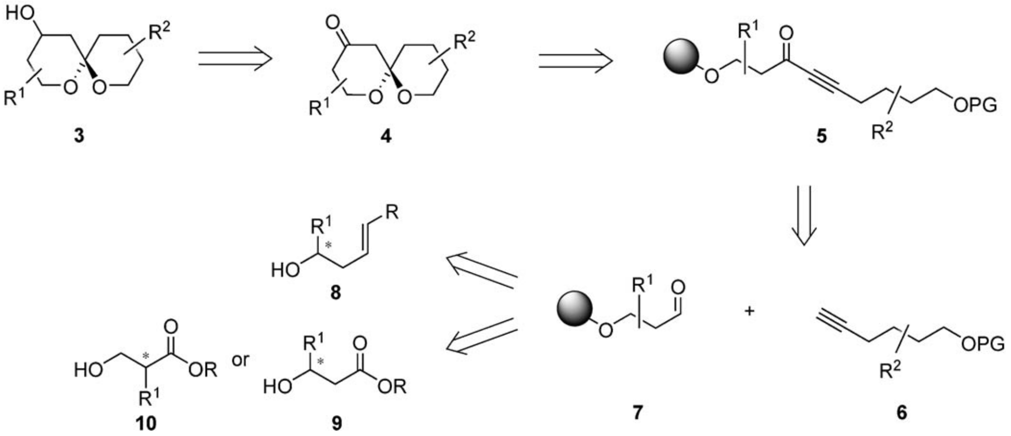
With the aim to synthesise a medium-sized library we searched for a reliable synthesis method to construct the spiroketal scaffold. It should allow a modular approach and variation of the stereochemistry. Furthermore, the building blocks should be readily accessible and the method should be amenable to solid-phase synthesis to facilitate library construction. Our interest was attracted to a method used successfully by Forsyth and co-workers which applies a double intramolecular hetero-Michael addition (DIHMA) for spiroacetal synthesis.[17,18]

DIHMA followed by reduction of the carbonyl group gives access to 4-hydroxy-1,7-dioxaspiro-[5.5]undecanes. This moiety can be found in a variety of potent natural products reaching from structurally simple but highly toxic talaromycins to complex oligomycins, rutamycins, avermectins, milbemycins and spongistatins.[6–8]

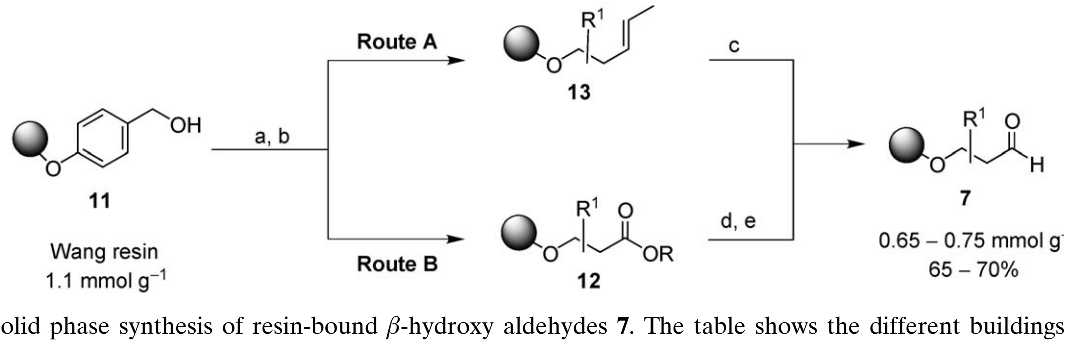
Spiroketal **3** was traced back in the retrosynthetic sense to ketone-bearing spiroketal **4** which itself should be accessible from solid support-linked alkynone **5** (Scheme 1). A disconnection was planned between the ketone and the alkyne leading to fragment **6**, a protected 5-hexyn-1-ol, and fragment **7**, a $\beta$-hydroxy aldehyde linked to a solid phase. The aldehyde can be derived from homoallylic alcohols **8** or $\beta$-hydroxy esters **9** and **10**.

The choice of the linker is crucial for every synthesis on a solid phase. Since Forsyth and co-workers described that DIHMA proceeds preferentially under acidic conditions[17] we decided to employ an acid-labile linker to affect cleavage from the support and cyclisation in one step, and the Wang linker turned out to be the right choice.

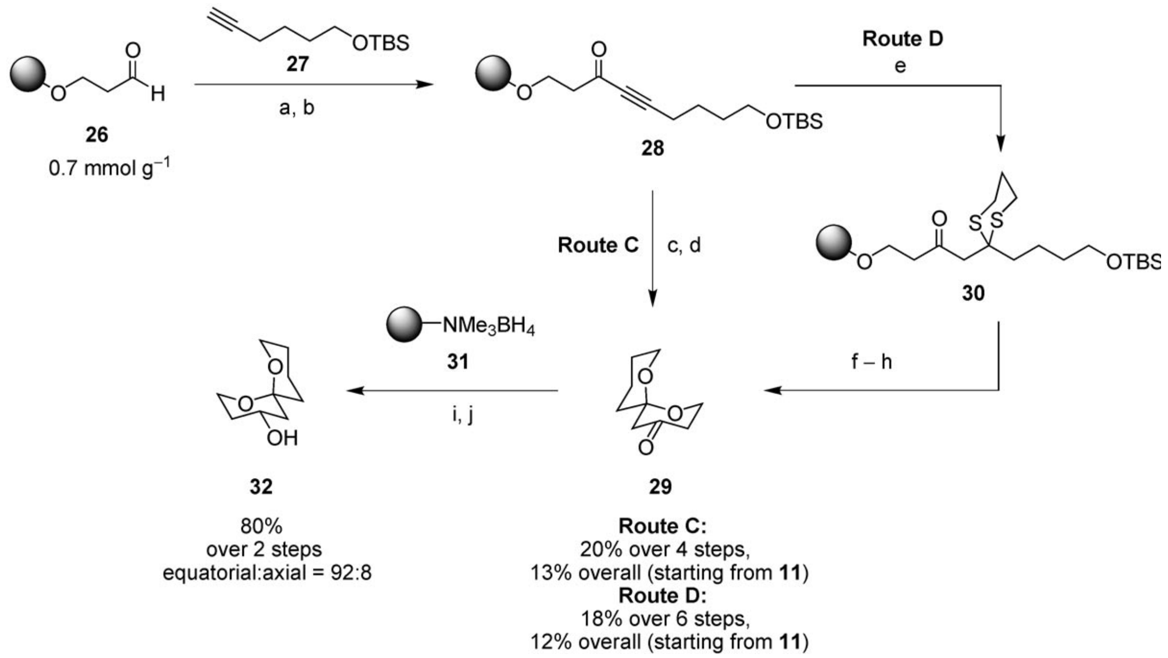
Polystyrene resin **11** equipped with Wang linker (loading 1.1 mmol g$^{-1}$) was activated as trichloroacetimidate,[19] which was then subjected to nucleophilic displacement by a chiral $\beta$-hydroxy ester or a homoallylic alcohol (Scheme 2). The resin-linked esters **12** were reduced with DIBAH and the corresponding alcohols were oxidised using IBX to yield the immobilised $\beta$-hydroxy aldehydes **7**. The polymer-bound homoallylic alcohols **13** were subjected to ozonolysis[20] and the ozonide was reduced to aldehydes **7** by addi-



**Scheme 1.** Retrosynthetic analysis of the [5.5]-spiroketal structures **3** and **4**.



**Scheme 2.** Solid phase synthesis of resin-bound $\beta$-hydroxy aldehydes **7**. The table shows the different buildings blocks used in this sequence. a) $Cl_3CCN$ (19.0 equiv.), DBU (0.88 equiv.), $CH_2Cl_2$, 0 °C, 40 min; b) alcohol (2.50 equiv.), $BF_3{\cdot}Et_2O$ (0.33 equiv.), cyclohexane/$CH_2Cl_2$ = 1/1, 15 min, 91% over two steps; c) $O_3$, −78 °C, $CH_2Cl_2$, 7-8 min; $PPh_3$ (5.00 equiv.), −78 °C to room temperature, 16 h, 70%; d) DIBAH (5.00 equiv.), THF/toluene, room temperature, 5 h, 90%; e) IBX (5.00 equiv.), DMSO/THF = 1/1, room temperature, 16 h, 83%.



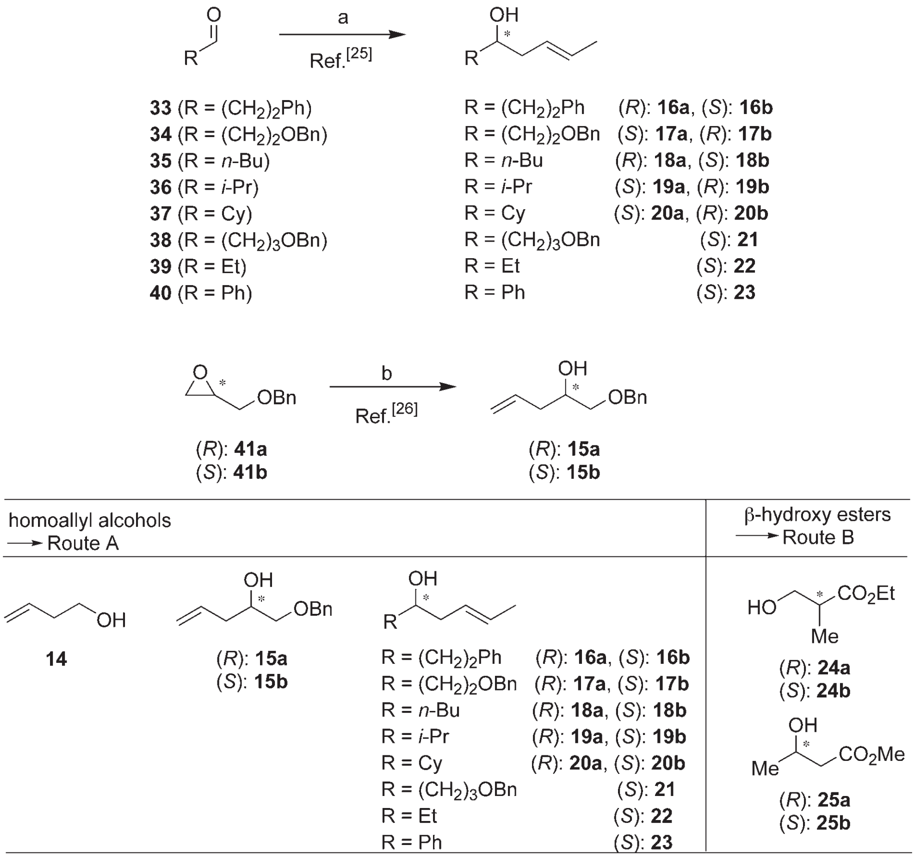
**Scheme 3.** Solid-phase synthesis of spiroketal **29** and solution-phase synthesis of the spiroketal **32**. a) alkyne (7.00 equiv.), 1 M EtMgBr in THF (7.00 equiv.), THF, room temperature, 16 h; b) IBX (5.00 equiv.), DMSO/THF = 1/1, room temperature, 16 h; c) 2% $MeSO_3H$ in $CH_2Cl_2$, room temperature, 30 min; d) (i) solvent exchange to MeOH, 40 °C to room temperature, 30 min; (ii) solvent exchange to toluene, room temperature, 2 h, 21% over 4 steps; e) 1,3-mercaptopropane (5.00 equiv.), NaOMe (5.00 equiv.), $CH_2Cl_2$/MeOH = 1/1, room temperature, 16 h; f) bis[trifluoroacetate]iodobenzene (2.50 equiv.), $CH_2Cl_2$/EtOH/$H_2O$ = 2/2/1; g) TBAF (5.00 equiv.), room temperature, 16 h; h) 5% TFA in $CH_2Cl_2$, room temperature, 30 min, 18% over 6 steps; i) borohydride on Amberlite IRA 400 (~2.5 mmol g$^{-1}$, 3 × 1.0 equiv.), MeOH, room temperature, 4.5 h; j) Dowex 50 X8, H$^{+}$-form, MeOH, room temperature, 30 min, 80% over two steps.

tion of triphenylphosphine. A minimum of 6 min in ozone-saturated dichloromethane was necessary for complete conversion of the support-bound olefin while reaction times longer than 9 min already led to lower aldehyde loading due to oxidative cleavage of the Wang linker. These two sequences could be conveniently monitored by FT-IR (C=O stretching band at 1721 cm$^{-1}$). For different substrates (see below), resin loading at this stage was determined to be 0.65–0.75 mmol g$^{-1}$ by application of a method which is based on formation of the corresponding dinitrophenylhydrazone.[4a,b,21]

The second part of the synthesis was optimised for the sequence which led to the simple spiroketals **29** and **32**. Under inert conditions seven equivalents of metallated terminal alkyne **27** were necessary to achieve conversion of achiral aldehyde **26** to the corresponding propargylic alcohol (Scheme 3). Disappearance of the strong carbonyl band at 1721 cm$^{-1}$ and the alkyne's weak vibration band at 2230 cm$^{-1}$ indicated successful conversion. Subsequent oxidation with IBX proceeded smoothly to give alkynone **28** (strong alkyne vibration band at 2209 cm$^{-1}$). Methanesulfonic acid in dichloromethane effected cleavage of the substrate from the Wang linker which was followed by a solvent exchange to methanol to remove the silyl protecting group (Scheme 3, Route C). A second solvent exchange to toluene was necessary to avoid 1,4-addition of methanol to the alkynone and to favor intramolecular Michael addition of the free hydroxy functions. Spiroketal **29** was obtained in 13% overall yield over seven steps on the support as a single diastereomer (determined by NMR of the crude product). Purification was achieved by means of column chromatography.

An alternative way to spiroketalisation was found by adding deprotonated 1,3-mercaptopropane to alkynone **28** (Scheme 3, Route D).[22] A double hetero-Michael addition introduced the second ketone protected as thioacetal. Oxidative deacetalisation of **30** followed by desilylation with TBAF and cleavage with spontaneous cyclisation under acidic conditions yielded spiroketal **29** in 12% overall yield over nine steps on the support. Although the conditions found for the second route are milder and may be the appropriate choice for sensitive substrates, yields were found to be in the same range as for the first route. Since the second route is more time-consuming we decided for the first route to build up the library.

Reduction of spiro[5.5]ketal-4-one **29** was achieved by treatment with polymer-bound borohydride **31**.



**Scheme 4.** Synthesis of homoallylic alcohols. a) (*R*)-configuration: (−)-crotylmenthol (1.10 equiv.), PTSA (0.10 equiv.), $CH_2Cl_2$, room temperature, 24 h, 56–79%, ≥98% *ee*; for (*S*)-configuration: (+)-crotylmenthol (1.10 equiv.), PTSA (0.10 equiv.), $CH_2Cl_2$, room temperature, 24 h, 57–87%, ≥98% *ee*; b) CuI (0.05 equiv.), (vinyl)MgBr in THF (1.30 equiv.), THF, −40 °C, 40 min, 90%, ≥98% *ee.*

Repeated addition of fresh reagent was required to drive the reaction to completion.

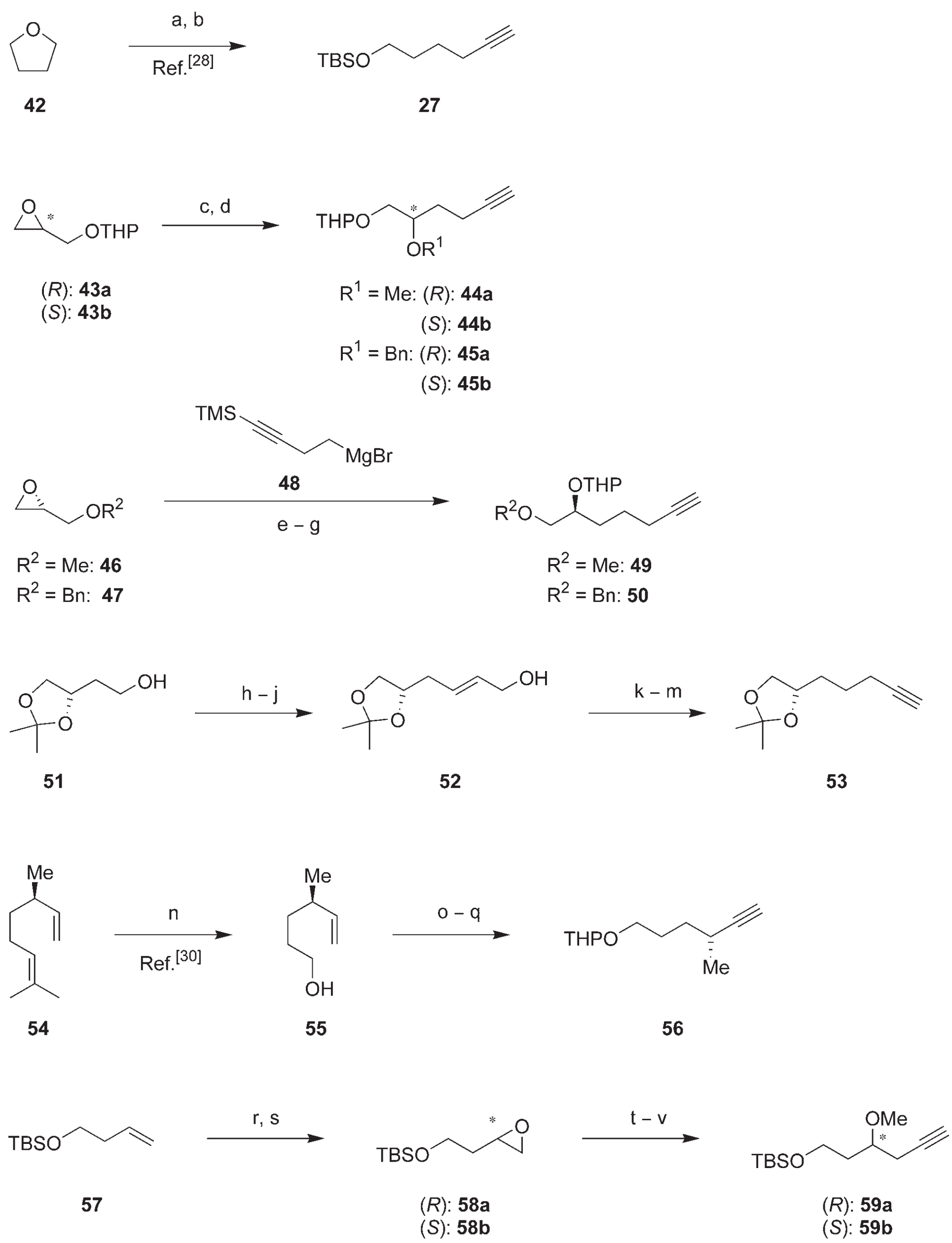
We expected that the nucleophilic attack of the hydride on the carbonyl group would occur from the equatorial direction giving rise to an axial alcohol.[23] However, the observed stereoselectivity was only low (53:47 in favour of the axial alcohol). Acidic protic conditions may lead to isomerisation of the spiro carbon as described by Mori et al.[24] In this process ring opening and reclosure led to formation of the thermodynamically more stable equatorial alcohol **32**. Upon treatment with acidic ion exchange resin in methanol equatorial alcohol **32** was formed in a ratio of 92:8. Compound **32** is a pheromone of the olive fly *Dacus oleae*.[17,24]

With a solid-phase sequence for the preparation of spiroketals in hand, very practicable methods for the synthesis of appropriate enantiomerically pure building blocks in multi-gram amounts were developed.

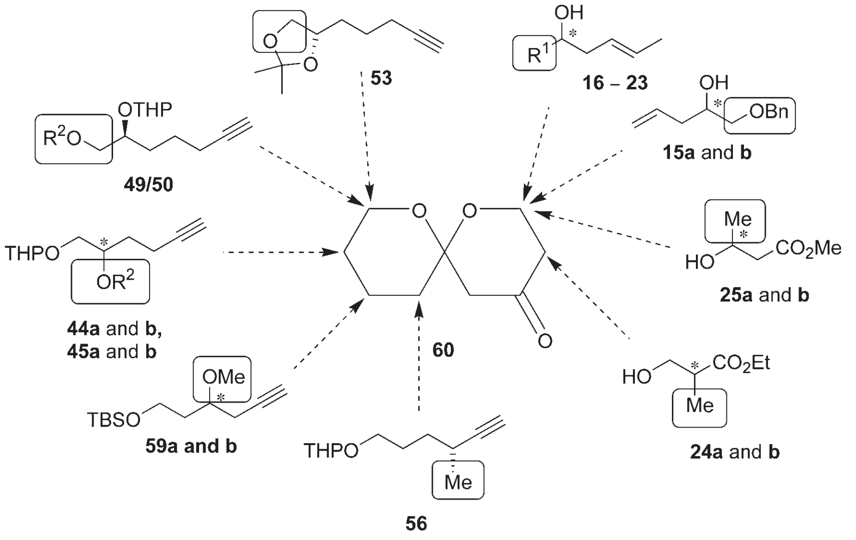
For the solid-phase synthesis of the *β*-hydroxy aldehydes **7** the chiral homoallylic alcohols **16–23**[25] and **15a** and **15b**[26] were synthesised following known procedures (Scheme 4). In addition, commercially available 3-buten-1-ol **14** and *β*-hydroxy esters **24a**, **24b**, **25a** and **25b**[27] were appropriate starting materials.

Except for alkyne **27**[28] new synthetic routes to different 5-hexyn-1-ols were developed (Scheme 5). Addition of allenyl-Grignard to THP-protected glycidol **43a** or **43b** followed by alkylation gave alkynes **44a**, **44b**, **45a** and **45b**. In a similar manner, epoxide opening of alkylated glycidol **46** or **47** with alkynyl-Grignard **48**, desilylation and THP-protection of the secondary alcohol gave alkynes **49** and **50**. Homologation of malic acid-derived alcohol **51**,[29] Swern oxidation and alkynylation with trimethylsilyl diazomethane gave alkyne **53**. Starting from (−)-*β*-citronellene-derived alcohol **55**[30] protection, bromination of the double bond and double elimination gave alkyne **56**. Epoxidation of TBS-protected 3-buten-1-ol **57** followed by enantioselective hydrolytic kinetic resolution[31] gave the chiral epoxides **58a** and **58b**. Ring opening with metallated trimethylsilylacetylene, desilylation and methylation of the secondary alcohol led to alkynes **59a** and **59b**.

With these building blocks in hand nearly all positions of spiroketal **60** are addressable (Scheme 6).



**Scheme 5.** Synthesis of protected 5-hexyn-1-ols. a) THF (2.50 equiv.), NaI (2.00 equiv.), TBSCl (1.00 equiv.), $CH_3CN$, 55 °C, 16 h, 100%; b) LiC≡CH·EDTA (1.50 equiv.), pentane/DMSO = 1/1, room temperature, 4 h, 88%; c) (allenyl)MgBr (2.00 equiv.), $Et_2O$, −10 °C, 35 min, 92%, ≥98% *ee*[a]; d) NaH (1.50 equiv.), MeI (2.00 equiv.), THF, 0 °C to room temperature, 71% or NaH (1.50 equiv.), BnBr (2.00 equiv.), room temperature, 16 h, 52%; e) **48** in THF (1.30 equiv.), CuI (0.05 equiv.), THF, −40 °C, 99% for epoxide **46** and 100% for epoxide **47**; f) $K_2CO_3$, MeOH, room temperature, 5 h, 71% and 70%, ≥98% *ee*[a]; g) DHP (1.35 equiv.), PTSA (0.03 equiv.), $CH_2Cl_2$, room temperature, 2 h, 94% for **49** and 100% for **50**; h) aqueous NaOCl (1.10 equiv.), TEMPO (0.01 equiv.), KBr (0.10 equiv.), 0 °C, 30 min, 79%; i) $Ph_3P{=}CHCO_2Me$ (1.00 equiv.), $CH_2Cl_2$, room temperature, 5 h, 83%; j) DIBAH in toluene (2.50 equiv.), −78 °C, 1 h, 100%; k) $MnO_2$ (22.0 equiv.), $CH_2Cl_2$, 0 °C to room temperature, 90 min, 80%; l) $H_2$, $Pd(OH)_2/C$ (0.10 equiv.), EtOAc, 3.5 h, 99%; m) LDA in hexane/THF (1.20 equiv.), $TMSCHN_2$ (1.20 equiv.), −78 °C, 1 h, reflux, 1 h, 75%; n) (i) $O_3$, $CH_2Cl_2$, −78 °C; (ii) $NaBH_4$ (1.50 equiv.), $CH_2Cl_2$/MeOH, 0 °C to room temperature, 1 h, 91%, ≥98% *ee*[b]; o) DHP (1.35 equiv.), PTSA (0.03 equiv.), $CH_2Cl_2$, 0 °C to room temperature, 3 h, 95%; p) $Br_2$ (1.10 equiv.), $CH_2Cl_2$, −78 °C, 5 min, 93%; q) $NaNH_2$ (2.50 equiv.), THF, −78 °C to room temperature, 2 h, reflux, 19 h, 61%; r) *m*-CPBA (1.50 equiv.), $CH_2Cl_2$, room temperature, 8 h, 90%; s) (*S,S*)-(−)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (0.005 equiv.), $H_2O$ (0.52 equiv.), AcOH (0.02 equiv.), THF, room temperature, 47%; t) *n*-BuLi in hexane (2.50 equiv.), TMSC≡CH (2.50 equiv.), $BF_3·OEt_2$ (2.50 equiv.), THF, −78 °C, 93%; u) $K_2CO_3$, MeOH, room temperature, 5 h, 84%, ≥98% *ee*[a]; v) NaH (1.50 equiv.), MeI (4.00 equiv.), THF, 0 °C, 95%. [a] Determined *via* Mosher ester. [b] Determined *via* chiral GC.



$R^1$ = Ph, Cy, *n*-Bu, *i*-Pr, $(CH_2)_2Ph$, $(CH_2)_2OBn$, $(CH_2)_3OBn$, Et
$R^2$ = Me, Bn

**Scheme 6.** Building blocks and the corresponding variation of sites at the spiroketal core structure **60**.

To get access to the spiroketals in viable amounts the quality and the loading of the resin loaded with *β*-hydroxy aldehyde was crucial. Loadings had to be above 0.65 $mmol\,g^{-1}$ and the resin had to be dried thoroughly.

For the cleavage and cyclisation conditions methanesulfonic acid was found to be optimal. Trifluoroacetic acid turned out to be too nucleophilic since trifluoroacetates of intermediate α,*β*-unsaturated ketones were formed. Camphorsulfonic acid as used by Forsyth et al. to promote DIHMA did not cleave the Wang linker.

For the spiroketals derived from substrate **56** cleavage and cyclisation conditions had to be optimised. Under initial conditions (3% $MeSO_3H$ and longer reaction times) epimerisation at the spiroketal $\alpha$ carbon was observed due to enolisation.[7] Shortening reaction times and reducing the amount of acid (2%) avoided epimerisation. The stronger cleavage and cyclisation conditions used initially introduced a $CH_2OMe$ group in the 8-position on the spiroketal core of alkyne **53** instead of a free $CH_2OH$ group. The same changes as in the latter case helped to prevent substitution of the free alcohol by methanol.

Combination of the 5-hexyn-1-ols with the homoallylic alcohols or *β*-hydroxy esters led to 147 spiroketals of type **60**. Since most of the by-products were rather polar in comparison to the desired cyclised product, isolation could be achieved by simple column chromatography to obtain the spiroketals in high purity of 88 to ≥98%. 104 of the 147 compounds were obtained as single diastereomers (determined by GC-MS) whereas the other compounds were formed as isomer mixtures with ratios ranging from 97:3 to 50:50. The overall yield over 7 steps on the solid phase varied between 5 and 45% (Table 1).

**Table 1.** Examples for library members.

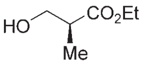
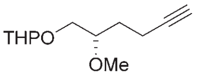
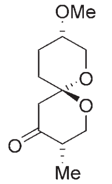
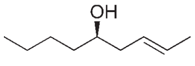
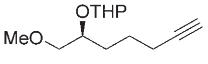
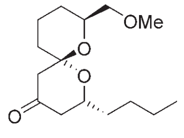
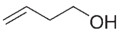
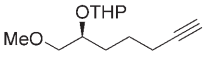
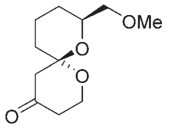
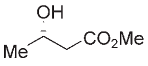
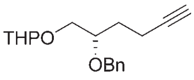
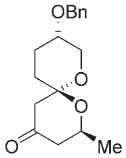
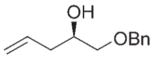
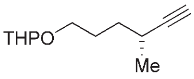
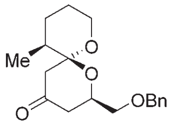
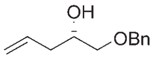
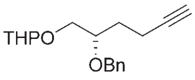
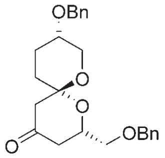
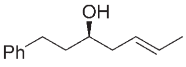
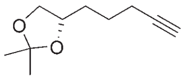
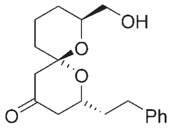
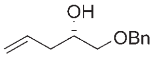
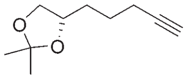
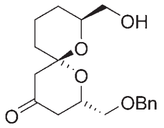
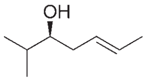
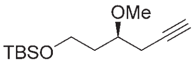
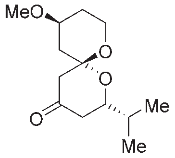
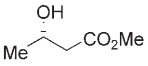
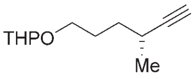
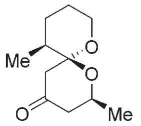
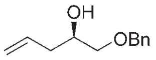
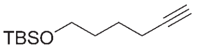
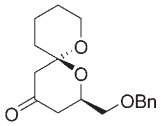
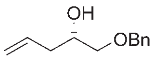
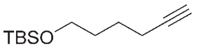
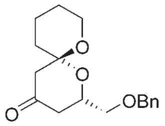
| No. | Building block 1 | Building block 2 | Product | Yield [%][a] | *dr*[b] |
|---|---|---|---|---|---|
| 1 |  <br>**24a** |  <br>**44b** |  | 45 | 80:20 |
| 2 |  <br>**18b** |  <br>**49** |  | 12 | [c] |

**Table 1.** (Continued)

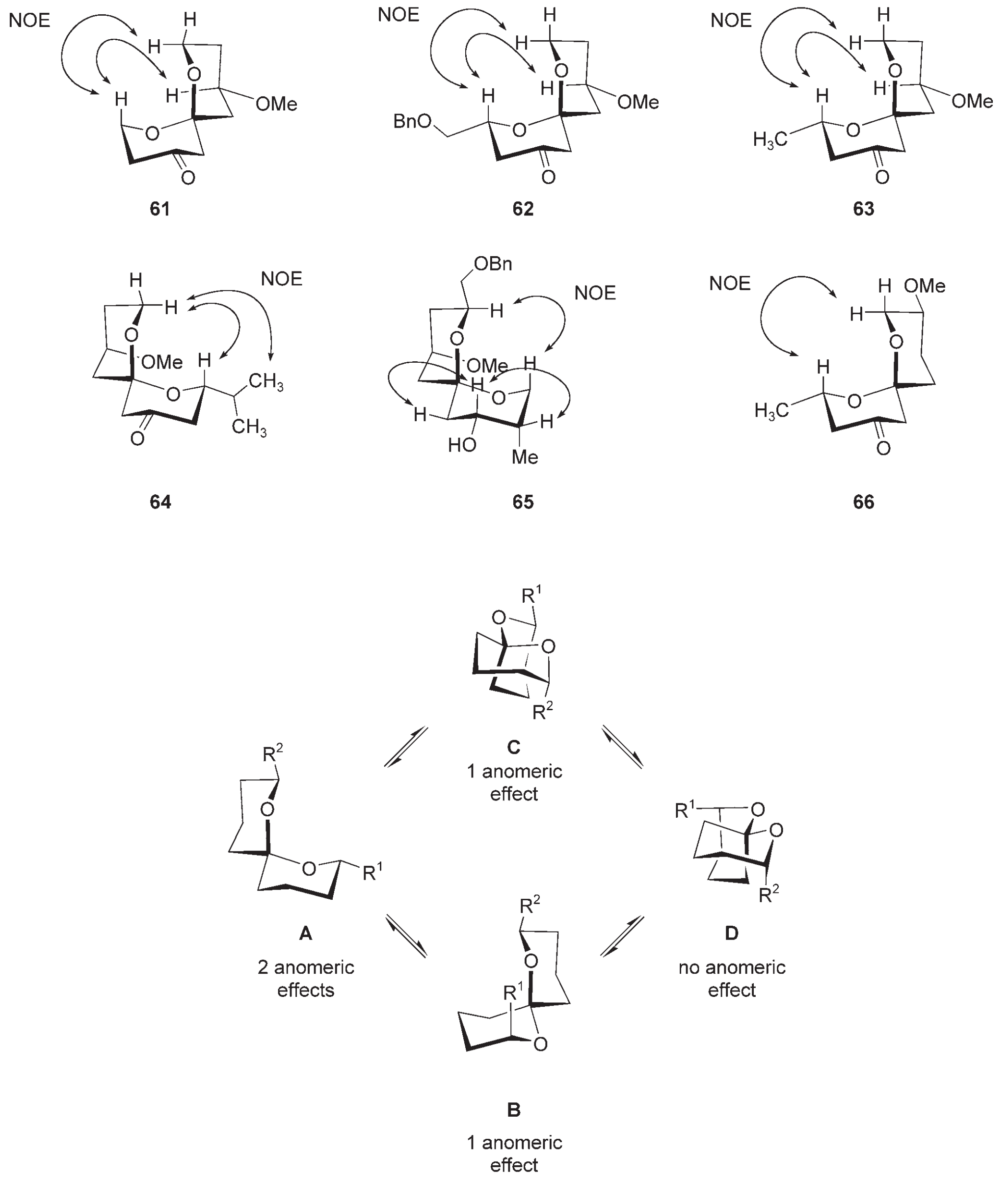
| No. | Building block 1 | Building block 2 | Product | Yield [%][a] | *dr*[b] |
|---|---|---|---|---|---|
| 3 |  **14** |  **49** |  | 38 | [c] |
| 4 |  **23b** |  **45b** |  | 31 | 90:10 |
| 5 |  **15a** |  **56** |  | 35 | 80:20 |
| 6 |  **15b** |  **45b** |  | 38 | [c] |
| 7 |  **16a** |  **53** |  | 5 | [c] |
| 8 |  **15b** |  **53** |  | 19 | [c] |
| 9 |  **19** |  **57b** |  | 12 | [c] |
| 10 |  **25b** |  **56** |  | 25 | 73:27 |
| 11 |  **15a** |  **27** |  | 27 | [c] |
| 12 |  **15b** |  **27** |  | 25 | [c] |

[a] Overall yields over 7 steps on the solid phase.

[b] Determined *via* GC-MS.

[c] Only one diastereomer detected.

As determined by 2D-NMR and NOE experiments for 6 representative compounds (Scheme 7) the spiroketals obtained as single diastereomers all adopted a conformation with a bisaxial arrangement of the spiro C–O bonds leading to a double anomeric stabilisation (conformer **A**). This was proven for these compounds by the close proximity of H-2 and H-8 which resulted in clear NOE signals. Additional NOE signals between the isopropyl group in the 2-position and H-8 as for spiroketal **64** or between H-2 and axially orient-



**Scheme 7.** Spiroketals in four different configurations and structural assignment of six library members by NOE signals.

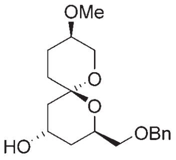
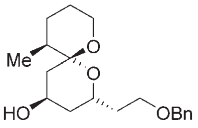
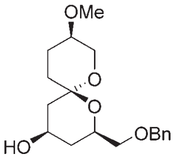
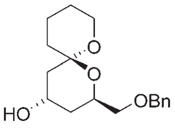
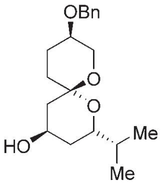
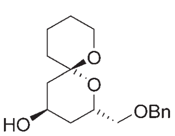
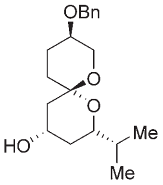
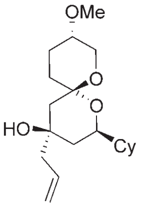
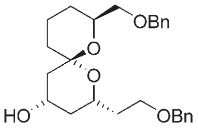
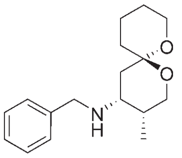
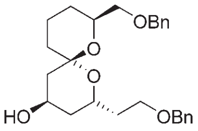
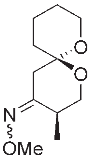
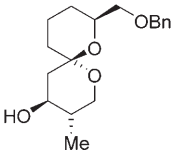
ed H-10 as for the compounds **62** and **63** gave further confidence in the structural assignment. For alcohol **65** the equatorial orientation of the OH in the 4-position was proven by NOE signals of the two equatorially oriented protons H-3 and H-5 with axially oriented H-4.

The two isomers of the spiroketals that occurred as mixtures were distinguished by $^{13}$C NMR shifts: for spiroketals with bisaxial orientation and two anomeric stabilisations the spiro carbon resonates at higher field than for spiroketals with just one anomeric stabilisation. In addition,equatorial methyl groups at the 2- or 8-position appear at lower field in the $^{13}$C spectrum than axial methyl groups.[32] In all mixtures the configuration with bisaxial arrangement of the spiro C–O bonds was favoured (Table 1). The minor isomer is expected to adopt configuration **B** or **C** stabilised by only one anomeric effect (Scheme 7).[6,7]

A loss of stereochemical information during synthesis could not be detected. NMR experiments using Eu(tfc)$_3$ as shift reagent and chiral GC (column: Lipodex-E) showed single enantiomers. Opposing enantiomers within the library showed opposite optical rotations (Table 1: entries 11 and 12, Table 2: entries 9 and 10).

A set of diastereomerically pure spiroketal ketones was subjected to reduction to yield spiroketals similar to **32**. As reported[7] the nucleophilic attack occurs preferentially from the equatorial face to give alcohols with preference for an axial OH group. Unfortu-

**Table 2.** Examples for functionalized library members.

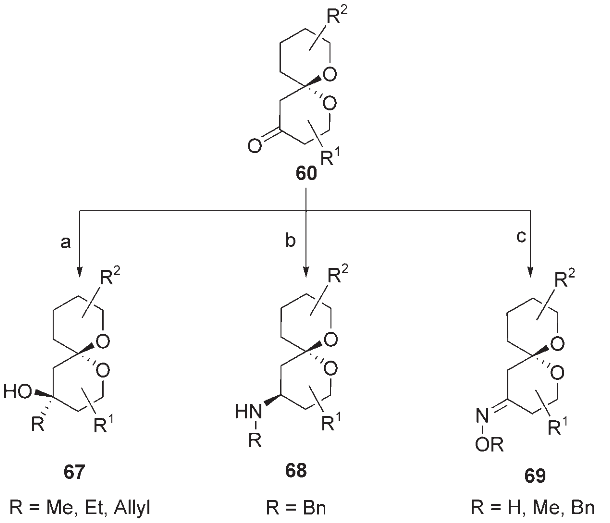
| No. | Product | Yield[%][a] | No. | Product | Yield [%][a] |
|---|---|---|---|---|---|
| 1 |  | 49 | 8 |  | 39 |
| 2 |  | 37 | 9 |  | 45 |
| 3 |  | 46 | 10 |  | 55 |
| 4 |  | 40 | 11 |  | 71 |
| 5 |  | 39 | 12 |  | 60 |
| 6 |  | 48 | 13 |  | 74 |
| 7 |  | 49 | | | |

[a] For one step starting from corresponding ketone.

nately, the diastereomeric differentiation with support-bound borohydride was low and led to epimeric mixtures ranging from 70:30 to 55:45 (determined by GC-MS) in favour of epimers with an axial hydroxy group (Table 2: entries 1–10). *Via* HPLC the epimers could be separated. After separation 55 reduced spiroketals were obtained in yields varying from 60 to 98% and 93% to ≥98% purity.

In addition to reduction of the keto group embedded into the spiroketals we sought to derivatise the scaffold further by means of solution-phase transformation of the keto group. To this end, the ketones were subjected to Grignard addition reaction, reductive amination and oxime formation (Scheme 8).

In accordance with a literature report,[33] in the case of the Grignard addition (allylMgBr, ethylMgBr, methylMgI) in solution at lower temperature (−60 °C) the nucleophilic attack occurs preferentially from the equatorial face to give tertiary alcohols with preference for an axial OH group (Scheme 8). The diastereomeric differentiation was substantial and led to isomer ratios from 85:15 to 97:3 (determined by GC-MS). After purification 41 spiroketals of type **67** were obtained in yields varying from 61 to 88% and



**Scheme 8.** Functionalisation of spiroketals. a) 1 M AllylMgBr in $Et_2O$ (2.00 equiv.) or 1 M EtMgBr in THF (2.00 equiv.) or 1 M MeMgI in $Et_2O$ (2.00 equiv.), THF, −78 °C; 10 min, −60 °C 3 h; b) benzylamine (2.00 equiv.), 3 Å mol sieves, MeOH, room temperature, 24 h, borohydride on Amberlite IRA 400 (~2.5 mmol g$^{-1}$, 4.00 equiv.), MeOH, room temperature, 24 h, polymer-supported benzaldehyde (excess), MeOH, room temperature, 24 h; c) $BnONH_2 \cdot HCl$ or $MeONH_2 \cdot HCl$ or $HONH_2 \cdot HCl$ (3.00 equiv.), EtOH, room temperature, 3.5 h.

85% to 98% purity (for an example see Table 2, entry 11).

For a reductive amination, the spiroketal was treated first with an excess of benzylamine for 24 h and then support-bound borohydride was added. Finally support-bound benzaldehyde was added to scavenge the excess benzylamine and to yield spiroketal **68**. In contrast to reduction of ketones yielding mixtures of isomers, only one diastereoisomer (determined by GC-MS) with an axial NH group (confirmed by NOE experiment) was found. According to this procedure three derivatives were synthesised in viable yields of 60 to 64% (see, for example, Table 2, entry 12).

Treatment of the spiroketal ketones with hydroxylamine and *O*-alkylhydroxylamines yielded spiroketals of type **69**. After purification five oximes were obtained in yields of 66 to 74% (for an example see Table 2, entry 13).

## Conclusions

We have developed a synthesis of spiroketals on a solid phase with varying stereogenic centres and substituents at nearly all sites of the spiroacetal core. Further derivatisation was achieved by application of support-bound borohydride for reduction and reductive amination, Grignard reaction and conversion to oxime derivatives in the solution phase. A library with 251 different members was successfully synthesised.

## Experimental Section

### General Procedure for the Activation of Wang Resin 11 as Trichloroacetimidate[19]

To a suspension of 1.00 g Wang resin **11** (1.10 mmol) in 10 mL dry dichloromethane 2.1 mL trichloroacetonitrile (22.8 mmol, 19.0 equiv.) were added and the mixture was stirred for 5 min at 0 °C. Over a time period of 5 min 0.13 mL of DBU (0.88 mmol, 0.80 equiv.) was added dropwise to the ice-cold suspension which changed colour from colourless to brown. The temperature was held for 40 min. The resin was filtered and washed successfully with $CH_2Cl_2$ (3×), DMSO (3×), THF (3×), $CH_2Cl_2$ (3×) and methanol (3×). It was dried with air for 1 h followed by drying under vacuum overnight to give a brown coloured trichloroacetimidate (TCA) resin. The FT-IR spectrum showed the disappearance of the hydroxy stretching band at 3500 cm$^{-1}$ with the appearance of strong bands at 1665 cm$^{-1}$ (C=N) and 3339 cm$^{-1}$ (N−H). The activation of Wang resin is believed to be quantitative.

### General Procedure for the Loading of Homoallylic Alcohols or β-Hydroxy Esters to Trichloroacetimidate (TCA) Resin[19]

TCA resin (0.80 g, 0.9 mmol) was washed twice with 8 mL of dry THF and twice with a 1:1 mixture of dry cyclohexane and dry dichloromethane under an argon atmosphere. Cyclohexane/dichloromethane (4 mL) was added followed by 2.18 mmol (2.50 equiv.) of the homoallylic alcohol or *β*-hydroxy ester. Under shaking and at room temperature 45 μL of $BF_3 \cdot Et_2O$ (0.36 mmol, 0.33 equiv.) were added in one portion to the suspension. A quick decolourisation was observed. After 15 min shaking at room temperature the resin was filtered and washed successfully with $CH_2Cl_2$ (3×), THF (3×), $CH_2Cl_2$ (3×) and methanol (3×). It was dried with air for 1 h followed by drying under vacuum overnight to give a bright yellow coloured resin. The characteristic bands for the TCA resin had disappeared and no IR band at 3300–3500 cm$^{-1}$ (O−H) could be observed. For the resin loaded with *β*-hydroxy ester **12** strong absorption at 1735 cm$^{-1}$ (C=O) was perceived. The loading was determined by cleavage with 5% TFA in dichloromethane over 30 min at room temperature (1.0 mmol g$^{-1}$, 91%).

### General Procedure for the Synthesis of Wang Resin Loaded with β-Hydroxy Aldehydes 7 Starting from Resin Loaded with Homoallylic Alcohol 13[20]

A suspension of 0.80 g of resin **13** loaded with homoallylic alcohol (0.8 mmol) in 15 mL dichloromethane in a three-necked flask was cooled to −78 °C. After 5 min stirring ozone was passed *via* a sintered frit through the suspension. After 1–3 min the colour changed to greenish blue indicating that saturation is reached. In general ozonolysis was stopped after 7–8 min. Ozone was removed by flushing with argon until decolourisation (~1 min). At −78 °C 1.05 g triphenylphosphine (4.00 mmol, 5.00 equiv.) were added and the suspension was shaken for 16 h at room temperature. The resin was filtered and washed successfully with $CH_2Cl_2$ (3×), THF (3×), $CH_2Cl_2$ (3×) and methanol (3×). The yellow resin was dried with air for 1 h followed by thorough drying under vacuum over 2 days. The *β*-hydroxy aldehyde linked to resin **7** showed no IR absorption at 3300–3500 $cm^{-1}$ (O–H) whereas, a strong band at 1721 $cm^{-1}$ (C=O) was observed. The loading was determined by the DNP method (0.65–0.75 $mmol\,g^{-1}$, 72–83%).[4a,b,21]

## General Procedure for the Synthesis of Wang Resin Loaded with β-Hydroxy Aldehyde 7 Starting from Resin Loaded with β-Hydroxy Ester 12

Resin **12** loaded with *β*-hydroxy ester (0.80 g, 0.8 mmol) was washed twice with 8 mL dry THF. To the swollen resin 4 mL of a 1 M solution of DIBAH in toluene (0.40 mmol, 5.00 equiv.) were added slowly at room temperature. After 5 h shaking at room temperature the bright, colourless resin was filtered and washed successfully with dry THF (2×), THF:methanol:AcOH = 47:47:6 (3×), THF (3×), $CH_2Cl_2$ (3×) and methanol (3×). It was dried with air for 1 h followed by drying under vacuum overnight. The IR absorption of the ester had disappeared while a broad band at 3433 $cm^{-1}$ was recognised. The loading was determined *via* Fmoc derivatisation, cleavage of the fluorenylmethyl group under basic condition and quantification by UV absorption (0.9 $mmol\,g^{-1}$, 90%).

A solution of 1.01 g IBX (3.6 mmol, 5.00 equiv.)[34] in a mixture of dry DMSO:dry THF = 1:1 was added to 0.80 g resin loaded with diol (0.72 mmol). After 16 h shaking at room temperature the yellow resin was filtered and washed successfully with DMSO (3×), THF (3×), $CH_2Cl_2$ (3×) and methanol (3×). It was dried with air for 1 h followed by thorough drying under vacuum over 2 days. The *β*-hydroxy aldehyde linked to resin **7** showed no IR absorption at 3300–3500 $cm^{-1}$ (O–H) whereas, a strong band at 1721 $cm^{-1}$ (C=O) was observed. The loading was determined as 0.75 $mmol\,g^{-1}$ (83%).[4a,b,21]

## General Procedure for Wang Resin Loaded with Alkynone Starting from Resin Linked to β-Hydroxy Aldehyde 7

A solution of 3.92 mmol alkyne (7.00 equiv.) in 4 mL dry THF was treated at 0 °C with 3.9 mL of a 1 M solution of ethylmagnesium bromide in THF (7.00 equiv.). After 2 h stirring at room temperature the solution was transferred under inert conditions to 0.80 g resin loaded with *β*-hydroxy aldehyde **7** that had been washed twice with dry THF and suspended in 4 mL dry THF. The reaction mixture was shaken for 16 h at room temperature, filtered and washed successfully with dry THF (1×), THF:methanol:AcOH = 47:47:6 (3×), THF (3×), $CH_2Cl_2$ (3×) and methanol (3×). The yellow resin was dried with air for 1 h followed by thorough drying under vacuum overnight. Completeness of the reaction was assumed when no IR absorption at 1721 $cm^{-1}$ (C=O) could be observed anymore and a weak band at 2230 $cm^{-1}$ (C≡C) and a broad band at 3432 $cm^{-1}$ (O–H) could be observed.

A solution of 1.01 g of IBX (3.6 mmol, 5.00 equiv.)[34] in a mixture of dry DMSO:dry THF = 1:1 was added to 0.80 g resin loaded with propargylic alcohol. After 16 h shaking at room temperature the yellow resin was filtered and washed successfully with DMSO (3×), THF (3×), $CH_2Cl_2$ (3×) and methanol (3×). It was dried with air for 1 h followed by thorough drying under vacuum overnight. The alkynone linked to resin **26** showed an IR absorption at 2209 $cm^{-1}$ (C≡C) whereas, no absorption between 3300–3500 $cm^{-1}$ could be observed.

## General Procedure for Cleavage from the Support and Spiroketalisation of the Alkynones

Resin loaded with alkynone **26** (0.80 g) was treated at room temperature with 8 mL of 2% solution of methanesulfonic acid in dichloromethane. After shaking for 30 min the resin was filtered and washed twice with 8 mL dichloromethane and twice with 8 mL methanol. At 40 °C and under reduced pressure dichloromethane was evaporated and the resulting solution was shaken for 30 min at room temperature. 20 mL toluene and 3 drops water were added and methanol was removed under reduced pressure. The toluene solution was shaken for 2 h and 0.30 mL triethylamine was added and the solution was immediately filtered through a plug of silica. Evaporation of the eluent gave a reddish brown oil that was purified by column chromatography (a gradient of cyclohexane/EtOAc = 8/1 to 6/1 was used) to afford the desired spiroketals as colourless or slightly yellow oils in overall yields ranging from 5 to 45% and 90 to ≥98% purity.

**(2*R*,6*R*,8*S*)-8-[(Hydroxy)methyl]-2-[2-(phenyl)ethyl]-1,7-dioxaspiro[5.5]undecan-4-one** (Table 1: entry 7): yield: 14.1 mg (0.046 mmol, 5%); $R_f$: 0.32 (cyclohexane/EtOAc = 2/1); purity: 98%; $[\alpha]_D^{20}$: 26.2° (*c* 0.95, $CHCl_3$); $^1H$ NMR (500.1 MHz, $CDCl_3$): $\delta = 7.14–7.30$ (m, 5 H, 5 × $C_{ar}H$), 3.89–3.97 (m, 1 H), 3.56 (tt, $^3J = 9.1$ Hz, $^3J = 2.9$ Hz, 1 H), 3.45 (dd, $^3J = 11.5$ Hz, $^3J = 3.3$ Hz, 1 H), 3.39 (dd, $^3J = 11.7$ Hz, $^3J = 6.7$ Hz, 1 H), 2.91 (ddd, $^3J = 13.9$ Hz, $^3J = 10.6$ Hz, $^3J = 5.3$ Hz, 1 H, $PhCH_2$), 2.68 (ddd, $^3J = 13.9$ Hz, $^3J = 10.3$ Hz, $^3J = 6.2$ Hz, 1 H, $PhCH_2$), 2.41 [s, 2 H, $C(5)H_2$], 2.38 (dd, $^3J = 15.2$ Hz, $^3J = 2.1$ Hz, 1 H), 2.23 (dd, $^3J = 14.1$ Hz, $^3J = 11.3$ Hz, 1 H), 1.82–2.22 (m, 4 H), 1.63–1.74 (m, 2 H), 1.45 (ddd, $^3J = 13.3$ Hz, $^3J = 13.3$ Hz, $^3J = 4.6$ Hz, 2 H), 1.28 (dddd, $^3J = 12.9$ Hz, $^3J = 12.9$ Hz, $^3J = 12.1$ Hz, $^3J = 4.1$ Hz, 1 H); $^{13}C$ NMR (125.8 MHz, $CDCl_3$): $\delta = 206.0$ (s), 150.2 (s), 128.6 (d), 128.4 (d), 126.1 (d), 99.4 (s), 71.0 (d), 68.5 (d), 65.9 (t), 51.9 (t), 47.1 (t), 37.7 (t), 34.8 (t), 31.9 (t), 25.7 (t), 18.5 (t); GC-MS(EI): $t_R$: 7.53 min; *m/z* (rel. int. [%]) = 304 (11) [$M^+$], 286 (15) [$M^+ - H_2O$], 273 (56), 199 (26), 174 (10), 155 (23), 128 (37), 117 (47), 91 (100) [$Bn^+$]; LC-MS(ESI): $t_R$: 8.39 min; *m/z* = 305.17 $[M+H]^+$; HR-MS (FAB: 3-NBA): *m/z* = 305.1734, calcd. for $C_{18}H_{24}O_4$ $[M+H]^+$: 304.1675.

## Representative Procedure for the Reduction of Spiroketals with Support-Bound Borohydride in Solution Phase

(2*R*,6*R*,9*R*)-2-[(Benzyloxy)methyl]-9-methoxy-1,7-dioxaspiro[5.5]undecan-4-one (41.1 mg, 0.128 mmol, 1.00 equiv.) was placed in a small vial and dissolved in 0.5 mL dry methanol. Three times after every 1.5 h 51 mg polymer-supported borohydride (~0.38 mmol, borohydride on Amberlite IRA

400, ~2.5 mmol g$^{-1}$; Aldrich Cat. No. 32,864–2) were added.[27] After 4.5 h completion of the reduction was controlled by TLC (cyclohexane/EtOAc = 1/1). The suspension was filtered and the eluent was evaporated to dryness. Purification and separation of the two epimers was achieved by means of HPLC.

**(2*R*,4*S*,6*R*,9*R*)-2-[(Benzyloxy)methyl]-9-methoxy-1,7-dioxaspiro[5.5]undecan-4-ol** (Table 2: entry 1): yield: 16.2 mg (0.050 mmol, 39%); $R_f$: 0.44 (cyclohexane/EtOAc = 1/1); purity: 94%; $[\alpha]_D^{20}$: −22.8° (*c* 1.73, $CHCl_3$); $^1$H NMR (500.1 MHz, $CDCl_3$): $\delta = 7.22–7.35$ (m, 5H, 5 × $C_{ar}H$), 4.58 (s, 2H, $CH_2Ph$), 4.05–4.13 (m, 2H), 3.75 (ddd, $^3J = 10.2$ Hz, $^3J = 4.8$ Hz, $^3J = 2.2$ Hz, 1H), 3.53 (d, $^3J = 1.8$ Hz, 1H), 3.52 (d, $^3J = 2.8$ Hz, 1H), 3.35 (s, 3H, $OCH_3$), 3.23–3.33 (m, 1H), 1.86–1.94 (m, 1H), 1.71–1.83 (m, 4H), 1.67 (d, $^3J = 3.5$ Hz, 1H), 1.62 (dd, $^3J = 10.7$ Hz, $^3J = 3.1$ Hz, 1H), 1.50–1.59 (m, 2H); GC-MS(EI): $t_R$:7.52 min; *m/z* (rel. int. [%]) = 322 (1) [$M^+$], 304 (2) [$M^+ - H_2O$], 216 (10), 201 (15), 183 (24), 157 (27), 129 (24), 107 (26), 91 (100) [$Bn^+$]; HR-MS (FAB: 3-NBA): *m/z* = 323.1875, calcd. for $C_{18}H_{26}O_5$ [M + H]$^+$: 322.1780.

**(2*R*,4*R*,6*R*,9*R*)-2-[(Benzyloxy)methyl]-9-methoxy-1,7-dioxaspiro[5.5]undecan-4-ol** (Table 2: entry 2): yield: 15.1 mg (0.047 mmol, 37%); $R_f$: 0.53 (cyclohexane/EtOAc = 1/1); purity: 98%; purity: 94%; $[\alpha]_D^{20}$: −10.4° (*c* 1.65, $CHCl_3$); $^1$H NMR (500.1 MHz, $CDCl_3$): $\delta = 7.23–7.36$ (m, 5H, 5 × $C_{ar}H$), 4.57 (s, 2H, $CH_2Ph$), 4.08 (sept, $^3J = 5.4$ Hz, 1H), 3.74–3.82 (m, 1H), 3.63–3.69 (m, 1H), 3.53 (dd, $^3J = 10.3$ Hz, $^3J = 5.3$ Hz, 1H), 3.49 (dd, $^3J = 10.3$ Hz, $^3J = 4.8$ Hz, 1H), 3.22–3.37 (m, 2H), 3.34 (s, 3H, $CH_3$), 1.87–2.01 (m, 3H), 1.69–1.86 (m, 2H), 1.53–1.60 (m, 2H), 1.28 (quint, $^3J = 12.0$ Hz, 2H); GC-MS(EI): $t_R$: 7.61 min; *m/z* (rel. int. [%]) = 322 (1) [$M^+$], 304 (2) [$M^+ - H_2O$], 216 (41), 201 (19), 183 (61), 157 (50), 129 (34), 107 (30), 91 (100) [$Bn^+$]; HR-MS (FAB: 3-NBA): *m/z* = 323.1885, calcd. for $C_{18}H_{26}O_5$ [M + H]$^+$: 322.1780.

## Representative Procedure for the Grignard Reaction of Spiroketals in Solution Phase

(2*R*,6*S*,9*S*)-2-Cyclohexyl-9-methoxy-1,7-dioxaspiro[5.5]undecan-4-one (10.7 mg, 0.038 mmol, 1.00 equiv.) was placed in a small vial and dissolved in 1.5 mL dry THF and cooled to −78 °C. A 1M solution of allylmagnesium bromide in $Et_2O$ (80 μL, 0.076 mmol, 2.00 equiv.) was added slowly at −78 °C and stirred then further 3 h at −60 °C. The reaction was quenched with saturated, aqueous ammonium chloride solution (2 mL). The biphasic mixture was separated, the aqueous layer was extracted with diethyl ether (3 × 10 mL), the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography to give (2*R*,4*S*,6*S*,9*S*)-4-allyl-2-cyclohexyl-9-methoxy-1,7-dioxaspiro[5.5]un-decan-4-ol (Table 2: entry 11): yield: 8.7 mg (0.027 mmol, 71%); $R_f$: 0.42 (cyclohexane/EtOAc = 2/1); purity: 91%; $[\alpha]_D^{20}$: −50.0° (*c* 0.87, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 5.89–5.73$ (m, 1H), 4.98 (m, 2H), 4.22 (s, 1H), 3.71–3.60 (m, 2H), 3.47 (ddd, $^3J = 11.8$ Hz, $^3J = 7.3$ Hz, $^3J = 2.2$ Hz, 1H), 3.30–3.28 (s, 3H, $OCH_3$), 3.20–3.15 (m, 1H), 2.17–2.02 (m, 2H), 2.01–1.96 (m, 1H), 1.95–1.87 (m, 1H), 1.85–1.54 (m, 8H), 1.38–1.09 (m, 7H), 0.95–0.87 (m, 2H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta = 133.8$, 117.6, 97.5, 72.7, 70.0, 69.8, 61.8, 56.1, 47.7, 43.6, 42.6, 39.5, 30.0, 29.1, 26.6, 26.2, 26.1, 21.4; GC-MS(EI): $t_R$: 8.20 min; *m/z* (rel. int. [%]) = 283 (81), 253 (15), 223 (7), 171 (28), 153 (100), 131 (91), 99 (75), 71 (64), 55 (48), 41 (48); HR-MS (EI): *m/z* = 325.2399, calcd. for $C_{19}H_{32}O_4$ [M + H]$^+$: 324.2301.

## Representative Procedure for the Reductive Amination of Spiroketals in Solution Phase

To a solution of (3*S*,6*R*)-3-methyl-1,7-dioxaspiro[5.5]undecan-4-one (19.6 mg, 0.106 mmol, 1.00 equiv.) and benzylamine (19.4 mg, 0.105 mmol, 2.00 equiv.) in 2.0 mL dry MeOH was added 3 Å mol sieves and this suspension was stirred for 24 h. Then 72 mg polymer-supported borohydride (~0.58 mmol, borohydride on Amberlite IRA 400, ~2.5 mmol g$^{-1}$; Aldrich Cat. No. 32,864–2) were added.[27] After 24 h an excess polymer-supported benzaldehyde was added to scavenge the excess amine. This suspension was stirred for further 24 h. The suspension was filtered. The eluent was evaporated to dryness to afford (3*R*,4*R*,6*R*)-*N*-benzyl-3-methyl-1,7-dioxaspiro[5.5]undecan-4-amine (Table 2: entry 12); yield: 17.6 mg (0.064 mmol, 60%); $R_f$: 0.30 (cyclohexane/EtOAc = 1/1); purity: 87%; $[\alpha]_D^{20}$: −1.1° (*c* 1.73, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.38–7.20$ (m, 5H, 5 × $C_{ar}H$), 3.98 (d, $^3J = 13.4$ Hz, 1H), 3.67 (d, $^3J = 13.6$ Hz, 2H), 3.58–3.51 (m, 2H), 3.39–3.33 (m, 1H), 2.60 (dd, $^3J = 6.8$ Hz, $^3J = 3.6$ Hz, 1H), 2.52–2.36 (m, 1H), 2.00 (dd, $^3J = 14.0$ Hz, $^3J = 2.7$ Hz, 1H), 1.86–1.76 (m, 2H), 1.59–1.41 (m, 6H), 0.89 (d, $^3J = 6.9$ Hz, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta = 141.5$, 128.3, 128.0, 126.5, 96.3, 62.0, 60.2, 53.6, 52.3, 37.7, 35.4, 34.2, 25.0, 18.3, 13.6; GC-MS (EI): $t_R$: 7.67 min; *m/z* (rel. int. [%]) = 275 (5), 232 (1), 216 (68), 176 (11), 160 (11), 132 (34), 106 (46), 91 (100), 65 (9), 55 (10).

## Representative Procedure for the Oxime Formation of Spiroketals in Solution Phase

(3*R*,6*R*)-3-Methyl-1,7-dioxaspiro[5.5]undecan-4-one (19.4 mg, 0.105 mmol, 1.00 equiv.) and 22 mg hydroxylamine hydrochloride (0.315 mmol, 3.00 equiv.) were stirred in 1.5 mL dry EtOH. After 3.5 h completion was controlled by TLC (cyclohexane/EtOAc = 2/1). The suspension was filtered and the eluent was evaporated to dryness. The residue was purified by column chromatography to afford (3*S*,6*R*)-3-methyl-1,7-dioxaspiro[5.5]undecan-4-one-*O*-methyl oxime (Table 2: entry 13); yield: 16.6 mg (0.078 mmol, 74%); $R_f = 0.29$ (cyclohexane/EtOAc = 2/1); purity = 89%; $[\alpha]_D^{20}$: 2.1° (*c* = 0.89, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 3.83$ (s, 3H), 3.69 (dd, $^3J = 10.8$ Hz, $^3J = 5.8$ Hz, 1H), 3.60 (d, $^3J = 2.5$ Hz, 1H), 3.59–3.56 (m, 1H), 3.45 (t, $^3J = 11.1$ Hz, 1H), 3.29 (d, $^3J = 14.5$ Hz, 1H), 2.52–2.41 (m, 1H), 1.83–1.76 (m, 2H), 1.74–1.69 (m, 1H), 1.61–1.52 (m, 4H), 1.02 (d, $^3J = 6.6$ Hz, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta = 156.0$, 97.2, 66.1, 61.3, 60.3, 36.0, 35.6, 34.8, 24.5, 18.6, 10.7; GC-MS(EI): $t_R$: 6.35 min; *m/z* (rel. int. [%]) = 213 (2), 183 (3), 169 (21), 152 (20), 113 (100), 98 (18), 83 (33), 68 (56), 55 (41), 41 (53); HR-MS (EI): *m/z* = 214.1454, calcd. for $C_{11}H_{19}NO_3$ [M + H]$^+$: 213.1365.

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## References

[1] For reviews see, e.g.: a) A. Reayi, P. Arya, *Curr. Opin. Chem. Biol.* **2005**, *9*, 240–247; b) Z. Gan, P. T. Reddy, S. Quevillon, S. Couve-Bonnaire, P. Arya, *Angew. Chem.* **2005**, *117*, 1390–1392; *Angew. Chem. Int. Ed.* **2005**, *44*, 1366–1368; c) R. Breinbauer, I. Vetter, H. Waldmann, *Angew. Chem.* **2002**, *114*, 3002–3015, *Angew. Chem. Int. Ed.* **2002**, *41*, 2878–2890; d) M. A. Koch, H. Waldmann, *Drug Discovery Today* **2005**, *10*, 471–483; e) A. Ganesan, *Curr. Opin. Biotechnol.* **2004**, *15*, 584–590.

[2] a) S. Shang, D. S. Tan, *Curr. Opin. Chem. Biol.* **2005**, *9*, 248–258; b) M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48–60; *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58.

[3] A. Nören-Müller, I. Reis Corrêa Jr. , H. Prinz, C. Rosenbaum, K. Saxena, H. Schwalbe, D. Vestweber, G. Cagna, S. Schunk, O. Schwarz, H. Schiewe, H. Waldmann, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 10606–10611.

[4] a) D. Brohm, S. Metzger, A. Bhargava, O. Müller, F. Lieb, H. Waldmann, *Angew. Chem.* **2002**, *114*, 319–323; *Angew. Chem. Int. Ed.* **2002**, *41*, 307–311; b) D. Brohm, N. Philippe, S. Metzger, A. Bhargava, O. Müller, F. Lieb, H. Waldmann, *J. Am. Chem. Soc.* **2002**, *124*, 13171–13178; c) O. Barun, S. Sommer, H. Waldmann, *Angew. Chem.* **2004**, *116*, 3258–3261; *Angew. Chem. Int. Ed.* **2004**, *43*, 3195–3199; d) M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 17272–17277; e) M. A. Koch, L. O. Wittenberg, S. Basu, D. A. Jeyaraj, E. Gourdzoulidou, K. Reinecke, A. Odermatt, H. Waldmann, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 16721–16726; f) S. Sommer, H. Waldmann, *Chem. Commun.* **2005**, 5684–5686; g) O. Barun, K. Kumar, S. Sommer, A. Langerak, T. U. Mayer, O. Müller, H. Waldmann, *Eur. J. Org. Chem.* **2005**, *22*, 4773–4478; h) B. Meseguer, D. Alonso-Diaz, N. Griebenow, T. Herget, H. Waldmann, *Angew. Chem.* **1999**, *111*, 3083–3087; *Angew. Chem. Int. Ed.* **1999**, *38*, 2902–2906; i) B. Meseguer, D. Alonso-Diaz, N. Griebenow, T. Herget, H. Waldmann, *Chem. Eur. J.* **2000**, *6*, 3943–3957; j) M. A. Sanz, T. Voigt, H. Waldmann, *Adv. Synth. Catal.* **2006**, *348*, 1511–1515; k) A. B. García, T. Leßmann, J. D. Umarye, V. Mamane, S. Sommer, H. Waldmann, *Chem. Commun.* **2006**, 3868–3870; l) T. Leßmann, H. Waldmann, *Chem. Commun.* **2006**, 3380–3389; m) V. Mamane, A. B. García, J. Umarye, T. Lessmann, S. Sommer, H. Waldmann, *Tetrahedron* **2007**, *63*, 5754–5767; n) T. Lessmann, M. G. Leuenberger, S. Menninger, M. Lopez-Canet, O. Müller, S. Hümmer, J. Bormann, K. Korn, E. Fava, M. Zerial, T. U. Mayer, H. Waldmann, *Chem. Biol.* **2007**, *14*, 443–451; o) I. Reis Corrêa Jr. , A. Nören-Müller, H.-D. Ambrosi, S. Jakupovic, K. Saxena, H. Schwalbe, M. Kaiser, H. Waldmann, *Chem. As. J.* **2007**, *9*, 1109–1126; p) M. Scheck, M. Koch, H. Waldmann, *Tetrahedron* **2008**, *64*, 4792–4801.

[5] For reviews, see: a) P. M. Abreu, P. S. Branco *J. Brz. Chem. Soc.* **2003**, *14*, 675–712; b) A. M. Boldi, *Curr. Opin. Chem. Biol.* **2004**, *8*, 281–286; c) R. Balamurugan, F. J. Dekker, H. Waldmann, *Mol. BioSyst.* **2005**, *1*, 36–45, and references cited therein.

[6] K. T. Mead, B. N. Brewer, *Curr. Org. Chem.* **2003**, *7*, 227–256; M. F. Jacobs, W. Kitching, *Curr. Org. Chem.* **1998**, *2*, 395–436; W. Francke, W. Kitching, *Curr. Org. Chem.* **2001**, *5*, 233–251.

[7] F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617–1661.

[8] A. F. Kluge, *Heterocycles* **1986**, *24*, 1699–1740.

[9] G. R. Pettit, Z. A. Cichacz, F. Gao, C. L. Herald, M. R. Boyd, J. M. Schmidt, J. N. A. Hooper, *J. Org. Chem.* **1993**, *58*, 1302–1304.

[10] A. B. Dounay, C. J. Forsyth, *Curr. Med. Chem.* **2002**, *9*, 1939–1980.

[11] P. Cohen, *Ann. Rev. Biochem.* **1989**, *58*, 453–508.

[12] S. B. Singh, D. L. Zink, B. Heimbach, O. Genilloud, A. Teran, K. C. Silverman, R. B. Lingham, P. Felock, D. J. Hazuda, *Org. Lett.* **2002**, *4*, 1123–1126.

[13] S. Mitsuhashi, H. Shima, T. Kawamura, K. Kikuchi, M. Oikawa, A. Ichihara, H. Oikawa, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2007–2012; H. Huang, C. Mao, S. T. Jan, F. M. Uckun, *Tetrahedron Lett.* **2000**, *41*, 1699–1702; F. M. Uckun, C. Mao, A. O. Vassilev, H. Huang, S. T. Jan, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 541–545; A. A. Birkbeck, S. V. Ley, J. C. Prodger, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2637–2642; W. Bell, M. H. Block, C. Cook, J. A. Grant, D. Timms, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2789–2801; X. D. Fan, G. R. Flentke, D. H. Rich, *J. Am. Chem. Soc.* **1998**, *120*, 8893–8894.

[14] A. Takai, G. Mieskes, *Biochem. J.* **1991**, *275*, 233–239.

[15] a) B. A. Kulkarni, G. P. Roth, E. Lobkovsky, J. A. Porco, *J. Comb. Chem.* **2002**, *4*, 56–72; b) R. P. Trump, P. A. Bartlett, *J. Comb. Chem.* **2003**, *5*, 285–291.

[16] a) R. Haag, A. G. Leach, S. V. Ley, M. Nettekoven, J. Schnaubelt, *Synth. Commun.* **2001**, *31*, 2965–2977; b) L.-G. Milroy, G. Zinzalla, G. Prencipe, P. Michel, S. V. Ley, M. Gunaratnam, M. Beltran, S. Neidle, *Angew. Chem.* **2007**, *119*, 2545–2548; *Angew. Chem. Int. Ed.* **2007**, *46*, 2493–2496; c) I. Paterson, D. Gottschling, D. Menche, *Chem. Commun.* **2005**, 3568–3570.

[17] J. L. Hao, C. J. Forsyth, *Tetrahedron Lett.* **2002**, *43*, 1–2; for a recent addition to the syntheses methods giving access to spiroketals, see: J. A. Marco, M. Carda, J. Murga.; E. Falomir, *Tetrahedron* **2007**, *63*, 2929–2958.

[18] J. Aiguade, J. L. Hao, C. J. Forsyth, *Org. Lett.* **2001**, *3*, 979–982.

[19] S. Hanessian, F. Xie, *Tetrahedron Lett.* **1998**, *39*, 733–736.

[20] C. Sylvain, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **1997**, *38*, 1043–1044.

[21] S. K. Shannon, G. Barany, *J. Comb. Chem.* **2004**, *6*, 165–170.

[22] M. J. Gaunt, D. F. Hook, H. R. Tanner, S. V. Ley, *Org. Lett.* **2003**, *5*, 4815–4818.

[23] I. R. Baxendale, S. V. Ley, C. Piutti, *Angew. Chem.* **2002**, *114*, 2298–2301; *Angew. Chem. Int. Ed.* **2002**, *41*, 2194–2197.

[24] K. Mori, T. Uematsu, K. Yanagi, M. Minobe, *Tetrahedron* **1985**, *41*, 2751–2758; K. Mori, H. Watanabe, K. Yanagi, M. Minobe, *Tetrahedron* **1985**, *41*, 3663–3672.

[25] a) J. Nokami, K. Nomiyama, S. Matsuda, N. Imai, K. Kataoka, *Angew. Chem.* **2003**, *115*, 1311–1314; *Angew. Chem. Int. Ed.* **2003**, *42*, 1273–1276; b) J. Nokami, M. Ohga, H. Nakamoto, T. Matsubara, I. Hussain, K. Kataoka, *J. Am. Chem. Soc.* **2001**, *123*, 9168–9169.

[26] K. Hashimura, S. Tomita, K. Hiroya, K. Ogasawara, *J. Chem. Soc. Chem. Commun.* **1995**, 2291–2292.

[27] Available from Aldrich.

[28] J. E. Nystrom, T. D. McCanna, P. Helquist, R. Amouroux, *Synthesis* **1988**, 56–58.

[29] D. Tanner, P. Somfai, *Tetrahedron Lett.* **1988**, *29*, 2373–2376.

[30] G. Li, W. C. Still, *Tetrahedron Lett.* **1993**, *34*, 919–922.

[31] S. E. Schaus, D. B. Bridget, J. F. Larrow, T. Makoto, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.

[32] L. C. Dias, L. G. de Oliveira, *Org. Lett.* **2004**, *6*, 2587–2590.

[33] I. Paterson, M. J. Coster, D. Y.-K. Chen, R. M. Oballa, D. J. Wallace, R. D. Norcross, *Org. Biomol. Chem.* **2005**, *3*, 2399–2409.

[34] M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537–4538; M. Frigerio, M. Santagostino, S. Sputore, G. Palmisano, *J. Org. Chem.* **1995**, *60*, 7272–7276.