Asymmetric Synthesis

Asymmetric Solid-Phase Synthesis of 6,6-Spiroketals**

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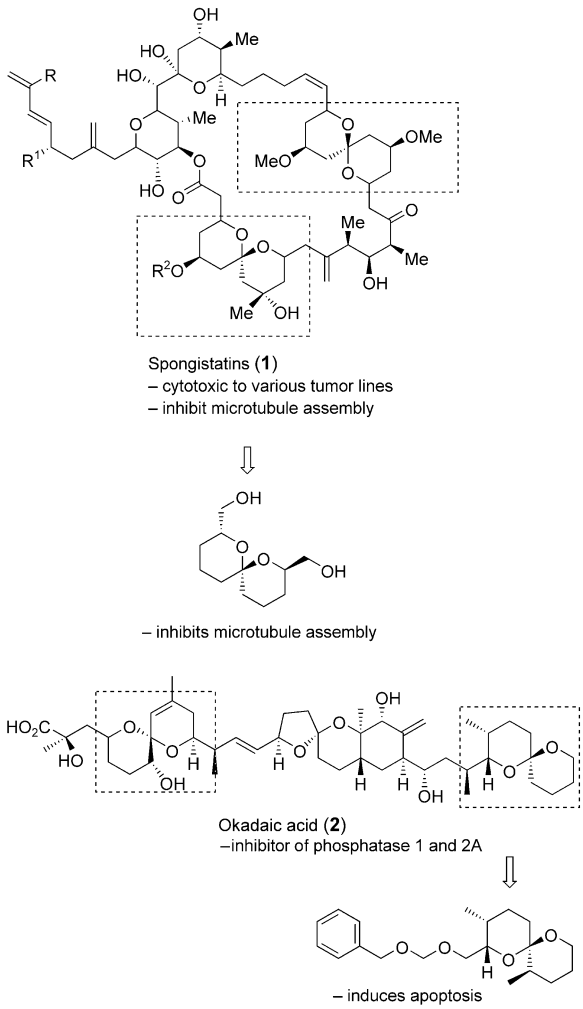
The solid-phase synthesis of compound libraries with a predetermined profile of properties has evolved as a key enabling technique in postgenomic chemical biology and medicinal chemistry. The underlying chemical structures of the compound libraries should have significance in nature. Ideally they should be biologically validated[1] and/or feature so-called privileged structures, that is, 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, which can be regarded as ligands selected by evolution for structurally conserved yet genetically mobile protein domains.[1] As this insight suggests, natural product derived compound libraries are promising starting points for research in chemical biology and lead development in medicinal chemistry.[1,3] The synthesis of such libraries requires the availability of efficient and practical methods for the multistep solid-phase synthesis (typically more than 10 linear steps) of frameworks of biologically promising natural products. The efficiency and selectivity of these methods must be comparable to those of competing solution-phase techniques. To date this goal has been attained in only a few cases.[1,4]

Herein we report a stereoselective solid-phase synthesis of 6,6-spiroketals[5] with stereoselective aldol reactions of boron enolates as key stereodifferentiating transformations. The synthesis proceeds in 12 linear steps and provides access to the desired spiroketals in preparatively viable overall yields and with very high stereoselectivity.

6,6-Spiroketals are the prevalent underlying structural element in a wide range of important natural products with differing biological activity, such as the spongistatins **1** and okadaic acid (**2**; Scheme 1).[6,7] Importantly, structurally simplified spiroketals derived from natural products retain their biological activity[7] (see Scheme 1), so that the underlying 6,6-spiroketal structure is suitable as a starting point for the development of natural product derived compound libraries. The usefulness of spiroketals in combinatorial



Scheme 1. Biologically active natural products with spiroketal substructures and structurally simplified biologically active analogues.

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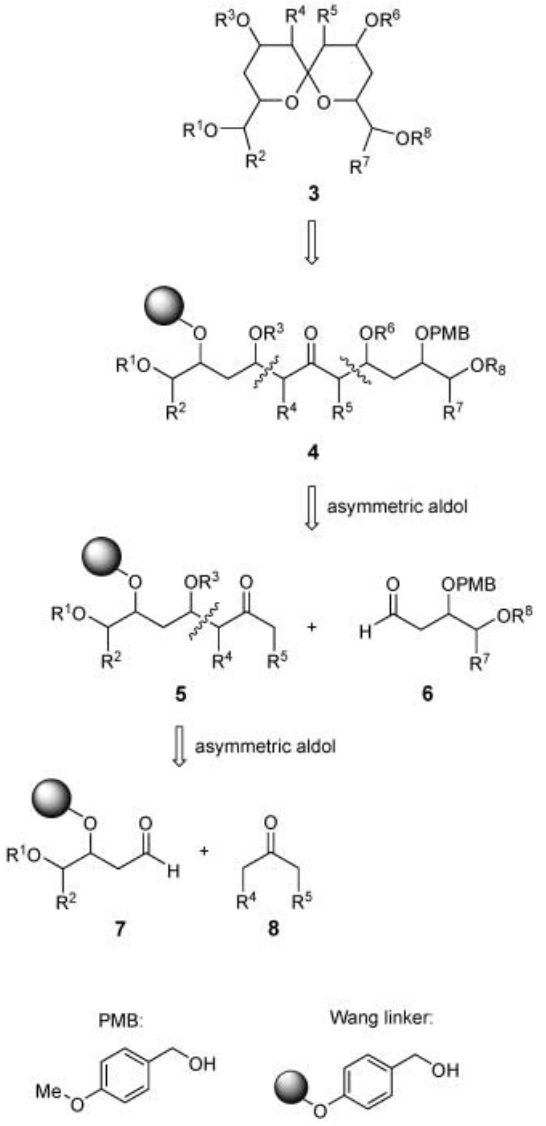
chemistry and a method for their synthesis on solid support have already been reported by Ley and co-workers.[8]

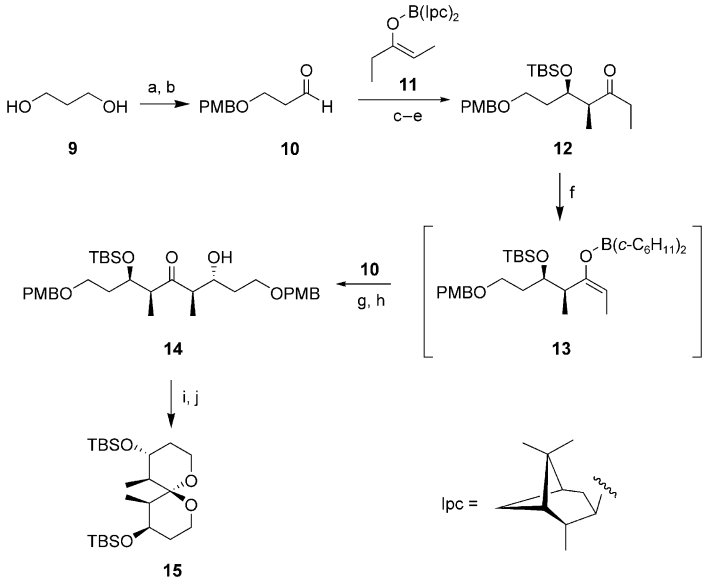
In planning the synthesis we chose compounds of the general structure **3** as targets (Scheme 2), which were traced back in a retrosynthetic sense to aldol adducts **4**, **5**, and **7**. We planned to attach one of the hydroxy groups required for acetal formation to the solid support. The other alcohol group was to be protected by a functional group of the same chemical type as the anchor. Thus, final release from the polymeric carrier would be accompanied by cleavage of the protecting group, and under appropriate conditions by spontaneous ketalization to give the desired spiroketals **3** in a single step. We anticipated that these conditions would be fulfilled by the *p*-methoxybenzyl (PMB) ether protecting group and the corresponding Wang linker (Scheme 2).



Scheme 2. Retrosynthetic analysis of the 6,6-spiroketal structures.

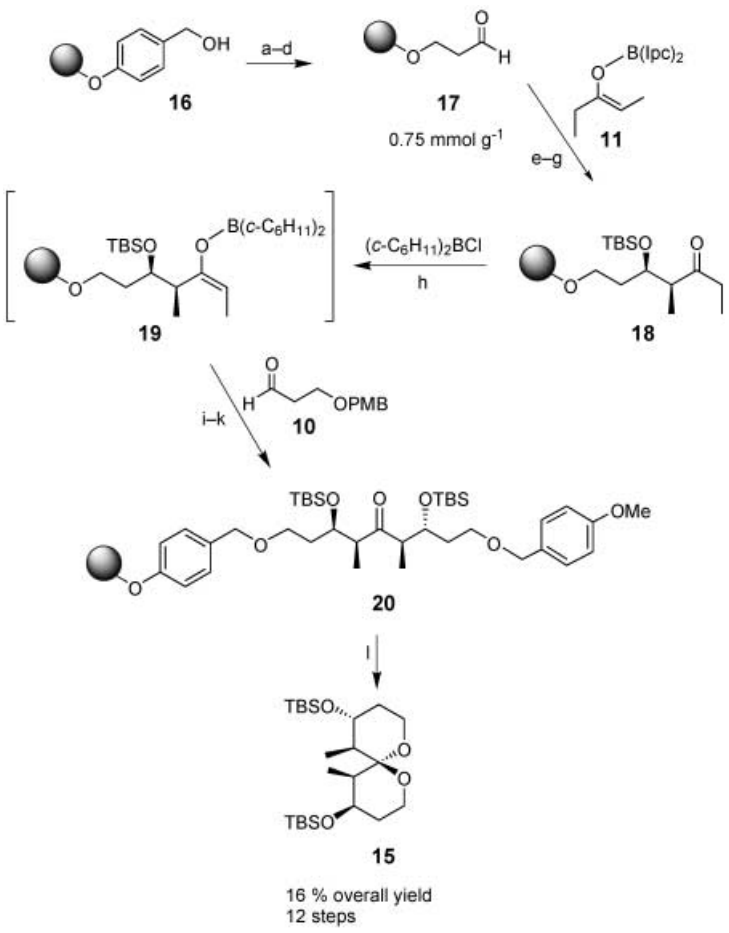
Immobilized aldol intermediates **4** and **7** might be formed by means of asymmetric boron-mediated aldol reactions with both polymer-bound and soluble chiral boron enolates. A few examples of stereoselective aldol reactions with soluble[9] and polymer-bound[10] chiral enolates have been described. However, the use of polymer-bound chiral boron enolates in aldol reactions has not yet been explored.

The feasibility of the strategy was investigated first in solution with the *Z* diisopinocampheyl borinate **11**[11] and the *E* enolate **13**,[12] which led to the formation of the corresponding *syn* and *anti* aldol adducts, respectively (Scheme 3).[13] The absolute configuration of the aldol adduct **14** was assigned based on the assumption that the stereochemical course of the reaction is analogous to that observed in related cases.[14] The simultaneous oxidative cleavage of both PMB protecting groups proceeded smoothly and was followed—as hoped—by the spontaneous formation of the spiroketal **15**, which was obtained as a single isomer. The configuration of compound **15** was ascertained after deprotection by means of NOE experiments and by comparison of spectroscopic data with those of known compounds.



Scheme 3. Solution-phase synthesis of the spiroketal **15**: a) NaH (1.5 equiv), PMBCl (1.1 equiv), DMF, 0 °C→RT, 24 h, 63%; b) $(COCl)_2$ (1.5 equiv), DMSO (2.5 equiv), Et_3N (4 equiv), CH_2Cl_2, −78→0 °C, 2 h, 93%; c) 3-pentanone (1 equiv), (−)-Ipc_2BOTf (1.2 equiv), DIEA (1.5 equiv), CH_2Cl_2, −78→−30 °C, 20 h; d) 30% aqueous H_2O_2/MeOH/buffer (pH 7) (1.5:5:1), 0 °C→RT, 2 h, 69%; e) TBSCl (1.3 equiv), imidazole (2.1 equiv), DMF, room temperature, 24 h, 91%; f) $(c\text{-}C_6H_{11})_2BCl$ (1.3 equiv), Et_3N (1.5 equiv), Et_2O, 0 °C, 4 h; g) **10** (1.4 equiv), Et_2O, −78→−30 °C, 24 h; h) 30% aqueous H_2O_2/MeOH/buffer (pH 7) (1.5:5:1), 0 °C→RT, 2 h, 89%; i) TBSCl (1.3 equiv), imidazole (2.5 equiv), DMF, room temperature, 24 h, 92%; j) DDQ (2.8 equiv), CH_2Cl_2/buffer (pH 7), 0 °C→RT, 3 h, 88%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIEA = *N*,*N*-diisopropylethylamine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

After the development of this reaction sequence in solution we investigated whether it could be transferred to the solid phase (Scheme 4). The Merrifield resin equipped with the Wang linker (**16**; loading 1.2 mmol g^{-1}) was activated



Scheme 4. Solid-phase synthesis of the spiroketal **15**: a) CCl_3CN (8 equiv), DBU (3 mol%), CH_2Cl_2, 0°C, 40 min; b) $TBSO(CH_2)_3OH$ (5 equiv), $BF_3{\cdot}Et_2O$ (3 mol%), cyclohexane, CH_2Cl_2, room temperature, 15 min; c) TBAF (8 equiv), THF, room temperature, 14 h; d) IBX (8 equiv), DMSO, room temperature, 36 h; e) 3-pentanone (6 equiv), (−)-Ipc_2BOTf (6.1 equiv), DIEA (7 equiv), CH_2Cl_2, −78→0°C, 20 h; filter and wash (two cycles); f) 30% aqueous H_2O_2/MeOH/DMF/buffer (pH 7) (1.5:4:4:1), 0°C, 8 h; g) TBSCl (10 equiv), DMAP (1 mol%), imidazole (10 equiv), DMF/CH_2Cl_2 (1:1), room temperature, 24 h (two cycles); h) $(c\text{-}C_6H_{11})_2BCl$ (8 equiv), Et_3N (9 equiv), Et_2O, 0°C, 24 h; filter and wash (two cycles); i) **10** (10 equiv), E_2O, −78→20°C, 26 h (2 cycles); j) 30% aqueous H_2O_2/MeOH/DMF/buffer (pH 7) (1.5:4:4:1), 0°C, 8 h; k) TBSCl (10 equiv), DMAP (1 mol%), imidazole (10 equiv), DMF/CH_2Cl_2 (1:1), room temperature, 24 h (two cycles); l) DDQ (10 equiv), CH_2Cl_2/buffer (pH 7) (20:1), 0°C→RT, 6 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine.

as the corresponding trichloroacetimidate,[15] which was then subjected to nucleophilic displacement by mono-TBS-protected 1,3-propanediol. 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 **17** by 2-iodoxybenzoic acid (IBX). At this stage resin loading was determined to be 0.75 mmol g^{-1}.[16] The polymer-bound aldehyde **17** was then treated at −78°C with the preformed *Z* enolate **11** in dichloromethane, and the reaction mixture was allowed to warm to 0°C. This procedure was repeated once. After oxidative workup to cleave the B–O bond the secondary alcohol was protected as its TBS ether to yield the immobilized aldol product **18** (monitored by FT-IR spectroscopy).

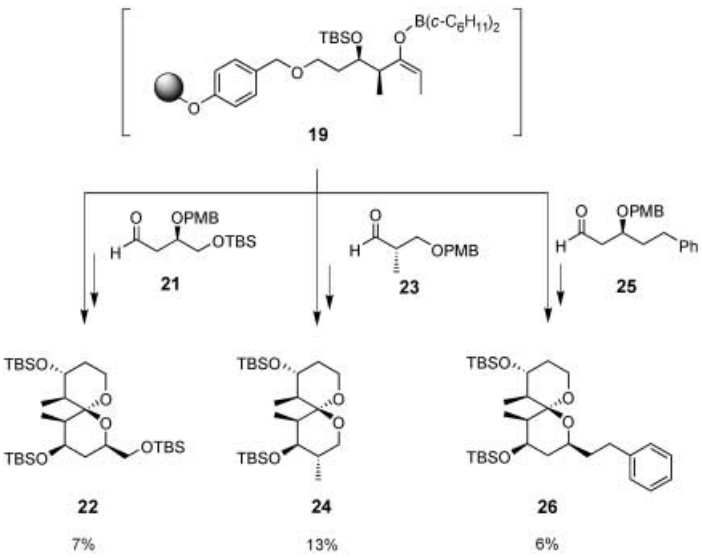
To form the polymer-bound chiral boron enolate required for the crucial second aldol reaction, the ketone resin **18** was swollen in diethyl ether and then a solution of chlorodicyclohexylborane and triethylamine in diethyl ether was added to the resin at 0°C. After 6 h the resin was washed and the addition of the reagents was repeated. As expected by analogy with enolate formation in solution (see above and reference [12]) the *E* dicyclohexylboron enolate **19** was formed on the solid support. The boron enolate resin **19** was then treated at −78°C with the aldehyde **10**, and after oxidative workup as described above the free secondary alcohol (strong absorption at 3504 cm^{-1} and 1714 cm^{-1} in the IR spectrum) was protected as the TBS ether **20**.

The treatment of the intermediate **20** with DDQ in a mixture of CH_2Cl_2 and an aqueous buffer (pH 7) resulted in the simultaneous cleavage of the PMB ether, release from the Wang resin, and spiroketalization. After purification by filtration through a short column of silica gel, the spiroketal **15** was obtained as a single stereoisomer, as determined by HPLC as well as ^1H and ^{13}C NMR spectroscopy.[13] NOE investigations and comparison of spectroscopic data and the specific rotation revealed that the product was identical to the spiroketal **15** synthesized in solution as described above.

The spiroketal **15** was obtained in this 12-step solid-phase synthesis in an overall yield of 16%, which corresponds to an average yield of 86% per step. This compares very favorably with the overall yield of 27% recorded for the 10-step synthesis in solution described above. The fact that the spiroketal obtained from the solid-phase synthesis had the same configuration as that obtained from the solution-phase synthesis is evidence that both aldol reactions on the polymeric support proceed by full analogy with the corresponding asymmetric transformations in solution. Furthermore, the degree of stereodifferentiation is very similar in both cases.

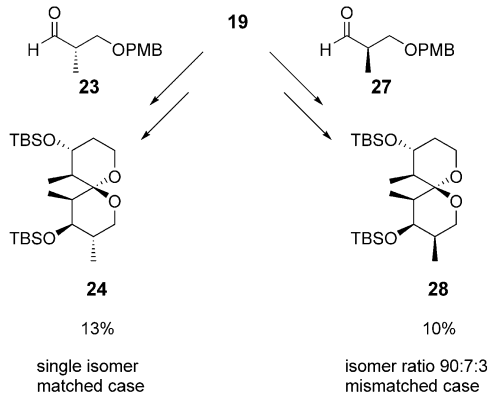
To demonstrate that the reaction sequence shown in Scheme 4 is amenable to the synthesis of compound libraries, three different functionalized spiroketals were synthesized. Thus, the chiral aldehydes **21**, **23**, and **25** were prepared[17] and subjected to aldol reactions with the boron enolate **19** (Scheme 5). After workup and release from the solid support the spiroketals **22**, **24**, and **26** were obtained as single isomers in overall yields of 7, 13, and 6%, respectively.

To gain further insight into the stereoselectivity of the asymmetric boron-mediated aldol reactions on the solid support, we investigated whether the principle of double diastereodifferentiation also operates in this case. To this end, the aldehyde **27** was prepared and treated with **19** under the aldol reaction conditions. The spiroketal **28** was obtained in 10% overall yield as an inseparable mixture with two other



Scheme 5. Solid-phase synthesis of the spiroketals **22**, **24**, and **26**; for reaction conditions, see Scheme 4.

isomers in a ratio of 90:7:3 (Scheme 6; determined by GC–MS). Thus, in both aldol reactions of the chiral enolate **19** with the enantiomeric aldehydes **23** and **27** the *anti* adduct is



Scheme 6. Double diastereodifferentiation in the aldol reaction on the solid support.

formed as the major product. In accordance with related findings[18] the combination of **19** with **23** represents the matched case and the combination of **19** with **27** the mismatched case.

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[13] The *syn* configuration of the aldol adduct **12** was assigned based on the coupling constant of $J = 4.7$ Hz for C*H*(OH)CH(CH_3) and CH(OH)C*H*(CH_3) of the deprotected adduct and comparison with literature values.[11] The diastereomeric ratio was determined by HPLC of the crude product; the *ee* value by GC on a chiral phase and by NMR spectroscopy in the presence of a chiral europium shift reagent. The *anti* configuration of the aldol adduct **14** was assigned based on the coupling constant of $J =$ 9.7 Hz for C*H*(OH)CH(CH_3) and CH(OH)C*H*(CH_3) and comparison with literature values.[12] The diastereomeric ratio was determined by HPLC and ^{1}H NMR spectroscopy of the crude reaction mixture (see Supporting Information). Analysis of the crude product **15** (Scheme 4) by GC–MS showed only one spiroketal stereoisomer. Analytical data for compound **15**: $R_f =$ 0.34 (silica gel, cyclohexane), $[\alpha]_D^{20} = +104.4$ ($c = 0.80$, $CHCl_3$), IR (KBr): $\tilde{\nu}_{max} = 3015$, 2859, 1255 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.27$ (dt, $J_1 = 11.5$, $J_2 = 4.9$ Hz, 1H), 3.70–3.59 (m, 4H), 3.53–3.50 (m, 1H), 2.17–2.10 (m, 1H), 1.82–1.45 (m, 4H), 1.39–1.34 (m, 1H), 1.15 (d, $J = 6.6$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.51 (s, 3H), 0.04 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 102.7$, 72.7, 66.9, 59.3, 58.0,

44.4, 43.4, 35.5, 29.6, 26.1, 26.1, 18.4, 18.3, 14.0, 9.6, −3.9, −4.2, −4.4, −4.4 ppm; GC–MS (*m*/*z*, %): 444 (M^+, 8), 387 ([$M-57$]$^+$, 15); HRMS (EI, 70 eV) calcd for $C_{23}H_{48}O_4Si_2$: 444.3091, found: 404.3099.

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