Solid phase synthesis of a spiro[5.5]ketal library†

Stefan Sommer[ab] and Herbert Waldmann[ab]

Received (in Cambridge, UK) 4th August 2005, Accepted 16th September 2005
First published as an Advance Article on the web 19th October 2005
DOI: 10.1039/b511177c

A spiro[5.5]ketal library embodying the core structure of numerous biologically active natural products was synthesized employing a double intramolecular hetero Michael reaction as a key transformation.

Biologically active natural products can be regarded as evolutionarily selected and biologically pre-validated privileged ligands for the ligand-sensing cores of the limited set of structurally conserved yet genetically mobile domains found in proteins.[1] Therefore, the synthesis of compound collections derived from such natural product classes should yield promising starting points for research in chemical biology and medicinal chemistry.[1,2]

The spiro[5.5]ketal is the underlying structural motif of numerous natural products ranging from steroidal saponins *via* polyether ionophores and macrolide antibiotics to insect pheromones and marine toxins.[3] The observation that structurally simplified spiroacetals derived from natural products may retain biological activity[4] validates the spiro[5.5]ketal as a suitable starting point for the development of natural product derived compound libraries.

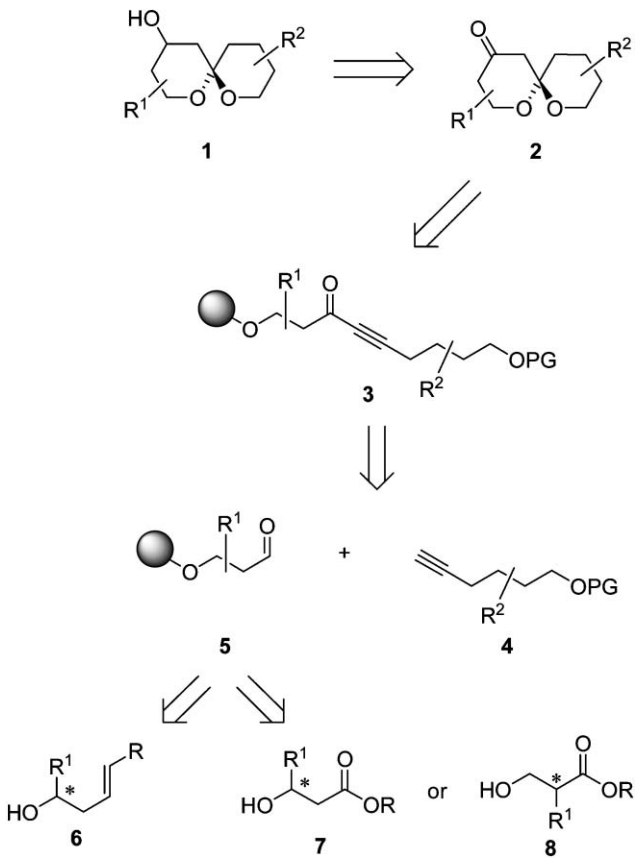
Here we report that spiro[5.5]ketal libraries can be synthesized efficiently on solid supports employing a double internal hetero Michael addition[5] as the key step. Solid phase syntheses of spiro[5.5]ketals on solid supports were reported in three cases[6–8] but the strategies followed therein were not translated into the construction of compound libraries. In particular, the application of the boron aldol reaction-based solid phase synthesis of spiro[5.5]ketals reported recently by us[7] to the synthesis of a larger compound collection proved to be experimentally challenging. Thus, we sought for an alternative that distinguishes itself by a high degree of practicality, robustness and amenability to compound library synthesis.

As target compound class 4-hydroxy-1,7-dioxaspiro[5.5]undecanes **1** were chosen, the characteristic structural spiroacetal unit occurring in natural products as complex as the antifungal mitochondrial F_0F_1-ATPase inhibitors oligomycin and rutamycin and the anthelmintic, acaricidal and insecticidal Avermectins but also the structurally simpler potassium flux inhibitor Talaromycin B.[3]

In a retrosynthetic sense secondary alcohols **1** were traced back to bis-β-oxo-substituted ketones **2** which could be formed by double intramolecular conjugate addition of two alcohols to a corresponding acetylenic ketone (Scheme 1). This strategy was successfully employed by Forsyth *et al.* before,[5] and in order to render it amenable to solid phase compound library synthesis we envisaged immobilized alkynones **3** as decisive intermediates. These compounds could be obtained by addition of alkynes **4** to polymer-bound aldehydes **5** which in turn were traced back to olefin- or β-hydroxy ester building blocks **6–8**.

In order to develop an efficient synthesis sequence and since acetal formation *via* conjugate addition requires acidic conditions, an acid-labile linker to the solid phase and acid sensitive protecting groups for the acetylenic building blocks were chosen (see below). Thereby, release from the solid support, removal of the blocking groups and spiroketal formation could occur in one step.

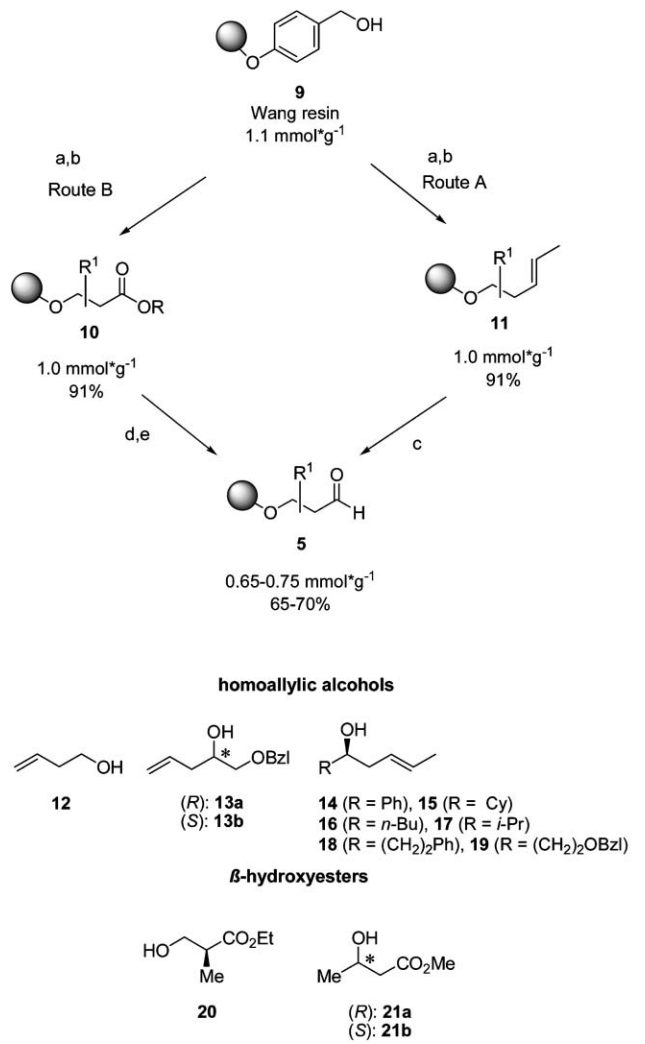
The synthesis was executed as shown in Schemes 2 and 3. Wang polymer **9** (loading 1.1 mmol g^{-1}) was converted into the corresponding trichloroacetimidate[9] which was subjected to nucleophilic substitution by different chiral homoallyl alcohols



Scheme 1 Retrosynthetic analysis of the [5.5]spiroketal structures **1** and **2**.

[a]*Max-Planck Institute of Molecular Physiology, Otto-Hahn-Str. 11, Dortmund, 44227, Germany. E-mail: herbert.waldmann@mpi-dortmund.mpg.de*
[b]*Department of Chemical Biology, University of Dortmund, Otto-Hahn-Str. 6, Dortmund, 44227, Germany. E-mail: herbert.waldmann@mpi-dortmund.mpg.de*

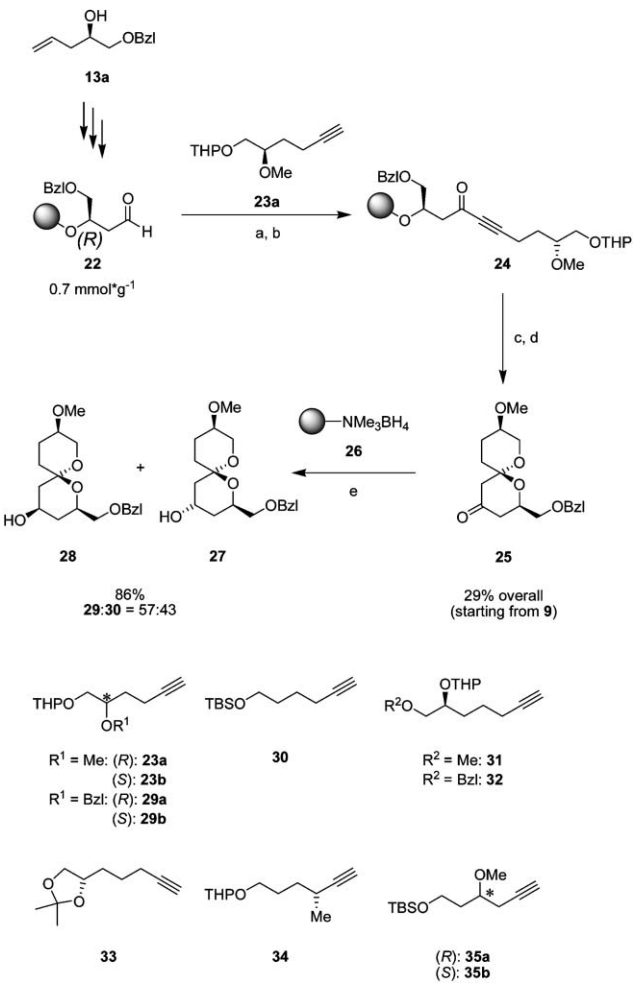
† Electronic supplementary information (ESI) available: General procedures and NMR data. See DOI: 10.1039/b511177c



Scheme 2 Solid phase synthesis of polymer-bound β-hydroxyaldehydes **5** and structures of homoallylic alcohols and β-hydroxyesters applied in the solid-phase synthesis. (a) Cl_3CCN (19 equiv.), DBU (0.88 equiv.), CH_2Cl_2, 0 °C, 40 min; (b) alcohol (2.50 equiv.), BF_3*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 equiv.), −78 °C to rt, 16 h, 70%; (d) DIBAH (5 equiv.), THF/toluene, rt, 5 h, 90%; (e) IBX (5 equiv.), DMSO/THF = 1/1, rt, 16 h, 83%.

12–**19** and hydroxy esters **20** and **21** to yield immobilized intermediates **10** and **11**. Alkenes **11** were converted into aldehydes **5** by ozonolysis[10] and reductive work-up with triphenylphosphine. Cleavage of the Wang linker under these conditions was prevented by restricting the time for ozonolysis to 7 min. β-Hydroxy esters **10** were converted into aldehydes **5** by means of reduction with DIBAH and subsequent oxidation with IBX. Aldehyde functionalized polymers **5** were obtained by either method with loadings of 0.65–0.75 mmol g^{-1}, *i.e.* in overall yields of 65–70%.[11]

Scheme 3 shows for one representative example how the second part of the synthesis sequence was carried out. Polymer-bound aldehyde **22** was generated from chiral homoallyl alcohol **13a** according to the procedure detailed above. Treatment with seven equivalents of alkyne **23a** led to complete conversion of the carbonyl compound to the secondary alcohol which was oxidized with IBX to yield polymer-bound alkynone **24**. The progress of



Scheme 3 Solid-phase synthesis of spiroketals **25**, **27** and **28** and structures of alkynes applied in the solid-phase synthesis. (a) **23a** (7.00 equiv.), 1 M EtMgBr in THF (0.99 equiv.), THF, rt, 16 h; (b) IBX (5.00 equiv.), DMSO/THF = 1/1, rt, 16 h; (c) 2% $MeSO_3H$ in CH_2Cl_2, rt, 30 min; (d) (i) MeOH, 40 °C to rt, 30 min; (ii) toluene, rt, 2 h, 21% over 4 steps; (e) borohydride on Amberlite IRA 400 (~2.5 mmol g^{-1}, 3 × 1.0 equiv.), MeOH, rt, 4.5 h, 86%.

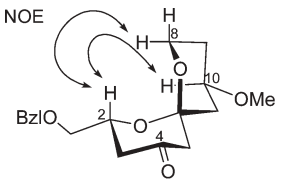
these transformations was conveniently followed by means of FT-IR, monitoring the disappearance of the C=O stretching band, and the appearance of bands at $\tilde{\nu}$ = 2230 cm^{-1} and 2209 cm^{-1} characteristic for the C≡C triple bonds of the intermediate secondary alcohol and alkynone **24** respectively. Release of the alkynone from the solid support was achieved by treatment with methanesulfonic acid in dichloromethane.

Upon successive exchange of the solvent to toluene and methanol the acid-labile THP protecting group was cleaved and the double intramolecular conjugate addition to the alkynone was initiated. Spiroketal **25** was obtained in 29% yield over seven steps as a single stereoisomer which was further purified by simple column chromatography to a purity of 98% (determined by GC-MS). Ketone **25** was efficiently reduced to epimeric alcohols **27** and **28** by means of polymer-bound borohydride reagent **26**[12] in 86% yield. The alcohols were separated by HPLC.

According to this method the polymer-bound aldehydes shown in Scheme 2 were combined with alkynes **23** and **29**–**35**[13] shown in Scheme 3 to yield 91 spiroacetals analogous to **25** in overall yields

of 5–45%. All compounds were obtained as crude products with at least 80% purity (determined by GC-MS od HPLC-MS) and further purified by means of column chromatography. For 12 representative examples the results of the syntheses are shown in the ESI (Table 1).†

The majority of the spiroacetal ketones (61) were obtained as single isomers, while the remaining 31 compounds were formed with isomer ratios of 97 : 3 to 50 : 50 (see ESI, Table 1† determined by GC-MS). Analysis of the compounds obtained as single isomers by means of 2D-NMR- and NOE-techniques revealed that they all have both C–O bonds in axial orientation, leading to double stabilization by the anomeric effect. For instance, in **36** clear NOE signal enhancements prove the spatial proximity of H-2 and H-8 and of H-2 and the axial proton at C-10.



36

Analysis of the ketones obtained as isomer mixtures by ^{13}C NMR revealed a high field shift of the spiro C-atom belonging to the major conformer relative to the signal recorded for the corresponding C-atom of the minor conformer. This indicates that in these cases the major isomer most likely also has both C–O bonds in axial orientation whereas the minor isomer probably has one C–O bond equatorially oriented, *i.e.* only one anomeric effect operates.[14]

To enlarge the spiroacetal collection 33 of the ketones were subjected to reduction with polymer-bound borohydride reagent **26** as described above and the resulting epimeric alcohols were separated by HPLC whenever possible. This yielded another 55 isomerically pure spiroacetals which were obtained with 93–98% purity and in 60–98% yield (see the ESI, Table 2† for representative examples). The configuration of the newly formed stereogenic centre was ascertained by means of NOE techniques (see above).

Taken together the solid-phase methodology described above yielded 146 spiro[5.5]ketals in a 7-step sequence with high overall yields and with high purity. This sequence is highly practical and makes the desired compounds rapidly available in multimilligram amounts sufficient for numerous subsequent analyses. It provides a viable and, in general, experimentally more practical method for the synthesis of spiro[5.5]ketal collections than for instance the solid phase method relying on enantioselective boron–aldol reactions reported by us recently.[7]

We thank Priv. Doz. Dr. B. Costisella for support in NOE experiments. This research was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. S.S. was supported by a Kekulé-Fellowship of the Fonds der Chemischen Industrie.

Notes and references

1 (*a*) M. A. Koch, L.-O. Wittenberg, S. Basu, D. A. Jeyaraj, K. Gourzoulidou, K. Reinecke, A. Odermatt and H. Waldmann, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 16721; (*b*) R. Breinbauer, I. R. Vetter and H. Waldmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 2879; (*c*) M. A. Koch and H. Waldmann, *Drug Discovery Today*, 2005, **10**, 471.

2 Recent Reviews: (*a*) J. Y. Ortholand and A. Ganesan, *Curr. Opin. Chem. Biol.*, 2004, **8**, 271; (*b*) A. M. Boldi, *Curr. Opin. Chem. Biol.*, 2004, **8**, 281; (*c*) R. Balamurugan, F. J. Dekker and H. Waldmann, *Mol. BioSyst.*, 2005, **1**, 36.

3 Reviews: (*a*) K. T. Mead and B. N. Brewer, *Curr. Org. Chem.*, 2003, **7**, 227; (*b*) M. F. Jacobs and W. Kitching, *Curr. Org. Chem.*, 1998, **2**, 395; (*c*) W. Francke and W. Kitching, *Curr. Org. Chem.*, 2001, **5**, 233; (*d*) A. F. Kluge, *Heterocycles*, 1986, **24**, 1699.

4 (*a*) F. M. Uckun, C. Mao, A. O. Vassilev, H. Huang and S. T. Jan, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 541; (*b*) S. Mitsuhashi, H. Shima, T. Kawamura, K. Kikuchi, M. Oikawa, A. Ichihara and H. Oikawa, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2007.

5 J. L. Hao and C. J. Forsyth, *Tetrahedron Lett.*, 2002, **43**, 1.

6 R. Haag, A. G. Leach, S. V. Ley, M. Nettekoven and J. Schnaubelt, *Synth. Commun.*, 2001, **31**, 2965.

7 (*a*) O. Barun, S. Sommer and H. Waldmann, *Angew. Chem., Int. Ed.*, 2004, **43**, 3195; (*b*) O. Barun, K. Kumar, S. Sommer, A. Langerak, T. U. Mayer, O. Müller and H. Waldmann, *Eur. J. Org. Chem.*, 2005, DOI: 10.1002/ejoc.200500605.

8 I. Paterson, D. Gottschling and D. Menche, *Chem. Commun.*, 2005, 3568.

9 S. Hanessian and F. Xie, *Tetrahedron Lett.*, 1998, **39**, 733.

10 C. Sylvain, A. Wagner and C. Mioskowski, *Tetrahedron Lett.*, 1997, **38**, 1043.

11 Routes **A** and **B** can be monitored by means of FT-IR spectroscopy monitoring the C=O stretching bands at $\tilde{\nu}$ = 1740 cm^{-1} (ester) or 1721 cm^{-1} (aldehyde). The loading of polymers **5** was determined by means of dinitrophenylhydrazone formation: D. Brohm, N. Philippe, S. Metzger, A. Bhargava, O. Muller, F. Lieb and H. Waldmann, *J. Am. Chem. Soc.*, 2002, **124**, 13171; S. K. Shannon and G. Barany, *J. Org. Chem.*, 2004, **69**, 4586; S. K. Shannon and G. Barany, *J. Comb. Chem.*, 2004, **6**, 165.

12 (*a*) I. R. Baxendale, S. V. Ley and C. Piutti, *Angew. Chem., Int. Ed.*, 2002, **41**, 2194; (*b*) R. Haag, A. Hebel and J.-F. Stumbe, in *Handbook of Combinatorial Chemistry, Vol. 1*, ed. K. C. Nicolaou, R. Hanko and W. Hartwig, Wiley-VCH, Weinheim, 2002, pp. 24–54.

13 Alkynes **23** and **29**–**35** were synthesized partly applying established methods: (*a*) J. E. Nystrom, T. D. McCanna, P. Helquist and R. Amouroux, *Synthesis*, 1988, 56; (*b*) D. Tanner and P. Somfai, *Tetrahedron Lett.*, 1988, **29**, 2373; (*c*) G. Li and W. C. Still, *Tetrahedron Lett.*, 1993, **34**, 919. The homoallyl alcohols and the β-hydroxy esters employed were either commercially available or prepared in multigram amounts and in enantiomerically pure form from readily available precursors following published procedures—see ref. 6.

14 L. C. Dias and L. G. de Oliveira, *Org. Lett.*, 2004, **6**, 2587.

