Traceless solid phase synthesis of natural product inspired *cis*-1,2-dehydrodecalins†

Masahito Yoshida,[a] Christian Hedberg,[a] Markus Kaiser[c] and Herbert Waldmann*[ab]

Received (in Cambridge, UK) 16th January 2009, Accepted 16th March 2009
First published as an Advance Article on the web 1st April 2009
DOI: 10.1039/b901041f

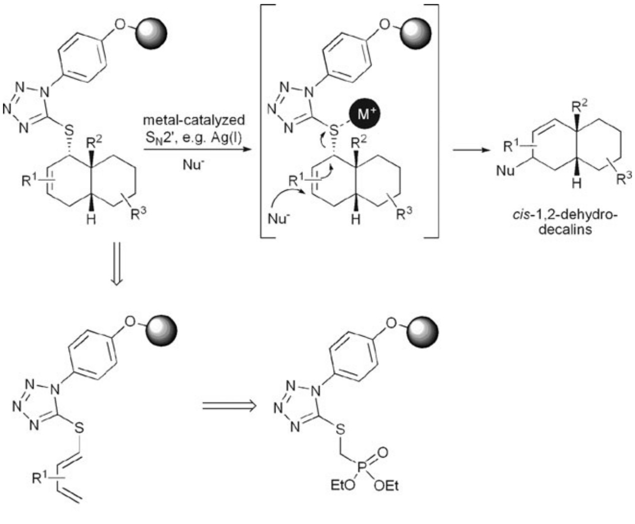
A tetrazole-based traceless linker for Diels–Alder reactions on solid support which can be cleaved by Pd(0)-, Cu(I)- and Ag(I)-assisted nucleophilic displacements has been developed and applied to the solid-phase/traceless release synthesis of natural product inspired *cis*-decalins.

Biologically relevant compound classes, for instance derived from or inspired by natural products (NPs), have proven to be powerful tools for chemical biology and medicinal chemistry research.[1] For the synthesis of compound libraries based on biological relevance, 'Biology oriented synthesis' (BIOS) provides guidance.[2] In BIOS relevance to nature is employed as the key criterion for the selection of the underlying scaffold of focussed libraries. Thus, for instance, compound collections based on the decalin-scaffold occurring in numerous natural products have yielded potent modulators of biochemical and biological activity.[3] For the synthesis of such libraries, highly efficient methods are in high demand.[3–6] In particular, for solid phase synthesis, traceless linkers that allow the release of the desired molecules from the solid support without any unwanted linker-derived functional groups remaining in the products are advantageous.[7a–f] In addition, the introduction of structural diversity in the release step is a desirable feature in compound library development allowing for the coverage of larger areas of chemical space in a given synthesis.

Here we describe the development of a new traceless linker system and its application in the diversity-generating release of dehydrodecalins synthesized by means of Diels–Alder cycloadditions on the solid phase.[7f–k]

We designed a traceless linker featuring a 5-thiotetrazole moiety as illustrated in Fig. 1. 5-Thiotetrazoles and derivatives have been recognized as versatile leaving groups, *e.g.* in the Julia–Kocienski olefination (after oxidation to sulfone) or during allylic substitutions.[8,9] We envisioned that a placement of this leaving group in an allylic position could enable a traceless cleavage by metal-catalyzed reactions. Linkage to the solid support was envisioned through a 1-(*p*-hydroxyphenyl)-5-thiotetrazole moiety. Its introduction to the required allylic position could be achieved through a Horner–Wadsworth–Emmons reaction with polymer-supported diethylphosphonate **1** and a subsequent Diels–Alder reaction. With carbocyclic dienophiles, this reaction sequence would lead to *cis*-1,2-dehydrodecalin systems which are for example found in the *cis*-clerodane diterpenoids solidagoic acid,[10] linaridial[11] and linarienone.[12] Importantly, a diverse substitution of the *cis*-1,2-dehydrodecalin scaffold can be achieved during each step of the reaction sequence, employing diverse aldehydes in the Horner–Wadsworth–Emmons (HWE) olefination, differently substituted dienophiles in the Diels–Alder reaction and various nucleophiles during release from the solid support.

For the synthesis of **1**, benzoate **2** was alkylated with the commercially available bromide **3** to obtain the ether **4** (Scheme 1). After deprotection and tosylation, **6** was coupled with the known 1-(*p*-hydroxphenyl)-5-thiotetrazole phosphonate[13] **9** to yield the desired HWE phosphonate **7**. Final deprotection of the allyl group with $Pd(PPh_3)_4$ and *N*-methyl morpholine afforded the linker **8** in 79% yield over 5 steps. The linker **8** was immobilized on polymeric support by amidation with HATU–DIEA, yielding resin-bound diethylphosphonate **1** with a loading efficiency of *ca.* 0.5 mmol g^{-1} based on gravimetric analysis after cleavage with 20% TFA–CH_2Cl_2. In order to investigate the feasibility of the traceless linker, cycloadduct **12** was synthesized on solid support. Horner–Wadsworth–Emmons olefination with methacrolein proceeded best (90% conversion into **10**) with



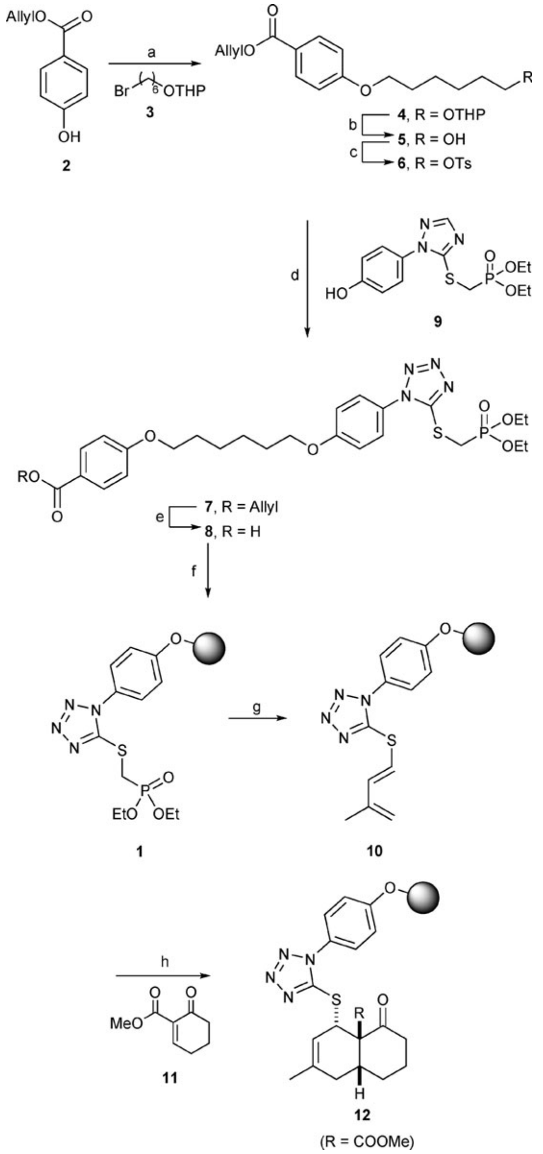
1

Fig. 1 Retrosynthetic analysis of a solid-phase synthesis of *cis*-decalins, using a 5-thiotetrazole based traceless linker.

---

[a] *Max-Planck-Institut für Molekulare Physiologie, Abteilung Chemische Biologie, Otto-Hahn-Str. 11, 44227 Dortmund, Germany. E-mail: herbert.waldmann@mpi-dortmund.mpg.de; Fax: +49 231-133-2499; Tel: +49 231-133-2400*
[b] *Technische Universität Dortmund, Fakultät Chemie, Chemische Biologie, Otto-Hahn-Str. 6, 44227 Dortmund, Germany*
[c] *Chemical Genomics Centre der Max-Planck-Gesellschaft, Otto-Hahn-Str. 15, 44227 Dortmund, Germany*

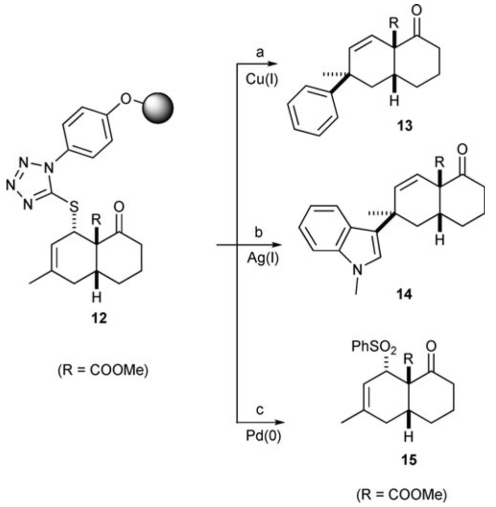
† Electronic supplementary information (ESI) available: Procedures for traceless linker and solid-phase synthesis and analytical data for compounds. See DOI: 10.1039/b901041f



Scheme 1 Synthesis of *cis*-decalins on solid support. (a) **3** (1.1 eq.), K_2CO_3 (1 eq.), DMF, 80 °C, 20 h, 97%; (b) 20% TFA–CH_2Cl_2, rt, 16 h, 93%; (c) TsCl (1.3 eq.), NEt_3 (2 eq.), DMAP (0.3 eq.), CH_2Cl_2, 0 °C, 4 h, 98%; (d) **9** (0.9 eq.), K_2CO_3 (1 eq.), KI (0.3 eq.), DMF, 80 °C, 6 h, 93% (based on **9**); (e) $Pd(PPh_3)_4$ (0.2 eq.), *N*-methyl morpholine (3 eq.), THF, rt, 1.5 h, 96%; (f) Rink amide or aminomethylated resin, **8** (0.1 M), HATU (0.1 M), DIEA (0.15 M), DMF, rt, 12 h; (g) methacrolein (0.3 M), LiHMDS (0.5 M), THF, rt, 16 h; (h) 2-methoxycarbonyl cyclohexenone **11** (0.1 M), $Sc(OTf)_3$ (0.02 M), CH_2Cl_2, 0 °C, 5 h.

LiHMDS as a base.[14] The subsequent Diels–Alder reaction with 2-methoxycarbonyl cyclohexenone **11**[15] as the dienophile in the presence of $Sc(OTf)_3$ afforded the desired polymer-supported *cis*-1,2-dehydrodecalin derivative **12** with full conversion estimated by NMR spectroscopy after TFA release from resin.

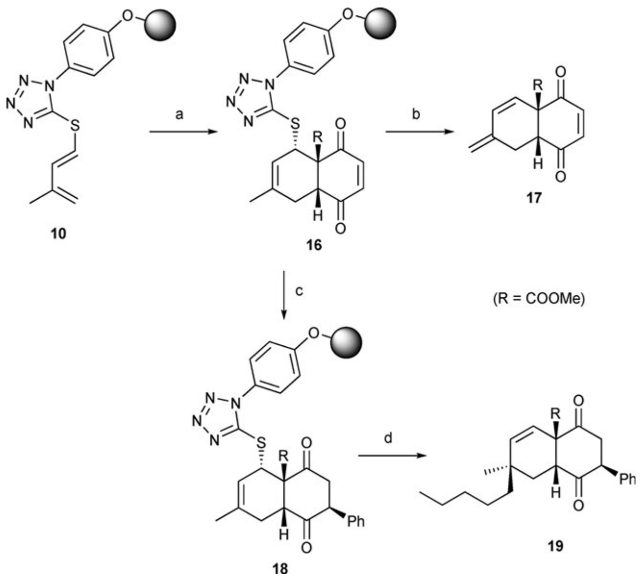
Next, we tested several metals for catalyzing the nucleophilic release of the *cis*-1,2-dehydrodecalin derivative **12** from the resin. Release of the 5-thiotetrazole moiety as originally anticipated could be achieved with Ag(I) and Cu(I) salts by direct S_N2' displacement by *exo*-attack from the least hindered side (Scheme 2).[9a] Interestingly, the use of Pd(0) led to replacement with stereochemical net retention (double inversion) of the 5-thiotetrazole moiety if phenylsulfinates were employed,[9b,c,16] resulting in the synthesis of *cis*-2,3-dehydrodecalins. This metal-dependent type of resin release significantly extends the scope of the linker system since it allows a diversity-generating cleavage of the polymer-supported decalin derivatives. All release reactions could be carried out under mild reaction conditions and gave the desired release products **13–15** in good to moderate overall yields of 23–38% for three steps, *i.e.* 61–67% average yield per step.



Scheme 2 Diversity generating cleavage of the 5-thiotetrazole linker by metal catalysis. (a) PhMgBr (0.1 M), CuBr (0.06 M), THF, 50 °C, 5 h, 29%; (b) 1-Me indole (0.1 M), AgOTf (0.1 M), CH_2Cl_2, rt, 3 h, 23%; (c) $PhSO_2Na$ (0.1 M), $Pd(PPh_3)_4$, THF–MeOH (2 : 1), 70 °C, 8 h, 38%; (yields were calculated after gravimetric analysis and are based on the initial loading of **1**).

In order to further extend the scope of the reaction sequence, we attempted to carry out the Diels–Alder reaction in an enantioselective fashion and several chiral ligand–metal Lewis acid combinations and 2-methoxycarbonylquinone[15] as a dienophile were employed (Scheme 3). The highest enantioselectivity (75% ee) and purity (>90%) for **16** was obtained if $Gd(OTf)_3$ and (*R*,*R*)-*i*PrPybox as a chiral ligand were used.[17] Due to the presence of the α,β-unsaturated carbonyl system, the subsequent release of the 5-thiotetrazole system represented a formidable challenge. The use of Ag(I) salts in the absence of a nucleophile yielded olefin **17**.[18] Alternatively, a cleavage with PhMgBr–CuBr in a two step process which consisted of a controlled Michael addition to the α,β-unsaturated Michael system to yield **18** followed by a traceless release with $C_5H_{11}MgBr$–CuBr in THF at 50 °C yielded the multi-substituted 1,2-dehydrodecalin derivative **19** in a 9% overall yield for five steps (*i.e.* 63% average yield per step) and 75% ee.

In summary, we have developed a traceless linker based on a 5-thiotetrazole moiety placed in an allylic position that can be easily cleaved with metal-assisted nucleophilic reactions employing Pd(0), Cu(I) and Ag(I) salts. The methodology proved suitable to perform even an enantioselective construction of the decalin scaffold on polymeric support.



Scheme 3 Enantioselective Diels–Alder reaction and traceless cleavage from solid support. (a) 2-methoxycarbonylquinone, Gd(OTf)$_3$, (*R*,*R*)-*i*PrPybox, CH_2Cl_2, −78 °C, 3.5 h; (b) Ag(OTf), CH_2Cl_2, rt, 5 h, 15%; (c) PhMgBr (0.15 M), CuBr (0.09 M), THF, rt, 5 h; (d) $C_5H_{11}MgBr$ (0.1 M), CuBr (0.06 M), THF, 50 °C, 3 h, 9% (75% ee); (yields were calculated after gravimetric analysis and are based on the initial loading of **1**).

This work was supported by the Alexander-von-Humboldt Stiftung (postdoctoral fellowship to M.Y.).

Notes and references

1 (*a*) D. R. Spring, *Chem. Soc. Rev.*, 2005, **34**, 472–482; (*b*) K. Hinterding, D. Alonso-Diaz and H. Waldmann, *Angew. Chem., Int. Ed.*, 1998, **37**, 688–749.

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

3 (*a*) P. Stahl, L. Kissau, R. Mazitschek, A. Giannis and H. Waldmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 1174–1178; (*b*) M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl and H. Waldmann, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 17272–17277; (*c*) L. Kissau, P. Stahl, R. Mazitschek, A. Giannis and H. Waldmann, *J. Med. Chem.*, 2003, **46**, 2917–2931; (*d*) P. Stahl, L. Kissau, R. Mazitschek, A. Huwe, P. Furet, A. Giannis and H. Waldmann, *J. Am. Chem. Soc.*, 2001, **123**, 11586–11593.

4 (*a*) A. Ganesan, *Curr. Opin. Chem. Biol.*, 2008, **12**, 306–317; (*b*) R. Breinbauer, I. R. Vetter and H. Waldmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 2879–2890.

5 For examples of natural product-based compound collections from our laboratories, see: (*a*) A. Nören-Müller, W. Wilk, K. Saxena, H. Schwalbe, M. Kaiser and H. Waldmann, *Angew. Chem., Int. Ed.*, 2008, **47**, 5973–5977; (*b*) A. B. Garcia, T. Lessmann, J. D. Umarye, V. Mamane, S. Sommer and H. Waldmann, *Chem. Commun.*, 2006, 3868–3870; (*c*) M. A. Koch, L.-O. Wittenberg, S. Basu, D. A. Jeyaraj, E. Gourzoulidou, K. Reinecke, A. Odermatt and H. Waldmann, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 16721–16726; (*d*) O. Barun, S. Sommer and H. Waldmann, *Angew. Chem., Int. Ed.*, 2004, **43**, 3195–3199; (*e*) B. Meseguer, D. Alonso-Díaz, N. Griebenow, T. Herget and H. Waldmann, *Angew. Chem., Int. Ed.*, 1999, **38**, 2902–2906; (*f*) B. Sauerbrei, V. Jungmann and H. Waldmann, *Angew. Chem., Int. Ed.*, 1998, **37**, 1143–1146; (*g*) H. Waldmann, V. Khedkar, H. Dückert, M. Schürmann, I. M. Oppel and K. Kumar, *Angew. Chem., Int. Ed.*, 2008, **47**, 6869–6872; (*h*) review: K. Kumar and H. Waldmann, *Angew. Chem., Int. Ed.*, 2009, **48,** DOI: 10.1002/anie.200803437.

6 (*a*) T. Leßmann and H. Waldmann, *Chem. Commun.*, 2006, 3380–3389; (*b*) I. Paterson and T. Temal-Laieb, *Org. Lett.*, 2002, **4**, 2473–2476.

7 For examples of traceless release from solid phase see: (*a*) C. Gil and S. Bräse, *Curr. Opin. Chem. Biol.*, 2004, **8**, 230–237; (*b*) F. Stieber, U. Grether and H. Waldmann, *Angew. Chem., Int. Ed.*, 1999, **38**, 1073–1077; (*c*) T. Takahashi, S. Tomida, H. Inoue and T. Doi, *Synlett*, 1998, 1261–1263; (*d*) K. C. Nicolaou, J. A. Pfefferkorn and G.-Q. Cao, *Angew. Chem., Int. Ed.*, 2000, **39**, 734–739; (*e*) W.-X. Gu, S.-X. Liu and R. B. Silverman, *Org. Lett.*, 2002, **4**, 4171–4174; (*f*) S. Bräse, *Acc. Chem. Res.*, 2004, **37**, 805–816; (*g*) review: F. Guillier, D. Orain and M. Bradley, *Chem. Rev.*, 2000, **100**, 2091–2157; (*h*) Diels–Alder reactions on solid support: W. C. Cheng, M. M. Olmstead and M. J. Kurt, *J. Org. Chem.*, 2001, **66**, 5528–5533; (*i*) L. Blanco, R. Bloch, E. Bugnet and S. Deloisy, *Tetrahedron Lett.*, 2000, **41**, 7875–7878; (*j*) D. Craig, M. J. Robson and S. J. Shaw, *Synlett*, 1998, 1381–1383.

8 P. R. Blakemore, W. J. Cole, P. J. Kocienski and A. Morley, *Synlett*, 1998, 26–28.

9 (*a*) K. Takeda, K. Tsuboyama, K. Torii, M. Murata and H. Ogura, *Tetrahedron Lett.*, 1988, **29**, 4105–4108; (*b*) K. Takeda, K. Torii and H. Ogura, *Tetrahedron Lett.*, 1990, **31**, 265–266; (*c*) H.-J. Gais, T. Jagusch, N. Spalthoff, F. Gerhards, M. Frank and G. Raabe, *Chem.–Eur. J.*, 2003, **9**, 4202–4221.

10 (*a*) T. Anthonsen, M. S. Henderson, A. Martin, R. D. H. Murray, R. McCrindle and D. McMaster, *Can. J. Chem.*, 1973, **51**, 1332–1345; (*b*) M. S. Henderson, R. McCrindle and D. McMaster, *Can. J. Chem.*, 1973, **51**, 1346–1358; (*c*) S. Manabe and C. Nishino, *Tetrahedron*, 1986, **42**, 3461–3470.

11 I. Kitagawa, M. Yoshihara, T. Tani and I. Yosioka, *Tetrahedron Lett.*, 1975, **16**, 23–26.

12 I. Kitagawa, M. Yoshihara and T. Kamigauchi, *Tetrahedron Lett.*, 1977, **18**, 1221–1224.

13 (*a*) H. Morita, S. Tashiro, M. Takeda, K. Fujimori, N. Yamada, Md. C. Shiekh and H. Kawaguchi, *Tetrahedron*, 2008, **64**, 3589–3595; (*b*) P. Mauleon, I. Alonso, M. R. Rodriguez and J. C. Carretero, *J. Org. Chem.*, 2007, **72**, 9924–9935.

14 The use of NaHMDS or KHMDS resulted in *E*/*Z* mixtures and incomplete conversion.

15 D. Liotta, C. Barnum, R. Puleo, G. Zima, C. Bayer and H. S. Kezar III, *J. Org. Chem.*, 1981, **46**, 2920–2923.

16 For a previous example of traceless release from solid support employing a Pd(0)-mediated allylic substitution, see: S. C. Schürer and S. Blechert, *Synlett*, 1998, 166–168.

17 D. A. Evans and J. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 10162–10163.

18 The regiochemistry of **17** was assigned by NMR spectroscopy by comparison with known compounds, see *e. g.*: B. Witte, L. Meyer and P. Margaretha, *Helv. Chim. Acta*, 2000, **83**, 554–561.