[20] Complexation of carbonyl compounds with zinc halides is well established, and NMR spectroscopy and X-ray structure analyses support the presence of this interaction: a) R. F. Childs, D. L. Mulholland, A. Nixon, *Can. J. Chem.* **1982**, *60*, 801; b) B. Müller, M. Ruf, H. Vahrenkamp, *Angew. Chem.* **1994**, *106*, 2164; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2089; c) B. Müller, H. Vahrenkamp, *Eur. J. Inorg. Chem.* **1999**, 129.
[21] For a review on nucleophilic additions of organozinc reagents to carbonyl compounds and proposed transition states, see: R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *103*, 34; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49.
[22] For a review that includes the use of metal complexes to catalyze additions to carbonyl compounds, see: D. A. Evans, *Science* **1988**, *240*, 420.
[23] C. Chuit, R. J. P. Corriu, C. Reye, J. C. Young, *Chem. Rev.* **1993**, *93*, 1371.
[24] Examples of dialkylzinc additions to imines promoted by silylating agents as Lewis acids have been reported: a) X. L. Hou, X. L. Zheng, L. X. Dai, *Tetrahedron Lett.* **1998**, *39*, 6949; b) C. Alvisi, S. Casolari, A. L. Costa, M. Ritiani, E. Tagliavini, *J. Org. Chem.* **1998**, *63*, 1330; c) C. Jimeno, A. Vidal-Ferran, A. Moyano, M. A. Pericas, A. Riera, *Tetrahedron Lett.* **1999**, *40*, 777.
[25] E. C. Ashby, R. S. Smith, *J. Organomet. Chem.* **1982**, *225*, 71.
[26] J. L. Fry, M. Orfanopoulos, M. G. Adlington, W. R. Dittman, Jr., S. B. Silverman, *J. Org. Chem.* **1978**, *43*, 374.
[27] D. A. Evans, G. L. Carroll, L. K. Truesdale, *J. Org. Chem.* **1974**, *39*, 914.
[28] H. Kunz, W. Sager, W. Pfrengle, D. Schanzenbach, *Tetrahedron Lett.* **1988**, *29*, 4397.
[29] D. J. Parks, J. M. Blackwell, W. E. Piers, *J. Org. Chem.* **2000**, *65*, 3090.
[30] I. Marek, D. Beruben, J.-F. Normant, *Tetrahedron Lett.* **1995**, *36*, 3695.

A Linker Scaffold to Present Dimers of Pharmacophores Prepared by Solid-Phase Syntheses**

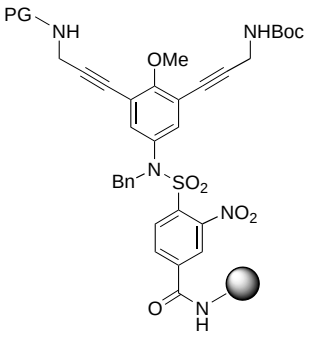
Mookda Pattarawarapan and Kevin Burgess*

Protein–protein interactions generally feature contact points ("hot-spots") situated on discontinuous sites on the protein surfaces.[1] It is therefore difficult to find small monomeric compounds that mimic or disrupt protein–protein interactions. This situation is unfortunate because this type of target is important, and is likely to become even more prevalent as data from The Human Genome Project are processed.

One apparent approach to mimick discontinuous hot-spots is to link potential pharmacophores on a scaffold that holds them apart. An early example of this is the coupling of FK506 ligands to form FK1012 and its analogues.[2] This approach featured rational design rather than high-throughput or combinatorial methods. More recently, NMR techniques have been used to design combinations of small pharmacophores wherein the monomers used are usually found by random screening.[3] Others have designed solution-phase approaches involving mixtures of compounds.[4, 5] However, none of the existing approaches capitalize on the advantages of separating the products from excess reagents in solid-phase syntheses. Moreover, the scaffolds featured in this solution-phase work were relatively flexible ones.

Solid-phase syntheses of combinations of pharmacophores from libraries of monomers can also provide a numerical advantage for the rapid generation of large libraries. A library of n components could, for instance, be attached in a one-compound-per-well format to one arm of a scaffold supported on a solid phase. If the samples of the resin were then distributed appropriately and the monomers coupled to the second arm of the scaffold it would be possible to form $n(n+1)/2$ dimers, one per well. If nonoverlapping libraries of n and m components were used then the number of combinations would be $n \times m$.

Herein we describe the synthesis of new "linker scaffolds" **1** for the solid-phase syntheses of dimeric combinations of pharmacophores. Linker scaffold **1a** has two orthogonally



	PG
1a	Fmoc
1b	Boc

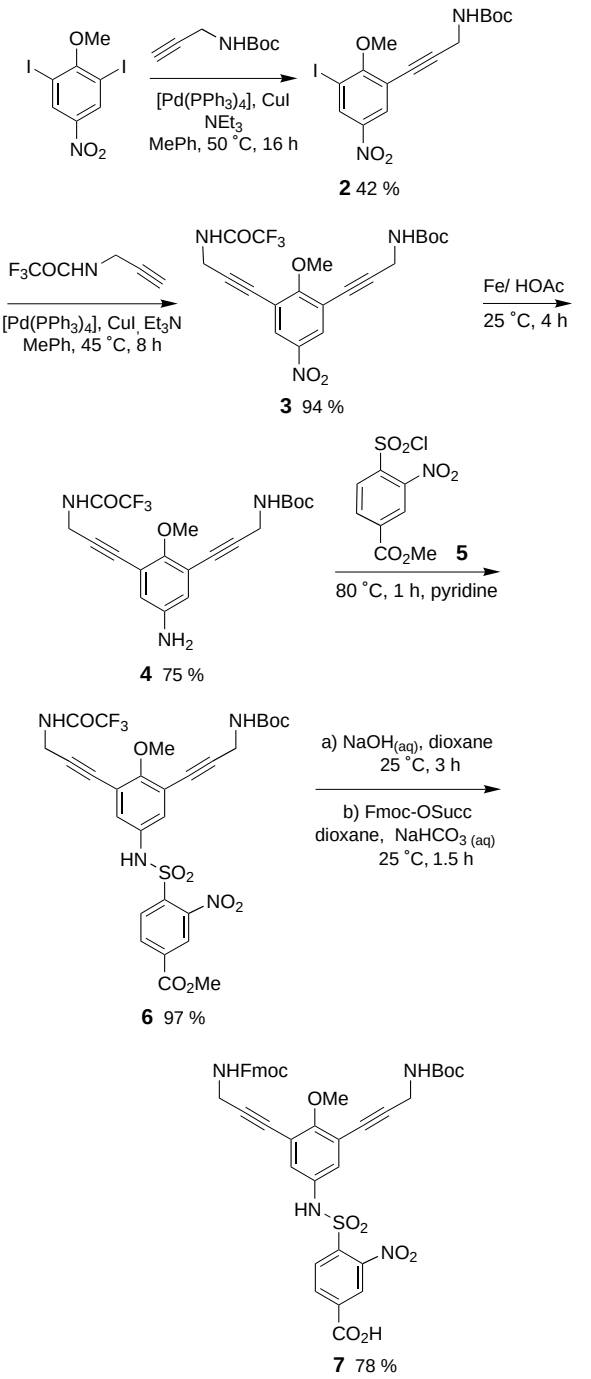
protected reactive groups on scaffold arms that can support pharmacophores at a relatively rigid separation of approximately 10 Å. The scaffold is attached to the resin through a cleavable linker that is stable to the coupling steps and to the acidic conditions typically used to remove side-chain protecting groups (for example, trifluoroacetic acid). Moreover, cleavage of the scaffold from the resin involves a reagent that gives only volatile or innocuous by-products, so the crude materials could be taken directly from the resin-cleavage step into biological assays.

Scheme 1 delineates a synthesis of linker scaffold **1a**. Sequential Sonogashira couplings were used to introduce the two scaffold arms in reactions that are promoted by the electron-withdrawing nitro group. Reduction of that nitro functionality gives an aryl amine **4** for coupling to a known[6]

[*] Prof. Dr. K. Burgess, M. Pattarawarapan
Department of Chemistry
Texas A & M University
PO Box 30012, College Station, TX 77842-3012 (USA)
Fax: (+1) 979-845-8839
E-mail: burgess@tamu.edu

[**] Financial support for this work was provided by the NIH (GM55013-02 and CA82642), the Robert A. Welch Foundation, and the Texas Advanced Technology Program.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.



Scheme 1. Synthesis of the linker scaffold unit **7**. Boc = *tert*-butoxycarbonyl; Fmoc = 9-fluorenylmethoxycarbonyl; Succ = succinimide.

sulfonyl chloride **5**. Ester hydrolysis and replacement of the trifluoroacetate **6** with a fluorenylmethoxycarbonyl protecting group gave the acid **7** (Table 1) for coupling to the resin. Full experimental details are provided in the Supporting Information.

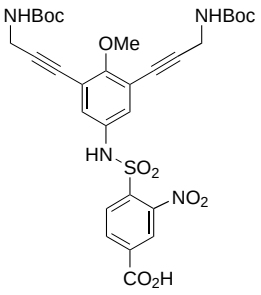
The development of appropriate linker modifications and cleavage conditions took a significant amount of time to achieve. The linker scaffolds **7** and **8** were coupled to aminomethyl polystyrene resin (Scheme 2) and the loadings of the resin were checked (Fmoc assay after coupling with Fmoc-protected glycines). Cleavage of the 2-nitrosulfonamide

Table 1. Spectroscopic data for key compounds.

7: yellow oil (78 %): ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 8.40$ (brs, 1H), 8.28 (d, $J = 7.8$ Hz, 1H), 8.01 (m, 1H), 7.82 (d, $J = 7.5$ Hz, 2H), 7.67 (d, $J = 7.5$ Hz, 2H), 7.37 (m, 3H), 7.30 (m, 4H), 7.05 (brt, 1H), 6.47 (brt, 1H), 4.35 (d, $J = 7.0$ Hz, 2H), 4.24 (m, 3H), 4.09 (d, $J = 5.7$ Hz, 2H), 3.87 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, [D$_6$]acetone): $\delta = 172.7$, 167.2, 161.8, 155.9, 151.8, 143.5, 139.2, 136.8, 131.2, 131.1, 129.2, 127.6, 125.9, 124.0, 123.2, 122.6, 122.1, 120.5, 115.5, 113.4, 113.3, 88.4, 75.9, 73.4, 62.7, 62.5, 56.9, 56.1, 42.5, 27.2, 26.8, 23.8; HR-MS (matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS)): calcd for $[C_{40}H_{36}N_4O_{11}SNa]^+$: 803.1999; found: 803.2030

8: yellow oil (95 %): ^{1}H NMR (300 MHz, [D$_6$]acetone): $\delta = 8.45$ (d, $J = 1.5$ Hz, 1H), 8.34 (dd, $J = 8.4$ Hz, 1.5 Hz, 1H), 8.00 (d, $J = 8.1$ Hz, 1H), 7.32 (s, 2H), 6.53 (brt, 2H), 4.14 (brs, 4H), 3.94 (s, 3H), 1.45 (s, 18H); ^{13}C NMR (75 MHz, [D$_6$]acetone): $\delta = 166.8$, 160.4, 156.5, 148.4, 141.1, 133.5, 133.1, 131.7, 131.4, 127.8, 125.97, 118.34, 92.9, 78.4, 76.8, 60.9, 30.6, 27.9; HR-MS (MALDI-MS): calcd for $[C_{30}H_{34}N_4O_{11}SNa]^+$: 681.1842; found: 681.1844

9: yellow oil (52 %, 99 % purity): ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 11.46$ (brs, 1H), 8.56 (brt, 1H), 7.32 (brs, 5H), 6.59 (brs, 2H), 4.44 (brd, 2H), 4.23 (brs, 4H), 3.85 (s, 3H), 3.67 (brs, 4H), 2.65 (m, 2H), 1.51 (s, 18H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 177.4$, 169.1, 163.2, 159.3, 155.6, 154.1, 153.0, 143.9, 138.7, 128.7, 127.4, 117.6, 117.2, 114.6, 88.2, 83.4, 79.7, 79.6, 61.6, 48.4, 36.4, 31.6, 28.2, 28.0, 24.5, 24.5. Analytical HPLC: homogeneous single peak, retention time = 19.0 min (5–90 % MeCN in H$_2$O over 30 min). HR-MS (MALDI-MS): calcd $[C_{35}H_{43}N_5O_8+H]^+$: 662.31; found: 462.20 $[M - 2t\text{BuOCO}]^+$

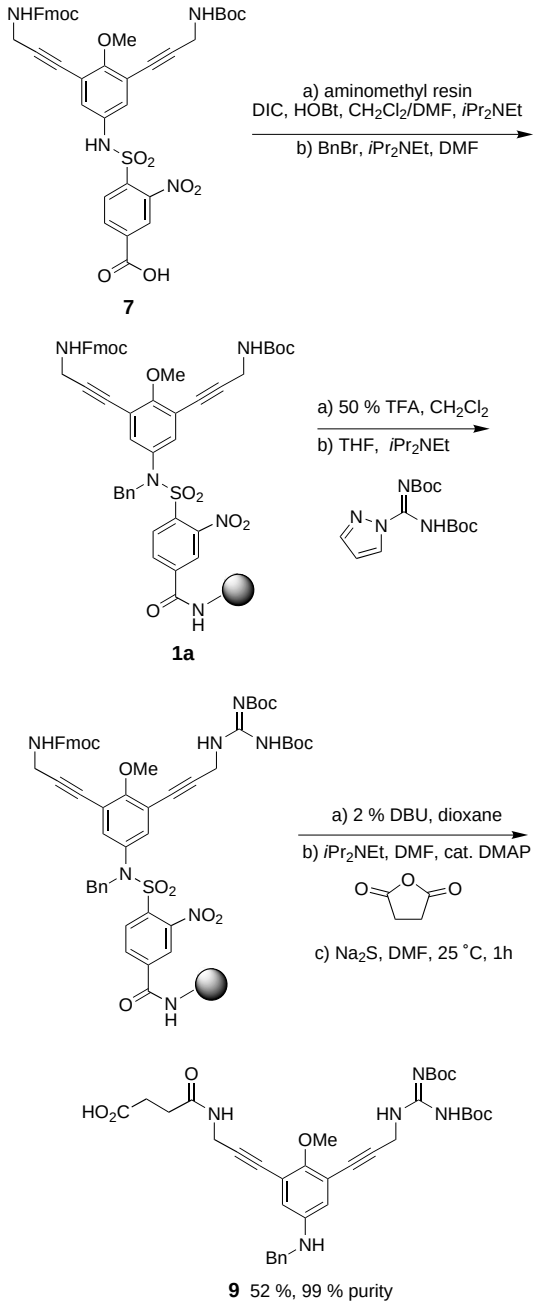


8

linkage is only facile after N-alkylation. It was shown that N-benzylation slightly attenuated the reactivity of the linkage relative to that in the *N*-methyl derivative. N-Benzylation of the linker scaffold was conveniently achieved by alkylation under mild conditions. Nosyl groups are normally cleaved using sodium thiophenylate or amines such as propylamine.[7] Sodium thiophenylate, however, would leave noxious residues that would likely interfere with biological assays. Cleavage of linker scaffold **1b** was investigated to optimize the rate and reaction efficiency. HPLC assays showed that while *n*-propylamine was insufficiently reactive for solid-phase work, treatment of **1b** with sodium sulfide/DMF caused clean and efficient cleavage in less than 1 h. The hydrolysis of excess sodium sulfide gives only hydrogen sulfide and sodium hydroxide. Though toxic, hydrogen sulfide is easily and completely removed by evaporation and/or lyophilization of the solvent media. The aqueous buffers typically used in biological assays will conveniently neutralize small amounts of sodium hydroxide; consequently both the by-products formed from the sodium sulfide mediated cleavage are relatively innocuous.

Scheme 2 illustrates how the linker-scaffold can be used to attach two different pharmacophores to the scaffold arms. The Boc-protecting group was removed first, the liberated amine was then coupled with the first component, and the Fmoc-protected amine was unmasked and coupled with the second component. It is important that a non-nucleophilic base be used in the Fmoc-deprotection step to avoid unwanted

  1433-7851/00/3923-4300 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2000**, *39*, No. 23



Scheme 2. Attachment of **7** to the resin, N-alkylation, and functionalization of the linker scaffold **1a**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DIC = diisopropylcarbodiimide; DMAP = 4-dimethylaminopyridine; HOBt = 1-hydroxy-1*H*-benzotriazole; TFA = trifluoroacetic acid.

cleavage of the linker fragment. Only one compound **9** (Table 1) is shown in Scheme 2, but a small library of homo- and heterodimeric ureas, pyridinium salts, carboxylic acids, and guanidines has been prepared. Full details of this library synthesis will be submitted shortly in the full account of this work.

The specific design of the linker scaffold **1** is special because it is the first to be produced to address the problem of making libraries of pharmacophores to mimic or disrupt protein–protein interactions. The most relevant prior research in this area involves scaffolds that do not have custom-made cleavable linkers, but have either flexible amines[8–10] or carbohydrate scaffolds.[11, 12] Many other linker scaffold systems using other skeletons attached to orthogonally cleavable linking groups could be envisaged. Indeed, slight modifications of the approaches presented here could be used to produce systems with longer or shorter arms, and more or less rigidity. It is likely that this type of work will evolve into an important area of solid-phase synthesis.

Received: June 30, 2000
Revised: August 11, 2000 [Z15373]

[1] J. A. Wells, *Science* **1996**, *273*, 449–450.
[2] S. N. Ho, S. R. Biggar, D. M. Spencer, S. L. Schreiber, G. R. Crabtree, *Nature* **1996**, *382*, 822–826.
[3] S. B. Shuker, P. J. Hajduk, R. P. Meadows, S. W. Fesik, *Science* **1996**, *274*, 1531–1534.
[4] D. L. Boger, W. Chai, *Tetrahedron* **1998**, *54*, 3955–3970.
[5] D. J. Maly, I. C. Choong, J. A. Ellman, *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 2419–2424.
[6] B. A. Bierbaum, J. J. Traverso, C. W. Whitehead, *J. Med. Chem.* **1963**, *6*, 272–275.
[7] T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
[8] I. R. Marsh, M. Bradley, *Tetrahedron* **1997**, *53*, 17317–17334.
[9] A. Nefzi, J. M. Ostresh, R. A. Houghten, *Tetrahedron* **1999**, *55*, 335–344.
[10] P. Seneci, C. Sizemore, K. Islam, P. Kocis, *Tetrahedron Lett.* **1996**, *37*, 6319–6322.
[11] T. Wunberg, C. Kallus, T. Opatz, S. Henke, W. Schmidt, H. Kunz, *Angew. Chem.* **1998**, *110*, 2620–2622; *Angew. Chem. Int. Ed.* **1998**, *37*, 2503–2505.
[12] S. Hanessian, H. K. Huynh, *Synlett* **1999**, *1*, 102–104.

First Generation Light-Harvesting Dendrimers with a $[Ru(bpy)_3]^{2+}$ Core and Aryl Ether Ligands Functionalized with Coumarin 450

Xiaoli Zhou, Daniel S. Tyson, and Felix N. Castellano*

Dendritic macromolecules are well defined, treelike structures that are typically prepared by a series of repetitive synthetic steps.[1–3] Dendrimer chemistry continues to rapidly develop as a field, since dendritic molecules are both fundamentally interesting and have many potential applications. Of particular interest are dendrimers that can be fabricated to control patterns of energy migration throughout the structure, enabling efficient light harvesting.[4, 5] Dendritic molecules constructed around Ru^{II} polypyridyl complexes that display metal-to-ligand charge transfer (MLCT) excited

[*] Prof. F. N. Castellano, X. Zhou, D. S. Tyson
Department of Chemistry
and Center for Photochemical Sciences
Bowling Green State University
Bowling Green, OH 43403 (USA)
Fax: (+1) 419-372-9809
E-mail: castell@bgnet.bgsu.edu

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  1433-7851/00/3923-4301 $ 17.50+.50/0