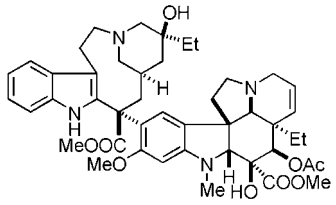
Library Synthesis

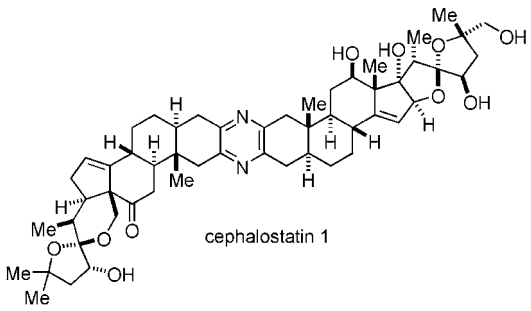
Convergent Diversity-Oriented Synthesis of Small-Molecule Hybrids**

*Chuo Chen, Xiaodong Li, Christopher S. Neumann, Michael M.-C. Lo, and Stuart L. Schreiber**

Nature uses convergent biosynthesis to yield natural product hybrids whose special properties derive from their enhanced protein-interacting capabilities; two examples are the vinca dimers and the cephalostatins (Scheme 1).[1]



vinblastine



Scheme 1. Structures of naturally occurring small-molecule hybrids.

We wish to determine whether non-natural small molecules comprising two elements, each of which has structural features reminiscent of those of natural products, might also have special properties when used in small-molecule screens. As a first step to address this question, we describe a synthesis that results in examples of "hybrid" synthetic small molecules.

[*] Dr. C. Chen,[+] X. Li,[+] C. S. Neumann, Dr. M. M.-C. Lo, Prof. S. L. Schreiber
Howard Hughes Medical Institute
Department of Chemistry and Chemical Biology
Harvard University and
The Broad Institute of Harvard and MIT
12 Oxford Street, Cambridge, MA 02138 (USA)
Fax: (+1) 617-495-0751
E-mail: stuart_schreiber@harvard.edu

[+] These authors contributed equally to this work.

[**] We thank the NIGMS for support of this research. C.C. is a research associate and S.L.S is an investigator with the Howard Hughes Medical Institute at the Department of Chemistry and Chemical Biology, Harvard University. C.S.N. acknowledges an NSF predoctoral fellowship.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/ange.200462798

We use a convergent diversity-oriented synthesis (DOS)[2,3] strategy with synthetic fragments common to natural products[4] and both solution-phase/solid-phase and solid-phase/solid-phase coupling methods (Figure 1).[5] The strategy should enable other such hybrids to be made in the future so that the above hypothesis can be tested.

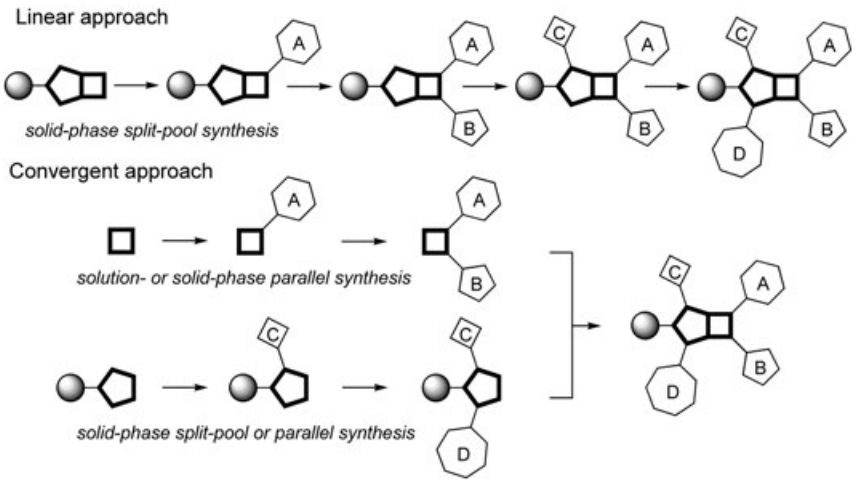
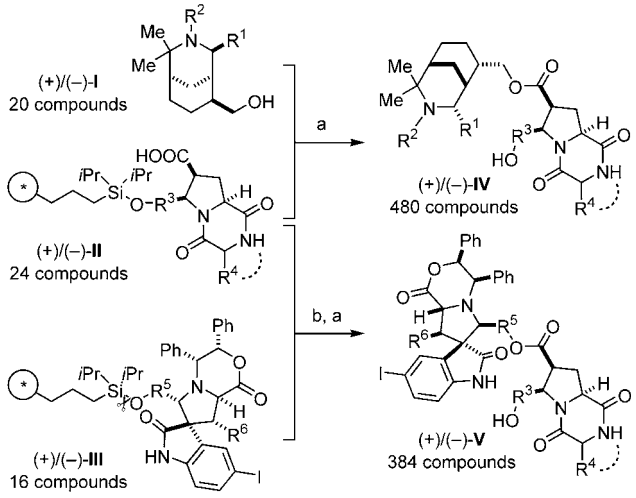


Figure 1. Linear and convergent approaches in diversity-oriented synthesis.

Three natural product subunits, based upon bridged piperidines, fused pyrrolidines, and spirocyclic oxindoles, were selected for two different hybrid-library syntheses. The key sublibrary-coupling steps are outlined in Scheme 2. The bridged-piperidine sublibrary **I** synthesized in solution was coupled to the fused-pyrrolidine sublibrary **II** immobilized on a macrobead solid support to provide the bridged-piperidine/fused-pyrrolidine hybrid library **IV**. The spirocyclic-oxindole sublibrary **III**[6] was released from a macrobead solid support and coupled to the fused-pyrrolidine sublibrary **II** to afford the spirocyclic-oxindole/fused-pyrrolidine hybrid library **V**. Sublibraries **I**, **II**, and **III** were synthesized in both enantiomeric forms by using chiral-pool, chiral-catalysis, and chiral-auxiliary approaches, respectively, to provide libraries **IV** and **V** in four diastereomeric forms.[7]



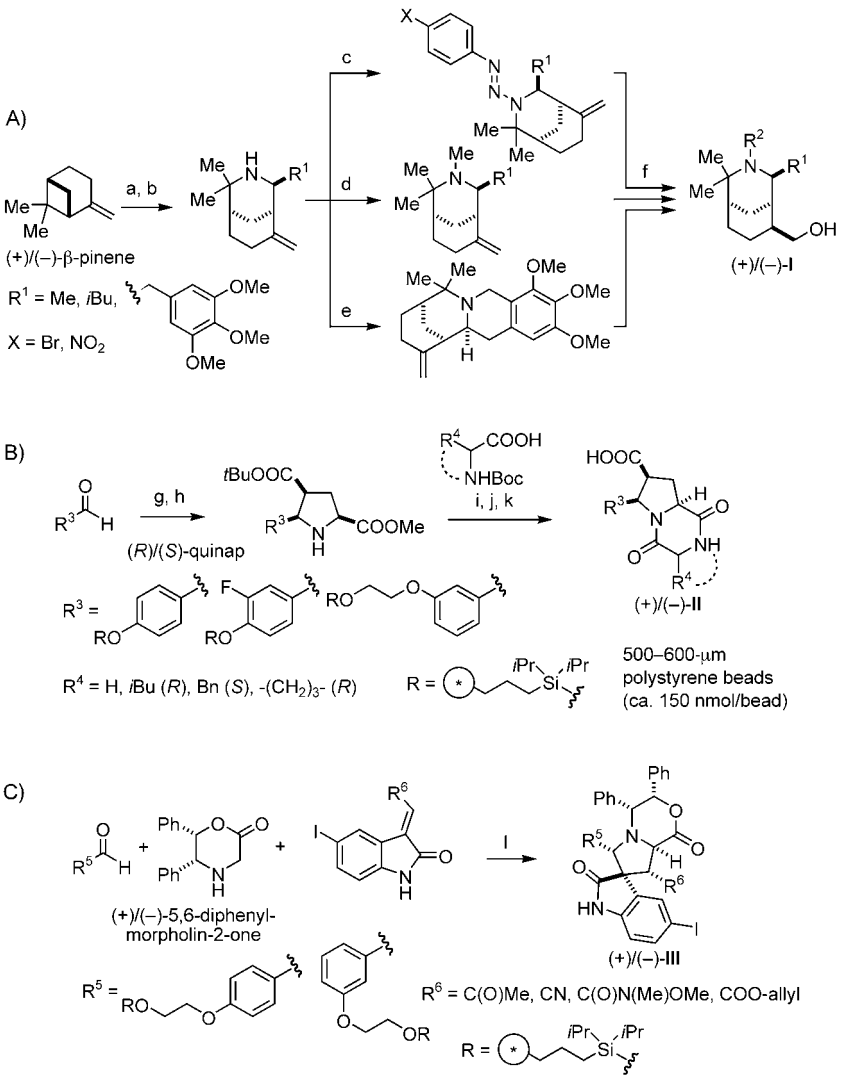
Scheme 2. Synthesis of libraries **IV** and **V** from sublibraries **I**, **II** and **II**, **III**. Only one diastereomer is shown for libraries **IV** and **V**. a) 1. PyBOP, DMAP, CH_2Cl_2, 23 °C, 16 h; 2. HF–py, THF, 23 °C, 2 h, then TMSOEt; b) **III**, HF–py, THF, 23 °C, 2 h, then TMSOEt. DMAP = 4-dimethylaminopyridine, py = pyridine, PyBOP = (1*H*-benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, TMS = trimethylsilyl.

The synthesis of sublibraries **I**–**III** is depicted in Scheme 3. The monoterpene (+)/(−)-β-pinene was chosen as the starting material for sublibrary **I** to introduce chirality, complexity, and rigidity (Scheme 3 A). The bicyclic skeleton of pinene was used to construct a chiral, nonracemic, structurally complex sublibrary with well-defined topography. The synthesis of sublibrary **I** started with a mercury(II)-mediated Ritter reaction of pinene, originally developed by Delpech and Khuong-Huu,[8] under modified conditions.[9] Analytically pure products were obtained after simple acid–base extractions. The bicyclic amines obtained after reduction with boron hydride were subjected to a diversification step comprising two processes to add an appending group (triazene formation and reductive methylation) and one skeleton-transforming reaction (Pictet–Spengler cyclization). A hydroxy group was then installed as a handle for the subsquent sublibrary-coupling reaction. A 20-membered bridged-piperidine sublibrary **I** with three different skeletons was synthesized in four steps in solution without recourse to column chromatography.

The parallel synthesis of the fused-pyrrolidine sublibrary **II** features a catalytic, asymmetric cycloaddition reaction of an azomethine ylide (Scheme 3 B) that was developed in the course of these studies.[10] Three phenolic aldehydes were loaded onto 500–600 μm polystyrene macrobeads,[11] condensed with methyl glycinate, and treated with *tert*-butyl acrylate in the presence of silver(I) acetate–(*R*)/(*S*)-quinap as the chiral catalyst. Amide coupling of the resulting pyrrolidines with *N*-Boc-protected amino acids (Gly, D-Leu, L-Phe, and D-Pro), followed by removal of both the *tert*-butyl and *N*-Boc protecting groups, provided the 24-membered fused-pyrrolidine sublibrary **II** on macrobeads in five steps.

The spirocyclic-oxindole sublibrary **III** was also synthesized in parallel on macrobeads by a Lewis acid catalyzed variant[6] of the Williams three-component coupling reaction[12] (Scheme 3 C). This 16-membered spirocyclic-oxindole sublibrary contains four different hydrogen-bond-acceptor appendages and two differently oriented "handles" for coupling to sublibrary **II**.

The final sublibrary-coupling step (**I**–**II** and **II**–**III**) involved a PyBOP/DMAP-promoted esterification (Scheme 2).[13] This convergent step provided a 480-membered bridged-piperidine/fused-pyrrolidine hybrid library **IV** and a 384-membered spirocyclic-oxindole/fused-pyrrolidine hybrid library **V**. For quality analysis, four representative compounds from **IV** and four representative compounds from **V**, which contain all building blocks, were analyzed by ^{1}H NMR spectroscopy. In all cases, good levels of purity were observed.[14] With the exception of the subset of



Scheme 3. Synthesis of sublibraries **I**, **II**, and **III**. a) $Hg(OTf)_2$, R^1CN (see Supporting Information for details); b) $NaBH(OAc)_3$, CH_2Cl_2, 23 °C, 3 h; c) ArN_2BF_4, pyridine, $MeOH/CH_2Cl_2$, 4 °C, 30 min, then KOH, 4–23 °C, 5 min; d) HCHO(aq), $NaBH(OAc)_3$, CH_3CN, 23 °C, 3 h; e) HCHO(aq), Ac_2O, CH_3CN, 60 °C, 18 h; f) BH_3·THF, THF, 23 °C, 3.5 h, then NaOH, H_2O_2, H_2O, 23 °C, 2 h; g) H_2NCH_2COOMe, benzene/DMF/MeOH, 90 °C, 16 h; h) AgOAc–(*R*)/(*S*)-quinap, iPr_2NEt, *t*BuOOCCH=CH_2, THF, −45 °C, 72 h; i) R^4(BocNH)CHCOOH, EDC, DMF/CH_2Cl_2, 23 °C, 16 h; j) TMSOTf, 2,6-lutidine, CH_2Cl_2, 40 °C, 4 h; k) NEt_3, MeOH, DMF/CH_2Cl_2, 23 °C, 24 h; l) $Mg(ClO_4)_2$, $HC(OMe)_3$, pyridine, toluene, 23 °C, 72 h. Boc = *tert*-butoxycarbonyl, DMF = *N*,*N*-dimethylformamide, EDC = 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride, Tf = trifluoromethanesulfonyl.

compounds containing the *p*-bromoaryl triazene functionality, standard conditions for cleavage from the macrobeads yielded 37 of 43 compounds with >80% purity by LCMS.[15]

The convergent strategy described herein allows the synthesis of complex small molecules through a short linear sequence on solid supports. The small-molecule products enable us to begin to determine whether the joining of fragments imparts special protein-binding and/or protein-modulating properties on the products in a manner reminiscent of natural product hybrids. The results of such experiments with the small molecules described herein and others synthesized in the future by other applications of this convergent strategy will be made available on the public database ChemBank.[16]

Received: December 3, 2004
Published online: March 3, 2005

Keywords: convergent synthesis · diversity-oriented synthesis · polycycles · small-molecule hybrids · solid-phase synthesis

[1] For reviews of small-molecule hybrids, see: a) L. F. Tietze, H. P. Bell, S. Chandrasekhar, *Angew. Chem.* **2003**, *115*, 4128–4160; *Angew. Chem. Int. Ed.* **2003**, *42*, 3996–4028; b) G. Mehta, V. Singh, *Chem. Soc. Rev.* **2002**, *31*, 324–334.

[2] M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48–60; *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58.

[3] For a discussion of the use of DOS to explore biology, see: S. L. Schreiber, *Chem. Eng. News* **2003**, *81*(9), 51–61.

[4] For a Review, see: R. Breinbauer, I. R. Vetter, H. Waldmann, *Angew. Chem.* **2002**, *114*, 3002–3015; *Angew. Chem. Int. Ed.* **2002**, *41*, 2878–2890.

[5] We are aware of only two reports of solution-phase convergent combinatorial parallel library synthesis: a) a 1600-membered library was made by an automated system: C. M. Baldino, D. S. Casebier, J. Caserta, G. Slobodkin, C. Tu, D. L. Coffen, *Synlett* **1997**, 488–490; b) an approximately 40-membered convergent library of HUN-7293 analogues was also reported: Y. Chen, M. Bilban, C. A. Foster, D. L. Boger, *J. Am. Chem. Soc.* **2002**, *124*, 5431–5440; c) for a discussion of solution-phase convergent library synthesis, see: D. L. Boger, J. Desharnais, K. Capps, *Angew. Chem.* **2003**, *115*, 4270–4309; *Angew. Chem. Int. Ed.* **2003**, *42*, 4138–4176.

[6] M. M.-C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086.

[7] Although ester functionalities can be vulnerable to cellular enzymatic cleavage, these two libraries possess highly hindered ester linkages that are not expected to suffer hydrolysis in cells.

[8] B. Delpech, Q. Khuong-Huu, *J. Org. Chem.* **1978**, *43*, 4898–4900.

[9] a) R. V. Stevens, P. M. Kenney, *J. Chem. Soc. Chem. Commun.* **1983**, 384–386; for improved procedures, see: b) D. Stoermer, C. H. Heathcock, *J. Org. Chem.* **1993**, *58*, 564–568; c) M. Dobler, H.-J. Borschberg, *Tetrahedron: Asymmetry* **1994**, *5*, 2025–2032.

[10] C. Chen, X. Li, S. L. Schreiber, *J. Am. Chem. Soc.* **2003**, *125*, 10174–10175.

[11] H. E. Blackwell, L. Pérez, R. A. Stavenger, J. A. Tallarico, E. C. Eatough, M. A. Foley, S. L. Schreiber, *Chem. Biol.* **2001**, *8*, 1167–1182; P. A. Clemons, A. N. Koehler, B. K. Wagner, T. G. Sprigings, D. R. Spring, R. W. King, S. L. Schreiber, M. A. Foley, *Chem. Biol.* **2001**, *8*, 1183–1195.

[12] P. R. Sebahar, R. M. Williams, *J. Am. Chem. Soc.* **2000**, *122*, 5666 – 5667.
[13] HPLC and ^{1}H NMR analyses, performed on eight products of the esterification reaction, revealed that minor stereoisomers made up 15–25 % of the product mixtures.
[14] For the structures of these eight compounds as well as their ^{1}H NMR spectra (of the crude and purified material), see Supporting Information.
[15] The *p*-bromoaryl triazene functionality proved problematic when subjected to our standard macrobead-cleavage reaction, which resulted in cleavage of the remote N–N bond. This undesired process can be prevented by the addition of Et_3N: In the case of IV-211121, cleavage with HF–py and Et_3N yielded the crude product with good purity by ^{1}H NMR spectroscopy.
[16] http://chembank.med.harvard.edu; R. L. Strausberg, S. L. Schreiber, *Science* **2003**, *300*, 294 – 295.

