JOC*Note*

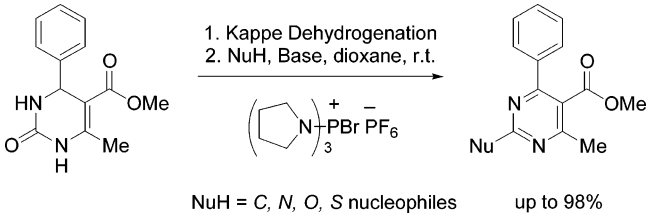
Efficient Conversion of Biginelli 3,4-Dihydropyrimidin-2(1*H*)-one to Pyrimidines via PyBroP-Mediated Coupling

Fu-An Kang,* Jason Kodah, Qunying Guan, Xiaobing Li, and William V. Murray

Johnson & Johnson Pharmaceutical Research and Development, LLC, 1000 Route 202, Raritan, New Jersey 08869

fkang@prdus.jnj.com

Received November 8, 2004



An efficient two-step procedure is described to convert the Biginelli 3,4-dihydropyrimidin-2(1*H*)-one to various multifunctionalized pyrimidines via the Kappe dehydrogenation and a new mild PyBroP-mediated coupling with *C*, *N*, *O*, and *S* nucleophiles, which provides a readily accessible multifunctionalized pyrimidine template for diversity-oriented synthesis.

Although the one-pot three-component Biginelli reaction has been known for more than a century,[1] the Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) were largely ignored in the early part of the 20th century.[2] In the past decades, the scope of the original cyclocondensation reaction was gradually extended by variation of all three building blocks, allowing access to a large number of structurally diversified multifunctionalized DHPMs.[3] These nonplanar heterocyclic compounds have received considerable attention from the pharmaceutical industry because of their interesting multifaceted pharmacological profiles. Synthesis of DHPMs resulted in the discovery of calcium channel modulators, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors and hepatitis B virus replication inhibitors.[4] Several marine-derived natural products such as Crambine, Batzelladine B (potent HIV gp-120CD4 inhibitors) and Ptilomycalin alkaloids also contain the DHPM core.[5]

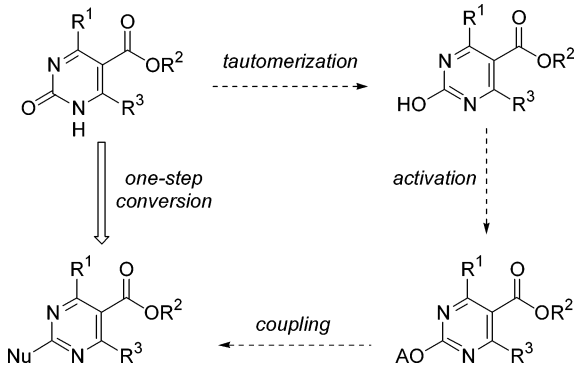
The Biginelli DHPMs are chemical precursors of multifunctionalized pyrimidines. However, despite the fact that pyrimidine is found in a wide range of biologically active molecules,[6] there has been a lack of a methodology to efficiently convert the Biginelli DHPMs to pyrimidines. A four-step process can be envisioned to realize such a chemical transformation. The Biginelli DHPMs are sequentially dehydrogenated, tautomerized, activated and coupled with a nucleophile. Dehydrogenation of the Biginelli DHPMs is known to be exceedingly difficult.[2] This is mainly due to the sensitivity of the methyl group at the *C*-6 position to oxidizing agents such as SeO_2, and the inertness of the DHPM ring toward a variety of other oxidizing agents such as DDQ, which makes the dehydrogenation very troublesome.[2,7] Consequently, since the discovery of the Biginelli reaction, there has been no preparatively useful general procedure available for the direct dehydrogenation of the Biginelli DHPMs.[2,7] It was not until 2001 that a general dehydrogenation of Biginelli DHPMs became available. Kappe et al.[8] reported an unexpected but clean dehydrogenation of the Biginelli DHPMs by using 50−60% nitric acid. In the conversion of pyrimidin-2(1*H*)-one to 2-substituted pyrimidine, conventional tautomerization-activation-coupling (TAC) process would normally include chlorination or sulfonylation, followed by coupling with a nucleophile. Chlorination[9] or sulfonylation[10] using $POCl_3$ or RSO_2Cl at high temperatures could be problematic for substrates with sensitive functionalities, particularly if this TAC process is attempted in one pot. Herein, we report our study of an efficient two-step conversion of the Biginelli DHPM to multifunctionalized pyrimidines via the Kappe dehydrogenation and a new mild one-step TAC process.[11]

(1) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
(2) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.
(3) (a) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879. (b) Bussolari, J. C.; McDonnell, P. A. *J. Org. Chem.* **2000**, *65*, 6777. (c) Byk, G.; Gottlieb, H. E.; Herscovici, J.; Mirkin, F. *J. Comb. Chem.* **2000**, *2*, 732. (d) Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. *J. Org. Chem.* **2002**, *67*, 6979. (e) Dzvinchuk, I. B.; Makitruk, T. V.; Lozinskii, M. O. *Chem. Heterocycl. Comput.* **2003**, *39*, 455. (f) Dondoni, A.; Massi, A.; Minghini E.; Sabbatini, S.; Bertolasi, V. *J. Org. Chem.* **2003**, *68*, 6172. (g) Abelman, M. M.; Smith, S. C.; James, D. R. *Tetrahedron Lett.* **2003**, *44*, 4559. (h) Gong, D.; Zhang, L.; Yuan, C. *Heteroatom Chem.* **2003**, *14*, 13. (i) Kappe, C. O. *QSAR Comb. Sci.* **2003**, *22*, 630. (j) Dondoni, A.; Massi, A. *Mol. Div.* **2003**, *6*, 261. (k) Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1. (l) Byk, G.; Kabha, E. *J. Comb. Chem.* **2004**, *6*, 596. (m) Bandyopadhyay, C.; Nag, P. P.; Sur, K. R.; Patra, R.; Banerjee, S.; Sen, A.; Ghosh, T. *J. Indian Chem. Soc.* **2004**, *81*, 132. (n) Shaabani, A.; Bazgir, A.; Bijanzadeh, H. R. *Mol. Div.* **2004**, *8*, 141.

(4) (a) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043. (b) Deres, K.; Schroder, C. H.; Paessens, A.; Goldmann, S.; Hacker, H. J.; Weber, O.; Kraemer, T.; Niewoehner, U.; Pleiss, U.; Stoltefuss, J.; Graef, E.; Koletzki, D.; Masantschek, R. N. A.; Reimann, A.; Jaeger, R.; Groβ, R.; Beckermann, B.; Schlemmer, K.-H.; Haebich, D.; Rubsamen-Waigmann, H. *Science* **2003**, *299*, 893. (c) Lengar, A.; Kappe, C. O. *Org. Lett.* **2004**, *6*, 771.
(5) (a) Snider, B. B.; Shi, Z. *J. Org. Chem.* **1993**, *58*, 3828. (b) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Gaulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westly, J. W.; Potts, B. C. *J. Org. Chem.* **1995**, *60*, 1182. (c) Overman, L. E.; Rabinowitz, M. H.; Renhowe, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (d) Aron, Z. D.; Overman, L. E. *Chem. Commun.* **2004**, 253.
(6) For representative drugs and biologicals containing pyrimidines (over 80 examples), such as amprolium, bispyribac, cetotiamine, diaveridine, ethirimol, fenarimol, glymidine, ipsapirone, lesopitron, mepanipyrin, nimustine, oxythiamine, peplomycin, quinapyramine, rimsulfuron, sulfabromomethazine,and tandospirone, see: *The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals*, 13th ed.; Merck & Co., Inc.: Whitehouse Station, 2001.
(7) Eynde, J. J. V.; Audiart, N.; Canonne, V.; Michel, S.; Haverbeke, Y. V.; Kappe, C. O. *Heterocycles* **1997**, *45*, 1967.
(8) Puchala, A.; Belaj, F.; Bergman, J.; Kappe, C. O. *J. Heterocycl. Chem.* **2001**, *38*, 1345.
(9) Kappe, C. O.; Roschger, P.; *J. Heterocycl. Chem.* **1989**, *26*, 55.
(10) (a) Matsushita, A.; Oda, M.; Kawachi, Y.; Chika, J. WO 03006439, 2003. (b) Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Seo, S.; Hirai, K. *Bioorg. Med. Chem.* **1997**, *5*, 437.

10.1021/jo040281j CCC: $30.25
Published on Web 02/03/2005

SCHEME 1. Proposed One-step Conversion of Pyrimidin-2(1*H*)-one to Pyrimidine

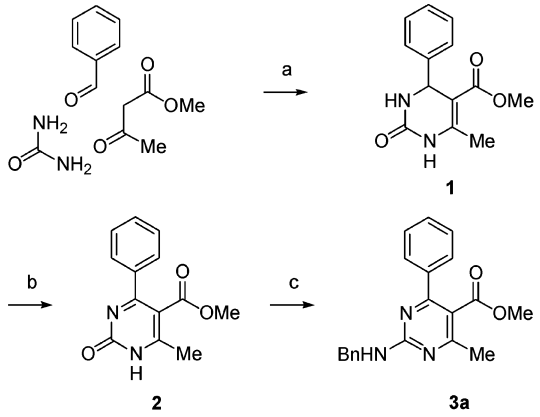


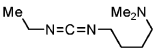
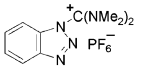
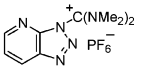
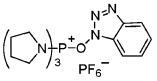
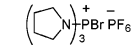
Since pyrimidine is an electron-deficient system and the presence of an electron-withdrawing group at the *C*-5 position should greatly enhance the overall electron-deficiency of the system, we thought that in the presence of a suitable activating reagent, 2-hydroxypyrimidine, the tautomerized pyrimidin-2(1*H*)-one, could form a highly reactive intermediate which could be easily attacked by a nucleophile to furnish the 2-substituted pyrimidine (Scheme 1). We recognize that there are various efficient activating reagents for peptide couplings, and they may be useful in our proposed study of a mild efficient one-step conversion of the dehydrogenated Biginelli DHPMs to multifunctionalized pyrimidines.

The Biginelli DHPM **1** and its dehydrogenated compound **2** were readily prepared according to the procedures by Hu[12] et al. and Kappe[8] et al. (Table 1). We screened some of the popular peptide coupling reagents, including DCC, EDCI, HBTU, HATU, PyBOP, and PyBroP, for the coupling reaction between **2**[13] and benzylamine in the presence of Et_3N in THF at room temperature (r.t.) (Table 1). To our delight, the phosphonium-based reagents PyBOP and PyBroP[14] were found to be very effective in this transformation affording **3a** in high yields, with PyBroP being slightly superior to PyBOP.[15]

With PyBroP as the coupling reagent of choice, we then investigated the solvent effect on this coupling reaction.

TABLE 1. Screening of Coupling Reagents for the Conversion of Pyrimidin-2(1*H*)-one to Pyrimidine[a]



entry	reagent	structure	yield of **3a** (%)
1	DCC		0
2	EDCI		0
3	HBTU		0
4	HATU		0
5	PyBOP		90
6	PyBroP		94

[a] Reagents and conditions: (a) CuCl, $BF_3{\cdot}OEt_2$, THF, refluxing, 18 h, 90%; (b) 60% HNO_3, 0 °C to rt, 0.5 h, 80%; (c) **2** (1 equiv), $BnNH_2$ (1.3 equiv), reagent (1.1 equiv), Et_3N (2.5 equiv), THF (0.1 M), rt, 24 h.

It turned out that among the common organic solvents, ethers led to faster and cleaner reactions. Dioxane[16] was found to be the best solvent, while DMF[17] was the worst solvent (**3a**, Table 2). With PyBroP and dioxane as the best reagent-solvent combination, we next studied the base effect on this coupling reaction. For strong nucleophiles, such as primary and secondary alkylamines (**3a** and **3b**), cycloalkylamines (**3c** and **3d**), α-amino ester (**3e**), α-amino alcohol (**3f**) and thiophenol (**3g**), Et_3N is a suitable base for achieving a complete coupling reaction (Table 2). On the other hand, for a weak nucleophile such as *N*-methyl methanesulfonamide, no coupling reaction was observed with Et_3N as the base. Screening of different bases for the coupling reaction between **2** and *N*-methyl methanesulfonamide revealed that sodium *tert*-butoxide is an excellent base to ensure a clean and complete reaction (**3h**, Table 2). Under similar conditions,

(11) For a preliminary communication of this study, see: Kang, F.-A.; Murray, W. V. *Abstracts of Papers*, 228th National Meeting of the American Chemical Society, Philadelphia, PA.; American Chemical Society: Washington, DC, 2004; ORGN 702.

(12) Hu, E. H.; Sidler, D. R.; Dolling, U.-H. *J. Org. Chem.* **1998**, *63*, 3454.

(13) (a) Interestingly, on the ^{13}C NMR spectrum of compound **2** determined at 25 °C, the four carbon signals of C_4, C_6 and their directly bonded carbons of the substituents (phenyl and methyl) are missing, which is due to the tautomerization between pyrimidin-2(1*H*)-one and pyrimidin-2(3*H*)-one. For a similar observation, see ref 8. The complete ^{13}C NMR data of **2** were obtained at 90 °C in DMSO-d_6, see the Supporting Information.

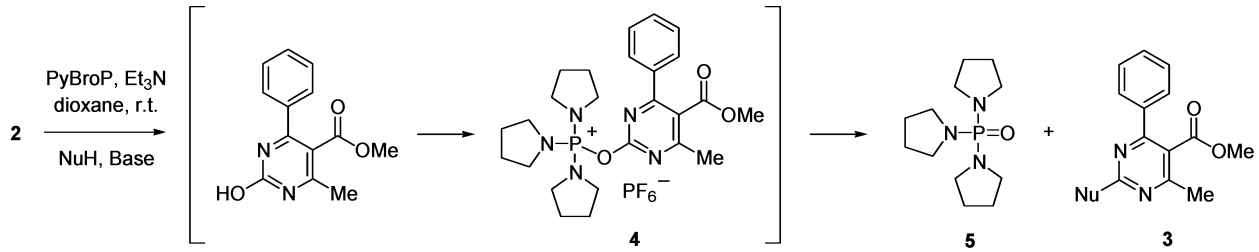
(14) (a) Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205. (b) Coste, J.; Frerot, E.; Jouin, P. *Tetrahedron Lett.* **1991**, *32*, 1967. (c) The coupling reactions by directly using commercial PyBOP or PyBroP usually produce about 5% of the pyrolidine-containing side-product **3c** (Table 2), which is attributed to the presence of a small amount of pyrrolidine as a contaminant to the commercial phosphonium salts. This side reaction does not occur when the reagents are recrystallized before their use in the coupling reaction. For recrystallization of PyBOP and PyBroP, and a similar observation of pyrolidine-containing side-product formation, see: Alsina, J.; Barany, G.; Albericio, F.; Kates, S. A. *Lett. Peptide Sci.* **1999**, *6*, 243.

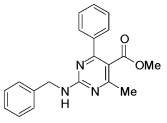
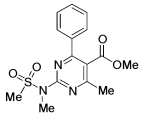
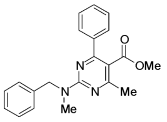
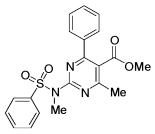
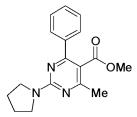
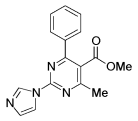
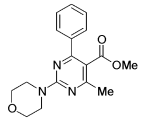
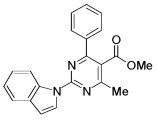
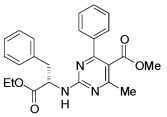
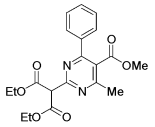
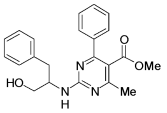
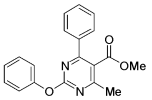
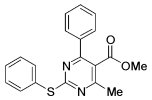
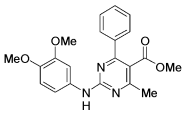
(15) PyBOP is slightly less efficient than PyBroP since it forms two transition intermediates with **2**, the more reactive **4** (Table 2) and the less reactive 2-*O*-(benzotriazol-1-yl)-pyrimidine which can be isolated from the incomplete coupling reaction.

(16) It is interesting to note that the less effective solvents, e.g. MeCN, DCM and DMF led to homogeneous reactions, while the more effective solvents, e.g. dioxane, THF and DME, resulted in heterogeneous reactions. Dioxane seems to cause a slightly less heterogeneous, faster and cleaner reaction than THF and DME.

(17) It is not surprising that DMF was the least effective solvent for the targeted coupling reaction, since it is known that DMF can form formamidines with amines in the presence of PyBroP; see: Delarue, S.; Sergheraert, C. *Tetrahedron Lett.* **1999**, *40*, 5487.

TABLE 2. Efficient Conversion of Pyrimidin-2(1*H*)-one to Pyrimidines via PyBroP-Mediated Coupling



entry	product	solvent / base / yield (%)	entry	product	solvent / base / yield (%)
		dioxane / Et_3N / 96			dioxane / $NaOBu^t$ / 90
		THF / Et_3N / 94			dioxane / DABCO / 10
3a[a]		DME / Et_3N / 90	**3h**[b]		dioxane / Cs_2CO_3 / 5
		MeCN / Et_3N / 80			dioxane / DBU / 0
		DCM / Et_3N / 45			dioxane / DMAP / 0
		DMF / Et_3N / 20			dioxane / Et_3N / 0
3b[a]		dioxane / Et_3N / 94	**3i**[b]		dioxane / $NaOBu^t$ / 92
3c[a]		dioxane / Et_3N / 98	**3j**[b]		dioxane / $NaOBu^t$ / 84
3d[a]		dioxane / Et_3N / 92	**3k**[b]		dioxane / $NaOBu^t$ / 78
3e[a,c]		dioxane / Et_3N / 82	**3l**[b]		dioxane / $NaOBu^t$ / 72
3f[a]		dioxane / Et_3N / 91	**3m**[b]		dioxane / $NaOBu^t$ / 88
3g[a]		dioxane / Et_3N / 95	**3n**[b,c]		dioxane / $NaOBu^t$ / 26

[a] Condition A: **2** (1 equiv), PyBroP (1.1 equiv), dioxane (0.1 M), Et_3N (2.5 equiv), NuH (1.3 equiv), rt, 24 h. [b] Condition B: **2** (1 equiv), PyBroP (1.1 equiv), dioxane (0.1 M), Et_3N (2.5 equiv); NuH (1.3 equiv), $NaOBu^t$(1.2 equiv), rt, 24 h. [c] rt, 72 h.

other weak nucleophiles such as *N*-methyl benzenesulfonamide (**3i**), imidazole (**3j**), indole (**3k**), diethyl malonate (**3l**), and phenol (**3m**) were coupled smoothly with **2** in high yields, except for the electron-rich aniline (**3n**). The proposed reaction pathway is supported by mass spectral analyses of the reaction mixture. A mass peak of 484.2 $[M+H]^+$, corresponding to the cation of the transition intermediate **4**, was observed at the beginning of the coupling reaction. This peak gradually disappeared, while mass peaks of 258.1 $[M + H]^+$ and 515.2 $[2M + H]^+$, corresponding to the byproduct **5**, gradually increased (Table 2).

It should be noted that while most of the coupling reactions were found to be complete at ambient temperature in 24 h, the reaction rate seems to depend on both the electronic and steric nature of the nucleophiles. For instance, the coupling reaction between **2** and morpholine was complete in 3 h (**3d**), whereas the coupling reaction between **2** and α-amino ester took 3 days (**3e**). In addition, attempts to couple **2** with primary sulfona-

mides, amides and electron-neutral anilines gave, at most, a trace of product **3** under similar conditions, which is probably due to their lower nucleophilicity.

In conclusion, we have demonstrated that the Biginelli DHPM can be efficiently converted to various multifunctionalized pyrimidines through Kappe dehydrogenation and PyBroP-mediated coupling with *C*, *N*, *O*, and *S* nucleophiles. Optimal conditions for this mild in situ activation coupling were obtained through reagent, solvent and base screenings. These coupling conditions could be potentially applicable to other electron-deficient heterocylic or aromatic systems. The present study also provides a readily accessible multifunctionalized pyrimidine template for diversity-oriented synthesis.[18]

Experimental Section

General Procedure A for the PyBroP-Mediated Coupling To Synthesize Pyrimidines 3a−g. To a stirred solution of compound **2** (48.8 mg, 0.2 mmol) in dioxane (2 mL) at room temperature were added PyBroP (102.5 mg, 0.22 mmol), Et_3N (69.2 μL, 0.5 mmol) and the nucleophile (0.26 mmol). After the mixture was stirred at room temperature for 24−72 h (TLC monitoring), it was diluted with EtOAc and washed with saturated NH_4Cl solution, brine and dried with Na_2SO_4. Filtration, evaporation, and flash chromatography (5−20% EtOAc in hexane) gave the products **3a**−**g**.

2-(*N*-Benzylamino)-4-phenyl-6-methylpyrimidin-2(1*H*)-one-5-carboxylic Acid Methyl Ester (3a). White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.58 (s, 3H), 4.69 (d, J = 6.0, 2H), 5.99 (br s, 1H), 7.2−7.6 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.0, 45.4, 52.0, 115.3, 127.3, 127.6, 127.9, 128.3, 128.6, 129.6, 138.9, 139.0, 161.2, 165.9, 167.4, 169.5. HRMS (FAB+): *m/z* calcd for $C_{20}H_{19}N_3O_2$ $[M + H]^+$ 334.1556, found 334.1546.

General Procedure B for the PyBroP-Mediated Coupling To Synthesize Pyrimidines 3h−n. To a stirred solution of compound **2** (48.8 mg, 0.2 mmol) in dioxane (2 mL) at room temperature were added PyBroP (102.5 mg, 0.22 mmol) and Et_3N (69.2 μL, 0.5 mmol); then, the nucleophile (0.26 mmol) and $NaOBu^t$ (23 mg, 0.24 mmol) were added. After the mixture was stirred at room temperature for 24−72 h (TLC monitoring), it was diluted with EtOAc, washed with saturated NH_4Cl solution and brine, and dried with Na_2SO_4. Filtration, evaporation, and flash chromatography (5−20% EtOAc in hexane) gave the products **3h**−**n**.

2-(*N*-Methylmethanesulfonylamino)-4-phenyl-6-methylpyrimidin-2(1*H*)-one-5-carboxylic Acid Methyl Ester (3h). White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59 (s, 3H), 3.52 (s, 3H), 3.59 (s, 3H), 3.69 (s, 3H), 7.47 (m, 3H), 7.67 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.3, 33.5, 42.9, 53.0, 120.0, 128.7, 129.0, 130.8, 137.9, 158.7, 164.8, 167.4, 169.0. HRMS (FAB+): *m/z* calcd for $C_{15}H_{17}N_3O_4S$ $[M + H]^+$ 336.1018, found 336.1004.

Acknowledgment. We thank Dr. Alexandra Shedlow and Ms. Amy Maden for analytical support and Drs. Zhihua Sui, Nareshkumar Jain, Raymond Ng, Bharat Lagu, and Shyh-Ming Yang for helpful discussions.

Supporting Information Available: Characterization data and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO040281J

(18) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Burke, M. D.; Lalic, G. *Chem. Biol.* **2002**, *9*, 535. (c) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613.