ORGANIC LETTERS

2011
Vol. 13, No. 10
2590–2593

# Facile and Unified Approach to Skeletally Diverse, Privileged Scaffolds

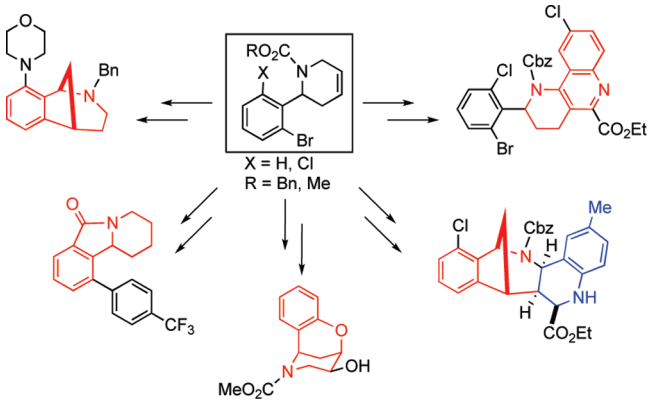
**James J. Sahn, Justin Y. Su, and Stephen F. Martin***

*Department of Chemistry and Biochemistry and The Texas Institute for Drug and Diagnostic Development, The University of Texas at Austin, Austin Texas 78712, United States*

*sfmartin@mail.utexas.edu*

**Received March 16, 2011**

## ABSTRACT




**A novel strategy has been developed to generate a diverse array of privileged scaffolds from readily available tetrahydropyridine precursors that may be prepared by a multicomponent assembly process followed by a ring-closing metathesis. The functionality embedded in these key intermediates enables their facile elaboration into more complex structures of biological relevance by a variety of ring-forming processes and refunctionalizations.**

The demand to identify new, selective agents to treat human diseases and to serve as tools to interrogate biological function has led to various approaches for generating molecular libraries for biological screening. Although traditional combinatorial synthesis has been employed to produce large numbers of novel compounds, these libraries have historically suffered from low hit rates and poor specificity, a consequence that has been attributed to poor physiochemical properties and insufficient structural diversity, coupled with a lack of stereocenters and molecular rigidity.[1] Accordingly, recent efforts in library design have focused upon developing more effective strategies. For example, libraries based on so-called privileged substructures typically exhibit higher hit rates in a variety of biological assays.[1,2] A single privileged scaffold can be easily modified via manipulation of either functional groups or ring substitution patterns. Because such alterations often induce marked changes in potency and target affinity, libraries based upon privileged scaffolds are well-suited for identifying new lead compounds for drug discovery.

We recently became interested in designing new strategies for diversity-oriented synthesis (DOS)[3] to prepare collections of biologically active small molecules having

(1) (a) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361. (b) Feher, M.; Schmidt, J. M. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 218–227.

(2) For leading references to privileged substructures, see: (a) Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235–2246. (b) Pippin, D. A.; Darrow, J. W.; Mitchell, S. A.; Currie, K. S.; DeSimone, R. W. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473–493. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930. (d) Constantino, L.; Barlocco, D. *Curr. Med. Chem.* **2006**, *13*, 65–85.

(3) See for example: (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58. (b) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74–84. (c) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149–1158.

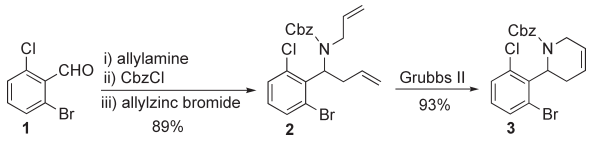
(4) For the first example of this process, see: Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161–6171.

10.1021/ol200709h 
**Published on Web 04/22/2011**

privileged ring systems as well as substructures found in natural products. One such strategy combines a multicomponent assembly process (MCAP) involving three or more reactants to prepare pivotal intermediates that are transformed into heterocyclic scaffolds by various ring-forming reactions that are directed by selective pairing of functional groups.[4−6] We have now developed a useful extension of this strategy, wherein tetrahydropyridines, which are accessed via a MCAP and a subsequent ring-closing metathesis (RCM), are transformed into a number of privileged scaffolds. We now present some of the details of these investigations.

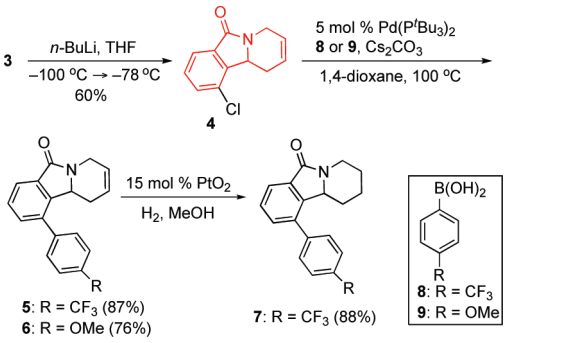
To develop this new approach to scaffold generation, a suitably functionalized tetrahydropyridine, such as **3**, was needed. Accordingly, reaction of 2-bromo-6-chlorobenzaldehyde (**1**),[7] allylamine, Cbz−Cl, and allylzinc bromide in a Mannich-like MCAP gave diene **2** in 89% yield (Scheme 1). Cyclization of **2** via a RCM reaction delivered the pivotal intermediate **3**. Tactics for its elaboration into various heterocyclic scaffolds, especially privileged substructures, were then explored.

**Scheme 1.** Synthesis of Tetrahydropyridine **3**




The isoindolinone ring system, which is found in the potent antiviral natural product stachyflin,[8] is one important member of the family of privileged scaffolds.[9] Intrigued by the possibility of preparing isoindolinones from **3** via a Parham cyclization,[10] we found that treatment of **3** with *n*-BuLi at −100 °C gave isoindolinone **4** in 60% yield (Scheme 2). To illustrate possible tactics for diversifying **4**, it was subjected to Suzuki cross-coupling reactions with electron-rich and electron-deficient arylboronic acids to give biaryls **5** and **6**; hydrogenation of **5** provided saturated amide **7**. Relative to possibilities for biological activity, it is notable that cyclohexyl-fused isoindolinones similar to **4** possess potent urotensin-II receptor antagonist activity,[11] and biarylisoindolinones similar to **5**−**7** exhibit KDR inhibitory activity.[12] Indeed, biaryls are privileged scaffolds that are present in 4.3% of all known drugs.[1,13]

**Scheme 2.** Synthesis of Isoindolinone Scaffold **4** and Subsequent Suzuki Cross-Coupling




Tetrahydropyridine **3** underwent facile Heck cyclization under Jeffrey's conditions[14] and microwave irradiation to provide the enecarbamate **10**, a versatile intermediate that is nicely functionalized for a number of diversification reactions (Scheme 3). For example, electron-rich enecarbamates are excellent inputs in imino Diels−Alder reactions, such as the Povarov reaction.[15,16] Although Povarov reactions involving substrates having the structural complexity of **10** are not known, we discovered that the reaction of **10** with *p*-toluidine and ethyl glyoxylate in the presence of Sc(OTf)$_3$ gave a readily separable mixture (1.2:1.0) of diastereomeric tetrahydroquinolines **11** and **12** in 84% yield. Formation of a mixture of stereoisomers was not unexpected because Povarov reactions often proceed with low stereoselectivity. The relative stereochemistry of **11** was verified by single X-ray crystallographic analysis, whereas the structure of **12** was tentatively assigned on the basis of a value of $J_{H2-H3}$ = 3.4 Hz, which is consistent with the proposed stereochemistry and not with the *trans*-diaxial relationship expected for the C(3)-epimer.[17] The indanyl quinoline **14**, the structure of which was secured by X-ray crystallography, was also isolated in 5−10% yield; **14** is presumably

(5) For a review of such strategies, see: Sunderhaus, J. D.; Martin, S. F. *Chem.—Eur. J.* **2009**, *15*, 1300–1308.

(6) (a) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4223–4226. (b) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Tetrahedron* **2009**, *65*, 6454–6469.

(7) Rawalpally, T.; Ji, Y.; Shankar, A.; Edward, W.; Allen, J.; Jian, Y.; Cleary, T. P.; Pierce, M. E. *Org. Process Res. Dev.* **2008**, *12*, 1293–1298.

(8) Minagawa, K.; Kouzuki, S.; Kamigauchi, T. *J. Antibiot.* **2002**, *55*, 165–171.

(9) Zhu, J.; Nueville, L.; Salcido, A. *J. Org. Chem.* **2008**, *73*, 3600–3603.

(10) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300–305.

(11) Lawson, E. C.; Luci, D. K.; Ghosh, S.; Kinny, W. A.; Reynolds, C. H.; Qi, J.; Smith, C. E.; Wang, Y.; Minor, L. K.; Haertlein, B. J.; Parry, T. J.; Damiano, B. P.; Maryanoff, B. E. *J. Med. Chem.* **2009**, *52*, 7432–7445.

(12) Curtin, M. L.; Frey, R. R.; Heyman, R. H.; Sarris, K. A.; Steinman, D. H.; Holmes, J. H.; Bousquet, P. J.; Cunha, G. A.; Moskey, M. D.; Ahmed, A. A.; Pease, L. J.; Glaser, K. B.; Stewart, K. D.; Davidsen, S. K.; Michaelides, M. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4505–4509.

(13) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443–3447.

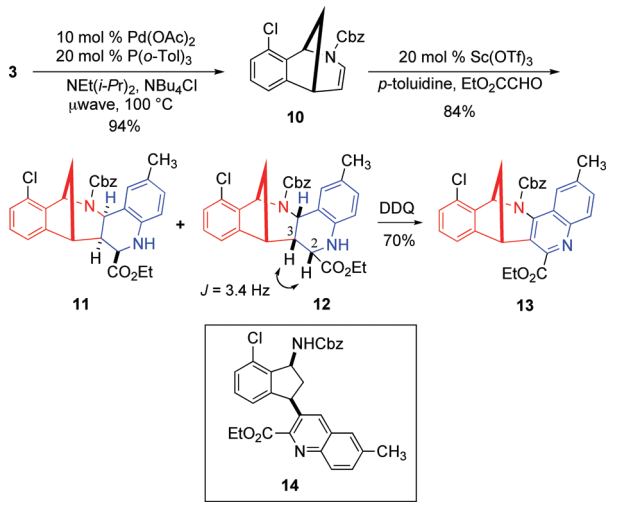
(14) Jeffrey, T. *Tetrahedron Lett.* **1985**, *26*, 2667–2670.

(15) For reviews on the Povarov reaction, see: (a) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656–670. (b) Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev.* **2008**, *77*, 137–159. (c) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721–2750.

(16) (a) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913–2916. (b) Yadav, J. S.; Reddy, B. V.; Sunitha, V.; Reddy, S. K.; Ramakrishna, K. V. *Tetrahedron Lett.* **2004**, *45*, 7947–7950. (c) Hu, Y. J.; Tomaszewski, M.; Walpole, C. PCT Int. Appl. WO 075476 A1 20050818, 2005.

(17) Adduct **12** undergoes spontaneous oxidation to **13** and could not be isolated in pure form.

**Scheme 3.** Imino Diels–Alder Reaction of Enecarbamate **10**

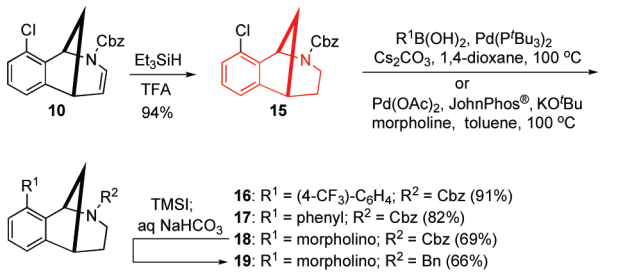



formed from **11** and/or **12** via an elimination-oxidation sequence.[18] Oxidation of the mixture of **11** and **12** with DDQ furnished **13** in 70% yield. It is noteworthy that **11**–**13** embody fused privileged substructures that can be diversified through elaboration of multiple functional handles.

The enecarbamate **10** can be easily converted into a number of norbenzomorphans, a privileged skeleton whose members exhibit a range of neurological activities such as AChE inhibitory[19] and codeine-like analgesic activity (Scheme 4).[20] In the event, the olefinic moiety in **10** was first reduced selectively under ionic conditions to furnish **15** in 94% yield.[21] Exemplary cross-coupling reactions of **15** with arylboronic acids and amines gave the biaryls **16** and **17** and the aniline **18** in good yield. In an application of a known, but rarely used reaction,[22] we found that treating **18** with TMSI, followed by workup with aqueous sodium bicarbonate, yielded benzylamine **19**.

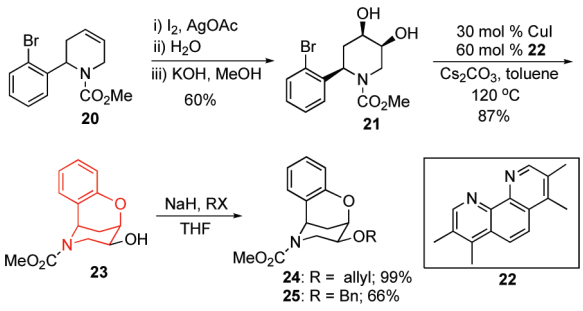
Tetrahydrobenzo[1,5]oxazocines are known to exhibit a diverse array of important biological properties, including CNS and analgesic activity,[23] as well as hepatitis C inhibitory activity.[24] Accordingly, we developed a novel entry to such compounds as exemplified by a facile synthesis of

**Scheme 4.** Synthesis of Norbenzomorphan Analogues **16**–**19**




benzoxazocine **23** that featured a ring-closing etherification (Scheme 5). We first prepared the piperidine **21** as a single diastereomer by highly selective vicinal dihydroxylation of **20** from the more hindered olefin face

**Scheme 5.** Tetrahydrobenzo[1,5]oxazocine **23** via an Intramolecular Ullmann Etherification




employing the conditions of Woodward.[25] When **21** was subjected to a copper-catalyzed intramolecular etherification,[26] benzoxazocine **23** was obtained in 87% yield. With both a free hydroxl group and protected nitrogen, benzoxazocine **23** is ideally suited for analogue synthesis, as exemplified by allyl and benzyl ethers **24** and **25**, respectively.

Compounds containing the 1,2,3,4-tetrahydrobenzo[*h*]-[1,6]naphthyridine motif exhibit a wide range of biological properities, including selective 5-$HT_4$ antagonist activity,[27] gastric ($H^+/K^+$)-ATPase inhibition,[28] and broad-spectrum antibacterial activity.[29] We thus queried whether we might be able to access this ring system from **3** via double-bond

(18) For a similar transformation, see: Vincente-García, E.; Catti, F.; Ramón, R.; Lavilla, R. *Org. Lett.* **2010**, *12*, 860–863.

(19) Yuhpyng, C. L.; Liston, D.; Nielson, J.; Chapin, D.; Dunaiskis, A.; Hedberg, K.; Ives, J.; Johnson, J.; Jones, S. *J. Med. Chem.* **1994**, *37*, 1996–2000.

(20) Mokotoff, M.; Jacobson, A. E. *J. Med. Chem.* **1970**, *13*, 7–9.

(21) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1991**, *56*, 2506–2512.

(22) D'Andrea, S. V.; Michalson, E. T.; Freeman, J. P.; Chidester, C. G; Szmuskzkovicz, J. *J. Org. Chem.* **1991**, *56*, 3133–3137.

(23) Raj, K. R.; Harry, G. P. Beecham Group LTD, DE1908324-(A1), 19690911.

(24) Narjes, F.; Crescenzi, B.; Ferrara, M.; Habermann, J.; Colarusso, S.; Ferreira, M.; Stansfield, I.; Mackay, A.; Conte, I.; Ercolani, C.; Zaramella, S.; Palumbi, M.; Meuleman, P.; Leroux-Roels, G.; Giuliano, C.; Fiore, F.; Di Marco, S.; Baiocco, P.; Koch, U.; Migliaccio, G.; Altamura, S.; Laufer, R.; De Francesco, R.; Rowley, M. *J. Med. Chem.* **2011**, *54*, 289–301.

(25) Woodward, R. B.; Brutcher, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209–211.

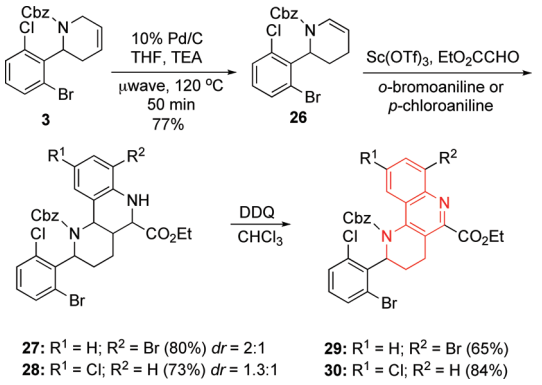
(26) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284–286.

(27) Hinschberger, A.; Butt, S.; Lelong, V.; Boulouard, M.; Dumuis, A.; Francois, D.; Bureau, R.; Pfeiffer, B.; Renard, P.; Rault, S. *J. Med. Chem.* **2003**, *46*, 138–147.

(28) Brown, T. H.; Ife, R. J.; Keeling, D. J.; Laing, S. M.; Leach, C. A.; Parsons, M. E.; Price, C. A.; Reavill, D. R.; Wiggall, K. J. *J. Med. Chem.* **1990**, *33*, 527–533.

(29) Inagaki, H.; Fujisawa, T.; Itoh, M.; Hayakawa, M.; Tsuda, T. PCT Int. Appl. WO 125808 A1 20091510.

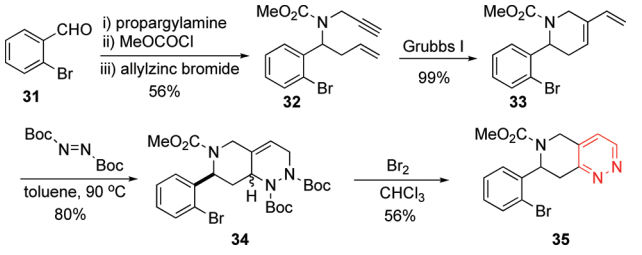
**Scheme 6.** Preparation of Hydrobenzonaphthyridines **29** and **30**




isomerization, followed by a Povarov reaction. Thermal, palladium-catalyzed isomerizations of tetrahydropyridines to enecarbamates are known,[30] but we found that heating **3** in the presence of 10% Pd/C using conventional heating methods gave irreproducible yields of **26**; reaction times were also lengthy. On the other hand, when this reaction was promoted with microwave heating (300 W, 120 °C), **26** was obtained in 77% yield after only 50 min; it is notable that there was no observable loss of halogen under these conditions (Scheme 6). When **26** was allowed to react with ethyl glyoxylate and either *o*-bromoaniline or *p*-chloroaniline in the presence of $Sc(OTf)_3$, the corresponding tetrahydroquinolines **27** and **28** were formed as mixtures of diastereomers in 80% and 73% yield, respectively. Oxidation of **27** and **28** with DDQ gave the corresponding tetrahydrobenzonaphthyridines **29** and **30**, each of which has multiple functional handles for further diversification. Moreover, varying the aniline and aldehyde inputs in the Povarov MCR would further expand the range of possible analogues.

Pyridazines display a wide range of biological activities and have shown promise as 11$\beta$-HSD1 inhibitors for treating type II diabetes[31] and as effective antitumor agents.[32] During the course of our efforts to synthesize novel heterocyclic scaffolds for DOS, we sought to extend our MCAP/RCM approach to access novel fused pyridazine ring systems such as **35**. The synthesis of this scaffold began by preparing the enyne **32** using propargylamine in an MCAP reaction (Scheme 7). A subsequent enyne RCM proceeded in excellent yield to furnish the diene **33**, which underwent a Diels–Alder reaction with di-*tert*-butyl azodicarboxylate to afford cycloadducts **34** as an inseparable mixture of diastereomers. We initially tried to prepare the pyridazine **35** from **34** by the acid-promoted removal of the *N*-Boc protecting groups followed by oxidation using a variety of oxidants. However, all of our efforts were unsuccessful, and the diene **33** was invariably obtained in near quantitative yield, presumably through a retro Diels–Alder pathway involving extrusion of molecular nitrogen. While exploring various alternative routes to generate an aromatic pyridazine ring, we fortuitously discovered that treatment of **34** with bromine provided **35** via an unprecedented tandem sequence of bromination, *N*-Boc deprotection, and aromatization. Pyridazine **35** bears several functional handles for further elaboration and derivatization.

**Scheme 7.** Pyridazine **35** via a Tandem Bromination, Deprotection, Oxidation Sequence




In summary, we have developed a novel strategy for the diversity-oriented synthesis of a variety of heterocyclic scaffolds, many of which embody privileged substructures that are suitably functionalized for further diversification. The key feature of the approach is a multicomponent assembly process followed by a ring-closing metathesis to give substituted tetrahydropyridines. These tetrahydropyridines then serve as pivotal intermediates for the facile generation of numerous functionalized scaffolds of biological relevance. Further applications of this and related approaches to the syntheses of novel compound libraries are in progress, and the results of these investigations will be reported in due course.

**Acknowledgment.** We thank the National Institutes of Health (GM 86192) and the Robert A. Welch Foundation (F-0652) for their generous support of this work. J.Y.S. is grateful for a Pfizer Summer Undergraduate Research Fellowship. We also thank Dr. Vince Lynch (The University of Texas) for performing X-ray analyses.

**Supporting Information Available.** Experimental procedures, spectral data and copies of $^1$H NMR and $^{13}$C NMR spectra for all new compounds, and X-ray data for **11** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

(30) For example, see: Paintner, F. F.; Wanner, K. T. *Tetrahedron* **1994**, *50*, 3113–3122.

(31) Amrein, K.; Hunziker, D.; Kuhn, B.; Mayweg, A. V.; Neidhart, W.; Hoffmann-La Roche Inc.; U.S. Patent US 0010519 (A1), 2007.

(32) Kuroiwa, S.; Odanaka, J.; Maruyama, S.; Sato, Y.; Tomura, A.; Sato, H.; Suzuki, Y. U.S. Patent US 7563893 (B2), 2009.