ORGANIC LETTERS

2011
Vol. 13, No. 17
4542–4545

Multicomponent Assembly Strategies for the Synthesis of Diverse Tetrahydroisoquinoline Scaffolds

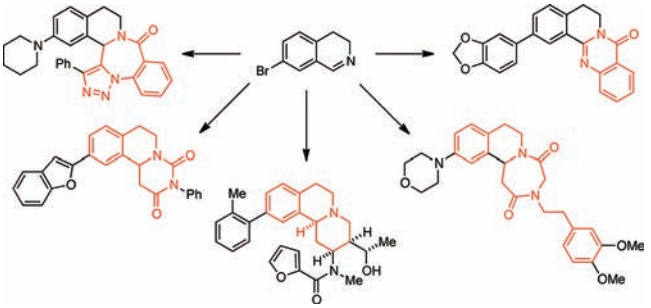
Brett A. Granger, Kyosuke Kaneda, and Stephen F. Martin*

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

sfmartin@mail.utexas.edu

Received June 28, 2011

ABSTRACT



Several novel multicomponent assembly processes have been developed for the rapid and efficient assembly of various heterocyclic scaffolds bearing a tetrahydroisoquinoline core, each of which allows for facile derivatization to access a diverse array of compounds. This work led to the serendipitous discovery of a new method for the synthesis of a fused quinazolone ring system, which was applied to a one-step total synthesis of the quinazolinocarboline alkaloid rutaecarpine.

The identification of potent and selective modulators of biological pathways is a key step in studying fundamental biology and discovering drug leads. Efforts to facilitate access to such compounds have fueled the development of several approaches for the generation of small molecule libraries.[1] Collections of small molecules containing privileged scaffolds, which are skeletal frameworks that bind to multiple receptors and display a wide range of biological activities,[2,3] often exhibit relatively high hit rates in screening assays. Initial hits can then be modified by introducing potency and selectivity enhancing substituents to give derivatives that exhibit favorable physiochemical properties.

We recently reported the design and development of a novel strategy for diversity-oriented synthesis (DOS) that featured a Mannich-type multicomponent assembly process (MCAP), followed by various cyclization reactions that were enabled by selective functional group pairing to construct substituted heterocyclic ring systems.[4–6] This approach has been extended to the synthesis and diversification of compounds based on the benzodiazepine,

(1) (a) Brenner, S.; Lerner, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 5381–5383. (b) Njardarson, J. T.; Gaul, C.; Shan, D.; Huang, X. -Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 1038–1040. (c) Kaiser, M.; Wetzel, S.; Kumar, K.; Waldmann, H. *Cell. Mol. Life Sci.* **2008**, *65*, 1186–1201. (d) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.

(2) 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.

(3) For leading references to privileged substructures, see: (a) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361. (b) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *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.

(4) For the first example of this process, see: Martin, S. F.; Benage, B.; Hunter, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 5925–5927.

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

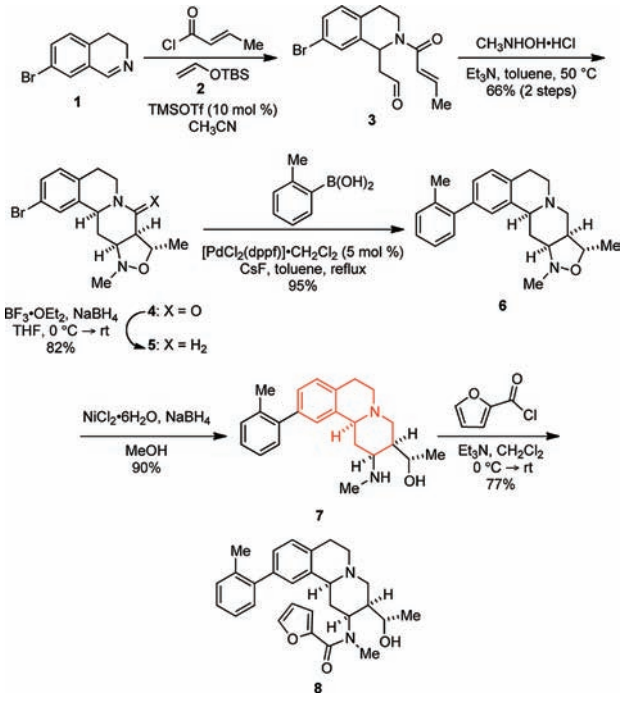
(6) (a) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4223–4226. (b) Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Tetrahedron* **2009**, *65*, 6454–6469.

10.1021/ol201739u
Published on Web 08/11/2011

tetrahydropyridine, and aryl piperidine scaffolds.[7–9] We now report a further expansion of this approach for DOS and the development of several MCAPs that provide ready access to various privileged structures fused to a tetrahydroisoquinoline core, which itself is found in molecules that exhibit a wide array of biological activities, including antihypertensive,[10] antitumor,[11] and antimalarial properties.[12]

We chose the readily available 7-bromodihydroisoquinoline (**1**)[13] as the common input for these MCAPs, because it allows for preparation of various derivatives via cross-coupling reactions with the aryl bromide moiety (Scheme 1). Inasmuch as compounds incorporating the highlighted tricyclic ring system in **7** are known to be potent α_2-adrenoceptor antagonists,[14] we sought to develop an efficient entry to this ring system.

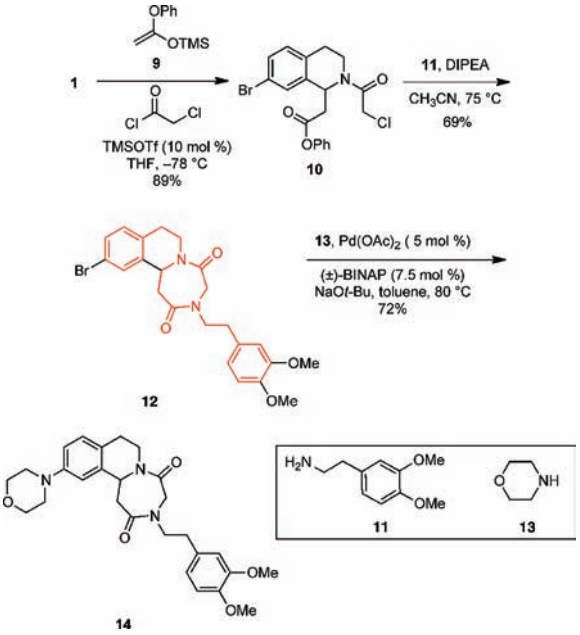
Scheme 1. Synthesis and Diversification of **7**



Accordingly, treatment of **1** with *trans*-crotonyl chloride and silyl enol ether **2** in the presence of a catalytic amount of TMSOTf provided the aldehyde **3**, which upon condensation with *N*-methylhydroxylamine gave an intermediate nitrone that underwent facile 1,3-dipolar cycloaddition to provide isoxazolidine **4** in 66% yield from **1**; no other stereoisomers were isolated. The relative stereochemistry in **4** was unambiguously determined by single crystal X-ray analysis. Notably, **4** is easily prepared on a multigram scale without column chromatography. Subsequent reduction of the lactam moiety in **4**, followed by a Suzuki cross-coupling, provided the biaryl isoxazolidine **6**. Upon treatment with nickel boride, **6** underwent *N,O*-bond cleavage to give the secondary amine **7** in 90% yield.[15] The amino group in **7** is an obvious point for further diversification as illustrated by its reaction with 2-furoyl chloride in the presence of triethylamine to furnish amide **8** in 77% yield.

We also wanted to explore methods for elaborating heterocyclic rings directly onto the parent dihydroisoquinoline **1**, and it occurred to us that appending a 1,4-diazepine-2,5-dione ring might be of considerable use. For example, *N,N'*-diphenethyl-1,4-diazepine-2,5-diones (highlighted portion of **12**) are of interest as inhibitors of the UCB13-UEV enzyme complex and hence may be useful as antitumor agents.[16] Since **12** represents a novel, constrained analog of these systems, we set to the task of preparing such compounds via our MCAP/cyclization strategy. In the event, reaction of **1** with silyl ketene acetal

Scheme 2. Synthesis of 1,4-Diazepine-2,5-diones



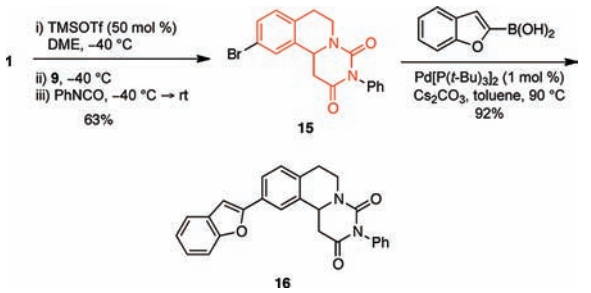
9 and chloroacetyl chloride in the presence of a catalytic amount of TMSOTf at −78 °C provided amide **10** in 89%

(7) Donald, J. R.; Martin, S. F. *Org. Lett.* **2011**, *13*, 852–855.
(8) Sahn, J. J.; Su, J. Y.; Martin, S. F. *Org. Lett.* **2011**, *13*, 2590–2593.
(9) Hardy, S.; Martin, S. F. *Org. Lett.* **2011**, *13*, 3102–3105.
(10) Gavras, I.; Vlahakos, D.; Melby, J. C.; Gavras, H. *J. Clin. Pharm.* **1984**, *24*, 343–350.
(11) Asaoka, T.; Yazawa, K.; Mikami, Y.; Takahashi, K. *J. Antibiot.* **1982**, *35*, 1708–1710.
(12) Francois, G.; Bringmann, G.; Phillipson, J. D.; Boyd, M. R.; Assi, L. A.; Schneider, C.; Timperman, G. U.S. Patent No. 5,639,761, 1994.
(13) (a) Worrall, D. E. *Org. Synth.* **1929**, *9*, 66. (b) Schumacher, R. W.; Davidson, B. S. *Tetrahedron* **1999**, *55*, 935–942. (c) Mjalli, A. M. M.; Gohimmukkula, D. R.; Tyagi, S. U.S. Patent No. 7,208,601, 2005.
(14) VanDyke, J. W., Jr.; Havera, H. J.; Johnson, R. D. *J. Med. Chem.* **1971**, *15*, 91–93.
(15) Jones, A. D.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3337–3344.
(16) Okatsu, T. T.; Sigmund, J. S.; Peypoch, A. M.; Ortiz, A. R.; Pérez De Rozas, G. S.; Masip, I. M.; Fernández, A. M.; Ruiz, D. G.; León, A. M. PCT Int. Appl. WO A1 2008009758, 2008.

yield (Scheme 2). When **10** was heated with primary alkyl amines in the presence of Hünig's base in CH_3CN the corresponding *N*-alkyl 1,4-diazepine-2,5-diones were obtained. For example, reaction of **10** with **11** provided **12** in 69% yield. Buchwald–Hartwig cross-coupling of **12** with morpholine (**13**) gave amine **14** in 72% yield.

The molecular framework embodied in **15** and **16** (6,7-dihydropyrimido[6,1-*a*]isoquinoline-2,4(3*H*,11*bH*)-dione) is present in compounds that exhibit hypotensive and diuretic effects.[17] We were thus intrigued by the possibility that we might exploit an MCAP/cyclization sequence to access this ring system by a route that would be more expedient than those previously reported.[17a,18] Indeed, sequential treatment of **1** with TMSOTf, the silyl ketene acetal **9**, and phenyl isocyanate provided **15** in 63% yield (Scheme 3). Because an isocyanate is implemented as the electrophilic component, this series of reactions represents a significant expansion of our MCAP chemistry to give products containing urea functionality. Preliminary studies using isothiocyanates as electrophilic inputs have not been as successful. Compound **15** was further elaborated via a Suzuki cross-coupling to give the aryl substituted tricyclic scaffold **16** in 92% yield.

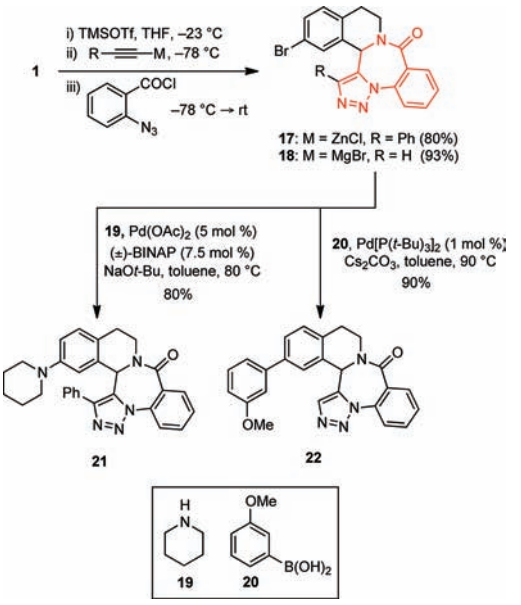
Scheme 3. Synthesis of Dihydropyrimidine-2,4-diones



The 1,5-benzodiazepin-2-one framework is present in many compounds that bind to multiple targets including the interleukin-1β converting enzyme (ICE)[19] and voltage-gated potassium channels.[20] More specifically, the triazolo 1,5-benzodiazepin-2-one scaffold, highlighted in **17** and **18**, is present in compounds reported to inhibit serine protease[21] and to bind to the benzodiazepine receptor.[22]

Toward incorporating this ring system in fused isoquinolines, **1** was first allowed to react with either zinc phenylacetylide or ethynylmagnesium bromide in the presence of TMSOTf (Scheme 4). The intermediate adducts were then trapped with *o*-azidobenzoyl chloride, and upon warming to room temperature, the amide thus produced readily underwent a dipolar cycloaddition to furnish the novel triazolo 1,5-benzodiazepin-2-ones **17** and **18** in 80% and 93% yields, respectively. Subsequent Buchwald–Hartwig or Suzuki cross-coupling reactions generated derivatives **21** and **22**.

Scheme 4. Synthesis of Triazolo 1,5-Benzodiazepin-2-ones



During initial experiments that were directed toward developing the sequence outlined in Scheme 4, we discovered that acylation of dihydroisoquinoline **23** with *o*-azidobenzoyl chloride at room temperature, followed by addition of ethynylmagnesium bromide, did not give the expected amide **26**; the benzaldehyde **24** and the quinazolone **25** were obtained instead (Scheme 5). Although **25** was isolated as a minor product, its formation suggested that we had serendipitously uncovered a new entry to quinazolones, a heterocyclic ring system present in a variety of pharmaceuticals and biologically active natural products.[3a,23]

After some optimization, we found that treatment of **1** with *o*-azidobenzoyl chloride in 1,2-dichloroethane under reflux provided quinazolone **27** in 62% yield (Scheme 6); no aldehyde was observed in the ^{1}H NMR spectrum of the crude reaction mixture. To the best of our knowledge, this represents the first example of an intramolecular cyclization

(17) (a) Kaneko, H.; Nagatsuka, T. Jpn. Kokai Tokkyo Koho JP 45009467, 1971. (b) Lombardino, J. G.; McLaMore, W. M.; Laubach, G. D. U.S. Patent No. 3,021,331, 1962.

(18) Angelov, P. A.; Ivanov, I. I.; Venkov, A. P. *Molecules* **2004**, *9*, 694–704.

(19) Batchelor, M. J.; Bebbington, D.; Bemis, G. W.; Fridman, W. H.; Gillespie, R. J.; Golec, J. M. C.; Gu, Y.; Lauffer, D. J.; Livingston, D. J.; Matharu, S. S.; Mullican, M. D.; Murcko, M. A.; Murdoch, R.; Nyce, P. L.; Robidoux, A. L. C.; Wannamaker, M. W.; Wilson, K. Y.; Zelle, R. E. U.S. Patent No. 6,008,217, 1999.

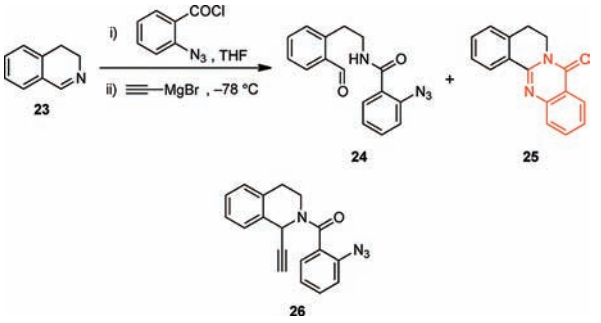
(20) Clareman, D. A.; Liverton, N.; Selnick, G. G.; Smith, G. R. U.S. Patent No. 5,726,171, 1998.

(21) Mohapatra, D. K.; Maity, P. K.; Shabab, M.; Khan, M. I. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5241–5245.

(22) Bertelli, L.; Biagi, G.; Giorgi, I.; Livi, O.; Manera, C.; Scartoni, V.; Martini, C.; Giannaccini, G.; Trincavelli, L.; Barili, P. L. *Farmaco* **1998**, *53*, 305–311.

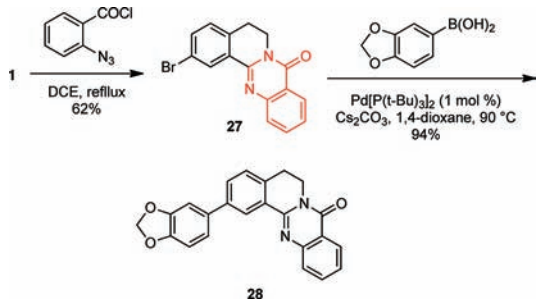
(23) (a) Hughes, A. N.; Rafi, I.; Griffin, M. J.; Calvert, A. H.; Newell, D. R.; Calvete, J. A.; Johnston, A.; Clendeninn, N.; Body, A. V. *Clin. Cancer Res.* **1999**, *5*, 111–118. (b) López-Gresa, M. P.; González, M. C.; Primo, J.; Moya, P.; Romero, V.; Estornell, E. *J. Antibiot.* **2005**, *58*, 416–419.

Scheme 5. Formation of Quinazolone **25** as a Minor Side Product



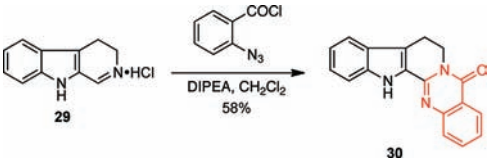
of an organic azide onto a putative *N*-acyliminium ion to form a quinazolone.[24] Subsequent Suzuki cross-coupling of **27** provided the biaryl quinazolone **28** in 94% yield.

Scheme 6. Synthesis of Quinazolones **27** and **28**



In order to showcase the utility of this novel route to quinazolones, we applied it to a one-step synthesis of the quinazolinocarboline alkaloid rutaecarpine (**30**). Rutaecarpine was isolated from the dried, unripe fruit of *Evodia rutaecarpa* and displays various biological activities including being a potent and selective inhibitor of cytochrome P450 in human liver microsomes.[25,26] Simply treating dihydro-β-carboline hydrochloride (**29**)[27] with *o*-azidobenzoyl chloride in the presence of Hünig's base in dichloromethane delivered rutaecarpine (**30**) in 58% yield (Scheme 7).[24a,28]

Scheme 7. Total Synthesis of Rutaecarpine (**30**)



In summary, we have developed several new MCAPs for the rapid synthesis of complex heterocyclic scaffolds in which tetrahydroisoquinolines are fused to 1,4-diazepine-2,5-dione, dihydropyrimidine-2,4-dione, 1,5-benzodiazepin-2-one, and quinazolone rings. These heterocycles bear functionality that may be further exploited in a variety of cross-coupling reactions to generate small compound libraries for submission to the NIH Molecular Libraries Small Molecule Repository (MLSMR). An important feature of this approach to DOS is that the members of these libraries typically have clog *P* values in the approximate range of 3.0−4.5; these compounds thus have excellent promise as potential leads. We also discovered a novel method to form fused quinazolone rings and have applied this discovery to a one-step synthesis of the quinazolinocarboline alkaloid rutaecarpine. Significantly, these novel reaction sequences can be applied to other imines, including those that are generated *in situ* by four-component assembly processes we have previously reported.[6−9] Further applications of this and related approaches to the syntheses of unique 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 24539 and 86192) and the Robert A. Welch Foundation (F-0652) for their generous support of this work. We also thank Dr. Vincent Lynch (The University of Texas at Austin) for performing X-ray crystallography.

Supporting Information Available. Experimental procedures, spectral data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and the CIF file for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

(24) For other methods of preparation, see: (a) Eguchi, S.; Takeuchi, H.; Matsushita, Y. *Heterocycles* **1992**, *33*, 153–156. (b) Wagner, E. C. *J. Org. Chem.* **1940**, *5*, 133–141. (c) Grout, R. J.; Partridge, M. W. *J. Chem. Soc.* **1960**, 3551–3557.

(25) Asahina, Y.; Kashiwaki, K. *J. Pharm. Soc. Jpn.* **1915**, 1293.

(26) Ueng, Y.-F.; Jan, W.-C.; Lin, L.-C.; Chen, T.-L.; Guengerich, F. P.; Chen, C.-F. *Drug. Met. Disp.* **2002**, *30*, 349–353.

(27) Späth, E.; Lederer, E. *Ber. Dtsch. Chem. Ges.* **1930**, *63*, 2102–2111.

(28) For selected synthesis of rutaecarpine, see: (a) Asahina, Y.; Manske, R. H. F.; Robinson, R. *J. Chem. Soc.* **1927**, 1708–1710. (b) Kametani, T.; Higa, T.; Von Loc, C.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 6186–6188. (c) Bergman, T.; Bergman, S. *J. Org. Chem.* **1985**, *50*, 1246–1255. (d) Zhang, C.; Kanta De, C.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416–417. (e) Kamal, A.; Reddy, M. K.; Reddy, T. S.; Santos, L. S.; Shankaraiah, N. *Synlett* **2011**, *1*, 61–64.