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Syntheses of Stereochemically Diverse Nine-Membered Ring-Containing Biaryls

Shyam Krishnan and Stuart L. Schreiber*

Department of Chemistry and Chemical Biology, Howard Hughes Medical Institute, Harvard University, and the Broad Institute of Harvard and MIT, Cambridge, Massachusetts 02138

stuart_schreiber@harvard.edu

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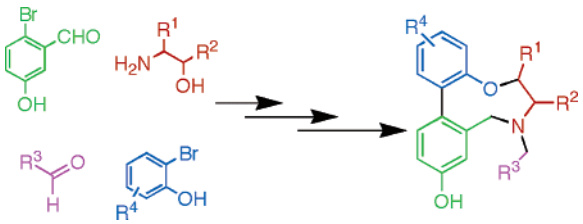
ABSTRACT

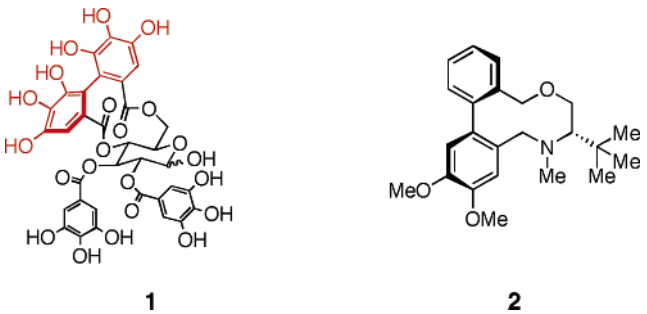


A library of nine-membered, biaryl-containing rings has been synthesized in parallel on polystyrene macrobeads. Dimeric medium rings were shown to be accessible via a regio- and stereoselective double cyclization.

Small molecules and small-molecule screening can illuminate cell circuitry and disease biology.[1] A promising approach to the creation of effective small-molecule modulators involves the use of diversity-oriented synthesis (DOS).[2] Here we report the generation of stereochemically diverse small molecules using DOS.

We were stimulated by the stereochemically complex ellagitannin family of natural products, a representative member of which is tellimagrandin I (**1**) (Figure 1). The rigidity of these compounds is due to the presence of an axially dissymmetric biaryl moiety implanted in a medium ring. The structural preorganization induced by biaryl bond formation may enhance the potential for selective recognition of protein targets, as suggested by the cellular activity displayed by ellagitannins.[3] This line of reasoning was supported by stereoselective copper-mediated syntheses of "ellagitannin-like" biaryl medium rings by adaptation of a protocol published by Lipshutz and co-workers[4a] and subsequent discovery of several biologically active small molecules using chemical genetic assays. An example is **2**, a modulator of zebrafish cardiovascular development.[4b,c]

Our earlier studies resulted in the split-pool synthesis of a library of (mostly) 10-membered ring-containing compounds. With the goal of increasing the rigidity of the resultant small molecules while maintaining the axially dissymmetric nature of the biaryl moiety, we embarked on the synthesis of a library of nine-membered rings. We



1 **2**

Figure 1. Natural (**1**, tellimagrandin I) and nonnatural (**2**, modulator of zebrafish cardiovascular development) biaryl-containing medium-ring compounds.

(1) Schreiber, S. L. *Chem. Eng. News* **2003**, *81*, 51−61. See also http://www-schreiber.chem.harvard.edu.
(2) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964−1968. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.
(3) Quideau, S.; Feldman, K. S. *Chem. Rev.* **1996**, *96*, 475−503.

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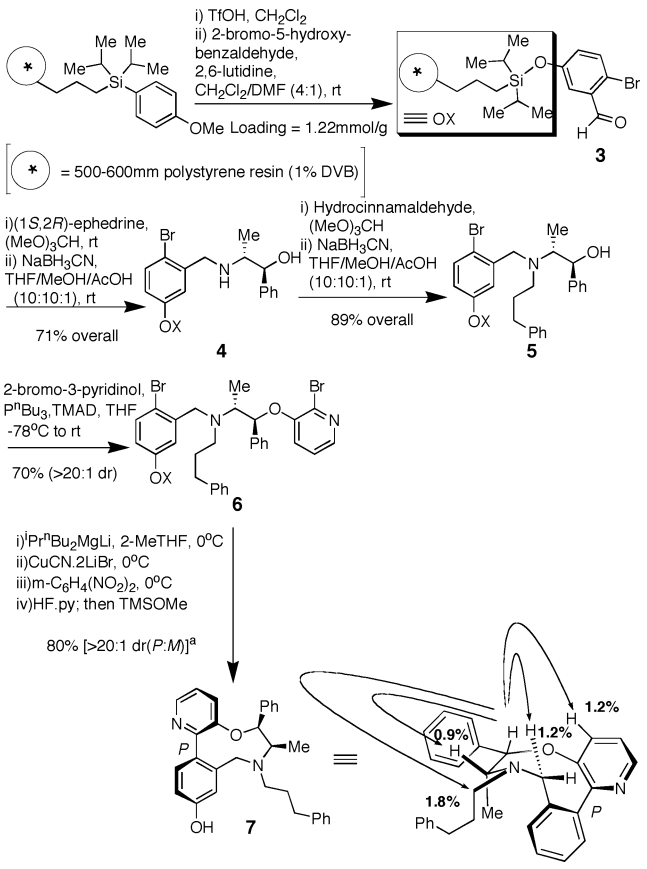
Scheme 1. Synthesis of Nine-Membered Biaryl Rings on Solid Phase



[a] NOEs indicated by arrows.

decided to use parallel solid-phase synthesis with the aim of generating 1−5 mg of each library member.

Our synthetic plan is depicted in Scheme 1. Polystyrene macrobeads functionalized with a silyl linker[5] were loaded with 2-bromo-5-hydroxybenzaldehyde via an intermediate silyl triflate. The polymer-supported aldehyde **3** was soaked in a solution of excess amino alcohol in trimethylorthoformate to form a Schiff base that was reduced using $NaBH_3CN$ in acidic solution to form the amino alcohol **4** (>90% purity by NMR and HPLC). The reductive alkylation of **4** was achieved by initial formation of an oxazolidine with a solution of excess hydrocinnamaldehyde in trimethylorthoformate; the resulting oxazolidine was reduced with $NaBH_3CN$ in acidic solution to form the amino alcohol **5** (>90% purity by NMR and HPLC). Amino alcohol **5** was transformed to the cyclization precursor **6** under Mitsunobu conditions. Reaction of **5** with 2-bromo-3-pyridinol in the presence of tri-*n*-butylphosphine and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD)[6] resulted in complete conversion to **6**. The stereochemistry of **6** resulted from retention of configuration at the center bearing the benzylic hydroxyl, presumably due to the involvement of an aziridinium ion intermediate[7] formed by anchimeric assistance from the tertiary amine β to the reacting center. Cyclization to the medium ring **7** was achieved by (i) magnesium−bromine exchange using *i*-$PrBu_2MgLi$,[8] (ii) magnesium to copper transmetalation using a solution of CuCN·2LiBr, and (iii) oxidation of the resulting cuprate with a solution of 1,3-dinitrobenzene. The greater rigidity of the nine-membered ring framework relative to a 10-membered ring results in **7** exhibiting configurational stability about the biaryl axis even though one of the ortho substituents on the biaryl nucleus is a pyridine nitrogen.[9] The relative stereochemistry of **7** was confirmed by NOE analysis and characteristic coupling constants[10] observed for protons on the amino alcohol backbone.

With the aim of deriving the diversity of the biaryl medium rings from readily available amino alcohols, aldehydes and 2-bromophenols, we selected building blocks individually on the basis of the success of their incorporation (>80% purity by NMR and LC-MS) with a chosen substrate under generalized reaction conditions. Figure 2 illustrates all the building blocks selected for use in a parallel library synthesis.[11] Amino alcohols with primary as well as secondary amines[12] (building blocks **B1**−**13**) could be used but were restricted to those that could undergo regioselective displacement with bromophenols in the subsequent Mitsunobu reaction. Several aliphatic aldehydes were suitable building blocks for the reductive alkylation of polymer-supported secondary amines (**C1**−**6**). Aromatic aldehydes were not used at this stage due to the reduced rate of the subsequent Mitsunobu reaction, a feature observed even in substrates in solution phase. This is presumably due to the increased steric hindrance around the carbinol carbon. While we tested a number of bromophenols for the Mitsunobu reaction, we chose building blocks **D1** and **D2** for incorporation in a library synthesis.

In the reductive alkylation of secondary amines, it was found that building block **B6** was not compatible with **C3**, **C4**, and **C5**.[13] The tertiary amine derived from building block **B9** underwent Mitsunobu displacement with phenols **D1** and

(4) (a) (i) Lipshutz, B. H.; Kayser, F.; Liu, Z.-P. *Angew. Chem., Int. Ed.* **1994**, *33*, 1842−1844. (ii) Lipshutz, B. H.; Kayser, F.; Maullin, N. *Tetrahedron Lett.* **1994**, *35*, 815−818. (iii) Lipshutz, B. H.; Liu, Z.-P.; Kayser, F. *Tetrahedron Lett.* **1994**, *35*, 5567−5570. (b) Spring, D. R.; Krishnan, S.; Schreiber S. L. *J. Am. Chem. Soc.* **2000**, *122*, 5656−5657. (c) Spring, D. R.; Krishnan, S.; Blackwell, H. E.; Schreiber S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1354−1363.

(5) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Schreiber, S. L.; Foley, M. A. *J. Comb. Chem.* **2001**, *3*, 312−318.

(6) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Ito, S. *Chem. Lett.* **1994**, *3*, 539−542.

(7) For Mitsunobu reactions proceeding via aziridinium ion intermediates, see: (a) Freedman, J.; Vaal, M. J.; Huber, E. W. *J. Org. Chem.* **1991**, *56*, 670−672. (b) Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585−4586. (c) Poelert, M. A.; Hulshof, L. A.; Kellogg, R. M. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 355−364.

(8) Kitagawa. K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481−2483. (b) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333−4339.

(9) 10-Membered rings with nitrogen and sulfur as ortho substituents show no evidence of restricted rotation around the biaryl bond.

(10) See Supporting Information.

(11) A complete list of building blocks tested for each step is included in the Supporting Information.

(12) Reductive aminations of secondary amines could be carried out with a modification of the procedure for primary amines, by initial formation of an oxazolidine, followed by reduction.

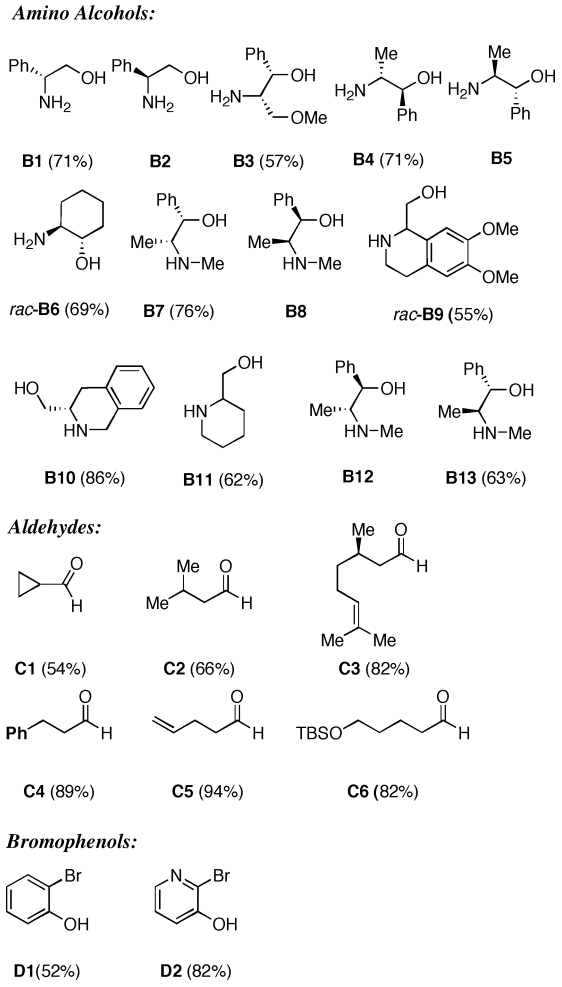


Figure 2. Building blocks used for the biaryl medium-ring library with yields in parentheses.

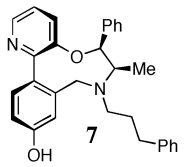
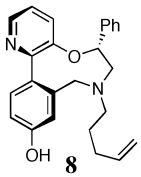
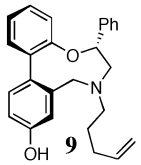
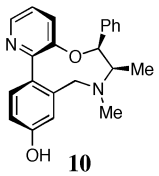
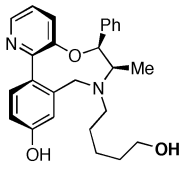
D2 to low conversion. These building blocks were not carried further for subsequent transformations in the library synthesis.

Representative examples of medium-ring-forming cyclizations on solid support are illustrated in Table 1.

202 compounds (biaryl medium rings and their intermediates) were synthesized in parallel on solid phase. Of the 202 compounds, 104 out of 124 intermediates were estimated to be >80% pure by LC-MS and ^{1}H NMR. Out of 78 cyclization reactions,[14] 57 resulted in products of >70% purity, while 16 resulted in products that were >50% pure. The library members were cleaved from the solid support purified by preparative HPLC and formatted into 5 mM stock solutions in DMSO for chemical genetic assays, as well as 1 mM stock solutions in DMF prepared for protein-binding assays using small-molecule microarrays.[15]

(13) (a) *rac*-B6 was not combined with enantiopure C3 in order to avoid producing an equimolar mixture of diastereomers. (b) Reaction of the polymer-supported secondary amine derived from *rac*-B6 with building blocks C4 and C5 resulted in the incorporation of a second molar equivalent of the aldehyde, presumably via an initially formed enamine. The difficulty of forming bicyclic oxazolidines from *trans*-2-aminocyclohexanol derivatives has been documented. See: Rona, M.; Ben-Ishai, D. *J. Org. Chem.* **1961**, *26*, 1446−1450.

Table 1. Medium-Ring-Forming Cyclizations on Solid Phase

entry	medium ring	% yield	dr (*P*:*M*)
1	 **7**	80	>20:1
2	 **8**	91	1:>20
3	 **9**	76	>20:1
4	 **10**	58	>20:1
5	 **11**	69	>20:1

Promoting protein−protein interactions as a means of regulating cellular processes can be achieved by using hybrid small molecules capable of inducing protein association.[16] We therefore investigated the formation of dimeric biaryl-containing medium rings in solution (Scheme 2).

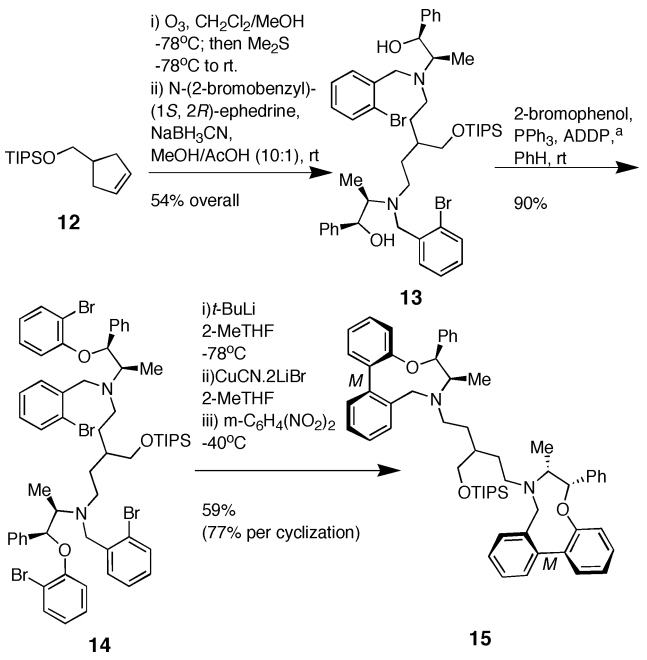
The triisopropylsilyl ether of 3-cyclopentenemethanol (**12**)[17] was subjected to ozonolysis and subsequent double reductive amination with *N*-(2-bromobenzyl)-(1*S*,2*R*)-norephe-

(14) Diastereoselectivities for all cyclization reactions were not determined. We earlier observed poor diastereoselection in nine-membered ring products derived from (*S*)-phenylalaninol and (*S*)-leucinol. In contrast, we observed good to excellent diastereoselection in medium-ring products bearing a phenyl substituent at C-1 of the 1,2-amino alcohol fragment (with the presence or absence of a cis-oriented methyl group at C-2) and with a substrate derived from *trans*-2-aminocyclohexanol. These results suggest a greater role for a substituent at C-1 than a substituent at C-2 of the 1,2-amino alcohol in influencing the atropdiastereoselection of the resulting nine-membered ring products.

(15) Barnes-Seeman, D.; Park, S. B.; Koehler, A. N.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 2376−2379.

(16) (a) Klemm, J. D.; Schreiber, S. L.; Crabtree, G. R. *Annu. Rev. Immunol.* **1998**, *16*, 569−592. (b) Diver, S. T.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 5106−5109.

Scheme 2. Synthesis of Dimeric Nine-Membered Biaryl Medium Rings in Solution



[a] ADDP = 1,1′-azodicarbonyldipiperidine.

drine to form dimeric amino alcohol (**13**). Further double Mitsunobu reaction with 2-bromophenol yielded cyclization precursor (**14**). Gratifyingly, lithium−bromine exchange followed by lithium to copper transmetalation and cuprate oxidation delivered *pseudo*-C_2-symmetric biaryl dimer (**15**) in high diastereoselection (>20:1 *M*,*M*:*P*,*P*) as the only doubly cyclized product.[18]

In conclusion, we have synthesized a library of nine-membered ring, biaryl-containing compounds in parallel on solid phase. We have also demonstrated the feasibility of performing a double cyclization yielding a bis(macrocycle) in solution phase. Small-molecule screening of the library members is now underway.

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Supporting Information Available: Representative experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048273C

(17) Prepared by silylation of the corresponding alcohol, which was prepared as in: Olah, G. A.; Surya Prakash, G. K.; Arvanaghi M.; Anet, F. A. L. *J. Am. Chem. Soc.* **1982**, *104*, 7105−7108.

(18) Traces of a product of single cyclization were observed (<5%) in the ^{1}H NMR and LC-MS analyses of crude reaction mixture.