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Stereochemical and Skeletal Diversity Employing Pipecolate Ester Scaffolds

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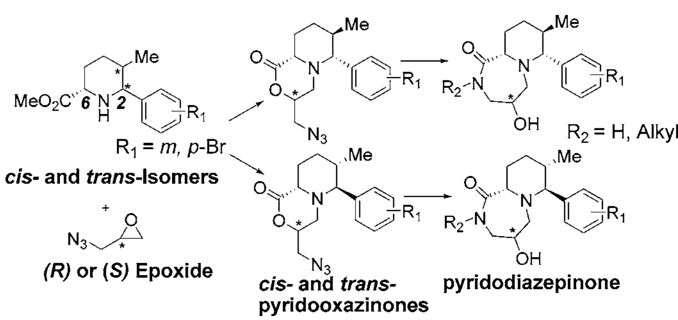
ABSTRACT



The stereocontrolled synthesis of pyridooxazinones by Mg(OTf)$_2$-promoted epoxide ring-opening with use of chiral pipecolates as nucleophiles is described. Pyridooxazinone products derived from azido-epoxides can be further rearranged to seven-membered pyridodiazepinones by azide reduction. The sequence of functional group interconversions generates diversity through topological and stereochemical variation.

The development of reaction methodology that allows rapid access to structurally and stereochemically diverse frameworks and scaffolds plays an important role in diversity-oriented synthesis (DOS).[1] Accordingly, methodology to access new chemotypes in a stereocontrolled manner would be a useful contribution to this area.[2] Bicyclic alkaloids such as quinolizidines and indolizidines incorporating a nitrogen at the ring junction have a rich and diverse history as pharmacological agents, and present an opportunity to create DOS strategies loosely based on the natural product scaffolds.[3]

This Letter describes the assembly of stereochemically and topologically diverse six- and seven-membered pyridooxazinones and pyridodiazepinones, respectively. The work also illustrates the use of our amino-functionalized silane reagents[4a] in the context of DOS. The approach makes efficient use of our annulation strategy that provides enantioenriched pipecolates **3** and **6** as stereochemically diverse building blocks.[4] An epoxide opening, lactonization, and ring expansion sequence highlight a series of functional group interconver-

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(2) (a) Wipf, P.; Stephenson, C. R. J.; Walczak, M. A. A. *Org. Lett.* **2004**, *6*, 3009−3012. (b) Gan, Z.; Reddy, P. T.; Quevillon, S.; Couve-Bonnaire, S.; Arya, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1366−1368. (c) Kesavan, S.; Su, Q.; Shao, J.; Porco, J. A., Jr.; Panek, J. S. *Org. Lett.*, **2005**, *7*, 4435−4438. (d) Beeler, A. B.; Acquilano, D. E.; Su, Q.; Yan, F.; Roth, B. L.; Panek, J. S.; Porco, J. A., Jr. *J. Comb. Chem.* **2005**, *7*, 673−681. (e) Adriaenssens, L. V.; Austin, C. A.; Gibson, M.; Smith, D.; Hartley, R. C. *Eur. J. Org. Chem.* **2006**, *22*, 4998−5001. (f) Dandapani, S.; Lan, P.; Beeler, A. B.; Beischel, S.; Abbas, A.; Roth, B. L.; Porco, J. A., Jr.; Panek, J. S. *J. Org. Chem.* **2006**, *71*, 8934−8945. (g) Fitzmaurice, R. J.; Etheridge, Z. C.; Jumel, E.; Woolfson, D. N.; Caddick, S. *Chem. Commun.* **2006**, *46*, 4814−4816. (h) Freifeld, L.; Holtz, E.; Dahmann, G.; Langer, P. *Eur. J. Org. Chem.* **2006**, *14*, 3251−3258. (i) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413−1419. (j) Franz, A. K.; Dreyfuss, P. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1020−1021.

(3) (a) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F. *J. Nat. Prod.* **1993**, *56*, 1016−1038. (b) Fantauzzi, P. P.; Yager, K. M. *Tetrahedron Lett.* **1998**, *39*, 1291−1294. (c) Jiang, W.; Alford, V. C.; Qiu, Y.; Bhattacharjee, S.; John, T. M.; Haynes-Johnson, D.; Kraft, P. J.; Lundeen, S. G.; Sui, Z. *Bioorg. Med. Chem.* **2004**, *12*, 1505−1515. (d) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556−1575.

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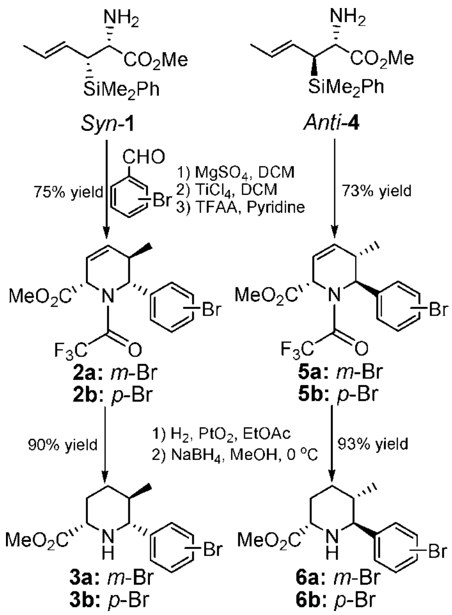
sions developed to access the target pyridooxazinone and pyridodiazepinone ring systems.

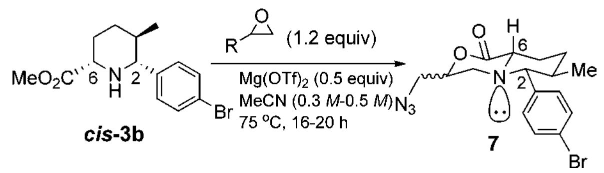
The pipecolate scaffolds were constructed by using [4+2]-annulation of aminosilanes *syn*-**1** and *anti*-**4** with *m*- or *p*-bromobenzaldehyde providing both 2,6-*cis*- and 2,6-*trans*-tetrahydropyridines **2** and **5** (Scheme 1).[4a] Diversification is established through variation in stereochemistry as well as positional variation of the aryl bromide. To avoid epimerization of the C6 stereocenter,[5] annulation products **2** and **5** (bearing a vinyl glycine-like moiety) were protected as trifluoroacetamides before hydrogenation of the tetrahydropyridine ring. Removal of the acetamide afforded the free secondary amines 2,6-*cis*-**3** and 2,6-*trans*-**6**.[4a]

Scheme 1. Preparation of Building Blocks



Initial experiments concerning epoxide ring-opening were carried out with 2,6-*cis*-pipecolate **3b** in an effort to prepare pyridooxazinone **7**.[6,7] Following literature precedent, a number of different Lewis acid[8] catalysts were evaluated for the ring-opening of both racemic and enantioenriched epoxides including 2-azidomethyl oxirane.[9] Best results were obtained by using a catalytic amount of $Mg(OTf)_2$ with pipecolate ester **3b** and epoxide (1.2 equiv) to provide the 2,6-*cis*-pyridooxazinone **7** in 16−20 h in good to excellent yields (Table 1). To our knowledge, the use of $Mg(OTf)_2$ to promote epoxide-ring opening has not been reported.[10]

Table 1. $Mg(OTf)_2$-Catalyzed Epoxide Ring-Opening of *cis*-Pipecolates

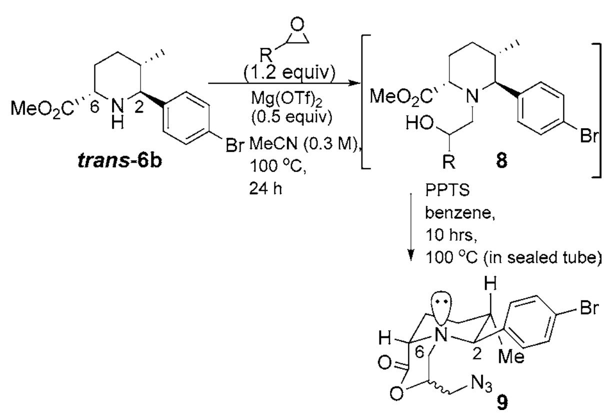


entry	R	isolate yield^a
1	(R)-N_3-CH_2−	**7a**, 90%
2	(S)-N_3-CH_2−	**7b**, 92%

^{a} Isolated yield after purification by SiO_2 chromatography.

These conditions were then applied to 2,6-*trans*-**6b** with mixed results; in comparison to reactions of 2,6-*cis*-pipecolates, longer reaction time was required to achieve full conversion for epoxide opening. Furthermore, cyclization was not observed and only hydroxy-ester **8** was obtained illustrating a stereochemical dependency on the lactone formation step (Table 2). The acyclic intermediate **8** was isolated and cyclized with PPTS[11] (6 mol %) at 100 °C for 10 h to give 2,6-*trans*-pyridooxazinone **9** as the major product with less than 5% of the C6 epimer as determined by ^{1}H NMR analysis of the crude reaction mixture. The lower reactivity observed

Table 2. $Mg(OTf)_2$-Catalyzed Epoxide Ring-Opening of *trans*-Pipecolates



entry	R	isolate yield^a
1	(S)-N_3-CH_2−	**9a**, 80%
2	(R)-N_3-CH_2−	**9b**, 73%

^{a} Isolated yield after purification by SiO_2 chromatography.

(4) (a) Huang, H.; Spande, T. F.; Panek, J. S. *J. Am. Chem. Soc.* **2003**, *125*, 626−627. (b) See ref 2f.

(5) (a) Agami, C.; Couty, F.; Daran, J.; Prince, B.; Puchot, C. *Tetrahedron Lett.* **1990**, *31*, 2889−2892. (b) Berkowitz, D. B.; McFadden, J. M.; Chisowa, E.; Semerad, C. L. *J. Am. Chem. Soc.* **2000**, *122*, 11031−11032.

(6) Representative literature on similar bicyclic lactones: (a) Kim, Y. B.; Choi, E. H.; Keum, G.; Kang, S. B.; Lee, D. H.; Koh, H. Y.; Kim, Y. *Org. Lett.* **2001**, *3*, 4149−4152. (b) Agami, C.; Comesse, S.; Kadouri-Puchot, C. *J. Org. Chem.* **2002**, *67*, 2424−2428. (c) Pave, G.; Leger, J.-M.; Jarry, C.; Viaud-Massuard, M.-C.; Guillaumet, G. *J. Org. Chem.* **2003**, *68*, 1401−1408.

(7) For epoxide opening of amino esters: (a) Lee, S.; Yi, K. Y.; Kim, S.-K.; Suh, J.; Kim, N. J.; Yoo, S.-E.; Lee, B. H.; Seo, H. W.; Kim, S.-O.; Lim, H. *Eur. J. Med. Chem.* **2003**, *38*, 459−471. (b) Babic, A.; Sova, M.; Gobec, S.; Pecar, S. *Tetrahedron Lett.* **2006**, *47*, 1733−1735.

(8) (a) For activity and selectivity classification of Lewis acids, see: Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Eur. J.* **2000**, *19*, 3491−3494.

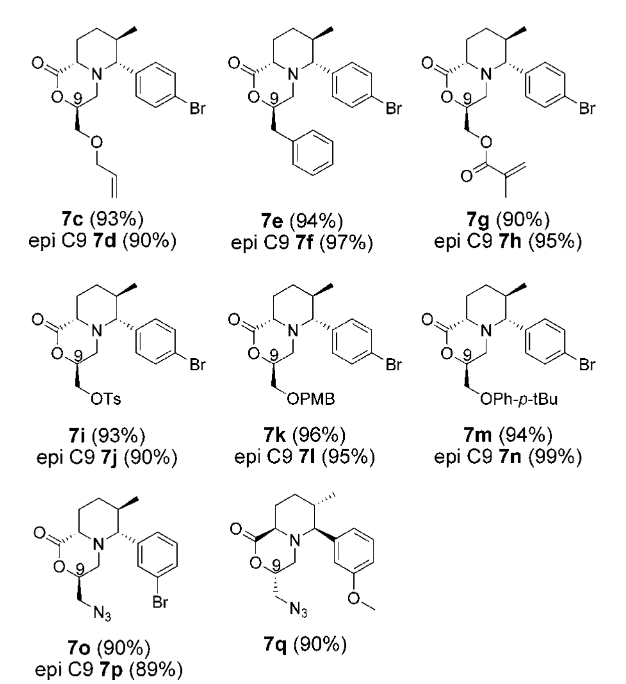


Figure 1. Pyridooxazinones from *cis*-pipecolates. Isolated yields after purification by SiO_2 chromatography are given.

in the conversion of **8** to **9** may be a result of destablizing 1,3-diaxial interactions during the formation of the tetrahedral intermediate leading to pyridooxazinone **9**. Using this strategy, we have created a small array of 2,6-*cis*- and 2,6-*trans*-pyridooxazinones depicted in Figures 1 and 2, respectively.

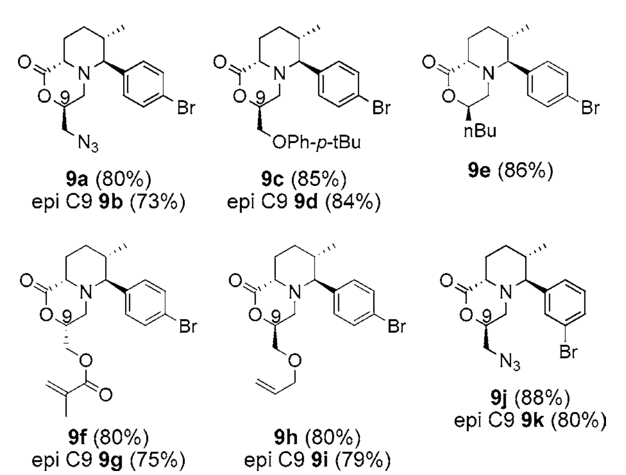
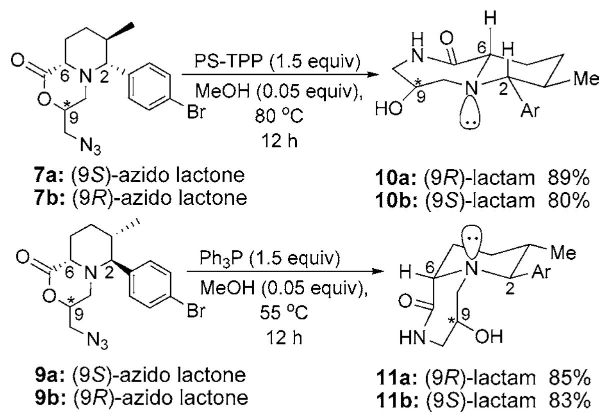


Figure 2. Pyridooxazinones from *trans*-pipecolates. Isolated yields after purification by SiO_2 chromatography are given.

Making use of a range of chiral epoxides, both 2,6-*cis*- and 2,6-*trans*-tetrahydropyridine afforded the desired pyridooxazinones **7c**−**p** (Figure 1) and **9c**−**k** (Figure 2) in good to excellent yield.

Having succeeded in developing conditions to obtain pyridooxazinones via $Mg(OTf)_2$-catalyzed epoxide ring opening with 2,6-*cis*- and 2,6-*trans*-methyl pipecolates, we next focused on the lactone-to-lactam ring expansion via azide reduction (Scheme 2).[12] Conversion of pyridooxazinones to the ring-expanded pyridodiazepinones was achieved by using the venerable Staudinger reaction.[13] Accordingly, treatment of (*S*)-azido 2,6-*cis*-pyridooxazinone **7a** with PS-TPP (polystyryl triphenylphosphine)[14] in methanol at 80 °C (sealed tube, 12 h) provided the ring expansion product 2,6-*cis*-pyridodiazepinone **10a** in one pot via the intermediate lactone amine.[15,16] At temperatures exceeding 60 °C, 2,6-*trans*-**9a** and 2,6-*trans*-**9b** epimerized at C6 to afford enantiomers of 2,6-*cis*-**10b** and 2,6-*cis*-**10a**. We have not established whether epimerization occurs during lactone or lactam formation. In contrast to PS-TPP, use of Ph_3P (1.5 equiv) in the solution phase allowed complete conversion to **11a** and **11b** without epimerization at temperatures below 60 °C. The sequences in Table 1 and Scheme 2 illustrate how subtle changes in the stereochemistry of the pipecolate ester building block provide the basis for variation of

Scheme 2. Pyridodiazepinone Formation via Ring Expansion of Aza-Pyridooxazinones[a]



[a]Isolated yields after purification by SiO_2 chromatography are given.

(9) For the synthesis of enantioenriched 2-azidomethyloxirane, see: Spelberg, J. H. L.; Tang, L.; Kellogg, R. M.; Janssen, D. B. *Tetrahedron: Asymmetry* **2004**, *15*, 1095−1102.

(10) Other less effective Lewis acids surveyed for epoxide ring opening include: $Yb(OTf)_3$, Yb(O-*i*Pr)$_3$, $Sc(OTf)_3$, $LiClO_4$, $ZrCl_4$, Zr(O-*i*Pr)$_4$, Mg-$(ClO_4)_2$, (*R*,*R*)-Co(Salen), $B(C_6F_5)_3$, $LiNTf_2$, NaH, $[Rh(CO)_2Cl]_2$, SmI_2-$(THF)_2$, Aliquat R336, Sm(O-*i*Pr)$_3$, La(O-*i*Pr)$_3$, $Bi(OTf)_3 \cdot nH_2O$, NaOMe, NaI, $ZnCl_2$.

(11) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772−3774.

(12) (a) Nyffeler, P. T.; Liang, C.; Koeller, K. M.; Wong, C. *J. Am. Chem. Soc.* **2002**, *124*, 10773−10778. (b) Pal, B.; Jaisankar, P.; Giri, V. S. *Synth. Commun.* **2004**, *34*, 1317−1323.

(13) (a) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635−644. (b) Staudinger, H.; Hauser, E. *Helv. Chim. Acta* **1921**, *4*, 861−868.

(14) Tunoori, A. R.; Dutta, D.; Georg, G. I. T. *Tetrahedron Lett.* **1998**, *39*, 8751−8754.

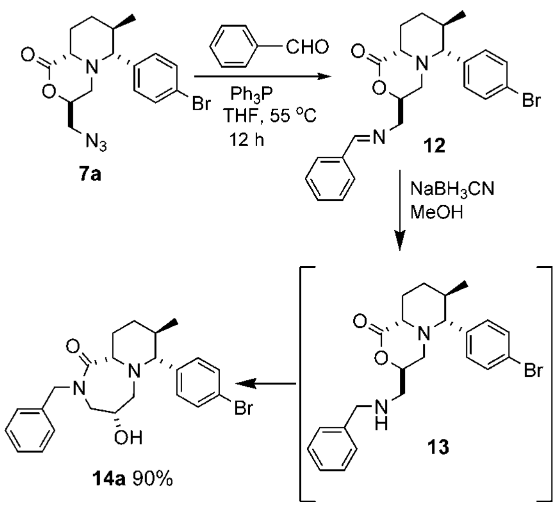
(15) Azido lactones **7a** and **7b** were initially obtained from the reaction of (*R*)- and (*S*)-tosyl lactones with use of sodium azide. However, use of (*R*)- and (*S*)-2-azidomethyloxirane in ring openings provided both *cis* and *trans* lactones **7** and **9** in excellent yields.

(16) (a) Zhang, W.; Mayer, J. P.; Hall, S. E.; Weigel, J. A. *J. Comb. Chem.* **2001**, *3*, 255−256. (b) Charette, A. B.; Boezio, A. A.; Janes, M. K. *Org. Lett.* **2000**, *24*, 3777−3779.

topology (*trans* and *cis* ring fusion) of pyridooxazinones **7** and **9** and pyridodiazepinones **10** and **11**.

The efficiency of the ring expansion prompted us to investigate a one-pot synthesis of *N*-substituted pyridodiazepinones via Staudinger[13a] reaction promoted with triphenylphosphine with the intent of expanding scaffold diversity. Unfortunately, a one-pot approach to *N*-substituted pyridodiazepinones was unsuccessful with use of the conditions optimized for pyridodiazepinones **10** and **11**. The desired *N*-substituted pyridodiazepinones were not observed during attempted one-pot addition of $NaBH_4$ or $NaBH_3CN$ in MeOH to a THF solution of the crude imine **12**. However, the *N*-substituted pyridodiazepinone **14** could be prepared by using a two-step process that included isolation of the intermediate imine **12** and treatment with $NaBH_3CN$ in MeOH at rt to give **14** in 90% yield (Scheme 3).

Scheme 3. *N*-Substituted Pyridodiazepinone Formation



Finally, a collection of pyridodiazepinones **14**−**22** bearing substitution of the lactam nitrogen was prepared. This series of scaffolds is shown in Figure 3, illustrating the versatility of the overall functional group interconversion sequence.

In conclusion, a reaction sequence employing $Mg(OTf)_2$-catalyzed epoxide opening with 2,6-*cis*- and 2,6-*trans*-methyl pipecolates, followed by lactone formation, has been developed to prepare functionalized pyridooxazinones. Azide reduction enabled ring expansion to seven-membered pyridodiazepinones. Further diversification was achieved by converting the intermediate aza-pyridooxazinones to secondary amines prior to pyridodiazepinone formation.[17] Further

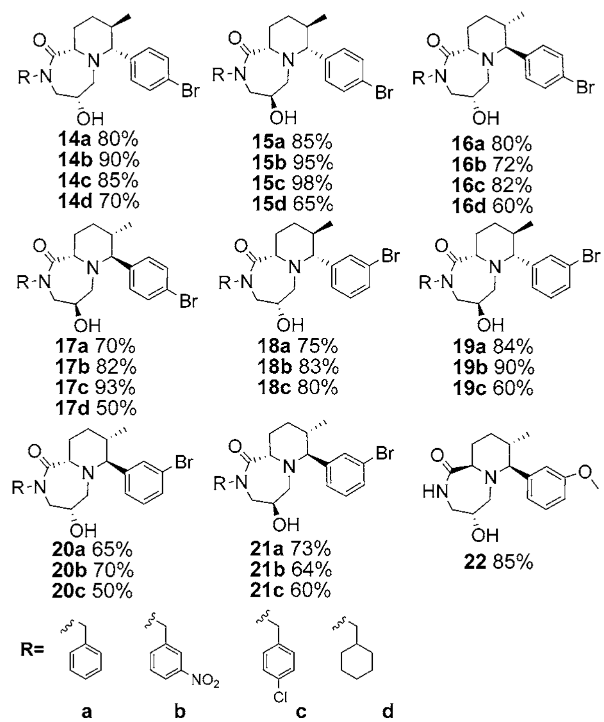


Figure 3. *N*-Substituted pyridodiazepinone scaffolds. Isolated yields after purification by SiO_2 chromatography are given.

studies concerning use of the pipecolate esters in library synthesis as well as biological evaluation of the pyridooxazinone/pyridodiazepinone scaffolds are in progress and will be reported in due course.

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

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(17) The ultility of the arylbromide functionality in building blocks **3** and **6** has been established earlier on our studies of diketopiperazines; see ref 1f.