1,2,3,4-Tetrahydro-1,5-naphthyridines and related heterocyclic scaffolds: exploration of suitable chemistry for library development

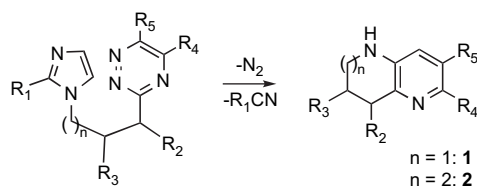Grace H. C. Woo, Aaron B. Beeler and John K. Snyder*

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Abstract—The chemistry of 1,2,3,4-tetrahydro-1,5-naphthyridines and 2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepines has been explored with the goal of discovering reactions at N1 suitable for library development. Epoxide openings, Pd-catalyzed N-arylations, DEPBT-promoted acylations, and urea formation through the reaction with isocyanates were all successful. The epoxide opening chemistry using homochiral epichlorohydrin followed by epoxide reclosure and a second nucleophilic opening led to the preparation of a small 24-membered library.
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1. Introduction

Recently we reported the details of a new procedure for the efficient synthesis of 1,2,3,4-tetrahydro-1,5-naphthyridines **1** and 2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepines **2** using an intramolecular inverse electron demand Diels–Alder reaction between an imidazole dienophile and a 1,2,4-triazine linked from the imidazole N1 position to the triazinyl C3 with a tri- or tetramethylene tether, respectively (Scheme 1).[1] Using this chemistry, a series of heterocycles were prepared, which demonstrated variation in ring size in the saturated ring as well as substitution diversity in both the saturated and pyridine rings (Chart 1). As small nitrogen heterocycles with variable substitution in the aromatized pyridine ring, this series presents an ideal 'drug-like' structure type for library development in the search for new biologically active compounds. Thus, the next goal was to examine the chemistry of the N1 position to determine the suitability of these scaffolds for library synthesis. There were no previous

reports in the literature addressing this issue of reactivity for these heterocycles. Thus, the degree of nucleophilicity of this nitrogen, how this nucleophilicity would be affected by pyridine ring substitution, and which reactions could be exploited for library synthesis were uncertain. We herein report the results of this investigation, which concludes with the preparation of a small, 24-membered library, setting the stage for larger library syntheses.

2. Results and discussion

Our probe into the chemistry of the tetrahydronaphthyridines with a few select models focused on derivatizations at N-1. Five basic reactions (Scheme 2) were initially examined: (1) epoxide opening to secondary alcohols **3** (Route **A**), (2) Pd-catalyzed aryl aminations to **4** (Route **B**),[2] (3) Petasis–Mannich chemistry[3] to **6** (Route **D**), (4) DEPBT-mediated acylation[4] to amides **7** (Route **E**), and (5) urea formation with isocyanates to **8** (Route **F**). In addition, *N*-tosylated **1h** could also serve as the aryl halide in Pd-catalyzed aryl aminations to produce **5** (Route **C**), as anticipated. While all of these reactions worked well, the homoenamine products from the Petasis–Mannich chemistry (e.g., **6**) formed with β-styrylboronic acid[5] proved to be very unstable and this chemistry was no longer pursued. All attempts at Mitsunobu couplings, even with ADDA, TMAD, and TIPA, and the more acidic of the naphthyridines **1g** with the two electron-withdrawing ester groups failed.[6] The products from the other exploratory reactions (**A**–**C**, and **E** and **F**) proved to be sufficiently stable for further exploration.

Scheme 1.

* Corresponding author. Tel.: +1 617 353 2621; fax: +1 617 353 6466; e-mail: jsnyder@bu.edu
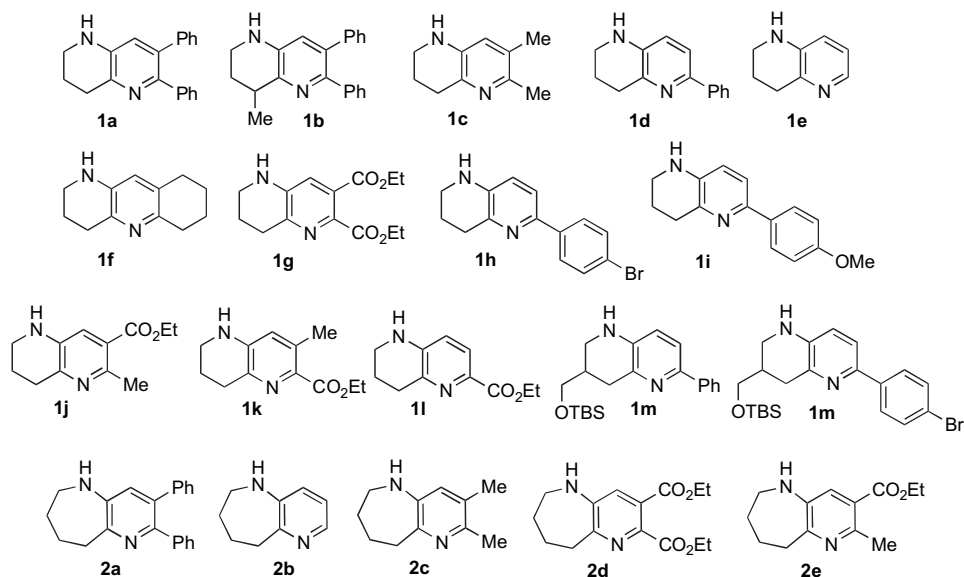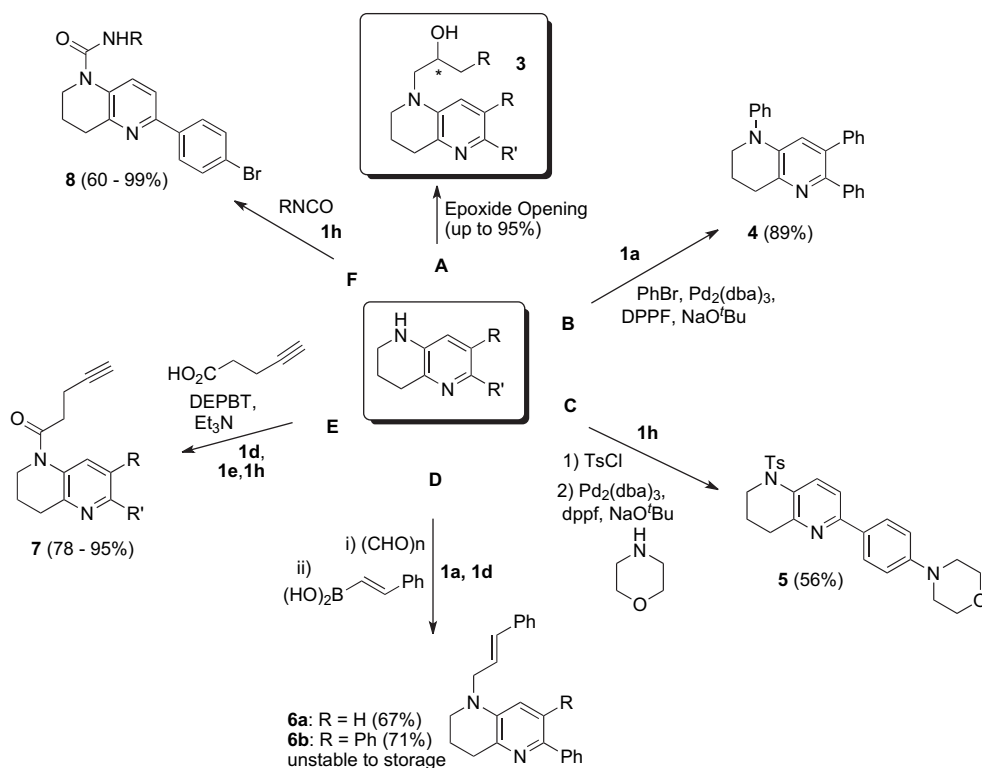
Chart 1.

Scheme 2.

Aryl amination of 5,6-diphenyltetrahydronaphthyridine **1a** proceeded in excellent yield with bromobenzene under Hartwig conditions[7] to give the 1,5,6-triphenyltetrahydronaphthyridine **4** (89%, Route **B**), thereby establishing that these tetrahydronaphthyridine N1 nitrogens are sufficiently nucleophilic to participate in Pd-catalyzed aryl aminations. Lower yields (65%) of **4** were obtained using the Pd(dba)$_3$/BINAP/ NaO^{t}Bu system.[8] The 6-*p*-bromophenyltetrahydronaphthyridine **1h**, protected as the *N*-tosylate, also participated in the

aryl amination with morpholine using the same conditions, demonstrating that appropriately substituted naphthyridines can serve as the oxidative addition substrates in these cross-couplings. Morpholine derivative **5** was produced in 56% unoptimized yield (Route **C**).

Direct acylation of the tetrahydronaphthyridines with carboxylic acids was then explored using **1d**, **1e**, and **1h** as models (Scheme 2, Route **E**). While EDCI/HOBt proved

ineffective in promoting the acylation, Goodman's 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4-one (DEPBT) reagent[4] was successful and amides **7d**, **7e**, and **7h** were isolated in 78–95% yield from the couplings with 4-pentynoic acid. The alkynyl functionality in **7d**, **7e**, and **7h** can serve as a diversification point for further chemistry such as dipolar cycloadditions.[9] In the ^{1}H NMR spectra of all the amides, H-8 suffered severe broadening, as did C-8 in the ^{13}C NMR, due to slow rotation about the amide bond. Heating the samples to 50 °C sharpened the resonances considerably.

**7d** (94%)   **7e** (78%)   **7h** (95%)
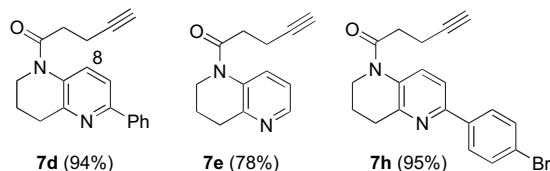
Somewhat more interesting was the potential use of the tetrahydronaphthyridines as scaffolds for preparing libraries via urea formation in the reaction with isocyanates or via epoxide ring opening reactions (Scheme 2, Routes **F** and **A**, respectively). Urea formation (Scheme 2, Route **F**) proceeded in good to excellent yields and could be accomplished with commercially available isocyanates such as phenylisocyanate, producing **8a** in 99+% yield, or by adding the naphthyridine to a solution of the isocyanate generated in situ from a carboxylic acid and DPPA/Et₃N (Scheme 3).[10] One advantage of this latter approach beginning with the carboxylic acids is the ability to use a greater variety of reagents for the isocyanate domain, as was done in the preparation of **8b** (60%) and **8c** (73%), rather than relying upon the more structurally limited, commercially available isocyanates.
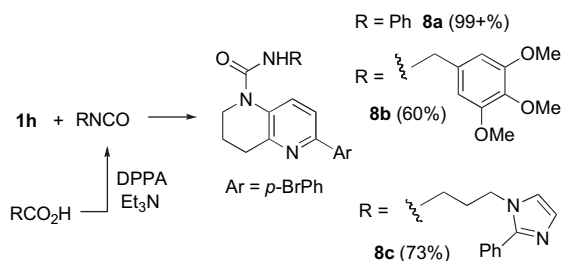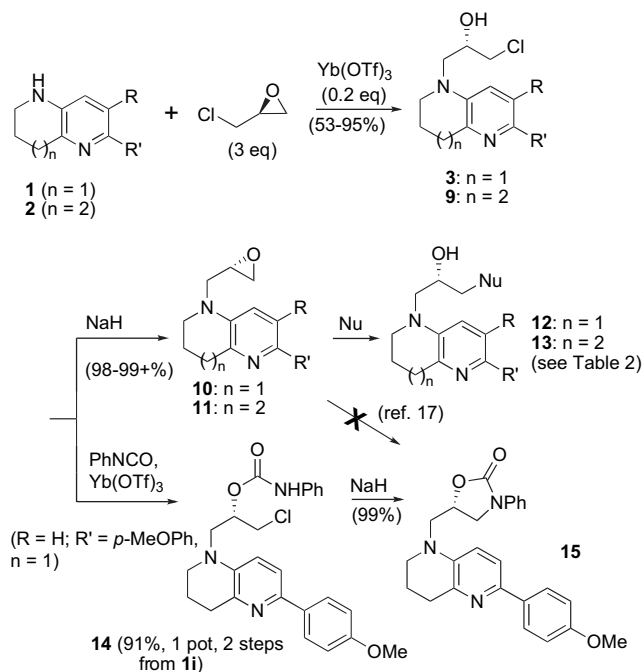

Scheme 3.

Our initial library work, however, focused on epoxide opening since this chemistry has the potential for adding a stereochemically encoded appendage to the naphthyridine scaffold (Scheme 2, Route **A**). The use of enantiomerically pure epoxides or a kinetic resolution in the course of opening a racemic mixture of epoxides would therefore be required in order to obtain enantiomerically pure individual library members. We briefly examined the application of Jacobsen's (*R*,*R*)-oligosalen-Co(III) catalyst[11] in the kinetically resolving epoxide opening of *rac*-propylene oxide (Scheme 4). By the use of a large excess of epoxide (10–15 equiv) at −78 °C, warming to −40 °C overnight, in the presence of 4 mol % catalyst and 8 mol % 2,6-lutidinium *p*-toluenesulfonate (LPTS), an excellent yield (95%) and ee (99+%) of secondary alcohol **3a** was obtained after passing through a solid–liquid extraction plug (SLE-Celite pre-conditioned with saturated aqueous NaHCO₃ solution), selecting for the (*S*)-epoxide. Only a single enantiomer was detected by chiral HPLC, which

also allowed assignment of the enantiomer upon comparison with that prepared from enantiomerically pure (*S*)-propylene oxide. At higher temperatures (0 °C), the ee was only 58%. Given the need for the large amount of epoxide and the ready availability of epoxides with high to complete enantioenrichment,[12] opening of enantiomerically pure epoxides was deemed a more suitable strategy for library development.

10 eq epoxide, THF, 0 °C, 12 h: 87%, 58% ee
15 eq epoxide, THF, -78 to -40 °C, 12 h: 95%, 99+% ee
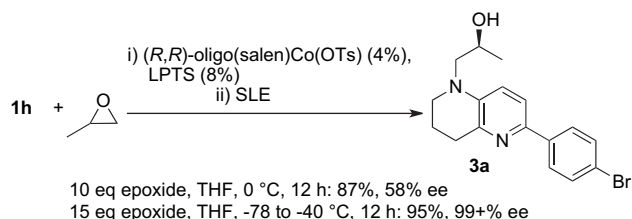
Scheme 4.

Preliminary work to optimize epoxide openings with enantiomerically pure epoxides used **1h** with epichlorohydrin (Scheme 5 and Table 1). A significant part of this effort optimized procedures for compound purification applicable to parallel synthesis. While several Lewis acid catalysts were examined in the epoxide opening, adaptation of Crotti's

Scheme 5.

Yb(OTf)₃[13,14] (0.2 equiv) protocol proved the most effective. Other Lewis acids examined, LiClO₄,[15] B(C₆F₅)₃,[16] Sc(OTf)₃,[14b] and ZrCl₄,[17] gave lower yields or were completely ineffective. Purification of the secondary alcohols was readily achieved by passage of the reaction mixture through an SLE-Celite cartridge as described above, then scavenging the small amount of unreacted tetrahydronaphthyridine from the eluant with MP-NCO resin.[18] From the available naphthyridines and pyridoazepines (Chart 1), **1c**,

Table 1. Chlorohydrin (**3/9**) and epoxide (**10/11**) formation (Scheme 5)[a]

Entry	1/2	Chlorohydrin 3/9	Epoxide 10/11
1	1c	**3c** (85%)	**10c** (98%)
2	1h	**3h** (95%)	**10h** (99%)
3	1i	**3i** (86%)	**10i** (98%)
4	1j	**3j** (53%)	—
5	2c	**9c** (70%)	**11c** (98%)

[a] Isolated yields.

1h, **1i**, and **2c** were then selected for conversion to the corresponding enantiomerically pure chlorohydrins **3/9** using these optimized conditions and purification protocols with (+)-(S)-epichlorohydrin (Scheme 5/Table 1). The intent was to then use these chlorohydrins as building blocks for library development. Tetrahydronaphthyridine **1j** with the ester substituent was also reacted with *rac*-epichlorohydrin under these conditions to form the chlorohydrin (**3j**), though in this case the reaction was considerably more sluggish, requiring 10 h to produce only a 53% yield of **3j** (Table 1, Entry 4). Presumably the electron-withdrawing ester substituent significantly reduces the nucleophilicity in comparison to the other naphthyridines. Given this reduced reactivity, **1j** was not further applied to library synthesis exploiting N1 nucleophilicity.
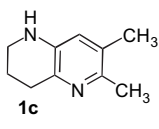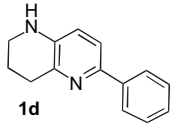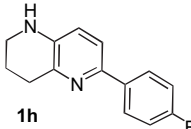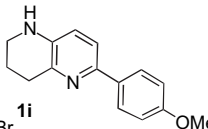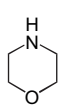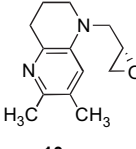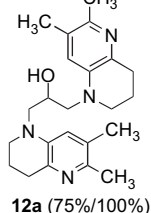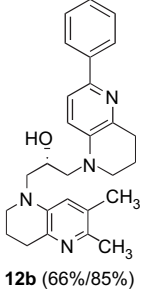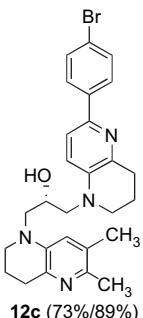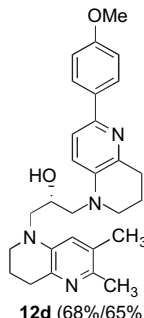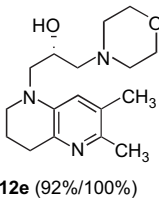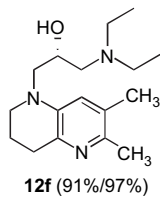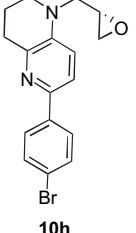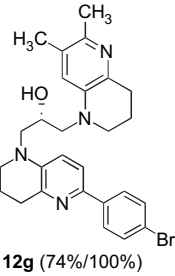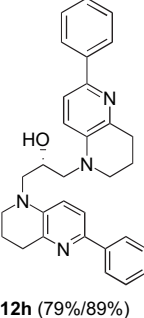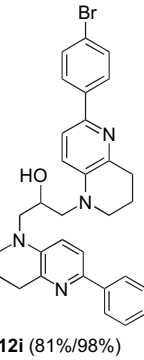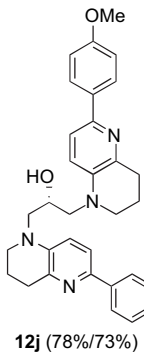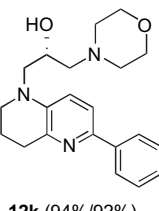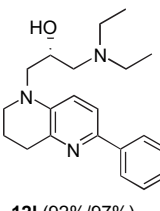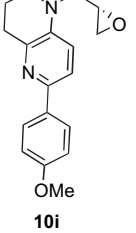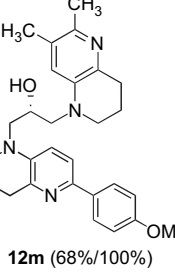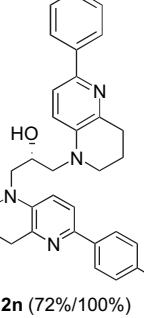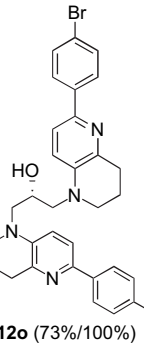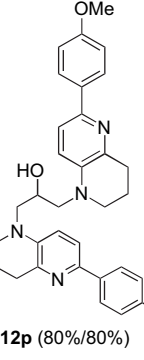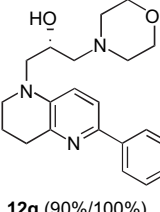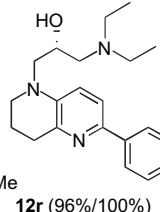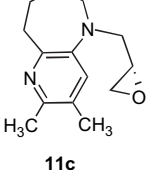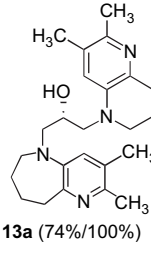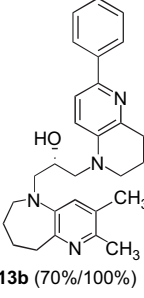
With epichlorohydrins **3c**, **3h**, **3i**, and **9c** in hand, two separate reactivities were then tested (Scheme 5): closure to epoxides **10/11** for a second nucleophilic epoxide opening to **12/13**, and conversion to the oxazolidinone **15**, the latter process adapting Qian's procedure (Scheme 5, above).[19] Qian's original procedure called for the reaction of epoxides with YbCl₃, generating a chlorohydrin in situ, which then condensed with an isocyanate to form the target oxazolidinones. Attempts to

use these protocols on epoxide **10i** were not successful and only starting epoxide was recovered. Beginning with chlorohydrin **3i** (R=H, R'=*p*-MeOPh), however, reaction with phenylisocyanate in the presence of Yb(OTf)₃ produced carbamate **14**. Furthermore, a one-pot procedure optimized the carbamate preparation wherein **1i** was treated with (S)-epichlorohydrin in the presence of Yb(OTf)₃ (0.2 equiv), excess epichlorohydrin was removed under reduced pressure, then the isocyanate was added to produce **14** in 91% yield from **1i**. Treatment of **14** with NaH then yielded the oxazolidinone **15** (99%). As with the amides **7**, the ¹H NMR spectrum of **14** at rt also showed slight broadening for the H-8 due to hindered rotation, which sharpened upon heating to 50 °C.

Alternatively, chlorohydrins **3/9** could be efficiently closed with NaH to the corresponding epoxides **10/11** (98–99%, Table 1), then these epoxides were subjected to a nucleophilic opening either with a second naphthyridine or another nucleophile under Yb(OTf)₃ catalysis using a small excess (1.2–2 equiv) of nucleophile (Scheme 5, above). Work up was accomplished by passage through an SLE-Celite cartridge, pre-conditioned with saturated aqueous NaHCO₃ solution, to remove the Lewis acid, followed by scavenging of the excess nucleophile with MP-NCO from the eluant. Some of the secondary alcohols **12/13** produced upon epoxide opening with amines were unstable to storage, some decomposing within 24 h of isolation. Stable products from the epoxide openings could be obtained following removal of the unreacted nucleophile by treatment with HCl/ether, forming the more stable HCl salts of **12/13**. Attempts to purify the product secondary alcohols by resin capture with PS–SiEt₂Cl[20] or PS–DHP[21] were not successful. Other efforts to remove excess nucleophile (naphthyridine) with PS–TsCl[22] and PM–MIA,[23] or to remove excess epoxide **10/11**, with the second nucleophile as the limiting reagent, using PS–thiophenol,[24] PS–Trisamine,[18c,18d] or PS–NH₂[18b] were also incomplete, though MP-MIA resin could be used to remove secondary amines other than the naphthyridines. The enantiomeric purity of epoxide **10h** was confirmed by chiral HPLC.

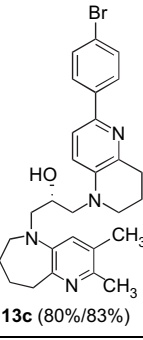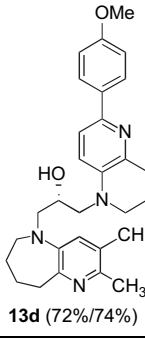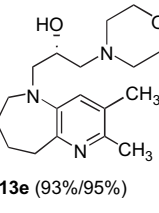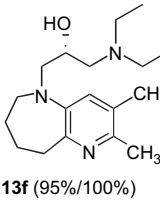A small, 24-membered library (Table 2) was then prepared in a block reactor from the four epoxides **10c**, **10h**, **10i**, and **11c** by reacting with six nucleophiles using the protocols described above, preparing a minimum of 10 mg per sample with an average yield of 80%. The yields were noticeably higher with morpholine and diethylamine as the nucleophile (90–96%, Table 2, columns 6 and 7) in comparison to a second naphthyridine as the nucleophile (66–81%, Table 2, columns 2–5). Purity analysis was accomplished by LC/MS and NMR, which determined that each library member was ≥65% pure with an average purity of 92.8%; only three members of the library were <80% pure. Prior to library preparation, model reactions to establish block reactor protocols were run, and the secondary alcohol products **12g**, **12i**, and **12j** (see Table 2) were purified by passing through an SLE cartridge followed by flash chromatography for accurate assessment of yields based on 100% purity, and full characterization (¹³C NMR and HRMS spectra). Included in this library are three naphthyridine dimers **12a**, **12i**, and **12p**, and 13 pseudodimers (**12b–d**, **12g,h**, **12j**, **12m–o**, **13a–d**). In addition, by reversing the naphthyridinyl

Table 2. Twenty-four membered library prepared by nucleophilic opening of naphthyridine and pyridoazepine epoxides (Scheme 5)[a]

Reagents						Et$_2$NH
1c	**1d**	**1h**	**1i**			

10c	**12a** (75%/100%)	**12b** (66%/85%)	**12c** (73%/89%)	**12d** (68%/65%)	**12e** (92%/100%)	**12f** (91%/97%)
10h	**12g** (74%/100%)	**12h** (79%/89%)	**12i** (81%/98%)	**12j** (78%/73%)	**12k** (94%/92%)	**12l** (92%/97%)
10i	**12m** (68%/100%)	**12n** (72%/100%)	**12o** (73%/100%)	**12p** (80%/80%)	**12q** (90%/100%)	**12r** (96%/100%)
11c	**13a** (74%/100%)	**13b** (70%/100%)	**13c** (80%/83%)	**13d** (72%/74%)	**13e** (93%/95%)	**13f** (95%/100%)

[a] % Yield/% purity as determined by ELSD-MS.

identities of the epoxide electrophile and amine nucleophile, three sets of enantiomers were also produced: **12c/12g**, **12d/12m**, and **12j/12o**. The remaining eight members of the library were prepared from the epoxide openings using diethylamine and morpholine, respectively.

3. Conclusions

The chemistry of 1,2,3,4-tetrahydro-1,5-naphthyridines has been explored to delineate the potential for the use of these heterocycles as scaffolds in library development, focusing

primarily upon the reactivity of the N1 nitrogen as a nucleophile. The nucleophilicity proved quite sensitive to the electronic effects of the substituents in the B-ring. Those with electron-withdrawing groups such as esters (e.g., **1j**) were not as reactive as other naphthyridines and were not included in libraries requiring N1 nucleophiles, such as epoxide openings. Ultimately, Yb(OTf)$_3$-catalyzed opening of the epoxides derived from epichlorohydrin was selected for library development leading to the preparation of a small series of linked naphthyridine dimers and related heterocycles **16**. The successful conversion of the intermediate chlorohydrins **3** to oxazolidinones was also intriguing and this chemistry is currently being pursued for a third library generation. Future libraries will also exploit the naphthyridine scaffolds as amines in Pd-catalyzed arylation chemistry.

4. Experimental procedures

4.1. General procedure A (Scheme 5): preparation of 1-(3-chloro-2-hydroxypropyl)-1,2,3,4-tetrahydro-1,5-naphthyridines 3c, 3h, 3i, 3j, and 1-(3-chloro-2-hydroxypropyl)-2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepine (9c)

(a) *Large scale*: To a solution of tetrahydro-1,5-naphthyridine **1** or tetrahydropyridoazepine **2** and Yb(OTf)$_3$ (typically 0.2 equiv) in CH$_2$Cl$_2$ was added epichlorohydrin (3–5 equiv) in a pressure tube, and the reaction mixture was heated to 60 °C for 3–5 h. After cooling to rt, the mixture was diluted with saturated aqueous NaHCO$_3$ and CH$_2$Cl$_2$, then the organic layer was separated and washed with saturated brine, then dried over Na$_2$SO$_4$. After filtration, the organic layer was concentrated in vacuo and the residue was purified by flash chromatography on a silica gel column.

(b) *Small scale*: To a solution of tetrahydro-1,5-naphthyridine **1** or tetrahydropyridoazepine **2** and Yb(OTf)$_3$ (typically 0.2 equiv) in CH$_2$Cl$_2$ was added epichlorohydrin (3–5 equiv) in a pressure tube, and the reaction mixture was heated to 60 °C for 5 h. After cooling to rt, the mixture was passed through an SLE-Celite cartridge, pre-conditioned with saturated aqueous NaHCO$_3$, and eluted with CH$_2$Cl$_2$. The organic eluant was concentrated in vacuo and the residue was purified by flash chromatography on a silica gel column.

4.2. General procedure B (Scheme 5): preparation of 1-(2,3-epoxypropyl)-1,2,3,4-tetrahydro-1,5-naphthyridines 10c, 10h, 10i, and 1-(2,3-epoxypropyl)-2,3,4,5-tetrahydro-1*H*-pyrido[3,2-*b*]azepine 11c

A suspension of chlorohydrin **3** or **9** (0.10–1.0 mmol) and NaH (60% in mineral oil, 2.0 equiv) in THF (1–10 mL) was stirred at rt overnight. The reaction mixture was quenched with water and then extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and the eluant concentrated in vacuo. The residue was purified by flash chromatography on silica gel column.

4.3. General procedure C (Scheme 5): nucleophilic opening of epoxides 10 and 11

A solution of epoxynaphthyridine **10** or **11** (1 equiv), nucleophilic amine (1.1 equiv), and Yb(OTf)$_3$ (1.0 equiv) in CH$_2$Cl$_2$ was stirred for 30 h at 60 °C in a pressure tube. After cooling to rt, the reaction mixture was passed through an SLE-Celite cartridge, pre-conditioned with saturated aqueous NaHCO$_3$, and eluted with CH$_2$Cl$_2$. The organic eluant was concentrated in vacuo, the crude product was placed in a pressure tube along with MP-NCO (3 equiv) and CH$_2$Cl$_2$ (500 μL), and heated to 60 °C for 24 h. After cooling to rt, the resin was removed by filtration and washed with CH$_2$Cl$_2$, then the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel column.

4.4. General procedure D: preparation of 24-membered library 12/13 by nucleophilic epoxide opening (Table 2)

Solutions of epoxides **10c**, **10h**, **10i**, or **11c** (0.05 mmol, 1 equiv), 1,2,3,4-tetrahydro-1,5-naphthyridines **1d**, **1h**, **1i**, or **11c** (0.06 mmol, 1.2 equiv each), or morpholine, or diethylamine (0.10 mmol, 2 equiv each), and Yb(OTf)$_3$ (0.05 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (250 μL, 0.2 M) were stirred for 30 h at 60 °C in capped microwave reactor tubes (10 mL CEM microwave tubes with aluminum cap) in a Bhodan MiniBlock XT block reactor for 24 reactions. After cooling to rt, the reaction mixtures were passed through SLE-Celite cartridges, pre-conditioned with saturated aqueous NaHCO$_3$, eluted with CH$_2$Cl$_2$ (3×1 mL), and collected in a CEM microwave tube (10 mL). The organic eluant was concentrated in vacuo using a Genevac centrifugal vacuum evaporator, and then nucleophile scavenger (MP-NCO, 0.15 mmol, 3 equiv) and CH$_2$Cl$_2$ (500 μL) were added and heated to 60 °C for 24 h in the block reactor after recapping the tubes. After cooling, the resin was removed by filtration and washed with CH$_2$Cl$_2$ (3×1 mL). The filtrate was collected in a test tube and then concentrated under reduced pressure using the Genevac centrifugal vacuum evaporator. The residue was treated with 2 M HCl in diethyl ether (500 μL), stirred for 15 min at rt, and the product was collected by filtration. Purity was established by LC/MS using ELSD as the primary detector and DAD as the secondary detector; column ACT ACE C3 3×50 mm, 3 μm; eluant: 5 mM formic acid in CH$_3$CN/water gradient. Characterization was accomplished by ^{1}H NMR.

Supplementary data

It includes reaction procedures and spectral characterization data for all compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.04.003.

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