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Enantioselective Synthesis of 3,4-Dihydro-1,2-oxazepin-5(2*H*)-ones and 2,3-Dihydropyridin-4(1*H*)-ones from β-Substituted β-Hydroxyaminoaldehydes

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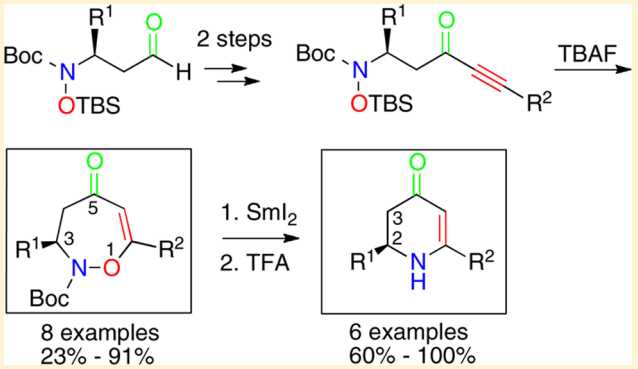
Supporting Information

ABSTRACT: The synthesis of 3,4-dihydro-1,2-oxazepin-5(2*H*)-ones and 2,3-dihydropyridin-4(1*H*)-ones from β-substituted β-hydroxyaminoaldehydes is reported. The β-hydroxyaminoaldehydes were prepared by enantioselective organocatalytic 1,4-addition of *N*-*tert*-butyl (*tert*-butyldimethylsilyl)-oxycarbamate to α,β-unsaturated aldehydes (MacMillan protocol). Alkyne addition to the aldehydes followed by alcohol oxidation furnished *N*-Boc *O*-TBS-protected β-aminoynones. Removal of the TBS protecting group initiated a 7-*endo*-*dig* cyclization to yield previously unknown 3,4-dihydro-1,2-oxazepin-5(2*H*)-ones. Reductive cleavage of the N−O bond of the oxazepinones and Boc-deprotection provided 2-substituted 2,3-dihydropyridin-4(1*H*)-ones via 6-*endo*-*trig* cyclization. 2,3-Dihydropyridin-4(1*H*)-ones are versatile intermediates that have been used for the synthesis of many alkaloids. The new protocol allows the synthesis of 3-dihydropyridin-4(1*H*)-ones carrying an array of substituents at C2 that cannot be prepared from commercial β-amino acids or by one-carbon homologation of proteinogenic amino acids. The use of readily available β-hydroxylaminoaldehydes expands the utility of our previously reported method to prepare 2,3-dihydropyridin-4(1*H*)-ones from β-amino acids as the source of diversity and chirality. A broad substrate scope is possible because β-aminoaldehydes can be prepared from α,β-unsaturated aldehydes by an enantioselective organocatalytic process.



INTRODUCTION

The objective of our work was to devise an enantioselective synthesis of 2,6-disubstituted 2,3-dihydropyridin-4(1*H*)-ones (Figure 1) that would expand the scope of existing methods.

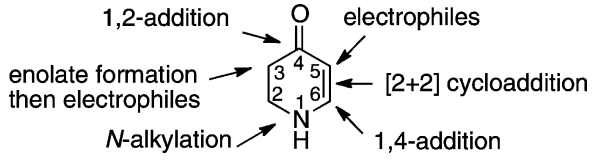


Figure 1. Reactivity profile of 2,3-dihydropyridin-4(1*H*)-ones.

2,3-Dihydropyridin-4(1*H*)-ones are versatile structures that have utility for the synthesis of piperidine-containing natural products, such as indolizidine and quinolizidine alkaloids,[1,2] and piperidine-containing bioactive molecules.[3−8] They can also be converted to substituted pyridines by oxidation.[9−11] Compared to the structurally closely related enamines, 2,3-dihydropyridin-4(1*H*)-ones are relatively more stable[12] as a result of the conjugation of the enamine moiety to a carbonyl functionality (vinylogous amides). They are therefore less sensitive to hydrolysis and oxidation reactions. The 2,3-dihydropyridin-4(1*H*)-ones feature multiple reactive groups that can be subjected to various synthetic transformations that modify the basic scaffold,[13,14] such as N-functionalization,[15,16] C3-functionalization,[17] 1,2-addition at C4, addition of electrophiles at C5,[18] 1,4-addition at C6, and [2 + 2] cycloaddition[19] with the C5−C6 double bond (Figure 1).

Several effective methods exist to prepare 2,3-dihydropyridin-4(1*H*)-ones enantioselectively (Figure 2).[20] These methods include Comins' synthesis of 2,3-dihydropyridin-4(1*H*)-ones, employing the addition of Grignard reagents to chiral *N*-acylpyridinium salts (Figure 2, eq 1).[1,13,21] This approach relies on a sterically demanding C3 tri-isopropylsilyl (TIPS) group to control regioselectivity and a carbamate linked chiral auxiliary to achieve excellent diastereoselectivities. Both auxiliary groups can be removed without racemization of the chiral center. Charrette's modification of Comins' methodology employs (*S*)-

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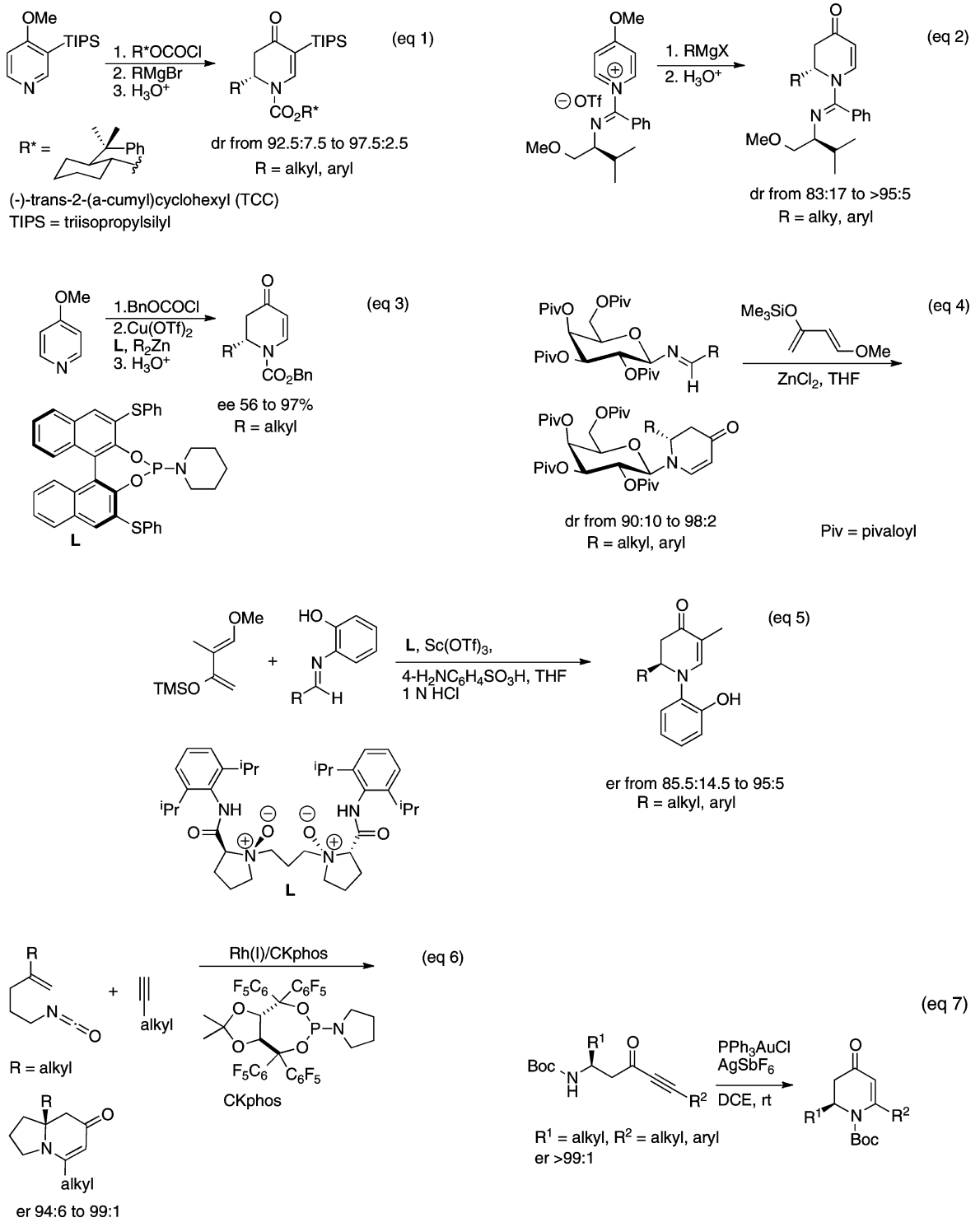

Figure 2. Methods for the synthesis of chiral nonracemic 2,3-dihydropyridin-4(1*H*)-ones.

N-(1-methoxy-3-methylbutan-2-yl)benzamide to generate nonracemic *N*-acylpyridinium salts (Figure 2, eq 2)[22] that furnish N-protected enaminones with excellent diastereo- and regioselectivity. This system does not require a sterically demanding group at C3 because the regioselectivity of the reaction is achieved by a chelation-controlled addition of the Grignard reagent to the pyridinium salt.

A catalytic enantioselective addition of organozinc reagents to *N*-acylpyridinium salts was reported by the Feringa group that furnished enantioselectivities with 56−97% ee with nonbranched alkylzinc reagents (Figure 2, eq 3).[23]

Other approaches utilize the asymmetric hetero-Diels−Alder reaction of imines with a Danishefsky's diene either by using chiral auxiliaries such as 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (Figure 2, eq 4) attached to the imine[24−28] or by employing a chiral catalyst (Figure 2, eq 5).[29−32] Recently, the Rovis group published a facile highly enantioselective synthesis of the bicyclic indolizidinone core via Rh(I)·CKphos-catalyzed

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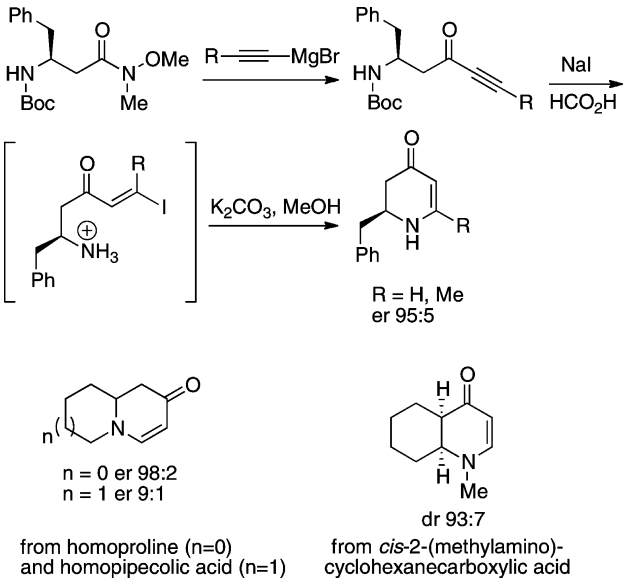
cycloaddition of alkynes and 1,1-disubstituted alkenyl isocyanates (Figure 2, eq 6).[33]

Gouault et al. developed a gold-catalyzed enantioselective synthesis of 2,6-disubstituted pyridones from the aminoynones, which were synthesized from the chiral pool of amino acids (Figure 2, eq 7).[34]

RESULTS AND DISCUSSION

Although many methods for the synthesis of chiral nonracemic 2,3-dihydropyridin-4(1*H*)-ones have proven to be effective, there are drawbacks depending on the exact method, such as multistep preparation of the starting material, limited scope for the introduction of substituents at C2, requirement to remove auxiliary groups, difficult-to-remove auxiliary groups, or the enantiomer of the chiral auxiliary or chiral catalyst may not be readily available. A limitation common to most procedures with the exception of the Rovis method is that they require multiple subsequent steps if bicyclic enaminones are the target compounds. In contrast to the above-mentioned approaches, our group developed a chiral pool method employing readily available chiral nonracemic *β*-amino acids as the starting materials (Scheme 1), thereby incorporating asymmetry as well as diversity into the target compounds.

Scheme 1. Synthesis of Amino Acid-Derived Enaminones[14,35]



This approach not only provides an enantioselective route to 2-substitited 2,3-dihydropyridin-4(1*H*)-ones but also is a concise and direct route to form bicyclic 2,3-dihydropyridin-4(1*H*)-ones when cyclic amino acids such as homoproline, homopipecolic acid, and *cis*-2-(methylamino)cyclohexanecarboxylic acid are employed as the starting *β*-amino acids (Scheme 1).[14,35−42]

As shown in Scheme 1, Weinreb amides of *β*-amino acids are reacted with readily available alkynyl Grignard reagents to form amino ynones. After Boc deprotection with formic acid and addition of NaI (or using HCl), the ynone is converted to a ketovinyl halide, which is not isolated. The addition of base to the reaction mixture deprotonates the amine, which undergoes a 6-*endo*-*trig* ring closure to form 2,3-dihydropyridin-4(1*H*)-ones. Using bicyclic 2,3-dihydropyridin-4(1*H*)-ones we accomplished the synthesis of indolizidine and quinolizidine alkaloids boehmeriasin A,[38] tylocrebrine,[40] antofine,[39,40] and ipalbidine.[39]

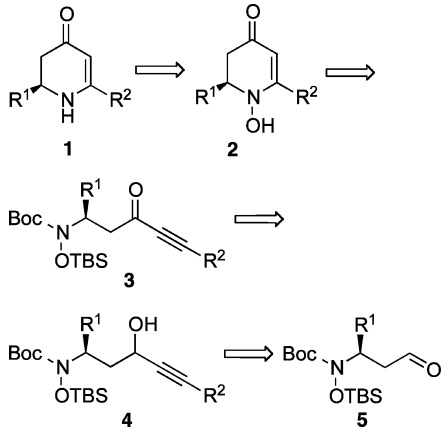
An advantage of this process is that many *β*-amino acids are commercially available or can be prepared from *α*-amino acids by Arndt−Eistert[43] or cyanohydrin homologation.[44] However, this method relies largely on the availability of the 20 proteinogenic amino acids and therefore limits the scope to the side chains to those present in the naturally occurring amino acids. In the case of the Arndt−Eistert homologation, the handling of explosive diazomethane reagent is required.[45−47]

Many other techniques have been developed to synthesize enantiopure *β*-amino acids. Detailed reviews on advances in the synthesis of *β*-amino acids and their derivatives have been published by Sibi[48] and by Juaristi and Soloshonok.[49,50]

MacMillan and co-workers recently developed a different strategy for generating *β*-amino aldehydes by enantioselective organocatalytic conjugate addition of *N*-siloxycarbamate nucleophiles to *α*,*β*-unsaturated aldehydes.[51] This methodology is operationally simple and uses an inexpensive and commercially available imidazolidinone catalyst that is available in both enantiomeric forms. A variety of functional groups are tolerated in this process, and the resulting *β*-amino aldehydes are synthesized with high enantiomeric purity. Given the synthetic utility of this well-developed strategy, we decided to employ it to generate *β*-hydroxylamino aldehydes as precursors for synthesizing novel chiral nonracemic 2,3-dihydropyridin-4(1*H*)-ones.

Our planned route to synthesize 2,6-disubstituted 2,3-dihydropyridin-4(1*H*)-ones **1**, is summarized in Scheme 2.

Scheme 2. Retrosynthetic Route to 2,3-Dihydropyridin-4(1*H*)-ones 1



The targeted 2,3-dihydropyridin-4(1*H*)-ones **1**, could be obtained by reductive cleavage of the N−O bond of *N*-hydroxy 2,3-dihydropyridin-4(1*H*)-ones **2**, which would be derived from the ynones **3**, after removal of the Boc- and TBS-protecting groups. The ynone could be prepared by oxidation of propargyl alcohol **4**, obtained by addition of alkynyl nucleophiles to *β*-hydroxylamino aldehydes **5**. The *β*-hydroxylamino aldehydes **5** can be prepared using MacMillan's procedure.[51]

The preparation of the *β*-hydroxylamino aldehydes **5** started with the synthesis of *N*-Boc-*O*-TBS-protected hydroxylamine **6** and *α*,*β*-unsaturated aldehydes **7** (Scheme 3). We prepared compound **6** from commercially available *N*-Boc-hydroxylamine by silylation of the hydroxyl group. Because only 2-

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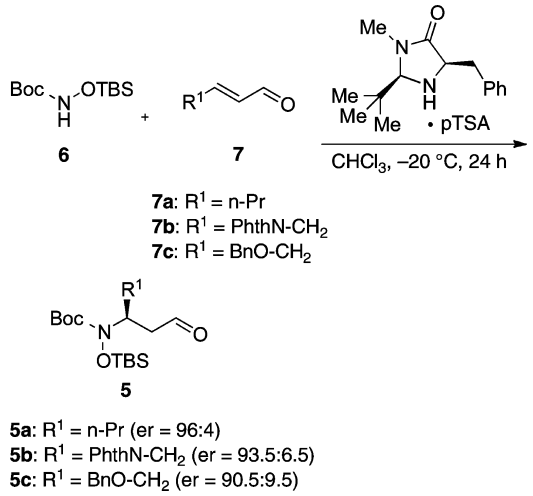
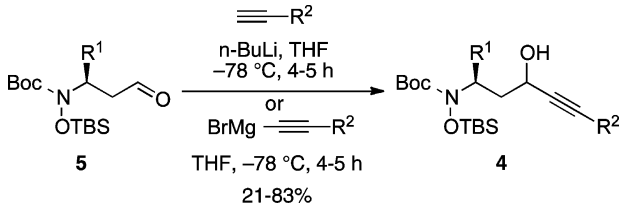
Scheme 3. Synthesis of β-Hydroxylamino Aldehydes 5



hexenal (**7a**) was commercially available, we prepared α,β-unsaturated aldehydes **7b** and **7c** from the corresponding aldehydes and commercially available (triphenylphosphoranylidene)acetaldehyde by a Horner–Wadsworth–Emmons reaction.[52] The β-hydroxylamino aldehydes **5** were synthesized using the MacMillan protocol (Scheme 3).[51] The spectral data and the optical rotation of aldehyde **5a** matched those reported by MacMillan. To confirm the optical purity of aldehyde **5b**, we converted **5b** to (3*R*,5*S*)-*tert*-butyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-5-hydroxyisoxazolidine-2-carboxylate. The optical rotation of this compound also matched MacMillan's report.[51] Aldehyde **5c** was reduced to the corresponding alcohol and then converted to a Mosher ester.[53] On the basis of the ^{19}F NMR spectrum of its Mosher ester, the enantiomeric ratio was determined to be 90.5:9.5.

For the synthesis of propargyl alcohols **4** (Table 1), alkynyl nucleophiles were generated by adding *n*-BuLi to a THF

Table 1. Synthesis of Propargyl Alcohols 4

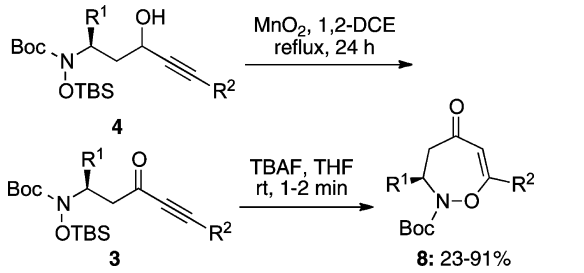


entry (compound)	R^1	R^2	yield (%)
1 (**4a**)	*n*-Pr	Ph	64
2 (**4b**)	*n*-Pr	4-MeO(C_6H_4)	33
3 (**4c**)	*n*-Pr	4-CF_3(C_6H_4)	83
4 (**4d**)	*n*-Pr	thiophen-3-yl	26
5 (**4e**)	*n*-Pr	Me	55
6 (**4f**)	*n*-Pr	*tert*-Bu	70
7 (**4g**)	PhthN–CH_2	4-MeO(C_6H_4)	21
8 (**4h**)	BnO–CH_2	4-MeO(C_6H_4)	46

solution of the alkynes at −78 °C. When R_2 was methyl, we used commercially available propynyl magnesium bromide. The aldehydes **5** were added to the alkynyl nucleophiles at −78 °C to provide propargyl alcohols **4** (Table 1) as a 1:1 mixture of diastereomers.

After subjecting the diastereomeric propargyl alcohols **4** to MnO_2 oxidation in refluxing 1,2-dichloroethane for 24 h, ynones **3** were obtained and directly used in the next step (Table 2). In an attempt to simultaneously remove both amine

Table 2. Two-Step Synthesis of 3,4-Dihydro-1,2-oxazepin-5(2*H*)-ones 8 from Propargyl Alcohols 4



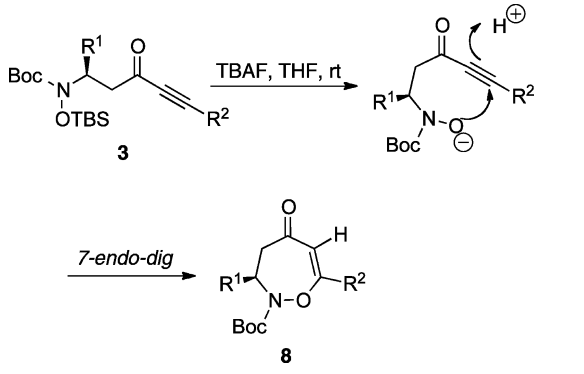
entry (compound)	R^1	R^2	yield (%)[a]
1 (**8a**)	*n*-Pr	Ph	77
2 (**8b**)	*n*-Pr	4-MeO(C_6H_4)	91
3 (**8c**)	*n*-Pr	4-CF_3(C_6H_4)	23
4 (**8d**)	*n*-Pr	thiophen-3-yl	64
5 (**8e**)	*n*-Pr	Me	73
6 (**8f**)	*n*-Pr	*tert*-Bu	52
7 (**8g**)	PhthN–CH_2	4-MeO(C_6H_4)	43
8 (**8h**)	BnO–CH_2	4-MeO(C_6H_4)	48

[a]Yield over two steps.

protecting groups, we treated ynone **3a** with 4 N HCl in dioxane followed by basification using excess K_2CO_3 and methanol. No product was formed, and starting material **3a** decomposed completely. Therefore, we decided to use an orthogonal strategy to deprotect the TBS group first. When a TBAF solution (1 M in THF) was slowly added to ynone **3a** at room temperature, TLC analysis of the reaction mixture showed complete disappearance of the starting material and the appearance of a single new product spot within a few minutes. NMR analysis of the product revealed that an unusual 7-*endo-dig* addition product (i.e., the novel seven-membered oxazepinone **8a**) had formed. Subjecting all ynones **3** to the same reaction conditions furnished oxazepin-5-ones **8a–8h** (Table 2).

The proposed mechanism of cyclization is shown in Scheme 4. After the removal of the silyl group, the oxygen anion attacks the triple bond in Michael fashion, yielding oxazepin-5-ones **8** as a 7-*endo-dig*-cyclization product.

Scheme 4. Proposed Mechanism of Cyclization



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We assigned the identity of the 7-*endo-dig* products on the basis of the ^{1}H NMR chemical shifts of the vinylic protons (Figure 3). For compounds **8**, we observed a chemical shift for

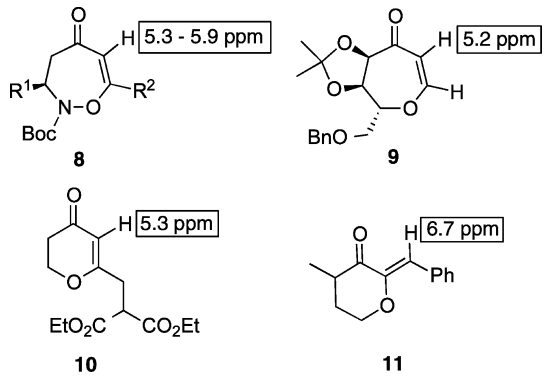


Figure 3. Chemical shifts of vinylic protons (5.3−5.9 ppm) for compounds **8** in comparison with 3a,4-dihydrooxepinone **9** (5.2 ppm),[54] 4-oxo-3,4-dihydro-2*H*-pyran **10** (5.3 ppm),[58] and (*Z*)-2-benzylidene-4-methyldihydro-2*H*-pyran-3(4*H*)-one **11** (6.7 ppm).[59]

the vinyl proton at 5.3 ppm for aliphatic R^2 groups and at 5.8−5.9 ppm for aromatic R^2 groups, which is in accordance with shifts reported in the literature for similar compounds like 6,7-dihydrooxepin-4(5*H*)-ones (5.3−5.8 ppm),[54,55] 5-substituted furanones (5.3 ppm),[56] and 2-substituted dihydropyranones (5.3 ppm).[56−58] This also ruled out the possibility that 6-*exo-trig* products had formed, in which case the ^{1}H NMR chemical shifts for the vinyl protons would be expected at 6.7 ppm.[59]

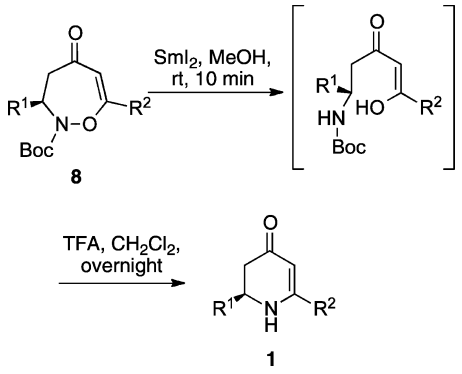
A literature search indicated that this particular seven-membered scaffold has not been reported before, although 1,2-oxazepines are a known class of compounds.[60] Various methods have been reported for the synthesis of the 1,2-oxazepine core. These include pyrolysis of cyclic N-oxides,[60−62] double Michael-type addition of hydroxylamine to heptadienone,[63] intramolecular N-alkylation of a hydroxylamine derivative,[64] intramolecular O-alkylation,[65] ring-closing metathesis of alkenes tethered by hydroxylamine,[66] Pd-catalyzed [4 + 3] cycloaddition of γ-methylidene-δ-valerolactones with nitrones,[67] ring enlargement of bicyclic dibromo-1,2-oxazines,[68] gold(I)-catalyzed 1,3-dipolar cycloaddition of alkynyl cyclopropyl oximes with nitrones,[69] and cyclocondensation of chalcone-based 1,5-diketones and hydroxylamine.[70] In all of these reports, the structures of the final 1,2-oxazepine derivatives obtained are different from 1,2-oxazepinones **8**. For example, some of the above-mentioned examples of oxazepines are fused with heterocycles or a benzene ring, do not possess unsaturation in the ring, and, many of those compounds, are devoid of a ketone moiety in their structures. Scaffold **8** contains an α,β-unsaturated ketone within the ring system that is bonded to oxygen at the β-position, thus featuring also an enol ether moiety.

Following MacMillan's precedence that the N−O bond can be cleaved easily with SmI_2, we subjected oxazepinones **8** to reduction with SmI_2 followed by treatment with TFA to remove the Boc group and isolated the 2,3-dihydropyridin-4(1*H*)-ones **1** (Table 3) as the reaction products.

CONCLUSIONS

We have extended the scope of our previously reported method for the synthesis of 3,4-dihydro-1,2-oxazepin-5(2*H*)-ones **1** by utilizing aminoaldehydes **5** instead of β-amino acids as starting

Table 3. Synthesis of 2,3-Dihydropyridin-4(1*H*)-ones 1



entry (compound)	R^1	R^2	yield (%)
1 (**1a**)	*n*-Pr	Ph	60
2 (**1b**)	*n*-Pr	4-$CF_3(C_6H_4)$	78
3 (**1c**)	*n*-Pr	thiophen-3-yl	88
4 (**1d**)	*n*-Pr	Me	100
5 (**1e**)	*n*-Pr	*tert*-Bu	100
6 (**1f**)	BnO−CH_2	4-MeO(C_6H_4)	75

materials. The advantage of this method is that a wide variety aminoaldehydes **5** with different substituents can be prepared from α,β-unsaturated aldehydes employing MacMillan's enantioselective organocatalytic method. The α,β-unsaturated aldehydes are readily accessible by reacting aldehydes with (triphenyphosphoranylidene)acetaldehyde. Another result from this research is the identification of 3,4-dihydro-1,2-oxazepin-5(2*H*)-ones **8** that represent a novel structural type. The one-flask reductive cleavage of the N−O bonds of these intermediates followed by Boc-deprotection furnished the targeted 2,3-dihydropyridin-4-(1*H*)-ones **1**. The 2,3-dihydropyridin-4-(1*H*)-ones **1**, and oxazepinones **8**, constitute unique six- and seven-membered scaffolds that can be used for the synthesis of diverse compound libraries. Additional chemical transformations can be carried out (Figure 1) to diversify these scaffolds further.

EXPERIMENTAL SECTION

All commercially available reagents and solvents were used without further purification. Flash column chromatography was carried out on silica gel. TLC was conducted on silica gel 250 μm, F254 plates. ^{1}H NMR spectra were recorded at 400 MHz on a NMR instrument. Chemical shifts are reported in ppm with TMS as an internal standard (TMS, 0.0 ppm). Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad; and m, multiplet), integration, and coupling constants (Hz). ^{13}C NMR spectra were recorded at 100 MHz with complete proton decoupling. Chemical shifts are reported in ppm with the solvent as internal standard ($CDCl_3$, 77.2 ppm). High-resolution mass spectrometry was carried out using ESI-TOF. IR spectra were recorded on a FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Optical rotations were measured on a polarimeter at a concentration (*c*) of grams per 100 mL.

General Procedure for the Synthesis of α,β-Unsaturated Aldehydes 7. (*E*)-Hex-2-enal (**7a**). This compound is commercially available.

General Procedure for the Synthesis of α,β-Unsaturated Aldehydes 7b and 7c.[52] A toluene solution (0.13 M) of (triphenylphosphoranylidene)acetaldehyde (1.0 equiv) and appropriate starting aldehyde (1.0 equiv) was heated under reflux for 4 to 5 h under an argon atmosphere. After the solvent was evaporated in vacuo, the residue was purified by silica gel chromatography.

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*(E)-4-(1,3-Dioxoisoindolin-2-yl)but-2-enal (**7b**).*[52] Purification of the crude reaction product by silica gel column chromatography (30% EtOAc/hexanes) provided the title compound as clear oil in 81% yield (1.8 g). IR (thin film) 1772, 1703, 1679, 1466, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.57 (dd, 2H, J_1 = 1.7 and J_2 = 5 Hz), 6.12−6.18 (ddt, 1H, J_1 = 1.7, J_2 = 7.6 and J_3 = 15.8 Hz), 6.83 (dt, 1H, J_1 = 5 and J_2 = 15.8 Hz), 7.77 (dd, 2H, J_1 = 3 and J_2 = 5.5 Hz), 7.90 (dd, 2H, J_1 = 3 and J_2 = 5.5 Hz), 9.57 (d, 1H, J = 8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.4, 123.7, 131.8, 133.1, 134.4, 149.0, 167.5, 192.5 ppm. HRMS m/z [M + Na] calcd for $C_{12}H_9NNaO_3$, 238.0480; found, 238.0484.

*(E)-4-(Benzyloxy)but-2-enal (**7c**).* Purification of the crude reaction product by silica gel column chromatography (20% EtOAc/hexanes) provided the title compound as clear oil in 85% yield (2.0 g). The spectral data of the title compound was in agreement with that found in the literature.[71]

Synthesis of *tert*-Butyl (*tert*-Butyldimethylsilyl)oxycarbamate (6). To a round-bottomed flask was added *N*-Boc hydroxylamine (1.0 equiv) in CH_2Cl_2 (0.2 M) and triethylamine (1.1 equiv), and the flask was cooled to 0 °C. To this solution was added TBSCl (1.0 equiv) as liquid, and the reaction mixture was allowed to warm to room temperature and stirred for an additional 12 h. Upon completion of the reaction, the reaction mixture was poured into a separatory funnel and washed with water and brine. The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by silica gel chromatography (10% ether/hexanes) to provide the title compound as a low-melting solid in 95% yield (0.88 g). The spectral data of compound **6** matched with that described in the literature.[51]

General Procedure for the Synthesis β-Hydroxylaminoaldehydes (5).[51] A round-bottomed flask equipped with a magnetic stirrer bar was charged with the *p*TSA salt of (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (0.2 equiv) and the appropriate α,β-unsaturated aldehyde (**7**) (3.0 equiv) in $CHCl_3$ (1.0 M for **7**) and was then cooled to −20 °C. *tert*-Butyl (*tert*-butyldimethylsilyloxy)-carbamate **6** (1.0 equiv) was added in one portion as a solid, and the reaction was maintained at −20 °C for 24−36 h. After completion of the reaction, the reaction mixture was filtered through a silica gel plug, eluted with diethyl ether, and concentrated in vacuo. The residue was purified by silica gel chromatography. The spectral data for new compounds **5b** and **5c** is given below.

*(R)-tert-Butyl (tert-Butyldimethylsilyl)oxy(1-(1,3-dioxoisoindolin-2-yl)-4-oxobutan-2-yl)carbamate (**5b**).* Purification by silica gel column chromatography (30% EtOAc/hexanes) provided the title compound as clear oil in 39% yield (168 mg, er 93.5:6.5). IR (thin film) 3442, 2945, 2909, 2849, 1719, 1395, 1364, 1252, 1169 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.16 (s, 3H), 0.86 (s, 9H), 1.45 (s, 9H), 2.70 (dd, 1H, J_1 = 1.5, J_2 = 6.1, and J_3 = 17.2 Hz), 2.98 (ddd, 1H, J_1 = 1.8, J_2 = 7.8, and J_3 = 17.2 Hz), 3.80 (dd, 1H, J_1 = 6.4 and J_2 = 13.8 Hz), 4.09 (dd, 1H, J_1 = 9.7 and J_2 = 16.6 Hz), 4.60 (p, 1H, J = 6.7 Hz), 7.69 (dd, 2H, J_1 = 3 and J_2 = 5.5 Hz), 7.82 (dd, 2H, J_1 = 3 and J_2 = 5.5 Hz), 9.73 (t, 1H, J = 1.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, 17.9, 25.8, 28.1, 39.0, 44.7, 56.8, 82.3, 123.3, 132.1, 134.0, 157.7, 167.9, 199.2. HRMS m/z [M + Na] calcd for $C_{23}H_{34}N_2NaO_6Si$, 485.2084; found, 485.2089. $[\alpha]_D^{25}$ −27.0 (c 0.500, $CHCl_3$). The enantiomeric ratio was determined by further derivatizing the title compound to form (3*R*,5*S*)-*tert*-butyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-5-hydroxyisoxazolidine-2-carboxylate following a literature procedure.[51] The spectral data and the specific optical rotation ($[\alpha]_D^{25}$ −60.0 (c 0.600, $CHCl_3$)) of this compound matched the literature value.[51]

*(R)-tert-Butyl 1-(Benzyloxy)-4-oxobutan-2-yl((tert-butyldimethylsilyl)oxy)carbamate (**5c**).* Purification by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as clear oil in 68% yield (583 mg). IR (thin film) 3430, 2945, 2930, 2858, 1728, 1479, 1455, 1388, 1368, 1310, 1251, 1168, 1109, 841, 786, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.14 (d, 6H, J = 1.7 Hz), 0.94 (s, 9H), 1.46 (s, 9H), 2.59 (ddd, 1H, J_1 = 2.1, J_2 = 7.3, and J_3 = 16.5 Hz), 2.76 (ddd, 1H, J_1 = 2.1, J_2 = 7.3, and J_3 = 16.5 Hz), 3.50 (dd, 1H, J_1 = 7.2 and J_2 = 9.4 Hz), 3.73 (dd, 1H, J_1 = 6.7 Hz and J_2 = 9.4 Hz), 4.52 (s, 2H), 4.59−4.65 (m, 1H), 7.32−7.35 (m, 5H), 9.75 (t, 1H, J = 2.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4, 18.1, 26.0, 28.1, 43.8, 57.8, 69.5, 73.1, 82.0, 127.6, 128.5, 131.8, 137.9, 158.6, 199.9. HRMS m/z [M + Na] calcd for $C_{22}H_{37}NNaO_5Si$, 446.2339; found, 446.2343. $[\alpha]_D^{25}$ +1.80 (c 0.500, $CHCl_3$). The enantiomeric ratio was determined by converting the title compound into the corresponding alcohol. For synthesizing the alcohol, the title compound was dissolved in MeOH (2.5 M) and cooled to 0 °C. To this was added $NaBH_4$ (4.0 equiv). After stirring for 1 h, the reaction mixture was quenched with 1.0 M $NaHSO_4$(aq) and then the extracted with diethyl ether (3 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude alcohol was then converted into the Mosher ester by reaction with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl). The ratio of the two resulting diastereomeric compounds was determined to be 90.5:9.5 by ^{19}F NMR. ^{19}F NMR (400 MHz, $CDCl_3$) δ −71.54 (major peak), −72.12 (minor peak).

General Procedure for the Synthesis of Propargyl Alcohols 4a−d and 4f−h. The alkyne (1.5 equiv) was dissolved in dry THF (2.0 M) and cooled to −78 °C. A solution of *n*-butyllithium (2.5 M in hexanes, 1.3 equiv) was then added dropwise. The mixture was stirred for 30 min at −78 °C, and then the β-hydroxylamino aldehyde (**5a−c**, 1.0 equiv) was added slowly. The mixture was stirred for 4 to 5 h. When the reaction was complete, as indicated by TLC, the mixture was quenched by adding an aqueous saturated solution of ammonium chloride. The aqueous layer was separated and extracted three times with ethyl ether. The organic layers were combined, washed with water and then with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo.

*tert-Butyl (tert-Butyldimethylsilyl)oxy((4S)-6-hydroxy-8-phenyloct-7-yn-4-yl)carbamate (**4a**).* Purification by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as pale yellow oil in 64% yield (631 mg). IR (thin film) 3350, 3028, 2925, 1708, 1600, 1384, 1364, 1158, 758, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.19−0.20 (m, 6H), 0.92−0.96 (m, 12H), 1.46−1.49 (m, 12H), 1.75−1.87 (m, 2H), 2.19−2.34 (m, 1H), 3.96−4.10 (br m, 1H), 4.66−4.73 (m, 1H), 7.28−7.30 (m, 3H), 7.40−7.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, 13.9, 18.2, 19.9, 26.0, 28.3, 35.6, 40.6, 60.2, 61.5, 81.5, 84.5, 89.8, 122.8, 128.2, 131.7, 158.3. HRMS m/z [M + Na] calcd for $C_{25}H_{41}NNaO_4Si$, 470.2703; found, 470.2692.

*tert-Butyl (tert-Butyldimethylsilyl)oxy((4S)-6-hydroxy-8-(4-methoxyphenyl)oct-7-yn-4-yl)carbamate (**4b**).* Purification by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as pale yellow oil in 33% yield (240 mg). IR (thin film) 3348, 2925, 2858, 1708, 1598, 1384, 1364, 1177, 835 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.18−0.20 (m, 6H), 0.91−0.95 (m, 12H), 1.36−1.43 (m, 3H), 1.45−1.48 (m, 9H), 1.72−1.89 (m, 2H), 2.17−2.32 (m, 1H), 3.79 (s, 3H), 3.97−4.09 (br m, 1H), 4.64−4.70 (m, 1H), 6.81 (d, 2H, J = 6.8 Hz), 7.35 (d, 2H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, 13.9, 18.1, 19.9, 26.0, 28.3, 35.6, 40.7, 55.2, 60.2, 61.5, 81.8, 84.5, 88.8, 113.8, 115.0, 133.1, 158.3, 159.5. HRMS m/z [M + Na] calcd for $C_{26}H_{43}NNaO_5Si$, 500.2808; found, 500.2799.

*tert-Butyl (tert-Butyldimethylsilyl)oxy((4S)-6-hydroxy-8-(4-(trifluoromethyl)phenyl)oct-7-yn-4-yl)carbamate (**4c**).* Purification by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as pale yellow oil in 83% yield (617 mg). IR (thin film) 3252, 2925, 2854, 1710, 1458, 1383, 1364, 1168, 875 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.18−0.20 (m, 6H), 0.91−0.96 (m, 12H), 1.46−1.49 (m, 12H), 1.81−1.91 (m, 2H), 2.19−2.35 (m, 1H), 3.92−4.10 (br m, 1H), 4.67−4.72 (m, 1H), 7.52−7.56 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, 13.9, 18.2, 19.9, 26.0, 28.3, 31.6, 40.4, 60.1, 61.4, 81.7, 82.1, 92.4, 125.12, 125.20, 127.9, 131.9, 131.9, 158.3. HRMS m/z [M + Na] calcd for $C_{26}H_{40}F_3NNaO_4Si$, 538.2576; found, 538.2566.

*tert-Butyl (tert-Butyldimethylsilyl)oxy((4S)-6-hydroxy-8-(thiophen-3-yl)oct-7-yn-4-yl)carbamate (**4d**).* Purification by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as pale yellow oil in 26% yield (149 mg). IR (thin film) 3258, 2960, 2932, 1708, 1456, 1383, 1369, 1158, 849 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.19−0.20 (m, 6H), 0.91−0.93 (m, 3H), 0.96 (d, 9H, J = 2.8 Hz), 1.48 (d, 12H, J = 9.1 Hz), 1.79−1.87 (m, 2H),

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2.20−2.33 (m, 1H), 3.95−4.09 (br m, 1H), 4.68 (dq, 1H, J_1 = 6.5 and J_2 = 11.8 Hz), 7.09 (m, 1H, J_1 = 1.2, J_2 = 2.4, and J_3 = 5 Hz) 7.24 (dd, 1H, J_1 = 3 and J_2 = 5 Hz), 7.42 (ddd, 1H, J_1 = 1.1, J_2 = 3.0, and J_3 = 4.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, 13.9, 18.1, 19.9, 26.0, 28.3, 35.6, 40.6, 60.2, 61.5, 79.6, 81.9, 89.8, 121.8, 125.1, 128.8, 129.9, 158.3. HRMS m/z [M + Na] calcd for $C_{23}H_{39}NNaO_4SSi$, 476.2267; found, 476.2260.

*tert-Butyl tert-Butyldimethylsilyloxy((4S)-6-hydroxynon-7-yn-4-yl)carbamate (**4e**).* To a solution of **5a** (1.00 equiv) in dry THF (0.05 M) at −78 °C under argon was slowly added 1-propynyl magnesium bromide (0.500 M in tetrahydrofuran, 4.00 equiv). The reaction mixture was stirred at −78 °C and monitored by TLC. After 4 to 5 h, when the reaction was complete as indicated by TLC, the mixture was quenched by adding an aqueous saturated solution of ammonium chloride. The mixture was diluted with ethyl ether and washed with brine. The separated organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the resulting residue by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as yellow oil in 55% yield (317 mg). IR (thin film) 3212, 2961, 2933, 1709, 1384, 1364, 1142 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.14−0.15 (m, 6H), 0.87−0.90 (m, 3H), 0.90−0.92 (d, 9H, J = 8 Hz), 1.34−1.40 (m, 3H), 1.44 (s, 9H), 1.69−1.72 (m, 2H), 1.79 (s, 3H), 2.01−2.17 (m, 1H), 3.86−4.00 (br m, 1H), 4.34−4.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, 3.6, 13.9, 18.1, 19.8, 26.1, 28.3, 35.6, 40.9, 59.8, 61.1, 80.0, 80.5, 81.8, 158.3. HRMS m/z [M + Na] calcd for $C_{20}H_{39}NNaO_4Si$, 408.2546; found, 408.2556.

*tert-Butyl (tert-Butyldimethylsilyl)oxy((4S)-6-hydroxy-9,9-dimethyldec-7-yn-4-yl)carbamate (**4f**).* Purification by silica gel column chromatography (15% Et_2O/hexanes) provided the title compound as pale yellow oil in 70% yield (277 mg). IR (thin film) 3224, 2964, 2934, 2874, 1709, 1459, 1383, 1369, 1163 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 3H), 0.17 (s, 3H), 0.93−0.95 (m, 12H), 1.21 (s, 9H), 1.48−1.50 (m, 12H), 1.70−1.77 (m, 2H), 2.07−2.22 (m, 1H), 2.47−2.52 (m, 1H), 3.80−4.01 (br m, 1H), 4.42−4.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.5, 13.9, 18.1, 19.9, 26.1, 27.3, 28.3, 31.0, 35.6, 41.2, 59.8, 61.2, 79.8, 81.7, 93.3, 158.3. HRMS m/z [M + Na] calcd for $C_{23}H_{45}NNaO_4Si$, 450.3016; found, 450.3011.

*tert-Butyl (tert-Butyldimethylsilyl)oxy((2R)-1-(1,3-dioxoisoindolin-2-yl)-4-hydroxy-6-(4-methoxyphenyl)hex-5-yn-2-yl)carbamate (**4g**).* Purification by silica gel column chromatography (20% EtOAc/hexanes) provided the title compound as pale yellow oil in 21% yield (40 mg). IR (thin film) 3352, 2900, 1711, 1667, 1384, 1364, 1177, 825 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15−0.19 (m, 6H), 0.87 (d, 9H, J = 6.1 Hz), 1.42 (s, 4H), 1.48 (s, 5H), 1.88−2.01 (m, 1H), 2.43 (ddd, 1H, J_1 = 3.2, J_2 = 7.8, and J_3 = 14.2 Hz), 3.80 (s, 3H), 3.89−4.04 (m, 1H), 4.11−4.20 (m, 1H), 4.28−4.39 (br m, 1H), 4.72−4.79 (m, 1H), 6.80 (m, 2H, J_1 = 2.6 and J_2 = 9.0 Hz), 7.28−7.35 (m, 2H), 7.69 (dd, 2H, J_1 = 3.0 and J_2 = 5.5 Hz), 7.82 (ddd, 2H, J_1 = 1.4, J_2 = 3.0, and J_3 = 5.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, 17.9, 25.8, 28.1, 37.5, 40.5, 55.2, 60.4, 61.4, 82.4, 85.0, 87.9, 113.8, 123.3, 132.1, 133.1, 134.0, 157.6, 159.5, 168.0. HRMS m/z [M + Na] calcd for $C_{32}H_{42}N_2NaO_7Si$, 617.2659; found, 617.2651.

*tert-Butyl ((2R)-1-(Benzyloxy)-4-hydroxy-6-(4-methoxyphenyl)-hex-5-yn-2-yl)((tert-butyldimethylsilyl)oxy)carbamate (**4h**).* Purification by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as pale yellow oil in 46% yield (240 mg). IR (thin film) 3350, 2967, 2900, 2833, 1713, 1384, 1364, 1178, 850 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18−0.19 (m, 6H), 0.95 (s, 9H), 1.44 (s, 5H), 1.46 (s, 4H), 1.90−2.08 (m, 1H), 2.19−2.29 (m, 1H), 3.61 (ddd, 1H, J_1 = 6.9, J_2 = 9.7, and J_3 = 26.2 Hz), 3.76−3.82 (m, 4H), 4.21−4.35 (m, 1H), 4.55−4.57 (m, 2H), 4.70−4.79 (m, 1H), 6.81 (d, 2H, J = 8.8 Hz), 7.32−7.37 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, 18.0, 26.0, 28.2, 38.1, 55.2, 60.4, 61.2, 71.0, 73.0, 81.8, 84.9, 88.2, 113.8, 114.9, 125.9, 127.6, 128.4, 133.1, 137.9, 158.4, 159.6. HRMS m/z [M + Na] calcd for $C_{31}H_{45}NNaO_6Si$, 578.2914; found, 578.2909.

General Procedure for the Synthesis of Ynones 3a−h. The propargyl alcohol (**4a−h**, 1.0 equiv) was dissolved in 1,2-dichloroethane (0.035 M), and activated MnO_2 (30 equiv) was added. The reaction mixture was refluxed overnight. After completion of the reaction, as indicated by TLC, the reaction mixture was filtered through a pad of Celite. The solution was concentrated in vacuo to give the title compound as a crude oil. The crude product was used in the next step assuming quantitative yield because complete conversion was observed.

General Procedure for the Synthesis of Oxazepin-5-ones 8a−h. The ynone (**3a−h**, 1.0 equiv) was dissolved in THF (0.028 M), and tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 2.5 equiv) was added at room temperature. After stirring for 1 min, the reaction was complete, as indicated by TLC. The reaction mixture was quenched with silica gel and concentrated in vacuo. The yields shown below refer to the two-step conversion of propargyl alcohols **4** to oxazepin-5-ones **8**.

*(S)-tert-Butyl 5-Oxo-7-phenyl-3-propyl-4,5-dihydro-1,2-oxazepine-2(3H)-carboxylate (**8a**).* Purification by silica gel column chromatography (25% Et_2O/hexanes) provided the title compound as yellow oil in 77% yield (173 mg). IR (thin film) 3402, 3069, 3026, 2925, 1710, 1664, 1619, 1493, 1452, 1384, 1367, 1158, 759, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, J = 7.3 Hz), 1.40 (q, 2H, J = 7.4 Hz), 1.49 (s, 9H), 1.65−1.74 (m, 1H), 1.79−1.88 (m, 1H), 2.85−2.93 (m, 2H), 4.59 (dq, 1H, J_1 = 7.2 and J_2 = 9.3 Hz), 5.89 (s, 1H), 7.41−7.49 (m, 3H), 7.92 (dt, 2H, J_1 = 1.3 and J_2 = 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.0, 28.3, 35.3, 47.3, 58.3, 83.1, 108.3, 127.6, 127.9, 131.7, 132.0, 153.2, 173.5, 197.9. HRMS m/z [M + Na] calcd for $C_{19}H_{25}NNaO_4$, 354.1682; found, 354.1680. $[\alpha]_D^{25}$ −2.40 (c 0.500, $CHCl_3$).

*(S)-tert-Butyl 7-(4-Methoxyphenyl)-5-oxo-3-propyl-4,5-dihydro-1,2-oxazepine-2(3H)-carboxylate (**8b**).* Purification by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as yellow oil in 91% yield (112 mg). IR (thin film) 3400, 2961, 2933, 1709, 1659, 1604, 1510, 1458, 1384, 1369, 1332, 1256, 1177, 841 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, J = 7.3 Hz), 1.38−1.42 (m, 2H), 1.49 (s, 9H), 1.64−1.73 (m, 1H), 1.78−1.85 (m, 1H), 2.83−2.94 (m, 2H), 3.86 (s, 3H), 4.57 (dq, 1H, J_1 = 7 and J_2 = 9.9 Hz), 5.80 (s, 1H), 6.93 (d, 2H, J = 9 Hz), 7.87 (d, 2H, J = 9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.0, 28.3, 35.4, 47.1, 55.5, 58.4, 82.9, 106.8, 114.1, 124.3, 129.8, 153.2, 162.6, 174.0, 197.9. HRMS m/z [M + Na] calcd for $C_{20}H_{27}NNaO_5$, 384.1787; found, 384.1782. $[\alpha]_D^{25}$ −6.20 (c 0.500, $CHCl_3$).

*(S)-tert-Butyl 5-Oxo-3-propyl-7-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1,2-oxazepine-2(3H)-carboxylate (**8c**).* Purification by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as yellow oil in 23% yield (19.5 mg). IR (thin film) 3400, 2925, 2854, 1737, 1683, 1650, 1459, 1384, 1364, 1324, 1246, 1169, 875 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, J = 7.3 Hz), 1.37−1.40 (m, 2H), 1.50 (s, 9H), 1.63−1.75 (m, 1H), 1.79−1.88 (m, 1H), 2.92 (d, 2H, J = 8.5 Hz), 4.59 (dq, 1H, J_1 = 7 and J_2 = 9.6 Hz), 5.95 (s, 1H), 7.68 (d, 2H, J = 8.3 Hz), 8.05 (d, 2H, J = 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.9, 28.3, 35.3, 47.4, 58.5, 83.4, 109.9, 125.5, 125.6, 128.1, 133.0, 135.4, 153.1, 171.7, 197.7. HRMS m/z [M + Na] calcd for $C_{20}H_{24}F_3NNaO_4$, 422.1555; found, 422.1553. $[\alpha]_D^{25}$ +3.00 (c 0.500, $CHCl_3$).

*(S)-tert-Butyl 5-Oxo-3-propyl-7-(thiophen-3-yl)-4,5-dihydro-1,2-oxazepine-2(3H)-carboxylate (**8d**).* Purification by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as yellow oil in 64% yield (45.4 mg). IR (thin film) 3401, 2961, 2931, 1709, 1662, 1618, 1457, 1383, 1369, 1254, 1158, 1088, 849 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, J = 7.3 Hz), 1.38−1.44 (m, 2H), 1.47 (s, 9H), 1.63−1.72 (m, 1H), 1.78−1.87 (m, 1H), 2.84−2.95 (m, 2H), 4.54 (dq, 1H, J_1 = 7 and J_2 = 9.6 Hz), 5.82 (s, 1H), 7.31−7.33 (dd, 1H, J_1 = 1.3 and J_2 = 5.1 Hz), 7.36 (dd, 1H, J_1 = 3 and J_2 = 5.1 Hz), 8.08 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 19.0, 28.3, 35.4, 47.3, 58.0, 82.9, 107.9, 125.8, 126.8, 128.9, 134.3, 153.1, 168.9, 197.9. HRMS m/z [M + Na] calcd for $C_{17}H_{23}NNaO_4S$, 360.1246; found, 360.1237. $[\alpha]_D^{25}$ −1.80 (c 0.500, $CHCl_3$).

*(S)-tert-Butyl 7-Methyl-5-oxo-3-propyl-4,5-dihydro-1,2-oxazepine-2(3H)-carboxylate (**8e**).* Purification by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as yellow oil in 73% yield (60.1 mg). IR (thin film) 3400, 2962, 2933, 1710, 1667, 1384, 1365, 1254, 1142 cm^{-1}. ^{1}H NMR (400 MHz,

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$CDCl_3$) δ 0.95 (t, 3H, J = 7.3 Hz), 1.36−1.40 (m, 2H), 1.48 (s, 9H), 1.55−1.61 (m, 1H), 1.74−1.81 (m, 1H), 2.10 (s, 3H), 2.82 (d, 2H, J = 7.9 Hz), 4.38−4.46 (dq, 1H, J_1 = 7 and J_2 = 9.6 Hz), 5.31 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 19.9, 28.2, 35.1, 47.4, 56.7, 82.6, 110.2, 152.6, 173.9, 197.6. HRMS m/z [M + Na] calcd for $C_{14}H_{23}NNaO_4$, 292.1525; found, 292.1512. $[\alpha]_D^{25}$ +5.80 (c 0.500, $CHCl_3$).

*(S)-tert-Butyl 7-tert-Butyl-5-oxo-3-propyl-4,5-dihydro-1,2-oxazepine-2(3H)-carboxylate (**8f**).* Purification by silica gel column chromatography (10% Et_2O/hexanes) provided the title compound as yellow oil in 52% yield (52.4 mg). IR (thin film) 3402, 2964, 2934, 2874, 1739, 1710, 1628, 1459, 1383, 1369, 1318, 1255, 1163 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.3 Hz), 1.24 (s, 9H), 1.35−1.43 (m, 2H), 1.48 (s, 9H), 1.55−1.64 (m, 1H), 1.74−1.83 (m, 1H), 2.72 (dd, 1H, J_1 = 7.8 and J_2 = 14.9 Hz), 2.86 (dd, 1H, J_1 = 7.8 and J_2 = 14.9 Hz), 4.46 (dq, 1H, J_1 = 7.3 and J_2 = 9.6 Hz), 5.34 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.2, 28.26, 28.29, 34.4, 36.7, 47.1, 57.1, 82.7, 105.4, 153.3, 181.9, 199.0. HRMS m/z [M + Na] calcd for $C_{17}H_{29}NNaO_4$, 334.1995; found, 334.1988. $[\alpha]_D^{25}$ +14.2 (c 0.500, $CHCl_3$).

*(R)-tert-Butyl 3-((1,3-Dioxoisoindolin-2-yl)methyl)-7-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1,2-oxazepine-2(3H)-carboxylate (**8g**).* Purification by silica gel column chromatography (30% EtOAc/hexanes) provided the title compound as yellow oil in 43% yield (13.7 mg). IR (thin film) 3400, 2900, 1718, 1667, 1603, 1450, 1384, 1364, 1256, 1177, 826 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.88 (m, 1H, J_1 = 5.8 and J_2 = 12.9 Hz), 3.08 (m, 1H), 3.85−3.89 (m, 4H), 4.14 (dd, 1H, J_1 = 7.6 and J_2 = 14.1 Hz), 5.00 (dq, 1H, J_1 = 6.6 and J_2 =10.8 Hz), 5.83 (s, 1H), 6.93 (d, 2H, J = 8.9 Hz), 7.74 (dd, 2H, J_1 = 3 and J_2 = 5.4 Hz), 7.87−7.90 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 39.1, 44.8, 55.4, 56.9, 83.4, 106.7, 114.1, 123.5, 123.9, 129.9, 132.1, 134.1, 152.5, 162.8, 168.0, 175.1, 196.2. HRMS m/z [M + Na] calcd for $C_{26}H_{26}N_2NaO_7$, 501.1638; found, 501.1632. $[\alpha]_D^{25}$ −80.6 (c 0.500, $CHCl_3$).

*(R)-tert-Butyl 3-(Benzyloxymethyl)-7-(4-methoxyphenyl)-5-oxo-4,5-dihydro-1,2-oxazepine-2(3H)-carboxylate (**8h**).* Purification by silica gel column chromatography (20% Et_2O/hexanes) provided the title compound as yellow oil in 48% yield (80.0 mg). IR (thin film) 3400, 2967, 2900, 2833, 1750, 1733, 1667, 1604, 1384, 1364, 1257, 1178, 850 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.86−2.99 (m, 2H), 3.58−3.62 (dd, 1H, J_1 = 8 and J_2 = 12 Hz), 3.74−3.78 (dd, 1H, J_1 = 8 and J_2 = 10 Hz), 3.85 (s, 3H), 4.56 (m, 2H), 4.83 (dq, 1H, J_1 = 6.6 and J_2 =10.8 Hz), 5.82 (s, 1H), 6.93 (d, 2H, J = 8.9 Hz), 7.26 (m, 3H), 7.33 (m, 2H), 7.87 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 44.2, 55.4, 57.8, 69.6, 73.1, 83.1, 106.9, 114.1, 124.2, 127.6, 127.7, 128.4, 129.9, 137.8, 153.3, 162.7, 173.9, 197.2. HRMS m/z [M + Na] calcd for $C_{25}H_{29}NNaO_6$, 462.1893; found, 462.1886. $[\alpha]_D^{25}$ −50.8 (c 0.500, $CHCl_3$).

General Procedure for the Synthesis of 2,3-Dihydropyridin-4(1*H*)-ones 1a−f. To an oven-dried 10 mL round-bottomed flask charged with corresponding oxazepin-5-one **1** (1.00 equiv) in degassed MeOH (1 mL) was added SmI_2 (0.100 M in tetrahydrofuran, 3.00 equiv) under an argon atmosphere. The deep-blue solution was allowed to stir at room temperature until the reaction turned pale yellow (2 min) or was deemed complete by TLC. The solvent was removed in vacuo, and the residue was then resuspended in dichloromethane (20 mL). The organic layer was washed successively with aqueous 1 M $NaHSO_4$, H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo to give crude compound. To a solution of this crude compound in dichloromethane (1 mL) was added trifluoroacetic acid (TFA). The reaction mixture was stirred until TLC showed that the reaction was complete (~24 h). The reaction mixture was then diluted with DCM (20 mL) and washed with saturated $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford the pure title compound.

*(S)-6-Phenyl-2-propyl-2,3-dihydropyridin-4(1H)-one (**1a**).* (60% yield, 13.7 mg). IR (thin film) 3403, 2900, 2858, 1617, 1531, 1384, 1325, 759, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.3 Hz), 1.43−1.57 (m, 2H), 1.64−1.74 (m, 2H), 2.40 (dd, 1H, J_1 = 12.9 Hz and J_2 = 16.1 Hz), 2.51 (dd, 1H, J_1 = 4.9 Hz and J_2 = 16.1 Hz), 3.81 (dq, 1H, J_1 = 5.1, J_2 = 5.8, and J_3 = 11.6 Hz), 4.89 (br s, 1H), 5.40 (s, 1H), 7.42−7.53 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 18.8, 36.5, 41.5, 53.2, 98.8, 126.1, 129.1, 130.9, 135.9, 161.2, 193.3. HRMS m/z [M + Na] calcd for $C_{14}H_{17}NNaO$, 238.1208; found, 238.1198. $[\alpha]_D^{25}$ −61.4 (c 0.500, $CHCl_3$).

*(S)-2-Propyl-6-(4-(trifluoromethyl)phenyl)-2,3-dihydropyridin-4(1H)-one (**1b**).* (78% yield, 9.80 mg). IR (thin film) 3401, 2900, 1625, 1533, 1384, 1325, 827 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, J = 7.3 Hz), 1.44−1.50 (m, 2H), 1.69−1.74 (m, 2H), 2.41 (dd, 1H, J_1 = 13 Hz and J_2 = 16.2 Hz), 2.53 (dd, 1H, J_1 = 4.9 Hz and J_2 = 16.2 Hz), 3.79−3.86 (m, 1H), 4.88 (br s, 1H), 5.38 (s, 1H), 7.64 (d, 2H, J = 8.2 Hz), 7.71 (d, 2H, J = 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.8, 36.5, 41.4, 53.4, 99.7, 126.0, 126.1, 126.6, 132.8, 139.42, 159.6, 193.2. HRMS m/z [M + Na] calcd for $C_{15}H_{16}F_3NNaO$, 306.1082; found, 306.1078. $[\alpha]_D^{25}$ −21.4 (c 0.500, $CHCl_3$).

*(S)-2-Propyl-6-(thiophen-3-yl)-2,3-dihydropyridin-4(1H)-one (**1c**).* (88% yield, 19.6 mg). IR (thin film) 3271, 2925, 1605, 1573, 1526, 1384, 1261, 787 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, 3H, J = 7.3 Hz), 1.43−1.49 (m, 2H), 1.64−1.75 (m, 2H), 2.37 (dd, 1H, J_1 = 12.8 Hz and J_2 = 16.1 Hz), 2.49 (dd, 1H, J_1 = 4.8 Hz and J_2 = 16.1 Hz), 3.74−3.82 (m, 1H), 5.03 (br s, 1H), 5.42 (s, 1H), 7.25 (dd, 1H, J_1 = 1.3 Hz and J_2 = 5.1 Hz), 7.40 (dd, 1H, J_1 = 2.9 Hz and J_2 = 5.1 Hz), 7.60 (dd, 1H, J_1 = 1.3 Hz and J_2 = 2.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 18.8, 36.5, 41.6, 53.1, 98.3, 124.5, 125.3, 127.2, 137.2, 155.7, 193.4. HRMS m/z [M + Na] calcd for $C_{12}H_{15}NNaOS$, 244.0772; found, 244.0764. $[\alpha]_D^{25}$ −128.2 (c 0.5000, $CHCl_3$).

*(S)-6-Methyl-2-propyl-2,3-dihydropyridin-4(1H)-one (**1d**).* (100% yield, 11.0 mg). IR (thin film) 3271, 2967, 2926, 1617, 1592, 1533, 1384 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, J = 7.3 Hz), 1.37−1.43 (m, 2H), 1.55−1.61 (m, 2H), 1.96 (s, 3H), 2.25 (dd, 1H, J_1 = 13.1 Hz and J_2 = 16 Hz), 2.38 (dd, 1H, J_1 = 4.9 Hz and J_2 = 16.1 Hz), 3.59−3.67 (m, 1H), 4.57 (br s, 1H), 4.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.6, 21.3, 36.6, 41.2, 53.2, 99.5, 161.3, 192.8. HRMS m/z [M + Na] calcd for $C_9H_{15}NNaO$, 176.1051; found, 176.1045. $[\alpha]_D^{25}$ −15.8 (c 0.500, $CHCl_3$).

*(S)-6-tert-Butyl-2-propyl-2,3-dihydropyridin-4(1H)-one (**1e**).* (100% yield, 32.4 mg). IR (thin film) 3301, 2959, 2925, 1605, 1513, 1465, 1384, 1364 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, J = 7.3 Hz), 1.19 (s, 9H), 1.39−1.43 (m, 2H), 1.56−1.66 (m, 2H), 2.24 (dd, 1H, J_1 = 12.6 and J_2 = 16.1 Hz), 2.40 (dd, 1H, J_1 = 4.9 and J_2 = 16.1 Hz), 3.55−3.63 (m, 1H), 4.76 (br s, 1H), 5.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.8, 28.6, 35.3, 36.3, 41.1, 53.1, 96.0, 172.6, 193.5. HRMS m/z [M + Na] calcd for $C_{12}H_{21}NNaO$, 218.1521; found, 218.1518. $[\alpha]_D^{25}$ −73.4 (c 0.500, $CHCl_3$).

*(R)-2-(Benzyloxymethyl)-6-(4-methoxyphenyl)-2,3-dihydropyridin-4(1H)-one (**1f**).* (75% yield, 16.4 mg). IR (thin film) 3401, 2918, 1604, 1508, 1384, 1258, 833 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30−2.42 (m, 2H), 3.62−3.67 (m, 2H), 3.85 (s, 3H), 3.99−4.07 (m, 1H), 4.59 (s, 2H), 5.37 (s, 1H), 5.47 (br s, 1H), 6.94 (d, 2H, J = 8.8 Hz), 7.32−7.37 (m, 5H), 7.46 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.7, 52.7, 55.5, 71.6, 73.4, 97.9, 114.4, 127.5 127.8, 128.1, 128.6, 137.4, 160.9, 161.8, 191.8. HRMS m/z [M + Na] calcd for $C_{20}H_{21}NNaO_3$, 346.1419; found, 346.1418. $[\alpha]_D^{25}$ −86.4 (c 0.500, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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