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

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ABSTRACT: The synthesis of 3,4-dihydro-1,2-oxazepin-5(2H)-ones and 2,3-dihydropyridin-4(1H)-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(2H)-ones. Reductive cleavage of the N−O bond of the oxazepinones and Boc-deprotection provided 2-substituted 2,3-dihydropyridin-4(1H)-ones via 6-endo-trig cyclization. 2,3-Dihydropyridin-4(1H)-ones are versatile intermediates that have been used for the synthesis of many alkaloids. The new protocol allows the synthesis of 3-dihydropyridin-4(1H)-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-hydroxyaminoaldehydes expands the utility of our previously reported method to prepare 2,3-dihydropyridin-4(1H)-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(1H)-ones (Figure 1) that would expand the scope of existing methods.

2,3-Dihydropyridin-4(1H)-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(1H)-ones are relatively more stable12 as a result of the conjugation of the enamine moiety to a carbonyl functionality (vinyllogous amides). They are therefore less sensitive to hydrolysis and oxidation reactions. The 2,3-dihydropyridin-4(1H)-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] cycloaddition19 with the C5−C6 double bond (Figure 1).

Figure 1. Reactivity profile of 2,3-dihydropyridin-4(1H)-ones.
N-(1-methoxy-3-methylbutan-2-yl)benzamide to generate non-racemic N-acylpyridinium salts (Figure 2, eq 2)\(^2\) that furnish N-protected enamiones 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)\(^2\)\(^3\)

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-galactopyranosamine (Figure 2, eq 4) attached to the imine\(^2\)\(^4\)\(^−\)\(^2\)\(^8\) or by employing a chiral catalyst (Figure 2, eq 5).\(^2\)\(^9\)\(^−\)\(^3\)\(^2\) Recently, the Rovis group published a facile highly enantioselective synthesis of the bicyclic indolizidinone core via Rh(I)-CKphos-catalyzed
cycloaddition of alkynes and 1,1-disubstituted alkenyl isocyanates (Figure 2, eq 6).

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

**RESULTS AND DISCUSSION**

Although many methods for the synthesis of chiral nonracemic 2,3-dihydropyridin-4(1H)-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 enamines 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

\[
\begin{align*}
\text{Ph} & \text{HN} \overset{\text{Me}}{\text{N}} \overset{\text{O}}{\text{Me}} \overset{\text{R}}{\text{H}} \overset{\text{O}}{\text{Me}} \overset{\text{H}}{\text{N}} \overset{\text{Boc}}{\text{Me}} \overset{\text{Me}}{\text{N}} \overset{\text{O}}{\text{Me}} \overset{\text{R}}{\text{H}} \overset{\text{O}}{\text{Me}} \overset{\text{H}}{\text{N}} \overset{\text{Boc}}{\text{Me}} \overset{\text{Me}}{\text{N}} \overset{\text{O}}{\text{Me}} \overset{\text{R}}{\text{H}} \overset{\text{O}}{\text{Me}} \overset{\text{H}}{\text{N}} \overset{\text{Boc}}{\text{Me}} \\
\text{Ph} & \text{HN} \overset{\text{Me}}{\text{N}} \overset{\text{O}}{\text{Me}} \overset{\text{R}}{\text{H}} \overset{\text{O}}{\text{Me}} \overset{\text{H}}{\text{N}} \overset{\text{Boc}}{\text{Me}} \overset{\text{Me}}{\text{N}} \overset{\text{O}}{\text{Me}} \overset{\text{R}}{\text{H}} \overset{\text{O}}{\text{Me}} \overset{\text{H}}{\text{N}} \overset{\text{Boc}}{\text{Me}} \\
\text{Ph} & \text{HN} \overset{\text{Me}}{\text{N}} \overset{\text{O}}{\text{Me}} \overset{\text{R}}{\text{H}} \overset{\text{O}}{\text{Me}} \overset{\text{H}}{\text{N}} \overset{\text{Boc}}{\text{Me}} \overset{\text{Me}}{\text{N}} \overset{\text{O}}{\text{Me}} \overset{\text{R}}{\text{H}} \overset{\text{O}}{\text{Me}} \overset{\text{H}}{\text{N}} \overset{\text{Boc}}{\text{Me}}
\end{align*}
\]

from homoproleine (n=0) from cis-2-(methylamino)-cyclohexanecarboxylic acid

This approach not only provides an enantioselective route to 2-substituted 2,3-dihydropyridin-4(1H)-ones but also is a concise and direct route to form bicyclic 2,3-dihydropyridin-4(1H)-ones when cyclic amino acids such as homoproleine, homoprolepic acid, and cis-2-(methylamino)cyclohexanecarboxylic acid are employed as the starting β-amino acids (Scheme 1).

As shown in Scheme 1, Weinreb amides of β-amino acids are reacted with readily available alkynyl Grignard reagents to form aminoynes. After Boc deprotection with formic acid and addition of NaI (or using HCl), the ynone is converted to a ketonic aldehyde, 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(1H)-ones. Using bicyclic 2,3-dihydropyridin-4(1H)-ones we accomplished the synthesis of indolizidine and quinolizidine alkaloids boehmerianis A, tylocrebrine, anotine, and ipalbidine.

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 or cyanohydrin homologation. 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.

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 and by Juaristi and Soloshonok.

MacMillan and co-workers recently developed a different strategy for generating β-amino aldehydes by enantioselective organocatalytic conjugate addition of N-siloxy carbamate nucleophiles to α,β-unsaturated aldehydes. 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(1H)-ones.

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

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

The targeted 2,3-dihydropyridin-4(1H)-ones 1, could be obtained by reductive cleavage of the N-O bond of N-hydroxy 2,3-dihydropyridin-4(1H)-ones 2, which would be derived from the ynone 3, after removal of the Boc- and TBS-protecting groups. The ynene 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.

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-
hexenal (7a) was commercially available, we prepared α,β-
unsaturated aldehydes 7b and 7c from the corresponding
aldehydes and commercially available (triphenylphosphor-
anylidene)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 (3R,5S)-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 19F
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
solution of the alkynes at -78 °C. When R2 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.

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

Yield over two steps.

Table 1. Synthesis of Propargyl Alcohols 4

After subjecting the diastereomeric propargyl alcohols 4 to
MnO2 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 3. Synthesis of β-Hydroxylamino Aldehydes 5

Table 4. Proposed Mechanism of Cyclization
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 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-dihydroxepin-4(SH)-ones (5.3–5.8 ppm),54,55 S-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 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-methylenediel-6-valorolactones with nitrones,67 ring enlargement of bicyclic dibromo-1,2-oxazines,68 gold(I)-catalyzed 1,3-dipolar cycloaddition of alkenes with nitrones69 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.

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(1H)-ones 1 (Table 3) as the reaction products.

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

| entry (compound) | R$^1$ | R$^2$ | yield (%) |
|------------------|-------|-------|-----------|
| 1 (1a) | n-Pr | Ph | 60 |
| 2 (1b) | n-Pr | 4-CF$_3$(C$_6$H$_4$)$_2$ | 78 |
| 3 (1c) | n-Pr | thiophen-3-yl | 88 |
| 4 (1d) | n-Pr | Me | 100 |
| 5 (1e) | n-Pr | tert-Bu | 100 |
| 6 (1f) | BrO–CH$_2$ | 4-MeO(C$_6$H$_4$)$_2$ | 75 |

**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:** A toluene solution (0.13 M) of (triphenylphosphoranylidene)acetaldheyde (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.
Purification of the crude reaction product by silica gel column chromatography (30% EtOAc/hexanes) provided the title compound as clear oil in 85% yield (2.0 g). The spectral data of the compound was in agreement with that found in the literature.  

**Synthesis of tert-Butyl (tert-Butyldimethylsilyloxy)carbamate (6).** To a round-bottomed flask was added N-Boc hydroxylamine (1.0 equiv) in CH₂Cl₂ (0.2 M) and triethylamine (1.1 equiv), and the flask was cooled to 0 °C. To this solution was added TBSCI (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 MgSO₄, 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.  

**General Procedure for the Synthesis of β-Hydroxyaldehyde (5).** A round-bottomed flask equipped with a magnetic stirrer bar was charged with the pTSA salt of (2R,5R)-5-benzyl-2-methylimidazolidin-4-one (0.2 equiv) and the appropriate α,β-unsaturated aldehyde (7) (3.0 equiv) in CHCl₃ (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-Butyldimethylsilyloxy)(1-(1,3-dioxoisindolin-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 93% yield (688 mg, 1.89 g).  

**tert-Butyl (tert-Butyldimethylsilyloxy)(4S)-6-hydroxy-8-(4-methoxyphenyl)oct-7-yn-4-yl)carbamate (4b).** Purification by silica gel column chromatography (20% EtOAc/hexanes) provided the title compound as pale yellow oil in 85% yield (240 mg).  

**tert-Butyl (tert-Butyldimethylsilyloxy)(4S)-6-hydroxy-8-(4-trifluoromethyl)phenyl)oct-7-yn-4-yl)carbamate (4c).** Purification by silica gel column chromatography (20% EtOAc/hexanes) provided the title compound as pale yellow oil in 83% yield (617 mg).
2.20−2.33 (m, 1H), 3.95−4.09 (br d, 1H), 4.68 (dq, 1H), 6.5 and J2 = 11.8 Hz), 7.09 (m, 1H, J1 = 1.2, J2 = 2.4, and J3 = 5 Hz). 7.24 (dd, 1H, J1 = 3 and J2 = 5 Hz), 7.42 (dd, 1H, J1 = 1.1, J2 = 3.0, and J3 = 4.2 Hz).

13C NMR (100 MHz, CDCl3) δ = 4.5, 13.9, 18.1, 19.9, 26.0, 28.3, 35.6, 40.6, 62.0, 61.5, 79.6, 81.9, 89.8, 121.8, 121.5, 128.8, 129.9, 158.3. HRMS m/z [M + Na] calcd for C20H27NNaO5, 384.1787; found, 384.1782.

General Procedure for the Synthesis of Yrones 3a−h.

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.

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 tetrahydroammonium 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-4-propyl-4,5-dihydro-1,2-oxazepin-2(3H)-carboxylate (8B).

Purification by silica gel column chromatography (25% EtO/hexanes) provided the titled compound as yellow oil in 77% yield (173 mg). IR (thin film) 3400, 3009, 2932, 2925, 1710, 1664, 1619, 1493, 1452, 1384, 1367, 1158, 759, 699 cm−1.

1H NMR (400 MHz, CDCl3) 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), 1.78−1.88 (m, 1H), 2.85−2.93 (m, 2H), 4.59 (dq, 1H, J1 = 7.2 and J2 = 9.3 Hz), 5.89 (s, 1H), 7.41−7.49 (m, 3H), 7.92 (dt, 2H, J1 = 1.3 and J2 = 7 Hz). 13C NMR (100 MHz, CDCl3) δ 13.8, 19.0, 28.3, 35.3, 47.8, 58.3, 81.3, 108.3, 127.6, 127.9, 131.7, 132.0, 153.2, 173.5, 197.9. HRMS m/z [M + Na] calcd for C16H17NaNO5, 354.1682; found, 354.1680.

(S)-tert-Butyl 7-(4-Methoxyphenyl)-5-oxo-4-propyl-4,5-dihydro-1,2-oxazepin-2(3H)-carboxylate (8B).

Purification by silica gel column chromatography (20% EtO/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, 1339, 1322, 1157, 841 cm−1.

1H NMR (400 MHz, CDCl3) 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, J1 = 7 and J2 = 9.9 Hz), 5.80 (s, 1H), 6.93 (d, 2H, J = 9 Hz), 7.87 (d, 2H, J = 9 Hz).

13C NMR (100 MHz, CDCl3) δ 13.8, 19.0, 28.3, 35.4, 47.1, 55.5, 58.4, 82.9, 86.6, 114.1, 124.3, 129.8, 153.2, 162.6, 174.0, 197.9. HRMS m/z [M + Na] calcd for C16H17NaNO5, 384.1787; found, 384.1782.

(S)-tert-Butyl 7-(4-Methoxyphenyl)-5-oxo-4-propyl-4,5-dihydro-1,2-oxazepin-2(3H)-carboxylate (8B).

Purification by silica gel column chromatography (20% EtO/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, 1339, 1322, 1157, 841 cm−1.

1H NMR (400 MHz, CDCl3) 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, J1 = 7 and J2 = 9.9 Hz), 5.80 (s, 1H), 6.93 (d, 2H, J = 9 Hz), 7.87 (d, 2H, J = 9 Hz).

13C NMR (100 MHz, CDCl3) δ 13.8, 19.0, 28.3, 35.4, 47.1, 55.5, 58.4, 82.9, 86.6, 114.1, 124.3, 129.8, 153.2, 162.6, 174.0, 197.9. HRMS m/z [M + Na] calcd for C16H17NaNO5, 384.1787; found, 384.1782.

(S)-tert-Butyl 7-(4-Methoxyphenyl)-5-oxo-4-propyl-4,5-dihydro-1,2-oxazepin-2(3H)-carboxylate (8B).

Purification by silica gel column chromatography (20% EtO/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, 1339, 1322, 2014, 79, 984 cm−1.
CDCl₃ 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 (dd, 1H, J₁ = 7 and J₂ = 9.6 Hz), 5.31 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 13.7, 19.1, 29.9, 32.5, 47.4, 56.7, 82.6, 110.2, 152.6, 173.9, 197.6. HRMS m/z [M + Na]⁺ calcul for C₁₇H₁₈N₃NaO₂, 292.1525; found, 292.1521. [α]ᵢ° = +5.80 (c 0.500, CHCl₃).

(S)-tert-Butyl 7-tert-Butyl-5-oxo-3-propyl-4,5-dihydro-1,2-oxazepine-2(3H)-carboxylate (8B). Purification by silica gel column chromatography (10% EtOAc/hexanes) provided the title compound as yellow oil in 48% yield (80.0 mg). IR (thin film) 3401, 2900, 1625, 1533, 1384, 1325, 827 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 0.99 (t, 3H, J = 7.3 Hz), 1.44—1.50 (m, 2H), 1.69—1.74 (m, 2H), 2.41 (dd, 1H, J₁ = 13 Hz and J₂ = 16.2 Hz), 2.53 (dd, 1H, J₁ = 4.9 Hz and J₂ = 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). ¹³C NMR (100 MHz, CDCl₃) δ 13.3, 18.8, 36.5, 41.4, 53.4, 99.7, 126.0, 126.1, 126.3, 132.8, 139.4, 156.9, 193.2. HRMS m/z [M + Na]⁺ calcul for C₁₉H₁₈F₂NaO₂, 306.1082; found, 306.1078. [α]ᵢ° = −21.4 (c 0.500, CHCl₃).

(S)-Propyl-6-(trifluoromethyl)phenyl)-2,3-dihydropyridin-4(1H)-one (1b). (88% yield, 19.6 mg). IR (thin film) 3271, 2925, 1605, 1573, 1526, 1384, 1261, 873 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) 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, J₁ = 12.8 Hz and J₂ = 16.1 Hz), 2.49 (dd, 1H, J₁ = 4.8 Hz and J₂ = 16.1 Hz), 3.74—3.82 (m, 1H), 5.03 (br s, 1H), 5.42 (s, 1H), 7.25 (dd, 1H, J₁ = 1.3 Hz and J₂ = 5.1 Hz), 7.40 (dd, 1H, J₁ = 2.9 Hz and J₂ = 5.1 Hz), 7.60 (dd, 1H, J₁ = 1.3 Hz and J₂ = 2.9 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 14.0, 18.8, 36.5, 41.6, 53.1, 98.8, 126.1, 129.1, 130.9, 152.6, 193.3. HRMS m/z [M + Na]⁺ calcul for C₁₀H₁₄F₃NaO, 191.2. Corresponding Author

Notes

The authors declare no competing financial interest.
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