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Synthesis of the Enantiomers of Tedanalactam and the First Total Synthesis and Configurational Assignment of (+)-Piplaroxide

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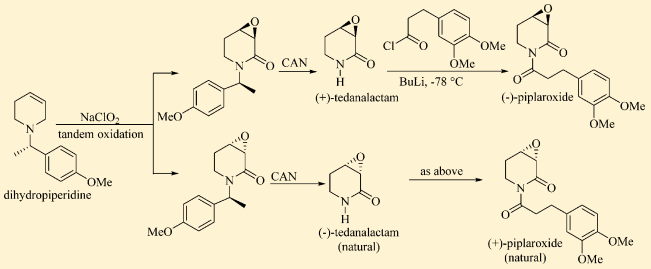
Supporting Information

ABSTRACT: Highlighting the recently established methodology for the direct synthesis of glycidic amides from tertiary allyl amines, the synthesis of the enantiomers of tedanalactam were completed in two steps from the corresponding chiral dihydropiperidine. Additionally, the (+)- and (−)-enantiomers of piplaroxide were obtained from their respective tedanalactam precursor, and the absolute configuration of the naturally occurring (+)-piplaroxide was determined. The present approach represents not only the shortest synthesis of (−)-tedanalactam but also the first total synthesis of (+)-piplaroxide, a repellent against the leafcutter ant *Atta cephalotes*.



The 3,4-epoxy-2-piperidone motif is not only a versatile building block for total synthesis[1] but also a common skeleton encountered in numerous biologically active compounds such as (−)-tedanalactam (**1**)[2] (isolated from the sponge *Tedania ignis*[2a] and the leaves of *Piper crassinervium*[2b]), (+)-kaousine (**2**)[3] (isolated from the aerial parts of *Piper capense* L.f), (−)-3,4-epoxy-5-pipermethystine (**3**)[4] (isolated from the aerial parts of kava, *Piper methysticum*), and (+)-piplaroxide (**4**)[5] (isolated from the leaves of *Piper tuberculatum*) (Figure 1). Despite the interesting biological activity of the naturally occurring 3,4-epoxy-2-piperidones depicted in Figure 1, in which, for instance, alkaloid **2**[3] showed antiplasmodial activity and (+)-piplaroxide (**4**)[5] showed repellency activity against the leafcutter ant *Atta cephalotes*, (−)-tedanalactam (**1**) is the only alkaloid that has been synthesized and has had its absolute configuration defined.[6]

Since the epoxidation of α,β-unsaturated amides in some cases is difficult to achieve,[7] organic chemists have chosen longer strategies for the elaboration of the 3,4-epoxy-2-amide moiety.[1,8] For example, in order to prepare the 3,4-epoxy-2-piperidone motif of (−)-tedanalactam (**1**), Tilve and co-workers[6a] employed Wittig olefination to introduce the α,β-unsaturated ester functionality, which was dihydroxylated under Sharpless conditions, followed by monotosylation, S_N2 cyclization, and lactamization under basic conditions. On the other hand, Nagarapu and co-workers[6b] took advantage of the hydroxy groups at C-3 and C-4, and C-2 of the diacetone-D-glucose to form the oxirane ring and the carbonyl group, respectively (Scheme 1).

As seen in Scheme 1, in order to achieve the relatively simple structure of (−)-tedanalactam (**1**), up to or more than 10 steps have been required. Therefore, a shorter and an efficient route for the synthesis of compounds **1**−**4** is highly desirable. Herein, a more efficient approach to the synthesis of the enantiomers of tedanalactam and the first total synthesis and determination of the absolute configuration of (+)-piplaroxide, a repellent against the leafcutter ant *Atta cephalotes*, are described.

In 2012, the first chemical method for preparing 2,3-epoxyamides (glycidic amides) was reported (Scheme 2).[9] Since $NaClO_2$ is the sole oxidizing reagent used in the double sequential oxidation of the tertiary allyl amines, this methodology not only reduces the cost for preparing glycidic amides but also considerably reduces the environmental impact; that is, C−H oxidation and olefinic epoxidation are generally mediated by transition metals, which are more expensive and toxic than $NaClO_2$. Additionally, this synthetic methodology has shown its utility in the synthesis of norbalasubramide[10] and the synthesis of a potent inhibitor of glycolipid biosynthesis.[11] Thus, the best way to construct the 3,4-epoxy-2-piperidone motif of (−)-tedanalactam (**1**) and subsequently (+)-piplaroxide (**4**) would be by applying this straightforward methodology to chiral dihydropiperidine **5**. Since the absolute configuration of naturally occurring (−)-tedanalactam (**1**) is known, the absolute configurational assignment of (+)-piplaroxide (**4**) can be deduced by chemical correlation with the acylation products from the reaction between either (−)-**1** or (+)-**1** and propanoyl chloride derivative **6** (Scheme 3).

The synthesis started with the (*S*)-α-methylbenzylamine **7**, which was converted in three steps into the dihydropiperidine (*S*)-**5**. Homoallylation of (*S*)-**7**, followed by allylation of (*S*)-**8**, and subsequent ring-closing metathesis (RCM) of the

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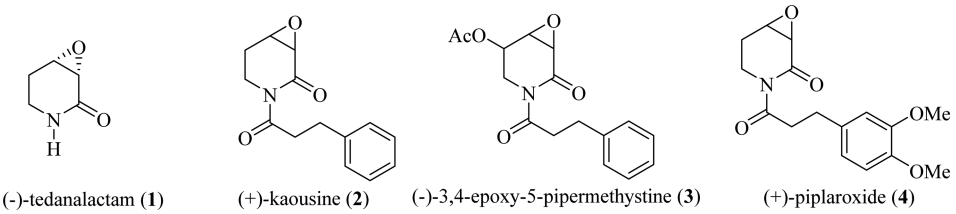
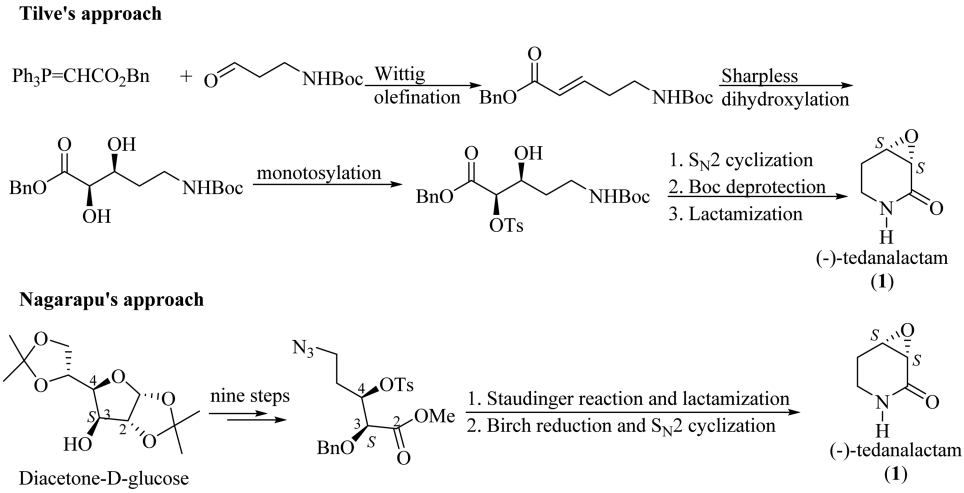
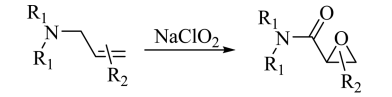


Figure 1. Representative naturally occurring compounds containing the 3,4-epoxy-2-piperidone motif.

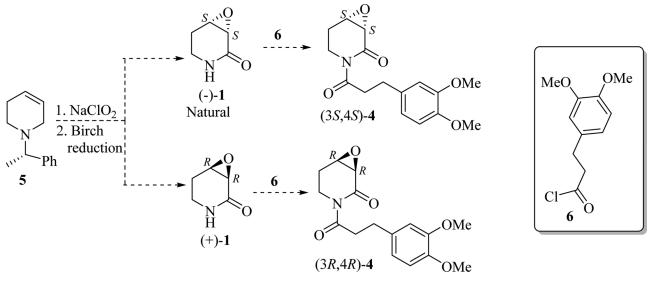
Scheme 1. Synthesis Strategies toward Naturally Occurring (−)-Tedanalactam (1)



Scheme 2. Direct Synthesis of 2,3-Epoxyamides from Tertiary Amines Mediated by $NaClO_2$



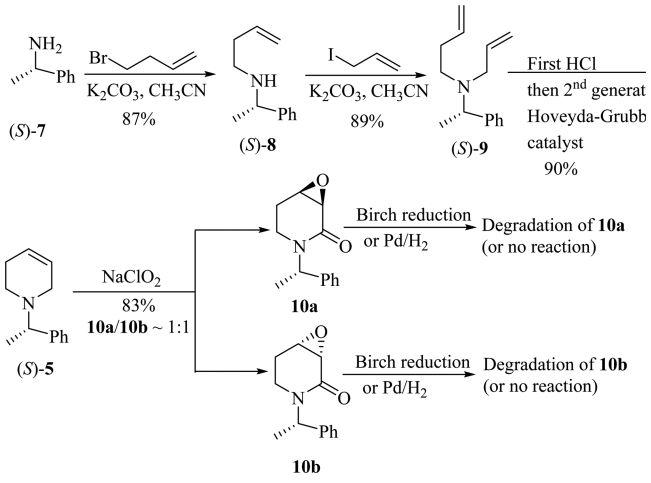
Scheme 3. Synthesis Plan for (−)-1 and (+)-1 and for the First Total Synthesis and Absolute Configurational Assignment of (+)-Piplaroxide (4)



corresponding hydrochloride of (*S*)-**9** with the second-generation Hoveyda−Grubbs catalyst[12] afforded the target cyclic amine (*S*)-**5** in excellent overall yield (70%). RCM attempts with the free amine (*S*)-**9** were unsuccessful.[13]

The treatment of (*S*)-**5** with $NaClO_2$[9] afforded an equimolar diastereomeric mixture of glycidic amides **10a** and **10b** in 83% combined yield (Scheme 4). However, debenzylation either under Birch conditions or Pd-catalyzed hydrogenolysis did not afford the target (−)- and (+)-tedanalactams (**1**), but led to degradation of the starting material or no reaction at all

Scheme 4. Initial Approach for the Synthesis of (−)- and (+)-Tedanalactams



(Scheme 4). Since the removal of the chiral auxiliary under reductive conditions was problematic,[14] a reasonable solution would be the preparation of a chiral dihydropiperidine that could be debenzylated under oxidative conditions. Accordingly, chiral piperidine (*S*)-**11**, which contains the (*S*)-4-methoxy-α-methylbenzylamine chiral auxiliary (**12**) and can be removed under mild oxidizing condition, e.g., in the presence of ceric ammonium nitrate,[15] was prepared in similar yields following the same route as for (*S*)-**5** (Scheme 5).

Like the allyl amine (*S*)-**5**, the application of the tandem oxidation to allyl amine (*S*)-**11** gave a similar yield and diastereomeric ratio of (*S*)-**13a** and (*S*)-**13b** (73% and ∼1:1 ratio). Glycidic amides **13a** and **13b** were separately treated with ceric ammonium nitrate (CAN) in aqueous MeCN to

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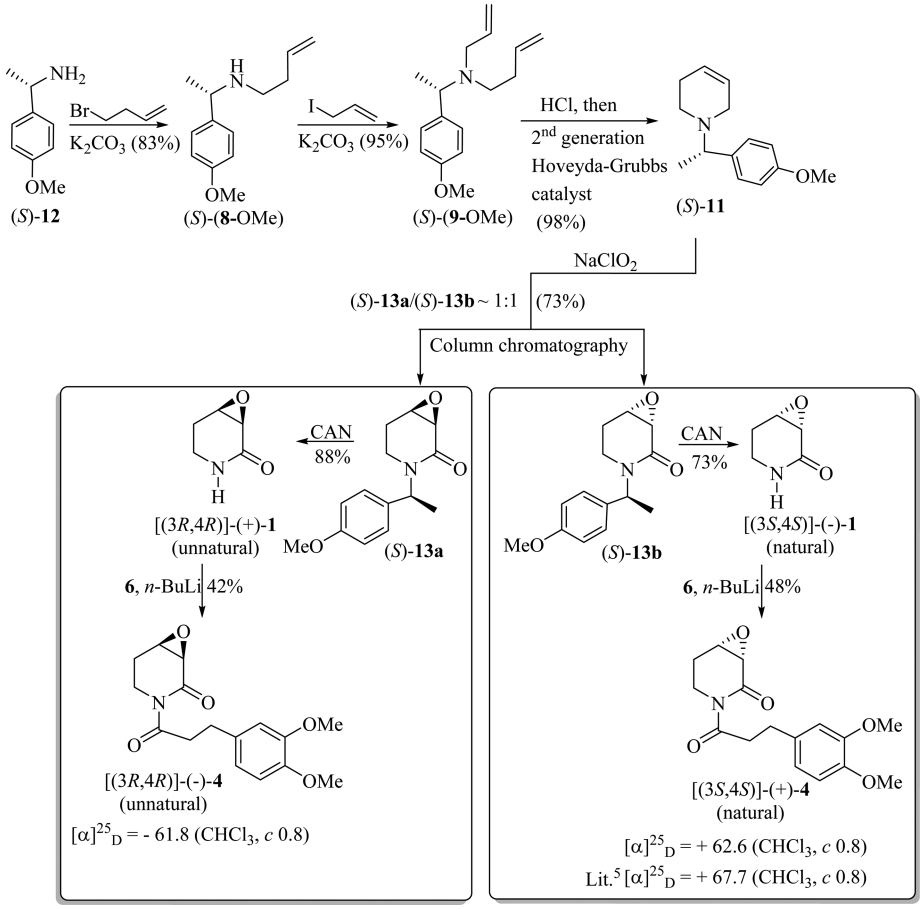
Scheme 5. Five-Step Synthesis of (−)-Tedanalactam and Its Enantiomer and the First Total Synthesis and Absolute Configurational Assignment of Naturally Occurring (+)-Piplaroxide (4)



afford [(3*S*,4*S*)]-(−)-tedanalactam **1** (natural enantiomer) from (*S*)-**13b** and [(3*R*,4*R*)]-(+)-tedanalactam **1** (unnatural) from (*S*)-**13a**. While acylation of naturally occurring (−)-**1** with acyl chloride **6** and *n*-BuLi at −78 °C gave the naturally occurring [(3*S*,4*S*)]-(+)-piplaroxide (**4**) in moderate yield, the synthetic enantiomer **4** [(3*R*,4*R*)-(−)-**4**] was obtained from unnatural (+)-tedanalactam [(+)-**1**] in moderate yield (Scheme 5). The spectroscopic data and specific rotation of (+)-piplaroxide (**4**) are in full agreement with the compound isolated from the air-dried leaves of *P. tuberculatum* by Wiemer and Capron[5] and also defined the absolute configuration of (+)-**4** as 3*S*,4*S*. Additionally, this chemical correlation also suggests that (−)-tedanalactam [(−)-**1**] might be the biosynthetic precursor of (+)-piplaroxide [(+)-**4**] (Scheme 5).

In summary, taking advantage of the tandem oxidation of tertiary allyl amines to glycidic amides mediated by $NaClO_2$ led to the development of an affordable and efficient five-step synthesis of (−)-tedanalactam [(−)-**1**]. In addition, the first total synthesis and absolute configurational assignment of the naturally occurring (+)-piplaroxide [(+)-**4**] has also been achieved.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were carried out under an inert argon atmosphere and anhydrous conditions, unless otherwise noted. Reagents of the highest commercial quality were purchased and used without further purification. Solvents were used as technical grade and freshly distilled prior to use. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. NMR spectra were recorded on a Bruker Ascend 500 NMR spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane as internal reference for ^{1}H (δ 0.00 ppm) and $CDCl_3$ for ^{13}C (δ 77.00 ppm). ^{1}H NMR shift values are reported as chemical shifts δ, relative integral, multiplicity, and coupling constant (J in Hz). High-resolution mass spectra (HRMS) were recorded on a Jeol MStation JMS-700 spectrometer using FAB-QMS (fast atom bombardment). Melting points were recorded on a Fischer Scientific 12-144 melting point apparatus and are uncorrected. Optical rotations were obtained on a PerkinElmer 341 polarimeter.

General Procedure for N-Homoallylation. To a stirred suspension of K_2CO_3 (3.07 g, 22.2 mmol) in MeCN (30 mL) at room temperature was added either (*S*)-(−)-α-methylbenzylamine or (*S*)-(−)-4-methoxy-α-methylbenzylamine (17.8 mmol). The mixture was stirred for 15 min before adding 4-bromobut-1-ene (2.0 g, 14.8 mmol) in MeCN (5 mL) and was then heated at reflux for 6 h. Upon completion, the mixture was cooled to 25 °C, solids were filtered, and the resultant organic phase was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc, 3:1) to afford the corresponding product.

*(S)-N-(1-Phenylethyl)but-3-en-1-amine [(S)-**8**]:* 2.25 g of a light yellow oil (87%); $[\alpha]^{25}_D$ = −21.4 (*c* 0.86, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, J = 6.5 Hz, 3H), 1.78 (bs, 1H), 2.23 (apparent q, J = 7.0 Hz, 2H), 2.50 (dt, J = 11.5, 6.5 Hz, 1H), 2.57 (dt, J = 11.5, 6.5 Hz, 1H), 3.76 (q, J = 6.5 Hz, 1H), 5.02 (m, 1H), 5.07 (m, 1H), 5.74 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H), 7.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 34.2, 46.6, 58.2, 116.3, 126.5, 126.8, 128.4, 136.4, 145.5; HRMS (FAB-QMS) *m*/*z* 176.1403 $[M + H]^+$ (calcd for $C_{12}H_{18}N$, 176.1439).

*(S)-N-[(1-(4-Methoxyphenyl)ethyl)]but-3-en-1-amine [(S)-(**8**-OMe)]:* 2.52 g of a light yellow oil (83%); $[\alpha]^{25}_D$ = −42.5 (*c* 1.0,

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$CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (d, J = 6.5 Hz, 3H), 1.57 (bs, 1H), 2.22 (apparent qq, J = 7.0, 1.5 Hz, 2H), 2.49 (dt, J = 11.5, 7.0, Hz, 1H), 2.55 (dt, J = 11.5, 7.0 Hz, 1H), 3.72 (q, J = 6.5 Hz, 1H), 3.80 (s, 3H), 5.01 (ddt, J = 10.0, 2.0, 1.0 Hz, 1H), 5.06 (apparent dq, J = 17.0, 1.5 Hz, 1H), 5.74 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H), 6.86 (apparent d, J = 8.5 Hz, 2H), 7.22 (apparent d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.2, 34.2, 46.6, 55.2, 57.5, 113.7 (2C), 116.3, 127.5 (2C), 136.5, 137.6, 158.4; HRMS (FAB-QMS) m/z 206.1541 $[M + H]^+$ (calcd for $C_{13}H_{20}NO$, 206.1539).

General Procedure for N-Allylation. To a stirred suspension of K_2CO_3 (2.08 g, 15.1 mmol) and (*S*)-**8** (2.20 g, 12.6 mmol) in MeCN (30 mL) at room temperature was added dropwise over 10 min allyl iodide (2.53 g, 15.1 mmol) in MeCN (5 mL). The mixture was stirred at room temperature for 1.5 h. Upon completion, the mixture was filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc, 4:1) to afford the corresponding product.

*(S)-N-Allyl-N-(1-phenylethyl)but-3-en-1-amine [(S)-**9**]:* 2.40 g of a light yellow oil (89%); $[\alpha]^{25}_D$ = −29.9 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (d, J = 7.0 Hz, 3H), 2.19 (m, 2H), 2.48 (ddd, J = 13.0, 8.5, 7.0 Hz, 1H), 2.58 (ddd, J = 13.0, 8.5, 7.0 Hz, 1H), 3.04 (dd, J = 14.5, 7.0 Hz, 1H), 3.12 (dd, J = 14.5, 7.0 Hz, 1H), 3.87 (q, J = 7.0 Hz, 1H), 4.95 (ddt, J = 10.5, 2.0, 1.0 Hz, 1H), 5.00 (dq, J = 17.0, 1.5 Hz, 1H), 5.08 (m, 1H), 5.16 (dq, J = 17.0, 1.5 Hz, 1H), 5.75 (ddt, J = 17.0, 10.5, 7.0 Hz, 1H), 5.84 (ddt, J = 17.0, 10.5, 7.0 Hz, 1H), 7.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.0, 31.9, 49.0, 53.1, 58.8, 115.2, 116.4, 126.6, 127.6, 128.0, 136.9, 137.1, 144.3; HRMS (FAB-QMS) m/z 216.1751 $[M + H]^+$ (calcd for $C_{15}H_{22}N$, 216.1752).

*(S)-N-Allyl-N-[(1-(4-methoxyphenyl)ethyl)]but-3-en-1-amine [(S)-(**9**-OMe)]:* 2.83 g of a light yellow oil (95%); $[\alpha]^{25}_D$ = −24.5 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.32 (d, J = 6.5 Hz, 3H), 2.19 (apparent qq, J = 7.0, 1.5 Hz, 2H), 2.46 (ddd, J = 13.0, 8.5, 6.5 Hz, 1H), 2.56 (ddd, J = 13.0, 8.5, 6.5 Hz, 1H), 3.02 (ddt, J = 14.5, 6.5, 1.5 Hz, 1H), 3.10 (ddt, J = 14.5, 6.5, 1.5 Hz, 1H), 3.80 (s, 3H), 3.83 (q, J = 6.5 Hz, 1H), 4.95 (ddt, J = 10.0, 2.0, 1.5 Hz, 1H), 5.00 (dq, J = 17.0, 1.5 Hz, 1H), 5.07 (ddt, J = 10.0, 2.0, 1.5 Hz, 1H), 5.15 (dq, J = 17.0, 1.5 Hz, 1H), 5.75 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H), 5.83 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H), 6.85 (apparent d, J = 9.0 Hz, 2H), 7.27 (apparent d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.9, 31.9, 48.9, 53.0, 55.2, 58.0, 113.3 (2C), 115.2, 116.3, 128.6 (2C), 136.2, 137.1, 137.2, 138.2; HRMS (FAB-QMS) m/z 246.1856 $[M + H]^+$ (calcd for $C_{16}H_{24}NO$, 246.1852).

General Procedure for the Ring-Closing Metathesis. To a stirred solution of (*S*)-**9** (2.0 g, 9.29 mmol) in THF (30 mL) at room temperature was added dropwise 5 N HCl until a pH ∼1 was reached (3 mL). After the addition of HCl was completed, the reaction mixture was stirred for 10 min, and the solvent was evaporated under reduced pressure. Then, H_2O (30 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 2.30 g of a yellow oil, which was used directly for the next step without purification. To a stirred solution of crude hydrochloride salt of (*S*)-**9** in anhydrous CH_2Cl_2 (15 mL) at room temperature was added second-generation Hoveyda−Grubbs catalyst (0.174 g, 0.29 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred for 3 h; then, 10 mL of H_2O and a saturated solution of NaOH (pH > 12) were added. The biphasic mixture was extracted with EtOAc (3 × 50 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc, 1:1) to yield the corresponding product.

*(S)-1-(1-Phenylethyl)-1,2,3,6-tetrahydropyridine [(S)-**5**]:* 1.56 g of a brown oil (90%); $[\alpha]^{25}_D$ = +6.5 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (d, J = 7.0 Hz, 3H), 2.05 (m, 1H), 2.16 (m, 1H), 2.38 (ddd, J = 12.5, 7.5, 5.0 Hz, 1H), 2.60 (dt, J = 11.0, 5.0, 1H), 2.87 (ddt, J = 16.5, 5.5, 3.0 Hz, 1H), 3.17 (apparent ddt, J = 16.5, 5.5, 3.0 Hz, 1H), 3.42 (q, J = 7.0 Hz, 1H), 5.66 (m, 1H), 5.74 (m, 1H), 7.28 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.2, 26.5, 47.3, 50.4, 64.9, 125.3, 125.6, 126.8, 127.6, 128.2, 144.2; HRMS (FAB-QMS) m/z 188.1478 $[M + H]^+$ (calcd for $C_{13}H_{18}N$, 188.1439).

*(S)-1-[(1-(4-Methoxyphenyl)ethyl)]-1,2,3,6-tetrahydropyridine [(S)-**11**]:* 2.16 g of a brown oil (98%); $[\alpha]^{25}_D$ = −4.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (d, J = 7.0 Hz, 3H), 2.06 (m, 1H), 2.14 (m, 1H), 2.37 (ddd, J = 11.0, 7.5, 5.0 Hz, 1H), 2.59 (dt, J = 11.0, 5.0, 1H), 2.86 (ddt, J = 16.5, 5.5, 3.0 Hz, 1H), 3.14 (ddt, J = 16.5, 5.5, 3.0 Hz, 1H), 3.40 (q, J = 7.0 Hz, 1H), 3.80 (s, 3H), 5.65 (m, 1H), 5.73 (m, 1H), 6.85 (apparent d, J = 8.5 Hz, 2H), 7.25 (apparent d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0, 26.5, 47.1, 50.3, 55.2, 64.1, 113.4 (2C), 125.2, 125.6, 128.6 (2C), 136.0, 158.4; HRMS (FAB-QMS) m/z 218.1541 $[M + H]^+$ (calcd for $C_{14}H_{20}NO$, 218.1539).

General Procedure for the Synthesis of 2,3-Epoxyamides. Dihydropiperidine (*S*)-**5** (1.52 g, 8.11 mmol) and $NaH_2PO_4{\cdot}H_2O$ (11.2 g, 81.2 mmol) were dissolved in a mixture of *t*-BuOH/THF/H_2O (7:3:3) (104 mL), and the mixture was vigorously stirred at room temperature until the NaH_2PO_4 was completely dissolved. The mixture was cooled to 0 °C followed by the addition of 2-methyl-2-butene (17.8 g, 243.5 mmol); then, $NaClO_2$ (5.87 g, 51.9 mmol) dissolved in H_2O (10 mL) was added. After 12 h of stirring, the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexanes/EtOAc, 2:1) to give the diastereomeric glycidic amides **10a** and **10b**.

*(1R,6R)-3-[(S)-1-Phenylethyl)]-7-oxa-3-azabicyclo[4.1.0]heptan-2-one (**10a**):* 0.56 g of a white solid (43%); mp = 84−85 °C; $[\alpha]^{25}_D$ = −148.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.49 (d, J = 7.0 Hz, 3H), 1.66 (ddd, J = 14.0, 12.5, 6.0 Hz, 1H), 2.17 (m, 1H), 2.72 (dd, J = 12.5, 5.5 Hz, 1H), 3.18 (td, J = 12.5, 4.0 Hz, 1H), 3.56 (apparent s, 2H), 5.99 (q, J = 7.0 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.6, 24.2, 34.3, 50.4, 51.1, 52.6, 127.1, 127.4, 128.4, 139.9, 166.4; HRMS (FAB-QMS) m/z 218.1179 $[M + H]^+$ (calcd for $C_{13}H_{16}NO_2$, 218.1181).

*(1S,6S)-3-[(S)-1-Phenylethyl)]-7-oxa-3-azabicyclo[4.1.0]heptan-2-one (**10b**):* 0.52 g of a white solid (40%); mp = 99−101 °C; $[\alpha]^{25}_D$ = −138.3 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.48 (d, J = 7.0 Hz, 3H), 1.89 (ddd, J = 15.0, 11.0, 9.0 Hz, 1H), 2.24 (apparent dq, J = 15.0, 2.5 Hz, 1H), 2.77 (m, 2H), 3.57 (m, 2H), 5.95 (q, J = 7.0 Hz, 1H), 7.29 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.3, 24.5, 35.3, 50.5, 51.1, 52.8, 127.2, 127.4, 128.4, 139.2, 166.4; HRMS (FAB-QMS) m/z 218.1179 $[M + H]^+$ (calcd for $C_{13}H_{16}NO_2$, 218.1181).

*(1R,6R)-3-[(S)-1-(4-Methoxyphenyl)]ethyl-7-oxa-3-azabicyclo-[4.1.0]heptan-2-one [(S)-**13a**]:* 0.88 g of a white solid (39%); mp = 54−55 °C; $[\alpha]^{25}_D$ = −164.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (d, J = 7.0 Hz, 3H), 1.62 (ddd, J = 15.0, 11.0, 6.0 Hz, 1H), 2.16 (ddt, 15.0, 4.0, 2.0 Hz, 1H), 2.72 (apparent dd, J = 12.5, 6.0 Hz, 2H), 3.15 (td, J = 12.5, 4.0 Hz, 1H), 3.55 (m, 2H), 3.80 (s, 3H), 5.94 (q, J = 7.0 Hz, 1H), 6.86 (apparent d, J = 9.0 Hz, 2H), 7.20 (apparent d, J = 9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.8, 24.2, 34.0, 49.9, 51.1, 52.6, 55.2, 113.7 (2C), 128.3 (2C), 131.9 158.8, 166.3; HRMS (FAB-QMS) m/z 248.1284 $[M + H]^+$ (calcd for $C_{14}H_{18}NO_3$, 248.1281).

*(1S,6S)-3-[(S)-1-(4-Methoxyphenyl)]ethyl-7-oxa-3-azabicyclo-[4.1.0]heptan-2-one [(S)-**13b**]:* 0.77 g of a light yellow solid (34%); mp = 110−111 °C; $[\alpha]^{25}_D$ = −120.41 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (d, J = 7.0 Hz, 3H), 1.88 (ddd, J = 15.0, 11.0, 8.0 Hz, 1H), 2.23 (apparent d, J = 14.0 Hz, 1H), 2.75 (m, 2H), 3.56 (m, 2H), 3.79 (s, 3H), 5.89 (q, J = 7.0 Hz, 1H), 6.86 (apparent d, J = 8.5 Hz, 2H), 7.17 (apparent d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.5, 24.4, 35.2, 50.0, 51.1, 52.8, 55.1, 113.7 (2C), 128.4 (2C), 131.2, 158.7, 166.2; HRMS (FAB-QMS) m/z 248.1283 $[M + H]^+$ (calcd for $C_{14}H_{18}NO_3$, 248.1281).

General Procedure for the *N*-Debenzylation under Oxidative Conditions. Glycidic amide **13b** (0.51 g, 2.06 mmol) was dissolved in MeCN (40 mL), and the solution was cooled to 0 °C followed by the addition of CAN (3.37 g, 6.18 mmol) dissolved in H_2O (10 mL) (previously cooled). The mixture was stirred at 0 °C for 4 h. Upon completion, the mixture was warmed to 25 °C, and brine (30 mL) was added. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic

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J. Nat. Prod. 2016, 79, 1174−1178

phases were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 1:2) to afford 0.170 mg (73%) of (−)-tedanalactam [(−)-**1**] as a yellow oil: $[\alpha]^{25}_D$ = −9.7 (*c* 1.0, MeOH); lit.[6] = $[\alpha]^{27}_D$ = −7.6 (*c* 0.13, MeOH); the ^{1}H and ^{13}C NMR data matched the literature values.[6]

*(+)-Tedanalactam [(+)-**1**]:* 0.185 mg (88%) of a pale yellow oil; $[\alpha]^{25}_D$ = +6.4 (*c* 1.0, MeOH); lit.[2] = $[\alpha]^{30}_D$ = +8.7 (*c* 0.118, MeOH); the ^{1}H and ^{13}C NMR data matched the literature values.[6a]

*3-(3,4-Dimethoxyphenyl)propanoyl chloride (**6**).* To a stirred solution of 3-(3,4-dimethoxyphenyl)propanoic acid (0.08 g, 0.38 mmol) in CH_2Cl_2 (6 mL) at room temperature were added CH_2Cl_2 (3 mL) and DMF (22 μL). The resultant mixture was cooled to 0 °C followed by the addition of oxalyl chloride (0.24 g, 1.9 mmol). The ice bath was removed, and the mixture was stirred at room temperature for 1 h. The resulting clear, pale yellow solution was concentrated in vacuo to afford crude **6** as a yellow oil, which was used immediately for the next reaction without further purification.

To a stirred solution of (−)-tedanalactam [(−)-**1**] (16.4 mg, 0.145 mmol) in anhydrous THF (1.5 mL) at −78 °C was added dropwise *n*-BuLi (12 mg, 0.19 mmol). The reaction mixture was stirred for 40 min before adding acyl chloride **6** (0.38 mmol) dissolved in THF (1.5 mL), and stirred at −78 °C for 6 h. Upon completion, the mixture was warmed to 25 °C, H_2O (2 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 3:1) to afford 21.2 mg of (+)-piplaroxide [(3*S*,4*S*)-(+)-**4**] as a white solid (48%): mp = 86−87 °C; $[\alpha]^{25}_D$ = +62.6 (*c* 0.8, $CHCl_3$); lit.[5] $[\alpha]^{25}_D$ = +67.7 (*c* 0.8, $CHCl_3$); the ^{1}H and ^{13}C NMR data matched those reported by Capron and Wiemer.[5]

*(−)-Piplaroxide[(3R,4R)-(−)-**4**]:* 17 mg of a white solid (42%); mp = 85−87 °C; $[\alpha]^{25}_D$ = −61.8 (*c* 1.0, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b01041.

Copies of ^{1}H NMR and ^{13}C NMR of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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