

An Efficient Synthesis of 2- and 2,6-Substituted Piperidines Using Pd^{II}-Catalyzed 1,3-Chirality Transfer Reaction

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An efficient and general method for 2- and 2,6-substituted piperidine syntheses using Pd^{II}-catalyzed 1,3chirality transfer reaction has been developed. The various *N*-protected ζ -amino allylic alcohols cyclize in the presence of PdCl₂(CH₃CN)₂ to give substituted piperidines with high stereoselectivities. The syntheses of (*S*)-(+)- and (*R*)-(-)-coniine were achieved in 3 steps from the optically pure allylic alcohols (*S*)-**14c** and (*R*)-**14c**, respectively. Although the rates of reactions were significantly accelerated in CH₂Cl₂, THF gave the highest stereoselectivity. PdCl₂(CH₃CN)₂ was found to be the best catalyst for this transformation. A plausible reaction pathway involving the formation of the Pd π -complex directed by the chiral secondary allylic alcohol followed by *syn*-azapalladation, and subsequent *syn*-elimination of PdCl(OH) is proposed.

1. Introduction

Piperidine alkaloids and their analogues comprise a large family of pharmacologically important compounds.¹ Particularly, piperidines bearing the alkyl substituent group at the 2- and/or 2,6-position on the ring can be found as a core structure in many naturally occurring alkaloids that possess a large spectrum of interesting biological activities. They serve as attractive scaffolding for medicinal agents to bind to biological targets. Among them, (S)-(+)- and (R)-(-)-coniine (**1a**) and (**1b**),² (-)-lobeline

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(2),³ alkaloid 241D (3),⁴ and (-)-cassine (4)⁵ are some of the representative examples having simple substituted piperidine rings, which are known to be inhibitors of the neuromuscular, ganglionic, central neuronal nicotinic acetylcholine receptors and HIV-protease. Because of the known dependence between the biological activity of a molecule and its absolute configuration, stereoselective synthesis of various substituted piperidines have evoked immense interest from a both synthetic and

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biological standpoint. Although there are many synthetic methods of piperidines reported in literature,1,6-10 including Mannich-type reaction,⁶ Michael addition,⁷ ring-closing metathesis,8 iminium ion cyclization,9 aza Diels-Alder reaction10 etc. a more efficient, convenient, and highly stereoselective synthetic method is desired.

Pd^{II}-catalyzed C-N bond formation reactions have been documented well in literature,11 and they proceed under milder conditions with high functional group tolerance and high stereoselectivities.¹² Both syn- and anti-azapalladation were discussed with their stereochemistry; however, the exact mechanistic course of this reaction remains unknown. Several reports have demonstrated the anti-azapalladation process,¹³ whereas some recent studies show that the nitrogen nucleophiles bearing electron-withdrawing groups such as sulfonamides and carbamates undergo oxidative coupling with alkenes through synazapalladation.¹⁴ Most recently, Stahl and co-workers illustrated that, although syn-azapalladation is more favored in such type of a reaction, anti-azapalladation could occur as well.¹⁵ This depends upon the substrate, the catalyst, and reaction conditions.

Recently we have reported the Pd^{II}-catalyzed stereospecific synthesis of 5-, 6-, and 7-membered oxaheterocycles by 1,3-

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SCHEME 1. Pd^{II}-catalyzed Cyclizations of Oxygen

IOCArticle



SCHEME 2. Pd^{II}-catalyzed Cyclizations of Nitrogen Nucleophile to Chiral Allylic Alcohols



ζ-amino allylic alcohol R = H or alkyl PG = protecting group

chirality transfer reaction using chiral allylic alcohols (Scheme 1).¹⁶ In this reaction, the stereochemistry at the newly formed chiral center is produced by syn-oxypalladation and synelimination processes. The advantages of this method are; (i) No oxidant such as CuCl₂ is required, because the Pd^{II}-catalyst is regenerated during the reaction. This is how it differs from other oxidative cyclizations to an alkene¹⁷ by Wacker-type reactions. (ii) The reaction proceeds smoothly at 0 °C with excellent selectivities. Since only a few examples of piperidine synthesis using Pd^{II}-catalyzed cyclization of ζ -amino allylic alcohols were reported in literature,¹⁸ there is not much known about the reaction mechanism. Because of our continuous interest in this area, we decided to apply this methodology to the synthesis of chiral 2- and 2,6-disubstituted piperidines (Scheme 2). To establish this as a general method, we synthesized various N-protected ζ -amino allylic alcohols and examined the cyclization reaction using different Pd^{II}-catalysts and solvents. Herein, we report the full account of our study in the synthesis of chiral piperidines and discuss the mechanistic details of this reaction.

2. Results and Discussion

2.1. Synthesis of Various N-Protected ζ -Amino Allylic Alcohols. As is mentioned above, the protecting group on amino functionality is expected to be important in the Pd-catalyzed cyclization for piperidine synthesis. We planned the synthesis of precursors 14a-f possessing six protecting groups on the nitrogen atom via their common intermediate 12. The synthesis is shown in Schemes 3 and 4.

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12 92%

OH

OB₂

OBz

OBz

Compound 12 was synthesized from δ -silyloxypentanal 5¹⁹ in seven steps. Wittig olefination of **5** gave the α,β -unsaturated ketone 6^{20} in 85% yield. Reduction of ketone by sodium borohydride in the presence of CeCl₃ and protection of the resultant allylic alcohol 7 with benzoyl chloride gave benzoate 8 in quantitative yield in two steps. Desilylation of 8 with TBAF followed by mesylation with methanesulfonyl chloride gave 10 in 87 and 99% yields, respectively. Treatment of 10 with sodium azide in DMF afforded azide 11 in 92% yield, which on subsequent reduction with triphenylphosphine in the presence of H₂O gave 12 in 92% yield.

The nitrogen atom of 12 was then protected with methyl carbonate, Boc, Cbz, Fmoc, Ts, and trifluoroacetyl groups. Using the standard procedures,²¹ 13a-f were obtained in good yields as shown in Scheme 4. Basic hydrolysis of benzoates 13a-cand 13e gave cyclization precursors 14a-c and 14e in 93-97% yields. In the case of 13d, deprotection of Fmoc group took place faster than hydrolysis of the benzoate. Therefore, deprotection of benzoate by DIBAL-H was carried out to provide 14d in 75% yield. Methanolysis of 13f afforded 14f in 54% yield along with 30% recovery of starting material. Elongation of reaction time for this reaction resulted in hydrolysis of trifluoroacetamide.

SCHEME 4. Preparation of Precursors 14a-f for Cyclizations



2.1.1. Cyclization of 14a-f Using Pd^{II}-Catalysts in Different Solvents. With precursors 14a-f in hand, the cyclization reaction was investigated. First, we chose the four most efficient Pd^{II}-catalysts-PdCl₂(CH₃CN)₂, PdCl₂(PhCN)₂, $Pd(OAc)_2$, and $Pd(OCOCF_3)_2$ —from the exhaustive screening in the study of oxy-palladation for tetrahydropyran synthesis. Then, we selected some common solvents such as CH₂Cl₂, THF, toluene, and acetonitrile. Primary screenings were performed in a multiple reaction kit using dry solvents under an argon atmosphere. Among the four catalysts, $PdCl_2(CH_3CN)_2$ and PdCl₂(PhCN)₂ were found to be the best catalysts to give

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| | | CH ₂ Cl ₂ | | | THF | | | |
|-------|---------------------------|---------------------------------|-----------|-----------|------------|-----------|-----------|-----------------|
| entry | substrate (PG) | time (min) | temp (°C) | yield (%) | time (min) | temp (°C) | yield (%) | product |
| 1 | 14a (COOCH ₃) | 15 | 0 | 89 | 30 | rt | 82 | 15a, see ref 22 |
| 2 | 14b (Boc) | 5 | 0 | 93 | 60 | 0 | 91 | 15b, see ref 23 |
| 3 | 14c (Cbz) | 10 | 0 | 95 | 45 | rt | 95^a | 15c |
| 4 | 14d (Fmoc) | 30 | 0 | 85 | 90 | rt | 92 | 15d |
| 5 | 14e (Ts) | 5 | 0 | 83 | 30 | rt | 91 | 15e |
| 6 | 14f (COCF ₃) | 30 | rt | | 120 | rt | b,c | 15f |

^{*a*} The results with the use of 1, 5, and 10 mol % of catalyst, see coniine synthesis in the main text. ^{*b*} No cyclization was observed. ^{*c*} Complex mixtures were obtained at 40 °C.

SCHEME 5. Pd^{II}-Catalyzed Synthesis of (S)-(+)- and (R)-(-)-Coniine



cyclized product 15 in CH₂Cl₂ or THF in excellent yields. The reaction with PdCl₂(CH₃CN)₂ was quite slower in toluene at 0 °C because of the reduced solubility of the catalyst. Note that Pd(OCOCF₃)₂ was also effective in THF to complete the reactions, generally in 20 min at room temperature for 14b and in 5 min at room temperature for 14e, whereas reactions with Pd(OAc)₂ required heating at 40 °C for a longer period of time. Among the solvents used, CH₂Cl₂ was found to be the best in reaction at 0 °C. THF and toluene are the next choice of solvents in which the transformation is clean but slower than that in CH₂Cl₂ at room temperature. Reactions in CH₃CN were even slower, and in most cases, a majority of the starting materials were recovered. The coordination of CH₃CN on the catalyst might decrease the reaction rate, which can retard the formation of π -complex or the attack of nucleophile in the azapalladation reaction. This could be the reason why the rate of reaction in THF was also slower and far slower in CH₃CN.

Table 1 lists selected results. The reactions in THF required higher temperature and longer period of time than those in CH_2Cl_2 . Nucleophilicity of nitrogen and stereic factor are important for the rate of reactions. The results indicate *N*-carbamoyl and *N*-sulfonyl groups can be used for cyclization (entries 1–5), although the *N*-trifluoroacetyl group is unsuitable for this purpose in both solvents (entry 6).

2.1.2. Enantioselective Synthesis of (S)-(+)- and (R)-(-)-Coniine. In view of these findings, we now focus on the stereochemical outcome of this reaction and the related reaction

mechanism. For this purpose, we choose the synthesis of (*S*)-(+)- and (*R*)-(-)-coniine² using (*S*)-(-)-14c and (*R*)-(+)-14c as the chiral starting materials. Although Hirai et al. reported the synthesis of (*R*)-coniine from (*S*)-(-)-14c using PdCl₂(CH₃CN)₂ catalyst,²⁴ the structure in their report indicated the (*R*)-configuration but the (+)-sign was shown. As per our prediction, the stereospecific attack of the nucleophile based on the stereochemistry of oxaheterocycles¹⁶ should take place from syn with respect to the chiral alcohol to afford (*S*)-(+)-coniine from (*S*)-(-)-14c, contrary to the results that appeared in their report. Therefore, re-examinations were carried out. Our results are depicted in Scheme 5.

Lipase (Candida Antarctica lipase; Novozyme 435) catalyzed kinetic acetylation of racemic **14c** gave (*R*)-acetate **16** in 40% yield along with an (*S*)-**14c** in 41% yield with >99% ee. Although methanolysis of **16** gave (*R*)-**14c** in 99% yield with 87% ee, the enzymatic acetylation and methanolysis of the resulted acetate were repeated to raise its ee value up to 99%. Treatment of enantiomerically pure (*S*)-(-)-**14c** with 10 mol % of PdCl₂(CH₃CN)₂ in THF at room temperature for 75 min afforded (*R*)-(+)-**15c**²⁵ in 92% yield with 93% ee. This result was reproducible when the reaction of (*R*)-(+)-**14c** in THF at room temperature for 80 min gave (*S*)-(-)-**15c** in 93% yield with 92% ee. When this reaction was carried out in CH₂Cl₂ at

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SCHEME 6. Preparation of 25a, 25b, and 27



0 °C for 30 min, (S)-(-)-15c was obtained with 91% ee. On the other hand, catalysts can be reducible to 5 mol %. The reaction took for 2 h in THF at rt leading to the cyclized product in 89% yield. However, when 1 mol % of PdCl₂(CH₃CN)₂ was used, the reaction stopped after 3.5 h and the cyclized product was obtained in 58% yield along with the recovery of starting material in 39% yield. Having successfully effected the key chirality transfer step, we then deprotected the Cbz group and reduced the double bond of (R)-(+)-15c all in one step using Pearlman's catalyst under a H_2 atmosphere. This gave (S)-(+)coniine 1a, which was then treated with HCl gas in ether to give (S)-(+)-coniine hydrochloride in two steps with 95% yield. (R)-(-)-Coniine **1b** hydrochloride was obtained in 90% yield from (S)-(-)-15c using the same two steps. The absolute configurations of **1a** and **1b** indicated in Scheme 5 were determined by specific degrees, which were consistent with the data of (+)- and (-)-coniine reported in literature.² Therefore, the stereochemical outcome in the piperidine synthesis is similar to that in the tetrahydropyran synthesis. Thus, in both the reactions, the formation of the product was directed by the chiral secondary allylic hydroxy group. However, it should be noted that the diastereoselectivity was nearly 92-3% de (96:4 to 97:3 ratio), which meant an occurrence of 3-4% of antiazapalladation. In comparison, the synthesis of the tetrahydropyran ring was exclusively stereospecific by syn-oxypalladation.¹⁶

2.2. Stereocontrolled Synthesis of 2,6-Disubstituted Piperidine.

2.2.1. Synthesis of Precursors of Cyclization Bearing Two Chiral Centers. Knowing the importance of solvent, catalyst, and protecting group for this cyclization reaction, the chemistry was developed for the synthesis of optically active 2,6-disustituted piperidines. The preparation of precursors **25a**, **25b**, and **27** are shown in Scheme 6.

The key chiral alcohols were generated by Carreira's asymmetric alkynylation.²⁶ Alkynylation of cyclohexanecarboxaldehyde with (S)-6-sililoxy-1-heptyne 17^{27} in the presence of $Zn(OTf)_2$ and (+)-N-methylephedrine produced (R)-propargyl alcohol 18a in 89% yield with 96% de.^{16b} Similarly, when (-)-N-methylephedrine was used instead of (+)-N-methylephedrine, the diastereomer 18b was obtained in 73% yield with 94% de. A partial reduction of 18a and 18b with Red-al followed by benzoylation of the generated allylic alcohols 19a and 19b gave benzoates 20a in 89% yield and 20b in 81% yield in two steps, respectively. The O-TBS group of 20 was transformed to a NHCOOCH₃ group in 6 steps. Desilylation of 20a and 20b with TBAF and the resultant alcohols 21a and 21b were treated with methanesulfonyl chloride in the presence of triethylamine to afford **22a** and **22b** both in 89% yield in two steps, respectively. The SN2 displacement of the mesylate with NaN₃ gave azides 23a in 94% yield and 23b in 90% yield. The reduction of azido group in 23a was effected by PPh3 in THF/H2O, and the produced amine was protected in situ with methyl chlorocarbonate in the presence of triethylamine, giving 24a in 80% yield. A similar reaction with 23b afforded 24b in 74% yield. Hydrolysis of benzoate by NaOH in aq. methanol gave 25a in 96% yield with 96% ee and also gave 25b in 91% yield with 94% ee, respectively. After the reduction of 23a, in situ protection of the amine with Boc anhydride gave 26 in 85% yield in 2 steps, and the subsequent hydrolysis of benzoate provided 27 in 98% yield.

2.2.2. Diastereoselective Synthesis of Cis and Trans 2,6-Disubstituted Piperidine Derivatives. Next, we examined the cyclization reaction on 25a and 25b. The results are listed

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| | | PG H NH | $PdCl_2(CH_3CN)_2$ (30 mol%) conditions $PG = COOCH_3$ | PG H I R' |] | |
|-------|------------------------|--------------------------------------|--|---------------------------------------|------------|-------------|
| | | 25a : R = ····OH | | 28a : R' = ── H (<i>tra</i> | ns) | |
| | | 25b: R =OH | | 28b : R' = ·····H (<i>cis</i> | <i>S</i>) | |
| entry | substrate ^a | solvent | time $(h)^b$ | product | yield (%) | de $(\%)^c$ |
| 1 | 25a | THF | 6.5 | 28a | 81 | 88 |
| 2 | 25a | CH_2Cl_2 | 0.5 | 28a | 79 | 49 |
| 3 | 25a | ClCH ₂ CH ₂ Cl | 0.75 | 28a | 75 | 69 |
| 4 | 25a | toluene | 15 | 28a | 83 | 82 |
| 5 | 25a | CH ₃ CN | 6 | 28a | 68 | 44 |
| 6 | 25b | THF | 3.5 | 28b | 85 | 86 |
| 7 | 25b | CH_2Cl_2 | 11^{d} | 28b | 82 | 19 |

^{*a*} Compounds **25a** with 96% de and **25b** with 94% de were used. ^{*b*} Reactions were conducted at room temperature except stated otherwise. ^{*c*} The de values were calculated based on ¹H NMR spectra. ^{*d*} The reaction was conducted at 0 °C.



FIGURE 2. Plausible mechanistic and stereochemical pathway for piperidine synthesis by 1,3-chirality transfer process.

in Table 2. First, cyclization of **25a** with 96% de was conducted under the same conditions described for the synthesis of coniine.

However, the reaction was slow and did not go to the completion even after 24 h. When Pd^{II}-catalyst was increased to 30 mol%, the cyclization of 25a occurred faster at room temperature to give 28a in 81% yield with 88% de (entry 1). The reactions of 25a were faster in halogenated solvents, CH_2Cl_2 or dichloroethane, and were completed in 30 and 45 min at room temperature to give 28a in 79 and 75% yields, respectively (entries 2 and 3). However, surprisingly, the diastereoselectivity decreased to 49% de and 69% de. The higher selectivity with 82% de obtained in toluene (entry 4) was similar to that in THF (entry 1). The reaction in CH₃CN was not clean, resulting in a poor yield with less selectivity (entry 5). Similarly, the reaction of diastereomer 25b with 94% de in THF was completed in 3.5 h to give cis piperidine 28b in 85% yield with 86% de, whereas that in CH₂Cl₂ was completed in 11 h at 0 °C to give 28b in 82% yield with only 19% de. It is interesting that the formation of cis 2,6-substituted piperidine is faster than that of trans piperidine in both solvents. Overall, the use of THF was proved to be the best for the synthesis of 2,6-disubstituted piperidines. Using **27** bearing Boc group instead of methoxy-carbonyl group on the nitrogen atom resulted in no reaction. The stereochemistry of **28a** and **28b** was confirmed by NOE experiments.

2.2.3. Mechanism of the Cyclization. A proposed reaction mechanism for the Pd^{II}-catalyzed stereoselective ring formation of piperidine by 1,3-chirality transfer is outlined in Figure 2. Coordination of the Pd^{II}-catalyst to both the chiral allylic alcohol and the double bond forms the palladium π -complex I, from syn to the chiral secondary allylic alcohol.²⁸

In the next step, a ligand exchange occurs to give complex II, which is in an equilibrium with I. The step is important for the chiral induction in which the nitrogen nucleophile attacks

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the alkenyl carbon from the same side of Pd π -complex. Synazapalladation gives σ -Pd intermediate III by elimination of a HCl molecule, which on subsequent syn-elimination of Pd-Cl(OH) delivers the major isomer (trans) in this case. Depending on the substrate and reaction conditions, the reaction may proceed partially through the antiazapalladation pathway from the palladium π -complex I to give the complex IV, which on syn-elimination of PdCl(OH) gives the minor isomer (cis) in this case. The catalyst is regenerated by the reaction of PdCl(OH) with HCl during the reaction sequence. The low selectivity obtained in solvents like CH2Cl2 can be justified based on the stability of complex II. If complex II is less stable than complex I, the antiattack of nucleophile leading to IV (i.e., from the opposite side of the Pd π -complex) may take place, which will give the minor product. When compared, the corresponding complex II of the 2-substituted piperidine (i.e., $R_1 = H$) is more stable than the complex II of 2,6-disubstituded piperidine (i.e., $R_1 = CH_3$), because in the latter case it is under more steric demand. Because of this reason, the better selectivity was obtained in monosubstituted piperidine (Scheme 5) than that in the 2,6-disubstituted piperidine (Table 2).

3. Conclusions

In conclusion, we have described a PdII-catalyzed intramolecular cyclization of N-protected ζ -amino allylic alcohols and the stereospecific synthesis of 2-substituted and 2,6disubstituted piperidines. The concise syntheses of (S)-(+)and (R)-(-)-coniine were achieved using this method. The reaction gives a syn SN2' product majorly through syncoordination of the PdII-catalyst to the allylic alcohol followed by syn-azapalladation and syn-elimination of PdCl(OH), leading to the product. Although the syn-azapalladation is found to be more favored, the formation of a minor isomer suggests that the anti-azapalladation is also plausible and it depends upon the substrate and solvent. The reaction and its rate suffer in a steric environment with an N-protecting group and an alkyl group. For the formation of 2,6-disubstituted piperidine, the reaction rate was slower than that of 2-substituted piperidine due to the steric hindrance. The reaction in dichloromethane was generally faster as compared to other solvents, although THF indicated higher stereoselectivity in the case of 2,6-disubstituted piperidine. This method will allow efficient and flexible synthesis of chiral 2- or 2,6substituted piperidines.

4. Experimental Section

(*E*)-8-(*tert*-Butyldimethylsilyloxy)oct-3-en-2-one (6). 1-(Triphenylphosphoranylidene)-2-propanone (17 g, 53.37 mmol) was added to a solution of aldehyde **5** (10.5 g, 48.52 mmol) in toluene (240 mL), and the reaction mixture was stirred at 80 °C for 15 h. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 10% EtOAc in hexane gave **6** (10.62 g, 85%): colorless oil; $R_f = 0.28$ (10% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 6.78 (dt, 1H, J = 16.0, 6.8 Hz), 6.05 (dt, 1H, J = 16.0, 1.5 Hz), 3.60 (m, 2H), 2.22 (s, 3H), 2.17–2.25 (m, 2H), 1.40–1.59 (m, 4H), 0.87 (s, 9H), 0.02 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 198.6, 148.2, 131.3, 62.6, 32.2, 32.1, 26.8, 25.9, 24.4, 18.3, -5.4; IR (film, cm⁻¹) 2930, 2854, 1677, 1253, 1100; MS (CI) m/z 257 (M + H⁺); HRMS calcd for C₁₄H₂₉O₂Si (M + H⁺) 257.1937; Found: m/z 257.1931.

(E)-8-(tert-Butyldimethylsilyloxy)oct-3-en-2-ol (7). NaBH₄ (2.31 g, 61.1 mmol) was added in small portions to a stirred solution of 6 (10.45 g, 40.75 mmol) and CeCl₃•7H₂O (15.18 g, 40.75 mmol)

in methanol (300 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction was recooled to 0 °C, quenched with water, acidified with 1N HCl to its pH between 5-6and extracted with EtOAc. The combined organic layer was dried over MgSO₄. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 25% EtOAc in hexane gave 7 (10.52 g, quant): colorless oil; $R_f = 0.25$ (10% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 5.62 (dt, 1H, J = 15.4, 6.8 Hz), 5.50 (dd, 1H, J = 15.4, 6.4 Hz), 4.25 (dq, 1H, J = 6.4, 6.2 Hz), 3.60 (t, 2H, J = 6.3 Hz), 2.02 (dt, 2H, J =7.2, 6.8 Hz), 1.70 (br, 1H), 1.35-1.56 (m, 4H), 1.24 (d, 3H, J =6.4 Hz), 0.89 (s, 9H), 0.04 (s, 6H); 13 C NMR (75 MHz, CDCl₃) δ 134.3, 130.8, 68.9, 63.0, 32.3, 31.8, 25.9, 25.4, 23.4, 18.3, -5.3; IR (film, cm⁻¹) 3349, 2930, 2857, 1472, 1254, 1102. MS (FAB) m/z 281 (M + Na⁺); HRMS calcd for C₁₄H₃₀O₂SiNa (M + Na⁺) 281.1913; Found: m/z 281.1918.

(E)-2-Benzoyloxy-8-(tert-butyldimethylsilyloxy)oct-3-ene (8). Benzoyl chloride (9.65 mL, 83.03 mmol) was added at 0 °C to a stirred solution of 7 (10.72 g, 41.5 mmol), Et₃N (28.9 mL, 207.6 mmol) and DMAP (0.507 g, 4.15 mmol) in CH₂Cl₂ (250 mL). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with H₂O, and the organic layer was separated. The aqueous layer was extracted (CH₂Cl₂), and the combined organic extract was dried over MgSO₄. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 10% EtOAc in hexane gave 8 (14.96 g, 99%): colorless oil; $R_f = 0.75$ (20% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.04 (d, 2H, J = 7.1 Hz), 7.54 (t, 1H, J =7.1 Hz), 7.42 (t, 2H, J = 7.1 Hz), 5.73–5.85 (m, 1H), 5.48–5.70 (m, 2H), 3.60 (t, 2H, J = 6.2 Hz), 2.07 (dt, 2H, J = 7.2, 7.0 Hz) 1.40-1.57 (m, 4H), 1.42 (d, 3H, J = 6.0 Hz), 0.89 (s, 9H), 0.04(s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 133.2, 132.7, 130.9, 129.7, 129.5, 128.2, 71.7, 63.0, 32.3, 31.9, 26.0, 25.2, 20.5, 18.3, -5.3; IR (film, cm⁻¹) 2930, 2857, 1729, 1451, 1271, 1108; MS (CI) m/z 363 (M + H⁺); HRMS calcd for C₂₁H₃₅O₃Si (M + H⁺) 363.2355; Found: m/z 363.2359.

(*E*)-2-Benzoyloxy-8-hydroxyoct-3-ene (9). TBAF (1.0 M in THF, 45.4 mL, 45.4 mmol) was added to a stirred solution of **8** (14.94 g, 41.24 mmol) in THF (196 mL) at room temperature. The reaction mixture was stirred overnight. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with 50% EtOAc in hexane to give **9** (8.86 g, 87%): colorless oil; $R_f = 0.25$ (20% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.03 (dd, 2H, J = 7.7, 1.5 Hz), 7.54 (tt, 1H, J = 7.3, 1.1 Hz), 7.42 (t, 2H, J = 7.7 Hz), 5.78 (dt, 1H, J = 14.3, 6.6 Hz), 5.51–5.62 (m, 2H), 3.63 (t, 2H, J = 6.3 Hz), 2.08 (dt, 2H, J = 7.1, 6.6 Hz), 1.44–1.62 (m, 5H), 1.42 (d, 3H, J = 6.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 165.9, 132.9, 132.7, 130.8, 129.8, 129.5, 128.2, 71.7, 62.7, 32.1, 31.8, 25.0, 20.5; IR (film, cm⁻¹) 3374, 2933, 2861, 1716, 1451, 1273, 1111; MS (CI) *m*/*z* 249 (M + H⁺); HRMS calcd for C₁₅H₂₁O₃ (M + H⁺) 249.1491; Found: *m*/*z* 249.1493.

(E)-2-Benzoyloxy-8-(methanesulfonyloxy)oct-3-ene (10). MsCl (5.5 mL, 71.2 mmol) was added to a stirred solution of 9 (8.44 g, 35.61 mmol) and Et₃N (24.8 mL, 178.1 mmol) in CH₂Cl₂ (200 mL) at 0 °C. The reaction mixture was stirred for 30 min at room temperature. The reaction was then quenched with H₂O, and the organic layer was separated. The aqueous layer was extracted (CH₂Cl₂), and the combined organic layer was dried over MgSO₄. Filtration and evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 30% EtOAc in hexane gave 10 (11.52 g, 99%): colorless oil; $R_f = 0.25$ (20% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.04 (d, 2H, J = 7.2 Hz), 7.55 (t, 1H, J = 7.3 Hz), 7.43 (t, 2H, J = 7.3Hz), 5.75 (dt, 1H, J = 14.5, 6.7 Hz), 5.52-5.63 (m, 2H), 4.22 (t, 2H, J = 6.4 Hz), 2.99 (s, 3H), 2.00 (dt, 2H, J = 7.2, 6.7 Hz), 1.70-1.80 (m, 2H), 1.47-1.57 (m, 2H), 1.42 (d, 3H, J = 6.2 Hz);¹³C NMR (75 MHz, CDCl₃) δ 165.8, 132.8, 132.1, 130.7, 130.5, 129.5, 128.3, 71.5, 69.8, 37.4, 31.4, 28.5, 24.7, 20.5; IR (film, cm⁻¹)

2938, 1714, 1451, 1274, 1112; MS (FAB) m/z 349 (M + Na⁺); HRMS calcd for C₁₆H₂₂O₅SNa (M + Na⁺) 349.1086; Found: m/z 349.1091.

(E)-8-Azido-2-benzoyloxy-oct-3-ene (11). A mixture of 10 (11.5 g, 35.23 mmol) and sodium azide (6.87 g, 105.7 mmol) in dry DMF (120 mL) was stirred at room temperature for 24 h. After a removal of DMF under vaccum, water was added and the mixture was extracted with EtOAc. The extract was dried over MgSO4. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 10% EtOAc in hexane gave 11 (8.83 g, 92%): colorless oil; $R_f = 0.77$ (20% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.05 (dd, 2H, J = 7.3, 1.5 Hz), 7.55 (tt, 1H, J = 7.3, 1.5 Hz), 7.43 (dt, 2H, J = 7.3, 1.5 Hz), 5.77 (dt, 1H, J = 14.5, 6.8 Hz), 5.52–5.64 (m, 2H), 3.26 (t, 2H, J = 6.7 Hz), 2.08 (dt, 2H, J = 7.2, 6.8 Hz), 1.56–1.63 (m, 2H), 1.44-1.52 (m, 2H), 1.43 (d, 3H, J = 6.2 Hz); 13 C NMR (75 MHz, CDCl₃) & 165.8, 132.7, 132.4, 130.8, 130.2, 129.5, 128.3, 71.5, 51.3, 31.6, 28.3, 26.0, 20.5; IR (film, cm⁻¹) 2935, 1716, 1451, 1271, 1110; MS (CI) m/z 274 (M + H⁺); HRMS calcd for C₁₅H₂₀N₃O₂ $(M + H^+)$ 274.1555; Found: m/z 274.1554.

(*E*)-8-Amino-2-benzoyloxy-oct-3-ene (12). A mixture of 11 (4 g, 12.8 mmol) and triphenylphosphine (7.68 g, 25.61 mmol) in H₂O (6 mL) and THF (120 mL) was stirred at room temperature for 24 h. Evaporation of solvents and purification of the residue by column chromatography on silica gel eluted with 20% MeOH in chloroform gave 12 (3.34 g, 92%): colorless oil; $R_f = 0.33$ (10% MeOH in chloroform); ¹H NMR (300 MHz, CDCl₃) δ 8.04 (dd, 2H, J = 7.1, 1.3 Hz), 7.54 (tt, 1H, J = 7.3, 1.3 Hz), 7.42 (dt, 2H, J = 7.1, 1.3 Hz), 5.78 (dt, 1H, J = 14.5, 6.6 Hz), 5.30–5.63 (m, 2H), 2.69 (t, 2H, J = 6.6 Hz), 2.06 (dt, 2H, J = 6.8, 6.6 Hz), 1.88 (br s, 2H), 1.42 (d, 3H, J = 6.0 Hz), 1.40–1.57 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 133.0, 132.7, 130.8, 129.8, 129.5, 128.2, 71.7, 41.8, 32.8, 31.9, 26.2, 20.5; IR (film, cm⁻¹) 3370, 2979, 1715, 1451, 1272, 1111; MS (EI) m/z 247 (M⁺); HRMS calcd for C₁₅H₂₁NO₂ (M⁺) 247.1572; Found: m/z 247.1577.

General Procedure for Pd^{II} -Catalyzed Cyclization. A mixture of precursor 14a-f (0.1 mmol) and $PdCl_2(CH_3CN)_2$ (10 or 20 mol %) was stirred in dry solvent (2.5 mL) at 0 °C to room temperature. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 10% EtOAc in hexane gave the corresponding 15a-f. The chemical yields and their characteristic data are indicated in Table 1 and in the Supporting Information.

Lipase Catalyzed Kinetic Acetylation of Racemic 14c. MS 4 Å (1.78 g), Novozyme 435 (0.45 g), and vinyl acetate (3.04 mL, 44.55 mmol) were added to a solution of **14c** (1.5 g, 8.91 mmol) in diisopropyl ether (175 mL) at room temperature. The mixture was stirred for 20 h and filtered through a celite pad. The filtrate was condensed, and the residue was purified by column chromatography on silica with 15% EtOAc in hexane as an eluent to give (*S*)-**14c** (621 mg, 41%) with 99% ee and with 25% EtOAc in hexane as an eluent to give **16** (811 mg, 40%) with 87% ee. Compound (*S*)-**14c**: amorphous solid, mp 28–29 °C; $[\alpha]_{D}^{23}$ –2.9 (*c* 0.51, CHCl₃); other spectroscopic data were all matched with those in racemic **14c** described above. The enantiomeric purities were determined by chiral HPLC, the details for which are described in the Supporting Information.

Preparation of (*R***)-14c.** A solution of **16** (811 mg, 2.54 mmol) with 87% ee in methanol (20 mL) and aq. K₂CO₃ (702 mg, 5.08 mmol) in H₂O (1 mL) was stirred overnight at room temperature. After removal of solvent under vaccum, water was added to the residue and the mixture was extracted with EtOAc. The organic layer was dried over MgSO₄ and purified by column chromatography on silica gel eluted with 50–60% EtOAc in hexane to give (*R*)-**14c** (695 mg, 99%) with 87% ee. This was subjected to the above lipase catalyzed kinetic acetylation to give **16** in 84% yield with 99% ee: colorless oil; $[\alpha]_{10}^{20}$ +38.0 (*c* 0.2, CHCl₃): *R_f* = 0.65 (40% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.26–7.36 (m, 5H), 5.65 (dt, 1H, *J* = 15.2, 6.6 Hz), 5.45 (dd, 1H, *J* = 15.2,

6.7 Hz), 5.29 (dq, 1H, J = 6.7, 6.4 Hz), 5.09 (s, 2H), 4.85 (br, 1H), 3.18 (q, 2H, J = 6.4), 2.02 (s, 3H), 1.98–2.07 (m, 2H), 1.39–1.49 (m, 4H), 1.28 (d, 3H, J = 6.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 170.3, 156.3, 136.5, 132.5, 129.9, 128.4, 128.0 (2C), 71.0, 66.5, 40.8, 31.6, 29.3, 25.9, 21.3, 20.3; IR (film, cm⁻¹) 3346, 2934, 1730, 1532, 1243, 1136; MS (FAB) *m/z* 342 (M + Na⁺); HRMS calcd for C₁₈H₂₅NO₄Na (M + Na⁺) 342.1681; Found: *m/z* 342.1676. This optically pure (*R*)-acetate was hydrolyzed again to give pure (*R*)-**14c** in 98% yield with 99% ee.; [α]₆²⁴ +1.7 (*c* 0.53, CHCl₃).

Preparation of (R)-15c and (S)-15c. The reaction was performed by the general procedure for Pd^{II}-catalyzed cyclization. Compound (*R*)-15 c^{25} was obtained from (*S*)-14c in 92% yield with 93% ee; colorless oil; $[\alpha]_D^{22}$ +37.3 (*c* 0.72, CHCl₃). $R_f = 0.74$ (40% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.25–7.35 (m, 5H), 5.41-5.58 (m, 2H), 5.13 (q, 2H, J = 12.3 Hz), 4.82 (br s, 1H), 4.01 (d, 1H, J = 12.8 Hz), 2.91 (dt, 1H, J = 12.8, 2.7 Hz), 1.68 (dd, 3H, J = 4.6, 1.5 Hz), 1.37–1.69 (m, 6H); ¹³C NMR (75 MHz, $CDCl_3$) δ 155.6, 137.0, 129.0, 128.3, 127.7, 127.6, 126.8, 66.8, 52.1, 39.9, 29.3, 25.5, 19.3, 17.7; IR (film, cm⁻¹) 2936, 2857, 1697, 1497, 1255, 1171; MS (EI) m/z 259 (M⁺); HRMS calcd for C₁₆H₂₁NO₂ (M⁺) 259.1572; Found: *m/z* 259.1578. Compound (S)-15c was obtained from (R)-14c in 93% yield with 92% ee; colorless oil, $[\alpha]_D^{22}$ –38.2 (*c* 0.62, CHCl₃). These enantiomeric purities were determined by chiral HPLC, the details for which are described in the Supporting Information.

Synthesis of Coniines 1a and 1b Hydrochlorides. A mixture of (R)-15c (96 mg, 0.3 mmol) and Pd(OH)₂/C (8 mg) in methanol (10 mL) was stirred under H₂ atmosphere at room temperature for 24 h. The reaction mixture was then filtered through a ceilite bed. Then, HCl gas was bubbled into the obtained filtrate. Evaporation of the solvent gave the corresponding coniine hydrochloride, (S)-(+)-Coniine 1a hydrochloride, in 95% yield in two steps. White solid; $[\alpha]_D^{21}$ +7.1 (c 1.00, EtOH); colorless crystals, mp 214–216 °C (methanol), lit.^{2d} mp 213-215 °C; ¹H NMR (300 MHz, CDCl₃) δ 9.48 (br s, 1H), 9.18 (br s, 1H), 3.44 (d, 1H, J = 10.5 Hz), 2.93 (br s, 1H), 2.83 (br s, 1H), 1.62–1.96 (m, 7H), 1.37–1.52 (m, 3H), 0.94 (t, 3H, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 57.2, 44.8, 35.3, 28.2, 22.4, 22.2, 18.6, 13.7; MS (EI) m/z 127 (M⁺); HRMS calcd for C₈H₁₇N (M⁺) 127.1361; Found: *m*/*z* 127.1357. (*R*)-(-)-Coniine **1b** hydrochloride. HCl was obtained from (S)-**15c** in 90% yield in two steps. White solid; $[\alpha]_D^{21}$ -6.3 (c 1.00, EtOH); colorless crystals, mp 218–220 °C (methanol); MS (EI) m/z 127 (M⁺); HRMS calcd for $C_8H_{17}N$ (M⁺) 127.1361; Found: m/z 127.1353.

(1S,7S)-7-(tert-Butyldimethylsilyloxy)-1-cyclohexyloct-2-yn-1ol (18b). Et₃N (0.257 mL, 1.8 mmol) was added in one portion to a stirred suspension of Zn(OTf)₂ (618 mg, 1.65 mmol, predried overnight at 125 °C under vacuum) and (-)-N-methylephedrine (332 mg, 1.8 mmol) in dry toluene (4.9 mL). After the white slurry was stirred at room temperature for 3 h, alkyne 17 (350 mg, 1.5 mmol) was added. The mixture was stirred for 30 min and then treated with freshly distilled cyclohexanecarboxaldehyde (173 mg, 1.5mmol). After the mixture was stirred for 3 h at room temperature, a saturated NH₄Cl solution was added to the mixture, and the aqueous layer was extracted (EtOAc). After filtration and evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with 5% of EtOAc in hexane to give product **18b** (382 mg, 73%): colorless oil; $[\alpha]_D^{23}$ +11.6 (*c* 1.08, CHCl₃) (>94% de, based on chiral HPLC); $R_f = 0.32$ (10% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 4,13 (br, 1H), 3.81 (qt, 1H, J = 6.0, 5.5 Hz), 2.19–2.24 (m, 2H), 1.43–1.85 (m, 10H), 1.13 (d, 3H, J = 6.0 Hz), 1.02–1.26 (m, 5H), 0.88 (s, 9H), 0.05 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 86.2, 80.3, 68.2, 67.4, 44.4, 38.8, 28.6, 28.1, 26.4, 25.9, 25.9, 25.0, 23.8, 23.7, 18.8, 18.1, -4.4, -4.7; IR (film, cm⁻¹) 3367, 2927, 1450, 1374, 1254, 1186, 1136, 1023, 892, 835, 774; MS (FAB) m/z 361 (M + Na⁺). HRMS calcd for $C_{20}H_{38}O_2SiNa$ (M + Na⁺): 361.2539; Found: m/z 361.2544. The enantiomeric purities were determined by chiral HPLC, the details for which are described in the Supporting Information.

(E,1S,7S)-7-(tert-Butyldimethylsilyloxy)-1-cyclohexyloct-2-en-1ol (19b). Red-al (70% in toluene solution, 1.27 mL, 4.37 mmol) was added to a solution of 18b (370 mg, 1.09 mmol) in THF (39 mL). The mixture was refluxed for 2 h, quenched with a saturated NH₄Cl and was extracted with EtOAc. The extract was dried over MgSO4 and evaporated. The residue was purified by column chromatography on silica gel eluted with 5% of EtOAc in hexane gave **19b** (311 mg, 84%): colorless oil $[\alpha]_D^{23}$ +8.90 (c 1.10, CHCl₃); $R_f = 0.32 (10\% \text{ EtOAc in hexane}); {}^{1}\text{H NMR} (300 \text{ MHz, CDCl}_3) \delta$ 5.59 (dt, 1H, J = 15.4, 6.6 Hz), 5.45 (dd, 1H, J = 15.4, 7.3 Hz), 3.78 (m, 2H), 2.03 (m, 2H), 1.63-1.87 (m, 5H), 1.31-1.51 (m, 6H), 1.11 (d, 3H, J = 6.0 Hz), 0.95–1.24 (m, 5H), 0.88 (s, 9H), 0.04 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 132.8, 131.6, 77.7, 68.4, 43.7, 39.2, 32.2, 28.8, 28.7, 26.5, 26.1, 26.0, 25.9, 25.4, 23.8, 18.1, -4.4, -4.7; IR (film, cm⁻¹) 3366, 2927, 2855, 1450, 1374, 1254, 1135, 1005, 891, 835, 774; MS (FAB) *m*/*z* 363 (M + Na⁺). HRMS calcd for $C_{20}H_{40}O_2SiNa$ (M + Na⁺): 363.2696; Found: m/z363.2689.

Benzoylation of 19. Et₃N (1.08 mL, 7.79 mmol), DMAP (9.5 mg, 0.078 mmol), and benzoyl chloride (0.271 mL, 2.34 mmol) were succesively added to a stirred solution of 19a^{16b} (265 mg, 0.78 mmol) in CH₂Cl₂ (15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 14 h and was quenched with water. The mixture was extracted with CH₂Cl₂, and the extract was dried over MgSO₄. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 3% EtOAc in hexane gave **20a** (337 mg; 98%): colorless oil; $[\alpha]_{D}^{23}$ -3.53 (c 0.65, CHCl₃); $R_f =$ 0.5 (5% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.06 (dd, 2H, J = 7.8, 1.5 Hz), 7.54 (tt, 1H, J = 7.3, 1.5 Hz), 7.43 (dt, 2H, J = 7.8, 7.3 Hz), 5.76 (dt, 1H, J = 15.2, 6.4 Hz), 5.49 (dd, 1H, J = 15.2, 7.7 Hz), 5.26 (dd, 1H, J = 7.2, 6.9 Hz), 3.77 (m, 1H), 2.05 (m, 2H), 1.65-1.85 (m, 5H), 1.04-1.53 (m, 10H), 1.09 (d, 3H, J = 6.0 Hz), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 135.1, 132.6, 130.9, 129.5, 128.3, 126.8, 79.5, 68.4, 42.0, 39.1, 32.2, 28.8, 28.7, 26.4, 26.0, 25.9, 25.8, 25.2, 23.8, 18.1, -4.4, -4.7; IR (film, cm⁻¹) 2928, 2855, 1719, 1270, 1109; MS (FAB) m/z 467 (M + Na⁺). HRMS calcd for $C_{27}H_{44}O_3SiNa$ (M + Na⁺): 467.2958; Found: *m*/*z* 467.2963. The diastereoisomer **20b** was obtained from **19b** in 97% yield: colorless oil; $[\alpha]_D^{23} + 11.00$ (*c* 1.29, CHCl₃); $R_f = 0.5$ (5% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.06 (dd, 2H, J = 7.7, 1.5 Hz), 7.54 (m, 1H), 7.43 (t, 2H, J = 7.7 Hz), 5.76 (dt, 1H, J = 15.2, 6.8 Hz), 5.49 (dd, 1H, J = 15.2, 7.7 Hz), 5.27 (dd, 1H, J = 7.2, 7.0 Hz), 3.75 (m, 1H), 2.04 (m, 2H), 1.60-1.81 (m, 5H), 1.31-1.51 (m, 5H), 1.04-1.26 (m, 5H), 1.11 (d, 3H, J = 6.0Hz), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) & 165.8, 135.1, 132.7, 132.6, 129.4, 129.5, 128.3, 128.2, 126.9, 79.5, 68.4, 42.0, 39.1, 32.2, 28.7, 28.6, 26.4, 26.0, 25.9, 25.8, 25.2, 23.8, 18.1, -4.4, -4.8; IR (film, cm⁻¹) 2928, 2855, 1720, 1272, 1109; MS (FAB) m/z 467 (M + Na⁺). HRMS calcd for C₂₇H₄₄O₃SiNa (M + Na⁺): 467.2958; Found: *m*/*z* 467.2965.

Deprotection of TBDMS Ether of 20. A mixture of 20a (322 mg, 0.72 mmol) and TBAF (1.0 M in THF, 5.73 mL, 5.79 mmol) in THF (8 mL) was stirred at room temperature overnight. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with ether to give 21a (230 mg, 96%): colorless oil; $[\alpha]_D^{24}$ –9.07 (*c* 0.65, CHCl₃); $R_f = 0.33$ (40% Et₂O in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.05 (d, 2H, J = 7.0 Hz), 7.53 (t, 1H, J = 7.3 Hz), 7.43 (t, 2H, J = 7.0 Hz), 5.75 (dt, 1H, J = 15.4, 6.8 Hz), 5.49 (dd, 1H, J = 15.4, 7.5 Hz), 5.24 (dd, 1H, J = 7.3, 7.0 Hz), 3.77 (m, 1H), 2.07 (m, 2H), 1.64 - 1.84 (m, 6H), 1.16 (d, 3H, J = 6.2 Hz), 0.86 - 1.52 (m, 10H);¹³C NMR (75 MHz, CDCl₃) δ 165.8, 134.8, 132.6, 130.8, 129.5, 128.2, 127.0, 79.5, 67.8, 41.8, 38.7, 32.2, 28.7, 28.6, 26.3, 25.8, 25.9, 25.1, 23.4; IR (film, cm⁻¹) 3387, 2927, 2854, 1716, 1272, 1112; MS (FAB) m/z 331 (M + H⁺). HRMS calcd for C₂₁H₃₁O₃ $(M + H^+)$: 331.2273; Found: *m*/*z* 331.2265. The diastereoisomer **21b** was obtained from **20b** in quantitative yield: colorless oil; $[\alpha]_D^{22}$ +13.2 (c 1.05, CHCl₃); $R_f = 0.33$ (40% Et₂O in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.05 (d, 2H, J = 7.0 Hz), 7.54 (t, 1H, J =7.3 Hz), 7.42 (t, 2H, J = 7.0 Hz), 5.75 (dt, 1H, J = 15.4, 6.8 Hz), 5.49 (dd, 1H, J = 15.4, 7.5 Hz), 5.24 (dd, 1H, J = 7.3, 7.0 Hz), 3.78 (m, 1H), 2.07 (m, 2H), 1.49–1.85 (m, 6H), 1.16 (d, 3H, J =6.2 Hz), 0.86–1.46 (m, 10H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 134.8, 132.6, 130.8, 129.5, 128.2, 127.0, 79.5, 67.8, 41.9, 38.7, 32.2, 28.7, 28.6, 26.4, 25.9, 25.8, 25.0, 23.4; IR (film, cm⁻¹) 3385, 2928, 2854, 1718, 1271, 1111; MS (FAB) m/z 331 (M + H⁺). HRMS calcd for C₂₁H₃₁O₃ (M + H⁺): 331.2273; Found: m/z331.2266.

Mesylation of Alcohol 21. MsCl (0.34 mL, 4.4 mmol) was added to a stirred solution of 21a (940 mg, 2.93 mmol) and Et₃N (1.22 mL, 8.8 mmol) in CH2Cl2 (69 mL) at 0 °C. The mixture was stirred for 30 min at room temperature and then poured into water and extracted with CH2Cl2. The extract was dried over MgSO4. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 10% EtOAc in hexane gave **22a** (1.08 g; 93%): colorless oil; $[\alpha]_D^{23}$ -8.26 (*c* 0.52, CHCl₃); $R_f = 0.41$ (40% Et₂O in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.05 (dd, 2H, J = 7.2, 1.5 Hz), 7.54 (tt, 1H, J = 7.5, 1.5 Hz), 7.43 (dt, 2H, J = 7.5, 7.2 Hz), 5.72 (dt, 1H, J = 15.4, 6.8 Hz), 5.50 (dd, 1H, J = 15.4, 7.3 Hz), 5.24 (dd, 1H, J = 7.2, 7.0 Hz), 4.78 (tq, 1H, J = 6.4, 5.8 Hz), 2.96 (s, 3H) 2.09 (m, 2H,), 1.42–1.85 (m, 10H), 1.39 (d, 3H, J = 6.4 Hz), 1.03–1.40 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 133.9, 132.7, 130.8, 129.5, 128.3, 127.7, 79.9, 79.3, 41.8, 38.6, 35.9, 31.7, 28.8, 28.6, 26.3, 25.9, 25.8, 24.3, 21.1; IR (film, cm⁻¹) 2930, 2854, 1714, 1272, 1112; MS (FAB) m/z 409 (M + H⁺). HRMS calcd for $C_{22}H_{33}O_5S$ (M + H⁺): 409.2048; Found: *m/z* 409.2040. Diastereoisomer 22b was obtained from **21b** in 89% yield: colorless oil; $[\alpha]_{D}^{22} + 14.7$ (*c* 1.03, CHCl₃); $R_f = 0.41 \ (40\% \ \text{Et}_2\text{O in hexane}); \ ^1\text{H NMR} \ (300 \ \text{MHz}, \ \text{CDCl}_3) \ \delta$ 8.05 (dd, 2H, J = 7.1, 1.5 Hz), 7.54 (tt, 1H, J = 7.5, 1.5 Hz), 7.43 (dt, 2H, J = 7.5, 7.1 Hz), 5.72 (dt, 1H, J = 15.4, 6.6 Hz), 5.51 (dd, 1H, J = 15.4, 7.5 Hz), 5.24 (dd, 1H, J = 7.2, 7.0 Hz), 4.78 (tq, 1H, J = 6.2, 5.5 Hz), 2.96 (s, 3H) 2.09 (m, 2H,), 1.37-1.85 (m, 10H), 1.39 (d, 3H, J = 6.2 Hz), 1.03–1.25 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 134.0, 132.7, 130.8, 129.5, 128.3, 127.7, 79.9, 79.3, 41.8, 38.6, 35.9, 31.7, 28.8, 28.6, 26.3, 25.9, 25.8, 24.3, 21.1; IR (film, cm⁻¹) 2929, 2854, 1714, 1272, 1112; MS (FAB) m/z 431 (M + Na⁺). HRMS calcd for C₂₂H₃₃O₅SNa (M + Na⁺): 431.1868; Found: *m*/*z* 431.1861.

Substitution of Methanesulfonate with Azide. A mixture of 22a (1.036 g, 2.53 mmol) and sodium azide (989 mg, 15.22 mmol) was stirred in dry DMF (25 mL) at room temperature for 24 h. After removal of DMF under vaccum, water was added and the mixture was extracted with EtOAc. The extract was dried on MgSO4 and condensed. The residue was purified by column chromatography on silica gel eluted with 5% ether in hexane to give 23a (847 mg; 94%): colorless oil; $[\alpha]_D^{23}$ -35.2 (*c* 1.14, CHCl₃); $R_f = 0.66$ (10%) EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.06 (dd, 2H, J = 7.0, 1.5 Hz), 7.55 (tt, 1H, J = 7.3, 1.5 Hz), 7.44 (dt, 2H, J = 7.3, 7.0 Hz), 5.74 (dt, 1H, J = 15.2, 6.8 Hz), 5.50 (dd, 1H, J =15.2, 7.5 Hz), 5.26 (dd, 1H, J = 7.3, 7.0 Hz), 3.42 (m, 1H), 2.08 (m, 2H,), 1.40–1.85 (m, 10H), 1.23 (d, 3H, J = 6.6 Hz), 1.04–1.28 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 134.3, 132.7, 130.8, 129.5, 128.3, 127.4, 79.4, 57.7, 41.9, 35.5, 31.9, 28.8, 28.6, 26.4, 25.9, 25.8, 25.3, 19.4; IR (film, cm⁻¹) 2928, 2854, 1716, 1270, 1111; MS (FAB) m/z 378(M + Na⁺). HRMS calcd for $C_{21}H_{29}N_3O_2Na$ (M + Na⁺): 378.2157; Found: m/z 378.2163. Diastereomer 23b was obtained from 22b in 90% yield: colorless oil; $[\alpha]_{D}^{24}$ -7.8 (*c* 1.00, CHCl₃); $R_f = 0.66$ (10% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.07 (dd, 2H, J = 7.0, 1.5 Hz), 7.55 (tt, 1H, J = 7.3, 1.5 Hz), 7.44 (dt, 2H, J = 7.3, 7.0 Hz), 5.75 (dt, 1H, J = 15.4, 6.6 Hz), 5.50 (ddt, 1H, J = 15.4, 7.5, 1.2 Hz),5.26 (dd, 1H, J = 7.2, 7.0 Hz), 3.42 (m, 1H), 2.08 (m, 2H,), 1.38-1.86 (m, 10H), 1.23 (d, 3H, J = 6.6 Hz), 1.04-1.27 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 134.3, 132.7, 130.8, 129.5, 128.3, 127.4, 79.4, 57.7, 41.9, 35.5, 31.9, 28.8, 28.6, 26.4, 25.9, 25.8, 25.3, 19.4; IR (film, cm⁻¹) 2929, 2854, 1717, 1270, 1111; MS (FAB) m/z 378 (M + Na⁺). HRMS calcd for $C_{21}H_{29}N_3O_2Na (M + Na^+)$: 378.2157; Found: m/z 378.2164.

Preparation of 24a and 24b. Triphenylphosphine (885 mg, 3.37 mmol) and H₂O (0.45 mL) were added to a stirred solution of 23a (300 mg, 0.84 mmol) in THF (22 mL), and the reaction was stirred for 30 h at room temperature. Solvent was removed and the residue was dried under high vaccum. The residue was then dissolved in CH₂Cl₂ (10 mL), and methyl chloroformate (0.13 mL, 1.68 mmol) and Et₃N (0.45 mL, 3.37 mmol) were added at 0 °C. After the addition, it was allowed to warm to room temperature and was stirred for an additional 1 h. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 5% EtOAc in hexane gave 24a (244 mg; 80%): colorless oil; $[\alpha]_D^{24} - 8.78$ (c 1.07, CHCl₃); $R_f = 0.37$ (25% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.05 (d, 2H, J = 7.0 Hz), 7.53 (t, 1H, J = 7.3 Hz), 7.42 (t, 2H, J = 7.7 Hz), 5.72 (dt, 1H, J = 15.4, 6.6 Hz), 5.48 (dd, 1H, J = 15.4, 7.7 Hz), 5.24 (dd, 1H, J = 7.2, 7.0 Hz), 4.45 (br, 1H), 3.64 (br, 1H), 3.62 (br s, 3H), 2.03 (m, 2H,), 1.64–1.84 (m, 6H), 1.40 (m, 4H), 1.16-1.25 (m, 5H), 1.10 (d, 3H, J = 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃) & 165.9, 156.4, 134.5, 132.7, 130.9, 129.5, 128.3, 127.3, 79.5, 51.8, 46.9, 41.9, 36.5, 32.0, 28.8, 28.6, 26.4, 26.0, 25.9, 25.3, 21.3; IR (film, cm⁻¹) 3339, 2929, 2854, 1714, 1530, 1271, 1111; MS (FAB) m/z 388 (M + H⁺). HRMS calcd for C₂₃H₃₄NO₄ (M + H⁺): 388.2488; Found: m/z 388.2483. Diastereisomer **24b** was obtained from **23b** in 74% yield: colorless oil; $[\alpha]_D^{23}$ +18.5 (c 0.53, CHCl₃); $R_f = 0.37$ (25%) EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.05 (d, 2H, J = 7.0 Hz), 7.54 (t, 1H, J = 7.5 Hz), 7.43 (t, 2H, J = 7.7 Hz), 5.72 (dt, 1H, J = 15.4, 6.6 Hz), 5.48 (dd, 1H, J = 15.4, 7.7 Hz), 5.23 (dd, 1H, J = 7.2, 7.0 Hz), 4.48 (br, 1H), 3.66 (br, 1H), 3.64 (br s, 3H), 2.05 (m, 2H,), 1.64–1.85 (m, 6H), 1.16–1.39 (m, 8H), 1.09 (d, 3H, J = 6.6 Hz) 1.03–1.11 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 156.4, 134.7, 132.7, 130.8, 129.5, 128.2, 127.2, 79.5, 51.8, 46.8, 41.8, 36.4, 32.0, 28.7, 28.6, 26.4, 25.9, 25.8, 25.2, 21.3; IR (film, cm⁻¹) 3341, 2928, 2854, 1714, 1530, 1271, 1111; MS (FAB) m/z 388 (M+ H⁺). HRMS calcd for $C_{23}H_{34}NO_4$ (M + H⁺): 388.2488; Found: m/z388.2479.

Preparation of 26. Triphenylphosphine (295 mg, 1.12 mmol) and H₂O (0.15 mL) were added to a stirred solution of 23a (100 mg, 0.28 mmol) in THF (7.5 mL), and the reaction was stirred for 30 h at room temperature. Solvents were evaporated and the residue was dried under high vaccum. The residue was then dissolved in CH₂Cl₂ (4.5 mL), and Boc anhydride (119 mg, 0.54 mmol) and Et₃N (0.15 mL, 1.1 mmol) were added at room temperature, and the mixture was stirred for 3 h. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 5% EtOAc in hexane gave **26** (103 mg; 85%): colorless oil; $[\alpha]_D^{24} - 10.37$ (*c* 1.32, CHCl₃); $R_f = 0.45$ (20% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.04 (d, 2H, J = 7.1 Hz), 7.53 (t, 1H, J = 7.3 Hz), 7.42 (t, 2H, J =7.1 Hz), 5.73 (dt, 1H, J = 15.4, 6.7 Hz), 5.47 (dd, 1H, J = 15.4, 7.7 Hz), 5.25 (dd, 1H, J = 7.1, 7.0 Hz), 4.27 (br, 1H), 3.61 (br, 1H), 2.03 (m, 2H,), 1.62–1.85 (m, 6H), 1.42 (s, 9H), 1.15–1.50 (m, 9H), 1.07 (d, 3H, J = 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 165.7, 155.3, 134.7, 132.6, 130.8, 129.5, 128.2, 127.1, 79.4, 46.2, 41.8, 36.7, 32.0, 28.7, 28.6, 28.3, 27.3, 26.3, 25.9, 25.8, 25.3, 21.3; IR (film, cm⁻¹) 3371, 2929, 2854, 1714, 1517, 1271, 1113; MS (FAB) m/z 430 (M + H⁺). HRMS calcd for $C_{26}H_{40}NO_4$ (M + H⁺): 430.2957; Found: m/z430.2952.

Hydrolysis of Benzoates 24a, 24b, and 26. A solution of benzoate (0.4 mmol) in methanol (15 mL) and aq NaOH (3.2 M solution, 1.5 mL, 4.8 mmol) was stirred for 24 h at room temperature. Solvent was removed under vaccum, water was added to the residue, and the mixture was extracted with EtOAc. The organic extract was dried on MgSO₄. Evaporation of the solvent and purification of the residue by column chromatography on silica gel eluted with 40% EtOAc in hexane gave the corresponding alcohol 25a, 25b, and 27.

Compound 25a. was obtained from **24a** in 96% yield; colorless oil $[\alpha]_{D}^{25}$ -2.19 (*c* 1.05, CHCl₃); $R_f = 0.16$ (25% EtOAc in hexane);

¹H NMR (300 MHz, CDCl₃) δ 5.70 (dt, 1H, J = 15.4, 6.2 Hz), 5.46 (dd, 1H, J = 15.4, 7.1 Hz), 4.45(br, 1H), 3.75 (t, 1H, J = 6.8 Hz), 3.67 (br, 1H), 3.64 (br s, 3H), 2.05 (m, 2H,), 1.63–1.85 (m, 7H), 1.34–1.46 (m, 5H), 1.16–1.32 (m, 4H), 1.12 (d, 3H, J = 6.6 Hz),; ¹³C NMR (75 MHz, CDCl₃) δ 156.4, 132.2, 132.1, 77.5, 51.8, 46.7, 43.6, 36.4, 31.8, 28.8, 28.7, 26.5, 26.1, 26.0, 25.3, 21.1; IR (film, cm⁻¹) 3325, 2924, 1698, 1537, 1256, 1085; MS (FAB) *m/z* 306 (M + Na⁺). HRMS calcd for C₁₆H₂₉NO₃Na (M + Na⁺): 306.2045; Found: *m/z* 306.2041.

Compound 25b. was obtained from **24b** in 91% yield; colorless oil $[\alpha]_{2^6}^{2^6}$ +8.2 (*c* 1.26, CHCl₃); $R_f = 0.16$ (25% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 5.70 (dt, 1H, J = 15.2, 6.2 Hz), 5.46 (dd, 1H, J = 15.2, 7.0 Hz), 4.48 (br, 1H), 3.75 (t, 1H, J = 6.8 Hz), 3.68 (br, 1H), 3.64 (br s, 3H), 2.04 (m, 2H), 1.54–1.86 (m, 6H), 1.12 (d, 3H, J = 6.6 Hz), 1.12–1.40 (m, 10H); ¹³C NMR (75 MHz, CDCl₃) δ 156.4, 132.2, 132.0, 77.5, 51.8, 46.9, 43.6, 36.6, 32.0, 28.8, 28.6, 26.5, 26.1, 26.0, 25.4, 21.2; IR (film, cm⁻¹) 3324, 2924, 1698, 1537, 1256, 1085; MS (FAB) *m/z* 306(M + Na⁺). HRMS calcd for C₁₆H₂₉NO₃Na (M + Na⁺): 306.2045; Found: *m/z* 306.2054.

Compound 27. was obtained from 26 in 98% yield; colorless oil $[\alpha]_{2^3}^{2^3}$ –3.78 (*c* 0.95, CHCl₃); R_f = 0.18 (25% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 5.55 (dt, 1H, J = 15.2, 6.2 Hz), 5.44 (dd, 1H, J = 15.2, 7.1 Hz), 4.33 (br, 1H), 3.73 (t, 1H, J = 6.8 Hz), 3.62 (br, 1H), 2.02 (m, 2H,), 1.62–1.85 (m, 6H), 1.41 (s, 9H), 1.29–1.47 (m, 6H), 1.07 (d, 3H, J = 6.6 Hz), 0.87–1.22 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 155.3, 132.3, 132.0, 78.9, 77.5, 46.0, 43.6, 36.6, 31.9, 28.7, 28.7, 28.3, 26.5, 26.1, 26.0, 25.4, 21.1; IR (film, cm⁻¹) 3343, 2926, 1693, 1527, 1248, 1078; MS (FAB) *m/z* 326 (M + H⁺). HRMS calcd for C₁₉H₃₆NO₃ (M + H⁺): 326.2695; Found: *m/z* 326.2702.

Pd(II)-Catalyzed Cyclization. A mixture of 25 (20 mg, 0.064 mmol) and PdCl₂(CH₃CN)₂ (5.6 mg, 0.021 mmol) was stirred in THF (1.6 mL) at room temperature for 6.5 h. After removal of the solvent, the residue was purified by column chromatography on silica gel eluted with 5% EtOAc in hexane to give 28. Compound **28a** was obtained from **25a** in 81% yield: colorless oil; $[\alpha]_{D}^{25}$ -31.11 $(c \ 1.26, \text{CHCl}_3); R_f = 0.77 \ (20\% \text{ EtOAc in hexane}); ^1\text{H NMR} \ (300)$ MHz, CDCl₃) δ 5.42 (m, 2H), 4.41(m, 1H), 4.03 (m, 1H), 3.67 (s, 3H), 1.87-1.97(m, 2H), 1.40-1.80(m, 10H), 1.23(d, 3H, J =6.8 Hz), 0.99–1.32 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 156.5, 135.8, 128.8, 52.6, 52.0, 47.5, 40.3, 32.9, 32.8, 29.7, 26.5, 26.2, 26.0, 25.7, 20.6, 13.8.; IR (film, cm⁻¹) 2924, 2852, 1698, 1445, 1360; MS (EI+) m/z 265(M⁺). HRMS calcd for C₁₆H₂₇NO₂ (M⁺): 265.2042; Found: m/z 265.2037. Compound 28b was obtained from **25b** in 85% yield: colorless oil; $[\alpha]_D^{24} + 17.4$ (*c* 0.78, CHCl₃); $R_f =$ 0.77 (20% EtOAc in hexane); ¹H NMR (300 MHz, CDCl₃) δ 5.47 (m, 2H), 4.70(m, 1H), 4.35 (m, 1H), 3.69 (s, 3H), 1.49-1.76 (m, 9H), 1.14 (d, 3H, J = 6.9 Hz), 0.99–1.35 (m, 8H); ¹³C NMR (75 MHz, CDCl₃) δ 156.5, 136.4, 128.9, 52.3, 50.9, 46.4, 40.5, 32.8, 32.7, 30.2, 29.7, 28.2, 26.2, 26.0, 20.5, 14.2; IR (film, cm⁻¹) 2924, 2852, 1698, 1443, 1360; MS (FAB) m/z 266 (M+H⁺). HRMS calcd for C₁₆H₂₈NO₂ (M+H⁺): 266.2120; Found: *m*/*z* 266.2113.

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Supporting Information Available: Copies of ¹H NMR and ¹³C NMR spectra for all new compounds and synthetic procedures and physical and characterization data for **13a**–**f**, **14a**–**f**, **15a**–**b**, and **15d**–**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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