A Dirhodium(II)−Carbenoid Route to (−)- and (+)-Geissman−Waiss Lactone: Synthesis of (1*R*,7*R*,8*R*)-(−)-Turneforcidine

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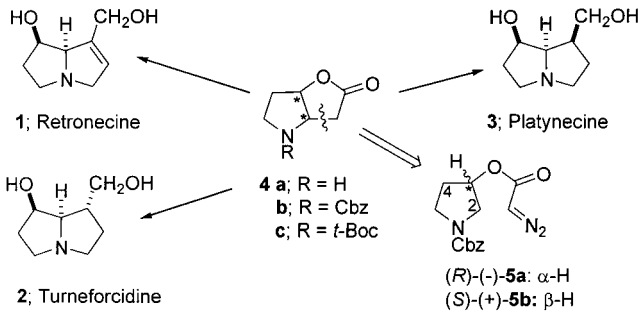
(−)- and (+)-Geissman−Waiss lactone, **4b**, was efficiently prepared via the intramolecular C−H insertion reaction of the chiral nonracemic diazoacetates (−)-**5a** and (+)-**5b** catalyzed by dirhodium(II) tetrakis[methyl (5*R* and 5*S*)-3-phenylpropanoyl-2-imidazolidinone-5-carboxylate]. The cyclization was found to proceed with excellent regioselectivity and cis-diastereoselectivity. The bicyclic lactone (−)-**4b** was successfully used in the synthesis of the necine base, (−)-turneforcidine **2**.

Introduction

The necine group of pyrrolizidine alkaloids is found in many plant families.[1] Structurally, these alkaloids are aliphatic ester or macrocyclic lactone derivatives of a pyrrolizidine mono-, di-, or triol core, exemplified by **1**−**3**. Pyrrolizidine alkaloids, especially the ones that possess the retronecine nucleus, have generally been found to be hepatotoxic; however, other interesting biological properties,[1b,c] such as antitumor, hypotensive, antiinflammatory, and antispasmolytic activities,[1,2] have been recorded. In some instances, the extracts of plants containing these alkaloids have been employed as herbal remedies in traditional, ethnic medicine.[2c]

Because of their structural diversity and interesting bioactivity profile, much interest has been directed at devising strategies for the synthesis of these alkaloids, and especially the construction of the pyrrolizidine base. Recent efforts have addressed the enantioselective construction of the pyrrolizidine moiety,[2] wherein the Geissman−Waiss lactone **4a**[3] and its N-protected derivatives, **4b,c**, have proven to be versatile building blocks (Chart 1). Nonracemic **4** has been prepared, using routes of varying lengths, from starting material derived from (1) the "chiral pool",[4a−g] (2) kinetic resolution of racemates,[4h−k] and (3) chiral auxiliary-based diastereoselective reactions.[4k−m] More direct routes to nonracemic **4** would be invaluable in pyrrolizidine alkaloid synthesis and, to our knowledge, only one such approach[4h] has been reported.

Chart 1. Examples of Pyrrolizidine Bases Synthesized from the Geissman−Waiss Lactone (4) and the Retrosynthetic Analysis of 4



We have investigated a route for the synthesis of **4b** based on the dirhodium(II)−carbenoid mediated C−H insertion reaction of the chiral nonracemic 3-pyrrolidinyl diazoacetates **5**. In this approach, there is a potential for carbenoid insertion into the C-2 and C-4 positions in **5**. Optimal conditions that favor C−H insertion reaction at C-2 (Chart 1, **5** → **4b**) were developed, and we now provide the details of our study.[5] The C−H insertion reaction was found to proceed with excellent regioselectivity and high cis-diastereoselectivity. This new method

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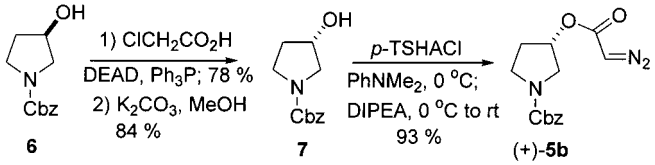
Scheme 1



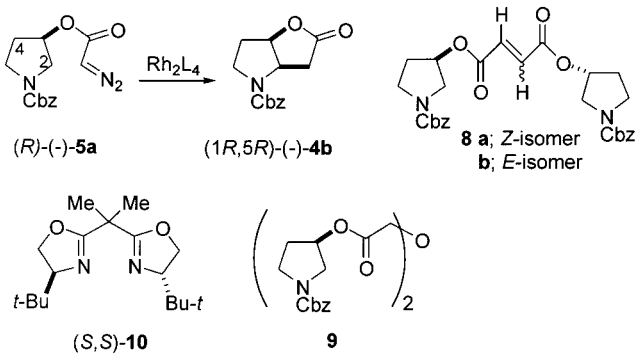
provided ready access to both enantiomers of the Geiss-man−Waiss lactone, (−)[4a,c,g,h]- and (+)[4a,h]-**4b**. The bicyclic lactone product, (−)-**4b**, was successfully used for the synthesis of the necine base (−)-turneforcidine **2**.

Results and Discussions

The studies commenced with the preparation of the (*R*)-*3*-pyrrolidinyl α-diazoacetate (**5a**) from commercially available (*R*)-3-pyrrolidinol. Thus, treatment of the latter alcohol with benzyl chloroformate (Cbz-Cl; Na_2CO_3, ether-H_2O; 98%) gave the known[6a] (*R*)-(−)-*N*-CBz-3-hydroxy-pyrrolidine (**6**).[6b] Subsequent acylation of **6** with α-(*p*-toluenesulfonylhydrazone)acetyl chloride (*p*-TSHACl)[7] under Corey−Myers conditions[8] gave **5a** in 97% yield. The preparation of the enantiomer, (*S*)-**5b**, is shown in Scheme 1. The (*R*)-alcohol **6** was subjected to Mitsonobu inversion ($ClCH_2CO_2H$, DEAD,[9] Ph_3P, THF) reaction to provide the chloroacetate derivative (78%). Base hydrolysis of the chloroacetate proceeded uneventfully to give an 84% yield of the known[10] (*S*)-alcohol **7**. Treatment of **7** with *p*-TSHACl[7,8] afforded the diazoacetate **5b** in 93% yield.

The metal-catalyzed reaction of diazoacetate **5a** (eq 1 in Table 1) was first investigated to ascertain the optimal reaction conditions for C−H insertion reaction, and the results are summarized in Table 1. It is clear from the Table that achiral catalysts do not effectively promote the desired C−H insertion reaction (**5a** → **4b**). The widely used $Rh_2(OAc)_4$ gave a poor yield (11%) of the desired (−)-**4b** (entry 1); however, we were encouraged to find that C−H insertion had occurred with excellent C-2 regioselectivity and cis-diastereoselectivity. The use of $Rh_2(Cap)_4$ only resulted in the formation of dimers **8a,b** although this catalyst is electronically more selective than $Rh_2(OAc)_4$ and has been shown to be effective for C−H insertion reaction (entry 2).[11] These initial results indicate that olefin formation via the dimerization of the initially formed metallocarbenoid is a significant competitive pathway in the reaction of (*R*)-**5a**. To improve on the yield of (−)-**4b** as well as to suppress dimer formation, the cyclization of diazoacetate (*R*)-**5a**, catalyzed by $CuPF_6$/**10**[12] complex and by three enantiomeric sets of chiral catalysts, $Rh_2(MEPY)_4$,[13] $Rh_2(MEOX)_4$,[14] and

Table 1. Metal-Catalyzed Reaction of Diazoacetate (−)-5a



entry	catalyst	yield (%)[a]	(−)-**4b**[b,c]	**8a**,**b** (*Z*:*E*)[b,c]	**9**[b,c]
1	$Rh_2(OAc)_4$	14	78	22 (1:2)	0
2	$Rh_2(Cap)_4$	36	0	100 (3.2:1)	0
3	$CuPF_6$/(*S*,*S*)- **10**	13	0	68 (1:8.7)	32
4	Rh_2(4*R*-MEPY)$_4$	5	72	28 (1:3)	0
5	Rh_2(4*S*-MEPY)$_4$	33	0	77 (1.6:1)	23
6	Rh_2(4*R*-MEOX)$_4$	15	72	28 (1:4)	0
7	Rh_2(4*S*-MEOX)$_4$	54	86	10 (1.5:1)	4
8	Rh_2(4*R*-MPPIM)$_4$	78[d]	100	0	0
9	Rh_2(4*S*-MPPIM)$_4$	25	74	26 (1:1.3)	0

[a] Combined yield of (−)-**4b**, **8a**,**b**, and/or **9**. [b]Relative yields were based on the integration of the α-CH_2 signals (δ 2.64−2.93) in the γ-lactone moiety of **4b**, the singlet at δ 6.25 of **8a**, the singlet at δ 6.85 of **8b**, and the singlet at δ 4.25 of **9**. [c]With the exception of entry 8, the balance of the material yield was due to polar, intractable baseline material. [d]Isolated yield.

$Rh_2(MPPIM)_4$,[15] was investigated. With $CuPF_6$/**10**, dimerization was still the preferred pathway (entry 3), but the ether product **9**, arising from reaction of water and two molecules of the reactive Rh(II)−carbenoid intermediate, was also produced in significant amounts. The desired C−H insertion product, (−)-**5a**, was not detected.

The chiral dirhodium(II) catalysts exhibited varying degrees of effectiveness in promoting the desired C−H insertion reaction. With Rh_2(4-MEPY)$_4$, the (*R*)-catalyst gave a low yield (3.6%) of the C−H insertion product, as well as the dimers **8a**,**b**, whereas the (*S*)-catalyst did not yield the C−H insertion product, but instead **8a**,**b** and the ether **9** were obtained. On the other hand, Rh_2(4*S*-MEOX)$_4$ gave a good yield (48%, entry 7) of (−)-**4b** accompanied by smaller amounts of **8a**,**b**. A very small amount of the ether **9** was also obtained. The corresponding (*R*)-catalyst, however, gave a lower yield (11%) of (−)-**4b** (entries 5 and 6) as well as dimers. Rh_2(4*R*-MPPIM)$_4$ was found to be the best catalyst (entries 8 and 9) for effecting the cyclization of (−)-**5a**, which provided a 78% yield of (−)-**4b** {$[\alpha]_D^{25.2}$ −115.5 (*c* 1.12, $CHCl_3$), lit.[4h] $[\alpha]_D^{26}$ −122.3 (*c* 4.7, $CHCl_3$)}; dimer formation was suppressed and the ether **9** was not observed. This result can be contrasted to the markedly lower yield (19%) of the (−)-**4b** produced when the enantiomeric Rh_2(4*S*-MPPIM)$_4$ was used as the catalyst.

The C−H insertion reaction mediated by the chiral dirhodium(II) catalysts was found to proceed with excellent regio and diastereoselectivity and this is also in accord with the result obtained with $Rh_2(OAc)_4$. The

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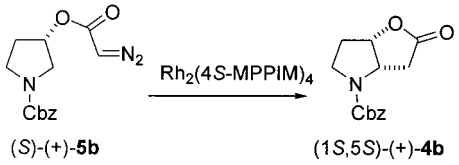
preference for metallocarbenoid insertion into the C_2−H bond is likely due to activation of this sigma bond by the adjacent carbamoyl nitrogen atom.[16]

The observed regio- and diastereocontrol in the cyclization of (−)-**5a** catalyzed by the chiral dirhodium(II) catalysts deserve some comments. Doyle and co-workers[17] had shown that C−H insertion reactions in select chiral nonracemic diazoacetates exhibited enhanced regio- and diastereoselectivity; that is, for one enantiomer of the diazoacetate, an (*R*)-configurated dirhodium(II) catalysts will promote the formation of one regio- and diastereomer whereas the (*S*)-catalyst favors another regio- and diastereomer. The fact that only the cis bicyclic lactone (−)-**4b** was formed in the C−H insertion reaction of diazoacetate (*R*)-**5a** and that both Rh_2(4*R*-MPPIM)$_4$ and Rh_2(4*S*-MEOX)$_4$ efficiently catalyzed the formation of (−)-**4b** from (*R*)-**5a** suggests that a "matched/mismatched" relationship does not manifest itself in the present system.

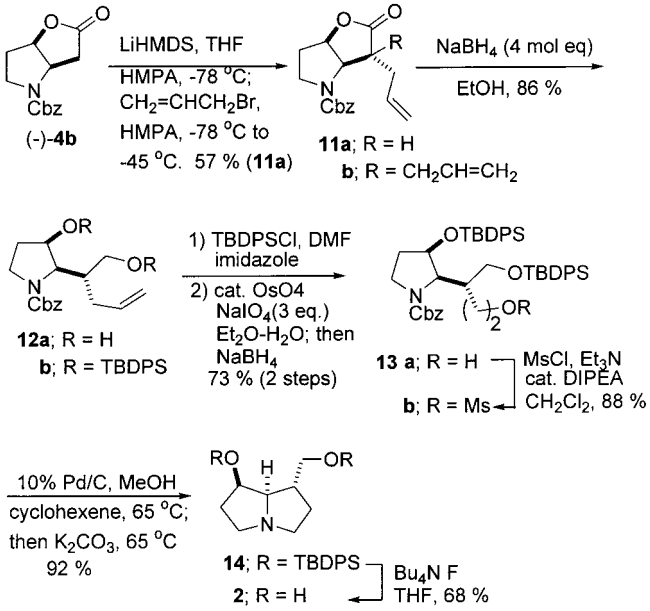
The encouraging results described above indicated that the enantiomeric cis bicyclic lactone, (+)-**4b**, should be accessible via the Rh_2(4*S*-MPPIM)$_4$-catalyzed C−H insertion reaction of (*S*)-(+)-**5b**. This notion was readily confirmed. Thus, treatment of (*S*)-(+)-**5b** with Rh_2(4*S*-MPPIM)$_4$ led to a high yield (76%) of the (1*S*,5*S*)-Geissman-Waiss lactone, (+)-**4b** (eq 2).



Since our method provides ready access to both (+)- and (−)-**4b**, we next investigated the synthesis of the pyrrolizidine base, (−)-turneforcidine (**2**), starting from (−)-**4b**. (−)-Turneforcidine is a naturally occurring necine base found in pyrrolizidine alkaloids typified by cropodine, retusine[1a] and the recently isolated racemozine.[18] Hitherto, two racemic[19a,b] and two enantioselective[19c,d] routes have been described for its synthesis.

To construct ring B in turneforcidine (**2**), we needed to install a functionalized side-chain at C-4 of the bicyclic lactone (−)-**4b**. Thus, alkylation of (−)-**4b** with allyl bromide afforded a respectable yield (57%) of the desired allylated product **11a** as well as the diallylated compound **11b**, and in a 4.8:1 ratio (Scheme 2). Bicyclic lactone **11a** was then efficiently reduced[19a] with 4 equiv of sodium borohydride ($NaBH_4$) to provide the diol **12a** in high yield. The reduction was incomplete when 2 equiv of $NaBH_4$ were used. Subsequent bis-silylation of diol **12a** with *tert*-butylchlorodiphenylsilane (TBDPS-Cl) afforded the corresponding very nonpolar bis-silyl ether **12b**, which was contaminated by a small amount of the *tert*-butyldiphenylsilanol byproduct. Attempted separation of the latter from **12a** by careful column chromatography was in vain.

Scheme 2



It was reasoned that the relatively nonpolar *tert*-butyldiphenylsilanol byproduct would be readily removed at the stage of primary alcohol **13a**.

Thus, the double bond in **12a** was subjected to Lemieux−Johnson oxidation[20] to provide the corresponding aldehyde, which was not isolated but immediately reduced with $NaBH_4$ to obtain, after chromatography, the primary alcohol **13a**. Mesylation of **13a** followed by catalytic transfer hydrogenolysis[21] of the *N*-Cbz protecting group in **13b** and base-mediated intramolecular alkylation provided an excellent yield of the pyrrolizidine bis-silyl ether, **14** {$[\alpha]_D^{27.7}$ −7.6 (*c* 1.05, $CHCl_3$)} (Scheme 2). Interestingly, attempted hydrogenolysis of the *N*-Cbz group in **13b** over 10% Pd/C using a pressure of either 1 or 2.4 atm of hydrogen only returned unreacted **13b**. Desilylation of **14** with TBAF gave (−)-**2** {$[\alpha]_D^{26}$ −13.9 (*c* 0.36, MeOH). Lit.[19c] $[\alpha]_D^{23}$ −12 (*c* 0.82, MeOH), lit.[19d] $[\alpha]_D^{23}$ −12.5 (*c* 1.3, MeOH)}as a highly polar product, whose ^{1}H NMR and ^{13}C NMR data are in accord with those reported in the literature. The overall yield of (−)-**2** starting from (−)-**4b** is 20%.

Conclusions

In conclusion, a method for the facile synthesis of both enantiomers of the *N*-Cbz protected Geissman−Waiss lactone via the Rh_2[5(*R*- and *S*)-MPPIM]$_4$ catalyzed reaction of nonracemic diazoacetates (*R*)-**5a** and (*S*)-**5b**, respectively, was developed. The utility of this method in pyrrolizidine alkaloid synthesis was demonstrated by the successful construction of (−)-turneforcidine (**2**) in an overall yield of 20% starting from (−)-**4b**. Further work using this Rh(II)−carbenoid approach in the synthesis of naturally occurring saturated N-heterocycles is in progress and will be reported in the future.

Experimental Section

General. Infrared spectra were recorded as thin films on sodium chloride plates on a Nicolet IMPACT 400D spectrophotometer, and only diagnostic absorptions are reported. ^{1}H

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(Bruker 250 or Varian Unity 300 MHz) and ^{13}C (62.5 or 75 MHz) NMR spectra were recorded from deuteriochloroform solutions unless otherwise stated. Tetramethylsilane ($\delta = 0$) was used as internal reference in ^1H NMR spectra and the $CDCl_3$ triplet ($\delta = 77.0$) was used as internal reference in ^{13}C NMR spectra. FAB high-resolution mass spectra were obtained using a JEOL HX110A Sector instrument. All reactions were conducted under a static pressure of argon. Optical rotations were measured from $CHCl_3$ solutions, unless stated otherwise, using a JASCO 1000 polarimeter. Dichloromethane and 1,2-dichloroethane were dried by distillation from CaH_2; tetrahydrofuran was dried by distillation from sodium/benzophenone ketyl. All reagents were purchased from Aldrich and used without further purification. Catalysts used: $Rh_2(OAc)_4$, $Rh_2(Cap)_4$, $Rh_2[(5R)\text{-MEPY}]_4$: MEPY = methyl (5R/5S)-2-pyrrolidinone-5-carboxylate, $Rh_2[(4R)\text{-MEOX}]_4$: MEOX = methyl (4R/4S)-2-oxazolidinone-4-carboxylate, $Rh_2[(4R)\text{-MPPIM}]_4$: methyl (4*R*/4*S*)-1-(3-phenylpropanoyl)-2-imidazolidinone-4-carboxylate, $Rh_2[(4S)\text{-MPPIM}]_4$ and $Cu(MeCN)4PF_6$.[22]

General Procedure for the Rh(II)- and Cu(I)-Catalyzed Reaction of Pyrrolidinyl Diazoacetate (*R*)-5a. Reactions were conducted in dry $Cl(CH_2)_2Cl$ (0.03 M) at 60 °C, under Ar, and using 2 mol % of Rh(II) catalyst or $Cu(MeCN)_4PF_6$/ligand **10** complex. Diazoacetate was added via syringe pump over 2 h. The progress of the reaction was monitored by TLC. After the reaction was complete, the $Cl(CH_2)_2Cl$ was evaporated and the crude residue was filtered through a short pad of silica gel (60 μm) using hexanes−ethyl acetate (1:1) as eluent. The combined filtrate was concentrated, and the mixture was analyzed using ^1H NMR to determine the ratio of product (−)-**4b**, dimer **8a**,**b**, and ether **9**. Please refer to Table 1 for details. Note that the reaction mixture from the $Rh_2(OAc)_4$ and $CuPF_6$/**10** experiments was separated via careful chromatography to obtain pure compounds for full characterization purposes (vide infra).

(1*R*,5*R*)-6-(Benzyloxycarbonyl)-6-aza-2-oxa-bicyclo-[3.3.0]-3-octanone [(−)-4b]. The (*R*)-**5a** (874 mg, 3.02 mmol) was dissolved in dry $Cl(CH_2)_2Cl$ (16 mL), and the solution was added dropwise (syringe pump), under Ar, over a period of 2 h to a solution of $Rh_2[(R)\text{-MPPIM}]_4$ (81 mg, 0.06 mmol) in dry $ClCH_2CH_2Cl$ (8 mL) heated at 60 °C (oil bath). The cooled reaction mixture was concentrated and filtered through a short plug of silica gel (1:1 hexanes−EtOAc). The filtrate was concentrated and the ^1H NMR of the crude product revealed little dimerization product (<1%) was formed. Chromatographic purification (2:1 and then 1:1 hexanes−EtOAc) of the crude product gave the (*R*)-bicyclic lactone (619 mg, 78%). $[\alpha]_D^{25.2}$ −115.5 (*c* 1.12, $CHCl_3$); lit.[4h] $[\alpha]_D^{26}$ −122.3 (c 4.7, $CHCl_3$). ν_{max}: 3061, 3037, 1789, 1709, 1610, 1586, 1536 cm^{-1}. ^1H NMR δ: 1.93−2.11 (m, 1H), 2.28 (dd, 1H, J = 14.2, 6.1 Hz), 2.64−2.93 (m, 2H), 3.41 (ddd, 1H, J = 11.2, 11.2, 6.2 Hz), 3.17−3.91 (m, 1H), 4.43−4.52 (m, 1H), 5.01−5.09 (m, 1H), 5.10−5.20 (m, 2H). ^{13}C NMR δ: 29.9 (30.4), 35.3 (36.3), 43.9 (44.3), (57.5) 58.2, 66.9 (67.1), 82.7 (83.7), 127.7, 127.9, 128.0, 128.3, 136.0, (153.6) 153.9, (174.9) 175.3. FAB-HRMS calcd for $C_{14}H_{16}NO_4$ (M + 1): 262.1071, Found: 262.1081.

Bis[(*R*)-3-pyrrolidinyl]maleate (7a). ν_{max}: 3061, 3055, 1715, 1641, 1586 cm^{-1}. ^1H NMR δ: 2.00−2.20 (m, 2H), 3.35−3.82 (m, 8H), 5.20 (s, 4H), 5.30−5.45 (m, 2H), 6.25 (s, 2H), 7.27−7.42 (m, 10H). FAB-HRMS calcd for $C_{28}H_{31}N_2O_8$ (M + 1): 523.2082, Found: 523.2092.

Bis-[(*R*)-3-pyrrolidinyl]fumarate (7b). ν_{max}: 3068, 3031, 1709, 1653 cm^{-1}. ^1H NMR δ: 2.05−2.20 (m, 4H), 3.45−3.72 (m, 8H), 5.15 (s, 4H), 6.85 (s, 2H), 7.30−7.45 (m, 10H). FAB-HRMS calcd for $C_{28}H_{31}N_2O_8$ (M + 1): 523.2082, Found: 523.2079.

(*R*)-3-Pyrrolidinyl [(*R*)-3-pyrrolidinyloxycarbonyl-methyloxy]acetate (9). ν_{max}: 3061, 1752, 1702, 1586 cm^{-1}. ^1H NMR δ: 2.05−2.20 (m, 4H), 3.40−3.70 (m, 8H), 4.25 (s, 4H), 5.15 (s, 4H), 5.35−5.45 (m, 2H), 7.30−7.45 (m, 10H). FAB-HRMS calcd for $C_{28}H_{33}N_2O_9$ (M + 1): 541.2186, Found: 541.2178.

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(1*S*,5*S*)-6-(Benzyloxycarbonyl)-6-aza-2-oxa-bicyclo-[3.3.0]-3-octanone [(+)-4b]. Similarly a solution of (S)-diazoacetate (160 mg, 0.553 mmol) was treated with $Rh_2[(S)\text{-MPPIM}]_4$ (20 mg, 0.0138 mmol) in dry $ClCH_2CH_2Cl$ (60 °C). ^1H NMR analysis of the crude mixture again showed very little dimer products (<1%). Chromatographic purification (2:1 and then 1:1 hexanes−EtOAc) yielded the bicyclic lactone (110 mg, 76%). $[\alpha]_D^{26.8}$ +122.9 (*c* 1.14, $CHCl_3$); lit.[4h] $[\alpha]_D^{24}$ +122.3 (c 1.42, $CHCl_3$). ν_{max}: 3061, 3031, 1783, 1703, 1610, 1586, 1536 cm^{-1}. ^1H NMR δ: 1.94−2.13 (m, 2H), 2.29 (dd, 1H, J = 14.2 Hz, 6.1 Hz), 2.65−2.92 (m, 2H), 3.41 (ddd, 1H, J = 11.2, 11.2, 6.2 Hz), 3.72−3.92 (m, 1H), 4.45−4.53 (m, 1H), 5.03−5.10 (m, 1H), 5.10−5.22 (m, 2H), 7.35 (s, 5H). ^{13}C NMR δ: (29.9) 30.3, 35.4 (36.3), 44.0 (44.3), (57.5) 58.2, 67.0 (67.2), 82.8 (83.8), 127.8, 127.9, 128.1, 128.4, 136.0, (153.6) 154.1, (175.0) 175.4. FAB-HRMS calcd for $C_{14}H_{16}NO_4$ (M + 1): 262.1081, Found: 262.1080.

(1*R*,4*R*,5*R*)-6-(Benzyloxycarbonyloxy)-4-(3-propenyl)-6-aza-2-oxa-bicyclo[3.3.0]-3-octanone (11a). Compound (*R*)-**4b** (259.5 mg, 0.994 mmol) was dissolved in dry THF (6 mL) containing HMPA (0.17 mL, 0.994 mmol), and the solution was cooled to −78 °C, under Ar. LiHMDS (0.994 mL, 0.994 mmol, 1 M in THF) was added dropwise to the solution and the mixture was stirred at −78 °C for 1 h. Then a mixture of allyl bromide (0.082 mL, 0.994 mmol) and HMPA (0.17 mL, 0.994 mmol) in dry THF (4 mL) was added, and the resulting mixture was stirred at −78 °C for 1 h and then at −45 °C for 30 min. The mixture was quenched by addition of saturated NH_4Cl (2 mL) at −45 °C, and then the mixture was allowed to warm slowly to room temperature. EtOAc (20 mL) and brine (10 mL) were added, and then the aqueous phase was removed. The aqueous phase was re-extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried, filtered, and evaporated to leave a pale yellow oil. Chromatographic purification (2:1 hexanes−EtOAc and then 1:1 hexanes−EtOAc) of the oil yielded the allylated lactone **11a** (170.5 mg, 57%) and the diallylated compound **11b** (41 mg, 12%). For **11a**: ν_{max}: 3068, 3031, 1771, 1704, 1637, 1589 cm^{-1}. ^1H NMR δ (mixture of rotamers): 1.90−2.10 (m, 1H), 2.29 (dd, 1H, J = 13.8, 5.8 Hz), 2.34−2.66 (m, 2H), 2.76 (dd, 0.4H, J = 8.0, 5.8 Hz), 2.97 (dd, 0.6H, J = 8.0, 5.7 Hz), 3.40 (ddd, 1H, J = 11.5, 11.5, 6.9 Hz), 3.78 (dd, 0.5H, J = 11.5, 9.2 Hz), 3.87 (dd, 0.5H, J = 11.5, 9.2 Hz), 4.20 (d, 0.5H, J = 5.0 Hz), 4.27 (d, 0.5 H, J = 5.0 Hz), 4.94−5.30 (m, 5H), 5.46−5.64 (m, 0.4H), 5.78−5.97 (m, 0.6H), 7.37 (s, 5H). ^{13}C NMR δ: 30.1 (30.5), 34.1, 43.9 (44.3), 46.7 (47.7), 62.2 (63.0), 67.0 (67.5), 81.7 (82.6), 118.6 (118.8), 127.8, 128.1, 128.5, 133.1, 135.8 (136.1), 153.6 (154.1), 1773 (177.7). FAB-HRMS calcd for $C_{17}H_{19}NO_4$ (M + 1): 302.1392, Found: 302.1391. **(1*R*,4*R*,5*R*)-6-(Benzyloxycarbonyloxy)-4-di(3-propenyl)-6-aza-2-oxa-bicyclo[3.3.0]-3-octanone (11b).** ν_{max}: 3074, 3030, 1771, 1703, 1641, 1586 cm^{-1}. ^1H NMR δ: 1.82−2.02 (m, 1H), 2.16 (dd, 1H, J = 13.2, 4.4 Hz), 2.22−2.60 (m, 4H), 3.07−3.23 (m, 1H), 3.90 (dd, 0.6H, J = 13.2, 8.8 Hz), 3.96 (dd, 0.4H, J = 13.2, 8.8 Hz), 4.52 (d, 0.4H, J = 7.9 Hz), 4.61 (d, 0.6H, J = 7.9 Hz), 4.82−5.29 (m, 7H), 5.50−5.69 (m, 0.5H), 5.70−5.95 (m, 1.5H), 7.30−7.45 (m, 5H). ^{13}C NMR δ: 31.2 (31.8), 36.7, 41.7 (41.9), 44.5 (44.7), 49.8 (50.4), 64.4 (65.4), 67.3 (67.7), 80.3 (81.0), 117.5 (117.8), 120.3, 127.9, 128.1, 128.4, 128.7, 131.5 (131.7), 132.8 (133.3), 135.6 (136.1), 154.1 (155.0), 179.0. FAB-HRMS calcd for $C_{20}H_{24}NO_4$ (M + 1): 342.1705, Found: 342.1716.

(3*R*)-1-(Benzyloxycarbonyl)-3-hydroxy-2-[2-(4-pentenyl-1-ol)]pyrrolidine (12a). A solution of **11a** (167 mg, 0.555 mmol) in 95% ethanol (5 mL) was treated with $NaBH_4$ (84 mg, 2.22 mmol), under Ar. The mixture was stirred at room temperature for 22 h and then cooled to 0 °C. Glacial acetic acid was carefully added to the reaction mixture, and when effervescence stopped, the mixture was concentrated. CH_2Cl_2 (10 mL) was added to the residue and followed by solid anhydrous K_2CO_3 and Na_2SO_4. The mixture was allowed to stand at room temperature for 1 h and then filtered and concentrated. The residual oil was chromatographed (1:1 hexanes−EtOAc and then EtOAc) to yield the diol **12a** as a viscous oil (148 mg, 86%). ν_{max}: 3622−3117, 3062, 3026, 1674, 1583, 1502 cm^{-1}. ^1H NMR δ: 1.80−2.50 (m, 5H, 2H-4, CH,

CH_2C═), 3.30−3.60 (m, 3H, CH_2O, OH), 3.65−3.76 (m, 1H, H-5), 3.95−4.10 (m, 1H, H-5′), 4.37 (dd, 1H, J = 13.2, 6.5 Hz, H-2), 4.50−4.90 (br hump, 1H, OH), 4.95−5.20 (m, 5H, ═CH_2), OCH_2Ph, H-3), 5.60−5.90 (m, 1H, ═CH), 7.35 (s, 5H, PhH). FAB-HRMS calcd for $C_{17}H_{24}NO_4$ (M + 1): 306.1705, Found: 306.1713.

(3*R*)-1-(Benzyloxycarbonyl)-3-(*tert*-butyldiphenylsilyloxy)-2-[2-(4-pentenyl-1-(*tert*-butyldiphenylsilyloxy-4-hydroxybutyl)]pyrrolidine (13a). The diol **12a** (124.6 mg, 0.4085 mmol) was dissolved, under Ar, in dry DMF (1.5 mL) containing imidazole (139 mg, 2.04 mmol). *t*-$BuPh_2SiCl$ (0.254 mL, 0.980 mmol) was added, and the mixture was stirred at room temperature for 20 h. Then DMF was removed in vacuo, and brine (5 mL) was added to the residue. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine (2 × 10 mL). The organic layer was dried, filtered, and concentrated to leave a thick oil. Column chromatography of the oil gave the product **12b** that was contaminated by *t*-$BuPh_2SiOH$ (coeluted with desired product). The mixture **12a**,**b** (381 mg) was dissolved in ether (5 mL), and to this solution was added distilled water (3 mL). OsO_4 (82 mg, 0.322 mmol) was added followed by powdered $NaIO_4$ (312 mg, 1.46 mmol) The mixture was vigorously stirred, under Ar, at room temperature for 36 h. Then EtOAc (10 mL) was added, and the aqueous phase was separated and back-extracted with EtOAc (5 mL). The combined organic layers were washed with brine (10 mL), dried, filtered, and concentrated to give a dark brown oil. The oil was taken into 95% ethanol (10 mL), and the solution was cooled to 0 °C. $NaBH_4$ (40 mg) was added, and the mixture was stirred at 0 °C for 2 h. Then glacial AcOH was carefully added dropwise until effervescence stopped. The mixture was concentrated, and the residue was dissolved in CH_2Cl_2 (15 mL). The solution was dried over a mixture of anhydrous K_2CO_3 and Na_2SO_4, and after 1 h, the mixture was filtered and concentrated. The crude oil was purified by chromatography (6:1 and then 2:1 hexanes−EtOAc) to afford the primary alcohol **13b** (238.4 mg, 73%). $[\alpha]_D^{25.7}$ +12 (*c* 1.56, $CHCl_3$). ν_{max}: 3555−3284, 3068, 3049, 1703, 1585 cm^{-1}. ^1H NMR δ: 0.98 (s, 9H), 1.01 (s, 9H), 1.40−1.95 (m, 5H), 2.45−2.65 (m, 1H), 3.05−3.20 (m, 2H), 3.65−4.05 (m, 5H), 4.25−4.40 (m, 1H), 4.90−5.10 (m, 2H), 7.15−7.75 (m, 25H). FAB-HRMS calcd for $C_{48}H_{60}NO_5$ (M + 1): 786.4002, Found: 786.4019.

(3*R*)-1-(Benzyloxycarbonyl)-3-(*tert*-butyldiphenylsilyloxy)-2-[2-(1-(*tert*-butyldiphenylsilyloxy-4-methanesulfonyloxybutyl)]pyrrolidine (13b). The alcohol **13a** (132.4 mg, 0.169 mmol) was dissolved in dry CH_2Cl_2 (4 mL) containing dry Et_3N (58.7 uL, 0.422 mmol), and the solution was cooled to 0 °C under Ar. Methanesulfonyl chloride (26.1 uL, 0.337 mmol) was added, and the mixture was stirred at 0 °C for 30 min. Saturated $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL) were added. The organic layer was separated, and the aqueous phase was re-extracted with CH_2Cl_2 (5 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4), filtered, and concentrated. Chromatographic purification (3:1 hexanes−EtOAc) of the crude oil gave the primary mesylate **13b** (129 mg, 88%). ν_{max}: 3074, 3049, 1703, 1586 cm^{-1}. ^1H NMR δ: 0.98 (s, 9H), 1.02 (s, 9H), 1.43−1.78 (m, 2H), 1.83−2.12 (m, 2H), 2.35−2.57 (m, 1H), 2.84 and 2.86 (s, 3H), 3.07−3.30(m, 2H), 3.70−4.10 (m, 3H), 4.95−5.10 (m, 2H), 7.15−7.75 (m, 25H). FAB-HRMS calcd for $C_{49}H_{62}NO_7SSi_2$ (M + 1): 864.3785, Found: 864.3760.

(1*R*,7*R*,8*R*)-7-(*tert*-butyldiphenylsilyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)pyrrolizidine (14). 10% Palladized charcoal (25 mg) was added, under Ar, to a solution of the mesylate **13b** (129 mg) in dry MeOH (5 mL). Then cyclohexene (0.3 mL) was added to the mixture, and the mixture was refluxed for 75 min. The reaction mixture was briefly cooled, anhydrous K_2CO_3 (61.2 mg, 0.443 mmol) was added, and the mixture was refluxed for 1 h. The cooled reaction mixture was filtered through Celite, and the residue washed thoroughly with 5% MeOH−Et_3N. The filtrate was concentrated, and the residue was purified by chromatography (20:1:1 and then 10:1:1 $CHCl_3$−MeOH−concentrated NH_4OH) to afford 86 mg (92%) of the pyrrolizidine **14**. $[\alpha]_D^{27.7}$ −7.6 (*c* 1.05, $CHCl_3$). ν_{max}: 3074, 3049 cm^{-1}. ^1H NMR δ: 1.02 (s, 9H), 1.10 (s, 9H), 1.60.1.94 (m, 3H), 2.10−2.25 (m, 1H), 2.65−2.90 (m, 3H), 3.01 (ddd, 1H, J = 9.8, 6.8, 3.2 Hz), 3.12 (ddd, 1H, J = 9.3, 6.7, 3.1 Hz), 3.21 (dd, 1H, J = 6.0, 4.1 Hz), 3.51 (dd, 1H, J = 9.8, 6.9 Hz), 3.63 (dd, 1H, J = 9.8, 6.2 Hz), 4.21 (dd, 1H, J = 6.1, 3.4 Hz), 7.25−7.46 (m, 12H), 7.57−7.70 (m, 8H). ^{13}C NMR δ: 19.27, 19.30, 26.7, 27.1, 31.7, 36.9, 39.7, 51.9, 55.9, 66.1, 71.9, 73.8, 127.5, 127.6, 129.5, 129.6, 129.7, 133.5, 133.8, 134.4, 135.6, 135.8. FAB-HRMS calcd for $C_{40}H_{52}NO_2Si_2$ (M + 1): 634.3537, Found: 634.3513.

(1*R*,7*R*,8*R*)-7-(Hydroxy)-1-(hydroxymethyl)pyrrolizidine [(−)-turneforcidine (2)]. The bis-silyl ether **14** (85.6 mg, 0.135 mmol) was dissolved in dry THF, under Ar, and Bu_4NF (0.297 mL, 0.297 mmol) was added. The mixture was allowed to stand at room temperature for 20 h. The reaction mixture was concentrated, and the residual oil was chromatographed (8:2:0.5 and then 5:5:1 $CHCl_3$−MeOH−concentrated NH_4OH) to provide 4.2 mg of pure (−)-turneforcidine and 18.2 mg of a 1.3:1 (on the basis of ^1H NMR integration) mixture of turneforcidine and Bu_4NF. The yield of synthetic (−)-turneforcidine (**2**) was 68%. $[\alpha]_D^{26}$ −13.9 (*c* 0.36, MeOH). Lit.[19c] $[\alpha]_D^{23}$ −12.5 (*c* 1.3, MeOH), lit.[19d] $[\alpha]_D^{23}$ −12 (*c* 0.82, MeOH) ν_{max}: 3568−3129, 2919, 2851 cm^{-1}. ^1H NMR δ (300 MHz, CD_3OD): 1.69 (dddd, 1H, J = 12.2, 12.2, 9.7, 6.8 Hz), 1.85−2.20 (m, 2H), 2.09 (dddd, 1H, J = 12.6, 6.6, 6.6, 3.3 Hz), 2.48−2.66 (m, 2H), 2.73 (q, 1H, J = 9.1 Hz), 3.03−3.16 (m, 2H), 3.21 (dd, 1H, J = 6.6, 4.5 Hz), 3.51 (dd, 1H, J = 10.5, 7.2 Hz), 3.56 (dd, 1H, J = 10.5, 6.6 Hz), 4.17 (q, 1H, J = 3.3 Hz). ^{13}C NMR δ (75 MHz, CD_3OD): 32.4, 37.4, 40.7, 52.8, 56.3, 65.5, 71.8, 73.9. FAB-HRMS calcd for $C_8H_{16}NO_2$ (M + 1): 158.1181, Found: 158.1185.

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Supporting Information Available: Preparation, analytical and spectral data of compounds **5a**, **5b**, **6**, and **7**, and NMR data for (−)-turneforcidine (**2**). This material is available free of charge via the Internet at http://pubs.acs.org.

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