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Reactivity of Chiral α-Amidoalkylphenyl Sulfones with Stabilized Carbanions. Stereoselective Synthesis of Optically Active 1-Aminopyrrolizidine

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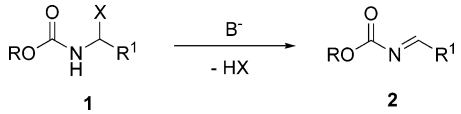
Metal enolates and functionalized allylzinc reagents react with optically active α-amidoalkylphenyl sulfones to give *N*-carbamoylamino derivatives with variable levels of *anti* diastereoselectivity. Zinc enolates provide comparable results with respect to lithium enolates in terms of diastereoselectivity but afford *β*-amino ester derivatives in lower yield. The synthetic utility of the obtained chiral *N*-carbamoylamino esters is demonstrated by the first enantioselective synthesis of (−)-1-aminopyrrolizidine a central intermediate for the preparation of various biologically active substances.

Introduction

Nucleophilic addition to imino derivatives represents a viable procedure to many synthetic targets containing primary or secondary amino groups.[1] The electrophilic character of the carbon−nitrogen double bond can be suitably enhanced by linking electron-withdrawing substituents to the nitrogen atom.[2] Among these imino derivatives, *N*-acyl and *N*-carbamoylimines have emerged as strong electrophilic compounds that react with a wide range of nucleophilic reagents giving the corresponding *N*-carbamoylamino derivatives.[3] The consistent reactivity of *N*-acylimines obtained from aliphatic aldehydes is often associated with their instability that causes some troubles in their preparation. Indeed, these *N*-acylimines undergo to a fast tautomerization that leads to the formation of the corresponding enecarbamates with consequent loss of any electrophilic character. For this reason, *N*-acylimines **2** are more profitably prepared from *N*-acyl-α-substituted amines **1** by a base-promoted elimination (Scheme 1).

SCHEME 1



The ready availability of derivatives **1** is therefore mandatory for a successful utilization of *N*-acylimino intermediates.[4] In this context, α-amidoalkylphenyl sulfones (**1**, X = $PhSO_2$) are easily prepared by reaction of a carbamate with an aldehyde and sodium benzenesulfinate in the presence of formic acid.[5] When acid-labile groups are present in the aldehyde, a modified procedure using benzenesulfinic acid in anhydrous conditions can be suitably used to access precursors **1**. Asymmetric induction in reactions involving imino derivatives can be realized introducing stereogenic *N*-substituents that

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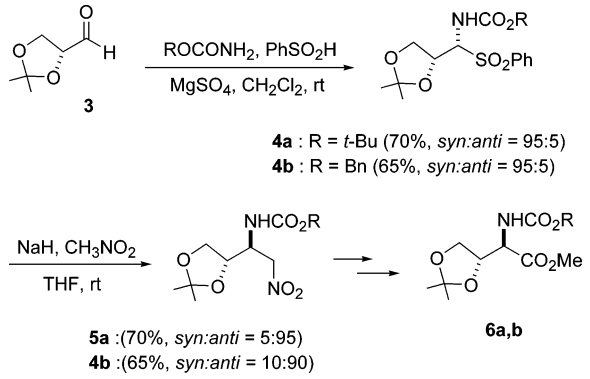
SCHEME 2



provide a diastereofacial discrimination at the carbon−nitrogen double bond.[6] However, this practice is poorly effective with *N*-acylimines **2** since the stereogenic center in the carbamoyl group is too far from the reactive double bond to produce consistent levels of diastereoselection.[7] Alternatively, the chiral group can be included in the alkyl framework of *N*-acylimine **2** as close as possible to the reaction center in order to realize the maximum stereodirecting effect toward the incoming nucleophilic reagent.

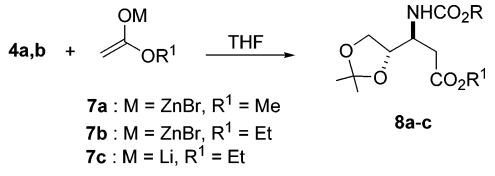
Recently, we have demonstrated that (*R*)-2,3-isopropylideneglyceraldehyde **3** as well as other chiral aldehydes, can be converted into the corresponding α-amidoalkylphenyl sulfones **4** with enhanced *syn* diastereoselectivity.[8] Reaction of sulfones **4** with nitromethane anion provides the nitro adduct **5** with high *anti* diastereoselectivity and after a Nef reaction ultimately leads to optically active *β*-hydroxy-α-amino acid esters **6** (Scheme 2).

In this paper, we report on the reactivity of chiral α-amidoalkylphenyl sulfones with other nucleophilic reagents and the application of the obtained adducts to the first enantioselective synthesis of (−)-1-aminopyrrolizidine.

Results and Discussion

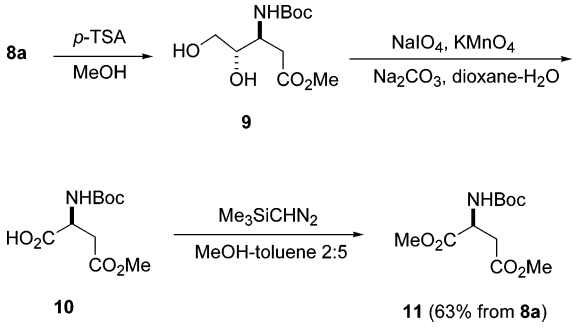
Reaction of imines with ester enolates provides a straightforward entry to functionalized *β*-amino esters, an emerging class of compounds present in a certain number of biologically active compounds.[9] Lithium and zinc ester enolates **7** can be added to sulfones **4** under different conditions to afford *N*-carbamoyl *β*-amino esters **8** (Scheme 3).[10] The addition is *anti* diastereoselective, and the utilization of the Reformatzky reagent **7a** produces the corresponding *β*-amino ester with higher diastereoselectivity than lithium enolate **7c** even though

SCHEME 3



4	7	T°C	8	yield(%)	*syn:anti*
4a	**7a**	20	**8a**	70	5:95
4a	**7c**	-78	**8b**	91	10:90
4b	**7a**	20	**8c**	75	15:85

SCHEME 4



the former addition is carried out at room temperature.[11] Furthermore, as previously observed, sulfone **4a** bearing a *N*-Boc protecting group gives better diastereoselectivities than the *N*-Cbz derivative **4b**.[8]

The absolute configuration of the newly formed stereocenter in compound **8a** has been evaluated by chemical correlation (Scheme 4).

Cleavage of the acetonide group in amino ester **8a** using *p*-TSA in methanol gives the corresponding diol **9** that is oxidized using $NaIO_4$−$KMnO_4$ to the *N*-Boc-L-aspartic acid monoester **10**.[12] Methyl esterification of monoacid **10** can be realized using Me_3SiCHN_2 in a mixture of methanol−toluene,[13] giving diester **11** that shows the sign of the optical rotation congruent with natural *N*-Boc-L-aspartic acid dimethyl ester.[14] As expected, sulfones **4** are also reactive toward functionalized allylzinc reagents giving *N*-carbamoyl homoallylamino derivatives **13** (Scheme 5).

Allyl bromide **12a** efficiently adds to sulfone **4a** in the presence of zinc metal with modest diastereoselectivity (*syn*/*anti* = 3:7), while substituted allylzinc reagent obtained from bromoacrylate **12b** gives the corresponding adduct **13b** with better diastereoselectivity (*syn*/*anti* = 1:9). The organozinc reagent prepared from 3-bromo-1-

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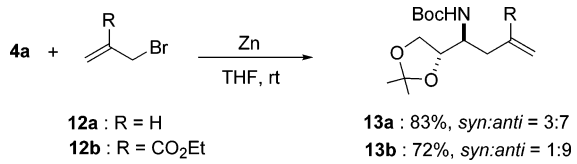
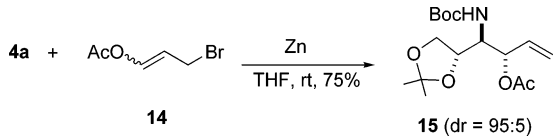
SCHEME 5



12a : R = H
12b : R = CO_2Et

13a : 83%, *syn:anti* = 3:7
13b : 72%, *syn:anti* = 1:9

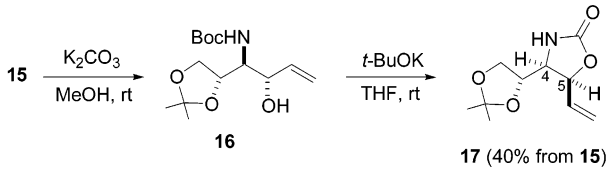
SCHEME 6



14

15 (dr = 95:5)

SCHEME 7



16

17 (40% from **15**)

acetoxy-1-propene **14** is a useful reagent recently reported by Lombardo et al. for the stereoselective synthesis of functionalized 1,2-diols from aldehydes and ketones.[15] Sulfone **4a** reacts with **14** in the presence of zinc metal to afford fully protected amino polyol **15** in good yield and diastereoselectivity (Scheme 6).

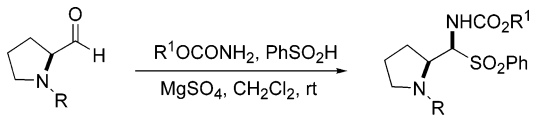
As previously observed, the attack of the nucleophile would preferentially occur from the *si* face of the intermediate *N*-acylimine giving the *anti* stereoisomer with respect to the 1,3-dioxolane ring oxygen. To establish the relative stereochemistry between the newly created stereocenters, compound **15** has been deacetylated in basic conditions to the hydroxy derivative **16** that has been cyclized using *t*-BuOK to the parent oxazolidin-2-one **17** (Scheme 7).

A measurement of the NOE effect between H-4 and H-5 in compound **17** allowed us to assign the *anti* relationship between the amino and the acetoxy groups. On the other hand, a marked preference for the *anti* diastereomer has been also observed in the reaction of **14** with racemic α-amidoalkylphenyl sulfones in similar conditions.[5d]

The pyrrolidine ring is an important structural unit present in alkaloids and other biologically active substances.[16] Many approaches devoted to the stereoselective synthesis of compounds featuring the pyrrolidine nucleus employ L-proline or its derivatives as pivotal building blocks. In particular, *N*-carbamoyl prolinals **18** can be converted by the usual procedure into the corresponding sulfones **19** with a variable degree of diastereoselectivity, depending on the nature of the *N*-carbamoyl group (Scheme 8).

The carbamate combination in compounds **19** has been chosen in order to ensure a chemoselective cleavage of the carbamoyl groups in the resulting adducts **20**−**22**.

SCHEME 8



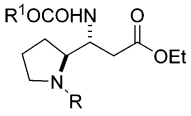
18a : R = Cbz
18b : R = Boc

19a : R^1 = *t*-Bu, 81%, *syn:anti* = 5:95
19b : R^1 = Bn, 90%, *syn:anti* = 15:85

SCHEME 9

20a : R = H, 77%, *syn:anti* = 3:7
20b : R = CO_2Et, 78%, *syn:anti* = 15:85

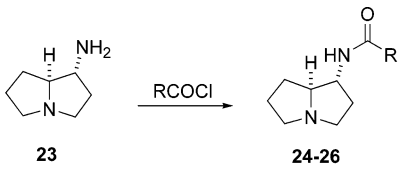
21: 84%, *syn:anti* = 15:85



22

19	**7**	T°C	**22**	yield(%)	*syn:anti*
19a	**7b**	20	**22a**	68	15:85
19a	**7c**	-78	**22a**	85	8:92
19b	**7c**	-78	**22b**	95	10:90

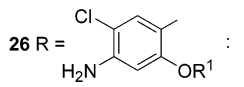
SCHEME 10



23

24-26

24 R = (*E*)-4-$MeOC_6H_4CH$=CH : (-)-absouline
25 R = $CH_3CH_2CH(CH_3)$: (-)-laburnamine



: serotonine 5-HT_3 antagonists

Sulfones **19** react with Reformatzky reagent **7b** and lithium enolate **7c** giving the corresponding adducts **20**−**22** in good yield but with lower diastereoselectivity compared to the same reaction of sulfones **4** (Scheme 9).

Specifically, reaction of enolate **7c** with sulfones **19** is able to produce the corresponding amino esters **22a**,**b** with respectable *anti* diastereoselectivity. It is worth noting that the epimeric composition of sulfones **19** does not affect the stereochemical outcome of the subsequent nucleophilic addition. Indeed, using pure *syn*-**19b** or epimeric mixtures of the same sulfone gives the same results in terms of diastereoselectivity. This probably means that a common *N*-acylimine intermediate is formed from each epimer of sulfone **19**. Amino esters **22** are ideal candidates for the synthesis of 1-aminopyrrolizidine **23** that constitutes the heterocyclic core of a number of biologically active compounds (Scheme 10).

The natural product (+)-absouline **24** isolated from the New Caledonian plants *Hugonia oreogena* and *Hugonia penicillanthenum* possess a slight antivral activity.[17] The

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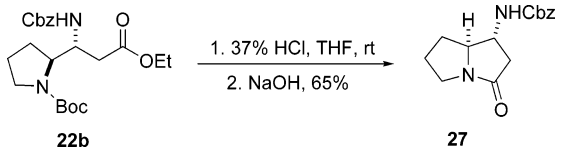
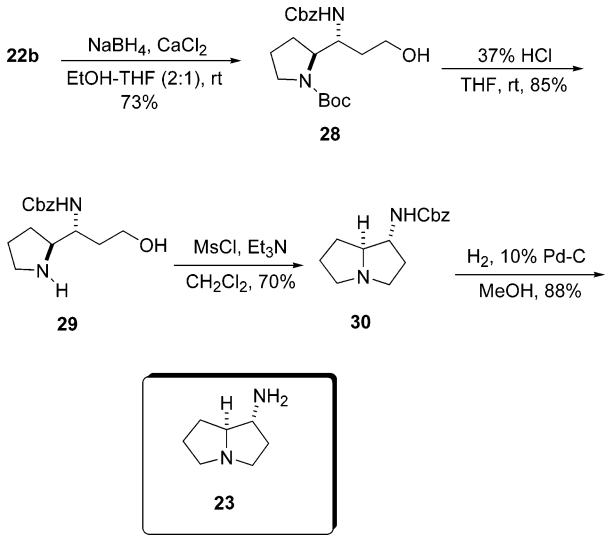
SCHEME 11



22b **27**

SCHEME 12



28 **29** **30** **23**

two enantiomers of absouline have been previously prepared by resolution of the racemic mixture on a preparative chiral column, and therefore, our procedure represents a synthetic approach toward the first enantioselective total synthesis of (−)-**24**. Furthermore, 1-amidopyrrolizidines **26** act as potent and selective 5-HT_3 antagonists for serotonine receptor.[18] As a first attempt we planned to originate the pyrrolizidine ring system by cleavage of the carbamoyl protecting group in compound **22b** followed by a lactamization under basic conditions (Scheme 11).

Although the formation of pyrrolizidinone **27** was successful, the subsequent reduction to the saturated byciclic derivative was proved to be quite troublesome. Thus, we exploited an alternative synthetic procedure that involves a preliminary selective reduction of the ester function in compound **22b** with $NaBH_4$−$CaCl_2$ in EtOH−THF[19] to afford primary alcohol **28** followed by the *N*-Boc cleavage to give amino alcohol **29** (Scheme 12).

Ring closure of compound **29** to the bicyclic derivative **30** can be carried out by intramolecular S_N2 displacement of the corresponding in situ generated mesylate.[20] Removal of the carbamoyl group in **30** by hydrogenolysis leads to (−)-1-aminopyrrolizidine **23** that has been previously prepared only in racemic form[17b] and this synthesis also served us to confirm the stereochemical assignment of the configuration of the amino stereocenter in compounds **22**.

Conclusion

Chiral α-amidoalkylphenyl sulfones **4** and **19** react with metal enolates and allylzinc reagents to afford the corresponding amino derivatives with enhanced *anti* diastereoselectivity. Sulfones **4** provide the corresponding adducts with better diastereoselectivities than sulfones **19** expecially when are made to react with functionalized organozinc reagents. The addition products obtained using the present procedure are amenable of further transformations as demonstrated by the enantioselective synthesis of (−)-1-aminopyrrolizidine **23** prepared in four steps from amino ester **22b**. This optically active pyrrolizidine is a pivotal intermediate for the synthesis of alkaloids endowed of interesting biological activity.

Experimental Section

General Procedure for the Preparation of *N*-Carbamoylamino Esters 8 and Allyl Derivatives 13, 15, 20, and 21 Using Organozinc Reagents. To a suspension of zinc dust (5 mmol) in dry THF (10 mL) was added the corresponding allyl bromide or bromoester (3 mmol) at room temperature. After the mixture was stirred for 30 min, the appropriate sulfone **4**, **19** (2 mmol) dissolved in dry THF (8 mL) was added dropwise. Stirring was continued for 1 h, and then the mixture was quenched by addition of satd NH_4Cl (8 mL). The mixture was extracted with CH_2Cl_2 (4 × 15 mL) and dried over $MgSO_4$. The crude product obtained after removal of the solvent was purified by column chromatography (7:3 hexanes−ethyl acetate).

Methyl (3*S*)-3-[(*tert*-butoxycarbonyl)amino]-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propanoate 8a: yield 70%; waxy solid; $[\alpha]^{20}_D = +4.2$ (*c* 1.3, $CHCl_3$); IR (cm^{-1}, neat) 3350, 1716; ^1H NMR δ 1.33 (s, 3H), 1.41 (s, 3H), 1.43 (s, 9H), 2.64−2.69 (m, 2H), 3.70 (s, 3H), 3.85 (dd, 1H, J = 5.2, 8.4 Hz), 3.90−4.01 (m, 1H), 4.04 (dd, 1H, J = 6.2, 8.4 Hz), 4.09−4.22 (m, 1H), 5.24 (d, 1H, J = 9.2 Hz); ^{13}C NMR δ 25.4, 26.8, 28.4, 35.1, 52.0, 60.3, 66.2, 77.0, 80.3, 110.0, 155.1, 172.3. Anal. Calcd for $C_{14}H_{25}O_6$ (303.35): C, 55.43; H, 8.31; N, 4.62. Found: C, 55.49; H, 8.27; N, 4.66.

***tert*-Butyl *N*-(1*S*)-1-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-butenylcarbamate 13a:** yield 83%; mp 60−62 °C; $[\alpha]^{20}_D = +6.9$ (*c* 1.05, $CHCl_3$); IR (cm^{-1}, KBr) 3350, 1680; ^1H NMR δ 1.33 (s, 3H), 1.42 (s, 12H), 2.15−2.47 (m, 2H), 3.62−3.90 (m, 2H), 3.98−4.10 (m, 2H), 4.48 (d, 0.7H, J = 9.2 Hz), 4.67 (d, 0.3H, J = 9.2 Hz), 5.05−5.16 (m, 2H), 5.71−5.91 (m, 1H); ^{13}C NMR δ 25.2, 26.5, 28.5, 35.5, 52.4, 67.1, 77.8, 79.6, 109.7, 118.2, 134.2, 155.8. Anal. Calcd for $C_{14}H_{25}NO_4$ (271.35): C, 61.97; H, 9.29; N, 5.16. Found: C, 62.02; H, 9.24; N, 5.19.

General Procedure for the Preparation of *N*-Carbamoylamino Esters 8 and 22 Using Lithium Enolates. To a solution of diisopropylamine (6 mmol) in dry THF (20 mL) was added BuLi (1.6M in hexanes, 6.5 mmol, 4.1 mL) at 0 °C, and stirring was continued for 0.5 h at 0 °C. Dry ethyl acetate (6 mmol) was then added at −78 °C, and after the mixture was stirred at the same temperature for 0.5 h sulfone **4**, **19** (2 mmol) dissolved in dry THF (8 mL) was added. Stirring was continued for 1 h at −78 °C, and then the mixture was quenched by addition of satd NH_4Cl (8 mL).The mixture was extracted with CH_2Cl_2 (4 × 15 mL) and dried over $MgSO_4$. The crude product obtained after evaporation of the solvent was purified by column chromatography (75:25 hexanes−ethyl acetate).

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***tert*-Butyl (2*S*)-2-((1*R*)-1-[(Benzyloxy)carbonyl]amino-3-ethoxy-3-oxopropyl)tetrahydro-1*H*-1-pyrrolecarboxylate 22b:** yield 95%; oil $[\alpha]^{20}_D = -21.7$ (*c* 2.5, $CHCl_3$); IR (cm^{-1}, neat) 3360, 1715; ^1H NMR δ 1.23 (t, 3H, $J = 7.0$ Hz), 1.46 (s, 9H), 1.68−2.05 (m, 4H), 2.40−2.60 (m, 2H), 3.15−3.32 (m, 1H), 3.35−3.58 (m, 1H), 3.88−4.20 (m, 4H), 5.05−5.20 (m, 2H), 6.20−6.35 (m, 1H), 7.29−7.40 (m, 5H); ^{13}C NMR δ 14.3, 23.9, 28.5, 29.1, 36.1, 46.9, 47.6, 51.5, 60.8, 66.8, 80.0, 128.1, 128.2, 128.6, 136.7, 156.2, 156.3, 171.9. Anal. Calcd for $C_{22}H_{32}N_2O_6$ (420.50): C, 62.84; H, 7.67; N, 6.66. Found: C, 62.88; H, 7.65; N, 6.63.

Cleavage of Amino Ester 8a. Synthesis of *N*-Boc-L-dimethyl Aspartate 11. *N*-Boc amino ester **8a** (0.32 g, 1.0 mmol) was dissolved in methanol (10 mL), and *p*-toluenesulfonic acid (0.025 g) was added at room temperature. The solution was stirred for 18 h at room temperature, and methanol was then removed at reduced pressure to give crude diol **9** that was dissolved in dioxane−water (7:3, 10 mL). This mixture was treated sequentially with Na_2CO_3 (0.065 g, 0.6 mmol) dissolved in water (0.6 mL), $NaIO_4$ (0.86 g, 4 mmol), and $KMnO_4$ (0.035 g, 0.2 mmol) and was stirred at room temperature for 45 min after which time reaction was complete. The reaction mixture was diluted with ethyl acetate (20 mL) and acidified with 1 N HCl until pH = 1. The resulting organic phase was washed with brine and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was dissolved in MeOH−toluene (2:5, 12 mL) and treated with Me_3SiCHN_2 (2.0 M in ether, 1.2 mL). The mixture was stirred for 30 min, and excess of Me_3SiCHN_2 was destroyed with AcOH (0.1 mL). After evaporation of the solvent, the crude diester was purified by column chromatography (7:3 hexanes−ethyl acetate) giving 0.165 g of pure **11** as a white solid: mp 64−65 °C; $[\alpha]^{20}_D = +27.3$ (*c* 3.5, $CHCl_3$) [lit.[14a] mp 65−66 °C; $[\alpha]^{20}_D = +28.02$ (*c* 5, $CHCl_3$)]. Spectroscopic data for compound **11** are in agreement with those reported.

(4*S*,5*S*)-4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5-vinyl-1,3-oxazolidin-2-one 17. *N*-Boc amino ester **15** (0.30 g, 0.9 mmol) was dissolved in methanol (10 mL), and 2 M K_2CO_3 (2 mL) was added at room temperature. After the mixture was stirred for 30 min at room temperature, methanol was partially removed at reduced pressure and the resulting solution was extracted with $CHCl_3$ (3 × 15 mL). The crude product obtained after evaporation of the solvent was dissolved in THF (6 mL), and *t*-BuOK (0.11 g, 1 mmol) was then added at room temperature. The mixture was stirred for 1 h at room temperature, and after removal of the solvent at reduced pressure the residue was taken up with ethyl acetate (25 mL), washed with brine (3 × 5 mL), and dried over $MgSO_4$. After evaporation of the solvent the crude oxazolidinone was purified by column chromatography (6:3:1 hexanes−ethyl acetate−ethanol) giving 0.077 g (40%) of pure **17** as a waxy solid: $[\alpha]^{20}_D = +4.45$ (*c* 0.2, $CHCl_3$); IR (cm^{-1}, neat); ^1H NMR δ 1.32 (s, 3H), 1.42 (s, 3H), 3.74 (dd, 1H, $J = 5.6$, 8.4 Hz), 4.01 (dd, 1H, $J = 6.2$, 8.4 Hz), 4.11−4.20 (m, 2H), 5.14−5.24 (m, 1H), 5.37−5.69 (m, 2H), 5.79−5.97 (m, 2H); ^{13}C NMR δ 24.9, 26.6, 57.3, 65.1, 74.7, 78.3, 109.4, 119.8, 130.8, 158.9. Anal. Calcd for $C_{10}H_{15}NO_4$ (213.23): C, 56.33; H, 7.09; N, 6.57. Found: C, 56.28, H, 7.12; N, 6.54.

Benzyl *N*-[(1*S*,7a*R*)-3-Oxoperhydro-1-pyrrolizinyl]carbamate 27. *N*-Boc amino ester **22b** (0.63 g, 1.5 mmol) was dissolved in THF (10 mL), and 37% HCl (5 mL) was then added at room temperature. The mixture was stirred for 30 min at room temperature, cooled in an ice bath, and made alkaline by addition of NaOH pellets. After being stirred for 15 min, the solution was extracted with $CHCl_3$ (4 × 15 mL) and dried over $MgSO_4$. After evaporation of the solvent, the crude lactam was purified by column chromatography (95:5 dichloromethane−methanol) giving 0.27 g (65%) of pure **27** as a yellow oil: $[\alpha]^{20}_D = -27.5$ (*c* 1.3, $CHCl_3$); IR (cm^{-1}, neat) 3350, 1670; ^1H NMR δ 1.80−2.20 (m, 4H), 2.63 (dd, 1H, $J = 10.6$, 14.1 Hz), 2.78 (dd, 1H, $J = 8.4$, 14.1 Hz), 2.98−3.15 (m, 1H), 3.45−3.77 (m, 2H), 3.95−4.15 (m, 1H), 5.08 (s, 2H), 5.46 (d, 1H, $J = 7.0$ Hz) 7.29−7.37 (m, 5H); ^{13}C NMR δ 26.8, 30.9, 41.7, 53.5, 62.2, 67.2, 68.5, 128.4, 128.5, 128.8, 136.4, 156.1, 171.9. Anal. Calcd for $C_{15}H_{18}N_2O_3$ (274.52): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.73; H, 6.57; N, 10.25.

***tert*-Butyl (2*R*)-2-((1*S*)-1-[(Benzyloxy)carbonyl]amino-3-hydroxypropyl)tetrahydro-1*H*-1-pyrrolecarboxylate 28.** To a solution of amino ester **22b** (2.0 g, 4.75 mmol) in ethanol−THF (2:1, 24 mL) were added $CaCl_2$ (1.1 g, 10 mmol) and $NaBH_4$ (0.78 g, 20 mmol) at 0 °C. After the mixture was stirred overnight at room temperature, the solvent was partially removed at reduced pressure, and the resulting slurry was taken up in ethyl acetate (50 mL) and then quenched with citric acid (1 M, 20 mL). The aqueous solution obtained after separation of the organic phase was extracted with ethyl acetate (3 × 15 mL), and the collected organic phases were dried over $MgSO_4$. The crude product obtained after removal of the solvent was purified by column chromatography (6:3:1 hexanes−ethyl acetate-ethanol) affording 1.31 g (73%) of alcohol **28** as a colorless oil: $[\alpha]^{20}_D = -11.7$ (*c* 1.4, $CHCl_3$); IR (cm^{-1}, neat) 3300, 1710; ^1H NMR δ 1.44 (s, 9H), 1.80−2.03 (m, 5H), 2.07−2.20 (m, 1H), 3.08−3.26 (m, 1H), 3.42−3.70 (m, 4H), 3.75−4.00 (m, 2H), 5.05−5.15 (m, 2H), 7.21 (d, 1H, $J = 8.9$ Hz), 7.29−7.43 (m, 5H); ^{13}C NMR δ 24.3, 28.5, 30.7, 32.2, 48.4, 51.9, 58.6, 62.0, 67.0, 80.3, 128.3, 128.4, 128.7, 136.0, 156.5, 158.0. Anal. Calcd for $C_{20}H_{30}N_2O_5$ (378.46): C, 63.47; H, 7.99; N, 7.40. Found: C, 63.42; H, 8.04; N, 7.36.

Benzyl *N*-(1*S*)-3-Hydroxy-1-[(2*R*)tetrahydro-1*H*-2-pyrrolyl]propylcarbamate 29. *N*-Boc-amino alcohol **28** (1.2 g, 3.2 mmol) was dissolved in THF (20 mL), and 37% HCl (10 mL) was then added at room temperature. The mixture was stirred for 30 min at room temperature, cooled in an ice bath, and made alkaline by addition of NaOH pellets. THF was partially removed at reduced pressure, and the resulting solution was extracted with ethyl acetate (6 × 15 mL) and dried over $MgSO_4$. After evaporation of the solvent, the crude amino alcohol was purified by column chromatography (90:9:1 dichloromethane−methanol−35% NH_4OH) giving 0.75 g (85%) of pure **29** as a white solid: mp 106−108 °C; $[\alpha]^{20}_D = -13.1$ (*c* 1.0, $CHCl_3$); IR (cm^{-1}, KBr) 3300, 1718; ^1H NMR δ 1.40−1.95 (m, 6H), 2.81−2.98 (m, 2H), 3.10−3.30 (m, 1H), 3.40−3.73 (m, 4H), 3.75−3.90 (m, 1H), 5.08 (s, 2H), 5.43 (d, 1H, $J = 9.5$ Hz), 7.28−7.43 (m, 5H); ^{13}C NMR δ 25.9, 30.1, 35.1, 46.8, 53.1, 58.7, 62.1, 67.1, 128.3, 128.4, 128.7, 136.5, 156.9. Anal. Calcd for $C_{15}H_{22}N_2O_3$ (278.35): C, 64.73; H, 7.97; N, 10.06. Found: C, 64.76; H, 8.01; N, 10.03.

Benzyl *N*-[(1*S*,7a*R*)-Perhydro-1-pyrrolizinyl]carbamate 30. To a solution of amino alcohol **29** (0.7 g, 2.5 mmol) in dry dichloromethane (15 mL) was added MsCl (0.34 g, 3 mmol) at −10 °C followed by dropwise addition of Et_3N (0.38 g, 3.8 mmol). After being stirred for 1 h at −10 °C, the cooling bath was removed and stirring was continued for a further 2 h. The solvent was evaporated at reduced pressure, and the residue was directly purified by column chromatography (55:30:15) dichloromethane−methanol−35% NH_4OH) affording 0.46 g (70%) of pyrrolizidine **30** as a yellow oil: $[\alpha]^{20}_D = -18.15$ (*c* 2.7, $CHCl_3$); IR (cm^{-1}, neat) 3350, 1715; ^1H NMR δ 1.80−2.30 (m, 6H), 2.65−2.83 (m, 2H), 3.25−3.42 (m, 1H), 3.51−3.70 (m, 1H), 3.71−3.83 (m, 1H), 3.92−4.10 (m, 1H), 5.07 (s, 2H), 6.46 (d, 1H, $J = 7.7$ Hz), 7.23−7.38 (m, 5H); ^{13}C NMR δ 25.3, 30.2, 31.9, 53.3, 55.2, 56.4, 67.0, 71.3, 128.2, 128.3, 128.7, 136.6, 156.5. Anal. Calcd for $C_{15}H_{20}N_2O_2$ (260.33): C, 69.20; H, 7.74; N, 10.76. Found: C, 69.24; H, 7.71; N, 10.79.

(1*S*,7a*R*)-Perhydro-1-pyrrolizinamine 23. Carbamate **30** (0.9 g 3.5 mmol) dissolved in MeOH (20 mL) was hydrogenated (2 atm) in the presence of 10% Pd−C (0.1 g) for 5 h at room temperature. After removal of the catalyst by filtration, the solvent was evaporated to give 0.38 g (88%) of pure pyrrolizidine **23** as a waxy solid: $[\alpha]^{20}_D = -24.1$ (*c* 5.5, MeOH); IR (cm^{-1}, neat) 3200; ^1H NMR δ 1.78−2.35 (m, 6H), 2.90−3.15 (m, 2H), 3.27−3.40 (m, 2H), 3.45−3.70 (m, 2H), 4.90 (s, 2H); ^{13}C NMR δ 25.8, 30.4, 34.4, 54.2, 56.1, 57.7, 74.4. Anal. Calcd

for $C_7H_{14}N_2$ (126.20): C, 66.62; H, 11.18; N, 22.20. Found: C, 66.66; H, 11.14; N, 22.24.

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Supporting Information Available: Spectral and physical data for the following compounds not included in the Experimental Section: **8b**,**c**, **13b**, **15**, **19b**, **20a**,**b**, **21**, and **22a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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