the mixture was filtered. The filtrate was cooled to 0 °C, and 10% Pd/C was added. The mixture was then shaken under H_2 (40 psi) for 3 h at rt. Filtration of the mixture and concentration of the filtrate gave the pure amino amide **20** (0.085 g, 98%): mp 202 °C dec; $[\alpha]^{20}_D$ -20.4° (*c* 1, H_2O); ^1H NMR (D_2O, int. std. 4.78 ppm) δ 0.92, 0.93 (2d, 6 H), 1.35-1.45 (m, 1 H), 1.52-1.64 (m, 1 H), 1.68-1.80 (m, 1 H), 2.50 (AB, *J* = 10.50 Hz, 1 H), 2.53 (AB, *J* = 3.5, 10.7 Hz, 1 H), 3.4 (ddd, *J* = 3.06, 7.14, 9.8 Hz, 1 H), 4.0-4.10 (m, 1 H); ^{13}C NMR (D_2O, CH_3OH int. std. 48.98 ppm) δ 21.01, 22.10, 23.93, 38.50, 41.42, 53.97, 68.27, 178.72. Anal. Calcd for $C_8H_{18}N_2O_2 \cdot H_2O$: C, 49.98; H, 10.49; N, 14.57. Found: C, 49.83; H, 10.49; N, 14.37.

(3*R*,4*S*)-4-Amino-3-hydroxy-6-methylheptanamide (21). Similar treatment of **17** (0.1 g, 0.5 mmol) gave **21** (0.083 g, 96%): mp 203 °C dec; $[\alpha]^{20}_D$ -18.1° (*c* 1, H_2O).

(3*R*,4*R*)-4-Amino-3-hydroxy-6-methylheptanamide (22). Treatment of **18** (0.1 g, 0.5 mmol) in a similar manner gave **22** (0.080 g, 92%): $[\alpha]^{20}_D$ +19° (*c* 1, H_2O).

(3*S*,4*R*)-4-Amino-3-hydroxy-6-methylheptanamide (23). Similar treatment of **19** (0.1 g, 0.5 mmol) gave **23** (0.086 g, 99%): $[\alpha]^{20}_D$ +18.3° (*c* 1, H_2O); ^1H NMR (D_2O int. std. 4.78 ppm) δ 0.91 (2d, 6 H), 1.35-1.70 (m, 3 H), 2.4-2.66 (m, 2 H), 3.37-3.48 (m, 1 H), 4.24-4.38 (m, 1 H); ^{13}C NMR (DCl 0.2 N, CH_3OH int. std. 48.95 ppm) δ 17.47, 18.33, 20.34, 34.66, 38.06, 58.01, 67.85, 175.54. Anal. Calcd for $C_8H_{18}N_2O_2 \cdot 0.6H_2O$: C, 51.92; H, 10.46; N, 15.14. Found: C, 51.63; H, 10.42; N, 14.78.

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Supplementary Material Available: ^{13}C NMR spectra for compounds **1**, **2**, **5**, **7**, **8**, **11**, **12**, **15**, **16**, **19**, **20**, and **23** (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Asymmetric Tandem Mannich-Michael Reactions of Amino Acid Ester Imines with Danishefsky's Diene

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Imines **1** derived from aromatic, aliphatic, and functionalized aldehydes and various amino acid esters react with Danishefsky's diene under Lewis acid catalysis via a tandem Mannich-Michael mechanism to give cyclic 6-substituted 2,3-didehydro-4-piperidinones in good to high yields and with diastereomeric ratios reaching from 92:8 up to 97:3. The chiral auxiliary is removed by conversion of the α C atom of the amino acid into an acetalic center, employing a Curtius reaction as the key step. For the elucidation of the absolute configuration, the alkaloids (*S*)-coniine and (*R*)-δ-coniceine are synthesized from the enaminones **5i** and **5r**.

Introduction

Reactions of compounds containing C-N double bonds with dienes to give six-membered azaheterocycles open up a wide variety of opportunities for organic synthesis, in particular for the construction of alkaloids and analogues thereof.[1] The widespread use of these methods has for a long time been hampered by the low reactivity of easily accessible and common unactivated imines, making the application of activated Schiff bases necessary, which carry electron-withdrawing substituents, e.g. CF_3, acyl, and tosyl groups. However, recently Danishefsky et al.[2a-c] demonstrated that unactivated aromatic and aliphatic imines react smoothly with electron-rich dienes like **2** (Danishefsky's diene) in the presence of $ZnCl_2$. The mechanism of this conversion is a matter of debate and may vary with the structure of the heteroanalogous carbonyl compound employed. Whereas Danishefsky et al. seem to favor a Diels-Alder type process, Kunz et al.[3] have substantiated that alternatively a Lewis acid induced addition of the silyl enol ether moiety of **2** followed by a cyclization via nucleophilic intramolecular attack of the amine generated, may occur. The principle has subsequently been applied by several groups for the construction of various heterocyclic frameworks and natural products.[2,3] Despite the great potential of this synthetic method, only isolated efforts have thus far been made to carry out corresponding transformations asymmetrically using removable chiral auxiliary groups, i.e. only a carbohydrate derived amine has been applied for the steric steering of reactions between the diene **2** and respective imines.[3]

In this paper we report on the use of the easily accessible amino acid esters as mediators of chirality in the reaction of unactivated imines with Danishefsky's diene **2**.[5] These esters have already been used as effective chiral auxiliaries

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(4) (a) Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 5741. (b) Grieco, P. A.; Parker, D. T.; Fobare, W. F.; Ruckle, R. *J. Am. Chem. Soc.* **1987**, *109*, 5859. (c) Grieco, P.; Larsen, S.; Fobare, W. *Tetrahedron Lett.* **1986**, *27*, 1975. (d) Waldmann, H.; Braun, M. *Liebigs Ann. Chem.* **1991**, 1045. (e) Waldmann, H.; Braun, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1231. (f) Waldmann, H. *Angew. Chem.* **1988**, *100*, 307; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 274; *Liebigs Ann. Chem.* **1989**, 231.

(5) Preliminary communication: Waldmann, H.; Braun, M.; Dräger, M. *Angew. Chem.* **1990**, *102*, 1445; *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1468.

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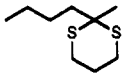
Table I. Synthesis of 2,3-Didehydropiperidin-4-ones with Varying Aldehydes

entry	no.	R^1	amino acid	temp (°C)	Lewis acid/solvent	yield (%)	5:6
1	**5a**	phenyl	Phg-OMe	0	$ZnCl_2$/THF	25	60:40
2	**5b**	*p*-methoxy-Ph	Phg-OMe	−20	$ZnCl_2$/THF	63	67:33
3	**5c**	*p*-nitro-Ph	Phg-OMe	0	$ZnCl_2$/THF	53	62:38
4	**5d**	*n*-prop	Phg-OMe	0	$ZnCl_2$/THF	69	71:29
5	**5e**	phenyl	Val-OMe	−20	$ZnCl_2$/THF	45	92:8
6	**5f**	*p*-methoxy-Ph	Val-OMe	0	$ZnCl_2$/THF	54	92:8
7	**5g**	*p*-nitro-Ph	Val-OMe	0	$ZnCl_2$/THF	65	94:6
8	**5l**	*p*-nitro-Ph	Ile-OMe	−10	$ZnCl_2$/THF	57	93:7
9	**5m**	*p*-nitro-Ph	Ile-OBzl	−10	$ZnCl_2$/THF	60	93:7
10	**5n**	*p*-methoxy-Ph	Ile-OMe	−10	$ZnCl_2$/THF	56	91:9
11	**5i**	*n*-prop	Ile-OMe	0	2 equiv of $ZnCl_2$/THF	11	15:85
12	**5o**	*i*-prop	Ile-OMe	−78 to −20	$EtAlCl_2/CH_2Cl_2$	48	97:3
13	**5o**	*i*-prop	Ile-OMe	−78 to −20	Me_2AlCl/CH_2Cl_2	50	93:7
14	**5p**	*n*-bu	Ile-OMe	−78 to −20	Me_2AlCl/CH_2Cl_2	77	90:10
15	**5q**	$MeOOC(CH_2)_3$	Val-OBzl	−78 to −20	$EtAlCl_2/CH_2Cl_2$	46	93:7
16	**5r**	$EtOOC(CH_2)_2$	Val-OBzl	−78 to −20	$EtAlCl_2/CH_2Cl_2$	50	93:7
17	**5s**		Ile-OMe	−78 to −20	$EtAlCl_2/CH_2Cl_2$	75	93:7
18	**5t**	*n*-prop	Phe-OMe	−10	$ZnCl_2$/THF	65	66:34

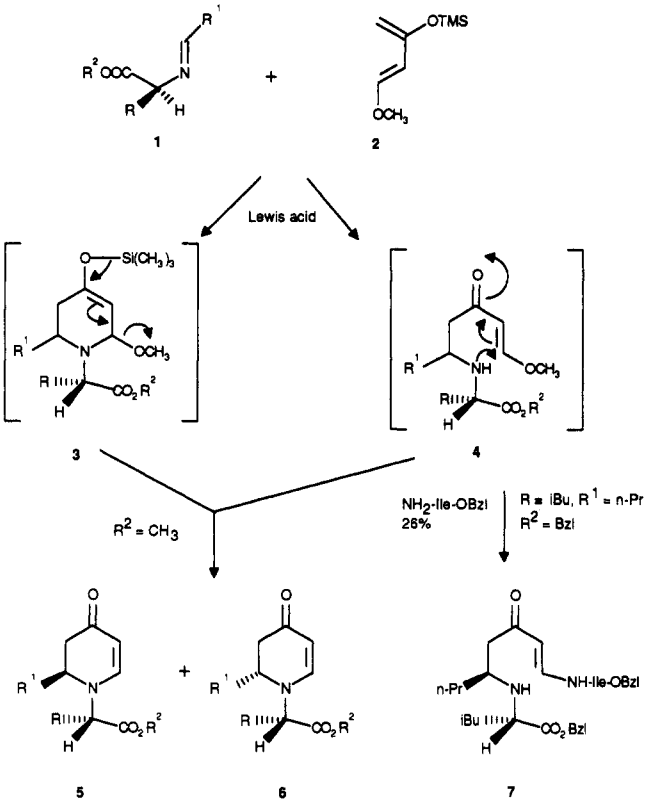
in asymmetric hetero-Diels–Alder reactions,[4] carbo-Diels–Alder reactions,[6] 1,3-dipolar cycloadditions,[7] radical additions to carbonyl groups,[8] and a variety of further reactions.[9]

Results and Discussion

The Danishefsky diene **2** reacts with amino acid ester imines **1** in the presence of 1 equiv of a Lewis acid to deliver the enaminones **5** and **6** in high yield and, depending on the structure of the amino acid used, with good to excellent stereoselectivity (Scheme I, Tables I and II). The diastereomeric ratios can be determined directly from the crude reaction mixtures by analytical HPLC. The major diastereomers **5** are conveniently isolated by flash chromatography. Their absolute configurations were determined by conversion of **5i** and **5r** into the naturally occurring alkaloids (*S*)-coniine and (*R*)-δ-coniceine (vide infra). In neither case could an intermediate **3** be detected, which according to Danishefsky et al.,[2] would result from a Diels–Alder process, neither was an intermediate **4** isolated, which according to observations of Kunz et al.,[3] would result from a stepwise tandem Mannich–Michael process. However, in the synthesis of **5h/6h** using $ZnCl_2$ as catalyst, the vinylogous amide **7** was formed in 26% yield as a byproduct. This compound must have been formed by nucleophilic attack of free amino acid ester, which was present in the reaction mixture probably because of incomplete formation of the imine at the Mannich base intermediate **4**. To confirm this assumption and to rule out the possibility of an alternative reaction of the ester with the final enaminones **5h/6h**, the free amino acid ester was treated with **5h** and $ZnCl_2$ under identical conditions and finally at reflux temperature. However, formation of **7** could not be detected. From these results a definite proof of the course of the reaction cannot be obtained, but the occurrence of **7** suggests that most probably the tandem Mannich–Michael sequence is followed if amino acid ester imines are used as electrophiles.

The application of phenylglycine and phenylalanine as chiral auxiliaries resulted in only low diastereomeric ratios

Scheme I



(Table I, entries 1–4 and 18). In addition, the Schiff bases of phenylglycine are prone to racemization.[10] This was confirmed by treating the benzaldimine of phenylglycine methyl ester with $ZnCl_2$ under the respective reaction conditions, reisolation of the amino acid ester, and comparison of its specific rotation (−40 °, c = 1.3, CH_2Cl_2) with the value obtained for a reference sample (−128°, c = 1.1, CH_2Cl_2). However, imines derived from valine and isoleucine esters yielded the enaminones with uniformly high diastereomeric excess. The size of the ester moiety remarkably seems only to be of subordinate influence on the diastereomeric ratio, as there is no significant difference between amino acid methyl and benzyl esters (Table II, entries 1 and 2). Electronic effects, too, seemingly play no important role in this process since aldehydes bearing

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(8) Waldmann, H. *Synlett* **1990**, 627; *Liebigs Ann. Chem.* **1991**, 1317.
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(10) Grigg, R. *J. Chem. Soc., Chem. Commun.* **1982**, 384.

Table II. Variation of Lewis Acid

entry	no.	R^1	amino acid	temp (°C)	Lewis acid/solvent	yield (%)	5:6
1	**5h**	*n*-prop	Ile-OBzl	0	$ZnCl_2$/THF	65	90:10
2	**5i**	*n*-prop	Ile-OMe	−15	$ZnCl_2$/THF	50	90:10
3	**5i**	*n*-prop	Ile-OMe	−78 to −20	$TiCl_4/CH_2Cl_2$	37	91:9
4	**5i**	*n*-prop	Ile-OMe	−78 to −20	$EtAlCl_2/CH_2Cl_2$	80	94:6
5	**5i**	*n*-prop	Ile-OMe	−78 to −20	Et_2AlCl/CH_2Cl_2	80	92:8
6	**5i**	*n*-prop	Ile-OMe	−78 to −20	$MeAlCl_2/CH_2Cl_2$	74	93:7
7	**5i**	*n*-prop	Ile-OMe	−78 to −20	Me_2AlCl/CH_2Cl_2	80	93:7
8	**5i**	*n*-prop	Ile-OMe	−78 to −20	$BF_3{\cdot}Et_2O/CH_2Cl_2$	64	80:20
9	**5k**	phenyl	Ile-OMe	−15	$ZnCl_2$/THF	62	92:8
10	**5k**	phenyl	Ile-OMe	−78 to −20	$EtAlCl_2/CH_2Cl_2$	21	95:5
11	**5k**	phenyl	Ile-OMe	−78 to −20	Et_2AlCl/CH_2Cl_2	28	89:11

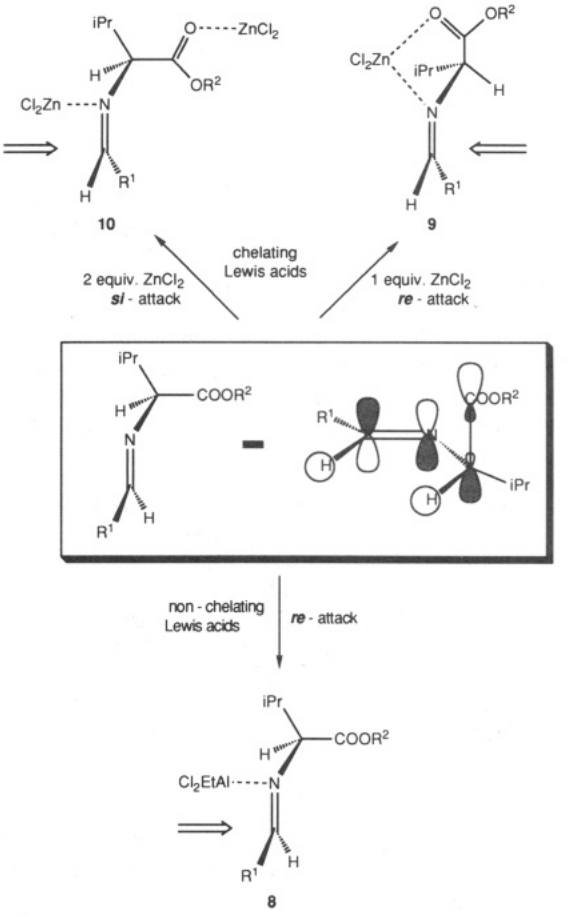
electron-withdrawing or -donating groups deliver nearly the same results (Table I, entries 5–7). In the reaction sequence shown in Scheme I, derivatives of differently substituted aromatic, aliphatic, and functionalized aldehydes can be used. With Schiff bases of aliphatic aldehydes, the best results are obtained if aluminum compounds are added as catalysts at low temperature and dichloromethane is employed as solvent (Table II). On the other hand, for imines of aromatic aldehydes the best catalyst system is $ZnCl_2$ in THF at 0 °C to −20 °C. However, $TiCl_4$ and $BF_3{\cdot}Et_2O$ may also be used (Table II, entries 3 and 8). These results markedly differ from earlier observations[2,3] that only upon treatment with $ZnCl_2$ in THF the diene **2** reacts with imines to give the desired products in high yields and/or stereoselectivities.

A further surprising result is the fact that the sense of the stereoselection is identical for both the chelating Lewis acids ($ZnCl_2$ and $TiCl_4$, Table II, entries 2, 3, and 9) as well as for the catalysts which are usually only capable of tetracoordination ($BF_3{\cdot}Et_2O$, and aluminum Lewis acids, Table II, entries 4–8, 10, and 11).

In analogy to observations obtained for aza-Diels–Alder reactions with amino acid ester imines in aqueous and in organic solution,[4] (*S*)-phenylethylamine is less efficient as a chiral mediator in the Mannich–Michael reactions presented here than the valine and isoleucine esters. The Schiff base obtained from this chiral amine and butyraldehyde gave the respective enaminones with a diastereomeric ratio of 75:25 (the absolute configuration of the predominating diastereomer was not determined), whereas the isoleucine methyl ester delivers the corresponding vinylogous amides **5i** and **6i** in a ratio of 93:7. Also phenylethylamine could not be removed from the heterocycles by hydrogenation.

To rationalize the steric course of the tandem Mannich–Michael reactions and to account for the lacking reversal of the stereochemistry upon switching from a chelating to a nonchelating catalyst, we propose the working model illustrated in Scheme II. The nonchelating boron and aluminum Lewis acids most probably coordinate to the imine nitrogen. The amino acid ester then adopts a conformation **8** in which, by analogy to the Felkin–Anh model[11] for nucleophilic additions to carbonyl groups, the α C–COOR bond is oriented perpendicular to the C–N double bond, resulting in a parallel arrangement and thus an overlap of the respective σ^* and π^* orbitals (see Scheme II). The attack of the diene then should preferably occur from the *re* side. According to this model, the chelating Lewis acids $ZnCl_2$ and $TiCl_4$, which can additionally coordinate the ester carbonyl group, are expected to reverse the direction of the induction. However, NMR spectroscopic investigations indicate that, in the presence of these Lewis acids, the imine double bond isomerizes under the

Scheme II



reaction conditions ($ZnCl_2$: 0 °C to −20 °C; $TiCl_4$: warming from −78 °C to rt), as previously observed by Ojima et al.[12] for $TiCl_4$-mediated [2 + 2]-cycloadditions between amino acid ester imines and ketene silyl acetals. Thus, the ^{1}H-NMR spectrum of a solution of valine methyl ester butyraldimine and 1 equiv of $ZnCl_2$ in THF-d_8 shows two sets of signals for the aldimine proton, and for the amino acid α H, with nearly equal chemical shifts, which differ from the shifts obtained from the uncomplexed imine (0.4 and 1.7 ppm, respectively). The occurrence of these signals (ratio 1:4) points to an equilibrium between cis and trans imine from which the cis imine **9** seems to react faster. It is again attacked preferentially from the *re* side and, therefore, also delivers the diastereomer **5** in excess.

The assumption that $ZnCl_2$ is chelated by the amino acid ester imines is supported by the observation that with 2 equiv of this Lewis acid the sense of the asymmetric induction is reversed (Table I, entry 11; Table II, entry 2).

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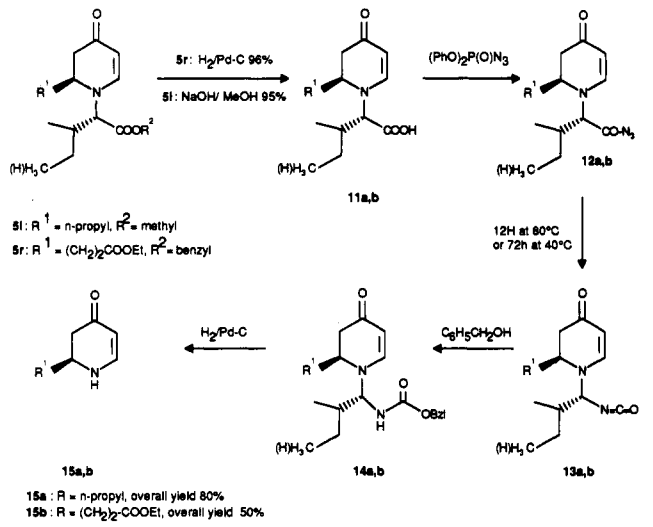
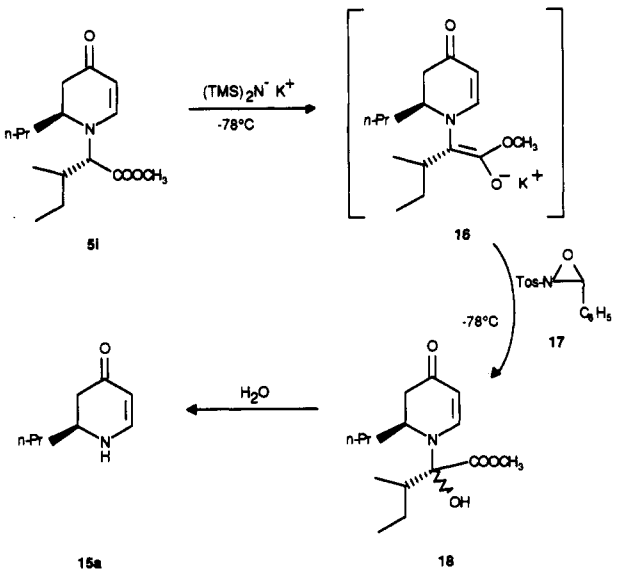
Scheme III



This result can be understood by the formation of a complex **10** in which both the imine and the ester carbonyl group are complexed by a $ZnCl_2$ so that the chelation is broken. The working hypothesis illustrated in Scheme II is, in addition, strengthened by findings made for the reaction of tryptophan methyl ester-derived Schiff bases with Danishefsky's diene.[13] In these cases, too, the outcome of the tandem reactions can be rationalized by the intermediate formation of a nonchelated complex analogous to **10**. It is interesting to note that in contrast to the reaction of the imines **1** with the diene **2** the similar transformations with the so-called Brassards diene (CH_2=$CH(OCH_3)$-CH=$C(OCH_3,O(SiCH_3)_3)$ proceed via different steric courses and, probably, as a Diels–Alder process. We have discussed the differences between the reactions of the Schiff bases **1** with these electron-rich siloxy dienes in detail elsewhere.[4e]

To cleave the chiral auxiliary from the enaminones **5**, the chemically stable bond between the α carbon of the amino acid and the nitrogen has to be broken. This goal was achieved by making use of a strategy developed by us,[4e,5] which consists in the conversion of the amino acid α C atom into an easily hydrolyzable acetalic center (Scheme III). For this purpose a Curtius rearrangement served as the key step. The application of a Hofmann degradation by means of a hypervalent iodine compound[14] or of a Lossen[15] rearrangement gave inferior results. To achieve the desired degradation, the methyl ester **5i** and the benzyl ester **5r** were first converted to the carboxylic acids **11a** and **11b** by alkaline saponification of the methyl ester and hydrogenation of the benzyl ester, respectively. Treatment of the liberated carboxylic acids with diphenyl phosphorazidate[16] either at 80 °C for 12 h or at 40 °C for 72 h resulted in the formation of the carboxylic acid azides **12a** and **12b**, which underwent smoothly Curtius rearrangements to yield the isocyanates **13a** and **13b**. These rearrangement products were trapped as the urethanes **14a** and **14b** by added benzyl alcohol. Finally, hydrogenolysis and subsequent chromatography delivered the free enaminones **15a** and **15b** in overall yields of 50–80%. The yield is higher if the rearrangement is carried out at 40 °C.

Scheme IV



If desired, the carboxylic acids **11a,b** and the acylated acetals **14a** and **14b** may be isolated and characterized, but for preparative purposes it is more convenient to run the whole reaction sequence as a one-pot procedure without diminishing the overall yield. It should be noted that the final hydrogenolysis is faster if the phosphoric acid ester and the added tertiary amine are first removed by extraction.

An alternative route to the desired vinylogous amides **15** consists in the oxidation of the amino acid ester enolates, e.g. **16**, with the sulfonyloxaziridine **17**, introduced by Davis[17] (Scheme IV). Unfortunately, from **5i** the enaminone **15a** could only be obtained in 30% yield by this one-step procedure. A competitive oxidation at C-5 of the heterocycle was not observed. Attempts to remove the amino acid ester via oxidation with lead tetraacetate[18] were not successful.

Enaminones like **15a** and **15b** are versatile intermediates for the construction of different alkaloids.[3,9,13,19] To elucidate the absolute configuration of the vinylogous amides obtained from the tandem Mannich–Michael reactions, **5r** was converted into the indolizidine alkaloid (*R*)-δ-coniceine **28**, and **5i** was transformed into the alkaloid (*S*)-coniine **22** (Scheme V). To this end, the enaminone **15a** obtained from **5i** as shown in Scheme III first was acylated to yield the urethane **19** which was then chemoselectively reduced with L-Selectride (Aldrich) to the ketone **20** according to the procedure described by Kunz et al.[3] The acylation of the amide function proved to be necessary to effect the desired reduction of the double bond; the direct reduction of the free enaminone **15a** was not successful. Finally, after thioketalization, treatment of the acetal **21** with Raney nickel at 80 °C resulted in the simultaneous desulfurization and the removal of the Z protecting group from **21** and yielded (*S*)-coniine which was isolated as the hydrochloride **22**. Similarly, the piperidinone **15b** obtained from **5r** was cyclized to the lactam **23** by heating in benzene in the presence of DBU, and subsequently the double bond was

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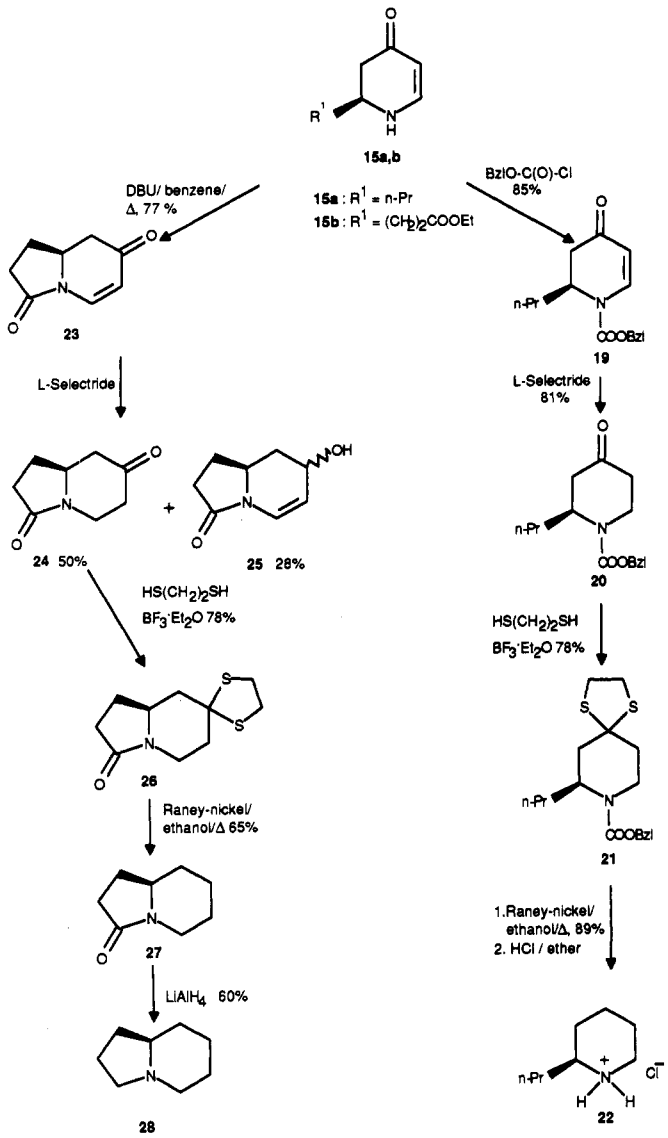
Scheme V



reduced to the lactam **24** with L-Selectride. The reaction, however, was not completely chemoselective and the allylic alcohol **25** was found in 28%. The keto function was then deoxygenated via Raney nickel mediated desulfurization of the thioacetal **26**, obtained from **24** and ethanedithiol in the presence of BF_3-Et_2O. Finally, desulfurization and reduction of the amide **27** with $LiAlH_4$ afforded (*R*)-δ-coniceine **28**. The specific rotations of both synthetic alkaloids **22** and **28** are in agreement with literature data[20,21] and thereby prove the absolute configuration of the adducts **5i** and **5r** and the enaminones **15a,b**.

In conclusion, amino acid esters prove to be efficient chiral auxiliaries for the Mannich-type transformations. These chiral auxiliaries provide the addition products with high diastereomeric ratios. They may be removed by a straightforward, experimentally simple one-pot procedure. We note that the process described in this paper can readily be extended to the construction of the polycyclic framework of the yohimbine-type alkaloids in enantiomerically pure form by employing imines derived from tryptophan esters.[13] Both enantiomers of amino acid esters are readily available at low cost, so that their loss during the removal of the auxiliary can easily be tolerated.

(20) Tallent, W.; Horning, E. *J. Am. Chem. Soc.* **1956**, *78*, 4467.
(21) Rindahl, B.; Pinder, A.; Pereira, W.; Oppenheimer, N.; Craig, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1.

Experimental Section

The analytical instruments and general experimental techniques used have already been described elsewhere.[4e,f,6,7] A 1 M solution of zinc chloride was prepared by dissolving 13.6 g of anhydrous zinc chloride in 50 mL of THF and, after cooling to room temperature, adding CH_2Cl_2 to a total volume of 100 mL.

General Protocol for the Preparation of the Imines 1. To a solution of 1 mmol of the free amino acid ester in 10 mL of ether or petroleum ether was added 1 mL of the corresponding aldehyde rapidly in one portion. The solution was stirred for 15–20 min, it was then dried with $MgSO_4$, and the solvent was removed in vacuo. The resulting imines **1** were directly used in the subsequent reactions without further purification.

General Protocol for the Synthesis of the 2,3-Didehydropiperidinones 5 and 6. (1) Using $ZnCl_2$. To a solution of 1 mmol of the respective imine in 10 mL of THF (at 0 to −15 °C) was added 1 equiv of the Lewis acid (1 M solution in THF/CH_2Cl_2) slowly within 2 min via syringe. The mixture was stirred for 5 min, and then 1.3 equiv of the diene **2** was added during 7 h by a motor-driven syringe to minimize any undesired polymerization of the diene.

(2) Using Aluminum Lewis Acids. A 0.1 M solution of the respective imine in CH_2Cl_2 was cooled to −78 °C, 1 equiv of the corresponding Lewis acid was added, and the diene was added in one portion. The cooling bath was removed, and the reaction mixture was allowed to warm to rt over 1 h, after which time the reaction mixture turned a deep red or black.

For workup in both cases the solution was poured into saturated aqueous $NaHCO_3$ and extracted twice with 100 mL of ether, followed by one extraction with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, and the solvent was evaporated in vacuo. The resulting dark-colored oil was subjected to flash chromatography using petroleum ether/acetone mixtures (5–6:1) to yield the enaminones **5** as yellowish oils.

According to the procedure described above, the following 2,3-didehydropiperidinones were prepared.

***N*-[(*R*)-(Methoxycarbonyl)benzyl]-(6*S*)-2,3-didehydro-6-phenylpiperidin-4-one (5a):** $[\alpha]^{23}_D$ = 0.45° (*c* = 0.93, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.5 (m, 10 H, Ph), 6.9 (d, $J_{2\text{-H},3\text{-H}}$ = 8.1 Hz, 1 H, 2-H), 5.03 (d, 1 H, 3-H), 4.86 (s, 1 H, α-H), 4.63 (dd, $J_{6\text{-H},5\text{-Ha}}$ = 5.7 Hz, $J_{6\text{-H},5\text{-Hb}}$ = 10.2 Hz, 1 H, 6-H), 3.7 (s, 3 H, OCH_3), 2.84 (dd, $J_{5\text{-Ha},5\text{-Hb}}$ = 15.1 Hz, 1 H, 5-H_a), 2.76 (dd, 1 H, 5-H_b); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 190.9 (C-4), 171.4 (C=O), 151.5 (C-2), 138.4 (C-ipso), 133.7 (C-ipso), 129.3, 129.1, 129.0, 128.9, 128.83, 128.7, 127.2 (7 C, Ph), 101.0 (C-3), 65.6 (C-α), 63.1 (OCH_3), 52.4 (C-6), 47.37 (C-5). Anal. Calcd for $C_{20}H_{19}NO_3$: C 74.74; H 5.95; N 4.35. Found: C, 75.05; H, 5.73; N, 4.68.

***N*-[(*R*)-(Methoxycarbonyl)benzyl]-(6*S*)-2,3-didehydro-6-(4-methoxyphenyl)piperidin-4-one (5b):** $[\alpha]^{23}_D$ = −51° (*c* = 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.5 (m, 3 H, Ph, 2-H), 6.9 (m, 7 H, Ph), 5.03 (d, $J_{3\text{-H},2\text{-H}}$ = 7.9 Hz, 1 H, 3-H), 4.85 (s, 1 H, α-H), 4.55 (dd, $J_{6\text{-H},5\text{-Ha}}$ = 5.3 Hz, $J_{6\text{-H},5\text{-Hb}}$ = 13.1 Hz, 1 H, 6-H), 3.76 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 2.80 (dd, $J_{5\text{-Ha},5\text{-Hb}}$ = 16.4 Hz, 1 H, 5-H_a), 2.65 (dd, 1 H, 5-H_b); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.2 (C-4), 170.3 (C=O), 159.8 (C-ipso), 151.6 (C-2), 133.7 (C-ipso), 130.1–129 (5 C, Ph), 100.9 (C-3), 65.2 (C-α), 63.1 (OCH_3), 55.1 (C-6), 47.7 (C-5). Anal. Calcd for $C_{21}H_{21}NO_4$: C, 71.57; H, 6.02; N, 3.99. Found: C, 71.69; H, 5.95; N, 3.95.

***N*-[(*R*)-(Methoxycarbonyl)benzyl]-(6*S*)-2,3-didehydro-6-(4-nitrophenyl)piperidin-4-one (5c):** $[\alpha]^{23}_D$ = 166.8° (*c* = 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, *J* = 8.7 Hz, 2 H, Ph), 7.9 (d, *J* = 7.6 Hz, 2 H, Ph), 7.5–7.39 (m, 5 H, Ph), 6.97 (d, $J_{2\text{-H},3\text{-H}}$ = 8.0 Hz, 1 H, 2-H), 5.10 (d, 1 H, 3-H), 4.82 (s, 1 H, α-H), 4.70 (dd, $J_{6\text{-H},5\text{-Ha}}$ = 9.2 Hz, $J_{6\text{-H},5\text{-Hb}}$ = 6.3 Hz, 1 H, 6-H), 3.77 (s, 3 H, OCH_3), 2.93 (dd, 1 H, $J_{5\text{-Ha},5\text{-Hb}}$ = 16.4 Hz, 5-H_a), 2.70 (dd, 1 H, 5-H_b); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 189.5 (C-4), 170.2 (C=O), 150.7 (C-2), 148.1 (C-ipso), 145.9 (*p*-C, $PhNO_2$), 132.8 (C-ipso), 129–126 (5 C, Ph), 101.6 (C-3), 66.8 (C-α), 62.6 (OCH_3), 52.8 (C-6), 43.6 (C-5). Anal. Calcd for $C_{20}H_{19}NO_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.49; H, 5.01; N, 7.34.

***N*-[(*R*)-(Methoxycarbonyl)benzyl]-(6*R*)-2,3-didehydro-6-*n*-propylpiperidin-4-one (5d):** $[\alpha]^{23}_D$ = −8.1° (*c* = 0.95, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.3 (m, 5 H, Ph), 6.55 (d,

$J_{2\text{-H},3\text{-H}}$ = 7.9 Hz, 1 H, 2-H), 5.07 (s, 1 H, α-H), 4.77 (d, 1 H, 3-H), 3.7 (s, 3 H, OCH_3), 3.4 (m, 1 H, 6-H), 2.84 (dd, $J_{5\text{-H}a,5\text{-H}b}$ = 15.1 Hz, $J_{6\text{-H},5\text{-H}a}$ = 6.4 Hz, 1 H, 5-H_a), 2.76 (dd, 1 H, 5-H_b), 1.7 (m, 1 H, 7-H_a), 1.67 (m, 1 H, 7-H_b), 1.36 (m, 1 H, 8-H_a), 1.26 (m, 1 H, 8-H_b), 0.9 (t, J = 6.9 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.2 (C-4), 170.9 (C=O), 148.9 (C-2), 132.6 (C-ipso), 129.3, 129.0, 128.4 (3 C, Ph), 98.6 (C-3), 67.6 (C-α), 58.1 (OCH_3), 52.4 (C-6), 39.2 (C-2), 31.6 (C-7), 18.7 (C-8), 14.0 (C-9). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.84. Found: C, 70.89; H, 7.13; N, 4.73.

***N*-[(*S*)-1-(Methoxycarbonyl)-2-methylpropyl]-(6*R*)-2,3-didehydro-6-phenylpiperidin-4-one (5e)**: $[\alpha]^{23}_D$ = −22.4° (c = 1.07, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.24 (m, 6 H, Ph, 2-H), 5.17 (d, $J_{3\text{-H},2\text{-H}}$ = 7.9 Hz, 1 H, 3-H), 4.46 (dd, $J_{6\text{-H},5\text{-H}a}$ = 5.8 Hz, $J_{6\text{-H},5\text{-H}b}$ = 11.4 Hz, 1 H, 6-H), 3.56 (s, 3 H, OCH_3), 3.10 (d, J = 10.8 Hz, 1 H, α-H), 2.76 (dd, $J_{5\text{-H}a,5\text{-H}b}$ = 14.5 Hz, 1 H, 5-H_a), 2.64 (dd, 1 H, 5-H_b), 2.16 (m, 1 H, β-H), 0.9 (d, J = 6.6 Hz, 3 H, CH_3), 0.75 (d, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 190.8 (C-4), 171.8 (C=O), 151.7 (C-2), 138.3 (C-ipso), 128.8, 128.4, 127.8 (Ph), 101.2 (C-3), 68.6 (C-α), 62.9 (OCH_3), 51.8 (C-6), 44.3 (C-5), 28.4 (C-β), 19.2, 19.1 (2 CH_3). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.33; N, 4.87. Found: C, 71.07; H, 7.53; N, 4.87.

***N*-[(*S*)-1-(Methoxycarbonyl)-2-methylpropyl]-(6*R*)-2,3-didehydro-6-(4-methoxyphenyl)piperidin-4-one (5f)**: $[\alpha]^{23}_D$ = 7.8° (c = 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.24 (d, $J_{2\text{-H},3\text{-H}}$ = 7.9 Hz, 1 H, 2-H), 7.16 (d, J = 8.7 Hz, 2 H, Ph), 6.83 (d, 2 H, Ph), 5.13 (d, 1 H, 3-H), 4.39 (dd, $J_{6\text{-H},5\text{-H}a}$ = 5.5 Hz, $J_{6\text{-H},5\text{-H}b}$ = 12.4 Hz, 1 H, 6-H), 3.75 (s, 3 H, OCH_3), 3.58 (s, 3 H, OCH_3), 3.10 (d, J = 10.8 Hz, 1 H, α-H), 2.74 (dd, $J_{5\text{-H}a,5\text{-H}b}$ = 16.4 Hz, 1 H, 5-H_a), 2.58 (dd, 1 H, 5-H_b), 2.13 (m, 1 H, β-H), 0.86 (d, J = 6.6 Hz, 3 H, CH_3), 0.75 (d, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.1 (C-4), 170.8 (C=O), 151.7 (C-ipso), 150.9 (C-2), 130.1 (p-C, $PhOCH_3$), 128.8 (2 C, Ph), 114.2 (2 C, Ph), 101.2 (C-3), 67.9 (C-α), 62.6 (OCH_3), 55.1 (OCH_3), 51.8 (C-6), 44.4 (C-5), 28.2 (C-β), 19.1, 19.0 (2 CH_3). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 65.24; H, 6.99; N, 4.23. Found: C, 65.02; H, 6.64; N, 4.11.

***N*-[(*S*)-1-(Methoxycarbonyl)-2-methylpropyl]-(6*R*)-2,3-didehydro-6-(4-nitrophenyl)piperidin-4-one (5g)**: $[\alpha]^{23}_D$ = 4.8° (c = 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, J = 8.6 Hz, 2 H, Ph), 7.40 (d, 2 H, Ph), 7.23 (d, $J_{2\text{-H},3\text{-H}}$ = 7.9 Hz, 1 H, 2-H), 5.07 (d, 1 H, 3-H), 4.63 (dd, $J_{6\text{-H},5\text{-H}a}$ = 6.5 Hz, $J_{6\text{-H},5\text{-H}b}$ = 8.5 Hz, 1 H, 6-H), 3.43 (s, 3 H, OCH_3), 3.09 (d, J = 10.8 Hz, 1 H, α-H), 2.72 (dd, $J_{5\text{-H}a,5\text{-H}b}$ = 16.4 Hz, 1 H, 5-H_a), 2.54 (dd, 1 H, 5-H_b), 2.17 (m, 1 H, β-H), 0.87 (d, J = 6.6 Hz, 3 H, CH_3), 0.75 (d, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 189.0 (C-4), 169.8 (C=O), 151.0 (C-2), 147.5 (C-ipso), 145.8 (p-C, $PhNO_2$), 127.1 (2 C, Ph), 124.3 (2 C, Ph), 101.2 (C-3), 70.1 (C-α), 60.3 (OCH_3), 51.7 (C-6), 43.2 (C-5), 28.1 (C-β), 18.9, 18.8 (2 CH_3). Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.47; H, 5.88; N, 8.45. Found: C, 61.34; H, 6.07; N, 8.54.

***N*-[(*S*)-1-(Benzyloxycarbonyl)-(*S*)-2-methylbutyl]-(6*S*)-2,3-didehydro-6-*n*-propylpiperidin-4-one (5h)**: $[\alpha]^{23}_D$ = −120.7° (c = 1.24, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.3 (m, 5 H, Ph), 6.99 (d, $J_{2\text{-H},3\text{-H}}$ = 7.6 Hz, 1 H, 2-H), 5.15 (s, 2 H, OCH_2Ph), 4.95 (d, 1 H, 3-H), 3.40 (m, 2 H, 6-H, α-H), 2.45 (dd, $J_{5\text{-H}a,5\text{-H}b}$ = 11.2 Hz, $J_{5\text{-H}a,6\text{-H}}$ = 6.7 Hz, 1 H, 5-H_a), 2.2 (dd, $J_{5\text{-H}b,6\text{-H}}$ = 16 Hz, 1 H, 5-H_b), 2.0 (m, 1 H, β-H), 1.69 (m, 1 H, 7-H_a), 1.53 (m, 1 H, 7-H_b), 1.29 (m, 2 H, CH_2-Ile), 1.1 (m, 2 H, 8-H), 0.9 (m, 9 H, 3 CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 192 (C-4), 171.1 (C=O), 148.5 (C-2), 134.9 (C-ipso), 128.6, 128.5, 128.3 (Ph), 98.9 (C-3), 69.8 (C-α), 67.0 (OCH_2Ph), 57.14 (C-6), 38.8 (C-5), 33.8 (C-β Ile), 31.2 (C-7), 24.7 (C-8), 18.3 (CH_2 Ile), 15.3 (CH_3 Ile), 13.4 (C-9), 10.4 (CH_3). Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.32; H, 8.77; N, 4.06. Found: C, 73.55; H, 8.58; N, 4.16.

***N*-[(*S*)-1-(Methoxycarbonyl)-(*S*)-2-methylbutyl]-(6*S*)-2,3-didehydro-6-*n*-propylpiperidin-4-one (5i)**: $[\alpha]^{23}D$ = −178.4° (c = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.97 (d, $J_{2\text{-H},3\text{-H}}$ = 7.6 Hz, 1 H, 2-H), 4.93 (d, 1 H, 3-H), 3.69 (s, 3 H, OCH_3), 3.60 (m, 2 H, 6-H, α-H), 2.6 (dd, $J_{5\text{-H}a,5\text{-H}b}$ = 13 Hz, $J_{5\text{-H}a,6\text{-H}}$ = 7 Hz, 1 H, 5-H_a), 2.5 (dd, $J_{5\text{-H}b,6\text{-H}}$ = 16 Hz, 1 H, 5-H_b), 1.96 (m, 1 H, β-H Ile), 1.73 (m, 1 H, 7-H_a), 1.56 (m, 1 H, 7-H_b), 1.29 (m, 2 H, CH_2-Ile), 1.2 (m, 1 H, 8-H_a), 1.0 (m, 1 H, 8-H_b), 0.9 (m, 9 H, 3 CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.0 (C-4), 171.0 (C=O), 149.0 (C-2), 98.9 (C-3), 69.7 (C-α), 61.7 (OCH_3), 57.0 (C-6), 38.9 (C-5), 34.2 (C-β Ile), 31.2 (C-7), 24.7 (C-8), 18.4 (CH_2 Ile), 15.1 (CH_3), 13.8 (C-9), 10.4 (CH_3). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 67.27; H, 9.42; N, 5.24. Found: C, 67.27; H, 9.38; N, 5.20.

***N*-[(*S*)-1-(Methoxycarbonyl)-(*S*)-2-methylbutyl]-(6*R*)-2,3-didehydro-6-phenylpiperidin-4-one (5k)**: $[\alpha]^{23}_D$ = −32° (c = 1.12, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30 (m, 6 H, Ph, 2-H), 5.14 (d, $J_{3\text{-H},2\text{-H}}$ = 7.9 Hz, 1 H, 3-H), 4.44 (dd, $J_{6\text{-H},5\text{-H}a}$ = 5.8 Hz, $J_{6\text{-H},5\text{-H}b}$ = 11.5 Hz, 1 H, 6-H), 3.54 (s, 3 H, OCH_3), 3.19 (d, J = 10.7 Hz, 1 H, α-H), 2.74 (dd, $J_{5\text{-H}a,5\text{-H}b}$ = 14.6 Hz, 1 H, 5-H), 2.63 (dd, 1 H, 5-H_b), 1.9 (m, 1 H, β-CH), 1.64 (m, 1 H, Ile CH_{2a}), 0.95 (m, 1 H, Ile CH_{2b}), 0.76 (t, J = 7.7 Hz, 3 H, Ile CH_3), 0.70 (d, J = 6.3 Hz, 3 H, Ile CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 190.7 (C-4), 170.7 (C=O), 151.0 (C-2), 138.2 (C-ipso), 128.3, 128.1, 127.8 (Ph), 101.1 (C-3), 67.2 (C-α), 62.9 (OCH_3), 51.7 (C-6), 44.2 (C-5), 34.3 (C-β), 24.7 (Ile CH_2), 15.2 (Ile CH_3), 10.4 (Ile CH_3). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.35; H, 7.74; N, 4.62.

***N*-[(*S*)-1-(Methoxycarbonyl)-(*S*)-2-methylbutyl]-(6*R*)-2,3-didehydro-6-(4-nitrophenyl)piperidin-4-one (5l)**: $[\alpha]^{23}_D$ = −2.5° (c = 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.14 (d, J = 8.6 Hz, 2 H, Ph), 7.42 (d, 2 H, Ph), 7.25 (d, $J_{2\text{-H},3\text{-H}}$ = 7.9 Hz, 1 H, 2-H), 5.12 (d, 1 H, 3-H), 4.64 (dd, $J_{6\text{-H},5\text{-H}a}$ = 6.3 Hz, $J_{6\text{-H},5\text{-H}b}$ = 8.7 Hz, 1 H, 6-H), 3.43 (s, 3 H, OCH_3), 3.20 (d, J = 10.7 Hz, 1 H, α-H), 2.7 (dd, $J_{5\text{-H}a,5\text{-H}b}$ = 16.4 Hz, 1 H, 5-H_a), 2.60 (dd, 1 H, 5-H_b), 2.0 (m, 1 H, β-CH), 1.64 (m, 1 H, Ile CH_{2a}), 0.95 (m, 1 H, Ile CH_{2b}), 0.81 (t, J = 7.7 Hz, 3 H, CH_3), 0.75 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 189.2 (C-4), 169.9 (C=O), 151.2 (C-2), 147.7 (C-ipso), 145.8 (p-C, $PhNO_2$), 127.1 (2 C, Ph), 124.3 (2 C, Ph), 101.5 (C-3), 68.9 (C-α), 60.8 (OCH_3), 51.8 (C-6), 43.4 (C-5), 34.2 (C-β), 24.7 (Ile CH_2), 15.1 (Ile CH_3), 10.4 (Ile CH_3). Anal. Calcd for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.08. Found: C, 62.25; H, 6.68; N, 8.05.

***N*-[(*S*)-1-(Benzyloxycarbonyl)-(*S*)-2-methylbutyl]-(6*R*)-2,3-didehydro-6-(4-nitrophenyl)piperidin-4-one (5m)**: $[\alpha]^{23}_D$ = 16.4° (c = 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, J = 8.7 Hz, 2 H, Ph), 7.5–7.3 (m, 8 H, Ph, 2-H), 5.15 (d, $J_{2\text{-H},3\text{-H}}$ = 7.9 Hz, 1 H, 3-H), 5.1–4.9 (2 d, J = 11.8 Hz, 2 H, OCH_2), 4.52 (t, 1 H, 6-H), 3.20 (d, J = 10.8 Hz, 1 H, α-H), 2.62 (d, $J_{5\text{-H},6\text{-H}}$ = 8.0 Hz, 1 H, 5-H). 2.04 (m, 1 H, β-CH), 1.68 (m, 1 H, Ile CH_{2a}), 0.98 (m, 1 H, Ile CH_{2b}), 0.84 (t, 3 H, Ile CH_3), 0.78 (d, J = 6.5 Hz, 3 H, Ile CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 189.5 (C-4), 169.5 (C=O), 150.9 (C-2), 147.9 (C-ipso), 145.6 (p-C, $PhNO_2$), 134.8 (C-ipso), 128-126 (6 C, Ph), 102.1 (C-3), 68.8 (C-α), 60.0 (OCH_3), 51.6 (C-6), 43.6 (C-5), 34.3 (β-C), 24.8 (CH_2 Ile), 15.2 (CH_3), 10.5 (CH_3). Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.32; H, 6.46; N, 6.39.

***N*-[(*S*)-1-(Methoxycarbonyl)-(*S*)-2-methylbutyl]-(6*R*)-2,3-didehydro-6-(4-methoxyphenyl)piperidin-4-one (5n)**: $[\alpha]^{23}_D$ = −9.2° (c = 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, $J_{2\text{-H},3\text{-H}}$ = 7.9 Hz, 1 H, 2-H), 7.14 (d, 2 H, Ph, J = 8.6 Hz), 6.82 (d, 2 H, Ph), 5.12 (d, 1 H, 3-H), 4.37 (dd, $J_{6\text{-H},5\text{-H}a}$ = 5.3 Hz, $J_{6\text{-H},5\text{-H}b}$ = 12.5 Hz, 1 H, 6-H), 3.73 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3), 3.48 (d, J = 10.7 Hz, 1 H, α-H), 2.74 (dd, $J_{5\text{-H}a,5\text{-H}b}$ = 16.4 Hz, 1 H, 5-H_a), 2.55 (dd, 1 H, 5-H_b), 1.8 (m, 1 H, β-CH), 1.64 (m, 1 H, Ile CH_{2a}), 0.95 (m, 1 H, Ile CH_{2b}), 0.75 (t, J = 7.7 Hz, 3 H, Ile CH_3), 0.71 (d, J = 6.3 Hz, 3 H, Ile CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.3 (C-4), 170.9 (C=O), 159.6 (C-ipso), 151.0 (C-2), 130.0 (p-C, $PhOCH_3$), 128.8 (2 C, Ph), 114.2 (2 C, Ph), 101.1 (C-3), 66.6 (C-α), 62.7 (OCH_3), 55.1 (OCH_3, Ph), 51.7 (C-6), 44.4 (C-5), 34.4 (C-β), 24.7 (CH_2 Ile), 15.2 (Ile CH_3), 10.5 (Ile CH_3). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.68; H, 7.60; N, 4.26. Found: C, 68.71; H, 7.69; N, 4.45.

***N*-[(*S*)-1-(Methoxycarbonyl)-(*S*)-2-methylbutyl]-(6*S*)-2,3-didehydro-6-(2-methylpropyl)piperidin-4-one (5o)**: $[\alpha]^{23}_D$ = −134.2° (c = 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.1 (d, $J_{2\text{-H},3\text{-H}}$ = 7.6 Hz, 1 H, 2-H), 5.00 (d, 1 H, 3-H), 3.7 (s, 3 H, OCH_3), 3.40 (m, J = 10.6 Hz, 1 H, α-H), 3.2 (ddd, J_1 = 4.4 Hz, J_2 = 7.7 Hz, J_3 = 8.3 Hz, 1 H, 6-H), 2.5 (dd, $J_{5\text{-H}a,5\text{-H}b}$ = 9.6 Hz, $J_{5\text{-H}a,6\text{-H}}$ = 7.7 Hz, 1 H, 5-H_a), 2.37 (dd, $J_{5\text{-H}b,6\text{-H}}$ = 16 Hz, 1 H, 5-H_b), 2.06 (m, 2 H, 7-H, β-H Ile), 1.73 (m, 1 H, Ile CH_{2a}), 1.3 (m, 1 H, Ile CH_{2b}), 0.9 (m, 12 H, 4 CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.6 (C-4), 171.5 (C=O), 149.3 (C-2), 99.5 (C-3), 69.7 (C-α), 62.9 (OCH_3), 52.2 (C-6), 35.2 (C-5), 34.2 (C-β Ile), 29.2 (C-7), 25.6 (CH_2 Ile), 19.3, 17.0 (CH_3), 15.1 (CH_3), 11.0 (CH_3). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.39; H, 9.42; N, 5.42. Found: C, 67.21; H, 9.52; N, 5.16.

***N*-[(*S*)-1-(Methoxycarbonyl)-(*S*)-2-methylbutyl]-(6*S*)-2,3-didehydro-6-*n*-pentylpiperidin-4-one (5p)**: $[\alpha]^{23}_D$ = −155.7°

(c = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.98 (d, $J_{2\text{-H},3\text{-H}}$ = 7.0 Hz, 1 H, 2-H), 4.9 (d, 1 H, 3-H), 3.7 (s, 3 H, OCH_3), 3.39 (m, 2 H, 6-H, α-H), 2.6 (dd, $J_{5\text{-Ha},5\text{-Hb}}$ = 11 Hz, $J_{5\text{-Ha},6\text{-H}}$ = 6.3 Hz, 1 H, 5-H_a), 2.3 (dd, $J_{5\text{-Hb},6\text{-H}}$ = 0.8 Hz, 1 H, 5-H_b), 1.96 (m, 1 H, β-H Ile), 1.73 (m, 1 H, 7-H_a), 1.6 (m, 1 H, 7-H_b), 1.30 (m, 6 H, 8-H, 9-H, Ile CH_2), 0.9 (m, 9 H, 3 CH_3). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.1 (C-4), 171.0 (C=O), 149.1 (C-2), 98.9 (C-3), 69.8 (C-α), 62.2 (OCH_3), 57.2 (C-6), 39.0 (C-5), 34.1 (C-β Ile), 28.9, 27.4, 27.3, 22.0 (CH_2), 15.4 (CH_3), 13.8 (C-10), 10.4 (CH_3). Anal. Calcd for $C_{18}H_{26}NO_3$: C, 68.54; H, 9.35; N, 5.00. Found: C, 68.62; H, 9.24; N, 4.78.

***N*-[(*S*)-1-(Benzyloxycarbonyl)-2-methylpropyl]-(6*S*)-6-[3-(methoxycarbonyl)propyl]-2,3-didehydropiperidin-4-one (5q)**: $[\alpha]^{23}_D$ = −131.5° (c = 1.21, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.3 (s, 5 H, Ph), 7.0 (d, $J_{2\text{-H},3\text{-H}}$ = 7.8 Hz, 1 H, 2-H), 5.15 (s, 2 H, OCH_2Ph), 4.98 (d, 1 H, 3-H), 3.62 (s, 3 H, OCH_3), 3.45 (m, 1 H, 6-H), 3.3 (d, J = 10.9 Hz, 1 H, α-H), 2.45 (dd, $J_{5\text{-Ha},5\text{-Hb}}$ = 12.0 Hz, $J_{5\text{-Ha},6\text{-H}}$ = 6.2 Hz, 1 H, 5-H_a), 2.25 (dd, 3 H, 5-H_b, β-H, 7-H_a), 1.8–1.1 (m, 5 H, 7-H_b, 8-H, 9-H), 0.9 (m, 6 H, Val CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 190.8 (C-4), 173.3 (C=O), 170.2 (C=O), 148.7 (C-2), 135.0 (C-ipso), 128.7, 128.6, 128.5 (Ph), 99.2 (C-3), 71.2 (C-α), 67.3 (OCH_2Ph), 57.6 (OCH_3), 51.6 (C-6), 38.5 (C-5), 33.5 (C-β Val), 28.7 (C-7), 28.0 (C-8), 20.3 (C-9), 19.2, 19.1 (CH_3 Val). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.36; H, 7.55; N, 3.61. Found: C, 68.55; H, 7.59; N, 3.53.

***N*-[(*S*)-1-(Benzyloxycarbonyl)-2-methylpropyl]-(6*S*)-6-[2-(ethoxycarbonyl)ethyl]-2,3-didehydropiperidin-4-one (5r)**: $[\alpha]^{23}_D$ = −137.5° (c = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.3 (s, 5 H, Ph), 7.22 (d, $J_{2\text{-H},3\text{-H}}$ = 6.8 Hz, 1 H, 2-H), 5.17 (s, 2 H, OCH_2Ph), 4.9 (d, 1 H, 3-H), 4.10 (q, J = 12 Hz, 2 H, OCH_2), 3.45 (m, 1 H, 6-H), 3.39 (d, J = 10.6 Hz, 1 H, α-H), 2.47 (dd, $J_{5\text{-Ha},5\text{-Hb}}$ = 11.0 Hz, $J_{5\text{-Ha},6\text{-H}}$ = 7.0 Hz, 1 H, 5-H_a), 2.3 (m, 4 H, 5-H_b, β-H, 7-H), 1.9 (m, 1 H, 8-H_a), 1.69 (m, 1 H, 8-H_b), 1.2 (t, 3 H, OCH_2CH_3), 0.9 (dd, 6 H, Val CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 190.4 (C-4), 172.0 (C=O), 170.3 (C=O), 148.3 (C-2), 135.0 (C-ipso), 128.7, 128.6, 128.5, (Ph), 99.3 (C-3), 71.6 (C-α), 67.3 (OCH_2Ph), 60.6 (OCH_2), 56.6 (C-6), 38.5 (C-5), 31.8 (C-β Val), 29.7 (C-7), 27.9 (C-8), 19.3, 19.2 (CH_3 Val), 14.1 (CH_3). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.32; H, 7.54; N, 3.61. Found: C, 68.70; H, 7.45; N, 3.62.

***N*-[(*S*)-1-(Methoxycarbonyl)-(*S*)-2-methylbutyl]-(6*S*)-2,3-didehydro-6-[3-(2-methyl-1,3-dithian-2-yl)propyl]-piperidin-4-one (5s)**: $[\alpha]^{23}_D$ = −99.1° (c = 1.15, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.9 (d, $J_{2\text{-H},3\text{-H}}$ = 7.0 Hz, 1 H, 2-H), 4.93 (d, 1 H, 3-H), 3.7 (s, 3 H, OCH_3), 3.40 (m, 2 H, 6-H, α-H), 2.7 (m, 4 H, SCH_2), 2.67 (dd, $J_{5\text{-Ha},5\text{-Hb}}$ = 14.4 Hz, $J_{5\text{-Ha},6\text{-H}}$ = 6 Hz, 1 H, 5-H_a), 2.3 (dd, $J_{5\text{-Hb},6\text{-H}}$ = 3 Hz, 1 H, 5-H_b), 1.8 (m, 5 H, β-H Ile, 7-H, SCH_2CH_2), 1.5 (m, 7 H), 1.2 (m, 8 H), 0.9 (m, 9 H, 3 CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.0 (C-4), 171.0 (C=O), 148.9 (C-2), 99.2 (C-3), 70.0 (C-α), 65.3 (SCS), 61.7 (OCH_3), 57.1 (C-6), 48.5 (CH_2S), 41.5 (CH_2S), 39.1 (C-5), 34.2 (C-β Ile), 29.2 (C-7), 27.3 (C-11), 26.4, 25.2, 25.0, 22.6 (CH_2), 15.1 (CH_3), 10.4 (CH_3). Anal. Calcd for $C_{20}H_{33}NO_3S_2$: C, 60.11; H, 8.32; N, 3.51. Found: C, 59.86; H, 8.44; N, 3.45.

***N*-[[(*S*)-1-(Methoxycarbonyl)ethyl]phenyl]-(6*S*)-2,3-didehydro-6-*n*-propylpiperidin-4-one (5t)**: $[\alpha]^{23}_D$ = −196.7° (c = 2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.3 (m, 6 H, 2-H, Ph), 4.95 (dd, $J_{3\text{-H},2\text{-H}}$ = 7.3 Hz, J = 0.8 Hz, 1 H, 3-H), 4.0 (dd, J = 6.7 Hz, J = 7.8 Hz, 1 H, α-H), 3.7 (s, 3 H, OCH_3), 3.40 (m, 1 H, 6-H), 3.28 (dd, J = 11 Hz, J = 6.6 Hz, 1 H, β-H), 3.0 (dd, 1 H, β-H), 2.65 (dd, $J_{5\text{-Ha},5\text{-Hb}}$ = 11 Hz, $J_{5\text{-Ha},6\text{-H}}$ = 6.8 Hz, 1 H, 5-H_a), 2.2 (dd, $J_{5\text{-Hb},6\text{-H}}$ = 3 Hz, 1 H, 5-H_b), 1.40 (m, 1 H, 7-H_a), 1.1–0.9 (m, 3 H, 7-H_b, 8-H), 0.75 (m, 9 H, 3 CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.0 (C-4), 170.5 (C=O), 148.4 (C-2), 135.7 (C-ipso), 128.6, 128.4, 127.9 (Ph), 98.6 (C-3), 65.8 (C-α), 58.0 (OCH_3), 52.5 (C-6), 39.1 (C-5), 36.2 (C-β Phe), 31.4 (C-7), 18.2 (C-8), 13.8 (C-9). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.29; H, 7.82; N, 4.64.

Removal of the Chiral Auxiliary Group: Liberation of the Carboxylic Acids. (a) From the Methyl Ester 5i. To a solution of 1 g (3.7 mmol) of **5i** in 100 mL of aqueous methanol (4:1) was added 100 mg of LiOH, and the mixture was heated to 40 °C for 3 h. The solvent was removed in vacuo; the remaining oily residue was taken up in water and extracted with ether. The aqueous phase was acidified and extracted three times with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, and the solvent was evaporated to give 900 mg (95%) of the acid **11a** which was used without further purification.

(b) From the Benzyl Ester 5r. To a solution of 1.2 g (3.4 mmol) of **5r** in 70 mL of methanol was added 100 mg of 5% Pd/charcoal, and the mixture was stirred under 1 atm of hydrogen for 5 h (monitored by TLC). The reaction mixture was filtered through a Celite pad and washed with methanol. The filtrate was evaporated to dryness to afford 850 mg (96%) of **11b** which was used without further characterization.

***N*-[(*S*)-1-Carboxy-(*S*)-2-methylbutyl]-(6*S*)-2,3-didehydro-6-*n*-propylpiperidin-4-one (11a)**: $[\alpha]^{23}_D$ = 120° (c = 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 11.4 (s, 1 H, COOH), 7.1 (d, $J_{2\text{-H},3\text{-H}}$ = 7.0 Hz, 1 H, 2-H), 5.1 (d, 1 H, 3-H), 3.51 (m, 1 H, 6-H), 2.75 (d, J = 10.6 Hz, 1 H, α-H), 2.75 (dd, $J_{5\text{-Ha},5\text{-Hb}}$ = 12.1 Hz, $J_{5\text{-Ha},6\text{-H}}$ = 7 Hz, 1 H, 5-H_a), 2.38 (dd, $J_{5\text{-Hb},6\text{-H}}$ = 13 Hz, 1 H, 5-H_b), 1.98 (m, 1 H, β-H Ile), 1.76 (m, 1 H, 7-H_a), 1.54 (m, 1 H, 7-H_b), 1.42 (m, 2 H, Ile CH_2), 1.36 (m, 2 H, 8-H), 0.9 (m, 9 H, 3 CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 192.1 (C-4), 172.0 (C=O), 151.7 (C-2), 97.3 (C-3), 70.6 (C-α), 57.3 (C-6), 37.6 (C-5), 34.2 (C-β Ile), 30.0 (C-7), 25.0 (C-8), 18.4 (CH_2 Ile), 15.4 (CH_3), 13.9 (C-9), 10.9 (CH_3). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.06; H, 9.10; N, 5.23.

General Procedure for the Curtius Rearrangement and Subsequent Hydrogenation. To a suspension of 1 g (3.9 mmol) of the acid **11** in 50 mL of toluene under an argon atmosphere was slowly added 0.6 mL (4 mmol) of triethylamine until all of the acid dissolved. The solution was cooled to 0 °C, and 0.9 mL (5 mmol) of diphenyl phosphorazidate and 0.6 mL (5.5 mmol) of benzyl alcohol were added during 10 min. The cooling bath was removed, and the solution was stirred at rt until the evolution of nitrogen ceased and then stirred for an additional 72 h at 40 °C or kept at 80 °C overnight. The reaction mixture was poured into water and extracted three times with ether. The combined organic phases were washed three times each with 1 N $NaHCO_3$ and 1 N HCl and dried with $MgSO_4$, and the solvent was removed in vacuo. The crude product was taken up in 70 mL methanol, 250 mg of 5% Pd/charcoal was added, and the mixture was stirred under 1 atm of hydrogen at rt for 5 h. After filtration of the mixture through a Celite pad, the solvent was removed in vacuo, and the residue was subjected to flash chromatography using petroleum ether/acetone (3:1 v/v) as eluent. If the rearrangement starting from **11a** was carried out at rt for 3 d, 440 mg (80%) of the enaminone **15a** was obtained as a colorless oil. When the reaction was carried out at 80 °C overnight, the yield was 50%.

(6*S*)-2,3-Didehydro-6-*n*-propylpiperidin-4-one (15a): $[\alpha]^{23}_D$ = 325.5° (c = 1.07, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.13 (dd, $J_{2\text{-H},3\text{-H}}$ = 6.9 Hz, $J_{2\text{-H,NH}}$ = 7.2 Hz, 1 H, 2-H), 6.43 (s, 1 H, NH), 4.83 (d, 1 H, 3-H), 3.55 (m, 1 H, 6-H), 2.32 (dd, $J_{5\text{-Ha},5\text{-Hb}}$ = 11.0 Hz, $J_{5\text{-Ha},6\text{-H}}$ = 5.4 Hz, 1 H, 5-H_a), 2.2 (dd, $J_{5\text{-Hb},6\text{-H}}$ = 13 Hz, 1 H, 5-H_b), 1.5 (m, 1 H, 7-H_a), 1.45 (m, 1 H, 7-H_b), 1.25 (m, 2 H, 8-H), 0.9 (t, J = 7.4 Hz, 3 H, 9-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 192.4 (C-4), 151.5 (C-2), 97.6 (C-3), 52.7 (C-6), 41.6 (C-5), 35.9 (C-7), 18.3 (C-8), 13.9 (C-9). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.03; H, 9.44; N, 9.79.

(6*S*)-6-[2-(Ethoxycarbonyl)ethyl]-2,3-didehydropiperidin-4-one (15b). The benzyl ester **5r** (11.1 g, 28.4 mmol) was dissolved in 250 mL of methanol, and 200 mg of 5% Pd/charcoal was added. The mixture was stirred under hydrogen gas for 4 h and then evaporated in vacuo. The carboxylic acid **11b**, thus liberated, was used immediately in the subsequent reaction. The Curtius reaction was carried out at 80 °C overnight as described for **15a** to give 2.81 g (50%) of the enaminone **15b**: $[\alpha]^{23}_D$ = 224.1° (c = 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.13 (t, $J_{2\text{-H},3\text{-H}}$ = 7.0 Hz, 1 H, 2-H), 5.99 (s, broad, 1 H, NH), 4.93 (d, 1 H, 3-H), 4.10 (q, J = 12 Hz, 2 H, OCH_2), 3.65 (dddd, J_1 = 5.8, J_2 = 6.1, J_3 = 11.7, J_4 = 12.1 Hz, 1 H, 6-H), 2.40 (m, 4 H, 5-H, 7-H), 1.96 (m, 1 H, 8-H_a), 1.80 (m, 1 H, 8-H_b), 1.2 (t, 3 H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 192.4 (C-4), 173.3 (C=O), 151.1 (C-2), 98.8 (C-3), 60.9 (OCH_2), 52.8 (C-6), 41.7 (C-5), 30.4 (C-7), 28.6 (C-8), 14.1 (CH_3). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.1. Found: C, 60.57; H, 7.81; N, 6.87.

***N*-(Benzyloxycarbonyl)-(6*S*)-2,3-didehydro-6-*n*-propylpiperidin-4-one (19).** To a solution of 1.36 g (9.6 mmol) of enaminone **15a** in 70 mL of THF was added a solution of 6 mL (9.6 mmol) of butyllithium (1.6 M in hexane). A white precipitate formed which dissolved again when 1.3 mL (1.1 equiv) of (ben-

zyloxy)carbonyl chloride was added via syringe. The reaction mixture was gradually warmed to rt within 50 min, the THF was evaporated, and 70 mL of CH_2Cl_2 was added. After extraction with 1 N $NaHCO_3$ and drying of the organic phase with $MgSO_4$, the solvent was removed in vacuo. The amide **19** (2.18 g, 85%) was purified by flash chromatography with petroleum ether/acetone (4:1, v/v) as eluent: $[\alpha]^{23}_D = -86.7°$ (c = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.7 (s, broad, 1 H, 2-H), 7.3 (s, 5 H, Ph), 5.27 (m, 3 H, 3-H, OCH_2Ph), 4.6 (s, broad, 1 H, 6-H), 2.75 (dd, $J_{5\text{-}Ha,5\text{-}Hb}$ = 11.2 Hz, $J_{5\text{-}Ha,6\text{-}H}$ = 6.6 Hz, 1 H, 5-H_a), 2.39 (dd, $J_{5\text{-}Hb,6\text{-}H}$ = 17 Hz, 1 H, 5-H_b), 1.52 (m, 2 H, 7 H), 1.32 (m, 1 H, 8-H_a), 1.28 (m, 1 H, 8-H_b), 0.85 (t, J = 7.2 Hz, 3 H, 9-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 192.4 (C-4), 151.5 (C=O), 141.0 (C-2), 134.3 (C-ipso), 128.6, 128.3, 127.8 (Ph), 107.6 (C-3), 69.8 (OCH_2Ph), 53.1 (C-6), 39.5 (C-5), 32.6 (C-7), 18.7 (C-8), 13.6 (C-9). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.03; H, 7.01; N, 5.10. Found: C, 70.10; H, 7.12; N, 5.47.

***N*-(Benzyloxycarbonyl)-(6*S*)-6-*n*-propylpiperidin-4-one (20).** To a solution of 2.1 g (7.63 mmol) of the enaminone **19** at −78 °C was slowly added 7.7 mL of a 1 M solution of L-Selectride via syringe over 5 min. The reaction mixture was kept at that temperature for 15 min and was then warmed to rt over 30 min. Water (2 mL) was added, and the solvent was evaporated. Chromatography of the residue with petroleum ether/acetone (4:1, v/v) yielded 1.7 g (81%) of the ketone **20**: $[\alpha]^{23}_D = -13.8°$ (c = 1.05, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.3 (s, 5 H, Ph), 5.14 (d, J = 3.5 Hz, 2 H, OCH_2-Ph), 4.6 (s, br, 1 H, 2-H_a), 4.3 (s br, 1 H, 2-H_b), 3.18 (m, 1 H, 6-H), 2.6 (dd, $J_{5\text{-}Ha,5\text{-}Hb}$ = 10.5 Hz, $J_{5\text{-}Ha,6\text{-}H}$ = 6.3 Hz, 1 H, 5-H_a), 2.4 (s, br, 1 H, 5-H_b), 2.27 (m, 2 H, 3-H), 1.3 (m, br, 4 H, 7-H, 8-H), 0.85 (t, J = 7.2 Hz, 3 H, 9-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 204.5 (C-4), 155.3 (C=O), 136.3 (C-ipso), 128.6, 128.3, 127.8 (Ph), 67.4 (OCH_2Ph), 53.1 (C-6), 49.3 (C-2), 40.3 (C-3), 38.5 (C-5), 34.3 (C-7), 18.7 (C-8), 13.5 (C-9). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.70; H, 7.68; N, 5.09. Found: C, 69.36; H, 7.51; N, 5.50.

***N*-(Benzyloxycarbonyl)-(6*S*)-4-(1,3-dithiolan-4-yl)-6-*n*-propylpiperidine (21).** To a solution of 1.5 g (5.5 mmol) of ketone **20** in 70 mL of CH_2Cl_2 were added 0.7 mL of ethanedithiol and 3 g of molecular sieves (4 Å). The mixture was cooled to 0 °C, and 3.26 mL (25.5 mmol) of $BF_3{\cdot}Et_2O$ was added. The reaction mixture was stirred overnight, poured into 50 mL of 1 N $NaHCO_3$, and extracted twice with 50 mL of CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, and the solvent was removed in vacuo. After flash chromatography of the residue with petroleum ether/acetone (5:1, v/v) 1.49 g (78%) of the thioketal **21** was obtained: $[\alpha]^{23}_D = -12.6°$ (c = 1.07, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.3 (s, 5 H, Ph), 5.14 (d, J = 3.5 Hz, 2 H, OCH_2Ph), 4.32 (dd, J = 7.2 Hz, J = 13 Hz, 1 H, 2-H_a), 4.0 (dd, 1 H, 2-H_b), 3.3 (m, 4 H, SCH_2), 3.1 (ddd, J_1 = 3.5 Hz, J_2 = 6.0 Hz, J_3 = 11.1 Hz, 1 H, 6-H), 2.6 (dd, $J_{5\text{-}Ha,5\text{-}Hb}$ = 16.0 Hz, $J_{5\text{-}Ha,6\text{-}H}$ = 6.0 Hz, 1 H, 5-H_a), 2.15 (dd, $J_{5\text{-}Hb,6\text{-}H}$ = 14.2 Hz, 1 H, 5-H_b), 1.9 (m, 2 H, 3-H), 1.75 (m, 1 H, 7-H_a), 1.62 (m, 1 H, 7-H_b), 1.27 (m, 2 H, 8-H), 0.85 (t, J = 7.8 Hz, 3 H, 9-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 155.3 (C=O), 136.3 (C-ipso), 128.6, 128.3, 127.8 (Ph), 67.2 (OCH_2Ph), 64.3 (C-4), 51.7 (C-6), 42.9 (C-2), 42.1, 40.1 (SCH_2-CH_2S), 38.5 (C-3), 37.4 (C-5), 33.6 (C-7), 19.9 (C-8), 13.5 (C-9). Anal. Calcd for $C_{18}H_{25}NO_2S_2$: C, 61.86; H, 6.68; N, 4.01. Found: C, 61.91; H, 6.86; N, 4.07.

(*S*)-2-Propylpiperidine [(*S*)-Coniine, 22]. To a solution of 1.1 g (3.1 mmol) of the thioketal **21** in 70 mL of 2-propanol was added 2.5 g of freshly prepared neutral washed Raney nickel, and the mixture was heated under a hydrogen atmosphere at reflux overnight. The suspension was filtered through Celite, and the pad was thoroughly washed with methanol. The filtrate was acidified with a solution of HCl in methanol. The solvent was evaporated, and the residue was recrystallized from CH_2Cl_2/ether to yield 0.28 g (89%) of (*S*)-coniine hydrochloride: $[\alpha]^{23}_D = -5.8°$ (c = 0.5, ethanol) (lit.[21] −6.9°, c = 1.5, ethanol); mp 209 °C (lit.[21] mp 215 °C); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 57.1 (CH_2), 44.6 (CH), 35.2, 27.9, 22.3, 22.0, 18.5 (5 CH_2), 13.5 (CH_3).

(6*S*)-2,3-Didehydroindolizidine-4,9-dione (23). To a solution of 1.7 g (8.62 mmol) of the enaminone **15b** in benzene was added 1.28 mL (8.6 mmol) of DBU, and the reaction was heated at reflux for 18 h. The solvent was removed in vacuo, and 1 g (77%) of the desired lactam was isolated by flash chromatography of the residue, eluting with petroleum ether/acetone (1.5:1, v/v): $[\alpha]^{23}_D$ = 449.0° (c = 1.04, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, $J_{2\text{-}H,3\text{-}H}$ = 7.9 Hz, 1 H, 2-H), 5.43 (dd, J = 0.7 Hz, 1 H, 3-H), 4.16 (dddd, J_1 = 4.4, J_2 = 5.9, J_3 = 8.6, J_4 = 10.5 Hz, 1 H, 6-H), 2.68 (dd, J_1 = 0.9, J_2 = 4.5 Hz, 1 H, 5-H_a), 2.60 (m, 3 H, 5-H_b, 7-H), 1.85 (m, 2 H, 8-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 193.2 (C-4), 171.5 (C=O), 137.6 (C-2), 109.0 (C-3), 55.4 (C-6), 43.2 (C-5), 30.8 (C-7), 26.0 (C-8). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.42; H, 5.93; N, 9.08.

(6*S*)-Indolizidine-4,9-dione (24). As described for **20**, 900 mg (5.95 mmol) of the enaminone **23** was treated with 6.25 mL of a 1 M solution of L-Selectride. Chromatography was performed with CH_2Cl_2/MeOH (50:1, v/v) to yield 0.45 g (50%) of the lactam **24** and 0.26 g (28%) of the allylic alcohol **25**: $[\alpha]^{23}_D = -34.9°$ (c = 1.6, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.36 (ddd, J_1 = 2.9 Hz, J_2 = 6.7 Hz, J_3 = 9.7 Hz, 1 H, 2-H_a), 3.7 (dddd, J_1 = 3.83 Hz, J_2 = 5.6 Hz, J_3 = 7.5 Hz, J_4 = 9.4 Hz, 1 H, 6-H), 2.9 (ddd, J_1 = 5.4 Hz, J_2 = 9.7 Hz, J_3 = 10.9 Hz, 1 H, 2-H_b), 2.53 (dd, $J_{5\text{-}Ha,5\text{-}Hb}$ = 14.1 Hz, $J_{5\text{-}Ha,6\text{-}H}$ = 7 Hz, 1 H, 5-H_a), 2.45–2.2 (m, 4 H, 5-H, 3-H, 7-H_a, 8-H), 1.72 (dddd, J_1 = 5.4 Hz, J_2 = 7.2 Hz, J_3 = 9.4 Hz, J_4 = 12.7 Hz, 1 H, 7-H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 206.3 (C-4), 173.5 (C=O), 56.3 (C-6), 48.5 (C-2), 39.7 (C-5), 37.9 (C-3), 29.5 (C-7), 24.9 (C-8). Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.50; H, 7.20; N, 9.20.

(6*S*)-4-(1,3-Dithiolan-4-yl)indolizidin-9-one (26). As described for **21**, 440 mg (2.87 mmol) of **24** was reacted with 1.1 mL (3 equiv) of $BF_3{\cdot}Et_2O$ and 0.36 mL (1.5 equiv) of ethanedithiol. Chromatography was performed with CH_2Cl_2/MeOH (30:1, v/v) to afford 520 mg (78%) of the thioketal **26**: $[\alpha]^{23}_D = 38.7°$ (c = 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.12 (ddd, J_1 = 3.3 Hz, J_2 = 4.8 Hz, J_3 = 8.7 Hz, 1 H, 2-H_a), 3.6 (dddd, J_1 = 3.2 Hz, J_2 = 3.5 Hz, J_3 = 3.9 Hz, J_4 = 7.4 Hz, 1 H, 6-H), 3.3 (s, 4 H, SCH_2CH_2S), 2.86 (ddd, J_1 = 3.1 Hz, J_2 = 9.1 Hz, J_3 = 13.0 Hz, 1 H, 2-H_b), 2.3 (m, J_1 = 13.1 Hz, J_2 = 7.4 Hz, 2 H, 3-H), 2.2 (m, 2-H), 2.0 (m, 1 H), 1.9 (ddd, J_1 = 4.9 Hz, J_2 = 11.6 Hz, J_3 = 12.6 Hz, 1 H), 1.7 (m, 1 H), 1.5 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.3 (C=O), 65.5 (C-4), 56.2 (C-6), 48.9 (C-2), 40.5 (C-5), 39.6 and 39.5 (SCH_2CH_2S), 37.9 (C-3), 30.1 (C-7), 24.5 (C-8). Anal. Calcd for $C_{10}H_{15}NOS_2$: C, 52.27; H, 6.59; N, 6.11. Found: C, 51.98; H, 6.66; N, 6.08.

(6*R*)-Indolizidin-9-one (27). As described for **22**, 480 mg (2.07 mmol) of the thioketal **26** was treated with 2.5 g of Raney nickel (neutral washed). After filtration through Celite and evaporation of the solvent, the residue was purified by chromatography with CH_2Cl_2/MeOH (20:1, v/v) to yield 180 mg (65%) of the amide **27**: $[\alpha]^{23}_D = 17.4°$ (c = 0.93, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.08 (ddd, J_1 = 4.6 Hz, J_2 = 6.5 Hz, J_3 = 8.5 Hz, 1 H, 2-H_a), 3.6 (dddd, J_1 = 3.4 Hz, J_2 = 3.6 Hz, J_3 = 3.9 Hz, J_4 = 7.4 Hz, 1 H, 6-H), 2.58 (ddd, J_1 = 3.1 Hz, J_2 = 9.1 Hz, J_3 = 13.0 Hz, 1 H, 2-H_b), 2.3 (m, 2 H, 3-H), 2.2 (m, 2-H), 1.8 (m, 1 H), 1.6 (m, 1 H), 1.5 (m, 2 H), 1.3–1.1 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 174.3 (C=O), 57.2 (C-6), 40.2 (C-2), 33.5 (CH_2), 30.2, 25.3, 24.4, 23.6 (CH_2). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.87; H, 9.63; N, 9.68.

(6*R*)-Indolizidine [(*R*)-δ-Coniceine, 28]. To a solution of 120 mg (2.5 mmol) of $LiAlH_4$ in 10 mL of ether was added a solution of 120 mg (0.86 mmol) of amide **27** in ether, and the mixture was heated at reflux overnight. The reaction mixture was poured onto 10 g of ice, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$ and evaporated to dryness in vacuo to yield 64.7 mg (61%) of (6*R*)-indolizidine **28**: $[\alpha]^{23}_D = -7.9°$ (c = 0.15, EtOH) [lit.[20] $[\alpha]^{23}_D = 10.2°$ (c = 1.76, EtOH)]; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 64.4 (C-6), 54.3 (C-2), 53.1 (C-9), 31.0 (CH_2), 29.7, 25.5, 24.6, 20.6 (CH_2).

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