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Divergent Synthetic Strategy Leading to Structurally Diverse Pyrrolidines and Piperidines from Common γ-Aminoalkyl Butenolide and Aldehyde Precursors†

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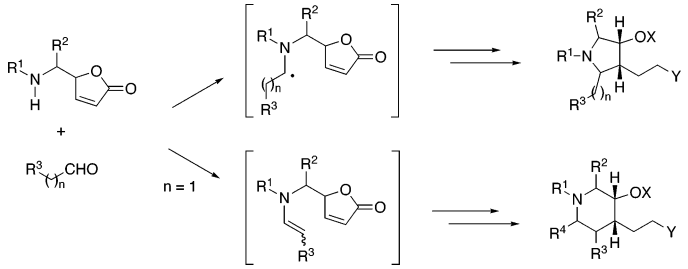


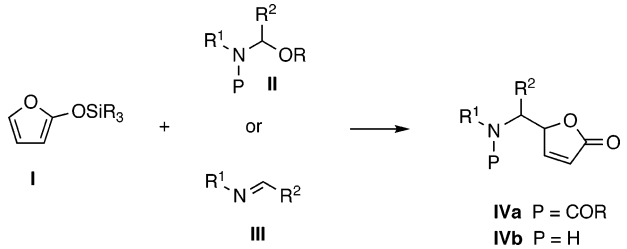
Condensation between aldehydes and the secondary amino function of 5-(aminoalkyl)furan-2(5*H*)-ones, obtained by the silyloxyfuran dienolate addition to imine-type derivatives, produces either aminoalkylbenzotriazoles or 1,2,3,4-tetrahydropyridines. The former can be reduced with SmI_2 to generate α-aminoalkyl radicals that are trapped by the α,*β*-unsaturated lactone moiety yielding substituted pyrrolidines diastereoselectively, while catalytic hydrogenation of the latter affords isomeric piperidine analogues. Alternatively, SmI_2-promoted reduction of tetrahydropyridines in the presence of acid also leads to intermediate α-aminoalkyl radicals that participate in inter- or intramolecular olefin addition reactions. Further manipulation of the lactone functionality in various ways gives access to a number of interesting derivatives based upon either a pyrrolidine or a piperidine structural motif. As a result, a high degree of structural diversity is obtained in a few steps starting from a common set of simple materials.

Introduction

The aminoalkyl-substituted furan-2(5*H*)-one substructure present in amines **IVa**,**b** (Scheme 1) has attracted particular attention not only for being present in natural products[1] but also for the synthetic applications of their derivatives, which have recently found extensive use in the synthesis of natural products.[2] As indicated in Scheme 1, compounds **IVa**,**b** are commonly accessible by Mannich-type reactions.

For synthetic applications, the formation of **IV** is often followed at some stage by manipulation of the α,*β*-unsaturated γ-lactone moiety, which may commonly undergo reduction,[1,2f,g] oxidation,[2a−e] or nucleophilic conjugate addition[2h] reactions. On the other hand, the corresponding conjugate radical additions[3] to **IV** or derivatives thereof are unprecedented. It was initially envisaged that the strategic combination of a vinylogous Mannich reaction and an intramolecular addition of α-aminoalkyl radicals[4] **VII**, derived from amines **IVb** and aldehydes **V** through the intermediacy of benzotriazoles **VI**,[5] would provide a conveniently rapid and practical access to pyrrolofuranone

SCHEME 1. Vinylogous Mannich Reaction of Silyloxyfurans I



† Dedicated to the memory of Professor Marcial Moreno-Mañas.

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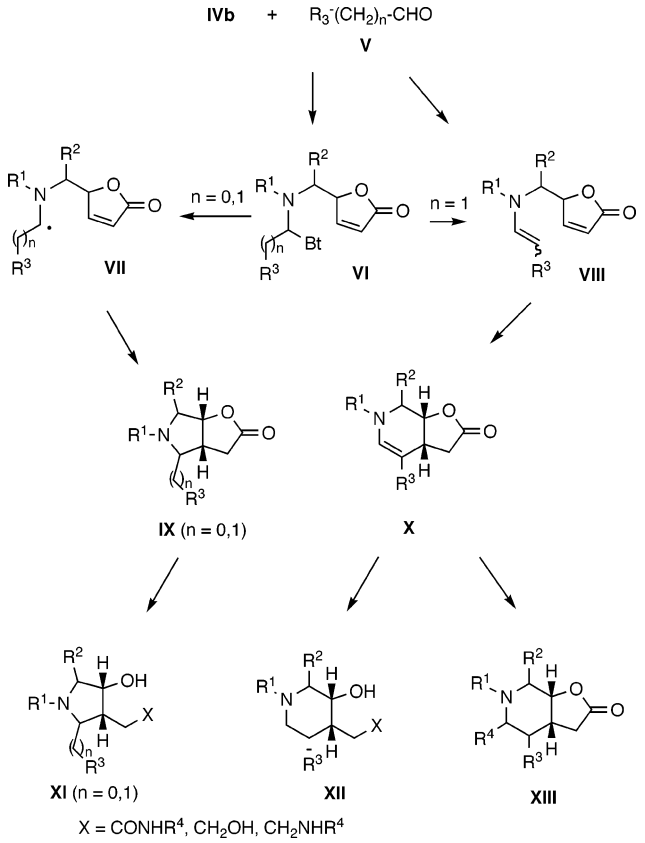
derivatives **IX** (Scheme 2).[6−9] Different combinations of readily incorporated substituents R^1, R^2, and R^3, along with various manipulations of the lactone functionality in bicycles **IX**, would then be expected to lead to structurally diverse 3-hydroxypyrrolidines **XI**, as suggested in Scheme 2. During the course of work directed to this end, it was found that, depending on reaction conditions, condensation between **IVb** and **V** could be directed either toward the formation of benzotriazole derivatives **VI** or toward cyclic enamines **X**,[10,11] and, therefore, the corresponding synthesis of piperidines **XII** and **XIII** became an additional goal of this work. Thus, similar to the preparation of **XI**, manipulation of the lactone moiety could be expected to provide 3-hydroxypiperidines **XII**, whereas the presence of an enamine-type double bond in **X** would provide an opportunity for the additional introduction of functionality at a piperidine α-position, leading to **XIII**. In this manner, a divergent strategy emerged that would give access to a range of structurally diverse pyrrolidines and piperidines **XI**−**XIII** in a few steps starting from common materials **IVb** and **V** (Scheme 2). Products **IX**−**XIII** are worthy synthetic targets. Thus, the basic skeleton of **IX** is present in natural products,[12] besides serving as a precursor of 3-azaprostaglandins, a type of 3-hydroxypyrrolidine with potential in the treatment of glaucoma.[13,14] The basic pyrrolidine-diol and -aminoalcohol substructures of **XI** (X = CH_2OH, CH_2-NHR^4) are found in natural products with a wide range of biological activities,[15] while many other 3-hydroxy-pyrrolidines and -piperidines are also found as structural components of compounds with interesting biological profiles.[16] This paper describes our results in this area.

SCHEME 2. Divergent Strategy for the Preparation of 3-Hydroxypyrrolidines and 3-Hydroxypiperidines from Amines IV and Aldehydes V



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(4) For a review, see: Aurrecoechea, J. M.; Suero, R. *ARKIVOC* **2004**, 10−35.

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(10) For a preliminary communication of parts of this work see: Aurrecoechea, J. M.; Suero, R. *Tetrahedron Lett.* **2005**, *46*, 4945−4947.

(11) For an application in alkaloid synthesis, see: Aurrecoechea, J. M.; Gorgojo, J. M.; Saornil, C. *J. Org. Chem.* **2005**, *70*, 9640−9643.

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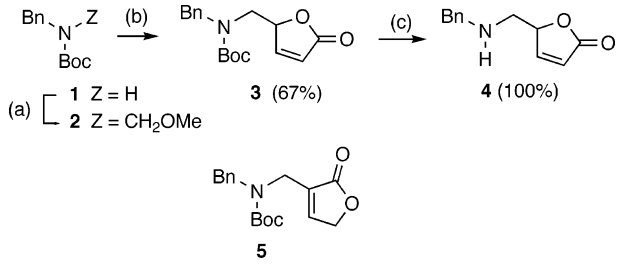
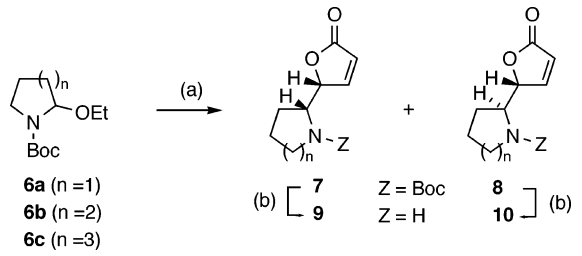
SCHEME 3. Preparation of 5-Aminomethylbutenolide 4[a]



[a] Reagents and conditions: (a) *n*-BuLi, MOMCI, THF, −78 °C → rt. (b) TMSOF, TMSOTf, CH_2Cl_2, −78 °C. (c) TFA, CH_2Cl_2, 0 °C → rt.

SCHEME 4. Preparation of Cyclic Amines 9 and 10[a]



[a] Reagents and conditions: (a) *t*-Butyldimethylsilyloxyfuran (TBSOF), TMSOTf, CH_2Cl_2, −80 °C. (b) TMSOTf, CH_2Cl_2, −25 → −5 °C (for **9a**) or TFA, CH_2Cl_2, 0 °C → rt (for **9b**,**c**, and **10b**).

Results and Discussion

(A) Radical Cyclizations. Amines of general structure **IVb** were prepared using the vinylogous Mannich reaction[2] between silyloxyfurans of type **I** and Boc-protected α-alkoxyamines **II** (P = Boc), followed by hydrolysis of the N-protecting group (Schemes 1, 3, and 4). Thus, coupling between **2** and trimethylsilyloxyfuran (TMSOF) was carried out using trimethylsilyltriflate (TMSOTf) as a promoter resulting in the formation of the corresponding 5-(aminomethyl)furan-2(*5H*)-one, **3**, that was isolated in good yields (Scheme 3). Formation of a regioisomer **5** was also observed in this reaction as a result of competitive α-alkylation.[17] Deprotection under acidic conditions afforded the free amine **4** in quantitative yield from **3**. A more direct preparation of amine **4** has been reported starting from TMSOF and a triazine derivative acting as a synthetic equivalent of benzylmethyleneamine.[18] However, the alternative indirect route depicted in Scheme 3 was preferred because it allowed us to conveniently store multigram quantities of the more stable *N*-Boc protected derivative **3** and deprotection afforded an essentially pure crude free amine **4** that could be used without purification.

Cyclic protected amines **7** and **8** were similarly obtained following a literature procedure[17a] (Scheme 4).[19] A high diastereoselectivity favoring isomer **7** was observed, which is in line with previous reports.[17a] Thus, five- and seven-membered protected amines **7a** and **7c**, respectively, were isolated as single diastereoisomers after column chromatography, whereas a 5:1 (**7b**/**8b**) diastereomeric ratio was obtained in the case of the six-membered analogue. Acidic removal of the Boc-protecting group afforded the free amines **9** and **10**, which needed to be handled with care. Thus, they have a tendency to epimerize,[20] particularly in the absence of solvent, and this is also accompanied by gradual decomposition.[21] Nevertheless, we have been able to isolate pyrrolidine **9a** in 84% yield and characterize it as the partially epimerized material. On the other hand, amines **9b**,**c** and **10b** were best manipulated as a partially evaporated CH_2Cl_2 solution obtained after workup of the mixture derived from the deprotection step. As a consequence, yields for subsequent reactions are always referred to Boc-protected amines **7b**,**c** and **8b** as the starting point. Stereochemical assignments for amines **7**−**10** relied on crystallographic data previously reported for the Boc-derivatives **7a**−**c**[17a] and were further supported by independent spectroscopic studies performed on their derived cyclization products described herein (vide infra and Supporting Information).

The SmI_2-mediated one-electron reduction of condensation adducts derived from aldehydes, secondary amines, and benzotriazole[4] has become a practical method for generation of α-aminoalkyl radicals capable of radical cyclization, as shown by the corresponding reports on the preparation of cyclopentylamines,[22a] pyrrolidines,[22b−e] and piperidines.[22f] At the outset, the possibility of applying this methodology using amines **4**, **9**, or **10** raised some concerns. For example, in the α-aminoalkyl radicals **VII**, the delocalization of the single electron into the nitrogen lone pair would give some π character to the C−N bond,[23] and its cyclization into the bicyclic or tricyclic arrangement (with formation of an endocyclic C−N bond) could be hindered as a result of strain development. Another point of concern was stereocontrol in the formation of pyrrolidines of type **IX**. While the relative configuration at C-3 and C-4 (5-hexenyl radical numbering) is already set during preparation of the amines (vide supra) and a cis-fusion between the pyrrolidine and lactone rings is readily expected based on thermodynamic considerations, control of the 1,5-relative stereochemistry would be defined in the radical cyclization step. Related α-aminoalkyl radical cyclizations have been shown to give preferentially 1,5-syn relationships in agreement with the Beckwith−Houk model;[24] however, in the present case, this would lead to apparently severely congested polysubstituted all-syn bicyclic or tricyclic systems.

The possibility of preparing bicyclic and tricyclic systems of type **13** was explored first. In that event, treatment of **4**, **9**,

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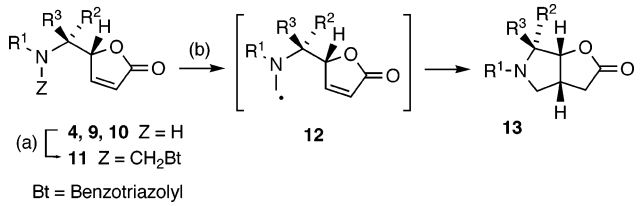
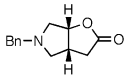
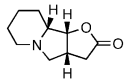
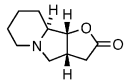
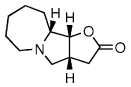
SCHEME 5. Preparation of Pyrrolofuranones 13 from 4, 9, or 10 and a Formaldehyde Equivalent[a]



[a] Reagents and conditions: (a) *N*-Hydroxymethylbenzotriazole, 4 Å MS, CH_2Cl_2, rt. (b) SmI_2, *t*-BuOH, THF, −78 °C → rt.

TABLE 1. Preparation of Bicyclic Pyrrolidines 13

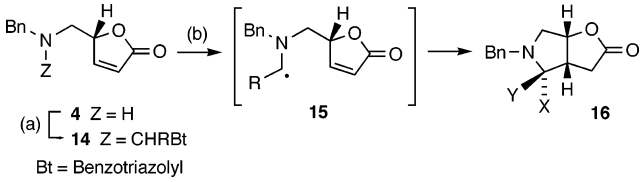
Amine	Product 13 (Yield)[a]	
4		**13a** (67)
9a	[b]	
9b		**13c** (61)[c]
10b		**13d** (65)[c]
9c		**13e** (54)

[a] Isolated yield (%) of pure products for three steps starting from **3**, **7**, or **8**. [b] The corresponding product (**13b**) was formed, as determined by ^{1}H NMR, but could not be conveniently isolated and purified. [c] Yield was corrected for epimerization.

or **10** with commercial *N*-hydroxymethylbenzotriazole (a surrogate for benzotriazole and formaldehyde) afforded the corresponding condensation adducts **11**, which were directly treated with excess SmI_2/*t*-BuOH to afford pyrrolidine lactones **13** (Scheme 5 and Table 1) in good overall yields, which are given for three steps starting from *N*-Boc derivatives **3**, **7**, or **8**.

Therefore, starting from a furanone dienolate of type **I**, the combination of a vinylogous Mannich reaction and SmI_2-promoted intramolecular conjugate aminomethylation gives ready access to fused bicyclic or tricyclic systems with remarkable ease. As expected, only cis-fused lactones were obtained, and this was confirmed by the observation of strong NOEs between the lactone bridgehead protons. The same technique served to confirm the relative configuration of the stereogenic center adjacent to nitrogen in tricyclic **13c**−**e** (see Supporting Information). The reaction of piperidine **9b** afforded, besides **13c**, small amounts of a minor product that was identified as epimer **13d** on the basis of spectroscopic data. Product **13d** arises from epimerization of the starting amine **9b**, the extent of which was estimated to be about 10% from the ^{1}H NMR spectrum of the crude cyclization mixture. The identity of **13d** was further confirmed by starting the condensation/cyclization sequence from epimeric amine **10b**. In this manner, **13d** was obtained (49%) along with **13c** (16%), confirming the facile epimerization of these amines, as previously noted in the literature.[20] That epimerization was taking place before cyclization was corroborated by inspection of the corresponding ^{1}H NMR spectra of the crude benzotriazole adducts that already showed signals associated to the other epimer.

SCHEME 6. Preparation of Pyrrolofuranones 16 from Amine 4 and Aldehydes[a]



[a] Reagents and conditions: (a) RCHO, Bt-H, 4 Å MS, CH_2Cl_2, rt. (b) SmI_2, *t*-BuOH, THF, −78 °C → rt.

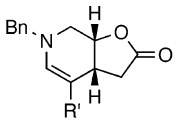
TABLE 2. Preparation of Pyrrolofuranones 16 from Amine 4 and Aldehydes

		major diastereoisomer		
	16	X	Y	yield (dr)[a]
1	**16a**	*n*-Pr	H	71 (94:6)[b]
2	**16b**	$(CH_2)_2Ar$[c]	H	47[d]
3[e]	**16b**	$(CH_2)_2Ar$[c]	H	84 (91:9)
4	**16c**	$(CH_2)_4CO_2Me$	H	66 (94:6)[f,g]
5	**16d**	*i*-Pr	H	84 (83:17)
6	**16e**	H	Ph	44 (61:39)[g]

[a] Yield (%) of isolated purified products. Unless otherwise indicated, diastereoisomer ratios were measured in the crude products. [b] Tetrahydropyridine **17a** was isolated in 6% yield. [c] Ar = 3,4-dimethoxyphenyl. [d] Tetrahydropyridine **17b** was isolated in 9% yield. [e] Benzene was used as the solvent in the formation of adduct **14**. [f] Tetrahydropyridine **17c** was isolated in 6% yield. [g] Isomer ratio determined from the isolated purified products.

The same cyclization conditions were applied successfully to benzotriazole adducts derived from aldehydes other than formaldehyde. Thus, starting from amine **4**, the corresponding pyrrolofuranones **16** were obtained in a process which, overall, represented the intramolecular aminoalkylation of an α,β-unsaturated lactone (Scheme 6, Table 2). The reaction proceeded with both good yields and good stereoselectivities for aliphatic aldehydes, while benzaldehyde gave poorer results (entry 6).

The use of aldehydes containing an unsubstituted methylene unit α to the carbonyl group (entries 1−4), in addition to the expected pyrrolidines **16**, led to the isolation of small amounts (6−9%) of tetrahydropyridines **17**. These six-membered side

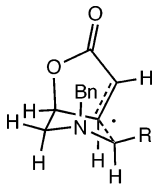


17a-c (R' = Et, CH_2Ar, $(CH_2)_3CO_2Me$)

products originated during formation of benzotriazole adducts **14**, as shown by the presence of the characteristic enamine proton resonance at $\delta \sim 6.0$ in the ^{1}H NMR spectrum of crude adducts **14**. The generation of enamines **17** from amine **4** and aldehydes was found to be dependent on the solvent used in the condensation step leading to **14**. Thus, CH_2Cl_2 as solvent promoted their formation, whereas benzene largely suppressed it, as shown by comparison between entry 2 and entry 3 (Table 2). Incidentally, the improved isolated yield of **16b** in entry 3 is mainly due to a notably simplified chromatographic purification in the absence of **17b**. Details on the independent formation of **17** from **4** and aldehydes will be discussed later on in this paper (vide infra).

Pyrrolofuranones **16a**−**d** derived from aliphatic aldehydes formed with good levels of stereoselectivity (Table 2). Improved

control of the 1,5-relative stereochemistry (5-hexenyl radical numbering) was observed in these reactions when compared to related cyclizations starting either from the all-carbon substituted hex-5-enyl radical[25] or from the simple acyclic 2-azahex-5-enyl radicals[22b] analogously activated with EWG on the alkene moiety. The radical ring closure produced only two pyrrolidine products that were diastereomeric at the newly created stereogenic center adjacent to N; in addition, a cis-ring fusion was observed in all cases, as expected. The major diastereoisomers of products **16a**−**d** derived from aliphatic aldehydes (X = alkyl) presented in these cases an all-syn relationship between the pyrrolidine methine hydrogens. Therefore, this reaction succeeds in producing a rather congested stereoisomer in an overall preparatively useful yield, and this stereochemical outcome can be rationalized within the framework of the Beckwith−Houk model for radical cyclizations.[24] According to this model, the major product derived from radical **15** in a kinetically controlled cyclization would form through a chairlike transition state of type **18** where the R substituent occupies a pseudo-equatorial

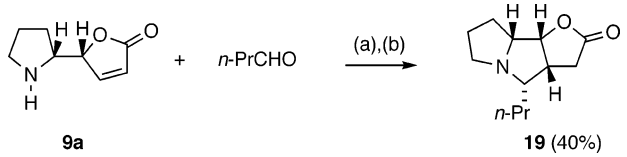


18

position. As noticed previously,[22e] for a 2-azahex-5-enyl radical, this arrangement would be expected to place the N-substituent in a pseudo-axial position in order to allow for some interaction between the unpaired electron and the N lone pair during cyclization. Therefore, further steric congestion would be expected involving the N-Bn unit, making the observed stereochemistry all the more remarkable. In apparent support of the model, radicals **15** derived from aldehydes with linear aliphatic chains gave the highest stereoselectivities (up to ∼16:1, entries 1−4), whereas α-branching resulted in a somewhat reduced diastereoisomer ratio (entry 5), and this effect was more noticeable for R = Ph (entry 6), derived from an aromatic aldehyde, which produced a major isomer with a 1,5-anti relationship (5-hexenyl radical numbering). However, it is not clear whether in this latter case the stereochemical preference results from kinetic control or is, rather, the consequence of the reversible cyclization of a particularly stable benzylic α-aminoalkyl radical.[26−28]

The similar radical cyclizations starting from cyclic amine substrates **9** were much less successful. Thus, starting from pyrrolidine **9a** and butyraldehyde, application of the above sequence afforded the corresponding cyclized tricyclic product **19** as a single diastereoisomer containing four contiguous stereocenters, albeit in only moderate chemical yield (Scheme 7). This stereochemical assignment is in line with the results reported above and was supported by NOE studies (see Supporting Information).

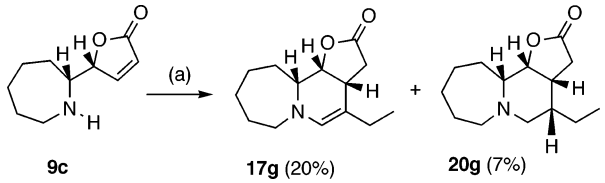
SCHEME 7. Preparation of a Tricyclic Pyrrolidine with Four Contiguous Stereocenters[a]



9a **19** (40%)

[a] Reagents and conditions: (a) Bt-H, 4 Å MS, CH_2Cl_2, rt. (b) SmI_2, *t*-BuOH, THF, −78 °C → rt.

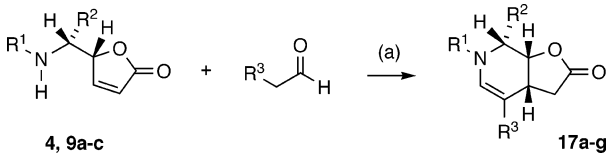
SCHEME 8. Reaction of Amine 9c with Butyraldehyde[a]



9c **17g** (20%) **20g** (7%)

[a] Reagents and conditions: (a) *n*-PrCHO, Bt-H, 4 Å MS, CH_2Cl_2, rt. (b) SmI_2, *t*-BuOH, THF, −78° → rt.

SCHEME 9. Preparation of Tetrahydropyridines 17 from Amines 4 or 9 and Aldehydes[a]



4, 9a-c **17a-g**

[a] Reagents and conditions: 4 Å MS, CH_2Cl_2, rt.

In contrast, only a complex mixture of products was obtained when butyraldehyde was used in combination with piperidine **9b**, and the similar use of azepane **9c** (Scheme 8) afforded a mixture of tetrahydropyridine **17g** and its reduction product **20g** in low yields instead of the expected pyrrolidine product. While tetrahydropyridine **17g** was a reasonable product given the above precedents, the formation of **20g** was intriguing, and this reaction was investigated further. The corresponding results will be discussed below in the context of the preparation and applications of tetrahydropyridine derivatives.

To summarize this part of the work, the intramolecular aminoalkylation of γ-butenolides can be effected through the intermediacy of α-aminoalkyl radicals derived from amines **IVb** and aldehydes **V**, and this provides a viable strategy to prepare pyrrolofuranones of general structure **IX** with very good control of the relative stereochemistry of up to four contiguous stereogenic centers. In terms of scope, the use of aldehydes RCHO where R ≠ H appears to be restricted to amines **IVb** unsubstituted at C-2 (R^2 = H), whereas the use of formaldehyde is of a more general application.

(B) Formation of Cyclic Enamines. Tetrahydropyridines **17** (Scheme 9) are interesting compounds containing a basic bicyclic enamine substructure that can be found in naturally occurring alkaloids of the Corynanthe type.[29] Results discussed above indicated formation of **17** to be a facile process already

(25) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418−7429.

(26) The trans-selectivity observed in cyclizations of benzylic radicals has usually been explained by postulating a reversible cyclization[22b,27] so that the product ratios would be a reflection of their thermodynamic stabilities. However, this explanation has been challenged, and some experimental evidence for a kinetic origin of the product distribution, based on dilution studies, has been alternatively offered.[28]

(27) (a) Walling, C.; Cioffari, A. *J. Am. Chem. Soc.* **1972**, *94*, 6064−6069. (b) Taber, D. F.; Wang, Y.; Pahutski, T. F. J. *J. Org. Chem.* **2000**, *65*, 3861−3863.

(28) Miranda, L. D.; Zard, S. Z. *Chem. Commun.* **2001**, 1068−1069.

(29) (a) Takayama, H.; Kurihara, M.; Kitajima, M.; Said, I. M.; Aimi, N. *J. Org. Chem.* **1999**, *64*, 1772−1773. (b) Takayama, H.; Kurihara, M.; Kitajima, M.; Said, I. M.; Aimi, N. *Tetrahedron* **2000**, *56*, 3145−3151.

TABLE 3. Preparation of Tetrahydropyridines 17 from Amines 4 or 9 and Aldehydes

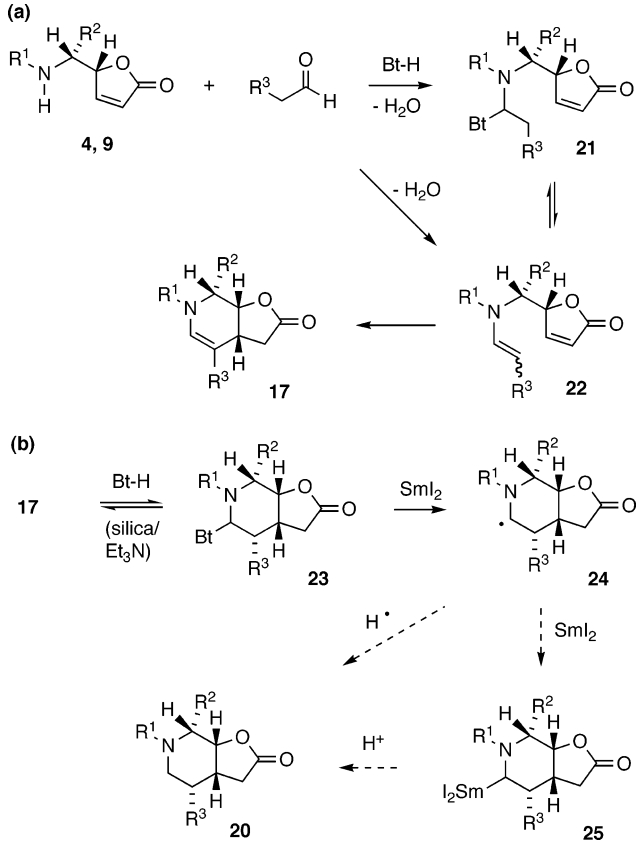
4, **9**	R^1	R^2	R^3	**17** (yield)[a]
4	Bn	H	Et	**17a** (73)
4	Bn	H	CH_2Ar[b]	**17b** (100)[c]
4	Bn	H	$(CH_2)_3CO_2Me$	**17c** (78)
4	Bn	H	$(CH_2)_2CH{=}CHY$[d]	**17d** (81)[e]
9a	$(CH_2)_3$		Et	**17e** (42)
9b	$(CH_2)_4$		Et	**17f** (42)[f,g]
9c	$(CH_2)_5$		Et	**17g** (68)[e,f]

[a] Percent yield (%) of isolated, purified product. [b] Ar = 3, 4-dimethoxyphenyl. [c] Yield of crude product. [d] (*E*)-Isomer. Y = CO_2Et. [e] Prepared under refluxing conditions. [f] Two-step yield starting from *N*-Boc derivatives **7b** or **7c**. [g] Corrected for epimerization.

at room temperature. Furthermore, subsequent manipulation of the functionality present in **17** would allow the rapid synthesis of structurally diversified polysubstituted piperidine derivatives from readily available amine and aldehyde building blocks. Therefore, the condensation between amines **4** or **9** and α-unsubstituted aldehydes was studied as a new entry into the synthesis of hydroxypiperidine derivatives under very mild reaction conditions.[10] Related direct condensations leading to 1,2,3,4-tetrahydropyridine formation via spirocyclization have been described starting from 3-(aminoethyl)cyclohex-2-enones and arylacetaldehydes under harsh conditions;[30] more recently, we have reported an application to alkaloid synthesis using a simpler acyclic amine under refluxing conditions.[11] In the present case, it was found that by using amines **4** or **9** and representative aldehydes, tetrahydropyridines **17** were produced in good yields as single stereoisomers under milder reaction conditions (Scheme 9, Table 3). As expected, cis-fused lactones were formed in all cases. These compounds were somewhat unstable to chromatographic conditions, and some mass loss was observed. Thus, the low yield of enamine **17e** appears to be associated to its chromatographic instability, as suggested by the substantially improved yield of its derived piperidine obtained by catalytic hydrogenation of the crude enamine product (vide infra). The preparation of enamine **17f**, on the other hand, was complicated by partial epimerization (about 10%) of the starting amine **9b** (vide supra), and the corresponding epimeric tetrahydropyridine product had to be separated by column chromatography, similarly resulting in a diminished yield.

The ease of formation of enamines **17** is remarkable. Presumably, acyclic enamines **22** are involved (Scheme 10a), and these are accessed from the aldehyde and secondary amine starting materials either directly, as in Scheme 9, or, alternatively, by partial elimination[31] of adducts **21** when condensations are carried out in the presence of benzotriazole (Scheme 10a). Ring closure of **22** to cyclic enamine **17** has precedent in the intramolecular enamine endocyclic addition to an α,β-unsaturated carbonyl derivative found in a key step of the synthesis of karachine from berberine[32] and in some related reactions starting from activated enaminone-type substrates.[33] In any case, to check the possibility

SCHEME 10. Mechanistic Proposals for Formation and SmI_2-Promoted Reduction of 17



of formation of **17** via intermolecular enamine conjugate addition, we treated amine **4** with the enamine derived from butanal and piperidine.[34] After 16 h at room temperature, only trace amounts of **17a** had formed, if at all, in a very complex reaction mixture, probably indicating that formation of the key C−C bond of **17** takes place intramolecularly. This conclusion appears to be further supported by the efficient formation of **17d** (Table 3) from an aldehyde containing an α,β-unsaturated carbonyl unit, a functionality that would have been expected to interfere had the conjugate addition step taken place intermolecularly.

As mentioned above, the formation of **17g** from azepane **9c**, butyraldehyde, and benzotriazole was examined in more detail. Thus, the ^1H NMR spectrum of the crude condensation product revealed the presence of free benzotriazole together with some tetrahydropyridine **17g** and a product tentatively assigned the structure **23g** [R^1 and $R^2 = (CH_2)_5$; R^3 = Et in Scheme 10b]. Attempted separation of the mixture by flash chromatography afforded only **17g** in overall yields that ranged from 64 to 84% depending on the particular run. The identity of the benzotriazole derivative **23g** was established after mixing **17g** with benzotriazole in $CDCl_3$ at room temperature, whereupon formation of a **17g**/**23g** mixture was immediately observed by ^1H NMR, in an approximately 1:1 ratio that did not change over time. This behavior appears to be general,[35a] as treatment of tetrahydropyridine **17a** with benzotriazole also led to the formation of a similar mixture where diastereomeric adducts **23a** (R^1 = Bn; R^2 = H; R^3 = Et in Scheme 10b) presented characteristic sets of resonances at δ 8.08−8.14 and δ 5.28−5.74 corresponding

(30) Grewe, R.; Arpe, H. J.; Petersen, E. *Liebigs Ann. Chem.* **1962**, *653*, 97−104.

(31) The preparation of enamines from simple α-(dialkylamino)alkylbenzotriazoles upon treatment with NaH has been reported: (a) Katritzky, A. R.; Long, Q. H.; Lue, P.; Jozwiak, A. *Tetrahedron* **1990**, *46*, 8153−8160. (b) Katritzky, A. R.; Long, Q. H.; Lue, P. *Tetrahedron Lett.* **1991**, *32*, 3597−3600.

(32) Stevens, R. V.; Pruitt, J. R. *J. Chem. Soc., Chem. Commun.* **1983**, 1425.

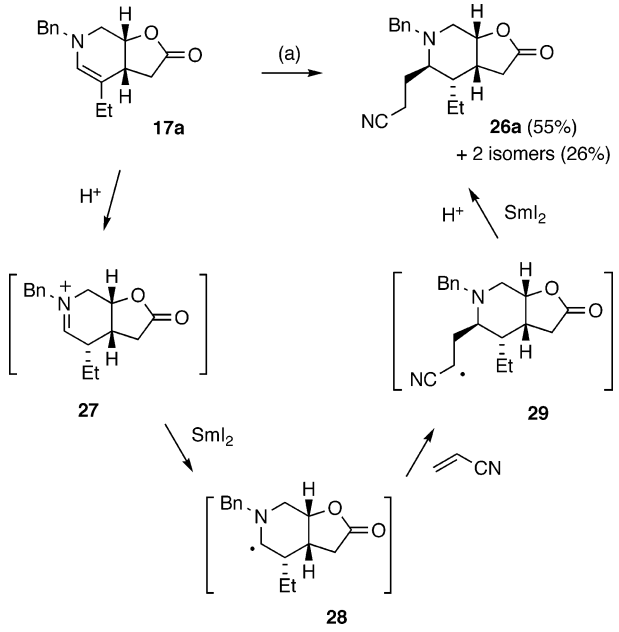
(33) Kucklaender, U.; Ulmer, P.; Zerta, G. *Chem. Ber.* **1989**, *122*, 1493−1498.

(34) Norman, M. H.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 3370−3371.

to benzotriazole ring and aminal-type protons, respectively.[35b] An additional interesting observation was made when a presumably similar mixture of **17g** and **23g**, obtained from **17g** and benzotriazole in THF, was treated with SmI_2/*t*-BuOH. A slow reaction took place that eventually led, after 14 days, to the isolation of piperidine **20g** [R^1 and $R^2 = (CH_2)_5$; $R^3 = Et$ in Scheme 10b; see also Scheme 8] in a 46% yield. The formation of **20g** implies the intermediacy of an α-aminoalkyl radical **24**,[4,22] which is further reduced to the organosamarium **25** or, alternatively, abstracts a H atom from the solvent (Scheme 10b). This outcome was somewhat surprising since, in the absence of efficient radical traps (e.g., electron-deficient alkenes), **24** would instead be expected to dimerize to afford a vicinal diamine.[36] It is likely that steric congestion around the radical center slows down dimerization so that other processes (e.g., H abstraction or reduction) become competitive. While this reaction does not have preparative value, it opens, nevertheless, the very interesting possibility of further building up of molecular complexity by combining condensations between amines of type **4** or **9** and aldehydes with radical chemistry at the piperidine 2-position through α-aminoalkyl radicals derived from cyclic enamines **17**. The application of these ideas will be demonstrated in the section that follows.

(C) Derivatization of Cyclization Products. The possibility of generating synthetically useful α-aminoalkyl radicals from enamines **17** was explored with ethyl derivative **17a**. Thus, treatment of **17a** with excess benzotriazole and SmI_2, at room temperature, in the presence of acrylonitrile, afforded coupling product **26a**, accompanied by two other diastereoisomers, in good overall yield (81%; Scheme 11). The relative configuration of the major diastereoisomer **26a** was assigned on the basis of spectroscopic studies (see Supporting Information) and is seen to follow the trend observed in the formation of piperidine **20g** (Scheme 8), with enamine protonation taking place from the less hindered side of the double bond. The resulting stereogenic center then directs the subsequent radical−alkene coupling so that the new C−C bond is preferentially formed anti to the Et substituent. The formation of **26** is readily interpreted in terms of formation of an iminium ion **27** (in equilibrium with a benzotriazole adduct **23a**; see Scheme 10)[35b] upon enamine protonation, followed by one-electron transfer, trapping of the resulting nucleophilic α-aminoalkyl radical **28** with the electron-deficient olefin, further reduction to an enolate-type intermediate, and protonation. Lowering the temperature with benzotriazole as the protonating agent resulted in sluggish reactions. On the other hand, the coupling reaction could alternatively be performed at lower temperatures using TFA to first generate cation **27**, followed by treatment with SmI_2, acrylonitrile, and *t*-butanol from −78 °C to room temperature. Formation of coupling product **26** under these conditions confirmed the proposed reaction pathway, and, furthermore, a better stereoselectivity (∼87:13 dr) was observed. However, about 50% of the starting enamine was recovered in this case. It is likely that intermediate α-aminoalkyl radical **28** partially undergoes *β*-H elimination[37] to regenerate enamine **17a**. Apparently, in the presence of an excess of a protonating agent (e.g., benzotriazole), effective recycling of enamine **17a** back to iminium ion **27** takes place, eventually resulting in complete reactions. The use of excess TFA also led to complete consumption of the starting material; however, the isolated yields of **26** never exceeded 50%, and reactions were noticeably less clean. In any case, the overall reaction is unusual in that it achieves the stereoselective coupling of an electron-deficient alkene to the enamine α-position by performing a double polarity inversion, first by conversion of a nucleophilic enamine into an electron-deficient iminium ion and then by reduction of this to a nucleophilic α-aminoalkyl radical. This also appears to represent the first example of the use of an enamine as a starting material to perform an α-aminoradical C−C coupling.[38,39]

SCHEME 11. Intermolecular Radical Functionalization of Enamine 17a[a]



[a] Reagents and conditions: (a) SmI_2, benzotriazole, acrylonitrile, THF, rt.

A suitably modified tetrahydropyridine **17d** was used to exemplify the possibility of doing an analogous intramolecular coupling to an electron-deficient alkene (Scheme 12). As previously shown in Scheme 9 and Table 3, tetrahydropyridine **17d** was available in good yield by condensation between amine **4** and the functionalized aldehyde ethyl (*E*)-7-oxohept-2-enoate.[22a,40] Generation of an α-aminoalkyl radical **31** and cyclization were triggered by simultaneous treatment with

(35) (a) The addition of benzotriazole to enamines has been reported: Katritzky, A. R.; Jurczyk, S.; Rachwal, B.; Rachwal, S.; Shcherbakova, I.; Yannakopoulou, K. *Synthesis* **1992**, 1295−1298. (b) Katritzky, A. R.; Yannakapoulou, K.; Kuzmierkiewicz, W.; Aurrecoechea, J. M.; Palenik, G. J.; Koziol, A. E.; Szczesniak, M.; Skarjune, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2673−2679.

(36) Aurrecoechea, J. M.; Fernández-Acebes, A. *Tetrahedron Lett.* **1992**, *33*, 4763−4766.

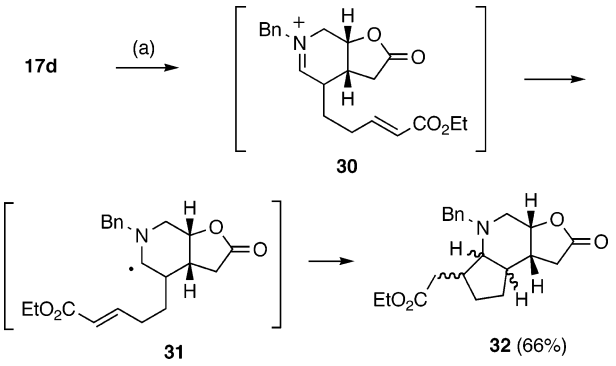
(37) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 84−91.

(38) The generation of α-aminoalkyl radicals from enamines by addition of electrophilic radicals has been reported: (a) Renaud, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 433−434. (b) Renaud, P.; Björup, P.; Carrupt, P. A.; Schenk, K.; Schubert, S. *Synlett* **1992**, 211−213. (c) Schubert, S.; Renaud, P.; Carrupt, P. A.; Schenk, K. *Helv. Chim. Acta* **1993**, *76*, 2473−2489.

(39) A related SmI_2-mediated intermolecular coupling with electron-deficient alkenes has been reported using nitrones as starting materials: (a) Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2265−2268. (b) Riber, D.; Skrydstrup, T. *Org. Lett.* **2003**, *5*, 229−231. (c) Masson, G.; Zeghida, W.; Cividino, P.; Py, S.; Vallee, Y. *Synlett* **2003**, 1527−1529. (d) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459−1462. (e) Cardona, F.; Goti, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7832−7835.

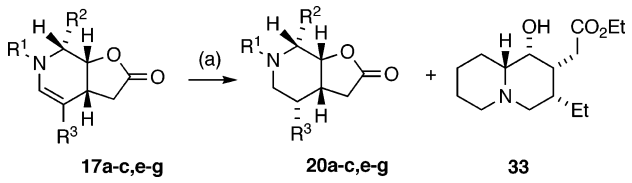
(40) Nishida, A.; Kawahara, N.; Nishida, M.; Yonemitsu, O. *Tetrahedron* **1996**, *52*, 9713−9734.

SCHEME 12. Intramolecular Radical Cyclization from an Enamine Precursor[a]



[a] Reagents and conditions: (a) SmI_2, benzotriazole, THF, rt.

SCHEME 13. Catalytic Hydrogenation of Enamines 17[a]



[a] Reagents and conditions: (a) H_2, 10% Pd/C, EtOH, rt.

TABLE 4. Preparation of Piperidines 20 from Enamines 17

17	R^1	R^2	R^3	20	yield[a] (dr)
17a	Bn	H	Et	**20a**	77[b] (90:10)
17b	Bn	H	CH_2Ar[c]	**20b**	75[b,d] (90:10)
17c	Bn	H	$(CH_2)_3Y$[e]	**20c**	95 (94:6)
17e	$(CH_2)_3$		Et	**20e**	62[b] (92:8)
17f	$(CH_2)_4$		Et	**20f**	88[f,g]
17g	$(CH_2)_5$		Et	**20g**	94 (99:1)

[a] Percent yield (%) of isolated, purified product. [b] Yield for two steps starting from amine **4** or **9a**, as appropriate. [c] Ar = 3,4-dimethoxyphenyl. [d] Yield of isolated major isomer alone. [e] Y = CO_2Me. [f] Hydrogenation conducted at 60 psi. Also isolated was ethyl ester **33** (3%). [g] A single isomer was isolated.

benzotriazole and SmI_2 at room temperature, as described above for the intermolecular coupling. This resulted in formation of the expected tricyclic product **32**, that was obtained in good yield (Scheme 12). Therefore, the partial goal of increasing structural complexity considerably, in just two steps, is readily achieved with this simple reaction sequence, but for synthetic applications, the very low observed diastereoselectivity will diminish the appeal of this novel procedure.

Cyclic products of general types **IX** and **X** (see Scheme 2), besides being variable at R^1, R^2, and R^3, contain functionality that offered different possibilities to introduce structural diversity around the pyrrolidine and tetrahydropyridine core. For example, tetrahydropyridines **17** turned out to be excellent substrates for the stereocontrolled preparation of substituted piperidines under catalytic hydrogenation conditions. Thus, in all cases, polysubstituted piperidines **20** were obtained in excellent yields (Scheme 13, Table 4). Some enamines (**17a**,**b**,**e**) were used in a crude form, and this proved advantageous as reflected by overall two-step yields of **20a**,**b**,**e** (Table 4) that were comparable or even higher than those of the purified enamines. In general, enamines **17** underwent efficient hydrogenation under a 1 atm hydrogen pressure. However, in the case of **17f**, the reaction was sluggish, and competitive lactone ring-opening of the hydrogenated major product, with formation of ester **33**, took place leading to poor results in terms of yields and stereoselectivity. Conducting the reaction at 60 psi largely avoided formation of **33** (3%), and **20f** was isolated in excellent yield as a single stereoisomer (Table 4).

The lactone moiety fused to either a pyrrolidine or a piperidine offered further opportunities for structural diversification (Scheme 14). For example, LAH reduction of **16a** and **20a** at 0 and −78 °C, respectively, led to the corresponding diols **34a**,**b**. Alternatively, performing the reduction of **16a** at −78 °C allowed the stereocontrolled preparation of lactol **35**, containing functionality that has participated in Wittig-type reactions leading to biologically active 2-azaprostaglandins from closely related analogues.[13,14] Lactol **35** can be alternatively elaborated into aminals **36** and then aminoalcohol **37** in high yields. Finally, lactone aminolysis under mild conditions[41] provided piperidine-based amides **38a** and **38b** in excellent yields (Scheme 14). A similar transformation was attempted starting from pyrrolidine **16a**; however, even after prolonged reaction times, conversions were only in the order of 50%, and upon attempted isolation, the presumed amide product reverted back to the starting lactone.

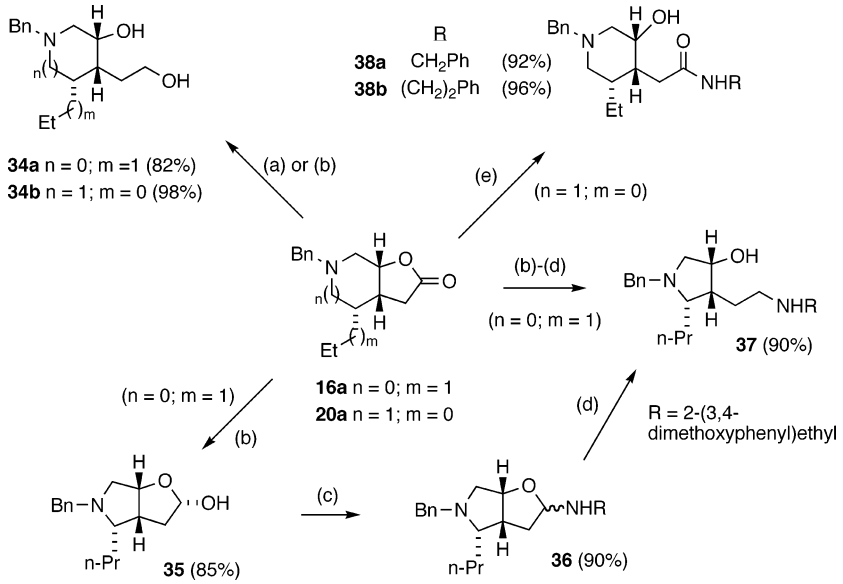
Conclusion. The strategic combination of a vinylogous Mannich reaction and either a radical- or an enamine-type ring closure provides expeditious entries into pyrrolidine- and piperidine-type structures, respectively, from a common set of simple amine and aldehyde building blocks. Structural diversity can be directly incorporated at three ring positions based on the choice of starting materials while subsequent manipulation of the lactone and enamine functionalities in the cyclization products introduces further diversification via either conventional procedures or novel radical-mediated enamine-alkene coupling. The compounds, thus obtained, are related to materials with interesting biological profiles.

Experimental Section

General Reductive Cyclization Procedures. In a typical experiment, a mixture of amine **4** or **9a** (1.00 mmol), the appropriate aldehyde (1.00 mmol), benzotriazole (0.119 g, 1.00 mmol), and 4 Å molecular sieves (0.50 g) in CH_2Cl_2 (or THF or benzene, as indicated; 12 mL) was stirred at rt for 14 h. Alternatively, *N*-(hydroxymethyl)benzotriazole (0.149 g, 1.00 mmol) was used as a substitute for formaldehyde and benzotriazole. In any case, the resulting suspension was filtered over Celite, the solid residue was washed with CH_2Cl_2 (2 × 10 mL), and the solution was evaporated to dryness to yield the crude adduct **11** or **14**. Without further manipulation the adduct was dissolved with *t*-BuOH (0.19 mL, 2.00 mmol) in THF (20 mL), and the resulting solution was added dropwise over 30 min to a solution of SmI_2 (ca. 0.1 M in THF, 31 mL, 3.08 mmol) at −78 °C. The mixture was stirred at −78 °C for an additional 30 min and allowed to warm to room temperature. After further stirring for 2 h, the reaction mixture was quenched with a 1:1 mixture of saturated K_2CO_3 solution and water (50 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were washed with brine (20 mL) and dried (Na_2SO_4). The residue after evaporation was purified by flash column chromatography in silica gel saturated with Et_3N to yield pyrrolidines **13**, **16**, and **19** as oils. For reactions that employed amines **9b**,**c** or **10b**, the following integrated procedure, starting from carbamates **7b**,**c**, or **8b**, was used: In a typical experiment, TFA (1.31 mL, 17.0 mmol) was

(41) Liu, W.; Xu, D. D.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2001**, *42*, 2439−2441.

SCHEME 14. Lactone Transformations in Cyclization Products[a]



[a] Reagents and conditions: (a) LAH, THF, 0 °C (for **34a**). (b) LAH, THF, −78 °C (for **34b** and **35**). (c) RNH_2, $NaBH_3CN$, $ZnCl_2$, MeOH, rt. (d) LAH, THF, 0 °C → rt. (e) RNH_2, sodium 2-ethylhexanoate, THF, rt.

added dropwise over a solution of protected amine **7b**,**c**, or **8b** (1.00 mmol) in CH_2Cl_2 (12 mL) at 0 °C. After stirring for 15 min, the reaction mixture was allowed to reach room temperature and stirred further 90 min. The solution was washed with saturated K_2CO_3 solution (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (5 mL), and dried ($MgSO_4$). The solvent was partially evaporated to an approximate volume of 12 mL, and the resulting solution of amine **9b**,**c**, or **8b** in CH_2Cl_2 was used according to the general reductive cyclization procedure described above. Structural information, yields, and diastereomeric ratios of all compounds prepared according to these procedures are collected in Schemes 5−7 and Tables 1 and 2. Purification and separation details, as well as characterization data, are provided in the Supporting Information.

General Procedures for Tetrahydropyridine Formation. In a typical experiment, a mixture of amine **4** or **9a** (1.00 mmol), the appropriate aldehyde (1.00 mmol), and 4 Å molecular sieves (2.00 g) in CH_2Cl_2 (12 mL) was stirred at room temperature for 14 h. The solid was filtered out and washed with CH_2Cl_2 (3 × 5 mL). The crude after solvent evaporation was elaborated, as indicated in the Supporting Information for the individual cases, to afford tetrahydropyridines **17**. For reactions that employed amines **9b** or **9c**, the following integrated procedure, starting from protected amines **7b** or **7c**, was used: In a typical experiment, TFA (1.31 mL, 17.0 mmol) was added dropwise over a solution of protected amine **7b** or **7c** (1.00 mmol) in CH_2Cl_2 (12 mL) at 0 °C. After stirring for 15 min, the reaction mixture was allowed to reach room temperature and stirred further for 90 min. The solution was washed with saturated K_2CO_3 solution (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried ($MgSO_4$). The solvent was partially evaporated to an approximate volume of 12 mL, and the resulting solution of amine **9b** or **9c** in CH_2Cl_2 was used according to the general procedure described above. Structural information and yields of all compounds prepared according to these procedures are collected in Scheme 9 and Table 3. Purification and separation details, as well as characterization data, are provided in the Supporting Information.

Procedure for Enamine−Alkene Intermolecular Reductive Coupling. Preparation of 8-Benzyl-7-(2-cyanoethyl)-6-ethyl-2-oxa-8-azabiciclo[3.4.0]nonan-3-one (26). SmI_2 (0.1 M in THF) was added dropwise to a solution of **17a** (0.083 g, 0.32 mmol), benzotriazole (0.114 g, 0.96 mmol), and acrylonitrile (42 μL, 0.64 mmol) in THF (1 mL) at room temperature at such a rate as to allow for the disappearance of the SmI_2 characteristic blue color before the next drop was added. The addition was continued until the blue color persisted (at that point approximately 8.8 mL, 2.8 equiv, had been consumed). The reaction mixture was poured over a saturated K_2CO_3 solution (15 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine (6 mL) and dried (Na_2SO_4). The residue after evaporation was purified by flash column chromatography (silica gel saturated with Et_3N, 50:48:2 hexanes/EtOAc/Et_3N) to yield **26** (81 mg, 81%) as a 17:68:15 diastereomeric mixture. The isomers were separated by HPLC (μ-Bondapak-NH_2, 10 μ, 19 mm ×15 cm; 65:35 hexanes/EtOAc; 10 mL/min). Data for the less polar isomer **26b**: t_R = 8 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H), 1.46−1.56 (m, 3H), 1.80−1.85 (m, 1H), 1.96−2.02 (m, 1H), 2.41−2.47 (m, 4H), 2.66 (td, J = 9.5, 4.0 Hz, 1H), 2.73 (dd, J = 17.5, 8.0 Hz, 1H), 2.80 (dd, J = 15.0, 4.0 Hz, 1H), 3.19 (dd, J = 15.0, 4.0 Hz, 1H), 3.54 (d, J = 13.6 Hz, 1H), 3.84 (d, J = 13.6 Hz, 1H), 4.50 (dt, 1H, J = 5.4, 3.9 Hz), 7.26−7.36 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 9.2 (CH_3), 13.5 (CH_2), 22.3 (CH_2), 25.9 (CH_2), 35.5 (CH_2), 35.9 (CH), 36.8 (CH), 49.0 (CH_2), 53.8 (CH_2), 59.4 (CH), 77.2 (CH), 119.9 (C), 127.4 (CH), 128.6 (CH), 138.4 (C), 176.6 (C); MS (EI) *m*/*z* (%) 312 (M), 259 (18), 258 (base), 91 (37); HRMS calcd for $C_{19}H_{24}N_2O_2$, 312.1838; found, 312.1830. Data for the major isomer **26a**: t_R = 9 min; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, J = 7.0 Hz, 3H), 1.07−1.26 (m, 1H), 1.62−1.71 (m, 2H, H-6, 1 CH−CH_3), 1.94−2.04 (m, 2H), 2.37−2.57 (m, 5H, 1 H-9, 2 H-4, CH_2−CN), 2.61−2.69 (m, 1H, H-7), 2.88−3.03 (m, 2H, H-5, 1 H-9), 3.57 (d, J = 13.5 Hz, 1H), 3.75 (d, J = 13.6 Hz, 1H), 4.57−4.66 (m, 1H, H-1), 7.23−7.36 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 11.6 (CH_3), 13.5 (CH_2), 23.3 (CH_2), 24.4 (CH_2), 28.8 (CH_2), 34.3 (CH), 38.3 (CH), 49.3 (CH_2), 55.6 (CH_2), 57.9 (CH), 76.7 (CH), 119.6 (C), 127.5 (CH), 128.3 (CH), 128.6 (CH), 137.8 (C), 176.4 (C); IR (neat) ν 2240 (CN), 1770 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 312 (M, 2), 259 (17), 258 (base), 91 (67); HRMS calcd for $C_{19}H_{24}N_2O_2$, 312.1838; found, 312.1834. Data for the more polar isomer (**26c**): t_R = 10 min; ^{1}H NMR (250 MHz, $CDCl_3$; from a 93:7 mixture with **26a**) δ 0.89 (t, J = 7.3 Hz, 3H), 0.95−1.17 (m, 1H), 1.69−1.80 (m, 4H), 2.04−2.30 (m, 2H), 2.39−2.53 (m, 2H), 2.71 (dd, J

= 17.2, 6.9 Hz, 1H), 2.81−2.94 (m, 2H), 3.21 (d, J = 15.9 Hz, 1H), 3.81 (d, J = 13.3 Hz, 1H), 4.02 (d, J = 13.1 Hz, 1H), 4.33 (br s, 1H), 7.26−7.31 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$; from a 1:1 mixture with **26a**) δ 11.0 (CH_3), 14.3 (CH_2), 20.6 (CH_2), 22.5 (CH_2), 33.0 (CH), 36.2 (CH_2), 36.7 (CH), 44.0 (CH_2), 54.2 (CH), 59.3 (CH_2), 77.8 (CH), 120.0 (C), 127.4 (CH), 128.4 (CH), 129.1 (CH), 139.1 (C), 176.6 (C); GC/MS t_R = 20.0 min, MS (EI) *m*/*z* (%) 312 (M), 258 (24), 126 (11), 106 (31), 105 (38), 91 (base), 77 (23); HRMS calcd for $C_{19}H_{24}N_2O_2$, 312.1838; found, 312.1852; t_R = 20.5 min, MS (EI) *m*/*z* (%) 312 (M), 258 (12), 106 (48), 105 (52), 91 (base), 77 (37); HRMS calcd for $C_{19}H_{24}N_2O_2$, 312.1838; found, 312.1852.

Procedure for Enamine−Alkene Intramolecular Reductive Coupling. Preparation of Ethyl (3a*R,8b*R**)-(5-Benzyl-2-oxo-decahydro-3-oxa-5-aza-*as*-indacen-6-yl)acetate (32).** SmI_2 (0.1 M in THF) was added dropwise to a solution of **17d** (0.100 g, 0.28 mmol) and benzotriazole (0.100 g, 0.84 mmol) in THF (5.6 mL) at room temperature at such a rate as to allow for the disappearance of the SmI_2 characteristic blue color before the next drop was added. The addition was continued until the blue color persisted (at that point approximately 9 mL, 3.2 equiv, had been consumed). The reaction mixture was poured over a saturated K_2CO_3 solution (20 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). The residue after evaporation was purified by flash column chromatography (silica gel saturated with Et_3N, 70:28:2 hexanes/EtOAc/Et_3N) and HPLC (μ-Bondapak-NH_2, 10 μ, 19 mm × 15 cm; 85:15 hexanes/EtOAc; 10 mL/min) to yield **32** (67 mg, 66%) as a 42:37:6 (two isomers):15 diastereomeric mixture. Further separation by HPLC provided samples of some of the individual isomers. Characterization data are given in order of elution. Data for **32a**: t_R = 12 min; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 1.38−1.45 (m, 1H), 1.67−1.72 (m, 2H), 1.93−2.27 (m, 5H), 2.30−2.41 (m, 1H), 2.64−2.89 (m, 4H), 3.11−3.20 (m, 2H), 3.97 (d, J = 13.9 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 4.68 (dd, J = 15.1, 8.2 Hz, 1H), 7.26−7.32 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2 (CH_3), 28.3 (CH_2), 28.9 (CH_2), 33.6 (CH_2), 33.8 (CH_2), 37.7 (CH), 38.0 (CH), 39.3 (CH), 51.5 (CH_2), 59.2 (CH_2), 60.4 (CH_2), 67.4 (CH), 78.0 (CH), 127.3 (CH), 128.5 (CH), 137.9 (C), 173.6 (C), 176.9 (C); IR (neat) ν 1770 (C═O), 1730 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 357 (M, 6), 242 (82), 91 (base), 71 (13), 57 (29), 55(16); HRMS calcd for $C_{21}H_{27}NO_4$, 357.1940; found, 357.1942. Data for isomer **32b** (from a 9:1 mixture with **32a**): t_R = 13 min; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 4H), 1.52−2.54 (m, 9H), 2.69−3.13 (m, 5H), 4.03−4.16 (m, 3H), 4.51−4.60 (m, 1H), 7.26−7.30 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2 (CH_3), 24.6 (CH_2), 27.3 (CH_2), 27.4 (CH_2), 34.6 (CH_2), 34.8 (CH), 36.8 (CH), 38.9 (CH), 53.7 (CH_2), 59.4 (CH_2), 60.4 (CH_2), 64.5 (CH), 77.5 (CH), 127.3 (CH), 128.4 (CH), 137.5 (C), 173.4 (C), 176.5 (C); IR (neat) ν 1780 (C═O), 1730 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 357 (M, 8), 243 (12), 242 (base), 91 (72); HRMS calcd for $C_{21}H_{27}NO_4$, 357.1940; found, 357.1931. Data for a 2:3 **32c/32d** mixture: t_R = 16 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, J = 7.3 Hz, 4H), [1.48−1.95 (m, 3H), 2.00−2.80 (m), 2.90−2.97 (m), 3.01 (dd, J = 13.3, 5.1 Hz) 3.08 (dd, J = 12.6, 6.3 Hz) (total 10H)], [3.19 (d, J = 12.5 Hz), 3.41 (d, J = 13.6 Hz) (total 1H)], [3.93 (d, J = 13.6 Hz), 4.03 (d, J = 12.4 Hz) (total 1H)], 4.10−4.16 (m, 2H), 4.52 (dd, J = 11.5, 6.0 Hz), 4.55−4.60 (m, 1H), 7.25−7.31 (m, 5H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 14.3 (CH_3), 25.7 (CH_2), 27.6 (CH_2), 29.1 (CH_2), 29.9 (CH_2), 34.5 (CH_2), 35.0 (CH), 36.6 (CH), 37.2 (CH), 37.4 (CH), 38.4 (CH), 40.2 (CH_2), 41.2 (CH_2), 43.5 (CH), 49.3 (CH_2), 54.1 (CH_2), 58.3 (CH_2), 58.9 (CH_2), 60.5 (CH_2), 66.9 (CH), 67.6 (CH), 76.3 (CH), 76.8 (CH), 127.2 (CH), 127.4 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 138.4 (C), 138.8 (C), 172.4 (C), 172.7 (C), 176.6 (C), 176.8 (C); GC/MS t_R = 19.7 min, MS (EI) *m*/*z* (%) 357 (M, 9), 243 (11), 242 (73), 91 (base); HRMS calcd for $C_{21}H_{27}NO_4$, 357.1940; found, 357.1945; t_R = 20.2 min, MS (EI) *m*/*z* (%) 357 (M, 9), 243 (12), 242 (77), 91 (base); HRMS calcd for $C_{21}H_{27}NO_4$, 357.1940; found, 357.1945. Data for **32e**: t_R = 25 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.1 Hz, overlapped with signals from another proton, total 4H), 1.64−1.90 (m. 2H), 2.02−2.11 (m, 1H), 2.21−2.29 (m, 3H), 2.45−2.73 (m, 4H), 2.75−2.78 (m, 2H), 2.95 (d, J = 13.8 Hz, 1H), 3.05 (d, J = 13.8 Hz, 1H), 4.06−4.14 (m, 3H), 4.47−4.49 (m, 1H), 7.20−7.31 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.2 (CH_3), 28.0 (CH_2), 30.5 (CH_2), 34.5 (CH), 34.5 (CH_2), 39.2 (CH), 40.2 (CH), 41.0 (CH_2), 52.9 (CH_2), 58.3 (CH_2), 60.4 (CH_2), 69.6 (CH), 78.2 (CH), 127.1 (CH), 128.2 (CH), 128.4 (CH), 138.6 (C), 172.4 (C), 177.6 (C); IR (neat) ν 1770 (C═O), 1730 (C═O) cm^{-1}; MS (EI) *m*/*z* (%) 357 (M, 5), 242 (71), 97 (12), 91 (base), 85 (272), 83 (12), 71 (18), 57 (30), 55 (19); HRMS calcd for $C_{21}H_{27}NO_4$, 357.1940; found, 357.1926.

General Hydrogenation Procedure. In a typical experiment, H_2 was bubbled through a suspension of **17** (2.00 mmol) and 10% Pd/C (0.028 g) in absolute ethanol (24 mL), and the mixture was stirred under a H_2 atmosphere (1 atm) at room temperature for 2−24 h. The catalyst was filtered off over Celite and the solid residue was washed with CH_2Cl_2 (3 × 10 mL). The crude after evaporation was purified by flash column chromatography to afford piperidines **20**. Structural information, yields, and diastereomeric ratios of all compounds prepared according to this procedure are collected in Scheme 13 and Table 4. Purification and separation details, as well as characterization data, are provided in the Supporting Information.

(3*R,4*R**,5*S**)-1-Benzyl-4-(2′-hydroxyethyl)-5-propylpyrrolidin-3-ol (34a).** A solution of **16a** (50 mg, 0.19 mmol) in THF (3.0 mL) was added dropwise to a stirred suspension of LAH (9 mg, 0.23 mmol) in THF (2.5 mL) at 0 °C. The reaction mixture was allowed to reach room temperature, stirred further for 14 h, and then quenched at 0 °C with 1 M NaOH (2 mL). After allowing the mixture to reach room temperature, CH_2Cl_2 (4 mL) and saturated sodium potassium tartrate (5 mL) were added. The resulting emulsion was vigorously stirred for 4 h, becoming a clear biphasic liquid. After separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic layers were dried (Na_2SO_4), and the residue after evaporation was purified by flash column chromatography (silica gel saturated with Et_3N, 18:80:2 hexanes/EtOAc/Et_3N) to yield **34a** (49 mg, 98%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, J = 7.3 Hz, 3H), 1.31−1.60 (m, 4H), 1.67−1.96 (m, 2H), 2.24−2.35 (m, 1H), 2.42 (dd, J = 10.5, 5.4 Hz, 1H), 2.57−2.65 (m, 2H), 2.84 (dd, J = 10.5, 2.2 Hz, overlapped with br signal, total 2H), 3.25 (d, J = 13.1 Hz, 1H), 3.64−3.81 (m, 2H), 4.06 (d, J = 13.0 Hz, 1H), 4.20 (td, J = 5.6, 2.2 Hz, 1H), 7.20−7.32 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.5 (CH_3), 20.5 (CH_2), 27.1 (CH_2), 32.7 (CH_2), 43.7 (CH), 58.9 (CH_2), 60.7 (CH_2), 61.7 (CH_2), 65.0 (CH), 71.5 (CH), 127.0 (CH), 128.3 (CH), 128.7 (CH), 138.8 (C); IR (neat) ν 3350 (O−H) cm^{-1}; MS (EI) *m*/*z* (%) 262 (M, 1), 221 (18), 220 (base), 202 (1), 174 (2), 160 (2), 155 (1), 91 (82); HRMS calcd for $C_{16}H_{25}NO_2$, 263.1885; found, 263.1884.

(1*R,3*S**,5*R**,6*S**)-7-Benzyl-3-hydroxy-2-oxa-6-propyl-7-azabicyclo[3.3.0]octane (35).** A suspension of LAH (36 mg, 0.95 mmol) in THF (1.0 mL) was added dropwise to a stirred solution of **16a** (50 mg, 0.19 mmol) in THF (4.0 mL) at −78 °C. Stirring was continued at the same temperature for 90 min, and the reaction mixture was quenched with 1 M NaOH (2 mL) and then allowed to reach room temperature. After diluting the mixture with CH_2Cl_2 (4 mL), saturated sodium potassium tartrate (6 mL) was added, and the resulting emulsion was vigorously stirred for 14 h, resulting in a clear biphasic liquid. After separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic layers were dried (Na_2SO_4), and the residue after evaporation was purified by flash column chromatography (silica gel saturated with Et_3N, 78:20:2 hexanes/EtOAc/Et_3N) to yield **35** (42 mg, 85%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (t, J = 7.3 Hz, 3H), 1.25−1.35 (m, 1H), 1.42−1.55 (m, 2H), 1.83−1.94 (m, 2H, 1 H-1′, 1 H-4), 1.97 (dd, J = 11.0, 4.8 Hz, 1H, H-8), 2.02 (d, J = 13.6 Hz, 1H, 1 H-4), 2.22 (ddd, J = 10.9, 6.8, 4.0 Hz, 1H, H-6), 2.86 (dt,

J = 10.0, 7.2 Hz, 1H, H-5), 2.93 (d, J = 11.0 Hz, 1H, H-8), 3.07 (d, J = 12.7 Hz, 1H), 4.17 (d, J = 12.7 Hz, 1H), 4.60 (dd, J = 7.2, 4.8 Hz, 1H, H-1), 5.24 (d, J = 4.6 Hz, 1H, H-3), 7.14−7.33 (m, 6H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.4 (CH_3), 19.3 (CH_2), 31.0 (CH_2), 35.0 (CH_2, C-4), 42.9 (CH, C-5), 56.8 (CH_2, PhCH_2), 61.6 (CH_2, C-8), 66.1 (CH, C-6), 79.8 (CH, C-1), 97.9 (CH, C-3), 127.4 (CH), 128.6 (CH), 128.8 (CH), 137.1 (C); IR (neat) ν 3180 (O−H) cm^{-1}; MS (EI) *m*/*z* (%) 261 (M, 1), 260 (2), 219 (16), 218 (base), 160 (3), 146 (4), 120 (7), 110 (3), 91 (80); HRMS calcd for $C_{16}H_{23}NO_2$, 261.1729; found, 261.1724.

(1*R,3*R**,5*R**,6*S**)- and (1*R**,3*S**,5*R**,6*S**)-7-Benzyl-3-(3,4-dimethoxyphenethylamino)-6-propyl-2-oxa-7-azabicyclo[3.3.0]-octane (36).** A mixture of $NaBH_3CN$ (6 mg, 0.10 mmol) and $ZnCl_2$ (7 mg, 0.05 mmol) in MeOH (0.5 mL) was stirred for 1 h at room temperature and was added dropwise to a stirred solution of **35** (26 mg, 0.10 mmol) and homoveratrylamine (0.07 mL, 0.40 mmol) in MeOH (1.0 mL). The reaction mixture was stirred for 40 h at room temperature, diluted with CH_2Cl_2 (5 mL), and poured over saturated K_2CO_3 solution (5 mL). After separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were washed with brine (2 mL) and dried (Na_2SO_4). The residue after evaporation was purified by flash column chromatography (silica gel saturated with Et_3N, 78:20:2 hexanes/EtOAc/Et_3N) to yield **36** (38 mg, 90%, 3:1 dr): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94 and 0.98 (2 t, J = 7.1 Hz, total 3H), 1.21−1.56 (m, 4H), 1.70−2.27 (m, 5H), 2.46−3.15 (m, 7H), 3.84−3.86 (4 s, 6H), 4.02 (d, J = 13.3 Hz, 1H) and 4.06 (d, J = 12.5 Hz, 1H, total 1H), 4.40 (dd, J = 7.3, 5.4 Hz) and 4.50 (dd, J = 7.7, 5.8 Hz, total 1H), 4.73 (dd, J = 6.7, 2.4 Hz) and 4.92 (t, J = 5.6 Hz, total 1H), 6.62−6.81 (m, 3H), 7.18−7.34 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 14.5 (CH_3), 14.6 (CH_3), 19.6 (CH_2), 19.6 (CH_2), 31.1 (CH_2), 31.6 (CH_2), 32.5 (CH_2), 32.9 (CH_2), 36.4 (CH_2), 36.7 (CH_2), 43.7 (CH), 44.4 (CH), 47.3 (CH_2), 48.3 (CH_2), 55.7 (CH_3), 55.8 (CH_3), 57.0 (CH_2), 57.5 (CH_2), 61.9 (CH_2), 62.4 (CH_2), 66.2 (CH), 66.5 (CH), 78.2 (CH), 79.3 (CH), 92.0 (CH), 111.0 (CH), 111.2 (CH), 111.8 (CH), 120.4 (CH), 120.5 (CH), 126.6 (CH), 127.0 (CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 129.1 (CH), 132.5 (C), 133.1 (C), 138.7 (C), 139.2 (C), 147.1 (C), 147.3 (C), 148.6 (C), 148.8 (C); IR (neat) ν 3260 (N−H) cm^{-1}; MS (FAB) *m*/*z* (%) 425 (M + 1, base), 424 (M, 23), 423 (74), 244 (83); HRMS calcd for $C_{26}H_{37}N_2O_3$ (M + 1), 425.2804; found, 425.2797.

(3*R,4*R**,5*S**)-1-Benzyl-4-[2-(3,4-dimethoxyphenethylamino)-ethyl]-5-propylpyrrolidin-3-ol (37).** A solution of **36** (19 mg, 0.045 mmol) in THF (1.0 mL) was added dropwise to a stirred suspension of LAH (2 mg, 0.054 mmol) in THF (1.0 mL) at 0 °C. The reaction mixture was allowed to reach room temperature, stirred further for 40 h, and then quenched at 0 °C with 1 M NaOH (1 mL). After allowing the mixture to reach room temperature, CH_2Cl_2 (2 mL) and saturated sodium potassium tartrate (2 mL) were added. The resulting emulsion was vigorously stirred for 4 h, becoming a clear biphasic liquid. After separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic layers were dried (Na_2SO_4). The residue after evaporation was purified by flash column chromatography (silica gel saturated with Et_3N, 98:2 CH_2Cl_2/Et_3N and then 95:3:2 CH_2Cl_2/MeOH/Et_3N) and then dissolved in CH_2Cl_2 (2 mL), and the solution was washed with 1 M NaOH (0.5 mL) to yield **37** (17 mg, 90%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.91 (t, J = 7.1 Hz, 3H), 1.25−1.78 (m, 8H), 2.10−2.22 (m, 1H), 2.49−2.93 (m, 9H), 3.32 (d, J = 13.3 Hz, 1H), 3.85 and 3.85 (2 s, 6H), 3.99 (d, J = 13.3 Hz, 1H), 4.18 (td, J = 5.7, 3.8 Hz, 1H), 6.70−6.81 (m, 3H), 7.18−7.32 (m, 5H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.6 (CH_3), 20.4 (CH_2), 24.8 (CH_2), 32.8 (CH_2), 35.7 (CH_2), 46.2 (CH), 48.4 (CH_2), 51.0 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 59.2 (CH_2), 60.3 (CH_2), 65.4 (CH), 71.0 (CH), 111.4 (CH), 112.0 (CH), 120.6 (CH), 126.7 (CH), 128.1 (CH), 128.6 (CH), 132.1 (C), 139.9 (C), 147.5 (C), 149.0 (C); IR (neat) ν 3300 (N−H, O−H) cm^{-1}; MS (FAB) *m*/*z* (%) 427 (M + 1, 97), 426 (M, 14), 275 (24), 262 (10), 246 (base), 226 (33), 201 (41), 184 (36), 172 (13), 165 (91), 162 (15); HRMS (FAB) calcd for $C_{26}H_{39}N_2O_3$ (M + 1), 427.2961; found, 427.2949.

(3*R,4*R**,5*S**)-1-Benzyl-5-ethyl-4-(2-hydroxyethyl)piperidin-3-ol (34b).** The procedure described above for the preparation of **35** was followed starting from **20a**. The crude product was purified by flash column chromatography (silica gel saturated with Et_3N, 98:2 EtOAc/Et_3N) to yield **34b** (82%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$, 50 °C) δ 0.84 (t, J = 7.3 Hz, 3H), 1.28−1.46 (m, 2H), 1.50−1.62 (m, 2H), 1.69−1.83 (m, 1H), 1.87−1.95 (m, 1H), 2.06−2.56 (m, 6H), 3.46 (d, J = 13.1 Hz, 1H), 3.59 (d, J = 13.1 Hz, overlapped with other signals, total 2H), 3.72−3.84 (m, 2H), 7.20−7.31 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 45 °C) δ 12.3 (CH_3), 22.5 (CH_2), 26.9 (CH_2), 40.6 (CH), 40.6 (CH), 54.5 (CH_2), 57.0 (CH_2), 62.3 (CH_2), 62.7 (CH_2), 69.9 (CH), 127.0 (CH), 128.2 (CH), 129.0 (CH), 138.2 (C); IR (neat) ν 3360 (O−H) cm^{-1}; MS (EI) *m*/*z* (%) 263 (M, 11), 262 (6), 246 (6), 202 (15), 172 (17), 120 (21), 91 (base); HRMS calcd for $C_{16}H_{25}NO_2$, 263.1885; found, 263.1882.

(3′*S,4′*R**,5′*R**)-*N*-Benzyl-2-(1-benzyl-3-ethyl-5-hydroxypiperidin-4-yl)acetamide (38a).** A mixture of **20a** (100 mg, 0.39 mmol), $BnNH_2$·HCl (140 mg, 0.98 mmol), and sodium 2-ethylhexanoate (227 mg, 1.36 mmol) in THF (2.0 mL) was stirred for 5 days under Ar. Brine (2.0 mL) and EtOAc (4.0 mL) were added, and the mixture was stirred 5 min. After separation, the aqueous layer was extracted with EtOAc (2 × 2 mL), and the combined organic layers were dried (Na_2SO_4). The residue after evaporation was purified by flash column chromatography (silica gel saturated with Et_3N, 18:80:2 hexanes/EtOAc/Et_3N) to yield **38a** (132 mg, 92%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$, 50 °C) δ 0.82 (t, J = 7.3 Hz, 3H), 1.32−1.44 (m, 2H), 1.59−1.70 (m, 1H), 2.09−2.18 (m, 2H), 2.32−2.51 (m, 4H), 2.60 (dd, J = 11.2, 3.4 Hz, overlapped with br signal, total 2H), 3.47 and 3.55 (2 d, J = 13.1 Hz, 2H), 3.84 (dt, J = 7.3, 3.6 Hz, 1H), 4.39 and 4.46 (2 dd, J = 14.7, 5.7 Hz, 2H), 6.02 (br s, 1H), 7.19−7.36 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 45 °C) δ 12.4 (CH_3), 22.6 (CH_2), 32.3 (CH_2), 39.2 (CH), 40.1 (CH), 43.8 (CH_2), 54.8 (CH_2), 57.2 (CH_2), 62.7 (CH_2), 69.6 (CH), 127.0 (CH), 127.4 (CH), 127.7 (CH), 128.2 (CH), 128.6 (CH), 128.9 (CH), 138.4 (C), 173.6 (C); IR (neat) ν 3290 (N−H), 3290 (O−H), 1640 (C═O), 1560 (N−CO) cm^{-1}; MS (EI) *m*/*z* (%) 366 (M, 1), 348 (38), 257 (11), 200 (77), 168 (9), 134 (4), 120 (7), 91 (base); HRMS calcd for $C_{23}H_{30}N_2O_2$, 366.2307; found, 366.2290.

(3′*S,4′*R**,5′*R**)-2-(1-Benzyl-3-ethyl-5-hydroxypiperidin-4-yl)-*N*-phenethylacetamide (38b).** A mixture of **20a** (100 mg, 0.39 mmol), $Ph(CH_2)_2NH_2$·HCl (155 mg, 0.98 mmol), and sodium 2-ethylhexanoate (227 mg, 1.36 mmol) in THF (2.0 mL) was stirred for 6 days under Ar, and the mixture was poured over a saturated K_2CO_3 solution (4.0 mL). After separation, the aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4). The residue after evaporation was purified by flash column chromatography (silica gel saturated with Et_3N, 18:80:2 hexanes/EtOAc/Et_3N) to yield **38b** (142 mg, 96%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$, 50 °C) δ 0.81 (t, J = 7.3 Hz, 3H), 1.21−1.45 (m, 2H), 1.57−1.68 (m, 1H), 1.90−2.11 (m, 2H), 2.28−2.41 (m, 4H), 2.60 (dd, J = 11.2, 3.3 Hz, 1H), 2.80 (t, J = 7.0 Hz, 2H), 3.32 (br s, 1H), 3.43−3.58 (m, 4H), 3.77−3.82 (m, 1H), 5.88 (br s, 1H), 7.16−7.31 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$, 45 °C) δ 12.3 (CH_3), 22.6 (CH_2), 32.0 (CH_2), 35.6 (CH_2), 39.1 (CH), 40.1 (CH), 40.7 (CH_2), 54.6 (CH_2), 57.0 (CH_2), 62.6 (CH_2), 69.5 (CH), 126.4 (CH), 127.0 (CH), 128.2 (CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 138.2 (C), 138.8 (C), 173.8 (C); IR (neat) ν 3380 (O−H, N−H), 1640 (C═O), 1560 (N−CO) cm^{-1}; MS (EI) *m*/*z* 380 (M, 1), 362 (38), 271 (19), 214 (12), 200 (base), 168 (5), 134 (6), 120 (6), 105 (11), 91 (93); HRMS calcd for $C_{24}H_{32}N_2O_2$, 380.2464; found, 380.2469.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2**−**5**, **7**−**9**, **13**, **16**, **17**, **19**, **20**, and **33**, stereochemical elucidation details, and copies of ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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