

Efficient and Expeditious Protocols for the Synthesis of Racemic and Enantiomerically Pure Endocyclic Enecarbamates from *N*-Acyl Lactams and *N*-Acyl Pyrrolidines

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A mild, practical, and straightforward protocol for the construction of endocyclic enecarbamates starting from *N*-acyl lactams and *N*-acyl pyrrolidines is presented. Lactams were reduced to the corresponding α -hydroxycarbamates in good to excellent yields using DIBAL-H, SuperHydride, or NaBH₄ followed by β -elimination (dehydration) promoted by trifluoroacetic anhydride in the presence of hindered nitrogenated bases such as 2,6-lutidine, diisopropylethylamine, or triethylamine. Small variations of this protocol permitted the preparation of several endocyclic enecarbamates (12 examples) in good to excellent overall yields (56–96%). The protocol was demonstrated to be applicable to several ring sizes, compatible with different protecting groups, and to be mild enough to prevent racemization of racemization-prone stereocenters. The efficacy of the procedure in the preparation of enantiomerically pure endocyclic enecarbamates was also demonstrated and compared to the commonly used Shono's protocol, which in our hands led to partial racemization of the endocyclic enecarbamate **18c**.

Introduction

Endocyclic enecarbamates are heterocyclic compounds whose structural motif, a deactivated enamine group, makes them useful building blocks for the synthesis of nitrogen-containing heterocycles of biological significance.¹ Despite the fact that these valuable compounds have been known for quite some time, there is a renewed interest in them as can be perceived from the recent increasing number of publications on the subject.² Of the methodologies available for their preparation,³ only a few are applicable to the construction of more complex endocyclic enecarbamates, especially the five-membered ones. This has probably functioned as a limiting factor for a more extensive use of these moderately reactive *N*-acyl enamines in organic synthesis.

In the past few years we have focused on a general protocol for the preparation of enantiomerically pure enecarbamates in conjunction with some ongoing synthetic programs.⁴ We then sought to develop general methodology for the preparation of endocyclic enecarbamates under mild conditions with consistently good yields.

Shono's protocol,^{3e,f} probably the most used one for the synthesis of enecarbamates, involves methanol elimination from α -methoxycarbamates and has been considered the methodology of choice. Recently, two efficient procedures for the synthesis of endocyclic enecarbamates from lactams were reported.^{3a,c} Although Dieter's procedure^{3c} is efficient, it uses HMPA, a toxic and expensive solvent, under rather harsh conditions (160–190 °C for 2–4 h). An attractive alternative reported by Cossy^{3a} employs catalytic amounts of the weakly acidic quinolinium camphorsulfonate to promote dehydration of α -hydroxycarbamates. However, some enecarbamates are unstable under these conditions, which might explain some of the low yields obtained in a few cases as well as the rather short reaction periods enecarbamates can be exposed to under these conditions. Prompted by these two rather recent publications, we report herein our results on the development of a general and mild protocol for the preparation of endocyclic enecarbamates from lactams, which we have been using routinely for quite some time in our laboratories. This protocol produces the desired enecarbamates in good to excellent overall yields, and is compatible with a number of protecting groups and with racemization-prone stereogenic centers.

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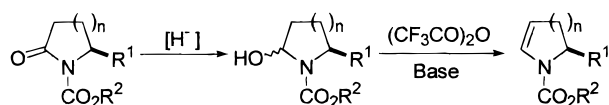
(1) For reviews, see: (a) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421. (b) Lenz, G. R. *Synthesis* **1978**, 489. Although these reviews focused on enamides, the authors use the term enamide in a rather broad sense including enecarbamates.

(2) For some selected examples, see: (a) Bueno, A. B.; Hegedus, L. S. *J. Org. Chem.* **1998**, 63, 684. (b) Bach, T.; Brummerhop, H. *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 3400. (c) Cossy, J.; Cases, M.; Pardo, D. G. *Synlett* **1998**, 507. (d) Wolf, L. B.; Tjen, K. C. M. F.; Rutjes, F. P. T.; Hiemstra, H.; Schoemaker, H. E. *Tetrahedron Lett.* **1998**, 39, 5081. (e) Paquette, L. A.; Tae, J. *Tetrahedron Lett.* **1997**, 38, 3151. (f) Matsumura, Y.; Yoshimoto, Y.; Horikawa, C.; Maki, T.; Watanabe, M. *Tetrahedron Lett.* **1996**, 37, 5715. (g) Foti, C. J.; Comins, D. L. *J. Org. Chem.* **1995**, 60, 2656. (h) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, 115, 3030. (i) Martin, S. F.; Rein, T.; Liao, Y. *Tetrahedron Lett.* **1991**, 32, 6481.

(3) In addition to refs 1 and 2, for specific references on the synthesis of enecarbamates consult the following: (a) Cossy, J.; Cases, M.; Pardo, D. G. *Synth. Commun.* **1997**, 27, 2769. (b) McDonald, F. E.; Chatterjee, A. K. *Tetrahedron Lett.* **1997**, 38, 7687. (c) Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, 61, 4180. (d) Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, 47, 1311. (e) Shono T. *Tetrahedron* **1984**, 40, 811. (f) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, 104, 6697. (g) Kraus, G. A.; Neuenschwander, K. *J. Org. Chem.* **1981**, 46, 4791.

(4) (a) Oliveira, D. F.; Severino, E. A.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, 40, 2083. (b) Pohl, A. M.; Correia, C. R. D. *Heterocycles* **1997**, 45, 2321. (c) Carpes, M. J. S.; Miranda, P. C. M. L.; Correia, C. R. D. *Tetrahedron Lett.* **1997**, 38, 1869. (d) Correia, C. R. D.; Faria, A. R.; Carvalho, E. S. *Tetrahedron Lett.* **1995**, 36, 5109. (e) Faria, A. R.; Matos, C. R.; Correia, C. R. D. *Tetrahedron Lett.* **1993**, 34, 27.

Scheme 1



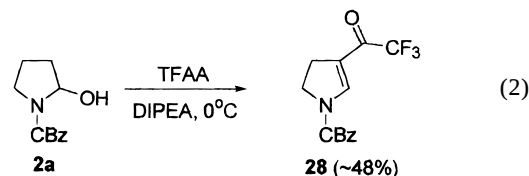
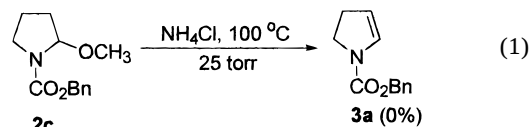
Results and Discussion

The strategy for the synthesis of enecarbamates involves reduction of *N*-acyl lactams to α -hydroxycarbamates followed by dehydration promoted by trifluoroacetic anhydride (TFAA) and a hindered base: 2,6-lutidine, triethylamine (TEA), or diisopropylethylamine (DIPEA). Special attention was placed on the preparation of enantiomerically pure endocyclic enecarbamates (Scheme 1).

α -Hydroxycarbamates (also termed hemiaminals or lactamols) were readily obtained from *N*-acyl lactams by reduction employing DIBAL-H,⁵ SuperHydride (LiEt₃BH),⁶ or NaBH₄.⁷ Use of DIBAL-H and LiEt₃BH led to α -hydroxycarbamates in high yields (80–97%), whereas NaBH₄ provided the corresponding α -hydroxycarbamates in slightly lower yields (50–80%). As pointed out by Dieter, this latter process requires more stringent control of the reaction conditions than does reduction with DIBAL-H and LiEt₃BH to prevent formation of byproducts resulting from over-reduction.^{7c} For this reason, reduction of *N*-acyl lactams using NaBH₄ was used here only on a few occasions, but was preferred in multigram scale reactions for economic reasons. Alternatively, α -hydroxycarbamates can be obtained by mild acetic acid hydrolysis of α -methoxycarbamates,⁸ which in turn can be readily obtained through anodic oxidation of the corresponding carbamate according to Shono's protocol.^{3e,f} That was the specific case for the preparation of α -hydroxycarbamate **17c** as shown in Scheme 2. All *N*-acyl lactams used as starting materials in this study were prepared by coupling the lactams with the corresponding chloroformate or with an acyl imidazole derivative (generated from the precursor alcohols) under standard conditions (see the Supporting Information for details), or by oxidation of the carbamate precursor with Ru(VIII).⁹ This latter procedure was found advantageous when preparing enecarbamates derived from L-proline (compounds **18b** and **18c**; Scheme 2) which bear a stereocenter susceptible to racemization.

Similarly to the results obtained by other research groups,^{3c} attempts to perform dehydration of the α -hydroxycarbamates employing some of the available methodologies proved more difficult than anticipated. For example, attempts to obtain five-membered enecarbamates **3a/3b** from **2a/2b** (see Table 1) using MsCl/Et₃N/CH₂Cl₂, Tf₂O/pyr/CH₂Cl₂, refluxing in toluene, CuSO₄/SiO₂, and FeCl₃/SiO₂ failed completely or provided the desired enecarbamates in very low yields (5–10%).

Besides, attempts to generate enecarbamate **3a** or **3b** directly from α -methoxycarbamate **2c** (derived from **2a** with MeOH/PPTS) employing Shono's conditions (NH₄Cl, 100 °C, ~25 Torr)^{3f} led to decomposition (eq 1). However, when we reacted hydroxycarbamate **2a** with (CF₃CO)₂O (~2 equiv) at 0 °C, in the presence of *i*-Pr₂EtN, the 3-acyl enecarbamate **28** was obtained as the main reaction product (eq 2) in moderate yields (~48% yield).



We thus changed reaction conditions to ensure stoichiometric formation of the trifluoroacetate intermediate (1 equiv of TFAA, –78 °C, 7 h), followed by elimination with *i*-Pr₂EtN (20 equiv, –78 °C to room temperature). Gratifyingly, these conditions provided reasonable yields (65–69%) of the corresponding endocyclic enecarbamate **3a** (Table 1, entry 1, procedure B). This protocol was later refined, resulting in five slightly different procedures, applicable to a broad range of α -hydroxycarbamates as described in Table 1 below. All α -hydroxycarbamates examined afforded the corresponding endocyclic enecarbamate in good to excellent yields in a scale ranging from 30 mg to 2 g.

These procedures were compatible with a number of nitrogen protecting groups and also allowed the preparation of enecarbamates of different ring sizes (entries 1, 2, 3, and 4; Table 1). Several enantiomerically pure enecarbamates were also prepared without noticeable racemization (entries 5, 6, 7, and 9; Table 1). As described in Table 1, procedures B, D, and E allowed the preparation of enecarbamates at room temperature, thus making it an appropriate procedure for the preparation of thermolabile enecarbamates. However, in several occasions yields were somewhat lower when using *i*-Pr₂EtN (procedure B) or Et₃N (procedure D) with a concomitant increase in the amounts of side products.¹⁰

Procedure A was found to be the most reliable one in preparing endocyclic enecarbamates. It is worth mentioning that enecarbamates are rather unstable under acidic conditions. Nevertheless, the slightly acidic lutidinium trifluoroacetate salt formed as a byproduct in the reaction medium did not cause any noticeable decomposi-

(5) (a) Adapted from Langlois, N.; Rojas, A. *Tetrahedron* **1993**, *49*, 77. (b) See also ref 3c.

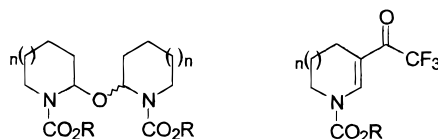
(6) Adapted from the work of Choi, J. K.; Ha, D. C.; Hart, D. L.; Lee, C. S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279. See also ref 3c.

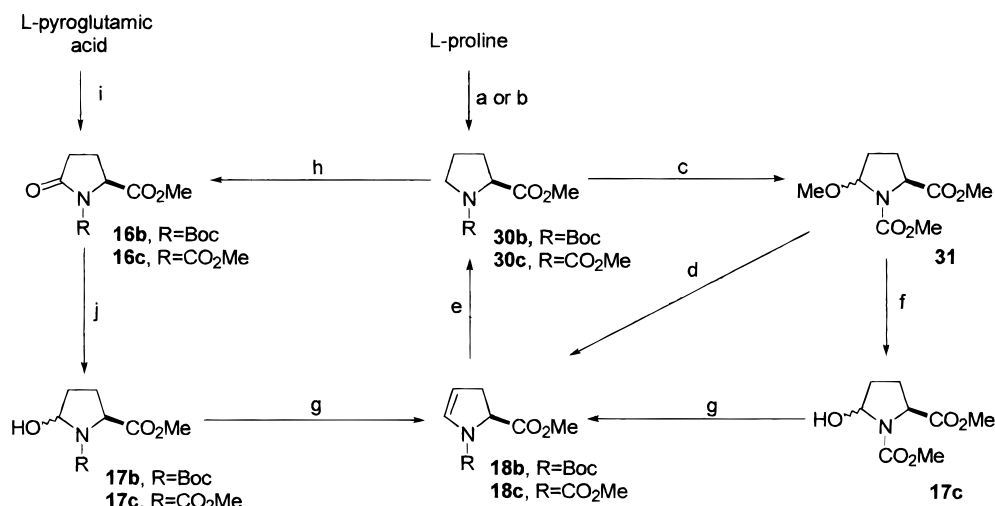
(7) Adapted from the following: (a) Altman, K. W. *Tetrahedron Lett.* **1993**, *34*, 7721. (b) Chamberlin, A. R.; Nguyen, H. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682. (c) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(8) Procedure adapted from the work of Nagasaka, T.; Tamano, H.; Maekawa, T.; Hamaguchi, F. *Heterocycles* **1987**, *26* (3), 617.

(9) Yoshifuji, S.; Tanaka, K.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3873.

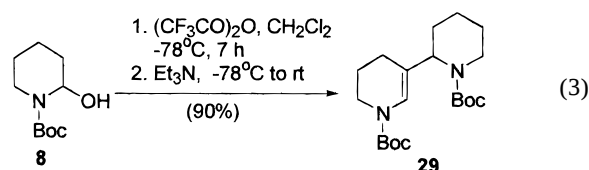
(10) Use of Et₃N or *i*-Pr₂EtN seems very effective in promoting elimination, yielding the corresponding enecarbamates even at 0 °C as detected by TLC. 2,6-Lutidine, on the other hand, promotes elimination of the trifluoroacetates only after heating. Despite this higher effectiveness, use of Et₃N and *i*-Pr₂EtN frequently led to the formation of side products in variable yields.



Scheme 2^a

^a Reagents and Conditions: (a) preparation of **30b**, (i) SOCl₂, MeOH (86%); (ii) Boc₂O, Et₃N, THF (82%); (b) preparation of **30c**, MeCO₂Cl, MeOH, K₂CO₃ (93%); (c) MeOH, Et₄NOTs (75%); (d) NH₄Cl, 150 °C, 1–2 h (61%); (e) H₂, Pd/C 10%, 40 psi (78–95%); (f) H₂O/HOAc (83%); (g) (i) TFAA (1 equiv), toluene, 0 °C; (ii) 2,6-lutidine, 0 °C to rt; (iii) reflux, 20 min (78% for **18b** and 46% for **18c**); (h) RuCl₃ (cat.), NaIO₄, AcOEt (78–82%); (i) (i) SOCl₂, MeOH (85%); (ii) Boc₂O, Et₃N, DMAP, CH₂Cl₂ (89%); (j) DIBAL-H, toluene, –78 °C or LiEt₃BH (72–89%).

tion. Actually most of the endocyclic enecarbamates prepared in this work can be refluxed in the presence of lutidinium trifluoroacetate for a period of 2 h without significant reduction in yields. Interestingly, procedure D was found more suitable for the synthesis of five-membered enecarbamate than for the preparation of six-membered enecarbamates. For instance, when procedure D was applied to α -hydroxycarbamate **8**, the “dimeric” enecarbamate **29** was obtained in 90% isolated yield (eq 3).¹¹ Apparently, the six-membered enecarbamate un-



dergoes self-condensation promoted by CF₃CO₂Et₃NH generated in the reaction medium. This type of self-condensation is largely suppressed when 2,6-lutidine is used as base (e.g., procedure A).

Overall yields of the endocyclic enecarbamates were consistently good, ranging from 56 to 96%. The only exception was entry 6 for enecarbamate **18c**. This lower overall yield for **18c** was credited to the volatility of the compound. Of the several chiral, nonracemic, enecarbamates depicted in Table 1 (entries 5, 6, 7, and 9) special mention is made of enecarbamates **18b** and **18c**, bearing a potentially racemizable stereocenter, which were obtained in enantiomerically pure form.

The procedures developed employ conditions that are essentially neutral or slightly acidic, and the option of choosing between toluene and CH₂Cl₂ (in which trifluoroacetic anhydride is more soluble at –78 °C) as reaction solvent also extends the potential applicability of this methodology.

Enantiomeric Purity of the Chiral Endocyclic Enecarbamates **18b and **18c**.** To confirm that the TFAA/2,6-lutidine protocol causes no racemization, the endocyclic enecarbamates **18b** and **18c** were converted to the known chiral proline derivatives **30b** and **30c** according to Scheme 2. Furthermore, a comparison between our protocol and Shono's protocol for preparing enantiomerically pure enecarbamates was also carried out. Along the way interesting observations were made and some important conclusions obtained.

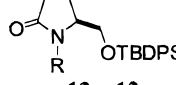
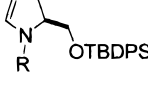
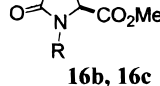
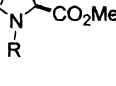
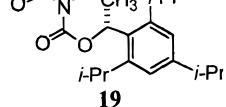
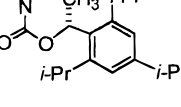
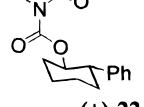
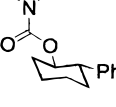
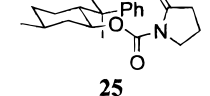
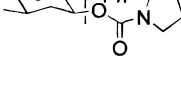
This comparative study was found necessary because enecarbamate **18b**—obtained by the sequence L-pyrroglutamic acid $\rightarrow$ **16b** $\rightarrow$ **17b** $\rightarrow$ **18b** (Scheme 2)—had a specific rotation value of –64.7, which was ~60% of the value reported in the literature ([α]_D = –108).⁹ In addition, enecarbamate **18c**, used by us in previous work^{4c} (sequence L-proline $\rightarrow$ **30c** $\rightarrow$ **31** $\rightarrow$ **18c**; Scheme 2) was found to be only 80–90% enantiomerically pure by chiral phase HPLC, as well as by comparing specific rotations after conversion of **18c** to **30c**.¹²

In the case of Shono's protocol (**30c** $\rightarrow$ **31** $\rightarrow$ **18c**; Scheme 2), it was critical to determine which was the racemization step in the process: the anodic oxidation, the methanol elimination, or both. Thus, with the objective of determining the racemization step, proline derivative **30c** was oxidized to methoxy proline **31** (75% yield) and immediately converted into enecarbamate **18c** by methanol elimination (NH₄Cl, 150 °C, 2–3 h; 61%). Catalytic hydrogenation afforded proline derivative **30c** possessing a [α]_D value of –55, meaning an estimated 10% racemization along the sequence of reactions. On the other hand, catalytic hydrogenation of enecarbamate **18c** obtained from α -hydroxycarbamate **17c**⁸ provided the proline derivative **30c** with a [α]_D value of –69, identical to that measured for **30c** used as starting material. These

(11) This dimeric compound contains the basic skeleton of the bispiperidine alkaloid ammodendrine (see: Pinder, A. R. *Nat. Prod. Rep.* **1989**, 515) and also the enamine form of tetrahydroanabasine (see: Koomen, G.-J.; Wanner, M. J. *J. Org. Chem.* **1996**, 61, 5581).

(12) Although Shono's protocol calls for a 30 min heating at 150 °C in the presence of NH₄Cl, in our hands this procedure led to low conversion of the α -methoxycarbamate, resulting in low overall yields of the corresponding enecarbamate. To ensure higher conversions, it was necessary to heat the reaction mixture for 1–2 h. It is conceivable that the longer reaction times were responsible for the degree of racemization observed, in the range of 5–10%.

Table 1. Conversion of *N*-Acyl Lactams into Endocyclic Enecarbamates

Entry	Lactam	Hydroxycarbamate (yield, %)	Enecarbamate Procedure (yield, %) ^{a, b, c}
1	 1a 1b	 2a , (88%) 2b , (92%)	 3a (C) (70%) 3a (B) (69%) 3b (D) (81%)
2	 4	5 , (80%)	 6 (E) (84%)
3	 7	8 (89%)	 9 (A) (63%)
4	 10	11 (88%)	 12 (A) (78%)
5	 13a , 13c	14a , (97%) 14c , (93%)	 15a (A) (99%) 15c (A) (95%)
6	 16b , 16c	17b , (84%) 17c , (72%)	 18b , (A) (78%) 18c , (A) (46%) ^d
7	 19	20 (93%)	 21 (A) (98%)
8	 (±)-22	23 (90%)	 (±)-24 (A) (92%)
9	 25	26 (87%)	 27 (A) (82%)

^a Yields refer to isolated compounds. ^b Letter **a** after the number of the compound indicates R = CBz; **b**, R = Boc; and **c**, R = CO₂Me. ^c Procedures; A, (i) TFAA, toluene, 2,6-lutidine; (ii) reflux; B, (i) TFAA, toluene; (ii) DIPEA; C, (i) TFAA, toluene; (ii) 2,6-lutidine, reflux; D, (i) TFAA, CH₂Cl₂; (ii) TEA; E, (i) TFAA, CH₂Cl₂, 2,6-lutidine; see Experimental Section for details. ^d This lower yield is due to the higher volatility of **18c** when compared to **18b**.

results permitted the conclusion that partial racemization was occurring exclusively during methanol elimination in Shono's protocol. It was also clear that the presence of the racemization-prone C-2 stereocenter of L-proline was fully compatible with the (CF₃CO)₂O/2,6-lutidine protocol.

In the case of enecarbamate **18b** (R = Boc) obtained from L-pyroglyutamic acid ([α]_D = −64.7), it was assumed that partial racemization was taking place during installation of the Boc protecting group (Et₃N, DMAP, Boc₂O). To circumvent this problem and also to demonstrate that racemization was indeed occurring at the stage of Boc installation, enecarbamate **18b** was synthesized through the sequence **30b** → **16b** → **17b** → **18b** (Scheme 2). This time, the specific rotation value observed for **18b** ([α]_D = −102) was very close to that reported in the literature.¹³

Unequivocal confirmation that no significant racemization was occurring was obtained when **18b** was catalytically hydrogenated to **30b**, which showed specific rotation ([α]_D = −69.0) almost identical to that measured for the proline derivative we started with ([α]_D = −69.4).¹⁴ Thus, to obtain enantiomerically pure endocyclic enecarbamates of type **18b** (R = Boc), the longer route starting from

(13) (a) Dormoy, J.-R. *Synthesis* **1982**, 753. [α]_D²⁰ = −108 (c 0.71, MeOH) for compound **18b**. (b) Cossy, J. (see ref 3a). [α]_D²⁰ = −101.1 (c 1.22, EtOH) for an ethyl analogue of **18b**. (c) Schumacher, K. K.; Jiang, J.; Joullie, M. M. *Tetrahedron: Asymmetry* **1998**, 9, 47. [α]_D²⁰ = −98.0 (c 0.89, CHCl₃).

(14) The [α]_D values obtained for compounds **30b** and **30c** were very similar. The literature value for compound **30b** is −69.4 (see ref 9). Since the [α]_D value for **30c** is not reported in the recent literature, we checked its enantiomeric excess (ee) by chiral phase GC. The ee found for **30c** was >98%.

L-proline was preferred over the one starting from pyroglutamic acid.¹⁵

Conclusion

An efficient and inexpensive protocol was developed for the synthesis of racemic and enantiomerically pure endocyclic enecarbamates in good to excellent overall yields starting from *N*-acyl lactams. The *N*-acyl lactams were reduced to the corresponding α -hydroxycarbamates in excellent yields using DIBAL-H and SuperHydride or with NaBH₄ in slightly lower yields. Conversion of the α -hydroxycarbamates into the desired endocyclic enecarbamates was accomplished in good to excellent overall yields using stoichiometric amounts of trifluoroacetic anhydride in the presence of triethylamine, diisopropylethylamine, or 2,6-lutidine. The conditions employed were very mild and essentially neutral and should prove suitable to a considerable number of synthetic applications.

Experimental Section

For general experimental details, see the Supplementary Information.

General Procedures for the Synthesis of Endocyclic *N*-Carbamoyl Enamines (Endocyclic Enecarbamates).

Procedure A. To a stirred solution of the lactamol, 2,6-lutidine, and toluene (in a 1 mmol:20 mmol:20.5 mL ratio), at 0 °C under N₂, was added 1 equiv of (CF₃CO)₂O. After being stirred for approximately 7 h at 0 °C, the reaction mixture was slowly warmed to room temperature overnight. The mixture was refluxed for 20 min, cooled to room temperature, and, after addition of saturated NaHCO₃ (22 mL/mmol of lactamol), stirred for 1 h. The toluene layer was separated and the aqueous layer extracted with toluene or hexane. The combined toluene/hexane extract was dried over anhydrous Na₂SO₄ and concentrated in vacuo, and the residue obtained purified by silica gel flash chromatography (hexane/EtOAc).

Procedure B. To a solution of 1 mmol of lactamol in 20 mL of toluene cooled to -78 °C was added 1 equiv of (CF₃CO)₂O under N₂. After 7 h, 4 equiv of *i*-Pr₂NEt was added and the resulting solution stirred overnight, during which time it slowly warmed to room temperature. Saturated NaHCO₃ (22 mL/mmol of lactamol) was then added, and the reaction mixture was stirred for 1 h. The toluene layer was separated and the aqueous layer extracted with toluene. The organic extracts were combined and concentrated in vacuo (1 Torr) to afford a residue that was purified by silica gel flash chromatography (hexane/EtOAc).

Procedure C. To a solution of 1 mmol of lactamol in 20 mL of toluene cooled to -78 °C was added 1 equiv of (CF₃CO)₂O under N₂. After 7 h, 2,6-lutidine (20 equiv) was added, and the resulting solution was stirred overnight, during which time it slowly warmed to room temperature. The reaction mixture was refluxed for 20 min and then cooled to room temperature, followed by addition of saturated NaHCO₃ (22 mL/mmol of lactamol). After the resulting mixture was stirred for 1 h, the toluene layer was separated and the aqueous layer extracted with hexane. The combined toluene and hexane extracts were washed with water, dried over anhydrous Na₂SO₄, concentrated in vacuo (water pump), and purified by silica gel flash chromatography (hexane/EtOAc).

Procedure D. The same as described in C, but using CH₂Cl₂ and Et₃N instead of toluene and 2,6-lutidine, respectively. The major difference between procedure C and procedure D is the fact that reflux of the reaction is not necessary to carry out elimination of the intermediate trifluoroacetate.

Procedure E. Used for the conversion of lactamol **5** into enecarbamate **6**. To a solution of lactamol **5** (307 mg, 1.5 mmol) in 6 mL of CH₂Cl₂ at -78 °C were added successively 2,6-lutidine (0.27 mL, 2.3 mmol) and trifluoroacetic anhydride (0.21 mL, 1.5 mmol, dissolved in 2 mL of CH₂Cl₂) over a period of 15 min. The mixture was slowly warmed to room temperature and stirred for a total of 12 h. The reaction was quenched with 3 mL of a saturated solution of NaHCO₃ and stirred for 15 min. After extraction with CH₂Cl₂ the combined organic layer was washed with brine and dried over anhydrous Na₂SO₄. The solvent was evaporated in vacuo to provide a colorless liquid that was flash chromatographed (SiO₂, 10% EtOAc in hexane) to give 239 mg (84% yield) of colorless enecarbamate **6**, whose spectroscopic data were in full agreement with those described.^{3c}

Note. Although 2,6-lutidine was routinely used in procedures A and C, it can be effectively replaced by 2,4-lutidine. Also, on several occasions the amount of 2,6-lutidine was reduced from 20 equiv to 5–10 equiv without any noticeable changes in yields.

1-(Benzyloxycarbonyl)-2-pyrroline (3a).^{3g} A 68.2 mg sample of **2a** afforded 33.3 mg (69% yield) of **3a** as a clear liquid by procedure B. When procedure C was employed, 70.8 mg of **2a** afforded 46.2 g (69% yield) of **3a**. *R*_f = 0.33 (EtOAc/hexane, 1:4). ¹H NMR (CCl₄, 80 MHz) (mixture of rotamers): δ 2.6 (dd, *J* = 9.9 Hz, 2H), 3.8 (dd, *J* = 9.9 Hz, 2H), 5.1 (br s, 1H), 5.2 (s, 2H), 6.6 (br s, 1H), 7.3 (s, 5H). MS: *m/z* (rel intens) 203(4) [M⁺], 159 (7), 92 (9), 91 (100), 65 (8), 41 (18).

1-(tert-Butoxycarbonyl)-2-pyrroline (3b).^{3c} Employing procedure D, 0.152 g (0.9 mmol) of **2b** yielded 0.112 g (81% yield) of **3b**. When procedure C was used, 0.150 g (0.80 mmol) of **2b** provided 0.073 g (54% yield) of **3b**. *R*_f = 0.32 (EtOAc/hexane, 1:10). FTIR (neat): 1704, 1410, 1365, 1134 cm⁻¹. ¹H NMR (CCl₄, 80 MHz) (rotamers): δ 1.4 (s, 9H), 2.6 (m, 2H), 3.6 (d, *J* = 13 Hz, 1H), 3.7 (d, *J* = 13 Hz, 1H), 4.9 (br s, 1H), 6.4 (br s, 1H, H). MS: *m/z* (rel intens): 169(8) [M⁺], 113 (26), 96 (16), 69 (38), 68 (60), 57 (100), 41(88).

(5S)-1-(Benzyloxycarbonyl)-5-[(tert-butylidiphenylsilyloxy)methyl]-2-pyrrolidinone (13a). To a solution of *i*-Pr₂NH (0.53 mL, 3.7 mmol) in 4 mL of THF at -78 °C was slowly added 2.86 mL of 1.3 N BuLi (3.7 mmol). After 15 min, a solution of (S)-5-[(tert-butylidiphenylsilyloxy)methyl]-2-pyrrolidinone¹⁶ (1.200 g, 3.4 mmol) in 6.8 mL of THF was added to the LDA solution, followed by addition of benzyl chloroformate (0.66 mL, 3.7 mmol) 30 min later. After 2 h at -78 °C, saturated NH₄Cl (12 mL) was added to the reaction mixture and the cooling bath removed. Once at room temperature, the reaction mixture was extracted with EtOAc (3 $\times$ 5 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated in vacuo to provide an oily residue that was purified by flash column chromatography (SiO₂, EtOAc/hexane, 1:2) to afford 1.40 g (85% yield) of the carbobenzyloxy derivative **13a** as a viscous liquid. TLC: *R*_f = 0.49 (EtOAc/hexane, 1:2). FTIR (neat): 1789, 1751, 1716, 1294, 1110, 702 cm⁻¹; [α]_D²⁰ = -18.4 (c 2.08, EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 1.00 (s, 9H), 2.02–2.20 (m, 2H), 2.42 (ddd, 1H, *J* = 3.6, 8.3, 17.8 Hz), 2.79 (ddd, 1H, *J* = 10.4, 10.4, 17.8 Hz), 3.67 (dd, 1H, *J* = 2.5, 10.6 Hz), 3.86 (dd, 1H, *J* = 4.0, 10.6 Hz), 4.22 (m, 1H), 5.09 (d, 1H, *J* = 12.3 Hz), 5.16 (d, 1H, *J* = 12.3 Hz), 7.36 (m, 11H), 7.57 (m, 4H).

(5S)-[(tert-Butylidiphenylsilyloxy)methyl]-1-(methoxycarbonyl)-2-pyrrolidinone (13c). Prepared according to the procedure described above, using methyl chloroformate instead

(15) We adopted Grieco's procedure to attach the Boc protecting group (Boc₂O, DMAP, Et₃N CH₂Cl₂); see: Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424. Under these conditions the agent causing partial racemization is most probably Et₃N. Near the conclusion of this study we learned of another procedure to introduce the Boc group on pyroglutamic acid without racemization (Boc₂O, DMAP, CH₃CN): Coudert, E.; Acher, F.; Azerad, R. *Synthesis* **1997**, 863.

(16) (S)-Pyroglutamic acid was converted to (S)-5-(hydroxymethyl)-2-pyrrolidinone according to the procedure described in Saijo, S.; Wada, M.; Ishida, A.; Himizu, J.-I. *Chem. Pharm. Bull.* **1980**, *28*, 1449. The hydroxy group was then protected by standard procedures as described in Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Academic Press: London, 1988.

of benzyl chloroformate. After flash column chromatography (SiO₂, EtOAc/hexane, 1:1), the carbomethoxy derivative **13c** was obtained in 86% yield as a white solid. Mp = 125–127 °C. TLC: *R_f* = 0.36 (EtOAc/hexane, 1:1). FTIR (KBr): 1753, 1715, 1305, 1103, 700 cm⁻¹. [α]_D²⁰ = -25.0 (1.28, EtOAc). ¹H NMR (CDCl₃, 300 MHz): δ 1.05 (s, 9H), 2.14 (m, 2H), 2.47 (ddd, 1H, *J* = 3.5, 8.6, 17.8 Hz), 2.83 (ddd, 1H, *J* = 10.4, 10.4, 17.8 Hz), 3.73 (dd, 1H, *J* = 2.4, 10.8 Hz), 3.98 (dd, 1H, *J* = 3.8, 10.8 Hz), 4.27 (m, 1H), 7.41 (m, 6H), 7.62 (m, 4H). MS: *m/z* (rel intens) 354 (96) [M⁺ - *t*-Bu⁺], 213 (100), 183 (24), 135 (12), 105 (14), 91 (7), 77 (5).

Typical Procedures for the Reduction of the *N*-Acylpyrrolidinones Employing DIBAL-H to the Corresponding *N*-Acyl-2-hydroxypyrrolidines. Illustrated for the preparation of compounds **14a**.^{5a} To a solution of **13a** (0.884 g, 1.8 mmol) in 5.2 mL of THF at -78 °C was slowly added DIBAL-H (1 M solution in hexanes, 2.5 mL, 2.5 mmol). After the solution was stirred for 1 h, saturated NH₄Cl (6.5 mL) was added and the reaction warmed to room temperature. The mixture was then treated with 10% Na₂CO₃ (4.5 mL) and more 15 mL CH₂Cl₂ added. After 10 min the organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (4 × 10 mL). The combined organic extract was dried over anhydrous Na₂SO₄ and concentrated in vacuo. Flash column chromatography (SiO₂, Et₂O) of the residue afforded 0.858 g (97% yield) of **14a** as a homogeneous material by TLC (mixture of diastereomers). TLC: *R_f* = 0.27 (EtOAc/hexane, 1:3). FTIR (neat): 3494, 1687, 1423, 1113, 703 cm⁻¹. ¹H NMR (CCl₄, 300 MHz) (rotamers + diastereoisomers): δ 1.03 (s, 9H), 1.72–2.06 (m, 3H), 2.10–2.30 (m, 1H), 3.12 (br s, 0.2H), 3.40–3.50 (m, 0.2H), 3.50–3.80 (m, 1.6H), 3.80–4.00 (m, 2H), 4.81–4.98 (m, 1.5H), 5.09 (br s, 0.5H), 5.34–5.50 (m, 1H), 7.0–7.4 (m, 11H), 7.56 (m, 4H).

(2*S*)-1-(Benzoyloxycarbonyl)-2-[(*tert*-butyldiphenylsilyloxy)methyl]-4-pyrroline (15a**).** Using procedure A, 0.862 g of **14a** afforded 0.821 g (99% yield) of **15a** as a viscous liquid. *R_f* = 0.36 (EtOAc/hexane, 1:7). Chiral HPLC was performed on a Chiralcel OD column from Daicel Chemical Industries: retention time *t_r* = 12.20 min (0.2% 2-propanol in hexane) corresponding to an ee > 98%. Racemic **15a** was used as standard to give the following *t_r*: (S) 12.20 min; (R) 14.62 min. [α]_D²⁰ = -26.8 (c 0.71, hexane). IR (neat): 1707, 1417, 1113 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) (rotamers): δ 1.09 (s, 9H), 2.81 (br s, 0.7H), 2.86 (br s, 1.3H), 3.70–4.00 (m, 2H), 4.30 (br s, 0.5H), 4.39 (br s, 0.5H), 4.95–5.23 (m, 3H), 6.57 (br s, 0.5H), 6.65 (br s, 0.5H), 7.15–7.50 (m, 11H), 7.65–7.75 (m, 4H). ¹³C NMR (CDCl₃): δ 19.2 (C), 26.7 (CH₃), 32.1 (CH₂), 33.2 (CH₂), 57.8 (CH), 58.3 (CH), 63.5 (CH₂), 64.0 (CH₂), 66.8 (CH₂), 108.0 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 129.1 (CH), 129.7 (CH), 133.5 (C), 133.7 (C), 135.6 (CH), 135.7 (CH), 136.4 (C), 136.6 (C), 152.2 (C), 152.8 (C). MS: *m/z* (rel intens): 414 (20), 370 (40), 270 (10), 202 (25), 135 (10), 91 (100). Anal. Calcd for C₂₉H₃₃NO₃Si: C, 73.85; H, 7.06; N, 2.97. Found: C, 74.09; H, 7.05; N, 2.98.

(2*S*)-1-[(*tert*-Butyldiphenylsilyloxy)methyl]-1-(methoxycarbonyl)-4-pyrroline (15c**).** Applying procedure A, 0.775 g of **14c** provided 0.711 g (95% yield) of **15c** as a viscous liquid. *R_f* = 0.30 (EtOAc/hexane, 1:6). [α]_D²⁰ = -74.6 (c = 0.80, hexane). FTIR (neat): 1708, 1450, 1394, 1112 cm⁻¹. ¹H NMR (CCl₄, 300 MHz) (mixture of rotamers): δ 1.03 (s, 9H), 2.74 (br s, 0.9H), 2.79 (br s, 1.1H), 3.46 (br s, 1.3H), 3.63 (br s, 2.5H), 3.80 (br s, 2H), 4.15 (br s, 0.4H), 4.24 (br s, 0.6H), 4.90 (br s, 0.7H), 4.93 (br s, 0.3H), 6.38 (br s, 0.6H), 6.51 (br s, 0.4H), 7.30–7.35 (m, 6H), 7.52–7.63 (m, 4H). ¹³C NMR (CCl₄) (mixture of rotamers): δ 19.2 (C), 26.8 (CH₃), 32.2 (CH₂), 33.3 (CH₂), 51.9 (CH₃), 57.7 (CH), 58.1 (CH), 63.6 (CH₂), 64.1 (CH₂), 106.4 (CH), 106.8 (CH), 127.8 (CH), 129.8 (CH), 130.7 (CH), 133.7 (C), 135.7 (CH), 135.8 (CH), 152.0 (C). MS: *m/z* (rel intens) 338 (100), 213 (60), 183 (25), 135 (5), 105 (5). Anal. Calcd for C₂₃H₂₉NO₃Si: C, 69.84; H, 7.39; N, 3.54. Found: C, 69.64; H, 7.22; N, 3.48.

(2*S*,5*RS*)-1-(*tert*-Butoxycarbonyl)-5-hydroxy-2-(methoxycarbonyl)pyrrolidine (17b**).** A 0.416 g sample of **34b** afforded 0.354 g (84% yield) of **35b** as a viscous liquid after column chromatography (SiO₂, EtOAc/hexane, 1:2, *R_f* = 0.28

and 0.35 for the diastereomers).^{3c} IR (neat): 3454, 1744, 1700 cm⁻¹. ¹H NMR (CCl₄, 80 MHz) (mixture of diastereoisomers and rotamers): δ 1.4 (s, 9H), 1.8–2.4 (m, 4H), 3.6–3.8 (m, 3H), 3.8–4.3 (m, 2H), 5.5 (br s, 1H).

(2*S*,5*RS*)-1,2-Dimethyl-5-hydroxypyrrolidine-1,2-dicarboxylate (17c**).** TLC: *R_f* = 0.30 (30% EtOAc in hexane). IR (film): 3465, 1747, 1709, 1456, 1379, 1201, 1128, 1011 cm⁻¹. ¹H NMR (CDCl₃) (mixture of diastereomers plus rotamers): δ set of several closed signals at 5.68 (dd, *J* = 2.7 and 5.6 Hz), 5.60 (br d, *J* = 5.1 Hz), 5.56 (br d, *J* = 5.4 Hz), 5.49 (br d, *J* = 5.3 Hz) all integrating for 1H, two triplets at 4.44 (*J* = 14.2 Hz), and 4.41 (*J* = 13.8 Hz) integrating for 1H, a set of eight singlets at 3.77, 3.76, 3.73, 3.72, 3.71, 3.69, 3.67, and 3.66 integrating for 6H, 2.58–2.29 (m, 1H), 2.17–1.82 (m, 3H). ¹³C NMR (CDCl₃): δ 173.1 (C), 173.0 (C), 155.7 (C), 155.0 (C), 89.1 (CH), 88.9 (CH), 88.8 (CH), 82.6 (CH), 81.7 (CH), 59.2 (CH), 59.0 (CH), 58.9 (CH), 58.8 (CH), 58.7 (CH), 52.7 (CH₃), 52.5 (CH₃), 52.2 (CH₃), 52.1 (CH₃), 31.9 (CH₂), 31.8 (CH₂), 30.7 (CH₂), 30.3 (CH₂), 27.8 (CH₂), 26.7 (CH₂).

(5*S*)-*N*-(*tert*-Butoxycarbonyl)-5-(methoxycarbonyl)-2-pyrroline (18b**).**^{3c} Starting from (S)-pyrrolutamic acid, and employing procedure A, 0.158 g of **17b** yielded 0.115 g (78% yield) of **18b** as a viscous liquid. *R_f* = 0.34 (EtOAc/hexane, 1:5). [α]_D²⁰ = -64.7 (c = 0.79, MeOH). Lit.¹³ [α]_D²⁰ = -108 (c = 0.71, MeOH). Optical rotation for **18b** prepared as described in Scheme 2; [α]_D²⁰ = -102.0 (c = 0.89, CDCl₃). FTIR (neat): 1759, 1700, 1402, 1129 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) (mixture of rotamers): δ 1.43 (s, 5H), 1.48 (s, 4H), 2.62 (br d, *J* = 14.6 Hz and 0.5H), 2.68 (br d, *J* = 14.3 Hz, 0.5H), 3.01 (br d, *J* = 14.3 Hz, 0.5H), 3.10 (br d, *J* = 14.6 Hz, 0.5H), 4.58 (dd, *J* = 5.5 and 12.1 Hz, 0.5H), 4.66 (dd, *J* = 5.3 and 11.9 Hz, 0.5H), 4.91 (br s, 0.5H), 4.95 (br s, 0.5H), 6.51 (br s, 0.5H), 6.65 (br s, 0.5H). MS: *m/z* (rel intens): 227 (4), 127 (12), 68 (100), 57 (84), 41 (58). HRMS (EI): calcd for C₁₁H₁₇O₄N [M⁺] 227.1157, found: 227.1159.

(5*S*)-*N*-(Methoxycarbonyl)-5-(methoxycarbonyl)-2-pyrroline (18c**).**^{3f} [α]_D²⁰ = -180.6 (c 1.0, acetone). IR (film): 3114, 1755, 1712, 1624, 1454, 881, 762, 771 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 6.69 and 6.56 (two br s, 1H), 5.02 and 4.99 (two br s, 1H), 4.68 (dt, *J* = 5.0, 12.5 Hz, 1H), 3.77 and 3.72 (two s, 6H), 3.20–3.02 (m, 1H), 2.69 (br t, *J* = 12.5 Hz, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 172.3, 153.0, 130.2, 129.4, 106.3, 106.0, 57.9, 52.7, 52.3, 35.4, 34.0. MS: (*m/z*) (rel intens) 185 (51) [M⁺], 126 (100), 59 (37), 67 (38), 59 (37). HRMS (EI): calcd for C₈H₁₁NO₄ [M⁺] 185.0688, found 185.0590.

Preparation of (1*R*)-1-(2,4,6-Triisopropylphenyl)ethyl-2-oxo-1-pyrrolidinecarboxylate (19**).** A solution of (1*R*)-1-(2,4,6-triisopropylphenyl)ethyl-1*H*-1-imidazolecarboxylate (see preparation in the Supporting Information) in 3 mL of 2-pyrrolidinone was heated at 85 °C under nitrogen for 52 h. After this period the reaction mixture was cooled to room temperature followed by addition of 10 mL of ether and 5 mL of water. The resulting heterogeneous system was then stirred vigorously. Next, the phases were separated, and the organic layer was washed twice with water (2 × 2 mL). The organic layer was dried over MgSO₄ and the solvent evaporated in vacuo to give a residue which was flash chromatographed (10% EtOAc/hexane) to afford 168 mg (55% yield) of an oil corresponding to *N*-acyl lactam **19** and 73 mg (35%) of the starting carbonyl-imidazole. TLC: *R_f* = 0.25 (10% EtOAc/hexanes). [α]_D = 48.2 (c 1.1, EtOAc). FTIR (film, NaCl): 2960, 2931, 2870, 1790, 1759, 1712, 1608 cm⁻¹. ¹H NMR (CDCl₃): δ 7.02 (br s, 2H), 6.61 (q, *J* = 6.8 Hz, 1H), 3.81 (t, *J* = 7.1 Hz, 2H), 3.60 (br s, 2H), 2.86 (sept, *J* = 7.0 Hz, 1H), 2.51 (t, *J* = 8.2 Hz, 2H), 2.02 (quint, *J* = 7.6 Hz, 2H), 1.70 (d, *J* = 7.0 Hz, 3H), 1.30 (d, *J* = 7.0 Hz, 6H), 1.23 (t, *J* = 6.6 Hz, 12H). ¹³C NMR (CDCl₃): δ 174.4 (C), 151.3 (C), 148.6 (C), 146.2 (C), 131.6 (C), 123.1 (CH), 121.4 (CH), 70.7 (CH), 46.2 (CH₂), 33.9 (CH), 32.6 (CH₂), 29.0 (CH), 24.7 (CH₃), 23.7 (CH₃), 23.6 (CH₃), 22.0 (CH₃), 17.4 (CH₂).

(1*R*,2*RS*)-1-(2,4,6-Triisopropylphenyl)ethyl-2-hydroxy-1-pyrrolidinecarboxylate (20**).** FTIR (film, NaCl): 3440, 2956, 1684, 1606, 1417, 1384 cm⁻¹. ¹H NMR (CDCl₃) (mixture of epimers and rotamers): δ 7.03 (s, 2H), 6.52 (q, *J* = 6.8 Hz, 1H), 5.54 and 5.48 (two br s, 1H), 3.75–3.49 (m, 2H), 3.47–3.26 (m, 2H), 2.90–2.80 (m, 1H), 2.18–1.83 (m, 4H), 1.69–

1.53 (m, 3H), 1.31 (d, $J = 6.6$ Hz, 6H), 1.26–1.14 (m, 12H). ^{13}C NMR (CDCl_3): δ 155.6 (C), 154.1 (C), 148.2 (C), 132.6 (C), 132.4 (C), 129.0 (C), 123.1 (CH), 121.3 (CH), 82.1 (CH), 82.0 (CH), 81.1 (CH), 69.6, 69.3, 69.1, 46.0 (CH_2), 45.5 (CH_2), 33.9 (CH), 33.5 (CH), 32.4 (CH), 29.1 (CH_3), 29.0 (CH_3), 24.6 (CH_2), 23.7 (CH_2).

(1R)-1-(2,4,6-Triisopropylphenyl)ethyl-2,3-dihydro-1H-1-pyrrolicarboxylate (21). $[\alpha]_D^{20} = 2.8$ (c 1.3, hexanes). FTIR (film, NaCl): 2958, 2929, 2868, 1705, 1616 cm^{-1} . ^1H NMR (CDCl_3): δ 6.87 (s, 2H), 6.55–6.47 (m, 1H), 6.44–6.36 (m, 1H), 4.92 and 4.89 (two br s, 1H), 3.82–3.60 (m, 2H), 3.52 (br s, 2H), 2.79 (quint, $J = 7.0$ Hz, 1H), 2.69–2.52 (m, 2H), 1.58 and 1.50 (two close d, $J = 7.0$ Hz, 3H), 1.27 (d, $J = 6.6$ Hz, 6H), 1.21 and 1.13 (two d, $J = 7.0$ Hz, 12H). ^{13}C NMR (CDCl_3): δ 151.6 (C), 150.9 (C), 147.5 (C), 132.5 (C), 130.9 (CH), 129.6 (CH), 122.0 (CH), 106.8 (CH), 106.3 (CH), 76.8 (CH), 68.2 (CH), 45.1 (CH_2), 44.8 (CH_2), 44.5 (CH_2), 33.8 (CH), 32.0 (CH), 29.4 (CH_2), 28.7 (CH), 28.1 (CH_2), 24.5 (CH_3), 24.1 (CH_3), 23.8 (CH_3), 23.7 (CH_3), 22.1 (CH_3). MS: m/z (rel intens) 343 (6) [M^+], 231 (100), 230 (79), 215 (37), 147 (9). HRMS (EI): calcd for $\text{C}_{22}\text{H}_{33}\text{NO}_2$ [M^+] 343.2511, found 343.2514.

(1R,2SR)-2-Phenylcyclohexyl-2-oxo-1-pyrrolidincarboxylate (22). FTIR (film, NaCl): 2933, 1786, 1753, 1711, 1603, 1282 cm^{-1} . ^1H NMR (CDCl_3): δ 7.30–7.16 (m, 5H), 4.95 (dt, $J = 4.4$; 10.6 Hz, 1H), 3.62–3.54 (m, 1H), 3.38–3.30 (m, 1H), 2.74 (dt, $J = 3.5$; 11.6 Hz, 1H), 2.40 (t, $J = 8.1$ Hz, 2H), 2.30 (br s, 1H), 1.93–1.72 (m, 5H), 1.67–1.30 (m, 4H). ^{13}C NMR (CDCl_3): δ 174.4 (C), 150.9 (C), 143.0 (C), 128.4 (CH), 127.7 (CH), 126.7 (CH), 78.8 (CH), 49.5 (CH), 45.9 (CH_2), 33.4 (CH_2), 32.3 (CH_2), 32.0 (CH_2), 25.5 (CH_2), 24.4 (CH_2), 17.0 (CH_2).

(1R,2SR)-2-Phenylcyclohexyl-2-hydroxy-1-pyrrolidincarboxylate (23). FTIR (film, NaCl): 3435, 2933, 1693, 1603, 1417 cm^{-1} . ^1H NMR (CDCl_3) (mixture of epimers and rotamers): δ 7.37–7.14 (m, 5H), 5.33 and 5.23 (two br s, 1H), 4.86–4.71 (m, 1H), 3.54–3.09 (m, 2H), 2.94–2.63 (m, 2H), 2.43–2.05 (m, 1H), 1.96–1.69 (m, 6H), 1.62–1.26 (m, 5H). ^{13}C NMR (CDCl_3): δ 155.4 (C), 153.8 (C), 143.8 (C), 143.4 (C), 129.3 (CH), 128.4 (CH), 127.7 (CH), 127.2 (CH), 126.6 (CH), 126.4 (CH), 81.9 (CH), 81.7 (CH), 81.1 (CH), 80.7 (CH), 50.3 (CH), 50.1 (CH), 49.9 (CH), 45.7 (CH_2), 45.4 (CH_2), 45.1 (CH_2), 34.0 (CH_2), 33.7 (CH_2), 33.1 (CH_2), 32.8 (CH_2), 32.2 (CH_2), 25.7 (CH_2), 25.6 (CH_2), 24.6 (CH_2), 24.4 (CH_2), 22.3 (CH_2), 21.6 (CH_2).

(1R,2SR)-2-Phenylcyclohexyl-2,3-dihydroxy-1H-1-pyrrolicarboxylate (24). FTIR (film, NaCl): 3028, 2936, 2859, 1705, 1618 cm^{-1} . ^1H NMR (CDCl_3): δ 7.23–7.03 (m, 5H), 6.38 and 6.14 (two br s, 1H), 4.82 (sl) and 4.74 (dt, $J = 4.2$, 10.6 Hz) integrating for 2H, 3.59–3.48 (m) and 3.15–3.12 (m) integrating for 2H, 2.64–2.49 (m, 3H), 2.27–2.24 (m, 1H), 1.94–1.77 (m, 3H), 1.62–1.48 (m, 2H), 1.41–1.28 (m, 2H). ^{13}C NMR (CDCl_3): δ 151.7 (C), 143.5 (C), 130.9 (CH), 129.8 (CH), 128.5 (CH), 127.5 (CH), 126.5 (CH), 106.6 (CH), 106.4 (CH), 76.5 (CH), 50.0 (CH), 44.8 (CH_2), 44.4 (CH_2), 34.2 (CH_2), 32.8 (CH_2), 29.4 (CH_2), 28.3 (CH_2), 25.9 (CH_2), 24.7 (CH_2). MS: m/z (rel intens) 271 (53) [M^+], 227 (6), 159 (54), 117 (33), 91 (100). HRMS (EI): calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_2$ [M^+] 271.1572, found 271.1581.

(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl-2-oxo-1-pyrrolidincarboxylate (25). $[\alpha]_D^{20} = -51.6$ (c 2.3, EtOAc). FTIR (film, NaCl): 2956, 2922, 1786, 1755, 1707, 1599, 1298 cm^{-1} . ^1H NMR (CDCl_3): δ 7.32–7.22 (m, 4H), 7.20–7.09 (m, 1H), 4.94 (dt, $J = 4.5$; 10.8 Hz, 1H), 3.19 (dt, $J = 7.8$; 11.5 Hz, 1H), 2.55–2.47 (m, 1H), 2.35 (t, $J = 8.1$ Hz, 2H), 2.09 (dt, $J = 3.5$, 11.4 Hz, 1H), 1.92–1.81 (m, 2H), 1.79–1.67 (m, 3H), 1.51–1.42 (m, 1H), 1.35 (s, 3H), 1.28–0.82 (m, 3H), 1.19 (s, 3H), 0.88 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (CDCl_3): δ 174.4 (C), 152.4 (C), 150.2 (C), 128.0 (CH), 125.6 (CH), 124.8 (CH), 75.7 (CH), 50.4 (CH), 45.3 (CH_2), 41.8 (CH_2), 39.3 (C), 34.2 (CH_2), 32.4 (CH_2), 31.0 (CH), 29.5 (CH_3), 26.0 (CH_2), 22.6 (CH_3), 21.5 (CH_3), 16.9 (CH_2).

(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl-2-hydroxy-1-pyrrolidincarboxylate (26). FTIR (film, NaCl): 3435, 2954, 1693, 1599, 1415 cm^{-1} . ^1H NMR (CDCl_3) (mixture of rotamers and epimers): δ 7.35–7.21 (m, 4H), 7.17–7.11 (m, 1H), 5.40–5.03 (two s, 1H), 4.94–4.75 (m, 1H), 3.77; 3.65; 3.53 (three br s) together with 3.45–3.41 (m) integrating for 1H, 3.18–2.78 (m, 1H), 2.39–2.32 (m, 1H), 2.13–1.99 (m, 1H), 1.94–1.78 (m, 3H), 1.76–1.41 (m, 3H), 1.37 (s, 3H), 1.32–0.94 (m) overlapping with three s at 1.23, 1.22, and 1.19 for a total of 8H, 0.90–0.85 (m, 3H). ^{13}C NMR (CDCl_3) (mixture of rotamers and epimers): δ 154.6 (C), 153.0 (C), 152.7 (C), 152.2 (C), 128.0 (CH), 127.8 (CH), 127.7 (CH), 125.3 (CH), 125.2 (CH), 124.8 (CH), 124.7 (CH), 82.0 (CH), 81.9 (CH), 80.2 (CH), 74.9 (CH), 74.7 (CH), 50.9 (CH); 50.7 (CH), 45.7 (CH_2), 44.8 (CH_2), 44.7 (CH_2), 42.6 (CH_2), 42.5 (CH_2), 42.4 (CH_2), 39.6 (C), 39.4, 34.6 (CH_2), 33.0 (CH_2), 32.5 (CH_2), 32.4 (CH_2), 31.3 (CH), 30.2 (CH_2), 29.7 (CH_3), 29.4 (CH_3), 28.7 (CH_3), 28.4 (CH_3), 26.6 (CH_2), 26.5 (CH_2), 26.3 (CH_2), 24.6 (CH_3), 24.1 (CH_3), 22.6 (CH_2), 22.4 (CH_2), 21.9 (CH_3), 21.8 (CH_3).

(1R,2S,5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl-2,3-dihydro-1H-1-pyrrolicarboxylate (27). $[\alpha]_D^{20} = -25.4$ (c 1.1, hexanes). FTIR (film, NaCl): 2954, 2922, 1699, 1620, 1599, 1417 cm^{-1} . ^1H NMR (CDCl_3): δ 7.36–7.20 (m, 4H), 7.19–7.05 (m, 1H), 6.52 and 5.58 (two br s, 1H), 5.42–4.94 (m, 1H), 4.90–4.74 (m, 1H), 3.66–3.30 (m, 1H), 3.22–2.78 (m, 1H), 2.54–2.42 (m, 1H), 2.40–2.16 (m, 1H), 2.04–1.57 (m, 6H), 1.55–1.43 (m, 1H), 1.42–1.30 (m, 3H), 1.22 (br s, 3H), 1.18–0.94 (m, 2H), 1.02–0.82 (m, 3H). ^{13}C NMR (CDCl_3): δ 152.2 (C), 151.9 (C), 130.9 (C), 130.0 (C), 128.1 (CH), 128.0 (CH), 127.9 (CH), 125.5 (CH), 125.3 (CH), 125.1 (CH), 124.8 (CH), 106.1 (CH), 82.8 (CH), 74.1 (CH), 74.0 (CH), 73.7 (CH), 50.9 (CH), 44.5 (CH_2), 42.7 (CH_2), 43.3 (CH_2), 39.7 (C), 39.6 (C), 34.7 (CH_2), 31.3 (CH), 31.2 (CH), 28.7 (CH_3), 26.7 (CH_3), 26.6 (CH_3), 26.5 (CH_3), 22.0 (CH_3), 21.9 (CH_3). MS: m/z (rel intens) 327 (8) [M^+], 199 (6), 119 (69), 105 (100), 91 (42).

(RS)-1-(tert-butoxycarbonyl)-3-[1'-(tert-butoxycarbonyl)-2'-piperidinyl]-4,5,6,1-tetrahydropyridine (29). Using procedure D for the synthesis of endocyclic enecarbamates, 207 mg of the lactamol **8** afforded 171 mg (90% yield) of **29** after purification by flash column chromatography. TLC: $R_f = 0.32$ (EtOAc/hexane, 1:5). FTIR (neat): 1705, 1653, 1373, 1170, 1115 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) (mixture of rotamers): δ 6.80 (br s, 0.5H, H_2), 6.60 (br s, 0.5H, H_2), 4.74 (br s, 0.5H), 4.70 (br s, 0.5H), 3.96 (br s, 0.5H), 3.92 (br s, 0.5H), 3.51 (br m, 0.6H), 3.47 (br s, 1.4H), 2.76 (br d, $J = 13.2$ Hz, 0.5H), 2.67 (br d, $J = 13.7$ Hz, 0.5H), 2.08–1.72 (br m, 4H), 1.71–1.52 (m, 2H), 1.48 (s, 9.4H), 1.45 (s, 9.6H), 1.27 (br s, 1H), 0.86 (m, 2H). MS: m/z (rel intens) 366 (5) [M^+], 209 (61), 165 (20), 84 (20), 57 (100), 41 (88).

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Supporting Information Available: Characterization data of compounds **2a/b**, **8**, **9**, **11**, **12**, and **16b/c**, experimental procedures for the synthesis of **14a/c** (with NaBH_4), **17c** (hydrolysis of **31**), **22**, **25**, **28**, and **31**, and copies of ^1H and ^{13}C NMR spectra of compounds **3a/b**, **6**, **9**, **12**, **13a/c**, **15a/c**, **17c**, **18b/c**, **19**, **21**, **22**, **24**, **25**, **27–29**, and **31**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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