The Preparation and Intra- and Intermolecular Addition Reactions of Acyclic *N*-Acylimines: Application to the Synthesis of (±)-Sertraline

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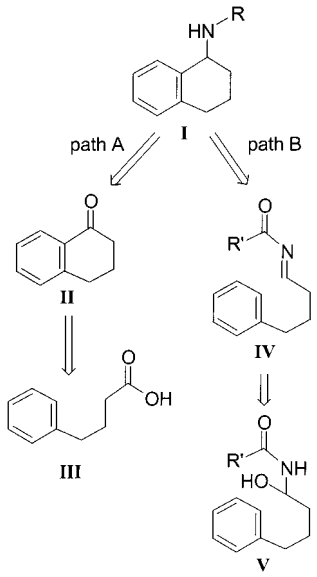
Intramolecular endo-cyclization reactions of *N*-acyliminium ions have seen wide application for the synthesis of heterocyclic compounds. The corresponding exocyclic variant, which would provide 1-aminotetralin derivatives, for example, has little precedent. We have discovered that acyclic *N*-acylcarbamates can be readily reduced to the corresponding *N*-acylhemiaminal derivatives in high yield using DIBAL as the reducing agent. These intermediates are remarkably stable and, if desired, can be purified and stored. The acyclic *N*-acylhemiaminals undergo both intra- and intermolecular nucleophilic addition reactions mediated by strong Lewis acids, such as $TiCl_4$. Diastereoselectivity, induced either by a substituent on the newly formed ring, or by utilizing a chiral ester on the carbamic acid, was disappointingly low. This methodology was successfully applied to the synthesis of the racemic form of the marketed antidepressant sertraline.

Introduction

Amino tetralins such as **I** are commonly found as a substructure in compounds of biological interest and as intermediates in the synthesis of natural products. This functional motif is most often prepared from the corresponding tetralones **II** (Scheme 1), which in turn are products of intramolecular Friedel−Crafts acylation reactions. Certain functionalized substrates are incompatible with the strong acids and elevated temperatures often required for Friedel−Crafts acylations. An alternate strategy for the synthesis of **I** was envisioned (path B) in which the amino tetralin is prepared in one step from an acylimine such as **IV**. Although the intramolecular endo cyclization of acylimines has been extensively explored (e.g., to provide *N*-acyltetrahydroquinoline derivatives),[1] the exocyclic variant has little precedent.[2] Herein, we report a novel method for the synthesis of acyclic *N*-acylimine precursors (**V**) and the inter- and intramolecular nucleophilic addition reactions thereof.

Scheme 1



Results and Discussion

The proposed synthetic sequence is outlined in Scheme 2. Literature methods for the preparation of acyclic *N*-acylimine precursors, such as **3,** include the degradation of amino acids with lead tetraacetate,[3] as well as electrochemical oxidation.[4] Newer methods for generating acylimine precursors have also appeared.[5] However, we explored an alternate general approach, namely the reduction of the acyl carbamates **2**.[6] Acyl carbamates were chosen to avoid regiochemical issues in the reduction. In addition, the products (**4**) would contain a

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(1) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(2) For examples of exocyclic imine ring closures, see: (a) Urban, F. J. *Tetrahedron Lett.* **1988**, *29*, 5493. (b) Ben-Ishai, D.; Sataty, I.; Peled, N.; Goldshare, R. *Tetrahedron* **1987**, *43*, 439. (c) Bosch, J.; Bonjoch, J.; Diez, A.; Linares, A.; Moral, M.; Rubiralta, M. *Tetrahedron* **1985**, *41*, 1753. (d) Katritzky, A. R.; Rachwal, B.; Rachwal, S. *J. Org. Chem.* **1995**, *60*, 3993. (e) Katritzky, A. R.; Rachwal, B.; Rachwal, S.; Abboud, K. A. *J. Org. Chem.* **1996**, *61*, 3117. (f) Padwa, A.; Brodney, M. A.; Marino, J. P., Jr.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78. (g) Dinsmore, C. J.; Zartman, C. B.; Baginsky, W. F.; O'Neill, T. J.; Koblan, K. S.; Chen, I.-W.; McLoughlin, D. A.; Olah, T. V.; Huff, J. R. *Organic Lett.* **2000**, *2*, 3473.

(3) Corcoran, R. C.; Green, J. M. *Tetrahedron Lett.* **1990**, *31*, 6827.

(4) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.

(5) (a) Johnson, A. P.; Luke, R. W. A.; Boa, A. N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 895. (b) Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997. (c) Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* **1996**, *37*, 3255. (d) Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970. (e) Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997. (f) Chao, W.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 9199.

(6) DeNinno, M. P.; Eller, C. *Tetrahedron Lett.* **1997**, *38*, 6545.

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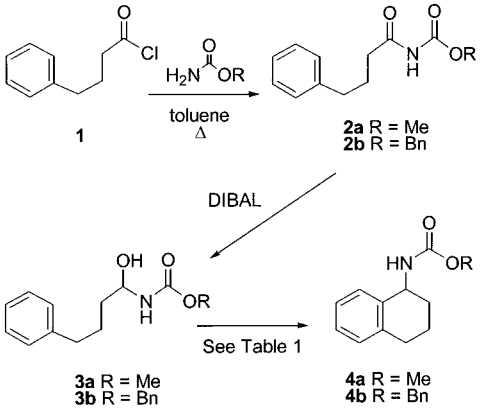
Published on Web 09/21/2001

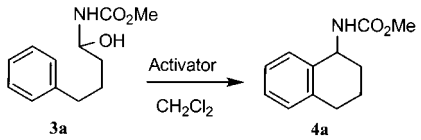
Scheme 2



carbamate-protected nitrogen that could undergo subsequent transformations. Although the reductive preparation of cyclic *N*-acylhemiaminals[7] has been widely used, the corresponding reaction in acyclic systems (e.g., **2** → **3**) had not been previously reported.[8] This lack of literature precedent raised concerns about the stability of such products and the viability of the approach. Nonetheless, the directness of this sequence outweighed these concerns and the route was investigated.

The acyl carbamates **2a** and **2b** were the first targets. They could be readily prepared[9] by reaction of methyl or benzyl carbamate with phenyl butyryl chloride (**1**) in toluene, and the products were isolated in high yield (90−95%) as crystalline solids. Although many reducing agents have been used successfully for the reduction of cyclic imides,[7] only DIBAL gave satisfactory results in the present system. Moreover, excess reducing agent (2.2 equiv) was required to ensure complete consumption of starting material, possibly due to the acidity of the imide NH. Under these conditions, **2a** and **2b** reduced cleanly at −78 °C in near-quantitative yield, thus removing the need for purification. Our initial concern about the stability of these products was unnecessary because the colorless solids **3a** and **3b** were stable for months at room temperature.[10] The cyclization of compound **3a** was now examined. Unlike the related endocyclization reactions, the choice of catalyst proved critical. The literature has shown that a wide variety of protic and Lewis acids can be effective in activating cyclic *N*-acylhemiaminals for the addition of carbon based nucleophiles.[1] In the present case, only strong Lewis acids were successful (Table 1). This difference may be attributed to the lower reactivity of the presumed *N*-acylimine intermediates as compared to the *N*-acyliminium ion intermediates in endocyclization reactions. From this survey, 1.5 equiv of $TiCl_4$ at −78 °C was chosen as optimal cyclization conditions, affording an 80% yield of product (**4a**). Reaction of **3b** under the identical conditions furnished **4b** in 78% yield. The use

Table 1. Survey of Various Activators for the Cyclization Reaction



entry	activator (equiv)	*T* (°C)	yield (%)
a	Tf_2O (1.0)	0 → 25	<5
b	CSA (0.1)	25	<5
c	TFA (2.0)	25	<5
d	$(^iPrO)_2TiCl_2$ (2.0)	0 → 25	<5
e	TFA (2.0)	−78 → 0	12
f	BF_3OEt_2 (2.0)	−60	55
g	$TiCl_4$ (0.5)	−78	15
h	$TiCl_4$ (1.0)	−78	25
i	$TiCl_4$ (1.5)	−78	80

of fewer equivalents of $TiCl_4$ resulted in a much slower reaction and incomplete conversion of starting material. A number of other substrates were investigated, and the results are displayed in Table 2. Generally, the overall yields for the reduction−cyclization sequence were very good (>75%). The reaction times varied on the basis of the reactivity of the aryl ring. For products **4e** and **4f**, $BF_3{\cdot}OEt_2$ proved to give higher yields due to the precipitation of a presumed catalyst-substrate complex when $TiCl_4$ was used. Exploring the formation of alternate ring sizes proved interesting. The seven membered rings **4i** and **4j** could be produced in moderate yields; however, the five-membered ring **4h** would not form even under more forcing conditions. This result is in contrast with intramolecular Friedel−Crafts acylation reactions in which five-membered rings are quite readily prepared.[11]

The phenyl-substituted analogues **5a** and **5b** were prepared and subjected to the standard two-step protocol (Scheme 3) to explore the diastereoselectivity of the cyclization reaction. The products (**7**) were isolated in good yields as 1:1 mixtures of isomers. This lack of selectivity was unexpected based on the literature reports of similar ring closures.[12] These results, combined with the inability to form the five-membered ring, suggested a possible nonobvious mechanism of ring closure. One unlikely but easily tested mechanism involves the direct displacement of a $TiCl_4$-complexed hemiaminal, without passing through an acylimine precursor. To rule out this possibility, the 1:1 mixture of diastereomers **6a** were separated by silica gel chromatography and individually subjected to the cyclization conditions. Both isomers produced the same 1:1 mixture of products, ruling out this pathway. The stability of the *N*-acylhemiaminals to chromatography and lack of subsequent isomerization are noteworthy. Another possible mechanism would involve an initial ipso attack on the aromatic ring followed by bond migration and rearomatization. Although we have not seen direct evidence for this pathway in any of the examples run thus far, additional experiments are planned to directly address this question.

Several strategies were envisioned for the synthesis of enantiomerically enriched products. One attractive

(7) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(8) Concurrent with our earlier work,[6] Fisher et al. reported on the reduction of N-acyl dihydroisoquinolone derivatives: Fisher, M. J.; Gunn, B. P.; Um, S.; Jakubowski, J. A. *Tetrahedron Lett.* **1997**, *38*, 5747.

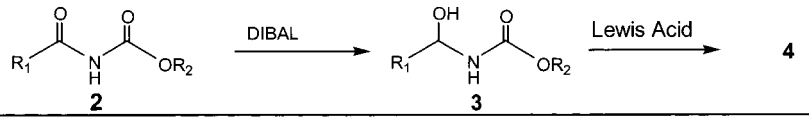
(9) See, for example: (a) Ben-Ishai, D.; Katchalski, E. *J. Org. Chem.* **1951**, *16*, 1025. (b) Atanassova, I. A.; Petrov, J. S.; Ognjanova, V. H.; Mollov, N. M. *Synth. Commun.* **1990**, *20*, 2083. (c) Pöpel, W.; Laban, G.; Faust, G.; Dietz, G. *Pharmazie* **1980**, *35*, 266.

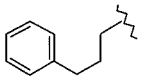
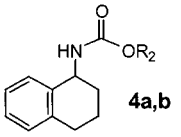
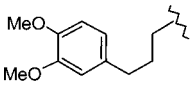
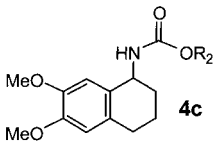
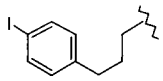
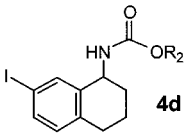
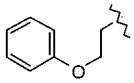
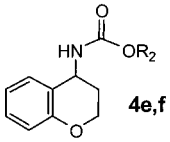
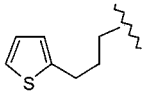
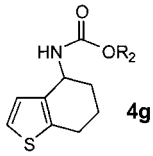
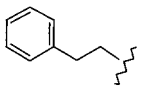
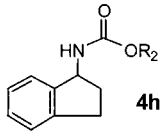
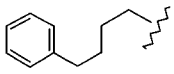
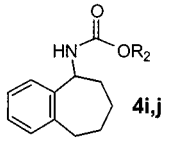
(10) An X-ray crystal structure of an analogue of **3a** (compound **10**) did not lend any insight as to the reason for this stability (e.g., intramolecular hydrogen bonding).

(11) (a) Olah, G. Ed. *Friedel−Crafts and Related Reactions*; Interscience Publishers: New York, 1964, Vol. III. (b) Snyder, H. R.; Werber, F. X. *J. Am. Chem. Soc.* **1950**, *72*, 2965.

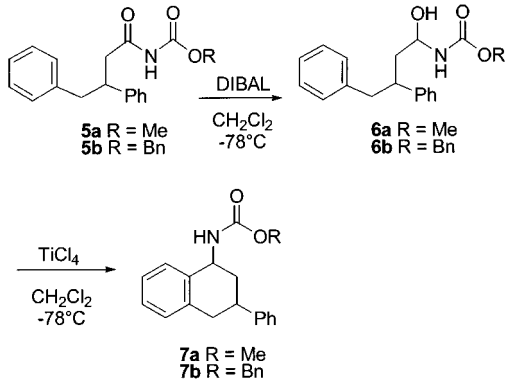
(12) (a) Katritzky, A. R.; Rachwal, B.; Rachwal, S. *J. Org. Chem.* **1995**, *60*, 7631. (b) Kuznet, V. V.; Aliev, A. E.; Prostakov, N. S. *Chem. Heterocycl. Compd. (Engl. Trans.)* **1994**, *30*, 64. (c) Talukdar, S.; Chen, C.-T.; Fang, J.-M. *J. Org. Chem.* **2000**, *65*, 3148.

Table 2



Entry	R_1	R_2	Lewis Acid (1.5 equiv)	Time	Overall Yield	Product
a		Me	$TiCl_4$	1 h	83 %	 **4a,b**
b	"	Bn	$TiCl_4$	1 h	80 %	
c		Me	$TiCl_4$	15 min	79 %	 **4c**
d		Bn	$TiCl_4$	2 h	84 %	 **4d**
e		Me	BF_3OEt_2	40 min	76 %	 **4e,f**
f	"	Bn	BF_3OEt_2	40 min	86 %	
g		Bn	$TiCl_4$	1 h	81 %	 **4g**
h		Me	$TiCl_4$	4 h	0 %	 **4h**
i		Me	$TiCl_4$	2 h	38 %	 **4i,j**
j	"	Bn	$TiCl_4$	2 h	39 %	

Scheme 3



approach would be to use a chiral Lewis acid, a strategy that has been successfully applied to numerous systems.[13] Unfortunately, the generally less active chiral catalysts are not strong enough to promote ring closure. Therefore, a chiral auxiliary based approach was investigated. The acyl carbamates **8** were prepared from three chiral alcohols. After reduction and cyclization with $BF_3{\cdot}OEt_2$, the products were analyzed by HPLC. The best result was realized with the (1*R*,2*S*)-2-phenylcyclohexanol auxiliary (**8c**), which furnished the product with a disappointing 40% de. Employing $TiCl_4$ as catalyst led to diminished diastereoselectivity (Table 3).

To expand the utility of this methodology, we examined the intermolecular variant as well.[14] The results are summarized in Table 4. It was optimal to use a several-fold excess of the nucleophile in the reactions and the yields were generally good. Care must be taken with the use of electron-rich nucleophiles (e.g., thiophene) to avoid

(13) For a recent example of a Ti-catalyzed enantioselective addition of TMSCN to unactivated imines, see: Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284.

(14) (a) Zaugg, H. E. *Synthesis* **1984**, 85. (b) Zaugg, H. E. *Synthesis* **1984**, 181.

Table 3

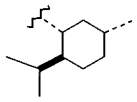
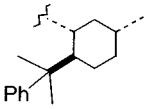
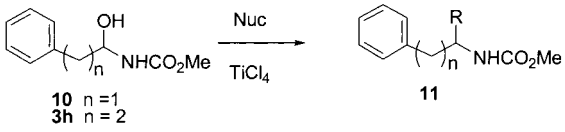
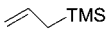
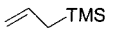
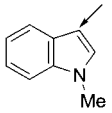
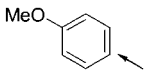
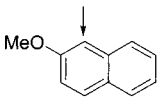
Entry	R	Yield	de
a		65%	0%
b		73%	25%
c		70%	40% 11% ($TiCl_4$)

Table 4. Intermolecular Nucleophilic Addition Reactions



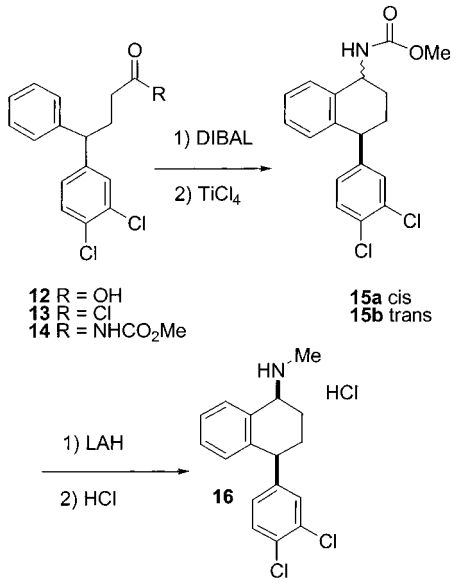
Entry	n	Nuc	Yield
a	2		72%
b	1		80%
c	2		68%[a]
d	2		78%[a]
e	1		77%[b]
f	2		68%[a]

[a] The designated position represents the only isomer formed. [b] An additional 5% of the ortho isomer was produced.

reionization of the product and the addition of a second equivalent of the nucleophile. In these cases, a short reaction time (e.g., 15 min) was the key for obtaining useful yields of the monoadducts.

We have applied the acyl imine cyclization methodology to the synthesis of (±)-sertraline. The acid **12**,[15] prepared for an earlier process route to the molecule, was converted to the acyl carbamate **14** in 88% yield. Reduction with DIBAL and cyclization promoted by $TiCl_4$ afforded a 2:1 mixture of cis (**15a**) and trans (**15b**) isomers in a combined 89% yield (Scheme 4). As expected, the closure occurred exclusively on the unsubstituted aryl

Scheme 4



ring. The desired cis product **15a** could be readily separated by column chromatography and was reduced with LAH in THF. Isolation of the product as the hydrochloride salt furnished pure (±)-sertraline **16** in 95% yield, which was identical spectroscopically and chromatographically to an authentic sample of (+)-sertraline.[16]

A new and general method for the generation of acyclic *N*-acylhemiaminals has been established. These remarkably stable intermediates are versatile precursors to *N*-acylimines, which undergo inter- and intramolecular nucleophilic addition reactions to furnish a number of synthetically useful products. This methodology was applied to the synthesis of (±)-sertraline. Several unusual results in this work have brought into question the precise mechanism of the intramolecular exocyclization reaction. Determination of this pathway remains an active goal.

Experimental Section

(4-Phenylbutyryl)carbamic Acid Methyl Ester (2a). Methyl carbamate (2.0 g, 0.0266 mol) was added to a solution of **1** (2.5 g, 0.0137 mol) in dry toluene (5 mL) at room temperature. The mixture was heated to 80 °C for 6 h, cooled, diluted with ethyl acetate (75 mL), and washed with water (2×) and brine (1×), dried, Na_2SO_4, filtered, and concentrated. The product was crystallized from ethyl acetate/hexanes to afford 2.85 g of **2a** as a colorless solid (94% yield). Mp: 121.5−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.5 (bs, 1H); 7.25 (m, 2H); 7.19 (m, 3H); 3.78 (s, 3H); 2.8 (m, 2H); 2.7 (m, 2H); 2.0 (m, 2H). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.46; H, 6.99; N, 6.47.

(4-Phenylbutyryl)carbamic Acid Benzyl Ester (2b). The procedure for the synthesis of the benzyl esters is the same as for the methyl esters, except that chromatography is usually required to separate the product from the excess benzyl carbamate. Mp: 105−106 °C. MS: 298 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.4 (bs, 1H); 7.38−7.1 (m, 10H); 5.12 (s, 2H); 2.78 (t, 2H, J = 7.3 Hz); 2.64 (t, 2H, 7.4 Hz); 1.95 (m, 2H). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.73; H, 6.47; N, 4.77.

(1,2,3,4-Tetrahydronaphthalen-1-yl)carbamic Acid Methyl Ester (4a). Step 1. A solution of diisobutylaluminum

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hydride (1.5 M in toluene, 1.7 mL, 2.5 mmol) was added to a stirred solution of compound **2a** (250 mg, 1.13 mmol) in CH_2Cl_2 (5 mL) at −78 °C. After 1.5 h, the reaction was quenched with methanol (0.5 mL), and the dry ice bath was removed. Florisil (4 g) was added followed by saturated aqueous NaCl (0.5 mL), and the mixture was diluted with ethyl acetate (10 mL). After the mixture was stirred for 15 min, $MgSO_4$ was added (4 g), and the mixture was stirred for 15 min. The mixture was filtered through sintered-glass and the solids were washed thoroughly with EtOAc. The filtrate was concentrated in vacuo to provide the hemiaminal **3a** as a colorless solid. This product was used directly in the next reaction.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (m, 2H); 7.18 (m, 3H); 5.4 (bd, 1H); 5.19 (bs, 1H); 3.78 (m, 1H); 3.64 (s, 3H); 2.6 (m, 2H); 1.8−1.5 (m, 4H). MS: 206 $(M - OH)^+$.

Step 2. The crude hemiaminal **3a** (1.13 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to −78 °C. Titanium tetrachloride (1 M solution in CH_2Cl_2, 1.7 mL, 1.7 mmol) was added and the mixture stirred for 1 h. The cold reaction mixture was poured into a stirred aqueous solution of $NaHCO_3$. The mixture was extracted with EtOAc (2×), the combined extracts were washed with brine, dried (Na_2SO_4), and filtered, and the filtrate was concentrated in vacuo. The product was purified by flash chromatography (20% EtOAc/hexanes) to afford 186 mg of compound **4a** (80%) as a colorless crystalline solid. Mp: 76−77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (m, 4H); 4.90 (bs, 1H); 3.65 (s, 3H); 2.75 (m, 2H); 2.0 (m, 1H); 1.8 (m, 4H). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.61; H, 7.37; N, 6.88.

(3,4-Diphenylbutyryl)carbamic Acid Methyl Ester (5a). Methyl carbamate (1.74 g, 23 mmol) was added to a solution of 3,4-diphenylbutyryl chloride (2 g, 7.7 mmol, prepared from the corresponding acid[17] in toluene. The mixture was heated at 80 °C for 6 h. The mixture was cooled, diluted with ethyl acetate (75 mL), washed with water (2×) and brine (1×), dried with Na_2SO_4, filtered, and concentrated. The product was crystallized from ethyl acetate/hexanes to afford 1.8 g of compound **5a** as a colorless solid (80% yield). Mp: 100−101 °C. MS: 298 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.2 (m, 8H); 7.03 (m, 2H); 3.73 (s, 3H); 3.52 (m, 1H); 3.22 (dd, 1H, J = 8.7, 17 Hz); 3.02 (dd, 1H, J = 6.3, 17 Hz); 2.95 (m, 2H). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.76; H, 6.36; N, 4.60.

(3,4-Diphenylbutyryl)carbamic Acid Benzyl Ester (5b). Mp: 79−81 °C. MS: 374 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 4H); 7.2 (m, 9H); 7.02 (m, 2H); 5.12 (s, 2H); 3.5 (m, 1H); 3.22 (dd, 1H, J = 8.5, 17 Hz); 3.03 (dd, 1H, J = 6.2, 17 Hz); 2.92 (m, 2H). Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.14; H, 6.14; N, 3.65.

(3-Phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)carbamic Acid Methyl Ester (7a). Compound **5a** was converted to compound **7a** by the general procedure described for compound **4a**. The crude product was purified by flash chromatography (5% EtOAc/hexanes) to afford an inseparable 1:1 mixture of diastereomers in 76% yield. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.56; H, 6.98; N, 4.98.

(3-Phenyl-1,2,3,4-tetrahydronaphthalen-1-yl)carbamic Acid Benzyl Ester (7b). Compound **5b** was converted to compound **7b** by the general procedure described for compound **4a**. The crude product was purified by flash chromatography (10% EtOAc/hexanes) to afford an inseparable 1:1 mixture of diastereomers in 80% yield. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.65; H, 6.53; N, 3.84.

(3-Phenoxypropionyl)carbamic acid (1*R*,2*S*)-2-Phenylcyclohex-1-yl Ester (8c). Carbamic acid (1*R*,2*S*)-2-phenylcyclohex-1-yl ester[18] (1.78 g, 8.1 mmol) was added to a solution of 3-phenoxyproprionyl chloride (1.0 g, 5.4 mmol) in dry toluene (5 mL), and the mixture was heated to reflux temperature. After 6 h, the mixture was cooled, diluted with EtOAc (30 mL), washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography (20% EtOAc/hexanes) to afford 1.85 g of **8c** (93%) as a waxy solid. Mp: 72−74 °C. MS: 368 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.3 (m, 5H); 7.2 (m, 3H); 6.95 (m, 1H); 6.85 (m, 2H); 4.90 (m, 1H); 4.20 (d, 2H, J = 8.1 Hz); 3.02 (m, 2H); 2.2 (m, 1H); 1.95 (m, 2H); 1.9 (m, 1H); 1.6−1.3 (m, 5H). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.63; H, 6.80; N, 3.97.

Chroman-4-ylcarbamic Acid (−)-Menthyl Ester (9a). Compound **8b** was reduced and cyclized (using $BF_3{\cdot}OEt_2$) as described for compound **2a**. The product was analyzed by chiral HPLC (Chiralpak AD column, 10% EtOH/hexanes with 0.1% DEA mobile phase) and shown to be a 1:1 mixture of diastereomers. MS: 330 $(M + H)^+$.

(1-Phenethylbut-3-enyl)carbamic Acid Methyl Ester (11a). Compound **2h** (200 mg, 0.97 mmol) was reduced with DIBAL as described previously for compound **2a**. The crude product was dissolved in CH_2Cl_2 (5 mL), and allyl trimethylsilane (0.5 mL, 2.9 mmol) was added. The mixture was cooled to −78 °C and treated with $TiCl_4$ (1.45 mL of a 1 M solution in CH_2Cl_2, 1.45 mmol). After 1 h, the mixture was poured into $NaHCO_3$ solution and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (15% EtOAc/hexanes) afforded 154 mg (68%) of **11a** as a colorless solid. Mp: 42−43 °C. MS: 234 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.2 (m, 5H); 5.78 (m, 1H); 5.02 (m, 2H); 4.5 (bs, 1H); 3.74 (bs, 1H); 3.61 (s, 3H); 2.62 (m, 2H); 2.22 (m, 2H); 1.82−1.6 (m, 2H). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.83; H, 7.99; N, 5.61.

[4-(3,4-Dichlorophenyl)-4-phenylbutyryl]carbamic Acid Methyl Ester (14). Oxalyl chloride (850 uL, 9.75 mmol) was added to a solution of 4-(3,4-dichlorophenyl)-4-phenylbutyric acid (2 g, 6.5 mmol) in CH_2Cl_2 (15 mL) at 0 °C. Two drops of DMF were added, and the mixture was allowed to warm to ambient temperature at which time vigorous evolution of gas commenced. After 6 h, the mixture was concentrated in vacuo and reconcentrated from toluene 2×. The residue was dissolved in toluene (10 mL) and treated with methyl carbamate (2.4 g, 32.5 mmol). The mixture was heated at 100 °C for 8 h, cooled, diluted with ethyl acetate, washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. The product was crystallized from EtOAc/hexanes to afford 2 g of **14** (85%) as a colorless solid. Mp: 140−141 °C. MS: 366 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.4−7.2 (m, 7H); 7.14 (dd, 1H, J = 2.1, 8.5 Hz); 3.97 (t, 1H, J = 7.9 Hz); 3.73 (s, 3H); 2.72 (m, 2H); 2.39 (m, 2H). Anal. Calcd for $C_{18}H_{17}Cl_2NO_3$: C, 59.03; H, 4.68; N, 3.82. Found: C, 59.32; H, 4.75; N, 3.82.

[4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl]carbamic Acid Methyl Ester (15). DIBAL (2.0 mL of a 1.5 M solution in toluene, 3 mmol) was added to a solution of **14** (0.5 g, 1.37 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After 2 h, the reaction was quenched with methanol (1 mL), and the dry ice bath was removed. Florisil was added, and the mixture was diluted with ethyl acetate (30 mL). Saturated NaCl solution was added (1 mL) and the mixture stirred for 20 min. The mixture was dried ($MgSO_4$), filtered, and concentrated. The crude product was dissolved in CH_2Cl_2 (10 mL) and treated with $TiCl_4$ (2.7 mL of a 1 M solution in CH_2Cl_2, 2.7 mmol) at −78 °C. After 1 h, the mixture was poured into vigorously stirred aqueous $NaHCO_3$ solution. The mixture was extracted with ethyl acetate (2×), and the combined extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (20% EtOAc/hexanes) afforded two products in a combined 87% overall yield.

High R_f Cis Isomer **(15a)**. Yield: 55%. Mp: 170.5−172 °C. MS: 350 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (m, 2H); 7.2 (m, 1H); 7.15 (m, 2H); 6.9 (d, 1H, J = 8.1 Hz); 6.8 (d, 1H, J = 8.1 Hz); 4.95 (m, 2H); 4.0 (m, 1H); 3.7 (s, 3H); 2.12 (m, 1H); 1.9 (m, 3H). Anal. Calcd for $C_{18}H_{17}Cl_2NO_2$: C, 61.73; H, 4.89; N, 4.00. Found: C, 61.84; H, 5.03; N, 3.90.

Low R_f Trans Isomer **(15b)**. Yield: 32%. Mp: 131−134 °C. MS: 350 $(M + H)^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, 1H,

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J = 7.9 Hz); 7.36 (d, 1H, J = 7.9 Hz); 7.22 (m, 1H); 7.18 (m, 2H); 6.88 (dd, 1H, J = 2, 8.3 Hz); 6.80 (d, 1H, J = 7.9 Hz); 5.02 (m, 1H); 4.91 (m, 1H); 4.1 (m, 1H); 3.70 (s, 3H); 2.2 (m, 2H); 1.85 (m, 1H); 1.75 (m, 1H). Anal. Calcd for $C_{18}H_{17}Cl_2NO_2$: C, 61.73; H, 4.89; N, 4.00. Found: C, 61.94; H, 4.95; N, 4.08.

[4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydronaphthalen-1-yl]methylamine (16) ((±)-Sertraline). LAH (22 mg, 0.57 mmol) was added to a solution of **15a** (100 mg, 0.29 mmol) in THF (3 mL) at rt. The mixture was heated at 70 °C for 1 h, cooled, and quenched by the sequential addition of water (22 μL), 15% NaOH (22 μL), and water (66 μL). The mixture was diluted with ether, dried with $MgSO_4$, filtered, and concentrated. The residue was dissolved in ether and treated with a solution of HCl in ether. The precipitate was filtered, washed with ether, and dried to afford 94 mg (96%) of product as a colorless solid. The chromatographic and spectral properties of **16** were identical to those of an authentic sample of (+)-sertraline. MS: 306 $(M + H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.22 (bs, 2H); 7.58 (m, 3H); 7.22 (m, 3H); 6.70 (d, 1H, J = 8.0 Hz); 4.39 (bs, 1H); 4.1 (m, 1H); 2.6 (s, 3H); 2.19 (m, 1H); 1.98 (m, 3H).

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Supporting Information Available: Spectral and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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