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A Highly Stereoselective Synthesis of Carbamate Protected *anti*-1,2-Aminoalcohols

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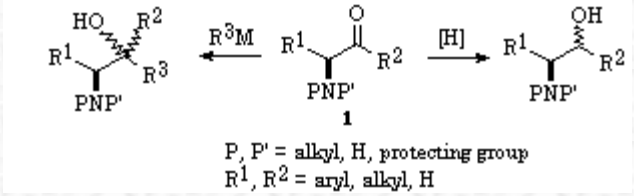
1,2-Amino alcohols are important and versatile synthetic intermediates for the preparation of a wide variety of natural products, drugs, and metal-binding ligands [1]. Consequently the development of synthetic methods for their preparation in a stereocontrolled manner has received significant attention for quite some time. In general, the hydroxyl group of the amino alcohol is installed either by the addition of an organometallic reagent to an aminocarbonyl compound **1** or by the reduction of an amino ketone **1** (R_2 not H) (Scheme 1) [2]. Moreover stereochemical control is good for either strategy when the amino group is a primary, secondary, or tertiary amine **1** (P, P'= alkyl, H), which is the most common class of amine used in these reactions [2].

Scheme 1

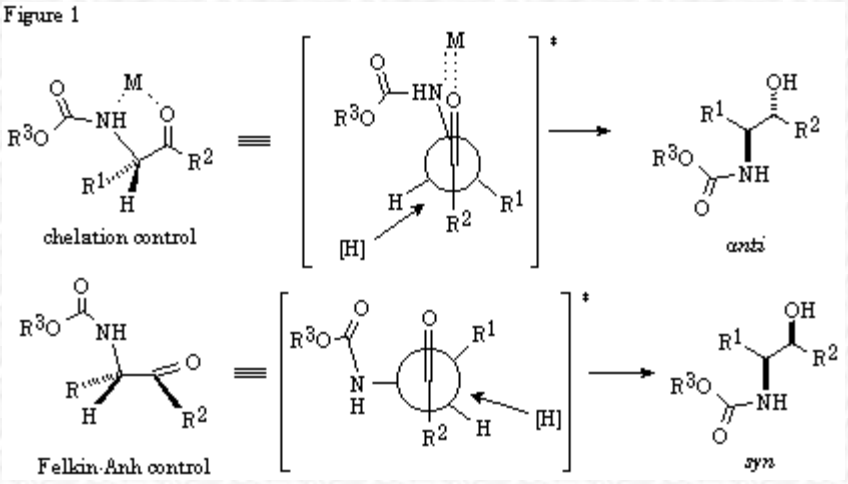


P, P' = alkyl, H, protecting group
R^1, R^2 = aryl, alkyl, H

In contrast, many syntheses of aminoalcohols from carbamate-protected aminocarbonyl compounds utilize the reduction of aminoketones **1** (R2= alkyl, aryl, P=carbamate group, P'= alkyl, H) and stereocontrol is unpredictable, relatively poor (diastereomer ratios commonly 2-6 : 1), and very poorly understood.2

There are two modes of stereocontrol that determine the major diastereomer. Chelation control enforces a *syn*-periplanar relationship between the amine and ketone groups and leads to the *anti*-diastereomer, whereas Felkin-Anh control, which utilizes a dihedral angle of about 90° between the amine and ketone groups to minimize stereoelectronic interactions, leads to the *syn*-diastereomer (Figure 1).

Figure 1

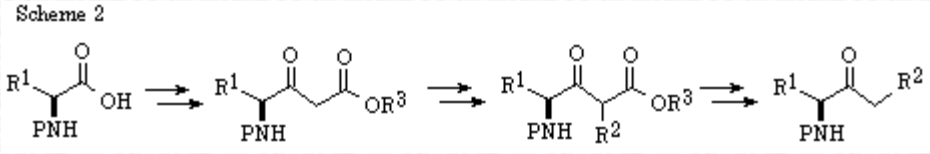


Examination of the literature reveals that there is no general method for the reduction of carbamate-protected amino ketones with predictable diastereoselection, and, in fact, contradictory results are the rule rather than the exception. For example, Fabio et al reported on the reduction of Boc-protected aminoketones with sodium borohydride in methanol, which had *anti*-diastereoselectivities ranging from 3 : 1 to 32 : 1. There was no obvious correlation between the substrate structure and the diastereoselectivity and other experiments led the authors to conclude that the reduction is "not markedly affected by the reducing agent or solvent" [3]. In contrast, Koskinen and Findland concluded that "solvent effects and reagent size are very important" effects on stereoselection in the reduction of a series of Boc-protected unsaturated aminoketones [4]. *Anti*-selectivity ranged from 6 : 1 to 1:4 for various reducing agents, and sodium borohydride was found to give the *syn* isomer selectively (3:1)!

The most common way to choose a reducing agent for carbamate-protected aminoketones is to prepare the aminoketone substrate and then screen 6-8 reducing agents to find the one which gives the highest diastereoselectivity. In the elegant synthesis of statine from leucine reported by Joullie, potassium borohydride gave a 10 : 1 *anti*-diastereoselectivity for the reduction of a Cbz-protected g-amino-b-ketoester and was clearly superior to other reductants examined [5]. More recently Dondoni prepared a Boc-protected acetylenic aminoketone during a sphingosine synthesis and screened eight reducing agents before finding that L-Selectride gives a 19:1 ratio of the *anti* product. (Normally L-Selectride gives Felkin-Anh selectivity.) These and many other studies clearly highlight the need for a general reduction protocol that is selective and predictable.

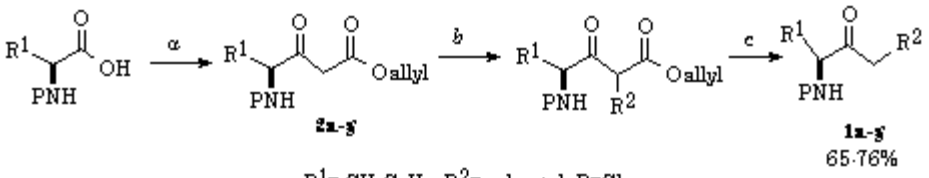
We had earlier developed a very simple and direct method for preparing N-carbamate-protected amino ketones with widely varying structures (Scheme 2). This methodolgy is very effective in the production of peptidomimetics [7] and sphingosines [8], but it also is a superior method for almost any aminoketone.

Scheme 2



Using this method, a series of seven carbamate-protected aminoketones **1a-g** were prepared via b-ketoesters **2a-g.** (Scheme 3). Noteworthy is that the method is compatible with a variety of functional groups and carbamate protecting groups. Surprizingly even the Fmoc-group of **1f** appears to pose no problem.

Scheme 3



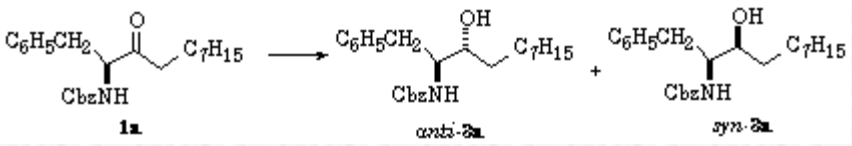
2a-g **1a-g** 65-76%

a. R^1= $CH_2C_6H_5$, R^2= n-heptyl, P=Cbz
b. R^1= $CH_2C_6H_5$, R^2= $CH_2C_6H_5$, P=Boc
c. R^1= CH_3, R^2= $(CH_2)_2C_6H_5$, P=Boc
d. R^1= $(CH_2)_4NHCbz$, R^2= $CH_2C_6H_5$, P=Boc
e. R^1= $CH_2CH=(CH_3)_2$, R^2= $(CH_2)_2C_6H_5$, P=Boc
f. R^1= $CH_2C_6H_5$, R^2= n-heptyl, P=Fmoc
g. R^1= $(CH_2)CO_2Me$, R^2= $CH_2CH=(CH_3)_2$, P=Boc

a. i. CDI *ii.* CH_3CO_2allyl/LDA. *b. i.* NaH *ii.* R^2OTf or R^2Br (for benzylic or allylic).
c. $Pd(PPH_3)_4$, $NH_4^+HCO_2^-$

Next amino ketone **1a** was reduced to *syn*- and *anti*-**3** with a variety of reducing agents and conditions that have been reported in the literature for the reduction of various carbamate-protected amino ketones. A selection of that data appears in Table 1. From these results several conclusions about the reduction can be reached. First, the reduction is very efficient for all the reducing agents as the yields, albeit crude, are very high. The crude product was nearly pure, since only trace amounts of contaminants could be detected.

Table 1. The Reduction of **1a** with Various Reducing Agents/ Conditions



1a *anti*-**3a** *syn*-**3a**

Entry	Reagent	Conditions	Yield (% crude)	*anti :syn*
1.	$NaBH_4$	EtOH, -78°C	98	7 : 1
2.	$LiBH_4$	EtOH, -78°C	97	7 : 1
3.	KBH_4	EtOH, -78°C	98	7 : 1
4.	$Me_4N^+BH_4$	EtOH, -78°C	97	7 : 1
5.	$NaBH_4$/ $CeCl_3$	EtOH, -78°C	97	7 : 1

6.	$Zn(BH_4)_2$	THF, -78 - 0°C	95	2 : 1
7.	$Zn(BH_4)_2$	ether, -78-0°C	94	1 : 2
8.	L-Selectride	THF, -78°C	91	1 : 9
9.	N-Selectride	THF, -78°C	93	1 : 9
10.	$LiAl(OtBu)_3H$	THF, -78- -20°C	95	1 : 1
11.	$LiAl(OtBu)_3H$	EtOH, -78°C	98	>95 : 5[a]

[a]Only one diastereomer could be observed in the nmr spectrum of the crude product.

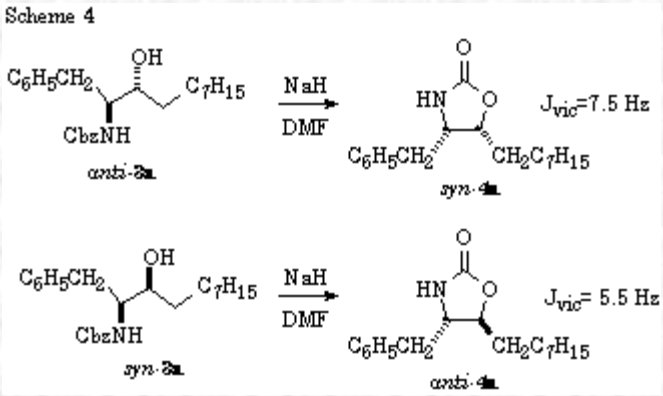
Second, borohydride reagents in alcohol solvents give chelation controlled reduction, but the chelating center must be the boron atom and not the metal. Identical results are found (Entries 1-5) irrespective of the metal (or none, Entry 4) present in solution. Third, solvent plays an important role in the diastereoselection. Our hypothesis is that hydroxylic solvents (EtOH and other alcohols) promote the exchange and/or disproportionation of ligands attached to boron so that the substrate can become bound to boron in a chelated fashion needed for effective chelation stereocontrol. Without hydroxylic solvents present (Entries 6,7), such exchange is slow and diastereoselection is nearly absent.

In support of this mechanistic rationale is the observation that Selectride reagents, which don't have exchangeable ligands on boron and thus should not readily chelate, give the Felkin-Anh product. These results should be viewed with caution, however, as we and others [4,6] have observed that relatively minor changes in the substrate structure can result in a switch to the *anti* product.

Since alkoxy ligands bound to aluminum are more labile than if they are bound to boron, lithium tri-*tert*-butoxyaluminum hydride was tested. In THF the diastereoselection was poor, presumably due to slow ligand exchange in the non-hydroxylic medium. These considerations culminated in the experiment shown in Entry 11. If solid $LiAl(OtBu)_3H$ is added to -78°C ethanol, very little hydrogen formation is observed upon dissolution and smooth reduction of **1a** to *anti*-**3a** as a single diastereomer in very high yield.

The stereochemistry of the reduction products *syn*- and *anti*-**3** was established by conversion to their cyclic oxazolidinone derivatives **4** with sodium hydride in DMF. *Anti*-**3a** cyclizes to *syn*-**4a** while *syn*-**3a** cyclizes to *anti*-**4a** (Scheme 4). Irradiation of the benzylic protons or the a-methylene protons allows the vicinal coupling constants between the methine protons of the aminoalcohol to be determined unambiguously. *Syn*-**4a** had the larger coupling constant J_{vic}= 7.5 Hz, while *anti*-**4a** had a smaller coupling constant J_{vic}= 5.5 Hz. Previous studies have established that *syn*-oxazolidinones have larger vicinal coupling constants than the *anti*-diastereomer [9]. Ab initio calculations on a truncated version of *syn*-**4a** and *anti*-**4a** show that the dihedral angle between the methine hydrogens is 25.5° in the most stable conformations of *syn*-**4a** and 107° in the most stable conformations of *anti*-**4a** [10]. These dihedral angles nicely support the assignment that *syn*-isomers of oxazolidinones have larger coupling constants than the *anti*-isomers.

Scheme 4



Having established a promising reduction protocol and a means to confidently assign the stereochemistry of the products, carbamate-protected aminoketones **1a-g** were reduced with $LiAl(OtBu)_3H$ in ethanol at -78°C. For the entire series the yields were very high and only one diastereomer could be detected in the crystalline crude products (Table 2). The products could be recrystallized to analytically pure products (75-80%), however, the nmr spectra of the crude material and the recrystallized products were nearly indistinguishable.

Table 2. The Reduction of Carbamate-Protected Aminoketones **1a-g** with $LiAl(OtBu)_3H$ in Ethanol at -78°C.

Compound	Yield (%, crude)	*anti* : *syn*
1a	97	>95 : 5
1b	96	>95 : 5
1c	94	>95 : 5
1d	97	>95 : 5
1e	93	>95 : 5
1f	95	>95 : 5
1g	96	>95 : 5

Noteworthy is that the method appears to be insensitive to the nature of the carbamate group and tolerates a range of functionality in the R_1 and R_2 substituents in aminoketones **1a-g**. This generality suggests that many other functional groups should be tolerated as well. Studies to further defing the scope of the reduction are currently ongoing.

Experimental Section

Infrared spectra were taken on as a KBr pellets or as solution in $CHCl_3$. ^1H NMR and ^{13}C NMR spectra

were recorded at 200 and 50 MHz, respectively. $CDCl_3$ or DMSO-d_6 were used as a NMR solvent. Thin layer chromatography was performed on silica gel 60 F_{254} plates from EM reagents and visualized by UV irradiation and by spraying $Ce(SO_4)_2$ solution and heating on a hot plate. Flash chromatography was performed using silica gel 60 (230-400 mesh). Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Tetrahydrofuran was distilled from benzophenone ketyl. Other solvents were HPLC grade and were used without further purification. Starting materiasl were purchased from Acros, Aldrich, Novabiochem and used as received.

General Procedure for the Preparation Carbamic N-Protected g-Amino b-Keto Allylester (2 a-g). CDI (carbonyl 1,1' diimidazole) (1.70 g, 10.5 mmol) was added at room temperature to a stirred solution of a carbamic N-protected a-amino acid (10 mmol) in dry THF (20 mL) under a N_2 atmosphere. The resulting solution was stirred for 1 h at the same temperature, and used for the next step without further purification. Meanwhile a solution of lithium enolate of allyl acetate was made from BuLi (2.5 M, 14 mL, 35 mmol), diisopropylamine (4.9 mL, 35 mmol) and allyl acetate (3.8 mL, 35 mmol). The above imidazole solution was added dropwise to this pale yellow solution of lithium enolate at –78°C under N_2 atmosphere. The resulting mixture was stirred for 30 min and then quenched with 10 % citric acid, extracted with ethyl acetate (3 x 50 mL). The organic extracts were combined, washed with sat. bicarbonate (2 x 50 mL), brine (50 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide the crude product, which can be purified by chromatography or recrystallization. Yield (90-94%).

General Procedure for the Preparation of the Carbamic N-Protected a-Amino Ketones (1a-g). Method A: With triflate as a alkylating agent: A solution of carbamic N-protected g-amino b-keto allylester **2** (2.6 mmol) in dry THF (10 mL) was added dropwise to a stirred suspension of NaH (125 mg of 60 % in oil, 3.1 mmol, 1.2 eq.) in dry THF (10 mL) at –20°C under nitrogen. The mixture was stirred for 20 min then the alkyl triflate (2.86 mmol, 1.1 eq.) in 5 mL THF was added. The resulting solution was allowed to warm up to room temperature and stirreqd for 3 h. After quenching with 10 mL 10% citric acid, the reaction mixture was then extracted with ethyl acetate (3 x 50 ml). The organic extracts were combined, washed with sat. bicarbonate, brine, dried ($MgSO_4$), passed through a short pad of silica gel and concentrated to provide a pale yellow oil. Without further purification, this oil was dissolved in THF (20 mL) and added dropwise to a stirred solution of palladium acetate (14.3 mg, 0.064 mmol), PPh_3 (33.8 mg, 0.13 mmol), formic acid (0.2 mL, 5 mmol) and Et_3N (0.9 mL, 6.5 mmol) in dry THF at room temperature under nitrogen. The mixture was vigorously stirred for 30 min then passed through a short silica column, flowed by ether washing. after the filtrate was concentrated in vacuo, the residue was chromatographed on SiO_2 with hexanes-ethyl acetate (90:10) to afford the ketone in 75-78% .

Method B: with alkyl bromide as a alkylating agent: A solution of carbamic N-protected g-amino b-keto allylester **2** (2.6 mmol) in dry THF (10 mL) was added dropwise to a stirred suspension of NaH (125 mg of 60 % in oil, 3.1 mmol, 1.2 eq.) in dry THF (10 mL) at –20°C under nitrogen. The mixture was stirred for 20 min then the alkyl bromide (2.6 mmol) in 5 mL THF and 10% NaI were added. The resulting solution was allowed to warm up to room temperature and refluxed for 2 h in order to complete the reaction. After quenching with 10 mL 10% citric acid, the reaction mixture was then extracted with ethyl acetate (3 x 50 ml). The organic extracts were combined, washed with sat. bicarbonate, brine, dried ($MgSO_4$), passed through a short pad of silica gel and concentrated to provide a pale yellow oil. Without further purification, this oil was dissolved in THF (20 mL) and added dropwise to a stirred solution of palladium acetate (14.3 g, 0.064 mmol), PPh_3 (33.8 mg, 0.13 mmol), formic acid (0.2 mL, 5 mmol) and Et_3N (0.9 mL, 6.5 mmol) in dry THF at room temperature under nitrogen. The mixture was vigorously stirred for 30 min then passed through a short silica column, flowed by ether washing. after the filtrate was concentrated in vacuo, the residue was chromatographed on SiO_2 with hexanes-ethyl acetate (10:1) to afford the ketone .

(1S-Benzyl-2-oxo-decyl)-carbamic acid benzyl ester (1a). This compound was prepared by the method A. Alkylation of 993 mg (2.6 mmol) of **2a** with 709 mg (2.86 mmol, 1.1 eq) of heptyl triflate afforded 770 mg (75%) of **1a** as a colorless solid after purification on silica gel eluting with 90:10 hexanes/EtOAc. Pure material could be obtained by recrystallization from hexanes: mp 52°C; $[a]_{21D}$ +4.5 (c 1.00, CH_2Cl_2); IR 3316, 2932, 2852, 1716, 1692, 1536, 1260; ^{1}H NMR ($CDCl_3$) d 0.88 (t, 3H), 1.23 (m, 10H), 1.49 (m, 2H), 2.36 (m, 1H), 3.03 (t, 2H), 4.61 (q, 1H), 3.83, 5.07 (s, 2H), 5.42 (d, 1H), 7.22-7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) d 14.1, 22.7, 23.3, 29.1, 29.3, 31.8, 38.0, 40.9, 60.4, 66.9, 76.4, 127.1, 128.1, 128.2, 128.6, 128.7, 129.3, 135.9, 155.7, 208.8.

(1S-Benzyl-2-oxo-4-phenyl-butyl)-carbamic acid 2,2-dimethyl-propyl ester (1b). This compound was prepared by the method B. Alkylation of 903 mg (2.6 mmol) of **2b** with 489 mg (2.86 mmol, 1.1 eq) of benzyl bromide afforded 703 mg (76%) of **1b** as a colorless solid after purification on silica gel eluting with 90:10 hexanes/EtOAc. Pure material could be obtained by recrystallization from hexanes: mp 84°C; $[a]_{23D}$ +3.4 (c 1.00, CH_2Cl_2); IR 3348, 2980, 1700, 1688, 1516, 1456, 1368, 1320; ^{1}H NMR ($CDCl_3$) d 1.40 (s, 9H), 2.69 (t, 2H), 2.84 (m, 2H), 2.96 (t, 2H), 4.52 (q, 1H), 5.08 (d, 1H), 7.09-7.27 (m, 10H); ^{13}C NMR ($CDCl_3$) d 28.3, 29.3, 37.8, 42.3, 60.1, 79.9, 126.3, 127.0, 128.2, 128.6, 128.7, 129.3, 135.6, 155.1, 208.3.

(1S-Methyl-2-oxo-5-phenyl-pentyl)-carbamic acid 2,2-dimethyl-propyl ester (1c). This compound was prepared by the method A. Alkylation of 705 mg (2.6 mmol) of **2c** with 727 mg (2.86 mmol, 1.1 eq) of phenethyl triflate afforded 553 mg (73%) of **1c** as a colorless solid after purification on silica gel eluting with 90:10 hexanes/EtOAc. Pure material could be obtained by recrystallization from hexanes: mp 46°C; $[a]_{23D}$ +1.1 (c 1.00, CH_2Cl_2); IR (KBr) 3332, 2984, 1684, 1528, 1452, 1368, 1252; ^{1}H NMR ($CDCl_3$) d 1.28 (d, 3H), 1.43 (s, 9H), 1.94 (qu, 2H), 2.50 (m, 2H), 2.6 (t, 2H), 4.27 (qu, 1H), 5.25 (d, 1H), 7.14-7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) d 17.9, 25.0, 28.3, 35.0, 38.2, 55.1, 79.7, 126.0, 128.4, 141.3, 155.1, 209.4.

(5S-tert-Butoxycarbonylamino-6-oxo-8-phenyl-octyl)-carbamic acid benzyl ester (1d). This compound was prepared by the method B. Alkylation of 1000 mg (2.1 mmol) of **2d** with 360 mg (2.1 mmol) of benzyl bromide afforded 740 mg (73%) of **1d** as a colorless solid after purification on silica gel eluting with 80:20 hexanes/EtOAc. mp 76°C; $[a]_{20D}$ +13.4 (c 1.00, CH_2Cl_2); IR 3366, 2974, 1726, 1696, 1526, 1377, 1267, 1167; ^{1}H NMR ($CDCl_3$) d 1.42 (broad, 13H), 2.46 (m, 2H), 2.85 (m, 4H), 3.13 (q, 2H), 4.25 (m, 1H), 4.80 (broad, 1NH), 5.09 (s, 2H), 5.22 (d, 1NH), 7.19-7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) d 22.3, 28.2, 29.3, 29.9, 34.0, 40.8, 57.1, 59.1, 66.0, 79.8, 118.9, 126.8, 128.3, 128.6, 128.8, 129.0, 131.3, 137.9, 156.4, 168.1, 203.4. 208.4.

(1S-Isobutyl-2-oxo-5-phenyl-pentyl)-carbamic acid benzyl ester (1e). This compound was prepared by the method A. Alkylation of 972 mg (2.8 mmol) of **2e** with 711 mg (2.80 mmol) of phenethyl triflate afforded 700 mg (68%) of **1e** as a colorless oil after purification on silica gel eluting with 90:10 hexanes/EtOAc. $[a]_{20D}$ +9.2 (c 1.00, CH_2Cl_2); IR ($CHCl_3$) 3445, 3037, 2967, 2877, 1521, 1466; ^{1}H NMR ($CDCl_3$) d 0.89 (d, 3H), 0.95 (d, 3H), 1.34 (m, 2H), 1.67 (m, 1H), 1.92 (qu, 2H), 2.51 (t, 2H), 2.57 (t, 2H), 4.38 (txd, 1H), 5.09 (s, 2H), 5.28 (d, 1NH), 7.18-7.34 (m, 10H). ^{13}C NMR ($CDCl_3$) d 21.9, 23.3, 25.0, 35.0, 39.0, 40.3, 40.7, 58.3, 67.0, 126.0, 128.1, 128.4, 129.0, 141.4, 156.2, 209.6.

(1S-Benzyl-2-oxo-decyl)-carbamic acid 9H-fluoren-9-ylmethyl ester (1f). This compound was prepared by the method A. Alkylation of 1173 mg (2.50 mmol) of **2f** with 620 g (2.50 mmol) of heptyl triflate afforded 785 mg (65%) of **1f** as a colorless solid after purification on silica gel eluting with 85:15 hexanes/EtOAc; Pure material could be obtained by recrystallization from hexanes: mp 104°C; $[a]_{20D}$ +35.0 (c 1.00, CH_2Cl_2); IR (KBr) 3326, 2937, 2847, 1725, 1691, 1541, 1322, 1262. 1088, 739; ^{1}H NMR ($CDCl_3$) d 0.88 (t, 3H), 1.23 (broad, 11H), 1.58 (m, 3H), 2.37 (m, 2H), 3.04 (t, 2H), 4.18 (t, 1H), 4.38 (m,

2H), 4.62 (q, 1H) 5.43 (d, 1NH), 7.12-7.77 (m, 13H); u, 2H), 2.51 (t, 2H), 2.57 (t, 2H), 4.38 (txd, 1H), 5.09 (s, 2H), 5.28 (d, 1NH), 7.18-7.34 (m, 10H). ^{13}C NMR ($CDCl_3$) d 14.1, 22.7, 23.4, 29.1, 29.3, 31.7, 31.8, 38.0, 40.9, 47.3, 60.4, 67.0, 120.1, 125.1, 127.1, 127.9, 128.7, 129.3, 136.0, 141.4, 143.9, 155.7, 208.8.

4S-tert-Butoxycarbonylamino-9-methyl-5-oxo-dec-8-enoic acid methyl ester (1g). This compound was prepared by the method B. Alkylation of 1063 mg (3.1 mmol) of **2g** with 462 mg (3.1 mmol) of prenyl bromide afforded 720 mg (71%) of **1g** as a colorless oil after purification on silica gel eluting with 90:10 hexanes/EtOAc. [a]$_{20D}$ +29.7 (c 1.00, CH_2Cl_2); IR ($CHCl_3$) 3435, 3026, 2986, 2927, 1741, 1710, 1506, 1451, 1381, 1182. ^{1}H NMR ($CDCl_3$) d 1.43 (s, 9H), 1.61 (s, 3H), 1.67 (s, 3H), 1.73 (q, 2H), 2.29 (m, 2H), 2.31 (m, 2H), 2.54 (m, 2H), 3.68 (s, 3H), 4.35 (txd, 1H), 5.04 (t, 1H), 5.25 (d, 1NH); ^{13}C NMR ($CDCl_3$) d 17.7, 22.3, 25.6, 26.8, 28.3, 29.7, 39.8, 51.7, 58.6, 79.9, 122.4, 133.1, 155.5, 173.3, 208.5.

General Procedure for the Reduction of the Carbamic N-Protected a**-Amino Ketones (1a-g).** Method A: Reduction using LiAlH(O-*t*-Bu)$_3$ in EtOH: 130 mg of LiAlH(O-*t*-Bu)$_3$ (0.50 mmol) were dissolved in EtOH (3 mL) at –78°C under nitrogen, then a solution of the ketone **1a-g** (0.25 mmol) in EtOH (4 mL) was added dropwise. After 2 h the solution was quenched with 10 % citric acid (2 mL), extracted by ethyl acetate (2 x 50 mL), washed by H_2O (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated to provide a white solid which can be recrystalized from an appropriate solvent.

Method B: Reduction using $NaBH_4$ in EtOH: 19 mg $NaBH_4$ (0.50 mmol) were dissolved in EtOH (3 mL) at –78°C under nitrogen, then a solution of the ketone **1a** (0.25 mmol) in EtOH (4 mL) was added dropwise. After 2 h the solution was quenched with 10 % citric acid (2 mL), extracted by ethyl acetate (2 x 50 mL), washed by H_2O (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated to provide a white solid, which can be recrystalized from an appropriate solvent..

Method C: Reduction using Selectride in THF: 0.5 mL of selectride solution in THF (1M) was cooled at –78°C under nitrogen, then a solution of the ketone **1a** (100 mg, 0.25 mmol) in THF was added dropwise. After 2 h the solution was quenched with 10 % citric acid (2 mL), extracted by ethyl acetate (2 x 50 mL), washed by H_2O (20 mL), brine (20 mL), dried ($MgSO_4$) quenched with 10 % citric acid (2 mL), extracted by ethyl acetate (2 x 50 mL), washed by H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide the crude product which can be recrystalized from an appropriate solvent.

(1S-Benzyl-2R-hydroxy-decyl)-carbamic acid benzyl ester (*anti***-3a).** Reduction of 100 mg (0.25 mmol) of **1a** using method A afforded 98 mg of crude *anti*-**3a** as a colorless solid which can be purified by recrystallization from hexanes with 90% recovery: mp 142°C; [a]$_{23D}$ -21.4 (c 1.00, CH_2Cl_2); IR 3324, 2920, 2852, 1692, 1544, 1456, 1316, 1264; ^{1}H NMR ($CDCl_3$) d 0.85 (t, 3H), 1.21 (m, 11H), 1.42 (m, 3H), 2.00 (s, 1H), 2.72-2.98 (m, 2H), 3.70 (m, 1H), 3.90 (m, 1H), 4.85 (d, 1H), 5.01 (s, 1H), 7.20-7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) d 14.4, 23.0, 26.4, 29.6, 29.8 29.9, 32.2, 34.5, 39.2, 56.4, 67.1, 74.9, 126,8, 128.3, 128.8, 128.9, 129.6, 137.0, 138.6, 156.9.

(1S-Benzyl-2S-hydroxy-decyl)-carbamic acid benzyl ester (*syn***-3a).** Reduction of 100 mg (0.25 mmol) of **1a** using method C afforded 96 mg of crude *syni*-**3a** as a colorless solid which can be purified by recrystallization from hexanes with 87% recovery: mp 141°C; [a]$_{23D}$ -17.5 (c 1.00, CH_2Cl_2); IR 3328, 2920, 2852, 1692, 1540, 1456, 1316, 1264; ^{1}H NMR ($CDCl_3$) d 0.85 (t, 3H), 1.21 (m, 11H), 1.42 (m, 3H), 2.00 (s, 1H), 2.72-2.98 (m, 2H), 3.70 (m, 1H), 3.90 (m, 1H), 4.85 (d, 1H), 5.00 (s, 1H), 7.20-7.31 (m, 10H); ^{13}C NMR ($CDCl_3$) d 14.4, 23.0, 26.4, 29.6, 29.8 29.9, 32.2, 34.5, 39.2, 56.4, 67.1, 74.9, 126,8, 128.3, 128.8, 128.9, 129.6, 137.0, 138.6, 156.9.

(1S-Benzyl-2R-hydroxy-4-phenyl-butyl)-carbamic acid 2,2-dimethyl-propyl ester (*anti***-3b).** Reduction of 90 mg (0.25 mmol) of **1b** using method A afforded 84 mg of crude *anti*-**3b** as a colorless

solid which can be purified by recrystallization from ethyl acetate with 86% recovery: mp 163°C; [a]$_{23D}$ -1.4 (c 1.00, CH_2Cl_2); IR 3360, 2932, 1688, 1524, 1452, 1316, 1268; ^{1}H NMR ($CDCl_3$) d 1.35 (s, 9H), 1.79 (t, 2H), 2.68 (m, 2H), 2.90 (m, 2H), 3.73 (m, 1H), 3.85 (m, 1H), 4.60 (d, 1H), 7.15-7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) d 28.3, 32.4, 35.2, 36.9, 57.1, 73.5, 79.8, 126.0, 126.4, 128.6, 129.3, 138.1, 142.0. 156.2

(2R-Hydroxy-1S-methyl-5-phenyl-pentyl)-carbamic acid 2,2-dimethyl-propyl ester (*anti*-3c). Reduction of 73 mg (0.25 mmol) of **1c** using method A afforded 71 mg of crude *anti*-**3c** as a colorless solid which can be purified by recrystallization from hexanes with 92% recovery: mp 79°C; [a]$_{23D}$ -8.2 (c 1.00, CH_2Cl_2); IR 3356, 2936, 1684, 1528, 1456, 1368, 1284; ^{1}H NMR ($CDCl_3$) d 1.05 (d, 3H), 1.43 (s, 9H), 1.64 (m, 2H), 1.82 (m, 2H), 2.25 (s, 1OH), 2.64 (t, 2H), 3.64 (m, 2H), 4.77 (d, 1NH), 7.15-7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) d 14.5, 27.8, 28.5, 32.8, 35.8, 50.8, 74.4, 79.6, 125.8, 128.4, 128.5, 142.2, 155.9.

(5S-tert-Butoxycarbonylamino-6R-hydroxy-8-phenyl-octyl)-carbamic acid benzyl ester (*anti*-3d). Reduction of 130 mg (0.28 mmol) of **1d** using method A afforded 127 mg (97%) of crude *anti*-**3d** as a colorless solid which can be purified by recrystallization from EtOH with 85% recovery: mp 113°C; [a]$_{20D}$ -15.8 (c 1.00, CH_2Cl_2); IR 3366, 2957, 1696, 1531, 1461, 1372, 1272, 1183, 1033; ^{1}H NMR ($CDCl_3$) d 1.42 (broad, 15H), 1.70 (m, 2H), 2.48 (broad, 1H), 2.69 (m, 2H), 2.84 (m, 1H), 3.16 (broad, 2H), 3.61 (m, 2H), 5.09 (s, 2H), 4.76 (broad, 1NH), 4.89 (broad, 1NH), 7.21-7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) d 23.1, 28.4, 28.9, 29.1, 32.4, 34.9, 40.6, 55.3, 66.7, 74.1, 79.7, 125.9, 127.6, 128.0, 128.4, 136.6, 141.9, 156.7.

(2R-Hydroxy-1S-isobutyl-4-phenyl-butyl)-carbamic acid benzyl ester (*anti*-3e). Reduction of 200 mg (0.54 mmol) of **1e** using method A afforded 195 mg (97%) of crude *anti*-**3e** as a colorless solid which can be purified by recrystallization from Hexanes with 87% recovery: mp 108°C; [a]$_{20D}$ -35.6 (c 1.00, CH_2Cl_2) IR 3325, 3036, 2957, 1867, 1696, 1556, 1466, 1287, 1262, 1122, 1062. 1028, 699. ^{1}H NMR ($CDCl_3$) d 0.90 (d, 6H), 1.23 (m, 2H), 1.40 (m, 2H), 1.61 (m, 2H), 1.84 (m, 1H), 2.25 (broad, 1OH), 2.63 (t, 2H), 3.67 (m, 2H), 4.86 (d, 1NH), 5.08 (s, 2H), 7.14-7.33 (m, 10H); ^{13}C NMR ($CDCl_3$) d 21.6, 23.7, 24.7, 27.8, 32.5, 35.8, 38.1, 54.0, 66.9, 74.6, 125.9, , 128.1, 128,4, 128.5, 136.5, 142.2, 156.8.

(1S-Benzyl-2R-hydroxy-decyl)-carbamic acid 9H-fluoren-9-ylmethyl ester (*anti*-3f). Reduction of 100 mg (0.20 mmol) of **1f** using method A afforded 95 mg (95%) of crude *anti*-**3f** as a colorless solid which can be purified by recrystallization from EtOH with 85% recovery: mp 172°C; [a]$_{20D}$ -20.8 (c 1.00, CH_2Cl_2), IR 3335, 3077, 3037, 2917, 2847, 1696, 1546, 1457, 1322, 1272, 1152, 1092, 1038. ^{1}H NMR (DMSO) d 1.23 (t, 3H), 1.62 (broad, 13H), 1.85 (m, 1H), 2.90 (m, 2H), 2.96 (m 1H), 3.42 (d, 1H), 3.83 (m, 1H), 4.51 (m, 3H), 5.09 (d, 1NH), 7.55-8.30 (m, 13H); ^{13}C NMR (DMSO) d 14.1, 22.2, 25.7, 29.3, 31.4, 32.1, 33.5, 35.9, 57.0, 57.6, 73.1, 73.5, 109.9, 120.2, 121.6, 125.9, 127.5, 128.2, 129.2, 135.5, 140.5, 157.1.

4S-tert-Butoxycarbonylamino-5R-hydroxy-9-methyl-dec-8-enoic acid methyl ester (*anti*-3g). Reduction of 100 mg (0.30 mmol) of **1g** using method A afforded 96 mg (96%) of crude *anti*-**3g** as a colorless solid which can be purified by recrystallization from EtOH with 85% recovery: mp 68°C; [a]$_{20D}$ -17.7 (c 1.00, CH_2Cl_2); IR 3366, 2986, 2947, 1756, 1691, 1536, 1536, 1457, 1381, 1267, 1187, 1053; ^{1}H NMR ($CDCl_3$) d 1.44 (broad, 11H), 1.62 (s, 3H), 1.69 (s, 3H), 1.94 (m, 2H), 2.19 (m, 2H), 2.41 (m, 2H), 2.54, 3.60 (m, 1H), 3.68 (s, 3H), 4.13 (m, 1H), 4.80 (broad, 1NH), 5.12 (d, 1H); ^{13}C NMR ($CDCl_3$) d 17.8, 23.4, 25.7, 28.4, 30.9, 33.6, 47.9, 51.7, 54.8, 74.4.9, 82.0, 122.8, 133.1, 155.1, 170.5.

General Procedure for the cyclization of the Carbamic N-Protected a-Amino alcohols (3a-c) to the corresponding oxazolidinones (4a-c). Method A: Aqueous sodium hydroxide (8 M, 0.5 mL) was added to a stirred solution of the a-Amino alcohol **3** (0.25 mmol) in 5 mL methanol-THF (1:2). The mixture was stirred for 3-5 h at room temperature and then evaporated. The residue was dissolved in 10 mL water and extracted twice with 10 mL ethyl acetate, washed by H2O (5 mL), brine (5 mL), dried

(MgSO4) and concentrated to provide the crude product which can be recrystalized from an appropriate solvent.

Method B: A solution of the a-amino alcohol **3** (0.25 mmol) in 2 mL DMF was added to a suspension of 18 mg NaH (0,75 mmol) in 3 mL DMF. The mixture was stirred for 3-5 h at room temperature . The mixture was dissolved in 10 mL water and extracted twice with 10 mL ethyl acetate, washed by H_2O (5 mL), brine (5 mL), dried ($MgSO_4$) and concentrated to provide the crude product which can be purified y chromatography or by recrystalization from an appropriate solvent.

4S-Benzyl-5R-octyl-oxazolidin-2-one (*syn*-4a). This compound was prepared by the method A treating 100 mg (0.25 mmol) of the alcohol **5a** with NaOH in THF-methanol to give **7a** as a colorless oil which was purified by chromatography to afford 64 mg (89%). ^{1}H NMR ($CDCl_3$) d 0.89 (t, 3H), 1.28 (m, 11H), 1.60 (m, 2H), 1.83 (m, 1H), 2.65 (dxd, 1H), 2.90 (dxd, 1H), 3.94 (m, 1H), 4.65 (m, 1H), 4.90 (s, 1NH), 7.17-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) d 14.1, 22.8, 26.0, 29.0, 29.2 29.6, 32.0, 36.3, 39.2, 57.0, 80.0, 127.3, 129.0, 129.1, 136.8, 158.7.

4S-Benzyl-5S-octyl-oxazolidin-2-one (*anti*-**4a).** This compound was prepared by the method A treating 100 mg (0.25 mmol) of the alcohol **6a** with NaOH in THF-methanol to give **8a** as a colorless oil which was purified by chromatography to afford 60 mg (83%). ^{1}H NMR ($CDCl_3$) d 0.88 (t, 3H), 1.23 (m, 11H), 1.50 (m, 2H), 1.65 (m, 1H), 2.83 (d, 2H), 3.64 (q, 1H), 4.28 (m, 1H), 4.45 (s, 1NH), 7.15-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) d 14.1, 22.8, 26.0, 29.3, 29.5 29.6, 31.9, 36.3, 39.2, 57.0, 80.1, 127.2, 129.0, 129.2, 136.8, 158.7.

4S-Benzyl-5R-phenethyl-oxazolidin-2-one (*syn*-4b). This compound was prepared by the method B treating 90 mg (0.25 mmol) of the alcohol **5b** with NaH in DMF to give **7b** as a colorless solid, which was purified by chromatography to afford 60 mg (86%). 1H NMR (CDCl3) d 1.95 (m, 1H), 2.17 (m, 11H), 2.72 (m, 4H), 3.92 (m, 1H), 4.62 (m, H), 5.10 (s, 1NH), 7.14-7.32 (m, 10H); 13C NMR (CDCl3) d 31.3, 32.0, 36.3, 56.7, 78.7, 126.2, 127.1, 128.5, 128.9, 129.0, 136.5, 140.5, 148.4.

4S-Methyl-5R-(3-phenyl-propyl)-oxazolidin-2-one (*syn*-4c). This compound was prepared by the method B treating 73 mg (0,25 mmol) of the alcohol **5c** NaH in DMF to give **7c** as a colorless solid, which was purified by chromatography to afford 50 mg (90%). From this compound was prepared a kristall in toluene for x-ray analysis. 1H NMR (CDCl3) d 1.11 (d, 3H), 1.74 (m, 4H), 2.67 (m, 2H), 3.87 (m, 1H), 4.55 (m, H), 6.22 (s, 1NH), 7.15-7.32 (m, 5H); 13C NMR (CDCl3) d 15.9, 27.6, 28.7, 35.5, 51.1, 80.0, 126.0, 128.4, 141.6, 142.8, 159.7.

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10. Calculations were carried out on *syn* and *anti*- i at the HF 6-31G* level using the Titan suite of programs from Wavefunction.