g, 4.3 mmol), which formed a heterogeneous reaction mixture. The suspension was cooled to -78 °C and boron trifluoride etherate (0.26 mL, 22 mmol) was added. The preformed Grignard reagent was added dropwise over a 10-min period. The mixture became a golden yellow color and appeared to become homogeneous during the addition of the Grignard reagent. After the addition of the Grignard was complete, the reaction mixture returned to a heterogeneous state. The suspension was stirred for 4 h at -78 °C and poured into an aqueous 20% $NH_4Cl/$ NH₄OH (50:50) solution (100 mL). After stirring the mixture 10 min, the organic layer was separated. The aqueous layer was extracted with diethyl ether $(2 \times 50 \text{ mL})$. The combined organic extracts were washed with brine (50 mL) and dried over MgSO4. The solution was filtered and concentrated to afford the crude product as a bright yellow oil. Purification by radial PLC (SiO₂, 30% EtOAc/hexanes) gave 380 mg (57%) of a light yellow oil. The isolated product consisted of two diastereomers (60:1 by ¹H NMR), which were separated by radial PLC (SiO₂, 20% acetone/hexanes) to give 370 mg (56%) of the cis isomer 6 and 5.2 mg of the trans isomer: ¹H NMR (CDCl₃) δ 7.5-7.3 (m, 5 H), 7.0-6.8 (m, 128.8, 128.7, 128.5, 128.3, 119, 118, 112, 109, 68, 56, 54, 52, 45, 36, 32, 24; IR (CDCl₃) 2938, 2835, 1717, 1691, 1602, 1589, 1518, 1455, 1410, 1327, 1257, 1147, 1026 cm⁻¹

Anal. Calcd for $C_{25}H_{30}CINO_5$: C, 65.28; H, 6.57; N, 3.05. Found: C, 65.11; H, 6.28; N, 3.04.

Preparation of 6 from 5a. The piperidone **5a** (539 mg, 1.22 mmol) was dissolved in 10 mL of DMF under N₂. To this solution was added 326 mg (2.44 mmol) of *N*-chlorosuccinimide and the solution was cooled to 0 °C (ice bath). Triphenylphosphine (640 mg, 2.44 mmol) was added slowly, and after all the triphenylphosphine had been added, the solution was warmed to 50 °C and held there for 4 h. To this solution was then added 1 mL of methanol to consume the excess reagents. This reaction mixture was poured into water and extracted with ether. The combined ether extracts were washed twice with water and once with brine and dried over MgSO₄. Concentration of the organic phase gave the crude product, which was purified by radial PLC (1% MeOH/CH₂Cl₂) to give 336 mg (60%) of **6** as a clear oil. This material was identical with that prepared above.

4-(3,4-Dimethoxyphenyl)quinolizidin-2-one (7). To a 500-mL Parr bottle was added **6** (0.78 g, 1.7 mmol) in ethyl acetate (15 mL). To this solution were added lithium carbonate (0.12 g, 1.7 mmol) and 5% Pd/C (0.14 g). The mixture was shaken under 40 psi of hydrogen for 12 h, filtered through Celite, and concentrated to afford the crude product. Purification by radial PLC (SiO₂, 5% MeOH/CH₂Cl₂) gave 370 mg (75%) of 7 as a clear oil. Crystallization from methanol gave colorless crystals: mp 82–84 °C (lit.^{4c} mp 83–84 °C); ¹H NMR (CDCl₃) δ 6.9 (s, 1 H), 6.8 (s, 2 H), 3.9 (s, 3 H), 3.8 (s, 3 H), 3.2 (dd, 1 H), 2.9–2.1 (m, 7 H), 1.9–1.1 (m, 6 H); ¹³C NMR (CDCl₃) δ 207, 135, 119, 111, 109, 69, 62, 56, 53, 51, 48, 34, 26, 24; IR (neat) 2900, 2770, 2725, 1710 cm⁻¹.

 (\pm) -Lasubine II (1). To a 5-mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added 4-(3,4-dimethoxyphenyl)quinolizidin-2-one (7) (73 mg, 0.25 mmol) in THF (1 mL). This solution was cooled to -78 °C in preparation for its delivery to the reducing agent. To a separate 10-mL round-bottomed flask equipped with a stir bar and purged with nitrogen was added LS-Selectride (Aldrich Chemical Co.) (0.31 mL, 0.31 mmol) in THF (2 mL) cooled to -78 °C. The solution of quinolizidinone 7 was transferred via a cannula to the reducing agent and stirring was continued for 30 min. After 30 min, pH 7.0 phosphate buffer (1 mL) was added and the solution was warmed to room temperature. The reaction mixture was extracted with diethyl ether (2 \times 25 mL), and the combined organic layers were washed with brine (25 mL). The solution was concentrated under reduced pressure to afford the crude boronate. The crude boronate was dissolved in ethanol, and 1 N NaOH (1 mL) was added. The mixture was refluxed for 1 h and then cooled to room temperature. The mixture was then poured into 5% aqueous NaHCO₃ (25 mL) and stirred for 10 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 \times 25 mL). The combined organic extracts were washed with brine (25 mL) and dried over K_2CO_3 . The solution was filtered and concentrated to afford the crude product. Purification by radial PLC (SiO₂, 5% CHCl₃/MeOH) gave 58 mg (81%) of (±)-lasubine II (1) as a viscous oil. The product was 98% pure containing only 2% of epilasubine II (8) as indicated by ¹H NMR: ¹H NMR (CDCl₃) δ 6.91 (s, 1 H), 6.86 (d, J = 7.2 Hz, 1 H), 6.79 (d, J = 8.2 Hz, 1 H), 4.15 (t, J = 2.6 Hz, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.31 (dd, J = 11.5and 3.2 Hz, 1 H), 2.69 (d, J = 11 Hz, 1 H), 2.35-2.41 (m, 1 H), 1.25-1.91 (m, 12 H); ¹³C NMR (CDCl₃) δ 148, 147, 137, 119, 111, 110, 64, 63, 56, 55.75, 55.7, 53.42, 40, 33, 25, 24; IR (CDCl₃) 3613, 3402, 3155, 3008, 2937, 2859, 2839, 2799, 2254, 1794, 1594, 1516, 1465, 1443, 1421, 1386, 1342, 1314, 1261, 1233, 1197, 1179, 1151, 1135, 1094, 1047, 1029, 908, 736 cm⁻¹. This is in agreement with reported spectra.⁵

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α -Amino Acids as Chiral Educts for Asymmetric Products. Alkylation of N-Phenylfluorenyl α -Amino Ketones. Synthesis of Optically Pure α -Alkyl Carboxylic Acids

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Abstract: Regioselective enolization and alkylation of N-(9-phenylfluoren-9-yl)amino ketones provides diastereomeric mixtures of α' -alkyl branched α -amino ketones. Separation of the diastereomers provides >99% enantiomerically pure α' -alkyl branched α -amino ketones which can be epimerized at the α' -carbon with no loss of chiral integrity at the α -carbon. Deprotection and subsequent oxidative degradation of the diastereomerically pure alkylated products provide enantiomerically pure α -alkyl-substituted carboxylic acids. α -Methylpentanoic acid and α -phenylpropanoic acid are synthesized in >99% enantiomeric purity from this seven step process that utilizes L-alanine as a one-carbon chiral building block.

Because of their abundance in nature and their application in pharmaceuticals, much attention has been devoted to the preparation of enantiomerically pure α -amino carbonyl compounds.¹ Although several methods are available to stereoselectively introduce different electrophiles at the α -center of α -amino acid and α -amino amide derivatives,^{1,2} no methodology existed for the

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regio- and stereoselective alkylation of α -amino ketones. Since α -amino ketones may possess two sites for possible carbon al-

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kylation, control must first be established for the regioselectivity of enolization before considering the problem of stereoselectivity. We present here our successful process for controlling both the enolization and stereoselective alkylation of α -amino ketones.

In the first study of the effect of an α -nitrogen substituent on ketone enolate formation,³ the direction of enolization was determined for tertiary amino, carbamato, trifluoromethanesulfonamido, and phthalimido ketones under kinetic and thermodynamic conditions, with both acid and base. This was done by trapping the enolates as their triethylsilyl enol ethers. For aminoacetone, the only acyclic example, the degree of enolization increases toward the α -amino carbon with an increase in the electron-withdrawing nature of the nitrogen substituent. Thus α -amino ketones which are N-protected as amides and carbamates provide a predominance of silyl enol ether products resulting from enolization at the nitrogen-bearing α -carbon. Under thermodynamic control N-alkyl-substituted α -amino ketones also enolize predominantly at the α -amino carbon; however, trapping N-alkyl-substituted α -amino ketone enolates prepared under kinetic control with lithium diisopropylamide as base results in a dominance of silyl enol ether products from enolization toward the non-nitrogen bearing carbon, the α' -carbon. Similar trends were observed in cyclic tertiary α -amino ketones, with the exception of 3-pyrrolidinones, which enolize predominantly at the α' -carbon under all conditions.

Since tertiary N-acyl- α -amino ketones enolize predominantly at the α - rather than α' -carbon, it was subsequently demonstrated⁴ that secondary (N-acylamino)acetone also may be enolized and regioselectively alkylated at the α -amino carbon. Use of 100 mol % of a strong base and an alkyl halide in THF provided α -alkyl-substituted α -amino ketones in moderate yields (60%). The regioselectivity of alkylation was explained as arising from kinetic deprotonation of the amide and proton transfer to generate the thermodynamically favored ketone enolate or its tautomeric, delocalized anion. More recently this strategy for enolate formation has been used to alkylate a series of α -formamido ketones.⁵

In previous investigations we have shown that optically pure N-blocked α -amino ketones can be prepared by acylation of primary organometallic reagents with the lithium salts of N-acyl, N-ethoxycarbonyl, or N-phenylsulfonyl α -amino acids⁶ or N-carbamato and N-benzenesulfonamido acid isoxazolidides.⁷ A parallel, synthetically useful acylation process with secondary or tertiary organometallics could not be developed to make α' -alkyl branched α -amino ketones.⁸ Thus our goal was to find a method for regiospecifically enolizing optically pure N-blocked α -amino ketones away from the chiral α -amino carbon center and alkylating the enolate at the α' -carbon to prepare optically pure α' -alkyl branched α -amino ketones.

Results and Discussion

Preparation, Enolization, and Alkylation of N-(Phenylsulfonyl)and N-(9-Phenylfluoren-9-yl)- α -amino Ketones. To test the effect of an electronegative nitrogen protecting group and a nitrogen anion in controlling α -amino ketone enolization, (2S)-2-[N-(phenylsulfonyl)amino]-3-heptanone (2) was synthesized from L-alanine by first nitrogen protection under standard Schotten-Baumann conditions to form N-(phenylsulfonyl)-L-alanine (1)^{6a} and then by acylation of *n*-butyllithium with the dianion of 1 (Scheme I). Regiospecific enolization of N-(phenylsulfonyl)amino ketone 2 at the α' -carbon is observed when 2 is exposed to 200

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Scheme I



mol % of lithium diisopropylamide (LDA) at -78 °C and the dianion is quenched with deuteriomethanol. Deuterium is incorporated specifically at the α' -carbon of 2 to form 2a, and a decrease in the proton NMR signal at δ 2.3 is observed. No decrease in the proton NMR signal at δ 3.95 occurs, indicating no deuterium incorporation at the α -carbon. This may be explained by initial sulfonamide deprotonation followed by enolization of the carbonyl distant from the existing charge and toward the α' -carbon, producing dianion 3 rather than 4 in which negative charges reside on adjacent atoms. The dianion is unreactive to alkylation with methyl iodide in THF at -78 °C. With HMPA as cosolvent, no C-alkylated amino ketone 6 is formed, rather methylation of the sulfonamide nitrogen occurs to yield (2S)-2-[N-methyl-N-(phenylsulfonyl)amino]-3-heptanone (5). Because ketone 5 is a compound similar to those previously studied³ and found to enolize at the α -carbon and therefore racemize, we abandoned use of arylsulfonyl nitrogen-protecting groups and turned to the use of a sterically hindered alkyl amino-protecting group.

Recently we described use of the N-(9-phenylfluoren-9-yl) (PhFl) protecting group to prepare configurationally stable α -amino aldehyde 7 from L-alanine in 66% overall yield.⁹ The PhFl protecting group acts as a pocket, shielding the α -carbon proton and preventing deprotonation and racemization of 7 during its preparation, purification, and subsequent reactions. These observations suggested the use of the PhFl protecting group in the synthesis and regiospecific enolization and alkylation of α -amino ketones.

Attempts to directly acylate *n*-butyllithium or *n*-butylmagnesium bromide with the lithium or potassium salts of L-N-(9-phenylfluoren-9-yl)alanine or L-N-(9-phenylfluoren-9-yl)alanine isoxazolidide failed to produce the target α -amino ketone 9. Amino ketone 9 can, however, be conveniently prepared by addition of excess *n*-butylmagnesium bromide to N-(9-phenylfluoren-9-yl)alaninal (7) and subsequent oxidation of the resulting diastereomeric amino alcohols 8 (Scheme II). Use of excess Grignard reagent is essential for good yields of 8 since some organometallic reagent may be quenched by deprotonation of the secondary amine during the nucleophilic addition. Oxidation of the sterically hindered alcohol is best accomplished with Nchlorosuccinimide and dimethyl sulfide in toluene,¹⁰ to give ketone 9 as a low melting solid.

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Scheme II. Preparation, Enolization, and Alkylation of N-(PhFl)amino Ketone 9 (Only Major Isomer 10 Shown)



2.2/1

Table I. Alkylation of N-(PhFl)amino Ketone 9



methyl α -bromopropanoate 8.5 38 (67)

^a Yields in parentheses based on consumed 9.

Enolization of N-(PhFl)amino ketone 9 is regioselective at the α' -carbon. Alkylation of 9 is both regioselective and dependent on the enolate counterion. Methyl iodide alkylation of the enolate prepared with potassium hexamethyldisilazide in THF at -78 °C yields ketone 10 as a mixture of diastereomers (only syn isomer shown). On the other hand, alkylation of enolate generated with LDA in THF at -78 °C is slow and occurs at the amine, producing N-methylamino ketone 11 in poor yield.¹¹ The potassium enolate of 9 can also be alkylated with allyl bromide and benzyl bromide (Table I). When similar alkylation conditions were employed with secondary alkyl halides, isopropyl bromide and α -methylbenzyl bromide failed to react with the enolate and only starting ketone 9 was recovered while alkylation with methyl α -bromopropanoate produced moderate yields of two of the four possible diastereomers.

Optical Purity of (2S,4R)-2-[N-(9-Phenylfluoren-9-yl)-amino]-4-methyl-3-heptanone (10). Diastereomeric N-(PhFl)-amino ketones 10 can be separated on silica gel by chromatog-raphy. To ascertain if any loss of enantiomeric purity at the α -carbon occurred during the enolization and alkylation of α -amino ketone 9, diastereomerically pure N-(PhFl)amino ketone 10 was oxidized to carboxylic acid 12, which was converted to diastereomeric amides with a chiral amine and analyzed for enantiomeric purity on HPLC. When the major isomer of 10 is

hydrogenolyzed in methanolic HCl with palladium on carbon as catalyst, the hydrochloride salt of the deprotected amino ketone is obtained. This intermediate is not isolated as the free base, which is optically labile and self condenses to form dihydropyrazine; instead, the salt is oxidized with periodic acid¹² in a methanol/water mixture to produce (R)- α -methylpentanoic acid (12) in 60% yield from 10. Conducting the periodate oxidation at pH 6 \pm 0.5 prevents racemization and dihydropyrazine formation during the oxidation step by limiting the concentration of nonprotonated amino ketone. Conversion of acid 12 to amides 13 with (R)- and (RS)-phenylethylamine and HPLC analysis show the carboxylic acid to be >99% enantiomerically pure. When the periodic acid oxidation is conducted at slightly alkaline pH (7.5), a lower yield of partially racemized carboxylic acid (97% ee) is obtained. Since the substrate amino ketone 10 was diastereomerically pure, the pH 6 oxidation also establishes complete conservation of enantiomeric purity at the α -amino carbon.

As in the case of α -amino alcohols,¹³ the rate of oxidation of α -amino ketones with periodic acid is dependent on the concentration of unprotonated amine and increases upon raising the pH. Lead tetraacetate in acetic acid proved to be a useful alternative method for effecting cleavage of the carbon–carbon linkage since it occurs at low pH in organic solvents.¹⁴ The N-protected α -amino ketone can be directly converted to carboxylic acid with lead tetraacetate in 3/1 acetic acid/water in 15 h at room temperature.¹⁵ In the absence of water the α -amino ketone is oxidized slowly to α -imino ketone (not isolated).¹⁶ By this process, car-

⁽¹¹⁾ Yield 20%; ¹H NMR δ 0.39 (d, 3 H, J = 6.6), 0.95 (t, 3 H, J = 7.2), 1.4 (m, 2 H), 1.6 (m, 2 H), 2.39 (s, 3 H), 2.61 (m, 1 H), 2.85 (m, 1 H), 3.22 (q, 1 H, J = 6.6), 7.25–7.7 (m, 11 H), 7.8 (m, 2 H).

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⁽¹⁵⁾ Isolation as described in the experimental section provides (R)- α -methylpentanoic acid (12) in 42% yield and (R)- α -phenylpropanoic acid (15) in 59% yield. When Baeyer-Villiger oxidation of 10 was attempted with *m*-chloroperbenzoic acid, monoperphthalic acid, or hydrogen peroxide, neither *N*-(9-phenylfluoren-9-yl)alanine *sec*-pentyl ester nor carboxylic acid 12 was obtained. Oxidation of 10 with potassium permanganate or periodic acid also failed to produce the desired acids.

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Scheme III. Synthesis of *a*-Phenylpropanoic Acid (15) (Only Major Isomer 18 Shown)



boxylic acid of >99% enantiomeric purity is obtained.

Diastereomeric selectivity of alkylation of amino ketone 9 might be influenced by altering the starting amino acid in the synthesis, the enolate cation, the solvent, or many other factors that effect alkylation. We chose to ignore the question of how to improve diastereomeric selectivity during alkylation and instead concentrated on developing methodology for epimerizing the α' -center of the alkylated α -amino ketone without racemizing the α -amino center. If the diastereomers produced from alkylation are separable, then with such methodology the undesired diastereomer may be recycled to desired product. Either isomer thus becomes obtainable in good yields and the question of the diastereoselectivity of alkylation becomes moot.

To epimerize the undesired isomer produced from alkylation of α -amino ketone 10, we initially investigated use of amines of increasing basicity (triethylamine; 1,8-diazabicyclo[5.4.0]-7-undecene; 1,1,3,3-tetramethylguanidine) in THF at room temperature and found that no epimerization occurred. Next potassium hexamethyldisilazide was used in THF from -78 to 0 °C to enolize 10 and the reaction mixture was quenched with methanol. These conditions either failed to produce epimerization or provided a mixture of diastereomers contaminated with 9-phenylfluorene. This hydrocarbon side product results from deprotonation of the α -amino carbon and subsequent loss of the stabilized aromatic phenylfluorenyl anion to form imine 14.9 Various concentrations of sodium alkoxides (methoxide, isopropoxide, and tert-butoxide) in 1/1 mixtures of THF and the respective alcohol were next examined. The best of these conditions (sodium methoxide, 100 mol %, 1/1 MeOH/THF, -25 °C) applied to pure minor S,S isomer 10 produced a 2/1 ratio of (S,S)-/(S,R)-10 after 1 h; however, prolonged exposure to these conditions resulted in 9phenylfluorene formation.

Lithium diisopropylamide in THF proved to be optimum for epimerizing the α' -center without loss of material. In practice, a precooled THF solution of S,S or S,R diastereomer 10 (>95%) de) is added to a solution of LDA (200 mol %) in THF (20 mL/1 mmol of 10) at -55 °C, stirred 1 h, and quenched with excess methanol. This produces a 1/1 mixture of diastereomers 10 with <5% side products (HPLC analysis). Products from the recycling procedure were shown to be of >99% enantiomeric purity by conversion to (phenylethyl)amides 13 and HPLC analysis.

In the search for a process to control both the regiochemistry of enolization and stereochemistry of alkylation of α -amino ketones at the α' -carbon, we have also developed a method that utilizes the chirality of α -amino acids to produce enantiomerically pure α -alkyl carboxylic acids. Starting from L-alanine, (R)- α methylpentanoic acid (12) is prepared in 25% overall yield and >99% enantiomeric purity. To further extend this method, it was next applied to the synthesis of α -arylpropanoic acids.

 α -Arylpropanoic Acids. The α -arylpropanoic acids are antiinflammatory agents used as alternatives to aspirin. They inhibit the enzyme cyclooxygenase and stop the arachadonic acid cascade to prostaglandins and thromboxane A2, which are necessary for inflammation. Because biological activity resides in only one

enantiomer, much effort has been focused on the asymmetric synthesis of these α -arylpropanoic acids.¹⁷ As a synthetic target, the simplest of these acids, α -arylpropanoic acid (15), was chosen to further study the versatility of this new process for preparing enantiomerically pure α -alkyl carboxylic acids from L-alanine as a chiral educt.

Three routes were considered to prepare α -arylpropanoic acids from N-(9-phenylfluoren-9-yl)alaninal (7). One may prepare (2S)-2-N-(9-phenylfluoren-9-yl)amino-3-pentanone from 7 and add aromatic electrophiles to its enolate anion, enol ether, or enol ester. Or one may prepare (3S)-1-aryl-3-N-(9-phenylfluoren-9yl)amino-2-butanones and alkylate them with iodomethane. Finally, secondary organometallic reagents may be added to aldehyde 7 to generate directly the necessary carbon framework.

Various methods exist to α -arylate carbonyl compounds. Halo aromatics have been used to arylate ketones and amides with strong base.¹⁸ Silyl enol ethers and enol acetates have been treated with aryl diazonium salts.¹⁹ Palladium-catalyzed phenylation of enol ethers and acetates with iodobenzene, benzovl chloride, or arylmercury salts provides aryl aldehydes and aryl ketones.²⁰ Silyl enol ethers react with aryl halides in the presence of a trialkyltin fluoride and palladium catalyst.²¹ Similarly, enol acetates react with aryl bromides in the presence of tributyltin methoxide and a palladium catalyst.²² Although these procedures and others²³ provide α -aryl carbonyl compounds, they are normally low yielding, especially when the α -position is alkyl-substituted and when an alkyl amine is present.²⁴ For these reasons we abandoned α' -arylation of the amino ketone and concentrated on the addition of benzylic organometallic reagents to aldehyde 7 to incorporate the aryl portion of the molecule.

When benzyllithium prepared from toluene and n-butyllithium/TMEDA is added to N-(9-phenylfluoren-9-yl)alaninal

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Scheme IV



(7), an excellent yield of the phenylethanols 16 is produced. Oxidation of alcohols 16 with N-chlorosuccinimide/dimethyl sulfide in toluene¹⁰ then provides the desired amino ketone 17 (Scheme III). Alkylation of 17 using potassium hexamethyldisilazide and methyl iodide under various conditions gives monomethylated product 18 and dimethylated product 19.25 Dimethylated product 19 may be avoided by using only 115 mol % of both base and alkyl halide whereupon a 4/1 mixture of diastereomers 18 (79%, only major isomer shown) and recovered ketone 17 (13%) is produced. Diastereomers 18 can easily be separated. When the major isomer is hydrogenolyzed with palladium on carbon in methanolic HCl and the resulting amino ketone hydrochloride oxidized with periodate at pH 6, (R)- α phenylpropanoic acid 15 is produced in 72% yield. When the major isomer is hydrogenolyzed with palladium on carbon in acetic acid and then oxidized with lead tetraacetate in acetic acid/water, 15 is obtained in 69% yield. The optical purity of 15 produced by both methods was determined by converting it to both (R)and (RS)- α -phenylethylamine diastereomeric amides 20. Analysis (HPLC) established 15 as >99% enantiomerically pure.

A second route to 15 was achieved by adding a secondary organometallic reagent to aldehyde 7 (Scheme IV). The vinyl Grignard reagent from α -bromostyrene²⁶ adds to aldehyde 7 in high yield to form a 2/1 mixture of diastereomeric allylic alcohols 21 that are separable by chromatography. When major isomer 21a is hydrogenated in benzene with a rhodium tris(triphenylphosphine) chloride catalyst²⁷ and hydrogen at atmospheric pressure, only a single isomer 22a is formed (>99% de by HPLC and NMR analysis). When the minor isomer 21b is reduced under the identical homogeneous conditions, a 2/1 mixture of inseparable

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Chart I. NMR of Cyclic Carbamates 25a and 25b from Amino Alcohols 24a and 24b, Respectively



diastereomers 22b is formed. Hydrogenolysis of 22a in methanolic HCl and subsequent periodate oxidation of the resulting amino alcohol hydrochloride with periodic acid in a methanol/water solution at pH 6 produced (R)- α -phenylpropanoic acid (15) in 53% yield and 97% ee (as determined via (α -phenylethyl)amides 20). The low yield and decreased optical purity of 15 is presumed to arise from incomplete oxidation and racemization of the α phenylpropanaldehyde intermediate. Addition of permanganate to the periodate mixture in an effort to facilitate oxidation produced a poorer yield of completely racemic acid 15. To avoid these losses in the direct conversion of amino alcohol 22a to carboxylic acid 15, alcohol 22a was first oxidized with dimethyl sulfide/Nchlorosuccinimide to α -amino ketone 18a in >80% yield. Oxidative degradation of 18a, as previously described, provided (R)- α -phenylpropanoic acid (15) of >99% enantiomeric purity (as determined via (α -phenylethyl)amides 20).

Although the benzylic methyl group of amino alcohol **22a** could be assigned the *R* configuration by conversion to (R)- α -phenylpropanoic acid,²⁸ the stereochemistry at the carbinol function of

^{(25) &}lt;sup>1</sup>H NMR δ 0.46 (d, 3 H, J = 7), 0.85 (s, 3 H), 1.16 (s, 3 H), 2.97 (q, 1 H, J = 7), 3.53 (br s, 1 H), 6.95–7.8 (m, 18 H). Anal. Calcd for C₃₁H₂₉NO: C, 86.3; H, 6.8; N, 3.2. Found: C, 86.2; H, 6.7; N, 3.2. (26) (a) Glaser, C. Liebigs Ann. Chem. **1870**, 154, 154. (b) Ashworth, F.;

⁽²⁸⁾ Absolute configurations of carboxylic acids were assigned by both the sign of optical rotation and the order of elution on HPLC. The *R*, *R* amide elutes second according to: (a) Helmchen, G.; Volter, H.; Schüle, W. *Tetrahedron Lett.* 1977, 1417. (b) Helmchen, G.; Nill, G.; Flockerzi, D.; Schüle, W.; Youssef, M. S. K. Angew. Chem., Int. Ed. Engl. 1979, 18, 62.

22a remained to be determined. Hydrogenolysis of 22a to remove the phenylfluorenyl group provides the free amino alcohol 24a in quantitative yield. Acylation of 24a with carbonyl-diimidazole produced the cyclic carbamate 25a. As a comparison for NMR analysis, the inseparable mixture of amino alcohols 22b obtained from hydrogenation of the minor allylic alcohol 21b was similarly converted to cyclic carbamates 25b. The chemical shifts and vicinal coupling constants of the three cyclic carbamate isomers are collected in Chart I. From these NMR data and a literature comparison,²⁹ the alcohol group of major isomer 22a is assigned the R configuration. This assignment was confirmed by NOESY ¹H NMR experiments on cyclic carbamates 25a and 25b. Dipolar coupling between the cis C2 and C3 ring hydrogens was observed only in carbamate 25a, while no dipolar coupling was observed between the trans hydrogens of carbamates 25b. Preference for this stereochemistry may be the result of attack of the organometallic reagent from the least sterically crowded side of a nonchelated transition state, in which the bulky PhFl-amine is assigned as the largest substituent.³⁰

When attempting to oxidize 21, we initially avoided the use of dimethyl sulfide/N-chlorosuccinimide, fearing allylic chloride formation.³¹ Instead manganese dioxide was employed and produced α,β -unsaturated ketone 23 in low yield along with a major side product resulting from oxidation of the alkyl amine and loss of protecting group. When other methods for oxidizing allylic alcohols (CrO₃/H₂SO₄, DDQ, TFAA/DMSO, SO₃/ pyridine) were employed, none of the desired α,β -unsaturated ketone 23 was produced. Finally, the dimethyl sulfide/Nchlorosuccinimide oxidation was tried and produced the desired α,β -unsaturated ketone 23 in >80% yield.

Although α,β -unsaturated ketone 23 opens up many synthetic doors to possible 1,2- and 1,4-addition reactions, we confined our exploration to reduction of the double bond. Rhodium tris(triphenylphosphine) chloride proved to be an effective catalyst for selectively reducing the double bond without reduction of the carbonyl group or hydrogenolytic cleavage of the phenylfluorenyl With 15 mol % of catalyst and a 48-h reaction in group. MeOH/EtOH, there was obtained an 85/15 ratio of diastereomeric amino ketones 18 and starting α,β -unsaturated ketone 23 in 85% yield after chromatography. The less polar major 2S,4Risomer of 18 can be isolated in pure form from the mixture and converted to carboxylic acid 15 of >99% enantiomeric purity. The mixture of minor isomer 18 and α,β -unsaturated ketone 23 can be recycled through the reduction process to produce pure diastereomers 18 in 75% yield after one recycle.

Stereoselectivity in Alkylation of Amino Ketones 9 and 17. The formation of (R)- α -methylpentanoic acid (12) and (R)- α phenylpropanoic acid (15) from oxidative degradation of the major diastereomers of 10 and 17 indicates that alkylation of the ketone enolate gives a predominance of the R configuration at the newly formed chiral center. Evidence supporting the Z enolate geometry is provided by trapping the potassium enolate of 9 with tert-butyldimethylsilyl chloride, producing silyl enol ether 26 as a single isomer. The Z double bond conformation of enol ether 26 was initially assigned by NOE difference spectroscopy³² of enol ether 26 which showed a nuclear Overhauser effect between the vinyl proton (δ 5.27) and both the α -proton (δ 2.76) and the methylene protons adjacent to the enol double bond (δ 2.2) with no NOE between the α -proton and the methylene protons. The Z assignment was confirmed with a NOESY ¹H NMR experiment. Because it avoids interaction between the alkyl chain and the PhFl-amine, the Z bond geometry of amino ketone enolate and enol ether is the more stable enol conformation.

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Figure 1. Influence of the enolate stereochemistry of α -(PhFl)amino ketones on diastereomer formation on alkylation at the α' -carbon.

The direction from which the electrophile approaches the Z enolate is dependent on the conformation about the α -center of the amino ketone. The two transition-state conformations that best minimize steric interactions and maximize polar effects necessary for alkylation are shown in Figure 1. They are (1) the chelated transition state A in which the nitrogen and enolate oxygen are held coplanar by electrostatic interaction with the potassium cation and (2) the nonchelated transition state B in which the amino and methyl groups are oriented gauche to the enolate oxygen.

Electrophilic attack of the prochiral enolate from the least hindered side provides the R isomer in the case of the chelated model and the S isomer from attack of the nonchelated transition state. The chelated transition state is more stable than the nonchelated since it avoids steric interactions of the α -proton with the enolate vinyl proton and the methyl group with the enolate oxygen anion. Alkylation of this more stable chelated conformation produces a preference for the R stereoisomer.

Conclusion

Regioselective enolization and alkylation of N-(PhFl)amino ketones has been used to prepare optically pure α' -alkyl branched α -amino ketones. Selective epimerization of the α' -center allows for control over diastereomeric selectivity after alkylation of the (PhFl)amino ketone by providing a means to recycle the undesired isomer. Deprotection and subsequent oxidation of diastereomerically pure α' -alkyl branched α -amino ketone produce α -alkyl-substituted carboxylic acids of >99% enantiomeric purity.

Experimental Section

General Procedures. Unless otherwise noted all reactions were run under a nitrogen or argon atmosphere. Tetrahydrofuran (THF) was distilled from LiAlH₄; dimethylformamide (DMF), hexamethylphosphoramide (HMPA), N,N,N',N'-tetramethylethylenediamine (TMEDA), diisopropylamine, hexamethyldisilazane, toluene, and benzene were distilled from CaH₂. Potassium hexamethyldisilazide was used either as a 1 M THF solution prepared from potassium hydride and hexamethyldisilazane or as a 0.6 M solution in toluene.³³ Final reaction mixture solutions were dried over Na₂SO₄. Chromatography was done on 230-400-mesh silica gel; TLC was done on aluminum backed silica plates. Melting points were determined on a Swissco melting point apparatus and are uncorrected. ¹H NMR spectra were recorded in CDCl₃ and are reported in ppm (δ units) downfield of internal tetramethylsilane ((CH₃)₄Si), and J values are given in hertz.

2(S)-[N-(Phenylsulfonyl)amino]-3-heptanone (2). *n*-Butyllithium in hexane (30 mL, 1.5 M) was added over 15 min to a -78 °C solution of N-(phenylsulfonyl)-L-alanine (1, 2.29 g, 10 mmol) in 50 mL of THF. The cooling bath was removed, the solution was allowed to attain room temperature, and after 4 h, the solution was poured into a rapidly stirred solution of 1 N NaH₂PO₄ (75 mL). The aqueous layer was separated

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⁽³³⁾ Available from Callery Chemical Co., Callery, PA.

and extracted with 3×75 mL of EtOAc, and the combined organic layers were washed with NaHCO₃ (2 × 50 mL) and brine (75 mL) and dried. Removal of solvent left an oil, which was chromatographed with 25% EtOAc in hexane as eluant. Concentration of the collected fractions under vacuum gave 1.44 g (54%) of solid 2: mp 64-66 °C after recrystallization from EtOAc/hexane; TLC (1/1 hexane/EtOAc) R_f 0.38; $[\alpha]^{20}_{D}$ 64° (c 0.72, CHCl₃); ¹H NMR δ 0.81 (t, 3 H, J = 7.1), 1.12 (m, 2 H), 1.31 (d, 3 H, J = 7.1), 1.35 (m, 2 H), 2.34 (m, 2 H), 3.94 (m, 1 H), 5.79 (d, 1 H, J = 5.9), 7.5 (m, 3 H), 7.83 (m, 2 H). Anal. Calcd for C₁₃H₁₉NO₃S: C, 58.0; H, 7.1; N, 5.2. Found: C, 57.8; H, 7.0; N, 5.2.

(2S)-2-[N-(Phenylsulfonyl)-N-methylamino]-3-heptanone (5). To a solution of diisopropylamine (0.4 mL, 2.9 mmol) in 8 mL of THF was added a 1.5 N solution of *n*-butyllithium in hexane (1.84 mL, 1.5 M) at -78 °C. The mixture was stirred 15 min and then a solution of 2 (323 mg, 1.2 mmol) in 2 mL of THF was added. After stirring 1 h at -78 °C, the solution was treated with iodomethane (97 μ L, 1.56 mmol) and HMPA (2 mL) and stirred an additional 2 h at -78 °C. Methanol (1 mL) was added, the cooling bath was removed, 10 mL of 1 M NaH₂PO₄ was added, the mixture was extracted with 3 × 15 mL of EtOAc, and the combined organic layers were washed with 25 mL of brine. Drying and evaporating the solvent left an oil. Chromatography, eluting with 15% EtOAc in hexane, and concentration of the collected fractions in vacuum gave 257 mg (80%) of recovered 2 and 32 mg (9%) of 5: TLC (3/1 hexane/EtOAc) R_f 0.36; ¹H NMR δ 0.93 (t, 3 H, J = 6.9), 0.97 (m, 2 H), 1.03 (d, 3 H, J = 6.8), 1.27 (m, 2 H), 1.62 (m, 1 H), 2.69 (s, 3 H), 3.07 (m, 1 H), 4.75 (m, 1 H), 7.58 (m, 3 H), 7.8 (m, 2 H).

(2S,3R)- and (2S,3S)-2-[N-(9-Phenylfluoren-9-yl)amino]-3-heptanol (8).³⁴ A solution of [N-(9-phenylfluoren-9-yl)amino]-L-alaninal (7, 1.1 g, 3.5 mmol)⁹ in THF (30 mL) was chilled to -78 °C and treated with 10 mL of a freshly prepared 1 M solution of n-butylmagnesium bromide in THF over 5 min. The mixture was stirred an additional 10 min and then the cooling bath was removed and the reaction mixture was allowed to attain room temperature. After stirring 1 h, the mixture was treated with 1 M NaH₂PO₄ (40 mL) and extracted with EtOAc (3×25 mL), and the combined organic extractions were washed with saturated $NaHCO_3~(30~mL)$ and brine (30 mL) and dried and concentrated to an oil, which was chromatographed with a gradient of 5-25% ether in hexane. Concentration of the collected fractions yielded 1.18 g (90%) of 8. Eluting first was the minor 2S,3S isomer: TLC (3/1 hexane/ EtOAc) $R_f 0.31$; $[\alpha]^{20}_{D} 239^{\circ}$ (c 1.0, CHCl₃); ¹H NMR δ 0.47 (d, 3 H, J = 6.3), 0.74 (t, 3 H, J = 6), 1.05–1.4 (m, 6 H), 1.94 (m, 1 H), 2.72 (br m, 2 H), 2.99 (m, 1 H), 7–7.75 (m, 13 H). Eluting second was the major 2*S*,3*R* isomer: mp 78–79 °C; $R_f 0.28 [\alpha]^{20} D 214^\circ$ (*c* 1.15, CHCl₃); ¹H NMR δ 0.52 (m, 6 H), 0.8-1.18 (m, 6 H), 1.84 (br s, 1 H), 2.05 (m, 1 H), 2.85 (m, 1 H), 7.08-7.7 (m, 13 H). Anal. Calcd for C₂₆H₂₉NO: C, 84.1; H, 7.9; N, 3.8. Found: C, 84.3; H, 8.0; N, 3.7.

(2S)-2-[N-(9-Phenylfluoren-9-yl)amino]-3-heptanone (9). To a stirred solution of N-chlorosuccinimide (1.66 g, 12.5 mmol) in 40 mL of toluene at 0 °C was added dimethyl sulfide (1.2 mL, 16.6 mmol). After 20 min the suspension was cooled to -25 °C and a solution of (2S,3R)- and (2S,3S)-2-[N-(9-phenylfluorenyl)amino]-3-heptanol (8, 3.07 g, 8.3 mmol) in 10 mL of toluene was added over 10 min. Stirring at -25 °C was maintained for 3 h and then triethylamine (1.7 mL, 12.5 mmol) in 5 mL of toluene was added over 5 min. The cooling bath was removed, the solution was allowed to reach room temperature, 50 mL of H₂O was added, the aqueous layer was separated and extracted with 3×25 mL of EtOAc, and the combined organic phase was treated with 50 mL of brine and dried. Removal of the solvent left an oil which was chromatographed, with 25% EtOAc in hexane as eluant. Concentration of the collected fractions gave 300 mg (10%) of recovered 8 and 9, which solidified under vacuum to a low-melting white solid (2.46 g, 80%): mp 56-57 °C; TLC (3/1 hexane/EtOAc) R_f 0.52 $[\alpha]^{20}_D$ -22° (c 1.16, CHCl₃); ¹H NMR δ 0.74 (t, 3 H, J = 7), 0.97 (d, 3 H, J = 7.1), 1.1 (m, 4 H), 1.53 (m, 1 H), 2.04 (m, 1 H), 2.64 (q, 1 H, J = 7), 3.5 (br m, 1 H), 7.05-7.5 (m, 11 H), 7.65 (m, 2 H). Anal. Calcd for C₂₆H₂₇NO: C, 84.5; H, 7.4; N, 3.8. Found: C, 84.4; H, 7.3; N, 3.7.

General Procedure for Oxidation of Amino Alcohols to Amino Ketones. Dimethyl sulfide ($150 \ \mu$ L, 200 mol %) was added to a 0 °C suspension of *N*-chlorosuccinimide (200 mg, 150 mol %) in 4 mL of toluene and the mixture was stirred 20 min and then cooled to -25 °C. The amino alcohol (1 mmol) in 2 mL of toluene was added and then stirred for 5 h at -25 °C. Triethylamine ($280 \ \mu$ L, 200 mol %) in 1 mL of toluene was added and the mixture was stirred for 10 min and then allowed to warm to room temperature over an additional 15 min. Water (15 mL) was added, the aqueous layer was extracted with EtOAc ($3 \times 15 \ mL$), and the combined organic layers were washed with brine, dried, and concentrated to an oil, which was chromatographed, with 2.5–10% EtOAc in hexane as eluant.

(3S)-1-Phenyl-3-[N-(9-phenylfluoren-9-yl)amino]-2-butanone (17): yield 67%; mp 79-82 °C; TLC (3/1 hexane/EtOAc) $R_f 0.45$; $[\alpha]^{20}_{\rm D}$ -241° (c 1.04, CHCl₃); ¹H NMR δ 0.96 (d, 3 H, J = 7.1), 2.82 (q, 1 H, J = 7.1), 2.87 (d, 1 H, J = 6.6), 3.23 (d, 1 H, J = 6.6), 3.27 (br s, 1 H), 6.75 (m, 2 H), 7-7.8 (m, 16 H). Anal. Calcd for C₂₉H₂₅NO: C, 86.3; H, 6.2; N, 3.5. Found: C, 86.3; H, 6.2; N, 3.4.

Alcohol 16 was recovered in 8% yield.

(25,4*R*)-2-[*N*-(9-Phenylfluoren-9-yl)amino]-4-phenyl-3-pentanone (18a): yield 80%; TLC (5% EtOAc in hexane) $R_f 0.18$; $[\alpha]^{20}_D - 319^\circ$ (*c* 1.4, CHCl₃); ¹H NMR δ 0.68 (d, 3 H, J = 6.9), 0.83 (d, 3 H, J = 7), 2.76 (m, 2 H), 6.85-7.8 (m, 18 H). Anal. Calcd for C₃₀H₂₇NO: C, 86.3; H, 6.5; N, 3.3. Found: C, 85.9; H, 6.6; N, 3.3.

Alcohol 22a was recovered in 10% yield.

(4S)-2-Phenyl-4-[N-(9-phenylfluoren-9-yl)amino]-1-penten-3-one (23): yield 84%; TLC (5% EtOAc in hexane) R_f 0.16; ¹H NMR δ 0.98 (d, 3 H, J = 7.1), 3.27 (q, 1 H, J = 7.2), 5.24 (s, 1 H), 5.48 (s, 1 H), 7.2–7.8 (m, 18 H). Anal. Calcd for C₃₀H₂₅NO: C, 86.7; H, 6.1; N, 3.4. Found: C, 86.7; H, 6.3; N, 3.2.

General Procedure for Alkylation of Amino Ketone 9. A solution of 9 (370 mg, 1.0 mmol) in 10 mL of THF was treated with a solution of potassium hexamethyldisilazide in THF (1.4 mL, 1 M) at -78 °C. The solution was stirred for 1 h at -78 °C, and then the alkyl halide (1.4 mmol) was added. The mixture was stirred for 1.5-8.5 h at -78 °C (Table I) and quenched with 1 mL of methanol, the cooling bath was removed, and 10 mL of 1 M KH₂PO₄ was added. Extraction with 3 × 15 mL of EtOAc, washing the combined organic layers with 25 mL of brine, and drying, followed by evaporation of the solvent, left an oil, which was chromatographed with 2.5% EtOAc in hexane as eluant.

(25,4*R*)- and (25,4*S*)-2-[*N*-(9-Phenylfluoren-9-yl)amino]-4-methyl-3-heptanone (10): yield 94%. Eluting first was the major 2*S*,4*R* diastereomer as an oil: TLC (5% EtOAc in hexane) R_f 0.34; ¹H NMR δ 0.2 (d, 3 H, *J* = 7), 0.77 (t, 3 H, *J* = 7), 0.86 (m, 1 H), 0.99 (d, 3 H, *J* = 7.2), 1.05 (m, 2 H), 1.44 (m, 1 H), 2.14 (m, 1 H), 2.78 (m, 1 H), 3.61 (br m, 1 H), 7.04-7.5 (m, 11 H), 7.7 (m, 2 H). This was followed by the minor 2*S*,4*S* diastereomer: mp 89 °C; R_f 0.29; $[\alpha]^{20}_D$ -143° (*c* 0.3, CHCl₃); ¹H NMR δ 0.63 (t, 3 H), 0.68 (m, 2 H), 0.84 (d, 3 H, *J* = 6.7), 0.9 (m, 2 H), 1.0 (d, 3 H, *J* = 7.2), 2.19 (m, 1 H), 2.74 (m, 1 H), 3.67 (br m, 1 H), 7.1-7.5 (m, 11 H), 7.65 (m, 2 H). Anal. Calcd for C₂₇H₂₉NO: C, 84.6; H, 7.6; N, 3.6. Found: C, 84.6; H, 7.7; N, 3.6.

(25,4*R*)- and (25,45)-2-[*N*-(9-Phenylfluoren-9-yl)amino]-4-allyl-3heptanone:³⁵ yield 77% (85%). Eluting first was the minor 25,4*R* diastereomer: TLC (5% EtOAc in hexane) R_f 0.35; ¹H NMR δ 0.72 (t, 3 H, *J* = 7), 0.82 (d, 3 H, *J* = 6.4), 0.91 (m, 2 H), 1.2 (m, 2 H), 1.98 (m, 3 H), 3.27 (m, 2 H), 4.93 (m, 2 H), 5.46 (m, 1 H), 7.1-7.45 (m, 11 H), 7.7 (m, 2 H). This was followed by the major 25,4*R* diastereomer: R_f 0.3; ¹H NMR δ 0.77 (t, 3 H, *J* = 6.9), 1.0 (d, 3 H, *J* = 7.2), 1.1-1.6 (m, 6 H), 2.2 (m, 1 H), 2.75 (m, 1 H), 3.63 (br m, 1 H), 4.78 (m, 2 H), 5.25 (m, 1 H), 7.2-7.55 (m, 11 H), 7.75 (m, 2 H). Anal. Calcd for C₂₉H₃₁NO: C, 85.0; H, 7.6; N, 3.4. Found: C, 85.2; H, 7.8; N, 3.3.

(25,4*R*)- and (25,4*S*)-2-[*N*-(9-Phenylfluoren-9-yl)amino]-4-benzyl-3-heptanone:³⁵ yield 93%. Anal. Calcd for C₃₃H₃₃NO: C, 86.2; H, 7.2; N, 3.1. Found: C, 86.2; H, 7.2; N, 3.1. Eluting first was the minor 2S,4*R* isomer: TLC (5% EtOAc in hexane) R_f 0.28; ¹H NMR δ 0.5 (d, 3 H, *J* = 7.2), 0.62 (t, 3 H), 0.69–0.9 (m, 4 H), 2.46 (m, 2 H), 2.6 (q, 1 H, *J* = 7.2), 2.76 (m, 1 H), 3.55 (br s, 1 H), 6.95–7.75 (m, 18 H). This was followed by the major 2S,4S isomer: R_f 0.26; $[\alpha]^{20}_{D}$ -126° (*c* 0.6, CHCl₃); ¹H NMR δ 0.7 (t, 3 H), 0.85 (m, 2 H), 0.97 (d, 3 H, *J* = 7.2), 1.05 (m, 1 H), 1.46 (m, 1 H), 1.72 (m, 2 H), 2.41 (m, 1 H), 2.85 (q, 1 H, *J* = 7.2), 3.45 (br m, 1 H), 6.8–7.8 (m, 18 H).

Methyl (5S)-5-[(9-phenylfluoren-9-yl)amino]-2-methyl-4-oxo-3propylhexanoate: yield 67% as an oil. Anal. Calcd for $C_{30}H_{33}NO_3$: C, 79.1; H, 7.3; N, 3.1. Found: C, 79.3; H, 7.3; N, 3.1. Eluting first was the major isomer: TLC (9/1 hexane/EtOAc) R_f 0.26; ¹H NMR δ 0.65 (d, 3 H, J = 7.2), 0.77 (t, 3 H, J = 6.6), 0.99 (m, 3 H), 1.0 (d, 3 H, J= 7.1), 1.49 (m, 1 H), 1.62 (m, 1 H), 2.83 (m, 2 H), 3.57 (s, 3 H), 7.19–7.79 (m, 13 H). This was followed by the minor diastereomer: R_f 0.21; ¹H NMR δ 0.57 (t, 3 H, J = 6), 0.85 (m, 4 H), 1.01 (d, 3 H, J = 6.2), 1.06 (d, 3 H, J = 7.2), 2.66 (m, 2 H), 2.82 (m, 1 H), 3.6 (s, 3 H), 7.19–7.79 (m, 13 H).

Periodate Oxidation of Amino Ketones to Carboxylic Acids. To a solution of major 2S,4R diastereometric amino ketone (0.29 mmol) in methanolic HCl (10 mL, 1.5 M) was added 50 wt % of 10% palladium on carbon. The suspension was placed under an atmosphere of hydrogen at 50 psi on a Parr shaker for 15 h at room temperature. The mixture was filtered through Celite which was washed with MeOH (20 mL) and

⁽³⁴⁾ Assignment of the stereochemistry of the carbinol function is based on analogy with 22.

⁽³⁵⁾ Assignment of the stereochemistry at the α' -carbon is based on analogy with 10.

EtOAc (20 mL). The filtrate and washings were concentrated in vacuo to a residue which was partitioned between toluene (15 mL) and H_2O (10 mL), the organic layer was extracted with water (3 × 5 mL), and the aqueous layers were combined, washed with toluene (5 mL), and concentrated to an oil, which was redissolved in a solution of periodic acid (230 mg, 1 mmol) in 10 mL of H_2O . Methanol (10 mL) was added and the pH adjusted to 6 ± 0.5 with benzyltrimethylammonium hydroxide (40% in MeOH). The reaction vessel was flushed with nitrogen and stoppered, and the contents were stirred for 24 h at room temperature, cooled to 0 °C, acidified to pH 2 with concentrated HCl, and extracted with ether (4 × 10 mL). The ether layers were combined and extracted with saturated NaHCO₃ (4 × 10 mL), and the aqueous extracts were combined, chilled to 0 °C, acidified with concentrated HCl to pH 2, and extracted with ether (4 × 10 mL). Evaporation of the combined, washed (brine, 10 mL), and dried organic phase left a clear oil.

(*R*)- α -Methylpentanoic acid (12): yield 60%; TLC (1/1 hexane/ EtOAc) $R_f 0.47$; $[\alpha]^{20}_{D} -9.2^{\circ}$ (c 0.13, CHCl₃) (lit.³⁶ $[\alpha]^{20}_{D} -18.4^{\circ}$ (neat)); ¹H NMR δ 0.92 (t, 3 H, J = 7), 1.18 (d, 3 H, J = 7), 1.38 (m, 3 H), 1.67 (m, 1 H), 2.46 (m, 1 H).

(*R*)-*a*-Phenylpropanoic acid (15): yield 72%; TLC (1/1 EtOAc/ hexane) $R_f 0.42$; $[\alpha]^{20}_{D}$ -67.5° (*c* 0.4, CHCl₃) (lit.³⁷ $[\alpha]^{20}_{D}$ -75.3° (*c* 1.6, CHCl₃)); ¹H NMR δ 1.5 (d, 3 H, J = 7.1), 3.74 (q, 1 H, J = 7.1), 7.29 (m, 5 H).

Optical Purity of 12. To a solution of **12** (24 mg, 0.2 mmol) and N-methylmorpholine (29 μ L, 0.26 mmol) in THF (2 mL) at -18 °C was added 27 μ L (0.2 mmol) of isobutyl chloroformate. The solution was stirred for 60 s and then 80 μ L (0.6 mmol) of (*R*)- or (*RS*)- α -phenyl-ethylamine was added. The solution was stirred at -18 °C for 2 h and then partitioned between EtOAc (3 mL) and NaH₂PO₄ (1 M, 3 mL). The organic phase was washed with saturated NaHCO₃ (2 × 3 mL) and brine (5 mL) and dried and concentrated to a solid that was used for HPLC analysis with 12.5% EtOAc in hexanes as eluant. ¹H NMR δ 0.8 (m, 3 H), 1.07 (t, 3 H, J = 7.5), 1.35 (m, 2 H), 1.43 (d, 3 H), 1.59 (m, 1 H), 2.1 (m, 1 H), 3.77 (m, 1 H), 5.07 (m, 1 H), 5.72 (br d, 1 H, J = 0.7), 7.26 (m, 5 H). Anal. Calcd for C₁₄H₂₁NO: C, 76.7; H, 9.7; N, 6.4. Found: C, 76.5; H, 9.7; N, 6.3.

(3S)-1-Phenyl-3-[N-(9-phenylfluoren-9-yl)amino]-2-butanol (16).34 n-Butyllithium (15 mL, 1.5 M in hexanes) was added to a room temperature solution of 10 mL of toluene (distilled fresh from sodium metal) and 3.5 mL of TMEDA. The mixture was brought to reflux for 30 min, allowed to cool to room temperature, and then the benzyllithium solution was added over 15 min to a -78 °C solution of N-(9-phenylfluoren-9yl)alaninal (7, 1.22 g, 3.9 mmol) in THF (30 mL). After the addition the suspension was brought to 0 °C and stirred for 1.5 h. Methanol (3 mL) was added followed by 60 mL of 1 M KH₂PO₄. The mixture was allowed to attain room temperature, extracted with EtOAc (3×20 mL), and the combined organic extracts were washed with brine (50 mL), dried, and concentrated to an oil which was chromatographed with a gradient of 10-50% EtOAc in hexane as eluant. Removal of solvent under reduced pressure yielded 1.27 g (80%) of 16 as a foam. Anal. Calcd for C₂₉H₂₇NO: C, 85.9; H, 6.7; N, 3.4. Found: C, 85.7; H, 6.7; N, 3.4. Eluting first from the column was the major 2S,4R isomer: TLC $(3/1 \text{ hexane/EtOAc}) R_f 0.33$; ¹H NMR $\delta 0.62$ (d, 3 H, J = 6.3), 2.17 (m, 1 H), 2.37 (dd, 1 H, J = 13.9, 8.9), 2.67 (dd, 1 H, J = 13.8, 3.1),3.35 (m, 1 H), 7.0–7.8 (m, 18 H). This was closely followed by the minor 2S,4S isomer: R_f 0.24; ¹H NMR δ 0.78 (d, 3 H, J = 6.7), 2.14 (m, 1 H), 2.29 (dd, 1 H, J = 14, 5.3), 2.51 (dd, 1 H, J = 14, 8.3), 3.31 (m, 1 H), 6.8 (m, 2 H), 7-7.75 (m, 16 H).

(2S,4R)- and (2S,4S)-2-[N-(9-Phenylfluoren-9-yl)amino]-4-phenyl-3-pentanone (18). To a -78 °C solution of (3S)-1-phenyl-3-[N-(9phenylfluoren-9-yl)amino]-2-butanone (17, 0.4 g, 1 mmol) in THF (10 mL) was added 1.15 mL of potassium hexamethyldisilazane (1 M in THF). After the mixture was stirred for 1 h at -78 °C, methyl iodide (68 μ L, 1.1 mmol) was added, the reaction mixture was stirred for an additional 3.5 h at -78 °C, MeOH (0.5 mL) was added, and the cooling bath was removed. The solution was partitioned between 1 M $\rm KH_2PO_4$ (10 mL) and EtOAc (10 mL) and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were washed with brine, dried, and concentrated to an oil, which was chromatographed with 5% EtOAc in hexane as eluant. Removal of the solvent yielded 330 mg (79%) of a 4/1 mixture of 18. Eluting first was the major 2S,4R diastereomer: mp 94-96 °C; TLC (5% EtOAc in hexane) $R_f 0.18$; $[\alpha]^{20}$ -319° (c 1.4, CHCl₃); ¹H NMR δ 0.68 (d, 3 H, J = 6.9), 0.83 (d, 3 H, J = 7), 2.76 (m, 2 H), 6.85–7.8 (m, 18 H). Anal. Calcd for $C_{30}H_{27}NO$: C, 86.3; H, 6.5; N, 3.3. Found: C, 85.9; H, 6.6; N, 3.3. This was followed by the minor 2S,4S isomer $[R_f 0.16; {}^{1}H NMR \delta 0.96 (d, 3 H, 10.5)]$ J = 7.2, 1.18 (d, 3 H, J = 7), 2.74 (q, 1 H, J = 7.2), 3.63 (q, 1 H, J

= 7), 6.6 (m, 2 H), 7–7.6 (m, 16 H)] and 50 mg (13%) of recovered 17.

Lead Tetraacetate Oxidation of Amino Ketones to Carboxylic Acids. To a solution of N-(PhF)amino ketone (0.18 mmol) in acetic acid (4 mL) was added palladium on carbon (30 mg, 10 wt %) and the mixture was stirred under a hydrogen atmosphere for 1 h. Water (1.3 mL) was added and the suspension was filtered on Celite and washed with 3/1 acetic acid/water (4 mL). The filtrate and washings were combined, lead tetraacetate (0.54 mmol) was added, and the mixture was stirred for 3.5 h at room temperature. A solution of 10% sulfuric acid (4 mL) was added and the mixture filtered through Celite, which was washed with water (5 mL). The filtrate and washings were combined, diluted with brine (5 mL), and extracted with Et_2O (5 × 10 mL). The combined organic layer was evaporated to an oil, which was partitioned between ether (20 mL) and saturated NaHCO3 (10 mL). The organic phase was extracted with saturated NaHCO₃ (4×10 mL), and the basic washes were combined, cooled to 0 °C, acidified to pH 2 with concentrated HCl, and then extracted with Et₂O (5 \times 10 mL). The organic layers were washed with brine (10 mL), dried, and evaporated to an oil containing (R)- α -methylpentanoic acid (12) in 16% yield and (R)- α -phenylpropionic acid (15) in 69% yield.

Optical Purity of 15.³⁸ To a -18 °C solution of (R)- α -phenylpropanoic acid (**15**, 5 mg, 0.03 mmol) and *N*-methylmorpholine (5 μ L, 0.04 mmol) in THF (0.5 mL) was added 5 μ L (0.04 mmol) of isobutyl chloroformate. The solution was stirred 60 s and then 13 μ L (0.1 mmol) of (*R*)- or (*RS*)- α -phenylethylamine was added. After stirring for 30 min at -18 °C, the solution was partitioned between EtOAc (1 mL) and NaH₂PO₄ (1 mL, 1 M) and the aqueous layer was extracted with 1 mL of EtOAc. The combined organic phase was washed with saturated NaHCO₃ (1 mL) and brine (1 mL), dried, and concentrated to a solid that was used for HPLC analysis with 12.5% EtOAc in hexanes as eluant: ¹H NMR δ 1.39 (d, 3 H), 1.5 (d, 3 H, J = 7.1), 3.56 (m, 1 H), 5.08 (m, 1 H), 5.5 (m, 1 H), 7.0-7.4 (m, 10 H). Anal. Calcd for C₁₇H₁₉NO: C, 80.6; H, 7.6; N, 5.5. Found: C, 80.4; H, 7.4; N, 5.4.

(4S)-2-Phenyl-4-[N-(9-phenylfluoren-9-yl)amino]-1-penten-3-ol (21). To dry, finely ground magnesium turnings (1.4 g) was added 10 mL of a solution of 6 mL of α -bromostyrene and 40 mL of THF. The mixture was brought to reflux for 60 s when the heating bath was removed and the rest of the THF solution added dropwise over 15 min. After stirring for 45 min, the Grignard solution (35 mL) was added over 15 min to a -78 °C solution of N-(9-phenylfluoren-9-yl)alaninal (7, 2.4 g, 7.67 mmol) in THF (50 mL). When addition was complete, the suspension was brought to 0 °C and stirred for 1 h, and 3 mL of MeOH was added. The mixture was allowed to reach room temperature and was then washed with 100 mL of 1 M KH₂PO₄, and the aqueous layer was extracted with EtOAc (4 \times 40 mL). The combined organic phase was washed with brine (100 mL), dried, and concentrated to an oil, which was chromatographed with a gradient of 10-25% EtOAc in hexane as eluant. Removal of solvent under reduced pressure gave a 2/1 mixture of alcohols **21a** and **21b**, yield 2.68 g (84%), as a solid. Anal. Calcd for $C_{30}H_{27}NO$: C, 86.3; H, 6.5; N, 3.4. Found: C, 86.4; H, 6.5; N, 3.3. Eluting first was the major 3R, 4S isomer: TLC (3/1 EtOAc/hexane) $R_f 0.32$; ¹H NMR δ 0.62 (d, 3 H, J = 6.7), 1.65 (br s, 1 H), 2.17 (m, 1 H), 3.59 (s, 1 H), 4.14 (d, 1 H, J = 1.3), 5.2 (t, 1 H, J = 1.4), 5.3 (t, 1 H, J = 1.7), 6.55 (m, 2 H), 7.0-7.8 (m, 16 H). This was closely followed by the minor 3R,4S isomer: $R_f 0.24$; ¹H NMR $\delta 0.42$ (d, 3 H, J = 6.3), 2.3 (m, 2 H), 4.02 (d, 1 H, J = 8), 5.22 (s, 1 H), 5.30 (d, 1 H, J = 1.4), 7.05-7.75 (m, 1.05)18 H)

(2S,3R,4R)-4-Phenyl-2-[N-(9-phenylfluoren-9-yl)amino]-3-pentanol (22a). A solution of major 3R,4S isomer 21a (208 mg, 0.5 mmol) and Rh(P(C₆H₅)₃)₃Cl (20 mg) in benzene (5 mL) was stirred at room temperature for 23 h, after which the solvent was evaporated and the residue was chromatographed with a gradient of 10-50% EtOAc in hexane. Concentration of the collected fractions left 198 mg (94%) of 22a as an oil: TLC (25% EtOAc/hexane) $R_f 0.36$; $[\alpha]^{20}_{D} 66.3^{\circ}$ (c 1.04, CHCl₃); ¹H NMR δ 0.64 (d, 3 H, J = 7), 0.82 (d, 3 H, J = 6.7), 1.59 (br s, 1 H), 2.43 (m, 2 H), 2.8 (br s, 1 H), 3.06 (dd, 1 H, J = 2.2, 8.7), 6.95-7.8 (m, 18 H). Anal. Calcd for C₃₀H₂₉NO: C, 85.9; H, 7.0; N, 3.3. Found: C, 85.8; H, 7.2; N, 3.2.

Reduction of (4S)-2-Phenyl-4-[N-(9-phenylfluoren-9-yl)amino]-1-penten-3-one (23). To a solution of $Rh(P(C_6H_5)_3)_3Cl$ (100 mg, 0.1 mmol) in EtOH (5 mL) was added 23 (640 mg, 1.5 mmol) in 1/1

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⁽³⁸⁾ The mixed carboxylic-carbonic acid anhydride intermediate formed in this procedure may collapse to phenyl methyl ketene and react with phenylethylamine to produce amides with lower de's (90-99%) depending on reaction conditions. We have developed an alternative procedure to activate the carboxylic acid which uses N^3 -methyl-1,1'-carbonylbis(imidazole) triflate to make the carboxylic acid N-methylimidazolium, which couples to phenylethylamine without loss of enantiomeric purity. This method will be described in a forthcoming paper (Saha, A.; Rapoport, H., in preparation).

MeOH/EtOH (10 mL), and the mixture was stirred under a balloon of hydrogen for 48 h. The solvent was evaporated and the residue was chromatographed with 5% EtOAc in hexane. Eluting first was the major 2S,4R isomer **18a** (155 mg, 25%) followed by a mixture of minor 2S,4S isomer **18b** and starting material **23** (395 mg, 62%). The mixture of minor isomer **18b** and **23** (375 mg, 0.9 mmol) in MeOH (6 mL) was resubjected to Rh(P(C₆H₅)₃)₃Cl (140 mg, 0.15 mmol) in EtOH (4 mL) and stirred under a hydrogen atmosphere for 48 h. Removal of the solvent and chromatography yielded 315 mg of the diastereomers **18**.

(2S,3R,4R)-2-Amino-4-phenyl-3-pentanol (24a). (2S,3R,4R)-4-Phenyl-2-[N-(9-phenylfluoren-9-yl)amino]-3-pentanol (23a, 640 mg, 1.5 mmol) was dissolved in methanol (20 mL) and to this solution was added three drops of concentrated HCl followed by palladium on carbon (300 mg of 10%). The suspension was shaken in a Parr apparatus under hydrogen at 55 psi for 26 h. The mixture was filtered through Celite, which was washed with MeOH (20 mL) and EtOAc (20 mL), and the combined organic phase was concentrated to a solid which was partitioned between H₂O (15 mL) and toluene (10 mL). The aqueous layer was washed with toluene (2 × 10 mL) and then basified with saturated K₂CO₃ (20 mL), diluted with brine (10 mL), and extracted with 3/1 CHCl₃/isopropyl alcohol (3 × 15 mL). After drying and evaporating, the combined organic phase left 24a: yield, 260 mg, 95%; mp 74-76 °C; ¹H NMR (CD₃OD) δ 1.21, (d, 3 H, J = 7.1), 1.27 (d, 3 H, J = 6.7), 2.77 (m, 1 H), 3.5 (m, 1 H), 3.84 (dd, 1 H, J = 9.5, 2.2), 7.2 (m, 5 H). **Preparation of Cyclic Carbamates.** To a solution of (2S,3S,4R)- and

(2S,3S,4S)-2-amino-4-phenyl-3-pentanol (24b, 70 mg, 0.47 mmol) in 3/1 THF/DMF (4 mL) at 0 °C was added carbonyldiimidazole (175 mg, 1.08 mmol), and the reaction vessel was flushed with nitrogen, and stoppered, and the contents were stirred for 14 h at 0 °C. Water (4 mL) was added to the suspension and the mixture was extracted with EtOAc $(3 \times 5 \text{ mL})$. The combined organic phase was washed with brine (10 mL), dried, and concentrated to an oil which was chromatographed (radial chromatography) with a gradient of 25-50% EtOAc in hexane as eluant. Concentration of the collected fraction yielded 40 mg (50%) of **25b** as a 2/1 mixture of diastereomers: TLC (3/1 EtOAc/hexane) $R_f 0.39$; ¹H NMR $\delta 0.96$ (d, 3 H), 1.2 (d, 3 H), 1.42 (d, 3 H), 1.45 (d, 3 H), 2.92 (m, 1 H), 3.05 (m, 1 H), 3.58 (m, 1 H), 3.63 (m, 1 H), 4.17 (dd, 1 H, J = 8.5, 6), 4.28 (dd, 1 H, J = 5.9, 6), 7.3 (m, 5 H). Carbamate **25a** was prepared in a similar manner and purified on a plate of silica gel (1000- μ m thickness): mp 154-155 °C; $R_f 0.35$; $[\alpha]^{20}_D 24^\circ$ (c 0.75, CHCl₃); ¹H NMR δ 1.25 (d, 3 H, J = 7.2), 1.25 (d, 3 H, J = 6), 3.04 (m, 1 H), 3.9 (dq, 1 H, J = 6.4, 6.4), 4.6 (dd, 1 H, J = 10.6, 6.4), 7.3 (m, 5 H). Anal. Calcd for C₁₂H₁₅NO₂: C, 70.2; H, 7.4; N, 6.8. Found: C, 70.4; H, 7.5; N, 6.5.

tert-Butyldimethylsilyl Enol Ether 26. To a solution of amino ketone 9 (200 mg, 0.54 mmol) in 6 mL of THF was added a 1 M solution of potassium hexamethyldisilazide in THF (0.76 mL) at -78 °C; the solution was stirred for 1 h at -78 °C and then tert-butyldimethylsilyl chloride (0.8 mmol) was added. The solution was stirred for 1 h at -78 °C, the solution was stirred for 1 h at -78 °C, the solution was stored for 1 h at -78 °C, the solution was stored for 1 h at -78 °C, the solution was stored for 1 h at -78 °C, the solution was stored for 1 h at -78 °C, the solution was stored for 1 h at -78 °C, the solution was stored for 1 h at -78 °C, the solution was stored was evaporated, and the residue was chromatographed on a chromatotron with 5% EtOAc and 0.25% Et₃N in hexanes as eluant. 26: ¹H NMR δ 0.0 (s, 3 H), 0.17 (s, 3 H), 1.15 (s, 9 H), 1.24 (t, 3 H, J = 6.2), 1.24 (d, 3 H, J = 6.7), 1.64 (m, 2 H), 2.2 (m, 2 H), 2.77 (q, 1 H, J = 6.7), 5.27 (t, 1 H, J = 7.1), 7.45–8.1 (m, 13 H).

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H⁺-Induced Release of Contents of Phosphatidylcholine Vesicles Bearing Surface-Bound Polyelectrolyte Chains

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Abstract: A semisynthetic vesicular membrane was constructed by immobilization of a synthetic polyelectrolyte [poly(2-ethylacrylic acid)] on the surface of a phosphatidylcholine bilayer. Immobilization was accomplished via Michael addition of polymer-bound thiol functions to a reactive maleimide handle incorporated into the lipid membrane in the form of dimyristoyl-*N*-[[4-(maleimidomethyl)cyclohexyl]carbonyl]phosphatidylethanolamine. Semisynthetic membranes prepared in this way are sensitive to hydrogen ion concentration and are subject to large variations in permeability with small changes in pH. Rapid and quantitative release of vesicle contents can be achieved by mild acidification within the physiological pH range.

Although conformational transitions in membrane-bound macromolecules provide the most general and powerful mechanisms for chemical and physical signaling processes in biology, the molecular details of such processes are not well understood. For example, it is only very recently that even the primary structure of the synaptic vesicle protein synaptophysin has been reported,¹ despite the critical role that such membrane proteins must play in the exocytic release of neurotransmitters from their vesicular storage sites.² The complexity of the natural membrane precludes, for the present, a precise description of the role of protein conformation. We describe in the present paper the construction of a much simpler model system: a "semisynthetic" vesicular membrane in which a well-defined conformational transition in a surface-bound polyelectrolyte chain causes rapid and quantitative release of vesicle contents. The semisynthetic membrane thus shares with its natural counterparts important

elements of structure and function, but retains a remarkable simplicity.

The design of the membrane builds on our previous work on the interactions of the hydrophobic polyelectrolyte poly(2ethylacrylic acid) (PEAA, 1) with aqueous dispersions of natural or synthetic phosphatidylcholines (2). PEAA in aqueous solutions



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