Surrogates for Chiral Aminomalondialdehyde. Synthesis of *N*-(9-Phenylfluoren-9-yl)serinal and *N*-(9-Phenylfluoren-9-yl)vinylglycinal

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The cyclic carbamate of *N*-(9-phenylfluoren-9-yl)serinal (**5**) and *N*-(9-phenylfluoren-9-yl)aminomalondialdehyde mono(dimethyl acetal) (**16**) were prepared from L-serine. Exposure to silica and nonnucleophilic base and treatment in Wittig coupling reactions proceeded without loss of enantiomeric purity. D- and L-*N*-(9-phenylfluoren-9-yl)vinylglycinals also were prepared, purified on silica, and treated with methyllithium and sodium borohydride to produce optically pure allylic amino alcohols. Finally, α-aminobutanol **27**, prepared from L-serine by a route employing three different β-substituted *N*-(PhFl)-α-amino aldehydes, was shown to retain complete enantiomeric intregrity at the α-amino carbon.

Carbonyl addition reactions with chiral aldehyde substrates are effective means for obtaining a variety of asymmetric products in organic synthesis. Caution must be taken, however, when preparing and utilizing such chiral aldehydes possessing α-heteroatom substituents. Losses of enantiomeric purity by way of α-epimerization may result with deceptive ease from exposure of the chiral substrate to higher temperatures, to silica during purification, or to basic conditions during addition reactions.[1] We have overcome the problem of configurational instability of α-amino aldehydes through protection of the amine with the 9-phenylfluoren-9-yl (PhFl) group.[2] To further establish the limits of *N*-(9-phenylfluoren-9-yl)-amino aldehyde configurational stability, we now report syntheses of *N*-(9-phenylfluoren-9-yl)amino aldehydes possessing side chains that increase the acidity of the amino aldehyde α-proton.

Because serine-derived α-amino aldehydes are chiral educts for stereoselective synthesis of unusual amino acids,[3] polyamino acids,[4] amino sugars,[5] and sphingolipids,[6] we first prepared *N*-(9-phenylfluoren-9-yl)serinal **5** which can be exposed to silica and nonnucleophilic base and used in Wittig couplings without loss of enantiomeric purity. While examining the stability of amino aldehydes containing a potential second electron withdrawing α-substituent, *N*-(9-phenylfluoren-9-yl)aminomalondialdehyde mono(dimethyl acetal) (**16**), was prepared and also employed in Wittig reactions with no loss of enantiomeric purity. To test the affect of the 9-phenylfluoren-9-yl group in preventing conjugation of a β,γ-unsaturated α-amino aldehyde under nucleophilic basic conditions, *N*-(9-phenylfluoren-9-yl)vinylglycinal (**22**) was prepared, chromatographed on silica, and treated with methyllithium and $NaBH_4$. Finally, the configurational stability of *N*-(9-phenylfluoren-9-yl)-L-vinylglycinal (**22**) and *N*-(9-phenylfluoren-9-yl)-L-aminobutanal (**26**) under aqueous acidic conditions was examined.

Results and Discussion

Preparation of Aldehydes Derived from *N*-(9-Phenylfluoren-9-yl)-L-serine (Scheme I).

Selective nitrogen protection of L-serine with the 9-phenylfluoren-9-yl group requires protective silylation of both the carboxylic acid and the hydroxyl groups with chlorotrimethylsilane prior to alkylation of the amine with 9-bromo-9-phenylfluorene.[2,7] To insure silylation of both oxygens, L-serine was refluxed with 300 mol % of chlorotrimethylsilane and 300 mol % of triethylamine in methylene chloride. The trimethylsilyl group was then selectively cleaved from the amine with 100 mol % methanol, leaving the silyl ether and silyl ester intact.[8] Alkylation of the amine with 9-bromo-9-phenylfluorene followed by acidic hydrolysis of the silyl groups produced *N*-(9-phenylfluoren-9-yl)-L-serine (**1**) after a difficult isolation in variable yields; however, when the triethylamine hydrochloride produced in the silylation step was removed prior to alkylation, *N*-(9-phenylfluoren-9-yl)-L-serine (**1**) was convenently isolated in pure form after an aqueous quench in yields consistently >75% on a 100-mmol scale.

N-(9-Phenylfluoren-9-yl)-L-serine isoxazolidide (**2**) was prepared in high yield by coupling isoxazolidine to carboxylic acid **1** mediated by dicyclohexylcarbodiimide and hydroxybenzotriazole in THF. Reduction of isoxazolidide **2** with $LiAlH_4$ in THF at 0 °C provided aldehyde **3** in good yield (80–85%) after chromatography; however, the acidic hydrogen and nucleophilic properties of the unprotected hydroxyl group were detrimental in subsequent reactions.[9] To protect the hydroxyl group and secure the optimum defense for both the alcohol and secondary amine functions that can be removed selectively without loss of the 9-phenylfluoren-9-yl group, we turned to the cyclic carbamate. Cyclic carbamate **4** can be prepared quantitatively as a white crystalline solid by treating amino alcohol **2** with phosgene and triethylamine in toluene.[10]

Reduction of **4** with a solution of $LiAlH_4$ in THF at −78 °C produces aldehyde **5** contaminated with traces of al-

(1) The following provide examples of epimerization of α-heterosubstituted aldehydes where the hetero function is: (a) Oxygen: Williams, D. R.; Klinger, F. D. *J. Org. Chem.* **1988**, *53*, 2134. (b) Selenium: Danishefsky, S. J.; DeNinno, M. P.; Chen, S.-h. *J. Am. Chem. Soc.* **1988**, *110*, 3929. (c) Azide: Kuzuhara, H.; Emoto, S. *Tetrahedron Lett.* **1975**, 1853. (d) Nitrogen: ref 2 and references therein.

(2) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.

(3) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855.

(4) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1071.

(5) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609.

(6) (a) Tkaczuk, P.; Thornton, E. R. *J. Org. Chem.* **1981**, *46*, 4393. (b) Newman, H. *J. Am. Chem. Soc.* **1973**, *95*, 4098. (c) Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5320. (d) Nimkar, S.; Menaldino, D.; Merrill, A. H.; Liotta, D. *Tetrahedron Lett.* **1988**, *29*, 3037. (e) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354 and references therein.

(7) (a) 9-Bromo-9-phenylfluorene was prepared according to Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239. (b) Serine was silylated according to: Barlos, K.; Papaioannou D.; Theodoropoulos, D. *J. Org. Chem.* **1982**, *47*, 1324.

(8) Hils, J.; Ruhlmann, K. *Chem. Ber.* **1967**, *100*, 1638.

(9) When aldehyde **3** in THF is treated with the ylide prepared from methyltriphenylphosphonium iodide and dimsyl sodium in DMSO, allylic amine **21** is produced in 16% yield. When **21** is converted to ester **28** and analyzed by proton NMR doping experiments, allylic amine **21** is shown to be of 40% ee. Racemization during the Wittig reaction is presumed to result from an intramolecular Oppenauer/Meerwein–Ponndorf–Verley couple, catalyzed by sodium cation during the Wittig reaction, and not by a mechanism involving loss of the α-proton.

(10) When isoxazolidide **2** is heated with carbonyldiimidazole in DMF at 80 °C for 1 h, cyclic carbamate **4** is not produced, and the *O*-acyl imidazolide is obtained in 79% yield after chromatography: mp 155–158 °C; ^1H NMR δ 1.95 (m, 2 H), 2.6 (m, 1 H), 3.2 (m, 1 H), 3.38 (m, 1 H), 3.75 (m, 3 H), 4.3 (m, 2 H), 7–7.75 (m, 15 H), 8.07 (s, 1 H). Anal. Calcd for $C_{29}H_{26}N_4O_4$: C, 70.4; H, 5.3; N, 11.3. Found: C, 70.4; H, 5.4; N, 11.3.

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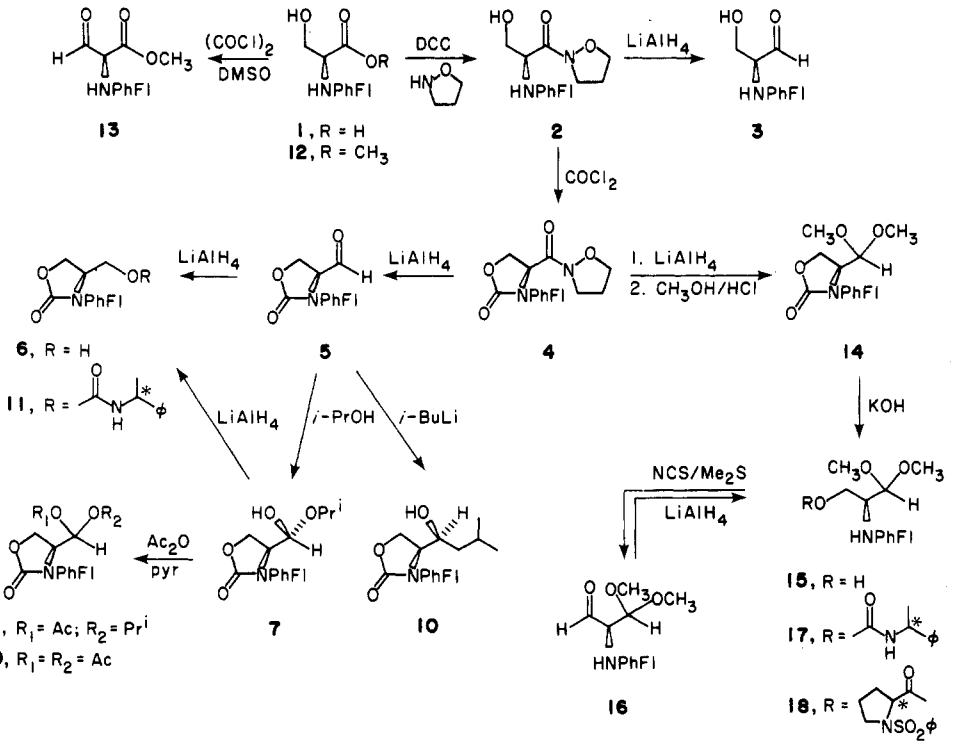
Scheme I. Synthesis of Aldehydes Derived from *N*-Phenylfluorenyl-L-serine



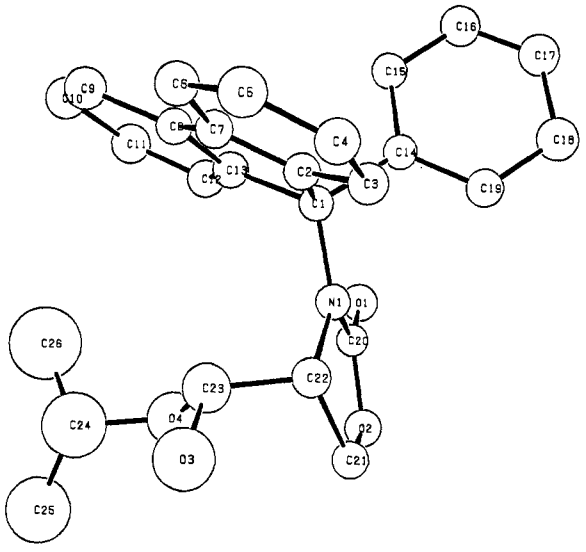


Figure 1. ORTEP stereodrawing of hemiacetal **7** (arbitrary numbering).

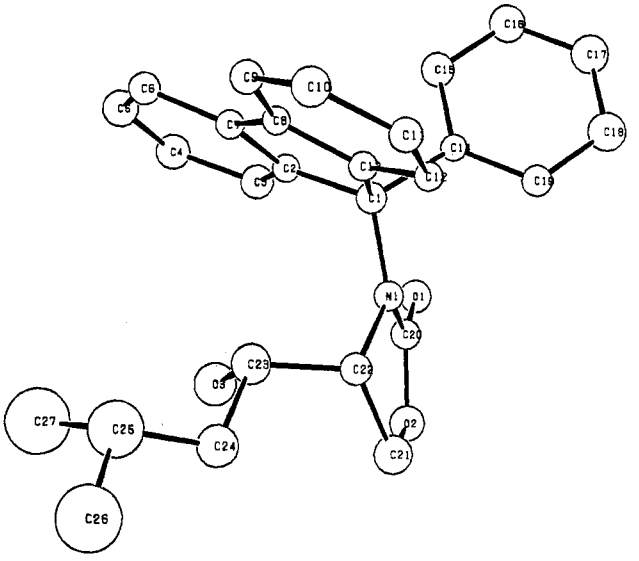


Figure 2. ORTEP stereodrawing of the product of isobutyllithium addition, secondary alcohol **10** (arbitrary numbering).

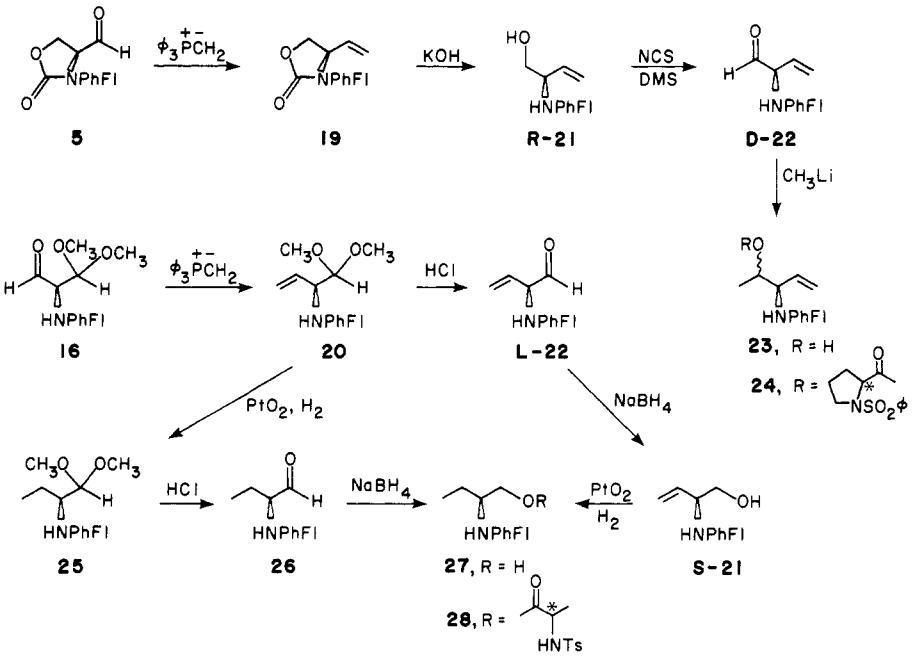
cohol **6**. Although only a 62% yield of aldehyde **5** was obtained after chromatography on silica, proton NMR spectroscopy showed crude aldehyde, obtained in 90% yield as a white foam, to be pure enough for direct use in subsequent addition reactions.

In an attempt to purify aldehyde **5** by recrystallization from isopropyl alcohol we obtained hemiacetal **7** as a single diastereomer. Hemiacetal **7** melts at 163–164 °C and can be stored at room temperature with no decomposition. Acylation of **7** with acetic anhydride in pyridine produces both acetate **8** and diacetate **9**. The ^{1}H NMR spectra of **8** and **9** show shifts for the acetal carbon proton of 0.6 and 1.4 ppm, respectively, downfield relative to **7**.

The configuration of the hemiacetal carbon of **7** was determined to be *R* by X-ray crystallography (Figure 1). Aware that this isomer may have arisen from resolution by crystallization of an equilibrium mixture, we were still curious to see if it might be of value in predicting the outcome of nucleophilic attack on aldehyde **5**. For this purpose, we added isobutyllithium to serinal **5** and obtained secondary alcohol **10** as a single diastereomer.[11] The configuration of secondary alcohol **10**, also determined by X-ray crystallography (Figure 2) was found to be *S*. Thus, although high diastereoselectivity was obtained in both nucleophilic additions, no correlation exists between these systems.

(11) Isomeric composition was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. No attempt was made to recover unreacted **5**. Addition of isobutylmagnesium bromide to **5** produced a 17% yield of diasteromerically pure **10** with 31% of primary alcohol **6**. Isobutyllithium was prepared from 1-bromo-2-methylpropane according to the procedure to prepare *n*-butyllithium described by Gilman, H.; Beel, J. A.; Brannen, C. G.; Bullock, M. W.; Dunn, G. E.; Miller, L. S. *J. Am. Chem. Soc.* **1949**, *71*, 1499.

Scheme II. Synthesis of D- and L-*N*-(Phenylfluorenyl)vinylglycinals



Reduction of serinal **5** with $NaBH_4$ in methanol or $LiAlH_4$ in THF provides alcohol **6**, which can also be obtained from reduction of hemiacetal **7** with $LiAlH_4$ in THF. Coupling of **6** to *R* or *S* α-methylbenzyl isocyanate in THF, catalyzed by cuprous chloride, provides carbamate **11**. The diastereomeric purity of **11** was established by proton NMR. As a further test of enantiomeric stability, serinal **5**, which had been purified on silica gel, was stirred in THF containing either 100 mol % Et_3N or 100 wt % SiO_2 for 1 h at reflux. It was then reduced to alcohol **6**, which was coupled to (*R*)- and (*S*)-α-methylbenzyl isocyanate. By this procedure, serinal **5** was shown to still be >99% enantiomerically pure. When hemiacetal **7** was stirred in THF with 100 mol % triethylamine or 100 wt % silica gel for 1 h at reflux and then converted to carbamate **11**, analysis again showed the carbamate to be of >99% diastereomeric purity. Thus serinal **5** and hemiacetal **7** are configurationally stable, maintaining enantiomeric integrity at the α-amino carbon after heating with silica and nonnucleophilic base.

Aminomalondialdehyde Monoacetal 16. A configurationally stable α-formylglycine derivative may allow for synthesis of amino acids of either configuration from a single intermediate.[12] Currently under study are the types of carbonyl and amino protection necessary to prevent racemization of the α-center of α-formylglycine derivatives. We now report preparation of the first configurationally stable aminomalonate derivative.

To test if minimal protection of the carbonyl function was sufficient to confer configurational stability to an amino malonate derivative, *N*-(9-phenylfluoren-9-yl)-α-formylglycine methyl ester (**13**) was synthesized. Phenylfluorenation of L-serine methyl ester hydrochloride provided crystalline *N*-(9-phenylfluoren-9-yl)-L-serine methyl ester (**12**) in high yield. Oxidation of **12** using DMSO and oxalyl chloride in the cold produced the desired malonate derivative **13**; however, it was unstable to purification on silica gel as well as storage at 0 °C under an inert atmosphere. Attempts to directly reduce **13** with $NaBH_4$ and to add CH_3Li to **13** without purification failed to produce the desired *N*-(9-phenylfluoren-9-yl)serine or threonine methyl esters. Instead the formation of multiple products, including 9-phenylfluorene, resulted.

Successful preparation of a configurationally stable aminomalonate derivative was achieved by masking one of the electron-withdrawing carbonyl functions as a dimethyl acetal. When serinal **5** is stirred in methanolic HCl containing trimethyl orthoformate as a water scavenger, dimethyl acetal **14** is obtained in 70% yield from isoxazolidide **4** after recrystallization. Hydrolysis of cyclic carbamate **14** in refluxing 1 M ethanolic potassium hydroxide cleanly provides amino alcohol **15**, which is oxidized at the primary alcohol with *N*-chlorosuccinimide and dimethyl sulfide in toluene to furnish, after chromatography on silica, aminomalondialdehyde monoacetal **16** as a solid in excellent yield (90%).[13] Reduction of aldehyde **16** with $LiAlH_4$ in THF smoothly reproduced alcohol **15**, which was coupled to a chiral auxillary to determine the enantiomeric purity of malondialdehyde **16**.

Although **15** reacted with (*R*)- and (*S*)-α-methylbenzyl isocyanate in the presence of cuprous chloride in refluxing THF, carbamates **17** were neither separable on HPLC nor were their ^1H NMR spectra sufficiently different to permit determination of enantiomeric purity. We then turned to preparation of the D- and L-*N*-(phenylsulfonyl)proline esters **18**, which was accomplished by using 1,1′-carbonyl-bis(3-methylimidazolium triflate) to activate the carboxyl group for ester formation.[14] The diastereomeric purity of proline esters **18** was determined by observation of the acetal methyl groups' ^1H NMR signals, which demonstrated **18** to be of >99% diastereomeric purity. When malondialdehyde **16** was stirred in THF with either 100 mol % triethylamine or 100 wt % silica gel for 1 h at reflux, reduction and conversion to ester **18** showed malondi-

(12) (a) Syntheses of racemic α-formylglycine equivalents are presented In *The Chemistry of Penicillin*; Clarke, H. T., Johnson, J. R., Robinson, R., Eds.; Princeton University Press: Princeton, NJ, 1949; p 492. (b) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 3089. (c) Sheehan, J. C.; Cruickshank, P. A. *J. Am. Chem. Soc.* **1956**, *78*, 3677. (d) Sheehan, J. C.; Johnson, D. A. *J. Am. Chem. Soc.* **1954**, *76*, 158. (e) Curtis, N. J.; Hammershøi, A.; Nicholas, L. M.; Sargeson, A. M.; Watson, K. J. *Acta Chem. Scand.* **1987**, *A41*, 36.

(13) (a) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1988**, *110*, 447. (b) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.

(14) Saha, A.; Rapoport, H. *J. Am. Chem. Soc.*, in press.

aldehyde **16** to still be of >99% enantiomeric purity.

Synthesis of Vinylglycinals (Scheme II). Attempts to prepare enantiomerically pure allylic amines, which are versatile synthetic intermediates, via the *N*-(*tert*-butoxycarbonyl)-α-amino aldehydes has led to significant racemization during Wittig coupling reactions.[15] On the other hand, when *N*-(9-phenylfluoren-9-yl)-α-amino aldehydes are subjected to similar Wittig conditions, no racemization occurs.[2] Treatment of *N*-(9-phenylfluoren-9-yl)-L-serinal **5** in THF with the ylide prepared from methyltriphenylphosphonium iodide and dimsyl sodium in DMSO produces allylic amine **19** in 77% yield from isoxazolidide **4**.[16] Exposure of aminomalondialdehyde monoacetal **16** to the ylide under similar conditions provides allylic amine **20** in 74% yield. Although nucleophilic addition to the amino aldehyde proceeded best at low temperature, avoiding decomposition through deprotonation of the aldehyde α-proton and subsequent loss of the 9-phenylfluoren-9-yl group, elimination of triphenylphosphine oxide and double-bond formation proceeded best at room temperature. Thus reactions were run initially in the cold and then warmed to room temperature for completion.

N-(9-Phenylfluoren-9-yl)-D-vinylglycinal (**22**) was prepared from allylic amine **19** by hydrolysis of the carbamate with ethanolic potassium hydroxide followed by oxidation of primary alcohol **21** with *N*-chlorosuccinimide and dimethyl sulfide in toluene.[13] When D-vinylglycinal **22**, which had been purified on silica gel, is treated with methyllithium in THF at −78 °C a 1/1 diastereomeric mixture of secondary alcohols **23** is produced. Since our objective was to observe if loss of configurational integrity at the α-center had occurred during the organometallic addition, no attempt was made to improve the diastereoselectivity of the addition reaction. Instead, the diastereomeric alcohol mixture **23** was acylated with D- and L-*N*-[(phenylsulfonyl)propyl]-3-methylimidazolium triflate[14] to obtain esters **24**. Although these esters were not separable by chromatography, they could be assayed for enantiomeric purity with 400-MHz ^{1}H NMR spectroscopy, which resolved all four methyl doublets of esters **24**. Thus, examination of the ^{1}H NMR spectra of esters **24** demonstrated that >98% of the enantiomeric integrity at the α-amino carbon had been conserved.

Hydrolysis of acetal **20** to produce *N*-(9-phenylfluoren-9-yl)-L-vinylglycinal (**22**) requires stronger acidic conditions and higher temperatures than those normally employed to deprotect less functionalized aldehydes.[17] Since vinylglycinal **22** is unstable to prolonged exposure to such conditions, a protecting group, alternative to the dimethyl acetal, may allow for a more effective conversion to *N*-(9-phenylfluoren-9-yl)-L-vinylglycinal. When, however, acetal **20** is subjected to our best hydrolysis conditions, 3/1, 5 M HCl/acetone at 50–60 °C for 3.5 h, a 35% yield of L-vinylglycinal **22** was obtained after purification on silica gel. Reduction of aldehyde **22** with $NaBH_4$ in methanol provided in good yield *N*-(9-phenylfluoren-9-yl)-L-vinylglycinol (*S*-**21**), which could be selectively reduced to α-aminobutanol **27** with hydrogen and platinum oxide as catalyst.

Selective catalytic hydrogenation of the double bond of acetal **20** gave crystalline α-aminobutanal dimethyl acetal **25**. Hydrolysis of acetal **25** with 5 M HCl at 50–60 °C for 3.5 h produced in 86% yield crystaline α-aminobutanal **26**, which was reduced with $NaBH_4$ in methanol to produce 2-aminobutanol **27**.

In both of these sequences to prepare 2-aminobutanol **27** three different amino aldehydes were prepared and treated in nucleophilic addition reactions. When alcohol **27** was derivatized with D- and L-*N*-[(tolylsulfonyl)alaninyl]-3-methylimidazolium triflate[14] in nitromethane, esters **28** were produced and analyzed by proton NMR in benzene-d_6 to ascertain if racemization at the α-amino carbon had occurred. Analysis of esters **28** synthesized from aminobutanal **26** and vinylglycinal **22** showed **28** to be of >99% diastereomeric purity and established that no loss of enantiomeric purity had occurred at the α-amino carbon in either synthesis.

Conclusion

N-(9-Phenylfluoren-9-yl)amino aldehydes possessing β-substituents that increase the acidity of the amino aldehyde α-proton were synthesized and exposed to silica and nonnucleophilic base without loss of enantiomeric purity. These aldehydes function as aminomalondialdehyde surrogates and react in Wittig couplings to prepare optically pure D- and L-*N*-(9-phenylfluoren-9-yl)-vinylglycinals. Nucleophilic additions to *N*-(9-phenylfluoren-9-yl)vinylglycinals proceed with no loss of chiral integrity and provide allylic amines of >98% enantiomeric purity. To illustrate the configurational stability of *N*-(9-phenylfluoren-9-yl)amino aldehydes, 2-aminobutanol **27** was prepared from L-serine via nucleophilic additions to three different α-amino aldehydes with no loss of enantiomeric purity.

Experimental Section

General. Unless otherwise noted all reactions were conducted under a nitrogen or argon atmosphere. Tetrahydrofuran (THF) was distilled from $LiAlH_4$; dimethylformamide (DMF), dimethyl sulfoxide (DMSO), CH_2Cl_2, nitromethane, chlorotrimethylsilane, and methanol (MeOH) were distilled from CaH_2; and triethylamine was distilled from barium oxide. Final reaction mixture solutions were dried over Na_2SO_4 and evaporated from a rotary evaporator. Chromatography was on 230–400-mesh silica gel. Melting points are uncorrected, ^{1}H NMR spectra were recorded in $CDCl_3$.

***N*-(9-Phenylfluoren-9-yl)-L-serine (1).** A suspension of L-serine (4.2 g, 40 mmol) and chlorotrimethylsilane (15.74 mL, 124 mmol) in CH_2Cl_2 (50 mL) under a N_2 atmosphere was heated under reflux for 30 min, cooled to room temperature, and treated with triethylamine (17.4 mL, 124 mmol) in CH_2Cl_2 (40 mL) at a rate sufficient to maintain gentle reflux. The mixture was heated under reflux for 1 h, cooled to 0 °C, treated with MeOH (1.78 mL, 44 mmol) in CH_2Cl_2 (10 mL), stirred for 10 min, and allowed to warm to room temperature over 45 min. Stirring was stopped, and the mixture was transferred, via Teflon tubing, through a sintered-glass funnel that was covered with a layer of diatomaceous earth (prewashed with Et_3N and benzene and oven-dried dried) into a solution of 9-bromo-9-phenylfluorene (PhFlBr, 12.84 g, 40 mmol) in CH_2Cl_2 (50 mL) in a Morton flask equipped with a mechanical stirrer. The triethylamine hydrochloride that remained on the filter was washed with CH_2Cl_2 (3 × 15 mL), and the washes were similarly transferred into the Morton flask. Triethylamine (5.58 mL, 40 mmol) and $Pb(NO_3)_2$ (13.25 g, 40 mmol) were added to the homogeneous solution, and the reaction

(15) (a) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487. (b) Moriwake, T.; Hamano, S.; Saito, S.; Torii, S. *Chem. Lett.* **1987**, 2085.

(16) In early experiments hemiacetal **7** was reacted under Wittig conditions and gave a 40% yield of allylic amine **19**.

(17) Attempts to hydrolyze the dimethyl acetal of allylic amine **20** with 1 M HCl in water/acetone (21/1) at 40 °C failed to produce L-vinylglycinal **22**, and the acetal was recovered unchanged. Stirring **22** at room temperature with trifluoroacetic acid in CH_2Cl_2 or trifluoroacetic acid in $CHCl_3/H_2O$ failed to remove either the acetal or the 9-phenylfluoren-9-yl group. When acetal **20** was heated at 40–50 °C with toluenesulfonic acid or methanesulfonic acid in aqueous THF and aqueous dioxane, ^{1}H NMR indicated the formation of aldehyde L-**22**; however, the aldehyde was unstable to prolonged exposure to these conditions. Trimethylsilyl bromide with catalytic iodine in refluxing chloroform removed only the phenylfluorenyl group.

vessel was flushed with N_2, sealed, and stirred for 48 h at room temperature. The mixture was filtered, and the filter cake was washed with THF (3 × 50 mL). The combined organic layer was evaporated, and the residue was redissolved in THF (250 mL) and treated with 5% citric acid in H_2O (100 mL) with vigorous stirring for 5 min. Ether (250 mL) was added, and the aqueous layer was separated and extracted with 1/1 THF/Et_2O (4 × 100 mL). The combined organic layers were extracted with 1 N NaOH (4 × 75 mL), and the combined NaOH extracts were washed with Et_2O (100 mL), cooled to 0 °C, and acidified with acetic acid to pH 6.5. The precipitate was extracted from the aqueous layer with 1/3 isopropyl alcohol/$CHCl_3$ (5 × 100 mL), and the combined organic layers were washed with brine, dried, and evaporated, leaving 11.4 g (83%) of 1, which was used without further purification. Recrystallization from THF/hexane gave 1: mp 172–174 °C; $[\alpha]^{20}_D$ −73° (*c* 1.0, MeOH); ^{1}H NMR δ 2.7 (t, 1 H, *J* = 3.7), 3.27 (dd, 1 H, *J* = 3.9, 11.6), 3.76 (dd, 1 H, *J* = 3.7, 11.5), 7.1–7.5 (m, 11 H), 7.75 (m, 2 H). Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.5; H, 5.5; N, 4.1. Found: C, 76.7; H, 5.5; N, 4.0.

***N*-(9-Phenylfluoren-9-yl)-L-serine Isoxazolidide (2).** Isoxazolidine hydrochloride[18] (6.54 g, 60 mmol) was vigorously stirred in 100 mL of THF, 2.5 mL of H_2O, and 2.5 mL of DMF. The mixture was treated with anhydrous K_2CO_3 (19.5 g) in three equal portions over 45 min. After the suspension was stirred for 30 min, it was transferred, via Teflon tubing, through a sintered-glass funnel, under a stream of N_2, into a solution of 1 (10.36 g, 30 mmol) and hydroxybenzotriazole monohydrate (6.08 g, 45 mmol) in THF (75 mL) in a Morton flask equipped with a mechanical stirrer. The K_2CO_3 was washed with THF (5 × 25 mL), and the washings were similarly transferred into the Morton flask. The solution was cooled to 0 °C, and dicyclohexylcarbodiimide (9.27 g, 45 mmol) was added. The reaction vessel was flushed with N_2, sealed, and stirred for 18 h at 0 °C. Water (510 μL, 28.3 mmol) and 1 M NaH_2PO_4 (30 μL) were added, and the reaction was stirred for an additional hour. Concentration of the heterogeneous solution onto 60 g of silica gel (230–400 mesh) in a rotary evaporator left a gel that was allowed to air dry for 2 h, and then chromatographed on silica gel (110 g) with a gradient of 50–100% EtOAc in hexane as eluant. Evaporation of the collected fractions gave a white solid, which was recrystallized from EtOAc yielding 2, 9.61 g, 80%: mp 182–185 °C; $[\alpha]^{20}_D$ −273° (*c* 1.31, $CHCl_3$); ^{1}H NMR δ 1.86 (m, 1 H), 2 (m, 1 H), 2.62 (m, 1 H), 2.8 (m, 1 H), 3.15 (m, 2 H), 3.4 (m, 2 H), 3.6 (m, 2 H), 3.7 (m, 1 H), 7.2–7.45 (m, 11 H), 7.66 (m, 2 H). Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 75.0; H, 6.0; N, 7.0. Found: C, 75.0; H, 6.1; N, 7.2.

***N*-(9-Phenylfluoren-9-yl)-L-serinal (3).** Isoxazolidide 2 (400 mg, 1 mmol) was dissolved in 10 mL of THF, cooled to 0 °C, and treated with $LiAlH_4$ (42 mg, 1.1 mmol). Reduction was complete after 30 min, and the solution was quenched with $KHSO_4$ (220 mg) in 10 mL of H_2O. The mixture was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine (30 mL), dried, and evaporated to an oil, which was chromatographed by radial chromatography with 20% EtOAc in hexane as eluant. Evaporation of the collected fractions gave 280 mg (85%) of aldehyde 3: ^{1}H NMR δ 2.75 (t, 1 H, *J* = 4.5), 3.0 (m, 1 H), 3.57 (m, 1 H), 7.16–7.74 (m, 13 H), 9.37 (s, 1 H).

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-carboxylic Acid Isoxazolidide (4). A solution of isoxazolidide 2 (5 g, 12.5 mmol) and triethylamine (4.36 mL, 31.3 mmol) in toluene (250 mL) was cooled to 0 °C, treated with a 20% solution of phosgene in toluene (13 mL, 25 mmol), and stirred for 15 min. Methanol (10 mL) was added, and the mixture was washed with $NaHCO_3$ (100 mL). The aqueous layer was extracted with $CHCl_3$ (4 × 50 mL), and the combined organic layer was washed with brine (2 × 50 mL), dried, and evaporated to a solid, which was recrystallized from CH_2Cl_2/hexane to give 4, 5.27 g, 99%: mp 224 °C; $[\alpha]^{20}_D$ 188° (*c* 1.17, $CHCl_3$); ^{1}H NMR δ 2.1 (m, 2 H), 3.0 (m, 1 H), 3.13 (m, 1 H), 3.4 (m, 1 H), 3.65 (m, 1 H), 4.08 (m, 1 H), 4.25 (m, 2 H), 7.1–7.9 (m, 13 H). Anal. Calcd for $C_{26}H_{22}N_2O_4$: C, 73.2; H, 5.2; N, 6.6. Found: C, 73.0; H, 5.3; N, 6.6.

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-carboxaldehyde (5). A solution of $LiAlH_4$ in THF (0.4 mL, 0.56 mmol) was added to isoxazolidide 4 (210 mg, 0.5 mmol) in THF (5 mL) at −78 °C. The mixture was stirred for 15 min, and then $KHSO_4$ (220 mg) in H_2O (5 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layer was washed with brine and dried. Radial chromatography with 1/1 EtOAc/hexane as eluant yielded 110 mg (62%) of 5: ^{1}H NMR δ 3.9 (dd, 1 H, *J* = 3.9, 5.5), 4.06 (dd, 1 H, *J* = 3.7, 5.5), 4.29 (t, 1 H, *J* = 9.3), 7.05–7.8 (m, 13 H), 8.99 (d, 1 H, *J* = 3.6).

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-carboxaldehyde Isopropyl Hemiacetal (7). A solution of isoxazolidide 4 (3 g, 7 mmol) in THF (100 mL) at −78 °C was treated with a 1.1 M solution of $LiAlH_4$ in THF (6.4 mL), stirred for 7 min, and then transferred via Teflon tubing into a rapidly stirring solution of $KHSO_4$ (4 g) in H_2O (100 mL) at 0 °C. The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layer was washed with brine, dried, and evaporated to a foam. This foam was redissolved in isopropyl alcohol (8 mL) from which 7 (2.3 g, 79%) crystallized as a single diastereomer: mp 163–164 °C; $[\alpha]^{20}_D$ −530° (*c* 1.31, $CHCl_3$);[19] ^{1}H NMR δ 0.6 (d, 3 H, *J* = 6.1), 0.87 (d, 3 H, *J* = 6.1), 2.0 (br d, 1 H, *J* = 5.8), 2.67 (septet, 1 H, *J* = 6.1), 3.88 (m, 1 H), 3.96, (d, 1 H, *J* = 8.3), 4.34 (t, 1 H, *J* = 8.4), 4.49 (d, 1 H, *J* = 8.7), 7.1–7.77 (m, 12 H), 8.2 (d, 1 H, *J* = 7.6); IR (KBr pellet) 3430, 2970, 1720, 1410, 1220, 750 cm^{-1}; MS *m/e* 355 (M − iPrOH, 40%), 241 (major). Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.2; H, 6.1; N, 3.4. Found: C, 75.5; H, 6.2; N, 3.3.

Acetates 8 and 9. Hemiacetal 7 (50 mg, 0.12 mmol) in 1 mL of pyridine was treated with acetic anhydride (100 μL, 1 mmol) and stirred for 16 h at room temperature. Water (2 mL) was added, the mixture was filtered, and the precipitate was washed with water (2 × 1 mL) and purified by radial chromatography with a gradient of 5–25% EtOAc in hexane as eluant. Eluting first was 9 (8 mg, 15%) (^{1}H NMR δ 1.75 (s, 3 H), 1.82 (s, 3 H), 4.1 (m, 1 H), 4.44 (m, 2 H), 5.75 (d, 1 H, *J* = 2.1), 7.15–8.15 (m, 13 H)), followed by 8 (20 mg, 36%): ^{1}H NMR δ 0.6 (d, 3 H, *J* = 6.2), 0.8 (d, 3 H, *J* = 6.1), 1.8 (s, 3 H), 2.63 (heptet, 1 H, *J* = 6.1), 3.96 (d, 1 H, *J* = 8.2), 4.34 (t, 1 H, *J* = 8.5), 4.5 (dd, 1 H, *J* = 8.6, 8.7), 4.97 (s, 1 H), 7.15–8.27 (m, 13 H).

(4*R*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-methanol (6) from 7. Hemiacetal 7 (415 mg, 1 mmol) was dissolved in 10 mL of THF, cooled to −78 °C, and treated with a 1.4 M solution of $LiAlH_4$ in THF (0.75 mL). The mixture was stirred for 45 min at −78 °C and for 15 min at 0 °C and then poured into a chilled solution of rapidly stirring $KHSO_4$ (500 mg) in H_2O (10 mL) The mixture was extracted with EtOAc (3 × 25 mL), and the combined organic layer was washed with brine, dried, and evaporated to an oil, which was chromatographed with 3/1 EtOAc/hexane. Evaporation of the collected fractions gave 270 mg (76%) of alcohol 6, which can be recrystallized from CH_2Cl_2/hexane: mp 225–227 °C; $[\alpha]^{20}_D$ −694° (*c* 1.08, $CHCl_3$); ^{1}H NMR δ 2.8 (m, 2 H), 3.88 (m, 1 H), 4.26 (dd, 1 H, *J* = 8.5, 8.6), 4.45 (t, 1 H, *J* = 8.4), 7.2–7.8 (m, 12 H), 8.2 (d, 1 H). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.3; H, 5.4; N, 3.9. Found: C, 77.0; H, 5.4; N, 3.9.

Optical Stability and Purity Studies of Aldehyde 5, Malondialdehyde Mono(dimethyl acetal) 16, and Hemiacetal 7. Aldehyde 5 (100 mg, 0.28 mmol, purified on silica gel with 3/1 EtOAc/hexane as eluant), aminomalondialdehyde 16 (60 mg, 0.16 mmol), and hemiacetal 7 (150 mg, 0.36 mmol) were separately dissolved in 2–4 mL of THF, treated with either triethylamine (100 mol %) or silica gel (100 wt %, 240–400 mesh), and stirred for 24 h at room temperature and for 1 h at reflux. Silica gel was removed by filtration, and reaction mixtures were evaporated and then reduced to alcohols 6 and 15 with $LiAlH_4$ according to the described procedures. Crude alcohol reaction mixtures were purified on silica gel and then coupled to (*R*)- and (*S*)-α-methylbenzyl isocyanate, or D- or L-*N*-(phenylsulfonyl)proline as described below, and analyzed by ^{1}H NMR to ascertain diastereomeric purity.[20]

(4*R*,1′*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-(3′-methyl)butan-1′-ol (10). Serinal 5, produced from reduction

(18) Prepared according to: (a) Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972. (b) King, H. *J. Chem. Soc.* **1942**, 432.

(19) In solution, hemiacetal 7 is in equilibrium with aldehyde 5. After standing for 48 h the same solution had a rotation of $[\alpha]^{20}_D$ −217°.

(20) Proton NMR analysis for isomeric composition was done according to: Maple, S. R.; Allerhand, A. *J. Am. Chem. Soc.* **1987**, *109*, 6609.

of isoxazolidide 4 (0.5 g, 1.17 mmol) at −78 °C with a 1.1 M THF solution of $LiAlH_4$ (1.1 mL) in THF (18 mL), was redissolved in 10 mL of THF, cooled to −78 °C, and treated with 2 mL of a 1.2 M solution of isobutyllithium in ether,[11] stirred 15 min, and treated with 2 mL more of the alkyllithium solution. After 15 min MeOH (1 mL) was added, and the mixture was partitioned between EtOAc (10 mL) and 1 M NaH_2PO_4 (10 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with brine, dried, and evaporated to an oil, which was chromatographed with 1/1 EtOAc/hexane as eluant. Evaporation of the collected fractions gave 120 mg (25% from 4) of crystalline 10, which was recrystallized from CH_2Cl_2/hexanes: mp 236–238 dec; $[\alpha]^{20}_D$ −557° (c 1.8, $CHCl_3$); ^1H NMR δ 0.38 (d, 1 H, J = 6.5), 0.42 (m, 1 H), 0.49 (d, 1 H, J = 6.6), 0.78 (br d, 1 H, J = 4.4), 1.05 (m, 1 H), 1.25 (m, 1 H), 2.87 (m, 1 H) 3.82 (m, 1 H), 4.3 (m, 2 H), 7.18–7.82 (m, 12 H), 8.3 (m, 1 H). Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.4; H, 6.6; N, 3.4. Found: C, 78.4; H, 6.6; N, 3.4.

***R* and *S* Carbamates 11.** Alcohol 6 (0.1 mmol) was dissolved in 2 mL of THF, treated with CuCl (30 mg) and either (*R*)- or (*S*)-α-methylbenzyl isocyanate (30 μL, 0.2 mmol), and stirred while refluxing for 2 h. The mixture was diluted with 4 mL of EtOAc, filtered, washed with H_2O (3 × 10 mL), washed with brine (10 mL), dried, and evaporated to a solid, which was analyzed without further purification. On TLC the *R* carbamate is eluted first (^1H NMR δ 1.38 (d, 3 H, J = 6.8), 3.17 (dd, 1 H, J = 11.8, 11.8), 3.32 (d, 1 H, J = 11.6), 4.0 (d, 1 H, J = 6.4), 4.1 (d, 1 H, J = 6.4), 4.44 (t, 1 H, J = 8.4), 4.55 (t, 1 H, J = 7), 4.76 (m, 1 H), 7.05–8.2 (m, 18 H) followed by the *S* carbamate: ^1H NMR δ 1.38 (d, 3 H, J = 6.7), 3.09 (dd, 1 H, J = 11.8, 11.8), 3.4 (d, 1 H, J = 11.4), 4.0 (d, 1 H, J = 6.7), 4.13 (d, 1 H, J = 8.5), 4.44 (q, 1 H, J = 8.1), 4.58 (m, 1 H), 4.76 (q, 1 H, J = 6.5), 7.1–8.04 (m, 18 H).

***N*-(9-Phenylfluoren-9-yl)-L-serine Methyl Ester (12).** A mixture of L-serine methyl ester hydrochloride (1.55 g, 10 mmol) and chlorotrimethylsilane (3.17 mL, 25 mmol) in CH_2Cl_2 (30 mL) at 0 °C was treated with triethylamine (4.86 mL, 35 mmol) and allowed to reach room temperature. The mixture was stirred while refluxing for 1 h, cooled to 0 °C, treated with MeOH (0.61 mL, 15 mmol) in CH_2Cl_2 (3 mL), allowed to warm to room temperature for 1 h, and then treated with PhFlBr (3.21 g, 10 mmol), triethylamine (1.39 mL, 10 mmol), and $Pb(NO_3)_2$ (3 g). The reaction vessel was flushed with N_2, and the mixture was stirred at room temperature for 48 h, filtered, and evaporated. The remaining solid was redissolved in citric acid (4 g) in MeOH (40 mL) and vigorously stirred for 1 h. Solvent was evaporated, and the remaining solid was chromatographed with 1/1 EtOAc/hexane as eluant. Evaporation of the collected fractions provided 2.82 g (78%) of 12: mp 114–115 °C; $[\alpha]^{20}_D$ −324° (c 2.85, $CHCl_3$); ^1H NMR δ 2.76 (t, 1 H, J = 5.1), 3.3 (dd, 1 H, J = 4.5, 5), 3.4 (m, 4 H), 7.2–7.4 (m, 11 H), 7.65–7.72 (m, 2 H). Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.9; H, 5.9; N, 3.9. Found: C, 77; H, 5.9; N, 3.8.

2-*N*-(9-Phenylfluoren-9-yl)-2-formylglycine Methyl Ester (13). Oxalyl chloride (29 μL, 0.33 mmol) was added to a solution of DMSO (47 μL, 0.66 mmol) in 1 mL of CH_2Cl_2 at −60 °C. After being stirred for 10 min, the solution was treated with **12** (40 mg, 0.11 mmol) in 1 mL of CH_2Cl_2. The mixture was stirred for 3 h at −60 °C, treated with 0.14 mL of triethylamine, and allowed to reach room temperature. Water (1 mL) was added, the aqueous layer was extracted with 2 mL of CH_2Cl_2, and the combined organic layer was washed with brine (3 mL), dried, and evaporated to an oil, which was rapidly purified by radial chromatography with 25% EtOAc in hexane as eluant. Evaporation of the collected fractions gave 26 mg (66%) of **13**: ^1H NMR δ 3.1 (s, 4 H), 7.2–7.4 (m, 11 H), 7.7–7.73 (m, 2 H), 9.56 (s, 1 H).

(4*S*)-2-Oxo-3-(9-phenylfluoren-9-yl)oxazolidine-4-carboxaldehyde Dimethyl Acetal (14). Serinal **5**, produced from reduction of isoxazolidide 4 (2.56 g, 6 mmol) at −78 °C with a 1.1 M THF solution of $LiAlH_4$ (5.4 mL) in THF (90 mL), was redissolved in methanol (50 mL), added to a methanol (10 mL)/acetyl chloride (430 μL) solution, and treated with trimethyl orthoformate (6 mL). The reaction vessel was flushed with N_2, stoppered, stirred for 48 h, and then evaporated to a solid, which was recrystallized from methylene chloride/methanol to give **14** (1.72 g, 71% yield from 4) as white needles: mp 222–223 °C; $[\alpha]^{20}_D$ −114° (c 1.4, $CHCl_3$); ^1H NMR δ 2.56 (s, 3 H), 2.73 (s, 3 H), 3.2 (d, 1 H, J = 1.64), 3.89 (dt, 1 H, J = 1.9, 8.3), 4.26 (t, 1 H, J = 8.5), 4.4 (dd, 1 H, J = 8.7, 2.1), 7.15–8.2 (m, 13 H). Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.8; H, 5.8; N, 3.5. Found: C, 74.7; H, 5.9; N, 3.4.

***N*-(9-Phenylfluoren-9-yl)-L-serinal Dimethyl Acetal (15).** Oxazolidinone **14** (1.67 g, 4.2 mmol) was dissolved in 90 mL of 1 M ethanolic potassium hydroxide, and dry N_2 was bubbled into the solution for 5 min while the solution was brought to reflux. The solution was stirred while refluxing under nitrogen atmosphere for 24 h, cooled, and partitioned between 1/1 H_2O/brine (90 mL) and EtOAc (90 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL), and the combined organic layer was washed with brine, dried, and evaporated to an oil, which later solidified. **15**: 1.45 g (92%); mp 91–92 °C; $[\alpha]^{20}_D$ −103° (c 1.49, $CHCl_3$); ^1H NMR δ 2.2 (q, 1 H, J = 4, 8), 2.94 (dd, 1 H, 11.2, 4.8), 3 (s, 3 H), 3.3 (s, 3 H), 3.4 (dd, 1 H, J = 3.4, 11.1), 3.89 (d, 1 H, J = 4) 7.2–7.7 (m, 13 H). Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.8; H, 6.7; N, 3.7. Found: C, 76.8; H, 6.7; N, 3.7.

Aminomalondialdehyde Mono(dimethyl acetal) 16. Dimethyl sulfide (620 μL, 8.4 mmol) was added to a suspension of *N*-chlorosuccinimide (940 mg, 7 mmol) in 12 mL of toluene at 0 °C and stirred for 20 min when a white precipitate was observed. The mixture was cooled to −25 °C, amino alcohol **15** (1.05 g, 2.8 mmol) in 6 mL of toluene was added to the cooled suspension, which was stirred for 5 h at −25 °C, triethylamine (1 mL, 7 mmol) was added, stirring was continued for 10 min at −25 °C, and the mixture was then allowed to warm to room temperature for an additional 10 min. Water (20 mL) was added, the aqueous layer was extracted with EtOAc (3 × 25 mL), and the combined organic layer was washed with brine, dried, and evaporated to an oil, which was chromatographed with 10% EtOAc in hexane as eluant. Evaporation of the collected fractions yielded **16** as an oil, which crystallized on exposure to high vacuum: 960 mg (92%); mp 65 °C; $[\alpha]^{20}_D$ 36° (c 1.27, $CHCl_3$); ^1H NMR δ 2.7 (d, 1 H, J = 2.3), 3 (s, 3 H), 3.28 (s, 3 H), 4.09 (d, 1 H, J = 3.4), 7.2–7.6 (m, 13 H), 9.38 (d, 1 H, J = 1). Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.2; H, 6.2; N, 3.7. Found: C, 77.2; H, 6.1; N, 3.7.

Reduction of Malondialdehyde Monoacetal 16 to Alcohol 15. A solution of malondialdehyde monoacetal **16** (125 mg, 0.33 mmol) in 3 mL of THF at −78 °C was treated with a solution (0.3 mL) of 1.1 M $LiAlH_4$ in THF, stirred for 20 min, warmed to 0 °C, stirred for an additional 20 min, and poured into a chilled rapidly stirring solution of $KHSO_4$ (200 mg) in 5 mL of H_2O. The mixture was extracted with EtOAc (4 × 10 mL), and the combined organic extractions were washed with brine, dried, and evaporated to an oil, which was chromatographed with a gradient of 10–25% EtOAc in hexane as eluant. Evaporation of the collected fractions yielded 106 mg (86%) of **15** as an oil, which crystallized on standing.

***N*-(Phenylsulfonyl)proline Esters 18 and 24.** L- or D-*N*-(phenylsulfonyl)proline (110 mg, 0.44 mmol) was added to a 0.66 M solution of 1,1′-carbonylbis(3-methylimidazolium) triflate[14] in nitromethane (0.6 mL), and the mixture was stirred for 10 min at 0 °C. Alcohol **15** or **23** (0.1 mmol) in THF (0.5 mL) was then added to the homogeneous solution, which was stirred for 50 min at 0 °C and then partitioned between EtOAc (10 mL) and water (3 mL). The organic layer was extracted with NaH_2PO_4 (8 mL) and $NaHCO_3$ (4 × 8 mL), washed with 10 mL brine, dried, and evaporated to an oil, which was redissolved, filtered through a short plug of silica gel with 25% EtOAc in hexane as eluant, and reevaporated to an oil, which was used for ^1H NMR analysis.[20]

L-Proline ester 18: ^1H NMR δ 1.78 (m, 1 H), 1.95 (m, 3 H), 2.5 (m, 1 H), 3.1 (s, 3 H), 3.18 (s, 3 H), 3.32 (m, 1 H), 3.48 (m, 1 H), 3.8 (m, 1 H), 3.87 (m, 1 H), 3.9 (d, 1 H, J = 4), 4.3 (m, 1 H), 7.15–7.85 (m, 18 H).

D-Proline ester 18: ^1H NMR δ 1.78 (m, 1 H), 1.95 (m, 3 H), 2.35 (m, 1 H), 3.12 (s, 3 H), 3.14 (s, 3 H), 3.3 (m, 1 H), 3.48 (m, 1 H), 3.8 (m, 1 H), 3.86 (m, 1 H), 3.91 (d, 1 H, J = 4), 4.27 (m, 1 H), 7.15–7.95 (m, 18 H).

L-Proline ester 24: ^1H NMR δ 1.03 (d, 3 H, J = 6.5), 1.15 (d, 3 H, J = 6.3), 1.75 (m, 2 H), 2 (m, 8 H), 2.58 (dd, 1 H, J = 3.7, 8.7), 2.77 (dd, 1 H, J = 5.6, 8.4), 3.35 (m, 2 H), 3.42 (m, 1 H), 3.55 (m, 1 H), 4.25 (m, 1 H), 4.3 (m, 1 H), 4.42 (dd, 1 H, J = 1.2, 10.2), 4.53 (dd, 1 H, J = 1.6, 10.2), 4.73 (m, 1 H), 4.9 (m, 1 H), 5.26 (m, 1 H), 5.35 (m, 1 H), 7.05–7.95 (m, 36 H).

D-Proline ester 24: ^1H NMR δ 0.98 (d, 3 H, J = 6.5), 1.2 (d, 3 H, J = 6.3), 1.77 (m, 2 H), 2 (m, 8 H), 2.6 (m, 1 H), 2.78 (dd,

1 H, J = 5.3, 8.4), 3.35 (m, 2 H), 3.44 (m, 2 H), 4.25 (m, 1 H), 4.3 (m, 1 H), 4.38 (dd, 1 H, J = 1.3, 10.2), 4.56 (dd, 1 H, J = 1.6, 10.2), 4.75 (m, 1 H), 4.83 (m, 1 H), 5.25 (m, 1 H), 5.35 (m, 1 H), 7.05–7.95 (m, 36 H).

(4*R*)-2-Oxo-3-(9-phenylfluoren-9-yl)-4-vinyloxazolidine (19). A solution of isoxazolidide **4** (1.28 g, 3 mmol) in THF (50 mL) at −78 °C was treated with a 1.1 M solution of $LiAlH_4$ in THF (2.7 mL), stirred for 7 min, and then transferred via Teflon tubing into a rapidly stirring solution of $KHSO_4$ (2.5 g) in H_2O (40 mL) at 0 °C. The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layer was washed with brine, dried, and evaporated to a foam (960 mg, 90%). The foam was redissolved in THF (25 mL), cooled to −40 °C, and treated with a suspension of ylide prepared from methyltriphenylphosphonium iodide (1.33 g, 3.3 mmol) and dimsyl sodium [NaH (150 mg, 3 mmol, 50 wt % dispersion) and DMSO (4 mL)] in THF (5 mL). The solution was stirred for 10 min at −40 °C, warmed to 30 °C, stirred for 10 min, chilled to 0 °C, treated with 25 mL H_2O, and extracted with EtOAc (4 × 25 mL). The combined organic extracts were washed with brine, dried, and evaporated to an oil, which was chromatographed with a gradient of 10–25% EtOAc in hexane as eluant. Evaporation of the collected fractions yielded 820 mg (77%) of **19**: mp 149–153 °C; $[\alpha]^{20}_D$ −510° (c 1.25, $CHCl_3$); ^1H NMR δ 3.9 (dd, 1 H, J = 8.6, 2.9), 4.1 (d, 1 H, J = 16.9), 4.18 (m, 1 H), 4.38 (d, 1 H, J = 10.2), 4.46 (t, 1 H, J = 8.3), 5.2 (dt, 1 H, J = 9.8, 16.6), 7.1–8 (m, 13 H). Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.6; H, 5.4; N, 4.0. Found: C, 81.6; H, 5.4; N, 3.9.

***N*-(9-Phenylfluoren-9-yl)-L-vinylglycinal Dimethyl Acetal (20).** Prewashed NaH (120 mg, 2.5 mmol, 50 wt % dispersion) was suspended in DMSO (3 mL) and heated at 80 °C for 30 min. The heating bath was removed, and methyltriphenylphosphonium iodide (1.11 g, 2.75 mmol, recrystallized from EtOH/ether) was added to the solution, which was stirred for 2 h, diluted with THF (3 mL), and transferred via Teflon tubing into a solution of malondialdehyde **16** (750 mg, 2 mmol) in THF (17 mL) at −10 °C. The mixture was stirred for 10 min at −10 °C and then for 10 min at room temperature before being cooled to 0 °C and treated with H_2O (25 mL). It was extracted with EtOAc (4 × 25 mL), and the combined organic layer was washed with brine, dried, and evaporated to an oil, which was chromatographed with a gradient of 10–25% EtOAc in hexane as eluant. Evaporation of the collected fractions yielded 550 mg (74%) of **20** as an oil: $[\alpha]^{20}_D$ −124° (c 1.35, $CHCl_3$); ^1H NMR δ 2.79 (dd, 1 H, 7.6, 4.4), 3.14 (s, 3 H), 3.25 (s, 3 H), 3.9 (d, 1 H, J = 4.4), 4.5 (dd, 1 H, J = 1, 17.3), 4.57 (dd, 1 H, J = 1, 10.3), 5.46 (ddd, 1 H, J = 7.6, 10.3, 17.3), 7.1–7.8 (m, 13 H). Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.8; H, 6.8; N, 3.8. Found: C, 80.8; H, 6.8; N, 3.8.

***N*-(9-Phenylfluoren-9-yl)-D-vinylglycinol (21).** Oxazolidinone **19** (1.45 g, 4.1 mmol) was dissolved in 80 mL of 1 M ethanolic KOH, N_2 was bubbled through the solution for 5 min while it was brought to reflux, and it was stirred while refluxing under a N_2 atmosphere for 24 h, cooled, and partitioned between 2/1 H_2O/brine (150 mL) and EtOAc (100 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL), and the combined organic layer was washed with brine, dried, and evaporated to an oil, which was chromatographed with a gradient of 10–50% EtOAc in hexane as eluant. Evaporation of the collected fractions gave 1.08 g (81%) of **21** as an oil: ^1H NMR δ 2.7 (q, 1 H, J = 6.4), 3.1 (dd, 1 H, J = 5, 10.6), 3.2 (dd, 1 H, J = 6.4, 10.6), 4.58 (d, 1 H, J = 17.2), 4.68 (d, 1 H, J = 10.2), 5.2 (ddd, 1 H, J = 7.4, 10.4, 17.4), 7.1–7.8 (m, 13 H). Anal. Calcd for $C_{23}H_{21}NO$: C, 84.4; H, 6.5; N, 4.3. Found: C, 84.3; H, 6.5; N, 4.2.

(2*R*,3*RS*)-2-[*N*-(9-Phenylfluoren-9-yl)amino]-1-penten-3-ol (23) via *N*-(9-Phenylfluoren-9-yl)-D-vinylglycinal (D-22). Dimethyl sulfide (730 μL, 10 mmol) was added at 0 °C to a suspension of *N*-chlorosuccinimide (1.1 g, 8.3 mmol) in 14 mL of toluene and stirred for 20 min when a white precipitate was observed. The mixture was cooled to −25 °C, and *N*-(9-phenylfluoren-9-yl)-D-vinylglycinol (**21**, 1.05 g, 2.8 mmol) in 6 mL of toluene was added to the cooled suspension, which was stirred for 5 h at −25 °C. Triethylamine (1.4 mL, 8.6 mmol) was added, and the mixture was stirred for 20 min at −25 °C and for 5 min at 0 °C. Water (20 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine, dried, and evaporated to an oil, which was chromatographed with 10% EtOAc in hexane as eluant. Evaporation of the collected fractions yielded **22** as an oil: 430 mg (40%); ^1H NMR δ 3.2 (d, 1 H, J = 6.8), 5 (d, 1 H, J = 1.3), 5.03 (d, 1 H, J = 1.4), 5.52 (m, 1 H), 7.1–7.75 (m, 13 H), 9.1 (s, 1 H).

Aldehyde D-**22** (430 mg, 1.3 mmol) was dissolved in 13 mL of THF, cooled to −78 °C, and treated with 0.8 mL of 1.6 M methyllithium in ether. The mixture was stirred for 20 min at −78 °C, MeOH (1 mL) was added, and the cooling bath was removed. The solution was partitioned between EtOAc (15 mL) and 1 M NaH_2PO_4 (15 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine, dried, and evaporated to an oil, which was chromatographed with a gradient of 10–25% EtOAc in hexane as eluant. Evaporation of the volatiles gave 210 mg (47%) of **23** as a 1/1 mixture of diastereomers: ^1H NMR δ 0.88 (d, 3 H), 0.93 (d, 3 H), 2.32 (t, 1 H, J = 8.5), 2.53 (dd, 1 H, J = 8.6, 3.8), 3.24 (m, 1 H), 3.4 (m, 1 H), 4.2 (d, 1 H, J = 17.4), 4.44 (d, 1 H, J = 10.1), 4.5 (d, 1 H, J = 17.1), 4.72 (d, 1 H, J = 10.3), 5.15 (ddd, 1 H, J = 8.7, 10.2, 17.1), 5.5 (ddd, 1 H, J = 8.7, 10.3, 17.2), 7.1–7.8 (m, 26 H). Anal. Calcd for $C_{24}H_{23}NO$: C, 84.4; H, 6.8; N, 4.1. Found: C, 84.2; H, 6.8; N, 4.0.

***N*-(9-Phenylfluoren-9-yl)-L-vinylglycinol (21) via *N*-(9-Phenylfluoren-9-yl)-L-vinylglycinal (L-22).** Dimethyl acetal **20** (120 mg, 0.32 mmol) was dissolved in 1.5 mL of acetone, treated with 4.5 mL of 5 M HCl, and heated at 50–60 °C for 3.5 H. The solution was cooled to 0 °C and treated with $NaHCO_3$ (1.9 g, 23 mmol). After CO_2 evolution ceased, the mixture was partitioned between EtOAc (15 mL) and H_2O (10 mL), and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layer was washed with brine, dried, and evaporated to an oil, which was chromatographed with 10–25% EtOAc in hexane as eluant. Eluting first was aldehyde L-**22** (24 mg, 23%), followed by 40 mg (33%) of recovered **20**.

Aldehyde L-**22** (24 mg, 0.07 mmol) was dissolved in methanol (2 mL), cooled to 0 °C, and treated with $NaBH_4$ (40 mg, 1 mmol). The solution was stirred for 30 min and then partitioned between 1 M NaH_2PO_4 (10 mL) and EtOAc (10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine, dried, and evaporated to an oil, which was purified by radial chromatography with 10–25% EtOAc in hexane as eluant. Evaporation of the collected fractions gave 16 mg (67%) of *S*-**21**.

(2*S*)-2-[(9-Phenylfluoren-9-yl)amino]butanal Dimethyl Acetal (25). Acetal **20** (330 mg, 0.89 mmol) in methanol (10 mL) was treated with platinum oxide (35 mg), and the mixture was stirred under 1 atm of hydrogen 4 h. The catalyst was removed by filtration through diatomaceous earth, which was washed with MeOH (3 × 10 mL), and the combined organic layer was evaporated to a solid, which was chromatographed with 25% EtOAc in hexane as eluant. Evaporation of the collected fractions gave 290 mg (87%) of **25**: mp 102–103 °C; $[\alpha]^{20}_D$ −204° (c 0.55, $CHCl_3$); ^1H NMR δ 0.8 (t, 3 H, J = 7.4), 1.17 (m, 1 H), 1.25 (m, 1 H), 2.15 (m, 1 H), 2.9 (s, 3 H), 3.15 (s, 3 H), 3.47 (d, 1 H, J = 3.3), 7.1–7.8 (m, 13 H). Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.4; H, 7.3; N, 3.8. Found: C, 80.5; H, 7.3; N, 3.7.

(2*S*)-2-[(9-Phenylfluoren-9-yl)amino]butanal (26). Dimethyl acetal **25** (290 mg, 0.78 mmol) was dissolved in 5 mL of acetone, treated with 15 mL of 5 M HCl, and heated at 50–60 °C for 3.5 h. The solution was cooled to 0 °C and treated with $NaHCO_3$ (6.3 g, 75 mmol). The solution was partitioned between EtOAc (20 mL) and H_2O (20 mL), and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layer was washed with brine, dried, and evaporated to a solid, which was recrystallized from EtOAc/hexane to give 160 mg (63%) of **26**: mp 107–108 °C. Chromatography of the mother liquor with a gradient 10–25% EtOAc in hexane as eluant gave another 60 mg (23%) of solid **26**: $[\alpha]^{20}_D$ −75° (c 1.05, $CHCl_3$); ^1H NMR δ 0.8 (t, 3 H, J = 7.4), 1.24 (m, 1 H), 1.36 (m, 1 H), 2.53 (m, 1 H), 7.1–7.8 (m, 13 H), 9.19 (d, 1 H, J = 2). Anal. Calcd for $C_{23}H_{21}NO$: C, 84.4; H, 6.5; N, 4.3. Found: C, 84.5; H, 6.4; N, 4.2.

(2*S*)-2-[(9-Phenylfluoren-9-yl)amino]butanol (27). Aldehyde **26** (190 mg, 0.58 mmol) was dissolved in methanol (9 mL), cooled to 0 °C, and treated with $NaBH_4$ (40 mg, 1 mmol). The solution was stirred for 30 min and then partitioned between 1 M NaH_2PO_4 (15 mL) and EtOAc (15 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic

layer was washed with brine, dried, and evaporated to an oil, which was chromatographed with 25% EtOAc in hexane as eluant. Evaporation of the collected fractions gave 170 mg (89%) of **27**, which solidified under vacuum: mp 100 °C; $[\alpha]^{20}_D$ 234° (*c* 1.43, $CHCl_3$); ^1H NMR δ 0.66 (t, 3 H, J = 7.4), 1.22 (m, 2 H), 2.07 (m, 1 H), 2.8 (dd, 1 H, J = 4, 10.6), 3.02 (dd, 1 H, J = 4, 10.5), 7.1–7.8 (m, 13 H); $C_{23}H_{23}NO$: C, 83.9; H, 7.0; N, 4.3. Found: C, 83.8; H, 7.0; N, 4.2.

Reduction of Vinylglycinol *S*-21 to 2-Aminobutanol 27. A solution of vinylglycinol *S*-**21** (30 mg, 0.09 mmol) in MeOH (3 mL) was treated with platinum oxide (10 mg) and stirred under 1 atm of hydrogen for 3 h. The catalyst was removed by filtration through diatomaceous earth, which was washed with MeOH (3 × 5 mL). The combined organic layer was evaporated to give 30 mg (99%) of **27**, which was directly coupled to *N*-(tolylsulfonyl)-L-alaninyl-*N*-methylimidazolium triflate as described below.

***N*-(Tolylsulfonyl)-L-alanine (*R*)- and (*S*)-2-[*N*-(9-Phenylfluoren-9-yl)amino]butanol Esters (28).** A solution of carbonyldiimidazole (50 mg, 0.32 mmol) in nitromethane (0.4 mL) was treated with 70 μL of methyl trifluoromethanesulfonate as described[14] and then treated with *N*-(tolylsulfonyl)-L-alanine (73 mg, 0.3 mmol) and stirred 10 min. To the solution was added a solution of (*R*)- or (*S*)-2-[*N*-(9-phenylfluoren-9-yl)amino]butanol (**27**, 30 mg, 0.09 mmol) in nitromethane (0.4 mL), the mixture was stirred at 0 °C for 30 min, and then EtOAc (12 mL) and water (3 mL) were added. The organic phase was extracted with NaH_2PO_4 (8 mL) and $NaHCO_3$ (4 × 8 mL), washed with 10 mL of brine, dried, and evaporated to an oil, which was redissolved, filtered through a short plug of silica gel with 25% EtOAc in hexane as eluant, and reevaporated to an oil, which was used for ^1H NMR analysis.[20]

***N*-(Tolylsulfonyl)-L-alanine (*S*)-2-[*N*-(9-phenylfluoren-9-yl)amino]butanol ester:** ^1H NMR δ (benzene-d_6) 0.59 (t, 3 H, J = 7.5), 1.04 (d, 3 H, J = 7.1), 1.1 (m, 2 H), 1.86 (s, 3 H), 2.2 (m, 1 H), 3.35 (dd, 1 H, J = 3.7, 11), 3.48 (dd, 1 H, J = 4.8, 11), 3.97 (m, 1 H), 5.4 (d, 1 H, J = 8.3), 6.7–7.9 (m, 17 H).

***N*-(Tolylsulfonyl)-L-alanine (*R*)-2-[*N*-(9-phenylfluoren-9-yl)amino]butanol ester:** ^1H NMR δ (benzene-d_6) 0.56 (t, 3 H, J = 7.3), 1.1 (m, 2 H), 1.12 (d, 3 H, J = 7.1), 1.92 (s, 3 H), 2.14 (m, 1 H), 3.4 (m, 2 H), 3.94 (m, 1 H), 5.28 (d, 1 H, J = 8.4), 6.75–7.85 (m, 17 H).

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Supplementary Material Available: The X-ray crystallographic determination of **7** and **10**, listings of fractional atomic coordinates with their estimated standard deviations, temperature factors, intramolecular distances and angles, and least-square planes (6 pages). Ordering information is given on any current masthead page.

Enantioselective Robinson Annulation: Synthesis of (+)-*O*-Methyljoubertiamine

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The α-formyl ester derived from 2-(1-naphthyl)-3-borneol, as the potassium salt in moist dimethoxymethane, adds to methyl vinyl ketone to give two adducts in a ratio of 95:5. The relative configuration of the major diastereomer has been confirmed by X-ray crystallography. This diastereomer is readily carried on to (+)-*O*-methyljoubertiamine. The addition of such naphthylbornyl esters to Michael acceptors should constitute a general laboratory-scale procedure for the enantioselective construction of enantiomerically pure quaternary stereogenic centers.

The two most common methods for the construction of cyclohexane derivatives are Diels–Alder cycloaddition and Robinson annulation. While a great deal of work has been directed toward enantioselective Diels–Alder cycloaddition,[2] work on the Robinson annulation has been limited to cyclic donors.[3] We now report the development of an enantiomerically pure Michael donor,[4-7] the optimization of selectivity in the Michael addition, and the

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