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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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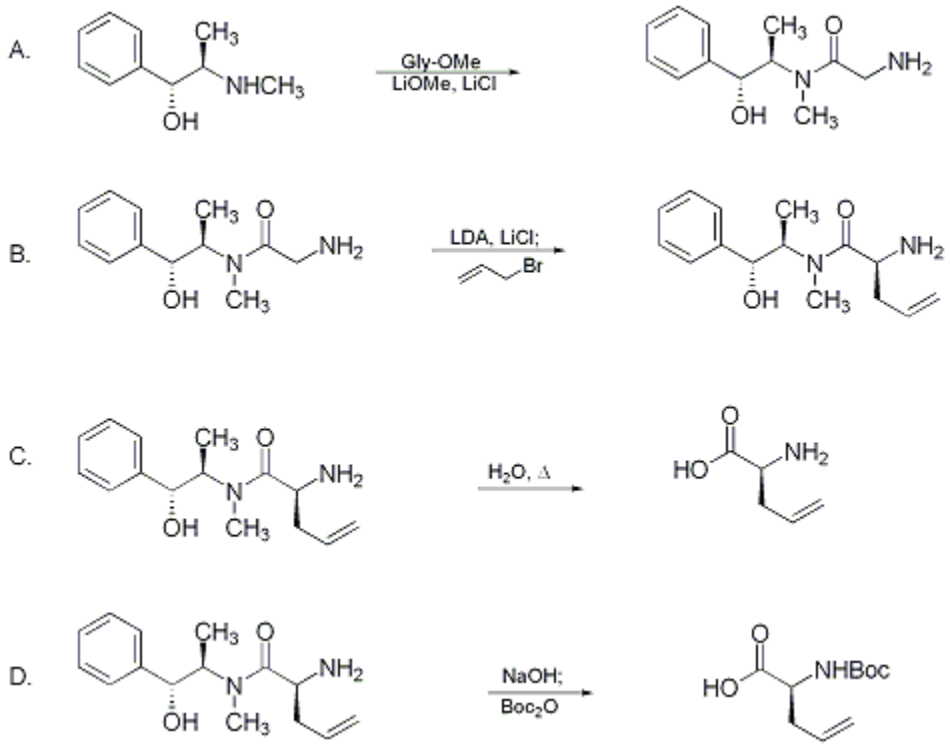
ASYMMETRIC SYNTHESIS OF α-AMINO ACIDS BY THE ALKYLATION OF PSEUDOEPHEDRINE GLYCINAMIDE: L-ALLYLGLYCINE AND N-BOC-L-ALLYLGLYCINE

[Acetamide, 2-amino-N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methyl-, [R-(R,R)]-, 4-Pentenoic acid, 2-amino-, (R)- and 4-Pentenoic acid, 2-[[(1,1-dimethylethoxy)carbonyl]amino]-, (R)-)]



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1. Procedure

A. (R,R)-(−)-Pseudoephedrine glycinamide. An oven-dried, 3-L, three-necked, round-bottomed flask is equipped with an argon inlet adapter, a rubber septum, a 150-mL pressure-equalizing addition funnel fitted with a rubber septum, and a Teflon-coated magnetic stirring bar. The flask is flushed with argon and charged with 30.8 g (0.726 mol, 2 equiv) of anhydrous lithium chloride (Note 1), 60.0 g (0.363 mol, 1 equiv) of (R,R)-(−)-pseudoephedrine (Note 2), and 500 mL of dry tetrahydrofuran (THF) (Note 3). The resulting slurry is cooled in an ice bath. After 15 min, 6.89 g (0.182 mol, 0.5 equiv) of solid lithium methoxide (Note 4) is added to the reaction flask in one lot. The resulting mixture is stirred at 0°C for 10 min, after which time the pressure-equalizing addition funnel is charged with a solution of 40.4 g (0.454 mol, 1.25 equiv) of glycine methyl ester (Note 5) in 100 mL of dry THF (Note 3), and dropwise addition of this solution is initiated. The addition is completed within 1 hr, and the reaction flask is maintained at 0°C for an additional 7 hr. The reaction is terminated by the addition of 500 mL of water. The bulk of the THF is removed from the resulting colorless solution by concentration under reduced pressure. An additional 250 mL of water is added to the aqueous concentrate, and the resulting aqueous solution is transferred to a 2-L separatory funnel and extracted sequentially with one 500-mL and four 250-mL portions of dichloromethane . The combined organic extracts are dried over anhydrous potassium carbonate and filtered, and the filtrate is concentrated under reduced pressure. The clear,

colorless, oily residue is dissolved in 300 mL of warm (50°C) THF (Note 3), 10 mL of water is added, and the resulting solution is allowed to cool to 23°C, whereupon the product crystallizes as its monohydrate within 1 hr. The crystallization process is completed by cooling the crystallization flask to −20°C. After standing for 2 hr at −20°C, the crystals are collected by filtration and rinsed with 200 mL of ether . The crystals are dried under reduced pressure (0.5 mm) at 23°C for 2 hr to provide 62.8 g (72%) of (R,R)-(−)-pseudoephedrine glycinamide monohydrate (Note 6).

Dehydration of the monohydrate is initiated by suspending the crystalline solid (62.8 g) in 1.2 L of dichloromethane ; the resulting suspension is stirred vigorously for 1 hr to break up any large lumps of solid. After 1 hr of vigorous stirring, 60 g of anhydrous potassium carbonate is added to the fine dispersion (Note 7). After the suspension is stirred for 10 min, it becomes translucent. At this point the mixture is filtered through 40 g of Celite in a 10 cm-i.d. Büchner funnel fitted with a Whatman #1 filter paper. The clear, colorless filtrate is concentrated under reduced pressure. The oily residue is dissolved in 200 mL of toluene , and the resulting solution is concentrated to remove any residual dichloromethane. The oily concentrate is then dissolved in 175 mL of hot (60°C) toluene , and the resulting solution is allowed to cool slowly to 23°C. Crystallization of the product may occur spontaneously within 1-3 hr at 23°C; however, if necessary, it can be initiated by scratching the side of the flask until crystals are observed. Once crystallization is initiated, the crystals are broken up periodically with a spatula to obtain a fine powder that is easily manipulated. After 30 min from the onset of crystallization, the flask is cooled to −20°C under an argon atmosphere to complete the crystallization process. After standing at −20°C for 2 hr, the crystals are collected by filtration and rinsed with 200 mL of ether . The product is dried by transferring the solid to a 500-mL, round-bottomed flask fitted with a vacuum adapter and evacuating the flask (0.5 mm). After 1 hr at 23°C, the flask is immersed in an oil bath at 60°C (Note 8). After 12 hr, the flask is cooled to 23°C to afford 53.8 g (67% overall) of anhydrous (R,R)-(−)-pseudoephedrine glycinamide (Note 9).

B. Pseudoephedrine L-allylglycinamide . A 1-L, single-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirring bar and a rubber septum through which is placed a needle connected to a source of vacuum and argon. The system is evacuated, the flask is flame-dried and then allowed to cool to 23°C under reduced pressure. When the reaction flask has cooled to 23°C, it is flushed with argon and charged with 200 mL of dry THF (Note 3) and 63.0 mL (0.450 mol, 1.025 equiv) of diisopropylamine (Note 10). The resulting solution is cooled to 0°C in an ice bath. With efficient stirring, the solution is deoxygenated at 0°C by alternately evacuating the reaction vessel and flushing with argon three times. After the solution is deoxygenated, 167 mL (0.439 mol, 1 equiv) of a 2.63 M solution of butyllithium in hexanes (Note 11) and (Note 12) is added via syringe over a 20-min period. After the addition is complete, the solution is stirred at 0°C for 15 min.

Separately, a 2-L, three-necked, round-bottomed flask is equipped with an inlet adapter connected to a source of vacuum and argon, two rubber septa, and a Teflon-coated magnetic stirring bar. The flask is charged with 57.2 g (1.35 mol, 6 equiv) of anhydrous lithium chloride (Note 1) and, with efficient stirring of the solid, the reaction vessel is evacuated and flame-dried. The flask and its contents are allowed to cool to 23°C under reduced pressure. When the flask has cooled to 23°C, it is flushed with argon, 50.0 g (0.225 mol, 1 equiv) of solid (R,R)-(−)-pseudoephedrine glycinamide is added, and one of the septa is replaced with a Teflon thermometer adapter fitted with a thermometer for internal measurement of the reaction temperature. The solids are suspended in 500 mL of dry THF (Note 3) and the resulting milky-white slurry is cooled to an internal temperature of 0°C in an ice bath. With efficient stirring, the slurry is deoxygenated by alternately evacuating the reaction vessel and flushing with argon three times.

The two reaction flasks are connected via a wide-bore (14 gauge) cannula so that one end of the cannula is immersed in the lithium diisopropylamide solution and the other is suspended above the (R,R)-(−)-pseudoephedrine glycinamide-lithium chloride slurry. The flask containing the lithium diisopropylamide solution and its ice bath are raised to a height just above that of the flask containing the glycinamide slurry. The reaction flask containing the glycinamide slurry is very briefly evacuated to initiate siphon transfer of the lithium diisopropylamide solution. Once the siphon flow is established, the flask containing the glycinamide slurry is flushed with argon. By raising or lowering the height of the flask containing the lithium diisopropylamide solution, the rate of addition is modulated so that the

temperature of the reaction mixture does not rise above 5°C (approximately 45 min addition time) (Note 13). After the addition is complete, the reaction mixture is stirred at 0°C for 30 min (Note 14). To the resulting pale yellow suspension is added 19.5 mL (0.225 mol) of allyl bromide (Note 15) via syringe over a 20-min period. The rate of addition of allyl bromide is also modulated to prevent the internal reaction temperature from rising above 5°C (Note 16). After the addition of allyl bromide is complete, the reaction mixture is stirred for 45 min at 0°C. The reaction is terminated by the addition of 500 mL of water. The resulting biphasic mixture is slowly acidified by the addition of 300 mL of 3 M aqueous hydrochloric acid solution. The biphasic mixture is transferred to a 2-L separatory funnel and is extracted with 1 L of ethyl acetate . The organic layer is separated and extracted sequentially with 300 mL of 3 M aqueous hydrochloric acid solution and 300 mL of 1 M aqueous hydrochloric acid solution. The aqueous layers are combined and cooled to an internal temperature of 5°C by stirring in an ice bath. The cold aqueous solution is then cautiously made basic (pH 14) by the slow addition of 120 mL of aqueous 50% sodium hydroxide solution. The temperature of the solution should not be allowed to rise above 25°C during the addition of base. The basic solution is extracted sequentially with one 500-mL portion and four 250-mL portions of dichloromethane (Note 17). The combined organic layers are dried over anhydrous potassium carbonate and filtered, and the filtrate is concentrated under reduced pressure. The oily residue is dissolved in 200 mL of toluene , and the resulting solution is concentrated under reduced pressure to remove residual dichloromethane and diisopropylamine. The solid residue is recrystallized by suspending it in 100 mL of toluene and heating the resulting suspension until the solids dissolve (ca. 70°C). The recrystallization mixture is allowed to cool to 23°C. After 3 hr, when crystallization of the product is nearly complete, the recrystallization flask is cooled to 0°C in an ice bath to complete the recrystallization process. After standing at 0°C for 1 hr, the crystals are collected by filtration and rinsed sequentially with two 50-mL portions of cold (0°C) toluene and one 100-mL portion of ether at 23°C. The crystals are dried under reduced pressure (0.5 mm) at 23°C for 2 hr to provide ~31.3 g (~53%) of diastereomerically pure pseudoephedrine L-allylglycinamide (Note 18). The mother liquors are concentrated and the oily residue is dissolved in 50 mL of toluene at 23°C. The resulting solution is cooled to −20°C and seeded with authentic pseudoephedrine L-allylglycinamide. After standing at −20°C for 6 hr, the crystals that have formed are collected by filtration and rinsed with 25 mL of cold (0°C) toluene and 50 mL of ether at 23°C. The product is dried under reduced pressure (0.5 mm) at 23°C for 2 hr to afford a second crop of the alkylation product. The second crop of crystals (~4.8 g) is recrystallized a second time by suspending it in 20 mL of toluene and warming to ca. 70°C to dissolve the solids (Note 19). The resulting solution is allowed to cool slowly to 23°C, whereupon the product crystallizes within 1 hr. The recrystallization flask is cooled to −20°C to complete the crystallization process. After standing at −20°C for 90 min, the crystals are collected by filtration and washed sequentially with two 10-mL portions of cold (0°C) toluene and one 25-mL portion of ether . The crystals are dried under reduced pressure (0.5 mm) at 23°C for 2 hr to afford ~3.6 g (~6%) of diastereomerically pure pseudoephedrine L-allylglycinamide. To obtain additional product, the mother liquors are concentrated under reduced pressure and the oily residue is purified by chromatography on silica gel (100 g, 5-cm i.d. column) eluting with 4% methanol , 4% triethylamine and 92% dichloromethane . The oily residue obtained after concentration of the appropriate fractions is dissolved in 25 mL of warm (50°C) toluene . The resulting solution is cooled to −20°C and held at that temperature for 12 hr. The crystals that form are collected by filtration and rinsed with 20 mL of cold (0°C) toluene and 30 mL of ether at 23°C. The crystals are dried under reduced pressure (0.5 mm) at 23°C for 2 hr to provide an additional ~5.0 g (~8%, total yield: 39.1-42.0 g, 66-71%) of diastereomerically pure pseudoephedrine L-allylglycinamide.

C. L-Allylglycine . A 1-L, single-neck, round-bottomed flask equipped with an efficient reflux condenser, a Teflon-coated magnetic stirring bar and a heating mantle is charged with 25.0 g (0.0953 mol) of pseudoephedrine L-allylglycinamide and 500 mL of water. The resulting suspension is heated to reflux, causing the solids to dissolve to afford a colorless, homogeneous solution. After 10 hr at reflux, the reaction mixture is allowed to cool to 23°C, whereupon (R,R)-(−)-pseudoephedrine is observed to crystallize (Note 20). Concentrated aqueous ammonium hydroxide solution (10 mL) is added (Note 21), whereupon the resulting aqueous slurry is transferred to a 1-L separatory funnel and extracted with three 200-mL portions of dichloromethane , reserving the aqueous layer. The three organic layers are individually and sequentially extracted with a single aqueous solution prepared by combining 250 mL of water and 5 mL of concentrated aqueous ammonium hydroxide solution. The aqueous extract is combined with the aqueous extract reserved earlier and the resulting solution is concentrated under

reduced pressure to provide a white solid residue. The solid is triturated, sequentially, with one 100-mL and one 50-mL portion of absolute ethanol . The triturated solid is collected by filtration and dried under reduced pressure (0.5 mm) at 23°C for 2 hr to afford 10.2 g (93%) of L-allylglycine of ≥99% ee (Note 22). If desired, (R,R)-(−)-pseudoephedrine can be recovered from the organic extracts. The organic extracts are combined and dried over anhydrous potassium carbonate and filtered, and the filtrate is concentrated under reduced pressure to afford a solid. The solid is recrystallized by dissolving it in a minimum volume of hot water (ca. 350 mL). The resulting solution is allowed to cool slowly to 23°C, by which time extensive crystallization of (R,R)-(−)-pseudoephedrine has occurred. The recrystallization flask is cooled to 0°C in an ice bath. After standing at 0°C for 1 hr, the crystals are collected by filtration and dried under reduced pressure (0.5 mm) at 23°C for 2 hr to afford 10.8 g of pure (R,R)-(−)-pseudoephedrine (mp 116-117°C). The mother liquors are concentrated and a second crop of crystals (2.6 g, total yield 13.4 g, 85%) is obtained in a similar manner by recrystallization from ca. 75 mL of water.

D. N-Boc-L-allylglycine . A 1-L, single-neck, round-bottomed flask equipped with an efficient reflux condenser, a Teflon-coated magnetic stirring bar and a heating mantle is charged with 14.7 g (0.056 mol, 1 equiv) of pseudoephedrine L-allylglycinamide and 224 mL (0.112 mol, 2 equiv) of 0.5 M aqueous sodium hydroxide solution. The resulting slurry is heated to reflux whereupon a clear, colorless homogeneous solution is obtained. After 2 hr at reflux, the reaction mixture is cooled to 23°C, inducing the crystallization of (R,R)-(−)-pseudoephedrine (Note 20). The reaction suspension is transferred to a 1-L separatory funnel and is extracted sequentially with one 200-mL and one 100-mL portion of dichloromethane , reserving the aqueous layer. The two organic layers are individually and sequentially extracted with a single 150-mL portion of water. The aqueous layer is combined with the earlier aqueous extract and the resulting solution is reserved. If desired, (R,R)-(−)-pseudoephedrine can be recovered from the organic extracts, as follows. The organic extracts are combined and dried over anhydrous potassium carbonate and filtered, and the filtrate is concentrated under reduced pressure to afford a solid. The solid is recrystallized by dissolving it in a minimum volume of hot water (ca. 250 mL). The resulting solution is allowed to cool slowly to 23°C, by which time extensive crystallization of (R,R)-(−)-pseudoephedrine has occurred. The recrystallization flask is cooled to 0°C in an ice bath. After standing at 0°C for 1 hr, the crystals are collected by filtration and are dried under reduced pressure (0.5 mm) at 23°C for 2 hr to afford 6.2 g (67%) of pure (R,R)-(−)-pseudoephedrine (mp 116-117°C). The mother liquors are concentrated and a second crop of crystals (1.5 g, total yield 7.7 g, 83%) is obtained in a similar manner by recrystallization from ca. 50 mL of water.

The combined aqueous layers are transferred to a 1-L, round-bottomed flask and 9.40 g (0.112 mol, 2 equiv) of solid sodium bicarbonate is added. The resulting solution is reduced to a volume of approximately 150 mL by concentration under reduced pressure. A Teflon-coated magnetic stirring bar is added, and the aqueous mixture is cooled to 0°C in an ice bath. To the cooled solution is added, sequentially, 150 mL of p-dioxane (Note 23) and 13.4 g (0.0615 mol, 1.1 equiv) of di-tert-butyl dicarbonate (Note 24). The reaction mixture is stirred for 90 min at 0°C, at which time the ice bath is removed and the solution is allowed to warm to 23°C. After stirring for 90 min at 23°C, the reaction mixture is diluted with 200 mL of water and the resulting solution is transferred to a 1-L separatory funnel and extracted sequentially with one 400-mL and one 200-mL portion of ethyl acetate , reserving the aqueous layer. The two organic layers are individually and sequentially extracted with a single 100-mL portion of 0.1 M aqueous sodium hydroxide solution. The aqueous layer is combined with the aqueous extract reserved earlier and the resulting solution is stirred while cooling in an ice bath. Before acidification of the aqueous layer, 100 mL of ethyl acetate is added to prevent excessive frothing. The resulting biphasic mixture is carefully acidified by the slow addition of 250 mL of a 1 M aqueous hydrochloric acid solution until the aqueous layer is pH 1. The biphasic mixture is transferred to a 2-L separatory funnel, 400 mL of ethyl acetate is added, and, after thorough mixing, the layers are separated. The organic layer is extracted with 200 mL of water. The two aqueous layers are individually and sequentially extracted with a single 200-mL portion of ethyl acetate . The organic layers are combined, and the resulting solution is dried over anhydrous sodium sulfate and filtered. The filtrate is concentrated under reduced pressure. The residue is dissolved in 100 mL of toluene , and the resulting solution is concentrated. The residue is then sequentially dissolved in and then concentrated from 100 mL of toluene , 100 mL of dichloromethane , and two 100-mL portions of ether , in order to remove residual dioxane and ethyl acetate. The oily residue is dried under reduced pressure (55°C, 0.2 mm) for

12 hr to afford 11.8 g (97%) of analytically pure N-Boc-L-allylglycine as a viscous oil (Note 25).

2. Notes

1. Reagent-grade anhydrous lithium chloride (Mallinckrodt Inc.) is further dried by transferring the solid to a flask equipped with a vacuum adapter. The flask is evacuated (0.5 mm) and immersed in an oil bath at 150°C. After 12 hr at 150°C, the flask is allowed to cool to 23°C and is flushed with argon for storage.
2. (R,R)-(−)-Pseudoephedrine was used as received from Aldrich Chemical Company, Inc.
3. Tetrahydrofuran was obtained from EM Science and was distilled under nitrogen (atmospheric pressure) from sodium benzophenone ketyl.
4. Lithium methoxide was purchased from Aldrich Chemical Company, Inc. , and used as received. Butyllithium (BuLi) (10 M in hexanes) may be substituted for lithium methoxide in this reaction and produces a more rapid reaction. For example, the use of 0.25 equiv of 10 M BuLi requires only 1-2 hr for complete reaction and affords 65-69% yield of anhydrous pseudoephedrine glycinamide on a 40-60-g scale.[2] The submitters describe the use of lithium methoxide as a less hazardous alternative to the highly pyrophoric 10 M BuLi.
5. Glycine methyl ester is prepared by the method of Almeida et al.[3] In a mortar and pestle, 80 g of glycine methyl ester hydrochloride (used as received from Aldrich Chemical Company, Inc.) is ground to a fine powder. The powder is suspended in 600 mL of dry ether in a 1-L Erlenmeyer flask equipped with a Teflon-coated magnetic stirring bar. Gaseous ammonia is bubbled rapidly through the vigorously stirred suspension. After 2 hr, the addition of ammonia is discontinued, the product slurry is filtered through a coarse-fritted glass filter, and the filtrate is concentrated under reduced pressure at 23°C. The liquid residue is distilled under reduced pressure (54-55°C at 18 mm) to provide 51.3 g (90%) of glycine methyl ester as a colorless liquid. Glycine methyl ester will polymerize upon storage at room temperature, but may be stored at −20°C for short periods (up to two weeks) without significant decomposition.
6. The monohydrate and anhydrous product show identical spectroscopic properties (Note 9). The monohydrate exhibits the following physical properties: mp 83-85°C; Anal. Calcd for $C_{12}H_{18}N_2O_2 \cdot H_2O$, C, 59.93; H, 8.32; N, 11.66; Found C, 59.81; H, 8.42; N, 11.51.
7. Alternatively, azeotropic drying with acetonitrile may be employed in lieu of dichloromethane/potassium carbonate.[2] A solution of 50.3 g of (R,R)-(−)-pseudoephedrine glycinamide monohydrate in ca. 200 mL of acetonitrile is concentrated under reduced pressure. The oily residue is dissolved in 250 mL of toluene and the resulting solution is concentrated under reduced pressure. The oily residue obtained may be carried on directly in the alkylation procedure with only a slight decrease in yield from the procedure described above. Alternatively, anhydrous (R,R)-(−)-pseudoephedrine glycinamide may be precipitated and the resulting solid dried and carried forward as outlined above.
8. Proper drying of (R,R)-(−)-pseudoephedrine glycinamide is essential to achieve high yields in the subsequent alkylation step. Complete drying may not be achieved at temperatures below 50°C. To prevent melting of the solid product, it should not be heated above 65°C. A preliminary indication of the hydration state of the product is its melting point. Material that is partially hydrated routinely has a melting point that is depressed relative to that of pure anhydrous product (mp 78-80°C). A more accurate determination of the water content may be obtained either from C,H,N analysis or by Karl Fischer titration. The product is somewhat hygroscopic. It may be weighed on the open benchtop without significant hydration; however, it should be stored under argon. The glycinamide should be redried at 60°C under reduced pressure (0.5 mm) if it has been stored for an extended period, or if the yield of the subsequent alkylation reaction is lower than expected.
9. The product shows the following physical and spectroscopic properties: mp 78-80°C; $[\alpha]^{23}_{D}$ −101.2° (CH_3OH, *c* 1.2); TLC R_f = 0.18 (5% CH_3OH, 5% NEt_3, 90% CH_2Cl_2); IR (neat) cm^{-1}: 3361, 2981, 1633, 1486, 1454, 1312, 1126, 1049, 926, 760, 703 ; ^1H NMR (1:1 ratio of rotamers, $CDCl_3$) δ: 0.99 (d, 1.5 H, J = 6.7), 1.09 (d, 1.5 H, J = 6.7), 2.11 [s(br), 3 H], 2.79 (s, 1.5 H), 2.97 (s, 1.5 H), 3.37 (d, 0.5 H, J = 17.1), 3.46 [d(obs)], 1 (H, J = 16.6), 3.72 (d, 0.5 H, J = 15.5), 3.88 (m, 0.5 H), 4.53-4.63 (m, 1.5 H), 7.29-7.40 (m, 5 H) ; ^{13}C NMR ($CDCl_3$) δ: 14.4, 15.3, 27.1, 30.1, 43.4, 43.7, 57.2, 57.5, 74.9, 75.8, 126.7, 126.9, 127.9, 128.2, 128.5, 128.7, 142.1, 142.3, 173.5, 174.1 . Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.65; H, 8.25; N, 12.53.
10. Diisopropylamine was purchased from Aldrich Chemical Company, Inc. , and distilled under nitrogen (atmospheric pressure) from calcium hydride prior to use.

11. It is absolutely imperative that the solution of butyllithium be accurately titrated. If an excess of butyllithium (or LDA) is used, reduced yields will result as a consequence of a decomposition reaction that releases pseudoephedrine. This is easily monitored by TLC analysis (5% methanol , 5% triethylamine , and 90% dichloromethane eluent; UV and ninhydrin visualization). It should be noted that even optimal reaction conditions produce small amounts of this cleavage product (2-4%); however, the amount of cleavage is greatly enhanced in the presence of excess base. To titrate the alkyllithium solution we recommend the method of Watson and Eastham.[4,5] A standard solution of 1.00 M 2-butanol (freshly distilled from calcium hydride) in toluene (freshly distilled from calcium hydride) is prepared in a volumetric flask. A 50-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum is charged with 5 mg of 2,2'-dipyridyl and 20 mL of ether . The flask is flushed with argon, and a small amount (ca. 0.5 mL) of the standard 1.00 M solution of 2-butanol in toluene is added to the solution. The butyllithium solution to be titrated is added slowly, dropwise, to a single-drop end point that turns the solution dark red. This initial titration eliminates complications due to moisture or oxygen and should not be used in the calculation of the titer of the butyllithium solution. Several repetitions of the titration cycle are conducted using the same indicator solution by using accurate, air-tight syringes and alternately adding aliquots of 1.00-M 2-butanol solution (1-2.5 mL) followed by titration of the butyllithium to a dark-red end point.

12. The checkers employed 163 mL of a 2.70-M solution of butyllithium in hexanes whose titer was determined by the procedure given in (Note 11).

13. The addition required 80 min in the hands of the checkers.

14. The reaction mixture was stirred for 40 min at 0°C by the checkers.

15. Allyl bromide was purchased from Aldrich Chemical Company, Inc. , and was distilled under argon (atmospheric pressure) from calcium hydride immediately prior to use.

16. The allyl bromide addition required 30 min in the hands of the checkers.

17. The pH of the aqueous layer is checked after each extraction to ensure that it is >12. If necessary, the pH of the aqueous layer is readjusted to 14 by the addition of aqueous 50% sodium hydroxide solution.

18. The product shows the following physical and spectroscopic properties: mp 71-73°C; $[\alpha]^{23}_{D}$ −86.4° (CH_3OH, *c* 1.1); TLC R_f = 0.59 (5% CH_3OH, 5% NEt_3, 90% CH_2Cl_2); IR (neat) cm^{-1}: 3354, 3072, 2978, 1632, 1491, 1453, 1109, 1051, 918, 762, 703 ; ^1H NMR (3:1 rotamer ratio, $CDCl_3$) major rotamer δ: 1.03 (d, 3 H, J = 6.4), 2.13 (m, 1 H), 2.23 (m, 1 H), 2.87 (s, 3 H), 3.65 (dd, 1 H, J = 7.5, 5.3), 4.55-4.59 (m, 2 H), 5.07-5.14 (m, 2 H), 5.64-5.85 (m, 1 H), 7.23-7.38 (m, 5 H); minor rotamer δ: 0.96 (d, 3 H, J = 6.7), 2.61-2.66 (m, 2 H), 2.93 (s, 3 H), 3.69 (m, 1 H), 4.03 (m, 1 H) ; ^{13}C NMR ($CDCl_3$) major rotamer δ: 14.4, 31.4, 39.6, 51.2, 57.6, 75.5, 118.1, 126.5, 127.6, 128.2, 133.7, 142.1, 176.1; minor rotamer δ: 15.5, 27.0, 39.8, 51.0, 74.9, 117.9, 126.8, 128.1, 128.5, 134.7, 141.8, 175.1 . Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.57; H, 8.59; N, 10.70. Determination of the diastereomeric purity of the product by NMR is complicated by the presence of amide rotamers. The diastereomeric purity of the product may be determined accurately and conveniently by preparing the corresponding diacetate and analyzing by capillary gas chromatography. To prepare the diacetate, a 10-mL, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and a rubber septum is charged with a 16-mg sample of the alkylation product to be analyzed and 1 mL of pyridine . The product is acetylated by adding 1 mL of acetic anhydride and a catalytic amount (5 mg) of 4-(N,N-dimethylamino)pyridine . The reaction mixture is stirred under argon for 1 hr and excess acetic anhydride is quenched by addition of 15 mL of water. The reaction mixture is extracted sequentially with one 30-mL portion and one 20-mL portion of ethyl acetate . The two organic extracts are individually and sequentially extracted with a single 15-mL portion of aqueous saturated sodium bicarbonate solution; the organic extracts are combined, dried over anhydrous sodium sulfate and filtered. The filtrate is concentrated under reduced pressure, and the residue is dissolved in ethyl acetate for capillary gas chromatographic analysis. Analysis was carried out using a Chirasil-Val capillary column (25 m × 0.25 mm × 0.16 μm, available from Alltech Inc.) under the following conditions: oven temp. 220°C, injector temp. 250°C, detector temp. 275°C. The following retention times were observed: (R,R)-(−)-pseudoephedrine glycinamide diacetate, 6.69 min; (R,R)-(−)-pseudoephedrine L-allylglycinamide diacetate, 6.94 min; (R,R)-(−)-pseudoephedrine D-allylglycinamide diacetate, 6.32 min. Note that the retention times can vary greatly with the age and condition of the column. The checkers obtained the following values using an identical new column from Alltech with a flow rate of 4 mL/min, split ratio of 50:1, and an injection volume of 1 μL: retention times (min) 18.33 (D-allyl

isomer), 19.24 (glycinamide SM), 20.24 (L-allyl isomer).
19. The second crop of product crystals (mp 69-71°C) was contaminated with 2% of the starting material, (R,R)-(−)-pseudoephedrine glycinamide (as determined by GC analysis, (Note 18)), and was recrystallized to provide analytically pure product.
20. Although the pseudoephedrine may be recovered by filtration at this stage, the recovery is not quantitative (ca. 50-60%). A more efficient recovery is achieved by the extraction procedure described.
21. Ammonium hydroxide is added to decrease the solubility of pseudoephedrine in the aqueous phase and to minimize the formation of emulsions.
22. The product shows the following spectroscopic and physical properties: mp 275-280°C (dec.); lit.[6] 241-243°C (dec.); lit.[7] 283°C (dec.); $[\alpha]^{23}_{D}$ −37.2° (H_2O, *c* 4); lit.[8] $[\alpha]^{23}_{D}$ −37.1 (H_2O, *c* 4) (Note 26); IR (KBr) cm^{-1}: 3130, 2605, 1586, 1511, 1406, 1363, 1345, 1307, 919, 539 ; ^1H NMR (D_2O) δ: 2.50 (m, 2 H), 3.67 (dd, 1 H, J = 7.0, 5.1), 5.13 (d, 1 H, J = 10.0), 5.14 (d, 1 H, J = 18.6), 5.64 (m, 1 H) ; ^{13}C NMR (D_2O) δ: 35.6, 54.6, 120.9, 132.0, 175.1 . Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.15; H, 7.74; N, 12.03.
The product is determined to be ≥99% ee by HPLC analysis on a Crownpak CR(+) column (pH 1.5 $HClO_4$ mobile phase, 0.4 mL/min, 205 nm detection). The minor enantiomer was identified by comparison with an authentic sample prepared from (S,S)-(+)-pseudoephedrine glycinamide. The following retention times are observed: D-allylglycine, 4.68 min; L-allylglycine, 5.45 min. Using an identical new column and the identical eluent at a flow rate of 0.8 mL/min, the checkers observed retention times of 13.86 min for D-allylglycine and 15.19 min for L-allylglycine.
23. Reagent grade p-dioxane was used as received from Mallinckrodt Inc.
24. Di-tert-butyl dicarbonate was used as received from Aldrich Chemical Company, Inc.
25. If necessary, residual ether may be removed by placing the oily product under reduced pressure (0.5 mm) and warming briefly with a heat gun. The oily residue is typically found to be analytically pure product and requires no purification. The product shows the following physical and spectroscopic characteristics: $[\alpha]^{23}_{D}$ +11.9° (CH_3OH, *c* 1.4), $[\alpha]^{23}_{D}$ −2.5° (CH_2Cl_2, *c* 1.1); lit.[9] $[\alpha]^{23}_{D}$ −3.9° (CH_2Cl_2, *c* 1) (Note 27); IR (neat) cm^{-1}: 3324, 3081, 2980, 2932, 1715, 1513, 1395, 1369, 1251, 1163, 1053, 1025, 922 ; ^1H NMR (2:1 rotamer ratio, $CDCl_3$) major rotamer δ: 1.44 (s, 9 H), 2.57 (m, 2 H), 4.40 (m, 1 H), 5.14-5.19 (m, 3 H), 5.73 (m, 1 H), 8.86 [s(br), 1 H]; minor rotamer δ: 4.19 (m, 1 H), 6.37 (d, 1 H, J = 5.2) ; ^{13}C NMR ($CDCl_3$) major rotamer δ: 28.1, 36.3, 52.7, 80.1, 119.1, 132.1, 155.4, 176.0; minor rotamer δ: 54.2, 81.7, 156.7 . Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.71; H, 8.14; N, 6.56.
In order to determine the enantiomeric excess of the product, the Boc protective group must be removed prior to HPLC analysis. The sample is prepared by dissolving 23 mg of N-Boc allylglycine in 1 mL of tetrahydrofuran and adding 2 mL of a 3 M aqueous hydrochloric acid solution. The mixture is allowed to stir at 23°C for 1 hr and then is concentrated under reduced pressure to provide a solid residue. The solid is dissolved in water for HPLC analysis. The product is determined to be ≥99% ee by analysis on a Crownpak CR(+) column (Note 22) and (Note 27).
26. The checkers obtained material having mp 240-242°C and $[\alpha]^{23}_{D}$ −37.2° (H_2O, *c* 4), and ≥99% ee by HPLC analysis on a Crownpak CR(+) column (Note 22) in good agreement with the cited literature values.[6,7]
27. The checkers obtained samples of material having rotations in methanol in the range $[\alpha]^{23}_{D}$ +8.6° to +11.4° (CH_3OH, *c* 1.4), and $[\alpha]^{23}_{D}$ −3.7° to −3.8° (CH_2Cl_2, *c* 1.1), all of which were determined to be ≥ 99% ee by HPLC analysis on a Crownpak CR(+) column (Note 22).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure describes a highly practical method for the asymmetric synthesis of α-amino acids by the alkylation of the chiral glycine derivative, pseudoephedrine glycinamide.[10] This methodology has been used for the synthesis of a wide variety of α-amino acids and is distinguished by the fact that the glycine amino group is not protected in the alkylation reaction. The method employs pseudoephedrine

as a chiral auxiliary. Pseudoephedrine is readily available and inexpensive in both enantiomeric forms, and many of its N-acyl derivatives are crystalline solids. The procedure that is described here for the enolization of pseudoephedrine glycinamide is modified from our previously reported metalation conditions[9] by reaction temperature (0°C versus −78°C employed earlier) and the order of mixing of reagents (addition of lithium diisopropylamide to pseudoephedrine glycinamide versus addition of pseudoephedrine glycinamide to lithium diisopropylamide). This modified procedure is more convienient for large-scale synthesis and is less sensitive to small errors in the titer of the butyllithium solution. The alkylation reaction proceeds in high yield using a wide variety of electrophiles and with excellent diastereoselectivity. Like the alkylation substrates, the products of the alkylation reaction are frequently crystalline and are readily recrystallized to ≥99% de.

The preparation of the alkylation substrate, pseudoephedrine glycinamide, is achieved in a single step from readily available and inexpensive reagents. This reaction accomplishes amide bond formation between the secondary amino group of pseudoephedrine and the carboxyl group of glycine methyl ester without protection of the glycine amino group. This is possible, it is speculated, by the operation of a base-catalyzed mechanism involving transesterification of the methyl ester with the hydroxyl group of pseudoephedrine, followed by intramolecular O → N acyl transfer. Pseudoephedrine glycinamide of both enantiomeric forms is easily prepared in large quantities by this procedure.

A particularly advantageous feature of this method for the synthesis of α-amino acids is the simplicity and mildness of the hydrolysis of the pseudoephedrine amide bond to reveal the α-amino acid. Two hydrolysis protocols are described, one for the isolation of enantiomerically pure α-amino acids, and the other for the preparation of N-acyl-α-amino acids of ≥99% ee. Simply heating aqueous solutions of the alkylation products results in spontaneous cleavage of the amide bond (presumably by intramolecular N→O acyl transfer, followed by hydrolysis of the resulting α-amino ester) and is ideal for isolation of the free α-amino acid under salt-free conditions, thus obviating the need for ion-exchange chromatography. Heating the alkylation products in the presence of alkali accelerates the cleavage reaction and allows the direct N-acylation of the hydrolysis products by the addition of an acylating agent to the aqueous alkaline α-amino acid solution. N-Protected α-amino acids are thus prepared in a single synthetic operation. Both hydrolysis procedures are highly efficient and proceed without significant racemization (≤1%). In both procedures, the chiral auxiliary is easily recovered in crystalline form in high yield.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R,R)-(−)-Pseudoephedrine glycinamide:
Acetamide, 2-amino-N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methyl-, [R-(R,R)]- (13); (170115-98-7)

L-Allylglycine:
4-Pentenoic acid, 2-amino-, (R)- (9); (54594-06-8)

N-Boc-L-allylglycine:
4-Pentenoic acid, 2-[[(1,1-dimethylethoxy)carbonyl]amino]-, (R)- (13); (170899-08-8)

Lithium chloride (8,9); (7447-41-8)

(R,R)-(−)-Pseudoephedrine:
Pseudoephedrine, (−)- (8);
Benzenemethanol, α-[1-(methylamino)ethyl]-. [R-(R,R)]- (9); (321-91-1)

Lithium methoxide:
Methanol, lithium salt (8,9); (865-34-9)

Glycine methyl ester (8,9); (616-34-2)

Pseudoephedrine L-allylglycinamide:
4-Pentenamide, 2-amino-N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methyl-, [1S-[1R(S),2R]]- (13);
(170642-23-6)

Diisopropylamine (8);
2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

Lithium diisopropylamide:
Butylamine, N,N-dimethyl-, lithium salt (8);
2-Propanamine, N-(1-methylethyl)-, lithium salt (9); (4111-54-0)

Allyl bromide:
1-Propene, 3-bromo- (8,9); (106-95-6)

Ethyl acetate:
Acetic acid, ethyl ester (8,9); (141-78-6)

Dichloromethane:
Methane, dichloro- (8,9); (75-09-2)

Ammonium hydroxide (8,9); (1336-21-6)

p-Dioxane: CANCER SUSPECT AGENT (8);
1,4-Dioxane (9); (123-91-1)

Di-tert-butyl dicarbonate:
Formic acid, oxydi-, di-tert-butyl ester (8);
Dicarbonic acid, bis(1,1-dimethylethyl) ester (9), (24424-99-5)

Glycine methyl ester hydrochloride:

Glycine methyl ester, hydrochloride (8,9); (5680-79-5)

Acetonitrile: TOXIC (8,9); (75-05-8)

2-Butanol:
sec-Butyl alcohol (8);
2-Butanol (9); (78-92-2)

2,2'-Dipyridyl:
2,2'-Bipyridine (8,9); (366-18-7)

Acetic anhydride (8);
Acetic acid anhydride (9); (108-24-7)

4-(N,N-Dimethylamino)pyridine:
Pyridine, 4-(dimethylamino)- (8);
4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

(S,S)-(+)-Pseudoephedrine glycinamide:
Acetamide, 2-amino-N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methyl-, [S-(R,R)]- (13); (170115-96-5)