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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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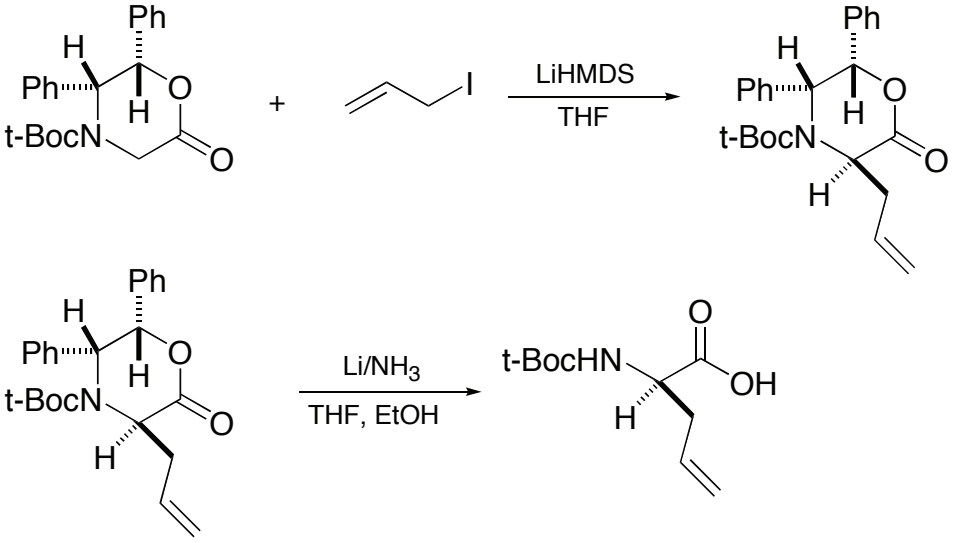
EFFICIENT ASYMMETRIC SYNTHESIS OF *N-tert*-BUTOXYCARBONYL α-AMINOACIDS USING 4-*tert*-BUTOXYCARBONYL- 5,6-DIPHENYLMORPHOLIN-2-ONE: (*R*)-(*N-tert*-BUTOXYCARBONYL)ALLYLGLYCINE

[(4-Pentenoic acid, 2-[[(1,1-dimethylethoxy)carbonyl]amino]-, (2*R*)-)]



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1. Procedure

A. (3R,5R,6S)-4-tert-Butoxycarbonyl-5,6-diphenyl-3-(1'-prop-2'-enyl) morpholin-2-one. A 250-mL, single neck, round-bottomed flask equipped with a magnetic stirring bar is charged with 1.0 g (2.83 mmol) of (5*R*,6*S*)-4-*tert*-butoxycarbonyl-5,6-diphenylmorpholin-2-one and placed under vacuum for 3 h. The evacuated flask is purged with argon, a rubber septum with an argon inlet is attached to the neck, and tetrahydrofuran (THF) (50 mL) is added via syringe (Note 1). After dissolution of the solid by stirring, 2 mL (10 mmol) of allyl iodide (Note 2) is added via syringe. With stirring, the flask and its contents are cooled to −78 °C with a dry ice/acetone bath, then 2.8 mL (2.83 mmol) of lithium bis(trimethylsilyl)amide (1M in THF) is added dropwise (Note 3). The mixture is stirred for 1 h at −78 °C (Note 4), then the solution is quenched by the addition of 100 mL of water. The

mixture is extracted with 250 mL of ethyl acetate in a separatory funnel. After separation of the aqueous phase, the organic phase is washed with brine, dried over anhydrous magnesium sulfate ($MgSO_4$), and concentrated by rotary evaporation under vacuum to afford an orange oil. The crude product is dissolved in a minimum amount of 4:1 hexanes:ethyl acetate, and purified by flash chromatography using 70 g of 35-75 mesh silica gel (eluting with 4:1 hexane:ethyl acetate followed by 2:1 hexanes:ethyl acetate). Removal of solvent from the appropriate fractions by rotary evaporation at room temperature affords 997 mg (90%) of (3*R*,5*R*,6*S*)-4-*tert*-butoxycarbonyl-5,6-diphenyl-3-(1'-prop-2'-enyl)-morpholin-2-one as a white solid (Notes 5, 6).

B. (R)-(N-tert-Butoxycarbonyl)allylglycine. A flame-dried, 100-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar is charged with 35 mL of liquid ammonia and 124 mg (17.8 mmol) of lithium metal (Note 7). The resulting solution is stirred at −33 °C. Meanwhile, a flame-dried 25-mL, round-bottomed flask fitted with a rubber stopper and an argon inlet is charged with 539 mg (1.37 mmol) of (3*R*,5*R*,6*S*)-4-*tert*-butoxycarbonyl-5,6-diphenyl-3-(1'-prop-2'enyl)morpholin-2-one 0.150 mL of absolute ethanol (Note 8), and 5 mL of anhydrous THF (Note 1). The resulting mixture is then transferred via cannula to the lithium/liquid ammonia solution. After 20 min, the reaction is carefully quenched with solid ammonium chloride and allowed to warm to room temperature (Note 9). After evaporation of the remaining ammonia, the residue is diluted with 35 mL of water and extracted twice with 35-mL portions of diethyl ether (Note 10). The aqueous phase is carefully acidified with 1N HCl to a pH of 2 while stirring with 35 mL of ethyl acetate (Note 11). Following separation of the organic phase, the aqueous phase is extracted three times with 20-mL portions of ethyl acetate. The organic extracts are combined, dried over $MgSO_4$, filtered, and concentrated under vacuum to yield 178 mg (60%) of crude (*R*)-(*N-tert*-butoxycarbonyl)allylglycine (% ee ≥ 96%) as a viscous oil (Notes 12-15).

2. Notes

1. Anhydrous tetrahydrofuran is obtained by distilling from sodium benzophenone ketyl.

2. Allyl iodide (98%) can be purchased from Aldrich Chemical Co., Inc.

3. Lithium bis(trimethylsilyl)amide (1M solution in tetrahydrofuran) can be purchased from Aldrich Chemical Co., Inc.

4. Phosphomolybdic acid (PMA) dissolved in ethanol is a suitable reagent for visualizing the product on TLC. After dipping the TLC plate in the PMA solution, the chromatogram is developed by heating on a hot plate.

5. Trace amounts of impurities can be removed by recrystallizing the product from either diethyl ether/hexanes or dichloromethane/hexanes. The yield obtained by the checker after the first recrystallization was 65%, although an additional crop of the product could be obtained by recrystallization of the mother liquor.

6. Analytical and spectral data are as follows: mp. 177-178 °C, $[\alpha]_D^{25}$ +45.7 (c 1.34, CH_2Cl_2); ^1H NMR (300 MHz) (DMSO-d_6 vs. DMSO) (120 °C) δ: 1.22 (9H, s broad); 2.87 (2H, m); 4.90 (1H, dd, J = 7.3, 7.0); 5.17-5.29 (3H, m); 5.89-6.04 (1H, m); 6.20 (1H, d, J = 3.3); 6.59-6.62 (2H, m); 7.1-7.3 (8H, m). IR (NaCl, CH_2Cl_2) cm^{-1}: 3050, 2970, 2920, 1755, 1690, 1375, 1350, 1260, 1155, 1110. Analysis (recrystallized from diethyl ether/hexanes or dichloromethane/hexanes); calcd for $C_{28}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 72.37; H, 6.85; N, 3.68. Note that the NMR spectrum must be recorded at high temperature due to slow conformational exchange of the urethane group on the NMR time scale.

7. Ammonia is distilled from sodium metal immediately prior to use.

8. Absolute ethanol is used as received from Pharmco Products Incorporated.

9. When quenching the reaction and warming to room temperature, caution must be exercised in order to prevent the reaction mixture from overflowing the flask if ammonium chloride is added too quickly or the reaction is warmed too rapidly.

10. Reagent grade diethyl ether is used as received from Fisher Scientific.

11. An Orion Research model 301 analog pH meter was used.

12. The crude product is typically analytically pure; however, the product can be further purified by flash chromatography using 15 g of 35-75 mesh silica gel (elution with 60 mL of 5% methanol in dichloromethane).

13. Analytical and spectral data are as follows: $[\alpha]_D^{25}$ = +3.3 (c, 1.5, CH_2Cl_2); ^{1}H NMR (300 MHz) (DMSO-d_6) (60 °C) δ TMS: 1.39 (9H, s); 2.29-2.46 (2H, m); 3.92-4.0 (1H, m); 5.02-5.13 (2H, m); 5.77 (1H, dddd, *J* = 17.2, 10.3, 7.0, 7.0); 6.73 (1H, br s); 12.13 (1H, br s). IR (neat) cm^{-1}: 3430, 3050, 2980, 1715, 1500, 1370, 1265, 1155; mass spectrum (NH_3, Cl) *m/e* 232.9 (M^+ +18, 1.8), 215.9 (M^+ +1, 2.1), 214.9 (M^+, 0.3), 116.0 (62.9).

14. Optical rotations were measured on a Rudolf Research Autopol III automatic polarimeter operating at 589 nm, corresponding to the sodium D line.

15. The enantiomeric excess of the product is determined by Mosher amide formation and NMR analysis as follows: (*R*)-(*N*-*tert*-butoxycarbonyl)allylglycine is dissolved in 3 mL of 1M ethanolic HCl and heated to reflux for 2 h. The reaction is cooled and the solvent removed under vacuum. The crude amino ester hydrochloride is dissolved in 0.3 mL of pyridine and 0.3 mL of CCl_4. To this mixture is added 25 mg (0.10 mmol) of (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and the reaction is stirred for 6 h at room temperature. The reaction is quenched with 1 mL water, taken up in diethyl ether, and washed consecutively with 1M HCl, saturated aqueous $NaHCO_3$, and water. The ether layer is dried over anhydrous $MgSO_4$, filtered and evaporated. The Mosher amide formation is repeated with (±)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, and, now with this reference standard, the two products are compared by ^{1}H NMR.

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

The morpholinone glycine synthon, which can be obtained in both enantiomeric forms, can be employed as a versatile scaffold for the preparation of a wide range of *N*-*t*-Boc protected *R*- and *S*-α-amino acids.[2,3,4] Allylglycine, the example selected here to demonstrate this methodology, is useful for the construction of several amino acid derivatives, such as 2,7-diaminosuberic acid[5,6] and mechanism-based inhibitors of pyridoxal-dependent enzymes.[7] Allylglycine has also served as a starting material for the synthesis of several natural products.[8,9,10,11] The current procedure is the only direct method of synthesizing this *N*-*t*-Boc-protected amino acid. Other reports have appeared for preparing this amino acid[12,13] including an *Organic Syntheses* procedure by Myers.[14] The use of the dissolving metal reduction to remove the chiral auxiliary allows the direct isolation of the *N*-*t*-Boc-protected amino acid, thus eliminating the need to protect the free amino acid in a subsequent step. The by-product of the reduction of the diphenylamino alcohol moiety is bibenzyl, which is insoluble in water and conveniently removed by extraction as described above. The current procedure enables these alkylations to be carried out on a preparative scale in good yield and excellent ee.

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

(*R*)-(*N*-*tert*-Butoxycarbonyl)allylglycine: 4-Pentenoic acid, 2-[[(1,1-dimethylethoxy)carbonyl]amino]-, (2*R*)- (9); (170899-08-8)

(5*R*, 6*S*)-4-*tert*-Butyloxycarbonyl-5,6-diphenylmorpholin-2-one: 4-Morpholinecarboxylic acid, 2-oxo-5,6-diphenyl-, 1,1-dimethylethyl ester, (2S-cis)-(9); (112741-50-1)

Allyl iodide: 1-Propene, 3-iodo-(9); (556-56-9)

(3*R*,5*R*,6*S*)-4-*tert*-Butoxycarbonyl-5,6-diphenyl-3-(1'-prop-2'-enyl)morpholin-2-one:
4-Morpholinecarboxylic acid, 2-oxo-5,6-diphenyl-3-(2-propenyl)-,1,1-dimethylethyl ester, 3*R*-(3α,5β,6β)]-(9); (143140-32-3)

Lithium bis(trimethylsilyl)amide: Silanamine, 1,1,1-trimethyl-*N*-(trimethylsilyl)-, lithium salt (9); (4039-32-1)

Lithium: Lithium (8,9); (7439-93-2)