An Improved Synthesis of Optically Pure 4-Boc-5,6-Diphenylmorpholin-2-one and 4-Cbz-5,6-Diphenylmorpholin-2-one

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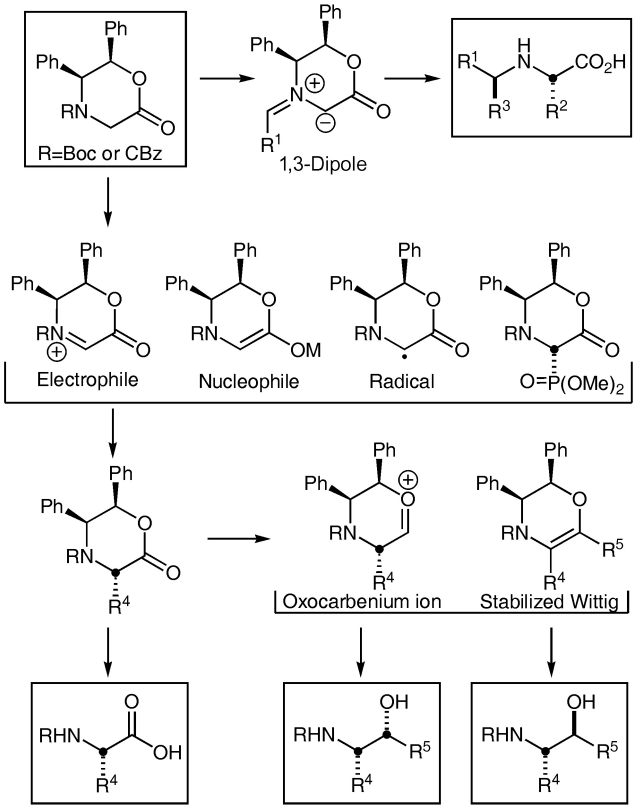
Abstract: A convenient synthesis of optically pure 4-Boc-5,6-diphenylmorpholin-2-one and 4-Cbz-5,6-diphenylmorpholin-2-one by reaction of (+)- or (–)-2-amino-1,2-diphenylethanol with ethyl bromoacetate, followed by N-protection, and *p*-TsOH-mediated ring-closure is described. The title compounds can be used as synthons for the asymmetric synthesis of N-protected α-amino acids. These lactones are quite stable to storage and handling.

Key words: amino acids, asymmetric synthesis, lactones, 2-amino-1,2-diphenylethanol, ring-closure

It is well-established that (+)- and (–)-4-*tert*-butoxycarbonyl-5,6-diphenylmorpholin-2-ones, as well as the corresponding 4-benzyloxycarbonyl compounds, are useful intermediates for the asymmetric synthesis of α-amino acid derivatives.[1–3] These intermediates serve as chiral, non-racemic templates for the construction of α-amino acids, which are found in a large number of biologically important metabolites and natural products (Scheme 1).[4] Several methods have been developed for the asymmetric synthesis of α-amino acids such as alkylation of chiral Schiff bases, catalytic asymmetric C-H, C-C and C-N bond forming reactions and the asymmetric Strecker reaction among other methods.[4] However, none of these methods can provide the range of chemical reactivity for C-C bond-forming processes that the morpholinone-based chiral templates provide. The great versatility that these glycine templates offer for preparing structurally diverse amino acids in high optically purity has been illustrated in the synthesis of several complex alkaloid natural products.[1–3] Among the transformations reported for these glycine templates is the asymmetric [1,3] dipolar cycloaddition reaction, which enables diastereoselective double alkylation in the construction of densely functionalized pyrrolidines (Scheme 1).[2p,3c] We have also demonstrated that the methylene carbon of the morpholinone can be coupled with a variety of electrophiles and nucleophiles to provide optically pure α-homologated amino acids after cleavage of the chiral template. Furthermore, the morpholinone can be selectively *trans*-homologated through Wittig olefination[2q] followed by reduction. Alternatively, the morpholinone can be *cis*-homologated through Lewis acid-mediated addition of allylsilane to the intermediate oxocarbenium ion generated from the corresponding hemiacetal.[2q,5]

A variety of both reductive and oxidative conditions have been developed for removing the chiral auxiliary from the functionalized adducts to generate the corresponding amino acid or amino alcohol products.[1] Furthermore, the lactones are quite stable to storage and handling.



Scheme 1 Synthesis of L- and D-amino acid derivatives from morpholinones

Our group has reported the synthesis of the title compounds starting from benzoin and have reported a practical procedure for the synthesis of (5*S*,6*R*)-4-*tert*-butoxycarbonyl-5,6-diphenylmorpholin-2-one (**6**) from (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol [(–)-**2**].[6] Herein, we wish to report an improved and more efficient preparation starting from non-racemic amino alcohols (+)- and (–)-**2**. The non-racemic amino alcohols, (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol and (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol, are commercially available. Alterna-

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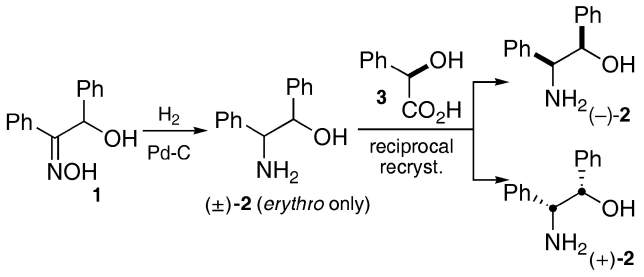
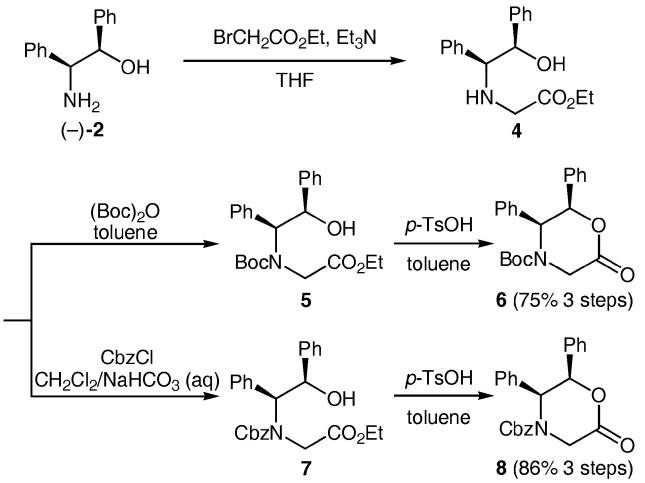
tively, these compounds can be easily prepared by converting benzoin to its corresponding oxime (**1**),[7] followed by stereoselective oxime reduction which gives exclusively, the *erythro*-amino alcohol,[8] and subsequent optical resolution of the resulting *erythro*-amino alcohol (±)-**2** (Scheme 2). This robust reduction that can be performed on a large scale, provides the racemic amino alcohols as a crystalline solid in a high state of purity. Resolution was accomplished through reciprocal crystallization of the corresponding (–)-mandelic acid salts.[9] The new protocol provides higher resolution efficiency and requires fewer recrystallizations than the fractional L-glutamic acid resolution reported previously.[6a,8] Alternatively, the non-racemic amino alcohols can be prepared through initial lipase resolution of benzoin, followed by requisite oxime formation and subsequent reduction.[10]



Scheme 2 Preparation of (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol and (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol[7]

Following resolution, either (+)- or (–)-**2** was reacted with ethyl bromoacetate to form the corresponding chiral glycinate as illustrated for compound **4** in Scheme 3. Our previously reported procedure was reported on a 25 g (117 mmol) scale and was accomplished by slow addition of Et_3N (2.0 equiv) to a solution of either (+)- or (–)-**2** and ethyl bromoacetate (1.5 equiv) in anhydrous THF (0.26 M).[5] After stirring for 20 hours at room temperature, the crude product was isolated and was subsequently recrystallized from absolute ethanol to yield 29 g (84%) of the enantiomerically pure glycinate bearing the desired configuration. We have since found that this reaction can be significantly improved by changing the addition sequence of the reagents. Specifically, slow addition of ethyl bromoacetate to the amino alcohol/Et_3N/THF solution resulted in complete reaction after an additional 1 hour of stirring at room temperature. We were able to decrease the quantities of Et_3N (1.55 equiv) and THF (0.45 M) required, and successfully conducted the reaction in reagent grade THF, obviating the use of anhydrous solvent. Importantly, the resulting crude product was isolated in adequate purity as a solid after rinsing with water and can be subjected to subsequent transformations without recrystallization. Furthermore, **4** and the corresponding antipode can now be routinely prepared on >100 g scale (0.5 mol) using this modified procedure.

Amine **4** [from (–)-**2**, 0.5 mol] was then acylated by reaction with either di-*t*-butyl dicarbonate [$(Boc)_2O$] or benzyl chloroformate (CbzCl). Our previous procedure for preparing **5** entailed refluxing **4** with $(Boc)_2O$ (2.0 equiv) in a biphasic $CHCl_3$/aqueous $NaHCO_3$–NaCl mixture for 20 hours. This was followed by an aqueous work-up, drying of the organic layer overnight, and removal of excess $(Boc)_2O$ (5 mmHg, 130 °C) to afford **5** (33.2 g, 99% from **4**). Alternatively, due to efforts to obviate the use of chlorinated solvents, it was discovered that the reaction could be performed in toluene. Therefore, a solution of $(Boc)_2O$ (1.35 equiv) in toluene was slowly added to crude **4** in refluxing toluene. After 10 hours, a portion of the solvent was distilled from the reaction mixture effecting azeotropic removal of excess water that remained from the isolation of **4** in the previous step. The resulting solution of **5** in toluene was used in the following step, therefore avoiding product isolation. This modified procedure is advantageous in that it (1) requires less $(Boc)_2O$ reagent; (2) obviates halogenated solvents, (3) utilizes a solvent that can, in practice, be recycled, and (4) is significantly more time efficient.



Scheme 3 Synthesis of (5*S*,6*R*)-4-*t*-Boc-5,6-diphenylmorpholin-2-one and (5*S*,6*R*)-4-Cbz-5,6-diphenylmorpholin-2-one from (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol

If the *N*-Cbz lactone **8** is ultimately desired, Schotten–Bauman acylation conditions are used to produce **7** from intermediate **4** as previously described (1.1 equiv CbzCl, sat. $NaHCO_3$ solution, CH_2Cl_2).[8] Interestingly, by applying minor modifications to the original procedure,[8] including maintaining the reaction at 0 °C rather than room temperature and slowly adding CbzCl to the biphasic mixture of **4** in aqueous $NaHCO_3/CH_2Cl_2$, we were able to reduce the reaction time from 12 hours to one hour.

Reaction of the crude N-protected products, **5** or **7**, with catalytic amounts of *p*-TsOH promotes ring-closure to **6** and **8**, respectively. The former protocol entailed refluxing the esters (**5** or **7**) in benzene with catalytic *p*-TsOH (0.1 equiv) using a Soxhlet extractor packed with $CaCl_2$ to remove water from the reaction. However, in accord with our recently developed distillation protocol, the reaction could be successfully performed in toluene. Therefore, removal of a portion of the reaction solvent through simple distillation, as before, effected azeotropic dehydration of

the reaction. This modification effectively provides the desired morpholinones after three distillation cycles. Finally, the products are recrystallized from ethanol or toluene to provide optically pure 4-Boc-5,6-diphenylmorpholin-2-one (**6**) and 4-Cbz-5,6-diphenyl-morpholin-2-one (**8**) in 75% and 86% yield, respectively, over three steps. Importantly, while the modified procedure requires three days for completion, the previous procedure typically required six to seven days and yielded 59% and 66% of **6** and **8**, respectively, over three steps.

Utilizing this convenient procedure, it is possible to prepare optically pure 4-Boc-5,6-diphenyl-morpholin-2-one and 4-Cbz-5,6-diphenylmorpholin-2-one on a 100 g scale with reproducibly high yields. Exclusion of air during the synthesis was not necessary, and the entire sequence from benzoin was accomplished without any chromatographic separations. The products can be stored on the shelf at room temperature over several years without decomposition.

Procedure for the Preparation of (5*S*,6*R*)-4-(*t*-Butoxy-carbonyl)-5,6-diphenyl-morpholin-2-one (6)

(1*R*,2*S*)-(–)-2-Amino-1,2-diphenylethanol [(–)-**2**, 106 g, 0.5 mol] was dissolved in a mixture of THF (1100 mL, ACS grade) and Et_3N (108 mL, 78.4 g, 0.775 mol, 1.55 equiv) with gentle warming. Ethyl bromoacetate (86 mL, 129 g, 0.775 mol, 1.55 equiv) was slowly dropped into the vigorously stirred solution over 1 h at r.t. The reaction was stirred for an additional 1 h, then cooled to 0 °C and filtered. The filter cake was thoroughly rinsed with ice cold THF (2 × 100 mL). The combined filtrates were evaporated to dryness, and the solid residue was washed with warm H_2O (500 mL, 50 °C), dissolved in toluene (600 mL), and brought to reflux temperature. A solution of di-*t*-butyl dicarbonate (147 g, 0.675 mol, 1.35 equiv) in toluene (400 mL) was slowly added to the stirred mixture over 2 h. The reaction remained at reflux for an additional 10 h, then 300–500 mL of solvent was distilled off to remove any residual water. The reaction volume was adjusted back to 1000 mL with fresh toluene, *p*-TsOH·H_2O (9.52 g, 0.05 mol, 0.1 equiv) was added, and the excess solvent was slowly distilled until approx. 500 mL remained. The reaction was cooled to r.t., the resulting crystals were collected by filtration, rinsed with toluene–hexane (1:3, 200 mL), followed by hexane (200 mL). The mother liquor and washes were combined, and the solvent was removed by distillation (until 300 mL remained). The cooling, filtration, and washing sequence was repeated to provide a second crop of crystals. The washes and mother liquors were again combined along with additional *p*-TsOH·H_2O (2.38 g, 0.012 mol, 0.025 equiv) and the sequence was repeated to provide a third crop of crystals. The combined solids were recrystallized from ethanol to give the product as a white crystalline solid (132 g, 75%); mp 207 °C; $[\alpha]_D^{22}$ –87.3 (*c* 1.0, CH_2Cl_2). IR (NaCl, CH_2Cl_2): 3050, 2975, 1755, 1690, 1380, 1255, 1150, 1100, 1045 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6 vs. DMSO, 120 °C): δ = 1.25 (9 H, s), 4.52 (2 H, d, *J* = 1 Hz), 5.16 (1 H, d, *J* = 3 Hz), 6.17 (1 H, d, *J* = 3 Hz), 6.63–6.68 (2 H, m), 7.00–7.30 (8 H, m). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.08; H, 6.44; N, 3.98.

(5*R*,6*S*)-4-(*t*-Butoxycarbonyl)-5,6-diphenyl-morpholin-2-one is obtained from the antipode, (1*S*,2*R*)-(+)-2-amino-l,2-diphenylethanol, using the procedure described above. Mp 207 °C; $[\alpha]_D^{22}$ +87.3 (*c* 1.0, CH_2Cl_2).

Procedure for the Preparation of (5*S*,6*R*)-4-(Benzyloxy-carbonyl)-5,6-diphenyl-morpholin-2-one (8)

(1*R*,2*S*)-(–)-2-Amino-1,2-diphenylethanol [(–)-**2**, 106 g, 0.5 mol) was dissolved in a mixture of THF (1100 mL, ACS grade) and Et_3N (108 mL, 78.4 g, 0.775 mol, 1.55 equiv) with gentle warming. Ethyl bromoacetate (86 mL, 129 g, 0.775 mol, 1.55 equiv) was slowly dropped into the vigorously stirred solution over 1 h at r.t. The reaction was stirred for an additional 1 h, then cooled to 0 °C and filtered. The filter cake was thoroughly rinsed with ice cold THF (2 × 100 mL). The combined filtrates were evaporated to dryness and the residue diluted with CH_2Cl_2 (750 mL) and sat. $NaHCO_3$ (750 mL). The mixture was cooled in ice and benzyl chloroformate (83 mL, 98.8 g, 0.55 mol, 1.1 equiv) was slowly added to the stirred solution over 1 h. The reaction was stirred for an additional 1 h at 0 °C, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the combined organic extracts were washed with H_2O and dried (Na_2SO_4). The solvent was removed, the residue was dissolved in toluene (1100 mL, ACS grade), *p*-TsOH·H_2O (9.52 g, 0.05 mol, 0.1 equiv) was added, and the excess solvent was slowly distilled at atmospheric pressure until approximately 500 mL remained. The reaction was then cooled to r.t. The resulting crystals were collected by filtration, and subsequently rinsed with toluene–hexane (1:3, 300 mL), followed by hexane (300 mL, 163 g, 84%). The mother liquor and washes were combined and evaporated to dryness under reduced pressure, and the residue was recrystallized from toluene to provide a second crop of product (2.43 g, 2%). The combined crops afforded 166 g (86%) of white crystalline product. Mp 206–207 °C; $[\alpha]_D^{22}$ –68.7 (*c* 1.0, CH_2Cl_2). IR (NaCl, paraffin oil): 1745, 1705, 1455, 1440, 1375, 1325, 1215, 1120, 1055 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6 vs. TMS, 120 °C): δ = 4.60 (2 H, ABq, *J* = 18 Hz), 5.06 (2 H, ABq, *J* = 13 Hz), 5.29 (1 H, d, *J* = 3 Hz), 6.20 (1 H, d, *J* = 3 Hz), 6.66 (1 H, s), 6.60 (1 H, s), 7.00–7.30 (13 H, m). Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.61. Found: C, 73.85; H, 5.38; N, 3.50.

(5*R*,6*S*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-morpholin-2-one is obtained from the antipode, (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol using the procedure described above. Mp 206–207 °C; $[\alpha]_D^{22}$ +68.7 (*c* 1.0, CH_2Cl_2).

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