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A Convenient Asymmetric Synthesis of Thalidomide

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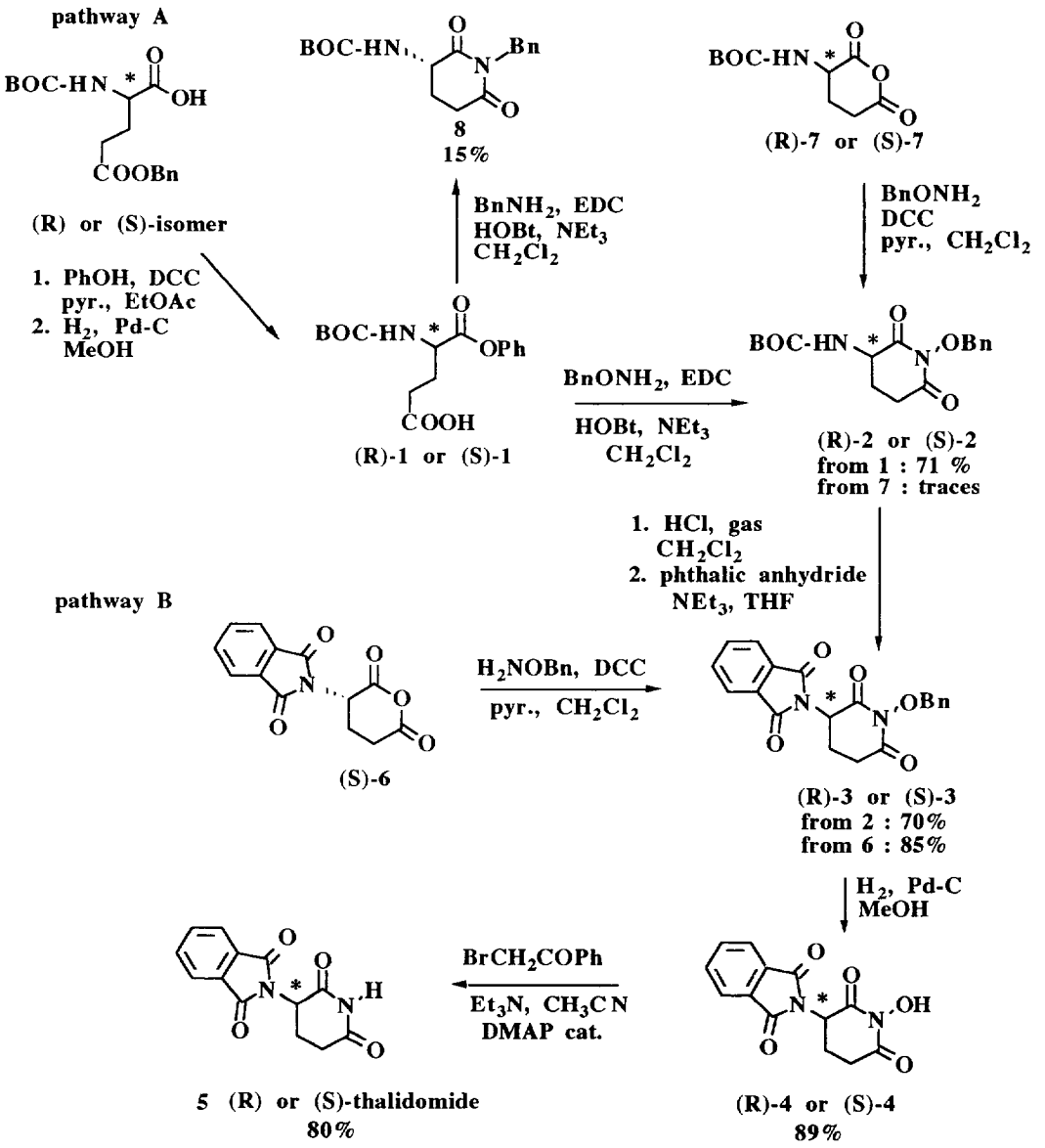
Abstract : Benzyloxyamine reacted with BOC-glutamic-α-phenyl ester in the presence of carbodiimide to give BOC-amino-N-benzyloxypiperidinedione. Deprotection of the amino group followed by phthaloylation led to N-benzyloxythalidomide which was then converted into thalidomide.

The development of asymmetric syntheses of drugs currently used as racemates is one of the major approaches to decrease side effects.[1] It is particularly relevant in the case of toxic drugs of increasing interest such as thalidomide. This orphan drug[2] has found several therapeutic applications in conjunction with its immunosuppressive property. Briefly, it is mainly used in leprosy therapy[3] and so far, it is the only active substance against Behcet's syndrome[4] and is also used as a substitute for, or in association with, cyclosporin derivatives for graft-versus-host disease (GvHD).[5] Recently its interesting activity on AIDS has led to clinical trials.[6]

Thalidomide **5** is currently used in therapy as a racemate. Although the relationship between chirality, immunosuppression and toxicity has been the subject of several research projects,[7, 8] the results are not conclusive and need further studies. The only reported asymmetric synthesis of thalidomide is tedious[9] and whenever the pure enantiomers are needed, they are obtained by preparative chiral chromatography.[10] The main difficulty confronted in the asymmetric synthesis of thalidomide is the easy racemisation due to the high acidity of the proton located on the asymmetric center.[11]

We wish to report here a simple asymmetric synthesis of thalidomide and some of its derivatives. Two pathways depicted in the scheme were examined. In pathway A, the key step is the condensation of benzyloxyamine with BOC-glutamic α-phenyl ester[12] allowing the formation of the glutarimide ring under very mild conditions. The structure of this intermediate was confirmed by X-ray crystallography.[13] The acidolysis of the BOC protective group followed by the phthaloylation step,[14] without isolation of the intermediate hydrochloride salts, led to N-benzyloxythalidomide **3**.[15] Similarly, in pathway B the commercially available (S)-phthaloylglutamic anhydride gave in one step[16] N-benzyloxythalidomide providing a short route to **5**.

In the presented synthesis, the benzyloxy group located on the nitrogen plays two roles : It allows the easy formation of the glutarimide ring by enhancing the nucleophilicity of nitrogen, since we observed that benzylamine gave a low yield (15%) of the benzylglutarimide derivative **8**.[13] The benzyloxy group can also be considered as a protecting group of the glutarimide ring due to its electron donating effect by lowering the reactivity of the C=O groups and it presumably reduces the acidity of the hydrogen on the stereogenic center.



The removal of the benzyloxy group was achieved in two steps. Although the hydrogenolysis (Pd-C) of the N-O bond in methanol/water/5% HCl solvent system has been previously described,[17] in the case under study, thalidomide could not be detected in the reaction mixture when N-benzyloxythalidomide was hydrogenated on Pd/C. Only N-hydroxythalidomide **4** was formed under these conditions. Reduction by zinc in acetic acid[18] or in the presence of Raney nickel W6[19] led only to degraded products. It can be noticed that the reductive cleavage of the N-O bond is easier for hydroxamic acids than for N-hydroxy imides : Recently, Miller reported that the reduction of the benzyl group in N-benzyloxyamides was concomitant with that of the benzyl group.[20] The hydrogenation of benzyloxyamides requires a special catalyst in order to avoid the cleavage of the N-O bond and the formation of amides.[21]

The hydroxy group was eliminated by nucleophilic cleavage of the phenacylether.[22] This method was improved by the use of a catalytic amount of DMAP as a base.[23] The purity of compound **5** obtained by both pathways was verified by chiral HPLC.[24]

In conclusion, the presented synthesis is simple and it could be applied to the preparation of thalidomide derivatives in particular to non racemisable compounds[25] and then useful in the search for new immunosuppressors with reduced toxicities.

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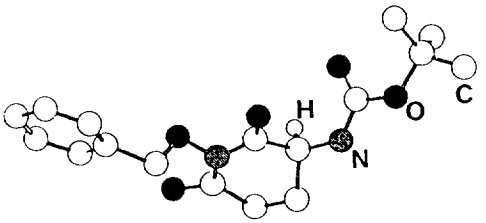
12. **N-Tertbutyloxycarbonyl glutamic acid α-phenyl ester (1).** A solution of BOC-Glu(OBn)-OH (1 g, 2.9 mmol), phenol (278 mg, 2.9 mmol), dicyclohexylcarbodiimide (DCC) (609 mg, 2.9 mmol) and pyridine 250 µl, 2.9 mmol) in 15 ml of ethyl acetate, was stirred at room temperature overnight. The precipitated dicyclohexylurea was filtered. The filtrate was washed with saturated $NaHCO_3$ solution, 10% citric acid solution and water respectively and the organic layer dried over Na_2SO_4. The solvent was removed under reduced pressure. Chromatography (SiO_2, 2:1 petroleum ether-ethyl acetate) gave 1.1 g (94%) of BOC-Glu(OBn)-OPh : mp 84 °C ; $[\alpha]_D$ = -1.09 (c = 1.1, $CHCl_3$), NMR spectra were recorded on a BRUKER 270 MHz ^1H NMR δ 1.5 (s, 9H), 2.1-2.2 (m, 1H), 2.3-2.4 (m, 1H), 2.6-2.7 (m, 2H), 4.6 (m, 1H), 5.1 (s, 2H), 5.15 (dd, 1H), 7.2-7.4 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 27.65, 28.31, 30.34, 53.21, 66.60, 80.47, 121.27, 126.13, 128.27, 128.31, 128.58, 129.48, 135.74, 150.43, 171.23, 172.43. Anal. Calcd for $C_{23}H_{27}O_6N$: C, 66.81; H, 6.58; N, 23.22. Found: C, 66.63; H, 6.75; N, 23.60. This product was dissolved in 20 ml of methanol and hydrogenated on 10% Pd-C (115 mg) for 2 hours. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. Chromatography (SiO_2, 3:1 petroleum ether-ethyl acetate) gave 852 mg (99%) of **1** : mp 75°C; ^1H NMR δ 1.5 (s, 9H), 2.0-2.2 (m, 1H), 2.4 (m, 1H), 2.6 (m, 2H), 4.6 (m, 1H), 5.25 (dd, 1H), 7.0-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.53, 28.27, 30.00, 50.29, 80.54, 120.51, 121.22, 126.17, 129.49, 150.39, 177.11. Anal. Calcd for $C_{16}H_{21}O_6N$: C, 59.43; H, 6.54; N, 4.33. Found: C, 59.09; H, 6.82; N, 4.57.
13. **(S)-1-Benzyloxy-3-tertbutyloxycarbonylamino piperidine-2,6-dione (2).** 1-(3-Dimethylamino-propyl-3-ethyl-carbodiimide hydrochloride (498 mg, 2.6 mmol) was added at 0°C to a solution of compound **1** (568 mg, 1.7 mmol), 1-hydroxybenzotriazole (279 mg, 2 mmol), triethylamine (1.2 ml, 8.7 mmol) and benzyloxyamine (264 µl, 2 mmol) in 25 ml of CH_2Cl_2. The mixture was stirred for 3 days at room temperature. The organic layer was washed with saturated $NaHCO_3$ solution, 10% citric acid solution and water and then dried with Na_2SO_4. The solvent was removed under reduced pressure. Chromatography (SiO_2, 1:2 cyclohexane-diethyl ether) gave 403 mg (71%) of **2** : mp 146-150°C; (S)-isomer $[\alpha]_D$ = -3,9 (c = 1.0, MeOH), ^1H NMR ($CDCl_3$) δ 1.49 (s, 9H), 1.78 (ddd, 1H), 2.35-2.5 (m, 1H), 2.7 (ddd, 1H), 2.85 (ddd, 1H), 4.3 (m, 1H), 5.1 (s, 2H), 5.3 (s, 1H), 7.2-7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.82, 28.27, 31.18, 52.81, 78.25, 80.62, 128.42, 129.21, 130.0, 133.63, 155.38, 167.27, 168.29. Anal. Calcd for $C_{17}H_{22}O_5N_2$: C, 61.06; H, 6.63; N, 8.38. Found: C, 60.79; H, 6.84; N, 8.58. A suitable crystal of (S)-**2** measuring 0.425 mm x 0.425 mm x 0.075 mm was investigated on a Syntex $P2_1$ diffractometer (Mo Kα radiation = 0.71069 Å, graphite monochromator). Crystal data : $C_{17}H_{22}N_2O_5$; Monoclinic, space group $P2_1$ Z = 4, a = 10.260 (7) Å, b = 10.819 (5) Å, c = 16.266

(9) Å, b = 106.07 (7)°, Dcalcd = 1.27 g.cm^{-3}; reflections up to 2 θ = 50° of which 1384 with F > 4σ(F) were kept in refinement calculations. The structure was solved by direct methods using SHELXS86 and refined with SHELX76. Convergence was reached at R = 0.058 and Rw = 0.06. (Hydrogens are omitted except for the stereogenic center).



(S)-1-Benzyl-3-tertbutyloxycarbonylamino piperidine-2,6-dione (8). This product was obtained under conditions identical to those used for compound **2.** Yield 15 %, ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.80 (m, 1H), 2.40 (m, 1H), 2.65 (ddd, 1H), 2.83 (ddd, 1H), 4.28 (m, 1H), 4.91 (2d, 2H), 5.4 (s, 1H), 7.2-7.4, (m, 5H).

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15. **(S)-1-Benzyloxy-3-phthalimidopiperidine-2,6-dione (3).** (Pathway A) : Compound **2** (1.3 g, 3.9 mmol) was dissolved in 20 ml of CH_2Cl_2. HCl gas was bubbled into the solution for 10 minutes and the mixture was stirred for half an hour. Dichloromethane was removed under reduced pressure and the chlorhydrate derivative was dissolved in THF (50 ml). Triethylamine (3.3 ml, 23.4 mmol), phthalic anhydride (692 mg, 4.7 mmol) and 4Å sieves were added. After heating for 2 hours, the mixture was filtered and the solvent was removed under reduced pressure. Chromatography (SiO_2, 1:1 cyclohexane-diethyl ether) gave 993 mg (70%) of **3** : mp 129°C; $[\alpha]_D$ = -40,9 (*c* = 1.0, $CHCl_3$); ^{1}H NMR δ 1.95-2.15 (m, 1H), 2.6-2.8 (m, 2H), 2.8-3.0 (m, 1H), 4.9 (s, 2H), 4.9 (dd, 1H), 7.2-7.5 (m, 5H), 7.65-7.9 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.04, 31.29, 50.41, 78.46, 123.84, 128.42, 129.12, 130.02, 131.74, 133.77, 134.52, 165.02, 166.78, 167.16. Anal. Calcd for $C_{20}H_{16}O_5N_2$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.71; H, 4.17; N, 7.95.

16. (Pathway B) : A solution of compound (S)-**6** (200 mg, 0.8 mmol), benzyloxyamine (140 µl, 1.2 mmol) and pyridine (82 µl, 0.96 mmol) was stirred at room temperature overnight. DCC (175 mg, 0.8 mmol) was added and the mixture stirred for two additional days. The precipitate was filtered. The filtrate was washed with 10% citric acid solution and with water. The organic layer was dried over Na_2SO_4 and the solvent removed under vacuum. Chromatography (SiO_2, 1:1 cyclohexane-diethyl ether) gave 247 mg (85%) of **3.**

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23. **(S)-1-Hydroxy-3-phthalimidopiperidine-2,6-dione (4).** Compound **3** (327 mg, 0.9 mmol) was dissolved in 30 ml of methanol and 10% Pd-C (35 mg) was added. The suspension was stirred for two hours under an hydrogen atmosphere and then filtered. The solvent was removed under reduced pressure. Chromatography (SiO_2, 1:1 petroleum ether-ethyl acetate) gave 219 mg (89%) of **4** : mp 224.8 °C; $[\alpha]_D$ = -19.8 (*c* = 1.0, MeOH); ^{1}H NMR δ 2.1 (m, 1H), 2.7 (m, 2H), 2.9 (m, 1H), 5.1 (dd, 1H), 7.8 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.13, 30.29, 49.54, 123.93, 131.67, 134.61, 159.52, 165.67, 167.08. Anal. Calcd for $C_{13}H_{10}O_5N_2$: C, 56.94; H, 3.67; N, 10.20. Found: C, 56.91; H, 3.7.5; N, 10.09.

Thalidomide (5). A solution of compound **4** (164 mg, 0.6 mmol), triethylamine (83 µl, 0.6 mmol), bromoacetophenone (120 mg, 0.6 mmol) and DMAP (7 mg, 0,06 mmol) in 30 ml of acetonitrile was stirred at room temperature for two hours. (The intermediate phenacylether could be isolated when the reaction was stopped after 30 mn). The solvent was removed under reduced pressure. Chromatography (SiO_2, 1:1 cyclohexane-diethyl ether) gave 124 mg (80%) of **5** : mp 269°C; (S)-isomer $[\alpha]_D$ = - 60.6 Lit[11] : $[\alpha]_D$ = - 63 (c = 2 .03 , DMF), (R)-isomer $[\alpha]_D$ = + 61.2 (c = 2, DMF); Lit[11] : $[\alpha]_D$ = + 63.3 (c = 2 .03, DMF). ^{1}H NMR δ : 2.1 (m, 1H), 2.7 (m, 2H), 2.9 (m, 1H), 3.5 (s, 1H), 5.1 (dd, 1H), 7.8 (m, 4H). Anal. Calcd for $C_{13}H_{10}O_4N_2$: C, 60.47; H, 3.90; N, 10.85. Found **(S)-5**: C, 60.53; H, 3.92; N, 10.75. Found **(R)-5**: C, 60.37; H, 3.81; N, 10.65.

24. Separation by chiral HPLC have been done on a Chiracel OJ column (DAICEL Chemical Industries Ltd) with ethanol as mobile phase. Sample analysis was made by an UV detector at 220 nm. $R_S \approx 3$.

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