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# A CONCISE ENANTIOSELECTIVE SYNTHESIS OF *N*-BOC-*(S)*-2-AMINOSUBERIC ACID

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**ABSTRACT:** The title compound has been enantioselectively obtained by a four-step process involving the catalytic asymmetric epoxidation of allyl alcohol **3**, regio- and stereoselective oxirane opening with benzhydrylamine and one-pot oxidative cleavage-amine reprotection.



L-α-Aminosuberic acid (**1**) has found application as a metabolically stable ethylene isostere for the Cys-Cys disulfide linkage in a variety of bioactive peptides such as oxytocin,[1] vasopressin,[2] somatostatin[3] and calcitonin,[4] among others.

Up to now, no asymmetric synthesis of this interesting compound has been reported, and the described preparations of **1** involve either resolution of the racemic compound[5] or rather lengthy elaborations of homochiral natural amino acids.[6]

We report in the present communication a short enantioselective preparation of *N*-Boc **1** by an extension to dicarboxylic systems of a recently reported enantioselective synthesis of *N*-Boc-α-amino acids.[7]

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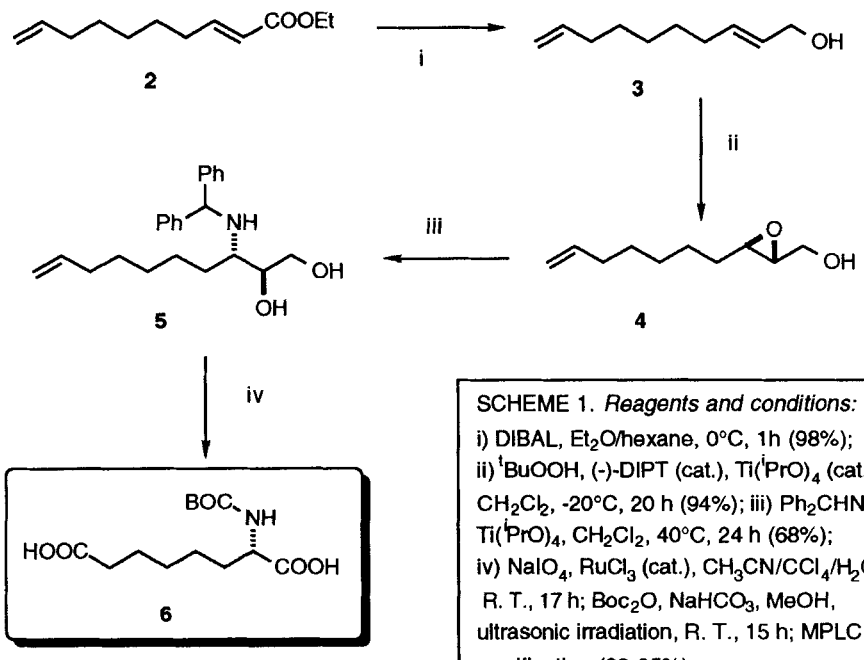
The method has the clear advantage of furnishing the target compound in a protected form, suitable for peptide synthesis, and appears to be applicable to the enantioselective preparation of other dicarboxylic α-amino acids.




SCHEME 1. *Reagents and conditions:* i) DIBAL, $Et_2O$/hexane, 0°C, 1h (98%); ii) $^tBuOOH$, (-)-DIPT (cat.), $Ti(^iPrO)_4$ (cat.), $CH_2Cl_2$, -20°C, 20 h (94%); iii) $Ph_2CHNH_2$, $Ti(^iPrO)_4$, $CH_2Cl_2$, 40°C, 24 h (68%); iv) $NaIO_4$, $RuCl_3$ (cat.), $CH_3CN/CCl_4/H_2O$, R. T., 17 h; $Boc_2O$, $NaHCO_3$, MeOH, ultrasonic irradiation, R. T., 15 h; MPLC purification (22-25%).

Ethyl *(E)*-2,9-decadienoate (**2**),[8] the starting material for the synthesis (see Scheme 1), was readily secured by Wittig reaction of 7-octenal.[9] Diisobutyl aluminum hydride reduction in diethyl ether at 0 °C provided *(E)*-2,9-decadien-1-ol (**3**) in essentially quantitative yield. Catalytic Sharpless epoxidation[10] of **3** with D-(-)-diisopropyl tartrate afforded a 94% yield of (2*R*, 3*R*)-2,3-epoxy-9-decen-1-ol (**4**) in very high enantiomeric purity ( > 95% e.e., according to the $^1H$ NMR spectrum of the corresponding Mosher ester[11]). When **4** was submitted to nucleophilic ring opening with diphenylmethylamine in the presence of

titanium tetraisopropoxide, a highly regioselective process took place,[12] and (2*S*, 3*S*)-*N*-diphenylmethyl-3-amino-9-decen-1,2-diol (**5**) was obtained in 68% yield after chromatographic purification. Very pleasingly, **5** could be directly converted to *N*-Boc-*(S)*-2-aminosuberic acid (**6**) by means of a multireaction one-pot procedure. Thus, simultaneous oxidative cleavage of the 1,2-diol, vinyl and diphenylmethylamino moieties occurred upon exposure of **5** to the $RuCl_3$ / $NaIO_4$ system;[13] subsequent treatment with $Boc_2O$ / $NaHCO_3$[14] afforded **6** in a reproductible 22-25% yield, corresponding to an approximate 70% yield per individual step.

The enantiomeric purity of **6** was checked by chiral HPLC analysis of the corresponding dimethyl ester on a Chiralcel OD-R column.[15] In agreement with the enantiomeric purity of epoxy alcohol **4**, only one enantiomer could be detected, so that the crucial oxidative process is racemization free.[7]

In summary, we have developed a practical, highly enantioselective synthesis of **6**, which takes place in four steps starting from the known, readily available ethyl decadienoate **2**.

## EXPERIMENTAL

### *(E)*-2,9-decadien-1-ol, 3.

To a solution of Ethyl *(E)*-2,9-decadienoate **2** (2.20 g, 11.2 mmol) in anhydrous diethyl ether (168 mL), DIBAL (1 M solution in hexanes; 28 mL, 28 mmol) was added dropwise at 0 °C under nitrogen. The resulting solution was stirred for 1 hour at 0 °C; methanol (25 mL) was then added and the stirring continued for 10 minutes. Following dilution with dichloromethane (150 mL), the solution was washed with saturated brine, dried over magnesium sulfate and the solvents removed under vacuum, to afford allyl alcohol **3** (1.69 g, 98% yield) pure enough for the continuation of the synthesis. The product can be purified by column chromatography on silica gel eluting with hexane / ethyl acetate mixtures (1.55 g, 90% yield).

IR (film, NaCl): 3640-3040, 3050, 2990, 2970, 2920, 2850, 1670, 1635, 1460, 1440, 1090, 995, 970, 910 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz); δ(TMS): 1.1-1.5 (m, 8H); 2.04 (m, 4H); 4.09 (d, J = 5 Hz, 2H); 4.85-5.05 (m, 2H); 5.6-5.9 (m, 2H); 5.83 (m, 1H).

$^{13}C$ NMR ($CDCl_3$, 50.1 MHz); δ(TMS): 28.6 (t), 28.7 (t), 28.9 (t), 32.1 (t), 33.6 (t), 63.6 (t), 114.1 (t), 128.8 (d), 133.2 (d), 139.0 (d).

MS (c. i., $NH_3$): 172 (M+18, 16%), 153 (M-1, 32%).

MS (i. e.): 153 (M-1, 6%), 135 (7%), 97 (15%), 83 (100%).

**(2*R*,3*R*)-2,3-Epoxy-9-decen-1-ol, 4.**

To a suspension of powdered, 4 Å molecular sieves (1.0 g)in anhydrous $CH_2Cl_2$ (100 mL), under dry nitrogen and at -22 °C, a solution of diisopropyl D-(-)-tartrate (0.19 g, 0.80 mmol) in dry $CH_2Cl_2$ (4.3 mL) was added *via* canula. Titanium tetraisopropoxide (0.16 mL, 0.54 mmol) was then added, followed by (*via* canula) a solution of allyl alcohol **3** (1.67 g, 10.8 mmol) in anhydrous $CH_2Cl_2$. The resulting mixture was stirred for 1 hour at -22 °C, and a solution of *tert*-butyl hydroperoxide (3 M in isooctane, 7.2 mL, 21.6 mmol) in dry $CH_2Cl_2$ (4.3 mL) was added *via* canula. Stirring was continued for 20 h at -20 °C; 0.9 mL of a 30% aqueous NaOH solution saturated with NaCl were then introduced and, after stirring for 10 min., diethyl ether (11 mL) was added. The reaction mixture was allowed to warm up to 10 °C, was stirred for 10 min. at the same temperature and subsequently treated with $MgSO_4$ (0.9 g) and Celite (0.11 g). After an additional 15 min. period of stirring, the reaction mixture was filtered through Celite, washing with diethyl ether, and the resulting clear solution was concentrated under vacuum. Excess hydroperoxide was removed by azeotropic distillation with toluene, and the residue was chromatographed on silica gel, eluting with hexane / ethyl acetate mixtures, to afford the epoxy alcohol **4** (1.72 g, 94% yield).

$[\alpha]_D$ = +31.6 (c=2.34, $CHCl_3$).

IR (film, NaCl): 3700-3120, 3080, 3000, 2930, 2860, 1645, 1470, 1090, 1040, 1000, 910 $cm^{-1}$.

$^1$H NMR ($CDCl_3$, 200 MHz); δ(TMS): 1.1-1.5 (m, 6H); 1.55 (m, 2H); 2.03 (m, 2H); 2.5 (br s, OH); 2.93 (m, 2H); 3.58 (dd, J = 12 Hz, J' = 5.5 Hz, 1H); 3.90 (dd, J = 12 Hz, J' = 2.7 Hz); 4.92-5.03 (m, 2H); 5.7-5.9 (m, 1H).

$^{13}$C NMR ($CDCl_3$, 50.1 MHz); δ(TMS): 25.7 (t), 28.6 (t), 28.7 (t), 31.4 (t), 33.5 (t), 56.0 (d), 58.6 (d), 61.7 (t), 114.3 (t), 138.8 (d).

MS (c. i., $NH_3$): 205 (M+35, 14%), 153 (M-17, 100%).

MS (i. e.): 169 (M-1, 3%), 153 (M-17, 20%), 137 (26%), 109 (79%), 95 (100%).

### (2*S*,3*S*)-*N*-Diphenylmethyl-3-amino-9-decen-1,2-diol, 5.

A stirred solution of epoxy alcohol **4** (1.70 g, 10 mmol), titanium tetraisopropoxide (8.90 mL, 29.9 mmol) and benzhydrylamine (3.65 g, 19.9 mmol) in anhydrous dichloromethane (135 mL) was refluxed under nitrogen for 24 hours. Aqueous 10% NaOH solution (40 mL) and saturated brine (40 mL) were then added, and the resulting mixture was stirred for 12 hours and filtered through Celite, washing with dichloromethane. The organic phase was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on triethylamine-pretreated silica gel (2.5% v/v), eluting with hexane / ethyl acetate mixtures, to afford 2.39 g (68% yield) of **5**, $[\alpha]_D$ = +30.9 (c=1.97, $CHCl_3$), contaminated with less than 4% of the regioisomer resulting from C-2 opening, according to $^{13}$C NMR spectroscopy.

IR (film, NaCl): 3700-3000, 3090, 3070, 3035, 3010, 2930, 2860, 1650, 1610, 1590, 1500, 1460, 1150, 980, 910, 750, 710 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, 200 MHz); δ(TMS): 1.1-1.7 (m, 8H); 2.03 (m, 2H); 2.45 (br s, 2OH + NH); 2.73 (m, 1H); 3.65 (m, 3H); 5.00 (s, 1H); 4.8-5.1 (m, 2H); 5.7-5.9 (m, 1H); 7.0-7.5 (m, 10H).

$^{13}$C NMR ($CDCl_3$, 50.1 MHz); δ(TMS): 25.3 (t), 28.6 (t), 29.0 (t), 29.9 (t), 33.5 (t), 57.3 (d), 64.1 (t), 64.3 (d), 71.3 (d), 114.2 (t), 127.1 (d), 127.3 (d), 128.5 (d), 138.7 (d), 142.9 (s), 143.7 (s).

MS (c. i., $NH_3$): 354 (M+1, 3%)., 248 (100%), 197 (30%), 103 (17%).

### (2*S*)-*N*-*tert*-Butoxycarbonyl-2-aminosuberic acid, 6.

To a mixture of aminodiol **5** (0.49 g, 1.39 mmol), acetonitrile (13.9 mL), carbon tetrachloride (13.9 mL) and water (20.8 mL), sodium periodate (4.45 g, 20.8 mmol) and hydrated $RuCl_3$ (0.021 g) were added, and the system stirred for 17 hours at room temperature. Dichloromethane (40 mL) was then added and the phases were separated. The aqueous layer was washed with $CH_2Cl_2$ (20 mL) and concentrated under vacuum. Following dilution with methanol (10 mL), $Boc_2O$ (0.302 g, 1.39 mmol) and $NaHCO_3$ (0.346 g) were added to the solution and the resulting mixture was sonicated for 15 hours. The solvent was evaporated at reduced pressure, and the residue was treated with water (10 mL), acidified to pH = 4 with 10% aqueous HCl, and extracted with ethyl acetate (4x10 mL). The solution was dried over $MgSO_4$, concentrated under vacuum and the residue submitted to medium pressure liquid chromatography on C-18 silica gel (Fluka, Art Nr. 60756), eluting with water / acetonitrile mixtures, to afford 90-103 mg (22-25% yield) of *N*-Boc-aminosuberic acid **6**.

$[\alpha]_D$ = +11.3 (c=0.85, $CHCl_3$).

IR (film, NaCl): 3600-2500, 2980, 2920, 2850, 1700 (br), 1160, 925 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz); δ(TMS): 1.44 (s, 9H); 1.2-1.8 (m, 8H); 2.35 (t, J = 7 Hz, 2H); 4.2 (br s, 1H); 5.15 (br s, NH); 7.5 (br s, 2OH).

$^{13}C$ NMR ($CDCl_3$, 50.1 MHz); δ(TMS): 24.3 (t), 24.8 (t), 28.3 (q), 32.1 (t), 33.8 (t), 53.3 (d), 80.8 (s), 157.5 (s), 177.6 (s), 179.3 (s).

MS (c. i., $NH_3$): 307 (M+18, 100%), 290 (M+1, 19%).

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