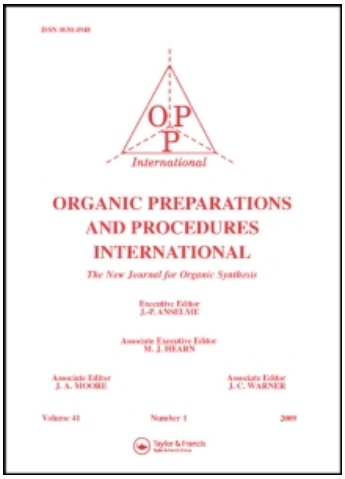

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A NOVEL AND SIMPLE SYNTHESIS OF (*1S, 2S*)-2-AMINO-l-(*p*-NITROPHENYL)-3-TRITYLOXYPROPANOL

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A NOVEL AND SIMPLE SYNTHESIS OF (*1S, 2S*)-2-AMINO-1-(*p*-NITROPHENYL)-3-TRITYLOXYPROPANOL

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(02/24/03)

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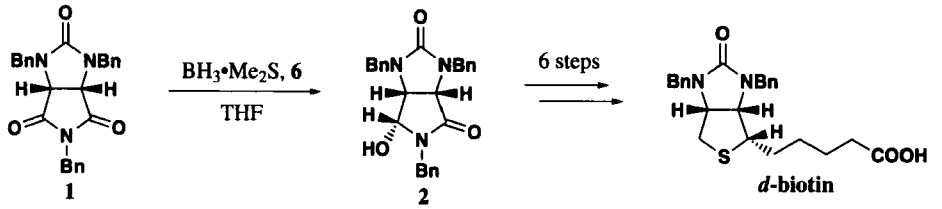
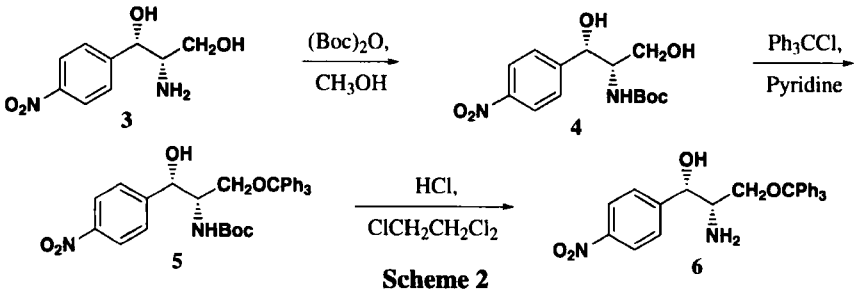
During the course of our investigation on the synthesis of (3*aS*,6*R*,6*aR*)-1,3,5-tribenzyl-6-hydro-xytetrahedro-4*H*-pyrolo [3,4-*d*] imidazole-2, 4(1*H*)-dione (**2**), a key intermediate in *d*-biotin synthesis, the high enantiomeric purity and yield in the one-pot catalytic enantioselective reduction of *N*-benzyl-*cis*-1,3-dibenzyl-2-imidazolidone-4,5-dicarboximide (**1**) mediated by an oxazaborolidine catalyst (generated *in situ)* from (1*S*,2*S*)-*threo*-1-(*p*-nitrophenyl)-2-amino-3-trityloxypropanol (**6**) and borane methyl sulfide (BH_3•Me_2S) to **2** was achieved (*Scheme 1*).[1,2] To



Scheme 1

the best of our knowledge, only one report of the pre-paration of **6** has appeared in the literature,[3] it involves a three-step synthesis of **6** starting from (1S,2S)-(+)-*threo*-1-(*p*-nithrophenyl)-2-amino-1,3-propanediol (**3**). However, this approach suffers from low overall yield (24%), long reaction times and requires chromatographic purification.

Herein, we report a simple method for synthesis of **6** as outlined in *Scheme 2*. Regioselective protect-ion of the amino group of **3** with *di-tert*-butyl dicarbonate [$(Boc)_2O$] gave intermediate **4** which was *O*-alkylated with trityl chloride in pyridine followed by deprotection with 18% hydrochloric acid in dichloro-ethane, to afford compound **6** with a 98% *ee* in an overall yield of 64%.



Scheme 2

In conclusion, we have developed a new three-steps route to **6** which proceeds on a reasonably large scale in high yield and high enantiometric excess.

EXPERIMENTAL SECTION

^{1}H NMR (500MHz) and ^{13}C NMR (125MHz) spectra were recorded on a spectrometer using $CDCl_3$ as solvent with TMS as an internal standard. Chemical shifts are reported δ. The mass spectra were obtained on HP 5989A Mass spectrometer using electrospray. IR spectra were determined on a Dynamin alignment FTS 175C Fourier transform infrared spectrophotometer. All reagents and solvents were obtained form commercial sources and were used as received without further purification.

(1*S*,2*S*)-1-(*p*-Nitrophenyl)-2-(carbo-*tert*-butoxyamino)-1,3-propanediol (4).- To a stirred solution of **3** (2.50 g, 11.8 mmol) in MeOH (25 mL) was added *di-tert*-butyl dicarbonate (2.6 g, 11.8 mmol) in one portion. The reaction mixture was refluxed for 20min. After cooling to room temperature, the pH of the mixture was adjusted to 10 with 10% aqueous NaOH. After concentration under reduced pressure, CH_2Cl_2 (30 mL). 10% aqueous HCl (10 mL) were added. The organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic phases were washed with water, saturated brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give **4** (2.84 g, 90%) as a pale yellow solid, mp. 112-114°C; $[\alpha]_D^{20}$ = +74.1°C (*c* 0.1, CH_2Cl_2); IR (KBr): 3431, 3379, 3241, 1713, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.31 (s, 9H, CH_3), 1.82 (s, 1H, OH), 2.81 (s, 1H, OH), 3.76 (s, 3H, CH, CH_2), 5.17 (s, 1H, NH), 5.22-5.23 (d, 1H, CH), 7.55-8.20 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$): δ 152.3, 148.75-123.46, 80.29, 73.68, 63.96, 56.65, 28.15; EI-MS (m/z, %): 312.

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.83; H, 6.47; N, 8.97. Found: C, 53.58; H, 6.28; N, 8.68

(1*S*,2*S*)-1-(*p*-Nitrophenyl)-2-(carbo-*tert*-butoxyamino)-3-trityloxypropanol (5).- To a suspension of **4** (1.04 g, 0.415 mol) in anhydrous pyridine (20 mL) was added trityl chloride (1.26 g, 0.415 mol) and the reaction mixture was stirred at 90°C for 30min. After cooling to room temperature, water (20 mL) and dichloroethane (40 mL) were added. The organic phase was separated, and the aqueous phase was extracted with dichloroethane (3 x 35 mL). The combined organic phases were washed with water, saturated brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give the crude pro-duct, which was recrystallized from acetonitrile to afford **5** (1.94 g, 85 %) as a yellow solid. mp. 75-76°C, $[\alpha]_D^{20}$ = +39.2°C (*c* 0.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 9H, CH_3), 3.24-3.47 (m, 2H, CH_2), 3.64 (s, 1H, CH), 3.90 (s 1H, OH), 7.25-8.10 (m, 19H, ArH); ^{13}C NMR ($CDCl_3$): δ 155.99, 148.49-123.28, 80.03, 73.68, 64.25, 55.80, 28.21; IR (KBr): 3430, 1690, 1521, 1448, 1347 cm^{-1}; EI-MS (m/z, %): 550.

Anal. Calcd for $C_{30}H_{38}N_2O_6$: C, 68.93; H, 7.34; N, 5.36. Found: C, 68.78; H, 7.29; N, 5.27

(1*S*,2*S*)-1-(*p*-Nitrophenyl)-2-amino-3-trityloxypropanol (6).- To a stirred solution of **5** (1.11 g, 2.02 mmol) in CH_2Cl_2 (5 mL) was added 18% aqueous HCl (15 mL). The reaction mixture was heated to 50°C for 2 h. The pH of reaction mixture was adjusted to 7-8 with 10% Na_2CO_3. The

organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic phases were washed with water, saturated brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give the crude product, which was recrystallized from methanol-ether to afford **6** (0.75 g, 84 %) as a yellow solid, mp. 194-195°C, $[\alpha]_D^{20}$ = +43°C (*c* 3, pyridine), *lit.*[4] 192°C; $[\alpha]_D^{20}$ = +43.8°C (*c* 3.08, pyridine); IR (KBr): 3364, 3061, 1598, 1515, 1350, 1215, 765 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55 (s, 2H, NH_2), 2.88-2.90 (t, 1H, CH), 3.07-3.33 (m, 2H, CH_2), 4.09 (s, 1H, OH), 4.69-4.70 (d, 1H, CH), 7.24-8.05 (m, 19H, ArH); ^{13}C NMR ($CDCl_3$): δ 152.63-123.24, 86.33, 73.34, 65.61, 57.61; EI-MS (m/z, %): 454.

Anal. Calcd for $C_{25}H_{30}N_2O_4$: C, 71.03; H, 7.06; N, 6.54. Found: C, 70.88; H, 7.14; N, 6.42

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SYNTHESIS OF 2-SUBSTITUTED THIAZOLIDINE-4-CARBOXYLIC ACIDS

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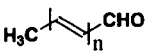
In our ongoing[1] work on chemical and pharmacological activity of polyconjugated aldehydes **1**, our attention was turned to the synthesis of 2-substituted thiazolidine-4- carboxylic acids. Preliminary *in vitro* and *in vivo* pharmacological tests carried out on polyenals **1** which are structurally related to carotenoids, have shown potential anti-proliferative and antioxidant activities. It is known that, in enzymes, the interaction between the α,β-unsaturated carbonyl compounds and the SH groups of glutathione and cysteine play an important role in the mechanism by which these molecules exert their pharmacological activity.[2-7] In fact, thiazolidine-4-carboxylic



1
n = 2-7