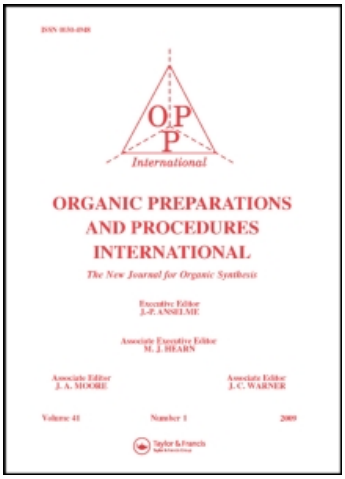

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(R)-2-HYDROXY-3-TRIPHENYLMETHYLTHIOPROPANOIC ACID, AN INTERMEDIATE IN THE SYNTHESIS OF HYDROXY ANALOGS OF OXYTOCIN

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5. S. Watanabe, T. Fujita, M. Sakamoto, M. Takeda, T. Kitazume and T. Yamazaki, *J. Fluorine Chem.*, **82**, 1 (1997).

6. W. Dmowski and T. Kozlowski, *J. Fluorine Chem.*, **83**, 187 (1997).

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(R)-2-HYDROXY-3-TRIPHENYLMETHYLTHIOPROPANOIC ACID, AN INTERMEDIATE IN THE SYNTHESIS OF HYDROXY ANALOGS OF OXYTOCIN

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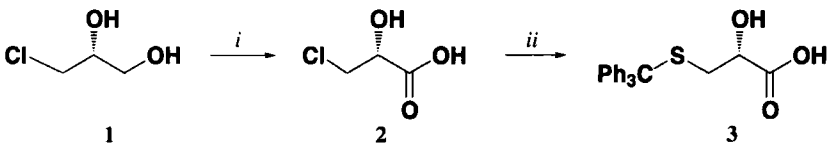
For our ongoing vasopressin and oxytocin (OT) projects, we needed to synthesize the potent oxytocin agonist [L-Hmp[1],Thr[4]]OT as a reference compound. The peptide, proposed by Manning's group in the mid-seventies,[1] is an analog of 4-threonine oxytocin in which a hydroxyl group replaces the N-terminal amino group. In the original synthesis of the peptide, (R)-2-hydroxy-3-benzylthiopropanoic acid was used. This protected hydroxythioacid was obtained in three steps by the procedure of Hope and Walti[2] which comprises a) oxidation of racemic 3-chloro-1,2-propanediol with nitric acid; b) conversion of the obtained D,L-β-chlorolactic acid to D,L-β-benzylthiolactic acid and c) resolution of the racemic mixture by crystallization of diastereoisomeric salts with brucine. An earlier attempt to synthesize this compound by nitrous acid deamination of (R)-S-benzylcysteine[3] resulted in a substance with different physicochemical properties due to thiiran formation.[4] Most recently, the synthesis of (S)-2-hydroxy-3-*tert*-butylthiopropanoic acid by regioselective epoxide ring opening of potassium glycidate was reported.[5]

For continuous-flow mode of peptide synthesis,[6] an acid labile S-protecting group was needed. The S-trityl group,[7] which can be removed with TFA, was a preferred candidate. The synthesis of (R)-2-hydroxy-3-S-triphenylmethylthiopropanoic (**3**) acid does not appear to have been reported and none of the methods used for the synthesis of (R)-2-hydroxy-3-benzylthiopropanoic acid appeared directly applicable to the synthesis of (**3**). A convenient, high-yield synthesis of (**3**) from (R)-3-chloro-1,2-propanediol (**1**) in only two steps is described here (*Scheme*).



1 **2** **3**

i) HNO_3; *ii)* NaH, TrtSH, DME

Chemical[8] and enzymatic[9] syntheses of the enantiomers of the key intermediate, 3-chloro-2-hydroxypropanoic acid (β-chlorolactic), (**2**) have been reported. However, oxidation of the now commercially available (R)-3-chloro-1,2-propanediol (**1**) with nitric acid according to procedure by Hope and Walti[2] appeared to be a more expedient alternative. Indeed, oxidation of the primary hydroxyl group of **1** occurred without racemization to give (R)-3-chloro-2-hydroxypropanoic acid (L-β-chlorolactic acid), (**2**), in good yield. Treatment of **2** with triphenylmethyl thiol anion in dimethoxyethane resulted in clean nucleophilic substitution of chlorine to give the final product, **3**. After standard aqueous workup and recrystallization from ethanol-water, the product was obtained in high yield and optical purity, without the need for column chromatography.

To assess the extent of racemization during the above procedure, the material obtained was applied to the synthesis of [L-Hmp^1,Thr^4]OT. A chromatographic standard mixture containing [D-Hmp^1,Thr^4]OT, the peptide derived from racemized **3**, was prepared from racemic (R,S)-2-hydroxy-3-S-triphenylmethylthiopropanoic acid, which was obtained from racemic **1** by the above procedure. HPLC analysis of crude [D,L-Hmp^1,Thr^4] OT showed two equal peaks corresponding to both diastereoisomers. Analysis of crude [L-Hmp^1,Thr^4] OT obtained from **3** showed one major peak with no more than 0.2% of [D-Hmp^1,Thr^4]OT. Therefore the synthetic procedure for **3** appears to be racemization free.

In summary, a simple procedure to obtain a synthetically useful hydroxy analog of cysteine, compatible with flow-continuous mode of peptide synthesis, was developed. The procedure does not involve chromatographic work-up and could be applied to the synthesis of other derivatives (e.g. protective groups) of 2-hydroxy-3-thiopropanoic acid.

EXPERIMENTAL SECTION

^{1}H-NMR, ^{13}C-NMR spectra as well as the elemental analysis were performed by NuMega Resonance Labs, Inc, San Diego; CA. HPLC-RP chromatography was performed on Waters 600 liquid chromatograph. Vydac C18, 5μ column, 250 x 4.6 mm was used. Following gradients were applied: X: 40→100%B, 30 min., flow rate: 2mL/min. (A = 0.1%TFA, B = 0.1%TFA, 90% CH_3CN); Y: 10→70%B, 30 min., flow rate: 2mL/min. (A = 0.1%TFA, B = 0.1%TFA, 90% CH_3CN). For TLC Merck aluminium sheets coated with silica containing UV indicator were used. Following solvent systems were applied: A: $CHCl_3$/MeOH/AcOH 10:1:1; B: 1-BuOH/AcOH/H_2O 4:1:1. TLC plates were visualized with UV and with bromocresol green. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Electrospray mass spectra (ESI) were recorded on a Finningan MAT spectrometer. Optical rotations were measured on a Perkin-Elmer Polarimeter 341. HPLC grade acetonitrile as well as the other solvents were purchased from Fischer Scientific. 3-Chloro-1,2-propandiols were purchased from Aldrich. Peptides were assembled on Tentagel-S-RAM resin (Peptide International) using a 9050 Plus PepSynthesiser and cleaved from the resin with TFA/H_2O/TIS 93/5/2 mixture. The peptides were subsequently dissolved in 10% aqueous TFA and oxidized with 0.1M methanolic I_2. The crude peptides were analyzed by HPLC in gradient Y.

(R)-3-Chloro-2-hydroxypropanoic Acid (L-β-Chlorolactic Acid, 2).- (R)-3-Chloro-1,2-propanediol (10.00 g, 90.5 mmol) was dissolved in 31 mL of conc. nitric acid at 0°. The solution was heated to ca

70°. Vigorous reaction started with the release of dark fumes and lasted for ca 10 min. The reaction mixture was then heated to 100° until gas evolution ceased. The mixture was cooled to room temperature and partially neutralized with 7 g of $NaHCO_3$. The product was extracted with ethyl ether (8 x 100 mL) and dried over $MgSO_4$. The solvent was then evaporated at RT and the temperature was raised to 60° towards the end of evaporation to remove residual nitric acid. The crude product solidified on standing at room temperature and was recrystallized from chloroform to yield 7.2 g (72%) of colorless crystals, mp. 91.5-93°. $[\alpha]_D^{20} = +3.95°$ (c=9, H_2O)[8,9]. R_f (A)=0.21, (tailing), R_f (B)=0.56. ^{1}H-NMR (DMSO-d_6): δ 3.76 (2H, CH^{β}), 4.30 (1H, CH^{α}).

Anal. Calcd for $C_3H_5ClO_3$: C, 28.94; H, 4.05. Found: C, 28.94; H, 3.94.

(R)-2-Hydroxy-3-S-triphenylmethylthiopropanoic Acid (L-Hmp(Trt)-OH, 3).- To a magnetically stirred solution of 5.92 g (47.5 mmol) of (R)-3-chloro-2-hydroxypropanoic acid in 50 mL of dry dimethoxyethane (DME) cooled to 0°, was added 1.9g (47.5 mmol) of sodium hydride (60% oil dispersion). A solution of 13.11 g (49.8 mmol) of triphenylmethyl thiol and 1.9 g of sodium hydride (60% oil dispersion) in 50 mL DME was added portionwise within 0.5h. The progress of the reaction was monitored by analytical HPLC in gradient X. The reaction mixture was stirred at room temperature until no further changes in concentration of product were detected (ca 3h). The solvent was then evaporated and the residue was partitioned between 200 mL of water and 200 mL of Et_2O. The aqueous phase was extracted twice with 100 mL Et_2O and acidified with 1M H_2SO_4. The product was extracted with EtOAc (3 x 100 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The oily residue was treated with hexanes containing a few drops of *i*-Pr_2O to afford 14.04g (81%) of finely powdered white product. Although sufficiently pure for the peptide synthesis the product was recrystallized from EtOH/H_2O, mp. 89-93°. $[\alpha]_D^{20} = +48.9°$ (c =2, EtOH). Rf (A)=0.68. ^{1}H-NMR ($CDCl_3$): δ 2.71 (2H, CH_2^{β}), 3.89 (1H, CH^{α}), 7.20-7.44 (15H, Trt). ^{13}C-NMR ($CDCl_3$): δ 36.25 (CH_2^{β}), 67.24, 69.12 CPh_3, CH^{α}), 127.12, 128.13, 129.72, 144.48 aromatic; 176.77 (COOH). MS: (negative mode): 275.3 $[TrtS]^-$, 363.2 $[M-H]^-$; (positive mode): 243.2 $[Trt]^+$, 387.1 $[M+Na]^+$.

Anal. Calcd for $C_{22}H_{20}O_3S \cdot 1/2H_2O$: C, 70.75; H, 5.67; S, 8.58. Found: C, 70.74; H, 5.68; S, 8.59

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REFERENCES

1. M. Manning, J. Lowbridge, J. Haldar and W. H. Sawyer, *J. Med. Chem.*, **19,** 376 (1976).

2. D. B. Hope and M. Walti, *J. Chem. Soc. C*, 2475 (**1970**).

3. J. A. Stekol, *J. Biol. Chem.*, **140**, 827 (1941).

4. C. D. Maycock and R. J. Stoodley, *J. Chem. Soc. Perkin I,* 1852 (**1979**).

5. F. Cavelier and A-M. Yim, *Org. Prep. Proced. Int.*, **30,** 103 (1998).

6. E. Atherton and R. C Sheppard, *Solid Phase Peptide Synthesis, A Practical Approach,* IRL Press at Oxford University Press, 1989.

7. G. B. Fields and R. L. Noble, *Int. J. Peptide Protein Res.*, **35,** 161 (1990).

8. C. Morin and G. Sawaya, *Synthesis,* 479 (**1987**).

9. B. L. Hirschbein and G. M. Whitesides, *J. Am. Chem. Soc.*, **104,** 4458 (1982).

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PREPARATION OF *N*-TRITYLPYRROLIDINE AND *N*-TRITYLPIPERIDINE

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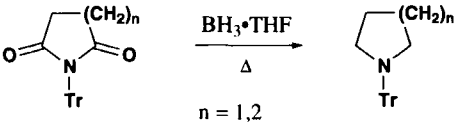
In connection with our ongoing radiopharmaceutical program, it became necessary to synthesize *N*-tritylpyrrolidine (*N*-triphenylmethylpyrrolidine) and *N*-tritylpiperidine (*N*-triphenylmethylpiperidine) in large quantities. It has been reported[1] that the reduction of *N*-tritylsuccinimide with lithium aluminum hydride results in the formation of *N*-trityl-γ-hydroxybutyramide but none of the expected *N*-tritylpyrrolidine. We recently reported[2] the use of borane to reduce various alkyl diphenimides to dibenz[c,e]azepines which are potent antihyperlipidemics.[3] We also described the preparation of hindered *N*-aryl cyclic amines *via* the reduction of *N*-aryl cyclic imides utilizing borane-THF.[4] We now report a convenient preparation of *N*-tritylpyrrolidine and piperidine *via* the reduction of *N*-tritylsuccinimide and *N*-tritylglutarimide with borane-THF.



The requisite *N*-tritylsuccinimide or *N*-tritylglutarimide was prepared by reaction of *N*-bromosuccinimide or *N*-bromoglutarimide with trityl bromide in refluxing chloroform.[1] The reduction of these imides with borane in refluxing tetrahydrofuran afforded *N*-tritylpyrrolidine and *N*-tritylpiperidine in 81% and 69% yield, respectively.

EXPERIMENTAL SECTION

N-Bromosuccinimide, trityl bromide and borane-THF were used as received from the Aldrich Chemical Company. *N*-Bromoglutarimide was prepared from glutarimide according to literature method.[5]