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Preparation of N,N-Bis[2-[N',N'-Bis[(Tert-Butoxycarbonyl)Methyl]-Amino]Ethyl-L-Aspartic Acid: An Intermediate in the Synthesis of MRI Contrast Agents

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PREPARATION OF N,N-BIS[2-[N',N'-BIS[(TERT-BUTOXYCARBONYL)METHYL]-AMINO]ETHYL-L-ASPARTIC ACID: AN INTERMEDIATE IN THE SYNTHESIS OF MRI CONTRAST AGENTS

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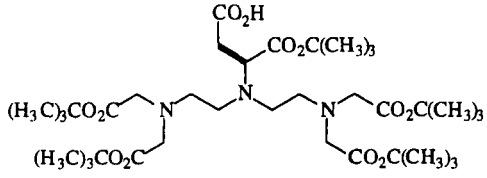
Abstract: A preparation of DTPA carboxylic acid **1,** a suitable intermediate in the synthesis of MRI contrast agents **2**, is described starting from α-*tert*-butyl-β-benzyl-L-aspartate hydrochloride. In addition, an alternative procedure for the synthesis of bromide **3b** is presented.

In our search for a suitable diethylenetriaminepentaacetic acid (DTPA) chelating agent for the complexation of the gadolinium ion, we needed to prepare large quantities of carboxylic acid **1**.[1]



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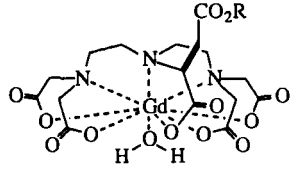

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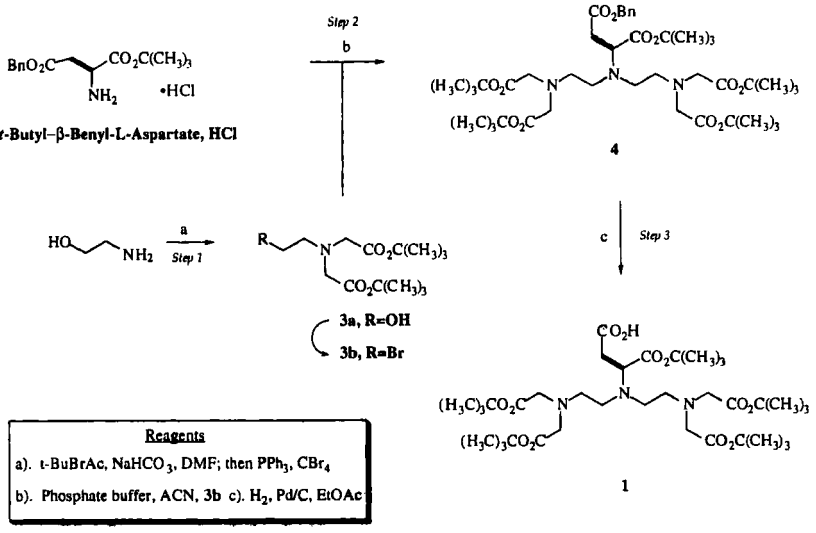
To this end, a modification of known chemistry was investigated. In this paper we describe an efficient preparation of bromide **3b** and carboxylic acid **1**.[2] Our approach is outlined in Scheme I.

Scheme I



The synthesis commenced with the dialkylation of ethanolamine using t-butyl bromoacetate and sodium bicarbonate in DMF. The isolated crude alcohol **3a** was subjected to carbon tetrabromide and triphenylphosphine in methylene chloride, providing bromide **3b** after column chromatography (34% over two steps). Combining α-*tert*-butyl-β-benzyl-L-aspartate hydrochloride[3] and bromide **3b** in the presence of 2.2M phosphate buffer in acetonitrile provided benzyl ester **4** (94% isolated yield). Exposure of benzyl ester **4** to a hydrogen atmosphere (45 psi) and 10% Pd/carbon in ethyl acetate gave the desired DTPA carboxylic acid **1**. The acid **1** was prepared in 26% overall yield in four synthetic steps.[4]

Results and Discussion

Step 1: N,N-bis[(tert-butoxycarbonyl)methyl]-2-bromoethylamine, 3b

The reported preparation of bromide **3b** proceeds through alcohol **3a** by treatment with N-bromosuccinimide and triphenylphosphine in methylene chloride. Whereas this preparation produced **3b** in respectable yield on small scale, large scale runs proved cumbersome. The yields were low and difficulty was encountered removing reaction by-products. Using bromination conditions comprising of carbon tetrabromide and triphenylphosphine[5] in methylene chloride, we were able to carrying out this reaction on large scale. Isolation of purified **3b** was accomplished from the reaction mixture via i. addition of hexanes, which facilitated by-product precipitation (mainly triphenylphosphine oxide), ii. removal of excess t-butyl bromoacetate using distillation, which minimized the amount of silica gel required for chromatography, and iii. silica gel column chromatography (see experimental). This sequence provided **3b** in 34% yield (two synthetic steps).

Step 2: N,N-Bis[2-[N',N'bis[-[bis[(tert-Butoxycarbonyl)-methyl]-amino]ethyl]-L-aspartic acid, benzyl ester, 4

Literature reports the preparation of **4** via dialkylation of α-*tert*-butyl-β-benzyl-L-aspartate hydrochloride with bromide **3b**.[1] These described conditions utilize diisopropylethylamine as the base in acetonitrile. Our attempts at reproducing these conditions provided **4** in low yield (10-15%). Further modifications using organic solvents (DMF, THF) and bases (triethylamine, lutidine, collidine and imidazole) were unsuccessful. Similar results were obtained when 10N aqueous sodium hydroxide in ethanol was used for the alkylation.[6] The long reaction times and low yields were unacceptable. Therefore, we turned our attention to the conditions developed by Rapoport *et al.* used in the N-alkylation of

amino acid esters.[2] A 2.2M phosphate buffer/acetonitrile combination in the presence of bromide **3b** and α-*tert*-butyl-β-benzyl-L-aspartate hydrochloride furnished benzyl ester **4** in 94% yield isolated yield. This procedure was reproducible on a 0.4 mol scale (based on starting amino acid).

Step 3: N,N-Bis[2-[N',N'bis[-[bis[(tert-Butoxycarbonyl)-methyl]-amino]ethyl]-L-aspartic acid, 1

The removal of the benzyl ester was achieved under standard conditions. The benzyl ester **4** was subjected to hydrogen gas in the presence of 10% palladium on carbon, with ethyl acetate as the reaction solvent. The reaction was carried out on a 0.2 mol scale and produced DTPA carboxylic acid **1** as an oil (82% yield).

Conclusion

DTPA carboxylic acid **1** was prepared in four synthetic transformations from readily available starting materials. Herein we developed suitable conditions for a large scale preparation of bromide **3b**, and hence report the first detailed preparation of DTPA carboxylic acid **1**.

Experimental

N,N-bis[(tert-butoxycarbonyl)methyl]-2-bromoethylamine, 3b

A 5.0 L Morton flask, equipped with a mechanical stirrer and internal temperature probe was charged with tert-butyl bromoacetate (1265 g, 6.41 mol), sodium bicarbonate (608 g, 7.15 mol) and DMF (462 mL) under a nitrogen flow. Ethanolamine (160 mL, 2.85 mol) was added over 45 minutes while maintaining an internal temperature of 22-25 °C. The reaction mixture was stirred for 16.0 hours

while maintaining an internal temperature of 22-25 °C . The reaction mixture was then diluted with diethyl ether (1730 L) and saturated sodium bicarbonate (1000 mL), stirred for 10 minutes and an additional 1300 mL of saturated sodium bicarbonate was added. After stirring for 20 minutes the layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate (1730 mL). The combined aqueous layers were washed with diethyl ether (1730 mL). The combined organic layers were washed with saturated sodium chloride (1730 mL), dried over sodium sulfate, filtered under suction and concentrated under reduced pressure (25-45 °C water bath, 45-20 mm Hg) to obtain a mobile oil (1000 g) [Analysis of the oil by ^{1}H NMR indicated a 2:1 mixture of alcohol **3a** to tert-butyl bromoacetate].

The above oil (2.85 mol theoretical maximum) was added to a 12.0 L Morton flask under a nitrogen flow. To this was added methylene chloride (4000 mL) and carbon tetrabromide (1340 g, 4.033 mol). To the reaction mixture was added triphenylphosphine (910 g, 3.47 mol) over 1.5 hours while maintaining an internal temperature of 23-30 °C [Following the addition of approximately 680 g of triphenylphosphine the reaction mixture became dark red in color]. The reaction mixture was stirred for 12.0 hours. To the reaction mixture was added 10.0 L of hexanes. The mixture was stirred for 30 minutes. The precipitated solids were collected by suction filtration. The filtrate was concentrated under reduced pressure (25-45 °C water bath, 45-20 mm Hg) to give a thick pasty oil. The oil was diluted with 14.0 L of hexanes and stirred for 30 minutes. The precipitated solids were collected by suction filtration. The filtrate was concentrated under reduced pressure (25-45 °C water bath, 45-20 mm Hg) to give an oil. The excess tert-butyl bromoacetate remaining in the oil was removed under reduced pressure (rotovap, 50-55 °C, 1 mm Hg. Typically less than 10% of the crude material was tert-butyl

bromoacetate after distillation) to provide an oil (522.6 g). The oil was diluted with methylene chloride (200 mL) and loaded onto 10 kg of silica gel. The silica gel column was eluted with a 5 to 20% ethyl acetate/hexanes gradient. The column fractions were analyzed by thin layer chromatography (ethyl acetate/hexanes, $KMnO_4$ stain) with like fractions combined and concentrated under reduced pressure (25-45 °C water bath, 45-20 mm Hg) to provide bromide **3b** as an oil (341.6 g, Yield: 34.0% from ethanolamine, Purity by HPLC, area %: 90.5%). See reference 2 for spectroscopic analysis. HPLC Method: Gradient HPLC system with UV detection, 10% to 80% ACN (0.1% trifluoroacetic acid) over 22 minutes, 8 minute hold at 80% ACN minutes, flow at 1.5 mL/minute, wavelength = 220 nm, Inertsil C4 column, 150 x 4.6 mm, 5 micron. Sample at 1.0 mg/mL in starting mobile phase.

N,N-Bis[2-[N',N'bis[-[bis[(tert-Butoxycarbonyl)methyl]-amino]ethyl]-L-aspartic acid, benzyl ester, 4

A 5.0 L Morton flask, equipped with a mechanical stirrer and internal temperature probe was charged with bromide **3b** (341.6 g, 0.970 mol), acetonitrile (890 mL) and 2.2 M pH 7.0 phosphate buffer (890 mL [Prepared by dissolving 326.0 g K_2HPO_4 and 36.0 g of NaH_2PO_4 in 1000 mL of water]). To this mixture was added α-*tert*-Butyl-β-benzyl-L-aspartate hydrochloride (127.7 g, 0.404 mol) while maintaining an internal temperature of 22-25 °C. The reaction mixture was stirred for 3.0 hours and the layers were separated. The aqueous phase was washed with acetonitrile (790 mL) and the combined organic phases were placed into the 5.0 L Morton flask. A fresh solution of 2.2 M pH 7.0 phosphate buffer was added and the mixture was stirred for 22 hours while maintaining an internal temperature of 22-25 °C. The layers were separated and the aqueous layer was

washed with acetonitrile (340 mL). The combined organic layers were concentrated under reduced pressure (25-45 °C water bath, 45-20 mm Hg) to give an oil. The oil was dissolved into ethyl acetate (4000 mL) and washed with water (200 mL), then saturated sodium chloride (1000 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure (25-45 °C water bath, 45-20 mm Hg) to give a yellow oil (424.0 g). The oil was purified in two lots (212 g each) on a Biotage system (5.0 kg) using a 10 to 30% ethyl acetate/hexanes gradient. The column fractions were analyzed by thin layer chromatography (ethyl acetate/hexanes, $KMnO_4$ stain) with like fractions combined and concentrated under reduced pressure (25-45 °C water bath, 45-20 mm Hg) to provide benzyl ester **4** as an oil (313.0 g, Yield: 94.0%, Purity by HPLC, area %, 90.3%). ^{1}H NMR ($CDCl_3$): δ 1.44 (s, 45H), 2.75 (m, 8H), 3.4 (m, 8H), 3.8 (m, 1H), 5.15 (q, 2H), 7.35 (m, 5H); MS: *m/z* 822$[M + H]^+$, 844$[M + Na]^+$.

HPLC Method: Gradient HPLC system with UV detection, 10% to 80% ACN (0.1% trifluoroacetic acid) over 22 minutes, 8 minute hold at 80% ACN minutes, flow at 1.5 mL/minute, wavelength = 220 nm, Inertsil C4 column, 150 x 4.6 mm, 5 micron. Sample at 1.0 mg/mL in starting mobile phase.

N,N-Bis[2-[N',N'bis[-[bis[(tert-Butoxycarbonyl)-methyl]-amino]ethyl]-L-aspartic acid, 1

A 2.0 L thick walled stainless steel reactor, equipped with a mechanical stirrer, was charged with benzyl ester **4** (157 g, 0.191 mol), 10% palladium on carbon (19.8 g, 9.3 mol %) and ethyl acetate (1800 mL). The reactor was closed and purged with hydrogen. The process was repeated two additional times allowing a final pressure of 45 psi.. The reaction mixture was stirred for 12 hours.

The mixture was filtered through a celite pad and concentrated under reduced pressure (25-45 °C water bath, 45-20 mm Hg) to give an oil (approximately 140.0 g). Upon repeating this reaction a second time the combined crude oil was 279.6 g . The combined oil was dissolved in a minimal amount of ethyl acetate/hexanes (1:1). Purification was conducted on a Biotage system (5.0 Kg) with one (1) column volume of ethyl acetate/hexanes (1:1), followed by six (6) column volumes of ethyl acetate. The column fractions were analyzed by thin layer chromatography (ethyl acetate/hexanes, $KMnO_4$ stain) with like fractions combined and concentrated under reduced pressure (25-45 °C water bath, 45-20 mm Hg) to provide DTPA carboxylic acid **1** as an oil (230.2 g, Yield: 82.3%, Purity by HPLC, area %: 95.5%). ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 45H), 2.65 (d, 2H), 2.9 (m, 8H), 3.4 (m, 8H), 4.3 (t, 1H). MS: *m/z* 732[M + H]$^+$, 754[M + Na]$^+$.

HPLC Method: Gradient HPLC system with UV detection, 10% to 80% ACN (0.1% trifluoroacetic acid) over 22 minutes, 8 minute hold at 80% ACN minutes, flow at 1.5 mL/minute, wavelength = 220 nm, Inertsil C4 column, 150 x 4.6 mm, 5 micron. Sample at 1.0 mg/mL in starting mobile phase.

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