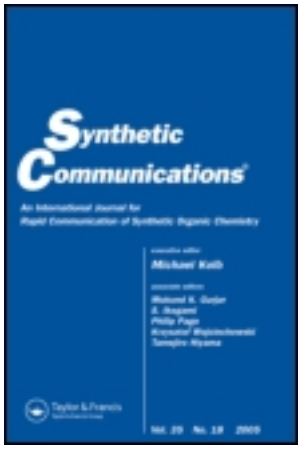

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Improved Synthesis of 10-(2-Alkylamino-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid Derivatives Bearing Acid-Sensitive Linkers

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IMPROVED SYNTHESIS OF 10-(2-ALKYLAMINO-2-OXOETHYL)-1,4,7,10-TETRAAZACYCLODODECANE-1,4,7-TRIACETIC ACID DERIVATIVES BEARING ACID-SENSITIVE LINKERS

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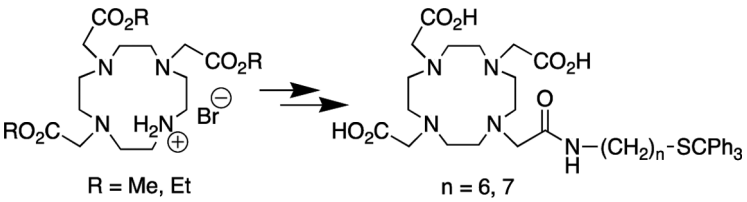
GRAPHICAL ABSTRACT



Abstract *Alkylation of the hydrobromide salts of 1,4,7-tris(methoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane and 1,4,7-tris(ethoxycarbonylmethyl)-1,4,7,10-tetraaza cyclododecane with appropriate α-bromoacetamides, followed by hydrolysis, provides convenient access to 10-(2-alkylamino-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid derivatives that contain acid-sensitive functional groups. The utility of the method is demonstrated by improved syntheses of two known 1,4,7,10-tetraaza cyclododecane-1,4,7,10-tetraacetic acid monoamides bearing acid-sensitive ω-tritylthio alkyl chains in much greater yields based on cyclen as the starting material.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Cyclen; DO3A monoamide; DOTA monoamide; medical imaging; synthesis

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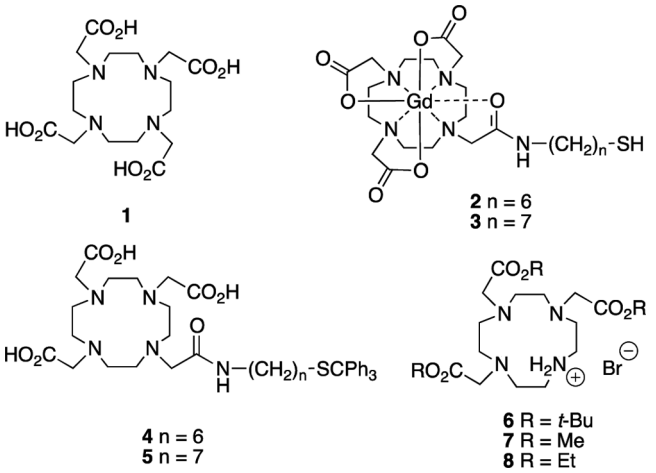
INTRODUCTION

1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA, **1**) forms stable complexes with lanthanides and radio metals.[1,2] As a result, DOTA-derived metal complexes are utilized as contrast agents in magnetic resonance imaging (MRI),[3–5] in radiopharmaceuticals, and radionuclide imaging.[6–8] In recent years, efforts to deliver bio molecules, such as proteins,[9,10] peptides,[11] and monoclonal antibodies,[12,13] labeled with metal ions or radioactive metal ions to specific cellular targets for imaging and therapy have gained importance. A common approach to linking the metal ion to a biomolecule is by means of a modified DOTA chelate that has been rendered bifunctional.[14] Many bifunctional derivatives of DOTA have been obtained by conversion of one of the pendant acid groups into an N-substituted acetamido derivative.[1] The chelate strongly coordinates with the chosen metal ion, while a functional group incorporated in the nitrogen substituent of the acetamido group conjugates with the biomolecule. Several precursors to DOTA monoamides have been described,[15–17] and some are commercially available. However, very little has been published relating to the synthesis of DOTA monoamides bearing acid-labile functional groups in the linker.

Previously we reported the synthesis of the gadolinium(III) DOTA monoamide complex **2** bearing a hexyl side chain that terminated with a thiol group.[18] The complex **2** was bound to human serum albumin (HSA) in a redox-sensitive manner. More recently, we demonstrated the utility of **2** as a magnetic resonance imaging biomarker of redox-active drugs in tumor-bearing mice.[19] We also synthesized Gd-DOTA monoamide complex **3** bearing an ω-thioheptyl side chain that showed higher binding affinity for HSA as compared to **2**.[21] DOTA monoamides **4** and **5**, intermediates in the published syntheses[18,20] of complexes **2** and **3**, respectively, were prepared by monoactivation of **1** with isobutyl chloroformate, followed by reaction with 6-tritylthiohexylamine and 7-tritylthioheptylamine, respectively, in good yields based on the amine starting materials. However, based on DOTA, the yields of **4** and **5** were 27% and 23%, respectively.[21] Assuming a yield of 82% in the conversion of cyclen to DOTA,[22] the yields of **4** and **5** based on cyclen were 22% and 19%, respectively. Existing procedures for the synthesis of DOTA monoamides that employ an excess of DOTA to avoid mixtures of products are not optimal, given the high cost of DOTA.[23] Other shortcomings of some published methods are the use of high dilution conditions and long reaction times. These issues limit large-scale preparations of DOTA monoamides. We describe in this article an efficient and scalable synthesis that is amenable to preparations of a series of DOTA monoamides, including compounds with acid-labile functionality in the linker, such as **4** and **5**.

[1] There is some ambiguity in the literature as to whether compounds such as **4** and **5** should be termed "DOTA monoamides" or "DO3A monoamides." CAS names such compounds as 10-(2-alkylamino-2-oxoethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid derivatives, which is inconsistent with both of these common usages. We employ "DOTA monoamide" in this article because this usage is consistent with use of the term "DOTA tetraamide" to indicate that all four acetate arms of the DOTA are present as amides.



RESULTS AND DISCUSSION

Of the methods reported for the preparation of DOTA monoamides,[24] two are well suited for large-scale synthesis. The first involves monoalkylation of 1,4,7,10-tetraazacyclododecane (cyclen, **9**) with an α-bromoacetamide, followed by incorporation of three acetate ester arms (methyl, ethyl, or *tert*-butyl) and their subsequent hydrolysis or cleavage to afford the DOTA monoamide. The second method involves the preparation of a DO3A tris-ester, such as the hydrobromides **6–8**, followed by neutralization, alkylation with an α-bromoacetamide, and subsequent hydrolysis or cleavage to afford the DOTA monoamide. In either method, one can choose methyl, ethyl, or *tert*-butyl ester groups, depending on the acid or base sensitivity of moieties on the acetamide arm. In the first method, an excess of cyclen is generally used to promote monoalkylation. This method can work well for the synthesis of a single DOTA monoamide, but for the synthesis of a series of DOTA monoamides, will involve the preparation and characterization of many more intermediates than will the second method. Barge et al.,[25] prepared a set of DOTA monoamide derivatives from **6** by the second method. For our work, the necessary acidolysis of the *t*-butyl ester moieties undermines the application of this synthetic method. However, the use of **7** or **8** in place of **6** would substitute base hydrolysis for acidolysis and permit preparations of DOTA monoamides such as **4** and **5** possessing acid-labile functionality in the linker, possibly on large scales.

While commercially available **6** has been used in the synthesis of many bifunctional chelates,[26,27] the related methyl and ethyl esters **7** [28–31] and **8**[32–37] have found limited use. Few methods for the synthesis of **7** and **8** have been published. Ester **7** was obtained as a free base in 54% yield by alkylation of **9** with 4 equivalents of methyl bromoacetate in refluxing methanol in the presence of triethylamine, followed by preparative thin-layer chromatography (TLC) purification.[28] Alternatively, **7** was obtained as a triflate salt by alkylation of *N*-formylcyclen[36]

with 3.3 equivalents of methyl bromoacetate, followed by removal of the formyl group.[29] Ester **8** was reportedly isolated in 72% yield after reaction of cyclen with 2.24 equivalents of ethyl bromoacetate in dichloromethane without an additional base.[37] More recently, Natrajan et al.,[38] prepared **8** in 63% yield as a hydrobromide salt by reaction of cyclen with 3.3 equivalents of ethyl bromoacetate in acetonitrile in the presence of sodium bicarbonate.

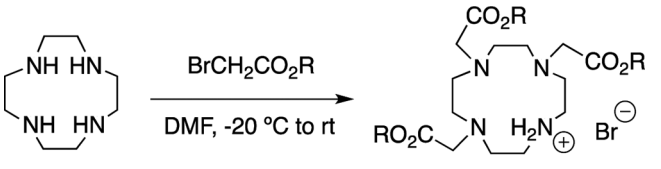
We described a synthesis of **6** as a hydrobromide salt in 79% yield by reaction of **9** with 3.3 equivalents of *t*-butyl bromoacetate and sodium acetate in dimethylacetamide at −20 °C.[39] The workup procedure involved adding the reaction mixture to water and isolating the hydrobromide salt by addition of potassium bicarbonate. Following this procedure, **9** was allowed to react with 3 equivalents of methyl bromoacetate and sodium acetate in dimethylacetamide at −20 °C. However, the hydrobromide salt **7** could not be isolated from the aqueous solution upon addition of potassium bicarbonate, presumably because of its greater solubility in water. To avoid a water workup, dimethylformamide (DMF) was used as solvent instead of dimethylacetamide.

In a typical procedure, 3 equivalents of methyl bromoacetate in DMF were added to a stirred suspension of one equivalent of **9** and 3.3 equivalents of sodium acetate in DMF at −20 °C (Scheme 1). After stirring for 6 h at room temperature, the reaction mixture was diluted with dichloromethane (DCM) and the salts removed by filtration. The filtrate was evaporated under reduced pressure and the crude oil was purified on a flash silica-gel column eluted with DCM and DCM 5% methanol. The hydrobromide salt **7** was obtained as a tan-colored oil, which solidified to a white solid upon scratching in the presence of ether at −20 °C. The yield of **7** was 78%.

Recrystallization of **7** from toluene produced a shiny amorphous solid. However, slow evaporation of a toluene solution produced crystals that were suitable for x-ray crystallographic analysis. The hydrobromide salt **7** crystallized in space group $P2_1/c$ with one molecule in the asymmetric unit and four molecules in the unit cell (Fig. 1).

Following a similar protocol, the hydrobromide salt **8** was synthesized in 77% yield by reaction of **9** with 3 equivalents of ethyl bromoacetate. With **7** and **8** in hand, we set about preparing **4** and **5** by an alternate synthetic route as described below.

Treatment of **10** [18] and **11**[20] with bromoacetyl bromide in DCM in the presence of 1 N NaOH gave **12** and **13** in 92% and 94% yields, respectively (Scheme 2).[34] While it was previously reported that alkylations of the hydrobromide salt of **6** gave



9

7 R = Me (78%)
8 R = Et (77%)

Scheme 1. Synthesis of **7** and **8**.

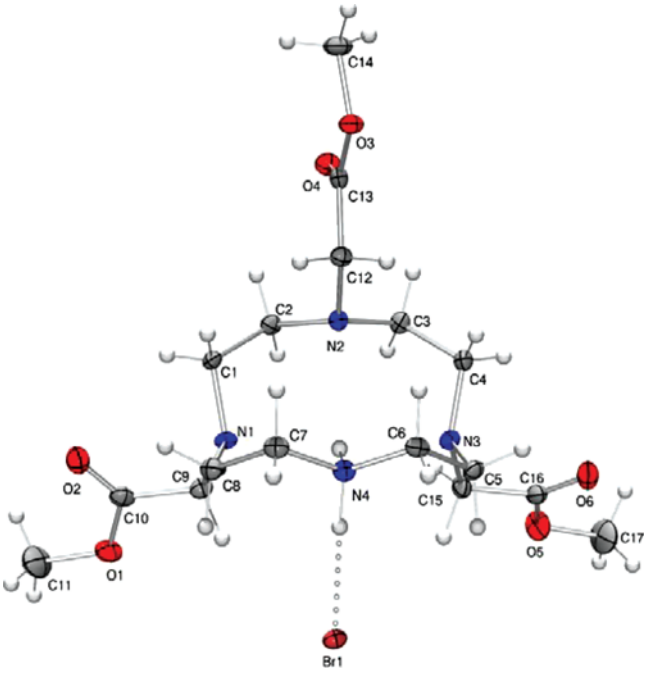
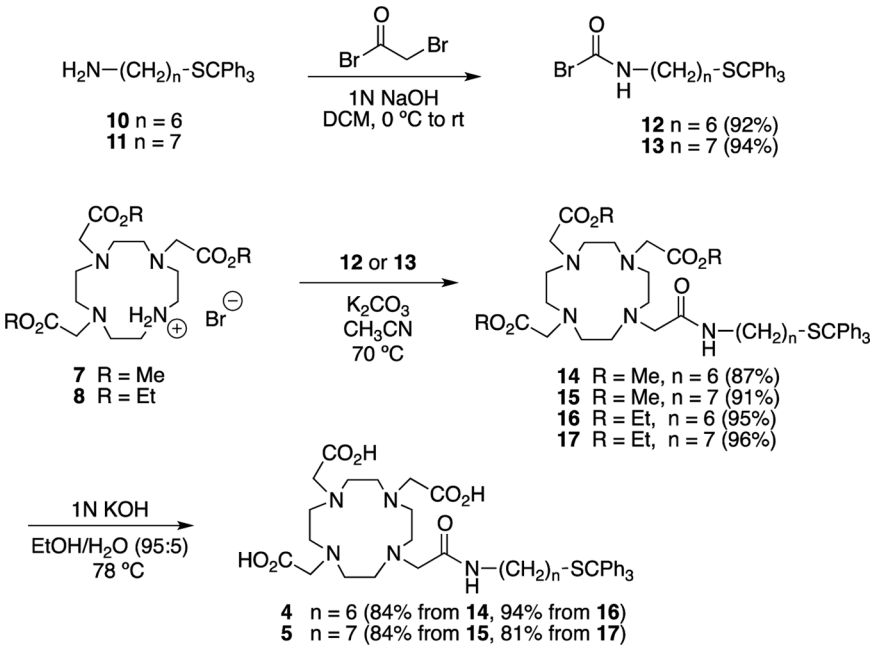


Figure 1. The structure of hydrobromide salt **7**. A hydrogen bond interaction is present between N4-H and Br with a donor-acceptor distance of 3.277(4) Å. Displacement ellipsoids are at the 50% probability level. (Figure is provided in color online.)



Scheme 2. Synthesis of DOTA monoamides **4** and **5**.

poor yields, even in the presence of K_2CO_3,[25] we found that treatment of the hydrobromide salt **7** with K_2CO_3 in acetonitrile for 1 h at 70 °C prior to the addition of bromoacetamide **12**, followed by reaction at this temperature for 1 h produced **14** in 84% yield (Scheme 2). Reactions of **7** with **13, 8** with **12**, and **8** with **13** under similar conditions gave **15, 16**, and **17** in excellent yields. Finally, hydrolysis of esters **14** and **16** in refluxing 1 N ethanolic KOH for 30 min gave DOTA monoamide **4** in 84% and 94% yields, respectively, while hydrolysis of esters **15** and **17** under these conditions gave the DOTA monoamide **5** in 84% and 81% yields, respectively.

CONCLUSIONS

Efficient gram-scale syntheses of the hydrobromide salts **7** and **8** have been developed, and the procedures seem amenable to further scale–up. The first x-ray crystal structure of hydrobromide salt **7** has been obtained. Neutralization of the hydrobromide salts **7** and **8** with K_2CO_3 prior to addition of α-bromoacetamides **12** and **13** produced alkylation products **14**–**17** in excellent yields. Saponification of **14**–**17** gave **4** and **5** in good yields. Overall, the three-step reaction sequences starting from cyclen (**9**) produced DOTA monoamides **4** and **5** in 57–69% yields based on cyclen, about three-fold greater yields than the literature syntheses of these same compounds.[18,20] Thus, hydrobromide salts **7** and **8** can be used as alternatives to **6** in the preparation of sets of DOTA monoamides, avoiding the synthesis and characterization of intermediates that would result from monoalkylation of **9** followed by incorporation of three acetate arms, or of single DOTA monoamide targets on large scales, and will be especially useful in cases where the DOTA monoamide derivatives contain acid-sensitive moieties.

EXPERIMENTAL

[1,4,7-Tris(methoxycarbonylmethyl)]-1,4,7,10-tetraaza cyclododecane Hydrobromide (7)

To a suspension of cyclen (1.00 g, 5.81 mmol) and sodium acetate (1.57 g, 19.17 mmol) in DMF (8 mL) at −20 °C was added a solution of methyl bromoacetate (2.66 g, 1.70 mL, 17.43 mmol) in DMF (4 mL) drop wise over 10 min. The temperature was maintained at −20 °C during the addition, after which the reaction mixture was allowed to come to room temperature. After 6 h of vigorous stirring, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and the salts were removed by filtration. The filtrate was evaporated under reduced pressure and the resulting oil was loaded onto a flash silica-gel column (100 g). Elution with CH_2Cl_2 (200 mL), followed by CH_2Cl_2/MeOH (95:5), gave a tan oil. Scratching of the oil under ether at −20 °C gave **7** (2.12 g, 4.53 mmol, 78%) as a white solid, mp 113–114 °C, R_f 0.42 (CH_2Cl_2/MeOH 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85 (4, m), 2.91 (8, m), 3.10 (4, m), 3.42 (2, s), 3.48 (4, s), 3.69 (9, s), 9.97 (1, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.3, 48.3, 49.3, 51.4, 51.6, 57.0, 170.6, 171.4. Anal. calcd. for $C_{17}H_{33}BrN_4O_6$: C, 43.50; H, 7.09; N, 11.94. Found: C, 43.25; H, 7.05; N, 12.01.

2-Bromo-*N*-(6-trityl-thiohexyl)acetamide (12)

Bromoacetyl bromide (5.75 g, 2.5 mL, 28 mmol) dropwise was added to a well stirred, ice-cold mixture of amine **10** (5.34 g, 14 mmol) in CH_2Cl_2 (45 mL) and 1 N NaOH (45 mL, 45 mmol). After 45 min, water (25 mL) was added, the layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3×25 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluted with hexanes/EtOAc (6:4) to afford **12** (6.36 g, 12.8 mmol, 92%) as a white solid, mp 78–79 °C, R_f 0.58 (EtOAc/hexanes 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16–1.22 (2, m), 1.23–1.29 (2, m), 1.38 (2, quintet, $J = 7.5$ Hz), 1.48 (2, quintet, $J = 7.5$ Hz), 2.13 (2, t, $J = 7.5$ Hz), 3.19–3.24 (2, m), 3.85 (2, s), 6.41 (1, s), 7.17–7.23 (3, m), 7.25–7.29 (6, m), 7.38–7.41 (6, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.3, 28.4, 28.5, 29.0, 29.3, 31.8, 40.1, 66.4, 126.5, 127.7, 129.5, 144.9, 165.0. Anal. calcd. for $C_{27}H_{30}BrNOS$: C, 65.31; H, 6.09; N, 2.82; S, 6.46. Found: C, 64.93; H, 6.48; N, 2.52; S, 6.84.

[1,4,7-Tris(methoxycarbonylmethyl)-10-[*N*-(6-trityl-thiohexyl)carbamoyl]-1,4,7,10-tetraazacyclo-dodecane (14)

Anhydrous K_2CO_3 (1.10 g, 8 mmol) was added to a stirred solution of **7** (0.94 g, 2 mmol) in dry CH_3CN (20 mL) and the mixture was heated at 70 °C. After 1 h, heating was discontinued, bromoacetamide **12** (1.04 g, 2.1 mmol) was added, heating was resumed, and the reaction mixture was stirred for an additional 1 h at 70 °C. The reaction mixture was cooled and filtered, and the filtrate evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography on silica gel (100 g). Elution with MeOH/CH_2Cl_2 (98:2, 200 mL) followed by MeOH/CH_2Cl_2 (95:5) gave **14** (1.39 g, 1.74 mmol, 87%) as a white foam, R_f 0.52 (CH_2Cl_2/MeOH 5:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14–1.26 (4, m), 1.34–1.40 (2, quintet, $J = 7.5$ Hz), 1.46–1.52 (2, quintet, $J = 7.5$ Hz), 2.15 (2, t, $J = 7.5$ Hz), 2.20–3.30 (24, m), 3.39 (2, s), 3.70 (6, s), 3.72 (3, m), 7.18–7.21 (3, m), 7.26–7.29 (6, m), 7.38–7.40 (6, m), 8.52 (1, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6, 28.5, 28.6, 29.2, 31.9, 39.1, 52.1, 53.3, 55.0, 56.5, 66.2, 126.3, 127.6, 129.4, 144.9, 171.6, 173.4. HRMS (ESI$^+$, m/z) calculated for $C_{44}H_{62}N_5O_7S$ 804.43645; found 804.43563.

[1,4,7-Tris(carboxymethyl)-10-[*N*-(6-trityl-thiohexyl)carbamoyl]-1,4,7,10-tetraazacyclododecane (4)

The triester monoamide **14** (0.80 g, 1 mmol) was added to 1 N KOH solution in EtOH/H_2O (95:5, 20 mL) and the mixture was heated to reflux. After 0.5 h, the solvent was removed under reduced pressure and the residue loaded onto a flash silica-gel column. Elution with CH_2Cl_2 / MeOH / aqueous NH_4OH (5:3:0.3) followed by removal of solvents gave a viscous oil, which was dissolved in a minimal amount of water and freeze-dried. By this procedure, **4** (0.64 g, 0.84 mmol, 84%) was obtained as a white fluffy solid. The ^{1}H NMR, ^{13}C NMR, and mass spectra were in agreement with results of the published procedure.[18]

Crystal Data for Hydrobromide Salt 7

$C_{17}H_{33}N_4O_6Br$, $M_r = 469.38\,g\,mol^{-1}$; colorless block $0.46 \times 0.17 \times 0.14\,mm^3$; $T = 100.31$ K. MoKα, radiation (0.71073 Å); space group $P2_1/c$, unit cell parameters $a = 6.6414(12)$ Å, $b = 6.6414(12)$ Å, $c = 26.354(5)$ Å, $V = 2445.6(7)$ Å^3; 24,826 measured reflections., 8025 unique reflections; final $R1 = 0.0383$ ($F^2 > 2\sigma$), $wR2 = 0.0822$ (all data)

Supporting Information

Complete experimental details, ^1H and ^{13}C NMR spectra of compounds **7, 8**, and **12–17**, and an x-ray crystallographic report for compound **7** can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENTS

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