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The syntheses and applications of β-benzylmercaptoethylamine derivatives

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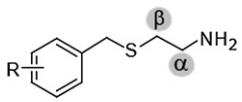
1. Introduction

The β-benzylmercaptoethylamine (β-BMEA) functionality and its derivatives are the most widely used synthons for the incorporation of the cysteamine moiety into many natural and non-natural products. The utility of this functionality arises from distinct advantages, including: ease of preparation, stability, compatibility with diverse reaction conditions, commercial availability, and scope of functional group manipulation through the reactive amine terminal, thioether linkage, or substituents in the aryl ring.

The general structure of these functionalities is represented below (Fig. 1). In accordance with IUPAC nomenclature, the NH_2 group receives priority over thioether, and therefore its attached carbon atom is denoted α. Occasionally this functionality has been referred to in the literature as 2-(benzylthio)ethylamine.



R = H or substitutents

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Figure 1. General structure of β-BMEA derivatives.

Abbreviations: β-BMEA, β-benzylmercaptoethylamine; TFA, trifluoroacetic acid; DCM, dichloromethane; TBAB, tetrabutylammonium bromide; DMF, *N*,*N*-dimethylformamide; CIP, 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate; DIEA, *N*,*N*-diisopropylethylamine; DIPC, *N*,*N*′-diisopropylcarbodiimide; DMAP, 4-dimethylaminopyridine; TEA, triethylamine; THF, tetrahydrofuran; LDA, lithium diisopropylamide; LAH, lithium aluminum hydride; TMSI, trimethylsilyl iodide; DCC, *N*,*N*′-dicyclohexylcarbodiimide; BOP, benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate; *m*-CPBA, *meta*-chloroperoxybenzoic acid; HOBt, 1-hydroxybenzotriazole; HBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HOAt, 1-hydroxy-7-aza-benzotriazole; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; MW, microwave; rt, room temperature.

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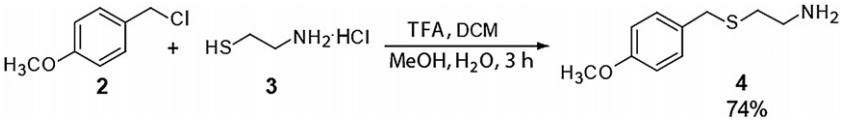
The range of utility of the β-BMEA has spanned from the synthesis of natural products and respective analogs to critical building blocks for the synthesis of heterocycles. Due to the presence of the highly reactive terminal amine, the primary route of synthetic utility stems from a reaction with an amine coupling partner. Apart from their wide ranging applications in organic synthesis, this functionality has been further utilized in a range of applications that span from materials to cosmetics. This functionality has gained traction especially in polydentate metal complexation, due to the presence of both the thioether linkage and amine functionality.[1,2] Recently in our own work, the β-BMEA proved a critical component in the synthesis of a panel of molecules that modulate α-secretase activity.[3] This review is responsive to our observation that despite the utility of the β-BMEA, no comprehensive reviews had been compiled to date. This review will provide a complete overview of currently developed methods for the preparation of β-BMEA derivatives and the wide ranging research of the application of these functionalities in the diverse fields of chemistry.

2. Survey of synthetic procedures

2.1. Acid mediated synthesis

The availability of acid mediated syntheses of β-BMEA has been limited. This is surprising given our own work showing that the reaction pathway likely proceeds via a borderline/S_N1-type reaction.[3] Regardless, Bierbach group reported the acid catalyzed synthesis of β-BMEA derivatives using a strategy entailing the dropwise addition of a solution of 4-methoxybenzyl chloride **2** in dichloromethane to a mixture of 2-aminoethanethiol hydrochloride **3** and trifluoroacetic acid in dichloromethane at 0 °C (Scheme 1). Extraction with a mixture of water and methanol followed by crystallization was the only purification necessary to afford pure β-BMEAs.[4]

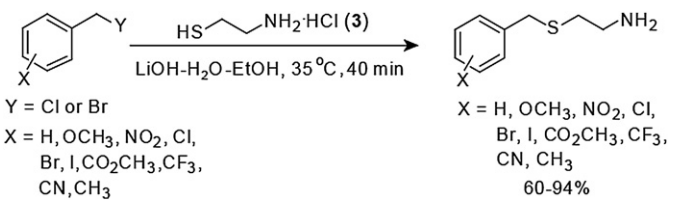


Scheme 1. Synthesis of β-(4-methoxybenzylmercapto)ethylamine **4**.

2.2. Base mediated synthesis

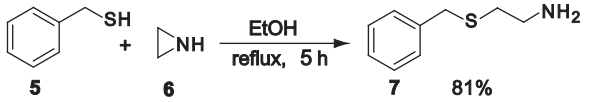
Among all of the synthetic strategies developed so far for the preparation of β-BMEA derivatives, base mediated syntheses dominate the literature. Generally, benzyl halides react with 2-aminoethanethiol hydrochloride in the presence of an alkali metal base in alcoholic solution to furnish the corresponding β-BMEA derivatives. This generalized scheme takes advantage of the enhanced nucleophilicity of the thiol as compared to the amine. Alkali metal bases such as NaOH,[5] NaOMe,[6] NaOEt,[7] Na/liq. NH_3,[8] TBAB–NaOET,[9] and K_2CO_3[10] are typically employed as the base.

Very recently our research group developed a synthetic methodology for the preparation of β-BMEA derivatives employing LiOH as an alkali metal base (Scheme 2).[3] We hypothesized that the general reaction could possibly be proceeding via a borderline/S_N1-type reaction mechanism, in contrast to the prototypical S_N2-type pathway we had originally hypothesized at the outset of the work. Lending support to this hypothesis, we were able to identify high dielectric mixtures of water and ethanol as ideal for smooth conversions. In this strategy, benzyl chlorides/bromides react with cysteamine hydrochloride **3** in the presence of a solution of LiOH in H_2O/EtOH (1:3) mixture at 35 °C in 40 min. After carrying out a number of experiments, we concluded that the varying amounts of water played an important role in both reaction time and yield and the 1:3 ratio of water/ethanol provided a balance between solvent dielectric and substrate solubility for the reaction pathway.



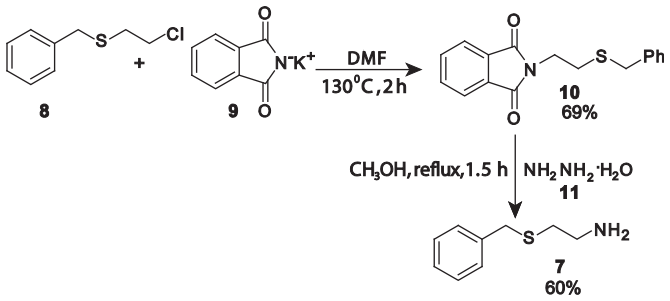
Scheme 2. LiOH mediated synthesis of β-BMEA derivatives.

During the synthesis of β-BMEA **7**, Chu et al. used ethyleneimine **6** as an alternative strategy that opened the aziridine in the process of forming the β-BMEA. In this approach, the ethyleneimine acted as both reagent and catalyst. The reaction between α-toluenethiol **5** and ethyleneimine **6** in absolute ethanol under refluxing condition furnished β-BMEA **7** in 81% yield (Scheme 3).[11]



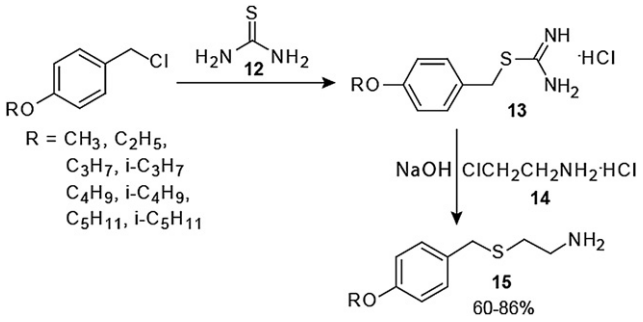
Scheme 3. Ethyleneimine mediated synthesis of β-BMEA.

Reisner et al. reported another base mediated synthetic strategy utilizing a combination of *N*-(β-benzylmercapto)-ethylphthalimide **10** and hydrazine hydrate **11** under refluxing conditions in methanol (Scheme 4).[12] This was a two-step procedure that first involved conversion of the β-benzylmercaptoethyl chloride **8** to the *N*-(β-benzylmercapto)-ethylphthalimide **10** using potassium phthalimide **9** as a reagent, which was followed by reaction with hydrazine hydrate **11** to produce β-BMEA **7**.



Scheme 4. Synthesis of β-BMEA from β-benzylmercaptoethyl chloride.

Thiourea has also been used as an efficient reagent for the synthesis of alkoxy functionalized β-BMEA derivatives **15** in a two-step procedure.[13] First, thiourea **12** is reacted with 4-alkoxybenzyl chlorides to form the corresponding *S*-(4-alkoxybenzyl)isothiourea **13**, which upon treatment with 2-chloroethylamine hydrochloride **14** in the presence of NaOH produced the corresponding β-(4-alkoxybenzylmercapto)ethylamines **15** in good yields (Scheme 5).



Scheme 5. Synthesis of β-(4-alkoxybenzylmercapto)ethylamines.

3. Applications in organic synthesis

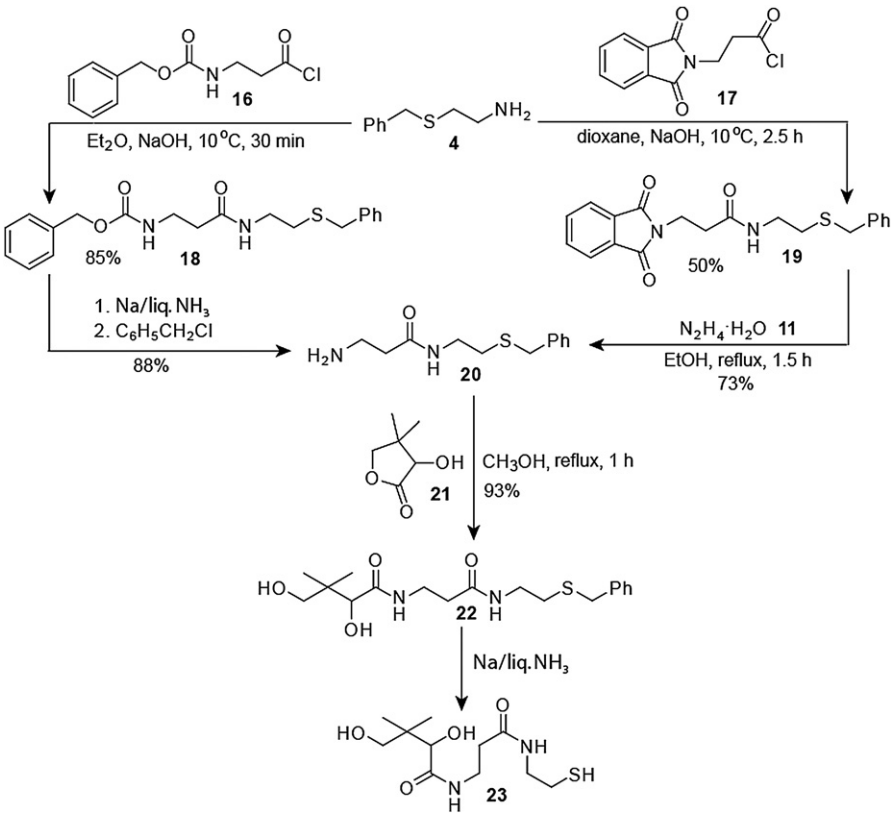
3.1. In the synthesis of natural products and natural product-like molecules

β-BMEA has been used extensively in the synthesis of many natural products, primarily as a synthon for the incorporation of the cysteamine functionality. The broad importance of these functionalities comes from the presence of the highly reactive terminal amine in its role as a nucleophile. Further, the resultant thioether can be readily converted to a thiol through the removal of the benzyl group by number of reagents, e.g., Na/liq. NH_3.

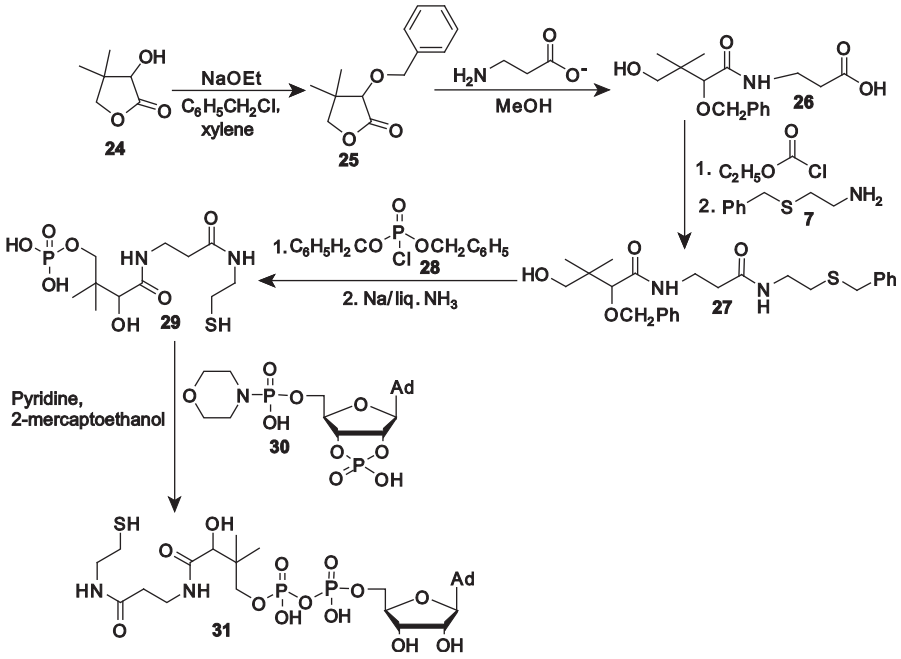
The first example in this section exemplifies the idea of the β-BMEA acting as a cysteamine synthon. Pantetheine **23** is the β-aminoethanethiol amide analog of vitamin B_5 (pantothenic acid) and an intermediate in the production of coenzyme A, a fundamental component of most living systems. During the synthesis of pantetheine and *S*-acetylpantetheine, Walton et al. used β-BMEA extensively as a co-building block.[6] They developed two different synthetic strategies for pantetheine employing β-BMEA to incorporate the cysteamine functionality into the pantetheine moiety (Scheme 6). The main aim for both synthetic strategies was the preparation of an important intermediate, *N*-(β-alanyl)-*S*-benzyl-β-aminoethanethiol **20**. The reaction of β-BMEA **7** and *N*-carbobenzyloxy-β-alanyl chloride **16** produced the corresponding *N*-(*N*-carbobenzyloxy-β-alanyl)-*S*-benzyl-β-aminoethanethiol **18**. The debenzylation and subsequent rebenzylation of **18** produced the intermediate **20**. In another strategy, the reaction between β-BMEA **7** and *N*-phthaloyl-β-alanyl chloride **17** yielded *N*-(*N*-phthaloyl-β-alanyl)-*S*-benzyl-β-aminoethanethiol **19**, which upon treatment with hydrazine hydrate produced the intermediate **20**. The condensation between **20** and (−)-pantolactone **21** yielded *S*-benzyl-pantetheine **22**, which upon debenzylation afforded the desired pantetheine **23**.

Subsequently, Sato et al. developed another synthetic strategy for the synthesis of pantetheine whereby the condensation between methyl D-pantothenate and β-BMEA under their newly developed conditions produced pantetheine in almost quantitative yield.[14]

A large number of synthetic approaches have been developed for the synthesis of coenzyme A after its discovery by Lipmann.[15–17] Coenzyme A is ubiquitous in metabolism, and plays a significant role in at least the synthesis and oxidation of fatty acids, the oxidation of pyruvate, and the transformation of amines to the corresponding acetyl derivatives. Khorana group undertook the total synthesis of coenzyme A and they found that the use of DL-pantetheine-4′ phosphate yielded 3′-dephospho coenzyme A whereas D-pantetheine-4′ phosphate produced coenzyme A and *iso*-coenzyme A.[18] β-BMEA was found to be an active material during the synthesis of DL-pantetheine-4′ phosphate (Scheme 7). First D(−)-pantoyl lactone **24** was benzylated to the corresponding DL-2-*O*-benzyl-pantoyl lactone **25**, which was converted to



Scheme 6. Synthesis of pantetheine.



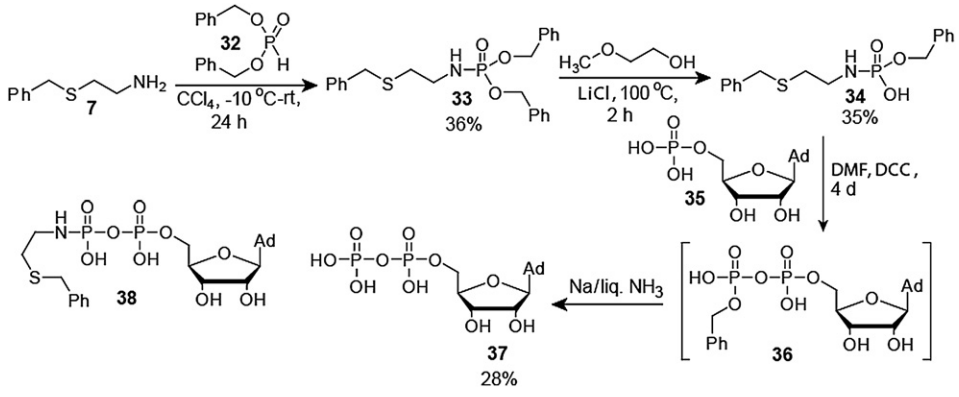
Scheme 7. Synthesis of 3′-dephospho coenzyme A.

DL-2′-*O*,*S*-dibenzyl pantetheine **27** in two steps, followed by the phosphorylation with dibenzylphosphorochloridate **28**. The Na/liq. NH_3 mediated reduction then produced DL-pantetheine-4′ phosphate **29**. The reaction between DL-pantetheine-4′ phosphate **29** and adenosine-5′-phosphoromorpholidate **30** in anhydrous pyridine produced 3′-dephospho coenzyme A **31**, whereas the reaction between D-pantetheine-4′ phosphate and adenosine-5′-phosphoromorpholidate followed by hydrolysis produced coenzyme A and *iso*-coenzyme A. D-Pantetheine-4′ phosphate was prepared by direct phosphorylation of D-pantetheine.

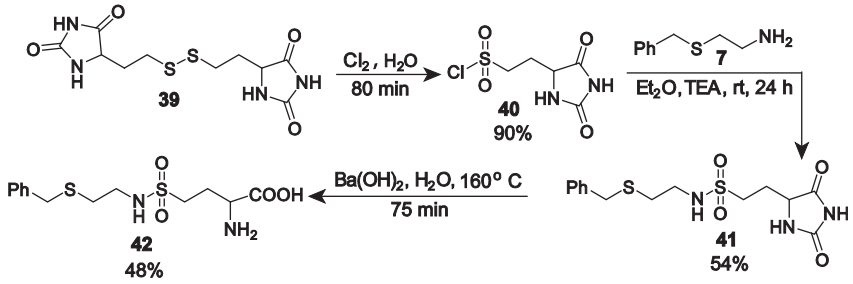
After the first chemical synthesis[18] of coenzyme A, Ikehara and co-workers synthesized analogs of coenzyme A to study the relationship between the structure of coenzyme A and its acylating activities.[19] It was during those studies that he was trying to synthesize one intermediate, P^1-5′-adenosine-P^2-*N*-(2-benzylthioethyl)pyrophosphoramidate **38**, but eventually the ultimate product he isolated was adenosine-5′-diphosphate (ADP) **37** and it was found that β-BMEA could be a reagent of choice for that synthetic strategy. It was hypothesized that the reaction proceeds through the formation of intermediate **36**. β-BMEA was phosphorylated with dibenzyl phosphate **32** to produce dibenzyl *N*-(benzylthioethyl)phosphoramidate **33**, which was further debenzylated to the corresponding monobenzyl derivative **34**. Thereafter, **34** was reacted with the pyridinium salt of adenosine-5′-phosphate **35** in the presence of DCC to yield **36**, which upon treatment with Na/liq. NH_3 furnished the desired ADP **37** (Scheme 8).

Since the pioneering metabolic work on Sulfa drugs by Woods in 1940 various synthetic anti-metabolites have been reported in the literature.[20] During the synthesis of DL-γ-sulfamyl-α-amino acids as potential anti-metabolites, Reisener and co-workers used the β-BMEA functionality as a building block.[12] In this synthetic strategy, homocystine hydantoin **39** was chlorinated to produce 5-(β-chlorosulfonyl)-ethylhydantoin **40**, which upon treatment with β-BMEA, furnished sulfonamido-hydantoin **41**. The hydrolysis of **41** afforded the desired amino acid **42** (Scheme 9).[12]

Interestingly, it has been established that cysteamine is one of the most effective antiradiation agents.[21] During their wide research on the synthesis of potential antiradiation agents, Chu et al. became interested in incorporating the bis(β-thioethyl)amino functionality into uracil using bis(β-benzylmercaptoethyl)amine as a key material in order to prepare pyrimidine derivatives with double-armed cysteamines. Although they made an attempt to

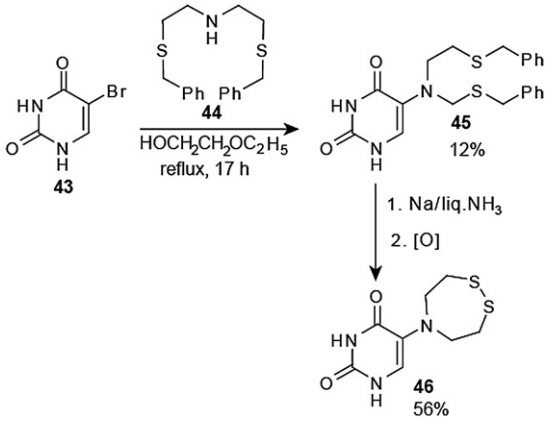


Scheme 8. Synthesis of ADP.



Scheme 9. Synthesis of DL-γ-sulfamyl-α-amino acid.

isolate the desired product 5-[bis(β-mercaptoethyl)amino]uracil, instead they ended up with 1,2-dithia-5-azepane **46** as the final product in good yield. 5-Bromouracil **43** was reacted with bis(β-benzylmercaptoethyl)amine **44** to produce the corresponding 5-[bis(β-benzylmercaptoethyl)amino]uracil **45**, which upon treatment with Na/liq. NH_3 followed by oxidation, yielded 1,2-dithia-5-azepane **46** (Scheme 10).[11]



Scheme 10. Synthesis of 1,2-dithia-5-azepane.

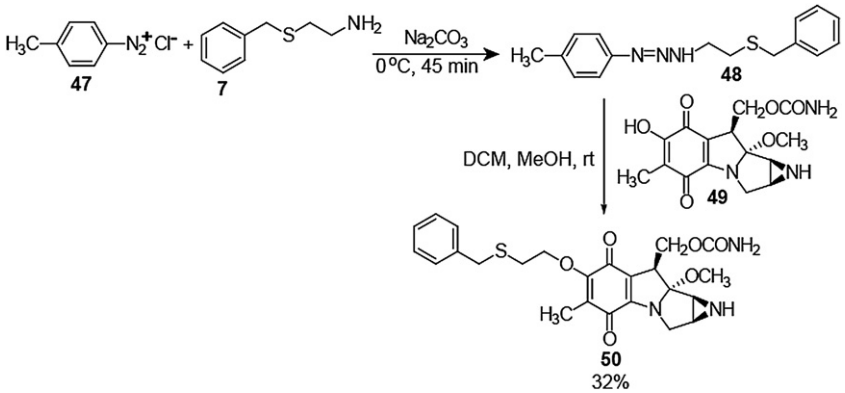
The mitomycins are a family of aziridine-containing natural products that bind covalently to DNA and are related chemically by a common structural nucleus, which has been assigned the name *mitosane*.[22] In particular, mitomycin A and its analogs have been found to posses antitumor activity.[23] Vays et al. developed a triazene-assisted alkylation strategy for the synthesis of mitomycin A and its analogs.[24] Eventually, they synthesized one mitomycin A analog based on β-BMEA (Scheme 11).[16] Reaction between *p*-toluenediazonium chloride **47** and β-BMEA **7** produced the corresponding triazene **48**,[25] which upon treatment with 7-hydroxy-9a-methoxymitosan **49**, furnished the desired β-BMEA-based mitomycin A analog **50**.

(−)-Mirabazole C was isolated by Moore group from *Scytonema mirabile* (Dillwyn) Bornet (strain BY-8-1).[26] It is a tetrathiazoline marine alkaloid and contains four consecutive thiazoline/thiazole rings. Two different synthetic strategies have been reported for the synthesis of (−)-mirabazole C using β-BMEA as an important co-building block.[27,28] The Kiso lab reported the convergent synthesis of (−)-mirabazole C[28] and showed that the use of β-BMEA was essential for the fabrication of the fourth thiazoline ring. Coupling of β-BMEA **7** with *N*-(carbobenzyloxy)-*S*-benzyl-(*R*)-2-methyl-cysteine **51** yielded the intermediate, *S*-protected-2-methyl-cysteine amide **52**, which was converted to another intermediate **53**. Subsequently, **53** was converted to the corresponding tetrathiol derivative **54**, which upon treatment with $TiCl_4$, produced the dihydromirabazole C **55** followed by the treatment with NiO_2 yielded the desired (−)-mirabazole C **56** (Scheme 12).

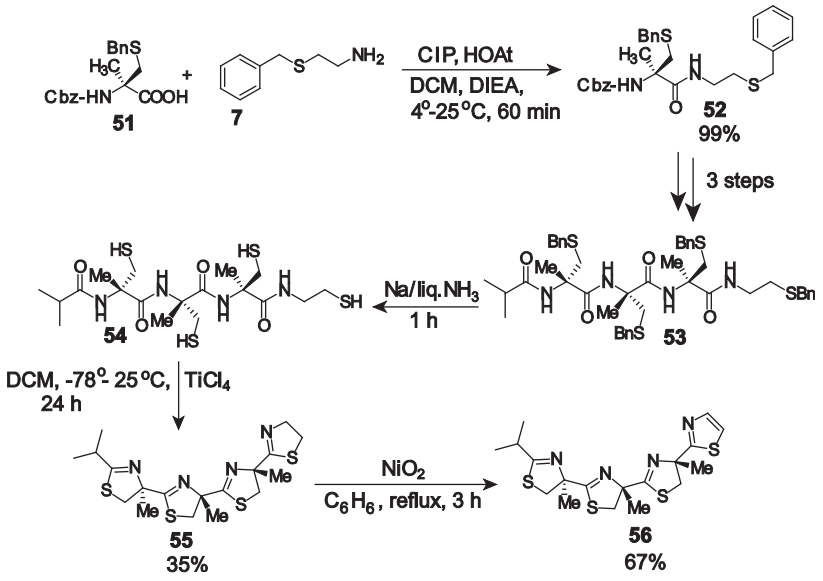
The Schreiber lab reported an efficient multistep synthetic strategy for the synthesis of a library of natural product-like small molecules.[29,30] During the course of reactions shikimic acid **57** was first converted to the iodobenzyl tetracycle **58** in a number of steps. This tetracycle **58** was then converted into the corresponding alkyne derivative **59** through a palladium-mediated cross-coupling reaction. Next, the alkyne derivative was treated with a number of various amines to produce γ-hydroxyamides. They found that β-BMEA could be used as an efficient amine component, which produced the corresponding γ-hydroxyamide **60**. Finally, these γ-hydroxyamides were converted to the corresponding γ-acyloxy amides **61** having structural features reminiscent of natural products (Scheme 13).

3.2. In the synthesis and derivatization of heterocycles

Apart from their wide applications in the synthesis of natural products or natural product-like molecules, β-BMEA derivatives



Scheme 11. Synthesis of mitomycin A analogs.



Scheme 12. Synthesis of (−)-mirabazole C.

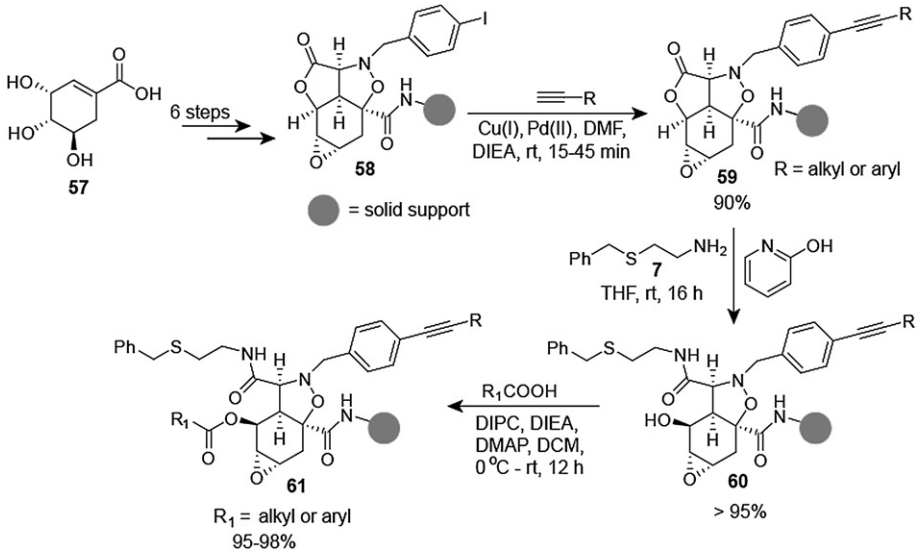
have been used extensively for the synthesis of many heterocyclic compounds.

3-(3-Hydroxyphenyl)-*N*-*n*-propylpiperidine (3-PPP) and 3-(3-hydroxyphenyl)-*N*-(2-phenylethyl)piperidine (phenethyl 3-PPP) are dopamine autoreceptor agonists.[31–34] Weintrab and co-workers were aiming to synthesize the thio-analogs of these two important heterocycles, based on the hypothesis that the structural modification might lead to the discovery of a more potent compound or a compound with a longer duration of action. During the synthesis of the analog of phenethyl 3-PPP, they used β-(3-methoxybenzylmercapto)ethylamine **62** as a key building block. The amine **62** was reacted with phenacetyl chloride **63** to yield the amide **64**, which upon treatment with borane–dimethylsulfide, produced the amine **65**. The reaction of **65** with methyl chloroformate yielded the corresponding urethane derivative **66**, which was converted to an amide **67** in the presence of LDA. The LAH reduction of **67** in diethyl ether yielded an important intermediate **68**, which upon treatment with TMSI in refluxing chloroform produced the desired analog of phenethyl 3-PPP, **69** (Scheme 14).[35]

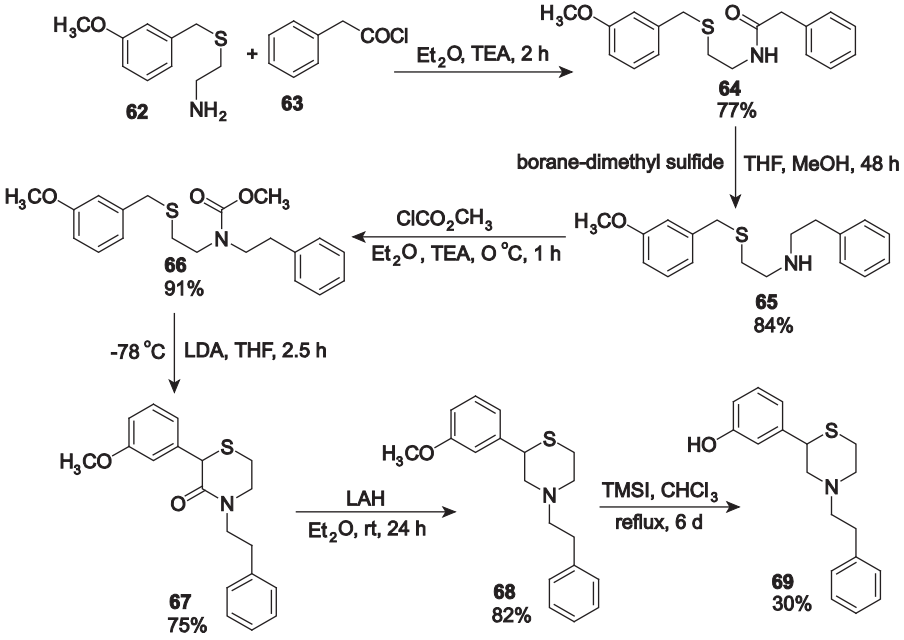
Ishikawa et al. introduced an excellent synthetic strategy for the preparation of thiomorpholines using β-BMEA as a key building block.[36] Initially β-BMEA **7** was reacted with benzaldehyde and ethyl chloroformate to furnish the intermediates **70** and **71**, respectively. After LDA treatment of both the intermediates, two different thiomorpholine derivatives **72** and **73** were obtained (Scheme 15).

N-Substituted-9-acridinamine derivatives are important class of heterocyclic bioactive molecules.[37,38] Roubaud et al. synthesized novel β-BMEA-based *N*-substituted-9-acridinamine derivative with a pendant polymerizable side chain for studies on polymers with biological activities.[39] By following a number of steps, 2-bromo-5-methoxybenzoic acid **74** was converted to an important intermediate **75**, which upon treatment with β-BMEA in the presence of triethylamine and phenol at 80 °C yielded the desired *N*-substituted-9-acridinamine derivative **76** (Scheme 16).

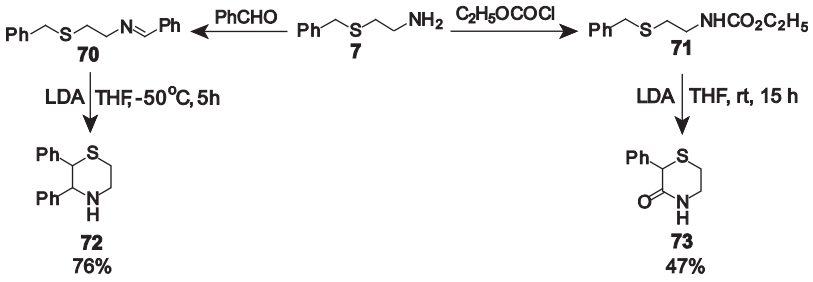
Pascal et al. synthesized one tripodal β-BMEA derivative as precursor of an amide-based 2,15,28-trioxo-3,16,29-triaza-6,19,32-trithia-[7.7.7](1,3,5)cyclophane **79** in order to mimic the anion



Scheme 13. Synthesis of natural product-like compounds.

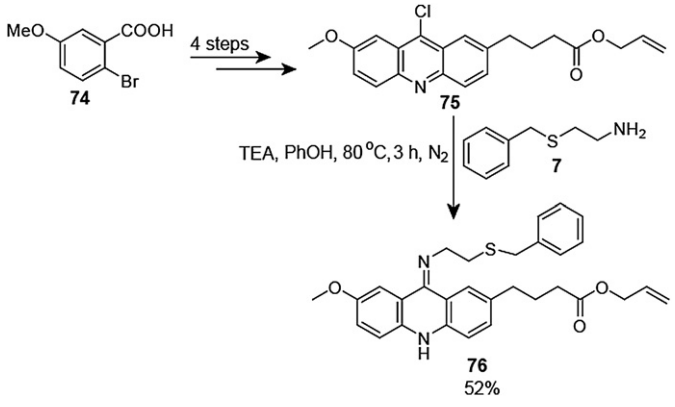


Scheme 14. Synthesis of a phenethyl 3-PPP analogue.



Scheme 15. Synthesis of thiomorpholine derivatives.

complexation mode of the sulfate binding protein of *Salmonella typhimurium*.[40] They hypothesized that this neutral organic macrocycle might form hydrogen bonds with an encapsulated inorganic anion. The tripodal amine **77** was reacted with the tri-acid chloride **78** in THF under refluxing conditions to yield the macrocycle **79** (Scheme 17). From X-ray crystallographic analysis, they determined that the cavity size of **79** should be suitable to fit small anions such as fluoride and hydroxide. They further postulated that the amide groups were well oriented to form strong hydrogen bonds with an encapsulated anion.

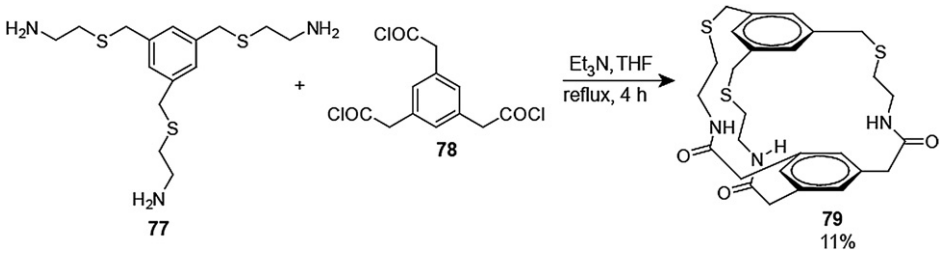


Scheme 16. Synthesis of an *N*-substituted-9-acridinamine derivative.

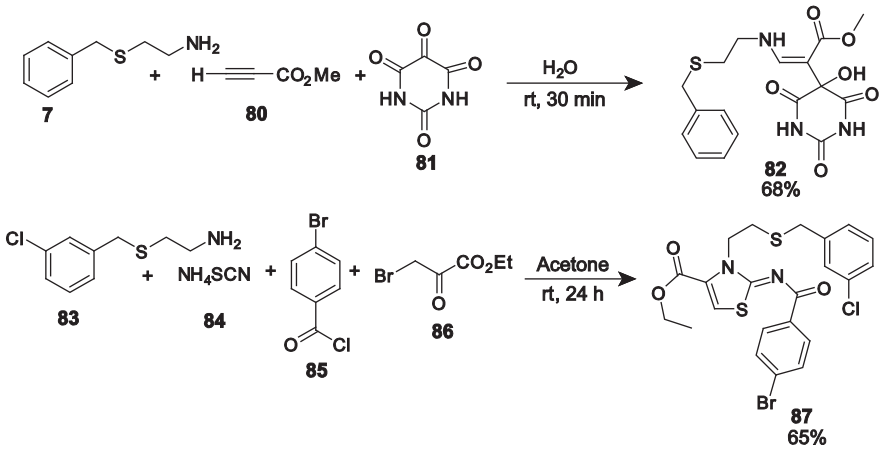
Our group recently reported[3] the utility of β-BMEAs as building blocks for several multi-component reactions (MCRs), which led to the synthesis of the analogs of many biologically active heterocycles like barbiturates[41,42] and thiazoles.[43–46] Following literature procedures,[47,48] the reaction between β-BMEA **7**, methyl propiolate **80**, and alloxan **81** in water yielded the desired barbiturate derivative **82**, whereas the reaction between β-(3-chlorobenzylmercapto)ethylamine **83**, ammonium thiocyanate **84**, 4-bromobenzoyl chloride **85**, and ethyl bromopyruvate **86** in acetone produced thiazole derivative **87** (Scheme 18).

3.3. Diverse applications in organic synthesis

Synthetic podands are open-chain multidentate ligands, which behave like crown ethers, for which a number of synthetic strategies have been developed for large scale preparation. Nature also produces many excellent podands such as monensin, lasalocid, etc.[49] Kumar et al. designed and synthesized a number of podands with two uracil units linked at N-3 with various spacers containing flexible chains with varied terminal binding sites at N-1. 6-Methyl-1,3-oxazine-2,4(3*H*)-dione **87** was reacted with bis(2-bromoethyl) ether **88** to produce intermediate **89**, which upon heating with β-BMEA, furnished the corresponding podand **90** (Scheme 19).[50] They



Scheme 17. Synthesis of (1,3,5)cyclophane.

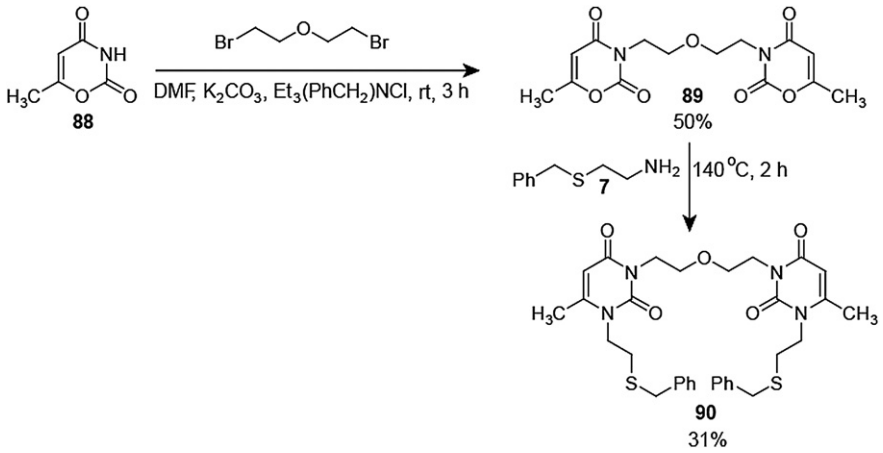


Scheme 18. Synthesis of heterocycles through MCRs.

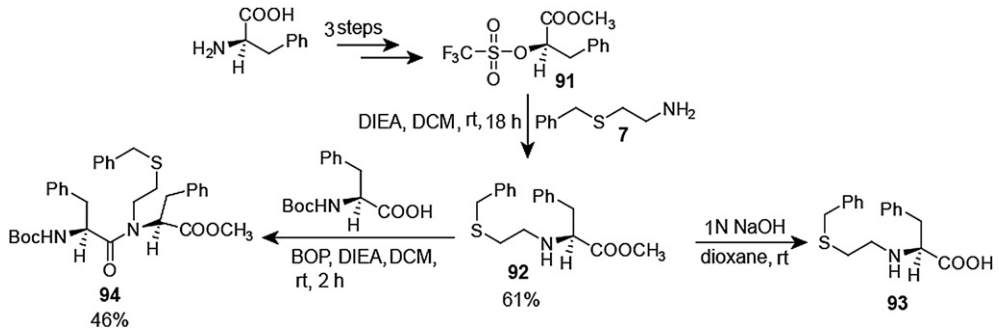
observed that the presence of two sulfur atoms as ligating sites makes the podand **90** more lipophilic and helps to extract and transport metal cations more efficiently.

Bitan et al. has applied β-BMEAs extensively in peptide chemistry.[51] Upon synthesis of a new family of amino acids containing an ω-thioalkylene group on the N^{α}-amino nitrogen by alkylation of ω-thioalkylamines with triflates of α-hydroxy acid **91**, they reported that β-BMEAs efficiently reacted with triflates to produce the corresponding N^{α}-(ω-thioalkylene)amino acid methyl esters **92**. The hydrolysis of these methyl esters yielded the corresponding N^{α}-(ω-thioalkylene)amino acid **93**. The protected N^{α}-(ω-thioalkylene)amino acid was subsequently used for the synthesis of peptide **94** (Scheme 20).

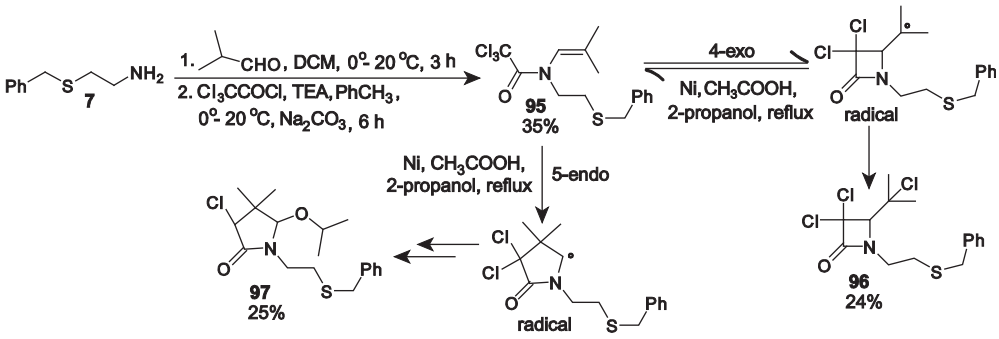
Radical cyclization reactions have been well investigated in organic synthesis[52] and they have been used extensively in natural product synthesis.[53] Cassayre et al. used a nickel powder and acetic acid mixture as an efficient reacting system to investigate the 4-*exo* versus 5-*endo* competitive cyclizations of *N*-alkenyltrichloroacetamides.[54] During those studies, they synthesized β-BMEA-based trichloroacetamide **95** as one of the starting materials. When they treated **95** with nickel powder and acetic acid in refluxing 2-propanol, they isolated 24% of β-lactam **96** (formed through 4-*exo* radical cyclization), and 25% of γ-lactam **97** (formed through 5-*endo* radical cyclization) (Scheme 21). In this case, the benzyl group did not act as an internal trap of the radical.



Scheme 19. Synthesis of β-BMEA-based podand.



Scheme 20. Synthesis of β-BMEA-based amino acids and peptides.

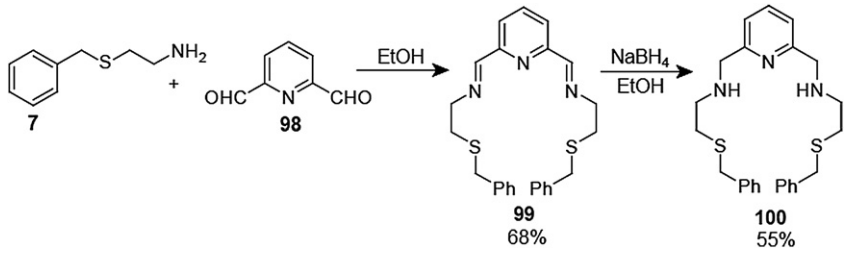


Scheme 21. Synthesis of β- and γ-lactam.

It has been reported that the ferric ion is coordinated with two nitrogen atoms, three thiolates, and a water molecule in octahedral geometry in the metal center of nitrile hydratase.[55] Therefore, there is a growing interest in the preparation of such pentadentate mixed N/S dithiolate ligands because these are expected to form octahedral ferric complexes of biomimetic importance. Because of the facile oxidation of thiol and thiolate compounds to the corresponding disulfide, the synthesis of these compounds requires thiol protection. When Zhang et al. synthesized a series of pentadentate mixed N/S dithiolate ligands, they synthesized one β-BMEA-based pentadentate ligand **100**.[56] The condensation between β-BMEA **7** and 2,6-pyridinedialdehyde **98** produced the corresponding imine **99**, which upon treatment with $NaBH_4$, yielded the pentadentate ligand **100** (Scheme 22).

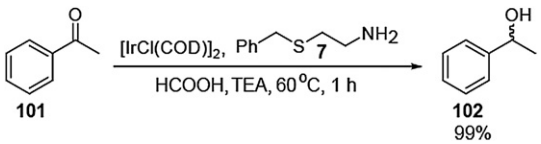
use of β-BMEA resulted in the formation of the most active catalyst (Scheme 23). Subsequently, they introduced various substituents in the carbon backbone of β-BMEA to synthesize a number of optically active ligands.

Masip et al. developed an excellent synthetic strategy toward a library of compounds containing 3-oxopiperazinium or perhydro-3-oxo-1,4-diazepinium moieties.[58] Upon the screening of the library of cyclic tetraalkylammonium derivatives, they found that these compounds can block vanilloid receptor TRPV1 and modulate the multidrug resistance phenomenon. During their synthetic studies, β-BMEA was found to be an efficient primary amine containing an aromatic residue. The synthetic pathway involved a homogeneous phase combined with a solid-phase scavenger for removing excess of reagents. The amine was initially reacted with



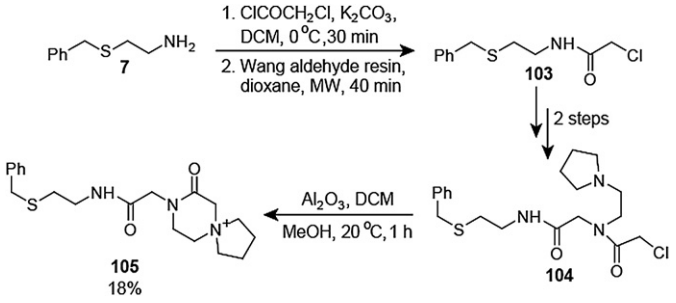
Scheme 22. Synthesis of pentadentate mixed N/S dithiolate ligands.

Optically active secondary alcohols have been widely used not only as an important class of intermediates for fine chemicals, but also in pharmaceuticals. Petra et al. developed iridium(I)-catalyzed asymmetric hydrogen transfer reactions of unsymmetrical ketones to furnish optically active secondary alcohols using a new class of efficient catalysts.[57] During this development, they first screened a series of achiral nitrogen-containing ligands and found that the



Scheme 23. Hydrogen transfer reactions of unsymmetrical ketones.

chloroacetyl chloride to produce the corresponding amide **103**, which was converted to an intermediate **104** following two steps. Finally, **104** was cyclized to the corresponding 3-oxopiperazinium derivative **105** (Scheme 24). The perhydro-3-oxo-1,4-diazepinium derivatives were subsequently synthesized following the same general synthetic pathway.

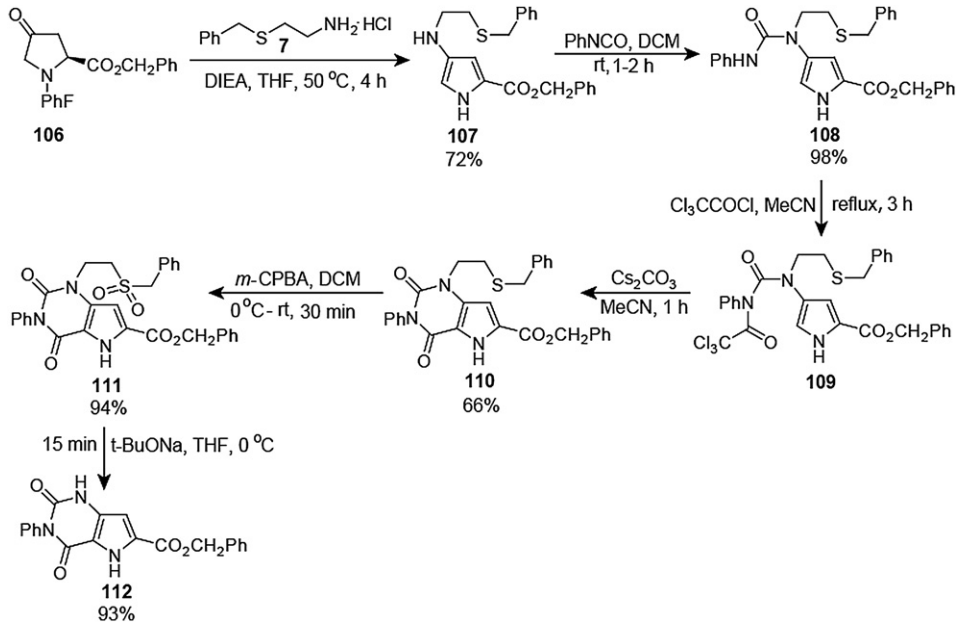


Scheme 24. Synthesis of 3-oxopiperazinium derivative.

Purines and pyrimidines are two of the main building blocks of nucleic acids; consequently they play important roles in cellular systems. The structural resemblance of pyrrolo[3,2-*d*]pyrimidines to purines and pyrimidines makes the former a key lead structure for biological investigations. For example, 3-(2,3-dimercaptopropyl)-substituted pyrrolo[3,2-*d*]pyrimidines have been found to be matrix metalloproteinase inhibitors,[59] and Rombouts et al. subsequently developed solid-phase methodology for the synthesis of analogs.[60] The solid-phase synthesis of pyrrolo[3,2-*d*]pyrimidine requires an effective linker, which will attach the 4-aminopyrrole-2-carboxylate to the resin prior to an acylation step using different isocyanates in order to introduce diversity at the N3 pyrimidine nitrogen.

Rombouts et al. showed that their cysteamine linking strategy was promising in the solid-phase synthesis in terms of yield as well as ease of cleavage of the desired products from the solid support. The main feature of this synthetic strategy is the ease of removal of the cysteamine 'traceless' linker. They first assessed the feasibility of this cleavage in solution phase synthesis with subsequent implementation in the solid-phase synthesis. The pyrrolo[3,2-*d*]pyrimidine derivatives were synthesized in solution phase starting from 4-oxo-*N*-(PhF)prolinate **106**. β-BMEA was subsequently reacted to yield the pyrrole derivative **107**, which upon acylation with phenyl isocyanate produced the corresponding ureidopyrrole **108**. This was converted to the corresponding β-BMEA-based pyrrolo[3,2-*d*]pyrimidine **110** through an intermediate **109** in two steps. Finally the oxidation of **110** with *m*-CPBA followed by the treatment with sodium *tert*-butoxide yielded the desired pyrrolo[3,2-*d*]pyrimidine **112** (Scheme 25). After a successful solution phase strategy, they started and completed the solid-phase synthesis of pyrrolo[3,2-*d*]pyrimidines.

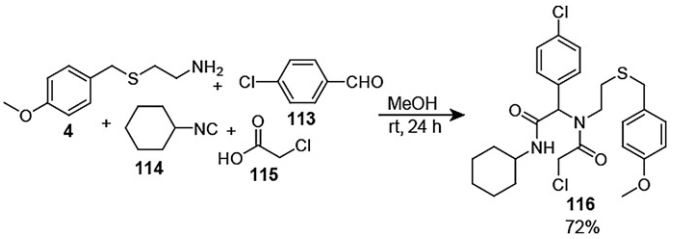
Recently our group has shown that β-BMEA derivatives can be used as efficient amine component in four-component Ugi reaction.[3] The Ugi reaction is one of the most popular multicomponent reactions[61,62] exploited to develop chemical libraries. We envisioned that the use of β-BMEA derivatives would result a new chemical library of compounds. For example, β-(4-methoxybenzylmercapto)ethylamine **4**, 4-chlorobenzaldehyde **113**, cyclohexyl isocyanide **114** and chloroacetic acid **115** yielded the corresponding desired bis-amide **116** through a one-pot condensation (Scheme 26).



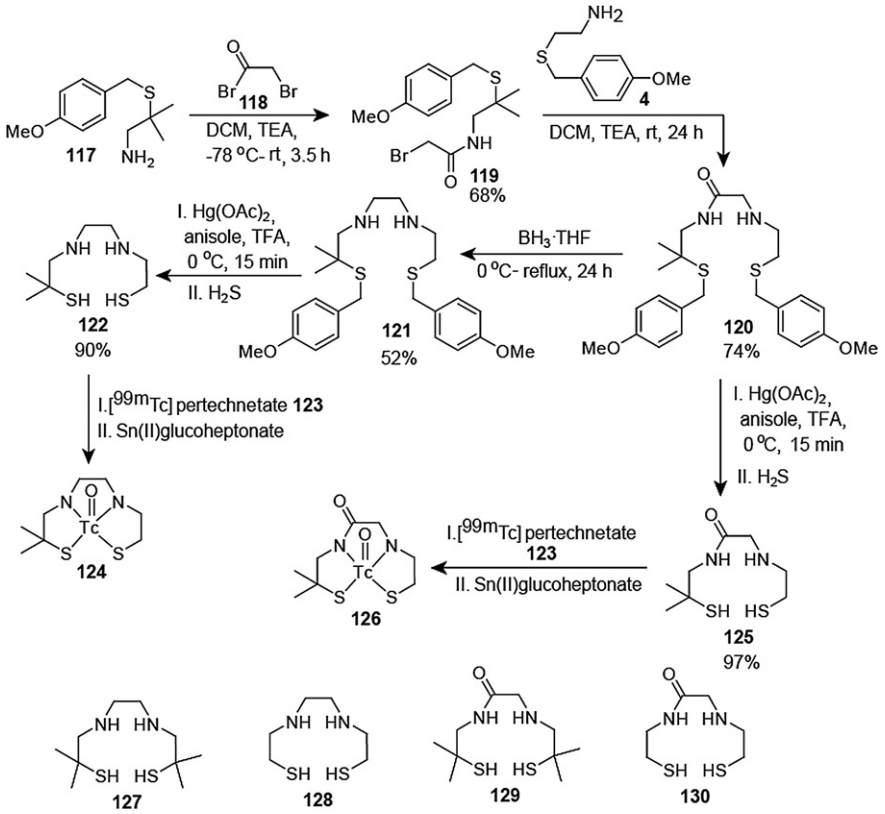
Scheme 25. Solution phase synthesis of a pyrrolo[3,2-*d*]pyrimidine derivative.

4. Applications in medicinal and cosmetic chemistry

As already stated, β-BMEA is an *S*-benzyl protected aminoethanethiol with a spacer of two carbons. Both the nitrogen and sulfur



Scheme 26. Ugi four-component reaction.



Scheme 27. Synthesis of BAT ligands and their ^{99m}Tc complexes.

atoms of β-BMEA can effectively coordinate metals to form the corresponding metal complexes. When two units of β-BMEA are integrated together, they can form very stable, neutral, lipophilic tetradentate bisaminoethanethiol (BAT, N_2S_2) ligands. Those ligands have been used extensively to synthesize metal complexes with Technitium-99m (^{99m}Tc), a metastable nuclear isomer of Technitium-99.[63–67] Technetium-99m (^{99m}Tc) has been extensively used as radionuclide for in vivo imaging studies in nuclear medicine.[68] The following examples will illustrate how the β-BMEA functionality plays a central role in fine tuning a number of N_2S_2 ligands. Apart from the synthesis of ^{99m}Tc-binding ligands, β-BMEA derivatives have also been used widely for the synthesis of histaminergic compounds.[69,70]

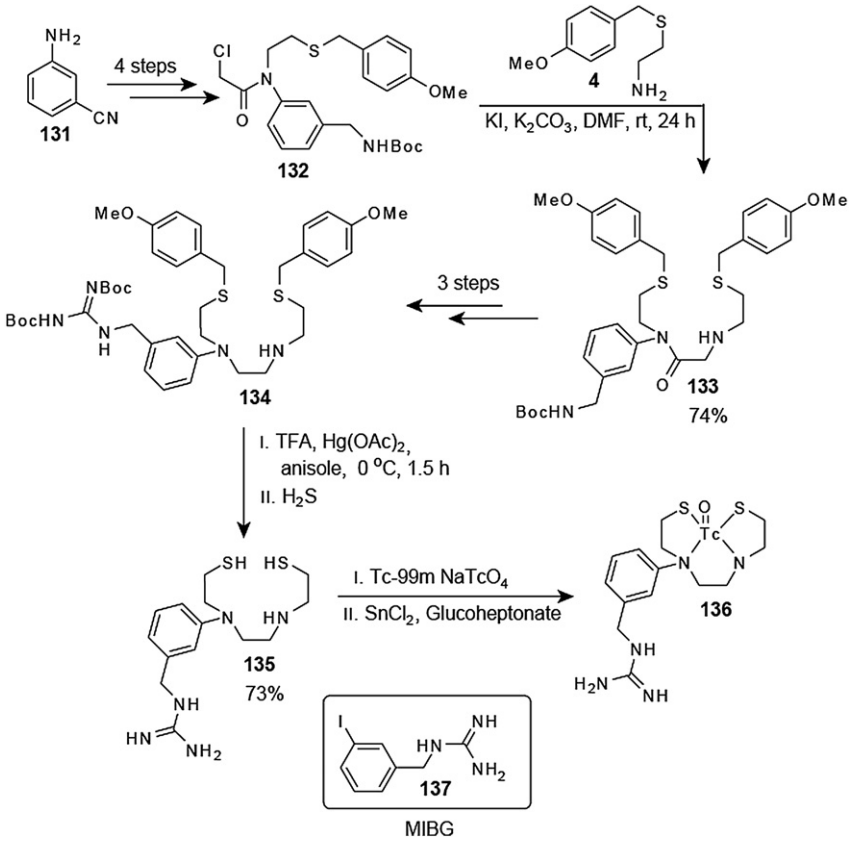
^{99m}Tc and bisaminoethanethiol (BAT, N_2S_2) complexes have been identified as some of the few potential brain perfusion imaging agents due to their ability to form neutral, stable, and lipophilic complexes. Kung group developed the synthesis of a number of BAT ligands with *gem*-dimethyl and amide groups and utilized those to make the corresponding neutral ^{99m}Tc complexes. Finally, the relative stabilities and brain uptakes of those complexes were examined thoroughly.[5] During the synthesis of BAT ligands (**122**, **125**, **127**–**130**), they identified β-(4-methoxybenzylmercapto)ethylamine **4** and another β-BMEA derivative **117** as key building blocks. The reaction between **117** and bromoacetyl bromide **118** produced intermediate 2-bromoethylamide derivative **119**, which was again reacted with **4** to yield the intermediate **120**. In order to get the amide-free ligand, **120** was treated with borane–THF complex to get the intermediate **121**. Finally, the desired ligands **122** and **125** were obtained by the removal of the *p*-methoxybenzyl group (Scheme 27). Radiolabeling of each ligand was done by ligand-exchange reaction with [^{99m}Tc]pertechnetate **123**, reduced by Sn(II)glucoheptonate. Interestingly, they observed that the ligands with amide functionality possessed better stability, but their ^{99m}Tc complexes displayed lower brain uptakes compared to those of non-amide ligands (Scheme 27).

Radioactive-iodine-labeled *m*-iodobenzylguanidine (MIBG) **137** is used as an in vivo imaging agent to detect certain types of tumors such as pheochromocytomas. Continuing their research on the synthesis and biological evaluation of ^{99m}Tc complexes, Kung group synthesized a series of MIBG derivatives containing suitable chelating groups, N_2S_2, in order to prepare $[Tc^{v}O]^{3+}$–N_2S_2 and ^{99m}Tc-labeled complexes.[71] In vivo studies on those compounds revealed that the iodine of MIBG could be replaced by a $[Tc^{v}O]^{3+}$–N_2S_2 complex.

During the synthesis of N_2S_2 ligand, they used β-(4-methoxybenzylmercapto)ethylamine **4** as one of the important building blocks (Scheme 28). 3-Aminobenzonitrile **131** was converted to **132** in four steps, which was reacted with **4** to produce the intermediate **133**, which was converted to **134** in three steps. Finally, the debenzylation of **134** produced the desired MIBG derivative **135**. This was used to synthesize the ^{99m}Tc complex **136** and subsequently evaluated as an imaging agent (Scheme 28).

Okarvi et al. reported another application of a β-BMEA central building block to fine tune the structure of N_2S_2 ligands.[72] ^{99m}Tc-MAG_3 (^{99m}Tc-mercaptoacetyltriglycine) **139** is already a well known replacement for ^{131}I-OIH (^{131}I-Hippuran) in renal functional studies. This is a polar, negatively charged complex and the oxotechnetium(V) core is bound to three nitrogen atoms and one sulfur atom of MAG_3 **138** (Fig. 2).[73]

Ease of renal excretion is one of the major characteristics of a clinical nuclear medicine and many attempts have been made to achieve that. Okarvi et al. synthesized a number of *S*-protected MAG_3 derivatives in which the terminal carbonylglycine sequence was substituted by an oxamide moiety (Scheme 29) and subsequently studied the effect of modification of carbonylglycine sequence on the renal handling characteristics.[72] Interestingly, they found that the oxamide derivative **144**, in which S-protection was done with β-(4-methoxybenzylmercapto)ethylamine **4**, showed excellent renal handling properties. Reaction of glycylglycinebenzyl



Scheme 28. Synthesis of MIBG derivative and its ^{99m}Tc complex.

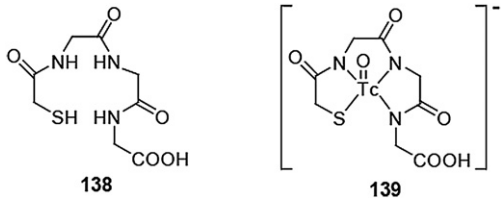
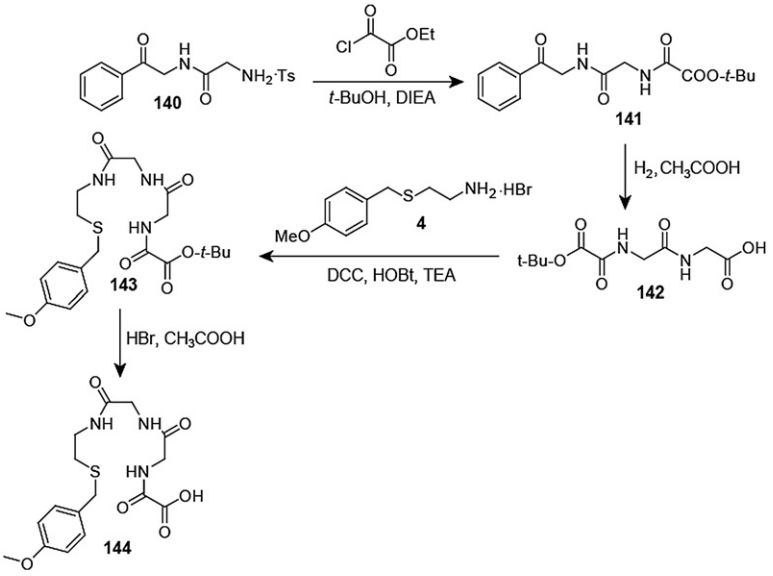


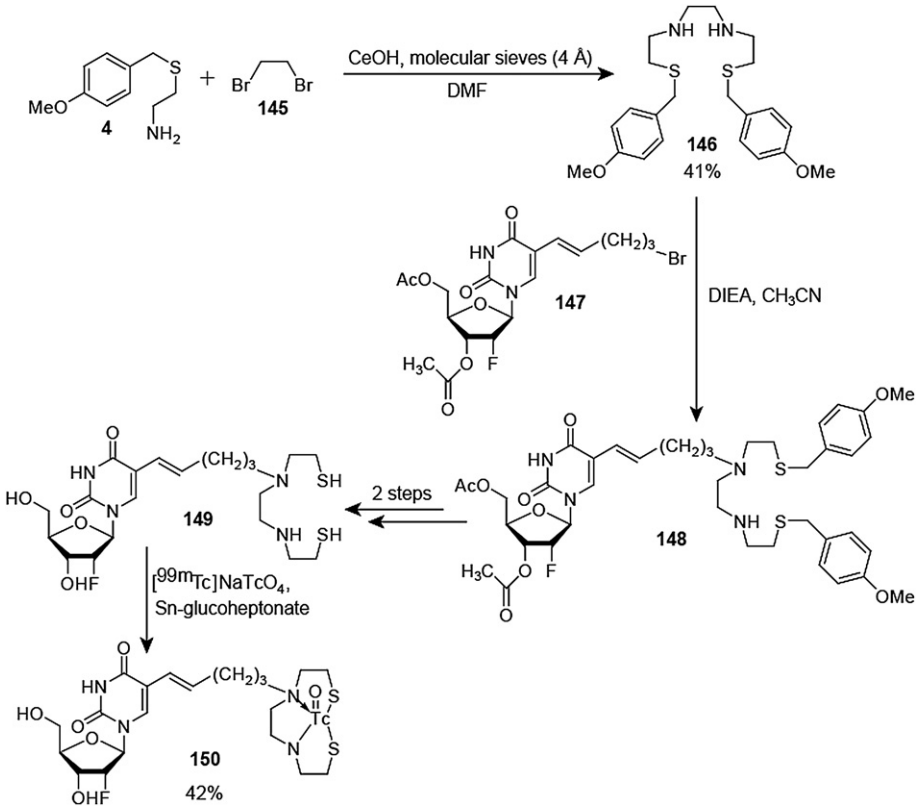
Figure 2. Structure of MAG_3 and ^{99m}Tc-MAG_3.

ester *p*-toluenesulfonate **140** with ethyloxalyl chloride and *tert*-butanol followed by hydrogenation afforded the intermediate **142**. The reaction between **142** and β-(4-methoxybenzylmercapto) ethylamine **4** yielded the intermediate *tert*-butyl ester derivative **143**, which was hydrolyzed to the corresponding oxamide derivative **144** (Scheme 29).

Zhang et al. described another potential use of β-(4-methoxybenzylmercapto)ethylamine **4** in the synthesis of a ^{99m}Tc-labeled thymidine analog.[74] Following a convergent synthetic strategy, the N_2S_2 radiometal chelator **146** was used to synthesize the {2-[5-(2′-



Scheme 29. Synthesis of an MAG_3 derivative.

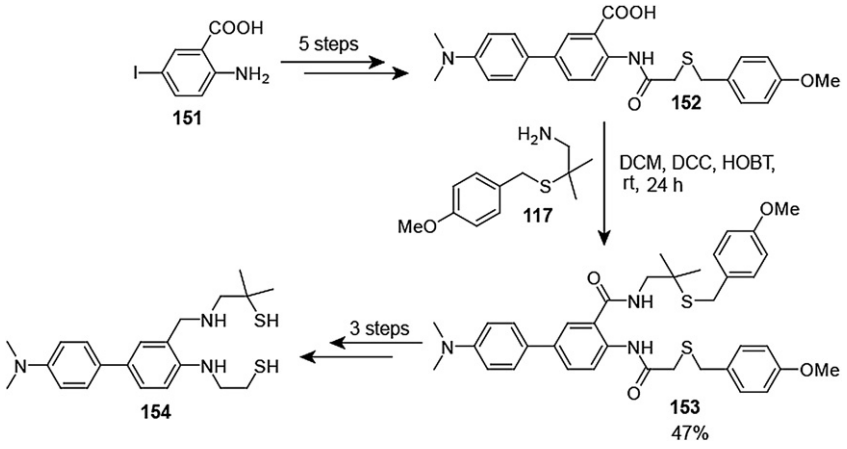


Scheme 30. Synthesis of FTcAU.

fluoro-2′-deoxyuridin-5-yl)-pent-4(*E*)-enyl][2-(2-mercaptoethyl)-aminoethyl]aminoehanethiolato(3)-*N*,*N*′,*S*,*S*′}oxo-[^{99m}Tc]technetium(V), (FTcAU), a viral thymidine kinase (HSV1-TK) substrate. β-(4-Methoxybenzylmercapto)ethylamine **4** was reacted with dibromoethylene **145** to produce the diamine **146**, which was coupled with thymidine analog **147** (synthesized from 2′-fluoro-2′-deoxyuridine in four steps) to furnish **148**. This intermediate was converted to the corresponding N_2S_2 radiometal chelator **149** in two steps. Finally, **149** was used to prepare the target compound FTcAU **150** (Scheme 30).

The formation and accumulation of amyloid beta (Aβ) plaques in the brain play an important role in developing Alzheimer's disease. Zhuang et al. prepared several biphenyl derivatives containing N_2S_2 (BAT)-chelating groups and used for the synthesis of ^{99m}Tc-labeled N_2S_2–biphenyl derivatives. Finally, these derivatives were used as diagnostic imaging agents for the detection of Aβ plaques.[75] During the synthesis of these N_2S_2 ligands, they used β-BMEA derivatives extensively as important building blocks. As a representative example, 2-amino-5-iodo-benzoic acid **151** was converted to an acid **152** in five steps, which was then coupled with the β-BMEA derivative **117** to produce the diamide **153**. The diamide **153** was subsequently converted to the desired ligand **154** in three steps (Scheme 31). Finally, **154** was complexed with ^{99m}Tc to form the corresponding ^{99m}Tc-labeled diagnostic imaging agent.

Tropane is a bicyclic nitrogen-containing heterocyclic compound. In order to reduce the molecular weight of ^{99m}Tc-labeled tropanes, Cleynhens et al. showed the potential applications of β-BMEA derivatives during the synthesis of tropane–BAT ligands



Scheme 31. Synthesis of biphenyl–BAT ligand.

(Fig. 3) as well as their ^{99m}Tc complexes. Eventually, they found that these ^{99m}Tc-tropane–BAT complexes are potential dopamine transporter tracers.[66,67]

Nicolaou et al. reported a structure–activity relationship (SAR) on the Psammaplin A targeted toward methicillin-resistant *Staphylococcus aureus* (MRSA).[78] In this study, they probed the functional

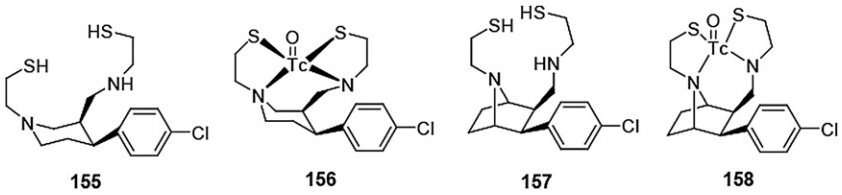


Figure 3. Structure of tropane–BAT ligands and a ^{99m}Tc-tropane–BAT complex.

Impromidine **159** is a highly potent and specific histamine H_2-agonist (Fig. 4).[76] Buschauer et al. replaced the 5-methyl-4-imidazolyl group of impromidine with a phenyl group and tested

importance of the disulfide moiety by synthesizing a number of homo- and heterodimeric molecules having no disulfide functionality. In their study β-BMEA was used as the thioether-containing

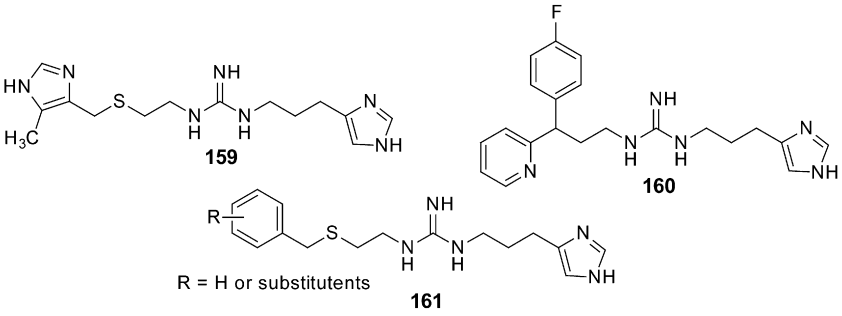
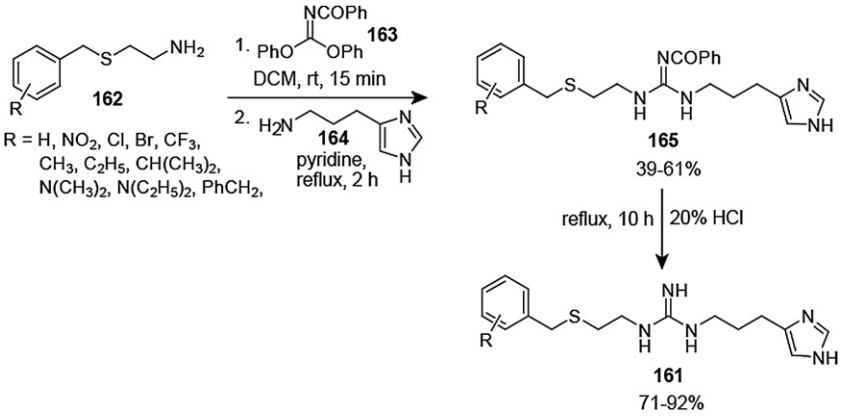


Figure 4. Structure of impromidine, arpromidine, and impromidine analogs.

the H_2-agonistic and H_1-antagonistic activities.[77] Arpromidine **160** is another well studied potent H_2-agonist and H_1-antagonist that is approximately four times more potent than the corresponding parent compound unsubstituted at the phenyl nucleus. A series of phenyl analogs of impromidine were synthesized, and the substitution pattern of the aromatic ring in **161** was studied with regard to the structure–activity relationships known from the arpromidine series. To synthesize this library, Buschauer et al. used β-BMEA derivatives as key building blocks (Scheme 32). β-BMEA derivatives **162** were reacted with diphenyl benzoylcarbonimidate

primary amine coupling partner to synthesize the analog **169**, which was subsequently assayed for antibacterial activity. The disulfide containing lead compound **170** was far more active than **169**, revealing the fact that the disulfide motif plays a key role in the biological activity of these compounds.

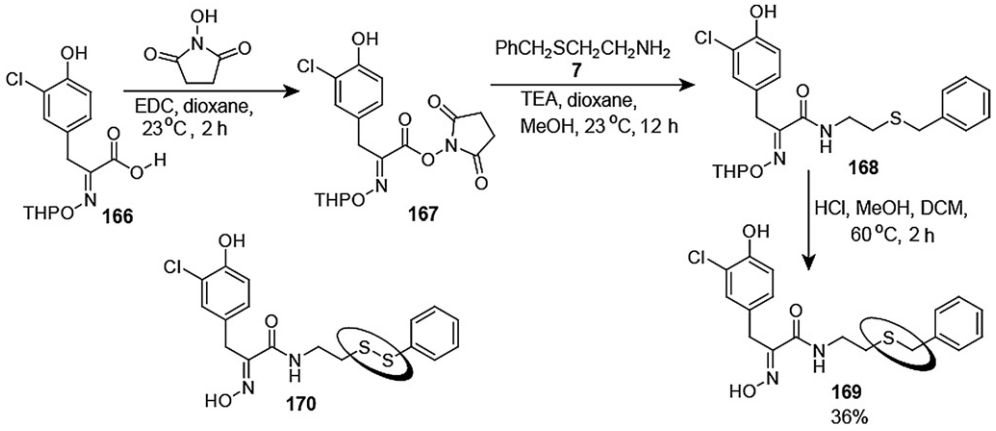
For the synthesis of these molecules, coupling of β-BMEA with carboxylic acid **166** was accomplished through the intermediacy of succinimate ester **167** to afford amide **168**. Finally, the THP group of **168** was removed under acidic conditions to produce **169** (Scheme 33).



Scheme 32. Synthesis of impromidine analogues.

163 and subsequent aminolysis of the intermediate *O*-phenyl isoureas with 3-(1*H*-imidazol-4-yl)propan-1-amine **164** produced the corresponding benzoylguanidines **165**. The benzoylguanidines **165** were converted to the corresponding guanidium salts **161** by acid hydrolysis (Scheme 32).

Seborrhea is simply a chronic skin disorder, and the Laporte lab found that various β-BMEA salts possess the ability to ameliorate this condition (Fig. 5).[79,80] In order to study the anti-seborrheic activity, they took the β-BMEA–malate salt **171** as a model compound, and studied its pharmacodynamic properties. It was



Scheme 33. Synthesis of heterodimeric molecules containing thioether linkage.

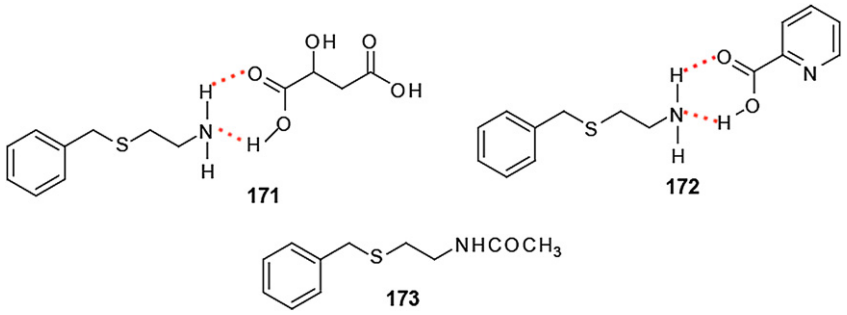


Figure 5. Various β-BMEA salts.

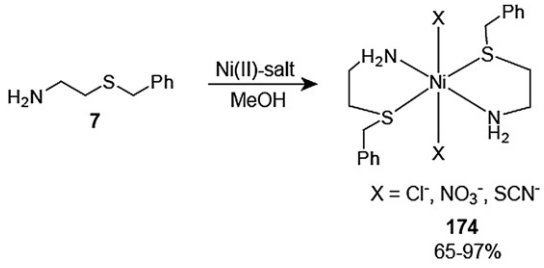
revealed that **171** crossed the cutaneous barrier and fixed itself on the surface of the sebaceous gland cells and upon the pilous follicle. Aubin et al. subsequently investigated the mechanism of action of several of these β-BMEA salts and found that these compounds have a direct action upon skin lipid metabolism.[81,82]

5. Applications in inorganic chemistry

Because of the presence of thioether donor system,[83,84] ligands containing β-BMEA moiety have been well received in coordination chemistry.[85] For example, Kennard et al. synthesized a series of thioether-containing Co(III) complexes of the general formula $[(en)_2Co(S(R)CH_2CH_2NH_2)]^{3+}$ [R=methyl, ethyl, cyclohexylmethyl, benzyl, 4-fluorobenzyl, 4-methylbenzyl, carboxymethyl, methylcarboxymethyl, carboxyethyl, carboxypropyl, 1-naphthylmethyl, and 2-naphthylmethyl][86] by alkylation of $[(en)_2Co(SCH_2CH_2NH_2)]^{2+}$. When benzyl chloride was used as an alkylating agent, a complex containing β-BMEA was obtained. Subsequently, they studied the kinetics and mechanism of the reduction of these complexes by Cr(II) salts in aqueous perchlorate media.[86] During those studies, they found that the thioether sulfur functions as an electron-transfer bridge.

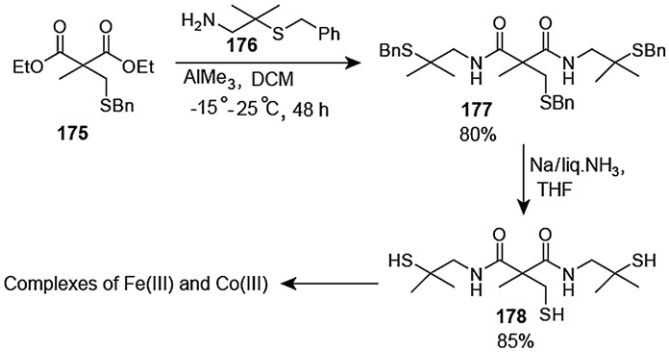
Galyer group reported that β-BMEA could be used as an efficient ligand for the synthesis of corresponding Cu(II) and Ni(II) complexes **174** (Scheme 34).[87] In these complexes, β-BMEA coordinates to metal ions in a *trans*-N_2S_2 arrangement in the equatorial plane where the anionic ligands occupy the axial sites. The infrared spectra of these complexes show the presence of hydrogen bonding between the NH groups and anions such as halogens.

Many efforts have been devoted toward the synthesis of biomimetic complexes of the nitrile hydratase (NHase) class of metalloenzymes. These metalloenzymes bear a non-heme iron(III) or a non-corrinoid cobalt(III), and catalyze the hydration of nitriles to



Scheme 34. Synthesis of Cu(II) and Ni(II) complexes.

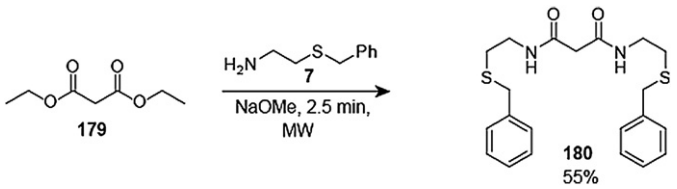
amides.[88–90] Heinrich et al. presented a synthetic pathway for three new N_2S_3-type and one N_2S_2-type ligands (with N=CONH and S=SH) (Scheme 35) and attempted to use those ligands for the synthesis of Fe(III)- and Co(III)-based biomimetic complexes of NHases. During the synthesis of these ligands, they found that



Scheme 35. Synthesis of N_2S_3-type ligand.

β-BMEA derivatives could be used as efficient building blocks to bring the thiolato moiety into the ligand structure.[91] The reaction between diethyl malonate derivative **175** and the β-BMEA derivative **176** produced the amide intermediate **177**, which upon debenzylation yielded the desired ligand **178**.

Daubinet et al. developed a new microwave-assisted synthetic strategy for the synthesis of several multidentate malonamide derivatives as silver(I)-selective ligands.[92] The reaction between diethyl malonate **179** and β-BMEA under microwave irradiation for 3.5 min yielded the malonamide derivative **180** as yellow crystals (Scheme 36). The silver(I) selectivity of these ligands was investigated by metal extraction studies and they found that a malonamide derivative of β-BMEA exhibited high silver(I) extraction efficiency over a broad pH range (2.7–9.0).



Scheme 36. Synthesis of β-BMEA-based malonamide derivative.

The Lippard group synthesized and structurally characterized a series of carboxylate-bridged diiron(II) complexes, as small molecule mimics of the catalytic sites of carboxylate-bridged non-heme diiron enzymes, with sterically hindered terphenyl carboxylate ligands and alkyl amine donors.[93] Their target was to study the oxygenation chemistry of these complexes. During those studies, β-BMEA was effectively used as nitrogen-donor ancillary ligand to prepare the complex $[Fe_2(\mu\text{-}O_2CAr^{Tol})_4(NH_2(CH_2)_2SBn)_2]$ **181** (Fig. 6). In this complex, each iron atom is coordinated by the four bridging carboxylates that form the base of a square pyramid with the β-BMEA ligand capping the metal center. When they studied the dioxygen reactivity of **181**, they observed that β-BMEA was oxidized (to an extent of 31%) to benzaldehyde. This fact indicates that the pendant benzyl group of β-BMEA is dealkylated oxidatively.

The dppa [dppa=bis(diphenylphosphanyl)amine] ligands are an important class of ligands in coordination chemistry and belong the category of short-bite ligands.[94,95] Braunstein group synthesized

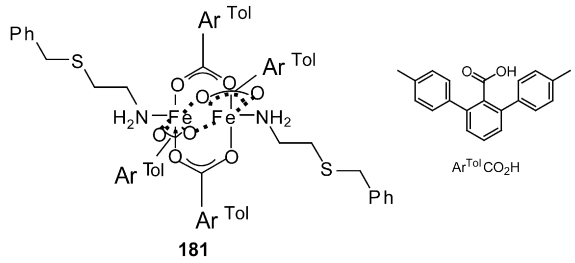
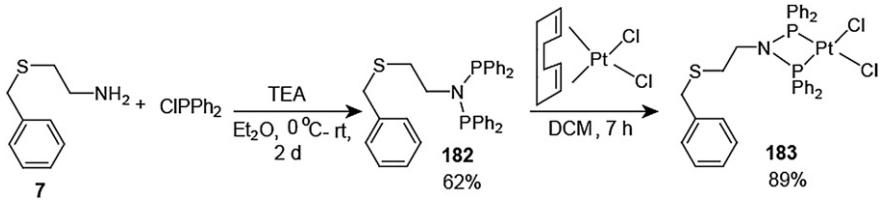


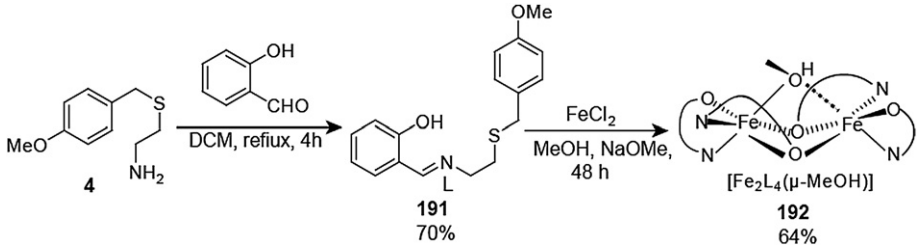
Figure 6. Binuclear carboxylate-bridged iron(II) complex.

various *N*-substituted dppa ligands and for this purpose they used β-BMEA as one of the starting amines in order to introduce the thioether function into dppa-type ligands (Scheme 37).[7] Their goal was to utilize these dppa ligands for synthesis of mononuclear *cis*-$[PtCl_2[\{Ph_2PN(R)PPh_2\}]$ complexes (Scheme 37) and heterotrinuclear clusters of formula $[PtCo_2(CO)_7\{Ph_2PN(R)PPh_2\}]$ (R= $-CH_2CH_2SCH_2C_6H_5$, $-CH_2CH_2S(CH_2)_5CH_3$, $-(CH_2)_9CH_3$, $-C_6H_5$)]. The crystal structure of the β-BMEA-based complex **183** revealed that the geometry around the platinum atom is distorted square planar. They subsequently studied the effect of functional group steric bulk (R) on the chelating ability of the ligand. From the thermodynamic studies, they came to the conclusion that in the case of mononuclear platinum complexes, the presence of a relatively bulky substituent on N entropically results in a higher chelating power of dppa(s), whereas for cluster compounds, the enthalpic factors govern the bridged form but entropic factors favor chelation.

In continuation of their research on the use of various dppa(s) ligands for the preparation of Pt(II) complexes, Braunstein lab reported the assembly of dendrimer-like Co_{12} and Co_{16} metal clusters **186** around a dppa-type polypodal ligand **185**.[96] In this centrosymmetric molecule, each dppa-type ligand is attached to a Co_3 cluster and bridges an edge opposite to that spanned by the ancillary dppa ligand. An X-ray diffraction study established all the CO ligands terminal, and each Co_3 triangle is capped by a μ_3-C–Cl ligand. This dppa-type polypodal ligand **185**[97] was synthesized from a tetrapodal β-BMEA derivative **184** (Fig. 7). This tetrapodal β-BMEA derivative has also been used for the synthesis of ferrocenyl end group containing bis-macrocyclic ligand and their tetranuclear di-copper(I)[97] complexes.[98]



Scheme 37. Synthesis of *N*-substituted dppa ligands and their metal complexes.



Scheme 38. Synthesis of the salicylaldimine ligand and its Fe(II) complex.

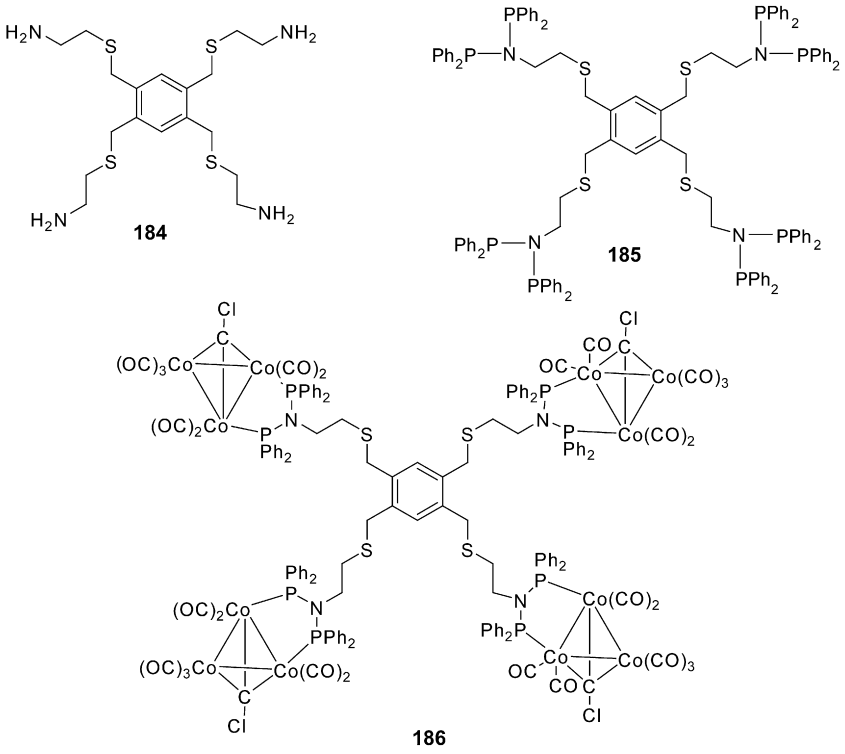


Figure 7. Tetrapodal β-BMEA-based polypodal ligands and their metal complexes.

2,2′-*o*-Phenylenebis(methylenethio)bis(ethanamine) **187**, a dipodal β-BMEA derivative has been used widely in inorganic chemistry.[99–101] Wei et al. used this bipodal ligand for the synthesis of 36- and 34-membered macrocycles, **188** and **189**, respectively. They described the high yielding synthesis of **188** and **189** via the 2+2 condensation reaction of terephthalaldehyde or isophthalaldehyde with **187** in acetonitrile. Subsequently, they used those macrocycles for the synthesis of air-stable di-copper(I) complexes **190** (only one example has been shown here). From the crystal structure it was clear that the two N_2S_2 donor sets are each tetrahedrally coordinated to the copper(I) (Fig. 8).[102]

The condensation between β-(4-methoxybenzylmercapto) ethylamine **4** and salicylaldehyde produces a thioether-containing tridentate Schiff base ligand *N*-(2-(4-methoxybenzylsulfanyl) ethyl)salicylaldimine **191**. Bierbach group synthesized and used this ligand **191** for the preparation of a dinuclear iron(II) complex **192** (Scheme 38).[4] The resulting dinuclear geometry is best described as face-sharing distorted octahedral with iron in a N_2O_4 mixed-donor environment. Interestingly, they observed that the ligand **191** acted as a bidentate N,O-donor although it was expected to be a tridentate N,O,S-donor. This resulted in an unexpected self-assembly of iron(II) into a triply bridged dimmer **192**.

Sun et al. used β-BMEA as a spacer for the synthesis of *N*,*N*′-bis(2-mercaptoethyl)ethylene-diamine-*N*,*N*′-diacetic acid **195**, an efficient ligand (Scheme 39).[103] Their target was to study the stability of some divalent and trivalent metal ions, such as In(III), Ga(III), Zn(II), Pb(II), and Cd(II) with this ligand. Interestingly, this ligand showed unusually high affinity for In(III) and Ga(III). They also revealed that the formation constant of In(III) complex with **195** is 10^{37} (0.1 M KCl, 25 °C), which was higher than those previously reported ligands for In(III).

In some metalloenzymes e.g., carbon monoxide dehydrogenase/acetyl-CoA synthase (CODH/ACS), Fe(II), and Co(III) nitrile hydratase (NHase), the catalytic center is bound by a Cys-Xxx-Cys motif in a tetradentate plane from the two cysteine thiolates and the

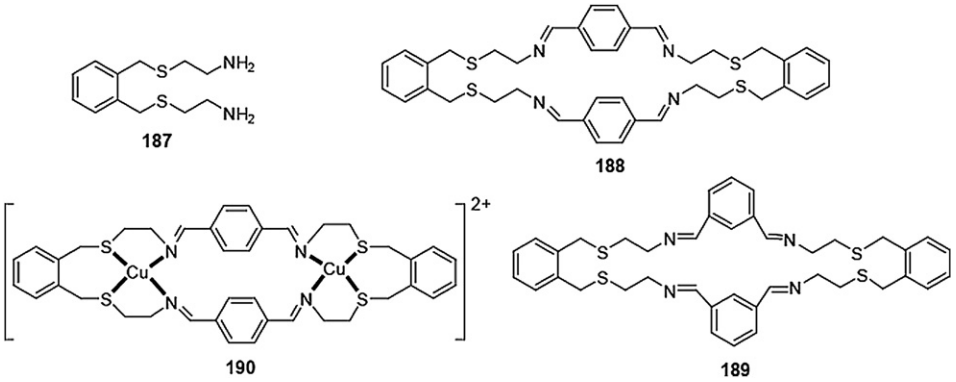
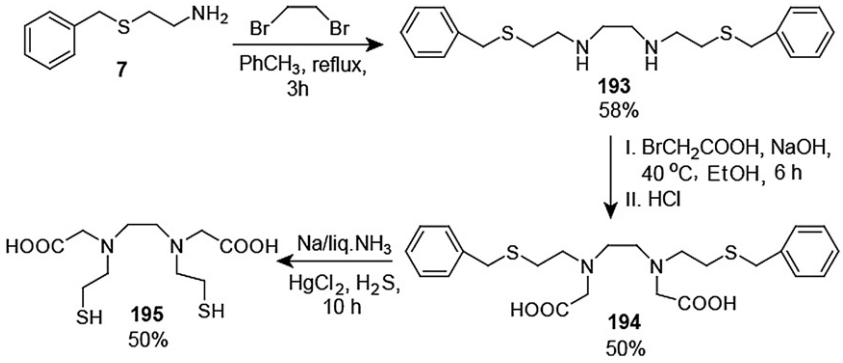


Figure 8. Bipodal β-BMEA-based macrocycles and their Cu(I) complexes.



Scheme 39. Synthesis of *N*,*N*′-bis(2-mercaptoethyl)ethylene-diamine-*N*,*N*′-diacetic acid.

backbone amide nitrogen of the central amino acid (Xxx: Gly for CODH/ACS; Ser for NHase) and the adjacent cysteine (Fig. 9).[104,105] Angelosante et al. made use of β-BMEA as a reagent of choice to develop a new synthetic strategy for the synthesis of biologically relevant Cys-Xxx-Cys synthetic ligand analogs (used in conjunction with metals as metalloenzyme models).

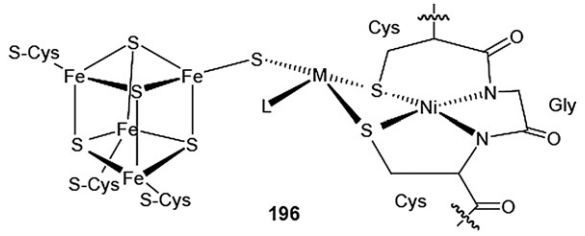
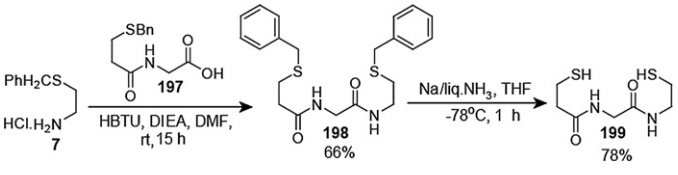


Figure 9. Representation of active site of CODH/ACS containing the Cys-Xxx-Cys fragment coordinated to the metal center through the cysteine sulfurs and two backbone amide nitrogens.[104]

The ease of debenzylation and presence of a primary amine have made β-BMEA a reagent of choice to get an access to free thiol group as well as to form an amide bond.

The reaction between β-BMEA **7** and the acid **197** yielded the diamide **198**, which upon debenzylation produced the desired ligand **199** (Scheme 40).[104]



Scheme 40. Synthesis of heterodimeric molecules containing a thioether linkage.

6. Conclusion

To incorporate the cysteamine moiety into many natural and non-natural products, β-BMEA derivatives have been used as efficient and important synthons in various fields of chemistry. These derivatives have also provided access to many heterocycles and biologically active compounds. Their use in the synthesis of a high number of ^{99m}Tc-binding ligands clearly shows their value in the nuclear medicine field. Further, the presence of thioether donor as well as reactive amine terminal has made this functionality broadly important as polydentate ligands in inorganic chemistry. Truly, this functionality is broadly applicable, and synthetically versatile. This report is meant to highlight this utility and versatility and serve as a resource for the further use of the β-BMEA.

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