Synthesis of Macrocyclic Derivatives of Polymethylene Amines of Natural Origin and Their Analogues

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Abstract

Data on synthesis routes and the possibilities for modification of the structure of macrocyclic alkaloids of natural origin – derivatives of biogenic polymethylene amines – are considered and generalized. The data on the synthesis of their synthetic analogues used to develop medical preparations of directed action are also reported.

Contents

INTRODUCTION

Natural compounds play the dominant part for developing medical preparations to cure various human diseases [1]. At present, attention to the natural compounds resumed because alternative methods of discovering medicines failed to detect basic compounds for such key therapeutic areas as immunosuppression, antiseptics and dysbolism.

Three previous publications of the authors presented systematisation of the literature data on structures and types of the biological activity of the alkaloids of natural origin – derivatives of polymethylene amines, as well as some promising synthetic analogues of these alkaloids [2–4]. In the recent publication [5], we considered the synthesis routes and the possibilities of structural modifications of the linear alkaloids of this type.

The present review concludes the series of works dealing with the derivatives of polymethylene amines of natural origin. Literature data on synthesis routes and the possibilities to modify the structure of macrocyclic alkaloids for the development of medical preparations of directed action are collected, systematized and analysed in the review. The works published mainly during the years 1993–2004 are considered. The review consists of the introduction and three chapters. The second chapter presents the syntheses of the cyclic polyamine fragments that have already been used to obtain the considered alkaloids or their analogues. The third and the fourth chapters contain the information on the methods of synthesis of natural alkaloids and their modified structures. It should be noted that the complete synthesis of the considered alkaloids clearly illustrates the value of the methods of protective groups [6].

SYNTHESIS OF THE CYCLIC POLYAMINE FRAGMENTS

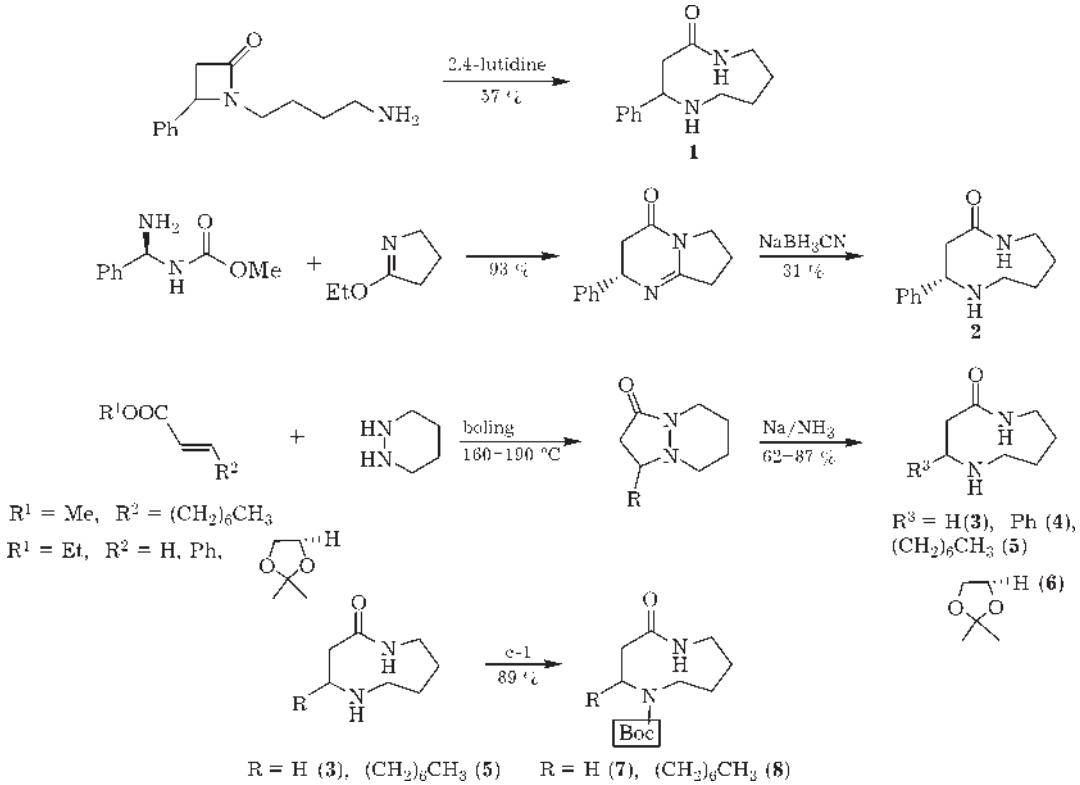
Various azalactams are necessary for the synthesis of the cyclic derivatives of the polymethylene amines of natural origin. As a rule, in these compounds, amine or oxygen-containing functional groups not involved in the synthesis of alkaloids are reversibly blocked with protective groups. The list of the used protective groups, reagents for their introduction/removal and designations of these processes in the synthesis schemes are listed in Table 1.

The syntheses of 9-membered azalactam **1** based on β-lactam [7] and azalactam **2** formed by the condensation of the methyl ether of (−)-(3*S*)-3-amino-3-phenylpropionic acid with 5-ethoxy-3,4-dihydro-2H-pyrrhol [8] are known. A higher yield of 9-membered azalactams **3–6** was achieved by condensation of the esters of α,β-unsaturated carboxylic acids and hexahydropyridazine with the intermediate formation of bicyclic lactams, followed by the rupture of the N−N bond by metal sodium in ammonium [7−10]. One of the amino groups of lactams **3** and **5** can be easily protected with Boc group [7, 9] (Scheme 1).

By means of N-alkylation of N-mehtylpiperazine with acrylonitrile, followed by hydrogenation of the resulting compound on a rhodium catalyst, N-methylpiperazinylpropylamine **9** [11] was obtained (Scheme 2).

The 8-membered azalactams **10–19** that are necessary to synthesize homaline alkaloids may be obtained using different methods: from (±)-N-methyl-β-phenyl-β-alanine [12] or ethyl esters of 3-(tosylamino)-3-alkylpropanoic acid [13] (Scheme 3), from β-lactam derivatives [12, 14] (Scheme 4) or using the reaction of pyrazolidine with optically active vinyl sulphoxides: *tert*-butyl-2-[(S)- and (R)-*para*-tolylsulphinyl]cynnamates [15] (Scheme 5).

The synthesis of alkaloids under consideration involves selectively protected linear polyamine intermediates **20** [16], **21** [17], **22** [18], **23** [19] and **24** [20], **25** [17], as well as free spermidine **26** and putrescine **27**.



Scheme 1. 9-Membered azalactams.

TABLE 1

Protective groups used in the synthesis of polymethylene amines of natural origin

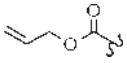
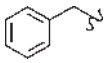
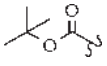
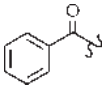
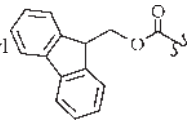
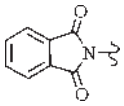
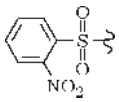
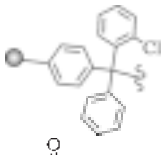
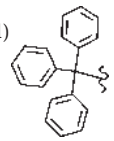
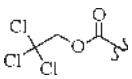
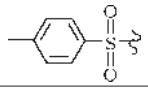
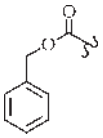
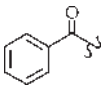
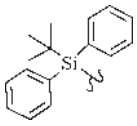
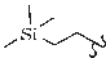
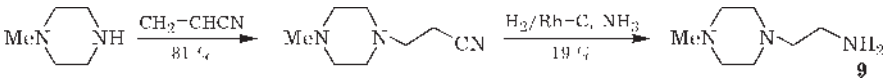
Designation	Name	Structure	Introduction of protective group		Removal of protective group	
			Designation	Reagent	Designation	Reagent
		Protective groups for N atoms				
Alloc	Allyloxycarbonyl		a-1	Alloc-Cl	m-1	$(Ph_3P)_4Pd$, Ph_3P, HOAc
Bn	Benzyl		b-l	$BnNH_2$	n-1	$H_2/Pd(OH)_2$-C
			b-2	$C_6H_5C(O)H$	n-2	$H_2/Pd(OH)_2$, HOAc
					n-3	Li/NH_3, ion exchange resin
Boc	*Tert*-butoxycarbonyl		c-1	Boc_2O	o-1	CF_3COOH
			c-2	Boc-ON	o-2	CF_3COOH, $HS(CH_2)_2SH$
					o-3	HCO_2H
					o-4	HCl, MeOH or EtOH
					o-5	HCl, dioxan
					o-6	CH_3SO_3H, dioxan
Bz	Benzoyl		d-1	$(C_6H_5CO)_2O_2$	p-1	NH_3, MeOH
					p-2	NH_4OH
Fmoc	9-Fluorenylmethoxycarbonyl		–	–	q-1	(*iso*-Pr)$_2$NEt, DMF/DMSO
					q-2	$CH_3(CH_2)_7SH$, DBU
Lr	Linker	$AllylOC(O)CH_2-OPhCH_2OC(O)$		LrONp	o-1	CF_3COOH
Phth	Phthaloyl		e-1	Phthalic anhydride	r-1	H_2NNH_2, MeOH or EtOH
			e-2	PhthC(O)OEt	r-2	H_2/Pd black
Ns	3-Nitrobenzenesulphanyl		f-1	NsCl	s-1	$HSCH_2CH_2OH$
PcTrt	3-Chlorotrityl resin			PcTrt-Cl	o-6	CF_3COOH, Et_3SiH
TFA	Trifluoroacetyl		g-1	$(CF_3CO)_2O$	t-1	aqueous Na_2CO_3, *iso*-PrOH
			g-2	$CF_3C(O)OEt$	t-2	NaOH, H_2O-MeOH
Trt	Trityl (triphenylmethyl)		h-1	TrtCl	o-1	CF_3COOH
					o-6	CF_3COOH, Et_3SiH
Troc	2,2,2-Trichloroethoxycarbonyl		i-1	Troc-Cl	u-1	Zn/HOAc
					u-2	Zn/NH_4OAc
Ts	4-Toluenesulphonyl		j-1	TsCl	v-1	Electrolysis

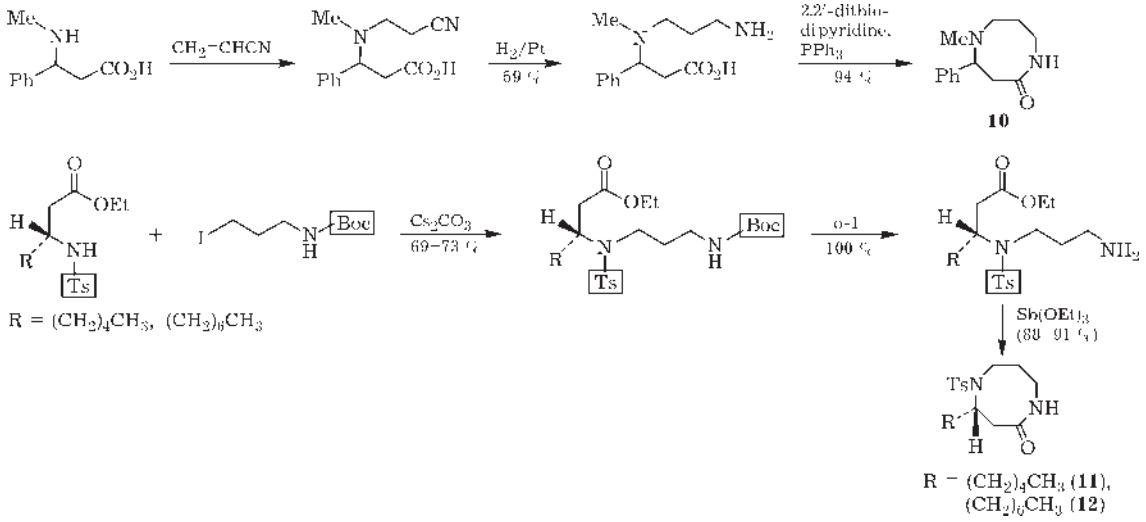
TABLE 1 (End)

Protective groups used in the synthesis of polymethylene amines of natural origin

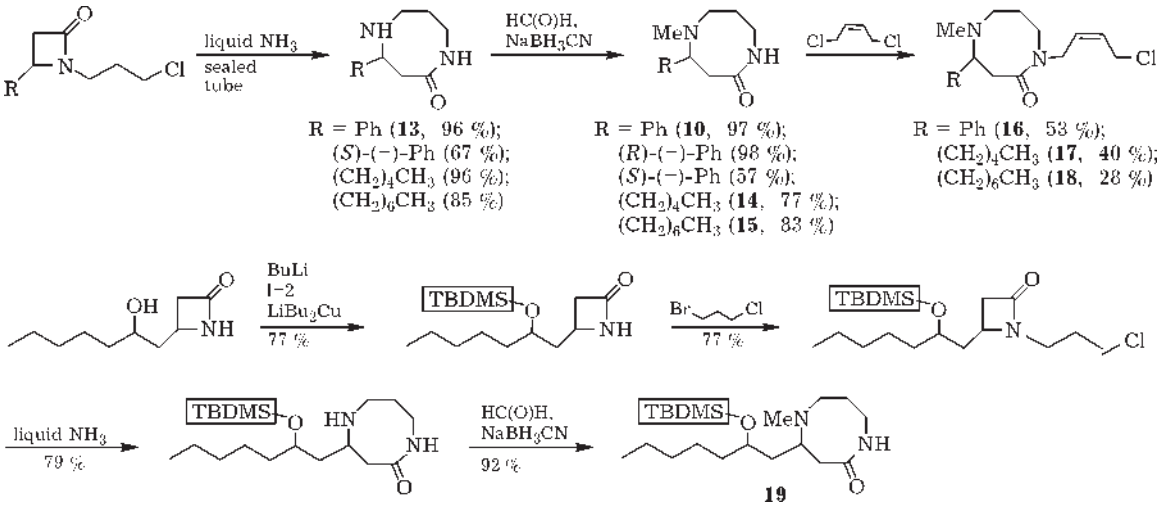
Designation	Name	Structure	Introduction of protective group		Removal of protective group	
			Designation	Reagent	Designation	Reagent
Z-	Benzyloxycarbonyl		k-1	ZC1	n-1	$H_2/Pd(OH)_2$–C
			k-2	ZCN	n-2	$H_2/Pd(OH)_2$, HOAc
					r-2	H_2/Pd black
					w-1	H_2/Pd–C, MeOH or EtOH
					w-2	H_2/Pd–C, HOAc
					w-3	H_2/Pd-C, CF_3COOH, HOAc
					w-4	Me_3SiCl
			Protective groups for O atoms			
Bz	Benzoyl		–	–	p-3	NaOH
MOM	Methoxymethyl		–	–	o-1	CF_3COOH
					o-5	HCl, dioxan
t-Bu	*Tert*-butyl		–	–	o-1	CF_3COOH
TBDMS	*Tert*-butyldimethylsilyl		l-1	TBDMSCl	x-1	HCl, MeOH
TBDPS	*Tert*-butyldiphenylsilyl		l-2	TBDPSCl	x-2	$[CH_3(CH_2)_3]_4NF$ (TBAF)
TMSE	Trimethylsilylethyl		l-3	$TMSEONH_2$	x-3	$BF_3 \cdot Et_2O$



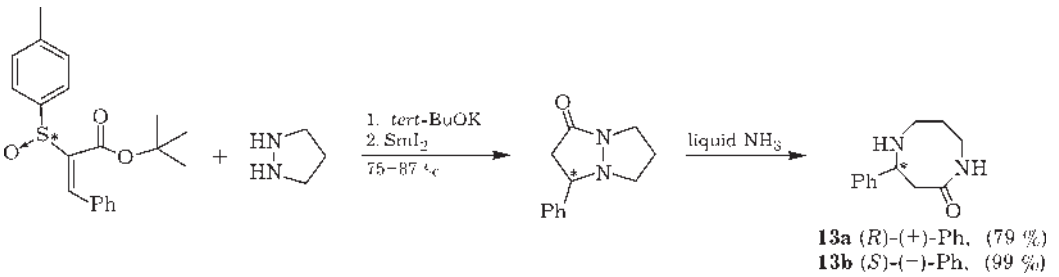
Scheme 2. Synton for the synthesis of the analogue of lunarine.



Scheme 3. 8-Membered azalactams based on amino acid derivatives.



Scheme 4. 8-Membered azalactams based on β-lactam derivatives.



Scheme 5. 8-Membered azalactams based on vinylsulphoxides and pyrazolidine.

SYNTHESIS OF NATURAL ALKALOIDS

Two methods are used at present to synthesize macrocyclic polyamines: expansion ring of aromatic precursor and macrolactamisation of linear precursors.

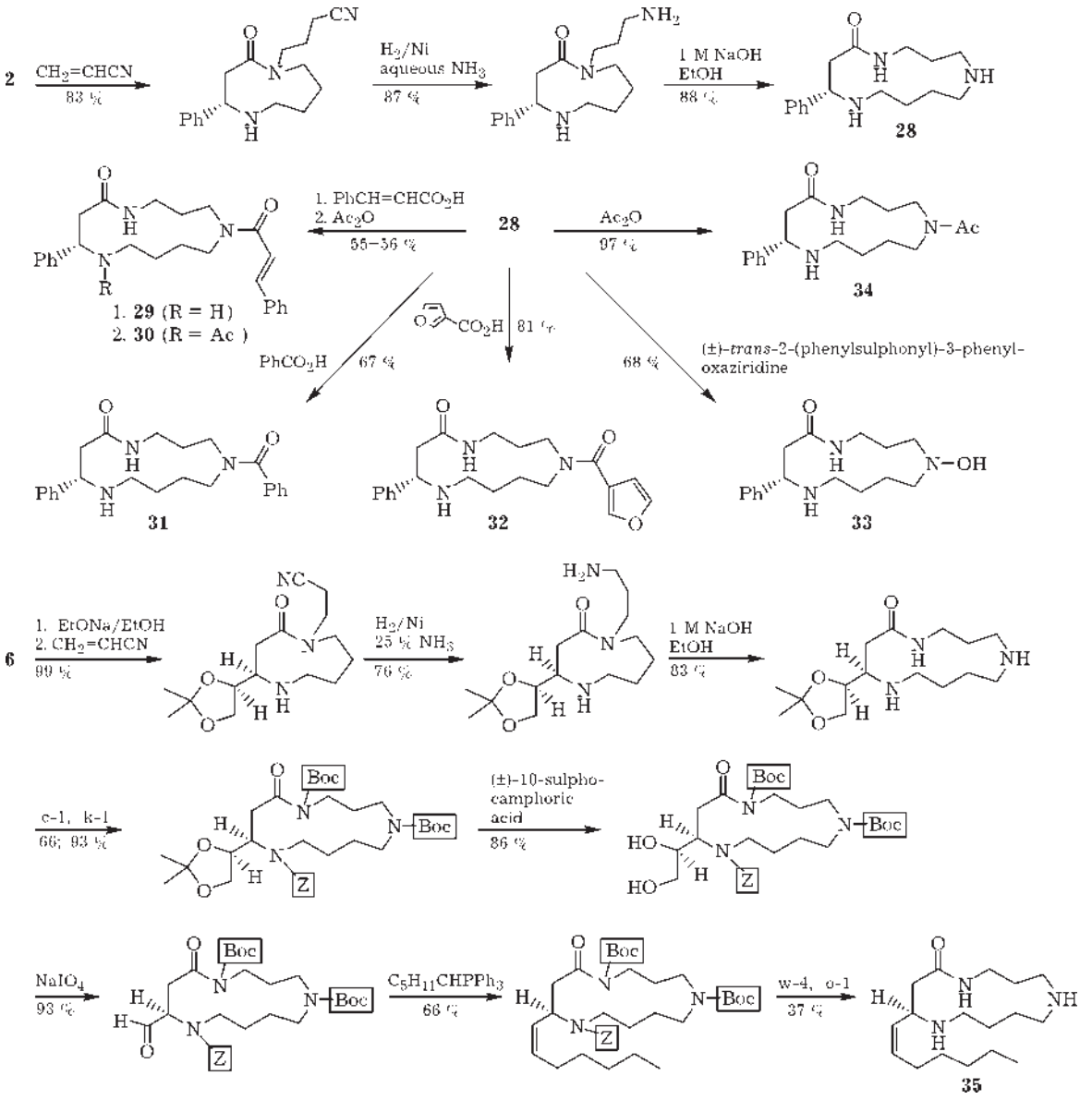
Ring expansion of cyclic precursor

Ring expansion of cyclic precursor with the help of 3-aminopropyl side chain or β-lactams allows one to obtain 13-membered spermidine alkaloids on the basis of 9-membered azalactams.

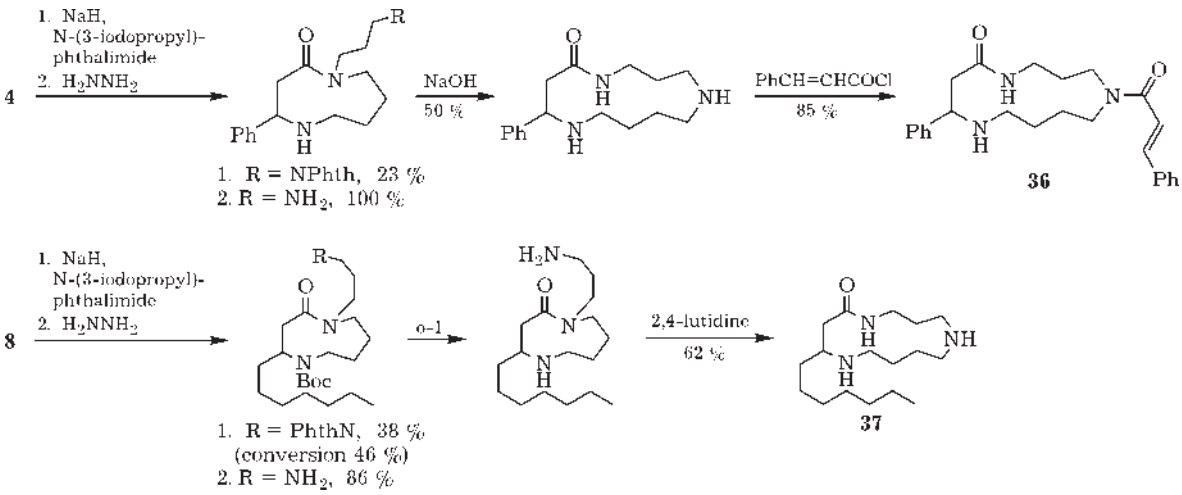
Two methods to obtain 3-aminopropyl side chain are known; each of them consists of two stages. The first method includes selective alkylation of the amide group NH of the ring with acrylonitrile, followed by reduction of CN group with hydrogen on Raney nickel. The second method includes selective alkylation of the amide group NH of the ring with N-(3-bromopropyl)phthalimide and transformations of the phthalimide group into amino group during the interaction with hydrazine.

Introduction of 3-aminopropyl side chain into optically active azalactam **2** and azalactam **6** using the first method was performed when obtaining diazalactam **28** and (−)-(2R)-dihydromyricoidine **35** [10] (Scheme 6). Optically active 13-membered diazalactam **28** serves as a precursor for a group of synthetic products **29–34**; they are equivalent to natural alkaloids of the type B (−)-(*S*)-celacynnine, (+)-(*S*)-viburnine, (0)-(*S*)-celabenzine, (−)-(*S*)-celafurine [21], (−)-(*S*)-maipholine and (−)-(*S*)-N(1)-acetyl-N(1)-deoxymaipholine [8]. The second method of the introduction of 3-aminopropyl side chain is demonstrated by the syntheses of spermidine 13-membered alkaloids of type B (±)-cellacinnine **36** [7] and (±)-tetrahydromyricoidine **37** [9] (Scheme 7).

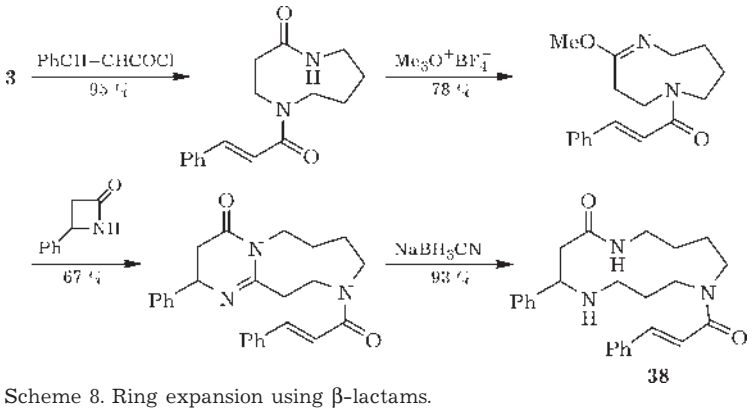
Ring expansion with the help of β-lactams was used to synthesize (±)-dihydroperiphylline **38** [7] (Scheme 8) and (+)-S-dihydroperiphylline **39** [22]. It is necessary to stress that these syntheses were carried out without using protective groups.



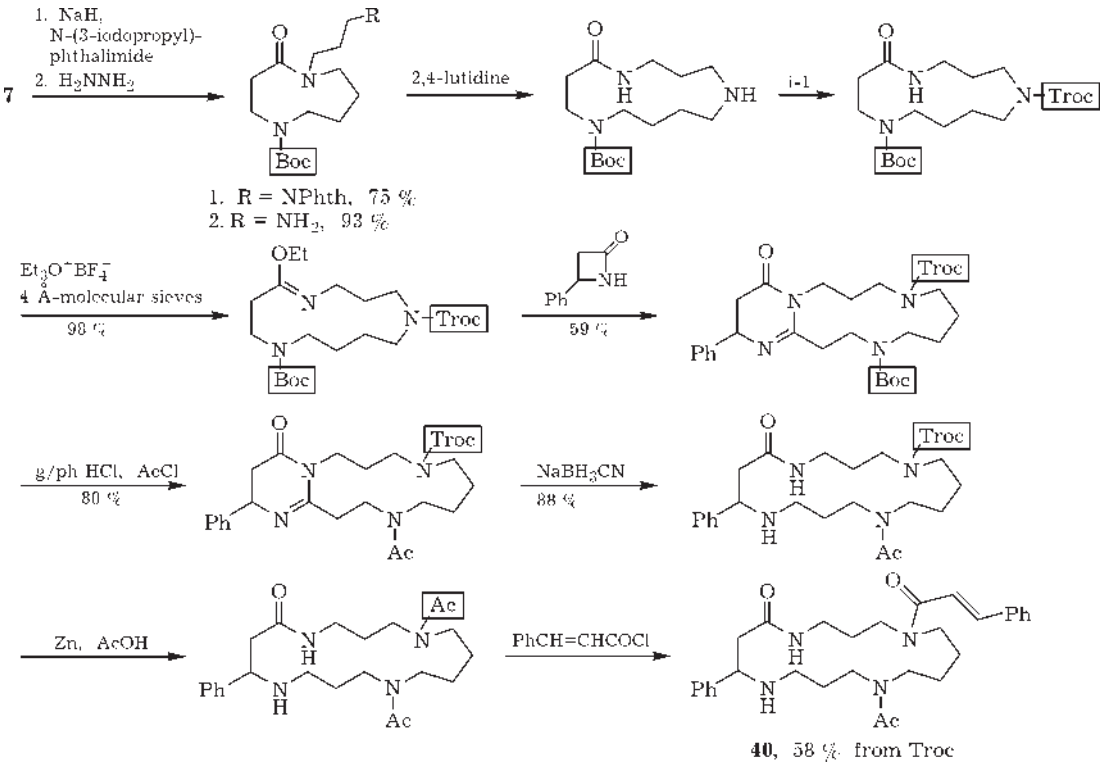
Scheme 6. Ring expansion using 3-aminopropyl side chain (method I).



Scheme 7. Ring expansion using 3-aminopropyl side chain (method II).



Scheme 8. Ring expansion using β-lactams.



Scheme 9. Combination of the methods of ring expansion.

Both methods of ring expansion were used sequentially to obtain (±)-verbascenine **40** [7] (Scheme 9). In order to form a 13-membered ring from 9-membered lactam ring **7**, it is necessary to have 3-aminopropyl side chain introduced using the second method, while in order to form a 17-membered cycle, it is necessary to perform condensation of 13-membered cycle with 4-phenylazetidine-2-one. To conserve Boc group in the presence of HBF_4 acid formed in the reaction of triethyloxonium ion with traces of water in the reaction mixture, it is necessary to use 4 Å molecular sieves and to limit the time of this reaction to 4–5 h.

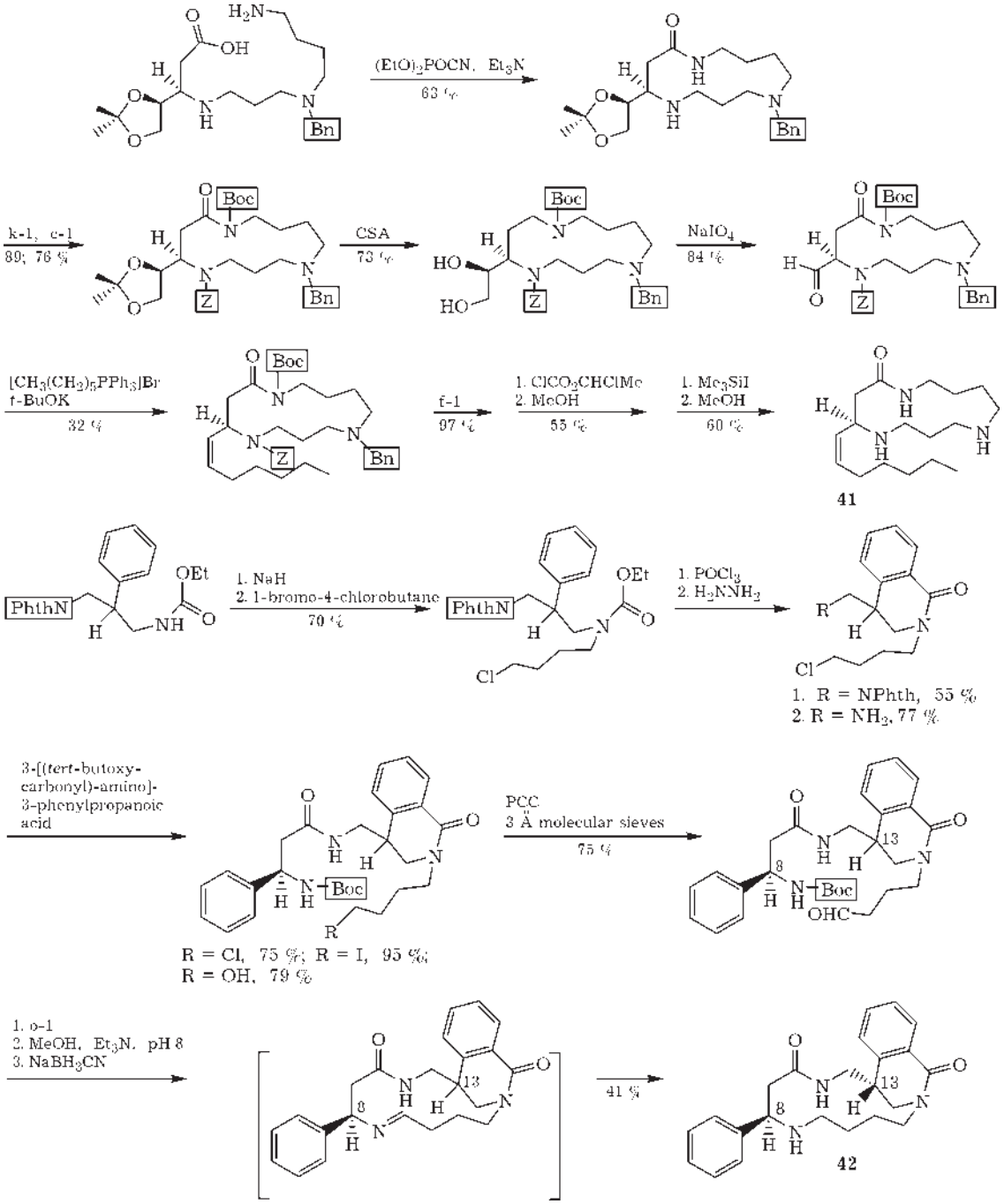
Macrolactamisation

Macrolactamisation is a convenient procedure used to obtain polyazamacrolactams with different cycle size and different numbers of nitrogen atoms. There are two versions of this method: intramolecular and intermolecular macrolactamisation.

Intramolecular macrolactamisation is based on aminolysis of bifunctional linear precursors; depending on the type of linear precursor, this reaction may proceed independently or under the action of templates.

As a rule, bifunctional precursor for macrolactamisation is a polyamino acid or its more

electrophilic derivatives. For example, the cycle of (−)-(4*R*)-dihydroisomyricoidine 41, a 13-membered aminolactam of type A, was synthesized under the action of diethyl-phosphorocyanidate from ω-amino acid with the middle nitrogen atom protected with Bn group [23] (Scheme 10). An important chiral block for the formation of the bifunctional precursor of spermidine 13-membered alkaloid of type B (+)-(8*S*,13*R*)-cyclocelabenzine **42** and its (−) isomer is optically active (+)-(3*S*)-3-amino-3-phenylpropanoic acid [24] (see Scheme 10). The formation of the bifunctional precursor in spermidine alkaloids of oncinotine type may occur *via* two routes. In the case of (−)-oncinotine **43**, two key compounds were used: carboxylic acid with a long unsaturated alkyl chain and N-propyl-1,4-butanediamine segment **20** [16]. The bifunctional precursor for oncinotine-11-one **44** was obtained by sequential operations of making

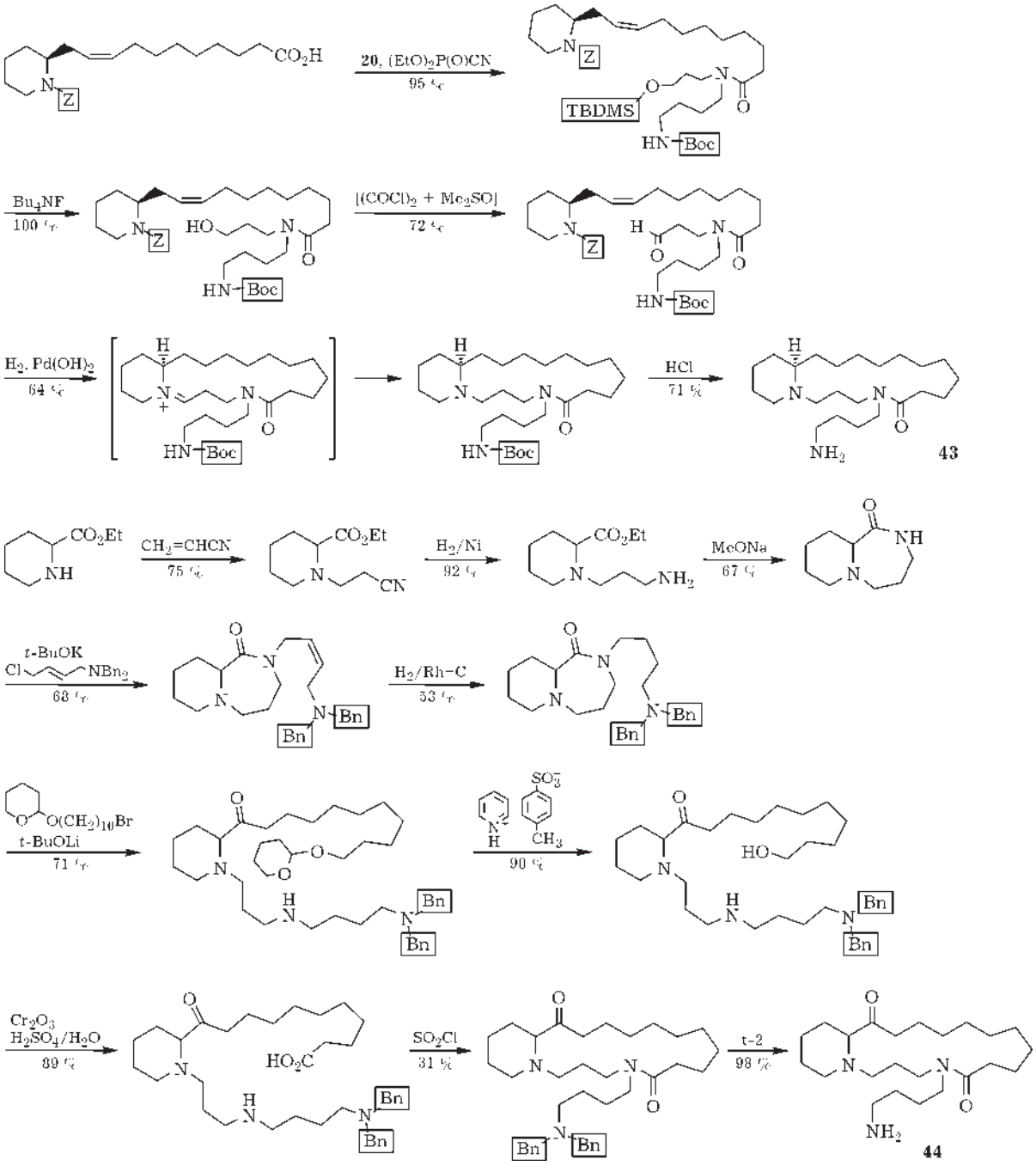


Scheme 10. Intramolecular lactamisation.

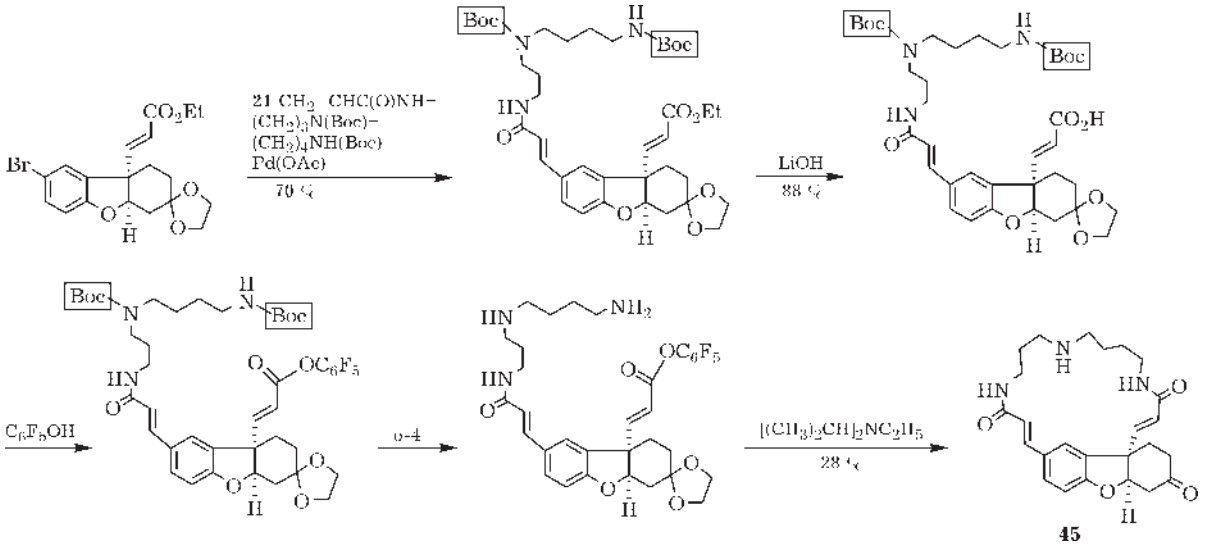
the spermidine and carbon parts in one molecule [25] (Scheme 11).

A pre-cyclic precursor of spermidine alkaloid **45** is activated pentafluorophenyl ester of carboxylic acid, obtained on the basis of selectively protected acrylamidospermidine **21** [17] (Scheme 12).

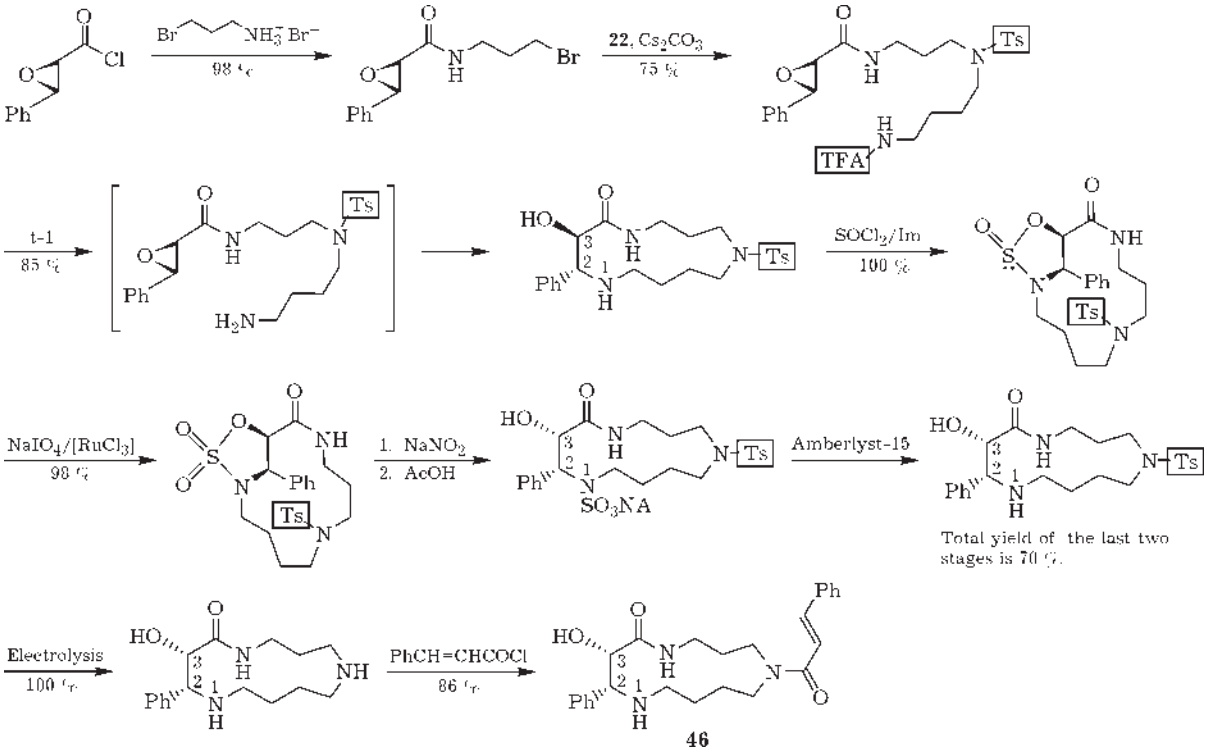
In the synthesis of natural spermidine 13-membered alkaloid of type B (−)-(2*R*,3*S*)-3-hydroxycelacinnine **46** [18] (Scheme 13), quite different linear bifunctional precursor was used; it has the oxiran ring and amino groups at different ends of the molecule. The oxiran cycle opens under the action of the terminal amino group; intramolecular cyclisation occurs. The authors studied the reactions of both *trans*- and *cis*-oxiran precursors and showed that only *trans*-oxiran compounds form macrocycles of the (2*R*,3*S*) configuration (with the yield higher than 85 %). The macrocycle of the natural



Scheme 11. Intramolecular lactamisation. Alkaloids of oncinotine type.



Scheme 12. Intramolecular lactamisation. Lunarine **45**.

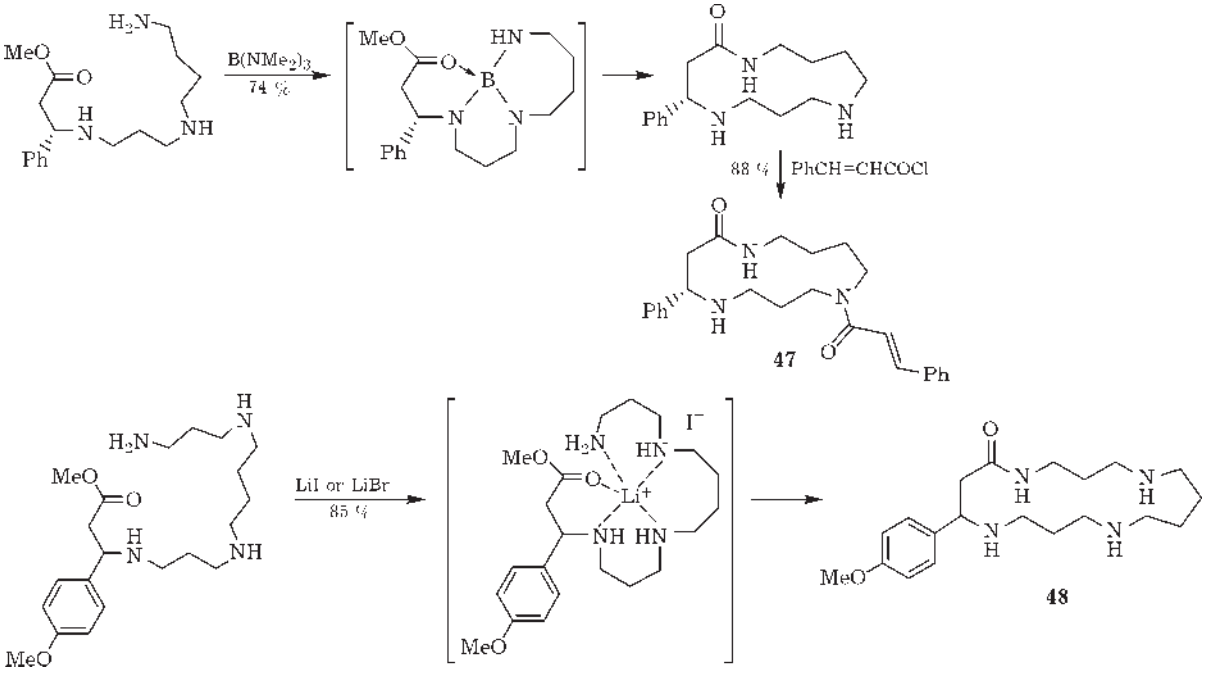


Scheme 13. Intramolecular lactamisation of the precursor possessing the oxiran ring.

(2*R*,3*S*) configuration was successfully obtained from the cyclic (2*R*,3*R*) precursor by inversion at the C(3) carbon atom under the action of cyclic sulphamidates.

The compounds possessing template effect for the intramolecular macrolactamisation are tris(dimethylamino)boron, antimony (III) ethoxide [26] and some lithium halides (lithium iodide and bromide) [27] (Schemes 14, 15). This method was applied to obtain spermidine 13-membered alkaloid of type A (+)-(S)-dihydroperiphylline **47** [26], spermine 17-membered alkaloids (±)-buchnerine **48**, (±)-protoverbine **49**, (±)-verbacine **50** [26, 27], (±)-verbaskine **51**, (±)-verbascenine **52** [26], (±)-budmunchiamines A–C **53–55** [28].

During intermolecular macrolactamisation, a linear precursor gets cyclised with another



Scheme 14. Intramolecular lactamisation of precursors under the action of $B(NMe_2)_3$ and lithium halides.

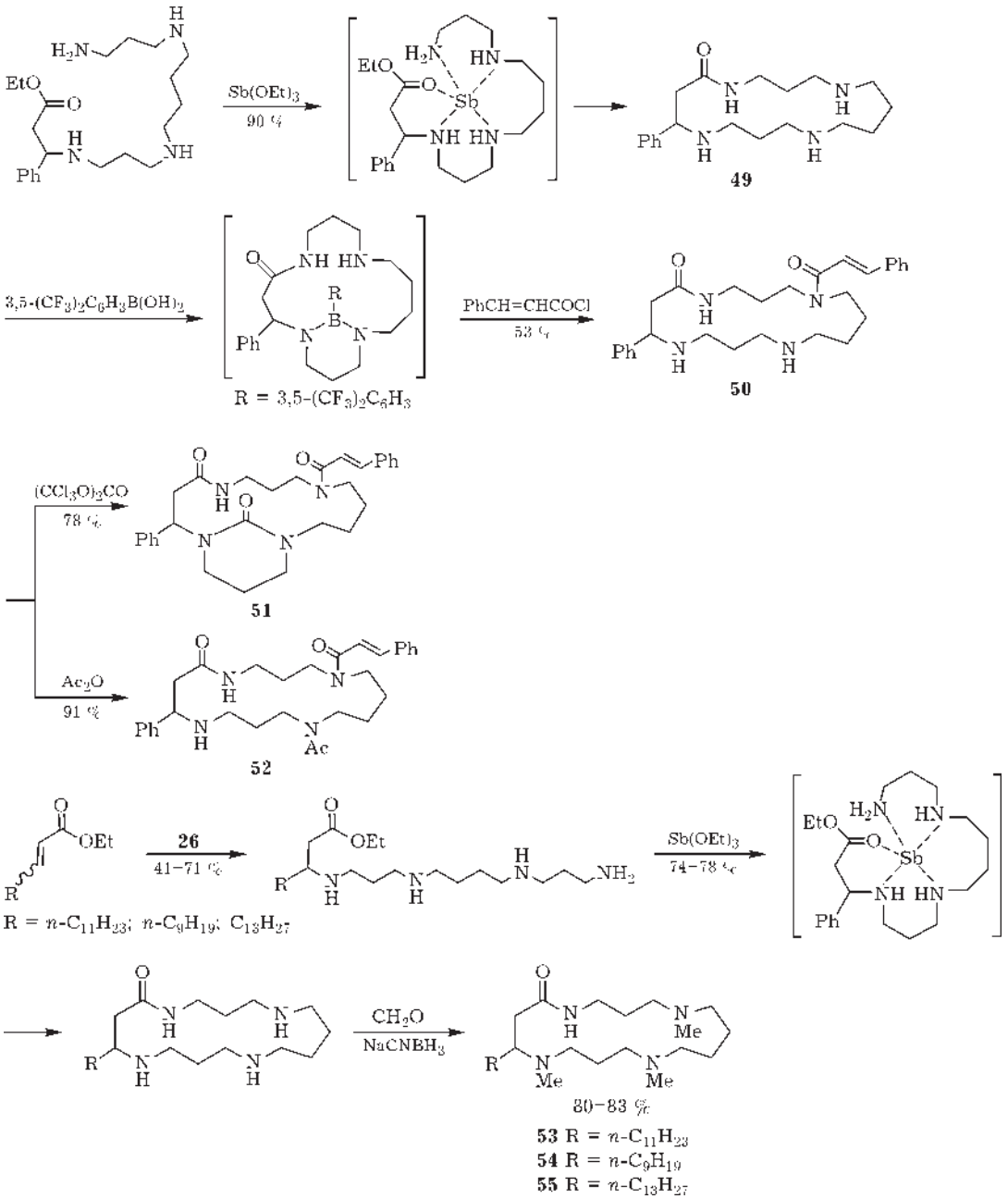
molecule to form a macrocyclic lactam in the presence of caesium carbonate Cs_2CO_3 (Scheme 16). For the synthesis of (+)-(*S*)-dihydroperiphylline **39**, (−)-(*S*)-protoverbine **56** and (−)-(*S*)-buchnerine **57**, (−)-(*R*)-bundmunchiamine A **58**, the second molecules for macrolactamisation were 1,3-bis(methylsulphonyl)propane [19], 1,4-dibromobutane [29] and 1,3-dibromopropane [20].

Other methods to synthesize polymerethylene amine alkaloids

To obtain chomaline alkaloids – homaline **59**, hopromine **60**, hoprominol **61** and hopromalinol **62** – 8-membered lactams **10**, **14**, **16–19** are necessary [13] (Scheme 17). Another method was proposed to synthesize natural (*S*,*S*)-(−)-homaline **63** [11] and (*R*,*R*)-(−)-hopromine **64** [12]: chiral azacyclooctanones **13b** and, respectively, **11** and **12**, get bound with the help of 1,4-dibromobutane (see Scheme 17).

SYNTHESIS OF THE ANALOGUES OF NATURAL ALKALOIDS

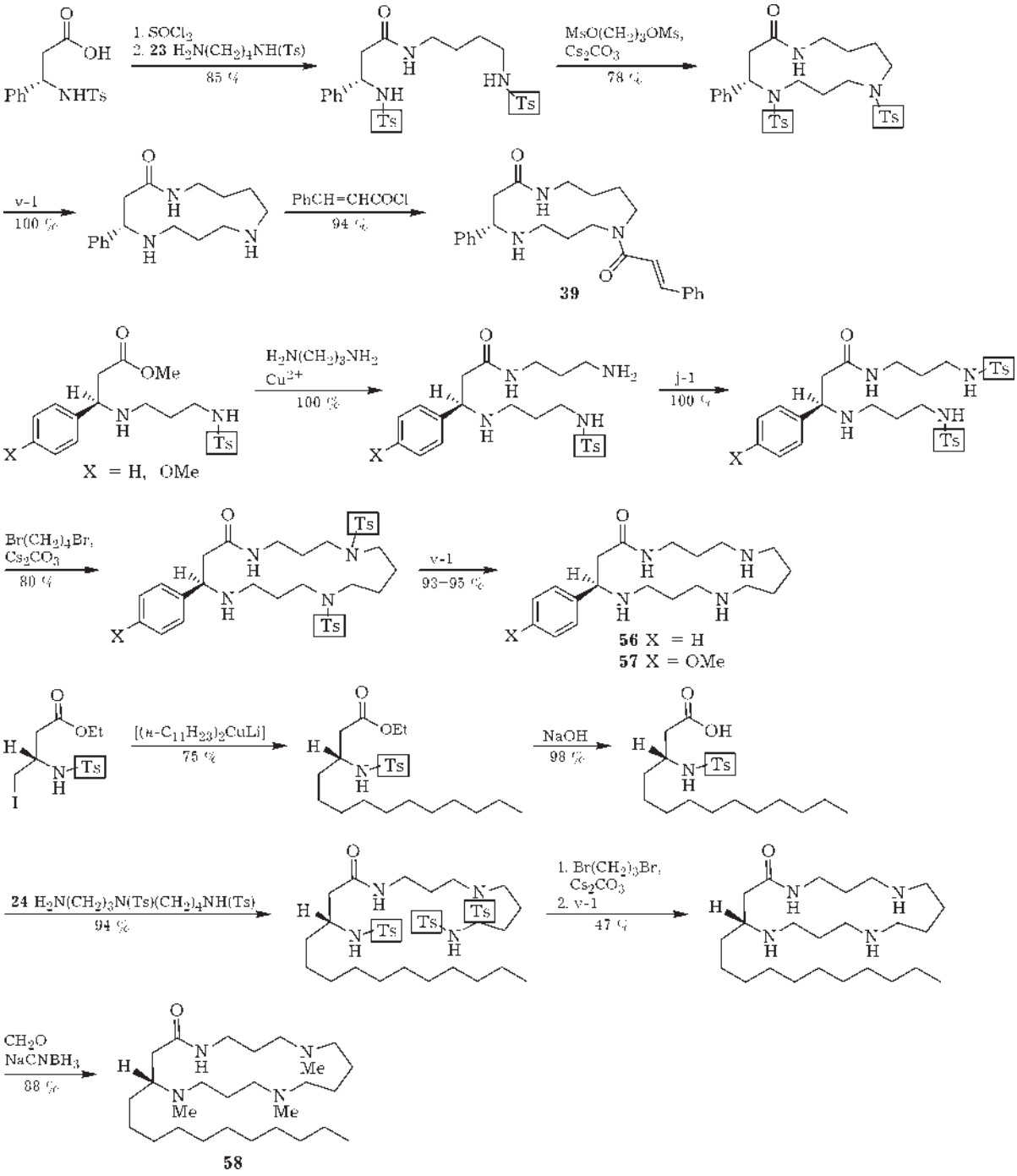
Due to the complicacy of the synthesis, lunarine **45** cannot serve as the basic structure for developing chemotherapeutic means to cure a number of diseases caused by trypanosomiatic parasites. For this reason, when developing the mimetics of this natural compound, it is important not only to simplify the chemical structure but also to conserve the given level of this rare type of biological activity. The major differences of the synthesized analogues **65–67** from the natural compound **45** are as follows. First of all, a bicyclic benzofuranyl fragment of dicarboxylic acid replaces a complicated tricyclic nucleus. Second, the polymethylene amine part is not included into the macrocycle but is represented by two independent linear substituents of the benzofuranyl nucleus. Finally, the structure of polyamine fragments varies taking into account the known interaction of linear bis-polyamines with trypanthioreductase enzyme. The compounds used for this purpose are 3-dimethylaminopropylamine, twice substituted spermidine **25** and N-methylpiperazinylpropylamine **9**. Two different procedures were used in the synthesis of analogues **65–67** to form the amide bond: dicarboxylic acid was used in the form of its complex anhydride with diphenylphosphine chloride or its more active bis-pentafluorophenyl



Scheme 15. Intramolecular lactamisation of precursors under the action of $Sb(OEt)_3$.

ester. Investigation showed that all the three compounds (**65**–**67**) are competitive inhibitors of trypanthione reductase, but only the compound with bis-4-methylpiperazine-1-yl-propylamide fragment exhibits the time-dependent activity. In spite of the essential structural modification, analogue **67** possesses the properties of time-dependent inhibitor of trypanthione reductase [30] (Scheme 18).

Macrocycles **68**–**70**, the analogues of spermidine 13-membered cyclic alkaloids and bundmunchiamines, containing heteroatom in the side chain were obtained with the help of intramolecular macrolactamisation [20] (Scheme 19). Due to this, it is possible to synthesize various polymethylene amine cyclic compounds for biological testing.

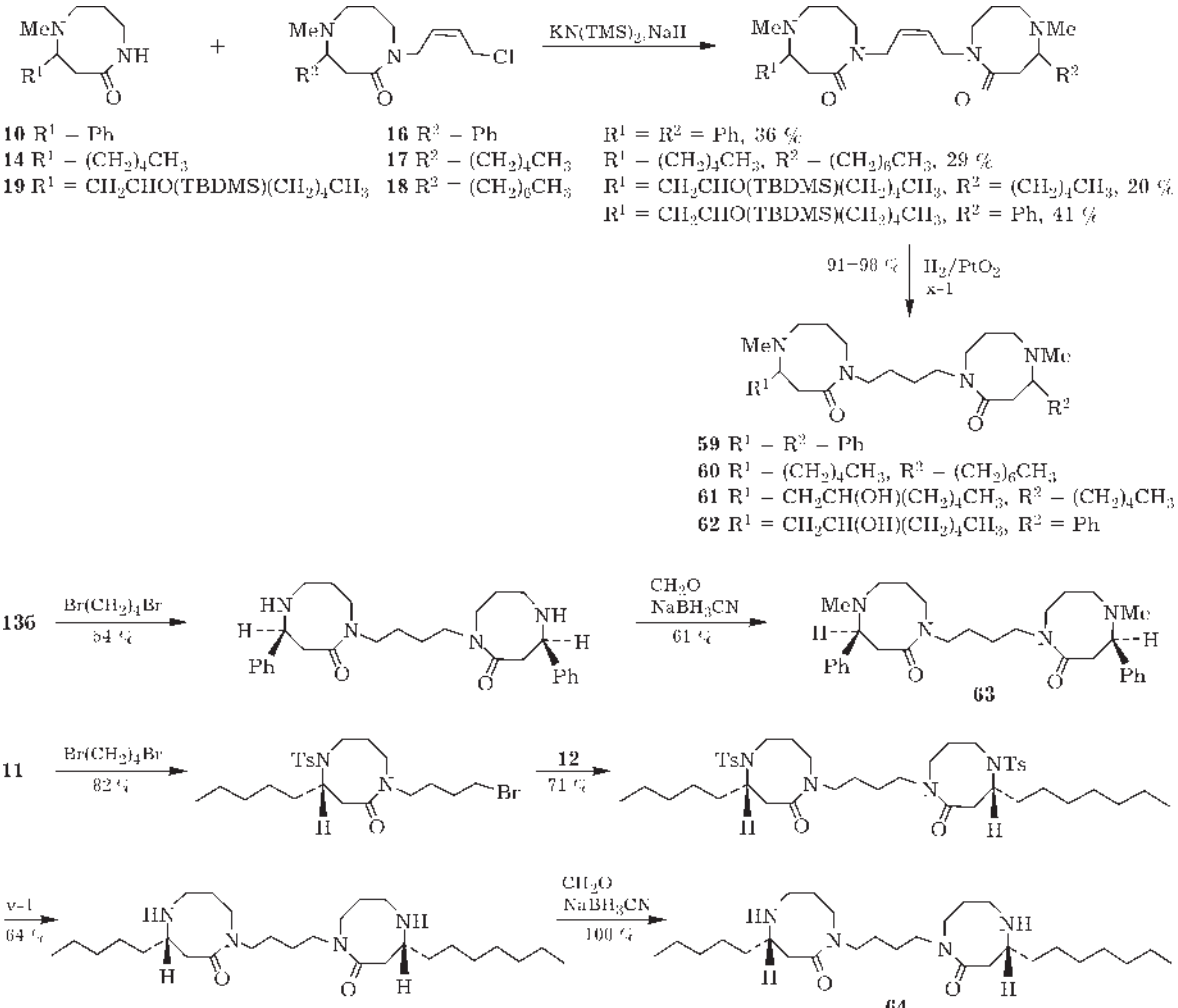


Scheme 16. Intermolecular macrolactamisation.

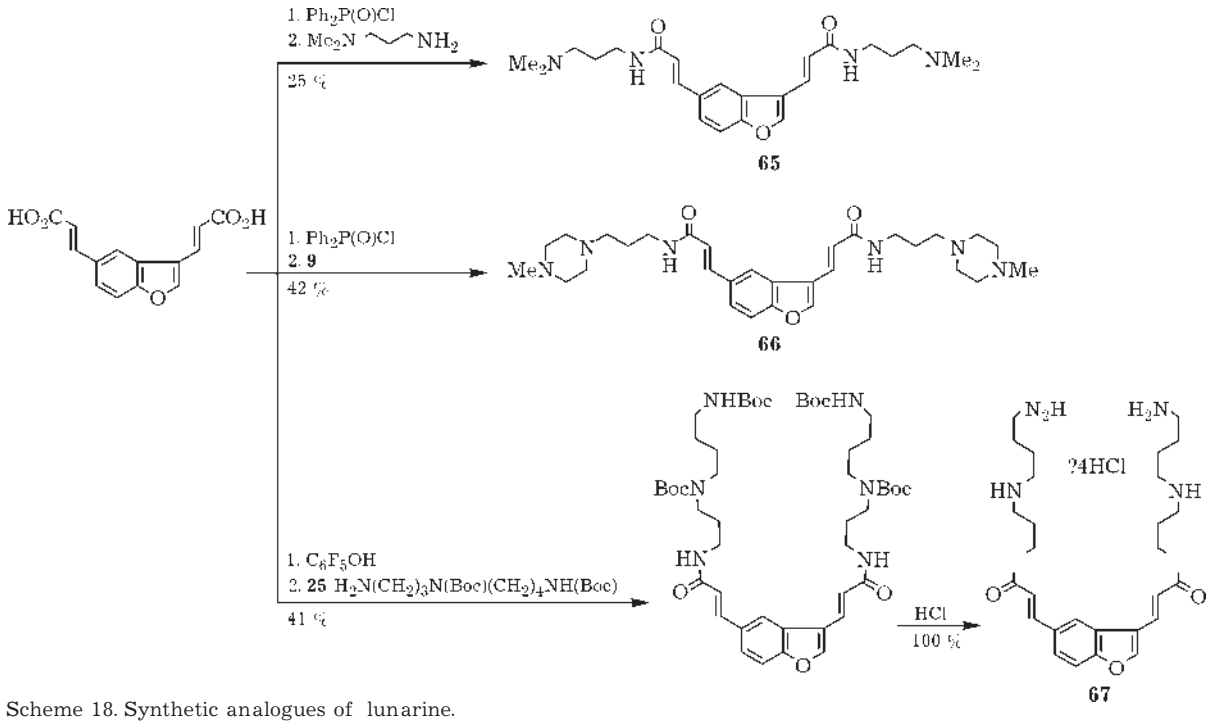
CONCLUSION

In the present review, we consider in detail such methods of the synthesis of macrocyclic derivatives of polymethylene amines of natural origin as broadening of the ring of the cyclic precursor and macrolactamisation of linear precursors. The methods of obtaining various cyclic polyamine fragments used to synthesize the considered alkaloids are described separately. As a rule, the method of protective groups is used in both cases.

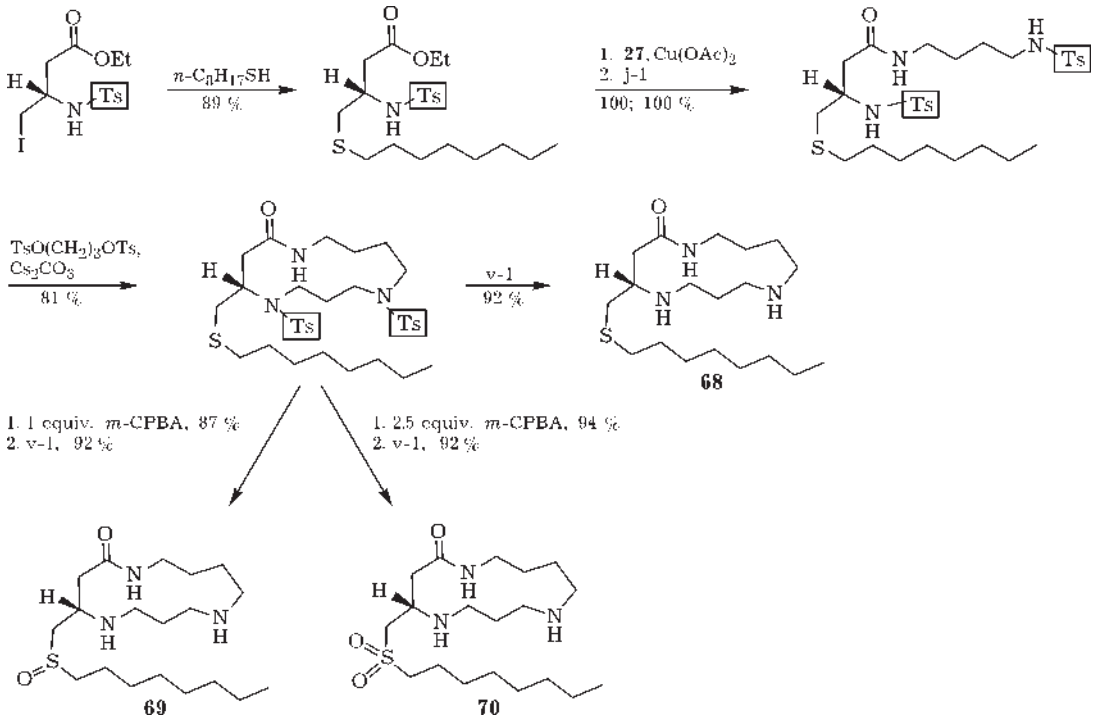
The same methods as those used to synthesize natural compounds were applied to obtain their synthetic analogues. One of them demonstrates good outlooks in the aspect of thera-



Scheme 17. Homaline alkaloids.



Scheme 18. Synthetic analogues of lunarine.



Scheme 19. Synthetic analogues of spermidine 13-membered cyclic alkaloids and budmunchiamines.

peutic action. Important structural elements of this synthetic analogue allowing it to conserve the given level of the rare type of biological activity in the case of substantial simplification of the chemical structure are specially stressed.

With the help of the available synthesis methods, one may obtain the macrocyclic derivatives of polymethylene amines and construct on this basis more efficient medical preparations through relying on the results of biological tests.

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