Макрогетероциклы
http://macroheterocycles.isuct.ru

DOI: 10.6060/mhc161066i

Functionalisation of Macroheterocycles with Preserving and Changing Their Sizes

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This review presents methods for functionalisation of macroheterocycles occurring both with preservation and alteration of their core. It is shown that the most common methods do not affect the main ring. While functionalisation of macroheterocycles accompanied by both a decrease and an increase of their size is less common, the examples given in the literature indicate the prospects of macroheterocycle functionalisation by described methods in direct synthesis of substances for different purposes: pharmacologically active compounds, selective ligands for various (mainly transient and rare-earth) metals, odorants, etc.

Keywords: Macroheterocycles, macrocyclic size, functionalisation, biological activity, application.

Функционализация макрогетероциклов с сохранением и изменением их размеров

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В данном обзоре литературы представлены методы функционализации макрогетероциклов, протекающие как с сохранением, так и изменением их остова. Показано, что наиболее распространенные методы не затрагивают их основного кольца. Тогда как функционализация макрогетероциклов, сопровождаемая как сокращением, так и увеличением их размеров, менее распространена, приведенные в литературе примеры свидетельствуют о перспективности функционализации макрогетероциклов описанными методами в направленном синтезе веществ различного назначения: фармакологически активных соединений, селективных лигандов для различных (в первую очередь переходных и редкоземельных) металлов, одорантов и др.

Ключевые слова: Макрогетероциклы, размер макроцикла, функционализация, биологическая активность, применение.

Introduction

Out of several hundred thousand secondary metabolites currently described that are isolated from various sources of natural origin, only a small part has the macrocyclic structure. However, compounds that have powerful antimicrobial, antiviral, antiparasitic, and antitumoral actions were detected precisely among them [1].This is driven by the relentless attention of chemists, biochemists, and pharmacologists to this class of natural metabolites and their synthetic derivatives.

Reviews[1, 2] describe in detail methods of development of macrocycles with ester, nitrogen-, and sulphur-containing functions, and also the use of these methods in streamlined synthesis of biologically active compounds was demonstrated on specific examples. This literature review presents methods for functionalisation of macroheterocycles themselves that proceed with both conservation and a change in their skeleton beginning with 1963 including 3 articles described in the review of 1999.[3]

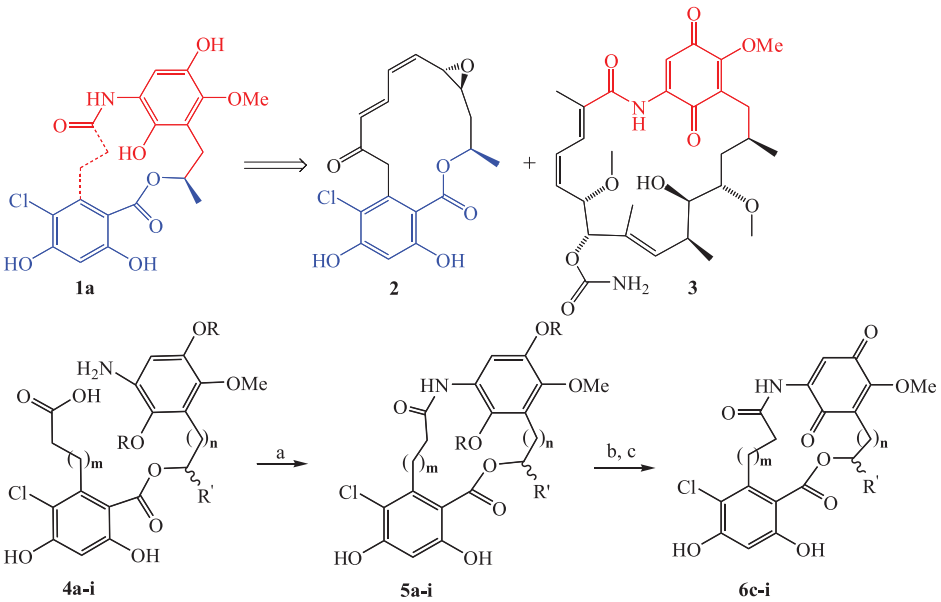
1.1. Functionalisation of Macrocycles with Preservation of Their Sizes

The most common methods for functionalisation of macroheterocycles do not affect the size of cycles.

One of them consists in oxidation of the hydroquinone fragment that is a part of a macromolecule. Thus, compounds with high antiproliferative activities and abilities to inhibit Hsp90-dependent protein degradation that are potential agents to cure cancer (Scheme 1)[4] are obtained in synthesis of radamicine (**1a**) and its seco analogues (**1b-i**) that represent series of macrocyclic chimeras radicicol (**2**) and geldanamycin (**3**) that are strong inhibitors of the Hsp90 N-terminal ATP-binding – macroamidation of acyclic precursors (**4a-i**) under the action of HATU and oxidation of the resulting hydroquinones (**5a-i**) into appropriate quinones (**6c-i**) (Scheme 1).

Unsaturated cycles, functionalization of which occurs on multiple bonds, are often formed resulting from macrocyclization. Thus, in target synthesis of biologically active macroheterocycles, after the stage of the formation of unsaturated cycles, the reaction of reduction of multiple bonds follows: exhaustive hydrogenation of C≡C, C=C and C=N bonds over Wilkinson's catalyst, Raney nickel and Pd/C,[6-11] reduction of C=N bonds using $NaBH_4$ or $LiAlH_4$ [6-12] and partial hydrogenation of the C-C triple bond to Z-double over Lindlar catalyst[13-18] that allow obtaining both isolated bonds, and conjugated systems.

For example, a method for hydrogenation of a double bond over palladium catalyst has been demonstrated in stereoselective synthesis of macrolactames of fluvirucines B_{2-5} (**7**) showing properties of antibiotics and strong inhibitors of A virus with low toxicity.[19] Construction of the macrocyclic skeleton of species **7** was carried out by the metathesis reaction of acyclic precursor, *i.e.* diene **8** over the second generation Grubbs catalyst leading to a mixture of *Z*- and *E*-isomers **9** easily separated by silica gel flash chromatography. Hydrogenation of both isolated isomers (**9***E*) and (**9***Z*) and their mixture proceeds highly stereoselectively over a palladium catalyst with the formation of 6*S*-isomer (7) as major (after



Experiment	n	m	R	R'	Experiment	n	m	R	R'
a	1	1	Me	Me	f	1	3	H	H
b	1	1	Me	H	g	2	3	H	H
c	1	1	H	H	h	3	3	H	H
d	1	1	H	Me	i	1	3	H	Me
e	1	2	H	H					

Scheme 1. a) HATU, HOBt, *i*-PrNEt, DMF, 70 °C (72-80 %); b) TMSCl, NaI, MeCN, CH_2Cl_2 (73-90 %); c) Pd/C, MeOH, air (70-80 %).

crystallization of *dr* 97:3). High stereoselectivity of hydrogenation process may be explained by depicting **10***Z*- and **10***E*-conformers of compound (**7**) with the minimum energy: the upper verges of the both isomers are most available (Scheme 2).

Crownophane-type macrocycles are especially attractive for selective recognition of inorganic and organic cations, anions and neutral substrates.They can also be used as a platform for the development of systems, *e.g.,* rotaxanes and catenanes. The authors[19-21] have reported of convenient and efficient synthesis of crownophanes (**10a-m**) with two amide and two hydroxyl groups by direct amidation of dichloroanhydride (**11**) with a series of achiral and chiral diamines (**12a-m**) followed by the involvement of the resulting macrocycles (**13a-m**) in the tandem Claisen rearrangement. The latter reaction allows obtaining macrocycles with naphthol fragments without using special conditions (high dilution) (Scheme 3).

The study of properties of the synthesized macrocyclic *bis*-amldonaphthol (**10**) in relation to anions testifies significant effects of the sizes of macrocyclic rings. For example, macrocycle (**10c**) shows selectivity towards F^- ion that has unique chemical properties and plays a significant part in stomatology, the treatment of osteoporosis, *etc*. It was also demonstrated that acidity of the hydroxyl group might be controlled by ring sizes, which enables it to differentiate a subtle difference to affinities of F^-, CH_3COO^- and $H_2PO_4^-$ ions.

Polyazamacrocycles have attracted much attention, since they have found applications in various areas, such as ion release, extraction and catalysis. The presence of additional functional groups at one or several nitrogen atoms broadens chelating properties and allows regulating solubility and behaviour in solutions.[22-27] *N*-Functionalized triazamacrocycles that are prepared mostly by *N*-alkylation reaction[28-31] are especially attractive compounds to prepare selective ligands that coordinate transition metals.

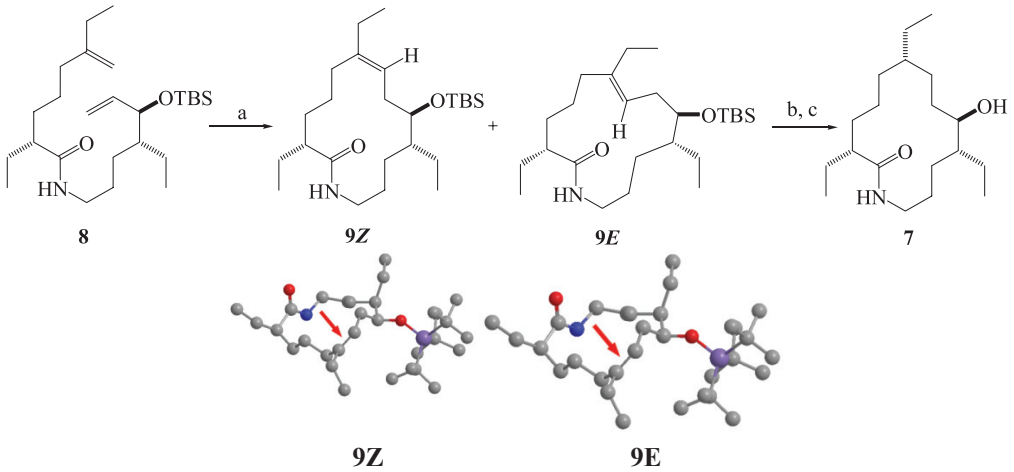
1,5,9-Triazacyclodecane (**14**) is an extremely basic azacrown compound (pK_{a_3}=12.3–12.7) used as an efficient extractant for gold dicyanate anion $[Au(CN)_2]^-$. Good solubility of the resulting complex in water significantly worsens its transfer to the organic phase. To increase hydrophobicity compound (**14**) was transformed into mono- (**15**), di- (**16**) and tri- (**17**) *N*-dodecyl derivatives.[32] Alkylation of triamine (**14**) with excess *n*-dodecyl iodide in DMF in the presence of $NaHCO_3$ proceeds with the formation of disubstituted compound (**16**). Selective alkylation of two out of three equivalent nitrogen atoms of compound (**14**) may be explained by high proton affinity of the ring. Reductive amination of compound (**14**) with *n*-dodecanal yielded trisubstituted product (**17**). Monoalkylated macrocycle (**15**) was prepared using the Parker approach involving condensation of a diethylmalonate and *bis*(3-aminopropyl)amine (**18**) in the presence of catalytic amounts of sodium methoxide in ethanol. The presence of unequal nitrogen atoms in the resulting cyclic aminodiamide (**19**) allows carrying out alkylation chemoselectively and obtaining monosubstituted amine (**15**) after reduction of amide groups (Scheme 4).

Synthesis [33] of two optically pure ligands (**20**) and (**21**) containing the *L*-lactic acid residues in side chains and used for coordination of Mn^{2+} ion included successive treatment of cyclic triamines (**23**) and (**24**) obtained from acyclic precursors (**18**) and (**22**)[34] with K_2CO_3 base in the polar aprotic solvent DMF and bromodiester (**26**) that is a product of chemoselective transformations of L-lactic acid (**25**) (Scheme 5).

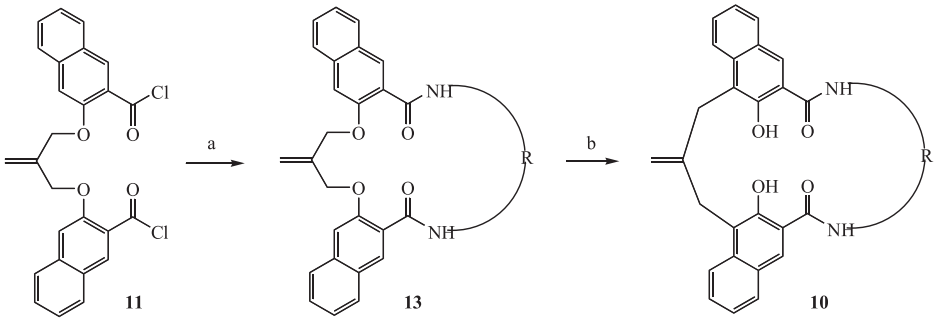
Alkaline treatment of *N*-macrocycle (**27**) obtained by condensation of *bis*-(3-aminopropyl)amine (**18**) with 2,6-pyridine dialdehyde (**28**) followed by hydride reduction, and then with 2-chloromethylpyridine (**29**) leads to trisubstituted derivative (**30**) able to form chelate complexes with a broad number of elements, such as Ca^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Ga^{3+}, Fe^{3+}, and In^{3+} (Scheme 6).[35]

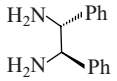
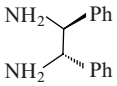
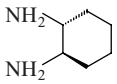
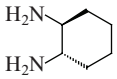
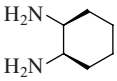
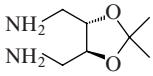
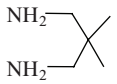
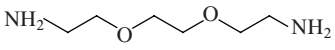
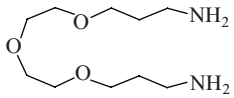
The presence of four secondary amine functions in tetraazacycloalkanes allows unlimitedly obtaining their derivatives showing better analytical properties (*e.g.* UV spectrum, fluorescence, thermal stability, volatility, *etc.*). Particularly, 1,4,7,10-tetraazacyclodecane (cyclen) (**31**) from *bis*(2-aminoethyl)amine (**22**)[36,37] and 1,4,8,11-tetraazacyclotetradecane (cyclame) (**32**) from *N,N*'-di-(2-aminoethyl)-1,3-diaminopropane (**33**)[38] are used as ligands for selective binding of metal ions into very stable complexes (Scheme 7).

Some derivatives of cyclen (**31**) and cyclam (**32**) completely substituted with identical functional groups show selective coordinative properties towards transition and heavy metal cations, lanthanide and actinide ions, and organic and inorganic anions with precise behaviour depending on cavity size and substituent nature.



Scheme 2. a) Grubbs-II, toluene, 80 °C (85 %); b) H_2 Pd/C, toluene; c) TBAF, THF.



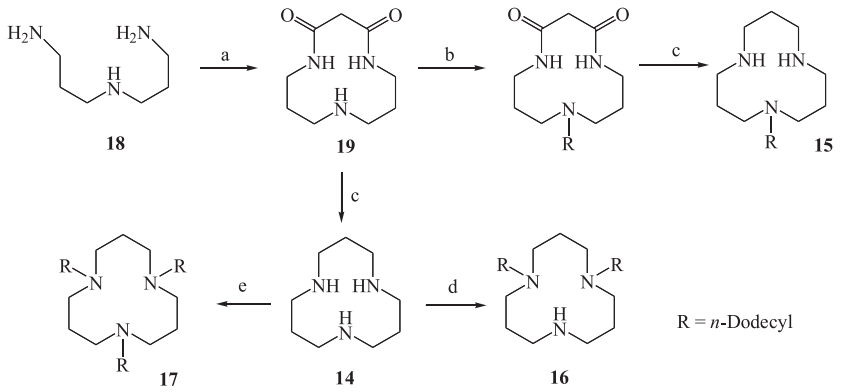
H_2N-R-NH_2	**12**	Yield of **13**	**13**, method	Yield of **10**	Ref.
$NH_2CH_2CH_2NH_2$	**12a**	43 %	**13a,** A	20 %	[96]
$NH_2(CH_2)_6NH_2$	**12b**	86 %	**13b,** B	81 %	[98]
$NH_2(CH_2)_8NH_2$	**12c**	69 %	**13c,** A	100 %	[97]
$NH_2(CH_2)_{12}NH_2$	**12d**	60 %	**13d,** B	83 %	[98]
	*(R,R)*-**12e**	30 %	**13e**, B	60 %	[96]
	*(S,S)*-**12f**	38 %	**13f**, B	80 %	[96]
	*(R,R)*-**12g**	30 %	**13g,** A	62 %	[96]
	*(S,S)*-**12h**	35 %	**13h,** A	55 %	[96]
	**12i**	66 %	**13i,** A	32 %	[96]
	*(S,S)*-**12j**	52 %	**13j**, B	88 %	[96]
	**12k**	83 %	**13k**, B	43 %	[96]
	**12l**	74 %	**13l**, B	81 %	[98]
	**12m**	52 %	**13m**, B	82 %	[98]

Scheme 3. a) H_2N-R-NH_2 (**12a-m**), Et_3N, C_6H_6, 50 °C; b) $PhNMe_3$, 180 °C (method A) or 150-180 °C (method B).

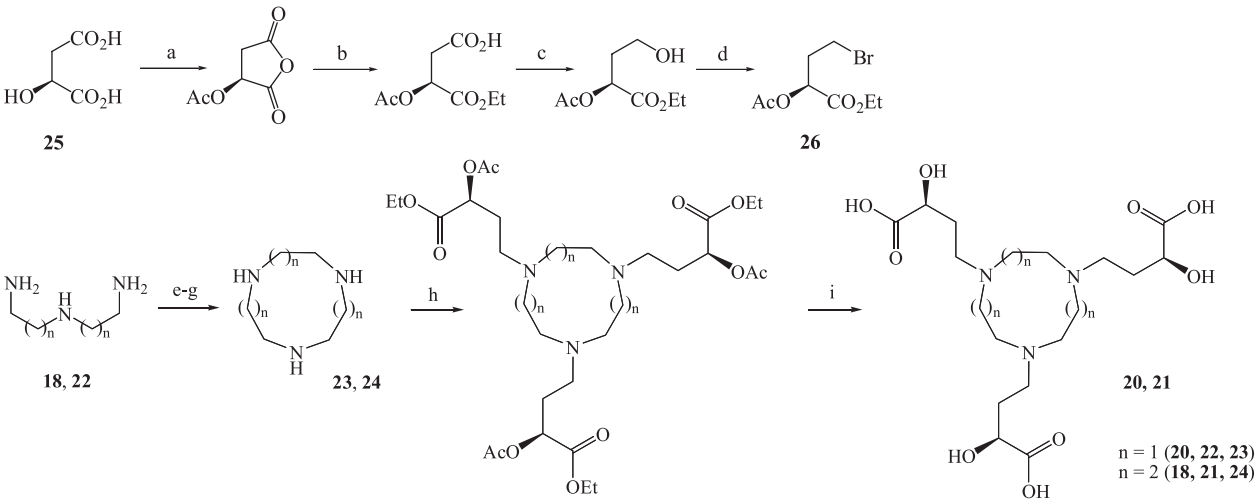
Tetraphenylsulfonyl- (**34**) and optically pure tetraphenylsulfenyl- (**35**) substituted with cycles used for complexation with Cu^{2+} and Eu^{2+} ions are accordingly obtained by the interaction of unsubstituted cyclam (**32**) and a slight excess of phenyl vinyl sulfone (**36**) and (*R*)-*p*-tolyl vinyl sulfoxide (**37**) under aza-Michael reaction conditions (Scheme 8).[39]

Tetra-*N*-substituted cyclen with carbamide side chains (**38**) are readily obtained by treatment with butyl isocyanate (4 equiv) of unsubstituted cyclen (**31**) (Scheme 9).[40]

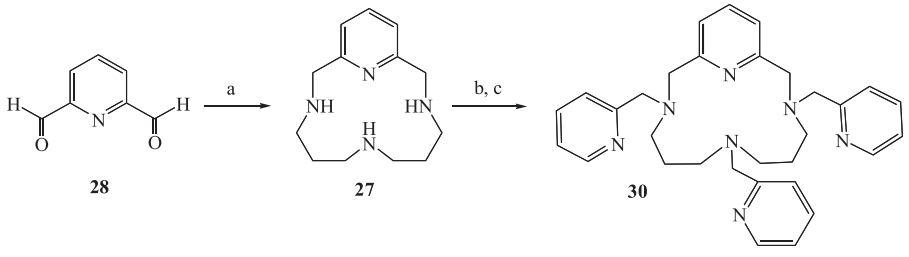
Aminocarboxylate derivatives turned out to be extremely valuable for obtaining highly stable chelates with lanthanoids. In turn, the latter have found applications



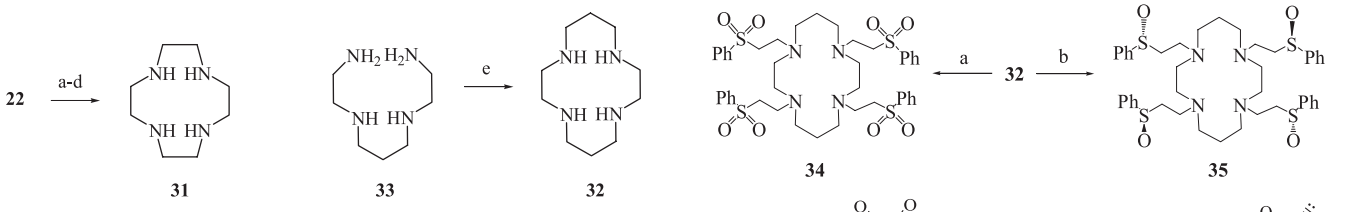
Scheme 4. a) EtO OEt, MeONa, EtOH, Δ (22 %); b) $C_{12}H_{23}I$, DMA (60 %); c) BH_3-THF, Δ (99 % for **12**, 95 % for **16**); d) $C_{12}H_{23}I$, $NaHCO_3$, DMA, 80 °C (88 %); e) $C_{11}H_{23}CHO$, $NaCNBH_3$, H_2O/MeCN, p*H*=4–5 (90 %).



Scheme 5. a) AcCl, Ac_2O; b) EtOH (100 %); c) BH_3-THF, 0 °C (70 %); d) Ph_3P, Br_2 (75 %); e) TsCl, NaOH, Et_2O, H_2O (97 % based on **18**, 57 % based on **22**); f) $Br(CH_2)_nCH_2Br$, K_2CO_3, DMF (24 % based on **18**, 8 % based on **22**); g) H_2SO_4, H_2O, 100 °C (88 % based on **18**, 79 % based on **22**); h) **26**, K_2CO_3, DMF (48 % based on **18**, 54 % based on **22**); i) HCl, H_2O, 100 °C (80 %).

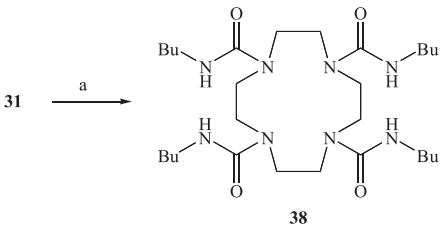


Scheme 6. a) **18**, $Cu(NO_3)_2$, EtOH, H_2O then $NaBH_4$ (86 %); b) NaOH, H_2O, CH_2Cl_2; c) ClH_2C (**29**) (55 %).



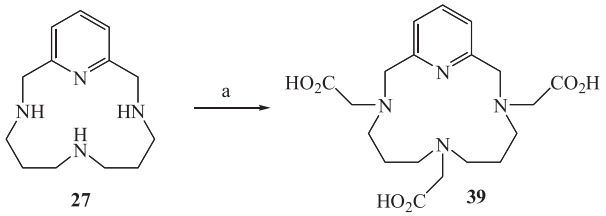
Scheme 7. a) TsCl, Py, 50 °C; b) EtONa, EtOH; c) DMF, 100 °C; d) H_2SO_4, H_2O, 100 °C (80 %); e) $Br(CH_2)_3Br$, KOH, EtOH (80 %).

Scheme 8. a) Ph (**36**), *i*-PrOH, H_2O (82 %); b) 3R-(**37**), *i*-PrOH, H_2O (69 %).



Scheme 9. a) 4 Bu-NCO, CH_2Cl_2 (90 %).

in medicine for diagnostics and as therapeutic agents. On the other hand, separation of f-elements (lanthanoids and actinoids) is of interest in production of nuclear fuel, since treatment is very difficult due to close chemical properties, moreover, cation radius size may turn out to be the key factor. Thus, in order to assess the effect of cavity size of macrocycles for complexation with the participation of cations 14-membered macroheterocycle (**39**) able to form stable complexes with some lanthanoids (La, Pr, Nd, Eu, Gd, Tb, Er, Yb, Lu) at various medium acidities is synthesised. Synthesis is based on alkylation of cyclic triamine (**27**) with acrylic acid under aza-Michael reaction conditions (Scheme 10).[41-44]



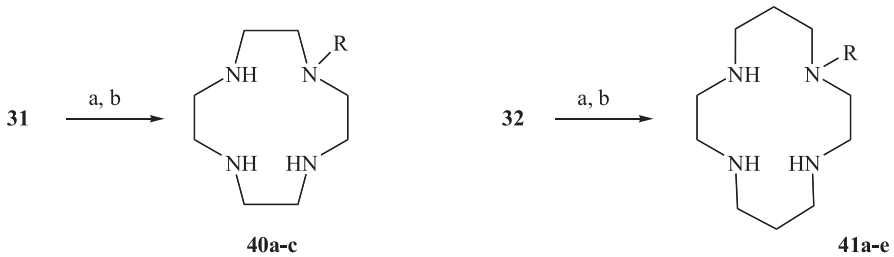
Scheme 10. a) CH_2=$CHCO_2H$, H_2O, 70 °C (35 %).

Due to the more complex synthesis of partially substituted tetraazaalkanes, they have received much less attention. However, these compounds are becoming increasingly popular, since they are important synthons for synthesis of macropolycycles or unsymmetrically substituted macrocycles. In fact, mixing various side substituents may increase ligand selectivity for a given ion and will allow carrying out fine tuning properties of complexes. Their use as agents for magnetic resonance therapy is one of the possible examples. Partial substitution may also include coupling complexes with antibodies for radioimmunotherapy or the attachment of ligands into organic or inorganic polymers for their use in the processes of solid-liquid extraction.

Syntheses of mono- and trisubstituted tetraazamacrocyclic derivatives have been described in detail in the review.[3] It proposes direct functionalisation for symmetric azacrown ethers, to which cyclen (**31**) and cyclam (**32**) are referred. Selective monoalkylation of tetraazacycloalkanes assumes the use of a large excess of macrocycles (5-10 equiv of cyclam (**32**) and 1.5-3 equiv of cyclen (**31**)) in relation to electrophiles (appropriate halocarboxylic acids) in the presence of LiOH in polar solvents (DMF, toluene, ethanol, acetonitrile or chloroform) and leads to monosubstituted cyclens (**40a-c**) and cyclames (**41a-e**) with yields up to 80 % (Scheme 11).

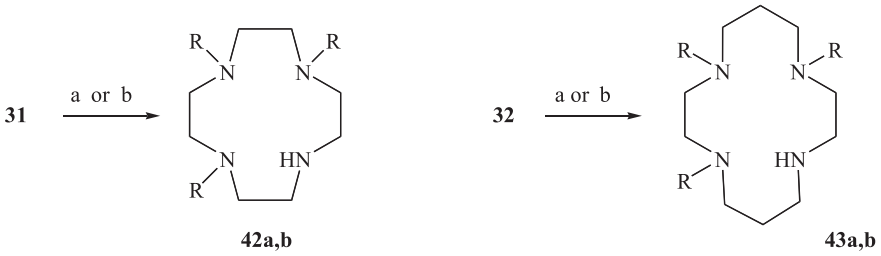
Tri-*N*-substitution of tetraazacycloalkanes has been more widely studied, since such trisubstituted derivatives are precursors for synthesis of monosubstituted macrocycles. The best result (51%) in synthesis of cyclam tritosylate (**43a**) has been reached when using a (2.1:1:2.2) molar ratio of tosyl chloride/cyclam (**32**)/Et_3N in dichloromethane. Tritosylcyclen (**42a**) was obtained with 80% yield upon the addition of tosyl chloride (5 equiv) to macrocycle (**31**) (1 equiv) in the presence of a large excess (17 equiv) of triethylamine. High yields of tetraazacycloalkanes (**42b**) and (**43b**) trisubstituted with tert-butyl carbonyl (Boc) groups (70% for cyclen (**31**) and 67% for cyclam (**32**)) were obtained using only 2.4 equiv of di-*tert*-butyl carbonate (Boc_2O). Large differences in polarity of the resulting di-, tri-, and tetra-substituted azamacrocycles facilitated chromatographic isolation of trisubstituted cyclens (**42a,b**) and cyclams (**43a,b**) (Scheme 12).[3]

The interaction of cyclam (**32**) with a large excess of iodoacetamide (**44**) in acetone in the presence of *i*-Pr_2NEt as a base is not following the usual pattern: only pure triamide (**45**) as powders almost insoluble in water and acetone is obtained. Afterwards, it is transferred to triacid (**46**). The formation of (**45**) is probably related to a high proton affinity

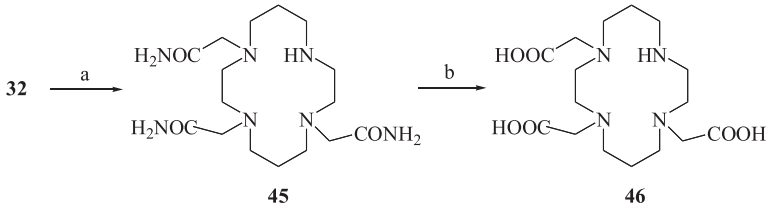


Experiment	R	Solvent	Yield of 40, %	Yield of 41, %
a	CH_2CO_2H	EtOH	74	77
b	$(CH_2)_2CO_2H$	EtOH	72	65
c	CH_2-*m*-Py	DMF	60	80
d	CH_2-*o*-Py	DMF	–	74
e	$(CH_2)_2$-*o*-Py	DMF	–	40

Scheme 11. a) LiOH, solvent; b) R-X, H_2O.



Scheme 12. a) TsCl, Et_3N, CH_2Cl_2; b) Boc_2O, CH_2Cl_2.

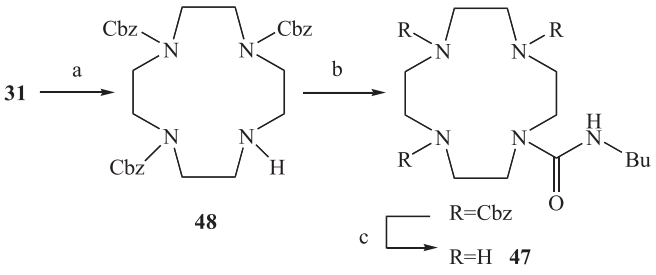


Scheme 13. a) ICH_2CONH_2 (**44**), *i*-Pr_2NEt, Me_2CO (99 %); b) 25 % HCl.

of the cyclam ring and low solubility of the ion pair formed by the macrocyclic cation and iodide ion (Scheme 13).[45]

Two-step synthesis of mono-*N*-substituted cyclen (**47**) with the carbamide side chain consisting in direct functionalization of cyclen (**31**) up to trisubstituted derivative (**48**) and its treatment with butyl isocyanate (Scheme 14) is an illustration of correlations between mono- and trisubstituted azacrowns. [40]

The literature describes numerous examples of synthesis, in which additional fragments to the already prepared

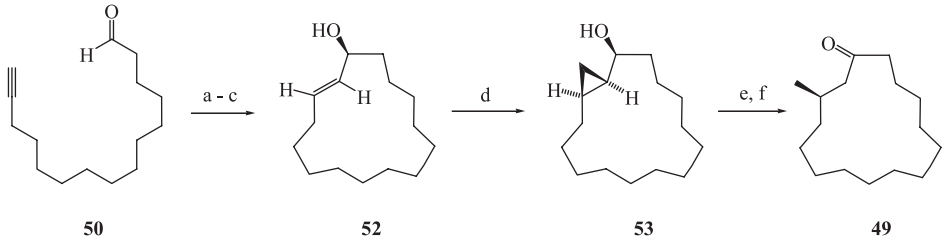


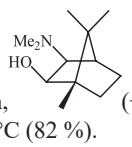
Scheme 14. a) $ClCO_2CH_2Ph$, CH_2Cl_2, Et_3N (49 %); b) Bu-NCO, CH_2Cl_2 (86 %); c) H_2, Pd/C, EtOH (98 %).

macrocyclic ring are being completed. Thus, the construction of three-membered rings is one of the methods for C=C bond functionalization.

For example, the cyclopropanation reaction is applicable in case of enantiomeric pure *R*-muscone (**49**) that is an odorous substance (muscus) isolated from glands of musk deer *Moschus moschiferus*.[46,47] Asymmetrically catalysed cyclization of 14-pentadecinal (**50**) consisting in hydroboration of its triple bond followed by transmetalation and interaction with the aldehyde functional group in the presence of (-)-3-*exo*-(dimethylamino) isoborneol (**51**) yielded *E*-allyl alcohol (**52**) with high (92% *ee*) enantiomeric purity. Hydroxy-directed cyclopropnation by the Denmark method followed by recrystallization yielded the sole diastereomer of alcohol (**53**), the Swern oxidation of which and reduction of the cyclopropyl functional group completed the synthesis (Scheme 15).

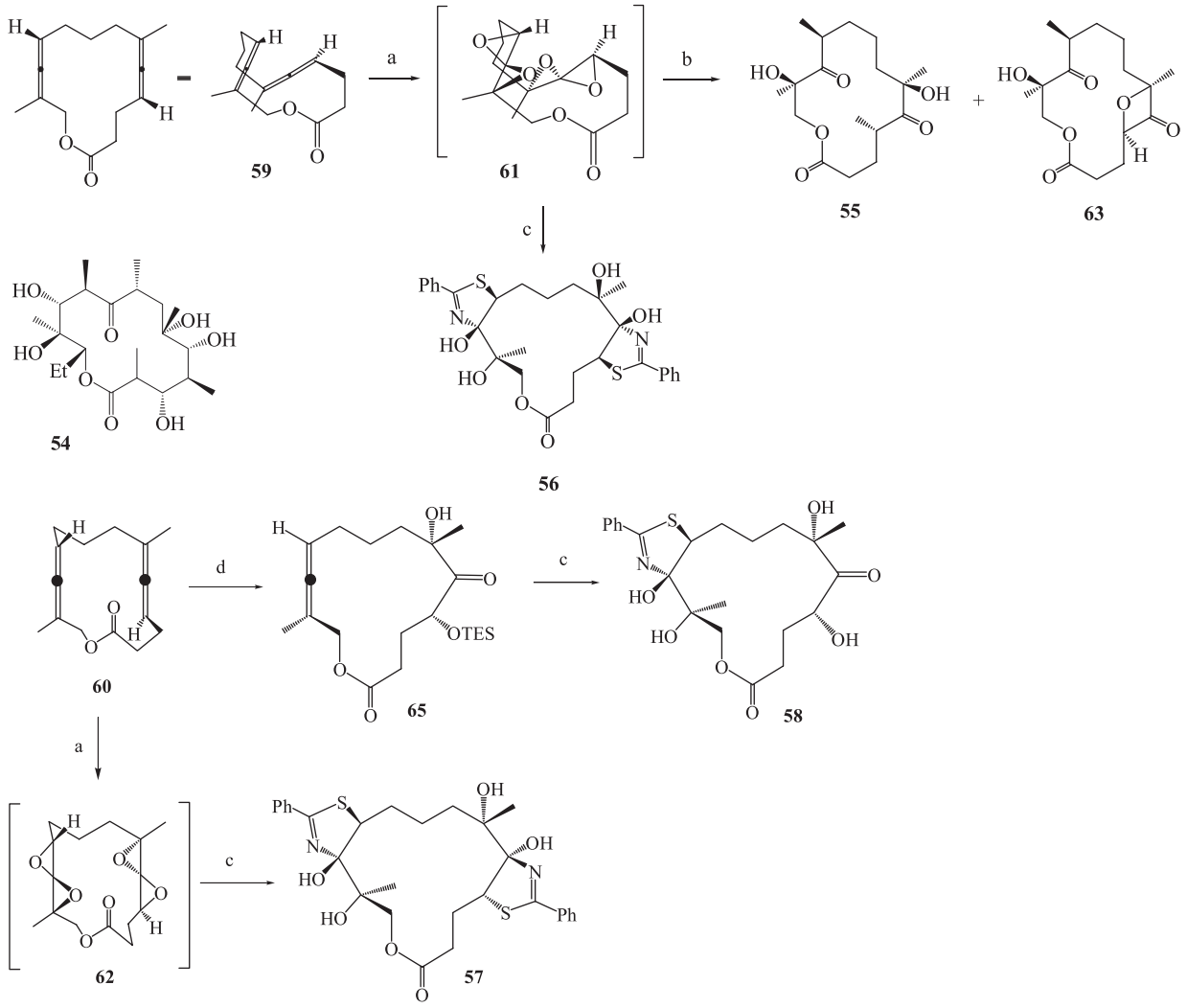
Oxidation of the double bond to epoxide is another option for the construction of a three-membered ring. This approach has been successfully carried out upon the action of metachloroperbenzoic acid on olefins in synthesis of ionophor units[48,49] and representatives of a very large family of chemically bound mycotoxins (trichothecins)[50] or 2,2'-dimethyl-



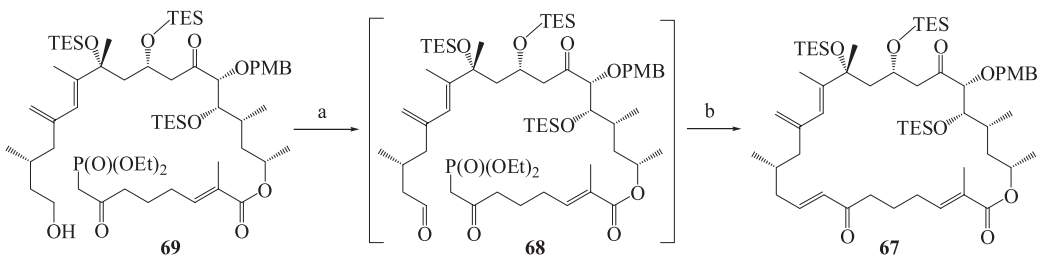
Scheme 15. a) $HB(\text{cyclohexyl})_2$, hexane, 0 °C; b) Et_2Zn,  (+)-DAIB (**51**); c) NH_4Cl, H_2O (75 %); d) Et_2Zn, $Cl(CH_2)_2Cl$, 0 °C then crystallization; e) Swern oxidation; f) Li/NH_3, -78 °C (82 %).

dioxirane (DMDO) in synthesis of epothilone A and B,[51] their analogues,[52] and antibiotic erythromycin derivatives A.[53] Thus, synthesis of erythronolide A (**54**) derivatives that are macroheterocycles (**55-58**) with potentially antibiotic properties[53] was carried out by the interaction between DMDO and cyclic *bis*-allenes (**59**) and (**60**) that led to appropriate *bis*[spirodiepoxides] (**61**) and (**62**). Subsequent addition of methyl cuprate to compound (**61**) leads to chiral macroheterocycle (**55**) with four stereocenters and side rearrangement product with C4-C6 oxetane fragments (**63**). Reduction of *bis*[spirodiepoxides] (**61**) and (**62**) with thiobenzamide (**64**) forms thiazoline rings into C-5 and C-11 positions of macrocycles (**56**) and (**57**) with 78 % and 74 % yields, respectively. A decrease in the amount of dimethyldioxirane in 3 times upon epoxidation of (**60**) leads to the selective formation of keto-alcohol (**65**) that is further transformed into mono-thiazoline (**58**) (Scheme 16).

The formation of the epoxide ring is possible under Sharpless conditions. This process has been carried out in stereselective synthesis[54-56] of amphidinolide B (**66**) that is a representative of a family of amphidinolides that are isolated from dinoflagellates *Amphidinium sp.* and show anticancer activity. Thus, the generation of macrocyclic structure (**67**) happens upon spontaneous cyclization by the intramolecular Wittig-Horner reaction of compound (**68**) that is an oxidation product of acyclic precursor (**69**) (Scheme 17).



Scheme 16. a) DMDO (6 eq.), $CHCl_3$, -40 °C; b) MeCuCNLi, Et_2O, -40 °C (22 % for **55**, 17 % for **63**); c) $PhCSNH_2$ (**64**), 0 °C (78 % for **56**, 78 % for **57**, 78 % for **58**); d) *i*. DMDO (3 eq.), $CHCl_3$, -40 °C, H_2O; *ii*. TESCl, imide, DMAP, CH_2Cl_2, 0 °C (77 %).



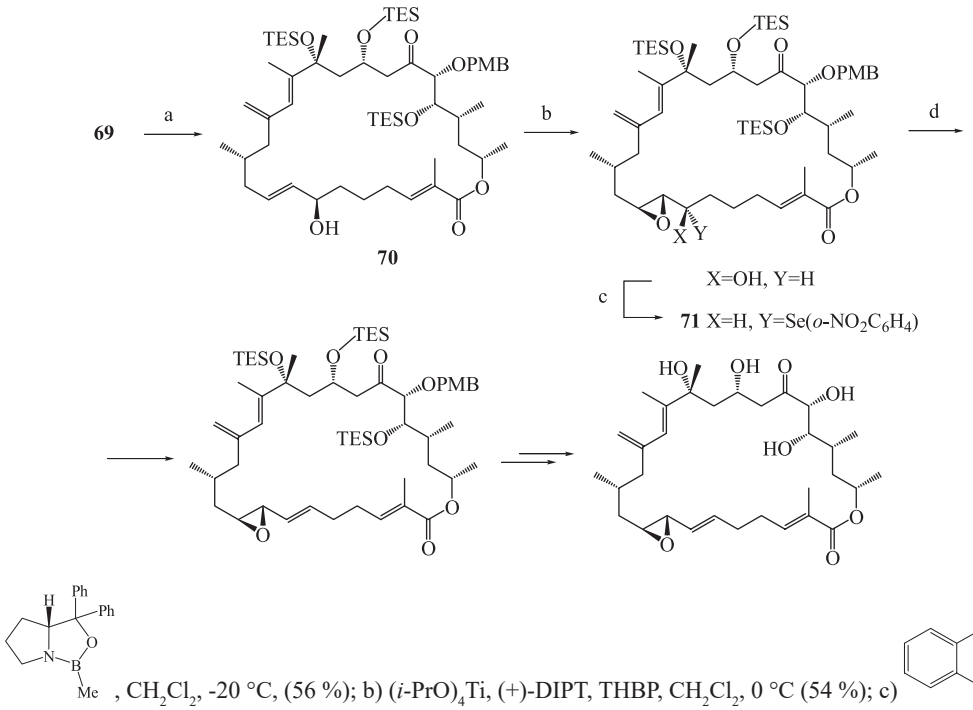
Scheme 17. a) TPAP, CH_2Cl_2; b) $Ba(OH)_2 \cdot 8H_2O$, THF/H_2O.

The introduction of the epoxide ring into macrocycle (**67**) was carried out in two steps. The first one consisted in stereoselective (*dr* 10:1) reduction with cathehol borane into allyl alcohol (**70**) involved in the stereoselective Sharpless epoxidation. In the presence of diisopropyltartrate, *dr*-selectivity of the latter reaction is 10:1,[54] and in its absence, it is drastically decreased to 1.5:1.[55] Dehydration was carried out via intermediate ortho-nitrophenyl selenide (**71**) (Scheme 18).

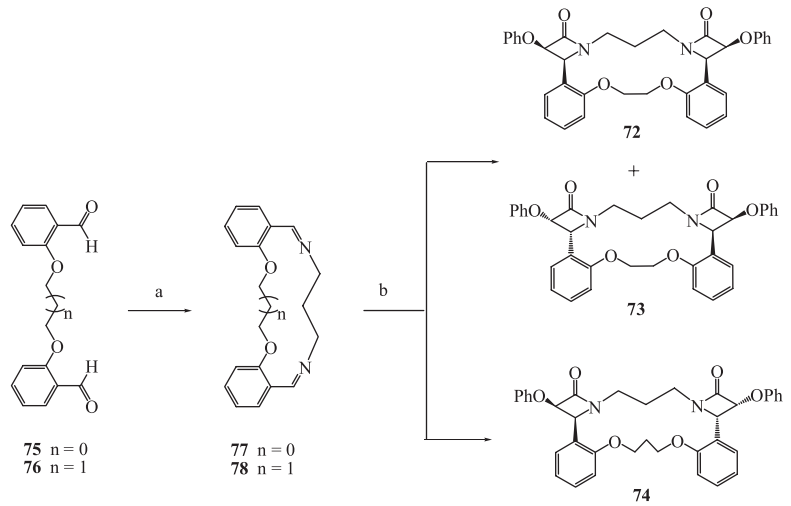
The formation of a four-membered ring was described in synthesis[57] of macrocyclic *bis*-azetidines (**72-74**) as convenient chelating agents for a series of metals, particularly, $Co_2(CO)_6$. It consists in transformations of diimines (**77**) and (**78**) readily available from dialdehydes (**75**) and (**76**), respectively, using the double Staudinger reaction accompanied by the formation of two additional four-membered rings. It is noteworthy that diimine (**77**) with closely located functional groups reacted low-selectively yielding a mixture (1:1) of *cys-syn-cys* (**72**) and *cys-anti-cys* (**73**) diastereomers, and diimine (**78**) almost exclusively turned into *cys-anti-cys* diastereomer (**74**) (Scheme 19).

The formation of a five-membered oxazol ring was carried out, for instance, in synthesis of the macrolide ulapualide A isolated from marine nudibranch[58] and oxygen analog (**79**) of the anti-inflammatory thiazole-containing drug halipeptin D (**80**) of sea sponges *Leiosella cf. arenifibrosa*. Synthesis of the latter includes cyclization of aminoacid (**81**) under the action of HATU and macrocycle (**82**) and the formation of the oxazole ring under the action of DAST on compound (**83**) (Scheme 20).[59]

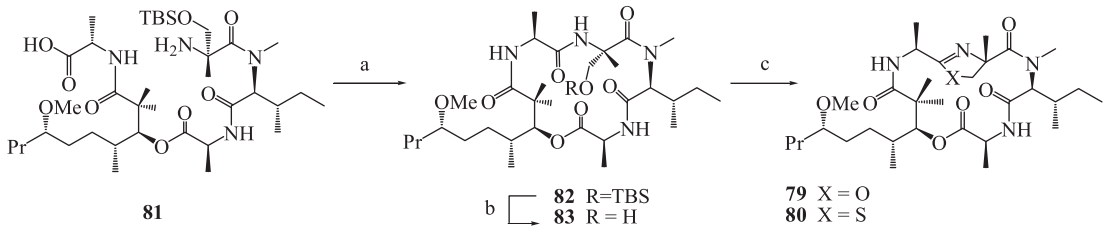
We managed to generate highly-stressed 13-membered macrocycle (**86**) by the intramolecular Ullmann etherification of compound (**85**) in synthesis of hirsutellone B (**84**) isolated from the pathogenic fungus *Hirsutella nivea* BCC



Scheme 18. a) , CH_2Cl_2, -20 °C, (56 %); b) $(i\text{-PrO})_4Ti$, (+)-DIPT, THBP, CH_2Cl_2, 0 °C (54 %); c) , PBu_3, THF (50 %); d) TPAP, NMO, Et_3N, CH_2Cl_2 (48 %).



Scheme 19. a) H_2N NH_2, MeOH, Δ (94 % for **75**), (95 % for **76**); b) $PhOCH_2COCl$, Et_3N, CH_2Cl_2, -78 °C (23 % for **72**, 27 % for **73**, 78 % for **74**).



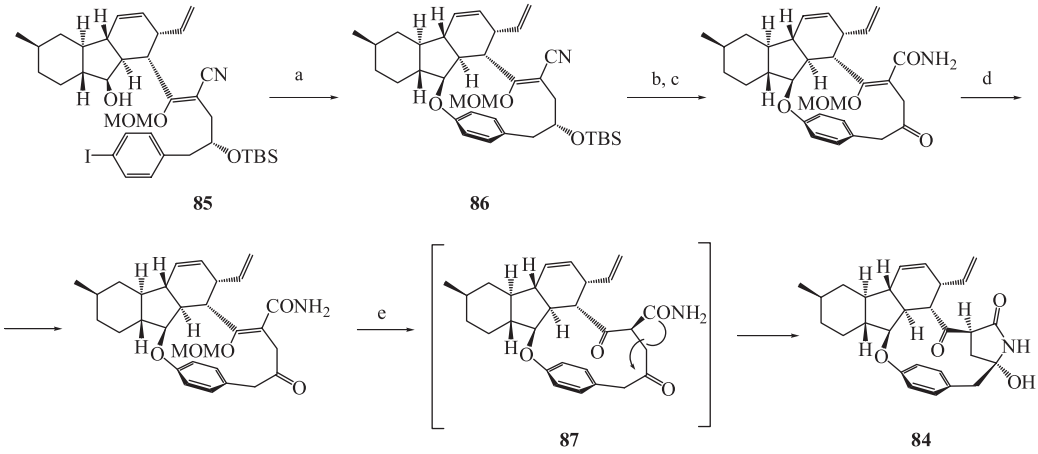
Scheme 20. a) HATU, HOAt, *i*-PrNEt, CH_2Cl_2 (74 %); b) TBAF, THF, -10 °C; c) DAST, CH_2Cl_2, -78 °C (74 %).

2594 and showing antituberculous activity, and spontaneous stereoselective cyclization into desired five-membered γ-hydroxylactam (**84**) proceeded after the removal of protective groups in cyclophane (**87**) (Scheme 21).[60]

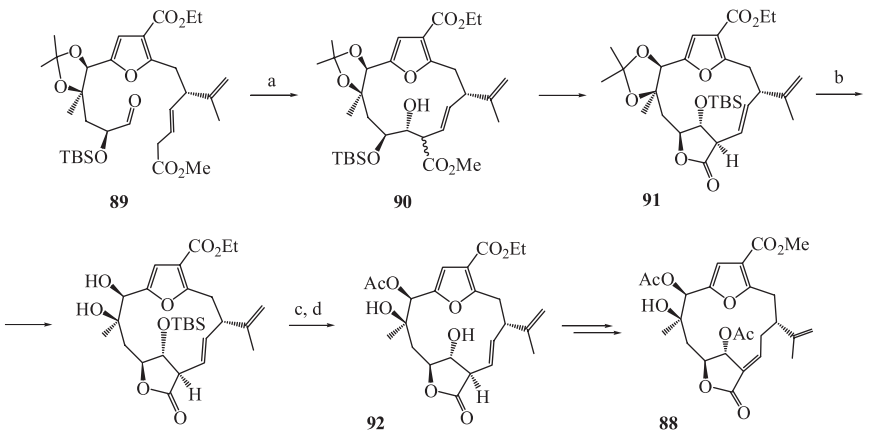
Another method to generate a five-membered ring was carried out in synthesis of natural danielid (**88**), *i.e.* oxygenated furan lactone-containing cembranoid[61] isolated from gorgonian. Treatment of α-siloxy aldehyde (**89**) with Li-HMDS proceeds with intramolecular cyclization to intermediate (**90**) that is accompanied with *in situ* lactonization with migration of the acyl group and leads to the sole diastereomer of furanocenbranoid (**91**). The removal of ethylene ketal protection and chemoselective acylation of secondary hydroxyl groups leads to macrocycle (**92**) that is semiproduct in synthesis of (**88)** (Scheme 22).

The intramolecular stereoselective Michael addition is one of the key steps in synthesis of leinamicyne (**93**) with the unique spiro-1-oxo-1,2-dithiolane-3-one structure. This compound is a new antitumor antibiotic. The intermediate thiolane fragment formed under the action of H_2S on bromoketone (**94**) is added to the third position of 18-membered α,β-unsaturated lactam yielding a mixture (10:1) of spirosulphides (**95a**) and (**95b**).[62] Isomer (**95a**) was the chiral intermediate for synthesis of leinamicyne (**93**) (Scheme 23).[63]

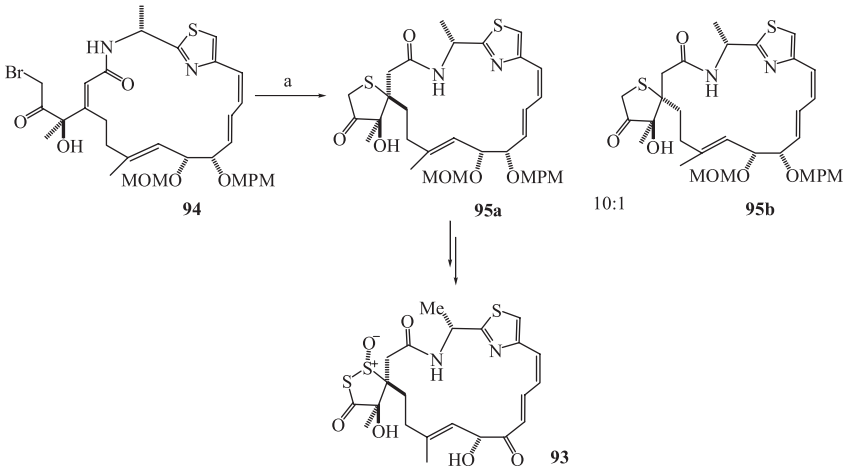
There are examples in the literature when six-membered rings, *e.g.* hexanolide [64] or tetrahydropyrane-4-one [65]



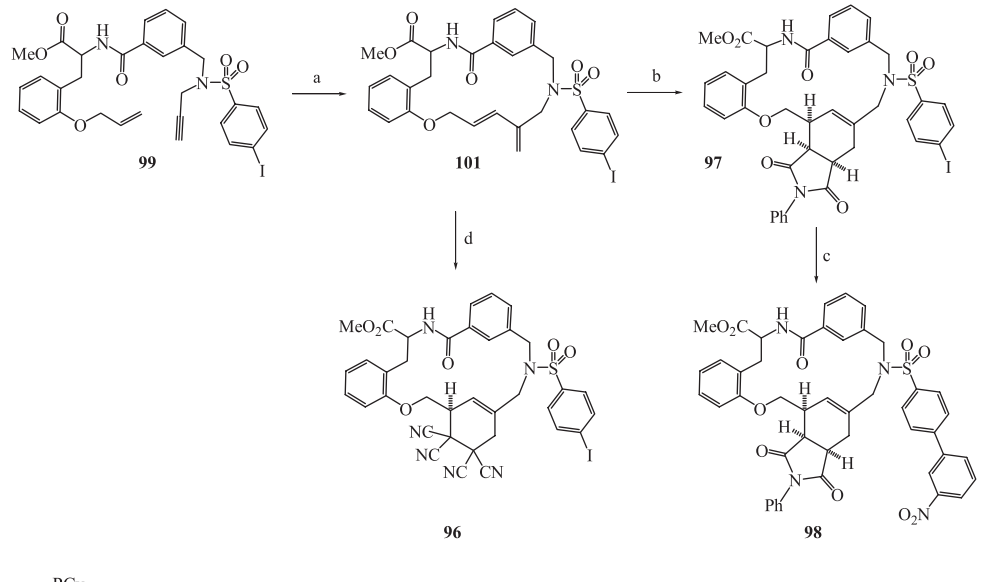
Scheme 21. a) CuI, Cs_2CO_3, 1,10-phenanthroline, toluene, 160 °C (42 %); b) TBAF, THF; c) DMP, CH_2Cl_2 (90 %); d) KOH, *t*-BuOH; e) HCl aq., *i*-PrOH, 60 °C (85 %).



Scheme 22. a) LiHMDS, LiCl, THF, -78 °C (51 %); b) H_2O/HOAc, 100 °C (98 %); c) TBAF, THF, 0 °C (90 %); d) Ac_2O/Py (65 %).



Scheme 23. a) H_2S, Et_3N (88 %).

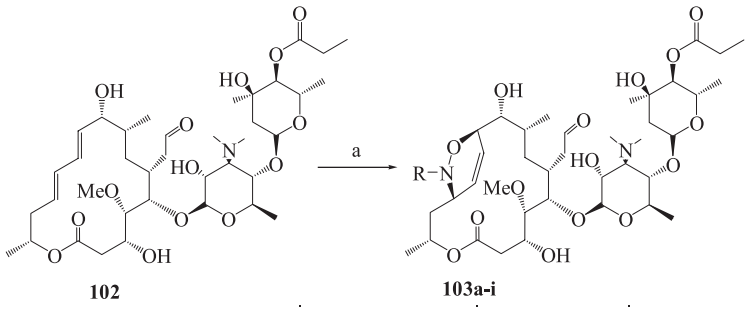


Scheme 24. a) (**100**), $(CH_2Cl)_2$, 60 °C; b) (60 %); c) , $Pd(dppf)Cl_2$, K_3PO_4 (76 %); d) $(NC)_2C=C(CN)_2$ (52 %).

are being completed in macrocyclic species during syntheses of biological objects.Thus, in synthesis of highly functionalised macrocyclic peptidomimetics (**96-98**) containing non-protein structural elements that are able to copy or counteract to biological activity of natural protein species, enyne (**99**) cross-metathesis reaction over catalyst (**100**) and functionalisation of the resulting diene (**101**) by the Diels-Alder reaction [66] that allows the formation of additional six-membered rings of compounds (**96**) and (**97**) are used (Scheme 24).

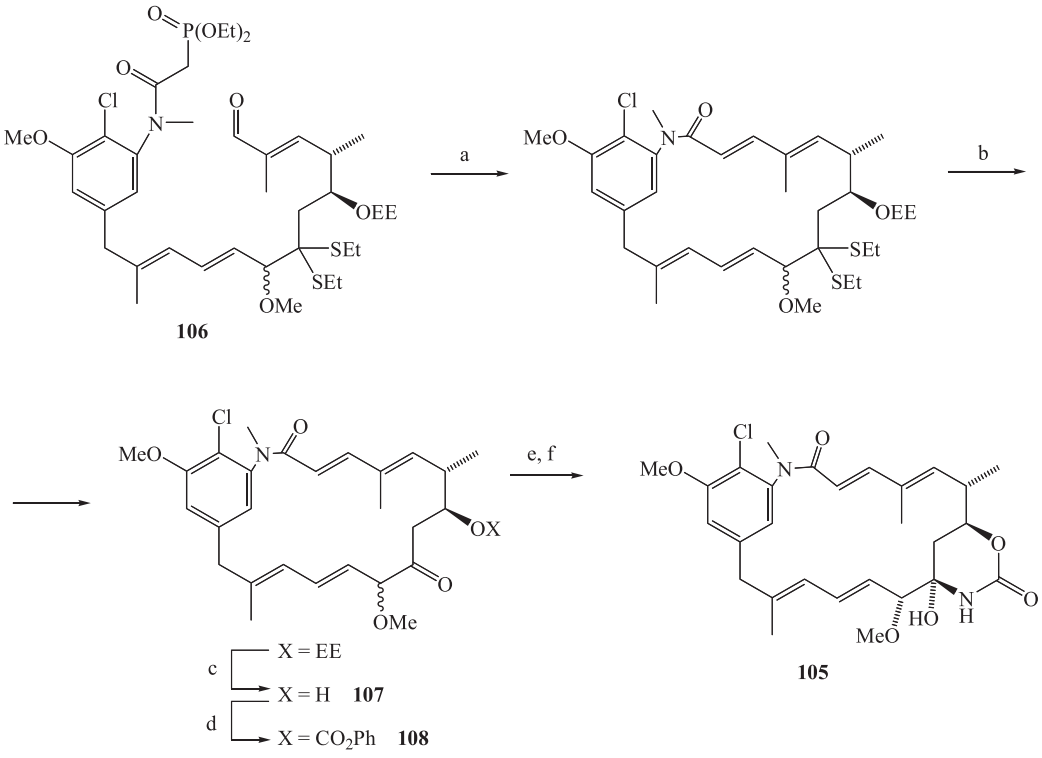
Since antibiotic resistance of pathogenic bacteria has become the challenge of the last decade, the study of new approaches to transformations of potentially biologically active compounds is relevant. For example, the nitroso Diels-Alder reaction, *i.e.* a heteroreaction with nitroso dienophiles was applicable for synthesis of some 10,13-disubstituted 16-membered macrolides (**103 a-i**) from the antibiotic leucomycin A7 (**102**).[67] Despite wide functionalities of the latter, heterocycloaddition proceeded highly regio- and stereoselectively:compounds (**103a-i**) were obtained as a sole isomer. As demonstrated in the carried out experiments, 2-nitrosopyridines (**104a-i**) were efficient dienophiles with selective sensitivities to electron and space structures of macrolide (**102**) with the diene system, which is probably related to their asymmetry. Low yields of compounds (**103b** and **103c**) can be explained by the labile nature of nitroso compounds (**104b** and **104c**), and also instability of leucomycin A7 (**102**) under oxidative conditions. Derivatives (**103a-i**) retained antibiotic properties similar to leucomycin (**102**), however unlike it, they additionally showed antiproliferative and cytoxic properties, which broadened biological activity profile (Scheme 25).

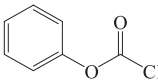
In synthesis of *N*-methylmaysenin (**105**) *i.e.* a macrolide that is isolated from several species of *Maytenus* and represents an extremely promising antitumour drug,



R–N=O	Adducts	Yield, %	R–N=O	Adducts	Yield, %
104a	**103a**	88	**104f**	**103f**	88
104b	**103b**	26	**104g**	**103g**	86
104c	**103c**	13	**104h**	**103h**	89
104d	**103d**	91	**104i**	**103i**	78
104e	**103e**	90			

Scheme 25. a) R–N=O (**104a-i**), CH_2Cl_2, 0 °C.



Scheme 26. a) *t*-BuOK, THF, -78 °C (74 %); b) $HgCl_2$-$CaCO_3$, MeCN-H_2O; c) HCl, THF-H_2O (81 %); d)  , THF; e) liq. NH_3, -78 °C (50 %); f) HPLC.

macrocyclization of compound (**106**) was carried out under Wadsworth-Emmons conditions to form an additional six-membered ring treatment of the hydroxy functional group of compound (**107**) with phenyl chloroformate was used. The resulting mixed carbonate (**108**) was transformed into a mixture of epimers (**105**) at C10 under the action of excess liquid ammonia. The required diastereomer was isolated using HPLC (Scheme 26).[68]

The formation of *cys*-bridged cycles (**109-113**) though with low yields during the interaction of unsubstituted cyclen (**31**) and cyclam (**32**) with *bis*-electrophiles (**114-118**) (Scheme 27) seems to be surprising.[3]

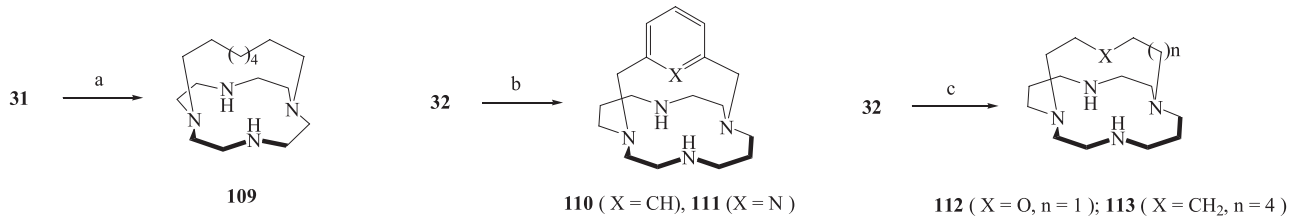
Locking two macro rings[69-73] is required in synthesis of some bicyclic compounds, including and biologically active.

Thus, the development of the bicyclic structure in synthesis of antitumor agents of spiruchostatin A (**119**)[74,75] and FK228 depsipeptide (FR901228) (**120**)[76-82] was carried out by consecutive macrocyclization reactions of hydroxy acids (**121**) or (**122**) by the Shiina's method or under Mitsunobu conditions, correspondingly, followed by the formation of the disulphide fragment in oxidation with iodine (Scheme 28).

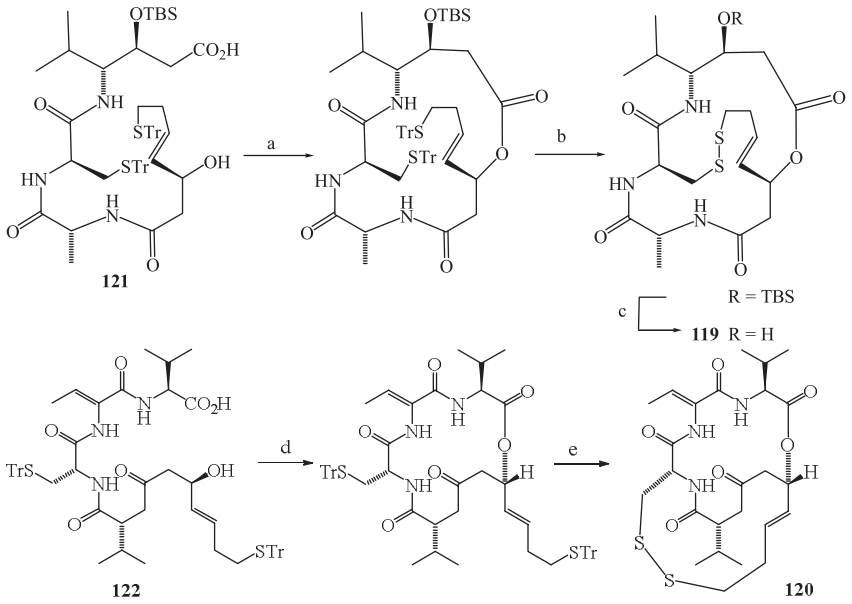
In synthesis[83,84] of the complex macrocyclic spermine alkaloid (-)-ephedradine A (**123**) that is one of the hypotensive components of the traditional Chinese drug Mao-con, the closure of the 16-membered ring of polyamine (**124**) was also carried out under Mitsunobu conditions, and construction of the 13-membered ring of macro-lactam (**125**) included cyclization of precursor (**126**) with an activated ester group using the Staudinger/intramolecular aza-Wittig reaction (Scheme 29).

Macrocyclic tetraazaparacyclophanes are an unique class of compounds that have found broad applications in studies of the "guest-host" interaction,[85] moreover, their structure itself has a high potential for modification. Thus, 1,8,22,29-dibridged derivatives of tetraaza[8,1,8,1] paracyclophane (**127**) and (**128**) are obtained by consecutive reactions of 1,8,22,29-tetraaza[8,1,8,1]paracyclophane (**129**) with 6-bromohexanoyl chloride (**130**) and resulting 1,8,22,29-tetra(6-bromohexanoyl)-1,8,22,29-tetraaza[8.1.8.1]paracyclophane (**131**) with benzene sulphonamide (**132**) (Scheme 30).[86]

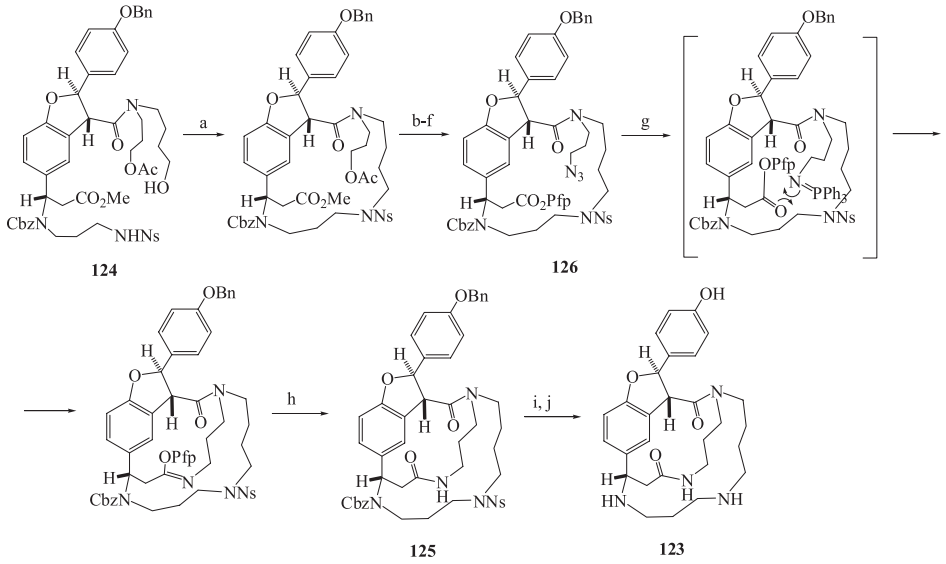
Many crown ethers show high selectivities of complexation against series of alkali metals. Thus, to improve binding metal cations due tothe expansion of macromolecule cavity, synthesis of *bis*-crown ethers (**133**) and (**134**) was carried out by the interaction of tri- (**135**) and tetra- (**136**) ethylene glycol ditosylates with tetramethoxy resorcinarene (**137**) (Scheme 31).[87]



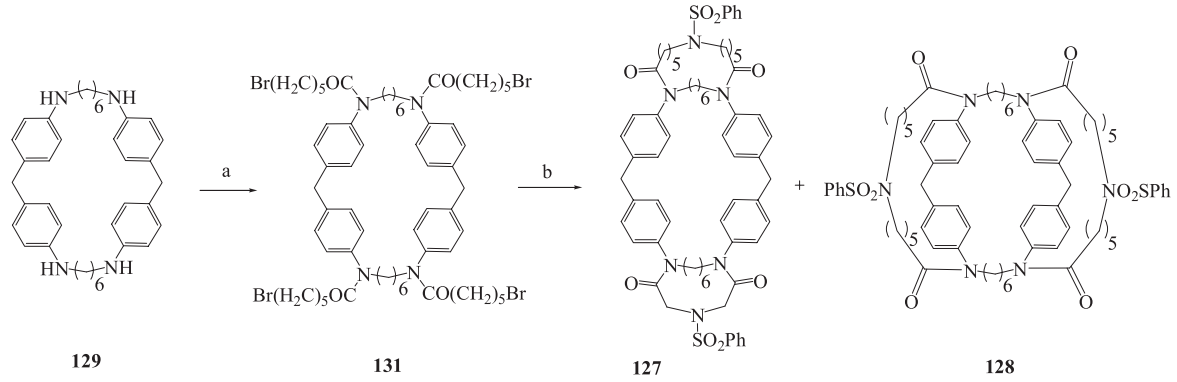
Scheme 27. a) $Br(CH_2)_8Br$ (**114**), Na_2CO_3, MeCN (17 %); b) $BrCH_2$–X–CH_2Br (**115** (X=CH), **116** (X=N)), Na_2CO_3, $CHCl_3$, (37 % for **110**, 14 % for **111**); c) $Br(CH_2)_2$-X-$CH_2(CH_2)$nBr (**117** (X=O, n=1), **118** (X=CH_2, n=4), (30 % for **112**, 35 % for **113**).



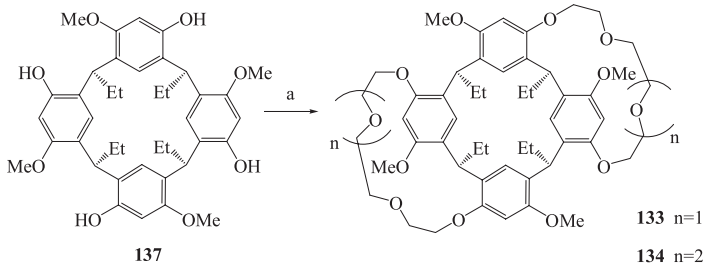
Scheme 28. a) MNBA, DMAP, CH_2Cl_2 (89 %); b) I_2, MeOH, CH_2Cl_2 (80 %); c) HF·Py, Py (92 %); d) DIAD, PPh_3, TsOH, THF, 0 °C (24 %); e) I_2, MeOH (81 %).



Scheme 29. a) PPh_3, DEAD, toluene (77 %); b) K_2CO_3, MeOH/THF (96 %); c) MsCl, Et_3N, CH_2Cl_2, 0 °C; d) NaN_3, DMF, 60 °C (82 %); e) LiOH, MeOH/THF/H_2O (97 %); f) pentafluorophenol, WSCDaHCl, CH_2Cl_2 (93 %); g) PPh_3, toluene, Δ; h) MeCN/H_2O, Δ (73 %); i) PhSH, KOH, MeCN, 50 °C (75 %); j) BCl_3, CH_2Cl_2, -78 to 0 °C (73 %).



Scheme 30. a) $Br(CH_2)_5COCl$ (**130**), $CHCl_3$, *i*-Pr_2NEt (61 %); b) $PhSO_2NH_2$ (**132**), K_2CO_3, DMF (13 %).

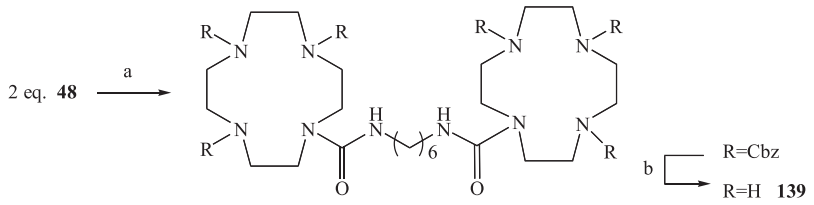


Scheme 31. a) TsO(CH$_2$CH$_2$O)$_n$OTs (**135** (n=1), **136** (n=2)), Cs_2CO_3, DMF (18 % for **133**), (22 % for **134**).

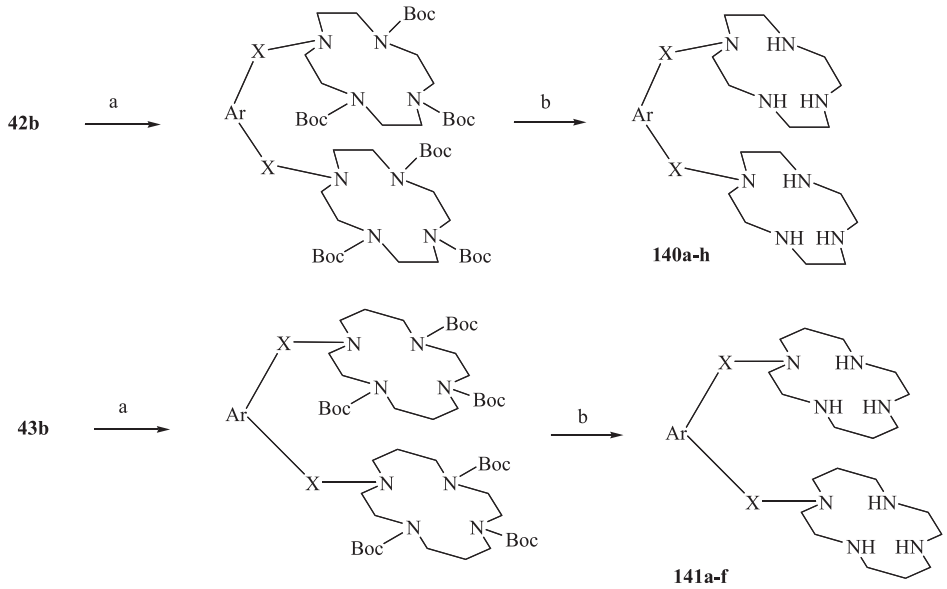
*Bis(*polyazamacrocycles) have attracted considerable attention due to their ability to form binuclear complexes. [88-90] Over the past decades, there has been an increase in the use of saturated *bis*-macrocyclic ligands instead of *bis*-porphyrin compounds containing two polyazamacrocycles coupled to each other by aliphatic or aromatic spacers. Some derivatives of *bis*-cyclams that are two macrocycles coupled by a spacer are able to strongly and selectively inhibit the human immunodeficiency virus (HIV-1 and HIV-2) with a unique mechanism of action.

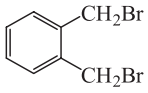
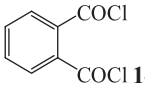
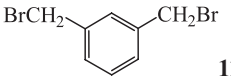
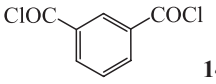
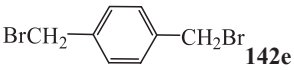
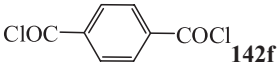
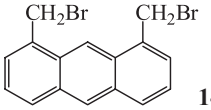
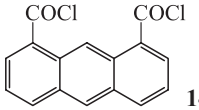
Introducing diisocyanate (**138**) into condensation allows "stitching" two cyclen (**48**) molecules with dicarbamide spacer in compound (**139**). The resulting cyclen derivatives (**38**), (**47**) and (**139**) are readily chelated with Cu^{2+} and Zn^{2+} ions (Scheme 32).[91]

Monoalkylation of trisubstituted cyclen (**42b**) and cyclam (**43b**) allows introducing such substituents as xylyl groups. Various *bis*-macrocycles coupled to each other *ortho*- (**140a**, **141a**, **140b**, **141b**), *meta*- (**140c**, **141c**, **140d**, **141d**) or *para*- (**140e**, **141e**, **140f**, **141f**) xylyl or anthracene-



Scheme 32. a) $OCN(CH_2)_6NCO$ (**138**), CH_2Cl_2 (69 %); b) H_2, Pd/C, EtOH (97 %).



Experiment	**142**	X	**140**	**141**
a	 **142a**	CH_2	**140a**	**141a**
b	 **142b**	CO	**140b**	**141b**
c	 **115**	CH_2	**140c**	**141c**
d	 **142d**	CO	**140d**	141d
e	 **142e**	CH_2	**140e**	**141e**
f	 **142f**	CO	**140f**	**141f**
g	 **142g**	CH_2	**140g**	–
h	 **142h**	CO	**140h**	–

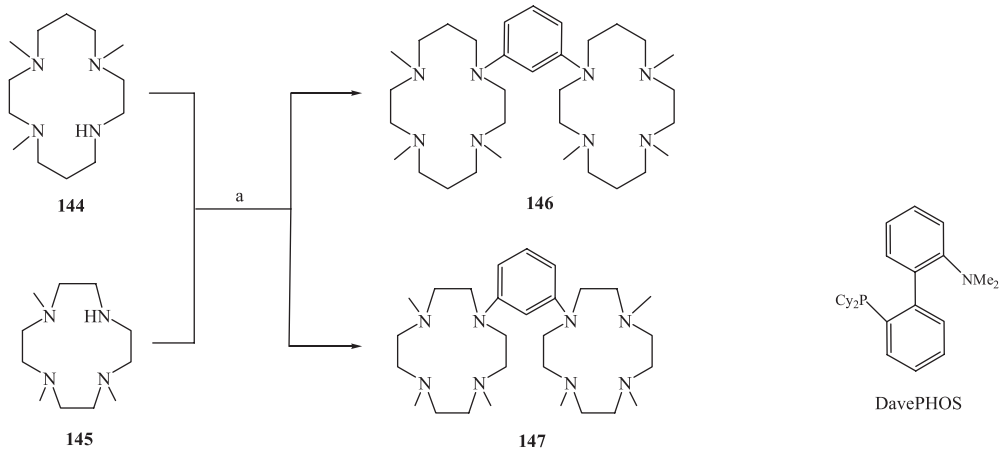
Scheme 33. a) Y-Ar-Y (**142a-h**); b) BH_3/THF when X=CO or HCl (6M).

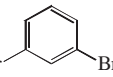
1,8-dimethylene (**140g**, **140h**) groups were synthesised in high yields during the interaction of compounds (**42b**) and (**43b**) with a number of electrophilic compounds (**115, 142a**,**b,d-h**) (Scheme 33).[3]

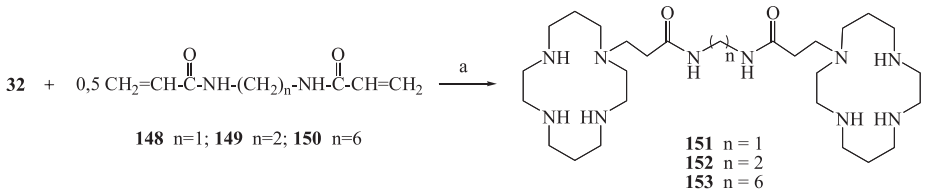
Direct Pd-catalysed arylation of cyclen (**31**) and cyclam (**32**) to obtain *bis*-polyaazamarocycles directly coupled with the aryl group is a complex task, since these cyclic tetraamines readily reduce halogen atoms in aryl halogenides. Therefore, trimethylcyclam (**144**) and trimethylcyclen (**145**) were introduced into reactions with *m*-dibromobenzene (**143**) during catalysis with $Pd(dba)_2$/DavePHOS that was most applicable for amine arylation, as a whole, and for diamination of 1,3-dibromobenzene, particularly, in the presence of sodium tret-butylate as a base yielding bis-macrocycles (**146**) and (**147**) (Scheme 34).[92]

The coupling reaction of two cyclam (**32**) species and diamide spacer under the action of methylene- (**148**), ethylene- (**149**) or hexamethylene- (**150**) *bis*-acrylamides in the presence of acid catalysts proceeds highly selectively with obtaining solely monosubstituted cyclams (**151-153**) (Scheme 35).[93]

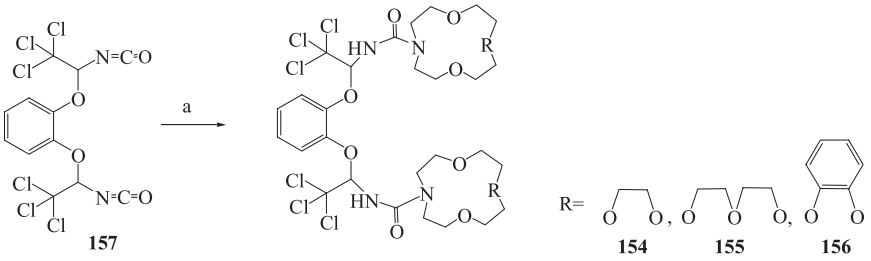
Lately, heteroditopic receptors containing binding sites of anions and cations various by nature have attracted much attention, which enables their capture of substrates as ion pairs (ion-pair recognition), thus, increasing lipophilicity and solubility of ion pairs in a non-polar medium and ensuring an opportunity of their efficient use in extraction systems and membrane transport processes. *Bis*(crown ethers), in which two crown ether cycles (cation binding sites) are connected by a relatively rigid chain containing urea fragments (anion binding sites) appear to be promising as ion pair receptors. Synthesis of compounds (**154-156**) was carried out by the interaction of 1,2-*bis*(2,2,2-trichloro-1-isocyanatoethoxy)benzene (**157**) and appropriate azacrown ether (2 equiv) (**158-160**) at room temperature (Scheme 36).[94]

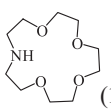
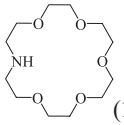
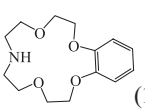


Scheme 34. a)  (**143**), $Pd(dba)_2$/DavePHOS, *t*-BuONa, dioxane (22 % for **146**, 32 % for **147**).



Scheme 35. a) TsOH, $CHCl_3$ (90 % for **151**, 82 % for **152**, 86 % for **153**).



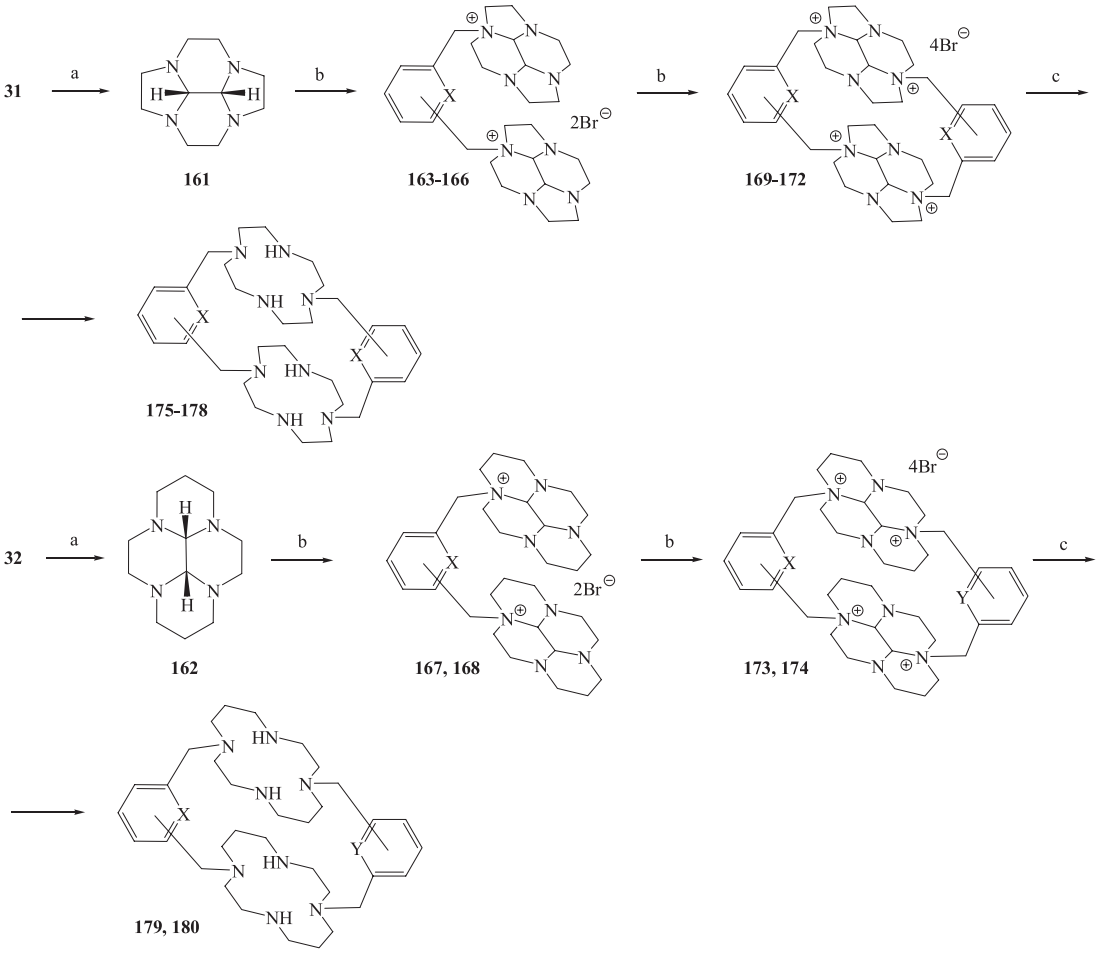
Scheme 36. a)  (**158**) or  (**159**) or  (**160**), $CHCl_3$, (73 % for **154**, 71 % for **155**, 84 % for **156**).

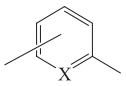
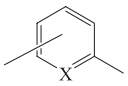
Cryptands comprising of two or more cycles containing O, S or N atoms coupled by ethylene bridges constitute a class of macrocyclic compounds.[95-97] They form stable complexes with alkali, alkaline earth, and some other metal cations. The former are cryptates, in which a metal ion is strongly shielded by the surrounding atoms from solvent and counterion species. Cryptands are used as catalysts, selective sorbents for extraction of metals, such exotic compounds as alkaloids comprising of alkaline metal cations ([Na(2,2,2-crypt]$^+$Na$^-$) were obtained using them.

The literature presents two approaches for synthesis of cryptands. The first one is based on consecutive reactions of cyclen- (**161**) or cyclam- (**162**) -glyoxal-*bis*-aminals (2 equiv) with a number of electrophilic compounds (1,2- (**142a**), 1,3- (**142c**) and 1,4- (**142e**) *bis*(bromomethyl)benzenes and 2,6-*bis*(bromomethyl)pyridine (**116**)), and the resulting diammonium salts (**163-168**) – with the same reactants in a 1:1 ratio. Deprotection of the resulting tetraamonium salts (**169-174**) leads to cryptands (**175-180**) (Scheme 37).[98-100]

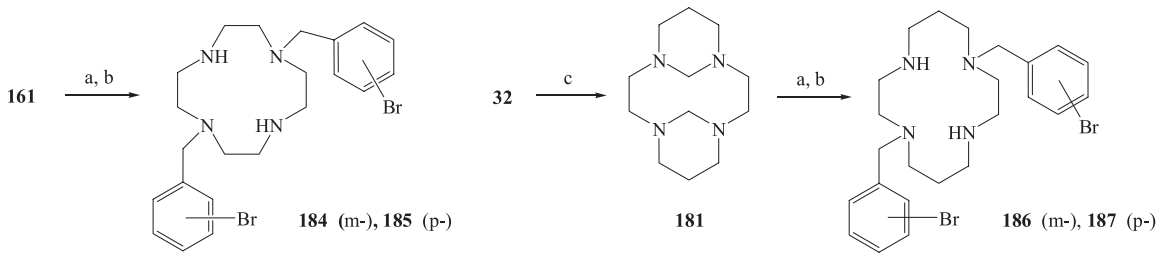
The reaction of *bis*-aminal (**161**) or *bis*-formaldehyde cyclam (**181**)[101,102] (1 equiv.) with 3-bromobenzyl- (**182**) and 4-bromobenzyl- (**183**) 1-bromides that have unequal substituents with obtaining tetraazaphenyl-substituted macrocycles (**184-187**) (Scheme 38) is the first step of the first approach to synthesis of cryptands.[103,104]

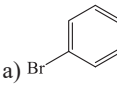
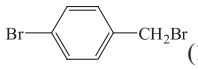
The subsequent reaction catalyzed by Pd salts of equimolar amounts of diphenyl-substituted macrocycle (**184**) with a number of diamines (**188a-e**) leads to the formation of a mixture of cryptands (**189a-e**) and their cyclodimers (**190a-e**) (Scheme 39).[103]

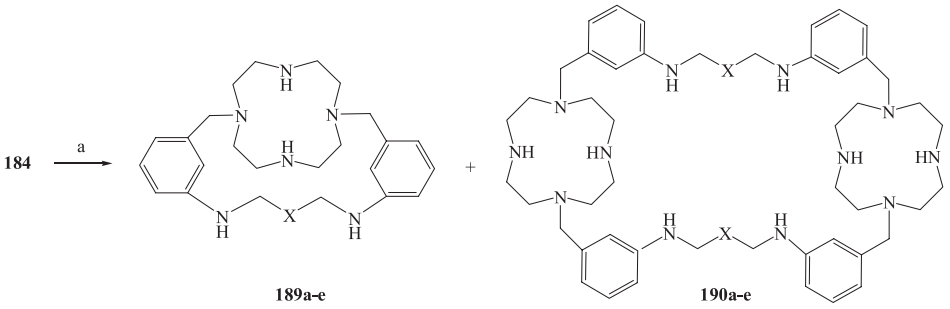


Bisaminal	Y-Ar-Y	Diammonium salt, 	Y-Ar-Y	Tetraammonium salt, 	Macrocycle, yield, %
161	**116**	**163**, X = CH_2, *o*-	**116**	**169**, X = CH_2, *o*-, *o*-	**175**, 60
161	**142a**	**164**, X = CH_2, *m*-	**142a**	**170**, X = CH_2, *m*-, *m*-	**176**, 98
161	**142c**	**165**, X = CH_2, *p*-	**142c**	**171**, X = CH_2, *p*-, *p*-	**177**, 91
161	**142e**	**166**, X = N	**142e**	**172**, X = N	**178**, 98
162	**142c**	**167**, X = CH_2, *m*-	**142c**	**173**, X = CH_2, *m*-, *m*-	**179**, 68
162	**142e**	**168**, X = CH_2, *p*-	**142e**	**174**, X = CH_2, *p*-, *p*-	**180**, 61

Scheme 37. a) OHC-CHO, MeOH; b) Y-Ar-Y, MeCN; c) NH_2OH, EtOH.

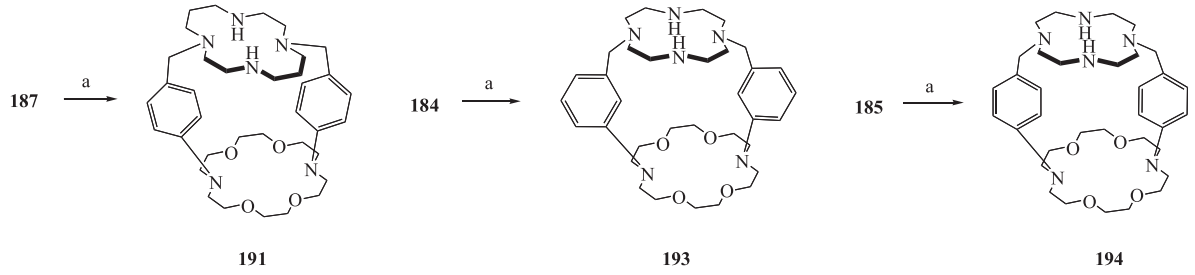


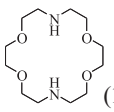
Scheme 38. a)  (**182**) or  (**183**), MeCN; b) NaOH, H_2O, 80 °C (94 % for **184**, 91 % for **185**, 78 % for **186**, 98 % for **187**); c) CH_2O, H_2O (90 %).



Experiment	**188**	**189**, yield %	**190**, yield %
a	**188a**, NH_2-$(CH_2)_3$-NH_2	**189a**, 13	**190a**, 5
b	**188b**, NH_2-$(CH_2)_3$-NH-$(CH_2)_3$-NH_2	**189b**, 26	**190b**, 53
c	**188c**, NH_2-$(CH_2)_2$-NH-$(CH_2)_3$-NH-$(CH_2)_2$-NH_2	**189c**, 38	**189c**, 44
d	**188d**, NH_2-$(CH_2)_3$-NH-$(CH_2)_2$-NH-$(CH_2)_3$-NH_2	**189d**, 45	**190d**, 34
e	**188e**, NH_2-$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$-NH_2	**189e**, 29	**190e**, 36

Scheme 39. a) H_2N-CH_2-X-CH_2-NH_2 (**188**), $Pd(dba)_2$/BINAP, *t*-BuONa, dioxane, Δ.



Scheme 40. a)  (**192**), $Pd(dba)_2$ / DavePHOS, *t*-BuONa, dioxane (12 %, for **191**, 30 % for **193**, 27 % for **194**).

One-step synthesis of a macrocyclic cryptand with cylindrical shape (**191**) used the reaction of equimolar amounts tetraazaphenyl substituted macrocycle (**187**) and diazacrown ether (**192**) with $Pd(dba)_2$/DavePHOS catalysis.[105,106] The yield of cryptands (**193**) and (**194**) based on cyclen derivatives (**184**) and (**185**) was somewhat higher (Scheme 40).

Macrobicycles containing 1,8-disubstituted cyclam fragment may be planar-chiral under the condition that a chain of atoms that form the second macrocycle cannot freely rotate around cyclam fragment. Hindered rotation can be achieved by two additional substituents on nitrogen atoms provided that a small chain length of the second cycle. *N,N',N'',N'''*-Tetrasubstituted cyclam (**195**) synthesised from *bis*-formaldehyde-cyclam (**181**)[101] by consecutive interactions with benzyl bromide (**196**) and 1-bromo-3-(bromomethyl)benzene (**182**) was introduced into Pd-catalysed amination reaction with 1,3-diaminopropane

(**188a**) with the formation of appropriate macrobicycle (**197**). This reaction explored chiral diphosphine ligands (**198**) and (**199**) based on 1,2-disubstituted ferrocene, and low asymmetric induction was noted (Scheme 41).[107]

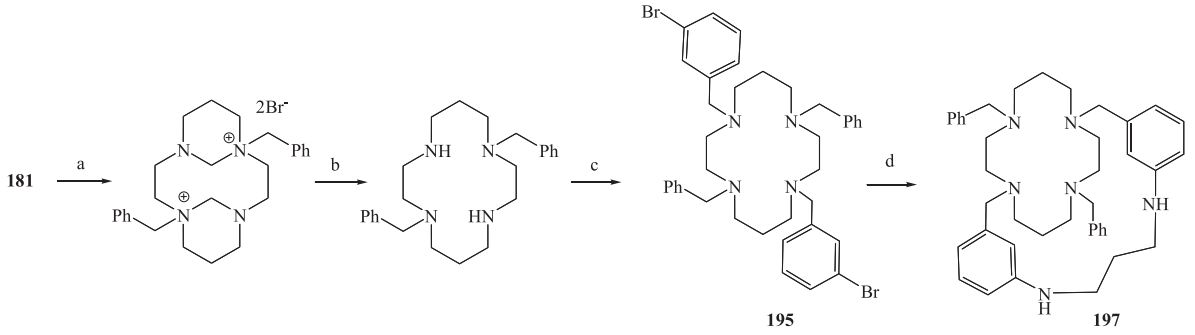
Cryptand (**200**) that forms a stable complex with the herbicide paraquat (**201**) was obtained by the interaction of *cis*(4,4')-di(carbomethoxybenzo)-30-crown-10 (**202**) and 2,6-piridinecarboxylic acid dichloroanhydride (**203**) (Scheme 42).[108]

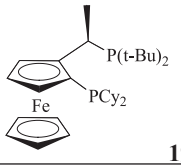
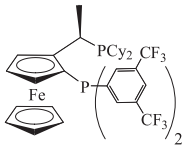
In addition to the above examples of functionalisation of macrocycles that consist in the formation of covalent bonds, there are synthetic methods for compounds with topological bonds that comprise of two or several independent parts not bound with each other by any valence bonds but nevertheless, held together. Catenanes comprised oftwo or several cycles bound as chain fragments and rotaxanes, the linear part of which is threaded through a macrocyclic ring and cannot slip out of it due to the presence of bulky end groups are referred to them. Species built without chemical bonding are found in animate and inanimate nature. Rotaxane and catenane forms of deoxyribonucleic acid (DNA) have been detected. It is interesting that an increase in the content of catenane DNA is observed during leukemia and various forms of cancer.[109] Rotaxanes are of interest as objects for information storage, and also can be used as molecular machines that operate during rotation of macrocycles around a linear axis or transition from one edge of the molecule to another.

When considering opportunities for synthesis of catenanes cases, when they are obtained as side or sole reaction products should be distinguished. The first method may be defined as statistical, and the second one – asa directed method, in which there are conditions, upon which the formation of catenane is inevitable. The statistical method may be illustrated by the following scheme: cyclization of a molecule with a long chain (**204**) containing terminal functional groups X in the presence of macrocycle (**205**) may lead to catenane (**207**), if in the moment of cycle closure the chain of (**204**) takes the intra-annular position (**206**) (Scheme 43).

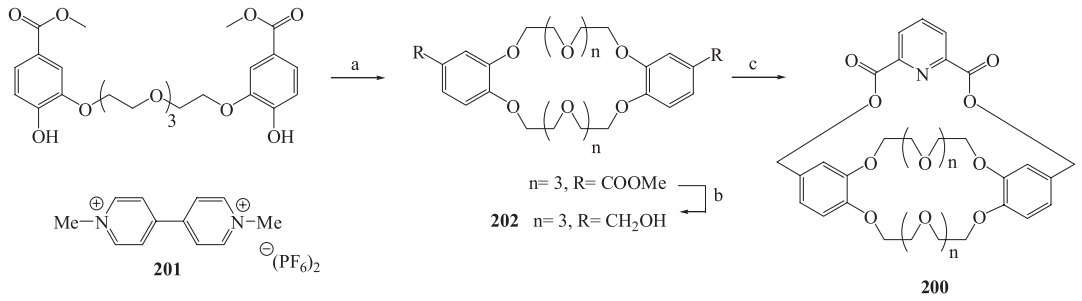
Thus, macrocyclization of aromatic dibasic acid chloroanhydride (**208**) and aromatic diamine (**209**) in the presence of macrocycle (**210**) were most preferable for the formation of catenane (**211**)[110,111] that was able to enter into the Diels-Alder reaction (Scheme 44).

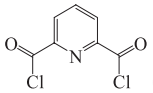
The probability of formation of catenane using the above method is low; however, it can be increased

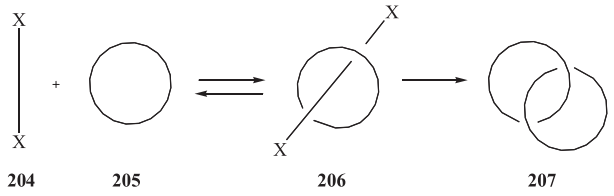


Ligand L	 **198**	 **199**
Yield of macrocycle (**197**), %	50	41
ee %	11	12

Scheme 41. a) CH_2O, H_2O (90 %); b) $PhCH_2Br$ (**196**), MeCN (78 %); c) NaOH, 80 °C (90 %); d) **182**, CH_2Cl_2/NaOH/H_2O (95 %); e) $H_2N(CH_2)_3NH_2$ (**188a**), $Pd(dba)_2$/L, *t*-BuONa, dioxane (50 %).



Scheme 42. a) $Ts(OCH_2CH_2)_4OTs$, KPF_6, K_2CO_3, MeCN (93 %); b) $LiAlH_4$, THF (94 %); c)  (**203**), CH_2Cl_2/Py (44 %).

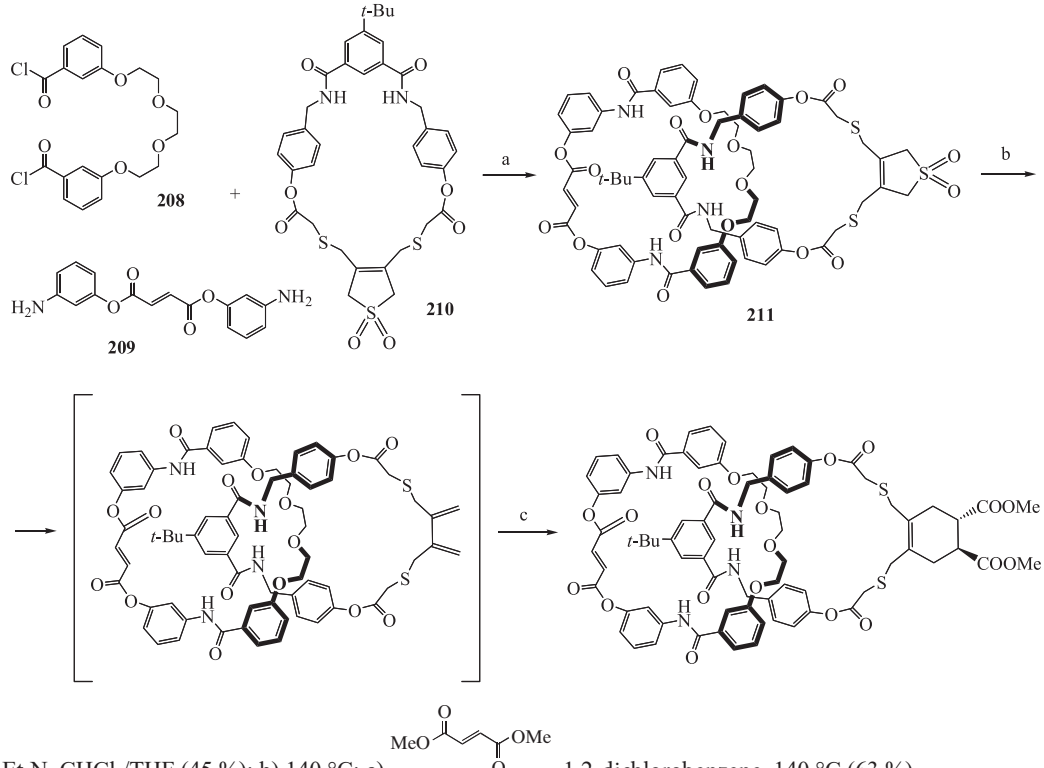


Scheme 43.

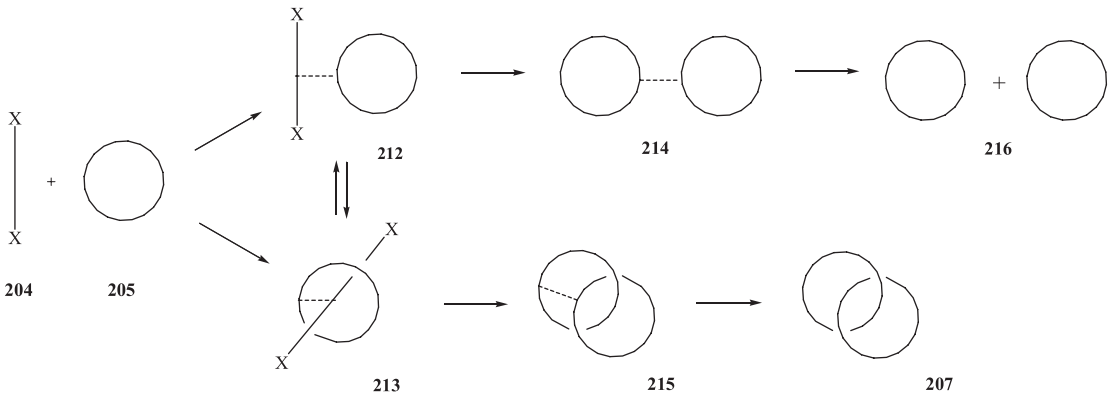
due to additional steric factors and through a temporary bond of macrocycle (**205**) with long-chain molecule (**204**). Compound with an open long chain (**204**) is added to (**205**) through an auxiliary bond (indicated by the dotted line) with the formation of adducts (**212**) and (**213**). Thus, the forced close convergence of two species is reached. By selecting a suitable auxiliary bond, one can affect the conformational equilibrium between adducts (**212**) and (**213**). Cyclization leads to the formation of cycles (**214**) and precatenane (**215**) coupled to each other that turn into two isolated macrocycles (**216**) and catenane (**207**), respectively, when breaking auxiliary bonds (Scheme 45).[109]

This was realised in synthesis of [2]catenane (**217**) when using Pd(II) directed cyclization of tridentate ligand (**218**) with monodentate macrocycle (**219**) (Scheme 46).[112]

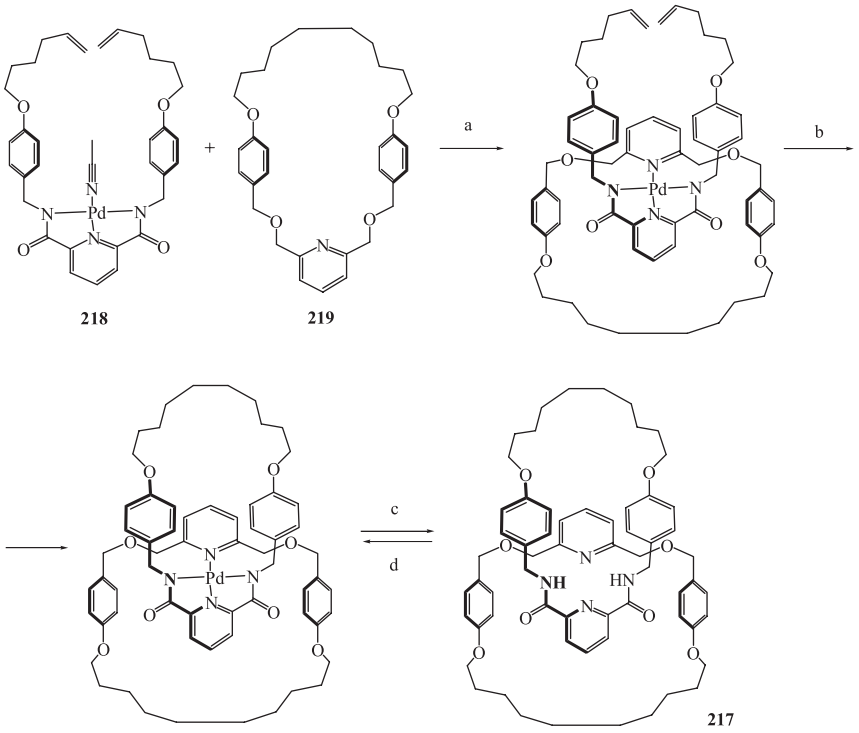
Similarly to catenanes, rotaxanes can be synthesized by both statistical and directed methods.[109] Rotaxanes are formed in statistic synthesis along with molecular components in a ratio defined by statistic laws. Thus, in the presence of macrocycle (**205**), bulky end groups of (**220**) are added to the chain of (**204**). Consequently, alongside with the initial macrocycle (**205**), some amounts of rotaxane (**221**) and molecular barbells of (**222**) are formed (Scheme 47).



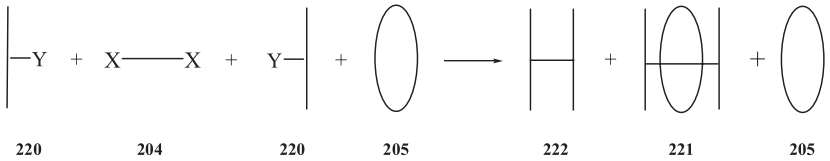
Scheme 44. a) Et_3N, $CHCl_3$/THF (45 %); b) 140 °C; c) , 1,2-dichlorobenzene, 140 °C (63 %).



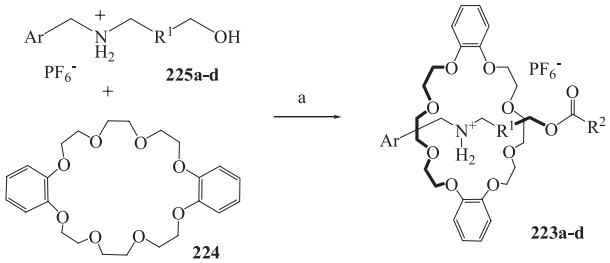
Scheme 45.

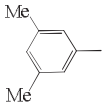
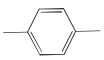
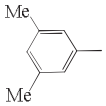
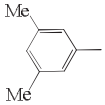
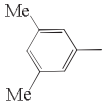
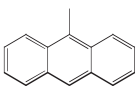
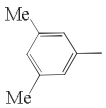
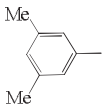
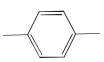


Scheme 46. a) CH_2Cl_2 (69 %); b) Grubbs catalyst I, CH_2Cl_2 then H_2, Pd-C, THF (78 %); c) KCN, MeOH, CH_2Cl_2, 40 °C (97 %); d) $Pd(OAc)_2$, MeCN, 60 °C (79 %).



Scheme 47.



225	Ar	R^1	R^2	Rotaxane	Yield, %
225a				**223a**	90
225b		–CH_2–		**223b**	78
225c		–CH_2–		**223c**	82
225a				**223d**	85

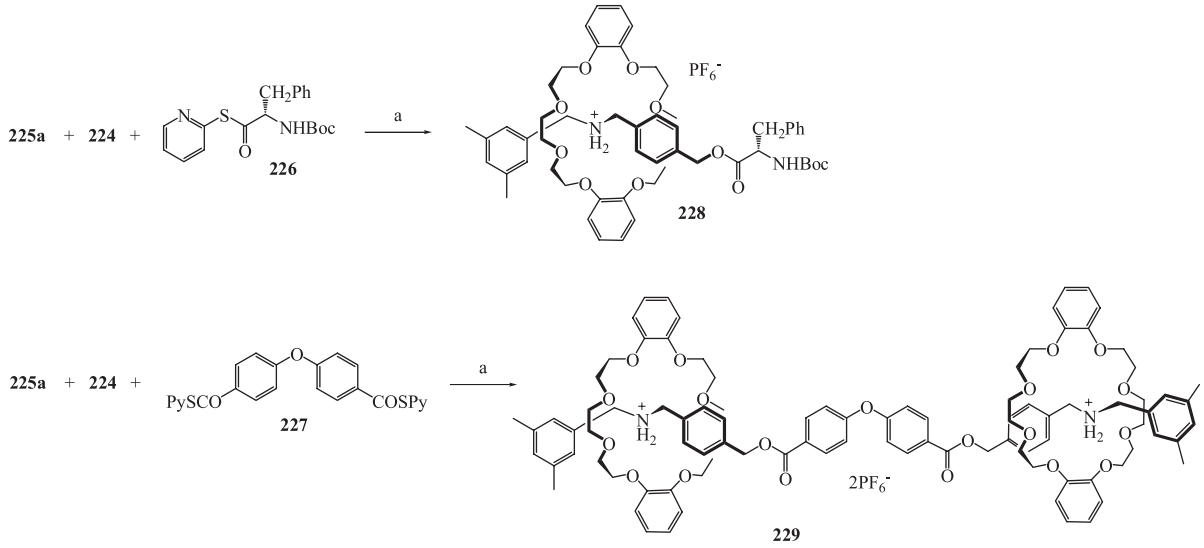
Scheme 48. a) $(R^3CO)_2O$, cat. Bu_3P, CH_2Cl_2.

Catalysed acylation with bulky acid anhydrides of pseudo-rotaxanes that have a hydroxyl group at the end of the axis is one of the most methods of synthesis of [2]rotaxanes comprising of crown ethers and secondary ammonium salts. Thus, a series of [2]rotaxanes (**223a-d**) were synthesized from dibenzo-24-crown-8 (**224**) and dibenzylammonium salts (**225a-d**) under catalysis by Bu_3P (Scheme 48).[113-115]

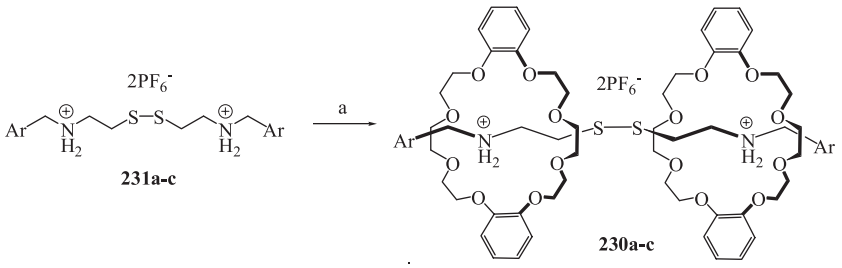
When a catalyst is a strong acid, *e.g.* triflic acid, the corresponding amine can be used as a base, since ammonium salts can be produced *in sutu*.[116] When using natural amino acids racemised in acid medium, and also for synthesis [3]rotaxanes as acylating agentsas the axis 2-pyridylthioesters are being applied successfully. Thus, acylation of alcohol (**225a**) with 2-pyridylthioesters (**226**) and (**227**) proceeds under neutral conditions under catalysis by Bu_3P and leads to [2]rotaxane (**228**) (without amino acid residue racemization) and [3]rotaxane (**229**) in good yields (Scheme 49).[117]

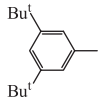
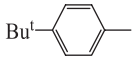
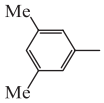
Disulphide-containing rotaxanes (**230a-c**) have been obtained by the interaction of symmetric dumbbell-like compounds (**231a-c**) containing by two secondary ammonium centers and the central disulphide fragment with crown ether (**224**) under catalysis by benzenethiol (Scheme 50).[118]

It is known that urethanes are more stable than esters and disulphides towards chemical reagents, heating, light, and radiation. Rotaxane (**232**) with a urethane functional group in the axis can be readily obtained in a high yield[119] from dibenzo-24-crown-8 (**224**) and benzylammonium salt (**225a**) by the interaction with



Scheme 49. a) Bu_3P, CH_2Cl_2 (82 %).



231	Ar	T, °C	Yield of **230**, %
231a		50	65
		20	81
231b		50	63
		20	81
231c		50	61
		20	79

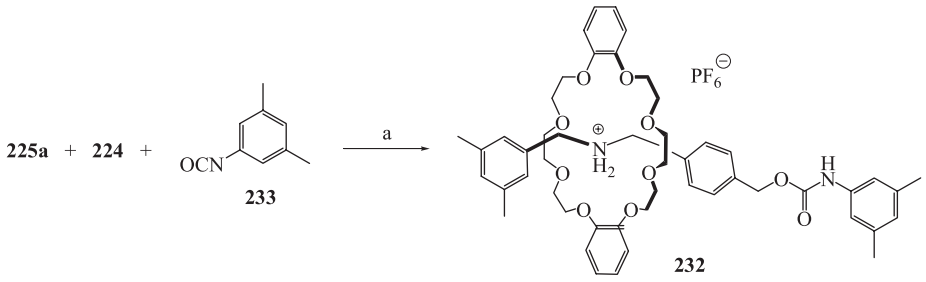
Scheme 50. a) **224**, PhSH.

3,5-dimethylphenylisocyanate (**233**) under soft conditions: *n*-$Bu_2Sn(OCO\text{-}n\text{-}C_{11}H_{23})_2$ in $CDCl_3$ at room temperature (Scheme 51).

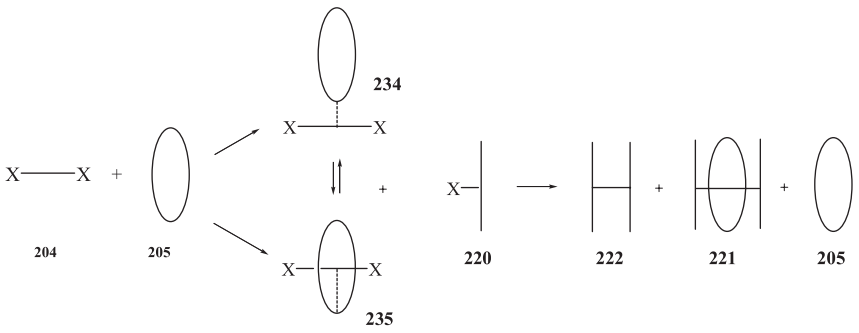
The yield of rotaxane (**221**) increases in temporary binding chain (**204**) with macrocycle (**205**). Herewith, extra- and intraannular isomers (**234**) and (**235**) should exist in the conformational equilibrium. A mixture containing rotaxane (**221**), compound (**222**) and macrocycle (**205**) is formed after the addition of bulky end groups (**220**) and cleavage of a temporary bond (Scheme 52).[109]

This approach was implemented in highly selective synthesis of rotaxanes (**236a-c**) using aminolysis of their precursors (**237a-c**) obtained by substitution of the hydroxyl group in phenols (**238a-c**) with bulky groups: the kinetically controlled approach of the amine (**239**) from the back part of the ring of pseudorotaxanes (**237a-c**) (Scheme 53).[120]

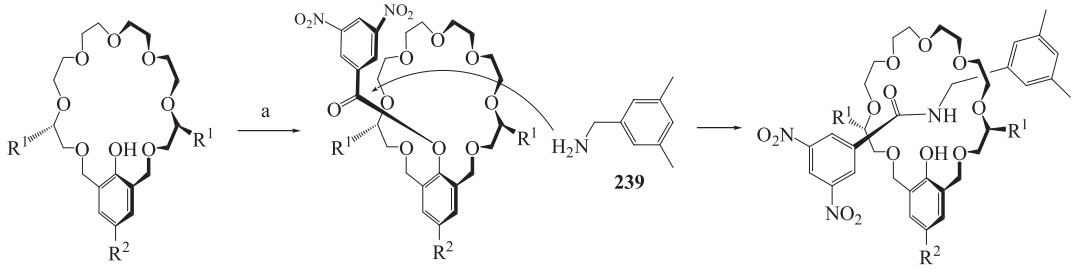
Another method of synthesis of [2]rotaxane (**240**) includes reactions occurring in sequence of treatment of tridentate palladium(II) complex obtained from macroheterocycle (**241**) with 2,6-disubstituted pyridine (**245**), protection of hydroxyl groups in the resulting (**243**) bulky isocyanate (**246**) and destruction of palladium complex (**244**) with carbon monoxide (Scheme 54).[121-123]



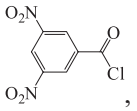
Scheme 51. a) *n*-$Bu_2Sn(OCO\text{-}n\text{-}C_{11}H_{23})_2$, $CDCl_3$ (90 %).



Scheme 52.



Experiment	R^1	R^2	Yield of **236**, %
a	H	Br	82
b	Ph	Br	81
c	H	NO_2	81

Scheme 53. a)  , C_6D_6.

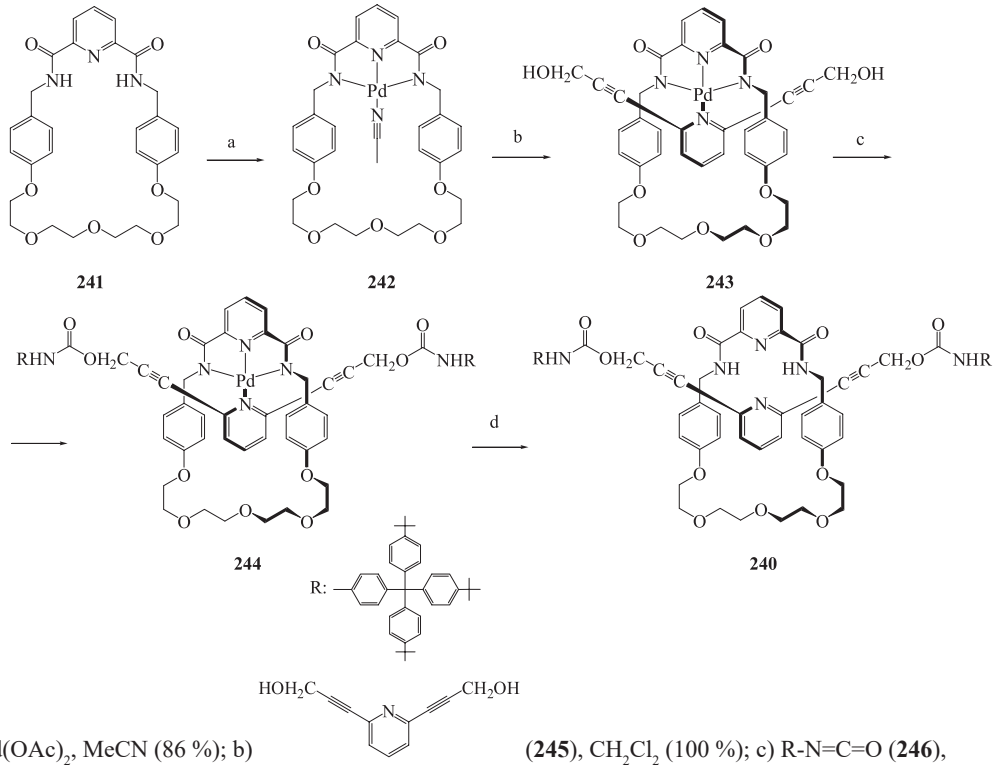
1.2. Functionalisation of Macrocycles with Decrease in Their Sizes

Functionalisation of macroheterocycles, including into synthesis of biologically active compounds may be accompanied by their cyclecontraction.

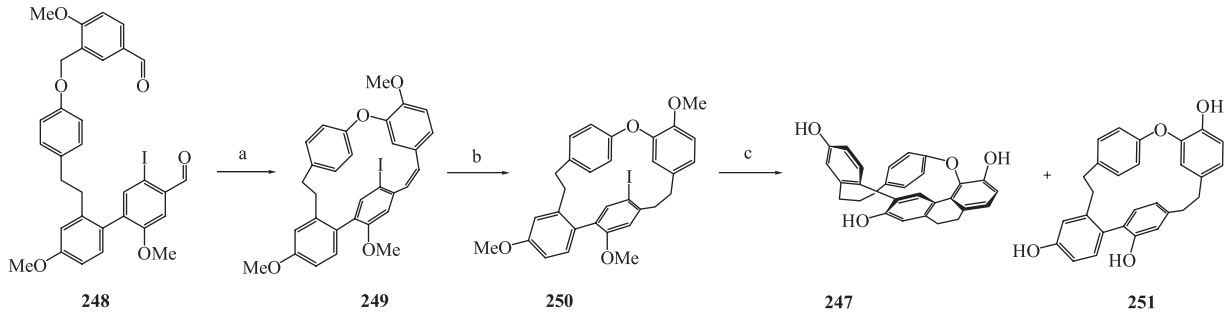
Thus, the key steps in synthesis of cavicularin (**247**) that is related to phenolic secondary metabolites isolated from *Cavicularia Densa* and representing the first natural compound with optical activity exclusively due to the presence of axial and planar chirality are macrocyclization of dialdehyde (**248**) into macrocycle (**249**) catalysed by a low valency titanium salt and a radical-induced transannular ring contraction in compound (**250**). The resulting target cavicularin (**247**) and riccardin C (**251**) that is present in Chinese liverwort *Plagiochasma intermedium* are readily separated using column chromatography (Scheme 55). [124]

The formation of the dihydropyran fragment occurs in the intramolecular interaction of the triple bond with the hydroxyl group, which is applicable to synthesis of bryastatines of sea mats *Bigula neritina*[125] and polycavernoside (**252**) that is glycosylated macrolide of poisonous red algae *Gracilaria edulis* (*Polycavernosa tsudai*).[126] Thus, metathesis cyclization of diyne (**253**) over a molybdenum catalyst (**254**) forms the required macrocycle (**255**), and transannular reaction therein over alkynophile gold catalyst (**256**) – an additional six-membered cycle. Further transformations of the resulting tricycle (**257**) (oxidation of the double bond and decreasing the pyranone cycle to hydroxyfurane) proceeded stereoselectively (Scheme 56).

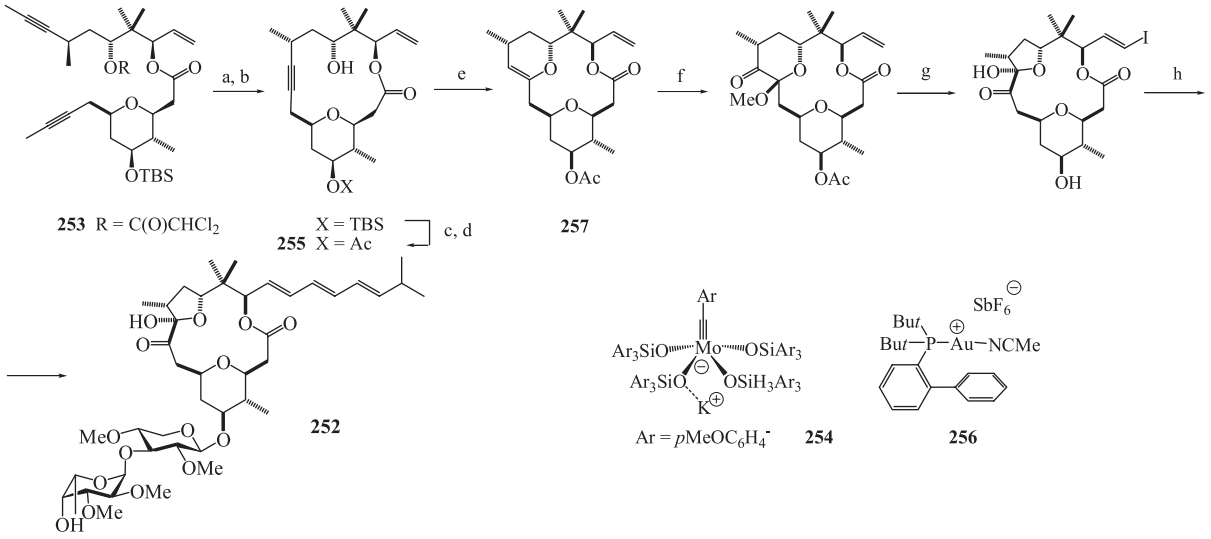
The generation of 2-hydroxytetrahydropyran happens in the intramolecular interaction of keto- and hydroxygroups, which is presented in synthesis of bryostatins of sea mats *Bigula neritina*[127] and the natural polyfunctional bicyclic immunosuppressant rapamycin (**258**) isolated from *Streptomyces hydroscopicus* and showing antifungal properties.[128] To form its 35-membered precursor that is macroheterocycle (**260**) DCC-initiated cyclization of bromo acid (**259**) was carried out. The intramolecular template Dieckmann condensation of two ester groups in macrolide (**260**) lead to a decrease in the cycle, and the removal of TES-pro-



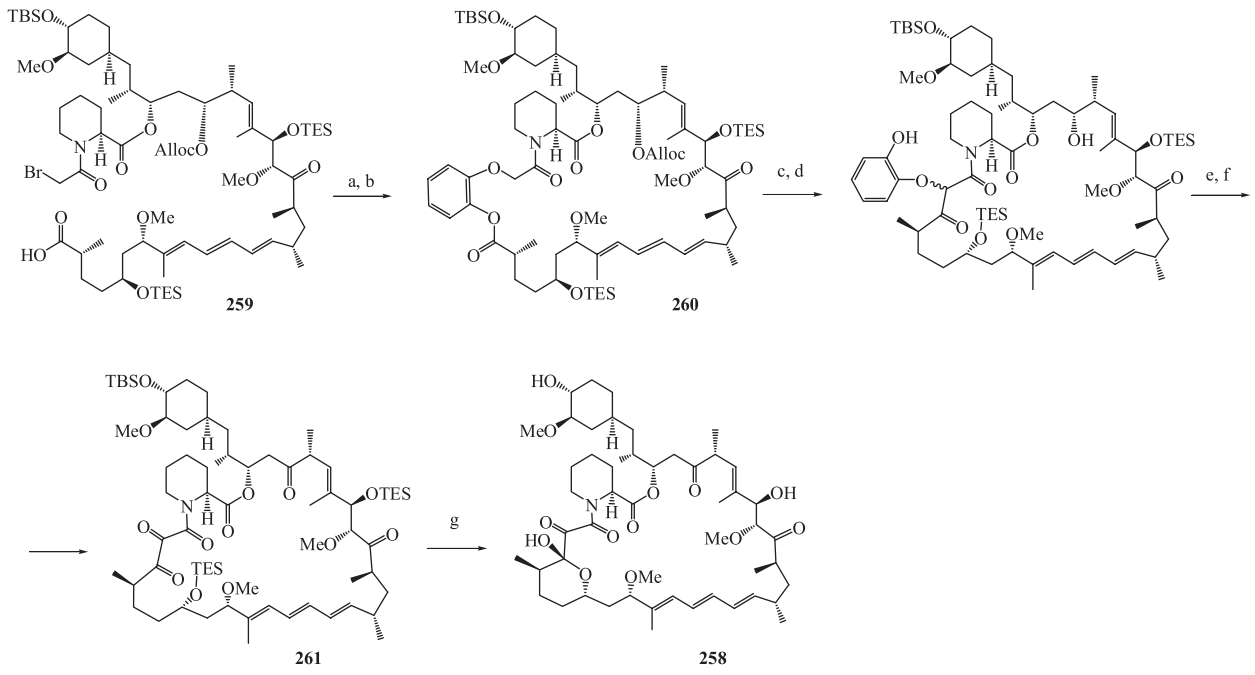
Scheme 54. a) $Pd(OAc)_2$, MeCN (86 %); b) (**245**), CH_2Cl_2 (100 %); c) R-N=C=O (**246**), *n*-$Bu_3Sn(OCOC_{11}H_{23})_2$, CH_2Cl_2 (96 %); d) CO (50 atm), MeOH, 80 °C (100 %).

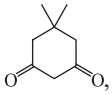


Scheme 55. a) $TiCl_4$, Mg, THF, -78 °C (35 %); b) $TsNHNH_2$ aq.THF, NaOAc (91 %); c) TTMSS, AlBN then BBr_3, CH_2Cl_2, toluene, 90 °C (95 %).



Scheme 56. a) **254**, toluene, MS 5Å, 80 °C (91 %); b) K_2CO_3, MeOH, 40 °C (80 %); c) TFA, CH_2Cl_2, 40 °C (76 %); d) Ac_2O, Py, CH_2Cl_2, 40 °C (97 %); e) **256**, MS 4Å, CH_2Cl_2 (84 %); f) DMDO, PPTS, MeOH then TPAP, NMO (72 %); g) O_3, PPh_3 then CHI_3, $CrCl_2$ then K_2CO_3 (54 %).



Scheme 57. a)  , DCC, DMAP, CH_2Cl_2, 0 °C (88 %); b) K_2CO_3, DMF (81 %); c) LiHMDS, THF, -78 °C (78 %); d) $[Pd(PPh_3)_4]$,  , THF (80 %); e) $PhI(OAc)_2$, $MeCN/H_2O$, 0 °C; f) DMP, Py, CH_2Cl_2 (61 %); g) HF·Py, THF, 50 °C (61 %).

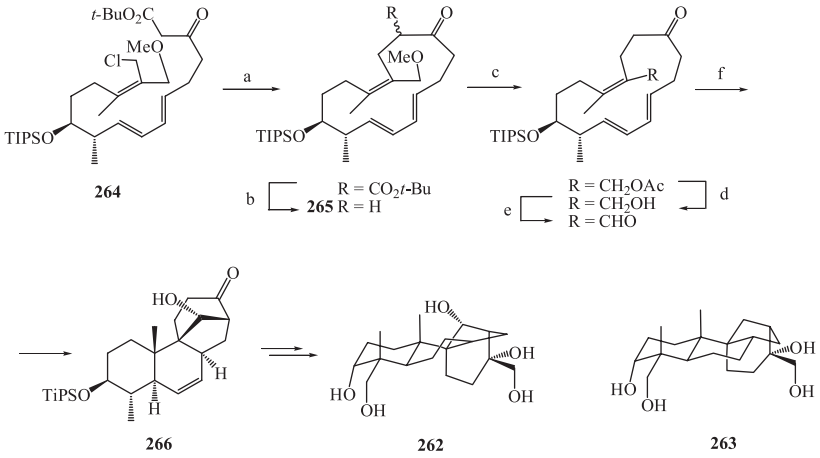
tection in compound (**261**) was accompanied by the spontaneous formation of a six-membered lactol ring of compound (**258**) (Scheme 57).

Macroheterocycles are successfully used to form polycyclic compounds using intramolecular reactions, *e.g.* Diels-Alder.[129]

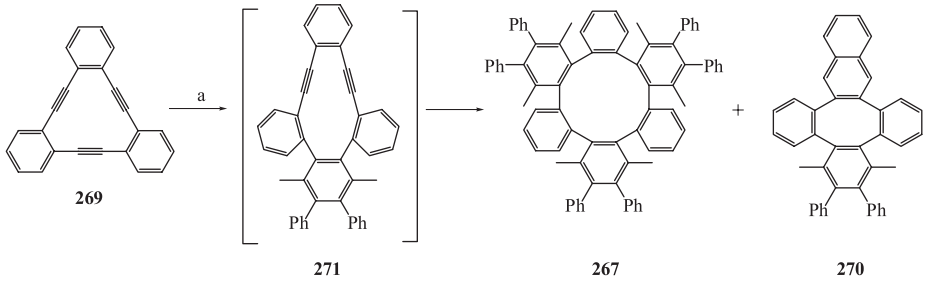
A macrocyclization reaction of compound (**264**) in synthesis of [(11R)-(–)-8-epi-11-hydroxyaphidicolin] (**262**) that is an unnatural derivative of tetracyclic diterpene (+)-aphidicolin (**263**) isolated from *Cephalosporium aphidicola fungus* as a potential anticancer agent led to the formation of polyfunctional *E,E,Z*-triene (**265**) involved in a tandem of highly stereoselective reactions, such as the trans-annular Diels-Alder sequence and aldolization into tetracyclic compound (**266**) as a precursor of (**262**) (Scheme 58).[130,131]

The Diels-Alder reaction is also used in the key step of the formation of hexaphenylene (**267**) as a representative with the carbon allotropic modification "cubic graphite", the conical cavity of which can be used as the "host" in molecular associates, and compound (**267**) itself – as a building block for porous solids.[132] Condensation of cyclopentadienone (**268**) with tribenzohexahydro[12]annulene (**269**) under high-temperature reflux conditions (300 °C) in diphenyl ether leads to the desired the triple addition product (**267**) of the Diels-Alder reaction in a mixture with compound (**270**) that are formed during the Bergman cyclization of intermediate adduct (**271**) (Scheme 59).

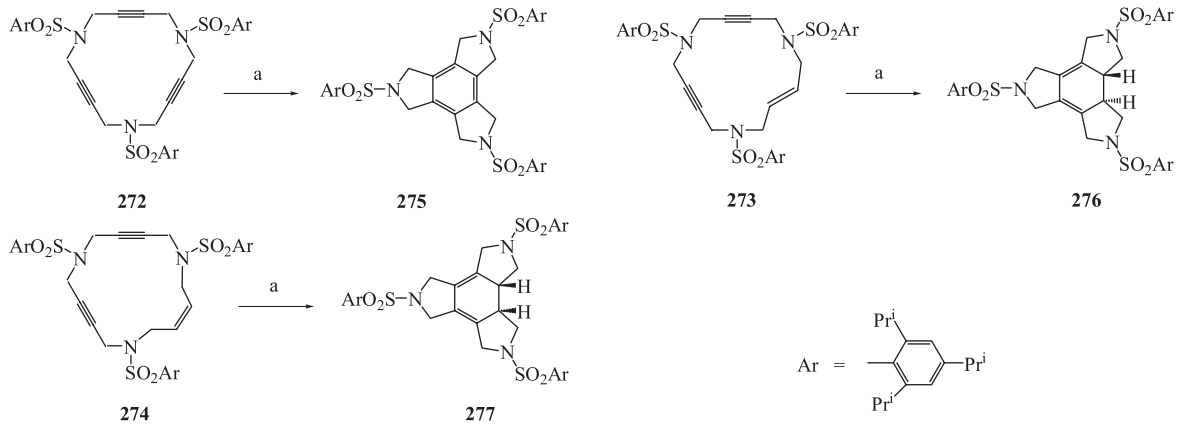
A highly-efficient method for the construction of tetracyclic organic species consists in the use of a domino process that combines the *ene*-reaction of two alkynes and the Diels-Alder cycloaddition. Thus, nitrogen-containing 15-membered triacetylene (**272**), enediyne (**273**) and (**274**) macrocycles were involved into [2+2+2] cycloisomerization processes that are catalysed by $PhCl(CO)(PPh_3)_2$ and lead to tetracyclic compounds (**275-277**) in high yields. Moreover,



Scheme 58. a) Cs_2CO_3, CsI, Me_2CO (79 %); b) LiI, 2,4,6-collidine, 100 °C (72 %); c) Me_2BBr, NaI, 15-crown-5, CH_2Cl_2, -78 °C then AcONa, DMF, 50 °C; d) K_2CO_3, MeOH (75 %), e) Dess-Martin periodinane, CH_2Cl_2 (88 %); f) Et_3N, PhMe, sealed tube , 230 °C (81 %).



Scheme 59. a)  (**268**), 300 °C



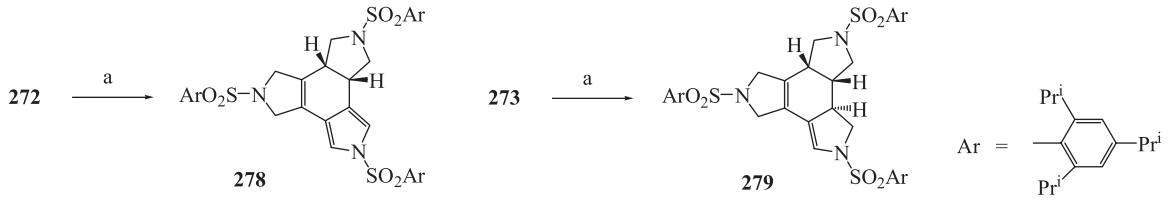
Scheme 60. a) $PhCl(CO)(PPh_3)_2$, toluene, 65 °C (96 % for **275**, 80 % for **276**, 68 % for **277**).

the reaction proceeds stereospecifically in case of enediyne macrocycles (Scheme 60).[133,134]

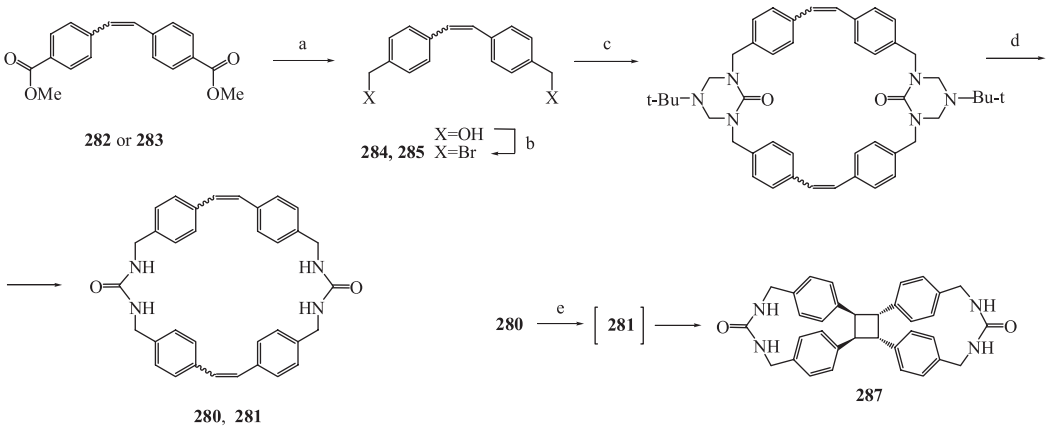
Other products (**278**) and (**279**) have been obtained in thermally induced [2+2+2] cycloisomerisation, though in moderate yields but high stereoselectivities: only isomers in *cys*-location of hydrogen atoms in unsaturated azacyclopentyl rings have been formed (Scheme 61).[133,134]

The [2+2] cycloaddition reaction of stilbenes during their UV irradiation is one of the most efficient methods of synthesis of cyclobutane-substituted derivatives. Thus, UV irradiation of both *cis*- (**280**) and *trans*- (**281**) macrolide stilbenes obtained from commercially available *cis*- (**282**) or *trans*- (**283**) stilbene-4,4'-dicarbolylic acid dimethyl ester led to the formation of the sole product (**287**) by their transfer in two steps to dibromides (**284**) and (**285**) followed by cyclization with triazinone (**286**) in the presence of NaOH in THF and the removal of protective groups under the action of diethanolamine. This can be explained by ready transfer of *cis*-stilbene (**280**) into its *trans*-isomer (**281**) that enters into a cycloaddition reaction (Scheme 62).[135]

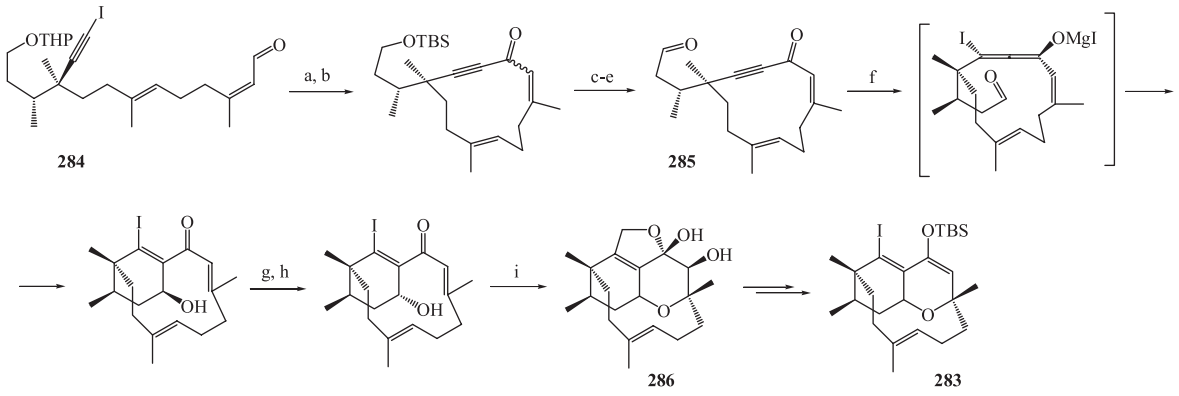
Enantioselective synthesis of phomactin (**283**) that is a natural compound isolated from a marine fungus *Phoma sp*. that grows in Chinoecetes opiloi crab shells is based on consecutive reactions of iodoacetylene and conjugated aldehyde functional group of compound (**284**) through the Nozaki-Hiyama-Kishi reaction with obtaining 12-membered macroheterocycle (**285**) and MgI_2-catalysed iodoallenoate cyclization of the latter into a precursor of phomactin (**283**) that is a tricyclic compound (**286**) (Scheme 63).[136,137]



Scheme 61. a) Δ, toluene (32 % for **278**, 45 % for **279**).



Scheme 62. a) $LiAlH_4$, THF (95 %, 99 %); b) NBS, PPh_3, THF (78 % for **284,** 74 % for **285**); c) *t*-Bu–N(NH)(C=O)–NH (**286**), NaH, THF (12 % or 20 %); d) $HO(CH_2)_2N(CH_2)_2OH$, MeOH (90 % for **280,** 92 % for **281**); e) *h*ν, DMSO-d_6 (100 %).

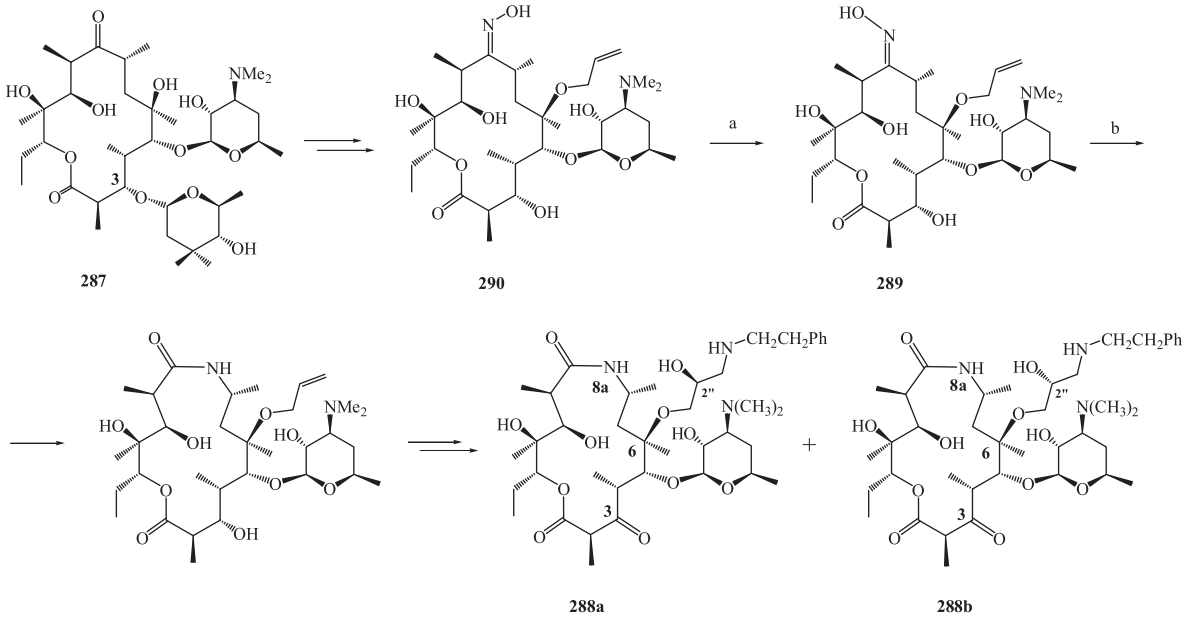


Scheme 63. a) $CrCl_2$, $NiCl_2$, THF (63 %); b) MnO_2, CH_2Cl_2 (69 %) (**250**); c) SiO_2; d) HF-pyridine, THF, 0 °C (98%); e) *n*-$Pr_4N^+RuO_4^-$, NMO, MS 4 Å, CH_2Cl_2 (73 %); e) MgI_2, THF, 0 °C (60 %); g) PNBOH, PPh_3, DEAD, benzene; h) K_2CO_3, MeOH (52%); i) TBSOTf, 2,6-lutidine, toluene (54 %).

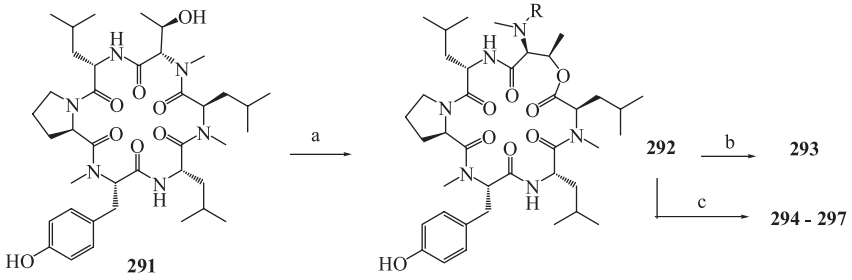
1.3 Functionalisation of Macrocycles with an Increase in Their Sizes

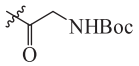
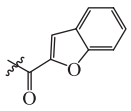
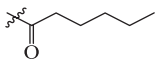
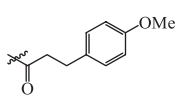
Functionalisation of biologically active macroheterocycles may also be accompanied by an increase in their sizes. One of the methods of transforming antibiotic erythromycin species (**287**) is the Beckmann rearrangement, that is the key step in highly efficient synthesis of a series of novel 6-*O*-substituted 8a-aza-8a-homoerythromycin A ketolides (**288a,b**) as epimers at the 2nd center. 3-*O*-Decladinosyl-6-*O*-allylerythromycin A (*Z*)-oxime (**289**) required for its implementation has been obtained by alkaline treatment of initially formed *E*-oxime (**290**).[138,139] *In vitro* testing of antibacterial activity of macrocycles (**288a,b**) against a series of erythromycin-sensitive and erythromycin-stable strains has demonstrated their high activity (Scheme 64).

N-*O*-Rearrangement accompanied by ring expansion with the formation of compound (**292**) may proceed in acidified solutions of cyclic peptide containing the amino acid residue of threonine (**291**). Amines (**293-297**) obtained by acylation of the latter with various carboxylic acids are characterised by high membrane permeabilities and conformations similar to the initial peptide (**291**) (Scheme 65).[140]



Scheme 64. a) $LiOH \cdot H_2O$, EtOH (80 %); b) *p*-TsCl, $NaHCO_3$, Me_2CO, H_2O (90 %).



Compound	R	Yield, %
292	H	
293	Ac	62
294		41
295		56
296		43
297		43

Scheme 65. a) EtOH, HCl, 50 °C; b) Ac_2O, CH_2Cl_2, 30 °C; c) RCOOH, DIC, 2,6-lutidine, CH_2Cl_2, 30 °C.

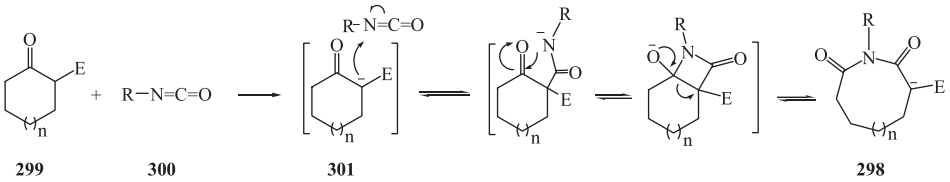
It is known that many macrocyclic imides show fungicide and bactericide properties may also are used as compositions for bleaching of textile products and the suppression of adsorption and desorption of pollutions or colourants. One of the methods[141] for obtaining macrocyclic imides (**298**) consists in the interaction of isocyanates (**300**) with cycloalkanols (**209**) substituted in the 2nd position with electron-acceptor groups that stabilize carbanion (**301**). Ring expansion proceeds by the following probable mechanism (Scheme 66).

Thus, 2-cyano-substituted dodecanone (**302**) enters into reactions with various *p*-substituted aryl isothiocyanates (**303a-c**) accompanied by ring expansion with obtaining appropriate CN-substituted cyclic imides (**304a-c**) (Scheme 67).[141]

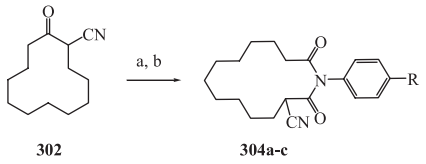
The use of CO_2R-substituted derivatives of cycloalkanones allows synthesizing both *N*-unsubstituted and various *N*-substituted cycloalkane dicarboximides. Thus, treatment of cyclododecanone (**305**) with sodium hydride and diallyl carbonate leads to oxoester (**306**),[141-144] in which the α-position to the (allyloxy)carbonyl group is activated under the influence of base, and ring expansion with obtaining 14-membered amide (**308**) happens in the interaction with various isocyanates (**307**). Its Pd(0)-catalysed *N*-deallylcarboxylation leads to both *N*-unsubstituted (**310**), and also *N*-alkyl and *N*-phenyl substituted (**309**) cyclic carboxyimides (Scheme 68).

The resulting derivatives may enter into repeated ring expansion reactions. For example, *N*-alkyl substituted cyclic carboxyimides (**311**) and (**312**) are rearranged into macrocyclic diamides (**313**) and (**314**) under the interaction with sodium azide and triphenylphosphine (Scheme 69).[144]

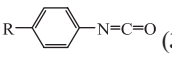
If reactive groups (Br, OH) are present in the *ortho*-position of aromatic isothiocyanate species; resulting *N*-aryl

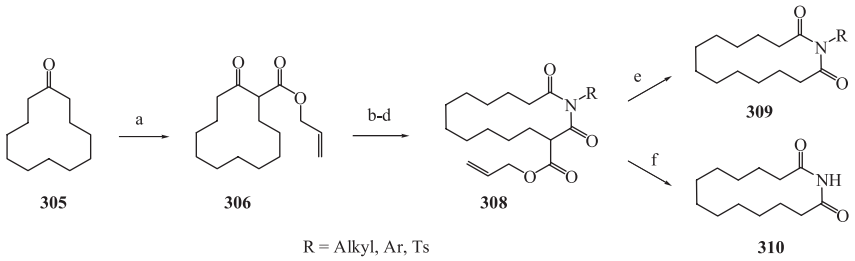


Scheme 66.

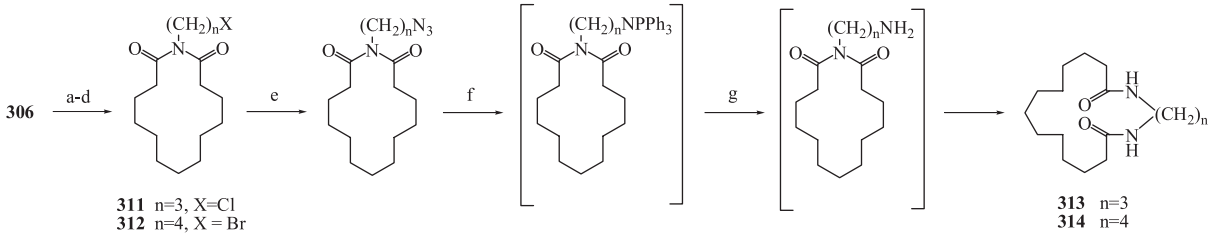


304	R	Yield, %
a	H	76
b	Cl	79
c	MeO	78

Scheme 67. a) NaH, THF; b)  (**303a-c**); c) HCl, H_2O.



Scheme 68. a) NaH, $CO(OCH_2CH{=}CH_2)_2$, benzene, Δ (70 %); b) NaH, THF; c) R-N=C=O (**307**); d) HCl, H_2O; e) $Pd(PPh_3)_4$, HCOOH, Et_3N, THF (100 %); f) $Pd(PPh_3)_4$, HCOOH, Et_3N, dioxane, 100 °C (100 %).



Scheme 69. a) NaH, THF; b) X-$(CH_2)_n$-N=C=O; c) HCl, H_2O (42 % or 55 %); d) $Pd(PPh_3)_4$, HCOOH, Et_3N, THF (92 %); e) NaN_3, H_2O, C_6H_6 (67 % or 87 %); f) PPh_3; g) H_2O (94 % for **313,** 84 % for **314**).

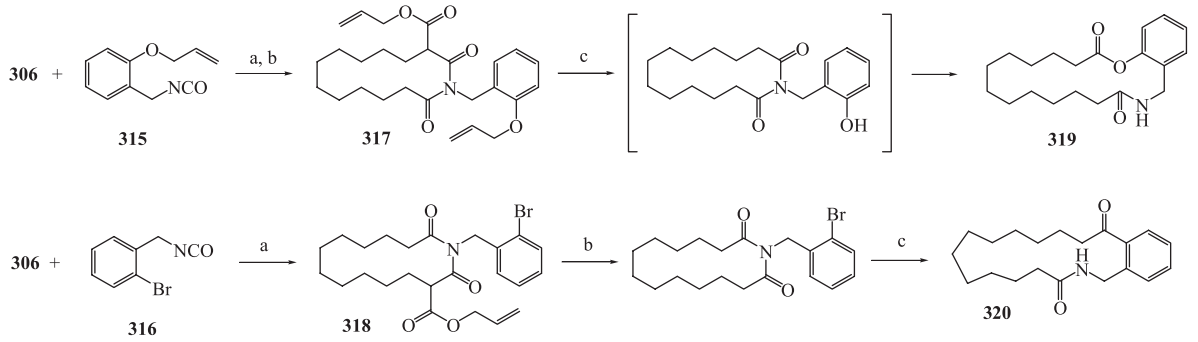
substituted macrolides (**317**) and (**318**) are transformed into appropriate cyclophanes (**319**) and (**320**) after deallylation (Scheme 70).[142]

Cyclophanes were also obtained using the Photo-Fries rearrangement.[143] Thus, irradiation of 12-membered *N*-phenylamide (**321**) in MeCN at 0 °C with a low pressure mercury lamp (110 W) leads to the formation of four products in the total yield of 97 %. *ortho*- (**322**) and *para*-(**323**) cyclophanes with the prevalence of the latter are main of them; moreover, bicyclic diketones (**324**) and (**325**) isomeric to them represent products of their secondary Photo-Fries rearrangement. Replacement of MeCN with EtOH allows excluding secondary processes and changes the *ortho*-/*para*-product ratio; *ortho*-cyclophane (**322**) is mainly formed (Scheme 71).

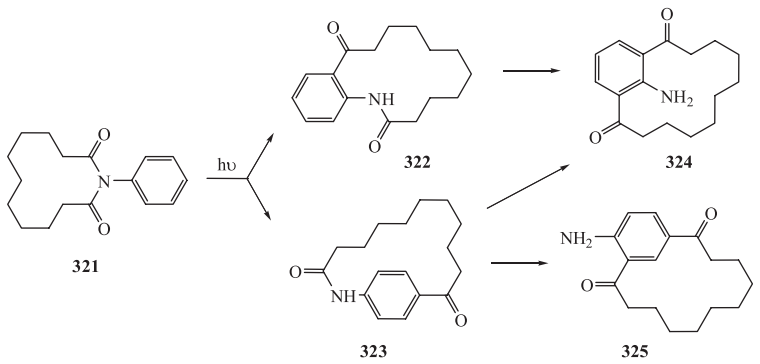
A large group of natural compounds that are metabolites of lower fungi and bacteria belongs to a class of cyclodepsipeptides. Many of them are significant antibiotics. Their synthesis consists in spontaneous isomerization of *N*-oxy- (**326**) and *N*-amino- (**327**) acyllactams and proceeds via the stage of the formation of cyclols (**328**) and azacyclols (**329**).[145-147] The latter are unstable and decompose with the formation of cyclopeptides (**330**) and (**331**). Additionally, transformation of *N*-α-aminoacyllactam (**326**) into bicyclic acylamides (**332**) that are dehydration products of intermediate azacyclols (**329**) (Scheme 72) is also possible.

The above method was used in synthesis of cyclotetradepsipeptides (**333a-h**) with regularly alternating residues of β-oxy- and α-amino acids. For this purpose, diketopiperazines (**334a-h**) were acylated with β-benzyloxy acid chloroanhydrides (**335a-h**) in boiling toluene and resulting *N,N*'-di(β-benzyloxy-acyl)diketopiperazines (**336a-h**) were subjected to hydrogenolysis in the presence of palladium oxide, which lead to the formation of cyclotetradepsipeptides (**333a-h**) in yields reaching 90 % in some cases (Scheme 73).[144-147]

Representatives of a family of macrolactam Fluvirucines A_1, A_2, and $B_{2\text{-}5}$ attract research attention, showing powerful activities against bacteria, fungi and especially the flu virus with their low toxicity. The aza Claisen rearrangement of amide enolate (**338**)[148] that proceeds stereoselectively with the formation of a mixture of diastereomeric 14-membered microlactams (**339**) in the 10:1 ratio is the key step of synthesis of fluvirucin A_2 (**337**). The regioselective oxidative cleavage of the *exo*-cyclic double bond in diyne (**339**)

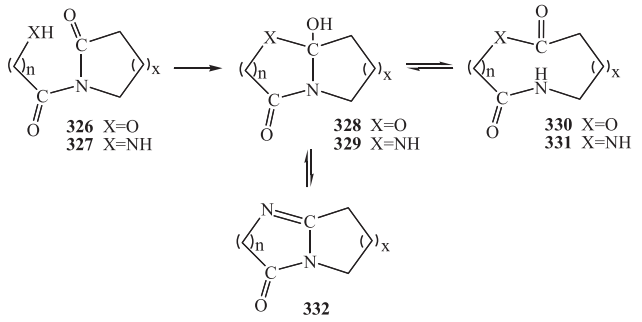


Scheme 70. a) NaH, THF; b) $Pd(PPh_3)_4$, HCOOH, Et_3N, dioxane, 100 °C; c) BuLi, Et_2O, hexane, -100 °C.



Products	High pressure mercury lamp, EtOH, 1.5 h	Low pressure mercury lamp, EtOH, 1.5 h	Low pressure mercury lamp, MeCN, 24 h
322	37 %	10 %	33 %
323	23 %	4 %	44 %
324	2 %	-	2 %
325	4 %	-	18 %
Total yield	66 %	14 %	97 %

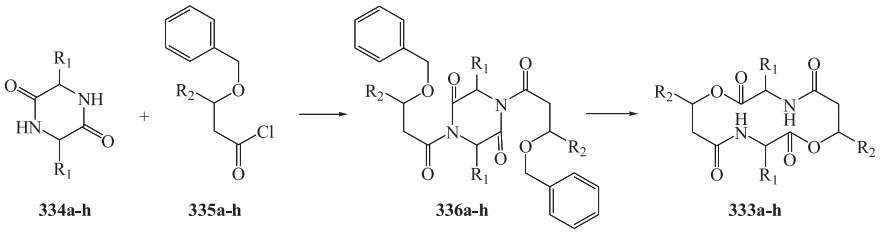
Scheme 71.



Scheme 72.

also used in the fragrance industry have been developed.

Synthesis of natural macrocyclic ketones, such as exaltone (**341**) (from the glands of muskrats) and muscone (**342**) (from the glands of deer) is based on oxidative fragmentation reactions of the double bond in macrocyclic bicycles (**343a,b**) and conjugated enones (**344a,b**). The simplest procedure is based on ozonolysis of olefins (**343a,b**) followed by reduction yielding symmetrical diketones (**345a,b**). Partial hydrogenation of the latter in the presence of an alkaline Raney nickel, dehydration of intermediate hydroxyketones (**346a,b**) and hydrogenation complete synthesis of compounds (**341**) and (**342**)



Compound	R^1	R^2	Compound	R^1	R^2
a	H	H	e	CH_2OAc	H
b	Me	H	f	CH_2OCHO	H
c	$CH(CH_3)_2$	H	g	CH_2OCH_2Ph	H
d	H	Me	h	CH_2OH	H

Scheme 73.

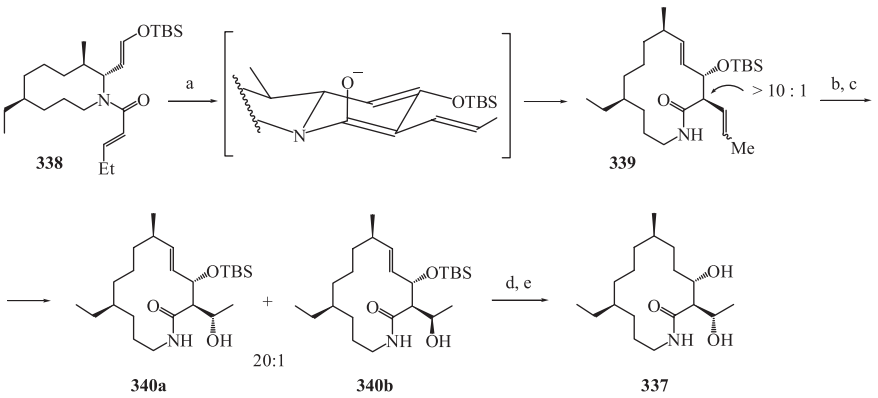
followed by stereoselective addition of a Grignard reagent to the resulting aldehyde leads to the formation of a mixture of lactam stereoisomers (**340a**) and (**340b**) in the 20:1 ratio. Its catalysed hydrogenation completes synthesis of bioactive 14-membered Fluvirucines A_2 (**337**) (Scheme 74).

Musks are an important class of odorants and have been used in perfumery more than ten centuries. Animals whose death is sometimes a requirement to extract essence are natural sources of musks. Therefore the prices for natural musks have remained high. In this regard, various methods of synthesis and transformation of their analogs[149] that are

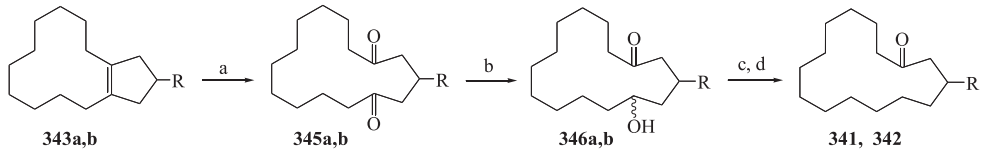
(Scheme 75).

Another approach assumes the impact of singlet oxygen on compounds (**343a,b**) with the formation of crystalline allylic hydroxyperoxides (**347a,b**). Hydroboration of the latter proceeds as an intramolecular redox reaction with the formation of *trans*-1,3-diols transformed into monotosylates (**348a,b**). Treatment of the latter with potassium *tert*-butylate and hydrogenation of macrocyclic precursors (**349a,b**) lead to target compounds (**341** and **342**) (Scheme 76).

One more approach consists in the generation of ketones (**341**) or (**342**) based on macrocyclic conjugated enones

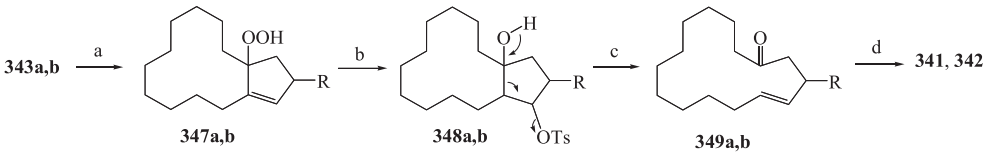


Scheme 74. a) LiHMDS, toluene, Δ (74 %); b) OsO_4, NMO then $NaIO_4$, Me_2CO, H_2O; c) MeMgI, Et_2O, 0 °C (93 %); d) TBAF, THF; e) H_2 Pd/C, MeOH (96 %).



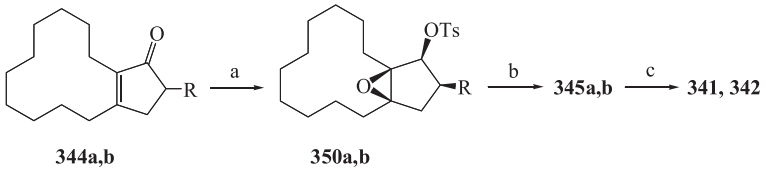
R = H (**343a, 345a, 346a, 341**), Me (**343b, 345b, 346b, 342**)

Scheme 75. a) O_3 then H_2; b) H_2, Ni-Ra; c) H_3O^+; d) H_2, Pd/C.



R = H (**347a, 348a, 349a, 341**), Me (**347b, 348b, 349b, 342**)

Scheme 76. a) $^1O_2$; b) BH_3 then TsCl, Py; c) *t*-BuOK, *t*-BuOH; d) H_2, Pd/C.



R = H (**344a, 345a, 350a, 341**), Me (**344b, 345b, 350b, 342**)

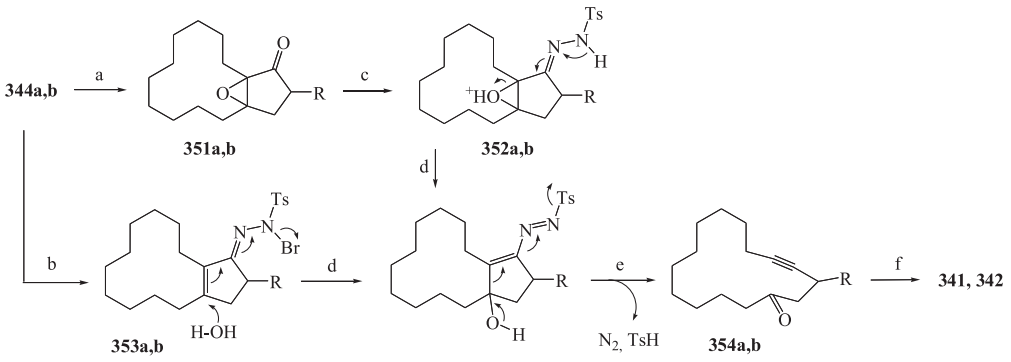
Scheme 77. a) *i*. DIBAH; *ii*. m-CPBA; *iii*. TsCl, Py; b) $CaCO_3$, Δ, 1,4-dioxane-H_2O; c) *i*. $TsNHNH_2$; *ii*. $NaBH_4$; *iii*. CrO_3, H_2SO_4, H_2O, acetone.

(**344a,b**). Consecutive reduction, epoxidation, and tosylation reactions lead to *cis*-epoxy tosylates (**350a,b**), treatment of which with hot calcium carbonate solution allows obtaining 15-membered cyclic diketones (**345a,b**). The latter are transformed into ketones (**341**) or (**342**) by the Cagliotti method that is based on reduction of monotosylhydrazons of (**345a,b**) with excess $NaBH_4$ followed by the Jones oxidation (Scheme 77).

The use of ozone or atomic oxygen in large scale production of natural musk-ketones (**341**) and (**342**) requires special equipment and poses a security threat. The Eschenmoser fragmentation of cyclic α,β-epoxyketones (**351a,b**) available from the epoxidation reaction of conjugated enones (**344a,b**) is one of the processes that allow avoiding the above issues. Tosylhydrazones (**352a,b**) that are subjected to a intramolecular rearrangements are obtained from keto-epoxides (**351a,b**).

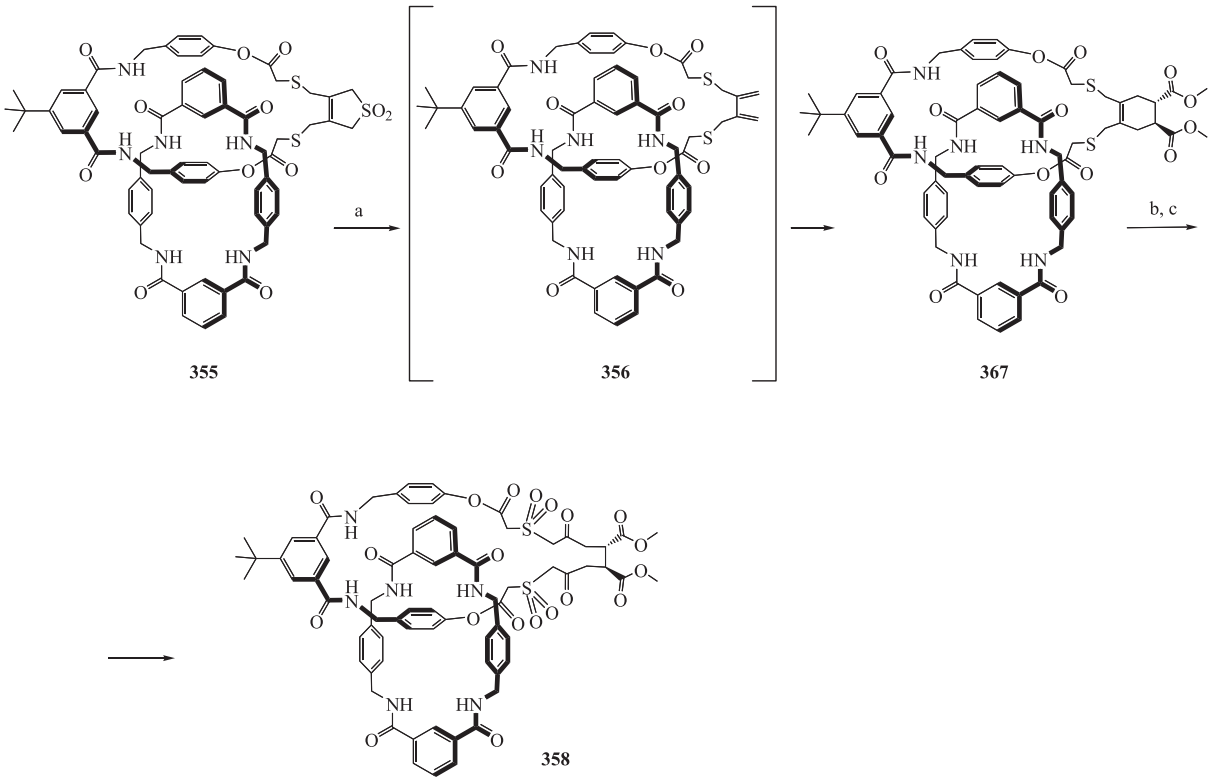
Since the yields of reaction products in the epoxidation stage are low, another way to transform enones (**344a,b**) is proposed. It consists in fragmentation of bromotosylhydrazones (**353a,b**) obtained by consecutive treatment with tosyl hydrazide and *N*-bromosuccinimide followed by exhaustive hydrogenation of the resulting alkyne ketones (**354a,b**) (Scheme 78).

The advisability of transformation of mechanically bound ring macromolecules into more complex molecular



R = H (**344a, 351a, 352a, 353a, 354a, 341**), Me (**344b, 351b, 352b, 353b, 354b, 342**)

Scheme 78. a) H_2O_2, NaOH; b) *i*. $TsNHNH_2$, *ii*. NBS, s-BuOH, $COMe_2$; c) $TsNHNH_2$, AcOH-CH_2Cl_2; d) warm; e) H_3O^+; f) H_2, Pd/C.



Scheme 79. a) (85 %); b) O_3, CH_2Cl_2/MeOH, -98 °C, Me_2S; c) *m*-CPBA, CH_2Cl_2 (40 %).

systems without structure destruction is driven by the need of studying the roles of catenanes and rotaxanes in living organisms. Thus, paper[123] demonstrated for the first time ring expansion of [2]catenane (**355**) without destruction of chained structures, and also the introduction of functional groups. The Diels-Alder reaction of bound ring macromolecules with dimethyl fumarate (10 equiv) proceeds under boiling with the formation of cyclohexane-condensed 4,5-disubstituted cyclohexen[2]catenane (**357**). The ozonolytic cleavage of the double bond in the cyclic species of the latter followed by reduction of peroxide ozonolysis products with dimethyl sulphide and further *m*-CPBA oxidation of sulphide groups expanded the ring of the catenane (**355**) macromolecule with obtaining catenane (**358**) (Scheme 79).

Thus, the presented review considered three approaches to functionalisation of macroheterocycles (with retaining, decreasing and increasing their sizes) in directed synthesis of compounds with various functionalities.

Acknowledgments. The work was carried out with the partial financial support of the Russian Foundation for Basic Research (Grant No. 17-03-01050-a).

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Received 06.10.2016
Accepted 28.12.2016