Quaternary ammonium derivatives of natural terpenoids. Synthesis and properties*

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In this review, we summarized and analyzed the literature data (from 1963 to March, 2014) on the synthesis and properties of quaternary ammonium derivatives of citronellal, menthol, camphor, lambertian acid, dehydroabietic acid, levopimaric acid, isosteviol, steviol, betulinic acid, dihydrobetulinic acid, platanic acid, oleanolic acid, ursolic acid, and polyprenols. Functionalization of terpenoids with ammnoium groups offers them new properties, such as cholinotropic, antiviral, and antimicrobial activities, or transforms them into chiral ionic liquids having a practical potential for application as chiral phase-transfer catalysts. The synthesis of ammonium derivatives of terpenoids possessing properties of cationic lipids or dimeric bis-quaternary ammonium surfactants was proved to have a promising outlook. A specific attention was paid to the method developed for transformation of any hydrophobic terpenoid or steroid into an amphiphilic water-soluble compound self-organized in the aqueous medium into vesicles (liposomes) forming cell-penetrating complexes with DNA.

Key words: quaternary ammonium compounds, terpenoids, camphor, resin acids, isosteviol, steviol, polylprenols, antimicrobial activity, DNA transport.

Over many years, mono- and bis-quaternary ammonium compounds are widely known by their bioactivities. First of all, they act as cholinesterase inhibitors,[1—3] curare-like muscle relaxants,[4,5] and ganglionic blocking agents.[6,7] Many ammonium compounds exhibit antimicrobial,[8] anticancer,[9,10] and antimalarial[11] activities. During the last decade, chiral quaternary ammonium salts became widely used as efficient phase-transfer catalysts for the enantioselective formation of carbon—carbon and carbon—heteroatom bonds under mild conditions.[12] Many ammonium compounds possess the properties of ionic liquids and are used as solvents.[13] It remains conventional to use the ammonium salts as corrosion inhibitors.[14] Recently, a novel class of surfactants called "*gemini surfactants*" or "*geminis*" (dimeric surfactants) loudly declared themselves in the colloid and supramolecular chemistry.[15] They are bis-quaternary ammonium compounds possessing long hydrophobic chains bound to two quaternary nitrogen atoms linked *via* any spacer. Compared to common surfactants,[16] dimeric cationic surfactants decrease more efficiently the surface tension of water and have a considerably less critical micelle concentration (CMC).[17] Due to these properties, dimeric cationic surfactants are superior dispersion stabilizers, efficient emulsifiers, dispersing agents, and foaming agents.[18,19] As many ammonium compounds, dimeric surfactants possess good antibacterial and antifungal activities.[20,21] An important field where cationic surfactants can be applied became DNA transport into cell (so called gene therapy).[22] It is obvious that one of the key reasons why the above-mentioned compounds have practically useful properties, including biological activity, is that they contain pharmacophore ammonium groups and, in some cases, hydrophobic polymethylene fragments. In this regard, introduction of the ammonium-group functionalization into the natural polycyclic terpenoids having a hydrophobic carbocyclic framework and possessing any bioactivity is of interest.

Functionalization of natural polycyclic terpenoids by pharmacophore groups is one of the conventional methods of their chemical modification,[23—28] which is carried out also by the changing the structures of their hydrocarbon fragments through the decrease[29—31] or increase[32—36] in the number of rings, as well as by the increase in the size of one ring.[30] In recent years, functionalization became to be carried out by combination of two or more terpenoid molecules into macrocycles.[37—39]

The present review summarizes the data on functionalization of natural terpenoids by the ammonium groups. The information is given in the order of terpene emergence during biogenesis.

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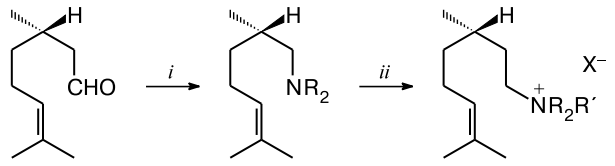
Acyclic monoterpenoids. A large series of chiral ionic liquids have been prepared based on available citronellal.[40] At the first step, (*S*)-citronellal **1** was subjected to reductive amination to give amines **2** or **3**. They were then quaternized with various alkyl halides to yield salts **4a**—**e** and **5a**—**e** (Scheme 1). The ammonium derivatives of enantiomeric (*R*)-citronellal **6** were prepared similarly. All compounds obtained, excluding salts (*S*)-**4a** and (*R*)-**4a**, are liquids at room temperature.

Scheme 1



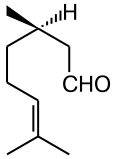
1 **2, 3** **4a—e, 5a—e**

R = Me (**2**, **4a**—**e**), Et (**3**, **5a**—**e**)

3, 5	R′	X	**3, 5**	R′	X
a	Me	I	**d**	Pr^i	Br
b	Et	I	**e**	Bu	Br
c	Pr	Br			

Reagents and conditions: *i*. NHR_2, H_2, Raney Ni, 20 °C; *ii*. R′X, MeCN.

Monocyclic terpenoids. One of the most known terpenoid representative of this class is (1*R*,2*S*,5*R*)-(−)-menthol **7**. The first data on its ammonium derivatives appeared in 1963.[41] Esterification of compound **7** with chloroacetic acid affords chloroacetic ester **8** suitable for quaternization of the nitrogen atom of trimethylamine, triethylamine, and procaine to yield salts **9a**,**b** and **10** (Scheme 2). Note that the first representative of bis-quarternized ammonium derivatives of natural terpenoids, *viz.*, compound **11**, was synthesized by the reaction of chloroacetic ester **8** with *N*,*N*,*N*′,*N*′-(tetramethyl)decamethylenediamine.[41]



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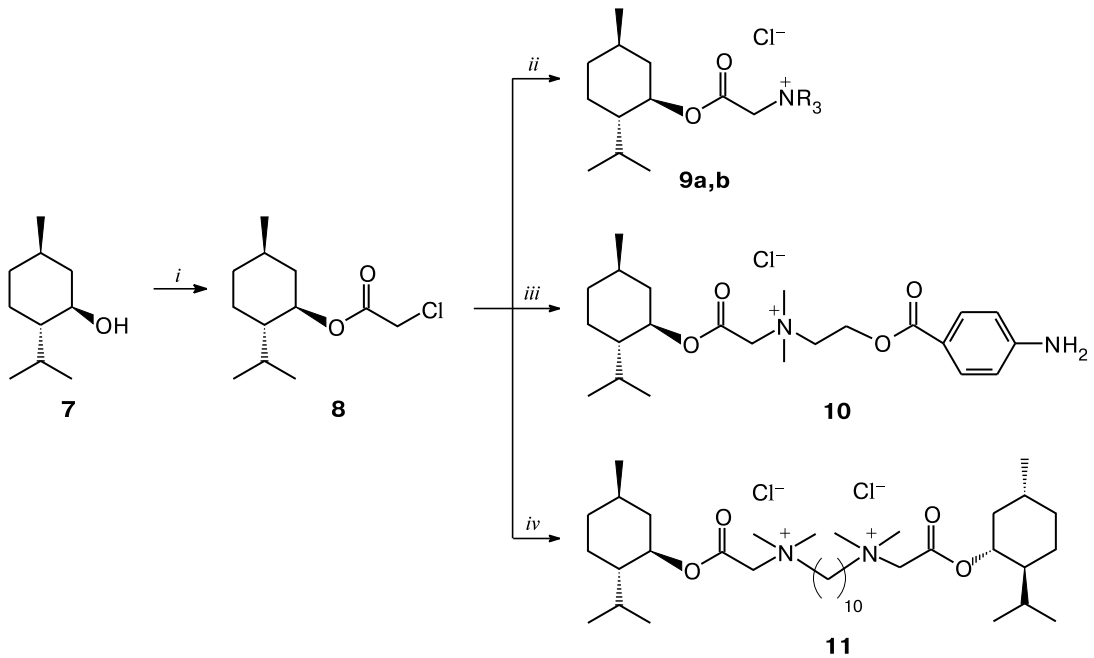
Only after 42 years, the ammonium derivatives of (−)-menthol attracted attention of chemists and, on its basis, a large series of catinoic lipids **13**—**17** have been synthesized through compound **12** (see Refs 42—47). The polar part of the molecules is represented by ammonium,[42] alkylimidazolinium,[43,44] (alkoxymethyl)imidazolinium,[45] and pyridinium[46] groups, while the hydrophobic part along with the menthane framework is represented by alkyl substituents R^1 at the quaternized nitrogen atom (Scheme 3). In all cases, the halide component upon quaternization of amines of different nature was chloromethyl menthyl ether **12**. The antibacterial activities of cationic

Scheme 2

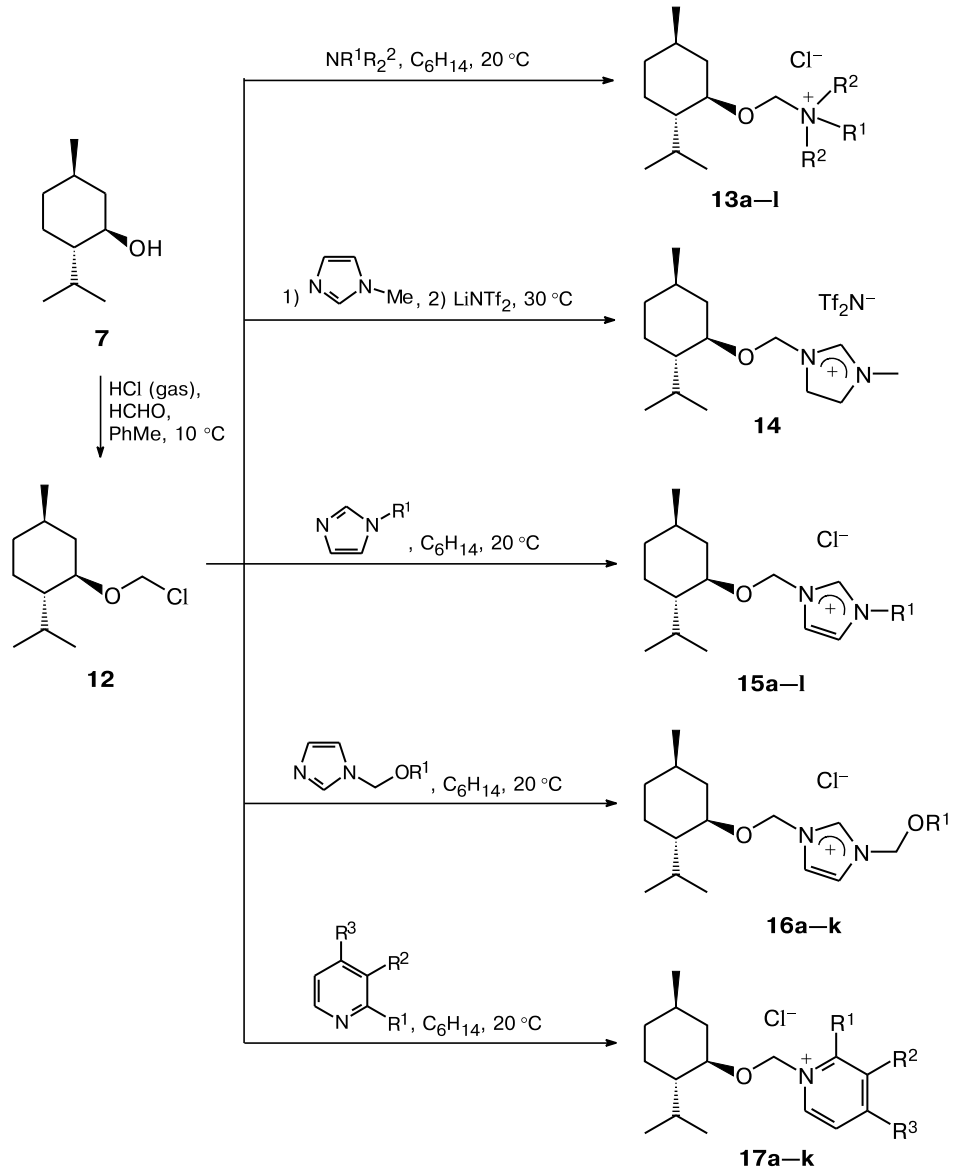


7 **8** **9a,b** **10** **11**

9: R = Me (**a**), Et (**b**)

Reagents and conditions: *i*. $ClCH_2COOH$, H_2SO_4 (conc.), 90 °C, 7 h.; *ii*. NMe_3 (for **9a**) or NEt_3 (for **9b**), toluene, 110 °C; *iii*. 4-$H_2NC_6H_4C(O)OCH_2CH_2NMe_2$, Et_2O, 30 °C; *iv*. $Me_2N(CH_2)_{10}Me_2N$, Et_2O, 30 °C.

Scheme 3



13	R^1	R^2	R^3
a	Et	Et	Et
b	Et	Et	Me
c	Et	Me	Me
d	Pr^i	Me	Me
e	Bu	Me	Me
f	C_6H_{13}	Me	Me
g	C_7H_{15}	Me	Me
h	C_8H_{17}	Me	Me
i	C_9H_{19}	Me	Me
j	$C_{10}H_{21}$	Me	Me
k	$C_{11}H_{23}$	Me	Me
l	$C_{12}H_{25}$	Me	Me

15	R^1
a	Me
b	Et
c	Pr
d	Bu
e	C_5H_{11}
f	C_6H_{13}
g	C_7H_{15}
h	C_8H_{17}
i	C_9H_{19}
j	$C_{10}H_{21}$
k	$C_{11}H_{23}$
l	$C_{12}H_{25}$

16	R^1
a	Et
b	Pr
c	Bu
d	C_5H_{11}
e	C_6H_{13}
f	C_7H_{15}
g	C_8H_{17}
h	C_9H_{19}
i	$C_{10}H_{21}$
j	$C_{11}H_{23}$
k	$C_{12}H_{25}$

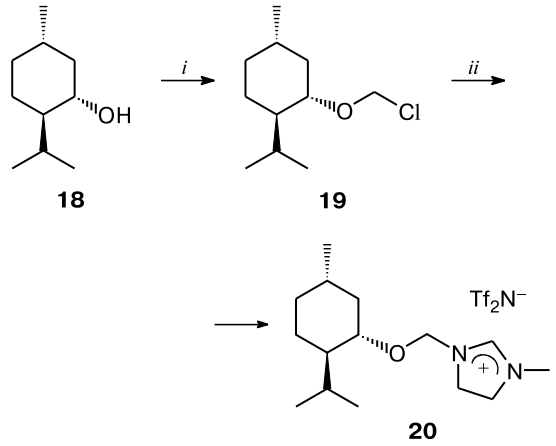
17	R^1	R^2	R^3
a	H	H	H
b	Me	H	H
c	H	Me	H
d	H	H	Me
e	H	H	Et
f	H	H	Bu^t
g	Me	H	H
h	H	$CONH_2$	H
I	H	OH	H
j	H	H	NMe_2
k	H	NMe_2	H

lipids **13**—**17** were found to increase dramatically with increasing the length of alkyl substituent at the quaternized nitrogen atom. The ammonium derivatives of menthol with ten or more carbon atoms in the alkyl substituent R^1 (compounds **13j**—**l**, **15j**—**l**, and **16i**—**k**) have a higher antibacterial activity against *M. luteus*, *S. Aureua*, *S. epidermidis*, *E. Faecium*, and *E. coli* compared to alkyldimethylbenzylammonium chloride (benzalkonium chloride, BAC)

with the analogous length of alkyl substituent at the quaternized nitrogen atom.[42,44,45] Among the pyridinium derivatives of (–)-menthol, only salts **17j—k** having no hydrophobic substituents surpassed the reference compound BAC in the antibacterial activity, but only against *M. Luteus*[46]. Thus, until now one cannot draw a final conclusion on the optimum nature (structure) of the ammonium group providing high and/or selective antibacterial activities of the (–)-menthol ammonium derivatives **13—17**.

For now, only one fact is obvious: on going from the reference compound BAC to the ammonium derivatives **13—17** involving the replacement of the benzene ring with the (–)-menthyl group, results in a pronounced increase in the antibacterial activity. Moreover, the mentioned activity was found to depend directly on the enantiomeric purity of the terpenoid fragment. For example, it was established that the racemic analogs of more active (–)-menthol ammonium derivatives **13k**, **15j**, and **16i** (see Scheme 3) are significantly less active.[47] Salt **14** prepared from (–)-menthol **7** (see Scheme 3) and salt **20** synthesized from (+)-menthol **18** through (+)-chloromenthyl ether **19** (Scheme 4) were used as both solvents and chiral inducers in photoisomerization of dibenzobicyclo[2.2.2]-octatriene diacid.[43] The enantiomeric excess achieved was not high (*ee* = 6.5); however, this is a single case described in the literature when the ammonium derivatives of terpenoids were used as chiral inducers.

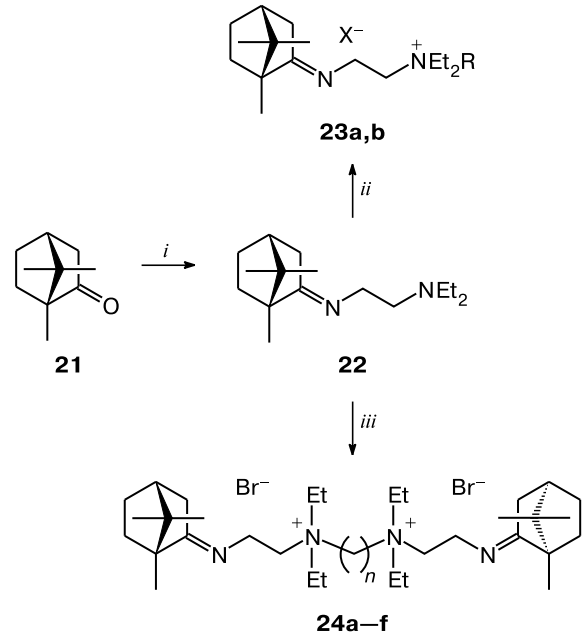
Scheme 4



Reagents and conditions: *i.* HCl (gas), HCHO, toluene, 10 °C; *ii.* 1)  ; 2) $LiNTf_2$, 30 °C.

Bicyclic monoterpenoids. The only representative of terpenoids of this class, for which ammonium derivatives have been described, is (+)-camphor **21**. The reaction of **21** with *N*,*N*-diethylethane-1,2-diamine in the presence of boron trifluoride diethyl etherate with azeotropic removal of water affords azomethine **22** whose amine nitrogen atom was subsequently quaternized with alkyl halides, including dibromoalkanes with different length of the polymethylene chain between the bromine atoms[48] (Scheme 5).

Scheme 5



23: R = Me, X = I (**a**), R = Et, X = Br (**b**)

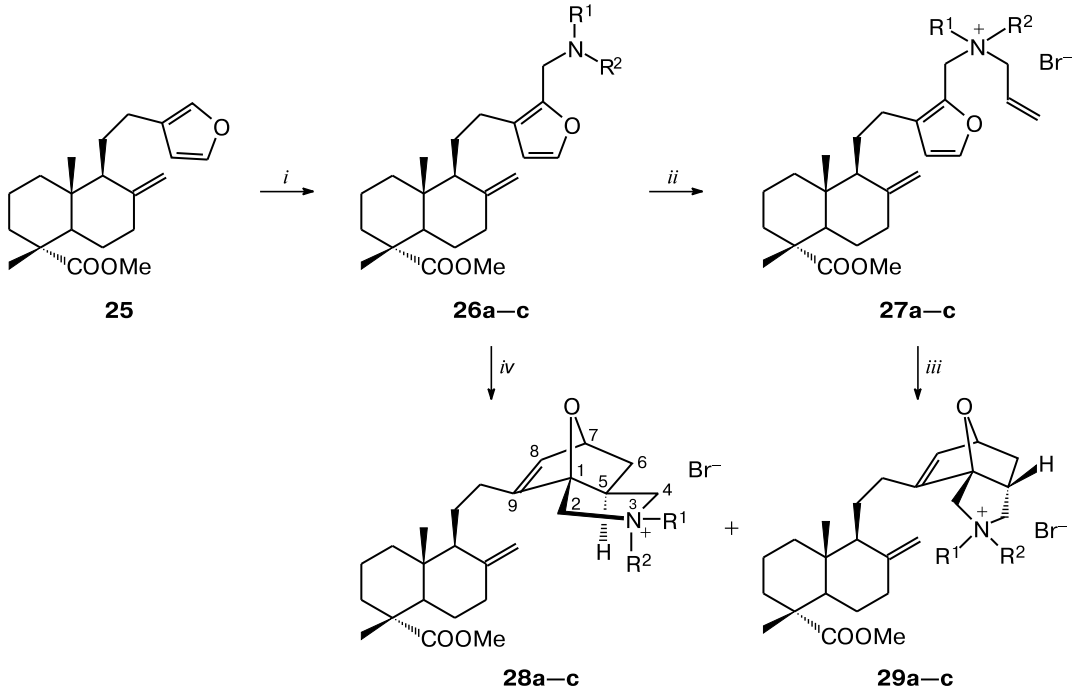
24: *n* = 5 (**a**), 6 (**b**), 8 (**c**), 9 (**d**), 10 (**e**), 12 (**f**)

Reagents and conditions: *i.* $H_2NCH_2CH_2NEt_2$, $BF_3 \cdot Et_2O$, toluene; *ii.* RX, MeCN, 80 °C; *iii.* $Br(CH_2)_nBr$, K_2CO_3, MeCN, 80 °C.

All compounds synthesized were studied for the activity against the pandemic influenza strain A(H1N1)pdm09. Compound **23a** was found to be 1.5-fold more active than remantadine and amantadine, but when the methyl substituent in the ammonium group was replaced with the ethyl group and the I^- counterion was replaced with Br^-, the loss of activity was observed.[48] On going to the bis-quaternary ammonium (+)-camphor derivatives **24**, the activity increases, which in compound **24d** with the nonamethylene spacer between the quaternary nitrogen atom is nine-fold higher than those of remantadine and amantadine.[48] It is interesting to note that further increase in the distance between the ammonium groups results in a decrease in the antiviral activity.[48]

Bicyclic diterpenoids. In this class of terpenoids, the ammonium derivatives were described only for the labdane group representative, *viz.*, lambertian acid.[49,50]. Methyl lambertianate **25** was converted to amines **26** by the Mannich reaction with methylene iminium salts prepared *in situ* from bis(dialkylamino)methanes and acyl chloride, which were then quaternized to the quaternary salts **27** by the reaction with allyl bromide (Scheme 6). Upon refluxing in benzene, compounds **26**, **27** underwent [4+2] cyclo-

Scheme 6



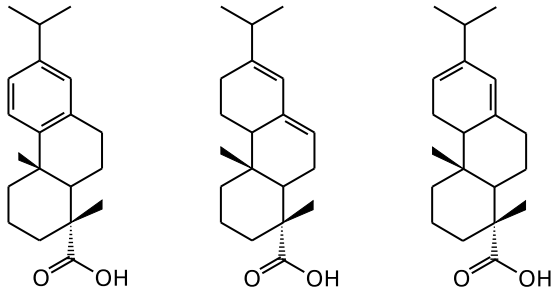
26—29	R^1	R^2
a	Me	Me
b	$(CH_2)_2O(CH_2)_2$	
c	$(CH_2)_5$	

Reagents and conditions: *i*. $(R^1R^2N)_2CH_2$, AcCl, CH_2Cl_2, 0—20 °C; *ii*. $CH_2{=}CHCH_2Br$, $Me_3N^+BnCl^-$, benzene, 20 °C; *iii*. Benzene, 80 °C; *iv*. $CH_2{=}CHCH_2Br$, $Me_3N^+BnCl^-$, K_2CO_3, KOH, MeCN, 80 °C.

addition to form the 1 : 1 mixture of (1′*R*,5′*S*,7′*S*)-*exo*-adducts **28** and (1′*R*,5′*R*,7′*S*)-*endo*-adducts **29**.[49,50] Compounds **28a** and **29b**,**c** were isolated in the individual state.[49,50] The cyclization can be performed omitting the isolation step of quaternary salts **27**, namely, by refluxing amines **26** with allyl bromide in acetonitrile[50] (see Scheme 6). It is interesting to note that while the reactions of amines **26b**,**c** with crotyl bromide under the same conditions also give intramolecular [4+2] cycloaddition products, the reaction of amine **26a** with crotyl bromide terminates at the step of quaternary salt formation.[50]

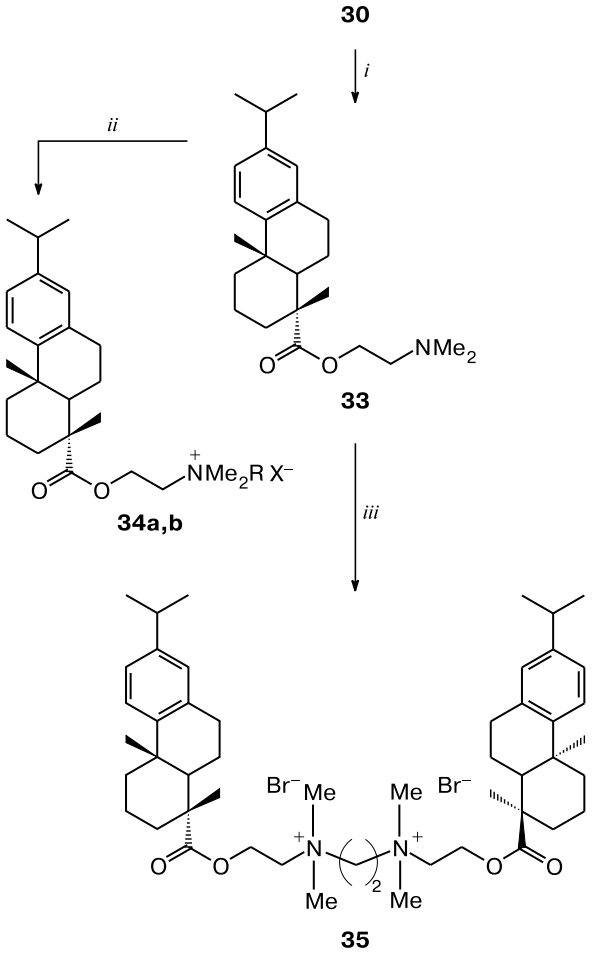
Tricyclic diterpenoids. The best known representatives of terpenoids of this class are resin acids (dehydroabietic acid **30**, abietic acid **31**, levopimaric acid **32**, *etc.*). Resin acids and their derivatives are widely used in the production of synthetic rubbers, industrial rubber products, varnishes, dyes, and other practically useful materials and products.[51] Resin acids since the mid XX century began to be used in the fine organic synthesis and, in the beginning of the present century, for the preparation of bioactive substances and high-efficiency therapeutic agents. To date, hundreds of resin acid derivatives of various structure, including amides, amines, imines, and others, have been described;[52,53] however, there are few data on their ammonium derivatives.

Due to the steric shielding by the geminal $C(4)H_3$ group, the carboxyl group of resin acids does not readily undergo typical reactions of carboxylic acids. Therefore, this group is frequently converted first to the acid chloride, which undergoes subsequent functionalization, for example, by the reaction with dimethylaminoethanol.[54] Amino ester **33** obtained in such way was then quaternized by the reaction with ethyl bromide and benzyl chloride (Scheme 7). The resulted salts **34a**,**b** are very soluble in water and organic solvents, act as surfactants, and possess bactericidal activity.[54] The reaction of amino ester **33** with ethylene dibromide afforded the bis-quaternary ammonium salt **35**, which was found to be a good emulsifier[55] (see Scheme 7).



The analogous surface-active properties were observed for the bis-quaternary ammonium derivative of abietic acid

Scheme 7



34: R = Et, X = Br (**a**), R = Bn, X = Cl (**b**)

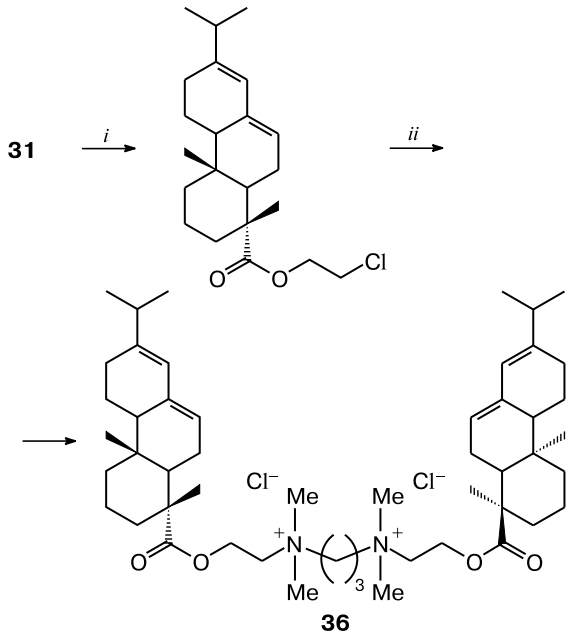
Reagents and conditions: *i*. 1) PCl_3, CCl_4, 2) $HOCH_2CH_2NMe_2$, NEt_3, CH_2Cl_2; *ii*. RX, MeCN, 80 °C; *iii*. $BrCH_2CH_2Br$, EtOH, microwave radiation.

36 (Scheme 8).[56] This is one of the rare cases when the carboxyl group of diterpenoid acids was involved in esterification under severe conditions (heating, conc. H_2SO_4).

Designing new surface-active systems for enantiomeric separation by micellar electrokinetic chromatography, the authors of Ref. 57 carried out amidation of dehydroabietic acid **30** by the reaction of its acid chloride with *N*,*N*-dimethylpropane-1,3-diamine and the resulted amine **37** was quarternized by the reaction with sodium 2-bromoethanesulfonate (Scheme 9). Using the betaine-type compound **38**, the enantiomeric mixtures of tryptophan, phenylalanine, and kynurenine were separated.[57]

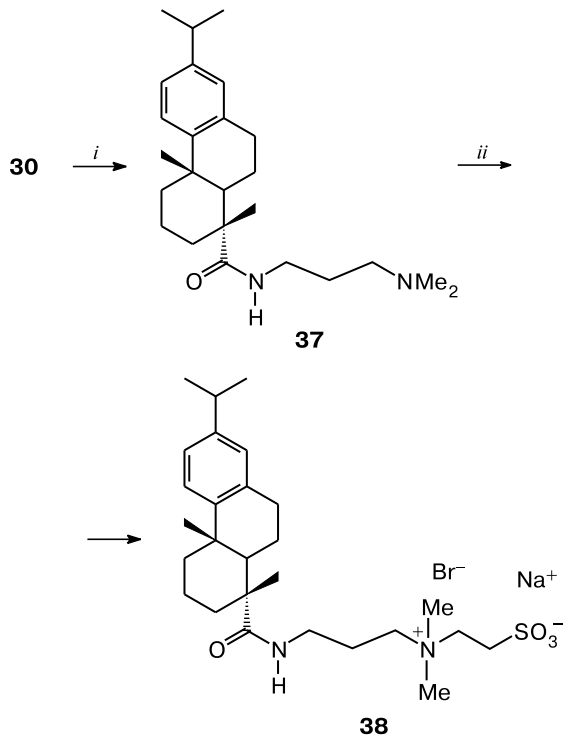
The ammonium derivative of dehydroabietic acid **30** was prepared using epichlorohydrin, which was involved in the reaction with its acid chloride. The resulted acid chloride **39** was used for quarternization of various amines[53,58]

Scheme 8



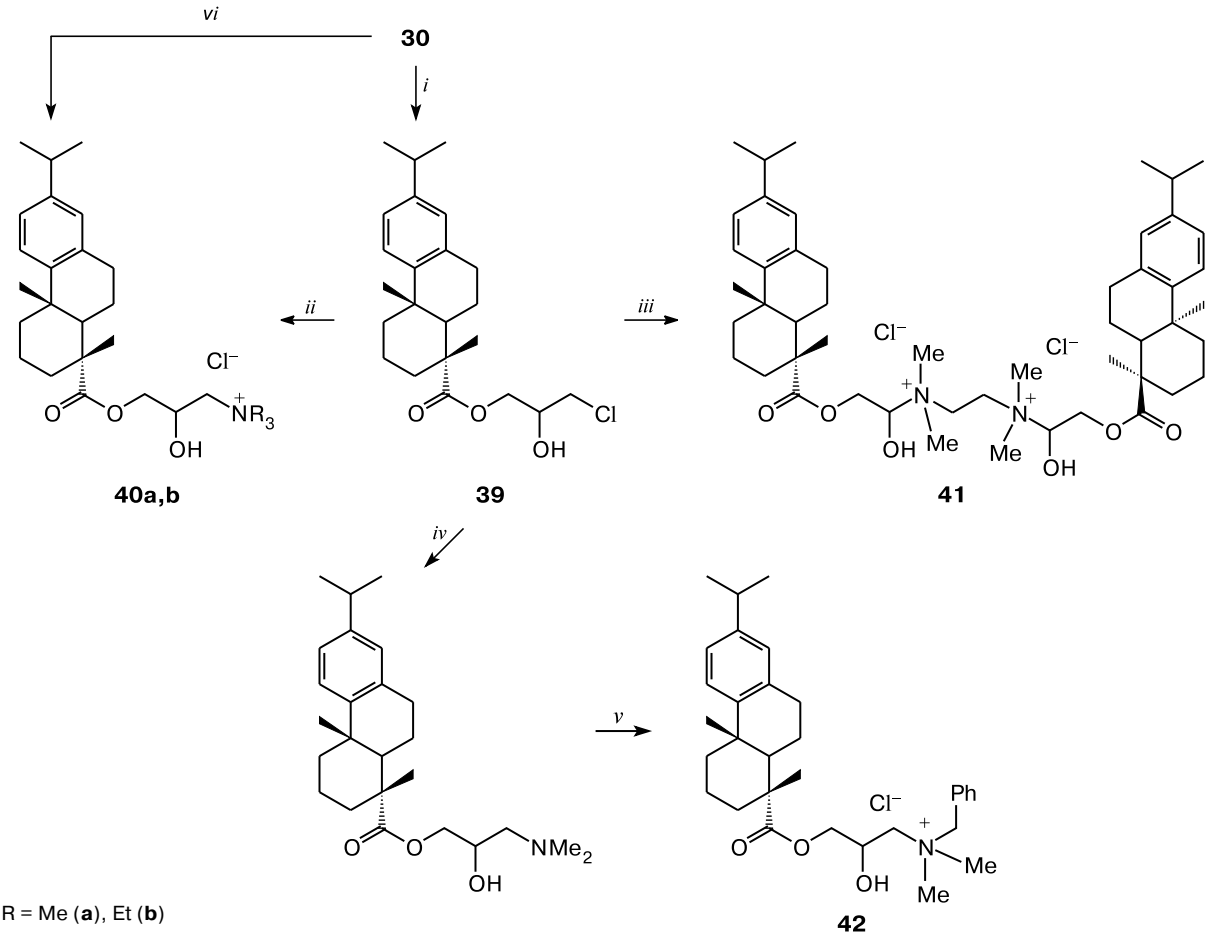
Reagents and conditions: *i*. $HOCH_2CH_2Cl$, H_2SO_4 (conc.), heating; *ii*. $Me_2N(CH_2)_3NMe_2$.

Scheme 9

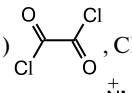
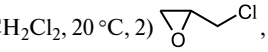
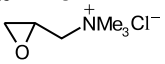


Reagents and conditions: *i*. 1) $SOCl_2$, benzene, 2) $H_2N(CH_2)_3NMe_2$, THF, K_2CO_3; *ii*. $[BrCH_2CH_2SO_3^-]Na^+$, EtOH, 78 °C.

Scheme 10



40: R = Me (**a**), Et (**b**)

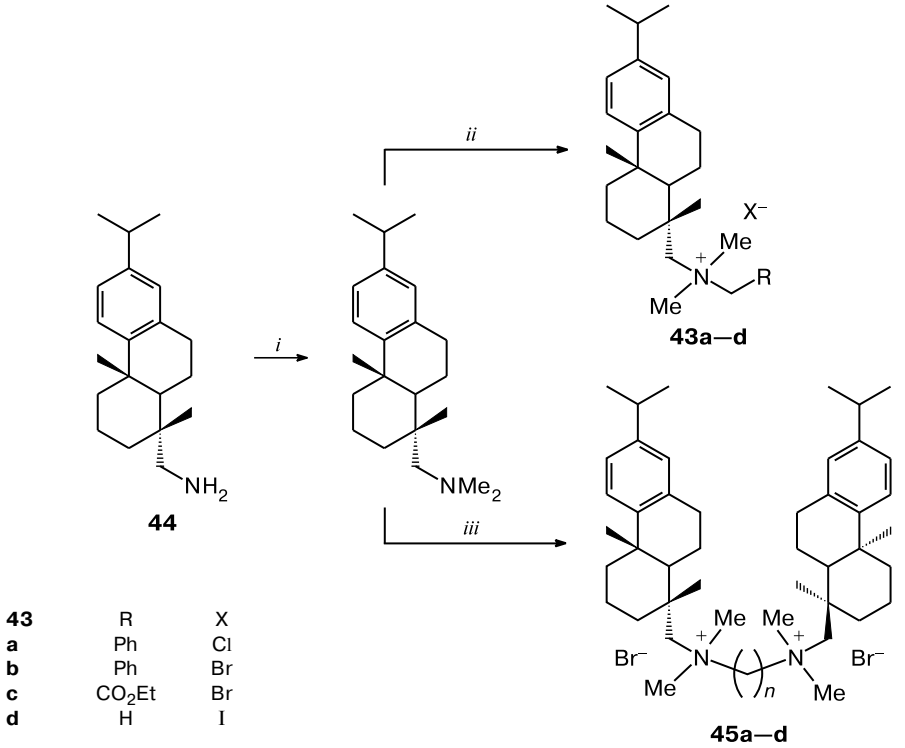
Reagents and conditions: *i.* 1)  , CH_2Cl_2, 20 °C, 2)  , TBAB, 50 °C; *ii.* NR_3, EtOH, H_2O, 85 °C; *iii.* $Me_2NCH_2CH_2NMe_2$; *iv.* $NHMe_2$; *v.* $PhCH_2Cl$; *vi.* 

to form salts **40**—**42** (Scheme 10). Hydroxy ammonium derivatives **40** were also synthesized directly from dehydroabietic acid **30** by the reaction with the oxirane ring of the ammonium salt obtained from epichlorohydrin and trimethylamine.[53] The "acid chloride pathway" was used also to synthesize the ammonium salt of type **40** based on perhydroabietic acid.[58] All ammonium salts obtained exhibited antifungal activity against *T. versicolor* and *G. trabeum*, the activity of the bis-quaternary derivative **41** being the highest in this series.[53]

The ammonium derivatives **43a**,**b** prepared from dehydroabietylamine **44** (Scheme 11) showed a capacity to act as chiral phase-transfer catalyst.[59,60] Catalyzed by compounds **43a**,**b** oxidation of chalcone with sodium hypochlorite yielded epoxide with *ee* equal to 18—20%.[60] The ability of compounds **43c**,**d** for the asymmetric catalysis was much worse.[59,60] The synthesis of bis-quaternary ammonium salts **45** based on dehydroabietylamine **44** (see Scheme 11) was reported;[53] however, there are no literature data on their properties.

The ammonium derivatives of levopimaric acid **32** are reported only in two papers.[58,61] Acryloyllevopimaric acid **46** obtained from these derivatives by [4+2] cyclization with acrylic acid was converted to diacyl dichloride **47**, whose reaction with epichlorohydrin afforded bischlorohydrin **48** used for quarternization of trimethylamine and triethylamine[58] to yield salts **49** (Scheme 12). The antifungal activities of the bis-quaternary ammonium salts **49** against *T. versicolor* and *G. trabeum* were higher than those of the analogous mono-quaternary salts **40** based on dehydroabietic and perhydroabietic acids.[58] The Diels—Alder adduct of ethyl levopimarate **50** with fumaric acid, *viz.*, diacid **51**, was easily transformed in 93% yield to the bis-quaternary ammonium salt **52** (Scheme 12).[61] This com-

Scheme 11



43	R	X
a	Ph	Cl
b	Ph	Br
c	CO_2Et	Br
d	H	I

44

45: *n* = 1 (**a**), 2 (**b**), 3 (**c**), 4 (**d**)

Reagents and conditions: *i*. HCHO, HCOOH; *ii*. RCH_2X, EtOH, 78 °C; *iii*. $Br(CH_2)_nBr$, EtOH, 78 °C.

pound exhibited a moderate antifungal activity against *T. versicolor*, *P. chrysosporium*, and *C. globosum*.[61]

Recently, dehydroabietic acid **30** was used for the synthesis of polymeric amphiphilic antibacterial agents containing ammonium groups.[62,63] At the first step, polymer **54** was obtained from *N*,*N*-dimethylaminoethyl methacrylate **53** by reversible addition-fragmentation chain transfer (RAFT) polymerization using cumyl dithiobenzoate (CDB) as the chain transfer agent and azobisisobutyronitrile (AIBN) as the initiator followed by quaternization with 3-chloropropyldehydroabietate **55** (Scheme 13).[62] Varying the molar ratio of reagents, the authors obtained a series of polymers **56** having different degree of quaternization (the number of groups containing the quaternary nitrogen atom).[62]

At the second step, RAFT polymerization of the monoquaternary ammonium salt **57** obtained by the reaction of abietate **55** with methacrylate **53** afforded[62] polymers **58** with a degree of quaternization of 100% (Scheme 14).

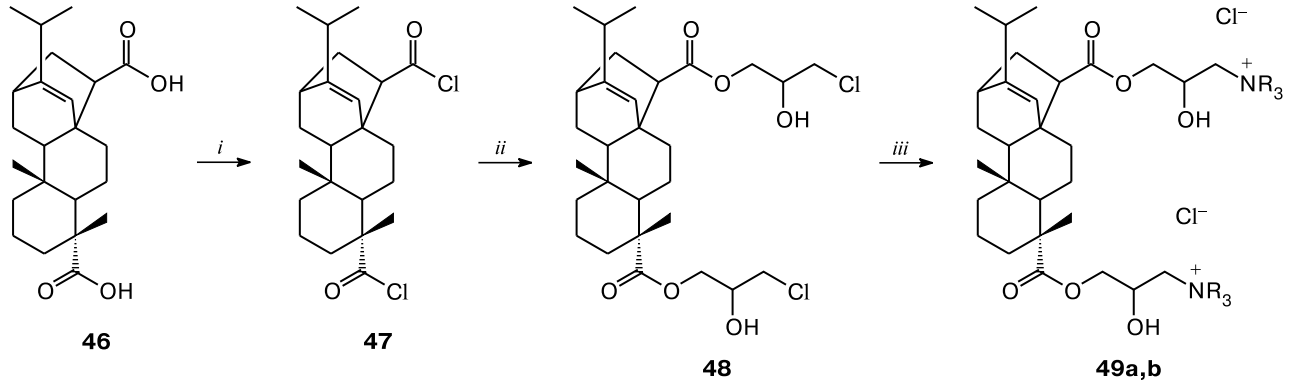
The results of the study of synthesized polymers **56** and **58** for the antibacterial activity against *E. coli* and *S. aureus* showed that this activity depends on the degrees of quaternization of compounds and their molecular weights. With increasing the degree of quaternization from 7 to 15%, the antibacterial activity increases, but the further increase in the number of dehydroabietyloxyethylammonium groups in copolymers **56** leads to a decrease in the activity.[62] Copolymers **58** with a degree of quaternization of 100% possessed the least antibacterial activity in this series.[62]

In the alternative approach[63] to the synthesis of polymeric cationic antibacterial agents (Scheme 15), the ammonium fragments were designed based on levopimaric acid **32**. The Diels—Alder reaction of levopimaric acid **32** with maleic anhydride afforded maleopimaric acid whose amidation with *N*,*N*-dimethylethane-1,2-diamine yielded amine **59**. Then, amine **59** was quaternized with ethyl bromide and the carboxyl group of the resulted quaternary salt **60** was esterified with propargyl alcohol. The click reaction of propargyl ester **61** with poly(ε-caprolactone) containing azide groups yielded the target polymers **62**.

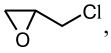
Both monomer **60** and polymers **62** on its basis showed a high antimicrobial activity against Gram-negative (*P. aeruginosa*, *E. coli*, *K. pneumoniae*, *P. vulgaris*, *E. agglomerans, S. typhimurium,* and *A. faecalis*) and Gram-positive (*S. aureus*, *B. cereus*, *S. pyogenes*, *M. luteus*, *M. smegmatis,* and *C. xerosis*) bacteria.[63] It should be noted that the activities of polymers **62** were higher than those of their analogs containing no maleopimaric groups.[63]

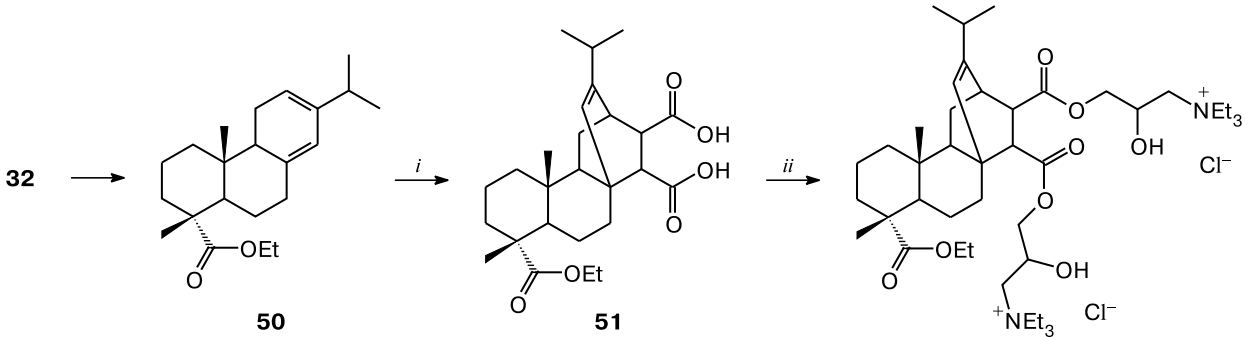
Tetracyclic diterpenoids. Only the ammonium derivatives of isosteviol **63** and steviol **64** are known in this group

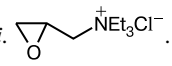
Scheme 12



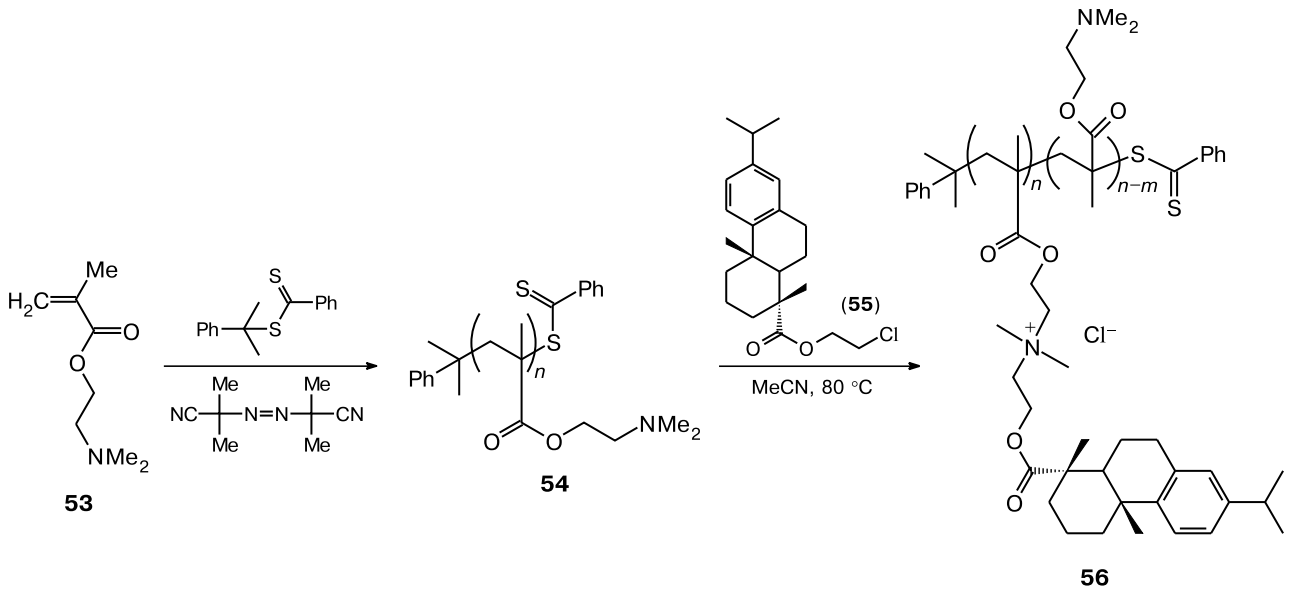
49: R = Me (**a**), Et (**b**)

Reagents and conditions: *i.*  , CH_2Cl_2, 20 °C; *ii.*  , TBAB, 50 °C; *iii.* NR_3, EtOH.

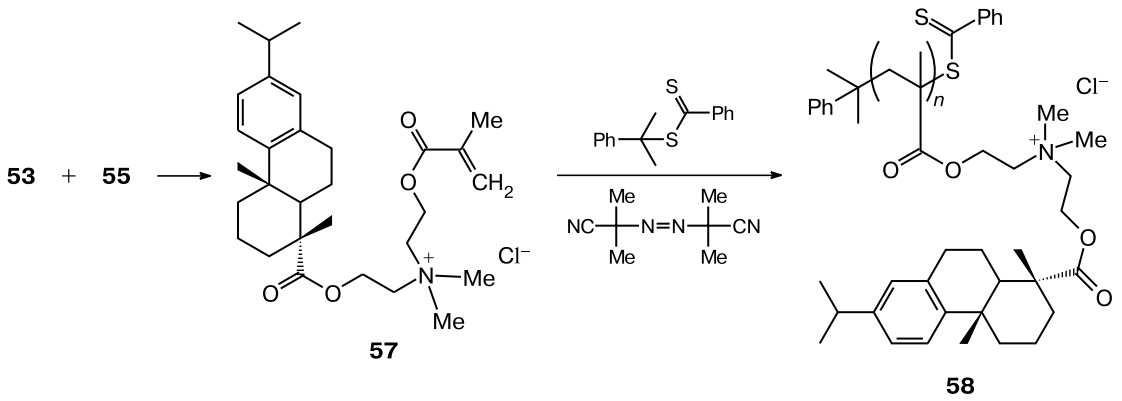


Reagents and conditions: *i.* HOOCCH=CHCOOH, 1,4-$(HO)_2C_6H_4$, N_2, 230 °C; *ii.*  .

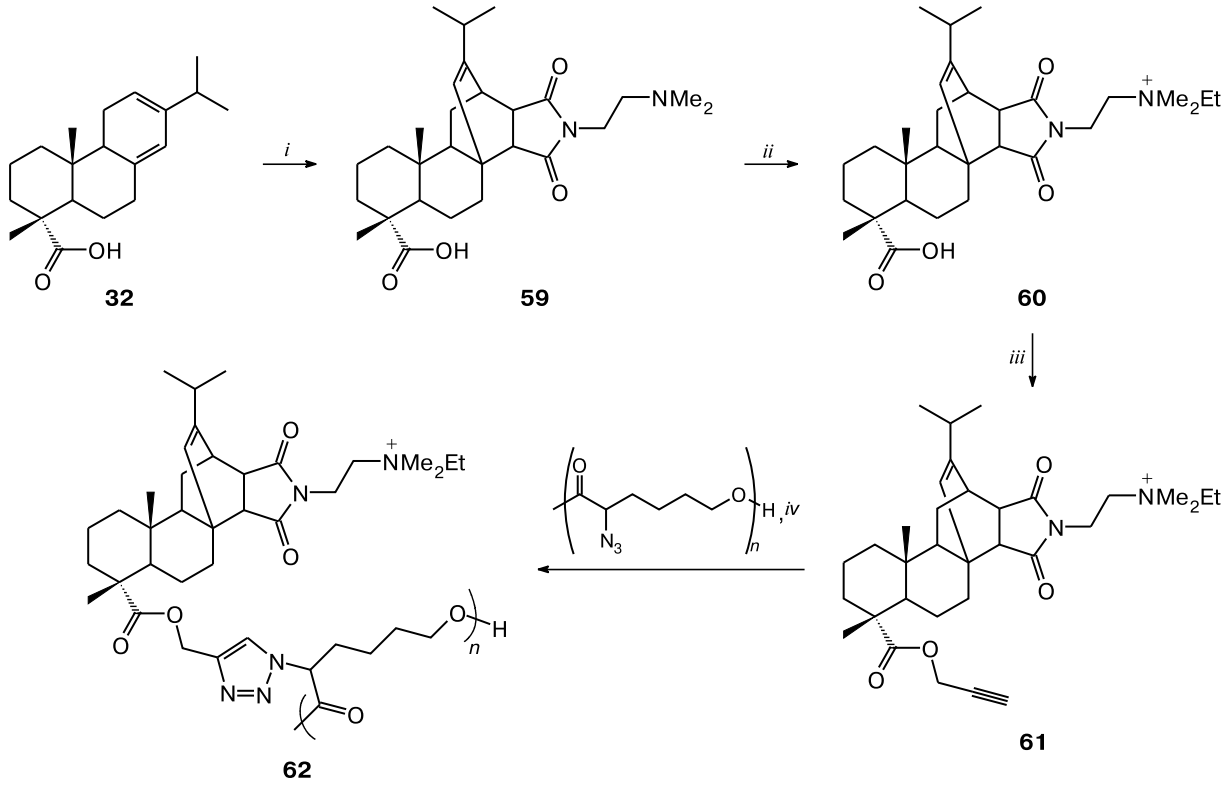
Scheme 13



Scheme 14



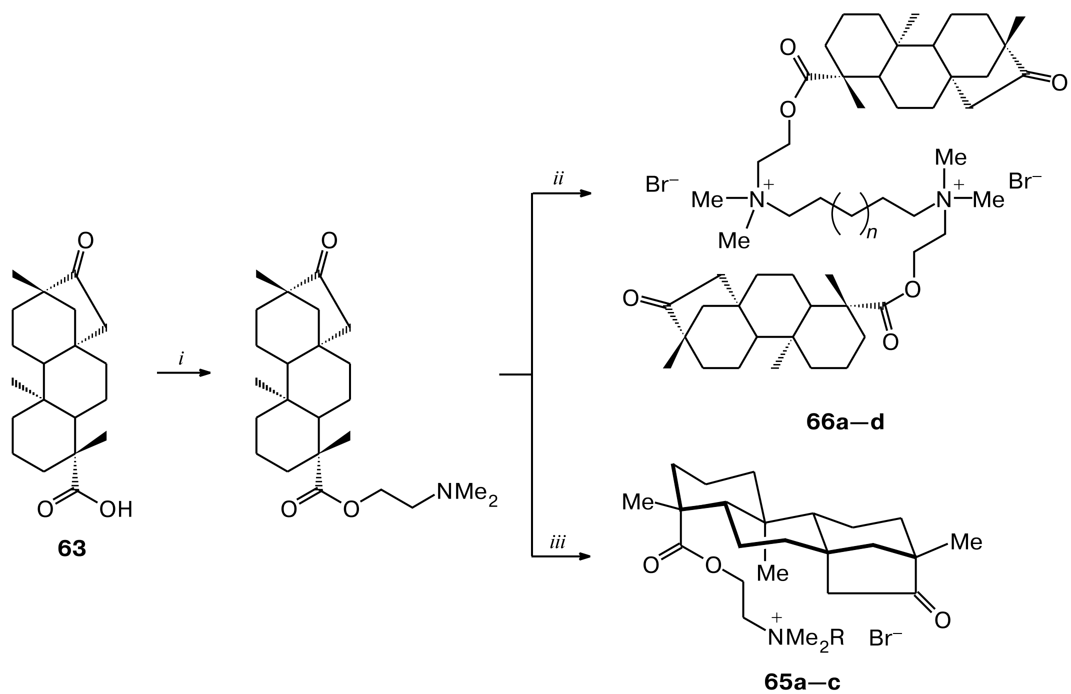
Scheme 15



Reagents and conditions: *i*. 1) maleic anhydride, 2) $H_2NCH_2CH_2NMe_2$, EtOH, 85 °C; *ii*. EtBr, THF, 50 °C; *iii*. $HC{\equiv}CCH_2OH$, $SOCl_2$, Et_3N; *iv*. CuI, DBU, THF, 35 °C.

of polycyclic terpenoids. These terpenoids are isomers differing in the geometry of the hydrocarbon skeleton: *trans* fusion of the rings B and C in isosteviol **63** (Scheme 16) and *cis* fusion of the rings B and C in steviol **64** (Scheme 17). Isosteviol **63** was transformed to mono-quaternary (compounds **65**) and bis-quaternary (compounds **66**) ammonium derivatives[64,65] (see Scheme 16). Among the mono-quaternary salts, only compound **65c** exhibited a noticeable antimicrobial activity, exclusively against *S. aureus 209p* bacteria and *T. gypseum* and *C. Albicans* fungi.[64] However covalent binding of two molecules of the low-activity mono-quaternary ammonium salt **65a** through the polymethylene linker resulted in a dramatic increase in the bacteriostatic and fungistatic activities, with the maximum value in a series of the compounds under study being observed for the bis-quaternary ammonium salt **66d**.[65] The

Scheme 16



65: R = Me (**a**), Pr (**b**), Bn (**c**)
66: *n* = 1 (**a**), 5 (**b**), 6 (**c**), 8 (**d**)

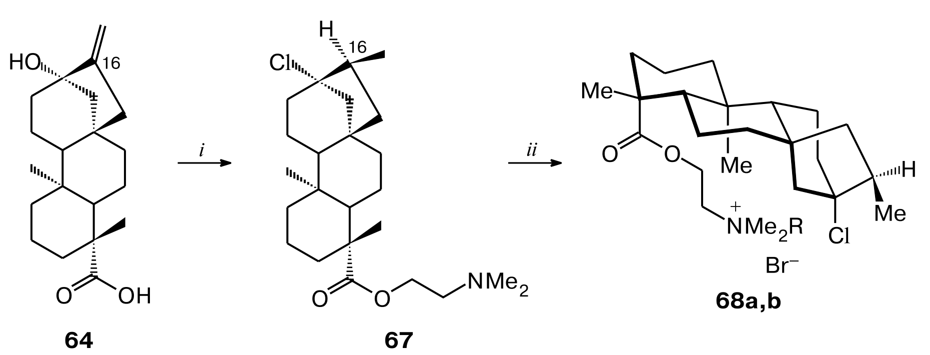
Reagents and conditions: *i*. 1) $SOCl_2$, 2) $HOCH_2CH_2NMe_2$, CCl_4; *ii*. $BrCH_2CH_2(CH_2)_nCH_2CH_2Br$, MeCN, 80 °C; *iii*. RBr, MeCN, 80 °C.

activity of salt **66d** against *S. aureus* and *C. albicans* was comparable with that of ciprofloxacin and clotrimazole, respectively.[65] Note that compound **66d** also possesses bactericidal activity, which is only two-fold less than that of ciprofloxacin.[65]

The isosteviol ammonium derivatives **65** and **66** also can inhibit human acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), the highest activities being observed for compound **65c** with the benzyl group at the nitrogen atom in a series of the mono-quaternary salts and compound **66d** with the dodecanediyl linker between the nitrogen atoms in a series of the bis-quaternary salts.[66]

To examine how the change in the hydrocarbon framework geometry influences the bioactivities of compounds **65**, the analogous derivatives of steviol **64** were synthesized[66] (Scheme 17). The hydroxyallylic system of steviol **64** undergoes readily the Wagner—Meerwein rearrangement; therefore, its double bond was preliminary

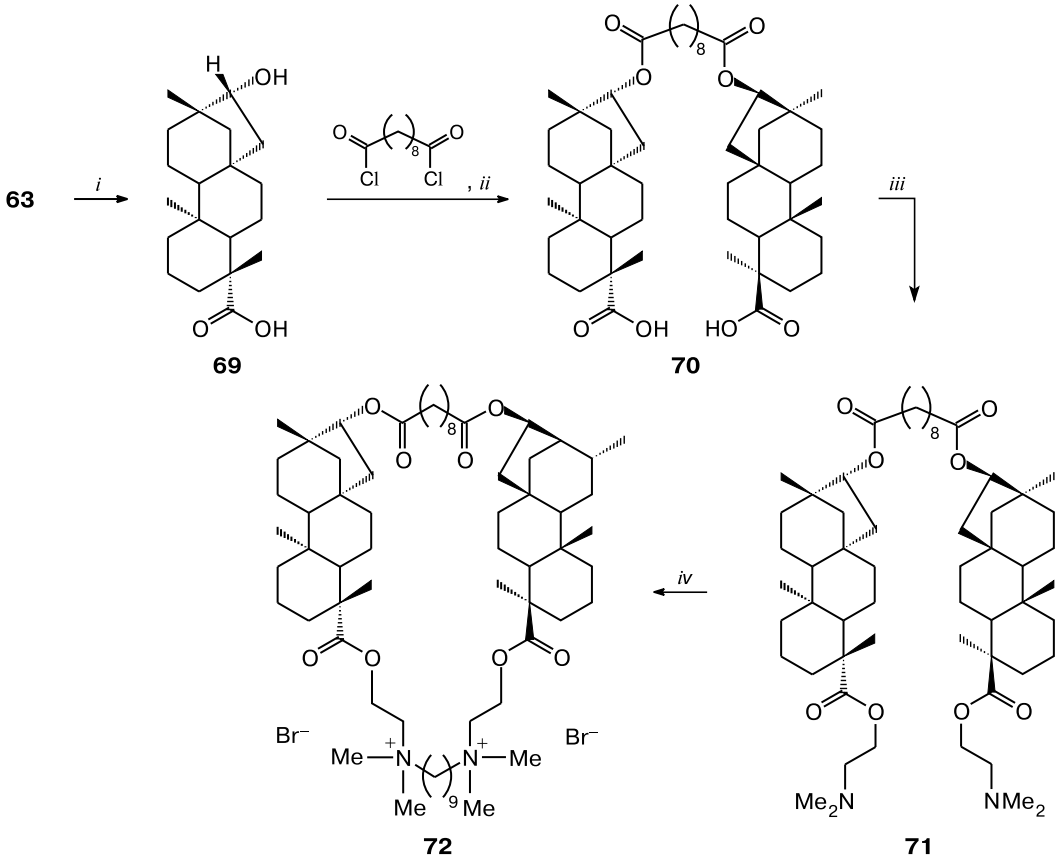
Scheme 17



68: R = Me (**a**), Bn (**b**)

Reagents and conditions: *i*. 1) Raney Ni, NH_2NH_2, H_2O, 80 °C, 2) $SOCl_2$, 3) $HOCH_2CH_2NMe_2$, CCl_4; *ii*. RBr, MeCN, 80 °C.

Scheme 18



Reagents and conditions: *i.* $NaBH_4$, MeOH; *ii.* DMAP, pyridine, CH_2Cl_2; *iii.* 1) $SOCl_2$, 2) $HOCH_2CH_2NMe_2$, CCl_4; *iv.* $Br(CH_2)_9Br$, MeCN, 80 °C.

reduced with diimide generated *in situ* by decomposition of hydrazine hydrate on Raney nickel.[66] The resulted 16(*S*)-dihydrosteviol was transformed into amine **67** whose quarternization afforded salts **68** (see Scheme 17).[66] The anticholinesterase activities of the salts were found to be slightly higher than those of the monoammonium isosteviol derivatives **65**.[66]

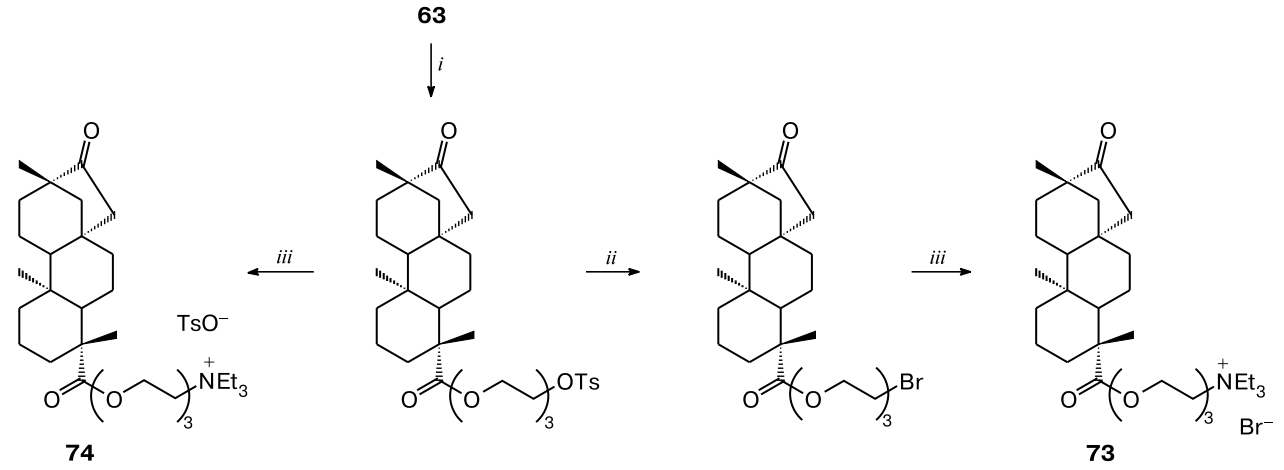
The same Ref. 66 reports on the synthesis of the first macrocycle containing the terpenoid groups and quarternized ammonium atoms (Scheme 18). The chemoselective and stereospecific reduction of the oxo group of isosteviol **63** with sodium borohydride afforded 16(*R*)-dihydroisosteviol **69** whose two molecules was then covalently bound to the diester linker by the reaction with decanedioic acid dichloride. The resulted diacid **70** was converted to diacyl dichloride, which, in turn, was transformed to bis(dimethylaminoethyl) ester **71** whose quaternization with 1,9-dibromononane yielded the macrocyclic compound **72**.

The results of the study of compound **72** for the anticholinesterase activity are of great interest. The macrocyclic compound **72** inhibits AChE as bis-quaternary ammonium isosteviol derivative **66d** with the dodecanediyl linker between the nitrogen atoms (IC_{50} is 2—5 μmol L^{-1}), *i.e.*, about 30-fold better than the isosteviol derivative **66c** with the dodecanediyl linker between the nitrogen atoms.[66] At the same time, the macrocyclic compound **72** inhibits BChE similarly to bis-quaternary ammonium isosteviol derivative **66c** (IC_{50} is 60—65 μmol L^{-1}), *i.e.*, 6-fold worse than the isosteviol derivative **66d**.[66] Thus, in a series of the compounds under study, the macrocyclic compound **72** exhibits the best selectivity in inhibition of AChE and BChE.

In the same Ref. 66, by the example of isosteviol **63**, the authors proposed for the first time a method of transformation of any hydrophobic terpenoid containing the carboxyl, oxo, aldehyde, or hydroxy group to the terpenoid derivative readily soluble in water. The method consists in introduction of the polyoxyethylene chain with the terminal triethylammonium group into the structure of the terpenoid (Scheme 19).

The thus synthesized amphiphilic isosteviol derivatives **73** and **74**, which differ in the nature of anion, are very soluble in water (up to 0.1 mol L^{-1}) and possess properties

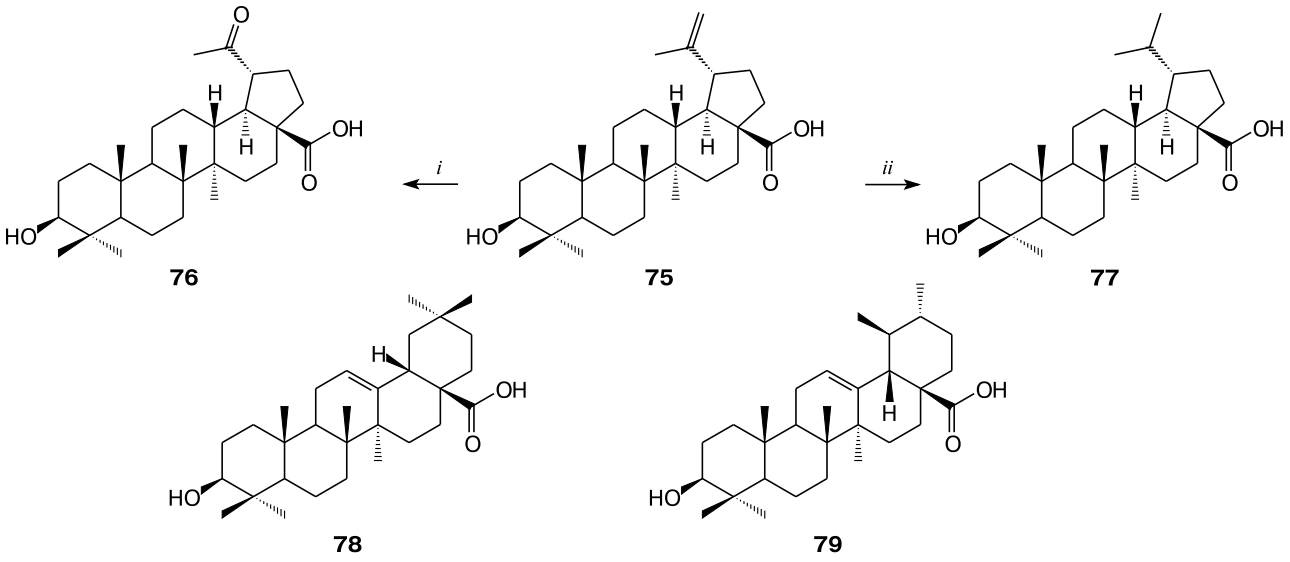
Scheme 19



Reagents and conditions: *i.* $Ts(OCH_2CH_2)_3OTs$, K_2CO_3, MeCN, 70 °C; *ii.* LiBr, acetone, 50 °C; *iii.* Et_3N, MeCN, 70 °C.

typical of surfactants.[67] Note that, by the example of amphiphiles **73** and **74**, the unique effect of the counter ion nature on self-organization of the surfactant with the nitrogen atom in water was found for the first time. Although the CMCs of amphiphiles **73** and **74** are close, their morphological characteristics differ drastically.[67] The ammonium isosteviol derivative **74** showed a classical behavior of surfactant, *i.e.*, the formation of spherical micelles with a hydrodynamic diameter of ≤10 nm. The ammonium derivative **73** displayed an essentially different mode of self-organization, namely, a spontaneous micelle—vesicle—micelle transition with increasing its concentration in water.[67] Moreover, it was established that amphiphile **73** readily incorporates into the lipid bilayer of synthetic liposomes and the vesicles (liposomes) that formed by itself in water form complexes with the model DNA (2661 base pairs), which penetrate into cells.[68] There are numerous papers dedicated to the DNA transfer into cells mediated by cationic lipids (see, for example, review[22]). The vital difference of the results obtained for the isosteviol ammonium derivative **73** (see Ref. 68), is that this compound is not a classical cationic lipid, but a water-soluble amphiphile having no hydrophobic polymethylene chain. Thus, the authors of Refs 66–68 demonstrated for the first time that the semisynthetic terpenoid molecule (just as steroid molecule) can be inserted direct-

Scheme 20



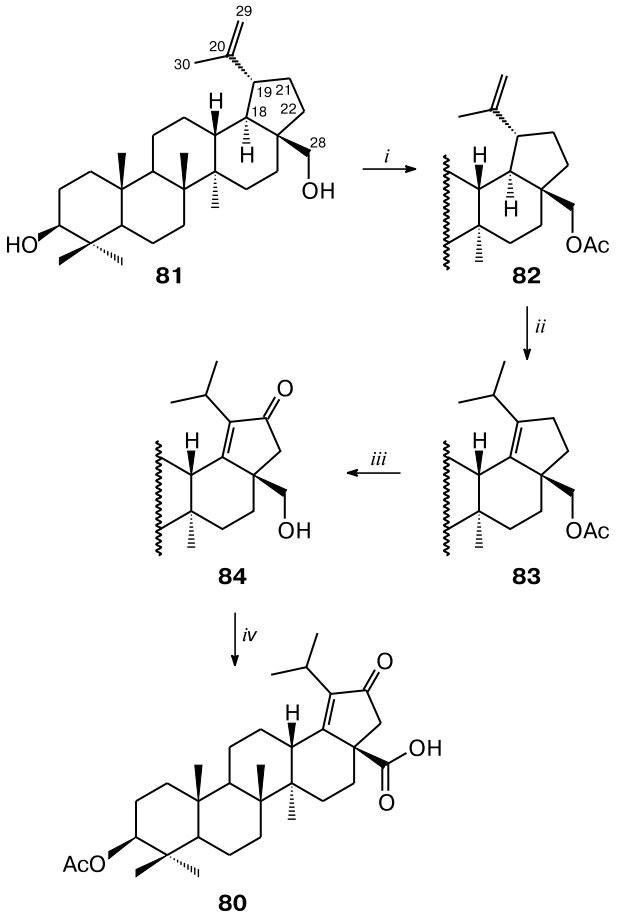
Reagents and conditions: *i.* 1) O_2, CH_2Cl_2, –80 °C, 2) Me_2S; *ii.* H_2, Pd/C, MeOH.

ly into cell. This fact is of fundamental importance to increase the efficiency of new therapeutic agents being designed from natural compounds.

Pentacyclic diterpenoids. In this group of natural terpenoids, a large series of the ammonium derivatives of triterpenoid acids possessing anticancer activity were synthesized.[69] As the starting compounds, betulinic (**75**), platanic (**76**), dihydrobetulinic (**77**), oleanolic (**78**), and ursolic (**79**) acids (Scheme 20), as well as 3β-acetoxy-21-oxolup-18-en-28-oic acid (**80**) were chosen. To prepare acid **80**, betulin **81** was subjected to acetylation. The acid-catalyzed isomerization of the C(20)=C(29) bond in acetate **82** gives compound **83**. Product **83** was then oxidized with chromium trioxide into hydroxy ketone **84** whose hydroxymethyl group was then oxidized to the carboxyl group to form acid **80** (Scheme 21).

Triterpenoid acids **75**—**80** were transformed to the corresponding 2-bromoethyl esters **85** by the reaction with 1,2-dibromoethane, from which the ammonium derivatives **86**—**88**[69] were obtained by the reaction with trimethylamine, triethylamine, and pyridine (Scheme 22). All compounds were studied for the *in vitro* cytotoxicity against human T-cell lymphoblastic leukemia. The maximum cytotoxicity (IC_{50} < 10 μmol L^{-1}) was observed for the triethylammonium derivatives **87b**,**d**,**f** and pyridinium derivatives **88b**,**d**.[69] Among them, the quaternary ammonium salts **87d**,**f** with the lupane or ursane triterpenoid framework, respectively, were the most efficient (IC_{50} < 5 μmol L^{-1}).[69]

Scheme 21



Reagents and conditions: *i*. Ac_2O, pyridine; *ii*. HBr, AcOH, Ac_2O, benzene; *iii*. 1) CrO_3, 2) MeONa, MeOH; *iv*. RuO_2, $NaIO_4$, CF_3COOH.

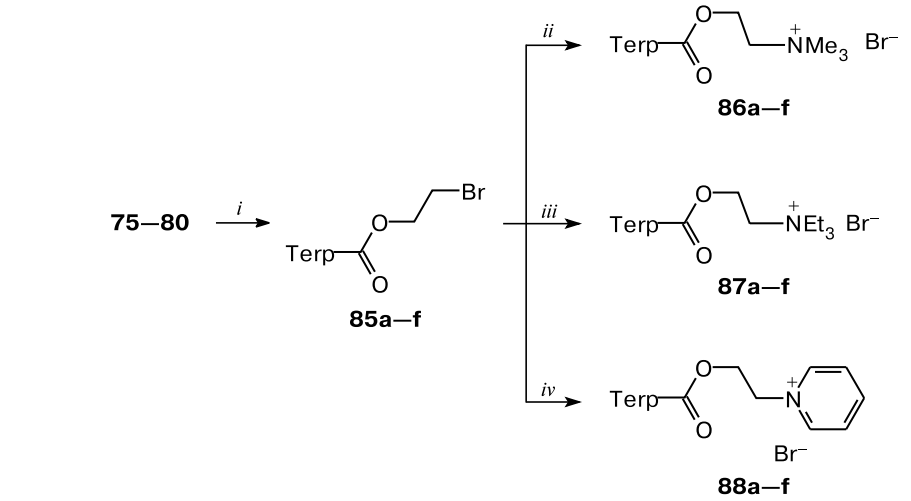
Polyprenoid compounds. In terms of bioactivity, polyprenols are important terpenoid representatives. During metabolism polyprenols transform into dolichol lipids and thereby favor restoration of the dolichol-phosphate cycle involved in the biosynthesis of glycoproteins and glycosaminoglycans, which is affected upon diabetes mellitus and hypertonia. Apparently, in order to enhance these properties, a one-pot method of functionalization of polyprenols from the mulberry leaves (called moraprenols) with the triethylammonium group was developed.[70] The method consists in quaternization of triethylamine in the presence of moraprenols **89** and phosphorus oxychloride to produce salts **90** (Scheme 23).

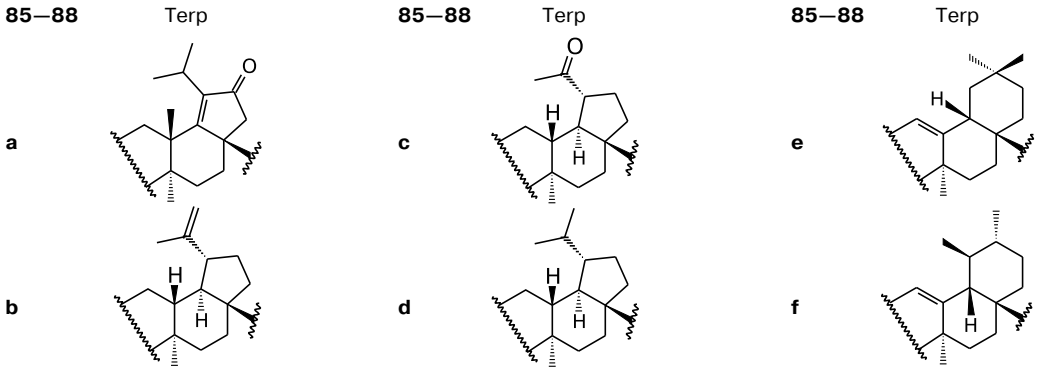
Probably, this method failed to be universal, because to prepare the triethylammonium, pyridinium, and imidazolinium derivatives of moraprenols **91**—**93**, the same authors used moraprenyl bromide **94** obtained by the reaction of moraprenols **89** with trimethylsilyl bromide.[71] Note that the *cis* configuration of the terminal isoprene group of the starting polyprenol reteins upon bromination. The bioactivities of cationic lipids **90**—**93** and their any applications have not been reported.

Taking all the aforesaid into consideration, one can conclude that functionalization of natural terpenoids with the ammonium groups first enhances the existing bioactivity, for example, anticancer activity of triterpenoid acids. Secondly, such functionalization offers terpenoids new properties, such as cholinotropic, antiviral, and antimicrobial activities, which were absent in these terpenoids; or transforms them into chiral ionic liquids whose practical potential for the application as chiral phase-transfer catalysts is obvious, but has not been studied yet.

In all cases, on going from the mono-quaternary ammonium derivatives of terpenoids to the bis-quaternary ones the bioactivity increases with the maximum activity in the series under study being observed for both the cationic lipids with a length of the polymethylene substituent at the nitrogen atom of about 10—12 methylene units and the dimeric cationic terpenoid surfactants with about the same length of the polymethylene linker between two quaternary nitrogen atoms. A specific success was achieved upon functionalization of the diterpenoid isosteviol with trioxyethylene chain having the terminal triethylammonium group. The resulted amphiphilic derivative is soluble

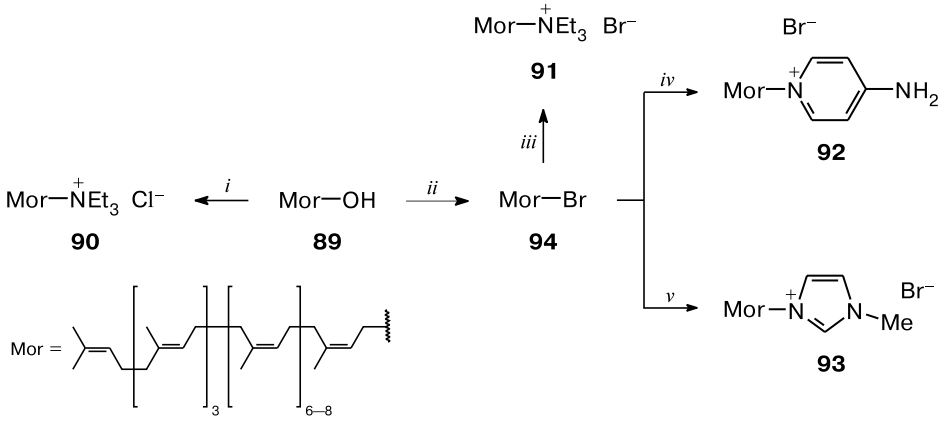
Scheme 22

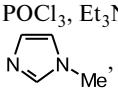




Reagents and conditions: *i.* $BrCH_2CH_2Br$, K_2CO_3, MeCN, DMF, 50 °C; *ii.* NMe_3, DMF; *iii.* NEt_3, DMF; *iv.* pyridine, DMF.

Scheme 23



Reagents and conditions: *i.* $POCl_3$, Et_3N, CH_2Cl_2, −60 °C; *ii.* Me_3SiBr, C_6H_{14}, −80 °C; *iii.* Et_3N, benzene, MeCN, 45 °C; *iv.* DMAP, benzene, MeCN, 60 °C; *v.*  , benzene, MeCN, 45 °C.

in water and forms vesicles (liposomes) therein, which bind DNA and penetrate into cells.

Thus, functionalization of natural and semisynthetic terpenoids by the ammonium groups is, undoubtedly, one of the promising trends in modern organic chemistry, chemistry of natural products, and medicinal chemistry.

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References

1. P. Thanei-Wyss, P. G. Waser, *Eur. J. Pharmacol.*, 1989, **172**, 165.
2. K. A. Anikienko, E. A. Bychikhin, V. K. Kurochkin, V. S. Reznik, V. D. Akamsin, I. V. Galyametdinova, *Dokl. Biochem. Bioph.* (*Engl.Transl.*), 2001, **376**, 39 [*Dokl. Akad. Nauk*, 2001, **376**, 818].
3. A. Conejo-García, L. Pisani, M. Del Carmen Núñez, M. Catto, O. Nicolotti, F. Leonetti, J. M. Campos, M. A. Gallo, A. Espinosa, A. Carotti, *J. Med. Chem.*, 2011, **54**, 2627.
4. D. P. Zlotos, *Mini-Rev. Med. Chem.,* 2005, **5**, 595.
5. N. F. Salakhutdinov, G. A. Tolstikov, *Mini-Rev. Med. Chem.*, 2010, **10**, 1248.
6. H. F. Oates, G. S. Stokes, in *Developments in Cardiovascular Medicine*, Eds A. Amery, R. Fagand, P. Lijnen, J. Staessen, Martinus Nijhoff Publ., Boston—London, 1982, **16**, p. 834.
7. M. Prat, D. Fernández, M. A. Buil, M. I. Crespo, G. Casals, M. Ferrer, L. Tort, J. Castro, J. M. Monleón, A. Gavaldà, M. Miralpeix, I. Ramos, T. Doménech, D. Vilella, F. Antón, J. M. Huerta, S. Espinosa, M. López, S. Sentellas, M. González, J. Albertí, V. Segarra, A. Cárdenas, J. Beleta, H. Ryder, *J. Med. Chem.*, 2009, **52**, 5076.
8. E. B. Walker, in *Handbook of Topical Antimicrobials. Industrial Applications in Consumer Products and Pharmaceuticals*, Ed. D. S. Paulson, New York—Basel, Marcel Dekker, Inc., 2003, p. 99.
9. J. S. Yang, D. Song, B. Lee, W. J. Ko, S.-K. Park, M. Won, K. Lee, H. M. Kim, G. Han, *Eur. J. Med. Chem.*, 2011, **46**, 2861.
10. D. Song, J. S. Yang, C. Oh, S. Cui, B.-K. Kim, M. Won, J.-I. Lee, H. M. Kim, G. Han, *Eur. J. Med. Chem.*, 2013, **69**, 670.
11. M. Tischer, L. Sologub, G. Pradel, U. Holzgrabe, *Bioorg. Med. Chem.*, 2010, **18**, 2998.
12. T. Ooi, K. Maruoka, *Angew. Chem., Int. Ed.*, 2007, **46**, 4222.
13. R. N. Das, K. Roy, *Mol. Divers.*, 2013, **17**, 151.
14. J. Zhang, D. Shi, X. Gong, F. Zhu, M. Du, *J. Surfactants Deterg.*, 2013, **16**, 515.
15. F. M. Menger, J. S. Keiper, *Angew. Chem., Int. Ed.*, 2000, **39**, 1909.
16. *Surfactants: A Practical Handbook*, Ed. K. R. Lange, Hanser Publ. and Hanser Gardner Publ., Münich—Cincinnati, 1999, 237 pp.
17. L. Zakharova, E. Zhiltsova, A. Mirgorodskaya, A. Konovalov, in *From Molecules to Functional Architecture. Supromolecular Interactions*, Ed. V. I. Rybachenko, East Publ. House, Donetsk, 2012, p. 415.
18. Y. You, X. Wu, J. Zhao, Y. Ye, W. Zou, *Colloids Surf., A*, 2011, **384**, 164.
19. Z. Huang, H. Zhong, S. Wang, L. Xia, G. Zhao, G. Liu, *Miner. Eng.*, 2014, **56**, 145.
20. E. Obłak, A. Piecuch, A. Krasowska, J. Łuczyński, *Microbiol. Res.*, 2013, **168**, 630.
21. M. S. Sheikh, A. J. Khanam, R.-U. H. Matto, Kabir-Ud-Din, *J. Surfactacts Deterg.*, 2013, **16**, 503.
22. S. Bhattacharya, A. Bajaj, *Chem. Commun.*, 2009, 4632.
23. I. Yu. Chukicheva, A. V. Kuchin, *Ross. Khim. Zh.,* 2004, **48**, No. 3, 21 (in Russian).
24. T. G. Tolstikova, I. V. Sorokina, G. A. Tolstikov, A. G. Tolstikov, O. B. Flekhter, *Russ. J. Bioorg. Chem.* (*Engl. Transl.*), 2006, **32**, 261 [*Bioorg. Khim.,* 2006, **32**, 291].
25. K. P. Volcho, N. F. Salakhutdinov, *Mini-Rev. Org. Chem.*, 2008, **5**, 345.
26. E. V. Buravlev, I. Y. Chukicheva, K. Y. Suponitsky, Y. B. Vikharev, V. V. Grishko, A. V. Kutchin, *Lett. Org. Chem.*, 2011, **8**, 301.
27. D. N. Sokolov, O. A. Luzina, N. F. Salakhutdinov, *Russ. Chem. Rev.*, 2012, **81**, 747.
28. C. Lohoelter, M. Weckbecker, S. R. Waldvogel, *Eur. J. Org. Chem.*, 2013, 5539.
29. Z. Ferjancic, R. Matovic, Z. Cekovic, Y. Jiang, J. P. Snyder, V. Trajkovic, R. N. Saicic, *Tetrahedron*, 2006, **62**, 8503.
30. O. B. Flekhter, N. I. Medvedeva, G. A. Tolstikov, O. V. Savinova, E. I. Boreko, F. M. Dolgushin, *Russ. J. Bioorg. Chem.* (*Engl. Transl.*), 2009, **35**, 118 [*Bioorg. Khim.*, 2009, **35**, 129].
31. V. V. Grishko, I. A. Tolmacheva, N. V. Galaiko, A. V. Pereslavceva, L. V. Anikina, L. V. Volkova, B. A. Bachmetyev, P. A. Slepukhin, *Eur. J. Med. Chem.*, 2013, **68**, 203.
32. O. B. Flekhter, N. I. Medvedeva, O. S. Kukovinets, L. V. Spirikhin, E. G. Galkin, F. Z. Galin, D. G. Golovanov, N. I. Pavlova, O. V. Savinova, E. I. Boreko, G. A. Tolstikov, *Russ. J. Bioorg. Chem.* (*Engl. Transl.*), 2007, **33**, 584 [*Bioorg. Khim.*, 2007, **33**, 629].
33. O. B. Kazakova, E. V. Tretyakova, O. S. Kukovinets, A. R. Abdrakhmanova, N. N. Kabalnova, D. V. Kazakov, G. A. Tolstikov, A. T. Gubaidullin, *Tetrahedron Lett.*, 2010, **51**, 1832.
34. I. E. Smirnova, O. B. Kazakova, E. V. Tretyakova, G. A. Tolstikov, L. V. Spirikhin, *Russ. J. Org. Chem.* (*Engl. Transl.*), 2011, **47**, 1576 [*Zh. Org. Khim.*, 2011, **47**, 1547].
35. I. E. Smirnova, D. T. Tkhu, O. B. Kazakova, G. A. Tolstikov, A. N. Lobov, K. Yu. Saponitskii, *Chem. Nat. Compd.* (*Engl. Transl.*), 2012, **48**, 816 [*Khim. Prir. Soedin.*, 2012, **48**, 727].
36. N. V. Galaiko, A. V. Nazarov, I. A. Tolmacheva, P. A. Slepukhin, Yu. B. Vikharev, O. A. Maiorova, V. V. Grishko, *Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2014, **50**, 65 [*Khim. Geterotsikl. Soedin.*, 2014, 72].
37. S. V. Larionov, A. V. Tkachev, *Ross. Khim. Zh.*, 2004, **48**, No. 4, 154 (in Russian).
38. R. N. Khaybullin, I. Yu. Strobykina, A. B. Dobrynin, A. T. Gubaydullin, R. V. Chestnova, V. M. Babaev, V. E. Kataev, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 6909.
39. O. V. Andreeva, I. Yu. Strobykina, O. N. Kataeva, O. B. Dobrynin, V. M. Babaev, I. Kh. Rizvanov, D. R. Islamov, V. E. Kataev, *Macroheterocycles*, 2013, **6**, 315.
40. D. Nageshwar, D. M. Rao, P. V. R. Acharyulu, *Synth. Commun.*, 2009, **39**, 3357.

41. A. I. Lopushanskii, A. K. Gorban´, V. V. Udovitskaya, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* (*Engl. Transl.*), 1963, **12**, 1046 [*Izv. Akad. Nauk SSSR, Ser. Khim.*, 1963, 1141].
42. J. Pernak, J. Feder-Kubis, *Chem. Eur. J.,* 2005, **11**, 4441.
43. J. Ding, V. Desikan, X. Han, T. L. Xiao, R. Ding, W. S. Jenks, D. W. Armstrong, *Org. Lett.*, 2005, **7**, 335.
44. J. Pernak, J. Feder-Kubis, A. Cieniecka-Roslonkiewicz, C. Fischmeister, S. T. Griffind, R. D. Rogers, *New J. Chem.*, 2007, **31**, 879.
45. J. Feder-Kubis, M. Kubicki, J. Pernak, *Tetraredron: Asymmetry*, 2010, **21**, 2709.
46. J. Pernak, J. Feder-Kubis, *Tetraredron: Asymmetry*, 2006, **17**, 1728.
47. J. Feder-Kubis, K. Tomczuk, *Tetrahedron*, 2013, **69**, 4190.
48. A. S. Sokolova, O. I. Yarovaya, A. V. Shernyukov, M. A. Pokrovsky, A. G. Pokrovsky, V. A. Lavrinenko, V. V. Zarubaev, T. S. Tretiak, P. M. Anfimov, O. I. Kiselev, A. B. Beklemishev, N. F. Salakhutdinov, *Bioorg. Med. Chem.*, 2013, **21**, 6690.
49. Yu. V. Kharitonov, E. E. Shults, M. M. Shakirov, G. A. Tolstikov, *Dokl. Chem.* (*Engl. Transl.*), 2004, **395**, 43 [*Dokl. Akad. Nauk*, 2004, **395**, 199].
50. Yu. V. Kharitonov, E. E. Shults, M. M. Shakirov, G. A. Tolstikov, *Russ. J. Org. Chem.* (*Engl.Transl.*), 2005, **41**, 1145 [*Zh. Org. Khim.*, 2005, **41**, 1167].
51. W. Sandermann, *Naturharze*, *Terperntinöl*, *Tallöl*, Springer Verlag, Berlin, 1960, 484 S.
52. G. A. Tolstikov, T. G. Tolstikova, E. E. Shults, S. E. Tolstikov, M. V. Khvostov, *Smolyanye kisloty khvoinykh Rossii. Khimiya, farmakologiya* [*Resin Acids of Russian Conifers. Chemistry and Pharmacology*]. Akad. izd-vo "Geo", Novosibirsk, 2011, 395 pp. (in Russian).
53. X. Rao, in *Rosin-based Chemicals and Polymers*, Ed. J. Zhang, Smithers Rapra Technol., Shrewsbury, 2012, p. 129.
54. B. A. Radbil´, S. R. Kushnir, A. B. Radbil´, E. N. Schmidt, V. F. Smirnov, N. B. Mel´nikova, *Russ. J. Appl. Chem.* (*Engl. Transl.*), 2008, **81**, 874 [*Zh. Prikl. Khim.*, 2008, **81**, 837].
55. W. Jia, X. Rao, Z. Song, S. Shang, *J. Surfact. Deterg.*, 2009, **12**, 261.
56. H.-F. Wang, Z.-G. Jiang, Y.-L. Ma, S.-Y. Han, *Xiandai Huagong* [*Mod. Chem. Ind.*], 2012, **32**, 79.
57. S. Zhao, H. Wang, Y. Pan, M. He, Z. Zhao, *J. Chromatogr. A*, 2007, **1145**, 246.
58. T. Liang, Y. Zhang, S. Li, T. T. H. Nguyen, *BioResources*, 2013, **8**, 735.
59. H. Wang, L. Tang, Y. Pan, M. Liang, *Chem. J. Internet*, 2004, **6**, 068056ne.
60. Y.-M. Pan, L.-D. Tang, H.-S. Wang, G.-F. Su, M. Liang, Y. Zhang, *Chin. J. Org. Chem.*, 2006, **26**, 349.
61. Z. Chen, S. Li, B. Tian, T. Liang, Y. Jin, *Env. Eng. Sci.*, 2012, **29**, 606.
62. Y. Chen, P. A. Wilbon, Y. P. Chen, J. Zhou, M. Nagarkatti, C. Wang, F. Chu, A. W. Decho, C. Tang, *RSC Adv.,* 2012, **2**, 10275.
63. J. Wang, Y. P. Chen, K. Yao, P. A. Wilbon, W. Zhang, L. Ren, J. Zhou, M. Nagarkatti, C. Wang, F. Chu, X. He, A. W. Decho, C. Tang, *Chem. Commun.*, 2012, **48**, 916.
64. M. G. Korochkina, R. R. Sharipova, I. Yu. Strobykina, A. D. Lantsova, A. D. Voloshina, N. V. Kulik, V. V. Zobov, V. E. Kataev, V. F. Mironov, *Pharm. Chem. J.* (*Engl. Transl.*), 2011, **44**, 597 [*Khim.-Farm. Zh.*, 2010, **44**, No. 11, 21].
65. M. G. Korochkina, V. M. Babaev, I. Yu. Strobykina, A. D. Voloshina, N. V. Kulik, V. E. Kataev, *Chem. Nat. Compd.* (*Engl. Transl.*), 2012, **47**, 914 [*Khim. Prir. Soedin.*, 2011, **47**, 802].
66. M. G. Korochkina, A. D. Nikitashina, R. N. Khaibullin, K. A. Petrov, I. Yu. Strobykina, V. V. Zobov, V. E. Kataev, *Med. Chem. Commun.*, 2012, **3**, 1449.
67. M. A. Voronin, D. R. Gabdrakhmanov, R. N. Khaibullin, I. Yu. Strobykina, V. E. Kataev, B. Z. Idiyatullin, D. A. Faizullin, Y. F. Zuev, L. Ya. Zakharova, A. I. Konovalov, *J. Colloid Interface Sci.*, 2013, **405**, 125.
68. D. R. Gabdrakhmanov, M. A. Voronin, L. Ya. Zakharova, A. I. Konovalov, R. N. Khaybullin, I. Yu. Strobykina, V. E. Kataev, D. A. Faizullin, N. E. Gogoleva, T. A. Konnova, V. V. Salnikov, Y. F. Zuev, *Phys. Chem. Chem. Phys.*, 2013, **15**, 16725.
69. D. Biedermann, B. Eignerova, M. Hajduch, J. Sarek, *Synthesis*, 2010, 3839.
70. O. V. Sizova, N. S. Utkina, N. A. Kalinchuk, L. L. Danilov, S. D. Maltsev, *Acta Biochim. Pol.*, 2007, **54**, 869.
71. N. S. Utkina, L. L. Danilov, O. V. Sizova, N. A. Kalinchuk, S. D. Mal´tsev, *Russ. Chem. Bull.* (*Int. Ed.*), 2010, **59**, 1459 [*Izv. Akad. Nauk, Ser. Khim.*, 2010, 1426].

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