Diterpenoids of Eunicellane Series

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Abstract

Sources, methods of isolation, structure and properties of diterpenoids of eunicellane series produced by sea organisms are considered. The schemes of complete synthesis of the urocanates of diterpenoids of 4,7-oxaeunicellane type possessing unique cytotoxic effect are discussed. The known routes of establishing the interconnections between structure and activity in the sarcodictyine series are presented.

Contents

1. INTRODUCTION

Terpenoids belong to the natural metabolites that permanently replenish the arsenal of medical preparations. Turning to the last decades of the past century we see that the list of remedies introduced into medical practice included unique antimalarial preparations based on sesquiterpenoid artemisinine, highly efficient carcinostatics obtained by the transformation of diterpenoid taxol, derivatives of terpenoid forskolin exhibiting activity against glaucoma, antiviral agents based on triterpenoid glycoside of glycyrrhizic acid.

A rich source of terpenoids possessing diverse and specific biological action is sea organisms. In middle 90s of the past century, a new diterpenoid eleutherobin was discovered among the metabolites of eunicellane type isolated from soft corals. This compound possesses the mechanism of cytotoxic action similar to that exhibited by taxol. After that, similar properties were discovered in sarcodictyines allied to eleutherobin; together with valdivones having a similar diterpenoid centre, these compounds formed a new class of eleuthesides. Unfortunately, the concentrations of these metabolites in natural objects are negligibly small (not more than 0.02 % of the dry mass of sea organisms), so it seems a difficult problem to organize economically acceptable production. Meanwhile, the potential value of eleuthesides for chemotherapy of cancer cannot but attract increasing attention. This circumstance

stimulates the efforts aimed at the search of alternative ways to solve the problem of eleutheside availability. Synthesis remains one of the most important ways to solve this problem.

2. STRUCTURE AND NATURAL SOURCES

2.1. Eunicelline and its analogues

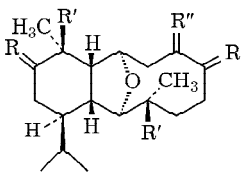
Eunicelline **1**, the first representative of the new group of sea terpenoids, was isolated in 1968 in the crystal state from gorgon *Eunicella stricta* [1]. Its structure was established with the help of physicochemical methods, as well the structural functional modification. According to those studies, eunicelline is a tricyclic terpenoid in which the menthane cycle is annelated with a ten-membered ring containing the oxygen bridge C^2–C^9. Some reactions related to the structure of eunicelline were investigated, for example, the presence of the $>C=CH_2$ group was confirmed by ozonolysis which was accompanied by the formation of noreunicellane **3**. Catalytic hydrogenation of **1** above $Pd/BaSO_4$ leads to the formation of dihydroeunicelline **4**.

Reduction with $LiAlH_4$ or alkaline hydrolysis of eunicelline **1** gives tetrole **5**; its acetylation results in the formation of diacetate **6**. Its oxidation with chromium trioxide CrO_3 in pyridine leads to the formation of diketone **7**. It was concluded on the basis of these results that among the four acetate groups of eunicelline **1** two groups are secondary and two are tertiary. According to the spectral characteristics, the product of the periodate oxidation of tetrole **5** contains a methyl ketone fragment and the aldehyde group, which points to the presence of the sequence $-CH(OAc)-C(CH_3)(OAc)-$ in eunicelline (Scheme 1).

Cis-coupling of the cycles was proven by means of the X-ray structural analysis of crystal dibromide **2**.

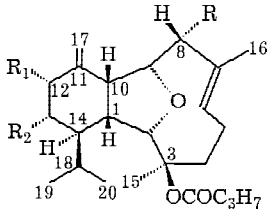
Later on [2–5], diterpenoid compounds litophynines A–J (**8–17**) (Scheme 2) were isolated from the extracts of marine invertebrates *Litophyton* sp. These compounds possess the eunicelline framework. All of them exhibited the juvenile activity towards silkworm *Bombyx mori* L. Litophynine A **8** was extracted in the form of colourless oil, while litophynine B **9** in the form of colourless needle-shaped crystals.

It was discovered that litophenynes I **16** and J **17** possess molluscicide and repellent activity, which causes a wide-scale destruction of the colonies of hexacorallians in the places inhabited by *Litophyton* sp. [6]. Other compounds of the eunicelline series were isolated from the methanol extract of *Calicogorgia* sp.: ophyrine

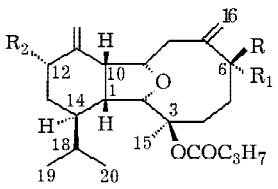


	R	R′	R″
1	(H)OAc	OAc	CH_2
2	(H)OAc	OAc	(Br)CH_2Br
3	(H)OAc	OAc	O
4	(H)OAc	OAc	(H)CH_2
5	(H)OH	OH	CH_2
6	(H)OAc	OH	CH_2
7	O	OH	CH_2

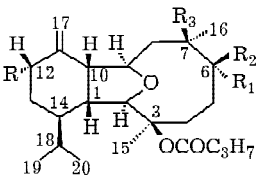
Scheme 1.



8 R = H, R_1 = H, R_2 = H
9 R = $OCOC_3H_7$, R_1 = H, R_2 = H
10 R = H, R_1 = OH, R_2 = H
11 R = H, R_1 = OAc, R_2 = OAc

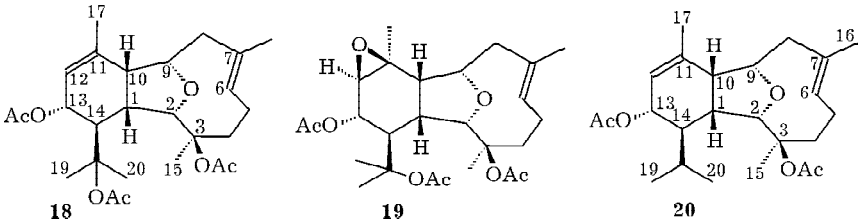


13 R = OH, R_1 = H, R_2 = H
14 R, R_1 = O, R_2 = H
15 R = OH, R_1 = H, R_2 = OH



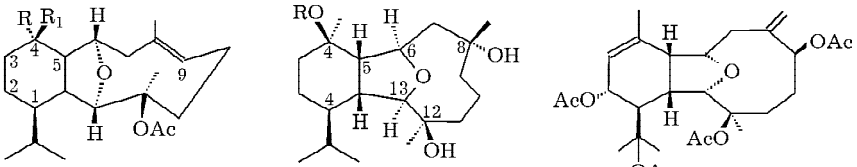
12 R = H, R_1 = H, R_2 = OH, R_3 = OH
16 R = OH, R_1 = H, R_2 = OH, R_3 = OH
17 R = OH, R_1 = O, R_2 = O, R_3 = CH_3

Scheme 2.



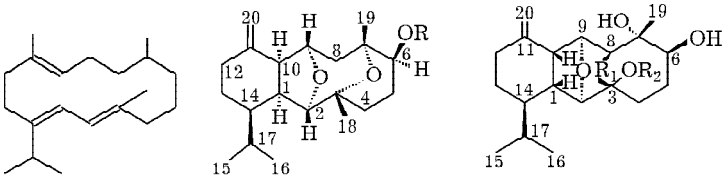
18 **19** **20**

Scheme 3.



21 R = CH_3, R_1 = OAc
22 R = R_1 = CH_2
23 R = H
24 R = Ac
25

Scheme 4.



26
27 R = H
28 R = Ac
29 R_1 = OH, R_2 = Ac
30 R_1 = OH, R_2 = H
31 R_1 = H, R_2 = Ac
32 R_1 = H, R_2 = H

Scheme 5.

18, calycophyrine A **19** and B **20**, which are C^3-acetates [7, 8] (Scheme 3).

A large number of new metabolites was extracted from the class of coelenterates: Gorgonaceae and Alcyonaceae. Two diterpenoids congener to eunicelline **1** were discovered in alcyonarians *Cladiella* sp.; they contain 14-membered cembranoid centre (acetoxycladielline **21** and cladielline **22**) and some other compounds containing the cladielline framework [9, 10, 12] (Scheme 4).

The diversity of di- and triterpenoids occurring in marine organisms is enormous. It was discovered that alcyonarians of *Lobophytum* genus contain isocembrene **26** and three other diterpenoids – cladielline **22**, ophyrine **18** and eunicelline **1**. Astrogorgine **25** inhibiting cell division [8, 11] was extracted from gorgonium coral *Astrogorgia* sp. The derivatives of cladielline **23**, **24** are produced by coral *Briareum steckiid.*

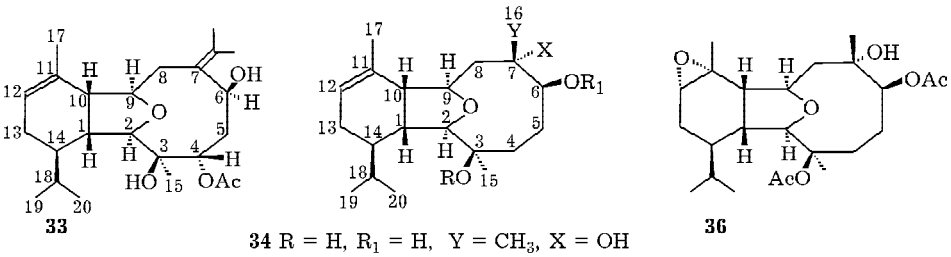
The presence of the second epoxide bridge is a characteristic feature distinguishing two other isocembrene derivatives of sclerophytine A **27** and B **28** extracted from the marine alcyonarian *Sclerophytum capitalis.* Sclerophytine A exhibited cytotoxic activity against L 1210 cells in the concentration of 0.001 mg/ml [13].

Further investigation of coral *Sclerophytum capitalis* allows one to extract other four diterpens – sclerophytines C–F (**29–32**) [14] (Scheme 5).

Another cladielline diterpenoid alcyonine **33** possessing a clearly exhibited cytotoxic activity was discovered in alcyonarian *Sinularia flexibilis* [15] (Scheme 6).

Coral *Cladiella* sp., one of the sorts of alcyonarians collected at Okinawa, produces diterpenoid with eunicelline centre **34**, as well as compounds **35–37** [16–18].

A characteristic structural fragment of all the eunicellanes considered is a menthane cycle annelated with a ten-membered ring containing 2,9-oxygen bridge.



33 **36**

34 R = H, R_1 = H, Y = CH_3, X = OH
35 R = Ac, R_1 = H, Y = CH_3, X = OH
37 R = H, R_1 = Ac, Y = X = CH_2

Scheme 6.

*2.2. Eleutesides**

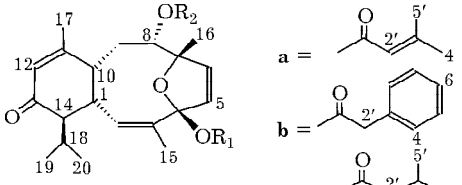
Historically, the most distinct representative of diterpenoids of the eunicellane type eleutherobin which gave the name to the new class of marine metabolites, was isolated in middle 90s of the past century after the discovery and identification of related valdivons and sarcodictyines.

The structure of these compounds has undeniable similarity with the structure of eunicelline **1** and differs only by the position of the oxygen bridge, so the tricyclic carbon framework of the new class of terpenoids was called the tricyclic centre of 4,7-oxaeunicellane type.

Valdivons. One of the first representatives of eleutesides extracted in 1968 from corals of the *Alcionium valdivae* genus growing near the coast of south Africa is valdivons. Five diterpenoid ethers were discovered in these corals: valdivons A **38** and B **39,** methoxyketals **40** and **41**, and dihydrovaldivon A **42**. Valdivons A **38** and B **39** possess pronounced anti-inflammatory activity; in addition, they inhibit the growth of bacteria and fungi (Scheme 7) [19].

Methylketals **40**, **41** and dihydrovaldivon A **42** that were likely to be formed during extraction were extracted as minor products.

Sarcodictyines. Investigation of the Mediterranean coral *Sarcodictyon roseum* has lead to the discovery and isolation of sarcodictyines A **43** and B **44** that are similar in structure to

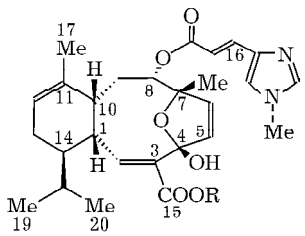


38 R_1 = H, R_2 = **a**
39 R_1 = H, R_2 = **b**
40 R_1 = Me, R_2 = **a**
41 R_1 = Me, R_2 = **b**
42 R_1 = H, R_2 = **c**

Scheme 7.

valdivons. The isolated compounds are esters of diterpene alcohols with N-methylimidazolylpropanoic (methylurocamic) acid (Scheme 8) [21, 22].

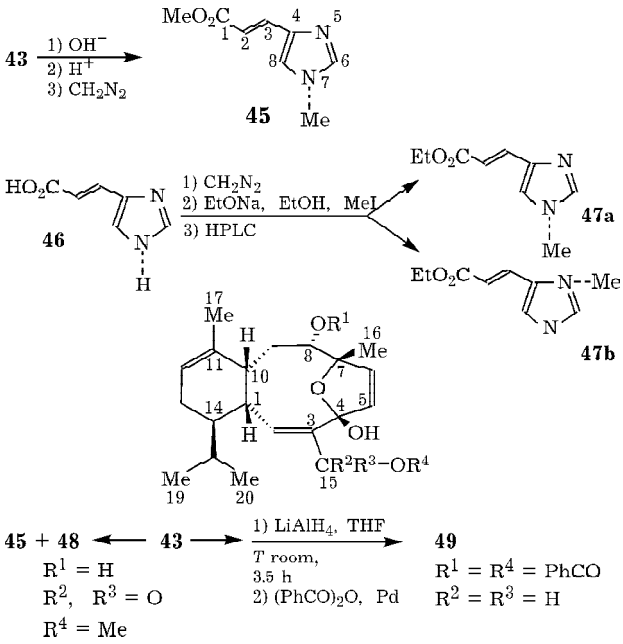
While establishing the structure of sacrodictyines, some chemical properties of these compounds were investigated. For instance, as a result of alkaline hydrolysis of sarcodictyine A **43** followed by treatment with diazomethane, only one carboxylic constituent of the molecule was successfully isolated: methyl ester of N-methylurocanic acid **45**. In these transformations, the diterpene component remained undisturbed. On the other hand, interesterification of **43** under the action of MeONa/MeOH leads to the formation of the methoxy derivative **48** and methylurocanate **45**. The structure



43 R = Me: sarcodictyine A
44 R = Et: sarcodictyine B

Scheme 8.

*There are two terms: eleuthosides and eleuthesides. In this paper we use the term eleuthesides [38, 39] to designate the representatives of eleutherobine class. Eleuthosides A, B, C are not only the compounds congener to eleutherobine [24] but also glycosides of condensed aromatic systems [20].

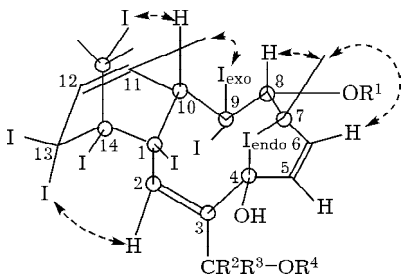


Scheme 9.

of **45** was confirmed by counter-synthesis of methyl substituted urocanate **47** from the acid **46** (Scheme 9).

The position of methyl group in ester **45** was established on the basis of the results of NOE experiment: suppression of δ-proton is recorded in C^3H, MeN, C^8H and C^6H.

Important data on the structure of the diterpene residue were obtained by transforming compounds **43** into dibenzoate **49**. The structure of **49** was established in course of NOE experiments. The interacting protons are indicated in the scheme below:



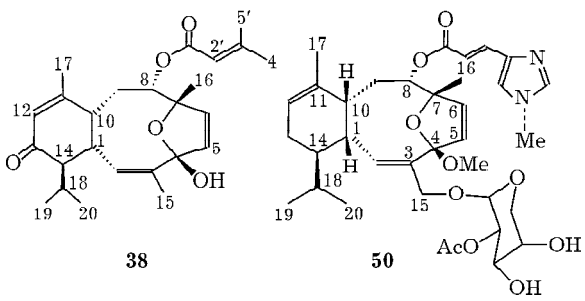
The structure of sarcodictyine B was proved in a similar manner.

In spite of the structural similarity between sarcodictyines and eunicelline **1** (which is likely to be an evidence of their biogenetic link with cembranoids), their characteristic distinguishing feature similar to that of eleutesides in general is not only the position of the oxygen bridge but also the acetale nature of the dihydrofuran fragment and the conjugated system of Michaelis acceptor, which together determine the features of the chemical properties of sarcodicyines.

Eleutherobine. Eleutherobine **50** was isolated in 1994 by means of column chromatography in the form of amorphous mass from the extract of alcyonarians *Eleutherobia* sp. [23] (Scheme 10). Another source of eleutherobine **50** was also alcyonarian *Erythropodium caribaeorum* discovered recently; it is rather widespread in the Caribbean sea [25].

The IR spectroscopic data provide evidence of the presence of one methoxyketal and two ester groups one of which (acetate, as it was established afterwards) belongs to the glycoside fragment of pentafuranose. The UV and NMR spectroscopic data point to the existence of an ester bond with N-methylurocanic acid in eleutherbine. Thorough ^{13}C NMR experiments, in the course of which the mutual positions of all the carbon atoms and protons bound with them were determined, showed that the presence of menthane fragment in *cis*-annelation with the ten-membered cycle and identical configurations of all the asymmetric centres of the nucleus are characteristic of the eleuthesides of sarcodictyine **43**, eleutherbine **50** and valdivone **38** [24].

A thorough investigation of eleutheside composition of natural sources and the processes of interacetylation, hydrolysis and some other transformations allowed researchers to propose a hypothetic scheme of the biogenetic connection within the entire variety of the derivatives of eleutherobine metabolizing



Scheme 10.

on the basis of geranylgeranylpyrophosphate. Relying on the biogenetic scheme, one may assume that urocanic acid gets added to the diterpene fragment at the stage of nucleus formation before C^{15} glycosylation. It was established that many compounds extracted from *Erythropodium caribaeorum* with methanol contain the methylketale group at C^4 and are artefacts [25].

3. INTERCONNECTION BETWEEN STRUCTURE AND ACTIVITY

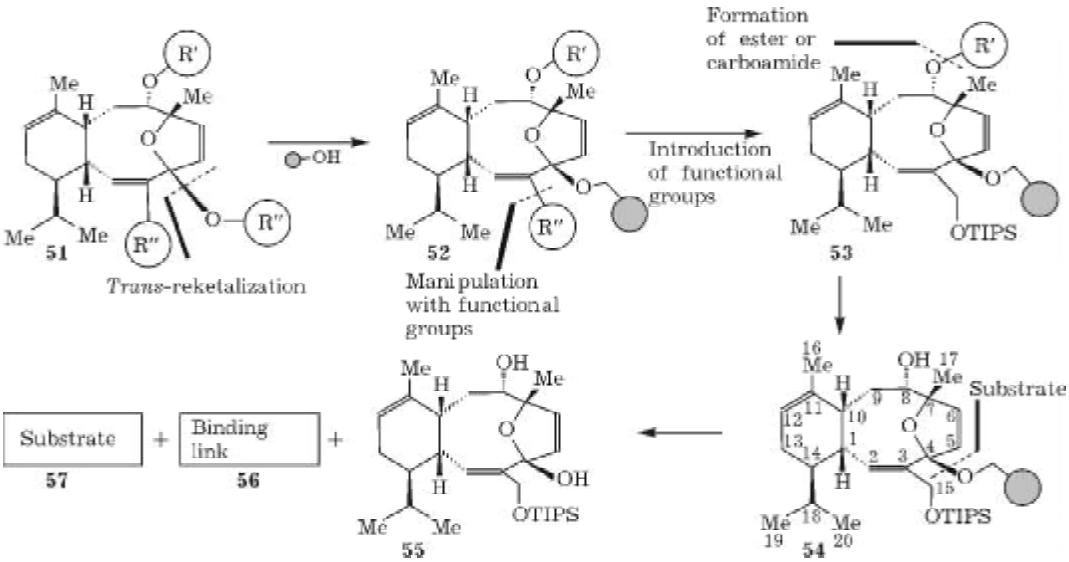
Biotesting of eleutherobine **50** *in vivo* showed the cytotoxic activity similar in the mechanism of action to that of taxol, at a level of 10–15 μM (IC_{50}) against various models of breast, kidney, ovary, lung tumour cells [23, 26, 29]. Similar properties were later revealed for epotylon [27, 30–32] and discodermolid [28].

After the realization of complete synthesis of eleutherobin **50** and sarcodictyine A **43** and B **44** (these schemes will be considered below), a series of sarcodictyine analogues was obtained using the solid-phase strategy, that is, by fixing the compound to be modified on a solid substrate [33–35]. Three important centres were determined for modification: C^3, C^4 and C^8, and were taken as the basis for the library. According to the retrosynthesis scheme, the synthesis fo the target analogue 51 is possible by means of reketalization of adduct **52**, which is obtained from **53** by introducing the necessary substituents at position C^3 (Scheme 11).

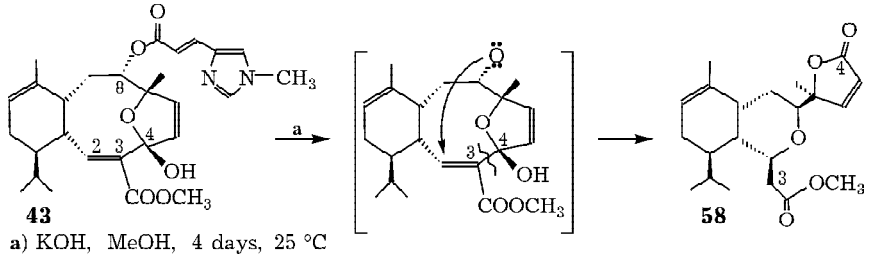
The structure of **53** implies esterification to transform adduct **54** into carbamate; in turn, this adduct may be obtained by cross-linking the basic intermediate **55** with substrate **57** through a connecting link **56**. Sarcodictyine analogues synthesized according to this retrosynthesis scheme were examined for the ability to decelerate polymerisation of tubulin. The cytotoxic activity of a number of synthetic analogues of sarcodictyines turned out to be higher than that of natural compounds **43** and **44**; for some new compounds, this activity was exhibited even against taxol resistant cancer cells.

At the same time, the efficiency of tubule polymerisation under the action of some analogues turned out to be lower than the general result of the cytotoxic activity. These observations suggest that a parallel mechanism of the biological action of these compounds according to the type of deoxyribonucleic acid alkylation is possible.

The importance of the side chain at C^8 became evident after screening of a series of C^8-modifying agents. For instance, replacement of the urocanic acid residue by the acetyl group caused a complete loss of the sytotoxic activity, while the introduction of the residue of phenylacrylic acid at C^8 resulted in the insignificant conservation of cytotoxicity. Replacement of the imidazole cycle by pyridine, thiazole and oxazole is accompanied by a substantial decrease in activity. So, to conserve the cyto-



Scheme 11.



Scheme 12.

toxic action, an important factor is the presence of both nitrogen atoms of the imidazole cycle.

Modification of the ketale function is not so unambiguous. For example, its methoxylation caused the appearance of biological activity against taxol resistant cancer cells. At the same time, the introduction of substituents ($-OC_3H_7$ or $-OCH_2CF_3$) is accompanied by the complete loss of cytotoxicity.

It is interesting to stress that the addition of dimethylacetale group at C^{15} instead of the ester group had no effect on the activity of the synthesized analogue. A change of the alcohol component of the ester group caused a substantial change of the biological activity in comparison with the natural products. Thus, replacement of methyl group by ethyl, *n*-propyl and allyl group is accompanied by an increase in the biological activity. A decrease in the activity was observed for the compounds with longer or branched substituents like *n*-butyl and isopentyl. At the same time, a series of esters containing the derivatives of hydroxyanthracenes, benzyloxyethanol and 4-phenylbutanol as the alcohol component exhibited the cytotoxicity similar to or higher than that of the prototypes, though their tubulin polymerisation ability was insignificant.

The data obtained are undoubtedly important for planning the syntheses of highly active cytostatics.

4. COMPLETE SYNTHESIS OF ELEUTHESIDES

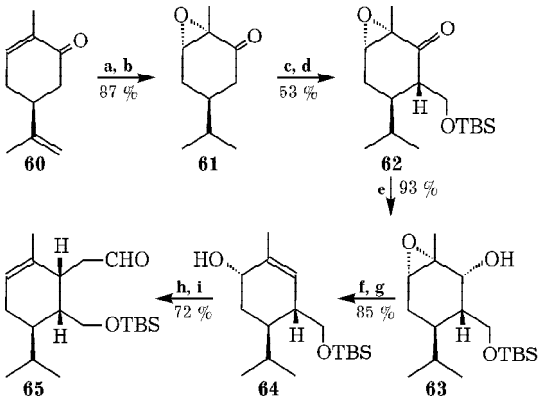
Investigation of the strain of the tricyclic framework of sarcodictyine A **43** gave the results important for better understanding of the chemical properties of the compounds of this class [22]. It was revealed that the treatment of this compound with the methanol solution of KOH leads to the formation of butenolid **58** (Scheme 12). The process is explained by strain relaxation in the cyclic system due to the intramolecular rearrangement initiated by the oxa-Michael reaction.

Thus, after the first stage of methanolysis of N-methylurocanate, the formed hydroxyl group attacks C^2, which is accompanied by the immediate fragmentation of C^3-C^4 bond according to Kleisen. The stereochemical structure of eleutherobine **50** had not yet been established by that time in the final form, so the results obtained provided a convincing confirmation of the absolute configuration typical for the diterpenois 4,7-oxaeunicellane framework. As far as the establishment of the structure of carbohydrate fragment is concerned, it should be noted that the *L*-enantiomer is predominant among arabinose enantiomers. Because of this, it is surprising that the carbohydrate part of eleutherobine **50** was unambiguously identified as that corresponding to *D*-arabinose. This result was later confirmed by the synthesis of diastereosiomeric neoeleutherobine containing *L*-arabinose in its structure [23].

The most successful investigations in this area were performed by two outstanding scientific schools (teams) headed by Nicolaou and Danishefsky who performed the complete synthesis of eleutherobine **50**, neoeleutherobine and sarcodictyines **43** [36–42].

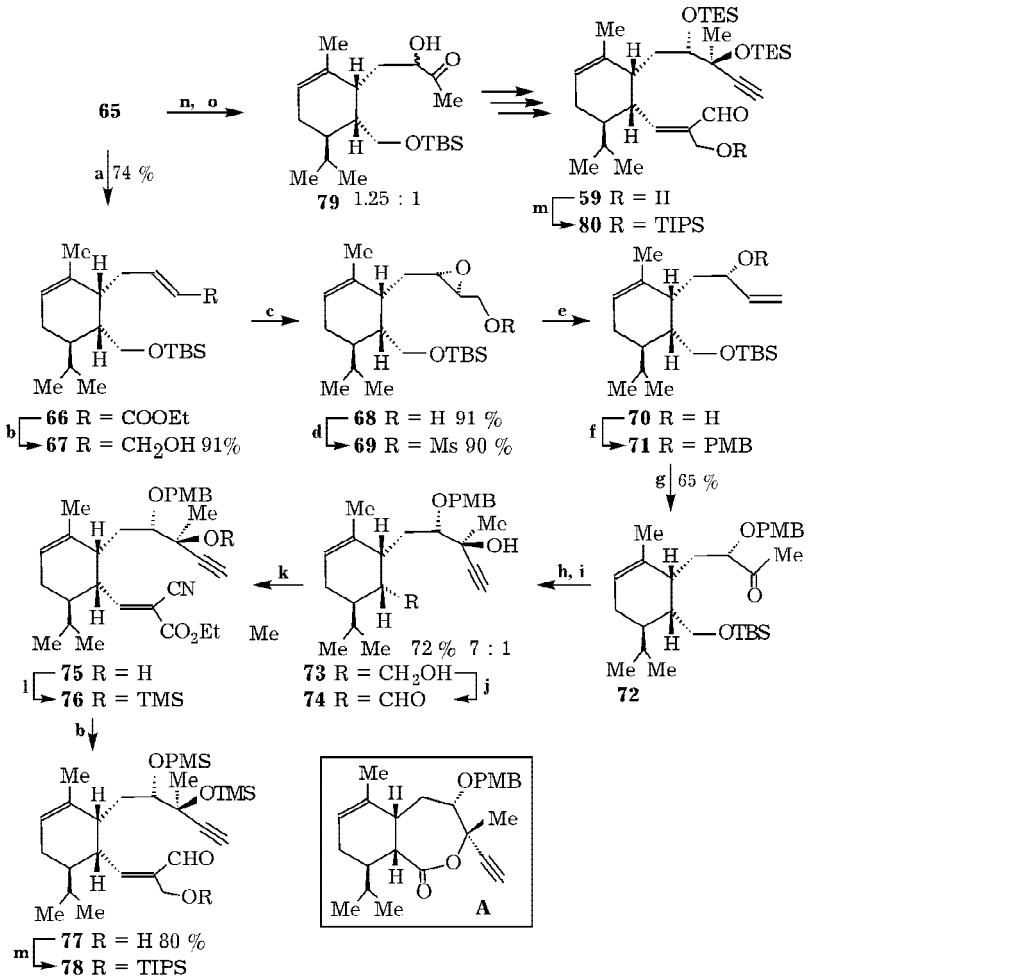
The synthesis strategy by Nicolaou and coworkers was developed on the basis of the retrosynthesis analysis; it is aimed at obtaining the derivative of menthane **59** with side chains containing terminal acetylene and aldehyde groups. Condensation of these groups opens the way to making the carbon framework of eleuthesides.

The complete synthesis of eleutherobine **50** starting from (+)-carvone **60** and some its ana-



a) H_2O_2, NaOH; **b**) H_2, PtO_2; **c**) LDA, CH_2O; **d**) TBSCl, Et_3N; **e**) *L*-селектрид; **f**) MsCl, Et_3N; **g**) нафталинид Na; **h**) $CH_3C(OEt)_3$, *n*-$PrCO_2H$; **i**) DIBAL.

Scheme 13.



a) $(EtO)_2P(O)CH_2COOEt$, NaH; **b**) DIBAL; **c**) $Ti(O\text{-}i\text{-}Pr)_4$, диэтил-*L*-тартрат, *t*-BuOOH; **d**) MsCl, Et_3N; **e**) нафталинид Na; **f**) $PMBOC(=NH)CCl_3$, PPTS; **g**) 1. $Hg(OAc)_2$, 2. Li_2PdCl_4, $CuCl_2$; **h**) HC≡CMgBr; **i**) TBAF; **j**) D–M [O]; **k**) $NCCH_2COOEt$, β-аланин; **l**) TMSOTf; **m**) TIPSOTf, Pr_2NEt; **n**) CH_2=CH(OEt), *t*-BuLi; **o**) H_2SO_4, Et_2O.

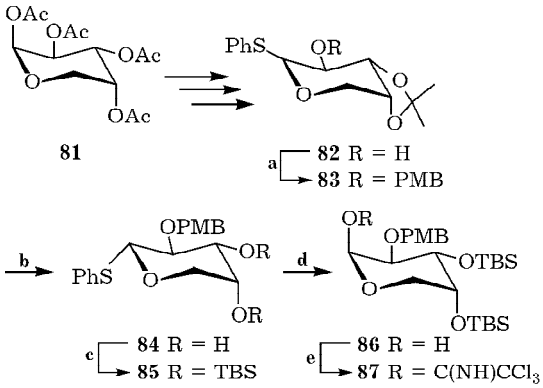
Scheme 14.

logues was realized according to the synthesis Scheme 13.

Matrix **65** was synthesized by the Kleisen rearrangement of allyl alcohol **64** synthesized from (+)-carvone according to Trost. On the basis of matrix **65**, two versions of obtaining synton **59** were studied. According to the first version, condensation of aldehyde **65** with the corresponding phosphonate according to Wittig–Horner leads to the formation of ester **66**. Its reduction under the action of $(i\text{-Bu})_2$AlH gives allyl alcohol **67**; its asymmetric epoxidation according to Sharpless leads to epoxide **68**. Transformation of epoxide **68** into alcohol **70** was performed through mesylate **69**. As a result of the blockage of hydroxyl group in the form of PMB ester and oxidation of terminal olefin **71** under the action of $Hg(OAc)_2$ and Li_2PdCl_4–$CuCl_2$, methylketone **72** is formed. Ethynylation of ketone **72** under the action of HC≡CMgBr followed by the removal of silyl protection gives diol **73** with the prevalence of α-diastereomer (7 : 1). Oxidation of primary alcohol **73** according to Dess–Martin finished with the formation of lactone A.

Soft oxidation of alcohol **73** in the presence of pyridine and $NaHCO_3$ gives the target aldehyde **74** with a good yield. Then aldehyde **74** is introduced into Knevenagel condensation with cyanoacetic ester. Blockage of hydroxyl group and simultaneous reduction of cyano and ethoxycarbonyl groups under the action of $(i\text{-Bu})_2$AlH result in the formation of hydroxyaldehyde **77**.

Another approach to building the "upper" chain of the similar type involves ethoxylation of aldehyde **65** followed by acetylenation of the formed epimeric mixture of hydroxyketone **79** by ethynylmagnesium bromide and the corresponding stages for the "lower" chain (Scheme 14).



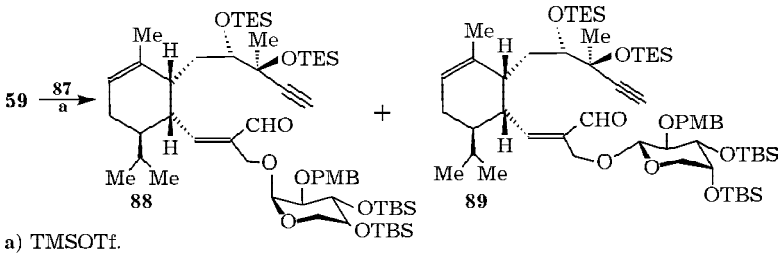
a) PMB–Cl, NaH; **b**) $TsOH \cdot H_2O$, этиленгликоль; **c**) TBS–OTf, Et_3N; **d**) NBS, Py; **e**) NaH, CCl_3CN.

Scheme 15.

According to the strategy, the next stage of the synthesis of eleutherobine involves Schmidt glycosylation of monocyclic allyl alcohol **59** by *D*-arabinose trichloroacetimidate.

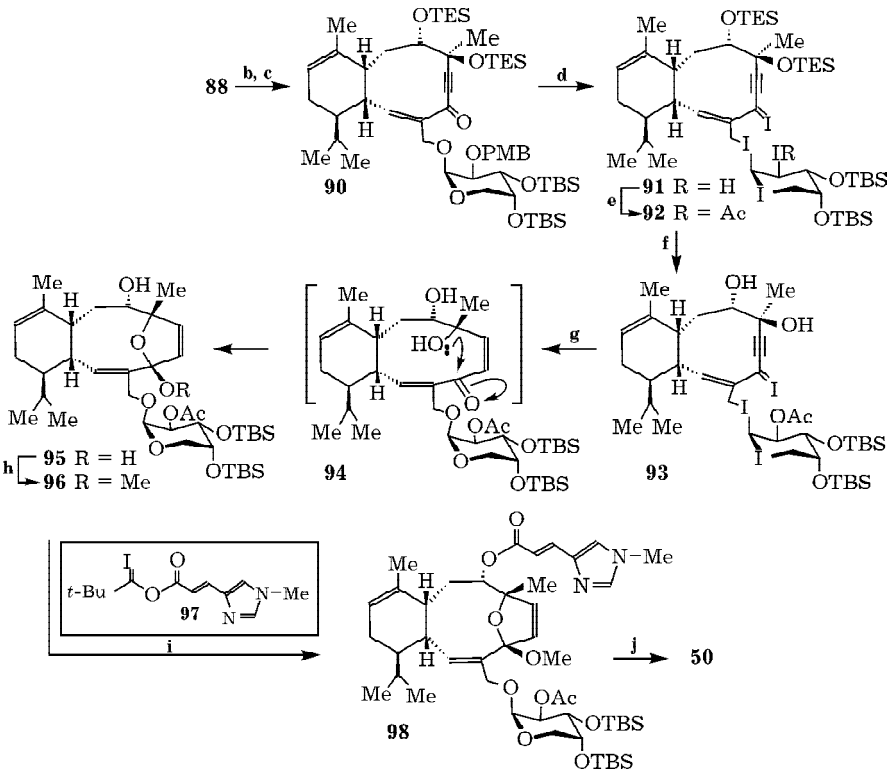
The necessary trichloroacetimidate **87** was obtained from tetraacetate **81** of *D*-arabinose (Scheme 15). Compound **81** is transformed into thioglycoside **82** in which the hydroxyl group is blocked in the form of *p*-methoxybenzoic ester into compound **83**. Then the acetonide group is hydrolysed to form diol **84**; after its transformation into bis-silylic ester **85**, the sulphide group at the anomer centre is removed by the action of NBS pyridine in aqueous acetone, which results in the formation of lactol **86** (2 : 1, a mixture of anomers). Finally, treatment of **86** with NaH followed by the addition of Cl_3CCN gives trichloroacetimidate **87**.

In the studies of the stage of glycosylation of hydroxyaldehyde **59** by trichloroacetimidate **87**, a broad range was established for the adjustment of stereoselectivity of glycosylation; the conditions for obtaining diastereomers at the



a) TMSOTf.

Scheme 16.



a) TMS–OTf; **b**) LIHMDS; **c**) D–M; **d**) DDQ; **e**) Ac_2O, Et_3N, 4-DMAP; **f**) Et_3N 3HF; **g**) H_2, Lindlar cat.; **h**) PPTS, MeOH; **i**) Et_3N, 4-DMAP; **j**) TBAF, AcOH.

Scheme 17.

ratio of α to β diastereomers from 8 : 1 to 2 : 1 were developed (Scheme 16) [38].

Treatment of β-anomer **88** with LiHMDS in THF at −30 °C results in the intramolecular cyclisation with the formation of secondary alcohol which is then immediately oxidized using Dess–Martin reagent to form ketone **90** (Scheme 17).

Subsequent stages of re-esterification of the arabinose fragment of glycoside **90** into C^2-acetate, hydrogenation at Lindlar catalyst during which the C^4–C^7 oxygen bridge is generated simultaneously, complete the construction of eleutheside nucleus in compound **95**. Stages of esterification into urocanate **98** and hydrolysis of TBS groups lead to the formation of the target eleutherobine **50** (see Scheme 17).

So, the synthesis sequence includes 28 stages.

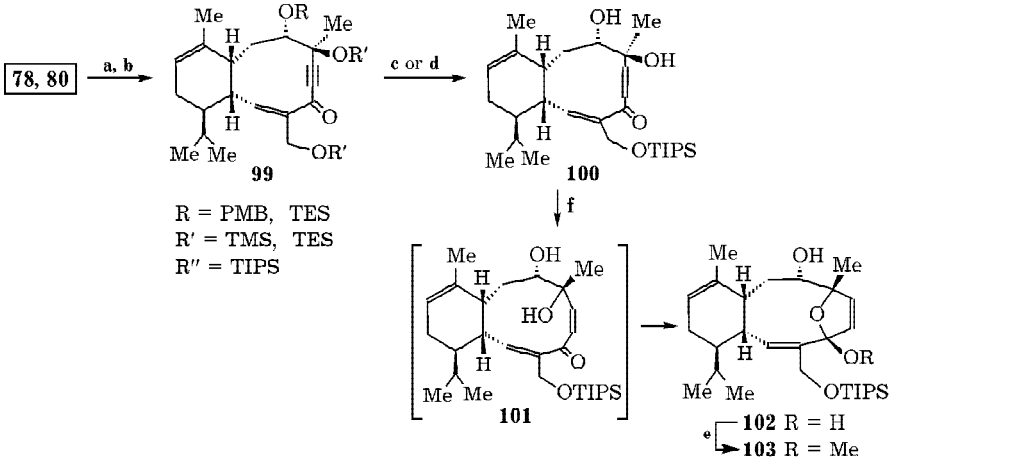
The α-glycoside analogue of eleutherobine was synthesized according to the similar scheme using α-anomer [23].

In order to synthesize sarcodictyine, acetylene-aldehyde cyclization of the key compounds **78** and **80** was carried out, followed by the formation of tricyclic nucleus (Scheme 18). However, the removal of PMB protective group in compound **99** by sodium in liquid ammonium results, in addition to the formation of the target tricycle, also in the formation of its C^5–C^6 saturated analogue at a ratio of 2 : 1. This complication was successfully overcome using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to remove this protective group. Nevertheless, it turned out that a more convenient way is that through intermediate **80** which excludes the use of PMB group.

Transformation into urocanate was carried out along the route similar to that described above.

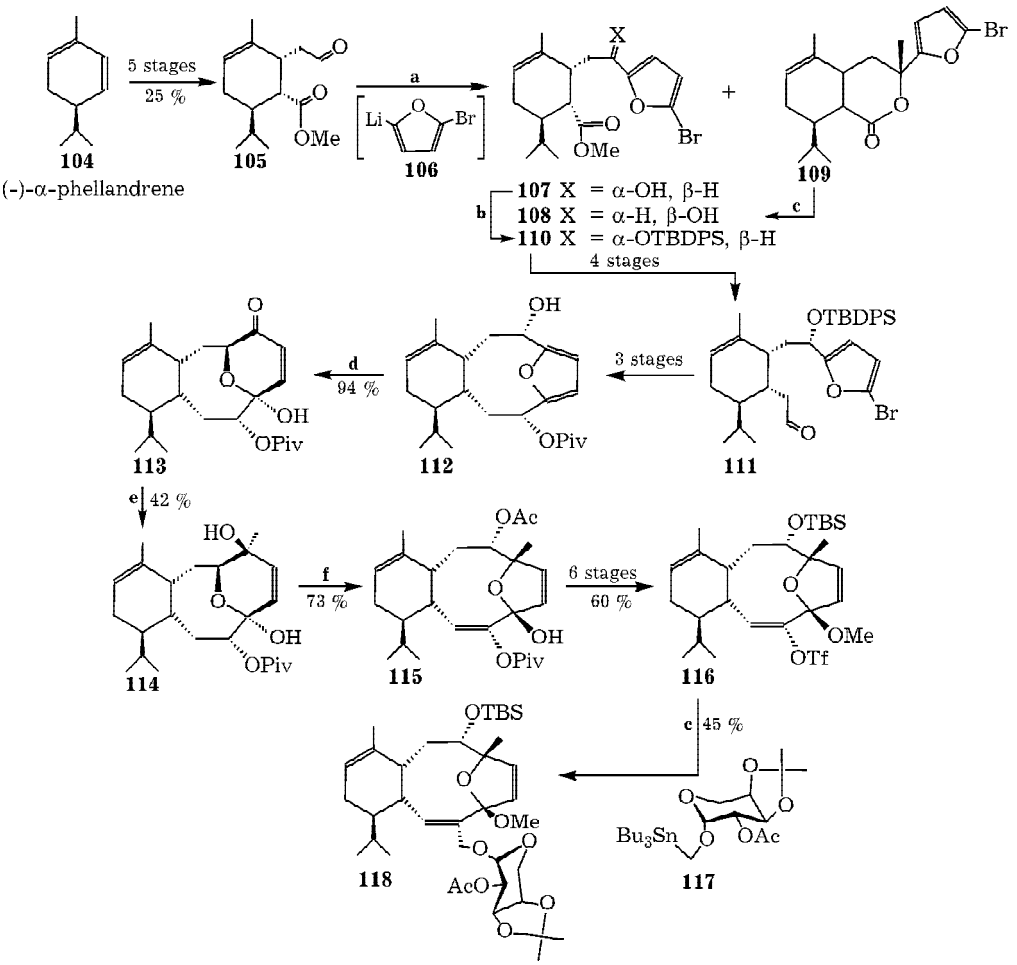
On the basis of eleutherobine, its analogues were obtained later. They are: eleuthosides A and B differing by the quantitative or regiomeric content of acetoxy groups in the carbohydrate fragment [36].

Another strategy of the synthesis of eleutherobine was presented in the investigations carried out by Danishefsky group for the purpose of developing the synthetic schemes of eleutherobine and neoeleutherobine [37, 41, 42]. It is



a) LiHMDS; **b**) D–M [O]; **c**) DDQ, CH_2Cl_2; **d**) Et_3N 3HF; **e**) MeOH, PPTS; **f**) H_2, $[Rh(nbd)(dppb)]BF_4$.

Scheme 18.



a) 2,5-dibromofuran + *p*-BuLi, THF → **106**; **106** + **105** in THF → **107**; **b**) TBDPSCl, imidazole, DMAP, 0 °C; **c**) tritone B, THF; MeI; **d**) DMDO, acetone, CH_2Cl_2, −78 °C; **e**) CH_3Li, THF, −78 °C; Ac_2O, DMAP, CH_2Cl_2; **f**) $Pd(PPh_3)_4$, LiCl, THF, 130 °C.

Scheme 19.

based on the formation of a ten-membered eleutheside framework by means of 1,2-addition of 2,5-dibromofuran to the stage-by-stage generated aldehyde functions at he ends fo chains, respectively, of disubstituted menthene **105**.

The initial compound was (−)-α-phellandrene **104**; after dichloroketenation, enamination, splitting of the ketoenamine fragment it gave aldehyde **105**. The interaction of the latter compound with 2-bromo-5-lithiumfuran **106** resulted in the formation of a mixture of diastereomers: the major alcohol **107** (57 %) and the side 8*R*-diastereomer which was isolated mainly in the form of lacton **109** (30–40 %). In one of the version of subsequent route, it was assumed that an alkoxycarbonyl-2-bromoethylene fragment would be formed at C^1; its intramolecular cyclization with the corresponding tributyltin derivative of the furan cycle was expected to proceed. Unfortunately, the attempt to perform Wittig olefination of the corresponding aldehyde failed.

An alternative route was realized: after the transformation into TBDPS ester and homologation of the lower chain using nitrile method, homoaldehyde **111** was obtained. It was then cyclized according to Nozaki–Kishi by treating **111** with the complex $CrCl_2$–$NiCl_2$ in DMF. Hydrolysis of the protective group resulted in the formation of compound **112**. Oxidation of the tricycle of **112** by dimethyldioxirane at −78 °C gives dihydropyranone **113**. Investigation of the properties of this unusual compound showed that it is able to undergo rearrangement into dihydrofuran derivative. Thus, selective acetylation of alcohol **114** obtained by methylation of ketone **113** is accompanied by shortening of the pyrane ring with the formation of tricycle **115**. After the corresponding replacement of protective groups in **115**, norditerpenoid tricycle **116** is obtained after six stages; total yield is 60 % (Scheme 19).

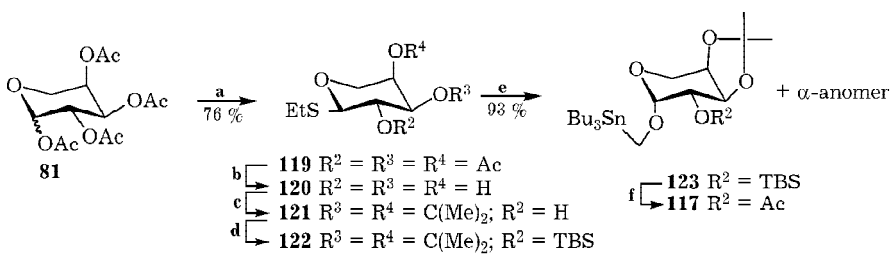
Subsequent glycosylation by coupling with arabinosyloxymethylstannane **117**, which was obtained, in its turn, in eight stages from *D*-arabinose (Scheme 20), resulted in the formation of glycoside **118** with the simultaneous introduction of the lacking carbon atom.

The complete synthesis of eleutherobine **50** is finished with the introduction of the fragment of (E)-N(6')-methyluricanic acid **125** by acylation of the free C^8-hydroxy group in the presence of DCC–DMAP, followed by the removal of TBS and isopropylidene protective groups. The synthesis sequence of the scheme includes **27** stages (Scheme 21).

The analogous compound neoeleutherobine was obtained using a similar route; this compound is glycoside of *L*-arabinose.

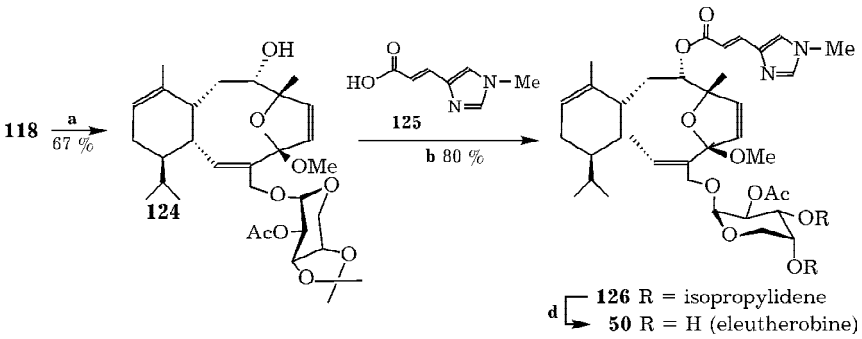
5. OTHER APPROACHES TO THE FORMATION OF ELEUTHESIDE FRAMEWORK

An attempt to make eleutheside core through a short semi-synthesis route was made in the works dealing with the investigation of transannular reactions of cembrane diterpenoids. It was discovered that cyclisation of isocembrol **127** or its 5-acetoxy derivative **128** leads under the conditions of acid catalysis (HCOOH) to the simultaneous formation of the compounds with the carbon framework of 2,11:3,8-dicyclocembrane **129**, **130** (57 %) and eunicellate derivatives 5α-acetoxy-2,11-cyclocembranoids **131**, **132** (17 %) (Scheme 22) [43, 44]. These com-



a) EtSH, BF_3 Et_2O, CH_2Cl_2 [10 : 1]; **b**) NaOMe, MeOH; **c**) 2,2-methyloxopropane, *p*-TsOH H_2O; **d**) (*t*-Bu)Me_2·SiCl, imidazole, DMAP, CH_2Cl_2; **e**) Bu_3SnCH_2OH, MeOTf, DTBP, CH_2Cl_2–Et_2O; **f**) TBAF–THF, Ac_2O, DMAP, CH_2Cl_2, DTBP.

Scheme 20.

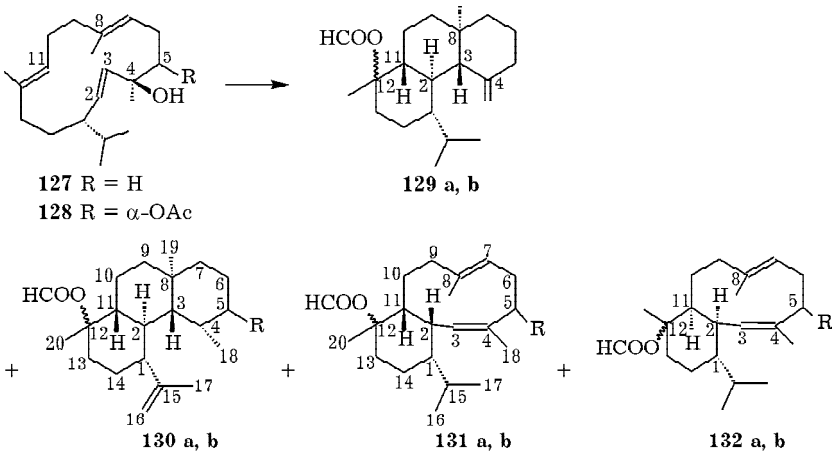


a) TBAF, THF; **b**) **133**, DCC, DMAP, $CHCl_3$, 50 °C; **d**) PPTS, MeO, boiling

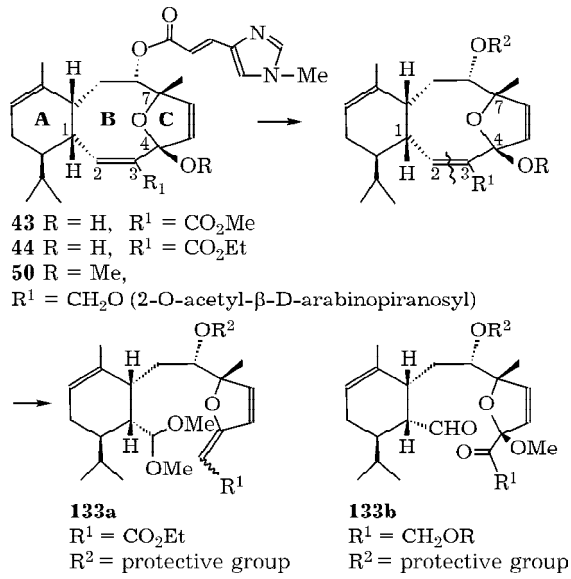
Scheme 21.

pounds are potential intermediates in the synthesis of eleutheside analogues.

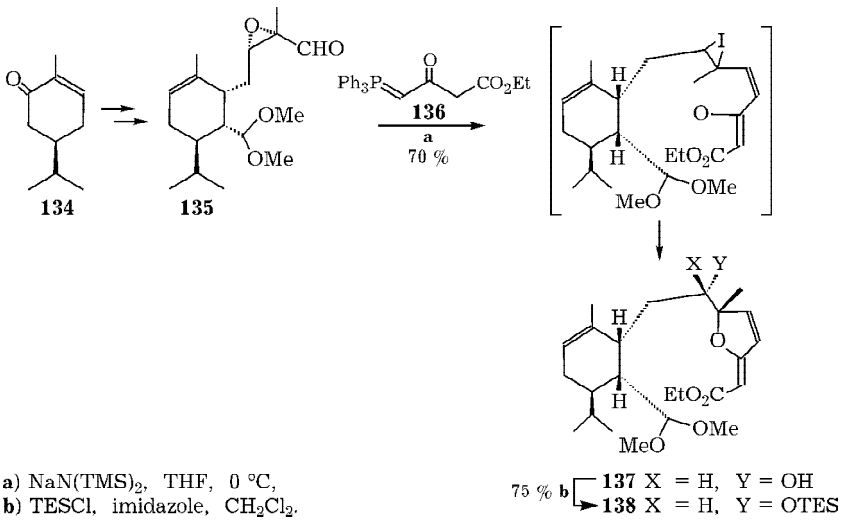
Many approaches to the synthesis of eleuthesides demonstrate the possibilities of alternative ways to compose the carbon core on the basis of the known syntons. For instance, one of the versions of compsing the tricyclic framework of eleuthesides, in agreement with the retrosynthesis Scheme 23, is cyclisation at C^2–C^3 (according to MacMury reaction) of com-



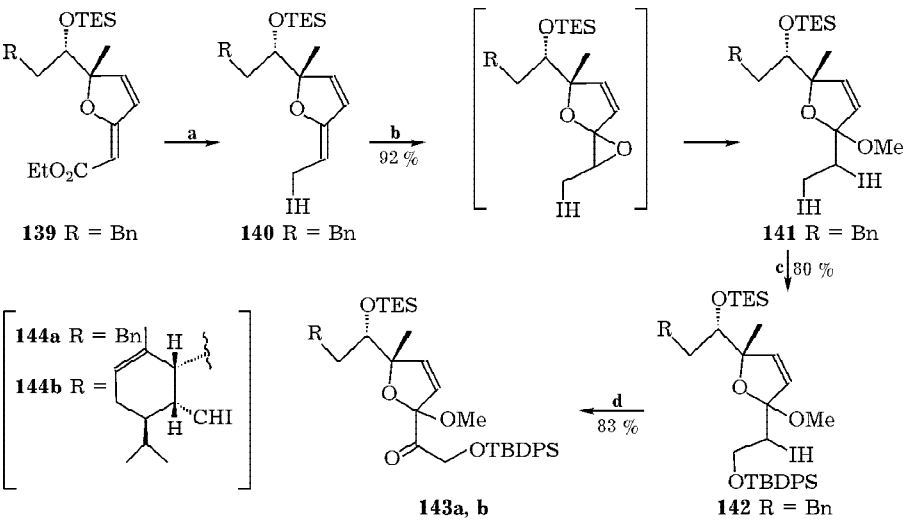
Scheme 22.



Scheme 23.



Scheme 24.



Scheme 25.

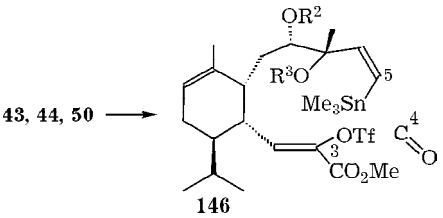
pound **133a** by aldol condensation of ketoaldehyde **133b**.

When realizing Scheme 24, starting from (−)-carvone **134**, epoxyaldehyde **135** was obtained in seven stages. The condensation of the latter compound with phosphoran **136** resulted in the successful introduction of the lacking carbon atoms with the simultaneous generation of dihydrofuran fragment in compound **137**.

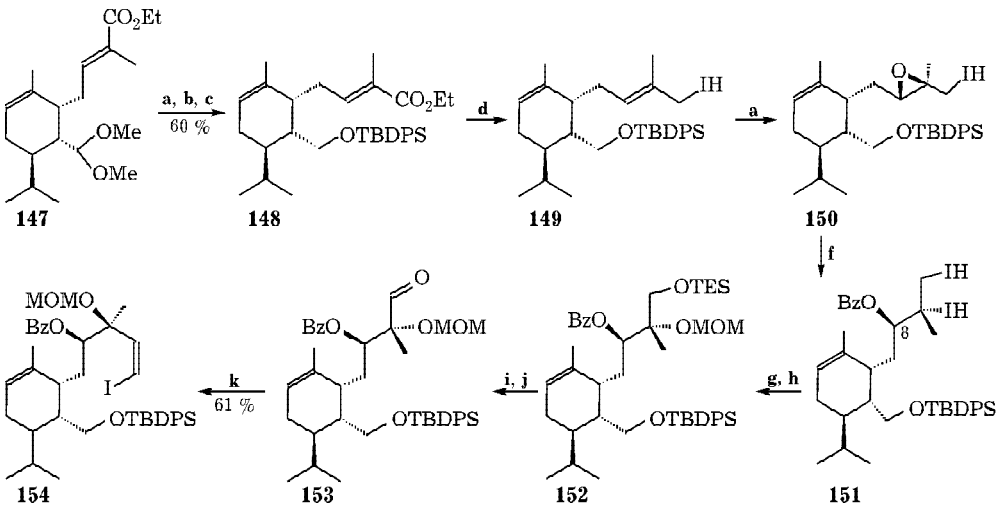
Another version of this synthesis, mastered with the model **139**, involves reduction of the ester group, oxidation of exocyclic double bond to form methoxydiol **141**; after blocking the primary alcohol group, oxidation into ketone **143a, b** is performed (Scheme 25).

Cyclisation of compounds **137** and **143b** is under investigation [45].

The key stage of another scheme under development (Scheme 26) is cyclisation of synton

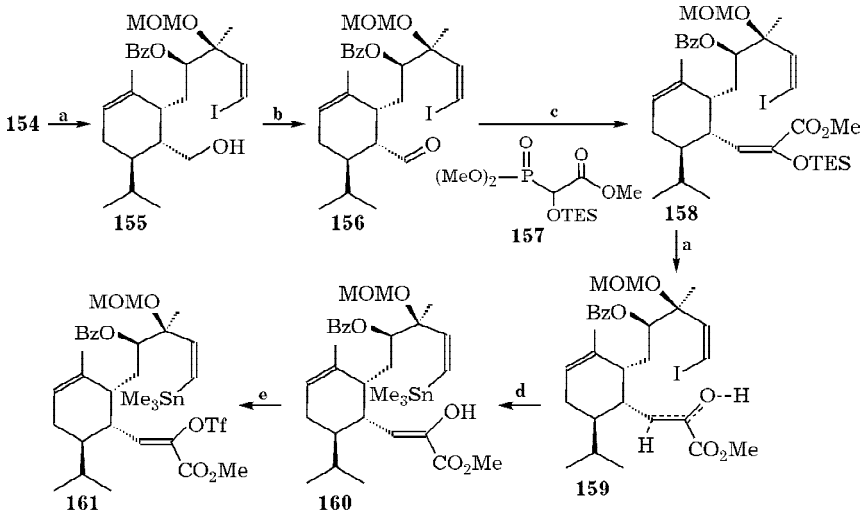


Scheme 26.



a) AcOH, THF, H_2O, 17 h; **b**) $NaBH_4$, EtOH; **c**) TBDPSCl, CH_2Cl_2; **d**) $LiAlH_4$, Et_2O; **e**) TBHP, Ti(O-*i*-Pr)$_4$, (+)-DET, CH_2Cl_2, −20 °C; **f**) Ti(O-*i*-Pr)$_4$, BzOH, $CHCl_3$; **g**) TESCl, CH_2Cl_2; **h**) MOMCl, DIPEA, CH_2Cl_2, 50 °C; **i**) TAS−F, DMF, H_2O; **j**) DMP, CH_2Cl_2; **k**) Ph_3PCHI, NaN(TMS)$_2$.

Scheme 27.



a) HF · Py, THF/Py; **b**) DMP, CH_2Cl_2; **c**) LiN(TMS)$_2$, THF, −78 °C; **d**) Pd_2dba_3, NMP, $(SnMe_3)_2$, 50 °C; **e**) NaN(TMS)$_2$, THF, −78 °C.

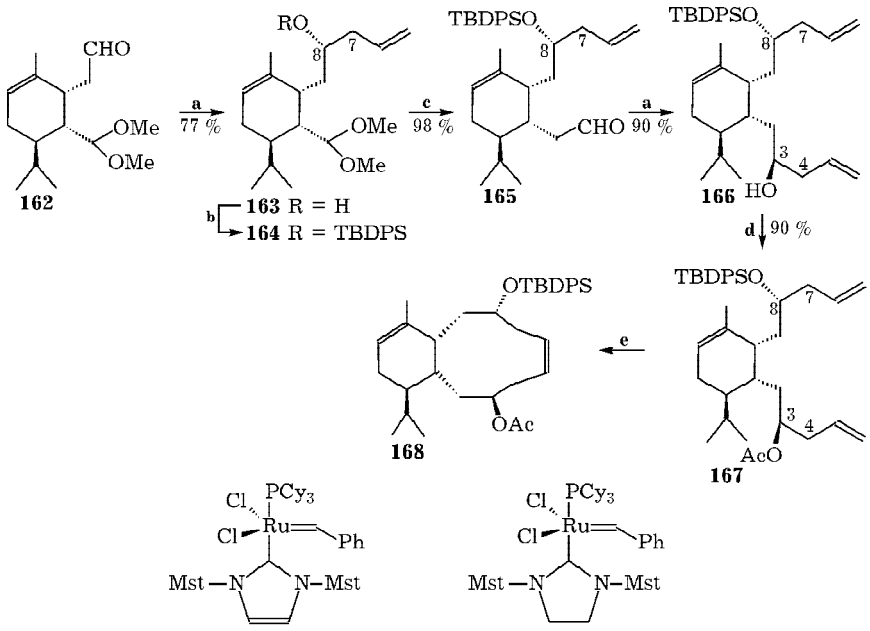
Scheme 28.

146 according to Still [46]. Thus, one may avoid complications encountered by the authors of [45]. The complications were due to the interaction of dimethylacetal group with Lewis acids.

Thus, ester **147** after the transformation of its acetale function into TBDPS ester **148**, reduction, epoxidation, opening of the epoxide to form diol **151**, manipulation with protective groups, oxidation into aldehyde **153** and its olefination according to Wittig gave Z-vinyliodide **154** (Scheme 27).

Hydrolysis of silyl ester **154** followed by oxidation of alcohol **155** results in the formation of aldehyde **156** which is then transformed into enolsilyl ester **158** under the action of phosphonate **157** (Scheme 28).

Hydrolysis of enolester **158** under the action of HF/Py gives a mixture composed of the tautomers of **159** (see Scheme 28). Subsequent substitution of iodide for trimethylstannyl group under the action of hexamethyldistannane in the presence of catalysts Pd_2dba_3



a) (*Z*)-γ-(methoxymethoxy)allyldiisocampheylborane, THF, −78 °C; H_2O_2, 6 M NaOH; **b**) TBDPSCl, imidazole, CH_2Cl_2; **c**) AcOH: THF : H_2O (3 : 1 : 1); $NaBH_4$, EtOH; MsCl, Et_3N, CH_2Cl_2, 0 °C; KCN, 18-crown-6, MeCN, 80 °C; DIBAL, −78 °C; **d**) Ac_2O, DMAP, Py; **e**) **169** (20 mol. %), CH_2Cl_2, (100 % *Z*); **170** (7 mol. %), CH_2Cl_2, (100 % *Z*).

Scheme 29.

resulted in the formation of Z-vinylstannane **160** but its yield was low (yield: 26 %, conversion degree: 63 %).

The possibility of cyclisation of triphlathe **161** into a 10-membered cycle is under investigation.

Somewhat later, as a part of this programme, the synthesis of a simplified eleutheside analogue was performed using metathesis reaction to lock the chains into a cycle [47–49].

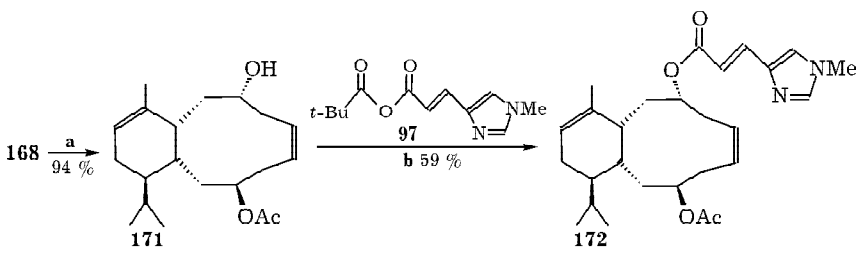
It should be noted that the known examples of metathesis cyclisation into medium- and large-sized rings are very rare, especially in the case of polyfunctional substrates.

The reaction of aldehyde **162** with allyldiisopinocampheylborane is stereospecific and leads to the formation of compound **163**. Subsequent homologation with the formation of aldehyde **165** after blocking the hydroxyl group, hydrolysis of acetale and repetition of stereoselective allylation give bis-homoallyl diol **167** which is differentially blocked with protective groups (Scheme 29).

Metathesis cyclization using catalysts **169** and **170** stereospecifically gives Z-isomer **168** with 80 % yield.

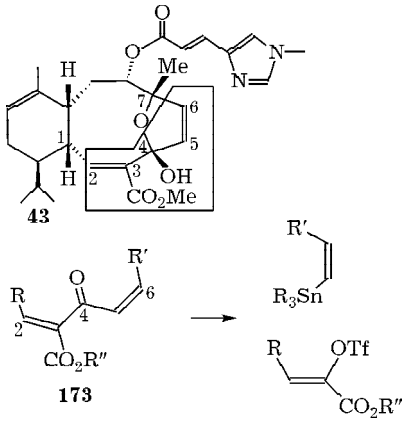
This approach is promising for the synthesis of analogues and mimetics of natural eleutherobine **172** (Scheme 30).

It should be noted that the obtained analogue **172** conserves the ability to stabilize microtubes [53].



a) TBAF, THF; **b**) Et_3N, DMAP, CH_2Cl_2.

Scheme 30.

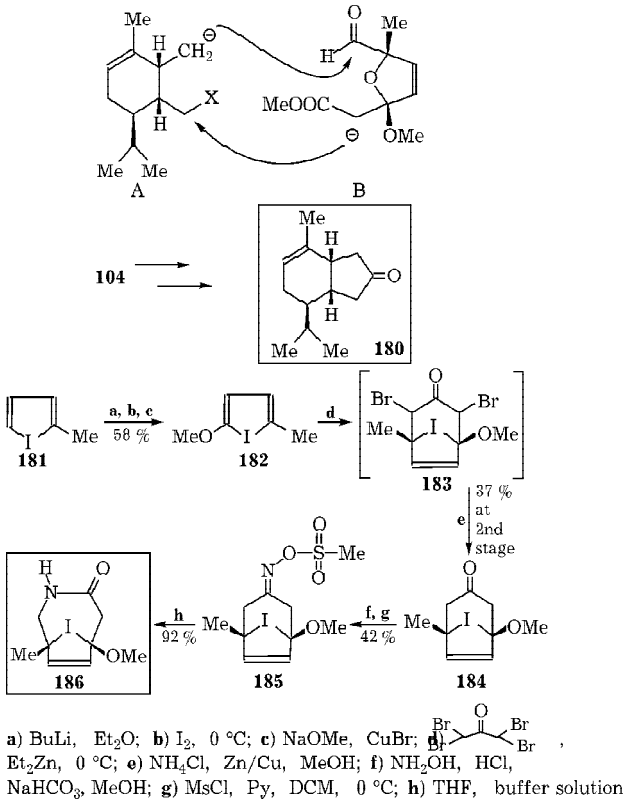


Scheme 31.

It is convenient to study the optimal ways to synthesize eleuthesides with the help of the models of conjugated systems like **173** (Scheme 31). These developments may be the basis of the synthesis strategy as the key stage of macrocyclisation [50].

To synthesize highly functionalised systems of this type, an original method was developed. It is based on couping vinyltrifluorosulphonates with vinyltributylstannanes in the presence of carbon monoxide, catalysed by palladium complexes (Scheme 32).

Another approach involves generation of a 10-membered cycle by the addition of substituted dihydrofuran unit according to the retrosynthesis Scheme 33. On the basis of (±)-phellandrene **104**, ketone **180** was obtained. It is an intermediate compound to form unit A. Approaches to unit B were implemented starting from 2-methylfuran **181**. Cycloaddition of tetrabromoacetone to 2-methoxy-5-methylfuran **182** in the presence of Et_2Zn leads to the formation of bicyclic amide **184**.

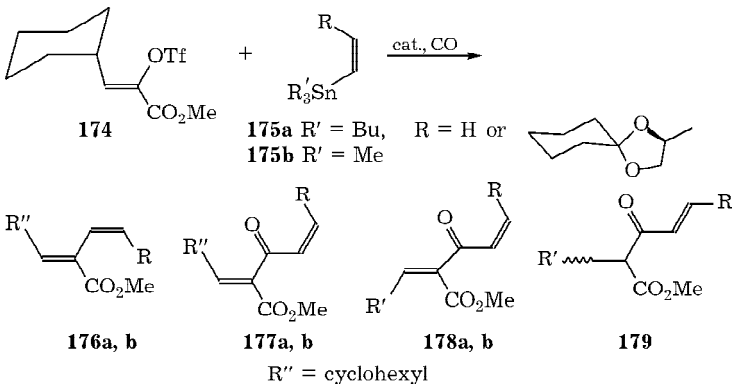


a) BuLi, Et_2O; **b**) I_2, 0 °C; **c**) NaOMe, CuBr; **d**) , Et_2Zn, 0 °C; **e**) NH_4Cl, Zn/Cu, MeOH; **f**) NH_2OH, HCl, $NaHCO_3$, MeOH; **g**) MsCl, Py, DCM, 0 °C; **h**) THF, buffer solution

Scheme 33.

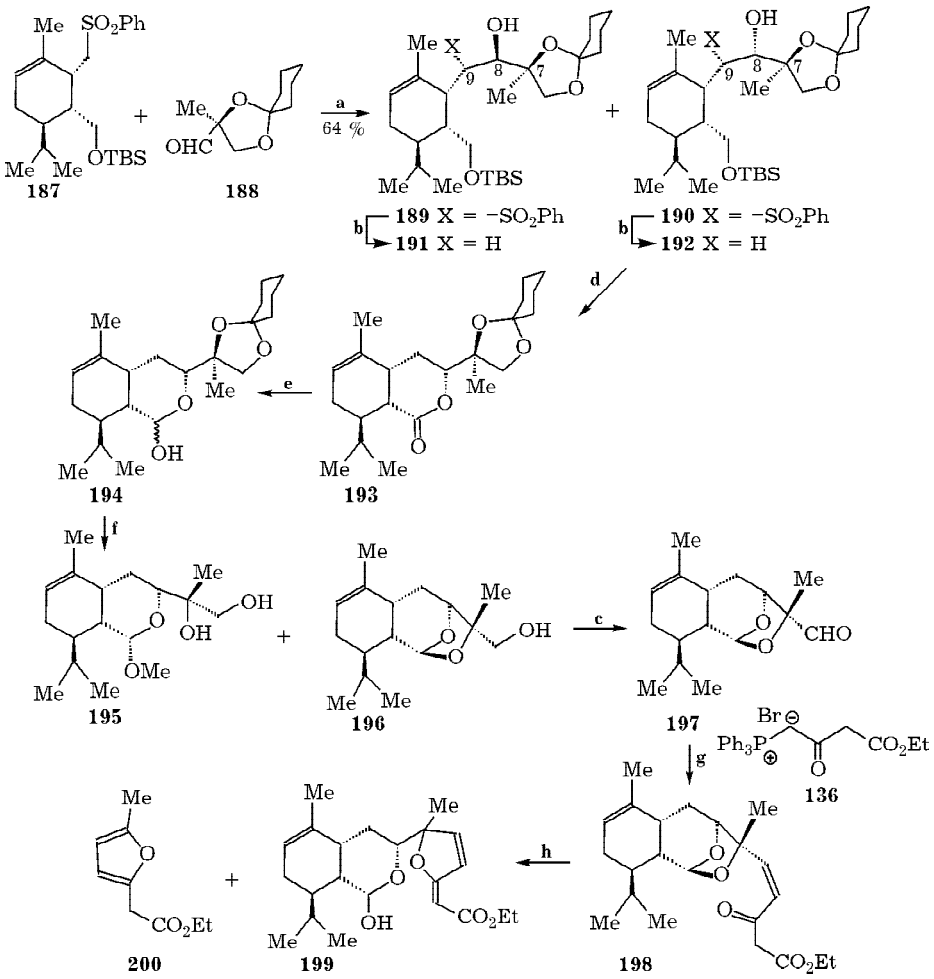
On the basis of the obtained units, the ways of their transformation into the eleutheside framework are under investigation [51].

In addition to the above considered approaches to the synthesis of eleuthesides, it is interesting to stress a convergent route [52]



R″ = cyclohexyl

Scheme 32.



Scheme 34.

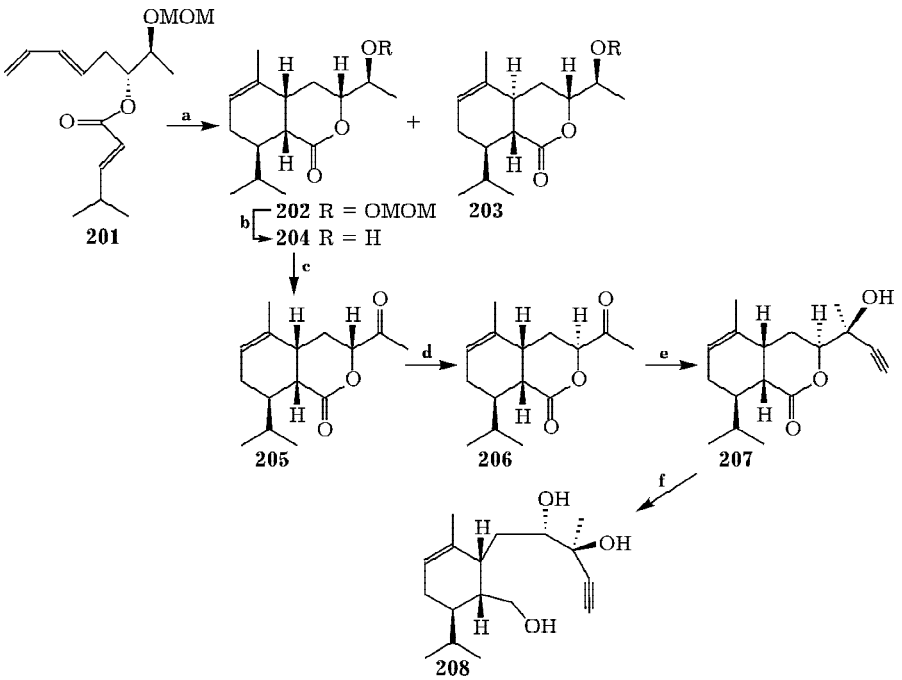
which involves coupling of sulphone **187** (derivative of (+)-carvone **60**) with aldehyde **188** which is a completely functionalized C^6–C^8 unit. As a result, a mixture of C^8 stereoisomers **189** and **190** at a ratio of 10 : 1 is formed (Scheme 34). Desulphonation under the action of Na/NH_3 gives alcohols **191** and **192**.

Oxidation of silyl ester **192** using TPAP leads to the formation of lactone **193**. Its reduction with $(i\text{-Bu})_2AlH$ proceeds stereoselectively with the formation of cyclic semi-acetale **194**. Its treatment with *p*-TsOH in methanol gives acetale **196** together with methoxyacetale **195**, with the total yield of 23 %.

Oxidation of acetale **196** with Dess–Martin reagent leads to the formation of aldehyde **197**; its Wittig condensation gives ketoester **198** (Z : E = 14 : 1). Attempts to split ester bonds using $BF_3 \cdot Et_2O/CH_2Cl_2$ leads to the formation of a complicated mixture of products; compound **199** and furan **200** were isolated from the mixture.

Synthesis using sulphone (see Scheme 34), in spite of its multistage character, ensures efficient stereocontrol of important asymmetric centres C^7, C^8 [52].

In addition to syntheses and approaches to the synthesis of eleuthesides on the basis of (+)-carvone **60** and (−)-α-phellandrene **104** (including racemic substance), chiral 3,5-hexadienylacrylate **201** was also used [53]. It enters the intramolecular Diels–Alder reaction and gives a mixture of epimeric bicyclic lactons **202** and **203** (Scheme 35). The necessary inversion of lacton carbinol centre corresponding to C^8 of eleutheside nucleus was performed by epimerization of the intermediate ketone **205** with the stereoselectivity 2.5 : 1 in favour of the necessary diastereomer which was later iso-



a) 200 °C, toluene; **b**) CBr_4, MeOH, boiling; **c**) PCC, CH_2Cl_2; **d**) DBU, CH_2Cl_2; **e**) HC≡CMgBr, $MgBr_2$–Et_2O, −70...−40 °C; **f**) $LiAlH_4$, Et_2O.

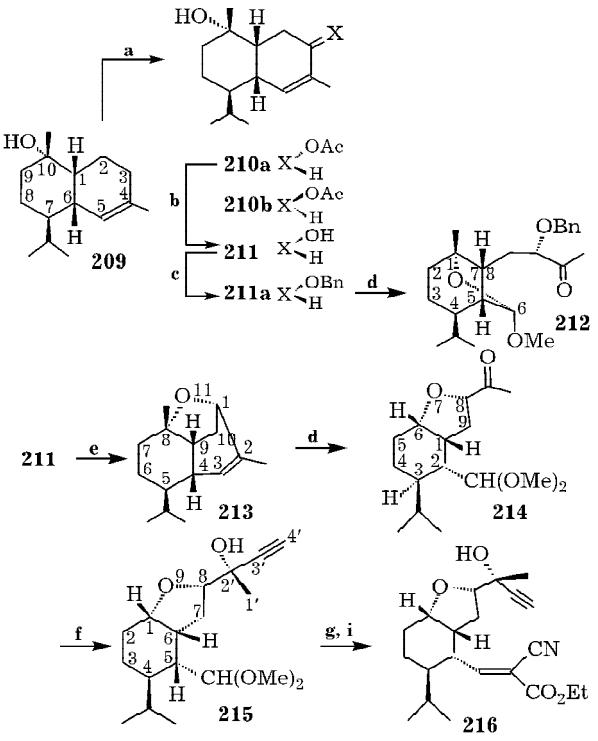
Scheme 35.

lated using HPLC. As a result of reduction of lacton **207**, compound **208** is formed. It is an unblocked synton **73** which is used in the scheme proposed by Nicolaou.

The use as substrate of sesquiterpenoid (+)-δ-cadinol **209** extracted from cedar turpentine is promising in the aspect of shortening the synthetic sequence based on (+)-carvone. For example, allyl oxidation of this sequiterpenoid leads to the formation of a mixture of epimeric acetates **210a, b**. On their basis, two alternative versions of obtaining important synthetic units were developed (Scheme 36).

In one case, after hydrolysis, chromatographic isolation and blocking, benzylate **211** was subjected to ozonolytic splitting; mixed acetale **212** was obtained. Subsequent transformations of the obtained compound in the direction of eleutheside nucleus fit within the scheme proposed by Nicolaou.

In the second version, the ability of allyl alcohol **211** to form 1,4-epoxide **213** is used. This is expected to allow one to shorten the synthesis sequence due to exclusion of the stages of manipulation with protective groups and to obtain the key compound **216** [54–56].



a) SeO_2–Ac_2O, 70 °C; **b**) MeONa–MeOH; **c**) BnCl, DMSO, 20 °C; **d**) O_3, MeOH, −78 °C, Me_2S; **e**) *p*-TsOH, C_6H_6, boiling; **f**) HC=CMgBr, THF, 0 °C; **g**) HCl, *i*-PrOH, $CHCl_3$; **i**) $NCCH_2CO_2Et$, β-alanine, EtOH.

Scheme 36.

6. CONCLUSIONS

A short time interval since the discovery of eleutherobine till the development of its complete synthesis and compilation of the combinatory library of sarcodictyine compounds is characterized by the high level of the development of directed synthesis. Investigations in this area initiated the works that are promising in the aspect of development of the methodology of organic synthesis in general and the methods to obtain carbocyclic structures of medium and large size in particular.

LIST OF ABBREVIATIONS

m-CPBA – *meta*-chloroperbenzoic acid
CSA – camphorsulphonic acid
DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC – dicyclohexylcarbodiimide
DDQ – 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET – diethyltartrate
DIBAL – diisobutylaluminium hydride
DIPEA – diisopropyletylamine
D–M – Diss–Martin reagent
DMDO – dimetyldioxirane
DMP – dimethylpyrazole
DMPU – 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidine
dba – dibenzylidene acetone
dppb – phosphine[4-diphenylphosphino)butyl]-diphenyl
DTBP – 2,6-di-tertbutylpyridine
Im – imidazole
LDA – lithium diisopropylamide
LiHMDS – lithium hexamethyldisilazide
MOM – methoxymethyl
MsCl – methanosulphochloride
nbd – bicyclo[2.2.1]heptadiene
NMO – 4-methylmorpholine-N-oxide
PMB – *para*-methoxybenzene
PPTS – pyridinium *para*-toluenesulphonate
i-Pr – isopropyl
Py – pyridine
TAS-F – tris(dimethylamino)sulphonium-difluorotrimethylsilicate
TBAF – tetra-*p*-butylammonium fluoride
TBDPS – *tert*-butyldiphenylsilyl
TBHP – *tert*-butyl hydroperoxide
TBS – *tert*-butyldimethylsilyl
TES – triethylsilyl
Tf – trifluoromethanosulphonyl
TIPS – triisopropylsilyl
TPAP – tetra-*p*-propylammonium perruthenate

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