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Plant metabolites of the Siberian flora. Chemical transformations and the scope of practical application

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Contents

I.	Introduction	655
II.	Results of the resource and structural analytical studies	655
III.	Chemical transformations of terpenoids and alkaloids	658
IV.	Practical applications of natural compounds and their derivatives	667

Abstract. The results of studies of some terpenoids, alkaloids and phenolic derivatives isolated from Siberian plants are summarised. The structures of the compounds studied are presented and the chemical transformations of the available terpenoids and alkaloids are considered. Examples of practical application of natural compounds and their derivatives are given. The bibliography includes 131 references.

I. Introduction

Natural compounds of plant origin, namely, secondary plant metabolites, are of interest from the scientific and practical standpoints. A fundamental basis for resource studies lies in taxonomy, determination of the chemical composition of plants and elucidation of the structure of particular components. Often, chemical compounds isolated from plants represent novel classes of chemical compounds, which favours the progress in new fields of organic chemistry. At the same time, many plant metabolites and products of their transformations possess practically useful properties, first of all, various biological activities.

At present, a great body of information on plants as sources of valuable compounds has been collected. Many of these compounds can easily be produced in amounts that meet current demands. The development of efficient methods for the isolation of natural compounds in individual form stimulates the design of new pharmaceuticals and agricultural preparations based on them.

Plant metabolites themselves can be the active principles of drugs. For instance, oriental medicine has long used camphor, which was recommended as an inhalation remedy during plague epidemy in the Middle Ages in Europe. A number of individual natural compounds were introduced into medicinal practice in the 19th century. These are quinine, morphine, strophanthin, *etc*. In the 1950s, drugs based on alkaloids vinblastine and vincristine were introduced into antitumour therapy.

However, at present the search for biologically active compounds is mainly associated with modification of the known plant metabolites aimed at either enhancing the original activity of the chemical compound or obtaining derivatives that exhibit other activities.

For a long time, researchers working at the N N Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, have been investigating the chemical composition of compounds isolated from forest trees and landscape plants of Siberia and Altai. The resource and structural analytical studies are being carried out to reveal plant producents of valuable metabolites and to develop new methods of processing of plant raw materials to isolate individual compounds that are either used in practice or are of interest for the design of chemical structures with novel properties. The structures of the compounds isolated are determined using all available modern physicochemical methods. In the last two decades, the research carried out at the Institute follows a programme that is aimed, on the one hand, at obtaining basic knowledge on the reactivity of three important classes of plant metabolites, namely, terpenoids, alkaloids and phenolic compounds and, on the other hand, at searching biologically valuable derivatives of these classes of compounds. The ultimate goal of these studies is the development of novel pharmaceuticals and environmentally safe pesticides.

The present review reports on the most important results obtained in the studies of secondary plant metabolites of the Siberian flora.

II. Results of the resource and structural analytical studies

In the 1960s, N N Vorozhtsov, the founder of the Novosibirsk Institute of Organic Chemistry (NIOCh), Siberian Branch of the Russian Academy of Sciences, initiated organisation of the laboratory for wood chemistry. The first two decades of studies headed by V A Pentegova gave a great deal of information on coniferous plants growing in Siberia and Far East (pine, cedar, abies, *etc*.) as unique sources of terpene compounds. Chemical compositions of oleoresins, turpentines and extracts including mono-, sesqui- and diterpenoids from several species of coniferae were determined. The results obtained in these studies

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were summarised in a monograph [1] and by right became part of the treasury of knowledge in the domestic and world science of resources and served as the basis of a new research avenue, which is rapidly developed at present.

Particular attention is paid to Siberian plants containing di- and triterpenoids. The interest of chemists and pharmacologists in these compounds is indicated by a number of publications.[2–7] In addition to terpenoids, researchers at the NIOCh study readily available alkaloids and phenolic metabolites present in some landscape plants. The resource and structural analytical studies of the Siberian flora included search for sources of promising plant metabolites, investigations of variation of the composition of the components depending on the species of plants, identification and structural elucidation of individual compounds and the development of optimum isolation procedures. As a result, researchers at the NIOCh created a database that includes the metabolites characterised by the following major features:

— availability of the plant source;

— efficiency of the isolation procedures;

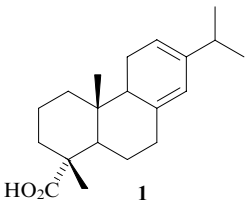
— chemical structure providing great potential for synthetic modification; and

— putative biological activity.

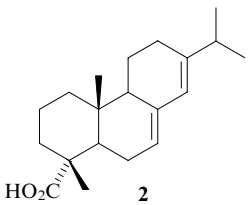
Here we shall consider a number of compounds that are of interest for further investigations isolation of which from Siberian plants relies on well-developed procedures.

1. Diterpenoids

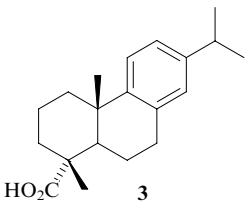
Undoubtedly, levopimaric acid (**1**), abietic acid (**2**) and their derivative, dehydroabietic acid (**3**) are the most available tricyclic diterpenoids. These compounds are isolated from pine resin and oleoresin, being of interest as substrates for targeted chemical transformations and pharmacological studies.[8]



1

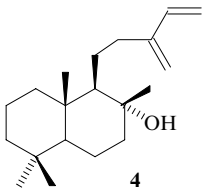


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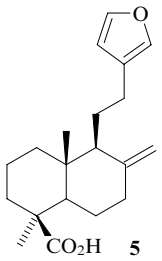


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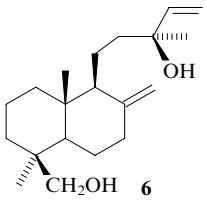
One of the key components of the extractives of pine needles is a labdane-type diterpenoid isoabienol (**4**). Labdanoids containing a conjugated diene system in the side chain are of interest as the starting compounds for the synthesis of fragrances [9] and pharmaceuticals.[10] Yet another labdanoid, lambertianic acid (**5**),[11,12] which can readily be isolated from cedar oleoresin and needles, also exhibits physiological activity. Labdanoids epitorusolol (**6**) and larixol (**7**) can be obtained from oleoresins of the Siberian and Gmelin larch.



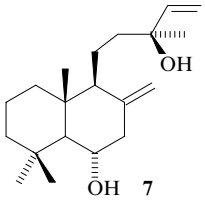
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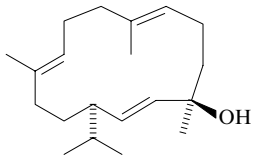


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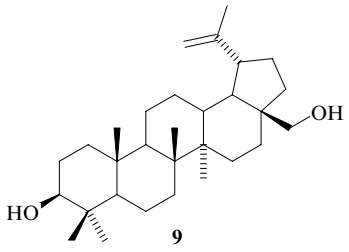
Among monocyclic diterpenoids isolated from the oleoresin of Siberian cedar, macrocyclic cembranoid isocembrol (**8**), a structural analogue of metabolites of marine organisms possessing high antitumour activity,[13] deserves attention.



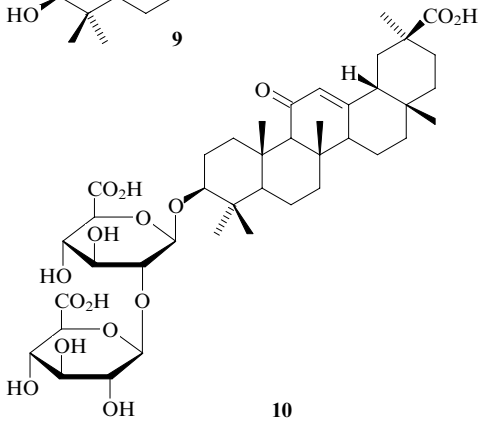
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2. Triterpenoids

As to triterpene compounds, betulin (**9**) isolated from birch bark [5,14] and glycyrrhizic acid (**10**), a metabolite of licorice [6] belonging to oleanane-type glycosides, should undoubtedly be ranked first in the availability and pharmacological potential.

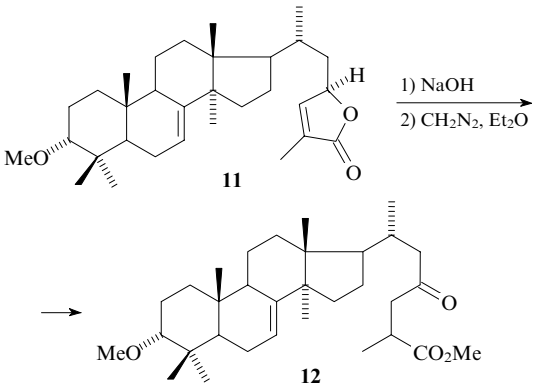


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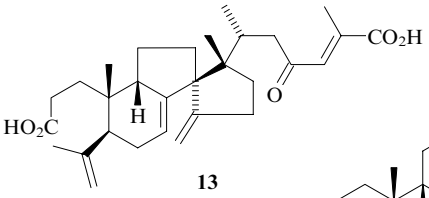
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From the standpoint of plant physiology, Firs (*Abies* genus) differ from Pines, Spruces and Larches belonging to the same botanical family in production of triterpenoids having a modified lanostane carbon skeleton. One of them, namely, abieslactone (**11**) present in bark of many species of Firs, can readily be isolated from extracts of plant raw materials by crystallisation.[15,16] Of particular interest is also an abieslactone derivative **12** with an antitumour activity.[17]

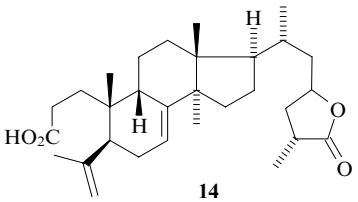


11 **12**

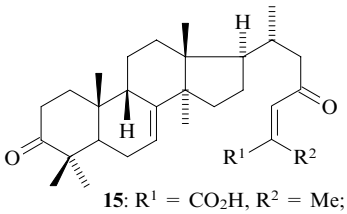
Triterpenoids **13**–**22** produced by Siberian fir (*Abies sibirica* Ledeb.) show structural diversity.[18–31] These compounds can affect the immune status of agricultural plants, thus enhancing their resistance against fungi.



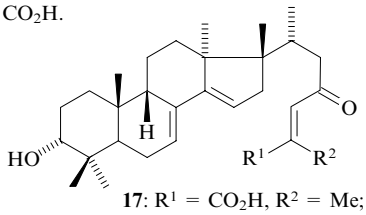
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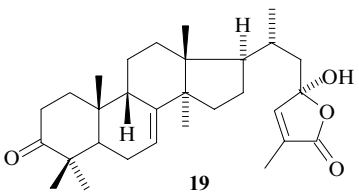
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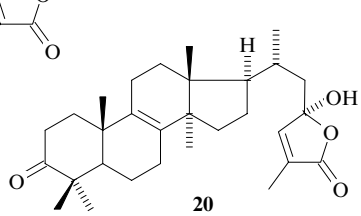
15: $R^1 = CO_2H$, $R^2 = Me$;
16: $R^1 = Me$, $R^2 = CO_2H$.



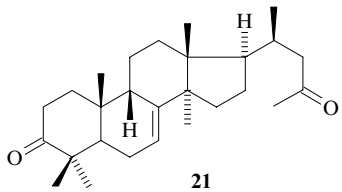
17: $R^1 = CO_2H$, $R^2 = Me$;
18: $R^1 = Me$, $R^2 = CO_2H$.



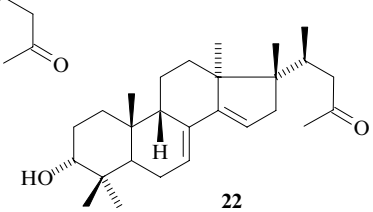
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21



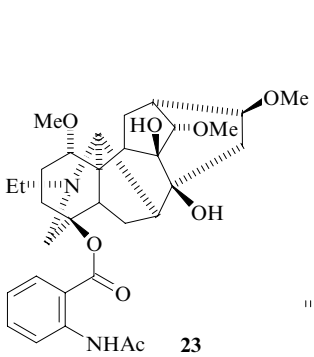
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3. Alkaloids

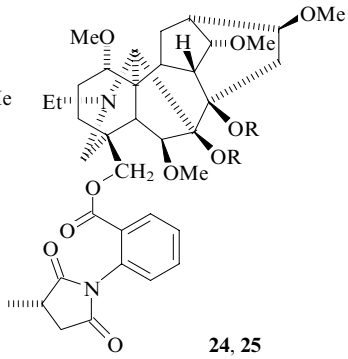
Classical investigations on alkaloids carried out by researchers from the scientific school headed by academician S Yu Yunusov (Uzbekistan) demonstrate a fruitful combination of the resource, taxonomic, structural analytical and processing studies that enabled the progress in medicinal chemistry and pharmaceutical industry. Despite the fact that most of these studies were carried out using Middle-Asian plant raw materials (see, *e.g.*, a review[32]), they played an important role in the studies of Russian alkaloid-containing flora.

The first results of studies on the chemistry, isolation techniques and pharmacological properties of alkaloids from Siberian and Altai plants carried out at the NIOCh clearly demonstrated that the methods and strategies developed by the researchers from Uzbekistan are well applicable for progress in this research avenue. Plants of West Siberia and Gornyi Altai are rich sources of alkaloids many of which also grow in mountain regions of the Middle Asian.

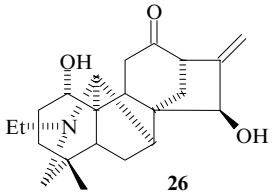
To date, the field and processing investigations made a number of alkaloids including lappaconitine (**23**), methyllicaconitine (**24**), elatine (**25**), songorine (**26**) and berberine (**27**) available for extensive studies.[33–35] For instance, the pilot plant at the NIOCh can produce several kilogrammes of lappaconitine (**23**) annually.



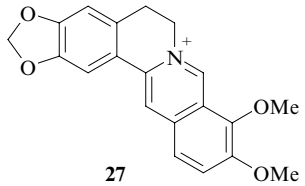
23



24, **25**
R = H (**24**), R–R = CH_2 (**25**)



26



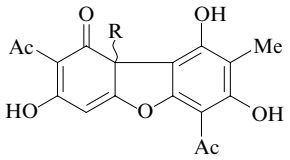
27

Lappaconitine (**23**) isolated from *Aconitum septentrionale* Koelle is the active principle of the anti-arrhythmic drug allapinine.[36] Alkaloids **24** and **25** isolated from *Delphinium retropilosum* Sambuk[34] and *Delphinium elatum* L (Ref. 33), respectively, are agonists of neuronal acetylcholine receptors (*N*-AChRs);[37] the former compound also shows insecticide activity.[38] The antiarrhythmic activity of songorine (**26**) produced by *Aconitum barbatum* Pers.[35] was reported by resear-

chers from Uzbekistan in the 1970s[39] and berberine (**27**) isolated from *Berberis sibirica* Pall. is known as choleretic and antimalarial agent.[40]

4. Phenolic compounds

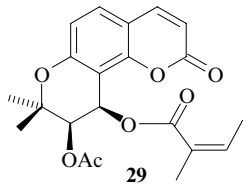
Phenolic plant metabolites represent one of the most important classes of natural bioregulators that can have beneficial effect on the vital functions of organisms.[41–43] Many of them inhibit tumorigenesis and exhibit antiviral (including anti-HIV) and antitubercular activities. Phenolic metabolites of the Siberian flora show a diversity of structural types and have a great resource potential. According to the data obtained by researchers from the Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences,[44] the total amount of larch wastewood permits large-scale production of phenolic metabolites used as substances for biologically active additives. Recent studies carried out at the NIOCh made many phenolic metabolites available,[45,46] first of all, the (+)- and (−)-usninic acids (**28**) isolated from lichens.



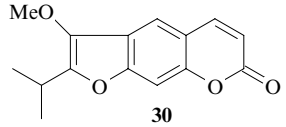
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R = β-Me [(+)-**28**], α-Me [(−)-**28**].

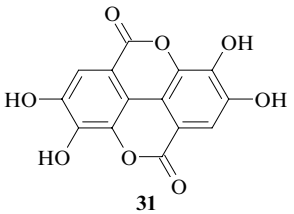
Phenolic compounds also include linear and angular coumarins, which are internal phenol esters. Some Umbelliferrae plants produce (+)-pterixin (**29**)[45] and peucedanin (**30**);[46] *Myricaria dahurica* is a producent of ellagic acid (**31**), a strong protein kinase inhibitor.[47]



29

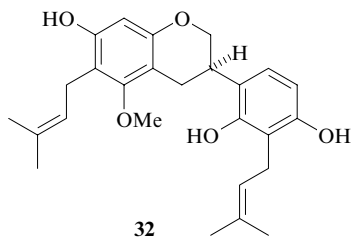


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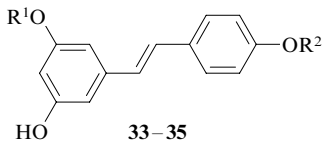


31

Licorice roots are a source of licoricidine (**32**), which exhibits antiulcer and antitumour activity.[48] Cedar bark contains readily extractable resveratrol (**33**), pinostilbene (**34**) and their glycoside derivatives, namely, resveratroloside (**35a**) and pinostilbenoside (**35b**).[49] The therapeutic action of stilbenes **33**–**35** has been comprehensively reviewed.[50]



32



33–**35**

$R^1 = R^2 = H$ (**33**), Me (**34**); R^2 = Glc: $R^1 = H$ (**35a**), Me (**35b**).

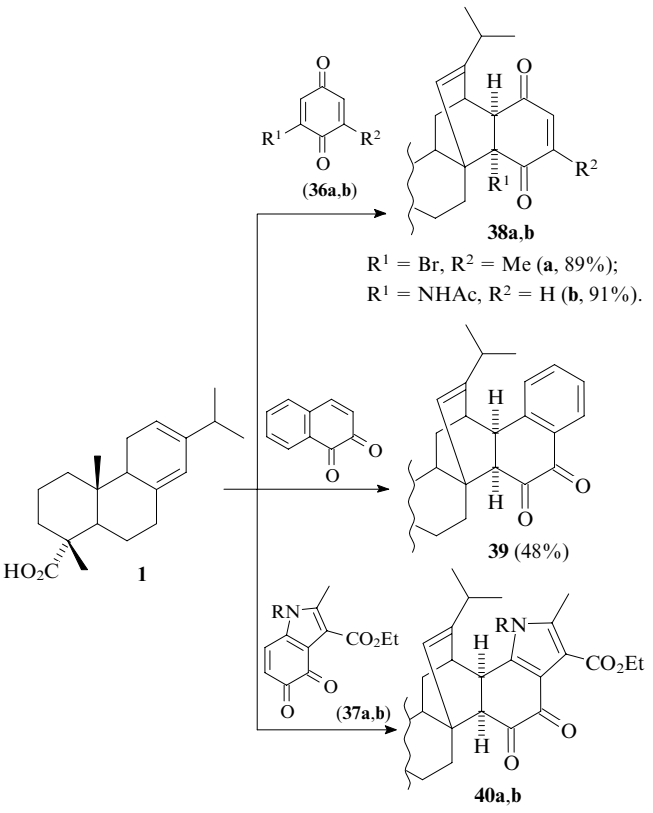
All these phenolic metabolites are considered as promising agents for further modification.

III. Chemical transformations of terpenoids and alkaloids

1. The Diels–Alder (retro-Diels–Alder) reactions

The availability of levopimaric acid (**1**) has made it a subject of synthetic studies. This diterpenoid has two conjugated double bonds and readily reacts with activated alkenes.[51] (Note that the Diels–Alder reaction adducts can be obtained from pine oleoresin containing up to 20% of levopimaric acid). Compound **1** readily reacts with quinone-type dienophiles to give high yields of adducts of unique structures.[52,53] The effect of the dienophile structure on the selectivity of [4 + 2]-cycloaddition was studied taking levopimaric acid as an example. It was established that 2,6-disubstituted benzoquinones **36a**,**b**, 1,2-naphthoquinone and indoloquinones **37a**,**b** add to diene **1** regiospecifically. Regioselectivity of the cycloaddition of asymmetric benzoquinones **36a**,**b** can be explained by the presence of electron-donor substituents (NHAc, Br) in their molecules; this favours the formation of a hydrogen bond between the carboxyl group and the carbonyl oxygen atom in position 1 of the quinone molecule. In addition, stabilisation of this transition state is also due to the shieding effect of the isopropyl group. Levopimaric acid derivatives **38**–**40** can be of interest as the starting compounds for the synthesis of pharmacologically valuable products (Scheme 1).

Scheme 1



38a,**b**

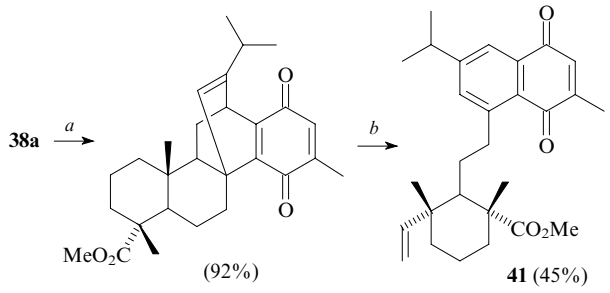
R^1 = Br, R^2 = Me (**a**, 89%);
R^1 = NHAc, R^2 = H (**b**, 91%).

39 (48%)

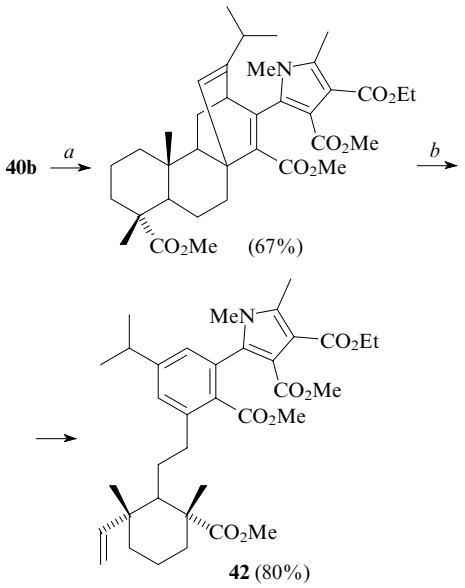
40a,**b**

R = H (**a**, 51%), Me (**b**, 64%).

Of particular interest is the ability of adducts, *i.e.*, bicyclooctadienes, to undergo a retro-diene cleavage. This reaction offers efficient ways for the synthesis of derivatives containing terminal vinyl groups, *e.g.*, 1,4-naphthoquinone (**41**) and pyrrole (**42**).[53]



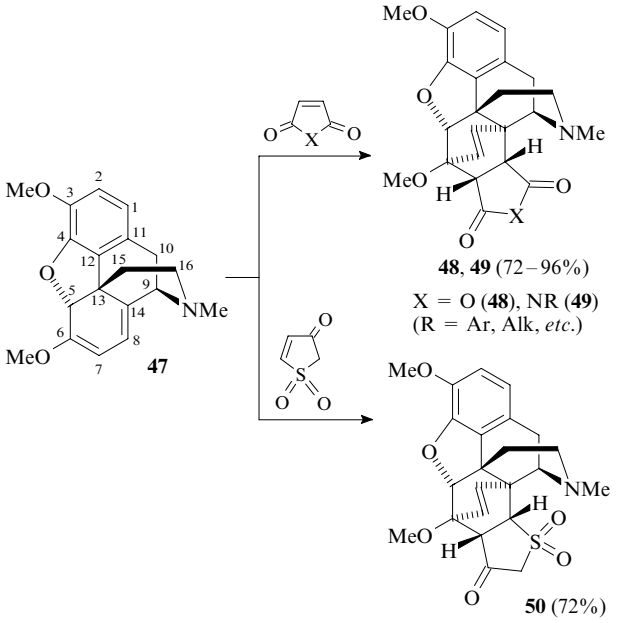
(*a*) 1) CH_2N_2; 2) Al_2O_3, HO^-; (*b*) DMF, 150 °C.



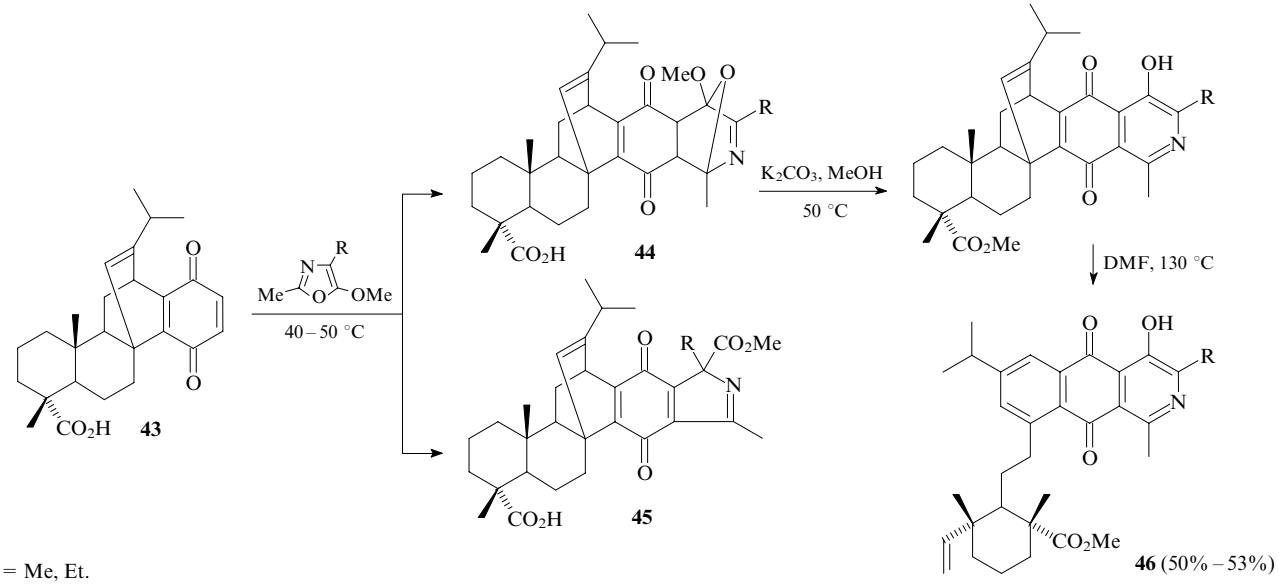
(*a*) 1) H_2O_2, HO^-, 50 °C; 2) CH_2N_2; (*b*) 260 °C.

Quinopimaric acid (**43**) turned out to be a highly reactive dienophile, which readily reacts with silyloxy- and sulfur-containing butadienes and their aza analogues.[54] For instance, the reactions of acid **43** with 5-alkoxyoxazoles (the Kondratyeva reagents) result in two compounds, *viz.*, a Diels–Alder adduct **44** and a 1,3-dipolar cycloadduct **45**.[55] In the latter case, the dipole is likely to be formed upon thermal decomposition of 5-alkoxyoxazole. The results of the reactions of quinopimaric acid (**43**) with alkoxyoxazoles depend on the nature of the solvent. In acetic acid, compounds **44** are the major products (yields 58%–67%), whereas the reactions in an AcOH–MeCN mixture afford adducts **44** (yields 40%–42%) and isoindole derivatives **45** (yields 25%–35%). Further transformations of compound **44** give terpenylazaanthraquinones **46** (Scheme 2).

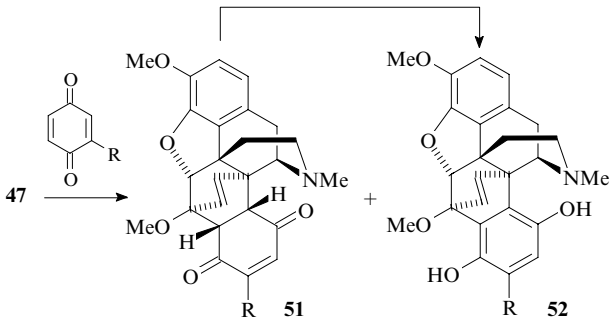
The behaviour of a morphinan-type alkaloid thebaine (**47**) in the Diels–Alder reaction was studied.[56] A new group of thebaine derivatives was synthesised, which includes compounds **48**–**54** containing additional carbocyclic and heterocyclic units.[57–63] Maleimides and maleic anhydride, 2,3-dihydrothiophen-3-one 1,1-dioxide, substituted benzoquinones (or the corresponding hydroquinones in the presence of Ag_2O) and indoloquinones **37a**,**b** served as the dienophiles. The cycloaddition of thebaine (**47**) to cyclic dienophiles results in 7,8-fused derivatives **46** of 6α,14α-ethenoisomorphinans; the reaction is regioselective in the case of non-symmetric dienophiles.



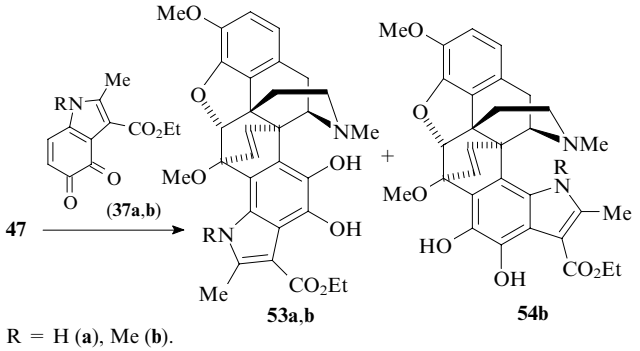
Scheme 2



R = Me, Et.



R = NHAc, SCH_2X (X = CH_2OH, CO_2H, CO_2Me, $CH(NH_2)CH_2OH$).

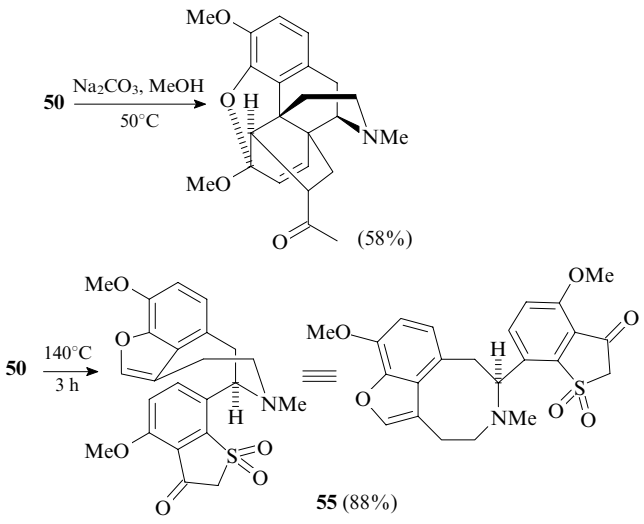


R = H (**a**), Me (**b**).

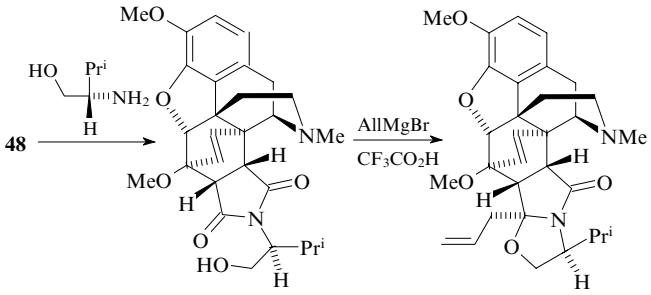
Thebaine (**47**) reacts with substituted benzoquinones (aqueous dioxane, 20 °C) or with a system hydroquinone–silver oxide (MeOH, 20 °C) to give adducts **51** and subsequent fused hydroquinones **52** (yields 75% – 90%). The product ratio varies from 1 : 8 to 1 : 10. Compounds **51** readily isomerise to hydroquinone derivatives **52** under the action of alkaline alumina in CH_2Cl_2 (yields 92% – 98%).

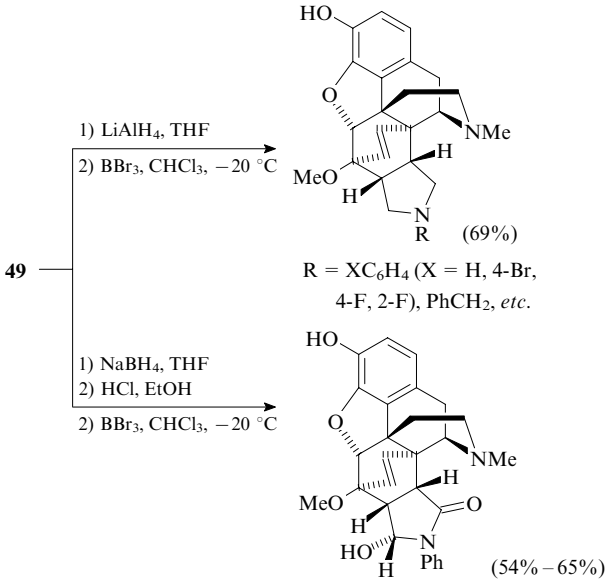
Indoloquinone **37a** adds to thebaine (**47**) in aqueous dioxane with simultaneous aromatisation to a dihydro derivative **53a** (yield 62%). Regioselectivity of the reaction is probably due to stabilisation of the transition state upon the interaction of the NH group in the pyrrole fragment with the methoxy group in position 6. The reaction of *N*-methylindoloquinone **37b** with diene **47** results in products **53b** and **54b** in a 3 : 2 ratio (overall yield 75%).

A thebaine adduct **50** is prone to skeletal rearrangements with elimination of SO_2.[57, 60, 61, 64] For the mechanism of this reaction, see Ref. 57. The retro-Diels–Alder cleavage of compound **50** results in a furobenzoazocine derivative **55**.[58, 61, 64]



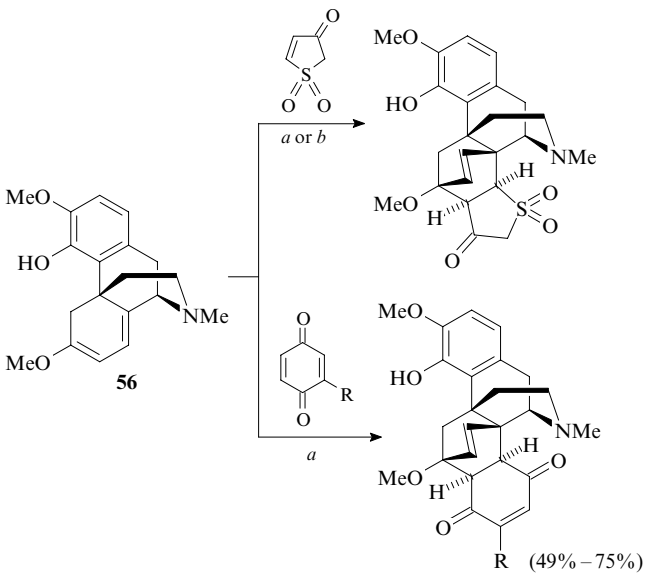
Here we present some transformations[62, 63] of adducts **48** and **49**, which made it possible to synthesise oripavines (promising psychotropic agents) from natural alkaloids.[61, 63]





R = XC_6H_4 (X = H, 4-Br, 4-F, 2-F), $PhCH_2$, *etc.*

Reactions of morphinandiene **56** with a number of dienophiles were also studied. Taking the Diels–Alder reactions of dienes **47** and **56** as examples, the factors affecting the regio- and stereoselectivity of these processes were studied. It was found that introduction of morphinandiene **56** devoid of the dihydrofuran fragment into the reaction changes the stereochemistry of the cycloaddition. This results in 6β,14β-ethenomorphinans.[59, 64]



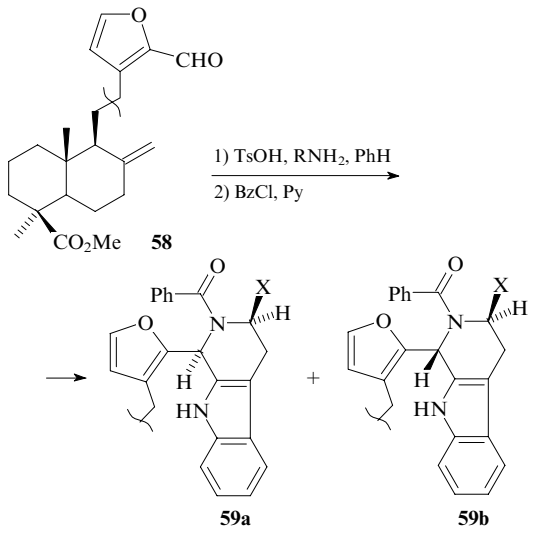
(*a*) aqueous dioxane; (*b*) Al_2O_3, CH_2Cl_2, 20 °C.

R = NHAc, SCH_2X [X = CH_2OH, CO_2H, CO_2Me, $CH(NH_2)CH_2OH$].

2. Diterpenoids in the synthesis of alkaloid-like compounds

Alkaloid-like compounds can be synthesised from structures that can be readily transformed to nitrogen-containing heterocycles. These are, *e.g.*, methyl lambertianate (**57**) and related derivatives.

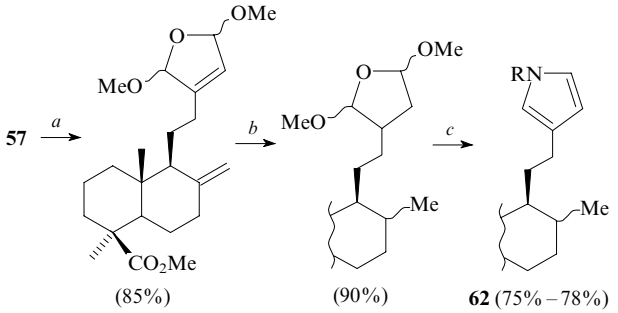
For instance, terpenocarbolines **59a**,**b** were synthesised from methyl 16-formyllambertianate (**58**) using the Pictet–Spengler reaction.[65]



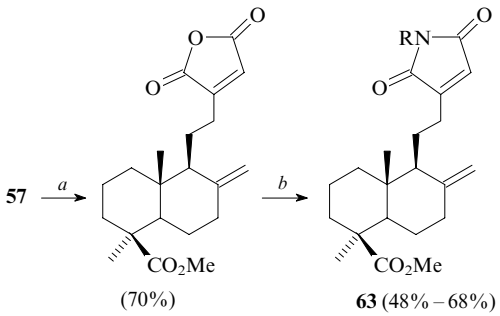
RNH_2 is triptamine, X = H; RNH_2 is L-tryptophan, X = CO_2H.

By choosing selective oxidants affecting different fragments of the molecule of lambertianic acid (**5**), it is possible to obtain various oxygen-containing derivatives suitable for further structural modifications. For instance, the oxidation of methyl lambertianate (**57**) followed by aminomethylation involving the furan ring led to *N*-heterocycles **60** and **61** (Scheme 3).[66, 67]

The synthesis of pyrrolyllabdanoids **62** and **63** from compound **5** has been reported.[68, 69] In the first stage lambertianic acid (**5**) is converted to methyl ester **57** under the action of dimethyl sulfate in ethanol; ester **57** is then oxidised using various reagents. Note that compound **62** was isolated as a 1 : 1 mixture of C(8)-epimers.



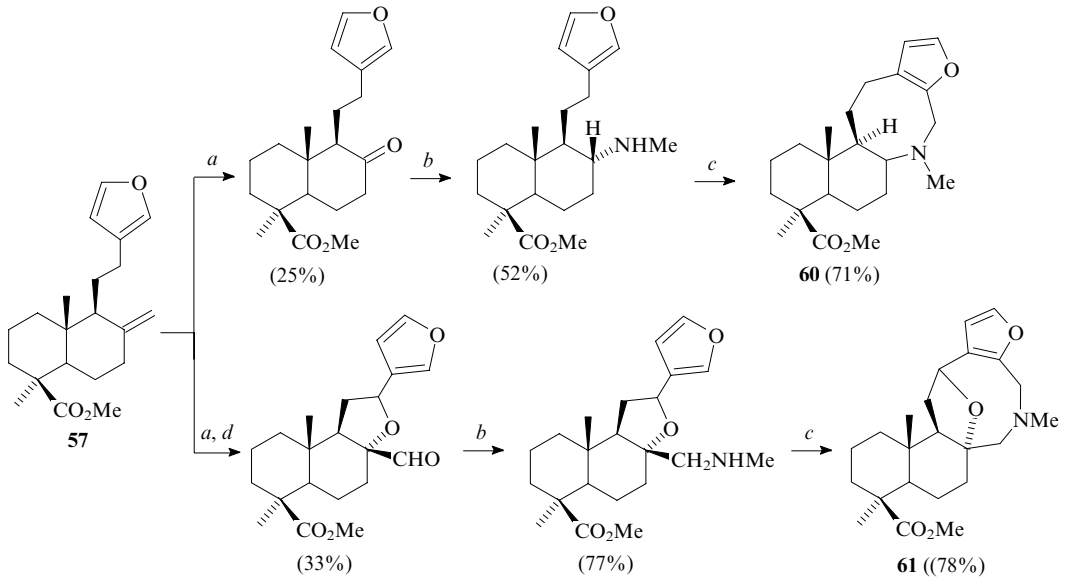
(*a*) $PhSO_2NHCl$, MeOH, 0–5 °C; (*b*) H_2/Ni-Ra, MeOH, 20 °C;
(*c*) RNH_2, AcOH, H_2O, 90 °C, 15 min.
R = Me, Et, cyclo-Pr, Bn.



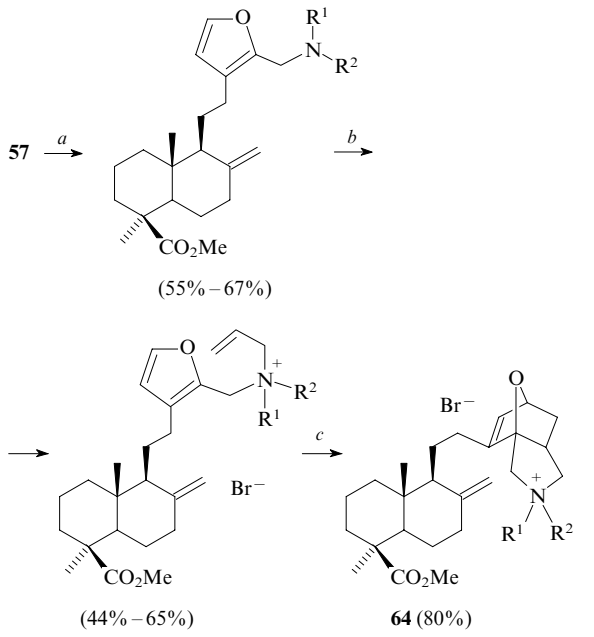
(*a*) CrO_3, H_2SO_4, Me_2CO, 0→20 °C; (*b*) RNH_2, AcOH, 100 °C, 5–8 h.
R = Bn, $(CH_2)_2Ph$, $(CH_2)_2C_6H_4OH$-4, $CH(CO_2H)Et$, $(CH_2)_3CO_2H$.

Synthetic routes to labdane derivatives **64** and **65** containing tricyclic nitrogen-containing fragments starting from lambertianic acid were developed.[70, 71]

Scheme 3

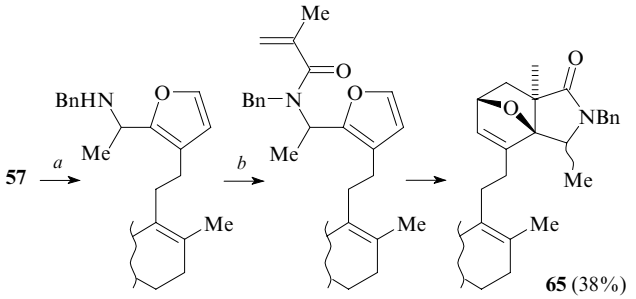


(*a*) $KMnO_4$–$MgSO_4$, PhH, H_2O, Bu^n_4NBr, 50 °C; (*b*) 1) $MeNH_2$, MeOH; 2) $NaBH_4$; (*c*) $(CH_2O)_n$, CF_3CO_2H, PhH, 80 °C;
(*d*) PCC, CH_2Cl_2, 20 °C; PCC is pyridinium chlorochromate.



(*a*) $(Me_2N)_2CH_2$ or *N*-bis(piperidino)methane, AcCl, CH_2Cl_2, 0→20 °C; (*b*) AllBr, PhH, KOH, K_2CO_3, Me_3BnNCl, 80 °C; (*c*) PhH, 80 °C. $R^1 = R^2 = Me$; $R^1–R^2 = (CH_2)_5$.

Alkylation of the amino derivative (step *b*) in acetonitrile as a solvent results in products **64** (yields 54%–58%) without isolation of salt. All stages of the synthesis of compound **65** are characterised by good yields (68%–84%), the last step, heterocyclisation, occurs spontaneously.

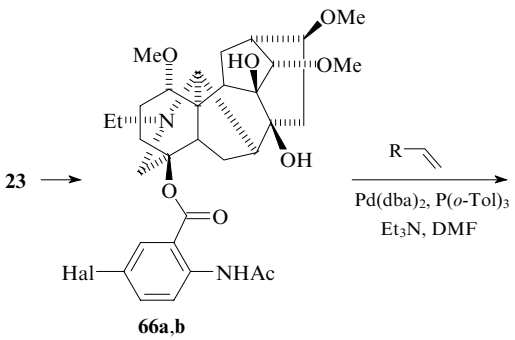


(*a*) 1) TsOH, PhH, 80 °C; 2) $Mg(ClO_4)_2$, Ac_2O, 20 °C; 3) $BnNH_2$, $NaBH_4$, $(Pr^iO)_4Ti$, 0–20 °C; (*b*) Et_3N, $CHCl_3$.

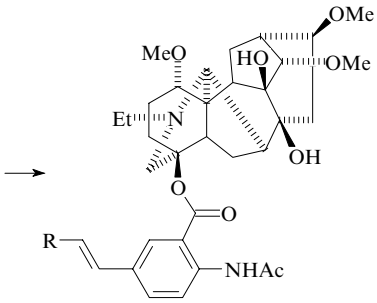
3. Reactions involving metal complex catalysis

The programme of studies on synthetic transformations of some available alkaloids carried out at the NIOCh [72–79] involves metal complex catalysis as a particular research avenue.

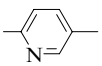
For instance, the aromatic fragment of lappaconitine (**23**) was modified using cross-coupling reactions.[80,81] Procedures for lappaconitine bromination and iodination were also developed, which made it possible to obtain the corresponding 5′-halogeno derivatives **66a**,**b**. Lappaconitine derivatives **67** and **68** containing alkenyl substituents conjugated with the benzene ring were first synthesised by condensation of these halides with ethyl acrylate or 5-vinyl-2-methylpyridine under the Heck reaction conditions.



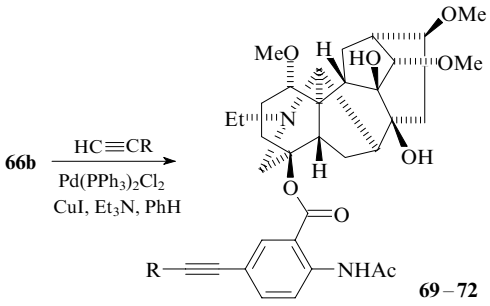
66a,**b**



67, **68** (65–86%)

Hal = Br (**66a**), I (**66b**); R = EtO_2C (**67**), Me  (**68**); dba is dibenzylidene acetone.

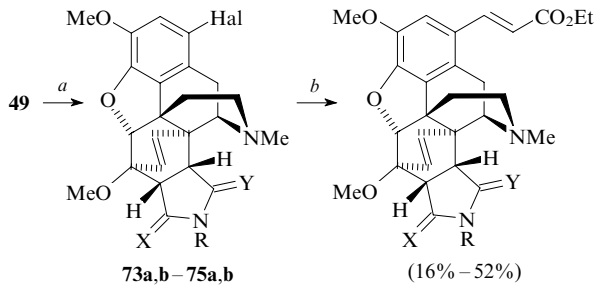
Condensation of 5′-iodolappaconitine **66b** with terminal acetylenes, namely, prop-2-yn-1-ol, 2-methylbut-3-yn-2-ol, phenylacetylene and 5-ethynylpyrimidine under the Sonogashira reaction conditions affords lappaconitine derivatives **69**–**72** containing aklynyl fragments.



69–**72**

R = CH_2OH (**69**), CMe_2OH (**70**), Ph (**71**),  (**72**).

Halogeno derivatives of *endo*-ethenotetrahydrothebaine (**73a**,**b**–**75a**,**b**) and dihydrothebainohydroquinone (**76a**,**b**) also react with various alkenes in the presence of palladium complex catalysts.[82,83] This strategy was used for the synthesis of some C(1)-substituted thebaine derivatives. Succinimido-annulated 1-iodotetrahydrothebaines **73b** are more reactive than pyrrolidine derivatives **74b** in the Heck reaction with ethyl acrylate; the reactions of the former compounds occur under milder conditions and in higher yields.



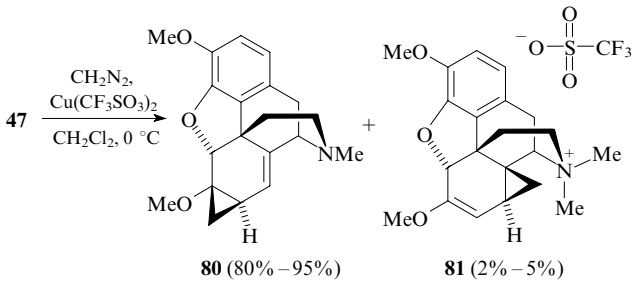
(*a*) Br_2 (or ICl), HCO_2H; (*b*) $CH_2{=}CHCO_2Et$, $Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, DMF.

X = Y = O (**73**); X = Y = H_2 (**74**); X = , Y = O (**75**);

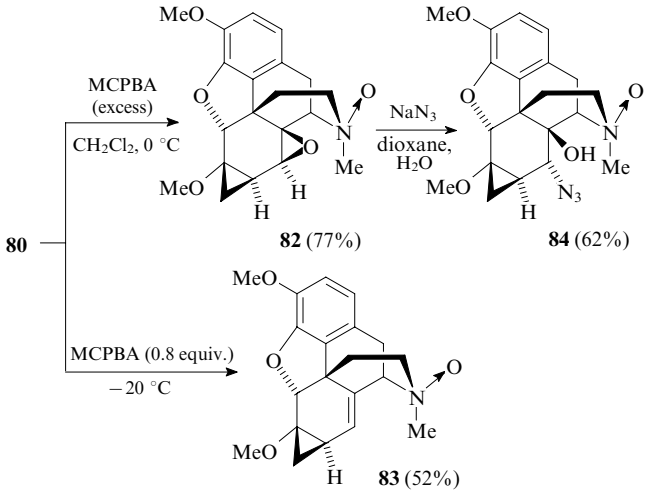
Hal = Br (**a**), I (**b**); R = H, Me, Ph, 4-BrC_6H_4.

The effect of the structure of alkenes (acrylates, 2-methyl-5-vinylpyridine, styrene, alkyl vinyl ethers) on the yield of 1-ethenyl-substituted dihydrothebainohydroquinones was studied. It was found that the reaction of 7,8-(1-acetoxy-4-hydrohybenzo)-1-iodo-6,14-*endo*-ethenodihydrothebaine (**76b**) with ethyl vinyl ether results in an arylation product at α-position of the ethyl vinyl ether molecule, but work up of the reaction mixture gives 1-acetyl-7,8-(1-acetoxy-4-hydroxybenzo)-6,14-*endo*-ethenodihydrothebaine (**77b**) as a result of hydrolysis. 1-[(*E*)-Pyridynylethenyl]dihydrothebainohydroquinone **78b** was used in the synthesis of hybrid structures **79b** containing fragments of indolizine- and isoquinoline-type alkaloids (Scheme 4).

Structural modification of thebaine (**47**) and its 7,8-annulated derivatives (*e.g.*, compounds **49** and **52**) using organometallic compounds made it possible to synthesise novel morphinan derivatives containing substituents at the C(8) and C(1) atoms. For instance, thebaine adds diazomethane in the presence of copper triflate (0.02 – 0.04 mol) to give 6β,7β-methylene-6,7-dihydrothebaine (**80**), a carbene addition product of to the C(6) – C(7) bond. A side reaction product, *N,N*-dimethyl-*N*-nor-8β,14β-methylene-8,14-dihydrothebainium trifluoromethanesulfonate (**81**), formed upon addition of two diazometane molecules to the C(8) – C(14) bond and the tertiary mitrogen atom was also isolated. The structure of compound **81** was established by spectral data and confirmed by X-ray diffraction analysis.[84,85]

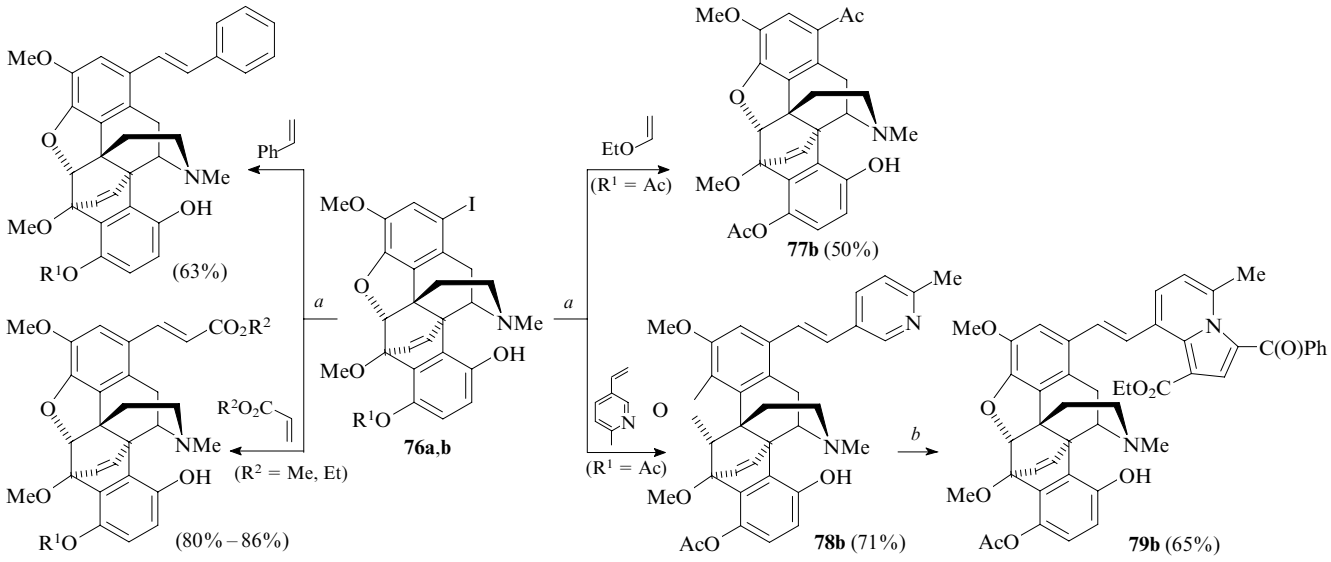


We studied the possibility of synthesis of 8α-substituted derivatives of 14β-hydroxy-6β,7β-methylenedihydrocodeine. For instance, the oxidation of compound **80** with excess *m*-chloroperoxybenzoic acid (MCPBA) in dichloromethane gives 8β,14β-epoxy-6β,7β-methylene-6,7,8,14-tetrahydrothebaine *N*-oxide (**82**).



The reaction occurs under kinetic control. *N*-Oxide **83** can be isolated from the reaction mixture at a reduced temperature using 0.8 equiv. of the oxidant. The epoxide ring opening in

Scheme 4

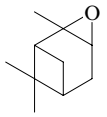


(*a*) $Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, DMF; (*b*) 1) $BrCH_2COPh$, Et_2O; 2) $HC{\equiv}CCO_2Et$, Et_3N, CH_2Cl_2. R^1 = H (**a**), Ac (**b**).

compound **82** under the action of sodium azide in aqueous dioxane gave the 8α-azido derivative of 6β,7β-methylene-7,8-dihydrocodein-14β-ol (**84**).[85]

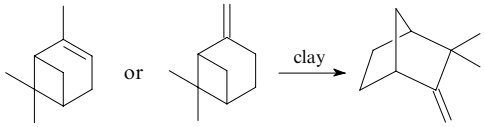
4. Reactions of monoterpenoids in the presence of crystalline aluminosilicate catalysts

Monoterpenoids are widespread in nature. They are produced by Coniferous plants and constitute their oleoresins, turpentines and resins, being also the major components of essential oils extracted from many other plants. Most monoterpenoids are highly reactive compounds and readily undergo various acid-catalysed cyclisation reactions and rearrangements. This often makes selective transformations difficult. For instance, isomerisation and polymerisation reactions occurring upon storage of α-pinene epoxide (**85**) in acid media can result in the formation of more than 200 different products.[86]



85

It turned out that the problem can be solved by carrying out the process under heterogeneous conditions, namely, on crystalline aluminosilicates (zeolites and clays). The first successful example of the use of aluminosilicates in the chemistry of monoterpenes is provided by the development, in the first half of the 20s century, of a large-scale method for isomerisation of α- (**86**) and β-pinenes (**87**) to camphene (**88**) in the presence of clays.[87]



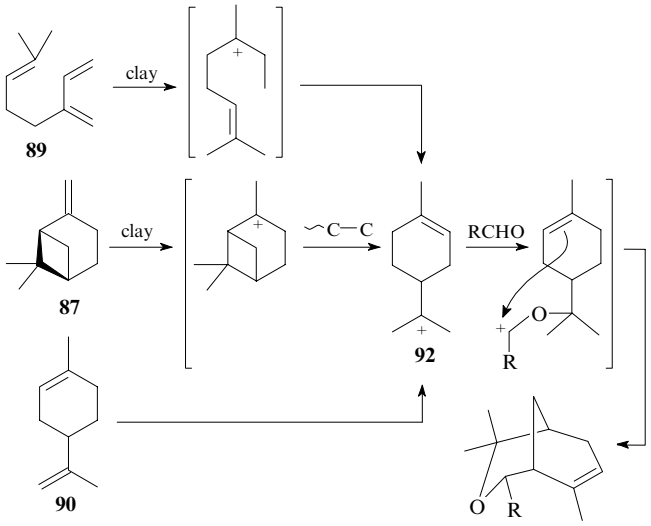
86 **87** **88**

However, systematic studies of the behaviour of terpenoids on crystalline aluminosilicates began only in the early 1990s.[88] It was found that the use of zeolites and clays as catalysts of acid transformations of terpenoids made it possible not only to carry out reactions under milder conditions, enhance reaction selectivity, simplify work up of reaction mixtures and solve the acid waste problem, but also often allows the reactions to follow unusual pathways, which cannot be realised under conditions of conventional homogeneous catalysis.

Intramolecular reactions of terpenoids in the presence of aluminosilicate catalysts have been reviewed in detail;[88–90] therefore, here we only present some examples of intermolecular reactions of monoterpenoids on zeolite and clay supports that were first carried out at the NIOCh. We present the most unusual reactions that demonstrate that the laws of homogeneous catalysis cannot always be directly applied to reactions of labile polyfunctional compounds (including monoterpenoids) in the presence of crystalline aluminosilicate catalysts.

a. Reactions of monoterpenes with carbonyl compounds

Studies of the reactions of some monoterpenes, namely, mircene (**89**), dipentene [(±)-limonene] (**90**) and β-pinene (**87**) with aliphatic and aromatic aldehydes in the presence of natural montmorillonite (askanite–bentonite) clay made it possible to develop a simple and efficient method of synthesis of bicyclic ethers **91** with the 3-oxabicyclo[3.3.1]nonane skeleton.[91,92] The interest in these compounds is due to, *e.g.*, recently found selectivity of binding to estrogen α- and β-receptors.[93] The highest yield of the target product (up to 56%) was attained in the case of β-pinene (**87**).

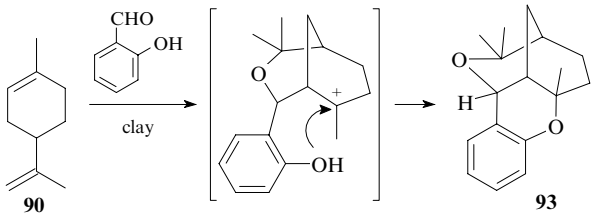


89 **87** **92** **90** **91**

R = Alk, Ar.

A possible mechanism of transformations of the three monoterpenes involves the formation of the same intermediate *p*-menthane carbocation **92**, which then interacts with the aldehyde molecule. It should be noted that α-pinene (**86**), which also forms a tertiary carbocation upon protonation, does not react with aldehydes under these conditions. This is apparently due to specific features of adsorption of monoterpenes **86** and **87** on aluminosilicate.

The reaction of dipentene (**90**) with salicylic aldehyde on clay does not stop after the formation of bicyclic ether.[94] Favourable spatial arrangement of the hydroxyl group in the intermediate carbocation leads to double heterocyclisation resulting in compound **93** with a new tricyclic skeleton.



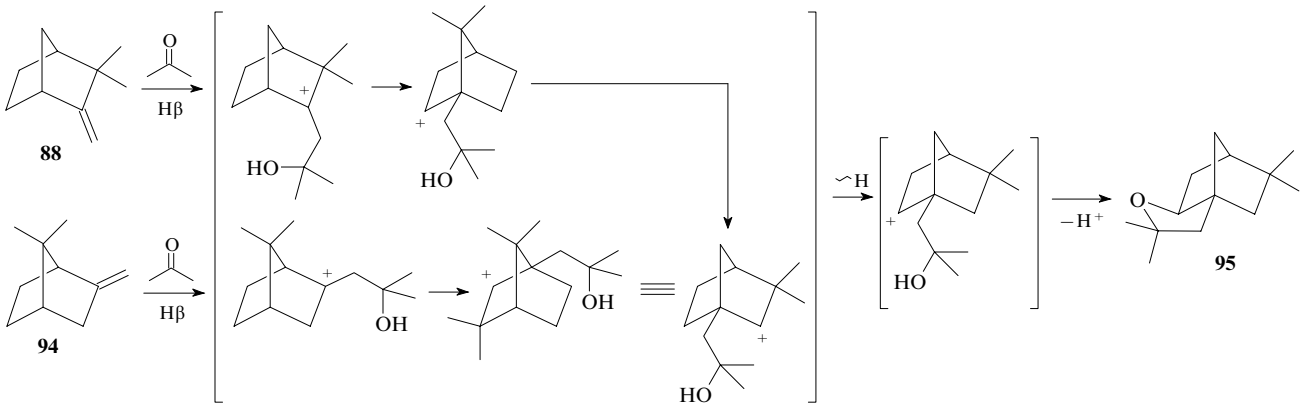
90 **93**

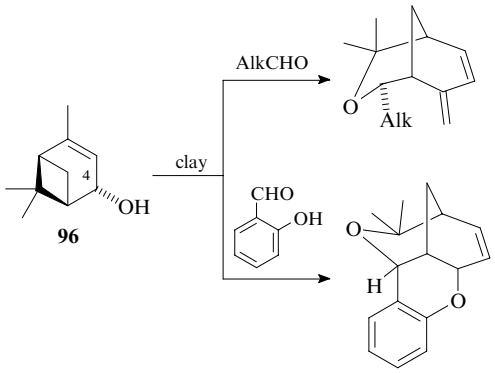
Reactions of (−)-camphene (**88**) and (+)-α-fenchene (**94**) with acetone in the presence of β-zeolite (Hβ) mainly give the same enantiomer of tricyclic compound **95**.[95] The yield and optical activity of the product depend on the solvent used. The best results were obtained for the reaction in CH_2Cl_2 (Scheme 5).

b. Reactions of monoterpene alcohols with aldehydes

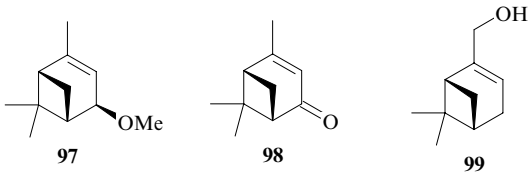
Reactions of aldehydes with natural monoterpene alcohols or hydroxymethylated monoterpenes in the presence of aluminosilicate catalysts result in polycyclic ethers. In particular, *trans*-verbenol (**96**) reacts with aldehydes on montmorillonite to give compounds that are structurally similar to products of β-pinene reactions with aldehydes (see Section III.4.a).[96]

Scheme 5





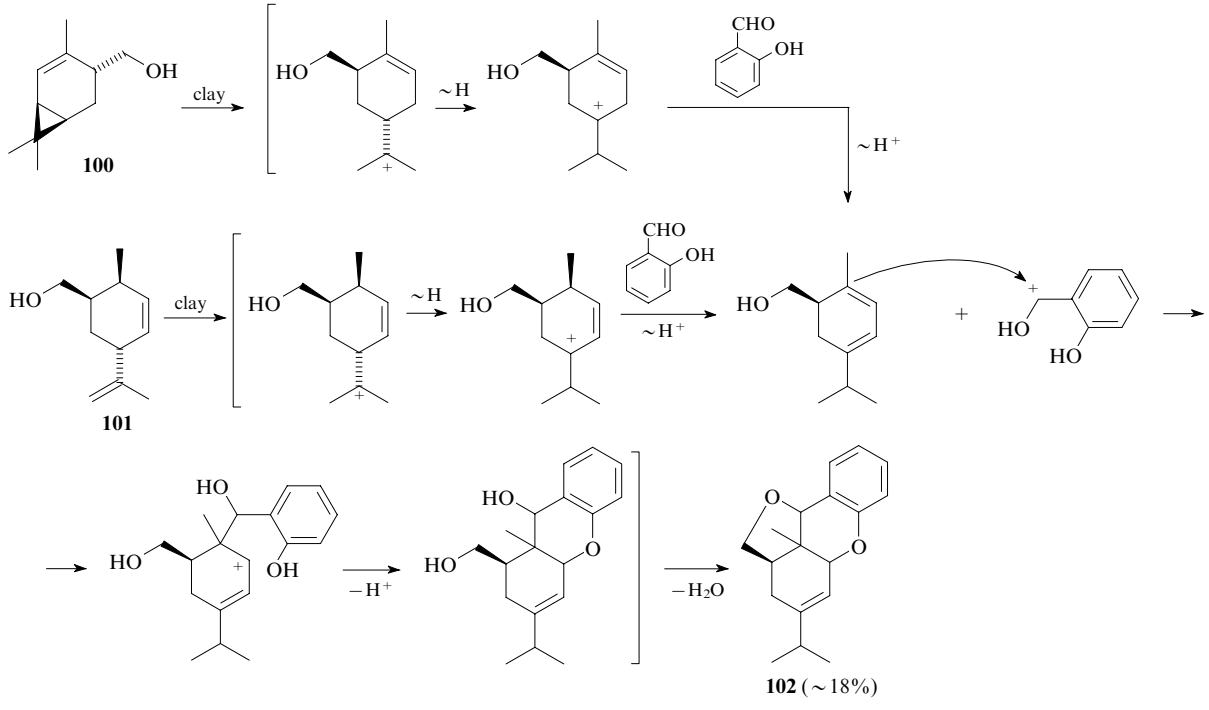
Reactions of *cis*-verbenol and *trans*-verbenol methyl ether (**97**) with aldehydes occur similarly. Therefore, the stereochemistry of the hydroxyl group (including alkylated one) has no effect on the direction of intermolecular reactions; only position of the hydroxyl group in the molecule does matter. Indeed, neither α-pinene (**86**) having no oxygen-containing substituents nor verbenone (**98**) (carbonyl group in position 4) nor myrtenol (**99**) (hydroxyl group in position 10) react with aldehydes on clays.[96,97]



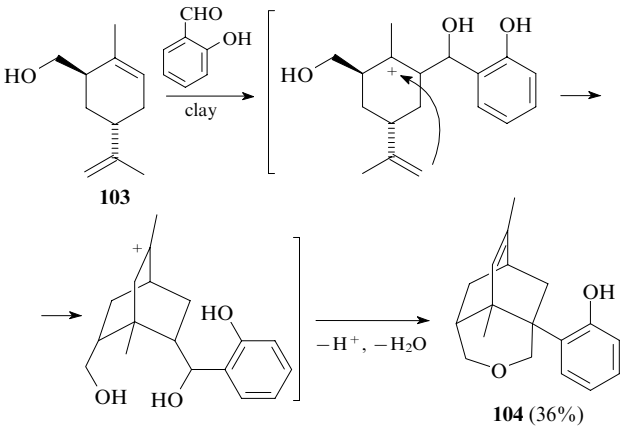
Reactions of 3-hydroxymethyl-2-carene (**100**) or 6-hydroxymethylisolimonene (**101**) with salicylaldehyde in the presence of clay gave a tetracyclic compound **102** with a furo[4,3,2-*kl*]xanthene skeleton.[98] The mechanism of formation of this compound involves a number of carbocationic rearrangements (Scheme 6).

At the same time, the reaction of 6-hydroxymethyllimonene (**103**), a double bond regio isomer of compound **101**, with salicylic aldehyde on clay affords product **104** having a 5-oxatricyclo[5.3.1.$0^{3,8}$]undecene skeleton.[98] Thus, monoterpenes **103** and **90** containing the same *p*-mentha-1,8-diene

Scheme 6



skeleton react with salicylaldehyde in different manner because they bear different functional groups.

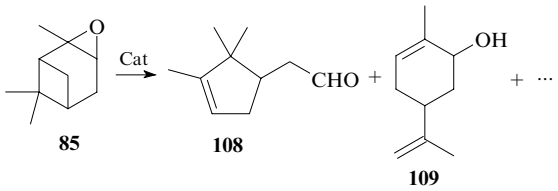


The reaction products of 3-hydroxymethyl-2-carene (**100**) with other aldehydes (α-methylacrolein and butyraldehyde) were also obtained in the presence of clay.[99] It was found that the direction of these reactions depended on the structure of the aldehyde. For instance, the reaction with α-methylacrolein resulted in indeno[1,7-*bc*]furan **105** as the major product. In the case of Pr^nCHO, the reaction involves the addition of two aldehyde molecules to give 6,10-dioxatricyclo[5.4.0.$0^{4,8}$]undecane **106** (Scheme 7). Unlike alcohol **100**, attempts to introduce compound **101** into reactions with other aldehydes failed.

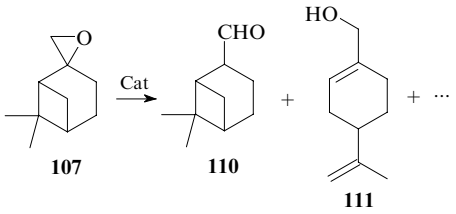
Thus, structurally similar, conformationally labile molecules form different products in the presence of montmorillonite clays.

c. Transformations of monoterpenoid epoxides

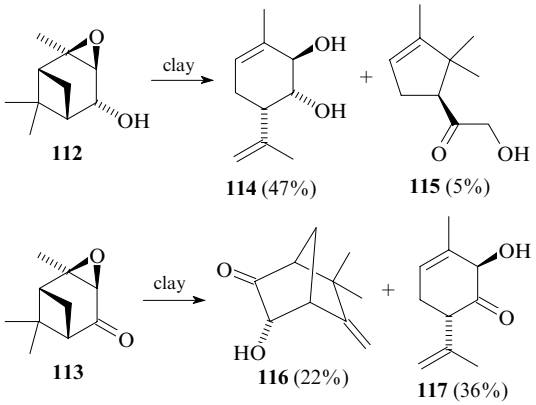
The behaviour of α-pinene epoxide (**85**) and β-pinene epoxide (**107**) in the presence of crystalline aluminosilicates was studied in detail.[88, 100] This is associated with both the availability of the starting compounds and the fact that many reaction products (*e.g.*, campholenic aldehyde (**108**), carveol (**109**),



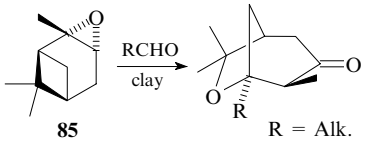
myrtenal (**110**), perillyl alcohol (**111**), *etc.*) are commercially valuable products. The product ratio depends strongly on the nature of the catalysts used (zeolites and clays) and varies over a rather broad range.



Recently,[97, 101] it has been shown that transformations of verbenol epoxide (**112**) and verbenone epoxide (**113**) in the presence of montmorillonite clays gives different products. Moreover, they significantly differ from the products synthesised using conventional homogeneous catalysts (analogues of campholenic aldehyde). For instance, isomerisation of verbenol epoxide (**112**) results in *trans*-diol **114** as the major product, whereas an analogue of campholenic aldehyde **115** was isolated as the minor product.[97] Isomerisation of verbenone epoxide (**113**) on clay afforded α-hydroxyketones with the camphane (**116**) and *p*-menthane (**117**) structures, whereas no campholenic-type products were detected.[101]

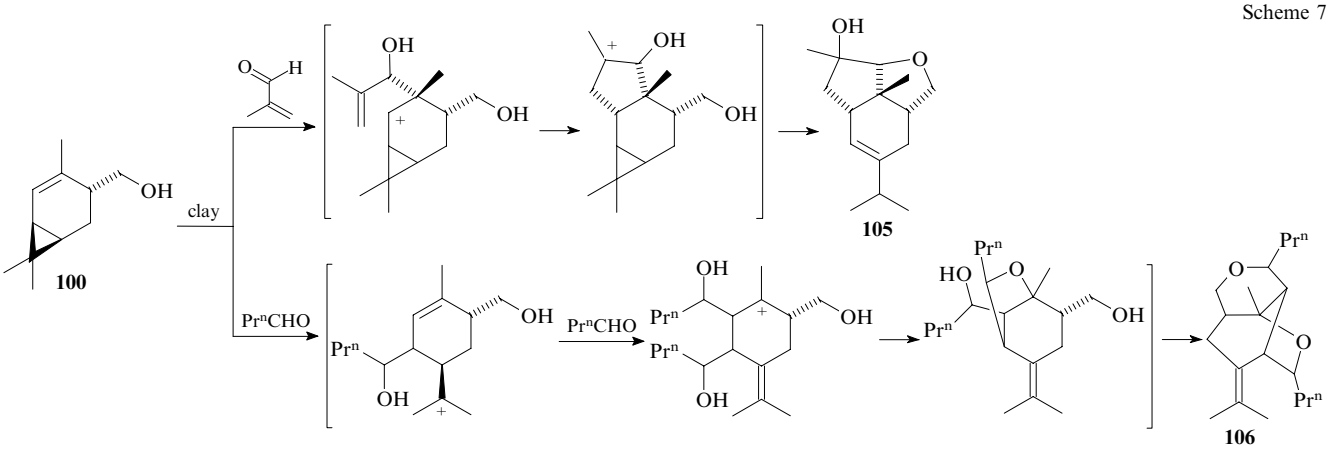


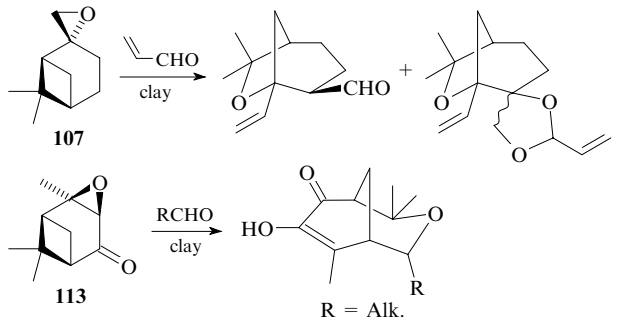
Some epoxides of the pinane series undergo intermolecular reactions with aldehydes in the presence of montmorillonite clays. The products formed on clay in the reacrions of α-pinene, β-pinene and verbenone epoxides (compounds **85**, **107** and **113**, respectively) with aliphatic aldehydes [96, 101] have



the 3-oxabicyclo-[3.3.1]nonane skeleton [see reactions of β-pinene (**87**) with aldehydes] with different reactive functional groups.

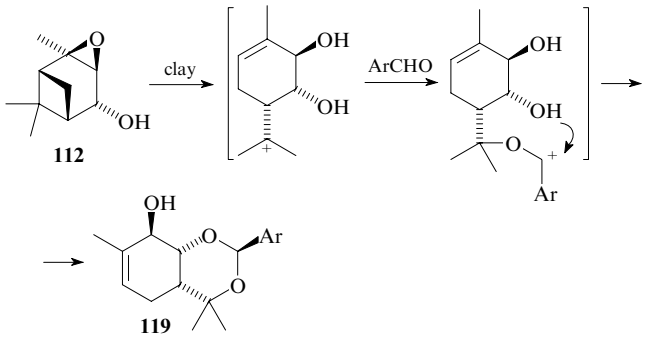
Scheme 7





The reaction of α-pinene epoxide (**85**) with salicylaldehyde [96] led to unexpected results; namely, an unusual tetracyclic ether **118** was isolated as the only product**.** The reaction scheme proposed to explain the mechanism of formation of compound **118** involves more than ten stages (Scheme 8).

Reactions of epoxide **112** with aromatic aldehydes in the presence of clay result not only in products of substrate isomerisation, compounds **114** and **115**, but also heterocycle **119**; the product ratio depends on the structure of the aldehyde.[97] Product **119** has the benzo[1,3-*d*]dioxine skeleton in contrast to the reaction products of other terpenoids with aldehydes (see Section III.4.a), which have the 3-oxabicyclo[3.3.1]nonane skeleton. This can be explained by different reaction mechanisms, namely, heterocyclisation in the last step of formation of compound **119** rather than carbocyclisation in the case of other terpenoids.[96, 97, 99, 101]



Thus, the use of crystalline aluminosilicate catalysts (clays and zeolites) for performing diverse reactions of monoterpenoids significantly extends the synthetic potential of these compounds and allows easy access to heterocyclic systems that are difficult to obtain. In addition, transformations of terpenoids occur with retention of optical purity under these conditions.[88, 97, 101]

Note that most reactions presented above do not occur in the presence of conventional homogeneous catalysts. Therefore, the aluminosilicate catalysts not only play the role of the acidic reagent, but also determine the mutual arrangement of the reactants and the site where the cationic centre appears. Because of this, even relatively small changes in the structure of the terpenoid or reagent can cause significant changes in the direction of the reaction.

IV. Practical applications of natural compounds and their derivatives

Studies in the properties of plant metabolites gave practically valuable results. Both natural compounds and their derivatives have found applications in agriculture and medicine.

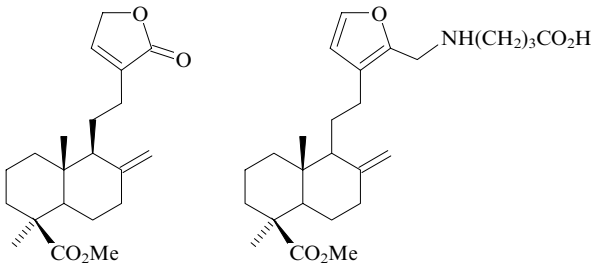
1. Triterpene acids isolated from fir as the basis for fungicides

Triterpene acids isolated from fir wood green enhance the stability of cotton-plant, crops and vegetables. A mixture of triterpene acids produced in a pilot plant [102–104] served as the basis for the preparation 'Novosil'. This has passed the Russian Federation State tests and was certified in 1995 as a plant growth regulator.[105–107] Its positive complex effect on plants consists in an increase in yield by 10%–30%, 2–4-fold enhancement of plant resistance to bacterial and fungal diseases, enhancement of freezing tolerance and drought resistance of plants and acceleration of ripening.[108]

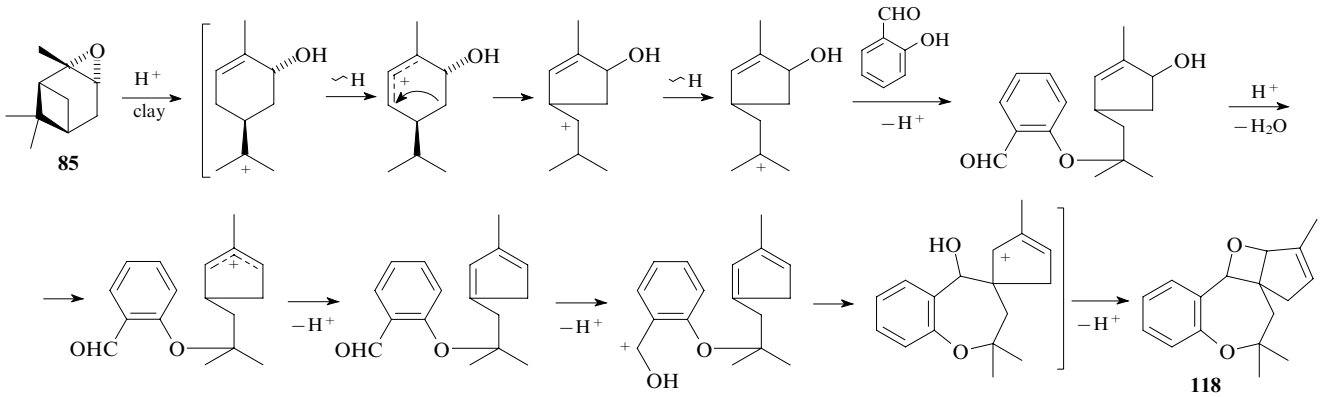
2. Pharmacological properties

a. Diterpenoids

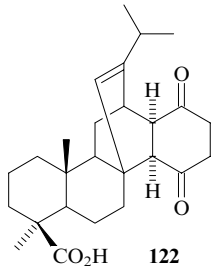
Two derivatives of lambertianic acid (**5**), namely, pinusolide (**120**) and a diterpene derivative of γ-aminobutyric acid **121** show pronounced physiological action. Pinusolide, an inductor of apoptosis, is active towards cells of juvenile lymphoblastic and mieloid leukemia,[109] while compound **121** exhibits nootropic activity determined from the rate of dissipation of conditioned passive avoidance reflex and from the degree of the anxiolytic effect.[110, 111]



Scheme 8



Levopimaric acid is the starting material for the synthesis of dihydroquinopimaric acid (**122**), which shows antiulcer activity, which compares well with modern drugs (*e.g.*, Venter).

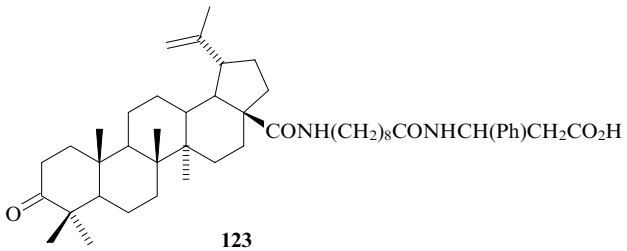


122

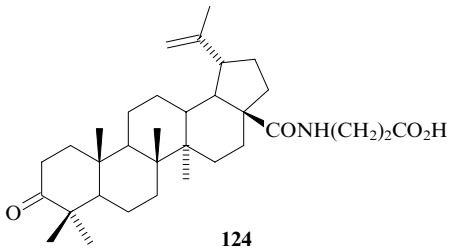
b. Triterpenoids

Among triterpene compounds, the most active are betulonic acid derivatives. For instance, betulonic acid-derived dipeptide **123** is a new HIV integrase inhibitor[112] and inductor of apoptosis of malignant cells.[113] At present, pre-clinical anti-HIV trials of this preparation are in progress.[114, 115]

Betulonic acid alanylamide **124** shows antioxidant action and is considered to be a promising corrector of toxic effects in cytostatic chemotherapy.[116–118]



123

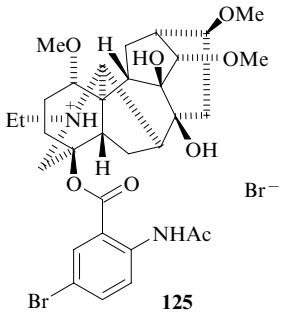


124

Glycyrrhizic acid (**10**) has been the subject of considerable attention of researchers for long. A particular manifestation of the physiological actvity is the complexation with various drugs, which ensures reduction of the therapeutic dose of the drug.[119–122]

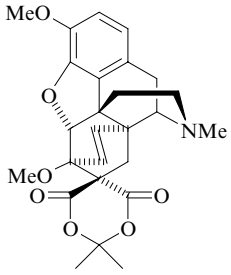
c. Alkaloids

Modification of diterpene alkaloids made it possible to synthesise novel derivatives of lappaconitine (**23**), which exhibit a much higher anti-arrhythmic activity compared to the well-known drug allapinine.[123, 124] An example is provided by 5′-bromolappaconitine hydrobromide (**125**). When introduced in a dose equal to one-tenth of the therapeutical dose of allapinine, compound **125** prevents the development of calcium chloride- and adrenaline-induced arrhythmia, being 4.8 times less toxic than allapinine.[124]

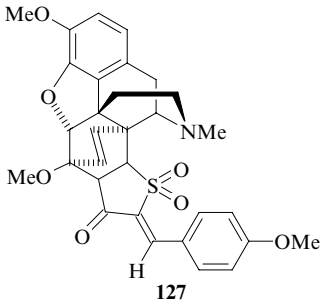


125

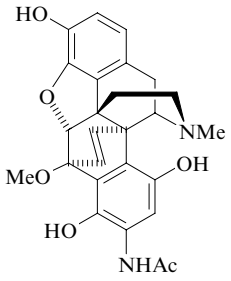
A number of highly efficient analgesics possessing no adverse effects typical of morphinans[63, 125–127] were synthesised from thebaine (**47**). Among the annulated morphinan derivatives, mention may be made of compounds **126**–**129**.



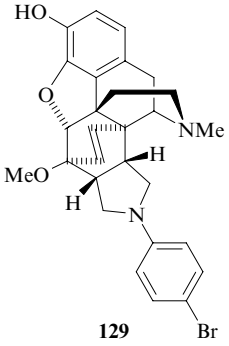
126



127



128



129

Compound **126**, in a lipophilic transport form, acts as blocker of pain caused by all types of stimulators. The ED_{50} value was 0.02 mg kg^{-1} for the electric pain stimulation model, 0.07 mg kg^{-1} for the hot-plate model and 0.009 mg kg^{-1} for the acetic acid writhing (AAW) model. These data characterise compound **126** as a μ-receptor agonist.[126] Compound **127** is a threefold times more efficient pain blocker for the AAW model. The effect of physical and visceral pain control was also observed upon introduction of compound **128**. In the dose corresponding to ED_{50} it only slightly changes the heart rate and has no effect on the bronchomotor tone in cats.[127] A morphinan derivative **129** shows a prolonged analgesic action on physical pain models.[63]

* * *

The material presented above shows that intensive developmemt of chemistry of low-molecular-mass plant metabolites is being continued. These compounds are important not only as

representatives of various structural types and information carriers in chemotaxonomic studies, but also as precursors for the synthesis of many valuable products and design of original drugs, cosmetics and agricultural preparations. At present, the available terpenoids and phenolic compounds are first of all used for directed synthesis of complex carbocyclic and heterocyclic structures. Recently, there have been increasing studies on transformations of those alkaloids, which in the native forms are of limited use in medicine owing to high toxicity or pronounced adverse effects. Considerable attention is paid to medicinal chemistry-oriented transformations of the metabolite classes described above (search for novel leader compounds and optimisation of their structures; fragment-oriented ligand design), as reported in recently published reviews.[2, 128–131]

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