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RECENT STUDIES OF (+)-3-CARENE TRANSFORMATIONS WITH THE RETENTION OF THE NATIVE FRAMEWORK

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Abstract. This review presents last decade and some past especially relevant studies in the field of (+)-3-carene synthetic transformations. The paper discusses exclusively the transformations of (+)-3-carene, proceeding with the retention of the native bicyclic carbon skeleton. The data concerning the features of epoxidation and oxidation reactions of (+)-3-carene, the synthesis of sulphur- and selenium-containing derivatives and their use in asymmetric synthesis are given. It also describes methods for producing amino derivatives of (+)-3-carene, substituted heterocycles based on it, reactions for the preparation of aziridines, azido-alcohols and azidoamines, as well as chiral phosphites as bidentate ligands.

Keywords: (+)-3-carene, epoxidation, sulphide, aminoalcohol, azidoalcohol, aziridine.

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List of abbreviations:

NBS	*N*-bromosuccinylamide
DMSO	dimethylsulphoxide
DBU	diazobicycloundecene
Py	pyridine
m-CPBA	m-chloroperbenzoic acid
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
THF	tetrahydrofuran
cat.	catalyst
atm.	atmosphere
DABCO	diazobicyclooctane
MS	molecular sieves
CAT	chloroamide-T hydrate
PTAB	phenyltrimethylammonium tribromide
ee	enantiomeric excess
acac	acetylacetone

Introduction

Plant metabolites extracts remain promising and interesting for medicine as evidenced by recent studies [1-8]. Thus, one of the main components of conifers' turpentine – (+)-3-carene or (1*S*,6*R*)-3,7,7-trimethylbicyclo[4.1.0]hept-3-ene **1** (Figure 1), has been discovered to have a positive effect on bone mineralization with reduction of devastating effects of osteoporosis [9]. Moreover, as an acetylcholinesterase inhibitor, it has also been proposed for the treatment of Alzheimer disease [10,11].

One of the promising areas of creation of new chemical compounds, including drugs, is the transformation of plant metabolites, which allows them to enhance or change their original properties [12,13].

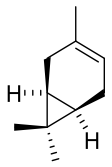

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Figure 1. (+)-3-carene.

In the last decade, the number of papers dedicated to the study of reactions proceeding with the preservation or modification of the natural carbon skeleton of **1** has increased [14]. Examples of the construction of bicyclo[4.1.0]heptanes in cycloaddition reactions and cycloisomerization of aliphatic compounds are also described, however, in some cases, the obtained products represent racemic mixtures [15-17].

The literature on the directed synthesis of optically active derivatives of 3,7,7-trimethylbicyclo[4.1.0]heptane was previously summarized [14,18,19]. Data on skeletal rearrangements of substances that occur *via* ionic or radical rearrangements of the carane series are also discussed in [20-22]. In this review, we will consider the ways of functionalization of **1**, described in papers of the last decade with preservation of the bicyclic carbon skeleton.

The review of the chemical transformations of **1** begins with an analysis of the work on the synthesis of monosubstituted caranes. Next, methods for obtaining of disubstituted caranes are discussed. Moreover, different transformations of mono- and disubstituted caranes into derivatives with different cycle size and heteroatoms will be presented.

Background

Monosubstituted caranes and their transformation pathways

α-3,4-Epoxycarane **2** and *β*-3,4-epoxycarane **3** (Figure 2) are saturated three-membered heterocyclic compounds that contain an oxygen atom in the cycle and have long attracted the attention of researchers as useful building blocks in organic synthesis [14]. In this regard, the development of selective methods for the preparation of isomeric oxides **2** and **3** still remains relevant.

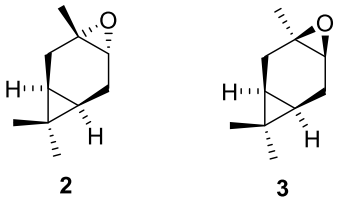


Figure 2. 3,4-Epoxycaranes.

Compound **2** is synthesized using peroxycarboxylic acids that attack the double bond of **1** from the less obstructed side, opposite to the gem-dimethyl group, giving predominantly isomer **2** [14,23,24].

An example of monoterpene **1** oxidation with a mixture of sodium periodate and dehydrocholic acid sodium salt in aqueous acetonitrile at room temperature is described in the literature [25].

In the case of oxidation with H_2O_2 catalysed by transition metals, the formation of epoxides is also observed. As a first example, the system polyoxometalate/Mn(III) porphyrin in combination with ammonium acetate can be mentioned [26]. The authors found that metalloporphyrin is the most active catalyst that is protected from degradation by polyoxanions.

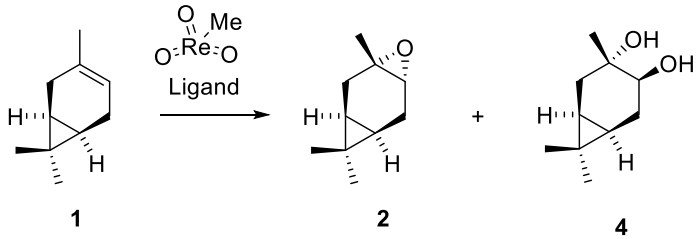
Monoterpene **1** oxidation process using a catalytic system: 60% hydrogen peroxide (1.3 eq.), Na_2WO_4 (0.04 eq.) with $PhP(O)(OH)_2$ (0.02 eq.) in the catalytic system, $[Me(n\text{-}C_8H_{17})_3N]$ HSO_4 (0.04 eq.) and NaOH (0.04 eq.) at room temperature for 12 hours resulted epoxide **2** with 87% yield [27].

The reactivity of methyltrioxorhenium in the epoxidation of olefins is associated with the presence of Lewis bases such as *p*-methoxyaniline, 2-aminomethylpyridine and *trans*-diaminocyclohane as ligands, a large excess of which is required to achieve high yields and selectivity of the process carried out in a CH_2Cl_2/CH_3CN with a 35% hydrogen peroxide solution (Scheme 1) [28].

Along with epoxide **2**, the formation of diol **4** was also observed in a 1:1 ratio with a total yield of 93%.

In order to eliminate this disadvantage, microencapsulation has been implemented. Microencapsulated Lewis base adducts of methyltrioxorhenium with nitrogen-containing ligands (2-aminomethylpyridine, 1,2-diaminocyclohexane) have been shown to be more effective. In the case of 4-methoxyaniline, the selectivity of the formation of substances **2** and **4** increased (amounted to 58% and 29%), while with the use of 2-aminomethylpyridine, the yield increased to 91% and 3%, respectively. During the transition to 1,2-diaminocyclohexane, an exclusive formation of *α*-3,4-epoxycarane **2** was observed (yield up to 98%).

Another group of researchers proposed an aqueous system of H_2O_2/*tert*-butyl acetate/ dimethyldecylammonium WO_4/ dimethyloctylammonium H_2PO_4/ dimethyloctylammonium HPO_4 for epoxidation of **1** [29]. As in the case of [28], the formation of the epoxide **2** mixture with diol **4** is detected in the ratio of 9:1.



Scheme 1. Epoxidation of monoterpene 1 with methyltrioxorhenium [28].

A similar result was recorded using the catalytic system $Na_2WO_4 \cdot 2H_2O$, $[(n\text{-}C_8H_{17})_3\text{-}NCH_3]$ HSO_4, and a 30% H_2O_2/phosphate buffer (obtained by mixing 0.1 M H_3PO_4 solution in H_2O_2 and 0.1 M NaH_2PO_4 solution in H_2O_2, in a ratio of 7:3) / Na_2SO_4 [30]. The oxidation system $[PO_4\{WO(O_2)_2\}_4]_3$/ imidazole/30% H_2O_2/aqueous acetonitrile [31] showed even lower selectivity (85%). It has been established that a mixture of Na_2WO_4, $[Me(n\text{-}C_8H_{17})_3N]HSO_4$, and $PhP(O)(OH)_2$ catalyzes epoxidation of **1** by H_2O_2 with the involvement of 0.3 equivalent of Na_2SO_4 [32].

The formation of product **4** during the epoxidation reaction with 35% aqueous H_2O_2 catalyzed by methyltrioxorenium was avoided by adding 1-methylimidazole to the reaction mixture [33]. The yield of the target epoxide **2** was 94%. The formation of **2** with a 79% yield was observed in the case of use of a mixture of ionic liquid $[Emmim]PF_6/H_2O_2$/CuCl complex with Schiff base (salicylic aldehyde with 2-hydrazinylpyridine) as oxidant [34]. The formation of 100% pure epoxide **2** with 88% conversion of the starting **1** within 24 hours was detected under microwave irradiation of the mixture of tris(pyrazolyl)methane molybdenum tricarbonyl complex with an excess of *tert*-butyl hydroperoxide in a solution of 1,2-dichloroethane at a temperature of 50°C [35]. A similar ratio of the reaction product and the conversion of the starting olefin using hexafluoroacetone as a catalyst and a solution of 60% H_2O_2 in 1,1,1,3,3,3-hexafluoroisopropanol was observed by the authors of another work [36]. In conclusion, it should be mentioned that under production conditions **1** is oxidized to **2** (yield 93%) by pinane hydroperoxide in the presence of molybdenum catalysts [37].

We also presented protocols for exclusive formation of *α*-oxide **2** *via* reusability of the catalytic system using nano-powder alumina as a heterogeneous catalyst and hydrogen peroxide as an oxidant [38]. As far as the oxidation reaction is concerned, employment of hydrogen peroxide as the oxidant agent offers several advantages: it is relatively cheap and environmentally friendly, since water is obtained as a by-product. (+)-3-Carene is converted to the *α*-oxide **2** with selectivity up to 98%, if an 8-10% solution of hydrogen peroxide in ethyl acetate and nano-powder alumina (2-4 nm) is present [39].

Bromonium electrophile, generated from bromosuccinimide, first attacks the olefin **1** from the less difficult to access side, after which the anti-nucleophilic attack of water passes to the more difficult side of the molecule. Cocker, W. *et al.* used this model to establish the stereochemistry of *β*-3,4-epoxycarane **3**, which was synthesized *via* bromohydrin **5** with a total yield of 70% in two stages (Scheme 2) [40].

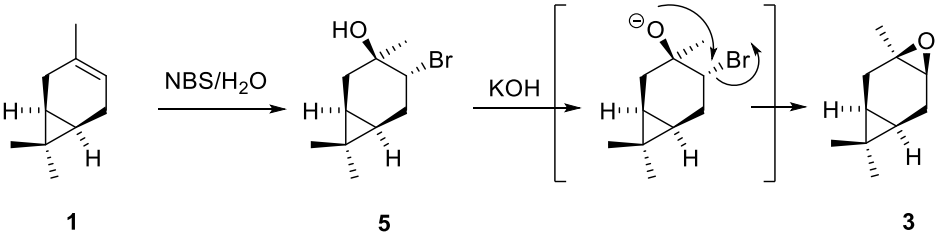
The formation of oxide **3** in trace amounts (4%) was observed during the oxidation of **1** with H_2O_2 catalysed by $[Ni_{0.63}Al_{0.37}(OH)_2](NO_3^-)_{0.27}(WO_4^{2-})_{0.05} \cdot 0.66H_2O$, while the main product was **5**. It was shown that 99% pure of the isomer **3** was isolated when treating the latter bromohydrin with NaOEt, but the authors did not indicate the total yield of the target product.

Olefin **1** can be converted in 73% yield to *β*-3,4-epoxycarane **3** under the conditions of the one-pot method by successively adding NBS and DBU to a solution of substance **1** in DMSO [41].

A scheme has been developed for the conversion of caranol **6** to diselenide **8** through tosylate **7** (Scheme 3) [42].

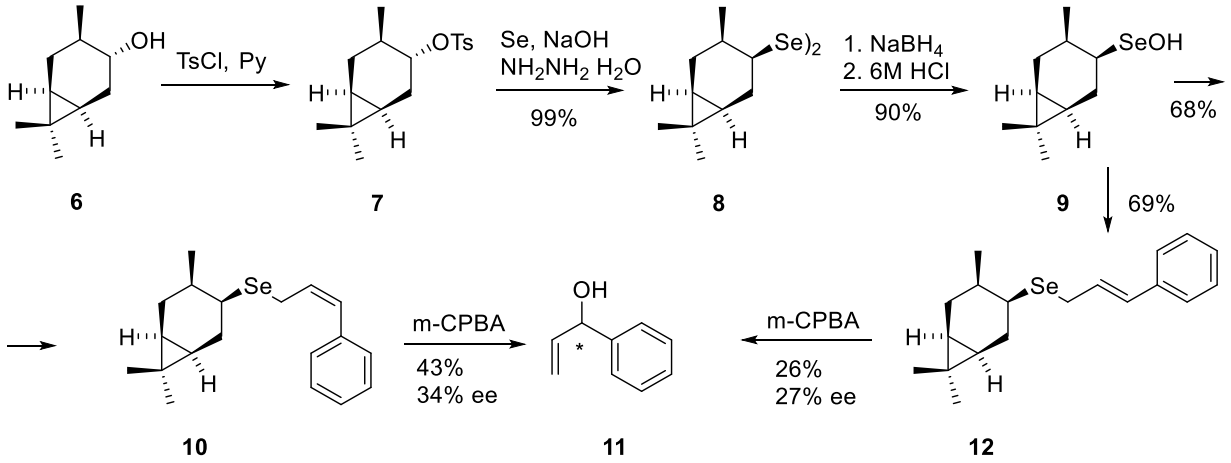
Low-temperature alkylation (-26°C) of selenol **9** with isomeric 3-chloroprop-1-enyl benzenes using *n*-BuLi as a base made it possible to synthesize selenides **10** and **12** with a yield of 68% and 69%, respectively. The latter upon oxidation with meta-chloroperbenzoic acid with low selectivity gave allyl alcohol **11** of the same enantiomeric series.

Synthesis of selenides **14-17** can be also carried out starting with alcohol **6** (Scheme 4). This approach included the initial formation of chloride **13**. It should be noted that similarly to the previous synthesis of alcohol **11** the enantioselectivity was low. At the same time, enantio-enriched linalools **18** can be obtained in two stages from selenol **15** by the oxidation of intermediated selenides **19** and **20** with *m*-CPBA (Scheme 5).

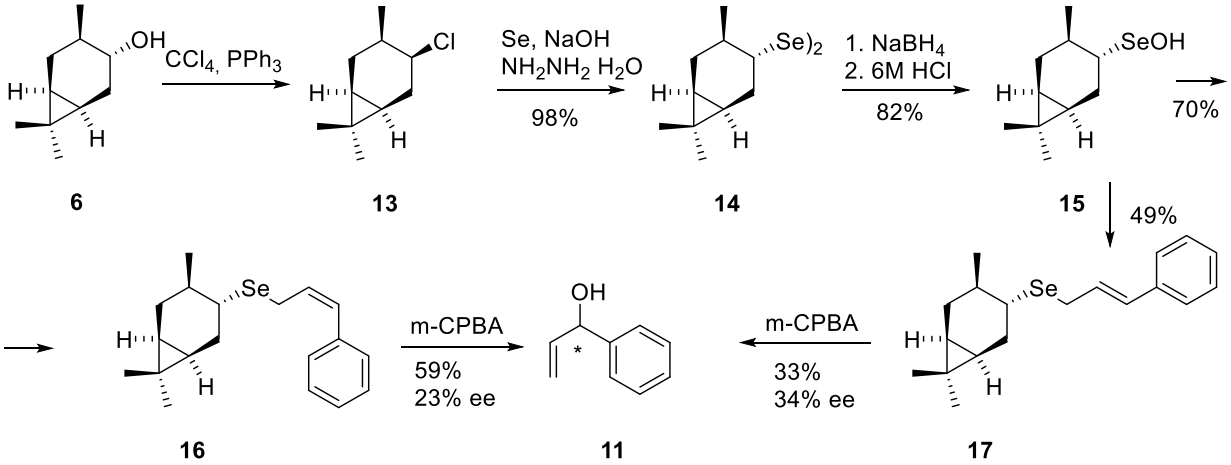


Scheme 2. Synthesis of *β*-3,4-epoxycarane 3 [40].

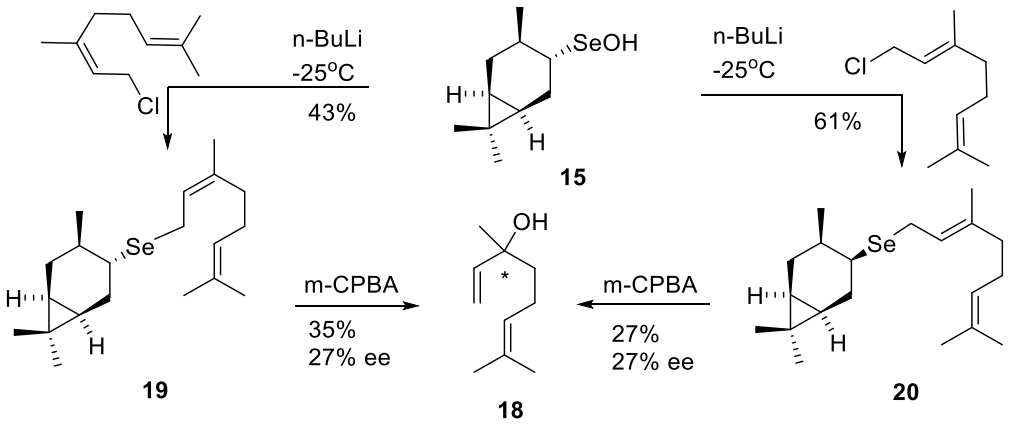
Synthesis of another type of selenides carried out from diselenide **14** involving formation of bromide, followed by anion metathesis, through triflate **21** interaction with *o*-allylphenol in dichloromethane/methanole at -78°C gave a mixture of selenides **21**, **22** in an approximately equal ratio (Scheme 6) [43]. During cyclization, an approximately equal mixture of diastereomeric selenides **22** was formed.



Scheme 3. Synthesis of optically active selenides [42].



Scheme 4. Synthesis of isomeric selenides [42].



Scheme 5. Synthesis of linalool [42].

Among the discussed substances, ether **23**, synthesized by the interaction of selenol **9** with trityl chloride [44], should also be noted (Scheme 7).

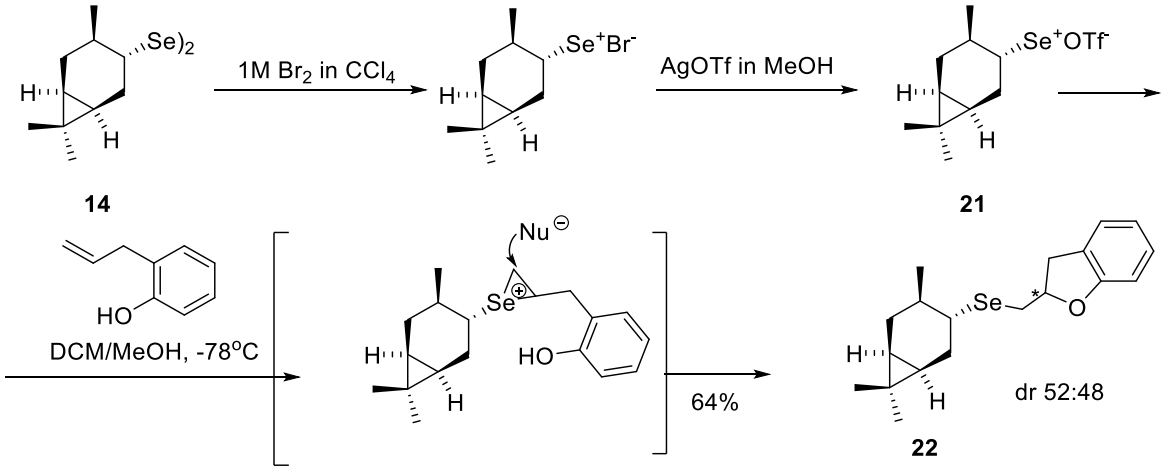
The tosylate **7** is a key starting compound for the one-pot synthesis of tellurides **24**, **25** by interaction with tellurium/$NaBH_4$ in EtOH/DMF (Scheme 8) [45]. The synthesized substances are quite stable and could be isolated through column chromatography.

Another type of symmetrically constructed substance of the carane series is *N*,*N*'-bis(caranyl) ethylenediamine **28** that could be synthesized in two stages from amine **26** (Scheme 9) [46].

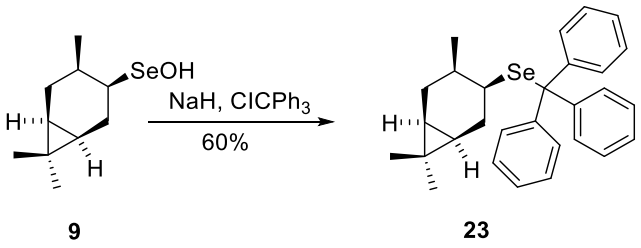
Diamine **28** was obtained by the reduction of diamide **27** by borohydride, which was used as an inducer of chirality in nitro-aldol condensation (Scheme 10).

The main products of the reaction of aldehyde **29** with nitromethane was alcohol **30**, the yield and enantiomeric purity of which depends on the nature of the aldehyde and is presented in the Table 1. The highest enantioselectivity was registered in the case of (*S*)-1-nitropropan-2-ol formation.

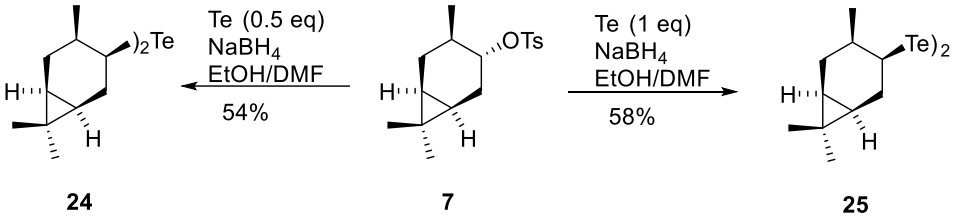
The synthesis of a diastereomeric mixture of caranones **31**, **32** under non-catalysed conditions by the oxidation of olefin **1** using N_2O was reported by Tkachev, A.V. *et al.* (Scheme 11) [47]. The authors also noted low conversion (up to 20%) and the formation of skeletal rearrangement products.



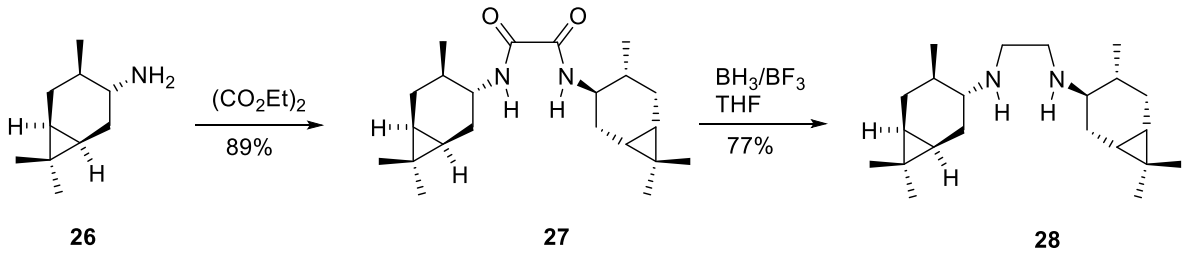
Scheme 6. Synthesis of selenides 21, 22 [43].



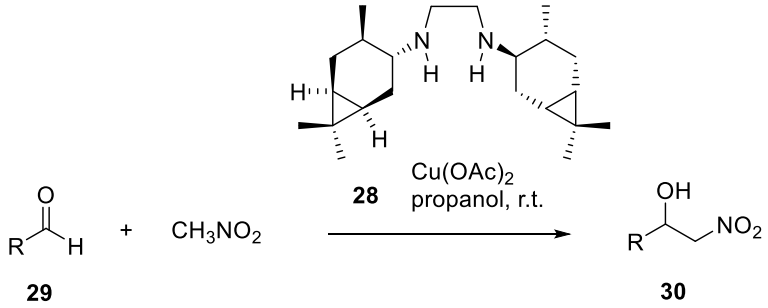
Scheme 7. Preparation of ether 23 [44].



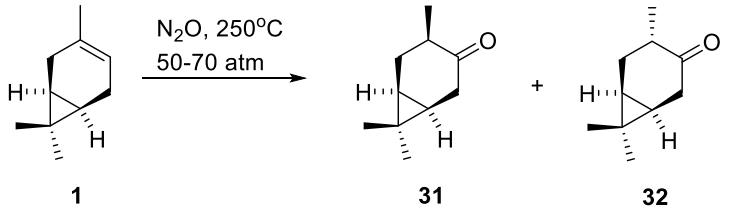
Scheme 8. Synthesis of mono- and ditellurides of the carane series [45].



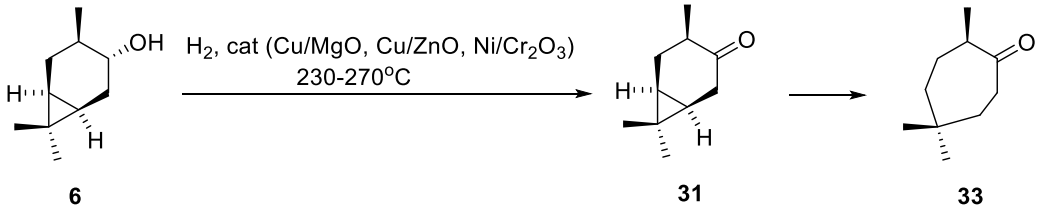
Scheme 9. Synthesis of symmetrical diamine [46].



Scheme 10. Nitro-aldol condensation of aldehydes with nitromethane [46].



Scheme 11. Synthesis of the diastereomeric mixture of caranones [47].



Scheme 12. Hydrogenation of caranol 6 [48].

Table 1

Yield and enantiomeric purity of nitro-aldol condensation adducts 30.

No	*Radical*	*Yield (%)*	*ee (%)*
1	Ph-	64	65
2	*o*-MeO-C_6H_4-	59	61
3	*m*-MeO-C_6H_4-	44	65
4	*p*-MeO-C_6H_4-	74	67
5	*p*-Cl-C_6H_4-	62	65
6	*p*-Br-C_6H_4-	58	69
7	*p*-F-C_6H_4-	76	79
8	1-Naphtyl-	65	71
9	*p*-NO_2-C_6H_4-	76	70
10	Cyclohexyl-	79	69
11	Butyl-	84	77

ee - enantiomeric excess, %.

The successive conversion of alcohol **6** to ketones **31**, **33** took place during the hydrogenation on the surface of the catalyst Cu / MgO, Cu / ZnO, Ni / Cr_2O_3 (Scheme 12) [48].

Aldehyde **34** synthesized according to scheme 13 and the corresponding acetals **35**, **36** have been proposed as fragrances for the perfume industry (Scheme 13) [49,50].

The available starting compound for the preparation of sulphur containing caranes **37**-**40** is tosylate **7** (Scheme 14) [51,52]. Thiol **39** under the action of sodium hydride gave disulphide **40** in a moderate yield.

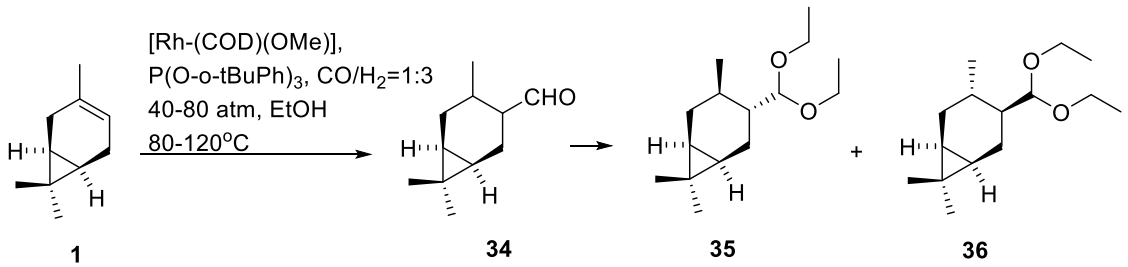
Sulphides **37**, **38**, **40** were used for the synthesis of optically active stilbene oxide (Scheme 15).

The yield, isomeric composition, and enantiomeric purity of the stilbene oxide are presented in Table 2.

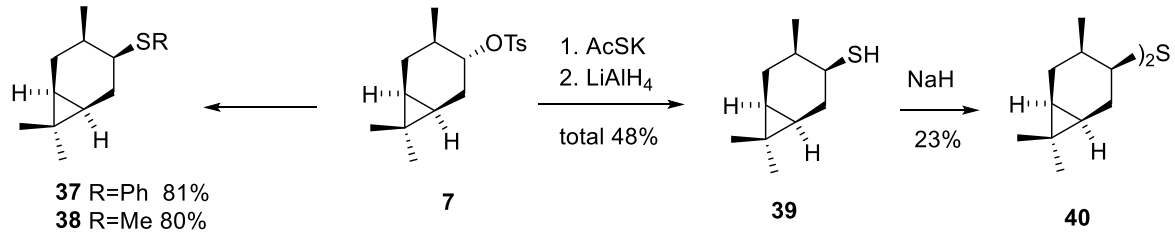
The synthesis of imidazoles **41**-**43** is based on the interaction of tosylate **7** with an alkaline solution of 2-sulphonyl-1*H*-imidazole, 1-methyl-2-sulphanil-1*H*-imidazole or 2-sulphanil-1*H*-benzimidazole, respectively (Scheme 16). It is possible to increase the yield of the substance **43** to 68% using a mixture of cesium carbonate and tetrabutylammonium iodide. Optimum conditions for diastereoselective oxidation of sulphides **41**-**43** to substances **44**-**46** were proposed.

The oxidation of thiol **39** by chlorine dioxide followed by hydrolysis results in the formation of sulphonic acid **47** in good yield (Scheme 17) [53].

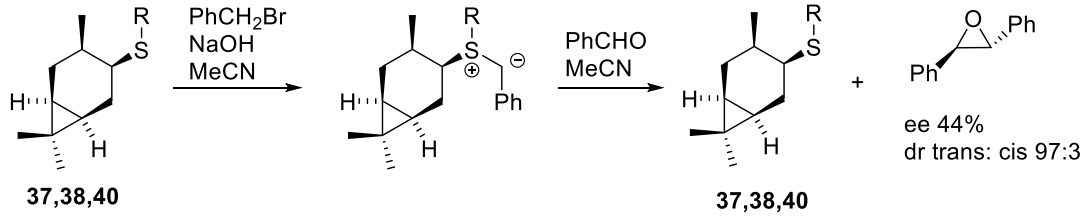
Synthesis of allyl alcohol **48** by the isomerization of epoxide **2** was reported (Scheme 18) [54]. The overall yield of the epoxide **2** → allylic alcohol **48** → aldehyde **49** → alcohol **50** scheme was 72%.



Scheme 13. Synthesis of acetals [49,50].



Scheme 14. Synthesis of sulphur-containing caranes [51,52].

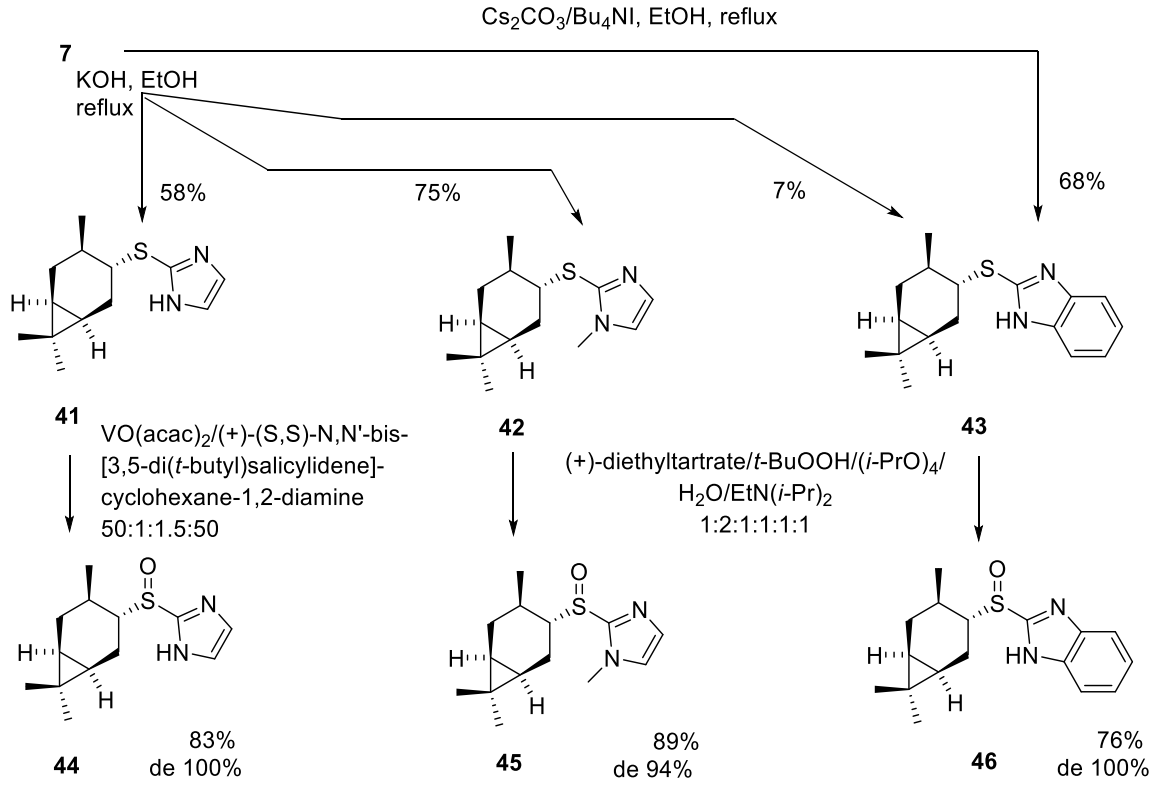


Scheme 15. Synthesis of the optically active stilbene oxide [51].

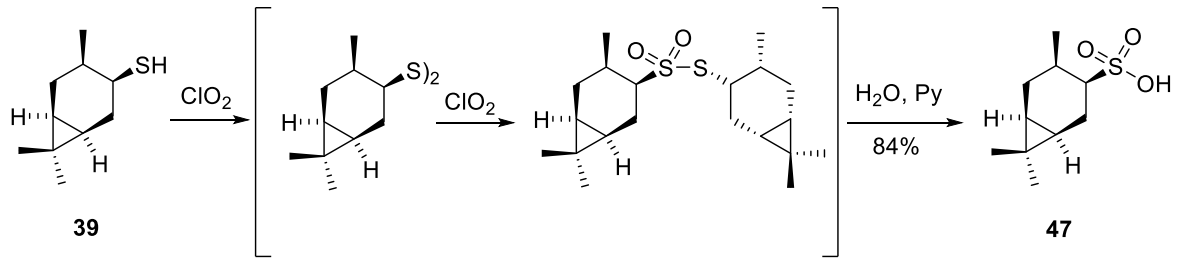
Table 2

The yield and enantiomeric purity of stilbene oxide.

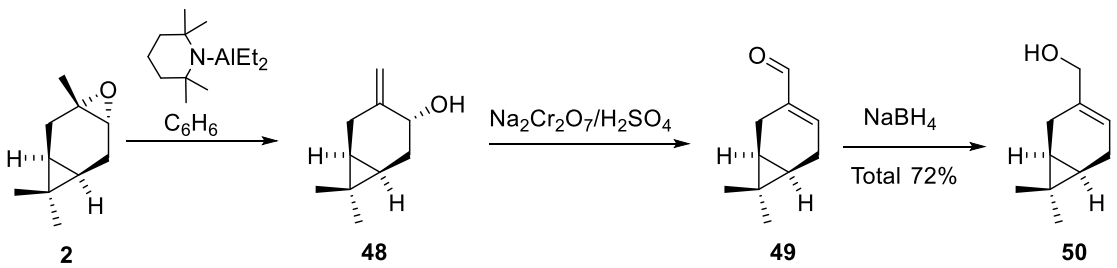
No	*Sulphide*	*Yield (%)*	*Ratio cis/trans*	*ee trans (%)*
1	37	13	55/45	44 (S,S)
2	38	53	3/97	8 (S,S)
3	40	14	71/29	8 (S,S)



Scheme 16. Synthesis of caranyl sulphonyl imidazoles [52].



Scheme 17. Synthesis of caranesulphonic acid [53].



Scheme 18. Synthesis of carane alcohols [54].

4-Substituted 2-carens are widely used for the synthesis of optically active 1,3-disubstituted 2,2-dimethylcyclopropanes [14,55], including the precursors of practically important insecticides [55-63]. Known methods for producing (+)-4*α*-acetyl-2-carene **51**, (+)-4*α*-hydroxymethyl-2-carene **52** and (+)-4*α*-acetoxymethyl-2-carene **53** include heating of **1** with $ZnCl_2$ in Ac_2O solution, or with paraform in AcOH solution, respectively (Scheme 19) [64-66]. Transitions from **51**, **52** to epimers **54** and **55** were also described [64,67].

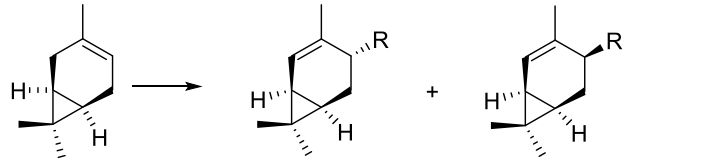
On the other hand, in the last decade there has been a significant increase in interest for the use of ionic liquids in organic synthesis, including the example of synthesis of **1** derivatives using ionic liquids **56**-**58** (Scheme 20) [68].

It was established that keeping the equimolar mixture of **1**, Ac_2O and 6% mol of the imidazole salts **56**-**58** at 50°C contributes to the Kondakov reaction (see Table 3).

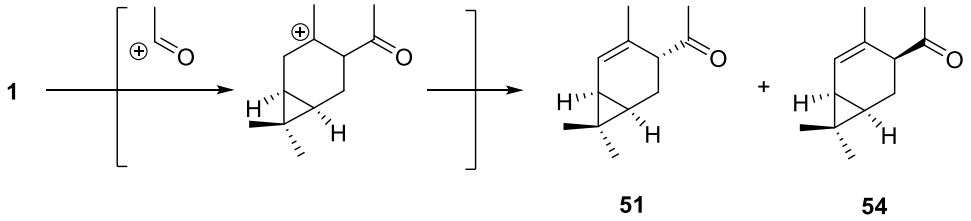
The catalytic effect of molten salts of imidazole is probably associated with the initial formation of an acyl ion from Ac_2O with the participation of the nitrile group associated with the anion.

The carbocation formed by attaching the acyl carbocation to the double bond of monoterpene **1** is stabilized by elimination of the proton with the regeneration of the double bond. The predominant formation of isomer **51** is associated with the directing effect of the 2,2-dimethylcyclopropane fragment present. Carrying out the reaction in the molten salt **56** leads to a double reduction of time with a slight increase in the yield of the final product and with the same degree (50%) of the conversion of the original **1**. It has been established that carrying out the reaction in the molten salt **57** or **58** along with the target reaction is accompanied by opening of 2,2-dimethylcyclopropan fragment, which ultimately leads to a complex mixture of products. Attempts of hydroxymethylation of **1** with paraform in the melt of the discussed salts and by addition of a catalytic amount of $ZnCl_2$ to the reaction mixture were unsuccessful.

It was found that only in the case of molten salt **57**, the addition of a stoichiometric amount of AcOH to the reaction mixture contributed to the Prins reaction.



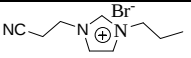
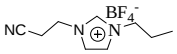
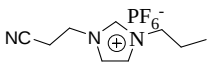
Scheme 19. Synthesis of 4-substituted 2-carenes [64-66].



Scheme 20. Synthesis of 4-acetyl 2-carenes [68].

Table 3

Reaction conditions and yields of acylation reaction products.

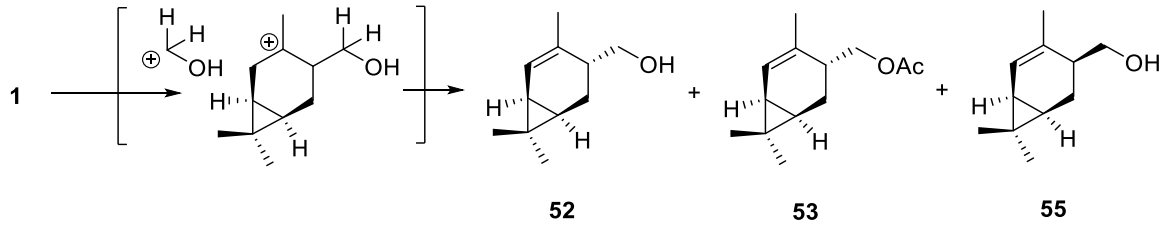
Products	*Ionic liquid*		*Ionic liquid quantity*	*Yield (%)*	*Time (hours)*
51, 52		**56**	6 % mol	33	49
			alloy	37	25
		**57**	6 % mol	38	46
		**58**	6 % mol	29	48

The *α*-hydroxyl carbocation produced by binding a proton to formaldehyde reacts with an olefin **1** to produce a *β*-hydroxycarbocation, which is stabilized by eliminating a proton with regeneration of the double bond. From a stereochemical point of view, the reaction proceeds as trans-addition, which in combination with the shielding effect of the gem-dimethyl group leads to selective hydroxymethylation. The ratio of epimers **52** and **55** was 9:1 (Scheme 21). The products of **51** reduction are proposed as intermediates in approaches to chiral blocks for the construction of epothilone carboanalogs [69]. However, the configuration of the emerging asymmetric center has not been established, and, moreover, the authors failed to separate diastereomers **59**, **60**. This is all the more important when it comes to obtaining carbon analogs of substances with a taxolon-like mechanism of action.

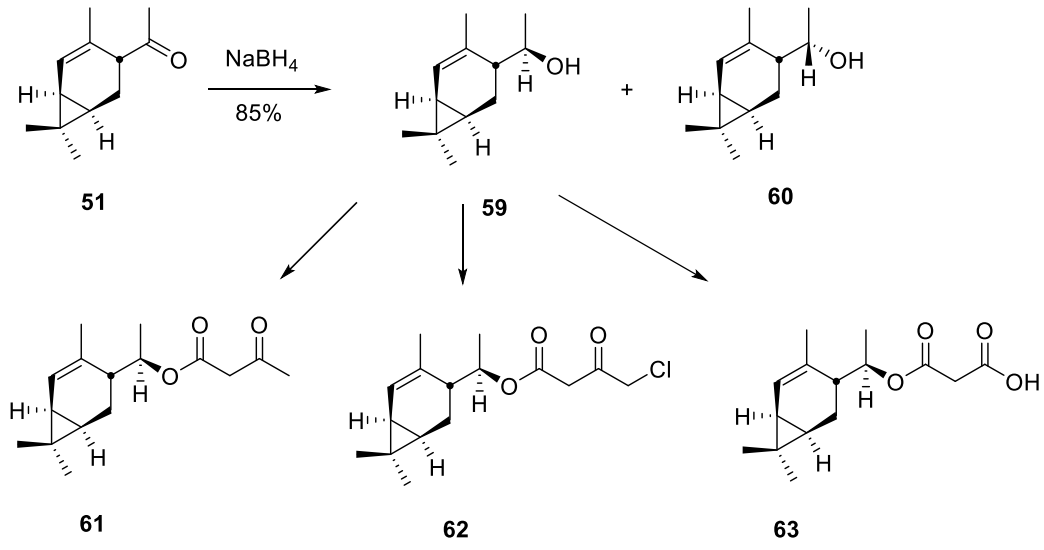
The literature describes the synthesis of alcohols **59**, **60** by borohydride reduction of ketone **51** (Scheme 22) [70]. It was found that the *R*-isomer **59** is easily separated from the *S*-isomer **60** by crystallization from hexane. Carrying out the reaction of borohydride reduction in a water-dioxane solution results in 85% yield of the mixture of epimers **59**:**60**= 3:2. In parallel, it was found that replacing solvents with MeOH and lowering the reaction temperature to -15°C does not reduce the overall yield of diastereomers and increases the epimer content of **59** to 60%.

The method of transesterification of acetoacetic ester, as applied to alcohol **59**, gave ester **61** (yield 51%). It is possible to increase the yield of the latter to 98% under Et_3N catalyzed condensation of alcohol **59** with diketene. Replacement of the acetoacetic ester with 4-chloroacetoacetic ester under conditions similar to the synthesis of ester **61** made it possible to prepare *α*-chloroketone **62** with 43% yield. Alcohol **59** interacts with 2,2-dimethyl-4,6-dioxo-1,3-dioxane giving malonic acid monoester **63** with a yield of 51%.

Nitrogen-containing substances and aminated derivatives of natural compounds take an increasingly significant place in the list of substances with practically important properties. For example, the enantiomerically pure anti-tuberculosis drug (+)-ethambutol contains (2*R*)-1-oxomethyl-2-aminopropyl fragment [71].



Scheme 21. Synthesis of substituted 2-carenes [69].



Scheme 22. Synthesis of acetoacetic esters [70].

A convenient and gentle method of introducing this fragment into the (+)-4*α*-acetyl-2-carene **51** molecule was the reaction with monoethanolamine in the presence of $NaBH_3CN$ as shown in the Scheme 23.

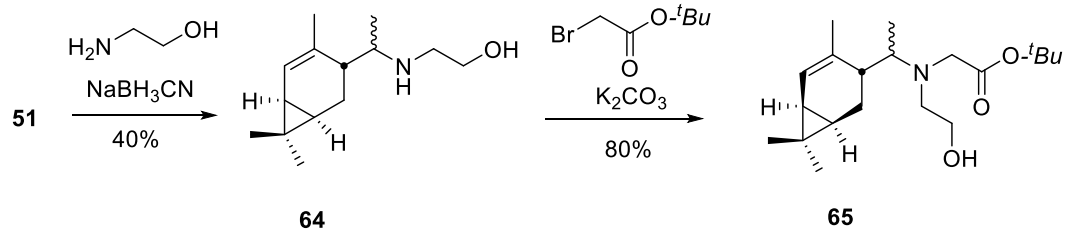
The reaction product **64** is a mixture (9:1) of epimers at the C1 atom of the side chain. A monobromoacetic acid *tert*-butyl ester was used to construct the aminoacetic acid fragment of compound **65**.

The *α*-activated acid ester **61** has found application in the synthesis of spiro-heterocyclic compounds **66**, **67** [72]. The condensation of substance **61** catalyzed by DABCO with isatin and malononitrile gives an equal mixture of diastereomeric spirans of structures **66** and **67** (Scheme 24).

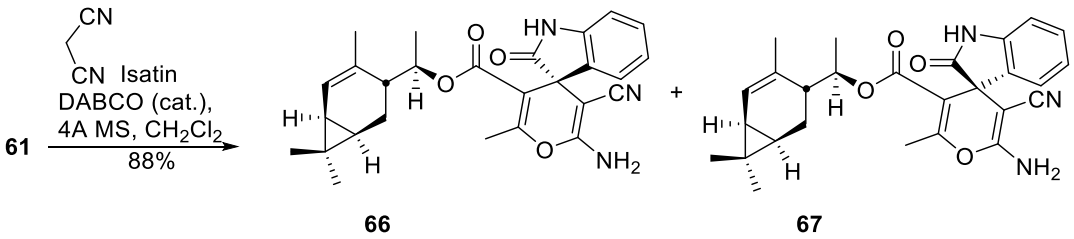
Disubstituted caranes and their transformation pathways

It was previously reported that the reaction of chlorosulphonyl isocyanate with (+)-3-carene **1** takes place with the formation of *β*-lactam **68** [73,74]. In the development of the approach to optically active lactam functionalized ionic liquids, the synthesis of **68** was repeated (Scheme 25) [75].

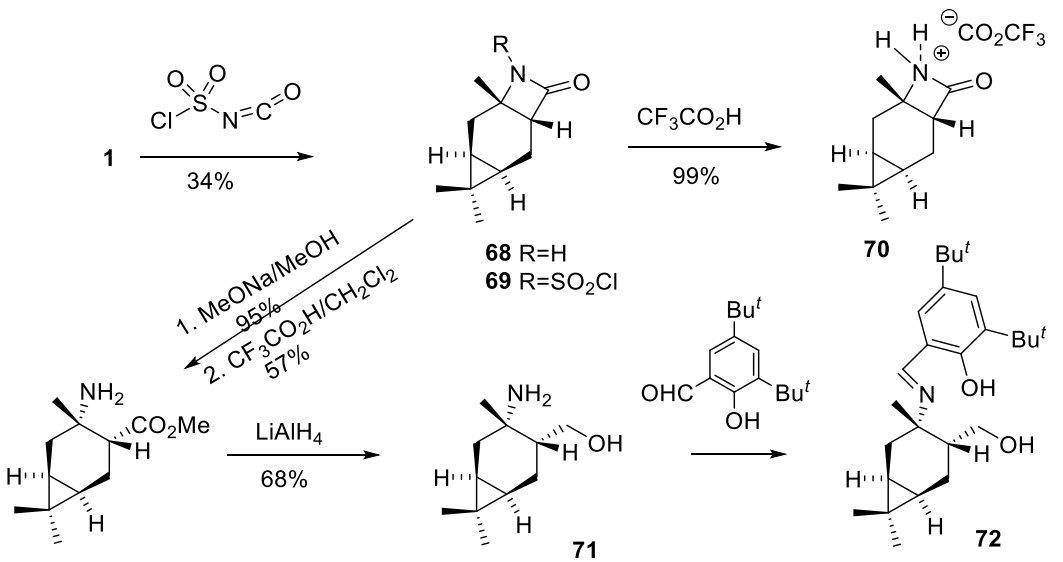
Instead of the expected product with a melting point of 108-111°C, substance **69** was isolated with a melting point of 66-67°C. Sequential treatment of sulphonyl chloride **69** with Et_3N and H_2O led to substance **68**, the reaction of which with trifluoroacetic acid gave salt **70**.



Scheme 23. Synthesis of aminated (+)-4*α*-acetyl-2-carene derivatives [71].



Scheme 24. Synthesis of spiro-heterocyclic compounds [72].



Scheme 25. Synthesis of amino alcohols [75].

The *β*-lactam **68** was transformed in three steps into the amino alcohol **71**, which, with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde, gave the Schiff base **72** [76,77]. By the combination of $VO(acac)_2$ - ligand **72** - *N*-ethyl-*N*,*N*-diisopropylamine - 86% solution of cumene hydroperoxide was performed the asymmetric synthesis of (*S*)-omeprazole by oxidation of its prochiral sulphide.

The transformation of olefin **1** to disulphide **75** included the preliminary formation of *cis*-aziridine **73** (Scheme 26) [78].

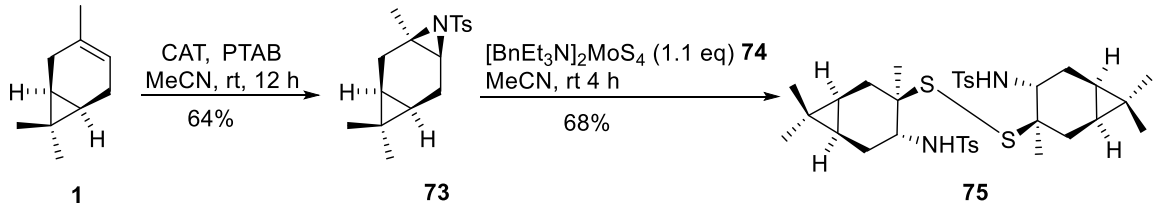
The regio- and stereoselectivity of the reaction of the aziridine cycle opening of **73** under the action of benzyltriethylammonium tetrathiomolybdate has been established.

Another type of disulphides of the carane series was synthesized *via* nitrosyl chloride **76** (Scheme 27) [79].

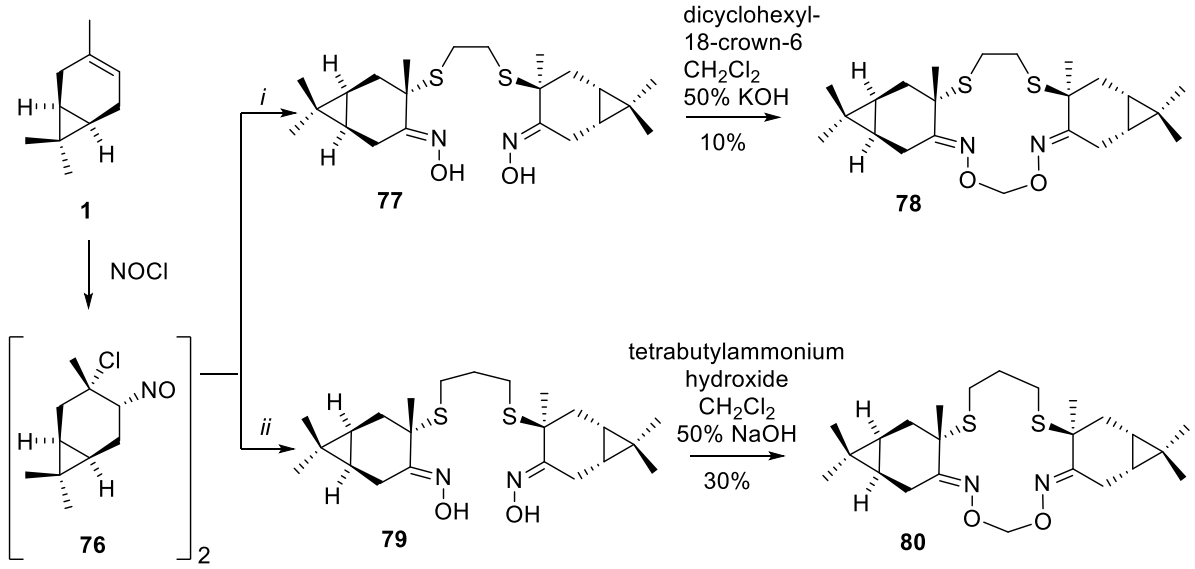
Dimer **76** interacts with $NaSCH_2CH_2SNa$(*i*) or $KSCH_2CH_2CH_2SK$(*ii*) with the formation of ketoxime **77** (yield 85%) or **79** (yield 60%), respectively. It was shown that cyclization of the **77** under the action of dicyclohexyl-18-crown-6 - 50% aqueous KOH system under the conditions of interfacial catalysis gives macrocycles **78**, whereas for the formation of **80** the use of the combination of tetrabutylammonium hydroxide and 50% aq. NaOH was proved to be the most efficient, but the yields did not exceed 10-30%.

Nitrosyl chloride **76,** when treated with acetone cyanhydrin is converted to ketoxime **81** (Scheme 28) [80].

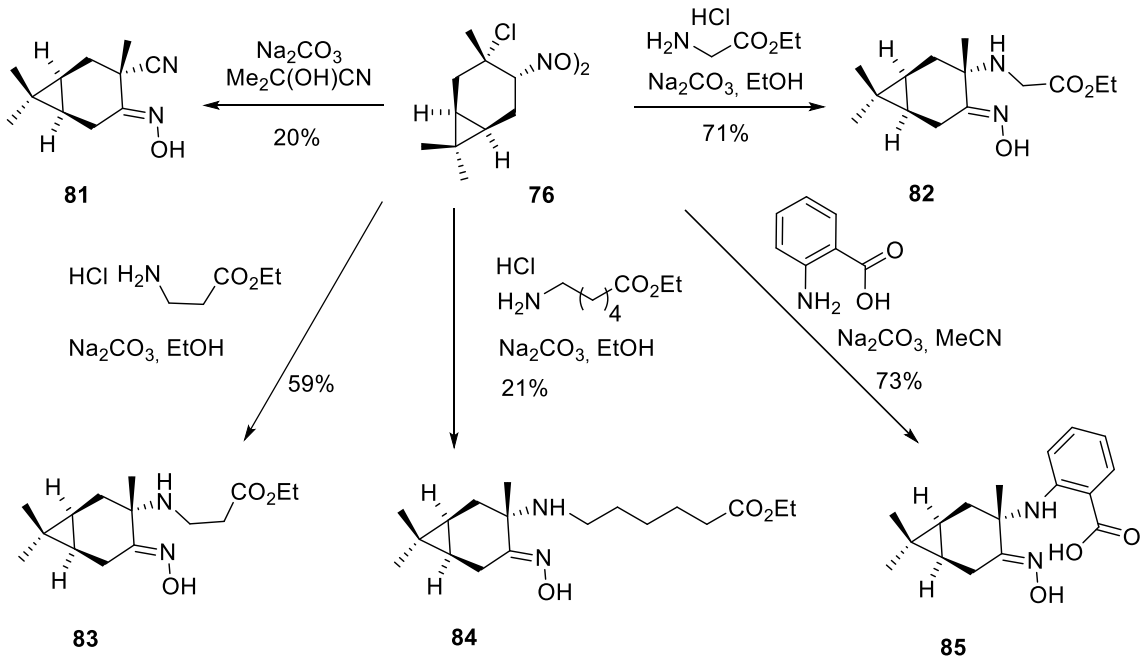
Functionalized ketoximes **82**-**85** were synthesized from dimer **76** and ethylacetic, aminopropionic, aminohexanoic and anthranilic esters, respectively [81]. The interaction of compound **76** with 1*H*-imidazole or benzotriazole gives **86** or **87** respectively (Scheme 29) [82]. Aminoketoximes **88**, **89** can be synthesized by the interaction of dimer **76** with ammonia and dimethylamine, respectively (Scheme 30) [83,84]. Dimethylaminoketoxime **89** is transformed into ether **90** by interaction with epichlorohydrin (yield 64%). The opening of the oxirane cycle **90** with aminohexane, morpholine, piperazine, and ketoxime **88** takes place with the formation of an inseparable mixture of alcohols **91**-**94**, the yield of which did not exceed 52%.



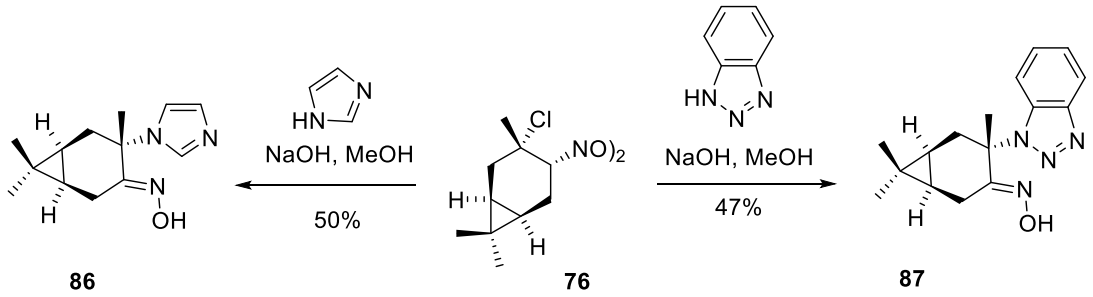
Scheme 26. Synthesis of *β*-sulphonamidodisulphides [78].



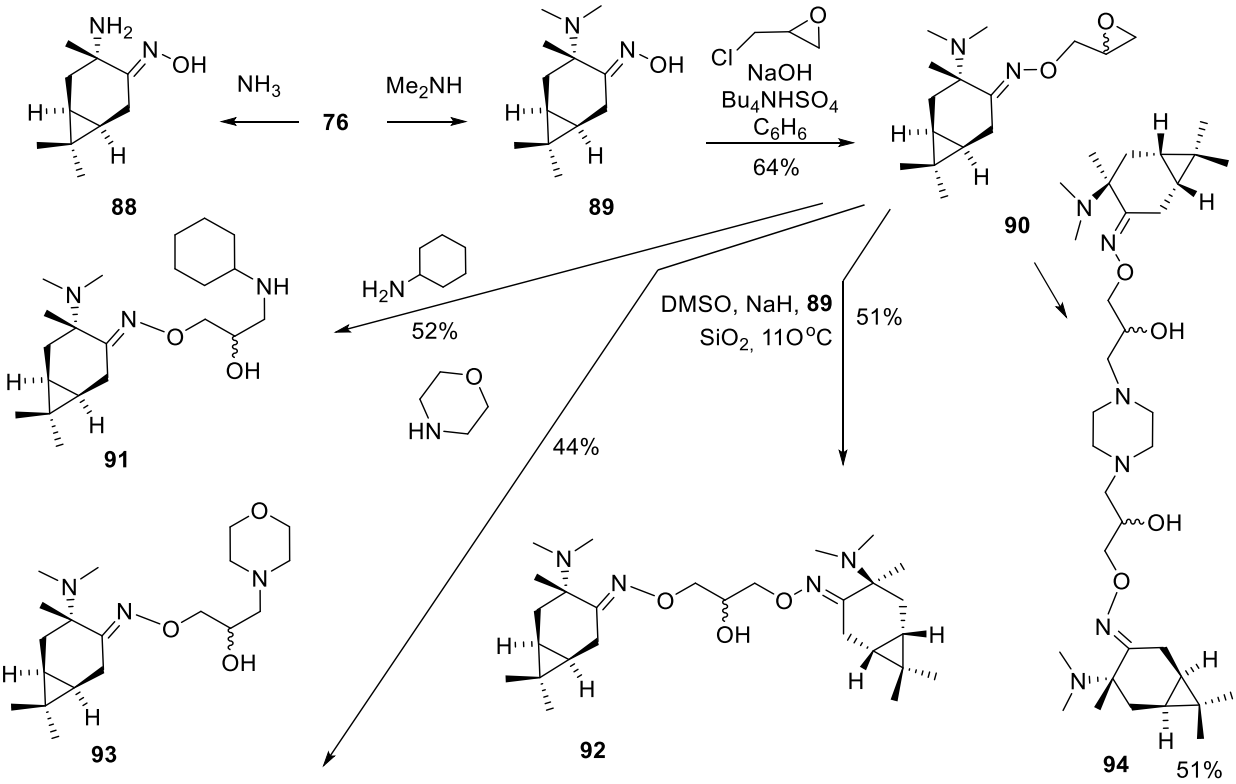
Scheme 27. Macrocycle synthesis [79].



Scheme 28. Amino acid synthesis [80,81].



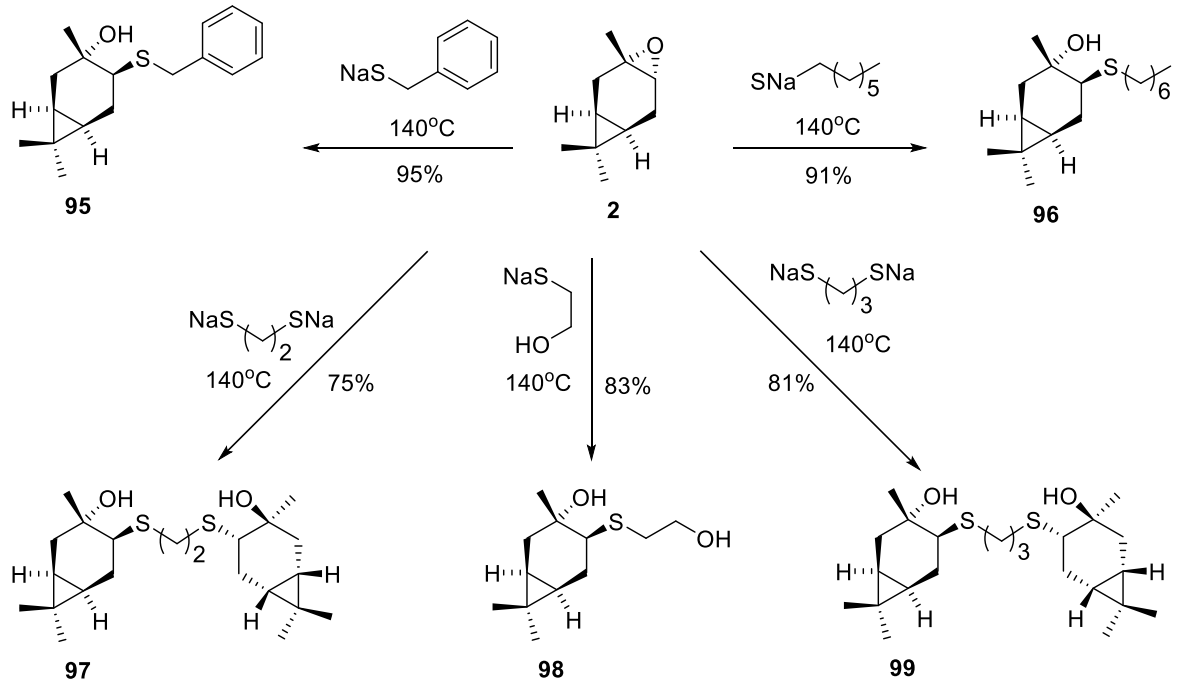
Scheme 29. Synthesis of imidazole and benzotriazole derivatives [82].



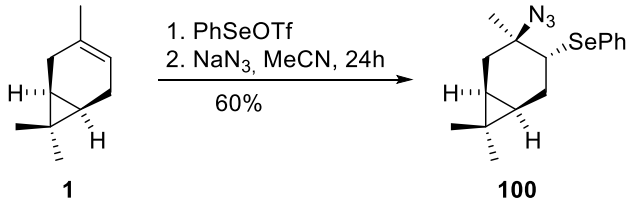
Scheme 30. Synthesis of amines of the carane series [83,84].

The microwave irradiation of epoxide **2** with sodium thiolates resulted in the formation of *β*-hydroxysulphides **95-99** with high yields (75-95%) (Scheme 31) [85].

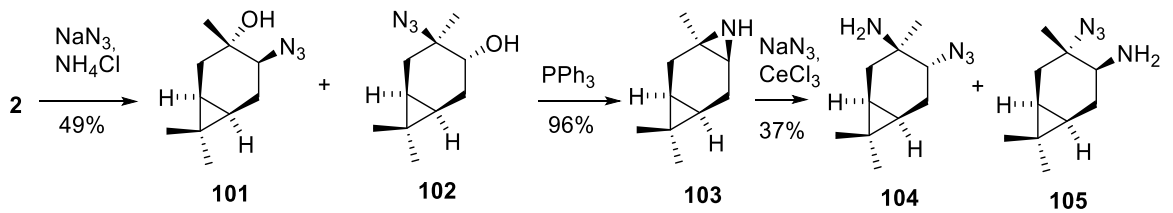
The method of obtaining azidoselenide **100** has been published also (Scheme 32) [86]. The reaction proceeds regioselectively according to the Markovnikov rule with the formation of a *trans*-diaxial product. The opening of the oxide **2** with sodium azide in the presence of ammonium chloride [87] occurs with lower selectivity (Scheme 33). It was possible to increase the yield of azide **102** to 65% when carrying out the reaction in aqueous acetic acid [88]. The regioselectivity of the reaction can be explained by the initial protonation of the oxide cycle, which leads to the formation of a positive charge on the tertiary carbon atom. As a consequence, a more substituted *α*-carbon atom is subjected to the nucleophilic attack by the azide ion with the formation of compound **102**. The opening of aziridine **103** with sodium azide catalysed by cerium chloride was highly selective, but the total yield of aminoazides **104**, **105** did not exceed 37%.



Scheme 31. Synthesis of *β*-hydroxysulphides of the carane series [85].



Scheme 32. Synthesis of *β*-azidoselenide of the carane series [86].

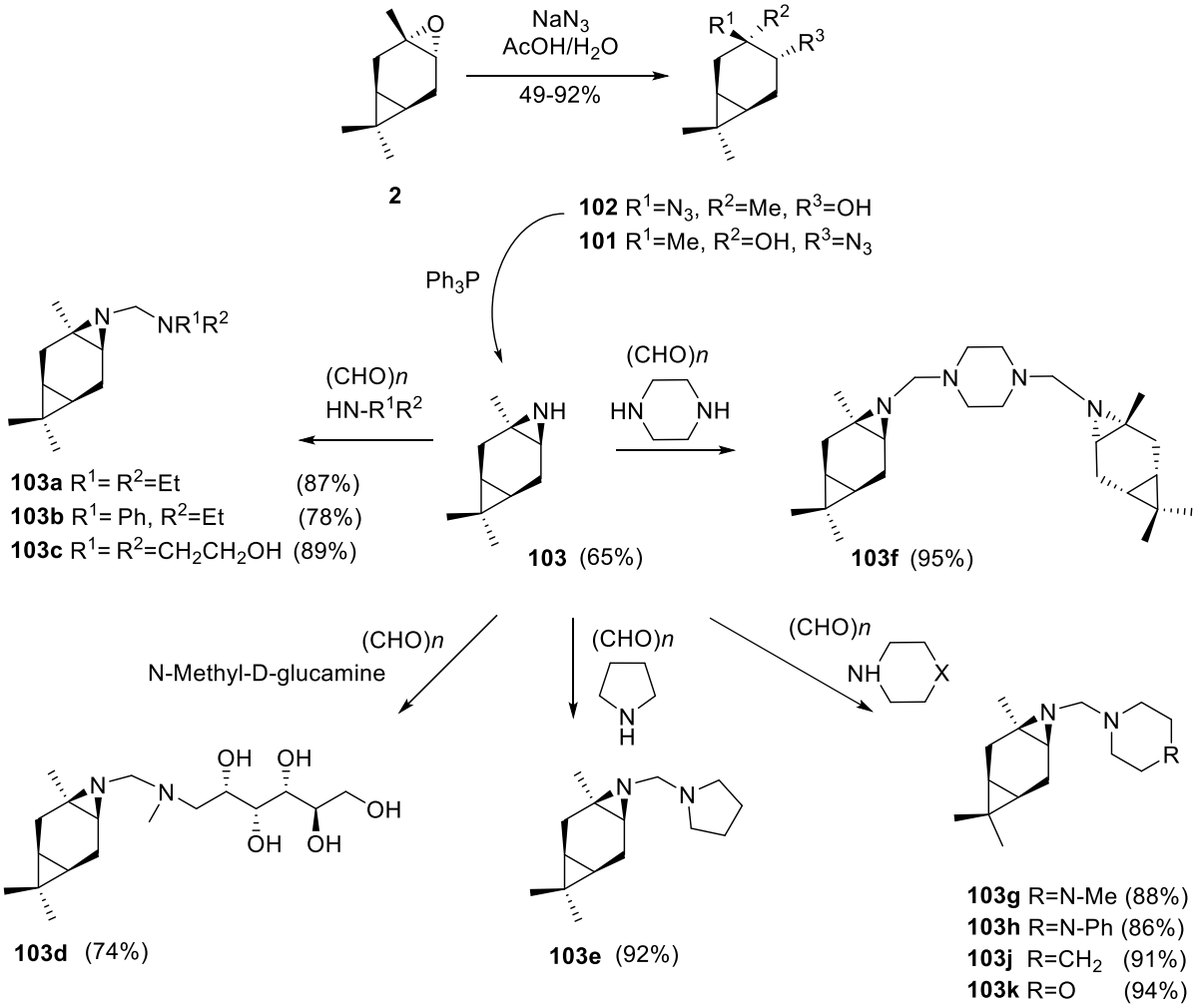


Scheme 33. Transformations of oxide 2 into azides [87].

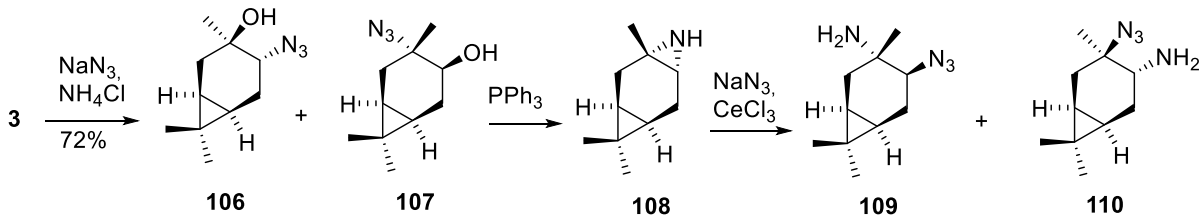
Synthesis of aminoalkylated aziridines **103a-k** has been performed *via* cyclization of azidoalcohol **102** with participation of Ph_3P, with a following condensation of aziridine **103** with formaline and the secondary amines (Scheme 34) [88].

It has been detected that the cytotoxicity of the aminoalkylated derivatives of aziridine with heterorganic substituents increases at transition from the five-membered pyrrolidine cycle to the six-membered piperidine cycle and is reduced at substitution of the piperidinic to morpholinic cycle or increased at transition to morpholinic cycle. The lowest toxicity has been detected for the aziridine **103** and azide **102** [88].

An equal mixture of isomeric azides **106**, **107** was synthesized based on epoxide **3** [87]. The latter azides are transformed into aziridine **108** with triphenylphosphine. However, a difference in reactivity has been observed: in the case of azido-alcohol **106**, the formation of aziridine took place at room temperature, whereas the conversion of azido-alcohol **107** to the desired product required long-term boiling in 1,4-dioxane. It should be noted that the reaction was diastereoselective since isomeric azido alcohols gave the same product, which at interaction with sodium azide in the presence of cerium chloride gave a mixture of substances **109**, **110** (Scheme 35).



Scheme 34. Synthesis of aminoalkylated aziridines [88].



Scheme 35. Transformations of oxide 2 into azides [87].

The opening of the epoxide **2** with diphenyldiselenide in MeOH led to *β*-hydroxyphenylselenide **112** (Scheme 36) [89].

By varying the selenium source, and conditions it is possible to synthesize selenide **111** or diselenide **113** in good yields. A similar approach applied for epoxide **3** allowed the authors of the cited paper to synthesize selenides with structures **114-116** (Scheme 37).

The reaction of the interaction of oxide **3** with diphenyldiselenide proceeds more smoothly as compared with **2** (yield 84% and 56%, respectively). It should be noted that in the case of products **114**, **116**, the yields are 11% lower and 23% lower than those of similarly constructed substances **111** and **113.**

The interaction of epoxide **117** with amines gave a series of secondary and tertiary aminodiols (Scheme 38) [90].

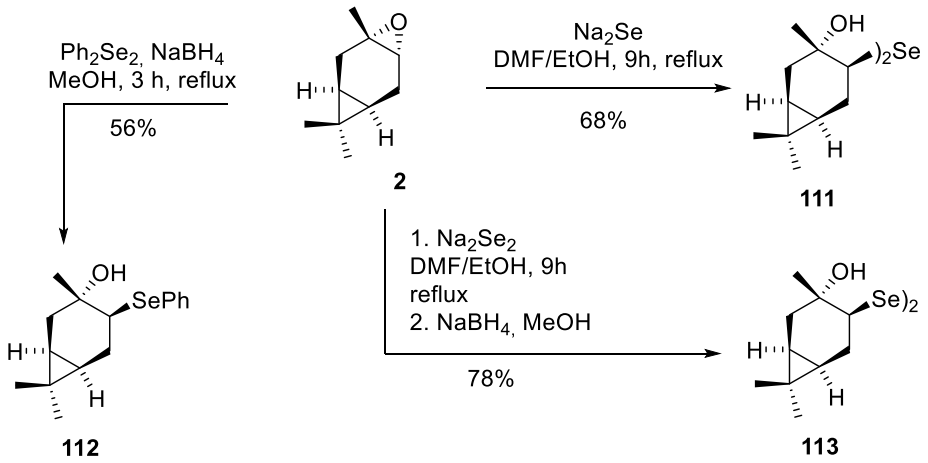
N-Benzylaminodiol **118c** was prepared by reacting benzylamine with oxide **117** in the same way as tertiary aminodiols **118a**, **118b**, **118d-g**, while *N*-methyl derivative **119a** and primary amine **119b** were synthesized under standard hydrogenation conditions of the corresponding *N*-benzyl derivatives **118a**, **118c**. Formalin reacts with secondary amines in high yields to form 1,3-oxazines **120a-d**.

Unlike the precursors **118c**, **118f**, **118g**, **119a**, oxazines **120a-d** exhibited high induction (77-97% of it) in the reaction of asymmetric addition of diethylzinc to aldehydes.

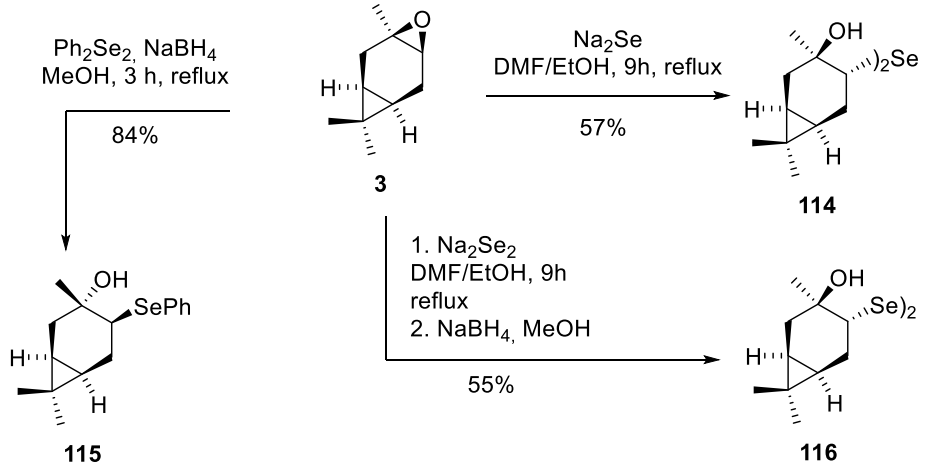
The method of synthesis of hydroxyamide **121** is based on the catalyzed OsO_4 interaction of **1** with chloramine T in aqueous *tert*-butanol (Scheme 39) [91].

Low-temperature treatment of *p*-toluenesulphonylamide **121** with sodium in ammonia with a yield of 72% gives hydroxyamine **122**.

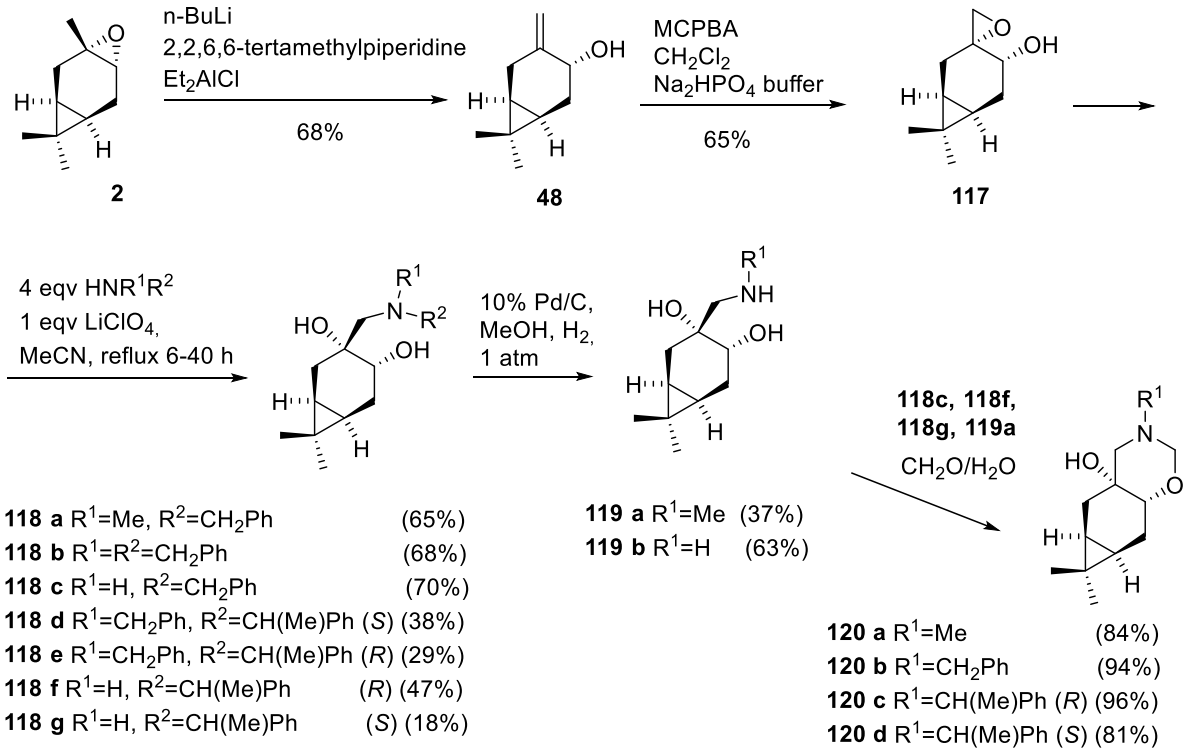
Azido alcohols **101**, **102** [87] under the action of $LiAlH_4$ in the ether are reduced to *trans*-amino alcohols **123**, **124** (Scheme 40) [92].



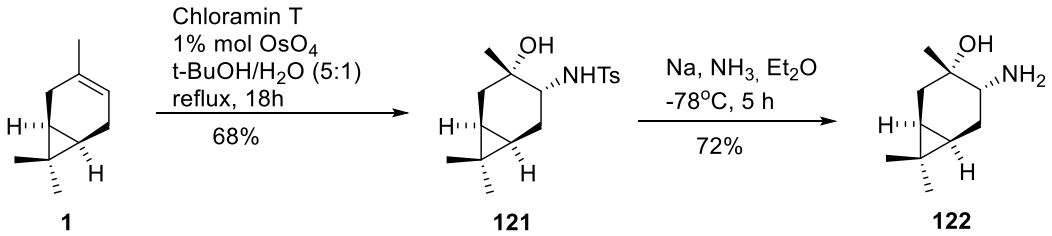
Scheme 36. Synthesis of *β*-hydroxyselenides [89].



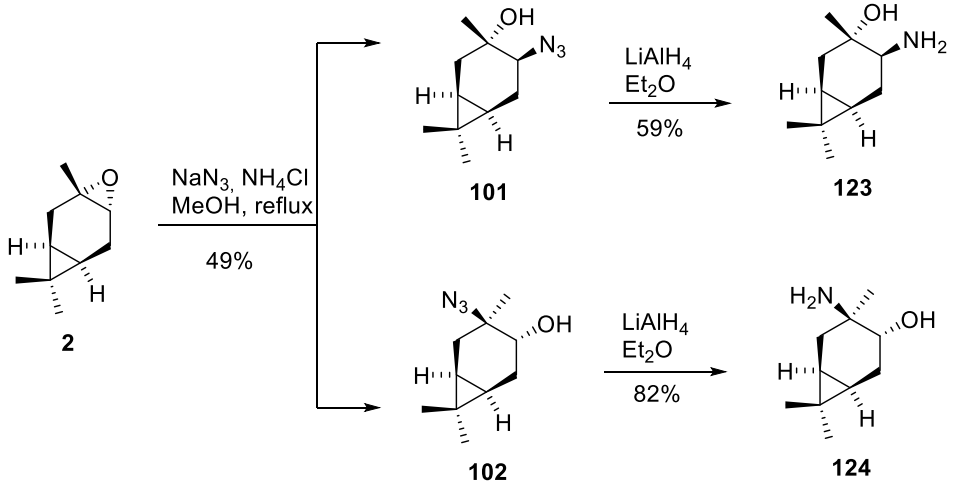
Scheme 37. Synthetic transformations of oxide 3 into selenides [89].



Scheme 38. Synthesis of *β*-hydroxyamine [90].



Scheme 39. Synthesis of *cis*-hydroxyamine 122 [91].



Scheme 40. Transformations of oxide 2 into *trans*-amino alcohols [92].

The same group of researchers described the synthesis of another pair of *trans*-amino alcohols **125**, **126** based on azido-alcohols **106**, **107** (Scheme 41).

Isatins **127a,b** have been the favoured template not only for the spectrum of biological activities, but also with respect to the development of methodologies.

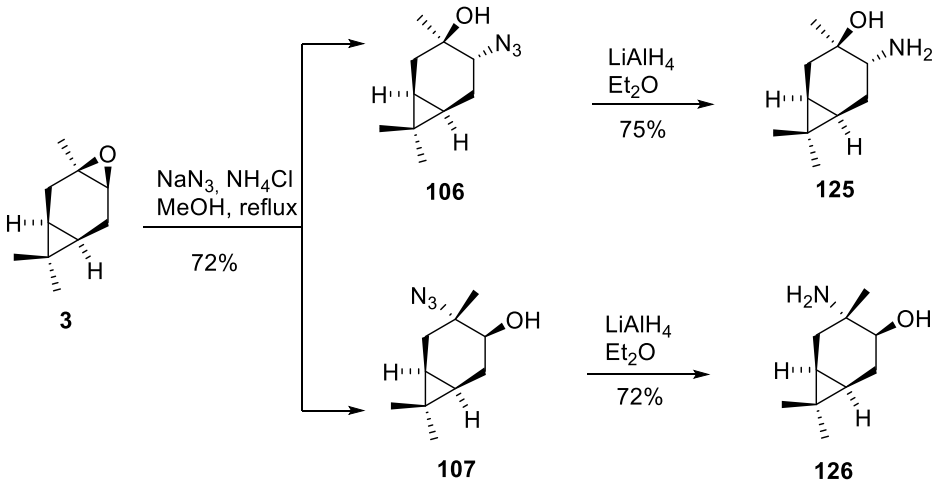
It is relevant to mention the synthetic approach employing organocatalyst **122**, prepared from **1** and used for the subsequent enantioselective synthesis of (*R*)-convolutamydine A **128a** (Scheme 42) that is a member of the oxindole subfamily, which exhibits a potent inhibitory activity on the differentiation of HL-60 human leukaemia cells.

It has been determined that water produces a moderate influence on the selectivity of the cross-aldol condensation of the 4,6-dibromoisatine **127a** with acetone catalysed by *cis*-aminoalcohol **122** [93]. The synthesized amino alcohols **125**-**126** were investigated as catalysts for the asymmetric cross-aldol condensation of isatin with acetone, the yield and enantiomeric purity of the reaction product are presented in the Table 4.

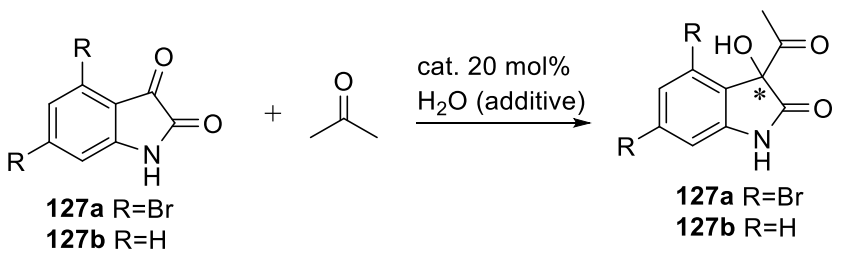
The reaction product with participation of isatine **127a** and catalysed by amino alcohol **126** was a racemic mixture **128b** (yield 74%), while the regioisomer **125** exhibited asymmetric induction up to 49% ee. A similar pattern was observed when using another pair of inductors. In the case of substance **123**, in which the amino group is at the tertiary carbon atom, the highest enantioselectivity has been registered, whereas with catalyst **124** the enantioselectivity did not exceed 5%.

The success in creating of highly efficient metal complex catalysts depends almost entirely on the correct choice of the chiral ligand, and the effectiveness of the latter is largely dependent on the right selection of the initial chiral synthon. This is completely true for optically active phosphorus-containing compounds that largely determine the modern view on catalysed asymmetric synthesis.

The use of chiral phosphorus-containing inductors based on **1** has been proposed [94].



Scheme 41. Transformations of oxide 2 into *trans*-amino alcohols [92].

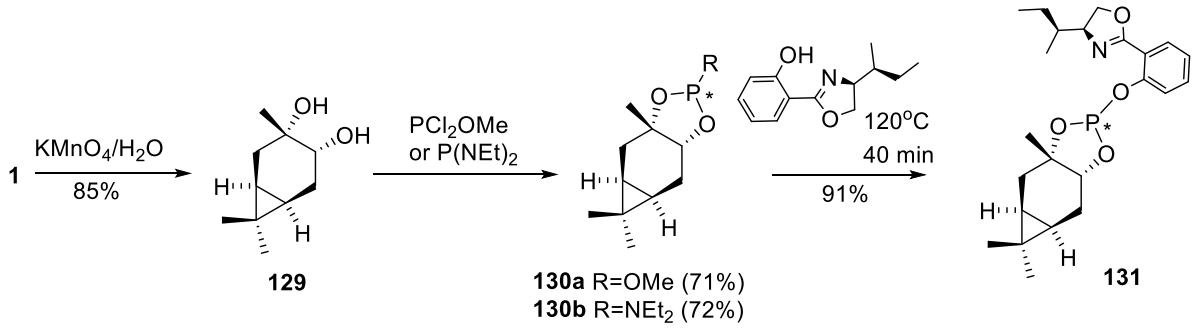


Scheme 42. Asymmetric condensation of isatines 127a,b with acetone [93].

Table 4

Reaction time, yield and enantiomeric purity of 3-hydroxy-3- (2-oxopropyl) indolin-2-one.

Entry	*Catalyst*	*Product*	*Water additive (mol %)*	*Time (hours)*	*Yield (%)*	*ee (%)*
1	**122**	**128a**	0	36	44	51(S)
2	**122**	**128a**	100	48	23	13(R)
3	**123**	**128b**	0	50	95	77(*R*)
4	**124**	**128b**	0	100	60	5(*S*)
5	**125**	**128b**	0	96	95	49(*R*)
6	**126**	**128b**	0	120	74	0



Scheme 43. Synthesis of *P - chiral phosphites [94].**

Phosphorylation of diol **129** yielded *P**-chiral phosphites **130a**, **130b** (Scheme 43). Synthesis of phosphite **130a** proceeds with high selectivity (95% of the main diastereomer). It should be noted that amidophosphite **130b** is formed as a single stereoisomer. New phosphites were tested in enantioselective Pd-catalysed allyl sulphonation with $TolSO_2Na$, alkylation with dimethyl malonate and amination with pyrrolidine (*E*)-1,3-diphenyl allylacetate. Regardless of the nature of the ligands and the ligand : Pd ratio, low optical yields were recorded, while the conversion level increased to 71% in the case of the phosphite **130b** / $[Pd(allyl)Cl]_2$ catalytic system at a ratio of 1:2. One approach to increasing the asymmetric activity of the ligand could be the use of the corresponding *P*,*N*-bidentate compounds with additional C* stereocenters in the peripheral nitrogen-containing group. For this purpose, oxazolinophosphite **131** was obtained using amidophosphite **130b**.

Compound **131** with respect to $[Pd(allyl)Cl]_2$ acts as a typical *P*,*N*-bidentate ligand, forming a chelate cationic complex, for which a high chiral induction of up to 90% is established at a conversion of 67% in the allylic amination reaction. In this case, the *R*-enantiomer is formed, whereas the previous catalytic systems based on ligands **130a**, **130b** led to the formation of a predominantly *S*-enantiomer. The use of the catalytic system based on oxazolinophosphite **131** and pyrrolidine as a nucleophile in allyl amination of (*E*)-1,3-diphenyl allylacetate led to an increase in the optical yield up to 91% at 100% conversion of (*E*)-1,3-diphenyl allylacetate.

Conclusions

The presented review has summarized scientific achievements in the field of (+)-3-carene synthetic transformations. The functionalization of (+)-3-carene leads to products with 3,7,7-trimethylbicyclo[4.1.0]heptane skeleton. However, a number of syntheses include many steps that lead to the appearance of a large number of by-products, and, therefore, a low yield of the target product.

A special attention is paid to epoxidation of (+)-3-carene, which is associated with the use of the resulting oxides as synthons in further transformations. Numerous studies descried synthetic pathways towards sulphur, selenium containing 3,7,7-trimethylbicyclo[4.1.0]heptans through opening of the (+)-3-carene α-epoxide. Synthesis of mono- or difunctionalized 3,7,7-trimethylbicyclo[4.1.0]heptanes, hydroxy-, amino-, azido-, *etc*., containing groups offer a wide possibility in their further application as ligands for metal complexes preparation, as well as their use as organocatalysts in asymmetric organic synthesis. The development of

new methods of selective synthesis of 3,7,7-trimethylbicyclo[4.1.0]heptanes, research of reactions with their participation and formation of new nitrogen-containing derivatives as well as application of water as catalyst, remain an important and prospective challenge.

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