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The chemistry of D_3-trishomocubane †

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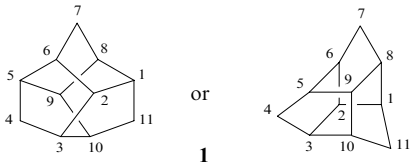
Abstract. Data on the chemistry of D_3-trishomocubane and its derivatives are described systematically. Different versions of construction of D_3-trishomocubane cage are presented. The methods of synthesis of mono-, di- and polysubstituted D_3-trishomocubanes and their heteroanalogues as well as their properties are considered. Data on biological activity of homocubanes are generalized. The bibliography includes 89 references.

I. Introduction

Among cage structures, adamantane is studied most of all.[1] Many adamantane derivatives have found application as medicines (*e.g.*, anti-viral and anti-parkinsonism drugs). Some polymeric materials and compositions with enhanced operation properties, thermostable lubricants, *etc.*, are based on adamantane. Diamantanes have been shown [2] to be useful in the fields of electron microscopy and lithography as well as components in production of new-generation flat monitors. The Department of Organic Chemistry of the Kiev Polytechnic Institute is currently investigating the other highly symmetrical cage hydrocarbon, D_3-trishomocubane (**1**).

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1

This hydrocarbon, like adamantane, possesses specific properties, *viz.*, a relatively large cage size (its diameter is 5.5 Å), high lipophilicity and conformational rigidity. The two latter properties are especially valuable for novel drug design.

Although D_3-trishomocubane was first synthesized in 1970,[3] its chemistry is still insufficiently studied, the only review on the synthesis of D_3-trishomocubane derivatives was published by Marchand [4] in 1989. The present paper covers data on this topic published over the recent 20 years along with some earlier data not discussed in the review cited.[4]

II. D_3-Trishomocubane and its isomers

Pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane (D_3-trishomocubane) is one of the few molecules belonging to the D_3 point symmetry group that has a threefold rotation axis and three twofold axes orthogonal to it. Despite the high symmetry, the molecule has chiral cage structure and can exist in the form of two optical isomers. Different graphical representations of the D_3-trishomocubane isomers are shown in Figure 1.

There are three possible isomers of a monosubstituted D_3-trishomocubane, with a substituent in position 1, 2 or 4. Like the alkane itself, its monosubstituted derivatives can exist in the form of two stereoisomers. Secondary carbon atoms (4, 7, 11) lie on the twofold symmetry axis, therefore

† Dedicated to the memory of professor A G Yurchenko (1934 – 2010).

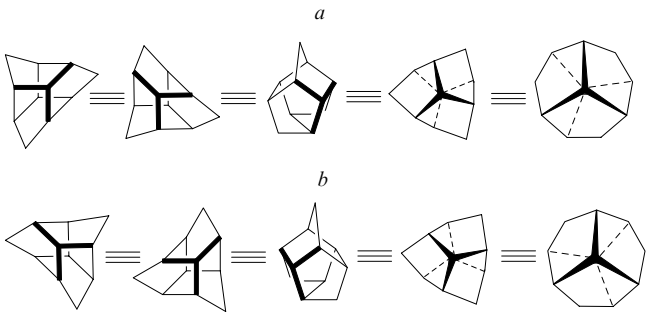


Figure 1. Different graphical representations of the D_3-trishomocubane stereoisomers: *a*, (−)-isomer, *b*, (+)-isomer.

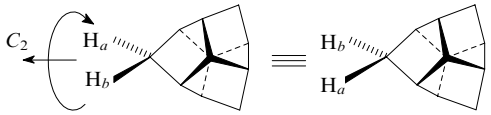
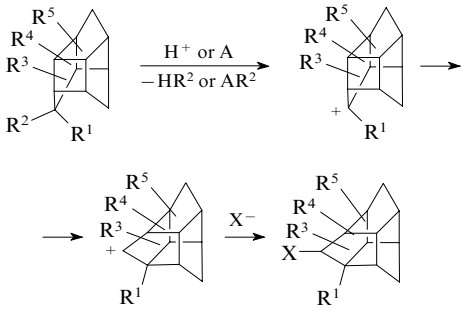


Figure 2. The 2-fold rotation axis in trishomocubane.

substitution at these positions does not result in diastereomers. (Fig. 2).

D_3-Trishomocubane is the most stable molecule among the cage structures with the empirical formula $C_{11}H_{14}$.[5] Table 1 contains data on the relative stabilities of various trishomocubanes as calculated by different methods.

The majority of synthetic routes to **1** and its derivatives are based on rearrangements of the carbon cage of isomeric cage structures. For instance, in acidic medium or in the presence of Lewis acids, pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (C_s-trishomocubane) derivatives are isomerized to D_3-trishomocubanes. The mechanism of this rearrangement can be represented as follows (particular examples and reaction conditions will be discussed below):



The starting C_s-trishomocubane can bear various functional groups (R^1–R^5) that are not involved in the rearrangements, but can react with an excess of the reagent when the D_3-structure has already been formed. (Hereinafter, the symbol of the point symmetry group D_3 or C_s is related only to the cage; introduction of substituents decreases the molecular symmetry). Such a rearrangement is characteristic of C_S-trishomocubane itself and its derivatives, *viz*., alcohols (R^1 = H, R^2 = OH), ethers (R^1 = H, R^2 = OAlk) and ketones (R^1–R^2 = O). In the latter case,

Table 1. Standard enthalpies of formation (ΔH_f° /kcal mol^{-1}) and strain energies (SE /kcal mol^{-1}) of trishomocubanes.

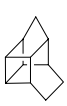
Structure	Name	ΔH_f°				SE		
		see [a]	see [b]	see [c]	see [d]	see [a]	see [b]	see [c]
	Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (D_3-trishomocubane)	9.38	11.32	8.4	6.3	42.05	44.13	39.7
	Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane	19.62	21.93	18.3	16.2	52.29	54.74	49.5
	Pentacyclo[5.4.0.0^{2,5}.0^{3,10}.0^{4,8}]undecane	18.82	22.00	17.9	15.8	51.49	54.81	49.1
	Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{4,8}]undecane	23.88	26.58	22.9	20.8	56.55	59.39	54.1
	Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{4,9}]undecane (C_{2v}-homobasketane)	48.24	53.35	42.9	40.8	80.91	86.16	74.1
	Pentacyclo[5.4.0.0^{2,5}.0^{3,11}.0^{4,8}]undecane (C_1-homobasketane, [2.1.0]triblattane)	40.99	43.82	40.3	38.2	73.66	76.63	71.6
	Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,8}]undecane	33.92	37.74	35.8	33.7	66.59	70.55	67.0
	Pentacyclo[5.4.0.0^{3,10}.0^{5,9}.0^{8,11}]undecane	33.17	40.84	36.8	34.7	65.84	73.65	68.1

Table 1 (continued).

Structure	Name	ΔH_f°				SE		
		see [a]	see [b]	see [c]	see [d]	see [a]	see [b]	see [c]
	Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{4,9}]undecane	31.81	36.08	31.2	29.1	64.48	68.89	62.4
	Pentacyclo[5.4.0.0^{2,5}.0^{3,11}.0^{4,9}]undecane	43.36	46.22	45.3	43.2	76.03	79.03	76.6
	Pentacyclo[5.4.0.0^{2,6}.0^{3,11}.0^{4,10}]undecane (C_s-homobasketane)	53.91	60.79	58.3	56.2	86.58	93.60	89.6
	Pentacyclo[5.4.0.0^{2,10}.0^{5,9}.0^{8,11}]undecane	58.05	62.46	59.5	57.4	90.72	95.27	90.7
	Pentacyclo[5.3.1.0^{2,5}.0^{3,10}.0^{4,9}]undecane	47.49	53.12	49.3	47.2	80.16	85.93	80.5
	Pentacyclo[5.4.0.0^{2,10}.0^{3,9}.0^{8,11}]undecane	85.34	90.14	84.7	82.6	118.01	122.95	116.0

Computed using: [a] the Schleyer forcefield (see [6]); [b] the Allinger forcefield (see [7]); [c] isodesmic equations (see [8]); [d] atomization energies.[8]

the reaction is complicated by subsequent transformations of the product.

Isomerization of other pentacycloundecanes are studied to much lesser extent because they are available with difficulty.[4]

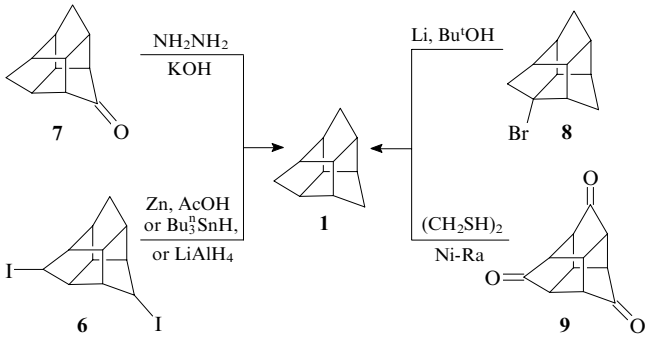
III. Synthesis of D_3-trishomocubane

Underwood[3] was the first to synthesize D_3-trishomocubane (**1**) and its derivative, 4,7-dibromotrishomocubane (**2**), from pentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diol (**3**) (Scheme 1, route *a*).

Dibromide **4** is initially formed, which eliminates HBr under the action of zinc to give a mixture of products that undergo partial isomerization during purification. In the course of bromination of diene **5**, the D_3-symmetric carbon cage is formed. Subsequent reduction of the dibromide **2** results in a mixture of diene **5** and alkane **1**, which is separated on SiO_2 with addition of 20% of $AgNO_3$.

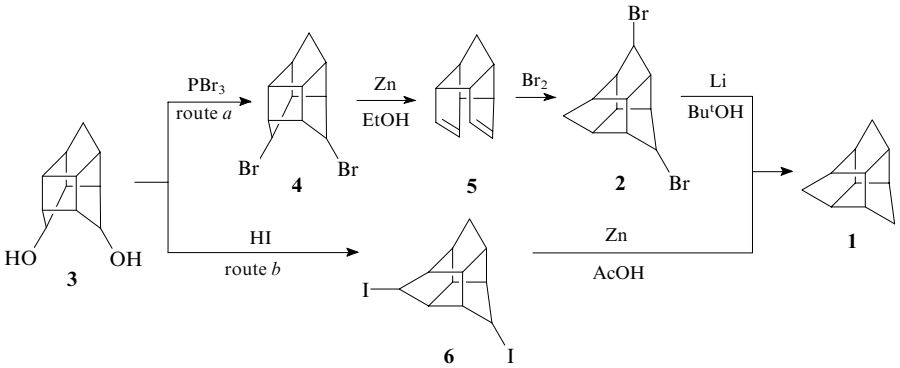
A shorter route to **1** that includes the formation of 4,7-diiodotrishomocubane (**6**) (route *b*) was proposed by Godleski *et al.*[9] High yields were reported (93% in each stage), however these yields could not be achieved by other investigators (see, *e.g.*, Ref. 10).

D_3-Trishomocubane was also obtained by reduction of its various derivatives, *e.g.*, compounds **7**–**9** (references to the original publications are given below, when discussing the syntheses).

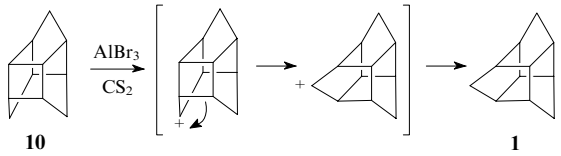


In most cases, the structures of the compounds obtained were confirmed by carrying out reduction reactions.

Scheme 1

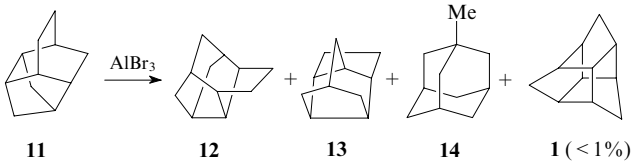


As it was noted in Section II, D_3-trishomocubane is formed as result of the rearrangement of C_s-trishomocubane (**10**) induced by Lewis acids, such as aluminium bromide.[5]

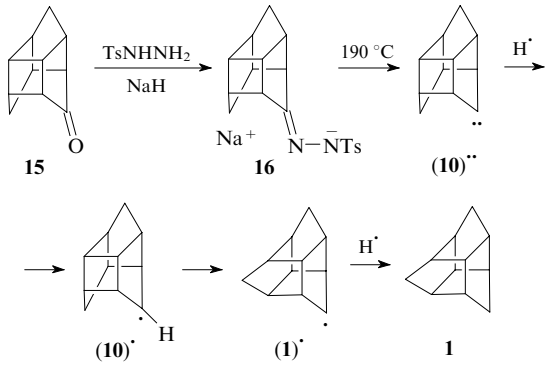


However, this route has a number of disadvantages. Alkane **10** is usually prepared from Cookson's diketone (see below). Despite the high yield (88%), compound **10** is contaminated by the tetracyclic alkene (6%), which then gives two isomeric ethanonoradamantanes (~7%) as an impurity in the target D_3-trishomocubane. Moreover, the volatility of alkane **1** makes problematic the removal of the solvent (toxic CS_2).

Trace amounts of D_3-trishomocubane were detected in the $AlBr_3$-catalyzed rearrangement products of some tetracyclic systems, such as methanotwistane (**11**), in carbon disulfide suspensions.[11] The major products of the transformation are 2,4-ethanonoradamantane (**12**), 2,8-ethanonoradamantene (**13**) and methyladamantane (**14**), the yield of trishomocubane formed being less than 1%.



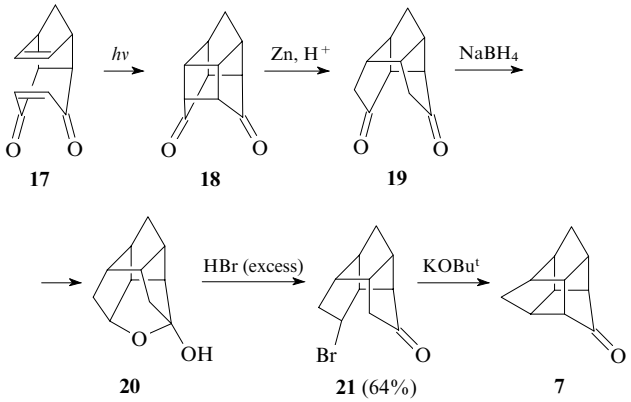
Marchand *et al.*[12] demonstrated the high stability of the D_3-trishomocubanyl radical. The C_s-trishomocubane ketone derivative **15** was converted to the corresponding tosylhydrazone sodium salt (**16**), which upon heating gives carbene (**10**)$^{\cdot\cdot}$. The C_s-trishomocubanyl radical formed upon hydrogen capture (**10**)$^{\cdot}$ undergoes rearrangement into the more stable D_3-symmetric radical. The GC-MS analysis of the hydrazone **16** pyrolysis products shows the alkane **1** content to be 13.7%.



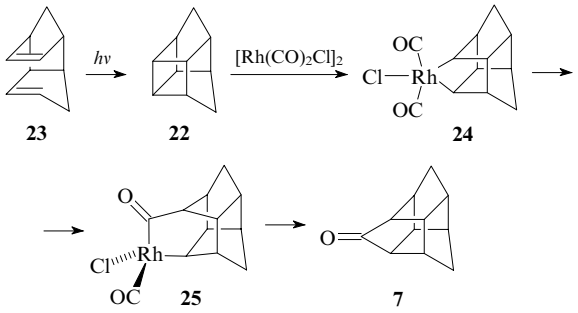
IV. Synthesis of monosubstituted D_3-trishomocubanes

1. 4-Substituted D_3-trishomocubanes

The most readily accessible are the monosubstituted D_3-trishomocubanes bearing a substituent in position 4, and the least studied isomers are those with a substituent in position 2. Historically, the first method of synthesis of 4-substituted D_3-trishomocubane was proposed by Eaton *et al.*[13] The cyclopentadiene–quinone Diels–Alder adduct (**17**) was photochemically [2+2] cyclized to pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (C_s-trishomocubanedione **18**), known as 'Cookson's diketone'. The latter was reduced with zinc in acetic acid giving the tetracyclic diketone **19**, which can be reduced with sodium borohydride to cyclic hemiketal **20**. Treatment of compound **20** with hydrogen bromide in acetic acid under high pressure and 100 °C leads to bromo ketone **21**. Dehydrobromination of **21** with potassium *tert*-butoxide results in cyclization to pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-one (D_3-trishomocubanone, **7**). All the steps except for the reaction with HBr proceeded with quantitative yields.

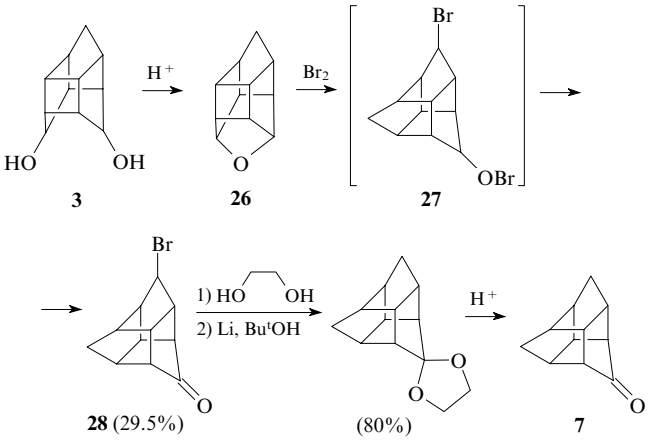


Another method of the synthesis of D_3-trishomocubane employs bishomocubane **22** as the starting material, which is obtained by photocyclization of dicyclopentadiene **23**.[14] The reaction of compound **22** with rhodium(I) binuclear complex leads to complex **24**, which is then decomposed to give D_3-trishomocubanone (**7**). It should be noted that the introduction of the CO-ligand into the hydrocarbon framework occurs first to give complex **25**, which is followed by demetallation. The yield of **7** obtained by pyrolysis of complex **24** is 40%–50%, but it can be increased up to 90%–95% if triphenylphosphine is used as an auxillary reagent. Rhodium is thus regenerated in the form of chlorocarbonylbis(triphenylphosphine)rhodium [Rh(CO).(PPh$_3$)$_2$Cl].



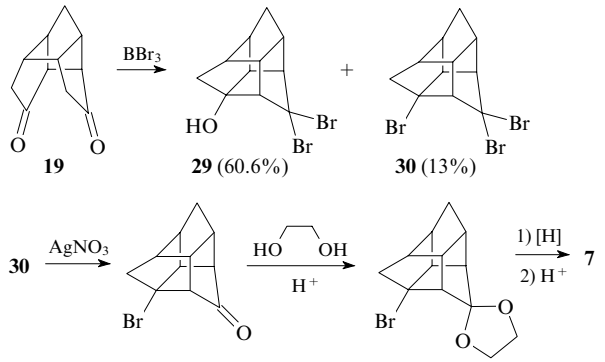
Kukhar and co-workers[15] found that ketone **7** can be synthesized from 12-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]-dodecane (**26**). The latter is formed from C_s-diol **3** under acidic conditions, often as an intermediate. The cyclic ether **26** is rearranged into unstable hypobromite **27** when treated with bromine, and after the elimination of HBr gives bromo ketone **28**. After protection of the carbonyl group, the corresponding bromo ketal was reduced with lithium in

tert-butyl alcohol, and the target ketone **7** was obtained upon removal of the ketal protecting group. The total yield in the described sequence, however, is not high, which does not allow this method to be considered as a preparative one.

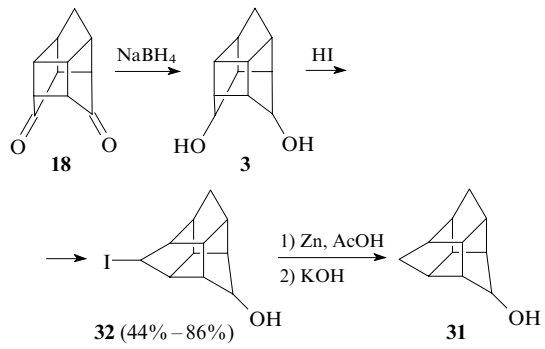


An alternative synthesis of D_3-trishomocubanone (**7**) was later suggested by the same authors,[16] tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione (**19**) serving as the starting compound (Scheme 2). But the reaction of diketone **19** with BBr_3 leads mainly to dibromide **29**, and the yield of the target compound **30** is only 13%. The necessity for isolation of the side product and numerous steps make this method of synthesis of ketone **7** inefficient.

Scheme 2



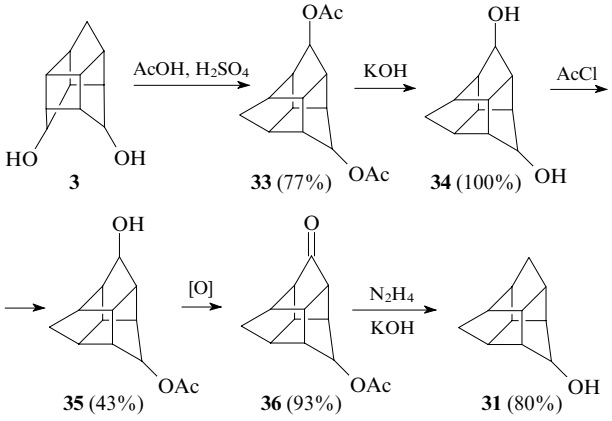
Another known representative of 4-monosubtituted D_3-trihomocubanes is pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-ol (D_3-trishomocuban-4-ol, **31**). The majority of synthetic procedures that afford this compound rely on the transformations of Cookson's diketone (**18**). Kent *et al.*[5] and Helmchen and Sataiger[17] simultaneously suggested a method in which compound **18** is first reduced to C_s-diol **3**. Refluxing of the latter in 42% hydriodic acid leads to iodo alcohol **32** in poorly reproducible and variable yields (from



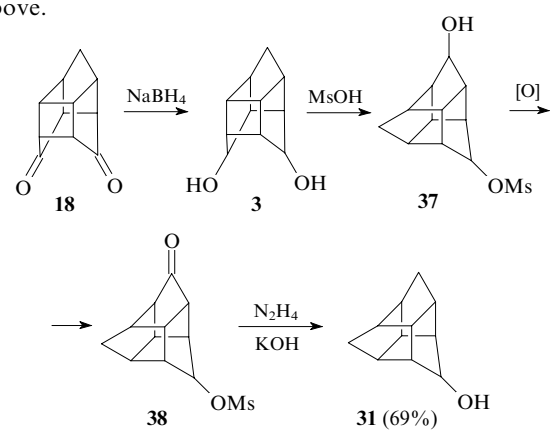
44% to 86%). This step involves the carbon skeleton isomerization and the formation of D_3-trishomocubane structure. Reduction of compound **32** with zinc in acetic acid followed by alkali treatment affords D_3-trishomocubanol **31**.

An alternative method of the synthesis of pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-ol (**31**) makes use of a longer reaction sequence (Scheme 3).[18] Cookson's diketone (**18**) is first reduced to diol **3**, which is transformed into pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4,7-diol diacetate (**33**) upon heating in glacial acetic acid in the presence of sulfuric acid. Treatment of compound **33** with alkali gives diol **34**. The reaction of the latter with a slight excess of acetyl chloride at ambient temperature affords monoacetate **35**, which is oxidized with the Jones reagent (a solution of CrO_3 in aqueous H_2SO_4) into the corresponding ketone **36**. The last step is the Kishner – Wolff reaction, which leads to D_3-trishomocubanol.

Scheme 3

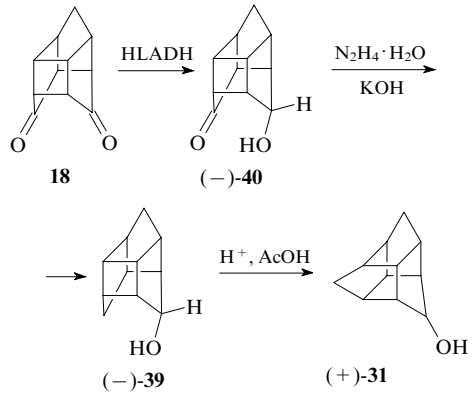


In an analogous sequence,[19] methanesulfonic acid was used instead of acetic acid. In this case, C_s-diol **3** gives 4-mesyloxypentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-7-ol (**37**) as a result of the rearrangement. The subsequent oxidation with the Jones reagent leading to ketone **38** and the Kishner – Wolff reduction afford trishomocubanol **31**. The hydrolysis of compound **37** leads to diol **34**. This method is characterized by high product yields in almost all the steps (except for the acetylation reaction **34** → **35**), which makes it more attractive compared with other methods described above.



A new in principle method for the synthesis of optically active D_3-trishomocubanol **31** from alcohol **39** with C_s-symmetric cage was described.[20] In the first step, enzymatic reduction of the carbonyl group with horse liver alcohol

dehydrogenase (HLADH) was employed. The reaction leads to the optically active compound **40**. The overall yield of compound **31** is ~40% based on the starting diketone **18**.

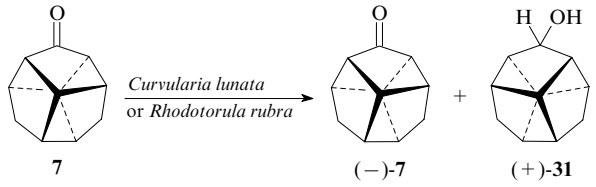


HLADH is horse liver alcohol dehydrogenase.

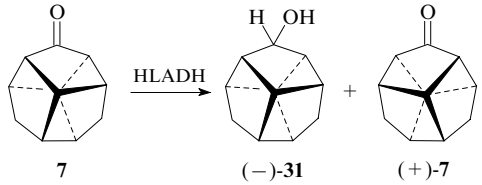
The described method is of a particular interest, since only one stereoisomer of D_3-trishomocubanol is formed.

Some other examples of synthesis of enantiopure trishomocubane derivatives should be noted. Nakazaki *et al.*[18] were the first to carry out in 1978 the separation of D_3-trishomocubanol optical isomers by reaction with phthalic anhydride and crystallization of salts with (+)-2-(1-aminoethyl)naphthalene. The same year, Eaton and Leipzig[21] managed to resolve racemic D_3-trishomocubanone into individual enantiomers through its aminal-acetal with *l*-ephedrine.

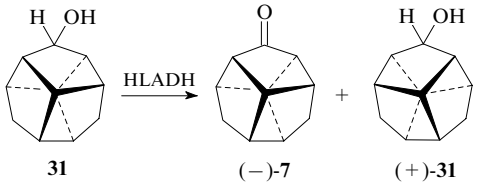
Biochemical methods play an important role in the synthesis of enantiopure D_3-trishomocubane derivatives. Thus microbiological studies showed[22] that the fungi *Curvularia lunata* and *Rhodotorula rubra* consume mainly the (+)-isomer of D_3-trishomocubanone (**7**). As a result of the reduction of the racemic compound **7** by the fungi *C. lunata* at ambient conditions for 1 h, alcohol **31** is produced in 25% yield with *ee* = 60.6%, while 40% of the (−)-stereoiomer **7** remain with 39.7% *ee*. The analogous reaction employing *R. rubra* proceeds with lower yields and smaller *ee* values for **31**. So far, enantiopure products cannot be isolated by this method.



At the same time, horse liver alcohol dehydrogenase utilizes the (−)-enantiomer of D_3-trishomocubanone (**7**) far more rapidly than its (+)-form.[23] In this reaction, a mixture of the alcohol (−)-**31** and (+)-isomer of the ketone **7** is formed in a ratio of 52:48. The optical purity of the obtained alcohol is 75% *ee*, and that of the remaining ketone, 93% *ee*.

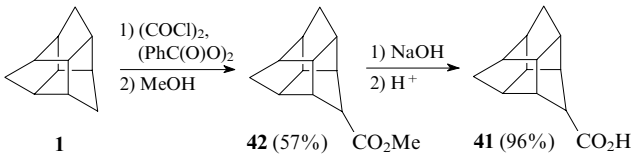


It was found later[24] that the oxidation of D_3-trishomocuban-4-ol (**31**) catalyzed by horse liver alcohol dehydrogenase resulted mainly in (−)-D_3-trishomocubanone (**7**), and the (+)-stereoisomer remained. Even prolonged (52 h) oxidation of the racemic alcohol **31** by the HLADH–NAD^+–FMN system (NAD is nicotinamide adenine dinucleotide, FMN is flavin mononucleotide) is characterized by low conversion, 32%. It was possible to isolate 54% of the intact alcohol with 23% *ee*, the yield of the ketone **7** was only 18% (63% *ee*).



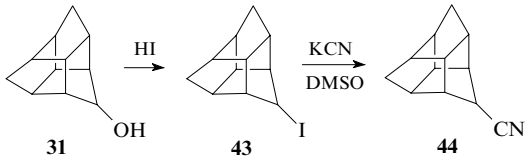
A significant influence of different co-enzymes on the enzymatic reduction of trishomocubanone **7** to alcohol **31** was demonstrated.[24] For instance, the use of the NAD^+–EtOH system instead of NADH resulted in a decrease in conversion of the starting ketone (from 52% to 38%), increased the reaction time (2.5-fold) and insignificantly increased the amount of the intact ketone (from 32% to 36%) with a decrease in its *ee* (from 93% to 59%). As for the alcohol, a reverse dependence was observed: the yield decreased (from 40% to 31%) and the optical purity slightly increased (from 76% to 81%).

Synthesis of D_3-trishomocubane-based carboxylic acid (**41**) and its methyl ester (**42**) was described by Kukhar and co-workers.[25] Compound **1** is treated with an equimolar amount of oxalyl chloride and benzoyl peroxide followed by methanol to form methyl pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-4-carboxylate (**42**). The resulting reaction mixture contained two other methyl esters (overall 3%), which could not be separated, and the intact starting compound. The yield of **42** after purification was 57%. Acid **41** was obtained upon alkaline hydrolysis of compound **42** and subsequent acidification.



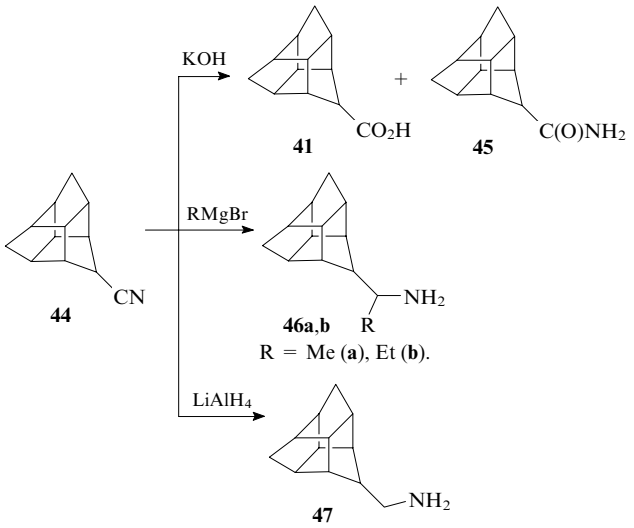
Various 4-substituted derivatives of D_3-trishomocubane, including D_3-trishomocubane-4-carbonitrile, were mentioned in a recently published patent.[26] However, no data on the methods of the synthesis and the properties of the substances obtained were given.

The authors of the present review synthesized[27] 4-iodo-D_3-trishomocubane **43** from trishomocubanol **31**. Reaction of iodide **43** with potassium cyanide leads to nitrile **44**, which was used to obtain a number of derivatives.



Thus alkaline hydrolysis of nitrile **44** leads mainly to amide **45** (the yield of the acid **41** was less than 20%).

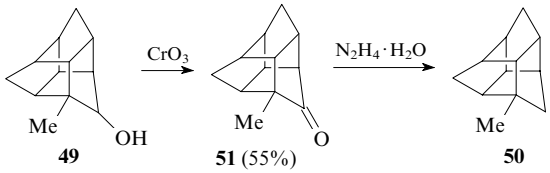
Reaction of nitrile **42** with the Grignard reagents afforded amines **46a**,**b**, and reduction with lithium aluminium hydride led to 4-aminomethyltrishomocubane **47**.



2. 1-Substituted D_3-trishomocubanes

A complicated reaction sequence was employed by Dekker *et al.*[28] to introduce a methyl group at position 1 of D_3-trishomocubane. The formation of D_3-symmetric carbon cage was achieved by rearrangement of 8-*endo*-hydroxy-8-methylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**48**) under acidic conditions. Two routes to compound **48** were proposed (routes *a* and *b* in Scheme 4). In both cases, Cookson's diketone (**18**) was used as the starting compound.

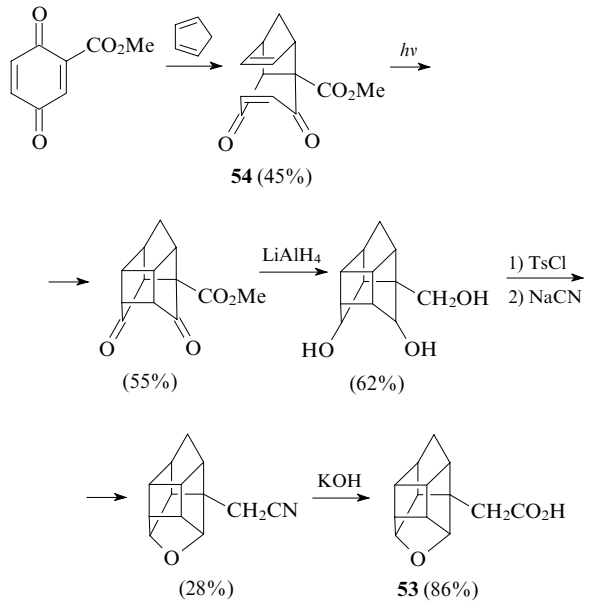
The key step of these reaction sequences is the isomerization of compound **48** to 3-methyl-D_3-trishomocuban-4-ol (**49**), which proceeds in a rather good yield. Subsequent oxidation with chromic anhydride and Kishner–Wolff reduction result in 1-methyl-D_3-trishomocubane (**50**) *via* ketone **51**.



It is of note that analogues of compound **52** that contain other hydrocarbon subtituents in position 3 can be obtained with other Grignard reagents instead of methylmagnesium iodide. For instance, 3-phenyl-D_3-trishomocuban-4-ol was synthesized in this manner.[29]

Rearrangement of substituted 12-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecane **53** obtained in several steps from 2-methoxycarbonyl-1,4-benzoquinone (Scheme 5) was investigated.[30] First, the Diels–Alder reaction of benzoquinone with cyclopentadiene occurs with the formation of adduct **54**. Photocyclization leads to the C_s-cage structure. Subsequent transformations include reduction with lithium aluminium hydride, tosylation, reaction with sodium cyanide and alkaline hydrolysis. Finally, racemic acid **53** was obtained.

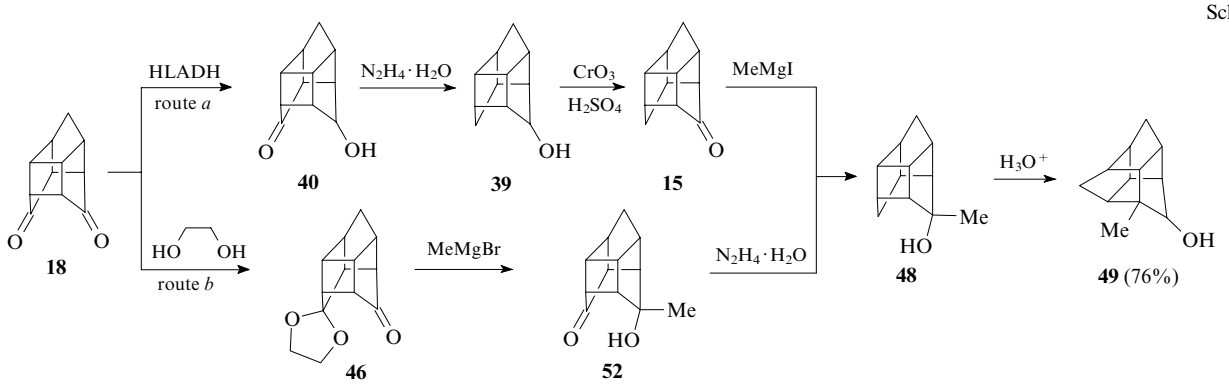
Scheme 5



The formation of its salt with the alkaloid cinchonidine allowed the isolation of the (−)-enantiomer from racemate **53**. Heating of compound (−)-**53** with concentrated H_2SO_4 at 150–160 °C followed by saponification and treatment with diazomethane and the Corey oxidation results in an equimolar mixture of diketo esters **55** and **56** from which compound (+)-**56** crystallizes (Scheme 6).

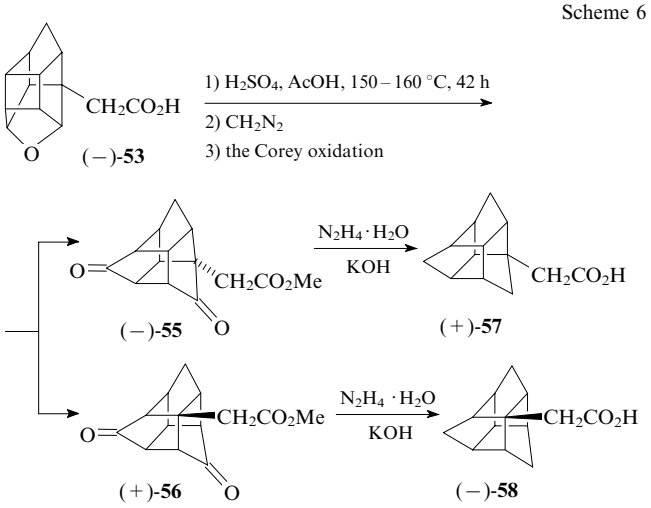
The mother liquor contains the isomeric rearrangement product (−)-**55**, which is transformed into acid (+)-**57** by reaction with hydrazine. Removal of carbonyl groups in compound (+)-**56** by the Kishner–Wolff method gave compound (−)-**58**, the first known D_3-trishomocubane derivative with a substituent in position 2. It is of note that the rearrangement of the carbon cage is insensitive to the presence of substituents at the bridgehead carbon atom.

Scheme 4

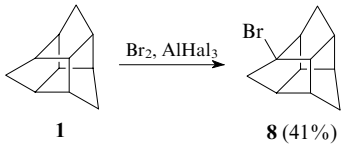


The overall yield of 1-substituted D_3-trishomocubane **57** based on the Diels–Alder adduct **54** was ~0.5%.

Scheme 6

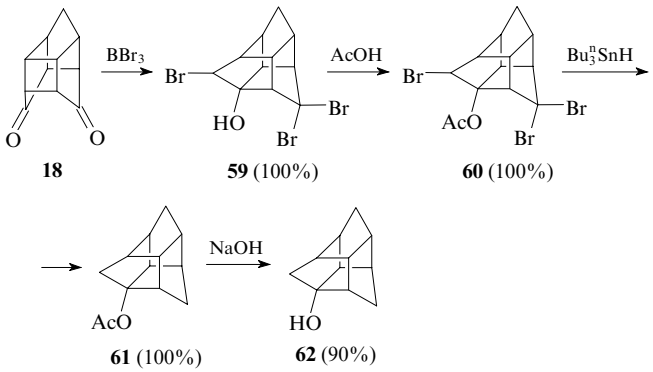


A number of papers devoted to the synthesis of 1-substituted D_3-trishomocubanes was published by Kukhar *et al.*[31–34] The first synthesis of 1-bromopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane (**8**) was achieved by direct bromination of D_3-trishomocubane (**1**).[31] The reaction proceeds only in the presence of aluminium chloride or bromide with moderate yields.

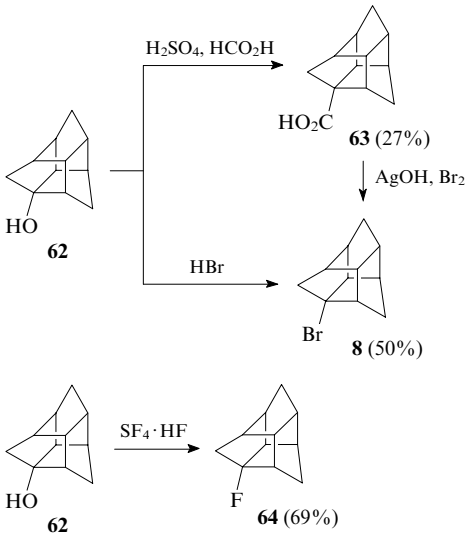


Hal = Cl, Br.

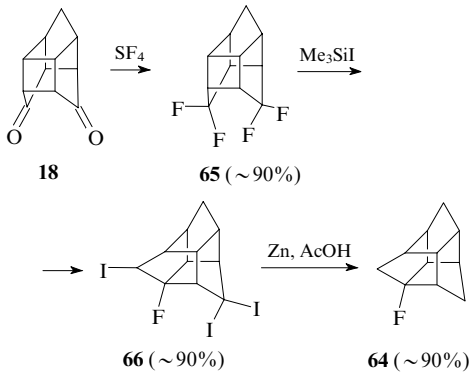
Various 1-monosubtituted trishomocubanes were obtained from Cookson's diketone (**18**).[32] Compound **18** reacts with boron tribromide to give 7,7,11-tribromopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-1-ol (**59**), which was first converted to the acetate **60** and then reduced with tributyltin hydride. Subsequent hydrolysis of compound **61** leads directly to D_3-trishomocuban-1-ol (**62**). The yields are very high in each step. The only drawback of the proposed scheme is the use of highly toxic boron tribromide.



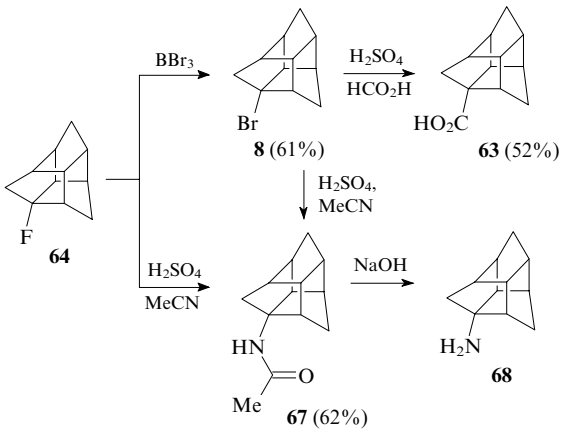
D_3-Trishomocuban-1-ol (**62**) served as a precursor for D_3-trishomocubane-1-carboxylic acid (**63**), 1-bromo- (**8**) and 1-fluoro-D_3-trishomocubanes (**64**), these transformations proceed with small yields.



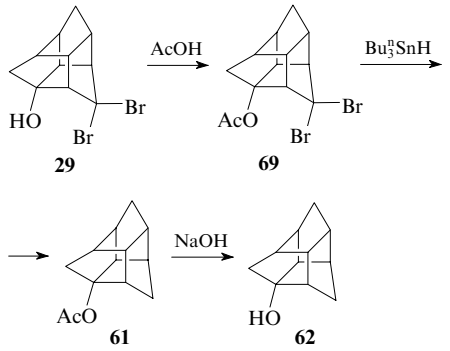
Prolonged heating of Cookson's diketone (**18**) with sulfur tetrafluoride in an autoclave affords 8,8,11,11-tetrafluoropentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**65**), which undergoes rearrangement upon treatment with trimethylsilyl iodide into 7,7,11-triiodo-1-fluoropentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**66**).[33] Reduction of the latter with zinc in acetic acid furnishes fluoride **64** in high yield.



Compound **64** served as the starting material for other D_3-trishomocubane derivatives, *viz.*, bromide **8**, acid **63**, carbamate **67** and amine **68**.



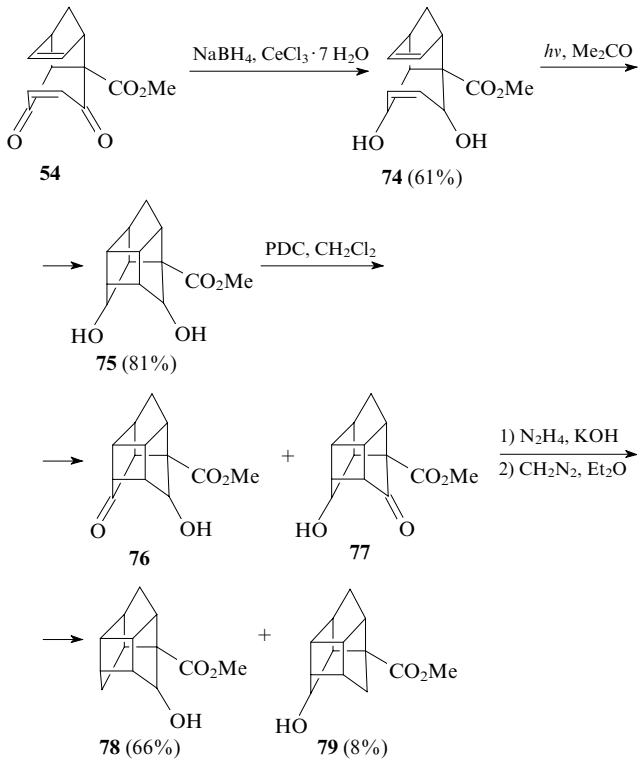
A method of synthesis of 1-acetoxy- (**61**) and 1-hydroxy-D_3-trishomocubanes (**62**) deserves attention. The starting compound **29** is the main reaction product of tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione (**19**) with boron tribromide (see Scheme 2).[34] The transformation of 7,7-dibromopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-1-ol (**69**) was carried out according to the procedure shown in Scheme 4.



3. 2-Substituted D_3-trishomocubanes

Besides the procedure developed by Nakazaki *et al.*[30] (Schemes 5 and 6), only one approach to 2-substituted D_3-trishomocubanes is reported. An intricate reaction sequence was effected[35] to afford pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-2-carboxylic acid (**70**), its amide (**71**) and methyl ester (**72**) and the respective alcohol **73** (Scheme 7).

The Diels–Alder adduct **54** served as the starting compound (see Scheme 5) for diol **74**. Its subsequent photocyclization furnished the cage compound **75** in high yield. The presence of the methoxycarbonyl group in methyl 8,11-dihydroxy-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-9-carboxylate (**75**) affects the process: the less sterically hindered hydroxyl is oxidized and a mixture of products **76**, **77** in the ratio 5.4 : 1 (88% overall yield) is formed. The Kishner–Wolff reduction followed by treatment with diazomethane affords compounds **78** and **79**, which were separated by chromatography on silica gel.

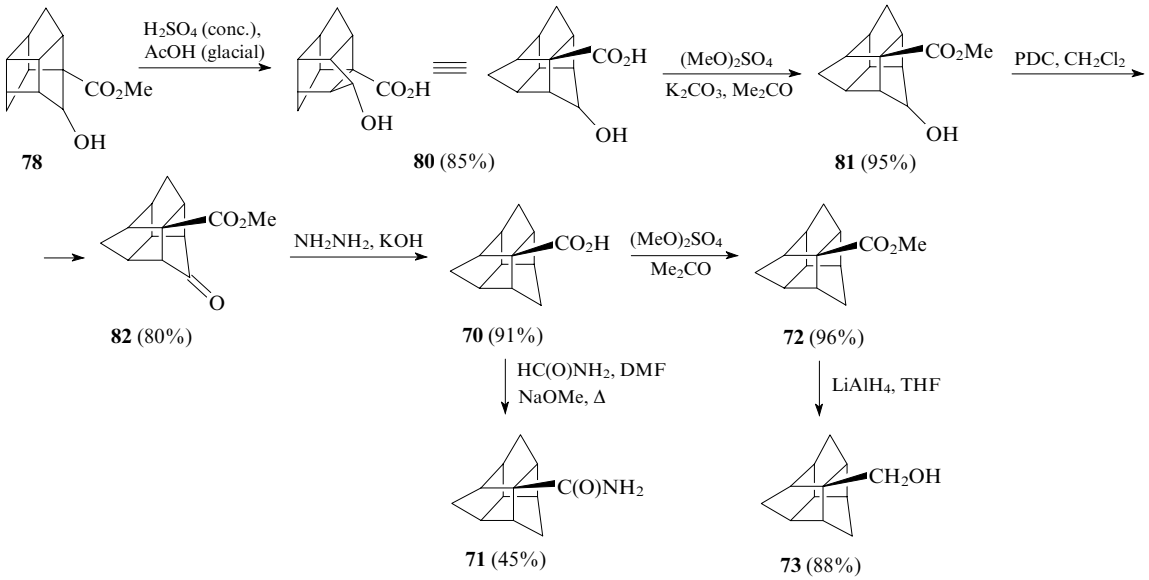


PDC is pyridinium dichromate.

The presence of a hydroxyl group in 8-hydroxy-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-9-carboxylic acid **78** facilitates the rearrangement of the C_s-structure to the D_3-cage. This results in 11-hydroxypentacyclo-[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-2-carboxylic acid (**80**), which was converted to hydroxy ester **81** and keto ester **82**. Reduction of the carbonyl group in the latter afforded the desired carboxylic acid **70**.

The overall yield of 2-D_3-trishomocubylmethanol **73** was $< 15\%$ based on the Diels–Alder adduct **54** (see Scheme 7).

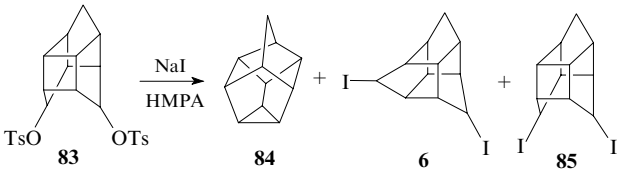
Scheme 7



V. Synthesis of di- and polysubstituted D_3-trishomocubanes

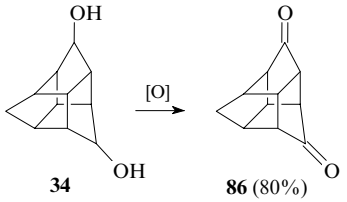
1. 4,7-Disubstituted D_3-trishomocubanes

The majority of disubstituted D_3-trishomocubanes were obtained by rearrangements of the corresponding C_s-structures. Historically, the first examples of these compounds were aforementioned 4,7-dibromotrishomocubane (**2**) and 4,7-diiodotrishomocubane (**6**). Marchand *et al.*[36] modified the Godleski procedure[9] by employing the C_s-ditosylate **83** as the starting compound instead of the diol **3** itself and using NaI solution in hexametapol (HMPA) instead of HI. Hexacyclic compound **84** was the target product, but a mixture of products was obtained including D_3-diiodide **6** and C_s-diiodide **85** (in a ratio 1.5 : 1, the overall yield of the diiodides being 43%). The spectroscopic properties of diiodide **6** and the mechanism of its formation were studied later.[10]



83 **84** **6** **85**

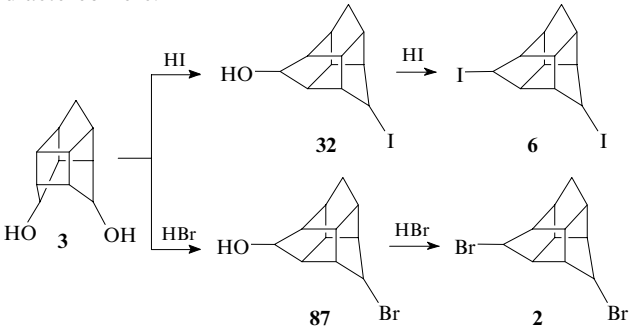
D_3-Trishomocubane-4,7-diol diacetate (**33**), 4,7-diol **34** and D_3-trishomocubane-4,7-dione **86** were synthesized from the diol **3** using the reaction sequence analogous to that depicted in Scheme 3.[37]



34 **86** (80%)

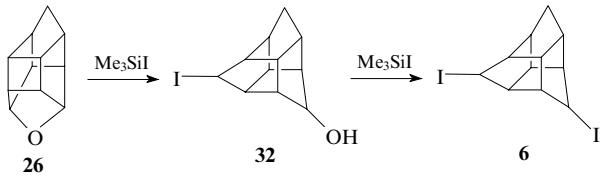
[O] is the Jones reagent.

Upon heating of diol **3** with hydrobromic acid, bromo-D_3-trishomocubanol **87** is formed, and refluxing with hydroiodic acid gives iodo-D_3-trishomocubanol **32**.[5] Prolonged reflux with the corresponding acids results in the formation of the dihalogeno compounds **2** and **6**. It should be noted that the products **2**, **6**, **32** and **87** are formed as diastereomers.



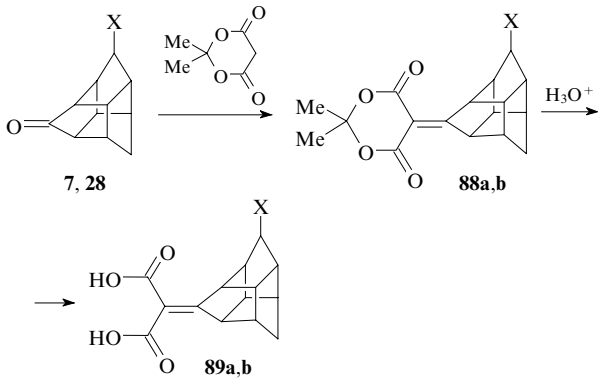
In some cases, 4,7-substituted D_3-trishomocubanes were synthesized with the aim of transformation ultimately into compound **1** [*cf.* the above-mentioned schemes of synthesis of compounds **27** and **28**,[15] **33**–**36**,[18] **37** and **38** (Ref. 19)].

Kukhar *et al.*[15] developed a method for synthesis of diiodide **6** and iodo alcohol **32** from cyclic ether **26**. The yield of a mixture of isomeric iodo alcohols formed upon 10-h heating of the ether **26** with trimethylsilyl iodide was 47%, while heating of the reaction mixture for 150 h afforded 73% of diiodide **6.** A drawback of the method is the use of the poorly accessible, trimethylsilyl iodide.



26 **32** **6**

The Knoevenagel reaction of ketone **7** or **28** with isopropylidene malonate (Meldrum's acid) was studied by Alexandrov *et al.*[38] As a result, cyclic esters **88a**,**b** were obtained, which gave upon hydrolysis free dicarboxylic acids **89a**,**b**. The presence of the substituent (a bromine atom) in the ketone molecule decreases the product yield (from 78% for compounds **88a** to 68% for compounds **88b**).



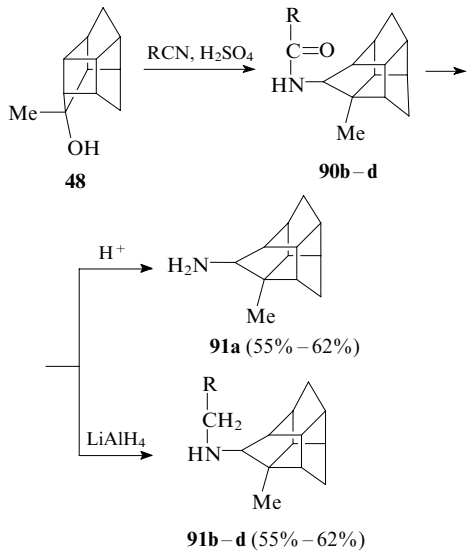
7, **28** **88a**,**b** **89a**,**b**

X = H (**7**, **88a**, **89a**), Br (**28**, **88b**, **89b**).

2. 3,4-Disubstituted D_3-trishomocubanes

The first representative of the 3,4-disubstituted D_3-trishomocubanes, *viz.*, 3-methyl-D_3-trishomocubane-4-ol (**49**), was synthesized by Dekker[26] (see Scheme 4), this was then transformed into 1-methyl-D_3-trishomocubane (**50**).

Amides **90b**–**d** were obtained by the Ritter reaction from tertiary alcohol **48**.[39] These amides are hydrolyzed to



48 **90b**–**d**

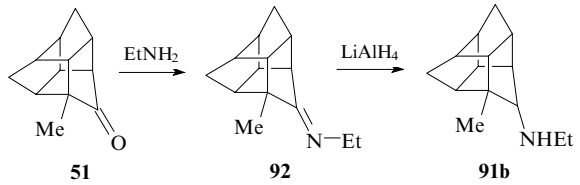
91a (55%–62%)

91b–**d** (55%–62%)

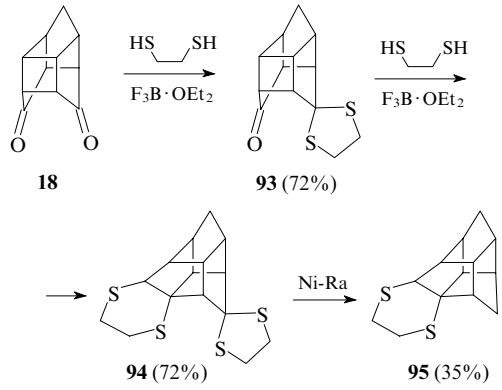
R = Me (**b**), Pr^n (**c**), Ph (**d**).

form 4-amino-3-methyl-D_3-trishomocubane (**91a**). Reduction of the amides with lithium aluminium hydride leads to the corresponding secondary amines **91b–d**. Later, 4-amino-3-phenyl-D_3-trishomocubane (**91e**) was synthesized analogously.[40] Replacement of the methyl group in the substrate **48** by the phenyl group resulted in an insignificant decrease in the product yield.

Secondary amine **91b** was obtained by reaction of the monoketone **51** with ethylamine followed by reduction of the resulting imine **92**.[41] However, neither the synthetic procedure nor physicochemical properties of compound **91b** were described.

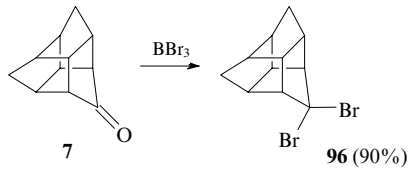


When Cookson's diketone (**18**) is treated with ethanedithiol in the presence of boron trifluoride, the dithioketal **93** is formed first followed by dithianodithioketal **94**.[42] The latter was reduced with Raney nickel to the dithiane derivative **95**.



3. 4,4-Disubstituted D_3-trishomocubanes

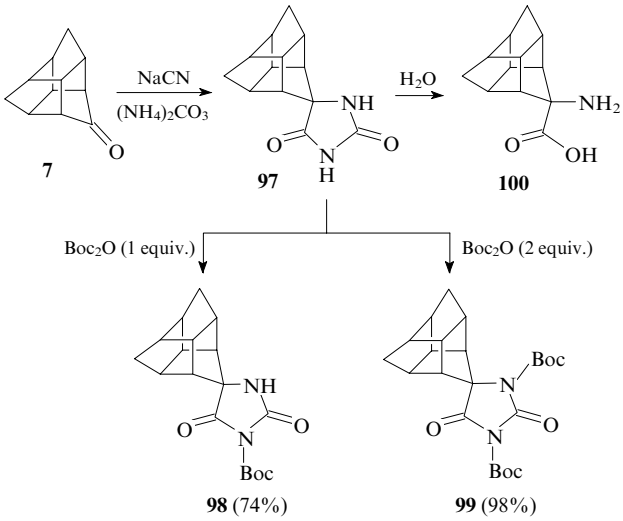
D_3-Trishomocubane derivative **96**, which bears two substituents (bromine atoms) in position 4, was first synthesized by the action of boron tribromide on D_3-trishomocubanone **7**.[31]



The same ketone affords under conditions of the Bucherer–Bergs reaction.[43] Reaction of hydantoin **97** with di-*tert*-butyl dicarbonate leads to mono- (**98**) and di-Boc-protected (**99**) hydantoins, and hydrolysis of compound **97** gives amino acid **100** (Scheme 8).

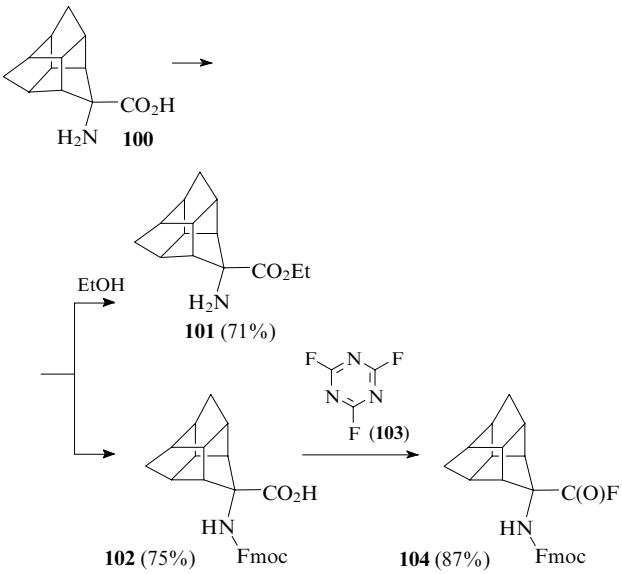
Protection of the carboxy and the amino groups of amino acid **100** furnished ethyl ester **101** and Fmoc-protected amino acid **102**.[44] Compound **102** reacts with 2,4,6-trifluoro-1,3,5-triazine (**103**) to give N-protected amino acid fluoride **104** (Scheme 9).

Scheme 8



Boc is *tert*-butoxycarbonyl.

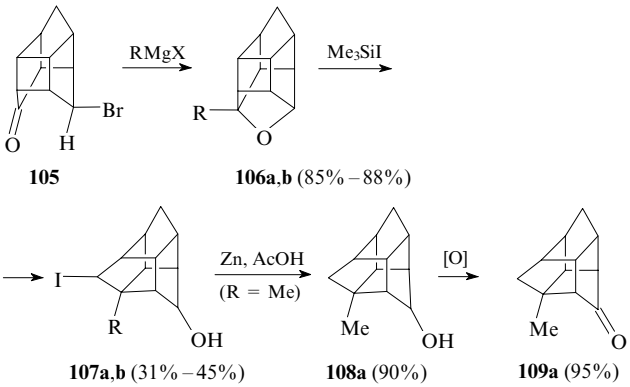
Scheme 9



Fmoc is 9-fluorenylmethoxycarbonyl.

4. Miscellaneous disubstituted D_3-trishomocubanes

11-Bromopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (**105**) was employed as the starting material for the syntheses of various D_3-trishomocubanes.[45]



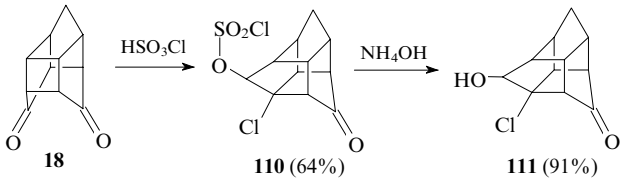
R = Me (**a**), Ph (**b**).

Reaction of bromo ketone **105** with the Grignard reagents gives 1-substituted 12-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecanes **106a**,**b**. Treatment of the latter with trimethylsilyl iodide results in the oxygen-containing ring opening and rearrangement to 11-iodo-1-methyl-pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-7-ol (**107a**) and the analogous phenyl derivative **107b**. Reduction of the iodo alcohol **107a** with zinc in acetic acid affords 1-methylpentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-7-ol (**108a**), which is then oxidized with the Jones reagent to methyltrishomocubanone **109a**. The reaction is characterized by high yields of ketone **109a**, while compound **51**, *i.e.* the oxidation product of methyltrishomocubanol **49** (see above), is formed only in 55% yield. This fact unambiguously demonstrates the effect of the substituent in the α-position relative to the hydroxyl group on the oxidation process.

The aforementioned compounds **80**–**82**[35] also belong to disubstituted D_3-trishomocubanones.

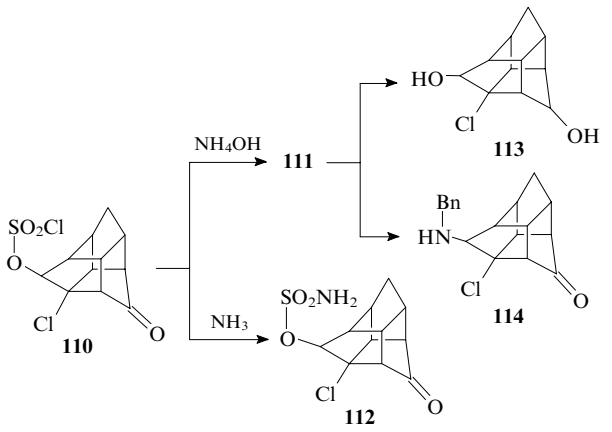
5. Polysubstituted D_3-trishomocubanes

In the reaction of Cookson's diketone (**18**) with chlorosulfonic acid, 1-chloro-11-chlorosulfonyloxypentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-7-one (**110**) was obtained for the first time;[46] this was hydrolyzed with aqueous ammonia to chloro hydroxy ketone **111**. An important characteristic feature of this transformation is the preferable *endo*-configuration of the chlorosulfonic (and then the hydroxy) group.



18 **110** (64%) **111** (91%)

This rearrangement was later investigated in detail, its mechanism was elucidated and this was employed in the synthesis of compounds **112**–**114**.[47,48] It should be noted that the yields of the products were not given in the cited papers.

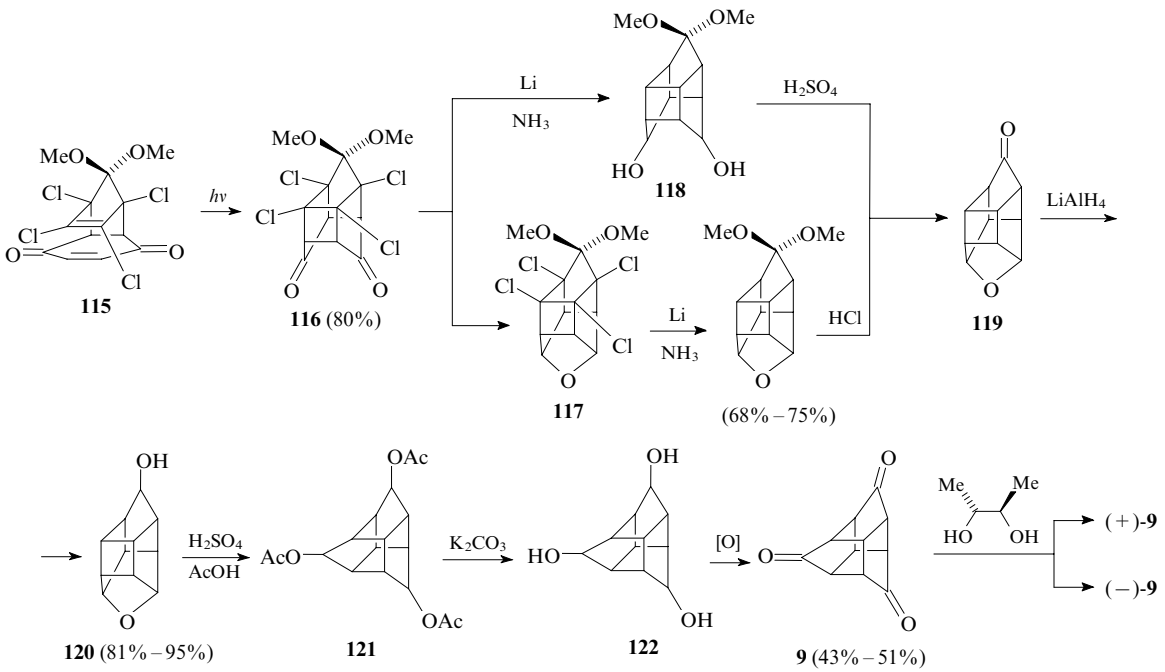


Fessner and Prinzbach[49] used the route presented in Scheme 10 to synthesize trishomocubanetrione **9**. The Diels–Alder reaction with perchlorocyclopentadiene ketal afforded adduct **115** instead of cyclopentadiene.

Dechlorination of the photocyclization product **116** or ether **117** took place under the action of lithium in liquid ammonia. It is of note that compound **117** affords the reduction product in 68%–75% yield, which is not always possible when four chlorine atoms must be simultaneously eliminated from a cage structure. The transformation of compound **118** to ketone **119** proceeds in acidic medium (47%–59% yield). Reduction of ketone **119** with lithium aluminium hydride gives a mixture of *syn*- and *anti*-isomers of alcohols **120** in a 3 : 1 ratio (the overall yield is 95%). Using sodium borohydride as a reducing agend not only decreases the yield to 81%, but changes the *syn*- to *anti*-ratio to 2 : 1.

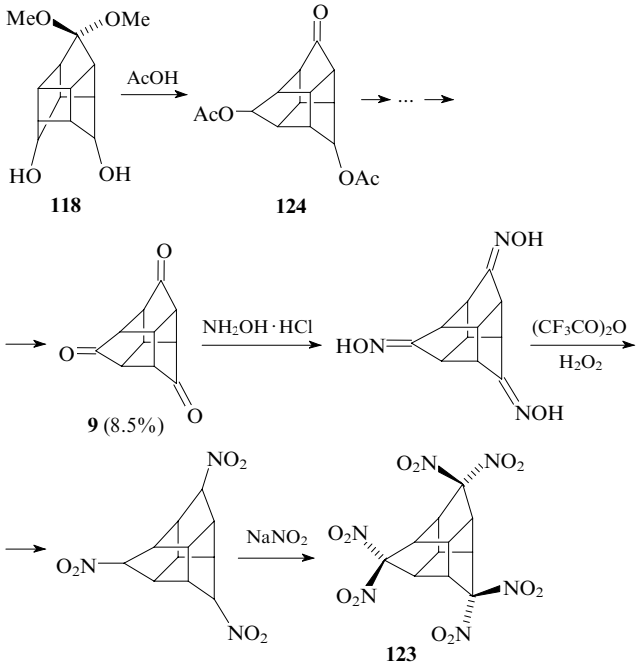
The rearrangement of compound **120** into the D_3-structure **121** with sulfuric and acetic acids faces certain difficulties. Pure *syn*-**120** isomer afforded one isomer of the triacetate, *viz.*, *syn*,*syn*,*syn*-**121**. However, from a mixture of the isomeric alcohols **120** (3:1 ratio), *syn*,*syn*,*syn*-triacetate **121** could be isolated only in 18% although the overall yield of the crude product was 93%. Hydrolysis of compound **121** in the presence of potassium carbonate proceeds

Scheme 10

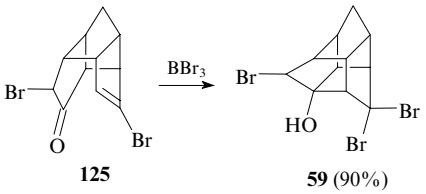


with 89%–97% yield. The triketone **9** is obtained by oxidation of the triol **122** with chromium(VI) oxide in sulfuric acid. Compound **9** was resolved into enantiomers using coupling with (*R*,*R*)-butane-2,3-diol.

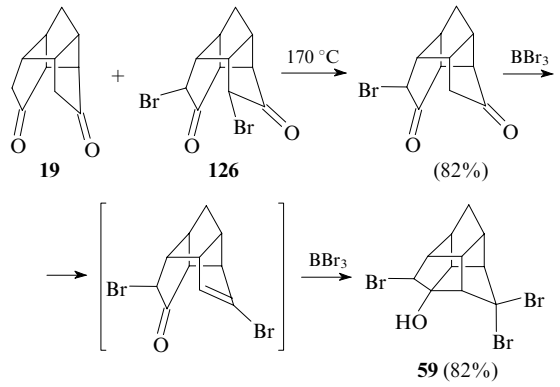
Transformation of D_3-trishomocubane-4,7,11-trione (**9**) to 4,4,7,7,11,11-hexanitro-D_3-trishomocubane (**123**) was described.[50] The formation of cyclic ether **120** in the synthesis of trione **9** could be avoided, C_s-diol **118** was converted directly to the diacetate **124**. This approach to the synthesis of trione **9** is remarkable by the fact that diacetoxy ketone **124** is formed together with the isomeric diacetoxy ketone, which has the C_s-trishomocubane cage (*i.e.* hydrolysis of the ketal is not necessarily accompanied by a rearrangement). Good solubility in water of the hydrolysis product of **124** and the failure to isolate the isomeric dihydroxy ketones by extraction with organic solvents necessitates the use of protecting groups. The C_s-isomer cannot be separated from the target D_3-product until the final step of the synthesis. The overall yield of compound **9** based on diacetate **124** was about 8.5%.



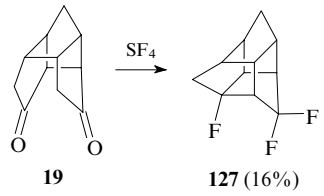
Mention has been made on the polyhalogenated D_3-trishomocubanes, *viz*., 7,7,11-triiodo-1-fluoropentacyclo[6.3.0. .$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane (**66**),[33] 7,7-dibromopentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-1-ol (**29**), 1,7,7-tribromopentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane (**30**)[16] and 7,7,11-tribromopentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecan-1-ol (**59**).[32] The latter is also formed in the reaction of 3,7-dibromotetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undec-6-en-2-one (**125**) with boron tribromide.[32]



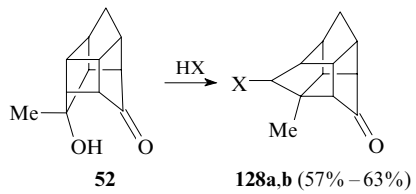
Compound **59** was also obtained from tetracyclo[6.3.0.$0^{4,11}$.$0^{5,9}$]undecane-2,7-dione (**19**) and its 3,6-dibromo derivative **126**.[51] The first step of this transformation requires fusion of the reactants at 170 °C for 4 h. The second step could be effected only on a microscale.



The reaction of dione **19** with sulfur tetrafluoride furnished 1,7,7-trifluoropentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**127**) (Ref. 32).

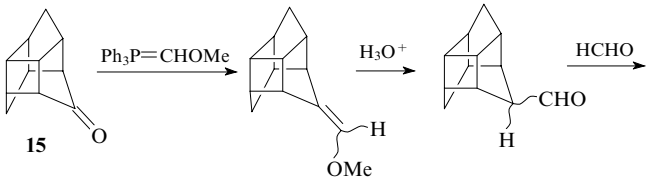


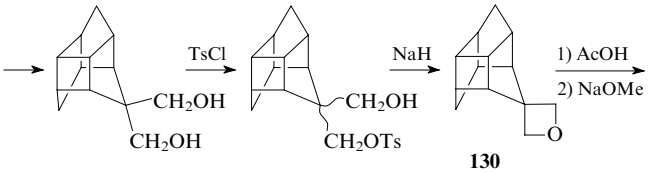
Treatment of compound **52**, which was obtained from Cookson's diketone (see Scheme 4), with hydrochloric acid or hydrogen bromide resulted in 11-chloro-1-methylpentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-7-one (**128a**) or its bromo analogue **128b** (Ref. 52).

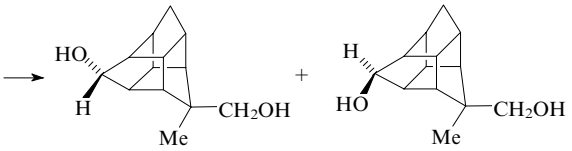


X = Cl (**a**), Br (**b**).

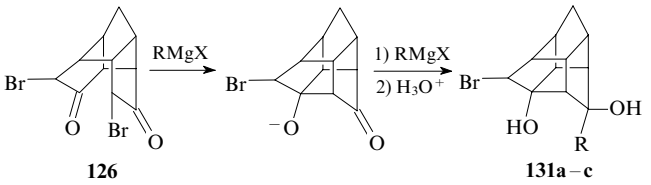
In 1992, Marchand *et al.*[53] synthesized isomeric diols **129** through ring-opening of spirooxetane **130**. Later, this transformation was repeated with the mono-deuterated ketone **15** in order to elucidate the reaction mechanism.[54] The key step of this process is the 1,5-hydride shift, which induces the oxetane ring-opening under the action of a cation, and results in rearrangement. Thus, the reacion that began as acid hydrolysis of the internal ether ends in CH_2-functionalization, isomerization and transformation of the oxetane into the hydroxy compounds **129** rather than 1,3-diol. Preferred formation of the *endo*-hydroxy isomer (*endo* : *exo* ratio is 4 : 1) demonstrates that the reaction mechanism is largely synchronous.







A method of synthesis of 4,4,6,7-tetrasubstituted D_3-trishomocubanes **131a–c** from dibromo ketone **126** and the Grignard reagent was developed.[55] A carbanionic mechanism similar to that of the Favorsky reaction is proposed for this reacion. However, in this case the negative charge is localized on the carbon atom; subsequent elimination of the bromine atom is followed by an intermolecular attack of the anion on the adjacent carbonyl group.

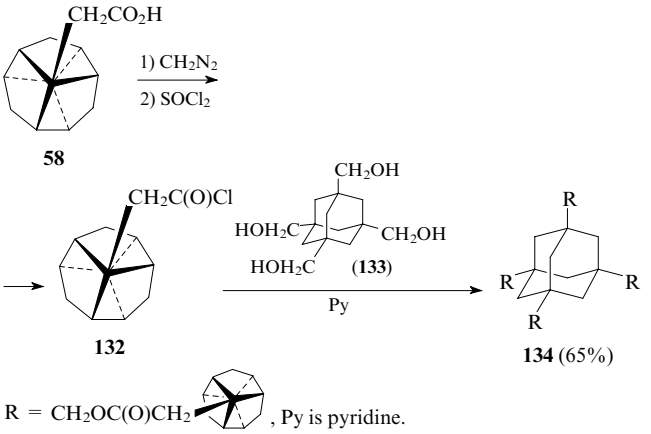


R = Me (**a**, 71%), Ph (**b**, 68%), C_6F_5 (**c**, 51%); X = Cl, Br ,I.

VI. Reactions of D_3-trishomocubane derivatives

1. Synthesis of substituted D_3-trishomocubanes bearing strained rings and highly symmetric molecules

The first optically active organic molecule with tetrahedral symmetry was synthesized from (−)-2-D_3-trishomocubylacetyl chloride **132** (see Scheme 6) and 1,3,5,7-tetrakis(hydroxymethyl)adamantane (**133**), this was (−)-1,3,5,7-tetrakis[2-(1*S*,3*S*,5*R*,6*S*,8*R*,10*R*)-D_3-trishomocubylacetoxymethyl]adamantane (**134**).[30,56] The reaction was carried out with an excess of acid chloride **132** in pyridine. The ^{1}H NMR and IR-spectroscopic data, as well as data from elemental analysis and recovery of the starting compounds upon hydrolysis of the product **134** were insufficient for unambigous determination of the structure of this compound.

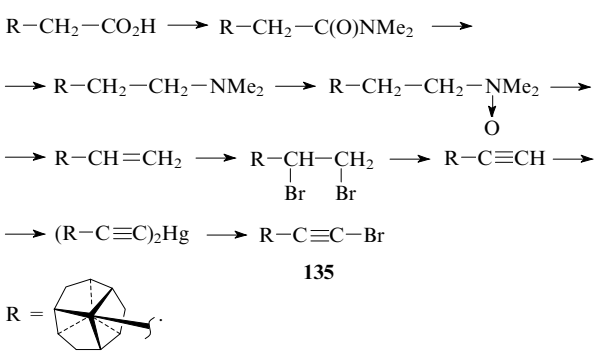


R = $CH_2OC(O)CH_2$, Py is pyridine.

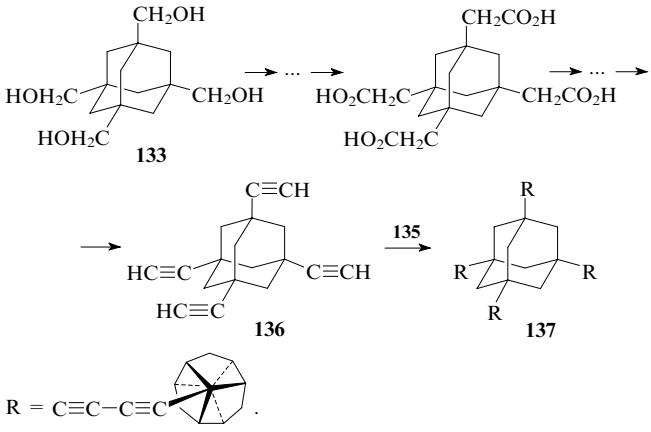
However, the ^{13}C NMR spectrum contained 10 groups of signals (the molecule has 66 carbon atoms), which corresponds to the theoretical spectrum predicted with account of geometry of molecule **134**.

According to Mislow's critisism,[57] the interposition of the acetoxymethyl ($CH_2CO_2CH_2$) groups destroys all threefold symmetry inherent in the four 2-D_3-trishomocubanyl groups and in the adamantane skeleton, and T symmetry is *ipso facto* unattainable for any conceivable conformation. Therefore, later the Japanese scientists using a complicated transformation sequence, linked[58] the trishomocubane and adamantane frameworks through rigid C–C-bond bridges. In the first step, compound **135** with D_3-symmetry was synthesized (Scheme 11).

Scheme 11



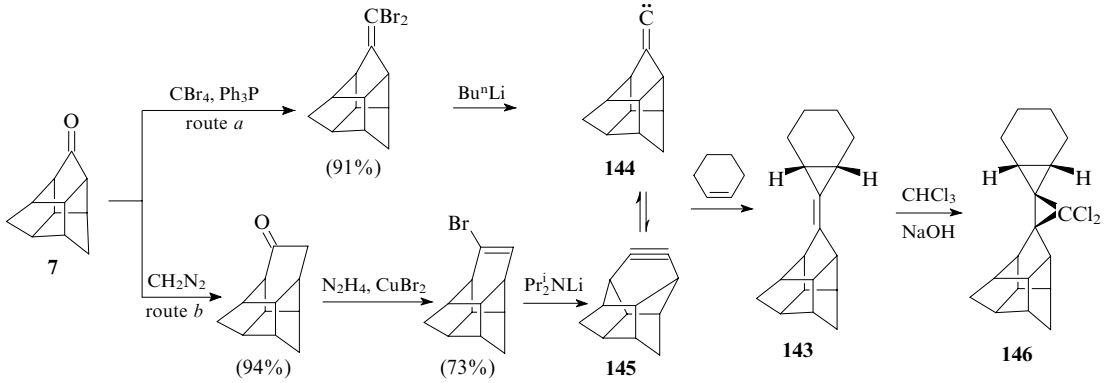
1,3,5,7-Tetrakis(hydroxymethyl)adamantane (**133**) was first transformed into the corresponding tetraacid and then to 1,3,5,7-tetraethynyladamantane **136** following the procedure depicted above (see Scheme 11); the total yield over all steps was 11%. In the final step, couplind of compound **136** with D_3-homocubane derivative **135** afforded (+)-1,3,5,7-tetrakis[2-(1*S*,3*S*,5*R*,6*S*,8*R*,10*R*)-D_3-trishomocubylbuta-1,3-diynyl]adamantane (**137**). 1,4-Bis(2-D_3-trishomocubyl)buta-1,3-diyne formed as a side product.

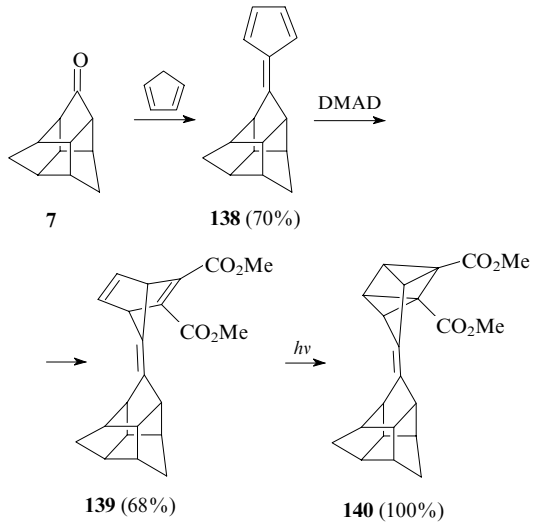


R = C≡C−C≡C .

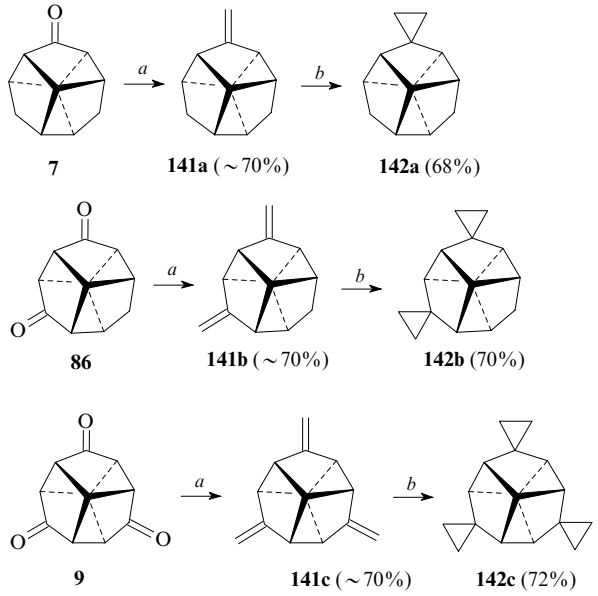
The reaction of D_3-trishomocubanone (**7**) with cyclopentadiene was used[59] to obtain fulvene **138**. Reaction of compound **138** with dimethyl acetylenedicarboxylate (DMAD) leads to triene **139,** which bears D_3-trishomocubane and norbornadiene fragments in its structure. Photocyclization of the norbornadiene part of the molecule gives 1,5-dimethoxycarbonyl-3-trishomocubylidenetetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptane (**140**) in quantitative yield.

Scheme 12





The ketones of D_3-trishomocubane series, compounds **7**, **9** and **86**, were transformed to the corresponding methylidene (**141a–c**) and spirocyclopropane (**142a–c**) derivatives.[60]



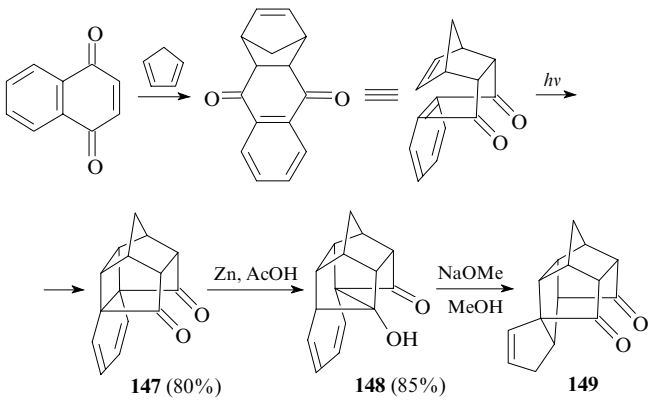
(*a*) $Ph_3P{=}CH_2$; (*b*) 1) $CHCl_3$, KOH, H_2O, $BnNEt_3Br$; 2) Li, NH_3, THF.

The multistep synthesis of 4-(bicyclo[4.1.0]hept-7-ylidene)-pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}] undecane **143**, performed by the Marchand group[61] deserves mentioning (Scheme 12).

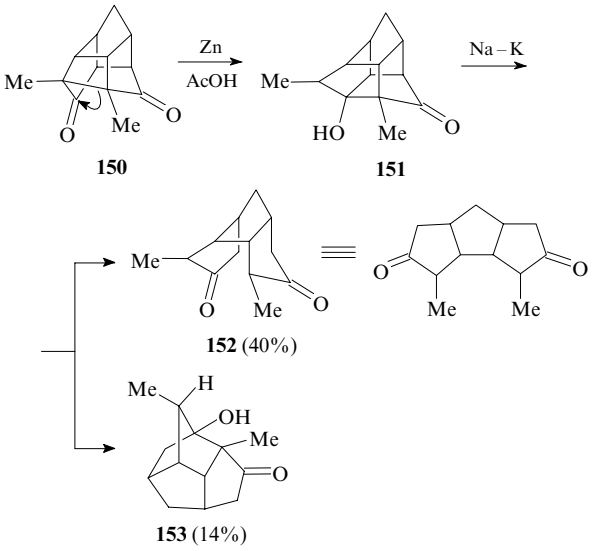
Compound **143** was synthesized by two routes. Presumably, the reaction intermediates are carbene **144** (route *a*) and the dehydrobenzene analogue **145** (route *b*). In the former case, the yield of product **143** was 60%, in the latter case, 36%. On treatment with dichlorocarbene, compound **143** is converted to dichlorocyclopropane derivative **146**.

2. Rearrangements of D_3-trishomocubane derivatives

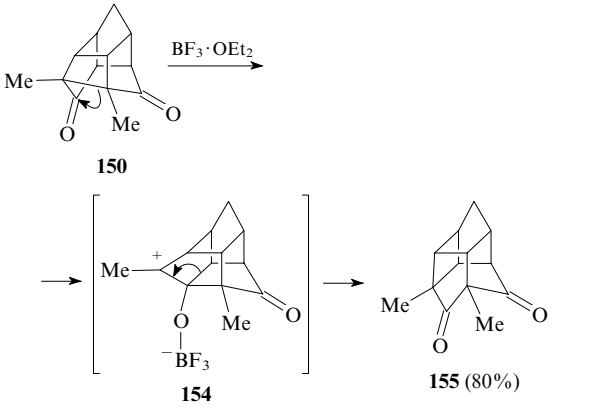
A considerable contribution to the studies of rearrangements of D_3-trishomocubane derivatives that are accompanied by changes in the carbon cage was made by the Mehta group. Some investigations from this group are discussed below. Photocyclization[62] of the Diels–Alder adduct of *p*-naphthoquinine to cyclopentadiene[63] affords C_s-hexacyclic compound **147**, which is converted to D_3-trishomocubane **148** under the action of zinc in acetic acid. When treated with sodium methoxide in methanol, compound **148** undergoes a rearrangement into diketone **149**, which is not typical of such species. In the course of the rearrangement, a spiro-cyclic system is formed and the six-membered ring of C_s-diketone **147** is expanded to seven-membered ring.



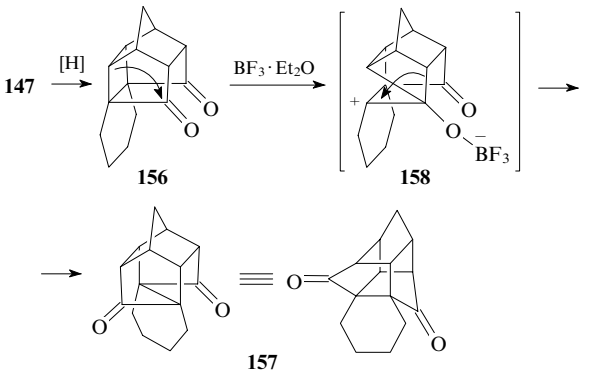
Reduction of 1,7-dimethylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione (**150**) with zinc in acetic acid furnishes 5-hydroxy-4,6-dimethylpentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-7-one (**151**). The action of sodium–potassium alloy on compound **151** leads to a mixture of polycyclic products **152** and **153**.[64]



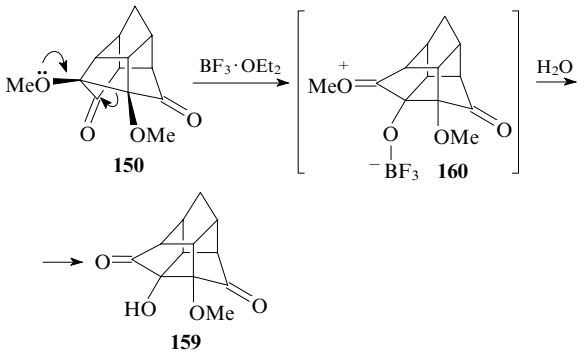
Studies of rearrangement of diketone **150** under the action of boron trifluoride etherate demonstrated[65,66] that it proceeds *via* D_3-derivative **154** formation. Nevertheless, the final product has quite a rare structure of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{4,8}]undecane (**155**).



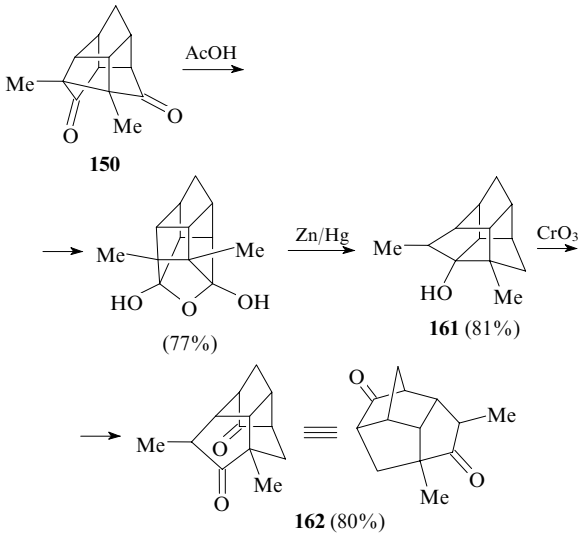
Reaction of compound **156**, which is the reduction product of diene **147** and has the structure of [4.4.2]-propellane, with boron trifluoride etherate gives a mixture of products from which propellane **157** was isolated. Apparently, the reaction proceeds *via* intermediate **158**.[66]



Under analogous conditions, substituted Cookson's diketone **150** furnishes tetrasubstituted D_3-trishomocubane **159**.[67] Presumably, the reaction proceeds *via* intermediate **160**. Unlike most rearrangements of the type, the increase in temperature from 0 to 25 °C does not decrease, but on the contrary increases the product yield (from 36% to 58%).

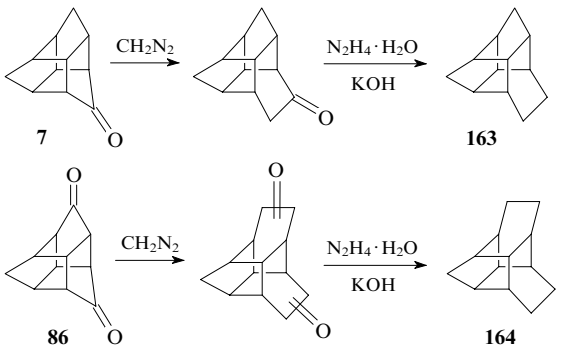


The Clemmensen reduction of preliminarily hydrated diketone **150** furnished D_3-alcohol **161**.[68] This alcohol was oxidized with chromium trioxide in acetic acid, which resulted in ring-opening product **162**.[69] It is of note that the selective C–C bond cleavage occurred in 80% yield. Analogous reactions were carried out for several other pentacyclic alcohols. However, the authors were not aware of studies by Ukrainian scientists who had synthesized unsubstituted 1-hydroxy-D_3-trishomocubane (**62**) ten years earlier (see Section IV.2).[32]



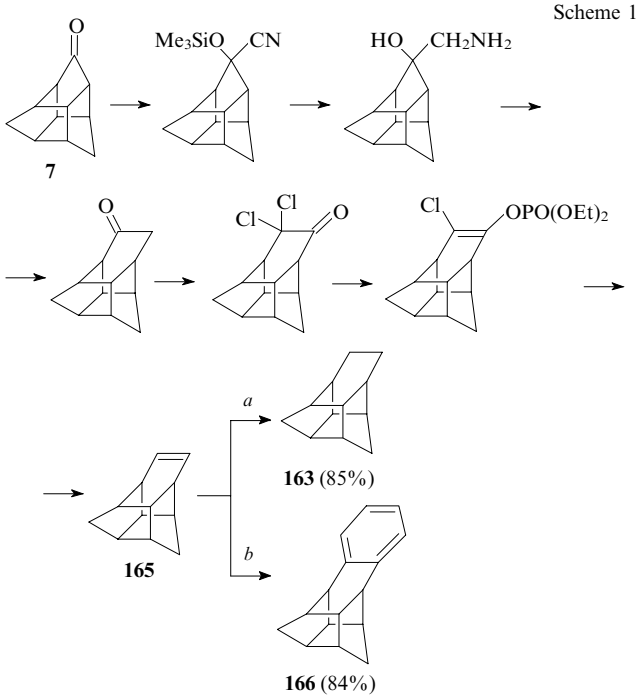
3. Synthesis of triblattanes

Some examples of transformation of D_3-trishomocubane cage structure to the triblattane cage are known. For instance, the action of diazomethane on trishomocubanone **7** and trishomocubanedione **86** with subsequent reduction afforded C_2-bismethanotwistane ([2.1.1]triblattane **163**) and



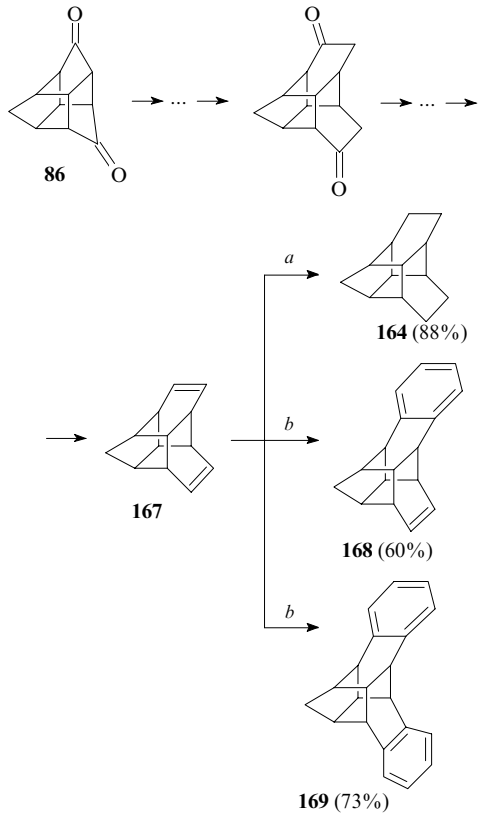
C_2-methanoditwistane ([2.2.1]triblattane **164**). The same research team later obtained [3.1.1]-, [4.1.1]- and [5.1.1]triblattanes.[71]

Scheme 13



(*a*) H_2, Pd/C, MeOH; (*b*) 1) tetrachlorothiophene 1,1-dioxide, PhMe, 110 °C, 13 h; 2) KOH, EtOH, Δ, 2 h; 3) Na, THF, Bu^{t}OH, Δ.

Scheme 14

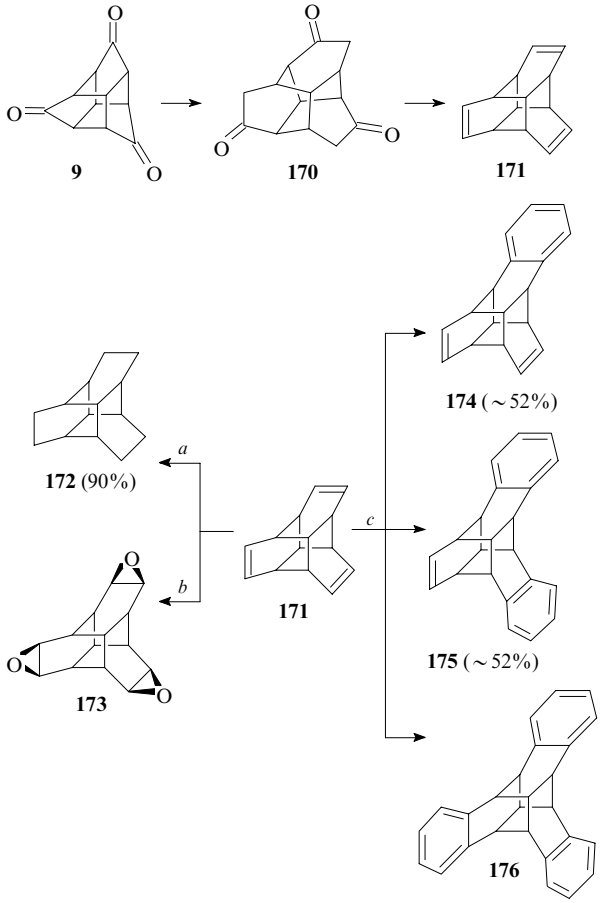


(*a*) H_2, Pd/C, MeOH; (*b*) 1) tetrachlorothiophene 1,1-dioxide, PhMe, 110 °C, 24 h; 2) KOH, EtOH, Δ, 2 h; 3) Na, THF, Bu^{t}OH, Δ.

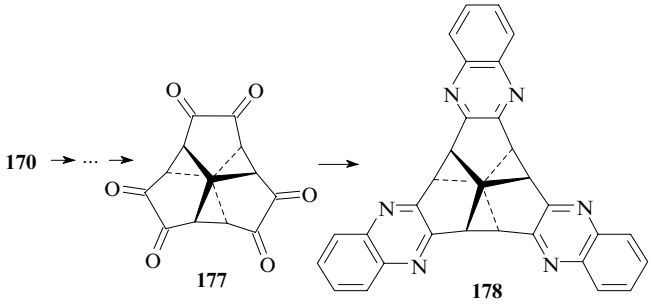
The Tiffeneau–Demjanov reaction was used[72] to expand five-membered rings in ketones of the D_3-trishomocubane series. By a multistep reaction sequence, trishomocubanone **7** was transformed to the corresponding alkene **165**, which was then reduced to triblattane **163**. Alkene **165** was also converted to triblattane **166** with an annulated benzene ring (Scheme 13).

An analogous route was employed in the transformations of diketone **86**: alkene **167** was converted to triblattanes **164**, **168** and **169** (Scheme 14).

Transformations of D_3-trishomocubanetrione (**9**) as the starting compound proceeded *via* triketone **170** and tritwistatriene **171**, yet another molecule with the D_3 symmetry, to afford triblattane **172**, triepoxide **173** and benzannulated triblattanes **174**–**176**. In addition, triblattane triketone **170** afforded hexaketone **177** and triquinoxaline **178**.



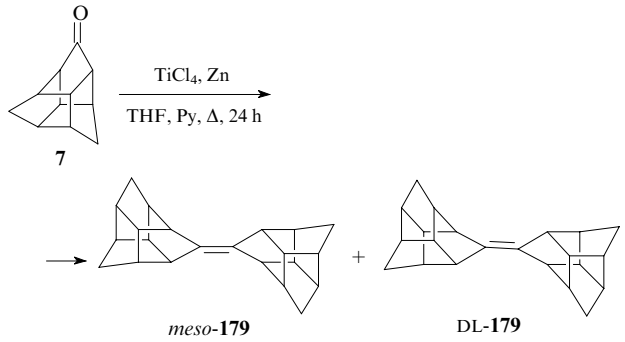
(*a*) H_2, Pd/C, MeOH; (*b*) 3-$ClC_6H_4C(O)OOH$ (MCPBA); (*c*) 1) tetrachlorothiophene 1,1-dioxide, PhMe, 110 °C, 3 days; 2) KOH, EtOH, Δ, 2 h; 3) Na, THF, Bu^{t}OH, Δ.



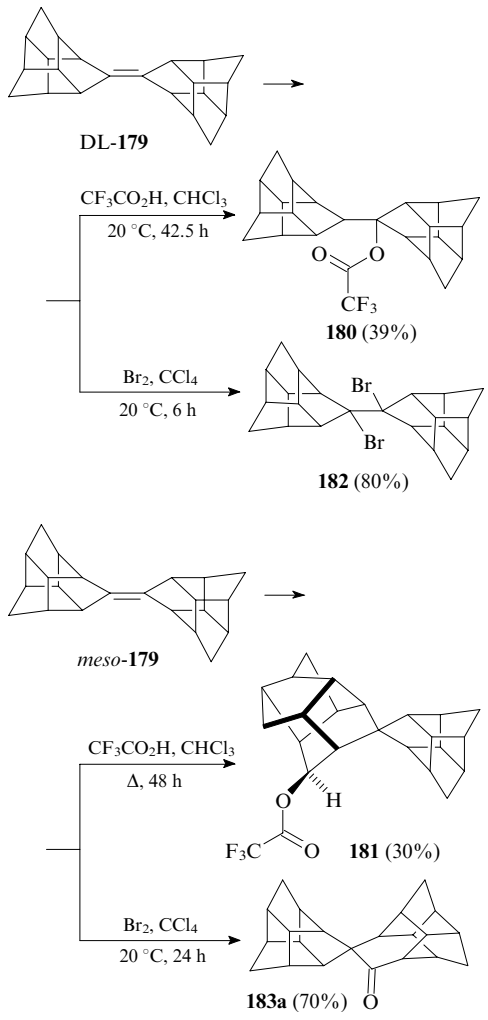
(*a*) 1) PhCHO, KOH, EtOH; 2) O_3, MeOH, −78 °C; 3) Me_2S; (*b*) 1,2-$(H_2N)_2C_6H_4$, MeOH, Δ.

4. D_3-Trishomocubane dimers

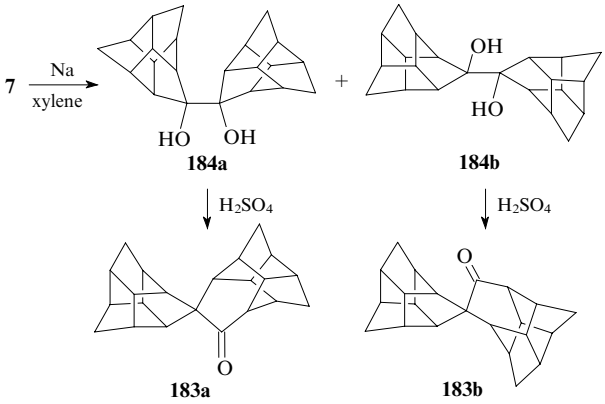
Reduction of D_3-trishomocubanone (**7**) with zinc in the presence of titanium tetrachloride gives dimeric trishomocubylidenetrishomocubane (**179**) in 60% yield.[73] This compound exists in the form of two geometrical isomers (*meso*-**179** and DL-**179**), which were separated by column chromatography and their structures were established by X-ray diffraction.



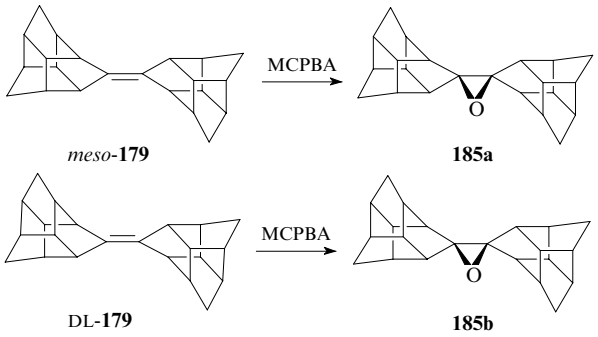
The isomers *meso*-**179** and DL-**179** possess different physicochemical properties. Thus compound DL-**179** reacts with trifluoroacetic acid in chloroform at ambient temperature with the formation of trifluoroacetate **180**. The analogous reaction of the *meso*-**179** isomer occurs only after prolonged refluxing of the reaction mixture and is accompanied by ring expansion resulting in spirocyclic trifluoroacetate **181**. Different products (dibromide **182** and diketone **183**) are formed upon electrophilic bromination of the isomers **179**.



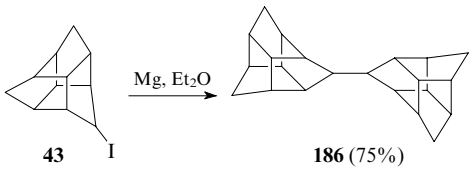
Rearrangement of pinacones **184a**,**b**, derived from D_3-trishomocubanone (**7**) into the corresponding pinacolines **183a**,**b** was studied.[73]



The action of *m*-chloroperbenzoic acid on *meso*- and DL-D_3-trishomocubylidene-D_3-trishomocubanes **179** resulted in their transformations to the corresponding oxiranes **185a**,**b**.[74]

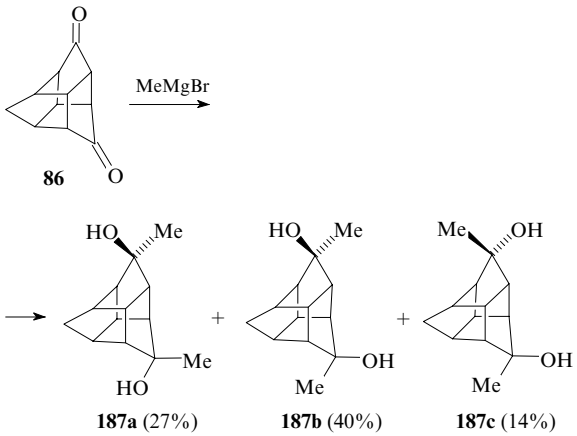


In an effort to synthesize D_3-trishomocubane-4-carboxylic acid (**41**) by treating iodide **43** with magnesium (in order to prepare the Grignard reagent) and carbon dioxide, the authors of the present review have recently obtained [75] 4,4′-bi(D_3-trishomocubyl) (**186**) in good yield. The same product is formed when iodide **43** reacts with magnesium turnings in ether, in the absence of carbon dioxide.



5. Synthesis of D_3-trishomocubane diols from diketones

Several papers describe syntheses of diols with the D_3-trishomocubane framework by reduction of the corresponding diketones. Thus the action of the Grignard reagent on D_3-trishomocubanedione **86** affords isomeric diols **187a**–**c**,[76] which were separated by fractional crystallization from acetone. The *syn*,*syn*-**187c** and *anti*,*anti*-**187a** isomers belong to the C_2 point symmetry group.



Four isomeric diols **188a–d** are formed in the reduction of 11-methyl-D_3-trishomocubane-4,7-dione (**189**) derived from ketone **124**.[77] The carbonyl group in compound **124** is first transformed into the methylene and then to the methyl group (Scheme 15).

For a detailed investigation into geometry of the intermediate benzyl ethers see Ref. 78.

VII. Heteroanalogues of D_3-trishomocubane

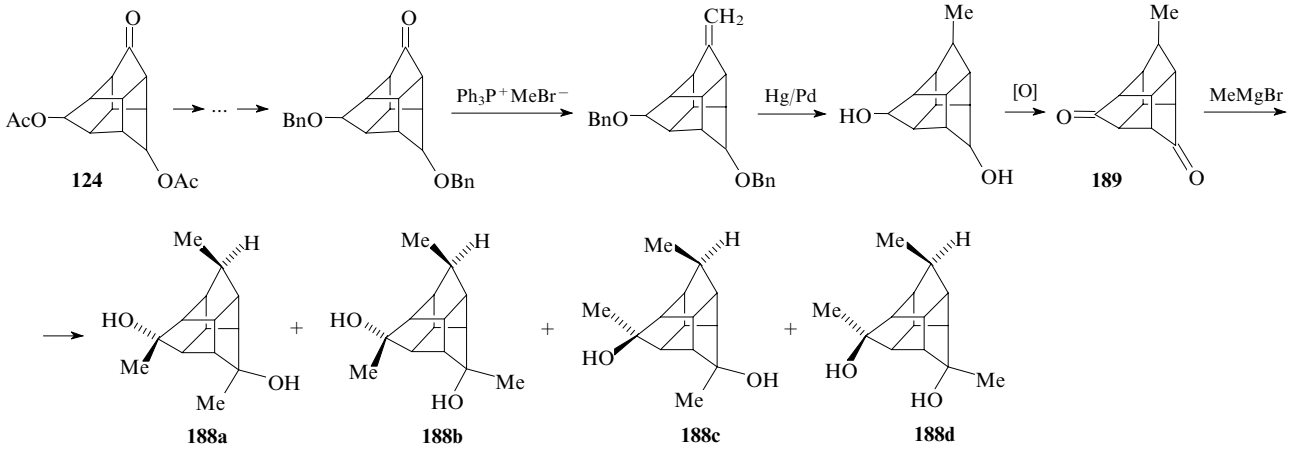
Analogues of D_3-trishomocubane are known that comprise a heteroatom, oxygen or nitrogen.

The Baeyer–Villiger oxidation of D_3-trishomocubanone (**7**) afforded lactone **190**.[79] Its reduction to diol **191** with lithium aluminium hydride followed by cyclization resulted in ether **192** (Scheme 16). Upon slight modification of the oxidation procedure of the ketone **7**, *viz*., the addition of triethyl orthoformate, cyclocarbonate **193** could be obtained, which was then reduced to diol **194**. Under the action of *p*-toluenesulfonic acid, diol **194** is transformed to the oxygen analogue of D_3-trishomocubane, *i.e*., 4-oxapentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**195**).

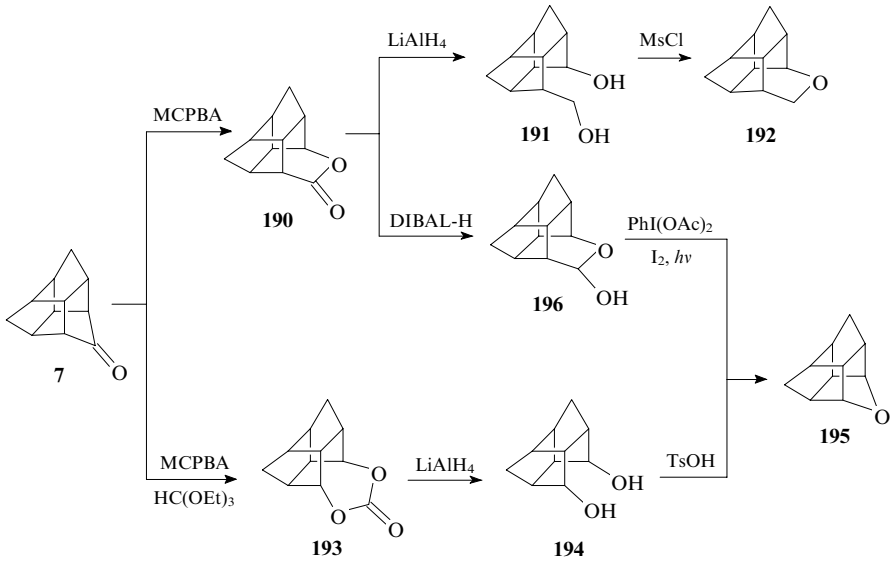
Compound **195** was also synthesized by another route. If the lactone **190** is reduced with diisobutylaluminium hydride (DIBAL-H), lactol **196** is formed, which can photochemically be oxidized with iodosobenzene diacetate in the presence of molecular iodine to the target compound **195** (see Scheme 16).[79]

Recently, a new in principle method has been described,[80] which allows the preparation of heterocyclic compounds with the D_3-trishomocubane cage containing heteroatoms in positions 4, 7 and 11. Barrelene (bicyc-

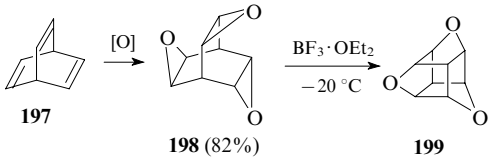
Scheme 15



Scheme 16



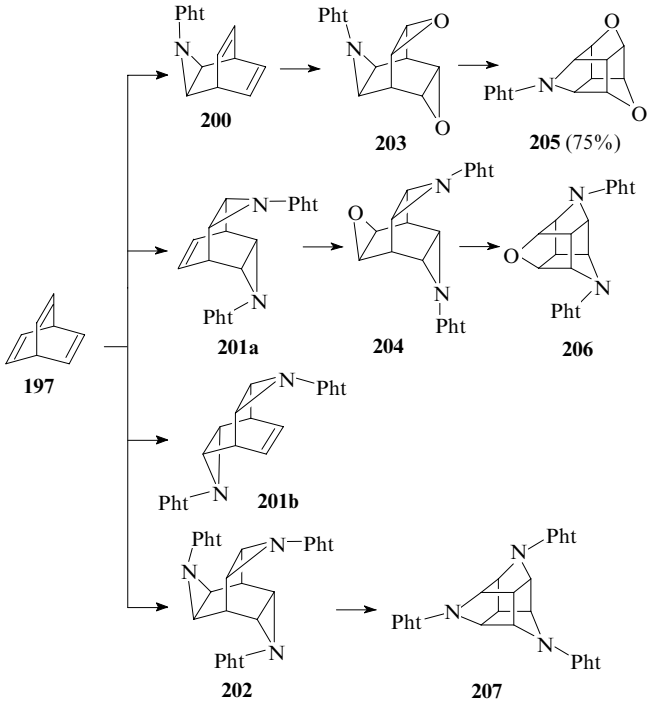
lo[2.2.2]octa-2,5,7-triene) (**197**) was used as the starting compound. Its oxidation with oxone (potassium peroxomonosulfate) furnished *endo–exo–syn*-3,7,10-trioxapentacyclo[3.3.3.$0^{2,4}$.$0^{6,8}$.$0^{9,11}$]undecane (barrelene trisepoxide or trioxatrishomobarrelene, **198**), which was then converted under the action of boron trifluoride etherate under very mild conditions to 4,7,11-trioxapentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (**199**) in quantitative yield.



197 **198** (82%) **199**

The reaction of barrelene **197** with *N*-aminophthalimide and lead tetraacetate in the presence of potassium carbonate resulted in a mixture of products (Scheme 17).[80] With 2 equiv. of *N*-aminophthalimide and the reaction time of 2 h, the major product was *N*-phthalimido-3-azatricyclo[3.2.2.$0^{2,4}$]nona-6,8-diene (**200**). In the case of sixfold excess and prolonged reation time (6 h), the main product was *endo–exo*-3,7-bis(*N*-phthalimido)-3,7-diazatetracyclo[3.3.2.$0^{2,4}$,$0^{6,8}$]dec-9-ene (**201a**) (the content in the reaction mixture was 45%, isolated in 21% yield). Besides, the reaction mixture contained *exo–exo*-3,7-bis(*N*-phthalimido)-3,7-diazatetracyclo[3.3.2.$0^{2,4}$,$0^{6,8}$]dec-9-ene (**201b**) (19% content, 8% isolated) and *endo–exo–syn*-3,7,10-tris(*N*-phthalimido)-3,7,10-triazapentacyclo[3.3.3.$0^{2,4}$.$0^{6,8}$.$0^{9,11}$]-undecane (**202**) (29% content, 19% isolated), while the monoadduct **200** amounted only to 7% of the reaction products.

Scheme 17

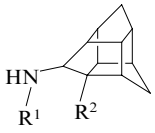


Pht is phthalimide.

Compounds **200** and **201a** were oxidized with *m*-chloroperbenzoic acid to the corresponding epoxides, *endo–exo–syn*-10-(*N*-phthalimido)-3,7-dioxa-10-azapentacyclo-[3.3.3.$0^{2,4}$.$0^{6,8}$.$0^{9,11}$]undecane (**203**) and *exo–exo–syn*-7,10-bis-(*N*-pthalimido)-3-oxa-7,10-diazapentacyclo[3.3.3.$0^{2,4}$.$0^{6,8}$.$0^{9,11}$]undecane (**204**). A rearrangement occurs upon stirring of chloroform solutions of azatrishomobarrelenes **202**–**204** with a cation-exchange resin. The yield of triazatrishomocubane **205** amounted to 75%, and compounds **206**, **207** were obtained in virtually quantitative yields. The optically active D_3-trishomocubane analogues are formed, as in the other described cases, as racemates.

VIII. Pharmacological properties of D_3-trishomocubane derivatives

In the 1990s, the antiviral activity of amines **91** was discovered.[39] However, in a recent study[81] of pharmacological properties of a series of aminocyclopentaundecanes and other cage compounds these data have been disproved.



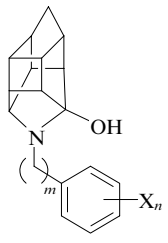
91a–h

R^1 = H: R^2 = Me (**a**), Ph (**e**); R^2 = Me: R^1 = Et (**b**), Bu^n (**c**), Bn (**d**), $Ph(CH_2)_2$ (**f**); R^1 = Et: R^2 = Et (**g**), Ph (**h**).

Thus the *in vitro* experiments did not reveal any noticeable antiviral (Herpes type II, influenza A2/Taiwan) activities of amines **91b**,**e**. It was suggested that the activity observed earlier was in fact the immune response to the chemicals that did not interact with the virus species themselves.

A series of amines **91a–h** was tested[81] for treatment of Parkinson's disease. It was found that the anticataleptic and anticholinergic activities of the studied substances (LD_{50} fall in the interval 10–34 and 10–100 mg kg^{-1}, respectively) are comparable with those of the reference drug, amantadine (17 and 100 mg kg^{-1}, respectively). Besides, it was found that the hydrophobicity of the cage compounds and the presence of aromatic substituents in their structure significantly influence both their activity and toxicity.

Four compounds with the azapentacycloundecane structure (**208a–d**) and aminotrishomocubane **91h** were tested for affinity to dopamine receptors.[81]



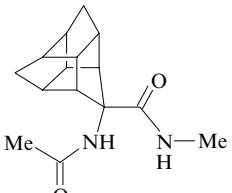
208a–d

m = 1, X_n = 3-F (**a**); m = 2, X_n = 3,4-Cl_2 (**b**), 3-F (**c**); m = 4, X_n = H (**d**).

Compounds **208a–d** demonstrated high sigma-binding constants, which conform to the amphetamine control. At the same time, amine **91h** is characterized by extremely low sigma-binding constants and represents a σ_2-antagonist, which diminishes the effect of amine **208c**. These findings coincide with the data obtained by other researchers.[82]

Syntheis of dipeptide **209** from amino acid **100** was described[83] (see Schemes 8, 9). The spatial structure of this dipeptide was investigated, and the functional groups were demonstrated to have helical arrangement, which

provides self-stabilization of the dipeptide by hydrogen bonding.



209

An assumption of designing medium-sized peptides[83] involving cage amino acids based on calculations was later confirmed experimentially.[84] A peptide containing a fragment of trishomocubanecarboxylic acid **100** in the middle of the chain built of seven alanine residues was synthesized. Its X-ray diffraction analysis was in good correlation with the computed structure.

In a recent investigation[85] (which cites the publications[5, 39, 82]), the biological properties of D_3-trishomocubane amines were summarized. It was shown that these substances having anti-Parkinsonism activity and affecting the dopamine receptors are also active against Herpes (types 1, 2), Taiwan influenza viruses and type 1A rhinoviruses.

IX. Conclusion

In the present review, we made an effort to generalize the currently known data on the chemistry of D_3-trishomocubanes. To give an exhaustive cover of original publications on this topic, we should mention the papers[86–89] where the structures of D_3-trishomocubane derivatives are given only as examples among other cage hydrocarbons.

Some conclusions can be made after summarizing the above data. D_3-Trishomocubane derivatives can be rather easily obtained from substituted C_s-trishomocubanes by cation rearrangements, racemates being formed in most cases. Biochemical methods of assymetric synthesis of the trishomocubane compounds are designed. Also, methods of resolution of racemic trishomocubanes into optical isomers are known. In some cases, D_3-trishomocubane derivatives are formed as rearrangement products of tetracyclic systems (usually in low yields).

The standard methods of synthesis of the D_3-trishomocubane framework are mainly based on Cookson's ketone. This is why 4-mono and 4,7-disubstituted D_3-trishomocubanes are the most accessible compounds. D_3-Trishomocubanes bearing a substituent in the position 1 may be synthesized under drastic conditions using such reagents as bromine, boron tribromide, sulfur tetrafluoride, chlorosulfonic acid. 2-Substituted D_3-trishomocubane derivatives can be obtained only from the substituted quinones because of the instability of both the corresponding cation and radical.

Since D_3-trishomocubane is the most stable compound among pentacycloundecanes, its derivatives are not prone to rearrangements into other isomers (although such reactions are known). The first optically active molecule with tetrahedral symmetry was synthesized based on D_3-trishomocubane. Among its derivatives are compounds with high anti-cataleptic activity. And the potential of this unique molecule, which still is not fully explored, goes beyond. The cage nature of trishomocubane substantially alters the course of many classical organic reactions and allows for better understanding of their mechanisms and factors influencing it.

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