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Usnic acid: preparation, structure, properties and chemical transformations

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Abstract. Published data on the chemistry of usnic acid since the time of its isolation in a pure state up to now are integrated and analyzed. The preparation methods, structure and properties of this compound are considered. The data on the chemical transformations of usnic acid comprise reactions that do not affect the carbon skeleton and reactions accompanied by carbon skeleton destruction. The bibliography includes 96 references.

I. Introduction

Studies of the properties of natural plant metabolites have been a key pursuit of scientists since chemistry originated as a science. Currently this area of science not only has not lost its significance but has also gained new goals and possibilities. The use of plant metabolites as the starting compounds for the development of new biologically active agents has become a key trend of modern medicinal chemistry. A very interesting plant metabolite is usnic acid (UA), which was first isolated from a lichen in the first half of the 19th century.

Interestingly, usnic acids with opposite signs of specific rotation and high optical purity are isolated from different lichen species. This fact can be employed to consider one more trend of recent decades in the development of new biologically active compounds, namely, transition to the use of chiral compounds. The simple isolation procedure from readily accessible plant raw material and the presence of a large number of functional groups makes usnic acid an interesting molecule for synthetic transformations. However, the combination of different functional groups in a natural molecule often leads to ambiguous outcomes of traditional reactions, and this precludes its wide use in synthetic practice.

Initially, the research was directed at the destruction of usnic acid in order to obtain simpler compounds with known structure and thus determine the chemical structure of usnic acid. As a result, a procedure for alternative synthesis of usnic acid was developed. Later, the researchers' attention was focused on the usnic acid reactivity, preparation of derivatives and their screening for various types of biological activity.

Although numerous publications deal with the chemical properties of usnic acid, these properties have not yet been integrated and analyzed as a whole in the scientific literature. Therefore, this review covers the published data on the chemistry of usnic acid over the whole time interval starting from the first publication reporting its isolation in an individual state.

II. Preparation, structure and properties of usnic acid

1. Structural features

Lichens (lat. *Lichenes*) comprise a group of lower plants formed by symbiosis of a fungus (mycobiont) and green alga and/or cyanobacterium partner (phycobiont). The symbiotic interactions between the lichen components are that the phycobiont provides the fungus with organic substances formed upon its photosynthesis and receives water with dissolved mineral salts from the fungus. Lichens have the unique ability to exist under extremely unfavourable conditions, because their complex nature allows them to gain nutrition from air, atmospheric precipitation, dew and mist moisture, dust particles that are deposited on the thallus or from soil. These symbiotic organisms are known to be valuable sources of biologically active compounds that have been used from long ago as medicines, food additives, dyes and so on.[1] Lichens are well-known for the diversity of secondary metabolites, so-called lichen substances, which are produced only by the mycobiont. Usnic acid, which is produced in *Cladonia* (Cladoniaceae family), *Usnea* (Usnea-

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ceae), *Lecanora* (Lecanoraceae), *Ramalina* (Ramalinaceae), *Evernia*, *Parmelia* (Parmeliaceae), *Alectoria* (Alectoriaceae) and in other lichen genuses is, perhaps, the best known secondary metabolite of lichens.[2] Usnic acid has antiviral, antibacterial, analgesic,[3] antitubercular[4] and insecticidal[5] properties.

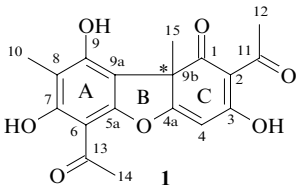
As mentioned above, UA is produced by the lichen mycobiont [this was first shown in 1949 (Ref. 6)] and subsequently UA was extracted from isolated mycobionts of *Ramalina* lichens.[7]

Usnic acid was first isolated in 1843 from the *Ramalina* and *Usnea* lichens;[8] a year later it was characterized as an individual substance and acquired its name.[9] Nine decades later its chemical structure was determined.[10]

Usnic acid is produced in lichens in large amounts, accounting for up to 8% of the dry matter of the thallus. The UA content in lichens is subject to large seasonal fluctuations, the highest level being observed at the end of spring and at the beginning of summer, while autumn and winter levels are generally low. The content of UA correlates with the summer solstice time, solar radiation levels and temperature conditions and also depends on the lichen vegetation area.[11,12]

Usnic acid is a yellow-coloured crystalline compound,[13] a derivative of dibenzofuran, existing as two enantiomers differing by the position of the angular methyl group at C(9b).

The dextrorotatory enantiomer of compound **1** has the *R*-configuration at C(9b);[14] its specific rotation is +478 [*c* 0.2, $CHCl_3$, (deg ml) (g dm)$^{-1}$]. A typical producer of (+)-UA is *Usnea Longissima*, while *Cladonia Stellaris* may serve as the source of the levorotatory enantiomer of UA [−458, *c* 0.2, $CHCl_3$, (deg ml) (g dm)$^{-1}$].



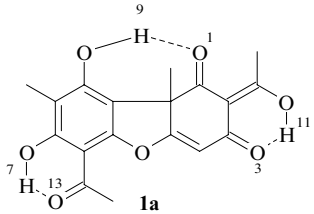
1

In all probability, the problem of determination of the absolute configuration of the asymmetric centre appeared immediately after the structure of UA was determined. In different years, researchers either ascribed the *S*-configuration to (+)-UA (for example, the Kutney group in 1976–1984; see also the Sigma-Aldrich catalogue[15]) or did not indicate the configuration at all (for example, publications of Takahashi and co-wokers of 1962–1985). In order to establish the absolute configuration of the asymmetric centre of UA, Huneck *et al.*[14] performed the reaction of (+)-UA with (*S*)-1-phenylethylamine and, based on the reaction outcome, assigned the *R*-configuration to the asymmetric centre. However, neither X-ray diffraction data no any spectral information was presented in the publication for the obtained compound. Some other publications[16,17] depicted (+)-UA with the *R*-configuration and confirmed this configuration by X-ray diffraction data for the reaction product obtained from (+)-UA and optically active 1,2-diaminocyclohexane.

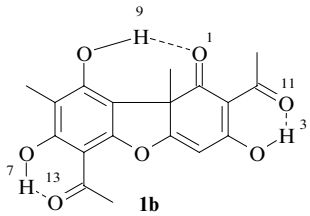
In this review, the configuration of the angular methyl group of UA and its derivatives is not indicated in those cases where it is not indicated by the authors of the cited studies and also in those cases where the authors indicated it incorrectly.

The hydroxy groups of UA are involved in the formation of strong intermolecular hydrogen bonds.[18] The dissociation constants of the OH groups of UA determined by spectrophotometric titration[19] are as follows: $pK_{a1} \approx 4.4$ [C(3)OH], $pK_{a2} \approx 8.8$ [C(7)OH], $pK_{a3} \approx 10.7$ [C(9)OH]. The acidity of the medium and the ratio of neutral to anionic UA forms was assumed[20] to be important for the lichen vital activity.

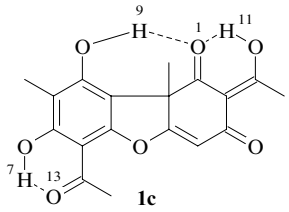
Buemi and Zuccarello[21] performed AM1 quantum-chemical calculations for the stability of the possible UA tautomers. According to the results, most probable is the equilibrium between three stable tautomers **1a**–**c** of which **1b** is most stable. The calculated hydrogen bond energies are summarized in Table 1. The hydrogen bond H(11)···O(3) in tautomer **1a** proved to be most strong being comparable in energy with the hydrogen bond in acetylacetone (32.76 kJ mol^{-1}). A comparison of the calculated and experimental absorption curves in the UV region demonstrated that tautomer **1b** predominates in solution, while the amounts of **1a** and **1c** are rather low.



1a



1b



1c

In a later work,[22] the molecular structure of UA was studied using the density functional theory (DFT). Two

Table 1. Energy of intramolecular hydrogen bonds in the tautomers of usnic acid according to AM1 and DFT calculation data.[21,22]

Tautomer **1a**			Tautomer **1b**			Tautomer **1c**	
bond	energy /kJ mol^{-1}		bond	energy /kJ mol^{-1}		bond	energy /kJ mol^{-1} (AM1)
	AM1	DFT		AM1	DFT		
H(11)···O(3)	32.66	37.7	H(3)···O(11)	29.78	36.6	H(11)···O(1)	29.03
H(7)···O(13)	19.07	20.3	H(7)···O(13)	18.50	20.1	H(7)···O(13)	19.68
H(9)···O(1)	14.10	12.7	H(9)···O(1)	14.40	13.1	H(9)···O(1)	14.05

tautomers (**1a** and **1b**) proved to be nearly isoenergetic and most stable among the possible tautomers. According to this calculation method, too, the most stable tautomer is **1b** (0.20 kJ mol^{-1} more stable than tautomer **1a**). According to calculations, the interconversion **1a** ⇄ **1b** has a barrier of 0.78 kJ mol^{-1} and occurs at room temperature. The authors also calculated the energy of intramolecular hydrogen bonds (see Table 1).

Due to the presence of the resorcinol moiety and the system of conjugated carbonyl groups, the UA molecule shows broad absorption bands in the near, medium and far UV ranges.[22] The hydroxy groups of the UA molecule can form not only intramolecular but also intermolecular hydrogen bonds.

It was shown that these systems effectively dissipate the excess energy obtained on exposure to UV irradiation.[23] It is believed that usnic acid serves as an efficient sun-protecting agent for lichens by reducing the adverse action of solar radiation [24] during long exposure to sunlight in hot deserts.

2. Preparation of usnic acid

Up to now, the key method for the preparation of UA is the extraction of lichens with organic solvents and subsequent precipitation of the target product from the extract or recrystallization. Usnic acid is readily soluble in benzene, chloroform, pentyl alcohol and glacial acetic acid; sparingly soluble in ethanol, petroleum ether and diethyl ether; and insoluble in water.[25] For example, UA was isolated [8,9] from a mixture of lichens *Ramalina* and *Usnea* by digestion in diethyl ether and subsequent precipitation with ethanol from the extract. Now this solvent is still used for the extraction of UA: Ingólfsdóttir *et al.*[26] extracted *Cladonia Arbuscula* in a Soxhlet apparatus, and the extract was recrystallized from ethanol. In other works,[27,28] UA was isolated from lichens by means of boiling petroleum ether. Sonication was used by Cetin *et al.*[5] to extract (+)- and (−)-UA from *Ramalina farinacea* and *Cladonia foliaceae* with acetone. One more method for the isolation of UA is the extraction of lichens with boiling chloroform followed by ethanol precipitation from the concentrated extract.[29] This procedure is suitable to recover (+)- and (−)-UA from *Usnea Longissima* and *Cladonia Stellaris* in amounts of 1.5%–2% relative to the raw material dry weight.

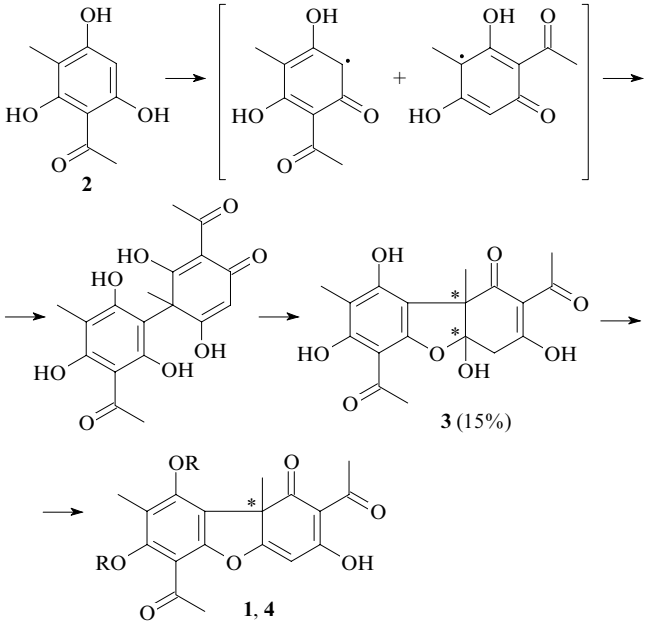
In a study [30] dealing with the chemical synthesis of UA, it was shown that it can be obtained in two steps by oxidative coupling of compound **2** induced by potassium ferricyanide (Scheme 1). The resulting compound **3** was treated with concentrated sulfuric acid to give racemic UA (**1**) in a 2% yield.

Another synthetic route comprised the preparation of diacetate **4** (yield 25%) by treating compound **3** with acetic anhydride in the presence of sulfuric acid.

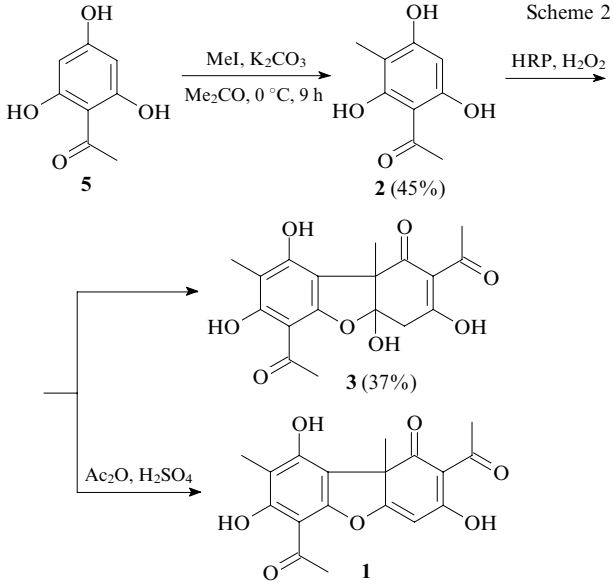
A relatively recent publication [31] was devoted to chemoenzymatic synthesis of UA. The authors used commercially available 2,4,6-trihydroxyacetophenone (**5**) (Scheme 2).

Compound **5** was methylated to give product **2**, which was then subjected to the action of horseradish peroxidase (HRP) and H_2O_2 to give compound **3**. When acetic anhydride and sulfuric acid were added during treatment of compound **2** with the enzyme HRP, the authors detected product **1** in the reaction mixture. The paper does not specify whether the obtained compounds **1** and **3** were optically active.

Scheme 1



Scheme 2

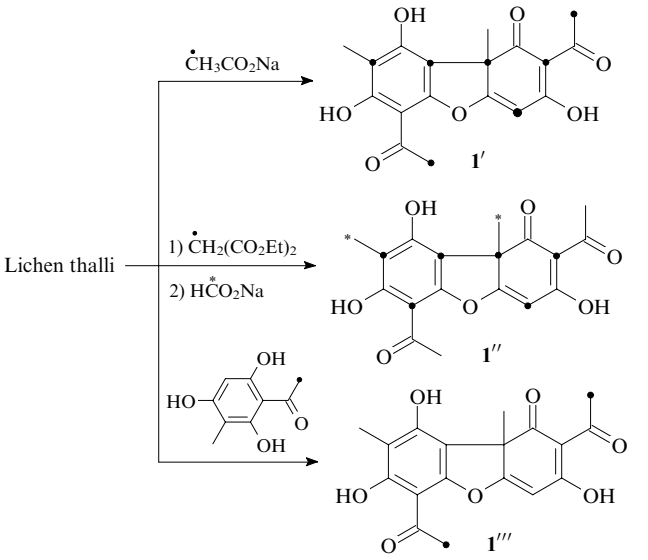


The sequence of stages in UA biosynthesis was elucidated using labelled compounds for the treatment of cultivated lichen thalli.[32,33] The experiment was carried out using sodium acetate, diethyl malonate, sodium formate and 3-methyl-2,4,6-trihydroxyacetophenone labelled at the appropriate positions, as indicated in Scheme 3. The ^{14}C-labelled compounds were used as aqueous or ethanol solutions for treating lichen thalli for 3 days at 25 °C under illumination.

The treatment of the thalli with sodium (^{14}C)-acetate gave UA **1′** labelled in positions 2, 4, 8, 9a, 9b, 12 and 14 (see Scheme 3). After treatment of lichen thalli with diethyl malonate (^{14}C) and sodium formate (^{14}C), labels were found in positions 2, 4, 6, 8, 9a, 9b, 10 and 15 (compound **1″**).†

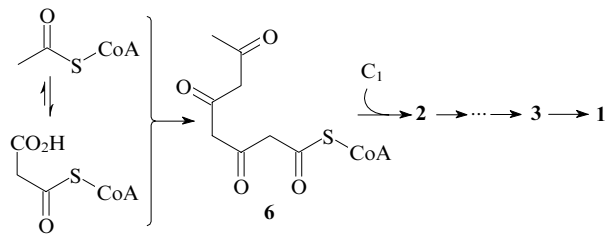
† The labelled C atoms are shown by circles; asterisks stand for sodium formate labels to avoid confusion with labels from diethyl malonate.

Scheme 3



Relying on this result, the authors concluded that C_8-polyketide intermediate **6** is involved in the initial stage of UA biosynthesis (Scheme 4). The experimental results on treatment of the thalli with labelled sodium formate gave rise to the hypothesis according to which the methyl groups at C(8) and C(9b) appear together with the formation of polyketide intermediate **6**. This assumption was also confirmed by experiments with labelled 2,4,6-trihydroxyacetophenone and 3-methyl-2,4,6-trihydroxyacetophenone; treatment of lichen thalli with 2,4,6-trihydroxyacetophenone (^{14}C) did not subsequently give rise to isotope-labelled UA. Conversely, treatment of the thalli with 3-methyl-2,4,6-trihydroxyacetophenone (^{14}C) resulted in the isolation of C(12)- and C(14)-labelled UA **1‴** (see Scheme 3).

Scheme 4



C_1 is one-carbon fragment

Thus, upon analysis of the obtained data, researchers proposed a chart for the biosynthesis of UA shown in Scheme 4 (the conversion of compound **2** *via* intermediate **3** to final product **1** is shown in Scheme 1).

III. Chemical transformations of usnic acid

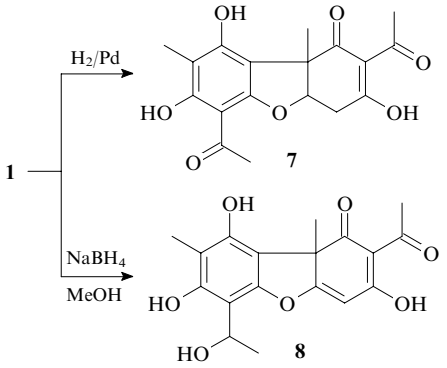
As has already been mentioned in the Introduction, destructive transformations of UA have been the main purpose of the studies for a long time, as the studies were aimed at determining its structure. Currently, of no less interest are reactions of introduction and replacement of functional groups with the UA skeleton remaining intact.

1. Reactions with retention of the carbon skeleton

a. Reduction

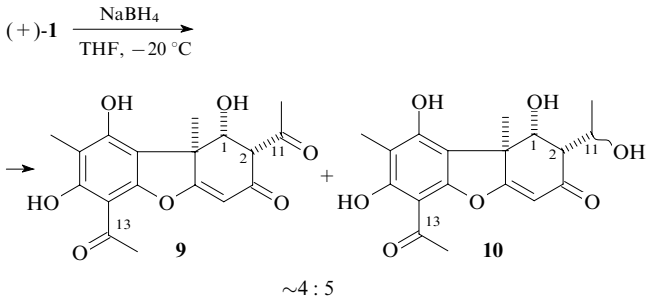
The hydrogenation of (+)-UA with hydrogen on palladium black under atmospheric pressure, resulting in the quantitative and stereoselective reduction of the C(4)=C(4a) double bond to give dihydrousnic acid **7**, was reported [34, 35] (Scheme 5). According to the authors,[35] the hydrogen atom in position 4a has the *cis*-configuration with respect to the angular methyl group at C(9b).

Scheme 5



When UA is treated with $NaBH_4$ in methanol, the carbonyl group at C(13) is reduced to give derivative **8**.[36] When THF was used as the solvent, the reaction gave a mixture of reduction products of one carbonyl group [C(1)=O] (compound **9**) and two carbonyl groups [C(1)=O) and (C(11)=O] (compound **10**) in a 57% total yield (Scheme 6).[37]

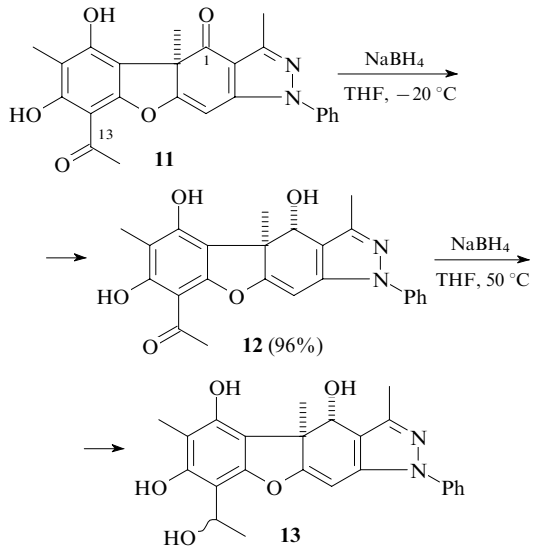
Scheme 6



The reaction of pyrazole derivative **11** with $NaBH_4$ under similar conditions affords the reduction product of only the C(1)=O carbonyl group (**12**). The reaction occurs with a high yield and stereoselectively in the temperature range from −40 to 0 °C; the yield of compound **12** decreases as the temperature increases to room temperature.

On further increase in the temperature to 50 °C, compound **12** reacts with an excess of $NaBH_4$, the carbonyl group C(13)=O (the numbering corresponds to the initial UA) being reduced to give product **13** [a ~ 2 : 3 mixture of stereoisomers at C(13) according to the ^1H NMR spectrum] (Scheme 7).

Scheme 7



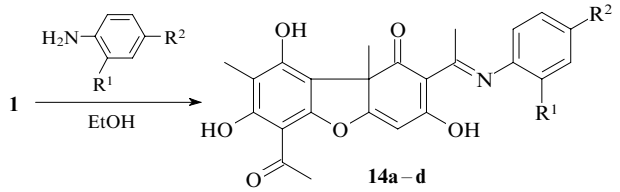
Thus, in the reaction of UA and its derivatives with $NaBH_4$ the endocyclic carbonyl group at C(1) is most active and the reduction is stereoselective.

b. Reactions with amines

The system of conjugated carbonyl groups in ring C of the UA molecule is reactive towards both aliphatic and aromatic amines. In a series of early works[38–41] devoted to the synthesis of amino derivatives of UA for testing their antibacterial activity, UA was made to react with aliphatic and aromatic amines, acylhydrazides, semicarbazides, cycloserine, *etc*. As a rule, all UA derivatives were prepared by refluxing equimolar amounts of the reactants in ethanol. Unfortunately, these publications do not present structures or spectral characteristics of the obtained compounds.

The reaction of UA with substituted anilines in absolute ethanol with heating gave compounds **14a–d** containing an imine group[42] (Scheme 8).

Scheme 8



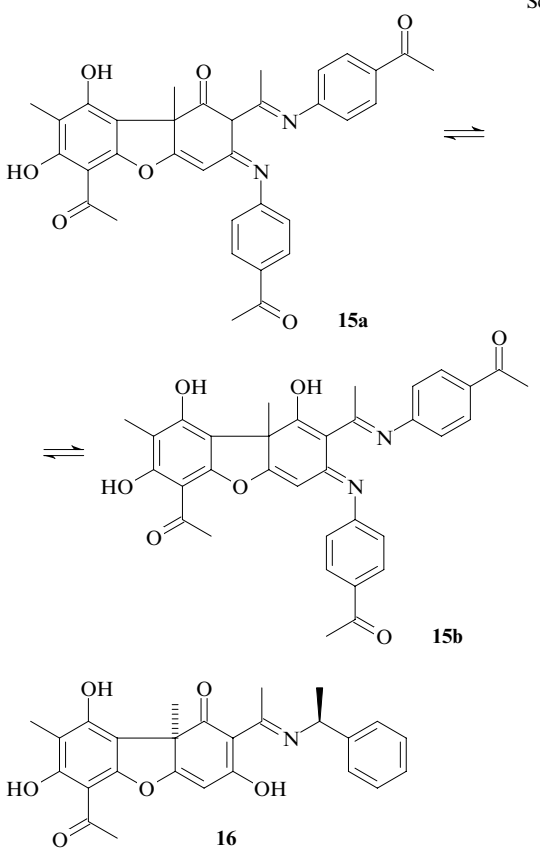
R^1 = H: R^2 = Ac (**a**), CO_2H (**b**), CO_2Et (**c**); R^1 = NH_2, R^2 = H (**d**)

The use of a twofold excess of *p*-aminoacetophenone in a similar reaction results in condensation product **15a**, which occurs in equilibrium with the enol form **15b** (Scheme 9).

According to the authors cited,[42] the carbonyl group at C(13) does not take part in the condensation with substituted anilines.

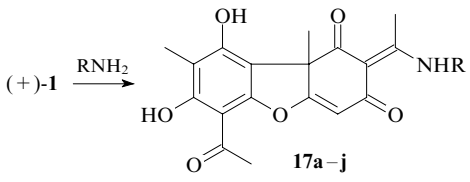
In order to determine the absolute configuration of the asymmetric centre C(9b), the reaction of (+)-UA with (*S*)-1-phenylethylamine was performed and gave imine **16**.[14]

Scheme 9

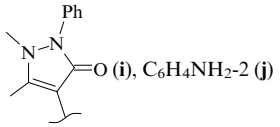


Kutney and Sanchez[43] carried out the reaction of (+)-UA with aliphatic amines by refluxing an equimolar mixture of amine and UA in ethanol for 1.5–4 h. The carbonyl group C(11)=O of usnic acid was the first to react, and the compounds thus formed were enamines **17a–c** (70% to 82% yields) rather than imines (Scheme 10). The structure of compound **17a** was confirmed by X-ray diffraction analysis.

Scheme 10



R = H (**a**), Me (**b**), Et (**c**), $(CH_2)_2NEt_2$ (**d**), C_6H_4Br-4 (**e**), C_6H_4Cl-4 (**f**), $(CH_2)_2C_6H_2Bu^t_2$-3,5-OH-4 (**g**), $(CH_2)_3C_6H_2Bu^t_2$-3,5-OH-4 (**h**),



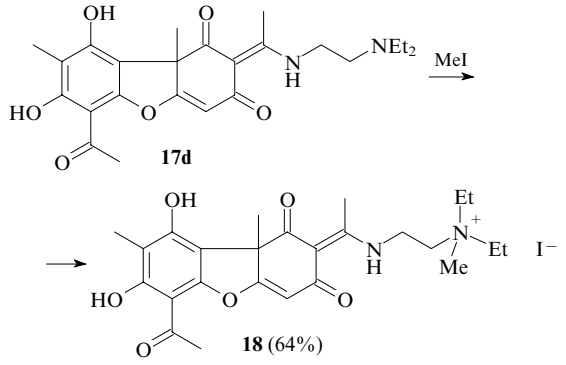
O (**i**), $C_6H_4NH_2$-2 (**j**)

With the view of incorporating pharmacophore groups into the UA molecules, Tazetdinova *et al*.[44] carried the reaction under similar conditions using amines that contained either a moiety with intrinsic biological activity or groups suitable for further chemical modification of the reaction products: *N*,*N*-diethylaminoethylamine, *p*-bromoaniline, *p*-chloroaniline, 4-(2-aminoethyl)-2,6-di-*tert*-butylphenol, 4-(3-aminopropyl)-2,6-di-*tert*-butylphenol and

4-aminoantipyrine. This method was used to prepare compounds **17d**–**i** in rather high yields (72%–93%) (see Scheme 10).

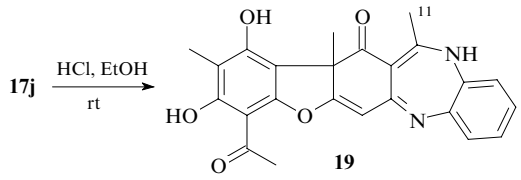
Compound **17d** is quaternized upon the reaction with MeI in CH_2Cl_2. The reaction occurs at room temperature over 72 h to give product **18** (Scheme 11).[44]

Scheme 11



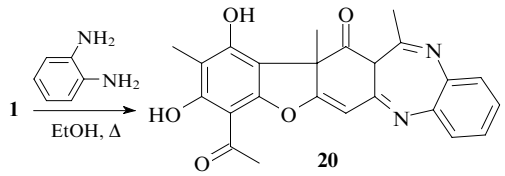
The reaction of (+)-UA with *o*-phenylenediamine giving rise to enamine **17j** in 94% yield (see Scheme 10) may proceed further until a benzodiazepine ring is formed (compound **19**). This reaction was carried out by stirring compound **17j** in ethanol in the presence of concentrated HCl at room temperature (rt) for 4 h (Scheme 12).[43]

Scheme 12



However, in an early study,[42] structure **20** with a different arrangement of double bonds in the benzodiazepine ring was ascribed to the product of UA condensation with *o*-phenylenediamine carried out in absolute ethanol on heating (Scheme 13).

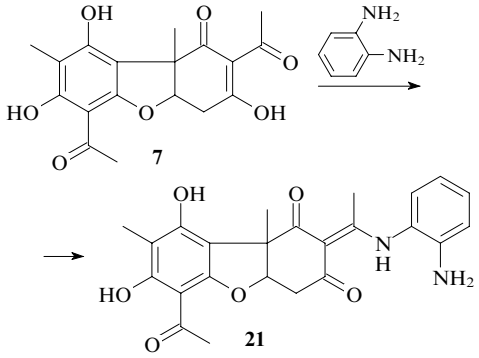
Scheme 13



In the ^{1}H NMR spectra of compounds **19** and **20**, the methyl groups in the diazepine ring have chemical shifts of 2.06 and 2.56 ppm, respectively. In addition, for compound **19**, the chemical shift of the proton at the benzodiazepine nitrogen is also reported (9.72 ppm). This provides grounds to believe that differences in the experimental conditions may lead to benzodiazepine rings with different positions of double bonds.

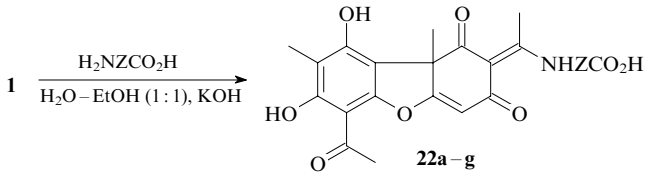
The reduction of the C(4)=C(4a) bond in UA does not affect its ability to condense with amines;[43] the reaction of compound **7** with *o*-phenylenediamine affords enamine **21** (Scheme 14).

Scheme 14



Unlike primary amines, amino acids do not react with (+)-UA on refluxing in ethanol. As noted by Luzina *et al.*,[45] in this case, the reaction occurs in a narrow range of pH values (9–10) in aqueous ethanol (1:1) in the presence of KOH, the mixture being refluxed for 10 min. The highest yield of the target product (**22a**) was obtained in the reaction with glycine (88%), the yields of compounds **22b**–**g** being 17% to 61% (Scheme 15) (L-amino acids were used to obtain compounds **22c**–**g**).

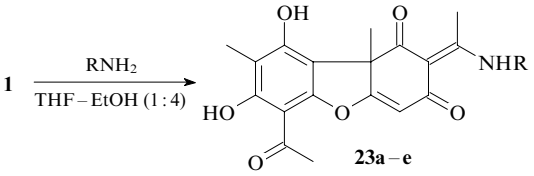
Scheme 15



Z = CH_2 (**a**), $(CH_2)_2$ (**b**), CHBn (**c**), $CHPr^i$ (**d**), $CHBu^i$ (**e**), $CH(CH_2CH_2SMe)$ (**f**), $CH(CH_2OH)$ (**g**)

Amino derivatives **23a**–**e** were prepared[16] using a THF–EtOH (1:4) solvent mixture and refluxing for 4 h. The product yields were 69% to 85% (Scheme 16).

Scheme 16

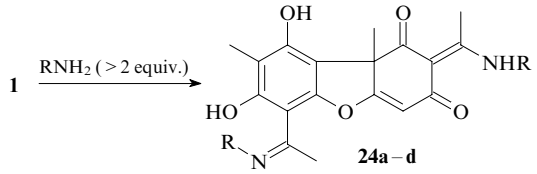


R = $(CH_2)_4OH$ (**a**), n-C_9H_{19} (**b**), $CHBu^sCO_2H$ (**c**), $CH(CHMePh)CO_2Et$ (**d**), $CH(CHMePr^i)CO_2Et$ (**e**)

At more than a twofold excess of the amine, the carbonyl group C(13)=O reacts: compounds **24a**–**d** (Scheme 17) contain both enamine and imine groups. Compounds **24a**,**b** were prepared in yields of 73%–82%,[43] and compounds **24c**,**d** formed in 20%–22% yields.[44] According to the authors,[44] 4-aminoantipyrine, *N*,*N*-diethylaminoethylamine, *p*-chloroaniline and *p*-bromoaniline do not form imines at the carbonyl group C(13)=O.

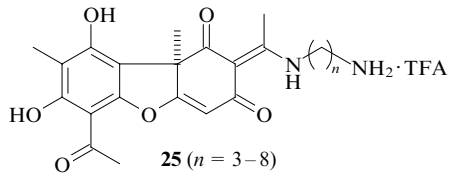
The reaction of (+)-UA with aliphatic di- and triamines with 3–8 carbon atoms in the chain has been studied.[46] However, unlike the reaction of UA with aliphatic monoamines, in this case, the use of equimolar amounts of the diamine resulted in a mixture of compounds, and the isolation of the desired product was difficult; an excess of diamine led to the formation of a dimeric derivative. The yield was found for the synthesis carried out on polymeric

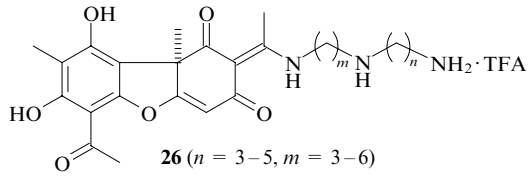
Scheme 17



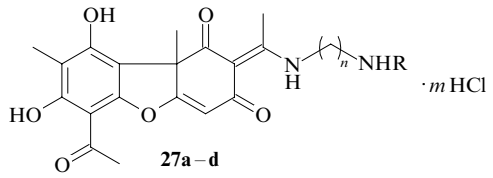
R = Me (**a**), Bn (**b**), $(CH_2)_3C_6H_2Bu^t_2$-3,5-OH-4 (**c**), $(CH_2)_2C_6H_2Bu^t_2$-3,5-OH-4 (**d**)

substrates. The reaction of UA with di- and triamines pregrafted on a polymeric substrate was carried out by heating the reactants in a THF – EtOH mixture (1 : 1) at 50 °C for 5 h. The yields of compounds **25** were 17% – 50% and those of compounds **26** were 30% – 40%. The condensation products were removed from the polymeric substrate by treating with a TFA – CH_2Cl_2 mixture (1 : 4) (TFA is trifluoroacetic acid) at room temperature for 1 h.





In a study[16] devoted to the reaction of (+)-UA with polyamines, the reaction was performed with *N*-Boc-substituted di-, tri- and tetraamines. This gave the series of compounds **27a – d** as hydrochlorides. The reaction was performed by refluxing in a THF – EtOH mixture (1 : 4) for 4 h. The protecting group was removed by stirring the reaction products in a 2.4 M solution of HCl in ethyl acetate.

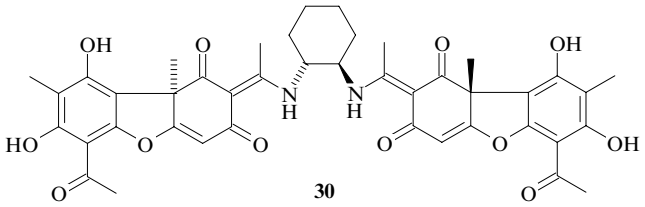


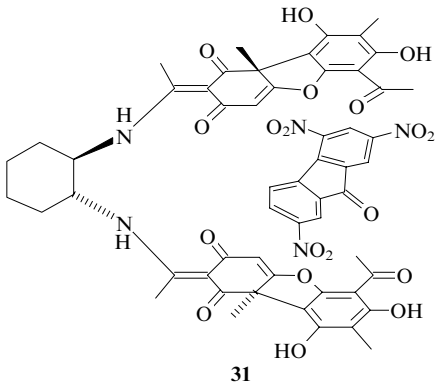
R = H: $n = 4$, $m = 1$ (**a**); $n = 8$, $m = 2$ (**b**);
$n = 3$: R = $(CH_2)_4NH_2$, $m = 3$ (**c**); R = $(CH_2)_4NH(CH_2)_3NH_2$, $m = 4$ (**d**)

The product that formed in the reaction of (+)-UA with ethylenediamine in 1 : 1 ratio (compound **28**) was used as the ligand to prepare copper and nickel complexes.[47] The reaction of UA with ethylenediamine occurs on refluxing in THF – EtOH (10 : 3) for 4 – 5 h (yield 84%).

Complexes **29a** (violet-coloured) and **29b** (orange-coloured) are rapidly formed upon the addition of a metal acetate solution in methanol to a solution of compound **28** in CH_2Cl_2 (Scheme 18).

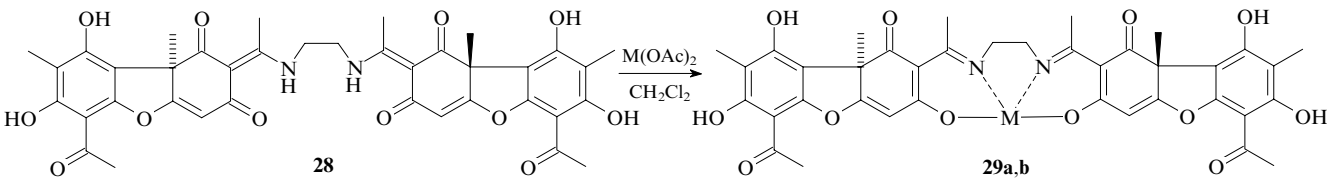
Legouin *et al.*[17] obtained dimer **30** by the reaction of UA with (1*R*,2*R*)-1,2-diaminocyclohexane [refluxing in a THF – EtOH mixture (1 : 4) for 4 h, yield 90%)] Product **30** is a sort of molecular forceps. According to X-ray diffraction data, the distance between the UA aromatic rings in this compound is 7.486 Å. Such a molecular forcep can form red complex **31** with 2,4,7-trinitrofluorenone *via* π – π stacking of the aromatic rings. The complex is formed on mixing compound **30** and 2,4,7-trinitrofluorenone in CH_2Cl_2 at room temperature.





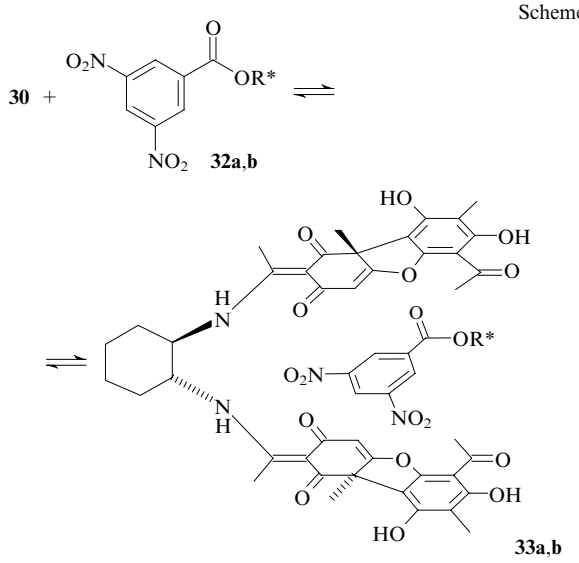
In a later work,[48] the authors obtained four stereoisomers of compound **30** by the reaction of (+)- and (−)-UA with (1*R*,2*R*)- and (1*S*,2*S*)-1,2-diaminocyclohexanes (yields 60% – 86%). The ability of the products to form host – guest complexes with compounds containing electron-deficient aromatic rings was investigated. Esters formed by chiral alcohols and 3,4-dinitrobenzoic acid, compounds **32a**,**b**, were used as guests. An attempt was undertaken to use compound **30** as a shift reagent for differentiating the esters formed by chiral secondary alcohols and 3,4-dinitrobenzoic acid **32** in the ^{1}H NMR spectra (Scheme 19).

Scheme 18



M = Cu (**a**), Ni (**b**)

Scheme 19



R* = Bu^s (**a**), CHMePh (**b**)

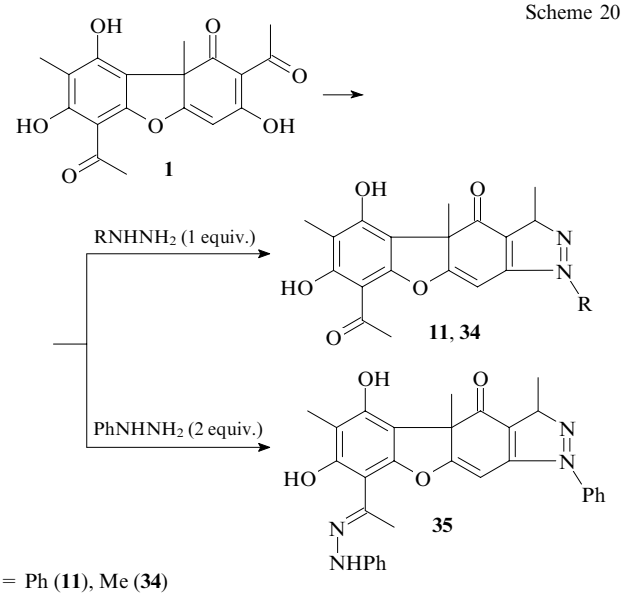
However, complexes **33** (with a mixture of enantiomers of **32**) did not show differences in the chemical shifts of NMR signals. This fact was attributed to fast exchange between enantiomers (*R*)-**32** and (*S*)-**32** in the complex occurring in solution and to the large distance between the stereogenic centres of compound **30** and the complexation site.

Thus, the reactions of UA with compounds containing amino groups clearly show the difference in the reactivity of the carbonyl groups of UA. The carbonyl group C(11)=O is the first to react with amines; this gives products containing either a enamine or imine moiety. The less active C(13)=O group reacts only in the presence of a more than twofold excess of amine, and the condensation gives an imine. The endocyclic carbonyl group C(1)=O does not react with the amino group.

c. Reactions with hydrazines

The reactions of UA with hydrazines produce derivatives that contain an annulated pyrazole ring. In the reaction of compound **1** with phenylhydrazine [42, 49] and methylhydrazine,[50] the carbonyl group C(11)=O reacts, and subsequent heterocyclization gives the pyrazole ring (compounds **11**, **34**); the addition of the second phenylhydrazine molecule to the carbonyl group C(13)=O does not involve heterocyclization and gives hydrazone **35** (Scheme 20).

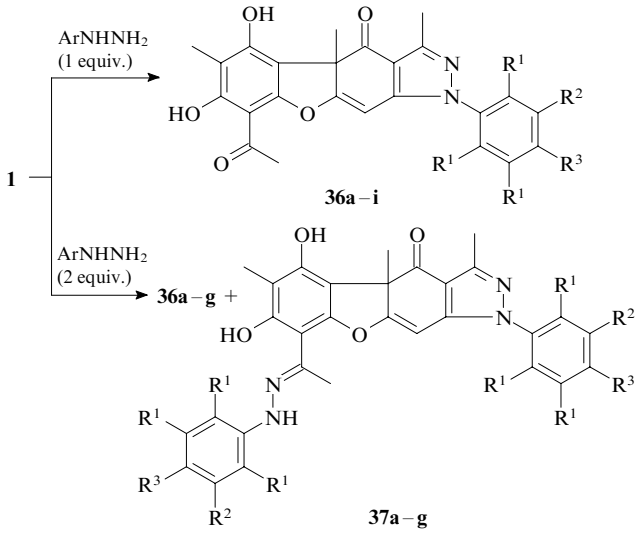
Scheme 20



R = Ph (**11**), Me (**34**)

By the reactions of (+)-UA with phenylhydrazines containing various substituents in the aromatic ring, series of compounds **36a**–**i**, **37a**–**g** were prepared [51] (Scheme 21). When two or more equivalents of phenylhydrazine are introduced in the reaction, the second molecule reacts to give hydrazones **37a**–**g**; however, the reaction is much slower, and in most cases, even a large excess of phenylhydrazine failed to fully convert UA to compounds **37**. In most experiments, hydrazones **37** were isolated together with impurities of compounds **36a**–**g** (10% to 40%). According to researchers' opinion, compounds **37a**–**g** were *E*-isomers of phenylhydrazones. *para*-Methoxy- and ethoxy-substituted phenylhydrazines do not form hydrazones at the carbonyl group C(13)=O of usnic acid.

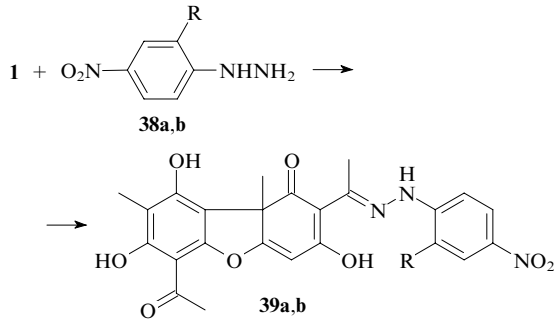
Scheme 21



$R^1 = R^3 = H$: R^2 = Cl (**a**), CF_3 (**b**); $R^1 = R^2 = F$, $R^3 = CF_3$ (**c**); $R^1 = R^2 = H$: R^3 = F (**d**), Cl (**e**), Br (**f**), Me (**g**), OMe (**h**), OEt (**i**)

Nitro-substituted phenylhydrazines **38a**,**b** do not condense at the carbonyl group C(13)=O either, and the reaction at C(11)=O does not involve the closure of the pyrazole ring (Scheme 22).[51] The authors attributed this outcome to reduced nucleophilicity of the nitrogen atom caused by the electron-withdrawing effect of the *para*- and *ortho*-nitro groups in the benzene ring.

Scheme 22

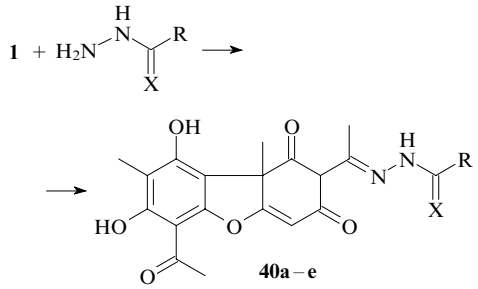


R = H (**a**), NO_2 (**b**)

According to ^{1}H and ^{13}C NMR data, the synthesis of hydrazones **39a**,**b** is not accompanied by double bond migration to give enamine typical of the reactions of UA with amines.

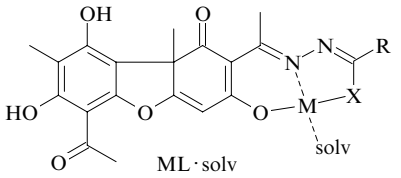
The reactions of UA with acylhydrazides also do not form products containing annulated pyrazole rings. A group of researchers [52, 53] synthesized ligands based on (+)-UA in order to obtain biologically active complexes. The reaction of compound **1** with hydrazides of some acids and thiosemicarbazide were carried out on refluxing in absolute ethanol for several hours. The compounds thus formed were typical hydrazones **40a**–**d** and thiosemicarbazone **40e** (Scheme 23).

Scheme 23



X = O: R = 1-Naph (**a**), 4-Py (**b**), n-C_7H_{15} (**c**), $C(O)NH_2$ (**d**);
X = S, R = NH_2 (**e**); Naph is naphthyl, Py is pyridyl

For preparing Pd^{II} and Cu^{II} complexes, compounds **40b**–**e** were mixed with K_2PdCl_4 or $CuSO_4$ in appropriate solvents and refluxed until a precipitate formed. The complex of compound **40a** was prepared by refluxing with an excess of $Cu(OH)_2$ in absolute ethanol. The precipitates were air-stable monosolvates of the metal complexes. Palladium complexes were formed as powders ranging from orange- to dark-red-coloured, while the copper complexes are all green.



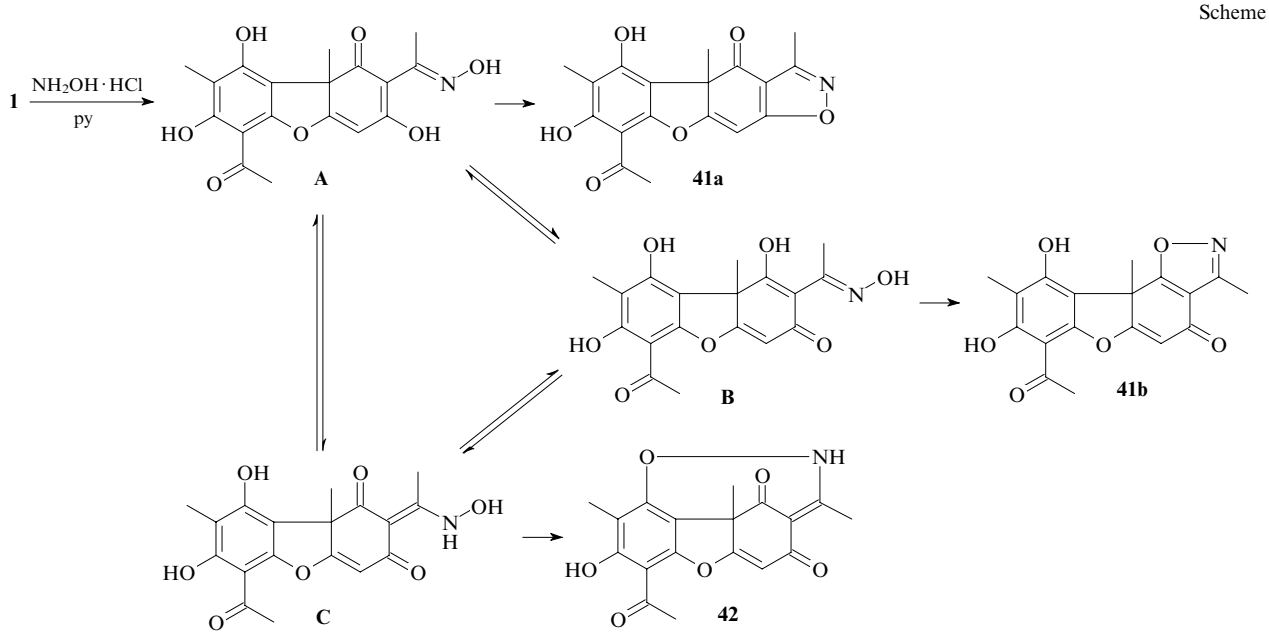
ML·solv

M	H_2L	solv
Cu	**40a**	EtOH
Pd	**40b**	EtOH
Cu	**40b**	EtOH
Pd	**40c**	EtOH
Cu	**40c**	MeC(O)Et
Cu	**40d**	THF
Pd	**40e**	EtOH
Cu	**40e**	MeC(O)Et

According to Kutney *et al.*,[54] the reaction of (+)-UA with hydroxylamine yields UA derivatives **41a**,**b** with an annulated isoxazole ring and also product **42** with an oxazocine ring. The reaction was carried out in the following way: UA and hydroxylamine hydrochloride were stirred at room temperature in dry pyridine (py), diluted with dry ethanol and refluxed (Scheme 24).

The authors believe that compounds **41** and **42** are formed *via* oxime **A**, which occurs in tautomeric equilibrium with forms **B** and **C**. Each tautomer is cyclized to give the corresponding product. According to TLC, the ratio of the reaction products can be affected by the reaction conditions. For the study of UA and hydroxylamine hydrochloride, the following experimental conditions were selected: (*a*) oxime formation in pyridine (rt, 1 h); (*b*) isolation of the oxime; (*c*) formation of annulated isoxazole derivative in absolute ethanol (90 °C, 1 h); (*d*) formation of annulated isoxazole derivative in anhydrous pyridine (110 °C, 1 h); (*e*) one-pot oxime synthesis and cyclization to the isoxazole ring in a pyridine–ethanol mixture (1 : 1;

Scheme 24



80 °C, 1.5 h). Different combinations of the above-listed stages gave the following yields of products:

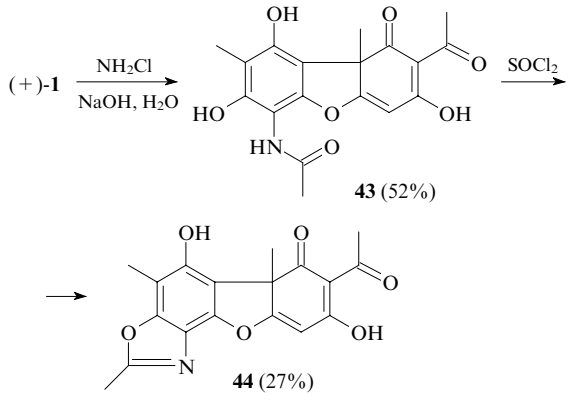
Conditions	Yield (%)			
	41a	**41b**	**42**	total
a, *c*	21	5.5	60.5	87
a, *b*, *c*	20	56.5	2	79
a, *b*, *d*	16	58	21	95
e	30.5	—	—	—

It can be seen that the one-pot reaction (conditions *e*) produces mainly product **41a**. The synthesis conducted by successive treatment of UA under conditions *a* and *c* gives a mixture of three products with predominance of compound **42**. The isolation of the oxide and the subsequent reaction under conditions *c* or *d* also affords three products where compound **41b** predominates.

Subsequently, it was shown [55] that compound **41b** rather than compound **42** as indicated above, is formed as the major product in the reaction of UA with hydroxylamine (conditions *a*, *c*). The authors of this work obtained products **41a**,**b**, and their structure was characterized by X-ray diffraction analysis.

Apart from UA derivatives containing an isoxazole ring annulated to ring C, products of UA modification containing an oxazole ring annulated to ring A are also known. In order to introduce an amide group into ring A of the UA molecule, (+)-UA was treated with monochloramine in a 0.6% aqueous solution of NaOH, and amide **43** was obtained.[56] At the next stage, this amide was treated with thionyl chloride at 55 °C to give oxazole derivative **44** (Scheme 25).

Scheme 25



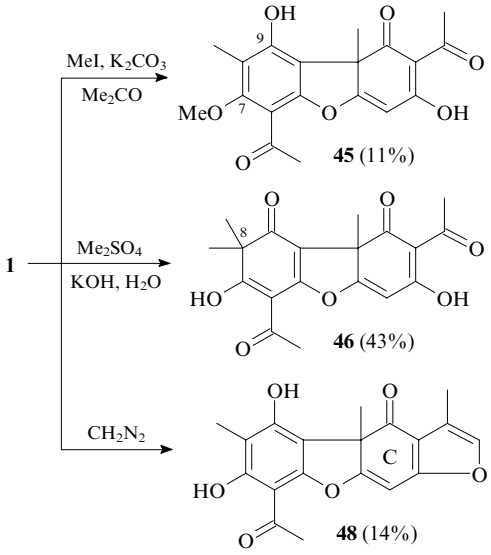
The same publication describes an attempt to involve (+)-UA into the Schmidt reaction to obtain amide **43**; however, upon use of an equimolar amount of sodium azide, only the starting UA was recovered in 93% yield from the reaction mixture. The Schmidt reaction performed under more rigorous conditions (4-fold excess of NaN_3 in the presence of concentrated H_2SO_4, 50–60 °C, 2 h) [57] gave compound **44** (yield 70%), *i.e.*, the expected amide derivative **43** was not formed but subsequent heterocyclization took place involving the phenolic hydroxy group located in the *ortho*-position to the reacting acyl group.

Thus, UA reacts with hydrazine and hydroxylamine, as with amines, first at the C(11)=O group to give annulated pyrazole or isoxazole derivatives. The presence of a strong electron acceptor in the substituted hydrazine prevents the formation of the pyrazole ring, and the reaction affords hydrazones. The hydrazides of some acids and thiosemicarbazide also do not form the pyrazole ring upon condensation with UA at the C(11)=O group.

d. Synthesis of ethers

In order to prepare UA methyl ether, Bertillson and Wactmeister [58] made (+)-UA to react with MeI in boiling acetone in the presence of K_2CO_3 and obtained ether **45** in a moderate yield (Scheme 26).

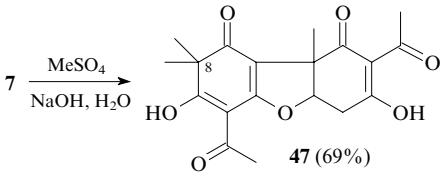
Scheme 26



On repeated introduction of compound **45** into the reaction with MeI for obtaining 7,9-dimethyl ether of UA, only product **45** is recovered. A different methylating agent, dimethyl sulfate, reacts with UA in an alkaline medium to give C-alkylation product **46** at position 8 (see Scheme 26).[59]

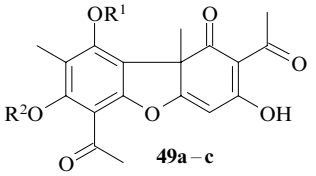
The same result (formation of compound **47**) is attained on using dihydrousnic acid **7** (Scheme 27).[60]

Scheme 27



The attempt to obtain the methyl ether of UA by the reaction of (+)-UA with diazomethane gave only a moderate yield of compound **48** containing a furan ring annulated to ring C of usnic acid (see Scheme 26).[61]

Kutney and Sanchez [62] implemented a more effective approach to the synthesis of ethers of usnic acid: (+)-UA was stirred with tetramethylammonium hydroxide in anhydrous hexamethylphosphoramide at 0 °C and then benzyl bromide was added. This gave a mixture of two compounds, monoether **49a** and diether **49b**, in 75% and 14% yields, respectively. As noted by the authors, compound **49b** is racemized during the synthesis.[62]



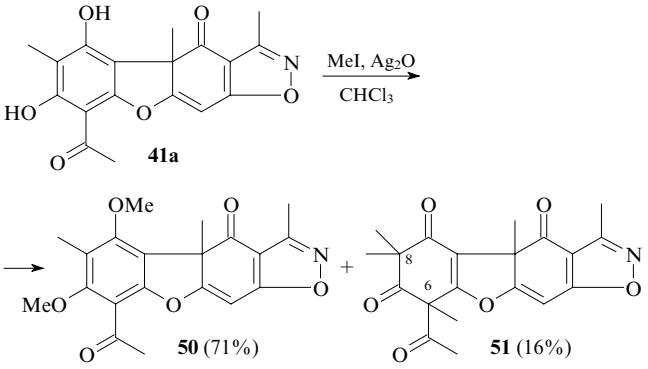
49a–c

R^2 = Bn: R^1 = H (**a**), Bn (**b**), Me (**d**);
R^1 = H, R^2 = $CH_2C_6H_4Br$-4 (**c**); R^1 = Me, R^2 = H (**e**)

Under similar conditions, the reaction with *p*-bromobenzyl bromide resulted in the formation of **49c** in a yield of 82%. Mixed diether **49d** was synthesized in 72% yield by the reaction of **49a** with dimethyl sulfate in anhydrous THF in the presence of NaH. The formation of compound **49d** is accompanied by racemization of the reaction product. By treating **49d** with trifluoroacetic acid at room temperature, monomethyl ether **49e** was obtained, also as a racemic mixture.

On heating (50–55 °C) with MeI in chloroform in the presence of Ag_2O for 20 h, isoxazole derivative of UA **41a** is converted to methyl ether at both hydroxy groups, product **50** (Scheme 28).[62] Compound **51** resulting from C-alkylation at C(6) and C(8) was isolated from the reaction mixture as a by-product.

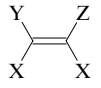
Scheme 28



41a

50 (71%) **51** (16%)

Furin *et al.*[63] considered the reactions of (+)-UA with some polyfluoroalkenes. The authors expected to obtain products of nucleophilic displacement of fluorine at the double bond of polyfluoroalkene. However, the reaction of compound **1** with polyfluoroalkenes **52a–c**



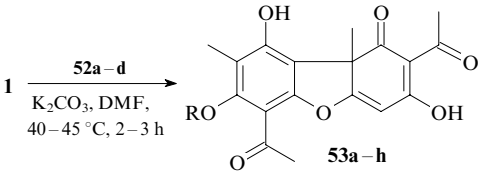
52a–d

X = Y = Z = F (**a**); X = Z = F, Y = Cl (**b**);
X = Y = F, Z = CF_3 (**c**); X = Cl, Y–Z = $(CF_2)_4$ (**d**)

in the presence of K_2CO_3 in DMF gave compounds **53a–c** (yields 94%, 87% and 52%, respectively) resulting from the addition of the C(7)OH group to the multiple bond of polyfluoroalkenes (Scheme 29). Only in the case of alkene **52c**, did the reaction give a small amount of compound **53d** ($Z:E \approx 1:1.6$) resulting from the nucleophilic displacement of fluorine at the perfluoroalkene double bond.

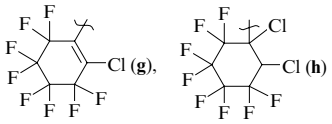
In the same study,[63] the effect of the solvent and the base on the degree of these transformations was investigated using perfluoroalkene **52c** as an example. The replacement of the K_2CO_3–DMF system by NaH–THF or Et_3N–MeCN changes the **53c** to **53d** ratio in the reaction mixture

Scheme 29



53a–h

53: R = CHF_2CF_2 (**a**), $CHClFCF_2$ (**b**), CF_3CHFCF_2 (**c**),
$CF_3CF{=}CF$ (**d**), $(CF_3)_2C{=}CC_2F_5$ (**e**), $(CF_3)_2CHCFC_2F_5$ (**f**),



from 3 : 1 to 1 : 1.6, the *Z*- to *E*-isomer ratio of **53d** remaining almost the same (~1 : 1.6).

It was noted[63] that the ratio of the substitution and addition products is affected by the solvent moisture content. The presence of water (0.2%) in DMF promotes the addition (52% **53c**), while in anhydrous DMF, the substitution takes place (76% **53d**). Also, in the latter case, minor amounts of compounds **53e**,**f** are also formed (see Scheme 29). The appearance of these by-products was attributed to the formation of perfluoro-2-methylpent-2-ene from hexafluoropropylene under the reaction conditions. The same trends in the distribution of addition and substitution products depending on the water content of the solvent were found in the reaction of UA with 1,2-dichlorooctafluorocyclohex-1-ene (**52d**) in the presence of K_2CO_3 in DMF (Scheme 29). When the water content of DMF is 0.2%, the major product is compound **53h** (85%), while in anhydrous DMF, compound **53g** is mainly formed (94%).

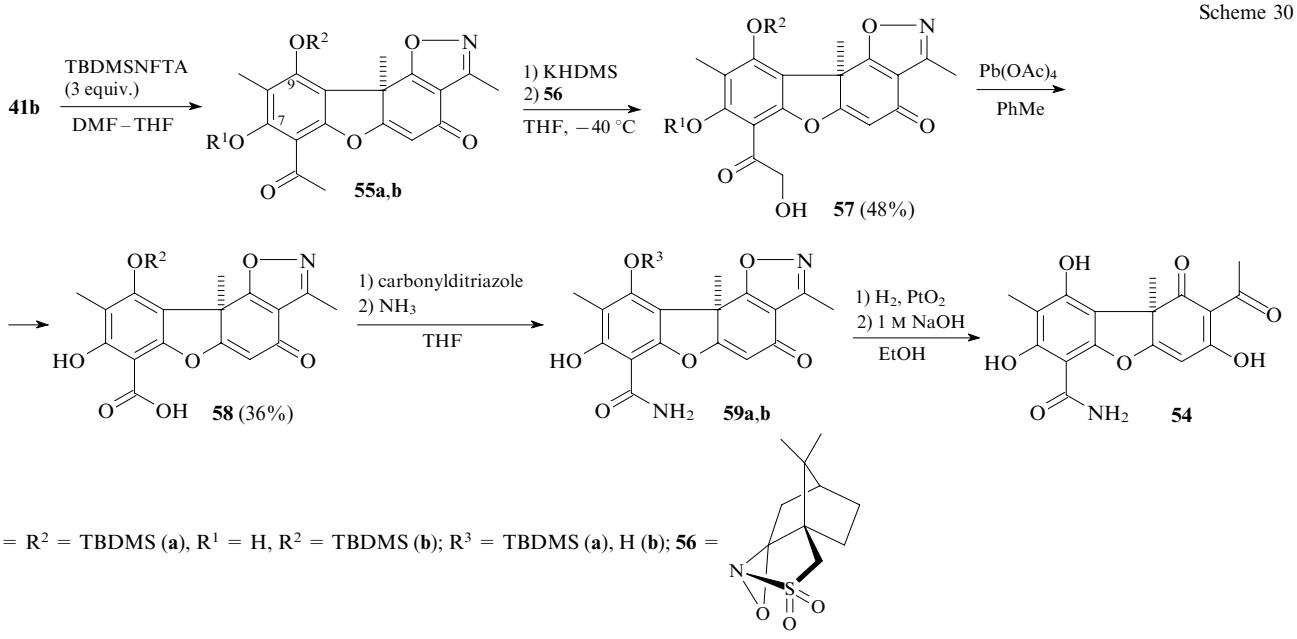
The *tert*-butyldimethylsilyl protection of the phenolic hydroxy groups was used[55] to prepare 8-methylcercosporamide (**54**), a structural analogue of (+)-UA, by a multistage synthesis. It is expedient to present the whole sequence of transformations of UA to 8-methylcercosporamide (Scheme 30).

The first stage is the preparation of the annulated isoxazole derivative **41b** by a known procedure;[54] then it is introduced in the reaction with *N*-*tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide (TBDMSNTFA). This gives diether **55a** in a yield of 95%; when the amount of TBDMSNTFA is halved, monoether **55b** is formed. During the subsequent transformations, on successive treatment with potassium hexamethyldisilazide (KHDMS) and (−)-(2*S*,8a*R*)-(camphorsulfonyl)oxaziridine (**56**), monoether **55b** is converted to α-hydroxy ketone **57** (diether **55a** gives α-hydroxy ketone in a yield of only 20%). The oxidation of compound **57** with $Pb(OAc)_4$ affords acid **58**. The latter is treated successively with carbonyldiimidazole and gaseous NH_3, resulting in a mixture of products **59a**,**b** in yields of 23% and 67%, respectively. This mixture is reduced with the H_2/PtO_2 system and then hydrolyzed in an alkaline medium; this affords compound **54** in 60% yield (see Scheme 30).

Note that in this case, the phenolic hydroxy group at C(9) turned out to be most reactive in the formation of the ether.

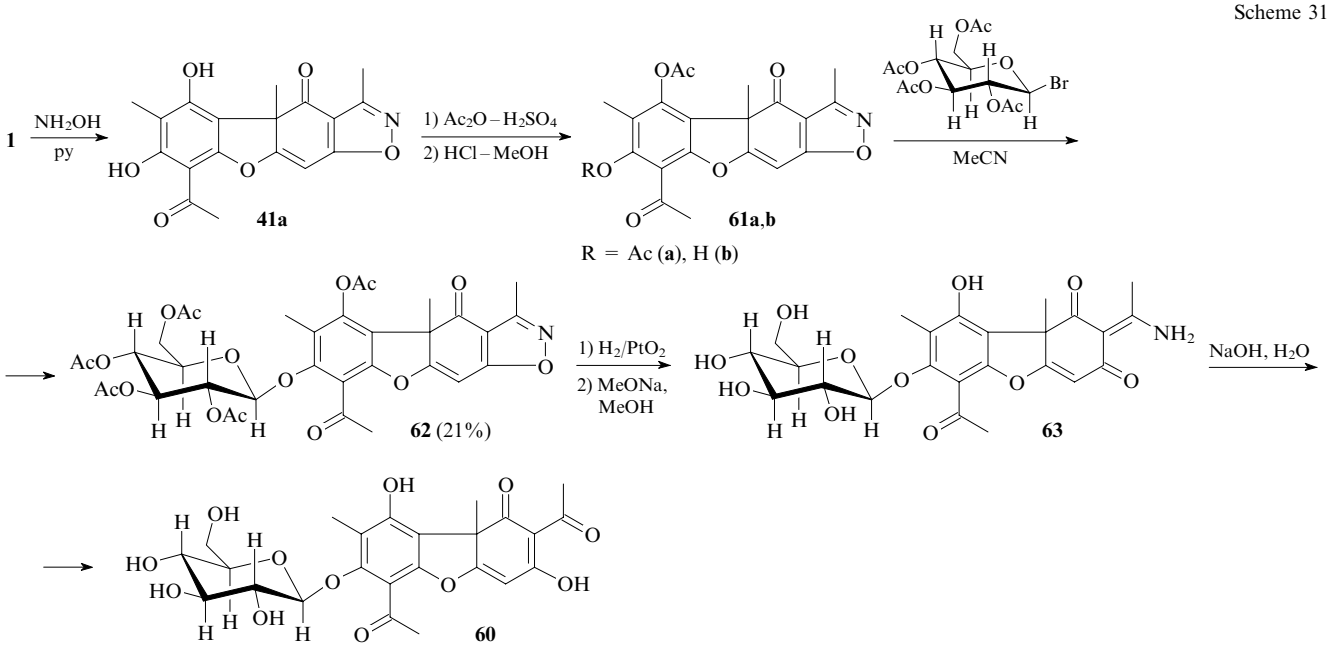
Glycoside **60**, an UA derivative that can also be regarded as ether, was synthesized[50] (Scheme 31). The first stage is the preparation of compound **41a** by a known procedure.[54] The second stage is the acetylation of the

Scheme 30



$R^1 = R^2 =$ TBDMS (**a**), $R^1 =$ H, $R^2 =$ TBDMS (**b**); $R^3 =$ TBDMS (**a**), H (**b**); **56** =

Scheme 31



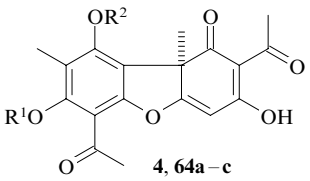
phenolic hydroxyls (compound **61a**, yield 70%) followed by selective removal of the acetyl group in position 7 (**61b**, 70%). Monoacetate **61b** reacts with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of Ag_2O on refluxing in acetonitrile to give compound **62**. The subsequent stages include isoxazole ring opening, removal of the acetyl groups from the glycoside residue (**63**, 86%) and alkaline hydrolysis of enamine **63** to give the target product **60**, glycoside, at the hydroxy group at the C(7) atom (yield 40%).

Thus, UA and its derivatives react with alkyl, alkenyl and aryl halides to give ethers at the phenolic hydroxyls, the hydroxy group at the C(7) atom being most reactive; an exception is the reaction giving *tert*-butyldimethylsylyl ether of an UA derivative **41b**, where the OH group at C(9) reacts more readily.

e. Synthesis of esters

Compound **4** was the first ester obtained by the acid-catalyzed reaction of UA and acetic anhydride over a period of 12 h (yield 98%).[64,65] Esterification involved both hydroxy groups of the benzene ring of UA. If UA reacts with acetic anhydride for 15 min,[58] ester **64a** at the C(7)-hydroxy group is formed in rather low yield (8%) and the substrate conversion is incomplete.

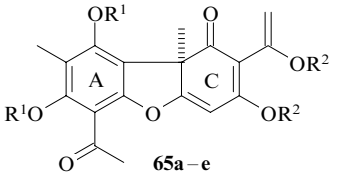
More recently,[66] the synthesis of esters **4**, **64b**,**c** and **65a**–**e** was reported. Esters **4** and **64b** at the C(7)- and C(9)-hydroxy groups were obtained by reactions of the corresponding acyl chlorides with (+)-UA in the presence of pyridine at room temperature for 3–4 h (yields 80%–82%). Product **64b** is also formed in the reaction of UA with propionic anhydride in the presence of H_2SO_4 (conc.) at 50 °C for 3 h but in a low yield (60%).



4, **64a–c**

64: R^1 = Ac, R^2 = H (**a**), R^1 = R^2 = EtC(O) (**b**), $CH_2ClC(O)$ (**c**)

The authors of this study obtained unexpected results when UA was made to react with aromatic acyl chlorides in the presence of pyridine. The first step gave enol esters in ring C, and only after that, esters in ring A were formed. Finally, tetrasubstituted derivatives were obtained. The reaction of UA with benzoyl chloride at room temperature for 3 h affords dibenzoate **65a** (yield 42%) and tetrabenzoate **65d** (yield 31%). Under the same conditions, the introduction of *p*-methoxybenzoyl chloride and *p*-chlorobenzoyl chloride into the reaction resulted in compounds **65b**,**c** as the major products in 43% and 40% yields, respectively. Diacetate **4** reacts with benzoyl chloride to give mixed ester **65e** in 35% yield.



65a–e

R^1 = H: R^2 = Bz (**a**), 4-$MeOC_6H_4C(O)$ (**b**), 4-$ClC_6H_4C(O)$ (**c**);
R^2 = Bz: R^1 = Bz (**d**), Ac (**e**)

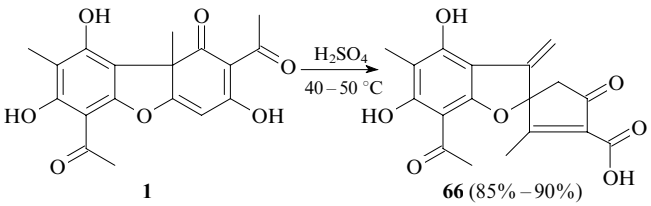
Thus, when reacting with aliphatic acylating reagents, UA forms esters at phenolic hydroxyls, C(7)OH being most reactive. Aromatic acylating reagents first react at the enol hydroxy group C(3)OH and with the enol form of the carbonyl group C(11)═O, and only after that, at the phenolic hydroxy groups of the substrate.

2. Reactions accompanied by the destruction of the carbon skeleton

a. Cleavage induced by various reagents

Publications [10, 67] devoted to determination of the UA structure describe the formation of spiro compound **66** on heating UA in concentrated H_2SO_4 for 2–3 h (Scheme 32). The structure of compound **66** was established by performing its chemical transformations.[67]

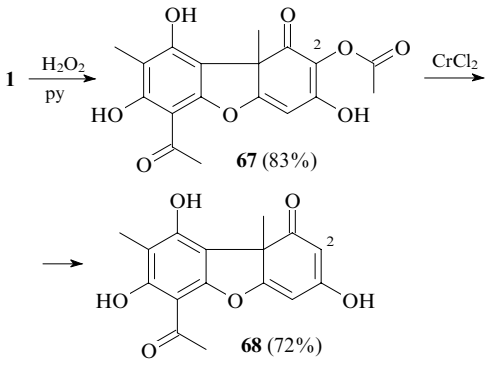
Scheme 32



1 **66** (85%–90%)

The deacetylation of UA at the C(2) atom was reported.[68] First, the reaction with H_2O_2 in pyridine produces 2-acetoxy derivative **67**, which is then treated with $CrCl_2$ to be converted to 2-deacetyl derivative **68** (Scheme 33).

Scheme 33

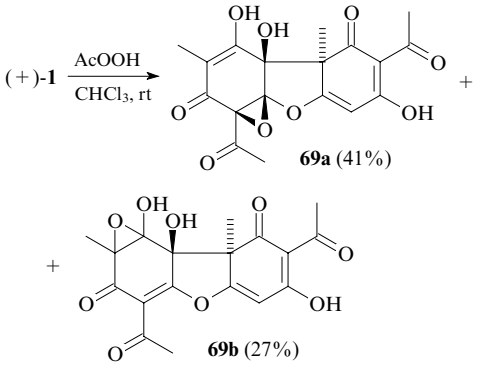


67 (83%)

68 (72%)

It was found [69] that oxidation of (+)-UA with organic peroxy acids involves ring A, and the aromatic system is destroyed to give compounds containing epoxide rings. The reaction with peracetic acid proceeds at room temperature and gives compounds **69a**,**b** (Scheme 34). The structure of compound **69a**, in particular the epoxide ring configuration, was confirmed by X-ray diffraction data (configuration of the epoxide ring in **69b** was not established).

Scheme 34

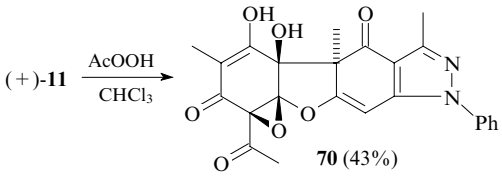


69a (41%)

69b (27%)

The pyrazole derivative of UA, compound **11**, can also be oxidized by peracetic acid at resorcinol ring A. This affords compound **70** (Scheme 35); the formation of the second oxidation product analogous to **69b** was not observed in the study cited.[69]

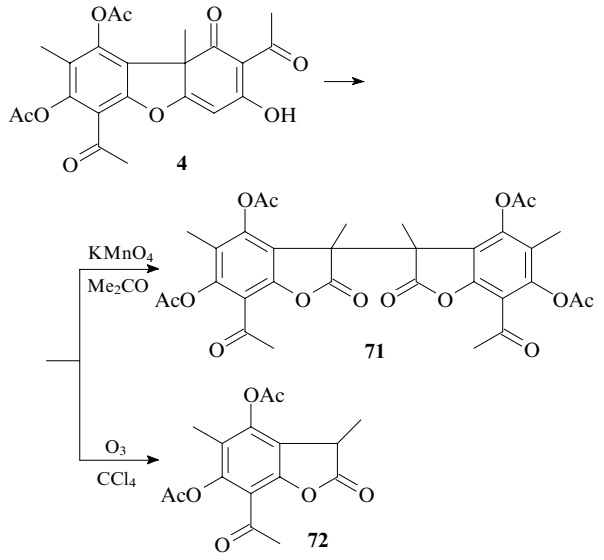
Scheme 35



70 (43%)

The oxidation of UA 7,9-diacetate (**4**) with potassium permanganate was reported [49] to involve ring C of the substrate and to give dimer **71** in a relatively low yield (Scheme 36).

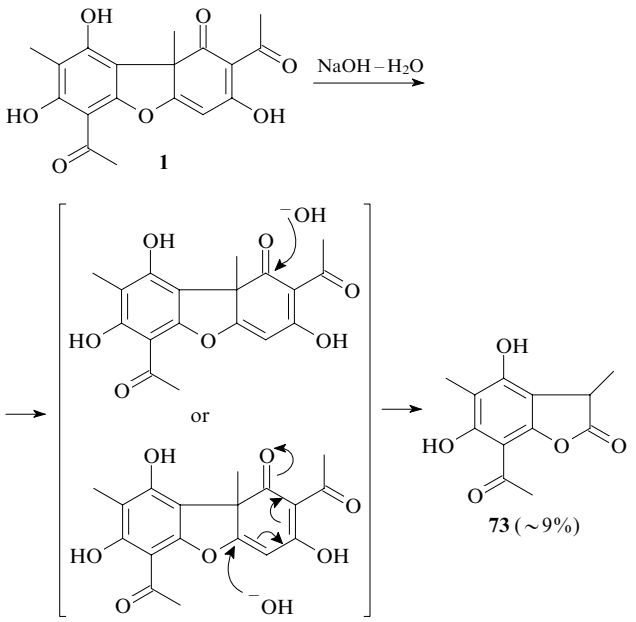
Scheme 36



In the same work, a solution of UA diacetate (**4**) in CCl_4 was treated with ozone. As a result, product **72**, produced upon destruction of ring C of the substrate, was isolated in a relatively low yield.

Cleavage of UA in a 50% solution of NaOH was carried out [70] in an oxygen stream at 100 °C for 1 h. After workup of the reaction mixture and chromatography on silica gel, product **73** was isolated in a low yield (Scheme 37).

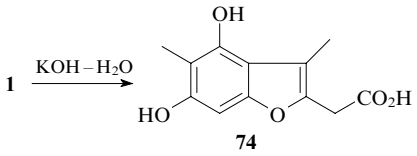
Scheme 37



Takahashi and Takani [70] suggest that the hydroxide anion attacks alternatively two positions of ring C; as a result, certain rearrangements lead to complete destruction of this ring (see Scheme 37).

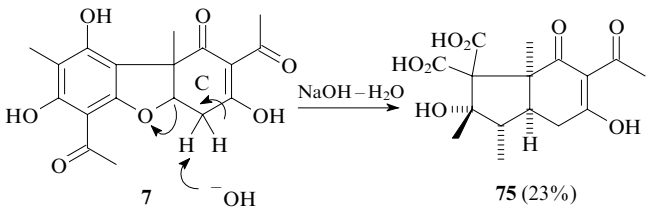
Under more rigorous conditions (50% KOH, 210 °C, 10 min), UA is deacetylated at position 6, and ring C is destroyed, thus giving compound **74** (Scheme 38).[71]

Scheme 38

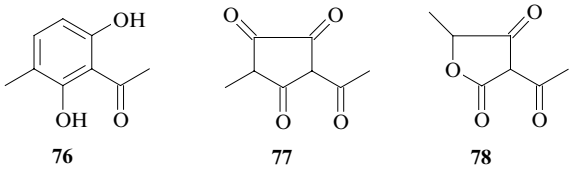


Dihydrousnic acid (**7**) is cleaved in a different way when refluxed on a water bath in 50% NaOH in a stream of oxygen. According to the authors,[72] the hydroxide anion attacks one of the methylene protons of ring C. During the subsequent rearrangements, destruction of rings A and B of the substrate takes place to give compound **75** (Scheme 39) with formally retained ring C and with two geminal carboxy groups (the structure of product **75** was confirmed by X-ray diffraction).

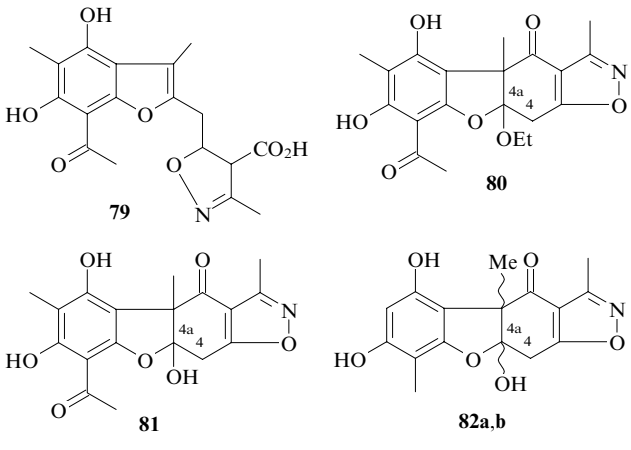
Scheme 39



On treatment with $KMnO_4$ in alkaline medium, dihydrousnic acid (**7**) is converted to products of extensive destruction, compounds **76**–**78**, in relatively low yields.[73]



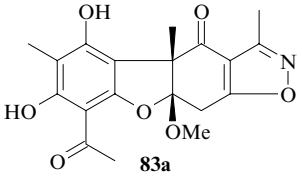
Usnic acid derivative **41a** with an annulated isoxazole ring also undergoes destruction of ring C in a water–ethanol solution of KOH at 70 °C, one of the major products being compound **79** containing a carboxy group, which is formed in 36% yield.[54,74] The minor products of this reaction, compounds **80** and **81**, are formed in yields of 3.1% and 2.2%, respectively, upon the addition of a solvent molecule to the C(4)=C(4a) bond. Apart from compounds **79**–**81**, this reaction gives compounds **82a**,**b** (yields 23%



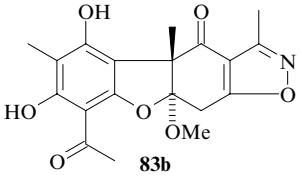
trans-Me,OH (**a**); *cis*-Me,OH (**b**)

and 26.8%, respectively), which have resulted from three reactions: addition of water molecule to the C(4)=C(4a) bond, deacetylation of aromatic ring A and its rearrangement.

Under milder conditions (50 °C, 20% KOH in MeOH), the reaction affords mainly the products of addition of a solvent molecule to the C(4)=C(4a) bond of the substrate.[65] Diastereomers **83a**,**b** are formed in a total yield of about 60% in a 1 : 4 ratio, respectively.



83a

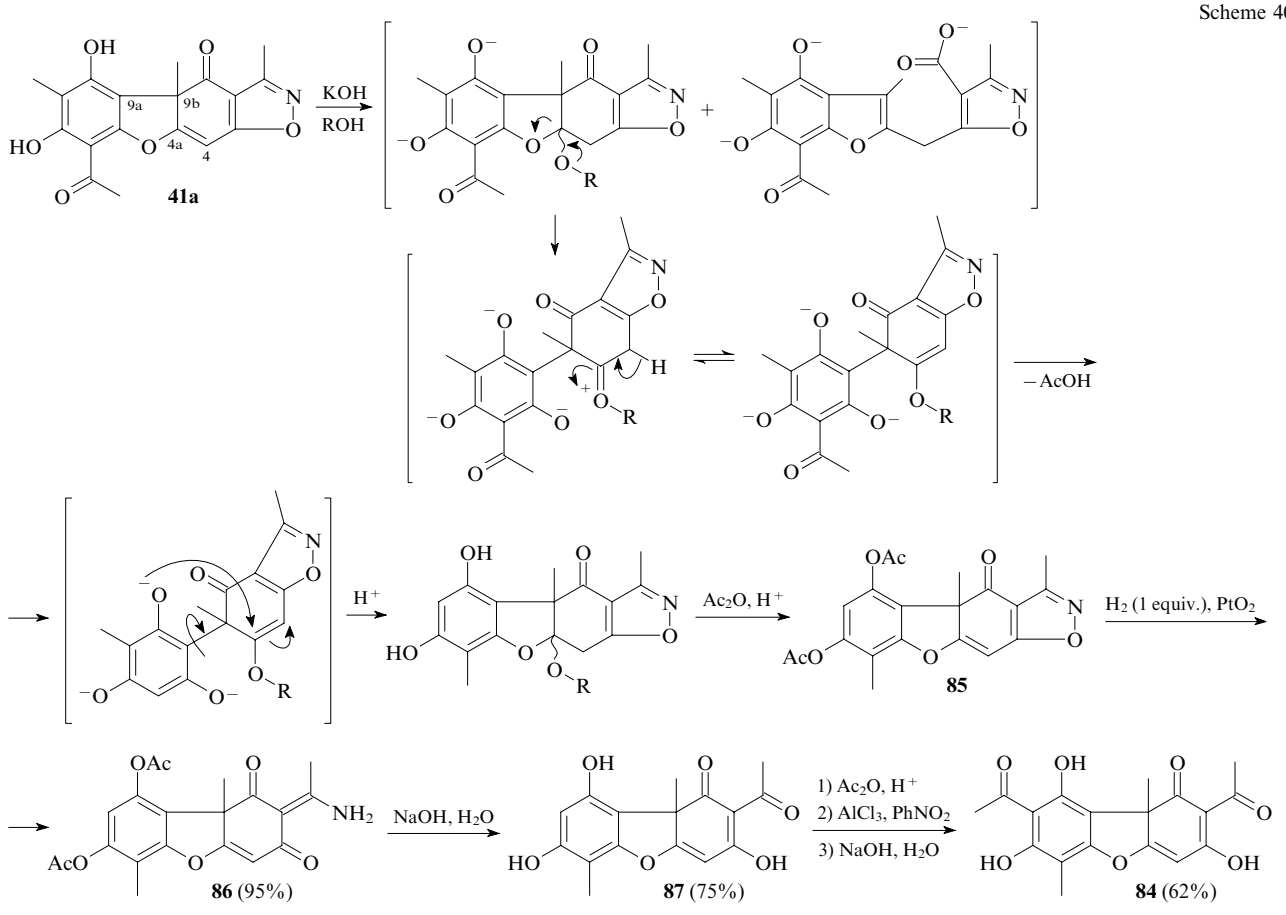


83b

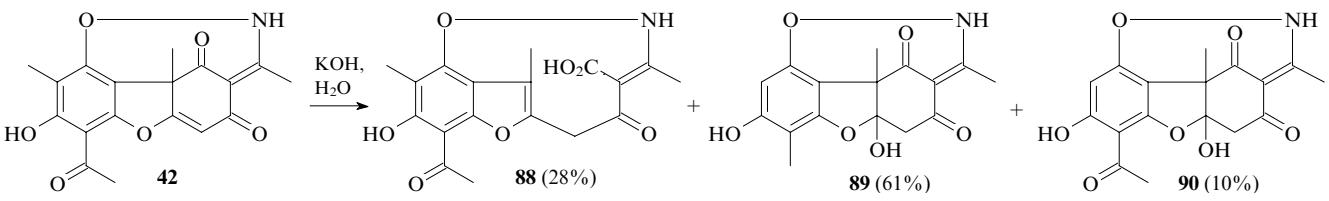
Kutney *et al.*[65,74] used the ability of ring A of UA derivative **41a** to rearrange in alkaline medium to prepare isousnic acid **84**. The authors[65] assumed that the rearrangement of ring A of compound **41a** in alkaline medium becomes possible after opening of the furan ring of the substrate upon the addition of a solvent molecule to the C(4)=C(4a) bond and the consequent possibility of rotation of ring A around the C(9a)–C(9b) bond (Scheme 40). Subsequently, on treatment with acetic anhydride in acidic medium, elimination of ROH at the C(4)–C(4a) bond and acetylation of the phenolic hydroxyls takes place to give compound **85**. This product is reduced with hydrogen on Adams' catalyst with isoxazole ring opening to give enamine **86**, which is hydrolyzed with 1 M NaOH at room temperature to give 8-deacetylisousnic acid **87** in 1 h. This compound is converted in three stages to isousnic acid **84**: first, it is acetylated at the phenolic hydroxyls (the yield of the diacetate is 87%), then the aromatic ring is acetylated at a temperature of 60 °C in dry nitrobenzene in the presence of $AlCl_3$, and the subsequent alkaline treatment of the reaction mixture gives isousnic acid **84** (see Scheme 40).[74]

Another product of UA condensation with hydroxylamine, compound **42**, was reported[75] to be converted in aqueous KOH for 1.5 h at room temperature to products of ring C cleavage and ring A deacetylation and rearrangement (compounds **88**–**90**) (Scheme 41).

Scheme 40

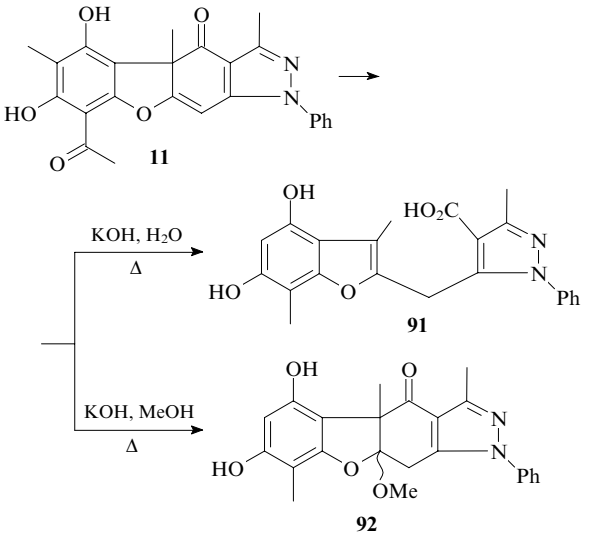


Scheme 41



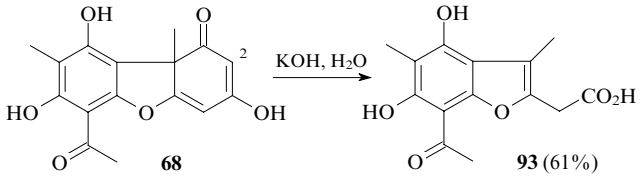
On heating in an aqueous solution of KOH, pyrazole UA derivative **11** is deacetylated, ring A rearranges and ring C is cleaved, thus giving compound **91**, which is structurally similar to compound **79**. On heating in a methanol solution of KOH, the same substrate is converted to the product of addition of a solvent molecule at the C(4)=C(4a) bond, namely, compound **92**, containing rearranged and deacetylated ring A (Scheme 42).[49]

Scheme 42



Treatment of UA derivative **68** deacetylated at the 2-position, for 25 min at a temperature of 95 °C in 75% aqueous KOH in a nitrogen stream induces destruction of ring C. The resulting compound **93** contains a carboxy group (Scheme 43).[10, 71, 76, 77]

Scheme 43



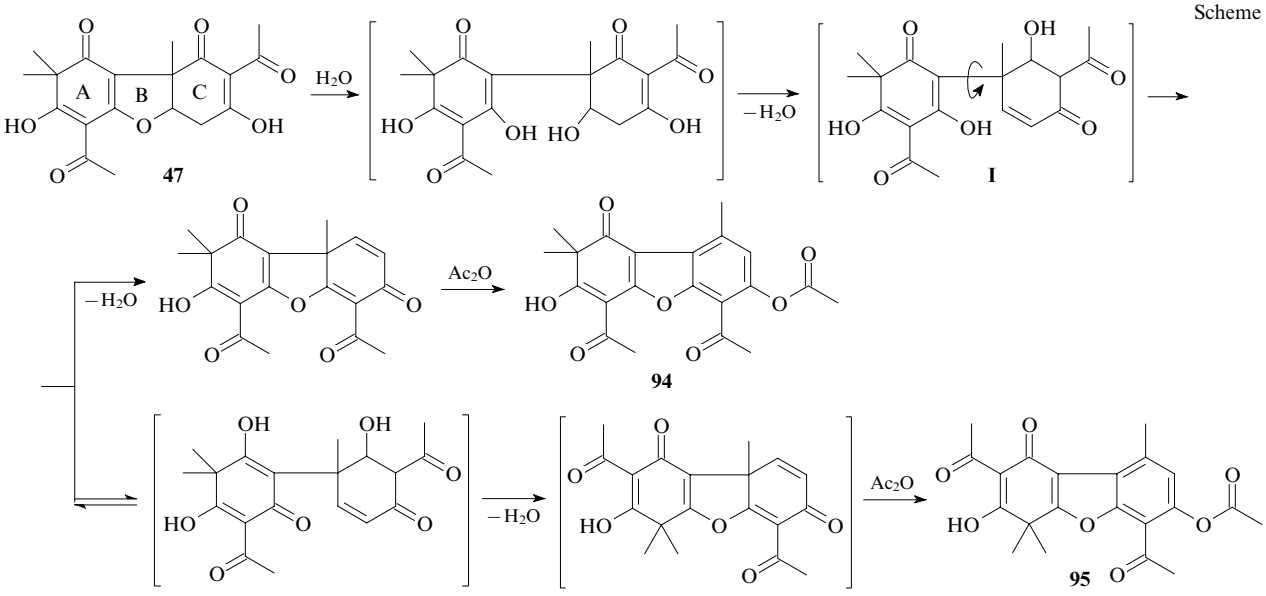
Thus, destruction of the carbon skeleton upon treatment of UA and some of its derivatives with alkalis involves initially ring C. Upon hydrogenation of the C(4)=C(4a) double bond in ring C, the route of cleavage changes, and the reaction is accompanied by destruction of rings A and B. In alkaline medium, deacetylation at the C(6) atom also takes place. One more process that proceeds in alkaline medium is the rearrangement of ring A in UA derivatives induced by furan ring opening; this gives compounds with the 'iso' arrangement of substituents in ring A. The oxidation of UA is also accompanied by destruction of ring C.

b. Dienone–phenol rearrangement

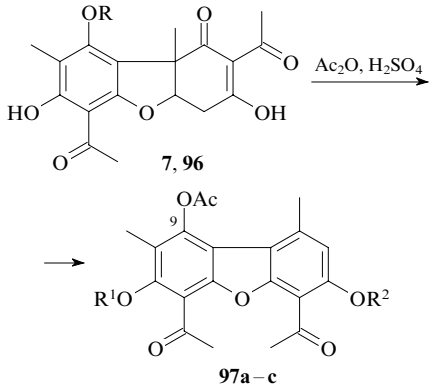
The so-called dienone–phenol rearrangement was observed [78, 79] at a step of acetylation of methyldihydrousnic acid (**47**) with acetic anhydride in the presence of H_2SO_4. This is accompanied by the rearrangement of all rings of the substrate. In the authors' opinion, compounds **94** and **95** are formed (Scheme 44) upon opening of ring B in compound **47**, which is accompanied by rotation around the C(9a)–C(9b) bond, and this subsequently affects the arrangement of substituents in ring A of the final reaction products. Opening of ring B is followed by elimination of the water molecule from the C(4)–C(4a) bond in ring C, and the resulting intermediate **I** undergoes rotation around the C(9a)–C(9b) bond, closure of the furan ring with the loss of the water molecule and the subsequent dienone–phenol rearrangement in ring C to give compound **94** with the 'normal' arrangement of substituents in ring A. The other tautomer of the intermediate undergoes closure of the furan ring and the subsequent dienone–phenol rearrangement in ring C to be converted to compound **95** with the 'iso' arrangement of substituents in ring A (see Scheme 44).

In a later study [80] devoted to the dienone–phenol rearrangement of UA derivatives, refluxing of dihydrousnic acid **7** and its monoacetate **96** in acetic anhydride in the presence of catalytic amounts of H_2SO_4 gave products **97a–c** in moderate yields (Scheme 45).

Scheme 44



Scheme 45

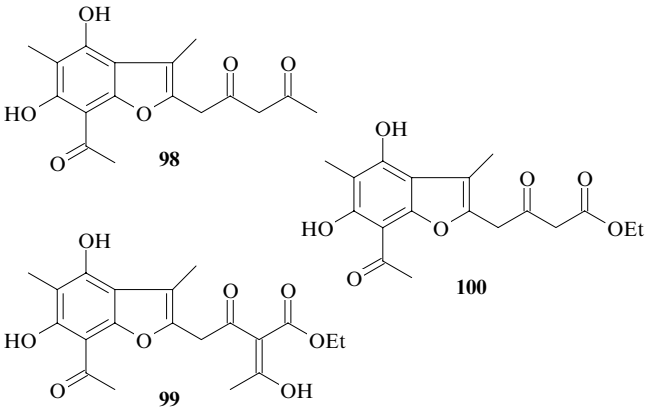


R = H (**7**), Ac (**96**); $R^1 = R^2$ = Ac (**97a**), H (**97b**); R^1 = Ac, R^2 = H (**97c**)

Note that in this case, ring A remained intact in the products. The authors suggest that the acetylated C(9)-hydroxyl prevents the furan ring from closing without rotation around the C(9a)–C(9b) bond and, hence, products with the 'normal' arrangement of substituents in ring A are formed.

c. Solvolysis in organic solvents

During determination of the UA structure, a number of investigations of its solvolysis in organic solvents at high temperature were performed. In all experiments, opening of ring C of the substrate took place. On heating of an ethanol–diethyl ether (20 : 1) solution of UA at 150–160 °C for 6 h, β-diketone **98** is formed in a yield of 61%.[10,81]



Hesse[82,83] carried out similar reactions in methanol, water, acetone and allyl alcohol with heating (150 °C); however, the product structure can be derived in this case only from elemental analysis data.

Solvolysis of UA in absolute ethanol occurs in a different way: heating for 4.5 h at 150 °C furnishes compound **99** in 60% yield.[84] An increase in temperature to 190 °C benefits the formation of compound **100** from UA.[85,86] It was shown[87] that 2-deacetylusnic acid is also converted to product **100** (yield 65%) when heated at 150 °C in absolute ethanol.

According to Sassa and Igarashi,[88] refluxing of UA in methanol containing 15% HCl for 6 h is not accompanied by destruction of ring C but leads to addition of the solvent molecule to the C(4)=C(4a) bond (products **101a**,**b**, substrate conversion ~60%) and, in addition, to the rearrangement of ring A of the substrate and, hence, the 'iso' arrangement of the methyl and acetyl groups in one of the products (compound **101b**) (Scheme 46). The authors presented the *cis*-configuration of the methoxy groups in compounds **101a**,**b** with respect to the angular C(9b)-methyl group.

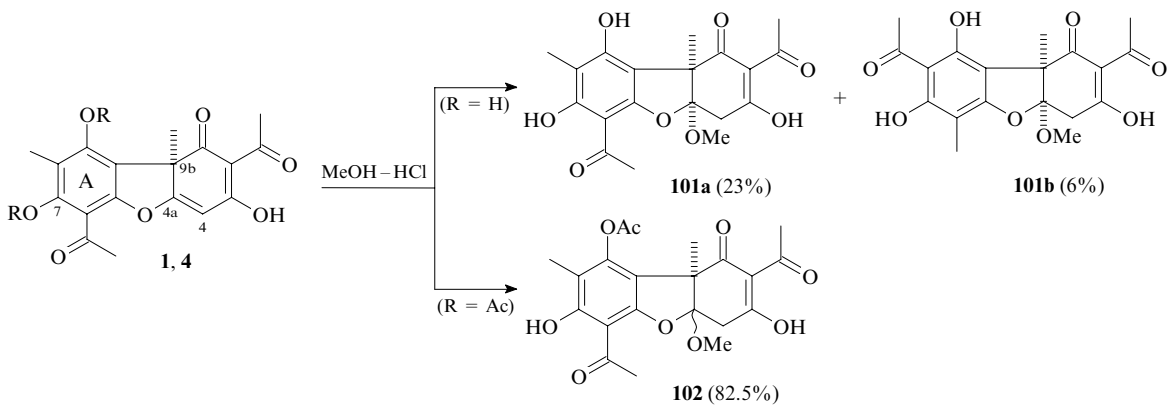
Considering the data on the synthesis of isousnic acid (**84**),[75] one may suggest that the formation of compound **101b** occurs *via* furan ring opening in UA. Under similar conditions (10% HCl in MeOH, reflux, 1.5 h), UA diacetate **4** is converted to compound **102** (*cis*- to *trans*-isomer ratio is 3 : 2) (see Scheme 46). Furthermore, selective deacetylation of C(7) occurs during the reaction.

Thus, solvolysis in organic solvents under rigorous conditions results in opening of ring C of the UA molecule to give products containing a β-diketone fragment and β-keto acid ester. Mild conditions of UA solvolysis lead to addition of the solvent (methanol) molecule to the C(4)=C(4a) bond with simultaneous rearrangement of ring A to give products with the 'iso' arrangement of substituents in the ring.

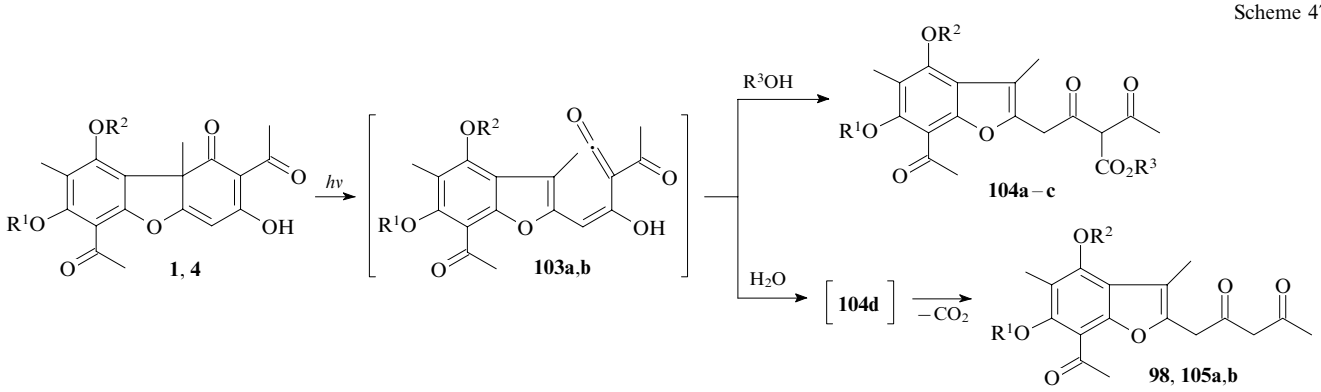
d. Photolysis

On UV irradiation of a solution of usnic acid in dioxane, racemization of UA took place (65%);[89,90] According to the authors,[90] this occurs *via* opening of the cyclohexadienone moiety giving ketene intermediate **103a** (Scheme 47). Note that no racemization of UA took place in chloroform. The presence of nucleophiles (water, alcohols) in the reaction medium during UV irradiation was reported[91] to favour the formation of addition products at the C=C bond of the

Scheme 46



Scheme 47

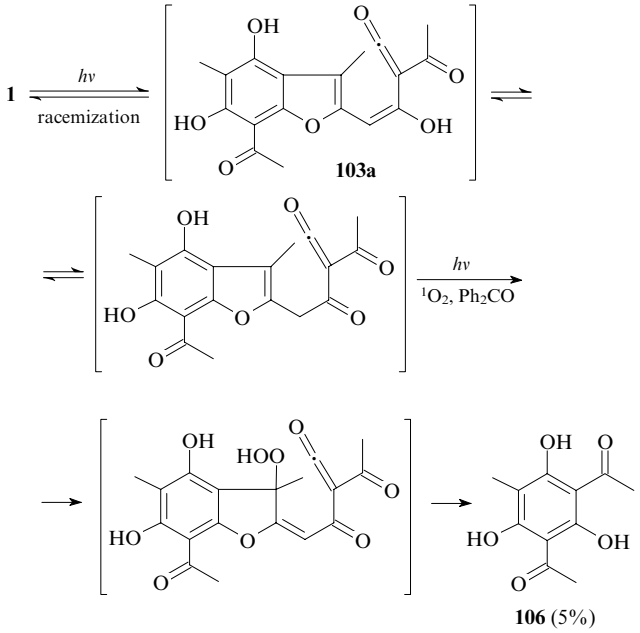


103: $R^1 = R^2 = H$ (**a**), Ac (**b**); **104**: $R^1 = R^2 = H$, $R^3 = Me$ (**a**); $R^1 = R^2 = Ac$: $R^3 = Et$ (**b**), Me (**c**), H (**d**);
105: $R^1 = H$, $R^2 = Ac$ (**a**); $R^1 = R^2 = Ac$ (**b**)

ketene. When a solution of UA (**1**) in THF is UV-irradiated at 0 °C in the presence of methanol, β-diketone **104a** (yield 21%) containing an ester group is formed. The photolysis of UA diacetate **4** under similar conditions in the presence of alcohols (methanol, ethanol) leads to intermediate **103b** to be converted to compounds **104b**,**c** in 44% and 46% yields, respectively (see Scheme 47). In the case of photolysis of UA diacetate **4** in the presence of water, partial deacetylation of the C(7)-hydroxy group and decarboxylation take place, resulting in the formation of compounds **105a**,**b** in yields of 13% and 65%, respectively. Probably, the ester group in β-diketones **104a**–**c** stabilizes these structures, unlike the carboxy group of compound **104d**, which is eliminated as CO_2 (see Scheme 47). Compound **98** was obtained in 37% yield upon UV irradiation of UA in acetonitrile for 3 h (Scheme 47).[92]

Takahashi and Takani[93] carried out photolysis of a solution of (+)-UA in THF at lower temperature (−20 °C). The same reaction in the presence of benzophenone and oxygen furnishes compound **106** in a low yield. In addition, it was found that this reaction is accompanied by

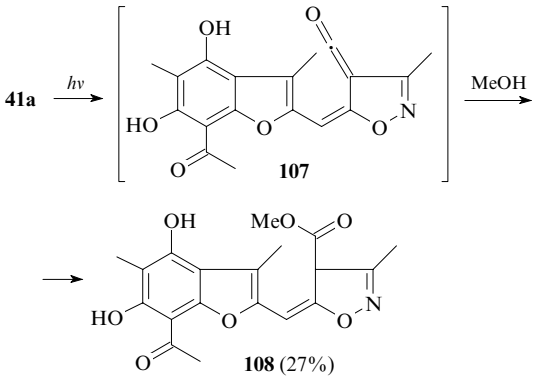
Scheme 48



UA racemization, the yield of racemic UA being 38%. When the reaction is conducted under similar conditions in the absence of benzophenone, the yield of compound **106** increases to 13%, and the content of racemic UA decreases to 6%. The presumptive mechanism also includes the formation of the ketene intermediate and participation of singlet oxygen (Scheme 48).

The isoxazole derivative of UA **41a** is photolyzed[91] in methanol *via* ketene intermediate **107** to give product **108** (Scheme 49).

Scheme 49

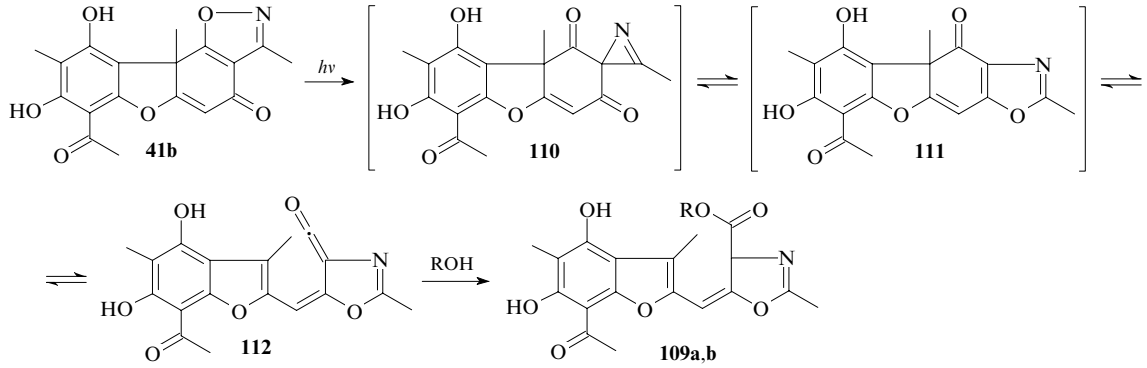


Photolysis in the presence of alcohols (methanol, ethanol) of another isoxazole derivative of UA, compound **41b**, gives mainly compounds **109a**,**b** containing an oxazole ring (Scheme 50). Thus, in this case, the isoxazole ring is rearranged to the oxazole ring, as was confirmed by ^1H and ^{13}C NMR data.

According to the authors, compounds **109** are formed in the following way. First, the isoxazole ring undergoes photoisomerization to the azirine ring (intermediate **110**), the latter rearranges to intermediate **111** containing an oxazole ring. This is followed by opening of the cyclohexadienone ring and addition of an alcohol molecule to the C=C bond of the ketene group of intermediate **112** to give compounds **109a**,**b** in 30% and 26% yields, respectively (see Scheme 50).[91]

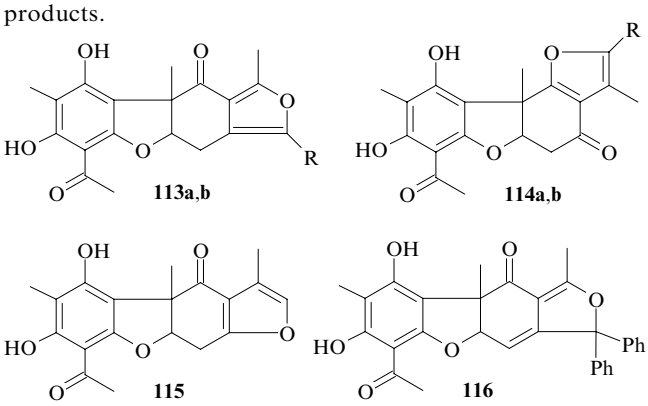
Photolysis of dihydrousnic acid **7** occurs without destruction of ring C of the substrate.[94] The reaction in methanol at −18 °C in the presence of benzophenone produces cyclization products, compounds **113a**, **114a** and **115**, in which the furan ring is in different ways fused to

Scheme 50



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

ring C (yields 2.6%, 17% and 1.4%, respectively). The same reaction at room temperature leads to lower yields of these products.

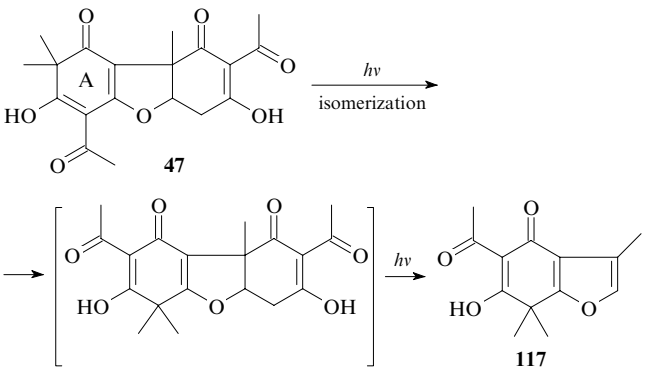


R = H (**a**), Me (**b**)

The replacement of methanol by ethanol for the photolysis of compound **7** gives products **113b**, **114b** and **116** in minor yields (2%, 3% and 1%, respectively). Compound **116** is presumably formed upon the addition of benzophenone to the substrate.

On UV irradiation in a methanol solution at −18 °C in the presence of benzophenone, methyldihydrousnic acid (**47**) is converted to product **117** in a very low yield (0.5%) *via* isomerization of ring A (Scheme 51).[94] Conduction of the reaction at room temperature and without benzophenone leads to an increase in the yield of compound **117** to 9%.

Scheme 51



The UV irradiation of compound **47** in another solvent, dioxane, at room temperature in the presence of benzophenone gives in a similar way compound **117** in a yield of 32%.[94]

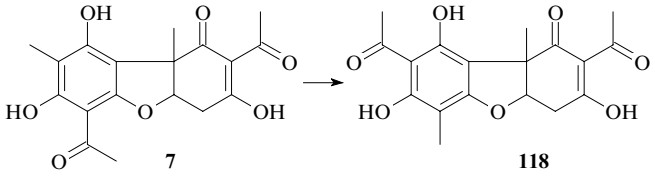
Thus, photolysis of UA is accompanied by opening of ring C *via* the formation of the ketene intermediate. When nucleophiles are present in the reaction medium, they react with the ketene group to afford β-diketones and β-keto acid esters, while in the absence of nucleophiles, substrate racemization takes place.

e. Thermolysis

To our knowledge, no data on the thermolysis of usnic acid are available from the literature, but thermolysis of some derivatives of this acid has been reported in a few publications.

Heating of dihydrousnic acid (**7**) *in vacuo* (5×10^{-3} mm Hg) in a hydrogen atmosphere at 230 °C leads to isomerization of the substrate giving isodihydrousnic acid **118** (Scheme 52).[34,35]

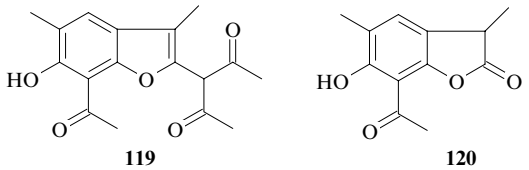
Scheme 52



The authors of this work note the change in the optical rotation sign during the reduction of UA to dihydrousnic acid **7** and during isomerization of the latter to product **118**. The change in the optical rotation sign concerns transformations of both enantiomers of UA, for example:

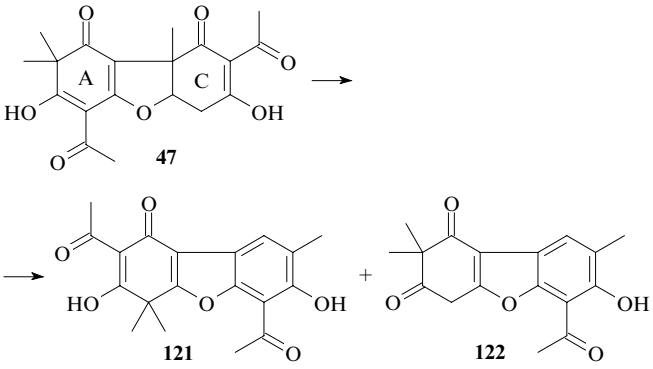
(+)-**1** ⟶ (−)-**7** ⟶ (+)-**118**

Heating of dihydrousnic acid (**7**) under more rigorous conditions (under atmospheric pressure and a temperature of 240–250 °C) affords compounds **119** and **120** in exceptionally low yields.[95]



Pyrolysis of methyldihydrousnic acid **47** under atmospheric pressure and at a temperature of 220–240 °C for 30 min produces compounds **121** and **122** in relatively low yields (Scheme 53).[96] In the authors' opinion, these products are formed *via* furan ring opening and closure accompanied by the loss of a water molecule and *via* 1,3-shift of the methyl group in ring C at the last stage.

Scheme 53



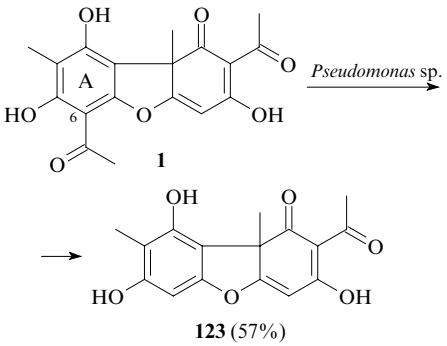
As regards the structure of ring C, compounds **121** and **122** are similar to **94** and **95**, which were obtained by the same authors by the dienone – phenol rearrangement of ring C of compound **47** in acetic anhydride in the presence of concentrated H_2SO_4. However, the positions of the methyl group in this ring are different for these compounds. In both cases, the authors describe the methods for determination of the structures of **94**, **95** and **121**, **122** in sufficient detail.

f. Biodegradation

The studies of the action of microorganisms on UA described below were driven by the interest of researchers in the mechanism of UA biodegradation in nature.

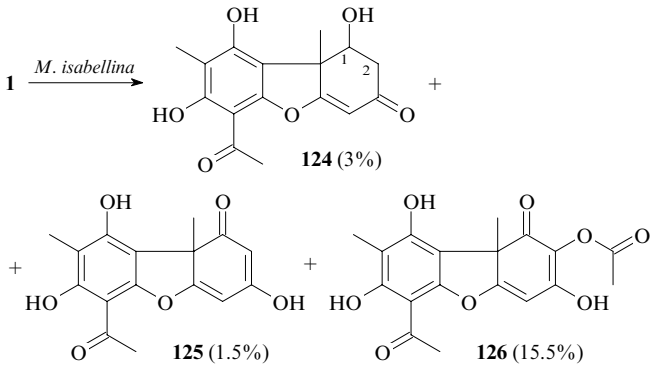
By treating UA with *Pseudomonas* sp. for two weeks (substrate conversion 68%), Kutney *et al.*[56] obtained 6-deacetyl derivative **123** (Scheme 54).

Scheme 54



In other biological media, UA forms derivatives at ring C. Treatment of UA with *Mortierella isabellina* for 10 days gave three metabolites, compounds **124**–**126**, in moderate yields[84] (Scheme 55). It can be seen that the transformation affects ring C of the substrate. Two minor metabolites (**124**, **125**) are 2-deacetyl derivatives, while the major metabolite **126** is the 2-acetoxy derivative of substrate **1**. The configuration of C(1) in compound **124** was determined from the spin – spin coupling constant of the protons at C(1) and C(2) atoms; the angular Me group at C(9b) and the OH group at C(1) are in *cis*-configuration.

Scheme 55



The introduction of the ^{14}C radioactive label into the acetyl group of ring A made it possible to reveal two routes of metabolization of UA induced by *M. isabellina*. One of the routes is the transformation of UA into compound **126**, while the other route is the transformation of UA into compounds **124** and **125**. The authors ascertained that compound **126** is not a precursor of compound **124**, as the latter is formed by a different route of substrate transformation. It was also shown that compound **124** is formed from compound **125**.

Later, 2-deacetyl derivative **125** was isolated in a yield of 32.4% by the action of the fungus *Mucor Globosus* on UA for two weeks.[68]

Thus, the action of biological media on UA affects predominantly the acetyl groups in positions 2 and 6.

IV. Conclusion

Initially, the reactions of usnic acid with various characteristic reagents have been used to prove its structure and later, they were used to study its reactivity and to prepare new derivatives. The principal process taking place on reagent treatment of UA and some its derivatives is destruction of ring C. This outcome, although probably *via* different intermediates, is observed upon the action of oxidants, in alkaline medium and upon photolysis and solvolysis. Other processes that take place in alkaline medium include the rearrangement of ring A in UA derivatives induced by furan ring opening as well as deacetylation. The photolysis of UA often leads to substrate racemization. All of the destructive reactions give products in low or very low yields; therefore, the use of the obtained compounds for further chemical transformations and for the search for substances with valuable biological processes is unlikely.

At the current state of research, chemical modification of UA is aimed at the preparation of its new derivatives — potential biologically active compounds. The reactions of UA with amines and hydrazines involving carbonyl groups have been studied most extensively. Compounds containing an enamine or imine moiety as well as annelated pyrazole and isoxazole derivatives have been obtained in good yields. Most reactive is the carbonyl group C(11)=O, while the less active C(13)=O group reacts only in the presence of a more than twofold excess of the reagent, and the endocyclic carbonyl group C(1)=O does not react with the amino group.

When being treated with alkyl, alkenyl and aryl halides, UA and its derivatives form ethers at the phenolic hydroxyls. The C(7)- hydroxy group seems to be most reactive. On

treatment with aliphatic acylating reagents, UA forms esters at the phenolic hydroxy groups, the C(7)OH group being again most reactive. When MeI and Me_2SO_4 are used, apart from O-alkylation, C-alkylation at the C(8) atom takes place. Aromatic acylating reagents form first of all esters at the enol hydroxy group C(3)OH and the enolyzed carbonyl group C(11)=O and only after that, they react with the phenolic hydroxy groups.

It can be seen that UA destruction reactions are usually of no value for preparative purposes, and the chemical modification of UA in order to prepare new derivatives has, most often, comprised reactions with amines at the carbonyl group and ester formation at hydroxy groups.

Thus, although usnic acid has been known to chemists since long ago and quite a few works have been devoted to its reactivity, it is to be admitted that due to a peculiar structure of the skeleton and a specific set and arrangement of functional groups, the chemical transformations of this metabolite are not fully known. Therefore, further studies of transformations of usnic acid, which shows a broad spectrum of biological activities in the native form remains a topical challenge for chemists.

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