In memory of my Teacher
Academician G.A. Tolstikov

Modification of Biologically Active Plant Metabolites *Via* the Transition Metal Catalyzed Reactions

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Abstract

Developed by the author's research laboratory methods of functionalization of some plant metabolites or their derivatives, *viz*., the eudesmane-type methylenelactones, diterpene and morphinane alkaloids, furanolabdanoids, and coumarins, using the transition metal catalyzed reactions, are reviewed. The activity of linear methylene lactone of the eudesmane type in the Heck reaction are analyzed. It is shown that the outcome of the Heck reaction is significantly influenced by the structure of methylidenelactone. The Pd-catalyzed arylation of isoalantolactone with arylhalogenides or 6-bromodeoxyvasicinone occurred with formation mainly of cross-coupling products with the (*E*)-configuration of the double bond. Synthesis of halogen derivatives of lappaconitine, tetrahydrothebaine and dihydrothebaine-hydroquinone and investigation of in the Heck or Sonogashira reactions gave the possibility for obtaining of new alkaloid derivatives with additional substituents in the aromatic rings. Homocoupling reaction or Sonogashira cross-coupling reaction of 5´-ethynyllappaconitine are used for synthesis of dimeric alkaloids of aconitane types. Pd-catalyzed amination of 2-(1,3-dibromoprop-2-ylidene)oreoselone and the transformations of oreoselone triflate, upon the action of palladium compounds allowed us to accomplish new modifications of linear furocoumarins. The method of enyne cycloisomerization of ω-alkynylfurans catalyzed with Au(III) was successfully obtained in the transformations of furanolabdanoids. The copper(I) salts catalyzed 1,3-dipolar cycloaddition reaction of azides to terminal alkynes belongs to the group of click-reactions was used in the synthesis of macrocyclic structures of labdane diterpenoids. The copper-catalyzed 1,3-dipolar cycloaddition reaction of 2-azidooreoselone with various alkynes yielded diverse 2-(1,2,3-triazolyl)furocoumarins. The advantages of transition metal catalyzed reactions to the transformations of plant metabolites and its derivatives shown the possibility of introduction of several bioisosteric groups, and other fragments providing additional interactions and selectivity of binding with receptors and enzymes.

Introduction

Synthetic transformation of plant metabolites in order to obtain pharmacologically active derivatives is an important direction in medicinal chemistry. The subject of our studies are metabolites of terpenoid, alkaloid, and coumarin types produced by Siberia and Altai flora. Let's briefly consider their characteristics. Sesquiterpene methylidenelactones, alloalantolactone 1 and alantolactone 2, are produced by the widely distributed and cultured flowering plant *Inula helenium* L. [1]. The northern wolfsbane *Aconitum septentrionale* Koelle roots contain the diterpene alkaloid lappaconitine 4 [2], which is the acting agent of the antiarrhythmic drug "Allapinine" and is successfully used in the synthesis of antiarrhythmia agents [3]. We transformed the aromatic fragment of alkaloid thebaine 5, obtained from the opiumpoppy, Papaver somniferum and used in the synthesis of medicinal drugs and

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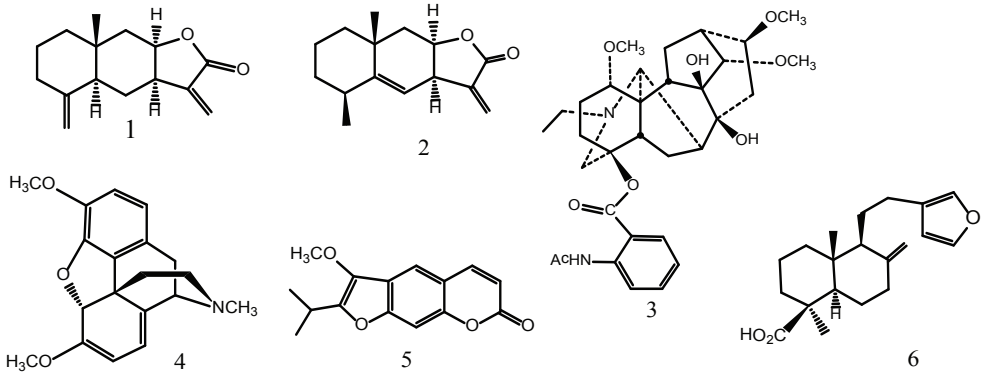
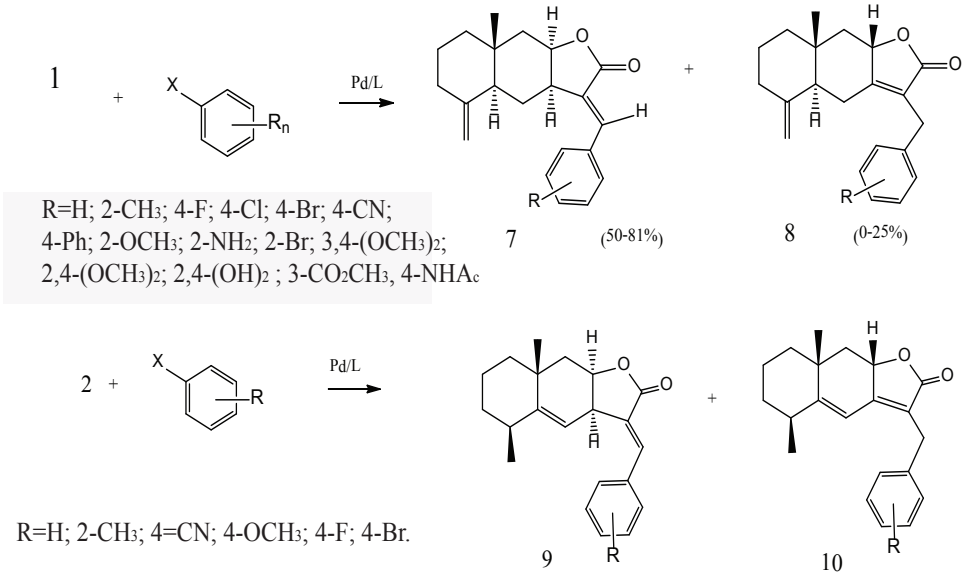
as tools in research [4]. The widely distributed in western Siberia *Peucedanum morisonii* Bess., was an accessible source of furocoumarin peucedanin (3) [5]. The Siberian pine *Pinus sibirica* R. Mayr. is a producer of the furanolabdanoid, lambertianic acid 7 [6], which can be easily obtained from a soft resin, as well as from needles and needleless sprouts [7].



Scheme 1. Accessible plant metabolites.

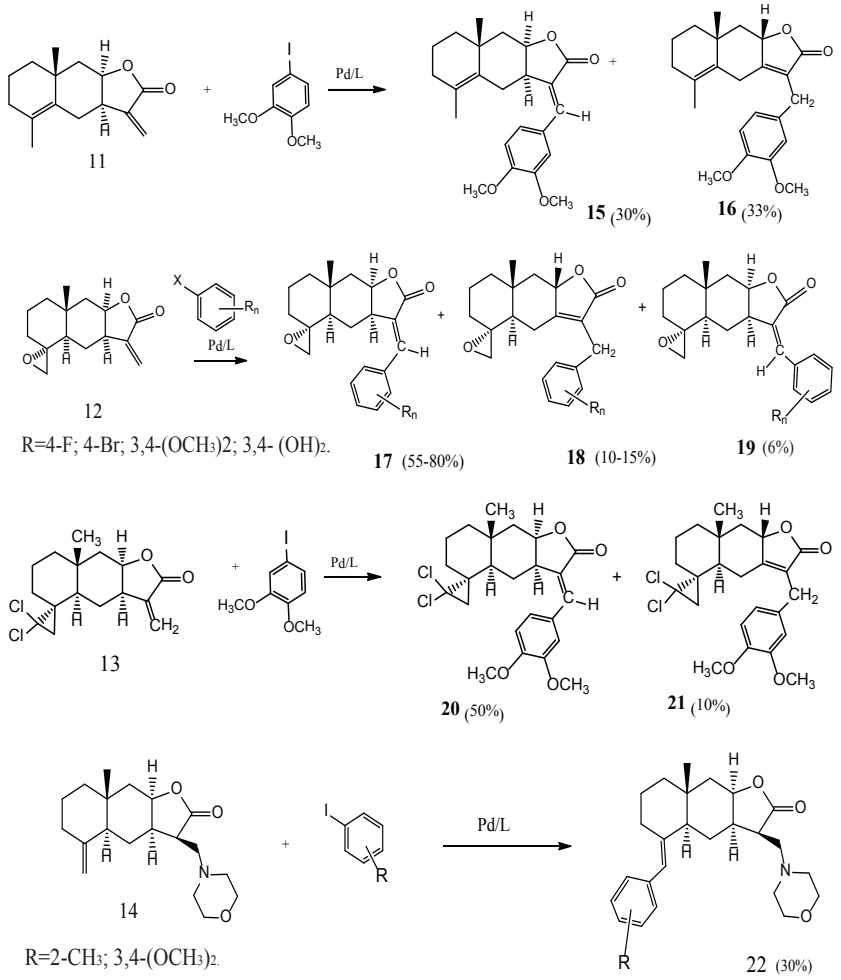
Sesquiterpene Lactones in the Cross-coupling Reactions

The Heck reaction proceeds between aryl or alkenyl halides and alkenes. In our experiments, plant metabolites were involved into the cross-couplin reaction as both the alkene and the aryl halide cross-component. Using sesquiterpene methylidenelactones 1, 2 as the alkene component, we showed a possibility of their modification by the introduction of aromatic substituents at position C(13). The reaction of alloalantolactone 1 with aryl iodides and aryl bromides catalyzed by the system $Pd(OAc)_2$—(o-Tol)$_3$P—Et_3N in DMF proceeded with the formation of arylated lactones 7 and 8 in up to 94% total yield (Scheme 1) [8, 9]. The ratio of isomers depended on the structure of aryl halide. Reaction of alantolactone 2 with bromobenzene, bromotoluele, 4-iodobenzonitrile, 4-iodoveratrole or 4-fluoroiodobenzene gave rise to aryl substituted derivatives 9 and 10 in considerably lower yield and in possibly equal amounts. For example, the reaction with 4- iodobenzonitrile led to compounds 9 and 10 in 18 and 15% yields, respectively [10].



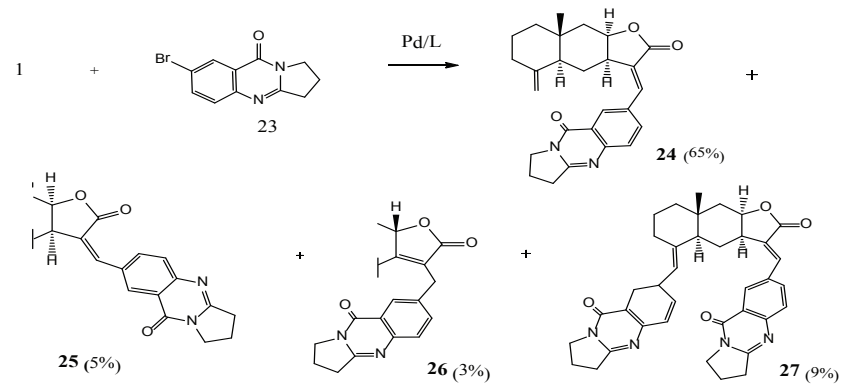
Scheme 2. Reagents and conditions: *i.* $Pd(OAc)_2$, (o-Tol)$_3$P, Et_3N, DMF, 120 ºC, 8-24 h; *ii.* $Pd(OAc)_2$, Et_3N, MeCN, 80ºC, 15 h.

As it is seen, the yield and the composition of the reaction products significally depended on the stricture of methylidenelactone. Isoalantolactone derivatives (11-14), with haloarenes under the Heck reaction conditions formed the following groups of compounds (15, 16), (17-19), (20, 21) and (22) [10,11]. We shown the activity of the 4,15-double bond of lactone 14 in the Heck reaction [10].



Scheme 3. Reagents and conditions: *i.* $Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, DMF, 120-130 °C, 12-30 h.

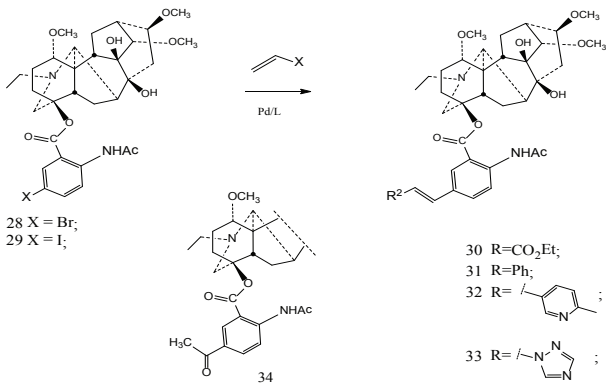
The use of aryl bromide of more complicated structure, viz., alkaloid 6-bromodeoxyvasicinone 23, allowed us to obtain the expected product 24, its isomers 25, and 26, and compound 27 [12].



Scheme 4. Reagents and conditions: *i.* $Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, DMF, 120ºC, 15 h.

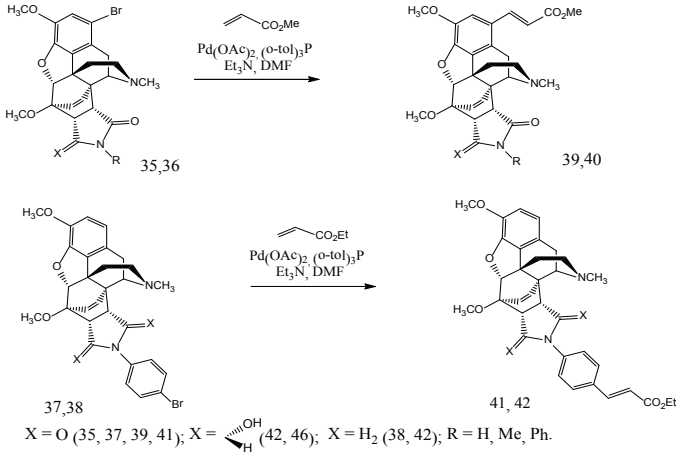
Palladium Catalyzed Transformations of Diterpene and Morphinane Alkaloids

The diterpene and morphinane alkaloids were studied in the bromination and iodination reactions for the further introduction of the halides obtained into the Heck reaction with terminal alkenes. Besides the catalytic system already mentioned, the system $Pd(dba)_2$—(*o*-Tol)$_3$P—Et_3N (dba stands for diben zylidenacetone) also showed good results [13-16]. 5′-Bromolappaconitine 28 has proved inactive in the reaction with terminal alkenes. Iodo derivatives 29 reacted with ethyl acrylate with the formation of cinnamic esters 30. The reaction of 5′-iodolappaconitine 29 with styrene, 2-methyl-5-vinylpyridine, *N*-vinyl-1,2,4-triazole led to compounds 31-33 in 51-86% yields (Scheme 5). The reaction with ethyl vinyl ether is a method for the introduction of the acetyl group in the own compound with the formation of a diperpenoid ketone 34 (41% yield).



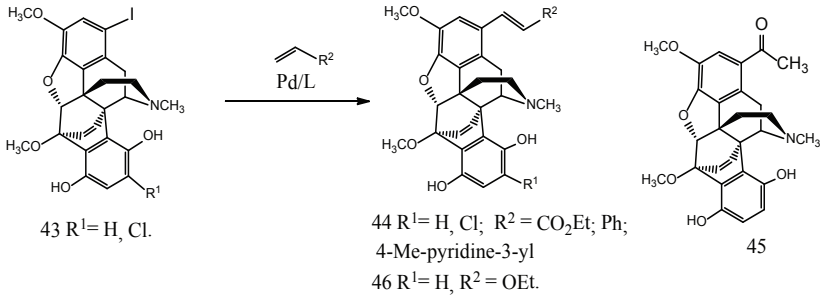
Scheme 5. Reagents and conditions: *i.* $Pd(dba)_2$, (*o*-Tol)$_3$P, Et_3N, DMF, 100-120ºC, 4-12 h.

Conducting fundamental studies of thebaine reactivity in order to search for the analgesics exceeding morphine and other known agents in their properties and side effects, we carried out the Heck reaction for the halosubstituted derivatives of dihydrothebaine and tetrahydrothebaine [17]. 1-Bromo-(2-R,5-R-pyrrolidino)[3,4-*h*]-6,14-*endo*-ethenotetrahydrothebaines 35-38 reacted with acrylic acid esters in the presence of the catalytic system $Pd(OAc)_2$-(*o*-Tol)$_3$P-Et_3N with the formation of dihydrothebaine derivatives 39-42 (Scheme 6) [18].



Scheme 6.

1-Iododihydrothebainehydroquinone derivatives 43 obtained from the phenolic-thebaine derivatives compounds shown the high analgesic activity [19], reacted with terminal alkenes to form compounds of type 44 [20]. The reaction of 1-iododihydrothebainehydroquinone 43 with vinyl ethyl led to a mixture of compounds 45, 46) (Scheme 7) [20].

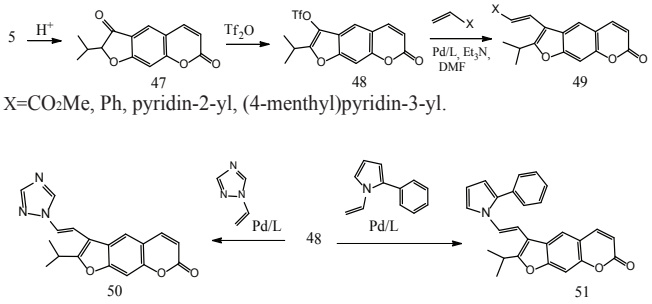


Scheme 7. Reagents and conditions: *i.* $Pd(OAc)_2$, $(o\text{-Tol})_3P$, Et_3N, DMF, 130-140 ºC, 7-12 h.

Peucedanin Derivatives in the Heck and Suzuki Reactions

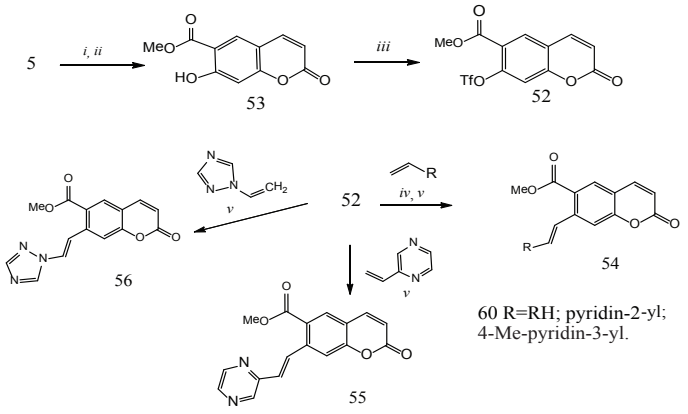
Detailed studies conducted on the conversion of peucedanin 5 derivative - furocoumarin oreoselone 47, upon the action of palladium compounds allowed us to accomplish new modifications of linear furocoumarins [21]. Oreoselone triflate 48 reacted with terminal alkenes with the formation of compounds type 49. The cross-coupling reaction indicated is characterized by the necessity to modify the catalytic system in order to obtain satisfactory yields.

In particular, besides the systems mentioned above, the following combinations were used: $Pd(OAc)_2$-(t-Bu)$_3$P-Et_3N; $Pd(OAc)_2$-BINAP-Et_3N; $Pd(dba)_2$-BINAP-Et_3N; and $Pd(dba)_2$-BINAP-(Ce_2CO_3). The reaction of triflate 48 with 2-phenyl-1-vinylpyrrole and 1-vinyl-1,2,4-triazole led to compounds 50 and 51.



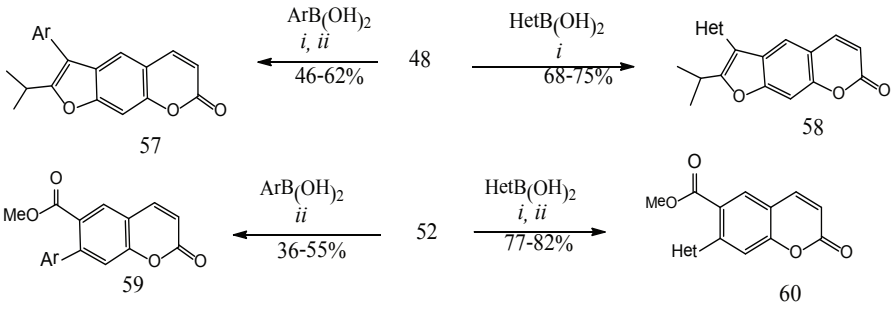
Scheme 8.

Peuruthenicin triflate 52 synthesized from peucedanin 5 through the step of preparation of peuruthenicin 53 [22] was involved into the cross-coupling reaction with styrene, 2-vinylpyridine, 2-methyl-5-vinylpyridine, 2-vinylpyrazine, as well as with 1-vinyl-1,2,4-triazole with the formation of compounds 54-56 (yield 38-78%) (Scheme 9) [23].



Scheme 9. Reagents, conditions, and yields: *i. m*-Cl-PBA, $CHCl_3$, 20°C $NaHCO_3$; *ii.* NaOH, aq. MeOH; *iii.* Tf_2O, pyridine; *iv.* $Pd(OAc)_2$, $(o\text{-Tol})_3P$, Et_3N, DMF, 135°C, 16 h (38%, R=Ph); *v.* $Pd(OAc)_2$, BINAP, base, DMF, 135°C, 16 h (43-78%).

The Suzuki reaction involving arylboronic acids, we accomplished using triflates 48 and 52 (Scheme 10). Their reaction with aryl- and hetarylboronic acids gave high yields of coupling compounds in the presence of the catalytic systems $PdCl_2$(dppf)-Bu_4NBr-K_2CO_3 [dppf stands for 1,1′-bis(diphenylphosphino)ferrocene] (*i*) and $Pd(PPh_3)_4$-Bu_4NBr-K_2CO_3 (*ii*). The reaction in both cases turned out to be sensitive to substituents in the aryl fragment of boronic acid. The reaction resulted in the synthesis of series of 3-aryl- or 3-hetarylpsoralenes 32 [24] or 7- (het)arylsubstituted coumarins 31 [23].

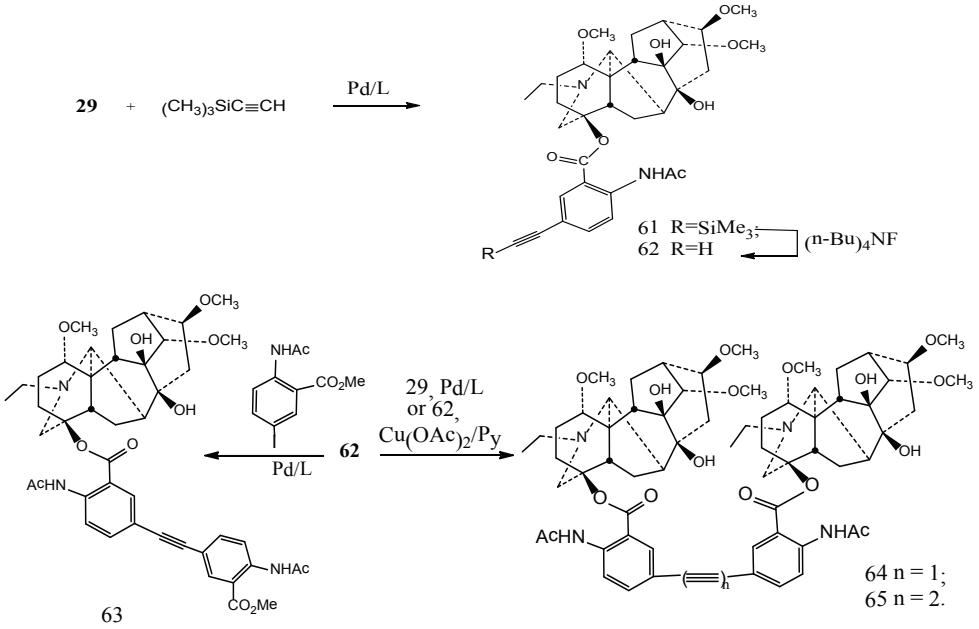


(57), 59 Ar = Ph; 2-Cl-4$CF_3C_6H_3$; 2-NH_2; (58), (60) Het = furan-3-yl; furan-2-yl; pyridin-3-yl; pyridin-4-yl; indol-5-yl.

Scheme 10. Reagents, and conditions: *i.* $PdCl_2$(dppf)-Bu_4NBr-K_2CO_3, MeCN, 80°C, 4-6 h; *ii.* $Pd(PPh_3)_4$-Bu_4NBr-K_2CO_3, dioxane, 100°C, 8-10 h.

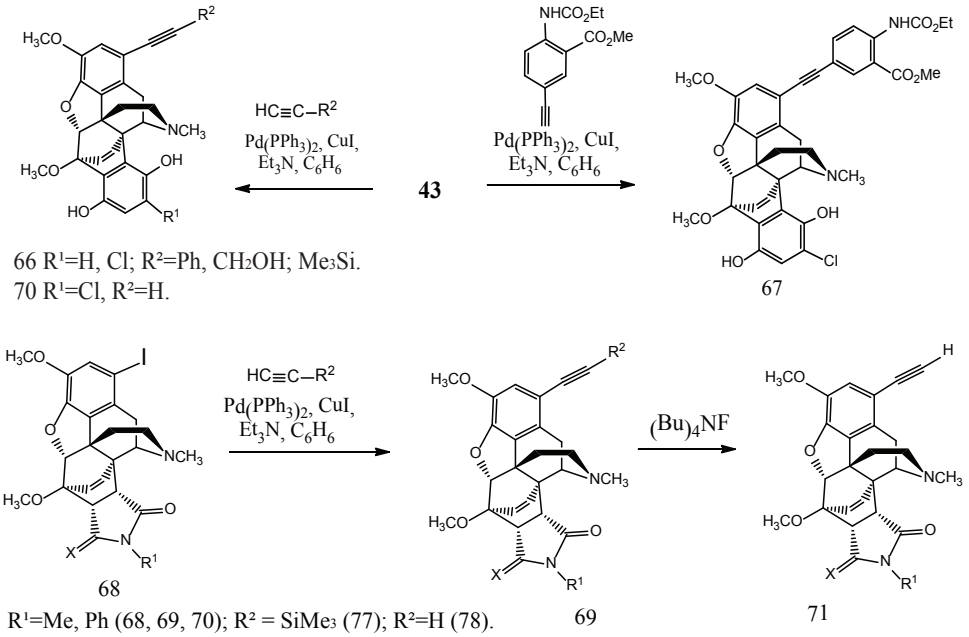
Sonogashira Reaction in the Synthesis of Acetylene Derivatives of Alkaloids, and Furocoumarins

We used the approach described above for the preparation of acetylene compounds belonging to diterpene and morphinane alkaloids, as well as to furocoumarins. The reaction of 5′-iodolappaconitine 29 with trimethylsilylacetylene catalyzed by the system $Pd(PPh_3)_2Cl_2$-PPh_3-CuI-Et_3N (PhH, 55-70°C) led to acetylene derivative of diterpene alkaloids 61 in 77% yield (Scheme 11). The latter was converted to 5′-ethynyllappaconitine 62, which was involved into the Sonogashira reaction with *N*-acetyl-3-iodoanthranilic acid ether (69) or 5′-iodolappaconitine 29 to give compounds 63 or 64 in 75-80% yields. The oxidative dimerization of terminal acetylene 62 by a standard method (the Glaser reaction) allowed us to obtain dimeric alkaloid 65 in 76% yield [25].



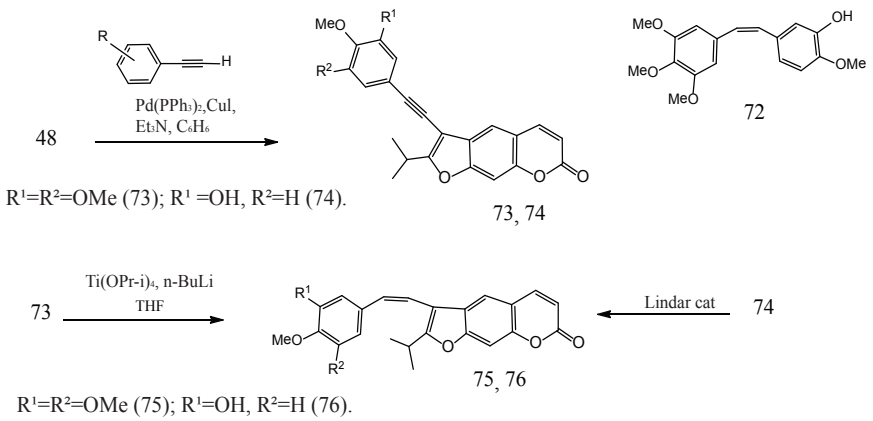
Scheme 11.

The Sonogashira reaction was used for the synthesis of the morphinane-type acetylene derivatives (Scheme 12). The reaction of iodo derivatives 43 with terminal alkynes catalyzed by the system $Pd(PPh_3)2Cl_2$-PPh_3-CuI-Et_3N led to products 66 and 67 in 44-90% yield. In the same reaction, 1-iodo-(2,5-dioxo-N-R-pyrrolidino)[3,4-*h*]-*endo*-ethenotetrahydrothebaines 68 were converted into the corresponding 1-ethynyl derivatives of alkaloids 69 (56-62% yield). The desilylation allowed us to obtain 1-ethynyl derivatives of morphinanes 70 and 71. By the reaction of 1-ethynyldihydrothebainehydroquinone 70 with 5-iodo-N-carboxyethylmethylanthranylate under the Sonogashira reaction conditions ($Pd(PPh_3)_2Cl_2$-PPh_3-CuI) the already mentioned compound 67 [26, 27] was obtained.



Scheme 12.

Based on oreoselone triflate 48, we carried out the synthesis of the structural analogs of a new type of the known anticancer metabolite combretastatine A-4, compound 72 (Scheme 13) [28]. A standard catalytic system $Pd(PPh_3)_2Cl_2$-PPh_3-CuI, allowed us to conduct the reaction of oreoselone triflate 48 with 3,4,5-trimethoxyphenylacetylene or 4-hydroxy-3-methoxyphenylacetylene. The yields of compounds 73 and 74 were 72 and 65%. The target compounds 75 and 76 were obtained by the reduction of alkynes 73 and 74 with the assistance by the system titanium(IV)-tetraisopropoxide-butyllithium [29] or by the hydrogenation on the Lindlar catalyst, respectively.



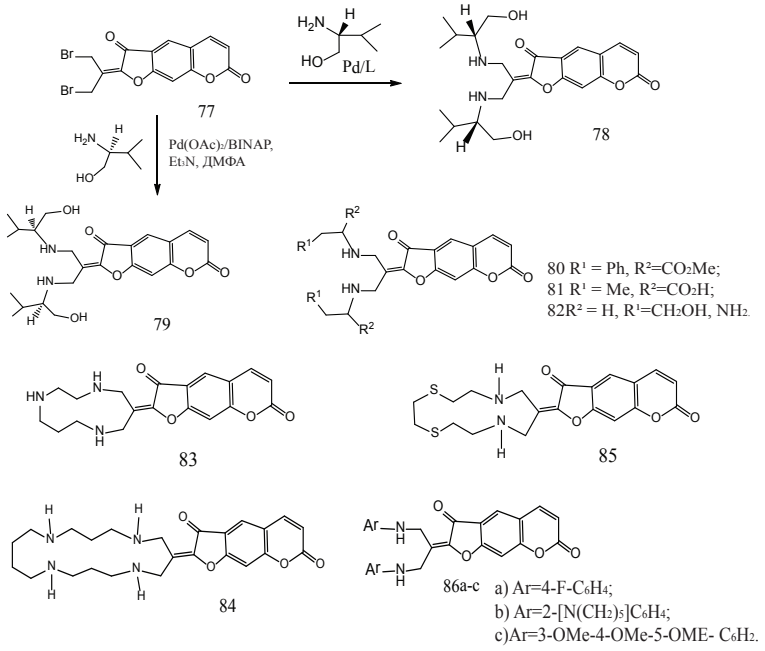
Scheme 13.

Palladium Catalyzed Amination of Furocoumarin Derivatives

Dibromide 91 obtained from peucedanin 6 [30] was used for the amination with various amino derivatives [31] (Scheme 14). The reaction of 2-(1,3-dibromoprop-2-ylidene)oreoselone 77 with L- or D-valinol catalyzed by the system $Pd(OAc)_2$-BINAP in DMF in the presence of Et_3N allowed us to obtain diamino derivatives 78 and 79 in 72 and 64% yields, respectively. The amination of dibromocoumarin 77 upon the action of L-phenylalanine methyl ester in the presence of the catalytic system $Pd(OAc)_2$-BINAP led to the formation of optically active coumarin derivative 80 (66% yield). The reaction of compound 77 with 2-aminobutanoic acid in the presence of $Pd(OAc)_2$)/(*o*-Tol)$_3$P (2/8 mol.%) resulted in furocoumarin 2,2-diaminopropylidene derivative 81 in 48% yield.

The reaction of coumarin 77 with aminopropanol or ethylenediamine in the presence of the catalytic system $Pd(OAc)_2$)/(*o*-Tol)$_3$P led to the formation of diaminosubstituted derivatives 82 in 36-42% yields.

Macrocyclic di-, tri-, and tetraamino derivatives 83-85 were obtained by the reaction with the corresponding polyamines. The use of different catalytic systems [$Pd(dba)_2$/BINAP; $Pd(OAc)_2$/BINAP; $Pd(OAc)_2$)/(*o*-Tol)$_3$P], bases (ButONa, Et_3N, Cs_2CO_3), and solvents (DMF, dioxane, toluene) allowed us to synthesize macrocyclic coumarin derivatives in satisfactory yields (44-55%). The reaction of dibromide 77 with substituted anilines resulted in compounds 86 (40-54% yields).

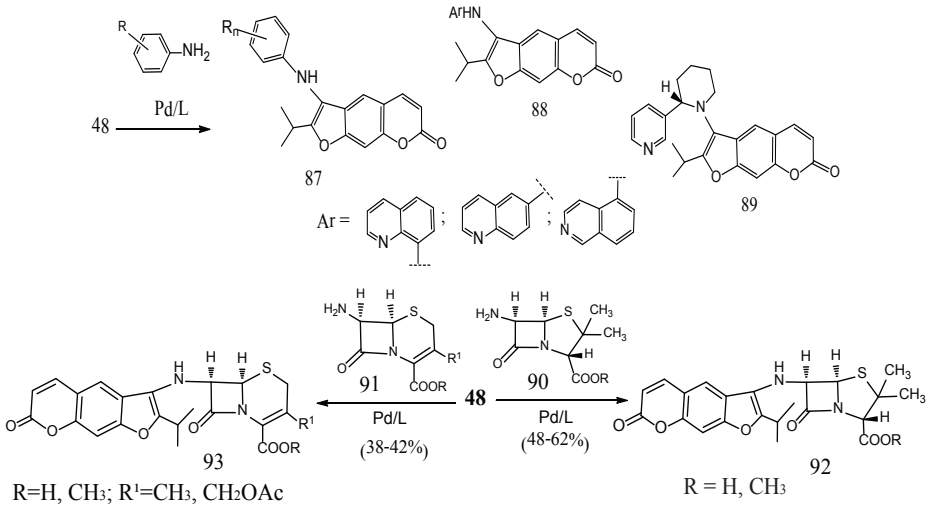


Scheme 14.

Palladium catalysed amination of aryl- vinyl and hetaryl halides and tryflates has rapidly emerged as a valuable tool in the synthesis of pharmaceuticals and novel materials. Breakthroughs in this area have typically been driven by the implemention of new classes of ligands. Notable examples include chelating diphenylphosphino ligands such as BINAP, DPPF and Xantphos and trialkylphosphines that have served to continually increase the substrate scope and to render the reaction more efficient.

The reaction of oreoselone triflate 48 with anilines in the presence of the catalytic systems $Pd(OAc)_2$-BINAP, $Pd(OAc)_2$-P(*o*-Tol)$_3$, or the system $Pd(OAc)_2$-Xantphos [Xantphos stands for 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene] led to 3-arylamino derivatives of psoralens type 87 in up to 74% yield (Scheme 15). The reaction of triflate 54 with aminoquinolines resulted in compound 88, whereas the reaction with anabasine led to a mixed compound of the furocoumarinoalkaloid type 89 (Scheme 15).

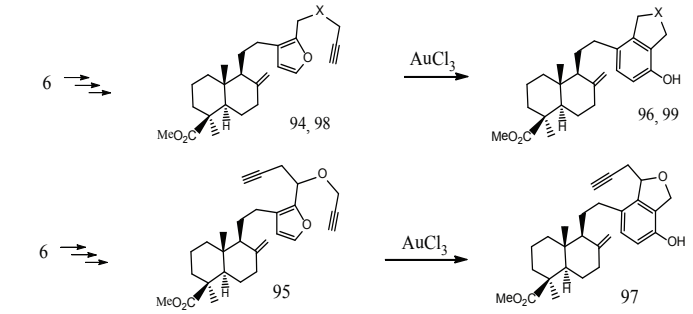
The reaction of triflate 48 with penicillins 90 or cephalosporanes 91 allowed us to carry out a new modification of the antibiotics and to synthesize the hybrid compounds 92 and 93 (Scheme 15) [32].



Scheme 15. Reagents and conditions: *i.* $Pd(OAc)_2$, BINAP, Et_3N, DMF, 100°C; *ii*. $Pd(OAc)_2$, (*o*-Tol)$_3$P, Et_3N, DMF, 100°C; *iii.* $Pd(OAc)_2$, BINAP, Et_3N, MeCN, 80°C; *iv*. $Pd(OAc)_2$, (t-Bu)$_3$P, Et_3N, DMF, 100°C, 4 h; *v.* $Pd(OAc)_2$, Xantphos, Et_3N, DMF, 100°C, 6 h; *vi*. $Pd(OAc)_2$, BINAP, Cs_2CO_3, PhMe, 110°C, 7 h.

Specific Catalytic Transformations of Furanoditerpenoids

Acetylenic ethers 94 and 95, obtained from lambertianic acid 6, underwent cycloisomerization upon the action of $AuCl_3$ giving rise to 7-hydroxydihydroisobenzofurans 96 and 97 in 70-78% yields (Scheme 16). The gold-catalyzed cycloisomerization of *N*-propargyl-*N*-tosylamine 95 led to 7-hydroxydihydroisoindoline 99 (yield 77%) [33].

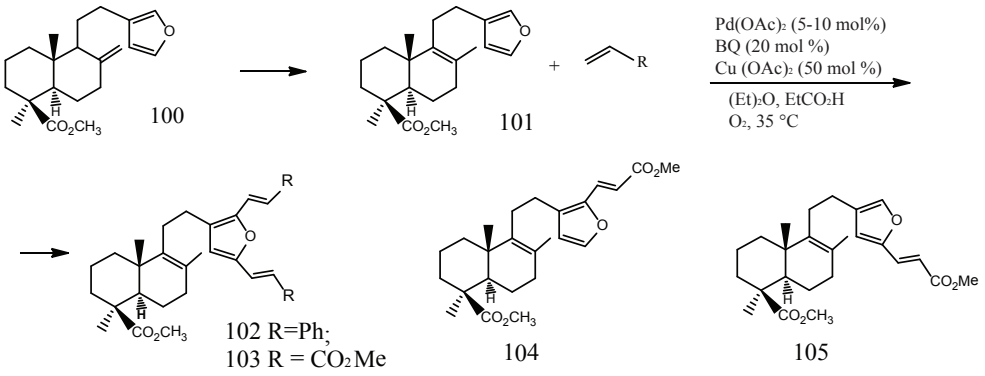


Scheme 16. Reagents and conditions: *i.* $AuCl_3$, MeCN, 20 °C.

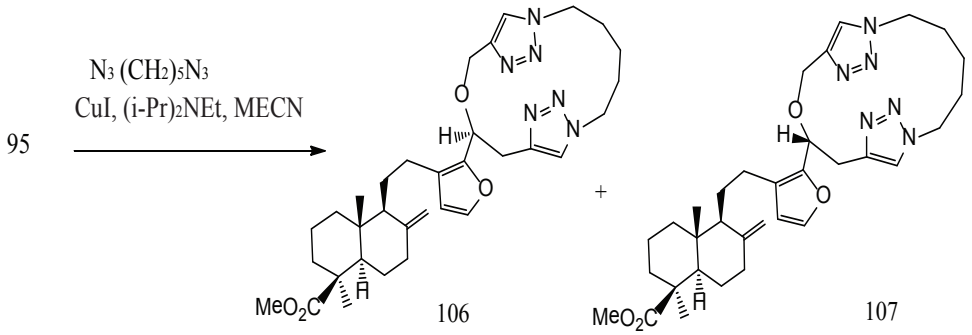
Methyl lambertianate 100 upon reflux in benzene in the presence of *p*-TsOH was smoothly converted to flomisoic methyl ester 101 [34]. Compound 101 in the presence of the oxidative catalytic system containing benzoquinone, $Pd(OAc)_2$, and $Cu(OAc)_2$ in an oxygen flow reacted with olefins, giving compounds 102-105 (Scheme 17). The reaction with styrene resulted in compound 102 as the main product (63% yield). The oxidative coupling of furanolabdanoid 101 with methyl acrylate under the indicated conditions led to a mixture of products of mono- (104 and 105; 24% yield, the ratio 104 : 105 = 3 : 1) and dialkenylation (103; 27% yield) at the furan ring [35].

Synthesis of 1,2,3-triazoles Based on Labdanoids and Coumarins

The copper(I) salts catalyzed cycloaddition of azides to terminal alkynes (CuAAC-reaction) belongs to the group of reactions distinguished by the simplicity of carrying out, regioselectivity, and high yields [36]. This reaction is widely used in the synthesis of macrocyclic structures of natural compounds such as steroids [37, 38], triterpenoids [39] and carbohydrates [40]. We were the first to accomplish the syntheses, in which alkyne-containing diterpenes or furocoumarin derivatives were involved as the reactants. Macrocyclic diterpenoid derivatives 106 and 107 (the ratio 1:1) were obtained from diacetylene diterpenoids 95 (Scheme 18) [41].

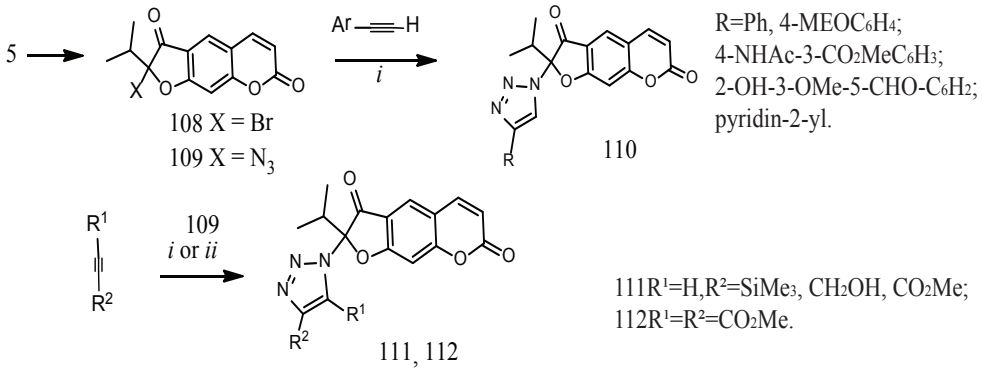


Scheme 17.



Scheme 18.

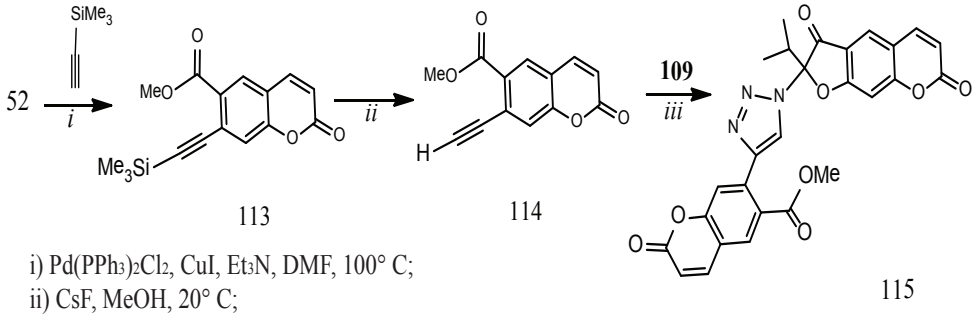
We obtained various triazoles from furocoumarin peucedanin 5 [42]. The bromination of compound 5 resulted in 2-bromooreoselone 108, from which azido ketone 109 was obtained under standard conditions (Scheme 19). The reaction of 2-azidooreoselone 108 with arylalkynes in the presence of sodium ascorbate and $CuSO_4$ in the system dichloromethane-water led to the synthesis of triazoles 110 (63-76% yields). The reaction with monosubstituted alkynes such as trimethylsilylacetylene, propargyl alcohol, or methyl propyolate led to triazoles 111, whereas with dimethyl acetylenedicarboxylate – to compound 112 (42-68% yields) (Scheme 19).



Scheme 19. Reagents and conditions: *i.* $CuSO_4$, sodium ascorbate, H_2O, CH_2Cl_2, 20→40°C; *ii.* CuI, Et_2N, H_2O, MeCN, 20°C.

In the view of interesting biological properties of dicoumarins [43], and the significant interest in 7 triazolyl-substituted coumarins [44], we synthesized a biscoumarin containing a coumarin and a linear furocoumarin moieties, and a 1,2,3-triazole ring as a linker (Scheme 20). Peuruthenicin triflate 52 was

involved in the Sonogashira reaction with trimethylsilylacetylene and converted to the corresponding alkyne 113 (Scheme 20). The desilylation proceeds smoothly with the formation of 7-ethynylcoumarin 114. The CuAAC reaction of alkyne 114 with azide 109 resulted in bis(coumarino)triazole 115 [42].



113 114 115

i) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF, 100° C;
ii) CsF, MeOH, 20° C;
iii) $CuSO_4$, sodium ascorbate, H_2O/CH_2Cl_2.

Scheme 20.

Conclusions

In conclusion, it should be noted that the conversion of plant metabolites under the metal complex catalysis conditions is very promising direction allowing one to obtain poly-substituted and multifunctional derivatives of chiral starting compounds. Different catalytic systems and various approaches to the activation create a possibility to efficiently control the chemoselectivity of the processes. The processes through which the introduction of pharmacophoric and polyfunctional groups can be accomplished have proved very useful in the search and design of new biologically active agents. The advantages of this approach consist in the possibility of introduction of bioisosteric groups, as well as various hydrophobic, hydrophilic, and other fragments providing additional interactions and selectivity of binding with receptors and enzymes.

In the present review, we mentioned a number of compounds very interesting from the biological point of view. Among 13-aryl-substituted derivatives of isoalantolactone 7 and 4,15-epoxy isoalantolactone 17, selectively acting antiulcer agents were discovered [9]. Besides the target compounds, the intermediate products of their synthesis frequently exhibit high activity. 5′- Bromolappaconitine 28 is of particular interest among the derivatives of lappaconitine 3. Hhydrobromide of compound 28 possessing the lower toxicity exceeds the known antiarrhythmia drugs “Allapinin” in its activity [15]. Among the amino derivatives of peuruthenicin 54, 56, and 60 and peucedanin 80-83, the agents worth of studies as stimulants of the central nervous system and antidepressants. Highly promising are lambertianic acid 6 [7] and its derivatives such as methyl esters of lambertianic and flomisoic acids 100 and 101. Based on these compounds, we are working on the development of neurotropic agents, as well as analgesics of a new structural type.

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