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FURANODITERPENOIDS OF THE LABDANE SERIES: OCCURRENCE IN PLANTS, TOTAL SYNTHESIS, SEVERAL TRANSFORMATIONS, AND BIOLOGICAL ACTIVITY

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*Structures of plant furanolabdanoids and synthetic schemes for a series of furanolabdanoids (coronarins A and E, hedychenone, acuminolide and 17-*O*-acetylacuminolide) from the available diterpenoids sclareol and larixol were reviewed. Attention was focused on transformations of available furanolabdanoids. Data on the biological activity of native metabolites and their synthetic derivatives were presented.*

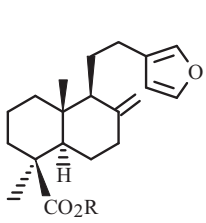
Keywords: labdanoids, lambertianic acid, phlomisoic acid, pinusolide, coronarins A and E, hedychenone, acuminolide, sclareol, sclareolide, larixol.

Di-, tri-, and sesterterpenoids, a structural feature of which is a furan ring or a derivative of it, are interesting as promising compounds for medical application. The furan ring in these natural terpenoids is transformed into a butenolide or dihydrofuran moiety. The transformation of the ring leads to the manifestation of new or enhanced biological activity of the original native terpenoid. Therefore, examples of the modification of furanoterpenoids are becoming more common.

Herein we review the structure and biological activity of plant furanolabdanoids and present schemes for the total synthesis of metabolites from terpenoids and chemical modifications of several available metabolites.

Plant Furanoditerpenoids. Furanolabdanoids are produced by plants of the families Acanthaceae, Alismaceae, Annonaceae, Apocynaceae, Asteraceae, Caprifoliaceae, Cistaceae, Euphorbiaceae, Lamiaceae, Pinaceae, Potamogetonaceae, Scrophulariacea, and Zingiberaceae.

Lambertianic acid (**1**) was first isolated from oleoresin of *Pinus lambertiana* Dogl. [1] and occurs in oleoresin of long-needle pines *P. sibirica* [2], *P. koraiensis* [3], and *P. wallichiana* [4]. Cones of *P. lambertiana* contained significant amounts of **1** (up to 25% of total acids) [5]. Acid **1** and its methyl ester **2** [2] occurred also in needles and needle-less shoots of *P. sibirica* [6]. Acid **1** has been isolated from other plants, e.g., *Gutierrezia dracunculoides* [7], *Sciadopitys verticillata* [8], *Platycladus orientalis* [9], *Biota orientalis* [10], *Thuja orientalis* [11], and *Caesalpinia echinata* [12]. Investigations of the pharmacological activity of **1** revealed its antidepressant activity with a sedative component [13]. The significant potential of **1** as an allergy treatment agent was noted [11]. Data on its action on allergy mediators, including the inhibition of interleukine-6 (IL-6), prostaglandin D_2 (PGD_2), and leukotriene C_4 (LTC_4) production; cyclooxygenase-2 (COX-2) expression; and β-hexosaminidase degranulation into PMA were obtained. The methyl ester of **1** (**2**) exhibited stimulating antidepressant properties [14].



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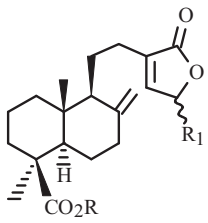

3 - 5

1: R = H; **2:** R = CH_3; **3:** R = R_1 = H
4: R = CH_3, R_1 = H; **5:** R = H, R_1 = OCH_3

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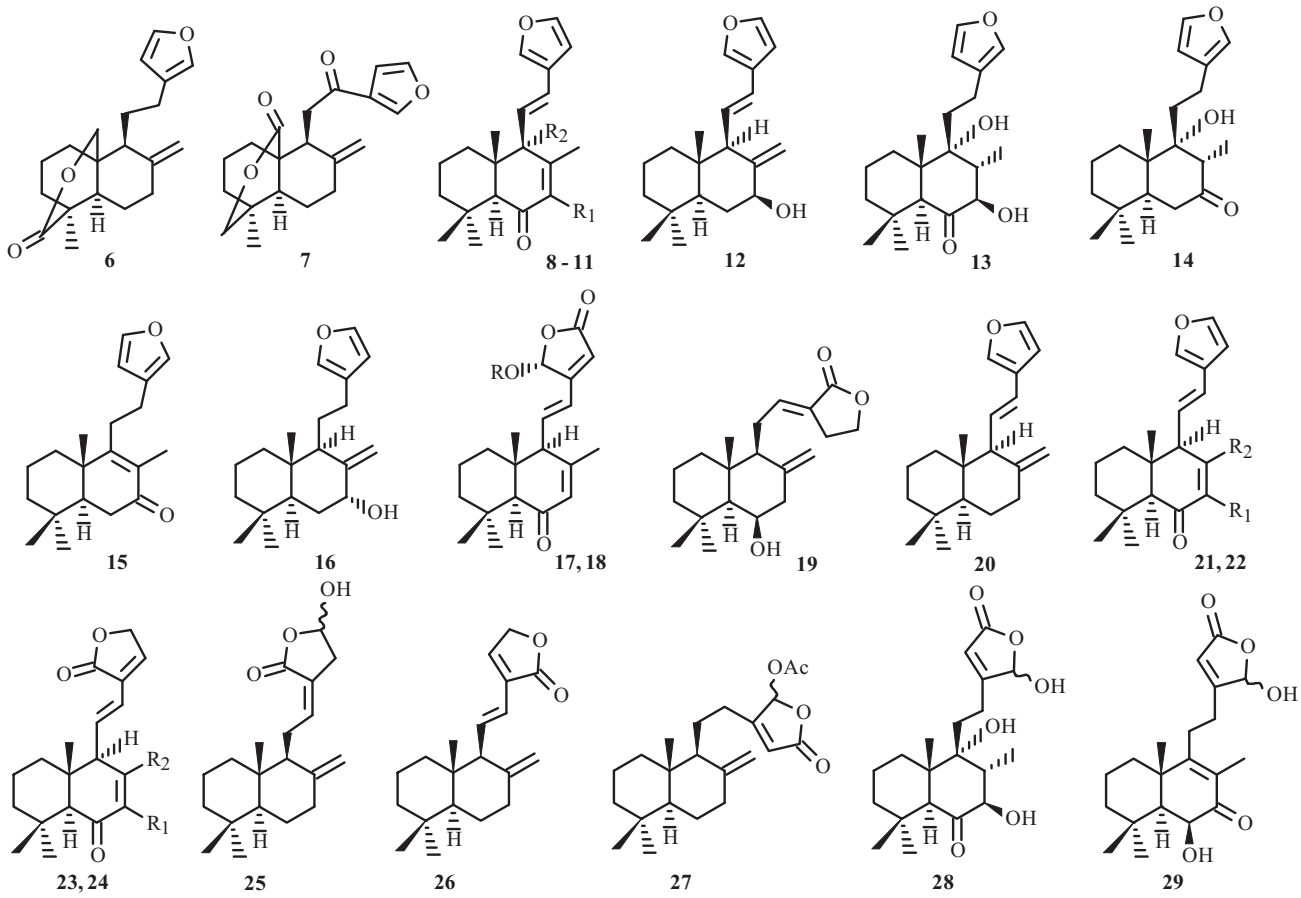


8: R_1 = H, R_2 = OH, 12,13-dihydro; **9:** R_1 = R_2 = H; **10:** R_1 = H, R_2 = OH; **11:** R_1 = OH, R_2 = H; **17:** R = H; **18:** R = CH_3
21: R_1 = H, R_2 = CH_2OH; **22:** R_1 = OH, R_2 = CHO; **23:** R_1 = H, R_2 = CHO; **24:** R_1 = OH, R_2 = CH_2OH

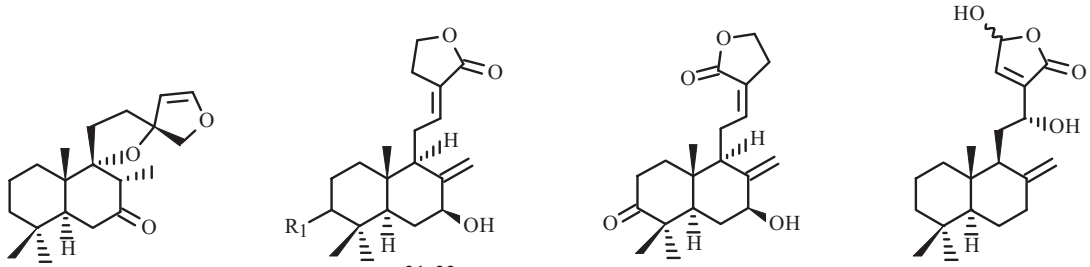
Oleoresin of *P. sibirica* and the medicinal plant *Biota orientalis* yielded products of oxidative metabolism at the C-13 atom, i.e., pinusolic acid (**3**) and pinusolide (**4**) [9, 15, 16]. Compound **4** was characterized as a new thrombocyte aggregation factor (TAF) antagonist [15–17]. IC_{50} values from 19 to 5 μM for thrombocyte aggregation caused by TAF upon lowering its concentration from 500 to 5 nM were obtained in tests using rabbit thrombocytes. The ED_{50} value *in vivo* was 1.1 mg/kg for i.v. injection and 69.0 mg/kg for *per os* administration. The anti-leukemia and prophylactic potential of **4** was studied *in vitro* on the BJAB Burkitt lymphoma cell line [18]. Furthermore, it was found that **4** *ex vivo* overcame the anthracycline resistance of primary lymphoblasts obtained from patients with a high risk of acute lymphoblastic leukemia (ALL) and a weak response to chemotherapy [18]. The neuroprotective activity of **4** and 15-methoxypinusolic acid **5** (from *Biota orientalis*) were investigated [19].

Extracts of aquatic plants of the genus *Potamogeton* possess antiviral, antibacterial, and antitumor activity. The plants produce diterpenoids of the labdane and *ent*-labdane types. Potamogetonin (**6**) [20] and ketofuran **7** [21] were isolated from *P. ferrugineus* Hagstr. and *P. nodosus* Poir., respectively.

Substituents in ring B are found in a large number of biologically active labdane-type metabolites. These include solidagenone (**8**) from *Solidago chilensis* Meyen. [22]; hedychenone (**9**) [23], 9-hydroxyhedychenone (**10**) [24], 7-hydroxyhedychenone (**11**) [25], and coronarin A (**12**) [26] (from *Hedychium* spp.); (+)-leoheterin (**13**) [27] (*Leonurus* sp.); and hispanolone (**14**) [28–30], hispanone (**15**) [30, 31] (from *Ballota* spp. and *Leonurus* sp.), and (+)-austrochaparol (**16**) [32] from *Acritopappus* spp. Metabolites of *Hedychium coronarium* Koen. (ginger lily) exhibited cytotoxic activity against human tumor cells [Colo-205 (colon cancer), L-431 (skin cancer), MCF-7 (breast cancer)]. Compound **10** was the most active [24]. Flowers of the medicinal plant *Hedychium spicatum* afforded metabolites that showed antihyperglycemic activity, among which **9**, butenolide derivatives spicatanol (**17**) and the methyl ether of spicatanol (**18**), 7-hydroxyhedychenone (**11**), and hedychialactone B (**19**), which contains an exocyclic double bond, are notable. All components and the extract inhibited α-glucosidase. Metabolite **17** had the lowest inhibiting concentration (IC 34.1 μg/mL) [33]. Subsequent research on the extracts of this plant isolated cytotoxic metabolites such as coronarin E (**20**), which is a furanolabdanoid that is unsubstituted in ring B, and the 6-ketosubstituted labdanoids yunnancoronarin D (**21**) and 7-hydroxyhydichinal (**22**) [34]. New cytotoxic

labdanoids with a transformed furan group (**23** and **24**) in addition to metabolites **19** and **20** were isolated from *H. coronarium* [35]. Hedychenone (**9**), coronarin E (**20**), hedychialactone B (**19**), coronarin D (**25**), and villosin (**26**) inhibited significantly the accumulation of nitric oxide (produced *in vivo* by oxidation of L-arginine by NO-synthase) through the inhibition of iNOS induction in macrophages activated by lipopolysaccharide [37]. The butenolide (–)-lagerstronolide (**27**), which was isolated from leaves of the medicinal plant *Lagerstroemia lancasteri*, was also characterized as having anti-inflammatory activity [38]. Antihypertensive, sedative, and uterotonic properties were found for metabolites of *Leonurus* spp., i.e., **12**, **14**, **15**, and sibiricinones A (**28**) and B (**29**) [39].

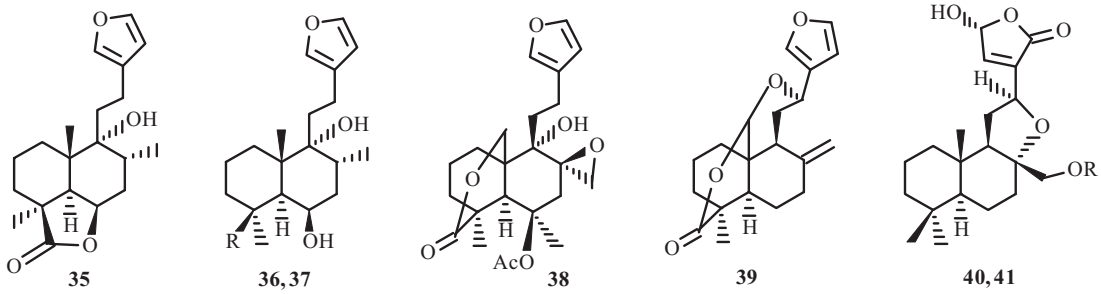
The metabolite of *Leonurus heterophyllus* Sw. prehispanolone (**30**) (a transformation product of **14**) was characterized as a selective TAF antagonist [40]. The plant *Renealmia exaltata* (Zingiberaceae) produced cytotoxic butenolides with exocyclic double bonds, pacovatinins A–C (**31**–**33**) [41]. Introduction of a hydroxyl into the C-3 position (**32**) reduced significantly the cytotoxicity. Pacovatinins A (**31**) and B (**32**) had the *E*-configuration of the C-12,13 double bond; pacovatinin C, the *Z*-configuration. (+)-Zerumin B (**34**), which occurs in various plants, was isolated from several derivatives of labdanoid hydroxylactones [42, 43]. A structural feature of this metabolite is the presence of a 12α-hydroxy group. It exhibited cytotoxic activity against various human tumor cells and was selective against MCF-7 breast tumor cells (IC_{50} 0.59 μM) [44].



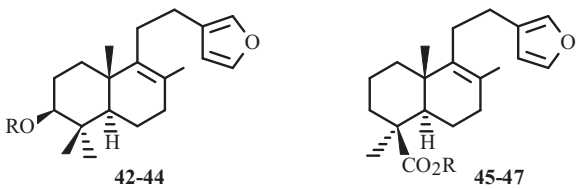
30 **31, 32** **33** **34**

31: R_1 = H; **32:** R_1 = OH

Medicinal plants of the genus *Marrubium* sp. produce a rich assortment of labdanoids. The principal constituents are marrubiin (**35**), marrubiinic acid (**36**), and marrubenol (**37**) [45], which possessed significant analgesic activity *in vivo* in the acetic-acid writhing test [46].



35 **36, 37** **38** **39** **40, 41**



42-44 **45-47**

36: R = CO_2H; **37:** R = CH_2OH; **40:** R = H; **41:** R = Ac; **42:** R = Glc^2-Xyl; **43:** R = Glc^2-Rha
44: R = Glc^2-Glc; **45:** R = Glc^2-Xyl; **46:** R = Glc^2-Rha; **47:** R = Glc^2-Glc

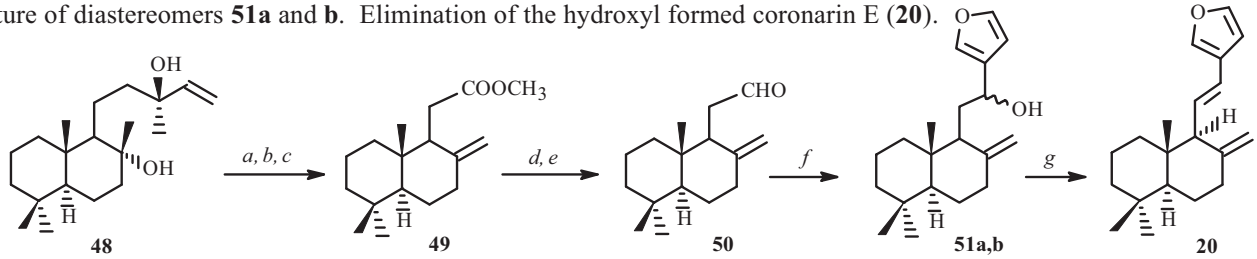
The previously known nepetaefuran (**38**) [47] and sciadin (**39**) [48] are other notable polyfunctional metabolites and derivatives of labdane acids.

Bark of the plant *Neouvaria acuminatissima* afforded the cytotoxic metabolites acuminolide (**40**) and 17-*O*-acetylacuminolide (**41**), which contain β-substituted γ-hydroxybutenolide and 8α,12-epoxide fragments in their structures [49]. Despite the similar structures of the compounds, they exhibited selective cytotoxicity for different tumor cells. Medicinal plants of the family Labiatae, Phlomis, and Eremostachys, which are widely represented in the flora of Central Asia and China, yielded the sweet diterpene glycosides baiyunoside (**42**), phlomisoside I (**43**), and phlomisoside II (**44**) in addition to the corresponding phlomisoic acid glycosides phlomisoside III (**45**), phlomisoside IV (**46**), and eremostachiin (**47**) [50, 51].

Thus, furanolabdanoids exhibit various biological activities. Labdanoids modified in ring B are characterized by broad spectra of pharmacological activity. Compounds that are inhibitors of α-glucosidase (**9**–**11** and **17**–**19**) and promising analgesics (**35**–**37**) have been isolated. Compounds with a transformed furan ring (**4** and **30**) were characterized as TAF antagonists and are promising antitumor agents.

Approaches to the Synthesis of Furanolabdanoids. The significant biological activity of furanolabdanoids is responsible for the interest in developing methods for total synthesis of these compounds. The principal preparation methods are based on transformations of available diterpenoids and monoterpenoids.

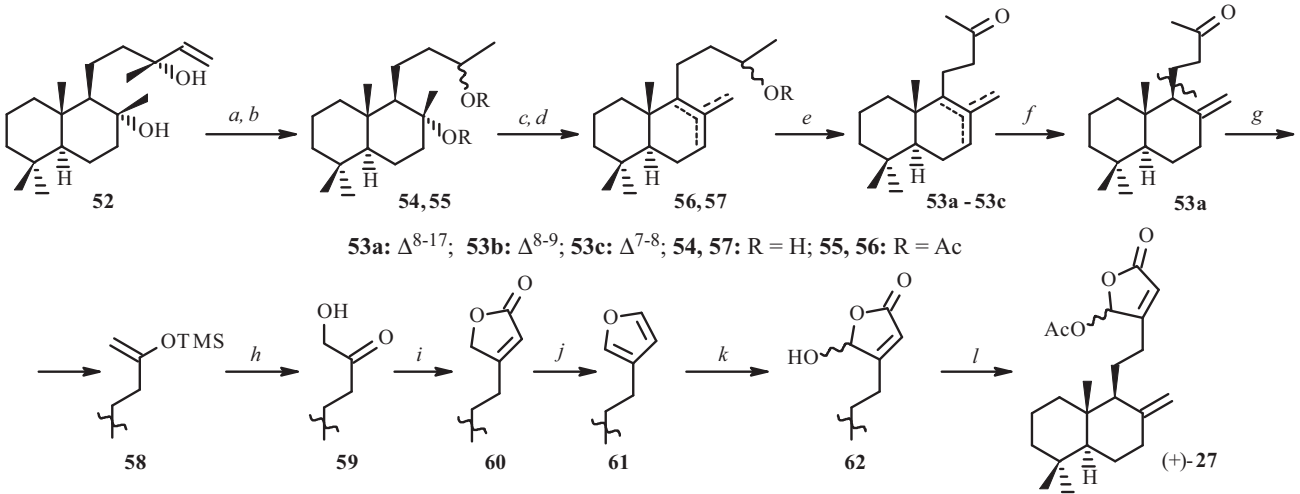
Sclareol in the Synthesis of Labdane Diterpenoids. The available labdane diterpenoid (–)-sclareol (**48**) (isolated from *Salvia sclarea*) was used in the synthesis of several furanolabdanoids. Scheme 1 illustrates the synthesis of (+)-coronarin E (**20**) from **48** [52]. The rate-limiting step was periodate cleavage of **48**, which occurred with formation of the corresponding acetoxy acid (30% sclareolide was also formed). Subsequent methylation by dimethylsulfate and thermal elimination of the C-8 acetoxy group produced **49** as the main product (the $\Delta^{7,8}$- and $\Delta^{8,9}$-isomers were also detected). Reduction to the corresponding alcohols, Swern oxidation, and reaction of aldehyde **50** with 3-lithiofuran afforded the coupling products as a mixture of diastereomers **51a** and **b**. Elimination of the hydroxyl formed coronarin E (**20**).



a. $RuCl_3 \cdot H_2O$, $NaIO_4$, H_2O–MeCN, CCl_4, 20°C (50%); *b*. Me_2SO_4, $LiOH \cdot H_2O$, DMF, 20°C (99%); *c*. $KHCO_3$, DMSO, 150°C (74%); *d*. $LiAlH_4$, THF, 50°C (97%); *e*. DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, –78→20°C (98%); *f*. 3-furyllithium, THF, –78→20°C (65%); *g*. Cl_3C-C(O)-CF_3, pyridinium *p*-toluenesulfonate, PhH, 80°C (50%)

Scheme 1

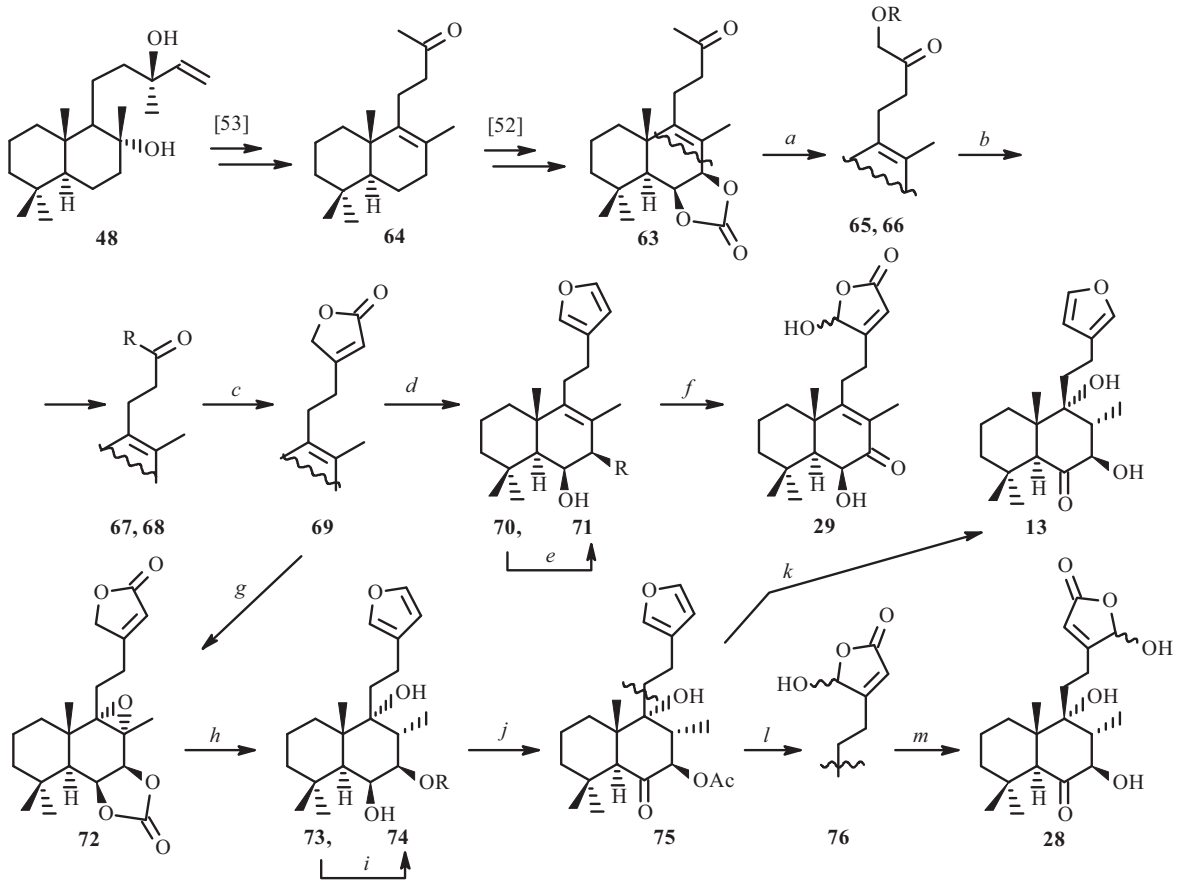
The γ-acetoxybutenolide (+)-lagerstronolide [(+)-**27**] was synthesized starting with (+)-13-epi-sclareol (**52**) (Scheme 2) [53]. Oxidation of **52** by $KMnO_4$ in neutral solution and reduction of the keto-derivative led to a mixture of C-13 epimeric diols **54**, acetylation of which formed a mixture of the corresponding epimeric acetates **55**. Elimination of the acetoxy group in the bicyclic system by pyrolysis over silica gel gave a mixture of olefins **56**. Subsequent hydrolysis of the secondary acetoxy group afforded an inseparable mixture of alcohols **57**, oxidation of which produced a difficultly separated mixture of keto-olefins **53a**–**c**. Epoxidation of the double bond allowed unreacted **53a** to be isolated. The next synthesis steps included formation of the butenolide ring in the side chain by oxidation of silylenol ether **58** into hydroxyketone **59** and treatment with ketene according to Bestman to produce butenolide **60**. Photochemical oxidation of furan derivative **61** by singlet oxygen led to hydroxybutenolide **62**, acetylation of which gave (+)-lagerstronolide [(+)-**27**], the optical isomer of the natural compound (–)-lagerstronolide [(–)-**27**]. The overall yield of (+)-**27** calculated as (+)-13-epi-sclareol (**52**) was about 10%.



a. $KMnO_4$, Me_2CO, $MgSO_4$, 20°C, then $LiAlH_4$ (80%); *b*. AcCl, *N*,*N*-dimethylaniline, DCM (93%); *c*. SiO_2, 100°C (90%); *d*. K_2CO_3–MeOH (90%); *e*. TPAP, NMO, DCM, molecular sieves 3 Å (100%); *f*. *m*-CPBA, DCM; *g*. LDA, TMSCl, THF, –78→20°C (100%); *h*. *m*-CPBA, DCM (90%); *i*. Ph_3P=C=C=O, PhH, 80°C (60%); *j*. DIBAL-H, DCM, –78→20°C, then SiO_2 (70%); *k*. $^1O_2$, Rose Bengal, DCM, –78°C (86%); *l*. Ac_2O, Py (92%)

Scheme 2

(–)-Sclareol (**48**) was used to synthesize leoheterin (**13**), sibiricinone A (**28**), and sibiricinone B (**29**) [54–56]. The starting material in the syntheses was 6,7-disubstituted ketone **63**, which was obtained from methylketone **64** [55]. Treatment of **63** with lead tetraacetate in MeOH produced a mixture of acetoxy- and methoxy-derivatives **65** and **66**. Basic hydrolysis of **65** led to hydroxyketone **67** with a small impurity of acid **68**. Treatment of **67** with ketene according to Bestman gave key lactone **69**. Scheme 3 presents the synthesis conditions for natural labdanoids **13**, **28**, and **29**.

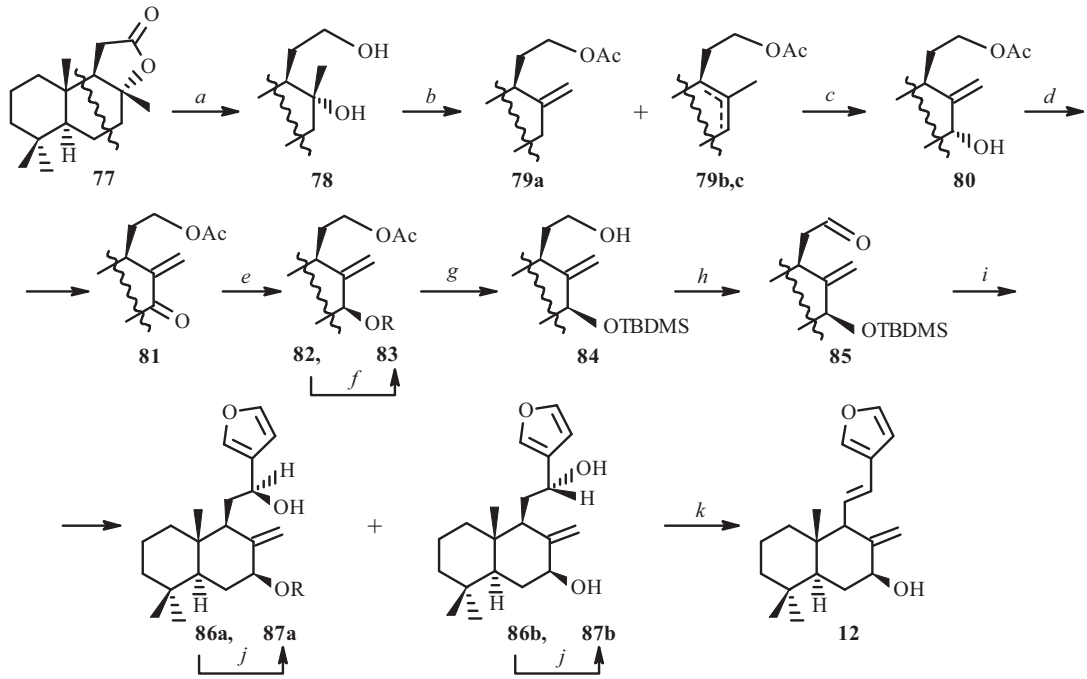


65: R = Ac; **66:** R = Me; **67:** R = CH_2OH; **68:** R = OH; **70:** R = β-OH; **71:** R = (=O); **73:** R = H; **74:** R = Ac

a. $Pb(OAc)_4$, $BF_3 \cdot Et_2O$, MeOH, PhH, 20°C (**65** – 60%, **66** – 21%); *b*. K_2CO_3, MeOH, 20°C (**67** – 81%, **68** – 13% from **65**); *c*. $Ph_3P{=}C{=}C{=}O$, PhH, 80°C, 40 min (84% from **67**); *d*. DIBAL-H, DCM, –78°C, 30 min; then LAH, Et_2O, 20°C (91%); *e*. MnO_2, DCM, 20°C (89%); *f*. $^1O_2$, Rose Bengal, DIPEA, DCM, –78°C, 2.5 h (85%); *g*. *m*-CPBA, DCM, 20°C, 40 h (98%); *h*. DIBAL-H, DCM, –78°C, 30 min; then LAH, THF, 50°C, 24 h (70%); *i*. Ac_2O, Py, 20°C (98%); *j*. TPAP, NMO, molecular sieves 3 Å, DCM, 20°C, 3 h (86%); *k*. K_2CO_3, MeOH, 20°C, 50 min (99%); *l*. $^1O_2$, Rose Bengal, DIPEA, DCM, –78°C, 5 h (92%); *m*. K_2CO_3, MeOH, 1 h, 20°C (97%)

Scheme 3

Sclareolide in the Synthesis of Labdane Diterpenoids. Several schemes for the total synthesis of furanolabdanoids are based on the use of the natural metabolite (+)-sclareolide (**77**), which is obtained by oxidative cleavage of several available labdane terpenes such as (–)-sclareol (**48**), (+)-*cis*-abienol, or (–)-labdanic acid. Scheme 4 shows the synthesis of coronarin A (**12**) from sclareolide (**77**) [57]. Hydride reduction of **77** produced diol **78**, treatment of which with acetic anhydride in collidine transformed it into a mixture of acetates with exo- (**79a**) and endocyclic (**79b** and **c**) double bonds (3:1:1 ratio). Allylic hydroxylation of **79a**–**c** led to 7α-hydroxybicyclane **80**, oxidation of which produced the corresponding 7-keto derivative **81**, reduction of which gave 7β-hydroxybicyclane **82** (natural configuration). Silyl protection of the alcohol afforded **83**, deacetylation of which produced **84**. Oxidation of **84** produced the unstable aldehyde **85** (75% yield from **80**), reaction of which with 3-lithiofuran gave furanolabdanoids **86a** and **b** (mixture of diastereomers). Removal of the silyl protection afforded corresponding alcohols **87a** and **b**, dehydration of which led smoothly to coronarin A (**12**).



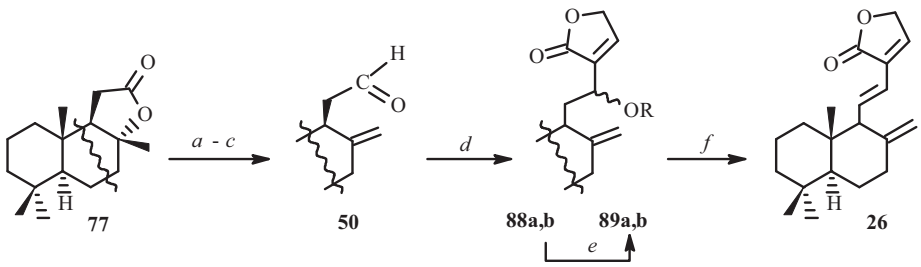
82, 87a, 87b: R = H; **83, 86a, 86b:** R = TBDMS

a. LAH, THF, 50°C, 5 h (97%); *b*. Ac_2O, collidine, reflux, 16 h (85%); *c*. SeO_2, *t*-BuOOH, CH_2Cl_2, 20°C, 2 h (45%); *d*. PCC, CH_2Cl_2, 20°C, 3 h (75%); *e*. $NaBH_4$, MeOH, 20°C, 1 h (98%); *f*. TBDMSCl, $AgNO_3$, DMF, 20°C, 1 h (89%); *g*. Na_2CO_3, MeOH, 20°C, 2 h (92%); *h*. PCC, CH_2Cl_2, 20°C, 3 h (98%); *i*. 3-bromofuran, *n*-BuLi, THF, –78→20°C (72%); *j*. $CuCl_2 \cdot 2H_2O$, Me_2CO–H_2O (95:5), reflux (90%); *k*. MsCl, 2,6-lutidine, MC, 20°C, 24 h, then gently warming to evaporate solvent (68%)

Scheme 4

It was demonstrated [58] that a more convenient method for introducing the C-11=C-12 double bond in the syntheses of coronarins A (**12**) and E (**20**) was to heat the corresponding hydroxy-derivatives **51a** and **b** or **87a** and **b** in alcohols in the presence of HMPA.

Villosin (**26**) was synthesized from (+)-sclareolide (**77**) [59]. The key step was formation of the (*E*)-(1-alkenyl)-2(5*H*)-furanones from the aldehydes (Scheme 5). Aldol condensation of aldehyde **50** with dibutylboron-2-furanolate that was generated *in situ* occurred regioselectively to form diastereomeric alcohols **88a** and **b** (3.8:1), the mesylates of which (**89a** and **b**) transformed smoothly into butenolide **26**.

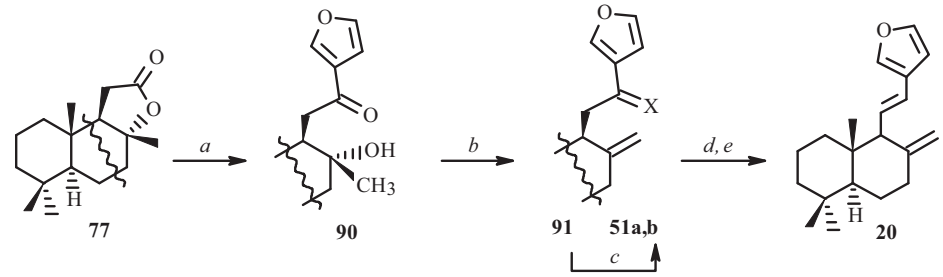


88a,b: R = H; **89a,b:** R = Ms; **a:** 12-(*R*), **b:** 12-(*S*)

a. MeNHOMe·HCl, Me_3Al, CH_2Cl_2, 0°C (87%); *b*. $SOCl_2$, Py, CH_2Cl_2, –78°C (88%); *c*. DIBAL, Et_2O, –78°C (93%); *d*. 2-(5*H*)-furanone, *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, –78°C, then **88**, –78°C, 2 h (95%); *e*. MsCl (4 equiv.), Et_3N, CH_2Cl_2, –78→0°C, 1 h (88%); *f*. DBU (2 equiv.), CH_2Cl_2, 20°C, 15 min (90%)

Scheme 5

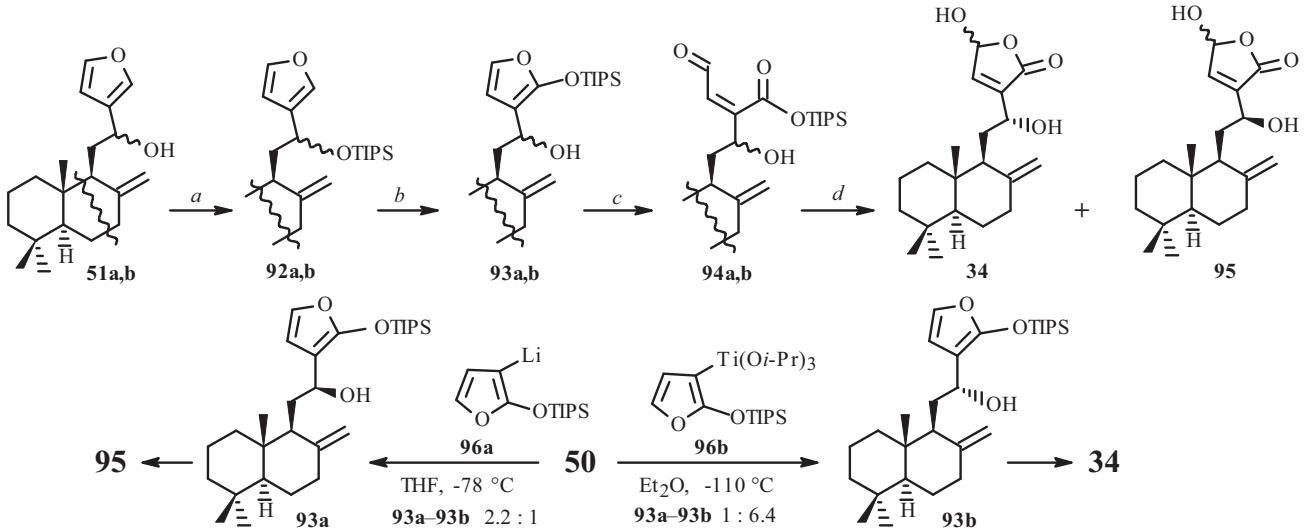
An effective method for preparing coronarin E (**20**) from metabolite **77** was proposed (Scheme 6) [60]. Opening of the lactone ring of sclareolide by 3-lithiofuran led to hydroxyketone **90**. Then, selective introduction of the exocyclic double bond, reduction of ketone **91**, bromination of alcohols **51a** and **b**, and elimination under basic conditions followed.



a. 3-Bromofuran, *n*-BuLi (85%); *b*. $SOCl_2$, Py (95%); *c*. $LiAlH_4$ (97%); *d*. Ph_3P, Br_2, Et_3N; *e*. DBU (57% on two steps)

Scheme 6

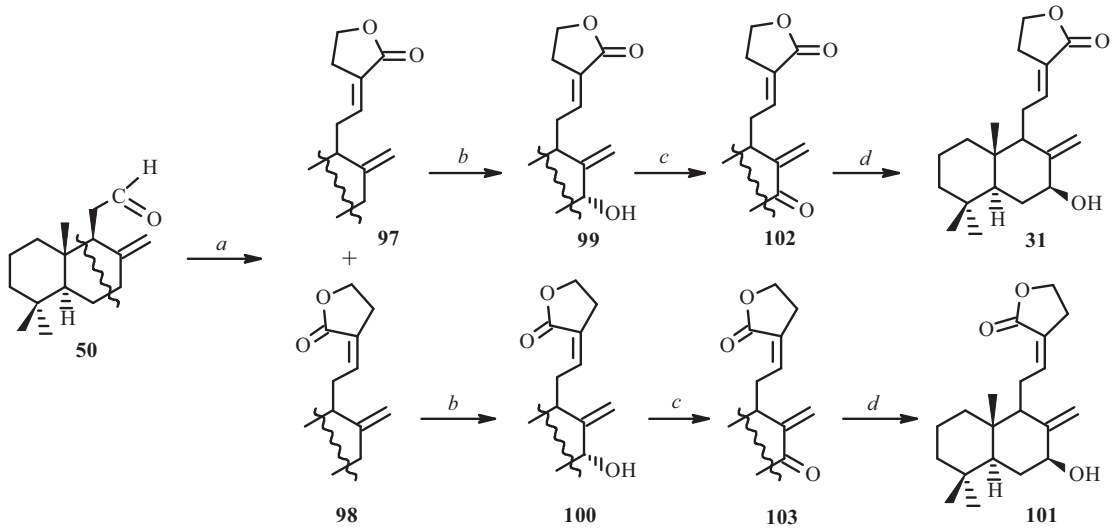
The total synthesis of the antitumor diterpenoid (+)-zerumin B (**34**) that was based on metabolite **77** was reported [61, 62]. The first step involved regioselective formation of the α-substituted γ-hydroxybutenolide moiety, which included [1,4] O→C migration of the triisopropylsilyl group in **92a** or **b** (obtained from pure alcohols **51a** or **b**) and subsequent oxidation by singlet oxygen of substituted 2-triisopropylsilyl-3-(α-hydroxy)alkylfurans **93a** and **b** (Scheme 7) [61]. The resulting silyl esters **94a** and **b** were hydrolyzed *in situ* to the corresponding γ-hydroxybutenolides (+)-zerumin B (**34**) and (+)-12-epi-zerumin B (**95**). A diastereo-divergent synthesis of zerumin (**34**) and its 12-epimer **95** using the reaction of aldehyde **50** with 2-isopropylsiloxy-3-lithio- or 2-isopropylsiloxy-3-[tri(isopropyloxy)titanium]furans (**96a** and **b**) as the key step was described [62]. The reaction of **50** with **96a** in THF produced a mixture of **93a** and **b**, from which 12(*S*)-isomer **93a** was easily isolated (65% yield). Condensation of **50** with **96b** gave primarily 12(*R*)-isomer **93b** (72% yield). Further oxidation by dimethyldioxirane in Me_2CO and hydrolysis produced pure γ-hydroxybutenolides **34** or **95**.



a. 2,6-Lutidine, TIPSOTf (91% for **92a** and 90% for **92b**); *b*. *n*-BuLi, HMPA (90% for **93a** and 91% for **93b**); *c*. O_2, methylene blue, hν; *d*. H_2O, SiO_2

Scheme 7

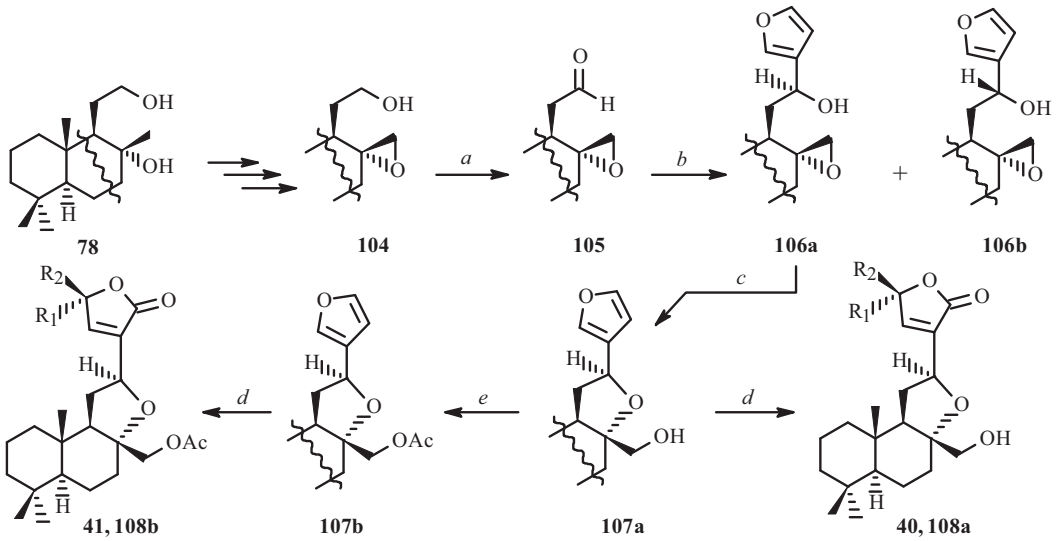
Aldehyde **50** that was obtained from sclareolide was used successfully in the total synthesis of (+)-hedychialactone A (pacovatinin A, **31**) (Scheme 8) [63]. Horner–Wadsworth–Emmons olefination of **50** led to a mixture of *E*- and *Z*-butyrolactones **97** and **98**. Allylic oxidation of both compounds by SeO_2 produced 7α-hydroxylabdanoids **99** and **100**. Sequential Swern oxidation of alcohols **99** and **100** and reduction of ketones **102** and **103**, which exhibited significant cytotoxicity against five human tumor cell lines, was used to prepare 7β-hydroxy-derivatives **31** or **101**.



a. Diethoxyphosphonobutyrolactone, NaH, PhMe, 20°C (for **97** – 51%, for **98** – 17%); *b*. SeO_2, *t*-BuOOH, CH_2Cl_2, 28°C (for **99** – 76%, for **100** – 82%); *c*. $(COCl)_2$, DMSO, CH_2Cl_2, –78→20°C (for **102** – 76%, for **103** – 83%); *d*. $NaBH_4$, MeOH, 0°C (for **31** – 92%, for **103** – 88%)

Scheme 8

Acuminolide (**40**) and 17-*O*-acetylacuminolide (**41**) were also synthesized from (+)-sclareolide (**77**) (Scheme 9) [64]. Diol **78** was converted into epoxide **104** using selective protection of the primary alcohol. Then, the furan ring was introduced (compounds **106a** and **b**; 46% and 32% yields). Treatment of the (12*S*)-hydroxy-derivative (**106a**) with *p*-toluenesulfonic acid in nitromethane gave exclusively tricyclane **107a**, reaction of which with singlet oxygen in the presence of base formed epimeric hydroxybutenolides acuminolide (**40**) and 15-epi-acuminolide (**108a**) (70:30 ratio). 17-*O*-Acetylacuminolide (**41**) was obtained from **107a** according to a scheme including acylation at the C-17 position and reaction of **107b** with singlet oxygen. Metabolite **41** was formed in a mixture with 16-epi-17-*O*-acetylacuminolide (**108b**) (66:34 ratio) [64].



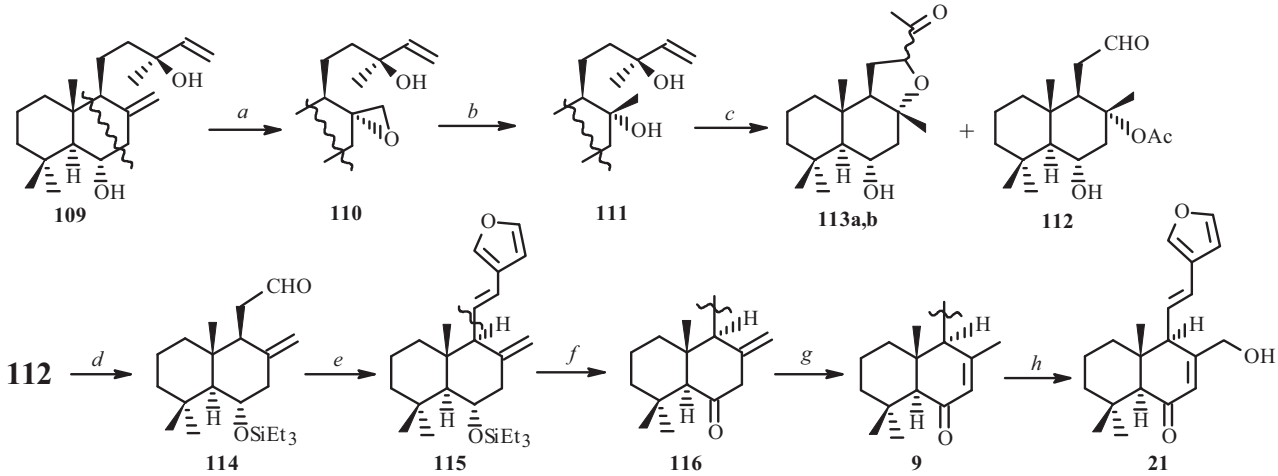
40, 41: R_1 = OH, R_2 = H; **108a,b:** R_1 = H, R_2 = OH

a. $CrO_3 \cdot 2Py$, CH_2Cl_2, 20°C (99%); *b*. 3-furyllithium, THF, –78→20°C, then NH_4Cl; *c*. *p*-TsOH·H_2O, $MeNO_2$, –20°C (90%); *d*. $^1O_2$, Rose Bengal, ethyl diisopropyl amine, CH_2Cl_2, –78→20°C (90%); *e*. Ac_2O, 4-DMAP, CH_2Cl_2

Scheme 9

Larixol in the Synthesis of Labdane Diterpenoids. Larixol (**109**) is an available sap constituent of various larch species. The syntheses of furanoditerpenoids hedychenone (**9**) and yunnancoronarin A (**21**) that are substituted in ring B were described [65]. Epoxidation of larixol (**109**) using oxone led to 8,17-epoxide **110** that was smoothly reduced to triol **111**. Oxidation of **111** by an excess of sodium periodate in the presence of a catalytic amount of osmium oxide gave a mixture of

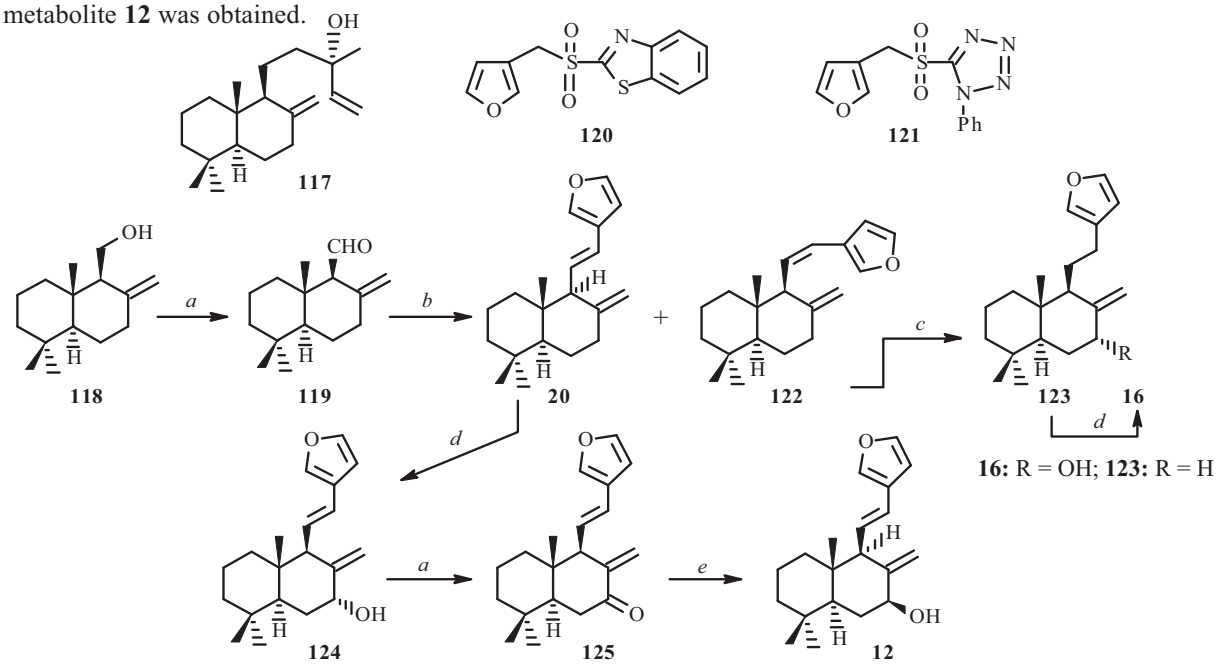
aldehydes **112** and **113a** and **b**. Elimination of the acetoxy group from the triethylsiloxyaldehyde that was formed *in situ* from **112** produced decaline aldehyde **114** with an exomethylene double bond (Scheme 10), reaction of which with 3-lithiofuran and dehydration of the resulting mixture of alcohols gave furanolabdanoid **115**, which was transformed into ketone **116**. Isomerization of the endocyclic double bond produced metabolite **9** (22% overall yield from **109**), from which metabolite **21** was obtained.



a. Oxone, Me_2CO, H_2O, CH_2Cl_2, [18] crown-6, $NaHCO_3$, 0°C (68%); *b*. $LiAlH_4$, THF, 0→20°C (94%); *c*. OsO_4 (cat.), $NaIO_4$, THF (90%, **113a,b** – **112** 1:2.2); *d*. Et_3SiCl, DMAP (cat.), Py, 8 h, then 2,4,6-collidine as solvent, 170°C, 12 h (79%); *e*. 3-furyllithium, –78°C, 2 h (68%), then 2,6-lutidine (7 equiv.), DCM, MsCl (3 equiv.), 20°C, 18 h (68%); *f*. AcOH–THF–H_2O (5:1:3), 20°C, 12 h, then IBX (3 equiv.), AcOEt, 60°C, 3 h (85%); *g*. MeONa (0.2 M in MeOH), 20°C, 2 h (99%); *h*. SeO_2 (1.5 equiv.), dioxane, 80°C, 8 h, then $NaBH_4$, EtOH, –78°C (60%)

Scheme 10

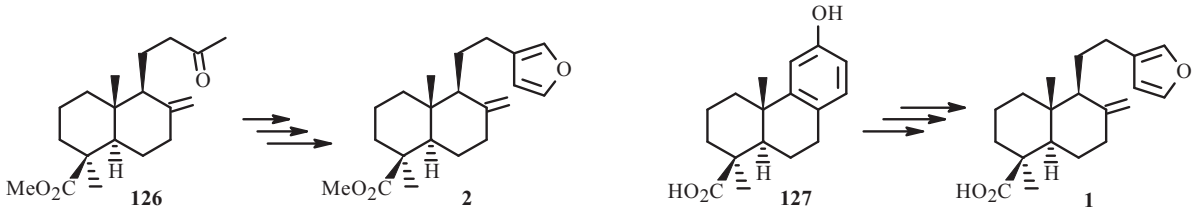
Other Terpenoids in the Synthesis of Furanolabdanoids. Many studies were focused on the development of preparation methods for key optically active bicyclic aldehydes suitable for further coupling reactions with furan derivatives. Thus, an effective synthesis of aldehyde **50** and correspondingly (+)-coronarin E (**20**) from (+)-manool (**117**) was described [66]. The available drimane-type diterpenoid (±)-albicanol was used as the starting material for synthesizing (+)-coronarin A (**14**), (+)-coronarin E (**20**), and austrochaparol (**16**) [67]. (+)-Albicanol (**118**) (prepared by lipase cleavage of the racemate) was oxidized by Dess–Martin periodinane to aldehyde **119**. Olefination of the aldehyde by β-furylmethylheteroaromatic sulfone **120** or **121** according to Julia produced a mixture of (+)-*trans*-coronarin E (**20**, 11%) and (+)-*cis*-coronarin E (**122**, 77%) (Scheme 11), which were hydrogenated to (+)-15,16-epoxy-8,13,14-labdatriene (**123**) (isolated from the marine sponge *Cacospongia* sp. [68]). Allylic oxidation of **123** produced metabolite **16**. Allylic oxidation of **20** led to alcohol **124**, from which metabolite **12** was obtained.



a. Dess-Martin periodinate, Na_2CO_3, CH_2Cl_2; *b*. **120**, $LiN(TMS)_2$, THF, or **121**, $KN(TMS)_2$, DME; *c*. H_2, Pd-$BaSO_4$, quinoline; *d*. SeO_2, CH_2Cl_2; *e*. $NaBH_4$, MeOH

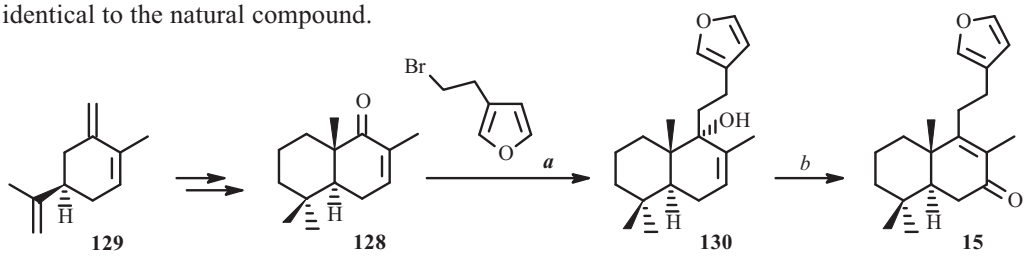
Scheme 11

The synthesis of methyl lambertianate (**2**) from the methyl ester of agatic acid (**126**) and metabolite **1** from podocarpic acid (**127**) was reported (Scheme 12) [69, 70].



Scheme 12

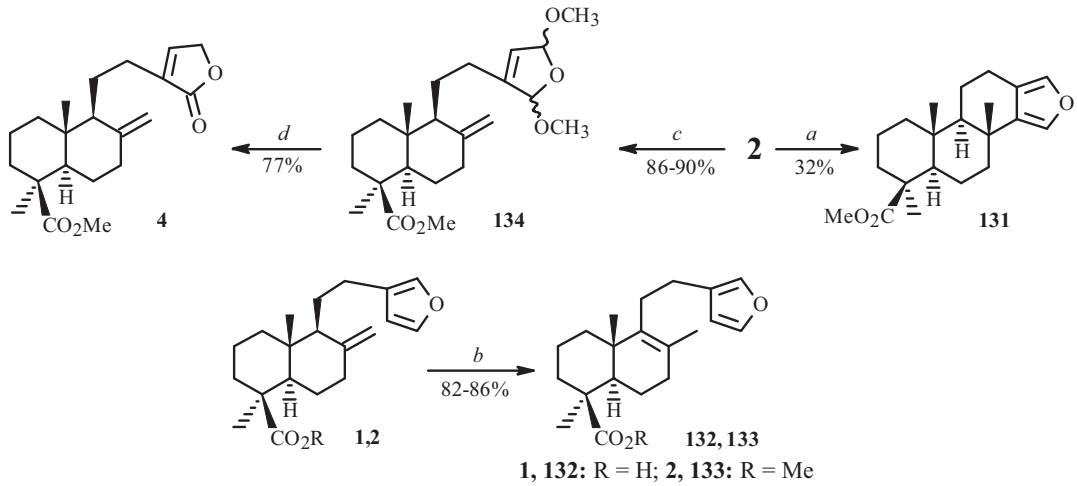
The use of C–C bond-forming reactions of *trans*-decaline-type ketones with organolithium compounds was proposed for the synthesis of labdanoids substituted in ring B. Such ketones included 11-nordrim-7-en-9-one (**128**), which was easily obtained from (*R*)-carvone (**129**) [31]. Scheme 13 shows that ketone **128** was used in the synthesis of hispanone (**15**). Reaction of **128** with 3-(2-lithioethyl)furan gave coupling product **130**, rearrangement and oxidation of which produced (+)-hispanone (**15**) that was identical to the natural compound.



a. *t*-BuLi, Et_2O, –78°C, 45 min, then NH_4Cl (68%); *b*. PCC, $CaCO_3$, CH_2Cl_2, 20°C, 12 h (51%)

Scheme 13

Transformations of Furanolabdanoids. Synthesis of Natural Metabolites from Furanolabdanoids. A structural analysis of furanolabdanoids and the availability of several metabolites led to the conclusion that their synthetic transformations were promising for preparing compounds that were structurally analogous to several natural metabolites and other practically valuable compounds. Thus, treatment of methyl lambertianate (**2**) with acid formed methyl spongia-13(16),14-dien-18-oate (**131**) (Scheme 14) [71].



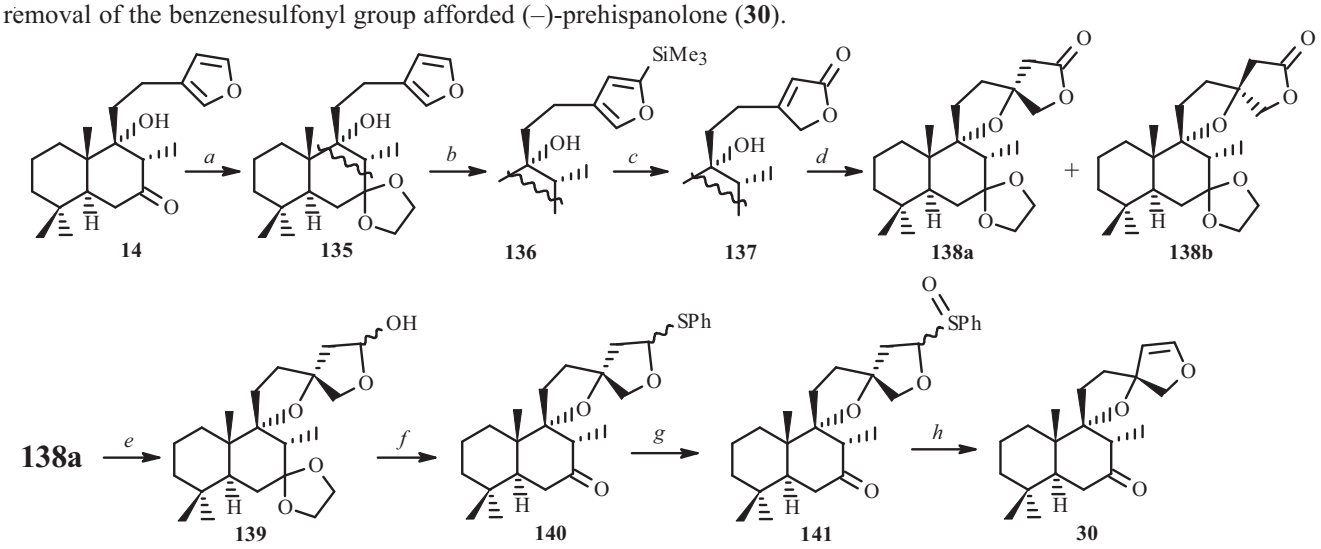
a. H_2SO_4, $MeNO_2$–PhMe; *b*. *p*-TsOH, C_6H_6, 80°C; *c*. $PhSO_2NHCl$ (2.1 equiv.), MeOH, 0–5°C, 30 min (90%), or NBS (2.1 equiv.), MeOH, 0°C, 10 min (86%); *d*. 20% HCl, 1,4-dioxane, 30 min (77%)

Scheme 14

Lambertianic acid (**1**) isomerized smoothly through the action of *p*-toluenesulfonic acid in refluxing benzene to phlomisoic acid (**132**), the aglycon of plant glycosides **45**–**47** (Scheme 14) [72]. Methyl lambertianate (**2**) underwent an analogous transformation to form **133** [73].

A practical synthesis of the diterpenoid pinusolide (**4**) (Scheme 14) that included oxidative methoxylation of **2** by chloramine B [or *N*-bromosuccinimide (NBS)] and subsequent treatment of diterpenoid 2,5-dimethoxydihydrofurans **134** with HCl was described [18].

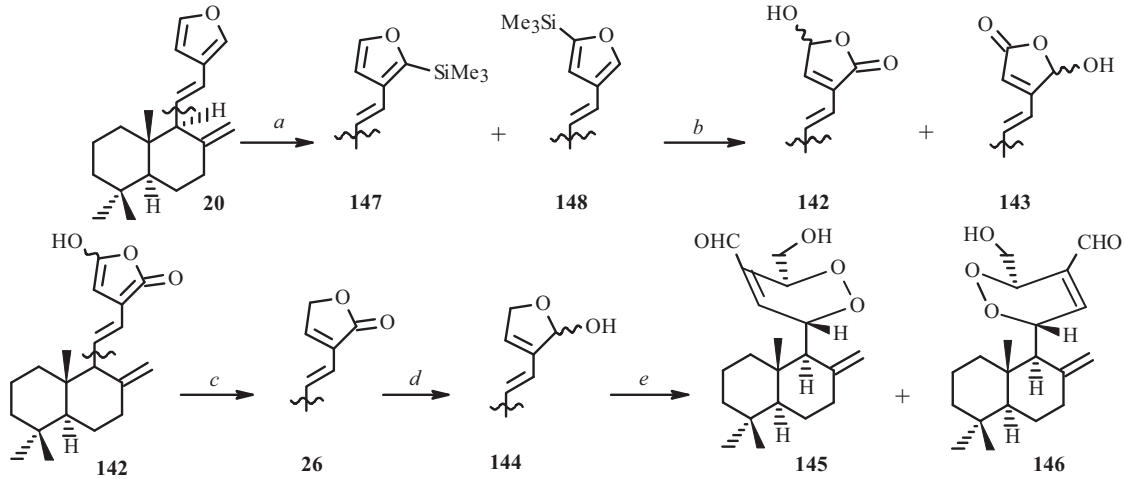
The synthesis of the valuable diterpenoid prehispanolone (**30**) from hispanolone (**14**) was reported (Scheme 15) [74]. Regioselective deprotonation and silylation of protected prehispanolone **135** produced trimethylsilyl derivative **136**, from which butenolide **137** was obtained. Intramolecular addition gave a mixture of 13(*R*)- and 13(*S*)-diastereomers (–)-**138a** and (+)-**138b** (1:1 ratio). Reduction of (–)-**138a** gave lactol **139** and then thioacetal **140**. Its oxidation into sulfoxides **141** and removal of the benzenesulfonyl group afforded (–)-prehispanolone (**30**).



a. $(CH_2OH)_2$, *p*-TsOH, PhH, 80°C (95%); *b*. *n*-BuLi, THF, –78→20°C, then Me_3SiCl; *c*. $MeCO_3H$, NaOAc, CH_2Cl_2, 0°C (69%, from (+)-**135**); *d*. DBU, Et_3N, 80°C (88%); *e*. DIBAL-H, CH_2Cl_2, –78°C (96%); *f*. PhSH, CF_3CO_2H, CH_2Cl_2, 0°C (45%); *g*. 0.5 M $NaIO_4$ in MeOH, 0→20°C (67%); *h*. $P(OEt)_3$, PhMe, 110°C (61%)

Scheme 15

The transformation of coronarin E (**20**) into natural antioxidants [75, 76] chinensines A–E (**142**–**146**) was investigated [60]. Silylation of **20** formed regioisomers **147** and **148** (3:1) (Scheme 16). Cycloaddition of singlet oxygen gave chinensines A and B (**142** and **143**). Reduction of **142** produced villosin (**26**), subsequent reduction of which led to chinensine C (**144**). [4+2]-Cycloaddition of singlet oxygen to lactol **144** synthesized **145** and **146**.

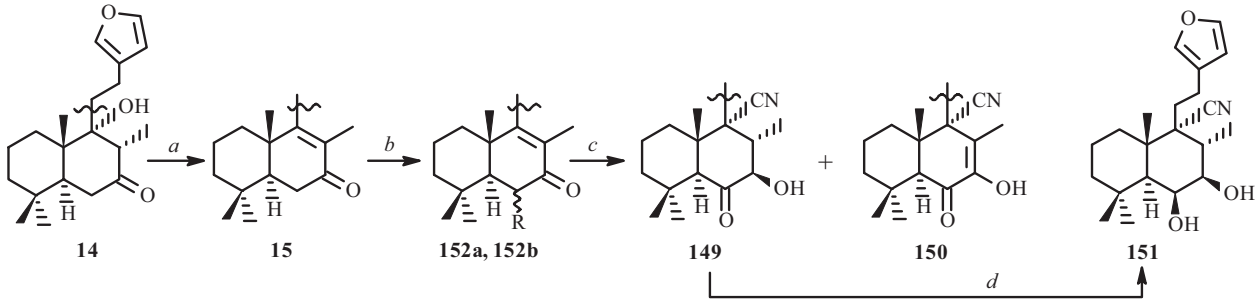


a. *n*-BuLi, Me_3SiCl; *b*. O_2, methylene blue, hν, CH_2Cl_2, –78°C, 2 min (80%); *c*. $NaBH_4$ (92%); *d*. DIBAL-H (96%); *e*. O_2, methylene blue, hν, CH_2Cl_2 (60%)

Scheme 16

Synthetic Transformations of Furanolabdanoids. We examined transformations of native metabolites that occurred mainly with retention of the labdanoid structure without including [4+2]-cycloaddition reactions of the furan moiety.

Modification of Furanolabdanoids on the Decaline Skeleton. The significant pharmacological activity of furanolabdanoids substituted in ring B stimulated interest in the corresponding modifications. Transformations in ring B were studied with respect to lambertianic acid (**1**), its ester (**2**), pinusolide (**4**), and hispanolone (**14**). The preparation of 9-α-cyano-derivatives of labdanoids **149**–**151** from **14** [77] included treatment with a catalytic amount of I_2 to give hispanone (**15**) [29]. Acetoxylation of **15** formed a mixture of epimeric 6-acetoxy-derivatives **152a** and **b** (5:2), treatment of which with KCN gave Michael reaction products **149** (45%) and **150** (9%) (Scheme 17). Compounds **149** and **150** and reduction product **151** showed significant growth inhibition of pathogenic plant fungi [77].



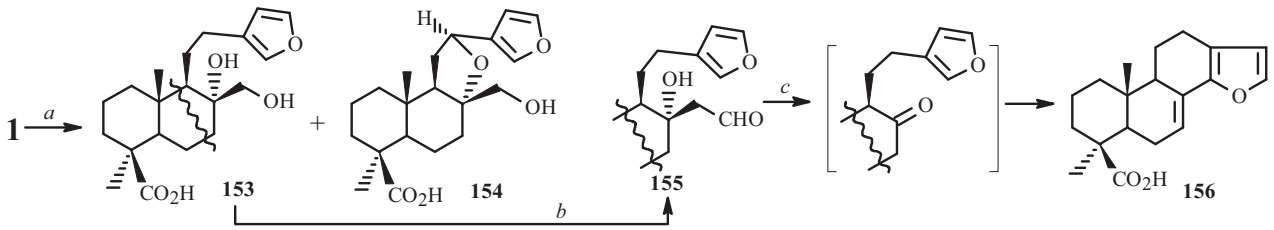
14 **15** **152a, 152b** **149** **150** **151**

152a: R = α-OAc; **152b:** R = β-OAc

a. I_2, PhH, 80°C (87%); *b*. $Mn(OAc)_3$, PhH, 80°C (60%); *c*. KCN, EtOH (95%); *d*. $LiAlH_4$, THF, 60°C (90%)

Scheme 17

A series of oxygen-containing derivatives of labdanoids **1** and **2** that became the subjects of further structural transformations were synthesized by an assortment of oxidants that affected selectively the exomethylene double bond. Hydroxylation of **1** by $KMnO_4$ in basic solution produced a mixture of 8,17-dihydroxy acid **153** (59%) and 8,12-epoxy acid **154** (5.5%) (Scheme 18) [78]. Periodate oxidation of **153** gave hydroxyaldehyde **155**, acid treatment of which (through a ketoacid step) afforded phenanthro[1,2-*b*]furan **156**, a structural analog of furanoabietanes, which occur among the active principles of Tanshen, a Chinese-medicine cardioactive agent [79].

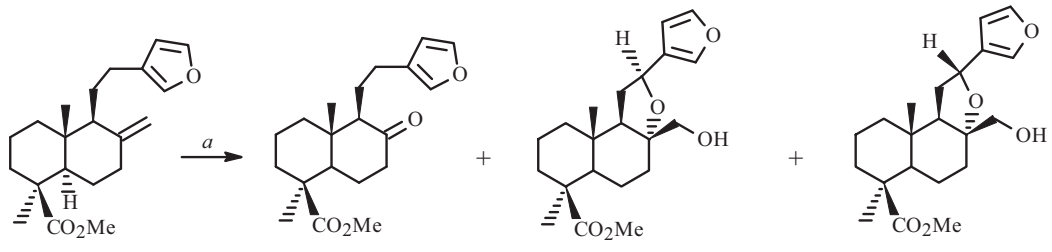


153 **154** **155** **156**

a. $KMnO_4$, 5°C; *b*. $NaIO_4$, AcOH, MeOH (77%); *c*. HCl, MeOH (74%)

Scheme 18

Oxidation of methyl lambertianate (**2**) by $KMnO_4$ under interphase catalysis conditions formed ketone **157** (21%), 8α,12α-epoxylabdanoid **158a** (39%), and its 12-diastereomer **158b** (11%) (Scheme 19) [80, 81].



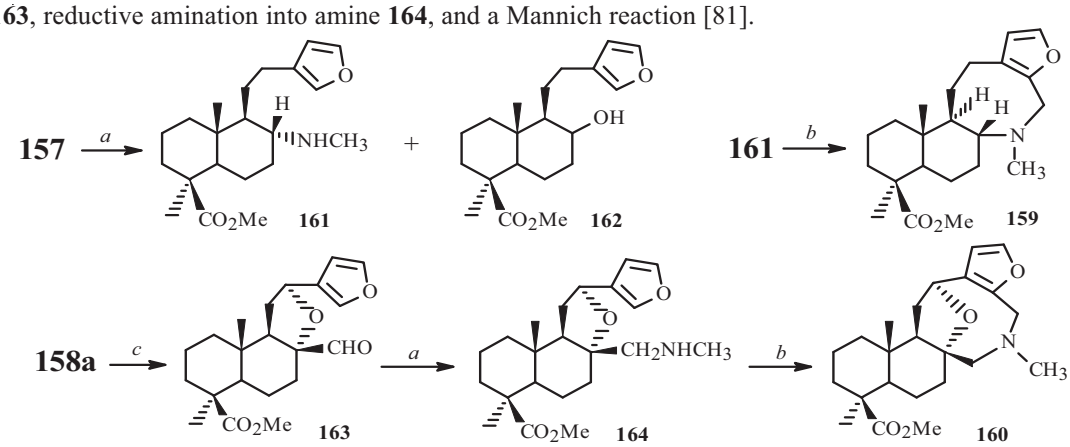
2 **157** **158a** **158b**

a. $KMnO_4$, PhH–H_2O, TBAB, 45°C

Scheme 19

Diterpene alkaloids of the new structural types **159** and **160** were synthesized by transformation of **157** and **158a** (Scheme 20). Reductive amination by methylamine of ketone **157** led to a mixture of 17-nor-8α-methylaminolabdanoid **161** and alcohol **162**. Intramolecular Mannich aminomethylation of diterpenoid amine **161** using formaldehyde produced

furobenzazocine derivative **159**. Transformation of labdanoid **158a** into furobenzazocine **160** included its oxidation into aldehyde **163**, reductive amination into amine **164**, and a Mannich reaction [81].

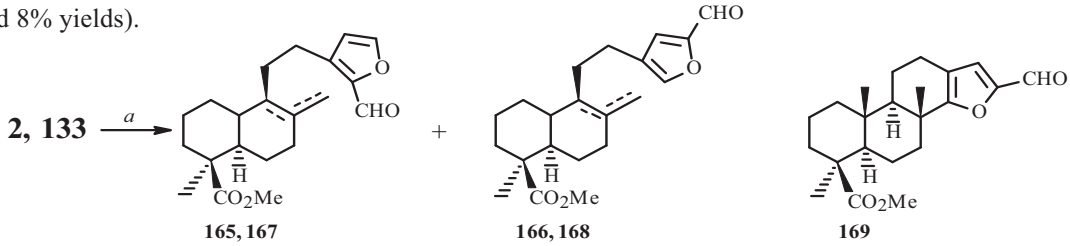


a. CH_3NH_2–MeOH, 20°C, then $NaBH_4$; *b*. $(CH_2O)_n$, CF_3COOH, PhH, 80°C, 15 min; *c*. PCC, CH_2Cl_2

Scheme 20

Derivatives and analogs of pinusolide (**4**) (primarily functionalized on ring B) were synthesized [17]. Data on the *in vitro* inhibitory activity against TAF were obtained. Epoxidation or hydroxylation of the exomethylene double bond and isomerization of the ring B double bond did not increase the inhibitory activity. 17-Nor-8-oxopinusolide showed the greatest activity (IC_{50} of 0.25 μM) that was comparable with that of **4**.

Modification of Furanolabdanoids in the Furan Ring. Formylation of methyl lambertianate (**2**) under Vilsmeier–Haack reaction conditions formed 16-formyl- and 15-formyllabdatrienoates **165** and **166** (10:1, 77% yield) (Scheme 21) [82]. Formylation of **133** produced tetracyclic isospongiane-type diterpenoid **169** [83] in addition to formyllabdatrienes **167** and **168** (79 and 8% yields).

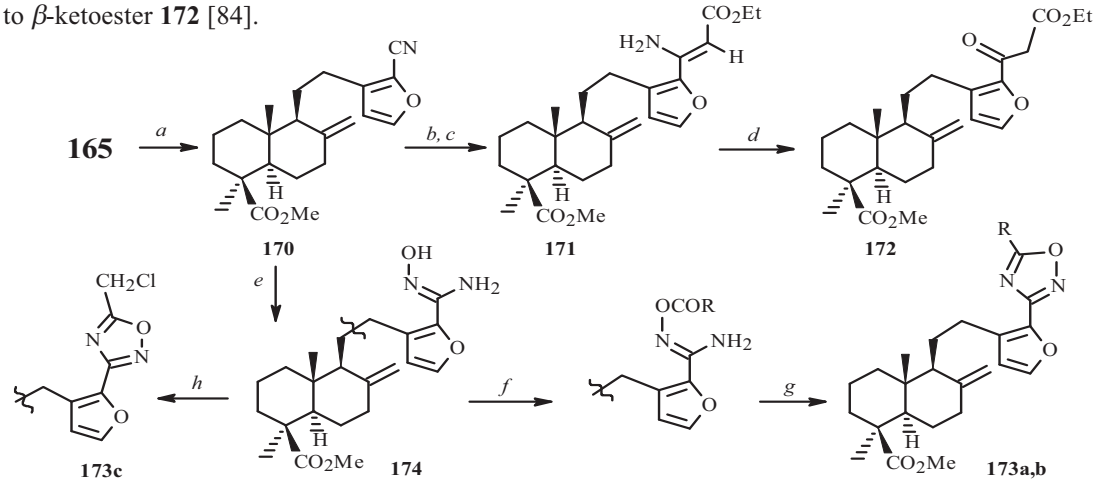


165, 166: $\Delta^{8,17}$; **167, 168**: $\Delta^{8,9}$

a. $POCl_3$–DMF, 20°C, 28 h

Scheme 21

Treatment of methyl 16-formyllambertianate (**165**) with ammoniacal I_2 in THF led smoothly to 16-cyanolabdatriene **170** (Scheme 22), reaction of which with the zinc enolate of ethylbromoacetate produced enaminoester **171**, which was hydrolyzed to *β*-ketoester **172** [84].



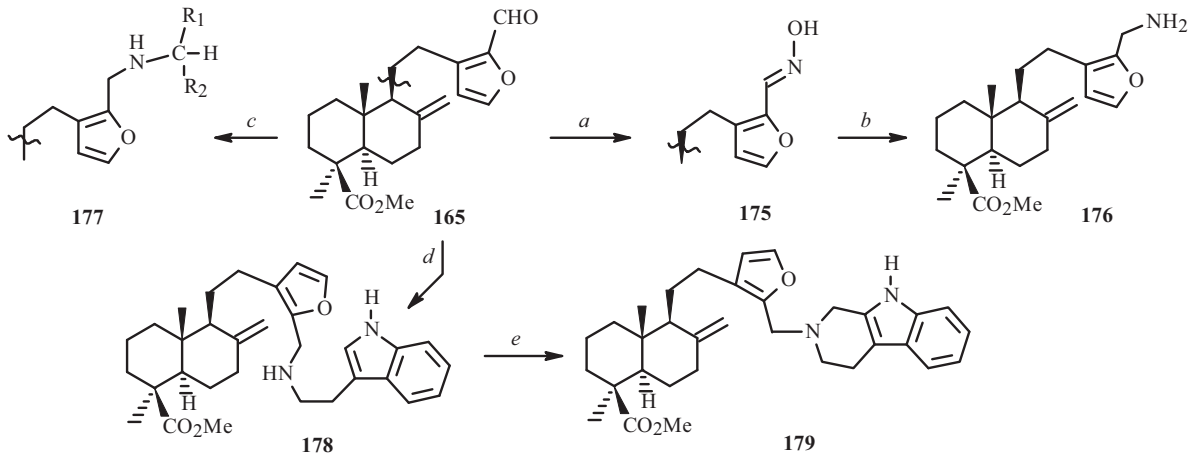
173a: R = Me; **173b:** R = Ph

a. NH_3–I_2, THF (91%); *b*. Zn, CH_2BrCO_2Et; *c*. K_2CO_3 (92%); *d*. HCl–THF (78%); *e*. NH_2OH ·HCl, Et_3N; *f*. RCOCl, Et_3N; g PhMe, 110°C; *h*. $CH_2ClCOCl$, Et_3N

Scheme 22

16-Cyanolabdatriene **170** was used to develop a route to 16-(1,2,4-oxadiazol-3-yl)-15,16-epoxylabdatrienoates **173a**–**c** (through amidooxime **174**) (Scheme 22). The products showed high cytotoxicity against human tumor cells ($CCID_{50}$ of 0.08 μM) [85].

The aminomethyl substituents in the furan rings of metabolites **1** and **2** were introduced in several ways. These included reduction of the oxime of methyl 16-formyllambertianate (**175**) [86], reductive amination of methyl 16-formyllambertianate (**165**), or Mannich aminomethylation of methyl lambertianate (**2**) [87]. Oximation of **165** occurred quantitatively to give pure (*E*)-oxime **175**, reduction of which led to methyl 16-aminomethyllambertianate **176** (97% yield) (Scheme 23). Reductive amination of aldehyde **165** by benzylamine and amino-acid derivatives afforded aminomethyl derivatives **177** [87]. Amides of labdanoids that were prepared via condensation of amine **176** with *N*-Boc-protected of *ω*-amino acids exhibited high cytotoxicity in CEM-13, MT-4, and U-937 tumor models ($CCID_{50}$ values of the most active compounds were 3.9–9.9 μM). Derivatives of **177** were used for further transformations [73].



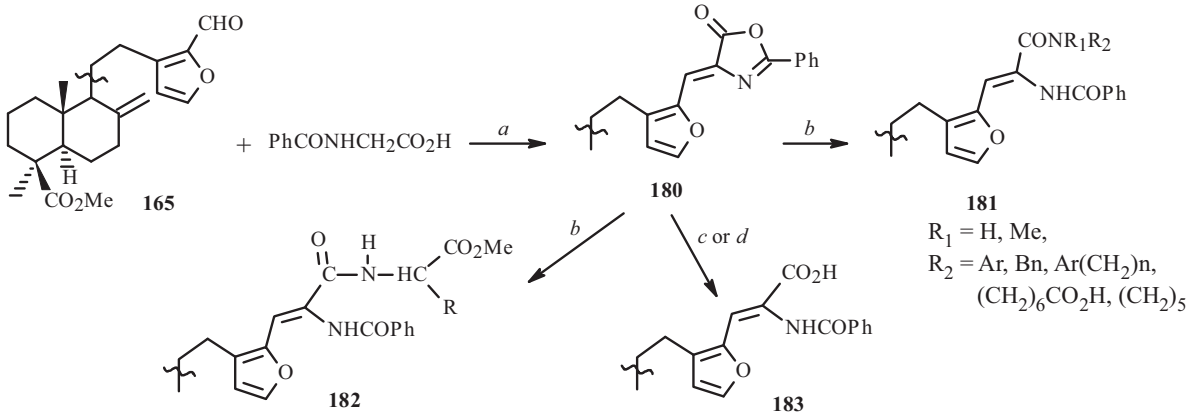
R_1 = Ph, $(CH_2)_nCO_2H$, R_2 = H; R_1 = *i*-Pr, R_2 = CO_2Me; R_1 = *i*-Pr, R_2 = CO_2Bu-*t*; R_1 = $(CH_2)_2SMe$, R_2 = CO_2Me

a. $NH_2OH{\cdot}HCl$, EtOH–H_2O 1:1, NaOH; *b*. H_2/Ni-Ra; *c*. $NH_2CHR_1(R_2)$, $NaBH_4$; *d*. tryptamine, $NaBH_4$ (87%); *e*. CH_2O, TsOH (71%)

Scheme 23

Hybrid structures with a tetrahydro-*β*-carboline group were synthesized from methyl 16-formyllambertianate (**165**) (Scheme 23) [88, 89]. The Pictet—Spengler reaction was used as the synthetic tool. The synthesis included reductive amination by tryptamine of aldehyde **165** to give indoloterpenoid **178** and subsequent condensation with formaldehyde to form *β*-carboline **179**.

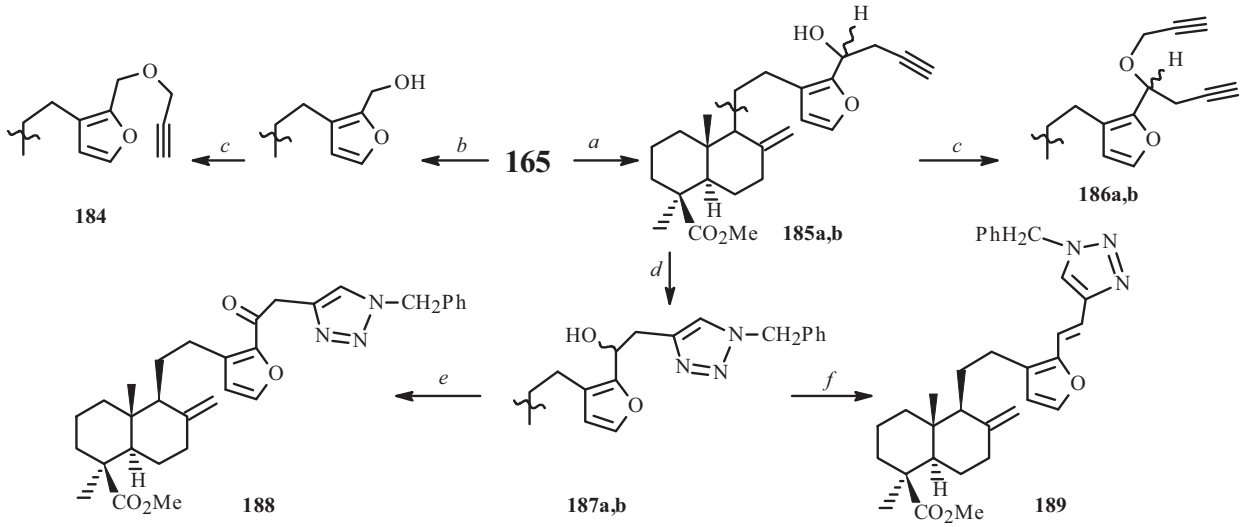
An Erlenmeyer reaction of diterpene aldehyde **165** with an acid group formed labdanoid 5(4*H*)-oxazolone **180** (76% yield) as the pure isomer with the *Z*-configuration of the double bond (Scheme 24) [90]. Condensation of azlactone **180** with amines or *α*-amino-acid esters (leucine and isoleucine) synthesized 4-substituted carbamoylvinylbenzamides **181** (69–91% yields) or esters of terpenoid 2-benzoylaminoacryloylamino acids **182** (62–78% yields). Hydrolysis of **180** produced *α*-acylamino acid **183**. 16-Carbamoylvinylbenzamides **181** acted as correctors for cytostatic polychemotherapy [91].



a. Ac_2O, K_2CO_3 (76%); *b*. $HN(R_1)R_2$, PhH, 75°C (62–91%); *c*. HCl-ether (72%); *d*. 10% NaOH–EtOH (67%)

Scheme 24

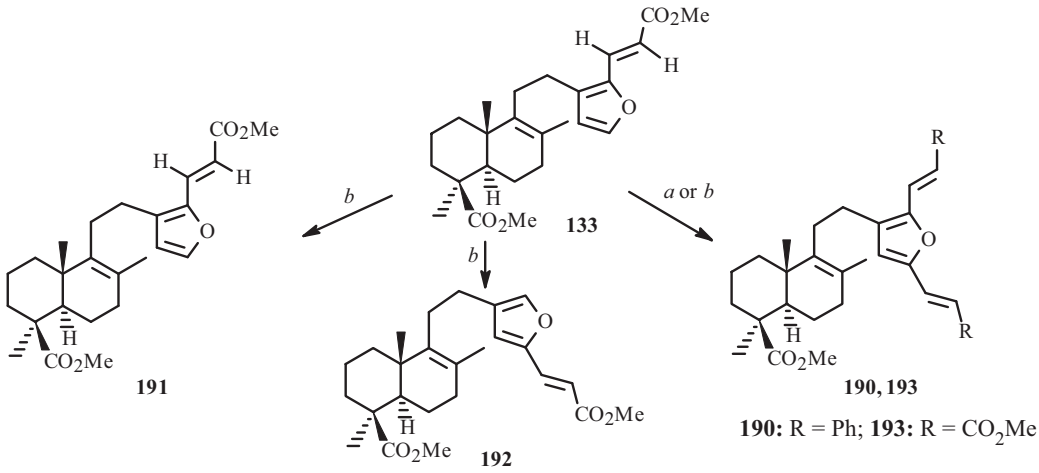
Labdanoid alkynes **184**, **185a** and **b**, and **186a** and **b** were synthesized (Scheme 25) [92, 93]. Their Cu(I)-catalyzed 1,3-dipolar cycloaddition reactions with mono- and diazides were investigated. The reaction of alkynes **185a** and **b** with benzylazide formed a mixture of diastereomeric labdatrienes **187a** and **b**. Oxidation of the stereoisomeric alcohols by Dess–Martin periodinane produced 1′-keto-derivative **188** (65% yield). Dehydration of **187a** and **b** led to *E*-triazolylvinyllabdanoid **189** (49% yield). Alkynes **184**, **185a** and **b**, and **186a** and **b** and triazolyl-substituted labdanoids were significantly cytotoxic in CEM-13, MT-4, and U-937 human tumor cell models ($CCID_{50}$ of the most active compound **188** was 7–12 μM) [93].



a. $BrCH_2C{\equiv}CH$, Zn, aq. NH_4Cl; *b*. $NaBH_4$, MeOH; *c*. $BrCH_2C{\equiv}CH$, NaH; *d*. $PhCH_2N_3$, CuI, $(i\text{-}Pr)_2NEt$, CH_3CN, 20°C; *e*. Dess-Martin periodinate, CH_2Cl_2, 20°C; *f*. MsCl, Et_3N, DMAP, EtOAc, 0°C, 1 h

Scheme 25

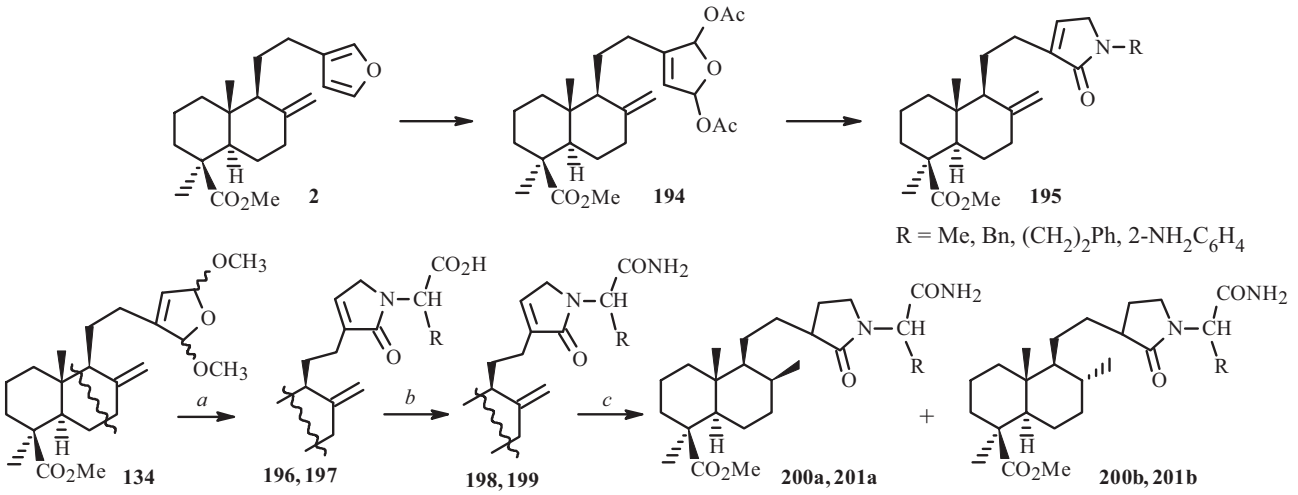
Oxidative coupling of methyl phlomisoate (**133**) with terminal olefins synthesized 16-alkenyl-substituted labdatrienes (Scheme 26) [94]. The $Pd(OAc)_2$–$Cu(OAc)_2$-catalyzed reaction of **133** with styrene in the presence of benzoquinone in a mixture of propionic acid and ether did not stop at the singly coupled products but proceeded to the formation of 15,16-distyryl-derivative **190**. The reaction time had to be increased to 80 h for complete reaction of **133** with methylacrylate. The ratio of formed products **191**, **192**, **193** changed with time. The values were 6:8:1, respectively, after 10 h; 2:1:1, after 30 h [94].



a. $C_6H_5CH{=}CH_2$; *b*. $CH_2{=}CHCO_2Me$, $Pd(OAc)_2$–$Cu(OAc)_2$, O_2, BQ, Et_2O–$CH_3CH_2CO_2H$

Scheme 26

An approach to the preparation of diterpenoid pyrrolidin-2-ones was proposed (Scheme 27) [95]. Treatment of methyl lambertianate (**2**) with lead tetraacetate gave stereoisomeric 2,5-diacetyldihydrofurans **194**, reaction of which with primary amines or *o*-phenylenediamine produced (5*H*)-pyrrol-2-ones **195**.

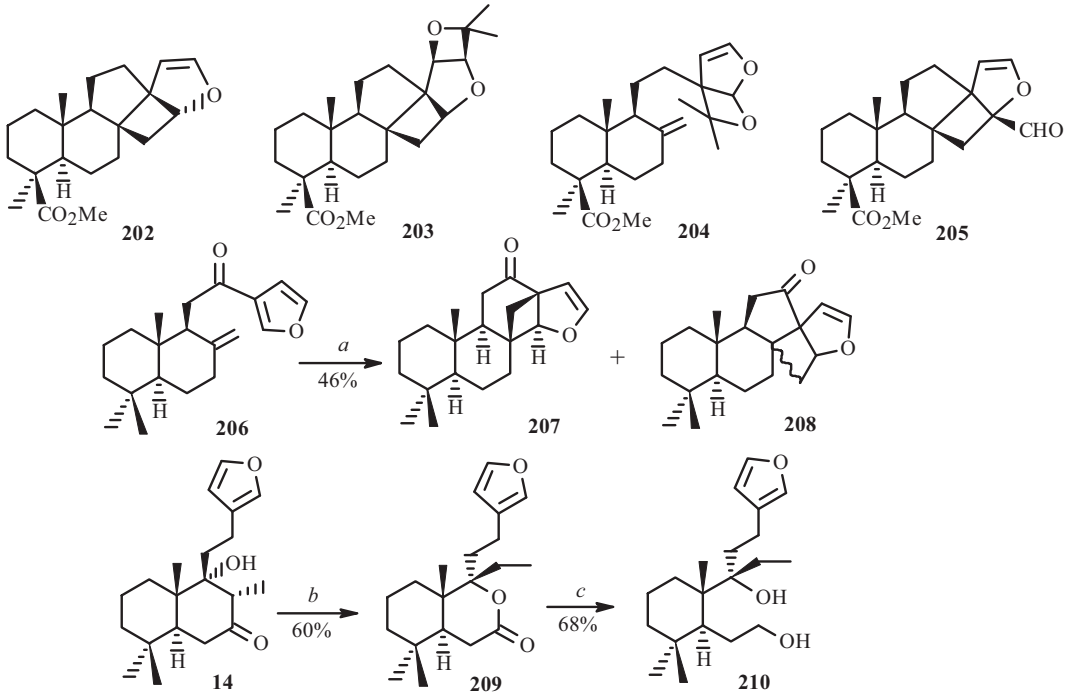


R = H (**196, 198, 200a, 200b**); Et (**197, 199, 201a, 201b**)

a. $RCH(NH_2)CO_2H$, 80% AcOH, 100°C; *b*. Me_3SiCl–MeOH, NH_3; *c*. Ni-Ra, MeOH, 20°C

Scheme 27

Diterpene analogs of levetiracetam were synthesized because of the significant interest directed at 1,3-disubstituted (5*H*)-pyrrol-2-ones as antiepileptic agents (Scheme 27) [96]. Oxidative methoxylation products **134** of methyl lambertianate were used as starting materials (Scheme 14). The reaction of **134** with glycine or α-aminobutyric acid gave labdanoid *N*-(1-carboxymethyl)- (**196**) or *N*-(1-carboxypropyl)-(5*H*)-pyrrol-5-ones (**197**), treatment of which with trimethylchlorosilane in MeOH and subsequent (without isolation) reaction with ammonia afforded corresponding amides **198** or **199** (Scheme 27). The overall yields of the terpenoid 2-(2-oxo-2,5-dihydropyrrol-1-yl)acetamides calculated for methyl lambertianate (**2**) were 48% and 42%, respectively. Hydrogenation of **198** and **199** was accompanied by reduction of the exomethylene double bond in the terpene skeleton and formed epimeric 2-(2-oxopyrrolidin-1-yl)acetamides **200a** and **b** or **201a** and **b**. Compounds **198**, **199**, and **200a** were patented as anticonvulsants [97, 98]. Analgesic activity was found for **200a** [98].



a. hν, MeCN; *b*. hν, PhH; *c*. $LiAlH_4$, THF

Scheme 28

Intramolecular photochemical [2+2]-cycloaddition involving the furan ring and the exomethylene double bond of **2** was described [99, 100]. The main reaction product was pentacyclic oxide **202**. As it turned out, the reaction was reversible. The degree of conversion of **2** depended on the solvent and varied in the order hexane < MeCN (0.4%) < C_6H_6 (10%) < Me_2CO (35%). Irradiation of **2** in Me_2CO by a high-pressure Hg lamp formed an equilibrium mixture of four compounds, i.e., oxide **202**, dioxide **203**, [2+2]-cycloaddition product of **2** to Me_2CO **204**, and starting **2** in a 1:0.8:0.7:8 ratio. Irradiation of **202** in Me_2CO gave dioxide **203**, which was a stable compound. Irradiation of methyl 16-formyllambertianate (**165**) in a mixture of hexane and Et_2O gave **205** (22.5% yield) (Scheme 28) [82].

[2+2]-Cycloaddition of furanolabdanoid **206** with a C-12 ketone formed a mixture of regioisomeric pentacyclanes **207** and **208** [101].

Photochemical transformations of hispanolone (**14**) resulted in the formation of δ-lactone **209** (60% yield) [102]. This transformation is a rare example of photochemical transformations of β-hydroxyketones into δ-lactones. The structure of **209** was proved by converting it to reduction product **210** (Scheme 28).

In conclusion, it is noteworthy that the presented information indicated that research on plant furanolabdanoids is highly promising. New sources of furanoditerpenoids are being discovered. These include woody (various *Pinus* species, plants of the species *Biota orientalis*), bushy (*Phlomis* spp., *Renealmia* spp., and *Eremostachys* spp.), and herbaceous plants [ginger, horehound, turmeric, goldenrod, galangal (*Alpinia*), and ginger lily (*Hedychium*)]

Studies of the biological activity of furanolabdanoids are expanding. Selective inhibitors of NO production (that inhibit induction of *i*NOS in macrophages activated by lipopolysaccharide), TAF antagonists, α-glucosidase inhibitors, and cytotoxic agents were found among such metabolites in the last decade.

The valuable pharmacological properties of these diterpene metabolites stimulated great interest in the development of their total syntheses. The starting materials have been primarily available diterpenoids such as sclareol, sclareolide, and larixol. Effective methods for preparing several valuable metabolites such as pinusolide, villosin, acuminolide, and hedychenone were proposed.

Modified derivatives of lambertianic acid, hedychenone, and coronarins A and E are highly interesting in the discovery of new agents with high biological activity and for solving problems of synthetic organic chemistry.

REFERENCES

1. W. G. Dauben and V. F. German, *Tetrahedron*, **22**, 679 (1966).
2. N. K. Kashtanova, A. I. Lisina, A. K. Dzizenko, and V. A. Pentegova, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, **2** (1), 126 (1967).
3. J.-M. Fang, C.-I. Lang, W.-L. Chen, and Y.-S. Cheng, *Phytochemistry*, **30**, 2793 (1991).
4. J. J. W. Coppen, L. M. Robinson, and A. N. Kaushal, *Phytochemistry*, **27**, 2873 (1988).
5. J. A. Micales, J. S. Han, J. L. Davis, and R. A. Young, in: *Biodeterioration Research. 4: Mycotoxins, Wood Decay, Plant Stress, Biocorrosion, and General Biodeterioration*, G. C. Llewellyn, W. V. Dashek, and C. E. O'Rear (eds.), Plenum Press, New York, 1994, pp. 317–332.
6. V. V. Grishko, S. A. Shevtsov, L. I. Demenkova, V. A. Raldugin, and G. B. Lyandres, *Sib. Khim. Zh.*, 94 (1991).
7. F. Bohlmann, M. Grenz, A. K. Dahr, and M. Goodman, *Phytochemistry*, **20**, 105 (1981).
8. S. Hasegawa and Y. Hirose, *Phytochemistry*, **24**, 2041 (1985).
9. J. Asili, M. Lambert, H. L. Ziegler, D. Stark, M. Sairafianpour, M. Wit, G. Asghari, I. S. Ibrahimi, and J. W. Jaroszewski, *J. Nat. Prod.*, **67**, 631 (2004).
10. K. A. Koo, S. H. Sung, and Y. C. Kim, *Chem. Pharm. Bull.*, **50**, 834 (2002).
11. H.-S. Chae and Y.-W. Chin, *Immunopharm. Immunotoxicol.*, **34**, 250 (2012).
12. B. B. Cota, D. M. de Oliveira, E. P. de Siqueira, E. M. Souza-Fagundes, A. M. C. Pimenta, D. M. Santos, A. Rabello, and C. L. Zani, *Fitoterapia*, **82**, 969 (2011).
13. T. G. Tolstikova, I. V. Sorokina, T. V. Voevoda, E. E. Shul′ts, and G. A. Tolstikov, *Dokl. Akad. Nauk*, **376**, 271 (2001).
14. T. G. Tolstikova, T. V. Voevoda, M. P. Dolgikh, and I. V. Sorokina, *Eksp. Klin. Farmakol.*, **65**, 9 (2002).
15. V. A. Raldugin, A. I. Lisina, N. K. Kashtanova, and V. A. Pentegova, *Chem. Nat. Compd.*, **6**, 559 (1970).
16. M. K. Lee, H. Yang, J. S. Yoon, E. J. Jeong, D. Y. Kim, N. R. Ha, S. H. Sung, and Y. C. Kim, *Arch. Pharm. Res.*, **31**, 866 (2008).

17. B. H. Han, H. O. Yang, Y.-H. Kang, D.-Y. Suh, H. J. Go, W.-J. Song, Y. C. Kim, and M. K. Park, *J. Med. Chem.*, **41**, 2626 (1998).
18. E. E. Shults, J. Velder, H.-G. Schmalz, S. V. Chernov, T. V. Rybalova, Y. V. Gatilov, G. Henze, G. A. Tolstikov, and A. Prokop, *Bioorg. Med. Chem. Lett.*, **16**, 4228 (2006).
19. K. A. Koo, M. K. Lee, S. H. Kim, E. J. Jeong, S. Y. Kim, T. H. Oh, and Y. C. Kim, *Br. J. Pharmacol.*, **150**, 65 (2007).
20. C. R. Smith Jr., R. V. Madrigal, D. Weisleder, K. L. Mikolajczak, and R. J. Highet, *J. Org. Chem.*, **41**, 593 (1976).
21. N. Qais, M. R. Mandal, M. A. Rashid, A. Jabbar, H. Koshino, K. Nagasawa, and T. Nakata, *J. Nat. Prod.*, **61**, 156 (1998).
22. I. B. Razmilic and G. Schmeda-Hirschmann, *Planta Med.*, 179 (1988).
23. S. C. Sharma, J. S. Tandon, H. Uprety, Y. N. Shukla, and M. M. Dhar, *Phytochemistry*, **14**, 1059 (1975).
24. P. P. Reddy, R. R. Rao, K. Rekha, K. S. Badu, J. Shashidhar, G. Shashikiran, V. V. Lakshmi, and J. M. Rao, *Bioorg. Med. Chem. Lett.*, **19**, 192 (2009).
25. S. C. Sharma, J. S. Tandon, and M. M. Dhar, *Phytochemistry*, **15**, 827 (1976).
26. H. Itokawa, H. Morita, K. Takeya, and M. Motidome, *Chem. Pharm. Bull.*, **36**, 2682 (1988).
27. P. Hon, E. S. Wang, S. K. M. Lam, Y. M. Choy, C. M. Lee, and H. N. C. Wong, *Phytochemistry*, **33**, 639 (1993).
28. G. Savona, F. Piozzi, and B. Rodriguez, *Heterocycles*, **9**, 257 (1978).
29. C. A. Gray, D. E. A. Rivett, and M. T. Davies-Coleman, *Phytochemistry*, **63**, 409 (2003).
30. P. M. Giang, P. T. Son, K. Matsunami, and H. Otsuka, *Chem. Pharm. Bull.*, **53**, 938 (2005).
31. U. Hersel, M. Steck, and K. Siefert, *Eur. J. Org. Chem.*, **8**, 1609 (2000).
32. F. Bohlmann, C. Zdero, R. K. Gupta, R. M. King, and H. Robinson, *Phytochemistry*, **19**, 2695 (1980).
33. P. P. Reddy, A. K. Tiwari, R. R. Rao, K. Madhusudhana, V. R. S. Rao, A. Z. Ali, K. S. Babu, and J. M. Rao, *Bioorg. Med. Chem. Lett.*, **19**, 2562 (2009).
34. P. P. Reddy, R. R. Rao, J. Shashidhar, B. S. Sastry, J. M. Rao, and K. S. Babu, *Bioorg. Med. Chem. Lett.*, **19**, 6078 (2009).
35. G. Suresh, P. P. Reddy, K. S. Babu, T. B. Shaik, and S. V. Kalivendi, *Bioorg. Med. Chem. Lett.*, **20**, 7544 (2010).
36. I. Kumrit, A. Suksamrarn, P. Meepawpan, S. Songsri, and N. Nuntawong, *Phytother. Res.*, **24**, 1009 (2010).
37. H. Matsuda, T. Morikawa, Y. Sakamoto, I. Toguchida, and M. Yoshikawa, *Bioorg. Med. Chem.*, **10**, 2527 (2002).
38. P. K. Chaudhuri, *Phytochemistry*, **26**, 3361 (1987).
39. D. M. Boalino, S. McLean, W. F. Reynolds, and W. F. Tinto, *J. Nat. Prod.*, **67**, 714 (2004).
40. P.-M. Hon, C.-M. Lee, H.-S. Shang, Y.-X. Cui, H. N. C. Wong, and H.-M. Chang, *Phytochemistry*, **30**, 354 (1991).
41. M. Sekiguchi, H. Shigemori, A. Ohsaki, and J. Kobayashi, *J. Nat. Prod.*, **64**, 1102 (2001).
42. H.-X. Xu, H. Dong, and K.-Y. Sim, *Phytochemistry*, **42**, 149 (1996).
43. R. Chokchaisiri, N. Chaneiam, S. Svatsi, S. Fucharoen, J. Vadolas, and A. Suksamrarn, *J. Nat. Prod.*, **73**, 724 (2010).
44. F. Abas, N. H. Lajis, K. Shaari, D. A. Israf, J. Stanslas, U. K. Yusuf, and S. M. Raof, *J. Nat. Prod.*, **68**, 1090 (2005).
45. W. Knoss and J. Zapp, *Planta Med.*, **64**, 357 (1998).
46. S. E. Bardai, N. Morel, M. Wibo, N. Fabre, G. Llabres, B. Lyoussi, and J. Quetin-Leclercq, *Phytomedicine*, **7**, 111 (2000).
47. J. D. White and P. S. Manchand, *J. Org. Chem.*, **38**, 720 (1973).
48. G. Suresh, P. P. Reddy, K. S. Babu, T. B. Shaik, and S. V. Kalivendi, *Bioorg. Med. Chem. Lett.*, **20**, 7544 (2010).
49. M. Sumimoto, *Tetrahedron*, **19**, 643 (1963).
50. M. Katagiri, K. Ohtani, R. Kasai, K. Yamasaki, C.-R. Yang, and O. Tanaka, *Phytochemistry*, **35**, 439 (1993).
51. A. Delazar, M. Moderassi, M. Shoeb, L. Nahar, R. G. Reid, Y. Kumarasamy, R. T. Majinda, and S. D. Sarker, *Nat. Prod. Res.*, **20**, 167 (2006).
52. M. Muller, J. Schroder, C. Magg, and K. Seifert, *Tetrahedron Lett.*, **39**, 4655 (1998).
53. P. Basabe, O. Bodero, I. S. Marcos, D. Diez, M. de Roman, A. Blanco, and J. G. Urones, *Tetrahedron*, **63**, 11838 (2007).
54. L. S. Marcos, L. Castaneda, P. Basabe, D. Diez, and J. G. Urones, *Tetrahedron*, **64**, 8815 (2008).
55. I. S. Marcos, A. Beneitez, L. Castaneda, R. F. Moro, P. Basabe, D. Diez, and J. G. Urones, *Synlett*, 1589 (2007).
56. I. S. Marcos, L. Castaneda, P. Basabe, D. Diez, and J. G. Urones, *Tetrahedron*, **64**, 10860 (2008).
57. S. Oh, I. H. Jeong, W.-S. Shin, and S. Lee, *Bioorg. Med. Chem. Lett.*, **13**, 2009 (2003).
58. M. Kolympadi, M. Liapis, and V. Ragoussis, *Tetrahedron*, **61**, 2003 (2005).

59. J. Boukouvalas, J.-X. Wang, and O. Marion, *Tetrahedron Lett.*, **48**, 7747 (2007).
60. I. Margaros and G. Vassilikogiannakis, *J. Org. Chem.*, **72**, 4826 (2007).
61. I. Margaros and G. Vassilikogiannakis, *J. Org. Chem.*, **73**, 2021 (2008).
62. J. Boukouvalas, J.-X. Wang, O. Marion, and B. Ndzi, *J. Org. Chem.*, **71**, 6670 (2006).
63. S. Oh, I. H. Jeong, W.-S. Shin, Q. Wang, and S. Lee, *Bioorg. Med. Chem. Lett.*, **16**, 1656 (2006).
64. P. A. Zoretic and H. Fang, *J. Org. Chem.*, **63**, 1156 (1998).
65. J. Aslaoui, H. Li, and C. Morin, *Tetrahedron Lett.*, **46**, 1713 (2005).
66. J. Villamizar, J. Fuentes, F. Salazar, E. Tropper, and R. Alonso, *J. Nat. Prod.*, **66**, 1623 (2007).
67. T. Miyake, K. Uda, M. Kinoshita, M. Fujii, and H. Akita, *Chem. Pharm. Bull.*, **56**, 398 (2008).
68. H. Akita, Y. Amano, K. Kato, and M. Kinoshita, *Tetrahedron: Asymmetry*, **15**, 725 (2004).
69. R. A. Bell and M. Fetizon, *Can. J. Chem.*, **54**, 141 (1976).
70. R. A. Bell, M. B. Gravestock, and V. Y. Taguchi, *Can. J. Chem.*, **50**, 3749 (1972).
71. P. F. Vlad and N. D. Ungur, *Chem. Nat. Compd.*, **20**, 685 (1984).
72. M. E. Mironov, Yu. V. Kharitonov, E. E. Shul′ts, M. M. Shakirov, I. Yu. Bagryanskaya, and G. A. Tolstikov, *Chem. Nat. Compd.*, **46**, 233 (2010).
73. Yu. V. Kharitonov, E. E. Shults, M. M. Shakirov, and G. A. Tolstikov, *Russ. J. Org. Chem.*, **44**, 516 (2008).
74. E. S. Wang, Y. M. Choy, and H. N. C. Wong, *Tetrahedron*, **52**, 12137 (1996).
75. L.-K. Sy and G. D. Brown, *J. Nat. Prod.*, **60**, 904 (1997).
76. H. Mohamad, N. H. Lajis, F. Abas, A. M. Ali, M. A. Sukari, H. Kikuzaki, and N. Nakatani, *J. Nat. Prod.*, **68**, 285 (2005).
77. A. W. W. van Wyk, C. A. Gray, R. A. Keyzers, D. E. A. Rivett, M. R. Caira, B. S. Nader, G. E. Davis, T. L. Werk, and M. T. Davies-Coleman, *Tetrahedron*, **61**, 8493 (2005).
78. S. V. Chernov, E. E. Shults, M. M. Shakirov, and G. A. Tolstikov, *Russ. J. Org. Chem.*, **42**, 36 (2006).
79. H. M. Chang, K.-P. Cheng, T. F. Choang, H. F. Chow, K. Y. Chui, P. M. Hon, F. W. L. Tan, Y. Yang, Z. P. Zhong, C. M. Lee, H. L. Sham, C. F. Chan, Y. X. Cu, and H. N. C. Wong, *J. Org. Chem.*, **55**, 3537 (1990).
80. S. V. Chernov, E. E. Shul′ts, M. M. Sakirov, and G. A. Tolstikov, *Russ. J. Org. Chem.*, **41**, 535 (2005).
81. S. V. Chernov, E. E. Shults, M. M. Shakirov, I. Y. Bagryanskaja, Y. V. Gatilov, and G. A. Tolstikov, *Arkivoc*, **13**, 172 (2003).
82. D. A. Klok, M. M. Shakirov, V. V. Grishko, and V. A. Raldugin, *Izv. Akad. Nauk, Ser. Khim.*, 2514 (1995).
83. M. E. Mironov, Yu. V. Kharitonov, E. E. Shul′ts, M. M. Shakirov, Yu. V. Gatilov, and G. A. Tolstikov, *Russ. J. Org. Chem.*, **46**, 1855 (2010).
84. Yu. V. Kharitonov, E. E. Shults, M. M. Shakirov, I. Yu. Bagryanskaya, and G. A. Tolstikov, *Russ. J. Org. Chem.*, **46**, 1339 (2010).
85. E. E. Shul′ts, Yu. V. Kharitonov, M. A. Pokrovskii, A. G. Pokrovskii, and G. A. Tolstikov, RU Pat. No. 2,473,550, Jan. 27, 2013; Appl. No. 2011135583/04, Aug. 25, 2011; *Byull. Izobret.*, No. 3, Jan. 27, 2013.
86. Yu. V. Kharitonov, E. E. Shul′ts, M. M. Shakirov, M. A. Pokrovsky, A. G. Pokrovsky, and G. A. Tolstikov, *Russ. J. Bioorg. Chem.*, **38**, 107 (2012).
87. S. V. Chernov, E. E. Shul′ts, M. M. Shakirov, and G. A. Tolstikov, *Russ. J. Org. Chem.*, **36**, 1493 (2000).
88. S. V. Chernov, E. E. Shults, M. M. Shakirov, and G. A. Tolstikov, *Dokl. Chem.*, **381**, 362 (2001).
89. S. V. Chernov, E. E. Shul′ts, M. M. Shakirov, and G. A. Tolstikov, *Russ. J. Org. Chem.*, **38**, 665 (2002).
90. S. V. Chernov, E. E. Shul′ts, M. M. Shakirov, and G. A. Tolstikov, *Russ. J. Org. Chem.*, **43**, 839 (2007).
91. I. V. Sorokina, T. G. Tolstikova, D. S. Baev, N. A. Zhukova, and Yu. V. Kharitonov, *Khim. Interesakh Ustoich. Razvit.*, **18**, 499 (2010).
92. Yu. V. Kharitonov, E. E. Shul′ts, M. M. Shakirov, I. Yu. Bagryanskaya, and G. A. Tolstikov, *Dokl. Chem.*, **446**, 166 (2012).
93. Yu. V. Kharitonov, E. E. Shul′ts, M. M. Shakirov, M. A. Pokrovsky, A. G. Pokrovsky, and G. A. Tolstikov, *Russ. Chem. Bull.*, 2046 (2013).
94. Yu. V. Kharitonov, E. E. Shul′ts, M. M. Shakirov, and G. A. Tolstikov, *Russ. J. Org. Chem.*, **36**, 602 (2011).
95. S. V. Chernov, E. E. Shul′ts, M. M. Shakirov, and G. A. Tolstikov, *Russ. J. Org. Chem.*, **42**, 828 (2006).
96. B. M. Kenda, A. C. Matagne, P. E. Talaga, P. M. Pasau, E. Differding, B. I. Lallemand, A. M. Frycia, F. G. Moureau, H. V. Klitgaard, M. R. Gillard, B. Fuks, and P. Michel, *J. Med. Chem.*, **47**, 530 (2004).

97. E. E. Shul′ts, S. V. Chernov, T. G. Tolstikova, M. P. Dolgikh, A. V. Bolkunov, and G. A. Tolstikov, RU Pat. No. 2,385,863 (2010), Apr. 10, 2010; Appl. No. 2008115710/04 (017643); *Byull. Izobret.*, No. 10, Apr. 10, 2010; http://www.freepatent.ru/patents/2385863.
98. S. V. Chernov, E. E. Shul′ts, T. G. Tolstikova, M. P. Dolgikh, A. V. Bolkunov, and G. A. Tolstikov, RU Pat. No. 2,385,864 (2010), Apr. 10, 2010; Appl. No. 2008115766/04; *Byull. Izobret.*, No. 10, Apr. 10, 2010; http://www.freepatent.ru/patents/2385864.
99. V. A. Raldugin, V. V. Grishko, Yu. V. Gatilov, M. M. Shakirov, I. Yu. Bagryanskaya, and L. I. Demenkova, *Sib. Khim. Zh.*, 66 (1992).
100. V. A. Raldugin, V. V. Grishko, I. Yu. Bagryanskaya, Yu. V. Gatilov, and M. M. Shakirov, *Sib. Khim. Zh.*, 69 (1993).
101. M. C. de la Torre, I. Garcia, and M. A. Sierra, *J. Org. Chem.*, **68**, 6611 (2003).
102. G. Fontana, G. Savona, N. Vivona, and B. Rodriguez, *Eur. J. Org. Chem.*, 2011 (1999).