Molecules **2012**, *17*, 1448-1467; doi:10.3390/molecules17021448

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Review

Communic Acids: Occurrence, Properties and Use as Chirons for the Synthesis of Bioactive Compounds

Alejandro F. Barrero [1,*], M. Mar Herrador [1,*], Pilar Arteaga [1], Jesús F. Arteaga [2] and Alejandro F. Arteaga [3]

[1] Departamento de Química Orgánica, Facultad de Ciencias, Instituto de Biotecnología, Universidad de Granada, Campus de Fuente Nueva, s/n. 18071 Granada, Spain; E-Mail: arteagaburon_pilar@hotmail.com

[2] Departamento de Ingeniería Química, Química Fisíca y Químíca Orgánica, Facultad de Ciencias Experimentales, Universidad de Huelva, Campus el Carmen, s/n, 21071, Huelva, Spain; E-Mail: jesus.fernandez@diq.uhu.es

[3] Departamento de Ingeniería Química, Facultad de Ciencias, Universidad de Granada, Campus de Fuente Nueva, s/n. 18071 Granada, Spain; E-Mail: jandro@ugr.es

* Authors to whom correspondence should be addressed; E-Mails: afbarre@ugr.es (A.F.B.); mmar@ugr.es (M.M.H.); Tel.: +34-958-243-318; Fax: +34-958-243-318.

Received: 25 November 2011; in revised form: 31 January 2012 / Accepted: 31 January 2012 / Published: 6 February 2012

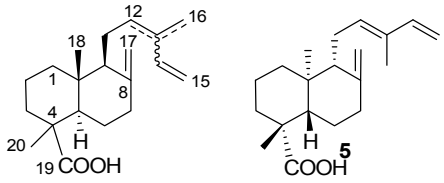
Abstract: Communic acids are diterpenes with labdane skeletons found in many plant species, mainly conifers, predominating in the genus *Juniperus* (fam. *Cupresaceae*). In this review we briefly describe their distribution and different biological activities (anti- bacterial, antitumoral, hypolipidemic, relaxing smooth muscle, *etc.*). This paper also includes a detailed explanation of their use as chiral building blocks for the synthesis of bioactive natural products. Among other uses, communic acids have proven useful as chirons for the synthesis of quassinoids (formal), abietane antioxidants, ambrox and other perfume fixatives, podolactone herbicides, *etc.*, featuring shorter and more efficient processes.

Keywords: communic acids; labdanes; bioactivity; synthesis; chirons

1. Introduction

Communic acids are a group of diterpenic natural products [1–4] with a labdane skeleton containing three double bonds and a carboxyl group at position 19 (Figure 1). Five communic acids have been described to date that differ in the location of the double bonds and the orientation of the carboxyl group: *trans*-communic acid (**1**) with the double bonds located in positions 8(17), 12 and 14, with Δ^{12} double bond *E* stereochemistry, and axial carboxyl group orientation, *cis*-communic acid (**2**) the *Z* isomer of the former, *mirceo*communic acid (**3**), also named *iso*communic acid, regioisomer of the former, where the Δ^{12} double bond moves to $\Delta^{13(16)}$, 4-*epi*-*trans*-communic acid (**4**), a C4 epimer of **1** and *ent*-*trans*-communic acid (**5**) is the (−) enantiomer of **1**. Of these, the most abundant in Nature is **1**.

Figure 1. Structure of the communic acids.



1 $E\Delta^{12}$ βCOOH
2 $Z\Delta^{12}$ βCOOH
3 $\Delta^{13(16)}$ βCOOH
4 $E\Delta^{12}$ αCOOH

2. Sources

Communic acids are widely distributed in *Cupresaceae* species, especially in the genus *Juniperus*. Although there are species that contain several of them, the most common case is the presence of only one. A tertiary mixture of **1**–**3** is found in *Juniperus nana* Willd. [5], *J. communis* [6] and *J. oxycedrus* [7]. A binary mixture of **1**–**2** is found in *J. chinensis* Linn [8–10], *J. phoenicea* [11], *J. thurifera* var. *africana* [11], *J. foetidissima* [12], *J. sabina* [13], *Cryptomeria japonica* [14], *Platycladus orientalis* [15], *Sabina vulgaris* [16], *Podocarups imbricatus* BI [17], *Agathis vitiensis*, *A. macrophylla* and *A. lanceolata* [18], *Thuja occidentalis* L. [19], and *Hermas villosa* [20] whereas a mixture of **3**–**4** is found in *J. excelsa* [21]. *Trans*-communic acid (**1**) was isolated from *Entada abyssinica* [22], *Thujopsis dolabrata* [23–25], *Pinus luchuensis* [26], *Chamaecyparis obtusa* Endl. [27–29], *Thuja standishii* [30,31], *Araucaria angustifolia* [32], *Chamaecyparis formosensis* [33], *Porella navicularis* [34], *J. oxycedrus* [35], *J. drupaceae* Labill [36], *Sciadopitys verticillata* [37], *Fritillaria thunbergii* [38], *Cunninghamia unicanaliculata* var. *pyramidalis* [39], *Chromolaena collina* [40], *Cupressus sempervirens* [41,42], *J. communis* [43], *Chloranthus spicatus* [44], *Sabina vulgaris* Antoine [45], *Torreya jackii* [46], *Dacrydium pierrei* [47], *J. phoenicea* [48], *Calocedrus formosana* [49], *Fleischmannia multinervis* [50], *Cretan propolis* [51], *Libocedrus chevalieri* [52], *Pinus densiflora* [53], and *Mikania aff. jeffreyi* [54], *Chamaecyparis lawsoniana* [55]. *Cis*-communic acid (**2**) was detected in *Larix dahurica* [56], *Pseudotsuga wilsoniana* [57], and *Cladonia rangiferina* L. Web. [58].

*Myrceo*communic acid (**3**) was isolated from *Juniperus oxycedrus* [59]. Moreover the main component of diterpene acids in *Cunninghamia lanceolata* (Lamb.) Hook was 4-*epi*-*trans*-communic acid (**5**) [60]. Additionally polymers of **1** and of their derivatives have been found in resins of different *Agathis* species [61,62] and in sandarac resin [63].

Although these acids have been isolated from different parts of the plant (fruits, wood, bark, leaves, roots, *etc.*), they are mainly founded in leaves, fruits, and bark.

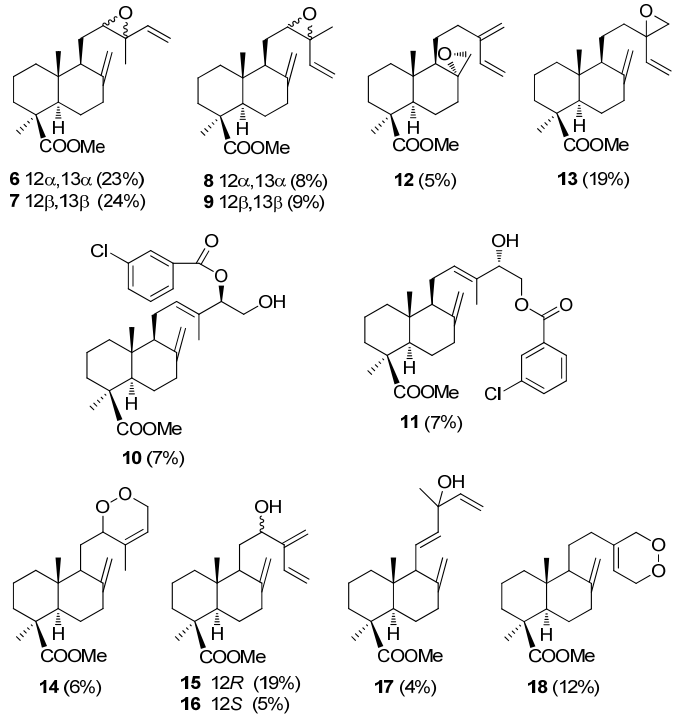
3. Biological Activity

The three communic acids **1**–**3** exhibited strong cytotoxic activity in a brine shrimp bioassay (LD_{50} 0.16 μg/mL) [46]. *Trans*-communic acid (**1**) and *cis*-communic acid (**2**) and plant extracts containing them were also active against different microorganisms such as *Staphylococcus aureus*, both standard ATCC strain and clinical isolates [55,64–69], *S. epidermidis* ATCC 12228 [70], *Aspergillus fumigatus* and *Candida albicans* [62]. Moreover, both acids have shown cytotoxic activity against BSC-1 cells [71]. Other activities described for **1** are: antimycobacterial (*Mycobacterium aurum*, *M. phlei*, *M. fortuitum* and *M. smegmatis*) [72], antitumoral [35,73], relaxant [74], hypolipidemic [75], testosterone 5α-reductase inhibitory [76], anti-inflammatory and antioxidant [77].

4. Chemical Reactivity

Years ago, Pascual-Teresa *et al.* [78,79] described two studies based on the oxidation of the lateral chain of methyl esters of communic acids **1a**–**3a**. First, the functionalization of the side chain by selective epoxidation [78], and later the singlet oxygen addition [79] was studied. In both cases the relative reactivity of the three double bonds was determined for each compound. Epoxidation of **1a** and **2a** with *m*-chloroperbenzoic acid mainly afforded a mixture of 12,13-epopxy derivatives **6**–**9** together with a mixture of 14- and 15-*m*-chlorobenzoates **10**–**11** (Figure 2). The epoxidation of **3a** with *m*CPBA gave methyl (8*R*)-8,17-epoxy-8,17-dihydro*mirceo*communate (**12**, 5%) and methyl 13,16-epoxy-13,16-dihydro*mirceo*communate (**13**, 19%), recovering 24% yield of **3a**. This result indicates greater reactivity at the trisubstituted double bond for **1a** and **2a** and terminal double bond on the side chain for **3a**.

Figure 2. Structures of the products obtained by epoxidation and singlet oxygen oxidation of **1a**–**3a**.

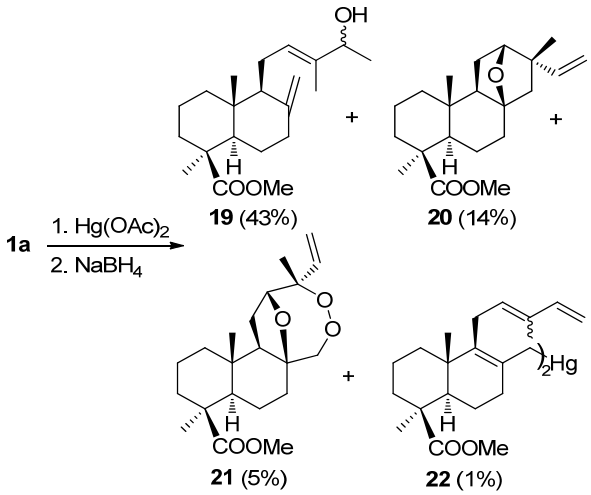


The singlet oxygen addition to **1a** led principally to the 12-hydroxyderivatives 12*R* (**15**, 19%) and 12*S* (**16**, 5%) together with minor proportions of the 12,15-dioxyderivative **14** (6%) and the tertiary alcohol **17** (4%), whereas in the case of **3a** afforded the only the 15,16-dioxyderivative **18** (12%).

Compound **1a** preferably underwent *ene*-reactions of the singlet oxygen on the trisubstituted double bond with *syn* stereospecificity, in accordance the with point established by Schulte-Elte [80]. Thus, the reaction produced mainly alcohols **15**–**17** and a minor proportion of the 12,15-dioxyderivative **14**, coming from a Diels-Alder reaction. In the case of methyl isocommunate **3a**, which does not have trisubstituted double bond and where the monosubstituted dienic system adopts the cisoid conformation with relative ease, the reaction that takes place with singlet oxygen is the Diels-Alder cycloaddition, slowly yielding a small amount of 15,16-dioxyderivative **18** due to the tendency of **3a** to polymerize.

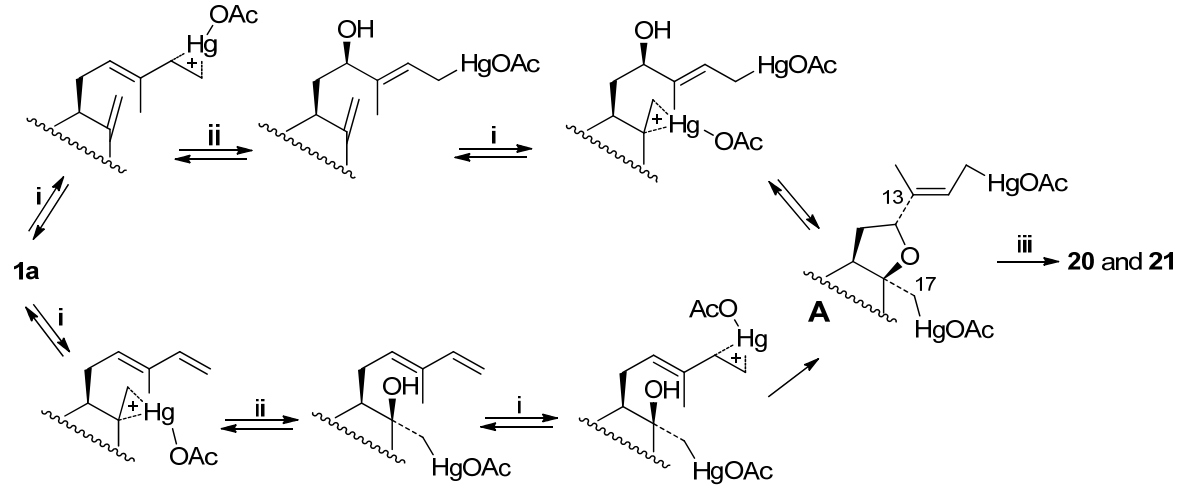
Furthermore, another oxygenation procedure, *i.e.*, the oxymercuration-demercuration (OM-DM) reaction of methyl esters of *trans*- and *cis*-communic acids (**1a**–**2a**) was studied [81–83]. Treatment of **1a** with mercuric acetate (1:2) in THF/H_2O and the subsequent reduction of mercurials with $NaBH_4$ afforded compounds **19**–**22** (Scheme 1).

Scheme 1. OM-OD reaction for compound **1a**. OD reaction with $NaBH_4$.



Compound **19** is the product corresponding to the OM-DM at C14-C15 double bond. The formation mechanism of compounds **20**, **21** is shown in Scheme 2. The formation of tetrahydrofuran derivatives **20**–**21** from **1a** can be explained by two routes, both converging at intermediate **A** and evolving to **20**, **21** via radical processes. In the first route, **A** results from the formation of mercurinium ion on the 14,15 double bond, followed by 1,4 addition of water at C12, and heterocyclization by attack of the hydroxy group on the other mercurinium ion formed on the 8,17 double bond. In a second possible route, **A** is obtained by the hydration of the 8,17 double bond on the β face, followed by attack of the hydroxy group on carbon C12 on the mercurinium ion of the monosubstituted double bond. Both routes converge at the organomercurial **A**, whose reduction with $NaBH_4$ in basic medium leads to the formation of a bis-radical intermediate, that by direct cyclization between carbons C13 and C17 originates **20**, and by reaction with atmospheric oxygen leads to **21**.

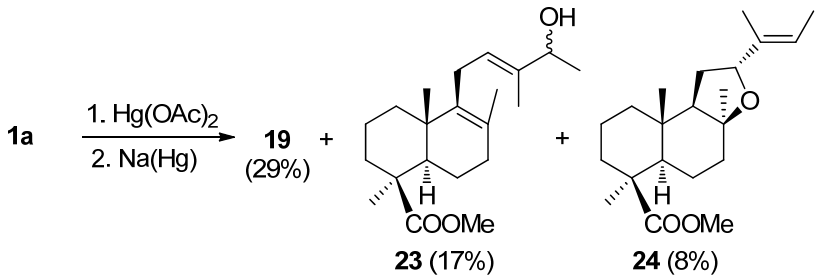
Scheme 2. Mechanism of formation of compounds **20**, **21**.



Reagents and conditions: (i) $Hg(OAc)_2$; (ii) H_2O; (iii) $NaBH_4$.

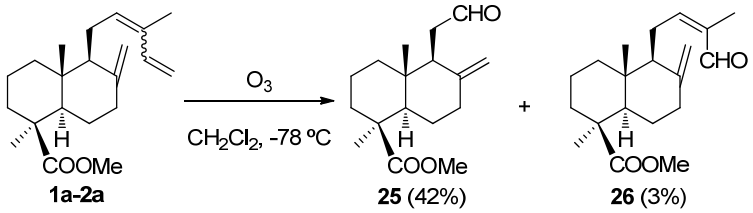
When the OM-OD reaction of compound **1a** was carried out using Na(Hg) as the demercuriating agent (Scheme 3), the products obtained were **19**, **23**–**24** and there was no evidence of the formation of either pimarane **20** or endoperoxide **21**. That is due to the fast reduction of the intermediate radicals coming from the corresponding type A organomercurials by sodium amalgam (Scheme 3).

Scheme 3. OM-OD reaction for compound **1a**. OD reaction with Na(Hg).



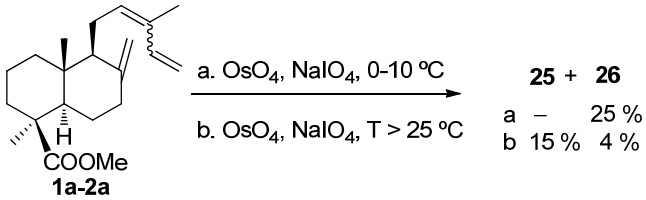
Another interesting reaction from the synthetic point of view is the oxidative degradation of the C12,C13 double bond of either *cis*-, *trans*-communic acids or their methyl esters. This transformation opens the possibility of using them in the preparation of bioactive molecules. In order to find appropriate experimental conditions for regioselective oxidative cleavage of the C12,C13 double bond in presence of the 8(17) and 14,15 ones, two methods of double bond cleavage were tried on **1a**–**2a**: Ozonolysis and $OsO_4/NaIO_4$ treatment [84,85]. First, ozonolysis of **1a** was performed under different conditions, such as type of solvent (hexane, methanol, CH_2Cl_2), temperature (room temperature, 0 °C, −78 °C) and different ozone stream flows. Better selectivity towards the C12,C13 double bond degradation was observed when the reaction was carried out at −78 °C in CH_2Cl_2 yielding aldehyde-esters **25** and **26** (Scheme 4). The ozonolysis of isomer **2a** under the same conditions also led to preferential attack on the C12,C13 double bond giving rise to the same products (Scheme 4).

Scheme 4. Ozonolysis of **1a**–**2a**.



The outcome of the reaction of **1a**–**2a** with $OsO_4/NaIO_4$ is, however, strongly dependent on experimental conditions. Thus, when the temperature was kept at 0 °C to 10 °C, only **26** was detected, whereas mixtures of **25** and **26** were isolated when the temperature was 25 °C or higher (Scheme 5).

Scheme 5. Oxidation of **1a**–**2a** with $OsO_4/NaIO_4$.

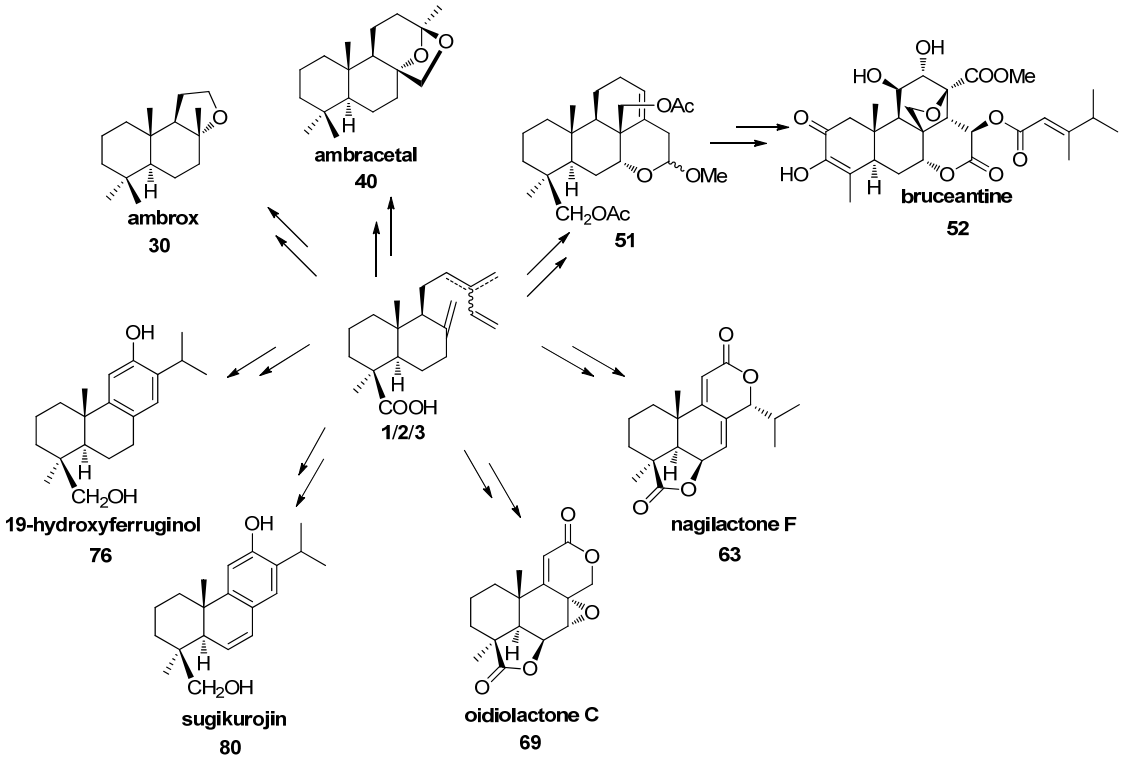


5. Use of Communic Acids as Starting Materials for the Synthesis of Compounds of High Added Value

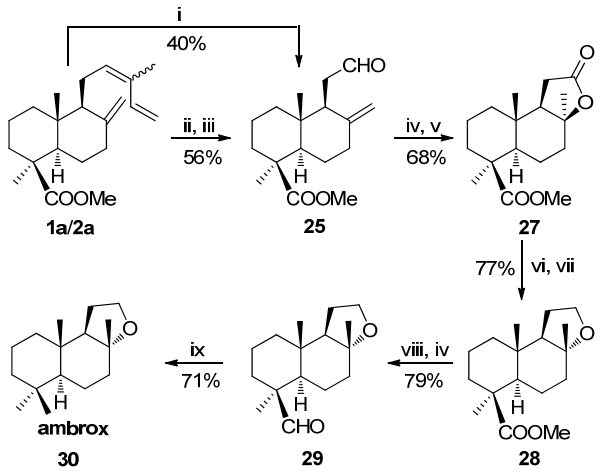
Communic acids **1**–**3** possess a labdane diterpene structure functionalised with a carboxylic group at C19, an exocyclic methylene at C8,C17 and a side chain dienic system appropriate for the preparation of a great variety of bioactive terpenoids, such as perfume fixatives [ambrox (**30**) and ambracetal (**40**)], antitumoral quassinoids [bruceantin (**52**)], antifungal podolactones [nagilactone F (**63**) and oidiolactone C (**69**)], and abietanes [19-hydroxyferruginol (**76**) a target for tolerance after transplant and in autoimmune diseases], and sugikurojin (**80**)] (Scheme 6).

Ambrox (**30**) and ambracetal (**40**) are perfume fixatives with a powerful amber-type aroma. Their syntheses were carried out alternatively from methyl *trans*-communate (**1a**) or methyl *cis*-communate (**2a**) or a mixture of the two [86,87]. Two different routes to ambrox from **1a**/**2a** are showed in Schemes 7 and 8. The key steps of these syntheses are selective degradation of the side chains, stereoselective formation of the tetrahydrofuran ring and reduction of the axial methoxycarbonyl group. In the first synthesis the transformation of **1a** and/or **2a** to aldehyde **25** was done using two different methods: (a) carefully controlled ozonolysis of **1a** and/or **2a** at low temperature or (b) Δ^{14} selective hydrogenation with diimide, followed by a C12–C13 degradation of the resulting 14,15-hydrogenated derivative with $OsO_4/NaIO_4$. Oxidation of **25** with Jones reagent followed of cyclization with *p*-TsOH in toluene at reflux stereoselectively yielded the γ-lactone **27** with the most stable *cis* interannular linkage. Its reduction with $LiAlH_4$ followed by kinetically controlled cyclization with *p*-$TsOH/CH_3NO_2$ at room temperature gave the tetrahydrofurane derivative **28** with the suitable *trans* stereochemistry. The conversion of the hindered methoxycarbonyl group into the methyl group was carried out in three steps by reduction of ester **28**, oxidation of the resulting alcohol to aldehyde **33** and finally reduction under Huang-Minlon conditions led to the target **30** (Scheme 7).

Scheme 6. Compounds synthesized from communic acids **1**–**3**.



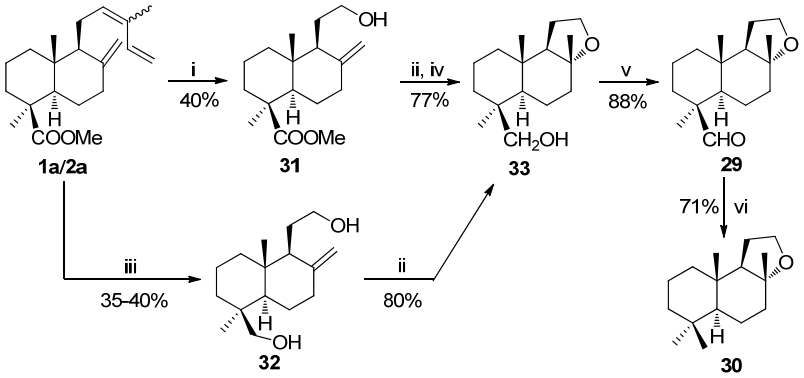
Scheme 7. Synthesis of ambrox **30**.



Reagents and conditions: (i) O_3, CH_2Cl_2, −78 °C, Me_2S; (ii) $N_2H_4{\cdot}H_2O$, EtOH, 30% H_2O_2, 0 °C; (iii) $NaIO_4$, 0.2% OsO_4, *t*-BuOH, H_2O, r.t., 60 h; (iv) Jones reagent, acetone, 0 °C; (v) *p*-TsOH, toluene, reflux, 1 h; (vi) $LiAlH_4$, THF, r.t., 1 h; (vii) *p*-TsOH, CH_3NO_2, r.t., 3 h; (viii) $LiAlH_4$, THF, reflux, 1.5 h; (ix) $N_2H_4{\cdot}H_2O$, KOH, triethyleneglycol, reflux, 1 h.

In the second route hydroxyolefin **31**, obtained by reductive ozonolysis from **1a**/**2a**, was treated with *p*-TsOH in CH_3NO_2 at room temperature and subsequently with $LiAlH_4$ to give the alcohol **33**. Oxidation of **33** with Jones reagent led to the aldehyde **29** whose reduction under Huang Minlon conditions yielded ambrox (**30**). This route was improved and shortened by direct conversion of **1a**/**2a** into diol **32** by reductive ozonolysis followed of cyclization with *p*-TsOH in CH_3NO_2 to yield the alcohol **33** (Scheme 8).

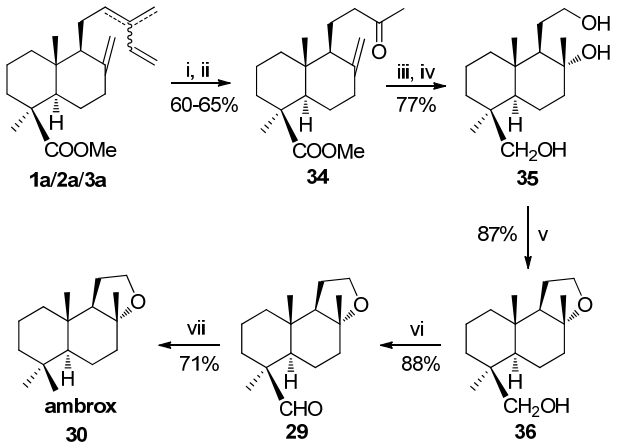
Scheme 8. Synthesis of ambrox.



Reagents and conditions: (i) O_3, CH_2Cl_2, −78 °C; $LiAlH_4$, THF, r.t.; (ii) *p*-TsOH, CH_3NO_2, r.t., 1–1.2 h; (iii) O_3, CH_2Cl_2, −78 °C; $LiAlH_4$, THF, reflux; (iv) $LiAlH_4$, THF, r.t., 1 h; (v) Jones reagent, acetone, 0 °C; (vi) $N_2H_4{\cdot}H_2O$, KOH, triethyleneglycol, reflux, 1 h.

Mixtures of **1–3** from *Juniperus communis* fruits are of great interest because they are byproducts of gin manufacturing. Schemes 8 and 9 show the syntheses of ambrox and ambracetal from a mixture of methyl esters of **1**–**3**. The key intermediate in both processes is methyl ketone **34**. This compound was obtained efficiently by a chemoselective reduction of the dienic system of a mixture of **1a**–**3a** with Na/*t*-BuOH at room temperature and subsequent oxidation with $OsO_4/NaIO_4$. The transformation of **34** to trihydroxy derivative **35** was carried out by stereoselective epoxidation with *m*-CPBA at room temperature followed by reduction with $LiAlH_4$ in THF at reflux. Stereo-selective cyclization of **35** with *p*-TsOH/CH_3NO_2 at room temperature led to **36**, which was transformed in ambrox **30** following the experimental procedure outlined in Scheme 7.

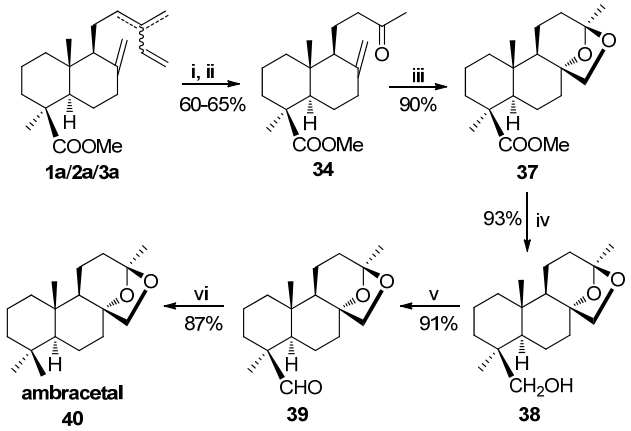
Scheme 9. Synthesis of ambrox.



Reagents and conditions: (i) *t*-BuOH, Na, r.t., overnight; (ii) $NaIO_4$, 0.2% OsO_4, *t*-BuOH, H_2O, r.t., 150 h; (iii) MCPBA, CH_2Cl_2, r.t., 5 days; (iv) $LiAlH_4$, THF, r.t., 1 h; (v) *p*-TsOH, CH_3NO_2, r.t., 1 h; (vi) Jones reagent, acetone, 0 °C; (vii) $N_2H_4{\cdot}H_2O$, KOH, triethyleneglycol, reflux, 1 h.

For ambracetal (**40**) synthesis, treatment of methyl ketone **34** with a catalytic amount of OsO_4 in a refluxing mixture of *t*-BuOH/pyridine/H_2O and trimethylamine oxide as co-oxidant, afforded the tetracyclic ester **37** (Scheme 10). Conversion of the methoxycarbonyl group into the methyl group was carried out as shown in Scheme 6.

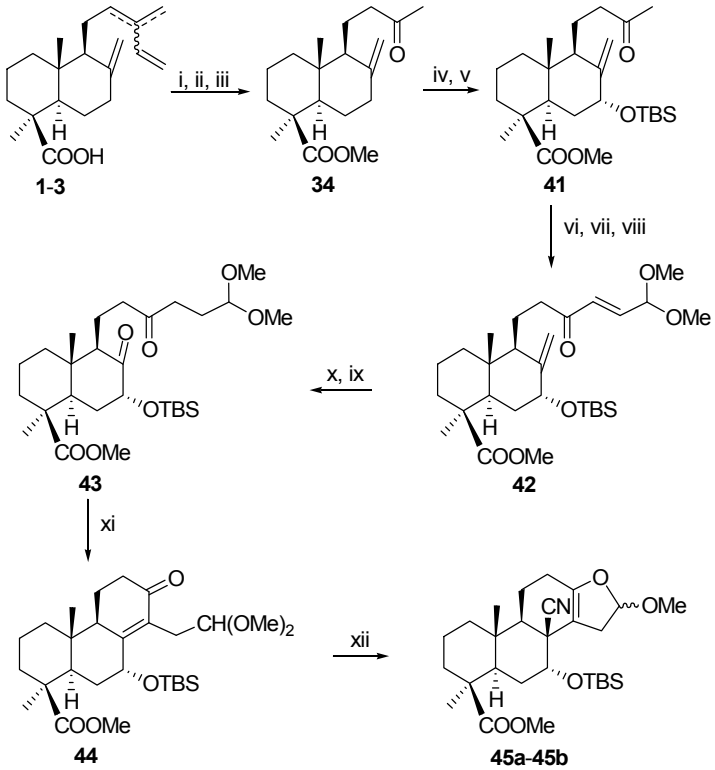
Scheme 10. Synthesis of ambracetal.



Reagents and conditions: (i) *t*-BuOH, Na, r.t., overnight; (ii) $NaIO_4$, 0.2% OsO_4, H_2O, *t*-BuOH, r.t., 150 h; (iii) Cat. 0.2% OsO_4, $Me_3NO{\cdot}H_2O$, *t*-BuOH, pyridine, H_2O, reflux, 24 h; (iv) $LiAlH_4$, THF, reflux, 1 h; (v) Jones reagent, acetone, 0 °C; (vi) $N_2H_4{\cdot}H_2O$, triethyleneglycol, reflux, 3 h.

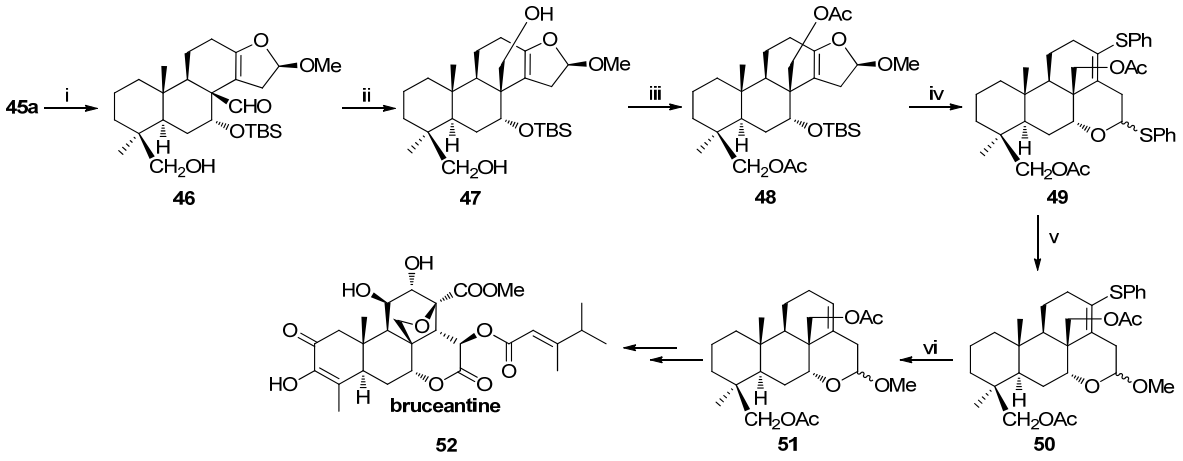
An approach to compound **51**, an intermediate in the synthesis of the antitumor agent bruceantin (**52**) has been developed from the communic acids **1**–**3** (Schemes 11 and 12) [88] *via* the methyl ketone **34**.

Scheme 11. Synthesis of the tetracyclic intermediate **45**.



Reagents and conditions: (i) CH_2N_2, Et_2O, 0 °C; (ii) Na, *t*-BuOH, Na, 60 °C, 18 h, 85%; (iii) OsO_4, 0.2% $NaIO_4$, *t*-BuOH-H_2O, r.t., 5 days; Jones, acetone, r.t., EtO_2/ac. Na_2CO_3; (iv) SeO_2, EtOH, 60 °C, 12 h 66%; (v) TBSCl, imidazole, DMF, r.t., 14 h, 94%; (vi) LDA, −78 °C, glyoxaldimethylacetal, THF, 30 min, 95%; (vii) MsCl, Py. r.t., 2.5 h, 94%; (viii) DBU, benzene, r.t., 3 h, 92%; (ix) Raney Ni, THF, r.t., 30 min, 94%; (x) O_3, CH_2Cl_2, −78 °C, 15 min, Ph_3P, r.t. 4 h, 91%; (xi) MeONa/MeOH, reflux, 11 h, 91%; (xii) KCN, Et_2AlCN, 18-crown-6 ether, toluene, 0 °C ~r.t., 20 h, 87%.

Scheme 12. Synthesis of the intermediate **51** (precursor of bruceantin **52**).



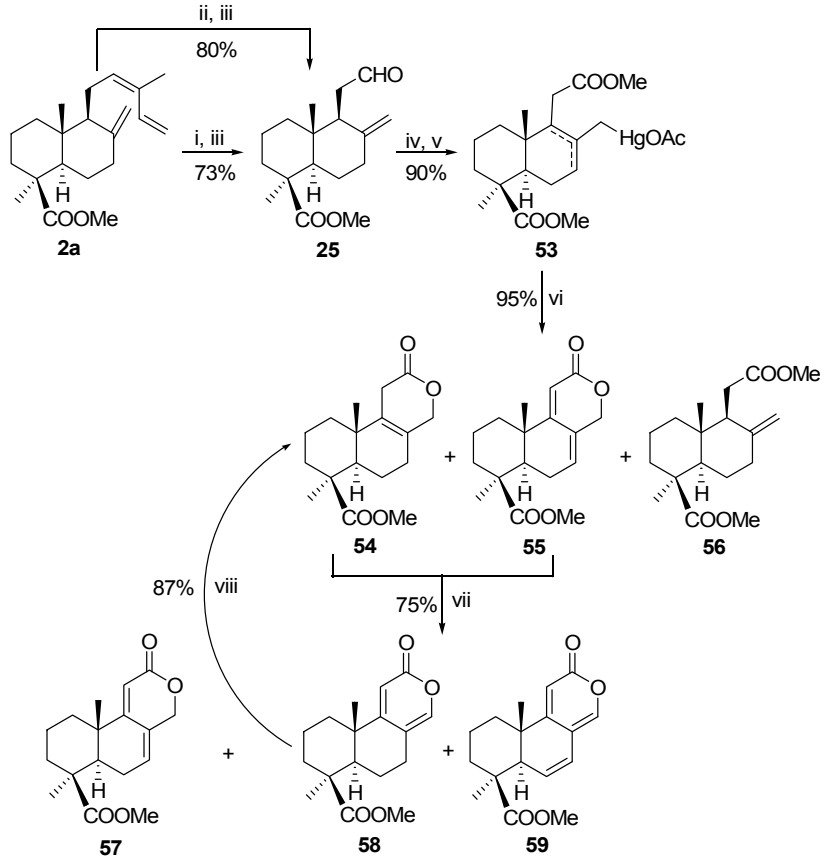
Reagents and conditions: (i) DIBAL, THF, r.t., 3.5 h; (ii) $NaBH_4$, EtOH, r.t., 45 min, 93%; (iii) Ac_2O, Py., r.t., 4 h, 95%; (iv) PhSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, r.t., 5 h; (v) $HgCl_2$, HgO, CH_3CN-MeOH, r.t., 14 h, 82%; (vi) $NaBH_4$, $NiCl_2$, THF, reflux, 12 h, 63%.

Allylic oxidation of **34** at C7 with SeO_2 at 60 °C and subsequent protection of the alcohol obtained with TBSCl yielded keto-ester **37** with high stereoselectivity. Subsequent condensation of the kinetic enolate of **41** with glyoxal dimethylacetal followed by mesylation and elimination with DBU led to the α,β-unsaturated ketone **42**. Chemoselective reduction of **42** with Raney nickel and subsequent ozonolysis afforded diketone **43**. At this point, an intramolecular aldol condensation gave the tricyclic ketone **44**, whose hydrocyanation with potassium cyanide, diethylaluminium cyanide and 18-crown-6 ether led with high stereoselectivity to an epimer mixture of acetals (**45a**–**b**) (6:1) (Scheme 11). Isomer **45a** was used to complete the synthetic sequence (Scheme 11). Thus, reduction of **45a**, first with DIBAL and then with $NaBH_4$ afforded the diol **47**, which was acetylated yielding **48**. Exposure of **48** to thiophenol and boron trifluoride etherate in CH_2Cl_2 at room temperature yielded thioacetal **49**. This compound was obtained as an epimeric mixture and the thioether groups were sequentially removed with mercury (II) chloride and mercury oxide in acetonitrile/methanol (1:1) at room temperature. Compound **51** was finally obtained as an epimer mixture after reductive desulfurization of **50** using nickel boride (Scheme 12).

Podolactones are nor-or bisnorditerpenic compounds isolated mainly from different plants of the genus *Podocarpus* (family *Podocarpaceae*) [89], and filamentous fungi (*Oidodendrum truncatum* [90], *Aspergillus wentii* [91], and *Acrostalamus sp*. [92]). These molecules present a wide range of biological activity, including antitumoral, insecticidal, antifeedant, allelopathic, and fungicidal activities, special attention being paid to their the antifungal activity. In this regard, LL-Z1271α (**62**) and oidolactone C (**69**) exhibited potent antifungal activities [93,94].

Considering their interesting properties, the podolactones nagilactone F (**63**) and LL-Z1271α (**62**) have been synthesized from a mixture of **1**, **2** (Schemes 13 and 14) [95]. Now the key steps are a δ-lactonization in order to form the C ring, γ-lactonization and finally 14-hydroxylation.

Scheme 13. Synthesis of nagilactone F, LL-Z1271γ and LL-Z1271α.



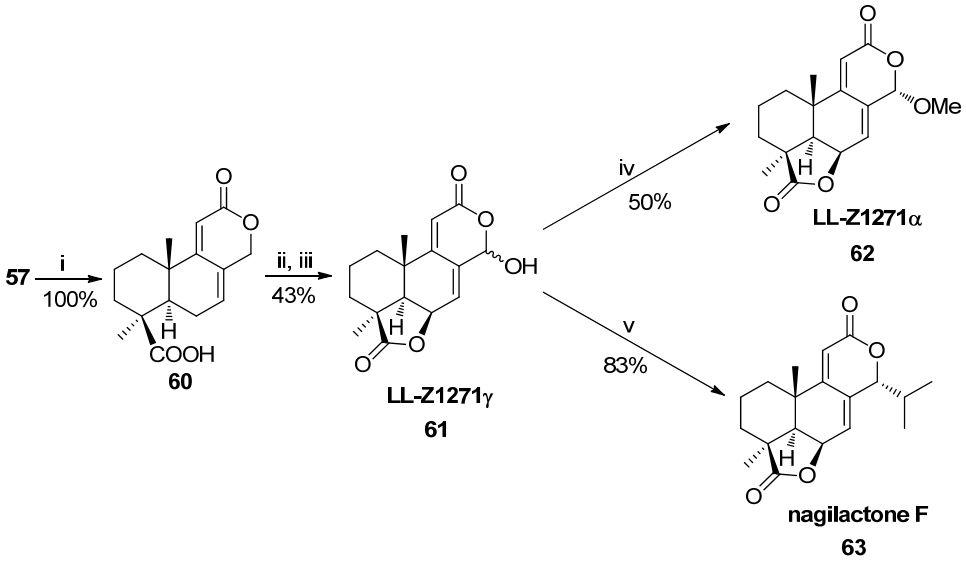
Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, $NaHCO_3$, −10~0 °C, 5H; (ii) $KMnO_4$, EtOH; (iii) HIO_4, THF, r.t., 30 min; (iv) 1. Jones, acetone, 0 °C, 30 min; 2. CH_2Cl_2, Et_2O, r.t.; (v) $Hg(OAc)_2$, toluene, reflux, 1 h; (vi) $NaBH_4$, O_2, DMF, r.t., 3 h; (vii) DDQ, PTSA, dioxane, reflux, 3 h; (viii) $NaBH_4$, NaOH, THF, reflux, 3 h.

The synthesis begins with the degradation of the side chain of the acids **1**,**2** by a different procedure to those previously described. Thus, oxidation with *m*-CPBA of the starting material and subsequent treatment of the crude product with HIO_4 led to the aldehyde **25** with good yield (73%). Compound **25** was better obtained by potassium permanganate oxidation and subsequent periodic degradation (80%). Oxidation of **25** to a carboxylic acid and esterification with CH_2N_2 followed by treatment with mercuric acetate (2.0 equiv.) in toluene at reflux gave the derivative **53** as an 8:1 mixture (Δ^8:Δ^7). This mixture was reduced with $NaBH_4$/DMF in the presence of an excess of bubbling O_2, producing lactone **54** (75%), dienolide **55** (15%) and the starting product **56** (5%). This mixture was dehydrogenated with DDQ and PTSA to give an 8:3:1 mixture of **57**–**59**.

The methyl ester **57** was hydrolyzed almost quantitatively with concentrated sulphuric acid to obtain the acid **60**. The treatment of **60** with lead tetraacetate under argon atmosphere and ten with SeO_2 led to the δ-hydroxylactone **61** permitting firstly γ-lactone closure and subsequently allylic oxidation at C14. Then the antibiotic LL-Z1271α (**62**) was prepared by treatment of **61** with methanol acidified with a drop of sulphuric acid. Moreover, treatment of **61** with isopropylmagnesium bromide at 0 °C yielded 83% of condensation products, being the most of the α isomer (90%), nagilactone F (**63**).

Related with the above-mentioned podolactone syntheses, the first synthesis of the antifungal oidiolactone C (**69**) was carried out from *trans*-communic acid (**1**) (Scheme 14) [96,97]. The key step of the synthesis is a new bislactonization reaction catalyzed by Pd(II), giving rise to the podolactone-type tetracyclic skeleton from a norlabdadienedioic acid. This synthetic scheme was also used by the authors to improve podolactone LL-Z1271α synthesis.

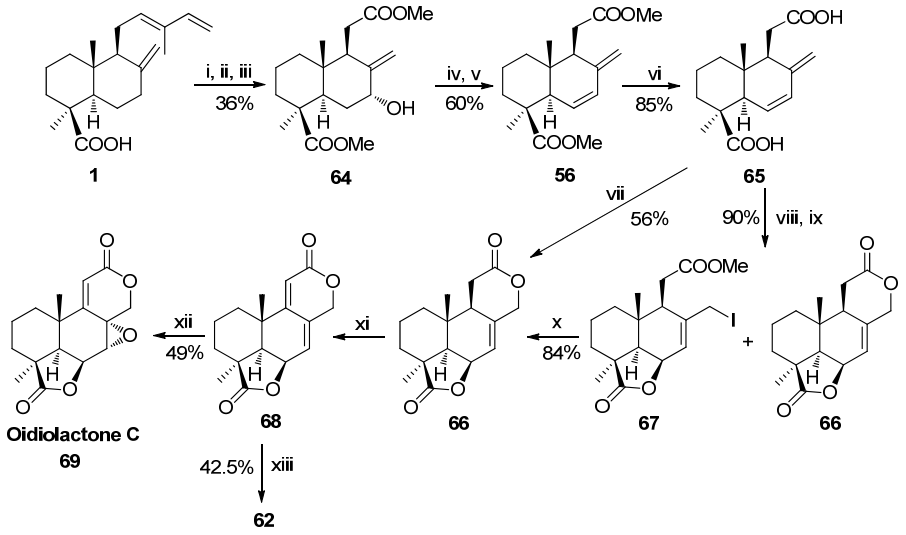
Scheme 14. Synthesis of nagilactone F, LL-Z1271γ and LL-Z1271α.



Reagents and conditions: (i) H_2SO_4, r.t., 24 h; (ii) $Pb(OAc)_4$, hυ, dry benzene, 10 °C, 62 h; (iii) SeO_2, dioxane, reflux, 2 h; (iv) MeOH, H_2SO_4, r.t., 2.5 h; (v) *i*-PrMgBr, dry THF, r.t., 4 h.

The selective ozonolysis of **1** and subsequent oxidation with Jones reagent, double esterification with diazomethane and allylic oxidation with SeO_2/*t*-BuOOH yielded 36% of the hydroxydiester **64**. Elimination of the trifluoroacetate of **64** with $Pd(PPh_3)_4$ led to diene **56**, whose hydrolysis with sodium propanethiolate afforded diacid **65**. Two different procedures were employed to carry out the double lactonization. First, the selective methylation of the carboxyl group at C12 with MeOH in the presence of 1,1′-carbonyldiimidazole and then iodolactonization under Barrett's conditions after strict deoxygenation of the reaction medium furnished the iodo derivative **67** (80% yield) along with a 20% yield of dilactone **66**. Iodo derivative **67** was exclusively converted in dilactone **66** by reaction with $AgNO_3/H_2O$/acetone (84% yield). Dilactone **66** was directly obtained from diacid **65** through a novel dilactonization process by treatment with substoichiometric Pd(II) (25%) and *p*-benzoquinone in a mixture of acetic acid and acetone as solvent (56%). The 9,11 double bond in diene-dilactone **68** was obtained, via the corresponding lithium enolate of **66** after adding phenylselenenyl chloride, and oxidation of the 11α-phenylseleno derivative to corresponding selenoxide by hydrogen peroxide with concomitant *syn*-elimination. Treatment of **68** with dimethyldioxirane afforded the natural oidiolactone C (**69**). Additionally, **62** was prepared by allylic oxidation as indicated in Scheme 15.

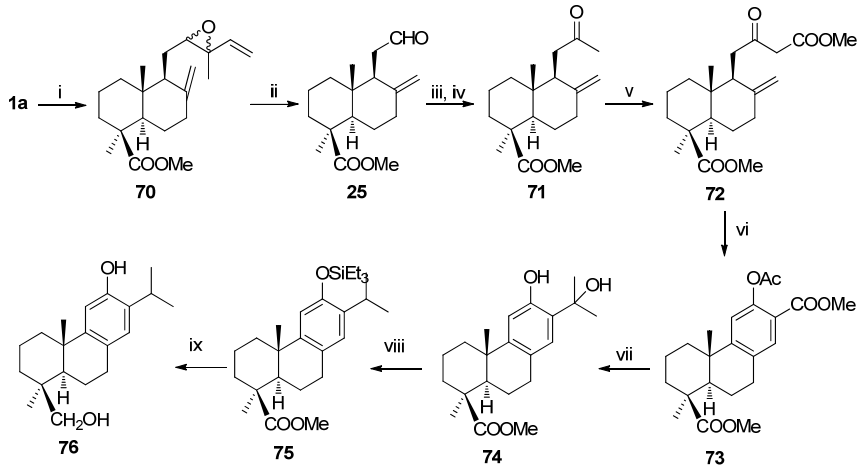
Scheme 15. Synthesis of oidiolactone C and LL-Z1271α.



Reagents and conditions: (i) O_3, CH_2Cl_2, −78 °C, Me_2S; (ii) 1. Jones reagesnt, acetone, 0 °C, 30 min; 2. CH_2N_2, Et_2O; (iii) SeO_2, *t*-BuOOH, CH_2Cl_2, 5–10 °C, 2 h; (iv) TFAA, DMPA, CH_2Cl_2, r.t., 45 min; (v) $Pd(PPh_3)_4$, K_2CO_3, dry toluene, 60 °C, 6.5 h; (vi) $CH_3CH_2CH_2SNa$, DMF, 50 °C, 24 h; (vii) $Pd(AcO)_2$, *p*-benzoquinone, glacial AcOH, acetone, r.t., 7 days; (viii) dry MeOH, carbonyldiimidazole, dry *t*-BuOMe, 4 A molecular sieves, r.t., 24 h; (ix) I_2, deoxygenated CH_3CN, −20 °C, 5 h; (x) AgBF4, collidine, acetone:H_2O (1:2), 60 °C, 2 h; (xi) 1. LDA, TMSCl, dry THF, −78 °C, 20 min; 2. PhSeCl, dry THF, to warm over 1 h; 3. H_2O_2, prridine, CH_2Cl_2, reflux, 5 min; (xii) dimethyldioxirane, acetone, r.t., 24 h; (xiii) 1. SeO_2, dioxane, reflux, 1 h; 2. MeOH, H_2SO_4, r.t., 2 h.

Synthesis of the phenol abietane diterpenes 19-hydroxyferruginol (**76**), isolated from *Podocarpus ferrugineus* [98], and sugikurojin A (**80**), isolated from *Cryptomeria japonica* [99], from *trans*-communic acid (**1**) is shown in Schemes 16 and 17, respectively [100]. The key steps of these procedures are the side chain degradation and the elaboration of the aromatic C ring by Mn(III) cyclization.

Scheme 16. Synthesis of 19-hydroxyferruginol (**76**).

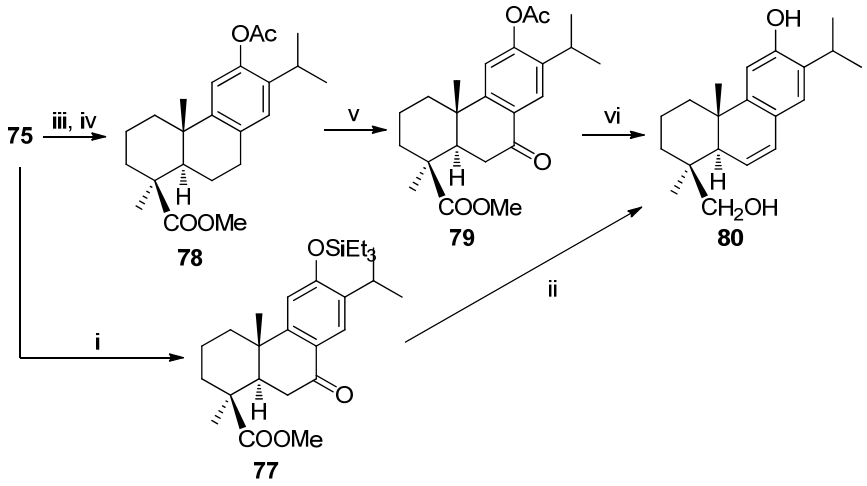


Reagents and conditions: (i) MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C~r.t., 12 h, 87%; (ii) HIO_4, THF, −10 °C, 1 h, 83%; (iii) MeMgBr, Et_2O, 0 °C, 96%; (iv) Jones reagent, acetone, 0 °C, 15 min, 92%; (v) $MeCO_3$, benzene, 3 h, 89%; (vi) $Mn(OAc)_3$, LiCl, Ac_2O, 120 °C, 12 h, 74%; (vii) MeMgBr, Et_2O, 0 °C, 15 min, 92%; (viii) Et_3SiH, CF_3COOH, CH_2Cl_2, −40 °C, 30 min, 87%; (ix) $LiAlH_4$, THF, r.t.~reflux, 12 h, 95%.

Epoxidation of ester **1a** by *m*CPBA followed by treatment with HIO_4 in THF led to aldehyde **25**, whose treatment with MeMgBr and further oxidation with Jones reagent gave methylketone **71**. Reaction of **71** with Me_2CO_3 and NaH in benzene afforded the β-ketoester **72**. Treatment of **72** with $Mn(OAc)_3 \cdot 2H_2O$ (4.0 equiv.) and LiCl (3.0 equiv.) in Ac_2O at 120 °C for 12 h led to the methyl *O*-acetyl salicylate **73** (74% yield). Transformation of **73** in abietane **74** was carried out by the addition of MeMgBr in excess. When this compound was treated with Et_3SiH and CF_3COOH was obtained silylether **75**, whose treatment with $LiAlH_4$ in THF at reflux afforded 19-hydroxyferruginol (**76**) (Scheme 16).

Heating of silylether **75** with Na_2CrO_4 and NaOAc in Ac_2O-AcOH led to 7-oxoderivative **77**. Compound **77** was refluxed with $LiAlH_4$ in THF giving sugikurojin A (**80**). An alternative route to compound **80** from **75** involved the removal of the silyl group and further acetylation and oxidation to obtain ketone **79**, which was then transformed into **80** (Scheme 17).

Scheme 17. Synthesis of sugikurojin (**80**).



Reagents and conditions: (i) $NaCrO_4$, NaOAc, Ac_2O, AcOH, 70 °C, 3 h, 83%; (ii) $LiAlH_4$, THF, r.t.~reflux, 12 h, 98%; (iii) TBAF, THF, r.t., 20 min, 94%; (iv) Ac_2O, pyridine, r.t., 24 h, 93%; (v) Jones reagent, acetone, r.t., 2 days, 76%; (vi) $LiAlH_4$, THF, r.t., 10 h, 88%.

6. Conclusions

This paper reveals the occurrence of the communic acids in fam. *Cupresaceae* especially in genus *Juniperus*. Furthermore they constitute appropriate building blocks for the efficient preparation of interesting bioactive natural products as ambrox, nagilactone F, bruceantin, 19-hydroxyferruginol and others.

References

1. Connolly, J.D., Hill, R.A., Eds. *Dictionary of Terpenoids*; Chapman & Hall: London, UK, 1991; Volume 2.
2. Hanson, J.R. Diterpenoids of terrestrial origen. *Nat. Prod. Rep*. **2011**, *28*, 1755–1772.
3. Peters, R.J. Two rings in them all: The labdane-related diterpenoids. *Nat. Prod. Rep*. **2010**, *27*, 1521–1530.
4. Hanson, J.R. Diterpenoids. *Nat. Prod. Rep*. **2004**, *21*, 312–320.

5. Sakar, M.K.; Er, N.; Dilek, E.; Del Olmo, E.; San Feliciano, A. (−)-Desoxypodophyllotoxin and diterpenoids from *Juniperus nana* Willd. berries. *Acta Pharm. Turcica* **2002**, *44*, 213–219.
6. De Pascual Teresa, J.; San Feliciano, A.; Barrero, A.F. Composition of *Juniperus communis* (common juniper) fruit. I. *An. Quim.* **1973**, *69*, 1065–1067.
7. De Pascual Teresa, J.; San Feliciano, A.; Miguel del Corral, J.M. Components of *Juniperus oxycedrus* fruits. *An. Quim*. **1974**, *70*, 1015–1019.
8. Fang, J.-M.; Chen, Y.-C.; Wang, B.-W.; Cheng, Y.-S. Terpenes from heartwood of *Juniperus chinensis*. *Phytochemistry* **1996**, *41*, 1361–1365.
9. Fang, J.M.; Sou, Y.C.; Chiu, Y.H.; Cheng, Y.S. Diterpenes from the bark of *Juniperus chinensis*. *Phytochemistry* **1993**, *34*, 1581–1584.
10. Chang, C.-I.; Chen, W.-C.; Shao, Y.-Y.; Yeh, G.-R.; Yang, N.-S.; Chiang, W.; Kuo, Y.-H. A new labdane-type diterpene from the bark of *Juniperus chinensis* Linn. *Nat. Prod. Res*. **2008**, *22*, 1158–1162.
11. Barrero, A.F.; Quilez del Moral, J.F.; Herrador, M.M.; Akssira, M.; Bennamara, A.; Akkad, S.; Aitigri, M. Oxygenated diterpenes and other constituents from Moroccan *Juniperus phoenicea* and *Juniperus thurifera* var. *africana*. *Phytochemistry* **2004**, *65*, 2507–2515.
12. Sakar, M.K.; San Feliciano, A. Diterpenoids of *Juniperus foetidissima* unripe berries. *Fitoterapia* **1994**, *65*, 304–306.
13. Barrero, A.F.; Sanchez, J.F.; Altarejos, J. Resin acids in the woods of *Juniperus sabina* L. and *Juniperus oxycedrus* L. *Ars Pharm.* **1987**, *28*, 449–457.
14. Su, W.-C.; Fang, J.-M.; Cheng, Y.-S. Diterpenoids from leaves of *Cryptomeria japonica*. *Phytochemistry* **1996**, *41*, 255–261.
15. Wang, Y.-Z.; Tang, C.-P.; Ke, C.-Q.; Weiss, H.-C.; Gesing, E.-R.; Ye, Y. Diterpenoids from the pericarp of *Plactycladus orientalis*. *Phytochemistry* **2008**, *69*, 518–526.
16. Fang, S.; Gu, Y.; Yu, H.; Musadillin, S. The chemical nature of antitumor compounds from *Sabina vulgaris* Ant. *Zhiwu Xuebao* **1989**, *31*, 382–388.
17. Gu, Y.; Xu, Y.; Fang, S.; He, Q. The chemical constituents from *Podocarpus imbricatus*. *Zhiwu Xuebao* **1990**, *32*, 631–636.
18. Smith, R.M.; Marty, R.A.; Peters, C.F. The diterpene acids in the bled resins of three Pacific kauri, *Agathis vitiensis*, *A. lanceolata*, and *A. macrophylla*. *Phytochemistry* **1981**, *20*, 2205–2207.
19. Hafez, S.S. New labdane-type diterpenoids from the stem bark of *Thuja occidentalis* L. *J. Pharm. Sci.* **2004**, *20*, 34–47.
20. Bohlmann, F.; Zdero, C. Naturally occurring terpene derivatives. XXXIII. Constituents of *Hermas villosa*. *Chem. Ber.* **1974**, *107*, 1416–1419.
21. Topcu, G.; Erenler, R.; Cakmak, O.; Johansson, C.B.; Celik, C.; Chai, H.-B.; Pezzuto, J.M. Diterpenes from the berries of *Juniperus excelsa*. *Phytochemistry* **1999**, *50*, 1195–1199.
22. Tchinda, A.T.; Fuendjiep, V.; Mekonnen, Y.; Ngo, B.B.; Dagne, E. A bioactive diterpene from *Entada abyssinica*. *Nat. Prod. Commun*. **2007**, *2*, 9–12.
23. Takahashi, K.; Nagahama, S.; Nakashima, T.; Suenaga, H. Chemotaxonomy on the leaf constituents of *Thujopsis dolabrata* Sieb. et Zucc.-analysis of acidic extracts. *Biochem. Syst. Ecol.* **2003**, *31*, 723–738.

24. Hasegawa, S.; Hirose, Y. Terpenoids from the seed of *Thujopsis dolabrata*. *Phytochemistry* **1981**, *20*, 508–510.
25. Nagahama, S.; Tajima, M.; Nishimura, K. Chemotaxonomy of ate (*Thujopsis dolabrata*) of Noto, Ishikawa Prefecture. *Mokuzai Gakkaishi* **1996**, *42*, 698–702.
26. Minami, T.; Wada, S.; Tokuda, H.; Tanabe, G.; Muraoka, O.; Tanaka, R. Potential antitumor-promoting diterpenes from the cones of *Pinus luchuensis*. *J. Nat. Prod*. **2002**, *65*, 1921–1923.
27. Fukushima, J.; Yatagai, M.; Ohira, T. Abietane-type and labdane-type diterpenoids from the cones of *Chamaecyparis obtusa*. *J. Wood Sci*. **2002**, *48*, 326–330.
28. Hanari, N.; Yamamoto, H.; Kuroda, K. Comparison of terpenes in extracts from the resin and the bark of the resinous stem canker of *Chamaecyparis obtusa* and *Thujopsis dolabrata* var. *hondae*. *J. Wood Sci*. **2002**, *48*, 56–63.
29. Yamamoto, H.; Asano, N.; Sawano, C.; Sone, T.; Gasha, T.; Ono, Y. Diterpenes Isolated from the Resin of the Resinous Stem Canker of Japanese Cypress, *Chamaecyparis obtusa*. *Mokuzai Gakkaishi* **1997**, *43*, 558–565.
30. Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. Aromatase inhibitory activities of standishinal and the diterpenoids from the bark of *Thuja standishii*. *Planta Med.* **2002**, *68*, 742–745.
31. Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. Anti-tumor promoting diterpenes from the stem bark of *Thuja standishii* (*Cupressaceae*). *Bioorg. Med. Chem*. **2001**, *9*, 1911–1921.
32. Fonseca, F.N.; Ferreira, A.J.S.; Sartorelli, P.; Lopes, N.P.; Floh, E.I.S.; Handro, W.; Kato, M.J. Phenylpropanoid derivatives and biflavones at different stages of differentiation and development of *Araucaria angustifolia*. *Phytochemistry* **2000**, *55*, 575–580.
33. Lin, T.-C.; Fang, J.-M.; Cheng, Y.-S. Terpenes and lignans from leaves of *Chamaecyparis formosensis*. *Phytochemistry* **1999**, *51*, 793–801.
34. Bungert, M.; Gabler, J.; Adam, K.-P.; Zapp, J.; Becker, H. Pinguisane sesquiterpenes from the liverwort *Porella navicularis*. *Phytochemistry* **1998**, *49*, 1079–1083.
35. Liu, Y.; Nair, M.G. Labdane diterpenes in *Curcuma mangga* rhizomes inhibit lipid peroxidation, cyclooxygenase enzymes and human tumour cell proliferatio. *Food Chem.* **2011**, *124*, 527–532.
36. Sakar, M.K. Diterpenes from ripe "fruits" of *Juniperus drupaceae* Labill. *Acta Pharm. Turcica* **1987**, *29*, 65–68.
37. Hasegawa, S.; Hirose, Y. Diterpenes from the seed of *Sciadopitys verticillata*. *Phytochemistry* **1985**, *24*, 2041–2046.
38. Kitajima, J.; Komori, T.; Kawasaki, T. Studies on the constituents of the crude drug "Fritillariae Bulbus." III. On the diterpenoid constituents of fresh bulbs of *Fritillaria thunbergii* Miq. *Chem. Pharm. Bull*. **1982**, *30*, 3912–3921.
39. Ding, T.; Liu, H.; Pu, Q. Studies on the resin constituents of *Taxodiaceae*. I. Sesquiterpene and diterpene components of the resin from *Cunninghamia unicanaliculata* var. *pyramidalis*. *Yunnan Zhiwu Yanjiu* **1982**, *4*, 307–311.
40. Bohlmann, F.; Fiedler, L. Naturally occurring terpene derivatives. Part 131. A new communic acid derivative from *Chromolaena collina* (DC) K. et R. *J. Indian Chem. Soc*. **1978**, *55*, 1161–1162.

41. Alvarez-Manzaneda Roldan, E.; Chahboun, R. Span. Procedure for isolation of *trans*-communic acid and derivatives from *Cupressus sempervirens*. Patent ES 2284341 A1 20071101, 2007.
42. Rawat, P.; Khan, M.F.; Kumar, M.; Tamarkar, A.K.; Srivastava, A.K.; Arya, K.R.; Maurya, R. Constituents from fruits of *Cupressus sempervirens*. *Fitoterapia* **2010**, *81*, 162–166.
43. De Pascual Teresa, J.; Barrero, A.F.; Muriel, L.; San Feliciano, A.; Grande, M. New natural diterpene acids from *Juniperus communis*. *Phytochemistry* **1980**, *19*, 1153–1156.
44. Xiao, Z.-Y.; Wang, X.-C.; Zhang, G.-P.; Huang, Z.-L.; Hu, L.-H. Terpenoids from roots of *Chloranthus spicatus*. *Helv. Chim. Acta* **2010**, *93*, 803–810.
45. Wang, W.; Ba, H.; Hajia, A.; Liao, L.; Duo, L. Study on chemical constituents of *Sabina vulgaris* Antoine. *Tianran Chanwu Yanjiu Yu Kaifa* **2005**, *17*, 588–591.
46. Chen, R.; Zhang, Y.; Fang, S. Inhibitors of human DNA polymerase β isolated from Jack Rorreya (*Torreya jackii*). *Zhongcaoyao* **1997**, *28*, 707–710.
47. Xu, Y.; Fang, S.; He, Q. The chemical constituents in *Dacrydium pierrei*. *Zhiwu Xuebao* **1991**, *33*, 646–648.
48. Dawidar, A.M.; Ezmirly, S.T.; Abdel-Mogib, M. Sesquiterpenes and diterpenes from *Juniperus phoenicea* L. *Pharmazie* **1991**, *46*, 472–473.
49. Lee, G.H.; Lin, C.C.; Cheng, Y.S.; Peng, S.M. Structure of methyl *trans*-communate. *Acta Crystallogr. C Cryst. Str.* **1987**, *C43*, 1382–1384.
50. Bohlmann, F.; Dhar, A.K.; Jakupovic, J.; King, R.M.; Robinson, H. A caryophyllene derivative from *Fleischmannia pycnocephaloides*. *Phytochemistry* **1981**, *20*, 1425–1426.
51. Popova, M.P.; Chinou, I.B.; Marekov, I.N.; Bankova, V.S. Terpenes with antimicrobial activity from *Cretan propolis*. *Phytochemistry* **2009**, *70*, 1262–1271.
52. Zhang, Y.-J.; Litaudon, M.; Bousserouel, H.; Martin, M.-T.; Thoison, O.; Leonce, S.; Dumontet, V.; Sevenet, T.; Gueritte, F. Sesquiterpenoids and Cytotoxic Lignans from the Bark of *Libocedrus chevalieri*. *J. Nat. Prod*. **2007**, *70*, 1368–1370.
53. Sultan, M.Z.; Jeon, Y.-M.; Moon, S.-S. Labdane-type diterpenes active against acne from pine cones (*Pinus densiflora*). *Planta Med.* **2008**, *74*, 449–452.
54. Mendes, C.C.; Cruz, F.G.; Guedes, M.L.S.; Roque, N.F. Terpenes from *Mikania aff. jeffreyi* (*Asteraceae*). *Zeitschrift Fuer Naturforschung B Chem. Sci.* **2005**, *60*, 875–879.
55. Smith, E.C.J.; Williamson, E.M.; Wareham, N.; Kaatz, G.W.; Gibbons, S. Antibacterials and modulators of bacterial resistance from the immature cones of *Chamaecyparis lawsoniana*. *Phytochemistry* **2007**, *68*, 210–217.
56. Shmidt, E.N.; Pentegova, V.A. Chemical composition of *Larix dahurica* soft resin. *Khimiya Prirodnykh Soedinenii* **1974**, 675–676.
57. Hsieh, Y.-L.; Fang, J.-M.; Cheng, Y.-S. Terpenoids and flavonoids from *Pseudotsuga wilsoniana*. *Phytochemistry* **1998**, *47*, 845–850.
58. Yoshikawa, K.; Kokudo, N.; Tanaka, M.; Nakano, T.; Shibata, H.; Aragaki, N.; Higuchi, T.; Hashimoto, T. Novel abietane diterpenoids and aromatic compounds from *Cladonia rangiferina* and their antimicrobial activity against antibiotics resistant bacteria. *Chem. Pharm. Bull.* **2008**, *56*, 89–92.
59. De Pascual Teresa, J.; San Feliciano, A.; Miguel del Corral, M.J. Components of *Juniperus oxycedrus* berries. I. *An. Quim*. **1972**, *68*, 1061–1062.

60. Zhou, X.; Cheng, C.; Roshchin, V.I. Study on the chemical composition of substances extracted from the green crown of *Cunninghamia lanceolata* Hook. *Linchan Huaxue Yu Gongye* **1997**, *17*, 55–60.
61. Carman, R.M.; Cowley, D.E. Diterpenoids. XII. Dundatholic acid. *Aust. J. Chem.* **1967**, *20*, 193–196.
62. Carman, R.M.; Cowley, D.E.; Marty, R.A. Diterpenoids. XXV. Dundathic acid and polycommunic acid. *Aust. J. Chem.* **1970**, *23*, 1655–1665.
63. Scalarone, D.; van der Horst, J.; Boon J.J.; Chiantore, O. Direct-temperature mass spectrometric detection of volatile terpenoids and natural terpenoid polymers in fresh and artificially aged resins. *J. Mass Spectrom.* **2003**, *38*, 607–617.
64. Trusheva, B.; Popova, M.; Bankova, V.; Tsvetkova, I.; Naydenski, C.; Sabatini, A.G. A new type of European *propolis*, containing bioactive labdanes. *Rivista Italiana EPPOS* **2003**, *36*, 3–7.
65. Hafez, S.S. New labdane-type diterpenoids from the stem bark of *Thuja occidentalis* L. *J. Pharm. Sci.* **2004**, *20*, 34–47.
66. Muhammad, I.; Mossa, J.S.; Al-Yahya, M.A.; Ramadan, A.F.; El-Feraly, F.S. Further antibacterial diterpenes from the bark and leaves of *Juniperus procera* Hochst. ex Endl. *Phytother. Res.* **1995**, *9*, 584–588.
67. Samoylenko, V.; Dunbar, D.C.; Gafur, M.A.; Khan, S.I.; Ross, S.A.; Mossa, Jaber S.; El-Feraly, F.S.; Tekwani, B.L.; Bosselaers, J.; Muhammad, I. Antiparasitic, nematicidal and antifouling constituents from *Juniperus* berries. *Phytother. Res.* **2008**, *22*, 1570–1576.
68. Hirayama, T.; Someya, K.; Kuroyanagi, M.; Nakane, T. Natural antibacterial agents containing labdatrienoic acid and oral hygiene compositions containing them. *Jpn. Kokai Tokkyo Koho*, JP 2009023920 A 20090205, 2009.
69. Jeon, Y.M.; Moon, S.S.; Lee, T.H.; Cho, S.C.; Yim, B.K. Extract of pine cone having antibacterial and antifungal activity against particularly bacteria causing acne or athlete's foot, and cosmetic composition for improving skin disease without side effects on skin comprising the same or compound isolated from the same. *Repub. Korean Kongkae Taeho Kongbo*, KR 2006104161 A 20061009, 2006.
70. Xue, J.-J.; Fan, C.-Q.; Dong, L.; Yang, S.-P.; Yue, J.-M. Novel antibacterial diterpenoids from *Larix chinensis* beissn. *Chem. Biodiver.* **2004**, *1*, 1702–1707.
71. Perry, N.B.; Foster, L.M. Antitumor lignans and cytotoxic resin acids from a New Zealand gymnosperm, *Libocedrus plumosa*. *Phytomedicine* **1994**, *1*, 233–237.
72. Gordien, A.Y.; Gray, A.I.; Franzblau, S.G.; Seidel, V. Antimycobacterial terpenoids from *Juniperus communis* L. (*Cuppressaceae*). *J. Ethnopharmacol*. **2009**, *126*, 500–505.
73. Tanaka, R.; Ohtsu, H.; Iwamoto, M.; Minami, T.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Yoshitake, A. Cancer chemopreventive agents, labdane diterpenoids from the stem bark of *Thuja standishii* (Gord.) Carr. *Cancer Lett.* **2000**, *161*, 165–170.
74. Ribeiro, L.A.A.; Tavares, J.F.; de Andrade, N.C.; da Silva, M.S.; da Silva, B.A. The (8)17,12*E*,14-labdatrien-18-oic acid (labdane 302), a labdane-type diterpene isolated from *Xylopia langsdorffiana* St. Hil. & Tul. (*Annonaceae*), relaxes the guinea pig trachea. *Revista Brasileira de Farmacognosia* **2007**, *17*, 197–203.
75. Kim, Y.-K.; Kim, W.-K. Hypolipidemic effects of Korean softwood components. *Han'guk Sikp'um Yongyang Kwahak Hoechi* **2001**, *30*, 1204–1214.

76. Ko, J.H.; Hwang, E.I.; Lee, K.W.; Choi, K.H. Testosterone 5α-reductase inhibitor for preventing and treating diseases associated with testosterone 5α-reductase comprising extract of pine needle or compounds isolated therefrom. *Repub. Korean Kongkae Taeho Kongbo*, KR 2006067255 A 20060619, 2006.
77. Shimizu, M.; Tsuji, H.; Shogawa, H.; Fukumura, H.; Tanaami, S.; Hayashi, T.; Arisawa, M.; Morita, N. Anti-inflammatory constituents of topically applied crude drugs. II. Constituents and anti-inflammatory effect of *Cryptomeria japonica* D. Don. *Chem. Pharm. Bull*. **1988**, *36*, 3967–3973.
78. De Pascual Teresa, J.; San Feliciano, A.; Miguel del Corral, J.M.; Barrero, A.F. Transformaciones químicas en la cadena lateral de los ácidos comúnicos. 1. Epoxidaciones. *Studia Chemica* **1984**, *9*, 255–267.
79. De Pascual Teresa, J.; Mateos, A.F.; Barrero, A.F.; Pollos, P. Adiciones de oxígeno singlete a mirceocomunato de metilo y *trans*-comunato de metilo. Síntesis de lambertianato de metilo. *Stud. Chem.* **1984**, *9*, 49–56.
80. Schulte-Elte, K.H.; Muller, B.L.; Rautenstrauch, V. Preference for *syn ene* additions of 1O2 to trisubstituted, acyclic olefins. *Helv. Chim. Acta* **1978**, *61*, 2777–2783.
81. Barrero, A.F.; Sánchez, J.F.; Altarejos, J. Biomimetic Cyclization of Communic Acids to Pimarane Skeleton Via Organomercurial Intermediates. *Tetrahedron Lett*. **1988**, *29*, 3713–3716.
82. Barrero, A.F.; Ramírez, A.; Salido, S.; Altarejos, J. Oxymercuriation-demedrcuriation reactions of methyl myrceocommunate. *An. Quim*. **1990**, *86*, 786–790.
83. Barrero, A.F.; Sánchez, J.F.; Altarejos, J.; Perales, A. Oxymercuriation-demercuriation of the methyl esters of communic acids. X-ray molecular structures of methyl (8*R*,12*R*)-8,12-epoxyisopimar-15-en-19-oate. *J. Chem. Soc. Perkin Trans. 1* **1991**, 2513–2523.
84. Barrero, A.F.; Sánchez, J.F.; Altarejos, J. Selective ozonolysis of methyl *trans*-communate. Synthesis of drimanes. *Tetrahedron Lett.* **1989**, *30*, 5515–5518.
85. Barrero, A.F.; Alvarea-Manzaneda, E.J.; Altarejos, J.; Ramos, J.M.; Salido, S. Preferential oxidation reactions of the side chain of unsaturated labdanes. *Bull. Soc. Chim. Fr*. **1993**, *130*, 700–707.
86. Barrero, A.F.; Altarejos, J.; Alvarea-Manzaneda, E.J.; Ramos, J.M.; Salido, S. Synthesis of ambrox from communic acids. *Tetrahedron* **1993**, *49*, 6251–6262.
87. Barrero, A.F.; Altarejos, J.; Alvarea-Manzaneda, E.J.; Ramos, J.M.; Salido, S. Amber-type odorants from communic acids. *Tetrahedron* **1993**, *49*, 9525–9534.
88. Barrero, A.F.; Alvarez-Manzaneda, E.J.; Alvarez-Manzaneda, R.; Chahboun, R.; Meneses, R.; Cuerva, J.M.; Aparicio, M.; Romera, J.L. Approach to the synthesis of antitumor quassinoids from labdane diterpenes: An efficient synthesis of a picrasane-related intermediate. *Org. Lett.* **2001**, *3*, 647–650.
89. Connolly, J.D., Hill, R.A., Eds. *Dictionary of Terpenoids*; Chapman-Hall, London, UK, 1991; Volume 2, pp. 853–857.
90. Andersen, N.R.; Rasmunsen, P.R.; Falshaw, C.P.; King, T.J. The relative and absolute configuration of clerocidin and its cometabolites. *Tetrahedron Lett*. **1984**, *25*, 469–472.
91. Dorner, J.W.; Cole, R.J.; Springer, J.P.; Cox, R.H.; Cutler, H.; Wicklow, D.T. Isolation and identification of two new biologically active norditerpene dilactones from *Aspergillus wentii*. *Phytochemistry* **1980**, *19*, 1157–1161.

92. Ellestad, G.A.; Evans, R.H.; Kunstmann, M.P.; Lancaster, J.E.; Morton, G.O. Structure and chemistry of antibiotic LL-Z1271α, an antifungal carbon-17 terpene. *J. Am. Chem. Soc.* **1970**, *92*, 5483–5489.
93. Hosoe, T.; Nozawa, K.; Lumley, T.C.; Currah, R.S.; Fukushima, K.; Takizawa, K.; Miyaji, M.; Kawai, K. Tetranorditerpene lactones, potent antifungal antibiotics for human pathogenic yeasts, from a unique species of Oidiodendron. *Chem. Pharm. Bull*. **1999**, *47*, 1591–1597.
94. Ichikawa, K.; Ikunaka, M.; Kojima, N.; Nishida, H.; Yoshikawa, N. Terpenoid lactone compounds and their production process. EP 0 933 273 A1, 1999.
95. Barrero, A.F.; Sánchez, J.F.; Elmerabet, J.; Jiménez-González, D.; Macías, F.A.; Simonet, A.M. Enantiospecific syntheses of the potent bioactives Nagilactone F and the mould metabolite LL-Z1271α. An evaluation of their allelopathic potential. *Tetrahedron* **1999**, *55*, 7289–7304.
96. Barrero, A.F.; Quilez del Moral, J.F.; Cuerva, J.M.; Cabrera, E.; Jimenez-González, D. preparation of bioactive podolactones via a new Pd-catalysed bislactonisation reaction. Synthesis of oidiolactone C. *Tetrahedron Lett.* **2000**, *41*, 5203–5206.
97. Barrero, A.F.; Arseniyadis, S.; Quilez del Moral, J.F.; Herrador, M.M.; Valdivia, M.; Jimenez, D. First synthesis of the antifungal oidiolactone C from *trans*-communic acid: Cytotoxic and antimicrobial activity in podolactone-related compounds. *J. Org. Chem*. **2002**, *67*, 2501–2508.
98. Cambie, R.C.; Cox, R.E.; Sidwell, D. Phenolic diterpenoids of *Podocarpus ferrugineus* and other podocarps. *Phytochemistry* **1984**, *23*, 333–336.
99. Arihara, S.; Umeyama, A.; Bando, S.; Imoto, S.; Ono, M.; Tani, M.; Yoshikawa, K. A new abietane and two dimeric abietane diterpenes from the black heartwood of *Cryptomeria japonica*. *Chem. Pharm. Bull*. **2004**, *52*, 354–358.
100. Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Lachkar, M.; Messouri, I. Synthesis of phenol abietane diterpenes based on the oxidative radical cyclization utilizing the $Mn(OAc)_3/Ac_2O$ system. *Synlett* **2007**, 2425–2429.