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Review

The Multiple Faces of Eugenol. A Versatile Starting Material and Building Block for Organic and Bio-Organic Synthesis and a Convenient Precursor Toward Bio-Based Fine Chemicals

Teodoro S. Kaufman*

Instituto de Química Rosario (IQUIR, CONICET-UNR) and Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, S2002LRK Rosario, Argentina

Phenylpropenes are produced by plants as part of their defense strategy against microorganisms and animals, and also as floral attractants of pollinators. Eugenol, the main component of clove's essential oil, is an inexpensive and easily available phenylpropene that has been known by humankind since antiquity, and used as a medicinal agent, but also for food flavoring and preservation. The review includes the most relevant results obtained during the last 15 years with regard to the synthetic uses of eugenol. Discussed here are the multiple applications of eugenol in organic synthesis, including its use as starting material or building block for the total synthesis of natural products, their analogs and derivatives, as well as other structurally interesting or bioactive compounds. The preparation technologically relevant macrocycles and polymeric derivatives of eugenol, is included, and the impact of biotechnology on the use of eugenol as feedstock for biotransformations, leading to other valuable small molecules is also addressed.

Keywords: eugenol, natural products synthesis, polymer science, macrocycles, bioactive compounds

1. Introduction

All the major groups of angiosperms biosynthesize phenylpropenes. These are stored in their vegetative parts, as a defense against herbivores, parasitic bacteria and fungi, or are easily volatilized, being toxic to insects and microbes. In addition, sometimes they are emitted from flowers to attract insect pollinators.

Eugenol (**1**, Figure 1)[1] is one of these key phenylpropenes. The natural product is a major aromatic constituent (up to approximately 80% by weight) of the essential oil of clove [*Eugenia caryophyllata* L. Merr. & Perry (Myrtaceae) = *Syzygium aromaticum*], which is commonly obtained by hydrodistillation, steam distillation, or Soxhlet (ethanol) extraction from leaves, buds, and stems of clove trees (Myrtaceae).[2] Eugenol is also found in *Myristica fragrans* Houtt. (nutmeg), *Cinnamomum verum* J. Presl (true cinnamon), *C. loureirii* Nees. (Saigon cinnamon), *Ocimum gratissimum* Forssk. (basil), *Ocimum basilicum* L. (sweet basil), pimento berry and bay oil, among others.

*e-mail: kaufman@iquir-conicet.gov.ar

Since the remote antiquity, medicinal plants have been the mainstay of traditional herbal medicine amongst rural dwellers worldwide. Natural products have been an integral part of the ancient traditional medicine systems including Ayurveda, Chinese and Egyptian. Currently, around 40% of the world population depends directly on plant based medicine for their health care. Hence, the traditional use of plants or parts of plants containing eugenol for medicinal purposes is not an exception.

Eugenol is a natural and generally acting antimicrobial and antianimal toxin, with mild analgesic properties. It is commonly used as a fragrance and flavoring agent in a variety of cosmetics, and food products. In addition, the natural product has shown a number of other interesting biological activities, including antioxidant, anti-inflammatory, antispasmodic, antidepressant, antigenotoxic, and anticarcinogenic. Proof of the interest in this subject is the surprisingly high number of articles reviewing these properties, which have been published in recent times.[3]

On the other hand, methyl eugenol (4-allyl-1,2-dimethoxybenzene, **2**) is the methyl ether derivative of eugenol. This is also a natural product,[4] which has a relevant role in nature, especially in relation to insect behavior

and pollination.[5] This chemical is easily available and has attracted some attention to the point that a green chemistry condition for its access (by alkylation of eugenol with dimethyl carbonate),[6] has been published. Compound **2** has been widely used as a test molecule for the development of organic synthetic methodologies,[7] it enjoys widespread use in carbohydrate chemistry, as a reagent to scavenge the PhSOTf formed during sulfoxide glycosylations,[8] and has found some applications as starting material or building block in organic synthesis.

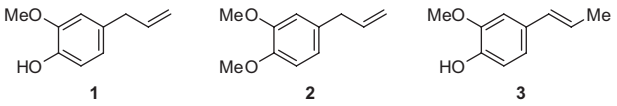


Figure 1. Chemical structures of eugenol (**1**), methyleugenol (**2**) and isoeugenol (**3**).

Eugenol is commercially available in large quantities with a market price around US$ 5 *per* kg; however, despite its easy access, it has been recently used as target for synthesis by a metal-free photoallylation of aryl halides with allyl-tetramethylsilane (TMS) in a MeCN-H_2O medium.[9] The particular structure and ready availability of eugenol has turned the natural product into an interesting starting material and a useful building block for complex synthesis, as well as into a valuable substrate for various biotransformations.

In 2000, Costa *et al.*[10] reviewed the chemical reactivity of eugenol and safrol, and their use in the synthesis of biologically active natural products and their derivatives. Therefore, in an attempt to complement and extend that work, this review will focus mainly on the advances which took place during the last 15 years, in the use of eugenol for different synthetic purposes.

Topics covered range from eugenol being a feedstock for biotransformations to the applications of the natural product as suitable starting material or key building block toward the synthesis of other natural products and their analogs, bioactive compounds, heterocycles, macrocycles and polymers.[11] However, the numerous applications of the related isoeugenol (**3**), a β-methylstyrene natural product, also available from eugenol, will not be covered.

2. Total Synthesis of Natural Products

Eugenol was found to be one of the most suitable starting materials for the total synthesis of structurally different natural products. Since various targets have been reached, the syntheses were grouped and arranged according to the type of objective, and a subjectively determined increasing degree of complexity.

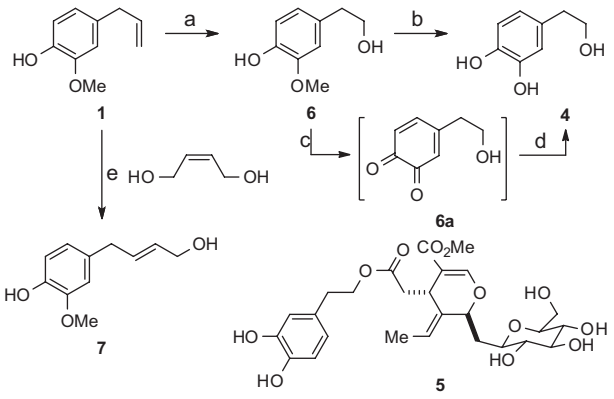
2.1. Hydroxytyrosol and (*E*)-4-(4-hydroxy-3-methoxyphenyl) but-2-enol

Among the wide variety of bioactive components found in olive oil, several phenolic compounds have been reported to express beneficial effects on human health.[12] The average concentration of phenolics can rise up to 1 g kg^{-1} in the first-pressed 'extra virgin' type olive oil. Hydroxytyrosol (**4**) is a simple catecholic compound and one of the major phenolic compounds present in the olive fruit and olive oil, together with oleuropein (**5**), from which it can be generated by hydrolysis.[13]

Due to its remarkable antioxidation activity,[14] hydroxytyrosol is suitable as a natural and non-toxic food preservative and a highly promising alternative to synthetic antioxidants. The natural product also contributes to the stability of virgin oil against rancidity caused by oxidation.[15]

A two-pot four-step synthesis of **4** from eugenol (Scheme 1) was reported by Deffieux *et al.*[16] The process was initiated by ozonolysis of the double bond of **1**, followed by an *in situ* hydride reduction of the ozonide to afford alcohol **6** in 98% yield. However, subsequent cleavage of the methyl aryl ether bond with aluminum iodide[17] and a catalytic amount of tetra-*n*-butylammonium iodide (TBAI) in MeCN,[18] afforded only 54% of the expected product. Therefore, a better alternative toward **4** was devised, through the dealkylative oxidation of the monomethyl catechol moiety of **6** with $NaIO_4$ to the unisolated quinone **6a**, followed by a reductive work-up with sodium thiosulfate, which furnished hydroxytyrosol (**4**) in an improved 78% yield.

On the other hand, (*E*)-4-(4-hydroxy-3-methoxyphenyl) but-2-enol (**7**) was originally isolated from the roots of *Zingiber cassumunar*, a medicinal plant from Southeast Asia possessing antioxidant and antiinflammatory

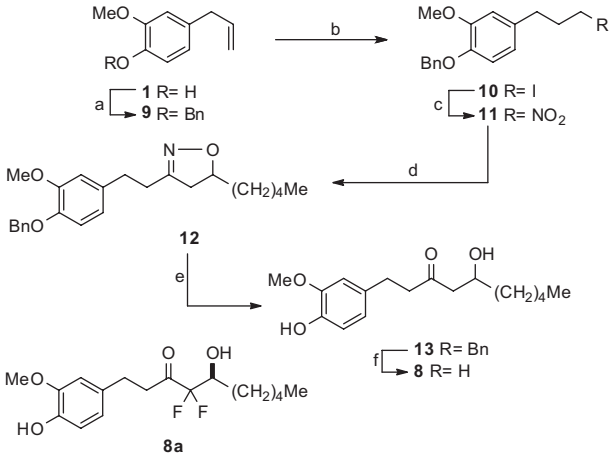


Scheme 1. Reagents and conditions: (a) 1. O_3, EtOH; 2. $NaBH_4$, EtOH (98%); (b) AlI_3, TBAI, MeCN, reflux (54%); (c) $NaIO_4$, EtOAc; (d) $Na_2S_2O_4$ (work-up, 78% overall); (e) Grubbs II in paraffin, *cis*-2-butene-1,4-diol, petroleum ether, room temperature (RT), 12 h (98%).

properties.[19] Taber *et al.*[20] performed a single-step synthesis of **7** from eugenol, by cross-metathesis with *cis*-2-butene-1,4-diol, and employing Grubbs II catalyst embedded in paraffin wax. Similarly, direct self-metathesis, and cross-metathesis of eugenol with symmetrical internal olefins and other alkenes,[21] and the use of ruthenium-catalyzed olefin cross-metathesis of eugenol with electron deficient olefins for the synthesis of polyfunctional alkenes have been reported.[22]

2.2. 6-Gingerol

6-Gingerol (**8**) is the key phenolic compound isolated from the rhizomes of ginger (*Zingiber officina*le Roscoe), a food spice and an important ingredient in Ayurvedic, Tibb-Unani and Chinese herbal medicines, for the treatment of various ailments like catarrh, rheumatism, gingivitis, toothache, asthma, stroke, constipation, and diabetes.[23] 6-Gingerol is responsible for the flavor and pungency of the spice, as well as for its bioactivity as antioxidant,[24] anti-inflammatory,[25] anti-tumor-promoting,[26] anti-platelet aggregation,[27] and antibacterial agent.[28]



Scheme 2. Reagents and conditions: (a) BnBr, K_2CO_3, MeCN, RT, 4 h (98%); (b) 1. $NaBH_4$, I_2, THF, 0 °C, 2.5 h; 2. **9**, RT, 3 h; 3. NaOMe, I_2, 0 °C, 3 h (75%); (c) $AgNO_3$, $NaNO_2$, H_2O, RT, 10 h (75%); (d) Ac_2O, 4-dimethylaminopyridine (DMAP), CH_2Cl_2, RT, 5-6 h (85%); (e) Ra-Ni, H_2 (30 psi), EtOH, 6 h; (f) Pd/C, H_2, EtOH, 3 h (60%, overall).

Isolation of this natural product is complicated by its low abundance and the presence of homologs and other structurally similar compounds. Therefore, Bettadaiah and co-workers[29] performed a total synthesis of 6-gingerol from eugenol (Scheme 2). To that end, these authors first protected its phenolic group as benzyl ether (**9**) and then converted the double bond into the primary iodide **10** in 75% yield, by hydroboration followed by iodination.[30]

Further transformation of the iodide **10** into the corresponding nitro derivative was best achieved with silver nitrate and sodium nitrite, which afforded **11** in 75% yield. In turn, this was subjected to a [3+2] cycloaddition reaction with 1-heptene in the presence of Et_3N and Ac_2O, to provide 40% of the intermediate isoxazoline **12**.[31]

The thus prepared heterocycle **12** was hydrogenolyzed in the presence of Raney nickel in moist ethanol to afford β-hydroxy carbonyl intermediate **13**, which was further debenzylated to furnish **8**, by catalytic hydrogenolysis with Pd/C, furnishing 60% of **8**. Interestingly, a chiral difluorinated analog of 6-gingerol (**8a**) was previously synthesized from eugenol, employing a different approach.[32]

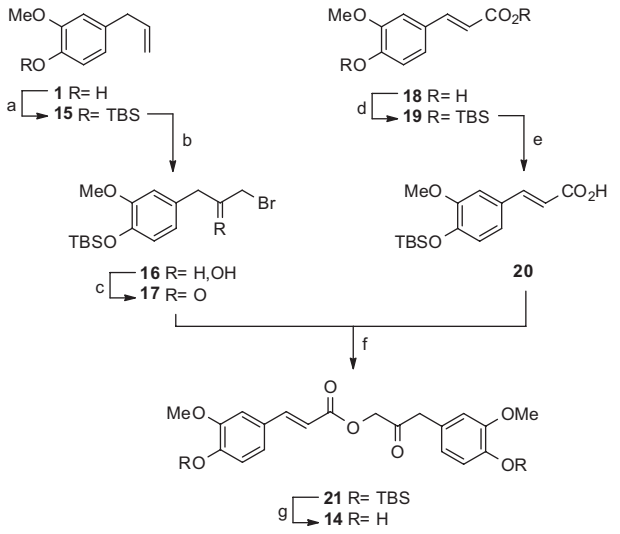
2.3. Cimiracemate B

The cimiracemates are phenylpropanoic acid esters isolated from the rhizomes of *Cimifuga racemosa*.[33] The plant containing these natural products is used in traditional medicine to treat menopausal symptoms[34] and inflammation.[35] In addition, it has been shown recently that cimiracemates could have additional health benefits, as scavengers of reactive oxygen species.[36]

However, the natural products are produced in extremely low amounts, as the abundance of cimiracemate B (**14**) is only 6 parts *per* million of the dry weight of the methanolic extract of the rhizome. Therefore, Piva and co-workers[37] reported a concise and convergent total synthesis of cimiracemate B (Scheme 3) starting from eugenol (**1**). Related compounds were also synthesized employing the same strategy.

The synthesis entailed the coupling of building blocks derived from eugenol (**17**) and cinnamic acid (**20**). For the synthesis of the former, eugenol (**1**) was protected as the *tert*-butyldimethylsilyl (TBS) ether **15** in 90% yield, which was converted into bromohydrin **16** under mild conditions with *N*-bromosuccinimide (NBS) in aqueous dimethyl sulfoxide (DMSO), thus avoiding the cleavage of the protecting group.[38] This was followed by a Dess-Martin oxidation[39] toward ketone **17**, which was accessed in 78% yield.

On the other hand, the synthesis of the cinnamic acid component **20** was performed in 81% overall yield by exhaustive silylation of **18** to the bis-silyl derivative **19**, followed by mild and selective hydrolysis of the silyl ester moiety (**20**).[40] The coupling between the acid and the α-bromoketone was achieved under phase transfer catalysis, resulting in 57% of the bis-silylated cimiracemate B derivative **21**, which was finally deprotected to furnish **14**, with aqueous HF in acetonitrile in rather low yield,[41] due to the lability of the ester bond.



Scheme 3. Reagents and conditions: (a) *tert*-Butyldimethylsilyl chloride (TBDMSCl), imidazole, 4-dimethylaminopyridine (DMAP), CH_2Cl_2 (90%); (b) NBS, H_2O-DMSO (5:95), 0 °C, (78%); (c) Dess-Martin, CH_2Cl_2 (78%); (d) TBDMSCl, imidazole, DMAP, CH_2Cl_2 (90%); (e) K_2CO_3, tetrahydrofuran (THF), MeOH, 30 min, RT (90%); (f) NaOH (aq.), $^nBu_4NBr$, toluene, RT, 12-14 h (57%); (g) 1. HF (aq.), MeCN, RT, 30 min; 2. 8% NaOH (10%).

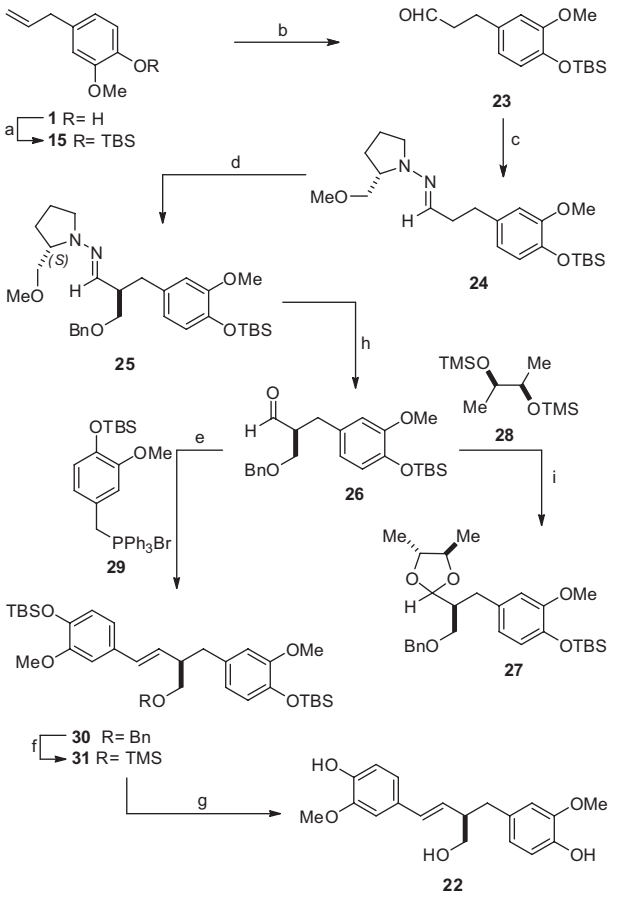
2.4. Imperanene

Imperanene (**22**), a phenolic compound which displays the rare C_6-C_4-C_6 pattern, was isolated from the rhizomes of *Imperata cylindrica.*[42] In traditional Chinese medicine, this plant is used as an anti-inflammatory and diuretic agent. However, in rabbits, the compound completely inhibits thrombin-induced platelet aggregation at concentrations as low as 6-10^{-4} mol L^{-1}. Other members of this rare class of natural products have also shown biological activity, as antiplatelet aggregation agents.[43]

The search for new platelet aggregation inhibitors to treat conditions such as heart attack, and the need to elucidate the absolute configuration of the natural product, prompted Shattuck and co-workers[44] to devise a total synthesis of both enantiomers of **22**, which was carried out in eight steps and 82-90% *ee* from eugenol (**1**).

The total synthesis of **22** (Scheme 4) was initiated with the protection of eugenol as the silyl ether **15**, in 78% yield. This was followed by the hydroboration of the double bond with disiamyl borane, and furthered by oxidation of the organoborane intermediate to the aldehyde **23** with pyridinium chlorochromate (PCC), in 75% yield.

Access to the aldehyde **23** set the stage for the diastereoselective introduction of the hydroxymethyl side chain (**25**), which was performed in approximately 80% yield via the asymmetric alkylation of the corresponding Enders' hydrazone (**24**) and its enantiomer, with BOMCl.[45]



Scheme 4. Reagents and conditions: (a) TBSCl, imidazole, dimethylformamide (DMF), RT, 19 h (78%); (b) 1. disiamylborane, 0 °C, 3 h; 2. PCC, CH_2Cl_2, reflux, 2 h (75%); (c) *S*AMP, 0 °C → RT, 20 h (84%); (d) 1. lithium di-isopropyl amide (LDA), 0 °C, 5.5 h; 2. benzyloxymethyl chloride (BOMCl), −120 °C, 20 min, then RT, 20 h (77%); (e) ^{n}BuLi (2 equiv.), **29** (2 equiv.), THF, 0 °C, 30 min → RT, 19 h (**30**, 72%); (f) $PhSSiMe_3$ (10 equiv.), $^nBu_4NI$ (1.5 equiv.), ZnI_2 (5 equiv.), 1,2-dichloroethane (DCE), RT (**31**, 65%); (g) tetra-*n*-butylammonium fluoride (TBAF) (3.3 equiv.), THF, RT, 30 min (**22**, 82%); (h) O_3, CH_2Cl_2, −78 °C, 30 min (79%); (i) TMSOTf (cat.), CH_2Cl_2, −78 °C, 3 h, then 0 °C, 1 h (76%).

The hydrazones **24** were prepared in high yield by reaction of **23** with (*S*)-1-amino-2-methoxymethylpyrrolidine (*S*AMP) and the (*R*)-enantiomer (*R*AMP), as chiral auxiliaries.[46] Only the route employing *S*AMP is shown.

The chiral auxiliary was removed ozonolytically to form the aldehyde **26**, and chiral acetal **27** was prepared with the aid of (*R*,*R*)-diol derivative **28**, in order to determine its enantiomeric excess by nuclear magnetic resonance (NMR) spectroscopy, employing $Eu(fod)_3$ as chiral shift reagent.[47] On the other hand, the aldehyde **26** was coupled under optimized conditions with the Wittig reagent **29**, furnishing alkene **30** in a ca. 5:1 *E/Z* ratio.

Transprotection of the benzyl group into a TMS ether (**31**) in 65% yield, followed by fluordesilylation with TBAF, enabled the smooth removal of both silicon-based protecting groups and afforded **22** in 82% yield. This

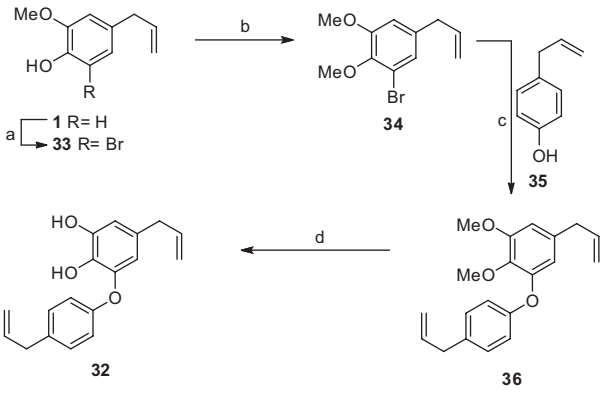
strategy avoided product instability associated with the hydrogenolytic debenzylation.

2.5. Obovatol

Obovatol (**32**) was isolated from a *Magnolia* species, which bark has traditionally been used in East Asia as a folk remedy for gastrointestinal disorders, cough, anxiety and allergic diseases.[48] The natural product was found to inhibit nitric oxide production, and the enzymes chitin synthase 2 and acyl-CoA:cholesterol acyltransferase.[49] Recently, it was also reported that obovatol has antitumor and anti-inflammatory activity through inhibition of NF-κB, a transcriptional factor significant to control cancer cell growth activity, and that this diaryl ether compound could be effective against photo-damaged skin.[50]

Jung and co-workers[51] recently reported a concise, four-steps total synthesis of the natural product (Scheme 5) from eugenol (**1**), which proceeds in 40% overall yield and relies on a chemoselective *ortho*-bromination of a phenol in the presence of a double bond.

Therefore, treatment of eugenol with *i*-PrMgCl as a base and 1,3-dibromo-5,5-dimethylhydantoin as an electrophile afforded 78% of bromoarene **33**.[52] Methylation of **33** furnished 90% of **34**, the required precursor for the diaryl ether coupling with *p*-allylphenol (**35**). This reaction was better performed under the conditions of Ma, affording 75% of the Ullmann product **36**, uncontaminated with β-methylstyrene derivatives resulting from double bond conjugative migration.[53] Final demethylation of the coupling product **36** with BBr_3 afforded 75% of the synthetic obovatol (**32**).



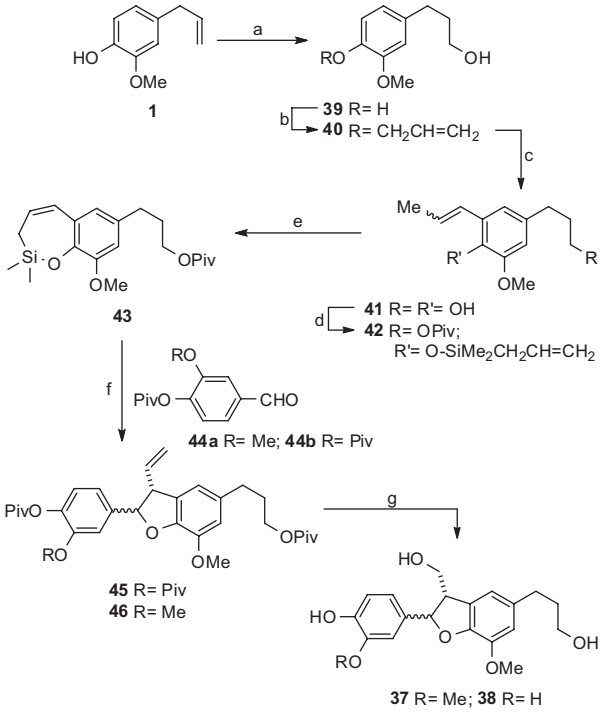
Scheme 5. Reagents and conditions: (a) 1. *i*-PrMgCl, THF, 30 min, –78 °C; 2. 1,3-dibromo-5,5-dimethyl hydantoin, 3 h, –78 °C (78%); (b) MeI, K_2CO_3, DMF, 2 h, RT (90%); (c) 4-HO–$C_6H_4CH_2CH{=}CH_2$, Cs_2CO_3, CuI, *N,N*-dimethylglycine hydrochloride, dioxane, 90 °C, 48 h (75%); (d) BBr_3, CH_2Cl_2, 30 min, –78 °C, RT, 2 h (75%).

2.6. Dihydrodehydroconiferyl alcohols

Neolignans are widely distributed natural products, which act as plant defense substances.[54] They also exhibit important biological activities as antitumor agents, bactericides, enzymatic inhibitors, antioxidants, etc. Several neolignans have been totally synthesized from eugenol, employing different approaches.

Cis- and *trans*-dihydrodehydro diconiferyl alcohols (**37**) are neolignans that were isolated from the twigs of *Taxus mairei*.[55] Rodríguez-García and co-workers[56] devised a six-step synthesis of neolignan **37** and its *O*-methyl analog **38** carrying a dihydrobenzo[*b*]furan skeleton (Scheme 6), based on a ring-closing metathesis reaction to produce a benzo[*f*][1,2]oxasilepine (**43**) intermediate, which was condensed with aromatic aldehydes **44**, in a modified Sakurai-Hosomi reaction.[57]

To that end, eugenol (**1**) was submitted to a hydroboration-oxidation reaction, which gave 84% of a mixture containing



Scheme 6. Reagents and conditions: (a) 1. $BH_3{\cdot}SMe_2$, THF; 2. H_2O_2, NaOH (84%); (b) $CH_2{=}CHCH_2Br$, K_2CO_3, Me_2CO (83%); (c) 1. *N,N'*-dimethylaniline, Δ (100%); 2. NaO^{t}Bu, DMSO, Δ (69%); (d) 1. PivCl, DMAP, pyridine, CH_2Cl_2 (83%); 2. $CH_2{=}CHCH_2SiMe_2Cl$, Et_3N, CH_2Cl_2 (86%); (e) Grubbs II, CH_2Cl_2, Δ (75%); (f) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (g) 1. OsO_4, KIO_4, THF-H_2O (95% from **45**; 91% from **46**); 2. $LiAlH_4$, THF, –60 °C (**37**, 84%; **38**, 90%).

mainly the primary alcohol **39**. Subsequent allylation of the free phenol afforded 83% of the allyl ether **40**, which was subjected to sequential Claisen rearrangement and double bond isomerization with Na^{t}BuO, furnishing **41** quantitatively.

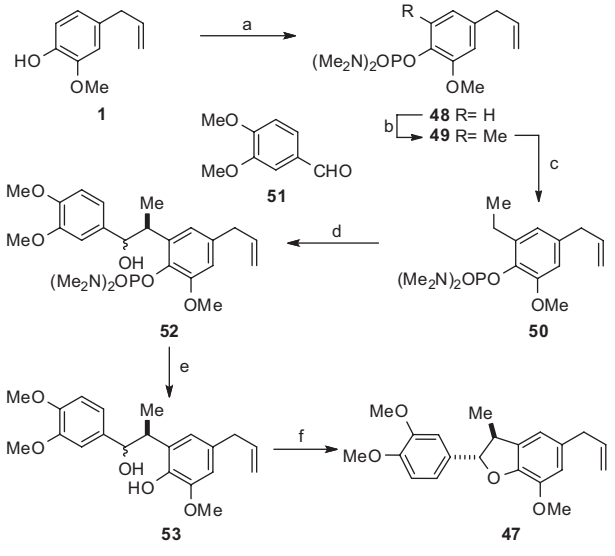
Selective protection of the alcohol as pivalate (83% yield) and silylation of the phenolic OH with allylchlorodimethylsilane, provided the intermediate

allylsiloxane **42** (86% yield) and set the stage for a ring-closing metathesis with Grubbs II catalyst, which gave the key benzo[*f*][1,2]oxasilepine **43** in 75% yield.

The modified Sakurai-Hosomi reaction of **43** with aldehydes **44a**,**b** under promotion by $BF_3{\cdot}OEt_2$ took place without diastereoselectivity,[58] affording 1:1 mixtures of the *cis*- and *trans*- dihydrobenzofurans **45** and **46** (70-78% yield), the relative stereochemistry of which was assigned after NMR analysis. Finally, oxidative fission of the double bond with OsO_4/KIO_4 afforded the corresponding aldehydes, whereas subsequent treatment with $LiAlH_4$ effected the simultaneous reduction of the aldehyde and deprotection of the pivalate ester, furnishing the target neolignans **37** and **38** in 84% and 90% yield, respectively.

2.7. Carinatol

Carinatol (**47**) is a neolignan isolated from the bark of *Virola carinata,* a tropical evergreen tree in the Myristicaceae family that is indigenous to Colombia, Venezuela and Brazil.[59] For the total synthesis of this natural product (Scheme 7), phosphamidate **50** was prepared in three steps and 94% yield from eugenol, by means of protection of the free phenol of **1** as the phosphamidate **48**, followed by heteroatom-directed *ortho* metalation-alkylation to **49** and final lateral metalation-methylation.

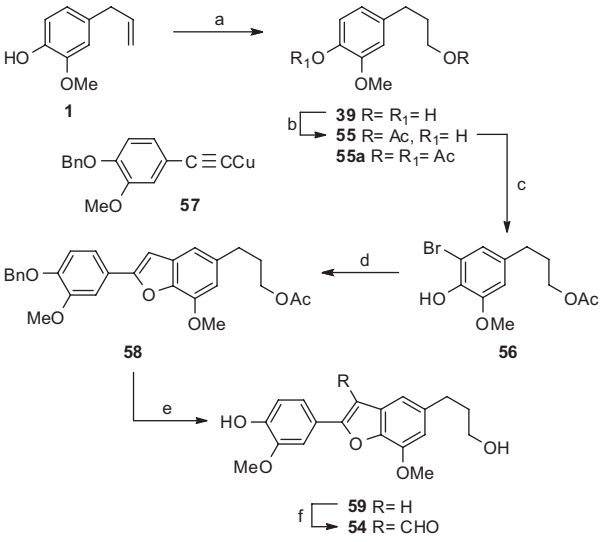


Scheme 7. Reagents and conditions: (a) 1. NaH, THF; 2. $ClPO(NMe_2)_2$ (97%); (b) 1. ^{s}BuLi; 2. MeI (96%); (c) 1. ^{s}BuLi; 2. MeI (96%); (d) ^{s}BuLi, tetramethylethylenediamine (TMEDA), $3,4\text{-}(MeO)_2C_6H_3CHO$, –108 °C (71%); (e) $LiAlH_4$ (51%); (f) AcOH (41%).

The ethylarene derivative **50** was submitted to an additional lateral metalation, at the benzylic methylene group *ortho* to the phosphamidoyl group, and reacted with 3,4-dimethoxy benzaldehyde (**51**), furnishing a 77:23 (*anti*:*syn*) mixture of carbinols **52** in 71% yield. Then, the phosphamidoyl protecting group was reductively removed in 53% yield toward phenol **53**, which was subsequently cyclized in 41% yield under acidic conditions, to afford carinatol (**47**).[60]

2.8. XH-14

The neolignan XH-14 (**54**) was isolated from the plant *Salvia miltiorrhiza* and found to be a potent antagonist of the A1 adenosine receptor.[61] Scammells and co-workers[62] reported a short total synthesis of the natural product from eugenol (Scheme 8).



Scheme 8. Reagents and conditions: (a) 1. $BH_3{\cdot}SMe_2$, THF; 2. H_2O_2, NaOH (84%); (b) 1. Ac_2O, $BF_3.Et_2O$, THF, 0 °C, 5 h (77%); (c) NBS, Et_2NH, CH_2Cl_2, RT, 16 h (39%); (d) CuC≡C(4-BnO-3-MeO)Ph, pyridine, 115 °C, 20 h (ca. 65%); (e) 5% Pd/C, AcOH-THF, RT, 10 h (ca. 92%); (f) 1. $Zn(CN)_2$, HCl, KCl, Et_2O, 0 °C, 30 min; 2. EtOH-H_2O, 50 °C (ca. 59%).

The synthesis was initiated with the hydroboration-oxidation of the double bond of **1**, with $BH_3.SMe_2$, followed by selective protection of the resulting primary alcohol **39** (obtained in 84% yield) with Ac_2O and $BF_3.Et_2O$,[63] which afforded 77% of a 92:8 mixture of mono- and di-acetylated compounds **55** and **55a**. Taking advantage of the activating and directing potential of the free phenol, **55** was selectively *ortho*-brominated with NBS in the presence of diisopropylamine, affording 39% of **56**.[64]

In turn, the bromide **56** was coupled with cuprous (4-benzyloxy-3-methoxy)phenyl acetylide (**57**) to afford 65% yield of **58**, which was subjected to catalytic debenzylation toward **58**, furnishing 92% of the product. Final formylation of **59** using a Gatterman-Adams reaction resulted in 59% yield of XH-14 (**54**).

2.9. Eupomatenoids **17** and **18**

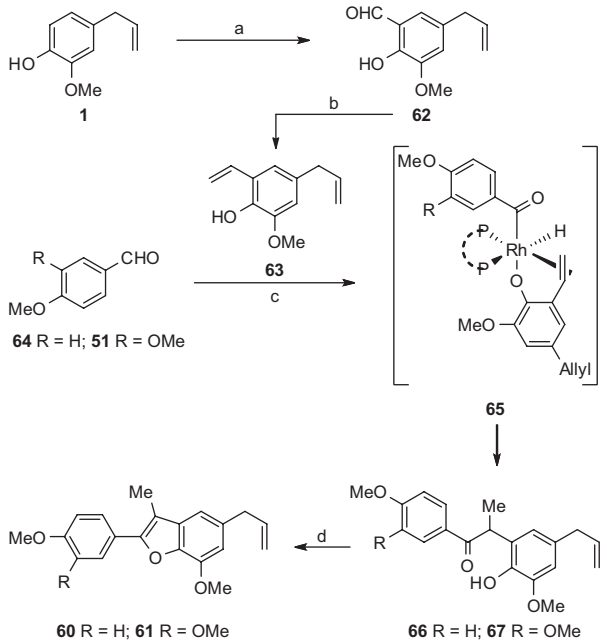
The eupomatenoids are a class of neolignans, which exhibit insecticidal, antimicrobial, antioxidant, and antitumor activity.[65] Eupomatenoid 17 (**60**) was isolated from *Eupomatia bennetti* F. Muell,[66] whereas eupomatenoid 18 (**61**) was obtained from *Virola pavonis*, *Eupomatia bennetti* F. Muell, and the bark of *Virola carinata* (Myristicaceae).[67]

Dong and co-workers[68] devised short syntheses of eupomatenoids 17 and 18, which employ a fully functionalized vinylphenol derived from eugenol and a hydroacylation and cyclocondensation/dehydration reaction to forge the benzofuran core (Scheme 9).

The synthesis of the eugenol derived component **63** was performed in two steps, by Duff formylation of **1**, which proceeded in 30% yield, followed by Wittig olefination of the resulting aldehyde **62** (82% yield). The vinyl phenol **63** was then coupled with benzaldehydes **64** and **51** under rhodium catalysis, furnishing the corresponding hydroacylation products, the ketones **66** and **67**, through the intermediacy of **65**. In turn, the phenolic ketones were cyclodehydrated with TFA, affording 78% and 82% of the targets **60** and **61**, respectively.

2.10. Santalin B

Red sandalwood, a rare hardwood, obtained from the tree *Pterocarpus santalinus* and related species, is one



Scheme 9. Reagents and conditions: (a) Hexamine, AcOH, 125 °C (30%); (b) PPh_3MeBr, ^nBuLi, THF, 0 °C → RT (81%); (c) Rh(COD) OMe_2 (4 mol%), bis(dicyclohexylphosphino)methane (dcpm, 8 mol%), dioxane, 70 °C, 24 h; (d) trifluoroacetic acid (TFA), CH_2Cl_2 (1:20), 40 °C, 3 h (**60**, 78%; **61**, 82%, overall).

of the colored materials found in nature that has been valued for millennia. In China, it was once reserved for the furniture of the imperial household, whereas in Ayurvedic medicine it is used for treating digestive tract problems and coughs.

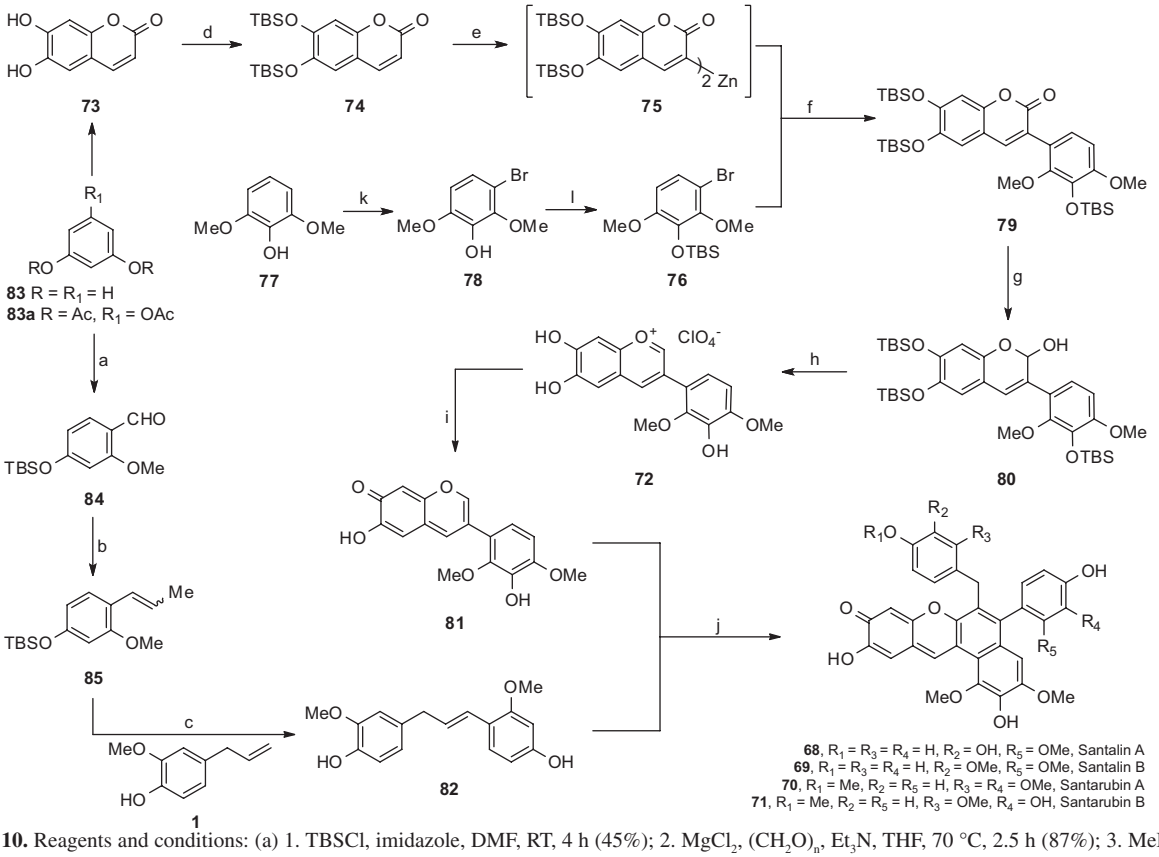
Despite chemical investigations of its colored constituents date back to the famous Pelletier,[69] the chemical structures of the santalins A and B (**68**, **69**) and the santarubins A and B (**70**, **71**), were unequivocally demonstrated in 1975.[70] These heterocycles, which share a common 9 h-benzo[*a*]xanthen-9-one core, were synthesized in 2013 by Strych and Trauner (Scheme 10),[71] employing pyrilium salt **72** as a common precursor, and a biomimetic strategy based on a previous speculation.[72] Their work demonstrated that complex molecular scaffolds can be assembled along biosynthetic lines, without the need of enzymatic catalysis.

The synthesis of santalin B (**69**) was performed by reaction of the building blocks **81** and benzylstyrene **82**. For the preparation of **82**, aldehyde **84**,[73] easily available in three steps from resorcinol (**83**), was subjected to a Wittig olefination to afford 63% of the β-methylstyrene **85**, as a 2.1:1 mixture of diastereomers. In turn, the mixture was submitted to a Grubbs II catalyst mediated olefin cross-metathesis reaction[74] with eugenol (**1**) to yield 41% of the expected benzylstyrene **82** after desilylation.

On the other hand, the synthesis of **81** commenced with esculetin (**73**), easily available in 52% yield from the H_2SO_4-mediated condensation of 1,3,4-trisacetoxybenzene **83**(**a**) with malic acid, at 120 °C for 2.5 h.[75] Esculetin was protected in 96% yield as the bis(silyl ether) **74** before it was subjected to a palladium-catalyzed cross-coupling[76] with bromoarene **76** via the di-organozinc intermediate **75**, to afford 84% of the isoflavonoid derivative **79**. Compound **76** was accessed in 95% overall yield from phenol **77** through the intermediacy of aryl bromide **78**.[77]

Compound **79** was then selectively reduced with DIBAL-H in 85% to the lactol **80**, which upon treatment with $HClO_4$ in AcOH, underwent protonation and subsequent dehydration with concomitant desilylation to furnish 76% of the isoflavylium perchlorate **72**.

Attempts to effect the biomimetic cascade reaction between isoflavylium perchlorate **72** and **82** in the presence of different bases met with limited success. However, santalin B (**69**) could be accessed in 62% yield when the isoflavylium salt was deprotonated in 89% yield to the anhydrobase **81** with 2,6-bis-*tert*-butylpyridine and then reacted with **82** under aerobic conditions. The mildness of the conditions of this final reaction raised the question whether the cycloaddition/oxidation cascade could take place spontaneously in nature.



Scheme 10. Reagents and conditions: (a) 1. TBSCl, imidazole, DMF, RT, 4 h (45%); 2. $MgCl_2$, $(CH_2O)_n$, Et_3N, THF, 70 °C, 2.5 h (87%); 3. MeI, Ag_2O, Et_2O, RT, 10 h (81%); (b) PPh_3EtBr, BuLi, THF, RT, 2 h (63%); (c) 1. Grubbs II (0.1 equiv.), CH_2Cl_2, 50 °C, 8 h (85%); 2. TBAF, THF, RT, 30 min (48%); (d) TBSCl, imidazole, DMAP (cat.), DMF, RT, 3 h (96%); (e) 1. $(TMP)_2Zn.MgCl_2.2LiCl$, THF, RT, 1 h; (f) **76**, $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), PhMe, 65 °C, 2 h (84% overall); (g) DIBAL-H, CH_2Cl_2 (85%); (h) $HClO_4$ (8 equiv.), AcOH, RT, 9 h (76%); (i) 2,6-di-*tert*-butyl pyridine, MeCN, 0 °C, 10 min (89%); (j) **82** (2.5 equiv.), MeCN/ MeOH (5:1), 80 °C (62%); (k) Br_2, CCl_4, −10 °C, 5 min (98%); (l) TBSCl, imidazole, DMAP (cat.), DMF, RT, 45 min (96%).

2.11. (–)-Plicatic acid

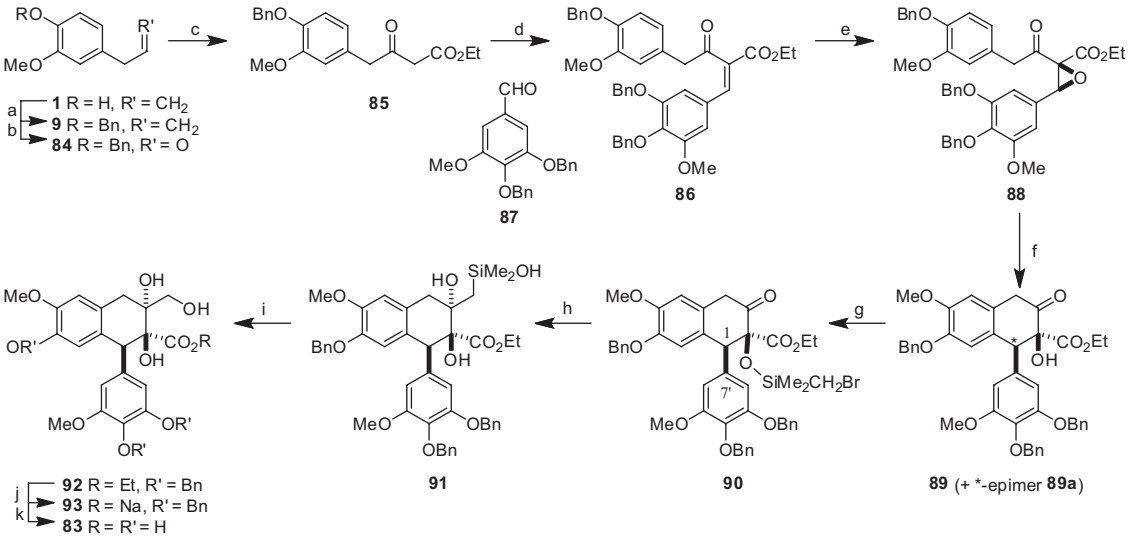
Plicatic acid (**83**) was isolated from western red cedar (*Thuja plicata*) and its structure was spectroscopically elucidated.[78] This lignan has an unusual skeleton, that is densely functionalized and bears a motif of three contiguous (quaternary-quaternary-tertiary) stereocenters. Plicatic acid has been shown to cause inflammatory and allergic reactions, which are characterized by increased concentrations of immunoglobulins, histamine, leukotrienes, eosinophils, and T-cell levels in the blood.[79] Furthermore, the natural product has been identified as the causative agent of occupational asthma.[80]

With the aim of gaining access to analogues that could be valuable for biomedical studies aimed to elucidate the molecular mechanism underlying the biological activities of plicatic acid, Deng and co-workers[81] performed the first asymmetric total synthesis of the natural product **83** (Scheme 11), employing eugenol (**1**) as starting material.

Thus, benzylation of eugenol to yield **9**, followed by oxidative cleavage of the olefin moiety afforded quantitative yield of the known aldehyde **84**, which was efficiently converted (92%) into β-ketoester **85**.[82] In turn, the Knoevenagel condensation of **85** and **87** gave a 5:3 *E/Z* separable mixture of olefins **86**. Since *Z*-**86** was readily isomerized to *E*-**86** with pyridine in refluxing benzene, it could be easily recycled, raising the overall yield of *E*-**86** to 80% in one cycle of the Knoevenagel condensation-isomerization process.

A modification of Seebach's asymmetric epoxidation with (*S*,*S*)-TADOOH as terminal oxidant[83] furnished 83% of epoxide **88** in 98% *ee*, whereas the regioselective Friedel-Crafts reaction leading to **89** (as a 4:1 diastereomeric mixture with **89a**, in favor of the desired diastereomer) was optimally performed in 70% yield, in the presence of trifluoromethanesulfonic acid (TfOH). Only the *R*-hydroxy ketone was isolated. Interestingly, broad and split peaks were observed in the ^1H and ^{13}C NMR spectra of this and more advanced intermediates, including the final product, resulting from the atropisomerism arising from the hindered rotation along the C1–C7' bond.

The easy enolizability of the ketone forced to implement the stereoselective addition of the hydroxymethyl group to the carbonyl, as an intramolecular stereospecific



Scheme 11. Reagents and conditions: (a) NaH, BnBr, DMF, 0 °C, 1 h (100%); (b) 1. OsO_4 (cat.), *N*-methylmorpholine-*N*-oxide (NMO), ^tBuOH:H_2O:THF (2:1:4), RT, 1 h; 2. $NaIO_4$ CH_2Cl_2-H_2O (1:1), 0 °C, 40 min (100%); (c) $N_2CHCOOEt$, $SnCl_2$ (cat.), CH_2Cl_2, −72°C, 5 min, RT, overnight (92%); (d) **87**, piperidine, PhCOOH, benzene, reflux, 2.5 h (80%, after one cycle, *E*/*Z* = 5:3); (e) (*S*,*S*)-TADOOH (cat.), LiOH, THF, 0 °C, 6 h; RT, overnight (83%, *ee* = 98%); (f) TfOH (4 mol%), CH_2Cl_2, −10 °C → RT, 15 min (**89**, 70%; **89a**, 17%); (g) $ClSi(Me)_2CH_2Br$, imidazole, DMF, RT, 1 h (75%; 94% brsm); (h) SmI_2, NiI_2 (0.1 equiv.), THF, 0 °C, 1 h (58%); (i) 35% H_2O_2, $NaHCO_3$, MeOH-THF, RT, overnight (87%; 90% brsm); (j) ^nPrSNa, DMF, 50 °C, 24 h (97%); (k) 1. H_2 (1 atm), Pd/C, MeOH, RT, 4 h; 2. Dowex-50, MeOH (72% overall).

addition of a masked hydroxymethyl group to the ketone, performing the critical C–C bond formation under nearly neutral conditions. Therefore, **89** was first silylated with $ClSi(Me)_2CH_2Br$ to yield 75% of **90**, which underwent a SmI_2-mediated, intramolecular Barbier reaction[84] in the presence of NiI_2[85] to afford 59% of silanol **91**.

The Fleming-Tamao-Kumada[86] oxidation of **91** furnished triol-ester **92** in 50% yield, the treatment of which with sodium propanethiolate afforded 97% of the sodium carboxylate **93**.[87] Exhaustive catalytic debenzylation of **93**, followed by treatment with a cationic exchange resin furnished 72% of synthetic (−)-plicatic acid (**83**).

2.12. Schefferine

Schefferine (tetrahydropalmatrubine, **94**) was isolated from the bark of *Schefferomitra subaequalis* Diels (Anonaceae), a New Guinea liana found as a climber on rain forest trees.[88] Schefferine was postulated as key intermediate in the biosynthesis of sinactine from reticuline and as a precursor of tetrahydropalmatine.[89]

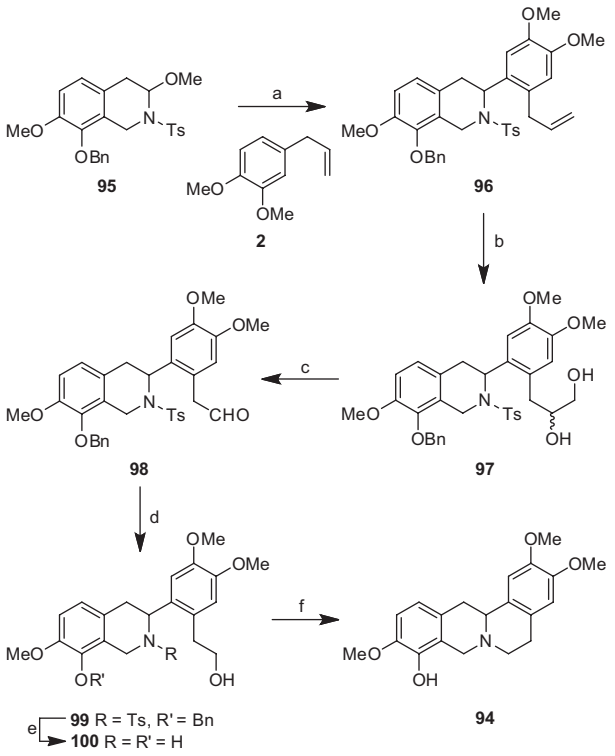
Ponzo and Kaufman[90] reported a convenient entry into 3-substituted tetrahydro-isoquinolines like schefferine (Scheme 12), featuring the reaction of silicon-based nucleophiles with tosyliminium ions, generated upon addition of Lewis acids to tosylamidals and employed this strategy for the synthesis of a natural product.[91] By capturing the resulting tosyliminium ions with electron rich aromatics, such as phenols and their ethers, Bianchi and Kaufman[92] extended the scope of this transformation to the elaboration of 3-aryl tetrahydroisoquinolines and also performed a total synthesis of schefferine.[93]

Thus, the known amidal **95** was reacted with methyleugenol (**2**) under $BF_3{\cdot}Et_2O$ promotion, to afford 88% of the 3-aryl tetrahydroisoquinoline derivative **96**. Next, a two-step dihydroxylation of **96** with OsO_4-NMO followed by a further treatment of the resulting diols **97** with $NaIO_4$ gave 89% of aldehyde **98** avoiding its over-oxidation. The latter was reduced with $NaBH_4$ to furnish 92% of alcohol **99**.

The reaction of **99** with sodium in liquid ammonia[94] was found to cleanly effect the simultaneous cleavage of both, the benzyl and tosyl protective groups,[95] providing amino alcohol **100** in 83% yield. Finally, the intramolecular Mitsunobu amination of **100** with the DEAD-PPh_3 couple in THF containing 1 equivalent of HBF_4 afforded 82% of schefferine (**94**). The addition of HBF_4 provoked protonation of the DEAD-derived hydrazide anion intermediate, avoiding its involvement as a competing nucleophile in the amination process.[96]

2.13. Ningalin C

Ningalin C (**110**) is a novel pyrrole-type aromatic alkaloid, isolated in 1997 together with other three congeners, from an unidentified ascidian of the genus *Didemnum* collected in ascidia-rich habitats near the Ningaloo Reef region, at the northwest cape of Western Australia.[97] Biogenetically, the ningalins appear to be derived from the condensation of 3,4-dihydroxyphenylalanine

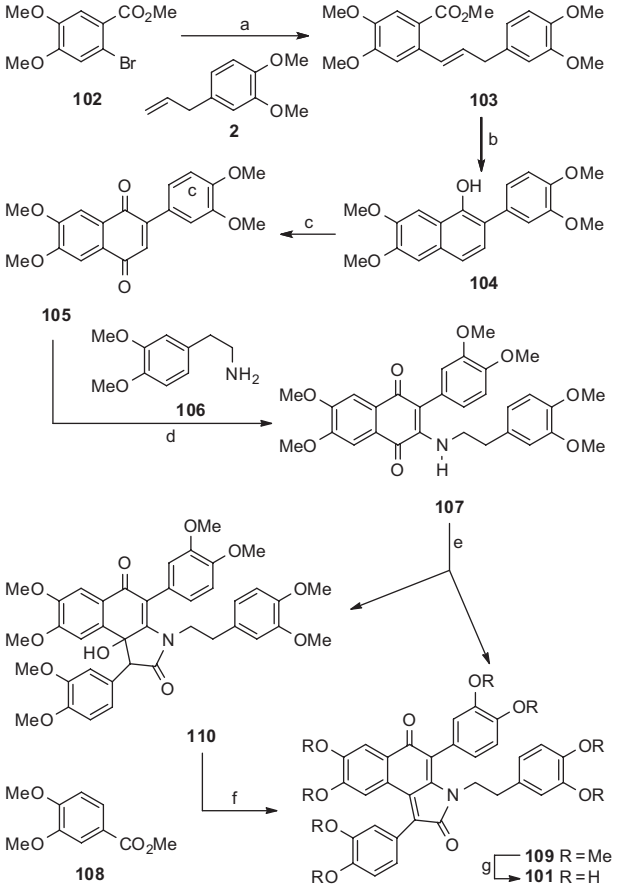


Scheme 12. Reagents and conditions: (a) **2**, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –78 °C, 15 min, –30 °C, 30 min (88%); (b) OsO_4 (cat.), NMO, Me_2CO-H_2O-^{t}BuOH (4:2:1) overnight, RT; (c) $NaIO_4$, THF-H_2O (3:1) overnight, RT (89%, overall); (d) $NaBH_4$, MeOH-Et_2O (4:1), 0 °C, 15 min (92%); (e) 1. Na, NH_3, –33 °C; 2. NH_4Cl, –33 °C → RT (83%); (f) PPh_3, diethyl azodicarboxylate (DEAD), HBF_4, THF, reflux (82%).

(DOPA).[98] Compound **110** exhibits anti-cancer activity, because of its ability to reverse multi drug resistance.[99]

The Namsa-aid-Ruchirawat synthesis of ningalin C (Scheme 13)[100] commenced with the Heck-type palladium-catalyzed coupling reaction[101] between methyl 2-bromoveratrate (**102**) and methyleugenol (**2**); this afforded 65% of ester **103**, which was further cyclized[102] with LDA to naphthol **104** (76%).[103] Next, oxidation of naphthol **104** with acidic H_2O_2 containing a trace of iodine, afforded 62% of the expected naphthoquinone **105**, which was converted into the key aminoquinone intermediate **107** by nucleophilic addition of homoveratrylamine (**106**).[104]

Treatment of the aminonaphthoquinone **107** with the carbanion of methyl homoveratrate (**108**) effected the selective addition of the anionic species to the right ketone group of **107**, in a process that was completed with the cyclization and subsequent dehydration towards the lactam, generating the pyrrolinone system of the ningalin C skeleton **109** in 69% yield, accompanied by 9% of the hydrated product **110**. The latter could be quantitatively dehydrated toward **109** by acid treatment. Finally, permethyl ningalin C (**109**) was demethylated[105] with BBr_3 to give 72% of ningalin C (**101**).



Scheme 13. Reagents and conditions: (a) $Pd(PPh_3)_4$, $NaHCO_3$, DMF, reflux, 24 h (65%); (b) LDA (2 equiv.), THF, –78 °C, 2 h, then RT 2 h (76%); (c) H_2O_2, I_2, H_2SO_4, MeOH (62%); (d) homoveratrylamine (**106**), EtOH, RT, 24 h (80%); (e) 1. LDA (2 equiv.), THF, –78 °C; 2. methyl homoveratrate (**109**, 1 equiv.), THF, –78 °C, 2 h then RT, 2 h (**110**, 73%; **108**, 15%); (f) 2M HCl, CH_2Cl_2, RT, 5 h (100%); (g) BBr_3, CH_2Cl_2 (73%).

2.14. (–)-Platensimycin

(–)-Platensimycin (**111**) was isolated from *Streptomyces platensis* MA7327, which originated from South Africa,[106] after a massive screen of 250000 extracts. Compound **111** is a potent inhibitor of fatty acid synthase that holds promise of being useful for the treatment of metabolic disorders, such as diabetes and "fatty liver", and pathogenic infections caused by drug-resistant bacteria. Eey and Lear[107] reported an original approach towards a key intermediate for the natural product starting from eugenol (**1**), which was later used for its total synthesis (Scheme 14).[108]

The first intermediate **117** was prepared in 75% overall chemical yield and 91% *ee*, in 7 steps from eugenol (**1**). The sequence entailed the *O*-benzylation of the free phenol of eugenol to give **9**, followed by a two-stage oxidative fission of the alkene toward **84**, through the intermediacy of the diol **112**. Next, olefination of the aldehyde **84** with phosphorane **113** followed by $LiAlH_4$-mediated

reduction of the resulting ester furnished 88% of **114**, which was subjected to a catalytic Sharpless epoxidation with *N*,*N*-diisopropyltryptamine, L-(+)-DIPT, to afford the expected epoxy alcohol. Regioselective opening of the oxirane with allyl magnesium chloride,[109] followed by Martinelli's regioselective catalytic monotosylation to give **115**[110] in 81% overall yield, established the desired C12 stereocenter and set the stage for accessing lactol **117**.

To that end, the diol mono-tosylate **115** was first converted into the related bromohydrine **116** in 91% overall yield, by way of a base-assisted epoxide ring closing followed by LiBr-mediated ring opening.[111] The sequence was completed by oxidative cleavage of the double bond, which took place with concomitant cyclization to the *cis*-bromolactol **117** in 91% yield over the last 2 steps.

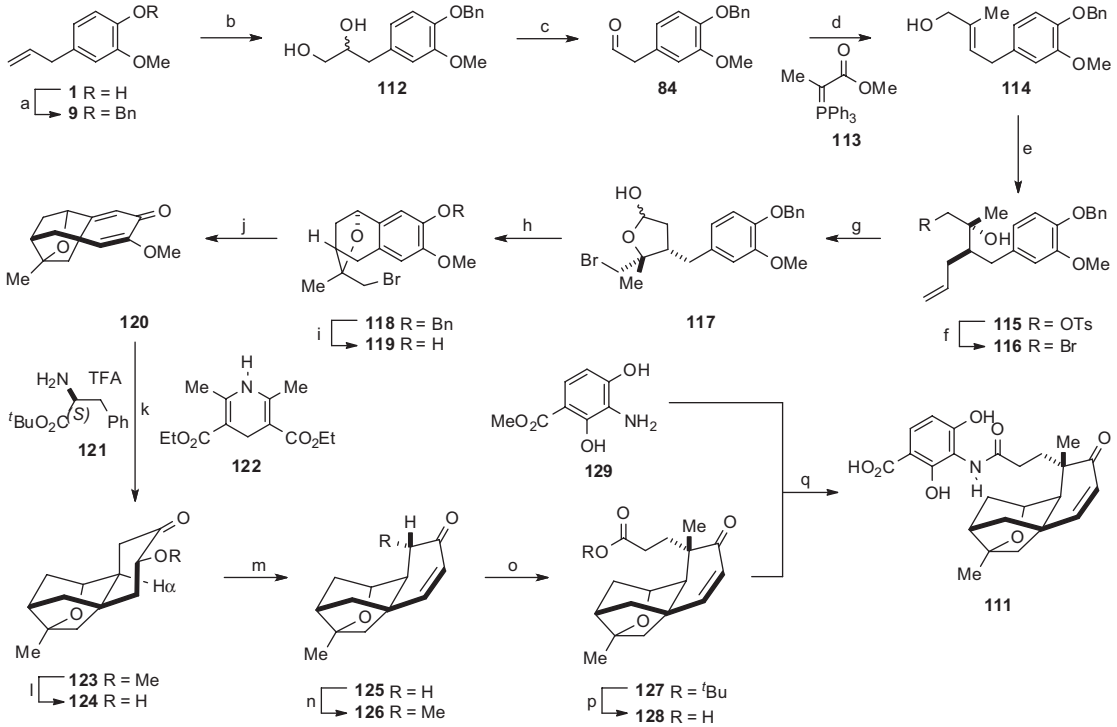
Cyclization of the lactol to afford **118** entailed a Friedel Crafts type alkylation, that was accomplished under Lewis acid promotion. Despite $SnCl_4$ afforded high yields of this compound, the reaction required a large excess of the Lewis acid. This was overcome by employing catalytic amounts of $Bi(OTf)_3$ in the presence of $LiClO_4$ as a co-catalyst,[112] to furnish **118** in 94% yield within 3.5 h.

Hydrogenolytic debenzylation of **118**, followed by exposure of the resulting phenol **119** to TBAF under high temperature produced the intramolecular alkylative dearomatization of the latter,[113] yielding 86% of the cage-like dienone **120**.

A sequential Hantzsch reagent-based (**122**) reduction of the dienone **120** in the presence of D-phenylalanine derivative **121**, followed by a Pd/C-mediated catalytic hydrogenation afforded 73% of the expected *cis*-decalinic methoxyketone **123**, admixed with the isomeric *trans*-decalin (*dr* = 4:1). This was employed as a scaffold to functionalize both α-positions of the ketone.

The installation of the conjugated double bond, which conducted to the synthesis of the key intermediate **125**, was accomplished in three steps and 60% overall yield. This was initiated by demethylation of **123** with $AlCl_3$/TBAI to yield 83% of **124**,[114] followed by mesylation of the resulting alcohol and thermally-assisted elimination of the mesylate with $LiBr/Li_2CO_3$ in DMSO.[115]

On the other hand, the stereochemically correct attachment of the methyl and propionate side chains was carried out by successive α-alkylations with MeI



Scheme 14. Reagents and conditions: (a) BnBr, TBAI (cat.), K_2CO_3, DMF, 55 °C, 16 h (99%); (b) OsO_4, NMO, THF-H_2O, RT, 16 h; (c) $NaIO_4$, THF-H_2O, RT, 4 h; (d) **113**, CH_2Cl_2, RT, 12 h (93% overall); 2. $LiAlH_4$, THF, −10 °C, 20 min; RT, 1.5 h (88%); (e) 1. L-(+)-DIPT, $Ti(O^iPr)_4$, *t*-butyl hydroperoxide (TBHP), CH_2Cl_2, −25 °C (98%, *ee* = 91%); 2. $ClMgCH_2CH{=}CH_2$, THF, −20 °C; 3. TsCl, $^nBu_2SnO$, Et_3N, CH_2Cl_2 (91%); (f) 1. K_2CO_3, MeOH (100%); 2. LiBr.H_2O, AcOH, THF, 90 °C (91%); (g) 1. OsO_4, NMO; 2. $NaIO_4$, THF-H_2O (2:1) (85%); (h) $Bi(OTf)_3$ (5 mol%), $LiClO_4$, CH_2Cl_2, 3.5 h; (i) H_2, Pd/C, THF; (j) TBAF, xylene, 130 °C, 4 h (86% overall); (k) 1. **121** (20 mol%), **122** (5 equiv.), dioxane, 60 °C, 130 h; 2. H_2, Pd/C, EtOAc-ethanolic KOH (2:1) (73% overall); (l) $AlCl_3$, TBAI, MeCN-CH_2Cl_2 (2:1), 0 °C (83%); (m) 1. MsCl, Et_3N, CH_2Cl_2, 0 °C to RT; 2. LiBr.H_2O, Li_2CO_3, DMSO, 150 °C (72% overall); (n) potassium bis(trimethylsilyl)amide (KHMDS), MeI, THF-HMPA, −78 °C → −10 °C (80%); (o) $H_2C{=}CHCO_2{}^tBu$, KO^tBu, ^tBuOH, THF, −10 °C → 0 °C (62%); (p) TFA, CH_2Cl_2, 0 °C (100%); (q) 1. **129**, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), Et_3N, DMF (71%); 2. 2 mol L^{-1} KOH (aq.), dioxane-MeOH, 35 °C (60%).

(80% yield of **126**) and *tert*-butyl acrylate to give 62% of ester **127**.[116] TFA-mediated removal of the *tert*-butyl ester moiety gave quantitative amounts of platensic acid (**128**). This was followed by a HATU-assisted amidation (in 71% yield) of the just uncovered carboxylic acid moiety of **128** with aniline derivative **129**[117] and final hydrolysis of the methyl ester to afford 60% of (−)-platensimycin (**111**). The synthesis took place in 21 steps for the longest linear sequence, with an overall yield of 3.8% from eugenol.

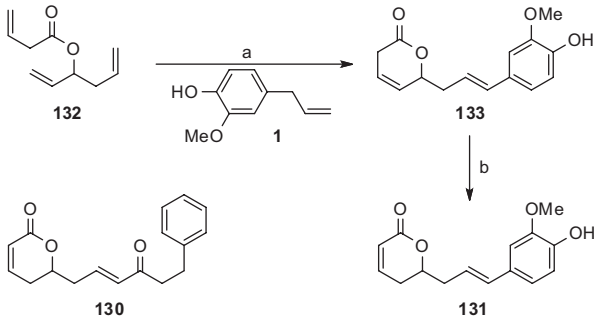
3. Synthesis of Analogs of Natural Products

3.1. Synthesis of chrysantemic acid esters

Taking into account that eugenol itself is a repellent against mosquitoes and expecting to achieve functional synergy, a series of pyrethroids was synthesized by connecting various eugenol derivatives to chrysanthematic acid and other carboxylic acids. The insecticidal activity of the compounds was evaluated by an immersion method on the fourth instar larvae of *Culex pipiens quinquefasciatus*. The results revealed that the larvae were sensitive to the synthesized compounds.[118]

3.2. Synthesis of an analog of rugulactone

Rugulactone (**130**), a naturally occurring pyrone, was isolated from the plant *Cryptocaria rugulosa*.[119] The compound is an efficient inhibitor of the nuclear factor (NK-κB) activation pathway. This factor has a major biological role, because once bonded to discrete DNA sequences, it can initiate gene expressions that are implicated in major diseases like cancer and diabetes.



Scheme 15. Reagents and conditions: (a) **1** (3 equiv.), Grubbs II (2.5 mol%), CH_2Cl_2, reflux (70%); (b) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.1 equiv.), THF, RT, overnight (52%).

The rugulactone analog **131** was prepared (Scheme 15) during the synthesis of the natural product as a test of the key ring closing metathesis/cross-metathesis strategy towards the functionalized pyrone core.[120] The synthesis entailed the Grubbs II-mediated reaction of triene **132** with eugenol, to afford 79% of intermediate **133**, followed by DBU-assisted conjugative isomerization of the internal double bond of the latter, achieved in 52% yield.

3.3. Synthesis of a brominated analog of dihydrodieugenol

5,5'-Biphenyl structures occur frequently in softwood lignins because they arise from the symmetrical coupling of the corresponding monomers. Dehydrodieugenol (**134**) is the symmetrical dimer of eugenol (**1**).[121] The compound (Scheme 16) is a conformationally flexible biphenyl derivative, which manifests biological activity comparable with that observed in eugenol, and others, such as antidepressant.[122]

The related *O*-methyldehydrodieugenol **134a**[123] and di-*O*-methyldehydrodieugenol **134c**[124] have been isolated from *Ocotea cymbanum* and *Nectandra polita*, respectively, whereas magnolol (**134b**), the symmetrical dimer of chavicol, was isolated from *Magnolia officinalis*.[125] The presence of the allyl chains and the four oxygenated groups seem to be a chemostructural requirement for pharmacological activity.[126]

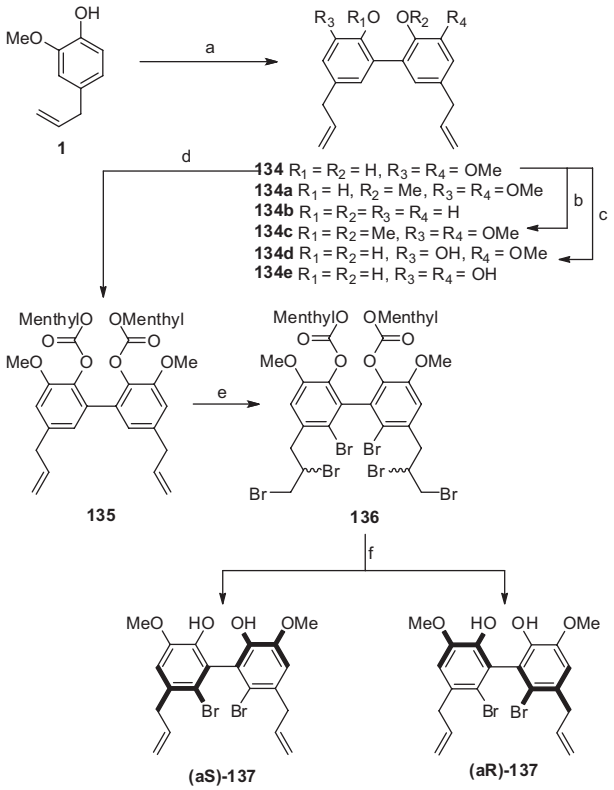
Dehydrodieugenol and **134b** have been studied as antioxidant and anti-inflammatory agents.[127] Compound **134** is less toxic than eugenol and exhibits a stronger scavenging ability for superoxide radicals with respect to hydroxyl radicals ($HO^{\bullet}$) and a stronger inhibitory effect on lipid peroxidation.[128] Therefore, it has inspired the synthesis of new biphenyls aiming to improved biological activities.[129]

During the last 60 years, compound **134** has been synthesized repeatedly by chemical[130] and biochemical[131] means, not always in satisfactory yield.[132] On the other hand, compounds **134d** and **134e** have been recently prepared in combined 95% yield from dehydrodieugenol (**134**) by $AlCl_3$-mediated demethylation.[133]

Dehydrodieugenol (**134**) enhances the function of the gamma-aminobutyric acid ($GABA_A$) receptor at concentrations higher than 3-10 mmol L^{-1}.[134] This compound, as well as its demethylated derivatives, were less potent as antiproliferative agents when evaluated against a panel of three cell lines (HL-60 PC-3 MOLT-4). Among the compounds **134** and **134a-c**, only dehydrodieugenol (**134**) was inactive as antimicrobial against *Staphylococcus aureus* ATCC 29213, Methicillin resistant *S. aureus* 15187 and Vancomycin resistant Enterococci.

Recently, atropoisomeric bromo-derivatives of **134** have also been prepared. Eugenol was oxidized with $K_3Fe(CN)_6$ in an open flask, affording 95% of **134**. This biphenyl was efficiently solved into the homochiral atropo-

diastereomeric bromo derivatives a*R*-**137** and a*S*-**137** by intermediacy of the di-(−)-menthyl dicarbonates **135**.

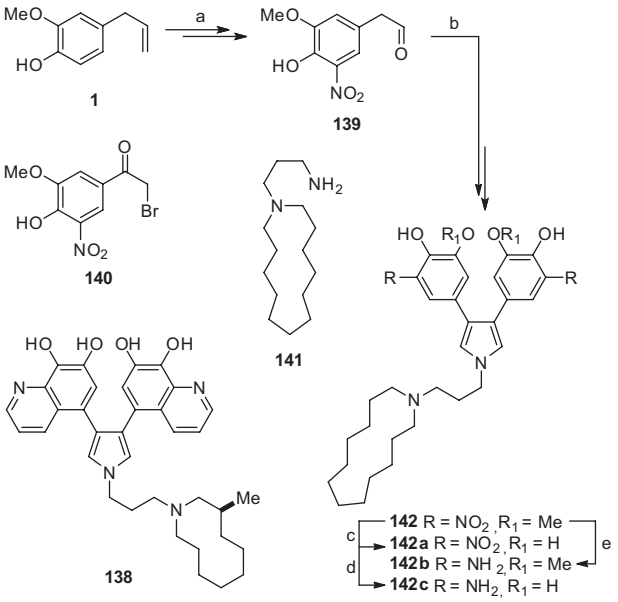


Scheme 16. Reagents and conditions: (a) $K_3Fe(CN)_6$, O_2, NH_4OH, Me_2CO-H_2O, RT (95%); (b) K_2CO_3, CH_3I, DMF, 60 °C, 8 h (90%); (c) $AlCl_3$, Me_2S, RT, 1 h (**134d**:**134e** = 1:4, 95%); (d) (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate, Et_3N, PhMe, RT, 1 h (95%); (e) BTEA.Br_3 (10 equiv.); (f) 1. $ZnCl_2$, AcOH, 80 °C, 24 h (*aS*, 90%; *aR*, 95%); 2. $LiAlH_4$, THF, 0 °C → RT (*aS***137**, 89%; *aR***137**, 90%).

An exhaustive bromination of **135** to afford **136**, followed by a selective zinc-mediated reductive dehydrodebromination[135] was devised in order to overcome the lack of selectivity for nuclear bromination, whereas a final reduction with $LiAlH_4$ was required to remove the menthylcarbonate moieties. The dibromo-derivative proved to be C_2-configurationally stable. The atropoisomers **137** was unable to modulate the function of the $GABA_A$ receptor. On the other hand, methylation of **134** with MeI/K_2CO_3 afforded natural product **134c** in quantitative yield.

3.4. Synthesis of analogs of hallitulin

A concise synthesis of *N*-substituted 3,4-diarylpyrroles structurally related to the cytotoxic marine alkaloid halitulin (**138**) was reported (Scheme 17).[136] The synthesis entailed the condensation of a phenacyl halide with a primary amine and a phenylacetaldehyde. Eugenol was employed as a starting material for the preparation of **139**, one of the phenylacetaldehyde components.



Scheme 17. Reagents and conditions: (a) 1. 70% HNO_3, AcOH (79%); 2. OsO_4, $NaIO_4$, THF-H_2O 0 °C → RT (82%); (b) **140**, **141**, NaI, MeOH (24%); (c) BBr_3, CH_2Cl_2, RT (92%); (d) H_2, Pd/C, EtOH (90%); (e) H_2, Pd/C, EtOAc (77%).

The synthesis entailed the anchimerically-assisted *ortho* nitration of the phenol, followed by oxidative fission of the double bond to produce the acetaldehyde side chain. Compound **139** was condensed with bromoketone **140** and diamine **141** to afford pyrrole derivative **142a**. In turn this was transformed into compounds **142b-d** by successive catalytic hydrogenations and BBr_3-assisted demethylations.

One of the eugenol derivatives (**142c**) was found to be the analog with the highest cytotoxic activity, the mechanism of which involved in part an autophagic response, without any caspase-dependent cell death mechanism. This compound might be a useful lead for anticancer drug development.

4. Synthesis of Bioactive Compounds

Several bioactive compounds have been synthesized employing eugenol (**1**), as part of medicinal chemistry endeavors (Figures 2 and 3). The EP_3 receptor is a member of the prostanoid G-protein coupled receptors. Prostanoids are products of the arachidonic acid cascade. Stark and co-workers[137] synthesized structures with different small molecule fluorophoric moieties via a dimethylene spacer, which resulted in human EP_3 receptor ligands such as **142**, with affinities in the nanomolar concentration range. The compounds were visualized within the cells by confocal laser scanning microscopy and characterized as antagonists on human platelets.

Quinoline moieties have been attached to the phenolic oxygen of eugenol, directly or through a spacer, in order to generate antiparasitary agents, potentially useful as antitrypanosomics against *Trypanosoma cruzi* (**143**)[138] or antileishmanial (**144**)[139] agents. The attachment of a ligustrazine (tetramethylpyrazine) residue afforded compounds with protective effects against hydrogen peroxide (H_2O_2)-induced oxidative damage on ECV-304 cells. Eugenol ether **146** proved to have a beneficial effect, protecting injured ECV-304 cells with an EC_{50} value of 0.20 μM.[140]

On the other hand, alkylation of the free phenol of eugenol and attachment of a trioxygenated aromatic ring to the end of the three-carbon side chain afforded cytotoxic compounds useful as breast cancer invasion inhibitors (**145**)[141] and cancer chemopreventive agents (**147**).[142] Other simple derivatives of eugenol have been prepared and examined as anticancer agents against different cell lines. Simple structure-activity relationships were obtained.[143]

Hydrothiolation of the double bond of eugenol with thiophenol derivatives afforded antioxidant compounds, such as **148**, which were more effective in inhibition of induced lipid peroxidation compared to the precursor eugenol.[144] Alkyl and aryl ethers of eugenol were effective in reducing lipid peroxidation, protein oxidative damage by carbonyl formation and increase total thiol content in cerebral cortex homogenates.[145]

1,3-Dipolar coupling of conveniently substituted eugenyl ethers with aldoximes resulted in pirazolines like **149**, endowed with anti-stress activity.[146] On the other hand, etherification of the free phenol of eugenol to produce mimetics of fibrates resulted in hipolipidemic compounds, such as **150**,[147] whereas introduction of the side chain of carvedilol afforded a new type of β-adrenoceptor blockers, with ancillary antioxidant activities; the receptor binding affinity of compound **151** was similar to that of propranolol.[148]

Alkylation of the free phenol moiety of eugenol with 3,5-diaryl pyrazoline amide derivatives resulted in antibacterial and antifungic agents. Compound **152** exhibited significant antibacterial activity compared with gentamycin and moderate antifungal activity in comparison with griseofulvin.[149] Simple derivatives of eugenol have also been evaluated for their antifungal activity.[150] In addition, eugenol was employed as starting material for the synthesis of substituted dihydronaphthalenes,[151] some of which exhibited activity as inhibitors of the efflux pump of *Staphylococcus aureus*. These agents have the ability to reduce the minimum inhibitory concentration of antibacterials, such as ciprofloxacin, when delivered associated with them.

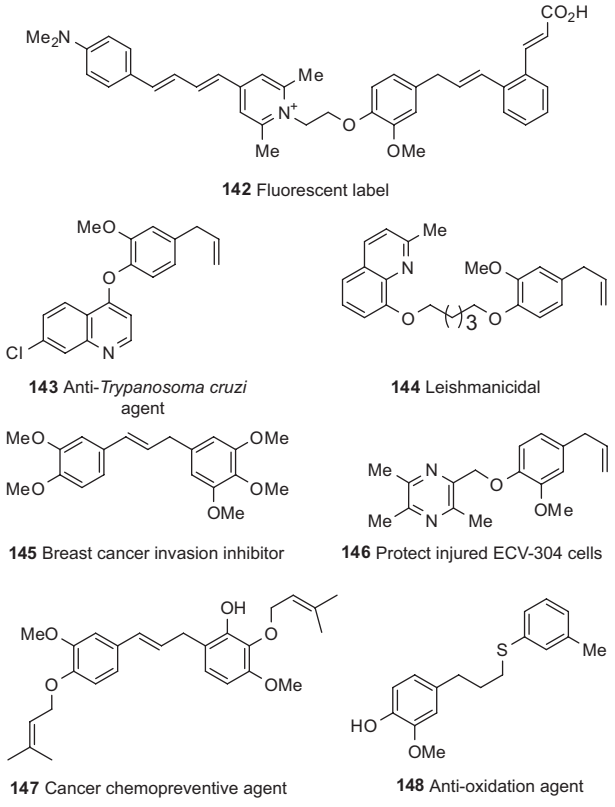


Figure 2. Selected synthetic bioactive compounds prepared from eugenol.

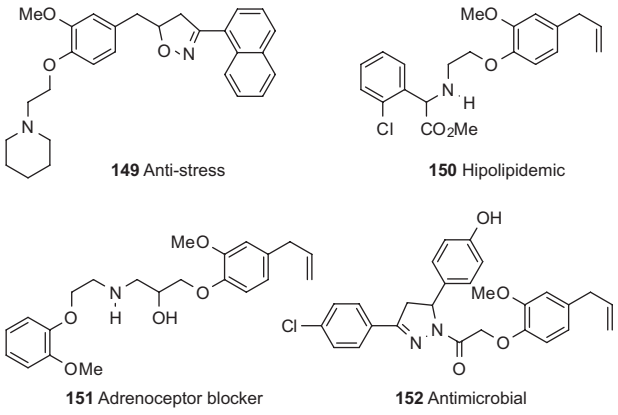


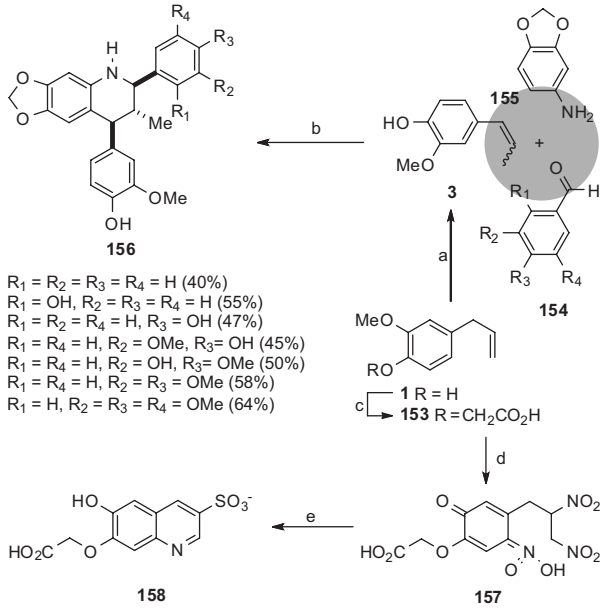
Figure 3. Selected synthetic bioactive compounds prepared from eugenol.

5. Cyclizations Involving Eugenol. Synthesis of Heterocycles

5.1. Synthesis of quinolines

The tetrahydroquinoline skeleton is an important heterocycle among natural products,[152] and polysubstituted tetrahydroquinolines display a wide range of biologic activities, including antimalarial, antitumoral and antioxidant.[153]

Kouznetsov and co-workers[154] designed a highly stereoselective synthesis of polysubstituted tetrahydroquinolines (**156**) from isoeugenol (**3**), obtained by solid base-mediated isomerization of eugenol (**1**), based on a three component imino Diels-Alder cycloaddition reaction (Scheme 18).[155] The *in situ* preformed aldimines derived from benzaldehydes (**154**) and 3,4-(methylendioxy) aniline **155** functioned as the azadiene component, whereas isoeugenol acted as the required dienophile.



Scheme 18. Reagents and conditions: (a) 10% KOH/Al_2O_3 (88%); (b) 10% $BF_3.Et_2O$, MeCN, 60 ºC, 6-10 h (40-64%); (c) $ClCH_2CO_2Na$; (d) HNO_3, AcOH, –5 ºC, 4 h; RT, 4 h (80%); (e) 1. $S_2O_4Na_2$, conc. NH_3, RT, 6 h; 2. AcOH, 72 h (68%).

The transformation was best performed in MeCN or polyethylenglycol (PEG) 400. A series of tetrahydroquinolines prepared after this methodology was tested as potential as cytotoxic and antitumor agents.[156] Interestingly, use of phthaldehydic acid as the aldehyde component enabled the formation of a isoindolo[2,1-*a*] quinolin-11(5 h)-one, by lactamization[157] of the acid moiety with the nitrogen atom of the tetrahydroquinoline. Compounds of this family were found to be active as protecting agents against N_2-induced hypoxia and inhibitors of human topoisomerase II and bacterial DNA-gyrase.[158]

On the other side, it is recognized that the quinolines are also an important class of heterocycles, and the quinoline skeleton is at the heart of numerous synthetic antimalarial, antibacterial, antifungal, anti-tuberculosis and anticancer compounds.[159] Dinh and co-workers[160] reported an efficient and simple new route towards substituted quinolines employing eugenol. Their sequence entailed protecting the free phenol with chloroacetic acid and subjecting the resulting compound (**153**) to nitration with fuming nitric acid in AcOH, which effected ether cleavage, a normal nitration, and then an unexpected electrophilic addition to the double bond to form 80% of the quinone-aci compound **157**.[161] In turn, derivative **157** was reductively cyclized in 68% yield, upon treatment with thiosulfate. It was conjectured that a Neff reaction of the primary nitro group afforded an intermediate aldehyde, which enabled the cyclization with the nitrogen atom attached to the cycle. The so obtained quinoline **158** could be further functionalized on C5 and on its free phenol moiety.

5.2. Synthesis of isoquinolines

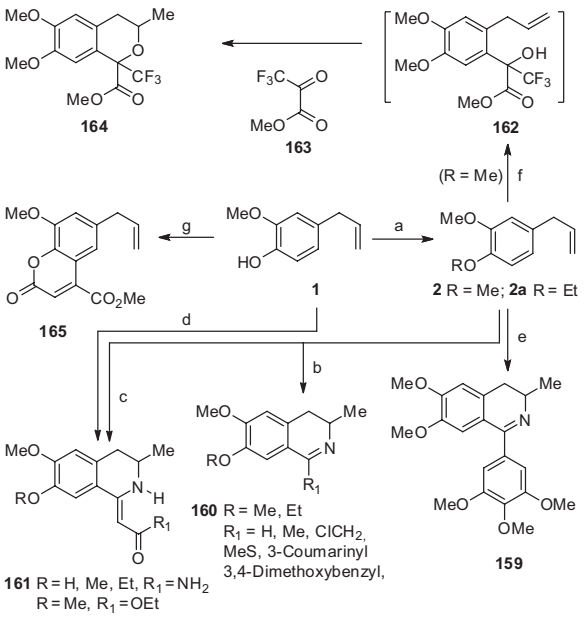
Since double bonds can be viewed as synthetic equivalents of alcohols, their hydrated counterparts, the capability of eugenol and eugenol derivatives to undergo cyclocondensations toward nitrogen and oxygen heterocycles was examined in several reaction sequences. One of them is a modification inspired in the Ritter-type[162] cyclocondensation of nitriles with dialkylbenzylcarbinols to access dihydroisoquinolines (Scheme 19), which was extended to allylbenzenes.[163]

The free hydroxyl of eugenol was alkylated (MeI, EtI) almost quantitatively (**2**, **2a**) under phase-transfer catalysis conditions (18-crown-6/KOH), and the Ritter cyclocondensation was performed with different nitriles, including HCN, MeCN, MeSCN, BnCN, $ClCH_2CN$, homoveratryl nitrile and 3-cyanocoumarin, to yield **160**.

Under HBF_4 as promoter, the reaction afforded 36% of the expected product (**159**),[164] whereas the reaction of **2** with cyanoacetamide afforded the expected enaminoamides **161**, even when eugenol itself was used as starting material. The use of 94% H_2SO_4 as cyclizing agent furnished lower yields of these latter compounds.[165]

5.3. Synthesis of isochromanes

On the other hand, the most commonly used approach toward the pyran ring of isochromanes is the oxa-Pictet-Spengler cyclization of β-phenylethyl alcohols with aldehydes and ketones.[166] Since some isochromanes are relevant for their bioactivity as hypotensive, growth-regulating and antitumor agents, modifications of this cyclization have been explored.[167] The reaction of methyleugenol (**2**) with methyl trifluoropyruvate (**163**) under TfOH promotion directly afforded 84% of the isochromane derivative **163**; the benzylic alcohol **162** was proposed as the intermediate, which undergoes cyclization with the allyl substituent.



Scheme 19. Reagents and conditions: (a) KOH, 18-crown-6, PhH, 40-60 °C, 2 h (ca. 100%); (b) AcOH, conc. H_2SO_4, 50-60 °C; 30 min or 94% H_2SO_4, 0 °C → RT, 15 min (52-82%); (c) AcOH, conc. H_2SO_4, 50-60 °C; 30 min (R = Me, $R_1 = NH_2$, 77%; R = Et, $R_1 = NH_2$, 73%); or 94% H_2SO_4, 0 °C → RT, 15 min (R = Me, R_1 = OEt, 22%); (d) AcOH, conc. H_2SO_4, 50-60 °C; 30 min (54%); (e) 54% HBF_4, Et_2O, overnight (36%); (f) **163**, TfOH, CH_2Cl_2, –20 °C, 1 h (84%); (g) dimethyl acetylenedicarboxylate (DMAD), PPh_3, MeCN, MW (70%).

5.4. Synthesis of coumarins

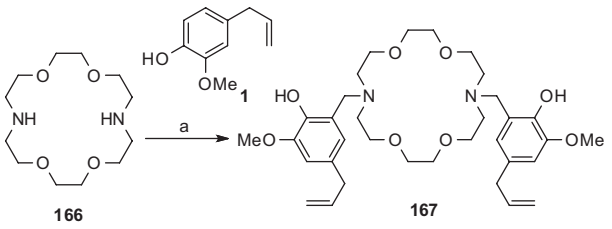
The reactivity of the free phenol moiety of eugenol was also employed to test the scope of a microwave-assisted synthesis of coumarins (**165**) from phenols, with DMAD and PPh_3.[168] Mechanistically, initial addition of PPh_3 to the acetylenic ester and concomitant protonation of the reactive 1:1 adduct, was proposed to be followed by electrophilic attack of the resulting vinyltriphenylphosphonium cation to the aromatic ring, at the *ortho* position relative to the phenolic strong activating group. The cyclized derivatives are then produced by lactonization.

6. Synthesis of Macrocycles

6.1. Synthesis of crown ether derivatives

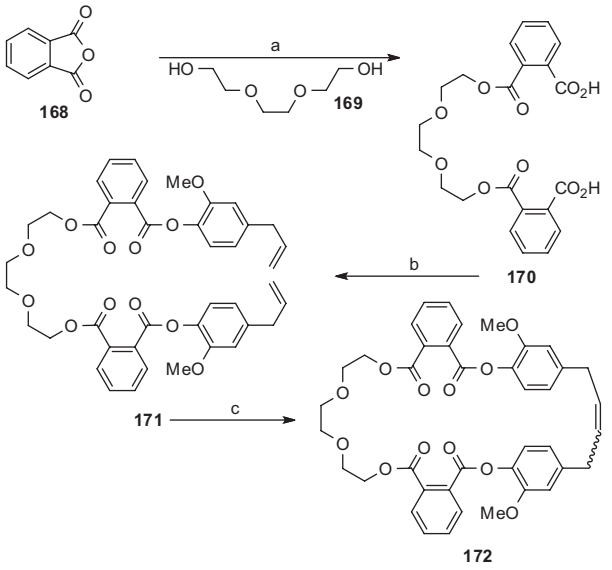
The Mannich reaction was employed for the synthesis in high yield of the bis-phenol aza-crown ether **167** (Scheme 20), as potential membrane-forming amphiphile, from diaza-crown ether precursor **166**.[169]

Functional tests revealed that the stability of the amphisomes formed from these monomers is lower possibly because intramolecular hydrogen bonding prevents formation of intermolecular hydrogen bonds.



Scheme 20. Reagents and conditions: (a) **1**, H_2CO, PhMe, 210 °C (78%).

A series of macrocyclic tetralactones were prepared (Scheme 21), employing a ring closing metathesis operated by Grubbs' I catalyst, as the key strategy toward the macroxyclization.[170]



Scheme 21. Reagents and conditions: (a) Diol **169**; PhH, reflux, Et_3N, 0 °C → RT, 9 h; (b) **1**, *N*,*N*'-dicyclohexylcarbodiimide (DCC), DMAP, CH_2Cl_2, 0 °C, 6 h (76%); (c) CsCl, Grubbs I (5 mol%), CH_2Cl_2, reflux, 36 h (67%, *E*:*Z* = 2:1).

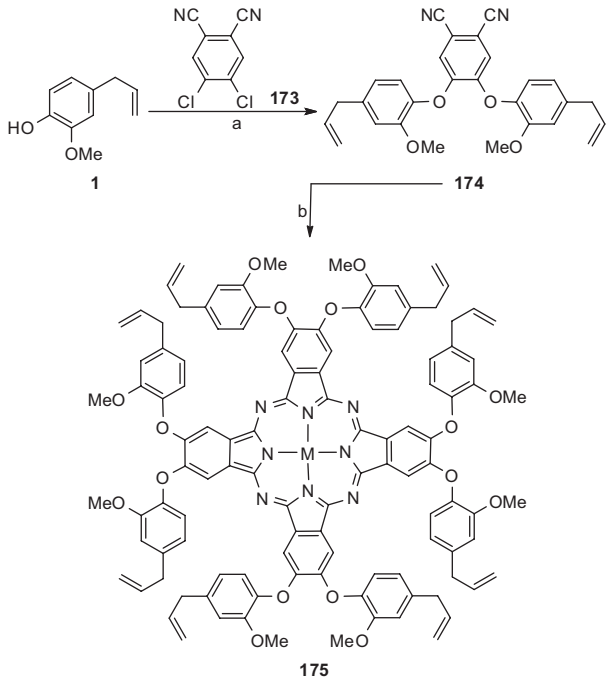
One of the examples included compound **172**, which contains a couple of eugenol (**1**) moieties. This was prepared by ring opening-esterification of phthalic anhydride (**168**) with triethyleneglycol (**169**), followed by Steglich esterification (DCC-DMAP) of the resulting diacid (**170**) with eugenol, to produce **171** in 76% yield. Cyclization of the latter furnished the expected 35-member macrocycle **172** in 67% yield, as a 2:1 (*E*/*Z*) mixture of isomers.

6.2. Synthesis of polysubstituted phthalocyanines

On the other hand, the phthalocyanines are an important group of organic functional materials. Their most important industrial application is the formation of color complexes with metal cations that are used as highly stable pigments

and dyes. Other uses include applications as photovoltaic materials in solar cells, systems for fabrication of light emitting diodes, liquid crystals and non-linear optical materials, sensitizers for photodynamic cancer therapy and dyes for recording layers for DVDs optical storage discs.

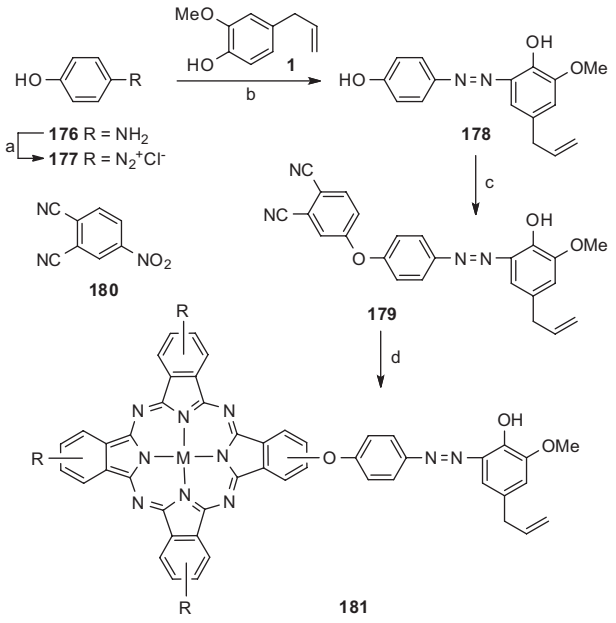
The unsubstituted phthalocyanine core is known for its insolubility in most common solvents. However, one of the main requirements for these compounds to be useful is that they should be soluble enough. In pursuit of that endeavor, Kantar and co-workers[171] devised a three step synthesis of a series of phthalocyanines containing eight pendant eugenol moieties.



Scheme 22. Reagents and conditions: (a) **173**, K_2CO_3, DMSO, 80 °C, 8 h (50%); (b) 1. 200 °C, 5 h (35%); 2. $CuCl_2$, $Zn(AcO)_2$, $CoCl_2$, $NiCl_2$, $Fe(CO)_5$, quinoline, 200 °C, 24 h (24-39%; M = Cu, Co, Ni, Zn, Fe).

Dichlorodicyanobenzene (**173**) was reacted with eugenol under base-catalyzed nucleophilic aromatic displacement conditions and the resulting bis-eugenyl ether (**174**) was tetramerized in refluxing quinoline (Scheme 22).[172] In order to obtain the corresponding metallophthalocyanines, anhydrous transition metal salts [CuCl, $NiCl_2$, $CoCl_s$, $Zn(AcO)_2$ and $Fe(CO)_5$] were employed under high temperature. The metallophthalocyanine products **175**, obtained in 24-39% yield, were intensely green and very soluble in common organic solvents.

Kantar and co-workers[171] also synthesized a series of phthalocyanines carrying more sophisticated side chains with four pendant eugenol units (Scheme 23). *p*-Hydroxyaniline (**176**) was diazotized and coupled with eugenol (**1**) and the phenolic moiety of the resulting product (**178**), obtained in 73% yield, was induced to displace the nitro group of 4-nitro-1,2-dicyanobenzene (**180**) under microwave irradiation, affording 76% of the monosubstituted phthalonitrile derivative intermediate **179**.[173] The next transformations, involving tetramerization of **179**, followed by introduction of the metallic cations toward **181** were performed under microwave irradiation.



Scheme 23. Reagents and conditions: (a) 1. $NaNO_2$, HCl, 0-5 °C; (b) **1**, NaOH (73%); (c) K_2CO_3, DMF, MW (360 W), 10 min (76%); (d) $CuCl_2$, $Zn(AcO)_2$, $CoCl_2$, $NiCl_2$, DBU, DMF, MW (360 W), 10 min (M = Co, Ni, Cu, Zn).

7. Synthesis of Polymeric Materials

The design and development of new materials is one of the main areas of research in polymer science. In recent years, bio-based polymers (derived from renewable resources) have been attracting attention because of their potential advantages with regards to conservation of fossil resources and biodegradability. Renewable polymers are more structurally diverse; in addition, these materials can be considered carbon sinks, which are generated from CO_2 by a combination of plant photosynthesis and chemical manipulation.

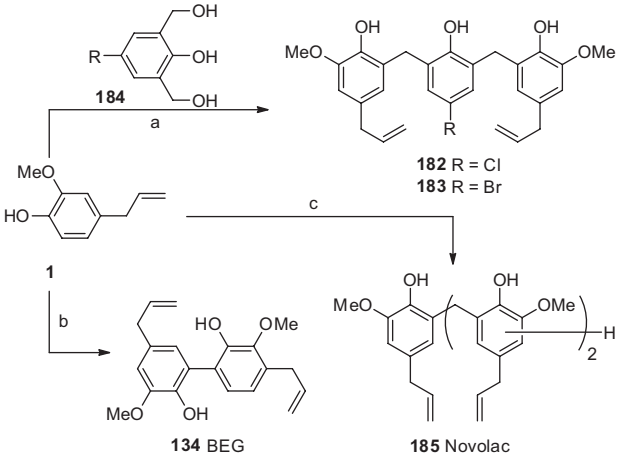
The increased use of sustainable polymers has the potential to reduce the amount of atmospheric CO_2 in the short term, while being carbon neutral in the long term. The structural characteristics of eugenol and its commercial availability at low cost, transformed the natural product into a valuable building block for the design of new polymers.[174]

Several researchers have attempted to use eugenol in synthetic polymer chemistry. For example, Ciszewsky and Milczarek[175] prepared polyeugenol by

electropolymerization, and examined its capacity to act as chemo- and biosensor. Bailly and co-workers[176] synthesized bisphenol-A polycarbonate/eugenolsiloxane copolymers, whereas Peppas *et al.*[177] studied the incorporation and release of eugenol from glassy hydrophilic copolymers.

De la Mata and co-workers[178] performed the hydrosilylation of the double bond of eugenol, preparing dendrimers with different properties, while Tappe *et al.*[179] examined Sharpless' asymmetric dihydroxylation as a strategy towards polymer-bound olefins of different structural types. On the other hand, Masuda and co-workers[180] studied the Rh, Mo, and W catalyzed-polymerization of eugenol derivatives carrying alkyne functionalities, and the synthesis of a bis(allyl)benzene diene derivative of eugenol, which was further submitted to acyclic diene metathesis polymerization,[181] were disclosed.

Eugenol can be engaged into oligomerization reactions. Triphenols **182** and **183** were prepared in 80% yields by tungstosilicic acid-assisted coupling of 2,6-bis-hydroxymethyl phenols (**184**)[182] with eugenol and related compounds, in aqueous medium (Scheme 24).[183] These polyhydroxy aromatics play a versatile role in organic synthesis, especially for the preparation of calixarenes and macrocyclic crown ethers.



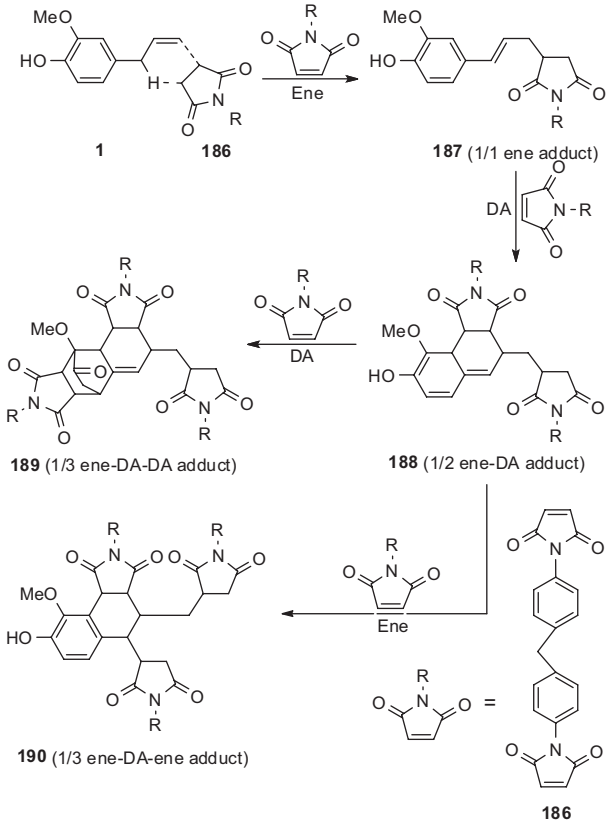
Scheme 24. Reagents and conditions: (a) **184** (R = Cl, Br), tungstosilicic acid, H_2O, reflux, 6 h; (R = Br, 81%; R = Cl, 80%); (b) $K_3Fe(CN)_6$; (c) H_2CO, AcOH, HCl. BEG: bis-eugenol.

On the other hand, Shibata and co-workers[184] oxidatively dimerized eugenol (**1**) to obtain 5,5'-bieugenol (**134**) and prepared the eugenol-formaldehyde polymer novolac (**185**). These authors pre-polymerized **1**, **134** and **185** with 4,4'-bismaleimide diphenylmethane (**186**) at 180 °C and then compression-molded the products at 250 °C for 6 h to produce cured **1/186** (EB), **134/186** (BB) and **185/186** (NB) resins with eugenol/maleimide unit ratios of 1/1, 1/2 and 1/3. Spectroscopic analysis suggested that EB resins arose from an ene reaction and subsequent Diels-Alder/ene reactions, involving intermediates like **187-190** (Scheme 25). However, BB resins and NB resins are the result of an ene reaction and subsequent thermal addition copolymerization.

The glass transition temperature (T_g) and 5% weight loss temperature (T_5) of the cured resin increased with increasing the content of **186**, and EB resins 1/3 showed the highest Tg (377 °C) and T_5 (475 °C). EB resins and NB resins exhibited higher flexural strengths and moduli than those of BB resins, with EB resin 1/2 showing the most balanced flexural strength and modulus (84.5 MPa and 2.75 GPa).

Bifunctional monomers containing maleimide and allylphenyl groups were synthesized by the condensation of maleimidobenzoic acid chloride and eugenol. The ene-addition reaction and Diels-Alder polymerization afforded new polyesters.[185]

Eugenol and rosin have been used as feedstocks for biobased epoxy resins. An epoxy component based on eugenol and an anhydride curing agent based on rosin were prepared and cured. The properties of the resulting material were studied, and the results suggest that the eugenol epoxy has similar reactivity, dynamic mechanical properties and thermal stability than commercial materials.[186]

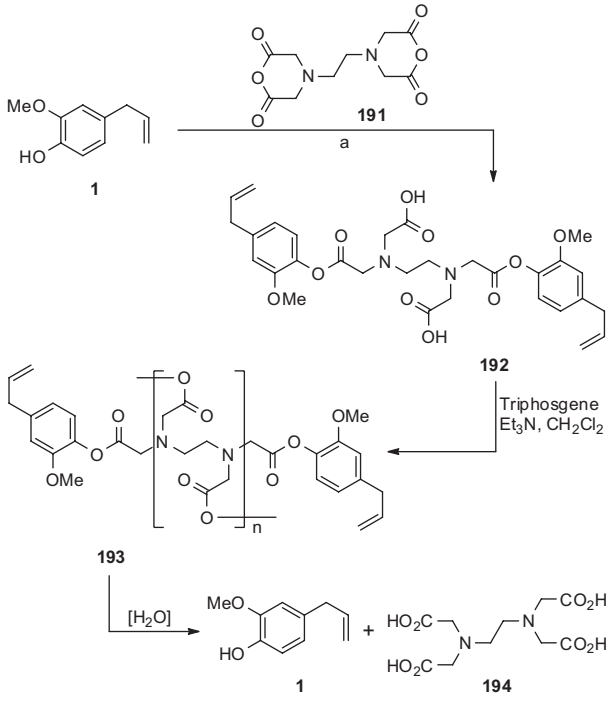


Scheme 25. Formation of some 1/1, 1/2 and 1/3 adducts between eugenol and 4,4'-bismaleimidediphenyl methane (**186**).

Eugenol derivatives of higher chlorocyclophosphazenes and related epoxy oligomers were prepared and characterized. Oligomers with epoxy numbers of 15-16% and molecular masses from 1400 to 1800 were achieved.[187]

Another important field of applied polymer science is the prevention of microbial contamination in the personal care and food industries for consumer protection. Taking into account that eugenol is known to possess antioxidant properties and antimicrobial activity against a range of bacteria, it was incorporated into poly(lactic-co-glycolic acid) (PLGA) nanoparticles. However, the nanoparticles exhibited a burst release of the active principle and nearly 50% of the antimicrobial was released in the first 8 h.[188]

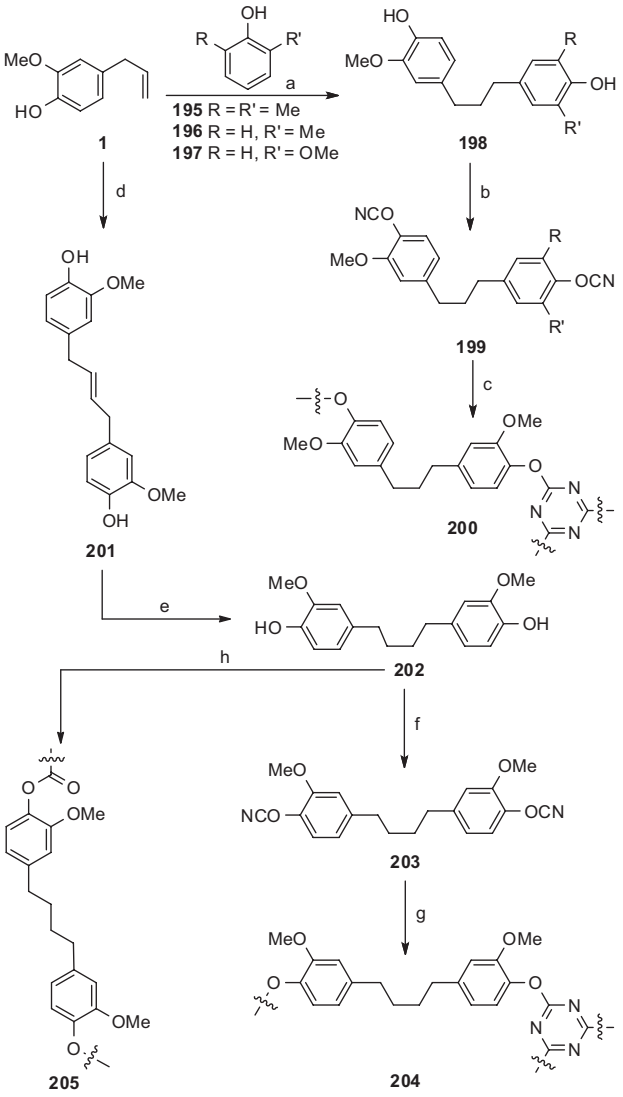
Attempting to design a slower and more controllable release solution, Uhrich and co-workers[189] synthesized, via solution polymerization, biodegradable poly(anhydride-esters) composed of an ethylenediaminetetraacetic acid backbone and pendant eugenol groups as antimicrobials. Other phenolics, such as carvacrol and thymol were also prepared and tested.



Scheme 26. Synthesis and degradation of the eugenol-ethylenediaminetetraacetic acid (EDTA) poly(anhydride-ester) **193**.

The synthesis of the polymer involved ring-opening transesterification of the phenol (**1**) with EDTA dianhydride (**191**) in the presence of triethylamine to afford diacid **192** in yields around 80% (Scheme 26), followed by solution polymerization to **193**, with triphosgene as the coupling reagent, which prevented potential ring closure and regeneration of the EDTA dianhydride.[190]

Functional assays demonstrated that the polymer exhibited bioactivity similar to that of eugenol and that the hydrolytic degradation of the polymer was complete in 16 days, resulting in the release of eugenol and EDTA (**194**).



Scheme 27. Reagents and conditions: (a) $AlCl_3$, 80 °C, 1.5 h (ca. 85%); (b) CNBr, Et_3N, Me_2CO, −15 °C, 1.5 h (87%); (c) 100 °C, 30 min; 150 °C, 30 min; 200 °C, 60 min; 250 °C, 3 h; (d) Grubbs I (0.4 mol%), 2.67 kPa, 48 h (93%); (e) H_2 (40-50 psi), 10% Pd/C, EtOH, 3 h (ca. 100%); (f) CNBr, Et_3N, Me_2CO, −50 °C → 10 °C, 1.5 h (73%); (g) 1. triphosgene, pyridine, −15 °C; 2. overnight, RT; 3. MeOH, 50 °C, 30 min (57% overall); (h) 150 °C, 30 min; 201 °C, 24 h.

Anuradha and Sarojadevi[191] prepared a series of bisphenols (**198**) containing a trimethylene spacer by treating eugenol (**1**) with 2,6-dimethyl phenol (**195**), *o*-cresol (**196**) and guaiacol (**197**) in the presence of $AlCl_3$[192] and transformed these products into their respective bis-cyanate esters **199** by treatment with CNBr (Scheme 27). Finally, the cyanate esters **199** were cyclotrimerized to **200** by thermal curing.[193]

The T_g values of the monomers were in the range of 208-239 °C, whereas the T_g of the cured network depended on the length and symmetry of the monomer. The T_{10} values of the resins were in the range of 364-381 °C, whereas physical parameters such as the limiting oxygen index (LOI) confirmed their thermal stability and flame retardancy capabilities.

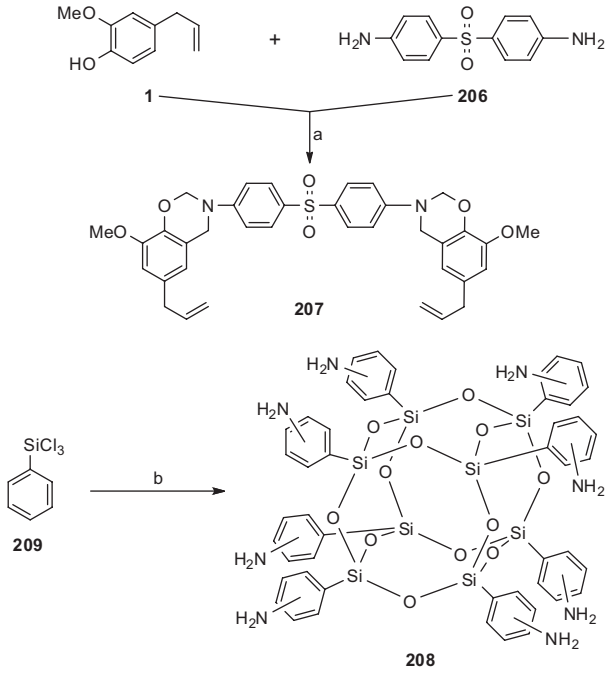
Harvey *et al.*[194] synthesized bisphenol **202** by the ruthenium-catalyzed cross-metathesis of eugenol, followed by hydrogenation of the resulting olefin **201**. This common intermediate **202** was transformed into polycyanurate **204** via the dicyanate **203**, and into polycarbonate **205**. The pure polycarbonate exhibited a T_g of 71 °C and polydispersity of 1.88. An 80:20 blend of cyanate ester:polycarbonate was prepared and thermally cured, observing that the presence of the polycarbonate had no significant effect on the cure behavior of the cyanate ester. No phase separation was observed either during or after cure, suggesting that a homogenous network was generated.

The resulting composite material exhibited a single T_g of 132 °C, 55 °C lower than the T_g of the pure polycyanurate and 60 °C higher than the polycarbonate. Furthermore, the polycarbonate could be quantitatively separated from the thermoset matrix after cure by solvent extraction, proving the absence of chemical grafting under the curing conditions. These polymeric blends may have applications for fabrication of toughened composite structures. Other dicyanate monomers containing methylene spacers have also been prepared.[195]

Polybenzoxazines are a class of phenolic resins that possess dimensional and thermal stability and can be used as matrices for high performance composites with superior physical and mechanical properties.[196] This is a relatively new family of phenolic resins which combine the thermal properties and flame retardance of phenolics, with the mechanical performance and design flexibility of epoxies. Polymerization takes place by thermal treatment, through the ring opening of the heterocyclic precursor monomers, without the need of catalysts and without producing by-products or volatiles.[197]

Benzoxazines are generated by the Mannich-like condensation of a phenol, formaldehyde and a suitable primary amine (Scheme 28);[198] in the presence of secondary amines, benzylamine derivatives are usually formed.[199] Some eugenol-derived benzoxazines demonstrated to be lethal in the brine shrimp assay.[200]

Muthusami and co-workers[201] has recently prepared and polymerized several benzoxazines (**207**) from various aromatic diamines, like **206**, and eugenol (**1**). They found that, unlike heterocycles resulting from other phenols, the allyl moiety of the eugenol-derived benzoxazines also participates during the curing process; this improves the cross-linking density of the polymer and leads to enhanced thermal stability (340 °C).

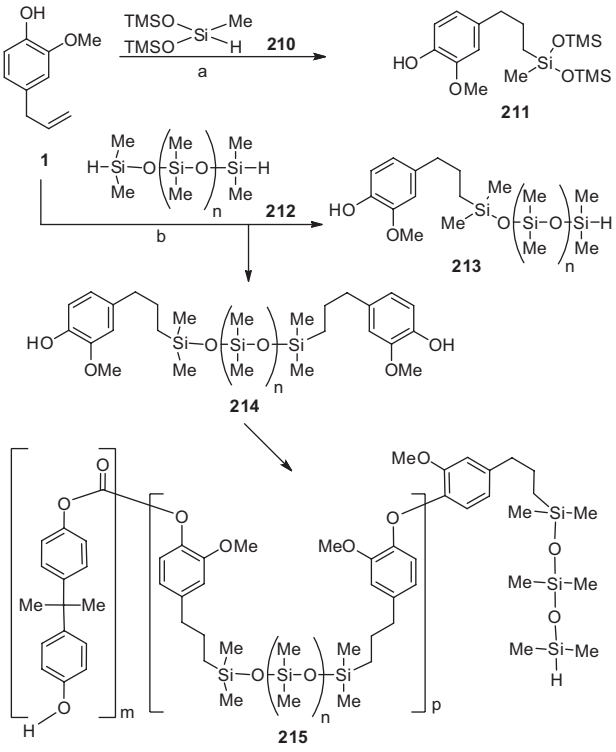


Scheme 28. Reagents and conditions: (a) H_2CO, DMSO, 130 °C, 5 h (80%); (b) 1. $BnNMe_3^+OH^-$, H_2O; 2. fuming HNO_3, RT, 20 h (90%); 3. 10% Pd/C, Et_3N, HCO_2H, THF, 60 °C, 5 h (82%).

Polymer nanocomposites are polymers that have been reinforced with small quantities of nanosized particles with large surface area and high aspect ratios (> 300). Their higher surface area to volume ratio convey to them enormous advantages over traditional micro or macroparticles.[202]

Nanocomposites of eugenol-based polybenzoxazines/amine-containing polyhedral oligomeric silsesquioxane (POSS, **208**) have been prepared through co-polymerization of an eugenol-derived benzoxazine with an amino-functionalized polyhedral oligomeric silsesquioxane (OAPS).[203] POSS, which can be prepared in three steps and 73% yield from phenyl trichlorosilane (**209**),[204] acts as good nanofiller and reduces the dielectric constant of the polybenzoxazines to 1.32, making them potentially suitable for use in microelectronics. In addition, the LOI values suggested that these products can be used for flame retardancy applications.

Silicone polycarbonates containing polydimethyl siloxane (**213**) and heptamethyl trisiloxane (**211**) moieties in the interior chain and terminal positions were recently synthesized (Scheme 29).[205] The polymeric chains were capped with eugenol moieties. A bifunctional eugenosiloxane (**214**) was also used to include this



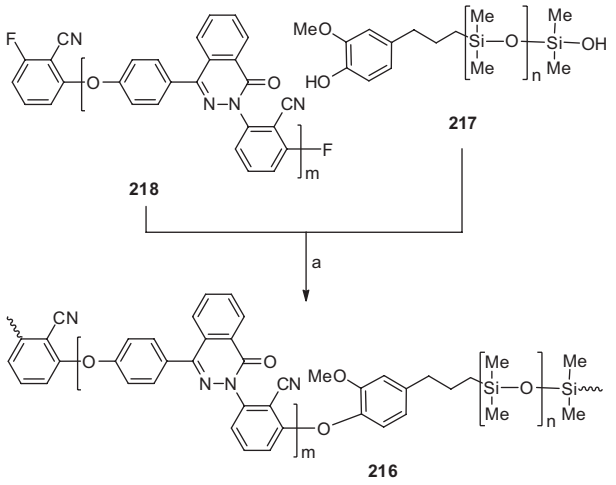
Scheme 29. Reagents and conditions: (a) Pt complex, C_6H_5Cl, reflux.

motif within the polymer (**215**). The silicon-derivatives of eugenol were prepared through a hydrosilylation reaction with **210** and **212**, using Karstedt's catalyst.[206] The polymers showed satisfactory thermo-oxidative stability and transparency. Their flexibility and wettability increased with increasing of the silicone content. Siloxane copolyesters containing phenylindane bisphenol, diphenyl terephthalate, and eugenol end-capped siloxanes, were prepared and characterized. The copolyesters were soluble in organic solvents and had film forming properties.[207]

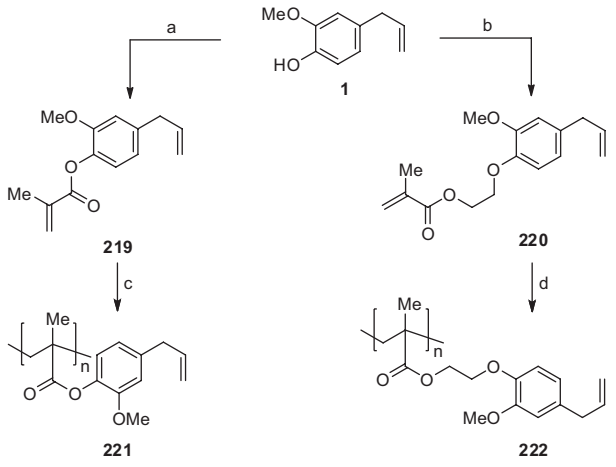
Poly(phthalazinone ether nitrile) (PPEN) block copolymers (Scheme 30) with an hydrophobic surface (**216**) were prepared by the nucleophilic aromatic substitution polycondensation of eugenol end-capped polydimethylsiloxane (PDMS, **217**) oligomers with fluoro-terminated PPEN oligomers (**218**).[208]

Polymers with eugenol moieties covalently bonded to the macromolecular chains were synthesized for potential application in orthopedic and dental cements (Scheme 31). The monomeric eugenol species were eugenyl methacrylate (**219**) and ethoxyeugenyl methacrylate (**220**), prepared in 80% yields by Fisher esterification.

Polymerization of each of the novel monomers, at low conversion, provided soluble polymers **221** and **222**, consisting of hydrocarbon macromolecules with pendant eugenol moieties. At high conversions, cross-linked polymers were obtained due to participation of the allyl



Scheme 30. Reagents and conditions: (a) K_2CO_3, 1,2-Cl_2-C_6H_4, DMSO, 180 °C.



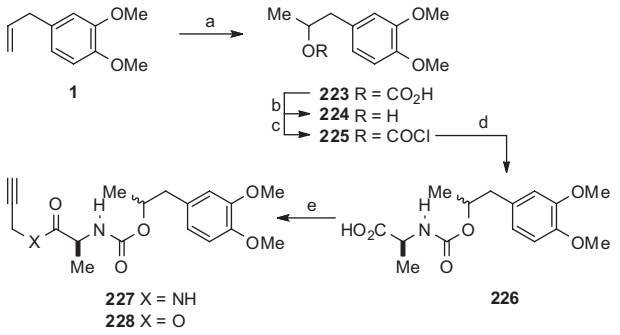
Scheme 31. Reagents and conditions: (a) Acryloyl chloride, Et_3N, Et_2O, RT, 48 h (ca. 80%); (b) 1. $ClCH_2CH_2OH$, KI, KOH, EtOH, reflux, 24 h; 2. acryloyl chloride, Et_3N, Et_2O, RT, 48 h (ca. 80%); (c) azobisisobutyronitrile (AIBN), PhMe, 50 °C, 24 h.

side chain in the polymerization reaction. Co-polymers with ethyl methacrylate were also prepared. Analysis of the thermal properties, suggested that the eugenyl methacrylate derivatives are potentially good candidates for dental and orthopedic cements.[209]

On the other hand, amino acid based synthetic polymers are expected to show biocompatibility and biodegradability similar to those of polypeptides.[210] Optically active amino acid-based poly (*N*-propargylamide)s and poly(*N*-propargyl ester)s bearing eugenol moieties were synthesized in good yields, employing (2,5-norbornadiene)$Rh^+[\eta_6$-$C_6H_5B^-(C_6H_5)_3$, a zwitterionic rhodium polymerization catalyst.[211]

The required eugenol-based monomers were prepared (Scheme 32) through the hydration of the double bond of methyl eugenol, achieved in 60% yield by reaction with formic acid, followed by hydrolysis of the

resulting formate **223** and conversion of the secondary alcohol **224** with triphosgene to afford 86% of the reactive chloroformate **225**. Reaction of the latter with alanine furnished the alanyl intermediate **226**, which was amidated (**227**) or esterified (**228**) in good yields.



Scheme 32. Reagents and conditions: (a) HCO_2H, 220 °C, 24 h (60%); (b) NaOH, EtOH, 30 °C, 2 h (97%); (c) $COCl_2$, Et_3N, Et_2O, 0 °C, overnight (86%); (d) L-alanine, $NaHCO_3$, Et_2O-H_2O, RT, 5 h (70%); (e) for **220**: 1. isobutyl chloroformate, NMO, THF, 0 °C; 2. propargylamine, RT, 1 h (75%). For **221**: propargyl alcohol, EDCI.HCl (95%).

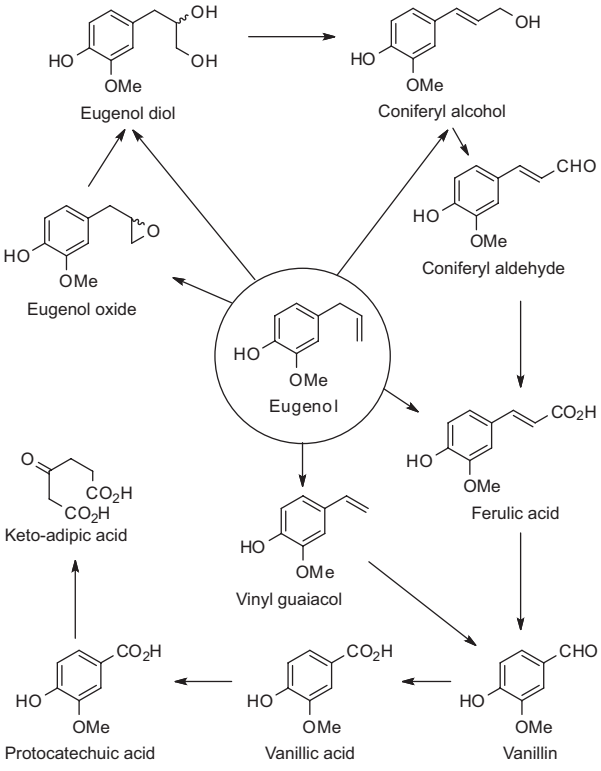
The molecular weights of the polymers ranged from 10800 to 17300. From their large specific rotation and circular dichroism signal, it was concluded that the polymers took a helical structure with a predominantly one-handed screw sense.[212] A different behavior was observed between the poly(*N*-propargylamide)s and poly(propargyl ester)s. This was attributed to the presence and absence of hydrogen bonding between the side-chain amide groups, which seems to play an important role in the formation of helical conformations.

8. Biotransformations and Biotechnology-Related Uses and Applications of Eugenol

8.1. Eugenol as feedstock. Production of fine chemicals

The TiO_2-photocatalyzed production of vanillin from eugenol has been studied.[213] However, biotechnological processes are usually less damaging to the environment than classical chemical processes and therefore considered as environmental friendly. Due to environmental concerns regarding the production processes for fine chemicals, recent research has shifted toward the exploitation of the metabolic and biocatalytic potential of microorganisms to transform readily available substrates into value-added products. The flavor and fragrances sector is a pioneer in this field.

Although eugenol is highly toxic for microorganisms even at low concentrations,[214] there is a growing body of reports that point out to the natural product as one of the most suitable substrates for biotransformations because it is economic and readily available.[215] The subject has been reviewed;[216] however, the selected examples of Table 1 and Scheme 33 evidenced that the biotechnology of the biotransformed products obtained from eugenol is still in its nascent stage.



Scheme 33. Biotransformation of eugenol into other valuable compounds.

Lambert and co-workers[217] was able to use eugenol as a feedstock for the production of coniferyl alcoholm by introducing in *S. cerevisiae* the *vaoA* gene native to *Penicillium simplicissimum*, which encodes for the enzyme flavoenzyme vanillyl-alcohol oxidase. The resulting strain produced up to 16.9 g L^{-1} of alcohol products after a few days of culture, suggesting the ability to develop these essential oils as constituents of growth media, to signal for greater cellular activity of resistant strains of yeast, for their use in alcohol production.

8.2. Enzymatically-assisted synthesis of esters of eugenol

Esters of eugenol have been traditionally produced by chemical esterification of eugenol with acid chlorides.[218] Several compounds were chemically synthesized and evaluated as potential inhibitors of the enzyme lipoxygenase.[219] In addition, eugenyl esters of aspirin, ibuprofen, 4-biphenylacetic acid (the active metabolite of fenbufen), mefenamic acid and indomethacin were

Table 1. Production of small molecules of interest employing eugenol as substrate

Microorganism	Product											Ref.
	A	B	C	D	E	F	G	H	I	J	K	
Amycolatopsis sp. HR167 (GM)	×		×					×	×		×	226
Bacillus cereus PN24		×	×	×	×						×	227
Corynebacterium sp.	×	×	×	×	×							228
Enterobacter sp.		×										229
Escherichia coli (GM)	×	×						×	×			230
Pseudomonas fluorescens E118								×				231
Pseudomonas nitroreducens Jin1	×	×	×					×				232
Pseudomonas resinovorans SPR1	×	×	×					×	×			233
Pseudomonas sp.	×		×			×	×	×	×			234
Pseudomonas sp. HR199	×	×	×					×	×			235
Pseudomonas sp. OPS1	×		×	×				×	×			236
Ralstonia eutropha H16 (GM)	×							×	×			237
Saccharomices ceevisae 92411 (GM)	×							×				238
Streptomyces sp.	×	×						×				239

A = ferulic acid; B = vanillin; C = vanillic acid; D = protocatechuic acid; E = keto-adipic acid; F = eugenol oxide; G = eugenol-diol; H = coniferyl alcohol; I = coniferyl aldehyde; J = guaiacol; K = 4-vinyl guaiacol. GM = genetically modified.

synthesized, in attempts to reduce the side-effects of the parent drugs,[220] or produce synergy with the known properties of the natural product.[221]

However, the enzymatic synthesis is an alternative to the chemical process.[222] It offers some advantages including milder reaction conditions, low energy requirements, high product yields and purity, shorter reaction times, and biocatalyst reusability. Reactions are usually carried out in water-containing media; however, the solventless enzymatic synthesis of eugenol esters has also been reported.[223]

The enzymatic synthesis of eugenol benzoate by immobilized *Staphylococcus aureus* lipase was informed, as a strategy to modulate the antioxidant activity of the natural product.[224] In the 1,1-diphenyl-2-picrylhydrazyl radical scavenging test, the IC_{50} values were found to be 18.2 *versus* 20.2 mg mL^{-1} for eugenol and eugenol benzoate, also evidencing antioxidant activities as high as 90% of that of butylated hydroxytoluene (BHT), employed as comparator.

Analogous preparations of eugenol caprylate and acetate have been reported. The former was synthesized using the commercial immobilized *Thermomyces lanuginose* lipase, Lipozyme TLIM, as the biocatalyst.[225] The biotransformation was statistically optimized, providing a maximum conversion yield of 72.2% under such conditions. On the other hand, eugenyl acetate was prepared employing Novozym 435, a commercial lipase from *Candida antarctica* immobilized on a macroporous anionic resin. The results indicated that the esterification of eugenol improved its antimicrobial properties.

8.3. Synthesis of eugenyl glycosides

Traditionally, glycosides have been synthesized by chemical means. For example, six eugenol glycosides, including **229** (Figure 4), were prepared by glycosylation of eugenol with various glycosyl bromides, followed by deacetylation with sodium methoxide in methanol, and their antifungal activity was assessed against Candida species. The peracetyl glycoside (**230**) was able to inhibit growth of *C. albicans*, *C. tropicalis* and *C. glabrata*, being 3.4 times more potent than fluconazole against *C. glabrata*, with low cytotoxicity (selectivity index of 45).[226]

However, the paradigm is slowly changing toward the enzymatic synthesis of useful glycosides. Floral aroma is an

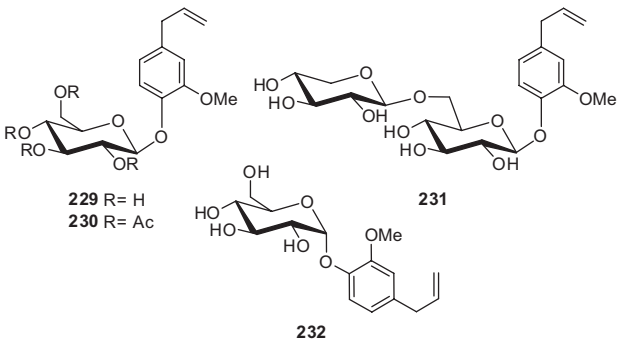


Figure 4. Selected relevant eugenyl glycosides.

important factor in determining the quality of various fruits, flowers and teas.[227] Various aroma constituents and other naturally occurring compounds are present in plants mainly as β-diglycoside precursors, such as β-primeverosides (6-*O*-β-D-xylopyranosyl-β-D-glucopyranoside); however, it is very difficult to obtain large amounts of the diglycosides from the natural sources.

Therefore, Yamamoto and co-workers[228] devised an enzymatic system, based on a partially purified β-diglycosidase from *Penicillium multicolor* IAM7153, for accessing several primaverosides. They prepared eugenyl β-primaveroside (**231**) in 12% yield by *trans*-glycosylation of *p*-nitrophenyl-β-primaveroside,[229] along with other analogous primaverosides. The rate of formation of eugenyl β-primaveroside was too rapid and the compound was hydrolyzed 25-fold faster than analogous aliphatic aroma β-primaveroside.

De Winter *et al.*[230] optimized a buffer/EtOAc biphasic system for the enzymatic transfer of glucose to a wide variety of acceptor molecules, taking advantage of the broad acceptor specificity of sucrose phosphorylase from *Bifidobacterium adolescentis*. Eugenol exhibited a rather moderate ability to undergo the transformation toward **232**. However, eugenyl-α-D-glucopyranoside (**232**), prepared through catalysis by an amyloglucosidase from a *Ryzopus*, was found to be a potent inhibitor of the angiotensin converting enzyme (ACE, $IC_{50} = 0.5 \pm 0.04$ mM),[231] and to display other useful bioactivities, behaving like a prodrug of eugenol.[232] The preparation of **232** by *Xanthomonas maltophilia* and with the aid of an α-glucosyl transfer enzyme of *Xanthomonas campestris* WU-9701 have also been reported.[233]

9. Concluding Remarks

Eugenol is a structurally simple, inexpensive and easily available small molecule natural product, which offers a wide range of application opportunities in bio/chemical synthesis. The various applications of eugenol, as feedstock for the chemo-enzymatic production of high valued low molecular weight compounds, as starting material for the synthesis of natural products and their analogs, and as building block for the elaboration of complexly functionalized bioactive compounds and co-drugs designed with improved physicochemical properties, macrocycles, heterocycles and polymers, fully justify considering eugenol as a highly versatile molecule.

Taking into account the growing pressure toward replacing fossil-derived resources with more sustainable alternatives with regard to the easy availability, structural characteristics and unique reactivity of eugenol, it can be foreseen that Chemists will be increasingly seduced to choose the natural product as part of future synthetic endeavors. Therefore, it is expected that new, more complex and imaginative synthetic and biotechnologically-assisted solutions will be published in the near future, with eugenol or its simple derivatives at the center of the scene.

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Teodoro S. Kaufman received his PhD (1987) from the National University of Rosario (UNR), working at the Institute of Synthetic Organic Chemistry (IQUIOS) under the guidance of Professor Edmundo A. Rúveda. After his post-doc at The University of Mississippi, he returned to IQUIOS-UNR as Research Assistant and Assistant Professor. Currently, he is full Professor of the UNR, Research Scientist of the Argentine National Research Council (CONICET) and Head of IQUIR (Institute of Chemistry of Rosario). He has co-authored 120 publications, 10 patents and five book chapters, and has edited three books. His scientific interests include heterocyclic chemistry, with emphasis in nitrogen and oxygen heterocycles, and the synthesis and evaluation of bioactive natural products and their analogs.

References

1. Koeduka, T.; Fridman, E.; Gang, E. R.; Vassao, D. G.; Jackson, B. L.; Kish, C. M.; Orlova, I.; Spassova, S. M.; Lewis, N. G.; Noel, J. P.; Baiga, T. J.; Dudareva, N.; Pichersky, E.; *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 10128.
2. Milind, P.; Deepa, K.; *Int. J. Res. Ayurveda Pharmacol.* **2011**, *2*, 47; Wenqiang, G.; Shufen, L.; Ruixiang, Y.; Shaokun, T.; Can, Q.; *Food Chem.* **2007**, *101*, 1558.
3. Chaieb, K.; Hajlaoui, H.; Zmantar, T.; Ben Kahla-Nakbi, A.; Rouabhia, M.; Mahdouani, K.; Bakhrouf, A.; *Phytother. Res.* **2007**, *21*, 501; Mittal, M.; Gupta, N.; Parashar, P.; Mehra, V.; Khatri, M.; *Int. J. Pharm. Pharm. Sci.* **2014**, *6,* 67; Pavithra, B.; *J. Pharm. Sci. Res.* **2014**, *6*, 153; Kamatou, G. P.; Vermaak, I.; Viljoen, A. M.; *Molecules* **2012**, *17*, 6953; Pramod, K.; Ansari, S. H.; Ali, J.; *Nat. Prod. Commun.* **2010**, *5*, 1999.
4. Miele, M.; Dondero, R.; Ciarallo, G.; Mazzei, M.; *J. Agric. Food Chem.* **2001**, *49*, 517.
5. Tan, K. H.; Nishida, R.; *J. Insect Sci.* **2012**, *12*, 1; Vargas,

R. I.; Shelly, T. E.; Leblanc, L.; Pinero, J. C.; Litwack, G.; *Vitam. Horm.* **2010**, *83*, 575.
6. Ouk, S.; Thiébaud, S.; Borredon, E.; Le Gars, P.; *Green Chem.* **2002**, *4*, 431.
7. Kulkarni, M. G.; Shaikh, Y. B.; Borhade, A. S.; Chavhan, S. W.; Dhondge, A. P.; Gaikwad, D. D.; Desai, M. P.; Birhade, D. R.; Dhatrak, N. R.; *Tetrahedron Lett.* **2013**, *54*, 2293; Hilt, G.; Lueers, S.; *Synthesis* **2002**, 609; Majetich, G.; Shimkus, J.; Li, Y.; *Tetrahedron Lett.* **2010**, *51*, 6830; Hilt, G.; Treutwein, J.; *Angew. Chem., Int. Ed.* **2006**, *46*, 8500; Okamoto, K.; Akiyama, R.; Kobayashi, S.; *J. Org. Chem.* **2004**, *69*, 2871; Colladon, M.; Scarso, A.; Sgarbossa, P.; Michelin, R. A.; Strukul, G.; *J. Am. Chem. Soc.* **2006**, *128*, 14006; Mochalov, S. S.; Gazeeva, R. A.; Fedorov, A. N.; Trofimova, E. V.; Trushkov, I. V.; Zefirov, N. S.; *Russ. J. Org. Chem.* **2004**, *40*, 1098; Hilt, G.; Paul, A.; Harms, K.; *J. Org. Chem.* **2008**, *73*, 5187.
8. Taylor, J. G.; Li, X.; Oberthuer, M.; Zhu, W.; Kahne, D. E.; *J. Am. Chem. Soc.* **2006**, *128*, 15084; Gildersleeve, J.; Smith, A.; Sakurai, K.; Raghavan, S.; Kahne, D.; *J. Am. Chem. Soc.* **1999**, *121*, 6176; Schueler, P.; Fischer, S.; Marsch, M.; Oberthuer, M.; *Synthesis* **2013**, *45*, 27; Gampe, C. M.; Tsukamoto, H.; Doud, E. H.; Walker, S.; Kahne, D.; *J. Am. Chem. Soc.* **2013**, *135*, 3776.
9. Protti, S.; Fagnoni, M.; Albini, A.; *Org. Biomol. Chem.* **2005**, *3*, 2868.
10. Costa, P. R. R.; *Quim. Nova* **2000**, *23*, 357.
11. Muheim, A.; Lerch, K.; *Appl. Microbiol. Biotechnol.* **1999**, *51*, 456.
12. Fogliano, V.; Sacchi, R.; *Mol. Nutr. Food Res.* **2006**, *50*, 5; Medina, I.; Sacchi, R.; Biondi, L.; Aubourg, S. P.; Paolillo, L.; *J. Agric. Food Chem.* **1998**, *46*, 1150.
13. Tuck, K. L.; Hayball, P. J.; *J. Nutr. Biochem.* **2002**, *13*, 636; Fernández-Bolaños, J. G.; López, O.; Fernández-Bolaños, J.; Rodríguez-Gutiérrez, G.; *Curr. Org. Chem.* **2008**, *12*, 442; Bernini, R.; Merendino, N.; Romani, A.; Velotti, F.; *Curr. Med. Chem.* **2013**, *20*, 655.
14. Mateos, R.; Domínguez, M. M.; Espartero, J. L.; Cert, A.; *J. Agric. Food Chem.* **2003**, *47*, 3535; Roche, M.; Dufour, C.; Mora, N.; Dangles, O.; *Org. Biomol. Chem.* **2005**, *3*, 423.
15. Baldioli, M.; Servili, M.; Perretti, G.; Montedoro, G. F.; *J. Am. Oil Chem. Soc.* **1996**, *73*, 1589; Carrasco-Pancorbo, A.; Cerretani, L.; Bendini, A.; Segura-Carretero, A.; Del Carlo, M.; Gallina-Toschi, T.; Lercker, G.; Compagnone, D.; Fernández-Gutiérrez, A.; *J. Agric. Food Chem.* **2005**, *53*, 8918.
16. Deffieux, D.; Gossart, P.; Quideau, S.; *Tetrahedron Lett.* **2014**, *55*, 2455.
17. Bhatt, M. V.; Babu, J. R.; *Tetrahedron Lett.* **1984**, *25*, 3497.
18. Andersson, S.; *Synthesis* **1985**, 437.
19. Masuda, T.; Jitoe, A.; *Phytochemistry* **1995**, *39,* 459.
20. Taber, D. F.; Frankowski, K. J.; *J. Org. Chem.* **2003**, *68*, 6047; Taber, D. F.; Frankowski, K. J.; *J. Chem. Educ.* **2006**, *83*, 283.
21. Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H.; *J. Am. Chem. Soc.* **2000**, *122*, 58; Vieille-Petit, L.; Clavier, H.; Linden, A.; Blumentritt, S.; Nolan, S. P.; Dorta, R.; *Organometallics* **2010**, *29*, 775; Broggi, J.; Urbina-Blanco, C. A.; Clavier, H.; Leitge, A.; Slugov, C.; Slawin, A. M. Z.; Nolan, S. P.; *Chem. Eur. J.* **2010**, *16*, 9215; Moïse, J.; Arseniyadis, S.; Cossy, J.; *Org. Lett.* **2007**, *9*, 1695.
22. Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C.; *RSC Adv.* **2012**, *2*, 9584.
23. Awang, D.; *Can. Pharm. J.* **1992**, *125*, 309; Tapsell, L. C.; Hemphill, I.; Cobiac, L.; Patch, C. S.; Sullivan, D. R.; Fenech, M.; Roodenrys, S.; Keogh, J. B.; Clifton, P. M.; Williams, P. G.; Fazio, V. A.; Inge, K. E.; *Med. J. Aust.* **2006**, *185*, S4.
24. Murad, N. A.; Ngah, W. Z. W.; Yusof, Y. A. M.; Abdul Aziz, J. M.; Semarak, J.; *Asian J. Biochem.* **2007**, *2*, 4214; Kim, J. K.; Kim, Y.; Na, K. M.; Surh, Y.-J.; Kim, T. Y.; *Free Radical Res.* **2007**, *41*, 603.
25. Ahui, M. L. B.; Champy, P.; Ramadan, A.; Pham Van, L.; Araujo, L.; Brou Andre, K.; Diem, S.; Damotte, D.; Kati-Coulibaly, S.; Offoumou, M. A.; Dy, M.; Thieblemont, N.; Herbelin, A.; *Int. Immunopharmacol.* **2008**, *8*, 1626.
26. Lee, H. S.; Seo, E. Y.; Kang, N. E.; Kim, W. K.; *J. Nutr. Biochem.* **2008**, *19*, 313; Lee, S. H.; Cekanova, M.; Baek, S.; *Mol. Carcinog.* **2008**, *47*, 197.
27. Hibino, T.; Yuzurihara, M.; Terawaki, K.; Kanno, H.; Kase, Y.; Takeda, A.; *J. Pharmacol. Sci.* **2008**, *108*, 89.
28. Nagoshi, C.; Shiota, S.; Kuroda, T.; Hatano, T.; Yoshida, T.; Kariyama, R.; Tsuchiya, T.; *Biol. Pharm. Bull.* **2006**, *29*, 443.
29. Vijendra Kumar, N.; Srinivas, P.; Bettadaiah, B. K.; *Tetrahedron Lett.* **2012**, *53*, 2993.
30. Brown, H. C.; Rathke, M. W.; Rogic, M. M.; De Lue, N. R.; *Tetrahedron* **1988**, *44*, 2751.
31. Maugein, N.; Wagner, A.; Mioskowski, C.; *Tetrahedron Lett.* **1997**, *38*, 1547.
32. Fukuda, H.; Tetsu, T.; Kitazume, T.; *Tetrahedron* **1996**, *52*, 157.
33. Chen, S.-N.; Fabricant, D. S.; Lu, Z.-Z.; Zhang, H.; Fong, H. H. S.; Farnsworth, N. R.; *Phytochemistry* **2002**, *61*, 409.
34. Lieberman, S. A.; *Int. J. Women's Health* **1998**, *7*, 525; Johnson, B. M.; van Breemen, R. B.; *Chem. Res. Toxicol.* **2003**, *16*, 838.
35. Sakai, S.; Ochiai, H.; Nakajima, K.; Terasawa, K.; *Cytokines* **1997**, *9*, 242.
36. Burdette, J. E.; Chen, S.-N.; Lu, Z.-Z.; Xu, H.; White, B. E. P.; Fabricant, D. S.; Liu, J.; Fong, H. H.; Farnsworth, N. R.; Constantinou, A. I.; van Breemen, R. B.; Pezzuto, J. M.; Bolton, J. L.; *J. Agric. Food Chem.* **2002**, *50*, 7022.
37. Fache, F.; Suzan, N.; Piva, O.; *Tetrahedron* **2005**, *61*, 5261.
38. Dalton, D. R.; Dutta, V. P.; Jones, D. C.; *J. Am. Chem. Soc.* **1968**, *90*, 5498.
39. Dess, D. B.; Martin, J. C.; *J. Org. Chem.* **1983**, *48*, 4155.
40. Solladié, G.; Gressot-Kempf, L.; *Tetrahedron: Asymmetry* **1996**, *7*, 2371.

41. Matsuno, M.; Nagatsu, A.; Ogihara, Y.; Mizukami, H.; *Chem. Pharm. Bull.* **2001**, *49*, 1644.
42. Matsunaga, K.; Shibuya, M.; Ohizumi, Y.; *J. Nat. Prod.* **1995**, *58*, 138.
43. Gulavita, N. K.; Pomponi, S. A.; Wright, A. E.; Garay, M.; Sills, M. A.; *J. Nat. Prod.* **1995**, *58*, 954; Chen, C. C.; Wu, L. G.; Ko, F. N.; Teng, C. M.; *J. Nat. Prod.* **1994**, *57*, 1271.
44. Shattuck, J. C.; Shreve, C. M.; Solomon, S. E.; *Org. Lett.* **2001**, *3*, 3021.
45. Connor, S. J.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K.; Medwid, J. B.; *Org. Synth.* **1988**, *52*, 16.
46. Enders, D.; Kipphardt, H.; Fey, P.; *Org. Synth.* **1987**, *65*, 183; Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., ed.; Academic: New York, 1984; Vol. 3; Enders, D.; Eichenauer, H.; Baus, U.; Schubert, H.; Kremer, K. A. M.; *Tetrahedron* **1984**, *40*, 1345; Enders, D.; Reinhold, U.; *Synlett* **1994**, 792.
47. Parker, D.; *Chem. Rev.* **1991**, *91*, 1441.
48. Fukuyama, Y.; Otoshi, Y.; Miyoshi, Y.; Nakamura, K.; Kodama, M.; Nagasawa, M.; Hasegawa, M.; Hasegawa, T.; Okazaki, H.; Sugawara, M.; *Tetrahedron* **1992**, *48*, 377; Ito, K.; Iida, T.; Ichino, K.; Tsunezuka, M.; Hattori, M.; Namba, T.; *Chem. Pharm. Bull*. **1982**, *30*, 3347; Huang, K. C.; *The Pharmacology of Chinese Herbs*, CRC Press: Ann Arbor, 1993.
49. Hwang, E.-I.; Kwon, B.-M.; Lee, S.-H.; Kim, N.-R.; Kang, T.- H.; Kim, Y.-T.; Park, B.-K.; Kim, S.-U.; *J. Antimicrob. Chemother.* **2002**, *49*, 95; Matsuda, H.; Kageura, T.; Oda, M.; Morikawa, T.; Sakamoto, Y.; Yoshikawa, M.; *Chem. Pharm. Bull*. **2001**, *49*, 716; Pyo, M. K.; Lee, Y. Y.; Yun-Choi, H. S.; *Arch. Pharm. Sci. Res*. **2002**, *25*, 325; Kwon, B.-M.; Kim, M.-K.; Lee, S.-H.; Kim, J.-A.; Lee, I.-R.; Kim, Y.-K.; Bok, S.-H.; *Planta Med.* **1997**, *63*, 550.
50. Lee, M.-S.; Yang, J.-E.; Choi, E.-W.; In, J.-K.; Lee, S. Y.; Lee, H.; Hong, J. T.; Lee, H. W.; Suh, Y.-G.; Jung, J.-K.; *Bull. Korean Chem. Soc*. **2007**, *28*, 1601; Lee, S. K.; Kim, H. N.; Kang, Y. R.; Lee, C. W.; Kim, H. M.; Han, D. C.; Shin, J.; Bae, K.; Kwon, B. M.; *Bioorg. Med. Chem*. **2008**, *16*, 8397; Lee, S. Y.; Yuk, D. Y.; Song, H. S.; Yoon, D. Y.; Jung, J. -K.; Moon, D. C.; Lee, B. S.; Hong, J. T.; *Eur. J. Pharm*. **2008**, *582*, 17; Choi, M. S.; Lee, S. H.; Cho, H. S.; Kim, Y.; Yun, Y. P.; Jung, H. Y.; Jung, J. K.; Lee, B. C.; Pyo, H. B.; Hong, J. T.; *Eur. J. Pharm*. **2007**, *555*, 181; Choi, M. S.; Yoo, M. S.; Son, D. J.; Jung, H. Y.; Lee, S. H.; Jung, J. K.; Lee, B. C.; Yun, Y. P.; Pyo, H. B.; Hong, J. T.; *J. Dermatol. Sci*. **2007**, *46*, 127.
51. Kwak, J.-H.; In, J.-K.; Lee, M.-S.; Choi, E.-H.; Lee, H.; Hong, J. T.; Yun, Y.-P.; Lee, S. J.; Seo, S. Y.; Suh, Y.-G.; Jung, J.-K.; *Arch. Pharm. Sci. Res.* **2008**, *31*, 1559.
52. Alam, A.; *Synlett* **2005**, 2403.
53. Cai, Q.; Zou, B. L.; Ma, D. W.; *Angew. Chem., Int. Ed.* **2006**, *45*, 1276; Ma, D. W.; Cai, Q.; *Org. Lett*. **2003**, *5*, 3799.
54. Ward, R. S.; *Nat. Prod. Rep.* **1993**, *10*, 1; Ward, R. S.; *Nat. Prod. Rep.* **1995**, *12*, 183; Ward, R. S.; *Nat. Prod. Rep.* **1997**, *14*, 43; Ward, R. S.; *Nat. Prod. Rep.* **1999**, *16*, 75; MacRae, W. D.; Towers, G. H. N.; *Phytochemistry* **1984**, *23*, 1207.
55. Yang, S.; Fang, J.; Cheng, Y.; *J. Chin. Chem. Soc.* **1999**, *46*, 811.
56. García-Muñoz, S.; Jiménez-González, L.; Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I.; *Synlett* **2005**, 3011.
57. Meyer, C.; Cossy, J.; *Tetrahedron Lett.* **1997**, *38*, 7861; Cassidy, J. H.; Marsden, S. P.; Stemp, G.; *Synlett* **1997**, 1411.
58. Miles, S. M.; Marsden, S. P.; Leatherbarrow, R. J.; Coates, W. J.; *J. Org. Chem.* **2004**, *69*, 6874.
59. Kawanishi, K.; Uhara, Y.; Hashimoto, Y.; *Phytochemistry* **1982**, *21*, 929; Kawanishi, K.; Uhara, Y.; Hashimoto, Y.; *Phytochemistry* **1982**, *21*, 2725.
60. Watanabe, M.; Kawanishi, K.; Akiyoshi, R.; Furukawa, S.; *Chem. Pharm. Bull.* **1991**, *39*, 3123.
61. Yang, Z.; Hon, M. H.; Chui, K. Y.; Xu, H. M.; Lee, C. M.; Cui, Y. X.; Wong, H. N. C.; Poon, C. D.; Fung, B. M.; *Tetrahedron Lett.* **1991**, *32*, 2061; Yang, Z.; Liu, H. B.; Lee, C. M.; Chang, H. M.; Wong, H. N. C.; *J. Org. Chem.* **1992**, *57*, 7248.
62. Hutchinson, S. A.; Luetjens, H.; Scammells, P. J.; *Bioorg. Med. Chem. Lett*. **1997**, *7*, 3081.
63. Nagao, Y.; Fujita, E.; Kohno, T.; Yagi, M.; *Chem. Pharm. Bull.* **1981**, *29,* 3202.
64. Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Dishida, A.; *Bull. Chem. Soc. Jpn.* **1993**, *66,* 1576.
65. Chauret, D. C.; Bernard, C. B.; Arnason, J. T.; Durst, T.; Krishnamurty, H. G.; Sanchez-Vindas, P.; Moreno, N.; San Roman, L.; Poveda, L.; *J. Nat. Prod.* **1996**, *59*, 152; Tsai, I.-L.; Hsieh, C.-F.; Duh, C.-Y.; *Phytochemistry* **1988**, *27*, 1371; Carini, M.; Aldini, G.; Orioli, M.; Facino, R. M.; *Planta Med.* **2002**, *68*, 193; Freixa, B.; Vila, R.; Ferro, E. A.; Adzet, T.; Caligueral, S.; *Planta Med.* **2001**, *67*, 873.
66. Carroll, A. R.; Taylor, W. C.; *Aust. J. Chem.* **1991**, *44*, 1627.
67. Marques, M. O. M.; Yoshida, M.; Gottlieb, O. R.; *Phytochemistry* **1992**, *31*, 4380; Watanabe, M.; Date, M.; Kawanishi, K.; Hori, T.; Furukawa, S.; *Chem. Pharm. Bull.* **1991**, *39*, 41; Date, M.; Kawanishi, K.; Hori, T.; Watanabe, M.; Furukawa, S.; *Chem. Pharm. Bull.* **1989**, *37*, 2884; Kawanashi, K.; Uhara, Y.; Hashimoto, Y.; *Phytochemistry* **1982**, *21*, 929.
68. Murphy, S. K.; Bruch, A.; Dong, V. M.; *Angew. Chem., Int. Ed.* **2014**, *53*, 2455.
69. Wisniak, J.; *Indian J. Hist. Sci.* **2013**, *48*, 239; Pelletier, P. J.; *Bull. Pharm.* **1814**, *6*, 432; cited in Poggendorf's *Ann. Phys. Chem.* **1833**, *29*, 102.
70. Arnone, A.; Camarda, L.; Merlin, L.; Nasini, G.; *J. Chem. Soc., Perkin Trans. 1* **1975**, 186; Arnone, A.; Camarda, L.; Merlini, L.; Nasini, G.; *J. Chem. Soc., Perkin Trans. 1* **1977**, 2118; Arnone, A.; Camarda, L.; Merlini, L.; Nasini, G.; Taylor, D. A. H.; *J. Chem. Soc., Perkin Trans. 1* **1977**, 2116.
71. Strych, S.; Trauner, D.; *Angew. Chem., Int. Ed.* **2013**, *52*, 9509.

72. Kinjo, J.; Uemura, H.; Nohara, T.; Yamashita, M.; Yoshihira, K.; *Tetrahedron Lett.* **1995**, *36*, 5599.
73. Tello-Aburto, R.; Harned, A.; *Org. Lett.* **2009**, *11*, 3998.
74. Chatterjee, A.; Choi, T.; Sanders, D.; Grubbs, R. H.; *J. Am. Chem. Soc.* **2003**, *125*, 11360; Chatterjee, A.; Toste, F.; Choi, T.; Grubbs, R. H.; *Adv. Synth. Catal.* **2002**, *344*, 634.
75. Jackson, Y. A.; *Heterocycles* **1995**, *41*, 1979.
76. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2005**, *127*, 4685.
77. Giles, R.; Hughes, A.; Sargent, M.; *J. Chem. Soc., Perkin Trans. 1* **1991**, 1581.
78. Gradner, J. A. F.; Barton, G. M.; MacLean, H.; *Can. J. Chem.* **1959**, *37*, 1703; Gradner, J. A. F.; Swan, E. P.; Sutherland, S. A.; MacLean, H.; *Can. J. Chem.* **1966**, *44*, 52; Swan, R. J.; Klyne, W.; MacLean, H.; *Can. J. Chem.* **1967**, *45*, 321.
79. Chan-Yeung, M.; *J. Allergy Clin. Immunol.* **1982**, *70*, 32; Vedal, S.; Chan-Yeung, M.; Enarson, D. A.; Chan, H.; Dorken, E.; Tse, K. S.; *J. Allergy Clin. Immunol.* **1986**, *78*, 1103; Chan-Yeung, M.; Chan, H.; Tse, K. S.; Salari, H.; Lam, S.; *J. Allergy Clin. Immunol.* **1989**, *85*, 762.
80. Chan-Yeung, M.; Giclas, P. C.; Henson, P. M.; *J. Aller. Clin. Immun.* **1980**, *65*, 333; Cartier, A.; Chan, H.; Malo, J.-L.; Pineau, L.; Tse, K. S.; Chan-Yeung, M.; *J. Allergy Clin. Immunol.* **1986**, *77*, 639; Frew, A.; Chang, J. H.; Chan, H.; Quirce, S.; Noertjojo, K.; Keown, P.; Chan-Yeung, M.; *J. Allergy Clin. Immunol.* **1998**, *101*, 841; Weissman, D. N.; Lewis, D. M.; *Occup. Med.* **2000**, *15*, 385.
81. Sun, B.-F.; Hong, R.; Kang, Y.-B.; Deng, L.; *J. Am. Chem. Soc.* **2009**, *131*, 10384.
82. Holmquist, C. R.; Roskamp, E. J.; *J. Org. Chem.* **1989**, *54*, 3258.
83. Aoki, M.; Seebach, D.; *Helv. Chim. Acta* **2001**, *84*, 187.
84. Park, H. S.; Lee, I. S.; Kwon, D. W.; Kim, Y. H.; *Chem. Commun.* **1998**, 2745; Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kuhlman, M. L.; Fuchs, J. R.; Flowers II, R. A.; *J. Am. Chem. Soc.* **2000**, *122*, 7718.
85. Machrouhi, F.; Hamann, B.; Namy, J. L.; Kagan, H.; *Synlett* **1996**, *7*, 633; Miquel, N.; Doisneau, G.; Beau, J.-M.; *Angew. Chem., Int. Ed.* **2000**, *39*, 4111.
86. Tamao, K.; Ishida, N.; Tanak, T.; Kumada, M.; *Organometallics* **1983**, *2*, 1694; Tamao, K.; Ishida, N.; Kumada, M.; *J. Org. Chem.* **1983**, *48*, 2122.
87. Vaughan, W. R.; Baumann, J. B.; *J. Org. Chem.* **1962**, *27*, 739; Lal, K.; Ghosh, S.; Salomon, R. G.; *J. Org. Chem.* **1987**, *52*, 1072.
88. Gellert, E.; Rudzats, R.; *Aust. J. Chem.* **1972**, *25*, 2477; Dutta, N. L.; Bradsher, C. K.; *J. Org. Chem.* **1962**, *27*, 2213.
89. Bhakuni, D. S.; Jain, S.; Gupta, D. S.; *Tetrahedron* **1980**, *36*, 2491; Bhakuni, D. S.; Jain, S.; Gupta, D. S.; *Tetrahedron* **1983**, *39*, 455.
90. Ponzo, V. L.; Kaufman, T. S.; *Synlett* **1995**, 1149.
91. Kaufman, T. S.; *J. Chem. Soc., Perkin Trans. 1* **1996**, 2497.
92. Bianchi, D. A.; Kaufman, T. S.; *Synlett* **2000**, 801.
93. Bianchi, D. A.; Kaufman, T. S.; *Can. J. Chem.* **2000**, *78*, 1165.
94. Kaufman, T. S.; *J. Chem. Soc., Perkin Trans. 1* **1993**, 403.
95. Larghi, E. L.; Obrist, B. V.; Kaufman, T. S.; *Tetrahedron* **2008**, *64*, 5236; Bracca, A. B. J.; Kaufman, T. S.; *Eur. J. Org. Chem.* **2007**, 5284.
96. Sammes, P. G.; Smith, S.; *J. Chem. Soc., Perkin Trans. 1* **1984**, 2415.
97. Kang, H.; Fenical, W.; *J. Org. Chem.* **1997**, *62*, 3254.
98. Bowden, B. F. In *Studies in Natural Products Chemistry*; Rahman, A., ed.; Elsevier Science: New York, New York, 2000, Vol. 23, pp. 233-283.
99. Tao, H.; Hwang, I.; Boger, D. L.; *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5979; Soenen, D. R.; Hwang, I.; Hedrick, M. P.; Boger, D. L.; *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1777.
100. Namsa-aid, A.; Ruchirawat, S.; *Org. Lett.* **2002**, *4*, 2635.
101. Amorese, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerini, S.; Fedili, W.; Ortar, G.; *Tetrahedron* **1989**, *45*, 813; Ikeda, M.; El Bialy, S. A. A.; Yakura, T.; *Heterocycles* **1999**, *51*, 1957; Amatore, C.; Jutand, A.; *Acc. Chem. Res*. **2000**, *33*, 314; Beletskaya, I. P.; Cheprakov, A. V.; *Chem. Rev*. **2000**, *100*, 3009; Poli, G.; Giambastiani, G.; Heumann, A.; *Tetrahedron* **2000**, *56*, 5959.
102. Sibi, M. P.; Dankwardt, J. W.; Snieckus, V.; *J. Org. Chem*. **1986**, *51*, 273; de Koning, C. B.; Michael, J. P.; Rosseau, A. L.; *Tetrahedron Lett*. **1997**, *38*, 893; Hattori, T.; Takeda, A.; Suzuki, K.; Koike, N.; Koshiishi, E.; Miyano, S.; *J. Chem. Soc., Perkin Trans. 1* **1998**, 3661.
103. Estevez, R. J.; Martinez, E.; Martinez, L.; Treus, M.; *Tetrahedron* **2000**, *56*, 6023.
104. Barret, R.; Roue, N.; *Tetrahedron Lett*. **1999**, *40*, 3889; Tohma, H.; Harayama, Y.; Hashizumi, M.; Iwata, M.; Egi, M.; Kita, Y.; *Angew. Chem., Int. Ed.* **2002**, *41*, 348.
105. Peschko, C.; Steglich, W.; *Tetrahedron Lett.* **2000**, *41*, 9477.
106. Wang, J.; Soisson, S. M.; Young, K.; Shoop, W.; Kodali, S.; Galgoci, A.; Painter, R.; Parthasarthy, G.; Tang, Y. S.; Cummings, R.; Ha, S.; Dorso, K.; Motyl, M.; Jayasuriya, H.; Ondeyka, J.; Herath, K.; Zhang, C.; Hernandez, L.; Allocco, J.; Basillo, A.; Tormo, J. R.; Genilloud, O.; Vicente, F.; Pelaez, F.; Colwell, L.; Lee, S. H.; Michael, B.; Felcetto, T.; Gill, C.; Silver, L. L.; Hermes, J. D.; Bartizal, K.; Barrett, J.; Schmatz, D.; Becker, J. W.; Cully, D.; Singh, S. B.; *Nature* **2006**, *441*, 358.
107. Eey, S. T.-C.; Lear, M. J.; *Org. Lett.* **2010**, *12*, 5510.
108. Eey, S. T.-C.; Lear, M. J.; *Chem. Eur. J.* **2014**, *20*, 11556.
109. Evans, D. A.; Bender, S. L.; Morris, J.; *J. Am. Chem. Soc.* **1988**, *110*, 2506.
110. Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R.; *Org. Lett.* **1999**, *1*, 447.
111. Bruno, M.; Rosselli, S.; Maggio, A.; Raccuglia, R. A.; Bastow, K. F.; Lee, K.-H.; *J. Nat. Prod.* **2005**, *68*, 1042.

112. Mukaiyama, T.; Suzuki, K.; Han, J. S.; Kobayashi, S.; *Chem. Lett.* **1992**, 435; Kawada, A.; Mitamura, S.; Kobayashi, S.; *Chem. Commun.* **1996**, 183; Chapman, C. J.; Frost, C. G.; Hartley, J. P.; Whittle, A. J.; *Tetrahedron Lett.* **2001**, *42*, 773; Bartoli, G.; Locatelli, M.; Melchiorre, P.; Sambri, L.; *Eur. J. Org. Chem.* **2007**, 2037.
113. Boger, D. L.; McKie, J. A.; Nishi, T.; Ogiku, T.; *J. Am. Chem. Soc.* **1997**, *119*, 311; Dai, M.; Danishefsky, S. J.; *Tetrahedron Lett.* **2008**, *49*, 6610.
114. Akiyama, T.; Shima, H.; Ozaki, S.; *Tetrahedron Lett.* **1991**, *32*, 5593.
115. Moëns, L.; Baizer, M. M.; Little, R. D.; *J. Org. Chem.* **1986**, *51*, 4497.
116. Tiefenbacher, K.; Mulzer, J.; *J. Org. Chem.* **2009**, *74*, 2937; Yeung, Y.-Y.; Corey, E. J.; *Org. Lett.* **2008**, *10*, 3877; Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S.; Ellery, S. P.; *J. Am. Chem. Soc.* **2009**, *131*, 16905.
117. Heretsch, P.; Giannis, A.; *Synthesis* **2007**, 2614; Nicolaou, K. C.; Li, A.; Edmonds, D. J.; *Angew. Chem., Int. Ed.* **2006**, *45*, 7086.
118. Wang, X.; Yi, M.; Du, Q.; Wu, A.; Xiao, R.; *Med. Chem. Res.* **2012**, *21*, 2827.
119. Meragelman, T. L.; Scuderio, D. A.; Davis, R. E.; Staudt, L. M.; McCloud, T. G.; Cardellina II, J. H.; Shoemaker, R. H.; *J. Nat. Prod.* **2009**, *72*, 336.
120. Cros, F.; Pelotier, B.; Piva, O.; *Eur. J. Org. Chem.* **2010**, 5063.
121. Jones, H. A.; Haller, H. L.; *J. Org. Chem.* **1940**, *62*, 2558; Taira, J.; Ikemoto, T.; Yoneya, T.; Hagi, A.; Murakami, A.; Makino, K.; *Free Radical Res. Commun.* **1992**, *16*, 197.
122. Amaral, J. F.; Silva, M. I. G.; Aquino Neto, M. R.; Moura, B. A.; Carvalho, A. M. R.; Vasconcelos, P. F.; Barbosa Filho, J. M.; Gutierrez, S. J. C.; Vasconcelos, S. M. M.; Macedo, D. S.; Sousa, F. C. F.; *Fundam. Clin. Pharmacol.* **2013**, *27*, 471.
123. De Diaz, A. M. P.; Gottlieb, H. E.; Gottlieb, O. R.; *Phytochemistry* **1980**, *19*, 681.
124. Suárez, M.; Bonilla, J.; De Díaz, A. M. P.; Achenbach, H.; *Phytochemistry* **1983**, *22*, 609.
125. Namba, T.; Tsunezuka, M.; Hattori, M.; *Planta Med.* **1982**, *44*, 100; Lo, Y.-C.; Teng, C.-M.; Chen; C.-C.; Hong, C.-Y.; *Biochem. Pharmacol.* **1994**, *47*, 549; Yahara, S.; Nishiyori, T.; Kohda, A.; Nohara, T.; Nishioka, I.; *Chem. Pharm. Bull.* **1991**, *39*, 2024; Kouno, I.; Morisaki, T.; Hara, Y.; Yang, C.-S.; *Chem. Pharm. Bull.* **1991**, *39*, 2606.
126. Watanabe, H.; Watanabe, K.; Hagino, K.; *J. Pharmacobio-Dyn.* **1983**, *6*, 184; Gustafson, K. R.; Cardellina II, J. H.; McMahon, J. B.; Pannell, L. K.; Cragg, G. M.; Boyd, M. R.; *J. Org. Chem.* **1992**, *57*, 2809; Zacchino, S. A.; López, S. N.; Pezzenati, G. D.; Furlán, R. L.; Santecchia, C. B.; Muñoz, L.; Giannini, F. A.; Rodríguez, A. M.; Enriz, R. D.; *J. Nat. Prod.* **1999**, *62*, 1353.
127. Taira, J.; Ikemoto, T.; Mimura, K.; Hagi, A.; Murakami, A.; Makino, K.; *Free Radical Res. Commun.* **1993**, *19*, S71; Fujisawa, S.; Kashiwagi, Y.; Atsumi, T.; Iwakura, I.; Ueha, T.; Hibino, Y.; Yokoe, I.; *J. Dent.* **1999**, *27*, 291; Fujisawa, S.; Atsumi, T.; Kadoma, Y.; Sakagami, H.; *Toxicology* **2002**, *177*, 39.
128. Gerosa, R.; Borin, M.; Menegazzi, G.; Puttini, M.; Cavalieri, G.; *J. Endodont.* **1996**, *22*, 532; Ogata, M.; Hoshi, M.; Urano, S.; Endo, T.; *Chem. Pharm. Bull.* **2000**, *48*, 1467; Fujisawa, S.; Okada, N.; Muraoka, E.; *Dent. Mater. J.* **2001**, *20*, 237.
129. Delogu, G.; Fabbri, D.; Dettori, M. A.; Forni, A.; Casalone, G.; *Tetrahedron: Asymmetry* **2004**, *15*, 275.
130. Asano, A.; Gisvold, O.; *J. Am. Pharm. Assoc.* **1948**, 169; Bassoli, A.; Di Gregorio, G.; Rindone, B.; Tollari, S.; Chioccara, F.; Salmona, M.; *Gazz. Chim. Ital.* **1988**, *118*, 763; Dias, A. F.; *Phytochemistry* **1988**, *27*, 3008; Krawczyk, A. R.; Lipkowska, E.; Wrobel, J. T.; *Collect. Czech. Chem. Commun.* **1991**, *56*, 1147; Marques, F. A.; Simonelli, F.; Oliveira, A. R. M.; Gohr, G. L.; Leal, P. C.; *Tetrahedron Lett.* **1998**, *39*, 943; Barba, I.; Chinchilla, R.; Gómez, C.; *J. Org. Chem.* **1990**, *55*, 3270; Jiang, Q.; Sheng, W.; Tian, M.; Tang, J.; Guo, C.; *Eur. J. Org. Chem.* **2013**, 1861; Bortolomeazzi, R.; Verardo, G.; Liessi, A.; Callea, A.; *Food Chem.* **2010**, *118*, 256.
131. Hernández-Vázquez, L. J.; Olivera-Flores, M. T.; Ruiz-Teran, F.; Ayala, I.; Navarro-Ocaña, A.; *J. Mol. Catal. B: Enzym.* **2011**, *72*, 102.
132. Vermillion, F. J.; Pearl, I. A.; *J. Electrochem. Soc.* **1964**, *111*, 1392; Iguchi, M.; Nishiyama, A.; Terada, Y.; Yamamura, S.; *Chem. Lett.* **1978**, 451.
133. Jada, S.; Doma, M. R.; Pal Singh, P.; Kumar, S.; Malik, F.; Sharma, A.; Khan, I. A.; Qazi, G. N.; Kumar, H. M. S.; *Eur. J. Med. Chem.* **2012**, *51*, 35.
134. Mascia, M. P.; Fabbri, D.; Dettori, M. A.; Ledda, G.; Delogu, G.; Biggio, G.; *Eur. J. Pharm.* **2012**, *693*, 45.
135. De Souza, N. J.; Kothare, A. N.; Nadkarny, V. V.; *J. Org. Chem.* **1966**, *9*, 618.
136. Egorov, M.; Delpech, B.; Aubert, G.; Cresteil, T.; García-Alvarez, M. C.; Collina, P.; Marazano, C.; *Org. Biomol. Chem.* **2014**, *12*, 1518.
137. Tomasch, M.; Schwed, J. S.; Kuczka, K.; Santos, S. M.; Harder, S.; Nusing, R. M.; Paulke, A.; Stark, H.; *ACS Med. Chem. Lett.* **2012**, *3*, 774.
138. Fonseca-Berzal, C.; Ruiz, F. A. R.; Escario, J. A.; Kouznetsov, V. V.; Gomez-Barrio, A.; *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1209.
139. Arango, V.; Domínguez, J. J.; Cardona, W.; Robledo, S. M.; Muñoz, S. L.; Figadere, B.; Sáez, J.; *Med. Chem. Res.* **2012**, *21*, 3445.
140. Chen, H.; Li, G.; Zhan, P.; Guo, X.; Ding, Q.; Wang, S.; Liu, X.; *Med. Chem. Commun.* **2013**, *4*, 827.
141. Abdel Bar, F. M.; Khanfar, M. A.; Elnagar, A. Y.; Badria, F. A.; Zaghloul, A. M.; Ahmad, K. F.; Sylvester, P. W.; El Sayed, K. A.; *Bioorg. Med. Chem.* **2010**, *18*, 496.

142. Ito, C.; Itoigawa, M.; Kanematsu, T.; Imamura, Y.; Tokuda, H.; Nishino, H.; Furukawa, H.; *Eur. J. Med. Chem.* **2007**, *42*, 902.
143. Carrasco, H.; Espinoza, L.; Cardile, V.; Gallardo, C.; Cardona, W.; Lombardo, L.; Catalan, K.; Cuellar, M.; Russo, A.; *J. Braz. Chem. Soc.* **2008**, *19*, 543.
144. Lenardão, E. J.; Jacob, R. G.; Mesquita, K. D.; Lara, R. G.; Webber, R.; Martinez, D. M.; Savegnago, L.; Mendes, S. R.; Alves, D.; Perin, G.; *Green Chem. Lett. Rev.* **2013**, *6*, 269.
145. Farias, M. A.; Oliveira, P. S.; Dutra, F. S. P.; Fernandes, T. J.; Pereira, C. M. P.; Oliveira, S. Q.; Stefanello, F. M.; Lencina, C. L.; Barschak, A. G.; *J. Pharm. Pharmacol.* **2014**, *66*, 733.
146. Maurya, R.; Ahmad, A.; Gupta, P.; Chand, K.; Kumar, M.; Rawat, P. J.; Rasheed, N.; Palit, G.; *Med. Chem. Res.* **2011**, *20*, 139.
147. Hernández, D.; Bernal, P.; Cruz, A.; Figueroa, Y. G.; Garduño, L.; Salazar, M.; Díaz, F.; Chamorro, G.; Tamariz, J.; *Drug Dev. Res.* **2004**, *61*, 19.
148. Huang, Y.-C.; Wu, B.-N.; Yeh, J.-L.; Chen, S.-J.; Liang, J.-C.; Lo, Y.-C.; Chen, I.-J.; *Bioorg. Med. Chem.* **2001**, *9*, 1739.
149. Bhat, K. I.; Hussain, M. M. M.; *Asian J. Chem.* **2009**, *21*, 3371.
150. Carrasco, H.; Raimondi, M.; Svetaz, L.; Di Liberto, M.; Rodriguez, M. V.; Espinoza, L.; Madrid, A.; Zacchino, S.; *Molecules* **2012**, *17*, 1002.
151. Thota, N.; Reddy, M. V.; Kumar, A.; Khan, I. A.; Sangwan, P. L.; Kalia, N. P.; Koul, J. L.; Koul, S.; *Eur. J. Med. Chem.* **2010**, *45*, 3607; Alhaffar, M.; Suleiman, R.; El Ali, B.; *Catal. Commun.* **2010**, *11*, 778.
152. López-Pérez, J.; Abad, A.; del Olmo, E.; San Feliciano, A.; *Tetrahedron* **2006**, *62*, 2370; Wang, E.-C.; Wein, Y.-S.; Kuo, Y.-H.; *Tetrahedron Lett*. **2006**, *47*, 9195; Angle, S. R.; Arnaiz, D.; *J. Org. Chem.* **1992**, *57*, 5937; Kam, T.-S.; Subramaniam, G.; Lim, T.-M.; *Tetrahedron Lett.* **2001**, *42*, 5977.
153. Jacquemond-Collet, I.; Benoit-Vical, F.; Mustofa, V.; Stanislas, A.; Mallié, E.; Fourasté, I.; *Planta Med.* **2002**, *68*, 68; Wallace, O. B.; Lauwers, K. S.; Jones, S. A.; Dodge, J. A.; *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1907; Dorey, G.; Lockhart, B.; Lestage, P.; Casara, P.; *Bioorg. Med. Chem. Lett.* **2000**, *10*, 935.
154. Arenas, D. R. M.; Ruíz, F. A. R.; Kouznetsov, V. V.; *Tetrahedron Lett.* **2011**, *52*, 1388.
155. Kouznetsov, V. V.; Romero, A. R. B.; Stashenko, E. E.; *Tetrahedron Lett.* **2007**, *48*, 8855; Kouznetsov, V. V.; Arenas, D. R. M.; Romero, A. R. B.; *Tetrahedron Lett.* **2008**, *49*, 3097; Hajbi, Y.; Neagoie, C.; Biannic, B.; Chilloux, A.; Vedrenne, E.; Baldeyrou, B.; Bailly, C.; Mérour, J.-Y.; Rosca, S.; Routier, S.; Lansiaux, A.; *Eur. J. Med. Chem.* **2010**, *45*, 5428; Muhuhi, J.; Spaller, M. R.; *J. Org. Chem.* **2006**, *71*, 5515.
156. Kouznetsov, V. V.; Arenas, D. R. M.; Arvelo, F.; Forero, J. S. B.; Sojo, F.; Muñoz, A.; *Lett. Drug Des. Discovery* **2010**, *7*, 632; Muñoz, A.; Sojo, F.; Arenas, D. M.; Kouznetsov, V. V.; Arvelo, F.; *Chem.-Biol. Interact.* **2011**, *189*, 215.
157. Khadem, S.; Udachin, K. A.; Enright, G. D.; Prakesch, M.; Arya, P.; *Tetrahedron Lett.* **2009**, *50*, 6661.
158. Ishihara, Y.; Kiyota, Y.; Goto, G.; *Chem. Pharm. Bull.* **1990**, *38*, 3024; Sui, Z. H.; Altom, J.; Nguyen, V.; Fernandez, J.; Bernstein, J. I.; Hiliard, J. J.; Barrett, J. F.; Podlogar, B. L.; Ohemeng, K. A.; *Bioorg. Med. Chem.* **1998**, *6*, 735.
159. Foley, M.; Tilley, L.; *Pharmacol. Ther.* **1998**, *79*, 55; Meshnick, S.; Dobson, M.; *Antimalarial Chemotherapy. Mechanisms of Action, Resistance, and New Directions in Drug Discovery*, Humana Press: Totowa, 2001; Mohammed, A.; Abdel-Hamid, N.; Maher, F.; Farghaly, A.; *Collect. Czech. Chem. Commun*. **1992**, *57*, 1547; Koseva, N.; Stoilova, O.; Manolova, N.; Rashkov, I.; Madec, J.-P.; *J. Bioact. Compat. Polym.* **2001**, *16*, 3; Savini, L.; Chiasserini, L.; Gaeta, A.; Pellerano, C.; *Bioorg. Med. Chem*. **2002**, *10*, 2193; Nayyar, A.; Malde, A.; Coutinho, E.; Jain, R.; *Bioorg. Med. Chem*. **2006**, *14*, 7302; Gemma, S.; Savini, L.; Altarelli, M.; Tripaldi, P.; Chiasserini, L.; Coccone, S.; Kumar, V.; Camodeca, C.; Campiani, G.; Novellino, E.; Clarizio, S.; Delogu, G.; Butini, S.; *Bioorg. Med. Chem*. **2009**, *17*, 6063; Dlugosz, A.; Dus, D.; *Farmaco* **1996**, *51*, 367.
160. Dinh, N. H.; Co, L. V.; Tuan, N. M.; Hai, L. T. H.; Van Meervelt, L.; *Heterocycles* **2012**, *85*, 627.
161. Dinh, N. H.; Huan, T. T.; Toan, D. N.; Kimpende, P. M.; van Meervelt, L.; *J. Mol. Struct.* **2010**, *980*, 137.
162. Ritter, J. J.; Murphy, F. X.; *J. Am. Chem. Soc.* **1952**, *74*, 763; Ho, T.-L.; Chein, R.-J.; *J. Org. Chem.* **2004**, *69*, 591.
163. Mikhailovskii, A. G.; Surikova, O. V.; Limanskii, E. S.; Vakhrin, M. I.; *Chem. Nat. Compd.* **2012**, *48*, 285.
164. Janin, Y. L.; Decaudin, D.; Monneret, C.; Poupon, M.-F.; *Tetrahedron* **2004**, *60*, 5481.
165. Shklyaev, Y. V.; Smolyak, A. A.; Gorbunov, A. A.; *Russ. J. Org. Chem.* **2011**, *47*, 239.
166. Larghi, E. L.; Kaufman, T. S.; *Eur. J. Org. Chem.* 2011, 5195; Larghi, E. L.; Kaufman, T. S.; *Synthesis* 2006, 187.
167. Dyachenko, V. I.; Semenov, V. I.; *Russ. Chem. Bull.* **2010**, *59*, 870.
168. Hekmatshoar, R.; Souri, S.; Rahimifard, M.; Faridbod, F.; *Phosphorus, Sulfur Silicon Relat. Elem.* **2002**, *177*, 2827.
169. Su, N.; Bradshaw, J. S.; Savage, P. B.; Krakowiak, K. E.; Izatt, R. M.; De Wall, S. L.; Gokel, G. W.; *Tetrahedron* **1999**, *55*, 9737.
170. Muthusamy, S.; Gnanaprakasam, B.; Suresh, E.; *J. Org. Chem.* **2007**, *72*, 1495.
171. Kantar, C.; Mert, F.; Sasmaz, S.; *J. Organomet. Chem.* **2011**, *696*, 3006.
172. Sasmaz, S.; Agar, E.; Agar, A.; *Dyes Pigm.* **1999**, *42*, 117.
173. Kantar, C.; Akdemir, N.; Agar, E.; Ocak, N.; Sasmaz, S.; *Dyes Pigm.* **2008**, *76*, 7; Kahveci, B.; Sasmaz, S.; Özil, M.; Kantar, C.; Kosar, B.; Büyükgüngör, O.; *Turk. J. Chem.* **2006**, *30*, 681.
174. Abdul Rahim, E.; Sanda, F.; Masuda, T.; *J. Macromol. Sci., Part A: Pure Appl.Chem.* **2004**, *41*, 133.

175. Ciszewsky, A.; Milczarek, G.; *Electroanalysis* **1998**, *10*, 791; Ciszewsky, A.; Milczarek, G.; *Anal. Chem.* **1999**, *71*, 1055; Ciszewsky, A.; Milczarek, G.; *Anal. Chem.* **2001**, *13*, 860.
176. Hagenaars, A. C.; Bailly, C. H.; Schneider, A.; Wolf, B. A.; *Polymer* **2002**, *43*, 2663.
177. Peppas, N. A.; Amende, D. J.; *J. Appl. Polym. Sci.* **1997**, *66*, 509.
178. Arevalo, S.; de Jesus, E.; de la Mata, F. J.; Flores, J. C.; Gomes, R.; *Organometallics* **2001**, *20*, 2583; Rasines, B.; Sánchez-Nieves, J.; Molina, I. T.; Guzmán, M.; Muñoz-Fernández, M. A.; Gómez, R.; de la Mata, F. J.; *New J. Chem.* **2012**, *36*, 360.
179. Riedl, R.; Tappe, R.; Berkessel, A.; *J. Am. Chem. Soc.* **1998**, *120*, 8994.
180. Rahim, E. A.; Sanda, F.; Masuda, T.; *Polymer Bull.* **2004**, *52,* 93.
181. Günther, S.; Lamprecht, P.; Luinstra, G. A.; *Macromol. Symp.* **2010**, *293*, 15.
182. Khalafi-Nezhad, A.; Rada, M. N. S.; Hakimelahi, G. H.; *Helv. Chim. Acta* **2003**, *86*, 2396.
183. Fareghi-Alamdari, R.; Khalafi-Nezhad, A.; Zekri, N.; *Synthesis* **2014**, *46*, 887.
184. Sakamoto, C.; Nakamoto, Y.; Nemoto, T.; Konish, G.; *J. Network Polym. Jpn.* **2006**, *27*, 218.
185. Gaina, V.; Gaina, C.; *Des. Monomers Polym.* **2007**, *10*, 91.
186. Qin, J.; Liu, H.; Zhang, P.; Wolcott, M.; Zhang, J.; Zhang, J.; *Polymer Int.* **2014**, *63*, 760.
187. Sirotin, I. S.; Bilichenko, Y. V.; Solodukhin, A. N.; Kireev, V. V.; Buzin, M. I.; Borisov, R. S.; *Polym. Sci., Ser. B* **2013**, *55*, 241.
188. Gomes, C.; Moreira, R. G.; Castell-Perez, E.; *J. Food Sci.* **2011**, *76*, N16.
189. Carbone-Howell, A. L.; Stebbins, N. D.; Uhrich, K. E.; *Biomacromolecules* **2014**, *15*, 1889.
190. Schmeltzer, R. C.; Johnson, M.; Griffin, J.; Uhrich, K.; *J. Biomater. Sci., Polym. Ed.* **2008**, *19*, 1295; Whitaker-Brothers, K.; Uhrich, K.; *J. Biomed. Mater. Res., Part A* **2006**, *76A*, 470.
191. Anuradha, G.; Sarojadevi, M.; *J. Appl. Polym. Sci.* **2008**, *110*, 938.
192. Lin, C. H.; Jiang, Z. R.; Wang, C. S.; *J. Polym. Sci., Part A-1: Polym. Chem.* **2002**, *40*, 4084.
193. Ramírez, M. L.; Walters, R.; Lyon, R. E.; Savitski, E. P.; *Polym. Degrad. Stab.* **2002**, *78*, 73.
194. Harvey, B. G.; Guenthner, A. J.; Yandek, G. R.; Cambrea, L. R.; Meylemans, H. A.; Baldwin, L. C.; Reams, J. T.; *Polymer* **2014**, *55*, 5073; Harvey, B. G.; Sahagun C. M.; Guenthner, A. J.; Groshens, T. J.; Cambrea, L. R.; Reams, J. T.; Mabry, J. M.; *ChemSusChem* **2014**, *7*, 1964.
195. Anuradha, G.; Sarojadevi, M.; *J. Appl. Polym. Sci.* **2008**, *110*, 938.
196. Yonghong, L.; Sixun, Z.; *J. Polym. Sci., Part A-1: Polym. Chem.* **2006**, *44*, 1168.
197. Lee, Y. J.; Huang, J. M.; Kuo, S. W.; Chen, J. K.; Chang, F. C.; *Polymer* **2005**, *46*, 2320.
198. Calo, E.; Maffezzoli, A.; Mele, G.; Martina, F.; Mazzetto, S. E.; Tarzia, A.; Stifani, C.; *Green Chem.* **2007**, *9*, 754.
199. Abrão, P. H. O.; Pizi, R. B.; Souza, T. B.; Silva, N. C.; Fregnan, A. M.; Silva, F. N.; Coelho, L. F. L.; Malaquias, L. C. C.; Dias, A. L. T.; Dias, D. F.; Veloso, M. P.; Carvalho, D. T.; *Chem. Biol. Drug Des.* **2014**, *in press*, DOI: 10.1111/cbdd.12504.
200. Rudyanto, M.; Ekowati, J.; Widiandani, T.; Hond, T.; *Int. J. Pharm. Pharm. Sci.* **2014**, *6*, 465.
201. Thirukumaran, P.; Shakila, A.; Muthusamy, S.; *RSC Adv.* **2014**, *4*, 7959; Thirukumaran, P.; Parveen, A. S.; Sarojadevi, M.; *ACS Sustainable Chem. Eng.* **2014**, *2*, 2790.
202. Zhou, Q.; Pramoda, K. P.; Lee, J. M.; Wang, K.; Leslie, S. L.; *J. Colloid Interface Sci.* **2011**, *355*, 222.
203. Thirukumaran, P.; Parveen, A. S.; Sarojadevi, M.; *Polymer Comp.* **2014**, *in press*, DOI: 10.1002/pc 1-10.
204. Tamaki, R.; Tanaka, Y.; Asuncion, M. Z.; Choi, J.; Laine, R. M.; *J. Am. Chem. Soc.* **2001**, *123*, 12416.
205. Mollah, M. S. I.; Kwon, Y.-D.; Islam, M. M.; Seo, D.-W.; Jang, H.-H.; Lim, Y.-D.; Lee, D.-K.; Kim, W.-G.; *Polymer Bull.* **2012**, *68*, 1551.
206. Lestel, L.; Cheradam, H.; Boileau, S.; *Polymer* **1990**, *31*, 1154.
207. Waghmare, P. B.; Deshmukh, S. A.; Idage, S. B.; Idage, B. B.; *J. Appl. Polymer Sci.* **2006**, *101*, 2668; Waghmare, P. B.; Idage, S. B.; Menon, S. K.; Idage, B. B.; *J. Appl. Polymer Sci.* **2006**, *100*, 3222.
208. Dong, L. M.; Liao, G. X.; Liu, C.; Yang, S. S.; Jian, X. G.; *Surf. Rev. Lett.* **2008**, *15*, 705; Dong, L. M.; Liao, G. X.; Liu, C.; Wang, M.; Jian, X. G.; *Acta Polym. Sin*. **2008**, 887.
209. Rojo, L.; Vazquez, B.; Parra, J.; Bravo, A. L.; Deb, S.; San Roman, J.; *Biomacromolecules* **2006**, *7*, 2751.
210. Sanda, F.; Endo, T.; *Macromol. Chem. Phys.* **1999**, *200*, 2651; Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S.; *Chem. Rev.* **2001**, *101*, 3893.
211. Gao, G.; Sanda, F.; Masuda, T.; *Macromolecules* **2003**, *36*, 3932; Gao, G.; Sanda, F.; Masuda, T.; *Macromolecules* **2003**, *36*, 3938; Sanda, F.; Araki, H.; Masuda, T.; *Macromolecules* **2004**, *37*, 8510.
212. Abdul Rahim, E.; Sanda, F.; Masuda, T.; *J. Polym. Sci., Part A-1: Polym. Chem.* **2006**, *44*, 810.
213. Augugliaro, V.; Camera-Roda, G.; Loddo, V.; Palmisano, G.; Palmisano, L.; Parrino, F.; Puma, M. A.; *Appl. Catal., B* **2012**, *111-112*, 555.
214. Friedman, M.; Henika, P. R.; Mandrell, R. E.; *J. Food Prot.* **2002**, *65*, 1545.
215. Priefert, H.; Rabenhorst, J.; Steinbuchel, A.; *Appl. Microbiol. Biotechnol.* **2001**, *56*, 296.
216. Mishra, S.; Sachan, A.; Sachan, S. G.; *J. Ind. Microbiol. Biotechnol.* **2013**, *40*, 545.
217. Lambert, F.; Zucca, J.; Ness, F.; Aigle, M.; *Flavour Fragrance J.* **2013**, *29*, 14.

218. Awasthi, P. K.; Dixit, S. C.; Dixit, N.; Sinha, A. K.; *J. Pharm. Res.* **2008**, *1*, 215.
219. Sadeghian, H.; Seyedi, S. M.; Saberi, M. R.; Arghiani, Z.; Riazi, M.; *Bioorg. Med. Chem.* **2008**, *16*, 890.
220. Zhao, X.; Chen, D.; Gao, P.; Ding, P.; Li, K.; *Chem. Pharm. Bull.* **2005**, *53*, 1246; Zhao, X. L.; Chen, D. W.; Gao, P.; Luo, Y. F.; Li, K. X.; *Pharmazie* **2005**, *60*, 883; Sharma, P. D.; Kaur, G.; Kansal, S.; Chandiran, S. K.; *Indian J. Chem.* **2004**, *43B*, 2159; Sawraj, S.; Bhardawaj, T. R.; Sharma, P. D.; *Med. Chem. Res.* **2012**, *21*, 834; Li, J.-Y.; Yu, Y.-G.; Wang, Q.-W.; Zhang, J.-Y.; Yang, Y.-J.; Li, B.; Zhou, X.-Z.; Niu, J.-R.; Wei, X.-J.; Liu, X.-W.; Liu, Z.-Q.; *Med. Chem. Res.* **2012**, *21*, 995; Dhokchawle, B. V.; Kamble, M. D.; Tauro, S. J.; Bhandari, A. B.; *Pharma Chem.* **2014**, *6*, 347; Redasani, V. K.; Bari, S. B.; *Eur. J. Med. Chem.* **2012**, *56*, 134.
221. Chandiran, S.; Vyas, S.; Sharma, N.; Sharma, M.; *Med. Chem.* **2013**, *9*, 1006.
222. Yadav, G. D.; Yadav, A. R.; *Chem. Eng. J.* **2012**, *192*, 146.
223. Chiaradia, V.; Paroul, N.; Cansian, R. L.; Junior, C. V.; Detofol, M. R.; Lerin, L. A.; Oliveira, J. V.; Oliveira, D.; *Appl. Biochem. Biotechnol.* **2012**, *168*, 742.
224. Horchani, H.; Ben Salem, N.; Zarai, Z.; Sayari, A.; Gargouri, Y.; Chaâbouni, M.; *Bioresour. Technol.* **2010**, *101*, 2809.
225. Chaibakhsh, N.; Basri, M.; Hani, S.; Anuar, M.; Rahman, M. B. A.; Rezayee, M.; *Biocatal. Agric. Biotechnol.* **2012**, *1*, 226.
226. de Souza, T. B.; Orlandi, M.; Coelho, L. F. L.; Malaquias, L. C. C.; Dias, A. L. T.; Carvalho, R. R.; Silva, N. C.; Carvalho, D. T.; *Med. Chem. Res.* **2014**, *23*, 496.
227. Guo, W.; Sakata, K.; Watanabe, N.; Nakajima, R.; Yagi, A.; Ina, K.; Luo, S.; *Phytochemistry* **1993**, *33*, 1373.
228. Tsuruhami, K.; Mori, S.; Sakata, K.; Amarume, S.; Saruwatari, S.; Murata, T.; Usui, T.; *J. Carbohydr. Chem.* **2005**, *24*, 849.
229. Yamamoto, S.; Okada, M.; Usui, T.; Sakata, K.; *Biosci., Biotechnol., Biochem.* **2002**, *66*, 801.
230. De Winter, K.; Desmet, T.; Devlamynck, T.; van Renterghem, L.; Verhaeghe, T.; Pelantováá, H.; Křen, V.; Soetaert, W.; *Org. Process Res. Dev.* **2014**, *18*, 781.
231. Lohith, K.; Vijayakumar, G. R.; Somashekar, B. R.; Sivakumar, R.; Divakar, S.; *Eur. J. Med. Chem.* **2006**, *41*, 1059; Vijayakumar, G. R.; Divakar, S.; *Biotechnol. Lett.* **2007**, *29*, 575.
232. Zhang, P.; Zhang, E.; Xiao, M.; Chen, C.; Xu, W.; *Appl. Microbiol. Biotechnol.* **2013**, *97*, 1043.
233. Chen, C.; Xiao, M.; Deng, L.; Yuan, L.; Zhang, P.; *Pharm. Biol.* **2012**, *50*, 727; Sato, T.; Takeuchi, H.; Takahashi, K.; Kurosu, J.; Yoshida, K.; Tsugane, T.; Shimura, S.; Kino, K.; Kirimura, K.; *J. Biosci. Bioeng.* **2003**, *96*, 199.

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