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Review

Synthesis of Marine Natural Products in Brazil

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So deadly is the force of this poison that it poisons not only those who took it in by mouth but also those who touched or looked at it, as Pliny reports, and if a pregnant woman sees it or even comes near it, especially if this happens to be a young woman, she immediately feels pain in the belly and nausea, and then has an abortion.
[J Grevin 1568]

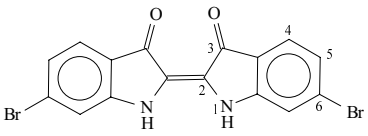
Descreve-se as sínteses de 23 produtos naturais marinhos, realizadas no Brasil ou por químicos brasileiros.

Syntheses of 23 marine natural products carried out in Brazil or by Brazilian chemists are comprehensively reviewed.

Keywords: *diterpenes, sesquiterpenes, macroliste, nitrogenarest metabolites*

Introduction

These are the words attributed to the greatest of the Latin naturalists, Gaius Plinius Secundus (known as Pliny the Elder A.D. 29-79), on describing the toxicity of the sea hare *Aplysia* in his encyclopedic work "Naturalis Historia"[1]. Later, it was reported that just touching *Aplysia depilans* would result in swelling of the body and depilation of hair[2]. Darwin also reported on an *Aplysia* which "exudes an acid secretion that causes a sharp stinging sensation"[3]. There are numerous references to the toxicity of mollusks; several date back to antiquity[3]. But there are not only unfavorable statements on mollusks. Tyrian purple is a good example. Phoenicians produced this dye from the snail *Murex brandaris*. It was prized so highly in ancient times that it was used as an emblem of royalty and in religious ceremonies. It had a high cost since 12,000 animals were necessary to produce only 1 g of dye. The dye production from mollusks is believed to go back at least to 1600 B.C., when the process was discovered by the Cretans[4]. With the advent of the Dark Ages, dyeing with Tyrian purple became a lost art that was to be rediscovered only in Ireland in 1684[5]. Tyrian purple is no doubt the oldest commercial marine natural product known and its production perhaps the oldest record of the industrial use of a photochemical reaction, since it is obtained by light exposure of the colorless secretion of *Murex* gland. It was also the first marine metabolite whose structure, **1**, was correctly deduced[6] and proven by *synthesis* of several dibromoindigo homologues[7].



1 Tyrian purple

Hence, synthesis accompanied the early steps of marine natural products chemistry. However, the advancement of spectroscopic analysis, and principally of the NMR techniques, made possible the structural investigation and complete determination of complex molecules without the need of chemical methods. This has drastically limited our knowledge to almost nothing of the chemistry of marine natural products. The extreme originality of marine metabolites that often possess new skeletons, originated from completely new biosynthetic pathways, represented new challenges that triggered organic chemists. Thus, synthesis, that practically did not exist in the early eighties, is now giving "a powerful contribution to the understanding and development of marine organic chemistry"[8].

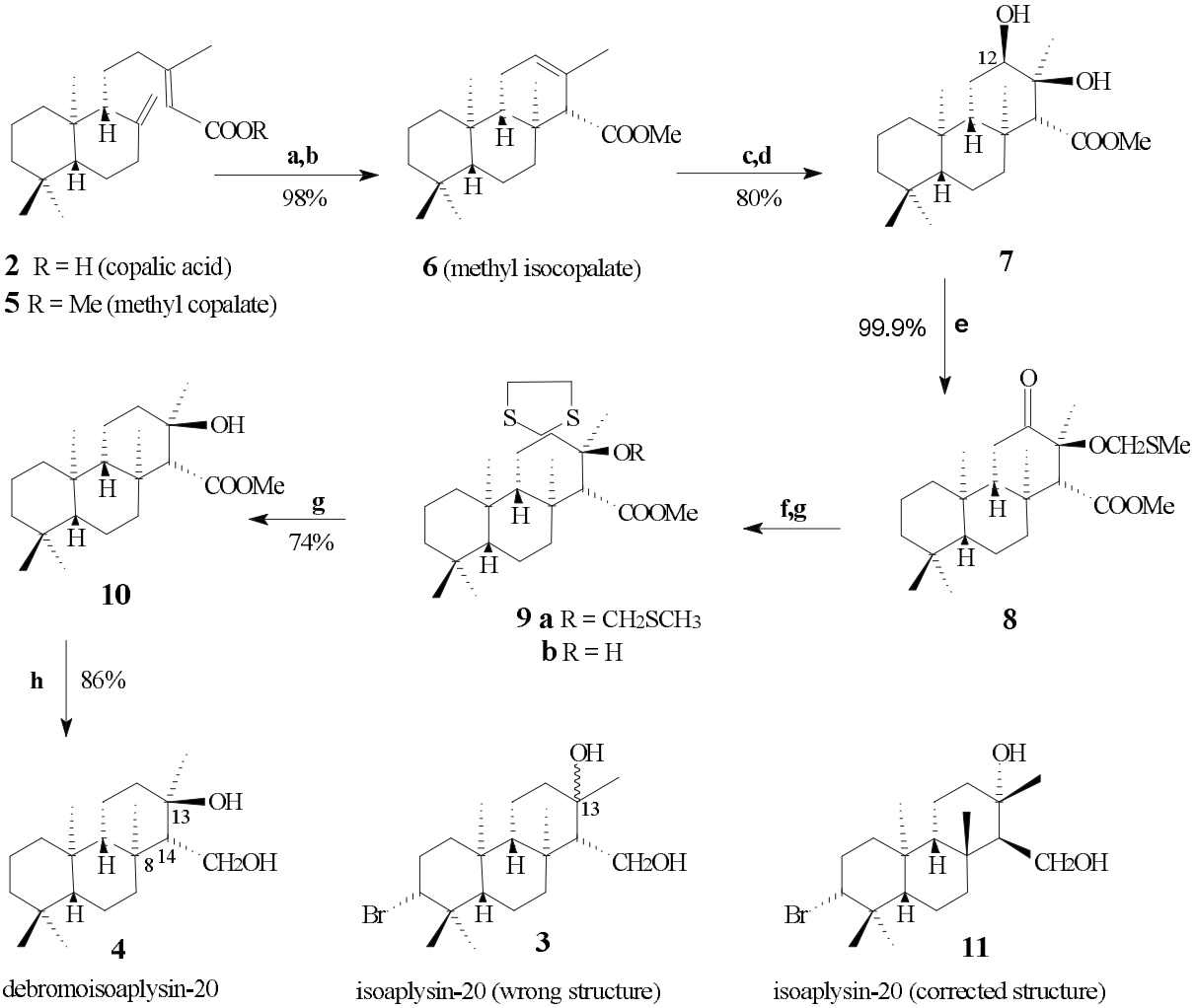
In Brazil, there has been a slow but continuous increase in the interest for marine natural products research along the past 20 years. In the first part of this review, studies related to isolation and structure determination were described[9]. The second part of this review is dedicated to synthesis. The major published results of works done in Brazil will now be discussed in the following sections. The content of meeting abstracts, usually inaccessible to most foreign scientists, is included.

Synthesis of Marine Natural Products

The first Brazilian contributions in the field of organic synthesis were made by Rúveda and co-workers who synthesized some diterpenes from sponges and sea hares diterpenes, or their enantiomers, from the readily available copalic acid **(2)**. Several sesquiterpenes were also the object of total syntheses. More recently, preliminary studies have appeared on the syntheses of one sesterterpene, one macrolide and nitrogen-containing metabolites.

Diterpenes

The first target was the tricyclic diterpene isoaplysin-20 **(3)**, that had been isolated from the sea hare *Aplysia kurodai*, collected in Japan, and for which the stereochemistry at C-13 had remained unclear[10]. The debromo homologue **4** was synthesized from copalic acid **(2)**, following Scheme 1, in an eight-step sequence with an excellent overall yield (49%)[11]. Thus, methyl isocopalate **6** was prepared by esterification of **2** into **5** and acid-catalyzed formation of the C-ring. Oxidation of the trisubstituted double bond with OsO_4 furnished the expected β-oriented α-glycol. The oxygen function at C-12 was then eliminated in the usual way, by oxidation to ketone **8**, thioketal formation and hydrogenolysis on Raney-Ni into **10**, which was finally reduced to debromo-isoaplysin-20 **(4)**[11]. This work fixed the rela-

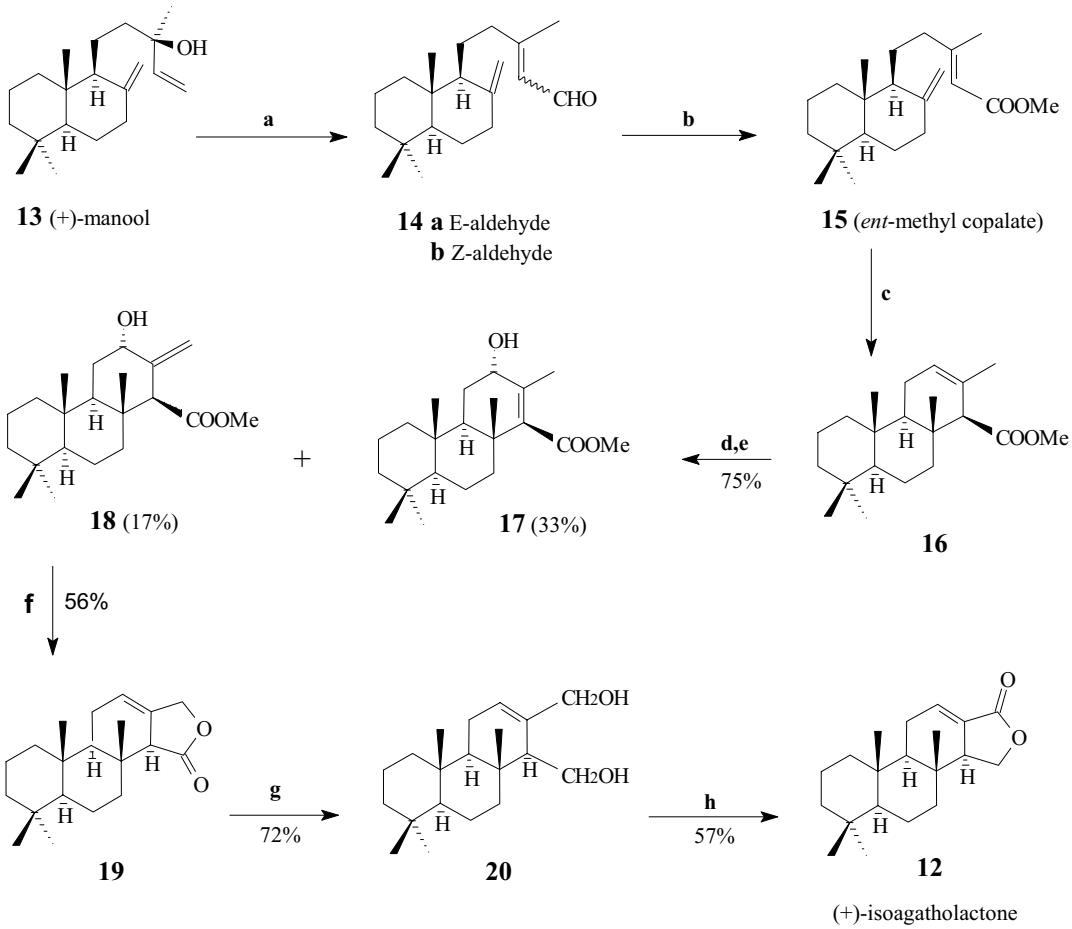


Scheme 1. Synthesis of the supposed structure of debromoisoaplysin-20.
a. CH_2N_2, Et_2O; **b.** HCOOH 98% aq; **c.** OsO_4, dry Py , r.t., 65 h; **d.** $Na_2S_2O_5$, Py/H_2O, 2,5 h ; **e.** DMSO / Ac_2O, r.t., 27h ; **f.** $HSCH_2CH_2SH$ / $BF_3.Et_2O$, AcOH, 1h ; **g.** Ni/Raney, EtOH reflux 8 h; **h.** LAH/THF, reflux 15 h - overall yield 49%.

tive stereochemistry at C-8, C-13 and C-14 as shown. However, some years later, the structure of isoaplysin-20 was corrected from **3** to **11**[12].

The second target was (+)-isoagatholactone **(12),** the first spongiane diterpene that had been isolated from some samples of the Mediterranean sponge *Spongia officinalis*[13]. Remarkably, other samples of apparently the same sponge furnished C-21 and C-25 furanoterpenes and no isoagatholactone at all[13]. This metabolite was successfully synthesized from (+)-manool **(13)** in an eight-step procedure whose key-step was the functionalization of the allylic methyl group of **16** through a sensitized photo-oxidation (Scheme 2)[14]. The desired allylic alcohol **(18)** was obtained in 17% yield. The overall yield of the synthesis cannot be calculated from published data, but is expected to be very low as the yield along the five final steps **16** → 12 was only 4%[14]. Noteworthy are the three-step transformation of (+)-manool **(13)** into *ent*-methyl isocopalate **(15)** shorter than the well-known sequence proposed by Fetizon and coworkers[15], the acid-catalyzed allylic rearrangement of **18** prior to lactonization and finally the two-step γ-lactone inversion **19** → **12**. Similarly, methyl isocopalate **(6**, *i.e.* *ent*-**16)** was transformed into *ent*-isoagatholactone **(***ent*-12) through the sequence of reactions **d-h** depicted in Scheme 2, in an overall yield of 8% (**d**, **e**: 16%; f:88%; **g**: 89% and **h**: 64%)[16]. An essentially identical total synthesis of (±)-isoagatholactone was subsequently published[17]. It started from *ent*-copalic acid (the corresponding acid of **15**) and differed only by the use of hematoporphyrin as photosentiziser, instead of methylene blue.

Three further diterpenes, *ent*-isocopal-12-en-15,16-dial **(21)**, 14-iso-*ent*-isocopal-12-en-15,16-dial **(22)** and 15-acetoxy-*ent*-isocopal-12-en-16-al **(23)** also isolated from *Spongia officinalis*[18], were synthesized from racemic methyl isocopalate **(**±16) according to Scheme 3[19]. It should be noted that the low yield photo-oxidation reaction (Scheme 2, step **d**, yield ≈17%) has been replaced by a two-step sequence of epoxidation and aluminium isopropoxide rearrangement to yield the desired allylic alcohol in 60% overall yield (Scheme 3, steps **a** and **b**). Interestingly, C-15 and C-20 terpenoids having two aldehyde groups in the same arrangement as exhibited in **22** usually taste very



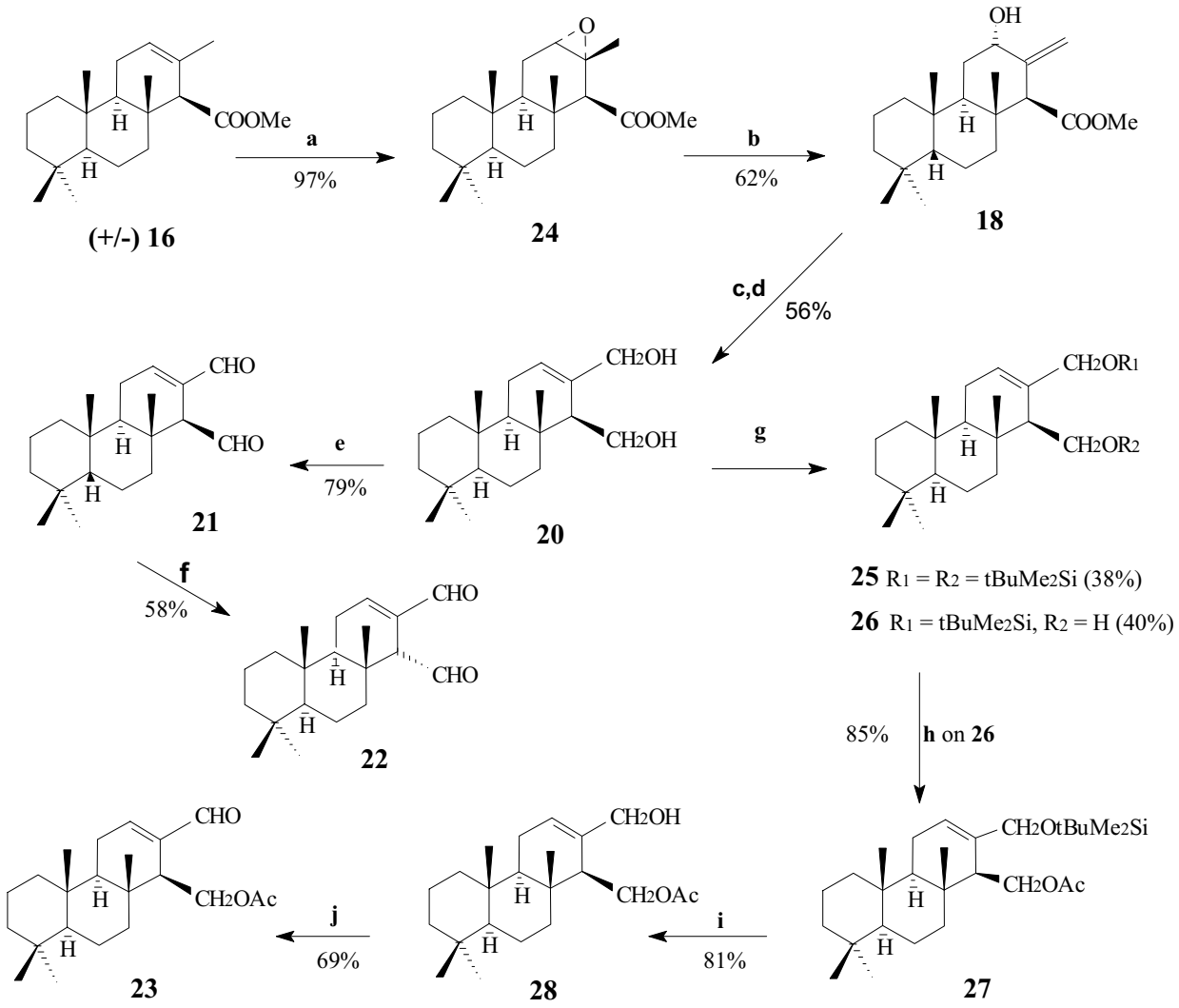
Scheme 2. Synthesis of (+)-isoagatholactone.

a. PCC; **b.** MnO_2 / HCN, MeOH and SiO_2 separation; **c.** HCOOH, reflux; **d.** $^1O_2$, methylene blue, EtOH/AcOEt (1:1), 14 h; **e.** $(CH_3O)_3P$; **f.** 6N H_2SO_4 H_2O- dioxane (1:13), 90 °C, 40 min; **g.** LAH / Et_2O; **h.** MnO_2, CH_2Cl_2.

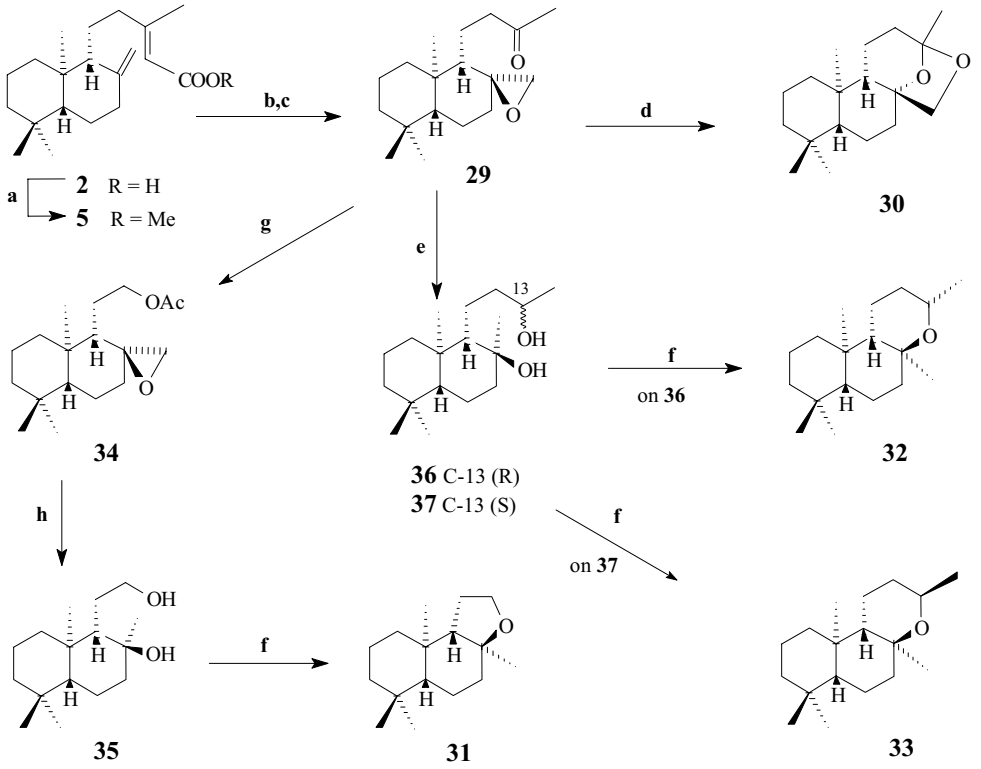
hot to humans and are endowed of potent phagorepellent activities[20]. Diterpene **22**, however, is devoid of such biological properties[18].

Ambergris is a concretion found in the gut of the sperm whales *Physeter* spp. It has been used for centuries because of its unique fragrance and fixative properties[21,22], but is now commercially abolished thanks to the Marine Mammalians Protection Act. Copalic acid **(2)** has been used as a chiral synthon for the obtention of several compounds related to the constituents of ambergris[23,24]. Scheme 4 depicts the syntheses of *ent*-8-epi-ambraketal **(30),** *ent*-ambrox **(31)** and related oxides **32** and **33**[23-25]. The key-step in the synthesis of *ent*-ambrox **(31)** is a smooth Baeyer-Villiger oxidation of the unstable epoxy-ketone **29** into **34**[24]. Spontaneous rearrangement of **29** into **30** has also been observed[23]; this reaction is assumed to be catalysed by traces of acid present in the reaction medium[25].

Finally, preliminary studies toward the synthesis of ambliol-B **(38),** from the Californian sponge *Dysidea amblia*[26,27] have resulted in the inter-conversion of hardwickiic acid **(39)** into dehydroambliol-B **(40)** (Scheme 5)[28]. The key intermediate **44** was prepared from alcohol **42** or its acetate **43**, through a reaction with nickel boride generated *in situ*. It should be emphasized that dehydration of ambliol-B **(38)** with phosphorous oxychloride in pyridine gave trisubstituted olefin **45** while acid-catalyzed dehydration produced tetrasubstituted olefin **40**[26,27]. The yields of the reactions have not been reported[28]. Further work is underway to achieve the synthesis of ambliol-B. Recently, a total synthesis of racemic ambliol-B has been published[29]. As reported above for *Spongia officinalis*, chemical analyses of individual animals have revealed, here again,

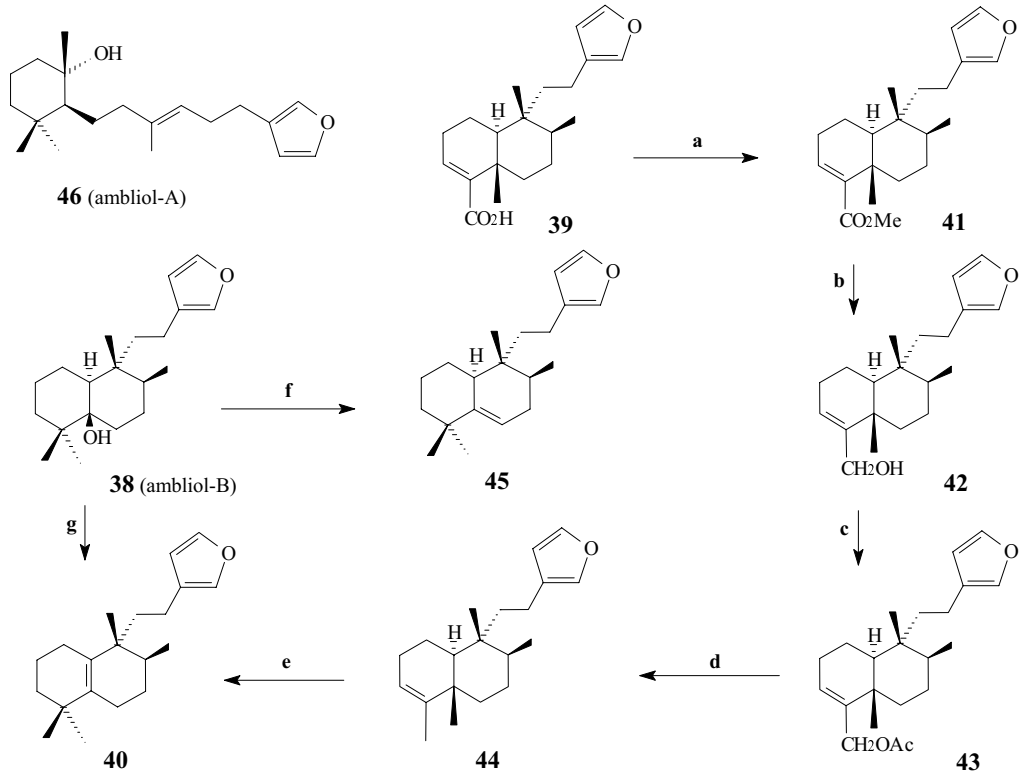


Scheme 3. syntheses of (+/-)-**21**, (+/-)-**22** and (+/-)-**23**.
a. MCPBA, CH_2Cl_2; **b.** Al(*i*-PrO)$_3$, toluene, reflux; **c.** 6N aq H_2SO_4, dioxane 1:13; **d.** LAH, Et_2O; **e.** DMSO, oxalyl chloride, CH_2Cl_2; **f**. basic alumina, CH_2Cl_2, r.t.; **g.** *t*-$BuMe_2SiCl$, imidazole, DMF, N_2; **h.** Ac_2O, TEA / DMAP, r.t.; **i.** THF-AcOH-H_2O (1:3:1), r.t.; **j.** MnO_2, benzene 18 h.



Scheme 4. Syntheses of ambergris-related compounds

a. CH_2N_2, Et_2O; **b.** MCPBA, CH_2Cl_2 (70%); **c.** O_3, CH_2Cl_2, -78 °C then Me_2S (53%); **d.** TsOH, benzene (54%); **e.** LAH, THF (43% in 36 and 40% in 37); **f.** MsCl, Py, benzene (66% in 31 and 32,61% in 33); **g.** MCPBA, CH_2Cl_2, r.t., 7 days (32%) and recovered material (32%); **h.** LAH, THF (97%).



Scheme 5. Towards the synthesis of ambliol-B (**38**).

a. CH_2N_2 , Et_2O; **b.** LAH, THF; **c.** Ac_2O/Py; **d.** *in situ* nickel boride; **e.** H^+; **f.** $POCl_3$/Py; **g.** TsOH/benzene.

that there are two chemical varieties of *Dysidea amblia*, one containing ambliol-A **(46)** the other ambliol-B **(38)**, that cannot be distinguished by classical taxonomic methods[26].

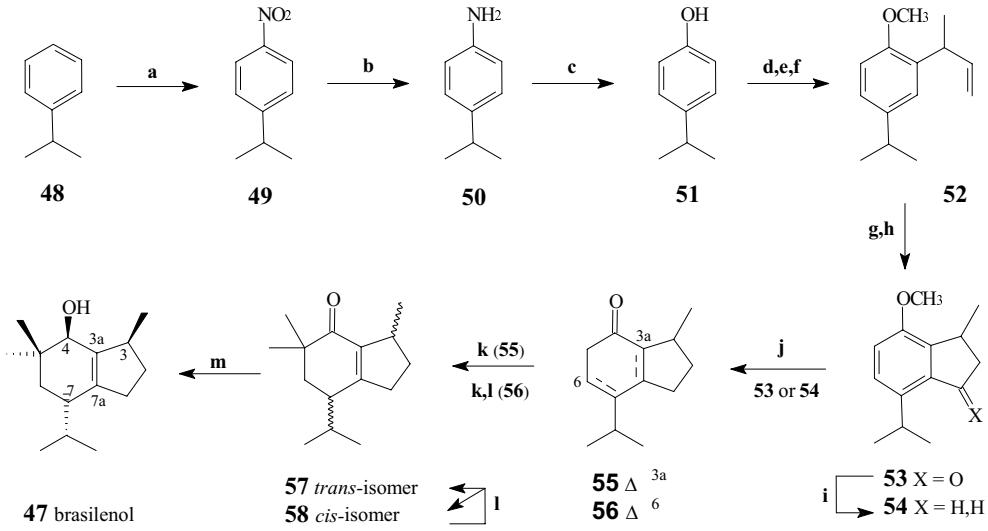
Sesquiterpenes

Brasilenol **(47)** is a sesquiterpene that had been isolated from the sea hare *Aplysia brasiliana*, collected in the Gulf of Mexico, and also from the Mediterranean red alga *Laurencia obtusa*[30]. While not totally conclusive, this strongly suggested that brasilenol may be produced by the algae on which the mollusk grazes[30]. Because of its non-isoprenoid new skeleton, this compound was chosen as target for a total synthesis that should confirm the structure (derived from spectral data only) and establish the unknown absolute configuration. Racemic brasilenol was obtained through a selective synthesis, which required 11 steps from 4-isopropylphenol **(51)** and proceeded in about 5% overall yield (Scheme 6)[31]. Phenol **51**, itself, had been prepared in 67% from cumene **(48)** by classical nitration, reduction and diazotization[32]. Anisole **52** was then obtained from **51** by Claisen rearrangement of the derived crotyl ether followed by methylation. Standard hydroboration of the terminal olefin and Jones oxidation furnished a carboxylic acid, which smoothly cyclized to give the indone **53**, by treatment with polyphosphoric acid. Partial reduction of the aromatic ring of **53** or **54**, followed by dimethylation (and eventual double bond isomerization) and finally stereoselective reduction of the carbonyl group furnished racemic brasilenol **(47)**.

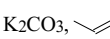
Starting from β-pinene **(59)**, the same group again synthesized racemic brasilenol **(47)**, as shown in Scheme 7, through a 16-step sequence in an approximate yield of 0.5%[32]. The two major problems of this synthesis were first the Michael addition (step *i*) that produced a mixture of isomers, and second the isomerization of **69** into **74** in a 4-step sequence of only 5% overall yield. Thus, it was assumed, from these results, that the *gem*-dimethyl group could be responsible for the observed lack of stereoselectivity of the Michael process, being however indispensable to insure the stereoselective reduction of brasilenone **(74)** to brasilenol **(47)**[32].

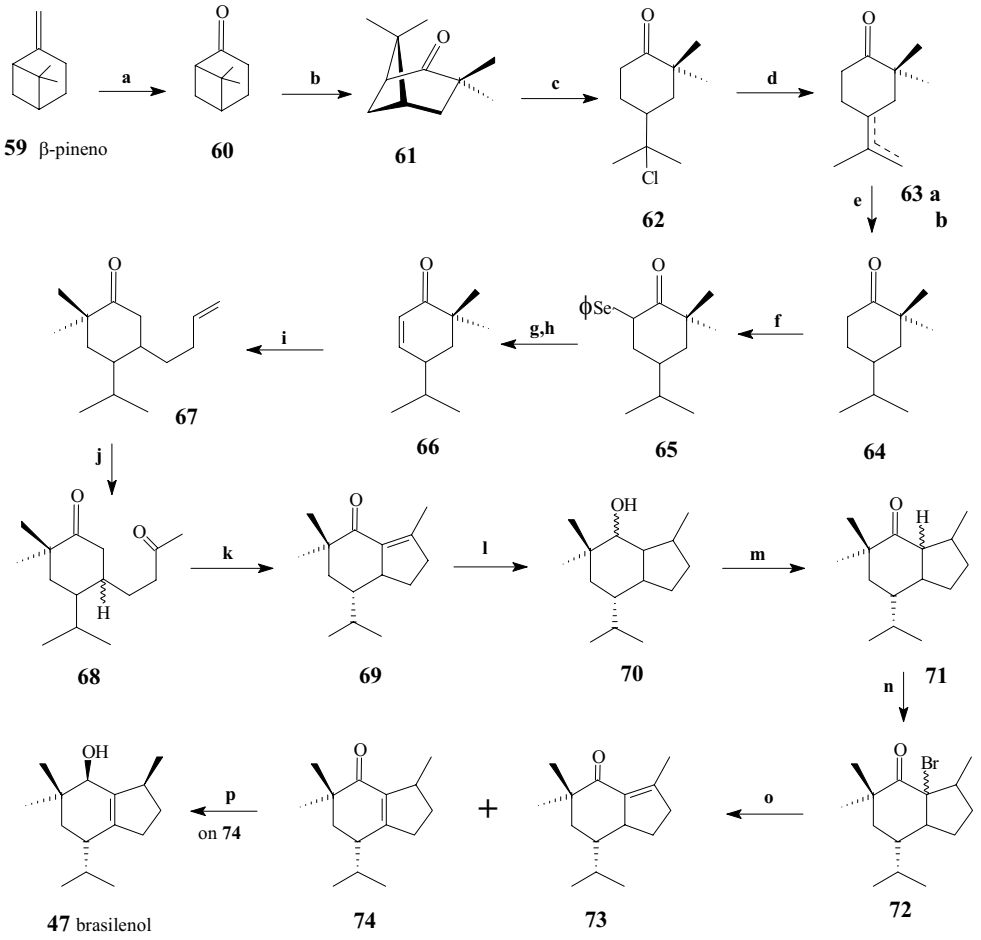
Finally, stereocontroled synthesis from (R)-(-)-cryptone **(75)** readily produced optically pure (+)-brasilenol ($[\alpha]_D$ +44.0° , lit. +33.4°) whose absolute configuration could thus be established as 3R,4S,7R (Scheme 8)[33]. The planned strategy used practically the same reactions as above, leaving the dimethylation for the penultimate step of the synthesis. The key step reaction resolved the upper-mentioned problem of double bond isomerization using a palladium-hydrogen-induced migration of the double bond of **78** to **79** that not only delivered the required double bond isomer, but also the necessary *trans* relationship at C-3 and C-7.

Africanol **(80)** has been isolated from the Indonesian soft-coral *Lemnalia africana* and was the first terpenoid reported from alcyonarians[34]. Its intriguing new skeleton, determined by X-ray diffraction analysis[34], and the rearrangements observed on acid treatment[34,35] have triggered organic chemists. As a result, four syntheses have already been reported for that compound[36-39]. Two alternative methods have now been proposed. Both planned the construction of the five-membered ring in the final steps: the first methods followed a 9-step procedure[40], and the second a 10-step one[41]. Scheme 9 depicts these syntheses. High

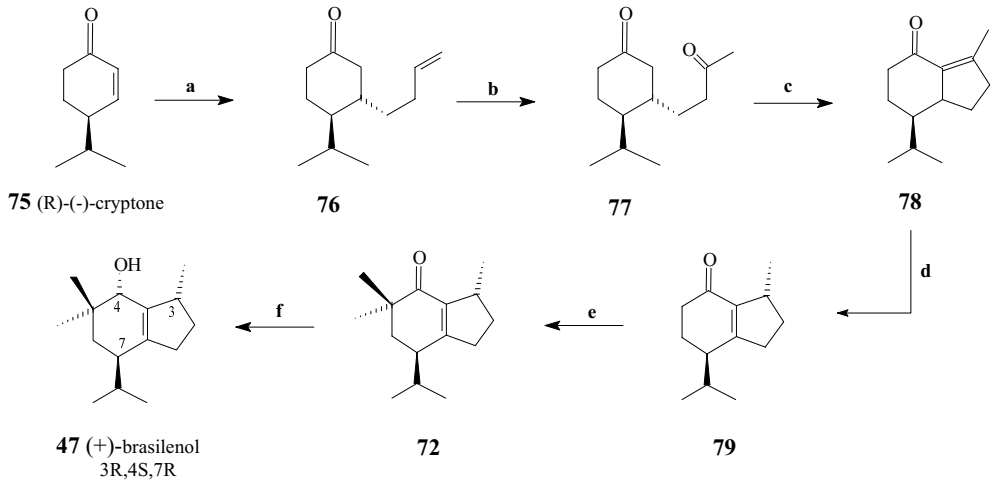


Scheme 6. Synthesis of racemic brasilenol from cumene.

a. HNO_3, $CHCl_3$ (98%); **b.** $SnCl_2$, HCl, Et_2O; **c.** $NaNO_2$, H_2SO_4 (a+b 70%); **d.** K_2CO_3,  (97%); **e.** Δ (93%); **f.** NaH, CH_3I (85%); **g.** BH_3; H_2O_2, NaOH; Jones (73%); **h.** PPA (63%); **i.** LAH; H_2, Pd/C (97%); **j.** Li, CH_3NH_2, t-BuOH; H^+; SiO_2 separation (43% from 156; 58% from 157); **k.** LDA, CH_3I (~83%); SiO_2 separation; **l.** $RhCl_3$, Δ, SiO_2 separation (70-85%); **m.** $LiB(Et)_3H$, THF (73%).



Scheme 7. synthesis of racemic brasilenol from β-pinene.
a. O_3, MeOH, Me_2S, -78 °C (86%); **b.** KH, CH_3I (93%); **c.** HCl; **d.** Py; **e.** H_2 /PtO_2, AcOEt (91%); **f.** PhSeCl, $(Me_3Si)_2NLi$, THF, -78 °C (78%); **g.** $NaIO_4$, MeOH, H_2O; h. D (g,h = 73%); **i.** $\rightleftharpoons$MgBr, CuI, THF, -20 °C ~ 0 °C 2h (75%); **j.** O_2; $PdCl_2$, CuCl, DMF, H_2O, THF, 3 h (79%); **k.** 3% NaOH, EtOH (60%); **l.** Li, NH_3 liq. (62%); **m.** CrO_3, Py, CH_2Cl_2 (58%); **n.** Br_2, AcOH (90%); **o.** $LiCO_3$, DMF (50%); **p.** $LiB(Et)_3H$, THF.

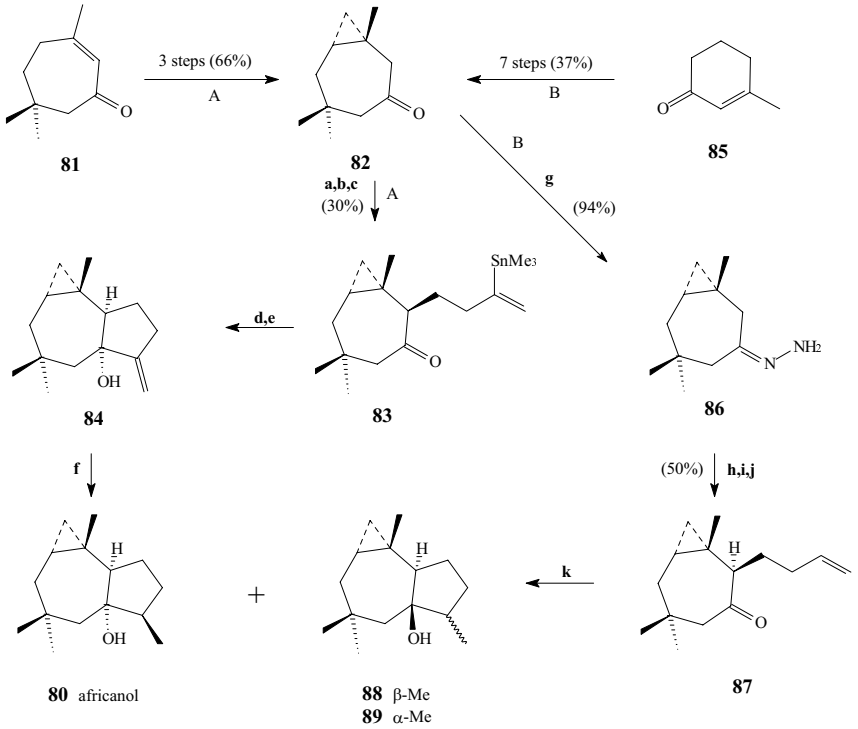


Scheme 8. synthesis of (+)-brasilenol from (R)-(-)-cryptone.
a. $\rightleftharpoons$MgBr, CuI, THF (97%); **b.** $PdCl_2$, CuCl, O_2, DMF-H_2O (79%); **c.** t-BuOK / t-BuOH (84%); **d.** 10% Pd/C, H_2, benzene (63%); **e.** $LiN(iPr)_2$, THF, CH_3I (84%); **f.** $LiB(Et)_3H$, THF (92%).

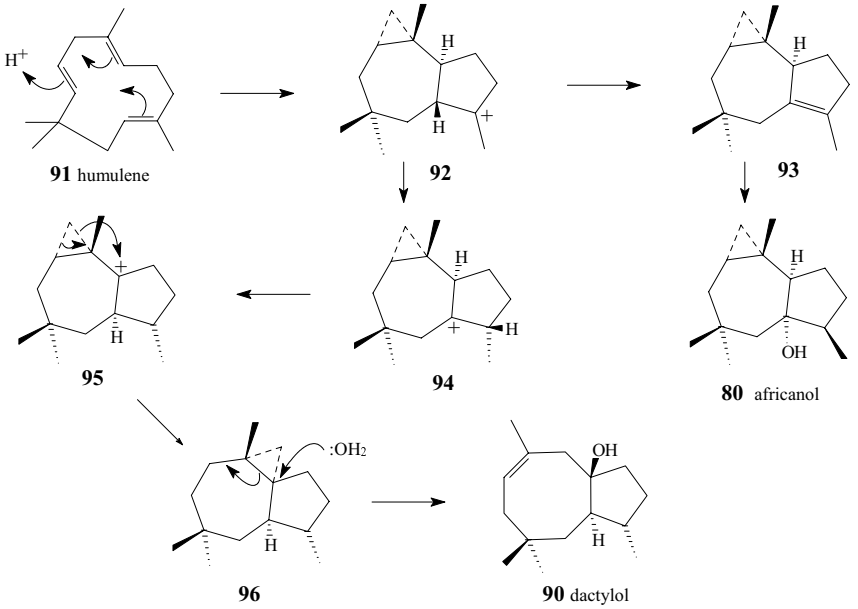
stereoselectivity was observed on alkylation of the dimethylhydrazone derived from **82** (method A)[40]. On the other hand, cyclization of **87** lacked stereoselectivity and yielded isomers **80**, **88** and **89** in a 1:0.6:1 ratio (method B)[41].

Dactylol **(90)** is an irregular isoprenoid alcohol isolated from the digestive glands of the Caribbean sea hare *Aplysia dactylomela* and from its putative dietary source, the red alga *Laurencia poitei* collected in the Florida Keys[42]. As with africanol **(80)**, dactylol is assumed to be biosynthetically derived from humulene **(91)** as illustrated in Scheme 10[34,43]. Although highly uncommon and *a priori* questionable, the 1,2-migration of the cyclopropane ring of **95** into **96** has been successfully achieved using $BF_3.OEt_2$ in Et_2O at -10 °C[43].

Dactylol is one of the simplest members of the interesting family of natural products possessing a cyclooctanoid structure. Such substances are the object of great interest[44]. Two syntheses of racemic dactylol **(90)** have already been



Scheme 9. Syntheses of africanol.
a. DMH, benzene; **b.** LDA, THF, RI; **c.** $NaIO_4$, THF, H_2O; **d.** I_2, CH_2Cl_2; **e.** n-BuLi, THF; **f.** H_2 / PtO_2, EtOAc; **g.** Me_2NNH_2, benzene, 80 °C; **h.** n-BuLi, THF, 0 °C ; **i.** RI, 20 °C; **j.** H_3O^+; **k.** SmI_2, THF, HMPA.

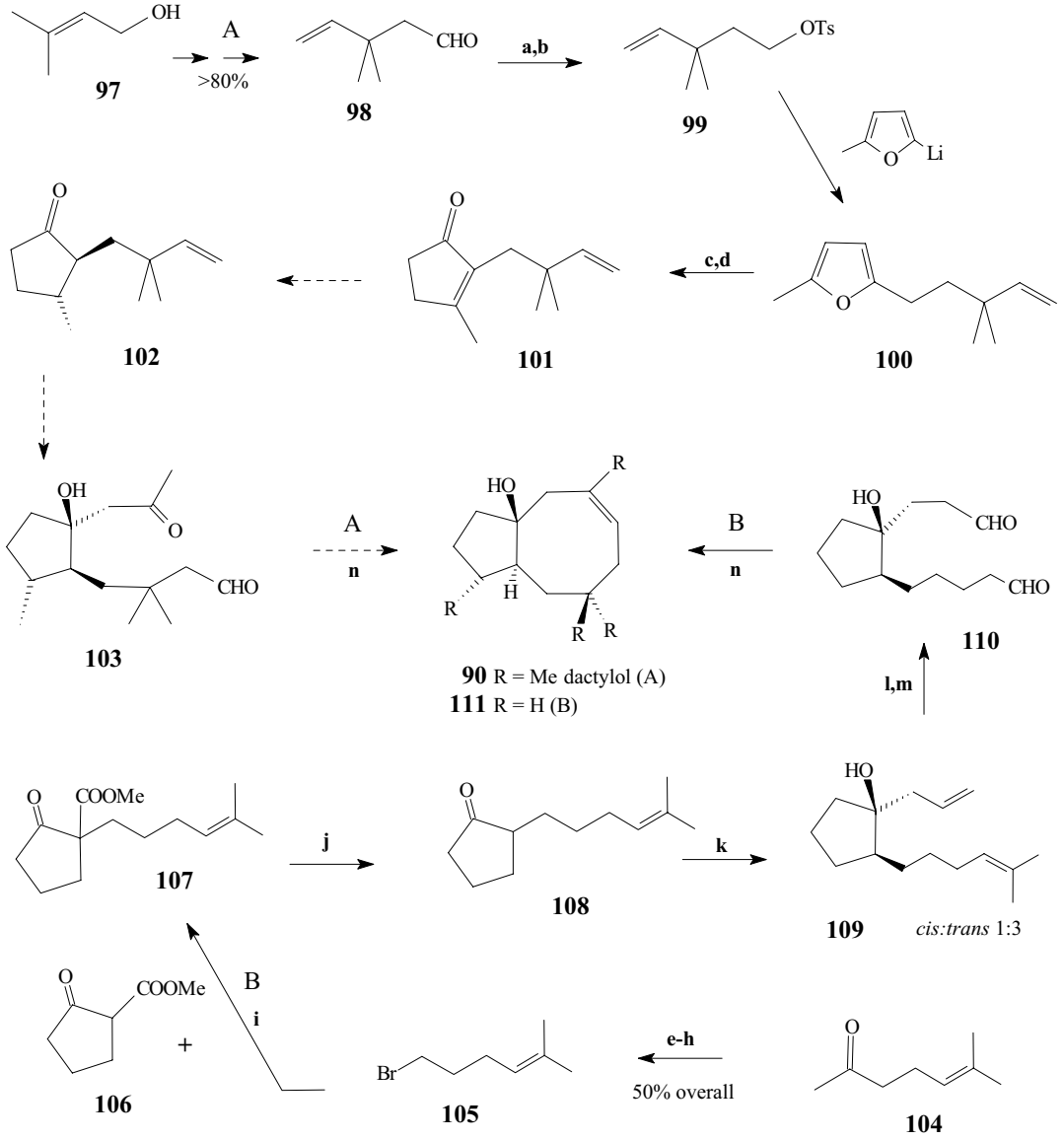


Scheme 10. biosynthetic proposal for africanol and dactylol.

reported[37,45]. Both used ring expansion methodology. Total synthesis of (+)-dactylol has now been reported and proceeds via a novel [3+5] annulation[46]. An alternative methodology planned the preparation of the skeleton **90**, through an intramolecular reductive coupling of keto-aldehyde **(103)** as shown in Scheme 11[47,48]. Although the carbonyl coupling appears direct, the potential lability of the β-hydroxy ketone moiety in **103** could prove troublesome. The model substrate **111** was thus prepared to first investigate the McMurry low-valent titanium promoted coupling (Scheme 11, step n)[49]. This coupling indeed proceeded, but in rather low yields (~10%) under a number of different experimental conditions[49].

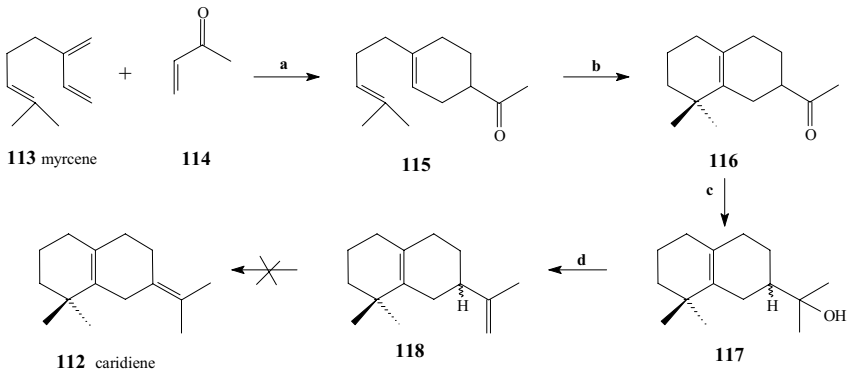
The sesquiterpene hydrocarbon caridiene **(112)**, a major constituent of the volatile fraction from the Cuban gorgonian *Pseudopterogorgia americana*[50], was the target of a total synthesis starting from a cycloaddition between myrcene **(113)** and methyl-vinyl ketone **(114)**. Isocaridiene **(118)** was obtained by acid-catalyzed cyclization, Grignard reaction and dehydration (Scheme 12)[51]. Attempts to isomerise **118** to **112** were unsuccessful.

The dorid nudibranch *Acanthodoris nanaimoensis*, collected in British Columbia, produces three aldehydic ses-



Scheme 11. Toward the synthesis of dactylol.

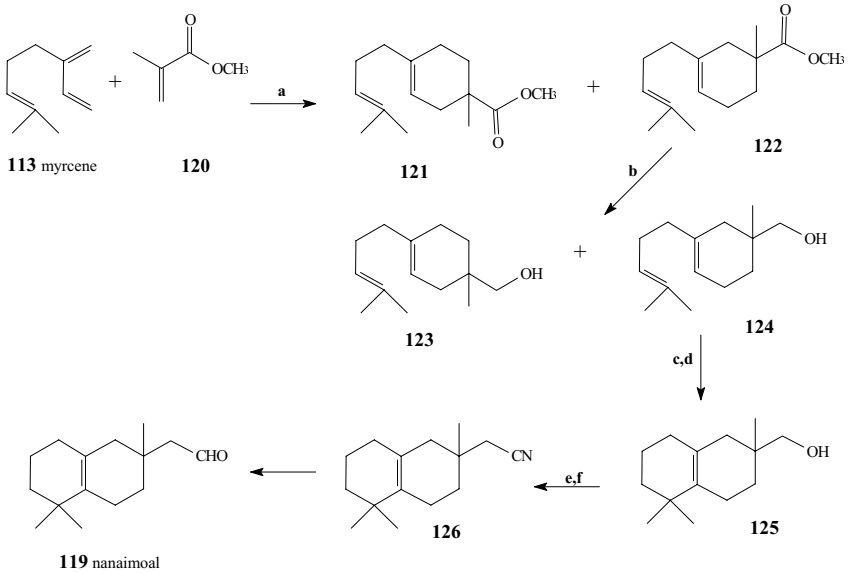
a. $NaBH_4$, THF-H_2O; **b.** TsCl, $CHCl_3$, Py; **c.** H^+/H_2O; **d.** aldolization; **e.** NaOBr, NaOH, dioxane/H_2O, 4 °C, 1 h then NH_4Cl (64%); **f.** LAH, THF, reflux, 3h (90-93%) ; g. MsCl, Et_3N, CH_2Cl_2, -10 °C, 5-10 min (97-99%); **h.** LiBr, THF, reflux, 3 h (86-89%); **i.** K_2CO_3, acetone, reflux, 60 h (78%) ; **j.** KCN, DMSO, 150 °C, 2 h (76%) ; **k.**  , $MgCl_2$, K, THF, r.t. (77%); **l.** DMAP, $NHiPr_2$, MEM-Cl, r.t. 14 h (92%); **m.** O_3 , CH_2Cl_2, -78 °C, then Me_2S -78 °C or H_2, Pd-C 60 psi, r.t., 4 h (60%); **n.** $TiCl_3$/K-graphite (1/3), DME, r.t. 40 h and reflux 5 h (10%).



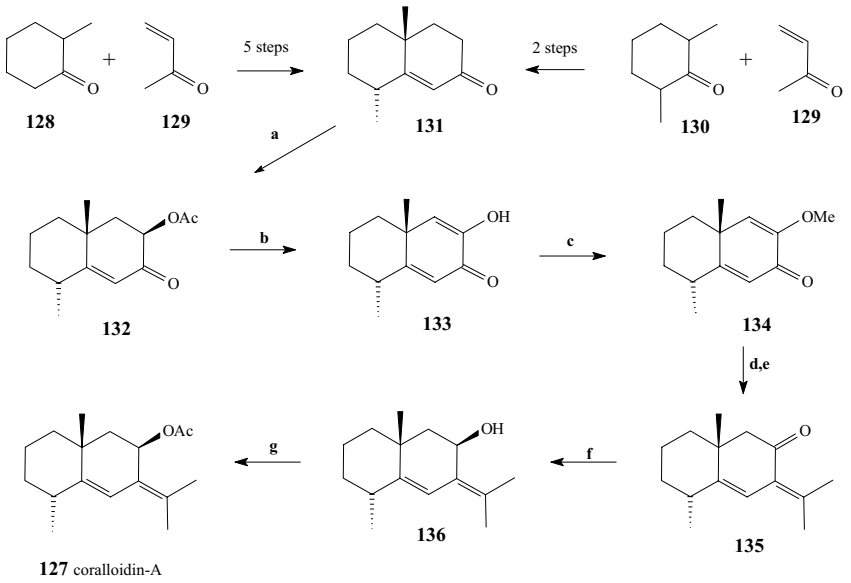
Scheme 12. Synthesis of isocaridiene.
a. $TiCl_4$, toluene (80%); **b.** HCOOH, 80 °C (85%); **c.** MeMgI, ether (70%); **d.** TsOH, benzene (75%).

quiterpenes[52]. Nanaimoal **(119)**, the major component, probably acts to control predation. Its structure was established from spectral data and synthesis, from myrcene **(113)**, of its p-bromo-phenyl-urethane derivative[52]. A short communication reports a similar total synthesis of **119**, following Scheme 13[53]. Thus, Diels-Alder reaction between myrcene **(113)** and methyl methacrylate **(120)** gave a mixture of regioisomeric esters **121** and **122**, that was subsequently reduced with lithium aluminium hydride to a 3:1 mixture of primary alcohols **123** and **124**. Acid-catalyzed cyclization of the less abundant **124** into **125** followed by tosylation, cyanation and reduction with DIBAL furnished racemic nanaimoal **(119)**. The key step in this synthesis was claimed to be the separation of the regioisomers **123** and **124**. Racemic nanaimoal has been obtained recently via Diels-Alder reaction of methacrylate with 1,1-dimethyl-2,3-dimethylenecyclohexane, a novel building block for cyclic terpenoids[54].

The eudesmane sesquiterpene (+)-coralloidin-A **(127)** was isolated from the Mediterranean soft coral *Alcyonium coralloides* living on a gorgonian of the genus *Eunicella*[55]. It was the first naturally occurring 5,6-dehydro-eudesmane to be described. Racemic coralloidin-A has now been synthesized in a seven-step sequence from the known enone **131**, as depicted in Scheme 14[56]. The first step was the acetoxylation of enone **131** into the key intermediate **132**. The acetate of **132** was then hydrolysed and oxidized to the unsaturated α-diketone **133**, and the enol form methylated, in low yield (62%), to the methoxy derivative **134**. Wittig addition of a C_3 unit completed the sesquiterpene skeleton and proceeded satisfactorily (79% after chromatographic purification). Reduction of the keto group furnished alcohol **136** in the desired β-orientation. The stereoselectivity of this reduction is probably controlled by the angular methyl group. Finally, acetylation of **136** gave racemic coralloidin-A in an overall yield, calculated from **131**, of about 30%[57].

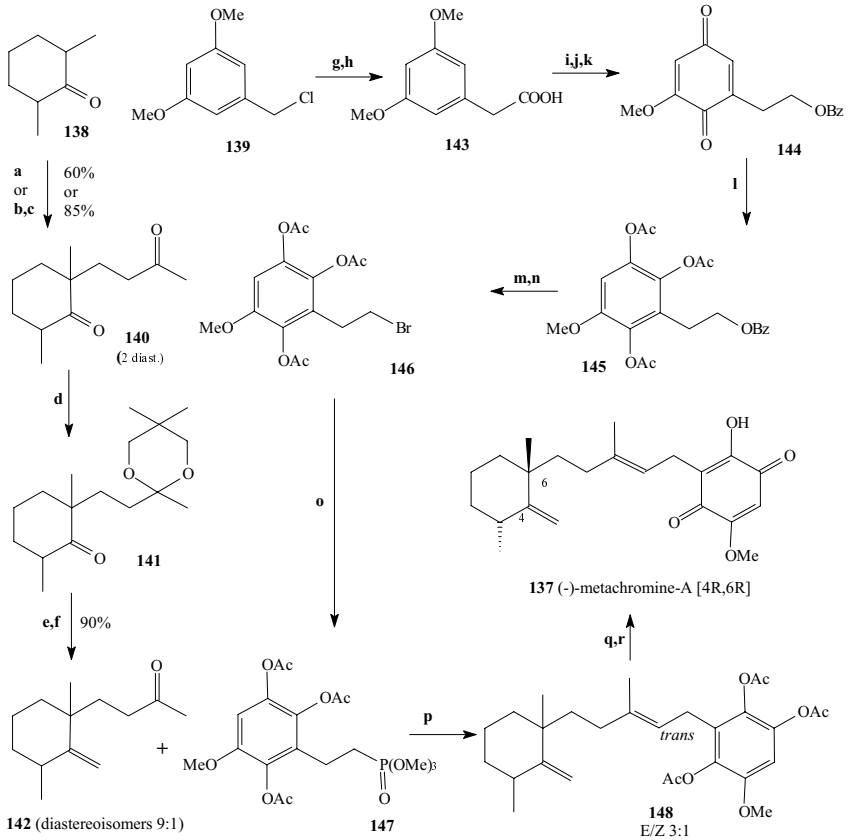


Scheme 13. Synthesis of (+/-)-nanaimoal.
a. Δ, 130 °C, 24 h; **b.** LAH, Et_2O; **c.** chromatography; **d.** HCOOH, 60 °C; **e.** TsCl, Py; **f.** NaCN, HMPA; **g.** DIBAL, hexane.



Scheme 14. Synthesis of coralloidin-A.

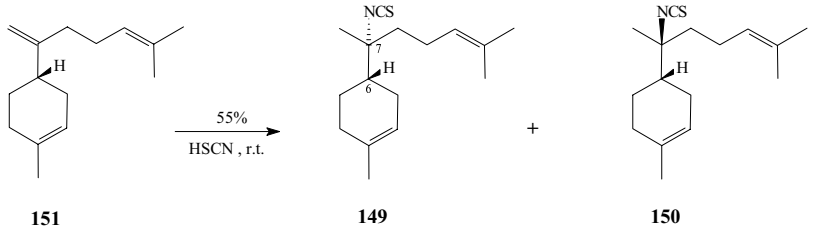
a. $Mn(OAc)_3.2H_2O$, benzene (82%); **b.** KOH, MeOH, O_2 (86%); **c.** t-BuOK, t-BuOH, MeI (62%); **d.** $iPrPPh_3Br$, Et_2O, THF; **e.** chromatography (79% from 134); **f.** LAH, Et_2O; **g.** Ac_2O, DMAP, CH_2Cl_2.



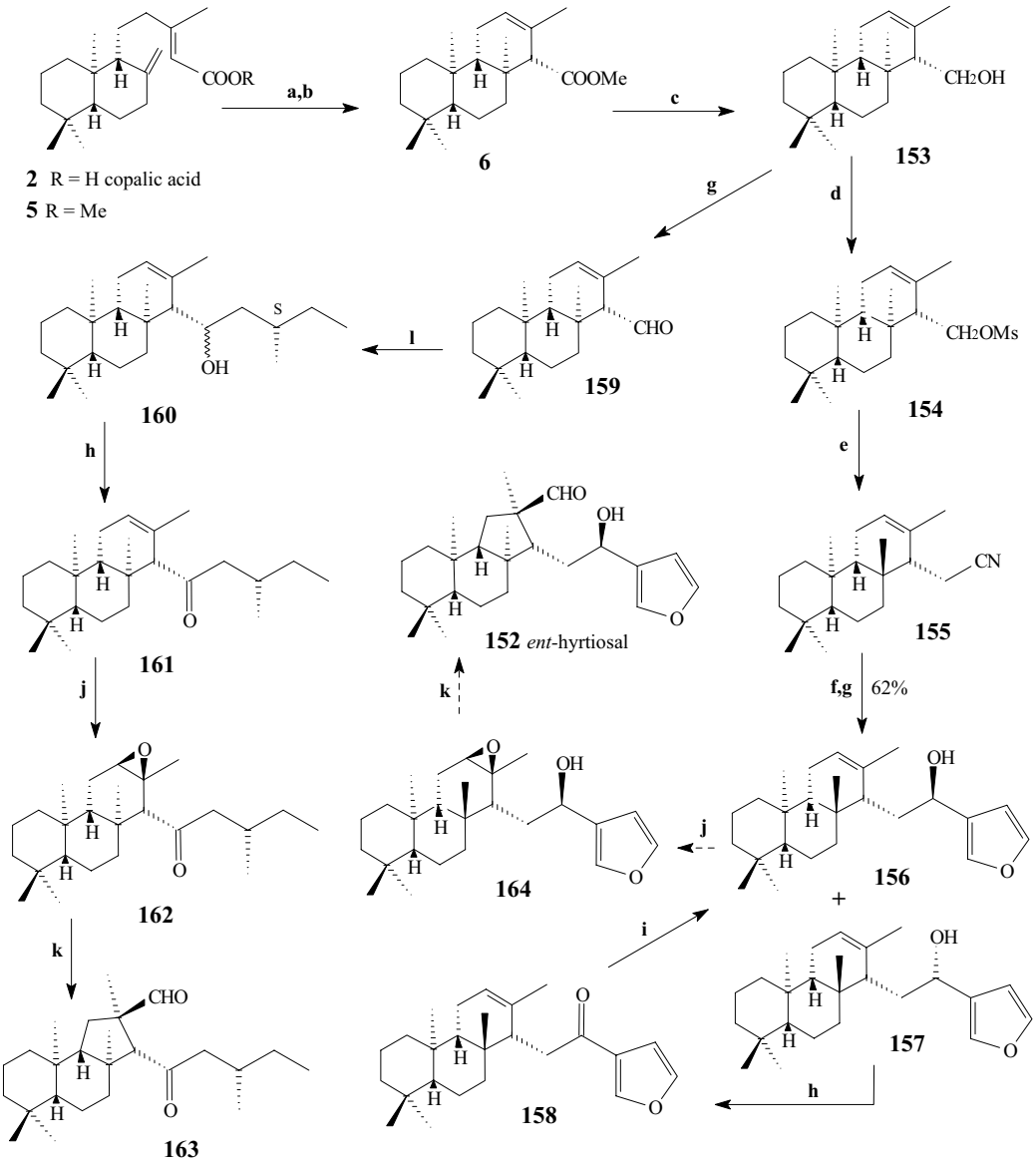
Scheme 15. synthesis of metachromine-A.

a. H_2SO_4 conc., MVK, benzene (53%); **b.** Et_3N, TMSCl, NaI, CH_3CN (82%); **c.** MVK, $BF_3.Et_2O$, $MeNO_2$, menthol (85%); **d.** p-TsOH,  , benzene, r.t. (95%); **e.** Ph_3PBr , CH_3I, t-BuOK, benzene (80%); f. PPTS, toluene (90%); **g.** NaCN , EtOH-H_2O, reflux, 4 h (93%); **h.** NaOH (40%), H_2O_2 reflux (90%); **i.** LAH, THF, reflux (98%); **j.** NaH, THF then BzBr, reflux (84%); **k.** CrO_3, AcOH,H_2O 0 °C then r.t. 2 h (84%); **l.** Ac_2O, H_2SO_4, r.t., 12 h (65%) ; **m.** H_2 , Pd-C, AcOH, r.t., 12 h (85%); **n.** CBr_4-Ph_3P, CH_2Cl_2, 0 °C then r.t., 6 h (80%); **o.** $(MeO)_3P$, DME, reflux, 3 h (56%); **p.** i. **147** in THF, -78 °C, nBuLi, 30 min then add **142** in THF (60% E/Z) or ii. **147** NaH, THF 0 °C then r.t. 30 min add **142** in THF, reflux, 4 h (40% E); **q.** LAH, Et_2O, 0 °C (55%); **r.** 1% aq. $FeCl_3$, benzene, r.t., 20 min (65%).

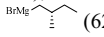
(-)-Metachromin-A **(137)** is one of the sesquiterpenoid quinones with an unprecedent skeleton that has been isolated from the Okinawan sponge *Hippospongia* cf. *metachromia*[58]. It exhibits a potent antitumor activity against L-1210 leukemia cells *in vitro* (IC_{50} 2.40 μg/ml) and potent coronary vasodilating activity in rabbit isolated artery (IC_{50} 3 x 10^{-6} M)[58]. Convergent synthesis of metachromin-A from 2,6-dimethylcyclohexanone **(138)** and the benzyl chloride **139** was achieved through the 16-step process shown in Scheme 15[59-61]. Thus, Michael



Scheme 16. Synthesis of a *Halichondria* metabolite (ent-**149**).

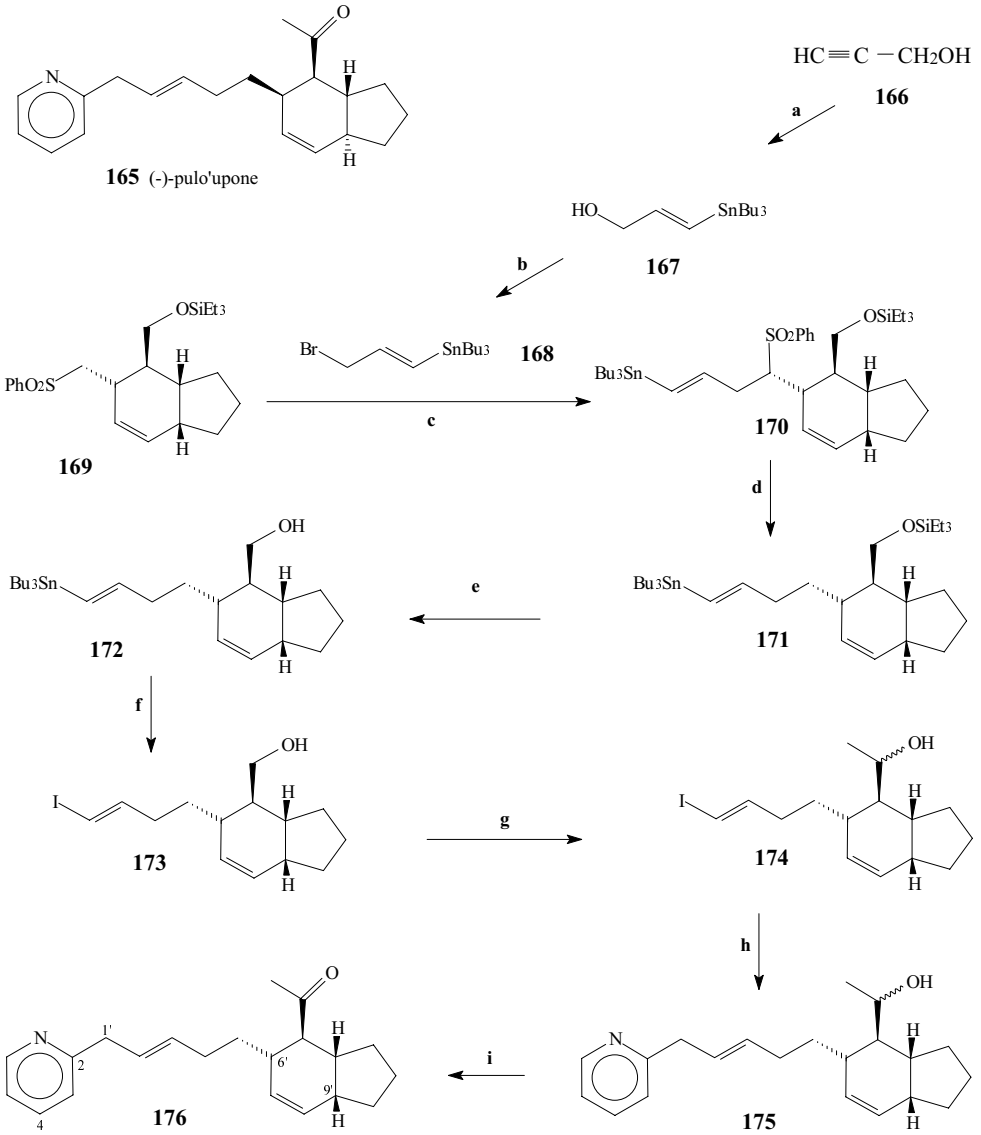


Scheme 17. Toward the synthesis of ent-hyrtiosal.

a. CH_2N_2, Et_2O; **b.** HCOOH 98% aq (a,b 98%); **c.** LAH (98%); **d.** MsCl; **e.** NaCN; **f.** DIBAL; **g.**  , -78 °C (73%) ; **h.** PCC, CH_2Cl_2; **i.** $NaBH_4$; **j.** MCPBA, $CHCl_3$; **k.** $BF_3.Et_2O$, benzene; **l.**  (62%).

addition of methylvinylketone on **138** furnished **140** as a 7:3 mixture of diastereoisomers. Protection of the less hindered keto group, olefination and removal of the protecting group yielded ketone **142** (two diastereoisomers) in 47% overall yield. On the other hand, quinone **144** was prepared from the commercially available benzyl chloride **139** by cyanation, basic hydrolysis to the corresponding acid, LAH reduction, protection of the primary alcohol and chromic acid oxidation of the aromatic ring. Then, Thiele acetoxylation followed by hydrogenolysis of the benzyl group, substitution by a bromine and phosphonation via a Michaelis-Arbuzov reaction delivered, in ~6% overall yield, the desired intermediate **147** that was subsequently coupled (HWE reaction) to ketone **142** affording a 3:1 mixture of the E/Z isomers. Metachromine-A **(137)** was finally obtained by reduction of the acetate groups and smooth ferric chloride oxidation in 16% yield from the coupling of **142** and **147**[61].

A number of isothiocyanosesquiterpenes have been isolated from sponges or from mollusks that feed on them[62]. Recently, an efficient methodology to introduce a tertiary NCS group has been described using *in situ* generated HSCN and mild operating conditions[63]. This eventually led to the synthesis of (6S,7R) and (6S,7S)-7-isothiocyano-7,8-dihydro-α-bisabolene **149** and **150**, the former being the enantiomer of a marine metabolite from an unspecified *Halichondria* sponge[64] and not from a *Ciocalypta* sponge[65] as reported[66] (see Scheme 16).

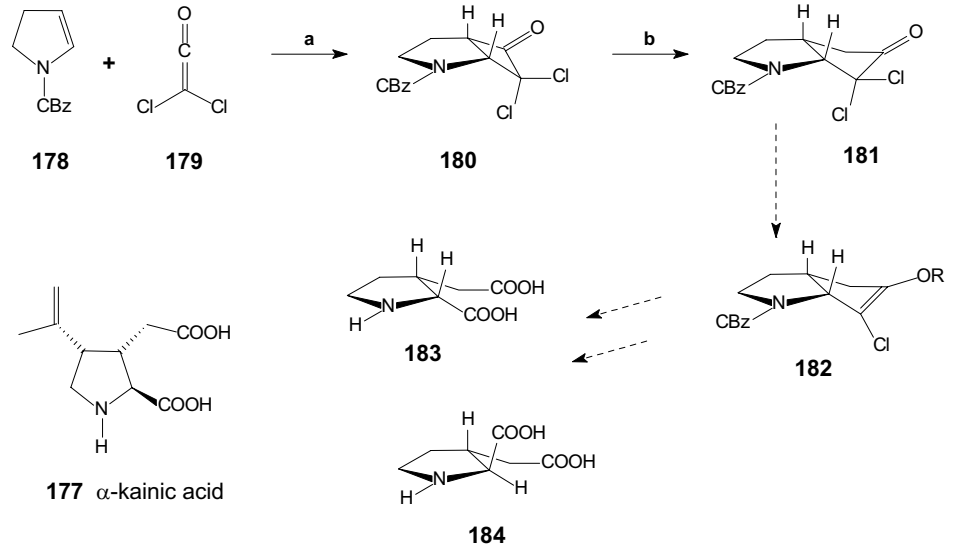


Scheme 18. Synthesis of pulo'upone side chain.

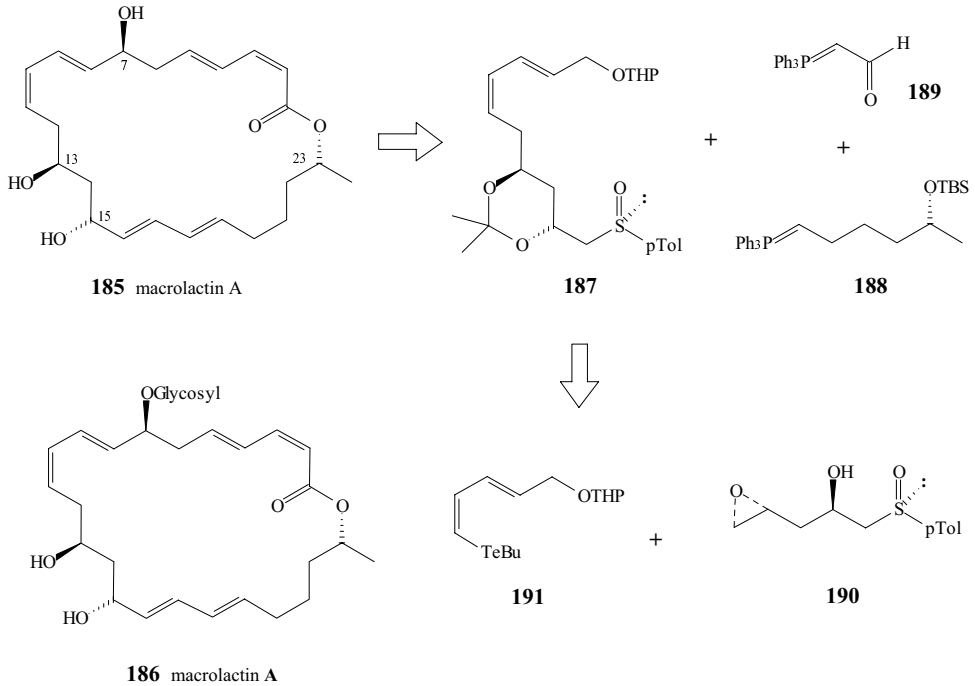
a. Bu_3SnH, AIBN, 80 °C, 2 h (50%); **b.** PPh_3, CBr_4, CH_2Cl_2, -20 °C to r.t., 5 h (55%); **c.** n-BuLi, THF, HMPA, -78 °C (42%); **d.** 6% Na(Hg), Na_2HPO_4, MeOH, 0 °C (76%); **e.** Bu_4N, THF (90%); **f.** I_2, CH_2Cl_2, -78 °C to 0 °C (88%); **g.** $(COCl)_2$, DMSO, Et_3N, THF, -78 °C to -35 °C; MeMgBr (70%); **h.**  , n-BuLi, THF, 0 °C ;CuCN , THF, -78 °C (83%); **i.** $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C (82%)

Miscellaneous

Hyrtiosal **(152)** is a sesterterpene isolated from the marine sponge *Hyrtios erectus* (= *erecta*?) and belongs to a new class of terpenoid named hyrtiosane[67]. It exhibits, *in vitro*, antiproliferative activity against KB cells. An elegant synthesis of its enantiomer has been planned, starting from copalic acid **(2)**. These efforts have led to the synthesis of the *ent*-hyrtiosane derivative **163**, according to Scheme 17, in 8 steps, with a rather good overall yield of 23%[68,69]. Hence, methyl isocopalate **(6)**, obtained from copalic acid **(2)** in the usual way (see Scheme 1), was transformed into the corresponding aldehyde **(159)** which was submitted to a Grignard reaction giving a 2:1 mixture of two sesterterpene alcohols **(160)** epimers at the carbinol carbon. PCC oxidation of this mixture and subsequent epoxidation of the trisubstituted double bond furnished intermediate **162** that could readily be rearranged into hyrtiosane **163** on treatment with boron trifluoride etherate. The overall yield of this synthesis is not available. Subsequently, the enantiomer of a possible biosynthetic precursor of hyrtiosal,



Scheme 19. Towards the synthesis of kainic acid analogues.
a. hexane, r.t., (90%); **b.** CH_2N_2, MeOH, Et_2O (~30%).



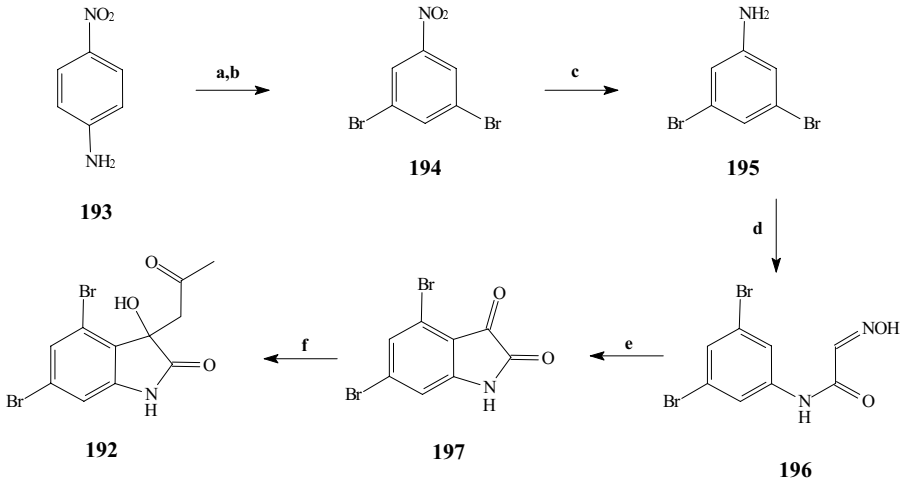
Scheme 20. Towards the total synthesis of macrolactin-A.

furane **156**, has been obtained from copalic acid **(2)** in seven steps (Scheme 17) by extention of the side chain of alcohol **153** and addition of a furane moiety that proceeds in good yield (62%). However, this latter step lacks stereoselectivity giving rise to a mixture of **156** and **157**, epimers at the carbinol carbon. A sequence of oxidation/reduction has been used to increase the yield of the desired intermediate **156**[70,71]. It may be anticipated that *ent*-hyrtiosal **(152)** will now be prepared from **156**, in two steps, through intermediate **164**.

(-)-Pulo'upone **(165)** is a minor metabolite isolated in 0.008% yield from the Hawaiian opistobranch mollusk *Philinopsis speciosa* (order Cephalaspidea). It is a highly uncommon pyridine derivative substituted at C-2 by a bicyclic polyketide derived C_{16}-alkadienone and has no close analogue among natural or synthetic products[72]. This has made **165** an interesting target for organic synthesis and racemic pulo'upone has already been obtained[73]. Subsequently, the absolute configuration of (-)-pulo'upone was determined by asymmetric total synthesis of both enantiomers[74]. A new approach to assemble the side chain of pulo'upone has now been described (Scheme 18). 6',9'-bis*epi*-pulo'upone **(176)**, a diastereoisomer of **165** was prepared starting from propargyl alcohol **(166)**, 2-picoline and the hydrindene moiety **(169)**[75,76]. Thus, the (E)-3-bromo-1-propen-tributylstannane **(168)** was prepared using a 2-step protocol from propargyl alcohol **(166)**, and coupled with the anion of the sulfone **169** to give the (E)-vinylstannyl sulfone **170**, along with 35% recovered starting substrate **169**. Desulfonylation to **171**, followed by deprotection of the hydroxyl group and treatment with iodine furnished intermediate **173** that was subsequently homologated in a one-pot Swern-Grignard procedure to a mixture of diastereoisomeric carbinols **174**. Treatment of the latter mixture with the cuprate derived from 2-picoline provided **175** as a mixture of 2 epimers, that was finally oxidized to bis*epi*-pulo'upone **176** in 12% overall yield from hydrindene **169**[75,76].

α-Kainic acid **(177)** is a pyrrolidine amino acid known for a very long time. It was first isolated from the red alga *Digenea simplex* and is endowed of anthelmintic properties justifying its use in popular medicine for centuries[4]. Kainic acid has more recently been implicated in the processes of learning and memory and has consequently received considerable attention in the area of neurosciences[77-81]. A number of syntheses of **177** have already been published and new approaches are being investigated[82-85]. Preliminary results towards the synthesis of kainic acid analogues have appeared and are described in Scheme 19[85]. [2+2]Cycloaddition of cyclic enecarbamate **178** and dichloroketene **179** furnished the dichloro-aza-cyclobutanone **180** that was transformed into the α,α-dichloro-cyclopentanone **181** through a regioselective ring expansion carried out with diazomethane in rather low yields (~30%)[86].

The macrolactins are the first members of a novel class of antiviral and cytotoxic macrolides. They were isolated from an unknown Gram-positive bacterium, isolate C-237, from a deep-sea sediment core[87]. Macrolactin-A **(185)** showed selective antibacterial activity and inhibited B16-F10 murine melanoma cancer cells *in vitro*. It also showed significant inhibition of mammalian *Herpes simplex* viruses (types I and II) and protected T-lymphoblast cells against human HIV viral replication[87]. The absolute (7S, 13S, 15R, 23R) stereochemistry of macrolactin-A has been proposed recently from a ^{13}C-NMR analysis of macrolactin-B **(186)**[88,89]. Studies toward the synthesis of macrolactin A have already generated the segments C_1-C_{11}, C_{16}-C_{24} and C_{15}-C_{24}[90,91]. Both works used organoiron methodologies. A convergent synthesis combining tellurium and sulfoxide chemistry has been planned in order to



Scheme 21. Synthesis of convolutamydine A.

a. Br_2, AcOH (98%); **b.** $NaNO_2$, H_2SO_4, EtOH (97%); **c.** (i) H_2, Ni-Ra, EtOH,%); (ii) HCl , EtOH aq. (86-96%); **d.** chloral, $(H_2NOH)_2$ H_2SO_4, Na_2SO_4, H_2O/EtOH(3:1v/v) (82-88%); **e.** 86% H_2SO_4 (80-86%); **f.** acetone, Et_2NH (77%).

provide gram quantities of **185** for further biological evaluation. The first step of the retrosynthetic analysis shown in Scheme 20, the coupling of tellurodiene **191** with the hydroxy-epoxide **190**, has been achieved in 90% yield[92]. The final steps of the synthesis are under investigation.

Convolutamydine A **(192)** is the first dibromohydroxyoxindole alkaloid isolated, from the bryozoan *Amathia convoluta*[93], together with a series of bromophenylethylamines and bromophenylethylamides[94,95]. This metabolite exhibits a potent activity in the differentiation of HL-60 human promyelocytic leukemia cells at 12.5~25 μg/mL[93,96]. A six-step synthesis of racemic **192** has very recently been reported[97]. Thus, bromination of *p*-nitroaniline **(193)**, followed by reductive deamination furnished 3,5-dibromonitrobenzene **(194)** that was subsequently hydrogenated to 3,5-dibromoaniline **(195)** using a freshly prepared Raney nickel catalyst. The key-step of the synthesis was the modified Sandmeyer reaction (step **d**) that delivered the expected isonitrosoacetanilide **196** in 82-88%, an excellent yield when compared to literature data[98]. Acid catalysed cyclization of **196** into **197** and aldol type addition of acetone resulted in the obtention of (±)-convolutamydine A in 53% overall yield [Scheme 21].

Conclusions

Synthetic studies have focused mainly on terpenes. Among them, 8 sesquiterpenes, 10 diterpenes and one sesterterpene have been the object of total synthesis or of the preparation by transformation of an abundant natural precursor. In addition, the synthesis of one dibromoindole metabolite has been achieved. The syntheses of two nitrogen-containing metabolites and one long-chain lipid are still under investigation.

Target metabolites had been isolated from sponges (8 compounds), mollusks (5), octocorals (3), bryozoan (1), red alga (1), bacteria (1) and mammalians (4), and were selected either because of their pharmacological activities (hyrtiosal, α-kainic acid, metachromine-A, and macrolactin-A, convolutamydine-A), industrial use (ambergris derivatives) or structure originality (isoagatholactone, brasilenol, africanol, dactylol, pulo'upone).

In most cases, racemic mixtures or the enantiomer of target compounds have been prepared. The syntheses of several of these metabolites had already been published by other groups, with the exception of the four diterpenes from *Spongia officinalis*, brasilenol, convolutamydine-A, coralloidin-A and metachromine-A. The synthesis of (+)-brasilenol is the only one that not only confirmed structural determination but, in addition, allowed determination of the unknown absolute configuration.

Some syntheses are still underway and have been reported here to present the state of art of what has been (and what is being) done in Brazil in the field of synthesis of marine natural products.

In the third part of this review, we will focus on the biological perspectives of marine natural product research in Brazil. We will describe works on chemosystematics, chemical ecology and marine pharmacology.

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