REVIEW

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Occurrence, biological activity and synthesis of drimane sesquiterpenoids

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In this review the names, structures and occurrence of all new drimanes and rearranged drimanes, which have been published between January 1990 and January 2003 have been collected. Subjects that have been treated are biosynthesis, analysis, biological activities, with special attention to cytotoxic activity and antifeedant and insecticidal activity and mode of action. An important part of the review deals with the synthesis of drimanes. This part has been subdivided into syntheses by transformation of natural products, syntheses starting from chiral compounds obtained by enzymatic resolution, syntheses by cationic polyolefin cyclizations, syntheses from trans-decalones, syntheses by radical cyclizations and syntheses by cycloaddition reactions. The review contains about 350 references.

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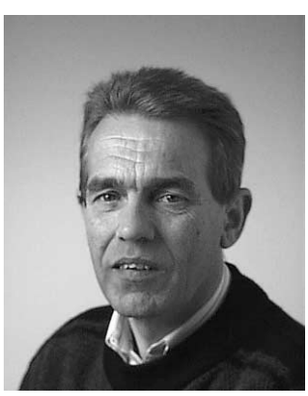

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Dr Bernardus J. M. Jansen was born in 1945 in Wehl, The Netherlands. He started his chemical career as a laboratory technician in 1962 in industry and in 1973 he continued as such at the laboratory of Organic Chemistry of Wageningen Agricultural University (WAU). Meanwhile he started his studies in chemistry at the State University of Utrecht and obtained his MSc in 1978. He completed his PhD thesis on the "Total synthesis of Insect Antifeedant Drimane Sesquiterpenes" at WAU in 1993 under the supervision of Professor Aede de Groot. His fields of research are the synthesis of insect antifeedant drimanes and clerodanes, and the synthesis of physiologically active sesquiterpenoids and steroids starting from carvone.

Ae. de Groot

Professor Aede de Groot received his MSc in Organic Chemistry and Technical Chemistry in 1964 from the University of Groningen in The Netherlands. He did his PhD in Organic Chemistry in 1967 under the supervision of Professor Dr Hans Wijnberg, also in Groningen, and he was a post doctoral fellow with Professor Dr E. E. van Tamelen where he got his first training in the synthesis of natural products. From 1969–1971 he gained industrial experience at the Dutch State Mines (DSM) on electro-organic synthesis, and after that he was an assistant professor at the Technical University of Eindhoven. In 1972 he was appointed as full professor in Bio-organic Chemistry at Wageningen University, a position he still holds today. His research interests concentrate on total syntheses of natural products, especially sesqui- and diterpenes with physiologically active properties in the field of crop protection (antifeedants, repellents, pheromones), flavour and fragrance and pharmaceuticals, and on syntheses starting from terpenes and steroids, which are abundantly available from Nature.

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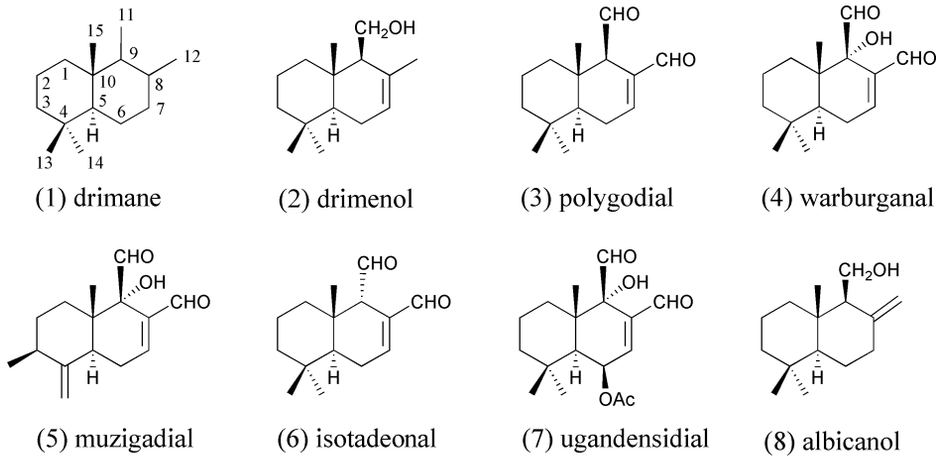

Fig. 1

8.4 Synthesis of drimanes by cationic polyolefin cyclizations
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1 Introduction

The continuing stream of publications on drimane sesquiterpenoids during the last two decades[1] has prompted us to update our previous review.[2] The format of this review is similar, but it will be focused more on bioorganic chemistry. Rearranged drimanes in which a 1,2 methyl shift from C4 to C3 has taken place are included in this review. Drimanic products belonging to sesquiterpenoid hydroquinones or quinones, a class of natural products of mixed biogenesis[3] and rearranged compounds with a 4,9-friedodrimane skeleton[4] are **not included** in this review. Likewise, naturally occurring coumarins with a drimane, *ent*-drimane or rearranged drimane skeleton are not treated extensively since there are excellent existing reviews.[5–9]

2 Structure and occurrence

The name *drimane* (1) was proposed for the saturated hydrocarbon[10] with the structure and absolute configuration depicted in Fig. 1. This structure is derived from (or related to) the sesquiterpenoid alcohol drimenol (2), isolated from the bark of *Drimys winterii* Forst.[11] This structure was elucidated by means of chemical conversions into known (natural) products and secured by crystallographic investigations.[12] Some important and well known biologically active drimanes are also shown in Fig. 1.

The first drimane, drimenol (2), was isolated from a species belonging to the Canellaceae. This family is a rich source of drimanes and includes, *Canella winterana*,[13–16] *Cinnamodendron corticosum*,[17] *Cinnamosma fragrans*,[18] *Capsicodendron dinisii*,[19,20] *Warburgia ugandensis*,[20,22] *W. stuhlmannii*,[21] and *W. salutaris*,[23,24] the Winteraceae species *Drymus winteri*,[25–27] *D. granadensis*,[28,29] *D. lanceolata* syn. *Tasmannia lanceolata*,[30,31] and the botanically related *Pseudowintera colorata*.[32] Canellaceae are grouped into four genera of which *Winterana* and *Cinnamodendron* are endemic to South America and *Warburgia* to South East Africa and *Cinnamosma* to Madagascar. Drimanes are scarcely isolated from other trees except from *Thuja standishii*[33a], *Cistus incanus* subsp. *Creticus*,[33b] *Taxus crispat*,[33c] and *Limeum pterocarpum* (Aizoaceae).[33d]

Some Thelypteridaceae like *Macrothelypteris torressiana*, *Dryopteris fragrans*, *Protowoodsia manchuriensis* and *Blechnum fluviatile* afforded drimanic products.[34a–c] The flowerheads of *Spilanthes acmella* contain drimane sesquiterpenoids.[34d]

Systematic investigations of active compounds in liverworts have also afforded drimanes as in *Porella vernicosa*,[35,36] *P. acutifolia*,[37] *P. canariensis*,[36,38] *P. cordeana*,[39] *P. navicularis*,[40] *Bazzania* species,[36,41–43] *Diplophyllum serrulatum*,[44] *Hymenophyton flabellatum*,[44] and *Makinoa crispata*.[45]

Polygonum hydropiper L is a very rich source of drimanes[46] and therefore other Polygonaceae, frequently used in folk medicine in different parts of the world, were also investigated including *Polygonum punctatum*,[47] *P. glabrum*,[48] and *Persicaria stagnina*.[49]

Compounds belonging to the drimane group have been identified in certain tobaccos, where they are partly responsible for the characteristic flavour notes.[50a–c] This is also the case in the essential oil from the rhizomes of Himalayan *Hedychium acuminatum*[51a] and from *Homalomena occulta*.[51b]

The Umbelliferae, a large family of higher plants, is well documented as a good source of biologically active compounds and drimanic coumarins have been found in *Ferula arrigoni*, *F. ceratophylla, F. kokanica, F. sinaic*, *F. sumbul*, *Heptaptera anisoptera*, and *H. triquetra.*[52] Drimenyl coumarin ethers have also been isolated from *Artemisia persica*, *A. pontica* and from the roots of *Tanacetum parthenium* transformed with *Agrobacterium rhizogenes*, *T. heterotomum* and from *Brocchia cinera.*[53] A striking phenomenon is the presence of drimenyl- and albicanyl coumarin ethers belonging to enantiomeric series within the same species.[5]

Fungi biosynthesize drimanes and several have been isolated from the fruiting bodies from the wild or from the fermentation cultures of fungi. The fairy ring fungus *Marasmius oreades* grown in still culture on PDY- or MEG medium produced a lot of highly oxidized drimane metabolites.[54] When cultivated in solid or liquid medium *Aspergillus* sp.,[55–57] *Kuehneromyces* sp.,[58] *Trichopezizella barbata*,[59] *Mniopetalum* sp. and *Panus* sp.,[60] *Penicillium brevicom-pactum*,[61] *Lactarius uvidus*,[62] *Polyporus ciliatus*,[63] *and P. arcularius*,[63,64] *Pestalotiopsis* spp., endophytic fungi of the yew tree, and *Lepista glaucocana*[65] afforded novel biologically active drimanes. A series of structurally related dimeric drimanes were isolated from *Cryptoporus volvatus* fruit bodies,[66] *Ganoderma neo-japonicum*,[67] *Cryptoporus volvatus* infected by *Paecylomyces varioti*,[68] *Haploporus odorus*,[69] and from *Roseoformes subflexibilis*.[70] Wood-rotting Basidiomycetes like *Gloeophyllum odoratum* and *Laricifomes officinalis* also produce drimanes.[71–74] *Peniophora polygonia*, which demonstrates a distinct antagonism against *Phellinus tremulae*, afforded several new active drimane sesquiterpenoids.[75]

With oceans covering a sizeable percentage of the earth, the potential of marine biodiversity has attracted many investigators and several biologically active drimane metabolites have been isolated.[76–79] Drimane sesquiterpenoids have been frequently isolated from temperate species of marine sponges of the genus *Dysidea*.[80–83] Chemical studies of the porostome family Dendrodorididae have revealed the presence of

Table 1 Recently isolated drimanes

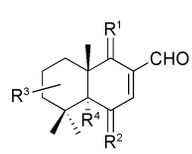
Compound	R^1	R^2	R^3	R^4	R^5	Ref.
3β-Acetoxypolygodial (9)	βCHO, H	H_2	3βOAc	H	—	15
3α-Acetoxypolygodial (10)	βCHO, H	H_2	3αOAc	H	—	14
Hodgsonal (11)	βCH_2OAc, H	H_2	2αOAc	H	—	93
Methoxycoumaroylpolygodial (12)	βCHO, H	H_2	1βOX[a]	H	—	28
Coumaroyl polygodial (13)	βCHO, H	H_2	1βOX[b]	H	—	28
Drimanial (14)	βCHO, H	H_2	1βOX[a]	OH	—	25*a*
RES-1149-1 (15)	βCHO, OH	βOX[c], H	H	H	—	55*a*
7-Ketoisodrimenin (16)	O	H_2	H	H_2	—	39
7-Keto-isodrimen-5-ene (17)	O	H, Δ		H_2	—	39
12-Hydroxyisodrimenin (18)	H_2	H_2	H	H, OH[d]	—	82
Ugandensolide (19)[e]	βOH, H	βOAc, H	H	H_2	—	21*a*
6-Deacetylugandensolide (20)	βOH, H	βOH, H	H	H_2	—	21*a*
Dendocarbin I (21)	βOH, H	H_2	H	ζOEt, H	—	92
Dendocarbin F (22)	—	—	—	—	—	92
6a-Hydroxy-7-chloroconfertifolin (23)	αCl, H	βOH, H	CH_3	CH_3	H_2	45
6,7-Dihydroxyconfertifolin (24)	αOH, H	βOH, H	CH_3	CH_3	H_2	45
6,7-Epoxyconfertifolin (25)	αH, –O–	αH	CH_3	CH_3	H_2	45
7-Hydroxyconfertifolin (26)	αOH, H	H_2	CH_3	CH_3	H_2	75
11-Hydroxyconfertifolin (27)	H_2	H_2	CH_3	CH_3	βOH, H	82
7,14-Dihydroxy-6-nitrobenzoylconfertifolin (28)	αOH, H	βOX[f], H	CH_2OH	CH_3	H_2	57
6,7-Dihydroxy-14-nitrobenzoylconfertifolin (29)	αOH, H	βOH, H	CH_2OX[f]	CH_3	H_2	57
Astellolide A (30)	H_2	βOX[g], H	CH_2OAc	CH_2OAc	H_2	116*d*
Astellolide B (31)	H_2	βOX[h], H	CH_2OAc	CH_2OAc	H_2	116*d*
11-Acetoxyconfertifolin (32)	H_2	H_2	CH_3	CH_3	αOAc, H	83
Dendocarbin J (33)	αOH, H	H_2	CH_3	CH_3	βOEt, H	92
Dendocarbin K (34)	αOH, H	H_2	CH_3	CH_3	αOEt, H	92
Dendocarbin L (35)	αOH, H	H_2	CH_3	CH_3	βOH, H	92
Dendocarbin M (36)	αOH, H	H_2	CH_3	CH_3	αOH, H	92
3-Hydroxycinnamolide (37)	H_2	H	H_2	3βOH	CH_3	21*a*
3-Acetoxycinnamolide (38)	H_2	H	H_2	3βOAc	CH_3	21*a*
3,9-Dihydroxycinnamolide (39)	H_2	OH	H_2	3βOH	CH_3	16*a*
6α-Hydroxycinnamolide (40)	αOH, H	H	H_2	H	CH_3	75
6β-Hydroxycinnamolide (41)	βOH, H	H	H_2	H	CH_3	75
Insilucolide A (42)	βOX[f], H	OH	H_2	H	CH_2OH	56*b*
9-Deoxyisulicolide A (43)	βOX[f], H	H	H_2	H	CH_2OH	57
11-Acetoxycinnamolide (44)	H_2	H	αOAc, H	H	CH_3	83
Stagninol (45)	αOH, H	H_2	H_2	H	2αOX[i], 3βOX[i]	49
Diangeloylisodrimeninol (46)	αOH, H	H_2	H_2	H	2αOX[j], 3βOX[j]	48
Angeloylmethylbutanoylisodrimeninol (47)	αOH, H	H_2	H_2	H	2αOX[j], 3βOX[k]	48
Angeloyl-2-methylpent-2-enoylisodrimeninol (48)	αOH, H	H_2	H_2	H	2αOX[j], 3βOX[l]	48
Angeloyl-2-methylpentanoylisodrimeninol (49)	αOH, H	H_2	H_2	H	2αOX[j], 3βOX[m]	48
1-Acetoxyisodrimeninyl acetate (50)	αOAc, H	H_2	H_2	H	1βOAc	34*a*
1,3-Diacetoxyisodrimeninyl acetate (51)	αOAc, H	H_2	H_2	H	1βOAc, 3βOAc	34*a*
1,6-Diacetoxyisodrimeninyl acetate (52)	αOAc, H	H_2	αOAc, H	H	1βOAc, H	34*a*
2-Hydroxydrimeninol (53)	βOH, H	H_2	H_2	H	2αOH, H	65*a*
RES-1149-2 (54)	O	H_2	βOX[c], H	OH	H_2	55*a*
Deoxo-RES-1149-2 (55)	H_2	H_2	βOX[c], H	OH	H_2	55*b*
Hydroxydeoxo-RES-1149-2 (56)	αOH, H	H_2	βOX[c], H	OH	H_2	55*b*
Hexadienoylhydroxydrimenin (57)	O	H_2	βOX[n], H	OH	H_2	55*b*
(*Z*,*E*,*E*)-2,4,6-Octatrienoylhydroxydrimenin (58)	O	H_2	βOX[o], H	OH	H_2	55*b*
11,12-Dimethoxy-11,12-epoxydrimene (59)	βOCH_3, H	ζOCH_3, H	H_2	H	H_2	28
Methoxycoumaroyl-11,12-dimethoxy-11,12-epoxydrimene (60)	βOCH_3, H	ζOCH_3, H	H_2	H	1βOX[a], H	28
11,12-Dimethoxy-3-acetoxy-11,12-epoxydrimene (61)	αOCH_3, H	αOCH_3, H	H_2	H	3βOAc, H	13
11,12-Dimethoxy-3-acetoxy-11,12-epoxydrimene (62)	αOCH_3, H	βOCH_3, H	H_2	H	3βOAc, H	13
Dimethoxy-11,12-epoxydrimene (63)	αOCH_3, H	αOCH_3, H	H_2	H	H_2	14
Dendocarbin A (64)	αOH, H	O	H_2	H	H_2	92
Dendocarbin B (65)	O	H_2	H_2	H	2αOH, H	92
Dendocarbin C (66)	αOH, H	H_2	αOH, H	H	H_2	92
Dendocarbin E (67)	O	O	H_2	H	2βOH, H	92
Dendocarbin G (68)	O	O	αOH, H	H	H_2	92
Dendocarbin H (69)	O	O	H_2	H	H_2	92
Desacetylpebrolide (70)	αH	βOX[g], H	CH_2OH	1βOH	—	61
1-Deoxypebrolide (71)	αH	βOX[g], H	CH_2OAc	H	—	61
3-Hydroxydihydroxyconfertifolin (72)	αH	H_2	CH_3	3βOH	—	75
Peniopholide (73)	αOH	H_2	CH_3	H	—	75
3α-Hydroxypeniopholide (74)	αOH	H_2	CH_3	3αOH	—	75
3β-Hydroxypeniopholide (75)	αOH	H_2	CH_3	3βOH	—	75
Limeolide (76)	βH	αOH, H	CH_3	3αOH	—	33*d*
Dendocarbin N (77)	—	—	—	—	—	92
Dihydrodrimeninol (78)	βOH, H	H_2	αH	—	—	81
Dihydroisodrimeninyl acetate (79)	αOAc, H	H_2	αH	—	—	81
Dihydro-isodrimeninol (80)	αOH, H	H_2	βH	—	—	82
Dihydrodrimenin (81)	O	H_2	βH	—	—	83
Dihydroisodrimeninol methyl ether (82)	αOCH_3, H	H_2	αH	—	—	83
Dihydroxydihydroisodrimeninol methyl ether (83)	αOCH_3, H	αOH, H	αOH	—	—	83
Dendocarbin D (84)	αOH, H	O	αOH	—	—	92

Table 1 (*Contd.*)

Compound	R^1	R^2	R^3	R^4	R^5	Ref.
9-Hydroxy-6-oxodrimenol (85)	βCH$_2$OH, OH	H	O	H$_2$	CH$_3$	55*b*
Drimenylcaffeate (86)	βCH$_2$OX^p, H	H	H$_2$	H$_2$	CH$_3$	41
Scopodrimol (87)	αCH$_2$OX^q, H	H	H$_2$	αOH, H	CH$_3$	53*a*
Drimenyl fatty acid ester (88)	βCH$_2$OX^r, H	H	H$_2$	H$_2$	CH$_3$	62*a*
Drimendiol (89)	βCH$_2$OH, H	OH	H$_2$	H$_2$	CH$_3$	27
6-*epi*-Albrassitriol (90)	βCH$_2$OH, OH	H	βOH, H	H$_2$	CH$_3$	56*a*
12-Hydroxy-6-*epi*-albrassitriol (91)	βCH$_2$OH, OH	OH	βOH, H	H$_2$	CH$_3$	56*a*
3-Hydroxydrimenol (92)	βCH$_2$OH, H	H	H$_2$	3βOH, H	CH$_3$	64
3,12-Dihydroxydrimenol (93)	βCH$_2$OH, H	OH	H$_2$	3βOH, H	CH$_3$	64
Conferol (94)	βCH$_2$OX^s, H	H	H$_2$	3βOH	CH$_3$	52*g*
Conferone (95)	βCH$_2$OX^s, H	H	H$_2$	O	CH$_3$	52*g*
7,9(11)-Drimadiene (96)	CH$_2$	H	H$_2$	H$_2$	CH$_3$	33*b*
Albicanyl caffeate (97)	βCH$_2$OX^p, H	CH$_2$	CH$_3$	H$_2$	—	41
Albicanyl 2,4-dihydroxycinnamate (98)	βCH$_2$OX^t, H	CH$_2$	CH$_3$	H$_2$	—	42
Isocryptoporic acid H (99)	βCH$_2$OX^u, H	CH$_2$	CH$_3$	H$_2$	—	67
Isocryptoporic acid I (100)	βCH$_2$OX^u, H	CH$_2$	CH$_3$	3βOH, H	—	67
14-Albicanic acid (101)	βCH$_2$OH, H	CH$_2$	COOH	H$_2$	—	68
3-Hydroxy-14-albicanic acid (102)	βCH$_2$OH, H	CH$_2$	COOH	3βOH, H	—	68
11-Albicanic acid (103)	βCOOH, H	CH$_2$	CH$_3$	H$_2$	—	44*a*
Albicanal (104)	βCHO, H	CH$_2$	CH$_3$	H$_2$	—	44*a*
Drim-8(12)-ene (105)	βCH$_3$, H	CH$_2$	CH$_3$	H$_2$	—	51*a*
3-Hydroxyalbicanol (106)	βCH$_2$OH, H	CH$_2$	CH$_3$	3βOH, H	—	64
Pectachol (107)	βCH$_2$OX^v, H	CH$_2$	CH$_3$	3βOH, H	—	53*e*
9-Epipectachol (108)	αCH$_2$OX^v, H	CH$_2$	CH$_3$	3βOH, H	—	53*c*
1,2-Diacetoxyalbicanyl acetate (109)	βCH$_2$OAc, H	CH$_2$	CH$_3$	1αOAc, 2αOAc	—	86
8βH Drimane (110)	βCH$_3$, H	αCH$_3$, H	CH$_3$	H$_2$	—	95*a*
8-Hydroxydrimanal (111)	βCHO, H	βCH$_3$, OH	CH$_3$	H$_2$	—	50*d*
8,11-Drimanediol (112)	βCH$_2$OH, H	βCH$_3$, OH	CH$_3$	H$_2$	—	94
8,9-Drimanedial (113)	βCHO, H	βCHO, H	CH$_3$	H$_2$	—	81
Isoalbicanal (114)	CHO, Δ	CH$_3$	CH$_3$	H$_2$	—	44*a*
3-Isovaleroyl albicanyl coumarine (115)	αCH$_2$OR^v, H	CH$_2$	CH$_3$	3αOX^k, H	—	53*d*
11,12-Diacetoxydrimane (116)	βCH$_2$OAc, H	βCH$_2$OAc, H	CH$_3$	H$_2$	—	83
12-Acetoxydriman-11-ol (117)	βCH$_2$OH, H	βCH$_2$OAc, H	CH$_3$	H$_2$	—	83
7-Deacetoxyolepupuane (118)	—	αOAc, H	—	—	—	80
11-Deacetylolepupuane (119)	—	βOH, H	—	—	—	81
Marasmene (120)	H$_2$	H$_2$	H$_2$	H$_2$	CH$_3$, CH$_3$	54*b*
Marasmone (121)	O	O	H$_2$	αOH, H	CH$_3$, CH$_3$	54*a*
Isomarasmone (122)	O	αOH, H	H$_2$	O	CH$_3$, CH$_3$	54*a*
Dihydromarasmone (123)	O	αOH, H	H$_2$	αOH, H	CH$_3$, CH$_3$	54*a*
3,15-Dihydroxymarasmene (124)	OH, H	H$_2$	H$_2$	αOH, H	CH$_3$, CH$_3$	54*b*
1,15-Dihydroxymarasmone (125)	OH, H	αOH, H	H$_2$	H$_2$	CH$_3$, CH$_3$	54*b*
15-Hydroxymarasmen-3-one (126)	OH, H	H$_2$	H$_2$	O	CH$_3$, CH$_3$	54*b*
Anhydromarasmone (127)	O	O	H, Δ	H	CH$_3$, CH$_3$	54*a*
13-Hydroxymarasmene (128)	H$_2$	H$_2$	H$_2$	H$_2$	αCH$_2$OH, CH$_3$	54*b*
14-Hydroxymarasmene (129)	H$_2$	H$_2$	H$_2$	H$_2$	βCH$_2$OH, CH$_3$	54*b*
Marasmal (130)	αOH, H	H$_2$	αOH, H	—	—	54*b*
Mniopetal F (131)	αOH, H	H$_2$	H$_2$	—	—	60*a*
Kuehneromycin A (132)	O	H$_2$	H$_2$	—	—	58
Mniopetal A (133)	αOH, H	αOX^w, H	H$_2$	—	—	60*a*
Mniopetal B (134)	αOH, H	αOX^x, H	H$_2$	—	—	60*a*
Mniopetal C (135)	αOH, H	αOX^y, H	H$_2$	—	—	60*a*
Mniopetal D (136)	αOX^x, H	αOH, H	H$_2$	—	—	60*a*
Mniopetal E (137)	αOH, H	αOH, H	H$_2$	—	—	60*a*
Panudial (138)	αH	αCHO, H	CHO, Δ	H	H$_2$	60*b*
11-Nordrimenone (139)	βCH$_3$	H, Δ	CH$_3$	O	H$_2$	50*b*
11-Nor-8-hydroxydriman-9-one (140)	βCH$_3$	O	βCH$_3$, OH	H$_2$	H$_2$	50*a*
3-Acetoxypolygonal (141)	βCH$_3$	H, Δ	CHO	αOH, H	3βOAc, H	14
Polygonic acid (142)	βCH$_3$	H, Δ	COOH	αOH, H	H$_2$	28
11-Nordriman-8,9-diol (143)	βCH$_3$	βOH, H	βCH$_3$, OH	H$_2$	H$_2$	50*d*
11-Nordriman-8-ol (144)	βCH$_3$	H$_2$	βCH$_3$, OH	H$_2$	H$_2$	50*d*
11-Nordrimen-12-al (145)	βCH$_3$	H, Δ	CHO	H$_2$	H$_2$	51*a*
12-Nordriman-8,11-diacetate (146)	βCH$_3$	βCH$_2$OAc, H	βOAc, H	H$_2$	H$_2$	83
12-Nor-8-hydroxymethylenedrimanone (147)	βCH$_3$	Δ, CHOH	O	H$_2$	H$_2$	83
Kuehneromycin B (148)	βH	βCHO	CHO, Δ	H	O	58
3-Acetoxyisopolygonal (149)	βCH$_3$	H, Δ	CHO	βOH, H	3βOAc	13
12-Nor-8-acetoxydrimanal (150)	βCH$_3$	βCH$_2$OH, H	βOAc, H	H$_2$	H$_2$	50*b*
Laricinolic acid (151)	βCH$_3$	βCOOH, H	CH$_2$	βOH, H	H$_2$	74
Muzigadiolide (152)	H$_2$	O	OH	—	—	21*a*
9-Deoxymuzigadial-12α-methyl acetal (153)	αOCH$_3$, H	αOCH$_3$, H	H	—	—	13
9-Deoxymuzigadial-12β-methyl acetal (154)	αOCH$_3$, H	βOCH$_3$, H	H	—	—	13
Salutarisolide (155)	H$_2$	O	OH	—	—	23*a*
11-Hydroxymuzigadiolide (156)	αOH, H	O	OH	—	—	22
9-Deoxymuzigadial (157)	βCHO, H	CH$_2$	βCH$_3$, H	—	—	15
9-Deoxyisomuzigadial (158)	βCHO, H	CH$_3$, Δ	CH$_3$	—	—	15
9-*epi*-Deoxymuzigadial (159)	αCHO, H	CH$_2$	βCH$_3$, H	—	—	13
Roseolal A (160)	See structure					70*b*
Roseolal B (161)	See structure					70*b*

Roseolide A (162)	See structure	70*a*
Haploporic acid A (163)	See structure	69
Cryptoporic acid F (164)	See structure	66
Cryptoporic acid G (165)	See structure	64

[a] X = *p*-methoxycinnamoyl. [b] X = *p*-hydroxycinnamoyl. [c] X = (*E,E,E*)-2,4,6-octatrienoyl. [d] Epimeric mixture at C12. [e] The authors named this natural product ugandensolide; the structure was confirmed after exhaustive NMR investigations but it is not the same structure as given before for ugandensolide.[21e] [f] X = *p*-nitrobenzoyl. [g] X = benzoyl. [h] X = *p*-hydroxybenzoyl. [i] X = tigloyl. [j] X = angeloyl. [k] X = 2-methylbutanoyl. [l] X = 2-methylpent-2-enoyl. [m] X = 2-methylpentanoyl. [n] X = (*E,E*)-2,4-hexadienoyl. [o] X = (*Z,E,E*)-2,4,6-octatrienoyl. [p] X = 3,4-dihydroxycinnamoyl. [q] X = 6-hydroxy-7-coumaryl, [r] X = fatty acid residue: hexadecanoyl, octadecanoyl, octadecadienoyl, 6-keto-octadecanoyl. [s] X = 7-coumaryl. [t] X = 2,4-dihydroxycinnamoyl. [u] X = isocitric acid ether. [v] X = isofraxidinyl [w] X = 2-acetoxydecanoyl. [x] X = 2-hydroxydecanoyl. [y] X = 2-hydroxyoctanoyl.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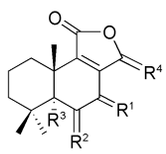
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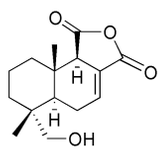
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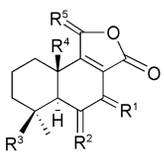
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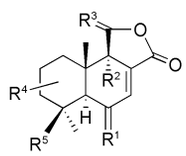
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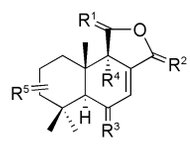
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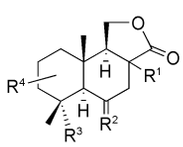
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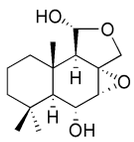
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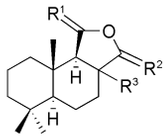
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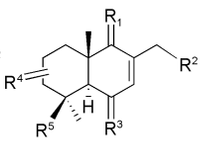
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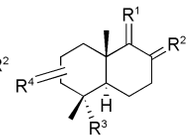
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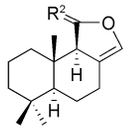
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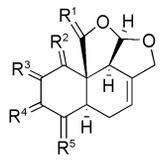
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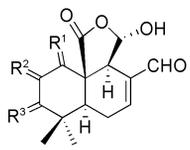
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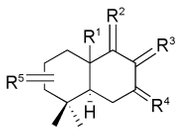
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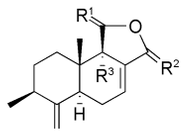
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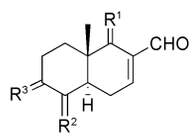
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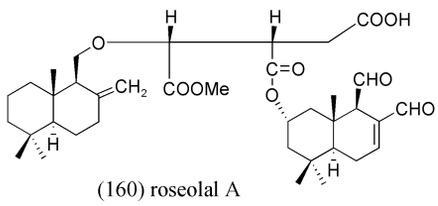
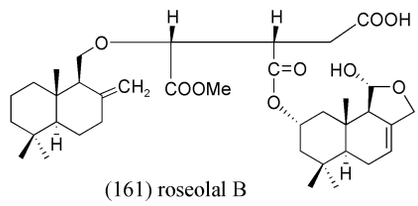

(160) roseolal A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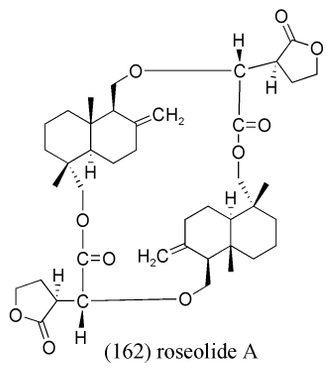
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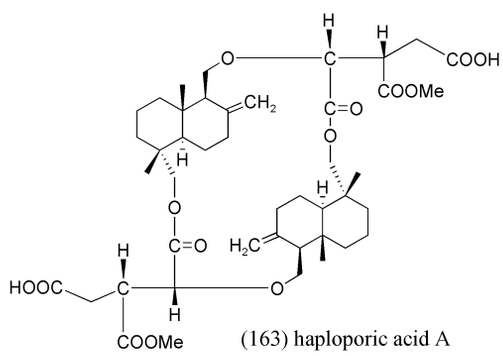
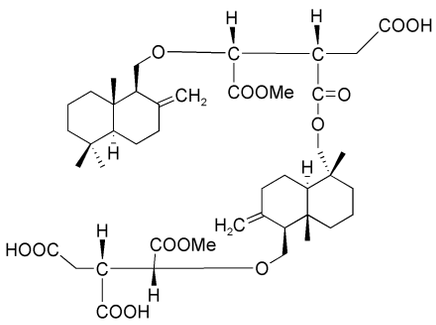
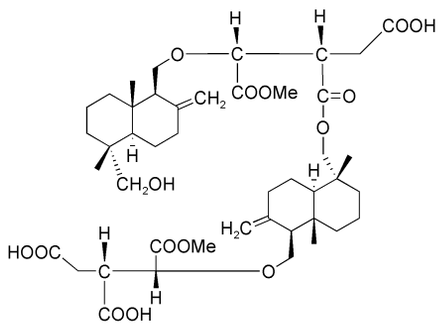
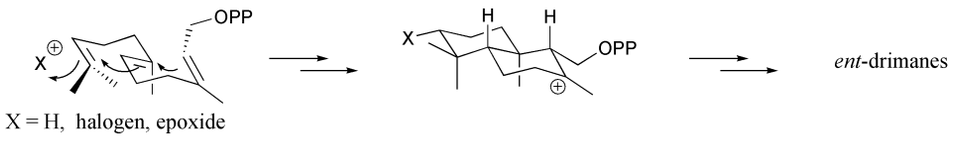
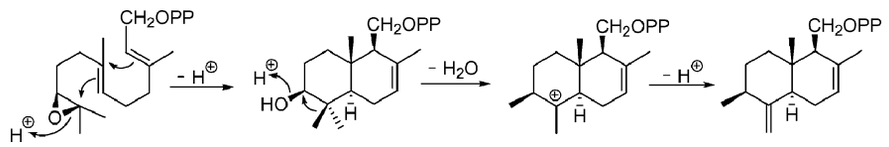

(163) haploporic acid A


(164) cryptoporic acid F

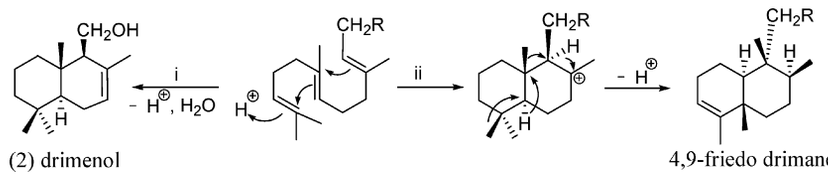

(165) cryptoporic acid G



Scheme 1



Scheme 2



Scheme 3 i: reaction pathway for R = OPP ii: reaction pathway for R = 1,4-dioxygenated aromatic substituent.

sesquiterpenoids of the drimane class. Drimanes are typical sponge metabolites which suggests a dietary origin of these compounds in the molluscs, although *de novo synthesis* has been unambiguously demonstrated. *Doriopsilla areolata*,[84,85] *D. albopunctata*,[85] *Cadlina luteomarginata*.[86–88] *Dendrodoris limbata and D. grandiflora*,[89–91] *D. krebsii*[85] *and D. carbunculosa*[92] and the antarctic nudibranch *Bathydoris hodgsoni*[93] all contain drimanes.

Extracts from temporal gland secretions of the African elephant have revealed for the first time a tobacco-derived drimane in an animal.[94]

Biological marker compounds are being used increasingly to provide information about the processes affecting organic matter in geological environments.[95–98] Some drimanes have been identified in petroleum and are probably derived from a microbial source.[95]

3 Biosynthesis

The vast majority of the sesquiterpenoids are biosynthesized by an enzyme-mediated solvolysis of the pyrophosphate group of farnesylpyrophosphate (FPP), which generates an incipient or actual carbocation at the *tail* position of the farnesyl chain. This process is accompanied by participation of either the central or the terminal double bond leading to six intermediate cations, which gives rise to several classes of sesquiterpenoids.[42,99] In contrast, drimane sesquiterpenoids arise from a cyclization which is initiated by an electrophilic attack, mostly a proton, on the double bond or onto the corresponding epoxide at the *head* position of FPP. Therefore they possess the characteristic features of the A,B ring of many di- and triterpenoids (Scheme 1). For this reason drimanes may be considered as the missing biogenetic link between the lower and the higher terpenoids.[44a,100]

The structure and the stereochemistry of the final product are determined by the relative positions of the double bonds in the conformation of the FPP chain before cyclization. The *trans* ring junction is consistent with the stereoelectronic requirements of a concerted mechanism in which the sequential addition of the non-conjugated double bonds takes place. The chair-chair conformation of the polyenic chain during cyclization can exist in two enantiomeric forms from which the enantiomeric drimane skeletons are derived (Scheme 1). Examples of both are found in Nature,[52g,101] although hardly ever in the same plant or animal. It nevertheless shows the danger in assigning absolute stereochemistry to drimanes based on speculative biosynthetic relationships.

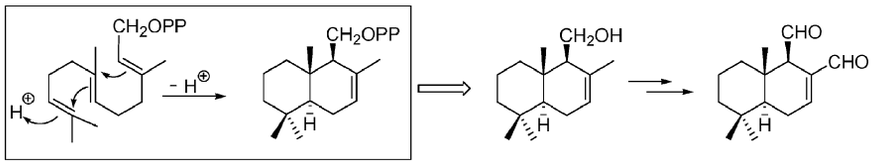
A hydroxyl group at C-3 probably originates from proton attack on an epoxy group positioned between C-10 and C-11 of the FPP chain but it is also proven that a hydroxylation catalyzed by cytochrome P-450 can occur after cyclization.[64,102] It is reasonable to assume that a carbocation is developed upon protonation of the C-3 hydroxyl group followed by dehydration, and that a 1,2 methyl shift accounts for the biogenesis of the rearranged drimanes (Scheme 2).

A prolific class of marine sponge metabolites is of mixed sesquiterpenoid and aromatic biosynthetic origin. They are related to drimane terpenoids biogenetically through an interesting *friedo*-rearrangement (Scheme 3, reaction path ii). These compounds are usually named rearranged drimanes, although their basic skeleton includes twenty one C atoms instead of fifteen.[76,103,104] When this rearrangement of farnesylated hydroquinones and/or quinones does not take place, the natural product has the drimane skeleton but with an aromatic substituent at C-11 (Scheme 3, reaction path i).[105,106]

The co-occurrence of drimanes and *nor* drimanes in some plants may arise through decarboxylation of drimanic carboxylic acids.[107]

Stable isotope incorporation studies have been used to investigate the origin of drimanes in nudibranches. It turned out that *de novo* synthesis *via* the classical acetate/mevalonate pathway had taken place.[86–88,91,108,109]

The biosyntheses of drimanes involve FPP, which is cyclized and converted to the final products by hydrolysis and oxidation. It is possible that only one enzyme is involved in the cyclization step that converts the FPP to drimenyl pyrophosphate, and because many organisms produce the cyclization substrate (FPP), cloning and expression of the cyclase gene from *P. hydropiper* in *E. coli* would enable production of drimenol by fermentation (Scheme 4).



Recombinant *E. coli* expressing cyclase gene (2) drimenol (3) polygodial

Scheme 4

Subsequent oxidation *via* cheap synthetic methods may then lead to useful products like the antifeedant polygodial. Expression of the cyclase gene, transferred to crop plants, could give rise to production of drimenyl pyrophosphate in the plants, which may be converted to antifeedants within the secondary metabolite system, provided that such an oxidative pathway is already present.[110] It was demonstrated in callus and suspension cultures of *P. hydropiper* that drimenol and especially the antifeedant polygodial were accumulated in *vitro.* Feeding experiments with 3*R*-[2-^{14}C]-mevalonate showed that the apparent synthetic ability for these sesquiterpenoids in callus was up to two-fold greater than in the parent plant.[111*a*] Drimenol cyclase was obtained from the homogenates of cultured cells of *P. hydropiper* and purified 2850-fold in a three-step procedure.[111*b*] The content of polygodial in the mixture of metabolites produced in cell suspension cultures of the liverwort *Porella vernicosa* was similar to that in field-grown plants but the yield of the crude extract from the suspension was higher.[35*b*]

4 Analysis

Several drimanic sesquiterpenoids are interesting by virtue of their biological activities. However, extensive biological testing is often not possible due to the limited availability of metabolites. Therefore these natural products have to be isolated preferably from renewable sources, *e.g.* plant crops with improved production of metabolites, plant tissue cultures or fermentation liquids. A prerequisite for this kind of study is the availability of a simple, reproducible, sensitive and fast quantitative determination of the compounds of interest, and methods to establish their absolute stereochemistry and optical purity. Several isolation procedures and analytical methods have been developed[30*a*,32,112–115] and X-ray crystallography and high field NMR applications have been successfully applied to determine the absolute configuration of drimanes either as such[12*a*,33*d*,116,197] or after transformation into a well-known drimane sesquiterpene.[81,117,118] To ensure that alkoxy acetals, sometimes found in extracts from natural material, are not artefacts the extraction and separation procedures had to be repeated without using alcohols.[28,119]

5 Biomarkers

Drimane sesquiterpenoids do not occur widely in Nature and therefore drimanes are useful as chemosystematic markers. Within the Canellaceae drimanic compounds constitute a neat unifying theme and a close affinity of the South American genus *Capsicodendron* with the African genus *Warburgia* rather than the Madagascarian genus *Cinnamosma* has been established.[20*a*] Infraspecific variation was found in *Pseudowintera colorata*, endemic to New Zealand, leading to two chemotypes: a mixed type with similar levels of polygodial and 9-deoxymuzigadial and a type with polygodial and very low levels of 9-deoxymuzigadial.[32*a*] The occurrence of polygodial classifies *Porella* species as a pungent type and differences in the chemical constituents make a further classification possible.[35*a*,36*a*,37,41–43,45] The existence of different chemical races of *P. canariensis* has been suggested based on their secondary metabolites.[38] Drimanic compounds are reported occasionally as biomarkers in geochemical research especially in petroleum investigations.[95–98,120,121]

6 Biological activity of drimanes

Tropical plants are exposed to attack by various parasites throughout the entire year and this has led to efficient built-in defense mechanisms. For this reason they offer a rich source of secondary metabolites possessing attractive biologically active properties including antibacterial, antifungal, antifeedant, plant-growth regulatory, cytotoxic, phytotoxic, piscicidal and molluscicidal effects.

6.1 Antifungal, antibacterial and antiviral activity

Bioassay-guided isolation has afforded many antifungal phytochemicals including the well-known drimanes polygodial (3), warburganal (4), and muzigadial (5) (Fig. 1).[47*a*,122,123] Polygodial occurs in roots, barks and leaves of several trees, in plants, liverworts, sponges and nudibranches. Polygodial (3) may be a promising antifungal agent against yeastlike- and filamentous fungi because of its effectiveness compared to potent antibiotics such as actinomycin D, rifampicin and amphotericin B (MIC's < 25 μg ml^{-1}). Polygodial showed an MIC of 1.56 μg ml^{-1} and an MFC of 3.13 μg ml^{-1} against *Saccharomyces cerevisiae*. Ca^{2+} did not protect the yeast from polygodial[124] as stated, but enhanced the MIC, as did EDTA.[125] Moreover, the combination of polygodial with very weak antifungal compounds including anethole, safrole, methyleugenol, maesanin and sorbic acid enhanced the activity significantly, sometimes up to 64-fold.[124–132] Several fungicides were applied together with polygodial and their activities were greatly enhanced (32–128-fold).[132*b*] A similar effect was found upon addition of polygodial to the food preservative EDTA.[132*c*] Surprisingly isotadeonal (6), the C-9 epimer of polygodial, which has been reported[133] to be devoid of antimicrobial activity exhibits only a slightly lower antibacterial (MIC for Gram-positive organisms 5–20 μg ml^{-1}) and antifungal activity (MIC 2–10 μg ml^{-1}) compared to polygodial.[134] Polygodial possesses antibacterial activity against the Gram-negative *Salmonella choleraesuis*, the cause of bacterial food-borne illness, with the minimum bactericidal concentration (MBC) of 50 μg ml^{-1} (0.17 μM).[135] Warburganal (4) also showed a related behaviour.[126] Muzigadial (5) was tested against *Candida albicans* and proved as active as amphotericin B (MIC 0.39 μg ml^{-1}), but after metabolism the activity was strongly decreased.[136,137] Extracts of the East African genus *Warburgia* show a broad spectrum of antimicrobial activity and warburganal (4), muzigadial (5), polygodial (3), mukaadial, ugandensidial (7) and isotadeonal (6) seem to be responsible for this activity.[119] A number of newly isolated drimanes have been tested for activity. Peniopholide (73) was active against *Phellinus tremulae*, one of the fungi causing trunk rot in aspen.[75]

Kuehneromycins A (132) and B (148) showed weak activity in the agar diffusion assay against a panel of bacteria and fungi.[58] Natural substances from the flora in Guadeloupe afforded canellal (5) (also known as muzigadial), which inhibited the growth of *Mycobacterium tuberculosis, M. avium* and *M. kansasii* for 99% at 100 μg ml^{-1}.[16*b*] Muzigadial (5) was tested against several bacteria and its activity was very weak compared to the antibiotic neomycin.[24] 7-Drimene-3,11,12-triol (93) and isodrimenediol (106) displayed moderate antimicrobial activity against *Staphylococcus aureus* (MIC: 10 μg ml^{-1}) and *Sporobolomyces salmonicolor* (MIC: 5 μg ml^{-1}).[64] Metabolites of the sponges of the genus *Dysidea* all showed a weak inhib-

ition (IC_{50} 90–145 μM) of the bioluminescence reaction of *Photobacterium leiognathi*, a symbiotic luminous bacterium of tropical fish,[80,83] but polygodial (3) exhibited a potent inhibition with an IC_{50} = 11.4 μM.[83] Cryptoporic acid H and isocryptoporic acids H (99) and I (100) were tested against some bacteria but proved to be inactive.[63]

A spontaneous outbreak of downy mildew in sunflower fields led to the accumulation of the phytoalexin scopoletin as self defence.[138]

Epi-albrassitriol (90) was moderately active in *in vitro* tests against influenza A- and myxovirus (MIC 44.4 μg ml^{-1}; maximum tolerated dose 133.3 μg ml^{-1}).[56a] Kuehneromycin A (132) proved to be a non-competitive inhibitor of the reverse transcriptase of avian myeloblastosis virus (IC_{50} 75 μg ml^{-1}) and Moloney murine leukemia virus (IC_{50} 10 μg ml^{-1}) and a weak inhibitor for HIV-1 reverse transcriptase (185 μg ml^{-1}).[58] A search for inhibitors of RNA-directed DNA-polymerases (reverse transcriptases) of the human immunodeficiency viruses revealed new biologically active compounds from fermentations of *Mniopetalum* sp. 87256, mniopetals A–F. Mniopetals A–D (133–136) had inhibition effects on the reverse transcriptase of avian myeloblastosis virus and Moloney murine leukemia virus at IC_{50} values of 41–77 μM and 1.7–7 μM, respectively. The reverse transcriptase of HIV-1 was moderately inhibited. In addition to the RNA-directed DNA-polymerase the mniopetals, with the exception of mniopetal E (137), inhibited the RNA-directed RNA-polymerase of vesicular stomatitis virus with IC_{50} concentrations of 47–64 μM.[139] The antibacterial and antifungal activities of mniopetal A-D (133–136) were quite weak with the exception of *Streptomyces* sp., which showed MIC values of 2, 0.22, 2.4, and 1.1 μM.

6.2 Cytotoxic activity

In the course of research programs designed to discover cytotoxic compounds, some drimane sesquiterpenoids were found to be active. Isotadeonal (6) showed a cytotoxic activity towards hamster lung fibroblasts in monolayer culture (cell line V79) with an IC_{20} of 4.3 μM, compared with 14 μM for mercury chloride. The very low activity of polygodial (3): 39 μM was unexpected.[140] Cytotoxic activity towards Ehrlich ascites tumor cells (ECA) and lyphocytic leukemia mouse L1210 cells revealed a 50% growth reduction at 10–20 μg ml^{-1} for the above-mentioned dialdehydes.[134] The nonmutagenicity of polygodial and isotadeonal in the Ames Salmonella/microsome assay was confirmed by the V79/HGPRT assay.[134,141] Insulicolide A (42), a marine isolate of the fungus *A. versicolor*, displayed significant cytotoxicity against HCT-116 human colon carcinoma cells (LC_{50} 0.44 μg ml^{-1}), comparable with the antitumor agent etoposide, and exhibited moderately selective cytotoxicity toward a panel of renal cell lines.[57] The dimeric drimane roseolide A (162) had little activity against P388 leukemia cell growth.[70a] The lactone drimenin was moderately, but reproducibly, toxic towards DNA-repair-deficient mutants of *Saccharomyces cerevisiae* (IC_{12} 200 μg ml^{-1}).[39] Albicanol (8) exhibited strong inhibitory effects on the Epstein–Barr virus early-antigen activation, induced by tetradecanoyl phorbol-13-acetate (TPA), an *in vitro* short-term assay for antitumor promoting agents. At a mol ratio of 100 (albicanol/TPA) 80% inhibition was observed using a 32 nanomolar solution of TPA. It also suppressed significantly an *in vivo* carcinogenesis on mouse skin. Upon treatment with 85 nanomol a reduction of 20–30% was found.[142] Other drimanes were also tested in this bioassay and showed potent effects.[143] Cryptoporic acids scavenge active oxygen species and prevent the formation of lipid peroxides and thus are useful as medicaments. In rats and mice, being weekly treated with cancer inducing agents, which were fed on a diet with cryptoporic acid E from the beginning, the incidence and the number of tumors per animal were reduced by 31% and 75%, respectively. Intrarectal deoxycholic acid-induced colonic mucosal ornithine decarboxylase activity was also significantly lowered in cryptoporic acid E fed animals, which demonstrated an antipromoting activity against colon carcinogenesis.[144] Cryptoporic acids A–G strongly inhibited the release of superoxide anion radical from guinea-pig peritoneal macrophage induced by the stimulant FMLP at a concentration of 0.05–25 μg ml^{-1}. A 5.9 μM solution of cryptoporic acid E gave a reduction from 73% to 20% in the tumor promoting activity of okadaic acid in two-stage carcinogenesis experiments on mouse skin whereby the number of tumors decreased from 4.2 to 0.5.[66,145,146] Hydroxypolygodials and their acetals, produced *via* fungal hydroxylation, showed strong activity against a panel of cell lines from human and murine origin. Interestingly, the deprotection of the acetal moiety led to lower activity.[113] Dendocarbins A–N (64)–(66), (84), (67), (22), (68), (69), (21), (33)–(36), and (77) respectively, new drimanes from *Dendrodoris carbunculosa*, were tested against sensitive murine P388 cells and against adriamycin- and vincristine-resistant P388 cells and IC_{50} values between 2.5 and 25 μg ml^{-1} were ascertained.[92] Uvidin A (175) inhibited the incorporation of ^{3}H-thymidine into HL-60 human leukemia cells by 97% and 21% at concentrations of 50 μg ml^{-1} and 0.05 μg ml^{-1}, respectively.[62a] Uvidin B gave 61% and 0% inhibition in the same test. Kuehneromycin A (132) exhibited cytotoxic properties on HeLa S3 and 3T3/MMSV cells (18–20 μM) and Kuehneromycin B (148) on L 1210 and HeLa S3 (22 μM).[58] In the Ames test for mutagenicity no induction of revertants of *S. typhimurium* TA 98 and TA 100 could be observed with 100 μg of the mniopetals A–D (133–136), isolated from the culture filtrate of *Mniopetalum* sp., per disc. Cytotoxic activities of mniopetals towards different mammalian cell lines were observed at IC_{50} values of 20–170 μM. The most sensitive cell line was HL-60, partly due to a lytic action on the cytoplasmic membranes.[139]

6.3 Plant-growth activity

Canella winterana afforded 14 drimanes, isolated from the leaves, of which eight exhibited phytotoxicity in a *Lemna minor* bioassay with IG_{50}'s of 8–100 μM. The 11,12-dialdehyde was the essential moiety, either as such or as its acetal, and compounds with an 11β-aldehyde showed greater activity than the corresponding α-isomers.[13,14] All cryptoporic acids completely inhibited elongation of the second coleoptile and germination of rice in the husk at a concentration of 200 ppm.[66] Polygodial (3) and isotadeonal (6) showed algaecidal activity against *Chlorella vulgaris* at MIC's of 30 μg ml^{-1} and 50 μg ml^{-1}, respectively.[134] Chinese cabbage leaves (*Brassica pekinensis* L.),[147] bean seedlings (*Vicia faba* Moench)[148] and oat plants (*Avena sativa* L. cv. 'Dula') showed phytotoxic effects after 24 h when treated with a 0.1% polygodial solution in 50% aqueous ethanol.[149] *Lactuca sativa* and *Setaria italica* were damaged by polygodial (3) and warburganal (4) with an IC_{50} of 10 μM.[150]

6.4 Piscicidal, molluscicidal and anthelmintal activity

Albicanol (8) and its acetate, isolated from Dryopteris species proved to be piscicidal compounds to killie-fish (*Oryzyas latipes*; medaka) at a median tolerance limit of 3.7 and 4.3 ppm respectively, after 24 h.[34b,151] Cinnamodial was active against adult *Biomphalaria glabrata* and embryos aged less than one day at 10.0 and 100 ppm, respectively.[20b] Polygodial inhibited an *in vitro* nematode larval motility assay against the sheep parasite *Trichostrongylus colubriformis* (IC_{50} 0.07 mg ml^{-1}).[152] A mixture of 2,3-substituted alkoxycarbonyl isodrimeninols (46–49) is used in Sudan as an anthelmintic agent.[48] Mukaadial and cinnamolide proved to be active when tested *in vitro*, using tissue cultures and *in vivo* using mice against *Trypanosoma congolense, T. evansi* and *T. brucei*.[153a] Synthetic drimanic quinone derivatives showed *in vitro* activity two to ten times higher than benzimidazole, the medicine of choice for the

treatment of American Trypanosomiasis, caused by *Trypanosoma cruzi*.[153b]

6.5 Taste and neurotransmission activity

Polygodial (3) was isolated as the active compound from the pungent principles of *P. hydropiper* L., a well-known ingredient in Japanese cuisine. Because it is a biologically active natural product, pungency may be a guide for potential activity. Human tongue pungency was determined for polygodial (0.1 μg) and its 9α-epimer (5 μg) and for warburganal (4) (0.5 μg) and its (synthetic) 9α-epimer (8 μg). The affinity for specific [^{3}H]-resinifereratoxin binding sites in rat spinal cord preparations was in line with the observed pungency.[150] Cinnamodial (7), cinnamosmolide, and drimenol (2) inhibited completely the specific binding of [^{3}H]-resinifereratoxin at concentrations of 0.6, 1.5, and 13.2 μM, respectively.[154,155] These results suggest that unsaturated dialdehydes exercise their pungency by interacting with vanilloid receptors on capsaicin-sensitive sensory neurons. Polygodial or a polygodial-containing plant extract added to mint flavourings enhanced the coolness and increased the duration of perception. It suppressed bitter flavours and when it was added at levels of 0.1–100 ppm it reduced the aftertaste caused by artificial sweeteners.[156] All cryptoporic acids isolated from the fruit body of *C. volvatus* had an intensely bitter taste.[66] Isodrimeninol, the major sesquiterpene isolated from *Dendrodoris carbunculosa* was found to have a sharp peppery taste.[92] The pungency of unsaturated drimanic dialdehydes indicates that they stimulate sensory neurons and therefore studies were undertaken on human neuroblastoma SH-Sy5Y cells as a model. Polygodial (3), warburganal (4) and isotadeonal (6) gave after 20 min incubation, an increase in membrane permeability of 20% at concentrations of 2.5 μM, 3.9 μM and 180 μM, respectively.[157] The aforementioned results gave rise to a study of the inhibition of a series of CNS receptors. Polygodial and its 9α epimer isotadeonal (6) gave 50% inhibition at 0.46 μM and 5.3 μM.[158] Tests with polygodial and isotadeonal were undertaken on SH-Sy5Y cells with the aim of investigating a possible relationship between pungency and [Ca^{2+}] concentration. Polygodial induced an increase in [Ca^{2+}] at 0.1 μg ml^{-1}, but isotadeonal only at 10 μg ml^{-1}, so pungency and the effect on [Ca^{2+}], which is in part mediated by mobilization of inositol phosphate, showed a relationship.[159] In the same test system, polygodial showed a significant [^{3}H]-noradrenaline release between 0.1 and 0.5 μg ml^{-1} (equal to 0.4–2 μM) with a maximum effect (40% release) at 0.2 μg ml^{-1}, which is dependent on a polygodial-induced increase in [Ca^{2+}].[160]

6.6 Antifeedant and insecticidal activity

Despite an enormous expenditure on agrochemicals worldwide there is still considerable loss of crops owing to damage caused by feeding insects. Much interest has been devoted towards behaviour-modifying chemicals that can be used in integrated pest control management programmes.[161] The probing and feeding behaviour of aphids can result in uptake of viruses from infected plants and subsequent transmission to healthy plants. *Myzus persicae*, settled on leaves of Chinese cabbage, grown in a [^{14}C] CO_2 atmosphere, showed that significant quantities of plant sap are taken in after 20–30 min, after the aphid has had time to penetrate the plant's deeper tissues.[162] Video recordings of *M. persicae* on Chinese cabbage (*Brassica pekinensis)* in a choice test revealed that the insects spent less time and make fewer penetrations on the side treated with a 0.1% solution of polygodial in 50% aqueous ethanol, but in a no-choice situation there was no discrimination.[148,163–165] It was shown that aphids detect polygodial upon contact with sensilla located on the antennal tips and repellent response occurs as a negative chemotropotaxis following unilateral simulation of these sensilla.[166] Several drimanic compounds were tested for their deterrence to nymphs of *M. persicae* and *Aphis gossypii*. Warburganal and polygodial were highly active and from 24 h interval observations and ablation studies it was concluded that nymphs of both detect polygodial with contact chemosensilla at the tips of their antennae.[167] Two cereal aphid species, *Sitobion avenae* and *Rhopalosiphum padi*, were tested on oat leaves treated with polygodial, applied as a 0.1% solution in ethanol, and the calculated antifeedant indexes (AI = C − T/C + T) were 0.6 and 0.7, respectively.[149] Polygodial (3) (AI 0.92), isodrimenin (AI 0.87), muzigadial (5) (AI 0.82), warburganal (4) (AI 0.79) and isotadeonal (6) (AI 0.51) tested on potato leaf discs at 5.0 mM against Colorado potato beetle larvae, *Leptinotarsa decimlineata*, exerted moderate to potent feeding inhibition.[168] Drimanes were tested for their feeding inhibiting activity in larvae of *Pieris brassicae* applied to leaf material of the host plant *Brassica oleraceea* L. Isodrimenin and its synthetic 4,4-di*nor* congener proved to be most potent with AI's of 0.88 and 0.77, respectively. Polygodial was moderately active (AI 0.55) and warburganal was less active (AI 0.24).[169] Polygodial and 9-deoxymuzigadial (157), isolated from *Pseudowintera colorata*, showed antifeedant activity at rates from 0.4–3.0 mg g^{-1} wool against the webbing clothes moth, *Tineola bisselliella*, and *Anthrenocerus australis*, a carpet beetle among the most resistant to insecticides. This result is comparable with the antifeedant activity of azadirachtin.[32b,170]

Predation by a spongivorous fish, *Pomacanthus imperator*, was deterred by 7-deacetoxyolepupuane (118), isolated from *Dysidea* spp.[83] Isodrimeninol from *Doriopsilla albopunctata* showed no antifeedant activity on *Carassius auratus* at 300 μg cm^{-2}.[85] Uvidin A (175) was moderately active against *S. littoralis* and *L. decemlineata*.[62a] Field tests showed that natural polygodial, extracted from *P. hydropiper* using ethyl ether, was an effective antifeedant against aphids. The half-lives of polygodial were 35, 34 and 16 days in air, under light and at temperatures of 55–60 °C, respectively.[171]

6.7 Vascular related activity

Endothelins are implicated in several human disease states. Drimanic lactones with an ester functionality at C-6 (15), (54–58) were tested and revealed IC_{50} values of 20–150 μM for the inhibition of ET-1 binding in the rabbit and human ET_A and ET_B receptor assays.[55b,172,173] Polygodial inhibited endothelin-1 induced contractions in rat portal vein at 300 μM but other agonists were inhibited at much lower concentrations.[174] Effects of drugs on vasorelaxant concentration–response curves of polygodial in rings of rabbit or guinea-pig pulmonary arteries with and without intact endothelium showed EC_{50} values between 0.4 and 2.9 μM. It was concluded that the vasorelaxation of polygodial is (partly) dependent on the release of nitric oxide (NO) or an NO-derived substance from the vascular endothelium and is not related with the opening of K^+ channels.[175] The relaxation produced by polygodial in the rabbit corpus cavernosum *in vitro* showed an EC_{50} value of 46.7 μM. The relaxation was inhibited by the nitric oxide (NO) synthase inhibitor L-NOARG for 79%, so the mechanism was partly dependent on the release of NO or a NO-derived substance.[176] RES-1149-1 (15) and RES-1149-2 (54) are endothelin type B (ET_B) receptor antagonists and selective inhibition by polygodial was found at IC_{50} of 1.5 μM and 20 μM, respectively. RES-1149-1 (15) also inhibited the increase of intracellular Ca^{2+} elicited by 1 nM ET-1 in cells expressing human ET_B receptor, but not in the case of cells expressing ET_A receptor.[177]

6.8 Toxicity assays

Uvidin A (175) showed an LC_{50} value of 48.8 ppm in the brine shrimp, *Artemia salina*, lethality assay.[62a] The validity of this system was tested in phosphate buffer at pH 7.2 and in cell culture medium, both of which are used in assays employing

mammalian cells. Polygodial and isotadeonal had LC_{50} of 0.75 and 12.5 μg ml^{-1}, respectively.[178] Polygodial is not toxic to *Myzus persicae*, even when applied at 0.8 μg per aphid but 1.0 μg applied to newly moulted *Aphis fabae* did increase mortality (50% survival after 15 days for treated insects and 28 days for solvent controls).[148] 7-Deacetoxyolepupuane (118) caused necrosis and damage to *Cacospongia* sp. by destroying its basal portions. This was tested in field experiments with agar strips containing this drimane in natural concentrations.[83]

6.9 Antiallergic, antiinflammatory and antinociceptive activity

Extracts of *Drimys winteri* inhibited carrageenan-induced paw oedema formation in rats in a dose-dependent manner, with an ID_{50} value of 49 mg kg^{-1}. When assessed in rats actively sensitized to ovalbumin (OVO) the oedema caused by OVO was significantly inhibited by the extract with an ID_{50} of 65 mg kg^{-1}. These results demonstrate the clear oral properties of the active principle present in the bark of *D. winteri*.[179] Polygodial, isolated from the bark of *Drimys winteri*, a plant widely used in folk medicine in Brazil, inhibited the contractions in the guinea pig ileum *in vitro*, induced by several mediators associated with the aetiology of respiratory diseases. It was shown that pre-incubation with polygodial (5–128 μM) resulted in a concentration dependent inhibition of acetylcholine, histamine and bradykinin with IC_{50} values of 87, 42, and 13 μM, respectively. When analyzed in guinea-pig trachea polygodial also caused marked inhibition at concentrations of 5–170 μM.[180,181] A long-lasting dose-related antinociception was produced when assessed against acetic acid, capsaicin and formalin in mice as well as against bradykinin and Substance P in rats. The calculated ID_{50} values were in the range 0.8–2.6 mg kg^{-1}.[182] Polygodial given intraplantarly, systemically or by spinal or supraspinal sites produced antinociception in mice, mainly preventing the neurogenic pain produced by formalin and capsaicin. This effect was not affected by GABA antagonists or potassium channel blockers and significantly attenuated by opioid antagonists.[183] Drimanial (14) and 1-β-(*p*-methoxycinnamoyl)polygodial (12), both also isolated from *Drimys winteri*, revealed ID_{50} values of 11.0 and 16.0 μmol kg^{-1}, i.p. administered, compared with 3.6, 125, and 133 μmol kg^{-1} for polygodial, acetaminophen and aspirin, respectively.[25a,26] In the formalin-induced licking test drimanial caused a dose-related inhibition of the neurogenic (0–5 min) and inflammatory (15–30 min) phases with ID_{50} of 66 and 47 μmol kg^{-1}, respectively. The antinociceptive action of drimanial (14) was not reversed by the non-selective opioid antagonist naloxone so it seems likely to be independent of interaction with opioid pathways. [^{3}H]-Glutamate binding in cerebral cortical membranes from mice was inhibited by drimanial with an IC_{50} value of 4.39 μM.[184] A long-lasting antiinflammatory and antiallergic effect was observed when polygodial was administered systemically to rats and mice. Inhibition of phospholipase A2 and neuropeptide release seem to account for the activity.[185]

6.10 Miscellaneous

Effects on *de novo* formation of cholesterol were observed in a HEP G2 cell assay of 6-*epi*-albrassitriol (90) and 12-hydroxy-6-*epi*-albrassitriol (91) to a level of 40% and 30% inhibition at a concentration of 10^{-8} M.[56a]

The diamondback moth *Plutella xylostella* is a world-wide pest of most crucifers and has shown a high ability to develop resistance to almost all groups of insecticides.[186] Additional management strategies such as the use of oviposition inhibitors might retard the development of resistance. It was found that polygodial and 13,14 di*nor*-polygonone inhibited the ovipositon by 91% and 88%, respectively in a dual choice test.[187]

Two 11-*nor* drimanes kuehneromycin B (148) (IC_{30} 3–40 μM) and panudial (138) (IC_{30} 6 μM) showed strong inhibition of bovine and human platelet aggregation stimulated with different inducers.[58,60b]

Polygodial (3), 11α-acetoxyconfertifolin (32) and 7,8-dihydrodrimenin (81) were moderate inhibitors of Na^+/K^+ ATPase (IC_{50} 82, 98, and 45 μM, respectively) and also 7,8-dihydrodrimenin (81) weakly inhibited PLA_2 enzyme with an IC_{50} of 113 μM.[83] Ethanol-induced gastric mucosal lesions in rats were potently inhibited by the methanolic extract of *Tasmannia lanceolata*. Bioassay-guided separation gave polygodial, polygodial 12α-acetal (63) and its 12β-acetal and methylisodrimeninol (82) as active principles. A dose of 0.2 mg kg^{-1}, *per os* gave inhibitions of 92.6, 53.8, 62.1, and 39.6%, respectively. Drimendiol (89) and some related semi-synthetic sesquiterpenes showed inhibitions of 27.6, 47.7, 37.8, and 29.1%, respectively at a dose of 1.0 mg kg^{-1}, *per os*.[188] Polygodial (0.2 mg kg^{-1}, *per os*) increased the amount of reduced glutathione in gastric mucosa of ethanol treated rats and the gastroprotection was attenuated by pretreatment with *N*-ethylmaleimide and ruthenium red. These results suggested that vanilloid receptor-mediated effects are involved in the protective effect of polygodial.[189] Mniopetals A (133), B (134), and D (136) caused 100% lysis of erythrocytes at concentrations of 10, 11, and 11 μM, respectively.[139]

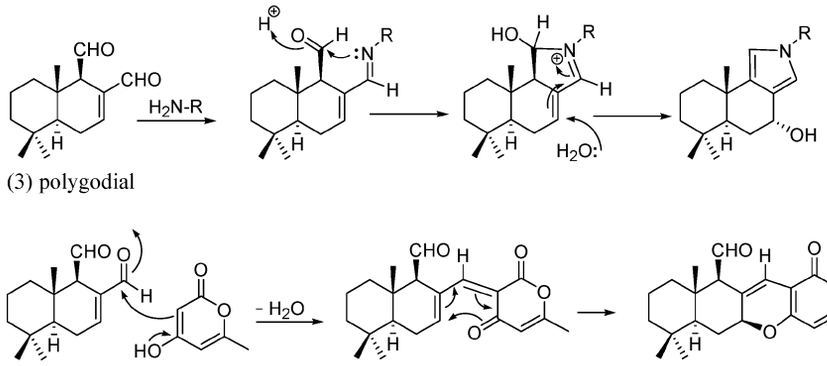
A highly potent attachment-inhibition was observed for the blue mussel *Mytilus edulis galloprovincialis* upon treatment with polygodial compared to cupric sulfate. The activity was increased 4-fold when used in combination with sorbic acid, anethole, and indole. The combination of 0.04 mg cm^{-2} with sorbic acid maintained activity after two months.[190]

7 Mode of action

Reactive oxygen species (ROS) are highly toxic oxidants causing lipid peroxidation and they can also induce disruption of plasma membrane phospholipids when not suitably eliminated. *S. cerevisiae* cells produced ROS upon polygodial treatment, which could be detected with a fluorescent probe. The cytoplasmic and mitochodrial glutathione level, one of the cellular defenses against oxidative stress, was decreased substantially. This polygodial-mediated depletion may result from a direct interaction between its enal moiety and the sulfhydryl group of the cysteine in glutathione by a Michael-type reaction.[191] Polygodial inhibits mitochondrial ATPase, in this way eliminating a major source of ATP and, because the plasma membrane is disrupted, an influx of protons collapse the proton motive force and inhibition of nutrient uptake coupled to this gradient. The internal pH decreases, which inhibits enzymes as they are shifted from their pH optima. Recovery of cells is possible by pumping protons out of the cell *via* the plasma ATPase, Pma1p, at the cost of large amounts of ATP. The combination of ATP consumption stimulated by proton permeability and ATPase synthase inhibition gives a decrease in ATP to levels below those necessary for normal metabolic functions.[123] The ability of polygodial to function as a nonionic surfactant may disrupt the lipid–protein interface and a reaction with sulfhydryl groups of plasma membrane H^+-ATPase may be important for inhibition.[192]

The unsaturated dialdehyde functionality and its reactivity towards biological nucleophiles is considered to be responsible for the general antibiotic properties, hot taste to humans, fish toxicant and antifeedant activity of these compounds. Structure–activity relationships of naturally occurring enedials with antifeedant activity against *Spodoptera* species have been extended *via* synthesis and bioassay with a series of compounds. A three-pronged mode of substrate binding *via* aromatic pyrrole formation, Michael addition of free sulfhydryl moieties and van der Waals interactions of the A ring of drimanes has been postulated to account for these observations.[193]

A thorough study was undertaken under biomimetic con-



Scheme 5

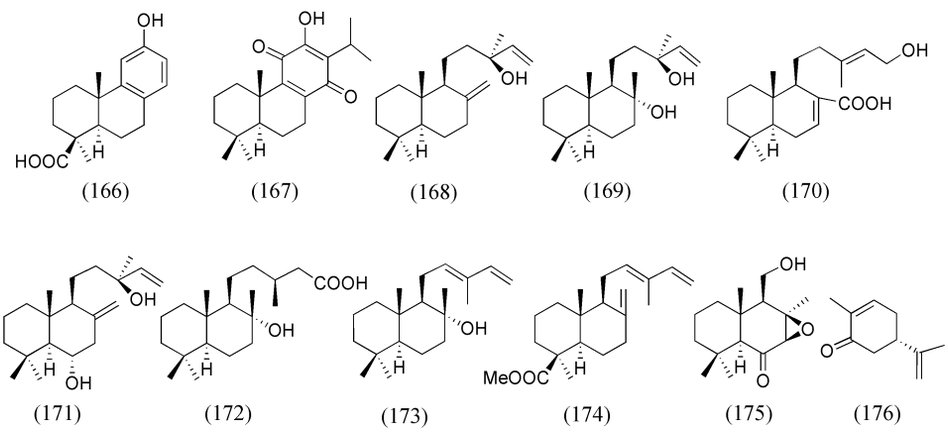


Fig. 2

ditions with amino acids, triacetic acid lactone and amines (Scheme 5).[150] Polygodial (3) reacted more than 200 times faster than its C-9 epimer isotadeonal (6) with lysine. This dramatic difference was expected since polygodial easily forms pyrroles, in contrast to isotadeonal (6) due to the larger distance between the aldehyde carbons of the latter.[194,195]

Polygodial was clearly reactive towards thiols since alanine, lacking the sulfhydryl group in cysteine, reacted considerably slower than the latter ($T_{1/2}$ 7.4 h and 0.28 h, respectively). Warburganal proved to be less reactive than polygodial although it is the better antifeedant of the two, so the suggestion that reactions with primary amines are responsible for antifeedant activity is contradicted. The natural triketide triacetic acid lactone is a bi-functional nucleophile and the mode of reaction with polygodial was studied.[196] An attack of the nucleophilic C-2 of the lactone on the unsaturated aldehyde carbon followed by an electrocyclic ring closure gave the adduct. Again, polygodial was the most reactive, and the results resemble those shown before.

8 Synthesis of drimane sesquiterpenoids

8.1 Introduction

The biologically active drimane-type sesquiterpenes have been an attractive target for organic synthesis since in most cases only minute amounts are available from natural sources. A classification of the numerous recent syntheses based on the starting materials and/or reaction types, is shown below.

8.2 Synthesis of drimanes by transformation of natural products.
8.3 Synthesis of drimanes by enzymatic resolution.
8.4 Synthesis of drimanes by cationic polyolefin cyclization.
8.5 Synthesis of drimanes from decalones.
8.6 Synthesis of drimanes by radical cyclizations.
8.7 Synthesis of drimanes by cycloaddition reactions.

8.2 Synthesis of drimanes by transformation of natural products

The semisynthesis of drimanes from other natural products gives the natural optically active forms. Drimanes have been prepared from the following terpenoids (+)-podocarpic acid (166), (+)-royleanone (167), (+)-manool (168), (−)-sclareol (169), zamoranic acid (170), (+)-larixol (171), (−)-labdanoic acid (172), (+)-*cis*-abienol (173), (+)-*trans*-communic acid (174), (−)-drimenol (2), (+)-uvidin A (175), (+)-albicanol (8) and (+)-carvone (176) (see Fig. 2).

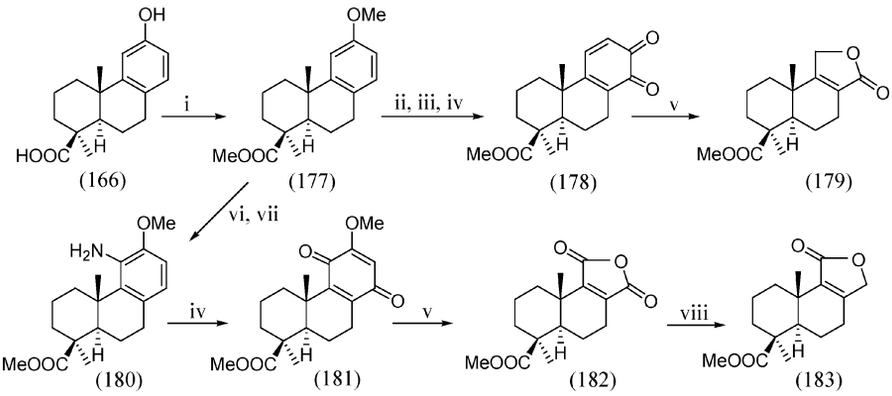
Intermediates have been prepared *via* oxidative procedures to remove extra carbon atoms. In the course of their studies on the conversion of (+)-podocarpic acid Cambie *et al.*[198] achieved a short synthesis of the C-13 oxidized congeners of (+)-confertifolin (179), (+)-winterin (182), and (+)-isodrimenin (183), albeit in low yield (see Scheme 6). These compounds are useful starting materials for the preparation of chiral analogues of biologically important drimanes.

(+)-Podocarpic acid (166) was converted *via* the *o*-quinone (178) to butenolide (179). The corresponding *p*-quinone (181) was synthesized *via* the amino derivative (180), and cleaved to the anhydride (182) in 35% yield. Reduction of the anhydride with lithium aluminium hydride afforded butenolide (183) in 63% yield.

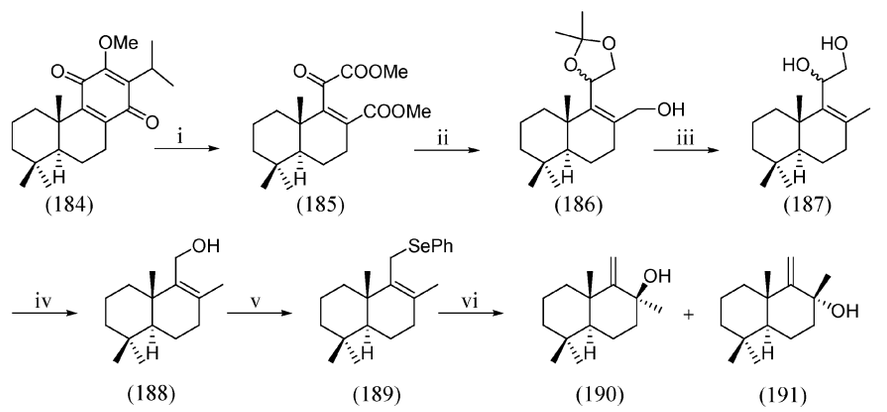
The periodate-based ruthenium tetroxide catalyzed oxidative degradation of aromatic rings is an attractive alternative for exhaustive ozonolysis, and for instance (+)-winterin was obtained from 11,14-dihydroxypodocarpa-8,11,13-triene in 60% yield.[199]

(+)-Royleanone (167), the main constituent of the root of several *Salvia* species,[200] was used to establish the normal drimane stereochemistry of the sesquiterpenes isolated from *Aspergillus oryzae*[201] (see Scheme 7).[202]

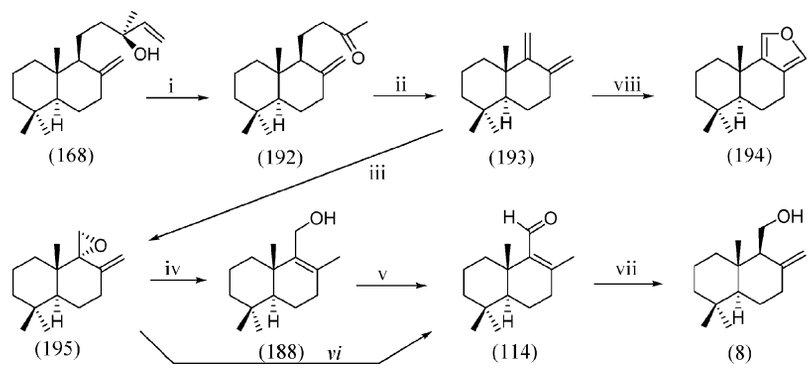
Acetonide (186), obtained in 49% yield from 12-*O*-methyl royleanone (184) was deoxygenated to afford diol (187) as an epimeric mixture. Cleavage of the diol and subsequent



Scheme 6 *Reagents*: i, CH_2N_2; ii, AcCl; iii, MCPBA, KOH, MeOH; iv, Fremy's salt; v, H_2, Pd/C; O_3, $NaBH_4$; vi, $Cu(NO_3)_2$, Ac_2O; vii, Pd/C, hydrazine hydrate; viii, $LiAlH_4$.



Scheme 7 *Reagents*: i, O_3; H_5IO_6; CH_2N_2; ii, $LiAlH_4$; acetone, $CuSO_4$; iii, MsCl, pyridine; $LiAlH_4$; AcOH, H_2O; iv, $Pb(OAc)_4$; $LiAlH_4$; v, *N*-(phenylseleno)phthalimide; vi, H_2O_2, CH_2Cl_2.



Scheme 8 *Reagents*: i, $KMnO_4$, CH_2Cl_2; ii, hv; iii, MCPBA; iv, $ZnBH_4$, silica gel; v, TPPA, NMO; vi, $MgBr_2$, benzene; vii, $NaBH_4$; viii, O_2, hv, *meso*-TPP, CCl_4; $FeSO_4$.

reduction produced (+)-bicyclofarnesol (188). The best way to proceed proved to be selenylation of the allylic alcohol (188) followed by a two-phase pyridine buffered oxidative selenoxide rearrangement gave the drim-9(11)-en-8-ols (+)-(190) and (−)-(191) in a 4 : 1 ratio, identical in all respects to the natural products. This conclusion contradicts earlier published data.[203]

Bicyclic diterpenoids of the labdane group are obvious starting compounds because the bicyclic carbon skeleton is closest in structure to that of drimanes.[204]

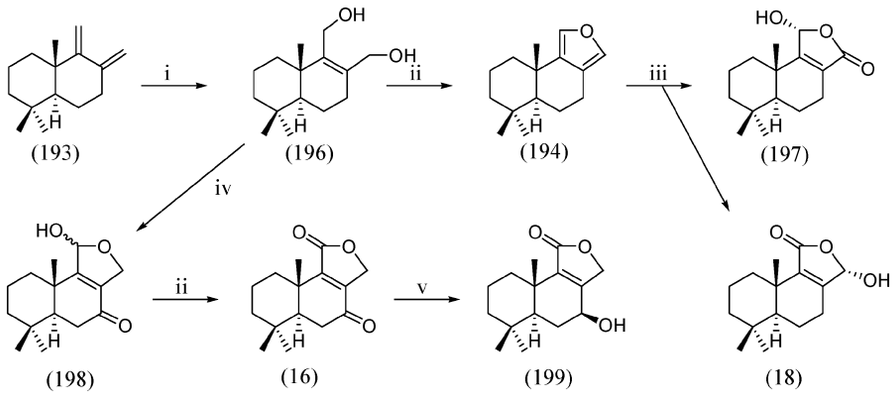
The side chain of (+)-manool (168) is easily cleaved by potassium permanganate[205] to give ketone (192), which upon UV irradiation in pentane undergoes a Norrish type II fragmentation. The resulting diene (193) is a convenient synthon for a variety of drimanes (see Scheme 8).[206,207]

Photooxygenation of diene (193) in the presence of *meso*-tetraphenylporphine gave an endoperoxide, which was reduced with ferrous sulfate or with tetracarbonyldi-μ-chloro-dirhodium to provide (+)-euryfuran (194) in 60% yield.

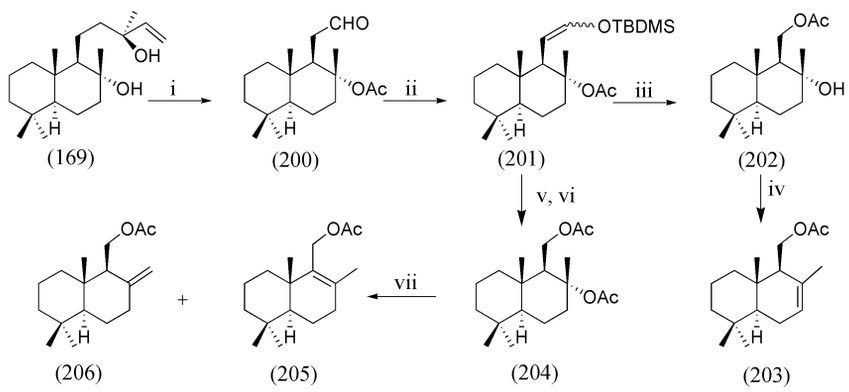
Epoxidation of diene (193) gave monoepoxide (195) as the main product. Reduction with silica gel supported zinc borohydride afforded (+)-bicyclofarnesol (188). Refluxing in benzene with magnesium bromide transformed epoxide (195) into (−)-bicyclofarnesal (114), identical with the product obtained in 76% yield by oxidation of (188) with tetra-*n*-propyl-ammonium perruthenate and *N*-methyl morpholine *N*-oxide as cooxidant. Reduction then gave (+)-albicanol (8) in 46% yield based on epoxide (195).

Diene (193) has also been used in the synthesis of some drimanes in a definitive proof of their structures (see Scheme 9).[208,209]

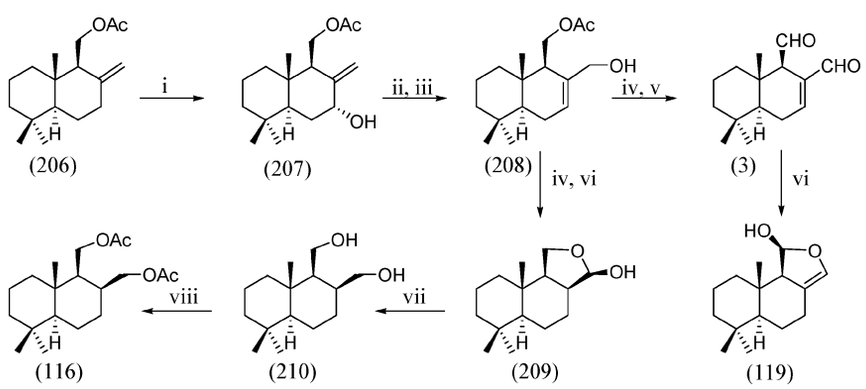
Photooxygenation of diene (193), and reduction of the peroxides afforded diol (196) in good yield. Oxidation with PCC again gave (+)-euryfuran (194). Irradiation in the presence of oxygen and eosin afforded (+)-valdiviolide (197) as the main product (50%) and 12α-hydroxyisodrimenin (18) as a minor product. Diol (196) was protected as its diacetate and then oxidized in acetic acid with CrO_3. Saponification with sodium hydroxide in methanol gave rise unexpectedly to the



Scheme 9 *Reagents*: i, O_2, hν, $NaBH_4$; ii, PCC; iii, hν, O_2, eosin; iv, Ac_2O; CrO_3, AcOH; NaOH, MeOH; v, $NaBH_4$.



Scheme 10 *Reagents*: i, OsO_4, $NaIO_4$; ii, TBDMSCl, NaH, THF; iii, O_3; $NaBH_4$; iv, $SnCl_4$, CH_2Cl_2; v, O_3; $LiAlH_4$; vi, Ac_2O, DMAP; vii, collidine, reflux.



Scheme 11 *Reagents*: i, *t*-BuOOH, SeO_2; ii, MsCl; iii, NaOAc, acetone, H_2O, reflux; iv, KOH, MeOH; v, oxalyl chloride, DMSO; vi, H_2, Raney Ni; vii, $NaBH_4$; viii, Ac_2O, pyridine.

acetals (198) as a 3 : 1 epimeric mixture due to aerial oxidation in basic medium. Oxidation to (+)-7-ketoisodrimenin (16) was performed with PCC in an overall yield of 30% based on diol (196). Reduction of the latter yielded in 86% (+)-7-*epi*futronolide (199).

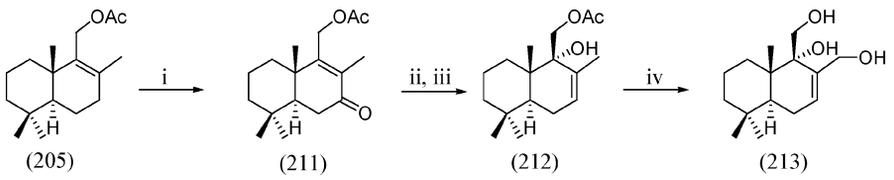
(−)-Sclareol (169), isolated from the flower heads of *Salvia sclarea*,[210] is also a convenient starting material for the syntheses of several drimanes. Participation of the C-8 hydroxyl group in oxidative degradations of the side chain, for instance using osmium tetroxide and sodium periodate as cooxidant, led to the acetoxy aldehyde (200) in 75% yield (see Scheme 10).[211,212]

Further shortening of the side chain to hydroxy acetate (202) was achieved in high yield *via* ozonolysis and reduction of the corresponding silyl enol ethers (201). Treatment of (202) with $SnCl_4$ gave the dehydrated product (+)-drimenyl acetate (203), an intermediate in the synthesis of (−)-polygodial (3),[213] (−)-warburganal (4),[214] and (+)-ugandensidial (7).[215] Ozonolysis of (201) and reduction with lithium aluminium hydride afforded a diol, which was acetylated to diacetate (204). Elimination of acetic acid gave (+)-bicyclofarnesyl acetate (205), and (+)-albicanyl acetate (206) in equimolar amounts. The diol has been transformed previously into (+)-drim-9(11)-en-8-ol.[216]

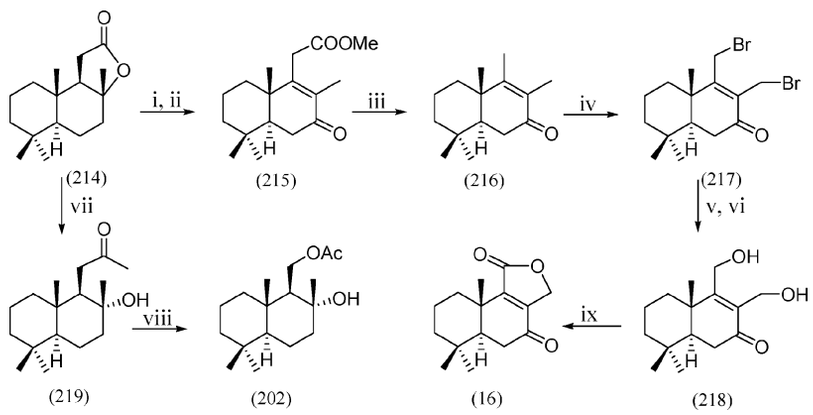
Albicanyl acetate (206) has been used as starting compound in the synthesis of (−)-polygodial (3) (see Scheme 11).

A regio and diastereoselective hydroxylation of albicanyl acetate (206) with selenium dioxide and *t*-butylhydroperoxide as cooxidant gave the alcohol (207) which was treated with mesyl chloride. Solvolysis of the mesylate gave hydroxy acetate (208), which was saponified and oxidized to polygodial (3). Reduction of polygodial afforded (+)-11,12-epoxydrim-8,12-en-11-ol (119).[217] This synthesis confirmed the structure and absolute configuration of this product, which had been isolated from a marine sponge.[218] Oxidation of the hydroxyl group and hydrolysis of the acetate group of (208) followed by reduction with hydrogen in the presence of Raney Ni gave *hemi*ketal (209) as the only product. This compound was converted into (+)-diacetate (116), identical to the natural sesquiterpene.[219]

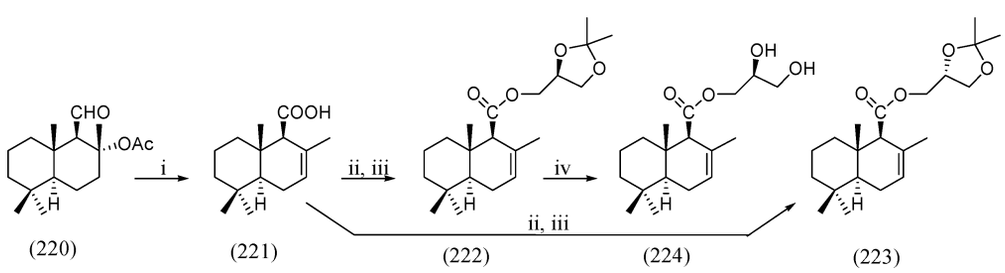
An efficient synthesis of the potent bioactive (−)-warburganal was achieved from bicyclofarnesyl acetate (205) (see Scheme 12).



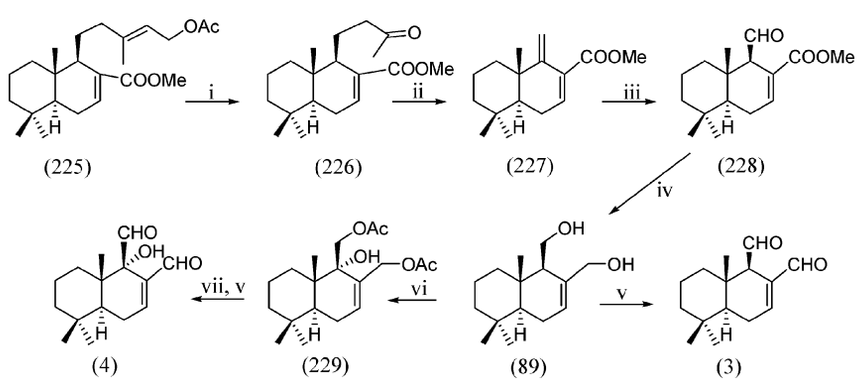
Scheme 12 *Reagents*: i, Na_2CrO_4, Ac_2O, AcOH; ii, $NaBH_4$; iii, MsCl, Et_3N, DMAP; iv, SeO_2, dioxane; KOH, MeOH.



Scheme 13 *Reagents*: i, MeOH, H_2SO_4; ii, $K_2Cr_2O_7$, AcOH or $e^-/LiClO_4$, MeOH; iii, KOH; iv, NBS, $CaCO_3$, CCl_4; v, AcOK, DMF; vi, K_2CO_3, MeOH; vii, CH_3Li, Et_2O; viii, H_2O_2 (50%), CH_2Cl_2, $(CF_3CO)_2O$, $NaHCO_3$; ix, PCC.



Scheme 14 *Reagents*: i, $NaClO_2$, NaH_2PO_4; KOH, MeOH; *p*-TsOH, benzene; ii, oxalyl chloride, benzene; iii, (−)-2,3-*O*-isopropylidene-*sn*-glycerol, NaH, CH_2Cl_2 or (+)-1,2-*O*-isopropylidene-*sn*-glycerol, NaH, CH_2Cl_2; iv, H_2SO_4.



Scheme 15 *Reagents*: i, MCPBA; H_5IO_6; ii, hv; iii, MCPBA; $BF_3{\cdot}Et_2O$; iv, $LiAlH_4$; v, Swern oxidation; vi, Ac_2O, pyridine; SeO_2; vii, K_2CO_3, MeOH.

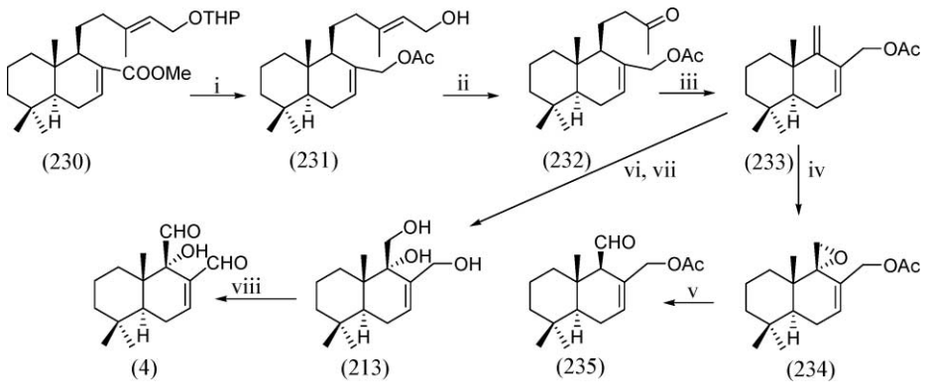
Allylic oxidation of (205) with sodium chromate gave enone (211) which was reduced and isomerized *via* the methane sulfonate to (212). Oxidation with selenium dioxide in dioxane and hydrolysis gave triol (213) in 55% overall yield. This triol has previously been converted into warburganal.[220]

(+)-Sclareolide (214) is a valuable product of oxidative cleavage of sclareol. Several improvements have been developed [221,222] and also bioconversion of sclareol may be a promising method.[223]

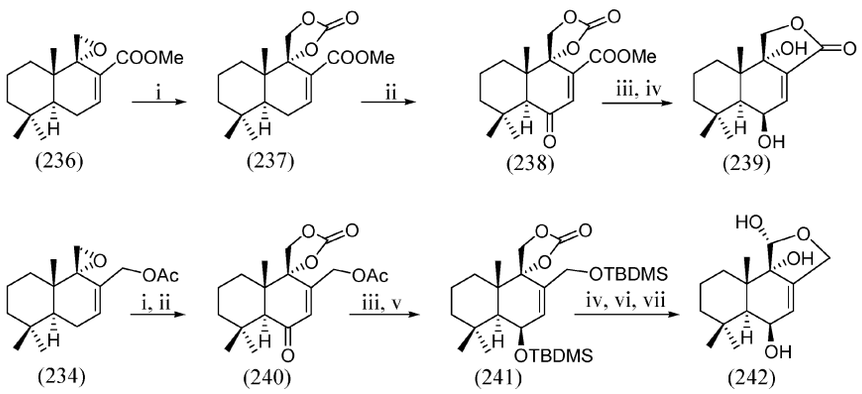
Esterification of sclareolide (214) gave a mixture of isomeric unsaturated esters and oxidation with potassium dichromate in acetic acid afforded ketoester (215) in 40% yield, despite many attempts at improvement.[224] Later an electrochemical oxidation proved the best method and afforded (215) in 63% yield.[225] Hydrolysis of the ester was accompanied by decarboxylation to give (+)-drim-8-en-7-one (216) (see Scheme 13). Bromination of (216) with NBS and treatment of dibromide (217) with potassium acetate gave a diacetate which was saponified to give diol (218).[226] Oxidation of this diol with PCC was chemo- and regioselective and (+)-7-ketoisodrimenin (16), a precursor for (−)-warburganal [227], was obtained in 56% yield.[228] A two-fold excess of methyl lithium converted sclareolide (214) into hydroxyketone (219). Oxidation with an excess of trifluoroperacetic acid gave a quantitative yield of monoacetate (202).[229]

To determine the absolute configuration in the glyceryl part of some drimenic glyceryl esters, isolated from dorid nudibranches, a total synthesis of these compounds was achieved starting with acetoxy aldehyde (220) (see Scheme 14). This revealed that the native diol had the *S* configuration.[230]

Zamoranic acid (170), isolated from *Halimium viscosum* as its methyl ester,[231] has the stereochemistry and functional groups that make it a potential precursor for the semisynthesis of drimanes. The first modification of the starting material is a five-carbon degradation of the side chain (see Scheme 15).[232]



Scheme 16 *Reagents*: i, $LiAlH_4$; Ac_2O, pyridine; *p*-TsOH, MeOH; ii, MCPBA; H_5IO_6; iii, hν; iv, MCPBA; v, $BF_3.Et_2O$; vi, OsO_4 (cat), NMO; vii, $LiAlH_4$; viii, Swern oxidation.



Scheme 17 *Reagents*: i, CSI; ii, CrO_3, AcOH; iii, $NaBH_4$, $CeCl_3$, MeOH; iv, NaOH, dioxane; v, TBDMSOTf, 2,6-lutidine; vi, Swern oxidation; vii, TBAF, THF.

Epoxidation of (225) and cleavage of the epoxides with periodic acid afforded ketone (226) in 50% yield. Irradiation with a high pressure Hg vapour lamp led to diene (227) in satisfactory yield and with a 50% conversion. Careful treatment of (227) with MCPBA and ring opening of the major epoxide with a Lewis acid gave the aldehyde (228). (−)-Polygodial (3) was prepared from (228) *via* reduction to diol (89) and a Swern oxidation of the latter. When diol (89) was protected as its diacetate, a selenium dioxide oxidation afforded the diacetoxy alcohol (229). Saponification and a Swern oxidation of the corresponding triol gave (−)-warburganal (4).

The synthesis outlined in Scheme 15 was modified to give much better yields in the side chain degradation (see Scheme 16).[233] Zomaric acid methylester was derivatized to its tetrahydropyranyl (THP) ether (230) and the ester was converted into an acetate *via* reduction and acetylation. Hydrolysis of the THP ether gave alcohol (231) in 94% yield. The degradation of the side chain was achieved as mentioned above in 60% yield, but the Norrish type II photochemical reaction still showed only a 50% conversion.

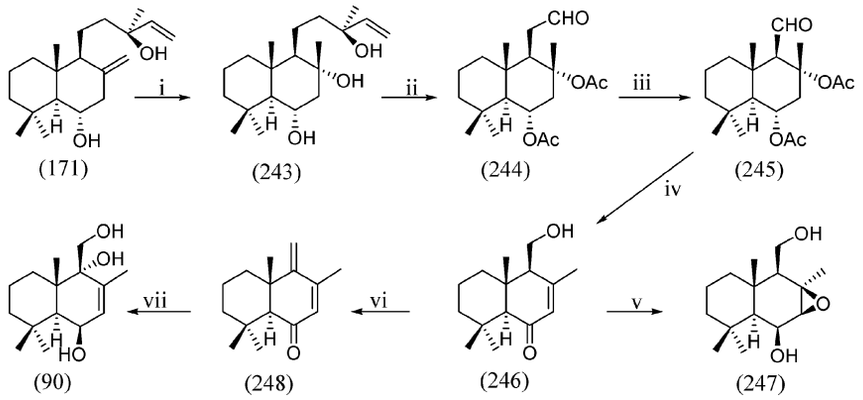
Diene (233) was epoxidized and rearrangement with Lewis acid of the major epoxide afforded mainly acetoxy aldehyde (235), a compound that has been used before in the synthesis of polygodial.[232] The ring-opening of a mixture of epoxides gave the same ratio of aldehydes as before, confirming that rearrangement goes through a cationic pathway and the hydride migration is directed by the C-10 methyl group. Warburganal was obtained by Swern oxidation of triol (213), which was prepared from diene (233) *via cis*-hydroxylation and reduction of the acetate group. The overall yields (55% for polygodial and 27% for warburganal) were much better than those previously reported.[233,234]

Synthesis of pereniporin B (239) was studied by Urones *et al.*[235] starting with epoxy ester (236) (see Scheme 17).

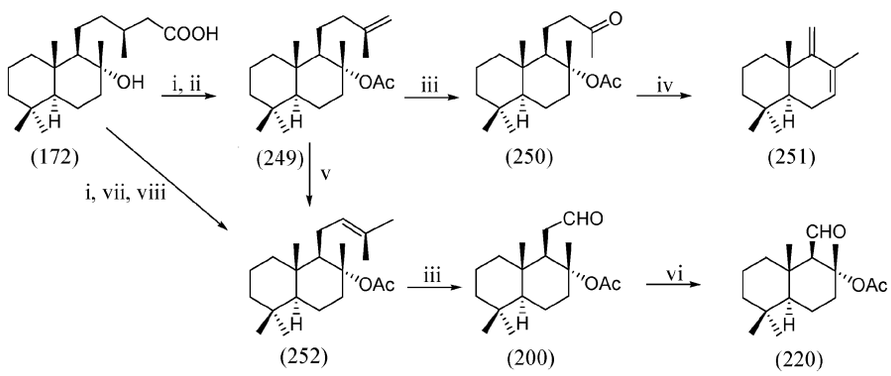
Reaction of (236) with chlorosulfonylisocyanate (CSI) gave carbonate (237) with retention of configuration. Allylic oxidation introduced the C-6 ketone, which was selectively reduced by sodium borohydride mediated by cerium trichloride. Saponification with base then afforded pereniporin B (239) in 19% yield based on epoxide (236). A similar sequence was undertaken with epoxy acetate (234) (see Scheme 17). The reduction of ketone (240) resulted in a diol, which was protected as its di-*t*-butyldimethylsilyl ether (241). Selective hydrolysis of the carbonate with base resulted in a hydroxymethyl group at C-9, which was oxidized to an aldehyde. Deprotection with tetrabutylammonium fluoride was followed by *hemi*acetal formation whereby pereniporin A (242) was obtained in 21% yield based on epoxide (234).[236]

The oleoresin of *Larix decidua* contains large amounts of the labdane diterpene (+)-larixol (171), which can be isolated easily in a pure form.[237] Since it has a hydroxyl group at C-6 as a characteristic structural element, it is particularly suited for the synthesis of drimanes that have a functional group at this position (see Scheme 18).[238] The methodology for a selective oxidative degradation of the side chain developed for sclareol has also been applied for triol (243), prepared in 80% yield from larixol (171), and the diacetate aldehyde (244) was obtained in 63% yield. A further degradation of the side chain was performed *via* ozonolysis of the silylenol ethers of aldehyde (244) to give diacetoxy aldehyde (245) in 75% yield. Complete reduction with lithium aluminium hydride afforded a triol, which was monoprotected at C-11. Oxidation of the secondary alcohol at C-6 with PCC, dehydration of the tertiary alcohol at C-8, and deprotection of the primary silyl ether gave rise to hydroxy enone (246). Stereoselective reduction of the ketone was performed by Dibal-H and epoxidation afforded (−)-uvidin C (247) in 10% overall yield.

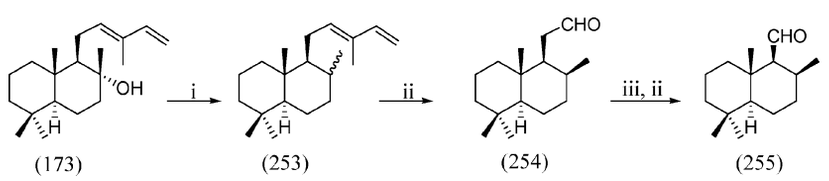
Hydroxy enone (246) was converted into its acetate from which acetic acid was eliminated to give dienone (248). Osmylation took place at the C-9(11) double bond and finally reduction with Dibal-H afforded (−)-*epi*-albrassitriol (90) in 4% overall yield.



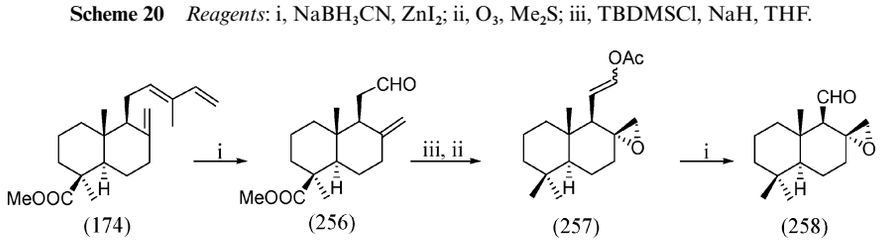
Scheme 18 *Reagents*: i, oxone, acetone, H_2O, CH_2Cl_2, $NaHCO_3$; $LiAlH_4$; ii, Ac_2O, pyridine; OsO_4 (cat), $NaIO_4$; iii, TBDMSCl, NaH, THF; O_3; Me_2S; iv, $LiAlH_4$; TBDMSCl; PCC; $SOCl_2$; TBAF, THF; v, Dibal-H; MCPBA; vi, Ac_2O; DBU, benzene, reflux; vii, OsO_4, pyridine; Dibal-H.



Scheme 19 *Reagents*: i, Ac_2O, Et_3N, DMAP; ii, $Pb(OAc)_4$, $Cu(OAC)_2$; iii, MCPBA; H_5IO_6; iv, hv; v, Li, ethylenediamine; MeCOCl, *N*,*N*-dimethylaniline; vi, TBDMSCl, NaH, THF; O_3; Me_2S; vii, IBDA, I_2, CCl_4, hv; viii, *t*BuOK, Δ.



Scheme 20 *Reagents*: i, $NaBH_3CN$, ZnI_2; ii, O_3, Me_2S; iii, TBDMSCl, NaH, THF.



Scheme 21 *Reagents*: i, O_3; Me_2S; ii, Ac_2O, Et_3N, DMAP; iii, MCPBA.

(−)-Labdanoic acid (172) is the main component from the acidic fraction of the *n*-hexane extract of air dried twigs and leaves of *Cistus labdaniferus* L. Labdanoic acid is best purified as its acetate and this is obtained in 47% yield based on the crude acidic fraction.[239] Degradation of the side chain is not an easy task because the carboxyl group is the only available functionality (see Scheme 19).[240] Acetoxy labdanoic acid was decarboxylated with lead tetraacetate and copper(II) acetate giving rise to alkene (249) with the isopropenyl double bond.

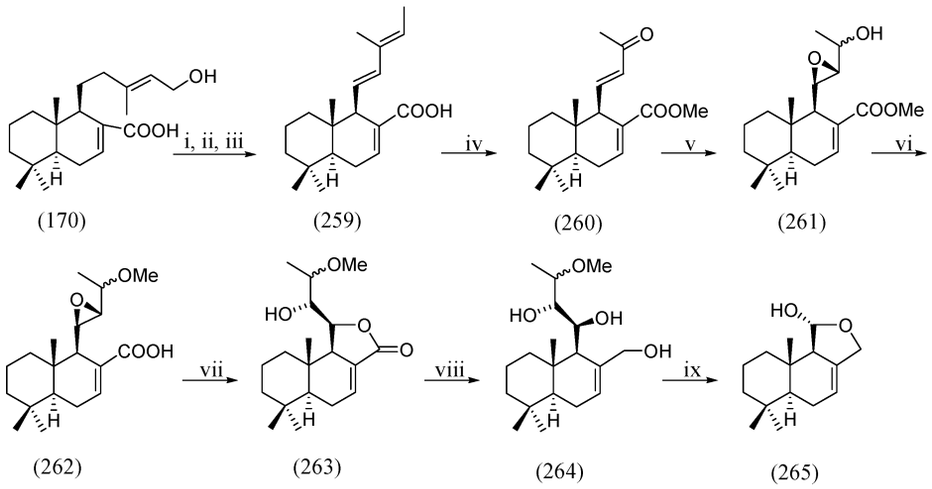
After epoxidation and treatment of the epoxides with periodic acid, acetoxy ketone (250) was obtained in 35% yield based on (172). A Norrish type II photochemical cleavage of the side chain took place with concomitant elimination of acetic acid to give diene (251) in 20% overall yield. This diene is a versatile synthon used in the synthesis of polygodial and warburganal.

If the double bond, formed upon decarboxylation, is isomerized to the more stable alkene (252) and then epoxidized and oxidized with periodic acid, acetoxy aldehyde (200) is obtained in 30% overall yield. The side chain in this aldehyde was shortened further to (220) *via* the method already described in Scheme 18 and this compound is a valuable synthon for drimanes. Aldehyde (200) was also obtained *via* iododecarboxylation of the acetate of labdanoic acid, elimination of the iodide, isomerization of the double bond and ozonolysis of the side chain by Bolster *et al.* in 40% overall yield.[239]

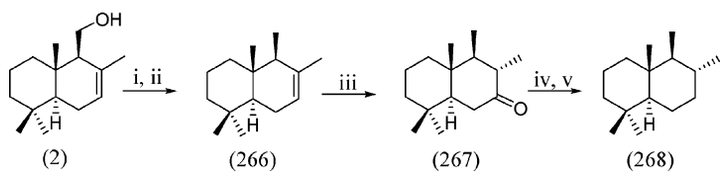
The side chain of the diterpene (+)-*cis*-abienol (173) [241] contains a conjugated double bond and therefore cleavage is easy. Treatment of (+)-*cis*-abienol with sodium cyanoborohydride in the presence of zinc iodide allowed a diastereoselective cationic reduction to a 4 : 1 epimeric mixture of (253) with the β epimer in excess (see Scheme 20).[242]

Ozonolysis and reduction of the ozonides afforded aldehyde (254), which was easily transformed in drimanic aldehyde (255) in 70% overall yield *via* known procedures (see Schemes 10, 18 and 19).

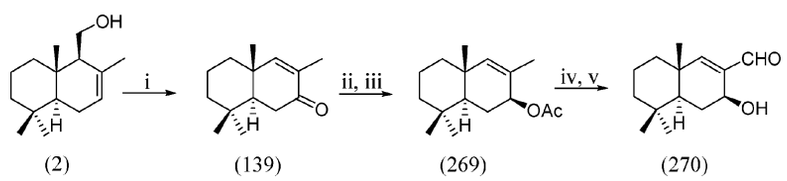
A similar side chain is found in *trans*-communic acid (174), a major component in the non-polar extracts of plant species from the Cupressaceae family.[243] Aldehyde (258) was obtained in four steps in an overall yield of 19% as outlined in Scheme 21.[244]



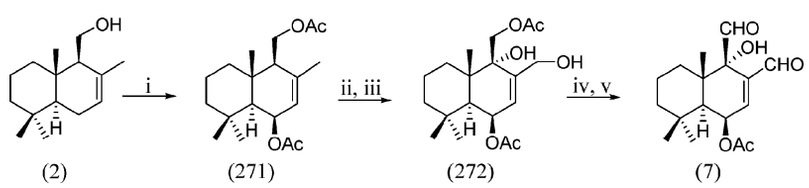
Scheme 22 *Reagents*: i, CH_2N_2; ii, Ac_2O, pyridine; iii, $SnCl_4$; iv, OsO_4, NMO; H_5IO_6; v, $NaBH_4$, $CeCl_3$; MCPBA; vi, CH_3I, NaH; NaOH; vii, *p*-TsOH; viii, Dibal-H; ix, $Pb(OAc)_4$.



Scheme 23 *Reagents*: i, $MeSO_2Cl$; ii, $LiAlH_4$; iii, $Me_2S.BH_3$; H_2O_2; Jones' oxidation; iv, ethanedithiol, $BF_3.Et_2O$; H_2, Raney Ni.



Scheme 24 *Reagents*: i, CrO_3; ii, $LiAlH_4$; iii, Ac_2O, pyridine; iv, SeO_2 (cat.), $(p\text{-}MeOC_6H_4)_2SeO$; v; K_2CO_3.



Scheme 25 *Reagents*: i, ref. 52; Ac_2O, pyridine, DMAP; ii, SeO_2 (cat.), $(p\text{-}MeOC_6H_4)_2SeO$; iii, K_2CO_3, MeOH; iv, Swern oxidation.

Elimination of the hydroxyl group in zamoranic acid (170) gave rise to diene (259) in 81% yield, but a convenient degradation of the side chain by ozone could not be achieved (see Scheme 22).[245] Selective oxidation proved only possible with osmium tetroxide to give ketone (260).

A cerium trichloride mediated sodium borohydride reduction afforded a 1 : 1 epimeric mixture of alcohols. Its epoxidation was diastereoselective due to double assistance by both the hydroxyl on C-13 and the carbonyl group in the methyl ester, to afford epoxy alcohol (261). The C-13 hydroxyl group was protected as a methyl ether and an acid mediated intramolecular epoxide ring opening in the carboxylic acid (262) afforded the δ lactones (263). Dibal-H reduction gave triol (264), which was transformed into isodrimeninol (265) by treatment with lead tetraacetate in 56% overall yield.

The drimane sesquiterpene (−)-drimenol (2) has been used extensively for the synthesis of other drimanes and additional functional groups have then to be introduced. The petroleum biomarker 8β(*H*)-drimane (268), which may be of microbiological origin, is easily synthesized from drimenol (2) (see Scheme 23).[246]

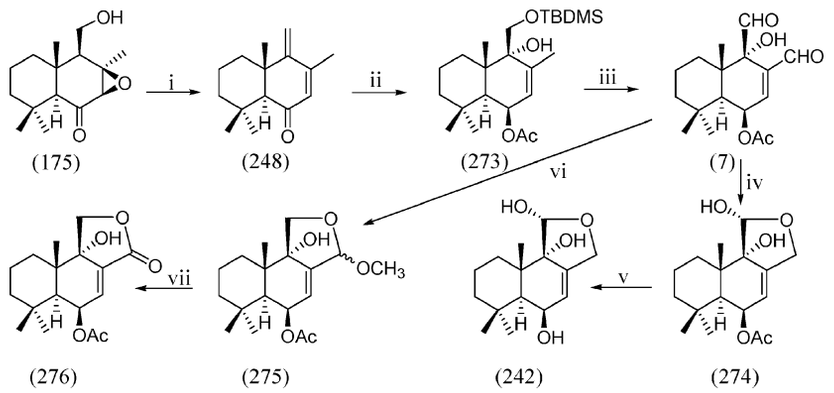
Drimenyl mesylate was reduced with lithium aluminium hydride in high yield. This contrasts with the reduction of the saturated drimanyl mesylate, whereby the starting alcohol was recovered. Hydroboration of (266) followed by Jones' oxidation gave rise to ketone (267). Transformation of the ketone into a methylene was achieved in a standard way to give (268) in 25% overall yield. The epimeric 8α(*H*)-drimane was also synthesized in order to fully establish the stereochemistry of (268).

The *nor*-drimanes isopolygonal (270) and its 7α epimer, polygonal, have both been synthesized from drimenol (see Scheme 24).[247]

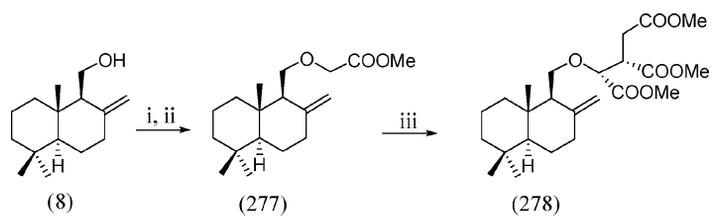
Oxidation of drimenol (2) with CrO_3 in dry pyridine led to a mixture of products from which enone (139) was isolated in 20% yield. Reduction of the carbonyl group afforded the 7β- and 7α-hydroxy isomers in 77% and 5% yield, respectively. The 7β-hydroxyl group was protected as its acetate (269) and allylic oxidation was performed with a catalytic amount of SeO_2 in the presence of bis-(*p*-methoxyphenyl)selenoxide as cooxidant. After saponification of the acetate (+)-isopolygonal (270) was obtained in a good overall yield of 35%, based on enone (139). The same sequence for the 7α-hydroxy isomer led to (+)-polygonal.

Cortes *et al.* synthesized (−)-ugandensidial (7) from (−)-drimenol in 10% overall yield (see Scheme 25).[248]

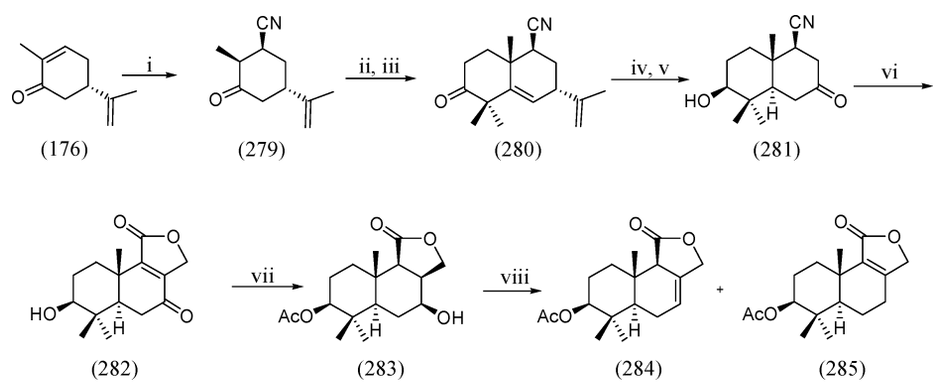
Allylic oxidation of drimenol afforded a diol[249] which was acetylated to its diacetate (271). The oxidation of the allylic methyl group was achieved by Ogura's method using a catalytic amount of selenium dioxide and bis-(*p*-methoxyphenyl)-selenoxide as cooxidant. Saponification of the primary acetate



Scheme 26 *Reagents*: i, Ph_3P, I_2, moist CH_3CN; Ac_2O, pyridine,; DBU; ii, OsO_4, pyridine; TBDMSCl, DMF; Dibal-H; Ac_2O, pyridine, DMAP; iii, SeO_2; TBAF; Swern oxidation; iv, $LiAl(O\text{-}t\text{-}Bu)_3H$; v, NaOH, H_2O; vi, glycol, PPTS; $LiEt_3BH$; H_2O_2, MeOH, PPTS; vii, H_2O, acetone; $BaMnO_4$.



Scheme 27 *Reagents*: i, bromoacetic acid, NaH; ii, CH_2N_2; iii, LDA, dimethylmaleate.



Scheme 28 *Reagents*: i, KCN, AcOH; ii, MVK, NaOMe; *p*-TsOH, benzene; iii, MeI, KO-*t*-Bu; iv, O_3, Ac_2O, Et_3N; $NaBH_4$; v MnO_2; H_2, Pd/C; vi, Bredereck's reagent; Ac_2O; vii, H_2, PtO_2; $NaBH_4$; viii, CF_3SO_2Cl, DMAP.

of (272) and subsequent oxidation by oxalyl chloride and dimethyl sulfoxide afforded (−)-ugandensidial (7), also known under the name of cinnamodial.

A major metabolite of *Lactarius uvidus* (Basidiomycetes) is (+)-uvidin A (175).[250] This natural product has been the starting material for a semisynthesis of (−)-cinnamodial (7).[251] In addition the reduction of cinnamodial was investigated (see Scheme 26).[252]

A new de-epoxidation procedure was developed[253] and applied to uvidin A (175), and after elimination of the C-11 hydroxyl group as acetic acid, a 70% yield of dienone (248) was obtained. Osmium tetroxide reacted selectively with the C-9(11) double bond. The primary alcohol was protected as its silyl ether and the carbonyl group at C-6 was reduced to a β hydroxy group. This sterically hindered, axial alcohol was slowly acetylated in only 60% to afford (273). Hydroxylation of the allylic methyl group and deprotection of the silyl ether gave a diol, which in a disappointing low yield using Ley's conditions for oxidation,[254] afforded (−)-cinnamodial (7) in 5% overall yield.

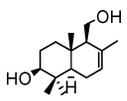
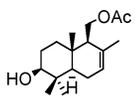
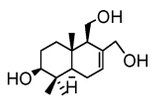
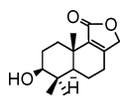
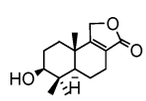
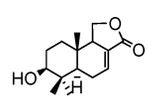
Reduction of (7) with lithium tri-*t*-butoxyaluminiumhydride afforded in high yield (274) with the acetoxy group still present. Evidently the formation of the highly congested sp^3 intermediate, which arises from attack of the hydride on the acetate group, is severely hindered by the two axial methyl groups at C-4 and C-10. Saponification of (274) gave (−)-pereniporin A (242). Protection of the α,β-unsaturated aldehyde in cinnamodial (7) as its acetal and reduction of the C-11 aldehyde with lithium triethylborohydride led to a cyclic boronate, which was treated with H_2O_2 and dry methanol to give (275). Hydrolysis of the acetal followed by oxidation of the *hemi*acetal afforded (−)-cinnamosmolide (276) in 25% yield based on cinnamodial.[255]

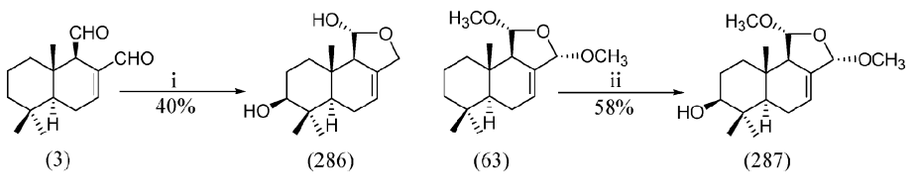
The antitumor promoter, (+)-cryptoporic acid A methyl ester, has been synthesized together with three other diastereomers starting from (+)-albicanol (8) (see Scheme 27).[256] The reaction of sodium albicanolate with bromoacetic acid afforded an acid, which was converted into ester (277). The enolate of this ester was added to methyl maleate to afford a mixture of trimethyl esters (3 : 3 : 1 : 1) in 22% yield. Separation by HPLC afforded ester (278), identical to the trimethyl ester derived from natural (+)-cryptoporic acid A.

S-(+)-Carvone (176) is the major component of caraway oil and for transformation into drimanes annelation has to take place and additional carbon atoms have to be introduced (see Scheme 28).[257,258] The conjugate addition of potassium cyanide proceeded selectively in 95% yield to give crystalline cyanocarvone (279).

Robinson annulation with methyl vinyl ketone was stereoselective and subsequent dehydration and dimethylation afforded the bicyclic keto nitrile (280) in good yield. The isopropenyl group was transformed *via* a Criegee rearrangement to an allylic alcohol, and the C-3 carbonyl group was reduced to give a diol in which the allylic alcohol was oxidized

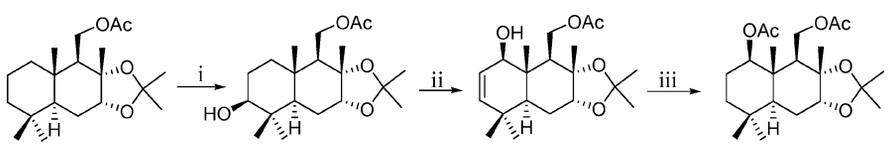
Table 2 Bioconversions of selected drimanes

						
A. niger	2	33	70 81	85	80 90	46
M. plumbens	7		66	90	90	
R. arrhizur	60			52	90	
C. elegans			70			



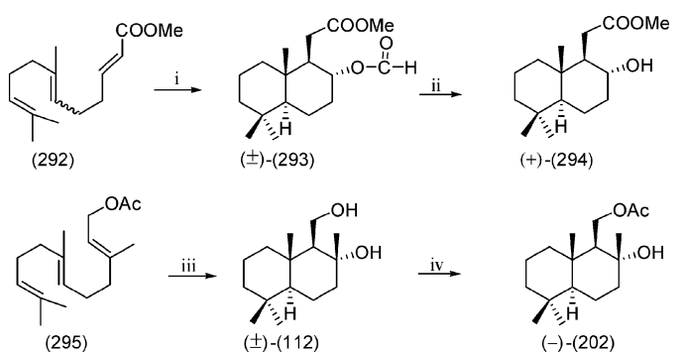
(3) (286) (63) (287)

Scheme 29 *Reagents*: i, *C. elegans*, 90%; ii, *S. racemosa*, 58%.



(288) (289) (290) (291)

Scheme 30 *Reagents*: i, *A. niger* ATCC 9142, 4 days; ii, Ph_3P, *p*-TsONa, THF; SeO_2; iii, Ac_2O, DMAP; H_2, PtO_2.



(292) (±)-(293) (+)-(294)

(295) (±)-(112) (−)-(202)

Scheme 31 *Reagents*: i, HCOOH, H_2SO_4; ii, immobilized lipase OF-360 (*Candida rugosa*), H_2O-saturated isooctane; iii, $ClSO_3H$, *i*-$PrNO_2$; KOH; iv, vinyl acetate, lipase PS-30 (*Pseudomonas* sp.), *i*-Pr_2O-benzene (1 : 1).

by MnO_2. Finally the *trans* fused decalone (281) was obtained upon reduction with hydrogen in the presence of palladium. Under neutral conditions using bis-(dimethylamino)-*t*-butoxymethane (Bredereck's reagent) the last carbon atom was introduced to give 3β-hydroxy-7-keto isodrimenin (282). This lactone was converted straightforwardly into hydroxy lactone (283). Treatment with trifluoromethanesulfonylchloride in the presence of DMAP gave a separable mixture of (−)-3β-acetoxydrimenin (284) and (+)-3β-acetoxyisodrimenin (285) in overall yields of 8.5% and 2%, respectively.

Much attention has been paid to the synthesis of hydroxylated drimanes due to their wide range of biological activities.[259–263] The direct microbial hydroxylation of 4,4-dimethyl substituted sesquiterpenes leading to 3β-hydroxy derivatives was best performed by filamentous fungi. After numerous experiments *Aspergillus niger* ATCC 9142, *Mucor plumbeus* ATCC 4740, *Rhizopus arrhizus* ATCC 11145, *Cunninghamella elegans* ATCC 36112 and *Syncephalostrum racemosa* were selected. *A. niger* proved to be the most efficient organism. *M. plumbeus* sometimes had a preference for 6α-hydroxylation. Some examples are given in Table 2.

Bioconversion of polygodial (3) was performed with *C. elegans* at pH 5.5 and a stereospecific oxidation occurred in high yield. A concomitant reduction of the C-8 aldehyde also took place to give 3β-hydroxyisodrimeninol (286) (see Scheme 29).[254]

Since polygodial is an unstable compound,[259] it was protected first as its dimethoxyacetal (63). Of 95 species studied, *S. racemosa* was selected as the best one for bioconversion of (63) to its 3β-hydroxy derivative (287) (see Scheme 29).

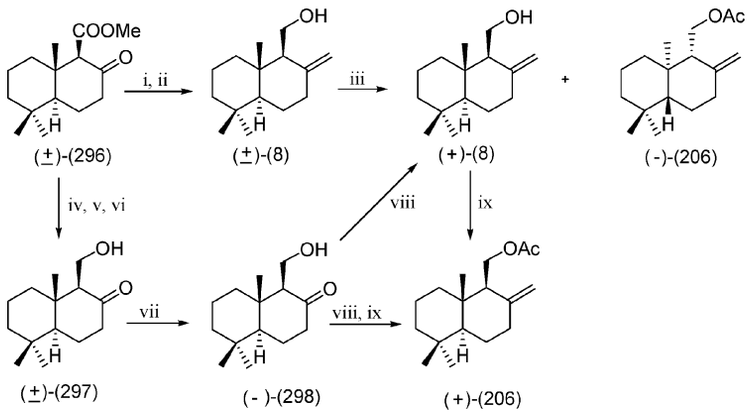
The hemisynthesis of an 1α-hydroxydrimane derivative is a nice illustration of a synthetic route involving the initial microbial 3β-hydroxylation of drimenol derivative (288) (Scheme 30).[259a]

After microbial hydroxylation of (288) in nearly quantitative yield, the 1α-hydroxy substituent was introduced by elimination of the 3β hydroxyl group followed by an allylic oxidation. Acetylation and subsequent hydrogenation afforded diacetate (291).

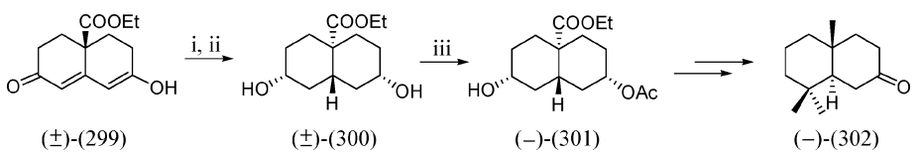
8.3 Synthesis of drimanes by enzymatic resolution

Chiral compounds containing the bicyclo [4.4.0] ring system with three pendant methyl groups are useful starting materials in drimane total synthesis. It should be noted that cyclization of achiral acyclic compounds affords racemic mixtures of decalins. Optical resolution has been achieved by converting the racemate into a pair of diastereomers which were separated.[265,266] For asymmetric synthesis the use of chiral auxiliaries is a well established method and the cyclization of (304) followed by reduction of the ester afforded (−)-drimenol with low chiral induction (20% *e.e.*) (*vide infra* Scheme 34).[267]

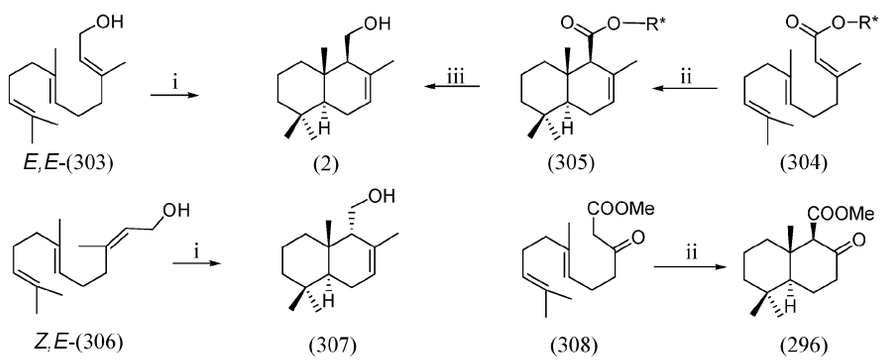
Optically pure intermediates were also obtained *via* enzymatic approaches. Acyclic polyenes were cyclized and exposed to lipases to achieve resolution of the racemic mixtures (see Scheme 31).



Scheme 32 *Reagents*: i, $Ph_3P{=}CH_2$; ii, $LiAlH_4$; iii, isopropenyl acetate, lipase PL-266 (*Alcaligenes* sp.), diisopropylether; iv, ethylene glycol; v, *p*-TsOH; vi, $LiAlH_4$; wet acetone, *p*-TsOH; vii, vinyl acetate, lipase (*Candida cylindracea*); viii, CH_2I_2, Zn, PbI_2, $TiCl_4$; ix, Ac_2O, pyridine.



Scheme 33 *Reagents*: i, H_2, Rh/C; ii, $NaBH_4$; iii, lipase AK (*Pseudomonas fluorescens*), vinyl acetate, *i*-Pr_2O.



Scheme 34 *Reagents*: i, FSO_3H, 1-nitropropane, −80° to −85 °C; ii, $SnCl_4$, benzene; iii, $LiAlH_4$.

Polyene ester (292), easily prepared from linalool, was cyclized to the formate ester (293) in 40% yield. Enantioselective hydrolysis was observed for (293) and (+)-hydroxy ester (294) was obtained in 40% chemical yield with > 99% *e.e.* [268] Farnesyl acetate (295) was subjected to a similar protocol and (−)-hydroxy acetate (202) was obtained after an enantioselective lipase catalyzed transacetylation of (±)-(112) in 20% chemical yield with 97% *e.e.* [269,270]

(−)-Albicanol (8) was synthesized from the well known β-ketoester (296) [271] as depicted in Scheme 32. A Wittig reaction of (296) with triphenylmethylenephosphorane followed by reduction of the ester group afforded racemic (8) in 87% yield. Enzymatic transacetylation of this racemate gave unchanged (+)-albicanol (8) in 46% yield with 75% *e.e.* and the unnatural acetate (−)-(206) in 50% yield with 76% *e.e.* [272] Optically pure products could be prepared by crystallization.

Hydroxyketone (297) was subjected to lipase catalyzed acylation with vinyl acetate and the unchanged (−)-alcohol (298) was once more subjected to lipase catalyzed acetylation to provide after crystallization, 48% of (−)-(298) with 97% *e.e.* [273,274] (−)-Keto alcohol (298) gave (+)-albicanol (8) upon methylenation using the Takai modification.[275] Natural (+)-albicanyl acetate (206) was obtained after acetylation of (8).

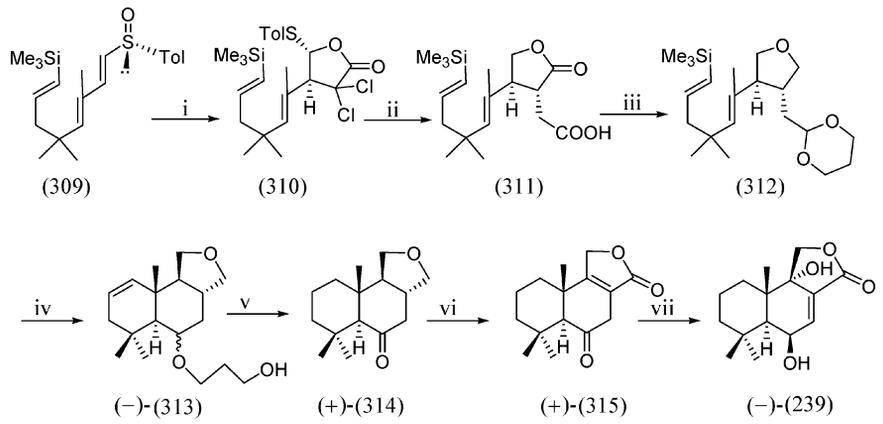
Desymmetrization of decalin *meso* glycols was achieved by lipase-mediated ring differentiation (see Scheme 33).[276–278]

Catalytic hydrogenation of (299) [278] followed by reduction with sodium borohydride gave *meso* diol (300) in 83% yield. Exposure of (300) to lipase AK (*Pseudomonas fluorescens*) immobilized on Celite and vinyl acetate in diisopropyl ether resulted in the formation of enantiopure monoacetate (301) in 96% isolated yield. The latter was converted into chiral decalone (302), a key intermediate for the synthesis of (−)-polygodial and (−)-warburganal.[279]

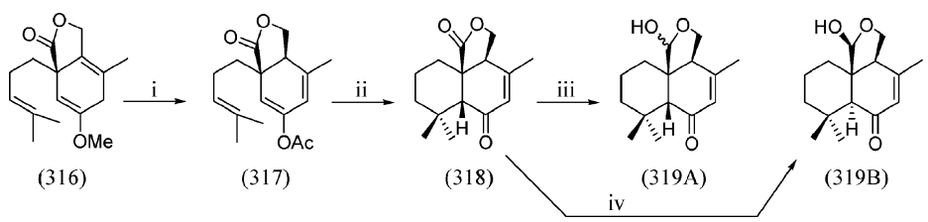
8.4 Synthesis of drimanes by cationic polyolefin cyclizations

The biogenetically patterned cyclization of acyclic polyenes has provided an elegant route to sesquiterpenoids and in the case of farnesol or its derivatives bicyclofarnesanes are obtained. Superacidic low-temperature cyclization of terpenols and their acetates by fluorosulfonic acid represents an efficient chemo- and structurally selective and stereospecific process (Scheme 34).[280–283]

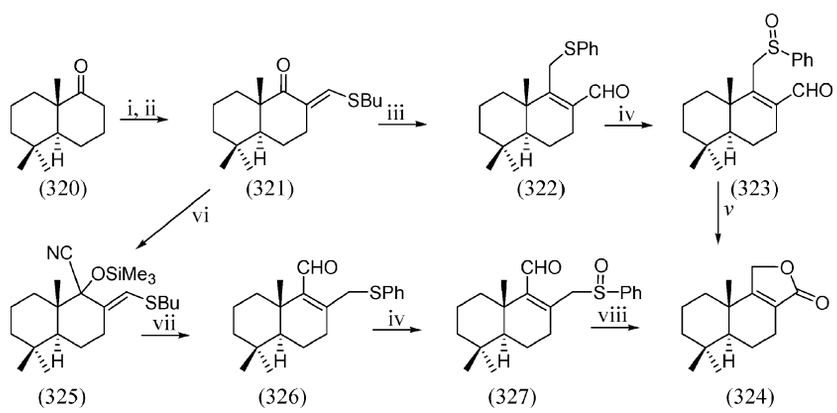
The configuration of C-9 in the cyclized products is determined by the configuration of the allylic double bond. (*E,E*)-Farnesol (303) and (*Z,E*)-farnesol (306) reacted in a clean reaction to afford drimenol (2) and *epi*-drimenol (307), respectively. This phenomenon may be related to the low nucleophilicity of the C(2)–C(3) double bond due to the influence of the hydroxyl group. Therefore conformational inversion of the C-7 cation proceeds faster than cyclization with participation of the C(2)–C(3) double bond.[281] If the reaction was interrupted after one minute, β-monocyclofarnesyl acetate was isolated in yields up to 90%. This fact points to a stepwise, rather than a concerted mechanism of the superacidic cyclization.[282] The corresponding farnesyl acetates reacted in the same way. (*R*)-(+)-1,1′-bis-2-naphthyl ester (304) was cyclized and reduced to give optically active (−)-drimenol with 20% *e.e.* [267] Acyclic ketoester (308) was prepared from geranylacetone in 82% yield and was cyclized to the bicyclic β-ketoester (296), which was transformed into drimenin *via* a three step improved procedure.[284]



Scheme 35 *Reagents*: i, CCl_3COCl, Zn-Cu; ii, Bu_3SnH; LDA, ICH_2CO_2Me; LiOH, H_2O; iii, *i*-BuOCOCl; $NaBH_4$; Swern oxidation; Me_2SO_4, DMF, 1,3-propane diol; $LiAlH_4$; *p*-TsCl, pyridine; iv, $TiCl_4$; v, Johnson's procedure[286]; Swern oxidation; H_2,Pd/C; vi, $RuCl_3$, $NaIO_4$; $PhMe_3NBr_3$; DBU; vii, $(PhSeO)_2O$; Dibal-H; Ag_2CO_3/Celite.



Scheme 36 *Reagents*: i, HCl, H_2O; LDA, Ac_2O; ii, BF_3 (gas), wet CH_2Cl_2; iii, Dibal-H; MnO_2; ref. 287*b*.



Scheme 37 *Reagents*: i, HCOOEt, NaH; ii, *n*-BuSH, *p*-TsOH, benzene; iii, $PhSCH_2Li$; $HgCl_2$, H_2O, HCl; iv, $NaIO_4$; v, wet dioxane, K_2CO_3 or Ac_2O, NaOAc; vi, Me_3SiCN; vii, Dibal-H; viii, $(CF_3CO)_2O$; $HgCl_2$, H_2O, HCl.

Enantioselective syntheses of (+)-fragolide (315) and (−)-pereniporin B (239) were performed by an effective acetal-initiated/vinylsilane-terminated cationic cyclization. The relative and absolute stereochemistry was induced by the sulfoxide stereocenter in triene (309) (see Scheme 35).[285]

Treatment of (309) with dichloroketene gave lactone (310) with the β and γ-carbon stereocenters in the lactone adjusted at the expense of the asymmetry at sulfur. Adjustment of the oxidation state in the *trans*-disubstituted lactonic acid (311) was achieved *via* reduction of the mixed anhydride, Swern oxidation and acetalization under non protic circumstances to prevent protodesilylation.

Prior to cyclization the lactone had to be reduced to the tetrahydrofuran derivative (312). Cyclization was easily performed and bicyclic compound (313) was formed in 30% overall yield. Conversion into (+)-fragolide (315) was straightforward and the latter was converted in three steps into (−)-pereniporin B (239) *via* an oxidative allylic transposition with benzeneseleninic anhydride.

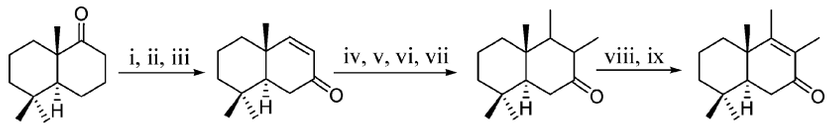
Fudecalone was isolated in 1995 from *Penicillium* sp. and the structure was reported to be (319A). To prove its structure a total synthesis was undertaken (see Scheme 36).[287*a*]

Trienic lactone (316) was converted into enol acetate (317), which cyclized on treatment with BF_3 in wet dichloromethane to form the tricyclic enone (318) as the sole product. Treatment with Dibal-H reduced the ketone and the lactone but upon reoxidation with MnO_2 only the allylic hydroxy group was oxidized and (319) was obtained as an inseparable crystalline diastereomeric mixture in 35% overall yield. However, the spectral data of synthetic (319A) and the natural product were different. Later another synthesis revealed the correct structure as (319B).

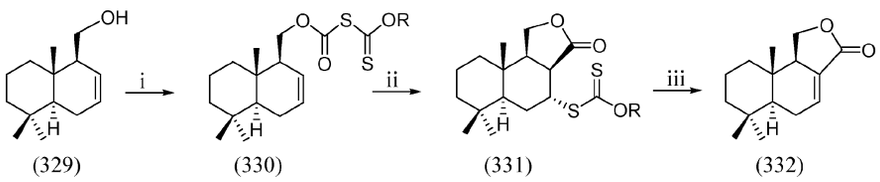
8.5 Synthesis of drimanes from *trans*-decalones

The readily available trimethyldecalone (320) has been used for the synthesis of confertifolin. C-12 was introduced *via* a formylation reaction and an addition of [phenylthiomethyl]lithium to the carbonyl group furnished the drimane skeleton (see Scheme 37).

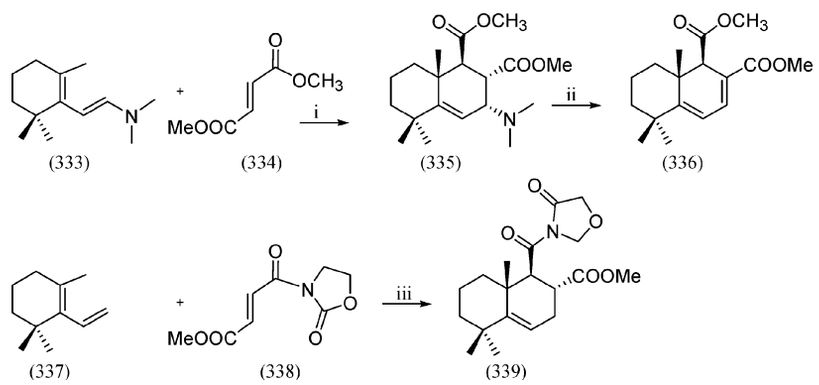
A mercuric chloride mediated hydrolysis of the adduct gave the γ-phenylthio-α,β-unsaturated aldehyde (322), which was oxidized to sulfoxide (323). Upon heating in wet dioxane or in acetic anhydride in the presence of sodium acetate, confertifolin (324) was obtained in 65% overall yield.[288] Another approach afforded the regioisomeric sulfoxide (327), which also gave confertifolin upon treatment with trifluoroacetic anhydride and hydrolysis of the intermediate phenylthiofuran.[289]



Scheme 38 *Reagents*: i, $LiAlH_4$; ii, *p*-TsOH on silica gel, toluene; iii, CrO_3; iv, $(CH_3)_2CuLi$; v, NaH, $CO(COOEt)_2$; vi, NaH, DMF, CH_3I; vii, DMSO, LiCl, H_2O, Δ; viii, Br_2, HOAc; ix, LiBr, Li_2CO_3, DMF.



Scheme 39 *Reagents*: i, $COCl_2$; $NaSC(S)OCH_2Bu^t$ ii, hν (500 W tungsten lamp); iii, DBU.



Scheme 40 *Reagents*: i, toluene, 150 °C, 48 h; ii, silica gel, cyclohexane, 80 °C; iii, toluene, 15 kbar, copper(II)-catalyst, room temperature.

Drim-8-en-7-one (216) was prepared starting with decalone (320) in 7% overall yield.[290] The carbonyl group in (320) was reduced and the resultant alcohol was dehydrated. Allylic oxidation then gave enone (328) (see Scheme 38).

The required methyl groups were introduced by conjugate addition of lithium dimethyl cuprate followed by alkylation with methyl iodide yielding (267). Finally the double bond was introduced *via* a bromination-dehydrobromination procedure.

8.6 Synthesis of drimanes by radical cyclizations

S-alkoxycarbonyl dithiocarbonates can be easily derived from alcohols. Upon irradiation with visible light, alkoxycarbonyl radicals are formed and their intramolecular addition to suitably located alkenes constitutes a direct route to lactones (see Scheme 39).[291]

Thus the known alcohol (329) was converted into the corresponding xanthate (330), and upon irradiation with visible light, cyclization took place to afford a single diastereomer (331) in 51% yield. Treatment with DBU yielded cinnamolide (332).[292,293]

8.7 Synthesis of drimanes by cycloaddition reactions

The use of inter- or intramolecular [4+2] cycloadditions as well as [3+2] dipolar cycloadditions to construct an appropriately functionalized decalin in a concise manner is an attractive approach to drimanes. An alternative to the Diels–Alder reaction is the tandem Michael reaction.[294]

The use of conjugated dienamines in [4+2] cycloadditions has been investigated but due to the steric encumbrance of the dienamines, the reactivity was low although a high stereoselectivity was observed (see Scheme 40).[295]

Dienamine (333) was heated for 48 h at 150 °C in the presence of dimethylfumarate (334) to yield the *endo* adduct (335) in 88%. The *exo* adduct was not detected in the crude reaction mixture. Dimethylamine was eliminated and (336) was obtained. This is a useful precursor for several drimanes.[254]

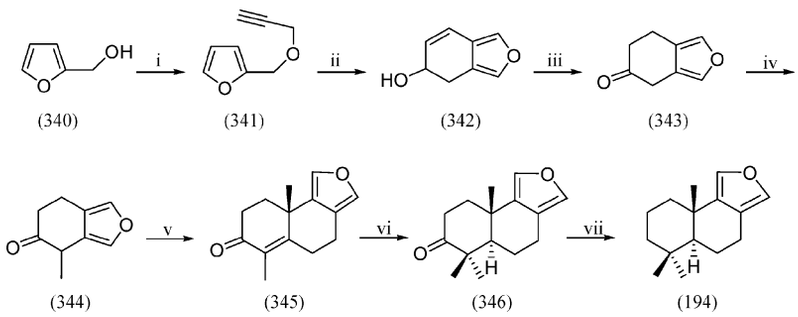
To prevent decomposition of the reactants at higher temperatures the Lewis acid catalyzed cycloaddition was developed. The use of chiral Lewis acid catalysts is an attractive possibility. Under high pressure (15 kbar) a complete conversion was observed at room temperature when the 1,3-oxazolidin-2-one derivative (338) was mixed with alkene (337) in the presence of a chiral bis-imine copper(II) complex. Drimane precursor (339) was obtained in 74% yield with 61% *e.e.* After one crystallization a nearly enantiomerically pure adduct (339) was isolated.[296]

Euryfuran was synthesized *via* furan ring transfer by an intramolecular Diels–Alder reaction as key step (see Scheme 41).[297]

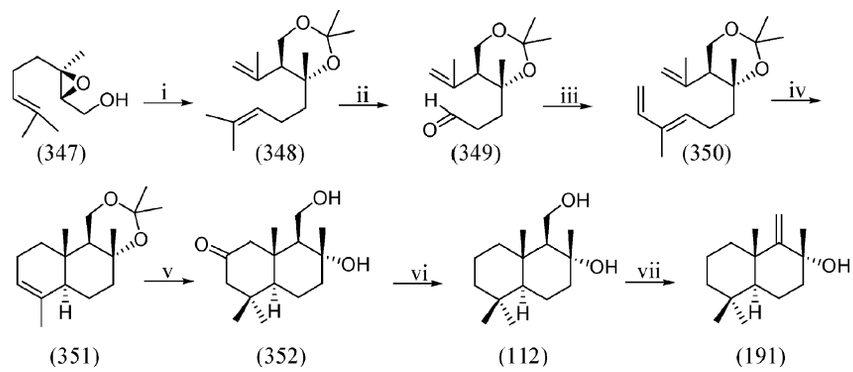
Furfuryl alcohol (340) was converted into propargyl ether (341). Treatment with base resulted in a smooth reaction to give bicyclic allylic alcohol (342), which after oxidation, methylation[298] and annelation with ethyl vinyl ketone afforded tricyclic furan (345). This intermediate could be converted into the *gem*-dimethylated product (346) and after reduction in two steps, euryfuran (194) was obtained in 13% overall yield.

A highly diastereoselective intramolecular Diels–Alder reaction was observed in the synthesis of (+)-driman-8,11-diol (112) and (+)-drim-9(11)-en-8-ol (191) starting from geraniol (see Scheme 42).[299] Chiral epoxide (347) was prepared from geraniol in 97% yield with 94% *e.e.* using the Sharpless asymmetric epoxidation procedure. Epoxide ring opening with *iso*propenylmagnesium bromide resulted in the exclusive formation of a 1,3-diol, which was converted into acetonide (348). Selective ozonolysis gave aldehyde (349), which was used to introduce the 1,3-diene unit. Cycloaddition of (350) was performed in a sealed tube and afforded *trans*-fused bicyclic (351) in 46% overall yield.

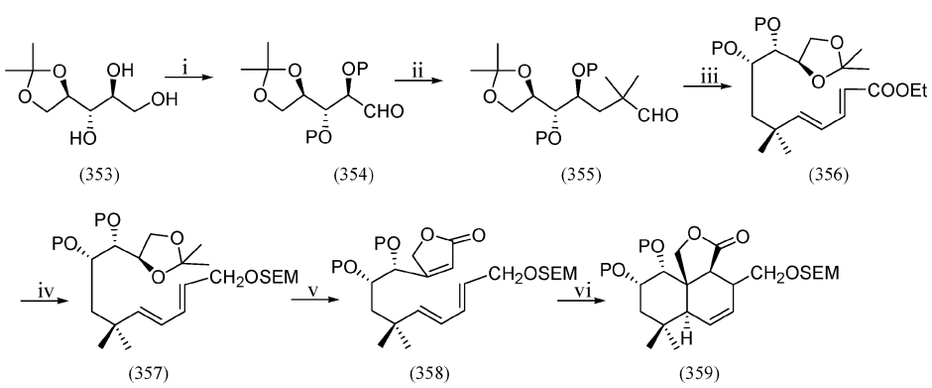
Allylic oxidation generated the substrate for a conjugated addition of methyllithium to introduce the *gem*-dimethyl group. Wolff–Kishner reduction of (352) gave (+)-driman-8,11-diol (98) and treatment of its monotosylate with zinc powder gave (+)-drim-9(11)-en-8-ol (191).



Scheme 41 *Reagents*: i, propargyl bromide; ii, *t*-BuOK; iii, H_2, Pd/C; Swern oxidation; iv, diallylcarbonate, NaH, benzene; MeI, K_2CO_3; $Pd(OAc)_2$; v, EVK, DBU; *t*-BuOK, THF; *p*-TsOH; vi, Li, NH_3, MeI; vii, $NaBH_4$; NaH, CS_2, MeI; Bu_3SnH.



Scheme 42 *Reagents*: i, 2-bromopropene, Mg, CuI; 2-methoxypropene, PPTS; ii, O_3, Me_2S; iii, $Ph_3P{=}C(Me)COOEt$; Dibal-H; PDC; $Ph_3P{=}CH_2$; iv, toluene, methylene blue, sealed tube, 210 °C; v, CrO_3; MeLi, CuI; vi, hydrazine hydrate, KOH; vii, *p*-TsCl, pyridine, DMAP; NaI, Zn.



Scheme 43 *Reagents*: i, TBDMSCl; MOMCl; TBAF; Dess–Martin oxidation; ii, $Ph_3P{=}C(Me)COO_2Et$; H_2,Pd/C; MeI, $KN(TMS)_2$; $LiAlH_4$; Dess–Martin oxidation; iii, $(EtO)_2P(O)CH_2COO_2Et$; Dibal-H; MnO_2; $(EtO)_2P(O)CH_2COO_2Et$; iv, Dibal-H; SEMCl; v, HOAc; $BrCH_2C(O)Br$; DMSO, Ac_2O; $P(OMe)_3$; LiCl, DIPEA; K_2CO_3; vi, toluene, sealed tube, 180 °C.

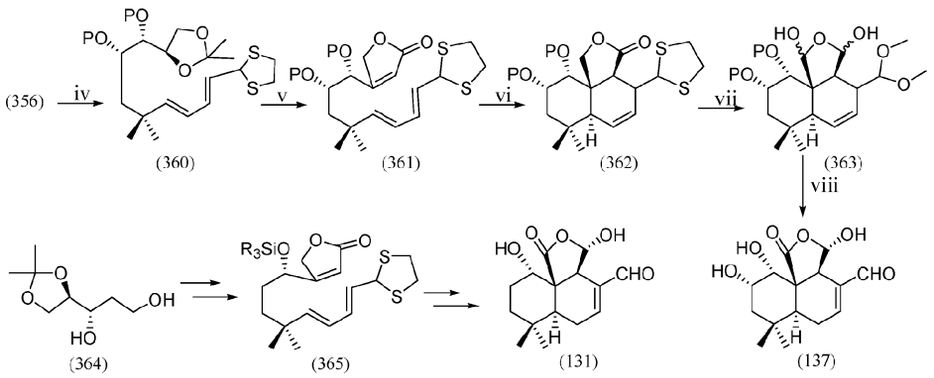
Owing to their biological interest, their challenging structures and the unsettled absolute stereochemistry, mniopetals were selected as targets for several total syntheses (see Scheme 43).[300–302] The enantiopure starting material D-4,5-*O*-isopropylidene-ribitol (353) was obtained from D-mannitol.[303] After protection of the secondary hydroxyl groups aldehyde (354) was prepared as a handle for chain elongation. This was performed in an elegant way to afford, after several high yielding steps, diene (356) in 41% overall yield. The ester group was reduced, the alcohol protected, and the acetonide group in (357) was converted into butenolide (358) in a moderate yield of 28%. The intramolecular Diels–Alder reaction of (358) proceeded well under thermal conditions to provide two *endo*-cycloadducts with preferential formation of the desired (359) in 49% yield.

However, no efficient route to mniopetal E (137) was found because the C-12 hydroxyl group could not be oxidized. The same route was then undertaken but with a synthetic equivalent of an aldehyde group instead of a protected alcohol (see Scheme 44). Dithiolane derivative (360) was obtained in 40% from (356) and the introduction of the butenolide (361) was achieved now in 40%. Cycloadduct (362) was isolated in 62% yield and this adduct could be transformed into (−)-mniopetal E (137)

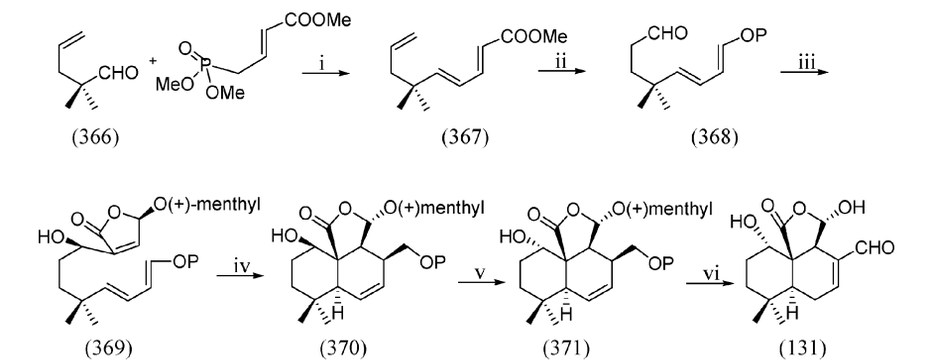
Based on the same strategy (−)-mniopetal F (131) was synthesized starting from the known D-2-deoxy-erythritol derivative (364), prepared from D-mannitol.[303] The key step was a stereoselective intramolecular Diels–Alder reaction of (365) in which the π-facial selectivity is controlled by the stereoelectronic effect of the trialkylsilyloxy substituent (see Scheme 44).[304]

Jauch's strategy to synthesize mniopetals is based on a highly diastereoselective Baylis–Hillman reaction with a chiral butenolide and on an *endo*-selective intramolecular Diels–Alder reaction (see Scheme 45).[305]

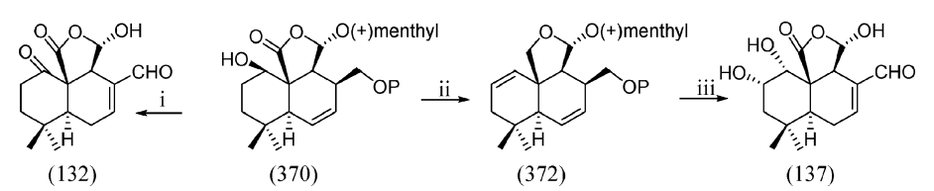
E,E-Triene ester (367) was regioselectively converted by a hydroboration-oxidation sequence into aldehyde (368). Because of its high nucleophilicity and very low basicity lithium phenylselenide was the nucleophile of choice in the Baylis–Hillman reaction of (368) with the chiral (+)-5-menthyloxy-2(5*H*)-furanone,[306] which gave one single diastereomer. Cycloaddition of (369) gave tricyclic lactone (370) in good yield.[307] Now the configuration of the hydroxyl group at C-2 in (370) had to be inverted and finally the method of Moriarty[308] was successful,



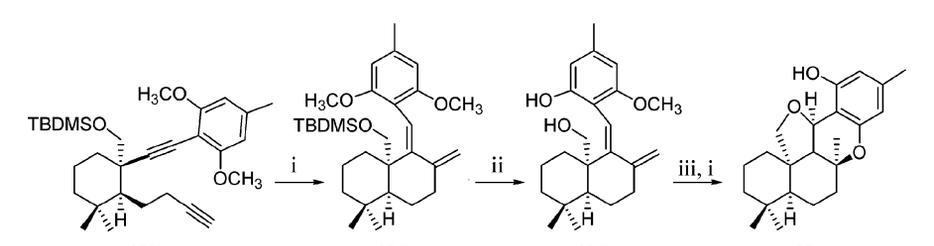
Scheme 44 *Reagents*: iv, Dibal-H; MnO_2; $HSCH_2CH_2SH$; v, HOAc; TBDMSCl; DMSO, $SO_3^{\bullet}$ pyridine; CSA; $(EtO)_2P(O)CH_2COOH$; K_2CO_3; vi, toluene, sealed tube, 180 °C; vii, MeOH, $Hg(ClO_4)_2$; Na_2RuO_4, KOH; Dibal-H; viii, trace aqueous HCl; DMSO, Ac_2O; aqueous HCl.



Scheme 45 *Reagents*: i, LiHMDS; ii, Dibal-H; TBDPSCl; 9-BBN, H_2O_2; $PhI(OAc)_2$, TEMPO; iii, LiSePh, (+)-5-menthyloxy-2(5*H*)-furanone; iv, xylene, 140 °C; v, Tf_2O, DMAP; KNO_2, DMF, 18-crown-6; vi, *p*-$O_2NC_6H_4COOH$; TBAF; SO_3.pyridine; K_2CO_3; TFA, H_2O, acetone.



Scheme 46 *Reagents*: i, PDC; TBAF; DMSO, SO_3.pyridine; TFA, H_2O; ii, Tf_2O, DMAP; 2,6-lutidine; iii, TBAF; DMSO, SO_3.pyridine; OsO_4 (cat.), NMO; TFA, H_2O.



Scheme 47 *Reagents*: i, $(dba)_3Pd_2.CHCl_3$, trifurylphosphine, $(C_2H_5)_3SiH$, HCOOH, toluene, 80 °C; ii, Tf_2O, 2,6 lutidine; iii, TBAF, DMSO, SO_3.pyridine; OsO_4, (cat.), NMO; TFA, H_2O.

which includes conversion of the hydroxyl group into a triflate and substitution of the latter by potassium nitrite in the presence of traces of water. In this way (−)-mniopetal F (131) was synthesized in fourteen steps in 10% overall yield.

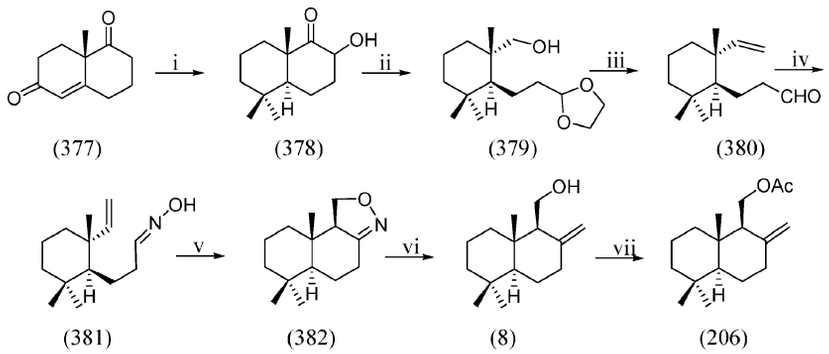
(−)-Kuehneromycin A (132)[309] and (−)-mnioptetal E (137)[310] were easily synthesized *via* cycloadduct (370)[311] (see Scheme 45) in 57% and 36%, respectively as illustrated in Scheme 46.

Palladium catalyzed reductive cyclization of diynes represents an attractive method for the synthesis of complex drimanes, *e.g*. siccanin (376), a clinically important antifungal agent with a *cis* fused AB ring system (see Scheme 47).[312] It is noteworthy that both *trans* and *cis* drimanes are accessible by this method.

Cycloreduction of (373) was effected in 80% yield to give a geometrically homogeneous diene (374). Deprotection of one of the aromatic methyl ethers with sodium ethylthiolate gave (375), and BF_3 etherate effected its direct cyclization to siccanin methyl ether. Demethylation gave siccanin (376).

A highly diastereoselective intramolecular [3+2] cycloaddition of a nitrile oxide as key step was involved in the total synthesis of (+)-albicanol (8) (see Scheme 48).[313,314]

Hydroxy ketone (378) was prepared from (+)-Wieland–Miescher ketone (377). Oxidative cleavage of (378) followed by immediate acetalization of the crude formyl ester and reduction of the ester, gave alcohol (379), which was still enantiomerically pure. Oxidation followed by a Wittig reaction and hydrolysis gave the aldehyde (380) in 53% overall yield. Oximation afforded an inseparable mixture of *syn* and *anti* oximes (381). When this mixture was stirred with sodium hypochlorite a clean reaction provided isoxazoline (382) as the sole product in 86% yield. (+)-Albicanol (8) and its (+)-acetate (206) were obtained straightforwardly from this intermediate.



Scheme 48 *Reagents*: i, pyridinium perbromide; NaOH; ii, $Pb(OAc)_4$; ethylene glycol, *p*-TsOH; $LiAlH_4$; iii, Swern oxidation; $Ph_3P{=}CH_2$; HCl, H_2O; iv, NH_2OH; v, NaOCl; vi, H_2, Raney Ni; Zn, CH_2Br_2, $TiCl_4$; vii, Ac_2O.

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