Synthesis of Polyquinane Natural Products: An Update†

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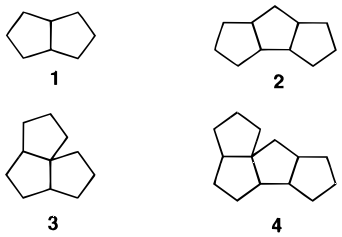
I. Introduction

Terpenoids are among Nature's more versatile and exciting creations. In a remarkable display of synthetic ingenuity and creativity, Nature has endowed terpenes with a bewildering array of carbocyclic frameworks with unusual assemblage of rings and functionalities. As a consequence of this phenomenal structural diversity, terpenes as a class of natural products hold special appeal to synthetic chemists and provide a fertile ground for developing and testing new synthetic strategies, particularly those directed toward carbocyclic ring construction. Among the terpenes, a relatively small but rapidly growing subgroup (~250 natural products) is of polyquinanes ("poly+quin+ane", *quin*, abbreviation of quintet or quintuplet, meaning five, f.L. *quintus*; this colloquial name has been commonly accepted), composed entirely of fused five-membered rings.

While polyquinanes have been known to Nature since time immemorial, they were revealed to humans only recently. In fact, the structure determination of the first "authentic" polyquinane natural product, hirsutic acid-C, was accomplished only in 1966. Despite this belated discovery, polyquinane natural products have rapidly proliferated and have been encountered among plant, marine, and microbial sources. Polyquinane skeleta have been found among sesqui-, di-, sesterterpenes and even in steroids. So far, natural products containing up to four fused five-membered rings have been unraveled with **1**−**4** representing the characteristic polyquinane carbocyclic skeleta.



The polyquinane natural products, quite expectedly, have aroused a great deal of interest among synthetic chemists in recent years, primarily on account of the architecturally pleasing assembly of five-membered rings, embellished with a number of methyl groups and the wide-ranging biological activity exhibited by some members of this family. Indeed, polyquinanes have spearheaded the drive and provided the impetus for the development of new strategies for cyclopentannulations. Throughout the decade of 1980s, polyquinane synthesis was considered as one of the "vibrant" areas of natural products synthesis and even in the 1990s, interest in them remains unabated. In view of this intense activity directed toward polyquinane synthesis, the literature

† Dedicated with affection and admiration to Professor Horst Prinzbach on his 65th birthday.

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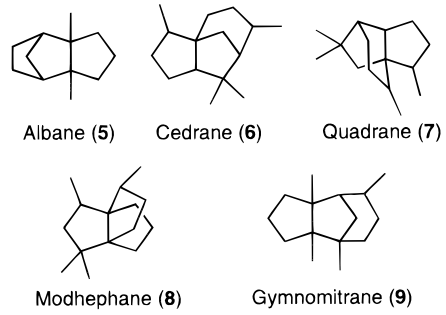
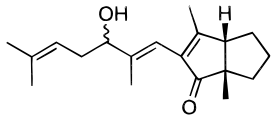
on the subject has been periodically reviewed,[1−6] particularly by Paquette *et al.*[1,3,5] However, the last monograph on the subject appeared in 1987 with literature coverage upto early 1986.

The accomplishments of the past decade in the area of polyquinane synthesis are extensive and impressive and have provided the motivation for preparing the present review. We have endeavored to cover the literature from 1986 to early 1996, but excluded the 1986 contributions covered earlier.[5] In order to provide a fairly comprehensive coverage, we have also included synthesis of those naturally occurring entities which contain a polyquinane moiety as a part structure, *e.g.* cedranoids and laurenene. However, general synthetic methodologies to polyquinanes, not specifically targeted toward a natural product, have been excluded from the scope of this review. For example, synthetic studies related to the "super polyquinane" dodecahedrane and its siblings, would not find coverage here. All the syntheses covered in this review have been presented schematically and chronologically, in easy to follow style, along with the reagents employed and yields obtained. In each case, the key strategy or reaction has been highlighted in the text. Wherever stereochemical nuances are involved and selectivity aspects (regio, stereo, and enantio) are critical, they have been duly commented upon. For the sake of completeness, while covering the literature during the period under review, we have also compiled the relevant earlier references on the total synthesis of polyquinane natural products.

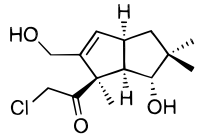
II. Diquinanes

While the occurrence of diquinane moiety as a part structure among terpenes has been known for quite sometime, *e.g.* albane (**5**), cedrane (**6**), quadrane (**7**), modhephane (**8**), gymnomitrane (**9**), etc., it was only recently that natural products composed only of this diquinane unit have been isolated. These are represented by xestenone (**10**)[7] and chloriolin (**11**)[8] among others. However, over the years, ring systems **5**−**9** have found much favor with the practitioners of total synthesis.





Xestenone (**10**)[7]



Chloriolin-A (**11**)[8]

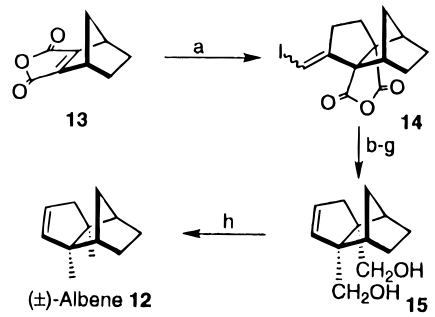
A. Albene

The trisnorsesquiterpene (−)-albene **12** was first isolated in 1962 from the plant *Petasites albus*.[9] The presence of a tricyclo[5.2.1.0^{2,6}]decane (2,4-ethanodiquinane) framework, incorporating two *endo*-methyl groups on two vicinal quaternary carbon atoms, has made it an interesting synthetic target,[10] and it continues to attract considerable attention. The new syntheses[11−13] of **12** reported during the period covered by the present review exhibit excellent stereoselectivity as they all exploit the proclivity of the norbornyl framework to react on the *exo* face.

Curran and Chen's[11] formal synthesis of (±)-albene (**12**) involves an atom transfer radical annulation

step as the key reaction (Scheme 1). Hexabutylditin-

Scheme 1[11]

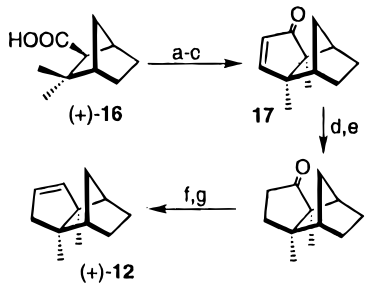


Reagents: (a) $HC{\equiv}CCH_2CH_2I$, $(^nBu_3Sn)_2$, AIBN, sun lamp; (b) NaOH; (c) CH_2N_2; (d) $^nBu_3SnH$, AIBN; 55% (for a-d); (e) O_3; $NaBH_4$; (f) MsCl, Δ; (g) LAH; 32% (for e-g); (h) ref. 10f.

catalyzed, stereoselective cyclopentannulation of the bicyclic anhydride **13** with butynyl iodide resulted in the *exo*-annulated product **14**. Degradation of the exocyclic olefin moiety in **14** and further functional group transformations led to the diol **15**, an intermediate in the Trost synthesis[10f] of (±)-**12**.

Sonawane and co-workers[12] have reported a synthesis of the unnatural antipode (+)-**12** of albene, starting from (+)-isocamphenilanic acid **16** (Scheme 2). The α-diazo ketone derived from **16** on rhodium

Scheme 2[12]

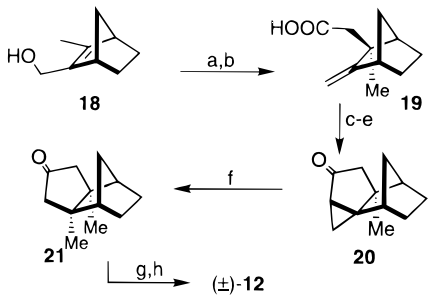


Reagents: (a) $(COCl)_2$; CH_2N_2; 93%; (b) $Rh_2(OAc)_4$, 88%; (c) $PdCl_2$, $Pd(OAc)_2$, O_2, 89%; (d) LDA, MeI, 82%; (e) H_2, Pd-C, 95%; (f) $TsNHNH_2$, 90%; (g) MeLi, 80%.

acetate-catalyzed, stereospecific intramolecular CH insertion into the *exo*-methyl group, followed by palladium(II)-mediated dehydrogenation furnished the tricyclic enone **17**. Regio- and stereoselective α-methylation at the more hindered *endo* face installed the second quaternary center and further functional group transformations led to (+)-**12**. The synthesis employs readily available chiral precursor, and very good yields have been claimed in all the steps.

The orthoester Claisen rearrangement within a norbornene derivative **18** was exploited by Srikrishna and Nagaraju[13,14] to stereoselectively install a quaternary carbon center on the norbornane framework (Scheme 3). Intramolecular cyclopropanation of the α-diazo ketone derived from the acid **19** and regiospecific cyclopropane cleavage (**20** → **21**) established the two vicinal quaternary carbon centers. Further functional group manipulations completed the synthesis of (±)-**12**.

Scheme 3[13,14]



Reagents: (a) $MeC(OEt)_3$, EtCOOH, Δ, 81%; (b) NaOH, 76%; (c) $(COCl)_2$; (d) CH_2N_2; (e) $CuSO_4$, 53%; (f) Li, liq. NH_3 or H_2, Pd-C, 81 or 99%; (g) $TsNHNH_2$, 86%; (h) ^nBuLi, 65%.

B. Cedranoids

The cedranoid sesquiterpenes composed of cedrane (**6**)[15] and isocedrane (**22**)[16] (also referred to as trixane) skeleta are widely distributed in Nature. The pres-

Cedrane (**6**) Trixane (Isocedrane) (**22**)

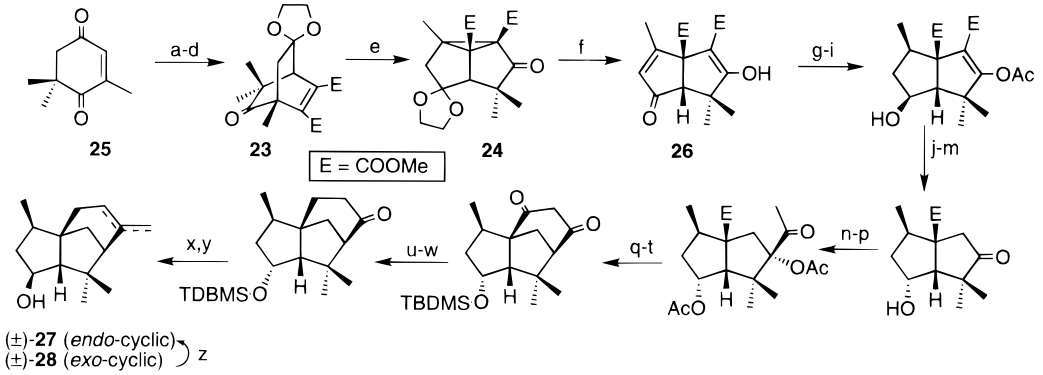
ence of a tricyclic framework, incorporating both the diquinane and bicyclo[3.2.1]octane moieties, makes these systems interesting to synthetic chemists; and despite several earlier syntheses,[17] new approaches continue to be explored. Besides the construction of the tricyclic carbon framework, a major concern in the synthesis of cedranoids is the stereocontrol of the remote secondary methyl group and build up of functionality in the case of highly oxygenated members.

Yates and co-workers[18−20] have employed a photochemical oxa-di-π-methane rearrangement in a bicyclo[2.2.2]octane derivative (**23** → **24**) for the construction of the diquinane part of cedranes (Scheme 4). The bridged bicyclic precursor **23** was assembled through a Diels−Alder reaction between the dienol acetate of cyclohex-2-ene-1,4-dione **25** and dimethyl acetylenedicarboxylate. Regioselective cyclopropane cleavage afforded the diquinane **26**, which on metal−ammonia reduction stereoselectively installed the secondary methyl group. Further elaboration through a series of functional group transformations, reminiscent of the Stork−Clarke synthesis,[17a] led to naturally occurring[21] (±)-α- and β-biotols **27** and **28** (Scheme 4).

An electrochemical route has been developed for the synthesis of (±)-cedranoxide (**29**)[22] by Yamamura and co-workers[23,24] in which an efficient anodic oxidation−cyclization of the phenol **30** and a series of selective transformations afforded the oxa-tetracyclic dione **31**. Double Wolff−Kishner reduction in **31** furnished (±)-cedranoxide (**29**) (Scheme 5). The brevity of this sequence is partly offset by the nonstereoselectivity in the initial electrocyclization step.

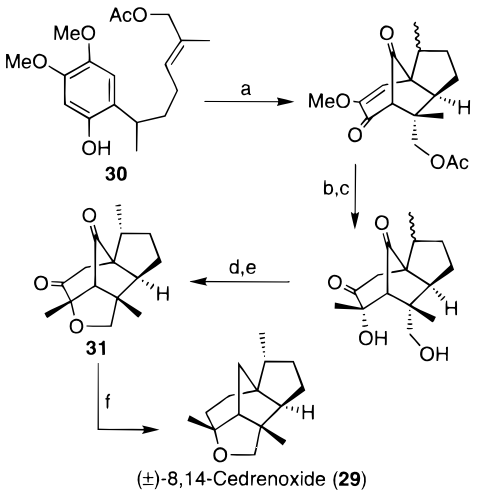
A short, tandem radical cyclization approach to *epi*-Δ^2-cedrene (**34a**) has been reported by Chen and coworkers.[25−27] Generation of a radical from the tertiary nitro compound **32** furnished the tricyclic compound **33** via two sequential 5-*exo*-*trig* cyclization

Scheme 4[18−20]



Reagents: (a) CH_2=C(Me)-OAc, H^+; (b) EC≡CE; (c) NaOMe; 83% (for a-c); (d) $(CH_2OH)_2$, H^+, 92%; (e) $PhCOCH_3$, hν, 94%; (f) H_2SO_4, 98%; (g) Li, liq. NH_3, 41%; (h) Ac_2O, py, 96%; (i) $NaBH_4$, 100%; (j) K_2CO_3, 99%; (k) NaCl, DMSO, Δ, 62%; (l) PPh_3, DEAD, BzOH, 68%; (m) K_2CO_3, 92%; (n) HC≡CLi, $CeCl_3$, 73%; (o) HgO, H_2SO_4, 94%; (p) Ac_2O, DMAP, 65%; (q) $^nBu_3SnH$, AIBN, 91%; (r) K_2CO_3, 100%; (s) TBDMSOTf, lutidine, 85%; (t) ^tBuOK, 96%; (u) LAH; (v) CrO_3, py; (w) H_2, Pd-C; 74% (for u-w); (x) MeLi, 95%; (y) $SOCl_2$, py, 81%; (z) HF, 70%.

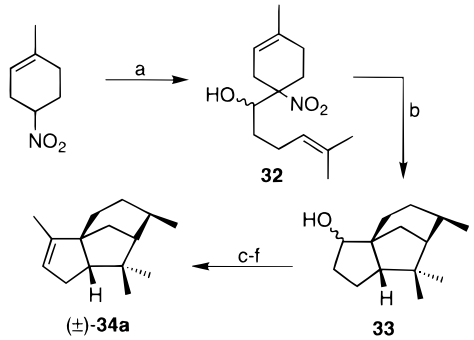
Scheme 5[23,24]



Reagents: (a) anodic oxdn., 80%; (b) MeMgI, 51%; (c) $(COOH)_2$, 93%; (d) separation; (e) $BF_3.OEt_2$, 72%; (f) W.K. redn., 64%.

reactions, which on further transformations led to (±)-8-*epi*-Δ^2-cedrene (**34a**) (Scheme 6).[25] Further

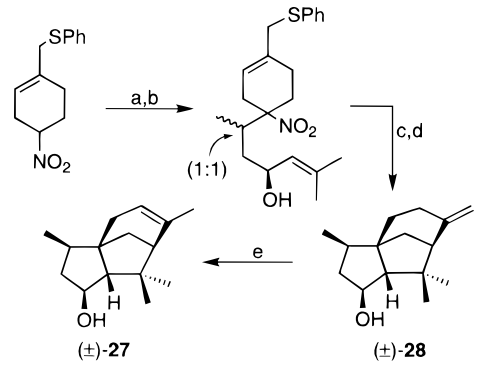
Scheme 6[25]



Reagents: (a) Me_2C=$CH(CH_2)_2CHO$, Amberlyst A-21, 62%; (b) $^nBu_3SnH$, AIBN, 52%; (c) CrO_3, 99%; (d) MeLi, 98%; (e) $SOCl_2$, py; (f) HI, 82%.

modifications of this approach, incorporating a thiophenyl leaving group,[26] led to an exceptionally short synthesis (cf. Scheme 4) of (±)-α- and *β*-biotols **27** and **28** (Scheme 7),[27] although separation of diasteromers had to be effected in the precursor employed for the tandem radical cyclization.

Scheme 7[27]



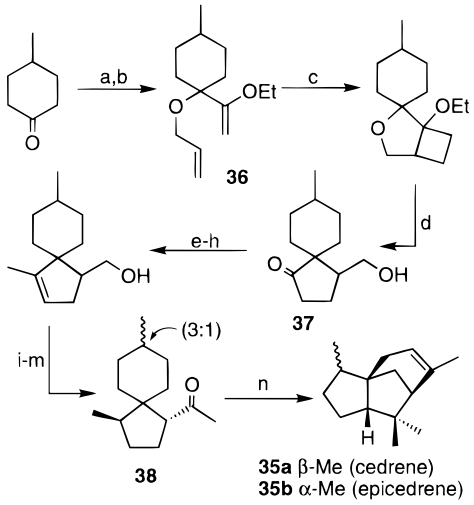
Reagents: (a) MeCH=CHCHO, DBU, 66%; (b) Me_2C=CH-MgBr, 60%; (c) separation; (d) $^nBu_3SnH$, AIBN, 55%; (e) HI, 93%.

Ghosh and Patra[28] devised a spirocyclopentannulation sequence toward a formal synthesis of (±)-cedrene (**35a**) and (±)-epicedrene (**35b**) (Scheme 8). Copper-catalyzed intramolecular [2+2]-photocycloaddition in the enol ether **36**, followed by trifluoromethanesulfonic acid-catalyzed rearrangement led to the spiro[4.5]decanone **37**. Further transformations furnished a 3:1 epimeric mixture of the spiro compound **38**, a known precursor of (±)-cedrene (**35a**) and (±)-*epi*-cedrene (**35b**).

Very recently, Mukherjee *et al.*[29] have reported the synthesis of (±)-Δ^2-cedrene (**34b**), a naturally occurring hydrocarbon from vetiver oil,[15d] employing intramolecular anionic cyclization (**39** → **40**) as the key step (Scheme 9). Stereoselective hydrogenation of the enol lactone **41**, obtained from the indanone **42**, and functional group manipulations generated the bromophenol **39**. Cyclization of the bromophenol **39** and further transformations involving the cyclohexanone ring contraction led to (±)-**34b**.

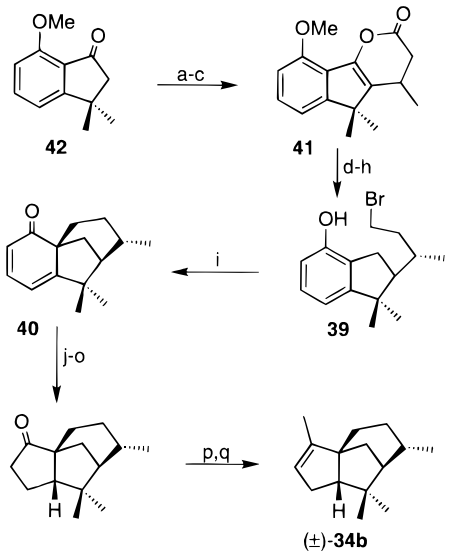
The total synthesis of highly oxygenated cedranoids, α- and *β*-pipitzols (**43** and **44**),[30] has been reported by two groups. An intramolecular Diels−Alder reaction (**45** → **46**) in a tropone derivative,

Scheme 8[28]



Reagents: (a) CH_2=CH-OEt, ^{t}BuLi, 81%; (b) NaH, CH_2=$CHCH_2Br$, 89%; (c) CuOTf, hν, 58%; (d) TfOH, 76%; (e) DHP, PPTs; (f) MeLi; (g) MeOH, PPTs; 67% (for e-g); (h) DMSO, Δ, 73%; (i) PtO_2, H_2, 99%; (j) Swern oxdn.; (k) MeLi; (l) Jones oxdn.; (m) NaOMe, MeOH; 55% (for j-m); (n) ref.17j.

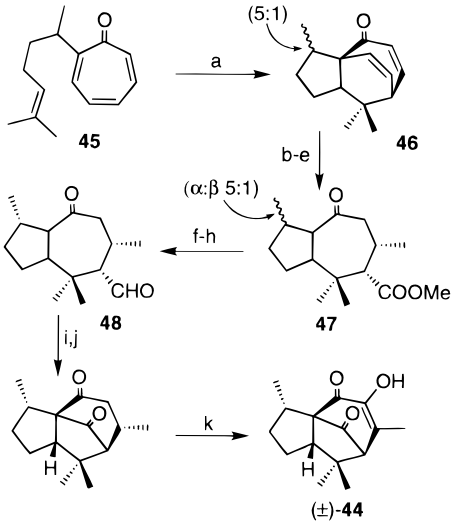
Scheme 9[29]



Reagents: (a) MeCH=CHCOOMe, NaOEt, 60%; (b) NaOH; (c) Ac_2O, NaOAc; 85% (for b-c); (d) H_2, catalyst; (e) CH_2N_2; 92% (for d-e); (f) LAH; (g) PBr_3; (h) BBr_3, 90%; (i) ^{t}BuOK, 74%; (j) H_2, catalyst, 96%; (k) HCOOEt, NaH; (l) H_2O_2, $^-$OH; 84% (for k-l); (m) CH_2N_2; (n) ^{t}BuOK; (o) -COOMe; 73% (for m-o); (p) MeMgI; (q) DMSO, Δ, 87%.

followed by conjugate addition of a methyl group and oxidative cleavage of the cyclohexene moiety for the generation of a 5−7 system **47**, were the key steps in the synthesis of α- and *β*-pipitzols by Funk and Bolton[31] (Scheme 10). Intramolecular aldol condensation and further oxidation transformed the major isomer of the ketoaldehyde **48** into (±)-*β*-pipitzol (**44**). The same sequence on the minor isomer of the keto ester **47** provided (±)-α-pipitzol (**43**). While the synthetic sequence leading to **43** and **44** is relatively short, it does require separation of diastereomers in the key intermediate **47**.

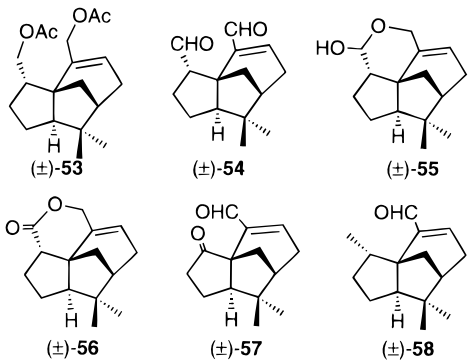
Scheme 10[31]



Reagents: (a) Δ or Et_2AlCl, 85%; (b) Me_2CuLi, 90%; (c) RuO_4, $NaIO_4$; (d) Δ; (e) CH_2N_2; 61% (for c-e); (f) separation; (g) LAH; (h) Swern oxdn.; 68% (for g-h); (i) NaOH, 96%; (j) PCC, 89%; (k) SeO_2, 50%.

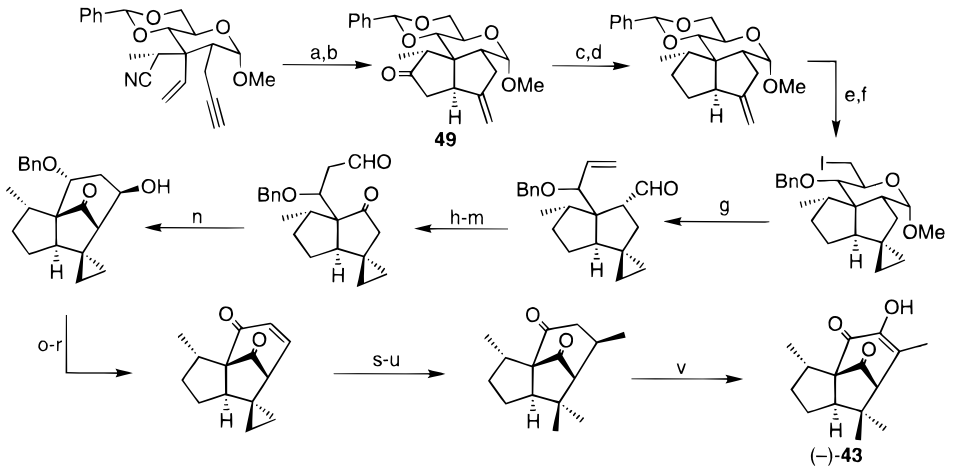
Fraser-Reid and co-workers[32] have employed the carbohydrates to carbocycles theme for an enantioselective synthesis of the unnatural antipode (−)-**43** of α-pipitzol (Scheme 11). The diquinane **49** was generated from methyl α-D-mannopyranoside using a nitrile-terminated tandem radical cyclization protocol. Restructuring of the carbohydrate portion to generate the six-membered ring and extensive functional group manipulations resulted in the unnatural enantiomer of α-pipitzol (−)-**43**.

Bohlmann and co-workers[33] have developed an intramolecular Diels−Alder strategy for accessing several functionalized isocedranes[16] (Scheme 12). A highly efficient and stereoselective intramolecular Diels−Alder reaction in a substituted cyclopentadiene **50** and functional group transformations afforded the tricyclic ketone **51**. Dichlorocarbene-mediated ring expansion and functional group readjustments eventuated in the synthesis of natural product (±)-**52**. The Bohlmann intramolecular Diels−Alder strategy is of general applicability and further adaptations of their scheme has led to the synthesis of isocedranoids (±)-**53**−**58**.[33]



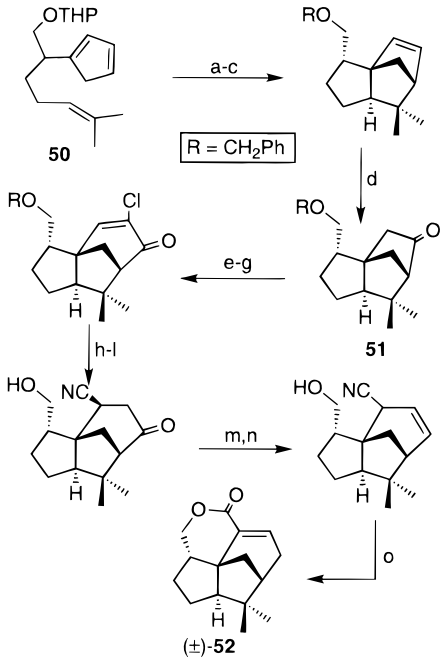
Paquette and Cheney[34] have reported their efforts toward the synthesis of (±)-trixikingolide (**59**),[35] a highly oxygenated, transannularly linked sesquiterpene belonging to the isocedrane family, via angularly fused tetraquinane precursors (Scheme 13).

Scheme 11[32]



Reagents: (a) $^{n}Bu_3SnH$, AIBN; (b) silica gel; 65%; (c) DIBALH, 88%; (d) PhOC(S)Cl; $^{n}Bu_3SnH$, AIBN; 70%; (e) $ZnEt_2$, CH_2I_2, 94%; (f) DIBALH; PPh_3, I_2; 54%; (g) Zn-Hg, 70%; (h) KHMDS, TBDMSCl; (i) m-CPBA; (j) TBAF; $NaBH_4$; 64% (for h-j); (k) $BH_3.SMe_2$; H_2O_2, ^{-}OH (l) $NaIO_4$; (m) PDC; 25% (for k-m); (n) Na_2CO_3, 90%; (o) TsCl, py; (p) H_2, Pd-C; (q) LiBr, DMF; (r) periodinane; (s) Me_2CuLi; (t) PtO_2, H_2; (u) periodinane; 24% (for o-u); (v) SeO_2,47%.

Scheme 12[33]

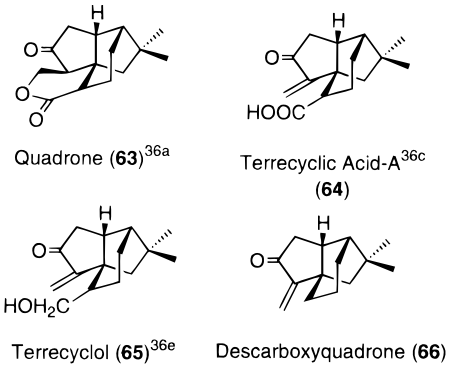


Reagents: (a) Δ; (b) H_3O^{+}; (c) NaH, BnBr; 94% (for a-c); (d) $(^{i}Am)_2BH$; H_2O_2, ^{-}OH; PCC; 92%; (e) LDA, TMSCl; (f) NaOEt, CCl_3COOEt; (g) HCl; 85% (for e-g); (h) $NaBH_4$, $CeCl_3$; (i) LAH; (j) MnO_2; 66% (for h-j); (k) KCN, NH_4Cl, 33%; (l) H_2, Pd-C, 95%; (m) $TsNHNH_2$, 97%; (n) NaOMe, 48%; (o) KOH, MeOH, 92%.

Readily assembled angular triquinane enone **60** was embellished into a highly functionalized derivative **61** via tetraquinane intermediates. However, the key intramolecular cyclization (**61** → **62**) thwarted further progress toward the natural product. The complex isocedranoid, trixikingolide (**59**), still remains an unattained synthetic objective.

C. Quadranoids

The promising biological activity and the presence of a novel structure closely resembling cedranoids, incorporating diquinane and bicyclo[3.2.1]octane moieties make the tetracyclic sesquiterpene lactone quadrone **63**[36a] and its ring-opened analogues terrecyclic acid-A (**64**)[36c] and terrecyclol (**65**), from the fungus *Aspergillus terreus*, attractive targets of synthesis.[37] Several new routes to these natural products and their descarboxy analogue **66** have appeared in the recent past employing imaginative strategies.

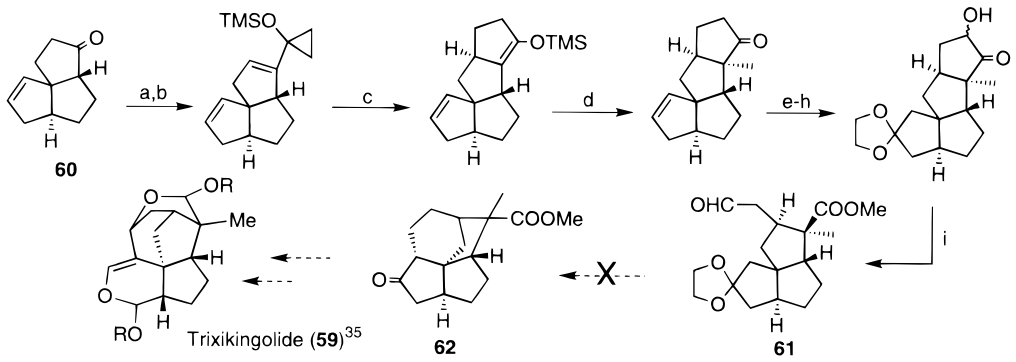


An acid-catalyzed rearrangement of the [3.3.3]-propellane derivative **67**, obtained from indene and vinyl acetate via arene−olefin meta-photocycloaddition and functional group manipulations, led to the tricyclo[4.3.2.0^{1,5}]undecanone (**68**), constituting a formal synthesis of (±)-descarboxyquadrone (**66**) (Scheme 14).[38]

In a similar approach, rearrangement of the [4.3.2]-propellane derivative **69**, obtained via [2+2]-photocycloaddition between hydrindenone **70** and vinyl acetate was exploited by Kakiuchi and co-workers[39] for the synthesis of (±)-descarboxyquadrone (**66**) (Scheme 15).

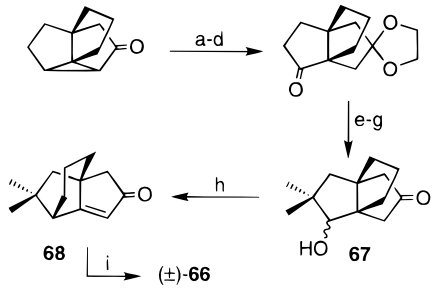
An Ireland−Claisen rearrangement-based approach leading to a formal synthesis of (±)-quadrone (**63**) has been reported by Funk and Ableman[40] (Scheme 16). Generation of the enol-TBDMS ether of the eight-membered lactone **71**, obtained from 4,4-dimethylcyclopentenone, on [3,3]-sigmatropic rearrangement afforded the diene acid **72**. Oxidative cleavage of the two olefinic moieties furnished the bicyclo[3.2.1]-octane-based diketo acid **73**, an advanced intermediate in Schlessinger's[37i] synthesis of (±)-quadrone (**63**).

Scheme 13[34]



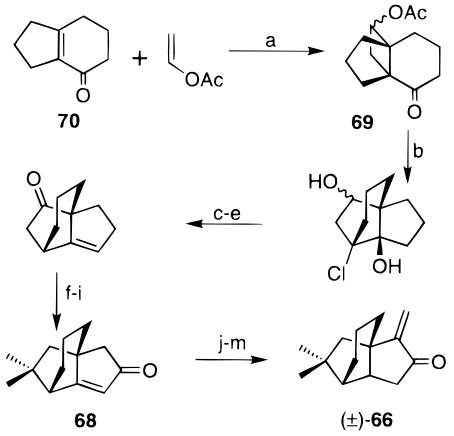
Reagents: (a) c-C_3H_5-S^+Ph_2 $^-BF_4$, KOH; (b) $LiNEt_2$, TMSCl; 58% (for a-b); (c) Δ; (d) MeLi; MeI; 44% (for c-d); (e) 9-BBN; H_2O_2, ^-OH, 94%; (f) Swern oxdn., 72%; (g) $(CH_2OTMS)_2$, TMSOTf, 84%; (h) LDA, MoOPh, 74%; (i) LTA, 94%.

Scheme 14[38]



Reagents: (a) HCOOH; (b) KOH; 95% (for a-b); (c) $(CH_2OH)_2$, H^+, 95%; (d) PCC, 82%; (e) ^{t}BuOK, MeI, 71%; (f) LAH, 95%; (g) Me_2CO, H^+, 95%; (h) $BF_3.OEt_2$, 25%; (i) ref. 37h,l.

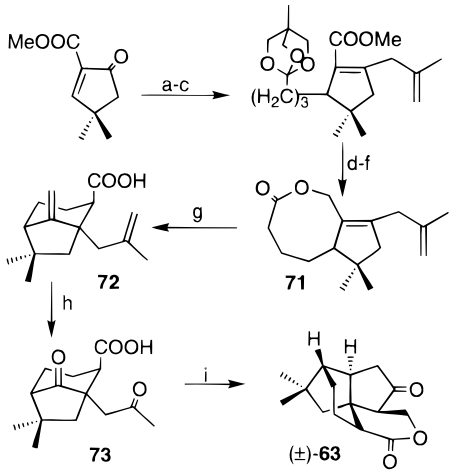
Scheme 15[39]



Reagents: (a) hν, 91%; (b) HCl, 72%; (c) PCC, 100%; (d) $SOCl_2$, py; (e) $^nBu_3SnH$, AIBN; 88% (for d-e); (f) NaH, MeI, 78%; (g) LAH, 98%; (h) NaH, CS_2; Me_2SO_4; $^nBu_3SnH$, AIBN; 33%; (i) CrO_3.DMP, 60%; (j) LDA, HCHO; (k) H_2, Pd-C; (l) MsCl, py, DMAP; (m) DBU; 52% (for j-m).

Regioselective cyclopropane cleavage in the tricyclic ketone **74** to deliver a functionalized bicyclo[3.2.1]-octane derivative and subsequent cyclopentannulation were the key elements in the Iwata's[41,42] synthesis of (±)-descarboxyquadrone (**66**) (Scheme 17). This methodology has been further extended[43] to (±)-quadrone (**63**), employing an intramolecular carboxylate-mediated, cyclopropane opening as the key step (**75** → **76**). Further elaboration of the lactone ring into cyclopentenone and functional group transformations led to the Danishefsky's[37a,b] precursor **77** of (±)-quadrone (**63**). In addition, Iwata and co-workers have published the details[44,45] of their earlier[37r] syntheses of (±)-quadrone (**63**) and (±)-terrecyclic acid-A (**64**).

Scheme 16[40]



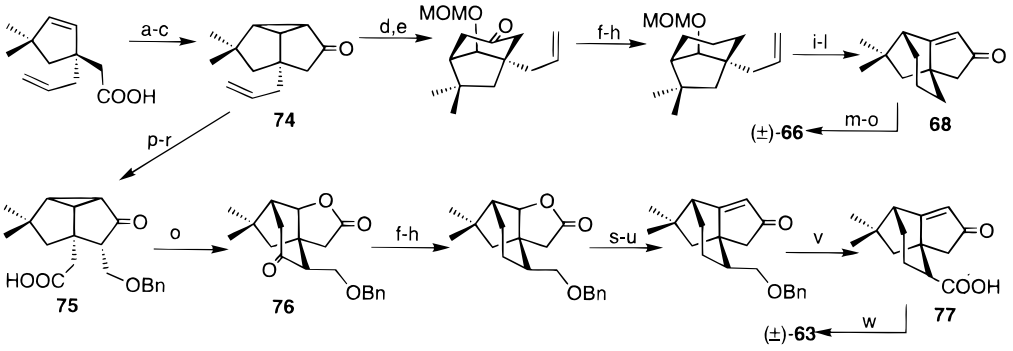
Reagents: (a) $[MeC(CH_2O)_3C(CH_2)_3]_2Cu(CN)Li_2$, 85%; (b) $PhNTf_2$, 83%; (c) $(CH_2=C(Me)CH_2)_2CuLi$, 96%; (d) LAH; (e) H_3O^+; (f) NaOH; 86% (for d-f); (g) LiHMDS, TBDMSCl, 79%; (h) $RuCl_3$; $NaIO_4$, 53%; (i) ref. 37i.

A stereoselective intramolecular Pauson−Khand bicyclization (**78** → **79**) was exploited by Magnus and co-workers[46] in their formal synthesis of (±)-quadrone (**63**) (Scheme 18). The precursor diquinane **79** on [2+2]-photocycloaddition with allene afforded the cyclobutane fused tricyclic compound **80** which was elaborated via ozonolysis and fragmentation to Isoe's[37m] precursor **81** of (±)-**63**.

Synthesis of natural quadrone (−)-**63**, from (−)-camphor-10-sulfonic acid (CSA) has been accomplished by Liu and Llinas-Brunet[47] (Scheme 19). Conversion to the cyclopenteneacetic acid **82** and setting up an intramolecular Horner−Wadsworth−Emmons reaction led to the diquinane **83**. Introduction of the acetate side chain was accomplished regioselectively via the allene [2+2]-photocycloaddition and degradative cyclobutane cleavage to give **84**. Further manipulation led to the keto ester **85**, which was elaborated to (−)-quadrone (**63**) employing Danishefsky's[37a,b] sequence.

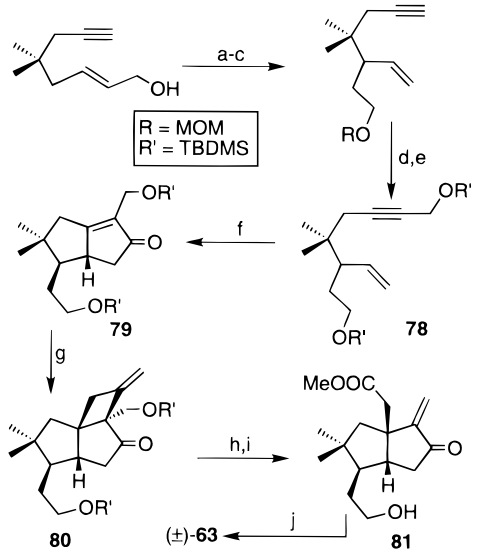
A vinyl radical cyclization (**86** → **87**) was the key reaction in Parsons and Neary's[48] novel approach to

Scheme 17[41−43]



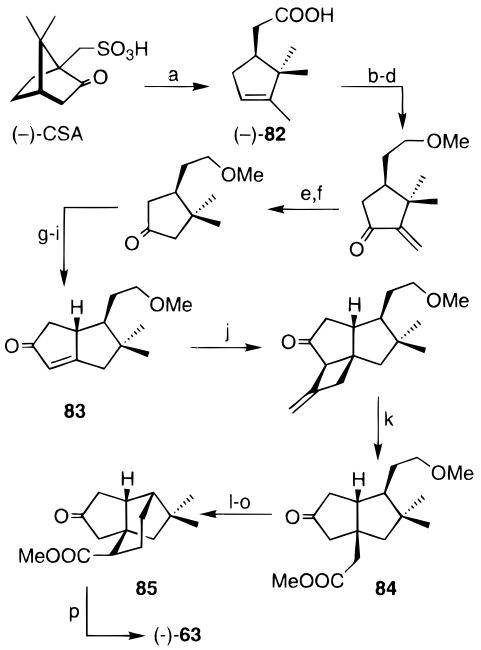
Reagents: (a) $(COCl)_2$; (b) CH_2N_2; (c) $CuSO_4$; 65% (for a-c); (d) HCOOH; NaOH; 29%; (e) MOMCl, $^iPr_2NEt$, 93%; (f) $NaBH_4$, 89%; (g) NaH, CS_2, MeI, 79%; (h) $^nBu_3SnH$, AIBN, 90%; (i) H_3O^+, 77%; (j) Jones oxdn., 75%; (k) $PdCl_2$, CuCl, O_2, 69%; (l) ^{t}BuOK, 81%; (m) LDA, MOMCl, 67%; (n) H_2, Pd-C, 88%; (o) TsOH, 97%; (p) LDA, $BnOCH_2Cl$, 83%; (q) O_3; AcOH, Zn; (r) Jones oxdn.; 61% (for q-r); (s) MeLi; (t) PCC; 60% (for f-h, s-t); (u) ^{t}BuOK, 60%; (v) Me_2S, $BF_3.OEt_2$; Jones oxdn.; 84%; (w) ref. 37a,b.

Scheme 18[46]



Reagents: (a) $MeC(OEt)_3$, EtCOOH, Δ, 73% (b) LAH, 92%; (c) MOMCl, Pr_2NEt, 79%; (d) BuLi, ClCOOEt, 86%; (e) LAH; NEt_3, TBDMSCl; 66%; (f) $Co_2(CO)_8$, CO, Δ, 45%; (g) $CH_2=C=CH_2$, hν, 84%; (h) H_3O^+, 96%; (i) O_3, MeOH; Me_2S, 90%; (j) ref.37m.

Scheme 19[47]



Reagents: (a) KOH; (b) LAH; (c) NaH, Me_2SO_4; 85% (for b-c); (d) O_2, TPP, hν, Ac_2O, DMAP, 78%; (e) H_2O_2; LiOH; (f) NaOH; 68% (for e-f); (g) LDA, $(EtO)_2P(O)CH=C(OEt)CH_2Br$; (h) H_3O^+; 48% (for g-h); (i) K_2CO_3, 18-C-6, 85%; (j) $CH_2=C=CH_2$, hν; (k) MeOH, O_3; Me_2S; 56% (for j-k); (l) TMSCl, NaI; (m) $(CH_2O)_2C(Me)Et$, H^+; 65% (for l-m); (n) LiHMDS; (o) H_3O^+; 60% (for n-o); (p) ref. 37a,b.

(±)-quadrone (**63**) (Scheme 20). An intramolecular aldol condensation−dehydration sequence was employed for the construction of the bicyclo[3.2.1]octane precursor **86**. The tricyclic enone **87** was restructured through oxidative cleavage and aldol cyclization to Danishefsky's[37a,b] precursor **77** of (±)-quadrone (**63**).

Little and co-workers[49] employed two sequentially orchestrated electrochemical reductive cyclizations (**88** → **89** + **90**; and **91** → **92**) for an elegant construction of the quadranoid framework (Scheme 21). The yields in the two electrochemical steps are extremely high and such cyclizations have the potential for further applications in polyquinane synthesis. Further transformations on **92** led to Kende's[37f] precursor **93** of (±)-quadrone (**63**).

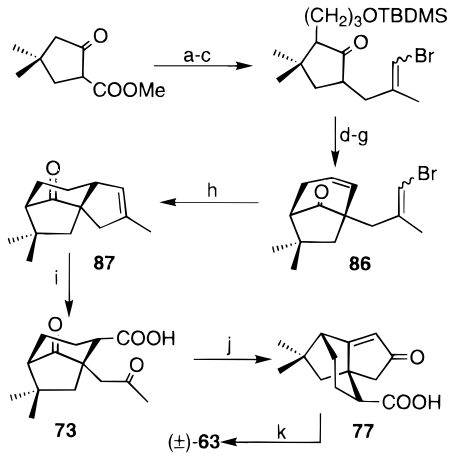
Hua *et al.*[50] have synthesized the quadranoid framework based on the acid-catalyzed rearrangement of a 1-methoxybicyclo[2.2.2]octane derivative into a bicyclo[3.2.1]octanone derivative (**94** → **95**) (Scheme 22).

Smith and co-workers[51] have disclosed the details of their synthesis[37h,q] of natural as well as racemic quadrone (**63**), involving the acid promoted rearrangement of a [4.3.2]propellane to the quadranoid framework as the pivotal step.

D. Pentalenolactones

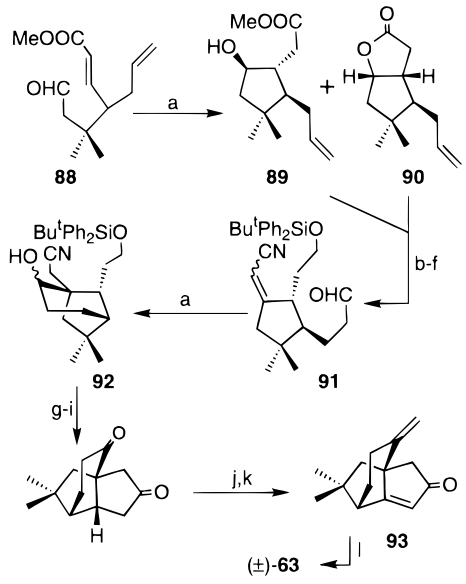
The diquinane-based pentalenolactone group (**96**−**105**, Chart 1) of antibiotics, isolated from *Streptomyces*, constitutes an interesting skeletal type among sesquiterpenes and has been known since 1969.[52] The interesting biogenesis through the humulene cycliza-

Scheme 20[48]



Reagents: (a) LDA, $I(CH_2)_3OTBDMS$, 75%; (b) NaH, $BrCH=C(Me)CH_2Br$; (c) LiI, lutidine; 88% (for b-c); (d) HF; (e) PCC; 64% (for d-e); (f) DBU, 72%; (g) NaH, Tol-OC(S)Cl; Δ; 30%; (h) $^nBu_3SnH$, AIBN, 80%; (i) RuO_2, $NaIO_4$, 100%; (j) ^{t}BuOK; (k) ref. 37a,b.

Scheme 21[49]

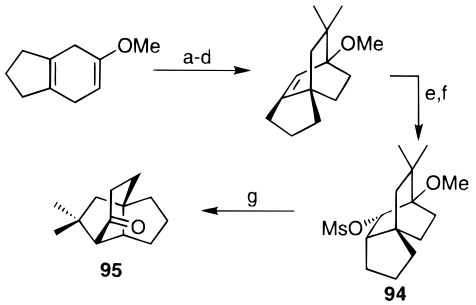


Reagents: (a) electro reductive cyclization, 89%; (b) LAH, 95%; (c) ^{t}BuPh$_2$SiCl, imidazole, 96%; (d) PCC; (e) $(OEt)_2P(O)CH_2CN$; 76% (for d-e); (f) 9-BBN; H_2O_2, $^-$OH; PCC; 85%; (g) PCC; TBAF; 92%; (h) $RuCl_3$, $NaIO_4$,90%; (i) $Na_2S_2O_8$, $AgNO_3$, 70-90%; (j)LiTMP, PhSeCl; H_2O_2; 93%; (k) $Ph_3P=CH_2$; 97%; (l) ref. 37f.

tion cascade and the promising biological properties of these compounds have aroused considerable interest in their synthesis,[53] and several approaches have been developed toward these natural products. Besides the construction of functionalized diquinane core, access to this family of sesquiterpenoids requires appending an α-oxy *δ*-lactone moiety in a stereoselective manner and creation of a quaternary carbon center.

Marino and co-workers[54] have explored a formal [3+2]-annulation strategy toward a synthesis of pentalenolactone-E methyl ester [(±)-**106**] (Scheme 23). A fluoride ion-mediated addition−cyclization sequence between the siloxy ester **107** and (thiophenyl)vinylphosphonium salt furnished the diquinane

Scheme 22[50]



Reagents: (a) $CH_2=C(Me)COOMe$, Δ, 79%; (b) LAH, 96%; (c) $(Me_2N)_2P(O)Cl$, NEt_3, DMAP, 86%; (d) Li, $EtNH_2$, 78%; (e) B_2H_6; H_2O_2, $^-$OH, 93%; (f) MsCl, NEt_3, 87%; (g) NaI, DMF, 65%.

diester **108** in very high yield, which on further functional group manipulations led to the lactone ester **109**. The latter has been converted into (±)-**106** by Paquette *et al.*[53e,f]

A combination of an intramolecular Pauson−Khand bicyclization (**110** → **111**) and a stereo- and regiospecific 1,4-addition of sulfinylallyl anion to enone (**111** → **112**) constitute the key steps in the formal synthesis of (±)-pentalenolactone-E methyl ester (**106**) by Hua and co-workers[55] (Scheme 24). Functional group modifications and oxidative cleavage of the olefinic moiety led to the tricyclic keto acetal **113**, which had been earlier transformed into (±)-pentalenolactone-E methyl ester **106** by the groups of Cane[53j] and Paquette.[53e,f]

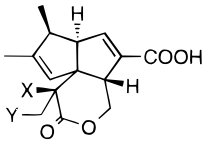
The Bakers' yeast-mediated kinetic resolution of the diquinane **114**, was exploited in the formal synthesis of chiral pentalenolactone-E methyl ester [(−)-**106**] by Mori and Tsuji[56] (Scheme 25). A series of functional group manipulations transformed the keto ester (+)-**114** into the hydroxy ketal (+)-**115**, which was elaborated into pentalenolactone-E methyl ester [(−)-**106**], following a methodology developed earlier for (±)-**106** by Cane *et al.*[53j]

As an application of their general methodology for the construction of α-methylenecyclopentanones, Demuth and co-workers[57] have in a short sequence synthesized the tricyclic lactone **116**, containing the pentalenolactone framework (Scheme 26). The [2+2]-photocycloaddition between cyclopentenone **117** and 2-siloxybutadiene afforded the (silyloxy)vinylcyclobutane **118**, which on palladium-catalyzed ring expansion (**118** → **119**) and lactonization led to the diketo lactone **116**.

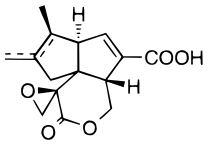
Pirrung and Thomson[58,59] have reported the first total synthesis of the methyl ester of pentalenolactone-G (**120**), one of the more complex members of this family (Scheme 27). The intramolecular allene−enone [2+2]-photocycloaddition in the acetal **121** and stereoselective reduction and epoxidation provided the key intermediate **122**. Regioselective ring expansion of the epoxycyclobutane **122** furnished the pentalenolactone skeleton **123**. A series of functional group manipulations eventuated in (±)-pentalenolactone-G methyl ester (**120**). Deoxygenation of the hydroxy group in the intermediate **122** and ring expansion also provided an entry into the (±)-pentalenolactone-E methyl ester (**106**), via **113**.

In 1989, Magnus and co-workers[60] reported an approach to (±)-pentalenolactone-H (**104**) (Scheme

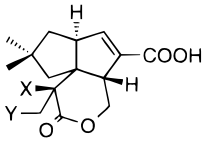
Chart 1



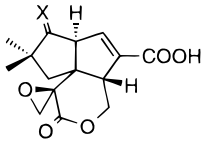
X-Y = O; Pentalenolactone (**96**)
X=Y=OH; Pentalenolactone-O (**97**)



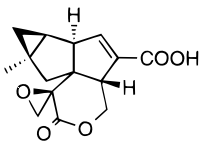
Pentalenolactones A & B
(**98** & **99**)



X=Y=H; Pentalenolactone-D (**100**)
X-Y=bond; Pentalenolactone-E (**101**)
X-Y = O; Pentalenolactone-F (**102**)

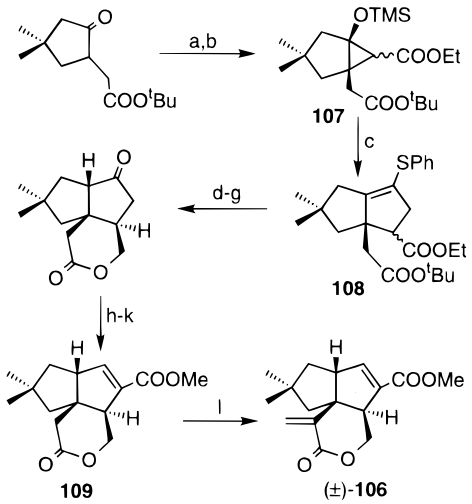


X=O; Pentalenolactone-G (**103**)
X=H,OH; Pentalenolactone-H (**104**)



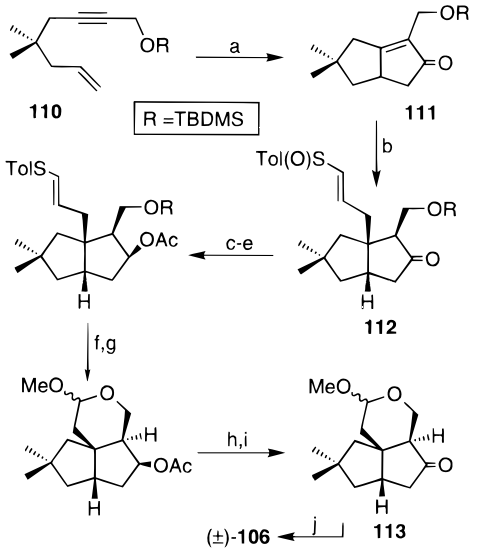
Pentalenolactone-P
(**105**)

Scheme 23[54]



Reagents: (a) TMSCl, NEt_3; (b) $N_2CHCOOEt$, $CuSO_4$; 65% (for a-b); (c) CH_2=C(SPh)-P^+Ph_3 BF_4^-, KF, 95%; (d) NaOH; (e) separation; (f) ClCOOEt, NEt_3; $NaBH_4$; (g) TFA; 43% (for d-g); (h) pyrrolidine, H^+; (i) ClCOOMe; (j) $NaCNBH_3$, HCl; (k) m-CPBA; 60% (for h-k); (l) ref. 53e,f.

Scheme 24[55]



Reagents: (a) $Co_2(CO)_8$, CO, Δ, 65%; (b) ^{n}BuLi, CH_2=$CHCH_2$S(O)Tol, 60%; (c) $NaBH_4$, 92%; (d) AcCl, py; (e) Zn, AcOH; 90% (for d-e); (f) O_3, MeOH; Me_2S; (g) HF; 83% (for f-g); (h) K_2CO_3, 96%; (i) PCC, 92%; (j) ref. 53e,f,j.

28). The intramolecular Pauson−Khand bicyclization of the enyne **124** and [2+2]-photocycloaddition with allene afforded the tricyclic enone **125**. Oxidative cleavage of the *exo*-methylene group and *in situ* fragmentation of the 1,3-diketone moiety, transformed the enone **125** into the enone ester **126**. Palladium-mediated carbonylation of the corresponding enol triflate followed by further functional group manipulations transformed the enone ester **126** into (±)-deoxynorpentalenolactone-H methyl ester (**127**).

Oppolzer and co-workers[61] have reported a formal synthesis of pentalenolactone-E methyl ester [(±)-**106**] in which they have employed a palladium-catalyzed intramolecular "allylation−methoxycarbonylation" cascade sequence (**128** → **129**) to generate the diquinane moiety in a highly diastereoselective manner (Scheme 29). The diquinane enone ester **129** was further carried to the Cane's (±)-pentalenolactone-E methyl ester intermediate **115**.[53j]

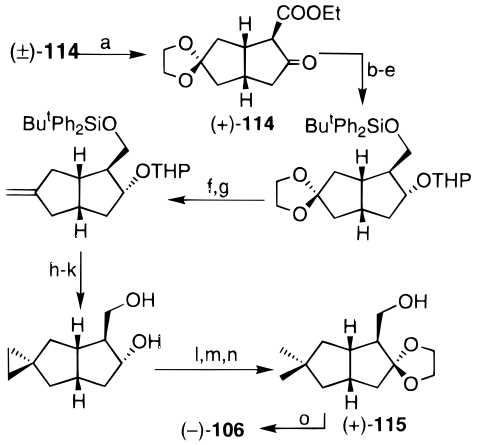
Recently, Paquette and co-workers[62,63] have reported the first total synthesis of the (±)-pentalenolactone-P methyl ester (**130**), a novel sesquiterpene[52h] containing a cyclopropane ring fused to the diquinane moiety (Scheme 30). The desired skeleton was assembled starting from the 1-methylnorcaradiene−dimethyl fumarate [4+2]-cycloadduct **131** which was obtained through a stereo- and regioselective high pressure Diels−Alder reaction. An efficient photochemical oxa-di-π-methane rearrangement on **132** was employed as the key step to generate a tetracyclic system **133**, embodying the tricyclic framework of pentalenolactone-P. Regioselective cleavage of the conjugated cyclopropane ring in **133** and further functional group transformations led to (±)-pentalenolactone-P methyl ester (**130**).

Taber and Schuchardt[64] have disclosed the details of their earlier reported[53k] synthesis of (±)-pentalenolactone-E methyl ester (**106**) based on an intramolecular CH insertion in an embellished α-diazo β-keto ester.

E. Modhephene

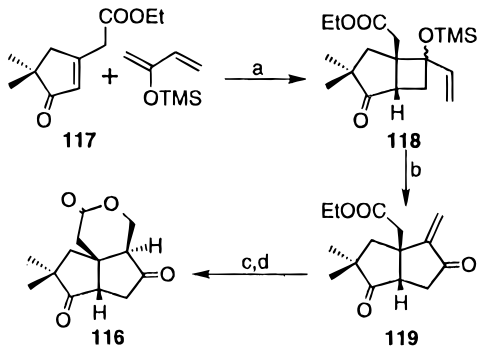
The sesquiterpene hydrocarbon modhephene (**134**) is the simplest member of a small group of sesquiterpenes containing a [3.3.3]propellane carbon framework and was isolated[65] from Rayless Goldenrod plant (*Isocoma wrightii*), known for its toxicity to cattle and sheep. The other members of this family

Scheme 25[56]



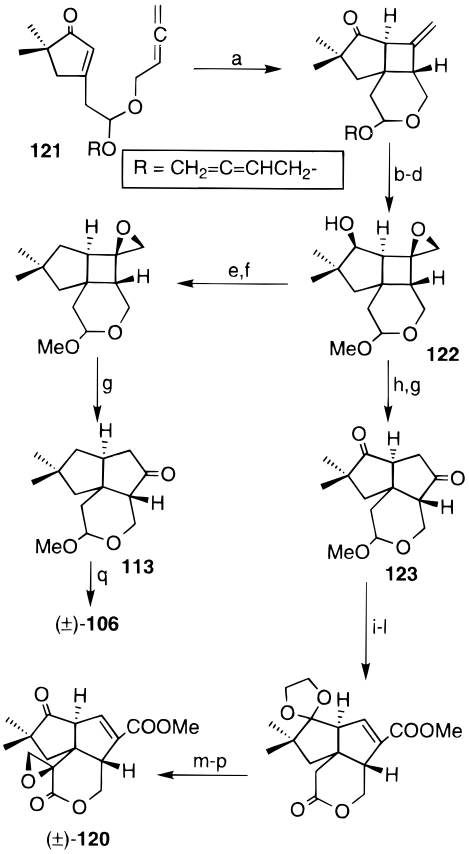
Reagents: (a) Baker's yeast, 32%; (b) $NaBH_4$, 72%; (c) DHP, PPTs; (d) LAH; 98% (for c-d); (e) $^tBuPh_2SiCl$, imidazole; (f) AcOH; DHP, PPTs; 60% (for e-f); (g) $Ph_3P{=}CH_2$; (h) H_3O^+; 87% (for g-h); (i) $CHCl_3$, NaOH; (j) TBAF; 87% (for i-j); (k) Li, liq. NH_3; (l) H_2, PtO_2; $^tBuPh_2SiCl$, imidazole; 54% (for k-l); (m) PCC; (n) $(CH_2OH)_2$, H^+; TBAF; 65% (for m-n); (o) ref. 53j.

Scheme 26[57]



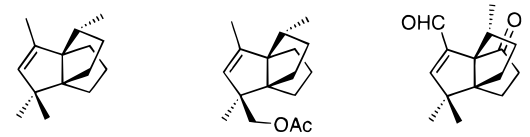
Reagents: (a) hν; (b) $PdCl_2(PhCN)_2$, benzoquinone; (c) HCl; (d) Δ.

Scheme 27[58,59]



Reagents: (a) hν, 70%; (b) L-selectride, 90%; (c) MeOH, H^+, 85%; (d) $VO(acac)_2$, ^tBuOOH, 85%; (e) NaH, CS_2, MeI; (f) $^nBu_3SnH$, AIBN; 73% (for e-f); (g) LiBr, HMPA, 85%; (h) PCC; LiBr, HMPA; 80%; (i) LDA, $PhNTf_2$, 65%; (j) $PdCl_2(PPh_3)_2$, CO, MeOH, 84%; (k) Jones oxdn.; (l) $(CH_2OH)_2$, H^+; 65% (for k-l); (m) LDA, $CH_2{=}N^+Me_2\ I^-$; (n) MeI; DBU; 50% (for m-n); (o) H_3O^+, 85%; (p) H_2O_2, ^-OH, 25%; (q) ref. 53e,f,j.

are the oxygenated derivatives **135** and **136**. The unique carbon skeleton of these propellanic sesquiterpenes continues to draw the attention of synthetic chemists, with the stereocontrolled placement of the remote secondary methyl group being a major concern.



Modhephene (**134**)[65a,b] 13-Acetoxymodhephene (**135**)[65d] Pulicaral (**136**)[65e]

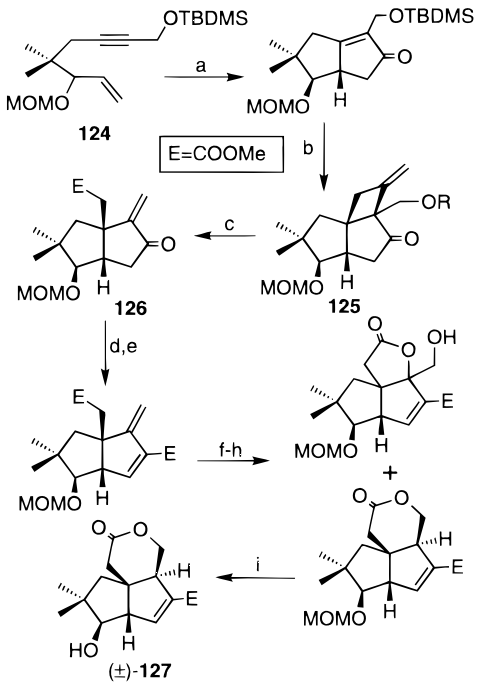
Fitzer and co-workers[67−69] have elegantly applied the facile acid-catalyzed rearrangement of the cyclobutane containing dispiranes toward a short synthesis of (±)- and (−)-modhephene (**134**) (Scheme 31). The key spirocyclic tertiary alcohol **137** was obtained from the dispiro ketone **138**, which in turn was assembled from isopropylidenecyclobutane (**139**) through dichloroketene addition (**139** → **140**), Wittig olefination with cyclobutylidinephosphorane (**140** → **141**) and ring expansion. Subsequently, the chiral alcohol corresponding to **137** was obtained through a kinetic resolution of the ketone **142** and rearranged to (−)-**134**.

Chiral auxiliary directed enantioselective cyclopropanation methodology has been applied by Mash *et al.*[70,71] for the chiral synthesis of unnatural enantiomer of modhephene [(+)-**134**] (Scheme 32). The readily available[66c] diquinane enone **143** was transformed into the chiral [3.3.1]propellane **144** via the chiral acetal **145**. Trimethylsilyl iodide-mediated cyclopropane cleavage in the ketone **144** and further elaboration afforded the ketoalkyne **146**, which was transformed into (+)-**134** employing a sequence developed earlier by Paquette.[66c,f]

Yamago and Nakamura[72] have developed a novel nickel- or palladium-catalyzed transannular methylenecyclopropane−olefin cycloaddition methodology for the rapid construction of the [3.3.3]propellane framework (**147** → **148**) (Scheme 33). Quite remarkably, near quantitative yields are obtained in this cycloaddition reaction. The propellane ester **148** was further elaborated into (±)-desmethylmodhephene (**149**), an analogue of the naturally available[65c] 13-acetoxymodhephene (**135**).

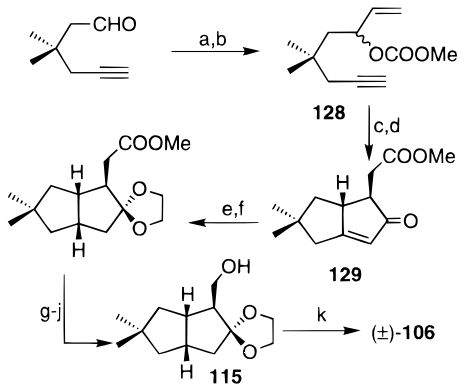
Sha *et al.*[73,74] have reported the synthesis of (±)-modhephene (**134**) and (±)-*epi*-modhephene (**150**), as an application of a radical cyclization-based general methodology for the cyclopentannulation of cyclic enones (Scheme 34). The commonly employed diquinane enone **143** was thus elaborated to the

Scheme 28[60]



Reagents: (a) $Co_2(CO)_8$, Δ, 64%; (b) $CH_2=C=CH_2$, hν, 80%; (c) O_3, MeOH; Me_2S, 62%; (d) Tf_2O; (e) $Pd(OAc)_2$, CO, PPh_3, NEt_3; 52% (for d-e); (f) m-CPBA; (g) $BF_3.OEt_2$; (h) $NaBH_4$; 15% (for f-h); (i) H_3O^+, 90%.

Scheme 29[61]



Reagents: (a) $CH_2=CHMgCl$; (b) ClCOOMe, py; 95% (for a-b); (c) $Pd(dba)_2$, CO, AcOH, PPh_3; (d) H_3O^+; CH_2N_2; 56% (for d-e); (e) H_2, $(PPh_3)_3RhCl$, 93%; (f) $(CH_2OH)_2$, H^+, 97% (g) LiOH; (h) $(COCl)_2$; N(ONa)pyridine-2-thione; (i) ^tBuSH, O_2; (j) $P(OMe)_3$; 41% (for g-j); (k) ref. 53j.

propellane **151** with stereoselective (4:1, α:*β*) placement of the *sec*-methyl group. Wittig methylenation of the propellane ketone **151** and olefin isomerization furnished a mixture of (±)-modhephene (**134**) and (±)-*epi*-modhephene (**150**). This approach is superior to the earlier reported[66f] intramolecular ene cyclization methodology which led to the *epi*-modhephene **150** predominantly.

Curran and Jasperse[75] have reported two vinyl radical cyclization-based approaches to (±)-modhephene (**134**). In their first approach, two sequential radical cyclization reactions (**152** → **153** and **154** → **155**) led to the [3.3.3]propellanic enone **155**. Addition of methyllithium to the enone **155** and *gem*-dimethylation of the tertiary alcohol furnished (±)-modhephene (**134**) and (±)-isomodhephene (**156**) (Scheme 35). While the two radical cyclization steps are fairly efficient, the efficacy of this approach is diminished due to the formation of regioisomeric mixture in the terminal step of the synthesis. In the second radical based route developed by Curran, 5-*exo*-*trig* radical cyclization reaction of the vinyl iodide **157**, derived from the ester **153**, and further transformations led to the exclusive formation of (±)-**134** (Scheme 36).

Subsequently, a tandem radical cyclization approach was devised by Curran and Shen[76] for a new synthesis of (±)-modhephene (**134**) and *epi*-modhephene (**150**) from cyclooctane-1,5-diol (Scheme 37). Barton's radical decarboxylation protocol on the dienic acid **158**, obtained via an Ireland−Claisen rearrangement (**159** → **158**), led to the propellane **160**. Further transformations completed the synthesis of (±)-**134** and (±)-**150**.

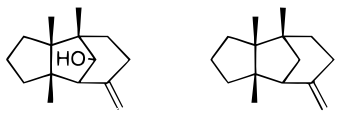
A Favorski-type ring contraction in a 1-bromobicyclo[3.3.1]nonanone derivative, mediated by the addition of diethylphosphonomethyl anion, leading to a diquinane ketophosphonate (**161** → **162**) was employed as the pivotal step by Kraus and Shi[77,78] in their synthesis of (±)-modhephene (**134**) (Scheme 38). The carbonyl-assisted, iridium-catalyzed hydrogenation of the olefinic moiety in **162** created the *sec*-methyl group in a stereoselective manner. Cyclization (**163** → **164**) of the ketophosphonate and functional group manipulations led to Curran's[75] precursor **155** of (±)-**134**.

Recently, Suri[79] has utilized the readily available[80] tricyclo[5.2.1.0^{2,6}]decane carboxylate **165** for a formal synthesis of (±)-modhephene **134** via the Oppolzer's[66g] advanced intermediate **166** (Scheme 39). The tricyclic system **165** was cyclopentannulated to the tetracyclic enone **167** incorporating the [3.3.3]propellane moiety of modhephene. Oxidative cleavage of the norbornane portion in **167** and functional group manipulations led to **166**.

The detailed account[81] of an earlier photochemical oxa-di-*π*-methane-based approach[66m] to (±)-modhephene (**134**) and (±)-*epi*-modhephene (**150**) by Mehta and Subrahmanyam has appeared.

F. Gymnomitrol

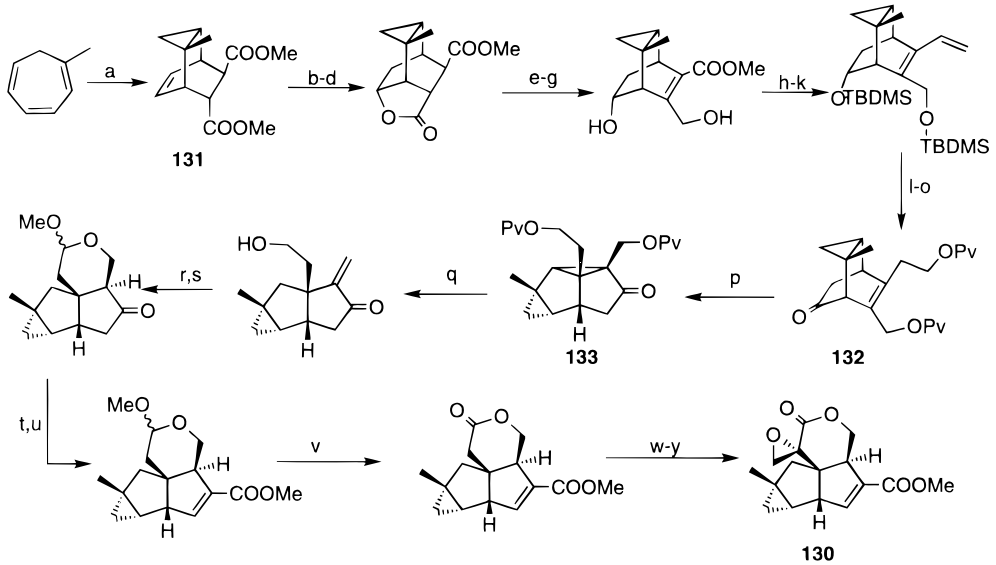
Gymnomitrol (**168**) along with gymnomitrene (**169**) and a few other derivatives have been isolated from the liverwort *Gymnomitrion obtusum* (Lindb.) Pears in 1970 by Connolly *et al.*[82] The presence of a novel tricyclic carbon framework incorporating three contiguous quaternary carbon centers has made these compounds attractive to synthetic chemists.[83]



Gymnomitrol (**168**)[82] Gymnomitrene (**169**)[82]

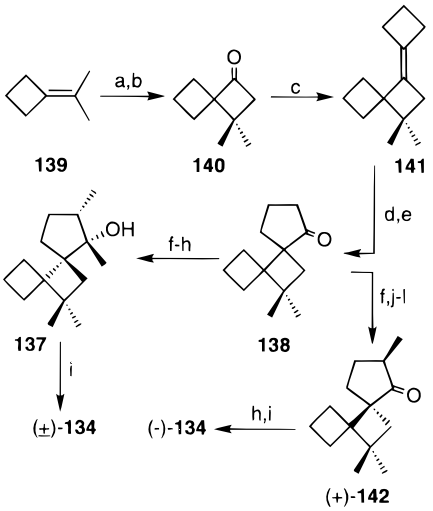
Imanishi and co-workers[84,85] reported the synthesis of (±)-isogymnomitrol **170**, wherein regioselective cyclopropane cleavage in the tetracyclic ketone **173** constituted the key step (Scheme 40). The diquinane **172**, prepared from **171**, was elaborated into the tetracyclic ketone **173** via α-diazo ketone insertion to an olefin. Acid induced cyclopropane cleavage (**173** → **174**) and functional group transformations led to

Scheme 30[62,63]



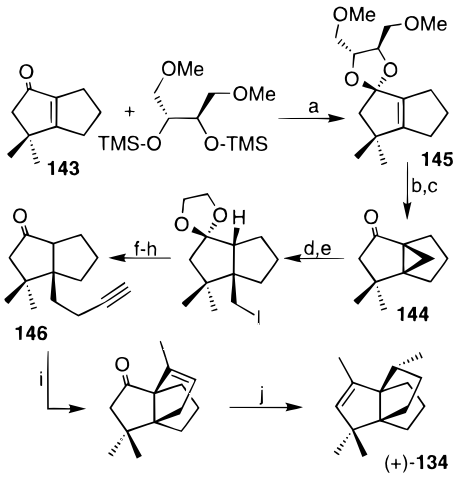
Reagents: (a) Fumaroyl chloride, 150000 psi; MeOH, py; 80%; (b) NaOH; (c) $Hg(OAc)_2$, $NaBH_4$; (d) CH_2N_2; 75% (for b-d); (e) $NaBH_4$; (f) $Me_2C(OMe)_2$, H^+; 76% (for e-f); (g) LDA, PhSeBr; m-CPBA, 72%; (h) TBDMSCl, imidazole; (i) DIBALH; 80% (for h-i); (j) TPAP, NMMO; (k) $Ph_3P{=}CH_2$; 93% (for j-k); (l) 9-BBN, $NaBO_3$; (m) PvCl, NEt_3; 87% (for l-m); (n) HF; (o) PvCl, DMAP; TPAP, NMMO; 70% (for n-o); (p) hv, 91%; (q) Li, liq. NH_3, 62%; (r) Swern oxdn.; (s) NaOMe, MeOH; 62% (for r-s); (t) LDA, $PhNTf_2$; (u) $Pd(OAc)_2$, PPh_3, NEt_3, CO; CH_2N_2; 66% (for t-u); (v) H_3O^+; TPAP, NMMO; (w) LDA, HCHO, 86%; (x) MsCl, NEt_3; DBU; 93%; (y) m-CPBA, 18%.

Scheme 31[67−69]



Reagents: (a) $Cl_2C{=}C{=}O$, 81%; (b) Zn, AcOH, 85%; (c) $Ph_3P{=}C(CH_2)_3$, 81%; (d) m-CPBA, 91%; (e) $BF_3{\cdot}OEt_2$, 54%; (f) LDA, MeI, 90%; (g) LDA, H^+, 66%; (h) MeLi, 69%; (i) TsOH, 65%; (j) (S)-Ph-S(O)(=NMe)CH_2Li, 84%; (k) separation; (l) Δ, 80%.

Scheme 32[70,71]



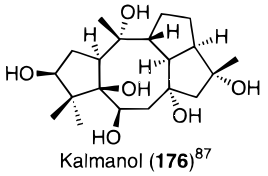
Reagents: (a) TMS-OTf, 70%; (b) Zn-Cu, CH_2I_2,84%; (c) H_3O^+, 94%; (d) TMSI, 85%; (e) $(CH_2OTMS)_2$, TMSOTf, 96%; (f) TMSC≡CCH_2Li; (g) H_3O^+; (h) TBAF; 82% (for f-h); (i) Δ, 57%; (j) ref. 66c,f.

the gymnomitrol methyl ether **175**, which on hydrolysis furnished (±)-isogymnomitrol (**170**).

Based on a photochemical oxa-di-π-methane rearrangement and regioselective cyclopropane cleavage methodology, Yamamoto and co-workers[86] reported the synthesis of the diquinane **172**, constituting a formal synthesis of (±)-gymnomitrol (**168**).

G. Kalmanol

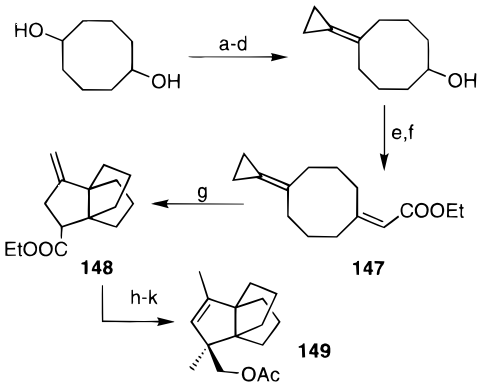
The unique diterpene kalmanol (**176**),[87] a minor constituent of *Ericaceae* leaves was isolated from *Kalmia angustifolia* L. in 1989, and possesses a complex tetracyclic structure composed of a diquinane fused to a bicyclo[6.3.0]undecane moiety as the basic framework.



Kalmanol (**176**)[87]

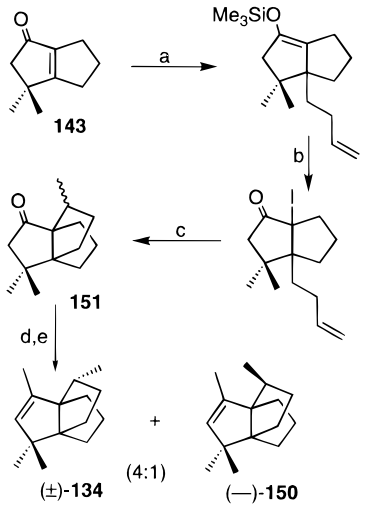
Recently, Paquette and Borrelly[88] reported the synthesis of a diquinane unit **177** for further elaboration to kalmanol **176** (Scheme 41). An intramolecular Pauson−Khand bicyclization was employed to construct the perhydrotriquinacene framework **178**. Functional group elaboration and oxidative cleavage of the cyclopentanone ring led to the diquinane **177**, comprising a subunit present in kalmanol (**176**).

Scheme 33[72]



Reagents: (a) TBDMSCl, Et_3N, DMAP, 64%; (b) PCC, 88%; (c) $Ph_3P{=}C(CH_2)_2$; (d) HF; 96% (for c-d); (e) Swern Oxdn., 91%; (f) Peterson reaction, 95%; (g) $Ni(acac)_2$, DIBALH, PPh_3 or $PdCl_2(PPh_3)_2$, DIBALH, 98%; (h) LDA, MeI, 74%; (i) TFA; (j) LAH; (k) Ac_2O, py; 64% (for i-k).

Scheme 34[73,74]



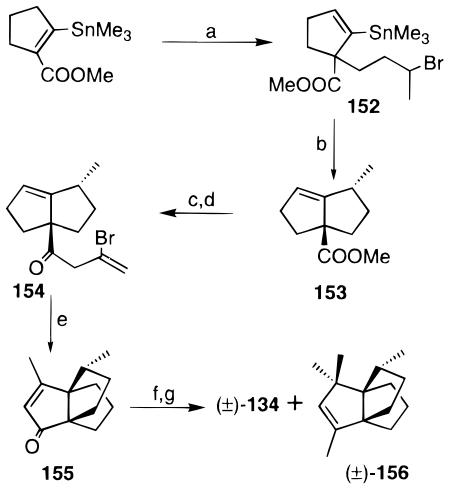
Reagents: (a) $CH_2{=}CH(CH_2)_2MgBr$, CuI, TMSCl, 80%; (b) NaI, m-CPBA, 67%; (c) $^nBu_3SnH$, AIBN, 85%; (d) $Ph_3P{=}CH_2$, 72%; (e) I_2, C_6H_6, 81%.

Subsequently, the same workers[89] have achieved an enantioselective synthesis of the complete framework of kalmanol in the form of an analogue (+)-**179** (Scheme 42). The diquinane based keto ester (−)-**180**, obtained from the chiral 4-siloxycyclopentenone (+)-**181** through a series of reactions, was coupled (**180** → **182**) with a cyclopentenyllithium **183** to set the stage for the Tebbe−Claisen sequence (**182** → **184**). The resulting tetracyclic derivative **184** was further carried to (+)-7-oxy-5,6-dideoxykalmanol (**179**) closely resembling the natural kalmanol [(+)-**176**].

H. Paniculatine and Magellanines

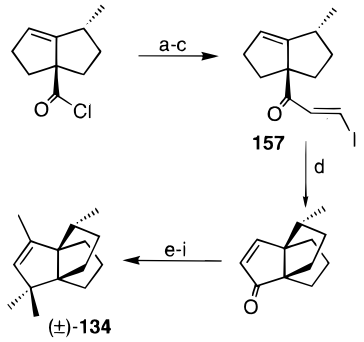
The interesting tetracyclic framework of lycopodium alkaloids, paniculatine (**185**)[90] isolated from *Lycopodium paniculatum*, and magellanine (**186**)[91] and magellaninone (**187**)[92] from *L. magellanicum*, consists of a doubly annulated diquinane moiety. Synthetic efforts toward these alkaloids have therefore centered around diquinane construction and

Scheme 35[75]



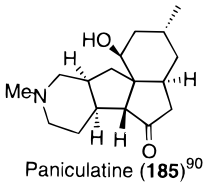
Reagents: (a) LDA, $Br(CH_2)_2CH(Br)Me$, 89%; (b) $^nBu_3SnH$, AIBN, 90%; (c) NaOH; $(COCl)_2$; (d) $TiCl_4$, $CH_2{=}C(Br)CH_2TMS$; (e) $^nBu_3SnH$, AIBN; 85% (for c-e); (f) MeLi; (g) Me_2Zn, $TiCl_4$.

Scheme 36[75]

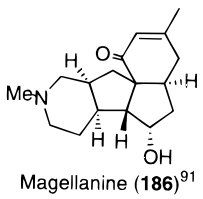


Reagents: (a) TMSC≡CZnCl, $Pd(PPh_3)_4$; (b) KF; (c) TMSI; $^iPr_2NEt$; 72% (for a-c); (d) $^nBu_3SnH$, AIBN, 88%; (e) MeLi; (f) Jones oxdn.; 95% (for e-f); (g) $Me_2CuCNLi$, 85%; (h) $Ph_3P{=}CH_2$; (i) TsOH; 53% (for h-i).

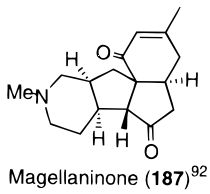
have aroused considerable interest in the past few years.



Paniculatine (**185**)[90]



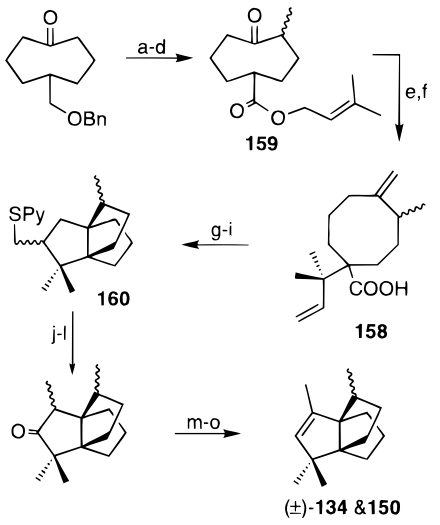
Magellanine (**186**)[91]



Magellaninone (**187**)[92]

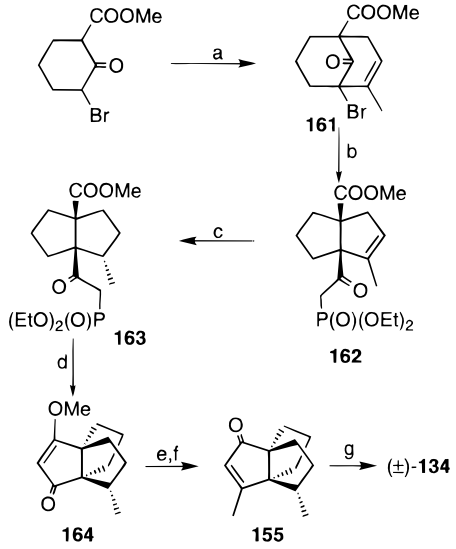
Mehta and co-workers[93−95] were the first to achieve the synthesis of the complete framework of these tetracyclic lycopodium alkaloids (Scheme 43). The cyclohexannulation of the readily available[96] triquinane-based dienone **188**, via an intramolecular Michael addition methodology, led to the tetracyclic bis-ketal **189**. Elaboration of the cyclopentene moiety in the bis-ketal **189** into the piperidine unit and

Scheme 37[76]



Reagents: (a) LDA, MeI; (b) H_2, Pd-C; (c) $RuCl_3$, $NaIO_4$; (d) $Me_2C{=}CHCH_2OH$, H^+; 67% (for a-d); (e) Zn, $TiCl_4$, CH_2Br_2, 76%; (f) LDA, TMSCl; Δ, 95%; (g) $(COCl)_2$; (h) N(OH)-pyridinethione; (i) Δ; 63% (for g-i); (j) $NaIO_4$, Δ, 71%; (k) $RuCl_3$, $NaIO_4$, 73%; (l) LDA, MeI, 91%; (m) LAH; (n) LDA, TsCl; (o) ^{t}BuOK; 43% (for m-o).

Scheme 38[77,78]

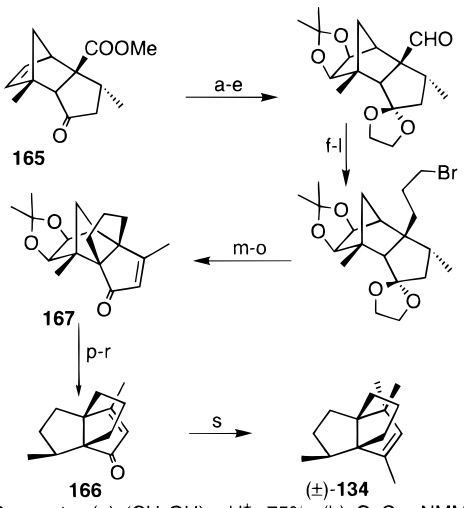


Reagents: (a) $CH_2{=}CHCOCH_3$, H_2SO_4, 77%; (b) $(EtO)_2P(O)CH_2^-{}^+Li$, 77%; (c) Iridium catalyst, H_2; (d) KH; 33% (for c-d); (e) MeLi; (f) H_3O^+; 65% (for e-f); (g) ref. 75.

further functional group manipulations led to (±)-deoxymagellaninone (**190**).

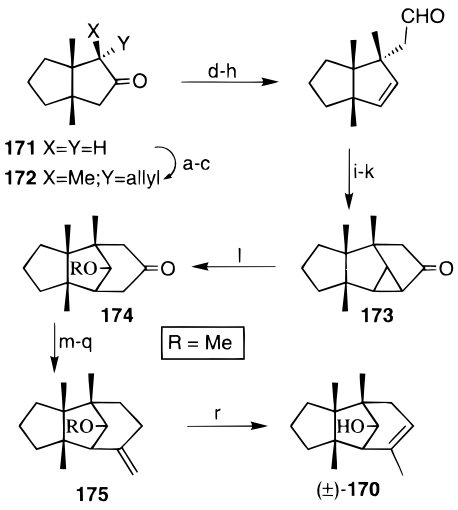
In 1993, Overman and co-workers[97] reported the enantioselective total synthesis of (−)-magellanine (**186**) and (+)-magellaninone (**187**) employing a stannic chloride-catalyzed Prins−pinacol rearrangement (**191** → **192**) as the key step (Scheme 44). The requisite diene acetal **191** was assembled via the coupling of iododiquinane **193** and chiral cyclopentanone derivative **194** and further functional group manipulations. Conversion of the cyclopentene unit in **192** into piperidine moiety and further functional group transformations led to (−)-magellanine (**186**), which on oxidation furnished (+)-magellaninone (**187**).

Scheme 39[79]



Reagents: (a) $(CH_2OH)_2$, H^+, 75%; (b) OsO_4, NMMO, 82%; (c) $CuSO_4$, Me_2CO, 96%; (d) LAH, 80%; (e) Swern oxdn., 81%; (f) AcOEt, LHMDS, 90%; (g) Ac_2O, py, 100%; (h) LHMDS, 90%; (i) H_2, Pd-C, 98%; (j) LAH, 100%; (k) TsCl, py, 90%; (l) LiBr, 100%; (m) H_3O^+, 89%; (n) $(PhSe)_2O$, 65%; (o) LDA, 79%; (p) Dowex, 95%; (q) KIO_4, 80%; (r) $(Ph_3P)_3RhCl$, 60%; (s) ref. 66a.

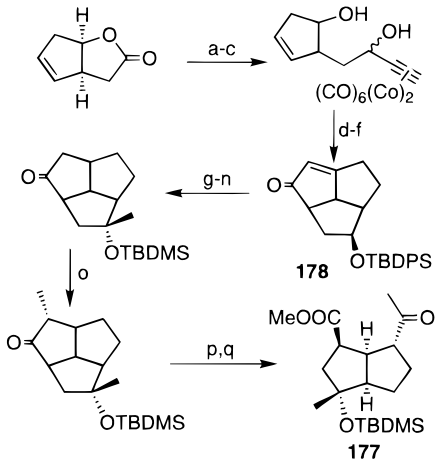
Scheme 40[84,85]



Reagents: (a) LDA, $(PhS)_2$, 64%; (b) LDA, allyl bromide, 79%; (c) Li, liq.NH_3; MeI, 48%; (d) O_3; Me_2S; (e) $(CH_2OH)_2$, H^+; 72% (for d-e); (f) LAH, 97%; (g) MsCl, py; NaI, DBU; 86%; (h) H_3O^+; (i) Jones oxdn.; 90% (for h-i); (j) $(COCl)_2$; CH_2N_2; (k) $Cu(acac)_2$; 64% (for j-k); (l) H^+, MeOH, 90%; (m) LDA, $(PhS)_2$, 93%; (n) LAH, 86%; (o) $SOCl_2$, 90%; (p) H_3O^+, 96%; (q) CH_2I_2, Zn, $TiCl_4$, 89%; (r) BBr_3, 100%.

Concurrently, Paquette and co-workers[99,100] have also reported the total synthesis of (±)-magellanine (**186**) and (±)-magellaninone (**187**), starting from the readily available[101] diquinane **195** (Scheme 45). Dehydration of the hydroxy ketone **195**, cyclohexannulation via two sequential Michael reactions and functional group manipulations led to the tricyclic dienone **196**. Annulation of a piperidone ring via the introduction of cyanomethyl and carboethoxy groups on the two olefinic carbon atoms of the enone **196** and further functional group adjustments, yielded the ene dione **197**. Alkylative 1,3-enone transposition in **197** furnished (±)-magellaninone (**187**). Stereo- and

Scheme 41[88]

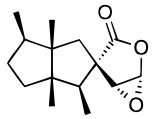


Reagents: (a) DIBALH; (b) H-C≡C-MgBr; 90% (for a-b); (c) $Co_2(CO)_8$, 87%; (d) $^tBuPh_2SiCl$, imidazole, 77%; (e) Et_3SiH, $BF_3.OEt_2$, 70%; (f) Me_3NO, 78%; (g) H_2, Pd-C, 92%; (h) TBAF, 76%; (i) $Me_2C(\text{-}CH_2O\text{-})_2CMe_2$, H^+, 95%; (j) PCC, 79%; (k) $Ph_3P{=}CH_2$, 85%; (l) $Hg(OAc)_2$; $NaBH_4$, 79%; (m) TBDMSOTf, DMAP, 86%; (n) Me_2CO, H^+, 91%; (o) LDA, MeI, 87%; (p) ^tBuOK, DMSO, O_2; (q) Me_2SO_4; 37% (for p-q).

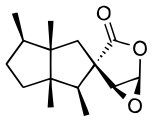
regioselective reduction of magellaninone **187**, followed by Mitsunobu inversion yielded (±)-magellanine (**186**).

I. Miscellaneous

Dreiding and co-workers[102] have published the details of their α-alkynone cyclization-based synthesis[103] of (±)-isoptychanolide (**198**), a stereoisomer of the pinguisane type sesquiterpene spirolactone ptychanolide (**199**).[104]

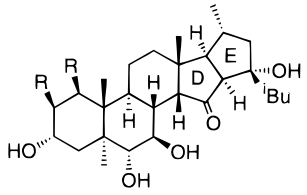


Ptychanolide (**199**)[104]



Isoptychanolide (**198**)

Xestobergosterol-A (**200**), a unique pentacyclic

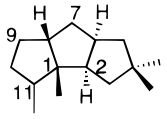


R=H Xestobergsterol-A (**200**)[105]
R=OH Xestobergsterol-B (**201**)

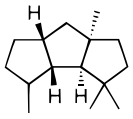
steroid containing a *cis* C/D ring junction, was isolated in 1992 from the crude extracts of the Okinawan sponge *Xestospongia berquista* Fromont, and has been shown to possess interesting biological activity.[105] Recently, Krafft and Chirico[106] reported the synthesis of a tricyclic system **202**, containing the CDE ring system of **200** (Scheme 46). Thus, Pauson−Khand bicyclization of the keto enyne **203**, obtained from the lactone **204**, resulted in a 1:1 epimeric mixture of the enone **202**.

III. Linear Triquinanes

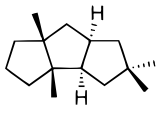
Among the natural products bearing a linear triquinane framework isolated so far, only the thermodynamically favored *cis,anti,cis*-ring fusion has been encountered. There are four different skeletal types (**205**−**208**) known among the linear triquinane natural products, representing variation in the location of the four carbon substituents and quaternary carbon centers. However, they all share a common biosynthetic origin through the humulene cyclization cascade. The main challenge in the synthesis of linear triquinane natural products has been the rapid construction of five-membered rings for which numerous new cyclopentannulation protocols have been developed. The control of ring junction stereochemistry in these natural products is not a serious problem as the *cis,anti,cis*-stereochemistry is overwhelmingly preferred.



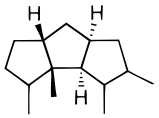
Hirsutane (**205**)



Capnellane (**206**)



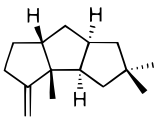
Ceratopicane (**207**)



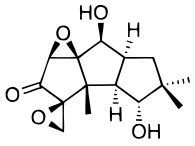
Pleurotellane (**208**)

A. Hirsutanes

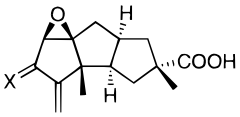
The hirsutanes constitute a group of fungal metabolites based on the *cis,anti,cis*-1,4,4,11-tetramethyltricyclo[6.3.0.$0^{2,6}$]undecane framework **205**. The extensive functionalization with stereochemical intricacies and the biological activity associated with various members **209**−**213** of this family continue to attract the attention of synthetic chemists.



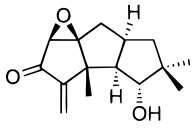
Hirsutene (**209**)



Coriolin (**212**)



X=H,OH; Hirsutic acid-C (**210**)
X=O, Complicatic acid (**211**)



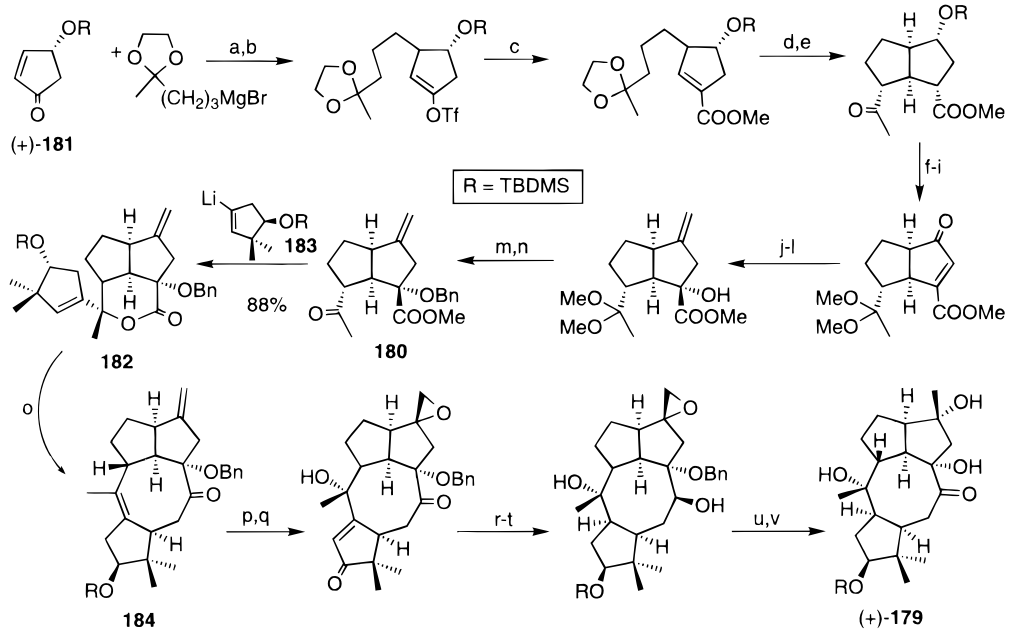
Hypnophilin (**213**)

1. Hirsutene

The sesquiterpene hydrocarbon hirsutene **209**, isolated[107a] from Basidomycete *Coriolus consors*, is the simplest member of the hirsutane group and has emerged as a popular target molecule[107] for developing and testing new methodologies for cyclopentannulations. Several new syntheses have been reported in the recent past.

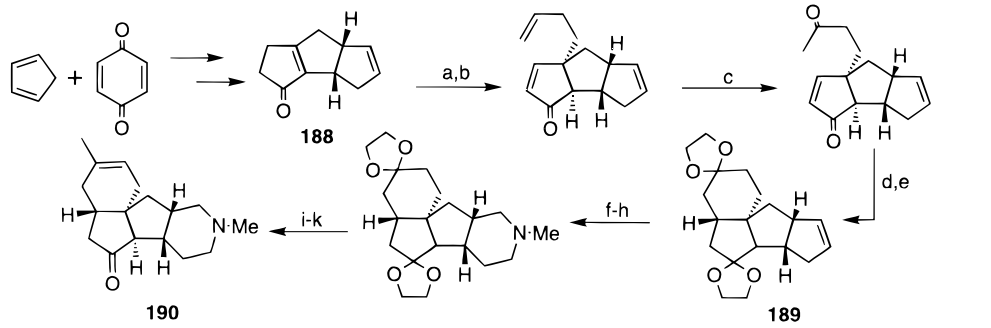
The trimethylsilyl iodide-mediated rearrangement of a bicyclo[4.2.0]octane-2,5-dione to a bicyclo[3.3.0]-oct-1(6)-en-2-one was utilized by Oda and co-workers[108] for a short and elegant synthesis of (±)-hirsutene (**209**) (Scheme 47). Thus, treatment of the tricyclic dione **214**, obtained via a [2+2]-photocycloaddition between cyclohex-2-ene-1,4-dione and 4,4-

Scheme 42[89]



Reagents: (a) $CuBrMe_2S$, TMSCl; (b) MeLi, $PhNTf_2$; 91% (for a-b); (c) $Pd(OAc)_2$, CO, NEt_3; PPh_3; MeOH; 87%; (d) TsOH, Me_2CO; (e) ^tBuOK; 60% (for d-e); (f) $HC(OMe)_3$, H^+, 93%; (g) TPAP, NMMO, 86%; (h) LDA, TMSCl; (i) NBS; 86% (for h-i); (j) NaOH, H_2O_2, 78%; (k) $Ph_3P{=}CH_2$, 50%; (l) $Pd(dba)_2$, $HCOONH_4$, PPh_3, 91%; (m) NaH, BnBr, TBAI; (n) TsOH, Me_2CO; 98% (for m-n); (o) Tebbe reagent; Δ; 85%; (p) TBAF, 91%; (q) m-CPBA; TPAP, NMMO; 70%; (r) H_2, Pd-C, 92%; (s) $LiEt_3BH$, 90%; (t) TBDMSOTf, imidazole, 93%; (u) $LiEt_3BH$; Li, liq. NH_3; 30%; (v) periodinane, 93%.

Scheme 43[93−95]



Reagents: (a) $CH_2{=}CH(CH_2)_2MgBr$, CuBr.SMe_2, 68%; (b) LDA, PhSeCl; H_2O_2, ^-OH; 48%; (c) $PdCl_2$, CuCl, O_2, 72%; (d) NaH, 75%; (e) $(CH_2OH)_2$, H^+, 88%; (f) O_3; $NaBH_4$; 82%; (g) MsCl, NEt_3, 80%; (h) $MeNH_2$, 40%; (i) H_3O^+, 50%; (j) $Ph_3P{=}CH_2$; (k) TsOH.

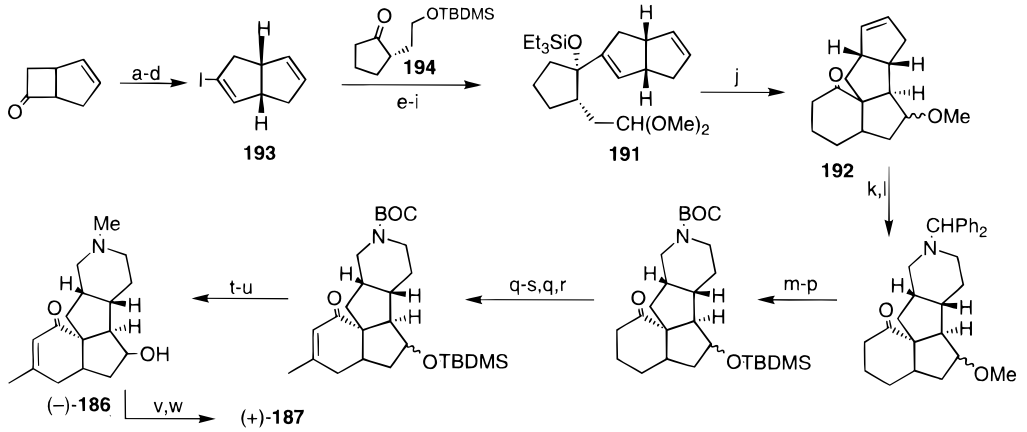
dimethylcyclopentene, with trimethylsilyl iodide generated the triquinane enone **215** in very high yield. Reductive methylation in **215** followed by Wittig olefination furnished (±)-**209**.

A photochemically induced alkyne−carbonyl reductive cyclization was the key step in the synthesis of (±)-hirsutene (**209**) by Cossy and co-workers[109,110] (Scheme 48). A palladium-catalyzed cyclopentannulation of cyclopentenone with trimethylenemethane equivalent and conversion of the exomethylene functionality into a *gem*-dimethyl group afforded the diquinane **216**, which was elaborated into the acetylenic ketone **217**. Photoirradiation of the ketone **217**, followed by nickel-catalyzed quaternization of the allylic tertiary alcohol **218** furnished (±)-**209**.

As an application of their notable work on the use of allylsilanes for different ring annulations, Majetich and co-workers[111] have explored an intramolecular allylsilane−cyclopentenone coupling methodology toward a synthesis of (±)-hirsutene (**209**) (Scheme 49). Conversion of the diester **219** into the allylsilane **220** and fluoride ion-induced construction of the central ring afforded the triquinane **221** with concomitant deacetoxylation. Further transformations led to the aldehyde **222**, which is yet to be elaborated to (±)-hirsutene (**209**).

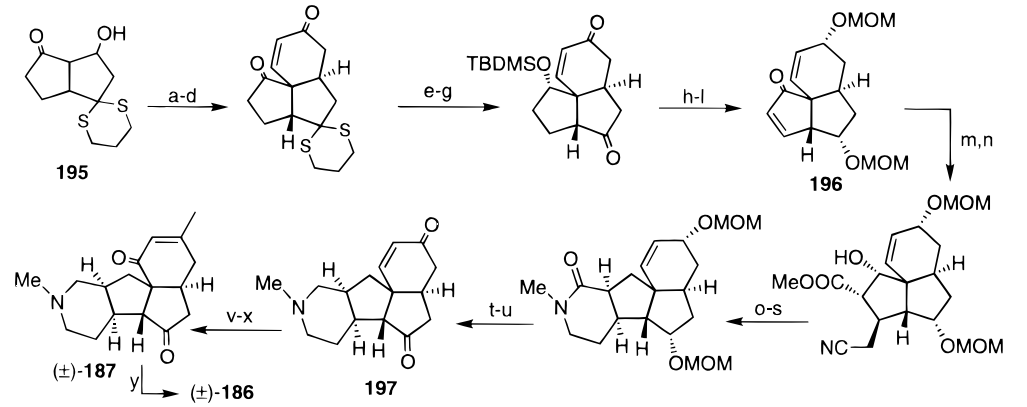
Cyclopentannulation, employing a formal [2+2]-cycloaddition of an enamine and an electron-deficient cyclopropene, and the regio- and stereospecific cleavage of the central bond in the resulting bicyclo[2.1.0]-pentane moiety was the key strategy in Franck-Neumann and co-workers' approach[112,113] to (±)-hirsutene (**209**) (Scheme 50). Addition of 3,3-dimethylcyanocyclopropene to the diquinane enamine **223** resulted in the stereospecific formation of the [2+2]-cycloaddition product **224**. Regio- and stereospecific cleavage (**224** → **226**) of the central bond of the bicyclo[2.1.0]pentane moiety and subsequent functional group manipulations led to (±)-**209**.

Scheme 44[97,98]



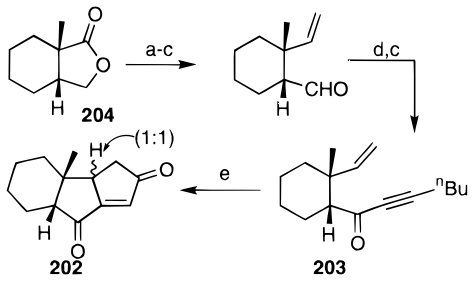
Reagents: (a) $LiCH(SMe)_2$, CuOTf, 70%; (b) Li, liq. NH_3, TMSCl; (c) MeLi, $PhNTf_2$; 49% (for b-c); (d) $^nBu_6Sn_2$, Pd(0), NIS, 80%; (e) ^{t}BuLi; (f) TBAF; 71% (for e-f); (g) Et_3SiCl, imidazole; (h) Swern oxdn.; 85% (for g-h); (i) $HC(OMe)_3$, H^+, 85%; (j) $SnCl_4$, 57%; (k) OsO_4, $NaIO_4$; (l) Ph_2CHNH_2, $NaBH_4$; 60% (for k-l); (m) TMSCl, NaI; (n) TBDMSCl, imidazole; 76% (for m-n); (o) H_2, $Pd(OH)_2$; (p) BOCCl; 89% (for o-p); (q) LDA, TMSCl; (r) $Pd(OAc)_2$; 85% (for q-r); (s) Me_2CuLi; (t) TFA; (u) HCHO, $NaCNBH_3$; 68% (for s,q,r,t,u); (v) HF, 85%; (w) Jones oxdn.

Scheme 45[99,100]



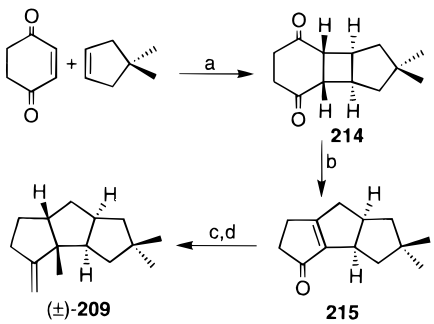
Reagents: (a) MsCl, NEt_3; (b) $(EtO)CH{=}CHCOCH_2COOEt$, K_2CO_3, Al_2O_3; 56% (for a-b); (c) TsOH; (d) NaCl, DMF, Δ; 89% (for c-d); (e) $NaBH_4$, 91%; (f) TBDMSOTf, imidazole, 96%; (g) $Tl(NO_3)_3$, 65%; (h) DIBALH, 76%; (i) MOMCl, $^iPr_2NEt$, 88%; (j) TBAF, 100%; (k) PCC, 89%; (l) LiHMDS, PhSeCl; H_2O_2, ^-OH; 56%; (m) $TMSCH(CN)Li$, 83%; (n) LDA, CNCOOMe; $NaBH_4$; 50%; (o) NaH, $COCl_2$, py, PhSeH, 95%; (p) $(TMS)_3SiH$, AIBN, 92%; (q) $NaBH_4$, $CoCl_2$; (r) NaH, MeI; 54% (for q-r); (s) LDA; (t) H_3O^+; (u) MnO_2; 47% (for s-u); (v) MeLi; (w) LAH; (x) Jones oxdn.; 67% (for v-x); (y) $NaBH_4$; DEAD, HCOOH; KOH; 73%.

Scheme 46[106]



Reagents: (a) DIBALH, 90%; (b) $Ph_3P{=}CH_2$, 74%; (c) PCC, 93%; (d) $BuC{\equiv}C$-Li; PCC; 80%; (e) $Co_2(CO)_8$, NMMO, 70%.

Scheme 47[108]

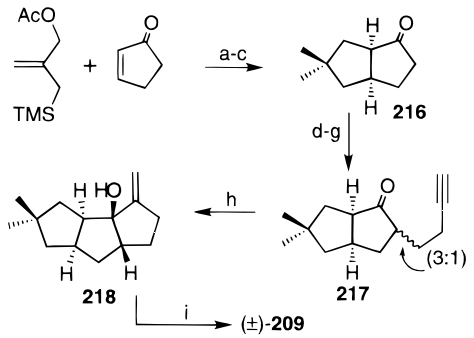


Reagents: (a) hν, 85%; (b) TMSI, 95%; (c) Li, liq. NH_3; MeI; 47%; (d) $Ph_3P{=}CH_2$, 96%.

Sternbach and Ensinger[114] adopted an intramolecular Diels–Alder reaction–oxidative double bond cleavage strategy for the synthesis of (±)-hirsutene (**209**) (Scheme 51). Thus, reduction and intramolecular [4+2]-cycloaddition of the fulvene **227** generated the adduct **228**. Oxidative cleavage of the olefinic moiety in **228** and stereospecific annulation of the third cyclopentane ring via an intramolecular aldol condensation led to (±)-**209**.

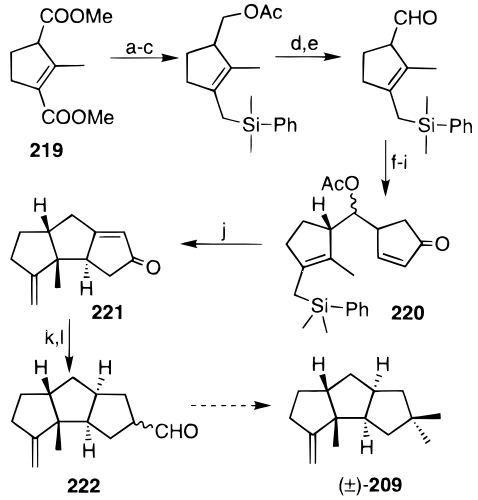
In a formal synthesis of (±)-hirsutene (**209**) by Sarkar and co-workers[115–117] (Scheme 52), an efficient

Scheme 48[109,110]



Reagents: (a) $Pd(OAc)_2$, $(^iPrO)_3P$, 60%; (b) CH_2N_2, $Pd(OAc)_2$, 99%; (c) H_2, PtO_2, 90%; (d) KH, $ICH_2CH{=}C(Cl)Me$, 71%; (e) LAH, 90%; (f) Potassium 3-aminopropylamide, 86%; (g) PCC, 96%; (h) hν, NEt_3, 58%; (i) $NiCl_2(PPh_3)_3$, MeMgBr, 35%.

Scheme 49[111]



Reagents: (a) LAH, 93%; (b) Ac_2O, py, 85%; (c) $PhMe_2SiCuLi$, 94%; (d) LAH, 87%; (e) py.CrO_3, 50%; (f) 3-ethoxycyclopentenone, LDA, 75%; (g) DIBALH; (h) H_3O^+; 84% (for g-h); (i) Ac_2O, py, 97%; (j) F^-, 40%; (k) MeCu, DIBALH, 78%; (l) $Ph_3P{=}CHOMe$; H_3O^+; 64%.

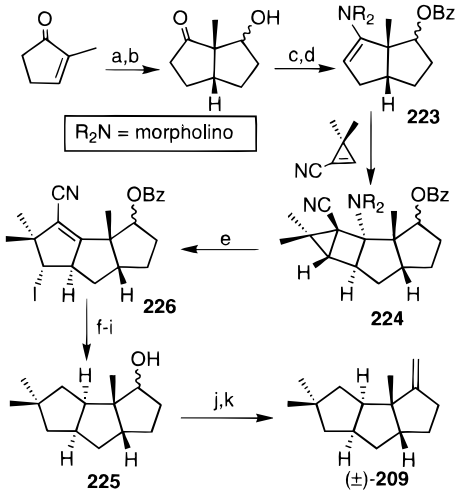
intramolecular ene reaction (**229** → **230**) and a titanium catalyzed epoxy−allylsilane cyclization (**231** → **232**) constituted the two key cyclopentannulation protocols leading to the diquinane **232**, which was further elaborated into the triquinane **233** via the classical aldol condensation.

Paquette and co-workers[118,119] have developed a new synthesis of (±)-hirsutene **209** employing an iodine catalyzed rearrangement of the methylenetricyclo[6.3.0.$0^{3,6}$]undecane derivative **234** into the norketone **235**, a frequently employed precursor of hirsutene (**209**) (Scheme 53). The requisite siloxyolefin precursor **234** was assembled via a stereoselective photochemical [2+2]-cycloaddition of ethylene and hydrindanone **236** and functional group transformations.

A novel, intramolecular bis-enolate oxidative coupling, mediated by iron(III), was the key reaction in the synthesis of (±)-hirsutene (**209**) by Cohen and coworkers[120,121] (Scheme 54). The one-pot procedure for the construction of the triquinane **237** comprises of a series of reactions: (a) conjugate addition of tris(phenylthio)methyllithium to 2-methylcyclopentenone to generate the lithium enolate **238**; (b) further metalation of **238** to the dilithio compound **239**; (c) Michael addition of **239** onto 5,5-dimethylcyclopentenone to form the bis-enolate **240**; and (d) ferric chloride-mediated oxidative coupling of **240** to furnish the triquinane **237**. Further functional group manipulations transformed the dione **237** into (±)-**209**.

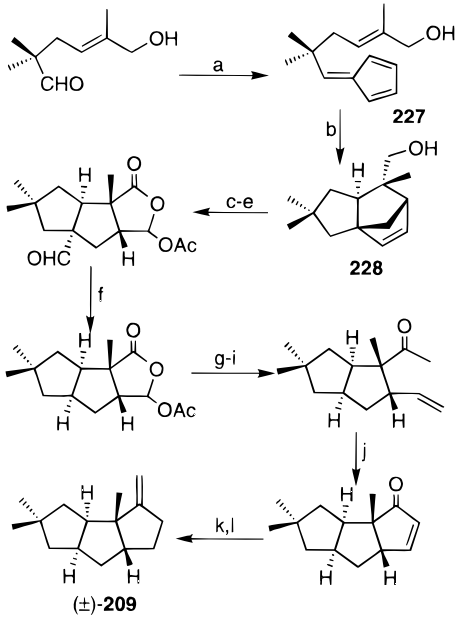
In the Fukumoto's[122,123] approach to (±)-hirsutene (**209**), a stereoselective, acid-catalyzed intramolecular Michael addition of the acetal **241** generated the functionalized cyclopentane precursor **242**. Palladium-mediated Kende-type cyclization of the TMS enol ether of the enone **243** furnished the diquinane **244**.

Scheme 50[112,113]



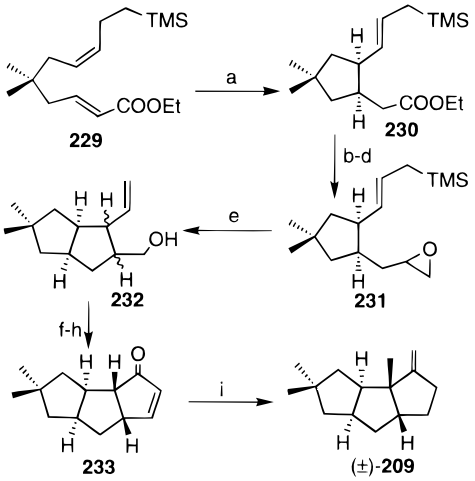
Reagents: (a) $(CH_2O)_2CHCH_2CH_2MgBr$, CuBr; (b) HCl; 84% (for a-b); (c) BzCl, py, 90%; (d) morpholine, H^+, 91%; (e) HI, 50% from **223**; (f) H_2, Pd-C, 91%; (g) Li, liq. NH_3, 28%; (h) NaOH, 95%; (i) electrolysis, 45%; (j) PCC, 100%; (k) $Ph_3P{=}CH_2$.

Scheme 51[114]



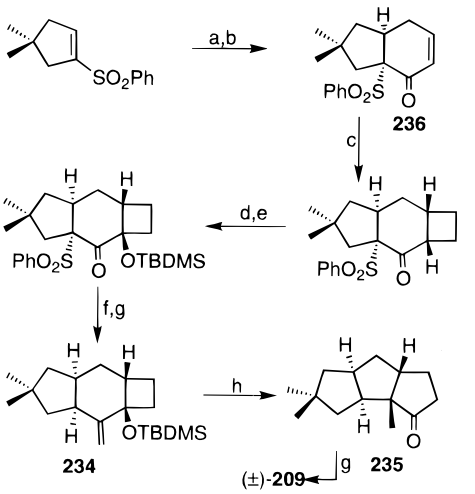
Reagents: (a) cyclopentadiene, piperidine, 99%; (b) LAH; Δ; 70%; (c) Jones oxdn., 97%; (d) O_3; Me_2S, 99%; (e) Ac_2O, NEt_3, 90%; (f) Jones oxdn.; Barton's decarboxylation; 78%; (g) MeOH, Et_3N, 95%; (h) $Ph_3P{=}CH_2$, 86%; (i) NaH; $(COCl)_2$; Me_2CuLi; 97%; (j) O_3, Me_2S; KOH; 77%; (k) H_2, PtO_2, 100%; (l) $Ph_3P{=}CH_2$, 93%.

Scheme 52[115–117]



Reagents: (a) Δ, 97%; (b) LAH, 90%; (c) PDC, 82%; (d) $Me_2S{=}CH_2$, 61%; (e) $TiCl_4$, 72%; (f) PCC, 70%; (g) $PdCl_2$, CuCl, O_2, 77%; (h) KOH, 40%; (i) ref. 107j.

Scheme 53[118,119]



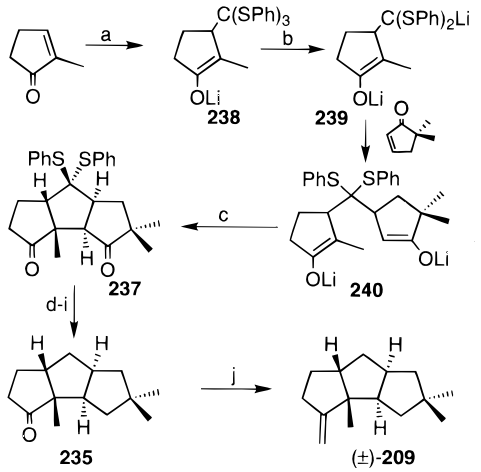
Reagents: (a) $CH_2{=}CHCH{=}CH$-OTMS; (b) Jones oxdn.; 72% (for a-b); (c) $CH_2{=}CH_2$, hv, 90%; (d) NaHMDS, TBDMSCl; (e) m-CPBA; 68% (for d-e); (f) Al-Hg, 91%; (g) $Ph_3P{=}CH_2$, 86%; (h) I_2, 91%.

Functional group adjustments leading to the installation of the *gem*-dimethyl group and an intramolecular aldol condensation reaction led to (±)-**209** (Scheme 55).

Weinges and co-workers[124] have developed a synthesis of (−)-hirsutene (**209**) starting from (*R*)-carvone (Scheme 56). Oxymercuration and radical cyclization reactions transformed (*R*)-carvone into the bicyclo[3.2.1]octanone **245**, which through a series of reactions was converted into the lactone **246**, an intermediate in the Curran's[107u] synthesis of (±)-hirsutene (**209**). Following the earlier sequence,[107u] an enantioselective synthesis of (−)-**209** was accomplished.

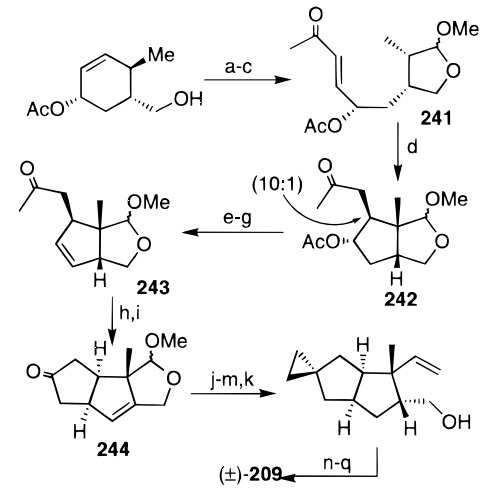
The "metallo ene reaction−carbonylation" cascade was the key reaction in the synthesis of (±)-hirsutene (**209**) reported by Oppolzer and co-workers[125] (Scheme 57). Palladium-catalyzed reaction of the carbonate derived from the alcohol **247** with carbon monoxide generated stereoselectively (85:15) the diquinane **248**, through a cascade of reactions: (a) an intramolecular

Scheme 54[120,121]



Reagents: (a) $LiC(SPh)_3$; (b) *sec*-BuLi; (c) $FeCl_3$; 64% (for a-c); (d) Raney Ni, 93%; (e) $(CH_2OH)_2$, H^+, 86%; (f) Li, liq. NH_3, 92%; (g) ^nBuLi, $Cl_2P(O)NMe_2$; (h) Li, $MeNH_2$; (i) H_3O^+; 82% (for g-i); (j) $Ph_3P{=}CH_2$, 96%.

Scheme 55[122,123]

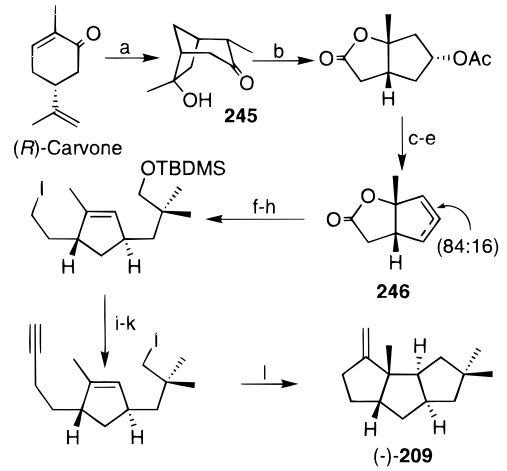


Reagents: (a) O_3; Me_2S; 93%; (b) $Ph_3P{=}C$-COMe; (c) PPTS, MeOH; 69% (for b-c); (d) TsOH, 95%; (e) LiOH; (f) PBu_3, o-$NO_2C_6H_4SeCN$; (g) H_2O_2; 66% (for e-g); (h) LDA, TMSCl; (i) $Pd(OAc)_2$; 99% (for h-i); (j) H_2, Pd-C; (k) $Ph_3P{=}CH_2$; (l) CH_2I_2, Et_2Zn; 50% (for j-l); (m) H_3O^+; $Ph_3P{=}CH_2$; 61%; (n) PCC; (o) $PdCl_2$, CuCl, O_2; (p) Bu_4NOH, KOH; (q) H_2, PtO_2; 74% (for n-q).

pallada ene cyclization; (b) addition of organopalladium species to carbon monoxide; (c) intramolecular acylpalladium−olefin insertion; and (d) addition of organopalladium species to carbon monoxide. The diquinane **248** was further elaborated into hirsutene **209** via the construction of the third ring employing a 5-*exo* trig radical cyclization in an organoselenium precursor **249**.

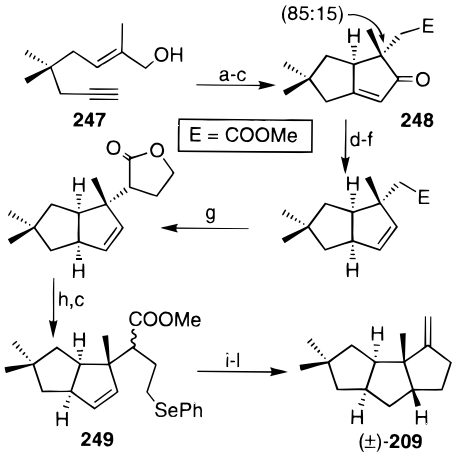
Rawal's approach to (±)-*endo*-hirsutene (**250**) (Scheme 58), consists of a series of interesting reactions: (a) an intramolecular Diels−Alder reaction (**251** → **252**); (b) an oxetane formation via Paterno−Buchi reaction (**252** → **253**); (c) base induced oxetane cleavage (**253** → **254**); and (d) a radical anion-mediated cleavage of the norbornane framework (**254** → **255**). The resulting triquinane **255** was deoxygenated to furnish (±)-*endo*-hirsutene **250**, which had earlier[107a] been converted to (±)-hirsutene (**209**).

Scheme 56[124]



Reagents: (a) $Hg(OAc)_2$, H_2O; $NaBH_4$; separation; 35%; (b) excess m-CPBA, 85%; (c) K_2CO_3, 88%; (d) PPh_3, $ZnBr_2$; DEAD; 83%; (e) DBU; (f) $LiCH_2C(Me)_2CH_2OTBDMS$; 98%; (g) LAH, 95%; (h) PPh_3, ZnI_2; DEAD; 79%; (i) TMSC≡CLi; (j) TBAF; 66% (for i-j); (k) Tf_2O, py; Bu_4NI, 82%; (l) $^nBu_3SnH$, AIBN, 72%.

Scheme 57[125]



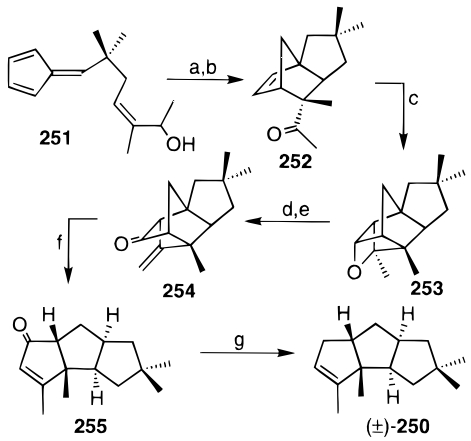
Reagents: (a) ClCOOMe, py, 90%; (b) $Pd(dba)_2$, PPh_3, CO, AcOH; (c) CH_2N_2; 72% (for b-c); (d) H_2, Pd-C, 100%; (e) $NaBH_4$, 97%; (f) $POCl_3$, 82%; (g) LDA, $(CH_2O)_2SO_2$, 48%; (h) PhSeNa; CH_2N_2, 77%; (i) $^nBu_3SnH$, AIBN, 92%; (j) LAH, 89%; (k) $o\text{-}NO_2C_6H_4SeCN$, 87%; (l) H_2O_2, ^-OH, 90%.

Greene and co-workers[127] have developed a synthesis of the chiral diquinane (−)-**256**, employing an asymmetric version of the versatile Pauson−Khand bicyclization on the enyne **257** (Scheme 59). The racemic diquinane **256** has been previously converted[107a] to (±)-hirsutene (**209**).

A Bakers' yeast-mediated asymmetric reduction of the diquinane dione **258** to keto alcohols **259** and **260** has been reported by Node *et al.*,[128] generating the chiral precursor[112,113] (−)-**260** of hirsutene (**209**) (Scheme 60).

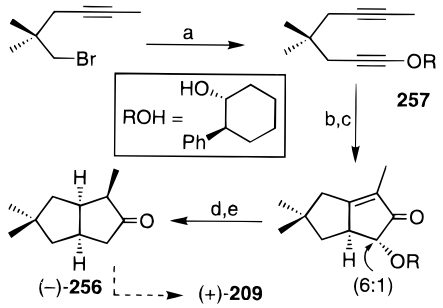
Mehta and co-workers[129] have published a detailed account of their synthesis[107h] of (±)-hirsutene (**209**) based on the photo-thermal olefin metathesis sequence. Weedon and Disanayaka[130] have published the details of their [2+2]-photocycloaddition−retroaldol−intramolecular McMurry coupling sequence based synthesis[107z] of (±)-**209**. Hua and co-workers[131] have disclosed the details of their asymmetric synthesis[107x] of (−)-hirsutene **209** starting from 2-methylcyclopentenone, employing (*R*)-allyl *p*-tolyl sulfoxide as the source of chirality.

Scheme 58[126]



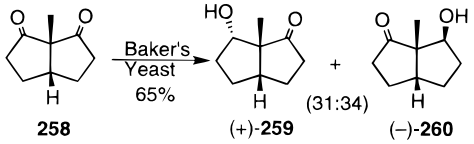
Reagents: (a) LAH; (b) $Al(O^iPr)_3$, Me_2CO; Δ; 66% (for a-b); (c) hν, 90%; (d) $^iPr_2NMgI$; (e) PDC; 65% (for d-e); (f) LDBB, 66%; (g) $NaBH_4$, CF_3COOH, 69%.

Scheme 59[127]



Reagents: (a) Mg, $ZnCl_2$, I-C≡C-OR, 57%; (b) LAH, 74%; (c) $Co_2(CO)_8$, 55%; (d) Li, liq. NH_3, 80%; (e) SmI_2, 85%.

Scheme 60[128]

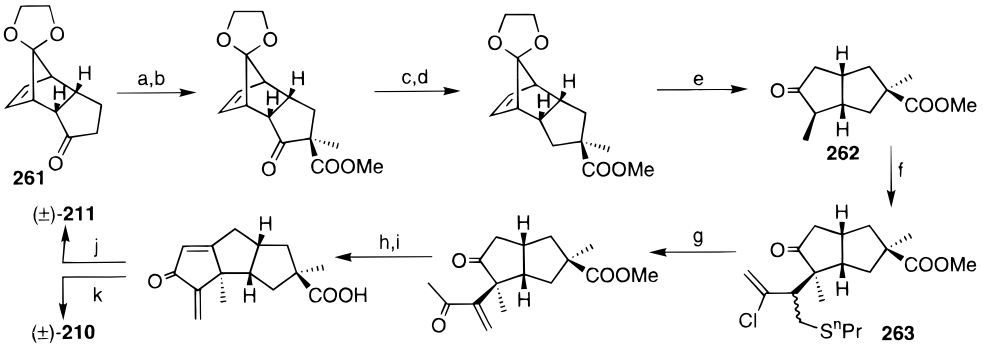


2. Hirsutic Acid-C and Complicatic Acid

Hirsutic acid-C (**210**), isolated from Basidomycetes *Stereum hirsutum*,[132a] was the first triquinane natural product to be isolated and characterized through incisive applications of spectroscopy and X-ray crystallography.[132c] Later, **210** along with a related sesquiterpene complicatic acid **211** was also found to occur in the Basidiomycetes *Stereum complicatum*.[132e] Several syntheses of hirsutic acid-C (**210**), in racemic and enantiomerically pure form have been reported earlier.[133]

Schuda and co-workers[134] have accomplished the total synthesis of (±)-hirsutic acid-C (**210**) and (±)-complicatic acid (**211**) by starting from the Diels−Alder dimer of cyclopentadienone via the keto ketal **261** (Scheme 61). The folded topology of the keto ketal **261** was exploited for the stereospecific introduction of the carbomethoxy bearing quaternary carbon center. Subsequent cleavage of the norbornene double bond afforded the diquinane **262**. A

Scheme 61[134]



Reagents: (a) LDA, MeI, 85%; (b) KHMDS, CNCOOMe, 58%; (c) $NaBH_4$, 99%; (d) Tf_2O, py; NaI; Zn; 65%; (e) RuO_2, $NaIO_4$; H_3O^+; LDA, MeI; 70%; (f) $^nPrSCH_2CH{=}C(Cl)CH_2OH$, H^+, Δ; 85%; (g) $Hg(OAc)_2$, HCOOH, $HCOONH_4$, 91%; (h) ^{t}BuOK; (i) TsOH, Δ; 59% (for h-i); (j) H_2O_2, $NaHCO_3$, 40%; (k) H_2O_2, NaOH; $NaBH_4$, 51%.

ketal Claisen rearrangement was employed for the stereoselective creation of the second quaternary center (**262** → **263**). Construction of the third ring employing an intramolecular aldol condensation and further functional group transformations furnished (±)-**210** and (±)-**211**.

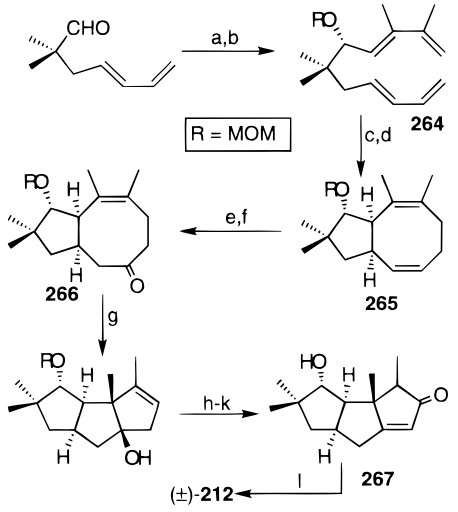
Ikegami *et al.*[135] have reported a detailed account of their enantioselective total synthesis[133h] of (+)-hirsutic acid-C (**210**).

3. Coriolin and Hypnophilin

Coriolins[136] and hypnophilins[137] constitute a group of closely related, highly oxygenated and densely functionalized triquinane sesquiterpenoids, isolated from Basidomycetes *Coriolus consors* and *Pleurotellus hypnophilus*, respectively. However, among them, coriolin (**212**) and hypnophilin (**213**) have been the most sought after synthetic targets.[138]

Wender and Correia[139] have reported a formal total synthesis of (±)-coriolin (**212**), employing a formal [4+4]-cycloaddition and transannular cyclization sequence (Scheme 62). Photochemical [2+2]-cycloaddition followed by thermal Cope rearrangement transformed the tetraene **264** into the 5−8 system **265**. Acid catalyzed transannular cyclization of enone **266**, obtained from the diene **265** and functional group manipulation led to the hydroxy enone **267**, Mehta's[129,138j] precursor of (±)-coriolin (**212**).

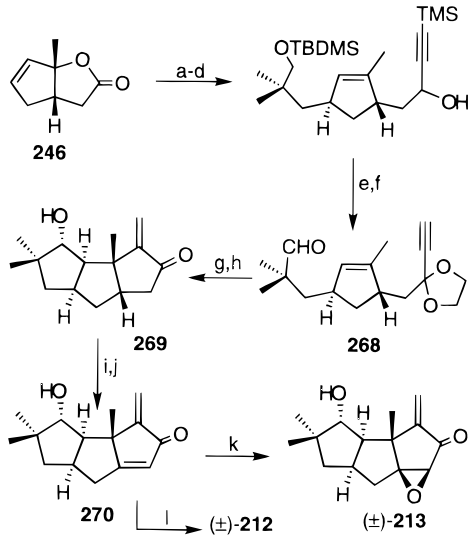
Scheme 62[139]



Reagents: (a) $CH_2{=}C(Me){-}C(Me){=}CHLi$, 64%; (b) KH, MOMCl, 77%; (c) hv; (d) Δ; 60% (for c-d); (e) 9-BBN; H_2O_2, $^-$OH; 74%; (f) PDC, 80%; (g) $BF_3.OEt_2$, 66%; (h) B_2H_6; H_2O_2, $^-$OH; 79%; (i) PDC, 90%; (j) MsCl, Et_3N, 82%; (k) 6N HCl, 66%; (l) ref. 129.

Curran and co-workers[140] have employed a samarium iodide-mediated tandem radical cyclization approach for the synthesis of (±)-hypnophilin (**213**) and (±)-coriolin (**212**) (Scheme 63). Essentially following their earlier methodology for hirsutene synthesis, the lactone **246** was converted into the ynal **268**, which on treatment with samarium iodide and hydrolysis, afforded the triquinane enone **269**. Introduction of the second olefinic moiety generated the dienone **270**, a frequently encountered precursor[138a] of (±)-**212**. Selective epoxidation of the dienone **270** furnished (±)-**213**.

Scheme 63[140]

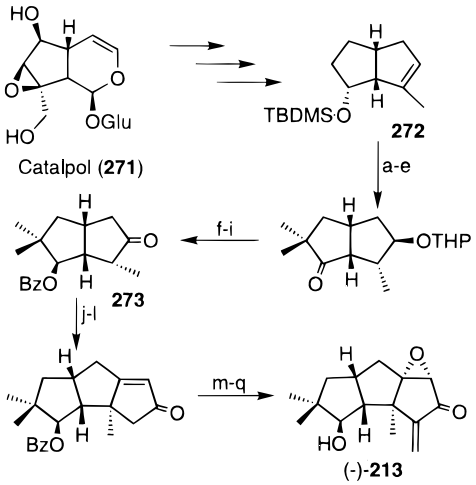


Reagents: (a) $BrCH_2C(Me)_2CH_2OTBDMS$, Li, CuBr; (b) LAH; 94% (for a-b); (c) PCC; (d) Li-C≡C-TMS; 98% (for c-d); (e) PCC; H^+, $(CH_2OH)_2$; (f) TBAF; PCC; 72% (for e-f); (g) SmI_2; (h) H^+, Me_2CO; 69% (for g-h); (i) LDA, TBDMSCl; (j) DDQ, 2,6-lutidine; 72% (for i-j); (k) H_2O_2, K_2CO_3, 75%; (l) ref. 138q.

Weinges and co-workers[141−143] have restructured the iridoid catalpol (**271**) into the diquinane **272** through a series of transformations. Further conversion of the diquinane **272** into Matsumoto's[138k] intermediate **273** constituted a formal synthesis of

coriolin (**212**) (Scheme 64). Cyclopentannulation of

Scheme 64[141−143]



Reagents: (a) B_2H_6; H_2O_2, ^-OH, 95%; (b) DHP, TsOH, 93%; (c) TBAF, 95%; (d) PDC, 76%; (e) ^{t}BuOK, MeI, 65%; (f) Li, liq. NH_3, 48%; (g) BzCl, py, 86%; (h) H_3O^+, 84%; (i) PCC, 85%; (j) CH_2=C(Cl)CH_2Cl, ^{t}BuOK, 60%; (k) $Hg(TFA)_2$, 80%; (l) ^{t}BuOK, 85%; (m) NaOH, 78%; (n) LDA, HCHO, 73%; (o) TsCl, py; (p) DBU; 75% (for o-p); (q) H_2O_2, K_2CO_3, 51%.

the diquinane **273** following the Lansbury methodology and functional group adjustments led to the first enantioselective synthesis of (−)-hypnophilin **213**.

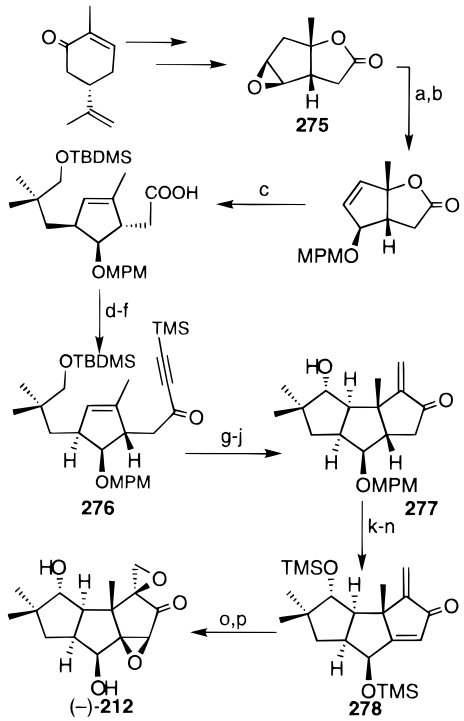
Weinges and co-workers[144,145] have also accomplished the enantioselective syntheses of (−)-coriolin (**212**) and (+)-coriolin-B (**274**) from (*S*)-carvone, through an extension of their hirsutene strategy (Schemes 65 and 66). The lactone **275** obtained from (*S*)-carvone was transformed into enyne **276**, and the triquinane **277** was assembled employing a samarium iodide-mediated tandem radical cyclization reaction. Further transformations of the triquinane **277** led to (−)-**212**. Elaboration of the protected dihydroxydienone **278** resulted in the total synthesis of natural (+)-coriolin-B (**274**).

In the formal total synthesis of (±)-coriolin (**212**), reported by Oppolzer and Ando,[146] a nickel-catalyzed "metallo ene reaction−methoxycarbonylation" cascade was the pivotal step (Scheme 67). The highlight of this methodology is the complete stereocontrol at the four stereogenic carbons in the formation of diquinane **279**. The diquinane **279** was transformed into **280**, an intermediate in the Magnus[138o] synthesis of (±)-**212**.

Demuth and co-workers[147] have reported the asymmetric synthesis of (−)-coriolin (**212**) from the chiral enedione (−)-**281** through an extension of their earlier oxa-di-π-methane rearrangement based strategy for the synthesis[138r] of the racemic coriolin [(±)-**212**]. The bridged bicyclic dione **281** was resolved through a tartrate derived ketal (Scheme 68).

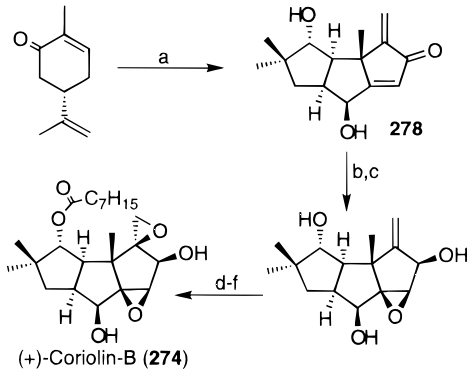
Little and co-workers,[148] while giving a detailed account of their[138s] synthesis of (±)-coriolin (**212**), have also reported the total synthesis of (±)-hypnophilin (**213**). They have elaborated an advanced intermediate (obtained via the intramolecular diyl trapping methodology) in their coriolin synthesis, to (±)-**213**.

Scheme 65[144]



Reagents: (a) NaSePh, 77%; (b) $CCl_3NHOMPM$, 91%; (c) $TBDMSOCH_2C(Me)_2CH_2Li$, CuBr; (d) LAH; 87% (for c-d); (e) PCC, 78%; (f) TMSC≡CLi; PCC; 80%; (g) $(CH_2OH)_2$, H^+; (h) TBAF; PCC; 40% (for g-h); (i) SmI_2 ; (j) H_3O^+; 60% (for i-j); (k) DDQ, 82%; (l) BSTFA; (m) LDA, TMSCl; (n) $Pd(OAc)_2$; (o) HF; 76% (for l-o); (p) H_2O_2, $NaHCO_3$.

Scheme 66[145]



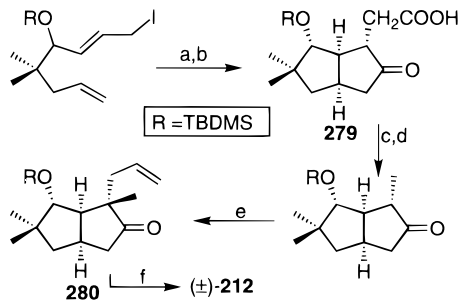
Reagents: (a) Scheme 65; (b) H_2O_2, $NaHCO_3$, 87%; (c) $NaBH_4$, 72%; (d) ^{t}BuOOH, $VO(acac)_2$, 75%; (e) $^nC_7H_{15}COCl$, DMAP; (f) K_2CO_3, 69% (for e-f).

Mehta and co-workers[129] have reported the details of their photothermal olefin metathesis[138j] based synthesis of (±)-coriolin (**212**).

B. Capnellanes

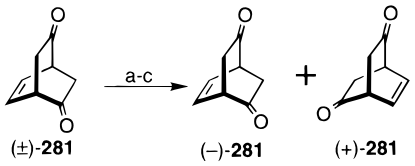
Capnellene (**282**), the simplest member of the capnellane group of marine sesquiterpenes, was isolated[149a,b] in 1978 by Djerassi *et al.* from the soft coral *Capnella imbricata*. Earlier,[149c−e] several oxygenated capnellanes **283**−**288** were also isolated from the same source. A combination of interesting structural features and potential biological activity has

Scheme 67[146]



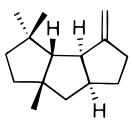
Reagents: (a) $Ni(COD)_2$, dppb, CO; (b) LiOH; 68% (for a-b); (c) N(OH)-pyridine-2-thione; (d) ^tBuSH, hv; 58% (for c-d); (e) NaH, allyl bromide, 49%; (f) ref.138o, 133l.

Scheme 68[147]

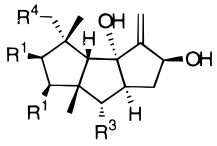


Reagents: (a) *(R,R)*-Diethyl tartrate, TsOH, 96%; (b) chromatography, 68% (1:1); (c) H_3O^+, 91%.

sustained the interest of synthetic chemists in this class of sesquiterpenoids.[150]



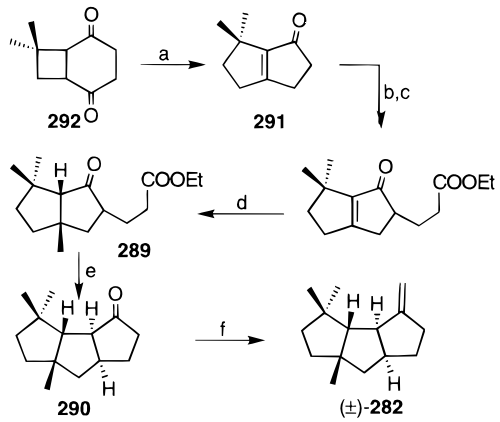
Capnellene (**282**)



283 $R^1=R^2=R^3=R^4=H$
284 $R^1=R^3=R^4=H$; $R^2=OH$
285 $R^1=R^2=R^4=H$; $R^3=OH$
286 $R^2=R^3=R^4=H$; $R^1=OH$
287 $R^1=R^3=H$; $R^2=R^4=OH$
288 $R^2=R^4=H$; $R^1=R^3=OH$

Oda and co-workers[151] have reported the synthesis of (±)-capnellene **282** employing an intramolecular Ti(0)-mediated ester−ketone reductive coupling as the key reaction (**289** → **290**) (Scheme 69). The

Scheme 69[151]

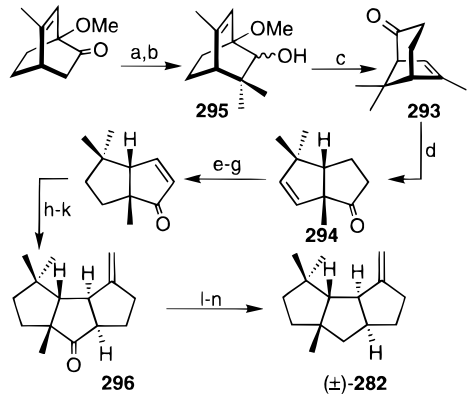


Reagents: (a) TMSI; (b) NaH, HCOOEt; (c) NEt_3, CH_2=CH-COOEt; 41% (for b-c); (d) Me_2CuLi, 88%; (e) LAH, $TiCl_4$, 72%; (f) $Ph_3P=CH_2$.

diquinane enone **291** was obtained by the trimethylsilyl iodide-mediated rearrangement of the bicyclo[4.2.0]octane-2,5-dione **292**. Introduction of the ethyl acrylate side chain and conjugate addition of the methyl group in enone **291** led to the keto ester **289** which on titanium(0) coupling furnished the penultimate precursor **290** of (±)-**282**.

Uyehara and co-workers[152] have explored the photochemical 1,3-acyl shift in a bicyclo[3.2.1]oct-6-en-2-one derivative for generating the diquinane unit (**293** → **294**) of capnellene (**282**) (Scheme 70). The

Scheme 70[152]



Reagents: (a) ^tBuOK, MeI; (b) LAH; 80% (for a-b); (c) TsOH, 80%; (d) hv, acetone, 51%; (e) H_2, Pd-C; (f) $ClCOOCH_2CH=CH_2$; (g) $Pd(OAc)_2$; 52% (for e-g); (h) $[-C(=CH_2)(CH_2)_2OTBDMS]_2CuLi$; (i) AcOH, H_2O; (j) TsCl, NEt_3; (k) LiHMDS; 86% (for h-k); (l) LAH; (m) NaH, CS_2; MeI; (n) $^nBu_3SnH$, AIBN, 26% (for l-n).

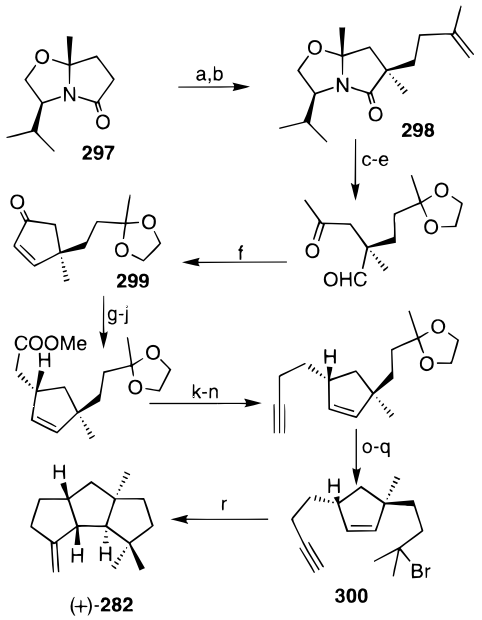
requisite bicyclo[3.2.1]octane precursor **293** was obtained through a regioselective rearrangement of bicyclo[2.2.2]oct-5-en-2-ol derivative **295**. The third cyclopentane ring was annulated via the conjugate addition of a functionalized vinyl cuprate and intramolecular alkylation to give the triquinane **296**. Deoxygenation of **296** completed the synthesis of (±)-**282**.

Meyers and Bienz[153] exploited the sequential alkylation on their chiral auxiliary, the bicyclic lactam **297**, to furnish **298** for an enantioselective synthesis of unnatural antipode (+)-**282** of capnellene (Scheme 71). Unmasking the functionalities and intramolecular aldol cyclization furnished the cyclopentenone **299**. A series of functional group modifications in **299** led to Curran's[150o] intermediate **300**. The tandem radical cyclizations in the bromo enyne **300** resulted in (+)-**282**.

A higher order intramolecular [6+2]-cycloaddition between fulvene and an aldehyde was the main strategy (**301** → **302**) employed by Houk and coworkers[154] for the rapid construction of the triquinane framework present in (±)-capnellene (**282**) (Scheme 72). Partial and regioselective reduction within the fulvene system **302** and further functional group manipulations led to the natural product.

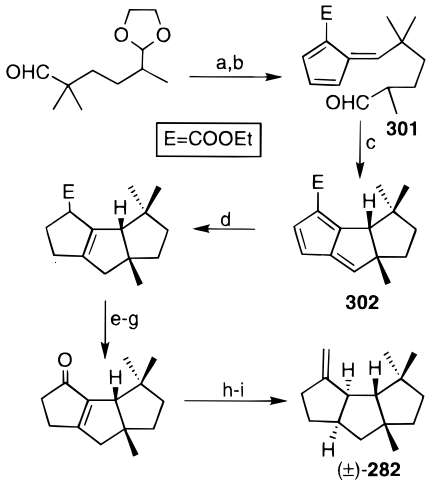
An intramolecular Diels−Alder reaction and ring contraction were the main elements of the strategy followed by Fukumoto and co-workers[155,156] for the synthesis of (±)-capnellene (**282**) (Scheme 73). The lactone **303**, prepared from 4,4-dimethylcyclopentenone, was elaborated into the bis-enone **304**. Formation of the dienol-TBDMS ether from **304** and thermolysis afforded the tricyclic compound **305** in excellent yield. Contraction of the cyclohexene ring

Scheme 71[153]



Reagents: (a) LDA, prenyi iodide, 79%; (b) LDA, MeI, 84%; (c) O_3; Me_2S, 98%; (d) $(CH_2OH)_2$, H^+, 95%; (e) RED-Al; (f) KOH; 78% (for e-f); (g) $NaBH_4$; separation; 43%; (h) ClCOOEt, py, 100%; (i) $Pd(PPh_3)_4$, $CH_2(COOMe)_2$, 90%; (j) NaCl, DMSO, 92%; (k) LAH, 99%; (l) MsCl, py, 99%; (m) NaI, 93%; (n) HC≡CLi, 86%; (o) H_3O^+, 89%; (p) MeMgCl, 98%; (q) TMSBr, 96%; (r) $^nBu_3SnH$, AIBN, 58%.

Scheme 72[154]



Reagents: (a) $MeNH_2$, AcOH, Cp-COOEt, 58%; (b) H_3O^+; (c) PhNHMe; 52% (for b-c); (d) Mg, MeOH, 64%; (e) NaOH, 100%; (f) LDA, O_2; (g) LTA; 57% (for f-g); (h) Li, liq. NH_3; (i) PDC; 62% (for h-i); (j) $Ph_3P{=}CH_2$.

was achieved through a classical Wolff rearrangement protocol. A series of routine reactions furnished the triquinane **296**, an advanced intermediate in Pier's[150k] synthesis of (±)-**282**.

An oxyanion-initiated fragmentation of 1-chlorobicyclo[3.3.1]nonane to a diquinane was the key step in the formal synthesis of (±)-capnellene (**282**) by Gambacorta and co-workers[157] (Scheme 74). The 9-oxobicyclo[3.3.1]nonan-1-carboxylate **306** obtained from 3,3-dimethylcyclohexanone was converted into the chloro diacetate **307**, which on base hydrolysis underwent a facile fragmentation to the diquinane **308**. The hydroxy aldehyde **308** was converted into the diquinane **309**, a known precursor[150b,d] of (±)-capnellene (**282**) and (±)-capnellene-8β,10α-diol (**283**).[150q]

Shono and co-workers[158] have employed two sequential electroreductive cyclization reactions of γ-cyano ketones (**310** → **311** and **312** → **313**) for the generation of the triquinane moiety **313**, in their formal synthesis of (±)-capnellene (**282**) (Scheme 75). Deoxygenation of the hydroxy ketone **313** led to the norketone **290**, a frequently encountered precursor of (±)-**282**.

A palladium-catalyzed tandem cyclization strategy was employed for the synthesis of (±)-capnellene (**282**) by Balme and Bouyssi[159] (Scheme 76). The malonate **314**, obtained from the lactone **315**, was transformed into the vinyl iodide **316**. Palladium-mediated cyclization of **316** furnished the triquinane **317**, in which the ester groups were transformed to a *gem*-dimethyl group to eventuate in (±)-**282**.

Sonawane and co-workers[160,161] have described the synthesis of both the enantiomers of the diquinane-based enone **318** from (+)-Δ^3-carene (Scheme 77). The racemic enone **318** has been transformed earlier[150k] to (±)-capnellene (**282**).

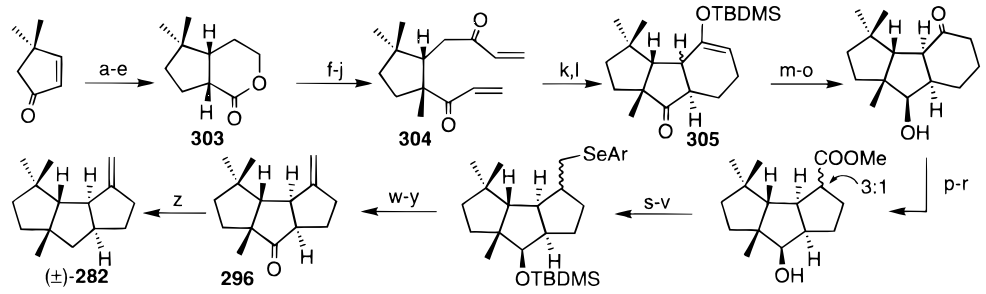
Asaoka and co-workers[162] have also reported a enantioselective synthesis of the chiral enone (−)-**318** (Scheme 78). Silyl group-directed conjugate addition on the cyclopentenone **319** and functional group manipulations led to (−)-**318**.

Singh and co-workers[163] have developed a photochemical oxa-di-π-methane rearrangement-based route to (±)-capnellene (**282**) (Scheme 79). The requisite bridged enone **320** was obtained via an inverse-electron demand Diels−Alder reaction between the dienone derived from the oxidation of 2,5-dimethylbenzyl alcohol and cyclopentadiene. Photochemical oxa-di-π-methane rearrangement (**320** → **321**) and functional group transformations led to (±)-**282**.

Pattenden and co-workers[164,165] have reported the detailed account of their earlier synthesis of (±)-8α,-10α-capnellenediol (**323**) along with its conversion into the natural capnellene, 8β,10α-capnellenediol (**283**) via superoxide-mediated inversion of the corresponding mesylate (Scheme 80).

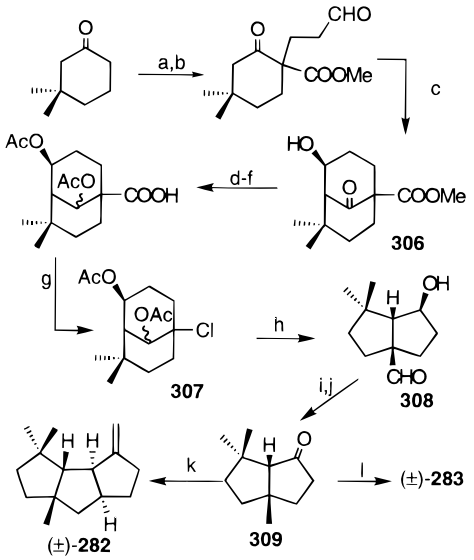
In continuation[150q] of their earlier synthesis of (±)-capnellenetriol (**284**), Shibasaki and co-workers[166] reported the first total synthesis of (±)-capnellenetetrol (**287**), along with an improved procedure for the triol (±)-**284** (Scheme 81). The diquinane-based enone **324** was elaborated into the triquinane dienone **325**. Conjugate addition of a methyl group and functional group manipulations led to the precursor **326** of (±)-**284**. Conjugate addition of a vinyl group, oxidative cleavage of the olefin moiety, and further elaboration furnished (±)-capnellenetetrol (**287**). Subsequently, Shibasaki *et al.*[167,168] have also developed

Scheme 73[155,156]



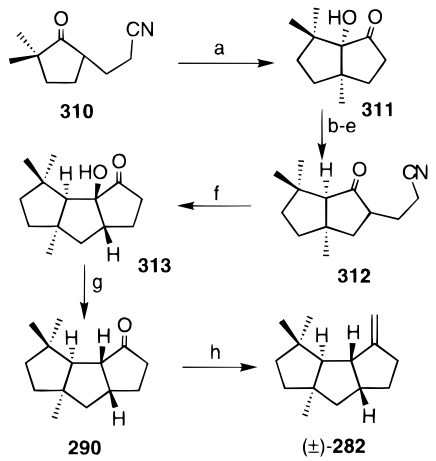
Reagents: (a) CH_2=CHMgBr, CuI; CNCOOMe; 89%; (b) $(CH_2SH)_2$, $BF_3.OEt_2$, 93%; (c) $(C_6H_{11})_2BH$; H_2O_2, ^-OH; 88%; (d) Raney Ni, 100%; (e) CSA, 97%; (f) LDA, MeI, 74%; (g) DIBALH, 100%; (h) Swern oxdn.; (i) CH_2=CHMgBr; 96% (for h-i); (j) Ph_3BiCO_3, 75%; (k) ^{t}BuOK, TBDMSCl; (l) Δ; (m) DBU; 55% (for k-m); (n) $NaBH_4$, 92%; (o) TBAF, 100%; (p) HCOOEt, NaOMe; (q) TsN_3, NEt_3; (r) hv; 48% (for p-r); (s) TBDMSOTf, DMAP, DMP, 98%; (t) DIBALH; (u) MsCl, NEt_3; (v) o-$NO_2C_6H_4SeCN$, $NaBH_4$; (w) H_2O_2; 70% (for t-w); (x) TBAF; (y) periodinane; 91% (for x-y); (z) ref. 150k, 152.

Scheme 74[157]



Reagents: (a) NaH, $(Me)_2CO_3$, 90%; (b) CH_2=CHCHO, NaOMe, 97%; (c) NaOMe, 62%; (d) $NaBH_4$, 95%; (e) NaOH, 90%; (f) Ac_2O, py, 97%; (g) Barton's chlorodecarboxylation; (h) NaOH; 84% (for g-h); (i) W.K. reduction, 88%; (j) PDC, 98%; (k) ref. 150b,d; (l) ref. 150q.

Scheme 75[158]



Reagents: (a) electrolysis, 68%; (b) H^+, 86%; (c) Me_2CuLi, 85%; (d) NaH, $(COOEt)_2$; (e) CH_2=CHCN, NEt_3; 62% (for d-e); (f) electrolysis, 37%; (g) H^+; Li, liq. NH_3; 82%; (h) Ph_3P=CH_2.

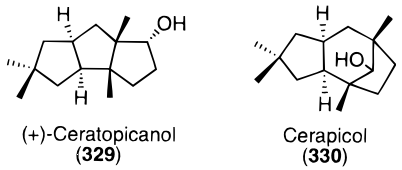
a methodology for the chiral synthesis of the triquinane **327** via an asymmetric Heck reaction on the *meso*-triflate **328** (Scheme 82).

Mehta *et al.*,[150i,129] Piers *et al.*,[150k,169] and Grubbs *et al.*[150p,170] have published full papers on their earlier syntheses of (±)-capnellene (**282**).

C. Ceratopicanol

Ceratopicanol (**329**), the only known member of this skeletal-type among triquinane natural products, was isolated in 1988 by Hanssen and Abraham[171] along with a closely related tricyclo[6.2.1.0^{2,6}]undecane-based alcohol cerapicol (**330**), from the fungus *Ceratocystis piceae* Ha 4/82. Besides the interesting biogenetic origin, the presence of two vicinal quaternary bridgehead methyl groups and five contiguous stereogenic centers on a *cis*,*anti*,*cis*-triquinane framework makes **329** a challenging synthetic target, and three syntheses have appeared since its isolation.

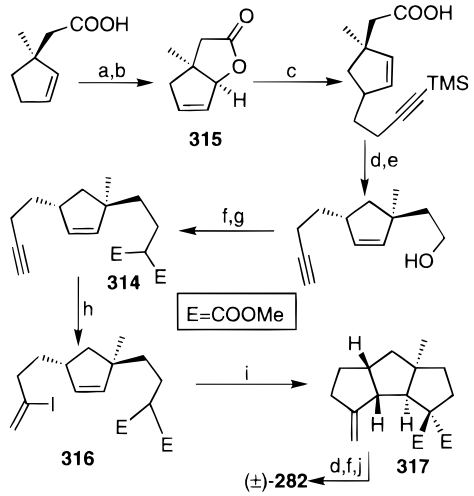
In 1991, Mehta and Karra[172] reported the first enantioselective total synthesis of the optical antipode of (−)-ceratopicanol (**329**), from (*R*)-limonene



(Scheme 83). An interesting feature of their strategy was the use of isopropyl group in chiron **331**,[173] as an internal, disposable, chiral director. A stereospecific orthoester-Claisen rearrangement (**331** → **332**) and an acid-catalyzed diazo ketone−olefin cyclization (**333** → **334**) were strategically used for the creation of the two quaternary carbon centers. Annulation of the third ring employing a recently developed[174] methodology for dimethylcyclopentannulation of cyclic ketones furnished the triquinane **335**. Functional group adjustments led to (−)-**329**.

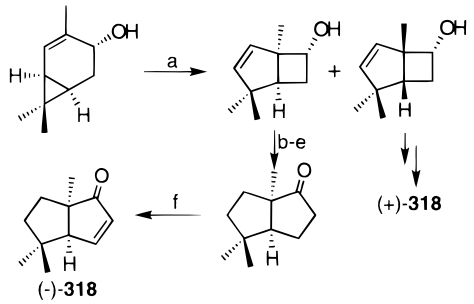
A titanium-mediated radical cyclization on an epoxy acetylene (**336** → **337**) was the key step in the synthesis of ceratopicanol **329** by Clive and Magnuson[175,176] (Scheme 84). The readily available[177] diquinane enone **338**, containing the two bridgehead

Scheme 76[159]



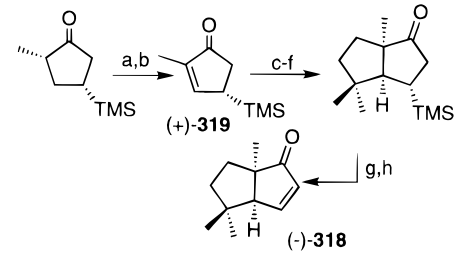
Reagents: (a) I_2, $NaHCO_3$, 95%; (b) DBU, 90%; (c) CuBr. Me_2S TMS-C≡C$(CH_2)_2$MgBr, 95%; (d) LAH, 95%; (e) KF, 95%; (f) NEt_3, MsCl; (g) $NaCH(COOMe)_2$, KI; 78% (for f-g); (h) TMSCl, NaI, 73%; (i) KH, $Pd(OAc)_2$, (2-Furyl)$_3$P, 65%; (j) $LiEt_3BH$, 49% (for d,f,j).

Scheme 77[160,161]



Reagents: (a) hν, 75%; (b) H_2, Pd-C, 90%; (c) Swern oxdn., 82%; (d) $N_2CHCOOEt$, $SbCl_5$, 85%; (e) DMSO, NaCl, Δ, 86% (f) $PdCl_2$, $Pd(OAc)_2$, O_2, 72%.

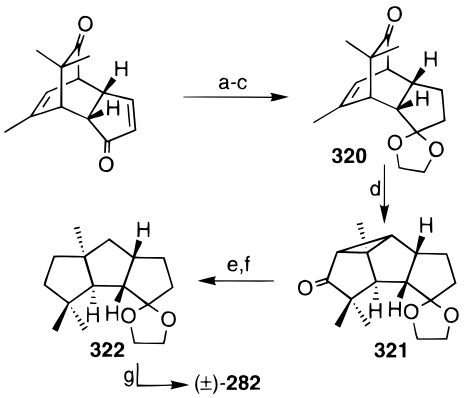
Scheme 78[162]



Reagents: (a) TMSOTf, NEt_3; (b) $Pd(OAc)_2$; 74% (for a-b); (c) $BnO(CH_2)_2C(Me)_2$-MgCl, CuBr.SMe_2, TMSCl; KF; (d) H_2, Pd-C; (e) TsCl, py; 40% (for c-e); (f) ^{t}BuOK; (g) TMSOTf, NEt_3; NBS; (h) TBAF; 61% (for g-h).

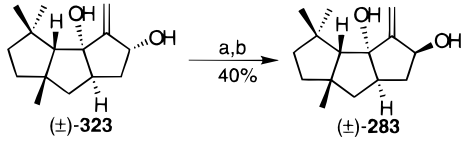
methyl groups, was transformed stereospecifically into the enyne **339**. Titanium-mediated radical cyclization of the epoxy acetylene **336**, generated the triquinane alcohol **337**, which on functional group manipulations provided (±)-**329**.

Scheme 79[163]



Reagents: (a) $NaBH_4$,89%; (b) Jones oxdn.,78%; (c) $(CH_2OH)_2$, H^+, 64%; (d) hν, 64%; (e) H_2, Pd-C, 85%; (f) $NaBH_4$; NaH, CS_2, MeI; ^{n}Bu$_3$SnH, AIBN; 69%; (g) H_3O^+; $Ph_3P{=}CH_2$, 63%.

Scheme 80[164,165]



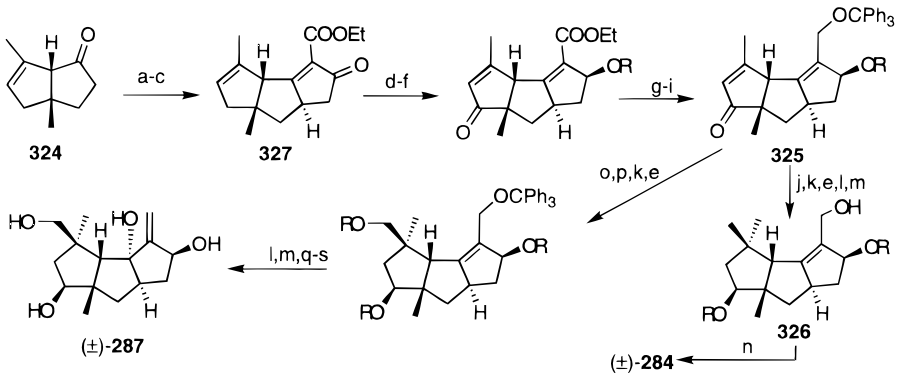
Reagents: (a) MsCl, NEt_3; (b) Potassium superoxide, 18-c-6.

Recently Chanon *et al.*[178] have accomplished a short synthesis of (±)-ceratopicanol **329** employing an intramolecular arene−olefin meta-photocycloaddition as the key step (Scheme 85). As the efficiency of the photochemical reaction was found to be poor with the dimethylated arene **340**, the reaction was carried out with monomethyl compound **341**, and the second bridgehead carbon atom was quaternized at a later stage. Irradiation of the arene **341** resulted in the formation of a 2:1 mixture of the vinylcyclopropane precursors for linear and angular triquinanes **342** and **343**, respectively. Regioselective cyclopropane cleavage in **342** and functional group adjustments including the installation of the second quaternary center through alkylation led to (±)-**329**. Interestingly, the Chanon *et al.* approach originated through computer-assisted analysis and illustrates the utility of the holosynthon concept in the rapid generation of complex frameworks.[178]

IV. Angular Triquinanes

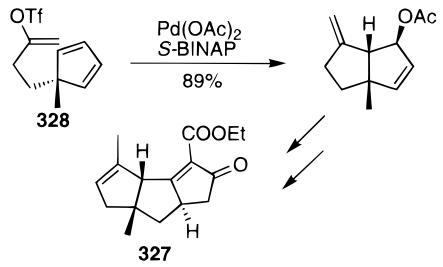
The sesquiterpene natural products containing an angular triquinane moiety, isolated so far, fall into four different skeletal types **344**−**347** on the basis of the arrangement of the four carbon substituents on the tricyclo[6.3.0.0^{1,5}]undecane core. In addition, di- and sesterterpene natural products, like laurenene and retigeranic acid also incorporate an angular triquinane unit corresponding to silphinane and silphiperfolane, respectively. The main challenge in the synthesis of angular triquinanes is the installation of a network of methyl groups and quaternary

Scheme 81[166]

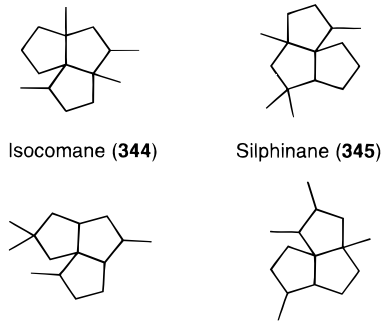


Reagents: (a) LDA, $ICH_2C(OMe)=CHCOOEt$, 85%; (b) $HClO_4$, 90%; (c) NaOEt, 85%; (d) $NaBH_4$, $CeCl_3$, 70%; (e) TBDMSCl, imidazole, 98%; (f) CrO_3.DMP, 60%; (g) DIBALH, 85%; (h) Ph_3CCl, DMAP, 95%; (i) MnO_2, 94%; (j) $Me_2CuCNLi_2$, 81%; (k) L-selectride, 75%; (l) OsO_4, py, 82% (for e, l); (m) Et_2AlCl, 96%; (n) ref. 150q; (o) $CH_2=CHCuCNLi_2$, 86%; (p) OsO_4, $NaIO_4$, 80%; (q) MsCl, NEt_3, 84%; (r) TMSLi, 70%; (s) TBAF, 96%.

Scheme 82[167,168]

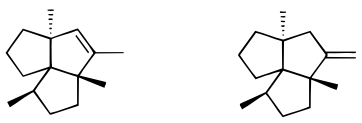


carbon centers in addition to the control of stereochemistry of the remote secondary methyl group.



A. α- and β-Isocomenes

α-Isocomene (**348**, usually referred to as isocomene) was the first angular triquinane sesquiterpene to be isolated and characterized.[179a,65b] Isocomenes,[179] isolated from *Isocoma wrightii*, are distinctive in the sense that their framework contains two angular methyl groups as part of three contiguous quaternary carbon centers. Understandably, their synthesis has aroused considerable interest.[180]



Dreiding and co-workers[181] have applied their α-alkynone cyclization strategy toward a formal synthesis of (±)-isocomene (**348**) (Scheme 86). Previously synthesized[182] diquinane enone **350** was elaborated into the α-alkynone **351**, which on flash vacuum pyrolysis furnished the angular triquinane **352**, an advanced intermediate in Paquette's[180c,g] synthesis of (±)-**348**.

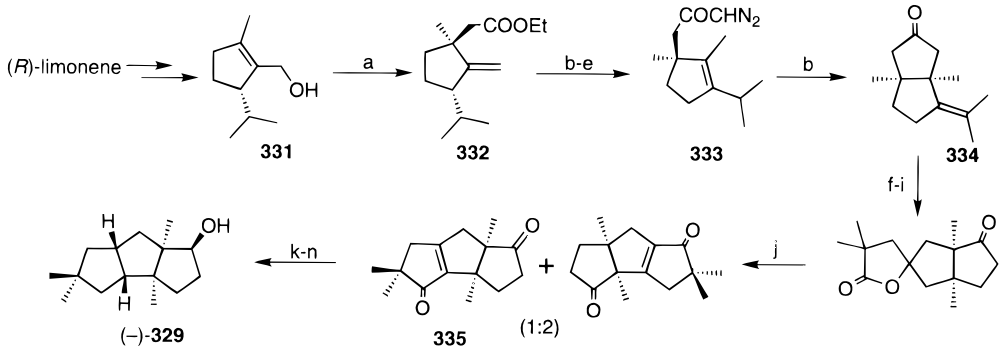
Fitzer and co-workers[67,69,183] have reported an elegant, one-pot, deep-seated cationic rearrangement of the dispirane-based tertiary alcohol **137** to furnish (±)-isocomene (**348**) (Scheme 87). Analogously, the chiral alcohol (−)-**137** afforded (−)-**348**.

An intramolecular olefin−ketene cycloaddition was the pivotal step in the formal synthesis of (±)-isocomene (**348**) by Snider and co-workers[184] (Scheme 88). The acetoacetate **353** was converted into the diene ester **354** through sequential Cargill−Claisen rearrangement (**353** → **355**) and Peterson olefination reaction (**355** → **354**). The vinylketene generated from the acid chloride of **354** furnished the cyclobutanone **356** via the intramolecular ketene−olefin cycloaddition. Olefin isomerization in **356** afforded the 5-5-4 tricyclic ketone **357**, which has been previously elaborated to (±)-**348** by Wenkert and co-workers.[180j]

Kennedy and co-workers[185] have reported the synthesis of (±)-β-isocomene (**349**) by employing a titanium tetrachloride-catalyzed intramolecular Prins reaction (**358** → **359**) and concomitant carbonium ion-mediated ring contraction (**359** → **360**) for the generation of the triquinane framework (Scheme 89). Further transformations on **360**, involving the introduction of the two bridgehead methyl groups and a Wittig olefination completed the synthesis of (±)-**349**.

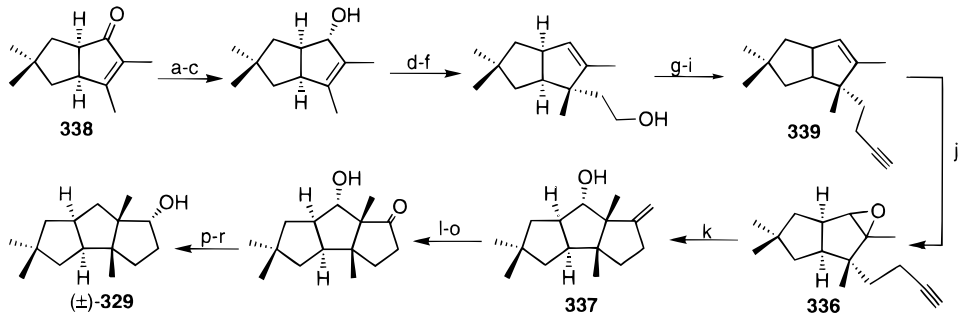
More recently, Rawal and co-workers[186] have described the synthesis of (±)-α-isocomene (**348**) and β-isocomene (**349**), employing a strategy similar to that developed by them for the synthesis of (±)-hirsutene **209** (Scheme 90). The synthesis seems to be quite efficient as high yields are reported in all the steps. The key features of their scheme are (a) an intramolecular Paterno−Buchi reaction in acetylnorbornene (**361** → **362**); (b) regioselective cleavage of oxetane and oxidation (**362** → **363**); and (c) LDBB-mediated C−C bond cleavage (**363** → **364**). Conversion of the diquinane **364** into the corresponding bromide followed by 5-*exo*-*trig* radical cyclization and Wittig methylenation led to (±)-**349**. On the other hand, carbanion-mediated cyclization in the iodide

Scheme 83[172]



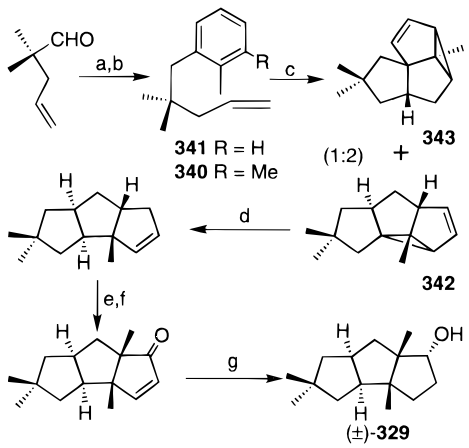
Reagents: (a) $MeC(OEt)_3$, EtCOOH, Δ, 80%; (b) $BF_3.OEt_2$, 82%; (c) NaOH; (d) $(COCl)_2$; (e) CH_2N_2; 68% (for c-e); (f) $BrCH_2C(Me)_2CH_2OTBDMS$, Li; 42% (for b,f); (g) O_3; Me_2S; (h) TBAF; 73% (for g-h); (i) TPAP, NMMO, 91%; (j) MsOH, P_2O_5, 70%; (k) $NaBH_4$, 87%; (l) Li, liq. NH_3, 66%; (m) Ac_2O, DMAP, 90%; (n) Na, HMPT, ^tBuOH, 20%.

Scheme 84[175,176]



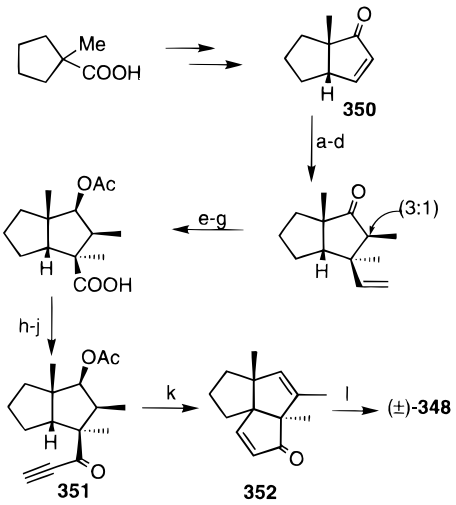
Reagents: (a) DIBALH, 89%; (b) PPh_3, $ClCH_2COOH$, DEAD; (c) LAH; 58% (for b-c); (d) $PhS(O)-CH=CH_2$, NaH; (e) Δ; (f) LAH; 73% (for d-f); (g) PPh_3, CBr_4, 94%; (h) LiC≡CTMS; (i) KOH, MeOH; 94% (for h-i); (j) m-CPBA; (k) Cp_2TiCl; 82% (for j-k); (l) Ac_2O, AcCl, DMAP, py; (m) OsO_4, NMMO; (n) K_2SO_3; (o) LTA, K_2CO_3 ; 80% (for l-o); (p) PhO-C(S)Cl, DMAP, 84%; (q) Bu_3SnH, BEt_3, 72%; (r) $NaBH_4$, 81%.

Scheme 85[178]



Reagents: (a) o-MeC_6H_4Li; (b) Li, liq. NH_3; 98% (for a-b); (c) hv, 72%; (d) PhSH; Li, liq.NH_3; 78%; (e) CrO_3.DMP, 60%; (f) LDA, MeI, 97%; (g) $NaBH_4$, 60%.

Scheme 86[181]



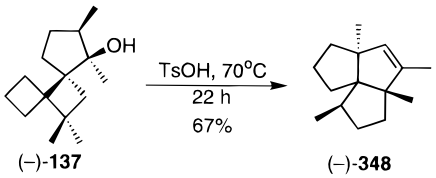
Reagents: (a) Me_2CuLi, 21%; (b) NaH, $TolSO_2Me$; Δ, 77%; (c) CH_2=CHMgBr, $(CuI.PBu_3)_4$; MeI; 91%; (d) equilibration, 95%; (e) $LiAl(O^tBu)_3H$, 60%; (f) Ac_2O, py, 92%; (g) $RuCl_3.3H_2O$, $NaIO_4$, 83%; (h) $SOCl_2$; (i) TMSC≡CTMS; (j) $Na_2B_4O_7$; 74% (for h-j); (k) 720°C; °OH; $POCl_3$, py; 60%; (l) ref.180c,g.

derived from **364**, trapping of the enolate as the enol triflate and coupling with lithium dimethyl cuprate led to (±)-**348**.

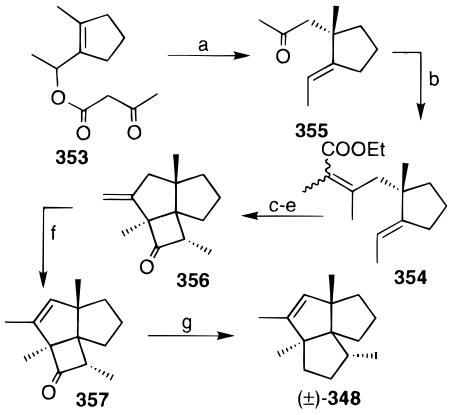
Lee and Lee[187,188] have reported a formal synthesis of (±)-isocomene (**348**) (Scheme 91). Cyclopentannulation of the diquinane-based enone **365** via conjugate addition of an appropriate cuprate and intramolecular alkylation sequence generated the triquinane **366**, which was further elaborated into Paquette's[180c,g] intermediate **352** of (±)-**348**.

Hudlicky and co-workers[189] have reported the details of their synthesis[180k,l] of (±)-α- and β-isocomenes **348** and **349** based on the intramolecular α-diazo ketone cyclopropanation and thermal vinylcyclopropane−cyclopentene rearrangement strategy.

Scheme 87[67,68]

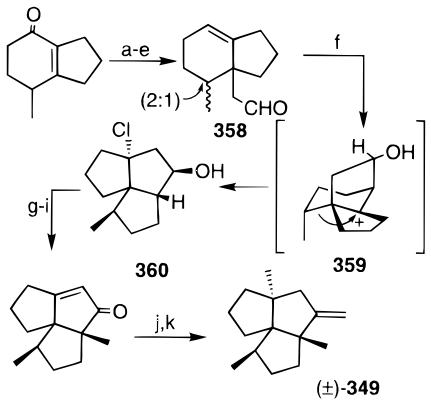


Scheme 88[184]



Reagents: (a) LDA; Δ; 72%; (b) MeCH(TMS)COOEt, LDA; (c) NaOH; 95% (for b-c); (d) $(COCl)_2$; (e) NEt_3; 41% (for d-e); (f) HI, 51%; (g) ref. 180j.

Scheme 89[185]

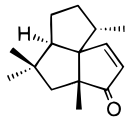


Reagents: (a) LAH, 95%; (b) Ac_2O, py; (c) TBDMSCl, LDA; Δ; (d) LAH; 85% (for b-d); (e) Swern oxdn., 84%; (f) $TiCl_4$, 67%; (g) PCC; (h) DBU; 98%; (i) LDA, MeI, 87%; (j) Me_2CuLi, 89%; (k) $Ph_3P{=}CH_2$, 98%.

B. Silphinene and 3-Oxosiliphinene

The angular triquinane silphinene **367** and its 3-oxo derivative **368** were isolated from the plants *Silphium perfoliatum* and *Dugaldia hoopesii*, respectively, by Bohlmann and co-workers.[190] Silphinenes have been popular synthetic targets[191] and several new approaches have appeared in the recent past.

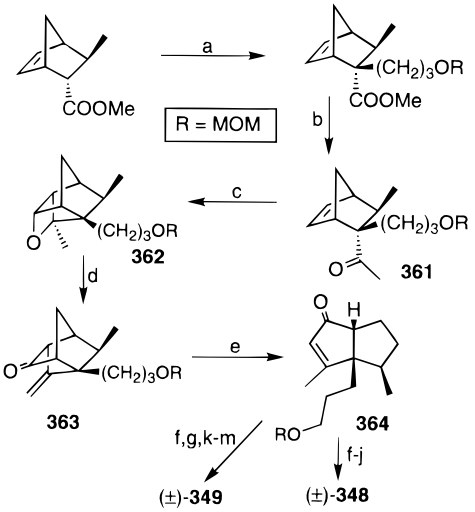
Silphinene (**367**)[190a]



3-Oxosilphinene (**368**)[190b]

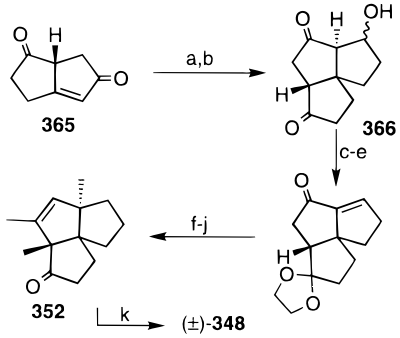
Crimmins and co-workers[192–194] have exploited an intramolecular [2+2]-photocycloaddition and regiospecific cyclobutane cleavage as the strategy for the synthesis of (±)-silphinene (**367**) (Schemes 92 and

Scheme 90[186]



Reagents: (a)LDA, $I(CH_2)_3OR$, 96%; (b) $MeSOCH_2Li$, Zn, NaOH, 92%; (c) hν, 92%; (d) LDA; Swern oxdn.; 80%; (e) LDBB, 65%; (f) LDA, MeI, 92%; (g) $LiBF_4$, 95%; (h) PPh_3, I_2, 98%; (i) ^nBuLi, $ArNTf_2$, 76%; (j) Me_2CuLi, 95%; (k) PPh_3, CBr_4, 84%; (l) $^nBu_3SnH$, AIBN, 91%; (m) $Ph_3P{=}CH_2$;

Scheme 91[187,188]

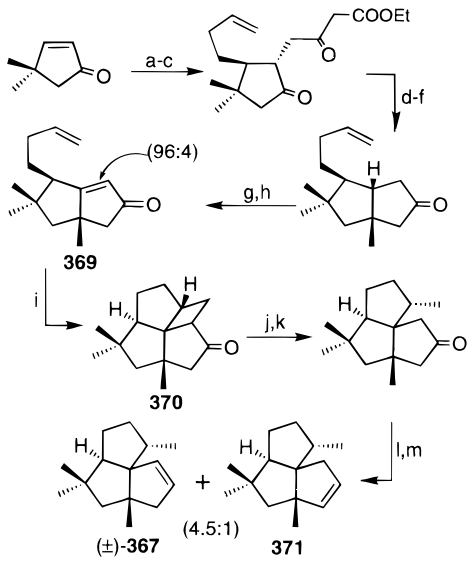


Reagents: (a) $(RO)_2CH(CH_2)_2Li$, CuBr; (b) H^+; (c) MsCl; (d) $(CH_2OH)_2$, H^+; (e) -MsOH; (f) Birch reduction- alkylation; (g) C-6 alkylation; (h) reduction; (i) $-H_2O$; (j) H_3O^+; (k) ref. 180c,g

93). The intramolecular [2+2]-photocycloaddition in the dienone **369**, obtained from 4,4-dimethylcyclopentenone through a series of reactions, afforded the cyclobutane fused triquinane **370** in high yield. Trimethylsilyl iodide-mediated regiospecific cleavage of the cyclobutane ring followed by conversion of the ketone to olefin led to a 4.5:1 mixture of (±)-siliphinene (**367**) and isosilphinene (**371**). Subsequently, the regiospecific formation of the olefin and the cyclobutane cleavage were achieved together via the tributyltin hydride reaction on the iodide **372** to furnish (±)-**367** in good yield.

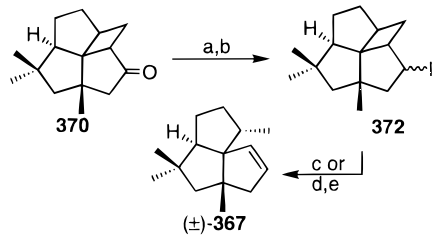
An intramolecular radical addition in a bicyclic enone was the key step in a formal synthesis of (±)-silphinene (**367**) devised by Nagarajan and Rao[195,196] (Scheme 94). The readily available 2,4,4-trimethylcyclopentanone was converted into the diquinane enone **373** through an intramolecular Horner–Wadsworth–Emmons reaction. The 5-*exo-trig* radical cyclization reaction of the thionocarbonate derived from the alcohol **373** afforded the Crimmin's[192] precursor **374** of (±)-**367** in a stereoselective manner.

Scheme 92[192,193]



Reagents: (a) CH_2=$CH(CH_2)_2MgBr$, $Bu_3P.CuBr$; (b) $ICH_2C(OMe)$=$CHCOOEt$; 58% (for a-b); (c) $HClO_4$; (d) NaOMe; 90% (for c-d); (e) Me_2CuLi, 90%; (f) LiCl, H_2O, DMSO, 90%; (g) $TMSCH_2COOEt$, TBAF; (h) $Pd(OAc)_2$; 70% (for g-h); (i) hν, 90%; (j) TMSI, 89%; (k) $^nBu_3SnH$, AIBN, 98%; (l) LDA, $(EtO)_2POCl$, 78%; (m) Li, $EtNH_2$ 99%.

Scheme 93[194]



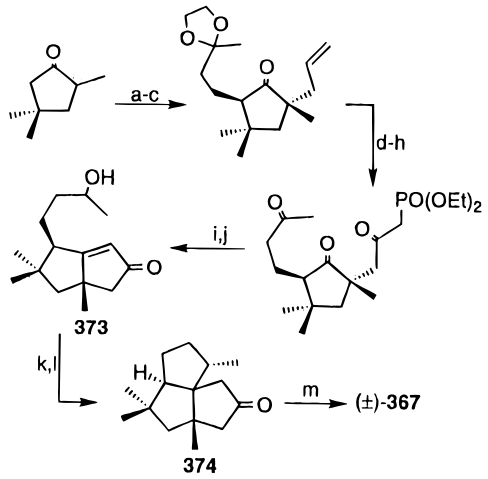
Reagents: (a) DIBALH, 97%; (b) TMSCl, NaI, 98%; (c) $^nBu_3SnH$ (slow addition), AIBN, 95%; (d) Bu_6Sn_2, AIBN, hν, 85%; (e) $^nBu_3SnH$, AIBN, 90%.

The theme of formal [2+2]-cycloaddition of an electron-deficient cyclopropene to an enamine and regiospecific cleavage of the resulting bicyclo[2.1.0]-pentane system has been extended to the synthesis of (±)-silphinene **367** by Franck-Neumann and co-workers[197] (Scheme 95). The diquinane **375** obtained by this strategy was elaborated into the triquinane **376**, employing a silicon-assisted Nazarov cyclization reaction. Further transformations including the regioselective introduction of the bridgehead methyl group led to (±)-**367**. Subsequently, the diquinane **375** was efficiently prepared via the cyclopropanation of the bicyclo[3.2.0]heptane system **377** with 2-diazopropane and further functionalization (Scheme 96).[198,199]

An electrochemical approach to (±)-silphinene (**367**) has been developed by Yamamura and co-workers[200,24] (Scheme 97). Anodic oxidation of the phenol **378** generated the methoxy enedione **379**. A series of functional group transformations and a glycolic cleavage transformed the dione **379** into the diquinane **380**. Intramolecular aldol condensation and 1,4-cuprate addition led to the triquinane **374**, a precursor[192] of (±)-**367**.

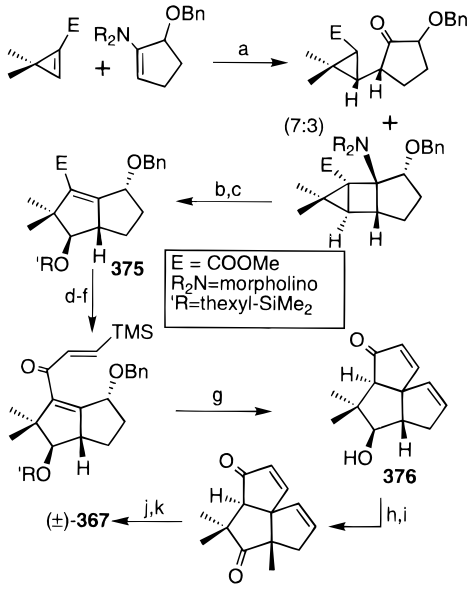
Fraser-Reid and Dickson,[201] as part of their carbohydrate to carbocycles theme, have reported the

Scheme 94[195,196]



Reagents: (a) NaH, CH_2=$CHCH_2Br$, 88%; (b) LDA, $MeC(OCH_2)_2CH_2CHO$, 90%; (c) Li, liq. NH_3, 60%; (d) $RuCl_3$, $NaIO_4$, 100%; (e) CH_2N_2, 100%; (f) $(CH_2OH)_2$, H^+, 60%; (g) ^nBuLi, $(EtO)_2P(O)CH_3$, 100%; (h) H_3O^+; (i) Bu_4NOH; 70% (for h-i); (j) $NaBH_4$, 72%; (k) Tol-OC(S)Cl, py, 70%; (l) $^nBu_3SnH$, AIBN, Δ, 70% (m) ref. 192.

Scheme 95[197]

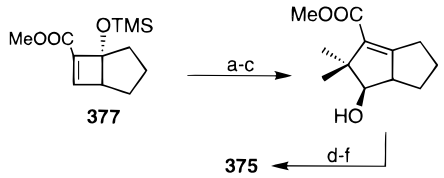


Reagents: (a) Et_2O, 97%; (b) H_2SO_4, 96%; (c) $Me_2Si(thexyl)OTf$, NEt_3; (d) DIBALH; PDC; 92% (for c-d); (e) TMSCH=CHMgBr, 92%; (f) MnO_2, 96%; (g) $BF_3.OEt_2$, 53%; (h) Swern oxdn., 89%; (i) LDA, MeI, 63%; (j) Me_2CuLi; (k) W.K. redn.

formal synthesis of silphinene **367** (Scheme 98). The diquinane intermediate **381** was obtained from a hexose through a series of selective transformations including a nitrile-terminated tandem radical cyclization reaction in the iodonitrile **382**. Restructuring of the carbohydrate portion and annulation of the third ring via an intramolecular alkylation led to the triquinane **383**, a precursor in the synthesis of (±)-**367** by Frank-Neumann *et al.*[197,198] The highlight of the sequence is the incorporation of all the six carbon atoms of the carbohydrate moiety into the final compound.

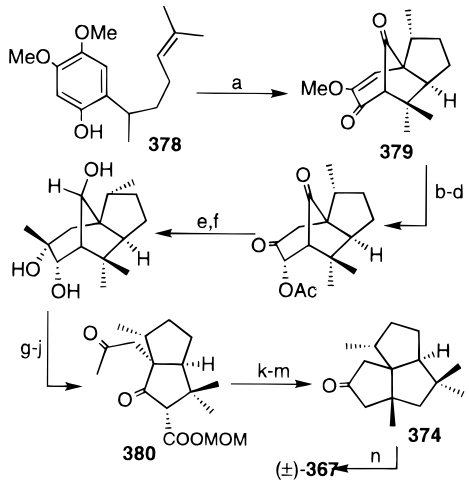
Fukumoto and co-workers[202,203] have utilized their intramolecular Diels−Alder reaction−ring contrac-

Scheme 96[198,199]



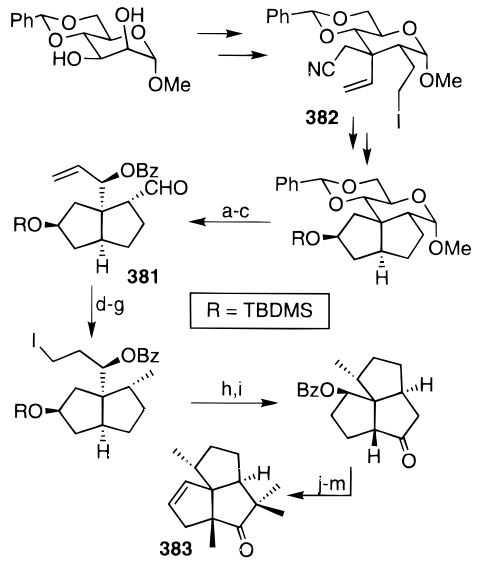
Reagents: (a) 2-diazopropane; hν; (b) TBAF; (c) H_2SO_4; 70% (for a-c); (d) Thexyl$(Me)_2$SiOTf; NEt_3; (e) SeO_2, 76%; (f) BnO-C(NH)CCl_3, 80%.

Scheme 97[200,24]



Reagents: (a) anodic oxdn., 54%; (b) DIBALH; (c) Ac_2O, py; 82% (for b-c); (d) $(COOH)_2$, 76%; (e) MeMgBr, 72%; (f) LAH, 98%; (g) LTA, 100%; (h) $NaClO_2$, 99%: (i) MOMCl, K_2CO_3, 97%; (j) PDC; (k) H_3O^+; 96% (for j-k); (l) NaOEt, 100%; (m) $Me_2CuCNLi_2$, 92%; (n) ref. 192.

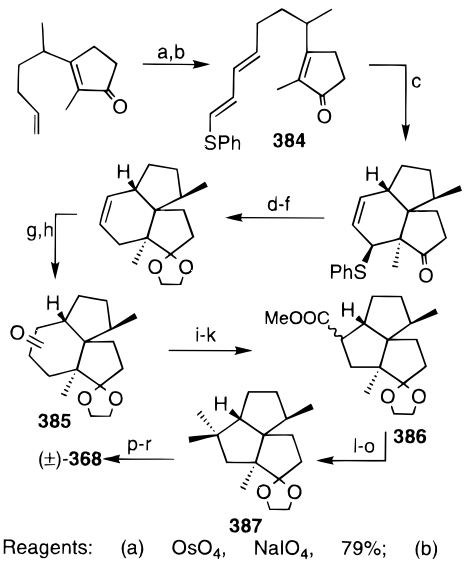
Scheme 98[201]



Reagents: (a) NBS, $BaCO_3$; (b) NaI; 84% (for a-b); (c) Zn-Hg, 81%; (d) $NaBH_4$, 92%; (e) $NaBH_4$, DMF, 85%; (f) BH_3; H_2O_2, ^-OH; (g) PPh_3, I_2; 82% (for f-g); (h) AcOH; PCC; (i) ^{t}BuOK; 75% (for h-i); (j) LiHMDS, MeI, 10%; (k) HCl; (l) PhOC(S)Cl; (m) $(^i PrO)_3C_6H_3$, Δ, 50% (for k-m).

tion strategy for the synthesis of (±)-3-oxosilphinene (**368**) (Scheme 99). As the intramolecular Diels–Alder reaction was found to be inefficient with the unsubstituted diene, a dienol thioether derivative **384** was employed. Thermal activation of **384** furnished a tricyclic adduct in a stereoselective fashion. Con-

Scheme 99[202,203]

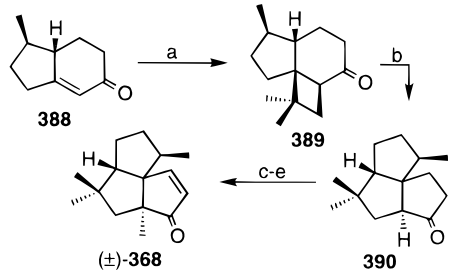


Reagents: (a) OsO_4, $NaIO_4$, 79%; (b) $(EtO)_2P(O)CH_2$ CH=CHSPh, ^{n}BuLi, 78%; (c) Δ, 76%; (d) Ca, liq. NH_3, 98%; (e) PCC, 88%; (f) H^+, $(CH_2OH)_2$, 91%; (g) $BH_3.SMe_2$; H_2O_2, ^-OH; (h) py.CrO_3; 78% (for g-h); (i) HCOOEt, NaH; (j) TsN_3, NEt_3; (k) hν; 60% (for i-k); (l) LDA, MeI, 80%; (m) DIBALH, 100%; (n) py.CrO_3, 84%; (o) W.K. redn., 99%; (p) H_3O^+, 87%; (q) LDA, TMSCl; (r) $Pd(OAc)_2$, 82% (for q-r).

traction of the six-membered ring using Wolff rearrangement (**385** → **386**) and conversion of the resulting ester into a *gem*-dimethyl group led to **387**. Further functional group readjustments led to (±)-**368**.

A novel aluminum chloride-catalyzed rearrangement of a bicyclo[4.2.0]octanone to a bicyclo[3.3.0]-octanone was the key reaction in the synthesis of (±)-3-oxosilphinene (**368**) by Kakiuchi and co-workers[204,205] (Scheme 100). Photochemical [2+2]-cycloaddition

Scheme 100[204,205]



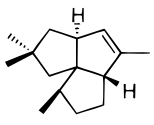
Reagents: (a) $Me_2C=CH_2$, silica gel, hν, 31%; (b) $AlCl_3$, 55%; (c) $PhNMe_3Br_3$; (d) LiBr, Li_2CO_3, DMF; (e) LDA, MeI, 34% (for c-e).

between isobutylene and hydrindenone **388** furnished the tricyclic ketone **389**, in which the regioselectivity was controlled by performing the reaction on a silica gel surface. Lewis acid-catalyzed rearrangement of the tricyclic ketone **389** led to the angular triquinane **390**, which was elaborated to (±)-**368**. While the yields in this synthesis are modest, the brevity of the approach is notable.

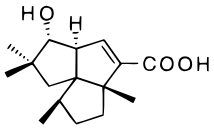
Reactions of cyclopentadienes using (η^5-indenyl)-molybdenum dicarbonyl complexes have been explored in the context of an approach to the synthesis of (±)-silphinene (**367**), by Taylor and co-workers.[206]

C. Pentalenene and Pentalenic Acid

Pentalenene (**391**), isolated[207] from the mycelia of *Streptomyces griseochromogenes*, is the parent hydrocarbon of the pentalenolactone group of fungal metabolites exhibiting antibiotic activity. Pentalenic acid (**392**) was isolated from the fermentation broth of *Streptomyces* sp. in 1978 along with pentalenolactone-H **104**.[52d] There has been a sustained interest in the synthesis of these compounds and several new approaches have appeared in the past decade.



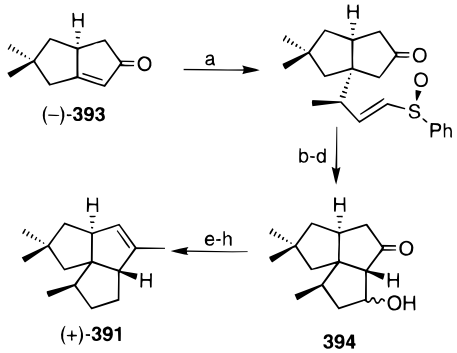
Pentalenene (**391**)[207]



Pentalenic Acid (**392**)[52d]

Hua[209] has reported an efficient enantioselective synthesis of the natural pentalenene [(+)-**391**] (Scheme 101). Stereoselective Michael addition of

Scheme 101[209]



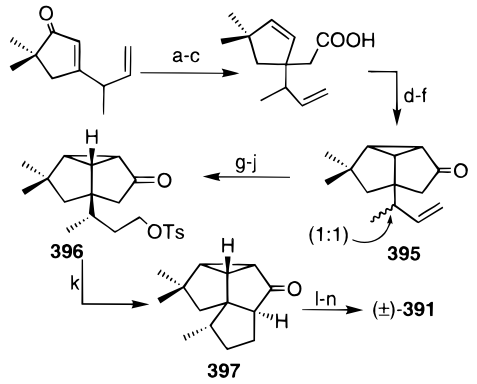
Reagents: (a) $MeCH{=}CHCH_2S(O)Ph$, LDA, 91%; (b) Zn, AcOH, 95%; (c) HCOOH, TFA, 60%; (d) K_2CO_3, 100%; (e) MeMgBr, 70%; (f) NEt_3, $(NMe_2)_2P(O)Cl$, 96%; (g) Li, $EtNH_2$, 97%; (h) $BF_3.OEt_2$, 99%.

crotyl phenyl sulfoxide to the diquinane enone (−)-**393**, obtained via a chiral sulfinyl anion-mediated kinetic resolution methodology, and annulation of the third cyclopentane ring through an intramolecular aldol condensation generated the chiral triquinane **394**. Further functional group manipulations in **394** led to (+)-**391**.

Iwata and co-workers[210,211] have developed a synthesis of (±)-pentalenene (**391**) in which an intramolecular α-diazo ketone-mediated cyclopropanation was effectively employed for the construction of the appropriately functionalized diquinane intermediate **395**. An intramolecular alkylation reaction (**396** → **397**) installed the third cyclopentane ring. Further functional group transformations, particularly the reductive cyclopropane ring cleavage led to (±)-**391** (Scheme 102). Iwata's second generation pentalenene synthesis[212] utilized the diquinane enone **74**, earlier reported by them[41−43] in their quadrone synthesis. A series of functional group adjustments led stereoselectively to (±)-**391** (Scheme 103).

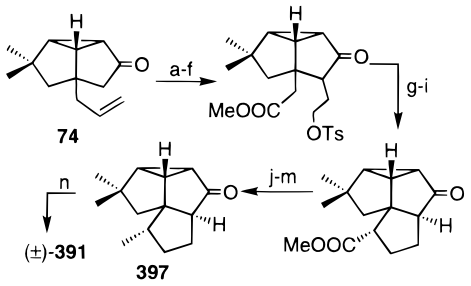
A vinylcyclopropane−cyclopentene rearrangement was the cornerstone of Hudlicky's[213,214] synthesis of (±)-pentalenene (**391**) and (±)-methyl pentalenate (**398**) (Schemes 104 and 105). LDA-mediated cyclo-

Scheme 102[210,211]



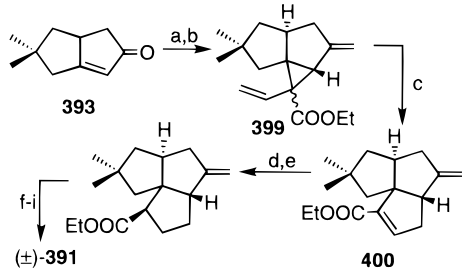
Reagnts: (a) LAH, 99%; (b) $CH_2{=}CH\text{-}OEt$, $Hg(OAc)_2$, Δ; (c) Jones oxdn.; 61% (for b-c); (d) $(COCl)_2$; (e) CH_2N_2; (f) Cu-Bronze; 82% (for d-f); (g)B_2H_6; H_2O_2, ^-OH; (h) TsCl, py; (i) separation; 24% (for g-i); (j) PCC, 100%; (k) ^tBuOK, 95%; (l) Li, liq. NH_3, 78%; (m) MeLi; (n) TsOH; 78% (for m-n).

Scheme 103[212]



Reagents: (a) LDA, $Br(CH_2)_2OTHP$, 88%; (b) H_3O^+; (c) TsCl, DMAP, Et_3N; 80% (for b-c); (d) O_3; Zn, 89%; (e) Jones oxdn.; (f) CH_2N_2; 60% (for e-f); (g) LiBr, 100%; (h) LHMDS, 90%; (i) separation, 74%; (j) LAH, 69%; (k) TsCl, py, 75%; (l) PCC, 100%; (m) Zn, NaI, 83%; (n) Scheme 102.

Scheme 104[213,214]

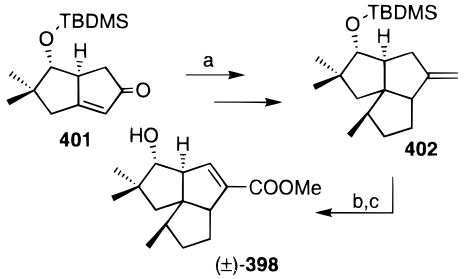


Reagents: (a) $MeCH{=}C(Br)COOEt$, LDA, 95%; (b) $Ph_3P{=}CH_2$, 90%; (c) Δ, 43%; (d) Mg, MeOH, 88%; (e) NaOEt, 58%; (f) LAH, 100%; (g) MsCl, py, 90%; (h) $LiEt_3BH$, 97%; (i) TsOH, 100%.

propanation of the diquinane enone **393** with ethyl α-bromocrotonate and Wittig olefination furnished the diene ester **399**. Thermal rearrangement of the vinylcyclopropane moiety in **399** afforded the triquinane ester **400**. A series of functional group transformations converted the keto ester **400** into (±)-pentalenene (**391**). In an analogous manner the TBDMS ether **401** led to (±)-**398** via the triquinane **402**.

An intramolecular double Michael reaction and ring contraction strategy was adopted by Fukumoto

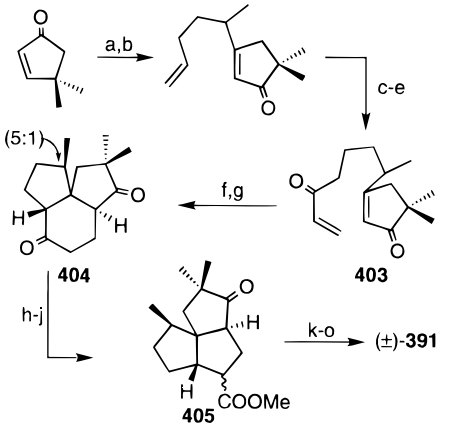
Scheme 105[213,214]



Reagents: (a) Scheme 104; (b) OsO_4, $NaIO_4$, 80%; (c) ref. 208d,e

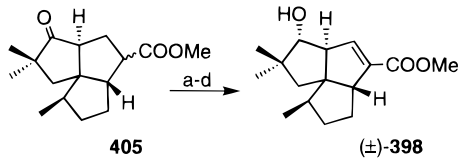
and co-workers[215,216] for the synthesis of (±)-pentalenene (**391**) and (±)-pentalenic acid methyl ester (**398**) (Schemes 106 and 107). Treatment of the bis-

Scheme 106[215,216]



Reagents: (a) CH_2=$CH(CH_2)_2CH(Me)Br$, Li, 70%; (b) PCC, 95%; (c) $(c\text{-}C_6H_{11}B)_2BH$; H_2O_2; ^-OH; PCC; 85%; (d) CH_2=$CHMgBr$, 73%; (e) PDC, 100%; (f) TMSCl, NEt_3, $ZnCl_2$; (g) H_3O^+; 52% (for f-g); (h) HCOOEt, NaOMe, 71%; (i) TsN_3, NEt_3, 100%; (j) hv, 100%; (k) $(CH_2SH)_2$, $BF_3.OEt_2$; (l) Raney Ni; 90% (for k-l); (m) PhSeCl; H_2O_2, ^-OH, 91%; (n) DIBALH; (o) SO_3.py; LAH, 47% (for n-o).

Scheme 107[215,216]

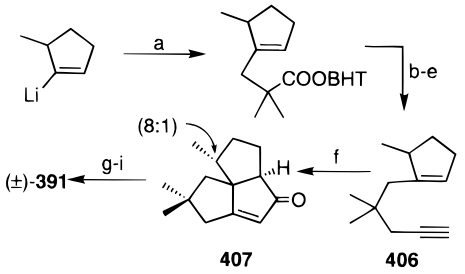


Reagents: (a) KOH; (b) Li, liq. NH_3; (c) CH_2N_2; 85% (for a-c); (d) PhSeCl; H_2O_2, ^-OH; 75%.

enone **403**, obtained from 4,4-dimethylcyclopentenone, with TMSCl and zinc chloride and hydrolysis resulted in the formation of the tricyclic compound **404**. Ring contraction of the cyclohexanone ring employing a Wolff rearrangement methodology afforded the triquinane **405**, which was separately transformed into (±)-pentalenene (**391**) and (±)-pentalenic acid methyl ester (**398**).

An intramolecular Pauson−Khand bicyclization methodology has been applied to the synthesis of (±)-pentalenene **391** by Schore *et al.*[217−219] (Scheme 108). Stereoselective intramolecular cyclization of the enyne **406**, obtained from 2-methylcyclopentenone, generated an 8:1 epimeric mixture of the triquinanes in which **407** was the dominant product. The major

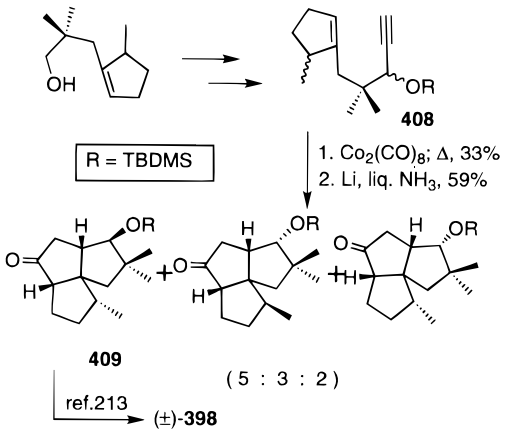
Scheme 108[217,219]



Reagents: (a) BHT methacrylate; MeI; 90%; (b) Li, liq. NH_3, 45%; (c) TsCl, py, 75%; (d) LiI, HMPA, 67%; (e) HC≡CLi.en, 65%; (f) $Co_2(CO)_8$, Δ, 51%; (g) Li, liq.NH_3, 89%; (h)Ph_3P=CH_2; (i) TsOH; 45% (for h-i).

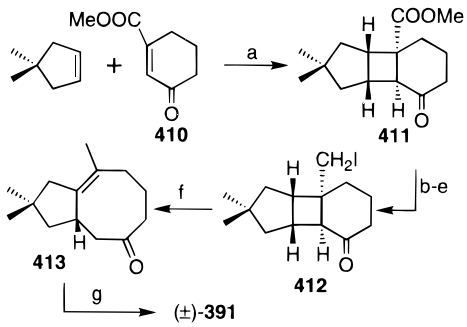
isomer **407** was converted into (±)-**391**. Analogously, intramolecular Pauson−Khand bicyclization of the siloxy enyne **408** and metal−ammonia reduction afforded a 5:3:2 mixture of the triquinanes, in which the Hudlicky's[213,214] advanced intermediate **409** of (±)-pentalenic acid methyl ester (**398**) was the major isomer (Scheme 109).

Scheme 109[218,219]



Grob-type fragmentation of the cyclobutane ring in a 5-4-6 fused tricyclic system was explored by Lange and Gottardo[220,221] for a formal synthesis of (±)-pentalenene (**391**) (Scheme 110). The [2+2]-photo-

Scheme 110[220,221]

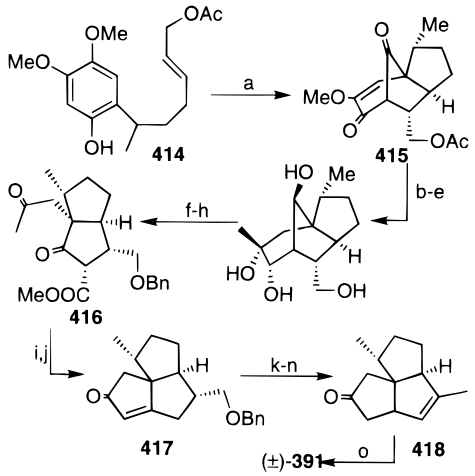


Reagents: (a) hv, 68%; (b) $(CH_2OH)_2$, H^+; (c) LAH; (d) H_3O^+; 91% (for b-d); (e) Ph_3P, I_2, 78%; (f) $^nBu_3SnH$, AIBN; silica gel; 68%; (g) ref. 208h.

cycloaddition of 4,4-dimethylcyclopentene and oxocyclohexencarboxylate **410** generated the 5-4-6 system **411**. Conversion of the ester **411** into iodide **412** and radical-mediated fragmentation led to **413**, Pattenden's[208h] precursor of (±)-**391**.

Yamamura and co-workers[222] have extended their electrochemical methodology to the formal synthesis of (±)-pentalenene (**391**) (Scheme 111). Anodic oxidation of the phenol **414**, stereoselectively generated the tricyclic methoxy enedione **415**, which through a series of functional group transformations was converted into the diquinane **416**. Intramolecular aldol condensation was used to generate the triquinane derivative **417**, which was elaborated to **418**, a precursor of (±)-**391**.

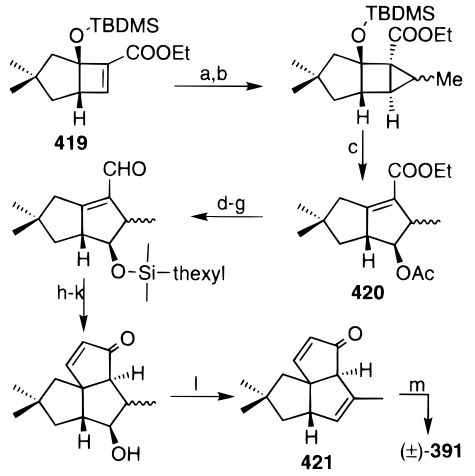
Scheme 111[222]



Reagents: (a) anodic oxdn., 64%; (b) DIBALH; (c) Ac_2O, py; 94% (for b-c); (d) $(COOH)_2$, 88%; (e) MeMgBr; (f) NaH, BnCl; 88% (for e-f); (g) PCC, 40%; (h) LTA, MeOH, 40%; (i) HCl, 94%; (j) NaOEt; (k) H_2, Pd-C; 83% (for j-k); (l) ArSeCN, Bu_3P; (m) H_2O_2; 82% (for l-m); (n) TsOH, 96%; (o) ref. 208k,229.

Synthesis of diquinanes via a [2+1]-cycloaddition to a bicyclo[3.2.0]hept-6-ene followed by selective cleavage of the central bond of the resulting bicyclo-[2.1.0]pentane moiety has been exploited by Franck-Neumann *et al.*[223] for a formal synthesis of (±)-pentalenene (**391**) (Scheme 112). Cyclopropanation of the bicyclic siloxy ester **419** and acid-mediated ring cleavage furnished the diquinane **420** in very good yield. Annulation of the third cyclopentane ring through a silicon assisted Nazarov cyclization and functional group manipulation led to the triquinane **421**, Paquette's[208d,e] precursor of (±)-**391**.

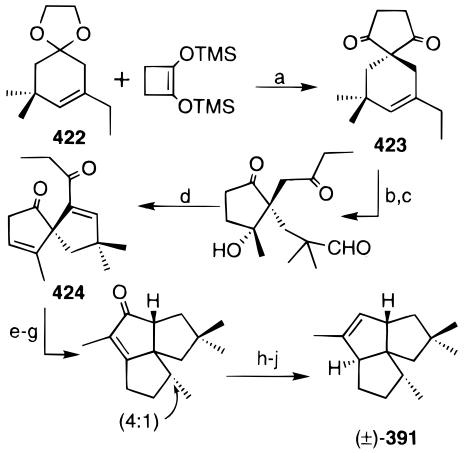
Scheme 112[223]



Reagents: (a) $MeCHN_2$; (b) hv; 75% (for a-b); (c) AcOH, 100%; (d) K_2CO_3, 100%; (e) Thexyl$(Me)_2$SiOTf; (f) DIBALH; (g) MnO_2; 81% (for e-g); (h) TMSCH=CHMgBr; (i) MnO_2; 71% (for h-i); (j) $BF_3.OEt_2$; (k) TBAF; 60% (for j-k); (l) H_2SO_4, 80%; (m) ref. 208d,e.

Burnell and co-workers[224,225] have explored the use of the acid-catalyzed spiroannulation of cyclic ketals with 1,2-bis(trimethylsiloxy)cyclobutene in the synthesis of (±)-pentalenene (**391**) (Scheme 113). Spiroannulation of the cyclohexenone ketal **422** afforded the spiro[4,5]decane derivative **423**. Regioselective addition of methyllithium to **423**, contraction of the six-membered ring via the oxidative cleavage and acid-catalyzed aldol condensation led to the spiro[4.4]-system **424**. Construction of the third cyclopentane ring using an intramolecular aldol condensation and further transformations led to (±)-**391** in a stereoselective manner.

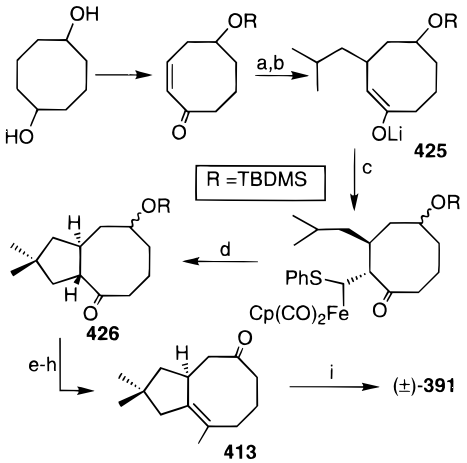
Scheme 113[224,225]



Reagents: (a) $BF_3.OEt_2$, 77%; (b) MeLi; (c) O_3; Me_2S; (d) TsOH; 63% (for b-d); (e) Li, liq. NH_3, 86%; (f) H_2, Pd-C, 100%; (g) ^{t}BuOK, 84%; (h) H_2, Pd-C; (i) $NaBH_4$; (j) TsOH; 88% (for h-j).

Helquist *et al.*[226] have reported a formal synthesis of (±)-pentalenene (**391**) from commercially available 1,5-cyclooctanediol (Scheme 114). Alkylation of the enolate **425**, with iron thiocarbene complex and

Scheme 114[226]

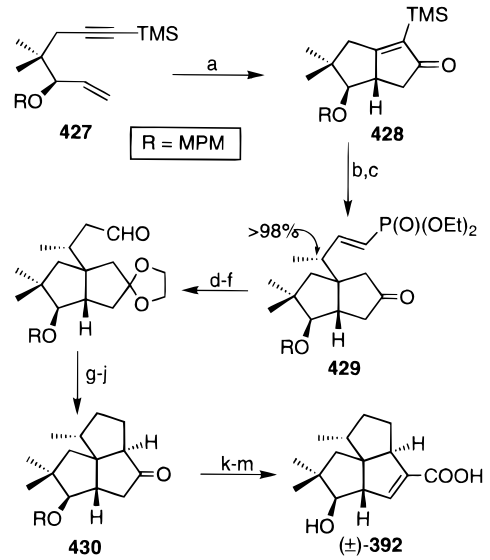


Reagents: (a) ^{i}BuMgBr, $CuBr.SMe_2$, TMSCl, 86%; (b) MeLi; (c) $Cp(CO)_2Fe^+$=CHSPh PF_6^+; (d) Me_3OBF_4; 37% (for b-d); (e) MeLi; (f) $SOCl_2$; 58% (for e-f); (g) TBAF; (h) CrO_3; 44% (for g-h); (i) ref. 308h

regiospecific intramolecular CH insertion of the iron carbene intermediate afforded the 5,8-fused bicyclic system **426** which was transformed into Pattenden's[208h] intermediate **413** of (±)-**391**.

A zirconium-promoted stereoselective enyne bicyclization−carbonylation (**427** → **428**) and allyl phosphonate Michael addition (**428** → **429**) were the key steps in the synthesis of (±)-pentalenic acid **392** by Agnel and Negishi[227] (Scheme 115). Both these steps

Scheme 115[227]



Reagents: (a) BuLi, $ZrCp_2Cl_2$, CO, 84%; (b) $MeCH{=}CH\text{-}CH_2\text{-}P(O)(OEt)_2$; (c) TBAF; 94% (for b-c); (d) $(CH_2OH)_2$, H^+; (e) BH_3; H_2O_2, ^-OH; (f) $NaHCO_3$; 57% (for d-f); (g) PPTS; (h) MsCl, NEt_3; (i) DBU; (j) H_2, Pd-C; 58% (for g-j); (k) LDA, $PhNTf_2$; $Pd(OAc)_2$, CO; (l) DDQ; (m) NaOH; 50% (for k-m).

are efficient and stereoselective. Cyclopentannulation via hydroboration−aldol sequence (**429** → **430**) and palladium-catalyzed carbonylation of the enol triflate-derived from the triquinane ketone **430** led to (±)-**392**.

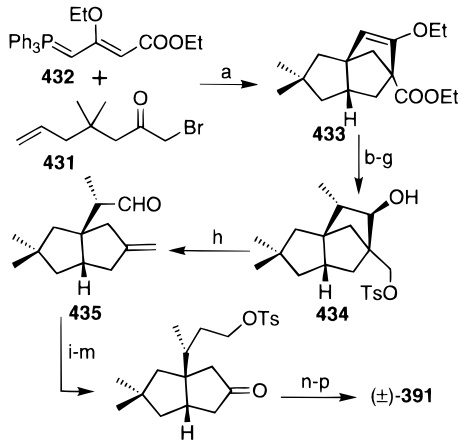
Very recently, Hatanaka and co-workers[228] have reported a new route to (±)-pentalenene (**391**) (Scheme 116). The formal [3+2]-cycloaddition between the α-bromo ketone **431** and the phosphorane **432**, followed by an intramolecular Diels−Alder reaction afforded the tricyclic ester **433** which was converted into the hydroxy tosylate **434**. Base-induced fragmentation in **434** led to the diquinane **435**. Construction of the third ring via an intramolecular alkylation reaction and introduction of the fourth methyl group completed the synthesis of (±)-**391**.

Mehta *et al.*[208k,229] and Pattenden *et al.*[208h,230] have reported the full details of their synthesis of (±)-pentalenene **391** based on the transannular cyclization of appropriately assembled 5,8-fused bicyclic systems. Piers and Karunaratne[208i,231] have also reported the details of their total synthesis of (±)-pentalenene (**391**) in which a methylenecyclopentannulation on a preformed diquinane was the key step.

D. Silphiperfolanes

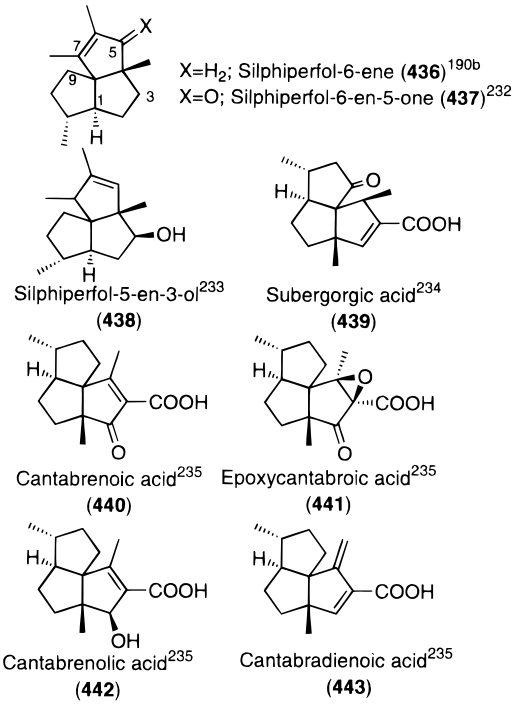
Angular triquinane sesquiterpenes silphiperfol-6-ene (**436**) and the silphiperfol-6-en-5-one (**437**) were isolated from *Silphium perfoliatum*[190a] and *Espeletiopsis quacharaca*,[232] respectively, by Bohlmann *et*

Scheme 116[228]



Reagents: (a) Cs_2CO_3; Δ; 60%; (b)LAH; H_3O^+; (c) TBDMSCl, imidazole; 84% (for b-c); (d) LiHMDS, MeI, 90%; (e) L-selectride; (f) TBAF; (g) TsCl, py; 79% (for e-g); (h) NaHMDS; (i) $Ph_3P{=}CHOMe$; 81% (for h-i); (j) TsOH, Me_2CO; (k) $NaBH_4$; (l) TsCl, py; (m) O_3; Me_2S; 62% (for j-m); (n) NaHMDS, 92%; (o) MeLi, $CeCl_3$; (p) TsOH; 98% (for o-p).

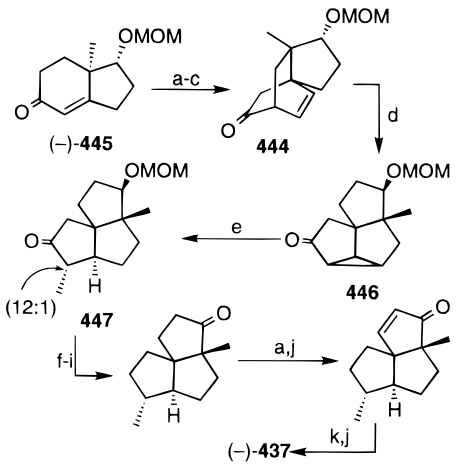
al. in 1980. With the isolation of several more oxygenated derivatives like silphiperfol-5-en-3-ol (**438**),[233] subergorgic acid (**439**),[234] and cantabronic acids **440**−**443**,[235] the interest in the synthesis of this family of triquinanes is at a high pitch[236] and several new approaches have been devised.



1. Silphiperfol-6-ene, Silphiperfol-6-en-5-one, and Silphiperfol-5-en-3-ol

Demuth and Hinsken[107bb,237] have employed an oxa-di-π-methane rearrangement based methodology for the synthesis of the natural (−)-silphiperfol-6-en-5-one **437** (Scheme 117). The requisite tricyclic enone **444** was obtained from the chiral enone (−)-**445** via a Diels−Alder methodology. The photoirradiation of the enone **444** afforded the cyclopropane fused triquinane **446**, which on regiospecific cyclopropane cleavage and *in situ* alkylation of the enolate, ste-

Scheme 117[107bb,237]

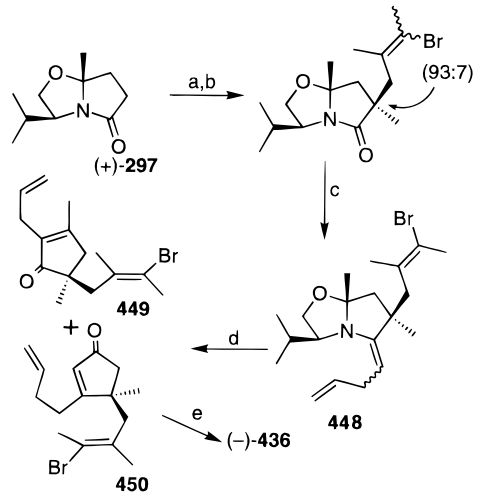


Reagents: (a) LDA, TMSCl; (b) maleic anhydride; 60% (for a-b); (c) electrolysis, 55%; (d) hν, 70%; (e) Li, Pr_2NH, TMSCl; $BnNMe_3F$, MeI; 45%; (f) $TiCl_4$; (g) $(CH_2SH)_2$, $Mg(OTf)_2$; 80% (for f-g); (h) $TiCl_4$, LAH, 63%; (i) $H_2Cr_2O_7$, 84%; (j) LDA, TMSCl; DDQ, BTTFA; 70%; (k) Me_2CuLi; MeI; 52% (for k,j).

reoselectively generated the triquinane **447**. Deoxygenation of the carbonyl group followed by further functional group alterations furnished (−)-**437**.

Meyers and Lefker[238,239] have achieved an enantioselective synthesis of (−)-silphiperfol-6-ene (**436**) employing lactam (+)-**297** as the chiral auxiliary (Scheme 118). Sequential alkylation of (+)-**297** and

Scheme 118[238,239]

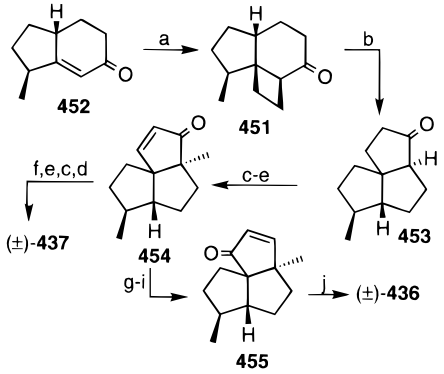


Reagents: (a) LDA, Me(Br)C=C(Me)CH_2Br; 81%; (b) LDA, MeI, 79%; (c) CH_2=CH$(CH_2)_2$Li; (d) H^+ (**449**:**450** 1:1); 79% (for c-d)(e) ref. 236c

addition of a four-carbon chain to the lactam carbonyl furnished **448**. Unmasking of the 1,4-dicarbonyl moiety and aldol cyclization afforded a 1:1 mixture of the cyclopentenones **449** and **450**. Application of Curran's tandem radical cyclization methodology[236c] on **450** led to the natural product (−)-**436**.

An apparently general, acid-catalyzed rearrangement of bicyclo[4.2.0]octanones to bicyclo[3.3.0]-octanones has been extended to a synthesis of (±)-silphiperfol-6-ene (**436**) and the (±)-silphiperfol-6-en-5-one (**437**) by Kakiuchi and co-workers[240,205] (Scheme 119). The aluminum chloride-mediated rearrangement of the tricyclic ketone **451**, obtained through a

Scheme 119[240,205]



Reagents: (a) CH_2=CH_2, hν, 73%; (b) $AlCl_3$, 93%; (c) $PhNMe_3Br_3$; (d) LiBr, Li_2CO_3, DMF; (e) LDA, MeI; 76% (for c-e); (f) Me_2CuLi; 63% (for f,e,c,d); (g) H_2O_2, NaOH; (h) N_2H_4, AcOH; (i) PDC; 51% (for g-i); (j) ref. 236a.

[2+2]-photocycloaddition of hydrindenone **452** to ethylene, afforded the triquinane **453** in high yield and was further elaborated to the enone **454**. Introduction of the two vicinal methyl groups, led to (±)-**437**, whereas 1,3-enone transposition led to Paquette's[236a] precursor **455** of (±)-**436**.

Fraser-Reid and Dickson[201] have extended their radical cyclization-based approach to polyquinanes from carbohydrates for the synthesis of (−)-silphiperfol-6-ene (**436**) (Scheme 120). The diquinane **456**, obtained via a radical cyclization reaction, was further elaborated through a series of reactions into (−)-**436**.

Vo and Snider[241] have reported a short synthesis of natural silphiperfol-6-ene [(−)-**436**], employing an intramolecular olefin−ketene cycloaddition (**457** → **458**) and manganese(III)-mediated rearrangement of ethynylcyclobutanol to α-methylenecyclopentanone (**459** → **460**) as the key reaction (Scheme 121). A stereoselective 1,4-conjugate addition of isopentenylmagnesium bromide to imine ester (+)-**461**, obtained from 3-methylcyclopentenealdehyde, and oxidation led to the requisite starting material **457**. The triquinane **460** was further elaborated into (−)-**436** via a Grignard reaction and deoxygenation of the resulting tertiary alcohol.

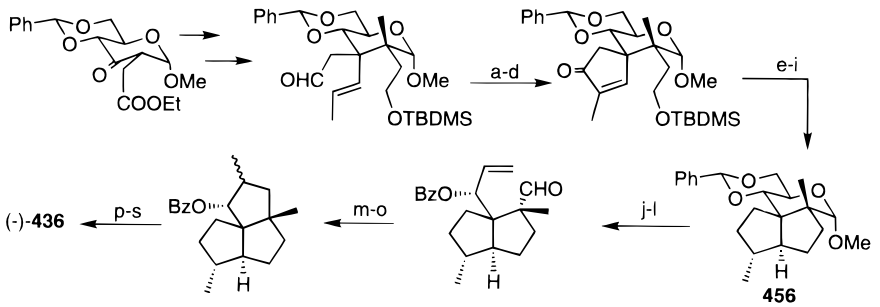
Weyerstahl and Brendel[242] have developed a synthesis of (±)-silphiperfol-5-en-3-ols (**438**) which have been recently isolated from the essential oil of *Artemisia laciniata*.[233] The diquinane enone **462**, obtained from 2-methylcyclopentenone, was elaborated to the triquinane based hydroxyketone **463**, employing a 1,4-conjugate addition and intramolecular aldol condensation. Further functional group manipulations led to the natural product (±)-**438** (Scheme 122). Application of the same sequence[243] starting from the chiral enone (+)-**462**, obtained from (*R*)-pulegone, led to the natural enantiomer of (−)-**438**.

Curran and co-workers[244] have reported the details of their vinyl radical-mediated tandem radical cyclization approach[236c] to (±)-silphiperfol-6-ene (**436**).

2. Subergorgic Acid

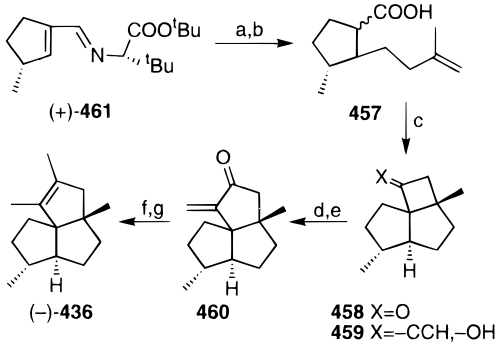
In 1985, subergorgic acid **439** was isolated from the Pacific gorgonian coral *Subergorgia suberosa* by Fenical *et al.*[234] The silphiperfolane framework and

Scheme 120[201]



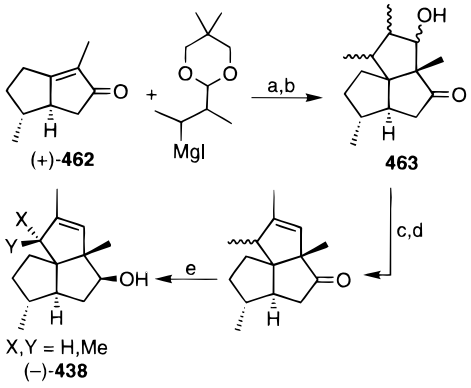
Reagents: (a) EtMgBr; (b) Swern oxdn.; (c) O_3; (d) ^{t}BuOK; 45% (for a-d); (e) TBAF; (f) PPh_3, I_2; 77% (for e-f); (g) ^{n}Bu$_3$SnH, AIBN, 81%; (h) LiHMDS, $PhNTf_2$; (i) H_2, Pd-C; 52% (for h-i); (j) NBS, $BaCO_3$; (k) NaI; (l) Zn-Hg; 82% (for j-l); (m) $NaBH_4$; (n) NaH, CS_2, MeI; 96% (for m-n); (o) ^{n}Bu$_3$SnH, AIBN; (p) LAH; (q) PDC; 54% (for o-q); (r) MeLi; (s) $POCl_3$, py; 34% (for r-s).

Scheme 121[241]



Reagents: (a) CH_2=C(Me)$(CH_2)_2$MgBr, 65%; (b) PDC, DMF, 84%; (c) $(COCl)_2$; ^{i}Pr$_2$NEt, DMAP, 79%; (d) LiC≡CH, 83%; (e) $Mn(OAc)_3$, 46%; (f) MeLi, 93%; (g) Li, liq. NH_3, 69%.

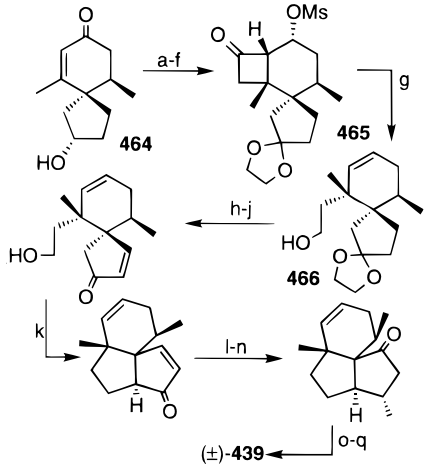
Scheme 122[242,243]



Reagents: (a) $CuBr_2.SMe_2$, TMSCl, 66%; (b) Me_2CO, HCl, 74%; (c) p-Tol-OC(S)Cl, py; (d) Δ; 67% (for c-d); (e) L-selectride, 90%.

the cardiotoxic activity of subergorgic acid **439** drew the attention of synthetic chemists, and soon Iwata and co-workers[245] reported the first total synthesis of (±)-**439** (Scheme 123). The spiro[4,5]decane derivative **464**, an intermediate in their synthesis of phytoalexin sesquiterpenes,[246,247] was elaborated into the ketomesylate **465** through a sequence of reactions involving [2+2]-photocycloaddition with allene and oxidative cleavage of the exomethylene group. Sodium borohydride reduction of **465** resulted in a fragmentation to the ketal alcohol **466**. Cyclopentannulation through routine methodology and contraction of the six-membered ring led to (±)-**439**.

Scheme 123[245]

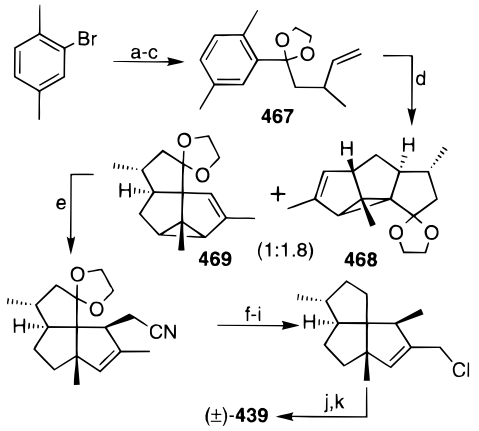


Reagents: (a) PCC; (b) $(CH_2OH)_2$, H^+; 79% (for a-b); (c) hν, allene, 90%; (d) L-selectride, 90%; (e) OsO_4, $NaIO_4$, 87%; (f) MsCl, py; (g) $NaBH_4$; 74% (for f-g); (h) Me_2CO, H^+; (i) MOMCl, ^{i}Pr$_2$NEt; 91% (for h-i); (j) LDA, $(PhS)_2$; $NaIO_4$; NEt_3; 80%; (k) MsCl, py;^{t}BuOK; 68%; (l) MeLi; (m) CrO_3; 83% (for l-m); (n) Li, liq. NH_3, 73%; (o) O_3; Zn, AcOH; 68%; (p) piperidine, AcOH, 77%; (q) $NaClO_2$, 98%.

Wender and deLong[248] have exploited benzylic ketal-assisted stereocontrolled intramolecular arene−olefin meta-photocycloaddition for the synthesis of (±)-subergorgic acid (**439**) (Scheme 124). Photolysis of the ketal **467**, afforded a 1.8:1 mixture of the linear and angular triquinane products (**468** and **469**) with excellent stereocontrol (at secondary methyl carbon). However, the required meta-photoadduct **469** was only the minor product of the reaction. Cyclopropane ring cleavage by conjugate addition of acetonitrile radical and a series of reactions transformed the tetracyclic compound **469** into (±)-**439**.

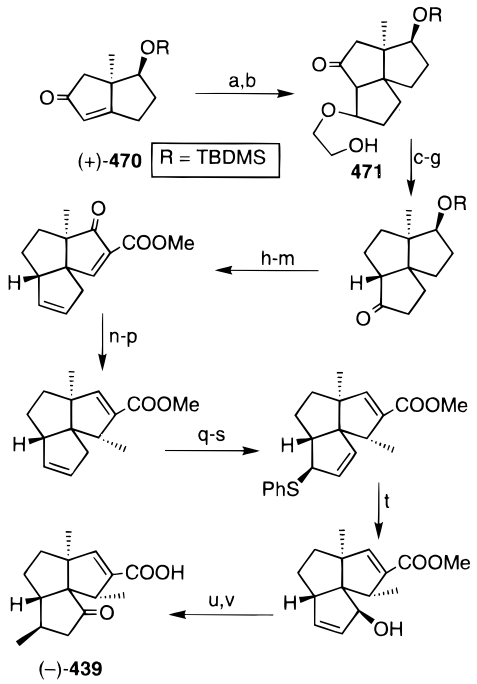
Recently, Paquette and co-workers[249] reported an enantioselective synthesis of natural subergorgic acid [(−)-**439**], starting from the diquinane (+)-**470**, obtained through a modified enzymatic procedure. Construction of the third ring through 1,4-conjugate addition and intramolecular Mukaiyama reaction afforded the triquinane **471**. A series of functional group alterations with stereocontrol led to (−)-**439** (Scheme 125).

Scheme 124[248]



Reagents: (a) Li, CH_2=CHCH(Me)CH_2CHO; (b) PCC; (c) $(CH_2OH)_2$, H^+; (d) hν, 61%; (e) $(BzO)_2$, MeCN, 67%; (f) K, 18-c-6, 90%; (g) m-CPBA, 80%; (h) $^iPr(C_6H_{11})NMgBr$, 70%; (i) $SOCl_2$, py 85%; (j) DMSO, $AgBF_4$, NEt_3, 85%; (k) $NaClO_2$.

Scheme 125[249]

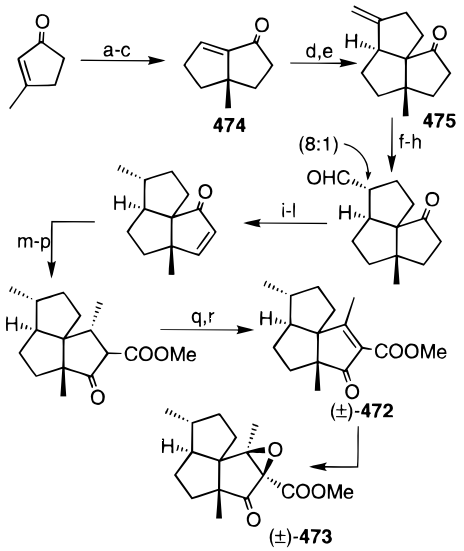


Reagents: (a) $(CH_2O)_2CH(CH_2)_2MgBr$, CuI, TMSCl; (b) $TiCl_4$; 63% (for a-b); (c) $PhI(OAc)_2$, I_2, hν, 75%; (d) LAH; (e) MsCl, py; (f) $LiEt_3BH$; 43% (for e-f); (g) H_3O^+, 85%; (h) KHMDS, $PhNTf_2$; (i) HCOOH, Bu_3P, $Pd(OAc)_2(PPh_3)_2$; (j) HF; 84% (for h-j); (k) PCC, 90%; (l) LDA, CNCOOMe, 71%; (m) DDQ, 67%; (n) Me_2CuLi, 74%; (o) $NaBH_4$, 79%; (p) MsCl, py; Al_2O_3, 87%; (q) PDC, ^tBuOOH, 69%; (r) $NaBH_4$, $CeCl_3$, 79%; (s) N(SPh)succinimide, 79%; (t) $NaIO_4$; $P(OMe)_3$, Et_2NH; 97%; (u) MnO_2, 96%; (v) Me_2CuLi; KOH, 80%.

3. Cantabronic Acids

In 1986, San Feliciano *et al.*[235] reported the isolation of four oxygenated silphiperfolenes, the cantabronic acids **440**−**443**, from *Artemisia cantabrica*. Piers and Renaud[250,251] have extended their methylenecyclopentannulation approach to the synthesis of methyl esters of cantabronic acid [(±)-**472**] and epoxy cantabronic acid [(±)-**473**] (Scheme 126). The bifunctional cuprate-mediated cyclopentannulation, converted the diquinane enone **474** into the triquinane **475**, which was further transformed into methyl cantabronates (±)-**472** and (±)-**473**, through a series of functional group manipulations.

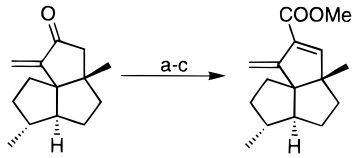
Scheme 126[250,251]



Reagents: (a) $(RO)_2C(CH_2)_2$-MgBr, $CuBr.SMe_2$, 70%; (b) H_3O^+, 73%; (c) MsCl, NEt_3; DBU; 74%; (d) $Cl(CH_2)_2C$-(=CH_2)$CuCNLi_2$; (e) HMPT; 73% (for d-e); (f) BH_3; H_2O_2, ^-OH; 96%; (g) Swern oxdn.; (h) NaOMe, MeOH; 80% (for g-h); (i) $(CH_2SH)_2$, $BF_3.OEt_2$, 85%; (j) Raney Ni, 74%; (k) LDA, TMSCl; (l) $Pd(OAc)_2$; 88% (for k-l); (m) MeLi, 96%; (n) PCC, 88%; (o) H_2, Pd-C, 98%; (p) LDA, CNCOOMe, 83%; (q) LDA, PhSeBr, 76%; (r) O_3, 77%; (s) H_2O_2, NaOH, 85%.

Recently, Snider and Vo[241] have reported the first total synthesis of (−)-cantabradienoic acid methyl ester (**476**) via palladium-mediated carbonylation of the enol triflate derived from the triquinane-based enone **460** (Scheme 127).

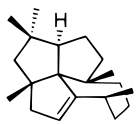
Scheme 127[241]



Reagents: (a) KHMDS, $PhNTf_2$, 85%; (b) $PdCl_2(PPH_3)_2$, CO; (c) CH_2N_2; 53% (for b-c).

E. Laurenene

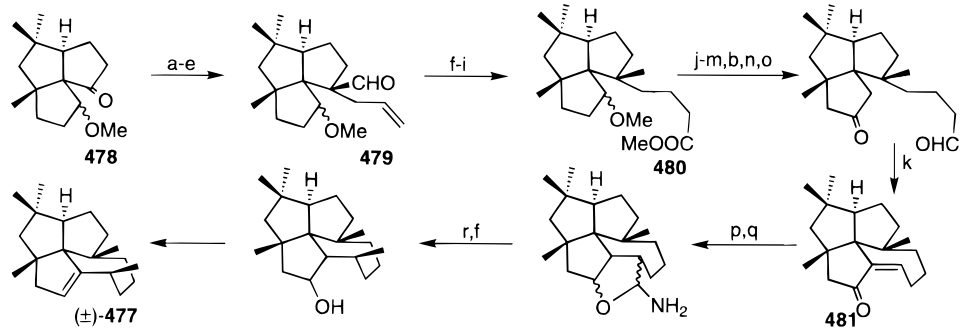
The unique diterpene laurenene **477**, the first



Laurenene (**477**)

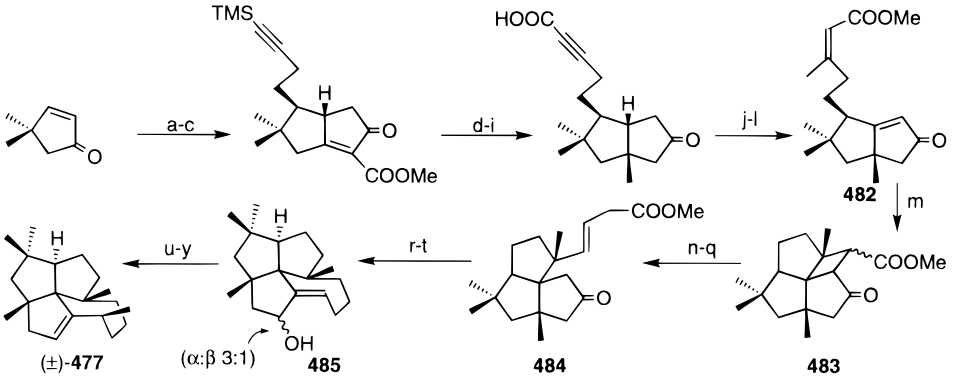
natural product comprising a fenestrane carbon framework, isolated by Corbett and co-workers[252] from the volatile oil of *Dacrydium cupressinum*, in 1979, has yielded to total synthesis. While Tsunoda[253] and Crimmins[254] groups simultaneously re-

Scheme 128[253]



Reagents: (a) $PPh_3=CH_2$, 99%; (b) $BH_3.SMe_2$; H_2O_2,$^-$OH; 94%; (c) Swern oxdn., 88%; (d) NaH, $CH_2=CHCH_2Br$; (e) Δ; 79% (for d-e); (f) W.K. redn., 73%; (g) OsO_4, $NaIO_4$; (h) $Ph_3P=CHCOOMe$; (i) H_2, Pd-C; 56% (for g-i); (j) AcCl, NaI; (k) NaOH; (l) CH_2N_2; 74% (for j-l); (m) $POCl_3$, py; (n) LAH; (o) PCC; 52% (for m-o); (p) KCN; (q) $NaBH_4$; (r) $NaNO_2$; 10% (for p-r,f); (s) $SOCl_2$, py, 71%.

Scheme 129[254]



Reagents: (a) $TMSC{\equiv}C(CH_2)_2MgBr$, CuI.$PBu_3$; $ICH_2(OMe)C=CHCOOMe$, 60%; (b) HCl; (c) NaOMe; (d) Me_2CuLi; (e) LiCl, DMSO, Δ; 71% (for b-e); (f) $(CH_2OH)_2$, H^+; (g) TBAF; (h) ^{n}BuLi, CO_2; (i) H_3O^+; (j) CH_2N_2; 90% (for f-j); (k) Me_2CuLi; $TMSCH_2COOEt$, TBAF; (l) $Pd(OAc)_2$; 80% (for k-l); (m) hν, 100 °C, 87%; (n) LAH; (o) Swern oxdn.; (p) $Ph_3P=CHCOOEt$; 89% (for n-p); (q) Na, liq. NH_3; (r) H_2, Pd-C; 80% (for q-r); (s) LAH; Swern oxdn.; TsOH; 75%; (t) $NaBH_4$, $CeCl_3$, 90%; (u) separation; (v) $^nBu_3SnCH_2I$, KH; (w) ^{n}BuLi; 60% (for u-w); (x) TsCl, py; (y) $LiEt_3BH$; 70% (for x-y).

ported the synthesis in 1987, two more by Paquette[255] and Wender[256] have appeared subsequently.

Tsunoda and co-workers[253] have exploited the relationship of the laurenene **477** with silphinene **367**, and elaborated an advance intermediate **478**[191c] of (±)-silphinene (**367**) into (±)-**477** (Scheme 128). The triquinane-based ketone **478** was converted into the allylated aldehyde **479**, which was further elaborated into the ester **480**. 1,2-Transposition of the oxygen functionality followed by construction of the seven-membered ring transformed the triquinane **480** into the fenestrane **481**, which was elaborated into (±)-**477**.

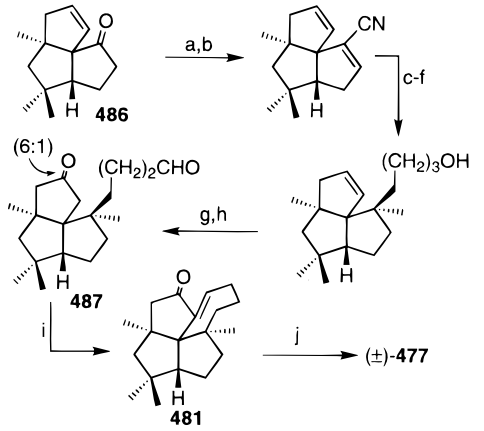
Crimmins and Gould[254] achieved the synthesis of (±)-laurenene (**477**), employing an intramolecular [2+2]-photocycloaddition and cyclobutane cleavage as the key strategy, analogous to their earlier synthesis of silphinene[192] (Scheme 129). The intramolecular [2+2]-photocycloaddition in the enone ester **482**, obtained from 4,4-dimethylcyclopentenone through a series of reactions, afforded the keto ester **483**. Further elaboration of the ester and regioselective cleavage of the cyclobutane ring transformed the keto ester **483** into the triquinane **484**, which was converted into the fenestrane **485**. Finally, introduction of the *secondary* methyl group using a stereospecific Wittig rearrangement furnished (±)-**477**.

Paquette and co-workers[255] have elaborated their silphinene intermediate,[191a,b] the triquinane enone **486**, into laurenene precursor **481** (Scheme 130). Transformation of the triquinane enone **486** into keto aldehyde **487** through a series of reactions, followed by acid-catalyzed aldol condensation led to the fenestrane **481**, which has been earlier converted into (±)-**477** by Tsunoda's[253] and Crimmin's[254] groups.

Wender and co-workers[256] have reported a complex example of an intramolecular arene−olefin meta-photocycloaddition enroute to their short and imaginative synthesis of (±)-laurenene (**477**) (Scheme 131). Synthesis of the lactone **488** starting from cycloheptadiene was achieved through a series of reactions involving a Grob-type fragmentation. Stereoselective alkylation of the lactone **488** with homoprenyl iodide and selective reduction generated the lactol **489**, which on irradiation afforded a single pentacyclic compound **490**. Regioselective cyclopropane cleavage and deoxygenation furnished (±)-**477**.

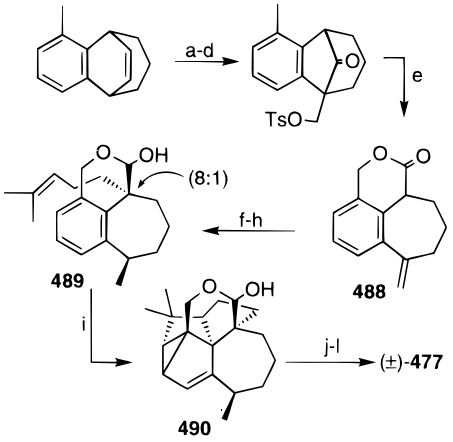
Mehta and Rao[257] have reported a short approach to [7.5.5.5]fenestrane ring system present in laurenene based on a transannular cyclization reaction

Scheme 130[255]



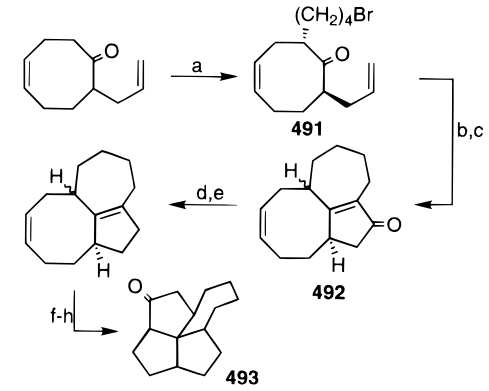
Reagents: (a) TMSCN, ZnI_2, 100%; (b) $POCl_3$, DBU, py, 92%; (c) Mg, MeOH, 95%; (d) LDA, Br-$(CH_2)_4$-OTMS, 83%; (e) DIBALH; (f) W.K redn.; 63% (for e-f); (g) $BH_3.SMe_2$; H_2O_2, ^-OH; (h) Swern oxdn.; 62% (for g-h); (i) TsOH, 78%; (j) ref. 253,254

Scheme 131[256]



Reagents: (a) O_3; Me_2S; 68%; (b) $Zn(BH_4)_2$, 98%; (c) TsCl, 72%; (d) PCC, 98%; (e) NBS, AIBN; KOH; 72%; (f) H_2, Pt, 96%; (g) LDA, $Me_2C{=}CH(CH_2)_2I$, 90%; (h) LAH, 95%; (i) hν, 51%; (j) Li, $MeNH_2$, 96%; (k) KHMDS, $(Me_2N)_2POCl$, 55%; (l) Li, $EtNH_2$, 65%.

Scheme 132[257]

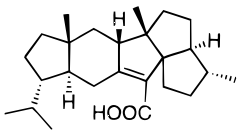


Reagents: (a) LDA, $Br(CH_2)_4Br$, 85%; (b) $PdCl_2$, CuCl, O_2, 78%; (c) NaH, 65%; (d) $(CH_2SH)_2$, H^+, 90%; (e) Na, liq. NH_3; (f) HCOOH; (g) KOH; (h) PCC; 25% (for e-h).

(Scheme 132). Wacker oxidation of the allyl compound **491**, followed by a combination of intramolecular aldol and alkylation reactions afforded the tricyclic diene **492**. Formic acid-mediated transannular cyclization of the diene **492**, hydrolysis and oxidation furnished the [7.5.5.5]fenestrane derivative **493**.

F. Retigeranic Acid

The novel sesterterpene retigeranic acid **494**, containing an angular triquinane moiety fused to a hydrindane framework, was isolated by Seshadri *et al.*[258] from various lichens belonging to *Lobaria retigera* group occurring in the Himalayas. The complex pentacyclic structure[259] present in retigeranic acid **494** has elicited widespread attention of synthetic chemists. Subsequent to Corey's first total synthesis of (±)-retigeranic acid (**494**) in 1985, three more syntheses have surfaced.



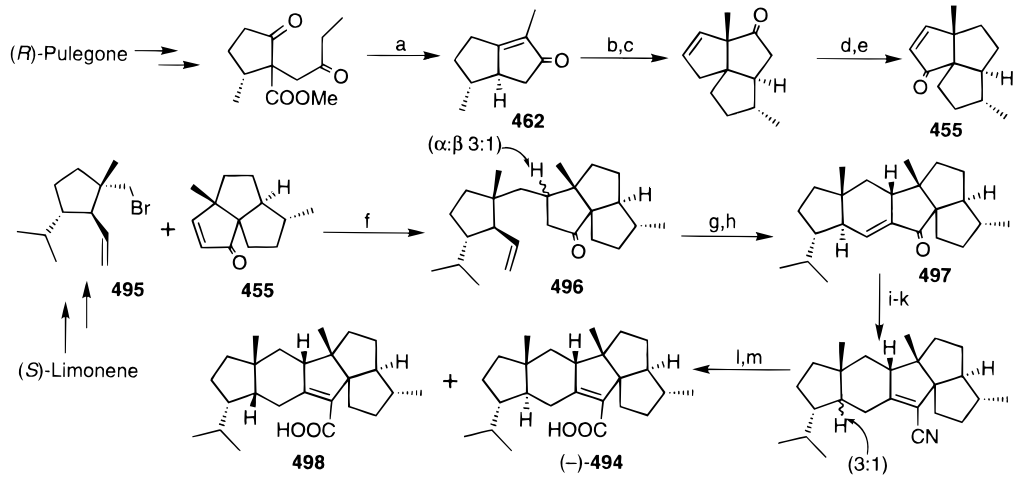
Retigeranic Acid (**494**)[258,259]

Paquette and co-workers[261,262] have reported an enantioselective synthesis of the natural (−)-retigeranic acid (**494**), starting from two monoterpenes, (*S*)-limonene and (*R*)-pulegone (Scheme 133). The triquinane segment **455** was obtained from (*R*)-pulegone, whereas the cyclopentane moiety (A-ring) **495** was derived from (*S*)-limonene. The diquinane enone **462**, obtained from (*R*)-pulegone, was transformed into the triquinane **455**, employing a combination of a 1,4-conjugate addition and acid catalyzed aldol methodology. Coupling of the triquinane **455** with the cyclopentane **495** afforded a 3:1 epimeric mixture of the coupled product **496**. Ozonolysis of the minor isomer followed by cyclization led to the pentacyclic compound **497**, which was further elaborated into (−)-**494** and its ring junction epimer **498**.

Hudlicky and co-workers[263,264] have reported a short and elegant synthesis of (−)-retigeranic acid (**494**) employing a formal [2+3]-annulation methodology (Scheme 134). Coupling of the hydrindane-based bromoacrylate **499**, obtained from dihydrolimonene, with the diquinane **462** afforded the cyclopropane carboxylate **500**. Thermal activation of the vinylcyclopropane **500** followed by deoxygenation and hydrolysis, furnished (−)-**494**.

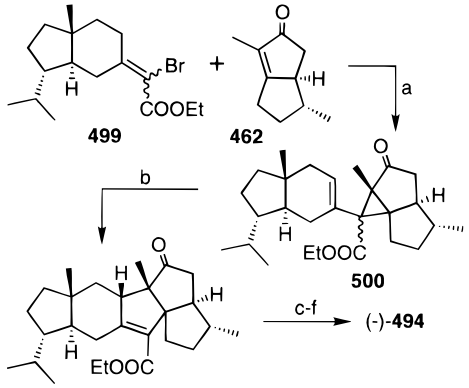
Wender and Singh[265] have applied the arene−olefin meta-photocycloaddition approach for a formal synthesis of (−)-retigeranic acid (**494**) (Scheme 135). Photolysis of the chiral olefin **501**, obtained from the half-ester of 3-methylglutaric acid, afforded a 2:1 mixture of the cyclopropane-fused angular triquinane **502** and linear triquinane **503**. Cyclopropane cleavage via the addition of formamide radical followed by allylic oxidation transformed the tetracyclic compound **502** into the triquinane **504**. Coupling of the triquinane **504** with the carboxylic acid **505**, derived from (*S*)-carvone, and intramolecular Diels−Alder

Scheme 133[261,262]



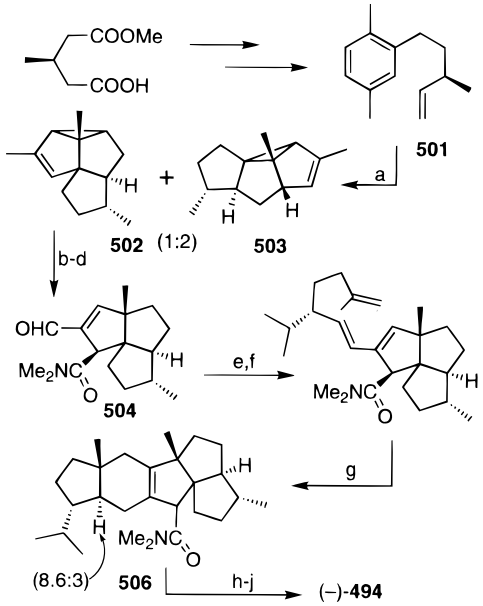
Reagents: (a) NaH; LiI, DMF, 57%; (b) $(RO)_2C(CH_2)_2MgBr$, $CuBr.SMe_2$, 72%; (c)$PPh_3.Br_2$, 55%; (d) W.K. redn., 72%; (e) Na_2CrO_4, 64%; (f) Mg, 53%; (g) O_3; Zn, AcOH; (h) piperidine, AcOH; 41% (for g-h); (i) PtO_2, H_2, 86%; (j) TMSCN, KCN, 100000psi, 96%; (k) $POCl_3$, DBU, 30%; (l) DIBALH; (m) $NaClO_2$, $NaHPO_4$; 56% (for l-m).

Scheme 134[263,264]



Reagents: (a) LDA, 66%; (b) FVP, 585 °C, $PbCO_3$, 80%; (c) $NaBH_4$; (d) NaH, CS_2, MeI; (e) $^nBu_3SnH$, AIBN; 72% (for c-e); (f) KOH.

Scheme 135[265]



Reagents: (a) hν, 72%; (b) $HCONH_2$, hν; (c) KOH, DMSO, MeI;80% (for b-c); (d) SeO_2, ^tBuOOH, 53%; (e) LDA, (*S*)-CH_2=C(Me)$(CH_2)_2$CH(^{i}Pr)CH_2COOH **505**; (f) $Me_2NCH(OEt)_2$, Δ; 65% (for e-f); (g) Δ, 64%; (h) LAH; (i) PDC; (j) ref. 260

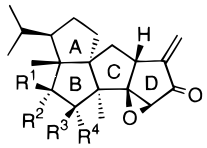
reaction led to a 8.6:3 epimeric mixture of the pentacyclic compound **506**. The major isomer was transformed to the natural product (−)-**494**.

V. Tetraquinanes

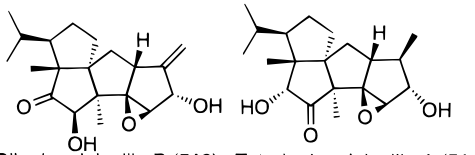
Only one group of natural products, crinipellins, comprising of a tetraquinane framework, has been isolated so far.

A. Crinipellins

An investigation of several strains of basidomycete *Crinipellis stipitaria* has led to the isolation of five new diterpenoids **507**−**511**,[266] containing a unique tetraquinane carbon framework, a combination of linear and angular triquinane moieties. Although several synthetic efforts have been initiated toward these novel natural products, endowed with biological activity, only one successful synthesis by Piers *et al.*[267] has appeared in the literature.

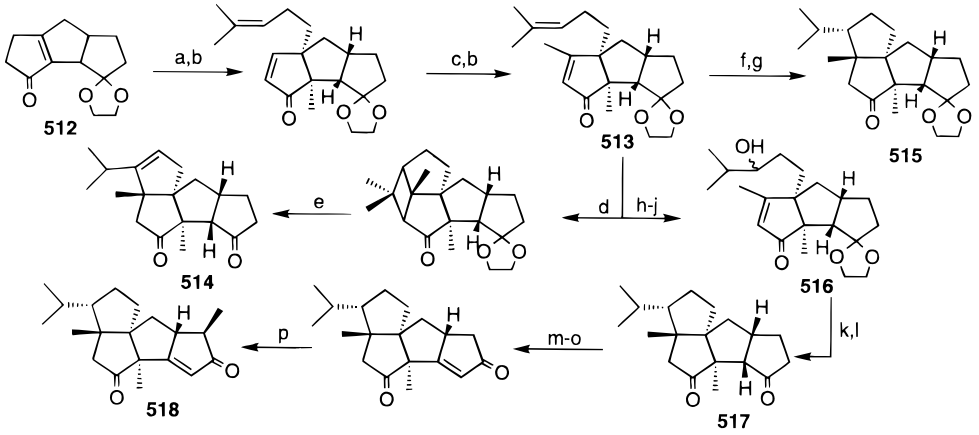


R^1=H;R^2=OH;R^3,R^4=O; Crinipellin-A (**507**)[266]
R^1,R^2=O;R^3=OH;R^4=H; Crinipellin-B (**508**)
R^1=H;R^2=OAc;R^3,R^4=O; O-Acetylcrinipellin-A (**509**)



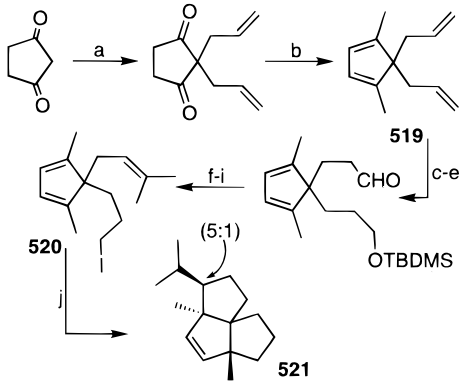
Dihydrocrinipellin-B (**510**) Tetrahydrocrinipellin-A (**511**)

Scheme 136[268,269]



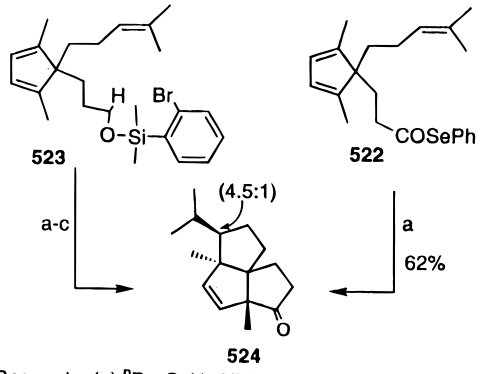
Reagents: (a) $Me_2C{=}CH(CH_2)_2MgBr$, $Me_2S.CuBr$; MeI, 87%; (b) LDA, PhSeCl; H_2O_2, ^-OH; 75%; (c) Me_2CuLi; 67% (for c,b); (d) hv, 83%; (e) NaI, TMSCl, 60%; (f) $HClO_4$, 82%; (g) H_2, Pd-C, 80%; (h) m-CPBA, 85%; (i) $BF_3.OEt_2$, 88%; (j) $NaBH_4$, 70%; (k) Tol-OC(S)Cl, py, 62%; (l) $^nBu_3SnH$, AIBN, 65%; (m) $NaBH_4$; MsCl, py;70%; (n) NaI, HMPA, 96%; (o) ^tBuOOH, PDC, 43%; (p) LiHMDS, MeI, 60%.

Scheme 137[271]



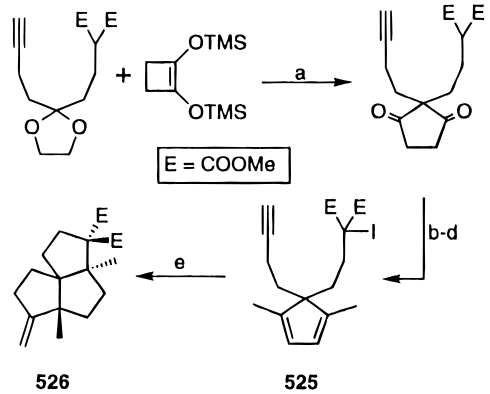
Reagents: (a) $CH_2{=}CHCH_2OAc$, DBU, Pd(0), 84%; (b) $TiCl_4$, Zn, CH_2Br_2; HI, 40%; (c) $(c\text{-}C_6H_{11})_2BH$; H_2O_2, ^-OH; (d) TBDMSCl, imidazole; 75% (for c-d); (e) Swern oxdn.; (f) $Ph_3P{=}CMe_2$; 66% (for e-f); (g) ^+TBAF, 94%; (h) MsCl; (i) NaI; 74% (for g-h); (j) $^nBu_3SnH$, AIBN, 88%.

Scheme 138[271]



Reagents: (a) $^nBu_3SnH$, AIBN; (b) TBAF; 65% (for a-b); (c) PDC, 80%.

Scheme 139[272]

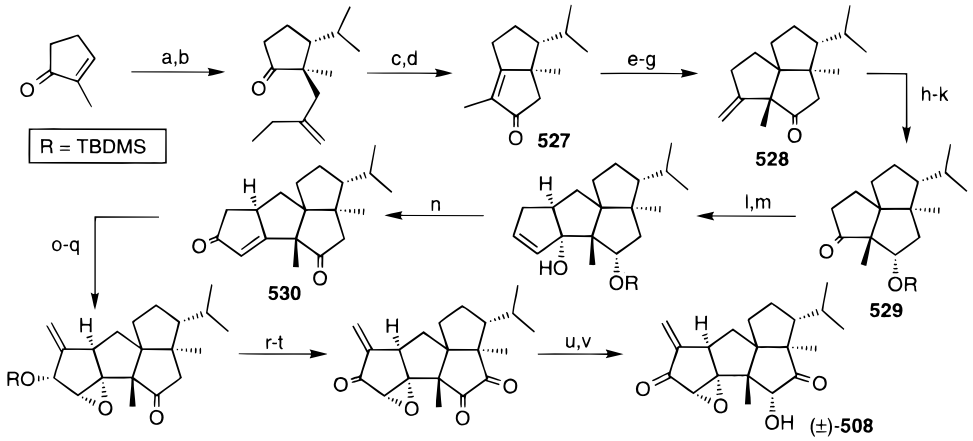


Reagents: (a) $BF_3.OEt_2$, 50%; (b) $TiCl_4$, Zn, CH_2Br_2; (c) HI; (d) NaH, NIS; (e) $^nBu_3SnH$, AIBN; 75% (for d-e).

The first approach to the crinipellins was reported in 1988 by Mehta *et al.*[268,269] (Scheme 136). The keto ketal **512**, obtained from benzoquinone and cyclopentadiene via the photothermal olefin metathesis sequence,[270] was elaborated into the dienone **513**. Intramolecular [2+2]-photocycloaddition in the dienone **513** and trimethylsilyl iodide-mediated cyclobutane cleavage led to the tetraquinane **514**, containing all but one carbon atom of crinipellins. An acid-catalyzed intramolecular olefin−enone cyclization in the dienone **513** and catalytic hydrogenation eventuated in tetraquinane **515**. Construction of the cyclopentane ring via a 5-*exo-trig* radical cyclization reaction through the hydroxy enone **516**, led to the tetraquinane **517**. Further transformations converted the dione **517** into an *epi*-crinipellin derivative **518**. However, in both the tetraquinanes **515** and **518**, the isopropyl group is epimeric with respect to the natural products.

In their model studies toward the angular triquinane part of crinipellins, Curran *et al.*[271] have explored tandem radical cyclization-based approaches. Conversion of the cyclopentane-1,3-dione into the tetraene **519**, followed by selective modifications of the terminal olefinic moieties, generated the requisite radical precursor, the iodotriene **520**. Tandem radical cyclization in **520** furnished a 5:1 epimeric mixture of the triquinane **521** (Scheme 137). In an analogous manner, tandem radical cyclization in either the selenoester **522**, or the silyl ether **523** followed by oxidation led to the same epimeric mixture of the triquinane ketone **524** (Scheme 138). In continuation of these studies, Curran's group has employed an atom transfer-mediated tandem cyclization for the conversion of the malonate **525** into the triquinane **526**[272] (Scheme 139).

Scheme 140[267]

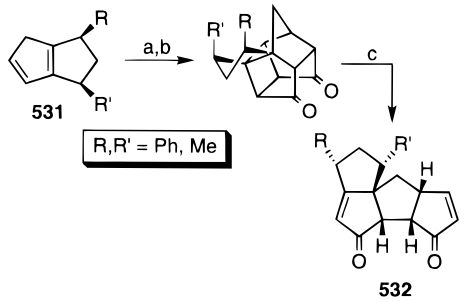


Reagents: (a) ^{i}PrMgBr, Me_2S.CuBr, TMSCl, 94%; (b) MeLi, CH_2=C(Et)CH_2Br, 76%; (c) O_3; Me_2S, 93%; (d) NaOMe, 97%; (e) CH_2=C($GeMe_3$)$(CH_2)_2$CuCNLi, TMSBr, 83%; (f) I_2,98%; (g) $Pd(PPh_3)_4$, ^{t}BuOK, 84%; (h) ^{n}BuLi+$^{i}Bu_2$AlH, 93%; (i) TBDMSOTf, NEt_3, 98%; (j) OsO_4; (k) LTA; 93% (for j-k); (l) LDA, ICH=$CHCH_2$Br, 76%; (m) ^{n}BuLi, 93%; (n) PCC, 51%; (o) H_2O_2, $NaHCO_3$, 84%; (p) LiHMDS, CH_2=$N^{+}Me_2$ $^{-}$I, 78%; (q) $NaBH_4$; TBDMSOTf, NEt_3; 80%; (r) KHMDS, 2-(SO_2Ph)-3-(Ph)-oxaziridene, 68%; (s) TBAF; (t) periodinane; 44% (for s-t); (u) ^{n}BuLi+$^{i}Bu_2$AlH; (v) py.SO_3, H_2O; 49%.

In 1993, Piers and Renaud[267] reported the first total synthesis of a crinipellin (Scheme 140). Conversion of 2-methylcyclopentenone into the diquinane **527**, followed by methylenecyclopentannulation using a combination of 1,4-cuprate addition and Heck coupling, furnished the triquinane **528**, which was transformed into the keto ether **529**. Alkylation of **529**, anion-mediated cyclization and oxidation transformed the keto ether **529** into the tetraquinane enone **530**. Further elaboration of **530** into (±)-crinipellin-B (**508**) was accomplished via selective functional group transformations.

Griesbeck and co-workers[273,274] have explored a variation of the photo thermal metathesis theme developed by Mehta *et al.*,[270] for the synthesis of a tetraquinane framework present in crinipellins (Scheme 141). The Diels−Alder reaction of the

Scheme 141[273,274]



Reagents: (a) p-benzoquinone, Δ, 50%; (b) hν, 96%; (c) Δ, 88%.

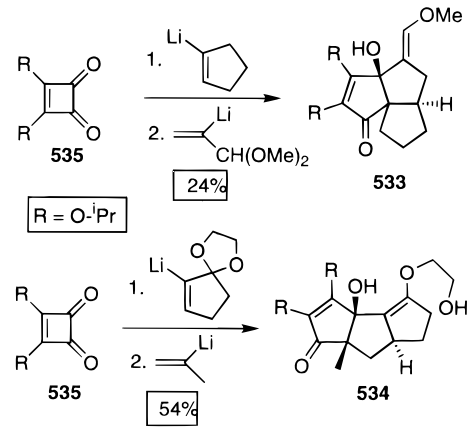
tetrahydropentalene **531** with *p*-benzoquinone followed by intramolecular [2+2]-photocycloaddition and flash vacuum pyrolysis furnished the tetraquinane bisenone **532**.

B. Miscellaneous

Some of the recently reported strategies for polyquinane synthesis have considerable potential for adoptation toward the synthesis of tetraquinane natural products.

Paquette *et al.*[275−277] have reported an interesting methodology for the construction of the angular and linear triquinanes **533** and **534** as well as tetraquinanes from the readily available squaric acid derivative **535** via an electrocyclic ring opening−closing and transannular cyclization cascade (Scheme 142).

Scheme 142[275−277]

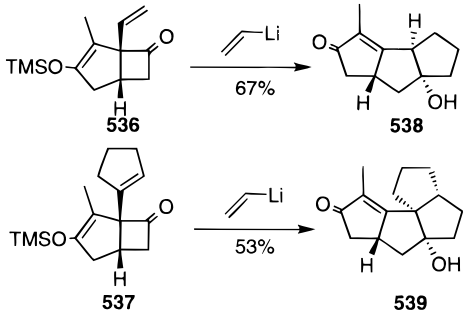


Recently, Moore and co-workers[278] outlined a tandem oxy-Cope rearrangement−transannular cyclization methodology for the construction of tri- and tetraquinanes (Scheme 143). This theme should find ready applications in the synthesis of natural products. Addition of vinyllithium to the dienones **536** and **537**, led to the tri- and tetraquinanes **538** and **539**, via the formation of "cyclooctenone" intermediates and transannular cyclization.

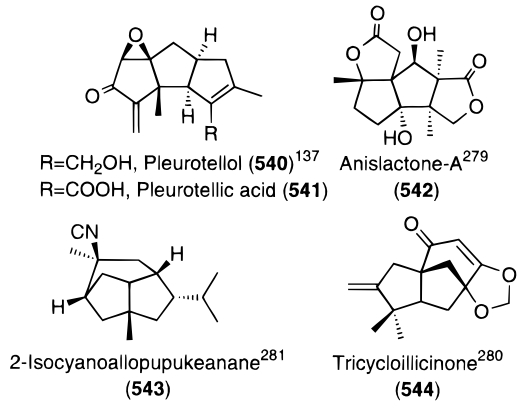
VI. Concluding Remarks

It is quite apparent that the progress in polyquinane synthesis has been quite spectacular, as evidenced by the number of total syntheses that have been accomplished. While some of the synthetic strategies

Scheme 143[278]



have been developed in the context of a particular target structure and exude their own flavor, many new methodologies, such as tandem radical cyclizations, arene−olefin meta-photocycloaddtions, vinylcyclopropane rearrangements, photothermal metathesis, oxa-di-π-methane rearrangements, tandem metallo ene−carbonylation cascade reactions, tandem oxy-Cope rearrangement−transannular cyclizations, higher order intramolecular cycloadditions, etc., have been developed/adopted in a more general context for the rapid assembly of five-membered rings. Many of these methodologies exhibit not only high stereo- and regioselectivity, but are also notable for their efficiency (high yields) and operational simplicity. Also, the recent developments in asymmetric synthesis have proved valuable in the polyquinane area and led to many enatioselective syntheses. Indeed, polyquinanes have proven to be a happy hunting ground for testing new themes and reagents during the past two decades, just as steroids were in previous decades. However, there still remain many methodological challenges, and several target molecules, *e.g.* **200**, **540**−**544**, await total synthesis. It is expected that the current upsurge of interest in polyquinane synthesis will be sustained in years to come as newer structures from Nature's bosom unfold and synthetic chemists remain ever-ready to meet the challenge.



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