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Hagemann's ester: a timeless building block for natural product synthesis

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Dedicated to Professor Achille Barco and Professor Augusto Cesare Veronese on the occasion of their retirement

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1. Introduction

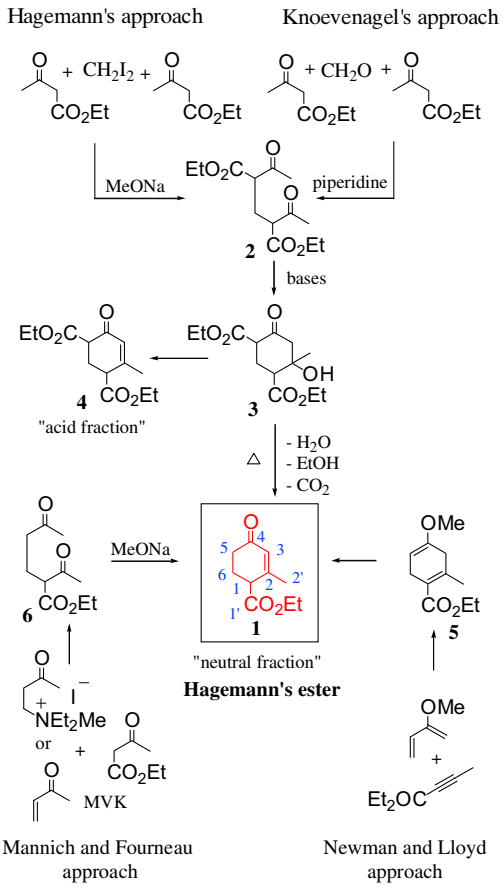
An article[1] entitled 'Carl Hagemann…ein Mensch von großer Güte, ein richtiger Chemiker…' that recently appeared in '*Chemie in unserer Zeit*' gave an excellent portrait of Carl Hagemann (1867–1940) as a well-known collector of German Expressionist paintings as well as a successful chemist and manager at Farbenfabriken Bayer, Cassella and IG Farben company. The efforts to assign the correct structure to the compound **1** prepared in 1893,[2] and, since then, named Hagemann's ester have been historically described. Moreover, a short description of several of its applications as a building block for the synthesis of a variety of important natural products has also been included. Almost contemporaneously, a paper[3] appeared in '*Journal of Chemical Education*' that described a detailed guided prelab exercise for the Hagemann's ester preparation, which has also been included in an organic chemistry laboratory manual[4] as a convenient intermediate to produce 3-methylcyclohex-2-enone. Moreover, a disconnection approach to Hagemann's ester has been used as an instructive example for students by Warren in his popular book, '*Designing Organic Syntheses*'.[5] This continuous attention around Hagemann's ester coupled with our long-standing appreciation of this compound as a tool for natural product synthesis[6,7] has prompted us to write a comprehensive overview with the aim of covering the development of its chemistry from the very beginning up to the present time. After this short introduction (Section 1), the material has been organized in sections and the papers listed in each section are discussed in chronological order. Thus, Section 2 has been dedicated to the different preparations of Hagemann's ester, the original protocol being continuously improved, and also covers the synthetic approaches to C-6 alkylated analogues, readily accessible by suitable modifications of the original procedures. The alkylation of the vinylogous β-keto ester system, the most common operation on the starting ester, has been discussed in detail in Section 3. Synthetic applications involving chemical modifications of the ester functionality, namely removal, preservation and elaboration, have been considered in Sections 4–6, while syntheses featuring Hagemann's ester fragmentation into linear carbon chains are collected in Section 7, regardless of the ester destiny. Section 8 has been dedicated to the preparation and synthetic applications of optically active Hagemann's ester derivatives. For the sake of clarity, the carbon-atom fragments of the different synthetic targets coming from Hagemann's ester or its analogues are marked in red.

2. Preparation

The original protocol[2] for the preparation of Hagemann's ester **1** has been continuously modified and three different procedures, which in some instances could be easily adapted to the preparation of C-1 as well as C-6 alkyl analogues, have been subsequently proposed by Knoevenagel,[8] Newman and Lloyd[9] and Mannich and Fourneau.[10] These are summarized in Scheme 1.

2.1. Hagemann's approach

Hagemann described the cyclization of the diethyl ester of 2,4-diacetylpentanedioic acid **2** obtained by the reaction between two equivalents of ethyl acetoacetate and methylene iodide in the presence of sodium methoxide. This operation led to the formation of two products, which could be easily separated by treatment with sodium hydroxide into 'acid' and 'neutral' fractions, compounds **4** and **1**, respectively. The formulae reported in the original paper contained several errors, which were corrected in the same issue at the end of the year.[2]



Scheme 1.

2.2. Knoevenagel's approach

A better method to prepare **1** in comparison to the original route was introduced soon after by Knoevenagel through the condensation of two equivalents of acetoacetic ester with one equivalent of formaldehyde in the presence of a catalytic amount of piperidine.[8] Thus, a first molecule of acetoacetic ester underwent a Knoevenagel condensation with formaldehyde to form an active Michael acceptor for a second molecule. The resulting primary condensation product **2** produced the cyclic ketol **3**, which was readily converted (even by steam distillation) into Hagemann's ester **1** in ca. 50% yield. This sequence may be considered a typical example of the widely used domino 'Knoevenagel–Michael–intramolecular aldol' reaction sequence. It has been generally accepted that the primary bisacetoacetate adduct **2** could be prepared without the use of a catalyst, but that a basic catalyst was necessary for its conversion into the ketol **3**, which was readily converted into **1** by loss of water and selective removal of the ethoxycarbonyl group α to the carbonyl group. This reaction has been extensively studied in detail as a tool to obtain substituted cyclohexenones and several groups[11–17] have made important contributions to elucidate the structure of the two compounds originally described as the 'acid fraction' and 'neutral fraction'.[2]

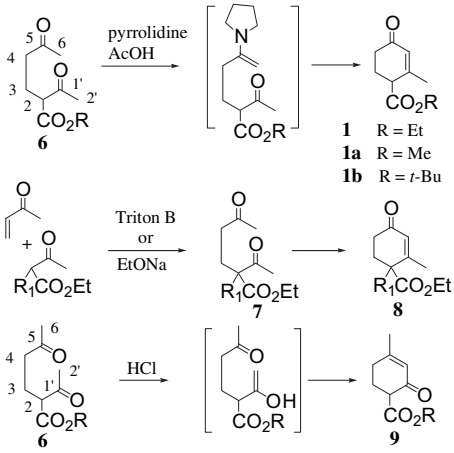
2.3. Newman and Lloyd approach

Newman and Lloyd[9] exploited the Diels–Alder reaction of 2-methoxy-1,3-butadiene and ethyl 2-butynoate as an alternative way to prepare Hagemann's ester. The Diels–Alder adduct **5** obtained in 51.5% yield was transformed into **1** by hydrolysis. This approach represented an alternative entry to this important starting material, the introduction of a variety of alkyl groups at the C-2 position being easily feasible by varying the starting alkynoate.

2.4. Mannich and Fourneau approach

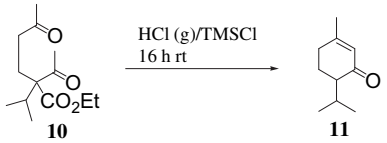
The preparation of **1**, although in poor yield, by the action of sodium ethoxide on the adduct **6** obtained in situ by the reaction of acetoacetic ester and diethyl-methyl-(3-oxo-butyl)-ammonium iodide used as precursor of methyl vinyl ketone (MVK) has been described by Mannich and Fourneau.[10]

The need for a convenient large-scale synthesis of the *t*-Bu analogue **1b**, led to the development of an alternative approach involving the aldol cyclization of esters of 2-acetyl-5-oxohexanoic acid (Scheme 2). Thus, Begbie and Golding[18] proposed a new, improved synthesis of **1** and its methyl and *t*-Bu analogues **1a** and **1b** through a regioselective cyclization of the Michael adduct of the appropriate ester of acetoacetic acid with MVK using pyrrolidinium acetate as the catalyst.



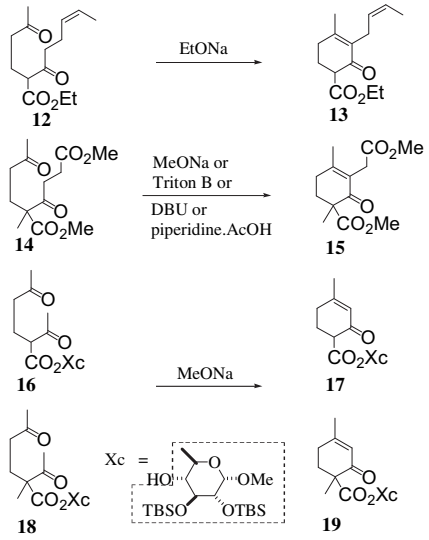
Scheme 2.

The same annulation has been successfully performed in a single step by the action of Triton B or sodium ethoxide on a mixture of MVK and ethyl acetoacetate.[19] Interestingly, using 2-alkyl acetoacetates as the Michael donors, the Mannich and Fourneau approach served to obtain C-1 alkyl Hagemann's ester derivatives **8** through cyclization of the adducts **7**. The direction of the aldol cyclocondensation of the Michael adducts has been claimed to be irrespective of the rule utilizing the carbonyl group of the original Michael acceptor. However, according to Blaise and Maire,[20] a reverse chemoselectivity in the aldol cyclization of **6** has been observed using hydrogen chloride as the catalyst, producing the isomeric cyclohexenone derivative **9**. Therefore, it is likely that the C-6/C-1′ carbon–carbon double bond formation in the presence of pyrrolidinium acetate as the catalyst occurred through an enamine intermediate, while the alternative C-5/C-2′ carbon–carbon double bond formation in the acid-catalyzed cyclization probably involved an enol intermediate (Scheme 2). The soundness of this hypothesis was corroborated several years later by Kreiser and Below,[21] who opened the way to a short synthesis of the monoterpenoid, piperitone **11**, putting into practice the regioselective cyclization of compound **10** by treatment of the corresponding silyl enol ether with HCl gas (Scheme 3).



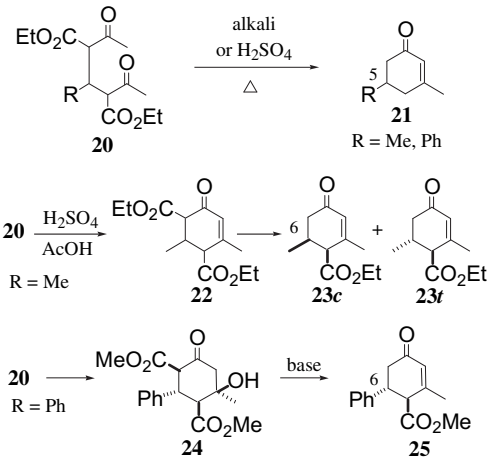
Scheme 3.

The ability of acid catalysts in *re*-directing the aldol cyclization has been observed in other instances,[22,23] the whole structure of the 1,5-dicarbonyl substrates being relevant (Scheme 4). Thus, basic promoted cyclocondensation reactions of compounds **12**,[24] **14**,[25] **16** and **18**[26] took place utilizing the carbonyl group of the original Michael acceptor, to form **13**, **15**, **17** and **19**.



Scheme 4.

Thus, Hagemann's ester analogues bearing alkyl or aryl groups at C-6 could be easily produced according to Knoevenagel's procedure,[8] by condensation of different aldehydes instead of formaldehyde with two equivalents of acetoacetic ester in the presence of piperidine. The prolonged heating of the resultant bis-ester adducts **20** with sulfuric acid or with aqueous or alcoholic alkali led to C-5 alkyl or aryl cyclohexenones **21** (Scheme 5). Under these conditions, cyclization, saponification and decarboxylation occurred in a single operation, but the overall yield was frequently low and variable. An improved general procedure took advantage of the use of AcOH containing H_2SO_4 where the carbethoxy groups could be retained, as in **22**, or in some cases removed selectively, as in **23**. Moreover, the reaction sequence could be carried out in a single operation.[27,28] It has been demonstrated that the C-6 methyl Hagemann's derivative was formed as a 3:2 separable mixture of *trans* **23*t*** and *cis* **23*c*** isomers.[29] Particular attention has been devoted to the reaction between benzaldehyde and



Scheme 5.

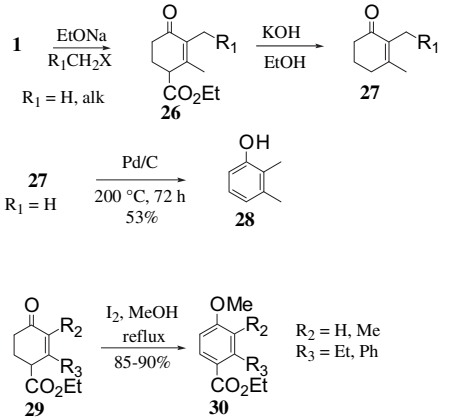
acetoacetic ester. A long and somewhat acrimonious history to assign the correct structure to the derived products involved many famous chemists including Hantzsch, Knoevenagel, Schiff and Rabe. A careful inspection of the NMR spectra of the three stereoisomeric compounds formed in the condensation of methyl acetoacetate and benzaldehyde led to their relative configurations being elucidated (Scheme 5). The predominant condensation product **24** has all but hydroxyl as equatorial substituents, a spatial arrangement accounting for the easily base-catalyzed transformation into the C-6 phenyl derivative **25** through an intermediate bicyclic lactone.[30]

3. Alkylation

Hagemann's ester **1** has four possible sites (C-1, C-3, C-5 and C-2′) at which alkylation could, in principle, occur. Thus, taking into account that this operation has been widely used in Hagemann's ester-based synthetic chemistry, separate subsections have been dedicated to C-3 vs C-1 competitive alkylation and to the synthetic procedures, which could favour the regioselective C-1 or C-5 attachment of electrophiles.

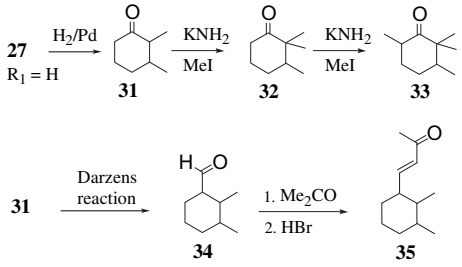
3.1. C-3 vs C-1 selectivity

The sequence involving C-3 alkylation of **1** with a suitable halide followed by one-pot hydrolysis and decarboxylation of the vinylogous β-keto ester **26**, usually performed in refluxing aqueous ethanolic KOH, has been conveniently used to obtain 2-alkyl-3-methyl-2-cyclohexen-1-ones **27**, which are useful starting materials for natural product syntheses. Smith and Rouault[31] prepared several cyclohexenone derivatives with the aim of producing different substituted phenols, but only 2,3-dimethylphenol **28** could be obtained by the action of a palladium catalyst (Scheme 6). More recently, the aromatization of 2,3-disubstituted cyclohexenone derivatives **29** was accomplished using iodine and methanol at reflux. The effectiveness of the protocol opened up a new entry to functionalized *p*-methoxybenzoates **30**, common subunits of many marine natural products.[19]



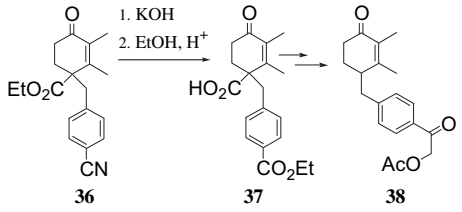
Scheme 6.

Hagemann's ester **1** has also been conveniently used for the preparation of several dihydroionone analogues,[32] modifying the number and the position of the methyl groups around the ring and retaining the exocyclic unsaturation (Scheme 7). Catalytic reduction of 2,3-dimethyl-2-cyclohexen-1-one **27** (R_1=H) afforded 2,3-dimethylcyclohexanone **31**, which could be further alkylated to produce **32** and **33** containing three and four methyl groups, respectively. It was found that methyl groups next to the carbonyl group greatly hampered the subsequent Darzens procedure, which was successful only for **31**. Thus, the dihydroionone analogue **35** was obtained submitting the aldehyde **34** to an aldolization–dehydration sequence.



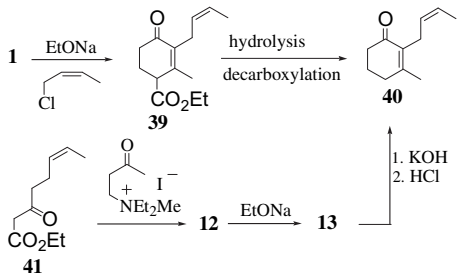
Scheme 7.

Methylation of **1** at C-3 followed by alkylation at C-1 with a suitably functionalized benzyl bromide gave the substituted cyclohexenone **36**, which has been conveniently used as the starting point of a synthetic study towards potential cortical hormone substitutes incorporating the α,β-unsaturated ketone and the α-ketol side-chain motifs of corticosterone (Scheme 8). Exhaustive hydrolysis and esterification gave the half-ester **37**, which was decarboxylated and further elaborated through classical chemical manipulations of the aromatic carbethoxy group to give the targeted analogue **38**.[33]



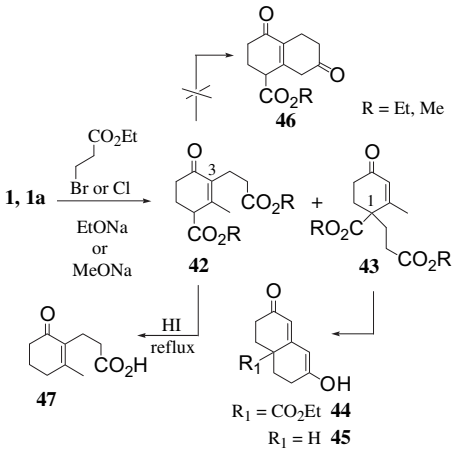
Scheme 8.

A convenient synthetic entry to a pyrethrin analogue **40** featuring a cyclohexenone ring system in place of the cyclopentenone entailed a C-3 alkylation of **1** with *cis*-crotyl chloride followed by one-pot hydrolysis and decarboxylation of the vinylogous β-keto ester **39** (Scheme 9). However, because of the slender evidence about the regioselectivity of the alkylation reactions, the authors[24] decided to seek more direct proof (Scheme 9). To this end, they were able to prepare compound **40** via a Mannich and Fourneau approach, starting from 4-diethylaminobutan-2-one methiodide and the sodium salt of ethyl 3-oxo-oct-6-enoate **41**. The resulting 1,5-diketone **12** underwent aldol cyclocondensation to yield **13**, easily transformed into **40** through saponification and decarboxylation.



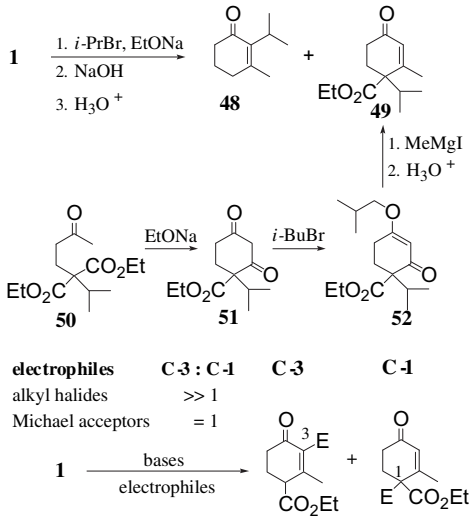
Scheme 9.

The alkylation of **1a** with ethyl bromopropionate in the presence of sodium methoxide has originally been described as occurring exclusively at C-3, producing **42** in 83% yield.[34] However, treatment of **1** in the presence of an excess of ethanolic sodium ethoxide was found to give the expected C-3 alkylated keto ester **42** together with a 25–30% yield of a new product, which on hydrolytic decarboxylation afforded the octal-2,7-dione **45** (Scheme 10). Therefore, the new product had the structure **44** and its formation was explained to occur via an initial alkylation of **1** at C-1 to give the keto ester **43**, which in turn underwent in situ Claisen condensation.[35] On the other hand, the isomeric C-3 alkylated compound **42** did not undergo a similar intramolecular condensation reaction leading to **46** and its acid hydrolysis-decarboxylation gave **47**.



Scheme 10.

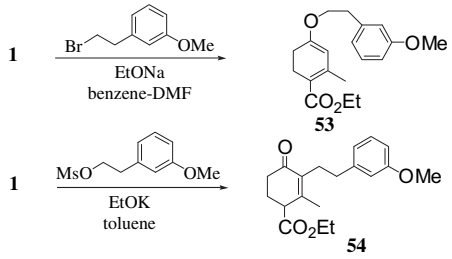
Moreover, a *re*-investigation of the reaction of **1** with isopropyl bromide led to the identification in the reaction mixture of the C-1 isopropyl derivative **49** together with the expected cyclohexenone **48** (Scheme 11). An authentic sample of **49** could be prepared by an independent route, starting from ethyl 2-carbethoxy-2-isopropyl-5-oxohexanoate **50** transformed into **51** by intramolecular Claisen condensation. The subsequent regioselective enol etherification gave **52**, easily transformed into **49** by treatment with methylmagnesium iodide followed by acid hydrolysis. In this way, it was found that the generally accepted prevalent C-3 alkylation of **1** might, in some cases, not be completely selective, as expected. The failure to identify the C-1 alkylation products in the past might be due to the fact that they



Scheme 11.

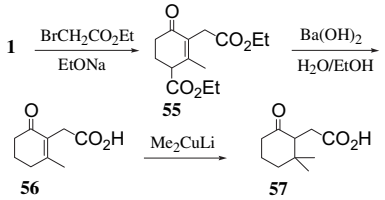
are more resistant to hydrolysis and were likely to have been lost as higher-boiling fractions in the distillation of the complex reaction mixture. As a matter of fact, it has been generally accepted that the site preference for alkylation was C-3, the resulting C-3-alkyl derivatives often being accompanied by small amounts (2–51%) of the C-1-alkyl products. The unwanted formation of small quantities of the C-1 alkylated compounds was circumvented taking advantage of their different rates of saponification which allowed an easy separation. Different protocols have been tested for the alkylation of **1** (EtONa–EtOH;[36–38] *t*-BuOK–*t*-BuOH;[39] NaH–DMF;[40] NaH–toluene or NaH–1,2-dimethoxyethane;[37] and $NaNH_2$–liquid ammonia[32]), but the ratio of the C-3/C-1 alkylation products (determined by GLC and NMR spectroscopy)[38] was found to be more dependent on the electrophilic agent than on the basic conditions (protic or non-protic medium) (Scheme 11). In particular, while reacting **1** with methyl iodide–sodium ethoxide gave monomethylated products at C-3 and C-1 in an approximate ratio of 4:1 in 83% yield, its reaction with Michael acceptors produced the corresponding C-1 and C-3 adducts in comparable yield. Both electronic and steric interactions in the transition states could explain the different extent of regioselectivity.[37]

Interestingly, the alkylation of the sodium enolate of **1** with *m*-methoxyphenethyl bromide in benzene–DMF gave predominantly the O-alkylation product **53**, whereas, on reacting the corresponding potassium enolate with the mesylate of *m*-methoxyphenethyl alcohol in toluene, the C-3 alkylated compound **54** was the prevalent product (Scheme 12).[41]



Scheme 12.

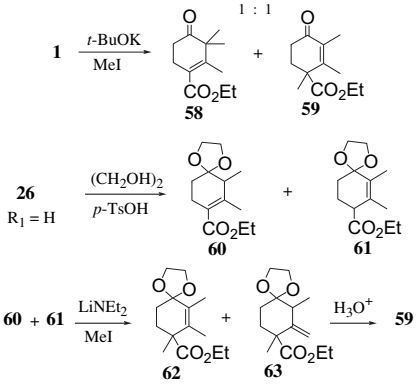
The most convenient of the six known synthetic routes to obtain 2,2-dimethyl-6-oxo-1-cyclohexaneacetic acid **57**, a useful isoprenoid building block, entailed the use of **1** as the starting material.[42] In the first step, substitution of ethyl bromoacetate for the chloroacetate ester served to increase the efficiency of C-3 alkylation (Scheme 13). Moreover, hydrolysis and decarboxylation of the resultant **55** to give **56** could be performed in a one-pot procedure using barium hydroxide. The successive conjugate addition of lithium dimethylcuprate (Gilman's reagent) afforded the keto acid **57** in 35% overall yield without any chromatographic purification.



Scheme 13.

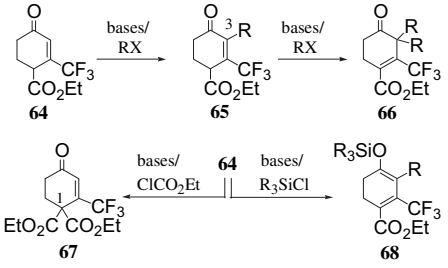
A careful study[39] of the alkylation of **1** aimed at producing the C-3, C-1 dimethylated derivative **59** showed that it was more convenient to protect the carbonyl group of the C-3 monomethylated compound **26** prior to effecting the second methylation. In this way, the formation of equimolar quantities of isomeric

dimethyl derivatives **58** and **59** was prevented (Scheme 14). Thus, alkylation of isomeric ketals **60** and **61** (as a 1:1 mixture) gave endocyclic **62** and exocyclic **63** dimethylated β,γ-usaturated esters (ca. 1:1). Acid hydrolysis furnished the keto ester **59** in 56% overall yield from **26**.



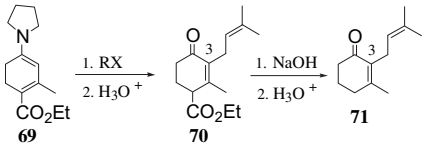
Scheme 14.

The Mannich and Fourneau approach performed using trifluoromethyl acetoacetate instead of ethyl acetoacetate led to the formation of the analogue **64**,[43,44] a new derivative, which showed a strong preference for the C-3 alkylation, while sequential double alkylation smoothly gave compound **66** via **65** (Scheme 15). Moreover, high C-1 selectivity has been shown in the reaction of **64** with ethyl chloroformate, producing compound **67**, while exclusive *O*-silyl enol-etherification occurred in the reaction with silyl chlorides, producing **68**.



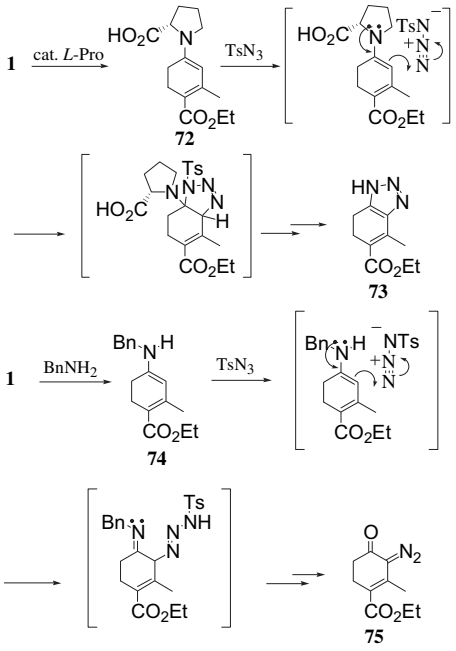
Scheme 15.

An alternative entry[37] to perform C-3 Hagemann's ester alkylation utilized its solid, fully conjugated dienamine **69** (Scheme 16). Thus, alkylation with 3-methylbut-2-enyl chloride gave, after hydrolysis, a moderate yield of **70**, from which 3-methyl-2-(3-methylbut-2-enyl)cyclohex-2-enone **71** could be easily derived.



Scheme 16.

The 'push–pull' dienamine **72** arising from the in situ condensation between **1** and L-proline has been reported to react with tosyl azide to give *N*H-1,2,3-triazole **73** via a [3+2]-cycloaddition/hydrolysis cascade (Scheme 17). On the other hand, the electrophilic azide reacted with dienamine **74** giving the diazo compound **75** via an enamine amination/elimination cascade. In both cases,

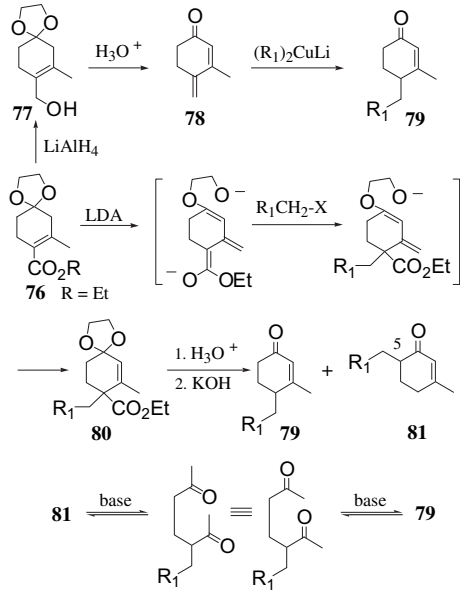


Scheme 17.

the C-3 regioselective trapping of the electrophilic reagent has been proposed as the starting step.[45]

3.2. C-1 selectivity

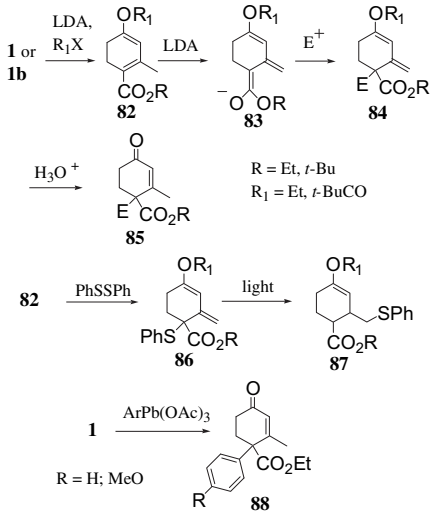
Reduction of the ketalized Hagemann's ester **76** with $LiAlH_4$ afforded the corresponding allylic alcohol **77**, which upon acid hydrolysis gave the dienone **78** (Scheme 18). The latter underwent lithium dialkylcuprate regioselective 1,6-addition, giving 4-alkyl-3-methyl-2-cyclohexen-1-one **79** (R_1=*n*-Bu), a compound otherwise preparable by regioselective C-1 alkylation of **1** followed by decarbethoxylation.[22] Moreover, it has been shown that hydrolysis of compound **80**, in turn derived by C-1 alkylation of **76**, furnished invariably a mixture of the C-1 and C-5 alkylated products **79** and **81**, respectively (Scheme 18). Interestingly,



Scheme 18.

a double deprotonation of **76** occurring with cleavage of the ethylene ketal group followed by regioselective alkylation at C-1 and rapid isomerization of the resulting dienol ether has been proposed to account for the formation of **80**.[46] Instead, the formation of the regioisomeric mixture of **79** and **81** has been accounted for by a base-catalyzed retro-aldol reaction, followed by cyclization in the opposite manner.

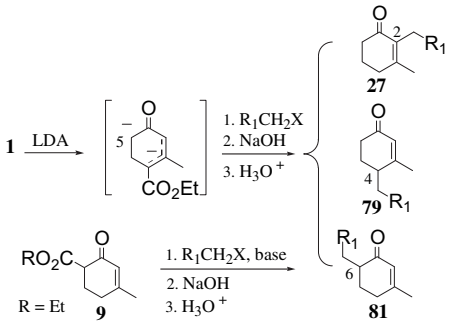
A communication by Australian authors[47] reported a seemingly facile method for a C-1 selective reaction of **1** with electrophiles. Thus, ester dienolates **83**, prepared by LDA deprotonation of the corresponding dienol ethers or dienol esters **82**, reacted rapidly at −78 °C with a variety of electrophiles (Scheme 19). The resulting products **84**, by virtue of mild acid hydrolysis, furnished the C-1 substituted Hagemann's derivatives **85**. Unexpectedly, the scant success of this protocol cannot be easily explained. Moreover, reacting **82** with diphenyl disulfide gave the α-(phenylsulfenyl) ester **86**, which, upon exposure to laboratory light, was quantitatively converted through a [1,3] shift of the phenylthio group into the γ-product **87**. Interestingly, a few years later, other authors from the same Department described the arylation of **1** with aryl-lead triacetates, furnishing regiospecifically a good yield of the 1-arylated compounds **88**.[48]



Scheme 19.

3.3. C-5 selectivity

The alkylation of the bisanion of **1** was contemplated as a suitable way to selectively introduce alkyl groups at C-5.[22] However, a mixture of 2-, 4- and 6-alkyl-3-methylcyclohexenones was invariably obtained after de-ethoxycarbonylation (Scheme 20). Thus,



Scheme 20.

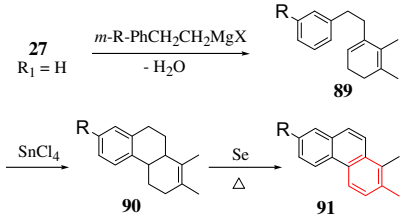
the preparation of compounds **81** was found to be more reliable through alkylation of the Hagemann's ester isomer **9** followed by saponification and decarboxylation.

4. Ester removal

The synthetic strategies towards natural targets in which the carboxy ester of **1** has served mainly to favour the C-3 alkylation, being subsequently removed, are collected in this section. This operation could be effected both by hydrolysis and decarboxylation (subsection 4.1) or by ozonolysis (subsection 4.2).

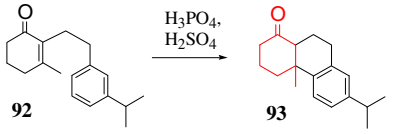
4.1. De-ethoxycarbonylation

As previously emphasised, **1** has been extensively used for the preparation of 2-alkyl-3-methyl-2-cyclohexen-1-ones **27**, which are useful starting materials for natural product syntheses. Thus, a pioneering approach to the substituted phenanthrene skeleton **91** entailed the 1,2-addition reaction of suitable Grignard reagents to **27**.[17] Dehydration of the resulting tertiary alcohols furnished **89**, which underwent tin (IV) chloride-mediated cycloisomerization to the tricyclic compound **90**, which eventually aromatized to **91** (Scheme 21).



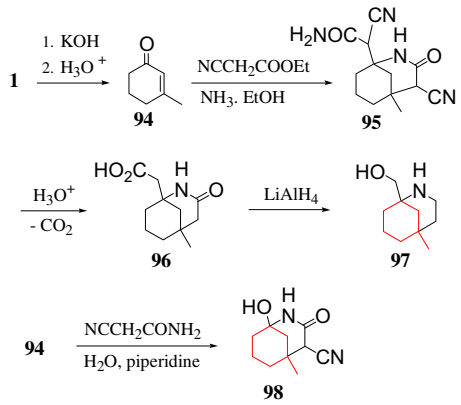
Scheme 21.

Stork and Burgstahler[40] described the construction of a tricyclic skeleton **93** related to dehydroabietic acid by acid-promoted cyclization of the cyclohexenone derivative **92** (Scheme 22).



Scheme 22.

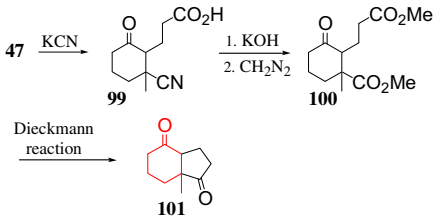
Interestingly, the latter was obtained by regioselective C-3 alkylation of **1** through a protocol involving NaH in DMF–benzene (1:3 mixture), which seems likely to be the first example of the utilization of DMF as an aprotic polar solvent in this kind of reaction.



Scheme 23.

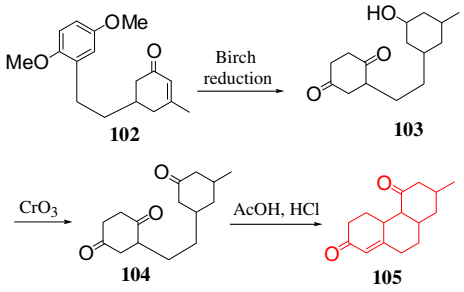
Compound **1** was also a convenient source of 3-methyl-2-cyclohexen-1-one **94**, which by reaction with ethyl cyanoacetate in alcoholic ammonia furnished the azabicyclononane **95**, the structure of which has been assigned through a rigorous study of its chemical properties (Scheme 23), its formation being likely to proceed through a domino Knoevenagel–Michael–annulation–aminolysis cascade.[49] Compound **95** upon hydrolysis and decarboxylation afforded the acid **96**, which was reduced with $LiAlH_4$ to give 5-methylmorphanethanol **97**. Interestingly, the reaction of **94** with cyanoacetamide in the presence of piperidine took a slightly different outcome, yielding the 1:1 condensation product **98** in 77% yield.

During their synthetic efforts towards vitamins D_2 and D_3, Inhoffen et al.[50,51] developed an easy entry to 8-methyl-hydrindan-1,4-dione **101** (Scheme 24). Thus, the already mentioned acid **47** (see Scheme 10) underwent conjugate addition of cyanide, yielding compound **99**, which was transformed into the keto diester **100** through sequential basic hydrolysis and esterification. A final Dieckmann reaction produced the useful intermediate **101**.



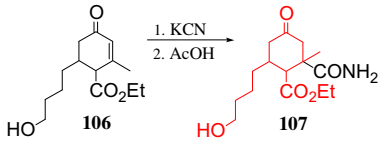
Scheme 24.

Approaches to steroid synthesis have often been inspired by **1**. A synthetic approach to the tricyclic diketone **105**, containing the elements of the steroid A, B and C rings with carbonyl groups and a double bond in the appropriate positions, has been described[52] (Scheme 25). The substituted cyclohexenone **102**, prepared by condensation of 2,5-dimethoxypropionaldehyde with ethyl acetoacetate according to Knoevenagel's procedure,[8] underwent Birch reduction to produce the hydroxy diketone **103**, which was subsequently oxidized to **104**. Intramolecular aldol condensation followed by double-bond isomerization eventually afforded compound **105**.



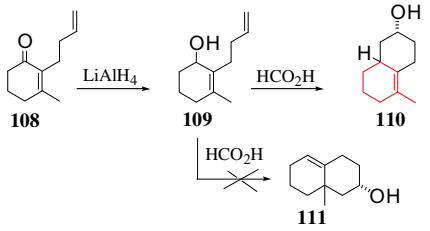
Scheme 25.

In the same paper, exploratory work directed towards the construction of the steroid D ring has also been described (Scheme 26). Thus, treatment of the C-6 substituted Hagemann's derivative **106** with potassium cyanide in an aqueous-ethanol solution containing 0.68 equiv of acetic acid per equivalent of potassium cyanide afforded the cyclohexanone **107** containing the elements for the construction of the steroid D ring.



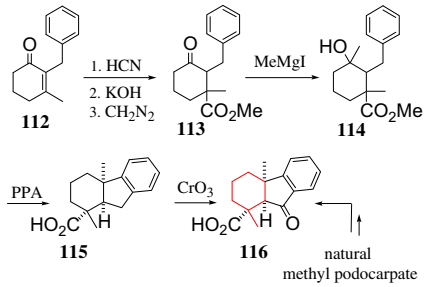
Scheme 26.

The cationic cyclization of **109** was studied with the aim of producing fused-ring systems bearing an angular methyl group.[53] Thus, cyclohexenone **108** was converted into the pivotal dienol **109** by reduction of the carbonyl group with $LiAlH_4$ (Scheme 27). Disappointingly, formolysis failed to give **111**, producing exclusively the methyloctalol **110**.



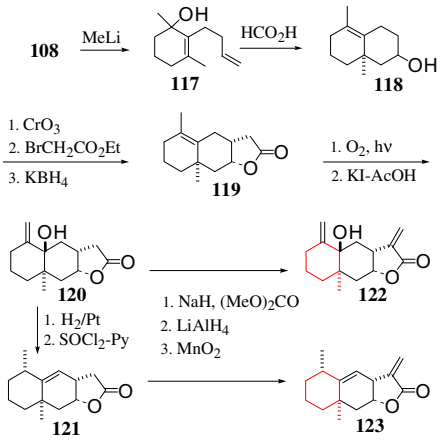
Scheme 27.

The first stereoselective total synthesis of the racemic hexahydrofluorenone derivative **116** began with the conjugate addition of hydrogen cyanide to the cyclohexenone **112**.[54a] The nitrile group was converted by standard chemistry into a methoxycarbonyl group, furnishing compound **113**, which reacted chemoselectively with methylmagnesium iodide to give the tertiary alcohol **114** (Scheme 28). Treatment of **114** with polyphosphoric acid (PPA) produced stereoselectively the tricyclic compound **115**, featuring a *cis* A/B-ring-fused hexahydrofluorene system. The final oxidation with chromic acid afforded the keto acid **116**, identical with that previously prepared from the natural methyl podocarpate.[54b,c]



Scheme 28.

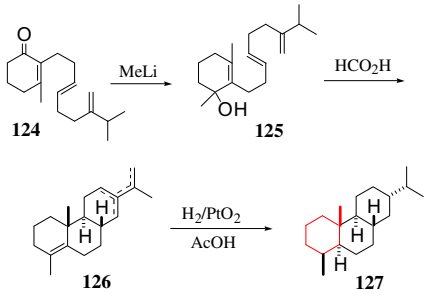
The synthesis via cationic olefin cyclization of the carbocyclic framework of racemic telekin **122** and alantolactone **123**, two lactone bitter principles of the eudesmane class of sesquiterpenes, featured the already described cyclohexenone **108** as the common starting point.[55,56] Its reaction with MeLi produced the tertiary cyclohexenol **117**, which was submitted to formolysis–hydrolysis following Johnson's conditions[53] to give the intermediate **118** (Scheme 29). The



Scheme 29.

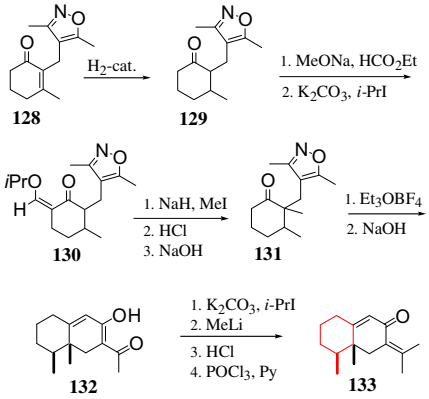
subsequent construction of the fused-ring lactone required oxidation to octalone, regioselective alkylation with ethyl bromoacetate and chemoselective reduction with methanolic potassium borohydride. The resulting compound **119** underwent stereoselective photooxygenation followed by reduction of the derived hydroperoxide with potassium iodide in acetic acid, furnishing the allylic alcohol **120**. Its catalytic hydrogenation followed by dehydration produced the intermediate **121**. The construction of the α-methylene moiety in **120** and **121** was achieved by a standard protocol including carbomethoxylation and reduction with lithium aluminium hydride. Final oxidation with activated manganese dioxide completed the synthesis of telekin **122** and alantolactone **123**, respectively.

Johnson's pioneering studies in biogenetic-like polycyclization have led to the discovery of a facile synthesis of racemic fichtelite **127** by exhaustive hydrogenation of the products formed in the cyclization of trienol **125**.[57,58] Thus, the MeLi addition to the carbonyl group of cyclohexenone **124** afforded the allylic alcohol **125**, a convenient substrate for the polyolefinic cyclization (Scheme 30). In detail, the action of anhydrous formic acid at room temperature gave a heterogeneous mixture that was shaken for 11 min before carrying out a saponification step. The crude residue was purified by chromatography, giving a hydrocarbon fraction containing four components. Interconversion experiments provided evidence that these substances were different only in the position of the double bond in ring C, as indicated in formula **126**. Conclusive proof of the tricyclic nature of these compounds and of the configurations at the ring junctures has been obtained by their conversion into the racemic form of the natural product, fichtelite **127**, by catalytic hydrogenation.



Scheme 30.

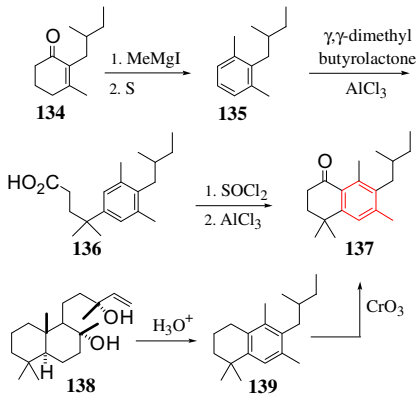
The synthesis of the sesquiterpene, dehydrofukinone **133**, commenced with the chemoselective hydrogenation of the cyclohexenone **128** to give **129** (Scheme 31).[59] Preventive protection of the methylene group α to the carbonyl via the isopropoxymethylene methodology was needed for the introduction of the C-2 methyl substituent. Thus, **130** was transformed into **131** by methylation–hydrolysis and a retro-Claisen reaction sequence. Isoxazole ring opening via quaternization with triethyloxonium fluoroborate and



Scheme 31.

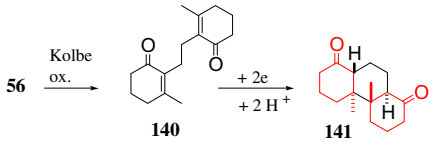
basic treatment, followed by intramolecular condensation of the demasked β-dicarbonyl system, produced the enol compound **132**. Its isopropyl enol ether was treated with MeLi to give, after hydrolysis and dehydration, *rac*-dehydrofukinone **133**.

Acid-catalyzed dehydration of sclareol **138** produced the hydrocarbon **139**. Its structure has been described by Ruzicka and Janot[60] and later confirmed by an independent synthesis of the related tetralone **137**, starting from the cyclohexenone **134**.[38] Its reaction with methylmagnesium iodide followed by aromatization afforded the trialkylbenzene **135** in 52% overall yield (Scheme 32). The subsequent Friedel–Crafts reaction with γ,γ-dimethylbutyrolactone gave the acid **136** as the sole product, albeit in 14% yield. In the final step the targeted tetralone derivative **137** was obtained through an intramolecular acylation reaction.



Scheme 32.

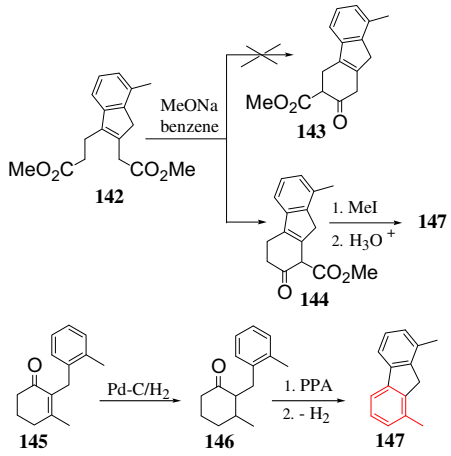
The electrochemical reduction of compound **140** was expected to be of potential utility for perhydrophenanthrene syntheses.[61] Thus, when the carboxylate anion of the already described cyclohexenone **56** was submitted to Kolbe oxidative dimerization in DMF solution, the diene dione **140** was obtained, albeit in poor yield (11%) (Scheme 33). Controlled potential reduction of the α,β-unsaturated ketone moieties took place with both regio- and stereospecificity, affording the *trans-anti-trans* compound **141**.



Scheme 33.

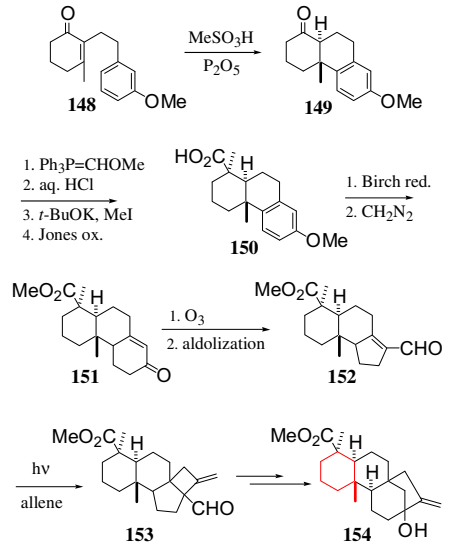
The Dieckmann cyclization of the indene derivative **142** has been claimed to produce the β-keto ester **143**.[62] However, because of some contradictory findings, it was considered important to carry out a *re*-investigation of this reaction. Thus, an unambiguous synthesis of 1,8-dimethylfluorene **147** was designed, starting from the cyclohexenone **145**.[63] Hydrogenation gave compound **146**, which upon treatment with polyphosphoric acid followed by dehydrogenation, furnished 1,8-dimethylfluorene **147** (Scheme 34). The latter compound was found to be identical with that prepared through methylation–hydrolysis–aromatization of the Dieckmann condensation product. In this way, it was demonstrated that the Dieckmann ring closure of **142** produced the expected β-keto ester **144**, instead of the previously reported isomer **143**.

A synthetic strategy coupling photochemical and solvolytic reactions for the construction of the 1-hydroxy-7-methylene-bicyclo[3.2.1]octane skeleton of steviol methyl ester **154** was designed starting from cyclohexenone **148**.[41] Acid-promoted cyclization gave **149**, which was converted into the key hydroindenal **152** through the



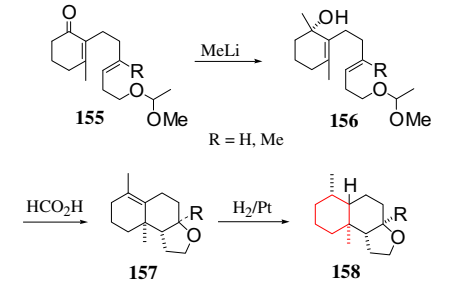
Scheme 34.

intermediates **150** and **151** by a number of steps (Scheme 35). Interestingly, a 10% solution of phosphorous pentoxide in 90% methanesulfonic acid (Eaton's reagent) was a superior acid medium for the cyclization, in comparison with the previously employed phosphoric acid-based reagents. Moreover, the stereochemical outcome of the photoaddition of allene to compound **152** was proved by conversion of the *cis* fused cycloadduct **153** into steviol methyl ester **154**.



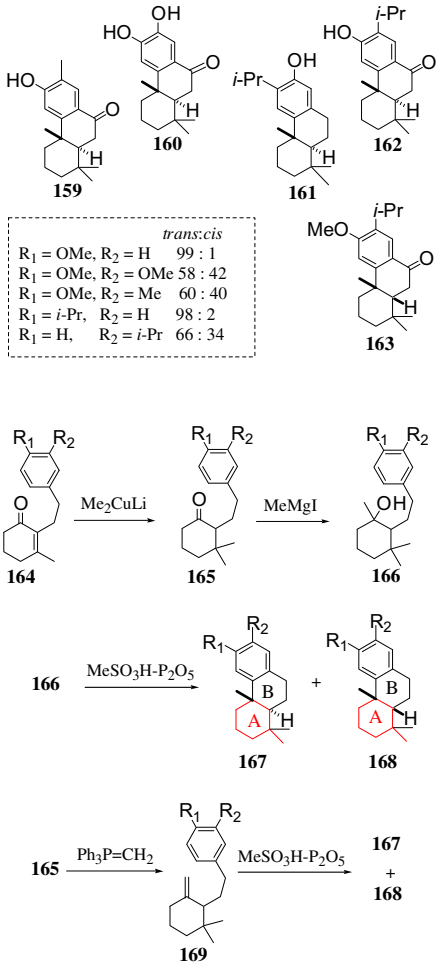
Scheme 35.

Regioselective 1,2-addition of methyllithium to cyclohexenones **155** afforded the cyclohexenols **156**, which underwent polycyclization to give **157** by treatment with formic acid (Scheme 36). Double-bond hydrogenation completed the synthesis of the odorous compounds, 4-desmethyl- and 4,8-didesmethyl-ambrox **158**.[64]



Scheme 36.

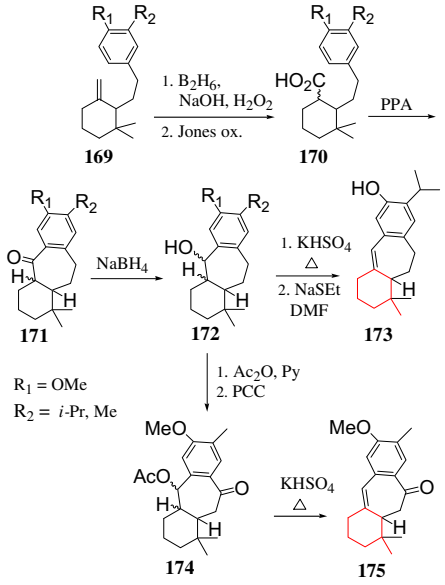
A simple acid-catalyzed cycloalkylation reaction has been conveniently used to prepare stereoselectively a series of natural diterpenoids having both the *trans*-A/B-ring-C aromatic nucleus (nimbiol **159**, nimbidiol **160**, sempervirol **161**, and sugiol **162**) as well as the *cis*-A/B junction (xantopherol methyl ether **163**). The approach took advantage of the stereochemical outcome of the $MeSO_3H$–P_2O_5-promoted reaction of the key intermediate tertiary cyclohexanols **166**, in turn derived from the corresponding cyclohexenones **164** by sequential 1,4-addition of Gilman's reagent to give **165** followed by 1,2-addition of Grignard reagent (Scheme 37). In the acid-promoted cycloalkylations, it was found that precursors bearing an unactivated aromatic ring formed almost exclusively the *trans* products **167**, while the presence of electron-donating substituents *para* to the site of attack favoured the formation of a mixture of **167** and the *cis* product **168**.[65–67] The same behaviour was observed for the acid-catalyzed cycloalkylations of **169**, in turn derived by Wittig methylenation of **165**.



Scheme 37.

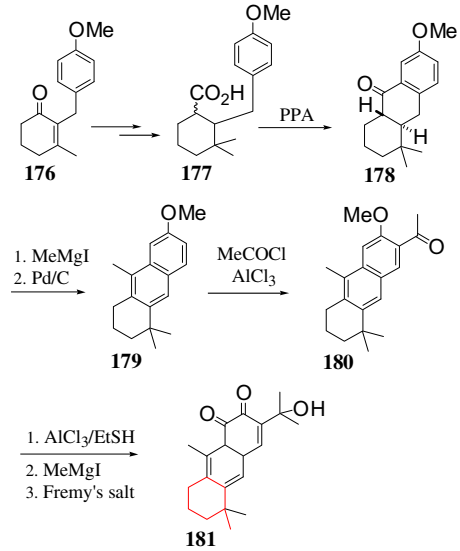
Performing a different chemical elaboration of the *exo*-methylene group of **169**, the same research group synthesized the related diterpenes, isopisiferin **173** and faveline methyl ether **175**.[68–70] Thus, a hydroboration–oxidation sequence of **169** gave the cyclohexanecarboxylic acids **170**, which underwent polyphosphoric acid cyclization to **171** (Scheme 38). The subsequent carbonyl group reduction with sodium borohydride furnished the alcohols **172**, from which the diterpene, isopisiferin **173**, was obtained by dehydration followed by O-demethylation with NaSEt in boiling DMF. On the

other hand, acetylation of **172** (R_2=Me) followed by chemoselective oxidation with PCC afforded the benzylic ketone **174** precursor of faveline methyl ether **175**.



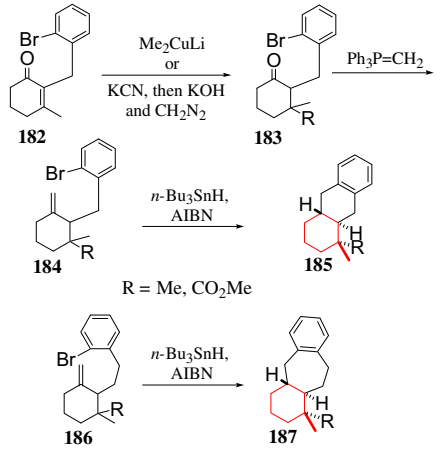
Scheme 38.

A synthetic approach to the rearranged linear abietane diterpenoid orthoquinone, umbrosone **181**, was designed in a similar way, starting from cyclohexenone **176**.[71] Thus, the cyclohexanecarboxylic acid **177** underwent PPA-promoted cyclization to the *trans*-ketone **178** (Scheme 39). Its reaction with methylmagnesium iodide followed by dehydration–aromatization led to tetrahydroanthracene **179**. At this stage, four steps were required to complete the total synthesis of umbrosone, namely a Friedel–Crafts acylation to give **180**, O-demethylation and addition of methylmagnesium iodide to give a relatively unstable phenolic alcohol derivative that was eventually oxidized to **181** with Fremy's salt.



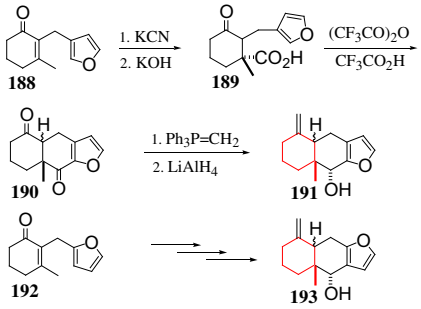
Scheme 39.

Gilman's reagent addition to cyclohexenone **182** or cyanide ion conjugate addition followed by nitrile conversion into a methoxycarbonyl group gave compounds **183** easily transformed into **184** by Wittig methylenation (Scheme 40). Their treatment with tri-*n*-butyltin hydride induced a 6-*endo* ring closure to the *trans*-octahydroanthracenes **185**.[72] The aryl radical cyclization strategy has also been successfully applied to the homologues **186**, giving rise to the formation of compounds **187** (Scheme 40), through a regioselective 7-*endo* cyclization.[73]



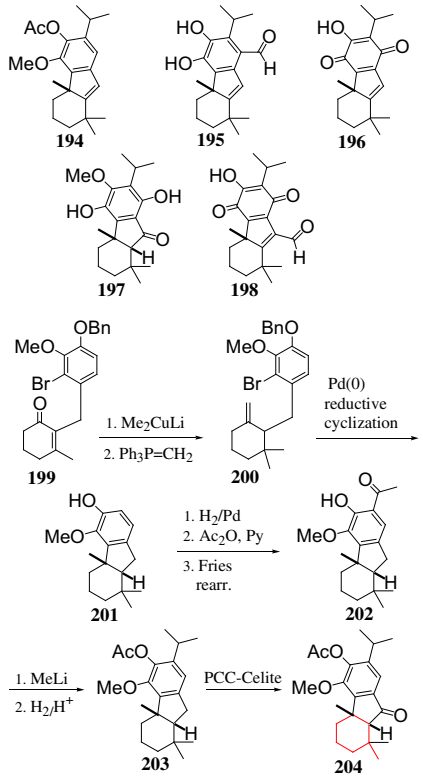
Scheme 40.

The furan-3-ylmethyl-cyclohexenone **188** was transformed into **189** by cyanide conjugated addition followed by saponification (Scheme 41).[74] Further connection of the cyclohexane and furan units by the action of the trifluoroacetic anhydride–trifluoroacetic acid system produced the linearly fused furodecalins **190** as a *cis*/*trans* ring-junction mixture. Differentiation of the carbonyl groups by selective Wittig methylenation followed by reduction of the remaining carbonyl function completed the assemblage of the functionalized intermediates **191**. The versatility of this approach has been further demonstrated through the synthesis of **193**, isomer of **191**, starting from **192**, both compounds being useful materials for the synthesis of many furosesquiterpenes.



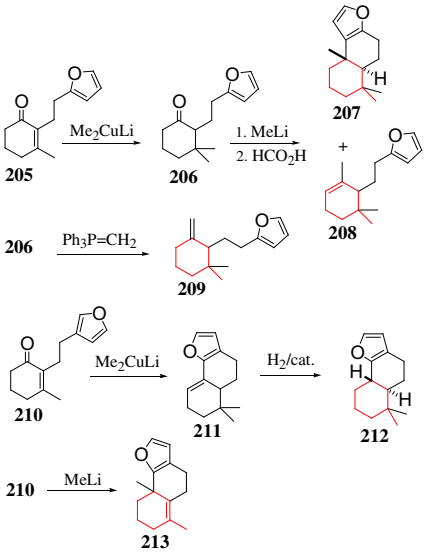
Scheme 41.

The syntheses of hydrofluorenone natural diterpenoids **194**–**198** have been approached using the common starting material **204**, in turn prepared through an interesting synthetic route featuring a Pd(0)-catalyzed reductive cyclization as the key step.[75,76] Thus, conjugate lithium dimethylcopper addition to the substituted cyclohexenone **199** followed by Wittig olefination produced **200**, which smoothly underwent cyclization to **201** by treatment with palladium-tetrakis(triphenylphosphine) and sodium formate (Scheme 42). Removal of the benzylic protecting group followed by a Fries rearrangement allowed the introduction of the *ortho*-acetyl group. Treatment of the resulting **202** with an excess of MeLi followed by acid-catalyzed hydrogenolysis afforded **203**, which underwent benzylic oxydation with PCC-Celite to provide the ketone derivative **204**.



Scheme 42.

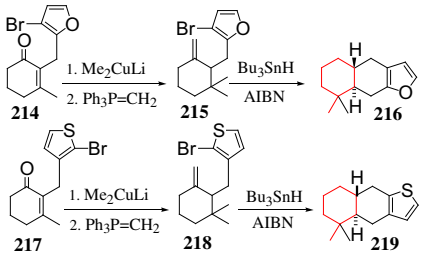
The regioisomeric cyclohexenone derivatives **205** and **210** were exploited as intermediates towards the total synthesis of some furosesquiterpenes and their analogues.[77] Thus, $BF_3 \cdot Et_2O$-promoted conjugate addition of Gilman's reagent to **205** produced the saturated cyclohexanone **206**, which on treatment with MeLi furnished the required tertiary alcohol for the acid-catalyzed cyclization which afforded a 3:2 mixture of isopallescensin-A **207** and isopallescensin-1 **208** (Scheme 43). On the other hand, 1,2-dihydroisopallescensin-2 **209** was directly prepared by Wittig olefination of **206**. However, attempts to extend the methodology to the synthesis of natural pallescensins met some hurdles. In fact, conjugated Gilman reagent addition to the isomer **210** yielded directly the tricyclic product **211** (Scheme 43). Therefore, 10-desmethylpallescensin-A **212** could be



Scheme 43.

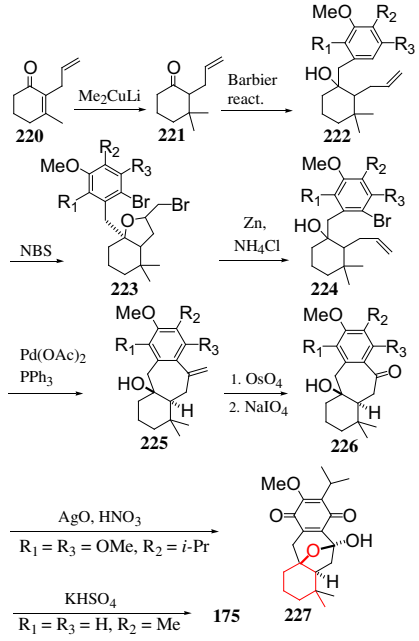
obtained under controlled catalytic hydrogenation. Moreover, the 1,2 methyllithium addition to **210** gave unexpected results, the only isolable product being 5-desmethyl-4,5-dehydromicrocionin-1 **213**.

A rapid access to a number of interesting natural and unnatural tricyclic frameworks entailed a 6-*endo*-*trig* selective radical cyclization of bromo heteroaryl alkenes prepared from **1**.[78] Thus, conjugate addition of Gilman's reagent followed by Wittig methylenation performed on cyclohexenones **214** and **217** afforded compounds **215** and **218**, respectively (Scheme 44). The corresponding radical species generated with *n*-Bu_3SnH and catalytic AIBN underwent intramolecular cyclization, giving rise to the linearly annulated tricyclic compounds **216** and **219** featuring a furan or a thiophene moiety fused to a *trans*-decalin core.



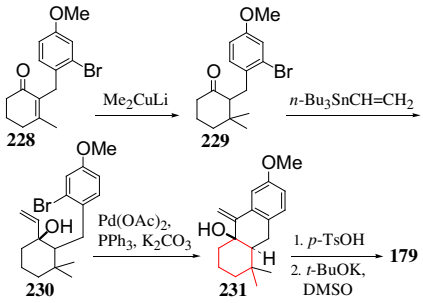
Scheme 44.

An intramolecular version of the Heck reaction was the crucial carbon–carbon bond-forming step of an efficient synthesis of rearranged abietane diterpenes featuring a functionalized 6,7,6-fused ring system.[79] Cyclohexenone **220** reacted with Gilman's reagent to give **221**, which, via Barbier reaction with the appropriate benzyl chloride, was transformed into **222** (Scheme 45). The subsequent aromatic bromination with concomitant bromoetherification led to the bromomethylfurans **223**. The restoration of the allyl group through a zinc-mediated debromination–fragmentation reaction produced **224**, which was converted via Heck cyclization into the tricyclic derivatives **225**. The oxidative cleavage of the *exo*-olefin yielded the *trans*-hydroxy ketones **226**, which were precursors of komaroviquinone **227** and faveline methyl ether **175**.



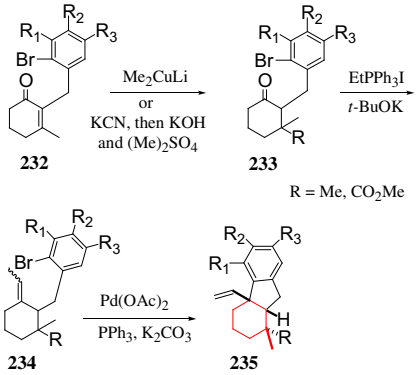
Scheme 45.

An intramolecular Heck reaction was also the featuring step of a recent synthetic approach to the already mentioned anthracene derivative **179**, a key intermediate along the synthesis of umbrosone **181**.[80] Addition of tri-*n*-butylvinyltin to the cyclohexanone **229**, in turn prepared from **228** through the usual Gilman reagent addition, afforded **230**, the required substrate for the pivotal Heck annulation (Scheme 46), which proceeded exclusively in the 6-*exo* mode, affording the tricyclic alcohol **231**. The latter was eventually taken to the key intermediate **179** through acid-promoted dehydration followed by base-induced aromatization.



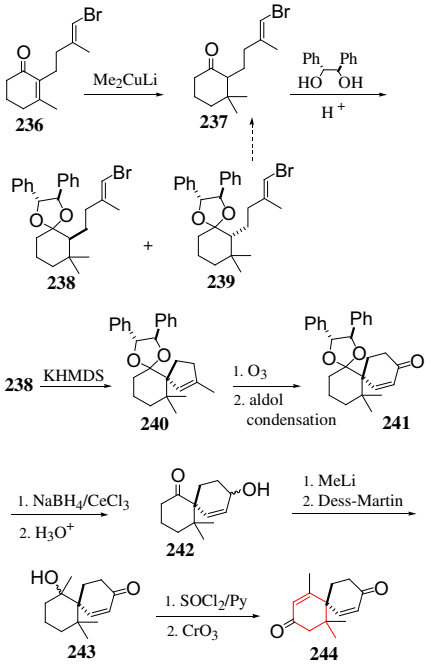
Scheme 46.

In contrast with **230**, a Heck reaction on **234** proceeded through a 5-*exo* cyclization, producing the angularly vinyl-substituted tricyclic systems **235**, which served as models towards gibberellins.[81] Once more, Gilman's reagent or cyanide conjugate addition to cyclohexenones **232** was the initial step (Scheme 47). Hydrolysis and esterification with dimethyl sulfate served to transform the nitrile into a methoxycarbonyl group. Wittig reaction of the resulting cyclohexanones **233** gave the corresponding olefins **234**, eventually submitted to Heck cyclization.



Scheme 47.

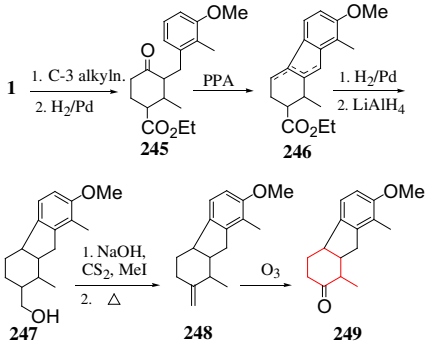
The primary challenge along the synthetic plan towards the total synthesis of (+)-majuscolone **244** was the construction of the spiro-fused six-membered ring at the C-3 carbon atom of **1**.[82] Thus, the trisubstituted cyclohexanone **237**, prepared in the usual way from **236**, was ketalized with (*R*,*R*)-(+)-hydrobenzoin (Scheme 48). The resulting diastereomeric ketals **238** and **239** (1:1 mixture) were separated through a combination of chromatographic and fractional-crystallization techniques. The undesired **239** was recycled, while its stereoisomer **238** entered the synthesis. The alkylidene carbene generated from its vinyl bromide with an excess of KHMDS underwent an intramolecular stereocontrolled insertion reaction on to the congested methine to afford the spiro derivative **240**. Ring enlargement through ozonolysis followed by aldol condensation led to the formation of the spirocyclohexenone **241**, which by chemoselective carbonyl reduction and removal of the ketal group furnished **242**. Generation of the tertiary alcohol and Dess–Martin oxidation of the secondary alcohol gave **243**, which was eventually taken to the natural target **244** by dehydration and allylic oxidation.



Scheme 48.

4.2. Ozonolysis

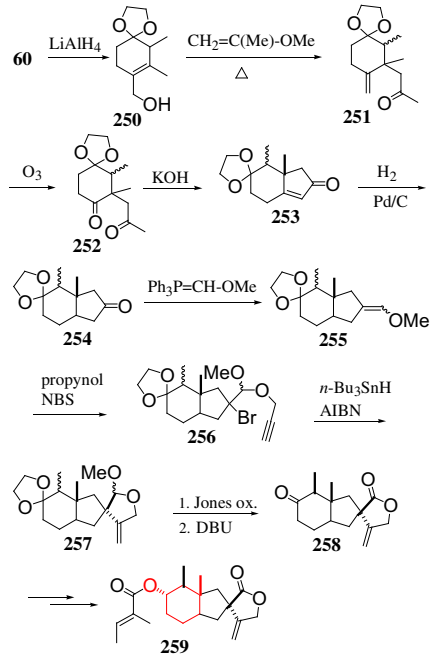
The preparation of **249**, which could be readily converted into a degradation product of jervine, has been achieved exploiting the successful acid-promoted cyclization of cyclohexanone **245**, in turn derived from **1** by regioselective C-3 alkylation and double-bond saturation.[83] The fluorene derivative **246** was transformed into **247** by hydrogenation and $LiAlH_4$ reduction of the carbethoxy functionality (Scheme 49). Dehydration of the primary alcohol by pyrolysis of the derived xanthogenate yielded the crystalline olefin **248** that was oxidized with ozone to the targeted tricyclic ketone **249**.



Scheme 49.

The synthesis of homogynolide-B **259**, a member of an interesting class of cytotoxic tricyclic sesquiterpenes, has been successfully accomplished selecting **60** as a convenient starting material (Scheme 50). Its conversion into the allylic alcohol **250** by $LiAlH_4$ reduction followed by reaction with 2-methoxypropene gave the Claisen-rearranged product **251**. The latter, submitted to ozonolysis, gave the diketone **252** as a chromatographically separable 3:2 mixture of epimers, both of which were usable to continue the

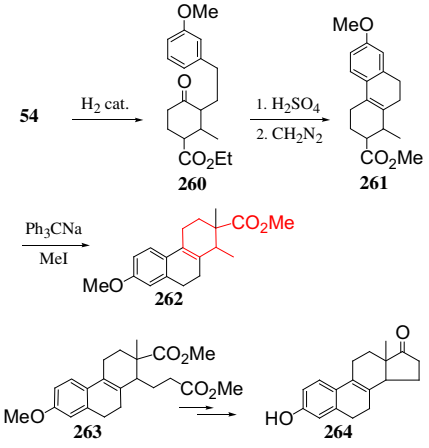
synthesis. Thus, intramolecular aldol condensation to **253** was followed by catalytic hydrogenation to the ketoketal **254**. Construction of the unusual α-spiro-β-methylene-γ-butyrolactone moiety led to the development of an efficient and general methodology featuring an intriguing radical cyclization as the key step.[84–86] In detail, compound **255**, in turn derived from **254** following Wittig reaction, underwent bromoacetalyzation with NBS and propargyl alcohol to give the bromo acetal **256**. The subsequent 5-*exo*-dig-radical cyclization triggered by *n*-Bu_3SnH gave the spiroacetal **257**, which by a one-pot hydrolysis–oxidation process followed by DBU-promoted epimerization furnished the ketospirolactone **258**, already taken to homogynolide-B **259** by Greene et al.[87]



Scheme 50.

5. Ester preservation

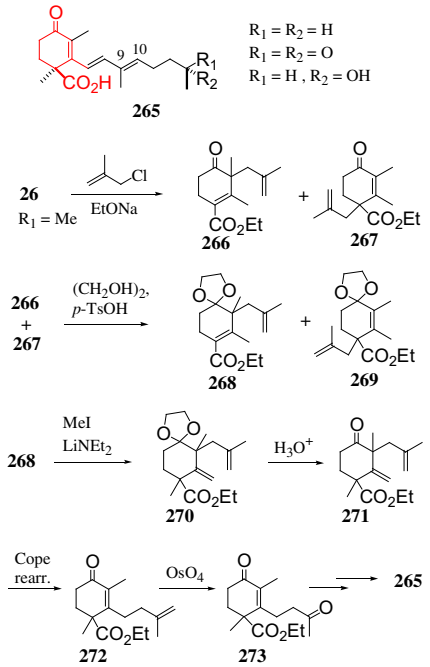
As already pointed out, a number of strategies towards the synthesis of the steroid framework starting from **1** are reported in the literature.[88] Thus, the cyclohexanone **260** obtained by hydrogenation of the already described C-3 alkylated derivative **54** on treatment with concentrated sulfuric acid followed by methyl esterification with diazomethane produced **261** featuring the tricyclic ABC-ring system of steroids (Scheme 51). Subsequent introduction



Scheme 51.

of a methyl group α to the methoxycarbonyl group using MeI-triphenylmethylsodium gave compound **262**. This scheme could be considered potentially useful for a synthetic approach to oestrone **264** using the tricyclic compound **263** with a suitably placed propanoic side chain for the construction of the D-ring.[89]

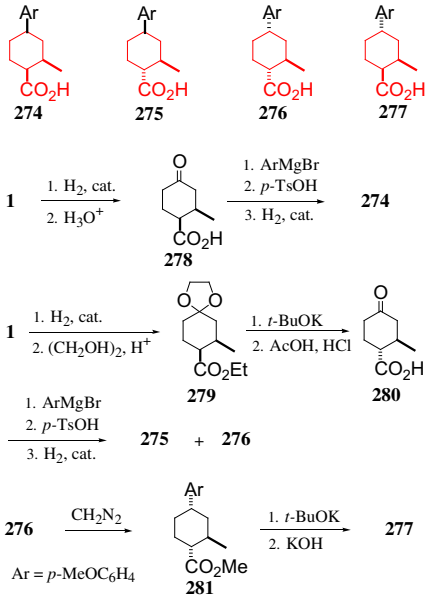
The diketo ester **273** has been envisaged as a very interesting intermediate for the construction of the skeleton of a family of naturally occurring fungal hormones known as trisporic acids **265**.[39] To put into practice the planned synthetic route, a detailed study of the sequential alkylation of **1** was undertaken, in order to find the experimental conditions for the preparation of **272**, a trialkylated Hagemann's ester derivative having the appropriate substitution pattern for conversion into **273**. The synthetic plan entailed the introduction, at the C-3 carbon of **1**, of both the methyl and methallyl groups, the translocation of the latter at C-2 being subsequently achieved via a Cope rearrangement (Scheme 52). Consequently, **26** was treated with methallyl chloride and sodium ethoxide to produce a mixture of **266** and **267**, which could be separated through conversion into the corresponding ketals **268** and **269**. The latter was hydrolyzed very rapidly in water, thus allowing a facile removal of **268** by distillation. Methylation of **268** and restoration of the carbonyl group in the derived **270** led to the formation of **271** featuring a 1,5-diene system. At this point, the stage was set to accomplish the Cope reaction, producing **272**. Selective double-bond oxidative cleavage furnished the diketo ester **273**, a versatile intermediate for the elaboration of the trisporic acid skeleton **265**.



Scheme 52.

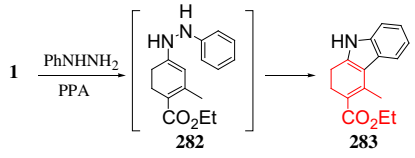
Compound **1** was the starting material for the preparation of **274**–**277**, the four possible diastereomeric racemates of 4-aryl-2-methylcyclohexanecarboxylic acids required for a structure–activity relationship study of potential antifertility agents.[90] Catalytic reduction of **1** gave essentially one isomeric ester, which was hydrolyzed without epimerization to the keto acid **278** (Scheme 53). Treatment of **278** with two equivalents of *p*-methoxyphenylmagnesium bromide followed by *p*-TsOH-promoted dehydration and catalytic reduction produced the all-*cis* isomer **274**. On the other hand, the two saturated 1,2-*trans* isomers **275** and **276** were obtained from the 1,2-*trans* keto acid **280**, in turn prepared through

epimerization and hydrolysis of the ketal **279**. Moreover, base equilibration of **281** gave the remaining diastereoisomer **277**. Fortunately, unsuccessful attempts to resolve the four racemates with chiral non-racemic alcohols and failure of the alternative enantioselective approach entailing the use of the optically active keto acid **278** were overcome by commercial facilities, which provided the authors with 10 g of (+)-**278** and 15.6 g of (−)-**278** from 260 g of (±)-**278**![91]



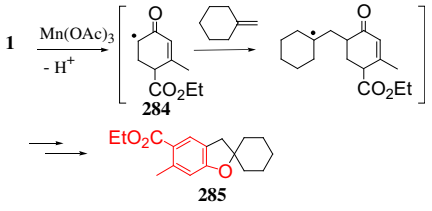
Scheme 53.

The synthesis of the interesting dihydrocarbazole **283**,[92] a ring system widely occurring in bioactive natural substances, has been accomplished via Fischer indolization of **1** with phenylhydrazine (Scheme 54). The regioselectivity observed in the heterocyclization was considered to be a consequence of the conjugation with the ester group in the crucial intermediate **282**.



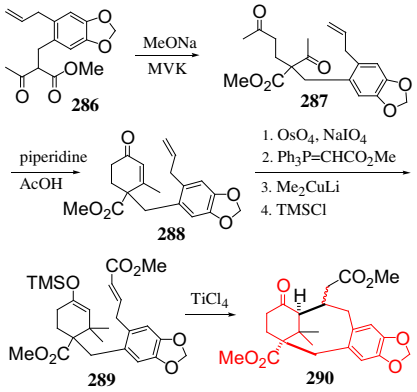
Scheme 54.

Oxidation of **1** by the action of dried $Mn(OAc)_3$ in benzene at 80 °C produced the related α′-keto radical **284**. Its one-pot reaction with methylenecyclohexane afforded via heterocyclization–aromatization a 25% yield of the dihydrobenzofuran **285** containing the griseofulvin skeleton (Scheme 55).[93]



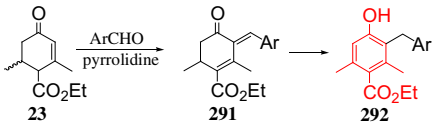
Scheme 55.

As already pointed out, C-1 alkyl substituted Hagemann's esters could be efficiently prepared according to Mannich and Fourneau's approach by regioselective Robinson annulation of substituted 1,5-diketones, in turn easily accessible through Michael addition of 2-alkyl acetoacetates to methyl vinyl ketone (MVK). Thus, efforts devoted to the construction of the eight-membered ring of taxanes led to the synthesis of the intermediate **289**, a suitable substrate for an intramolecular conjugate addition.[94] To this end, compound **286**, resulting from the alkylation of methyl acetoacetate with bromomethyl safrole, reacted with MVK to give the 1,5-diketone **287**, which was cyclized to **288** by the action of piperidinium acetate (Scheme 56). A series of steps including chemoselective oxidation of the methylene group, Wittig olefination of the resulting aldehyde, and Me_2CuLi conjugate addition with trapping of the enolate with TMSCl provided eventually the pivotal silyl enol ether **289**, which underwent a Mukaiyama-type cyclization to the expected tricyclic substrate **290**, related to the taxane core.



Scheme 56.

The reaction of the C-6 methyl Hagemann's derivative **23** with equimolecular quantities of aromatic aldehydes in DMF at room temperature in the presence of pyrrolidine as the catalyst proceeded in a highly regioselective manner, producing the Claisen–Schmidt condensation products **291** and/or the tandem Claisen–Schmidt/*iso*-aromatization products **292** (Scheme 57). This experimentally simple and environmentally friendly approach was used to construct highly substituted enones and phenols.[95]



Scheme 57.

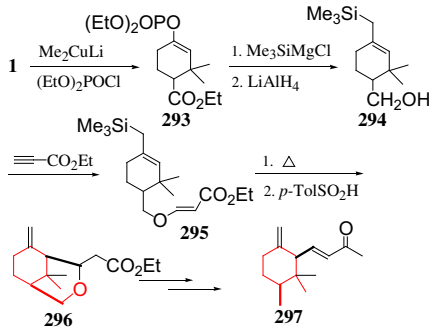
6. Ester elaboration

The elaboration of the ester group is an important operation in Hagemann's ester chemistry. A sub-classification of this section has been used, depending on whether the ester group has been fully or partially reduced. In the latter case, lengthening of the carbon chain and its use to construct different ring-fused systems will be described.

6.1. Reduction to methyl group

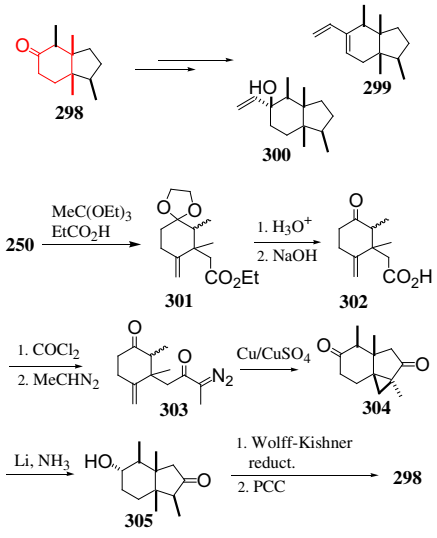
An intramolecular thermal H-ene reaction of an allylsilane prepared from **1** was the key step for the production of a useful intermediate for the diastereoselective synthesis of racemic *cis*-γ-irone **297**.[96] Thus, 1,4-addition of Gilman's reagent to **1** followed by quenching with chlorodiethyl phosphate gave the diethyl enol phosphate **293** (Scheme 58). The nickel(II)-catalyzed coupling reaction with trimethylsilylmagnesium chloride followed by $LiAlH_4$ reduction gave the allylsilane **294**, which by conjugate addition to

methyl propiolate furnished the (*E*)-β-alkoxyacrylate **295**. Heating at 250 °C for 96 h of a solution of this compound in decalin and subsequent desilylation with *p*-toluenesulfinic acid produced the 3-oxabicyclo[3.3.1]nonane derivative **296**, already transformed into the natural compound **297**.



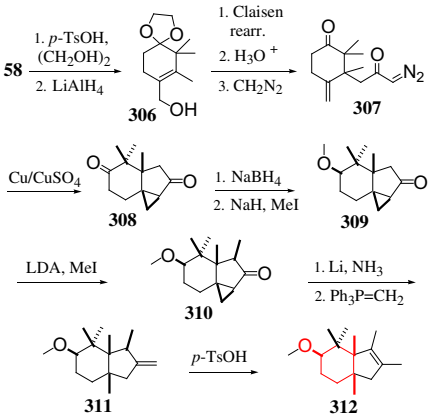
Scheme 58.

A *cis*-fused 1,2,6,7-tetramethylbicyclo[4.3.0]nonane system incorporating the interesting structural features of two vicinal quaternary carbon atoms and four contiguous carbon atoms oriented in an all-*cis* manner has made pinguisanes attractive and challenging synthetic targets. The synthesis of **298**, a key intermediate in Schinzer's approach[97] to α-pinguisene **299** and pinguisenol **300**, has been designed starting from the already described **250** through a route featuring a Claisen rearrangement and an intramolecular diazo ketone cyclopropanation reaction as the key steps.[98] Thus, an *ortho* ester Claisen rearrangement of the allyl alcohol **250** led to **301** incorporating a first quaternary carbon atom (Scheme 59). Hydrolysis of the ketal and ester moieties afforded the keto acid **302** precursor of the diazo ketone **303**, which upon copper-catalyzed decomposition underwent an intramolecular cyclopropanation to **304**. Controlled reaction with lithium in liquid ammonia effected both the regioselective carbonyl reduction and cyclopropane ring cleavage to yield **305**, incorporating the two vicinal quaternary carbon atoms. The final transformation into Schinzer's ketone **298** has been performed via a modified Wolff–Kishner reduction and oxidation protocol.



Scheme 59.

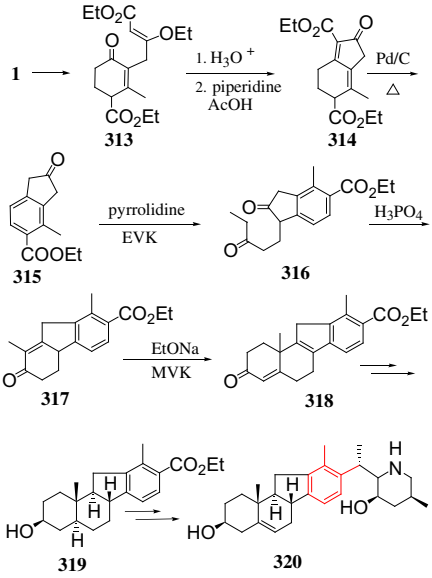
The same authors[99] described the synthesis of racemic 3-methoxythaps-8-ene **312**, starting from the γ,γ-dimethyl Hagemann's ester **58**, in turn obtained by regioselective dialkylation of the sodium dienolate of **1** with methyl iodide at −100 °C (Scheme 60). Subsequent ketalization and $LiAlH_4$ reduction gave the allylic alcohol **306**, which, subjected to Johnson's *ortho* ester Claisen rearrangement and the usual carboxylic group manipulation, afforded the diazo ketone **307** featuring two contiguous quaternary carbon atoms. Intramolecular cyclopropanation furnished the tricyclic dione **308**, which upon regio- and stereoselective reduction with one equivalent of $NaBH_4$ followed by methyl etherification gave **309**. Alkylation of **309** with LDA and MeI furnished the methylated ketone **310** in a highly stereoselective manner. Regioselective cyclopropane ring cleavage with lithium in liquid ammonia followed by Wittig methylenation gave compound **311**. The exocyclic double bond has been eventually isomerized by treatment with a catalytic amount of *p*-TsOH to furnish 3-methoxythaps-8-ene **312**.



Scheme 60.

6.2. Elongation

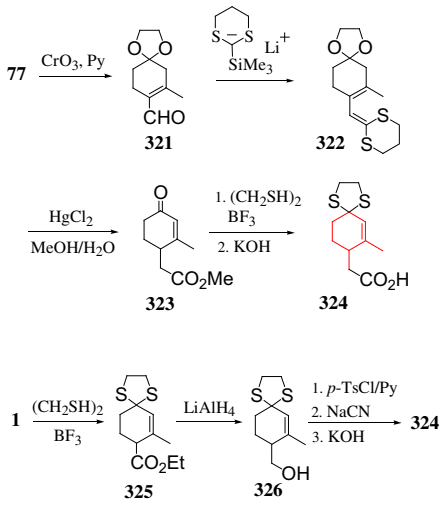
Alkylation of **1** with ethyl β-ethoxy-γ-bromocrotonate in the presence of potassium *tert*-butoxide produced **313**. Hydrolysis with aqueous hydrochloric acid in ethanol and cyclization of the resulting β-keto ester with piperidine and acetic acid yielded the bicyclic compound **314** (Scheme 61). A one-pot aromatization and decarbethoxylation produced **315**, which underwent regioselective addition of ethyl vinyl ketone (EVK) to furnish the diketone **316**. The latter was smoothly cyclized by acid treatment to the tricyclic



Scheme 61.

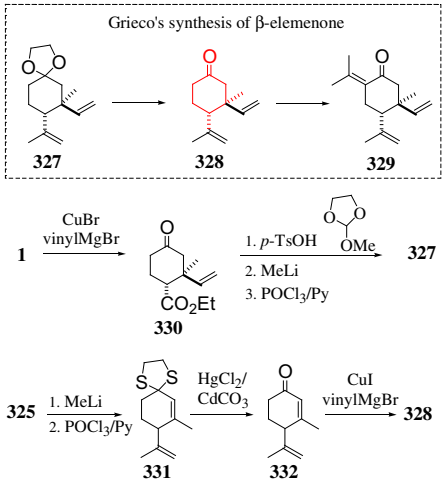
ketone **317**, which took part in a second Robinson annelation with MVK, producing the tetracyclic keto ester **318**. This intermediate represented a precursor of the 17-acetyl-5α-etiojerva-12,14,16-trien-3β-ol **319**, already transformed to veratramine **320** through carbon chain elongation of the original ester group of the starting material **1**.[100]

Two synthetic routes towards **324**, a useful intermediate for the synthesis of suitable polyenes for biomimetic cationic cyclization, have been described in the literature.[101] The first began with the controlled oxidation of the primary alcohol **77** to the corresponding aldehyde **321** (Scheme 62). The formyl group allowed the one-carbon homologation through addition of the anion of 2-trimethylsilyl-1,3-dithiane followed by $HgCl_2$-assisted methanolysis of the resulting ketene-*S*,*S*-acetal **322** proceeding with concomitant dioxolane removal. The derived compound **323**, a homologue of **1**, was transformed into the desired acid by carbonyl protection and saponification. A more convenient approach entailed the use of Hagemann's ester thioacetal **325** (Scheme 62), which was converted by $LiAlH_4$ reduction into the primary alcohol **326**, eventually subjected to one-carbon homologation to **324** by cyanide displacement of the corresponding tosylate and saponification.



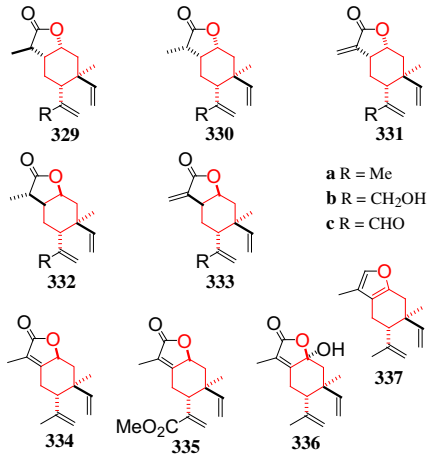
Scheme 62.

Two independent formal syntheses of the sesquiterpene, β-elemenone **329**, claiming to improve the previous Grieco's[102] approach appeared almost contemporaneously in the literature.[103,104] Both syntheses are based on the stereoselective vinylcuprate conjugate addition to 3,4-disubstituted cyclohexenones and share the method of deriving the isopropenyl group from the original ethoxycarbonyl group through the addition of methyllithium followed by dehydration with a phosphoryl chloride–pyridine system (Scheme 63). Thus, cuprous-catalyzed vinylmagnesium bromide addition to **1** gave a 71% yield of cyclohexanone **330**, eventually taken to Grieco's intermediate **327** by ketalization and isopropenyl assemblage. In the alternative approach, compound **325** was transformed into **331**, which, by carbonyl deprotection, furnished the cyclohexenone **332**. The latter, however, was shown to be a capricious substrate for the vinylcuprate conjugate addition, the known intermediate **328** being formed in only 20–30% yield.



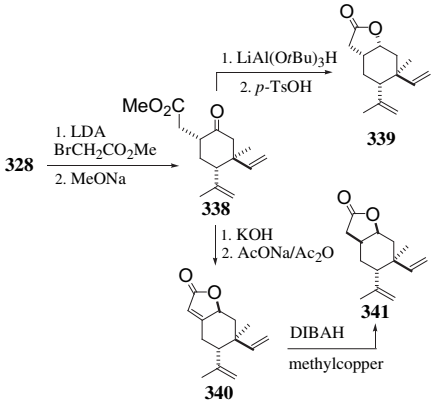
Scheme 63.

The divinylcyclohexanone **328** has been utilized as a suitable starting material for a synthetic approach to several 12.8-*cis*-elemanolides, a class of cytotoxic sesquiterpene lactones found in the plant family of *Compositae* (Scheme 64).[105]



Scheme 64.

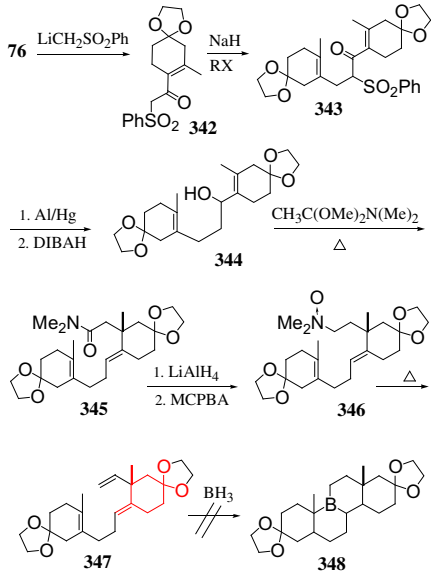
The alkylation of **328** with methyl bromoacetate followed by basic epimerization furnished the thermodynamically stable keto ester **338**, which served to prepare both the bis-epimeric nor-lactones **339** and **341** (Scheme 65). In detail, stereoselective carbonyl reduction of **338** followed by heating of the resulting hydroxy ester with *p*-TsOH afforded **339**, while the preparation of **341** required chemo- and stereoselective reduction of the butenolide **340**, in turn derived from **338** by a saponification–lactonization sequence. Hydride conjugate addition to **340** performed with DIBAH in the presence of methylcopper gave **341**. The subsequent stereocontrolled α-methylation of **339** and **341** furnished the dihydrolactones **329**, **330** and **332**, respectively. The preparation of the corresponding *exo*-methylene derivatives **331** and **333** was achieved via selenoxide *syn* elimination,



Scheme 65.

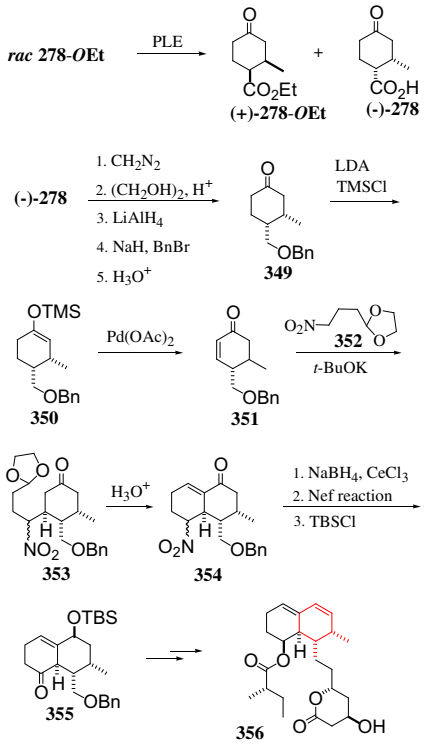
while the regiospecific allylic oxidation of **329**–**333** with *t*-BuOOH/SeO_2 led to the corresponding oxygenated naturally occurring elemanolides. Moreover, the butenolides **334**–**336** as well as the furan **337** have also been obtained starting from **338**.

The diketal triene intermediate **347** was designed with the aim of investigating the hypothesis of obtaining carbocycles via a boron annulation–carbonylation–oxidation sequence.[106] The enone sulfone **342**, in turn derived by reaction of the protected ester **76** with the anion of methyl phenyl sulfone, was transformed into **343** by the introduction of a suitable carbon framework by alkylation (Scheme 66). Desulfonylation and carbonyl reduction gave the allylic alcohol **344**, a substrate for a Claisen rearrangement leading to **345**. The third monosubstituted double bond in **347** was established through $LiAlH_4$ reduction of the amide **345**, followed by oxidation to **346** and thermal-induced elimination. However, all attempts to prepare the targeted boracyclane **348** failed, probably because of the sluggish addition of boron hydrides to tetrasubstituted olefins.



Scheme 66.

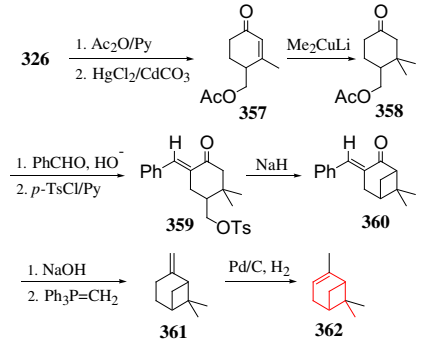
Difficulties encountered in the resolution of the racemic compound **278**[91] suggested the exploration of a different route for the construction of the hexahydronaphthalene nucleus of natural compactin **356** (Scheme 67). Thus, a suitable chiral non-racemic and properly functionalized cyclohexenone has been conveniently prepared, starting from **1**, through pig liver esterase (PLE)-catalyzed hydrolysis of the racemic ester ***rac* 278-*O*Et**.[7] The resolved acid (−)-**278** was transformed into the saturated cyclohexanone **349** through a sequence entailing temporary ketal protection to allow chemoselective reduction and benzyl etherification of the resulting primary alcohol. The next steps were devoted to setting up the conjugated enone system of **351** required for the projected annulation. Thus, a crucial step was the Pd(II)-catalyzed dehydrosilylation of **350**, in turn obtained by regioselective silyl enol-etherification of **349**. Interestingly, a rather unusual four-carbon bifunctional annulating reagent, namely 2-(3-nitropropyl)-1,3-dioxolane **352**, was utilized for the construction of the six-membered ring fused with the original **1**. Thus, the reaction of **351** with **352** in the presence of *t*-BuOK led to the Michael adduct **353**, which by hydrolysis and intramolecular aldol condensation furnished the annulated compound **354**. Its elaboration to an advanced precursor already taken to the natural target **356** entailed manifold chemical steps, among which was a Nef reaction to convert the nitro group into a carbonyl moiety, as in **355**.



Scheme 67.

6.3. Elongation-ring incorporation

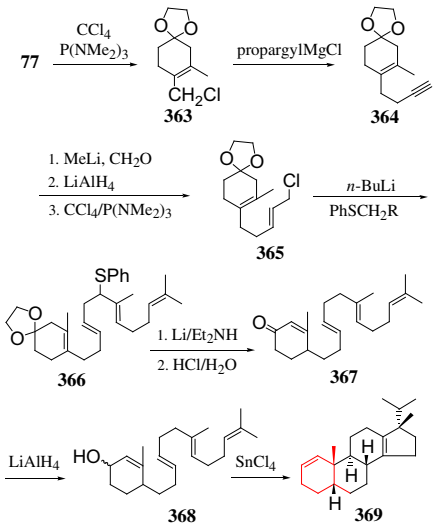
A regioselective intramolecular alkylation reaction into a substituted cyclohexanone was envisaged as the key step for the development of a general route to the bicyclo[3.1.1]heptane nucleus suitable for monoterpene hydrocarbon synthesis.[107,108] Thus, acetylation of the primary alcohol **326** followed by removal of the thioketal protective group allowed the cyclohexenone **357**, a convenient precursor of **358** (Scheme 68), to be obtained. Regioselective condensation of the latter with benzaldehyde followed by tosylation of the deprotected primary hydroxyl group afforded the crystalline monobenzylidene derivative **359**, which underwent a smooth intramolecular alkylation by treatment with sodium hydride in refluxing 1,2-dimethoxyethane to give the benzylidene nopinone **360**. Removal of the benzylidene function and Wittig methylenation produced (±)-β-pinene **361**, which could be quantitatively converted into (±)-α-pinene **362** by treatment with 5% Pd/C saturated with hydrogen.



Scheme 68.

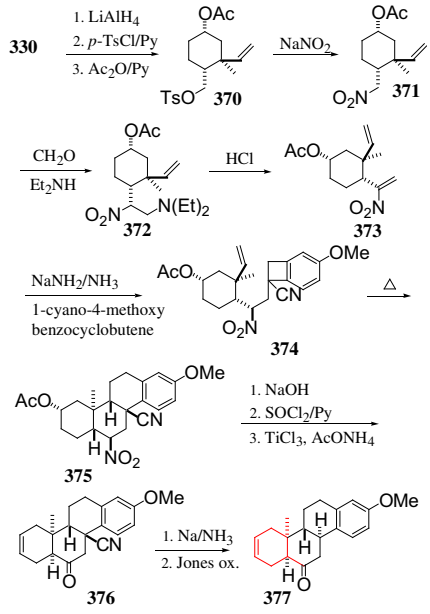
Johnson's approach to the synthesis of the tetraenol **368**, a useful substrate for the acid-catalyzed cyclization, began with the three-carbon elongation of the allyl alcohol **77** to produce **364** via

the corresponding chloride **363** (Scheme 69). Well-established protocols allowed the formation of the allyl chloride **365**, which was coupled with the anion of the appropriate thioether to produce **366**. Reductive removal of the phenyl thioether and restoration of the cyclohexenone moiety led to the formation of **367**, which underwent 1,2-reduction to the desired allylic alcohol **368**. Treatment of the latter with either stannic chloride or trifluoroacetic acid gave the expected polycyclization, yielding the steroidal tetracycle **369** through a series of trans antiplanar hydrogen and methyl shifts and a final trans elimination of a proton.[109]



Scheme 69.

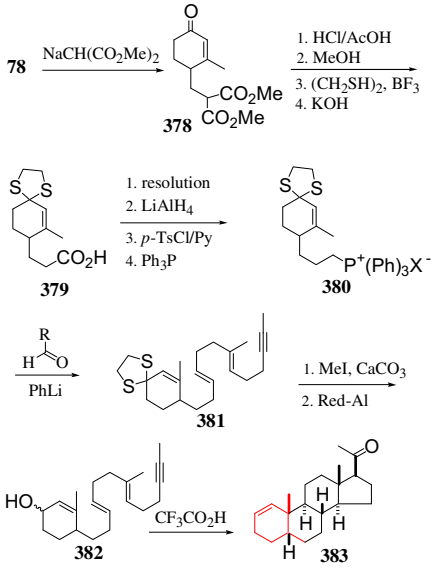
An intramolecular cycloaddition of a thermally generated *o*-quinodimethane was envisaged as the key step on the route to the D-ring aromatic steroid **377**, an intermediate for the synthesis of insect-molting hormones.[110,111] The pivotal benzocyclobutene derivative **374** was prepared in a convergent way by joining two half moieties through a Michael addition reaction (Scheme 70). Thus, the acceptor olefin **373** was derived from the already described cyclohexanone **330** by $LiAlH_4$ reduction followed by tosylation of the primary alcoholic group and acetylation of the secondary alcohol.



Scheme 70.

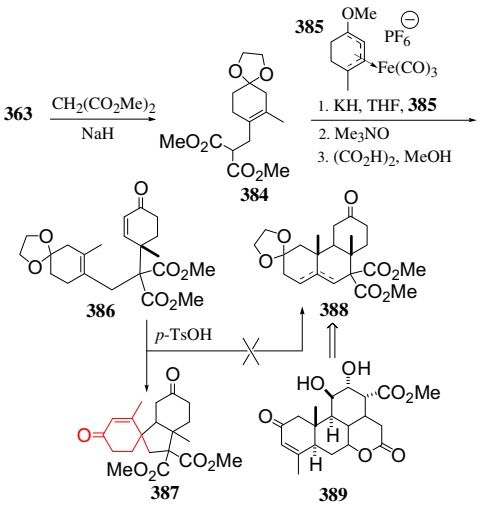
A tosyl displacement reaction of the derived compound **370** with nitrite ion gave **371**, which was taken to the nitro-olefin **373** via the Mannich base **372**. Michael addition of 1-cyano-4-methoxybenzocyclobutene in the presence of sodium amide in liquid ammonia yielded the key intermediate **374**, which was thermolyzed to the D-ring aromatic steroidal compound **375**, and subsequently converted to **376** in a few steps including hydrolysis of the acetate ester, dehydration to the olefinic nitro compound and Nef reaction with titanium trichloride in the presence of ammonium acetate. The targeted aromatic steroid **377** was eventually obtained through reductive decyanation of **376** with sodium in liquid ammonia followed by a Jones oxidation.

A stereoselective Wittig–Schlosser condensation of the appropriate aldehyde with the phosphonium salt **380** was envisaged as the key step of a convergent synthetic approach to the trienynol **382,** a suitable substrate to test the biomimetic polyene cyclization strategy as a tool to achieve steroid nuclei.[112] The preparation of compound **380** commenced with the 1,6-Michael addition of malonic acid dimethyl ester to the dienone **78** (Scheme 71). The resulting adduct **378** gave the racemic acid **379** by sequential dealkoxycarbonylation and thioketalization. Its resolution, efficiently performed with D-α-methylbenzylamine, allowed the preparation of both enantiomers of the phosphonium salt **380** through standard chemical steps. The subsequent Wittig reaction afforded the *trans*,-*trans*-trienyne thioketal **381**. Its deketalization, performed with methyl iodide under buffered conditions to suppress racemization, followed by carbonyl reduction furnished the allylic alcohol **382**, which underwent a stereocontrolled acid-promoted polyene cyclization to the tetracycle **383**, a useful intermediate for the preparation of steroid analogues.



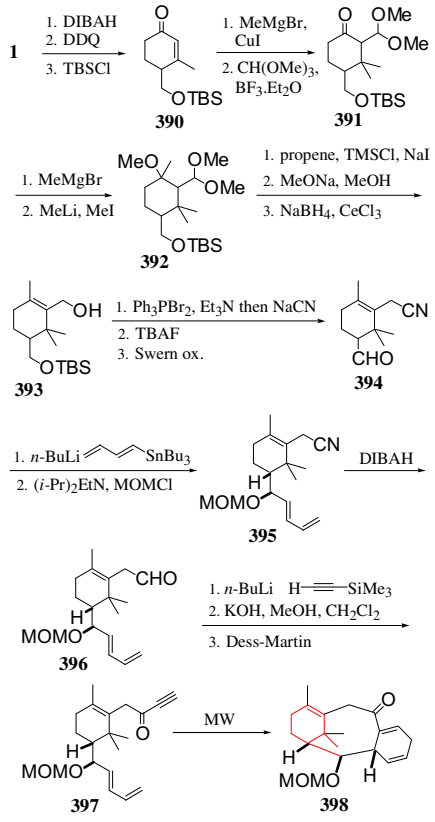
Scheme 71.

A projected approach to the synthesis of the polyoxygenated skeleton of klaineanone **389**, a member of the family of antitumour quassinoids, was centred on an intramolecular cyclization providing the tricyclic compound **388** as a useful intermediate.[113] Thus, alkylation of dimethyl malonate with the allyl chloride **363** gave **384**, which was submitted to alkylation with the iron tricarbonyl salt reagent **385**, followed by treatment with trimethylamine *N*-oxide to remove iron, and selective hydrolysis to demask the enone system. Unfortunately, treatment of the resulting **386** with *p*-TsOH led to the formation of the spirocyclic ketone **387**, instead of the desired tricyclic compound **388** (Scheme 72).



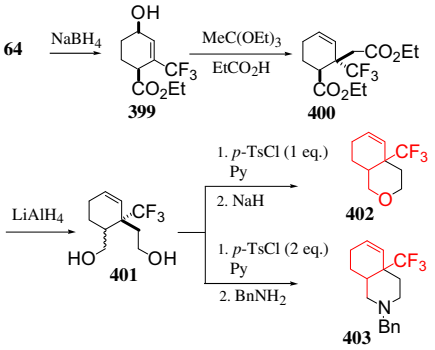
Scheme 72.

A highly convergent approach to the tricyclic intermediate **398**, having a suitably functionalized skeleton for the synthesis of Taxol®, relied on an intramolecular Diels–Alder cycloaddition reaction.[114] To this end, compound **397**, bearing the required diene and dienophile units attached to a preformed A-ring, in turn derived from **1**, was the synthetic goal (Scheme 73). The starting steps were the hydride reduction of **1** followed by allylic oxidation and protection of the primary alcoholic group to give **390**. The latter was converted into the keto-acetal **391** through conjugate addition of methylmagnesium bromide followed by BF_3-mediated reaction with methyl orthoformate. Methylmagnesium bromide addition to the carbonyl group produced the tertiary alcohol, which was etherified to **392**. Removal of the acetal protecting group, followed by a facile β-elimination of methoxide ion and reduction of the aldehyde, provided the allylic alcohol **393**, which was subjected to chain extension by cyanide displacement of the corresponding bromide. Deblocking of the silyl ether and Swern oxidation furnished the intermediate **394**, conveniently functionalized for the introduction of the diene moiety. Thus, nucleophilic addition of a suitable organometallic reagent followed by protection of the alcoholic group gave **395**, which was converted into **396** by DIBAH reduction of the nitrile functional group. A sequence involving addition of the acetylenic species, desilylation and Dess–Martin periodinane oxidation led to the formation of **397**, which eventually underwent stereoselective microwave-assisted thermal intramolecular cycloaddition to give **398**.



Scheme 73.

Hagemann's trifluoromethyl analogue **64** has been efficiently utilized for the preparation of angularly CF_3-substituted heterobicyclic compounds.[43,44] Thus, chemo- and diastereoselective reduction of **64** with $NaBH_4$ in EtOH at −30 °C gave smoothly the *cis* allylic alcohol **399**, which was subjected to a Johnson–Claisen rearrangement, providing the diester **400** (Scheme 74). Reduction with $LiAlH_4$ furnished the diol **401** that was the precursor of both tetrahydroisochromane **402** and the A/B *cis* octahydroisoquinoline **403**. Thus, the reaction of **401** with one equivalent of tosyl chloride in the presence of pyridine followed by the in situ addition of sodium hydride gave **402**, while ditosylation of **401** followed by reaction with benzylamine led to the formation of **403**.

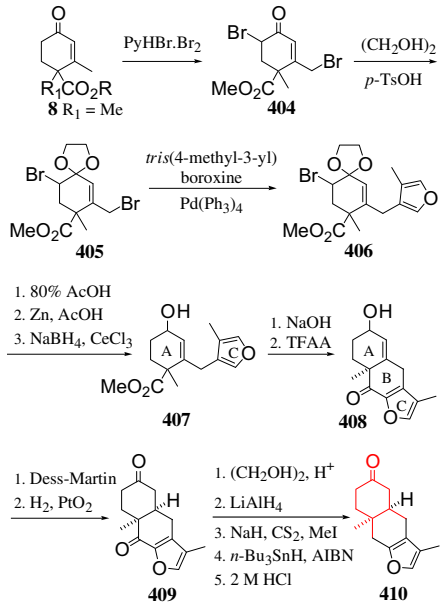


Scheme 74.

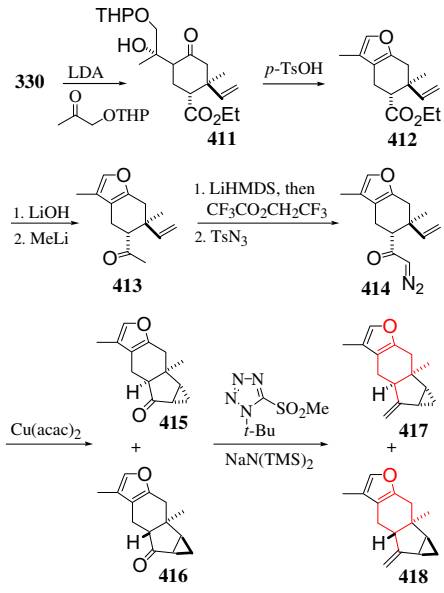
A synthetic approach to tricyclic sesquiterpenoid furanoeudesmanes has been successfully developed.[115] The key step involved the ring B closure on to the preformed A–C system **407**. Accordingly, the reaction of **8** with pyridinium bromide perbromide allowed the formation of compound **404**, subsequently ketalized to furnish **405**, which took part in a Suzuki coupling with *tris*(4-methyl-3-yl)boroxine to produce **406** (Scheme 75). Removal of both the acetal and the bromine residue followed by Luche reduction afforded **407**, which after saponification underwent the projected ring B construction by treatment with trifluoroacetic anhydride. The resulting **408** afforded the *cis*-decalin skeleton **409** by Dess–Martin periodinane oxidation and hydrogenation with Adam's catalyst. Selective protection of the ring-A carbonyl group allowed the removal of the carbonyl present in ring B through $LiAlH_4$ reduction/Barton–McCombie radical deoxygenation. Final restoration of the keto group furnished **410**, an advanced intermediate along the route to naturally occurring furanoeudesmanes.

The intramolecular cyclopropanation of the α-diazo ketone **414** was the key step of a synthetic approach to the furanosesquiterpenes, *epi*-lindenene **417** and *iso*-lindenene **418**.[116] Construction of the furan moiety of **412** entailed the reaction between THP-protected hydroxyacetone and **330** in the presence of LDA followed by treatment of the resulting aldol derivative **411** with *p*-TsOH (Scheme 76). Conversion of the ester group into the methyl ketone produced **413**, which furnished the α-diazo ketone **414** through a sequence involving kinetic deprotonation, trifluoroacetylation and reaction with tosyl azide. The subsequent metal-catalyzed

cyclopropanation led to the formation of the diastereomeric compounds **415** and **416**, eventually taken to the unnatural furanosesquiterpenes **417** and **418** by carbonyl methylenation using the modified Julia–Kocienski reaction.[117]



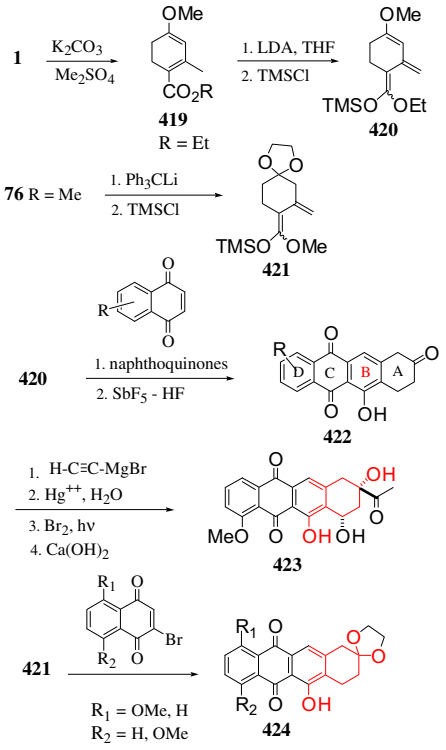
Scheme 75.



Scheme 76.

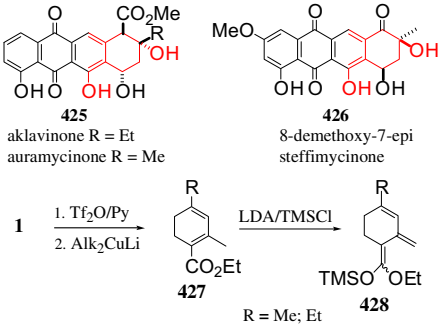
6.4. Construction of a diene system

Gesson[118] and Rapoport[119] reported almost simultaneously very similar synthetic approaches to anthracycline aglycones, featuring as the central step a Diels–Alder-type cycloaddition of naphthoquinones and silyl ketene acetals derived from **1**. Thus, the silyl ketene acetals **420** and **421** were, respectively, utilized as diene counterparts being suitably functionalized for the introduction of a carbonyl group into ring A of the resulting cycloadducts. In detail, enol etherification of **1** gave compound **419**, which afforded **420** by exocyclic deprotonation and quenching with trimethylsilyl chloride. On the other hand, treatment of the dioxolane derivative **76** (R=Me) with a threefold excess of Ph_3CLi followed by silyl enol-etherification furnished **421** (Scheme 77). The reaction of equimolar amounts of **420** and substituted naphthoquinones in anhydrous solvents at room temperature, followed by air oxidation and treatment with the superacid SbF_5–HF to cleave the ether groups, gave rise to the tetracyclic compounds **422**. The latter could be taken to 11-deoxy daunomycinone **423** through ring-A chemical manipulation including a difficult ethynylation, followed by hydration and final benzylic hydroxylation via bromination and basic treatment with $Ca(OH)_2$.[120] The 11-deoxyanthracyclinone precursors **424** could be prepared by a regiospecific cycloaddition reaction of **421** and regioisomeric bromojuglone methyl ethers (Scheme 77).



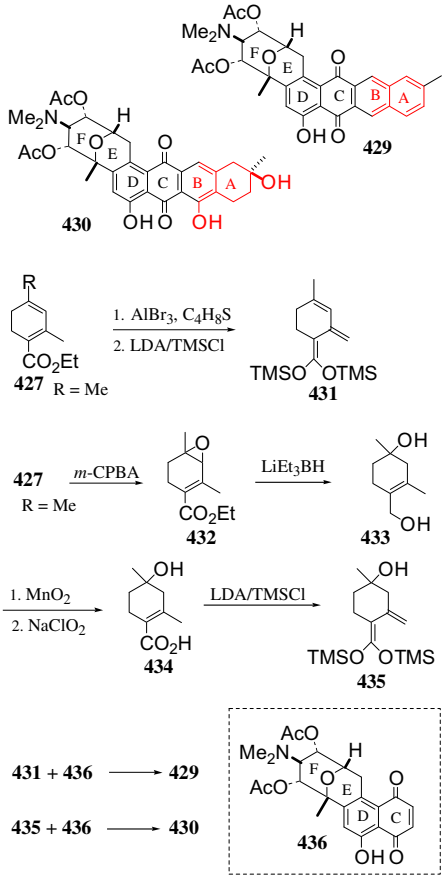
Scheme 77.

Similarly, the related aglycones **425** and **426** were prepared by reaction of the commercially available juglone with the vinyl ketenes **428** (Scheme 78). Their preparation required the introduction of a methyl or an ethyl group at the C-4 carbon of **1**. This operation has been accomplished by treatment of the corresponding enol triflate with the appropriate dialkylcopper lithium reagent, giving rise to **427**. Subsequent regiospecific deprotonation and quenching with trimethylsilyl chloride gave the pivotal dienes **428**. Manifold steps are then required for setting up the ring A of the antitumour antibiotics utilizing the derived tetracyclic adducts.[121,122]



Scheme 78.

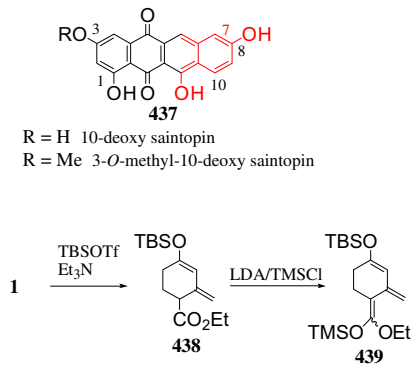
Accordingly, a synthetic approach to the 11-deoxyanthracyclinone skeleton of the nogalamycine congeners, nogarene **429** and 7-deoxynogarol **430**, has been described using bis(trimethylsilyloxy)dienes **431** or **435**, respectively, as the required partners of naphthoquinone **436** in the Diels–Alder reaction.[123] In detail, the preparation of **431** simply required O-dealkylation of **427** with aluminium bromide in tetrahydrothiophene followed by trapping with trimethylsilyl chloride of the dianion produced by treatment with LDA (Scheme 79). The preparation of **435** involved a selective double-bond epoxidation of **427** to **432** followed by regioselective reduction with Superhydride to give **433**. Stepwise oxidation of the primary alcohol gave **434**, eventually transformed to **435** upon treatment of the corresponding trianion with trimethylsilyl chloride. As expected, the regioselective Diels–Alder reaction of dienes **431** and **435**, respectively, with naphthoquinone **436** possessing the CDEF ring system, followed by concomitant air oxidation of the derived cycloadducts during mild acidic work-up, gave rise to the compounds **429** and **430**, featuring the ABCDEF ring system of the natural compounds.



Scheme 79.

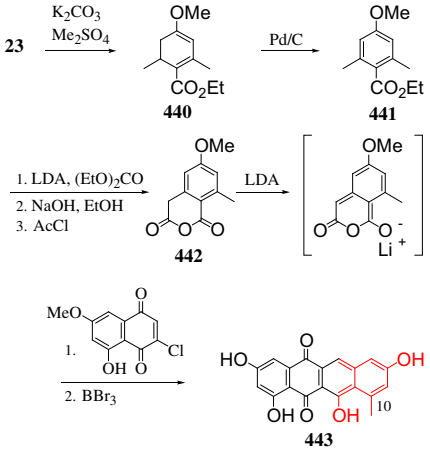
The Diels–Alder-type cycloaddition reaction of naphthoquinones and silyl ketene acetals derived from **1** has also been successfully employed in the preparation of fully aromatized naphthacenequinones **437**.[124] Accordingly, silyl enol-etherification of **1** gave the exocyclic dienes **438**, easily transformed into vinyl ketene acetals **439**. Their reaction with the dienophile quinones gave the corresponding cycloadducts, which underwent spontaneous or DDQ-promoted aromatization along the route to the natural cytotoxic naphthoquinones **437** (Scheme 80).

Alternatively, the oxidation step could be performed before the Diels–Alder-type cycloaddition reaction. Thus, tetracenomycin D **443** has been envisaged to result from the base-catalyzed



Scheme 80.

condensation of the appropriate naphthoquinone with the homophthalic anhydride **442** acting as the diene counterpart.[124] Thus, aromatization of the methyl enol ether **440** of the starting C-6 methyl Hagemann's ester derivative **23** gave **441**, which was converted into **442** through a three-step sequence including ethoxycarbonylation, saponification, and anydrification (Scheme 81). The diene system generated by deprotonation of **442** was trapped by the dienophile quinone and the derived cycloadduct eventually taken to tetracenomycin D **443** by demethylation.



Scheme 81.

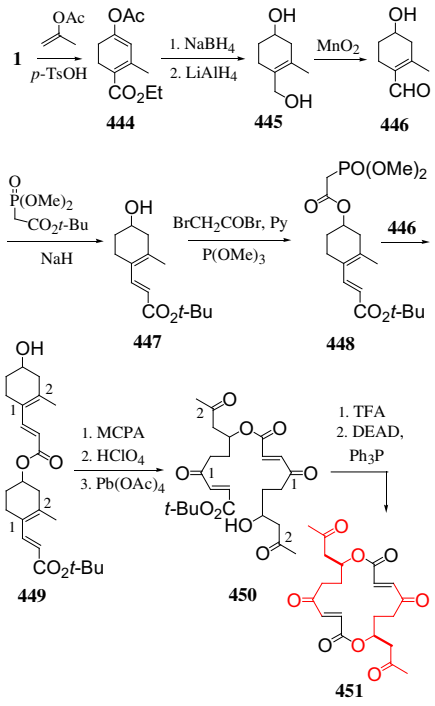
7. Ring opening

Linear chain compounds containing the structural elements required by a particular target could be conveniently obtained using the eight carbon atoms generated by ring opening of **1**. This operation could be accomplished in different ways, which have been collected in the following subsections. Thus, synthetic approaches based on oxidative deannulations are discussed in Subsections 7.1–7.3, while the ring opening of **1** as a consequence of a C_3–C_4 acylcarbene insertion-retro Claisen sequence is discussed in Subsection 7.4.

7.1. C_1–C_2 ring cleavage

Coupling of the two constituent halves has been a well-suited synthetic strategy towards the antibiotic, vermiculine **451**, featuring two identical C-10 hydroxy acid units lactonized in a head-to-tail fashion (Scheme 82). However, an alternative strategy has been proposed for the construction of a fully functionalized *seco*-hydroxy acid, which was lactonized in the final step via a Mitsunobu reaction.[125] Thus, the reaction of **1** with isopropenyl acetate

containing *p*-TsOH afforded the dienol acetate **444**, subsequently converted into the diol **445** through two consecutive reductive steps. Chemoselective oxidation of the primary alcohol afforded the hydroxycyclohexenecarbaldehyde **446**, which was converted by a Wittig reaction into **447**. Treatment of the latter with bromoacetyl bromide followed by reaction with trimethyl phosphite gave **448**, which took part in a Wittig reaction with **446**, furnishing **449**. The subsequent transformation into **450** required the oxidative opening of the two cyclohexene moieties through selective epoxidation with *m*-chloroperbenzoic acid followed by hydrolytic opening of the two epoxide functions with perchloric acid and oxidative cleavage with lead tetraacetate. Deprotection of the *t*-Bu ester with TFA furnished the corresponding *seco*-hydroxy acid, eventually taken to the lactone **451** via an intramolecular Mitsunobu reaction.

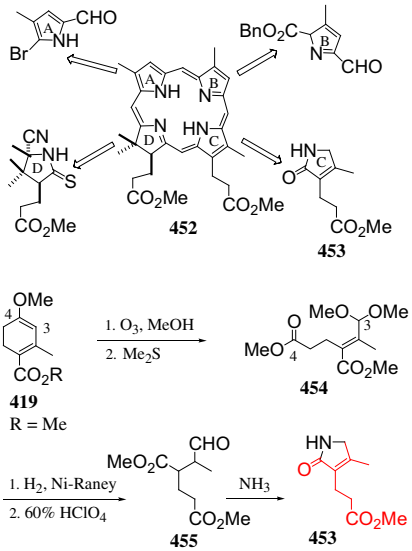


Scheme 82.

7.2. C_3–C_4 ring cleavage

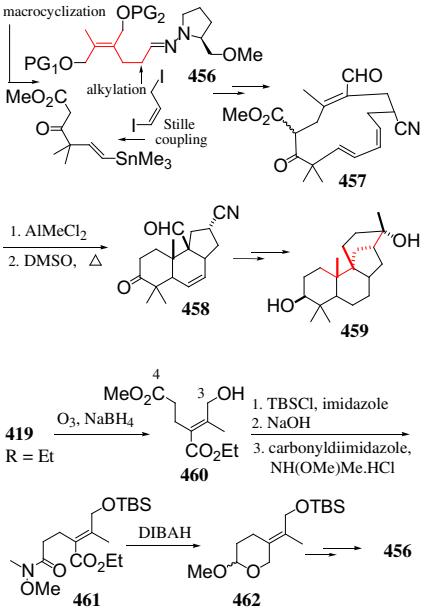
The synthesis of the marine natural substance, bonellin **452**, was envisaged by putting together four monocyclic building blocks and a malonate unit. The preparation of the ring-C dihydropyrrolone unit **453** has been successfully accomplished using **1** as the starting material.[126,127] Selective ozonolytic cleavage of the trisubstituted double bond of the methyl enol ether **419** and concomitant protection of the produced aldehyde function gave **454** (Scheme 83). Catalytic hydrogenation of the tetrasubstituted olefin followed by removal of the acetal group led to **455**, a convenient precursor of the five-membered heterocycle **453** easily obtained by reaction with methanolic ammonia.

The tricyclic core structure **458** of the diterpenoid, maritimol **459**, was stereoselectively obtained through a transannular Diels–Alder reaction (TADA strategy) of the 13-membered macrocycle **457** incorporating the eight-carbon fragment **456** in turn prepared from **1**.[128] A number of steps have been involved in the assemblage of the macrocycle **457** including diastereoselective alkylation of the SAMP hydrazone **456** with *cis*-1,3-diiodopropene, Stille coupling with a vinylstannane and intramolecular alkylation (Scheme 84). The preparation of **456** began with the reductive ozonolysis of the



Scheme 83.

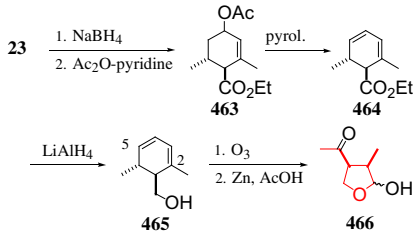
cyclohexadiene ring system of **419**. The resulting hydroxy diester **460** was protected as the silyl derivative, selectively hydrolyzed and converted into the Weinreb amide **461**. Reduction with DIBAH furnished the methoxytetrahydropyran **462**, which could be easily converted into the SAMP hydrazone **456**.



Scheme 84.

7.3. C_2–C_3 and C_5–C_6 ring cleavage

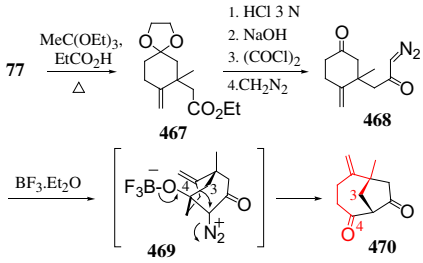
Reduction of **23** with $NaBH_4$ followed by acetylation provided the allylic acetate **463**. Pyrolytic elimination of acetic acid gave the cyclohexadiene **464** as the major product. Reduction with $LiAlH_4$ afforded the alcohol **465**, which by ozonolysis of both carbon–carbon double bonds produced the antibiotic, botryodiplodin **466** (Scheme 85). Assuming the relative configuration of **465** had been maintained in the ozonolytic step, the authors could ascertain a *cis* relationship of the non-anomeric centres in the natural substance.[129]



Scheme 85.

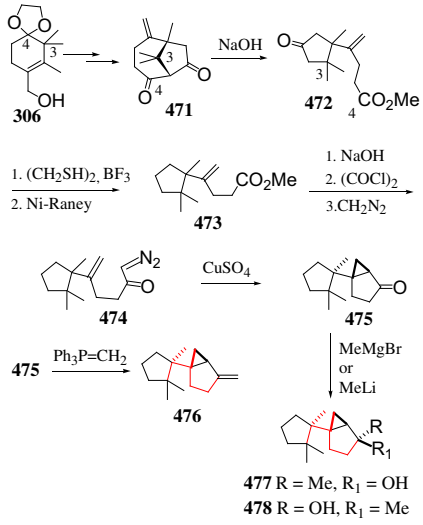
7.4. C_3–C_4 acylcarbene insertion-retro Claisen sequence

A $BF_3{\cdot}Et_2O$-mediated regioselective intramolecular diazo ketone insertion reaction occurring on a methylene cyclohexanone derivative prepared from **1** was the featuring step of an interesting approach to bicyclo[4.2.1]nonane, the key structural element of several natural products.[130] A Claisen rearrangement performed on the allylic alcohol **77** allowed the introduction of the acetic chain at the original C-2 carbon of **1** (Scheme 86). Removal of the dioxolane protecting group of **467** followed by the usual operations led to the key compound **468**, which furnished the bicyclo[4.2.1]nonane-2,8-dione **470** by treatment with BF_3 in a highly regioselective manner, presumably via transposition of the intermediate **469**. The ultimate effect was the selective insertion of the acylcarbene into the original C_3–C_4 bond of **1**. The easy formation of the chemically intriguing bicyclic 1,3-diketonic nucleus paved the way to the synthesis of several naturally occurring compounds.



Scheme 86.

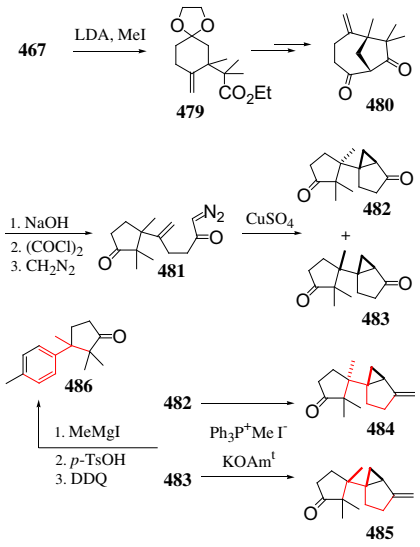
Thus, the first total synthesis of racemic β-microbiotene **476**, microbiotol **477** and cyclocuparenol **478** has been designed, starting from the allylic alcohol **306** in turn derived from **1**.[131] The chemical steps through which compound **77** had been transformed to **470** served to prepare the more densely substituted bicyclo[4.2.1]nonane **471** from the allylic alcohol **306** (Scheme 87). The subsequent



Scheme 87.

retro-Claisen reaction led to the definitive ring opening of the original Hagemann's ester through formal C-3/C-4 detachment. The resulting keto ester **472** was deoxygenated to **473** following a thioketalization–desulfurization sequence. Transformation of **473** into the diazo ketone **474** allowed the construction of the unique carbon framework of cyclocuparane sesquiterpenes by an intramolecular cyclopropanation reaction. The resulting bicyclo[3.1.0]hexanone **475** could be transformed into β-microbiotene **476** by Wittig methylenation, into microbiotol **477** by reaction with an excess of methylmagnesium iodide, and into **477** and cyclocuparenol **478** (1.5:1 mixture) by reaction with an excess of methyllithium. These cyclocuparanes have been later prepared in an optically pure form following a different synthetic route from cyclogeraniol.[132]

The bicyclo[4.2.1]nonanedione **480**, isomer of **471**, has been prepared in a similar way and transformed into the odorous sesquiterpene, grimaldone **484**, as well as into epigrimaldone **485** and α-cuparenone **486**.[133] Thus, the ester **467** was α-dimethylated to **479** and transformed into the bicyclic compound **480** (Scheme 88). The subsequent regioselective retro-Claisen condensation and elaboration of the carboxylic group afforded the diazo ketone **481**, which by copper-mediated intramolecular cyclopropanation yielded a 1.7:1 mixture of the stereoisomeric diones **482** and **483**, separable by chromatography. The selective Wittig methylenation of **482** furnished grimaldone **484** and, in a similar manner, compound **483** gave epigrimaldone **485**. Moreover, controlled reaction of a mixture of the diones with methylmagnesium iodide followed by dehydration and aromatization led to the formation of α-cuparenone **486**.



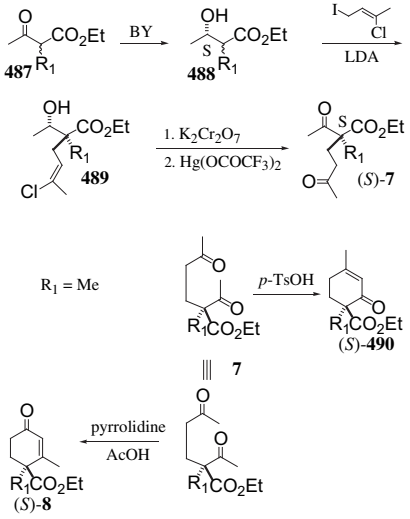
Scheme 88.

8. Optically active Hagemann's ester analogues

The preparation of optically active **1** has never been achieved, owing to the low configurational stability of the chiral C-1 carbon. However, a number of optically active analogues possessing a quaternary C-1 carbon or lacking the vinylogous system have been prepared in good ees.

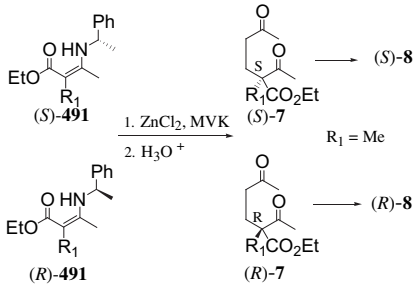
Thus, the successful preparation of enantiopure 2-acetyl-2-methyl-5-oxohexanoate (*S*)-**7** paved the way to the optically active 1-methyl analogue derivative (*S*)-**8** as well as the isomeric β-keto ester (*S*)-**490**, the regiochemical outcome of the Robinson's annulation being dependent on the use of basic or acid conditions.[23,134] The preparation of (*S*)-**7** took advantage of baker's yeast (BY) reduction of racemic 2-methyl acetoacetate **487**, furnishing the hydroxy ester **488** as a C-2 diastereomeric mixture (Scheme 89). The latter underwent enantioselective alkylation with (*E*,*Z*)-3-chlorobut-2-enyl iodide, giving **489** having the absolute (*S*) configuration

at the quaternary stereocenter. Oxidation of the alcoholic group followed by reaction with $Hg(OCOCF_3)_2$ gave the 1,5-dicarbonyl compound (*S*)-**7** as the convenient precursor of both the isomeric cyclohexenones (*S*)-**8** and (*S*)-**490** efficiently obtained with 86% ee.



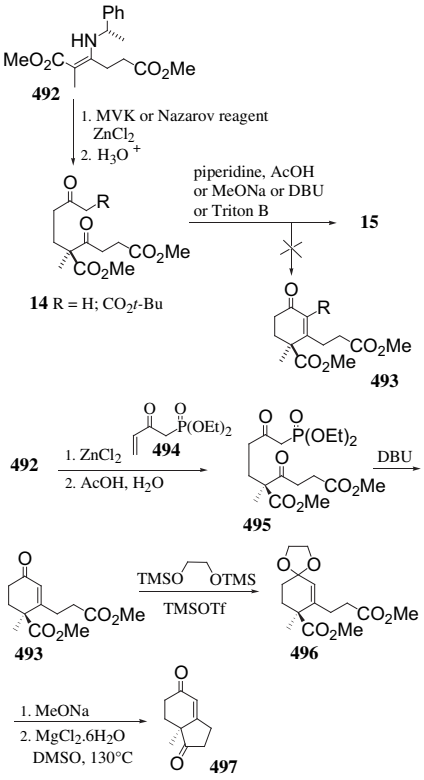
Scheme 89.

An alternative efficient enantioselective approach to both (*R*)- and (*S*)-**7** involved the Michael reaction between MVK and chiral β-enamino esters **491** in turn prepared by the reaction of (*R*)- or (*S*)-1-phenylethylamine with 2-substituted acetoacetate (Scheme 90). The Michael addition performed in the presence of 1 equiv of zinc chloride gave the expected adducts **7** with good ees. Their subsequent annulation furnished the optically active analogues of Hagemann's ester (*S*)- and (*R*)-**8**.[135]



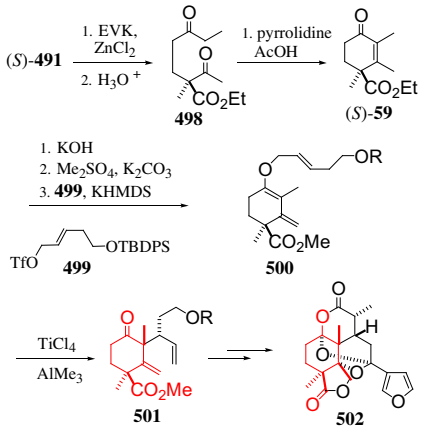
Scheme 90.

As discussed in Section 2, all the attempted protocols for the annulation of the intermediate **14** furnished exclusively the unwanted regioisomer **15**, instead of the Hagemann's ester-like structure **493** (Scheme 91). Moreover, the desired cyclohexenone **493** cannot be obtained by Robinson's annulation of the adduct between the β-enamino esters **492** and the Nazarov's reagent. However, the Horner–Wadsworth–Emmons annulation of compound **495** offered an efficient way of reversing the regiochemistry (Scheme 91). Thus, reaction of **492** with 2-oxo-3-vinylphosphonate **494** afforded enantioselectively the adduct **495**, which was smoothly cyclized by the action of DBU to furnish the Hagemann-like derivative **493**. Its conversion into the known hydrindenedione **497** served to ascertain both the structural and configurational assignments.[25] The sequence of steps leading ultimately to **497** included the carbonyl protection of **493** to form the ketal **496**, and Dieckmann cyclization followed by Krapcho demethoxycarbonylation with concomitant carbonyl deprotection.



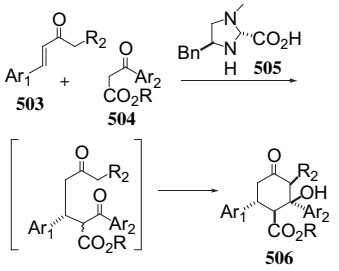
Scheme 91.

The long journey to establish the first total synthesis of saudin **502**, a highly oxidatively modified labdane diterpene with interesting biological properties, took advantage of the $ZnCl_2$-catalyzed Michael addition of (*S*)-**491** to ethyl vinyl ketone (EVK).[136] The adduct **498** underwent pyrrolidinium acetate regioselective Robinson annulation, yielding the chiral cyclohexenone (*S*)-**59** (Scheme 92). This scheme represented an elegant solution to the problems connected with the introduction of two methyl groups at C-3 and C-1 of **1**, already discussed in Section 3.1. (see Scheme 14). Transesterification of (*S*)-**59** followed by O-alkylation of the thermodynamic enolate with the allylic triflate **499** afforded **500**. Next, a carefully designed Lewis acid-promoted Claisen rearrangement produced the desired stereoisomer **501**. A series of steps were required for the transformation of the latter into the unnatural (+)-saudin **502**, thus establishing the absolute configuration of the natural target. Using (*R*)-α-methylbenzylamine as the chiral auxiliary, the above-described synthetic sequence served to prepare the natural labdane diterpene possessing hypoglycemic activity.



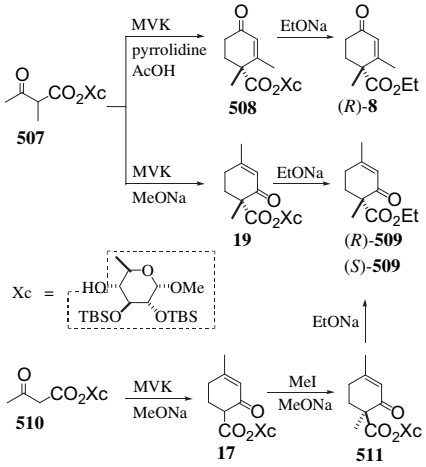
Scheme 92.

A regioselective domino Michael–aldol reaction between α,β-unsaturated ketones **503** and aromatic or heteroaromatic β-keto esters **504** catalyzed by the chiral phenylalanine-derived imidazolidine **505** has been recently described.[137] The organocatalytic asymmetric domino reaction, related to the proline-catalyzed Robinson annulation, provided a series of optically active cyclohexanones **506** with up to four stereogenic centres with excellent enantio- and diastereoselectivity (Scheme 93). A multiple role has been proposed for the organocatalyst **505**, i.e. an activator of the Michael acceptor and donor reagents, via iminium-ion formation and deprotonation of the β-keto ester, respectively, as well as a basic inducer for the intramolecular aldol reaction.



Scheme 93.

Exploration of a sugar template strategy for asymmetric access to synthetically useful chiral carbocycles led to the discovery that the reaction between MVK and the acetoacetate **507** could be conveniently carried out in order to obtain the isomeric cyclohexenones **508** or **19** simply by switching the basic activator in the tandem Michael–aldol condensation.[26] In detail, the pyrrolidinium acetate-mediated condensation produced **508**, while the MeONa-mediated reaction furnished **19**, respectively (Scheme 94). Thus, detachment of the sugar auxiliary group by ethanolysis produced the C-1 methyl-substituted Hagemann's ester (*R*)-**8** (80% ee) and its isomer (*R*)-**509** (86% ee). Interestingly, it was possible to obtain (*S*)-**509** (82% ee) by ethanolysis of **511** in turn derived from diastereoselective α-methylation of **17**, prepared from **510**.



Scheme 94.

9. Concluding remarks

The search for synthetic strategies towards complex and biologically active natural products has capitalized on the employment of Hagemann's ester and congeners as versatile starting materials, also contributing to the development of a wide range of new and modern chemistry.

The potential of Hagemann's ester as a building block in the synthesis of complex molecules has been demonstrated by its use in a variety of chemical transformations, allowing the development of diverse and creative applications.

Most importantly, the functionalities present make it a versatile building block, which could potentially be used in a variety of chemical transformations, still securing much room for research in this area.

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Biographical sketch

Carmela De Risi was born in Ferrara on May 22, 1967. She graduated in Chemistry in 1992 from the University of Ferrara, where she carried out her Ph.D. studies from 1992 to 1995 under the guidance of Prof. Gian Piero Pollini. In 1996, Carmela De Risi joined the laboratory of Prof. Pierre Vogel at the University of Lausanne (Switzerland) where she worked one year, and received the Ph.D. in Chemical Sciences from the University of Milan. After having spent a further two years as a postdoctoral researcher at the University of Ferrara, in 1999 Carmela De Risi was appointed as researcher at the University of Ferrara, Faculty of Pharmacy. Since then, Carmela De Risi has always worked at this Faculty, her main research interests including synthesis of biologically active natural compounds, general synthetic methodologies, amino acids and heterocycles.

Simonetta Benetti born in1947 in Ferrara Italy, Simonetta Benetti received her Degree in Chemistry in 1971 from the University of Ferrara. Since 1982 she has occupied the position of Associated Professor of Organic Chemistry at the 'Dipartimento di Chimica' of the same university. Since 1971 she has carried out research on the synthesis of natural organic substances and their structural analogues of particular pharmaceutical interest and had studied new synthetic methods of general applicability.

Gian Piero Pollini was born in Genoa and graduated in chemistry from Pavia University. He began his research and teaching career in the University of Perugia as assistant professor (1964–1967), then (1968) he moved to the University of Ferrara, Faculty of Sciences. In 1981 he was appointed as full professor of Organic Chemistry in the Faculty of Pharmacy of the same University. He was Chairman of the 'Dipartimento di Scienze Farmaceutiche' (1983–1990) and Dean of the Faculty of Pharmacy (1994–2000). His research interests include the development of new methods and reagents and their application to the synthesis of natural and non-natural targets with interesting biological and chemical properties.

Vinicio Zanirato was born in Rovigo (Italy) in 1957. He graduated in Chimica e Tecnologia Farmaceutiche from the University of Ferrara in 1982. In 1987, he completed his Ph. D working under the supervision of Professor Mario Guarneri on a synthesis of prostanoids. Three years later he became Researcher and in 1998 he was appointed as associate Professor of Organic Chemistry at the University of Siena (Italy). In 2003 he came back to the University of Ferrara and joined the group of Prof. Gian Piero Pollini at the Department of Pharmaceutical Sciences. His research interests broadly span the design and synthesis of biologically active molecules, as well as the development of new reaction methodologies.