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## Aromatic abietane diterpenoids: total syntheses and synthetic studies



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### 1. Introduction

Natural products have attracted synthetic chemist's attention from an academic point of view for a long time. However, natural product synthesis is still essential for confirming the molecular structure of a new natural product.<sup>1</sup> Natural products have played

a dominant role in the drug discovery efforts for the treatment of human diseases.<sup>2</sup> Many diterpenes offer attractive synthetic challenges because of their biological and pharmaceutical properties.

Abietane diterpenoids are widely distributed natural products in the plant kingdom, which exhibit a wide range of biological activities. During the last three decades, many new members of this family of natural products have been isolated and described in several specific reviews on naturally occurring diterpenoids by Professor Hanson.<sup>3</sup> These compounds have generated significant interest from the synthetic, medicinal and pharmacological communities. The biological activities of natural abietane acids and their derivatives have been reviewed up to 1992.<sup>4</sup> In this review, our attention is focused on the synthetic studies of diterpenoids characterised by tricyclic structures having the abietane ( $I$ ,  $C_{20}$ ) (Fig. 1) carbon framework, which is contained in abietic acid (**1**), and an aromatic ring C.

**Abbreviations:** AcCl, acetyl chloride;  $Ac_2O$ , acetic anhydride; BnCl, benzyl chloride;  $n\text{-BuLi}$ ,  $n$ -butyllithium; DCC, *N,N*-dicyclohexylcarbodiimide; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DIBAL-H, diisobutylaluminium hydride; DHA, dehydroabietic acid; DMAP, 4-(*N,N*-dimethylamino)pyridine; DMDO, dimethyldioxiirane; DMSO, dimethyl sulfoxide; HOAc, acetic acid; HOOAc, peracetic acid; IPA, isopropenyl acetate; MCPBA, *m*-chloroperbenzoic acid; MsCl, mesyl chloride; PDC, pyridinium dichromate; PCC, pyridinium chlorochromate; *p*-TSA, *p*-toluenesulphonic acid; TsCl, tosyl chloride; pyridine; R-BINOL, *R*-1,1'-bi(2-naphthol).

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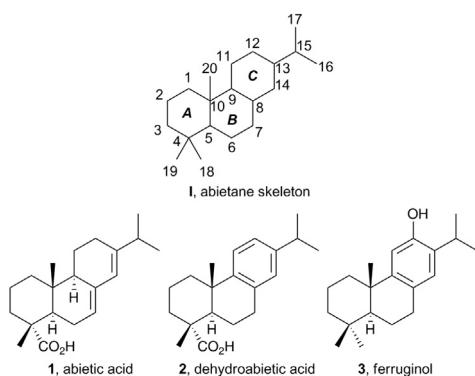


Fig. 1. Abietane numbering system and abietic acid (1).

Aromatic abietanes comprised the largest group of components of naturally occurring abietanes. They possess an aromatic ring C and a different degree of oxygenation at several positions. This group of abietanes is exemplified by dehydroabietic acid (2, DHA) and ferruginol (3) (Fig. 1), which were discovered more than 70 years ago.<sup>5,6</sup> Both structures were assigned based on chemical data. Dehydroabietic acid (2) was initially obtained from chemical studies starting from abietic acid (1), later, it was found in resin or extracts of conifers.<sup>7</sup> Ferruginol (3) was firstly isolated in 1939 from the resin of the Miro tree (*Podocarpus ferrugineus*), endemic to New Zealand.<sup>6</sup> Since the isolation of these compounds in the late 1930s, numerous research groups have embarked on their synthesis and the synthesis of related congeners.

Herein, we present synthetic aspects of the aromatic group of abietanes, which so far have not been covered in reviews. It is our intention to disclose the rich chemistry behind the efforts to synthesise 2,3 and related compounds.

## 2. Structure, occurrence and biological activity

The semisystematic naming and numbering of this family of diterpenoids was introduced in 1969, by Burgstahler,<sup>8</sup> following the synthesis of fichtelite, a fossil resin hydrocarbon, from abietic acid (7,13-abietadien-18-oic acid, 1). Thus, in accordance with the IUPAC recommendations the saturated hydrocarbon I, named 'abietane', was chosen as the fundamental parent structure with the numbering pattern as depicted in Fig. 1.

The main source of abietanes is colophony, the distillation residue of pine resins. In addition, abietanes are components of extracts or resins from many other conifers belonging to the families Araucariaceae, Cupressaceae, Phyllocladaceae, Pinaceae and Podocarpaceae, but they also occur in several Angiosperm species and, particularly in the families Asteraceae, Celastraceae, Hydrocharitaceae and Lamiaceae.<sup>4</sup> Some abietanes have also been isolated from fungal species.<sup>9</sup>

To date, there are around 200 known compounds belonging to this group of natural products, commonly known as dehydroabietic derivatives (dehydroabietanes). Generally, aromatic abietanes are not functionalised on A-ring carbons. Most of them present a different degree of oxygenation in their B- and C-ring carbons, as well as at carbons 18–20.

Most of these compounds play a key role as eco-physiological mediators (chemical defense) and are of interest for potential applications as therapeutic agents. In fact, the aromatic abietanes have displayed a wide spectrum of interesting biological properties including antimicrobial, antileishmanial, antiplasmodial, antifungal, antitumour, cytotoxicity, antiviral, antiulcer, cardiovascular, antioxidant as well as anti-inflammatory activity.<sup>3</sup>

## 3. Syntheses of aromatic abietane diterpenoids

A number of syntheses have appeared since the first isolations in the late 1930s. The earliest synthesis example, in 1938, addressed the synthesis of DHA (2) and was a semisynthetic route from abietic acid (1). The first total synthesis was in 1939 and dealt with racemic 4-epidehydroabietic acid (4, callitrisic acid) (Fig. 2) before its isolation from natural sources. From the mid-1950s until 1979, several racemic total syntheses were developed. In 1979, the first enantioselective total synthesis of (+)-ferruginol (3) was reported by a Japanese research group.<sup>10</sup> Only recently, in 2014, the enantioselective total synthesis of DHA (2) has been described by the Corey's research group at Harvard. I will classify all the synthetic studies in three main groups. Thus, I will describe firstly the syntheses from other natural products, total syntheses and, finally, other approaches. Most of the synthetic studies towards aromatic abietane diterpenoids have been focus on the synthesis of DHA (2) and ferruginol (3). Generally, despite the interesting molecular structures and biological properties of related congeners, there have been relatively few synthetic studies towards their preparation.

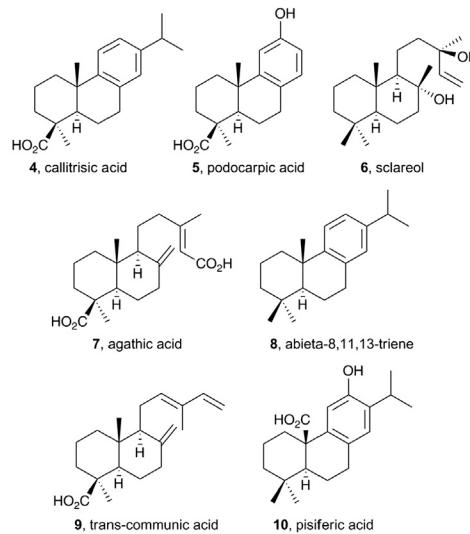
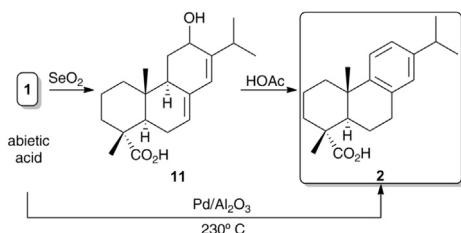


Fig. 2. Starting materials for the semisynthetic studies.

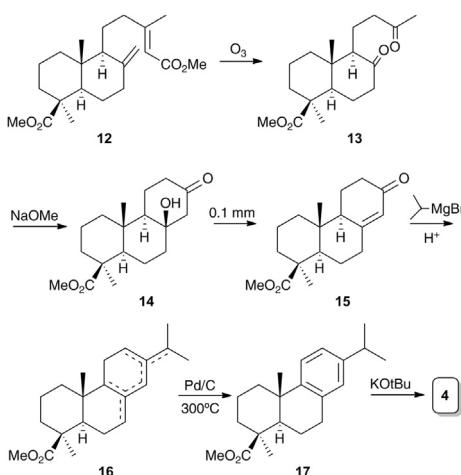
### 3.1. Syntheses from other natural products

Several naturally occurring compounds have been used as enantiomerically pure starting materials for the synthesis of bioactive abietanes. Some are commercially available as, for example, abietic acid (1), dehydroabietic acid (2) (Fig. 1), podocarpic acid (5), sclareol (6) and agathic acid (7) (Fig. 2). Other are obtained directly from natural sources as, for example, abeta-8,11,13-triene (8), trans-communic acid (9), pisiferic acid (10) and callitrisic acid (4) (Fig. 2). These starting materials are converted into versatile tricyclic intermediates having the characteristic ABC-ring system of abietanes, which are subjected to functionalisation to obtain the desired products.

In 1938, Fieser and Campbell reported the first synthesis of DHA (2).<sup>5</sup> It happened before this naturally occurring diterpenoid was isolated from natural sources. The synthesis started from abietic acid (1), which was converted into 12-hydroxyabietic acid (11) by treatment with  $\text{SeO}_2$  (Scheme 1). Heating of 11 at reflux in HOAc gave DHA (2). Contemporaneous studies by Littmann described the preparation of DHA (2) and its corresponding methyl ester directly from abietic acid (1) (Scheme 1). This simplified method consisted in the disproportionation of abietic acid (1) over a palladium catalyst.<sup>11</sup>

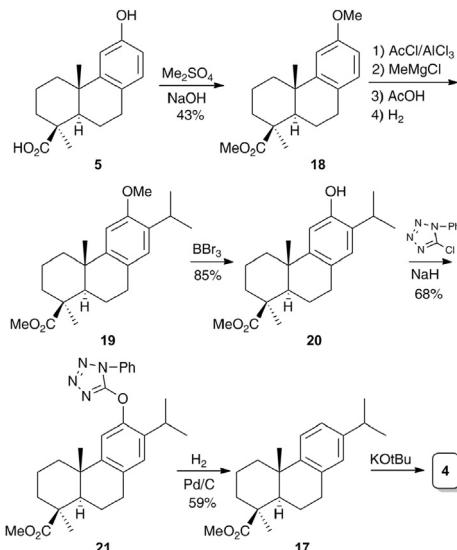
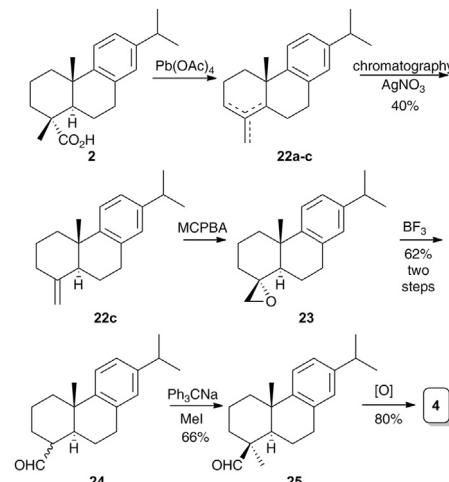
**Scheme 1.** Fieser's and Littmann's syntheses of dehydroabietic acid (**2**).

In 1968, a cooperative work from an Australian group and a Japanese group led to the synthesis of 4-epidehydroabietic acid (**4**, callitrisic acid) (Scheme 2).<sup>12</sup> The synthesis began with the ozonolysis of dimethyl agathate (**12**) followed by reductive workup, which gave principally diketone ester **13**. Diketone **13** was treated with sodium methoxide to give hydroxyketone **14**, which upon distillation at 0.1 mm gave the unsaturated ketone **15**. Ketone **15** was treated with isopropyl magnesium bromide, followed by acid hydrolysis and isomerisation to afford a mixture of esters **16**. The diene ester mixture **16** was dehydrogenated with palladium on charcoal at 300 °C. From the crude product, methyl 4-epidehydroabietate **17** was isolated and hydrolysed with potassium *tert*-butoxide (KO*t*-Bu) in DMSO to give acid **4**.

**Scheme 2.** Carman's and Mori's synthesis of 4-epidehydroabietic acid (**4**).

Two years later, Huffman described the synthesis of 4-epidehydroabietic acid (**4**, callitrisic acid) (Scheme 3) from podocarpic acid (**5**).<sup>13</sup> Thus, podocarpic acid (**5**) was treated with dimethyl sulfate and base to give methoxy-ester **18**, which was converted into methyl 12-methoxyabiet-8,11,13-trien-19-oate **19** by Friedel–Crafts acylation, reaction with methylmagnesium chloride followed by dehydration and catalytic hydrogenation. Then, cleavage of the methoxy group with BBr<sub>3</sub> gave methyl 12-hydroxyabiet-8,11,13-trien-19-oate **20**, which was treated with NaH and 1-phenyl-5-chlorotetrazole to afford phenyltetrazolyl ether **21**. The hydrogenolysis of **21** proceeded smoothly under mild conditions to give methyl 4-epidehydroabietate (**17**, methyl callitrisate), which could be hydrolysed as reported previously (KO*t*-Bu) to afford 4-epidehydroabietic acid (**4**, callitrisic acid).

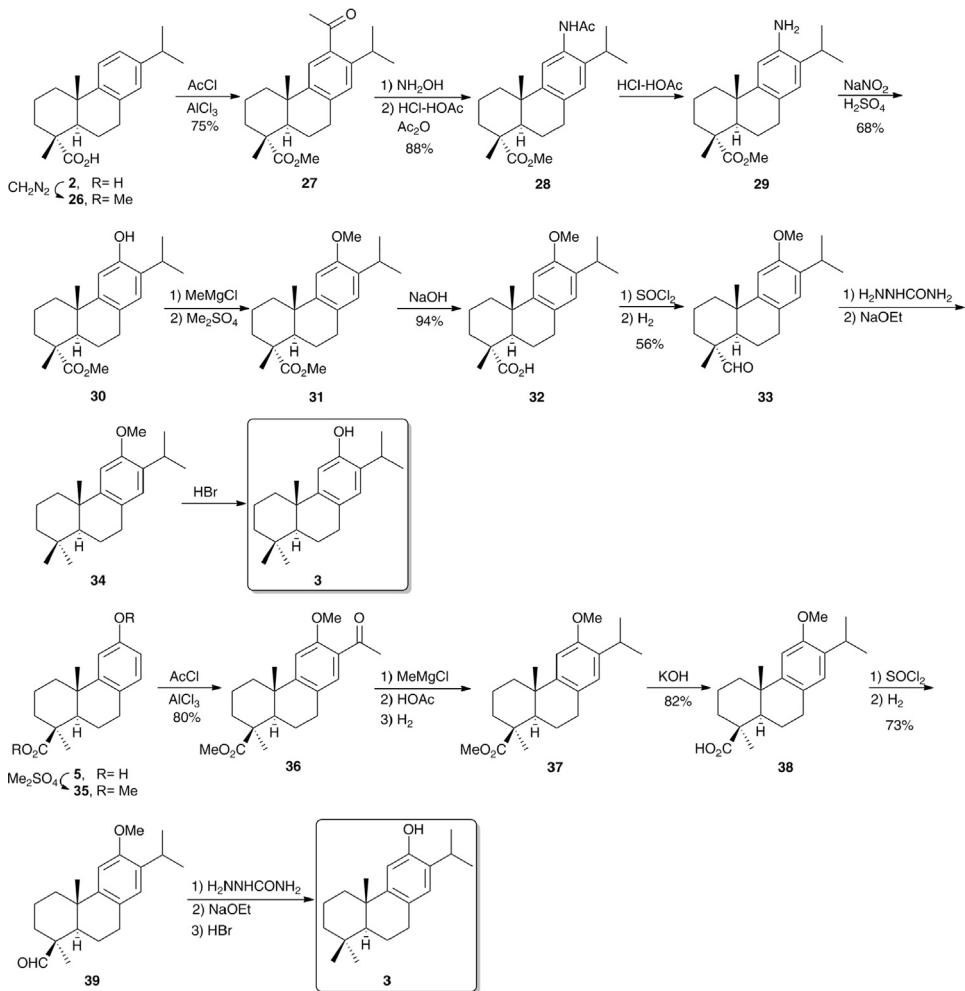
In 1971, Pelletier and Herald reported the inversion of the C-4 substituents in dehydroabietic acid (**2**) to obtain 4-epidehydroabietic acid (**4**, callitrisic acid) (Scheme 4).<sup>14</sup> Oxidative decarboxylation of **2** with lead tetraacetate resulted in the formation of a mixture of isomeric olefins **22a–c**, which were purified by chromatography over 10% silver nitrate impregnated silica gel. Thus, compound **22c** with the exocyclic double bond was obtained

**Scheme 3.** Huffman's synthesis of 4-epidehydroabietic acid (**4**).**Scheme 4.** Pelletier's synthesis of callitrisic acid (**4**).

and treated with *m*-chloroperbenzoic acid (MCPBA) to give epoxide **23**. Rearrangement of crude **23** with BF<sub>3</sub> etherate afforded a mixture of epimeric aldehydes **24**, which were methylated with excess MeI and tritylsodium as base to give callitrisaldehyde (**25**). Oxidation of **25** with silver oxide or Jones reagent provided callitrisic acid (**4**).

The synthesis of ferruginol (**3**) has been studied extensively. This bioactive phenol has attracted much attention from synthetic chemists and a number of synthetic routes have been described.

The first synthesis of ferruginol (**3**) was carried out in 1942 by Campbell and Todd from dehydroabietic acid (**2**, DHA) and podocarpic acid (**5**) (Scheme 5).<sup>15</sup> Thus, DHA (**2**) was treated with diazomethane to give methyl dehydroabietate (**26**), which was acylated by the Friedel–Crafts method to give methyl ketone **27**. Oxime formation of **27** followed by Beckmann rearrangement and acetylation afforded acetamide **28**. Hydrolysis of **28** with hydrochloric-acetic acid led to amine **29**, which was converted by diazotisation with nitrosylsulfuric acid in pyridine and by hydrolysis into phenol **30**. The methylation of **30** presented some difficulty since the hydroxyl group is highly hindered by the isopropyl group. The ether **31** was obtained by the action of dimethyl sulfate on the chloromagnesium salt, prepared by treating the phenol **30** with methylmagnesium chloride. Hydrolysis of **31** gave acid **32**, which was chlorinated and subjected to Rosenmund reduction to give aldehyde **33**. Formation of the semicarbazone of **33** and



Scheme 5. Campbell's syntheses of ferruginol (3).

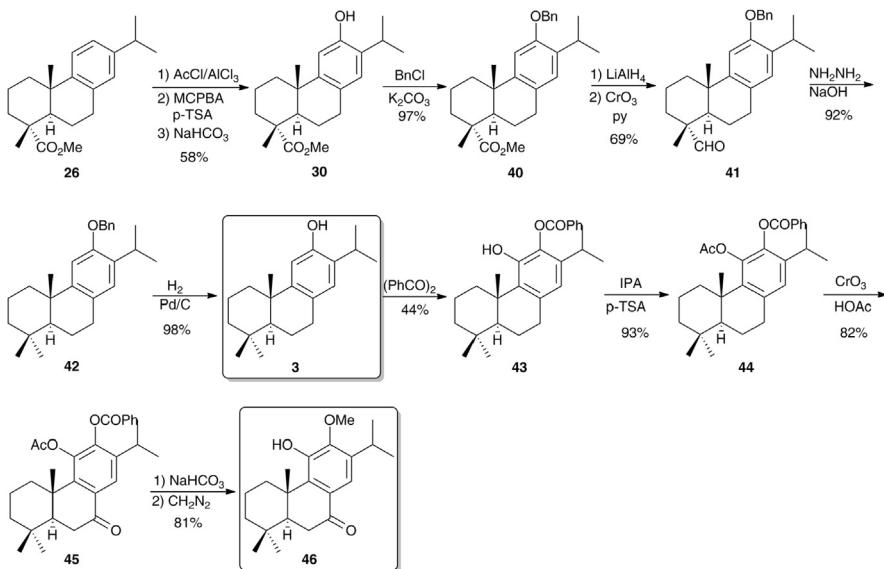
reduction with excess sodium ethylate furnished compound **34**, which was treated with hydrobromic acid to afford ferruginol (**3**). On the other hand, podocarpic acid (**5**) was methylated with dimethyl sulfate followed by Friedel–Crafts acylation to give methyl ketone **36**. The treatment of **36** with methyl magnesium chloride followed by dehydration and hydrogenation led to the compound **37** containing the isopropyl group typical of abietanes. Hydrolysis of the ester group in **37** with KOH gave acid **38**, which was subjected to chlorination and Rosenmund reduction to give aldehyde **39**. Formation of the semicarbazone of **39** and reduction with excess sodium ethoxide followed by treatment with hydrobromic acid afforded ferruginol (**3**).

In 1977, Matsumoto et al. reported the synthesis of ferruginol (**3**) and cryptojaponol (**46**) via known methyl 12-hydroxyabieto-8,11,13-trien-18-oate (**30**) prepared from methyl dehydroabietate (**26**) with the method of Cambie and Franich (Scheme 6).<sup>16</sup> Thus, Friedel–Crafts acylation of **26** followed by Baeyer–Villiger oxidation and hydrolysis gave known phenol **30** in 58% overall yield. Next, the treatment of **30** with benzyl chloride in the presence of K<sub>2</sub>CO<sub>3</sub> gave benzyl ether **40**, which, on reduction with LiAlH<sub>4</sub> followed by oxidation of the resulting alcohol with CrO<sub>3</sub>–pyridine complex yielded a formyl derivative (**41**). Huang–Minlon reduction of **41** gave ferruginol benzyl ether (**42**), which was then hydrogenolysed using Pd/C in acetic acid to give ferruginol (**3**). The oxidation of ferruginol (**3**) with benzoyl peroxide gave phenol **43**, which was acetylated to give acetate **44**. This was then oxidised with CrO<sub>3</sub> in HOAc to yield the corresponding 7-

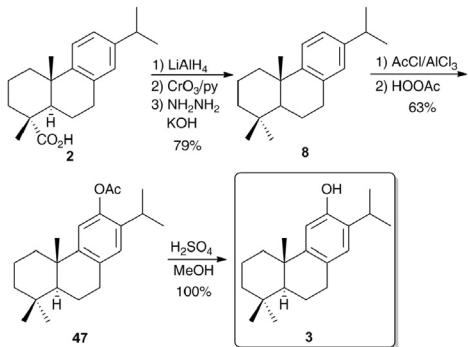
oxo compound (**45**). The hydrolysis of **45** followed by methylation with diazomethane gave cryptojaponol (**46**) in 27% overall yield from **3**.

Four years later, Oishi and Akita described another synthesis of ferruginol (**3**) via dehydroabietane (**8**) prepared from dehydroabietic acid (**2**) (Scheme 7).<sup>17</sup> Firstly, the carboxyl group in **2** is converted into a methyl group by reduction, oxidation to the aldehyde and modified Wolff–Kishner reduction in 79% overall yield. Then, Friedel–Crafts acylation of **8** followed by Baeyer–Villiger oxidation with HOOAc gave 12-acetoxy compound **47**, and this was hydrolyzed with concd H<sub>2</sub>SO<sub>4</sub> in MeOH to give ferruginol (**3**) in 63% overall yield.

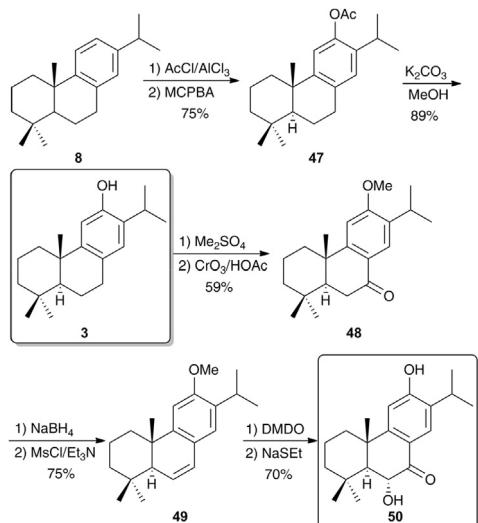
Recently, a paper from Córdova-Guerrero et al. described the diverted synthesis of oxidised abietane diterpenes, via oxidation of antimicrobial 6,7-dehydroferruginol methyl ether (**49**) with dimethyldioxirane (DMDO) starting from the natural dehydroabietane (**8**, abieta-8,11,13-triene) isolated from *Salvia clevelandii* (Scheme 8).<sup>18</sup> The synthetic route began with the preparation of ferruginol (**3**) from **8** following a synthetic sequence similar to Oishi's synthesis of ferruginol (**3**) (Scheme 7). Thus, compound **8** was reacted with AcCl in the presence of AlCl<sub>3</sub> to afford a methyl ketone that was subjected to Baeyer–Villiger oxidation to give acetate **47**. Acetate **47** was hydrolysed with K<sub>2</sub>CO<sub>3</sub> in MeOH/DCM to afford ferruginol (**3**) in 66% overall yield. Ferruginol (**3**) was methylated with dimethyl sulfate and LiOH as base to yield a methyl ether that was subjected to benzylic oxidation with CrO<sub>3</sub> in HOAc to give ketone **48**. This ketone was reduced with NaBH<sub>4</sub>



Scheme 6. Matsumoto's syntheses of ferruginol (3) and cryptojaponol (46).



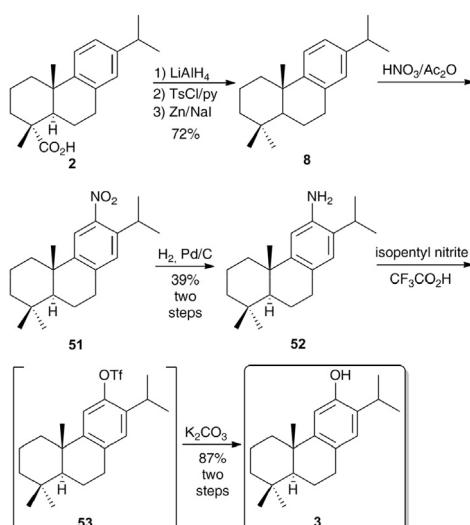
Scheme 7. Oishi's synthesis of ferruginol (3).



Scheme 8. Córdova-Guerrero's synthesis of 6α-hydroxysugiol (50).

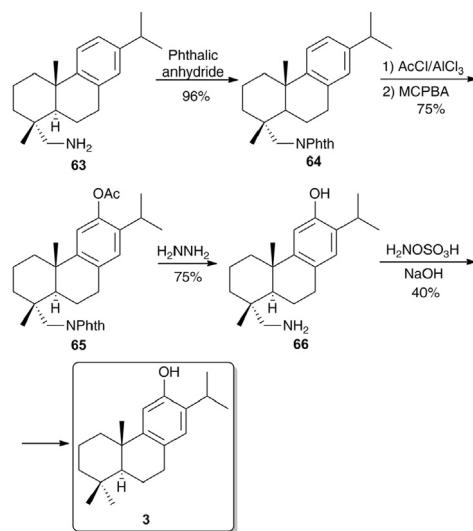
and the resulting mixture of diastereomeric alcohols was converted into methyl ether **49** by treatment with mesyl chloride (MsCl) in dry Et<sub>3</sub>N. Next, compound **49** was converted into natural 6α-hydroxysugiol (**50**) by treatment with DMDO and NaSET. Dehydroabietane (**8**, abiet-8,11,13-triene) has been used as precursor of

ferruginol (**3**), which was the intermediate for the synthesis of other bioactive abietanes. This time, **8** was synthesised from dehydroabietic acid (**2**) by a route different to that of Oishi's (Scheme 7) to convert the carboxyl group at C-4 into a methyl group (Scheme 9).<sup>19</sup> Compound **2** was reduced with LiAlH<sub>4</sub> to give an alcohol, which was converted to the tosylate with tosyl chloride (TsCl). The tosylate was reduced with Zn powder/NaI to give abietatriene **8**. Then, the introduction of the hydroxyl group at C-12 was carried out with two methods. The known Friedel-Crafts acetylation followed by Baeyer-Villiger oxidation and nitration-reduction followed by Sandmeyer reaction. Both synthetic routes successfully gave ferruginol (**3**), but the yield of the Baeyer-Villiger reaction of the former route was lower in the larger scale experiments. The latter route was selected in the synthesis. Thus, abietatriene **8** was nitrated with nitric acid in Ac<sub>2</sub>O to give as major compound 12-nitro-8,11,13-abietatriene **51**. This compound was hydrogenated over 10% Pd/C to produce 12-amino compound **52**, which was dissolved in CF<sub>3</sub>CO<sub>2</sub>H and then treated with isopentyl nitrite. The resulting trifluoroacetate **53** was not isolated and was hydrolysed in situ with aqueous Na<sub>2</sub>CO<sub>3</sub> to give ferruginol (**3**) in 23% overall yield from **2**.

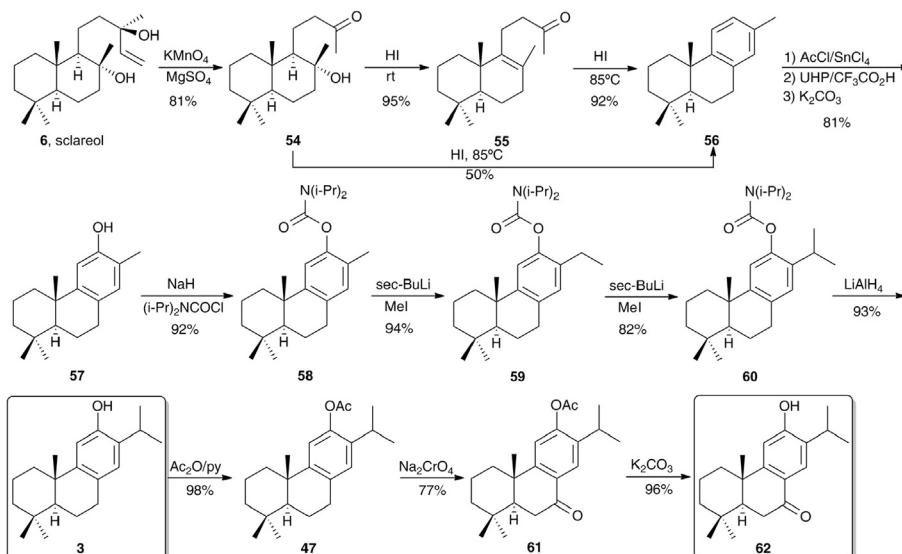


Scheme 9. Tada's synthesis of ferruginol (3).

In 2010, Marcos et al. described the synthesis of ferruginol (**3**) and sugiol (**62**) from sclareol (**6**) using as key step the side chain lithiation of a dinorditerpene precursor (**Scheme 10**).<sup>20</sup> Thus, sclareol was transformed into methylketone **54** by treatment with  $\text{KMnO}_4$  and  $\text{MgSO}_4$ . The podocarpane derivative **56** can be directly obtained in a 50% yield from **54** by treatment with  $\text{HI}$  and heating at  $85^\circ\text{C}$ , but the transformation could be achieved in a better yield in two steps. The treatment of **54** with  $\text{HI}$  at room temperature gave compound **55** in nearly quantitative yield, which on heating at  $85^\circ\text{C}$  with  $\text{HI}$  led to the podocarpane **56** in an excellent yield. The introduction of the hydroxyl group at C-12 followed the classical Friedel–Crafts acetylation followed by Baeyer–Villiger oxidation and hydrolysis to give phenol **57**. Compound **57** was converted into the carbamoyloxy derivative **58** since the carbamoyl was the chosen group for directing the side chain lithiation. Compound **58** was treated with a big excess of *sec*-BuLi at  $-78^\circ\text{C}$  and the lithiated species were made to react with an electrophile as  $\text{MeI}$  to give norditerpenoid **59**. The same process was repeated on **59** to complete the abietane carbon skeleton giving compound **60**, which was reduced with  $\text{LiAlH}_4$  to afford ferruginol (**3**). Acetylation of **3** with  $\text{Ac}_2\text{O}$  gave the acetyl derivative **47**, which by oxidation with  $\text{Na}_2\text{CrO}_4$  led to ketone **61**. Finally, hydrolysis of **61** with  $\text{K}_2\text{CO}_3$  gave sugiol (**62**).



**Scheme 11.** Gonçalves' synthesis of ferruginol (**3**).

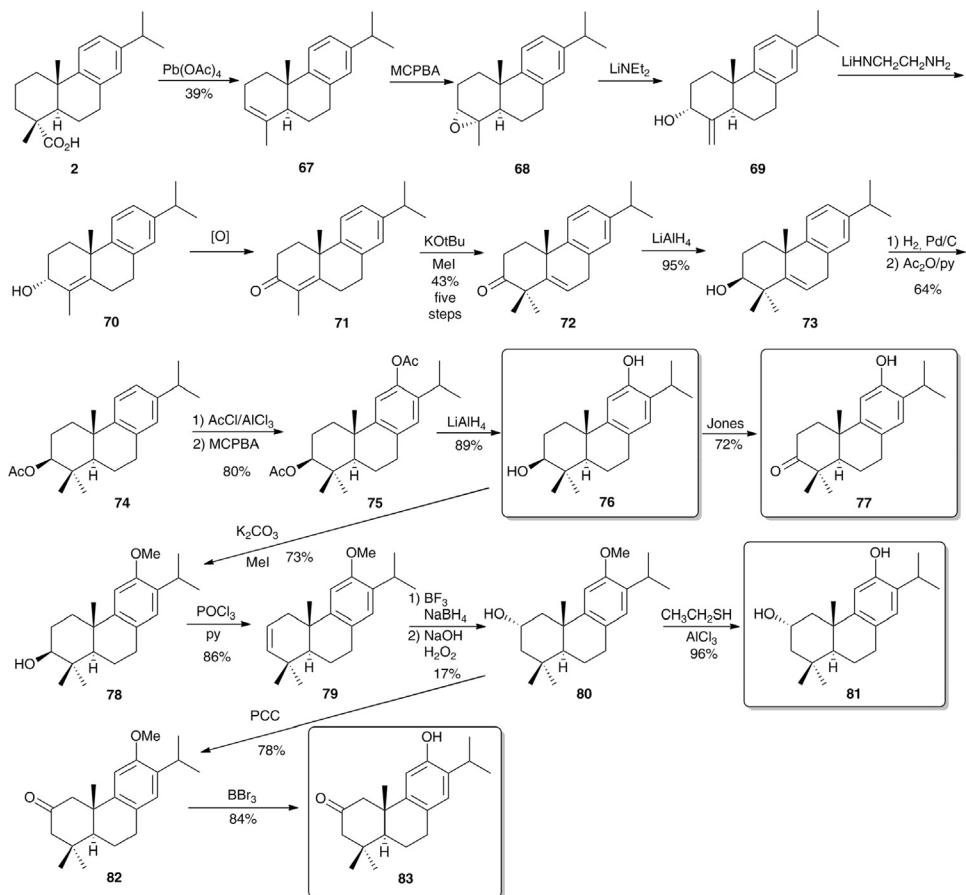


**Scheme 10.** Marcos' syntheses of ferruginol (**3**) and sugiol (**62**).

Recently, González and Pérez-Guaita reported a short synthesis of ferruginol (**3**) from commercially available (+)-dehydroabietylamine (**63**) (**Scheme 11**), which is not a natural product but derived from industrial rosin amine.<sup>21</sup> In order to prepare ferruginol (**3**) from **63**, the introduction of a hydroxyl group at C-12 and deamination was required. Thus, classical sequence of Friedel–Crafts acetylation followed by Baeyer–Villiger oxidation on phthaloyl protected dehydroabietylamine, compound **64**, led to phthaloyl-acetate **65** in high yield. Simultaneous cleavage of the acetate and phthaloyl groups was carried out by treatment with hydrazine leading to amino-phenol **66**. This was reductively deaminated upon treatment with hydroxylamine-O-sulfonic acid (HOS) in aqueous basic media to give ferruginol (**3**) on the gram scale, though in very moderate yield.

In the early 1980s, Matsumoto et al. described the syntheses of hinokiol (**76**), hinokione (**77**), salviol (**81**) and 2-oxoferruginol (**83**), starting from abieto-5,8,11,13-tetraen-3-one (**72**), which was prepared from dehydroabietic acid (**2**) (**Scheme 12**).<sup>22</sup> All these natural diterpenes possess the oxygen functions in both the rings A and C of the abietane skeleton. The syntheses began with the preparation of intermediate **72** from **2**. Thus, oxidative decarboxylation of **2** with

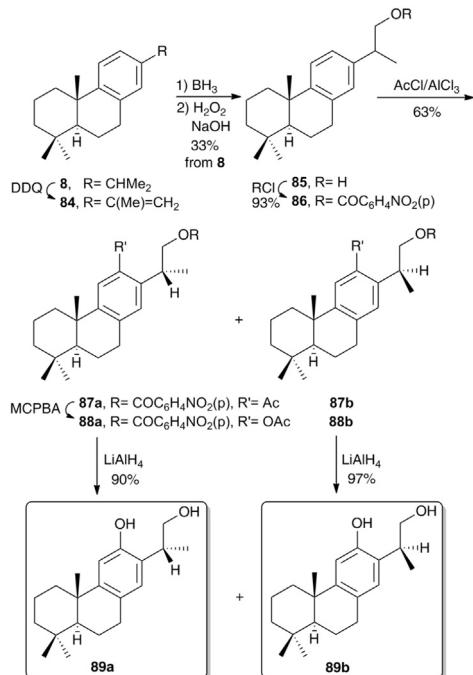
$\text{Pb}(\text{OAc})_4$  gave an alkene mixture with olefin **67** being one of the major products. Epoxidation of **67** and base-catalysed rearrangement gave allylic alcohol **69**, which by treatment with ethylenediamine lithium salt afforded unsaturated alcohol **70**. Oxidation of **70** gave ketone **71**, which was alkylated with  $\text{KOt-Bu}$  and  $\text{MeI}$  to give desired ketone **72**. Next, reduction of **72** to alcohol **73** followed by catalytic hydrogenation and acetylation gave acetate **74**. The Friedel–Crafts acetylation with  $\text{AcCl}$  in the presence of anhydrous  $\text{AlCl}_3$  followed by Baeyer–Villiger oxidation afforded 3 $\beta$ ,12-diacetoxyabietatriene **75**. Treatment of **75** with  $\text{LiAlH}_4$  yielded hinokiol (**76**), which was oxidised with Jones reagent to give hinokione (**77**). Methylation of hinokiol (**76**) with  $\text{MeI}$  and anhydrous  $\text{K}_2\text{CO}_3$  afforded hinokiol 12-methyl ether (**78**). This intermediate was used for the synthesis of salviol (**81**) and 2-oxoferruginol (**83**). Firstly, the methyl ether **78** was dehydrated with  $\text{POCl}_3$  in pyridine to yield tetraene **79**. Hydroboration of **79**, followed by oxidation with alkaline  $\text{H}_2\text{O}_2$ , afforded a mixture of alcohols. Among them, alcohol **80** was a minor product and was demethylated with ethanethiol and  $\text{AlCl}_3$  to afford salviol (**81**). Subsequently, the alcohol **80** was oxidised with PCC to give



Scheme 12. Matsumoto's syntheses of hinokiol (76), hinokione (77), salviol (81) and 2-oxoferruginol (83).

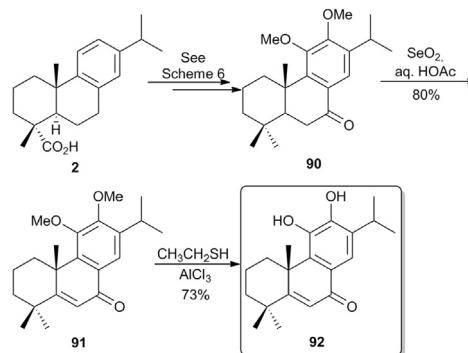
ketone **82**, which, on demethylation with BBr<sub>3</sub> afforded 2-oxoferruginol (**83**).

In 1991, Matsumoto et al. reported the synthesis of (15*R*)-16-hydroxyferruginol (**89a**) and its (15*S*)-epimer (**89b**) starting from natural abietatriene **8** (Scheme 13).<sup>23</sup> Dehydrogenation of **8** with

Scheme 13. Matsumoto's synthesis of 16-hydroxyferruginols **89**.

DDQ afforded the corresponding isopropenyl compound **84**, which was subjected to hydroboration–oxidation to give a C-15 epimeric mixture of alcohols **85**. These alcohols were further converted into 4-nitrobenzoates **86** by heating with 4-nitrobenzoyl chloride in pyridine. Then, Friedel–Crafts acetylation afforded a C-15 epimeric mixture (ca. 1:1) that was carefully chromatographed to give the (15*R*)-12-acetylabietatriene (**87a**) and (15*S*)-12-acetylabietatriene (**87b**) diastereomers. The Baeyer–Villiger oxidations of **87a** and **87b** with MCPBA and *p*-TSA, followed by reductions of the resulting acetates, **88a,b**, with LiAlH<sub>4</sub> afforded desired (15*R*)-16-hydroxyferruginol (**89a**) and its (15*S*)-epimer (**89b**).

Two years later, the same research group described the synthesis of salvinolone (**92**), via 11,12-dimethoxyabiet-8,11,13-triene-7-one (**90**), from dehydroabietic acid (**2**) (Scheme 14).<sup>24</sup> The key intermediate **90** was synthesised following the route for the synthesis of cryptojaponol (**46**) (Scheme 6). Then, compound **90**

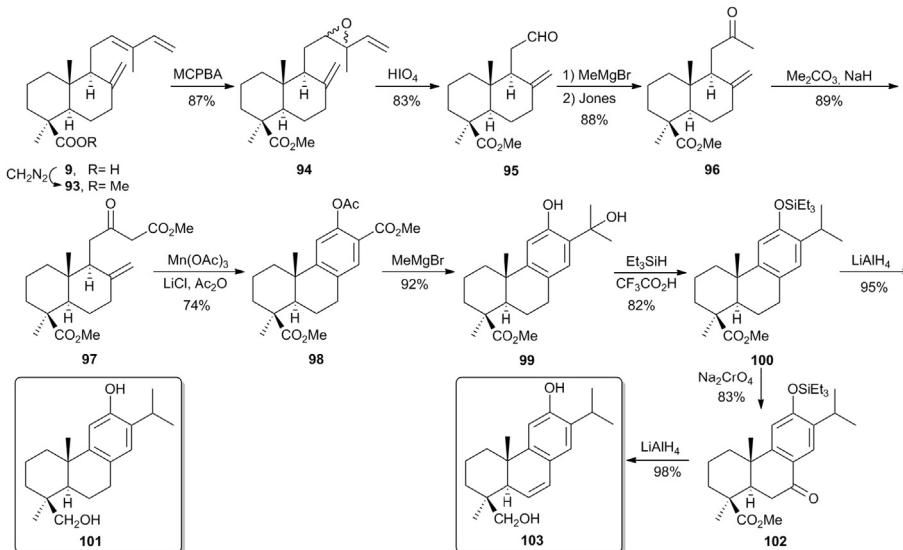
Scheme 14. Matsumoto's synthesis of salvinolone (**92**).

was refluxed with  $\text{SeO}_2$  in aqueous HOAc to give salvinolone dimethyl ether (**91**). Demethylation of **91** with ethanethiol and anhydrous  $\text{AlCl}_3$  afforded salvinolone (**92**).

A new strategy towards phenol abietane diterpenes using natural *trans*-communic acid (**9**) as starting material has recently been described by Alvarez-Manzaneda et al., as outlined in Scheme 15.<sup>25</sup> The key step is the formation of the aromatic C ring through a manganese(III)-based oxidative free-radical cyclisation of unsaturated  $\beta$ -ketoester **97**. The synthetic sequence allowed the preparation for the first time of immunosuppressive 19-hydroxyferruginol (**101**) and sugikurojin A (**103**). The synthesis of  $\beta$ -ketoester **97** starts with the treatment of communic acid (**9**) with diazomethane, followed by epoxidation of the resulting ester, compound **93**, with MCPBA to give a mixture of diastereomeric 12,13-epoxy derivatives **94**. The epoxides **94** were converted into aldehyde **95** by treatment with  $\text{HIO}_4$ . Treatment of compound **95** with  $\text{MeMgBr}$  and further oxidation with Jones reagent gave methylketone **96**, which was converted into  $\beta$ -ketoester **97** after treatment with  $\text{Me}_2\text{CO}_3$  and  $\text{NaH}$  in benzene. Next, the construction of the aromatic C ring was undertaken. After some investigation, it was found that 4 equiv of  $\text{Mn}(\text{OAc})_3$  and 3 equiv of  $\text{LiCl}$  in  $\text{Ac}_2\text{O}$  at 120 °C for 12 h affords the aromatic norabietane **98** in 74% yield. Treatment of this compound with  $\text{MeMgBr}$  in excess gave the abietane phenol **99**. When this phenol was treated with  $\text{Et}_3\text{SiH}$  and  $\text{CF}_3\text{CO}_2\text{H}$  the 15-hydroxy group was removed, producing the silyl ether **100**. Refluxing of compound **100** with  $\text{LiAlH}_4$  in THF caused reduction of the ester group and simultaneous deprotection of the silyl ether, affording 19-hydroxyferruginol (**101**). On the other hand, heating of silyl ether **100** with  $\text{Na}_2\text{CrO}_4$  and  $\text{NaOAc}$  in  $\text{Ac}_2\text{O}/\text{HOAc}$  led to the corresponding 7-oxoderivative **102**, which was treated with  $\text{LiAlH}_4$  under reflux in THF to afford directly sugikurojin A (**103**).

phenol (18-hydroxyferruginol) **104**, which was benzylated with benzyl bromide and  $\text{K}_2\text{CO}_3$  to give benzyl ether **105**. Oxidation with PCC of **105** gave aldehyde **106**, which was subjected to further oxidation with MCPBA to afford formate **107**. Heating of **107** in refluxing collidine led to the exocyclic olefin **108**. Hydroboration–oxidation of this substrate afforded alcohol **109**, which was then oxidised with PCC to the corresponding aldehyde **110**. Treatment of this with  $\text{MeI}$  in the presence of  $\text{KOt-Bu}$  led to the aldehyde **111** with inverted C-4 functionality. Aldehyde **111** was reduced with  $\text{NaBH}_4$ , to alcohol **112**, followed by hydrogenolysis to give 19-hydroxyferruginol (**101**). On the other hand, acetylation of **112** with  $\text{Ac}_2\text{O}$  in pyridine followed by oxidation with  $\text{CrO}_3$  in HOAc gave ketone **113**, which was subjected to hydrogenolysis and reduction with  $\text{LiAlH}_4$  and acidic workup to afford sugikurojin A (**103**). In an independent synthetic sequence starting from benzyl ether **105**, hanagokenol A (**119**) and fortunin H (**121**) were also synthesised. Similarly, starting from phenol **104**, fortunins E (**125**) and G (**126**) were obtained. In the first synthetic sequence, benzyl ether **105** was treated with tosyl chloride in pyridine and 4-(*N,N*-dimethylamino)pyridine (DMAP) to afford tosylate **114**, which was oxidised with  $\text{CrO}_3$  in HOAc to give ketone **115**. Then, ketone **115** was converted into enol acetate **116**. Treatment of **116** with MCPBA afforded acetoxy ketone **117**, which after treatment with  $\text{K}_2\text{CO}_3$  in MeOH gave compound **118**. Further hydrogenation led to hanagokenol A (**119**).

The treatment of ketone **118** with  $\text{NaBH}_4$  gave alcohol **120**, which after debenzylation afforded fortunin H (**121**). In the other sequence, 18-hydroxyferruginol (**104**) was first acetylated with  $\text{Ac}_2\text{O}$  and DMAP in pyridine. The corresponding diacetate, compound **122**, was oxidised with  $\text{CrO}_3$  in HOAc and the resulting ketone was then converted into enol acetate **123**. The treatment of **123** with MCPBA afforded the triacetoxy ketone **124**, which in two separate ap-

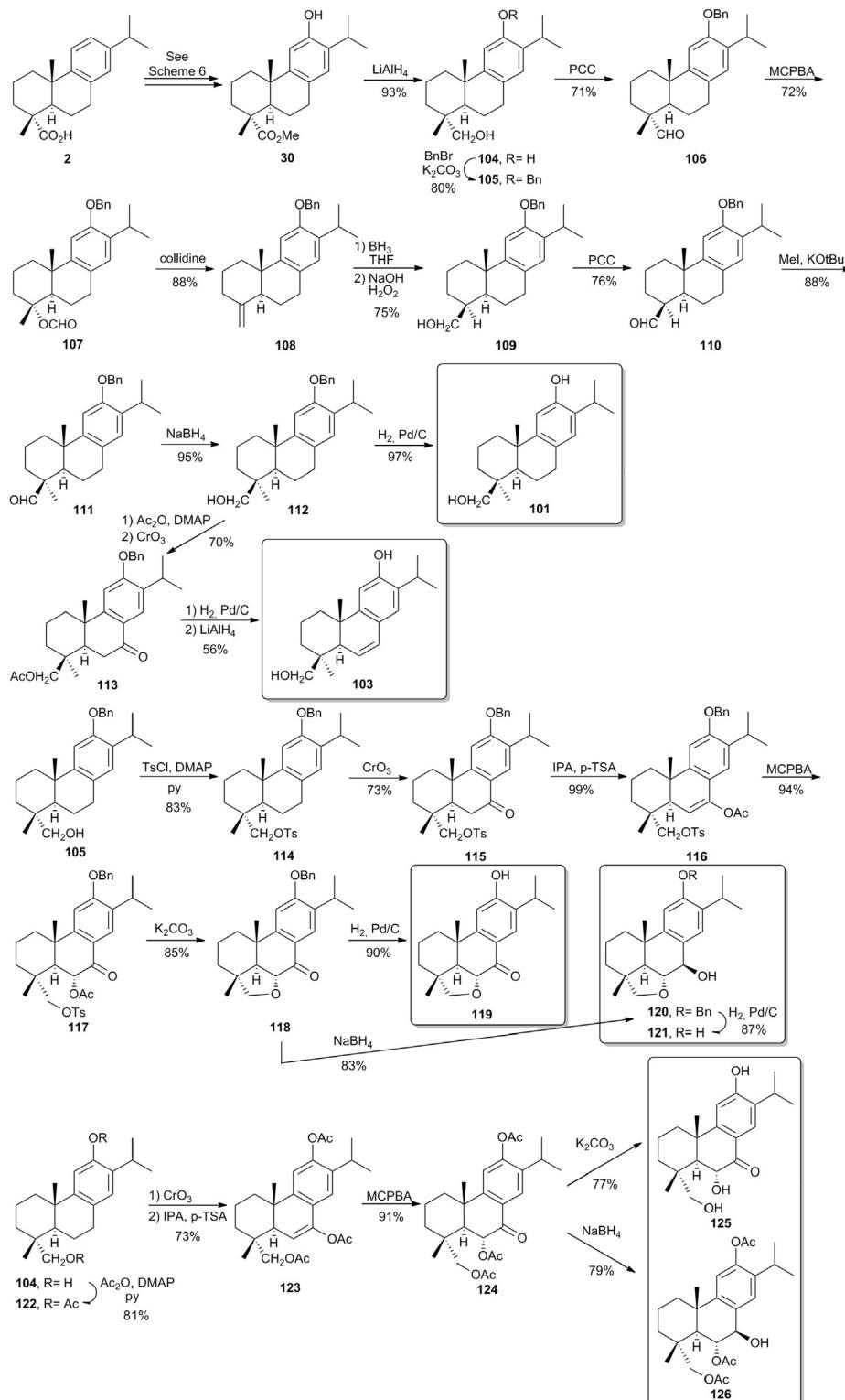


**Scheme 15.** Alvarez-Manzaneda's syntheses of 19-hydroxyferruginol (**101**) and sugikurojin A (**103**).

The same authors have published several papers on the synthesis of aromatic abietanes starting from abietic acid (**1**). For example, they developed a route to invert the C-4 carboxyl group in phenol **30** with the aim of obtaining 19-hydroxyferruginol (**101**) and sugikurojin A (**103**) (Scheme 16).<sup>26</sup> Phenol **30** was prepared via dehydroabietic acid (**2**) from abietic acid (**1**) as described by Cambie and Matsumoto (Scheme 6).<sup>16</sup> With intermediate **30** in hand, Alvarez-Manzaneda et al. inverted the C-4 stereochemistry using a formate transformation into an exocyclic alkene with complete regioselectivity. Thus, ester **30** was reduced with  $\text{LiAlH}_4$  to the

approaches led to fortunins E (**125**) and G (**126**). Firstly, saponification of **124** with  $\text{K}_2\text{CO}_3$  in MeOH gave fortunin E (**125**), and secondly reduction with  $\text{NaBH}_4$  in ethanol at –20 °C gave fortunin G (**126**).

In 2006, Alvarez-Manzaneda et al. reported the synthesis of picealactones A (**130a**) and B (**130b**), two natural abietanes, which contain a rare 5-dehydro-18,6-olide functionality, starting from abietic acid (**1**) (Scheme 17).<sup>27</sup> Thus, abietic acid (**1**) was converted into methyl 15-hydroxydehydroabietate (**128**), via known methyl abiet-8,13(15)-dien-18-oate (**127**).<sup>28</sup> by treatment with  $\text{SeO}_2$ . Methyl dehydroabietate (**26**) was used for the synthesis of

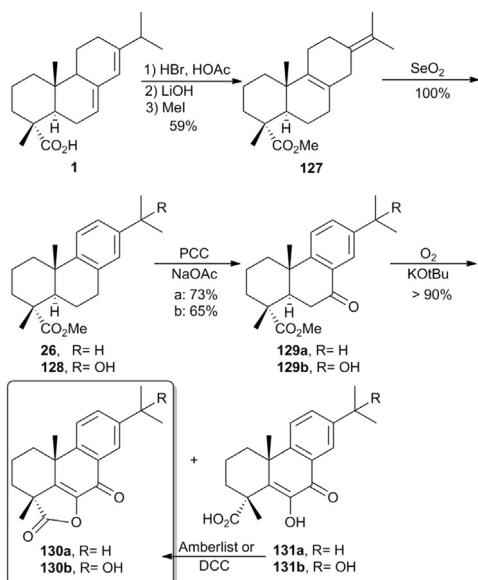


**Scheme 16.** Alvarez-Manzaneda's syntheses of 19-hydroxyferruginol (**101**), sugikurojin A (**103**), hanagokenol A (**119**) and fortunins H (**121**), E (**125**) and G (**126**).

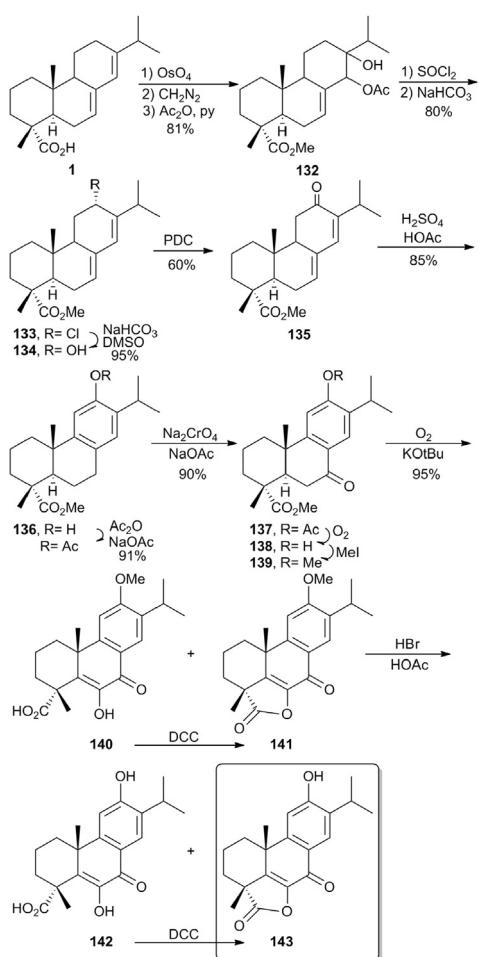
picealactone A (**130a**) and the 15-hydroxy derivative **128** for the synthesis of picealactone B (**130b**). The synthesis of both compounds was carried out by benzylic oxidation with PCC to give **129a,b**, followed by treatment with a stream of oxygen in the presence of KOt-Bu, to afford both picealactones A (**130a**) and B (**130b**) along with diosphenols **131a,b**.

The same synthetic methodology was used 1 year later by these authors to prepare picealactone C (**143**), this time, via methyl 12 $\alpha$ -chlor-

hydroxyabietate (**134**) obtained from abietic acid (**1**) (Scheme 18).<sup>29</sup> The synthesis began with the preparation of the acetate intermediate **132** by dihydroxylation with OsO<sub>4</sub>, methylation with diazomethane and acetylation with Ac<sub>2</sub>O in pyridine. When the acetate **132** was treated with SOCl<sub>2</sub> and Et<sub>3</sub>N at -78 °C and the reaction was quenched with aqueous NaHCO<sub>3</sub>, methyl 12 $\alpha$ -chloroabietate (**133**) was obtained in high yield. This chloride was transformed into alcohol **134** by treating with aqueous NaHCO<sub>3</sub> in



Scheme 17. Alvarez-Manzaneda's syntheses of picealactones A and B (130a,b).

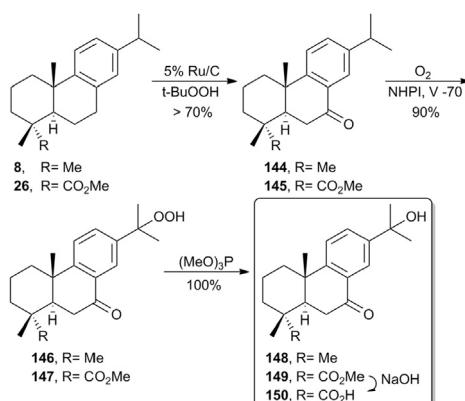


Scheme 18. Alvarez-Manzaneda's synthesis of picealactone C (143).

DMSO. The oxidation of alcohol 134 to ketone 135 was carried out with pyridinium dichromate (PDC). The isomerisation of dienone 135 to phenol 136 was achieved by refluxing a HOAc solution in the presence of H<sub>2</sub>SO<sub>4</sub>. After protecting the phenolic hydroxyl group of 136 as acetate, the 7-oxo group of the target molecule was

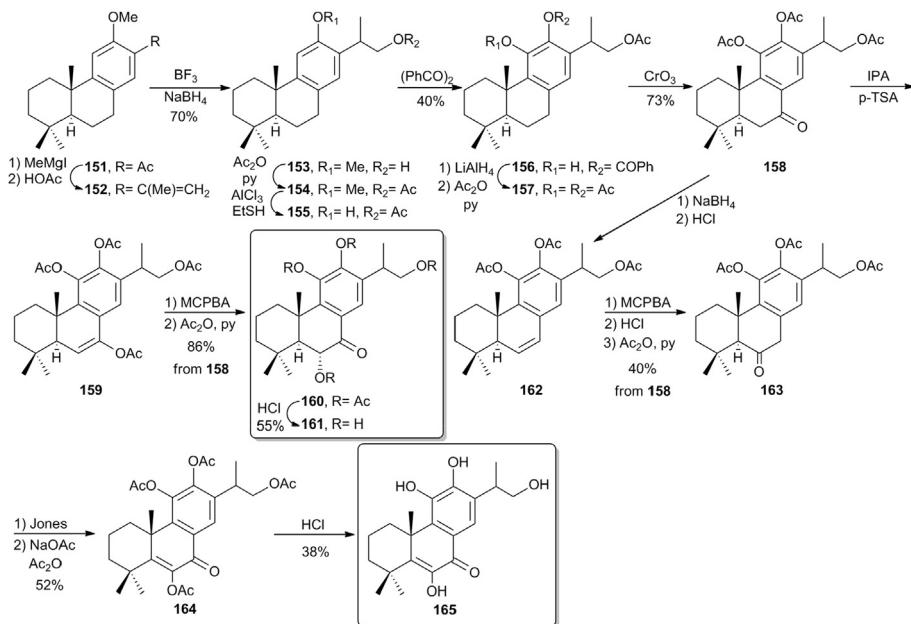
introduced by oxidation with Na<sub>2</sub>CrO<sub>4</sub> to give ketone 137. Then, it was applied the methodology for the synthesis of picealactones A (130a) and B (130b), that is, the treatment of a solution of 137 and KOt-Bu in *tert*-butanol with oxygen. However, only deacetylation was produced giving phenol 138. This was converted into the corresponding methyl ether 139 with MeI and K<sub>2</sub>CO<sub>3</sub>, which under the above-mentioned conditions gave a 1:1 mixture of the desired lactone 141 and diosphenol 140. Diosphenol 140 was converted into lactone 141 by treatment with DCC. Finally, the treatment of lactone 141 with HBr in HOAc gave a 1:2 mixture of diosphenol 142 and picealactone C (143), which was completely converted into the desired lactone 143 by treating with DCC.

A recent report by Matsushita et al. described how to prepare natural 15-hydroxy derivatives (148 and 150) by a novel aerobic oxidation under mild conditions with *N*-hydroxyphthalimide (NHPI) and the catalyst 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) (Scheme 19).<sup>30</sup> The synthesis started by oxidation of abiet-8,11,13-triene (8) and methyl dehydroabietate (26) to the corresponding 7-oxo compounds 144 and 145, using a catalytic system composed of 5% Ru/C and *tert*-BuOOH. Further oxidation at C-15 occurred by aerobic treatment with NHPI and V-70 as catalyst to give hydroperoxides 146 and 147, which were reduced in quantitative yield with (MeO)<sub>3</sub>P to afford 15-hydroxy derivatives 148 and 149. The latter was hydrolysed with NaOH to give naturally occurring 150.



Scheme 19. Matsushita's synthesis of 15-hydroxyabietanes 148 and 150.

Studies by Matsumoto et al. revised the structure of the nellionols (161) and (165) by chemical synthesis and comparison of the NMR spectra of their derivatives (Scheme 20).<sup>31</sup> They concluded that the two phenolic groups were located at positions C-11 and C-12 instead of C-11 and C-14. The synthesis started from 13-acetyl-12-methoxypodocarpa-8,11,13-triene (151) prepared methylation and Friedel–Crafts reaction on ferruginol (3) obtained from dehydroabietic acid (2) following the method of Oishi and Akita (Scheme 7).<sup>17</sup> Then, Grignard reaction of 151 with MeMgI followed by dehydration of the resulting alcohol in refluxing HOAc, afforded tetraene 152. This compound was converted into an epimeric mixture at C-15 of alcohols, compounds 153, by hydroboration and subsequent oxidation with alkaline H<sub>2</sub>O<sub>2</sub>. As the separation of these epimeric alcohols was not possible, the synthesis continued with the mixture. Acetylation of 153 with Ac<sub>2</sub>O in pyridine yielded the corresponding acetate (154), which was treated with AlCl<sub>3</sub> and ethanethiol to give phenol 155. The phenol 155 was oxidised with benzoyl peroxide to afford 11-hydroxy derivative 156. This was then converted into 11,12,16-triacetoxyabiet-8,11,13-triene (157) by treatment with LiAlH<sub>4</sub>, followed by acetylation with Ac<sub>2</sub>O in pyridine. Oxidation of 157 with CrO<sub>3</sub> in HOAc afforded the corresponding 7-oxo compound (158). The 7-oxo compound 158 was



Scheme 20. Matsumoto's syntheses of nelliol (161) and dehydronelliol (165).

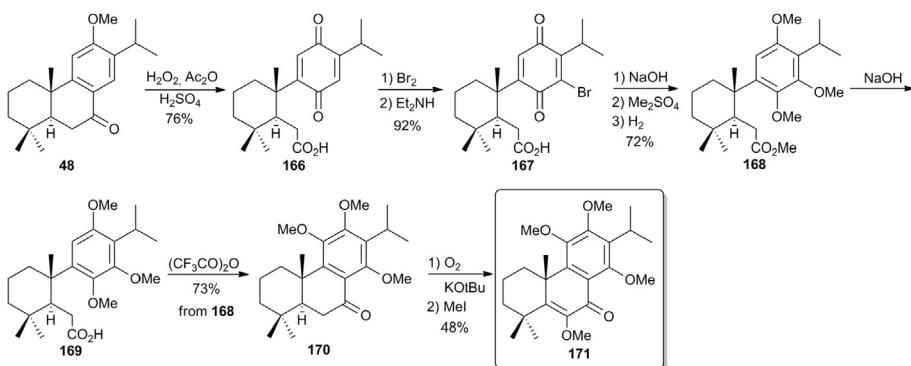
refluxed with IPA in the presence of *p*-TSA to give tetraene **159**. Oxidation of **159** with MCPBA, followed by acetylation gave tetraacetate **160**, which by hydrolysis with dilute HCl gave the desired nelliol **161**. The <sup>1</sup>H NMR spectra of **160** and **161** were in good agreement with those of natural nelliol and its tetraacetate. Subsequently the 7-oxo compound **158** was reduced with NaBH<sub>4</sub> to give a mixture of epimeric alcohols at C-7, which was immediately converted into tetraene **162** by treatment with dilute HCl and subsequent acetylation with Ac<sub>2</sub>O in pyridine. The tetraene **162** was further converted into 6-oxo compound **163** by a series of reactions: oxidation with MCPBA, treatment with dilute HCl and acetylation with Ac<sub>2</sub>O in pyridine. The oxidation of **163** with Jones reagent, followed by treatment with NaOAc in refluxing Ac<sub>2</sub>O, afforded the tetraacetate **164**. Hydrolysis of **164** with dilute HCl produced the desired dehydronelliol (**165**). The <sup>1</sup>H NMR spectra of **164** and **165** were in good agreement with those of natural dehydronelliol and its tetraacetate. Thus, the structures of natural nelliol and dehydronelliol were revised. However, the stereochemistry of the C-15 position in these natural compounds remained unsettled.

The synthesis of the related congener, coleon U as the tetra-O-methyl ether (**171**) (Scheme 21), was described by Burnell et al., in 1981, starting from sugiol methyl ether (**48**) prepared from podocarpic acid (**5**) following published methods (see Schemes 3 and 6).<sup>32</sup> Thus, peracetic acid oxidation of **48** afforded the expected

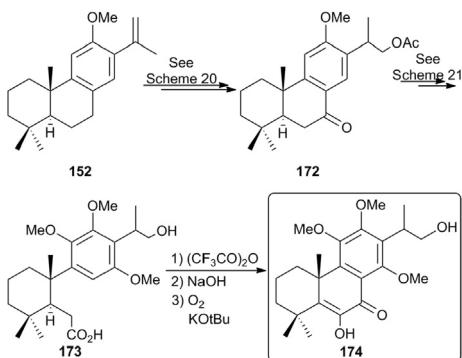
quinone **166** in excellent yield and the sequence of bromine addition and dehydrobromination gave regiospecifically the bromoquinone **167**. The facile exchange of the bromo substituent by hydroxyl with NaOH followed by catalytic reduction and immediate methylation in situ gave methyl ester **168**, which was hydrolyzed readily to the corresponding acid **169**. This acid smoothly cyclised in trifluoroacetic anhydride, to the expected ketone **170**. Oxygenation of **170** in basic media gave the corresponding enolic  $\alpha$ -diketone, which was methylated to give coleon U tetra-O-methyl ether (**171**).

Based on these results, a few years later, this research group described the synthesis of coleon C tri-O-methyl ether (**174**) (Scheme 22), following a similar route to Matsumoto's sequence for the introduction of the 16-hydroxyl group in the synthesis of dehydronelliol (**165**) (Scheme 20) via ketone **172**.<sup>33</sup> With the ketone **172** in hand, a similar route to that of the synthesis of coleon U tetra-O-methyl ether was used to afford coleon C **174** via cyclisation of compound **173** and similar aerobic oxidation in basic media (Scheme 21).

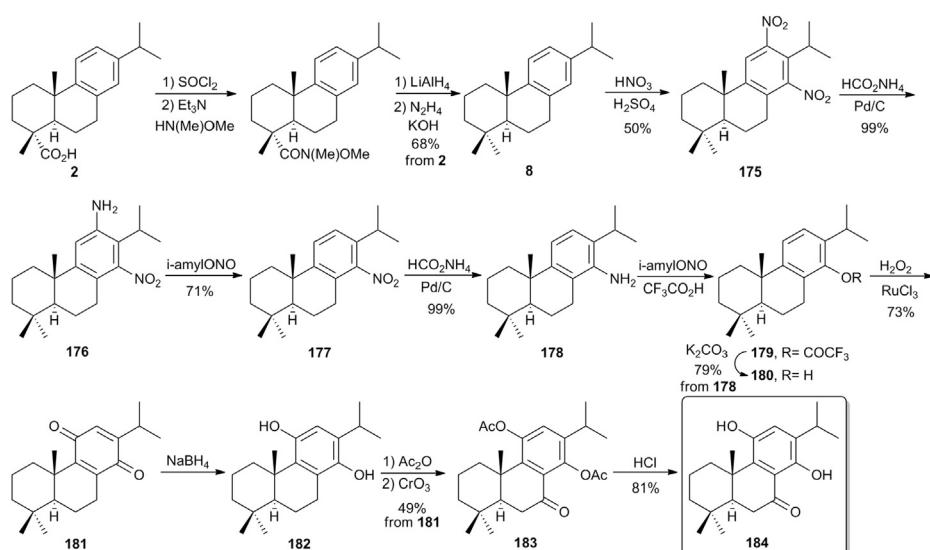
In 2005, Matsushita et al. reported the synthesis of naturally occurring hydroquinone (11,14-dihydroxy-8,11,13-abietatrien-7-one) **184**, along with other quinones, starting from dehydroabietic acid (**2**) via phenol **180** (Scheme 23).<sup>34</sup> Thus, compound **2** was converted into abietatriene **8** (68% overall yield), which was



Scheme 21. Burnell's synthesis of coleon U tetra-O-methyl ether (171).



**Scheme 22.** Burnell's synthesis of coleon C tri-O-methyl ether (**174**).



**Scheme 23.** Matsushita's synthesis of 11,14-dihydroxy-8,11,13-abietatriene-7-one (**184**).

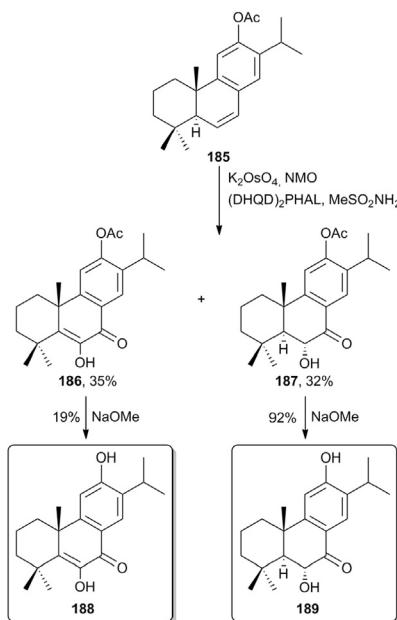
nitrated with  $HNO_3/H_2SO_4$  to afford dinitro compound **175**. This compound was reduced selectively with  $HCOONH_4$  in the presence of Pd/C as a catalyst to give 12-amino-14-nitro compound **176**. Deamination by diazotisation–reduction was achieved with isoamyl nitrite to afford nitro compound **177**, which was further reduced with  $HCOONH_4$ –Pd/C to 14-amino compound **178**. Diazotisation and treatment with  $CF_3CO_2H$  afforded 14-trifluoroacetoxy compound **179**, which was hydrolysed with  $K_2CO_3$  to give phenol **180**. The oxidation of **180** with  $H_2O_2$  catalysed by  $RuCl_3$  gave quinone **181**, which was reduced to hydroquinone **182** with  $NaBH_4$ . Acetylation of **182** and oxidation with  $CrO_3$  yielded ketone **183**, which was hydrolysed with HCl to yield the natural 11,14-dihydroxyketone **184**.

Recently, Gademann et al. reported the synthesis of the anti-cancer agents 6-hydroxy-5,6-dehydrosugiol (**188**) and 6-hydroxysugiol (**189**) from naturally derived 6,7-dehydroferruginyl acetate (**185**) under hydroxylation conditions ( $K_2OsO_4$ , hydroquinidine 1,4-phthalazinediyl diether [(DHQD)<sub>2</sub>PHAL], *N*-methylmorpholine *N*-oxide [NMO], and  $MeSO_2NH_2$ ) to give alcohols **186** and **187** (Scheme 24).<sup>35</sup> Deacetylation of both compounds was achieved by standard transesterification procedure using NaOMe in MeOH to provide sugiols **188** and **189**.

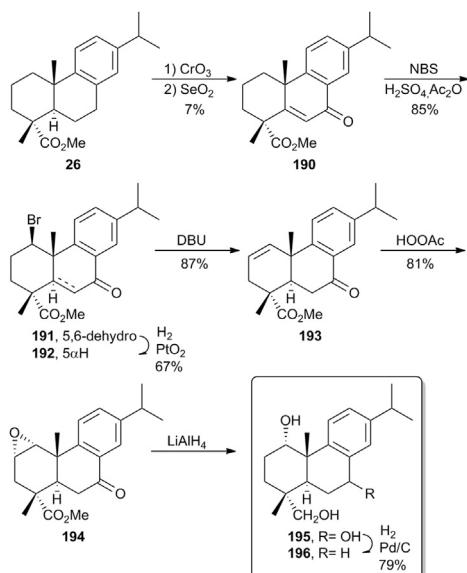
Tahara's group described the synthesis of an A-ring functionalised abietane such as teideadiol (**196**). In their strategy, they started from methyl dehydroabietate (**26**) and introduced a bromine atom at position C-1 via phenacylidene **190** (Scheme 25).<sup>36</sup> Thus,

compound **26** was treated with  $CrO_3$  followed by oxidation with  $SeO_2$  to give phenacylidene **190**. Treatment of **190** with *N*-bromosuccinimide and 5%  $H_2SO_4/Ac_2O$  gave bromide **191**, which was hydrogenated on a  $PtO_2$  catalyst to afford compound **192** with a trans A/B ring juncture. Dehydrobromination of **192** with diazabicyclo [5.4.0]-undecene (DBU) gave olefin **193**, which was treated with  $HOOAc$  in HOAc to yield  $1\alpha,2\alpha$ -epoxide **194**. The epoxide **194** was reduced with  $LiAlH_4$  into the triol **195**, which was submitted, without purification, to hydrogenolysis with 10% Pd/C to give teideadiol (**196**).

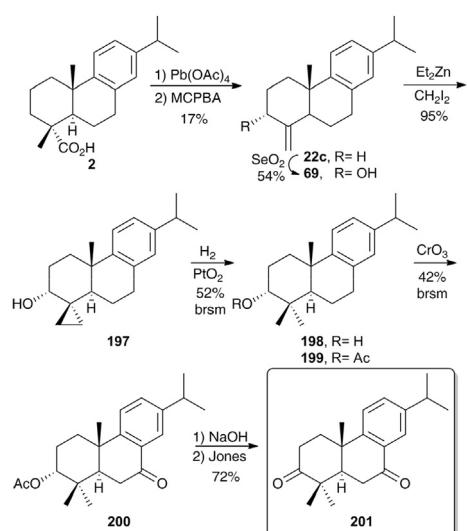
Another synthesis of an A-ring functionalised compound, marnocin (**201**), was reported by Burnell et al. starting from dehydroabietic acid (**2**) via known allylic alcohol **69** (Scheme 26).<sup>37</sup> Allylic alcohol **69** was obtained with the route presented in Scheme 12 and also from the exocyclic olefin **22c**, which was



**Scheme 24.** Gademann's synthesis of sugiols (**188** and **189**).



Scheme 25. Tahara's synthesis of teideadiol (196).



Scheme 26. Burnell's synthesis of margocin (201).

obtained from decarboxylation of dehydroabietic acid (**2**). Thus, the treatment of **2** with Pb(OAc)<sub>4</sub> gave a mixture of olefins in 50% yield, which after reaction with MCPBA the unreacted exocyclic olefin **22c** could be separated in 35% yield. Oxidation of **22c** with SeO<sub>2</sub> gave alcohol **69**, which was reacted under modified Simmons-Smith conditions to give cyclopropyl intermediate **197**. Hydrogenolytic opening of the three-membered ring proved more difficult than anticipated. Despite this, enough of the *gem*-dimethyl compound **198** was obtained to continue the synthesis. The hydroxyl group in **198** was protected as the acetate derivative **199**, and the C-7 benzylic position was oxidised with CrO<sub>3</sub> to give ketone **200**. After hydrolysis of the acetate in **200**, Jones oxidation gave the diketone **201**, margocin.

The synthetic studies of pisiferic acid (**10**) (Fig. 2) and the related 11-hydroxy derivative (carnosic acid) have been reviewed up to 2003.<sup>38</sup> Herein, we present the related syntheses of pisiferic acid (**10**) derivatives, pisiferol (**213**) and pisiferal (**214**) (Scheme 27).<sup>39</sup> These naturally occurring diterpenes are characterised by an oxidised angular methyl group and were synthesised from dehydroabietic acid (**2**) by transannular oxidation. Thus, compound **2**

was converted into abietatriene **8** by known methods (Scheme 23). Then, abietatriene **8** was converted into a mixture of 7α- and 7β-acetoxyabiet-8,11,13-triene **202**, which by treatment with 10% HCl afforded tetraene **203**. This compound was oxidised with MCPBA to give an epoxide, which, without purification, was converted into abieta-8,11,13-trien-6-one (**204**) by refluxing with *p*-TSA. Reduction of **204** with LiAlH<sub>4</sub> yielded abieta-8,11,13-trien-6β-ol (**205**), which was oxidised at the angular methyl group by treatment with Pb(OAc)<sub>4</sub> in the presence of I<sub>2</sub> to give epoxyabietane **206**. Treatment of **206** with *p*-toluenesulfonic anhydride produced a mixture of 20-acetoxyabiet-6,8,11,13-tetraene (**207**) and 20-acetoxyabiet-5,8,11,13-tetraene (**208**). This mixture was submitted to catalytic hydrogenation over PtO<sub>2</sub> in HOAc to afford a mixture of 20-acetoxyabiet-8,11,13-triene (**209**) and its *cis*-isomer (**210**). Because of the difficulty of the separation of **209** and **210**, the mixture was immediately treated with LiAlH<sub>4</sub>. After repeated column chromatography the alcohol abieta-8,11,13-triene-20-ol (**211**) was isolated, which was acetylated and subjected to Friedel-Crafts acylation with AcCl in the presence of AlCl<sub>3</sub>. The Baeyer-Villiger oxidation of the resulting acetyl derivative with MCPBA in the presence of *p*-TSA afforded diacetate **212**, which was treated with LiAlH<sub>4</sub> to yield pisiferol (**213**). Oxidation of **213** with Jones reagent afforded pisiferal (**214**).

Recently, Tada et al. reported the synthesis of bioactive carnosic acid (**215**) and carnosol (**216**) from natural pisiferic acid (**10**) (Scheme 28).<sup>40</sup> Thus, the oxidation of **10** to introduce a hydroxyl group at C-11 was carried out with several reagents. The best results were found after treatment of **10** with 2-iodoxybenzoic acid (IBX) giving an unstable *ortho*-quinone, which was reduced with NaBH<sub>4</sub> to carnosic acid (**215**). Benzylic oxidation of **215** with Ag<sub>2</sub>O gave desired carnosol (**216**) with in situ lactonisation.

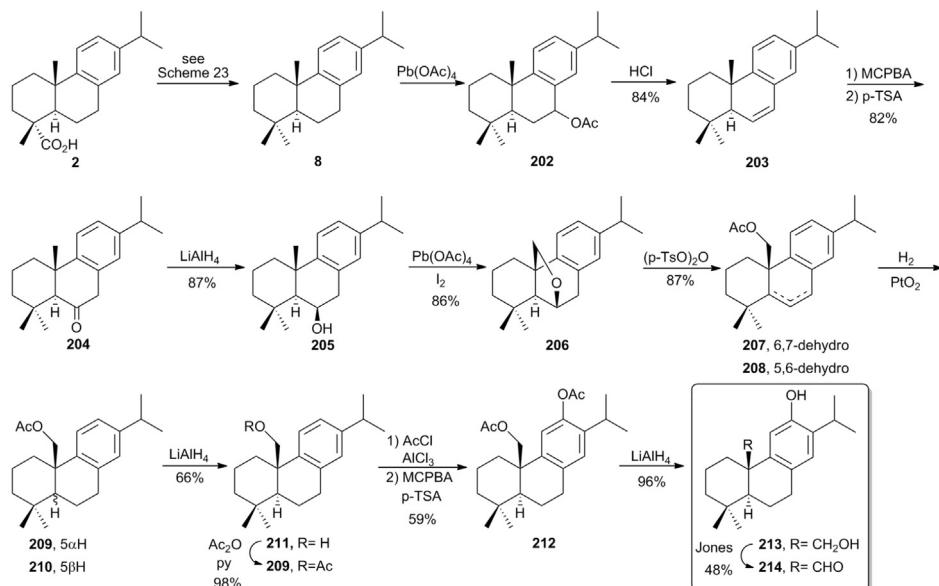
Contemporaneous studies by González et al. described the preparation of bioactive 7α-hydroxydehydroabietinol (**218**) and its corresponding 7-oxo derivative (**219**, 7-oxodehydroabietinol) from abietic acid (**1**) via oxidation of abietinol (**217**) (Scheme 29).<sup>41</sup> Thus, abietic acid (**1**) was reduced with LiAlH<sub>4</sub> to abietinol (**217**), which was oxidised with excess SeO<sub>2</sub> and *t*-BuOOH to give compound **218**. Further oxidation with MnO<sub>2</sub> afforded ketone **219**.

Finally, González and Zaragozá have just reported the synthesis of the antiviral diterpenoid jiadifenoic acid C (**222**) from callitrisic acid (**4**) isolated from sandarac resin (Scheme 30).<sup>42</sup> Callitrisic acid (**4**) was used as its methyl ester (**17**, methyl callitrisate), which was converted into tetraene **220** by treatment with DDQ. Allylic C-17 oxygenation with catalytic SeO<sub>2</sub> and *t*-BuOOH as co-oxidant gave, after treatment with NaBH<sub>4</sub>, alcohol **221**. Ester hydrolysis with LiI in collidine afforded jiadifenoic acid C (**222**) in 22% overall yield from methyl callitrisate (**17**).

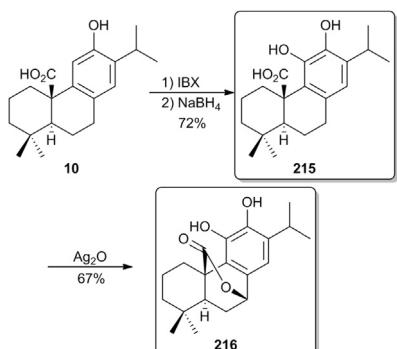
### 3.2. Total syntheses

As mentioned previously, most of the studies directed towards the total synthesis of aromatic abietane diterpenoids are racemic, including the synthesis of resin acids (±)-DHA (**2**), (±)-callitrisic acid (**4**), as well as the synthesis of (±)-ferruginol (**3**) and some of its congeners. The first enantioselective total synthesis of an aromatic abietane diterpenoid occurred in 1979, when (+)-ferruginol (**3**) was obtained by a Japanese research group.<sup>10</sup> Since then, several enantioselective total syntheses of this terpenoid have been achieved, including the synthesis of its enantiomer. Only recently, in 2014, the enantioselective total synthesis of DHA (**2**) has been described by the Corey's research group at Harvard.<sup>43</sup>

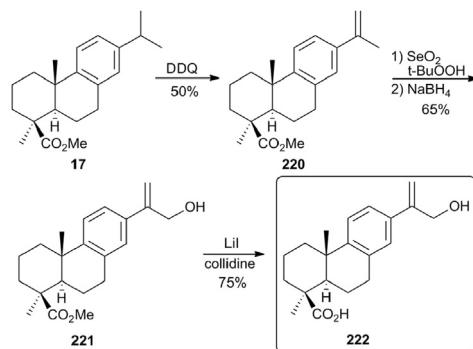
The first total synthesis of a diterpene resin acid, (±)-callitrisic acid (**4**), was reported by Haworth and Barker as early as 1939 (Scheme 31).<sup>44</sup> Interestingly, it occurred 28 years before the natural product was isolated.<sup>45</sup> The synthesis exploited the Bogert–Cook reaction on a cyclohexene **223**, which is appropriately substituted



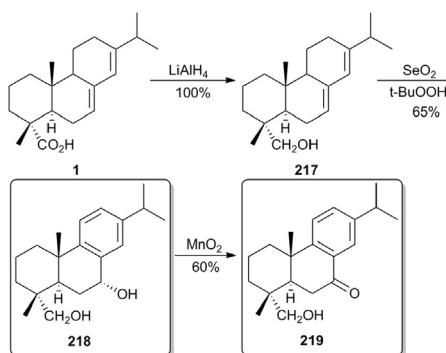
Scheme 27. Matsumoto's synthesis of pisiferol (213) and pisiferal (214).



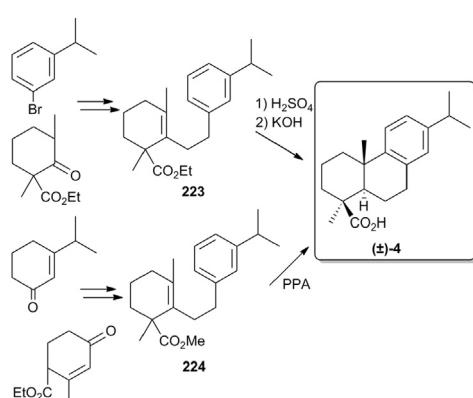
Scheme 28. Tada's synthesis of carnosic acid (215) and carnosol (216).



Scheme 30. González's synthesis of jiadifenoic acid C (222).



Scheme 29. González's synthesis of dehydroabietinols 218 and 219.

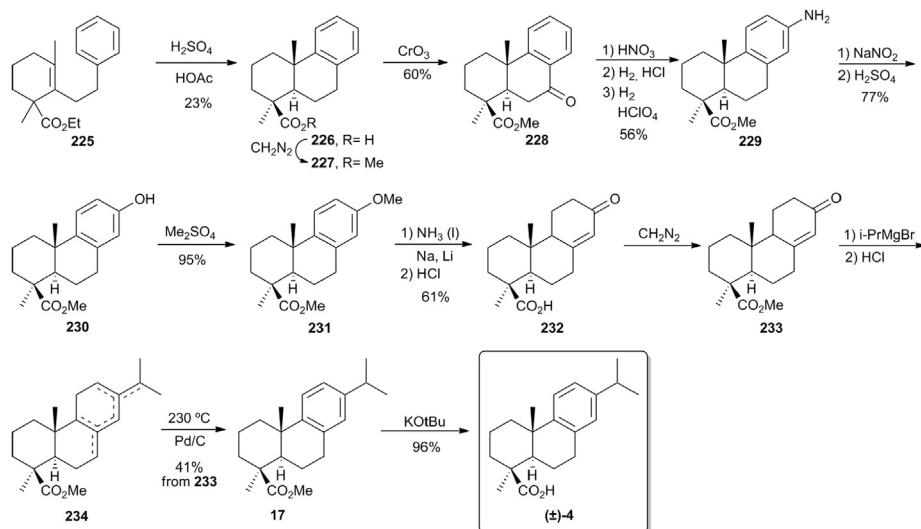


Scheme 31. Haworth's and Sharma's syntheses of callitrisic acid (4).

with a phenylethylene moiety. Cyclohexene **223** was obtained from 3-bromocumene and 2,6-dimethylcyclohexanone-2-carboxylate. Cyclisation of **223** with HOAc/H<sub>2</sub>SO<sub>4</sub> gave a tricyclic ester, which was hydrolysed with KOH to give ( $\pm$ )-**4**. In 1963, the same strategy was used by Sharma et al. using polyphosphoric acid (PPA) for the key cyclisation step on the cyclohexene **224**, prepared from 3-isopropylcyclohexenone and 4-carbethoxy-3-methyl-2-cyclohexen-1-one (Scheme 31).<sup>46</sup>

Based on these results, Mori and Matsui reported, in 1968, another synthesis of ( $\pm$ )-callitrisic acid (**4**) from cyclohexene **225**, via

methyl podocarpenoate **233** (Scheme 32).<sup>47</sup> Thus, according to the method of Haworth and Barker (cyclisation with HOAc/H<sub>2</sub>SO<sub>4</sub>) the cyclohexene **225** gave tricyclic acid **226** with a trans A/B ring juncture and an axial carboxyl group. Chromic acid oxidation of the corresponding methyl ester **227** gave ketone **228**, which was nitrated and hydrogenated in two steps to give amino ester **229**. Diazotisation of **229** and hydrolysis gave phenol **230**, which was methylated with Me<sub>2</sub>SO<sub>4</sub> to give methoxy-ester **231**. The Birch reduction and treatment with HCl of **231** gave acid **232**, which was



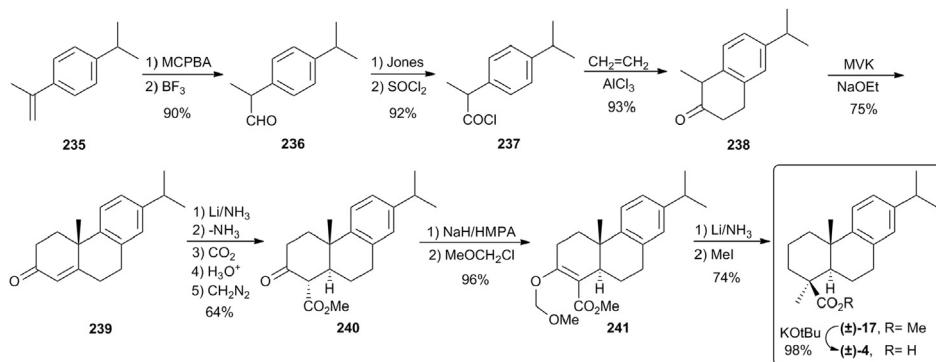
Scheme 32. Mori's and Matsui's synthesis of 4-epidehydroabietic acid (4, callitrisic acid).

converted into its corresponding methyl ester, compound **233**, with ethereal CH<sub>2</sub>N<sub>2</sub>. Treatment of keto ester **233** with *i*-PrMgBr and dehydration with acid gave a mixture of olefins **234**, which was heated at 230–240 °C with Pd/C to effect disproportionation. After chromatographic separation methyl (±)-4-epidehydroabietate (**17**, methyl callitrisate) was obtained in 41% yield from ester **233**. Hydrolysis with KOt-Bu in DMSO gave the racemic acid **4**.

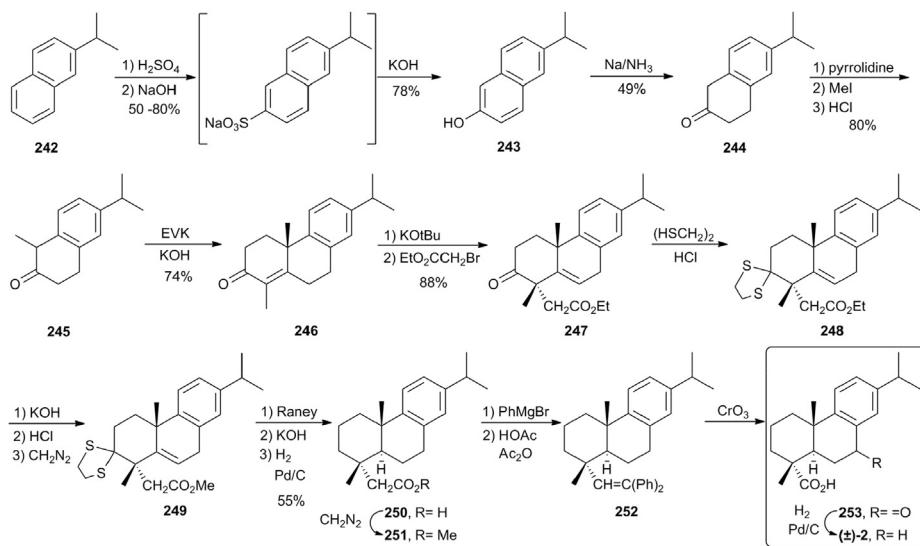
In 1976, the total synthesis of (±)-callitrisic acid (**4**) was reported by Welch et al. starting from 4-isopropenylisopropylbenzene (**235**), via β-keto ester **240** (Scheme 33).<sup>48</sup> Epoxidation of alkene **235** with MCPBA in the presence of Na<sub>2</sub>HPO<sub>4</sub>, followed by acid rearrangement using BF<sub>3</sub> etherate afforded aldehyde **236** in high yield. Oxidation of aldehyde **236** with Jones reagent produced the corresponding acid, which was treated with SOCl<sub>2</sub> to give acid chloride **237**. Acid chloride **237** was allowed to react with ethylene in the presence of anhydrous AlCl<sub>3</sub> at –15 °C to give bicyclic ketone **238**. Ring annelation of tetralone **238** with methyl vinyl ketone (MVK) in the presence of a catalytic amount of NaOEt afforded tricyclic enone **239**. Reductive carbomethoxylation of enone **239** by sequential treatment with Li in liquid ammonia/ether; quickly removing the ammonia; adding freshly sublimed, anhydrous dry-ice; carefully extracting to remove neutral side products; acidifying at 0 °C; and esterifying with CH<sub>2</sub>N<sub>2</sub> gave β-keto ester **240** in 64% yield. Ketoester **240** was O-alkylated using NaH in hexamethylphosphoramide (HMPA) followed by MeOCH<sub>2</sub>Cl to produce vinyl ether ester **241**. Finally, reductive-elimination–alkylation of vinyl ether ester **241** by treatment with Li in liquid ammonia followed by quenching with MeI afforded (±)-methyl callitrisate (**17**) as the

only isomer observed. Ester (±)-**17** was saponified quantitatively using KOt-Bu followed aqueous acid to give (±)-callitrisic acid (**4**).

The first total synthesis of (±)-dehydroabietic acid (**2**) was reported in 1956 by Stork and Schulenberg, starting from 2-isopropylnaphthalene **242** via phenanthrone **246** (Scheme 34).<sup>49</sup> The key step was the alkylation of **246** with ethyl bromoacetate, which defined the stereochemistry of the C-4 centre. Thus, sulfonation 2-isopropylnaphthalene **242** gave a sodium sulfonate salt, which was not purified and was directly converted into 6-isopropyl-2-naphthol **243** by fusion with KOH. Birch reduction of naphthol **243** gave 6-isopropyl-2-tetralone **244**, which was alkylated via pyrrolidine enamine with MeI to afford methyl ketone **245**. Ring annelation of tetralone **245** with ethyl vinyl ketone (EVK) in the presence of aqueous methanolic KOH afforded tricyclic enone **246**. Enone **246** was alkylated by treatment with KOt-Bu and EtO<sub>2</sub>CCH<sub>2</sub>Br to the desired keto ester **247**. Conversion of **247** into its thioketal **248** was accomplished by treatment with HSCH<sub>2</sub>CH<sub>2</sub>SH in the presence of anhydrous HCl. Then, thioketal **248** was converted into its methyl ester **249** by saponification and esterification with CH<sub>2</sub>N<sub>2</sub>. Desulfurisation with Raney nickel followed by ester hydrolysis and hydrogenation with Pd/C in HOAc afforded homodehydroabietic acid **250**, which was converted into its corresponding methyl ester, compound **251**, with CH<sub>2</sub>N<sub>2</sub>. Barbier–Wieland degradation of the ester **251**, via the diphenylcarbinol and diphenylethylene **252** with chromic acid, gave 7-oxo-dehydroabietic acid **253**, which was converted into (±)-dehydroabietic acid (**2**) by hydrogenation on Pd/C. This synthesis was a milestone in diterpene chemistry.



Scheme 33. Welch's synthesis of callitrisic acid (4).

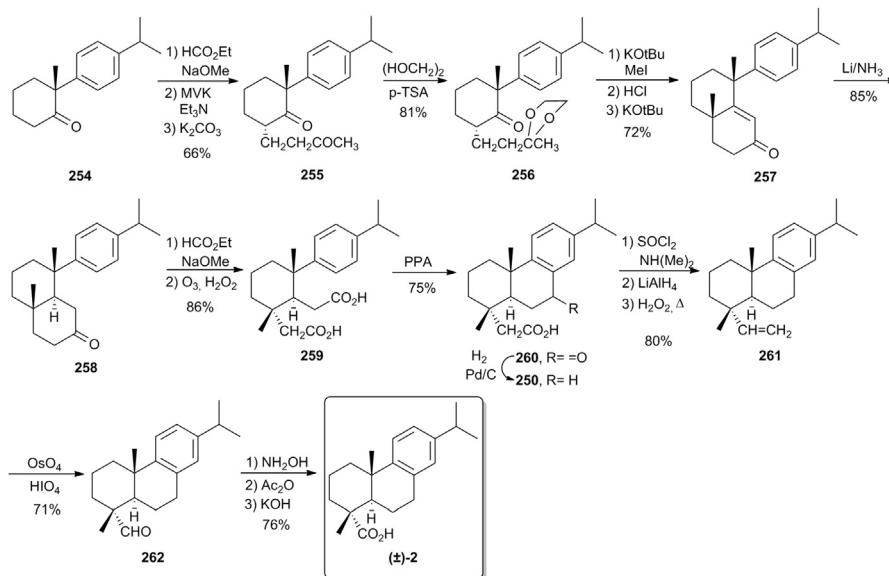


Scheme 34. Stork's and Schulenberg's synthesis of dehydroabietic acid (2).

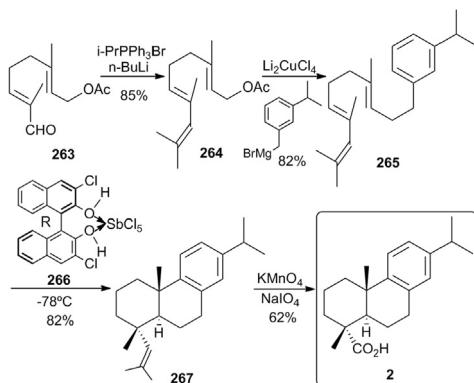
Another total synthesis of  $(\pm)$ -dehydroabietic acid (2) was reported in 1962 by Ireland and Kierstead, starting from 2-methyl-2-(*p*-isopropylphenyl)cyclohexanone 254 via decalone 258 (Scheme 35).<sup>50</sup> The key steps are: a stereoselective alkylation and a reduction with Li in liquid ammonia to give decalone 258 and a polyphosphoric acid (PPA) catalysed cyclisation to give tricyclic homoacid 260. Thus, cyclohexanone 254 was activated at position-6 towards alkylation with a formyl group, then methyl vinyl ketone (MVK) was added to introduce a four-carbon side chain and the activating formyl group was removed with aqueous  $\text{K}_2\text{CO}_3$  to give diketone 255. Selective ketalisation of the side chain ketone in 255 afforded ketal 256. Stereoselective alkylation of 256 with  $\text{KOt-Bu}$  and  $\text{MeI}$  gave the desired stereochemistry at the future C-4. Hydrolysis and treatment with  $\text{KOt-Bu}$  of the resulting diketone afforded enone 257, which was reduced with Li in liquid ammonia to introduce the last stereocenter, decalone 258, with the fused ring system. Cleavage of decalone 258 by ozonisation of the derived hydroxymethylene/decalone gave diacid 259, which was treated with polyphosphoric acid (PPA) to afford tricyclic keto acid 260. Hydrogenolysis of 260 gave homodehydroabietic acid 250,

which was degraded following a similar sequence to that of Barbier–Wieland process but under milder conditions to avoid oxidation of the B-ring at C-7, as it occurred in the synthesis of Stork (Scheme 34). Thus, compound 250 was converted into the vinylic compound 261 via tertiary amine by amine oxide pyrolysis. Treatment of 261 with  $\text{OsO}_4$  and  $\text{HIO}_4$  gave the corresponding aldehyde, compound 262, which was converted into  $(\pm)$ -dehydroabietic acid (2) via its derived nitrile by hydrolysis.

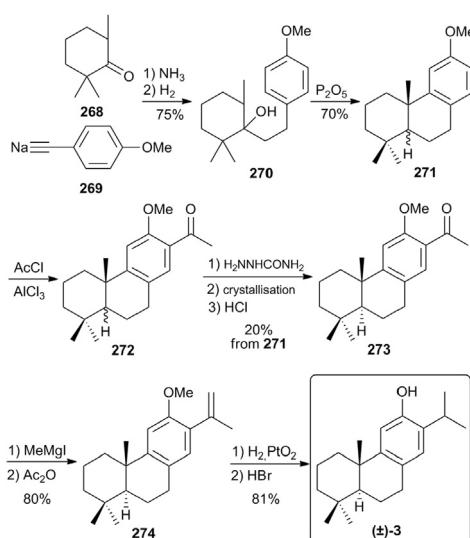
Very recently, Corey et al. reported a very short enantioselective synthesis of  $(+)$ -dehydroabietic acid (2) starting from a derivative of geranyl acetate, compound 263, using as key step an enantioselective cationic polycyclisation with  $o,o'$ -dichloro-*R*-BINOL (266) complex with  $\text{SbCl}_5$  (Scheme 36).<sup>43</sup> Compound 263 was converted into olefin 264 by Wittig reaction. Coupling of 264 with *m*-isopropylbenzylmagnesium bromide by copper catalysis ( $\text{Li}_2\text{CuCl}_4$ ) gave the cyclisation precursor 265. This substrate underwent smooth cyclisation with the complex 266/ $\text{SbCl}_5$  to the required tricyclic product 267 with high enantioselectivity (91% ee) and high yield (82%). Subsequent degradation of the olefin 267 with  $\text{KMnO}_4$  and  $\text{NaIO}_4$  afforded  $(+)$ -dehydroabietic acid (2).



Scheme 35. Ireland's and Kierstead's synthesis of dehydroabietic acid (2).

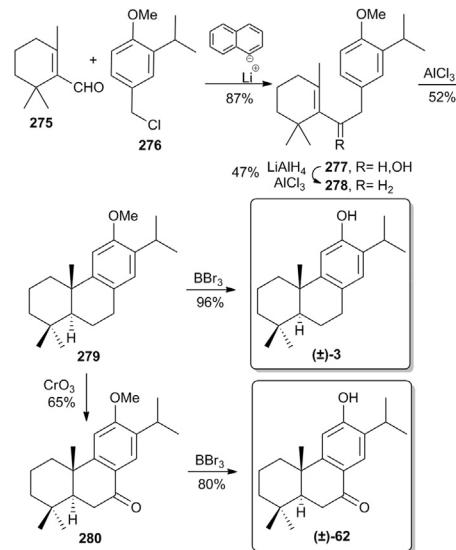
**Scheme 36.** Corey's synthesis of dehydroabietic acid (2).

Synthetic efforts directed towards ferruginol (**3**) have employed various permutations of the order in which the three rings are assembled. The earliest approach by King et al., 1957, utilised the Bogert–Cook ring-closure (Scheme 37), as in the synthesis of callictric acid (**4**) (Schemes 31 and 32), but suffered from a lack of stereoselectivity in the A/B ring fusion. However, this synthesis represented the first established synthesis of the racemic form of a naturally occurring tricyclic diterpene.<sup>51</sup> The synthesis started with the preparation of cyclisation precursor **270** by reaction of 2,2,6-trimethylcyclohexanone **268** and sodium-p-methoxyphenylacetylide **269** in liquid ammonia followed by hydrogenation with a palladium catalyst. Cyclisation of **270** with phosphoric oxide ( $P_2O_5$ ) gave a mixture of cis- and trans-isomers (**271**) in the A/B ring juncture. This mixture was subjected to Friedel–Crafts acylation with AcCl and AlCl<sub>3</sub> to give a mixture of ketones **272**, which were separated by fractional crystallisation of the corresponding semicarbazones. Regeneration of the ketone by hydrolysis with HCl gave pure trans-isomer **273** in 20% overall yield from mixture **271**. Reaction of pure isomer **273** with MeMgI gave a tertiary alcohol, which was dehydrated with Ac<sub>2</sub>O to the isopropenyl derivative **274**. This was hydrogenated with Adams (PtO<sub>2</sub>) catalyst and then demethylated with HBr to give ( $\pm$ )-ferruginol (**3**).

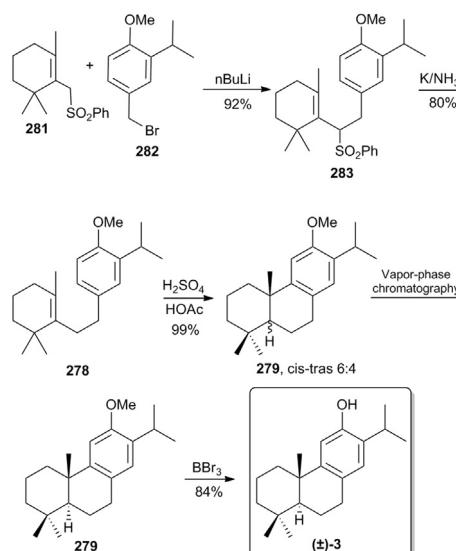
**Scheme 37.** King's synthesis of ferruginol (3).

In 1977, Matsumoto et al. used the same type of cyclisation to prepare racemic ferruginol (**3**) and sugiol (**62**), this time, starting from two C<sub>10</sub> units  $\beta$ -cyclocitral (**275**) and 3-isopropyl-4-methoxybenzyl chloride (**276**) via cyclisation precursor **278**

(Scheme 38).<sup>52</sup> Thus, condensation of **275** and **276** in the presence of lithium naphthalenide afforded alcohol **277**, which was reduced, to effect the cleavage of the hydroxyl group, with dichloroaluminium hydride to give **278**. Cyclisation of **278** with anhydrous AlCl<sub>3</sub> produced tricyclic compound ferruginyl methyl ether (**279**), which was demethylated with BBr<sub>3</sub> to give ( $\pm$ )-ferruginol (**3**). Subsequently, compound **279** was oxidised with CrO<sub>3</sub> to the corresponding 7-oxo compound **280**. The demethylation of **280** with BBr<sub>3</sub> gave ( $\pm$ )-sugiol (**62**).

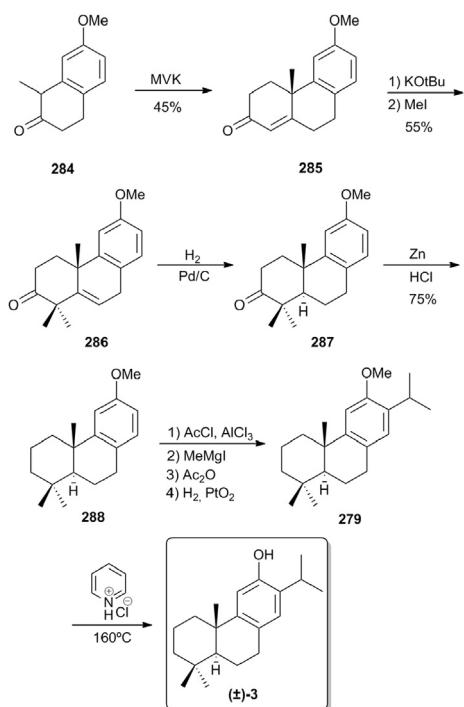
**Scheme 38.** Matsumoto's synthesis of ferruginol (3) and sugiol (62).

Contemporaneous studies by Torii et al. described a similar route to ( $\pm$ )-ferruginol (**3**) using phenylsulfone **281** and 3-isopropyl-4-methoxybenzyl bromide (**282**) as C<sub>10</sub> units for the synthesis of the cyclisation precursor **278** (Scheme 39).<sup>53</sup> Thus, the reaction of **281** with **282** afforded compound **283** on treatment with n-BuLi. Desulphonation of **283** to precursor **278** was accomplished selectively without reducing the anisole ring, by the action of potassium in liquid ammonia. Cyclisation of **278** in HOAc/H<sub>2</sub>SO<sub>4</sub> (9:1) afforded **279** as a mixture (6:4) of cis- and trans-isomers. The isomers were separated by vapour-phase chromatography (VPC).

**Scheme 39.** Torii's synthesis of ferruginol (3).

Demethylation of the trans-isomer **279** with BBr<sub>3</sub> gave ( $\pm$ )-ferruginol (**3**).

In 1958, Rao and Raman described a stereospecific synthesis of ( $\pm$ )-ferruginol (**3**) using a different synthetic strategy, a Robinson's annelation on bicyclic ketone **284** to build up the tricyclic ring system (Scheme 40).<sup>54</sup> Thus, condensation of ketone **284** with methyl vinyl ketone (MVK) afforded enone **285**. Introduction of a *gem*-dimethyl group by treatment of **285** with KOt-Bu and MeI led to unsaturated ketone **286**, which was hydrogenated with 10% Pd/C in HOAc to give the *trans* ketone **287**. The keto group in compound **287** was reduced by Clemmensen's method to afford compound **288** and an isopropyl group was then introduced by a procedure similar to that described by King et al. Compound **288** was subjected to Friedel-Crafts reaction with AcCl and AlCl<sub>3</sub>, Grignard reaction with MeMgI, dehydration with Ac<sub>2</sub>O, and hydrogenation on PtO<sub>2</sub> to give ferruginyl methyl ether (**279**). This was then demethylated with pyridine hydrochloride to give ( $\pm$ )-ferruginol (**3**).



**Scheme 40.** Rao's and Raman's synthesis of ferruginol (**3**).

Another different route to  $(\pm)$ -ferruginol (**3**) and  $(\pm)$ -sugiol (**62**) via enedione **293** was devised by Meyer et al., starting from *trans* decalone **289** (Scheme 41), which was prepared from 6-cyano-2,2-dimethylcyclohexanone.<sup>55</sup> Condensation of decalone **289** with ethyl formate produced hydroxymethylene ketone **290**, which was

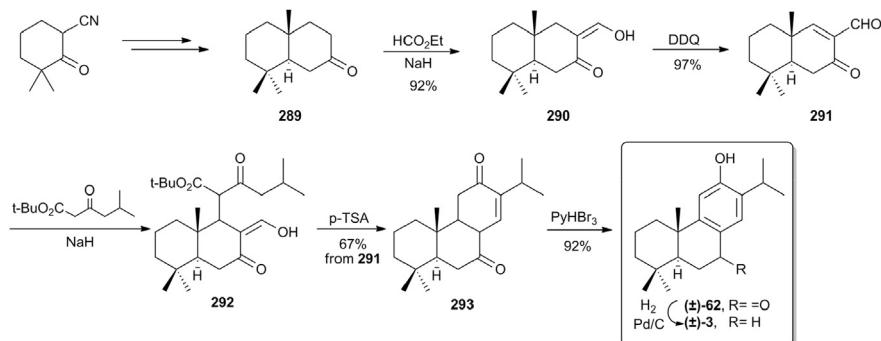
dehydrogenated with DDQ to give unsaturated keto aldehyde **291**. Michael addition of the sodium enolates of *tert*-butyl isovalerylacetate led to the adduct **292** as a mixture of two diastereomeric racemates. These were not purified but directly exposed to *p*-toluenesulfonic acid (*p*-TSA), which induced cleavage of the *tert*-butyl group, decarboxylation, and cyclodehydration to give enedione **293**. Next, facile aromatisation was achieved with pyridine hydrobromide perbromide (PyHBr<sub>3</sub>) in HOAc to the corresponding phenol ( $\pm$ )-sugiol (**62**). Hydrogenolysis of ( $\pm$ )-sugiol (**62**) over 30% Pd/C removed the benzylic ketone and produced ( $\pm$ )-ferruginol (**3**).

In 1978, Watt et al. reported the synthesis of  $(\pm)$ -ferruginol (**3**) and  $(\pm)$ -hinokione (**77**), in which the tricyclic ring system was assembled by two successive Robinson annelations on 2-carboethoxycyclohexanone **294** with ethyl vinyl ketone (Scheme 42).<sup>56</sup> The resulting intermediate **296** was then elaborated to introduce the appropriate functionality in the C ring, previous protection of the enone moiety in the A-ring. Thus, the ketalisation of compound **296** with ethylene glycol proceeded with concomitant lactonisation to give the bridged  $\delta$ -lactone **297**. The oxidation of **297** with  $\text{CrO}_3 \cdot 2\text{py}$  furnished the enone **298**, whose zinc enolate was condensed with acetaldehyde to give  $\beta$ -hydroxyketone **299** as a mixture of diastereomers. Dehydration of **299** with *p*-TSA then secured the cross-conjugated dienones **300** as an 8:1 mixture of *E/Z* isomers. The regioselective addition of lithium dimethylcuprate to the s-*cis* enone of **300** completed the introduction of the isopropyl group, giving compound **301**. Compound **301** was converted into dienone **302** by treatment with lithium diisopropylamide (LDA) and PhSeCl and then oxidation with  $\text{H}_2\text{O}_2$ . At this point, the acid-catalysed hydrolysis of the ketal in **302** proceeded with concomitant  $\beta$  elimination, decarboxylation, and aromatisation to furnish the phenol **303**. This was methylated with  $\text{Me}_2\text{SO}_4$  to give methyl ether **304**, which was reduced with lithium in ammonia and further methylated with MeI to give ketone **305**. The Wolff–Kishner reduction of **305** and demethylation with  $\text{BBr}_3$  provided  $(\pm)$ -ferruginol (**3**). In addition, similar demethylation of **305** provided  $(\pm)$ -hinokione (**77**).

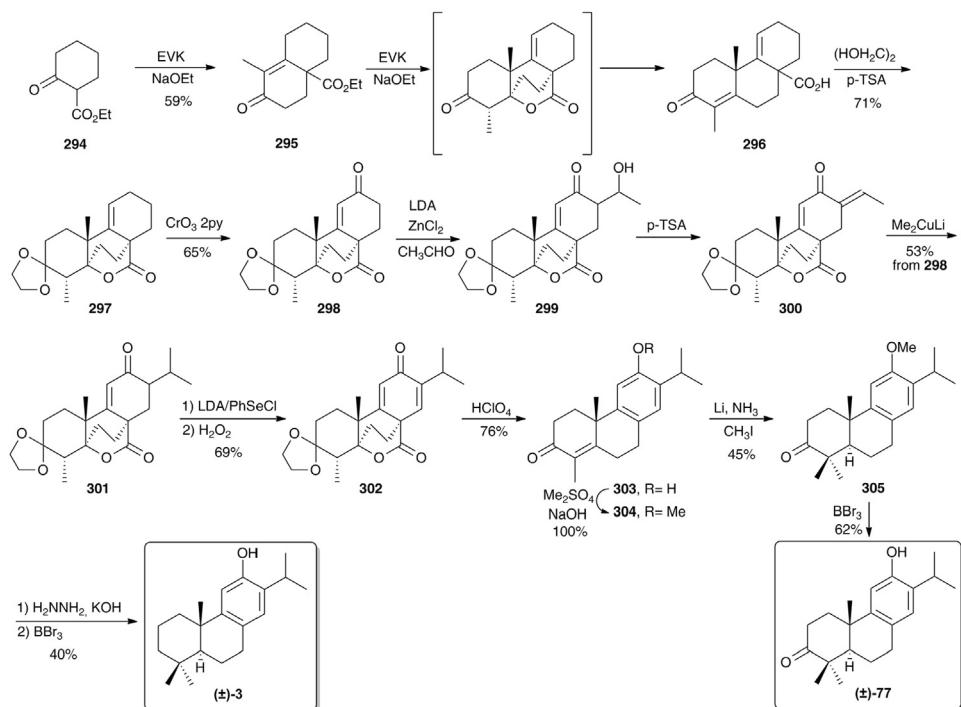
In 1993, Pan and Wang described the total synthesis of ( $\pm$ )-euphraticol (**308**) from cyclisation precursor **306** using the classical Bogert–Cook ring-closure (Scheme 43).<sup>57</sup>

In 2004, Ramana and Bhar reported the total synthesis of ( $\pm$ )-ferruginol (**3**) via domino acylation–cycloalkylation on acid **309** (Scheme 44).<sup>58</sup> Thus, acid **309** was subjected to domino acylation–cycloalkylation with anisole, using a 10:1 mixture of  $\text{MeSO}_3\text{H}/\text{P}_2\text{O}_5$ , to give tricyclic ketone **310**, which was subsequently reduced to compound **288**. Compound **288** has already been transformed to ( $\pm$ )-ferruginol (**3**) (see Scheme 40). These authors used a similar reaction sequence.

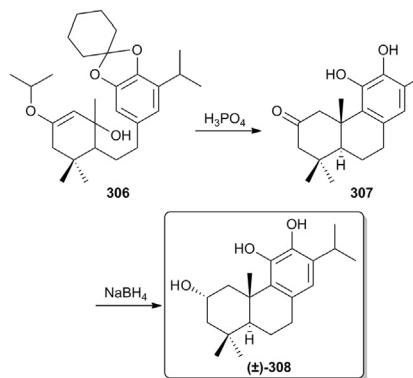
The first total synthesis of (+)-ferruginol (3) was achieved by Matsumoto and Usui in 1979 (Scheme 45).<sup>10</sup> They started the synthesis from (−)- $\alpha$ -cyclocitral (311), which was subjected to Wittig reaction with (3-isopropyl-4-methoxybenzyl)



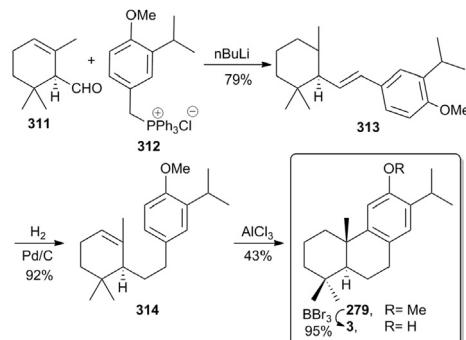
**Scheme 41.** Meyer's synthesis of sugiol (**62**) and ferruginol (**3**).



**Scheme 42.** Watt's synthesis of ferruginol (**3**) and hinokione (**77**).



**Scheme 43.** Pan's synthesis of euphraticol (**308**).

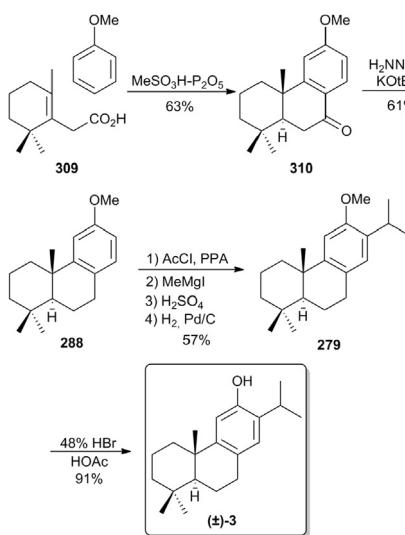


**Scheme 45.** Matsumoto's synthesis of ferruginol (**3**).

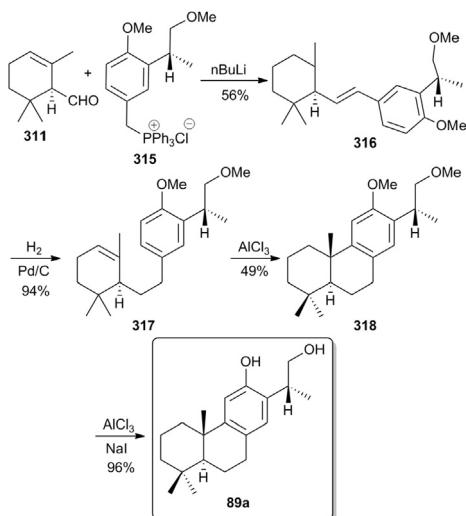
triphenylphosphonium chloride **312**. The resulting *trans* alkene **313** was submitted to partial catalytic hydrogenation to afford cyclisation precursor **314**. Treatment of **314** with anhydrous AlCl<sub>3</sub> gave a mixture of two tricyclic compounds. The chromatographic purification of the mixture afforded ferruginyl methyl ether (**279**) and its *cis*-isomer in a ratio of 1:1. Demethylation of **279** with BBr<sub>3</sub> gave (+)-ferruginol (**3**).

Later on, these authors reported the total synthesis of natural 16-hydroxyferruginol (**89a**) based on the same strategy starting from  $(-)$ - $\alpha$ -cyclocitral (**311**) (Scheme 46).<sup>59</sup> This time, the Wittig reaction was carried out with optically active phosphonium salt **315**, which was prepared by resolution by means of cinchonidine of the acid precursor. The Wittig reaction of  $(-)$ - $\alpha$ -cyclocitral (**311**) with **315** gave *trans* alkene **316**, which was submitted to partial catalytic hydrogenation over Pd/C to afford the corresponding phenethyl derivative **317**. The intramolecular cyclisation of **317** with anhydrous AlCl<sub>3</sub> gave a mixture of two tricyclic compounds. The chromatographic purification of the mixture afforded dimethyl ether **318** in 49% yield. Demethylation of **318** with AlCl<sub>3</sub> and NaI furnished  $(+)$ -16-hydroxyferruginol (**89a**).

In 2000, Pan et al. improved this synthetic strategy changing the cyclisation reagent and the cyclisation precursor to avoid mixtures after cyclisation. They reported the stereoselective synthesis of

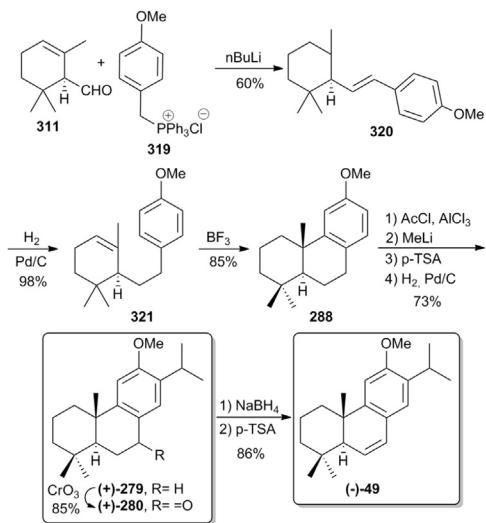


**Scheme 44.** Ramana's and Bhar's synthesis of ferruginol (**3**).



**Scheme 46.** Matsumoto's synthesis of 16-hydroxyferruginol (89a).

(+)-ferruginyl methyl ether (279), (+)-sugiy methyl ether (280), and (−)-6,7-dehydroferruginyl methyl ether (49) starting from (−)- $\alpha$ -cyclocitral (311) (Scheme 47).<sup>60</sup> Thus, the Wittig reaction of (−)- $\alpha$ -cyclocitral (311) with phosphonium chloride 319 in the presence of *n*-BuLi gave the styrene derivative 320, which was subjected to partial hydrogenation to give phenethyl derivative 321. Cyclisation of 321 with BF<sub>3</sub> etherate provided tricyclic derivative



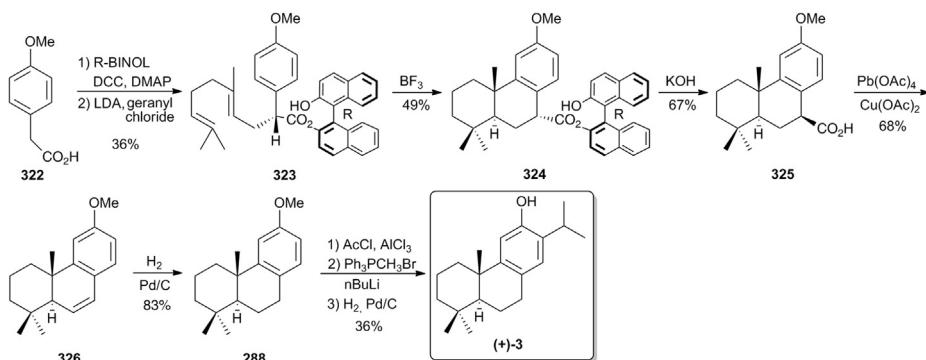
**Scheme 47.** Pan's synthesis of ferruginyl and sugiy methyl ethers (279, 280).

**288** in high yield and stereoselectivity (*de*>95%). Compound **288** was converted into (+)-ferruginyl methyl ether (**279**) following a similar sequence to those reported (see Schemes 40 and 44). Oxidation of **279** with CrO<sub>3</sub> gave (+)-sugiy methyl ether (**280**), which was converted into (−)-6,7-dehydroferruginyl methyl ether (**49**) by reduction and dehydration.

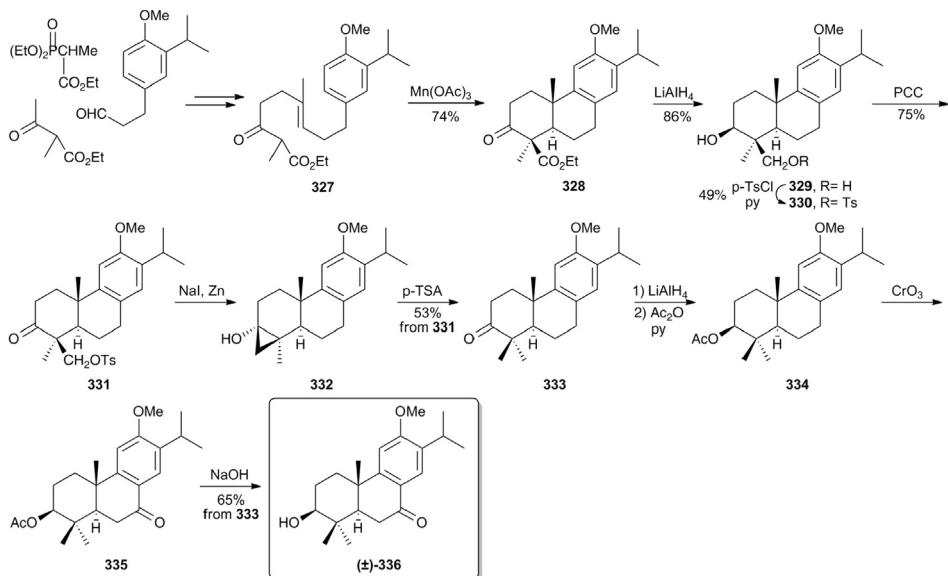
Contemporaneous studies by Tada et al. described the synthesis of (+)-ferruginol (**3**) and its unnatural enantiomer via asymmetric cyclisation of a polyene (Scheme 48).<sup>61</sup> To this end, the polyene derivative **323** was prepared from *R*-BINOL and *p*-methoxyphenyl acetic acid (**322**). Treatment of polyene **323** with BF<sub>3</sub> etherate provided tricyclic derivative **324**, which was hydrolysed with KOH to give acid **325**. Decarboxylation of **325** gave compound **326**, which was hydrogenated to give known **288**. Compound **288** was treated as in other reports to introduce the isopropyl group. In this case, Friedel–Crafts acylation with 4 equiv of AlCl<sub>3</sub> gave deprotection of the methyl ether in **288**, then, Wittig reaction with methyltriphenylphosphonium bromide and hydrogenation on Pd/C afforded (+)-ferruginol (**3**). (−)-Ferruginol (**3**) was synthesised by similar procedures starting from *S*-BINOL. This research group reported the synthesis of cryptojaponol (**46**) and salvinolone (**92**) using this methodology (asymmetric polyene cyclisation) for the synthesis of intermediate (+)-ferruginol (**3**) and a similar route to Matsumoto's synthesis of cryptojaponol (see Scheme 6) for further functionalisation.<sup>62</sup>

Another cascade-type cyclisation had been reported by Burnell et al. for the synthesis of racemic margocilin O-methyl ether (**336**) (Scheme 49).<sup>63</sup> In this work, the key step was a radically initiated cyclisation with Mn(OAc)<sub>3</sub> in HOAc on  $\beta$ -keto ester **327**, which led to tricyclic derivative **328**. Compound **328** was reduced with LiAlH<sub>4</sub> to the diol **329**, and subsequently was selectively tosylated at the primary alcohol to **330**. The remaining C-3 hydroxyl group was oxidised to the ketone **331**, which on reduction with NaI and Zn, afforded a hydroxycyclopropyl intermediate **332**. The latter was not isolated but immediately rearranged to the *gem*-dimethyl ketone **333** by refluxing with p-TSA in benzene. The ketone **333** was reduced to the alcohol and protected as the acetate **334**, then, this substance was oxidised with CrO<sub>3</sub> to the C-7 ketone **335**. Hydrolysis afforded the alcohol ( $\pm$ )-**336**, margocilin O-methyl ether, identical with the natural product in all respects.

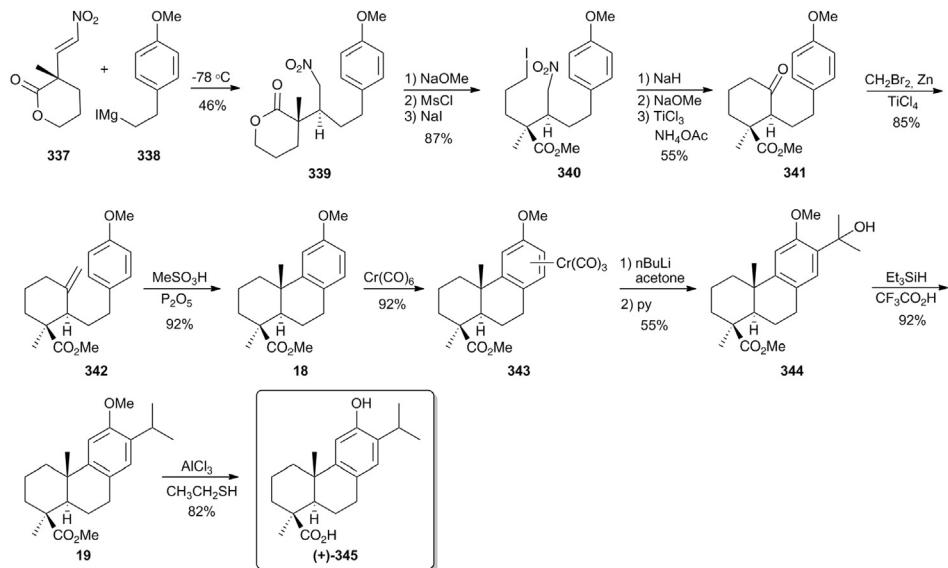
In the early 1990s, Fuji's research group described the total synthesis of (+)-lambertic acid (**345**) starting from chiral nitroalkene **337** via methyl O-methylpodocarpate (**18**) (Scheme 50).<sup>64</sup> Thus, the treatment of nitroalkene **337** with Grignard reagent **338** afforded a mixture where compound **339** was the major isomer. The lactone ring in **339** was opened with NaOMe to give a hydroxyl ester, which was further converted into the iodide **340** by mesylation followed by the substitution with NaI. Intramolecular alkylolation of **340** and the successive Nef reaction with TiCl<sub>3</sub>/NH<sub>4</sub>OAc provided cyclohexanone **341**. Methylenation of **341** with the Nozaki's reagent (CH<sub>2</sub>Br<sub>2</sub>/Zn/TiCl<sub>4</sub>) gave alkene **342** without



**Scheme 48.** Tada's synthesis of ferruginol (3).



Scheme 49. Burnell's synthesis of margocilin O-methyl ether (336).



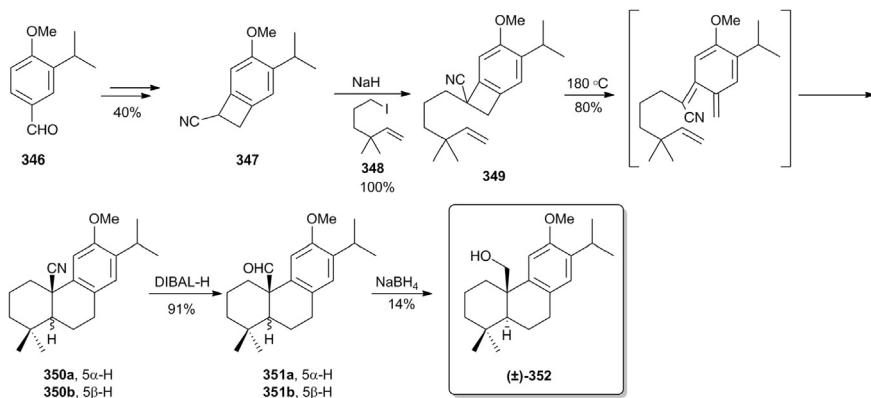
Scheme 50. Fuji's synthesis of lambertic acid (345).

epimerisation at C-5, while epimerisation occurred under the normal Wittig conditions ( $\text{Ph}_3\text{P}=\text{CH}_2/\text{KOT-Bu}$ ). Treatment of **342** with modified polyphosphoric acid ( $\text{MeSO}_3\text{H}/\text{P}_2\text{O}_5$ ) afforded a 92% yield of methyl O-methylpodocarpane (**18**). The desired trans A/B juncture was obtained selectively. Then, the synthetic problem was the introduction of the isopropyl group at C-13 for the formation of (+)-lambertic acid (**345**). Instead of the typical Friedel–Crafts acetylation (see Scheme 3), these authors used the chromium complex **343** as starting material, which was prepared by treatment of **18** with chromium hexacarbonyl ( $\text{Cr}(\text{CO})_6$ ). The chromium complex **343** was treated with *n*-BuLi to form a lithio anion *ortho* to the methoxy group, which reacted with acetone to furnish **344** after decomplexation in refluxing pyridine. Reductive removal of the hydroxyl group in **344** was accomplished by ionic hydrogenation with  $\text{Et}_3\text{SiH}/\text{CF}_3\text{CO}_2\text{H}$  to give **19**, which was converted into (+)-lambertic acid (**345**) by demethylation with a combination system of  $\text{AlCl}_3$  and ethanethiol.

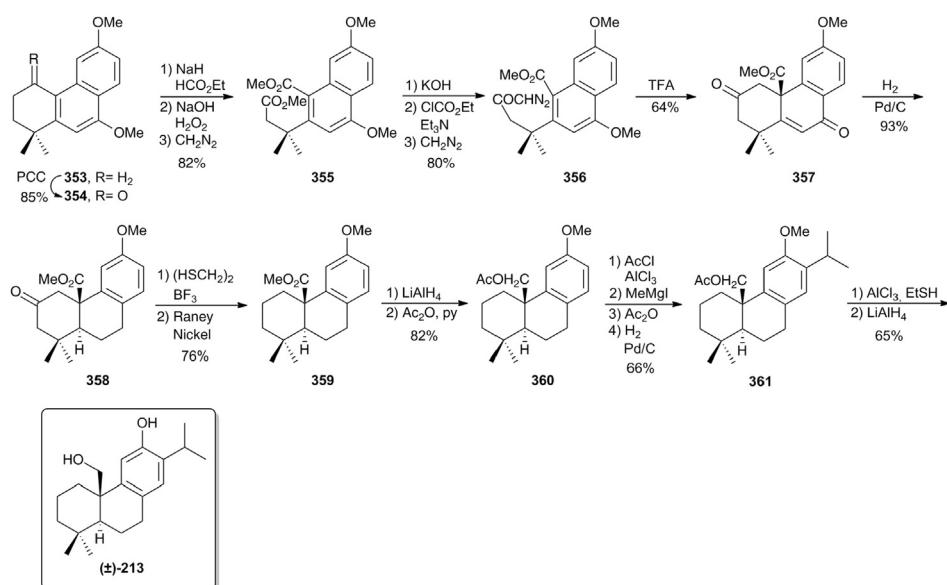
Contemporaneous studies by Honda et al. reported the total synthesis of racemic pisiferol methyl ether (**352**) using the

thermolysis of the olefinic benzocyclobutene **349** as the key step (Scheme 51).<sup>65</sup> The synthesis began with the preparation of benzocyclobutene **347** by a known method from aldehyde **346**. Then, compound **347** was alkylated with the iodide **348** to give olefinic benzocyclobutene **349** in quantitative yield. Thermolysis of **349** in *o*-dichlorobenzene at 180 °C proceeded through intramolecular Diels–Alder reaction of an *o*-quinodimethane to afford tricyclic compounds **350a,b** as an inseparable 1:4 mixture. Reduction of both nitriles **350a,b** with diisobutylaluminium hydride (DIBAL-H) afforded the corresponding aldehydes **351a,b**, which on reduction with  $\text{NaBH}_4$  gave the separable alcohol ( $\pm$ )-**352**, pisiferol methyl ether.

Finally, a total synthesis of ( $\pm$ )-pisiferol (**213**) has been reported by Mukherjee and Pati starting from the accessible tetrahydrophenanthrene **353** via the derivative **360** as key intermediate (Scheme 52).<sup>66</sup> Oxidation of **353** with PCC furnished the ketone **354**. This ketone was condensed with ethyl formate in the presence of NaH to give a hydroxymethylene derivative, which was treated with  $\text{H}_2\text{O}_2$  followed by  $\text{CH}_2\text{N}_2$  to afford diester **355**. Partial



Scheme 51. Honda's synthesis of pisiferol methyl ether (352).



Scheme 52. Mukherjee's synthesis of pisiferol (213).

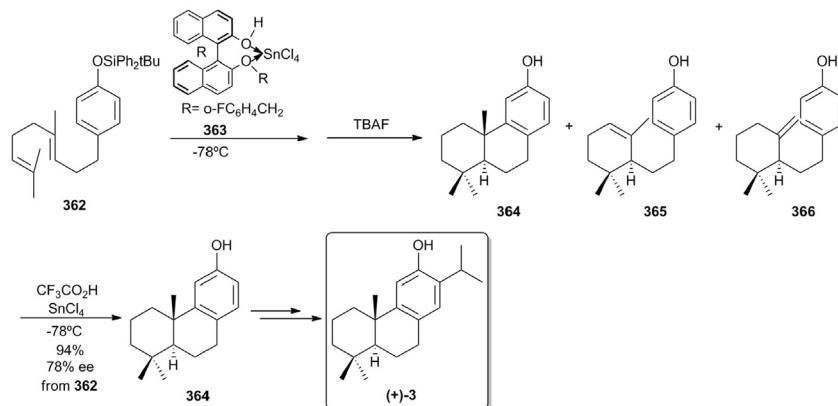
hydrolysis of the diester gave an acid, which was converted into diazomethyl ketone 356. Treatment of diazoketone 356 with CF<sub>3</sub>CO<sub>2</sub>H at -20 °C produced the intramolecular cyclisation to give the enedione 357, which on catalytic hydrogenation yielded the trans-fused keto ester 358 as the sole product. The carbonyl group in ring A was removed via the corresponding ethylene thioketal by desulfurisation with Raney nickel to afford compound 359. Reduction of 359 with LiAlH<sub>4</sub> followed by acetylation of the resulting primary alcohol provided the acetate 360, which was subjected to a typical procedure to introduce the isopropyl group, compound 361, through Friedel–Crafts acylation, reaction with MeMgI, dehydration and hydrogenation. Demethylation of 361 with AlCl<sub>3</sub> and ethanethiol followed by reduction with LiAlH<sub>4</sub> furnished (±)-pisiferol (213).

### 3.3. Other approaches

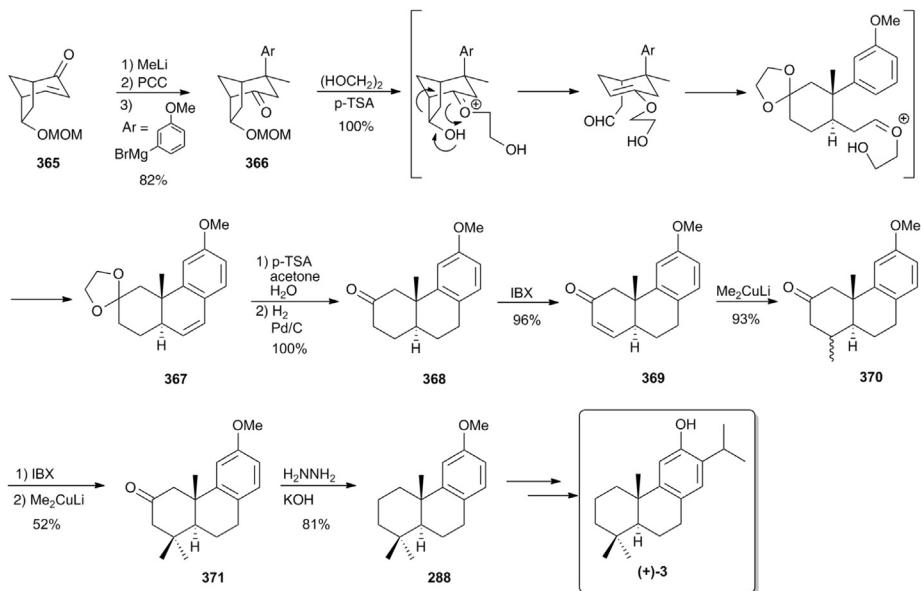
In this section, several approaches to natural abietanes including formal total synthesis, and synthesis of unnatural abietanes will be described. For example, Yamamoto et al. reported in 2001 the enantioselective polyene cyclisation of homogeranylbenzene derivative 362, induced by a Lewis acid-assisted chiral Brønsted acid 363, to obtain compound 364 (Scheme 53), which had

previously been converted into ferruginol (3).<sup>67</sup> Therefore, this method represented a formal enantioselective total synthesis of (+)-ferruginol (3). The cyclisation of 362 with 363 at -78 °C for 3 days gave a mixture of products, which were subjected to desilylation with tetrabutylammonium fluoride (TBAF) to give a mixture of compounds 364–366. Further treatment of the mixture 364–366 with SnCl<sub>4</sub>/CF<sub>3</sub>CO<sub>2</sub>H led to compound 364 in 78% ee and 94% yield from 362 in three steps.

Contemporaneous studies by Ogasawara et al. described another formal total synthesis of (+)-ferruginol (3). This method employed a tandem retro-aldol and intramolecular Friedel–Crafts alkylation sequence on compound 366, starting from the chiral building block 365 (Scheme 54).<sup>68</sup> Thus, compound 365 was submitted to sequential 1,2-addition, oxidation with PCC and 1,4-addition to obtain 366. Treatment of 366 with ethylene glycol in the presence of catalytic p-TSA gave a clean reaction in quantitative yield where the tricyclic A/B-trans-hexahydrophenanthrene 367 was formed. Then, compound 367 was transformed into compound 288, which had previously been converted into (+)-ferruginol (3). Deketalisation of 367 and hydrogenation gave the ketone 368. Reaction of 368 with 2-iodoxybenzoic acid (IBX) in the presence of p-TSA furnished the unsaturated ketone 369, which on 1,4-addition gave the β-methyl ketone 370. Repetition of



Scheme 53. Yamamoto's formal total synthesis of ferruginol (3).



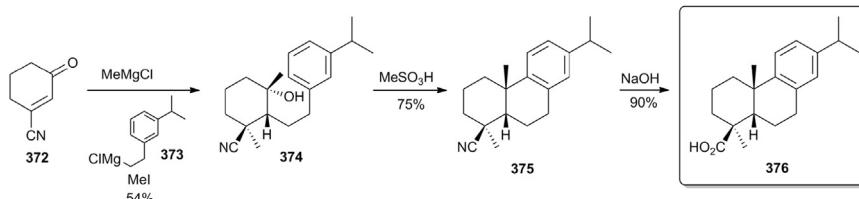
Scheme 54. Ogasawara's formal synthesis of ferruginol (3).

the same sequence of IBX oxidation and 1,4-addition afforded ketone 371, which was reduced under Wolff–Kishner conditions to give intermediate 288, completing a formal synthesis of (+)-ferruginol (3).

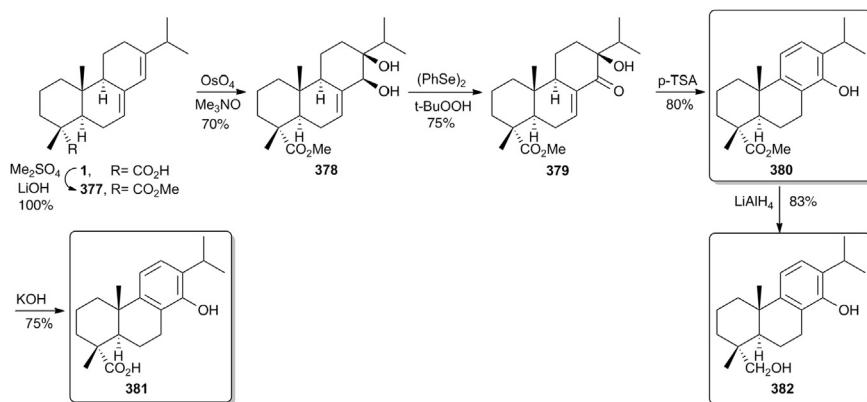
In 2008, Fleming et al. reported the racemic synthesis of less common cis-fused abietanes such as acid 376, starting from a cyclic nitrile 372 via hydroxy nitrile 374 by acid-catalysed intramolecular cyclisation (Scheme 55).<sup>69</sup> Thus, Grignard addition–alkylation of oxonitrile 372 with MeMgCl and the phenethyl Grignard 373 and MeI gave hydroxyl nitrile 374 with the entire abietane carbon skeleton. The treatment of hydroxyl nitrile 374 with MeSO<sub>3</sub>H

afforded nitrile 375 with the cis-fused ring junction stereochemistry. Hydrolysis of 375 furnished the dehydroabietic acid 376 completing a short synthesis of the cis-abietane carbon framework.

Finally and recently, González et al., based on the results of Matsushita and Alvarez-Manzaneda,<sup>34,70</sup> reported the synthesis of several 14-hydroxydehydroabietanes, compounds 380–382, starting from abietic acid (1) to carry out their biological evaluation (Scheme 56).<sup>71</sup> Firstly, abietic acid (1) was methylated by treatment with LiOH and Me<sub>2</sub>SO<sub>4</sub> to yield ester 377. Regioselective dihydroxylation of 377 with catalytic OsO<sub>4</sub> and Me<sub>3</sub>NO as co-oxidant gave diol 378. Oxidation of the allylic alcohol in 378 with



Scheme 55. Fleming's synthesis of 4,5-epidehydroabietic acid (376).



Scheme 56. González's synthesis of 14-hydroxydehydroabietanes (380–382).

PhSeSePh and *t*-BuOOH gave the hydroxyl ketone **379**. Subsequent aromatisation of **379** with *p*-TSA provided the phenol **380**, which was hydrolysed to acid **381** and reduced with LiAlH<sub>4</sub> to alcohol **382**.

#### 4. Summary of key reactions

To summarise the rich chemistry enclosed in this review, the key reactions applied to the abietane scaffold as well as the main retrosynthetic disconnections can be seen graphically in Fig. 3. The electrophilic aromatic substitution reactions are typical transformations, which have been applied to the dehydroabietane skeleton mainly at C-12 (Friedel–Crafts acetylation, see Schemes 5–8; nitration, see Scheme 9), and also the nitration at both C-12 and C-14 has been described (Scheme 23). The benzylic oxidation at C-7 is also characteristic of this skeleton (Schemes 6, 8, 10, and 15–19), and the selective benzylic oxidation at C-15 has also been described (Scheme 19).

The main synthetic strategy to build up the tricyclic ring system has been by large the intramolecular Friedel–Crafts cyclisation (Bogert–Cook reaction, see Schemes 31, 32, 37–39, and 45–48). This reaction has been part of a cationic polyene cyclisation sometimes, which even has been described enantioselectively (Schemes 36 and 53). A radical cyclisation approach has been described (Scheme 49). The Robinson annelation has also been applied to construct the abietane carbon framework (Schemes 33, 34, 40 and 42).

#### 5. Conclusions

The scientific investigations on the synthesis of abietane diterpenoids have been an active field since their first isolations from natural sources. For over 50 years, abietane diterpenoids have been synthesised by Friedel–Crafts cyclisations, but other different strategies have also been explored. Semisynthesis of abietanes has

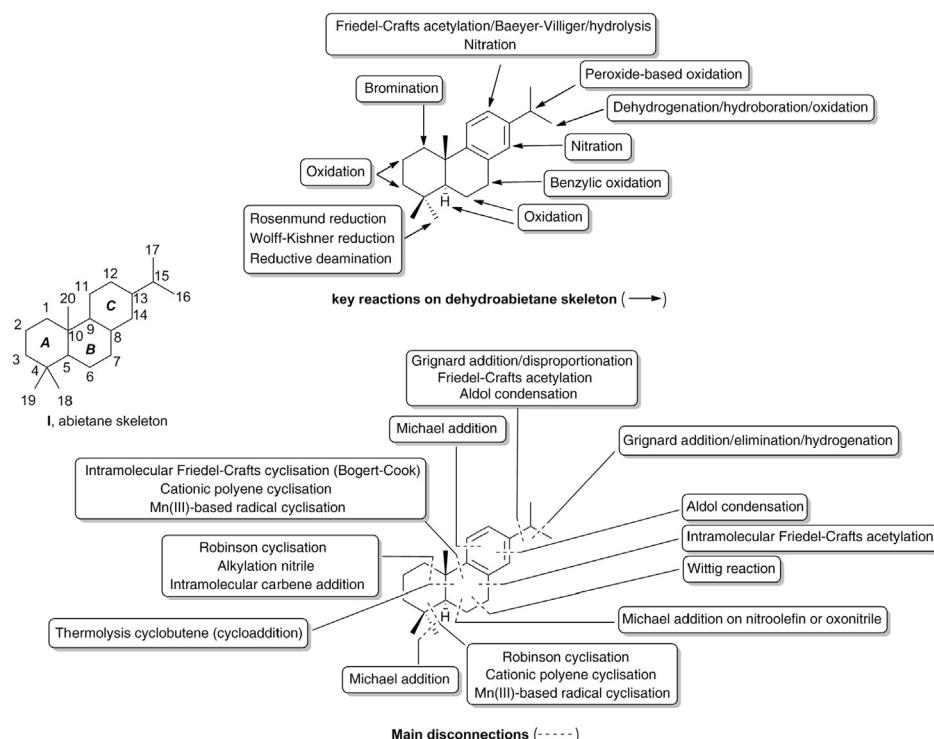


Fig. 3. Summary of key reactions on the abietane skeleton, including main retrosynthetic disconnections.

provided a wide variety of chemical entities, which usually present interesting biological properties. However, the synthetic studies on this family of natural products represent only a minor amount of the publications in the field, mainly related to isolation and structural characterisation, including preliminary biological studies. Future investigations in this area will continue providing new synthetic methods as well as potential biological probes and chemotherapeutic agents.

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## References and notes

1. Nicolaou, K. C.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012–1044.
2. Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311–335.
3. Hanson, J. R. *Nat. Prod. Rep.* **2013**, *30*, 1346–1356 and preceding contributions of the author.
4. San Feliciano, A.; Gordaliza, M.; Salinero, M. A.; Miguel del Corral, J. M. *Planta Med.* **1993**, *59*, 485–490.
5. Fieser, L. F.; Campbell, W. P. *J. Am. Chem. Soc.* **1938**, *60*, 159–170.
6. Brandt, C. W.; Neubauer, L. G. *J. Chem. Soc.* **1939**, 1031–1037.
7. (a) Harris, G. C. *J. Am. Chem. Soc.* **1948**, *70*, 3671–3674; (b) Norin, T.; Winell, B. *Acta Chem. Scand.* **1972**, *26*, 2289–2296; (c) Ulubelen, A.; Miski, M.; Mabry, T. J. *J. Nat. Prod.* **1981**, *44*, 119–124.
8. Burgstahler, A. W.; Marx, J. N. *J. Org. Chem.* **1969**, *34*, 1562–1566.
9. Van Beek, T. A.; Claassen, F. W.; Dorado, J.; Godejohann, M.; Sierra-Alvarez, R.; Wijnberg, J. B. P. A. J. *Nat. Prod.* **2007**, *70*, 154–159.
10. Matsumoto, T.; Usui, S. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 212–215.
11. Littmann, E. R. *J. Am. Chem. Soc.* **1938**, *60*, 1419–1421.
12. Carman, R. M.; Deeth, H. C.; Marty, R. A.; Mori, K.; Matsui, M. *Tetrahedron Lett.* **1968**, *30*, 3359–3360.
13. Huffman, J. W. *J. Org. Chem.* **1970**, *35*, 3154–3156.
14. Pelletier, S. W.; Herald, D. L. *J. Chem. Soc., Chem. Commun.* **1971**, 10–11.
15. (a) Campbell, W. P.; Todd, D. J. *Am. Chem. Soc.* **1942**, *64*, 928–935; (b) Campbell, W. P.; Todd, D. J. *Am. Chem. Soc.* **1940**, *62*, 1287–1292; (c) Fieser, L. F.; Campbell, W. P. *J. Am. Chem. Soc.* **1939**, *61*, 2528–2535.
16. (a) Cambie, R. C.; Franich, R. A. *Aust. J. Chem.* **1971**, *24*, 117–134; (b) Matsumoto, T.; Ohsuga, Y.; Harada, S.; Fukui, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 266–272.
17. Akita, H.; Oishi, T. *Chem. Pharm. Bull.* **1981**, *29*, 1567–1579.
18. Córdoba-Guerrero, I.; San Andrés, L.; Leal-Orozco, A. E.; Padrón, J. M.; Cornejo-Bravo, J. M.; León, F. *Tetrahedron Lett.* **2013**, *54*, 4479–4482.
19. Tada, M.; Ishimaru, K. *Chem. Pharm. Bull.* **2006**, *54*, 1412–1417.
20. (a) Marcos, I. S.; Beneitez, A.; Castañeda, L.; Moro, R. F.; Basabe, P.; Diez, D.; Urones, J. G. *Synlett* **2007**, *1589–1590*; (b) Marcos, I. S.; Beneitez, A.; Moro, R. F.; Basabe, P.; Diez, D.; Urones, J. G. *Tetrahedron* **2010**, *66*, 7773–7780.
21. González, M. A.; Pérez-Guaita, D. *Tetrahedron* **2012**, *68*, 9612–9615.
22. Matsumoto, T.; Usui, S.; Kawashima, H.; Mitsuki, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 581–584.
23. Matsumoto, T.; Terao, H.; Imai, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2855–2856.
24. Matsumoto, T.; Tanaka, Y.; Terao, H.; Takeda, Y.; Wada, M. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3053–3057.
25. Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Lachkar, M.; Messouri, I. *Synlett* **2007**, *2425–2429*.
26. Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Ramos, J. M.; Guardia, J. J.; Messouri, I.; Chayboun, I.; Mansour, A. I.; Dahdouh, A. *Synthesis* **2010**, *3493–3503*.
27. Alvarez-Manzaneda, E. J.; Chahboun, R.; Guardia, J. J.; Lachkar, M.; Dahdouh, A.; Lara, A.; Messouri, I. *Tetrahedron Lett.* **2006**, *47*, 2577–2580.
28. Abad, A.; Arno, M.; Domingo, L. R.; Zaragoza, R. J. *Tetrahedron* **1985**, *41*, 4937–4940.
29. Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Lachkar, M.; Messouri, I. *Tetrahedron Lett.* **2007**, *48*, 989–992.
30. Matsushita, Y.; Sugamoto, K.; Iwakiri, Y.; Yoshida, S.; Chaen, T. *Tetrahedron Lett.* **2010**, *51*, 3931–3934.
31. Matsumoto, T.; Imai, S.; Takeda, S.; Mitsuki, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2013–2017.
32. Burnell, R. H.; Andersen, A.; Néron-Desbiens, M.; Savard, S. *Can. J. Chem.* **1981**, *59*, 2820–2825.
33. Burnell, R. H.; Andersen, A.; Néron, M.; Savard, S. *Can. J. Chem.* **1985**, *63*, 2769–2776.
34. Matsushita, Y.; Iwakiri, Y.; Yoshida, S.; Sugamoto, K.; Matsui, T. *Tetrahedron Lett.* **2005**, *46*, 3629–3632.
35. Jana, C. K.; Scopelliti, R.; Gademann, K. *Synthesis* **2010**, 2223–2232.
36. Mizuno, H.; Ohsawa, T.; Tahara, A. *Chem. Pharm. Bull.* **1976**, *24*, 1527–1531.
37. Burnell, R. H.; Côté, C.; Théberge, N. J. *Nat. Prod.* **1993**, *56*, 1459–1467.
38. Banerjee, A. K.; Poon Ng, P. S.; Laya, M. S. *Stud. Nat. Prod. Chem.* **2003**, *29*, 169–221.
39. Matsumoto, T.; Endo, Y.; Okimoto, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2018–2022.
40. Tada, M.; Ohkanda, T.; Kurabe, J. *Chem. Pharm. Bull.* **2010**, *58*, 27–29.
41. González, M. A.; Pérez-Guaita, D.; Correa-Royer, J.; Zapata, B.; Agudelo, L.; Mesa-Arango, A.; Betancur-Galvis, L. *Eur. J. Med. Chem.* **2010**, *45*, 811–816.
42. González, M. A.; Zaragozá, R. J. *J. Nat. Prod.* **2014**, *77*, 2114–2117.
43. Surendra, K.; Rajendar, G.; Corey, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 642–645.
44. Haworth, R. D.; Barker, R. L. *J. Chem. Soc.* **1939**, 1299–1303.
45. Carman, R. M.; Deeth, H. C. *Aust. J. Chem.* **1967**, *20*, 2789–2793.
46. Sharma, M.; Ghatak, U. R.; Dutta, P. C. *Tetrahedron* **1963**, *19*, 985–994.
47. (a) Mori, K.; Matsui, M. *Tetrahedron* **1966**, *22*, 879–884; (b) Mori, K.; Matsui, M. *Tetrahedron* **1968**, *24*, 6573–6575.
48. (a) Welch, S. C.; Kim, J. H. *Synth. Commun.* **1976**, *6*, 27–31; (b) Welch, S. C.; Hagan, C. P.; Kim, J. H.; Chu, P. S. J. *Org. Chem.* **1977**, *42*, 2879–2887.
49. (a) Stork, G.; Schulenberg, J. W. *J. Am. Chem. Soc.* **1956**, *78*, 250–251; (b) Stork, G.; Schulenberg, J. W. *J. Am. Chem. Soc.* **1962**, *84*, 284–292.
50. (a) Ireland, R. E.; Kierstead, R. C. *J. Org. Chem.* **1962**, *27*, 703–704; (b) Ireland, R. E.; Kierstead, R. C. *J. Org. Chem.* **1966**, *31*, 2543–2559.
51. King, F. E.; King, T. J.; Topliss, J. G. *J. Chem. Soc.* **1957**, 573–577.
52. Matsumoto, T.; Usui, S.; Morimoto, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1575–1579.
53. Torii, S.; Uneyama, K.; Hamada, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2503–2504.
54. Rao, P. N.; Raman, K. *Tetrahedron* **1958**, *4*, 294–301.
55. Meyer, W. L.; Clemans, G. B.; Manning, R. A. J. *Org. Chem.* **1975**, *40*, 3686–3694.
56. Snitman, D. L.; Himmelsbach, R. J.; Watt, D. S. J. *Org. Chem.* **1978**, *43*, 4758–4762.
57. Pan, X.-F.; Wang, X.-L. *Youji Huaxue* **1993**, *13*, 192–194.
58. Bhar, S. S.; Ramana, M. M. V. *J. Org. Chem.* **2004**, *69*, 8935–8937.
59. Matsumoto, T.; Imai, S.; Miuchi, S.; Sugabayashi, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 340–345.
60. (a) Gan, Y.; Pan, X. *J. Chem. Res., Synop.* **2000**, 130–132; (b) Gan, Y.; Li, A.; Pan, X.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron: Asymmetry* **2000**, *11*, 781–787.
61. Tada, M.; Nishiiri, S.; Yang, Z.; Imai, Y.; Tajima, S.; Okazaki, N.; Kitano, Y.; Chiba, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2657–2664.
62. Yang, Z.; Kitano, Y.; Chiba, K.; Shibata, N.; Kurokawa, H.; Doi, Y.; Arakawa, Y.; Tada, M. *Bioorg. Med. Chem.* **2001**, *9*, 347–356.
63. Burnell, R. H.; Côté, C.; Girard, M. *J. Nat. Prod.* **1993**, *56*, 461–472.
64. (a) Node, M.; Hao, X.-J.; Nagasawa, H.; Fuji, K. *Tetrahedron Lett.* **1989**, *30*, 4141–4144; (b) Hao, X.-J.; Node, M.; Fuji, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, *1505–1509*.
65. Kametani, T.; Kondoh, H.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, *5–10*.
66. Pati, L. C.; Mukherjee, D. *Tetrahedron Lett.* **2004**, *45*, 9451–9453.
67. Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505–1506.
68. Nagata, H.; Miyazawa, N.; Ogasawara, K. *Org. Lett.* **2001**, *3*, 1737–1740.
69. Fleming, F. F.; Wei, G.; Steward, O. W. *J. Org. Chem.* **2008**, *73*, 3674–3679.
70. Alvarez-Manzaneda, E.; Chahboun, R.; Bentaleb, F.; Alvarez, E.; Escobar, M. A.; Sad-Diki, S.; Cano, M. J.; Messouri, I. *Tetrahedron* **2007**, *63*, 11204–11212.
71. Zapata, B.; Rojas, M.; Betancur-Galvis, L.; Mesa-Arango, A. C.; Pérez-Guaita, D.; González, M. A. *Med. Chem. Commun.* **2013**, *4*, 1239–1246.

**Biographical sketch**

**Miguel A. González** was born in Valencia, Spain, in 1972. He received his B.S. degree in Chemistry in 1995 and an M.Sc. (Honours) degree in Chemistry from the University of Valencia, in 1997. He then remained at the same University to undertake Ph.D. studies, under the direction of Professor Manuel Arnó and Professor Ramón J. Zaragozá, on the *Synthesis of Terpenes with Spongian, Scopadulane and Estrane skeletons*. Upon completion of his Ph.D. in 2001, he undertook postdoctoral research first in the group of Professor Gerald Pattenden at the University of Nottingham (UK), on the synthesis of Phorboxazole A, and then in the group of Professor Emmanuel A. Theodorakis at the University of California, San Diego (USA), on the synthesis of norzoanthamine. After 3 years of postdoctoral research abroad, he returned to Spain to work with a 'Ramón y Cajal' research contract at the University of Valencia. The synthesis of bioactive natural products, their derivatives and medicinal chemistry are his major interests.