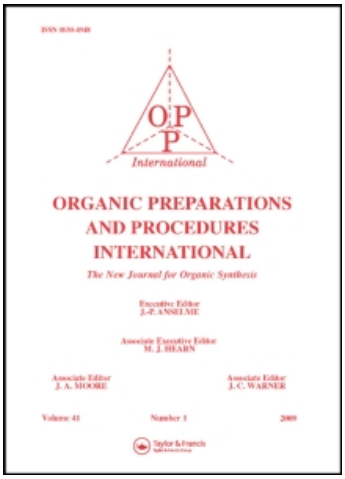

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Antonio Abad[a]; Consuelo Agulló[a]; Manuel Arnó[a]; Luis R. Domingo[a]; Ramón J. Zaragozá[a]
[a] Departamento de Química Orgánica, Universidad de Valencia, Burjassot, Valencia, SPAIN

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Departamento de Química Orgánica
Universidad de Valencia
46100 Burjassot, Valencia, SPAIN

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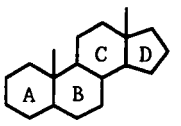
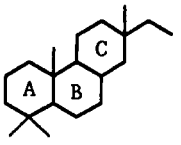
INTRODUCTION

When incisions are made in the bark of some conifers an oleoresin is exuded. Steam distillation of this oleoresin yields a volatile fraction (turpentine) and a residue known as rosin or colophony. After standing, many oleoresins deposit a crystalline cake known as galipot. Chemically, rosin and galipot are a mixture of diterpenoid acids whose composition varies according to their origin.[1a-c] These resin acids constitute a cheap and abundant source of chiral materials for the preparation of natural products. In particular, the structural analogy that exists, including identical absolute stereochemistry at C-5, C-9 and C-10,[1d] between steroids (**A**) and resin acids with a pimarane (**B**), abietane (**C**), or podocarpane (**D**) type of skeleton makes these resin acids and their derivatives attractive starting materials for the synthesis of optically active steroids.



A



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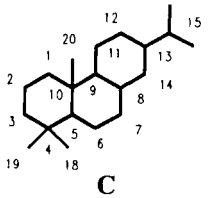

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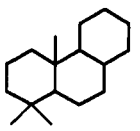


D

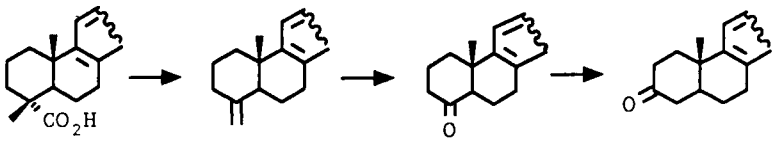
In this review, a description is given of the synthetic activities reported in the literature in this area of resin acids chemistry. It covers the literature published from

1970 up to the middle of 1990, although leading references prior to this period are also highlighted.

The review is divided into two main sections. The first discusses the way in which the functionality of the A-ring of resin acids may be modified to the functionality characteristic of steroids, with special emphasis on the methods which have been used for the degradation of the carboxyl group at C-4. In the second section, a descriptive account of reported tricyclic resin acids-to-steroid skeleton conversions is presented; the work described in this section is classified according to the carbon skeleton of the starting material leading to the steroidal D-ring: pimarane, abietane, and podocarpane.

I. MODIFICATION OF THE A-RING FUNCTIONALITY

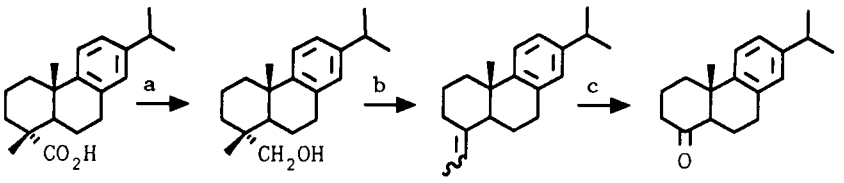
For conversion of tricyclic resin acids into steroidal derivatives that utilize the A-ring in the acids as the A-ring in the steroids, it is necessary to remove the methyl and carbomethoxy groups at C-4 and introduce an oxygen function at C-3. The relatively simple and direct approach towards this goal involves degradation of the corresponding resin acid to a $\Delta^{4(18)}$-olefin (Scheme 1), oxidation of the exocyclic double bond, and exchange of the resulting carbonyl function with the adjacent methylene (1,2-carbonyl transposition).



1.1 **1.2** **1.3** **1.4**

Scheme 1

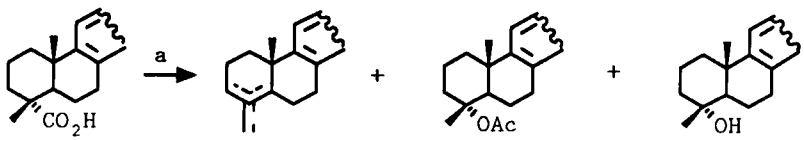
Considerable work has been directed towards the first two steps of this approach, usually using dehydroabietic and podocarpic acids as A-ring models, but only a few authors have worked out the completion of the steroid-type A-ring functionality. The earliest workers in this area[2,3] described the degradation of dehydroabietic acid (**2.1**) to ketone (**2.4**) *via* a dehydration-rearrangement of dehydroabietinol (**2.2**) followed by ozonolysis of the resulting alkene (**2.3**) (Scheme 2).



2.1 **2.2** **2.3** **2.4**

Scheme 2. (a) $LiAlH_4$; (b) PCl_5; (c) O_3 then $KMnO_4$

Since then, several degradation procedures with varying degrees of success have appeared in the literature. The single-step oxidative decarboxylation of resin acids with lead tetraacetate is the most direct way to obtain a compound with a $\Delta^{4(18)}$-double bond that is susceptible to further oxidation to a 4-oxoderivative. This method, which has been used for degradation of abietane[4,5,6,7] and podocarpane[8,9] type compounds, gives a mixture of Δ^3-, Δ^4-, and $\Delta^{4(18)}$-olefins (**3.2**) in a relative proportion that varies from 1:2:2 to 1:1:2 depending on the substrate, together with a small amount of 4-acetoxy and 4-hydroxy derivatives, (**3.3**) and (**3.4**), respectively (Scheme 3).



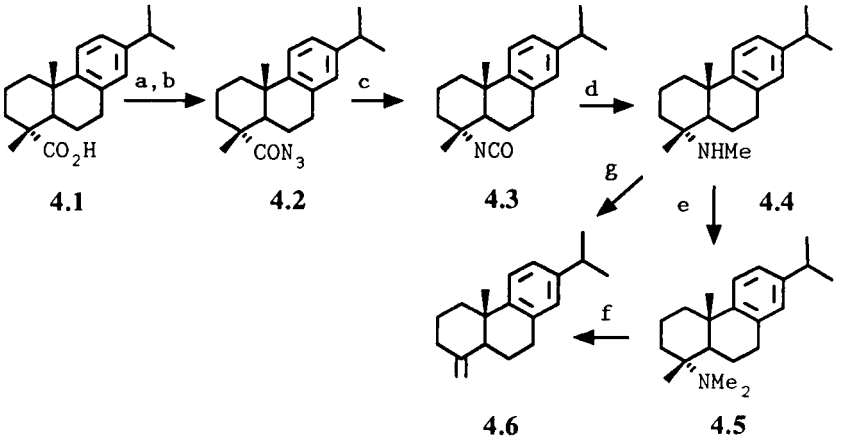
3.1 **3.2** **3.3** **3.4**

Scheme 3. (a) $Pb(OAc)_4$, benzene-pyridine

Although the exocyclic olefin can be isolated from the decarboxylation mixture,[5,6,7,10,11] its low percentage in the mixture seriously limits the utility of this method. In this context, methods for isomerization of the olefinic mixture have been examined.[9,12] As expected, isomerization of the olefinic mixture obtained by decarboxylation of podocarpic and dehydroabietic acids using iodine as the catalyst gives[9] a mixture enriched in the endocyclic Δ^4-olefin to the extent of 80%, and attempts to obtain a greater proportion of the $\Delta^{4(18)}$-isomer have been unsuccessful.[5,11,12]

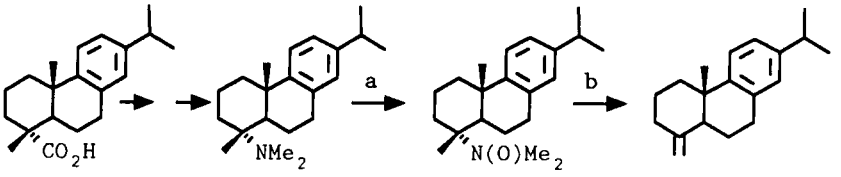
One of the most useful methods for obtaining the exocyclic double bond, in spite of the rather large number of steps that it involves, is that reported by Zeiss and

Martin.[13] In the original report, dehydroabietic acid was converted to the C-4α tertiary amine (**4.5**) (Scheme 4) and subjected to Hofmann elimination to give the exocyclic olefin (**4.6**) in 40% overall yield. Alternatively, the C-4α secondary amine (**4.4**) was quaternized directly with methyl iodide and decomposed to the exocyclic olefin with similar results. Utilizing this method, Burgstahler and Marx reported the conversion of an abietic acid derivative to the corresponding exocyclic olefin with an overall yield of 56%.[14]



Scheme 4. (a) $SOCl_2$; (b) NaN_3; (c) Xylene, Δ; (d) $LiAlH_4$; (e) Formalin, HCO_2H; (f) MeI then Ag_2O; (g) K_2CO_3, MeI

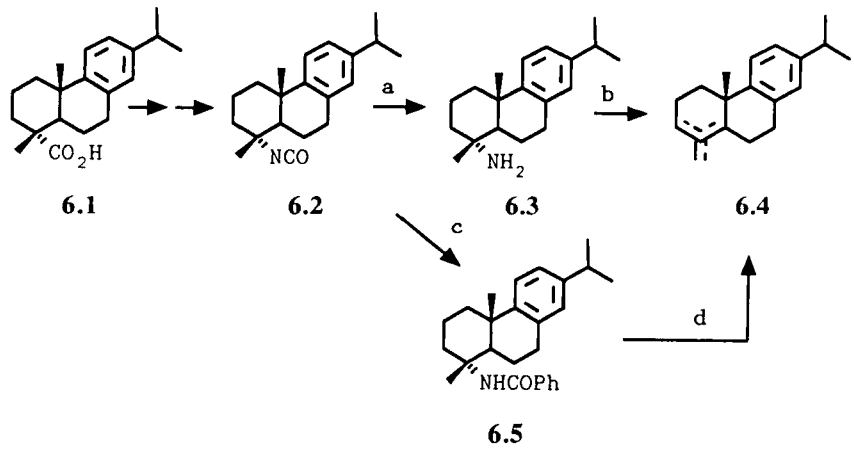
The orientation of the carboxyl group at C-4 has no influence on the relative proportion of olefins formed in the oxidative decarboxylation with lead tetraacetate.[11,12,15] This is not surprising since the olefins are probably elimination products of a C-4 carbonium ion. However, the orientation of the C-4 tertiary amino moiety proves decisive in the stereochemical outcome of the Hofmann degradation. In contrast with the conversion of (**4.5**) to (**4.6**), the axial C-4β amine derived from podocarpic acid undergoes Hofmann degradation to give a mixture of Δ^3- and Δ^4-olefins in a ratio of 3:2.[16] A modification of the Zeiss procedure, using a Cope elimination, was reported by Huffman.[17] The C-4α tertiary amine was converted to C-4 N-oxide (**5.3**) (Scheme 5) and pyrolyzed to give a good yield of the exocyclic olefin (**5.4**). Overall yields as high as 72% were obtained by this method with several dehydroabietic acid derivatives.[18,19,20,21,22]



5.1 5.2 5.3 5.4

Scheme 5. (a) HCO_3H-AcOH or MCPBA, CH_2Cl_2; (b) DMF, heat

In addition to the Hofmann and Cope elimination procedures, other methods for the formation of a $\Delta^{4(18)}$-olefin from related amino compounds were also reported.[23,24] Thus, nitrous acid deamination of the C-4α primary amine (**6.3**) derived from dehydroabietic acid (Scheme 6) gave a mixture of $\Delta^{4(18)}$-, Δ^3-, and Δ^4-olefins in an approximate ratio of 6:2:1.[25] A bimolecular elimination of the initially formed equatorial diazonium ion was proposed to explain the preferential formation of the Hofmann product ($\Delta^{4(18)}$-olefin).[24] In terms of yield this method is inferior to those previously discussed. Better results were obtained by dehydration of the benzamide (**6.5**) in a retro-Ritter reaction, which gave a good yield of the olefin mixture and a higher proportion of the $\Delta^{4(18)}$-olefin (80%).[26]



6.1 6.2 6.3 6.4

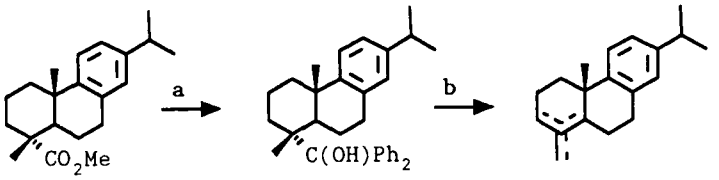
6.5

Scheme 6. (a) H_2SO_4; (b) HNO_2; (c) PhMgBr; (d) $SOCl_2$, pyridine, Et_2O

In the case of the C-4β primary amine derived from podocarpic acid, the mixture of olefins formed in the deamination reaction shows little resemblance to that obtained from (**6.3**); the Δ^4-, Δ^3-, and $\Delta^{4(18)}$-olefins are formed in a ratio of *ca.*

8:1:1.[16] A still higher proportion of the Δ^4-olefin is formed by dehydration of the corresponding benzamide.[16,26] A change in the mechanism from E2 to unimolecular elimination was proposed to explain the observed preference for elimination in the Saytzeff orientation in the case of the C-4 axial amine derived from podocarpic acid.[16]

An alternative method for introducing the $\Delta^{4(18)}$-double bond from the C-4α equatorial carboxyl group of resin acids was developed by Jeger *et al.*[27] and more recently improved by Matsumoto *et al.*[28] In this method the C-18 methyl ester (**7.1**) (Scheme 7) is transformed into a *gem*-diphenyl carbinol (**7.2**). Treatment of this alcohol with lead tetraacetate and calcium carbonate gives a mixture of Δ^3-, Δ^4-, and $\Delta^{4(18)}$-19-nor compounds (**7.3**) in a ratio of *ca.* 1:1:8. That this two-step process is, probably, the most convenient of the methods yet employed to effect this degradation is demonstrated by the high overall yields obtained (up to 70%) using several different dehydroabietic acid derivatives.[28,29,30]



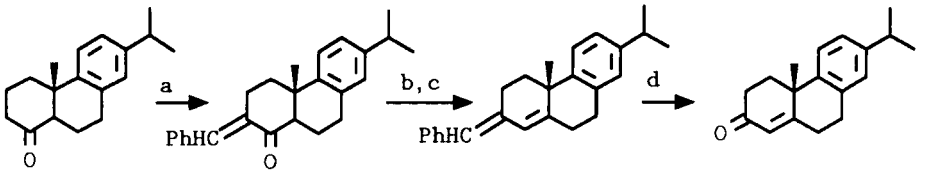
7.1 **7.2** **7.3**

Scheme 7. (a) PhMgBr; (b) $Pb(OAc)_4$, $CaCO_3$, benzene

Oxidative cleavage of the $\Delta^{4(18)}$-double bond, the second step in the elaboration of the C-4 carboxyl group to a ketone, has generally employed ozonolysis,[4,17,19,31] but other oxidizing agents frequently employed in this kind of transformation have also been used.[8,22,23,24,32] In general, good yields of 4-oxoderivatives have been obtained using the isomeric mixture of olefins as a starting material.

As pointed out at the beginning of this section, the last step of the general approach to transforming the A-ring functionality of resin acids into that of steroids (Scheme 1, **1.3** to **1.4**) requires a 1,2-transposition of the C-4 carbonyl function. Convenient methodology for this transposition as well as the incorporation of a Δ^4-double bond, which eventually produces the α,β-unsaturated ketonic system of steroidal hormones, was developed as early as 1953 by Zeiss and Martin.[13] Key

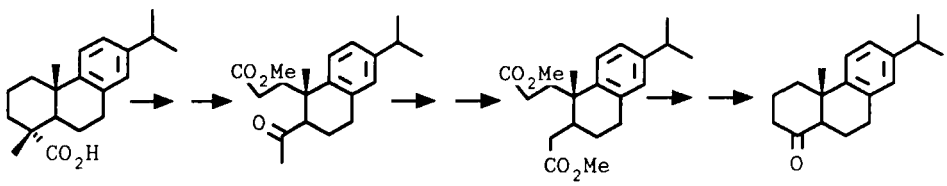
reactions were the introduction of an α-arylidene group by aldol condensation of an aromatic aldehyde with the carbonyl group, and its removal in the last step by ozonolysis to create the new carbonyl function in about 20% overall yield. This conversion was reinvestigated and modified by Cambie and co-workers,[32] who converted the 3-oxo compound (**8.1**) to the tricyclic steroid analog (**8.4**) in *ca.* 50% yield (Scheme 8). The same authors carried out the same transposition in the podocarpic acid series.[32]



8.1 **8.2** **8.3** **8.4**

Scheme 8. (a) PhCHO, NaOH; (b) $NaBH_4$, NaOH; (c) Al_2O_3, Δ;(d) OsO_4 then $NaIO_4$

In their synthetic approaches to steroids from dehydroabietic acid, A. Tahara and his colleagues[33] developed an alternative nine-step sequence for the 1,2-carbonyl transposition. The large number of steps and the low overall yield make this route rather unattractive. Tahara and his group also developed a totally different approach for transforming dehydroabietic acid into a 3-oxoderivative (**9.4**) (Scheme 9).[35,36] This transformation proceeded *via* oxo ester (**9.2**), which was prepared from dehydroabietic acid by two independent multistep sequences in very low yields (less than 10%). Finally, the steroid-type A-ring was constructed by Dieckmann condensation of diester (**9.3**), followed by decarboxylation of the resulting keto-ester. Because the sequence is long and the overall yield is low, and because it is not of general applicability to other resin acids, the approach reported by Tahara is of limited preparative value.



9.1 **9.2** **9.3** **9.4**

Scheme 9

It is somewhat surprising, in view of the number of methods that have been developed in the last 20 years to effect 1,2-carbonyl transpositions,[34] that only three reports of this significant step in the elaboration of the steroid-type A-ring have appeared, and this attests to the absence of short, efficient sequences for accomplishing this valuable transformation.

II. FORMATION OF THE D-RING

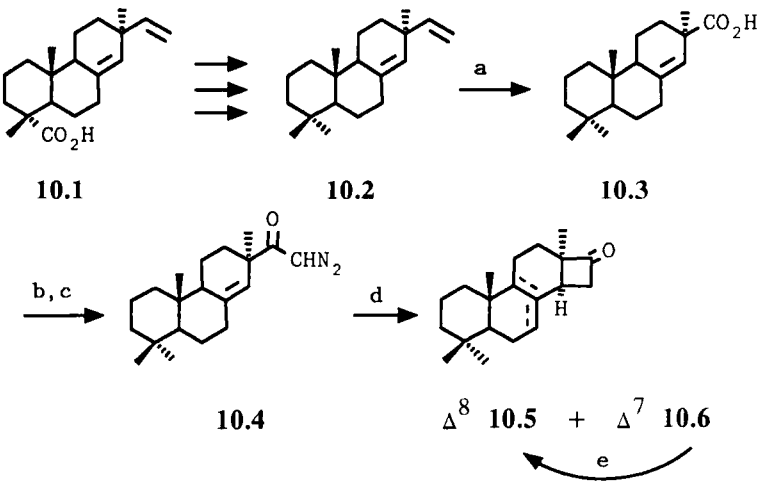
1. Pimarane- and Isopimarane-to-Steroid Skeleton Conversion

Due to their similar structural characteristics, compounds with the pimarane and especially the isopimarane (13-*epi*-pimarane) skeleton are very suitable starting material for synthesis of steroids. In particular, the presence of the methyl group at C-13 and the possible utilization of the 13α-vinyl group in the construction of the steroid D-ring make this interconnection exceedingly attractive. However, only a few recent contributions dealing with this transformation have appeared in the literature.

In general, the methodology used for construction of the D-ring is based on the different reactivity of the $\Delta^{8(14)}$- and Δ^{15}-double bonds.This allows the selective manipulation of the vinyl group and permits the introduction of a supplementary, functionalized carbon atom in order to effect the ring closure with C-14. Acid-catalyzed cyclization, intramolecular carbon-hydrogen insertion, and radical cyclization processes were used in the ring-forming step.

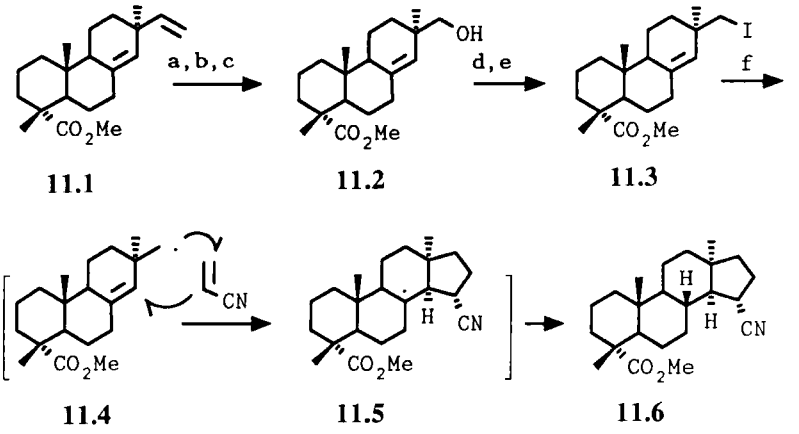
The first published work dealing with the pimarane-to-steroid conversion came from Ceccherelli in 1978, who completed the preparation of a D-nor-steroidal skeletal type from pimaric acid.[37] This short synthesis began with conversion of pimaric acid (**10.1**) into pimarane (**10.2**) by established procedures (Scheme 10). The Δ^{15}-double bond was cleaved with permanganate-periodate and the resulting carboxylic acid (**10.3**) was converted into olefinic diazoketone (**10.4**). Acid-catalyzed intramolecular cyclization gave a mixture of the two isomeric D-nor-steroidal ketones (**10.5**) and (**10.6**). These were treated with hydrogen chloride gas to give (**10.5**), having the more stable Δ^{8}-double bond, as the only product. Presumably, the exclusive formation of the cyclobutanone ring was due to preferential formation of the more stable carbonium ion at C-8 (formed by electrophilic attack of the olefinic double bond to the protonated diazomethyl carbonyl function) and the impossibility

of the alternative, less favored secondary carbonium ion at C-14 collapsing to an olefin because of the absence of α hydrogens. Using the same methodology, these authors also prepared other 4,4-dimethyl-D-nor-steroidal systems from related pimarane and sandaracopimaradiene precursors.[38]



Scheme 10. (a) $KMnO_4$-$NaIO_4$; (b) $(COCl)_2$; (c) CH_2N_2; (d) SiO_2, benzene; (e) HCl, $CHCl_3$

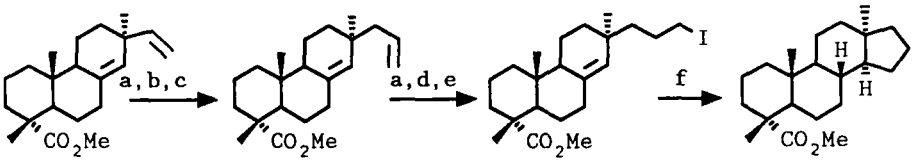
An interesting pimarane-steroid conversion was accomplished by Delmond and co-workers, who prepared several steroid compounds from methyl pimarate, using a free-radical cyclization for construction of the D-ring.[39] In a first approach, they transformed methyl pimarate (**11.1**) into the primary iodide (**11.3**) (Scheme 11). Generation of the corresponding radical (**11.4**) in the presence of an excess of



Scheme 11. (a) $KMnO_4$; (b) $NaIO_4$; (c) $NaBH_4$; (d) TsCl; (e) NaI; (f) Bu_3SnCl-$NaBH_4$, hν, acrylonitrile

acrylonitrile resulted in the formation of the steroid compound (**11.6**). The mechanism of this interesting reaction involved conjugate addition of the C-15 radical to acrylonitrile, followed by an intramolecular radical cyclization with the $\Delta^{8(14)}$-double bond.

In a second approach, both atoms of the vinyl moiety were used for the construction of the D-ring (Scheme 12). Regioselective hydroboration of the more accessible Δ^{15}-double bond was followed by oxidation of the initially formed primary hydroxyl group and Wittig reaction to afford the olefin (**12.2**), which was readily transformed into iodide (**12.3**). Irradiation of the latter in the presence of a catalytic amount of tri-*n*-butyltin hydride produced the corresponding primary radical that added intramolecularly to the $\Delta^{8(14)}$-double bond to give a high yield of the steroid compound (**12.4**).

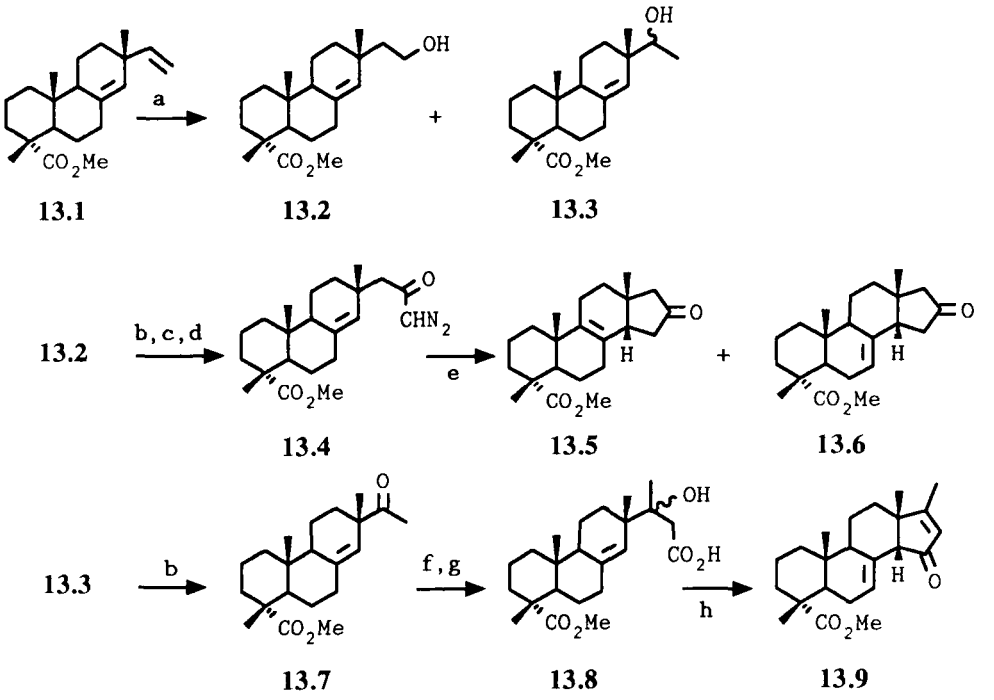


12.1 **12.2** **12.3** **12.4**

Scheme 12. (a) 9-BBN; (b) CrO_3, pyridine; (c) $Ph_3P=CH_2$; (d) TsCl; (e) NaI, acetone; (f) Bu_3SnCl-$NaBH_4$, $h\nu$, CH_3CN

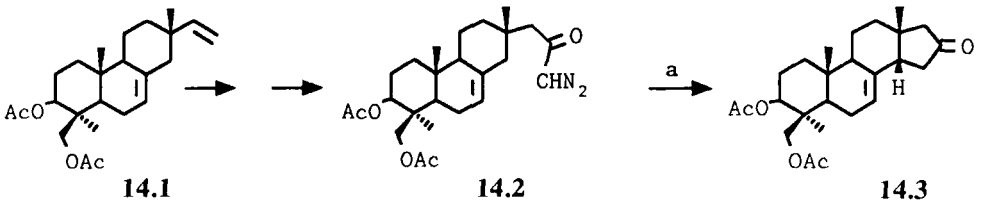
Sandaracopimaric acid (**13.1**) was transformed by Mateos[40] and co-workers into several androstane derivatives, using an acid-catalyzed cyclization in the D ring-forming step. Hydroboration of methyl sandaracopimarate gave a mixture of compounds from which alcohols (**13.2**) and (**13.3**) were isolated (Scheme 13). The former was converted into diazoketone (**13.4**), which upon acid treatment gave a mixture of tetracyclic ketones (**13.5**) and (**13.6**).

In a second approach to the androstane system[41] (Scheme 13), the alcohol (**13.3**) was transformed into the hydroxy acid (**13.8**) by oxidation to a methyl ketone (**13.7**), a Reformatsky reaction with ethyl bromoacetate, and controlled saponification. Acid-catalyzed cyclization gave the *cis*-fused enone (**13.9**), which was apparently the only isomer produced in the reaction.



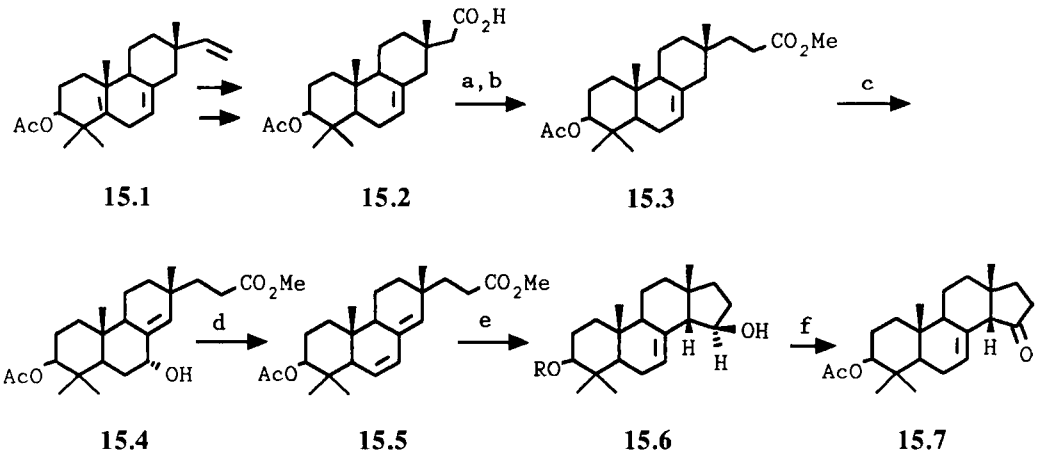
Scheme 13. (a) BH_3, H_2O_2; (b) Jones reagent; (c) $(COCl)_2$; (d) CH_2N_2; (e) TsOH, benzene; (f) $BrCH_2CO_2Et$, Zn; (g) KOH; (h) TsOH, acetic anhydride

A 16-androstane derivative similar to (**13.6**) was prepared by Wenkert from virescenol B diacetate (**14.1**), a diterpene structurally related to sandaracopimaric acid. The C-13 vinyl group was transformed[42] into a diazomethyl ketone group (Scheme 14) as described for (**13.1**). Intramolecular carbon-hydrogen insertion mediated by a dirhodium(II) tetraacetate-assisted decomposition of diazo ketone (**14.2**) produced cyclopentanone (**14.3**). The preferential intermediacy of the more stable allylic radical at C-14 was responsible for the regiospecificity observed.



Scheme 14. (a) $Rh_2(OAc)_4$, 1,2-dimethoxyethane

The same authors used a new carbon-carbon bond-forming reaction, based on reductive transfer of acetyl groups from ester side chains onto nuclear carbon sites, to transform the 19-deoxyvirescenol acetate (**15.1**) (Scheme 15) into an androstane derivative.[43] Straightforward elaboration of the 13-vinyl group of (**15.1**) gave acid (**15.2**), which was homologated to ester (**15.3**) by the Arndt-Eistert method. Photo-oxygenation of (**15.3**) followed by reduction of the resultant hydroperoxide led to hydroxy ester (**15.4**). The dehydration of (**15.4**) provided the key dienic ester (**15.5**), and its reduction with lithium in ammonia yielded tetracyclic diol (**15.6**, R = H) and its acetate (**15.6**, R = Ac). The further oxidation of (**15.6**) gave the 15-androstanone derivative (**15.7**). Presumably, the key step of this interesting carbon-carbon bond-forming reaction involved the intramolecular addition of a ketyl radical to the diene at C-14 followed by hydrogen capture by the resultant allyl radical from the solvent.

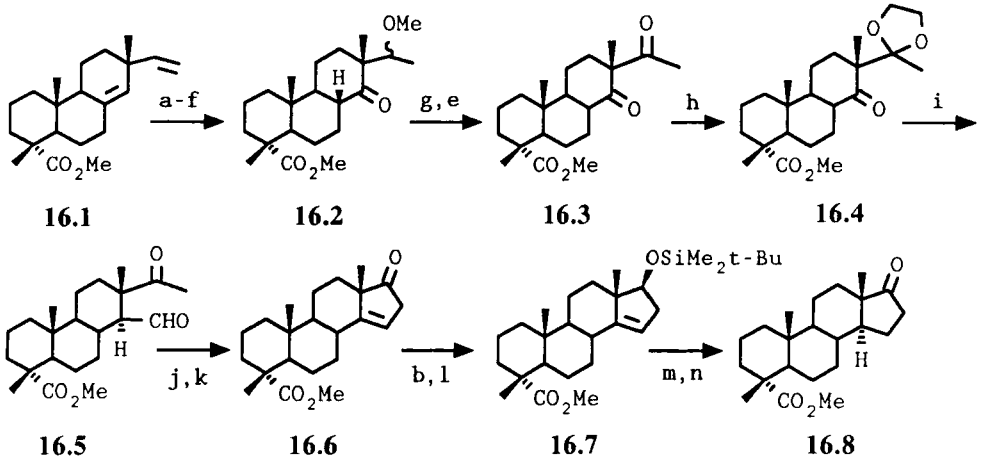


Scheme 15. (a) $(COCl)_2$ then CH_2N_2; (b) Ag_2O; (c) O_2, eosine, hν; NaI; (d) TsCl, pyridine; (e) Li, NH_3; (f) Collins reagent

It must be noted that in all of the above-mentioned pimarane- and isopimarane-to-steroid transformations, the stereochemistry of the ring closure step took place in a *cis* manner leading to C/D-*cis*-fused compounds. None of these steroidal products possessed the *trans-anti-trans* arrangements of BCD rings of natural steroids.

We have recently reported[44] the conversion of sandaracopimaric acid into an androstane analog steroid that utilized a new approach for construction of the D-ring and that eventually led to the *trans*-fused C/D-ring system. Key steps of this approach

(Scheme 16) were the reductive nucleophilic acylation of ketone (**16.4**) and intramolecular aldol condensation of keto aldehyde (**16.5**). Alkoxymercuration-demercuration of the vinyl group of (**16.1**), followed by regioselective hydroboration of the $\Delta^{8(14)}$-double bond gave a mixture of isomeric alcohols, which after oxidation and epimerization at C-8 afforded ketone (**16.2**). Methyl ether cleavage and oxidation of the resulting alcohol gave diketone (**16.3**) which, after chemoselective ketalization of the C-15 carbonyl group, gave the keto ketal (**16.4**). One-carbon homologation of (**16.4**) and hydrolysis of the ketal moiety provided key keto aldehyde (**16.5**), whose aldol condensation gave a mixture of cycloaldolization products, leading ultimately to the β,γ-unsaturated ketone (**16.6**) on acid treatment. Direct hydrogenation of (**16.6**) gave the C/D-*cis* fused cyclopentanone, so additional modification of the C-17 functionality was necessary in order to obtain the *trans* CD rings. Thus, reduction of (**16.6**), formation of the *t*-butyldimethylsilyl ether of the resulting alcohol, stereoselective hydrogenation of the Δ^{14}-double bond, and regeneration of the carbonyl group gave androstanone (**16.8**), the first steroidal system possessing the *trans-anti-trans* arrangements of BCD rings that has been prepared from a diterpene with the isopimarane skeleton. Curiously, the same tetracyclic compound (**16.8**) had been prepared many years ago in a transformation of testosterone into sandaracopimaric acid.[45]



Scheme 16. (a) $Hg(OAc)_2$, MeOH; (b) $NaBH_4$; (c) BH_3 then H_2O_2; (d) Jones reagent; NaOMe; (g) NaI, TMSCl; (h) $HO(CH_2)_2OH$, TsOH; (i) $Me_3SiCHLiOMe$ then HCO_2H; (j) KOH; (k) TsOH; (l) TBDMSCl, imid.; (m) H_2; (n) Jones reagent, KF

2. Abietane-to-Steroid Skeleton Conversion

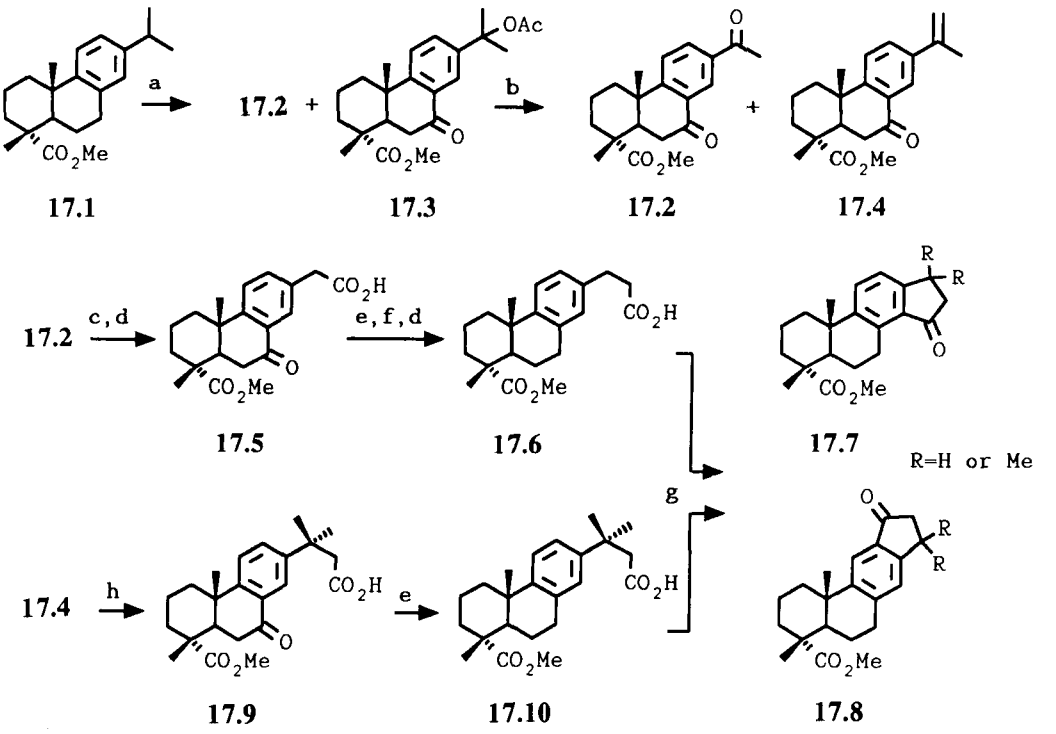
Several kinds of steroid compounds have been prepared from abietane-type resin acids such as abietic and dehydroabietic acids. Of particular interest was the development of syntheses of C-aryl-18-nor-steroids, a group of compounds used in petroleum exploration as geochemical "biomarkers" that have attracted increasing attention in recent years motivated by the hope of discovering hormone analogues with modified biological activity.[46] In general, these syntheses involved an ABC + D ring construction scheme, using part of the carbon units of the 13-isopropyl group for construction of the steroidal D-ring. A good deal of interest has also been focused on the preparation of androstane analogs from abietic and dehydroabietic resin acids, but so far no synthesis has been reported which uses the isopropyl group as a building block for the D-ring.

a. Ring-C Aromatic Steroidal Systems

One of the main problems associated with the use of abietane-type resin acids in the construction of C-aromatic steroids resided in the modification of the isopropyl group. Functionalization of the isopropyl group of abietic acid was only achieved by radical bromination of its Diels-Alder adducts with fumaric or maleic acid.[47] In the case of dehydroabietic acid, several attemps to functionalize the isopropyl group met with varying degrees of success. Oxidation with the common oxidizing agents such as oxygen,[48] CrO_3,[48,49,50] $KMnO_4$,[51,52,53] SeO_2,[54] or NBS,[55] led to moderate to low yields of products resulting from benzylic oxidation at C-15 or even at C-7. Although other methods involving the intramolecular cyclization of 12-carboxy derivatives[56] have given good yields of C-15 functionalized products, the best way of regioselectively functionalizing the isopropyl group of dehydroabietic acid is by dehydrogenation with certain quinones such as DDQ.[57,58,59]

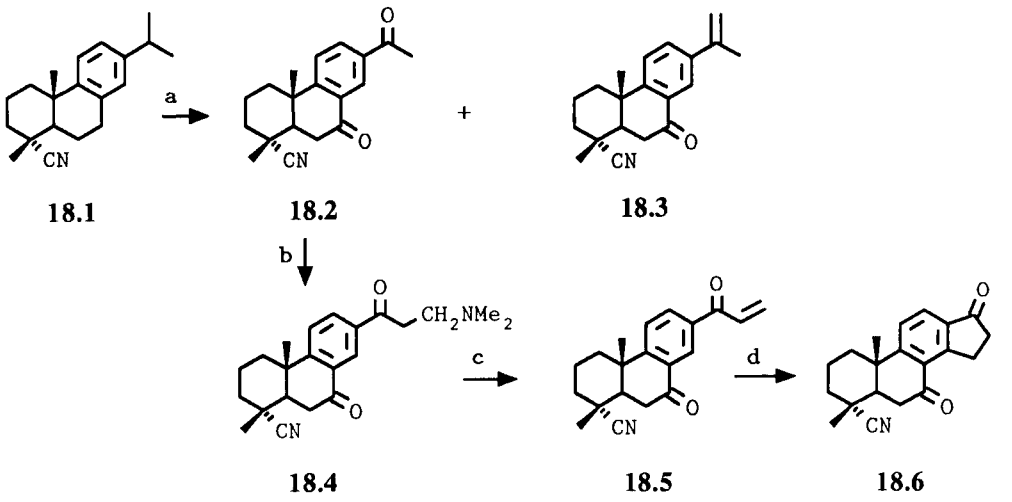
The first syntheses of C-aryl-18-nor-steroids from dehydroabietic acid came from Tahara and co-workers,[60,61] who used the oxidation products of the isopropyl group with CrO_3 to form a steroidal skeleton (Scheme 17). The initial oxidation products were the methyl ketone (**17.2**) and acetate (**17.3**), which were subsequently pyrolyzed as a mixture to give (**17.2**) and the isopropenyl derivative (**17.4**). The side chain at C-13 in both compounds was conveniently modified by oxidation of (**17.2**) with $Tl(ONO_2)_3$ followed by Arndt-Eistert reaction, or by an addition reaction of

1,1-dichloroethylene to the double bond of (**17.4**). After straightforward modifications, the resulting β-arylpropionic acids (**17.6**) and (**17.10**) underwent intramolecular Friedel-Crafts acylation to give the cyclized products (**17.7**) and (**17.8**) in a 3:1 ratio. It was noted that the intramolecular cyclization to C-14 in (**17.6**) and (**17.10**) predominated over that at C-12, in contrast to the intermolecular acylation of dehydroabietic acid which always occurred at C-12.



Scheme 17. (a) CrO_3; (b) pyrolysis; (c) $Tl(ONO_2)_3$-$HClO_4$; (d) KOH; (e) H_2, Pd-C; (f) $SOCl_2$ then CH_2N_2 and Ag_2O; (g) $AlCl_3$; (h) 1,1-dichloroethylene, BF_3

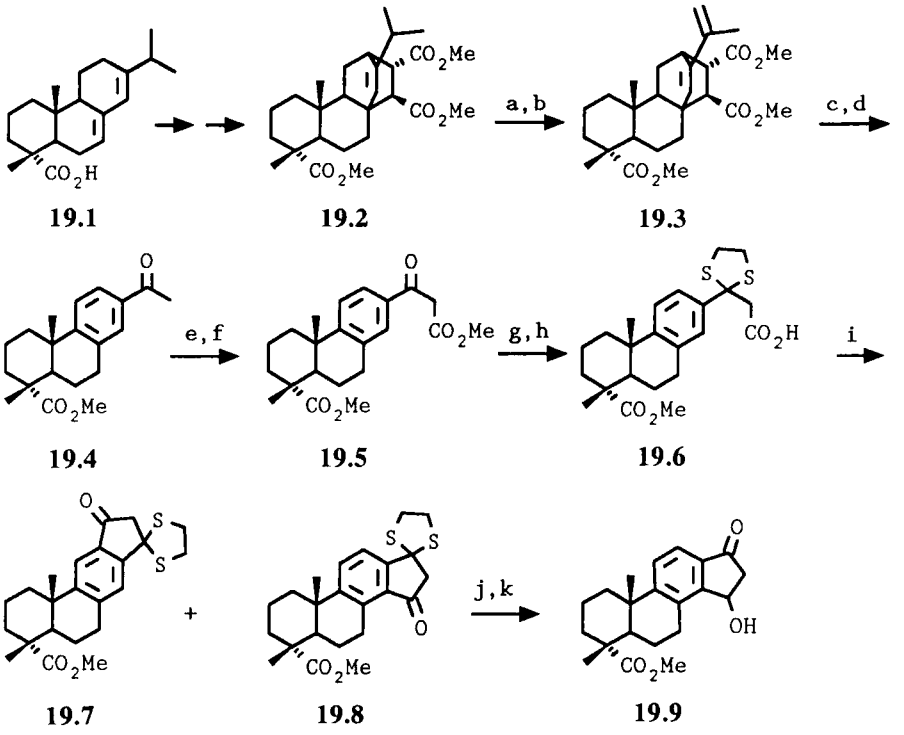
In a later synthesis, Settine and Gawish[62] used the same oxidation procedure to functionalize the isopropyl group of dehydroabietonitrile (**18.1**), which was converted to a 17-keto-C-aryl-18-nor-steroid (Scheme 18). In this sequence, the methyl ketone (**18.2**) was converted to the vinyl ketone (**18.5**) which, on treatment with $AlCl_3$ in melted sodium chloride, afforded the C-aryl-18-nor-steroid (**18.6**) in 70% yield as the sole product.



18.1 18.2 18.3 18.4 18.5 18.6

Scheme 18. (a) CrO_3, Ac_2O-AcOH then pyrolysis; (b) $(CH_2=NMe_2)Cl$; (c) MeI then heat; (d) $AlCl_3$, NaCl

Steindl and Haslinguer[63] achieved the synthesis of a 17-keto-C-aryl-18-nor-steroid from abietic acid (**19.1**), the resin acid most easily obtained from rosin (Scheme 19).

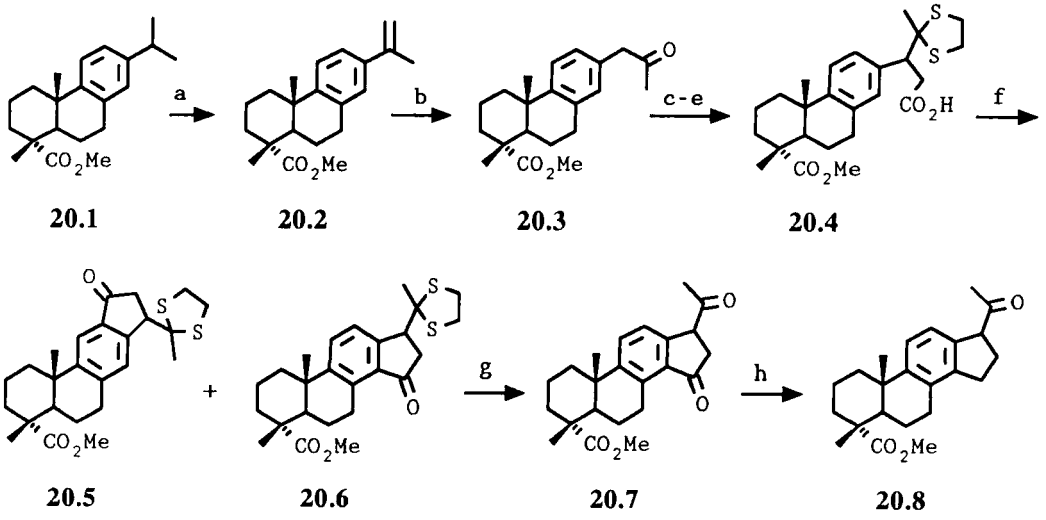


19.1 19.2 19.3 19.4 19.5 19.6 19.7 19.8 19.9

Scheme 19. (a) Br_2, $h\nu$; (b) pyridine; (c) OsO_4-$NaIO_4$; (d) Se, 310°C; (e) $MeOMgOCO_2Me$; (f) CH_2N_2; (g) $HS(CH_2)_2SH$, BF_3; (h) NaOH; (i) polyphosphoric acid, P_2O_5; (j) $NaBH_4$; (k) NBS, aq. acetone

The diene system of the resin acid was first protected by a Diels-Alder reaction with maleic or fumaric acid. Bromination of the allylic position of Diels-Alder adduct (**19.2**) followed by elimination afforded the diene (**19.3**). The selective cleavage of the terminal double bond, a reverse Diels-Alder reaction, and an aromatization of the C-ring gave the methyl ketone (**19.4**) in *ca.* 40% yield from (**19.2**). Carboxymethylation of (**19.4**), followed by protection of the ketone carbonyl group and selective saponification gave the key intermediate (**19.6**). Treatment of (**19.6**) with polyphosphoric acid resulted in D-ring formation, giving a mixture of (**19.7**) and (**19.8**) in a ratio of 1:4. Straightforward elaboration of the D-ring functionality afforded the final 15-hydroxy-17-keto-C-aryl-18-nor-steroid (**19.9**). It is interesting to note that no oxygen function was introduced in the B-ring during the whole procedure.

It was recently shown that the regioselective functionalization of the isopropyl group of dehydroabietic acid can be effected by dehydrogenation with DDQ.[58,59] On the basis of this procedure, we developed a short route to a 20-keto-C-aryl-18-nor-steroid from dehydroabietic acid (Scheme 20).[58] Dehydrogenation of methyl dehydroabietate with DDQ afforded the corresponding isopropenyl compound (**20.2**). Treatment with thallium (III) nitrate gave the methyl ketone (**20.3**) in 56% yield from dehydroabietic acid. Alkylation, thioketalization, and partial saponification led to acid (**20.4**). An intramolecular Friedel-Crafts acylation provided the cyclized

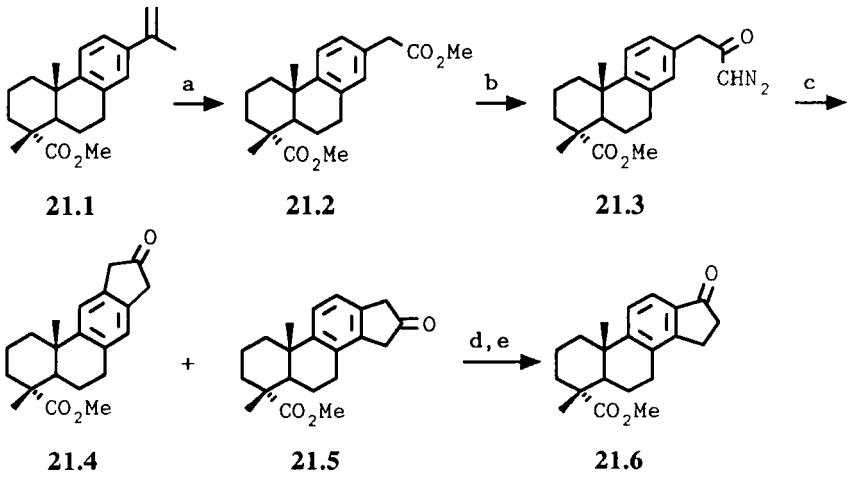


Scheme 20. (a) DDQ; (b) $Tl(ONO_2)_3$; (c) KH then BF_3 then $BrCH_2CO_2Me$; (d) $HS(CH_2)_2SH$, BF_3; (e) NaOH; (f) polyphosphoric acid, P_2O_5; (g) $Tl(ONO_2)_3$; (h) H_2, Pd-C

products (**20.5**) and (**20.6**) in a ratio of 1:1.7. Finally, unmasking of the C-17 acetyl function and removal of the C-15 carbonyl group of (**20.7**) gave the 20-keto-C-aryl-18-nor-steroid (**20.8**) as a 1:1 mixture of epimers at C-17.

In another application of the regioselective dehydrogenation with DDQ, we developed an alternative two-step process to prepare methyl ketone (**19.4**) (see Scheme 19) from dehydroabietic acid.[64] Dehydrogenation of dehydroabietic acid followed by oxidation of the resulting isopropenyl compound (**21.1**) with potassium permanganate in the heterogeneous two-phase water-benzene system and the phase-transfer agent methyltrioctylammonium chloride led to methyl ketone (**19.4**) in an overall yield of *ca.* 50%. This process considerably shortened the synthesis of the C-aromatic androstane (**19.9**) described by Haslinger.

As part of the same work, we also developed an alternative approach to 17-keto-C-aryl-18-nor-steroids from dehydroabietic acid, in which the D-ring was formed by an intramolecular insertion reaction of a diazo ketone into an aromatic carbon-hydrogen (Scheme 21). Treatment of the isopropenyl compound (**21.1**) with $Tl(ONO_2)_3$ afforded diester (**21.2**), which was transformed into diazo ketone (**21.3**). Decomposition of diazo ketone (**21.3**) in a dichloromethane solution of dirhodium(II) tetraacetate produced a high yield of an equimolecular mixture of cyclized products (**21.4**) and (**21.5**). The synthesis was completed by a Clemmensen reduction of the C-15 carbonyl group and regioselective oxidation of C-17. This route had the



21.1 21.2 21.3

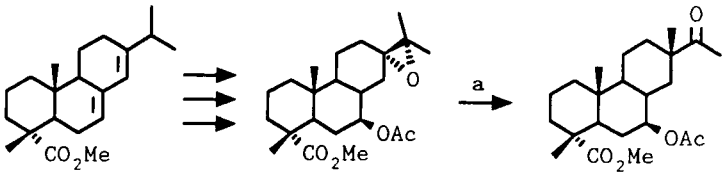
21.4 21.5 21.6

Scheme 21. (a) $Tl(ONO_2)_3$; (b) KOH then $SOCl_2$ then CH_2N_2; (c) $Rh_2(OAc)_4$; (d) Zn-Hg, HCl; (e) DDQ, water-AcOH

advantage of rapid access to the tetracyclic steroidal system, but this was countered by the disadvantage of uncontrolled regioselectivity in the cyclization step.

b. Ring-C Non-aromatic Steroidal Systems

As indicated earlier, no synthesis of the D-ring of androstane-type steroidal systems was yet achieved by the use of part or all of the carbon units of the isopropyl group of abietane-type resin acids. Shimagaki *et al.*[65] studied the possibility of using the isopropyl group in the construction of the steroidal skeleton. They showed that stereoselective migration of one methyl group of the isopropyl group to the 13β-position took place when the α-epoxide (**22.2**), derived from abietic acid through an eight-step sequence,[66] was treated with $BF_3.Et_2O$ (Scheme 22). The rearranged compound (**22.3**), with its 13β-methyl group, represented a potential intermediate for the preparation of androstane-type steroids. However, this possibility has not been explored.



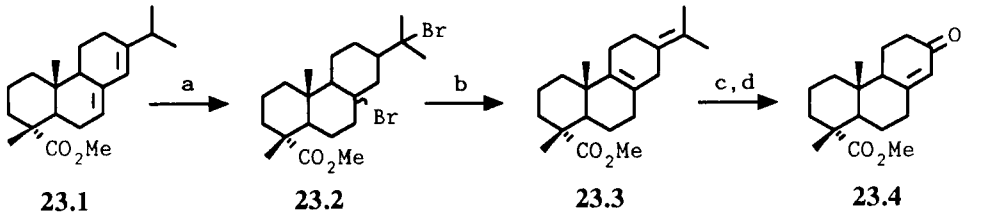
22.1 **22.2** **22.3**

Scheme 22. (a) $BF_3.Et_2O$

Practical approaches for the abietane-to-androstane skeleton conversion are of two general types. One involves initial removal of the isopropyl group and transforms the abietane skeleton into a tricyclic podocarpane system which is further elaborated to the steroidal nucleus (ABC + D ring construction strategy). The other approach modifies the A-ring of the resin acid, making it the D-ring of a BCD synthon, which is then converted to the tetracyclic steroidal skeleton (DCB + A approach).

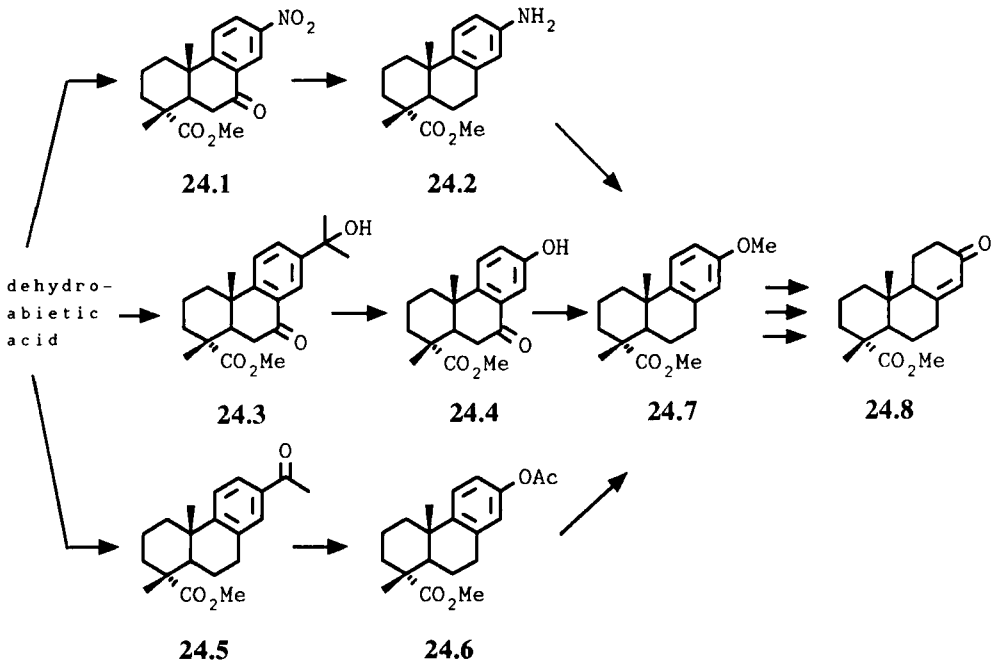
With respect to the first approach, several distinct strategies were applied to the excision of the isopropyl group of different resin acids and, in accordance with the organization of this review, the transformation of these tricyclic podocarpane-type systems into the steroidal nucleus will be discussed in the following section. The isopropyl group of abietic acid was removed by a three-step sequence in 25-30%

overall yield (Scheme 23).[67] Hydrobromation of methyl abietate gave dibromo derivative (**23.2**), which upon dehydrobromation and regioselective ozonolysis of the exocyclic double bond of diene (**23.3**) afforded podocarpenone (**23.4**). Due to its simplicity and the possibility of obtaining the dibromo derivative (**23.2**) directly from colophony, this transformation is suitable for large-scale preparation.



Scheme 23. (a) BrH-AcOH; (b) LiOH; (c) O_3 then Me_2S

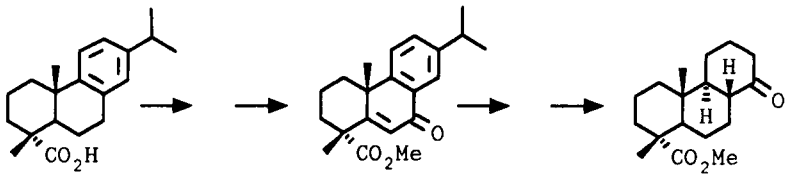
The same podocarpenone (**24.8**) (see Scheme 24) was obtained from dehydroabietic acid through several routes that converge on the methyl ether (**24.7**). Thus, transformation of dehydroabietic acid into deisopropyldehydroabietic acid by a



Scheme 24.

multistage oxidative deisopropylation, followed by oxidation at C-7 and nitration gave the 13-nitro compound (**24.1**) which, by reduction to amine (**24.2**), diazotization, and methylation, led to methyl ether (**24.7**).[68] Oxidation[59] and dehydrogenation[58,59] of the isopropyl group afforded tertiary alcohol (**24.3**) and olefin (**20.2**) (*vide supra*), respectively. Oxidation of the former with *t*-butyl hydroperoxide gave phenol (**24.4**), readily transformed into (**24.8**), while oxidation of the terminal olefin (**20.2**) to ketone (**24.5**) followed by Baeyer-Villiger rearrangement gave acetate (**24.6**), also easily converted to the required methyl ether (**24.7**).[69] The last approach has proved to be the most effective of the three (*ca.* 40% overall yield from dehydroabietic acid). Straightforward elaboration of the C-ring of methyl ether (**24.7**) eventually gives the target podocarpenone (**24.8**), whose conversion to steroids is described in section II.3.b.

Other podocarpanones suitable for transformation into steroidal compounds have also been obtained from dehydroabietic acid. Thus, the enone (**25.2**) (Scheme 25), derived from dehydroabietic acid, was converted[70,71] to podocarpanone (**25.3**) *via* nitration at the 14-position, conversion of the nitro group into the OH group, deisopropylation, reduction of the enone function, and oxidation of the 14-OH group to the oxo group. Although the conversion of (**25.3**) to steroids is already known in analogous compounds, the low overall yield obtained in the above sequence limits the potential interest of this intermediate in the synthesis of steroids.



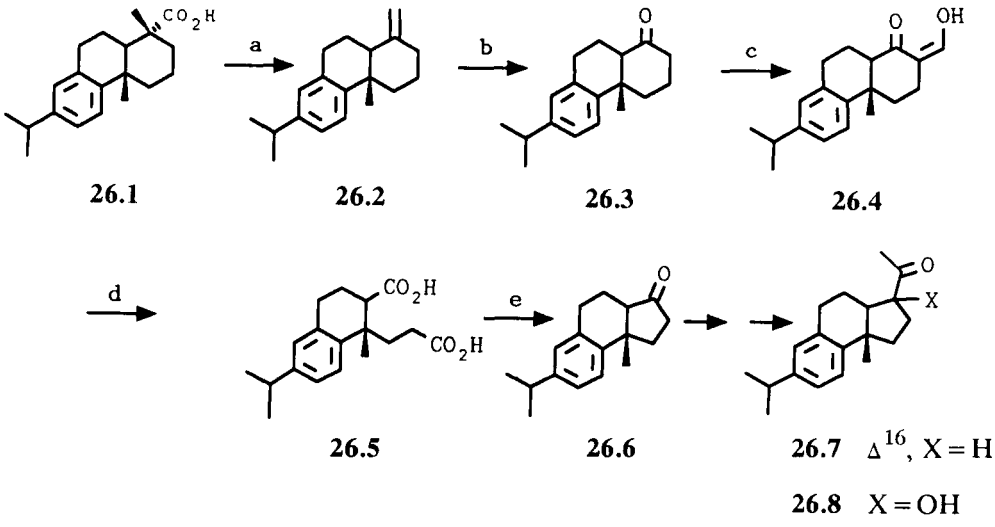
25.1 **25.2** **25.3**

Scheme 25

Studies on the DCB+A ring construction of the steroidal skeleton were described by several authors, using dehydroabietic acid as starting material. This approach was based on the conversion of the A-, B-, and C-rings of the diterpene skeleton to the D-, C-, and B-rings of the steroidal skeleton. The resulting des-A steroid thus generated must possess the *trans*-CD ring junction characteristic of

natural steroids and an appropriate B-ring functionality for the elaboration of the A-ring.

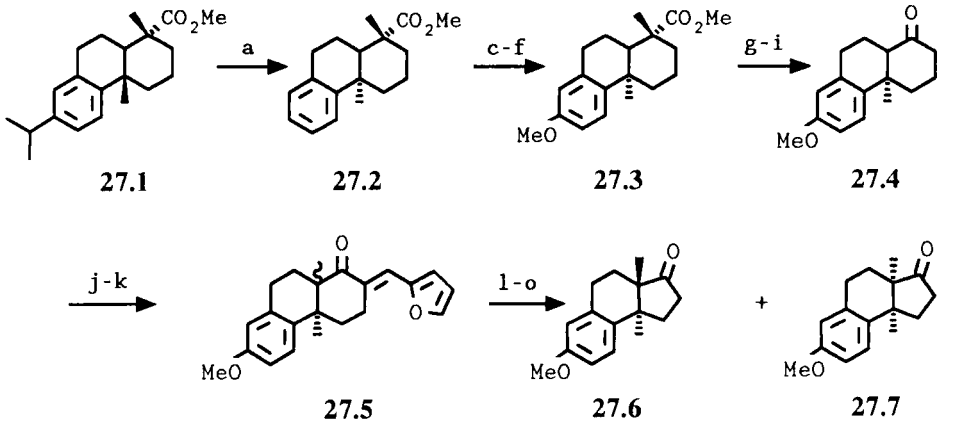
Huffman and Arapakos,[4] as part of their pioneering studies in the conversion of resin acids into steroids, described the preparation of several tricyclic steroid analogs from dehydroabietic acid (Scheme 26). Oxidative decarboxylation of dehydroabietic acid, followed by ozonization of the resulting olefin (**26.2**) (see Section I) gave 1-ketonordehydroabietane (**26.3**), which was transformed, *via* formyl derivative (**26.4**), into diacid (**26.5**). Dieckmann condensation of the diester of this acid followed by decarboxylation gave cyclopentanone (**26.6**), which was converted to Δ^{16}-20-keto and 17-hydroxy-20-keto steroid analogs (**26.7**) and (**26.8**), respectively. The main disadvantage of this approach was that it led to tricyclic steroid analogs of unnatural configuration, with the methyl group and hydrogen at the CD bridgehead interchanged.



Scheme 26. (a) $Pb(OAc)_4$; (b) O_3; (c) HCO_2Et, NaH; (d) KOH, H_2O_2; (e) CH_2N_2 then t-BuOK then HCl-AcOH

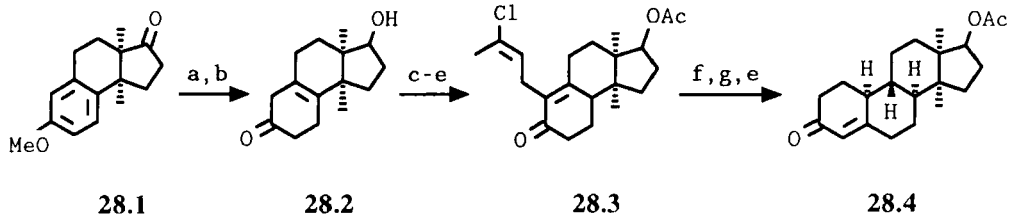
Jeger and colleagues[27] reported the conversion of dehydroabietic acid into the des-A B-aromatic 14-methylsteroid (**27.6**) (Scheme 27). One-step aluminum chloride-induced deisopropylation of methyl dehydroabietate (**27.1**) led to the A/B-*cis* compound (**27.2**) (note that configuration inversion occurs at C-10). This was converted to the 13-methoxy derivative (**27.3**) *via* nitration at the 13-position,

conversion of the nitro group into the OH group, and methylation of the 13-OH group. Successive C-4 decarboxylation and ozonolysis led to ketone (**27.4**). Introduction of the angular 13-methyl group (steroid numbering) and ring contraction of the cyclohexanone moiety of (**27.4**), following a route similar to that developed some time ago by Huffman, afforded the C/D-*trans* compound (**27.6**) in *ca.* 21% overall yield from (**27.4**), along with the C/D-*cis* isomer (**27.7**) in approximately 4% yield.



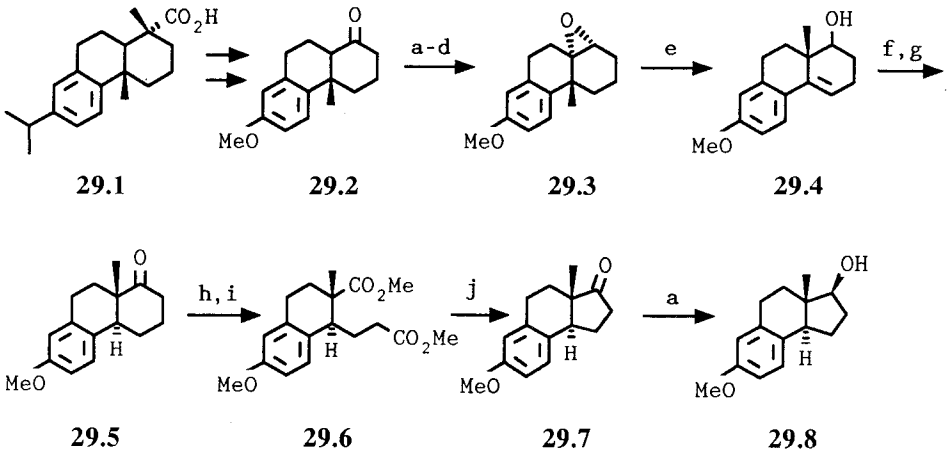
Scheme 27. (a) $AlCl_3$; (b) CrO_3; (c) H_2SO_4-HNO_3; (d) H_2, $PdCl_2$, Pd-C; (e) $NaNO_2$; (f) K_2CO_3, Me_2SO_4; (g) PhLi; (h) $Pb(OAc)_4$, $CaCO_3$; (i) O_3 then $LiAlH_4$ then CrO_3; (j) NaOH, $C_5H_4O_2$; (k) K(*t*-BuO), MeI; (l) NaOMe; (m) NaCl, KI, $Na_2S_2O_3$; (n) NaH; (o) NaOH

In accompanying experiments, the authors worked out the formation of the A-ring by transforming the minor isomer (**27.7**) into the 14α-methyl-13α-estrene (**28.4**) (Scheme 28).[72] Straightforward elaboration of the B-ring gave enone (**28.2**), which after alkylation with 1,3-dichloro-2-butene, hydrolysis of the vinyl chloride moiety, hydrogenation, and aldol condensation led to (**28.4**).



Scheme 28. (a) $NaBH_4$; (b) Li-NH_3 then $(CO_2H)_2$; (c) Ac_2O-pyridine (d) 1,3-dichlorobut-2-ene, Na(t-amylate); (e) HCl-AcOH; (f) H_2SO_4; (g) H_2, Pd-C

The last, and ultimately most practical sequence, involved the conversion of dehydroabietic acid into the des-A B-aromatic steroid (**29.8**) (Scheme 29),[73] a useful intermediate for the synthesis of steroids that has already been converted into estradiol and adrenosterone.[74] The initial stages of this synthesis involved transformation of dehydroabietic acid into methoxy ketone (**29.2**) by application of the above-described methods [cf. Scheme 24; (**24.3**) → (**24.4**) → (**24.7**); Scheme 27; (**27.3**) → (**27.4**)]. The authors were able to bring about the stereoselective migration of the angular methyl group at the C-10 position to the C-5 position (the C-13 position in the steroidal system) *via* rearrangement of the epoxide (**29.3**). Stereoselective hydrogenation of the olefin (**29.4**) followed by oxidation of the OH-group led to ketone (**29.5**). Oxidative cleavage of the cyclohexanone moiety in (**29.5**) and subsequent esterification afforded diester (**29.6**), which was transformed into indenone (**29.7**) by Dieckmann cyclization followed by hydrolysis and decarboxylation. Finally, reduction of the carbonyl group at C-17 led to the des-A B-aromatic steroid (**29.8**) in *ca.* 15% yield from (**29.2**).



Scheme 29. (a) $LiAlH_4$; (b) $MeSO_2Cl$-pyridine; (c) 2,4-lutidine; (d) MCPBA; (e) $BF_3.Et_2O$; (f) H_2, Pd-C; (g) PCC; (h) IOH; (i) CH_2N_2; (j) K(t-BuO) then HCl-AcOH

3.- Podocarpane-to-Steroid Skeleton Conversion

The majority of the syntheses described in this section made use of podocarpic acid as starting material for the preparation of steroid analogs, principally ring-C

aromatic steroids. A few syntheses aimed at saturated steroids that start from ring-C reduced podocarpane-type precursors are also discussed at the end of this section.

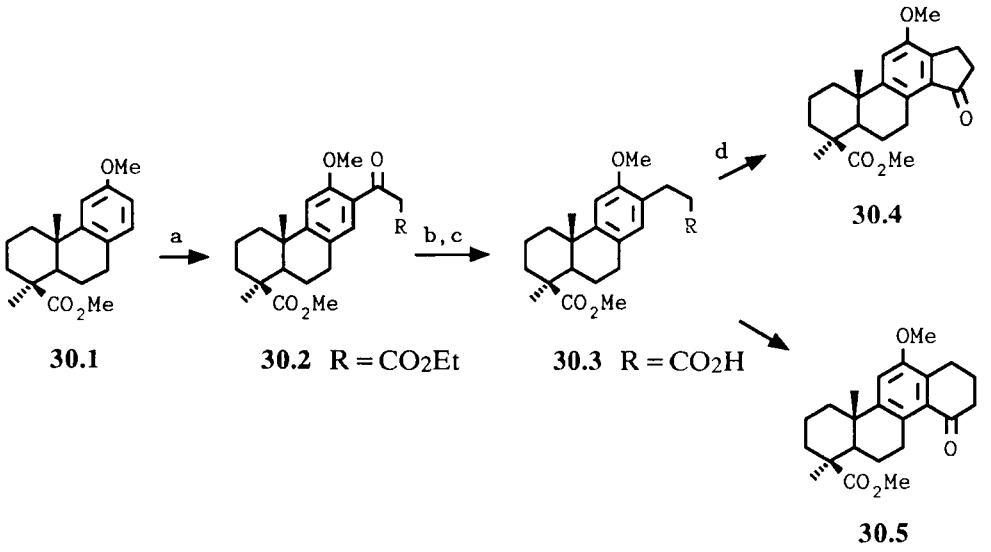
a. Ring-C Aromatic Steroidal Systems

The general strategy used for the preparation of ring-C aromatic steroids from podocarpic acid was based on the incorporation of a side chain at C-13 with the necessary functionality for further elaboration of the D-ring. Friedel-Crafts reactions were used for forming the two new carbon-carbon bonds, first at C-13 and then at C-14. The oxygen atom at C-12 serves not only to favor the initial attack at C-13, but also as a means to force subsequent ring closure with C-14. Recently, other methods involving transition metal-mediated processes to complete the cyclopenta-annulation step have also been reported.

The first preparation of a ring-C aromatic steroidal system from podocarpic acid came in 1957 from Bible,[75] who reported the preparation of steroids such as 4-methyl-4-carbethoxy-12-methoxy-18-nor-8,11,13-androstatriene-7,17-dione by Friedel-Crafts reaction of the appropriate podocarpic acid derivative with $CH_2=CHCOCl$ and $AlCl_3$ in nitrobenzene. No yields were reported for these syntheses.

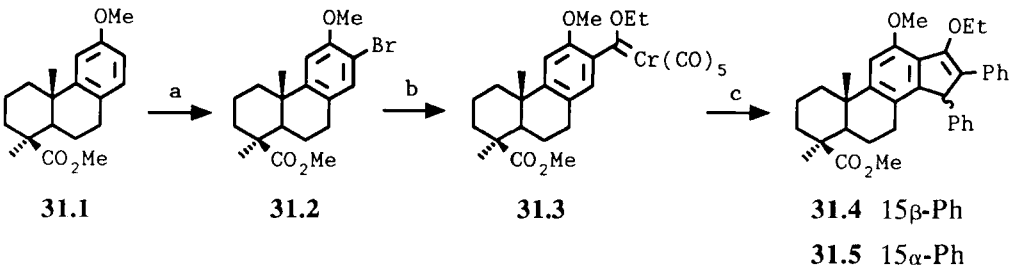
Some years later, Davis and Watkins[76] reported the synthesis of a 15-keto-C-aryl-18-nor-steroid (**30.4**) from podocarpic acid derivative (**30.1**) (Scheme 30). Friedel-Crafts reaction of (**30.1**) with ethyl malonyl chloride afforded β-ketoester (**30.2**). Clemmensen reduction followed by alkaline hydrolysis gave the acid (**30.3**), which was transformed, *via* its acid chloride, to 15-keto compound (**30.4**) in *ca.* 45% yield.

In other attempted syntheses of 15-keto compounds with substituents such as carboxyl or carboxyalkyl at C-17, the ring closure failed or resulted in very low yields of cyclization products. All attempts to obtain tetracyclic compounds with the D-ring possessing a carbonyl group at C-17 were unsuccessful and this gives an idea of the unreactivity of podocarpic acid and its derivatives towards electrophilic substitution at C-14. A similar route to that above, but using succinic anhydride in the initial acylation step, led to the D-homosteroid (**30.5**) (See Scheme 30, $R=CH_2CO_2H$).[77]



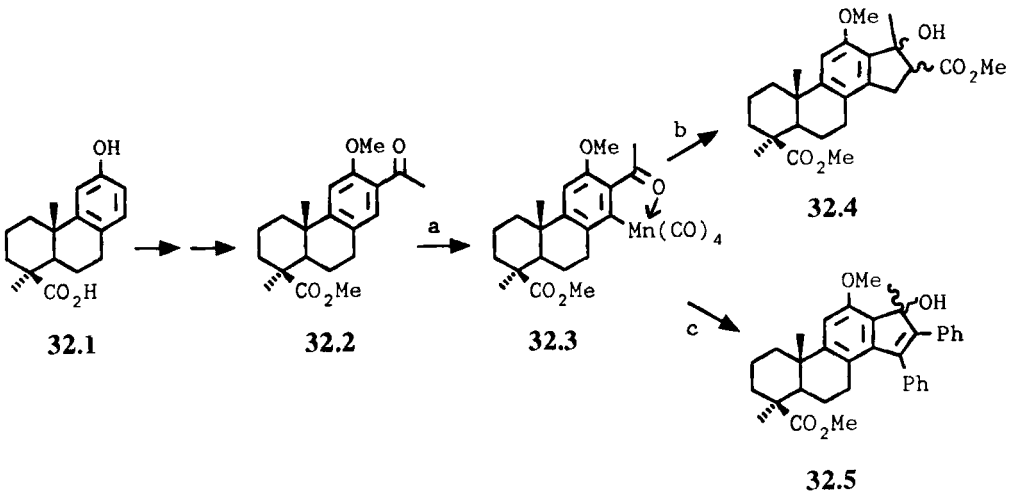
Scheme 30. (a) $AlCl_3$, $ClCOCH_2CO_2Et$; (b) Zn-Hg, HCl; (c) KOH; (d) PCl_5 then $AlCl_3$

More recently, an alternative strategy for the elaboration of the steroidal D-ring was developed by Woodgate and co-workers[78] in connection with their investigations into the functionalization of ring-C in podocarpic acid *via* transition metal-mediated processes. The key step in this new approach was the reaction of the chromium carbene complex (**31.3**) derived from methyl O-methylpodocarpate (**31.1**) with diphenyl-acetylene (Scheme 31). This approach resulted in cyclopenta-annulation to give ring-C aromatic steroid derivatives (**31.4**) and (**31.5**) in a ratio of 2:1 in moderate yield. These compounds possess two phenyl groups in the D-ring and are therefore of little value for further modifications leading to natural steroids. Attemps were made to prepare other steroidal compounds in which the phenyl groups at C-15 and C-16 were absent, but without success.



Scheme 31. (a) Br_2, $AlCl_3$; (b) BuLi, $Cr(CO)_6$ then $Et_3O^+BF_4^-$; (c) $PhC{\equiv}CPh$ then $h\nu$-O_2

Another more interesting transformation of podocarpic acid into ring-C aromatic steroids that also involved organotransition metal intermediates, was reported by the same authors.[79] In this approach (Scheme 32), the 13-acetyl compound (**32.2**) derived from podocarpic acid was transformed by ortho-manganation with benzylpentacarbonylmanganese(I) into the aryltetracarbonyl-manganese(I) complex (**32.3**) in high yield. Oxidative decarbonylation with Me_3NO generated a coordinatively unsaturated 16-electron intermediate that reacted with methyl acrylate to give the ring-C aromatic steroidal analog (**32.4**) directly in 72% yield. Reaction with diphenylethyne also led to cyclopenta-annulation to give a mixture of stereoisomeric tetracyclic steroidal analogs (**32.5**) in moderate yield.

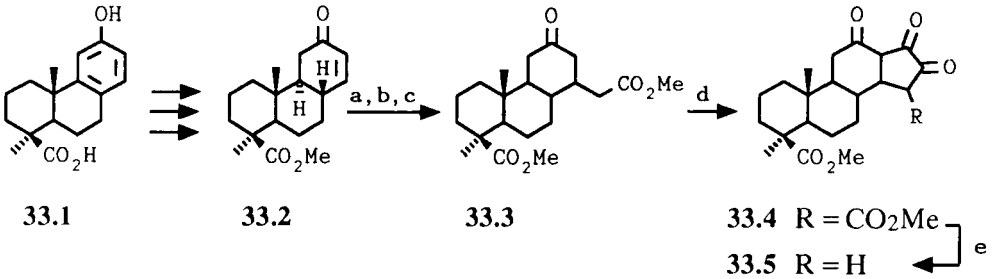


Scheme 32. (a) $PhCH_2Mn(CO)_5$; (b) Me_3NO then $CH_2=CHCO_2Me$; (c) Me_3NO then $PhC\equiv CPh$

b. Ring-C Non-aromatic Steroidal Systems

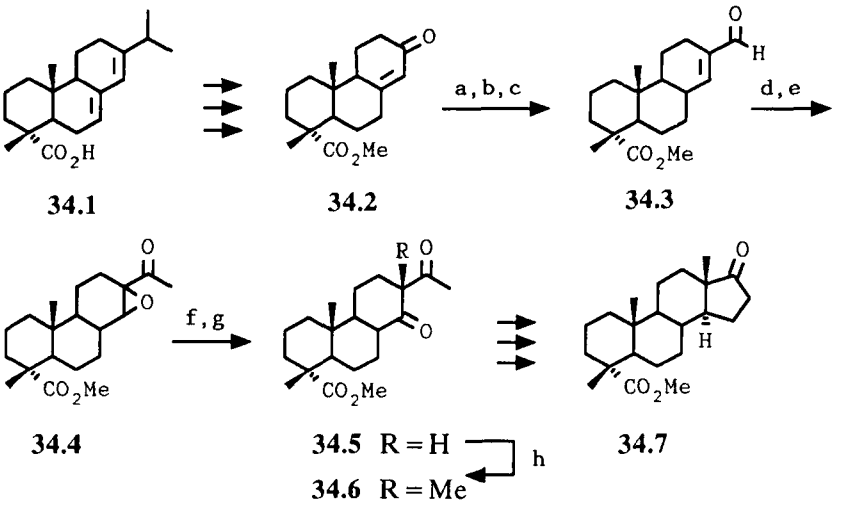
The preparation of steroidal compounds possessing a saturated C-ring from podocarpic acid has led to modifications of the A-ring in order to make it the D-ring of a tricyclic des-A steroidal system, in a similar fashion to those already described for dehydroabietic acid.[80] On the other hand, several methods were described for the elaboration of the ring-C of podocarpic acid to obtain chiral tricyclic intermediates which might be suitable for the synthesis of steroids[81,82,83] but only one report culminated in the conversion of podocarpic acid to an androstane-type steroid

analog, following the ABC+D ring approach.[84] It was based on the previous transformation of podocarpic acid into podocarpenone (**33.2**), which was then elaborated to an 18-nor steroid (Scheme 33). Thus, addition of diethyl malonate to enone (**33.2**), followed by hydrolysis, decarboxylation, and esterification, gave the methyl ester (**33.3**). The D-ring was completed by condensing keto ester (**33.3**) with dimethyl oxalate. When the condensation was performed in the presence of NaH, the tetracyclic compound (**33.4**) was isolated directly, and was then converted to 18-nor-steroid (**33.5**) by hydrolysis and decarboxylation under acid conditions.



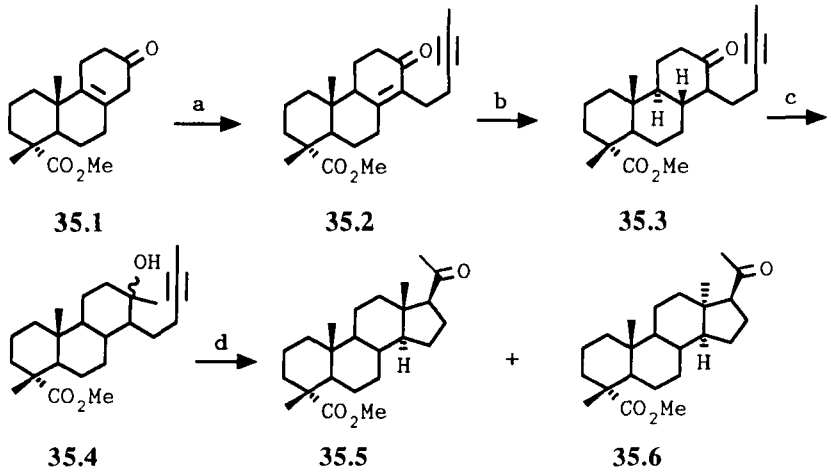
Scheme 33. (a) $NaCH(CO_2Et)_2$; (b) NaOH then heat; (c) CH_2N_2; (d) $(CO_2Et)_2$, NaH; (e) HCl-AcOH

As previously mentioned, other podocarpenones obtained from abietic and dehydroabietic acid were transformed into steroid compounds (see Section II.2.b). In particular, during the course of our own work in this field, we transformed podocarpenone (**34.2**) into isopimarone (**34.6**) (Scheme 34),[85] whose conversion to the androstane-type steroid (**34.7**) has already been described (see Scheme 16). This transformation, which also represented an abietane- and podocarpane-to-isopimarane skeleton conversion, began with a one-carbon homologation of podocarpenone (**34.2**) to the α,β-unsaturated aldehyde (**34.3**), which upon epoxidation, epoxide opening, and oxidation gave diketone (**34.5**). The angular methyl group at C-13 was stereoselectively introduced by addition of methyl iodide to the salt of the β-diketone, which afforded (**34.6**) in 14% overall yield from podocarpenone (**34.2**).



Scheme 34. (a) $Ph_2P(O)CHLiOMe$; (b) NaH; (c) HCO_2H; (d) MeLi then MnO_2; (e) *t*-BuOOH, Triton B; (f) NaTeH; (g) P_2O_5-DMSO; (h) NaOH, MeI

Finally, following earlier applications of cation-acetylene cyclization methodology to the steroids field, we also transformed podocarpenone (**35.1**)[67] into a pregnane-type steroid (Scheme 35).[86] Podocarpenone (**35.1**) was transformed into the saturated tricyclic ketone (**35.3**) by a straightforward sequence in almost 53% overall yield. The required acetylenic alcohol (**35.4**) was obtained, as a mixture of



Scheme 35. (a) LDA, $ICH_2CH_2C{\equiv}CCH_3$; (b) Li, liq. NH_3; (c) MeLi; (d) CF_3CO_2H-$(CF_3CO)_2O$ then NaOH

isomeric alcohols at C-13, by reaction of (**35.3**) with methyl lithium. The final step in the synthesis of the pregnane steroid analog (**35.5**) involved the acetylene-cation cyclization of (**35.4**). This was accomplished by treatment of the epimeric mixture of tertiary alcohols with a mixture of trifluoroacetic acid and trifluoroacetic anhydride, followed by hydrolysis of the initially formed enol trifluoroacetates, which gave a separable 5:1 mixture of tetracyclic ketones (**35.5**) and (**35.6**).

CONCLUSIONS

It is clear that the transformation of tricyclic resin acids into steroidal compounds has attracted considerable effort and ingenuity. It must be recognized that the tricyclic diterpene-to-steroid skeleton conversion represented a significant challenge and although several methods have been developed to effect this skeletal transformation, these conversions often proceed in modest overall yield. This area of resin acid chemistry is still far from fully developed.

Although the use of isopimarane-type resin acids, which already possess the methyl group with the required stereochemistry at C-13, leads to the most immediate syntheses of non-aromatic steroids, the use of abietane- and podocarpane-type resin acids allows access to a wider range of steroidal structures as well as greater versatility in the design of the synthetic plan to prepare them. Due to their availability, abietic and podocarpic acid are the most attractive starting materials for the preparation of steroidal compounds. Although the isopropyl group of abietic acid has been successfully used for the construction of the steroidal D-ring of C-ring aromatic steroids, no synthesis of saturated steroids was reported in which the D-ring derives from the isopropyl group. In practice, it has proved advantageous to remove the isopropyl group and transform the abietic acid into a tricyclic podocarpenone system before further elaboration to the desired steroidal nucleus.

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