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THE SYNTHESES OF C-NOR D-HOMOSTEROIDS

ERIC BROWN and MICHEL RAGAULT
Laboratoire de Synthèse Organique, Faculté des Sciences, Route de Laval, B.P. 535, 72017-Le Mans Cedex, France

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Abstract—A certain number of alkaloids (veratramine, jervine and related compounds) contain a C-nor D-homosteroid skeleton. Compared with classical steroids these form, at the present moment, a less numerous and, above all, less thoroughly studied family of compounds.

The present paper consists of two distinct parts. The first is a review of the recently discovered natural C-nor D-homosteroids, with a description of some pharmacological properties. In the second various studies on hemisyntheses and total syntheses of C-nor D-homosteroid compounds are analysed. This analysis shows that there is very little work published about the total synthesis of C-nor D-homosteroids and that, essentially, it can be put into two categories, that is, the synthesis of hydrochrysenes followed by contraction of the C-ring and the linear syntheses according to the DCBA and ABCD schemes.

CONTENTS

THE PRINCIPAL NATURAL COMPOUNDS CONTAINING THE C-NOR D-HOMOSTEROID SKELETON

Alkaloids having the steroid or the C-nor D-homosteroid skeleton were isolated from plants of the lily family and, in particular, of the *Veratrum Schoenocaulon* and *Zygadenus* species.[1]

Of the *Veratrum* species, two closely related types have been used for therapeutic purposes, the *Veratrum album* L. (White Hellebore or Hellebore) of Europe and northern Asia and the *Veratrum viride* Aiton (Green Hellebore or "boar's foot") of North America.

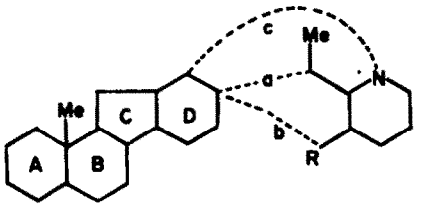
The Hellebore grows widely in France in mountainous areas: it is a tall herbaceous plant with a perennial rhizome, whose stem can reach a height of 1.5 m and which grows at between 600 and 2500 m in mountain pastures.

These plants, which are poisonous, especially for cold-blooded animals, have pharmaceutical properties which have been known for a very long time:[2,3] as early as the Middle Ages they were used for the purposes of witchcraft, in the treatment of fevers, as sedatives, cardio-tonics, emetics, poisons and insecticides.

The rhizome in particular has emeto-cathartic properties (Codex 1884); it is a source of hypotensive and vasodilatory alkaloids: the protoveratrines. These alkaloids are present in the form of alkamines, alkamine esters or glycosides. Two groups can be distinguished at the present time following a classification proposed by Fieser:[4] the alkaloids of the *jerveratrum* group which contain two or three atoms and those of the *ceveratrum* group which contain up to seven to nine O atoms (structure 1).

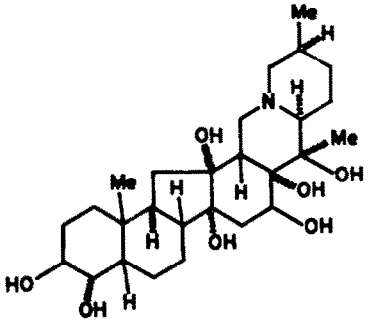
The rhizome extracts are well-known as hypotensives, this pharmaceutical property being due to the presence of alkaloids such as *sabine* **2**[2] and to other members of the *ceveratrum* family.[3]

Teratogenic properties have also been observed in certain members of the *jerveratrum* group, like jervine 3, for example.[5] Finally, it has been established that members of the *ceveratrum* family have the properties of insecticides.[6]

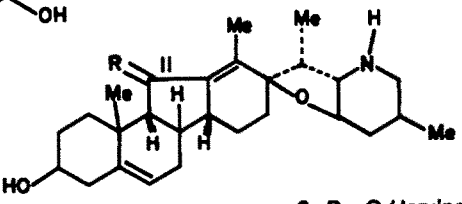


a: veratramine
a, b: jervanine
Jerveratrum group

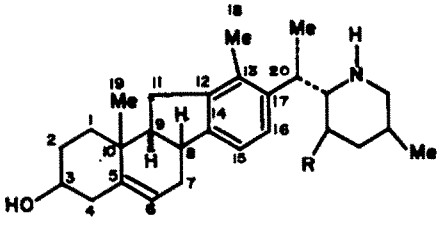
a, c: *ceveratrum* group



2 (sabine)



3: R = O (Jervine)
3a: R = H_2



4: R = H (verarine)

5: R = OH (veratramine)

According to Kupchan,[7] there are fifty or so known structures and approximately as many unknown.

Some of the best known alkaloids have been the objects of synthetic work; these are verarine **4**,[8] veratramine **5**,[9] jervine **3**[10] and some related compounds which all belong to the *jerveratrum* group; the only member of the *ceveratrum* group which has been the object of a synthesis is verticine **6** and that only recently.[11]

Some new structures have been established concerning the alkaloids of the "hexacyclic" *ceveratrum* group, these are edwardinine **7**,[12] germinalinine **8**,[13] sewertzidine **9**,[14] edpetisine **10**,[15] kashmirine **11**[16] and imperialine **12**[17] whose authors seem to agree as to their identical structure, and finally korsidine **13**,[18] korseveridine **14**[19] and veratrenone **15**.[20]

These are complex molecules which have six or even seven rings, two of them containing nitrogen, various functional groups and a high number of asymetric carbons.

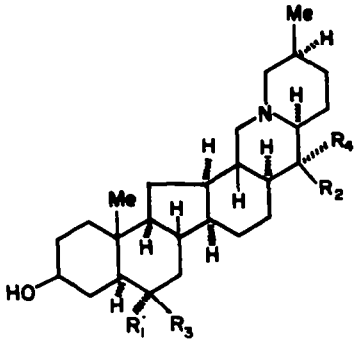
SYNTHESES OF C-NOR D-HOMOSTEROIDS

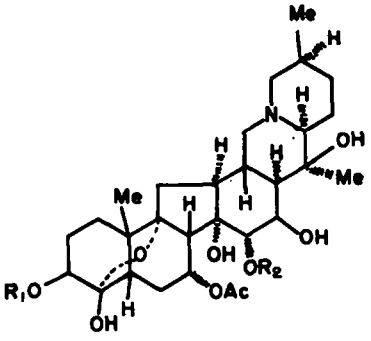
Introduction

The various syntheses of C-nor D-homosteroids known at the present time can be put into five categories.†

1. *Hemisyntheses.* These form a large group and have the advantage of starting from products of natural and therefore optically active origin, and whose stereochemistry is well defined. Unfortunately

†For detailed explanations of the terms "linear, convergent, ABCD and DCBA syntheses" (see Ref. 21).

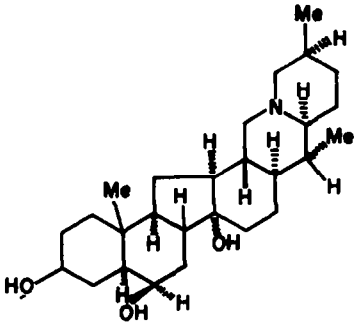




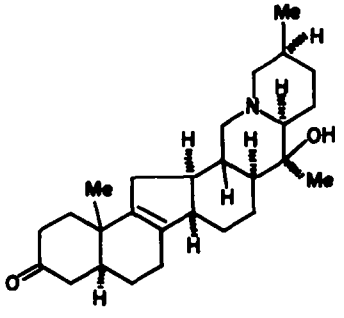
6 ($R_1 = R_2 = OH$; $R_3 = H$; $R_4 = Me$) (verticine)

7 ($R_1 = OH$; $R_4 = Me$; $R_2 = R_3 = H$) (edwardinine)

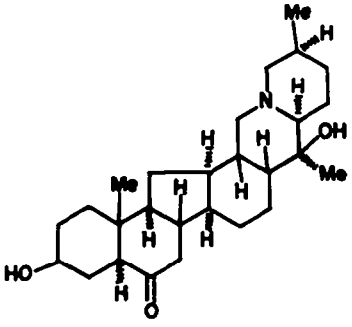
8 (R_1 = *d*-MeCH(OH)CMe(OH)CO; R_2 = *l*-EtCHMeCO) (germinalinine)



9 (sewertzidine)



10 (edpetisine)



11 (kashmirine)

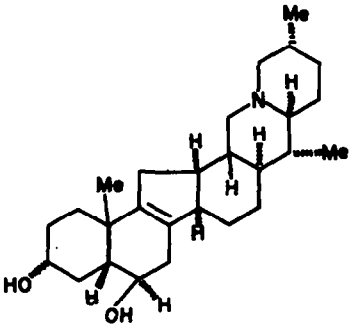
12 (imperialine)

they require the use of delicate degradation reactions, modifications of the skeleton or functional groups, with the same problems of stereochemistry and yield as in the case of total syntheses. Nevertheless hemisynthesis allows us to obtain highly elaborate products which would otherwise be almost unobtainable.

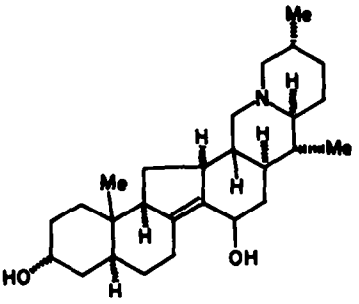
2. *Syntheses by chrysene ring-contraction.* Starting from a compound with a more or less hydrogenated chrysenic skeleton and of known stereochemistry, it is possible to obtain a C-nor D-homosteroid by contraction of the C-ring. The teams which have done research along this route have applied the methods which they had already used for ring-contractions in the steroid field, in general, oxidative cleavage followed by recyclisation by internal aldol reaction.

The starting chrysene is more or less readily accessible and, moreover, these syntheses often have the drawback of a poor yield at the key-step of the opening of the C-ring.

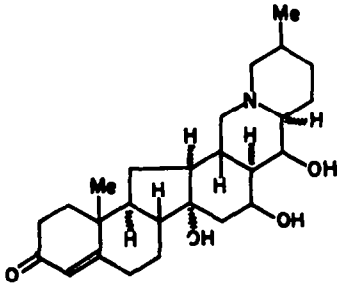
3. *Linear syntheses of the DCBA type.* Starting from a D-ring, a C-ring is constructed onto it, followed by a B-ring and finally an A-ring. These syntheses involve classical reactions and allow us to obtain the C-nor D-homosteroid system quickly.



13 (korsidine)



14 (korseveridine)



15 (veratrenone)

4. *Convergent synthesis.* The only convergent synthesis known at the present time has allowed the preparation of *O*-methyl C-nor D-homo equilenin by joining two blocks AB on the one hand and DC on the other.

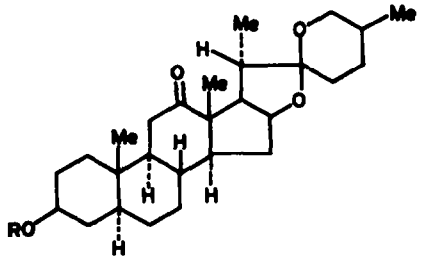
5. *Linear syntheses of the ABCD type.* The only author apart from ourselves who has published studies along this route does not seem to have obtained the desired tetracyclic compound.

This route seems interesting to us in more than one respect. A priori, it should reveal itself to be as fruitful as the DCBA route. Let us note that it requires the preparation of intermediates which possess the rare perhydrobenz(e)inden-2-one structure.

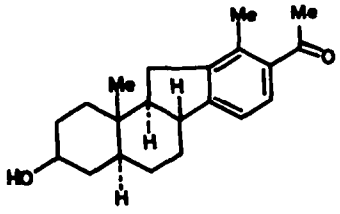
1. *Hemisyntheses*

The *jervisteroids* have led to important research into hemisynthesis which is quoted by Fieser.[4] Since the publication of this work in 1959, other important papers have appeared among which we can quote those of Masamune,[10,22,23] Johns and Laos,[24,25] Johns,[26-28] Kupchan,[29-32] Huffmann,[33] and more recently those of Kutney.[11,34]

Masamune's hemisyntheses.[10,22,23] The C-nor D-homosteroid system is obtained by degradation of hecogenin **16** or its derivatives such as acetate **16a**. Thus Masamune has successfully synthesized verarine **4**, jervine **3**, 11-deoxo jervine **3a** and veratramine **5** using as relay the C-nor D-homosteroid **17** derived from natural hecogenin **16**.[25,35]

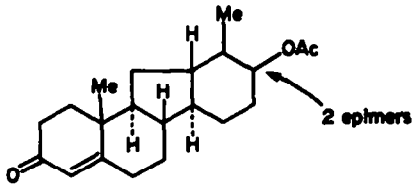


16 (R = H)
16a (R = $OCOCH_3$)



17

Kupchan's hemisyntheses. This author has successfully synthesized C-nor D-homosteroid analogues of the classical hormones: testosterone, cortisone and progesterone. Thus jervine 3 was transformed in nine steps into C-nor D-homotestosterone acetate 18,[30] the initial degradation reaction being that used by Fried[35] in his study on the structure of jervine 3. In another paper, Kupchan[31] transformed jervine 3 in eight steps into an analogue of C-nor D-homoprogesterone (19). Finally, attempts to obtain an analogue of cortisone[29] have only resulted in the C-nor D-homosteroids 20 and 21.



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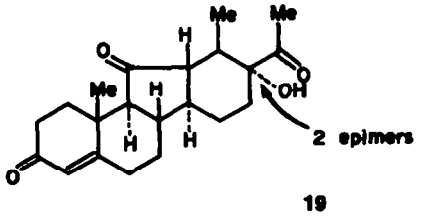

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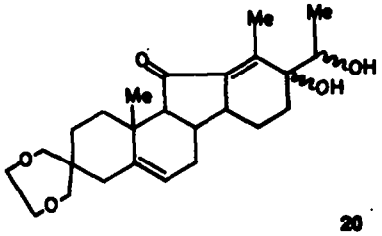

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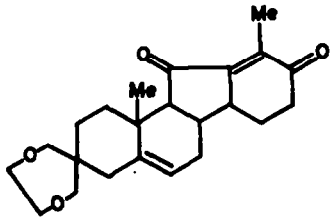
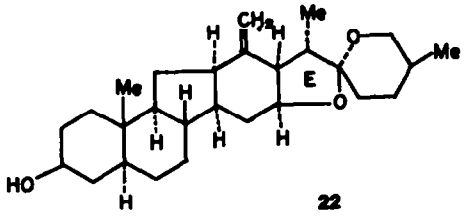


21

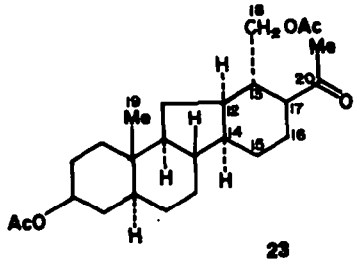
Kutney's hemisynthesis of verticine 6. Verticine 6 is one of the simplest members of the hexacyclic ceveratrum group. The synthesis recently described by Kutney[11,34] uses the acetate of natural hecogenin (16a) which is degraded according to a known method[26] then transformed into an exocyclic olefin 22 with an overall yield of 75%.

Starting with the compound 22 a first reaction sequence totalling nine steps is carried out and results in a functionalisation at C18 and then a degradation of the E-ring while leaving an acetyl group at position 17.

The thus obtained C-nor D-homosteroid 23 leads in ten steps to verticine 6.



22



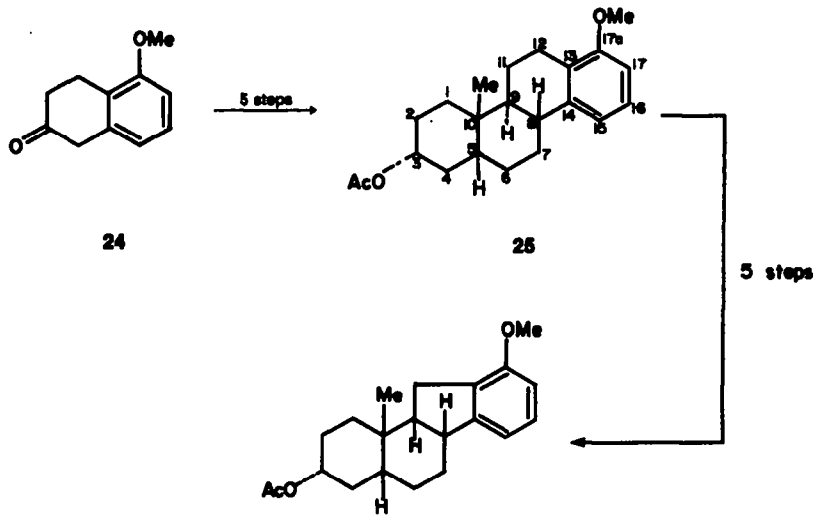
23

2. *Syntheses by contraction of the C-ring of a hydrochrysene*

Johnson's syntheses.[36,37] Johnson is the originator of this method, which he described in 1963[36] and which he used in the case of acetoxy methoxy methyl dodecahydrochrysene 25 which can be obtained in five steps starting from 5-methoxy 2-tetralone 24.[38,39]

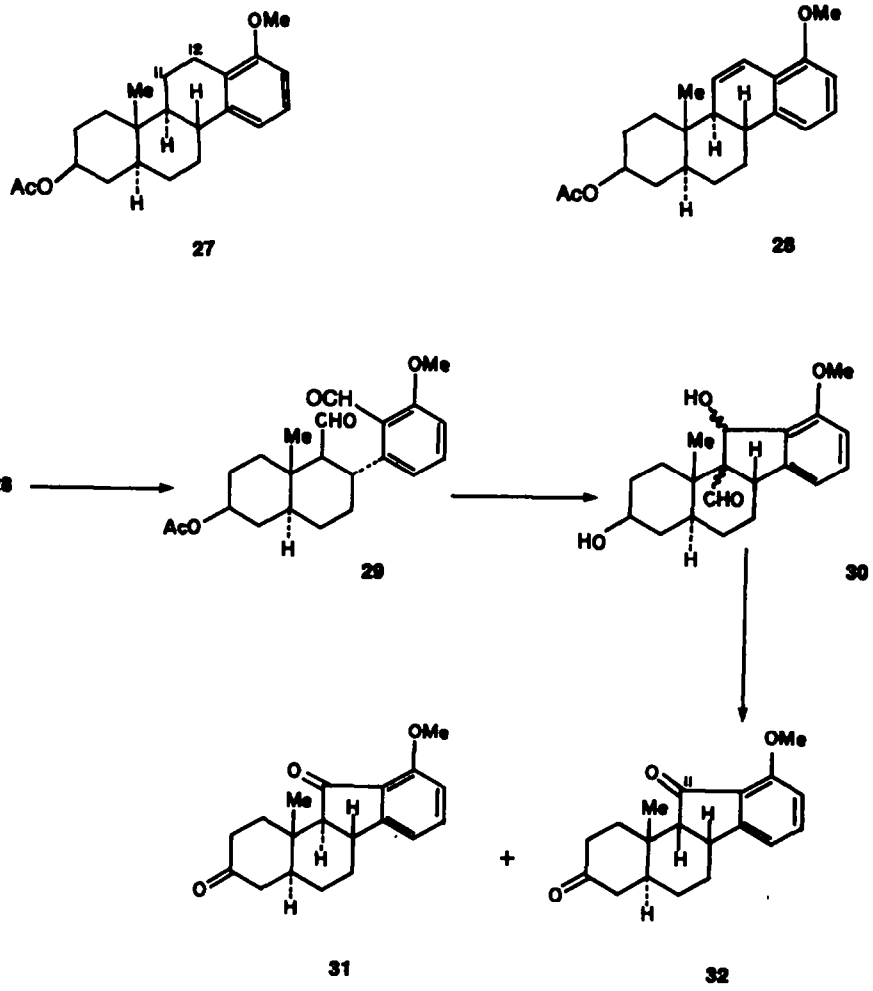
We should note that the hydrochrysene 25 does not have quite the same stereochemistry as the C-nor D-homosteroids of natural origin but is closer to biliary acids; in fact, the acetoxyl is in the 3α position, while the A and B rings are in a *cis* junction. Nevertheless, the use of the compound 25 helped Johnson *et al.*[36] to develop an interesting reaction sequence which allowed them to obtain the C-nor D-homosteroid 26 in five steps and which was then successfully used by Kutney[40] with a compound whose structure was similar to 25.

In the following we will describe in detail this method of synthesis by ring-contraction as used by Johnson[37] in the case of hydrochrysene 27 (which shows the same *trans–anti–trans* stereochemistry as in nature), which allowed him to synthesize the known relay 17.[9] Prepared in 4 steps starting from



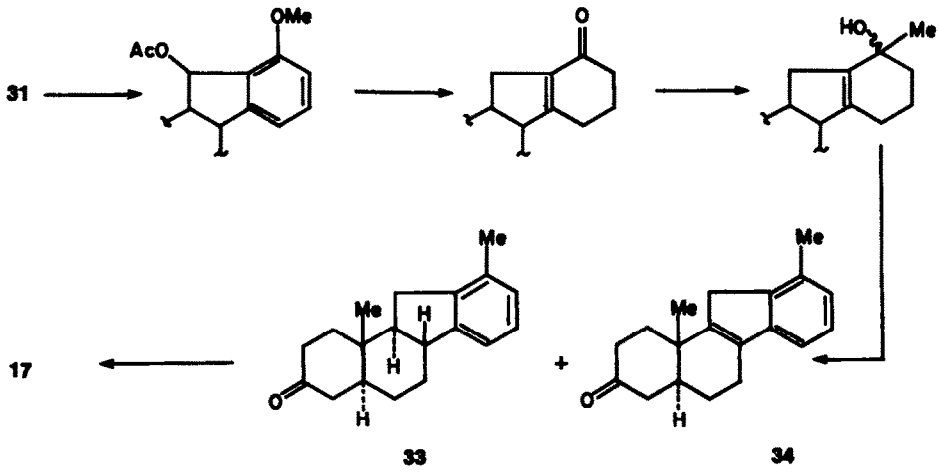
24 25 26

5-methoxy 2-tetralone **24**,[39,41] hydrochrysene **27** was oxidised by lead tetraacetate which resulted in the formation of an acetoxyl group at position 12.[42] Elimination of acetic acid afforded the 11,12-dehydro compound **28** which gave dialdehyde **29** after ozonolysis. This is easily cyclised; the resulting aldol **30** is oxidised by Jones' reagent and then deformylated by potassium hydroxide in aqueous dioxan which leads to a mixture of the C-nor D-homo steroid diketones **31** and **32**.



27 28 29 30 31 32

The mixture of diketones (31 and 32) is obtained in the ratio 9:1 with an overall yield of 38% starting from 27. The compound 31 is isolated by crystallisation. The change from diketone 31 to the mixture of monoketones (33+34) requires several steps: reduction by $LiAlH_4$ of the ketonic group at C_{11} and acetylation, Birch reduction of the aromatic ring leading to a cyclohexenone with hydrogenolysis of the 11-acetoxyl, condensation of methyllithium and rearomatisation of the D-ring, following which 33 and 34 can be separated by preparative thin layer chromatography.



Reduced by sodium borohydride, ketone 33 yields in three steps the racemic alcohol 17 one of whose enantiomers proved to be identical to the product obtained by degradation of 5,6-dihydroveratramine.

Kutney's synthesis of verarine 4. This synthesis, published in 1967, also involves a contraction of the C-ring of a hydrochrysene.[8,40,43]

Starting from 6-methoxy 2-tetralone 35, which will form the C and D-rings, the authors construct the B and A-rings by means of two Mannich–Robinson reactions; the reduction of the 4,5 and 8,9 double bonds (steroid number) followed by acetylation and finally oxidation at position 12 leads to hydrochrysene 36 where the A,B,C-ring junction is *trans–anti–trans* and where the acetoxyl is 3β.

The least favourable step of this sequence is the oxidation of the methylene at position 12, where the conversion yield does not exceed 16%.

Compound 36 then undergoes a contraction of the C-ring via an intermediary formation of dialdehyde 37 which gives diacetate 38 after intramolecular aldol reaction and acetylation. After alkaline elimination, this affords the C-nor D-homosteroid 39, which has the advantage of possessing, in position 8, a tertiary proton visible in NMR.

Birch reduction of 39 leaves intact the 9,11-ethylenic double bond and yields dienone 40, which, by hydrogenation followed by reductive alkylation with lithium in liquid ammonia and methyl iodide, then reintroduction of the double bond in 12,13 and finally acetylation, affords acetate 41 which has been resolved into its enantiomers, one of which is identical to the compound of natural origin resulting from the degradation of hecogenin 16 in thirteen steps.[24,43]

Kutney effected the final stages of the synthesis by using as relay the optically active acetate 41, obtained by degradation of hecogenin 16. The compound 41 leads in nine steps to verarine 4, identical to the naturally occurring product.

3. *Syntheses of the DCBA type*

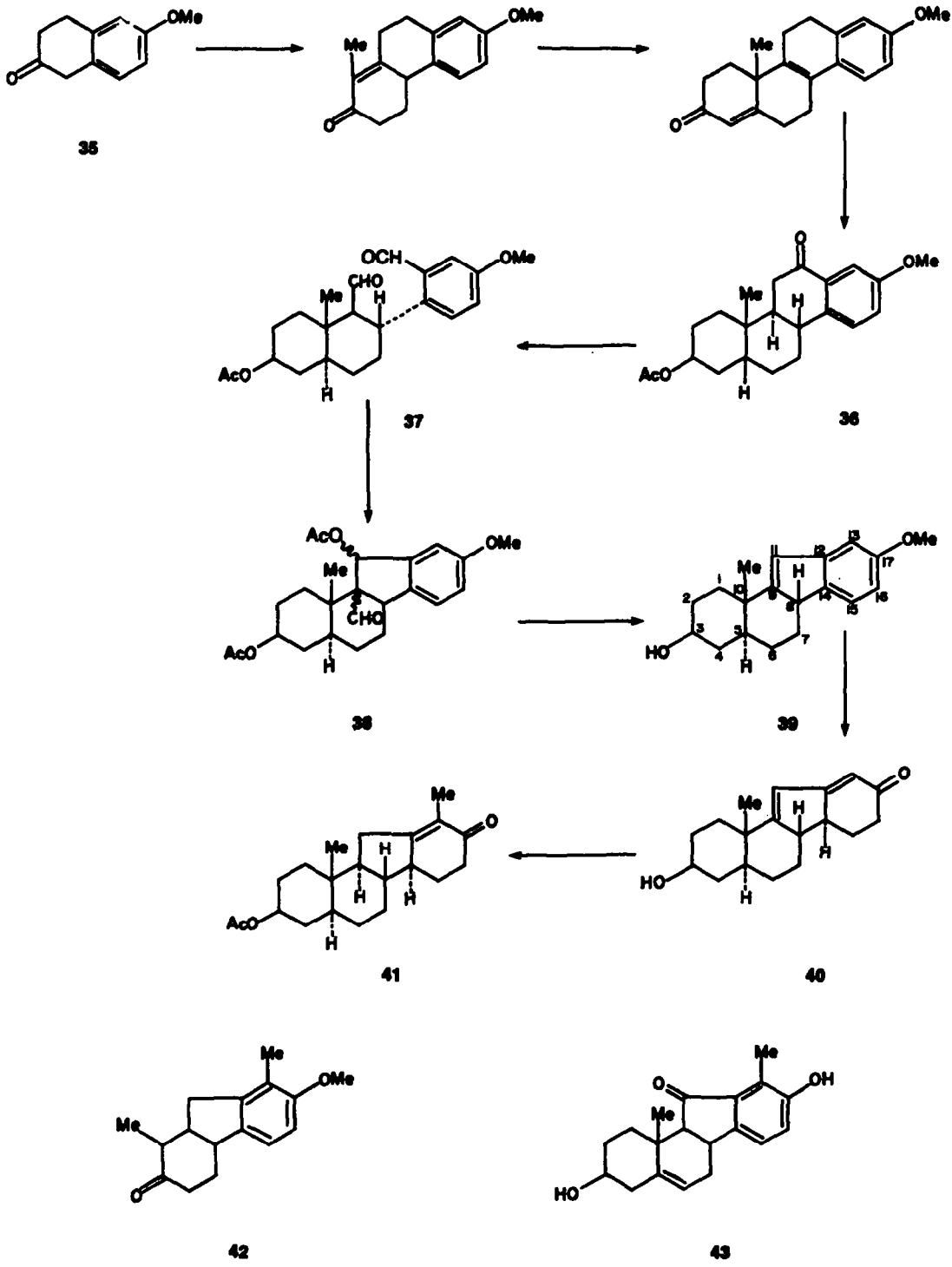
Barnes' work. Barnes *et al.*[44–46] thought of using fluorenes such as 42 to synthesize the tetracyclic compound 43 which had already been obtained by degradation of jervine 3.[35]

Various fluorenes analogous to 42 were thus prepared according to three different methods.

In the first, the key-step is a Diels–Alder reaction between the dienic acid 44 and crotonic acid, which gives the adduct 45 in 20–26% yields.

The cyclisation desired at position 12 requires the protection of position 16 of 45 by bromination.

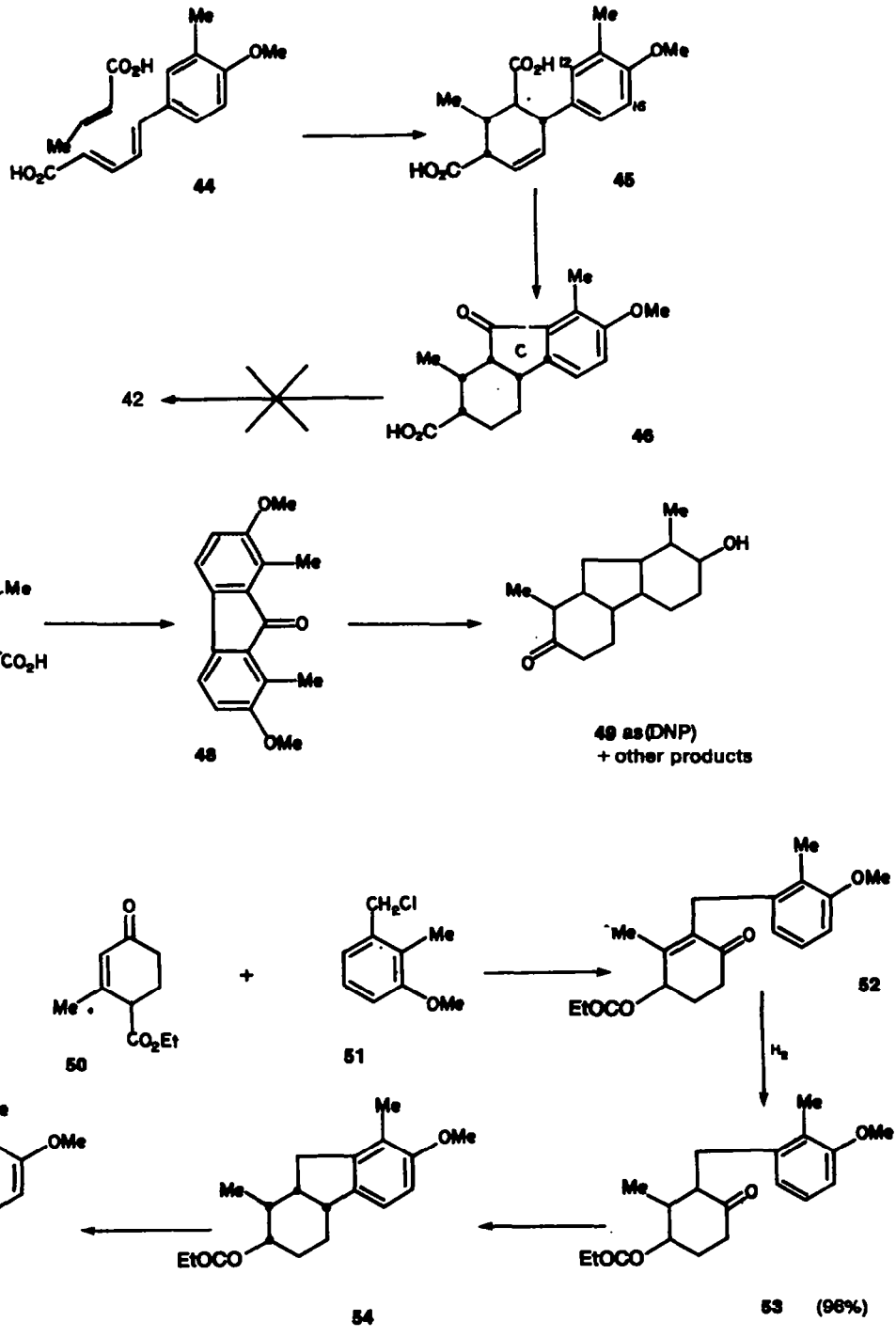
The tricyclic compound 46 obtained probably has a *cis* B,C-ring junction. Attempts to degrade it in hydrofluorene 42 by a Hunsdiecker reaction were unsuccessful.



The second synthesis calls for an Ullmann reaction between two molecules of the acid **47**, which yields the fluorenone **48** via the anhydride of a diphenic acid.

The reduction of **48** proved to be very disappointing and produced a mixture containing several stereoisomers of the compound **49** expected, of which only one was successfully isolated. No stereochemistry has been proposed for the perhydrofluorene **49** thus obtained.

In the third method, alkylation of Hagemann ester **50** by the substituted benzyl chloride **51** gives the intermediate **52** which, after hydrogenation, affords a product **53** likely to give hydrofluorene **54** in acceptable yields.



The ethoxycarbonyl group in **54** was successfully degraded into a ketonic group in four steps, which gave, although with a very poor overall yield, fluorenone **55** which probably has the indicated *cis* B,C-junction.

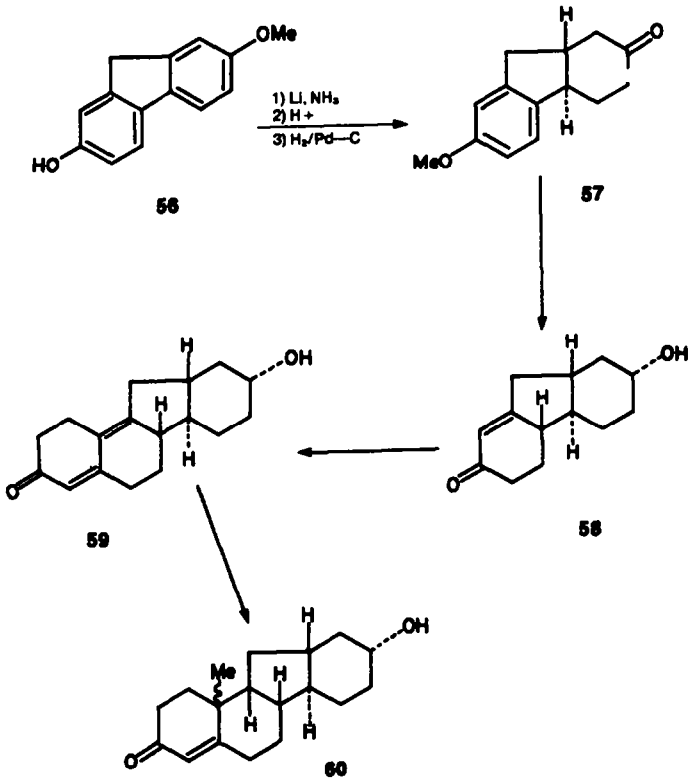
Barnes does not seem to have used these different tricyclic precursors to synthesize C-nor D-homosteroids. But, in any case, if he had brought his work to a conclusion, Barnes would have obtained compounds different from the C-nor D-homosteroids of natural origin, since these have a *trans–anti-trans* stereochemistry.

Fried's synthesis.[47,48] This synthesis allows the construction of the C-nor D-homosteroid skeleton in seven steps starting from fluorene **56** which is easily accessible. A Birch reduction of **56**, followed by hydrolysis, catalytic hydrogenation of the conjugated double bond and methylation, yields ketone **57**

where the junction of the C and D rings is *trans*. It is interesting to note that, in the course of the reduction, only the methoxylated ring of **56** was reduced.

A second Birch reaction gives ketol **58** after hydrolysis and this, after tritylation of the alcohol group, followed by direct alkylation with 3,3-ethylenedioxy 1-iodobutane (NaH, glyme at 80°), and elimination of the two protecting groups and finally intramolecular cyclisation, yields the tetracyclic compound **59**.

The angular methyl at the A,B-ring junction is introduced by reductive methylation of **59**, which yields the compound **60** as a mixture of two isomers differing only in their methyl stereochemistry, and which are, moreover, difficult to separate. Finally it must be emphasized that the B,C junction thus obtained is *cis* whereas it is *trans* in natural compounds.



The syntheses of Bhattacharyya and Mukherjee. These linear syntheses of chrysofluorenes following a scheme of the DCBA type use classical alkaline condensation reactions (Stobbe, Dieckmann) starting from a substituted indanone.[49,50]

1-indanone **61** leads after bromination and malonic condensation, followed by methylation and decarboxylation, to the ester **62** which already possesses the angular methyl at the junction of the A,B rings. By Stobbe condensation, followed by decarboxylation and esterification, **62** yields the ethylenic diester **63**.

The tricyclic keto ester **64** resulting from a Dieckmann condensation of the diester **63** yields, after saponification and decarboxylation, a mixture of ketones of which the compound **65** was isolated with a 10% yield.

By Mannich–Robinson annelation, followed by catalytic reduction, compound **65** affords the tetracyclic compound **66** (14% yield) where the junction of the B,C rings is *cis*, that of A,B being unknown.

Following on from this, various C-nor D-homosteroids were synthesized by Mukherjee[51,52] starting from the liquid mixture of isomeric tricyclic ketones **68**, prepared in the same way as that of **65** starting from 5-methoxy 1-indanone **67**. Treated with diethylaminobutanone methiodide in the presence of MeONa/MeOH, the mixture **68** yielded a tetracyclic ketone **69** whose dioxolan **70** was reduced according to Birch. The reduced compound **71** has been hydrolysed to give the ketone **72**, the latter being changed into the *trans–anti–trans* compound **73** by a Birch reduction. On the other hand, the unsaturated tetracyclic compound **69** has, by a Birch reduction, followed by hydrolysis and acetylation, yielded a unique C-nor D-homosteroid **74** in which the rings A, B and C are *trans–anti–trans*.

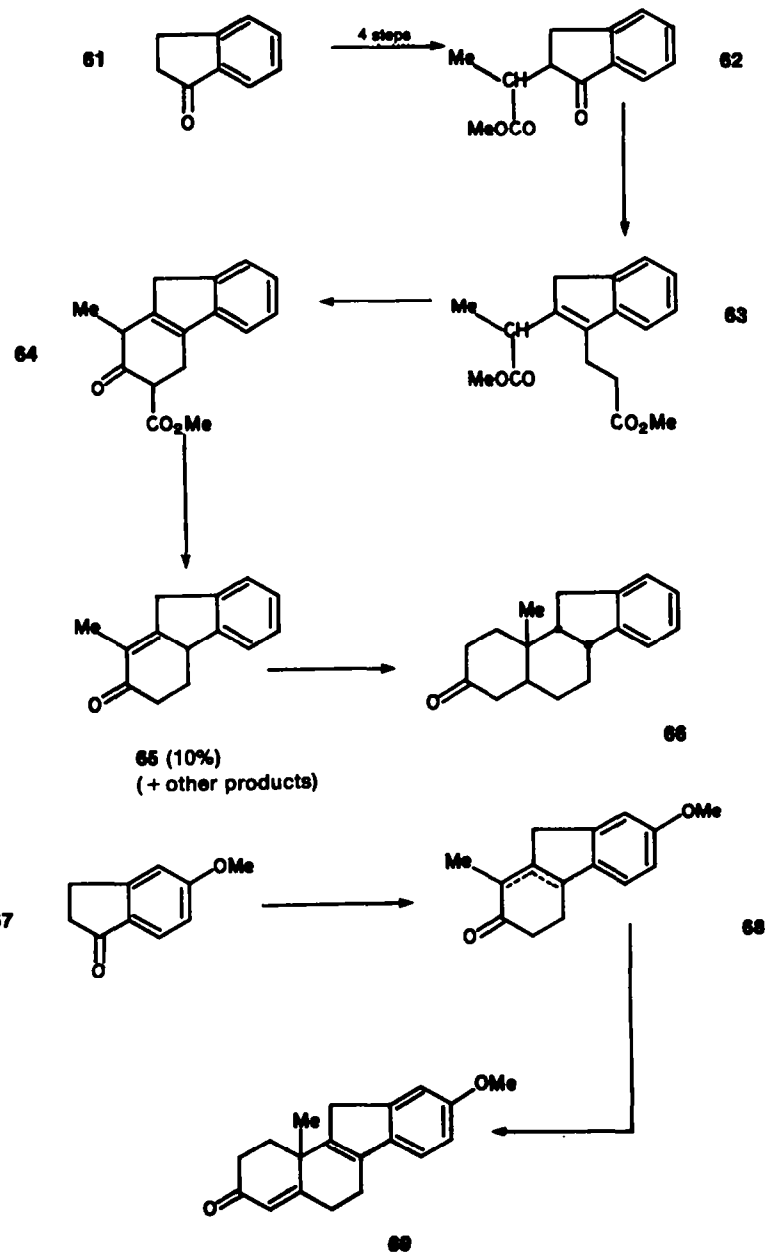
Johnson's total synthesis of veratramine **5**. This ingenious linear synthesis of the DCBA type allows us to obtain the desired compound quickly.[9,53]

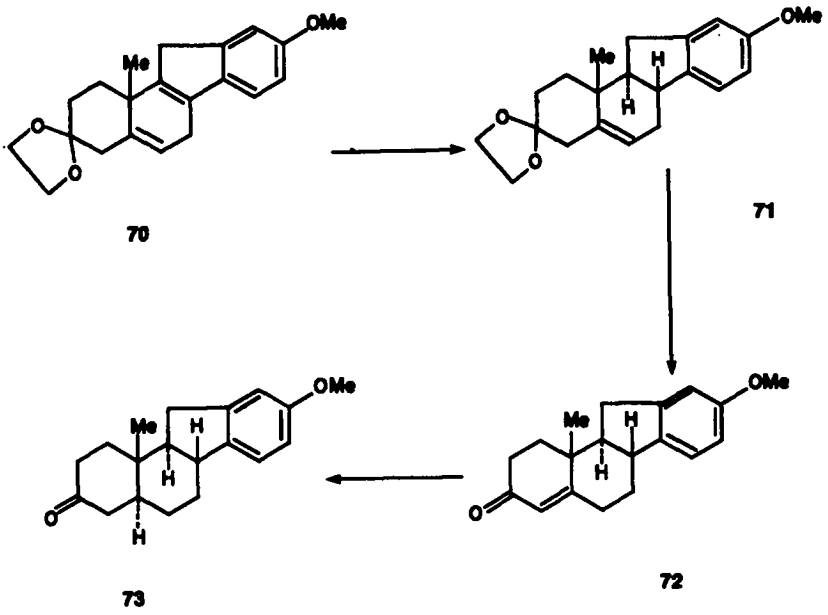
It can be divided into two parts: firstly, the total synthesis of the tetracyclic relay **17** already used in Masamune's work,[10] and, secondly, the change to veratramine **5** by linking up a suitable piperidinol ring.

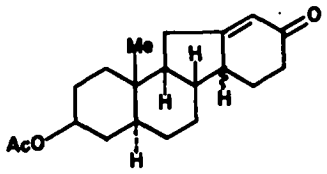
In the first sequence, the condensation of ethyl β-ethoxy γ-bromo crotonate on Hagemann ester **50** affords **75**, which, when cyclised, yields the bicyclic keto-diester **76**.

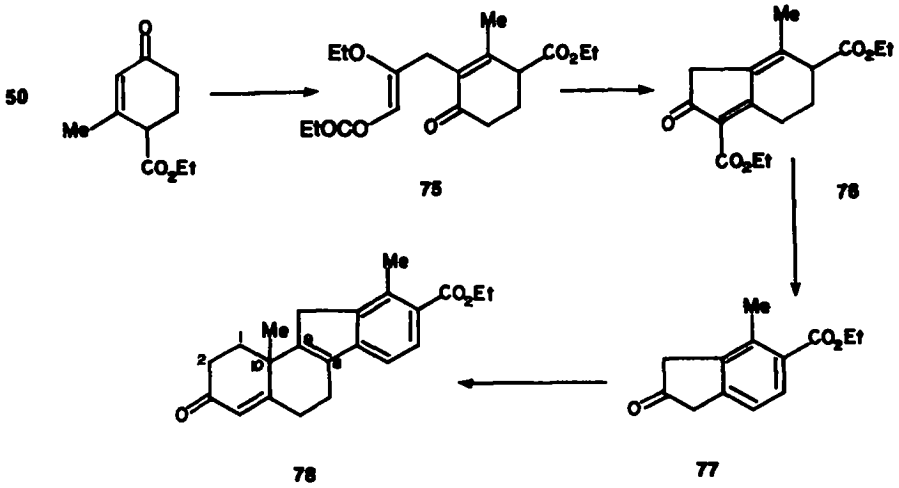
The compound **76** is aromatised immediately afterwards, which is interesting on a practical level, since general observation shows that aromatisation reactions are only really advantageous at the start of a synthesis because they often give poor yields in the case of elaborate multifunctional compounds.

With two successive annelations with vinylketones, following classical methods, Johnson *et al.* obtained the tetracyclic compound **78**. A Birch reduction results in a reduction of the 8,9 double bond and leads to the *trans* stereochemistry desired for the three centres 8, 9 and 10. It unfortunately involves a partial reduction of the D-ring which must then be rearomatised. After saponification followed by resolution into its antipodes, compound **79** was found to be identical to the product of natural origin obtained by degradation of veratramine **5**.



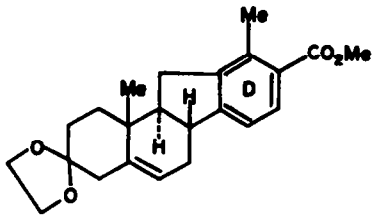






The synthesis of 17 starting from the optically active compound 79 has been concluded in six steps. One may regret that this admirable synthesis of compound 17 was described only in a preliminary paper which appeared in 1967,[53] and in which practically no yield is recorded.

The change of the relay 17 into veratramine 5 was effected in about ten main steps, of which several were required for the introduction of the double bond at C_5, C_6.



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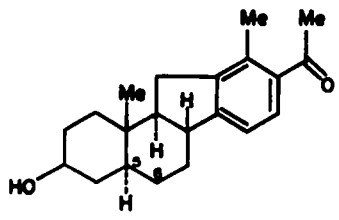
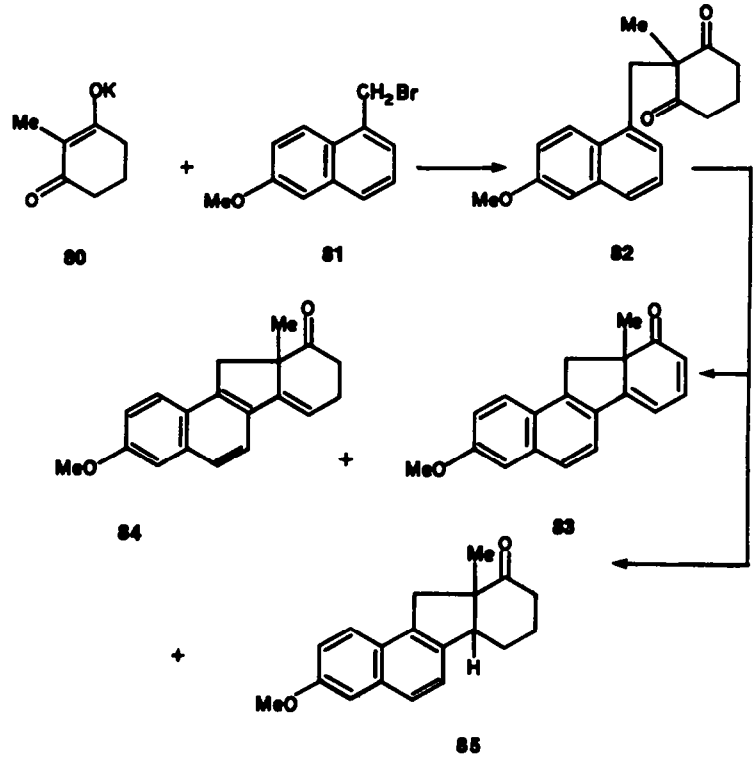


17

4. *Convergent synthesis*

This synthesis described by Wiechert[54] has the advantage of being quick to carry out, as one might expect when one takes account of the structural simplicity of the final product where the A and B rings are both aromatic.

The alkylation of the potassium salt **80** of 2-methyl cyclohexane-1,3-dione by 1-bromomethyl 6-methoxy naphtalene **81** affords the compound **82** with a 71.5% yield. The latter has been cyclised by means of polyphosphoric acid to give a separable mixture of the three C-nor D-homosteroids **83**, **84** and **85** with an overall yield of 14%.



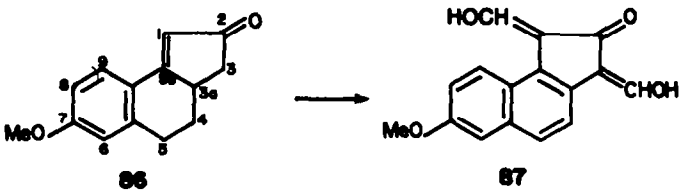
80 81 82 84 83 85

5. *Synthesis of the ABCD type*

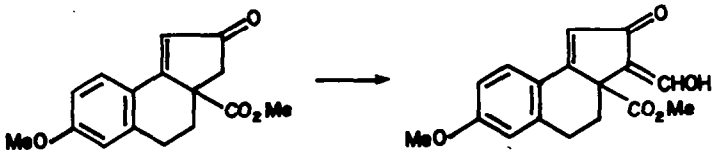
Roy's research, published in 1973,[55] gives a different approach to the problem, since it concerns a linear synthesis of the ABCD type according to a reaction scheme, the major elements of which we had already suggested in 1971[56,57] and which consists in passing via a suitable hydrobenz(e)inden-2-one, which possesses the A, B and C rings of the desired C-nor D-homosteroid.

The benz(e)inden-2-one **86**[58] used by Roy has an undeniably simple structure: no angular methyl, an aromatic A ring and only one asymetric centre.

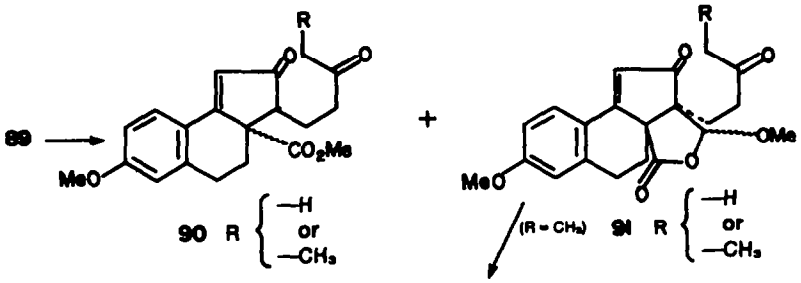
Treated by ethyl formate in order to obtain the corresponding 3-hydroxymethylene benz(e)inden-2-one, compound **86** actually yielded a totally conjugated 1,3-*bis*-hydroxymethylene benz(e)inden-2-one **87**, with migration of the ethylenic double bond at the junction of the B and C rings. It thus appeared



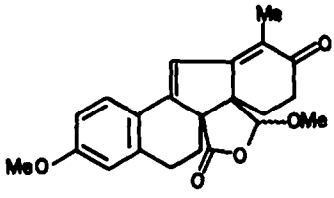
86 87



88 89

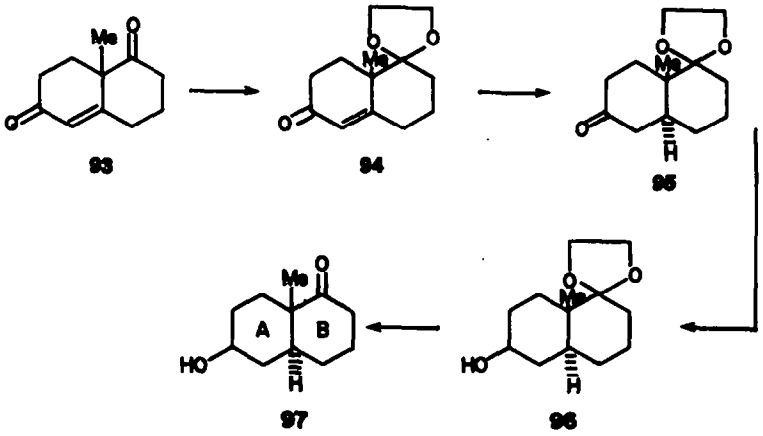


90 R = —H or —CH₃ (R = CH₃) 91 R = —H or —CH₃



92

that a selective hydroxymethylenation at position 3 could only be successfully effected with a benz(e)inden-2-one possessing, at position 3a a protecting substituent easy to remove at the end of the synthesis. These considerations dictated the choice of 3a-methoxycarbonyl benz(e)inden-2-one **88**[58] as the new starting compound. The α-hydroxymethylene ketone **89**, which derived from it in good yields, was treated with methylvinylketone, to afford the mixture of compounds **90** (R = H) and **91** (R = H) in which the desired compound **90** (R = H) is by far the minor product (isolated yield 4%).



93 94 95 96 97

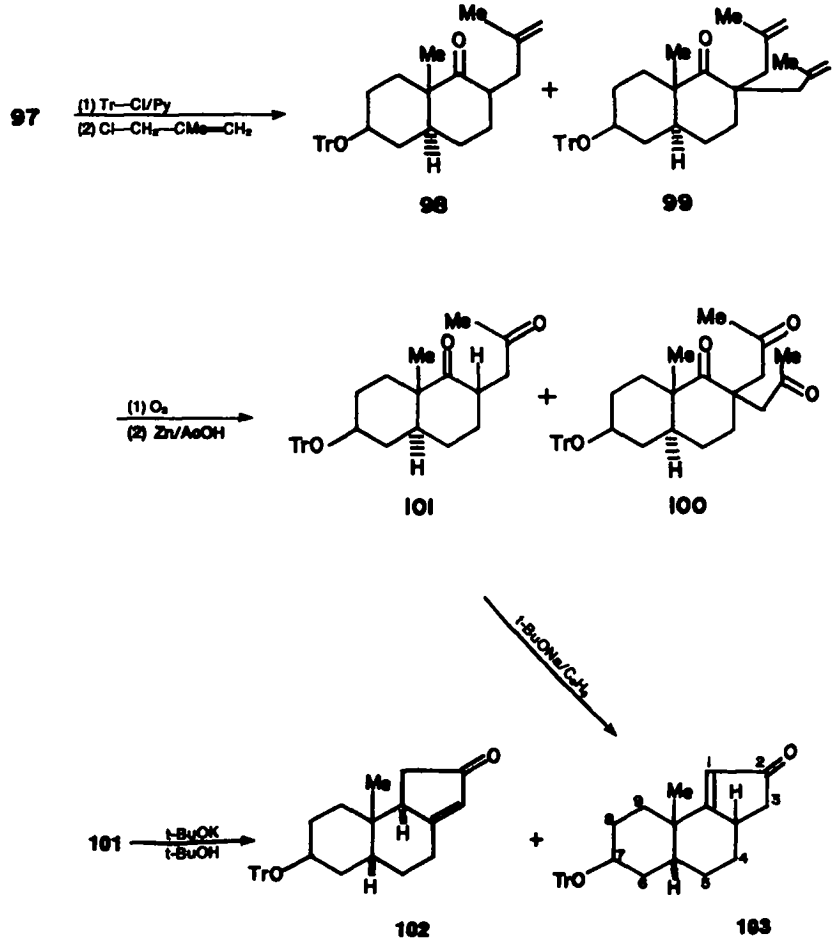
All the attempts at cyclisation of the δ-diketone **91** (R = H) were unsuccessful.

Numerous attempts have been made using ethylvinylketone, which has yielded the mixture of compounds **90** (R = Me) and **91** (R = Me), a mixture from which the authors were able to separate the desired compound **90** (R = Me) with only a 2% yield. By intramolecular cyclisation the δ-diketone **91** (R = Me) afforded the pentacyclic compound **92** with good yields. All attempts at removing the lactonic ring in the compounds **91** met with no success.

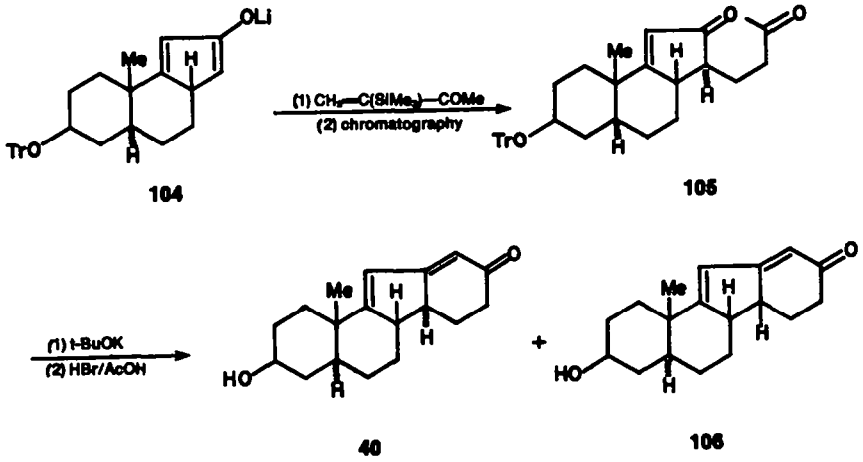
As far as we are concerned, after studying various annelation methods on model compounds,[56,57,59] we ultimately achieved a stereospecific total synthesis of Kutney's C-not D-homosteroid compound **40**, in eleven steps starting from the Wieland–Miescher ketone **93**, and following a linear scheme of the AB → C → D type.[60–62] Our synthesis can be grouped into three main stages: firstly the construction of the AB bicyclic ring system with the desired stereochemistry, secondly leading to a perhydrobenz(e)inden-2-one (ABC), and finally annelation of the C ring of the latter.

The protection of the saturated carbonyl group of the compound **93**, followed by Birch reduction of the double bond, afforded the decalone **95**, having a *trans* stereochemistry at the ring junction, and possessing the angular methyl group of the C-nor D-homosteroids. Reduction of the ketone **95** using sodium borohydride, gave the alcohol **96** in which the hydroxyl has the required β configuration. Finally, the hydrolysis of the dioxolan ring of **96** gave the hydroxy decalone **97** in good yield.

After protection of the OH group of **97** in the form of a trityl ether, alkylation with methallyl chloride using potassium t-butoxide as a base, afforded a separable mixture of mono and bis methallyl ketones **98** and **99**. Ozonolysis of this mixture, followed by reduction with zinc in acetic acid, gave the triketone **100** and the diketone **101** which can be separated much more easily than the starting mixture of **98** and **99**. Intramolecular cyclisation of the diketone **101** gave only the expected benz(e)inden-2-one **103** when using sodium t-butoxide in benzene. On the other hand, cyclisation of **101** in protic conditions (potassium t-butoxide in t-butanol) gave an isomeric mixture of **102** and **103**.



The construction of an extra 6-membered ring onto the C ring of the benz(e)inden-2-one **103** involves an alkylation at position 3 of the latter. We considered activating the carbon at position 3 of **103**, by formation of the corresponding α-hydroxymethylene, α-methoxalyl or α-ethoxycarbonyl derivatives. Since none of these intermediates could be obtained satisfactorily under a variety of experimental conditions, we next tried direct alkylation of **103** with various annelation reagents, such as methylvinyl-ketone, 4-chloro butan-2-one, 4-diethylamino butan-2-one 2,2-ethylenedioxy 4-iodobutane, and t-butyl iodotiglate, but here again without any success.



104 **105** **40** **106**

On the other hand, treatment of the ketone **103** with lithium diisopropyl amide in THF at 0° gave the kinetic enolate **104**, which reacted instantly with methyl (α-trimethyl silyl)-vinyl ketone, to give the δ-diketone **105** in 75% yield after chromatography. Intromolecular cyclisation of **105** using potassium t-butoxide in a t-butanol/toluene mixture, followed by treatment with HBr/AcOH to remove the trityl group, afforded the C-nor D-homosteroid compound **40**, m.p. 153–158°, which was identified as being Kutney's,[8] since it had the same IR, NMR and UV data. When the δ-diketone **105** was cyclised in a somewhat cruder state, apart from compound **40**, we isolated minute amounts of its isomer **106**, m.p. 199–208°.

CONCLUSION

The total syntheses of C-nor D-homosteroids belong in three main categories: syntheses by contraction of the C-ring of a hydrochrysene and linear syntheses of the DCBA and ABCD types.

The syntheses by ring-contraction were the earliest discovered. They are generally long and laborious and their main advantage is probably that of having allowed chemical correlations to be made between the natural C-nor D-homosteroids and the hydrochrysenes of known configuration, which correlations demonstrate that the C-nor D-homosteroids of natural origin indeed have the same *trans–anti–trans* stereochemistry as normal steroids.

Although the total linear syntheses of the D→C→B→A and AB→C→D types are apparently simpler and easier than earlier syntheses, up to now they have, however, given rise to only a limited number of publications.

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