The Total Synthesis of Natural Products

VOLUME 6

Edited by

John ApSimon

Ottawa—Carleton Institute for Research and Graduate Studies in Chemistry

and

Department of Chemistry
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Preface

The first five volumes in this series have been concerned with describing in a definitive manner the total synthetic approach to various classes of natural products.

This volume continues the series with chapters describing the reports and progress in the total synthesis of aromatic steroids, carbohydrates, genes, pyrrole pigments, and triterpenoids since the appearance of Volumes 1 and 2 some ten years ago.

There have been some delays in producing this volume at the Editor's end caused by the requirement of retyping and the structure drafting; however, this series of chapters brings the reader up to date with progress in the diverse classes of compounds examined herein. My particular thanks are due to Karl Diedrich of Carleton University for his efforts in the production of the various manuscripts.

The seventh volume in this series is in preparation and is planned for publication in about one year, covering the synthesis of diterpenes, diterpene alkaloids, macrocycles, and anthracyclinones.

JOHN APSIMON

Ottawa, Canada
January 1984

Contents

THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

The Total Synthesis of Aromatic Steroids 1972–1981

DAVID TAUB

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey

1. INTRODUCTION

This review covers the literature published during 1972–1981 and updates the chapter on the total synthesis of naturally occurring aromatic steroids that appeared in Volume 2 (pp. 641-725) of this series.

Extensive synthetic effort has continued to be directed toward the aromatic steroids exemplified by estrone—and toward the related 19-norsteroids—not only because of their practical medical and commercial importance but because they serve admirably as templates for the display of new organic synthetic methodology.

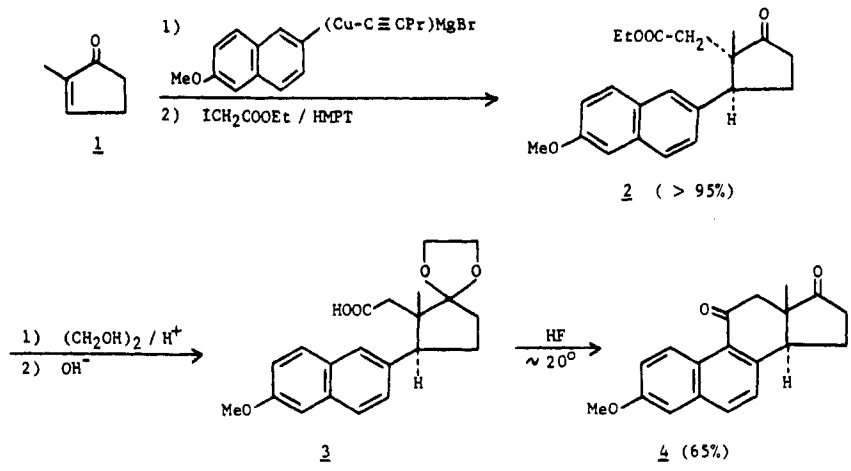
The major innovations include:

1. Development of asymmetric syntheses involving chirality transfer to prochiral substrates, in particular the use of amino acids as catalysts in chirally directed aldol cyclizations.
2. Development of synthetic routes based on generation and intramolecular cycloaddition of orthoquinodimethanes.

2. EQUILENIN

A. Posner Synthesis

Posner and co-workers have developed an efficient (52% overall yield) conversion of 2-methyl-2-cyclopentenone into (±)-11-oxoequilenin methyl ether, **4** (Scheme 1).[1] The latter had been hydrogenolyzed earlier to equilenin methyl ether by Birch (see Volume 2, p. 660).



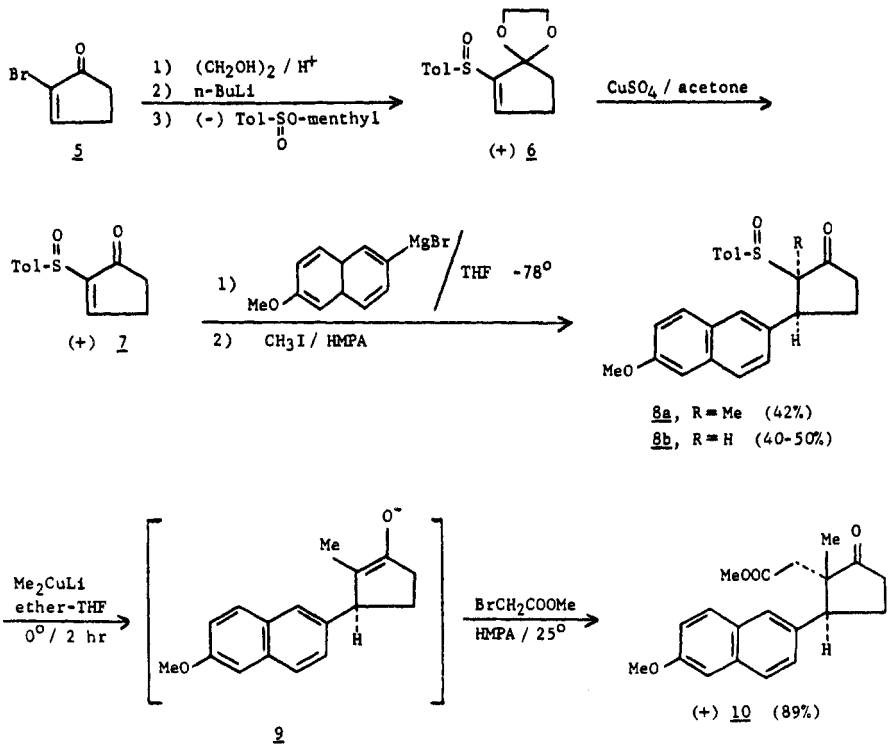
1 2 (> 95%) 3 4 (65%)

Scheme 1

2-Methyl-2-cyclopentenone **1** was treated sequentially with (6-methoxy-2-naphthyl)(1-pentynyl)coppermagnesium bromide and ethyl iodoacetate to give the stereochemically pure *trans* keto ester **2** in >95% yield (Scheme 1). The yield was considerably lower when the corresponding aryl(alkynyl)lithium cuprate and methyl bromoacetate were utilized. Analogous reactions with the smaller vinyl group instead of 6-methoxy-2-naphthyl were not as clean stereochemically, producing appreciable amounts of *cis* isomers (see below, orthoquinodimethane approach[36,40,53]). Conversion of **2** to the corresponding ethylene ketal, saponification, and Friedel–Crafts cyclization in liquid hydrogen fluoride led to (±)-11-oxoequilenin 3-methyl ether, **4**. Curiously, the cyclization yield was appreciably higher with the ethylene ketal acid **3** than with the corresponding 17-ketone.

Extension to the natural (+) series was accomplished by transfer of chirality from sulfur to carbon via (+)-2-tolylsulfinyl-2-cyclopentenone, **7**[2a] (Scheme 2). The latter was prepared in optically pure form from the ethylene ketal of 2-bromo-2-cyclopentenone **5** by lithiation and treatment with (−)-menthyl *p*-toluenesulfinate to yield (+) **6**, followed by deketalization. Conjugate addition of 6-methoxy-2-naphthylmagnesium bromide to (+) **7** followed by *in situ* methylation gave stereochemically pure **8a** in 42% yield along with 40-50% of unmethylated analog **8b**. More vigorous methylation conditions led to elimination of *p*-toluenesulfinic acid. Generation of enolate **9** with dimethylcopperlithium followed by alkylation with methyl bromoacetate then led to (+)-methyl ester **10**. The overall yield of (+) **4** is 25% based on the Friedel–Crafts procedure developed for the racemic series.

Sulfoxide (+) **7** has also been utilized in effective chiral syntheses of (3*S*)-2-methyl-3-vinylcyclopentanone **128**[46] and the corresponding trimethylsilyl enol



Scheme 2

ether [cf. (±) **95**[35,42,2b]], ring D synthons in orthoquinodimethane approaches discussed below. Conjugate addition of vinylmagnesium bromide to (+) **7** occurred with 100% asymmetric induction when zinc bromide was added first to preform the zinc chelate.

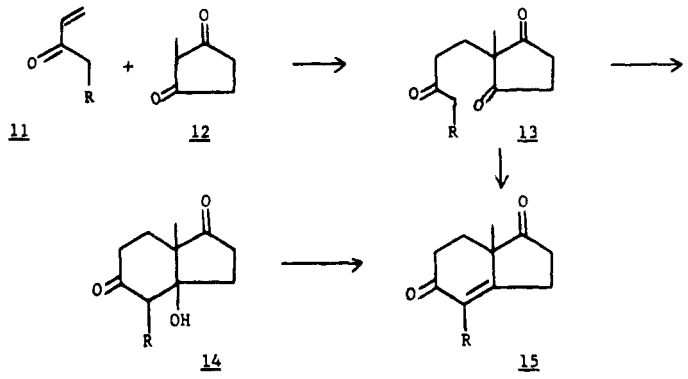
3. ESTRONE AND RELATED 19-NORSTEROIDS

A. Amino Acid Mediated Asymmetric Cyclizations

(a) Introduction

A major advance, of significance not only for steroid synthesis but also for organic synthesis in general,[3] is the finding that aldol type cyclizations of prochiral substrates can be catalyzed by chiral α-amino acids to yield chiral products of high optical purity. The discovery was made independently by groups at Schering A.G. (Berlin)[4] and Hoffman-LaRoche (Nutley, N.J.)[5] in the devel-

opment of routes to chiral hydrindenones as CD part structures in CD → ABCD approaches to 19-norsteroids. Some representative examples are shown here:



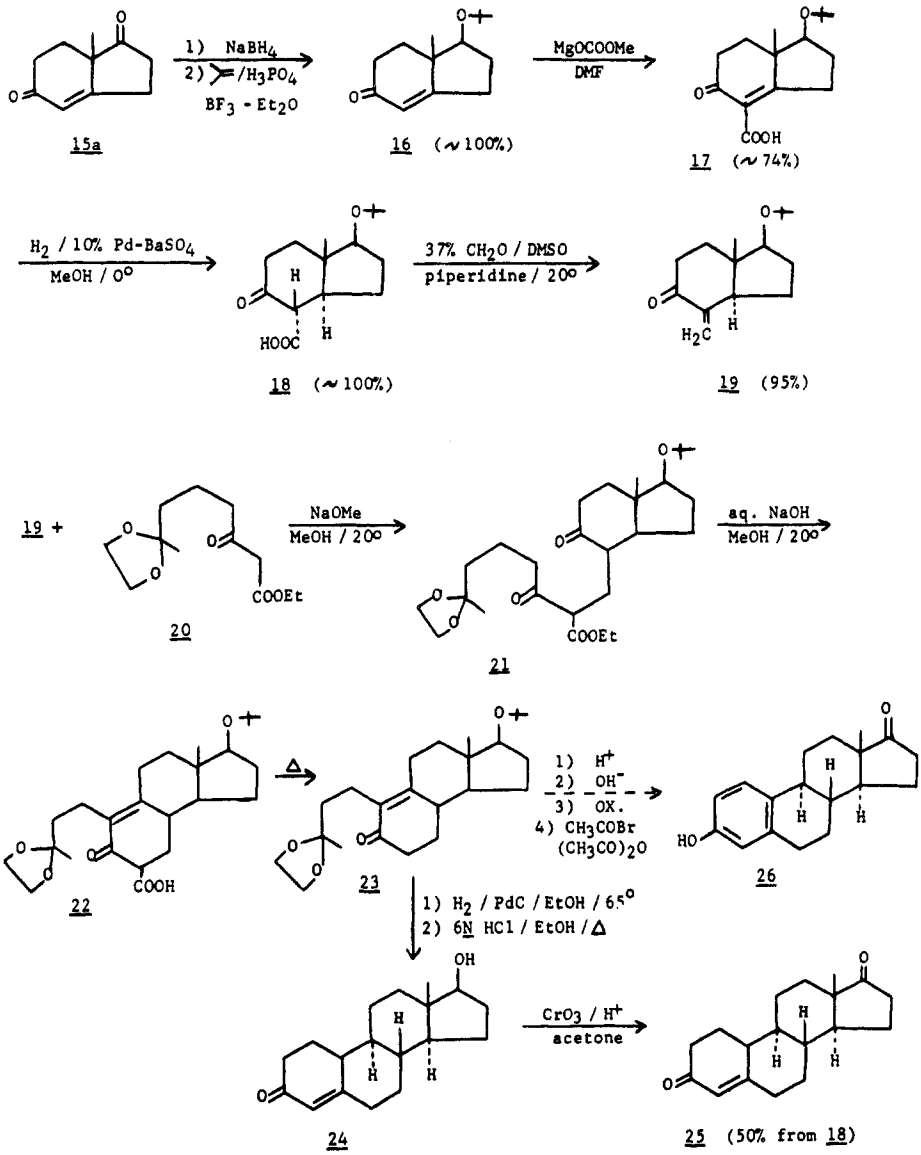
(a) R = H
(b) R = $CH_2CH_2COOCH_3$
(c) R = CH_2CH_2-C$_6$H$_4$-OCH_3

Yields in the Michael condensation for preparation of the triones **13** were improved by operating in aqueous media and omitting basic catalysis.[4,6] For example, trione **13a** was obtained in 88% yield by stirring a mixture of methyl vinyl ketone **11a** and 2-methylcyclopentane-1,3-dione **12** in water at 20° for 5 days.[6] This Michael condensation is considered to be self-catalyzed by the acidic 1,3-dione.[6]

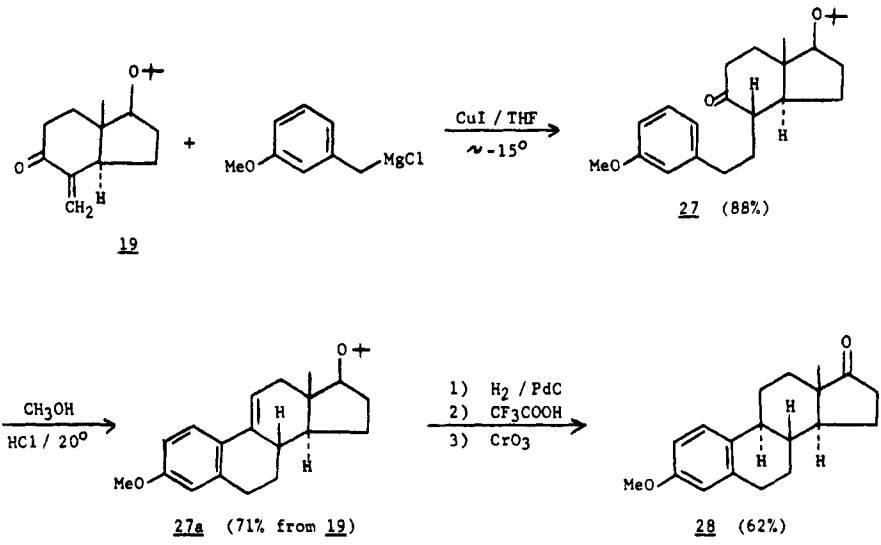
In the Schering route to **15a**,[4] trione **13a**, L-proline, and 1*N* perchloric acid (molar ratios 1:0.5:0.27) in refluxing acetonitrile for 22 hours afforded an 87% yield of (+) **15a** of 84% optical purity. Alternatively,[5,8a] **13a** in dimethyl formamide containing 0.05% water and 1% by weight of L-proline at 20° for 22.5 hours yielded ketol **14a**, which on treatment with *p*-toluenesulfonic acid in benzene gave (+) **15a** in 94% yield of 87% optical purity.

In the above examples, L-α-amino acids induce the natural 13β-chirality. Amines or amino acid derivatives (esters, amides) are much less effective, and a tertiary amino acid, hygrinic acid, was ineffective. For trione **13a**, secondary amino acids (e.g., proline) are best; for **13b** and **13c** [R > H, see also the Danishevsky (Scheme 8)[19] and Tsuji (Scheme 10)[22] syntheses below], a primary amino acid (e.g., L-phenylalanine) is preferred. The mechanism of the reaction has not yet been clarified.[5,7]

Applications of the chiral hydrindenone syntheses to industrially feasible routes to 19-norsteroids and their (of necessity) totally synthetic 18-ethyl counterparts (e.g., norgestrel) were then developed.


1) NaBH4
2) =/H3PO4
BF3 - Et2O
MgOCOOMe
DMF
H2 / 10% Pd-BaSO4
MeOH / 0°
37% CH2O / DMSO
piperidine / 20°
NaOMe
MeOH / 20°
aq. NaOH
MeOH / 20°
1) H+
2) OH-
3) OX.
4) CH3COBr
(CH3CO)2O
1) H2 / PdC / EtOH / 65°
2) 6N HCl / EtOH / Δ
CrO3 / H+
acetone
15a
16 (~100%)
17 (~74%)
18 (~100%)
19 (95%)
19 +
20
21
22
23
24
25 (50% from 18)
26

Scheme 3



19 27 (88%) 27a (71% from 19) 28 (62%)

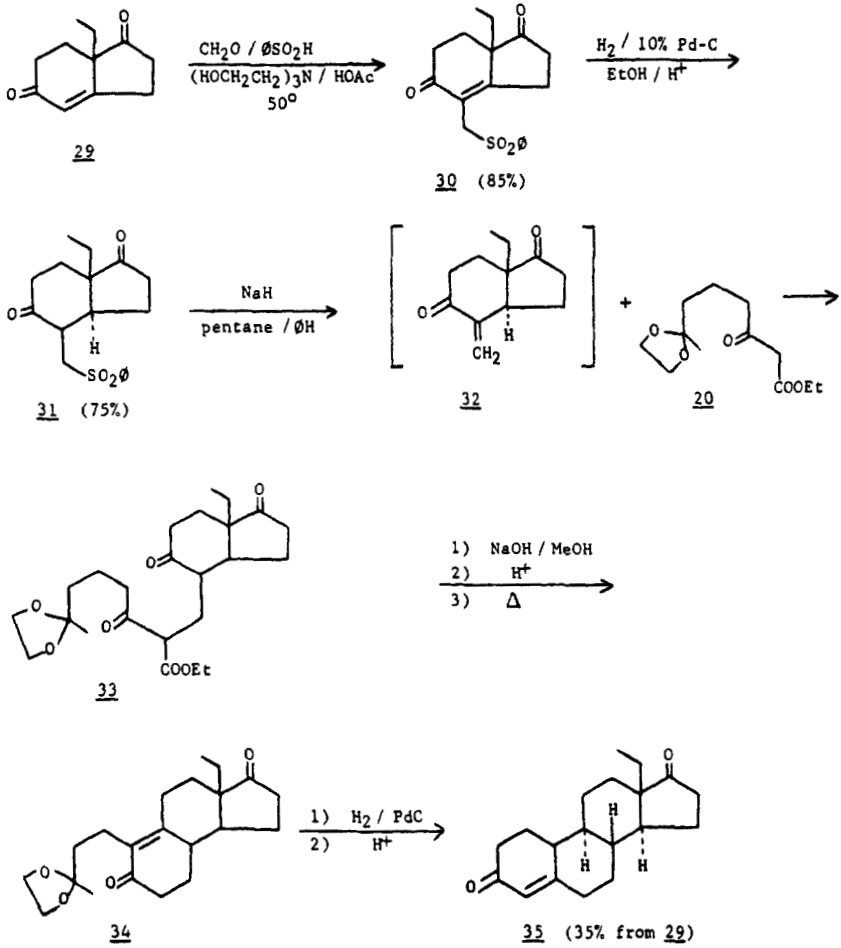
Scheme 4

(b) Hoffman-LaRoche Syntheses

At the outset of the Hoffman-LaRoche route[8] (Scheme 3), hydrindendione **15a** was converted into the corresponding 17β (steroid numbering) *t*-butyl ether **16**. Carbonation with magnesium methyl carbonate then yielded unsaturated acid **17**. The latter was the chosen intermediate because it was known that the direction of hydrogenation of the double bond in hydrindenones **15** is strongly dependent on the nature of the substituent R[9,10] and that carboxyl, ester, and methyl aryl sulfone[11a] functionality strongly favor reduction from the α-face to give the desired C/D *trans* stereochemistry. Furthermore, carboxyl was required as a removable activating group in the Mannich reaction step that followed reduction.

Hydrogenation was carried out at 0° to minimize decarboxylation of the saturated β-keto acid product **18**. Mannich reaction proceeded with *in situ* decarboxylation to afford α-methylene ketone **19**, which on Michael reaction with ketal β-keto ester **20**[8,11] yielded adduct **21**. Saponification, B ring closure, and decarboxylation then led to ketalenone **23** in high yield, which was converted into (+)-19-nortestosterone **24** and thence to (+)-19-norandrostenedione **25** in 50% yield from **18** or 27% overall yield from **12**. However, ketal hydrolysis, A ring closure, oxidation at C-17, and isomerization by the Roussel procedure (acetyl bromide–acetic anhydride in methylene chloride at 20°)[12] should yield (+)-estrone **26** efficiently.

Alternatively, Cohen et al.[13] (Scheme 4) reacted **19** with *m*-methoxybenzyl magnesium chloride in the presence of cuprous iodide to produce the 1,4-adduct

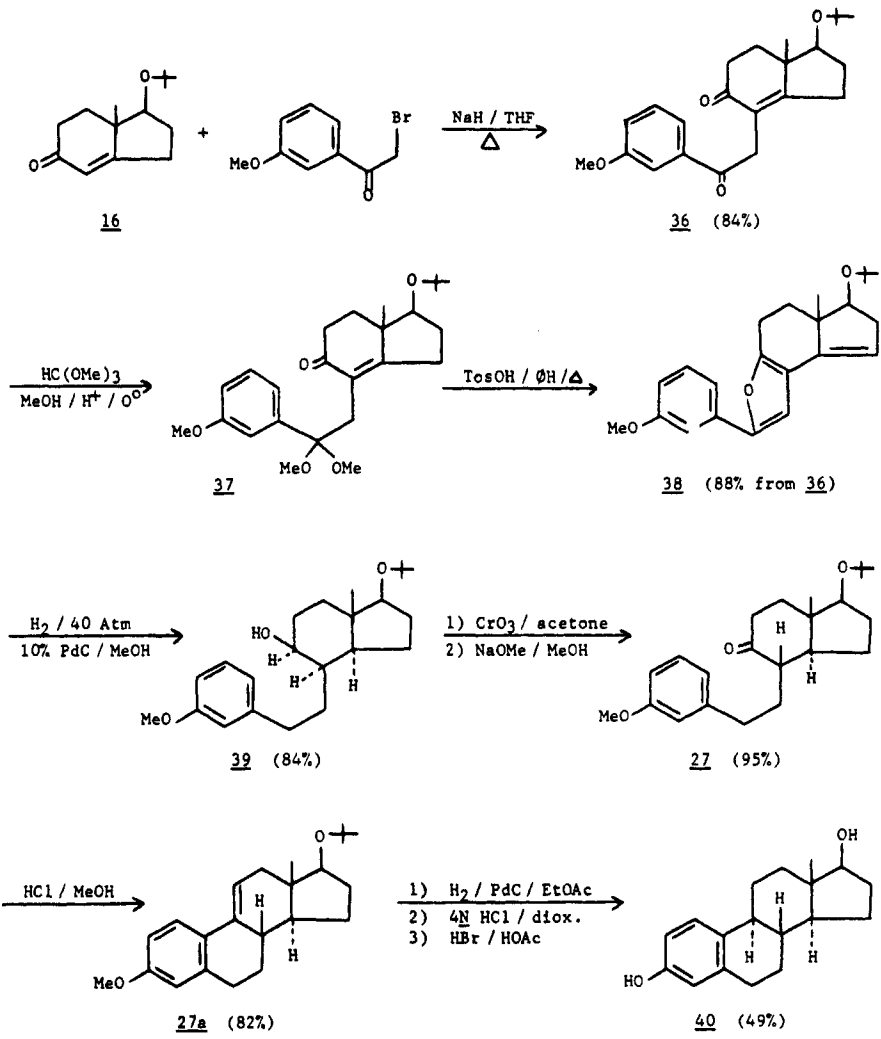


Scheme 5

27 in good yield. Acid catalyzed B ring closure, hydrogenation, and conversion to the 17-ketone then yielded (+)-estrone methyl ether **28**.

(c) Schering A.G. Syntheses

The Schering group described a route to (+)-13-β-ethylgon-4-ene-3,17-dione **35** (for conversion to norgestrel), which is clearly adaptable to estrone synthesis. The key step (Scheme 5)[11a] is a variant of the Mannich reaction involving sulfonylmethylation of **29** with formaldehyde and benzenesulfinic acid in 3:1 triethanolamine:acetic acid at 50° to yield unsaturated sulfone **30**. Hydrogenation of the latter in ethanol:1% 1*N* hydrochloric acid gave crystalline saturated sulfone



Scheme 6

31 in 75% yield, with hydrogenolysis of the allylic carbonyl group a minor side reaction. Condensation of **31** (via enedione **32**) with ketal β-keto ester **20** followed by saponification, β ring closure, and decarboxylation then gave tricyclic ketalenedione **34** (analogous to Hoffman-LaRoche intermediate **23**) and thence **35**.

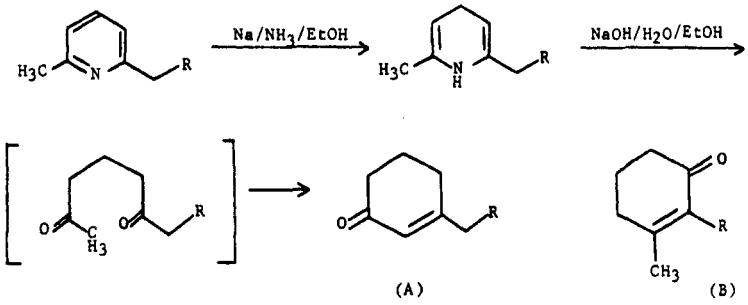
The Schering chemists also reported a synthesis of (+)-estradiol **40** based on direct alkylation of the anion of (+)-**16** with *m*-methoxyphenacyl bromide (Scheme 6).[14] The 84% yield obtained was considerably higher than that achieved

previously utilizing the less active *m*-methoxyphenethyl halide or tosylate as alkylating agent (Volume 2, pp. 712, 713). Direct acid-catalyzed formation of the indenofuran **38** was slow and occurred with some loss of the *t*-butyl group. However, prior conversion into the dimethyl acetal **37** permitted smooth furan formation under mild conditions. Hydrogenation of **38** under moderate pressure led in high yield to the 8a,14α-9β-hydroxy compound **39**, which on oxidation and side chain isomerization to the equatorial position afforded the 8β,14α-9-ketone **27**,[13] converted by standard procedures to **27a** and thence to (+)-estradiol **40**.

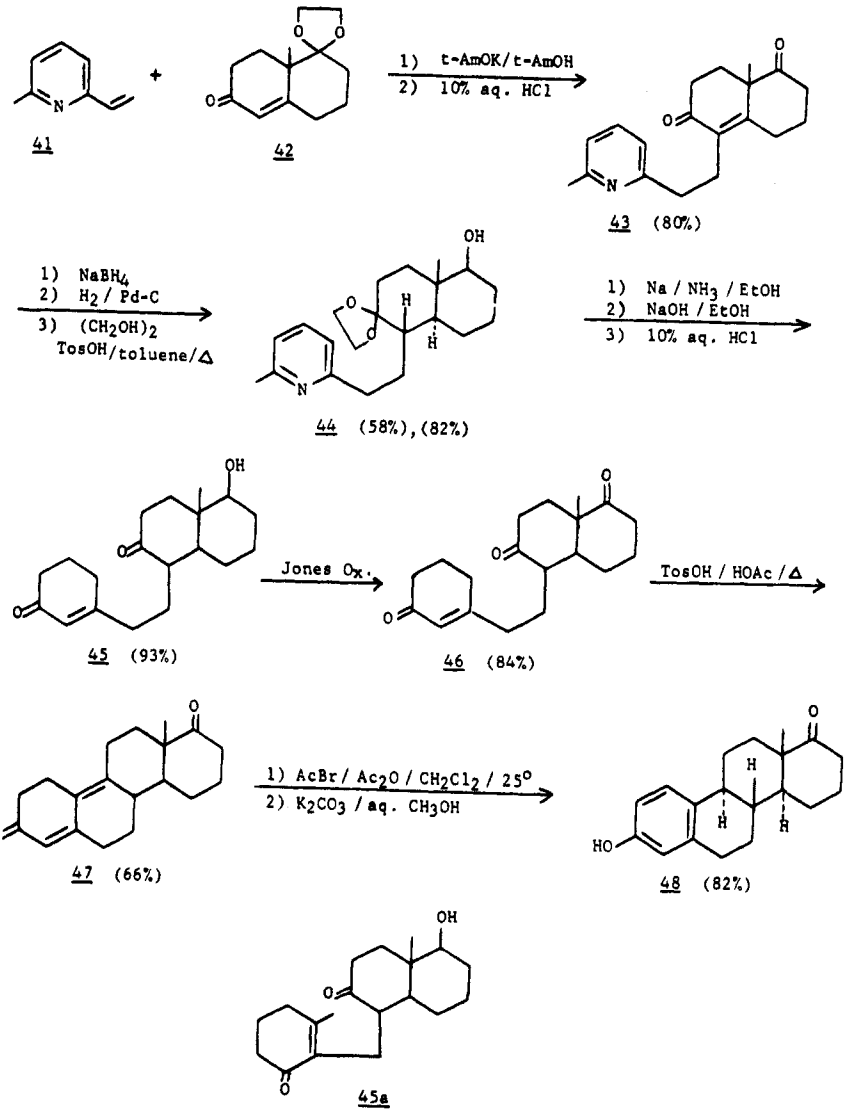
(d) Danishevsky Syntheses

Danishevsky and co-workers devised an ingenious synthesis of estrone (and other 19-nor-steroids) utilizing 6-substituted α-picolines as ring A synthons in a variant of the Robinson annulation process.[15] The synthesis was initially applied to (±)-D-homoestrone and an improved version was developed for (+)-estrone and related (+)-19-norandrostenones.

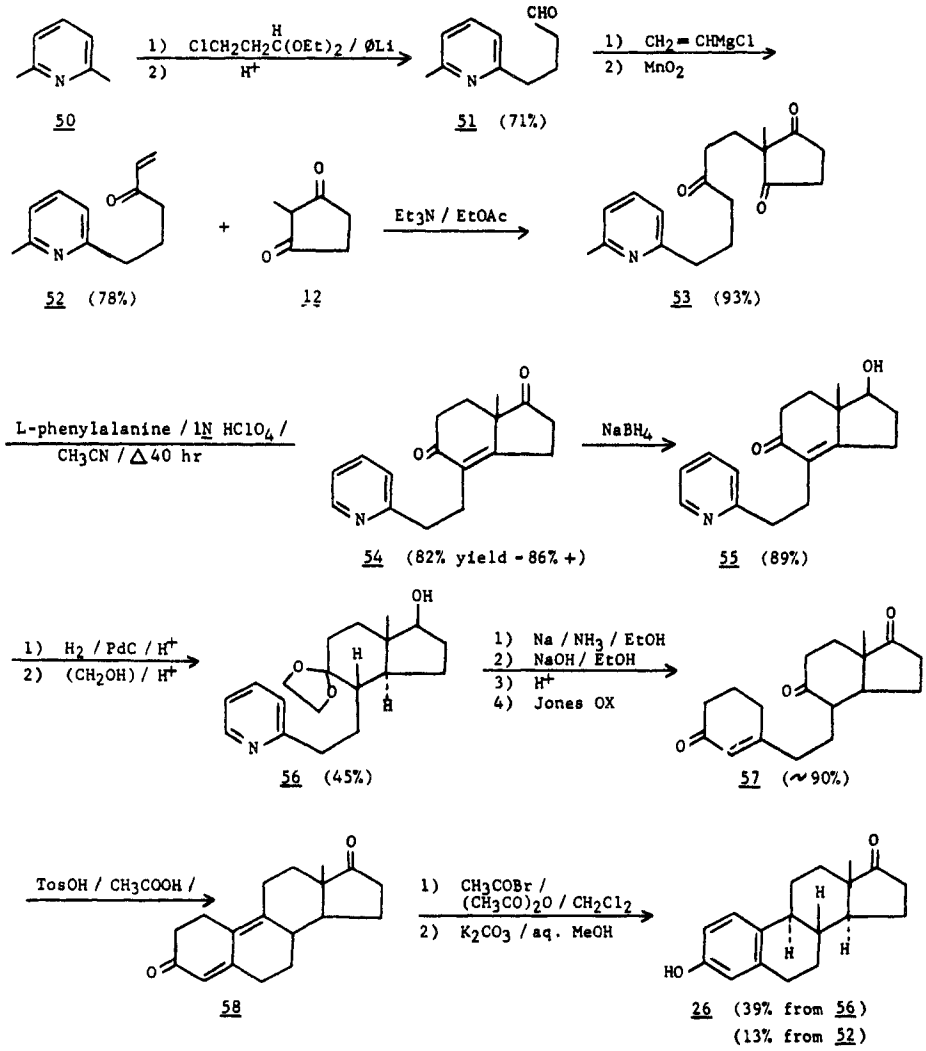
Model studies showed that Birch reduction of 6-substituted α-picolines and hydrolysis of the intermediate bisenamines yield 1,5-diketones, which can cyclize to enones A and/or B.[16] In fact, literature precedent[17] and experience with 1,4-diketones favored cyclization mode B (e.g., jasmone). However, the model studies showed substantial and in some cases predominant cyclization to A.



In the synthesis of (±)-D-homoestrone (Scheme 7),[18a,b] Michael addition of the monoketal **42** of the Wieland–Miescher enedione to 6-vinyl-2-methylpyridine **41** led to tricyclic adduct **43** in good yield. Reduction to the 17a-β-alcohol, double bond hydrogenation, and ketalization produced **44** with the requisite 8β,14α-stereochemistry in 58% yield. However, modification of the hydrogenation conditions from ethyl acetate-triethylamine to ethanol-perchloric acid raised the yield to 82%.[18c] Birch reduction, hydrolysis, cyclization, and ketal reversal


41
42
1) t-AmOK/t-AmOH
2) 10% aq. HCl
43 (80%)
1) NaBH4
2) H2 / Pd-C
3) (CH2OH)2
TosOH/toluene/Δ
44 (58%),(82%)
1) Na / NH3 / EtOH
2) NaOH / EtOH
3) 10% aq. HCl
45 (93%)
Jones Ox.
46 (84%)
TosOH / HOAc / Δ
47 (66%)
1) AcBr / Ac2O / CH2Cl2 / 25°
2) K2CO3 / aq. CH3OH
48 (82%)
45a

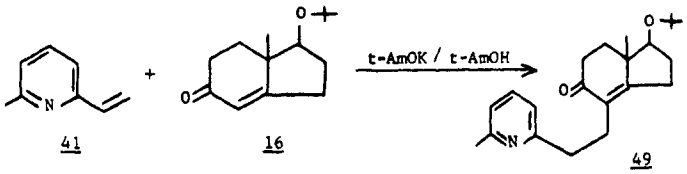
Scheme 7



Scheme 8

then led to a single enedionol **45** in 93% yield, converted to crystalline enetrione **46** and thence to (±)-D-homoestrone **48** in 21% overall yield from **42**. The absence of the alternative cyclization product **45a** anticipated from model studies may be rationalized on steric grounds.

In initial studies toward (+)-estrone, vinyl picoline **41** was condensed with hydrindenone **16** in analogy with the reaction of **41** with **42**. However, since



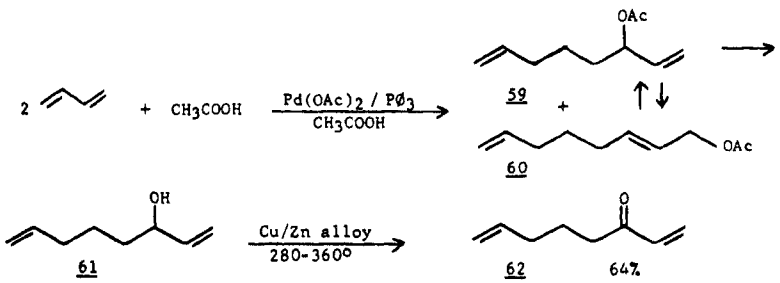
41 16 49

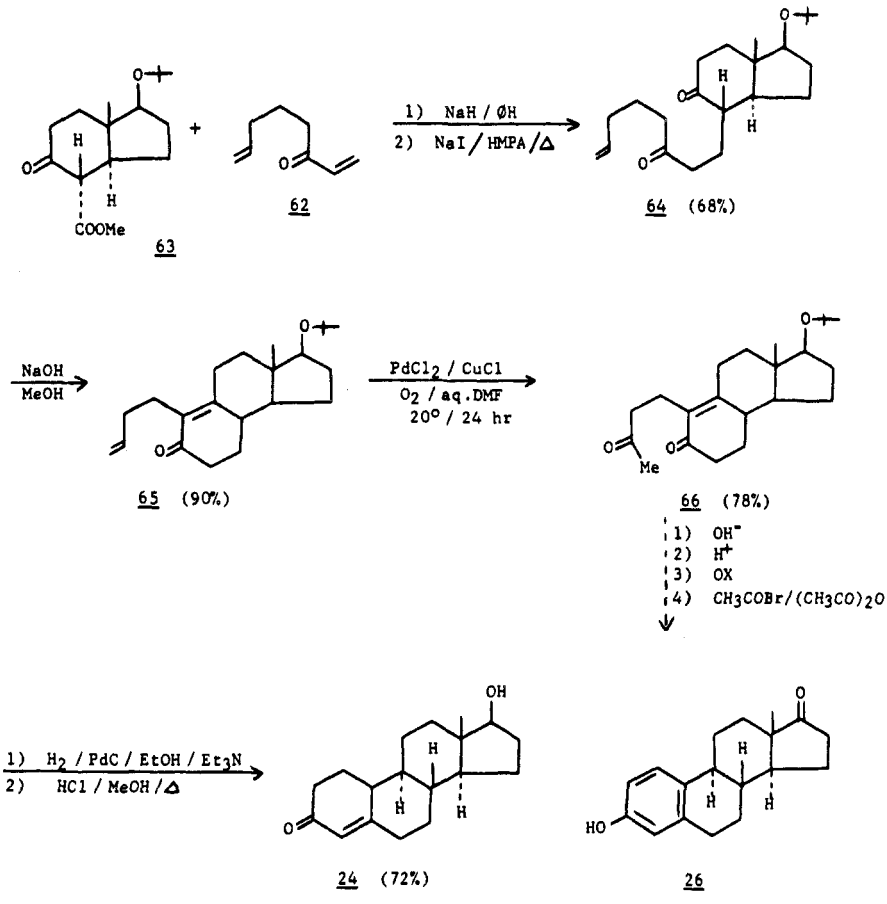
the yield in the present case was low, an alternative route was devised (Scheme 8).[19] 2,6,-Lutidine **50** was converted in 57% yield to the enone **52** (cf. **167**, Volume 2, p. 693), which readily added 2-methylcyclopentane-1,3-dione **12** to give the prochiral bicyclic trione **53** in high yield. Asymmetric cyclization of **53** in the presence of L-phenylalanine-1*N* perchloric acid (molar ratio 1:1.2:0.5) in refluxing acetonitrile by the Eder–Hajos technique[4,5] led to (+) **54** of 86% optical purity in 82% chemical yield. Selective borohydride reduction to **55**, followed by catalytic hydrogenation under acidic conditions, ketalization, and chromatography gave **56** in only 45% yield along with 17% of the C/D *cis* isomer and 21% of hydrogenolysis product (**55** C_9–H_2). The present hydrogenation difficulties are in sharp contrast with the clean high yield result in the analogous step in the D-homo series. Elaboration of the ring A enone occurred unidirectionally to give **57** in 90% yield. Closure of ring B and isomerization by the Roussel procedure[12] led to (+)-estrone **26** in 39% yield from **56** or 13% yield from **52**. The low yield in hydrogenation of the 8(14) double bond unfortunately negates the high yield of the asymmetric cyclization.

(e) Tsuji Syntheses

Tsuji and colleagues have synthesized 1,7-octadiene-3-one **62** from the readily available butadiene telomer **59**[20] and have explored the utility of **62** in natural product synthesis, including two routes to 19-norsteroids.[21,22]

Dimerization of butadiene catalyzed by palladium acetate-triphenylphosphine yielded a separable mixture of octadiene acetates **59** and **60** in high yield. Acetate





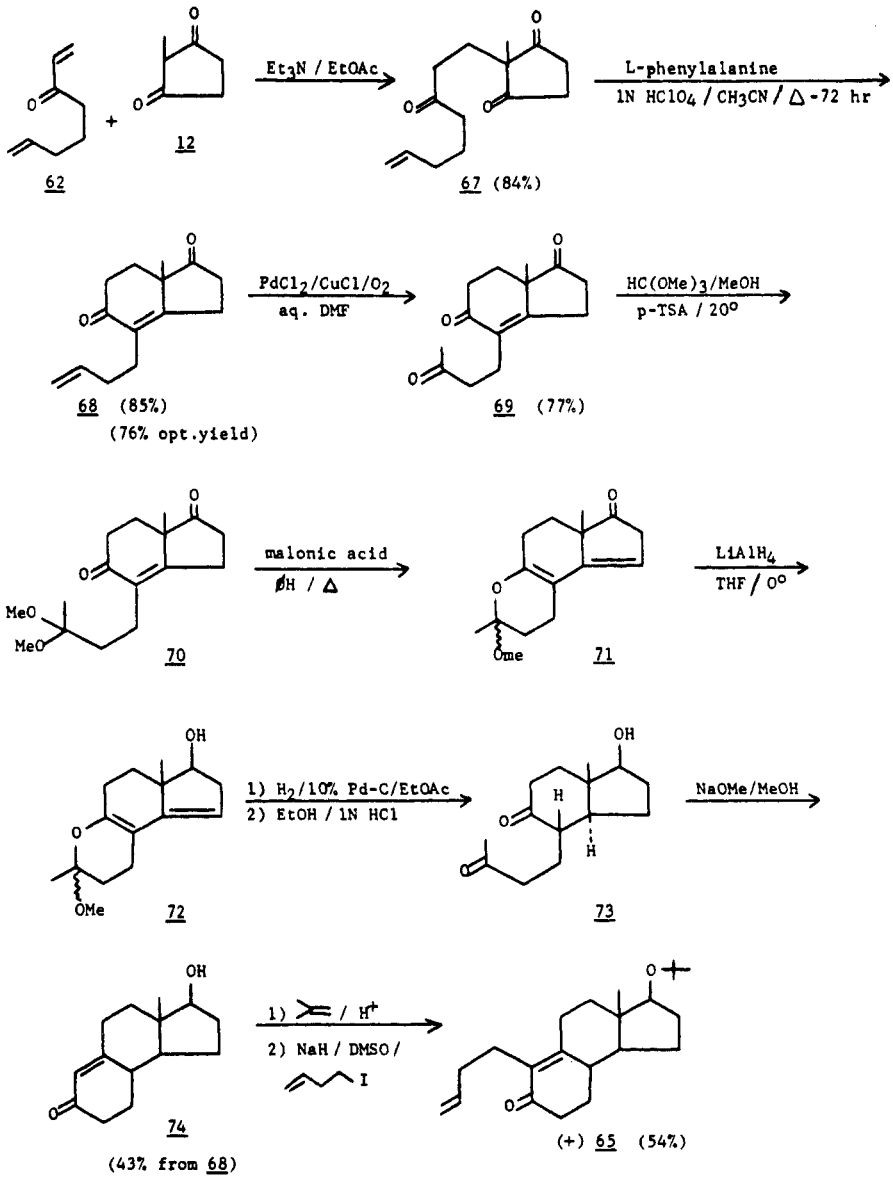
63 62 64 (68%) 65 (90%) 66 (78%) 24 (72%) 26

Scheme 9

60 could be rearranged to **59** by the palladium catalyst. Conversion of **59** to alcohol **61** and dehydrogenation over copper-zinc alloy in a packed column at 280-360° provided dienone **62** in good yield.[20,21,23]

The 1-ene-3-one part-structure in **62** can be utilized in Michael addition reactions and subsequently the remaining double bond can be oxidized to methyl ketone,[24] making **62** a bisannulation reagent synthetically equivalent to 7-octene-2,6-dione, as is Danishevsky's 6-vinyl-2-picoline (**41**, Scheme 7).

As shown in Scheme 9,[21] (+)-β-keto ester **63** [available by diazomethane treatment of **18** (Scheme 3)][8b] on Michael reaction with **62**, followed by decarbomethoxylation, yielded enedione **64**. Aldol cyclization to **65** and palladium chloride–cuprous chloride catalyzed oxidation of the terminal double bond then gave tricyclic enedione **66**. The latter was converted into (+)-19-nortestosterone


Et3N / EtOAc
L-phenylalanine
1N HClO4 / CH3CN / Δ -72 hr
PdCl2/CuCl/O2
aq. DMF
HC(OMe)3/MeOH
p-TSA / 20°
malonic acid
ØH / Δ
LiAlH4
THF / 0°
1) H2/10% Pd-C/EtOAc
2) EtOH / 1N HCl
NaOMe/MeOH
1) ⟩= / H+
2) NaH / DMSO /
62
12
67 (84%)
68 (85%)
(76% opt.yield)
69 (77%)
70
71
72
73
74
(43% from 68)
(+) 65 (54%)

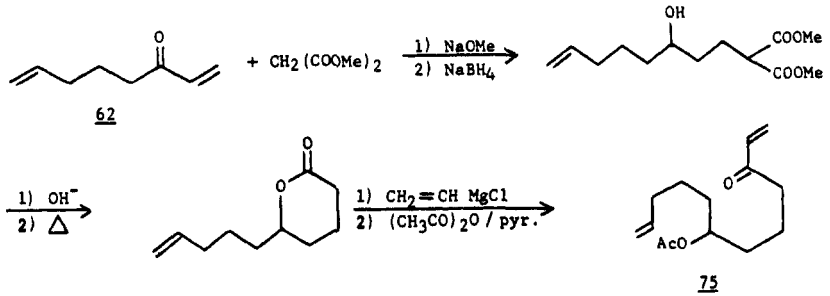
Scheme 10

24 but should also be convertible into (+)-estrone **26** as indicated earlier (cf. Scheme 3, **23** → **26**; Scheme 8, **58** → **26**).

In the route just described (CD → ABCD), the bisannulation reagent **62** is the source of rings A and B. In an alternative, somewhat more involved, approach[22] (D → BCD → ABCD; Scheme 10), reagent **62** is the source of rings B and C.

Michael reaction of **62** and 2-methylcyclopentane-1,3-dione led to adduct **67** in good yield. Asymmetric aldol cyclization with concomitant dehydration was accomplished using L-phenylalanine-1*N*-perchloric acid (molar ratio 1:1:0.4) in refluxing acetonitrile to produce (+)-**68** of 76% optical purity in 85% yield.[4,5,19] Palladium chloride catalyzed terminal olefin oxidation[24] then yielded enetrione **69**. The latter compound has been prepared by Eder et al.,[25] who developed an effective method for its α-face hydrogenation via the 17β-hydroxydiene system **72** (cf. Scheme 6) which in turn was obtained in good yield via intermediates **70** and **71**. Hydrogenation of the Δ^{14} double bond of **72** proceeded completely in the desired α sense, and the product was hydrolyzed to hydroxydione **73**. Base catalyzed aldol cyclization then provided the tricyclic enone **74**. Conversion of the 17β-hydroxy group to the t-butyl ether and base catalyzed addition of 3-butenyl iodide produced the butenylated ketone (+) **65** in 54% conversion yield. The latter had been produced by the earlier route (Scheme 9) and converted into (+)-19-nortestosterone **24**.

Tsuji has also prepared the trisannulation reagent **75** from dienone **62** as indicated and utilized it in a synthesis of (±)-D-homoandrost-4-ene-3,17a-dione.[26]



B. Orthoquinodimethane Approach

(a) Introduction

Thermolysis of benzocyclobutenes and trapping of the intermediate orthoquinodimethanes with external dienophiles was described some time ago by Cava[27] and by Jensen and Coleman.[28] The intramolecular version of this reaction was