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STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF
PENTACYCLIC TRITERPENES.

by

MICHEL GIRARD, B.Sc.(UQAC), M.Sc.(Carleton).

A thesis submitted to the Faculty of
Graduate Studies in partial fulfilment
of the requirements for the degree of
DOCTOR OF PHILOSOPHY.

Ottawa-Carleton Chemistry Institute

Departement of Chemistry

Carleton University

September 1985

c. Michel Girard

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PENTACYCLIC TRITERPENES".

submitted by Michel Girard in partial-fulfilment of
the requirements for the degree of Doctor of
Philosophy.

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à la mémoire de ma mère,

Germaine.

Two approaches to the synthesis of the pentacyclic triterpene friedelin (5) have been investigated. In the first approach, the preparation of (+)-1-(3-benzyloxybutyl)-5 β -hydroxy-4 α β -methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (118), corresponding to the CD ring system, in 30% ee is reported. The use of the recently reported trimethylsilylcyanation of conjugated enones proved highly stereoselective, and thus an efficient alternative to the Nagata's hydrocyanation for the introduction of the second axially oriented substituent at the C/D ring junction. Base catalyzed intramolecular aldol condensation of triketone 138 led to the formation of 1,7-dioxo-10 α β -methyl-perhydropheanthrene-4 α α -8 α α -carbolactam (142) by an unprecedented rearrangement. Confirmation of the structure came from an X-Ray diffraction analysis. The acid catalyzed counterpart led to the expected tricyclic enone 103. Studies of the reactivity and the functionalization of this intermediate are described and have led to successful routes for the preparation of intermediates in which potential precursors of rings A and B have been introduced. Attempts at trapping kinetically generated enolate of bicyclic β -cyanosilylenol ether 178 with α -silyl vinyl ketone are presented. In the second approach, the use of three successive Robinson annulation reactions to generate the tetracyclic intermediate 187, corresponding to the ABCD ring system, has been investigated.

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TABLE OF CONTENTS

ABSTRACT.....	iv
ACKNOWLEDGEMENTS.....	v
TABLE OF CONTENTS.....	vi
LIST OF FIGURE.....	vii
LIST OF TABLES.....	viii
LIST OF ABBREVIATIONS.....	ix
INTRODUCTION.....	1
Classification.....	5
Biosynthesis of pentacyclic triterpenes.....	6
Total synthesis of pentacyclic triterpenes.....	15
1. Germanicol.....	16
2. Alnusenone.....	22
3. Friedelin.....	30
Notable approaches to pentacyclic triterpenes synthesis.....	36
RESULTS AND DISCUSSION.....	51
PART I. A chiral approach to the synthesis of friedelin (5) via a CDE+A→ABCDE ring assemblage.....	55
A. Synthetic Strategy.....	55
B. Preparation of chiral synthon <u>102</u>	59
C. Attempted reduction of the cyano group in cyano-ketone <u>102</u>	91
D. Preparation of tricyclic enedione <u>103</u>	94
E. Introduction of ring A fragments.....	112
F. Attempted preparation of tricyclic substrates via direct alkylation of β -cyanosilylenolether.....	129
PART II. An approach to the synthesis of friedelin (5) via a ABC+E→ABCDE ring assemblage.....	142
A. Synthetic Strategy.....	142
B. Preparation of tricyclic enone <u>188</u> and bis-annulating reagent <u>194</u>	147
CONCLUSION.....	151
EXPERIMENTAL.....	157
REFERENCES.....	206
APPENDICES.....	214
FLOW CHARTS.....	232

LIST OF FIGURES

1. Structural representation of some natural triterpenoids...3
2. Structural similarities in pentacyclic triterpenes.....56
3. Resolved C*₁₄-CH₃ signal of hydroxy-enone 118
in the presence of 0.95M equivalents of CSR.....73
4. Comparative ¹³C-NMR spectra for compounds 134 and 135...87
5. Perspective view of lactam 142 from X-Ray data.....100
6. Bond lengths in 142 as determined by X-Ray.....101
7. Bond angles in 142 as determined by X-Ray.....102

LIST OF TABLES

1. Representative occurrences of triterpenoids in nature.....2

2. Shift differences for the $C^*_{14}-CH_3$ signals.....72

LIST OF ABBREVIATIONS

Ac	acetyl
acet.	acetone
Bn	benzyl
t-Bu	t-butyl
n-Bu	n-butyl
m-CPBA	m-chloroperbenzoic acid
CSR	chiral shift reagent
DHP	dihdropyran
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
EG	ethyleneglycol
elem. Anal.	elemental analysis
Et	ethyl
g	gram
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
IR	infrared
kg	kilogram
L	litre
LAH	lithium aluminum hydride
LDA	lithium N,N-diisopropyl amide
LHMDS	lithium N,N-bis(trimethylsilyl) amide
Me	methyl
mMOL	millimole
Mol	mole
mL	millilitre
M.S.	mass spectrum
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PPA	polyphosphoric acid
ppm	parts per million
pyr.	pyridine
TBDMS	t-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCN	trimethylsilylcyanide
Tol.	toluene
Ts	tosyl
UV	ultraviolet
xyl.	xylene

INTRODUCTION

The triterpenoids form a large class of the naturally occurring compounds, only equalled in number and structural diversity by the sesquiterpenes. Their 30 carbon atoms originate from the union of six isoprene units for which the arrangement follows the "biogenetic isoprene rule" (1). (A more detailed inspection of the biogenesis of triterpenoids will be presented in a following section.) The occurrence of triterpenoids in nature is ubiquitous as being found in both vegetable and animal species (TABLE I) (1). In plants, from which the vast majority of triterpenes have been isolated, they are found as constituents of the sap and in resins. Two of the best known triterpenes that can be isolated from animals are the acyclic squalene (2), first obtained from shark ("squal") liver oil and lanosterol (3) which is now widely recognized as the biogenetic precursor of sterols in many animal species.

Although structural studies of triterpenoids can be traced back to the end of the last century, it is with the advent of modern sophisticated spectroscopic methods of analysis developed over the last three decades (^1H - and ^{13}C -NMR, X-Ray crystallography, Mass Spectrometry) that

TABLE I

REPRESENTATIVE OCCURENCES OF TRITERPENOIDS IN NATURE^{*}

<u>TRITERPENOID</u>	<u>SOURCE</u> ¹
Malabaricol (<u>1</u>)	plant <u>Ailanthus malabarica</u>
Squalene (<u>2</u>)	shark liver oil
Lanosterol (<u>3</u>)	wool fat, marine invertebrates
Oleanic acid (<u>4</u>)	olive leaves
Friedelin (<u>5</u>)	corb

* The corresponding structures are presented on page 3 .

FIGURE 1

3

STRUCTURAL REPRESENTATION OF SOME NATURAL TRITERPENOIDs.

1

2

3

4

5

definite structures were deduced for many of the earlier described triterpenoids (2). The vast amount of spectroscopic data accumulated over the years now allows the structural identification of most new compounds without the tedious, and sometimes questionable, necessity to derivatize or chemically modify the substance. This is particularly valuable in the case of the labile triterpene-glycosides, some of which have been shown to undergo structural modifications upon hydrolysis of the glycosidic moiety (3).

Similarly the development of powerful separation and purification techniques (HPLC for the most part) has permitted a solution of the problem of homogeneity that interfered in earlier studies (4).

Despite this considerable technological progress one aspect of the triterpenoids that is still unresolved is the one associated with their existence, that is, their biological significance and role. As for most of the secondary metabolites isolated from living organisms, these aspects are still obscure for the vast majority of the triterpenoids (5).

CLASSIFICATION

The triterpenoids are generally subdivided into three main groups based on the skeletal frame work produced at precise stages of the biosynthetic pathways. They are:

- (1) the acyclic, for which squalene (2) is an example;
- (2) the tetracyclic, i.e. lanosterol (3);
- (3) the pentacyclic, i.e. friedelin (5).

The polycyclic species (groups 2 and 3) form the bulk of the more than 750 examples of triterpenoids reported in the first compendium published in 1972 (1b). The acyclic group is limited to only a few examples. Each of the tetracyclic and pentacyclic groups can be further subdivided into basic skeletons which differ in the structure and location of side chains as well as in the stereochemically diverse array of methyl groups appearing on the skeleton. No less than 30 different examples of common basic skeletons have been identified as well as an equal number of less commonly observed ones (1b).

In the remainder of this work we shall focus the attention on the chemistry related to the last group, the pentacyclic triterpenes, and more specifically to the

molecule friedelin (5). First, a brief inspection of the biosynthesis of this group will be presented.

BIOSYNTHESIS OF PENTACYCLIC TRITERPENES

It was mainly through the work of Ruzicka and his collaborators, (Eschenmoser, Arigoni and Jeger) in Switzerland on the structural elucidation of triterpenes that emerged the first rationalization of the biosynthesis of this class of compounds, and at the same time the development of the basic concept of terpenoid biosynthesis known as the "biogenetic isoprene rule" (7).

In fact a common biogenetic precursor had been suspected for a long time for those compounds whose empirical formulae were multiples of five carbon atoms and that could be dislocated, at least on paper, into isopentane skeletal units linked in a regular head-to-tail fashion. This working hypothesis was known as the "isoprene rule" also referred to as "the empirical isoprene rule" (7a). With great insight, Ruzicka et al. (7) proposed however that the carbon skeleton of the product is not necessarily identical to the one of the precursor, that is, the failure of a terpene to obey the "empirical isoprene rule" of

regular head-to-tail arrangement of isoprene units does not immediately disprove its origin from isoprene units. Thus they proposed that all triterpenes might arise from the same acyclic precursor, squalene (2), by a series of concerted cyclizations, and that subsequent transformations to the carbon skeleton, that is, Wagner-Meerwein-type rearrangement of methyl groups and 1,2-eliminations, could follow.

This first hypothesis was later refined (7b, 8) on the basis of stereochemical concepts related to the stereoelectronic control of electrophilic additions on olefins. The following rules for the cyclization of squalene in vivo were proposed:

- (i) the cyclization of squalene takes place in the all-trans configuration and in a well-defined sequence of chair-like or boat-like conformations.
- (ii) cyclizations occur by a series of trans- and coplanar additions on double bonds. Subsequent Wagner-Meerwein rearrangements, as well as, 1,2 eliminations arise when stereoelectronic requirements for these reactions are optimum, that is, whenever the groups are trans-and-periplanar.
- (iii) all transformations between squalene and the final product are concerted, that is, no stable intermediate produced by the loss of a proton or by addition of a nucleophile, (to neutralize the carbonium ion) will be formed.

Much experimental support for this theoretical model has been accumulated over the years (6). Thus, the natural squalene is invariably isolated in its all-trans form (9a). Tchen and Bloch (9b) demonstrated the relationship between squalene (2) and lanosterol (3) by using a synthetic ^{14}C -labelled squalene in incorporation experiments. On the other hand, when the unlabelled squalene was used in deuterated water as the medium, no incorporation of deuterium was observed, hence supporting the hypothesis of a concerted reaction pathway (rule iii).

Squalene (2) and squalene-2,3-epoxide (6), the latter formed by oxidation of the terminal olefin of squalene (10), are now widely accepted as the immediate precursors in the biosynthesis of all pentacyclic triterpenes. Moreover, the proposed concerted nature of the cyclization process requires that the (3S)-isomer of 6 be the direct precursor of the 3-oxygenated triterpenoids. This was recently confirmed by the preparation of both stereoisomers (the (3S)- and (3R)- 6) and their use in enzymatic cyclization studies (11).

Schemes I-V present the various modes of cyclization of squalene (or squalene epoxide) that can be derived to

SCHEME II

SCHEME III

11

SCHEME IV

12

SCHEME V

13

account for the various basic skeletons of pentacyclic triterpenes. Unlike the tetracyclic triterpenes, the polycyclic system of pentacyclic ones is not always obtained by a continuous series of cyclizations. Thus after adopting a suitable spatial arrangement, for which the enzyme of the system is believed to be responsible, the cyclization process is in many cases interrupted by a skeleton rearrangement, through the intermediacy of non-classical carbonium ions like 7 and 9 (Scheme I).

The many stereochemical variations among each class is best explained by 1,2-migration of methyl groups and hydrogen atoms and carbocation stabilization by the loss of protons. Friedelin (5) certainly represents the most complex case of all; the overall series of events can be visualized in structure 10.

10

TOTAL SYNTHESIS OF PENTACYCLIC TRITERPENES

The total synthesis of pentacyclic triterpenes has been the subject of many research efforts over the last two decades. At the outset, it is possible to distinguish two general principles that have guided these efforts. The first one concerns both the method and the sequence for the construction of the polycyclic system. The strategies involved here can be related to the methodology that has been developed in the field of total synthesis of steroids in the 1950's and 1960's (12-14). They are based on the choice of starting synthons that already incorporate one or more of the cycles present in the target molecule.

The second principle is more recent, both in concept and methodology, and involves the stereochemical control associated with the formation of an asymmetric centre. The application of this concept to the synthesis of pentacyclic triterpenes has permitted the difficult problem of the separation of isomers to be circumvented. This was not possible in the earliest synthetic efforts.

In the following we will present a brief account of those synthetic efforts that have incorporated these two

general principles, in relation with the preparation of pentacyclic triterpenes possessing the perhydropicene cyclic system (11).

The pioneering efforts in the total synthesis of pentacyclic triterpenes, as well as the more recent research work, have been ably reviewed by ApSimon and Hooper (15) and ApSimon, Greaves and Fyfe (16).

1. Germanicol (12)

The total synthesis of germanicol (12) has been reported by Ireland et al. (17) by an approach of the type $ABC + E \longrightarrow ABCE \longrightarrow ABCDE$ (Scheme VI). The initial tricyclic synthon 13, corresponding to the ABC ring system, was prepared by 2 successive Robinson annelations with

ethyl vinyl ketone, starting from the commercially available 2-methyl-1,3-cyclohexadione. The reductive alkylation sequence, developed by Stork (18), was then applied to provide the gem-dimethyls at C_4 as required in the final product. The ketone 14 thus obtained could be efficiently converted to the keto-acetate 15 by successive hydride reduction, acetylation of the C_3 -hydroxyl function, hydrolysis of the ketal and stereospecific hydrogenation of this olefin from the less hindered α face. This keto-acetate 15 was the starting point of two pathways to obtain the diketone 16, differing for the most part in the stage at which the oxidation at C_{13} occurred.

SCHEME VI

18

12

- ^a $\text{C}_2\text{H}_5\text{COCH}=\text{CH}_2, \text{NaOMe}, \text{MeOH}$; ^b $(\text{CH}_2\text{OH})_2, \text{H}^+$; ^c $\text{Li}/\text{NH}_3, \text{T-BuOH}, \text{MeI}$;
^d $\text{LiAl}(\text{O}-\text{T-Bu})_3\text{H}$; ^e H_3O^+ ; ^f $\text{Ac}_2\text{O}, \text{PYR.}$; ^g $\text{Pd-C}, \text{AcOH}$; ^h Br_2, AcOH ;
ⁱ $\text{OH}^-, \text{Me}_2\text{SO}_4$; ^j $\text{NACH}_2\text{SO}^+\text{Me}_2, \text{Ac}_2\text{O}, \text{PYR.}$; $\text{BF}_3 \cdot \text{Et}_2\text{O}$; $\text{NAH}, \text{DMSO}, \text{MeI}$;
^k $\text{PH}_3\text{P}=\text{CH}_2$; ^l $\text{R}_2\text{BH}, \text{H}_2\text{O}_2, \text{OH}^-$; ^m $\text{CrO}_3 \cdot 2\text{PYR.}$; ⁿ $\text{M-MEOC}_6\text{H}_4\text{MgBr}, \text{H}_2$;
 $\text{Pd-C}, \text{H}_3\text{O}^+$; ^p PPA ; ^q MeLi, DME ; $8\text{N H}_2\text{CrO}_4, \text{ACET.}$; $\text{SOCl}_2, \text{PYR.}$; TsOH ;
 $\text{C}_6\text{H}_6, (\text{CH}_2\text{OH})_2$; ^r O_2 , SENS., PYR. , LAH ; ^s $\text{M-MEOC}_6\text{H}_4\text{CH}_2\text{MgCl}, \text{Ac}_2\text{O}$;
^t $\text{MeLi}, \text{DME}, \text{MeI}$; ^u $\text{Li}/\text{NH}_3, \text{ALC.}$; ^v $\text{Et}_3\text{Al}, \text{HCN}, \text{THF}$; ^w $\text{N}_2\text{H}_4, \text{OH}^-, \text{TEG}$;
^x $\text{CaCO}_3, \text{DMA}$; ^y $\text{KOT-Bu}, \text{T-BuOH}, \text{MeI}$; ^z $(\text{i-Bu})_2\text{AlH}, \text{C}_6\text{H}_6$.

In the less efficient pathway, the diosphenol ether 17 was obtained by bromination of 15 and treatment of the dibromide with alkaline methyl sulfate, followed by reacetylation at C₃. The critical step of introducing the axial methyl group at C₁₄ proved to be difficult to achieve due to the highly congested nature of the intermediate aldehyde 18 that was prepared from 17 in three steps via a spiro-epoxide homologation. Nevertheless, 19 was produced as the sole product in about 50% yield. Aldehyde 19 was then converted in five steps to the lactone 20, for which the stereochemical identity was established by comparison with a degradation product of the tetracyclic triterpene euphol. The preparation of the diketone 16, which contains all of the carbon atoms of the pentacyclic system (with the exclusion of the gem-dimethyls at C₂₀) was subsequently accomplished in six steps.

In the more efficient pathway, keto-acetate 15 was converted to the olefin 21 in 4 steps by successive addition of methyl lithium to the ketone, oxidation of the deprotected C₃-alcohol, elimination of water and ketalization of the ketone at C₃. The preparation of diketone 16 from 21 was readily accomplished via the formation of the exocyclic α, β -unsaturated ketone 22 to which a 1,4-addition of the

Grignard reagent of p-methoxy benzyl chloride allowed for the facile introduction of the E cycle; the stereoselective introduction of the C₁₄-methyl group from the α face seemed to present no particular problems when this reaction was realized by cleavage of the enol acetate to the lithium enolate and trapping with methyl iodide. By this last route, the diketone 16 was prepared in an overall yield of 25% from 15.

At that stage of the synthesis, 6 of the 8 asymmetric centres had been stereoselectively elaborated. The remaining 2 non-contiguous asymmetric centres (at C₁₃ and C₁₇) were generated in the following way: polyphosphoric acid cyclization of 16 led to the pentacyclic intermediate 23 which can be reduced by lithium/ammonia in the presence of an alcohol to give the α, β -unsaturated ketone 24 with the required C₁₃- β H; the last, angularly situated methyl group at C₁₇ was introduced in a highly stereoselective fashion by the use of the kinetically controlled Nagata's hydrocyanation procedure (19) and conversion of the cyano to a methyl group by hydride reduction, followed by a modified Wolf-Kischner reduction of the intermediate aldimine. Thus hydroxy-ketone 25, possessing all of the 8 chiral centres in the proper configuration, was converted to germanicol (12) in

four steps that included the introduction of gem-dimethyl groups at C₂₀ and reduction of the ketone to the hydrocarbon.

2. Alnusenone (26)

Preliminary studies on the preparation of alnusenone (26)-type pentacyclic triterpenes by Ireland et al. (20-22) culminated in the report of the total synthesis of (dl)-alnusenone (26) in 1973 (23). In this highly convergent and stereoselective synthesis, the diether 27, containing the trans-anti-trans arrangement of BCD rings, was sought as the key intermediate with the anticipation that differentiation of the two aromatic A and E rings could be effected before their reduction to saturated systems. The general approach to the synthesis was of the type $DE + A \rightarrow ACDE \rightarrow ABCDE$ and is illustrated in Scheme VII.

An initial Robinson annelation of the tetralone 29 and the Michael acceptor 28 gave the tricyclic ketone 30, which contains all of the carbon atoms that are necessary to form the pentacyclic skeleton. This intermediate is particularly well suited for the introduction of the second angular methyl group at the C/D ring junction at an early stage of the synthesis. Thus, using the kinetically controlled Nagata's hydrocyanation conditions, as previously applied in the preparation of germanicol (12), (see preceding section), they obtained the cyano-ketone 31, with a trans-fused C/D ring junction, in high chemical and stereochemical yield. Prior to the reduction of the cyano to a methyl group, addition of methyl magnesium iodide, followed by elimination of water was achieved for the twofold purpose of protection of the functionality and introduction of the potential angular methyl group. The resulting olefin 32 was then readily converted to the pentacyclic diether 27 by way of an

^a Aq. KOH, MeOH; ^b Et_3Al , HCN, THF; ^c MeMgI ; ^d SOCl_2 , PYR.; ^e $(i\text{-Bu})_2\text{AlH}$, C_6H_6 ; ^f $\text{N}_2\text{H}_4 \cdot 2\text{HCl}$, $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$, TEG, KOH; ^g $p\text{-TsOH}$, C_6H_6 ; ^h LiPPh_2 , THF; ⁱ Li/NH_3 , GLYME, MeI; ^j $\text{Li}(\text{O } t\text{-Bu})_3\text{H}$, THF- C_6H_6 ; ^k CH_2I_2 , $\text{Zn}(\text{Cu})$, DME; ^l $\text{CrO}_3 \cdot 2\text{PYR.}$; ^m $\text{KO } t\text{-Bu}$, THF, MeI; ⁿ Li/NH_3 , THF; ^o LAH, THF- Et_2O ; ^p $n\text{-BuLi}$, DME; ^q $\text{HMPA-Et}_3\text{N}$, $\text{ClPO}(\text{NMe}_2)_2$; ^r Li/NH_3 , THF- EtOH ; ^s H_3O^+ ; ^t $\text{KO } t\text{-Bu}$, $t\text{-BuOH}$, MeI.

acid-catalyzed Friedel-Crafts-type cycloalkylation that had been previously reported (24) to give the trans-fused B/C ring junction.

In order to achieve the differentiation of the 2 aromatic rings in 27 during Birch reduction, it was envisaged to increase the reduction potential of one ring by its conversion to the free phenol. This, however, implied that a selective deprotection of one of the 2 aromatic alkyl ethers could be obtained. Indeed, the conversion of 27 to the ketone 33 was accomplished through the selective cleavage of the methoxyl group using the conditions reported by Mann (25) (lithium diphenyl phosphide) to give an alkoxyphenol that underwent preferential Birch reduction of the E aromatic ring, and finally remethylation of the free phenol. The Birch reduction also afforded the desired "anti" relationship at the bond joining the C and E rings.

The required cis-fused D/E ring system could not be obtained through conjugate addition of an organo-cuprate on the α,β -unsaturated ketone 33, due to steric factors. The last angular methyl group was therefore introduced via the formation of a cyclopropyl ring. They used the β -hydroxyl intermediate, obtained from hydride reduction of 33, to

direct the Simmons-Smith cyclopropylation on the same face of the molecule. Reoxidation and α,α -dialkylation of the ketone were then accomplished prior to the opening of the cyclopropyl ring. The ketone 35 was further reduced at the A ring to 36 which gave (dl)-alnusenone (26) after alkylation at C₄.

In a totally different approach, Ireland *et al.* (26, 27) envisaged the preparation of alnusenone (26) based on the "now-classical" biomimetic polyolefinic cyclization method developed by Johnson (28). This new strategy was investigated primarily to develop a more efficient synthesis that would be devoid of the necessity to differentiate the two aromatic A and E rings of diether 27 used in the preceding approach. Among other advantages was the possibility of direct formation of the troublesome trans-fused C/D ring junction with its 2 angular methyl groups. In model studies directed to the preparation of the tetracyclic triterpene shionone (29), the aldehyde 37 was shown to be a poor initiator for the cationic cyclization. However, its facile preparation prompted them to investigate the use of compounds that could be more effective sources of cationic character and, at the same time, that could be derived from 37.

37

Two such compounds were studied, the cyclic allylic alcohols 38 (Scheme VIIIa) and 42 (Scheme VIIIb). The 5-membered allylic alcohol 38 was prepared from 37 using a masked 2-butanone synthon, 4-trimethylsilylhomopropargyl magnesium chloride, in 5 steps. Despite success on a model system, the cyclization of 38 proceeded in low yield to give a mixture of ortho- and para-olefins 39 and 40. Oxidative ring enlargement of the major isomer 39 provided the target enone 33 thus completing the alternate formal synthesis of alnusenone (26). The identity of 40 was provided by converting both 39 and 40 to the same demethoxylated product 41.

The parallel study using the six-membered homolog 42 led to a complex mixture from the stannic chloride-initiated cyclization. The desired pentacyclic olefin 43 was isolated with a disappointing 12% yield which could not be greatly

(a)

(b)

^a $\text{Me}_3\text{SiC}\equiv\text{C}(\text{CH}_2)_2\text{MgCl}$; ^b $\text{HgSO}_4, \text{Ag}, \text{H}_2\text{SO}_4$; ^c $8\text{N H}_2\text{CrO}_4$; ^d $2\% \text{ NaOH}$,
 EtOH ; ^e LAH ; ^f SnCl_4 ; ^g $\text{OsO}_4, \text{DIOXANE}, \text{H}_2\text{S}$; ^h $\text{Pb}(\text{OAc})_4$; ⁱ $20\% \text{ NaOH}$,
 MeOH ; ^j $\text{LiPPH}_2, \text{TMEDA}$; ^k $\text{CLPO}(\text{NMe}_2)_2, \text{HMPA}, \text{Et}_3\text{N}$; ^l $\text{Li}/\text{NH}_3, \text{THF}, \text{EtOH}$;
ⁿ $\text{LDA}, \text{THF}, \text{HMPA}, \text{MeI}$; ^o LAH ; ^p $\text{C}_4\text{H}_9\text{N}, \text{MVK}$; ^q LAH ; ^r $\text{BH}_3, \text{THF}, \text{THF}, \text{H}_2\text{O}_2$,
 NaOH ; ^s H_2CrO_4 .

improved by using alternate reaction conditions. The subsequent attempts to convert 43 to the desired E ring of alnusenone were no more successful. While conversion to the ketone 44 could be accomplished by hydroboration-oxidation, the steric congestion resulting from the cis-D/E ring fusion and the proximity of the C-14a α -methyl group prevented several attempts to further transform it to the desired gem-dimethyl group.

3. Friedelin (5)

The naturally occurring pentacyclic triterpene friedelin (5), with its 9 contiguous asymmetric centres (of which 5 are situated at ring junctions and bear angular methyl groups), has been the target of numerous synthetic approaches from various groups. Ireland and Walba (30), by applying the strategy developed on the previous successful synthesis of alnusenone (26), reported the first total synthesis of friedelin (5) (Scheme IX). Some modifications to the alnusenone synthesis were introduced: the order of reduction of the two aromatic rings was reversed, that is, A before E rather than E before A, so as to avoid an anticipated backbone rearrangement which would occur if the

^a SEE a-g IN SCHEME VII; ^b SEE h,i IN SCHEME VII; ^c H₂O₂, NaOH, ME OH; ^d p-TsNHNH₂, AcOH, CH₂Cl₂; ^e MeLi, Et₂O; ^f CF₃CO₂H, (CF₃CO)₂O; ^g LDA, THF; ^h Zn(Ag), CH₂I₂, THF; ⁱ Li/NH₃, DME, EtOH; ^j 5N HCL, EtOH, C₆H₆; ^k Li(O t-Bu)₃Al, THF, C₆H₆, 0°; ^l DHP, POCL₃; ^m SEE j-n IN SCHEME VII; ⁿ CLPO(NMe₂)₂, DME, HMPA, N-BuLi; ^o Li, EtNH₂, t-BuOH; ^p p-TsOH, ME OH, THF; ^q CrO₃ . 2PYR.

cis-D/E ring junction system were present due to the acidic conditions required for the elaboration of ring A.

Thus, the pentacyclic diether 45 was prepared by a sequence identical to the one used for 27. Again using conditions previously reported for alnusenone, the reduction of the ethoxyl-bearing aromatic ring was accomplished selectively. The resulting unsaturated ketone 46 was converted to the acetylenic tertiary alcohol 47 by an Eschenmoser-type cleavage (31) on the derived α,β -epoxy-tosylhydrazone, followed by treatment with methyl lithium. The cationic cyclization of 47 in the presence of trifluoroacetic acid and trifluoroacetic anhydride afforded quantitatively the pentacyclic enol trifluoroacetate 48. The remaining β -methyl group at C₄ was introduced via a carbene addition on the lithium enolate obtained by treating 48 with lithium diisopropylamide. Although carbene addition occurred from the less hindered α -face, epimerization to the more stable β -methyl occurred during cleavage of the hydroxy-cyclopropane intermediate with lithium and ammonia followed by acid treatment. The ketone 49, which contains the correct stereochemistry at all asymmetric centres of rings A, B and C was then converted to friedelin (5) by a sequence of reactions involving the previously developed

elaboration of the E ring followed by deprotection and oxidation of the C₃-hydroxyl function. The overall synthesis provided the target molecule in 0.3% yield.

A few years later, Kametani et al. (32) reported a new and elegant approach to friedelin (5) and alnusenone (26). They prepared the diethers 27 and 45 by regio- and stereoselective intramolecular cycloaddition of ortho-quinodi- π methanes, an approach they had used successfully for the preparation of oestrone (33) and astisine (34). The starting cyano-benzocyclobutene derivative 55 (Scheme X) was prepared as previously described (35). On heating with an excess of isoprene they obtained the desired tetralin derivative 56 in 43% yield after chromatography. This first fragment was coupled with the iodide 58, obtained from the same cyano-benzocyclobutene 55 via alkylation with the THP ether of 2-bromo ethanol, to give the key intermediate 59 possessing a cis relationship of the cyano and isopropenyl groups (alkylation occurred from the less hindered side). In the following step, the benzocyclobutene portion underwent a simple electrocyclic ring opening to generate the o-quinodimethane system 60 upon heating in a sealed tube, and intramolecular [4 + 2] cycloaddition to the olefin resulted

^a THPOCH₂CH₂Br; ^b H⁺; ^c P-TsCl; ^d NaI; ^e LDA, NH₃(L); ^f (1-Bu)₂AlH;
^g N₂H₄·H₂O, N₂H₄·HCl.

in the stereo-selective formation of the pentacyclic dinitrile 61. The trans-anti-trans BCD ring system stereoselectivity was rationalized on the basis of cycloaddition occurring through the most favourable chair conformation 61a. The final conversion to diethers 27 and 45 was accomplished by the usual hydride reduction Wolf-Kishner sequence used by Ireland.

61a

NOTABLE APPROACHES TO PENTACYCLIC TRITERPENE SYNTHESIS

In addition to the total syntheses that were described in the preceeding pages, a number of reports have appeared on the preparation of various synthons generally suitable for incorporation into the synthesis of more than one pentacyclic triterpene.

An approach that attracted much effort was the preparation of synthons that would incorporate the troublesome cis-fused D/E ring junction at an early stage of the synthetic scheme. Heathcock et al. (36) reported the preparation of the bicyclic allylic bromide 62 that could be used in a convergent synthesis of several pentacyclic triterpenes of the germanicane family (Scheme XI). The synthesis of the key intermediate keto-ester 65 could be accomplished by a Nazarov-type annelation. Reaction of 2,5,5-trimethyl-cyclohexanone 63 with the keto-diesther 64 in refluxing benzene with a catalytic amount of mineral acid afforded 65 in 42% yield. Catalytic hydrogenation of 65 led to the single cis-fused stereoisomer 66 which interestingly exists totally in the chelate enolic form. Hydride reduction of 66 afforded the β -allylic alcohol 67 by an unusual axial attack of the hydride. The subsequent

^a H^+ ; ^b H_2 , Pd-C; ^c LAH; ^d MCPBA; ^e JONES REAG.; ^f $PH_3P=CH_2$;
^g Li/NH_2Et ; ^h PBr_3 .

transformation to the bromide 62 via the epoxidation-Wittig methylenation was chosen since elaboration through the derived enone gave poor yield of the desired product.

At the same period, ApSimon et al. (37) reported the preparation of a similar cis-fused D/E synthon 69. The work focused on the elaboration of a substrate in which the future C₂₈ methyl group is functionalized both for its activating effect in the synthesis and for the subsequent preparation of pentacyclic triterpenes possessing a oxidized methyl group. The reaction of 3,3-dimethylcyclohexanone (70) with refluxing dimethylcarbonate in the presence of sodium hydride provided the α -carbomethoxy ketone, which was then treated with ethyl vinyl ketone to give the bicyclic enone 71. After several unsuccessful attempts to catalytically hydrogenate 71 to a cis-fused ring system, they envisaged to direct the hydrogenation from the β -face by converting the ester to the corresponding primary alcohol, as suggested by literature precedents. Thus, the ketone group in 71 was protected as a 1,3-dioxolane prior to hydride reduction of the ester to the alcohol. Deketalization afforded the hydroxy-ketone 72 which underwent selective catalytic hydrogenation to the desired hydroxy-ketone 69.

^a $(\text{MeO})_2\text{CO}$, NAH ; ^b NAOMe , EVK ; ^c $(\text{CH}_2\text{OH})_2$, P-TsOH ; ^d LAH ; ^e HCL ;
^f H_2 , Pd-C ; ^g Ac_2O , HClO_4 ; ^h ALLYL BROMIDE , MELI .

Attempts at alkylation of 69 from the less hindered β -face gave disappointing results. In the best case, the alkylation of the enol acetate with allyl bromide gave the keto-acetate 73 in low yield.

Very recently another potential D/E ring system synthon was synthesized by Krishnamurthy and Rao (38) (Scheme XIII). The conversion of 2-naphtoic acid (74) to the aldehyde 75 was realized in 3 steps by successive reductive alkylation, reduction of the acid to the alcohol and selective oxidation to the aldehyde. After Wolf-Kishner reduction of 75, the resulting dimethyl-methoxy ether was subjected to Birch reduction followed by acid cleavage of the intermediate dienol ether to the α,β -unsaturated ketone 77. The introduction of the angular methyl group with a cis-stereochemistry was then accomplished by copper-catalyzed conjugate addition of methyl magnesium iodide. Dehydrogenation with DDQ furnished the target enone 78.

A variation of the strategy involved in the previous efforts would be to prepare a CDE ring system that would be suitably functionalized to accommodate the introduction of a potential A ring fragment (79) since Ireland showed that by a cycloalkylation reaction it is possible to generate the

^a $\text{NaNH}_3, \text{MeI}$; ^b $\text{Na}(\text{MeOCH}_2\text{CH}_2\text{O})_2\text{-AlH}_2, \text{C}_6\text{H}_6$ (VITRIDE REAGENT);
^c PCC ; ^d $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}, (\text{CH}_2\text{OH})_2\text{O}, \text{KOH}$; ^e $\text{Na}/\text{NH}_3, \text{T-BuOH}$; ^f HCl, MeOH ;
^g $\text{MeMgI}, \text{CuCl}_2, \text{Et}_2\text{O}$; ^h $\text{DDQ}, \text{C}_6\text{H}_6$.

desired trans-fused B/C ring junction of the pentacyclic system.

79

Such an approach was investigated by ApSimon et al. (39). Their synthesis of the tricyclic system 80 is presented in Scheme XIV. Alkylation of keto-ester 81 with the aromatic bromide 82, followed by acid-catalyzed cycloalkylation afforded the tricyclic ester 83. This time, conversion of the ester to the primary alcohol and catalytic ~~hydrogenation~~ of the alcohol gave a mixture of cis- and trans-fused isomers 84. Investigation of metal-ammonia reduction of the carboxylic acid however proved quite successful and they obtained the cis-saturated acid 85 in 75% yield. The final conversion to 80 proceeded through successive reduction of the acid to the alcohol 84a,

SCHEME XIV

43

^a T-BuOK; ^b P-TsOH, C₆H₆; ^c LAH; ^d 10% Pd-C, H₂; ^e KOH, DME; ^f Li/NH₃;
^g PCC; ^h N₂H₄·H₂O, THEN NAH, MeI; ⁱ Li/NH₃, T-BuOH.

oxidation to the aldehyde, Wolf-Kishner reduction to the methyl group and finally Birch reduction to the tetrasubstituted-unconjugated enone 80.

Studies on the ABC + E ring construction of the pentacyclic triterpene skeleton were recently reported by ApSimon et al. (40, 41). The underlying advantage of these routes was to rapidly provide the polycyclic species with preformed stereochemistry. The previously reported (42) tricyclic enone 86 was alkylated with the tosylate 87 via the dienolate anion generated with potassium t-amylloxide to yield an equimolar mixture of the diastereoisomeric keto-ketal 88 (Scheme XV) (40). At the outset it was believed that one of the diastereoisomer would cyclize preferentially with respect to the other one in the aldol condensation as suggested by recently published results (43). After several unsuccessful attempts at cyclizing the deketalized ketone 88, it was decided to hydrogenate the unconjugated double bond in 88 since it was believed that the failure of the cyclization was due to the lability of the cationic species 90 leading to more stable allylic or benzylic species in competing processes. Thus after catalytic hydrogenation and deketalization of 88, the resulting diketone could be cyclized and, contrary to the initial assessment, both diastereoisomers reacted.

a. $\text{KOT-AMYL}, \text{C}_6\text{H}_6$; b. OXALIC ACID; c. 10% $\text{Pd-C}, \text{H}_2, \text{XYL.}$; d. P-TsOH ,
CHROMATOGRAPHY.

However, after chromatography, the single compound 89 crystallized and its structure was unequivocally determined by X-Ray diffraction.

The same tricyclic enone 86 was also used in another route (41) (Scheme XVI) in which the bis-annulating synthon 91 was envisaged to lead to the formation of the D and E rings by two successive aldol-type condensations. Unlike the preceding route, this approach would not lead to the loss of 50% of the material since it doesn't involve the coupling of two racemates. However, the diketone 92 obtained from the reductive alkylation of ketone 86 with the α -silylated ketone 91, could not be cyclized using a variety of

^a T-BuOH, T-BuOK, CH₂=CHCN; ^b P-TsOH, EG, C₆H₆; ^c KOH, EG; ^d LAH, THF;
^e PCC; ^f CH₂=CHBrSiMe₃, Mg, THF; ^g PCC, NaOAc; ^h Li/NH₃, T-BuOH;
ⁱ TMSCL, Et₃N; ^j MeLi, DME.

conditions. After careful inspection of molecular models, the authors reached the conclusion that the presence of the gem-dimethyl groups, although seemingly distant from the reaction site, inhibits the approach of the correct enolate along a trajectory that allows for ready cyclization. This route was then abandoned for a more promising bis-normethyl series.

ApSimon et al. (44) have also reported a route aimed at preparing a BCDE ring system that would be a suitable synthon for the synthesis of pentacyclic triterpenes (Scheme XVII). This route parallels the one presented in Scheme XV and involved the preferential cyclization of one of a pair of diastereoisomeric diketones in an aldol-type cyclization. The diketones 94 were obtained from the alkylation of the tetralone 93 with the previously reported tosylate 87, followed by deketalization of the reaction products. The reaction of the diastereoisomeric mixture in dimethoxyethane with a solution of t-butyilmagnesium chloride led to the formation of the three compounds 95, 96 and 97 in a ratio of 15:1:10. These results indicated that a preferential cyclization of 94b, leading to the major tetracyclic anone 95, occurred. The other diketone 94a led mainly to the hydroxy-ketone 97 and to a minor extent the desired

SCHEME XVII

49

^a KO T-AMYL, C₆H₆; ^b OXALIC ACID; ^c T-BuMgCL, DME.

tetracyclic enone 96. Confirmation of these results was obtained by separating the two constituents of 94 and exposure of both 94a and 94b to the cyclization conditions. Although enone 96 was the initial subgoal in order to prepare friedelin, enone 95 was not devoid of interest since it could lead to the preparation of β -amyrin.

RESULTS AND DISCUSSION

The field of total synthesis of pentacyclic triterpenes has been for many years one of the major concerns of these laboratories. As seen in the previous section, the task of synthesizing polycyclic systems related to this class of compounds has often proved to be a challenging one and, despite some outstanding achievements in this field, the development of new approaches still remains of great interest.

In this respect, the main emphasis of the work accomplished in these laboratories has always been to devise a general entry to the pentacyclic array, with the elaboration of synthetic strategies that would incorporate synthetic intermediates suitable for the preparation of many pentacyclic triterpenes of a given class. The successful realization of such an objective has as its first implication the effective stereochemical control of all the asymmetric centres. In fact, at the outset, a multicentres-target molecule such as friedelin (5), which contains 9 asymmetric centres, represents only one of 512 theoretical stereoisomers and evidently it is totally impractical to venture in a non-stereospecific pathway.

Thus, the work that is presented in this thesis has been elaborated from these considerations. Using the pentacyclic keto-triterpene friedelin (5) as target molecule, the following two convergent approaches have been investigated and the results are described in the next two sections (Scheme XVIII shows a ring assemblage representation).

Part 1. The $CDE + A \longrightarrow ABCDE$ approach.

Part 2. The $ABC + E \longrightarrow ABCDE$ approach.

The first approach, the $CDE + A \longrightarrow ABCDE$, was especially attractive since a retrosynthetic analysis showed its potential application to a chiral synthesis of the target molecule. Few reports have appeared on the preparation of chiral synthons suitable for pentacyclic triterpene synthesis. In this respect, this is probably the only area for which the field of total synthesis of pentacyclic triterpenes has not followed the field of steroids total synthesis where a multitude of chiral syntheses and approaches have been investigated especially in studies aimed at the progestational 19-nor steroids (45). Thus, borrowing from that methodology, it was decided to

SCHEME XVIII

venture into the preparation of a chiral synthon that could be further elaborated into a chiral pentacyclic system.

PART I

A chiral approach to the synthesis of friedelin (5) via a
CDE + A $\longrightarrow$ ABCDE ring assemblage

A. SYNTHETIC STRATEGY

The keto-triterpene friedelin (5) probably constitutes one of the most challenging members of the perhydropicene group to synthesize. As mentioned earlier, nine contiguous asymmetric centres are present, of which five are quaternary carbon atoms bearing angular methyl groups at ring junctions. Furthermore, friedelin (5) carries a trans-anti-dis arrangement of the CDE rings, which undoubtedly brings a considerable amount of strain to the molecule, as well as ~~two~~ axially oriented methyl groups at the CD ring junction. These last two structural features are also shared by the pentacyclic triterpenes alnusenone (26) and multiflorenol (98) as indicated in figure 2 (p. 56).

In this respect, the preparation of a suitably functionalized synthon corresponding to the CDE ring system represents an attractive solution to the synthetic preparation of these examples of pentacyclic triterpenes.

STRUCTURAL SIMILARITIES IN PENTACYCLIC TRITERPENES.

5

26

98

Thus a bicyclic intermediate such as 102 (Scheme XIX), in which the problematic trans-disubstituted CD ring junction is present, would constitute a key intermediate since its subsequent elaboration to the pentacyclic system could be envisaged by two different pathways. On one hand, the introduction of the A ring fragment via a Grignard-type alkylation and further straightforward transformations would lead to intermediate 100 which contains all of the carbon atoms of the pentacyclic skeleton. From there, the necessary transformations in order to obtain the pentacyclic system would include an intramolecular aldol-type cyclization of the side chain to form the E ring and a cycloalkylation following the method developed by Ireland et al. (24) to generate the B ring.

On the other hand, the elaboration of the E ring could be effected initially to give a tricyclic species such as 103 and, after selective protection of the unsaturated carbonyl, the A-ring fragment would be introduced by applying the methodology developed in the previous pathway. The intermediate 101 thus obtained is well suited for the further elaboration of the E ring which includes the formation of the cis-DE ring junction.

SCHEME XIX

58

The choice of the bicyclic species 102 as the key intermediate was also based on the possibility of obtaining it in a single antipodal form by applying the methodology developed in the field of steroid synthesis (45). Thus, a Robinson-type annelation between the commercially available 1-methyl-1,3-cyclohexadione (104) and the enone 105, in the presence of an optically active catalyst, could lead to the formation of the enedione 106 in which the angular methyl group of the future C-14 position has the correct, absolute stereochemistry (Scheme XX). The regio- and stereoselective reduction of the saturated carbonyl residue followed by a stereoselective conjugate addition of a cyano group (Nagata's hydrocyanation) would provide the key intermediate 102 in a stereospecific fashion.

B. PREPARATION OF THE CHIRAL SYNTHON 102.

B.1. Synthesis of (+)-7-benzyloxy-oct-1-en-3-one (105).

Annelation reactions to form six-membered cyclic ketones using alkyl vinyl ketones or their equivalents is well known as the Robinson annelation and has wide application, particularly for the stepwise construction of polycyclic compounds such as steroids and terpenoids (46). A particularly important innovation based on the Robinson

SCHEME XX

60

procedure has been the introduction of a single reagent capable of forming two fused six-membered cyclic ketones. This new method of cyclization is called bis-annellation, and few compounds have been recommended for this purpose. The bis-annellation reagent was defined by Danishefsky (47) as a synthetic equivalent of 7-octene-2,6-dione, that is, a molecule incorporating a terminal enone or its equivalent in one side and a masked ketone to generate a 1,5-diketone system in the other side of the molecule. The usefulness of a bis-annulating reagent is determined by easy accessibility of the reagent itself and the facile procedure of unmasking.

In the synthetic strategy presented earlier, we envisaged the formation of the D and E rings of friedelin (5) from such a bis-annulating reagent. Its formulation as the benzyl ether 105 was dictated primarily from an inspection of the conditions required for the asymmetric aldolization step which involves lengthy reflux in the presence of mineral acid. Furthermore, there exist efficient methods for the removal of benzyl protecting groups under mild conditions that will allow for an easy unmasking procedure.

(Overall yield : 11%)

a: NaOEt ; b: $\text{Na}_2\text{CO}_3, \text{H}_2\text{O}$; c: $\text{NaBH}_4, \text{EtOH}$; d: $\text{NAH}, \text{PhCH}_2\text{Cl}, \text{DMF}$; e: KOH, EG ;
 f: LAH ; g: $\text{PCC}, \text{CH}_2\text{Cl}_2$; h: $\text{CH}_2=\text{CHMgBr}, \text{ETHER}$; i: JONES REAG..

Various methods for the preparation of similar bis-annulating reagents have been reported by Saucy (48), Stork and Ganem (49), Boeckman (50) and Tsuji *et al.* (51). In earlier studies from these laboratories (52), the preparation of 105 had been done according to the methodology of Saucy (48) as illustrated in Scheme XXI. However, the relatively high number of steps and the low overall yield of this sequence prompted us to look for a more efficient synthesis of this relatively simple molecule.

The commercially available and inexpensive 5-hexen-2-one (107) (Scheme XXII) possesses a functionalization pattern that is adequate for ready conversion to aldehyde 110 which can in turn be converted to 105 by straightforward procedures. Thus, 5-hexene-2-one (107) was reduced to the hydroxy-olefin 108 using lithium aluminium hydride, and the alcohol thus obtained was subjected to the standard conditions of benzylation (NaH , benzyl bromide) to give the benzyl ether 109 in moderate yield (50%), after 24 hrs. of stirring at room temperature. Significant improvement in both yield and reaction time was obtained upon addition of 0.1 equivalent of tetra-butyl ammonium iodide following the work of Czernecki *et al.* (53). Thus 109 was produced in 70% yield with 1 hour of stirring at room temperature. The

^a LAH, Et_2O , 25° ; ^b NaH, $\text{N-BuN}^+\text{I}^-$, PhCH_2Br , THF; ^c $\text{BH}_3 \cdot \text{ME}_2\text{S}$, CH_2Cl_2 ;

^d PCC, CELITE, CH_2Cl_2 ; ^e $\text{CH}_2=\text{CHMgBr}$, THF, 0° , THEN NH_4Cl ; ^f JONES

REAG., 0° ;

higher reactivity of the alkoxide anion is believed to be the result of the formation of a weaker ion pair $RO^-N^+(Bu)_4$ (53). The direct conversion of the terminal olefin in 109 to an aldehyde was accomplished by the one-pot hydroboration-oxidation procedure reported by Brown *et al.* (54) involving the regiospecific hydroboration of the olefin with the complex borane-dimethylsulfide followed by direct oxidation with pyridinium chlorochromate. Careful distillation under reduced pressure afforded aldehyde 110 in 60% yield.

The α,β -unsaturated ketone 105 was then obtained by the successive treatment of aldehyde 110 with vinyl magnesium bromide and oxidation of the resulting allylic alcohol with Jones reagent (two-phase procedure) in a combined yield of 50%. This moderate yield could not however be significantly improved by the use of other oxidizing agent such as pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), $KMnO_4$, $CuSO_4$ (55) or $NaOCl$ (56). Nevertheless, this sequence affords 105 in an improved yield and fewer steps when compared to the previous method (Scheme XXI).

B.2 Preparation of the chiral synthon 102: (+)-1-(3'-benzyloxybutyl)-8a α -cyano-5 β -hydroxy-4a β -methyl-3,4,4a,5,6,7,8,8a-octahydronaphtalen-2(1H)-one.

With the bis-annelating reagent 105 in hand, the next task was to examine the feasibility of preparing the bicyclic synthon 106 with a high enantiomeric excess (ee) using an asymmetrically biased intramolecular aldol condensation. This approach was inspired by the methodology developed in the field of steroid total synthesis (45) and was based on the discovery that prochiral triketones such as 112 (Scheme XXIII), upon exposure to optically active amino-acid, are converted into ketols 113 or enediones 114 in excellent chemical and optical yields (57, 58).

Several amino acids have been shown to induce appreciable enantiodifferentiation (45), but certainly the most widely used are L-proline and L-phenylalanine with the latter being the best suited when substituted enones are formed ($R = H$) (59). Another considerable advantage provided by such processes resides in the formation of a product with the required chirality at an early stage of the synthetic scheme.

Earlier studies in these laboratories (52b) had provided evidence that this methodology was applicable in our case, that is, the enantioselective cyclization of the triketone 115. Thus employing the conditions developed by Greaves (52b), the racemic triketone 115 was prepared from the Michael-acceptor enone 105 and 2-methyl-1,3-cyclohexanedione (104) in excellent yield (Scheme XXIV), and then subjected to intramolecular aldol condensation using L-phenylalanine and perchloric acid in refluxing acetonitrile. The bicyclic enone 106, $[\alpha]_D = +35^{\circ}$, was obtained in 80% yield after purification by chromatography.

In spite of numerous synthetic investigations, the mechanism of the enantiodifferentiation is still an open matter. Conceivably the chiral amine component may interact with either the side chain carbonyl or one of the two enantiotopic cyclohexanedione carbonyls. In the former case, an enamine-like intermediate 116 would be generated. The formation of the crucial bond between the future C₁₃ and C₁₈ can then take place through the formation of the immonium ion 117 as indicated, which upon hydrolysis yields the observed enedione 106. A recent report by Agami *et al.* (60) has brought some strong support in favor of this mechanism for the proline-catalyzed process.

a NaH, DME ; b $\text{L-PHEYLALANINE, HClO}_4, \text{MeCN}$; c $\text{NaBH}_4, \text{EtOH}$.

An alternative mechanism, as suggested by Hajos and Parrish in their pioneering study (57), would involve the formation of a carbinolamine intermediate 119 upon activation of one of the enantiotopic carbonyls. Cyclization would occur by a direct backside nucleophilic attack from the enol formed in the side chain.

Nevertheless, whatever the mechanism, what seems to be most significant is the beneficial effect of a free α -carboxyl group in the chiral reagent (45). Its function could involve either intramolecular protonation of the incipient tertiary hydroxyl group as in the cyclization of 116 to 117, or the enforcement, via hydrogen bonding, of a rigid asymmetrically biased arrangement in the transition state.

With the optically active enone 106 in hand, the determination of the enantiomeric excess became the task of highest priority. A rapid and efficient way for such a determination is provided by the use of chiral shift reagent (CSR) which induce differential chemical shifts for the signals of the component enantiomers, provided that a suitable anchor be in the vicinity of the chiral centre (61). Since the mode of action of CSR is to form weak addition complexes with organic bases, it was felt that this complexing effect could be maximize by transformation of the C_5 -ketone functionality into a stronger base. This was readily accomplished by a stereoselective sodium borohydride reduction (62) to the alcohol 118, $[\alpha]_D = +45^\circ$ (c. 2.15, methanol).

The enantiomeric composition was determined with the CSR tris-(3-heptafluorobutyl-d-camphorato)-europium (III) $Eu(hfbc)_3$ (120), introduced by Fraser *et al.* (63), using a XL-200 NMR spectrometer.

With increasing amounts of CSR (Table II), the signal due to the C_{14}^* -methyl singlet moved dramatically downfield, reaching a value of 4.7 ppm for a 0.95 molar ratio of CSR to substrate. Furthermore, the signal separated into two peaks, each arising from the C_{14}^* -methyl group of the component diastereoisomers. The best separation (≈ 11 Hz) was obtained with 0.95 molar equivalent of CSR (Figure 3), from which a computer-assisted deconvolution procedure allowed for the determination of the relative area for each peak. The results indicated that 118 comprises about 65% of the desired (R)- C_{14}^* diastereoisomer that is, an enantiomeric excess of 30%. (Here, the absolute stereochemistry at C_{14}^* has been assigned on the basis of the generalization that amino-acids of natural configuration (L) induce the desired β -alkyl configuration in compounds such as 118 (45, 59).) Little fluctuation ($\pm 2\%$) in the results was observed when the reaction was repeated under identical conditions, thus ascertaining the reproducibility of the process.

The modest optical yield obtained here contrasts with the generally high enantiomeric excesses reported for similar systems ($<65\%$) (45). On a quantitative basis,

TABLE II

Shift differences for the $C_{14}^*-CH_3$ signals^a.

CSR Molar ratio	$\delta C_{14}^*-CH_3$		$\Delta\delta$		$\Delta\Delta\delta'(\Delta\Delta\nu)^b$
	R	S	R	S	
0	1.158	1.158	-	-	-
0.19	1.794	1.772	0.636	0.614	0.022 (4.4)
0.33	2.580	2.541	1.422	1.383	0.039 (7.9)
0.55	3.927	3.881	2.769	2.723	0.046 (9.3)
0.95	5.855	5.801	4.697	4.643	0.054 (11.2)

^a The spectra were recorded for a 0.2 M solution of 118 in $CDCl_3$. The chemical shifts are expressed in ppm downfield from TMS as an internal standard. $\Delta\Delta\nu = Hz$

FIGURE 3. RESOLVED C₁₄-CH₃ SIGNAL OF HYDROXY-ENONE 118 IN THE PRESENCE OF 0.05 M OF CSR.

these results indicate that the desired (R)-C^{*}₁₄ enantiomer could be obtained with a maximum theoretical yield of 50% when calculated from the purified enedione 106.

Although we have not attempted to preparatively resolve the mixture into its components, it seems reasonable to assume that the desired enantiomer would be recuperated in high yield by using one of the various methods of resolution now available (64).

At that point in our work it became evident that one of the two objectives initially envisaged by that strategy, that is, the preparation in high enantiomeric excess of the bicyclic intermediate, could be accomplished only with modest success. However, on a strictly preparative point of view, this route still seemed quite viable and for this reason we decided to pursue our efforts towards the preparation of the target molecule along the lines initially described. It should be pointed out here that attempts to the chiral preparation of this particular bicyclic synthon via a different strategy will be described in a later section.

I am deeply indebted to Mr. Lee Collier for making the deconvolution procedure available.

With the hydroxy-enone 118 in hand, the next task was the introduction of the trans-methyl group at the C/D ring junction. The route of choice involved the conjugate addition of hydrogen cyanide across the double bond of 118 under kinetic conditions in order to generate the trans-carbon substituent -as a nitrile- according to the conditions of Nagata (65). It is now well established that the kinetic conditions to ensure the formation of the trans ring function involve the use of the $\text{HCN}/\text{Et}_3\text{Al}$ reagent, whilst the preformed reagent diethyl aluminum cyanide (Et_2AlCN) exerts thermodynamic control, and thus generates the cis ring fusion in six-membered polycyclic species similar to 118. On the other hand, Ireland *et al.* (29) have demonstrated that the presence of a proton source in the form of a hydroxyl group in a substrate converts the more convenient diethyl aluminum cyanide process to a kinetic one. In fact, this precedent was one of the contributing factors to the preparation of the hydroxy-enone 118 in the first place.

An additional advantage in the use of the nitrile group, as the alkylating agent lies into the fact that it can be easily converted to an hydroxy-methyl or carboxylic acid group, both of which have been reported to appear in naturally occurring triterpenes (1).

In the event, hydroxy-enone 118 was reacted with Et_2AlCN in a mixture of benzene:toluene (4:1) (Scheme XXV) to afford a single product, in 70% yield after purification, to which was assigned structure 102 on the basis of its spectral properties and by comparison with the product obtained from the "true" kinetic process ($\text{HCN}/\text{Et}_3\text{Al}$) (52b). Confirmation of this assignment was later provided by a single-crystal X-Ray diffraction experiment (vide infra).

SCHEME XXV

In a related series of experiments, we investigated the synthetic utility of a recently reported alternate method of conjugate addition using trimethylsilylcyanide (TMSCN) (66, 67). Thus, Utimoto and his group (66) showed that TMSCN reacted with the α,β -unsaturated ketone 121 (Scheme XXVI) to provide a mixture of cis- and trans- β -cyanosilyl enol ether 122 and 123 under the action of triethylaluminum (Et_3Al). Upon hydrolysis of the enol ether, the corresponding β -cyanoketones were obtained, thus providing a new method of hydrocyanation which has two distinct advantages over the conventional Nagata's hydrocyanation in that all reagents are commercially available and the manipulation is much simpler. They also determined that the kinetically-generated trans-adduct 123 was obtained as the major product when toluene was used as solvent whilst a reverse selectivity is observed in refluxing tetrahydrofuran (THF). The reaction may also be catalyzed by various other Lewis acids (67) from which the trans-adduct 123 is always obtained as the major product thus providing evidence that the reaction is kinetically controlled. The greatest selectivity was achieved using boron trifluoride etherate ($\text{BF}_3\text{Et}_2\text{O}$) or SnCl_2 from which the trans-adduct was obtained in 65% yield.

^a Et_3Al , THF OR TOLUENE; ^b LEWIS ACID, NO SOLVENT; ^c H_3O^+ .

Following that precedent, we first investigated the trimethylsilylcyanation on model compounds bearing an oxygen substituent at C₅ as in our substrate 118. The Wieland-Mischer ketone 125 and its homolog 126 possess such a functionalization pattern, and their easy preparation made them attractive as model compounds for our study. Both were prepared according to previously described procedures (68), from the condensation of 2-methyl-1,3-cyclohexanedione (104) with methyl and ethyl vinyl ketones, giving respectively the enediones 125 and 126 (Scheme XXVII). Further transformation to the hydroxy-enones 127 and 128 was achieved via stereoselective sodium borohydride reduction (62).

SCHEME XXVII

a KOH, MeOH; b NaBH₄, EtOH.

When hydroxy-enone 127 was subjected to the reported trimethylsilylcyanation conditions using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as catalyst (3 eq TMSCN/0.1 eq $\text{BF}_3 \cdot \text{Et}_2\text{O}$) (Scheme XXVIII), no starting material could be detected in the reaction mixture after 5 hours of heating at 73°C . The proton NMR spectrum of the crude mixture showed that equimolar quantities of 1,2- and 1,4-adducts were present as identified by the characteristic chemical shift of their respective olefinic proton (67). Thus, two signals at 5.38 and 5.50 ppm were observed for the isomeric 1,2-adducts whilst the signal associated with the 1,4-adducts appeared at higher field as a broad singlet centered at 4.58 ppm. Careful chromatography of the mixture, on a short silica gel column afforded three fractions. The major one (=75%) consisted of an inseparable mixture of the 1,2- and 1,4-adducts 129a and 129b (R = TMS) while the minor fraction (=10%) proved to be a mixture of the 1,2- and 1,4-adducts 129a and 129b (R = H) as indicated by the strong absorption band at 3400cm^{-1} in the IR spectrum. The third fraction was identified by IR and NMR as the ketone 130 resulting from the partial hydrolysis of the β -cyanosilylenol ether 129b (R = TMS). (It should be pointed out here that we also observed this hydrolysis process, although at a slow rate, even when 129b (R = TMS) was stored in the cold (-15°C) under an inert atmosphere over a relatively long period of time.)

SCHEME XXVIII

R H, TMS

Confirmation of these results was obtained from the analysis of the acid-hydrolysis products for each fraction.

Similar results were also obtained when 127 was reacted under the reported kinetic conditions of TMSCN (2.2 eq) and Et_3Al (2.0 eq) in toluene. In this case, the 1,2-adducts 129 were formed in slightly higher yield (=85%).

The simultaneous presence of the 1,2- and 1,4-adducts can be best explained by assuming the initial formation of the 1,2-adducts, as suggested by Utimoto et al. (67), and its subsequent transformation into the 1,4-adducts under the catalysis of the Lewis acid. A similar mechanism has been proposed for the well-documented kinetically controlled hydrocyanation process using Et_2AlCN (65). The incomplete conversion of the 1,2-adduct to the 1,4-adduct in our cases also seems to suggest that the formation of the conjugate addition product may be second order in cyanating species, as it is the case in the Et_2AlCN reaction (65), since the competing formation of a trimethylsilyl ether from the reaction of TMSCN with the hydroxyl function would leave an insufficient amount of TMSCN to effect that conversion under the reaction conditions used (2.2 eq TMSCN).

These hypotheses are strongly supported by the fact that the 1,4-adduct 129b (R = TMS) was obtained as the sole product upon reaction of the 1,2-adduct 129a (R = TMS) with TMSCN (1.1 eq) and Et₃Al (1.0 eq) in toluene. A singlet at 4.60 ppm was the only olefinic proton signal observed in the ¹H NMR spectrum. The ¹³C NMR spectrum showed the presence of two olefinic carbon resonances at 154.2 and 104.1 ppm indicative of a trisubstituted olefin bearing an oxygen substituent (69). Moreover, both spectra indicated that a single stereoisomer of the 1,4-adduct has been formed, which was identified as the trans-β-cyano-silyl enol ether 131 by comparison of its spectral properties with those of the trimethylsilylcyanation product of the tert-butyl ether 132.

Thus, enone 132, obtained in 50% yield from the acid-catalyzed O-alkylation of hydroxy-enone 128 with 2-methyl propene (Scheme XIX), was subjected to the Et_2Al -catalyzed trimethylsilylcyanation conditions previously used for enone 127, and afforded quantitatively the conjugate-adduct 133. Its ^{13}C -NMR spectrum showed the characteristic olefinic resonances of a tetrasubstituted olefin bearing an oxygen functionality (146.6 and 109.5 ppm), as well as a cyano group resonance (122.0 ppm). The trans stereochemistry at the ring junction was deduced from comparison of the spectral properties of its hydrolysis product 134t with those of an authentic sample of the cis- β -cyano ketone 134c, prepared by hydrocyanation of 132 under thermodynamic conditions (Et_2AlCN) (65). Thus, GLC analysis of the crude mixture 134t revealed the presence of a single compound with a slightly shorter retention time than the cis-isomer 134c. Mass spectrum analysis of both 134t and 134c gave the same molecular ion at m/z 277 with a nearly identical fragmentation pattern. Due to its extreme sensitivity to molecular geometry, ^{13}C -NMR spectroscopy proved to be very useful for differentiating between the two isomers. The results for 134t and 134c are presented in figure 4. The various resonances have been assigned by comparison with reported values for similar compounds (69, 70) and by the

SCHEME XXIX

a. $\text{H}_3\text{PO}_4, \text{BF}_3, \text{Et}_2\text{O}, \text{ISOBUTYLENE};$ b. $\text{TMSCN}, \text{Et}_3\text{Al}, \text{TOLUENE};$ c. $\text{Et}_2\text{AlCN}, \text{benz.}$
 d. $\text{HCL}, \text{THF},$

2

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FIGURE 4 COMPARATIVE ^{13}C -NMR SPECTRA FOR COMPOUNDS **134c** AND **134t**

use of APT technique which provided direct determination of the multiplicity for each signal, that is, methyl, methylene, methine and quaternary carbon atoms.

Significant chemical shift variations are observed for the angular methyl group resonance as well as for the two methine carbons C_4 and C_8 whilst the remaining of the resonances are practically unchanged. In 134t, the angular methyl group is shifted upfield by 6.5 ppm, when compared to 134c. A reverse trend (downfield shift) of similar magnitude is observed for the two methine carbons. These results suggest that 134c and 134t are isomeric around the ring junction, and this can be explained in terms of the shielding arising when two proton-bearing carbons are in γ -gauche relative orientation (70). Thus the angularly situated methyl group in 134c is engaged in 4 γ -gauche interactions with C_1 , C_3 , C_7 and C_9 carbons. The same carbon in 134t however is involved in only 2 such interactions, thus explaining the upfield shift observed. The average shielding contribution of one interaction has been observed to be 3.5 ppm which in our cases would amount to a 8 ppm shift. This value correlates well with the value observed here (6.5 ppm). The situation is reversed for the methine carbons C_4 and C_8 where the number γ -gauche interactions decreases from two to one in going from 134c to

134t , thus explaining the downfield shift, observed for these carbon resonances. These results thus clearly indicate that 134t is the kinetically formed trans-1,4-adduct.

However, the most remarkable feature of this reaction is the considerable enhancement of the stereoselectivity brought up by the presence of the C₃-oxygen functionality. (It is not possible at the moment to discuss whether this effect is electronic or steric in origin but this aspect is under continuing investigation in these laboratories.) Unlike Utimoto *et al.* (66, 67), the cis-1,4-adduct was not detected in any of the reactions performed.

We next subjected 135, the trimethylsilylether derivative of hydroxy-enone 118, to the Et₃Al-catalyzed trimethylsilylcyanation conditions described above (Scheme XXX). Again the reaction afforded solely the trans-conjugate adduct, the hydrolysis product of which was found to be identical to the previously prepared cyano-ketone 102. The 64% overall yield of 102 from hydroxy-enone 118 compares favourably to the one obtained from the Et₂AlCN process, thus making this method a viable alternative to the classical Nagata's hydrocyanation.

SCHEME XXX

90

^a $(\text{Me}_3\text{Si})_2\text{NH}, \text{TMSCL}$; ^b $\text{TMSCN}, \text{Et}_3\text{Al}, \text{TOLUENE}$; ^c H_3O^+ .

C. ATTEMPTED REDUCTION OF THE CYANO GROUP IN CYANO-KETONE
121

As we have seen earlier, cyano groups have been used on many occasions in triterpene syntheses as an indirect method of introducing an axially oriented angular methyl group (see Introduction). The usual method for the conversion of cyano group to methyl group involves as a first step the diisobutylaluminum hydride reduction of the nitrile function to an unsubstituted imine, which may then be directly subjected to the Huang-Minlon modification of the Wolff-Kischner reduction without prior hydrolysis to the aldehyde.

Prior to effect this transformation on the cyano group of our substrate, it was necessary to suitably protect the ketone functionality in order to avoid its simultaneous reduction. Thus, cyano-ketone 102 was converted to the cyano-ketal 136, with an excess of ethylene glycol in the presence of a trace of p-toluenesulfonic acid (p-TsOH) in refluxing benzene (Scheme XXXI). When the cyano-ketal 136 was subjected to the usual conditions of hydride reduction (excess diisobutylaluminum hydride in toluene), the starting material was recovered in almost quantitative

yield (95%). Similar results were obtained upon varying the reaction conditions (refluxing in various solvents such as toluene, THF or benzene for several days). This apparent lack of reactivity was also observed when the more powerful reducing agent lithium aluminum hydride (LAH) was used where again the expected imine 137 could not be detected in the reaction mixture which contained mostly the unchanged starting product 136.

SCHEME XXXI

a P-TsOH, EG, C₆H₆; **b** (t-Bu)₂ALH, TOLUENE; **c** LAH, THF.

These results can most probably be explained by the steric hindrance in the vicinity of the cyano group due in large part to the high degree of rotational freedom of the 3-benzyloxybutyl side chain which can inhibit the approach of the nucleophile towards the nitrile.

In view of these results, we decided to postpone the application of this transformation to a later stage where such hindrance would be greatly diminished like, for example, in a more rigid species resulting from the closing of ring E.

D. PREPARATION OF TRICYCLIC ENEDIONE 103

As discussed earlier in our synthetic strategy, the obtention of the bicyclic synthon 102 offers the dual possibility of studying the introduction of fragments corresponding to the A and B rings carbon atoms either directly, or after obtaining a tricyclic CDE ring system species (see section A of Part I). In order to pursue parallel investigations for each of these alternatives, we required the preparation of the tricyclic enedione 103.

The route of choice involved the unmasking of the side chain carbonyl in 102 to afford the 1,5-diketone system 138, followed by an intramolecular aldol condensation to yield the tricyclic species.

138

Cleavage of the benzyl ether of hydroxy-ketone 102 was easily accomplished using the transfer hydrogenolysis conditions recently reported by Hanessian *et al.* (71), which make use of cyclohexene as the hydrogen source and 20% palladium hydroxide on charcoal as catalyst. The reaction afforded a mixture of the dihydroxy-ketone 139 and the hemiacetal 140 (Scheme XXXII). Oxidation of this mixture to the crystalline triketone 138 could be achieved only in moderate yield by using Jones reagent. The use of other oxidizing agents such as PCC or PDC led to the formation of a complex mixture of unidentified, UV active products, probably resulting from the β -elimination of the cyano group.

A significantly better overall yield of triketone 138 was obtained by an alternate route where the carbonyl group in 102 had been protected as a 1,3-dioxalane group, thus eliminating the possibility of formation of the difficultly oxidized hemiacetal 140. Thus, the hydroxy-ketal 136, prepared in high yield as in Scheme XXXI, was quantitatively debenzylated using the previously described conditions and the resulting dihydroxy-ketal 141 was successively oxidized by Jones reagent and deketalized using aqueous oxalic acid to afford the triketone 138 in a 68% overall yield from 102.

^a $\text{Pd}(\text{OH})_2$, CYCLOHEXENE, EtOH; ^b JONES REAG.; ^c OXALIC ACID, H_2O .

With the crystalline triketone 138, in hand, we investigated the possibility of effecting an intramolecular aldol condensation to form the E ring. Treatment of 138 with, an excess of potassium hydroxyde in refluxing methanol for 20 hours led to the formation of a complex mixture of unidentified products. However, when triketone 138 was treated with an excess of sodium ethoxide in absolute ethanol we observed the complete disappearance of the starting material after 20 hours of stirring at room temperature, concurrently with the formation of a single new product which was isolated in very good yield (85%). We assigned structure 142 to this new compound on the basis of its spectral and chemical properties.

142

The molecular ion at m/z 275 (100%) in the mass spectrum indicated that the reaction product was isomeric to the starting ketone 138 thus excluding the expected enedione 103 as a possible structure. This was confirmed by the absence of any UV absorption above 210 nm. Similarly the possible formation of the β -hydroxy ketone 143 could be

ruled out since the product was recovered unchanged after a prolonged treatment with *p*-toluenesulfonic acid in refluxing benzene. Most significantly was the absence of the nitrile absorption band at 2220 cm^{-1} in the IR spectrum, along with the appearance of a new absorption band in the carbonyl region at 1680 cm^{-1} . This then suggested the unexpected transformation of the cyano group into a lactam as further confirmed by the presence of a resonance at 177.8 ppm in the ^{13}C -NMR spectrum (69).

Confirmation of the structure came from a single-crystal X-Ray diffraction experiment, performed by Dr. C. Huber of the National Research Council. A perspective view of 142 is shown in Figure 5 where the hydrogen atoms are shown as arbitrarily small spheres. The bond lengths and angles are presented in Figure 6 and Figure 7 respectively. Figure 5 shows a tetracyclic molecule composed of a trans-anti-trans perhydrophenanthrene ring system, with an amide moiety connecting the C4a and C8a carbon atoms by the carbonyl and nitrogen respectively. The trans-stereochemistry at the C/D ring junction observed here confirms our previous assignment of the hydrocyanation stereochemistry which was based on spectroscopic evidence.

The formation of the diketo-lactam 142 can be rationalized as shown in Scheme XXXIII. The cyclic six-centered transition state of the intramolecular aldol condensation most likely adopts the more stable chair conformation 144 which lead to an attack by the side-chain enolate anion on the β -face of the cyclic ketone at C₂; the resulting β -alkoxy ketone 145 then possesses the more stable trans-anti-trans configuration where all three rings are in chair conformation. Moreover, the axially oriented alkoxy function thus generated is ideally situated to attack

FIGURE 5 PERSPECTIVE VIEW OF LACTAM 142 FROM X-RAY DATA.

SCHEME XXXIII

103

the axial cyano group to give the intermediate cyclic imino-ether 146. Such an intramolecular base-catalyzed Pinner synthesis has been recently described by LeBorgne et al. (72).. The final transformation to the lactam 142 can be rationalized in terms of an initial base-induced deprotonation at C₈ in 146, which then lead to ring opening of the imino-ether and formation of an intermediate enone-amide anion 147; the latter can then undergo an intramolecular Michael-type addition to produce the tetracyclic diketolactam 142.

5

To the best of our knowledge such a transformation has not been reported before. The overall process can be described as the conversion of a formal 2-cyanomethyl-1,5-diketone system 148 to a bicyclic cis-fused keto-lactam 149. Further studies will be necessary to determine whether this reaction is of general applicability since such a system could be readily used in synthetic work directed towards a variety of alkaloids.

Thus, this base-catalyzed intramolecular aldol condensation provided the additional advantage of partially hydrolyzing the cyano group which had previously resisted all attempts of reduction. It was hoped at that point that the diketolactam 142 might be further hydrolyzed to the amino-acid 150 (Scheme XXXIV) which could in turn

SCHEME XXXV

lead to the preparation of enedione 151. However, when subjected to various acidic or basic hydrolysis conditions the diketo-lactam 142 was invariably recovered unchanged. Since lactones are generally more easily hydrolyzed than lactams we next investigated the transformation of lactam 142 to the corresponding lactone following the work of Huisgen (73). In this method, the lactam is first converted to the N-nitroso derivative which upon heating or the action of a weak base eliminates N_2 to give the corresponding lactone as illustrated in Scheme XXXV for the six-membered ring δ -valerolactone. The eight-membered ring rearrangement product 152 has been proposed as a likely intermediate in this transformation. The reaction was also reported to be successful for the N-nitro derivative, in which case N_2O is eliminated.

In this respect we subjected the diketolactam 142 to various nitrosation and nitration conditions (Scheme XXXVI). In our first attempt, the substrate was treated with the nitrosating agent nitrosyl chloride ($NOCl$) in anhydrous dichloromethane, this procedure being more convenient than the conventional aqueous nitrous acid conditions for water-insoluble lactams such as 142. However, the starting lactam 142 was recovered unchanged even after prolonged treatment.

^a NOCL, CH₂CL₂; ^b PYRH⁺BR₃⁻, NANO₂, ET₃BNN⁺CL⁻, CH₂CL₂; ^c NO₂⁺BF₄⁻, PYR.;
^d Cu(NO₂)₂·2H₂O, Ac₂O, NaOAc.

^a PHENYLALANINE, HClO₄, MeCN; ^b PYRROLIDINE, AcOH, Et₂O; ^c β-ALANINE,
 AcOH, MeCN.

Similar results were obtained when 142 was subjected to the recently reported phase-transfer conditions (74), using sodium nitrite, pyridinium bromide-perbromide and benzyltriethyl ammonium chloride as catalyst. We also attempted N-nitration by the methods of Olah (75a) and Campbell et al. (75b). The former utilizes the nitrating agent nitronium tetrafluoroborate ($\text{NO}_2^+\text{BF}_4^-$) in the presence of pyridine while the latter method generates the nitrating species acetyl nitrate (AcONO_2) in situ by reacting copper nitrate with acetic anhydride. In each case, the starting material was recovered quantitatively, hence demonstrating once again the very unreactive nature of 142.

Therefore it became evident to us that the obtaining of 142 created a dead end situation since the impossibility of modifying the lactam functionality prevented the differentiation of the two cyclic ketones as it is imperative to do so in order to pursue the elaboration of the pentacyclic system.

Concurrently to these studies, we also investigated the possibility of effecting the intramolecular aldol cyclization of 138 under acidic conditions (Scheme XXXVII). As we described earlier, amino-acids in conjunction with

mineral acids have been reported on many occasions to be efficient catalysts for intramolecular aldol cyclization particularly in the preparation of chiral products (see Section B). Thus, treatment of triketone 138 with phenylalanine and perchloric acid in acetonitrile gave a complex mixture of unidentified products. Similarly under the conditions described by Hajos et al. (76), using pyrrolidine and acetic acid in anhydrous ether, the reaction afforded the expected enedione 103 in low yield (= 20%) along with many other unidentified products. However, when treated with β -alanine (2 equivalents) and acetic acid in refluxing acetonitrile, a single UV-absorbing (λ_{max} 238 nm) product could be isolated in 75% yield after chromatography. This new crystalline compound was identified as enedione 103 on the basis of its spectral properties. The mass spectrum showed a molecular ion at m/z 257 (96%) along with a fragmentation pattern that could be explained in terms of structure 103 (see experimental section). The $^1\text{H-NMR}$ spectrum showed the disappearance of the methyl signal associated to the side-chain methyl ketone in 138, along with the appearance of a singlet at δ 6.00 ppm corresponding to the olefinic proton at C_8 . The presence of the α, β -unsaturated ketone was substantiated by the absorption band at 1680 cm^{-1} in the infrared spectrum and the UV absorption

band at 238 nm. Finally, the ^{13}C -NMR spectrum showed 16 well separated resonances among which two downfield signals at 209.6 and 197.4 ppm assigned to the two carbonyls at C_1 and C_7 respectively (69); the two signals at 158.2 and 128.2 are characteristic of a conjugated, trisubstituted olefin and were therefore assigned to C_{8a} and C_8 respectively; lastly the signal at 119.1 ppm was ascribed to the cyano carbon atom. The remaining resonances were assigned on the basis of literature precedents (69) and by comparison with compounds previously characterized in this work.

Our studies on the intramolecular aldol condensation have thus revealed that it is possible to effect that transformation both in acidic and basic media, although the end product differs. The usefulness of the base-catalyzed reaction resides in the concomittant modification of the nitrile functionality, to afford a lactam moiety, which had previously resisted all reaction attempts. Continuing studies directed to the modification of this lactam moiety are currently investigated.

L. INTRODUCTION OF RING A FRAGMENTS.

Having obtained the tricyclic enedione 103, the next task became the study of the incorporation of functionalized fragments that would allow for the formation of rings A and B in both enedione 103 and hydroxy-enone 102. In each case however, the substrate could not be used as such due to the presence of other potentially reactive functional groups and hence appropriate protection of these groups became necessary.

For hydroxy-enone 102 it seemed adequate to protect the D-ring ketone as a 1,3-dioxolane group. The hydroxy-ketal 136 was obtained as mentioned earlier by refluxing hydroxy-enone 102 with an excess of ethylene glycol in benzene, or alternatively by refluxing in the same conditions the β -cyano silyl enol ether 152 obtained from the trimethylsilylcyanation of the trimethylsilyl ether 135. (Scheme XXXVIIIa).

The enedione 103 presents a particular problem in that a chemo-selective method of protection must be used. There exist few methods by which one can selectively protect a α,β -unsaturated carbonyl group in the presence of a

(a)

(b)

a. P-TsOH, EG, C₆H₆; b. JONES REAG.; c. ETHANEDITHIOL, BF₃·ET₂O, MeOH.

saturated one as it is the case in tricyclic enedione 103. The use of ethylene glycol to form a 1,3-dioxolane group lead to a mixture of di- and mono-ketal. However, the use of the thio analog 1,2-ethanedithiol, in the presence of boron trifluoride etherate in anhydrous methanol (77) afforded a single crystalline compound which was identified as the keto-thioketal 153 (Scheme XXXVIIIb) on the basis of its spectroscopic properties. The high resolution mass spectrum provided the information about the molecular weight, showing a molecular ion at m/z 333.1243 for $C_{18}H_{23}NOS_2$ (theor. 333.1222). The disappearance of the UV absorption band at 238 nm and of the IR absorption band at 1675 cm^{-1} were evidence that thioketalization occurred at the desired site, that is, the α,β -unsaturated carbonyl group of the E ring. The ^1H - and ^{13}C -NMR spectra were also in agreement with structure 153.

The first functionalized synthon chosen as a precursor for rings A and B was the homobenzylic bromide 154. It possesses all of the necessary carbon atoms (with the exception of the methyl substituents) required for the preparation of pentacyclic or tetracyclic species by coupling with intermediates 153 and 136 respectively. The preparation of 154 was readily accomplished starting with

(m-methoxyphenyl)-acetic acid (155) (Scheme XXXIX). Lithium aluminium hydride reduction to the primary alcohol 156 was followed by nucleophilic displacement of the alcohol using PBr_3 to afford the bromide 154 in 71% overall yield.

In the first approach, we studied the use of 154 as a nucleophile. This was borne out of the fact that a complementary electrophilic centre was readily available, and adequately situated, in both of the two intermediates to be coupled with bromide 154. The natural polarity of the carbonyl group makes it an attractive electrophilic centre, and therefore the C_1 -carbonyl function in 155 and 157 (obtained by oxidation of 136, Scheme XXXVII) should prove effective for this first approach. The most trivial methodology for the coupling of a ketone functionality with halides is the conversion of the latter into an organomagnesium reagent, and we therefore investigated the preparation of the Grignard reagent 158 in satisfactory yields.

The use of classical conditions for the preparation of Grignard reagents, that is, using iodine, 1,2-dibromoethane or methyl iodide as initiators (in ether or THF) proved to be inadequate for the formation of 158 where a 10% maximum

a LAH, Et_2O ; b PBr_3 ; c MgBr_2 , POTASSIUM, THF

yield was obtained as determined by the titration method of Gilman et al. (78). Similar results were obtained from the iodo derivative which was prepared by displacement of the bromide with sodium iodide in refluxing, 2-butanone. We then turned to more elaborate methods of activation.

Rieke and Bales (79) prepared in high yields Grignard reagent from "super-activated" magnesium, formed by chemical reduction of magnesium bromide with potassium metal in refluxing THF as shown in equation 1:

The magnesium thus formed had the appearance of a fine black atomic powder. Addition of the bromide 154 to this suspension lead rapidly to the formation of 158 in 80% yield as determined by Gilman's titration.

The activity of the organomagnesium formed was checked by reacting it with cyclohexanone where the addition product 1-[2-(3-methoxyphenyl)-ethyl] cyclohexanol was isolated in 80% yield. With the preparation of 158 in satisfactory

yield in hand we set about to attempt addition on the two substrates 153 and 157 (Scheme XL). Thus, upon addition of the substrate to the suspension of super-activated Grignard reagent a new spot appeared when the reaction was monitored by TLC. In the best cases, the tertiary alcohols 159 and 160 could be isolated only with disappointing 15% and 19% yields respectively; in each case however the starting ketone was recovered in approximately 60% yield which then gives an effective yield of 50% for the tertiary alcohol. These low yields of addition could be explained by two complementary factors. First, each starting substrate bears two adjacent quaternary carbon atoms in the vicinity of the carbonyl group which undoubtedly brings about some steric hindrance to the approach of the nucleophilic reagent. Secondly, it is well known that Grignard reagents while being highly nucleophilic in character are also effective bases. In consequence, in the case of a sterically congested carbonyl group with α -hydrogen atoms, competition between addition and enolization would occur. In those cases where enolization predominates, the generation of the intermediate enolate 162 would lead mainly to the recovery of the starting ketone by protonation at the quenching stage. It seems quite likely that this situation occurs for both of our substrates 153 and 157.

SCHEME XL

119

R = OMe

Dehydration of the tertiary alcohol 160 with thionyl chloride in pyridine lead quantitatively to the olefin 161. Due to the small amount of alcohol 159 available, this last step could not be done but it is believed that the reaction should also lead to the expected product 163 in high yield.

The low overall yield obtained in these last two steps prompted us to investigate alternative ways to the formation of olefins 161 and 163. For instance, the bromide 154 was treated with triphenylphosphine to afford the corresponding phosphonium bromide which upon treatment with n-butyl lithium gave an orange solution of the phosphorane 164 (Scheme XLI); however addition of this solution to either 153 or 157 led to a quantitative recovery of the starting ketone even under forcing conditions (prolonged reflux in THF or benzene).

a PPh_3 ; b N-BuLi ; c 153 OR 157, THF, REFLUX.

Similar results were obtained from the addition of the organolithium derivative of bromide 154 (obtained by reacting 154 with either lithium metal or by halogen-metal exchange using two equivalents of tert-butyl lithium).

From these unsuccessful results it appears that the use of bromide 154 as a nucleophilic reagent suffers from severe steric interactions due in part to the bulkiness of the attacking species and on the congestion in the vicinity of the reactive site for both substrates. Therefore in order to attenuate these unfavorable interactions the only solution rested on the decrease of the bulkiness of the nucleophile. This however implied a substantial modification of the synthetic strategy as outlined here.

Recently, Corey et al. (80) reported that the use of β -nitro- α,β -unsaturated ketones such as 165 provided an effective way of reversing the normal way of cycloaddition of the corresponding α,β -enones (Scheme XLII). Further, the removal of the nitro group in the intermediate cycloadduct 166 is easily effected and an α,β -enone is produced. We have considered using this method to generate simultaneously the A and B rings by a cycloaddition using 165 as dienophile (Scheme XLIII). The diene system could be derived from ketonic substrates by Grignard addition of vinyl magnesium bromide which should prove a better reagent than 158 due to its reduced size, followed by dehydration. This particular strategy however requires that the future C₉-methyl group be introduced prior to the Grignard reaction. Since mono-alkylation of ketone is easily accessible through various methods, this last step should not present any particular problems. The Diels-Alder reaction between 165 and the diene substrate would provide after dehydronitration the dienone system 167 resulting from the dominant directing influence of the nitro-group. This system then possesses the necessary functionalities for further elaboration to the A and B rings of the target molecule.

SCHEME XLII

SCHEME XLIII

Reaction of ketones 153 and 157 with bases such as potassium tert-butoxide or lithium diisopropylamide (LDA), followed by addition of methyl iodide, led to the formation of mixtures containing various amounts of mono-, di- or non-alkylated products, depending upon the reaction conditions. The use of 1 equivalent of potassium hydride (81a) in anhydrous THF however afforded mainly the mono-methylated products 168 and 169 (Scheme XLIV), accompanied by small amounts of the corresponding dimethylated products. The structures 168 and 169 were confirmed by spectroscopic methods, particularly by ^1H -NMR spectrum where a new methyl doublet appeared around 1.1 ppm. The equatorial configuration of the new methyl group was assigned after quantitative recovery of the product when placed in equilibration conditions using sodium methoxide in methanol. Thus, it appears that alkylation of the intermediate potassium enolate by methyl iodide leads in these reaction conditions to the thermodynamically more stable product. The reaction of ketones 153 and 157 with lithium N,N,-bis(trimethylsilyl)-amide (LHMDS) in THF solutions containing 1.5 equivalents of hexamethylphosphoramide (HMPA) (81b), followed by addition of methyl iodide, also afforded a major product in excellent yields (90%) but not identical with the previous

^a KH, THF; ^b MeI; ^c HMDS, N-BuLi, HMPA, THF; ^d NaOMe, MeOH.

compounds. The presence of a new methyl doublet in the ^1H -NMR spectra suggested that the products were also mono methylated. Furthermore, the rapid and quantitative transformation of these products into 168 and 169 upon reaction with sodium methoxide indicated that the kinetic products 170 and 171 had been formed under these conditions. It should be noted here that the configuration of this new methyl group is of no importance since in this approach an unsaturation will be introduced at the carbon bearing this methyl group at a later stage.

With an efficient method of alkylation in hand, we next turned to the introduction of the vinyl group by means of a Grignard addition of vinyl magnesium bromide on the carbonyl of our substrates. The reaction of ketone 169 with an excess of Grignard reagent afforded a mixture of the tertiary allylic alcohol (undetermined configuration) and the starting ketone (Scheme XLV). Since the two products had identical mobilities on silica gel in various solvents, the mixture was treated directly with thionyl chloride and pyridine in dichloromethane. After purification of the resulting mixture the diene 173 was isolated in 40% yield, (non-optimized), calculated from the starting ketone 169. The starting ketone was recovered in 50% yield thus giving

^a $\text{CH}_2=\text{CHMgBr}$, THF; ^b SOCl_2 , PYR., CH_2Cl_2 .

in 90% effective yield of diene 173. Here again, the high yield of unreacted 169 can be attributed to a competitive enolization reaction. However, the increased yield obtained here when compared to the use of the Grignard reagent 158 supports our earlier assumption regarding the steric congestion of the carbonyl group. At the time of writing this thesis, only preliminary results had been obtained for the same reaction with ketone 168, and they suggest a similar behaviour. Continuing studies in these laboratories are now concerned with the cycloaddition reaction with the β -nitro- α,β -enone 165 as well as the optimization of the conditions of previously discussed reactions.

F. ATTEMPTED PREPARATION OF TRICYCLIC SUBSTRATES VIA DIRECT ALKYLATION OF β -CYANO-SILYL ENOL ETHERS.

We showed earlier that the chiral induction at the future C₁₄ position using a bisannulating reagent could be achieved only in moderate yield (see Section B.2). However, the preparation of simple bicyclic system devoid of side chains in high optical yield (>90%) is now common place in organic synthesis. We reasoned that an alternative way of preparing tricyclic substrates more readily would come from a direct trapping of the regiochemically pure enolate 174 of a bicyclic precursor as indicated in Scheme XLVI. Such a strategy would greatly reduce the number of steps to tricyclic substrates as well as provide high optical yield. Furthermore, the generally difficult problem of regiospecific generation of a particular enolate would be readily overcome by applying the trimethylsilylcyanation procedure used earlier in our studies to provide a β -cyanosilylenol ether. The usefulness of such silyl enol ether for the generation of various enolates has been recently reviewed (82).

At the outset it appeared to us that the most straightforward route to the tricyclic species would

involve trapping of the enolate with a Michael acceptor such as methyl vinyl ketone or one of its equivalent so as to afford rapidly the 3-oxo-butyl side chain, which could be readily cyclized by the intramolecular acid-catalyzed aldol condensation method developed earlier in our studies (vide supra). However, the choice of an appropriate Michael acceptor (and the reaction conditions thereupon) becomes critical in those cases where the use of a potentially regionunstable enolate is involved (83). We anticipated that such would be the case with a substrate of type 174 by analogy to the work of Stork et al. (84) who showed that the enolate 175 of the parent bicyclic system is less stable than its counterpart 176 by about 3 Kcal/mole. Thus, as a direct consequence of the reversibility of the Michael reaction, the potential problem of enolate equilibration would surface.

SCHEME XLVII

132

^a Et_3SiCl ; ^b Br_2 , THEN Et_2NH ; ^c Mg , THEN MECHO ; ^d JONES REAG,

The use of α -trialkylsilyl vinyl ketones as suitable Michael acceptors for the regiospecific trapping of kinetically generated enolates has been reported to be highly effective (83, 85), due presumably to the ability of Si to provide additional stabilization of the intermediate enolate by d-p- π overlap. We decided to study this class of Michael acceptor in our initial efforts. The preparation of α -trialkylsilyl vinyl ketones can be readily accomplished via trialkylvinylsilanes (86). Scheme XLVII shows the preparation of 3-triethylsilyl-3-buten-2-one (177) in 33% overall yield starting from vinyl magnesium bromide.

The bicyclic precursor was prepared as described earlier (see Scheme XXVII). The hydroxy-enone 127 was first converted to its tert-butyldimethylsilyl (TBDMS) ether by reaction with tert-butyldimethylsilyl chloride in the presence of imidazole (Scheme XLVIII), followed by stereospecific introduction of the nitrile functionality using trimethylsilylcyanide and triethylaluminum in toluene as described earlier. The resulting β -cyanosilylenol ether 178 was used immediately after purification on a short florisil column in order to avoid excessive contamination from the cyano-ketone 179 formed by partial hydrolysis.

In our first attempts, the regiochemically pure enolate was obtained by treatment of 178 with MeLi in anhydrous DME. Trapping at $-78^{\circ} \rightarrow 0^{\circ}$ with 177 afforded a complex mixture containing three major products, one of which was readily identified as ketone 179 by TLC comparison with an authentic sample.

Clean separation of the constituents of this mixture proved to be a rather difficult task since they all exhibited very close mobilities on silica gel. We therefore subjected the crude mixture to the action of sodium methoxide in methanol in order to effect intramolecular aldol condensation. This procedure afforded a solid residue which upon recrystallization in ethyl acetate gave a crystalline mixture of two closely related compounds in 18% overall yield from 178. The major component (95%) was identified as the linear tricyclic lactam 180 on the basis of

^a TBDMSCL, IMIDAZOLE; ^b TMSCN, Et_3Al , TOLUENE; ^c MeLi, DME OR Et_2O ;

^d 177; ^e NaOMe, MeOH. ^f JONES REAG.

spectroscopic and chemical data. The electron-impact (EI) mass spectrum did not show the molecular ion but the parent peak at m/z 334 was indicative of the loss of the labile tert-butyl group ($M^+ - 57$). The molecular ion at m/z 392 ($M^+ + 1$) was observed in the "chemical-ionization (CI)" mass spectrum. The ^{13}C -NMR spectrum showed a chemical-shift pattern similar to the one predicted from theoretical calculations (70). Particularly revealing was the signal due to the C_{4a} methine carbon atom which appeared at 36.7 ppm. (Here the multiplicity of the various resonances was determined using the spin-echo technique). The corresponding methine carbon in angularly fused tricyclic species such as 142 appears at much lower field (~52 ppm) (70). In a complementary way, the presence of two low-field methylene carbons at 46.9 and 50.0 ppm corresponding to C_9 and C_1 respectively further suggest the linear system. As a final verification, the TBDMS ether in 180 was cleaved (acetic acid/THF) and the resulting alcohol oxidized to provide the diketo-lactam 182 which showed a different mobility by TLC when compared to 142.

The minor component of the mixture was tentatively assigned structure 181 on the basis of IR and TLC comparison with 180. The minute quantities available did not permit a more detailed characterization.

Modifications of the reaction conditions to less Lewis-basic solvents such as ether (83) or the use of larger excess of Michael acceptors did not alter significantly the outcome of the reaction, where again the angularly fused tricyclic system was isolated in very small yield.

Several factors can be invoked to account for the failure to trap the regiospecifically generated enolate in these cases. The presence of the two axially oriented substituents at the ring junction must shield the approach of the electrophile from either face of the enolate, thus making the reaction at the desired site a very difficult process, and perhaps reversible. As the reaction proceeds to form 183 (Scheme XLIX), the free carbonyl group which is formed must provide a proton source sufficient to effect fast equilibration of 178 to the isomeric enolate 184. Once formed, conjugate addition of 177 to 184 proceeds more easily thus accounting for the larger amount of linear tricyclic system.

178a

R = TBDMS

We have also examined the same reaction but this time employing the titanium enolate generated by cleavage of the silyl enol ether with titanium tetrachloride in the presence of titanium tetra-isopropoxide (87-89). These enolates have been shown to add to Michael acceptors or their corresponding acetals to afford in very mild conditions the desired 1,5-dicarbonyl system. We had hoped, in this case that equilibration might be significantly reduced considering the much less basic conditions used. However, when 178 was treated at -78° in dichloromethane with $\text{TiCl}_4 \cdot \text{Ti}(\text{iPrO})_4$ followed by dropwise addition of the Michael acceptor (Scheme L), the major product was again identified as ketone 179 in all three cases. The use of the α -trialkylsilyl ketone 177 did not afford any alkylated product thus showing its lower reactivity (83) when compared to methyl vinyl ketone or its ethylene acetal derivative (90). In these last two cases, the linear tricyclic system was obtained in 25% and 30% respectively after treatment of the reaction mixture with sodium methoxide.

From these disappointing results it is possible to draw some conclusions regarding the reactivity of the bicyclic system **178** that might be considered in future studies. First the generally high yield of ketone **179** (>50%) obtained with both the lithium and titanium enolates suggests a rather low reactivity (for both kinetic and thermodynamic enolates) towards Michael acceptors, undoubtedly as a direct consequence of the proximity of two quaternary centers at the ring junction, combined with the reversibility of the Michael reaction. Furthermore, the very low yield of angularly fused tricyclic species demonstrates the strong

proclivity of the system to undergo fast enolate equilibration, even under mild conditions, which makes the trapping of the desired kinetic enolate a most difficult process. A possible solution to some of these problems would be the use of alkylating agents which could be readily converted to the 3-oxo-butyl side chain. The generally lower stereochemical requirements for alkylation (46) and the irreversibility of the process should contribute to effectively trap the desired enolate. Duhamel *et al.* (91) have recently reported the use of the vinyllogous hemiacetal 186 as an efficient alkylating agent for the trapping of kinetic enolates obtained from silylenol ethers in the presence of Lewis acid catalysts. The mild conditions of the reaction should prove adequate for use with the bicyclic system 178. Moreover, the 3-oxo-butyl side chain is formed readily in the reaction mixture.

186 (R = Me, Et)

PART II

An approach to the synthesis of friedelin (5) via a

A. SYNTHETIC STRATEGY

Earlier studies in these laboratories (52b) have demonstrated the possibility of obtaining the tetracyclic intermediate 187 by a series of three successive Robinson annulations (Scheme LI), employing the efficient method developed by Stork et al. (84-86). This method involves the reductive alkylation of an α, β -enone (Scheme LII) followed by ring closure by means of an aldol condensation on the 1,5-dicarbonyl system produced. The use of trialkylsilylvinyl ketones allows for the trapping of the kinetically generated enolate and the α -trialkylsilyl ketone produced can be readily converted to the enone with concomitant loss of the trialkylsilyl group. This highly convergent strategy certainly represents one of the more rapid ways to obtain the pentacyclic system. The elaboration of 187 to the pentacyclic system of friedelin (5) could be envisaged by the method developed in the previous sections.

SCHEME LI

143

However, a major obstacle in this approach was one of efficiency of trapping the lithium enolate with the trimethylsilylvinyl ketones, particularly in the reaction of tricyclic species 188 with the bis-annulating enone 189 where only low yield (<30%) of 187 were obtained in optimized conditions (Scheme LIII) (52b). Similarly, direct alkylation of the saturated ketone 190 via its highly reactive potassium enolate afforded only 25% yield of the tetracyclic species.

Ganem (86) was able to subject the bisannulating agent 191 to Michael addition using potassium tert-butoxide as base in high yield. This suggests that the trimethylsilyl enone 189 might not be as stable to such vigorous conditions as the triethylsilyl analog. We then decided to reinvestigate this approach using this time the triethylsilyl enones.

191

B. PREPARATION OF TRICYCLIC ENONE 188 AND BIS-ANNULATING REAGENT 194

The tricyclic enone 188 was prepared as shown in Scheme LIVa. The bicyclic enone 132, obtained as presented earlier (see Scheme XXVII and XXIX), was first treated with lithium in ammonia in the presence of tert-butanol to generate in situ the lithium enolate. Trapping with triethylsilylvinyl ketone 193 followed by base-catalyzed aldol condensation of the resulting diketone afforded the enone 188 in 50% overall yield, along with 25% of the saturated ketone 192. An alternate two steps procedure was also investigated. Thus, the bicyclic enone 132 was reduced to the saturated ketone 192 using lithium and ammonia (Birch reduction). The potassium enolate of ketone 192 was then alkylated with 193 and upon treatment with base furnished the enone 188 in 47% overall yield. Although this last procedure doesn't lead to improved yield of 188, the easier separation and purification steps made it the method of choice.

The bis-annelating reagent 194 (Scheme LIVb) was prepared in high yield by addition of aldehyde 110 (see Scheme XXII) to the Grignard reagent of 1-bromo-1-

a $\text{Li}/\text{NH}_3, \text{T-BuOH}$; b KOH, MeOH ; c KOBU ; d Mg, THF ; e PCC or $\text{PDC}, \text{CH}_2\text{Cl}_2$.

triethylsilylethylene (Scheme XLVII), followed by PCC or PDC oxidation of the resulting allylic alcohol.

With both enone 188 and the bis-annelating reagent 194 in hand, we set about to study their reaction. Because of the generally more difficult separation involved in the one-step reductive alkylation procedure and considering the higher reactivity of the potassium enolates over lithium enolates, we opted for the two-step procedure involving the generation of the saturated ketone. Birch reduction of enone 188 gave ketone 190 in moderate yield (Scheme LV).

SCHEME LV

^a Li/NH₃; ^b KOT-Bu, THEN 194; ^c KOH, MeOH.

The potassium enolate of ketone 190 was generated from reaction with potassium tert-butoxide in tert-butanol. Trapping of that enolate with silylated enone 194 afforded low yields of the tetracyclic enone 187 after the usual base-catalyzed intramolecular aldol condensation. The major product of the reaction was the unreacted ketone 190 (50%). Various changes in reaction conditions did not improve on the yields.

These results were very disappointing since we had placed high hopes in the improvement of the yield for this crucial step. The overall results further suggest that the use of triethylsilylated enones as trapping agent do not significantly improve over the use of the trimethylsilylated ones in highly congested molecules such as enone 188.

CONCLUSION

One of the most important aspect of any synthetic work is certainly to elucidate the many factors that delimit the chemistry of a given class of compounds. Although the total synthesis of the target molecule has not been achieved in this work, it is felt that the various routes investigated have contributed to increase the knowledge of those factors which influence the chemistry of compounds related to the terpene skeleton.

Contributions to knowledge and suggestions for future work.

It is convenient at this point to summarize some of the contributions to knowledge which could arise from this work as well as to provide suggestions for future work.

Part I

Reinvestigation of the preparation of optically active compound 106 showed that only moderate chiral induction could be obtained when chiral amino-acids were used as catalysts.

106

The newly reported trimethylsilylcyanation of α,β -enone has been explored in great details. These studies have shown that when the reaction is applied to substrates such as 127, 132 and 135, all possessing an oxygen functionality at C₅, a single stereoisomer is obtained in

127 132 135

the conjugated-addition. In all cases, the product bearing the axial cyano group (trans ring junction) was obtained in very good yield, thus making this method a good alternative to the kinetically controlled Nagata's hydrocyanation. The

failure to detect any of the thermodynamically generated cis-adduct, which was observed in parent systems (66, 67), suggests that the oxygen-functionality plays a non-negligible role in the mechanism of the reaction. Further studies will be necessary in order to determine the type of interactions involved here.

In an attempt to effect a base catalyzed intramolecular aldol condensation, lactam 142 was isolated in very good yield. We suggested its formation by a novel

intramolecular rearrangement which involved the conversion of a cyano group to a lactam moiety. Further studies will be necessary here to determine the scope of this new transformation in analogous systems and also to investigate its applicability to the synthesis of certain alkaloids.

The synthesis of intermediates 102 and 103 and their reactivity towards further elaboration to pentacyclic systems have been described. In both cases steric factors have been shown to limit the use of alkylating agents for the introduction of ring A fragments. Among other possible solutions not studied in this work, the use of the highly reactive lithium acetylide 195 should be considered in future studies since the extended conjugation between the aromatic ring and the triple bond should minimize the steric hindrance associated with the more flexible synthons studied in this work.

The preparation of diene 173 as a possible precursor for the formation of the pentacyclic system has been described. Preliminary results suggested that the tricyclic diene system 196 can be obtained by a similar sequence of reactions. Their reactivities towards activated dienophiles are under continuing investigations in these laboratories.

The preparation of tricyclic substrates by direct trapping of kinetically generated enolate 178a

using α -silylated vinyl ketones proved unsuccessful. Recent reports on the reactivity of methyl vinyl ketone equivalents, such as 186

186 (R = Me, Et)

suggest that they can efficiently trap kinetically generated enolates under very mild conditions. The use of such reagents would have the obvious advantage of eliminating the reversibility problem associated with the Michael reaction. Alternate solutions would include the

trapping of the enolates with reactive alkylating agent such as carbon dioxide to generate a 1,3-dicarbonyl system such as 197 which might be further elaborated the tricyclic system via the exocyclic enone 198.

Part II

Continuing studies on the ABC + E ring assemblage prove unsuccessful regarding the use of triethylsilyl-enones as more effective trapping agents than their trimethyl counterparts. Again here, future work should concentrate on the use of the generally more reactive "alkylating" agents which obviate the reversibility problem of the Michael reaction.

EXPERIMENTALGeneral

All melting points were determined on a Buchi SMP-20 and are corrected. IR spectra were recorded on a Perkin-Elmer 237-B grating spectrophotometer. Proton-nuclear magnetic resonances spectra were obtained on a Varian T-60 or Varian EM-360 for routine analysis. High resolution carbon-13 and proton-NMR spectra were recorded on a Varian instrument operating at 200 MHz for proton and 75 MHz for carbon-13. Chemical shifts are reported in ppm using tetramethylsilane as an internal standard. Only well-resolved areas of spectra were analyzed in first approximation as first-order systems. The following symbols are used: s = singlet, d = doublet, dd = doublet of doublet, br. s. = broad singlet, m = multiplet, t = triplet.

Mass spectra were obtained on a VG 7070-E instrument (from VG Analytical), at the Ottawa-Carleton Mass Spectrometry Centre, University of Ottawa. Optical rotations were measured on a Perkin-Elmer 141 polarimeter using the sodium D line. UV spectra were recorded on a

Perkin-Elmer 202 spectrophotometer. Elemental analysis were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan and Guelph Chemical Laboratories Ltd., Guelph, Ontario.

All reactions and chromatograms were routinely monitored by analytical thin-layer chromatography (TLC) (Merck-50 PF-254 plates). Spots were developed by exposing to iodine vapour, or by spraying with ceric ammonium nitrate solution and heating. Silica gel (Davison Chemical Co., grade 923, 100-200 mesh) was used for column chromatography. HPLC was performed using a Waters Prep. 500 High Performance Liquid Chromatograph.

Dry solvents were obtained by distillation over lithium aluminium hydride (dimethoxyethane and tetrahydrofuran), or sodium (benzene and toluene). "Anhydrous ether" was obtained from Mallinkrodt Canada Ltd. and redistilled over sodium.

In the following, when mention is made of "treatment in the usual way" it indicates that the solution was dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure.

PART I(±)-5-benzyloxyhexene (101)

A solution of 5-hexen-2-one (107) (Aldrich Chemical Co.) (26 g, 0.264 mole in 200 mL of ether) was added dropwise to a suspension of lithium aluminum hydride (5 g, 0.132 mole) in 200 mL of anhydrous ether. After 90 minutes of stirring at room temperature, the reaction is quenched by the successive addition of 5 mL of distilled H₂O, 5 mL of 15% NaOH and 15 mL of H₂O. The white inorganic precipitate is then filtered through celite and the resulting solution is evaporated under reduced pressure (35°C) to afford 25.4 g of 5-hexen-2-ol (108) (95%) as a colorless liquid that was used without any further purification in the next step.

¹H-NMR (CDCl₃) 1.20 (d, 3H, d = 7Hz, Me); 1.38-2.45 (m, 4H); 2.98 (s, 1H, OH); 3.80 (m, 1H, CHOH); 4.90-5.35 (m, 2H, C-6); 5.60-6.30 (m, 1H, CH=CH₂).

ν_{max} IR: 3480 cm⁻¹ (broad)

A solution of 5-hexen-2-ol (25 g, 0.250 mole) in dry THF (100 mL) was slowly added to a suspension of NaH (6.6 g, ✓

0.275 mole) in 250 mL of dry THF and the solution was stirred at room temperature for 45 minutes. After cooling at 0°C, tetra-butyl ammonium iodide (0.0250) was added, followed by dropwise addition of benzyl bromide (51.3 g, 0.300 mole). The solution was then allowed to warm up to room temperature. After stirring at that temperature for 1 hr, the excess NaH is then neutralized by addition of methanol (10 mL) and the solution stirred for an additional 30 minutes. The suspension was diluted with ether (300 mL) and water (300 mL). The aqueous phase was separated and reextracted with ether (2 X 300 mL). The combined ethereals were then successively washed with water (3 X 200 mL), NaCl saturated solution (3 X 200 mL) and treated in the usual way to afford after distillation under reduced pressure 33.2 g. (70%) of benzylic ether 109.

b.p.: 92-95°C / 0.05 mm Hg

¹H-NMR: see Appendix 1

(±)-5-benzyloxy-hexanal (110)

The benzyl ether 109 (50 g, 0.263 mole) was added dropwise, under an inert atmosphere of Argon, to a cooled (0°C) solution of borane-dimethyl sulfide complex (9.4 mL,

0.0922 mole) in anhydrous dichloromethane (200 mL). After stirring for 1 hr at that temperature, the solution was evaporated under reduced pressure, and anhydrous dichloromethane (100 mL) was added to the residue. The resulting solution was then transferred, using a double-tip needle, into a mechanically stirred suspension of pyridinium chlorochromate (170.1 g, 0.790 mole) in dichloromethane (450 mL) over a 90 minutes period; the thick brown suspension was then stirred for a period of 24 hrs. An equivalent volume of ether was added and the precipitate was filtered through a thick pad of florisil. The filtrate was evaporated and the residue was distilled under reduced pressure to afford 32.1 g of aldehyde 110:

b.p.: 100-105 °C / 0.05 mm HG

¹H-NMR: 1.20 (d, 3H, $J = 7$ Hz, CH_3); 4.55 (q, 2H, CH_2 phenyl); 7.44 (s, 5H, phenyl); 9.8 (s, 1H, CHO)

ν_{max} IR (Film): 1715 cm^{-1} (C=O)

MS (m/z): 206 (M^+ ; less 1), 91 (C_7H_7^+ , 100)

(±)-7-benzyloxy-oct-1-en-3-one (105)

To a cooled (0°C) solution of vinyl magnesium bromide (0.221 mole) in THF under Argon was added a solution of

aldehyde 110 (30.4 g, 0.147 mole) in dry THF (200 mL). The solution was allowed to warm up to room temperature and stirred for an additional 90 minutes. Saturated NH_4Cl solution (50 mL) was then added slowly, followed by the minimum amount of water to dissolve the inorganic salts. The aqueous layer was separated and extracted with ether (2 X 200 mL). The combined ethereal extracts were washed with water (2 X 100 mL), brine (2 X 100 mL) and treated in the usual way to afford 34.1 g (99%) of crude allylic alcohol 111 used as such in the next step.

$^1\text{H-NMR}$: 1.2 (d, 3H, $J = 6 \text{ Hz}$, CH_3); 4.9-5.4 (m, 2H, $\text{CH}_2=\text{C}$); 5.6-6.2 (m, 1H, $-\text{CH}=\text{C}$)

ν_{max} IR (Film): 3400 cm^{-1} (broad, OH), 1625 cm^{-1} (C=C).

The allylic alcohol 111 (34.0 g, 0.145 mole) dissolved in 300 mL of ether was cooled to 0°C and 68.1 mL of Jones Reagent (2.70M, 0.184 mole) was added dropwise over a 30 minutes period. The heterogeneous mixture is stirred at that temperature for an additional 15 minutes prior to the addition of isopropanol (30 mL). The mixture was stirred until the appearance of a blue color. Water (30 mL) is added aqueous layer is extracted with ether (3 X 100 mL).

Successive washings with saturated NaHCO_3 solution (4 X 100 mL), brine (2 X 100 mL) and treatment in the usual way afforded 32.9 g of crude enone 105 as a yellow thick syrup. Separation by preparative HPLC using 15% ethyl acetate in hexane gave 17.1 g (50%) of pure 105 as a thick colorless syrup: $^1\text{H-NMR}$: see Appendix

IR (Film): 1665 cm^{-1} (C=O); 1620 cm^{-1} (C=C)

MS (m/z, %): M^+ (undetected), 126 (10), 91 (100)

Elementary Analysis: for $\text{C}_{15}\text{H}_{20}\text{O}_2$ calc. C = 77.58, H = 8.62; exp. C = 77.69, H = 8.39

(+)-2-(7-benzyloxy-3-oxo-octyl)-2-methyl-1,3-cyclohexane-dione (115)

A suspension of 2-methyl-1,3-cyclohexandione (19.00 g, 0.151 mole) and sodium hydride (1.82 g, 0.076 mole) in anhydrous DME (500 mL) was stirred at room temperature for 15 minutes under Argon. Enone 105 (24.52 g, 0.108 mole) in dry DME (150 mL) was then added and the mixture was refluxed for 1 hr after which time the solution was cooled to room temperature and a saturated Na_2SO_4 solution (500 mL) was added slowly. The aqueous layer was extracted with chloroform (3 X 300 mL) and the combined organic layers were washed with saturated NaCl solution and treated in the usual

way to afford 37.6 g (97%) of crude 115. Purification by HPLC (37% EtOAc /Pet. ether) gave 34.0 g (90.0%) of pure triketone 115 as a thick colorless liquid.

¹H-NMR: 1.1 (d, 3H, J = 7 Hz, C-7 Me); 1.2 (s, 3H, C-2 Me); 4.5 (dd, 2H, CH₂ phenyl); 7.3 (s, 5H, phenyl)

$\nu_{\max}$ IR (Film): 1695-1720 cm⁻¹ (C=O)

MS (%): M⁺ (undetected), 267 (4), 252 (15), 139 (20), 127 (45), 109 (10), 91 (100), 55 (22)

(+)-1-(3-benzylloxybutyl)-4a β -methyl-4,4a,7,8-tetrahydro-naphtalen-2(3H),5(6H)-dione (106)

The triketone 115 (20.6 g, 57.5 mmole) was dissolved in mL of acetonitrile and the solution was poured into a round bottom flask fitted with a magnetic stirrer and a reflux condenser. L-phenylalanine (11.4 g, 69.0 mmole) was then added to the stirring solution, followed by perchloric acid (4.5 g of 60% aqueous solution). The heterogeneous solution was then refluxed for 72 hrs by which time no starting material could be detected by TLC. After evaporation of the solvent under reduced pressure, a saturated NaCl solution (250 mL) and chloroform (250 mL) were added. The aqueous layer was separated and extracted with chloroform (2 X 250 mL). The organics were combined,

washed with saturated NaCl solution (300 mL) and treated in the usual way to afford, after purification by HPLC (25% EtOAc/hexane), 15.5 g (81.5%) of enone 106 as a thick colorless liquid.

$$[\alpha]_D = + 31.4^\circ \text{ (c = 2.5, MeOH)}$$

λ_{max} UV: 253 nm, ($\epsilon = 10.9 \times 10^3$) (MeOH)

$^1\text{H-NMR}$: 1.2 (d, 3H; $J = 7$ Hz, C-4' Me); 1.4 (s, 3H, C-4a Me); 4.6 (d, 2H, CH_2 phenyl); 7.4 (s, 5H, phenyl)

ν_{max} IR (Film): 1665 cm^{-1} (α, β -unsaturated carbonyl)
1705 cm^{-1} (saturated carbonyl)

MS (%): 340 (5, M^+), 234 (10), 91 (100)

Elementary Analysis: for $\text{C}_{22}\text{H}_{28}\text{O}_3$ calc. C = 77.64, H = 8.23, exp. C = 76.96, H = 8.39

(+)-1-(3-benzyloxybutyl)-5 β -hydroxy-4a β -methyl-4,4a,5,6,7,8-hexahydronaphtalen-2(3H)-one (118)

To a solution of enedione 106 (10.53 g, 30.9 mmole) in ethanol (80 mL), cooled at 0°C with an ice-water bath, was added a solution of sodium borohydride (0.39 g, 10.2 mmole) in ethanol (10 mL). After 20 minutes of stirring at 0°C , the excess hydride was destroyed by addition of acetic acid (20 mL). The solvent was evaporated under reduced pressure and the residue was taken up in chloroform (200 mL) and

successively washed with NaCl saturated solution (2 X 200 mL). After the usual treatment, the crude mixture was purified by HPLC to afford 10.0 g (95%) of pure hydroxy-enone 118 as viscous syrup.

$$[\alpha]_D = +45^\circ \quad (c = 2.15, \text{MeOH})$$

¹H-NMR: see Appendix 3

ν_{max} IR (Film): 3425 cm^{-1} (OH); 1660 cm^{-1} (C=O);
1601 cm^{-1} (C=C)

λ_{max} UV 251 nm ($\epsilon = 11.1 \times 10^3$) (MeOH)

MS (%): 342 (5, M^+), 91 (100), 55 (25)

(+)-1-(3-benzyloxybutyl)-8a α -cyano-5 β -hydroxy-4a β -methyl-perhydronaphthalen-2-one (102)

Hydroxy-enone 118 (3.90 g, 11.4 mmol) was dissolved in a mixture of anhydrous benzene (48 mL) and toluene (12 mL), followed by cooling at 0°C with an ice-water bath. A solution of diethylaluminum cyanide (40 mL, 1.2 M in benzene) was then added dropwise and the reaction was stirred at that temperature for 15 minutes, for 45 minutes at room temperature and finally refluxed for 90 minutes. The cooled solution was poured on a mixture of aqueous 1 M sodium hydroxide (20 mL) and ice-water (100 mL) and stirred

vigourously for 15 minutes. After separation of the organic phase, the aqueous layer was extracted with CHCl_3 (4 X 100 mL). The combined organics were successively washed with 1% HCl solution (2 X 50 mL), saturated sodium bicarbonate solution (2 X 50 mL) and saturated sodium chloride solution (2 X 50 mL). After the usual treatment and purification by HPLC, 3.0 g of hydroxycyano ketone 102 were obtained as a visquous colorless liquid (70%).

$$[\alpha]_D = +23.4 \quad (c = 1.0, \text{C}_6\text{H}_6)$$

$^1\text{H-NMR}$: 1.15 (s, 3H, C-4a Me), 1.22 (d, $J = 7$ Hz, C-4' Me), 3.35-3.95 (m, 3H, CH-OBn, CH-OH, OH), 4.50 (q, 2H, $\text{CH}_2\text{-Ph}$), 7.40 (s, 5H, Ph)

ν_{max} , IR (Film): 3440 cm^{-1} (OH), 2225 cm^{-1} (CN), 1710 cm^{-1} (C=O)

MS (%): 369 (1%, M^+), 282 (4), 263 (23), 262 (13), 207 (20), 107 (15), 91 (100)

Elementary Analysis: for $\text{C}_{23}\text{H}_{31}\text{NO}_3$ calc. C = 74.79, H = 8.40, N = 3.79, exp. C = 74.48, H = 8.29, N = 3.55

$^{13}\text{C-NMR}$: 208.68 (C-2), 120.87 (CN), 74.1 (C-5), 72.6 (C-3'); 128.8-127.2 (Ph)

(+)-5 β -hydroxy-4 α β -methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (127)

2-methyl-1,3-cyclohexanedione (25 g, 0.20 mole) was stirred under Argon with one pellet of KOH in anhydrous methanol (60 mL). Methyl vinyl ketone (26 g, 0.37 mole) was then added and the reaction was refluxed for 3 hrs, then cooled and the solvent removed under reduced pressure. Benzene (200 mL) was then added and 30 mL of solvent was distilled off from a Dean-Stark apparatus followed by the addition of pyrrolidine (2 mL) to the cooled solution. The mixture was then refluxed for 10 hrs with a Dean-Stark apparatus. The volume of solvent was reduced in half and ether (100 mL) was added. The solution was extracted with 5% HCL solution (2 X 50 mL), water (3 X 50 mL) and saturated sodium chloride solution (2 X 50 mL). After the usual treatment and purification by HPLC, a visquous colorless oil (24 g, 69%) was obtained and identified as enedione 125. A solution of 125 (13.7 g, 77 mmole) in ethanol (200 mL) was cooled to 0°C and sodium borohydride (0.885 g, 23 mmole) dissolved in ethanol (100 mL) was added over a period of 45 minutes. The solution was stirred for an additional 20 minutes at 0°C and glacial acetic acid (8 mL) was added dropwise. The solvent was removed under reduced pressure

and water and chloroform were added. The layers were separated and the aqueous layer was reextracted with CHCl_3 (2 X 100 mL). Successive washings of the combined organic extracts with saturated NaHCO_3 solution (2 X 50 mL), water (2 X 50 mL) and saturated sodium chloride solution (2 X 50 mL), followed by the usual treatment afforded the hydroxy-enone 127 (13.4 g, 97%) as a thick colorless oil that slowly crystallized on standing in the cold.

$^1\text{H-NMR}$ (CDCl_3): 1.19 (s, 3H, C-4a Me), 3.20-3.49 (m, 1H, CHOH), 5.70 (s, 1H, CH=C)

ν_{max} IR (Film): 3400 cm^{-1} (OH), 1680 cm^{-1} (C=O)

UV (λ): 241 nm ($\epsilon = 12.4 \times 10^3$)

(±)-5β-hydroxy-1,4aβ-dimethyl-4,4a,5,6,7,8-hexahydronaph-talen-2(3H)-one (128).

The title compound was obtained following the procedure described above, using ethyl vinyl ketone. The thick colorless oil obtained (89%) had the following spectroscopic characteristics:

$^1\text{H-NMR}$ (CDCl_3): 1.16 (s, 3H, C-4a Me), 1.76 (s, 3H, C-1 Me), 3.20-3.55 (m, 1H, CH-OH)

ν_{max} IR (Film): 3440 cm^{-1} (OH), 1675 cm^{-1} (C=O)

Trimethylsilylcyanation1. General ProceduresA. $\text{BF}_3 \cdot \text{Et}_2\text{O}$ catalyzed reaction

The α, β -unsaturated ketone (1 mmole) is placed in a 3-neck round bottom flask fitted with a condenser and an inert gas inlet. Trimethylsilylcyanide (3 mmole) is then added, followed by $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.1 mmole) and the mixture is stirred for 5 hrs at 73°C . Saturated ammonium chloride solution (2 mL) is added to the cooled solution and the mixture is stirred for 15 minutes. The reaction is then extracted with ether (2 X 5 mL) and the combined organic extracts are washed with saturated NH_4Cl solution (3 mL), saturated NaHCO_3 solution (3 mL) and brine (3 mL). The ether layer is dried over anhydrous MgSO_4 and the solvent is removed under reduced pressure with a roto-evaporator (40°C).

B. Et_3Al catalyzed reaction

The unsaturated ketone (1 mmole) dissolved in 0.5 mL of dry toluene is added dropwise to a solution of Et_3Al (2.0 mmole, 1.4 mL of 25% hexane solution) and

trimethylsilylcyanide (2.2 mmole) in 3.5 mL of dry toluene. The solution is stirred at room temperature for 20 hrs. A few drops of saturated ammonium chloride solution are then added and the solution is cooled with an ice-bath. Saturated ammonium chloride (25 mL) are then added dropwise, followed by a 15 minutes period of stirring at room temperature. The mixture is extracted with ether (3 X 40 mL) and the combined organic extracts are washed with saturated ammonium chloride (2 X 10 mL), saturated NaHCO_3 solution (2 X 10 mL) and saturated sodium chloride solution (2 X 10 mL), dried on anhydrous MgSO_4 and the solvent is removed under reduced pressure.

2. Reaction with hydroxy enone 127

Hydroxy-enone 127 (180 mg, 1 mmole) was treated according to procedure A to afford a thick yellow oil (280 mg) of a mixture that was subsequently chromatographed on a short silica gel column using 20% ethyl acetate in hexane. Three fractions were obtained and identified as follows:

F-1 (175 mg, 63%): mixture of the 1,2-adduct 129a (R = TMS) and of the 1,4-adduct 129b (R = TMS)

$^1\text{H-NMR}$: 0.08 and 0.15 (s, OTMS), 1.05 (s, C-4a Me), 4.60 (s, $\text{CH}=\text{C}$, 1,4-adduct), 5.40 (s, $\text{CH}=\text{C}$, 1,2-adduct)

IR : 2220 cm^{-1}

F-2 (31 mg, 17%): cyano-ketone 130 obtained as tiny colorless needles.

m.p. 60-63°C

$^1\text{H-NMR}$: 0.18 (s, 9H, OTMS), 1.08 (s, 3H, C-4a Me), 1.4-2.0 (m, 8H, CH_2 's), 2.15-2.35 (m, 4H, C-1 CH_2 , C-3 CH_2 , 3.65 (dd, 1H, CHOTMS)

IR (ν_{max} , CHCl_3): 2220 cm^{-1} (CN), 1715 ($\text{C}=\text{O}$)

F--3 (20 mg, 11%): mixture of the 1,2-adduct 129a (R = H) and of the 1,4-adduct 129b (R = H)

$^1\text{H-NMR}$: 0.07, 0.18 (s, OTMS), 1.05 (s, C-4a Me), 4.58 (s, $\text{CH}=\text{C}$, 1,4-adduct), 5.40 (s, $\text{CH}=\text{C}$, 1,2-adduct)

ν_{max} IR : 3440 cm^{-1} (OH), 2220 cm^{-1} (CN)

Treatment of 127 with conditions of procedure B afforded similar results.

3. (±)-2,5-bistrimethylsilyloxy-8α-cyano-4aβ-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene (131).

The 1,2-adduct 129a (R = TMS) was treated under conditions B to afford quantitatively a single product which was identified as β-cyano-silylenol ether 131:

¹H-NMR (CDCl₃): 0.09 (s, 9H, OTMS), 0.12 (s, 9H, OTMS), 0.95 (s, 3H, C-4a Me), 1.6-2.2 (m, 10H, CH₂'s), 3.65 (dd, 1H, CHOTMS), 4.60 (s, 1H, CH=C OTMS)

¹³C-NMR (CDCl₃): see Appendix 4

ν_{max} IR (Film): 2220 cm⁻¹ (CN)

4. (±)-5-(tert-butoxy)-8α-cyano-1,4aβ-dimethyl-2-trimethylsilyloxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene (133).

Hydroxy-enone 128 (25.0 g, 130 mmoles) was dissolved in anhydrous methylene chloride (200 mL) and cooled at -78°C with a dry-ice/acetone bath. Boron trifluoride etherate (12.1 g, 85 mmoles) and phosphoric acid (8.33 g, 85 mmoles) were added simultaneously through a syringe. After 30 minutes of vigorous stirring, 150 mL of isobutylene (dry ice/acetone collected) was added and the reaction was refluxed for 3 hours using a dry-ice/acetone condenser. The excess isobutylene was removed using an argon stream and the remaining solution was poured into 2N aqueous NH₄OH with

stirring. The layers were separated and the aqueous layer extracted with methylene chloride. The combined organics were washed with 2N NH_4OH , water and brine and filtered on a florisil pad with ether elution. Purification by HPLC with 5% ethyl acetate in hexane afforded 17.0 g (50%) of pure enone 132 as a visquous liquid:

$^1\text{H-NMR}$ (CDCl_3): 1.05 (s, 3H, C-4a Me), 1.2 (s, 9H, t-butyl), 1.85 (s, 3H, C-1 Me), 3.25 (dd, 1H, CHO t-Bu), 5.80 (s, 1H, $\text{HC}=\text{C}$)

ν_{max} IR (Film): 1680 cm^{-1} (C=O), 1600 (C=C)

UV : 250 nm

MS (m/z, %): 250 (M^+ , 5), 126 (100), 124 (40)

Enone 132 was trimethylsilylcyanated using conditions B to afford quantitatively the trans- β -cyano-silylenol ether 133:

$^1\text{H-NMR}$ (CDCl_3): 0.15 (s, 9H, OTMS), 0.85 (s, 3H, C-4a Me), 1.10 (s, 9H, t-Butyl), 3.45 (dd, 1H, CHO t-Bu)

$^{13}\text{C-NMR}$ (CDCl_3): see Appendix 5

IR ν_{max} (Film): 2222 cm^{-1} (CN), 1665 (C=C-OTMS)

Acid hydrolysis of 133 was effected with a dilute HCL/THF solution at room temperature for 24 hrs and gave cyano-ketone 134 as a white solid:

m.p. 73-75°C

$^1\text{H-NMR}$ (CDCl_3): 1.10 (s, 9H, t-butyl), 1.15 (s, 3H, C-1 Me), 3.55 (dd, 1H, CHO t-Bu)

$^{13}\text{C-NMR}$ (CDCl_3): see Figure 4 and Appendix 6a

MS (m/z, %): 277 (M^+ , 3), 221 ($\text{M}^+ - \text{t-BU} + \text{H}$, 7), 194 (49), 138 (44), 57 (100)

ν_{max} IR (CDCl_3): 2220 cm^{-1} (CN), 1710 cm^{-1} (C=O)

5. ($\pm$)-1-(3-benzyloxybutyl)-8 α -cyano-5 β -hydroxy-4 α β -methyl perhydronaphthalene-2-one (102). (via trimethylsilyl ether 135).

To hydroxy-enone 118 (0.7 g, 2.04 mmole) dissolved in 10 mL of dry pyridine was added successively hexamethyldisilazane (HMDS) (0.7 mL, 3.3 mmole) and trimethylsilylchloride (0.3 mL) and the mixture was stirred at room temperature for 12 hrs. The mixture was poured on ice-water and extracted with ether (3 X 10 mL). The combined organics were washed with water (5 X 10 mL), brine and dried over magnesium sulfate. Purification by HPLC afforded 670 mg of pure trimethylsilyl ether 135:

$^1\text{H-NMR}$ (GDCl_3): 0.10 (s, 9H, OTMS), 1.05 (s, 3H, C-4 α Me), 7.3 (s, 5H, Ph)

ν_{max} IR (Film): 1662 cm^{-1} (C=O), 1601 cm^{-1} (C=C)

The ether 135 was trimethylsilylcyanated according to procedure B to afford quantitatively the 1,4-adduct 152:

$^1\text{H-NMR}$ (CDCl_3): 0.10, 0.15 (s, 9H each, OTMS), 0.95 (s, 3H, C-4a Me), 4.56 (s, 2H, CH_2 Ph), 7.3 (s, 5H, Ph)

ν_{max} IR (Film): 2220 cm^{-1} (CN), 1655 cm^{-1} ($=\text{C-OTMS}$)

This product was readily hydrolyzed using a dilute HCl solutions in THF after stirring at room temperature for 12 hrs. The hydrolyzed product was obtained in 80% yield and proved identical to the previously prepared hydroxy-cyanoketone 102.

($\pm$)-5 β -tert-butoxy-8a β -cyano-1 α ,4a β -dimethyl-perhydronaph-talen-2-one (134c).

To a solution of enone 132 (0.25 g, 1 mmole) in 20 mL of dry benzene was added a solution of diethylaluminum cyanide (1.5 mL of 1.5 M in C_6H_6 , 2.25 mmole) at 0°C . The reaction was stirred for 2.5 hrs at room temperature, then poured on an ice-cooled 1M NaOH solution (10 mL). The mixture was extracted with ether (3 X 10 mL) and the combined organics were washed with water, saturated NaCl solution and dried over magnesium sulfate. Purification by HPLC afforded the crystalline cis-adduct 134c (0.2 g, 72%):

m.p. 67-68°C

¹H-NMR (CDCl₃): 1.10 (s, 9H, t-Butyl), 1.15 (s, 3H, C-1 Me), 3.55 (dd, 1H, CHO t-Bu)

¹³C-NMR (CDCl₃): see Figure 4 and Appendix 6b

$\nu_{\max}$ IR (CCl₄): 2220 cm⁻¹ (CN), 1710 cm⁻¹ (C=O)

MS (m/z, %): 277 (M⁺, 4), 221 (M⁺ - t-Bu + H, 9), 194 (55), 138 (50), 57 (100)

([±]), 1-(3-benzyloxybutyl)-8a α -cyano-2,2-ethylenedioxy-5 β -hydroxy-4a β -methyl-perhydronaphthalene (136).

To a solution of hydroxyketone 102 (2.35 g, 6.37 mmole) in benzene (100 mL) were added ethylene glycol (20 mL) and a crystal of p-toluenesulfonic acid. After 4 hrs of reflux (azeotropic distillation with a Dean-Stark trap), the reaction mixture was cooled to room temperature and a saturated NaHCO₃ solution was added. The aqueous layer was extracted with chloroform (3 X 50 mL) and the combined organics were washed with saturated NaHCO₃, brine and after the usual treatment hydroxyketal 136 (2.40 g, 91.3%) were obtained as a thick syrup.

¹H-NMR (CDCl₃): 1.0 (s, 3H, C-4a Me), 1.25 (d, 3H, J = 7Hz, C-4' Me), 3.9 (m, 4H, O-(CH₂)₂-O), 7.3 (br. s., 5H, Ph)

ν_{max} IR (Film): 3440 cm^{-1} (OH), 2220 cm^{-1} (CN)

MS (m/z, %): 413 (M^+ , 4), 398 ($\text{M}^+ - \text{CH}_3$, 1), 307 (16), 250 (13), 100 (56), 99 (100), 91 (88), 86 (89)

Attempted reduction of cyano functionality in 136.

To a solution of 136 (121 mg, 0.33 mmole) in anhydrous THF (5 mL) is added lithium aluminum hydride (100 mg, 2.62 mmoles). The heterogeneous solution is heated to reflux for three days. The solution was then cooled to room temperature and a saturated solution potassium and sodium tartrate solution (10 mL) was added. The aqueous layer was extracted with chloroform (3 X 10 mL) and the organics were combined and treated in the usual way. The residue obtained was found identical to the starting material.

Similarly hydroxy-cyanoketal 136 (121 mg, 0.33 mmole) was dissolved in dry benzene (7 mL) and dry toluene (2 mL). To the stirred solution was added dropwise a 25.8% solution of diisobutyl aluminum hydride (1.5 mL). After stirring for 18 hrs, the solution was poured into 20 mL of 10% aqueous KOH and 5 g of ice. After stirring for 15 minutes, the reaction mixture was extracted with chloroform (3 X 10 mL) and the organics were then filtered through a pad of MgSO_4 .

Concentration and removal of residual solvents under vacuum gave a product which was identical in all respects to the starting material.

(±)-8 α -cyano-4 α -methyl-1 α -(3-oxobutyl)-perhydronaphthalene-2,5-dione (138).

(a) via direct debenzylation of 102.

To the hydroxy-cyanoketone 102 (4.9 g, 13.3 mmole) in 100 mL of anhydrous ethanol were added 50 mL of cyclohexene and 1.25 g of 20% Pd(OH)₂/C. The mixture was refluxed for 2.5 hrs after which it was filtered on a florisil pad (elution with ethyl acetate). After evaporation and removal of the residual solvent under high vacuum, 3.0 g (90%) of a mixture of dihydroxy-ketone 135 and hemiketal 140 was obtained. This mixture in acetone (100 mL) was treated directly with Jones reagent (17 mL of a 2.7 M solution) at 0°C. After stirring for 3 hrs at that temperature, 20 mL of isopropanol were added and the mixture stirred for 15 minutes. Separation of the insoluble inorganic salts was followed by addition of brine and extraction of the aqueous layer with chloroform (3 X 100 mL). The combined organics were washed with saturated NaHCO₃ solution, brine, and

treated in the usual way to afford 1.5 g (50%) of triketone 138 as colorless needles (recrystallized from ethyl acetate).

m.p. 160.5-162 °C

$^1\text{H-NMR}$ (CDCl_3): see Appendix 7a

$^{13}\text{C-NMR}$ (CDCl_3): see Appendix 7b

ν_{max} IR (CDCl_3): 2220 cm^{-1} (CN), 1700 cm^{-1} (C=O)

MS (m/z , %): 275 (M^+ , 17), 260 ($\text{M}^+ - \text{CH}_3$, 2), 232 (22), 218 (18), 205 (12), 204 (13), 176 (11), 58 (24), 43 (100)

High resolution mass spectrum: found: 275.1513
($\text{C}_{16}\text{H}_{21}\text{NO}_3$); calculated: 275.1519

(b) via hydroxy-cyanoketal 136.

The hydroxy-cyanoketal 136 (1.9 g, 4.60 mmole) was debenzylated according to the transfer hydrogenolysis procedure described above (2.5:10/catalyst:substrate in weight) to afford 1.48 g (98.7%) of dihydroxy-ketal 141 as a thick colorless syrup.

$^1\text{H-NMR}$ (CDCl_3): 1.15 (s, 3H, C-4a Me), 1.30 (d, 3H, J = 7 Hz, C-4' Me), 3.8-4.2 (m, 4H, O-(CH_2)₂-O)

ν_{max} IR (Film): 3460 cm^{-1} (OH), 2220 cm^{-1} (CN)

To the dihydroxy-cyanoketal 141 (1.33 g, 4.12 mmole) dissolved in 40 mL of acetone was added, at 0°C, Jones reagent (5.3 mL of a 2.7 M solution) in three portions of 1.8 mL each at 5 minutes intervals. The mixture was stirred at 0°C for an additional 2 hrs. After work-up (see preceeding section) the diketo-cyanoketal residue (1.05 g) was dissolved in acetone (100 mL) and saturated aqueous oxalic acid solution (80 mL) was added and the mixture was refluxed for 16 hrs. The mixture was then cooled to room temperature and extracted with chloroform (2 X 100 mL). The combined organics were washed with saturated NaHCO₃ solution (2 X 100 mL), brine and treated in the usual way to afford a solid residue (0.96 g) which was recrystallized in ethyl acetate/hexane to give triketone 138 (0.79 g, 75% from 141) described above.

(±)-1,7-dioxo-10aβ-methyl-4bα-perhydropheanthrene-4aα,8aα-carbolactam (142).

To a solution of triketone 138 (63 mg, 0.23 mmole) in absolute ethanol (10 mL) was added an ethanolic sodium ethoxide solution (7 mL of 0.44 M, 3 mmole). The mixture was stirred at room temperature for 20 hrs. After evaporation of ethanol, water was added and the mixture was

extracted with chloroform (3 X 10 mL). The combined organics were washed with dilute HCl solution (5 mL), saturated NaHCO₃ solution (5 mL), brine and treated in the usual way to afford 57 mg (91%) of lactam 142 which crystallized as thick prisms from chloroform/methanol:

m.p. 245-250°C (dec.)

¹H-NMR (CDCl₃): 1.3 (s, 3H, C-4a Me), 1.6-2.8 (br. m., 17H), 7.65 (br. s, 1H, NH)

$\nu_{\max}$ IR (CDCl₃): 3210 cm⁻¹ (NH), 1700 and 1680 cm⁻¹ (C=O)

¹³C-NMR (CDCl₃): 210.1 and 212.7 (q) (C-1 and C-7), 177.9 (q), (CO-NH), 61.3 (c-8a), 56.4 (C-4a)

MS (m/z, %): 275 (M⁺, 100), 247 (44), 220 (78), 190 (25), 163 (31), 91 (28), 55 (36), 41 (49)

X-Ray crystallography: see Figures 5, 6 and 7

(±)-4a α -cyano-10a β -methyl-3,4,4a,4b,5,9,10,10a-octahydro-4b α -phenanthrene-1(2H),7(6H)-dione (103).

To a solution of triketone 138 (200 mg, 0.73 mmole) in 15 mL of dry acetonitrile were added β -alanine (130 mg, 1.46 mmole) and acetic acid (0.146 mL). The mixture was first stirred at room temperature for 3 hrs, then refluxed for 24 hrs. The reaction mixture was cooled to room temperature

and the solvent evaporated in vacuo. A saturated NaCl solution (15 mL) was then added and extracted with chloroform (4 X 15 mL). The combined organics were washed with brine and treated in the usual way to afford 190 mg of crude tricyclic enone 103. Recrystallization from ethyl acetate/hexane afforded the pure 103 as thin colorless needles (140 mg, 75%).

m.p. 178-180°C

¹H-NMR (CDCl₃): 1.38 (s, 3H, C-4a Me), 1.8-2.6 (m, 15 H), 5.95 (s, 1H, CH=C)

¹³C-NMR (CDCl₃): see Appendix 8

$\nu_{\max}$ IR (CDCl₃): 2220 cm⁻¹ (CN), 1710 cm⁻¹ (C=), 1665 cm⁻¹ (conj. C=O)

$\lambda_{\max}$ UV (MeOH): 238 nm

MS (m/z, %): 257 (M⁺, 96), 242 (M⁺ - CH₃, 16), 214 (35), 186 (40), 149 (55), 148 (41), 122 (100), 107 (),

(±)-4α-cyano-7,7-ethylenedithio-10aβ-methyl-3,4,4a,4b,5,6,7,9,10,10a-decahydro-4bα-phenanthren-1(2H)-one (153).

To the tricyclic enone 103 (160 mg, 0.623 mmole) dissolved in dry methanol (12 mL) were added ethanedithiol (107 mg, 1.13 mmole) and boron trifluoride etherate (108 mg,

3 OF/DE 3

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0.76 mmole). The reaction mixture was stirred at room temperature for 1 hr. Water (50 mL) was then added and the mixture was extracted with ethyl acetate (4 X 15 mL). The combined organics were washed with water until neutral, then brine and treated in the usual way to afford 193 mg of crude thioketal 153. Purification on a short silica gel column gave the pure 153 (168 mg, 80%) as tiny colorless needles:

$^1\text{H-NMR}$ (CDCl_3): see Appendix 9

ν_{max} IR (CDCl_3): 2215 cm^{-1} (CN), 1710 cm^{-1} (C=O)

MS (m/z , %): 333 (M^+ , 44), 305 (100), 273 (38), 150 (37), 136 (43), 123 (35), 91 (57), 85 (52), 83 (80), 61 (40)

High resolution mass spectrum: found: 333.1243

(^{18}O , $^{18}\text{H}_{23}\text{NOS}_2$): calc. 333.1223

2-(*m*-methoxyphenyl)-ethanol (156)

To a suspension of lithium aluminum hydride (4.50 g, 0.12 mole) in anhydrous THF (150 mL) was added slowly *m*-methoxyphenyl-acetic acid (25.0 g, 0.15 mole) in anhydrous THF (150 mL) and the mixture was refluxed for 20 hrs. After cooling to room temperature, water (4.5 mL), aqueous 15% NaOH solution (4.5 mL) and water (13.5 mL) were added successively. The inorganic salts were filtered off on

athick celite pad and evaporation of the filtrates afforded alcohol 156 (22.2g, 98%) as a colorless liquid.

$^1\text{H-NMR}$ (CDCl_3): 1.8 (broad, 1H, OH), 2.6-3.0 (m, 4H, CH_2 's), 3.8 (s, 3H, OMe), 6.8-7.45 (m, 4H, Ph)

ν_{max} IR (Film): 3375 cm^{-1} (OH)

1-bromo-2-(m-methoxyphenyl)-ethane (154)

To the homobenzylic alcohol 156 (22.2 g, 0.15 mole) in anhydrous THF (200 mL) cooled to 0°C , under Argon was added dropwise phosphorus tribromide (7.05 mL) in anhydrous benzene (70 mL). After stirring at 0°C for 3 hrs and at 60°C for 4 hrs, the cooled solution was poured on an ice-water mixture (200 mL). The aqueous layer was separated and extracted with benzene (3 X 100 mL). The combined organics were washed with brine (3 X 100 mL) and after the usual treatment afforded 23.5 g (73%) of bromide 154 as a colorless liquid.

$^1\text{H-NMR}$ (CDCl_3): 3.0-3.6 (m, 4H, CH_2 's), 3.9 (s, 3H, OMe), 6.85-7.5 (m, 4H, Ph)

(±)-1 α -(3-benzyloxybutyl)-8 α -cyano-2,2-ethylenedioxy-5 β -hydroxy-4 α β -methyl-perhydronaphthalene (157).

To a solution of hydroxy-cyanoketal 136 (2.19 g, 5.3 mmole) in ether (40 mL) was added, at 0°C, a solution of Jones reagent (2.35 mL of 2.70 M solution) over a period of 15 minutes. After stirring at 0°C for 30 minutes, isopropanol (10 mL) was added and the mixture was further stirred for 15 minutes. Water (50 mL) was added and the mixture was extracted with ether (3 X 50 mL). The combined ethereal layers were washed with saturated NaHCO₃ solution (3 X 100 mL), brine (3 X 100 mL) and treated in the usual way to afford, after purification by HPLC (30% ethyl acetate in hexane), the keto-cyanoketal 157 (1.4 g, 63%) (crystallized from ethyl acetate/hexane).

m.p. 96-98°C

¹H-NMR (CDCl₃): 1.2 (d, 3H, J = 6Hz, C-4' Me), 1.25 (s, 3H, C-4a Me); 3.9-4.1 (m, 4H, O-(CH₂)₂-O), 4.6 (q, 2H, CH₂ Ph), 7.4 (s, 5H, Ph)

¹³C-NMR (CDCl₃): 210.0 (C-5), 127.5-128.2-139.0 (Ph), 120.3 (CN), 109 (C-2), 75.0 (C-3'), 70 (CH₂ Ph), 65.4-64.2 (O-(CH₂)₂-O), 50.5 (C-4a and C-8a)

$\nu_{\max}$ IR (Film): 2220 cm⁻¹ (CN), 1710 cm⁻¹ (C=O)

MS (m/z , %): 411 (M^+ , 99), 320 (5), 305 (10), 99 (100), 91 (70)

Elementary analysis: found: C: 72.99, H: 7.88, N: 3.39 ($C_{25}H_{33}O_4N$), calc. C: 72.89, H: 7.98, N: 3.4

($\pm$)-1 α -(3-benzyloxybutyl)-8 α -cyano-5-[2-(*m*-methoxyphenyl)-2,2-ethylenedioxy-5-hydroxy-4a β -methyl-perhydronaphtalene (160)].

To a solution of magnesium bromide (368 mg, 2 mmoles) in anhydrous THF (8 mL) was added freshly cut potassium metal (143 mg, 3.6 mmoles) and the mixture was refluxed for 2 hrs. under Argon. Bromide 154 was then added dropwise while maintaining a constant reflux. After addition, the mixture was cooled to room temperature and stirred for 1 hr. The Grignard reagent 158 thus obtained was cooled to -78°C and a solution of ketone 157 (100 mg, 0.243 mmole) in anhydrous THF was added. After 20 hours of stirring at room temperature, the reaction mixture was cooled to 0°C and neutralized by addition of saturated NH_4Cl solution (5 mL). The solution was extracted with chloroform (3 X 10 mL) and the combined organics were successively washed with saturated NaHCO_3 solution (10 mL) and brine (2 X 10 mL). After the usual procedure and purification by column chromatography (40% ethyl acetate in hexane), the tertiary

alcohol 160 (25 mg, 20%) and starting ketone 157 (59 mg, 50%) were obtained.

¹H-NMR (CDCl₃): - see Appendix 10

ν_{max} IR (Film): 3425 cm⁻¹ (OH), 2220 cm⁻¹ (CN)

()-1α-(3-benzyloxybutyl)-8α-cyano-5-[2-(m-methoxyphenyl)-ethyl]-2,2-ethylenedioxy-4aβ-methyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene (161).

To a solution of tertiary alcohol 160 (25 mg, 0.046 mmole) in anhydrous pyridine (5 mL), cooled to 0°C, was added thionyl chloride (0.1 mL, 1.4 mmole). After stirring at room temperature for 1 hr, the reaction mixture was poured on ice-water (10 mL) and extracted with ether (3 X 10 mL). The combined organics were washed with 1% HCl solution (2 X 10 mL), saturated NaHCO₃ solution (2 X 10 mL) and brine (2 X 10 mL) and after the usual treatment afforded quantitatively the olefin 161 (24.3 mg).

¹H-NMR (CDCl₃): 1.15 (s, 3H, C-4a Me), 1.30 (d, 3H, C-4' Me), 2.8-3.1 (m, 2H, CH₂ Ph), 3.80 (s, 3H, OMe), 4.55 (br. s., 2H, O-CH₂ Ph), 4.9-5.1 (m, 1H, HC=C), 6.70-7.50 (m, 10H, Ph)

ν_{max} IR (Film): 2220 cm⁻¹ (CN), 1600 cm⁻¹ (C=C)

(±)-4α-cyano-2α,10aβ-dimethyl-7,7-ethylenedithio-3,4,4a,4b,5,6,7,9,10,10a-decahydro-4bα-phenanthren-1(2H)-one (168).

To a suspension of 35% potassium hydride (10.8 mg, 3.6 mg of KH, 0.09 mmole) in anhydrous THF (1 mL) was added a solution of keto-dithioketal 153 (20 mg, 0.06 mmole) in anhydrous THF. After stirring at room temperature for 1 hr, the reaction mixture was cooled at 0°C and methyl iodide (13.6 mmg, 0.096 mmole) was added and the solution was stirred for 20 hrs. Addition of methanol (0.5 mL) and water were followed by extracted work-up with ether (3 X 2 mL). The combined organics were washed with water (2 mL) and brine (2 X 2 mL) and after the usual treatment afforded 17.2 mg of crude 168. Purification by thick-layer chromatography gave the pure 168 (11 mg, 55%) along with the isomeric product 170 (4 mg, 20%).

¹H-NMR (CDCl₃): 1.10 (d, 3H, J = 6 Hz, C-2 Me), 1.25 (s, 3H, C-4a Me), 3.45 (br. s., 4H, 5-(CH₂)₂-S), 5.85 (br. s., CH=C)

ν_{max} IR (Film): 2220 cm⁻¹ (CN), 1710 cm⁻¹ (C=O)

MS (m/z, %): 347 (M⁺, 3), 332 (M⁺ - CH₃, 2), 319 (5), 303 (3), 264 (9), 179 (38), 135 (82), 44 (100)

(±)-4α-cyano-2β,10αβ-dimethyl-7,7-ethylenedithio-3,4,4a,5,6,7,9,10,10a-decahydro-4bα-phenanthren-1(2H)-one (170).

To a solution of hexamethyldisilazane (21.2 mg, 0.13 mmole) in anhydrous THF (1mL) was added n-butyl lithium (0.16 mL of a 1.6 M solution, 0.13 mmole) at 0°C under Argon. After stirring for 1 hr the slightly yellow solution was cooled to -78°C (dry-ice/acetone bath) and ketone-dithioketal 153 (40 mg, 0.12 mmole) in 1.5 mL of dry THF was added dropwise. The mixture was stirred at that temperature for 1 hr. Hexamethylphosphoramide (33 mg, 0.18 mmole) and methyl iodide (35 mg, 0.24 mmole) were then added successively and the resulting mixture was stirred for 15 hrs at room temperature. Water (5 mL) and chloroform (5 mL) were then introduced and the aqueous layer was separated and reextracted with chloroform (3 X 5 mL). The combined organics were washed with water (5 mL) and brine (2 X 5 mL) and after the usual treatment afforded the crude 170 (37 mg). Purification by chromatography or silica gel gave 170 (33 mg, 79%) contaminated with a small amount of isomeric product 168 (10% by ¹H-NMR).

¹H-NMR (CDCl₃): see Appendix 11

ν_{max} IR (Film): 2220 cm⁻¹ (CN), 1715 cm⁻¹ (C=O)

Treatment of ketone 170 in methanol with a catalytic amount of sodium methoxide generated epimerization at C-6. After neutralization, ketone 168 was obtained as the sole product.

(±)-1 α -(3-benzyloxybutyl)-8 α -cyano-4 β ,6 α -dimethyl-2,2-ethylenedioxy-perhydronaphtalen-5-one (169).

Keto-cyanoketal 157 was treated with potassium hydride-methyl iodide as described above for ketone 153 to afford ketone 169 (40%) as a viscous colorless oil.

¹H-NMR (CDCl₃): 1.06 (d, 3H, J = 6 Hz, C-4' Me), 1.22 (d, 3H, J = 6 Hz, C-6 Me), 1.25 (s, 3H, C-4a Me), 4.52 (m, 2H, CH₂ Ph), 7.32 (br. s., 5H, Ph)

$\nu_{\max}$ IR (Film): 2220 cm⁻¹ (CN), 1722 cm⁻¹ (C=O)

MS (m/z, %): 425 (M⁺, 19), 334 (6), 184 (36), 99 (97), 91 (100)

(±)-1 α -(3-benzyloxybutyl)-8 α -cyano-4 β ,6 β -dimethyl-2,2-ethylenedioxy-perhydronaphtalen-5-one (171).

Keto-cyano ketal 157 was alkylated according to the procedure described above for obtaining 170. The resulting product was identified as ketone 171.

$^1\text{H-NMR}$ (CDCl_3): 1.20 (s, 3H, C-4a Me), 1.25 and 1.35 (2 doublets, 6H, $J = 4$ Hz and 6 Hz, C-6 Me and C-4' Me), 4.55 (m, 2H, CH_2 Ph), 7.4 (br. s., 5H, Ph)

ν_{max} IR (Film): 2220 cm^{-1} (CN), 1720 cm^{-1} (C=O)

Treatment of ketone 171 with a catalytic amount of sodium methoxide in methanol generated quantitatively the isomeric ketone 169.

($\pm$)-1 α -(3-benzyloxybutyl)-8 α -cyano-4 α ,6-dimethyl-2,2-ethylenedioxy-5-ethenyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene (173).

To a solution of ketone 169 (168 mg, 0.396 mmole) in anhydrous THF cooled to -10°C was slowly added vinyl magnesium bromide (1.98 mL of 1.2 M solution, 2.4 mmole). After 20 hrs of stirring at room temperature, saturated NH_4Cl solution (5 mL) was added dropwise, followed by water (10 mL). Extractive work-up with chloroform (4 X 10 mL) and treatment of the combined organics in the usual manner afforded a mixture of allylic alcohol 172 and starting ketone 169. The crude mixture (160 mg) in dichloromethane (5 mL) and anhydrous pyridine (5 mL) was cooled to -78°C (dry-ice/acetone) and thionyl chloride (0.040 mL) was added. After 5 hrs of stirring at -25°C , the excess thionyl chloride was destroyed by addition of ice-water (5 mL).

followed by extractive work-up with chloroform (3 X 20 mL). The combined organics were washed successively with 10% HCl solution (3 X 10 mL), saturated NaHCO_3 solution (3 X 10 mL) and brine (2 X 10 mL), and treated in the usual manner to afford the crude diene 173. Purification by silica gel chromatography gave the pure diene 173 (68.9 mg, 40%) as a thick syrup.

$^1\text{H-NMR}$ (CDCl_3): 1.15 (d, 3H, $J = 4$ Hz, C-4' Me), 1.3 (br. s., 6H, C-4a Me, C-6 Me), 2.6 (m, 2H, CH_2 Ph), 4.8-5.5 (m, 3H, $\text{CH}_2=\text{CH}$)

ν_{max} IR (Film): 2220 cm^{-1} (CN), 1650 cm^{-1} (C=C)

MS (m/z , %): 435 (M^+ , 49), 344 (14), 99 (100), 91 (88)

2-triethylsilyl-1-butene-3-one (177).

Preparation of the Michael acceptor 177 was accomplished according to the procedure of Ganem (86); to clean magnesium shavings (1.6 g) covered with 60 mL of freshly distilled THF was added a few drops of 1,2-dibromoethane. When reflux was started α -bromovinyltriethylsilane (86) (5.9 g, 0.033 mole) was added dropwise in order to maintain gentle reflux. At the end of addition, the mixture was refluxed for 45 minutes more, then

treated with dry distilled acetaldehyde (2.7 g, 0.066 mole) while maintaining gentle reflux, then refluxed for an additional 30 minutes. The cooled reaction mixture was treated with 1N HCl solution and extracted with ether (4 X 50 mL). The combined organics were filtered and concentrated under vacuum to give 3.7 g (79%) of crude 2-triethylsilyl-1-buten-3-ol:

$^1\text{H-NMR}$ (neat): 0.2-1.1 (m, 15H, TMS), 1.200 (d, 3H, Me), 5.3 and 5.7 (m, 2H, $\text{CH}_2=\text{C}$).

The crude alcohol (3.7 g) was dissolved in CH_2Cl_2 (30 mL) and pyridinium dichromate (14 g) was added. The solution was stirred at room temperature for 3 hrs. The heterogeneous mixture was diluted with ether-pentane (3 volumes) and filtered on a florisil pad. Evaporation of the solvent and distillation afforded the pure 2-triethylsilyl-1-buten-3-one (177) in 75% yield.

b.p. 83°C (7 mm Hg)

$^1\text{H-NMR}$ (CDCl_3): 0.4-1.1 (m, 15H, Ethyl), 2.15 (s, 3H, Me), 6.58, 6.11 (AB quartet, 2H, $\text{CH}_2=\text{C}$)

ν_{max} IR (Film): 1670 cm^{-1} (conj. C=O)

(+)-5 β -tert-butyldimethylsilyloxy-8a α -cyano-4a β -methyl-2-trimethylsilyloxy-3,4,4a,5,6,7,8,8a-octahydronaphthalene (178).

To hydroxy-enone 127 (2.8 g, 0.016 mole) in 60 mL of freshly distilled dimethylformamide (DMF) was added successively imidazole (5.3 g, 0.08 mole) and tert-butyldimethylsilyl chloride (TBDMS) (7.2 g, 0.048 mole) and the resulting mixture was stirred at room temperature for 24 hrs. The reaction mixture was then poured onto ice-water (100 mL) and extracted with ether (3 X 75 mL). The organics were washed with 100 mL of 5% HCl, saturated NaHCO₃ solution and brine, and treated in the usual way to afford, after purification by HPLC (25% ethyl acetate in hexane), 3.34 g (72%) of the corresponding TBDMS-ether:

¹H-NMR (CDCl₃): 0.15 (s, 6H, Si-Me₂), 0.95 (s, 9H, t-butyl), 1.25 (s, 3H, C-4a Me), 3.45 (m, 1H, CHO), 5.80 (s, 1H, CH=C)

$\nu_{\max}$ IR (Film): 1670 cm⁻¹ (conj. C=O)

The title compound 178 was obtained by trimethylsilylcyanation of the obtained TBDMS ether according to procedure B (p.170).

¹H-NMR (CDCl₃): 0.15 (s, 6H, SiMe₂ t-Bu), 0.25 (s, 9H, OTMS), 0.95 (s, 9H, t-Bu), 1.0 (s, 3H, C-4a Me), 3.85 (m, 1H, CH-OTBDMS), 4.60 (s, 1H, CH=C)

$^{13}\text{C-NMR}$ (CDCl_3): 154.4 (C-2), 122.8 (CN), 104.5 (C-1), 74.1 (C-5)

ν_{max} IR (Film): 2220 cm^{-1} (CN), 1665 cm^{-1} (C=C-OTMS)

Attempted alkylation of trimethylsilylenol ether 178 via the lithium enolate: ()-5 β -tert-butyltrimethylsilyloxy-10a β -methyl-2-oxo-5 α -perhydroanthracene-8 α ,9 α -carbolactam (180)

To methyl lithium (1.75 mL of 1.5 M solution, 2.63 mmoles) in freshly distilled dry dimethoxyethane (DME) (10.5 mL) was added 178 (0.98 g, 2.5 mmoles) dissolved in 10 mL of DME and the solution was stirred for 30 minutes. The mixture was then cooled to -78°C (dry-ice/acetone) and the vinyl ketone 177 was added dropwise (0.42 g, 3.05 mmoles). After stirring at -78°C for 60 minutes, the mixture was warmed up to -20°C and stirred for an additional 60 minutes. The mixture was then treated with saturated NH_4Cl solution (20 mL) and extracted with ether (3 X 10 mL). The combined organics were washed with NH_4Cl saturated solution, brine and treated in the usual way to afford 0.96 g of mixture of products. One of the three major products was readily identified as ketone 179:

$^1\text{H-NMR}$ (CDCl_3): 0.2 (s, 6H, SiMe_3), 0.95 (s, 9H, t-Butyl), 1.25 (s, 3H, C-4a Me), 3.65 (dd, 1H, CHOTBDMS)

^{13}C -NMR (CDCl_3): see Appendix 12

ν_{max} IR (Film): 2220 cm^{-1} (CN), 1710 cm^{-1} (C=O)

The crude mixture (150 mg) was treated with a methanolic 5% sodium methoxide solution (5 mL) at room temperature. After stirring 20 hrs the mixture was added to water (20 mL) and extracted with chloroform (2 X 40 mL). The combined organics were washed with water, brine and treated in the usual way to afford a solid residue which upon recrystallization in ethyl acetate gave the title compound 180 (27 mg, 18%) contaminated with a minor component (~5%) which was identified as lactam 181. Purification by HPLC provided the pure lactam 180.

m.p. 205-210°C

^1H -NMR (CDCl_3): see Appendix 13a

^{13}C -NMR (CDCl_3): see Appendix 13b

MS (m/z, %): a) EI: no M^+ observed, 334 (M^+ - t-Butyl, 100), 259 (21), 75 (28), 73 (22)

b) CI: 392 (M^+ + 1, 100), 334 (M^+ - t-Butyl, 20), 260 (15)

ν_{max} IR (CDCl_3): 3260 cm^{-1} (NH), 1710 cm^{-1} , 1680 cm^{-1} (C=O)

Oxidation of mixture of 180 and 181.

Lactam 180 obtained previously (10 mg) was treated with Jones reagent (0.1 mL of 2.7 M solution) at room temperature for 30 hrs. Addition of a few mLs of isopropanol followed by extractive work-up with chloroform and treatment in the usual manner afforded a mixture of diketolactam 182:

ν_{max} IR (CDCl_3): 1710, 1680 cm^{-1} (C=O)

TLC comparison with diketolactam 142 showed that the two products were different.

Attempted alkylation of silylenol ether 178 via titanium enolate.

To a solution of titanium tetrachloride (190 mg, 1 mmole) and titanium isopropoxide (285 mg, 1 mmole) in 4 mL of dry dichloromethane cooled at -78°C was added dropwise a solution of enol ether 178 (390 mg, 1 mmole) and methyl vinyl ketone ethylene acetal (125.4 mg, 1 mmole) in dichloromethane (1 mL). After stirring at -78°C for 60 minutes the mixture was let to warm up to room temperature gradually. The mixture was then treated with aqueous K_2CO_3 (0.7 g in 15 mL of water) and extracted with ether (3 X 10

mL). The combined organics were washed with water, brine and treated in the usual way to afford a mixture containing as the major product ketone 179.

The crude mixture was treated with sodium methoxide in the same way as described above to afford ketolactam 180 in about 30% yield.

PART II

(±)-8β-tert-butoxy-1,4aβ,8aβ-trimethyl-4,4a,4b,5,6,7,8,8a,9,10-decahydro-4bα-phenanthren-2(3H)-one (188).

Lithium (175 mg, 25.2 mmoles) was dissolved in distilled ammonia (60 mL) and enone 132 (1.58 g, 6.32 mmole), tert-butanol (374 mg, 5.06 mmoles) in dry ether were added dropwise over 15 minutes. After stirring for 60 minutes, the excess lithium was destroyed with bromobenzene (1.5 mL) and the ammonia was taken off under aspirator pressure. The residual salts were dissolved in dry DME (40 mL) and stirred for 20 minutes. The mixture was then cooled to -78°C and 2-triethylsilyl-1-penten-3-one (193), prepared in the same way as 177 (see p.193), (1.489 g, 9.48 mmoles) in DME (10 mL) was added. Stirring was continued at -78°C for 15-20 minutes then at room temperature for 2 hrs. Saturated NH₄Cl was added (50 mL) and the reaction mixture was extracted with ether (3 X 20 mL). The combined organics were filtered on a florisil pad with ether elution and then concentrated under pressure. The residue was taken up in 5% sodium methoxide in methanol (100 mL) and refluxed for 5 hrs. It was then poured into ether and water was added. The layers were separated and the aqueous layer extracted

with ether (x 2): The combined organic extracts were washed with water, brine and treated in the usual way. Purification by HPLC (6% ethyl acetate in hexane) afforded tricyclic enone 188 (1.0 g, 50%).

$^1\text{H-NMR}$ (CDCl_3): see Appendix 14

λ_{max} UV (CH_3OH): 247 nm ($\epsilon = 13.4 \times 10^3$)

ν_{max} IR (Film): 1660 cm^{-1} (C=O), 1615 cm^{-1} (C=C)

MS (m/z , %): 318 (M^+ , 18), 262 ($\text{M}^+ + \text{H} - t\text{-Bu}$, 67), 210 (34), 138 (46), 57 (100)

Elementary analysis: found: C = 79.41, H = 10.47, calculated: C = 79.25, H = 10.69; for $\text{C}_{21}\text{H}_{34}\text{O}_2$

Chromatography also afforded ketone 192 (24%):

$^1\text{H-NMR}$ (CDCl_3): 1.0 (d, 3H, $J = 6$ Hz, C-1 Me), 1.15 (s, 3H, C-4a Me), 1.2 (s, 9H, $t\text{-Butyl}$), 3.45 (dd, 1H, CHO $t\text{-Bu}$)

ν_{max} IR (Film): 1708 cm^{-1} (C=O)

In another experiment, saturated ketone 192 (1.85 g, 7.35 mmoles) dissolved in dry $t\text{-butanol}$ (25 mL) was added to a stirring solution of potassium $t\text{-butoxide}$ (663 mg, 5.9 mmoles) in $t\text{-butanol}$ (40 mL). After stirring for 30 mins, enone 193 (1.61 g) in 15 mL of $t\text{-butanol}$ was added dropwise over 40 minutes. The resulting red solution was stirred for an additional 20 hrs. Water and ether were then

added and the layers separated. The aqueous layer was extracted with ether and the combined organics were filtered on a florisil pad with ether elution. After evaporation of the solvent, the residue was taken up in methanol (100 ml) to which was added potassium hydroxide (0.75 g) and water (5 mL). The mixture was refluxed for 16 hrs. Upon extractive work-up with ether and column chromatography, the reaction afforded the tricyclic enone 188 (960 mg, 46%), identical to previously prepared sample.

(±)-7-benzyloxy-2-triethylsilyloct-1-en-3-one (194).

To magnesium shavings (800 mg) in 15 mL of dry THF. was added dropwise a solution of α -bromovinyltriethylsilane (308 g, 14 mmoles) in dry THF (6 mL) at a rate necessary to maintain gentle reflux. At the end of addition, the reaction was stirred for an additional 60 minutes, then cooled to 0° C. 5-benzyloxyoctanal (110) (2.82 g, 14.7 ~~mmoles~~) was then added at reflux and the mixture was further refluxed for 15 minutes. Saturated NH_4Cl solution was added (20 mL) and the mixture extracted with ether (3 X 20 mL). The combined organic extracts were washed with water, brine and treated in the usual way to afford, after purification on HPLC, 4.1 g (90%) of allylic alcohol. The alcohol was

dissolved in dichloromethane (20 mL) and added to a suspension of pyridinium dichromate (3.98 g) in 30 mL of dichloromethane. After 2 hrs of stirring at room temperature, the reaction mixture was diluted with ether-pentane and filtered on a florisil pad to afford the crude enone 194 (4.2 g) which was purified by HPLC (4% ethyl acetate in hexane). The pure enone 194 (2.8 g, 63%) was thus obtained as a thick liquid.

¹H-NMR (CDCl₃): 0.8 to 1.0 (m, 15H, SiEt), 1.20 (s, 3H, C-8 Me), 3.55 (m, 1H, CH-OBn), 4.60 (d, 2H, CH₂ Ph), 6.1 (d), and 6.5 (d) (1H each, CH=C), 7.4 (s, 5H, Ph)

²-1
^ν_{max} IR (Film): 1665 cm⁻¹ (conj. C=O)

MS (m/z, %): no M⁺, 127 (45), 91 (100), 73 (50)

(±)-8β-tert-butoxy-1,4aβ,8aβ-trimethyl-4b β,10aβ-perhydro-phenanthren-2-one (190).

Lithium (31 mg) was dissolved in freshly distilled dry ammonia (100 mL) and enone 188 (242 mg, 0.762 mmole) in tert-amylalcohol (85 microl) was added dropwise. After stirring for 2 hrs, the mixture was quenched by addition of NH₄ Cl (solid) and the ammonia was evaporated under reduced pressure. Water and ether were then added and the layers separated. The aqueous layer was extracted with ether, and

the combined organics were washed with water, brine and treated in the usual way. Purification by HPLC afforded the pure saturated ketone 190 (120 mg, 50%).

¹H-NMR (CDCl₃): 0.95 (s, 3H, C-4a Me), 1.0 (s, 3H, C-8a Me), 1.05 (d, 3H, C-1 Me), 1.15 (s, 9H, t-Butyl)

¹Umax IR (Film): 1705 cm⁻¹ (C=O)

MS (m/z, %): 320 (M⁺, 15), 200 (25), 140 (100)

(±)-1-(3-benzyloxybutyl)-7β-tert-butoxy-4aβ,6aβ,10bβ-trimethyl-4,4a,4b,5,6,7,8,9,10,10a,11,12-tetradecahydro-4bβ,10aβ-chrysen-2(3H)-one (187).

To ketone 190 (35 mg, 0.11 mmole) dissolved in tert-butanol (2 mL) was added potassium tert-butoxide (13 mg) and the reaction was stirred for 15 minutes. Enone 193 (100 mg, 0.30 mmole) in dry tert-butanol was then added and stirring was continued for 16 hours. Water and ether were then added and the layers separated. The combined organics were washed with water, brine and treated in the usual way to afford a residue to which was added methanol (10 mL) and potassium hydroxide (60 mg) in water (2 mL). The mixture was refluxed for 24 hrs, cooled and water and ether added. The aqueous layer was extracted with ether and the combined ethereal layers filtered on a florisil pad. Concentration followed by chromatography on silica gel afforded enone 187 (10 mg,

18%) as a colorless oil, which proved identical with an authentic sample of (52b).

$^1\text{H-NMR}$ (CDCl_3): 1.20 (s, 9H, t-Butyl), 4.5 (dd, 2H, CH_2Ph), 7.3 (s, 5H, Ph), see Appendix 15)

ν_{max} IR (Film): 1660 cm^{-1} (conj. C=O), 1601 cm^{-1} (C=C)

λ_{max} UV (CH_3OH): 252 nm ($\epsilon = 12.7 \times 10^3$)

MS (m/z, %): 534 (M^+ , 3), 443 (5), 428 (5), 107 (15), 91(100), 57 (90).

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APPENDICE 3. $^1\text{H-NMR}$ of hydroxy-enone 118

APPENDICE 4. ^{13}C -NMR of silylenol ether 131

APPENDICE 6a. ^{13}C -NMR of cyano-ketone 134t

APPENDICE 6b. ^{13}C -NMR of cyano-ketone 134c

138 APPENDICE 7a. ¹H-NMR of triketone 138.

APPENDICE 8. ^{13}C -NMR of tricyclic enone 103

APPENDICE 10. ¹H-NMR of tertiary alcohol 160

APPENDICE 11. ^1H -NMR of thio-ketal 168

APPENDICE 12. ^{13}C -NMR of ketone 179

APPENDICE 13a. $^1\text{H-NMR}$ of linear tricyclic lactam 180

APPENDICE 13b. ^{13}C -NMR of linear tricyclic lactam **180**

APPENDICE 14. ^1H -NMR of tricyclic enone 188

APPENDICE 15. ^1H -NMR of tetracyclic enone 187

PART II

R t-Bu

END

FIN

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87