Removable chirality inducing fragments in the synthesis of polycyclic natural products

REMOVABLE CHIRALITY INDUCING FRAGMENTS IN THE SYNTHESIS OF POLYCYCLIC NATURAL PRODUCTS

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PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE TECHNISCHE WETENSCHAPPEN AAN DE TECHNISCHE HOGESCHOOL EINDHOVEN, OP GEZAG VAN DE RECTOR MAGNIFICUS, PROF. DR. S. T. M. ACKERMANS, VOOR EEN COMMISSIE AANGEWEZEN DOOR HET COLLEGE VAN DEKANEN IN HET OPENBAAR TE VERDEDIGEN OP DINSDAG 21 SEPTEMBER 1982 TE 16.00 UUR

DOOR

CORNELUS GERARDUS MARIA JANSSEN

GEBOREN TE SCHAESBERG

DIT PROEFSCHRIFT IS GOEDGEKEURD DOOR
DE PROMOTOREN:
PROF. DR. E.F. GODEFROI
EN
PROF. DR. R.M. KELLOGG

Aan myn Ouders.

Aan myn Vrienden.

I have learned
that to be
with those
I like
is enough

Walt Whitman

CONTENTS

CHAPTER I

General Introduction

I.1 Historical Background

Past strategies underlying total synthesis of polycyclic natural products have most often involved stepwise annelation sequences with each individual ring being constructed sequentially. In spite of having generated innumerable ingenious approaches, such tactics suffer from being long and tedious and generally afford end products in low over-all yields. In particular, attainment of the correct stereochemistry has constituted the major challenge in such approaches.[1]

In 1955 natural product synthesis received a powerful impetus by the observation that certain 1,5-dienes with a *trans*-geometry could, under acidic conditions, be made to undergo so-called cationic polycyclizations, which proceeded with total stereospecificity to produce all-*trans* annelated ring systems. The process constituted an *in vitro* mimicry of a plausable biological pathway and has hence been referred to as a biomimetic approach. Its principles, experimentally demonstrated and rationalized by Stork[2] and additionally formalized by Eschenmoser[3] are considered to involve a concerted stereospecific *trans*-antiparallel intramolecular addition across an internal double bond. In a way cationic polyene cyclization may be seen as a one-step intramolecular version of a two-step intermolecular addition to a double bond in the same sense in which bromine is known to add stereospecifically to alkenes.

Storks' and Eschenmosers' studies are generally regarded as the dawn of modern biomimetically derived polyene cyclization strategies. The theory can be illustrated by considering the cyclization of squalene oxide, biologically derived

from squalene, and known to be the precursor of lanosterol which, in turn, gives rise to cholesterol and from there to a host of steroid hormones[1b] (Fig. I. 1).

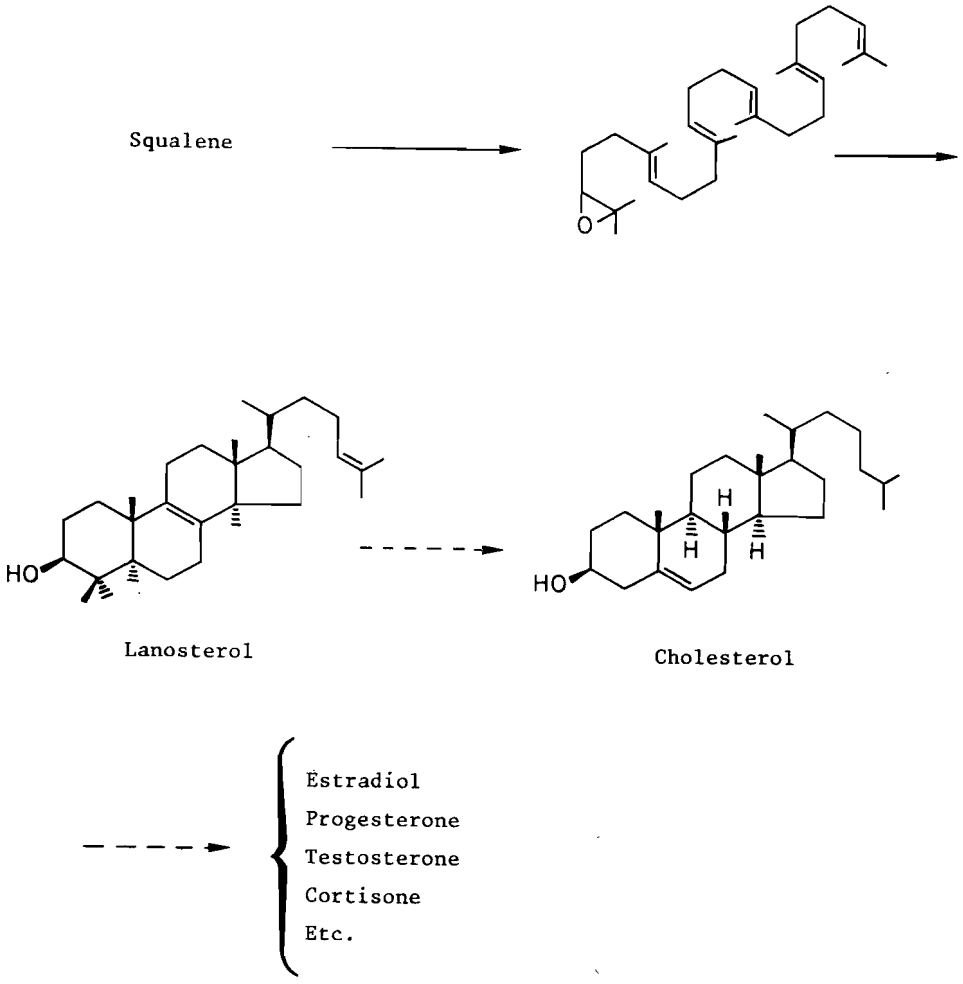


Figure I. 1.

In laboratory practice steroid synthesis especially has greatly benefited from this concept and a number of elegant and novel approaches have by now emerged as illustrated by routes to progesterone[4] and testosterone[5] (Fig. I. 2 and I. 3). The method depends foremost on having convenient access to a *trans*-dialkylated olefin featuring a cyclization init-

iator and a terminator on either of the olefin chains. The nature and function of these terms will be briefly discussed.

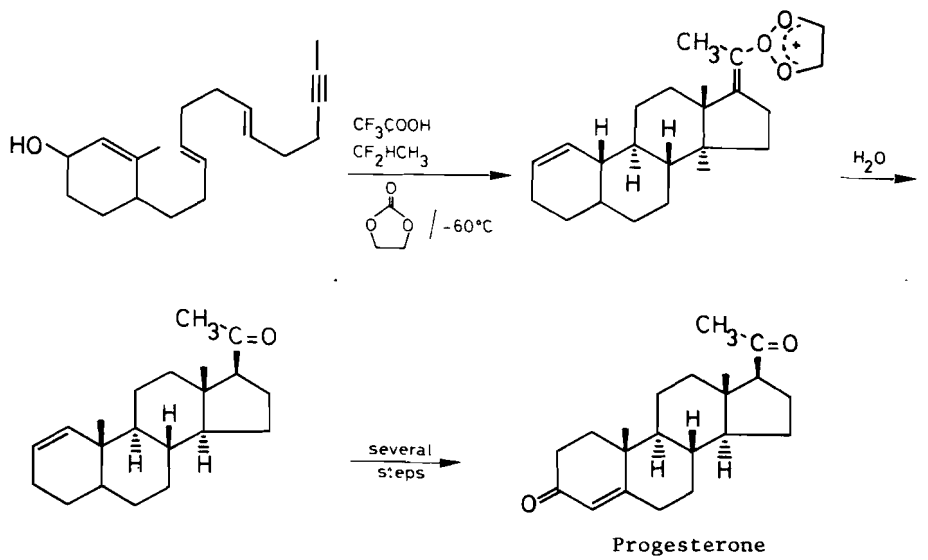


Figure I. 2.

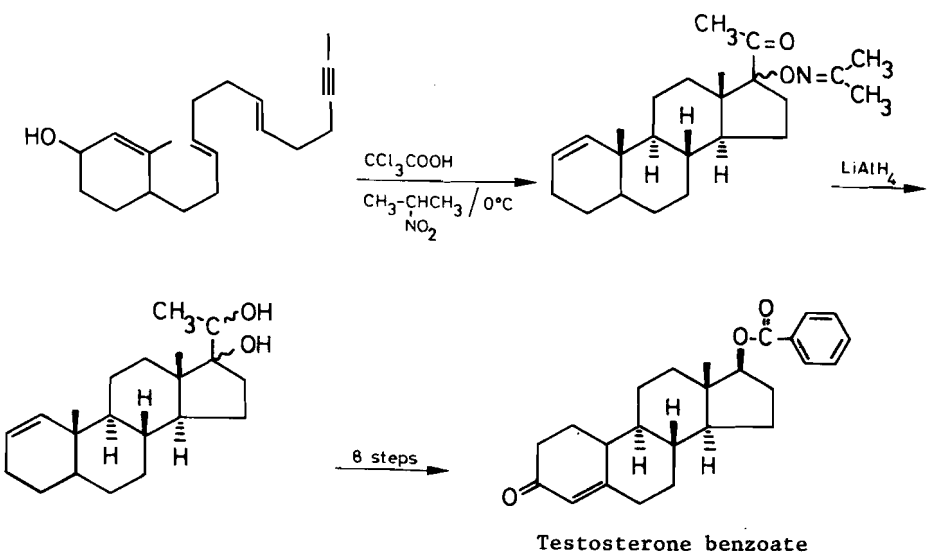


Figure I. 3.

Cationic polycyclization is ushered in by the generation within the substrate of a so-called cyclization initiator, which creates an electron-deficient site. This may be brought about by the action of proton- or Lewis acids on, for instance, allyl alcohols to provide cyclization-triggering allyl cations.[1b,c] Ionization of protonated epoxides[1a] or acetals[1b,c] likewise produce cyclization initiating centers. Efforts to have olefins serve as initiators have been disappointing[1c] probably because indiscriminate protonation of the substrate is found to lead to formation of a plethora of products. In practice, ionization of protonated or Lewis acid-coordinated allyl alcohols, epoxides or acetals has still proven to be the most advantageous starting point for initiating synthetically applicable polyene cyclizations.

Equally important are events bringing about the reactions' termination. In this context the expression "terminator" refers to the electron-donating fragment and constitutes the group destined to bear the ultimately most stabilized positive charge. The resulting species may then lose a proton to provide an olefinic end product or may be nucleophilically quenched to yield substitution-derived substances. The essence of poly-

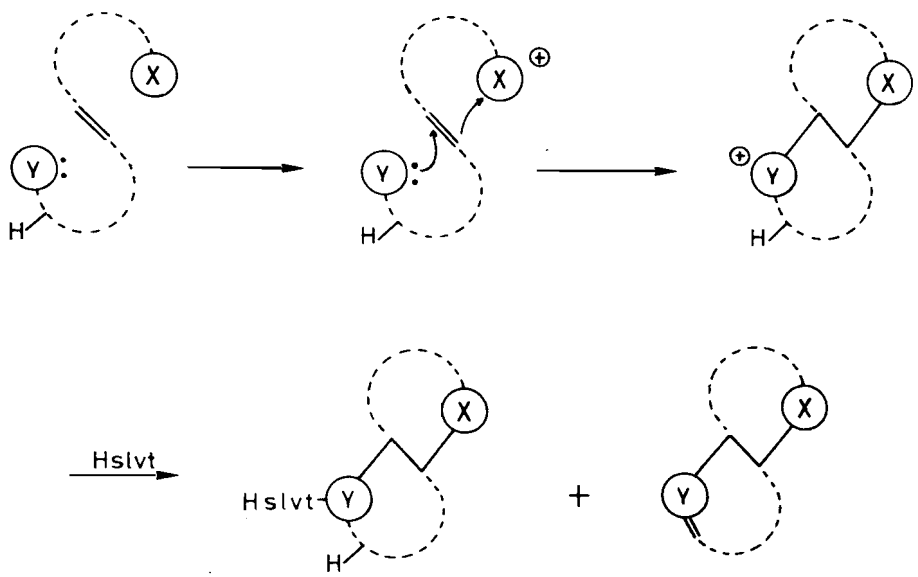
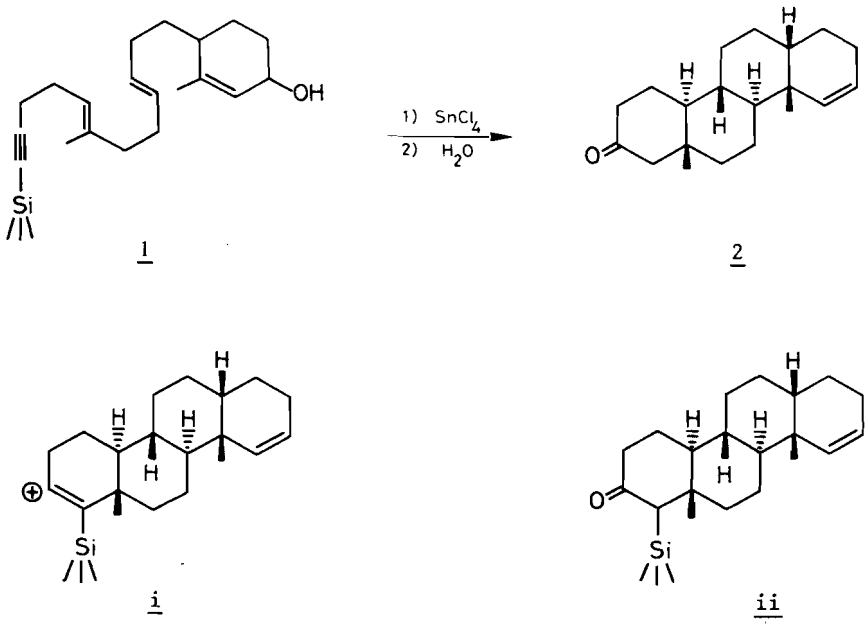


Figure I. 4.

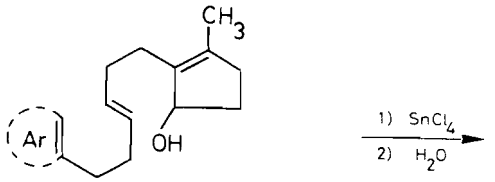
cyclization is schematically depicted in Fig. I. 4, with X and Y representing the initiating and terminating units respectively.

The above concepts are additionally demonstrated by the following examples of steroid-directed polycyclizations. Compound 1, with $SnCl_4$ in CH_2Cl_2 furnishes after aqueous work-up ketone 2 in good yield.[6] The driving force for the cyclization is considered to stem from silicons' ability to stabilize cationic centers on β-carbons.[7] Cation i, formed initially, is hydrated first to a vinyl alcohol and then tautomerized to β-silylketone ii; such species readily lose silylated fragments to produce ketones like 2. In this case the silylated acetylene is seen to serve as cyclization terminator.



Aromatic ring systems perform likewise. For instance 3a,b have given 4a,b on treatment with $SnCl_4$ followed by water-quenching, via a pathway almost certainly involving iii and its concluding deprotonation.[8] This example illustrates a terminator losing a proton in the end and corresponds to the classical mechanism of aromatic substitution. Stork-Eschenmoser postulates are obeyed in all these cases, causing *trans*-olefinic precursors

to produce *trans-anti-trans* ring systems.



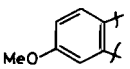
3a,b

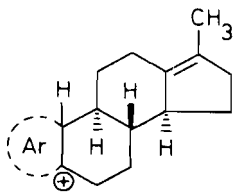
4a,b

a: Ar = m-anisyl

b: Ar = 2-thienyl

a: Ar = 

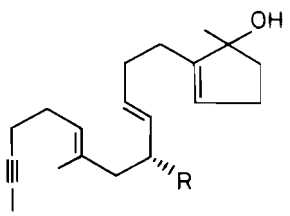
b: Ar = 



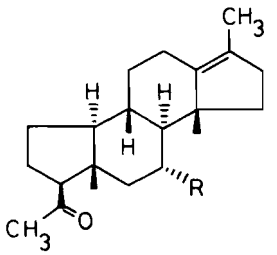
iii

The aforementioned examples involve cyclization of achiral precursors. Cationic cyclization strategy can be further refined by performing the ring closures on chiral substrates. If carried out on precursor racemates this will obviously give rise to ring systems containing two configurationally opposite isomers. Whereas each epimer consists of a 50:50 d,l-mixture, the epimeric sets are produced in unequal amounts; this is a reflection of a sum total of interaction factors operative during attainment of the most favorable transition state tending to give preference to one epimeric pair over the other. Reactions whereby racemic chiral substances are transformed into unequal amounts of racemic epimers are said to proceed enantioselectively. The same transformation carried out on enantiomerically pure substrates will necessarily also give enantiomerically pure products, obviously in the absence of racemization possibilities. Such conversions are then said to have proceeded with chiral (or asymmetric) induction. These

concepts are best illustrated by examples. Compounds 5a,b, as racemates, have been reported to undergo polyene cyclization under acidic conditions to give 6a,b. For R = CH_3 this resulted in complete enantioselectivity at C-11 (steroid numbering system) to give 100% of the α-methyl epimer while at C-17 an α:β ratio of 9:91 was observed; cyclization of 5b (R = OH) led to 100% enantioselectivity at C-11 with no α:β ratio for the C-17 being given.[9] A comparable situation has been noted during



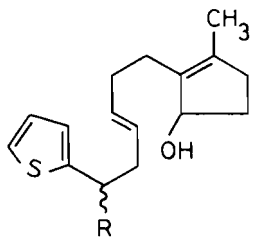
5a,b



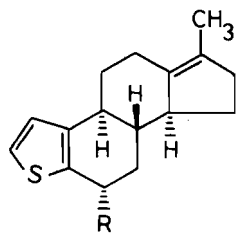
6a,b

a: R = CH_3
b: R = OH

$SnCl_4$-mediated cyclizations of 7a,b, where, in the case of 7a fair yields of 8a were obtained with 97% enantioselectivity having occurred in favor of the α-isomer. Cyclization of *tert.*-butyl analog 7b was found to proceed with 100% enantioselectivity to provide 8b.[10]



7a,b



8a,b

a: R = CH_3
b: R = $C(CH_3)_3$

In summary, the current state of the art regarding steroid--directed cationic cyclization routes is the following.

1°. Concerted ring closures will proceed 100% stereospecifically with *trans*-olefinic substrates furnishing *trans*-annelated systems solely and *cis*-analogs giving rise to the *cis*--fused condensed systems.

2°. Precursor aliphatically-bonded substituents will, on cyclization, tend to assume configurations least encumbered by unfavorable 1,3-interactions. Such processes are said to occur enantioselectively. When the same reaction is performed on enantiomerically pure systems it is considered to take place with chiral (or asymmetric) induction.

I.2 Aim and Scope of the Present Investigation

So far, the substituents examined under point 2 have, to our knowledge, been limited to alkyl- and hydroxy fragments. Such functionality on carbon is not readily removed. The present investigation was undertaken to examine possibilities of exploiting bulky, enantioselectivity-inducing fragments which, on having served their purpose, would lend themselves for ultimate detachment. If successfully performed on racemic mixtures the approach would ultimately be extendable to optically pure cyclized materials whose optical integrity would be retained on severing the chirality inducing functionality. It should provide access i.a. to optically pure naturally occurring polycyclic systems. Specific emphasis was to be placed on construction of steroidal frameworks containing aromatic A-rings for reasons of simplicity and hoped for medicinal implications. Location of the enantioselectivity effecting group was to be limited to C-6 (steroid numbering convention). The overall strategy is depicted in Fig. I. 5. Although conceived for elaboration of steroidal skeletons, the approach was to be tested out on the construction of some simpler bi- and tricyclic models first. The choice of chirality-inducing, removable units fell on the tosyl- and trimethylsilyl (TMS) fragments for a variety of reasons. Tosylated structures are often easily handled solid compounds, promptly characterizable by their CH_3-NMR signals around 2.40 ppm. Moreover, sulfonyl fragments constitute synthetically appealing

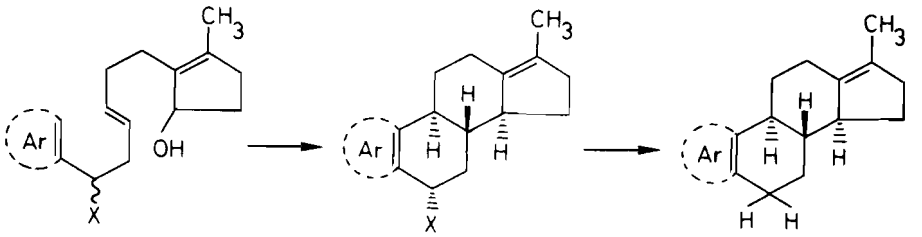


Figure I. 5.

auxiliaries which may contribute substantially to the ease of assembling an assortment of structural units.[11] There appear to be no data relating to the asymmetry inducing power of sulfonyl fragments in general and the tosyl group in particular. Tosyl removal from carbon has been investigated and has been shown to include the use of $Li/EtNH_2$,[12] $LiAlH_4/CuCl_2$,[13] Al-Hg,[13] Na-Hg,[14] Zn-AcOH[15] and $NaNH_2$.[16]

Selection of the TMS fragment as potential chirality controller rested on other considerations. Whereas tosylated derivatives are generally crystalline materials, TMS compounds tend to be thermally stable, distillable liquids. The fact that benzylic desilylation methodologies seem up to now not to have been exhaustively investigated was not considered to constitute an unsurmountable obstacle and would be dealt with when the need arose. Nothing appeared to be known about the ability of TMS fragments to elicit enantioselectivity during cationic cyclizations either; related work, though, involving the use of the less voluminous *tert.*-butyl group in similar ring closures had shown such processes to proceed with 100% enantioselectivity.[10] Such a group on saturated carbon is generally not removable; the related TMS moiety, almost certainly, would be.

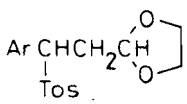
Since in these studies the extent of asymmetric induction would parallel the attained enantioselectivity, the main efforts were, for the time being, to be limited to preparing and ring closing substrate racemates. Their aromatic component was to consist of phenyl- and suitably substituted phenyl derivatives as well as 2- and 3-thienyl fragments.

Equally important in this work was to be the attention

given to the elaboration of simple, technologically applicable, high-yield processes, obviating as much as possible time-consuming chores such as chromatographic separations of whatever type.

I.3 Outline of the Present Investigation

Chapter II deals with a facile, one-pot conversion of 3-arylpropenals into 2-[2-aryl-2-(p-toluenesulfonyl)ethyl]--1,3-dioxolanes I. Some aldehydes derived therefrom, II, have been subjected to Wittig olefination conditions. The results are discussed.



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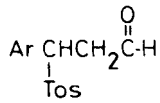
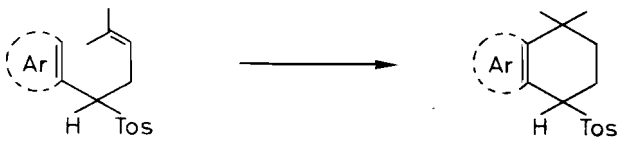
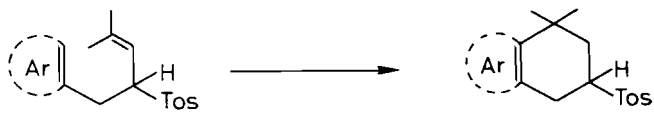


II

In chapter III construction of model olefins III and V and their cyclization in FSO_3H/SO_2 to IV and VI are discussed. The behavior of the latter towards diisobutylaluminum hydride (Dibal-H) in toluene will be described and rationalized.



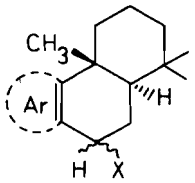
III IV



V VI

The strategy will be extended in chapter IV to include a new, short and efficient entry into aromatic resin acid types

VII and VIII. The enantioselectivity inducing power of the tosyl fragment on realizing such objectives is dwelt upon.



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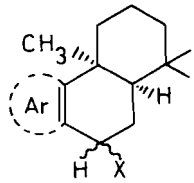
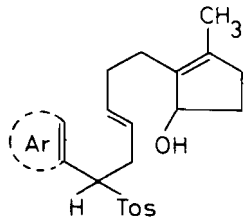


VIII

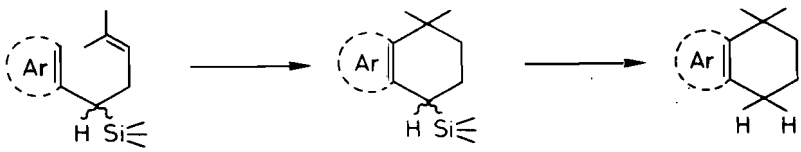
(X = tosyl or H)

Chapter V describes the synthesis of a tosylated steroidal alicyclic precursor of type IX via a route differing significantly from earlier reported ones. Efforts to bring about its cyclization to steroidal systems are discussed.

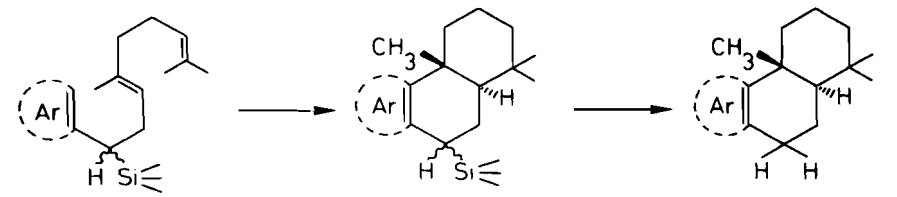


IX

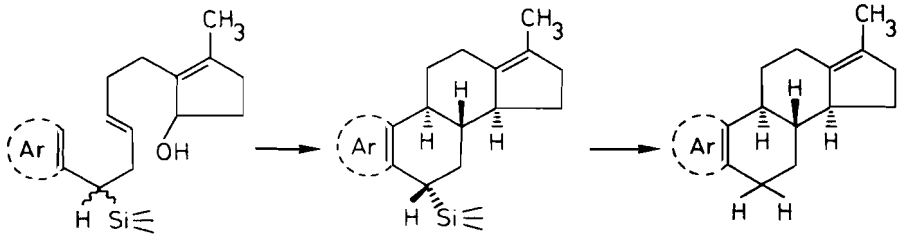
In chapter VI the capacity of the trimethylsilyl fragment to cause enantioselectivity during cationic cyclizations is demonstrated. The power of the TMS group in synthesis comes to the fore in preparing X, XIII and XVI. In a subsequent, novel desilylation tactic the TMS fragments are removed by treatment with potassium *tert.*-butoxide in DMSO to give XII and XV, identical to material obtained earlier via detosylation of related products. Steroidal skeletons XVIII are likewise shown to be thus accessible. In combination with the cyclizations it opens new entries into steroidal intermediates.



X XI XII



XIII XIV XV



XVI XVII XVIII

The thesis' summary constitutes an overall survey briefly unifying and interrelating the most important data described.

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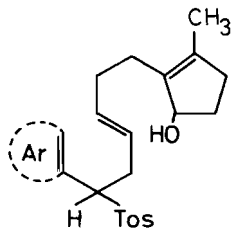
CHAPTER II

2-[2-Aryl-2-(p-toluenesulfonyl)ethyl] -1,3-dioxolanes as Potential Starting Materials for Tosyl-induced Enantioselectivity Studies

II.1 Introduction

For examination of the proposals outlined in Chapter I substantial amounts of *trans*-olefinic structures I were required. Several examples of compound type I had already



I

been reported by W. S. Johnson in connection with his cationic cyclization studies.[1] In some isolated instances this had involved *trans*-olefin production via Na/NH_3 reduction of preconstructed acetylenes;[2] precursor geometry was established in some other cases by $LiAlH_4$ reduction of suitably substituted propargylic alcohols.[3] Most examples, however, have centered on Wittig-like olefinations of aldehydes with properly designed phosphoran components. Because the ylids were usually unstabilized, significant amounts of *cis*-isomers were also produced. This drawback can be minimized by performing the reactions under Schlosser conditions[4] (addition of one extra equiv of phenyllithium or butyllithium to the formed betaines at $-30^{\circ}C$), which is known to steer the reaction towards production of *trans*-alkenes. Johnson's central feature for preparing cyclization precursors is depicted in Fig. II. 1. The ultimately required cyclization terminator Y is generally found on the aldehydic component of which the most commonly

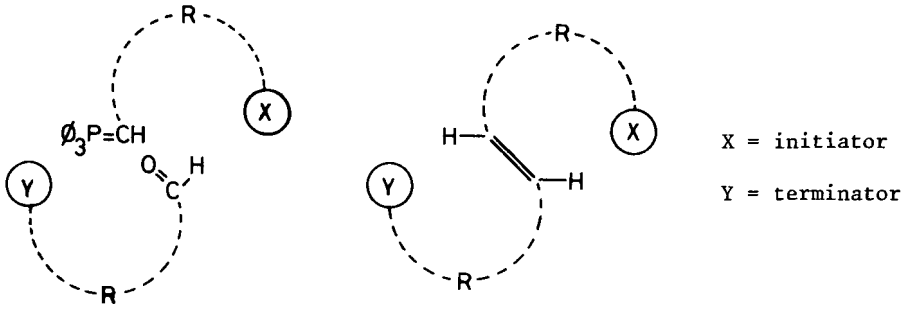
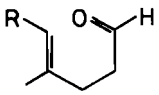


Figure II. 1.

encountered ones are collected in Table I.

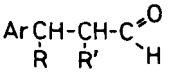
Table I. Representative Aldehydic Olefination Substrates



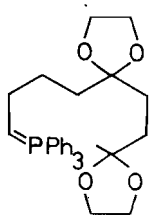
R	Reference
$CH_2CH_2C{\equiv}CCH_3$	5a-d
$CH_2CH_2C{\equiv}C$-phenyl	5e
$CH_2CH_2CH{\overset{t}{=}}CH$-phenyl	5f
$CH_2CH_2C{\equiv}CSi(CH_3)_3$	5g,h
$CH_2CH_2C{\equiv}CCH_2Si(CH_3)_3$	5i

3-Arylpropanals have served as starting materials for steroidal aromatic A-ring open precursors via Wittig-Schlosser *trans*-olefination techniques; they are given in Table II. Phosphoranes, having functioned as ylid fragment with the above aldehydes are exemplified by compounds 1-3.

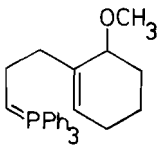
Table II. 3-Arylpropanals as Wittig-Schlosser Components



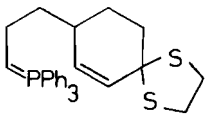
Ar	R	R'	Reference
phenyl	H	H	6a
m-anisyl	H	H	6b
m-anisyl	CH_3	H	6c
m-anisyl	H	CH_3	6d
m-chloro phenyl	H	H	6a
m-tolyl	H	H	6a
m-trifluoromethyl phenyl	H	H	6a
2-thienyl	H	H	6e
2-thienyl	CH_3	H	6f
2-thienyl	t-Bu	H	6f
3-thienyl	CH_3	H	6g



1

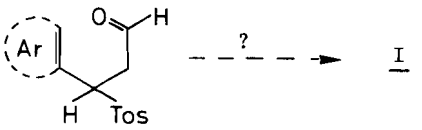


2



3

In the present investigation, Johnson's concept for preparing aromatic A-ring steroid precursors I would be contingent on facile entries into 3-aryl-3-tosylpropanals II.[1b] This chapter describes such a route whereby in a simple,

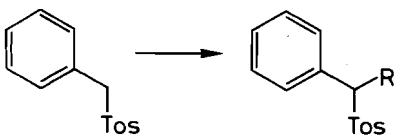


II

3 minute process, some representative 3-arylpropenals are converted into 1,1-ethylenedioxy-acetals derived from II.[7] The behavior of some corresponding aldehydes with triphenyl isopropylphosphoran as model phosphorus ylid is examined.[8]

II.2 Preparation of 2-[2-Aryl-2-(p-toluenesulfonyl)ethyl]--1,3-dioxolanes

Initial efforts to prepare an aldehyde of type II were concentrated on obtaining the unsubstituted phenyl derivative. Treatment of benzyl chloride with sodium-p-toluenesulfinate (NaTos) in DMF gave 4; this was deprotonated (BuLi) and alkylated with either benzyl chloride or propargyl bromide in THF to provide 5a and 5b. The anion failed to react with bromoacetal under these conditions. This contrasts with results of



4 5a,b

a: R = $CH_2C_6H_5$
b: R = $CH_2C{\equiv}CH$

Julia who did alkylate related sulfones with bromoacetal albeit in the presence of hexamethylphosphoramide (HMPA).[9] Other routes were opted for because of suspected health risks associated with HMPA exposure.[10]

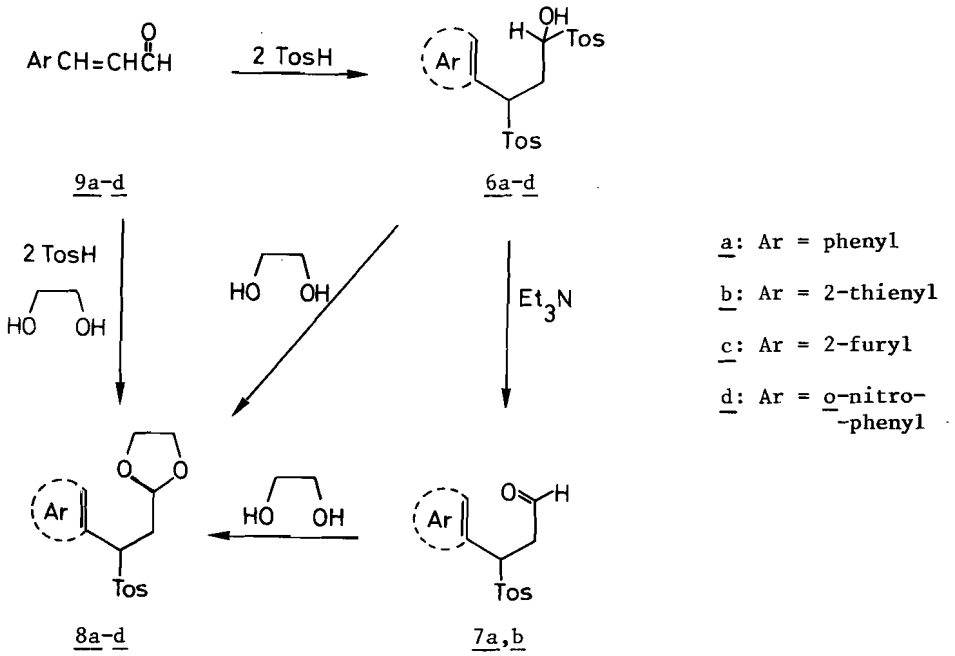
Aldehydes 7a-d formally represent 1,4-addition products of TosH to 3-arylpropenals; α,β-unsaturated aldehydes, however, most frequently undergo 1,2- rather than 1,4-addition. Examination of the literature revealed only one instance of an aromatic sulfinic acid having been added to cinnamaldehyde. Kohler and Reimer[11] in 1904 had described the reaction of

cinnamaldehyde with TosH and claimed to have obtained a 1,4--addition product ("mp 78°C, soluble in alcohol, ether and benzene, insoluble in water and ligroin") and a diaddition product ("mp at about 126°C, soluble in benzene, alcohol and water" and "analyses gave no concordant results"). Their data tend to be vague and ambiguous. On allowing one equiv of TosH to react with cinnamaldehyde at room temperature, instantaneous precipitation (43%) of a diadduct was observed, mp 128-129 °C, insoluble in hot water or benzene. Analytical and spectral data (see Experimental Section) were consistent with structure 6a. With 2 equiv of TosH, cinnamaldehyde gave 6a in 91% yield.

The diadduct was converted to aldehyde 7a in a variety of ways. These included aqueous $NaHCO_3$, Et_3N in DMF, and best, Et_3N in water-ether. Physical data derived from 7a (mp 122--123 °C, soluble in benzene) are at variance with the literature,[11] but analytical and spectral data (see Experimental Section) leave no doubt that the structure is correct. The aldehyde with ethylene glycol in refluxing benzene gave acetal 8a; this was also obtained directly from 6a in excess boiling ethylene glycol in an unexpectedly fast reaction (Method A, see Experimental).

The effect of aryl variation on TosH addition to 3-aryl-propenals was then briefly examined. This involved the 2-thienyl, the 2-furyl, and the o-nitrophenyl analogs and gave, after 18 h at ambient temperatures, 6b-d in 43, 58 and 86% yields. Extending the contact times did, in the one case studied, improve the yield: 3-(2-furyl)-propenal with 2 equiv of TosH for 42, 66 and 168 h gave 67, 73 and 76% yields, respectively of 6c. Like 6a, 6b-d reacted extremely rapidly with ethylene glycol to furnish 8b-d in good yields.

Literature precedent for concomitant HBr addition and acetalization of acrolein[12-15] plus the ease of converting 6a-d into acetals 8a-d prompted efforts to convert the 3-aryl-propenals directly into the desired dioxolanes. Cinnamaldehyde was therefore treated with 2 equiv of TosH in ethylene glycol at 125 °C to furnish, after 3 min, 8a in 90% yield (Method B, see Experimental). The 2-thienyl- and o-nitrophenyl propenals reacted likewise to give 8b,d; the furyl analog, on the other

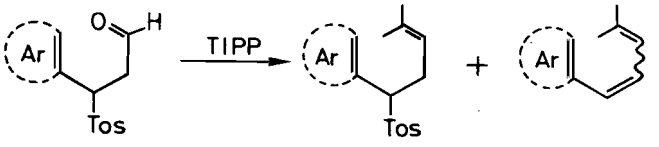


hand, produced intractable tars. Reaction conditions appear to be critical and differ from case to case. In the 2-thienyl series, for example, a contact time of 10 min at 125 ^{o}C or 5 min at 155 ^{o}C brought about total decomposition. The process most likely proceeds via the aforementioned ditosyl adducts, thus requiring participation of at least 2 equiv of TosH. This is substantiated by the observation that the use of only 1 equiv of TosH lowered the yield of 8b to 25%. Specific data related to the mode of preparation of 6b-d and 8b-d and their physical properties are presented in Table III.

II.3 Reactivity of 7a and b towards Triphenyl isopropylidene phosphoran (TIPP)

First trials in probing the potential of the Wittig olefination reaction involved TIPP as model phosphoran in the reaction with 7a. This gave 35% of solid 10a, but NMR examination of the mother liquors showed these to consist mostly of non-tosyl system 11a. This situation worsened when 7b, obtained from 8b was treated with TIPP; only minor amounts of 10b

resulted (NMR inspection), the major product consisting of detosylated material (based on the absence of the characteristic tosyl CH_3 signal and the appearance of extra olefinic protons at 6.20-6.90 ppm). This approach was abandoned in



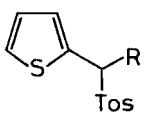
7a,b 10a,b 11a,b

a: Ar = phenyl

b: Ar = 2-thienyl

favor of one involving reversal of the Wittig components; attention was therefore directed to the preparation of 12e.

2-Thienyl(p-toluenesulfonyl)methane 12a was derived from 2(chloromethyl)thiophene[8] and NaTos, according to the procedure for the phenyl analog. Treatment in THF with BuLi followed by ethylene oxide led cleanly to 87% of 12b. The



12a-e

a: R = H

b: R = CH_2CH_2OH

c: R = CH_2CH_2OTos

d: R = CH_2CH_2I

e: R = $CH_2CH_2P^+(C_6H_5)_3I^-$

alcohol was converted to iodide 12d via tosyl ester 12c and treatment with sodium iodide. The reaction with triphenylphosphine then furnished phosphonium salt 12e. The ylid, derived from 12e on BuLi treatment gave in its reaction with acetone multi-component intractable mixtures. In retrospect, this is not surprising since in 12e all aliphatically bonded hydrogens are somewhat acidic. Both the tosyl and triphenylphosphonium fragments are potential leaving groups, so that deprotonation of any of the sp^3 carbon atoms of 12e could well lead to undesirable reactions.

II.4 Summary and Conclusions

The reaction of 3-arylpropenals 9a-d with 2 equiv of TosH has been shown to produce diadducts 6a-d, thus resolving a literature ambiguity.[11] The products lose a molecule of TosH under mildly basic conditions to provide 7a,b and give, on treatment with ethylene glycol the corresponding dioxolanes 8a-d. The latter are also obtained directly from 9a-d by treatment with 2 equiv of TosH in excess ethylene glycol at 100-125 °C.[7]

Aldehydes 7a,b are demonstrated to be unsuitable for model olefination reactions with triphenyl isopropylidene-phosphorane. It was therefore decided to abandon the Johnson--derived Wittig approach to the projected tosylated *trans*--olefinic cyclization precursors (i.e. II→I as depicted schematically in Fig. II. 1) in favor of potentially more productive strategies described in subsequent chapters.

II.5 Experimental Section

Nuclear resonance spectra (NMR) were recorded on a Varian EM 360-A spectrometer. Melting points were determined on a Fisher-Johns block and are uncorrected. 3-Phenyl-, 3-(o-nitrophenyl)-, and 3-(2-furyl)propenal were obtained from Aldrich Europe. 3-(2-Thienyl)propenal was prepared from diethyl-2--(cyclohexylamino)vinylphosphonate[16] and thiophene-2-carboxaldehyde in 80% yield, paralleling directions for synthesizing cyclohexylideneacetaldehyde.[17]

►*Phenyl-(p-toluenesulfonyl)methane (4).*

To a stirred mixture of 142 g (0.800 mol) of NaTos in 170 mL of DMF was added 101 g (0.800 mol) of benzyl chloride. The temperature was adjusted to 110 °C, initiating an exothermic reaction which made the temperature climb to 140 °C. After an additional hour of stirring at ambient temperature the suspension was poured onto 800 mL of water. Product was collected by filtration and was then washed successively with water, cold ethyl alcohol, and ether to give 162 g (82%) of air-dried 4; mp 145-146 °C (lit. mp 148-149 °C).[18]

► *1,2-Diphenyl-1-(p-toluenesulfonyl)ethane (5a).*

To 12.3 g (0.050 mol) of 4 in 120 mL of dry THF was added, at -65 °C, 42 mL (0.060 mol) of commercial 15% BuLi in hexane. After the mixture was stirred for 15 min, 7.48 g (0.060 mol) of benzyl chloride was introduced at -65 °C. After 0.5 h the mixture was allowed to come to room temperature, and stirring was continued overnight. Addition of 500 mL of water and 100 mL of ether, filtration, and washing of the product with water furnished 11.3 g (67%) of air-dried material, mp 176--178 °C. Analytical material was obtained from toluene: mp 181-182 °C; ^{1}H NMR δ ($CDCl_3$): 2.32 (s,3,$TosCH_3$), 3.03-4.36 (m,3,$CHCH_2$), 6.71-7.36 (m,14,ArH).

Anal. Calcd. for $C_{21}H_{20}O_2S$: C, 74.76; H, 5.99. Found: C, 75.23; H, 6.12.

► *4-Phenyl-4-(p-toluenesulfonyl)but-1-yne (5b).*

The anion of 4 was prepared as above from 1.23 g (0.005 mol) of 4 in 12 mL of dry THF and 4.2 mL (0.006 mol) of 15% commercial BuLi in hexane. Addition at -65 °C of propargyl bromide and stirring for 0.5 h at -65 °C and then room temperature for 18 h gave, on pouring into water, solid product. It was collected by filtration, was washed successively with water, ethyl alcohol and ether, and was then air-dried to give 0.85 g (60%) of 5b. Recrystallization from isopropyl alcohol gave analytically pure product: mp 182-183 °C. ^{1}H NMR δ ($CDCl_3$): 1.72-1.90 (m,1,CCH), 2.33 (s,3,$TosCH_3$), 2.87-3.30 (m,2,CH_2), 4.03-4.40 (m,1,CHTos), 6.88-7.57 (m,9,ArH).

Anal. Calcd. for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67. Found: C, 71.77; H, 5.65.

The synthesis of bis-sulfones 6b-d (Table III), is exemplified by the preparation of 6a.

► *3-Phenyl-1,3-bis(toluenesulfonyl)propan-1-ol (6a).*

To a stirred mixture of 13.2 g (0.100 mol) of 3-phenylpropenal in 200 mL of ether and 35.8 g (0.200 mol) of NaTos in 200 mL of water was added dropwise 200 mL of 1N hydrochloric acid.

A white precipitate formed immediately. Stirring was continued for 18 h; the solids were then filtered off and washed with water, ethyl alcohol and ether to give, after air drying, 40.5 g (91%) of product melting at 125-128 °C. Analytical material was obtained by recrystallization from THF-hexane: mp 128--129 °C. ^{1}H NMR δ (Me_2SO-d_6): 2.19-2.57 (m,2,CH_2), 2.57 (2 s, 6, TosCH_3), 3.18-3.41 (m,1,OH), 3.65-4.65 (m,2,CHTos and OCHTos), 6.82-7.70 (m,13,ArH).

Anal. Calcd. for $C_{23}H_{24}O_5S_2$: C, 62.14; H, 5.44. Found: C, 62.39; H, 5.70.

► *3-Phenyl-3-(p-toluenesulfonyl)propanal (7a).*

To a well-stirred suspension of 22 g (0.050 mol) of 6a in 150 mL of water and 100 mL of ether was added 5.05 g (0.050 mol) of triethylamine. After 18 h of stirring, the solids were filtered off and were rinsed with water and ether. The dried material, 12 g (83%), melted at 122-123 °C. Analytical material was obtained on recrystallization from toluene-hexane: mp 122-123 °C. ^{1}H NMR δ ($CDCl_3$): 2.34 (s,3,TosCH_3), 2.88-3.79 (m,2,CH_2), 4.49-4.81 (m,1,CHTos), 6.88-7.56 (m,9,ArH), 9.58 (t,1,CHO).

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59. Found: C, 66.50; H, 5.49.

The preparation procedure leading to 8b,c (Table III) is given in detail for 8a.

► *2-[2-Phenyl-2-(p-toluenesulfonyl)ethyl]-1,3-dioxolane (8a).*

Method A. *From* 6a *and Ethylene Glycol.*

To a beaker containing 7 mL of boiling ethylene glycol was added 4.44 g (0.01 mol) of 6a, immediately followed by 15 mL of ice-cold 2-propanol. The mixture was cooled on ice, and product was collected by filtration; it was rinsed with fresh isopropyl alcohol and then with diisopropyl ether to provide 2.5 g (75%) of dry product melting at 158-159 °C. ^{1}H NMR δ ($CDCl_3$): 2.28-2.70 (m,2,CH_2), 2.40 (s,3,TosCH_3), 3.55-3.92 (m,4,$(OCH_2)_2$), 4.08-4.85 (m,2,CHTos and $CH(OC)_2$), 6.87-7.35 (m,9,ArH).

Anal. Calcd. for $C_{18}H_{20}O_4S$: C, 65.03; H, 6.06. Found: C, 65.15; H, 6.10.

Method B. *From 3-Phenylpropenal, TosH, and Ethylene Glycol.* To a solution of 3.12 g (0.02 mol) of dry TosH (prepared freshly from the sodium salt) in 3 mL of ethylene glycol, preheated to 125 °C, was added 1.32 g (0.01 mol) of cinnamaldehyde. After 3 min more at 125 °C, 3 mL of isopropanol were added. Cooling, filtration and rinsing with isopropyl alcohol and diisopropyl ether gave 2.9 g (90%) of material, mp 158-159 °C, identical with the product obtained via method A.

► *2-Thienyl(p-toluenesulfonyl)methane (12a).*

Analogous to 4; yield 70%; mp 131-132 °C. Analytical material from ethyl alcohol had mp 132-133 °C. ^{1}H NMR δ ($CDCl_3$): 2.39 (s,3,TosCH$_3$), 4.30 (s,2,CH$_2$), 6.70-7.65 (m,7,ArH).

Anal. Calcd. for $C_{12}H_{12}O_2S_2$: C, 57.11; H, 4.79. Found: C, 57.28; H, 4.64.

► *1-(2-Thienyl)-1-(p-toluenesulfonyl)propan-3-ol (12b).*

To a stirred solution of 25.2 g (0.10 mol) of 12a in 50 mL of dry THF was added dropwise, at 0 °C, 84 mL of commercial 15% BuLi in hexane (0.20 mol). Lithiation was allowed to proceed for 0.5 h at room temperature; the temperature was then lowered to -30 °C and 8.8 g (0.20 mol) of ethylene oxide was introduced. After 0.5 h the mixture was allowed to come to room temperature, kept there for 0.5 h, and then quenched by addition of 200 mL of water. This afforded solid material, which was filtered and rinsed with fresh water. The product was taken up in a minimum of chloroform, dried and stripped, leaving 25.5 g (87%) of carbinol, mp 140 °C. A sample was purified from toluene: mp 143-144 °C. ^{1}H NMR δ ($CDCl_3$): 1.84-2.96 (m,3, CH$_2$CTos and OH), 2.39 (s,3,TosCH$_3$), 3.13-4.04 (m,2,CH$_2$O), 4.63 (dd,1,CHTos), 6.62-7.61 (m,7,ArH).

Anal. Calcd. for $C_{14}H_{16}O_3S_2$: C, 56.73; H, 5.44. Found: C, 56.96; H, 5.51.

► *1-(2-Thienyl)-1-(p-toluenesulfonyl)prop-3-yl-p-toluenesulfonate (12c).*

p-Toluenesulfonyl chloride, 14 g (0.073 mol), was added to 20 g (0.067 mol) of carbinol 12b in 40 mL of pyridine at -5 °C. After 18 h at -5 °C it was poured onto 500 mL of stirred ice-water, ultimately giving solid product. Filtration, washing with water, and finally trituration with isopropyl alcohol yielded 28.1 g of brown material, mp ca 95 °C. This was repeatedly leached out with small portions of boiling dibutyl ether, depositing, on cooling 14.7 g (48%) of crystals, which on isopropyl alcohol trituration had mp 104-105 °C. Analytical material was obtained on recrystallization from methyl alcohol: mp 106-107°C. ^{1}H NMR δ ($CDCl_3$): 2.01-3.26 (m,2,CH_2CTos), 2.38 2 s,6,2 TosCH_3), 3.26-4.27 (m,2,CH_2OTos), 4.43 (dd,1,CHTos), 6.53-7.77 (m,11,ArH).

Anal. Calcd. for $C_{21}H_{22}O_5S_3$: C, 55.97; H, 4.92. Found: C, 56.17; H, 5.01.

► *1-(2-Thienyl)-1-(p-toluenesulfonyl)-3-iodopropane (12d).*

A stirred solution of 14.8 g (0.033 mol) of 12c and 14.8 g (0.099 mol) of sodium iodide in 110 mL of acetone was allowed to reflux for 1 h. The solids were removed by filtration and the filtrate was evaporated; the residue was partitioned between benzene and water. Scrubbing of the organic phase with water, drying, and solvent removal left crude product which was triturated with methyl alcohol. This material, 12.4 g (93%), had mp 101 °C. A sample was recrystallized from methyl alcohol: mp 101-102 °C. ^{1}H NMR δ ($CDCl_3$): 2.40 (s,3,TosCH_3), 2.40-3.46 (m,4,CH_2CH_2), 4.51 (dd,1,CHTos), 6.75-7.52 (m,7,ArH).

Anal. Calcd. for $C_{14}H_{15}IO_2S_2$: C, 41.38; H, 3.72. Found: C, 41.60; H, 3.75.

► *1-(2-Thienyl)-1-(p-toluenesulfonyl)prop-3-ylphosphonium Iodide (12e).*

A solution of 4.06 g (0.01 mol) of 12d, 2.6 g (0.01 mol) of triphenylphosphine, and 10 mL of toluene was refluxed for 2 h. The mixture was cooled, and the toluene was then decanted from

the produced oily layer; this was rubbed with ether to give 4.7 g (70%) of solid product, mp 202-204 °C, which was recrystallized from ethyl alcohol-acetone-ether: mp 204-205 °C. ^{1}H NMR δ ($CDCl_3$): 2.08-3.50 (m,4,CH_2CH_2), 2.34 (s,3,$TosCH_3$), 5.78 (dd,1,CHTos), 6.65-8.02 (m,22,ArH).

Anal. Calcd. for $C_{32}H_{30}IO_2PS_2$: C, 57.49; H, 4.52. Found: C, 57.38; H, 4.70.

Table III. Preparation and Physical Properties of Compounds 6b-d and 8b-d

compd	exptl conds[a]	yield, %[b]	mp, °C (recrystn solvent)[c]	^{1}H NMR, δ
6b	a	43	107-109 (acetonitrile--isopropyl ether)	2.26-2.64 (m,2,CH_2), 2.41 (2 s,6,2 TosCH_3), 3.01-3.45 (m,1, OH), 3.87-5.27 (m,2,CHTos and OCHTos), 6.06-7.67 (m,11,ArH)
6c	a	61	98-101 (acetonitrile--isopropyl ether)	2.22-2.82 (m,2,CH_2), 2.40 (2 s,6,2 TosCH_3), 3.30-3.52 (m,1, OH), 3.92-4.74 (m,2,CHTos and OCHTos), 6.06-7.67 (m,7,ArH)
6d	a	86	109-111 (THF-petroleum ether)	2.22-2.68 (m,2,CH_2) 2.41 (2 s,6,2 TosCH_3), 3.29-3.58 (m,1, OH), 3.58-4.82 (m,2,CHTos and OCHTos), 6.95-8.02 (m,7,ArH)
8b	b	80	139-140 (benzene--isopropyl ether)	2.14-2.73 (m,2,CH_2), 2.34 (s,3,TosCH_3), 3.48-4.06 (m,4,$(OCH_2)_2$), 4.29-5.00 (m,2,CHTos and $CH(OC)_2$), 6.54-7.74 (m,7,ArH)
	c	69		
8c	b	77	126-127 (benzene--petroleum ether)	2.29-2.62 (m,2,CH_2), 2.39 (s,3,TosCH_3), 3.64-3.95 (m,4,$(OCH_2)_2$), 4.28-4.91 (m,2,CHTos and $CH(OC)_2$), 6.08-7.34 (m,7,ArH)
8d	b	77	111-112 (benzene--isopropyl ether)	2.38 (s,3,TosCH_3), 2.46-2.75 (m,2,CH_2), 3.41-4.00 (m,4,$(OCH_2)_2$), 4.76 (t,1,$CH(OC)_2$), 5.37-5.67 (m,1,CHTos), 7.00-7.98 (m,8,ArH)
	c	60		

[a](a) Reaction of appropriate 3-arylpropenals with 2 equiv of TosH for 18 h at room temperature as for 6a. (b) Identical with method A, given for 8a. (c) Method B, as described for 8a. [b]Figures correspond to crude yields of material melting not less than 5°C below the analytical melting point. [c]Satisfactory C, H analyses (± 0.30 %) were reported.

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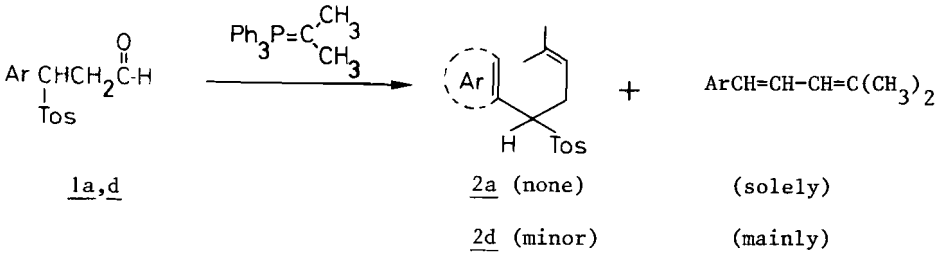
CHAPTER III

Some Tetrahydrobenzo[*b*]thiophenes and -naphthalenes via Dibal-H-mediated Detosylations of Cycloalkylation-derived Products: a New Approach.

III.1 Introduction

In the previous chapter efforts were described to prepare model structures 2a,d via olefination of aldehydes 1a,d for testing this key transformation to generate ultimately *trans*-olefinic tosylated steroidal precursors of type I. These studies had demonstrated that the β-tosyl aldehydes 1a,d suffer predominantly tosyl elimination on treatment with the strongly basic triphenyl isopropylidene phosphorane, thus effectively blocking Wittig-Schlosser-based approaches to I.



1a,d

2a (none)

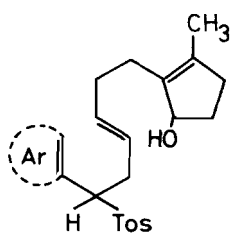
2d (minor)

(solely)

(mainly)

a: Ar = 2-thienyl

b: Ar = phenyl



I

The desirability of having model structures at ones' disposal for testing new procedures underlays continued efforts to prepare 2a,d via alternative non-olefinic routes. An obvious entry would involve prenylation of aryltosyl methanes 3a,d since these had already been described[1] and would no doubt be suitable for base-promoted alkylation with the highly electrophilic prenyl bromide. Section III. 2 of this chapter will deal with the preparation and prenylation of 3a-d, their subsequent cyclization to 4a-d and the concluding removal of the tosyl auxiliary to supply 5a-d. As our cyclization and detosylation modes are synthetically novel, some structural aspects relating to their scope and limitations have been investigated and are discussed in section III. 3.

III.2 Compounds 2a-d: Preparation and Conversion to 5a-d via Cyclization and Subsequent Detosylation [2]

Exploratory investigation mostly involved 2-thienyl-derived systems, primarily because the starting material, 2-thienyl-tosyl methane 3a, happened to be amply available at the time and also because cycloalkylation onto thiophenes is known to occur readily. Furthermore, the so produced tetrahydrobenzo[*b*]-thiophenes would be of interest in their own right. Clearly success of the overall scheme would hinge on uncovering reaction conditions of sufficient power to bring about cyclization, yet mild enough to allow the tosyl fragment to come through unscathed.

The experimental background in alkylating aryltosyl methanes (Chapter II) was put to use in prenylating 3a to 2a (76%) except that here the transformation was achieved under phase transfer conditions, partly because some publications bearing on similar alkylation of related systems had then just appeared.[3] Phase transfer techniques offer some distinct advantages over classical non-aqueous reaction procedures in being able to dispense with organic solvents and also in not having to operate under strictly anhydrous conditions and a nitrogen atmosphere. In practice the potential nucleophile and electrophile are merely stirred in 30-50% NaOH in the presence of catalytic amounts of a quaternary ammonium catalyst. Work-up of the

reaction mixture is extremely simple and is accomplished via extraction or filtration, if the product is a solid. Phase transfer technology is thus ideally suited for large scale operations and represents the method of choice for many modern industrial processes. Many of the reactions described in this dissertation were realized in this fashion. The growing interest in phase transfer techniques is reflected in several recent reviews and monographs.[4]

The preparation of aryltosyl methanes 3b-d paralleled that of 3a; compounds $ArCH_2Cl$ were allowed to react with NaTos in DMF. An ensuing phase transfer treatment of 3b-d with prenyl bromide in the system 50% NaOH-THF-tetrabutylammonium bromide then furnished prenylated derivatives 2b-d in 77-, 78- and 82% yields respectively.

Initial cyclization attempts were conducted on 2-thienyl derivative 2a and were monitored by observing the NMR shifts of the *gem*-dimethyl signals from 1.6 to 1.0 ppm in the ring closed materials. Results were extremely disappointing at first. Conditions such as trifluoroacetic acid in methylene chloride, reported earlier as effective for cyclizing the non-tosyl analog of 2a,[5] gave, at ambient temperatures after 6 h, no reaction and produced tars on raising the temperature. This also occurred in sulfuric acid, either concentrated at 0 °C, as a 50% solution at reflux temperatures, or as a refluxing 5% solution in acetic acid.[6] Ethereal BF_3[6] gave the same results. A system frequently used in cationic cyclization reactions is tin tetrachloride in methylene chloride.[7] With 2a this failed to bring about reaction at -78 °C (0.5 h) or at 0 °C (1.5 h), and led to decomposition in 2.5 h at 20 °C. A variety of other conditions such as P_2O_5 in CH_3SO_3H,[8a] polyphosphoric acid pure, or in chlorobenzene,[8b] $AlCl_3$ in $MeCl_2$,[6] $ZnCl_2$ in CH_3NO_2,[7] formic acid with trifluoroacetic acid or with sodium formiate, or acetic acid with its anhydride gave no reaction at 20 °C, and led to total resinification at higher temperatures.

The desired cyclization would undoubtedly proceed via spectrally detectable cationic species, which suggested the reaction to be performed in NMR tubes in order to follow any changes. When 2a was dissolved in SO_2, a solvent frequently

used for generating and demonstrating the presence of carbonium ions, no discernable NMR changes were noted. Addition of traces of fluorosulfuric acid, however, produced an almost instantaneous change of the thienyl signals into an AB-pattern as the *gem*-dimethyl signals moved from 1.61 to 0.95 and 1.10 ppm as expected if cyclization had occurred. The conditions for effectuating the ring closure were subsequently modified and adapted for synthetically productive conversions. It was ultimately found that treatment of 2a in liquid SO_2 at -78 °C with a 10% molar amount of freshly distilled FSO_3H (the purity of the acid turned out to be critical) and quenching the system in water after 1 minute afforded consistently 65% yield of solid, purified 4a in batches running up to 15 g. Although the system FSO_3H/SO_2 has been extensively used in spectroscopic studies, its application in steering processes unidirectionally towards synthetically usable transformations seems to have been rather limited.[9] Treatment of analogs 2b-d in FSO_3H/SO_2 produced 4b-d in good yields; in these cases cyclizations required the use of equivalent amounts of FSO_3H rather than the catalytic quantities sufficing for cyclizing 2a.

A number of aspects bearing on the FSO_3H/SO_2-induced cycloalkylation of aliphatically tosylated olefinic substrates deserve further comment. Failure to bring about ring closures in all but the SO_2-run reactions undoubtedly reflects the solvation and stabilization of the cationic intermediates in this medium, thereby affording them sufficient time for attaining cyclization--productive conformations. The process is unusually fast and clean, providing colorless reaction mixtures on work-up from which good yields of cyclized materials are readily isolated. The method is not restricted to electrophilically sensitive aromatic systems only, since thienyl- and dimethoxyphenyl-derived systems 2a-c as well as unsubstituted phenyl analog 2d also undergo the ring closure. Of paramount importance, though, is that the tosyl group survives the reaction conditions and emerges intact in the cyclized version. The synthetic power of sulfones in general and the tosyl group in particular has been amply documented.[10] These fragments all enhance adjacent C-H acidity and will stabilize any subsequently generated carbanion.

Such species have been shown to react with a variety of electrophiles after which the activating segment, having served its purpose, may be removed. In this sense, the tosyl group especially, represents a true auxiliary since it stabilizes a carbanion to which it is attached while being of sufficient nucleofugicity to be replacable by hydrogen.[11] Because this fragment emerges intact from the above cyclization conditions, any intended tosyl-dependent manipulations could hence be performed early at the acyclic stage or subsequently on the cyclized version. As discussed in section III. 3 however, this turned out to be only partially true.

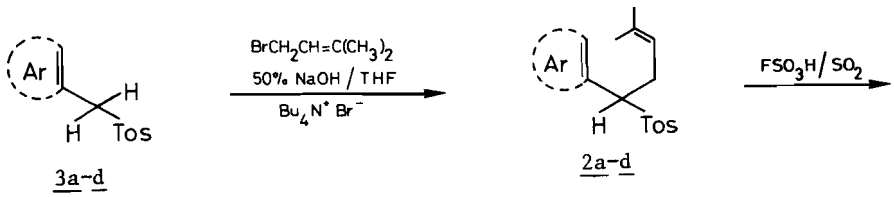
Attention was turned next to removal of the tosyl fragment from bicyclic material 4a-d with, again, the 2-thienyl--derived 4a serving as prototype. Detosylation of saturated carbon atoms is reported to be achieved by a number of methods. These include Li-$EtNH_2$,[12a,b] Na-Hg,[13a-d] and Zn-HOAc.[14] Such reagents have one thing in common: by analogy to reductions of other substrates they act via electron-transfer protonation. Thiophenes, however, have been shown to be vulnerable to such conditions,[15] prompting a search for alternative detosylation methods.

During the course of related work, there arose the need to deoxygenate 2a to its corresponding sulfide. Earlier work by Gardner had shown Dibal-H to be an effective agent for reducing sulfones to sulfides.[16] We chose to test the procedure on 2a; on reacting it with Dibal-H, however, the odor of p-thiocresol was soon unmistakable and work-up of the reaction mixture afforded a 70% yield of detosylated material. Dibal-H became therefore a logical potential detosylating agent for 4a-d.

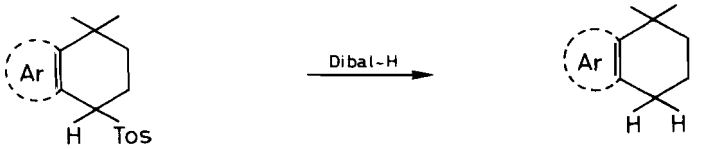
The reaction of 4a with 1.5 equiv of Dibal-H in toluene as monitored by TLC was highly exothermic and complete within 1 min. Isobutene evolved, which was trapped and characterized by NMR. Aqueous, alkaline work-up subsequently produced totally desulfonylated 5a in NMR-pure 70% isolated yield. Similar treatment of 4b-d with 3 equiv of Dibal-H provided the corresponding 5b-d.

These results are at variance with the Dibal-H-mediated sulfone→sulfide reductions reported by Gardner.[16] This discrep-

ancy was first thought to stem from the proximity of thiophene sulfur to the sulfone fragment, suggesting possible intermed-



3a-d 2a-d



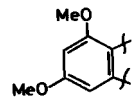
4a-d 5a-d

3 and 2 a: Ar = 2-thienyl
b: Ar = 3-thienyl
c: Ar = 3,5-dimethoxyphenyl
d: Ar = phenyl

4 and 5 a: Ar =

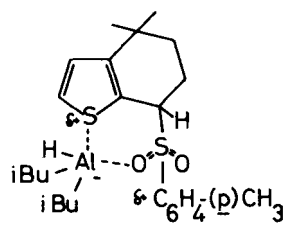
b: Ar =

c: Ar =



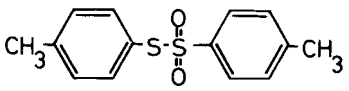
d: Ar =

iacy of a chelated or loosely bound cyclic S-Al-O complex 6 facilitating hydride delivery to the C-7 reaction site either from aluminum or the isobutyl β-carbon. However, as the



6

detosylation reaction had been shown to extend beyond the 2-thienyl derived substrates to encompass 3-thienyl analog 4b and phenyl systems 4c,d, this overall view had to be ruled out. Nonetheless, there is indirect but compelling evidence for singling out the detosylation of 4a as a special case that indeed involves the intermediacy of 6. The reasoning is the following. Dibal-H induced detosylation of 4a proceeded faster and more exothermically than all other cases examined and turned out to be the only reaction that required only 1 equivalent of reducing agent, as opposed to 4b-d, the detosylation of which demanded 3 equiv of Dibal-H and, even then, was shown to proceed much slower. Although the mechanistic study of this reaction was beyond the scope of the project some significant data soon emerged. The detosylation of 4a produced, besides 5a, significant amounts of thiosulfonate ester 7 identified by spectra and melting point.[17] Such esters are known to arise via Tishchenko-like disproportionation--esterification sequences out of sulfinic acids.[17] The more



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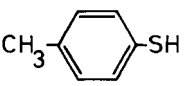


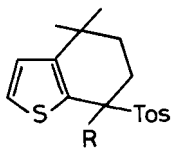
8

sluggish detosylations of 4b-d, having required 3 equiv of Dibal-H, unmistakably produced p-thiocresol 8 rather than 7, most likely by way of Dibal-H reduction of the displaced toluenesulfinate. This possibility was verified by control experiments which showed Dibal-H to reduce freshly prepared p-toluenesulfinic acid to p-thiocresol under the reaction conditions. The reagent would thereby be prematurely consumed thus accounting for Dibal-H having to be present in excess. The sum total of the data relating to the detosylation of 4a, i.e. the fast and highly exothermic process producing, besides 5a, 7 but not p-thiocresol 8, plus the need for only 1 equiv of Dibal-H can be accommodated by invoking the intermediacy of cyclic 6 which, owing to its rigidity, would promote rapid

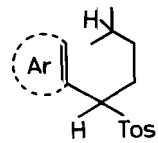
hydride delivery to C-7 to produce 5a; the Dibal-H would thus be used up quickly enough to prevent its premature destruction by sulfinate reduction, permitting it ultimately to be converted to thiosulfonate ester 7 instead. On the other hand, substrates 4b-d, being unsuitable for forming chelates like 6 would tend to detosylate more slowly, thus providing the Dibal-H sufficient time to reduce the slowly forming sulfinate to p-thiocresol 8. The inability of 4b-d to produce chelates would not preclude Dibal-H coordinating via oxygen only; this would certainly be in line with the expected behavior of such an electrophilic agent.

III.3 The Reaction of Variously Tosylated Substrates with Dibal-H

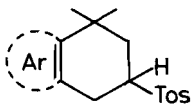
The discrepancy of the cited results with those in the literature[16] warranted a brief diversion to examine the effect of Dibal-H on some other tosylated substrates. Four modifications have been examined. Types II and III represent α-tosylated systems ("α" in this context denotes the position with respect to the aromatic fragment), either as 7-alkylated versions of 4a or as ring-disrupted variations of 4a,b,d. Systems featuring the tosyl fragment β to the aryl system and isomeric with 4a,b,d are represented by IV and are, as open ring analogs, depicted as V. The following subsections will deal with the preparation of representative examples of each type and their behavior towards Dibal-H



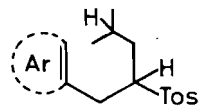
II



III



IV

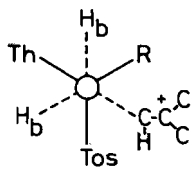


V

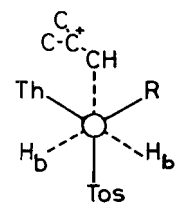
III.3.1 Compounds 11a-c: Synthesis and Reaction with Dibal-H

Compounds 11a-c were prepared via two routes. Treatment of 3a with ethyl bromide or benzyl chloride under phase transfer conditions produced 9b,c, but failed to give reproducable yields of methyl analog 9a. This was ultimately prepared by methylating the 3a-anion, generated by BuLi, in THF. Phase transfer prenylation of 9b,c yielded 10b,c systems which could also be obtained by ethylating or benzylating 2a under the same circumstances. The preparation of 10a was achieved by methylating the BuLi-derived anion of 2a. Drawing on previous experience, the behavior of 10a-c in FSO_3H/SO_2 was investigated next, progress of the reaction being followed via NMR observation of the *gem*-dimethyl shifts. Cyclization of methyl analog 10a in SO_2 using catalytic amounts of FSO_3H proceeded considerably slower than 3a, but gave, in the presence of 1 mol-equivalent of acid, 44% of isolated 11a after 5 h at -78 °C. Such conditions provided only 4% of 11b from 10b and no more than spectrally detectable 11c from 10c. Compounds 11b,c were, in practice, more conveniently accessible via phase transfer alkylation of 4a; methyl analog 11a was again obtained most easily by conventional methylation of the 4a anion in THF.

The cyclization results are best interpreted by inspection of the Newman projections. Ring closure requires suitably pre-positioned cations in conformation ii; other conformations, for instance i, would not be expected to furnish cycloalkylated materials. Non-bonded interactions generated on trying to ring close 10a-c would clearly impede such a process, as the steric demands in going from H through methyl and ethyl to benzyl increase. Failure to effect ring closure of compounds like 10



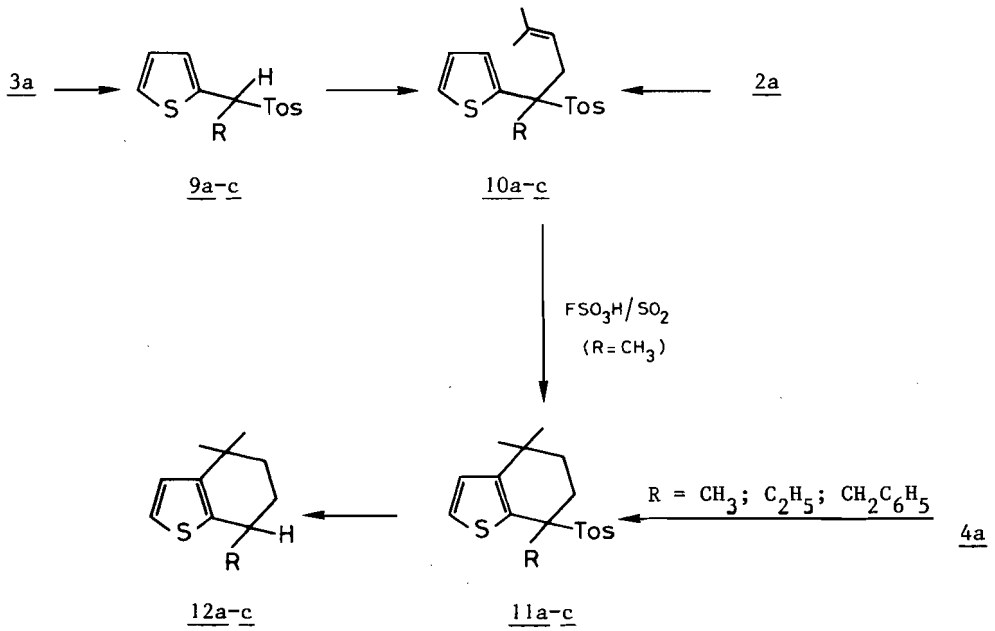
i



ii

carrying bulky α-substituents is therefore not surprising.

Optimal conditions for the Dibal-H reaction with 11a-c were again TLC-monitored. Whereas 2a had been previously shown to be completely consumed on using 1.5 equiv of Dibal-H, complete disappearance of 11a-c required 3 equiv of the reagent. All cases examined led to completely detosylated 12a-c in synthetically clean and good-yield processes (Table II). The more drastic conditions required for detosylating 11a-c might well stem from the sterically demanding alkyl substituents interfering with formation of chelates like 6. Unfavorable

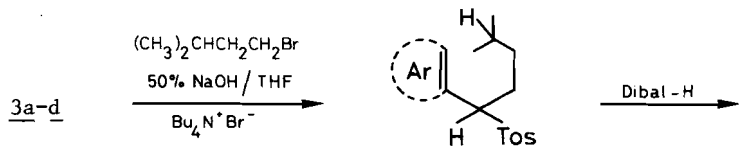


conformational factors operative at C-7 might also play a role, for instance, by reducing the tosyl groups' nucleofugicity, thereby slowing the process down. Substantiating data are, however, not available.

III.3.2 Compounds 13a-d: Synthesis and Reaction with Dibal-H[18]

Attention was turned next to preparing open systems 13a-d for purposes of comparing their reaction with Dibal-H to those of rigid structures 4a-d. The substrates were, as before, obtained via phase transfer techniques involving 4 equiv of isoamyl bromide to achieve optimum results. The need for excess of alkylating agent is in line with its documented limited reactivity.[19] The reaction co-produced some dialkylated byproducts which were removed by isopropyl ether trituration to leave 39-68% of 13a-d (Table III).

Initiation of the Dibal-H reaction called for higher temperatures than hitherto required as evidenced by the beginning of isobutene evolution and the measurement of an exotherm. For 13a with Dibal-H in toluene, the temperature had to be adjusted to 50 °C for reaction to commence; this occurred only at 80 °C for 13b and required 100 °C for 13c,d. These figures are approximate only but do suggest 2-thienyl-derived 13a to be the most detosylation-prone of the series, conceivably due to proximity of the thiophene sulfur to the sulfone array exerting a favorable effect on the reaction rate. The need for more elevated temperatures for inducing 13a-d to react would suggest these systems to be more resistent to detosylation than their cyclic congeners 4a-d. All reactions led to detosylated materials 14a-d in good yields (Table III).



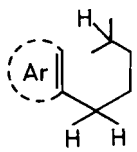
13a-d

a: Ar = 2-thienyl

b: Ar = 3-thienyl

c: Ar = 3,5-dimethoxyphenyl

d: Ar = phenyl

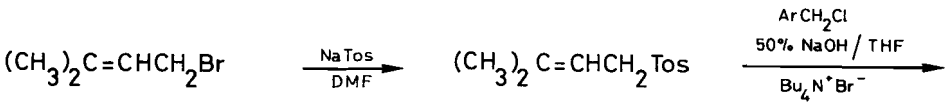


14a-d

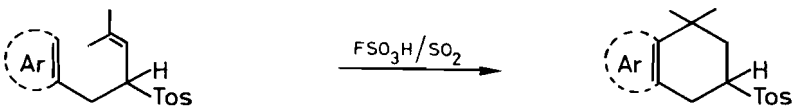
III.3.3 Compounds 17a-c and 20a-c: Synthesis and Reaction with Dibal-H[18]

Structures 17a-c, which differ from 4a,b,d in that the tosyl group is β rather than α to the aromatic component, were considered next. Their synthesis began with prenyl bromide which, when treated with NaTos in DMF, produced tosylated 15 in excellent yield.[20] The fact that the CH_2 group of 15 is flanked by two activating groups made satisfactory phase transfer alkylations with 2- and 3-thienyl- and benzyl chloride possible to furnish systems 16a-c (Table III). These compounds, although isomeric with 2a,b,d, differ strikingly as evidenced by their resistance to FSO_3H/SO_2 promoted cyclization. In contrast to their α-congeners, β-isomers 16a-c in SO_2 failed to cyclize in the presence of 1 equiv of acid but required at least 6 equiv of FSO_3H and contact times of 18 h in SO_2 to produce acceptable yields of ring closed 17a-c (Table III).

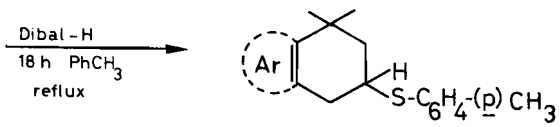
The behavior of these β-tosylated systems with Dibal-H was then determined and was, in this respect also, found to differ entirely from their α-substituted counterparts. Whereas



15



16a-c 17a-c



18a-c

a: Ar = 2-thienyl

b: Ar = 3-thienyl

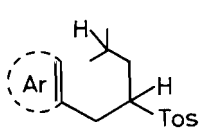
c: Ar = phenyl

4a,b,d had reacted vigorously and highly exothermically with 1.5-3 equiv of Dibal-H to produce detosylated materials, compounds 17a-c with Dibal-H gave neither an exothermic reaction nor any detectable isobutene after even 3 h. On refluxing such mixtures for 18 h, thus essentially reproducing Gardners' conditions,[16] small amounts of sulfides 18a-c were chromatographically separated from the reaction mixture, with the main components consisting of unreacted sulfones. Sulfide identification was based on NMR inspection, which showed the absence of CHTos at 3.00-3.60 ppm, with all other aromatic and aliphatic protons being accounted for. IR Data indicated also the absence of sulfone- and sulfoxide bands.

Compounds 20a-c represent monocyclic variants of β-tosylated bicyclics 17a-c and were prepared somewhat accordingly. Treatment of isoamyl bromide with NaTos in DMF gave the tosylated 19. This compound, whose terminal CH_2 was insufficiently activated to permit aqueous phase transfer alkylations, was deprotonated with BuLi in THF instead and gave then 20a-c on treatment with the appropriate arylmethyl chlorides (Table III). These sulfones were then subjected to the action of Dibal-H in refluxing toluene for 18 h to give minor amounts of sulfides 21a-c with mostly unreacted sulfones still being present.

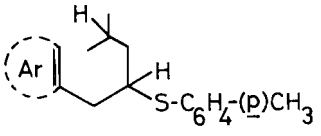
$$(CH_3)_2CHCH_2CH_2Br \xrightarrow[DMF]{NaTos} (CH_3)_2CHCH_2CH_2Tos \xrightarrow[2)\ ArCH_2Cl]{1)\ BuLi}$$

19



20a-c

Dibal-H



21a-c

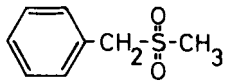
a: Ar = 2-thienyl

b: Ar = 3-thienyl

c: Ar = phenyl

III.3.4 The Dibal-H-induced Detosylation of Saturated Carbon Atoms: Concluding Remarks

The data presented clearly show Dibal-H to bring about detosylation of benzylic-type substrates only. Assuming this process to involve ionic hydride displacement of toluenesulfinate anion, the detosylation results appear to be a reflection of the susceptibility of benzylic substrates to nucleophilic substitution. In this sense our results would be expected to differ from those of Gardner.[16] Inspection of his table of reported examples shows all but one of them to have involved non-benzylic types, the exception being benzyl methyl sulfone 22. His described Dibal-H studies were carried out in refluxing



22

toluene; for 22 no product yield was cited. This is not surprising since the reaction would be expected to produce additional toluene which would escape detection: the same would not hold for the co-produced methyl mercaptan.

III.4 Summary and Conclusions

The preparation of α-tosylated systems 2a-d and 10a-c and some β-tosylated analogs 16a-c is reported. With the exception of 10b,c these are shown to undergo FSO_3H/SO_2-induced cycloalkylation in a synthetically useful process to produce bicyclic α- and β-tosylated systems 4a-d, 11a and 17a-c. Compounds 11b,c are described via ethylation and benzylation of 4a. The tosyl isomers are shown to differ markedly in their behavior towards Dibal-H. This reagent brings about rapid cleavage of tosyl moieties α with respect to an aromatic fragment, giving 5a-d, and 12a-c. β-Tosylated analogs 17a-c, on the other hand, are relatively unaffected by prolonged treatment with Dibal-H in refluxing toluene, giving, besides recovered sulfones, minor amounts of sulfides 18a-c. These results parallel the ones derived from the Dibal-H treatment of open-chained analogs 13a-d and 20a-c

which are shown to provide detosylated 14a-d and S-deoxygenated 21a-c respectively.

The FSO_3H/SO_2-mediated cycloalkylation of aliphatically tosylated substrates and the subsequent use of Dibal-H for removing tosyl fragments α to an aromatic component represent, to the best of knowledge, novel methodologies. Their scope and limitations relating to structural variations as well as some qualitative aspects bearing on the mode of the reactions are briefly examined and rationalized. In combination, the two reactions promise to offer considerable potential in the design and elaboration of practical syntheses.

III.5 Experimental Section

Nuclear resonance spectra (NMR) were recorded on a Varian EM-360A spectrometer. Melting points (recorded on a Fisher-Johns block) are uncorrected. Compounds 3b,c were prepared in 78- and 88% yield analogously to 3a,d as described in Chapter II (II-12a resp. II-4); their requisite chlorides were either obtained commercially or prepared from the corresponding benzyl alcohols via $SOCl_2$ chlorination. Prenyl bromide was prepared according to the literature;[21] the procedure was slightly modified by keeping the crude reaction mixture at reflux for 1 h prior to distillation.

The preparation procedure leading to 2b-d, 13a-d and 16a-c (Table III), to 2-substituted thiophenes 9b,c and 10b,c (Table I) and to bicyclics 11a-c (Table II) is given in detail for 2a.

► *1-(2-Thienyl)-1-(p-toluenesulfonyl)-4-methylpent-3-ene (2a).* A mixture of 6.3 g (0.025 mol) of 3a, 4.1 g (0.027 mol) of prenyl bromide, 37.5 mL of 50% sodium hydroxide, 10 mL of THF and 0.5 g of tetrabutylammonium bromide was thoroughly stirred for 18 h at room temperature. Water (500 mL) was added to give a solid product, which was then filtered off and washed with water, isopropyl alcohol, and diisopropyl ether respectively. The yield was 6.1 g (76%), mp 106 °C; analytical material from toluene gave mp 107-108 °C. ^1H NMR δ ($CDCl_3$): 1.61 (s,6, $(CH_3)_2$), 2.30-3.40 (m,2,CH_2C=), 2.37 (s,3,$TosCH_3$), 4.07 (dd,1,

CHTos), 4.85 (t,1,CH=), 6.52-7.54 (m,7,ArH).

Anal. Calcd. for $C_{17}H_{20}O_2S_2$: C, 63.71; H, 6.29. Found: C, 63.73; H, 6.12.

► *2-(2-Thienyl)-2-(p-toluenesulfonyl)-5-methylhex-4-ene (10a).*

To a stirred solution of 6.4 g (0.02 mol) of 2a in 20 mL of dry THF was added, dropwise at 0 °C, 14.1 mL of commercial 15% BuLi in hexane. After the mixture was stirred for 0.5 h at room temperature, 4.26 g (0.06 mol) of methyl iodide was introduced at room temperature. Stirring was continued for 1 h, whereupon the mixture was poured onto 300 mL of water. The formed solid was filtered, rinsed with fresh water, and triturated with fresh isopropyl alcohol to furnish 6.6 g (78%) of 10a, mp 73-74 °C. Analytical material was obtained on recrystallizing from low-boiling petroleum ether-benzene: mp 74-75 °C. ^{1}H NMR δ ($CDCl_3$): 1.60 and 1.64 (2 s,9,3 CH_3), 2.33 (s,3,TosCH_3), 3.00 (br d,2,CH_2), 4.80 (t,1,C=CH), 6.65-7.40 (m,7,ArH).

Anal. Calcd. for $C_{18}H_{22}O_2S_2$: C, 64.63; H, 6.63. Found: C, 64.84; H, 6.68.

The cyclization to compounds 4b-d, 17a-c (Table III) and 11a,b (Table II) is typified by the cyclization of 2a to 4a.

► *4,4-Dimethyl-7-(p-toluenesulfonyl)-4,5,6,7-tetrahydrobenzo[b]-thiophene (4a).*

To a solution of 15 g (0.047 mol) of 2a in 40 mL of liquid sulfur dioxide at -78 °C was added 0.4 mL of freshly distilled fluorosulfuric acid. The dark mixture was stirred for 1 min and was then quenched by pouring into an ether-water mixture. The ether layer was separated, washed with water, cold 4N ammonium hydroxide solution and water until neutral, dried and evaporated to leave 15 g of crude material. Trituration in the cold with diisopropyl ether provided 9.9 g (66%) of white product, mp 90 °C. Recrystallization from diisopropyl ether furnished the analytical sample: mp 91-92 °C. ^{1}H NMR δ ($CDCl_3$): 0.95 and 1.10 (2 s, 6,2 CH_3), 1.24-1.97 (m,2,CH_2CCTos), 1.97-2.50 (m,2,CH_2CTos), 2.39 (s,3,TosCH_3), 4.38 (t,1,CHTos), 6.67-7.73 (2 AB,6,ArH).

Anal. Calcd. for $C_{17}H_{20}O_2S_2$: C, 63.71; H, 6.29. Found: C, 63.80; H, 6.46.

Detosylation experiments, leading to 5b-d and 14a-d (Table III) and to 12a-c (Table II) are fully given for 5a.

► *4,4-Dimethyl-4,5,6,7-tetrahydrobenzo[b]thiophene (5a).*

To a stirred, nitrogen-covered solution of 1.6 g (0.005 mol) of 4a in 3 mL of dry toluene was added, in one portion at room temperature, 1.5 equiv (0.0075 mol) of Dibal-H in 5 mL of toluene. Immediate evolution of isobutene was observed, together with a temperature rise to ca 100 °C. After 5 min the mixture was cooled, and to it was carefully added 0.53 mL of ethanol, 2.21 mL of water and 1.11 mL of concentrated hydrochloric acid. The organic layer was decanted and the residue was extracted with diethyl ether. The combined organic layers were washed with water, 5N sodium hydroxide solution and water until neutral, dried and evaporated to leave 0.85 g of crude material. This was filtered through silica (5 g, 70-230 mesh ASTM) and eluted with petroleum ether 40/65, ca 30 mL, to give after evaporation 0.65 g of TLC-pure product. ^{1}H NMR δ ($CDCl_3$): 1.21 (s,6,2 CH_3), 1.40-2.32 (m,4,CH_2CH_2), 2.72 (t,2,$ThCH_2$), 6.87 (AB,2,ThH).

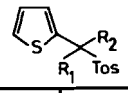
The preparation procedure leading to 20b,c (Table III) is given in detail for 20a.

► *1-(2-Thienyl)-2-(p-toluenesulfonyl)-4-methylpentane (20a).*

To a freshly prepared solution of 0.08 mol of BuLi in dry ether[22] was added, at room temperature, 16.3 g of 19 (0.075 mol) in 40 mL of ether. After the mixture was stirred for 1 h at room temperature 10.6 g of 2-thenylchloride (0.08 mol) was introduced. Stirring was continued for 1 h, whereupon the mixture was poured onto 100 mL of water. The organic layer was washed with water until neutral, dried and evaporated. Trituration in the cold with diisopropyl ether gave 4.3 g (37%) of solid material, mp 67-68 °C. Analytical material was obtained on recrystallization from diisopropyl ether and gave mp 68-69 °C. ^{1}H NMR δ ($CDCl_3$): 0.71 (dd,6,$(CH_3)_2$), 0.83-3.64 (m,6,CH_2CHCH_2CH), 2.43 (s,3,$TosCH_3$) 6.60-7.85 (m,7,ArH).

Anal. Calcd. for $C_{17}H_{22}S_2O_2$: C, 63.31; H, 6.88. Found: C, 63.24; H, 7.03.

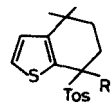
Table I. 2-Substituted Thiophenes



compd	R_1	R_2	method[a] (yield, %)[b]	mp, °C[c]
10b	ethyl	prenyl	ethylation of 2a (37) prenylation of 9b (89)	83-84
10c	benzyl	prenyl	benzylation of 2a (87) prenylation of 9b (88)	122 dec
9b	ethyl	hydrogen	ethylation of 3a (83)	116-117
9c	benzyl	hydrogen	benzylation of 3a (84)	159

[a]Phase transfer techniques as described for 2a (Experimental Section) using ethyl bromide, benzyl chloride or prenyl bromide. [b]Yield based on amount obtained with mp < 5 °C below analytical sample. [c]Satisfactory elemental analyses (C, H ± 0.30%) were found.

Table II. Substituted Tetrahydrobenzo[*b*]thiophenes



compd	R	method (yield, %)[c]	mp, °C
11a	methyl	cyclization of 10a (44)[a] methylation of 4a (78)[b]	129-130[e]
11b	ethyl	cyclization of 10b (4)[a] ethylation of 4a (69)[b]	117-118[e]
11c	benzyl	benzylation of 4a (62)[b]	dec[e]
12a	methyl	detosylation of 11a (75)[d]	liquid
12b	ethyl	detosylation of 11b (67)[d]	liquid
12c	benzyl	detosylation of 11c (63)[d]	liquid

[a]Cyclizations as for 2a, involving 1 equiv of HSO_3F. [b]Alkylations as for open systems 10a-c. [c]Yields based on amount with mp < 5 °C below analytical sample. [d]Detosylation for 5 min with 3.0 mol of Dibal-H per mol of substrate. [e]Satisfactory elemental analyses (C, H ± 0.30%) were found.

Table III. α and β Tosyl Bicyclic and Open Chain Models and their detosylation results with Dibal-H

Compd	Method	Yield %[a]	mp °C[b] recrystn. solv.
2b	A	78	99-100 diisopropyl ether
2c	A	78	118-119 diisopropyl ether
2d	A	82	116-117 diisopropyl ether
4b	B, 1 equiv of FSO_3H, 15 min	92	107-108 diisopropyl ether
4c	B, as for 4b	77	126-127 isopropyl alcohol
4d	B, as for 4b	55	148-149 diisopropyl ether
5b	C, 15 min	72	liquid
5c	C, 15 min	77	liquid
5d	C, 15 min	75	liquid
13a	A, 4 equiv of isoamyl bromide	38	92-93 diisopropyl ether
13b	A, as for 13a	58	95-96 diisopropyl ether
13c	A, as for 13a	53	80-82 diisopropyl ether
13d	A, as for 13a	69	108-109 diisopropyl ether
14a	C, 15 min, $T_{init.}$ = 50 °C	74	liquid
14b	C, 15 min, $T_{init.}$ = 80 °C	80	liquid
14c	C, 15 min, $T_{init.}$ = 100 °C	60	liquid
14d	C, 15 min, $T_{init.}$ = 100 °C	70	liquid
16a	A	82	83-84 diisopropyl ether
16b	A	61	86-87 diisopropyl ether
16c	A	80	94-95 diisopropyl ether

Table III. Continued

Compd	Method	Yield %[a]	mp °C[b] recrystn. solv.
17a	B, 12 equiv of FSO_3H, 18h	40	134-135 isopropyl alcohol
17b	B, as for 17a	40	136-137 isopropyl alcohol
17c	B, 6 equiv of FSO_3H, 15 min	54	122-123 isopropyl alcohol
18a	C, 18 h, 110 °C, N_2 atmosph	43% 17a 11% 18a	
18b	C, as for 18a	80% 17b 11% 18b	
18c	C, as for 18a	87% 17c 13% 18c	
19		87	liquid
20b	D	50	73-74 diisopropyl ether
20c	D	53	90-91 diisopropyl ether
21a	C, as for 18a	41% 20a 18% 21a	
21b	C, as for 18a	58% 20b 21% 21b	
21c	C, as for 18a	50% 20c 20% 21c	

A: Phase transfer techniques as described for 2a (see Experimental). B: Cyclizations as for 2a. C: Detosylation with 3.0 mol of Dibal-H per mol of substrate. D: BuLi alkylation of 19 as for 20a (see experimental).

[a]Yield based on amount obtained with mp < 5 °C below analytical sample. [b]Satisfactory elemental analyses (C, H ± 0.30%) were found for solid materials.

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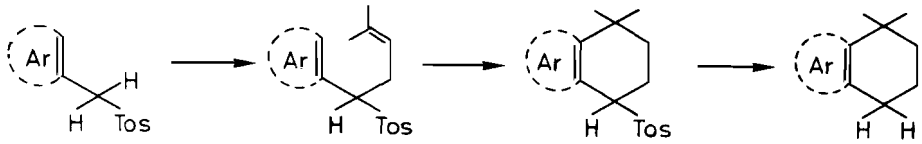
CHAPTER IV

Aromatic Resin Acid Ringsystems via Detosylation of Polyene Cyclization-derived Materials

IV.1 Introduction

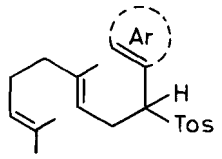
The synthesis of bicyclic sulfone III via FSO_3H/SO_2 promoted cycloalkylation from II and its Dibal-H mediated C-detosylation to afford IV were described in Chapter III. These results



I II III IV

offered sufficient perspectives to merit further investigation. In this chapter attention will be focussed on the synthesis and cyclization of some terminally prenylated homologs of II, namely V and VIII, obtained via geranylation or nerylation of I.[1]

These endeavors were undertaken for the following reasons. Assuming initiating protonation to occur mostly at the terminal double bond, ensuing concerted polycyclization *via a synchronous pathway* would, according to Stork-Eschenmoser postulates,[2] predict that V produces exclusively *trans*-fused VI, with opposite geometry, i.e. IX, being expected on cyclizing VIII. Secondly, the extent that the tosyl fragment brings about enantioselectivity in favor of the β-tosylated tricyclic derivatives would be of interest as this might perhaps give some indication for the enantioselectivity expected on ring closing pro-C-6 steroid precursors.Enantioselectivity will in this context be taken to mean the formation of unequal amounts of racemic epimers from racemic chiral substrates and had been observed in



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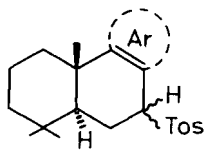

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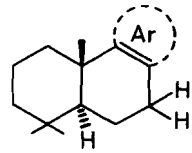

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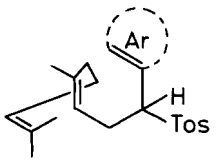
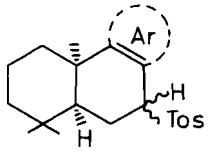


VIII



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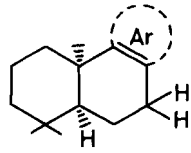
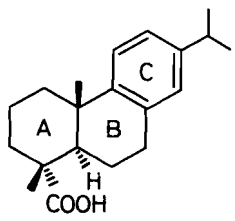


X

steroid synthesis on cyclizing, for instance, suitably alkylated alicyclics to 6-α-methylestrone intermediates[3] and also their thiophene A-ring counterparts.[4a,b] A third motivation underlying these efforts stemmed from the recognition that detosylated ring system VII agrees in framework, substitution pattern and mode of ring junction with those of dehydroabietic- and podocarpic acids 1 and 2. In resin acid types the aromatic



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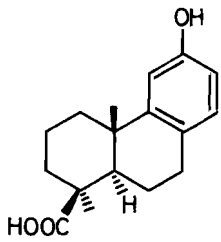
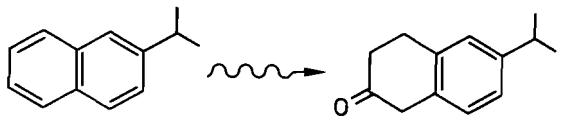


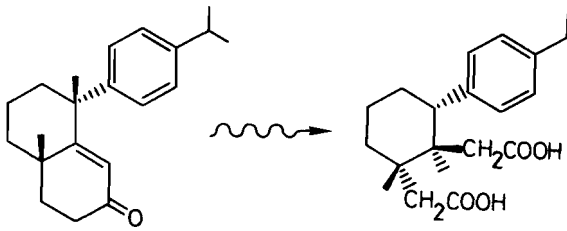
2

C-ring is fused to ring B which in turn is annelated to the A-ring as indicated in 1. Numerous already elaborated routes to 1 and 2 involve stepwise annelations and belong to three main categories. Storks' pioneering synthesis of dehydroabietic acid 1[5a,b] exemplifies approaches[5c-e] involving annelation of

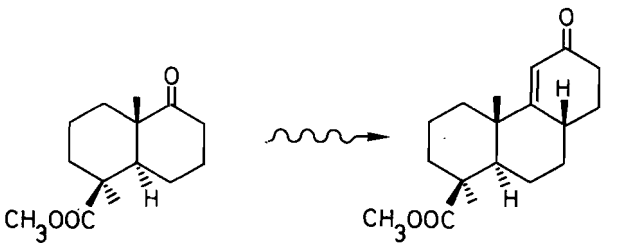
ring A to a preformed BC unit (equation I). Irelands' stereoselective, high-yield synthesis of 1[6a,b] represents a second type, whose salient feature consists of the B-ring being closed onto a preconstructed AC system (equation II). This tactic has found favor with a number of other investigators.[6c,d] Spencer and other workers[7a-c] in synthesizing podocarpic acid 2 have centered their research on an AB→ABC approach as depicted in equation III.



1 (eq. I)



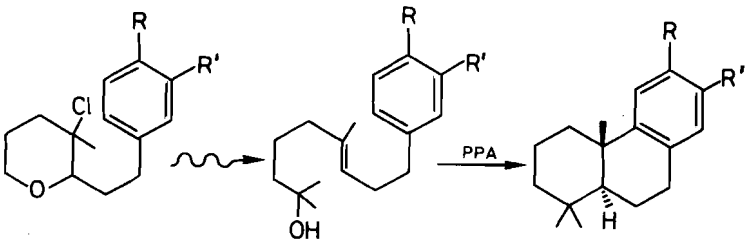
1 (eq. II)



2 (eq. III)

Construction by way of biomimetically-modelled polyenic cyclization schemes,[8] however, seems to have recieved scant attention, short of one related route elaborated by Ansell

and Gadsby[9] (equation IV). In this case it led to mixtures of *cis*- and *trans*-ring closed dehydroabietane (R = H; R' = iPr) and dehydropodocarpane (R = MeO; R' = H), thus not constitut-



(eq. IV)

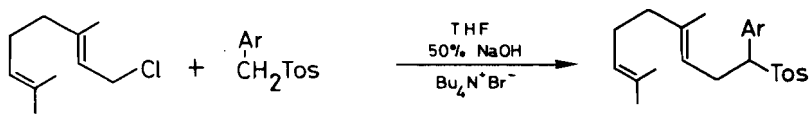
ing a truly biogenetic scheme since both ring fused systems are produced, probably via a multi-step sequence. The advantage of a really biomimetic entry would stem from its directness of purpose and, more important yet, the control of a cyclizations' stereochemical outcome.

IV.2 Preparation and Cyclization of 4a-c and 5a,b

The starting material used in these model studies, 4a-c and 5a,b, were prepared via phase transfer alkylation of sulfones 3a-c with geranyl-[10] and 3a,b with neryl chloride. TLC examination showed the crude mixtures to consist of unreacted sulfones, mono- and dialkylated products in addition to tarry contaminants. The required compounds were chromatographically isolated and their physical data are compiled in Table I.

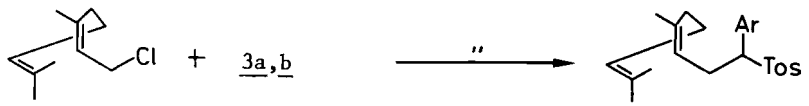
Ring closure conditions were based on those of the bicyclic compounds (see Chapter III), and involved dissolving the substrates 4a-c and 5a,b in 2 parts of liquid SO_2 containing catalytic or equivalent amounts of freshly distilled FSO_3H. Crude product mixtures were isolated after 15 min at -78 °C and were freed of polymeric byproducts by means of short column filtration. The resulting syrups were then examined via NMR.

Geranyl and neryl systems 4a and 5a,b furnished 60-80% of totally cyclized materials consisting of epimeric sets of α- and β-tosylated products. Estimation of component ratios and gross structural assignments were based on NMR inspection



(1)

3a-c 4a-c



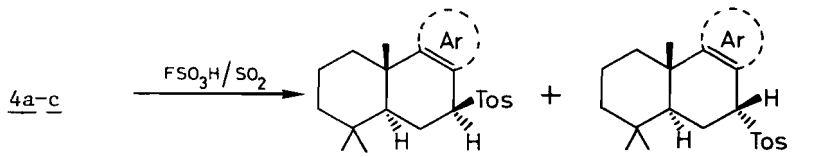
(2)

5a,b

a: Ar = 2- thienyl

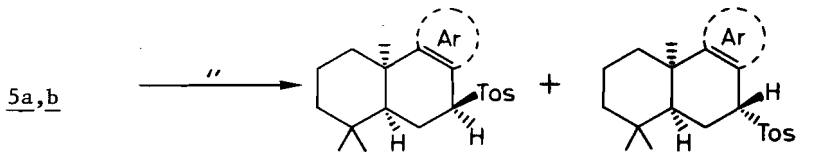
b: Ar = 3-thienyl

c: Ar = 3,5-dimethoxyphenyl



(3)

6a-c 7a-c



(4)

8a,b 9a,b

a: Ar =

b: Ar =

c: Ar =

of the C-4 and the C-10 methyl shifts (Table II). For material arising from 4a a 60:40 product distribution was noted; neryl systems 5a,b produced more pronounced product-spreads of 70:30. HPLC failed to bring about practically useful isomer separation but, fortuitously, all product-syrups eventually solidified. The crude solid obtained from cyclization of 4a with mp 133--151 °C ultimately provided the least soluble and most abundant component, mp 165-166 °C, via repeated trituration (10% acetone--hexane). A similar procedure provided the pure major constituents of the crude solidified mixtures from 5a,b. Reasoning by analogy with the amply documented precedents of bulky substituents adopting least encumbered conformations during polyenic cyclizations,[8] β-configurations 6a, 8a and 8b were tentatively assigned to the major isomers having arisen on cyclization of 4a and 5a,b since in these systems the tosyl fragments are clearly least encumbered by 1,3-interactions with the proximal C-9 proton; the minor components were therefore characterized as α-epimers 7a, 9a and 9b. Definitive configurational assignments and also the unequivocal establishment of the mode of B/C ring fusion rested on spectral examination of subsequently detosylated materials and will be discussed in section IV.3.

There is the possibility of epimerization occurring during work-up of the reaction, thus disturbing initial product-ratios. This was ruled out by ascertaining that pure 6a, for instance, when subjected to conditions of the isolation procedure (stirring for 18 h in ether-conc-NH_4OH) could be recovered unchanged.

The 3-thienyl geranyl system 4b produced on cyclization a considerably more complex mixture. NMR data again suggested the presence of a 60:40 mixture of epimers 6-/7b but ensuing detosylation (vide infra) produced two distinctly different compounds rather than the one expected on detosylating an epimeric pair. ^{13}C NMR inspection of the aromatic carbons confirmed the presence of detosylated 11 but showed it to contain ca 30% of isomeric 10b. The latter must have arisen from an uncommon cyclization of 4b onto the 4-thiophene position to produce 10a and, on detosylation, 10b. A similar cyclization anomaly, at low temperature, had been found earlier. This was attributed to the 3-thienyl substituent retarding attainment of suitably

conformations necessary for producing 2,3-annelated thiophenes only.[4b] It is interesting, though, to note that no detectable 3,4-thiophene annelation was observed on cyclizing neryl analog 5b. Crude material, obtained in 92% yield from the 3-thienyl prenyl analog III-2b had a melting point in agreement with that of the analytical sample and showed no NMR evidence of 3,4-ring closure having occurred (Chapter III). The crude solidified mixture resulting from cyclization of 4b ultimately provided homogeneous material on prolonged trituration with acetone-hexane and was spectrally identified as 6b.

The dimethoxyphenyl precursor 4c gave, after 15 min in SO_2/FSO_3H, an oily 60:40 mixture of ring closed epimers from which was isolated 12% of the major β-isomer 6c, mp 138-139 °C. The mother liquors ultimately deposited a small amount of the α-isomer, mp 129-131 °C, thereby providing the only instance of actually isolating both of the produced epimers. Physical data relating to all cyclized materials are gathered in Table III. The consistently high yields attained in the SO_2-conducted olefin-initiated polycyclization are at variance with the literature reports[8] ascribing disappointing polycyclization results to indiscriminate protonation of the polyene to give an assortment of products. The role played by SO_2 in solvating and stabilizing the intermediate cations may be crucial, thus allowing establishment of conformational equilibria required for the unidirectionality of ensuing processes.

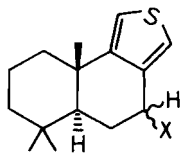
The α/β configurations as well as the B/C ring junction modes have thus far only been assigned tentatively. Definitive assignments ultimately relied on the spectral examination of detosylated materials discussed in section IV.3.

IV.3 Detosylation Experiments

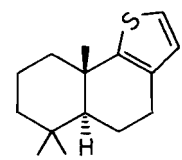
Pure β-isomers 6a,c and 8a,b were treated with Dibal-H in toluene for 5 min at 50 °C to provide detosylated systems 12-15. Exactly identical, homogeneous materials were arrived at on detosylating the binary mixtures 6-/7a, 6-/7c, 8-/9a and 8-/9b, thus providing unequivocal proof of the compounds of each mixture differing in configurational mode of the tosyl attachment only. Spectral examination provided conclusive evidence for the

nature of the B/C ring fusion of all systems in question, since closely related (*trans*) 16 and (*cis*) 17 had previously been described by Wenkert et al.[11] The close similarity of methyl shifts of 12 and 13 to those reported for 16 suggested 12 and 13 and therefore 6a,c and 7a,c to constitute of B/C *trans*-annelated systems. Likewise, the resemblance of methyl shifts of 14 and 15, together with their predecesors 8a,b and 9a,b represent the B/C *cis*-fused counterparts. Specific data are gathered in Table II, entries A and D. The products 10b/11, from the detosylation of the total cyclization harvest of 4b were also spectrally similar to 16 and were therefore designated as B/C *trans*--fused ring systems.

The spectral data also substantiated the previously tentative tosyl configurational assignments. Inspection of molecular models of *trans*-fused systems shows the C-4 and C-10 methyl groups to be in the shielding cone of the tosyl substituent. They are closer to the tosyl group in the β-configuration; hence the detosylation of all systems to 12-13 ought to bring about a greater upfield shift in methyl signals for β-isomers than for α-analogs. Similarly, *cis*-fused systems show the C-4 and C-10 methyl groups in the β-configuration to lie in the deshielding cone of the tosyl group; in the α-forms they are situated in the shielding cone. Hence detosylation of all systems to 14 and 15 should bring about a downfield shift for the β--isomers and an upfield shift for the α-isomers. This is borne out by experimental observations. As shown in Table II, entries B, C, E, F, all observed Δδ's are greater for β-isomers 6a,c than for α-epimers 7a,c, thus firmly establishing the nature



10a,b



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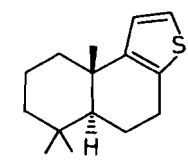
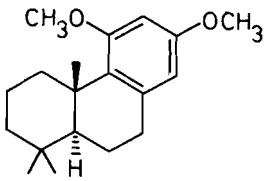


12

a: X = Tos

b: X = H



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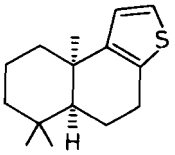

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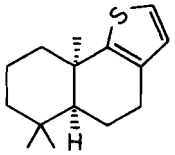

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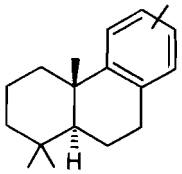

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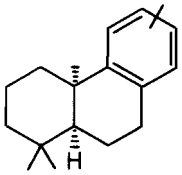

17

of the tosyl configuration at the C-6 position of all cyclic intermediates.

IV.4 Summary and Concluding Remarks

The synthesis of *trans*-alkenes 4a-c and two of their *cis*--counterparts 5a,b is described. These systems undergo totally stereospecific ring closure in FSO_3H/SO_2 at -78 °C to give 6-/7a-c and 8-/9a,b in NMR-determined 60:40 and 70:30 ratios respectively, thus showing the tosyl group being capable of eliciting significant enantioselectivity during cationic polycyclization processes. The stereospecificities of the ring closures conform to the Stork-Eschenmoser predictions and are accommodated by assuming the processes to occur via a one-step concerted mechanism. Polycyclization of 4b has been shown to co-produce ca 30% of anomalously 3,4-thienyl ring closed 10a. From all binary mixtures except 6-/7b, the least soluble and most abundantly present β-tosyl isomers 6a,c and 8a,b are obtained via trituration. Treatment of these pure systems with Dibal-H leads to rapid detosylation to produce 12-15; the identical compounds are produced by treating each of the binary mixtures with Dibal--H, thus showing them to have consisted of configurationally

differing tosyl epimers only. The nature and stereochemistry of the desulfonylated structures has been established by NMR--comparison with previously reported compounds. Detosylation of 6-/7b contaminated with 10a has given the corresponding mixture of 11-10b.

For practical purposes the outlined route constitutes the method of choice for preparing aromatic resin acid related systems VII and their *cis*-annelated isomers X. The concept features ready assembly of pre-cyclization substrates displaying the correct array of carbon atoms in a suitable geometry and utilizes processes whereby cheap and plentiful components are transformed via open vessel aqueous phase transfer techniques into the required systems. The concept has the tosyl group functioning as auxiliary which survives a totally stereospecific polycyclization and is ultimately removed by means of Dibal-H. The strategy is ideally suited for construction of aromatic A-ring variants of the resin acids[12] and could also serve to prepare 7-substituted homologs thereof.

IV.5 Experimental Section

Nuclear resonance spectra (NMR) were recorded on a Varian EM-360A spectrometer. Melting points (recorded on a Fisher--Johns block) are uncorrected. Chromatography was carried out over a 10-fold excess by weight of silica gel.

► *1-Chloro-3,7-dimethyl-2(Z),6-octadiene* was prepared according to the method described for the (*E*)-isomer:[10] yield 76%, bp 48-50 °C/0.25 mm. ^{1}H NMR δ (CCl_4): 1.59, 1.65 and 1.77 (3 s,9, 3 CH_3), 2.02 and 2.11 (2 s,4,2 CH_2), 3.89 (d,2,CH_2Cl), 4.75--5.52 (m,2,olefinic H).

The preparation of cyclization precursors 4a-c, 5a,b (Table I) is exemplified by the synthesis of 4a.

► *d,l-1-(2-Thienyl)-1-(p-toluenesulfonyl)-4,8-dimethyl-3(E),7--nonadiene (4a).*

A mixture of 12.6 g (0.05 mol) of 3a, 9.5 g (0.055 mol) of geranyl chloride,[10] 75 mL of 50% sodium hydroxide, 20 mL of

THF and 1.0 g of tetrabutylammonium bromide was thoroughly stirred for 18 h at room temperature. Water (500 mL) was then added. The organic layer was separated and diluted with ether. The ether phase was washed with brine until neutral, dried and evaporated to leave 20.0 g of crude material. Chromatography (eluent: hexane-10% acetone), evaporation and trituration with low-boiling petroleum ether gave 10.3 g (53%) of solid material, mp 60 °C. Recrystallization from pentane furnished analytical material, mp 62-63 °C. ^{1}H NMR δ ($CDCl_3$): 1.46 (s,3,=CCH_3), 1.54 (s,6,=$C(CH_3)_2$), 1.60-2.06 (m,4,CH_2CH_2), 2.38 (s,3,TosCH_3), 2.38-3.43 (m,2,TosCCH_2), 3.93-4.35 (dd,1,CHTos), 4.57-5.12 (m,2,olefinic H), 6.56-7.53 (m,7,ArH).

Anal. Calcd. for $C_{22}H_{28}O_2S_2$: C, 68.00; H, 7.26. Found: C, 68.20; H, 7.47.

The preparation procedure leading to 6- and 7a-c and 8- and 9a,b (Table III) is given in detail for 6a.

►*d,l-4aβ,7,7-Trimethyl-9β-(p-toluenesulfonyl)-4,4a,5,6,7,7aα,8,8-octahydronaphto[1,2-b]thiophene (6a).*

To a solution of 5 g (0.014 mol) of 4a in 10 mL of liquid sulfur dioxide at -78 °C was added 0.5 mL (0.008 mol) of freshly distilled fluorosulfuric acid. The mixture was stirred for 5 min and was then quenched by pouring it into a water-ether mixture. The ether layer was washed with water (3x), cold 5N NH_4OH solution (3x) and then with water until neutral. Drying and evaporation left 3.8 g of crude material. Chromatography gave 3.1 g (62%) of an oil which solidified on prolonged standing. Trituration with hexane-10% acetone gave 1.9 g of solid material (38%), consisting of an α/β mixture of tosyl epimers 6-/7a having mp 133-151 °C. Repeated trituration with hexane-10% acetone on ice provided 0.8 g (16%) of the pure β isomer, mp 165-166 °C. ^{1}H NMR δ ($CDCl_3$): 0.60, 0.87 and 0.94 (3 s,9,3 CH_3), 0.90-2.45 (m,9,4 CH_2 and CH), 2.38 (s,3,TosCH_3), 4.58 (dd,1,CHTos), 6.57--7.89 (2 AB,6,ArH).

Anal. Calcd. for $C_{22}H_{28}O_2S_2$: C, 68.00; H, 7.26. Found: C, 67.80; H, 7.25.

Detosylation experiments, leading to compounds 11-15 (Table IV) are typified by the hydrogenolysis of epimeric mixture 6-/7a.

► *d,l-4aβ,7,7-Trimethyl-4,4a,5,6,7,7aα,8,9-octahydronaphto [1,2-b]thiophene (12).*

To a stirred, nitrogen-covered solution of 0.39 g (0.001 mol) of 6-/7a in 0.4 mL of dry toluene at 50 °C was added, in one portion 0.21 g (0.0015 mol) of Dibal-H in 1 mL of toluene. Isobutene was evolved as the temperature rose to 80 °C. After 5 min the mixture was cooled, and to it was carefully added 0.1 mL of ethanol, 0.45 mL of water and 0.225 mL of concentrated hydrochloric acid respectively. The organic layer was decanted and the residue was extracted with diethyl ether. The combined organic layers were washed with water, 5N sodium hydroxide solution and water until neutral, dried and evaporated to leave 0.25 g of crude material. Filtration through silica with hexane gave 0.19 g of 12 (81%). The compound was ^{1}H NMR, TLC and HPLC pure. ^{1}H NMR δ ($CDCl_3$): 0.87, 0.91 and 1.15 (3 s,9,3 CH_3), 1.06-2.26 (m,9,4 CH_2 and CH), 2.61-3.00 (m,2,ThCH_2), 6.56-7.02(AB,2,ArH).

Table I. (*E*)- and (*Z*)-Cyclization Precursors

compd	yield, %[a]	mp, °C (recrystn solvent)[b]
4a	53	62-63 (pentane)
4b	51	49-50 (pentane-diisopropyl ether)
4c	74	69-70 (diisopropyl ether)
5a	33	46-47 (pentane)
5b	42	48-49 (pentane)

[a]Based on amount obtained with mp < 5 °C below that of analytical sample. [b]Satisfactory elemental analyses (C, H ± 0.30%) were found.

Table II. Methyl Chemical Shifts of Cyclized Materials[a]

Entry and Type	Compd	δ			Δδ		
		C-10- -β-Me	C-4- -α-Me	C-4- -β-Me	C-10- -β-Me	C-4- -α-Me	C-4- -β-Me
A B/C-*trans* detosyl'd derivs	11	1.30	0.93	0.93			
	12	1.15	0.91	0.87			
	13[b]	1.21	0.90	0.96			
	16[10]	1.18-1.22	0.94	0.94			
B B/C-*trans* β-tosyl'd derivs	6a	0.94	0.87	0.60	-0.21	-0.04	-0.27
	6b	0.88	0.82	0.62	-0.42	-0.11	-0.31
	6c	0.90	0.81	0.69	-0.31	-0.09	-0.27
C B/C-*trans* α-tosyl'd derivs	7a	1.02	0.90	0.79	-0.13	-0.01	-0.08
	7b	1.13	1.04	0.90	-0.17	+0.11	-0.03
	7c	1.15	1.01	0.85	-0.06	+0.11	-0.11
D B/C-*cis* detosyl'd derivs	14	1.17	0.63	0.99			
	15	1.27	0.67	1.00			
	17[10]	1.15	0.32	0.90			
E B/C-*cis* α-tosyl'd derivs	8a	0.90	0.40	0.62	-0.27	-0.23	-0.37
	8b	0.92	0.44	0.64	-0.35	-0.23	-0.36
F B/C-*cis* β-tosyl'd derivs	9a	1.36	0.84	1.17	+0.19	+0.25	+0.14
	9b	1.45	0.83	1.11	+0.28	+0.16	+0.11

[a]Data have been compiled according to chemical types. [b]This compound solidified and had mp 70-71°C.

Table III. Cyclized Sulfones

compd mixt	yield, %[a]	mp, °C	yield, %[b] (isol'd compd)	mp, °C
6a/7a	62	133-151	16 (6a)	165-166
6c/7c	66	108-124	12 (6c)	138-139
			4 (7c)	129-131
8a/9a	80	126-135	24 (9a)	149-150
8b/9b	78	116-129	20 (9b)	140-141

[a]Crude mixture of α- and β-isomers. [b]Yield of actually isolated material having reported mp.

Table V. Analytical Material

compd	recrystn solvent	formula	calcd., %		found, %	
4b	pentane	$C_{22}H_{28}O_2S_2$	68.00	7.26	68.05	7.35
4c	diisopropyl ether	$C_{26}H_{34}O_4S$	70.55	7.74	70.48	7.64
5a	pentane	$C_{22}H_{28}O_2S_2$	68.00	7.26	67.96	7.25
5b	pentane	$C_{22}H_{28}O_2S_2$	68.00	7.26	67.88	7.25
6c	hexane-10 % acetone	$C_{26}H_{34}O_4S$	70.55	7.74	70.73	7.84
9a	hexane-10 % acetone	$C_{22}H_{28}O_2S_2$	68.00	7.26	68.30	7.20
9b	hexane-10 % acetone	$C_{22}H_{28}O_2S_2$	68.00	7.26	68.32	7.44
13	pentane	$C_{19}H_{28}O_2$	79.12	9.78	79.21	9.85

Table IV. ^{1}H NMR Data

compd	^{1}H NMR, δ ($CDCl_3$)
4b	1.52, 1.56 and 1.60 (3 s,9,3 CH_3), 1.77-2.10 (m,4,CH_2CH_2), 2.38 (s,3,TosCH$_3$), 2.47-3.39 (m,2,TosCCH$_2$), 3.95-4.34 (dd,1,CHTos), 4.63-5.13 (m,2,olefinic H), 6.77-7.53 (m,7,ArH).
4c	1.52, 1.57 and 1.58 (3 s,9,3 CH_3), 1.76-2.11 (m,4,CH_2CH_2), 2.36 (s,3,TosCH$_3$), 2.52-3.20 (m,2,TosCCH$_2$), 3.60 (s,6,2 OCH_3), 3.73-4.06 (dd,1,CHTos), 4.59-5.06 (m,2,olefinic H), 6.03-6.34 (m,3,ArH), 6.93-7.54 (AB,4,sulfone ArH).
5a	1.53 (s,6,=C(CH_3)$_2$), 1.64 (s,3,=CCH_3), 1.84-2.13 (m,4,CH_2CH_2), 2.13-3.26 (m,2,TosCCH$_2$), 2.37 (s,3,TosCH$_3$), 3.87-4.23 (dd,1,CHTos), 4.64-5.20 (m,2,olefinic H), 6.50-7.48 (m,3,ArH).
5b	1.59, 1.60 and 1.69 (3 s,9,3 CH_3), 1.81-2.14 (m,4,CH_2CH_2), 2.38 (s,3,TosCH$_3$), 2.53-3.41 (m,2,TosCCH$_2$), 3.90-4.28 (dd,1,CHTos), 4.60-5.23 (m,2,olefinic H), 6.76-7.54 (m,7,ArH).
6b	0.48-2.63 (m,9,4 CH_2 and CH), 0.62, 0.82 and 0.88 (3 s,9,3 CH_3), 2.36 (s,3,TosCH$_3$), 4.14-4.69 (m,1,CHTos), 6.87-7.70 (m,6,ArH).
6c	0.49-3.25 (m,9,4 CH_2 and CH), 0.69, 0.81 and 0.90 (3 s,9,3 CH_3), 2.34 (s,3,TosCH$_3$), 3.69 (d,6,2 OCH_3), 4.32-4.81 (m,1,CHTos), 6.21-7.41 (m,6,ArH).
7c	0.77-3.23 (m,9,4 CH_2 and CH), 0.85, 1.01 and 1.15 (3 s,9,3 CH_3), 2.40 (s,3,TosCH$_3$), 3.69 (d,6,2 OCH_3), 4.19-4.50 (m,1,CHTos), 6.31-6.62 (AB,2,ArH), 7.06-7.74 (AB,4,sulfone ArH).
9a	0.56-2.64 (m,9,4 CH_2 and CH), 0.84, 1.17 and 1.36 (3 s,9,3 CH_3), 2.36 (s,3,TosCH$_3$), 4.14-4.59 (m,1,CHTos), 6.56-7.89 (m,6,ArH).
9b	0.66-2.53 (m,9,4 CH_2 and CH), 0.83, 1.11 and 1.45 (3 s,9,3 CH_3), 2.33 (s,3,TosCH$_3$), 4.01-4.48 (m,1,CHTos), 6.79-7.67 (m,6,ArH).
13	0.90, 0.96 and 1.21 (3 s,9,3 CH_3), 0.77-1.98 (m,8,4 CH_2), 2.54-3.23 (m,3,ArCH_2 and CH), 5.76-6.20 (m,2,ArH).
14	0.63, 0.99 and 1.17 (3 s,9,3 CH_3), 0.77-2.54 (m,9,4 CH_2 and CH), 2.63-3.06 (m,2,ThCH_2), 6.68-7.08 (AB,2,ArH).
15	0.67, 1.00 and 1.27 (3 s,9,3 CH_3), 1.00-2.45 (m,9,4 CH_2 and CH), 2.45-2.89 (m,2,ThCH_2), 6.41-6.99 (AB,2,ArH).

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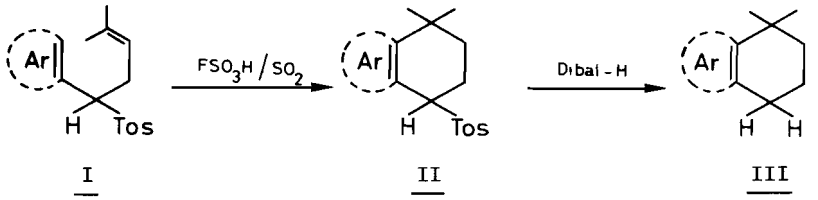
CHAPTER V

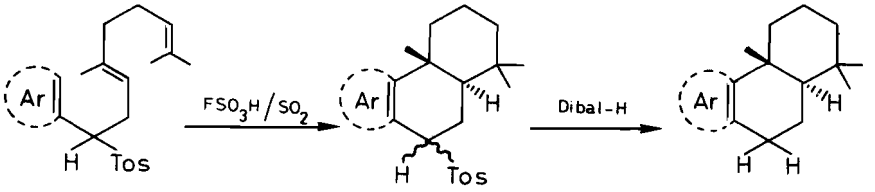
The Preparation of Some Aliphatically Tosylated pro-steroidal Cyclization Precursors

V.1 Introduction

In Chapters III and IV the FSO_3H/SO_2-promoted cycloalkylations of tosylated substrates I and IV and a new reaction using Dibal-H to remove tosyl fragments from the resulting cyclized materials were discussed. Systems I and IV were thus converted via II and V into III and IV. Polycyclizations of IV displayed pronounced selectivity in favor of sterically least encumbered β-tosylated epimers. These model-studies had now yielded sufficient data to justify tackling the main objective given in Chapter I, namely the synthesis of alicyclic

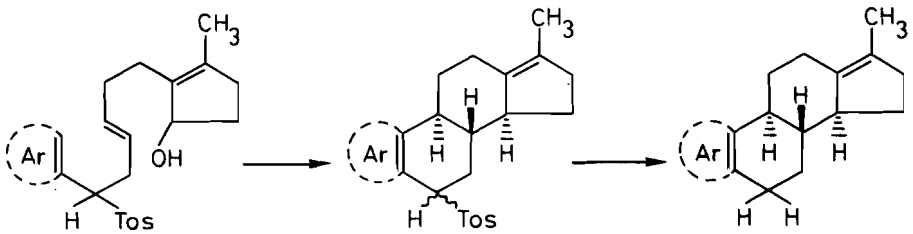


I II III



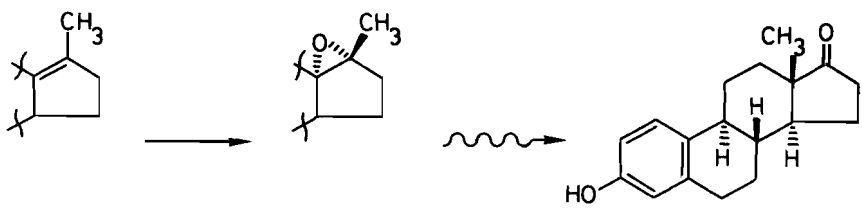
IV V VI

pro-C-6 tosylated steroidal precursors VII, their subsequent cyclization to VIII and ultimate detosylation of VIII to furnish steroidal frameworks IX. The latter, it should be noted,



VII VIII IX

had already served as d,l-estrone intermediates via a route involving rearside double bond epoxidation and subsequent Lewis-acid catalyzed methyl migration from C-17 to β-C-10 with the epoxide oxygen ending up as C-17 keto functionality.[1]



d,l-estrone

If a pro-C-6 d,l-mixture of VII cyclizes to VIII enantioselectively, identical transformations on the C-6 enantiomerically pure analogs should give chirally active ring systems whose optical properties would be retained on detosylation, thus providing optically active steroids IX. The newly formed chiral hydroxy in the pro-D ring does not influence the ring closure's stereochemical pathway; recent studies on a similar system showed complete racemization occurring on cyclizing an asymmetrically reduced ketone.[2] The approach was to be applied in preparing enantiomerically pure estrone and its analogs.

Johnsons' well-trodden path to non-tosyl containing VII features a stereochemically critical Wittig-Schlosser olefination step for constructing the central *trans*-olefinic linkage. Whereas such transformations had proceeded satisfactory for

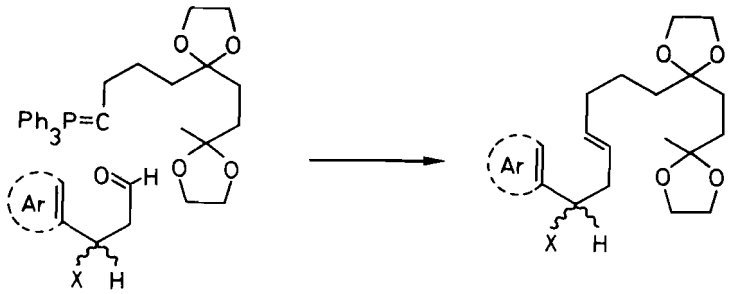
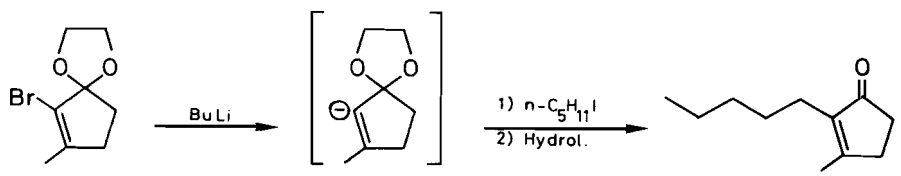


Figure V. 1.

cases where X = H or alkyl[1,3a-e] the model studies described in Chapter II portended its probable failure if X were to be a tosyl fragment. The development of a new route into VII became therefore imperative.

During the course of this work there appeared a publication describing compound 1 and its potential in synthesis.[4] Treatment of 1 with BuLi was shown to provide anion 2 which, on reaction with n-pentyl iodide ultimately produced dihydrojasmone 3. In combination with earlier acquired experience in



1 2 3

prenylating, geranylating and nerylating anions derived from aryltosyl methanes (Chapter II and IV), an alternate scheme for constructing VII suggested itself. The approach, a strongly convergent three component one, would involve construction of a suitably functionalized *trans*-2-pentenyl backbone fragment for purposes of incorporating a five carbon bridge between the aryltosyl fragment and the above cited 3-methyl-2-cyclopentenyl system. A concluding two step functionality manipulation would transform the ketal into the allylic alcohol array found in VII.

The concept is depicted in Figure V. 2. In this approach the *trans*-2-pentenyl unit is destined to appear as the C-7,8,9, 11,12 steroidal spine, with the D-ring, obviously, originating from cyclopentenyl unit 2. Attention was to be turned first to elaborating a suitable *trans*-C-5-unit and then to arriving at a suitable procedure for preparing convenient quantities of 1. These endeavors are covered in the subsequent sections.

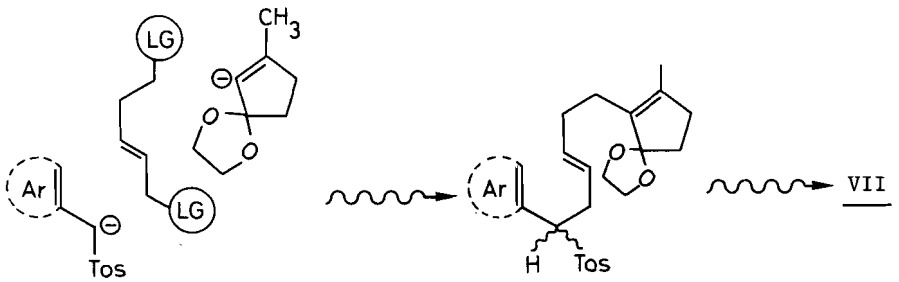


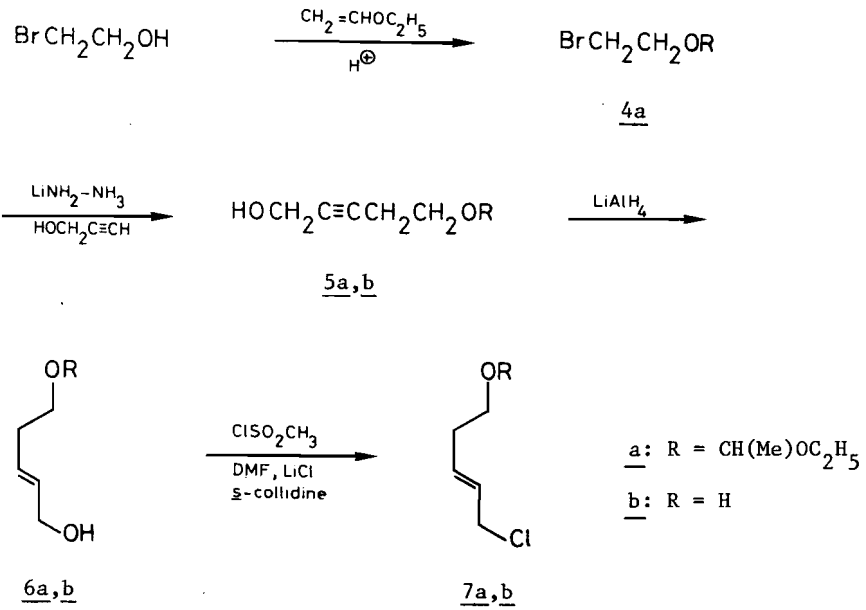
Figure V. 2.

V.2 Preparation and Investigation of trans-1-Chloro-5(ethoxy ethoxy)-pentene-2 as Potential Steroidal Backbone Unit

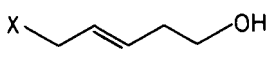
Literature examination revealed that, in contrast to a variety of *cis*-2-pentenyl units,[6] scant attention has been paid to their *trans*-counterparts. *trans*-1,5-Pentene-2-diol 6b, for instance, has been described only once, via a short, but operationally cumbersome reduction of glutacondialdehyde with sodium borohydride.[6a] The dihalides derived therefrom appear not to have been described. For practical purposes, *trans*-alkenols are best prepared by lithium aluminum hydride (LAH) reduction of acetylenic alcohols,[7] thus suggesting an approach centering the intermediacy of a 1,5-pentyne-2-diol derivative. Such systems have been prepared via hydroxymethylation of 3-butyne-1-ol[6b] or hydroxyethylation of propargyl alcohol.[6c,8] As such routes proceed via acetylenic anions, prior protection of base sensitive hydroxyl functionalities is often advisable. These and other considerations suggested the preparation of *trans*-1-chloro-5-(ethoxyethoxy)-pentene-2

7a, a system, featuring a highly reactive allylic chloride and a latent homoallylic functionality at the other terminus.

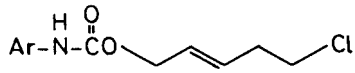
Compound 7a was prepared as follows. 2-Bromoethanol, on acid-promoted treatment with ethyl vinyl ether, gave the O--protected 4a.[9] Preference for the ethoxyethyl- rather than the more conventional tetrahydropyranyl- blocking group derived from the formers' greater ease of hydrolysis or methanolysis to yield readily removable breakdown fragments;[10] moreover, the ethoxyethyl group displays clearly distinguishable CH_3 NMR signals at 1.21 and 1.29 ppm (t and d resp.). Propargyl alcohol dianion, generated in $LiNH_2$-containing liquid NH_3, reacted rapidly with 4a to provide, after 1 h, 77% of 5a. Reduction thereof to 6a gave optimal yields on using 1.25 equivs of LAH in refluxing THF (1 h); characterization of 6a was based on ^{13}C NMR inspection and also by hydrolysis to 6b and its subsequent conversion to the earlier reported bis-phenylcarbamate.[6a] Transformation of 6a to 7a was realized via the method of Collington and Meyers.[11] This involved the system $MeSO_2Cl$ and LiCl in collidine-containing DMF and gave, in accord with the cited examples, unrearranged chloride 7a of at least 95% homogeneity.[12]



The reactivity of synthon 7a was briefly probed. Reactions in DMF with potassium phthalimide and with sodium p-toluenesulfinate proceeded cleanly to give, on mild hydrolysis, crystalline pentenols 8a,b. Acid-induced deprotection of 7a led to *trans*-5-chloro-3-penten-1-ol 7b, derivatized via treatments with phenyl- and naphthylisocyanate to solid carbamates 9a,b.



8a,b



9a,b

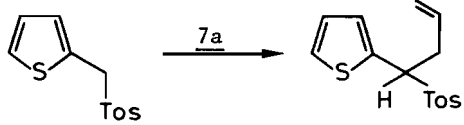
a: X = N-Phthalimide

b: X = p-$SO_2C_6H_4CH_3$

a: Ar = C_6H_5

b: Ar = α-Naphthyl

Thienyl derivative III-3a, being amply available at the time, was chosen as model for studying the alkylation with 7a. The reaction, carried out under phase transfer conditions, followed by an acidic methanolic work-up, produced a truly pitch-black tar. On subjecting this to prolonged continuous liquid-liquid extraction with petroleum ether, 57% of an amber-colored oil was obtained which crystallized on standing; trituration with a 10:1 mixture of isopropyl ether:isopropanol then gave 34% of pure carbinol 10b melting sharply at 73-74 °C. Transformation of 10b to iodide 10d was achieved via the tosylate ester. This involved phase-transfer treatment of the alcohol with tosyl chloride to produce tosylate 10c identified by NMR,



II-12a

10a-e

a: X = $OC(Me)OC_2H_5$

b: X = OH

c: X = OTos

d: X = I

e: X =

which produced 10d when refluxed in sodium iodide-containing acetone for 2 h; the overall yield amounted to 81%. In an exploratory probe, 10d in DMF with potassium phthalimide at 100 °C for 1 h gave the N-phthalimide derivative 10e. Having thus shown the iodide nucleofugicity of 10d to be sufficiently high for at least displacement by phthalimide ion and relying on the literature precedent alkylation of anion 2 to 3,[4] efforts were initiated towards preparing generous quantities of bromoketal 1. Data relating thereto and the behavior of 2 towards iodide 10d will be dealt with next.

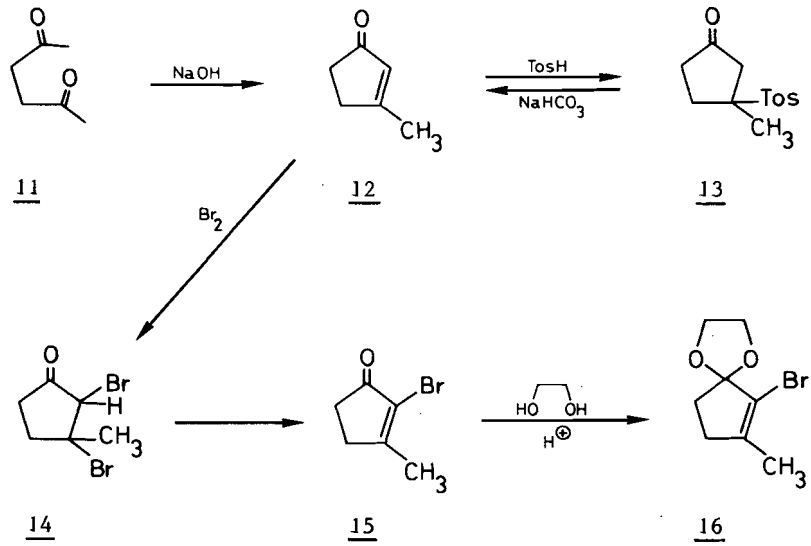
V.3 Synthesis of 1 and Reaction of its Derived Anion 2 with 10d

The concluding step to a *trans*-olefinic pro-steroidal cyclization precursor VII, exemplified by 18, was to involve attaching the potential D-ring to iodide 10d by its reaction with anion 2. The tactic presupposed ready access to 1, a compound recently described in passing as "being readily prepared from the parent enone 12 in 76-84% yield" via standard bromination, dehydrobromination and ketalization.[4] These steps had indeed furnished nor-methyl analog 16[4] but their application to prepare 1 posed, in our hands, considerable difficulties. The problems encountered were serious enough to warrant a reevaluation of Smith's approach and prompted the elaboration of new experimental conditions for preparing 1. The results are offered in this section. The method requires high-purity 12, a compound arising out of the intramolecular aldol condensation of acetonylacetone 11 but difficultly separable from it at the end. A simple highly economical technique for obtaining GLC-pure 3-methyl--cyclopent-2-enone 12 from this mixture will be presented.

The base-induced intramolecular aldolization of 11 to 12[14] was, as shown via NMR inspection of fractionated material, to still contain ca 20% of 11. Bromination of this mixture in carbon tetrachloride gave dibromide 14, which was converted directly into 15 on stirring with aqueous sodium bicarbonate. The tar-contaminated bromoenone was best isolated by repetitive extractions into boiling pentane. This step could be dispensed with on using prepurified 12. Earlier experiences with p-toluene sulfinic acid (TosH) additions to 3-arylpropenals,[15] described

in Chapter II, prompted treatment of an aqueous 12/11 mixture with TosH, causing, after 18 h at room temperature, the quantitative deposition of 11-derived Michael adduct 13. Methylene chloride extraction of the filtrate led to recovery of reusable 11. Compound 13 was next stirred with saturated sodium bicarbonate solution to regenerate GLC-pure 12 in 94% yield; the liberated TosH was recovered from the neutralized water phase on methylene chloride extraction.[16] Purified 12, when treated with bromine and sodium bicarbonate solution as above, then produced 61% of 15 cleanly and efficiently.

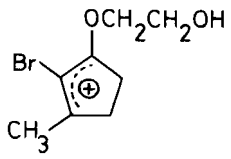
The p-toluenesulfonic acid (TSA)-promoted conversion of 15 to 1 in refluxing benzene was followed by NMR inspection of bicarbonate-scrubbed aliquots. The initial data were puzzling. On the one hand they showed a 70:30 mixture of 1 and 15 to be present after 24 h and replenishment of the system with fresh ethylene glycol and TSA failed to drive the reaction to completion. Extensive resinification was observed on prolonged reaction time. Work-up of the reaction mixture after 48 h, involving bicarbonate washing furnished 43% and 18% of chromatographically separable 1 and 15.



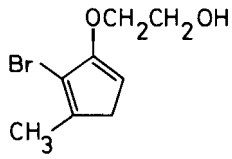
The unexpectedly low ketalization yield, the extensive resinification of the reaction mixture, the apparent resistance

of the ketalization to go to completion and the recovery of unreacted ketone deserve comment as they are relevant and interrelated. The reasoning hinges on the reasonable assumption that a ketalization process, which has already exceeded the 70% conversion point while still appearing to contain unreacted ketone, can be driven to completion on adding more ethylene glycol and TSA. The ketone detected on sampling had therefore to be an artifact which did not reflect the actual state of the reaction. The chance of 15 having undergone an acid-catalyzed, carbonyl consuming but bicarbonate-reversible transformation was ruled out because 14 was recovered unchanged after 48 h in refluxing TSA-containing benzene. This implied ethylene glycol being involved in the anomaly. The issue was resolved by allowing the ketalization to proceed for 24 h, scrubbing the organic phase with sodium bicarbonate solution, drying and recharging the system with fresh ethylene glycol and TSA. On repeating this cycle two or more times, 15 was used up completely, giving 1 essentially pure in 65% yield.

These results may be ascribed to the ketalization proceeding via intermediacy of the relatively long-lived allylic cation i; retardation of the expected ring closure-deprotonation sequence to yield 1 could, in this case, lead to β-deprotonation of i



i



ii

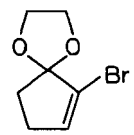
and polymerization to the thus produced cyclopentadiene ii. Periodic bicarbonate scrubbing would prevent i from accumulating by having it revert back to its parent ketone 15, thus giving ketalization a second chance.

A number of model experiments to establish optimal conditions for the ultimate conversion of 1, via anion 2, to intended 18 through alkylation of 2 with 10d, were carried out. Literature directions for generating 2 from 1[4] called for the use of BuLi

in THF at -78 °C, but subsequent NMR-inspection of some alkylated ketone derivatives showed these to be seriously contaminated with 2-butyl-3-methyl-cyclopent-2-enone 17b. This system must have arisen through a competing alkylation reaction of 2 with the butyl bromide originating from the reaction of 1 with the butyllithium employed. This side reaction was suppressed

$$1 + BuLi \longrightarrow 2 + BuBr \xrightarrow{\text{hydrol.}} 17b$$

by using 2 equiv of *tert.*-butyllithium instead as anion generating species; quenching of 2 developed in this fashion with H_2O or methyl iodide, led on acidic work-up to NMR-pure 12 and 17a



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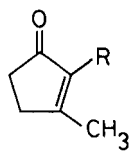
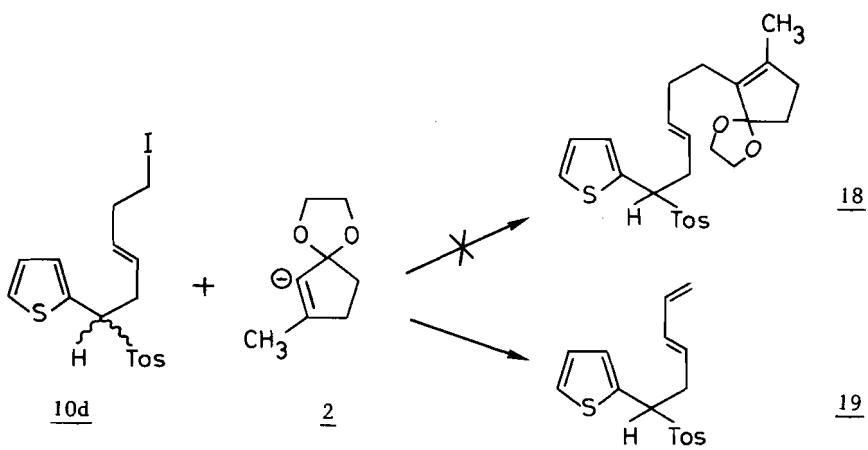


17a,b

a: R = H

b: R = n-C_4H_9

Having established optimal conditions for generating 2 from 1, the alkylation of 2 with 10d was examined next. The reaction, carried out in THF for 3 h gave crude product, the NMR of which showed the appearance of extra olefinic protons at 4.90-6.30 ppm, indicating the formation of 19. This course of events was sub-



10d 2 18 19

stantiated by treating 2 with the simplest homoallylic substrate, 1-butenyl bromide. Again, under identical conditions, elimination to butadiene instead of alkylation was observed.

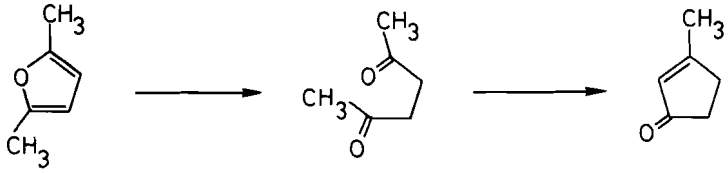
These data undoubtedly reflect the confluence of a number of factors, notably the propensity of homoallylic electrophiles towards elimination rather than substitution, the nucleophilic site of 2 enhancing its basic properties thus promoting elimination pathways and, of course, experimental conditions such as the choice of solvent and reaction temperature. The behavior of ion 2 might to some extent be modified by varying the nature of the cationic species associated with it. Time limitations, however, argued against initiating extensive investigations aimed at unraveling the parameter variations for steering the reaction of 2 with 10d towards substitution rather than elimination. Fortunately, an alternate approach towards VII had, by that time, progressed far enough to look extremely promising, thus making efforts to prepare 18 from 10d and 2 unnecessary.

V.4 The Synthesis of Steroidal Precursors 27a,b and their Behavior under Polycyclization Conditions

The previous section had demonstrated the failure to attach the potential D-ring synthon 2 onto preconstructed *trans*-olefin 10d which, had it been successful, would have opened the way towards constructing VII (Ar = 2-thienyl) via the desired 18. A related line of reasoning suggested preparing fragment 23, a system featuring the eventual steroid backbone already tied onto the ultimate D-ring, as alkylating agent in reactions with a series of aryltosyl methanes. The advantages of this strategy stem from the common intermediacy of 23 for assembling a variety of different aryl-containing cyclization precursors VII and hence a host of aromatically different steroidal A-ring analogs.

In earlier work Johnson[17] had started with the BuLi-promoted reaction of 2-methylfuran with 1,3-dibromopropane to give 20. The choice of 2-methylfuran as starting synthon in this approach was predicated on its synthetic equivalence to 3-methylcyclopent--2-enone 17a through successive acid catalyzed ring opening and base-induced aldolization (Figure V. 3). In the cited approach,

20 was ring-opened via an HBr-ethylene glycol treatment to give a bromo-diketal rather than a diketone, which was subsequently



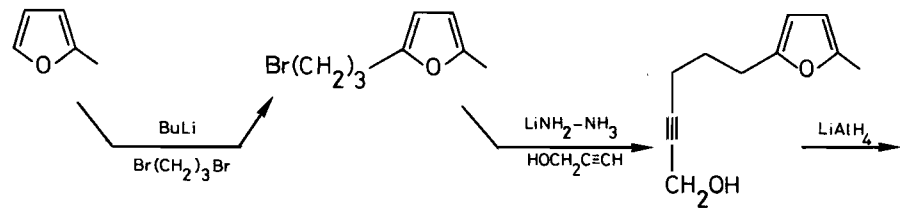
17a

Figure V. 3.

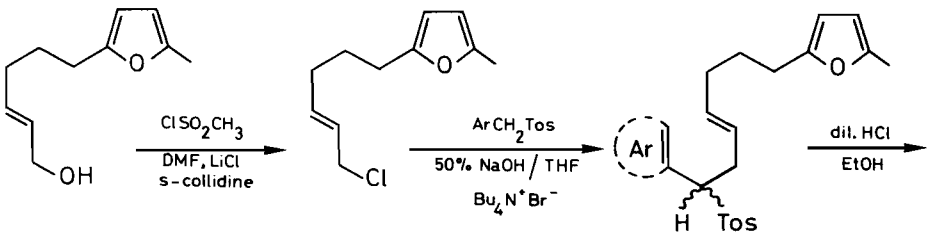
transformed into its phosphoran by way of triphenylphosphonium bromide and reacted as Wittig-Schlosser ylid in a subsequent olefination.

Based on experience gained earlier in constructing 7a, 20 was converted to chain-elongated propargylic alcohol 21 in liquid NH_3. The yield of distilled product was 87%. Subsequent LAH reduction gave, as in many related cases,[7] purely *trans*--allyl alcohol 22 (81%) as evidenced by ^{13}C NMR chemical shifts of the allylic carbons at 63.23 and 34.50 ppm.[18] The corresponding *trans*-allyl chloride 23 was aquired via the Collington--Meyers technique involving the use of the system mesyl chloride, lithium chloride, DMF and s-collidine to give 81% of sensitive and unstable chloride. Its isolation and semi-purification was best achieved via flash-distillation out of potassium carbonate stabilized product mixtures to give 90% NMR-determined product in good yield; it is stable if stored at low temperatures over traces of potassium carbonate.

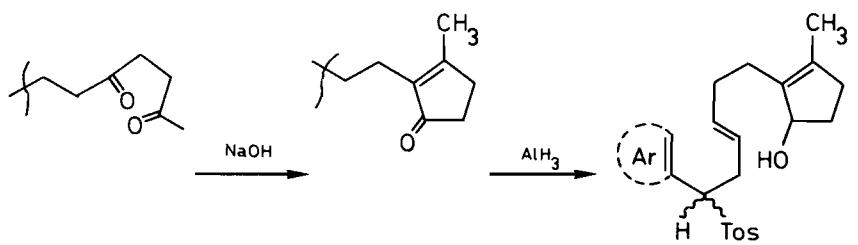
Having gained the necessary know-how for preparing 23 in quantity, its use in alkylating 2-thienyltosyl methane was examined next. Under aqueous phase transfer conditions, the reaction produced crystalline 24a in 55% yield. Elaboration of the furyl segment into the desired 3-methyl-cyclopent-2-enone array involved overnight refluxing in ethanol-0.5N hydrochloric acid to give diketone 25a, identified by NMR, as an oil; this was used directly in the subsequent base-catalyzed aldolization (0.34N NaOH, 2 h reflux) providing, in 89% overall yield,



20 21



22 23 24a,b



25a,b 26a,b 27a,b

a: Ar = 2-thienyl

b: Ar = phenyl

crystalline 26a. Parallel transformations, proceeding even better and more cleanly, brought about the conversion of phenyl analog 24b to 26b; phenyltosyl methane alkylation with 23 gave 65% of 24b, with the conversion yield of 24b to 26b amounting to 95%.

Literature directions for reducing non-tosyl containing α,β-unsaturated ketones like 26a,b to the corresponding allylic alcohols generally call for the use of LAH.[1,3a-e,17] In the case at issue, however, even inverse addition of LAH to 26a in THF at -30 °C produced significant amounts of totally reduced carbinols. This is not surprising in view of the many precedents of LAH reduction of conjugated enones resulting largely in 1,4--addition rather than carbonyl reduction.[19a] A number of reportedly carbonyl-selective reducing agents such as Dibal-H,[19b] zinc borohydride in dimethoxyethane[19c] and 9-borabicyclo[3.3.1]--nonane (9-BBN)[19d] were briefly examined but were, in all instances, found to produce mixtures of starting materials and partially and totally reduced products as determined by IR and NMR spectroscopy. Another method ultimately proved effective. Alane, freshly prepared from LAH and $AlCl_3$[19e] gave, on inverse addition to 26a in THF at -10 °C, clean and quantitative reduction to isolated 27a. This compound, which has two chiral centers, was used immediately as an oil in the subsequent cyclization experiments; most likely it consisted of a diastereomeric mixture. Alane reduction of phenyl enone 26b, on the other hand, gave on trituration with diisopropyl ether, 80% of isolated, crystalline alcohol 27b, melting sharply at 77-78 °C. Spectral and analytical data agreed with the proposed structure. Compound 27b would appear to represent then the first instance of a stable crystalline allylic alcohol cyclization precursor ever being isolated.

Compound 27a was subjected to the FSO_3H/SO_2 cyclization medium at -78 °C to produce a mixture of 75% tar and 25% of 7 chromatographically separated fractions. Their NMR spectra showed no change of the thienyl signals into an AB spectrum, which indicates that cyclization had not occurred. The tosyl fragment appeared to be unaltered with CHTos and $TosCH_3$ signals still being present. The D-ring methyl (NMR) and hydroxy absorption (IR), however had disappeared. Pronounced changes in the

aliphatic part of the spectrum were noted. Olefinic protons were still present but could not *per se* be adjudged to be the ones originally present. Phenyl analog 27b produced similar cyclization results. A number of other cyclization conditions were probed in trying to ring close 27a. These included P_2O_5/CH_3SO_3H[20] and HCl/isopropanol which produced no reaction at all at low temperatures and extensive resinification at more elevated temperatures. At -78 °C $SnCl_4/CH_2Cl_2$ or CF_3COOH/CH_2Cl_2 or SO_2 containing BF_3/Et_2O or $SnCl_4$ or SO_2 pure, produced product patterns resembling the ones obtained above with FSO_3H/SO_2. Efforts directed at cyclizing 27a,b were therefore abandoned.

V.5 Summary

Two new strategies for constructing tosylated steroid-directed cyclization precursors VII are examined. The first one, depicted in Figure V. 2, has involved the large-scale preparation of 1 and 7a. Synthon 1 is derived in three steps from acetonyl acetone 11 via considerable modification of existing literature directions.[13] An efficient and practical synthesis of 7a, centered on LAH *trans*-reduction of alkyn 5a, has also been achieved. On reaction with anionized 2-thienyl-tosyl methane, 7a gives 10a, which is transformed by way of 10b and c into 10d. This compound with the 1-derived anion, 2, undergoes predominantly elimination to 19 rather than substitution to 18. In a second strategy, unit 23 is produced in four steps from 2-methylfuran to serve as electrophile in alkylating 2-thienyl- and phenyltosyl methane to provide 24a,b. These undergo furan ring opening and aldolization to cyclopentenones 26a,b which are transformed by alane reduction into cyclization precursors VII exemplified by 27a,b. Efforts to bring about their acid-induced polycyclizations are presented.[21]

V.6 Experimental Section

Melting points, taken on a Fisher-Johns block, and boiling points are uncorrected. ^{1}H NMR spectra were taken on a Varian EM 360A spectrometer; ^{13}C NMR spectra were recorded on a Varian HA 100 equipped with a Digilab FTS-NMR-3. GLC data were obtained on a carbowax column of 30 m and 0.3 mm diameter at 170 ^{o}C.

► *1-Bromo-2-(ethoxyethoxy)ethane (4a).*

The following directions are based on those of Brandsma.[22] To 180 g (2.50 mol) of ethyl vinyl ether were added at 0 ^{o}C and with stirring 175 mg of p-toluene sulfonic acid (TSA) and 15.7 g (0.125 mol) of 2-bromoethanol. The cooling bath was removed, resulting in a rapid temperature rise to 6 ^{o}C; the mixture was recooled to 0 ^{o}C whereupon another 140.6 g (1.125 mol) of 2-bromoethanol and 120 mg of TSA were added. The mixture was slowly allowed to come to room temperature (1 h) and was then first basified by addition of 12.5 mL of saturated K_2CO_3. On bubbling NH_3 through the mixture for 10 seconds, the solids were removed by filtration and were rinsed with ether. The low-boiling components were removed from the filtrate at aspirator pressure below 50 ^{o}C; fractionation of the residue from anhydrous K_2CO_3 in NH_3-flushed equipment afforded 220 g (92%) of 4a, bp 63-64 ^{o}C/10 mm. ^{1}H NMR δ (CCl_4): 1.14 (t,3, $OCCH_3$), 1.25 (d,3,O_2CCH_3), 3.16-3.91 (m,6,3 CH_2), 4.62 (q,1,OCHO).

► *5-(Ethoxyethoxy)-2-pentyn-1-ol (5a).*

To a stirred, refluxing mixture of 1.1 mol of freshly prepared $LiNH_2$(from 7.7 g of Li wire and 0.10 g of $Fe(NO_3)_3$ in 1000 mL of liquid NH_3)[22] was added dropwise 28.0 g (0.50 mol) of propargyl alcohol. Stirring was continued for 15 min at which point 98.2 g (0.50 mol) of 4a was introduced. After 1 h the solvent was expelled and the residue was taken up in ice water-ether and filtered through Hy-Flow (Celite 545) to remove bothersome solids. The filtrate was then thoroughly extracted with 400 mL of ether. Drying and evaporation of the organic phase left a residue which, on fractionation from anhydrous K_2CO_3, provided 66.8 g (77%) of product, bp 86-89 ^{o}C/0.15 mm. ^{1}H NMR δ (CCl_4): 1.21 (t,3,$OCCH_3$),

1.29 (d,3,$OCOCH_2$), 2.20-2.62 (m,2,$\equiv CCH_2CO$), 4.63 (q,1,OCHO).

► *trans-5-(Ethoxyethoxy)-2-penten-1-ol (6a).*

To a stirred mixture of 6.25 g (0.164 mol) of LAH in 150 mL of dry THF was introduced dropwise 43.0 g (0.25 mol) of 5a in 50 mL of THF. The mixture was refluxed for 1 h and was then decomposed by consecutive additions of 6.25 mL of water, 4.7 mL of 5N NaOH and 20.3 mL of water. Filtration and filtrate--solvent removal gave a residue which was fractionated to furnish 37.8 g (87%) of product, bp 77-78 °C/0.1 mm. ^{1}H NMR δ (CCl_4): 1.21 (t,3,$OCCH_3$), 1.27 (d,3,O_2CCH_3), 2.08-2.56 (m,2,$=CCH_2$), 3.14-4.32 (m,7,$HOCH_2$ and CH_2OCOCH_2), 4.64 (q,1,OCHO), 5.23-5.97 (m,2,CH=CH). ^{13}C NMR δ (neat): 63.32 (C_1), 33.29 (C_4).[18]

For purposes of literature comparison and ^{13}C NMR ascertainment of the proper *trans*-geometry, 6a was hydrolyzed to 6b which was then derivatized to the known bis-phenylcarbamate.[6a]

► *trans-1,5-Pentene-2-diol (6b).*

A solution of 8.7 g (0.05 mol) of 6a in 100 mL of methanol containing 0.15 mL of sulfuric acid was kept at room temperature for 18 h. Sodium methoxide in methanol, equivalent to the acid used, was added and the solvent was removed and replaced with chloroform. The solids were filtered; removal of the solvent and fractionation of the residual oil provided 4.8 g (93%) of diol 6b, bp 88-89 °C/0.7 mm. ^{1}H NMR δ ($CDCl_3$): 2.10-2.50 (m,2,CH_2CO), 3.57 (t,2,CCH_2O), 3.85-4.38 (m,2,$OCH_2C=$ and 2 OH), 5.22-5.97 (m,2,CH=CH). ^{13}C NMR δ (neat): 63.82 (C_1), 36.29 (C_4).[18] This material was GLC-compared with authentic *cis*-isomer. It was 99% pure and contained none of the *cis*-isomer.

Diol 6b, 0.51 g (0.005 mol) was treated with 1.19 g (0.01 mol) of phenyl isocyanate for 4 h in refluxing THF, to give, on solvent removal and trituration of the residual solids with diisopropyl ether, 1.50 g (91%) of carbamate, mp 160-161 °C, lit[6a] mp 159-160 °C; the mp did not change after crystallization from diisopropyl ether.

► *trans-1-Chloro-5-(ethoxyethoxy)-pentene-2 (7a).*

To an ice cold mixture of 2.26 g (0.055 mol) of LiCl, 7.25 g (0.06 mol) of s-collidine and 8.7 g (0.05 mol) of 6a in 25 mL of dry DMF was introduced, with stirring, 6.87 g (0.06 mol) of methanesulfonyl chloride. After 1.5 h at 0 °C the mixture was poured into 50 mL of ice water. This was extracted with 100 mL of 50% ether-petroleum ether. The combined organic layers were then scrubbed with 15 mL of saturated copper nitrate solution and ultimately with water. Drying of the organic layer (K_2CO_3), solvent evaporation and fractionation of the residue from K_2CO_3 gave 7.7 g (80%) of product, bp 60-62 °C/0.3 mm.[12] ^{1}H NMR δ (CCl_4): 1.14 (t,3,$OCCH_3$), 1.26 (d,3,O_2CCH_3), 2.07-2.50 (m,2, $=CCH_2$), 3.05-3.79 (m,4,CH_2OCOCH_2), 3.79-4.25 (m,2,$ClCH_2$), 4.57 (q,1,OCHO), 5.25-6.07 (m,2,CH=CH). ^{13}C NMR δ (neat): 45.32 (C_1), 33.20 (C_4).[18]

Compound 7a was converted to 7b according to the procedure 6a→6b (see above). ^{1}H NMR δ ($CDCl_3$): 2.07-2.35 (m,2,CH_2CO), 3.62 (t,2,CCH_2O), 4.04 (d,2,$ClCH_2$), 4.20-4.53 (t,1,OH), 5.29-6.06 (m,2,CH=CH).

Treatment of 7b with one equiv of phenyl isocyanate, gave the phenyl carbamate 9a, mp 54-55 °C (diisopropyl ether).

Anal. Calcd. for $C_{12}H_{14}ClNO_2$: C, 60.13; H. 5.89; N, 5.85. Found: C, 60.25; H, 5.89; N, 5.81.

Similarly 7b, on treatment with α-naphthyl isocyanate, gave α-naphthyl carbamate 9b, mp 91-92 °C (diisopropyl ether).

Anal. Calcd. for $C_{16}H_{16}ClNO_2$: C, 66.32; H, 5.57; N, 4.84. Found: C, 66.54; H, 5.66; N. 4.76.

► *trans-5-(N-Phthalimido)-2-penten-1-ol (8a).*

A mixture of 3.85 g (0.02 mol) of 7a and 3.75 g (0.02 mol) of potassiumphthalimide in 15 mL of DMF was kept at 135 °C for 10 min. It was poured into water from which the product was extracted into ether, which was dried and evaporated. Methanol, 50 mL, and 0.10 g of sulfuric acid were added to the residue, which was kept at room temperature overnight and was then neutralized with sodium methoxide in methanol. Solvent was removed in vacuo and replaced with chloroform; the inorganics were filtered,

whereupon the chloroform was stripped to leave solid product, 4.5 g (97%). Recrystallization from ethanol gave white crystals melting at 83-84 °C.

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.24; H, 5.67; N, 5.93.

► *trans-5-(p-Toluenesulfonyl)-2-penten-1-ol (8b).*

Treatment of 7a with an equivalent amount of sodium-p-toluenesulfinic acid in DMF as described above, led to sulfone 8b (71%), recrystallized from isopropyl alcohol to melt at 48-49 °C.

Anal. Calcd. for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71. Found: C, 60.11; H, 6.73.

► *(E)-1-(2-Thienyl)-1-(p-toluenesulfonyl)-6-hydroxy-hex-3-ene (10b*

A mixture of 25.2 g (0.1 mol) of 2-thienyl-p-toluenesulfonyl methane, 21.2 g (0.11 mol) of 7a, 150 mL of 50% (w/w) sodium hydroxide 40 mL of THF and 2 g of n-tetrabutylammonium bromide was stirred for 3 h. Water, 1000 mL was added, the organic phase was separated and dissolved in 200 mL of chloroform. The solution was washed with water until neutral, dried over magnesium sulfate and the solvent was expelled to leave 45.1 g of crude material. This was dissolved in 150 mL of methanol containing 0.2 mL of concentrated H_2SO_4 and left overnight. The mixture was neutralized with sodium methoxide in methanol, equivalent to the amount of acid used, and the solvent was evaporated. Continued liquid-liquid extraction with warm low-boiling petroleum ether for 68 h left after evaporation 19.2 g of an oil. This was filtered over a 10 fold by weight of silica. Evaporation and trituration with ice cold diisopropyl ether containing 10% of isopropanol gave 11.5 g (34%) of solid 10b, mp 73-74 °C. ^{1}H NMR δ ($CDCl_3$): 1.83-3.75 (m,5,$CH_2C{=}CH_2$) and OH), 2.36 (s,3,$TosCH_3$), 3.41 (t,2,CH_2O), 4.08-4.56 (dd,1,CHTos), 4.94-5.81 (m,2,olefinic H), 6.57-7.64 (m,7,ArH). Analytical material was obtained from diisopropyl ether and had mp 75-76 °C.

Anal. Calcd. for $C_{17}H_{20}O_3S_2$: C, 60.68; H, 5.99. Found: C, 60.89; H, 6.10.

► *(E)-1-(2-Thienyl)-1-(p-toluenesulfonyl)-6-iodo-hex-3-ene (10d).*

To a stirred mixture of 3.4 g (0.01 mol) of 10b, 10 mL of benzene, 0.1 g of triethylbenzylammonium chloride and 10 mL of 30% (w/w) sodium hydroxide was added slowly, at 0 °C, 2.1 g (0.011 mol) of p-toluenesulfonyl chloride. The mixture was stirred for 18 h at room temperature. To it was then added 50 mL of water and 50 mL of ether. The organic layer was separated, washed with water until neutral, dried and evaporated to leave 6.3 g of an oil. This was dissolved in 20 mL of dry acetone and then refluxed with a solution of 3.0 g (0.02 mol) of sodium iodide in 70 mL of dry acetone. The mixture was cooled after 2 h, filtered and the solvent was evaporated. The residue was dissolved in ether and the solution was washed respectively with water, saturated thiosulfate solution and water. Drying over magnesium sulfate, evaporation and trituration with ice cold methanol left 3.68 g (81%) of solid product, mp 95 °C. ^{1}H NMR δ ($CDCl_3$): 2.14-3.51 (m,6,3 CH_2), 2.37 (s,3,TosCH$_3$), 4.11-4.47 (dd,1,CHTos), 4.89--5.74 (m,2,olefinic H), 6.57-7.60 (m,7,ArH). Analytical material was obtained from methanol, mp 99-100 °C.

Anal. Calcd. for $C_{17}H_{19}IO_2S_2$: C, 45.74; H, 4.29. Found: C, 46.02; H, 4.42.

► *(E)-1-(2-Thienyl)-1-p-toluenesulfonyl-6-(N-phthalimido)--hex-3-ene (10e).*

A mixture of 0.45 g (0.001 mol) of 10d and 0.185 g (0.001 mol) of K-phthalimide in 1 mL of dry DMF was kept for 5 min at 120 °C. It solidified on pouring into water. Filtration and washing with water, ice cold isopropyl alcohol and diisopropyl ether afforded 0.3 g (70%) of 10e; mp 112-113 °C. Analytical material was obtained from diisopropyl ether and had mp 114-115 °C.

Anal. Calcd. for $C_{25}H_{23}NO_4S_2$: C, 64.49; H, 4.98; N, 3.01. Found: C, 64.35; H, 5.05; N, 2.98.

► *3-Methyl-cyclopenten-2-one (12).*

This compound, bp 74-76 °C/16 mm, was prepared in 40% yield as described.[14] ^{1}H NMR inspection and comparison thereof with the spectrum of acetonyl acetone 11, showed it to contain a residual 20% of the starting material.

► *3-Methyl-3-(p-toluenesulfonyl)cyclopentanone (13).*

To a stirred solution of 12 (80% pure, containing 76.8 g (0.80 mol) of 12) and 178 g of NaTos (1.0 mol) was added slowly in a thin stream 1000 mL of 1N hydrochloric acid. After 18 h the produced solids were filtered off; washing with water, isopropanol and ether gave on air drying 196 g (97%) of adduct; mp 86-87 °C. ^{1}H NMR δ ($CDCl_3$): 1.40 (s,3,$TosCH_3$), 1.73-3.23 (m,6,3 CH_2), 2.42 (s,3,CH_3), 7.17-7.83 (AB,4,ArH). IR ($CHCl_3$): ν = 1755 cm^{-1} (C=O). An analytical sample was prepared from isopropanol: mp 86-87 °C.

Anal. Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39. Found: C, 61.83; H, 6.39.

Neutralization of the filtrate and extraction with methylene chloride provided acetonyl acetone; yield 21 g(94%).

► *Conversion of 13 to pure 3-methylcyclopenten-2-one (12).*

A supension of 91 g (0.355 mol) of 13 and 100 g of sodium bicarbonate in 200 mL of water was stirred for 18 h. Some insoluble material was filtered off. The filtrate was salted out and thoroughly extracted with methylene chloride. On drying with magnesium sulfate and evaporation of solvent, a residue of 32 g (94%) of essentially pure 12 was obtained; bp 70 °C/10 mm. ^{1}H NMR δ (CCl_4): 1.97-2.70 (m,4,2 CH_2), 2.10 (s,3,CH_3), 5.60--5.83 (m,1,=CH).

The TosH was recovered on acidification of the mother liquors and filtration of the solids. These, on being taken up in ether, and subsequently drying over magnesium sulfate, left after ether removal 38 g (70%) of pure TosH.

► *2-Bromo-3-methylcyclopenten-2-one (15).*

Into a stirred solution of 26 g (0.27 mol) of 12 in 150 mL of carbon tetrachloride kept at 10-15 °C was slowly introduced 43 g (0.27 mol) of bromine in 8 mL of carbon tetrachloride. After 30 min the organic phase was thoroughly scrubbed with water and saturated sodium bicarbonate solution. The organic layer was separated, washed with water, dried with magnesium sulfate and stripped of solvent leaving 35 g of solid product. On extraction

in boiling pentane and cooling 29.2 g (61%) of crystalline 15 was deposited, mp 52-53 °C. ^{1}H NMR δ (CCl_4): 2.10 (s,3,CH_3), 2.23-2.73 (m,4,2 CH_2); IR (CCl_4): ν = 1730 cm^{-1} (C=O). An analytical sample was obtained from diisopropyl ether and had mp 52-53 °C.

Anal. Calcd. for C_6H_7BrO: C, 41.17; H, 4.03. Found: C, 40.83; H, 4.12.

► *6-Bromo-7-methyl-1,4-dioxaspiro[4.4]non-6-ene (1).*

A stirred mixture of 16 g of 15 (0.09 mol), 25 mL of ethylene glycol (0.44 mol), a trace of TSA and 500 mL of benzene was refluxed for a total of 72 h in an apparatus equipped for continuous water removal. The reaction was interrupted after 24 h and 48 h. It was then scrubbed with saturated sodium bicarbonate solution and ultimately with water and was then dried. Fresh ethylene glycol, 12 mL, and traces of TSA were reintroduced each time and the reaction was started up again. The scrubbing procedure was repeated on termination of the reaction. Drying of the organic layer over potassium carbonate and solvent removal left crude product which was flash-distilled from solid potassium carbonate to give 13 g (66%) of ketone-free material which solidified on standing; bp 70 °C/0.07 mm; mp 32-33 °C. ^{1}H-NMR δ (CCl_4): 1.73 (s,3,CH_3), 1.83-2.62 (m,4,2 CH_2), 3.62-4.20 (m,4,OCH_2CH_2O). IR (CCl_4): ν = 1675 cm^{-1} (C=C); no C=O.

► *1-Hydroxy-6-[2-(5-methylfuryl)]-hex-2-yne (21).*

To 0.63 mol of $LiNH_2$ (freshly prepared from 5.0 g of Li, 0.06 g of ferric nitrate and ca 600 mL of refluxing NH_3, according to the directions of Brandsma)[22] was added 17.7 g (0.3 mol) of propargyl alcohol. After 10 min 60.9 g (0.3 mol) of 20[17] was introduced, and the mixture was stirred for 3 h. The ammonia was allowed to evaporate and the residue was taken up in ice water-ether and filtered through Hy-Flow (Celite 545). The filtrate was thoroughly extracted with ether. The combined ether layers were washed with brine, dried over magnesium sulfate and evaporated to leave 51 g of an oil. Fractionation gave

46.3 g (87%) of 21, bp 88-91 °C/0.005 mm. ^{1}H NMR δ (CCl_4): 1.47-2.03 (m,2,CH_2CFu), 2.03-2.40 (m,2,$CH_2C{\equiv}C$), 2.16 (s,3,CH_3), 2.62 (s,3,CH_3), 2.62 (t,2,CH_2Fu), 3.40 (s,1,OH), 4.08 (t,2, $OCH_2C{\equiv}C$), 5.57-5.84 (m,2,FuH).

► *(E)-1-Hydroxy-6-[2-(5-methylfuryl)]-hex-2-ene (22).*

To a slurry of 10 g of LAH in 75 mL of THF was dropped a solution of 39.5 g (0.22 mol) of 21 in 30 mL of THF. The stirred mixture was refluxed for 1 h and then cooled. To it was added respectively 10 mL of water, 7.5 mL of 5N NaOH solution and 32.5 mL of water. Filtration and filtrate-solvent removal gave a residue which was fractionated to afford 32 g (81%) of product, bp 90-92 °C/0.02 mm. ^{1}H NMR δ (CCl_4): 1.43-2.31 (m,4,2 CH_2), 2.19 (s,3,CH_3), 2.51 (t,2,CH_2Fu), 2.94 (s,1,OH), 3.81-4.03 (m,2,$OCH_2C{=}C$), 5.37-5.61 (m,2,olefinic H), 5.64 (s,2,FuH).

► *(E)-1-Chloro-6-[2-(5-methylfuryl)]-hex-2-ene (23).*

To an ice cold mixture of 5.52 g (0.13 mol) of LiCl, 17.0 g (0.14 mol) of s-collidine and 23.0 g (0.13 mol) of 22 in 50 mL of dry DMF was introduced, with stirring, 16.1 g (0.14 mol) of methane sulfonyl chloride. After 1.5 h at 0 °C the mixture was poured into 100 mL of ice water. This was extracted 5 times with a total amount of 200 mL of 50% ether-petroleum ether. The combined organic layers were then scrubbed with respectively water, saturated copper nitrate solution and water. Drying of the organic layers on K_2CO_3, solvent evaporation in the presence of a trace of K_2CO_3 and flash-vacuum distillation (K_2CO_3) gave 21 g (81%) of 90% pure material, bp 110-130 °C/0.5 mm. ^{1}H NMR δ (CCl_4): 1.32-2.31 (m,4,2 CH_2), 2.15 (s,3,CH_3), 2.52 (t,2,CH_2Fu), 3.80-4.00 (m,2,$ClCH_2$), 5.36-5.87 (m,2,olefinic H), 5.64 (s,2,FuH).

► *(E)-1-(2-Thienyl)-1-(p-toluenesulfonyl)-7-[2-(5-methylfuryl)]-hept-3-ene (24a).*

A mixture of 21.0 g (0.083 mol) of 2-thienyl-p-toluenesulfonyl methane, 20.0 g of 90% pure 23 (0.09 mol), 124 mL of 50% (w/w) of NaOH solution, 33 mL of THF and 1.6 g of n-tetrabutylammonium

bromide were stirred at room temperature. After 18 h, 1000 mL of water were added, the organic layer was separated and dissolved in chloroform. Washing with water, drying over $MgSO_4$ and evaporation gave 40.0 g of crude material. Filtration through silica, using hexane-10% acetone as eluent furnished after evaporation of the solvent and trituration with ice cold diisopropyl ether 19.0 g (55%) of solid product, mp 74 °C. Recrystallization from diisopropyl ether gave analytical material, mp 77-78 °C. ^{1}H NMR δ ($CDCl_3$): 1.25-3.34 (m,8,4 CH_2), 2.17 (s,3,$FuCH_3$), 2.37 (s,3,$TosCH_3$), 4.11-4.46 (dd,1,CHTos), 4.81--5.82 (m,2,olefinic H), 5.70 (s,2,FuH), 6.62-7.61 (m,7,ArH).

Anal. Calcd. for $C_{23}H_{26}S_2O_2$: C, 66.63; H, 6.32. Found: C, 66.87; H, 6.44.

► *(E)-1-Phenyl-1-(p-toluenesulfonyl)-7-[2-(5-methylfuryl)]--hept-3-ene (24b).*

Identical to 24a. Addition of a 10-fold of water to the phase--transfer mixture caused 24b to precipitate. The solid was filtered and washed with respectively water, isopropyl alcohol and diisopropyl ether to give 65% of 24b; mp 71-72 °C. Analytical material was obtained upon recrystallization from diisopropyl ether and melted at 73-74 °C. ^{1}H NMR δ ($CDCl_3$): 1.03-3.38 (m,8, aliphatic H), 2.19 (s,3,$FuCH_3$), 2.35 (s,3,$TosCH_3$), 3.83-4.23 (dd,1,CHTos), 4.76-5.66 (m,2,olefinic H), 5.50-5.88 (m,2,FuH), 6.88-7.54 (m,9,ArH).

Anal. Calcd. for $C_{25}H_{28}SO_3$: C, 73.50; H, 6.91. Found: C, 73.70; H, 7.19.

► *(E)-1-(2-Thienyl)-1-(p-toluenesulfonyl)-6[2-(3-methyl-2--cyclopenten-1-onyl)]-hex-3-ene (26a).*

A mixture of 10.0 g (0.024 mol) of 24a in 300 mL of ethanol and 150 mL of 0.5N hydrochloric acid was refluxed for 20 h. To it was then added 8.0 mL of 50% (w/w) NaOH solution (6.0 g of sodium hydroxide). The alkaline solution was refluxed for 2 h and then partly evaporated. To the residue was added chloroform and the organic layer was washed with brine, dried over $MgSO_4$ and filtered. Evaporation of the solvent followed by trituration

with ice cold diisopropyl ether gave 8.9 g (89%) of solid material, mp 110 °C. Analytical material was obtained upon crystallization from isopropyl alcohol, mp 114-115 °C. ^{1}H NMR δ ($CDCl_3$): 1.80-3.42 (m,10,aliphatic H), 1.92 (s,3, CH_3C=C), 2.37 (s,3,TosCH_3), 4.03-4.52 (dd,1,CHTos), 4.83--5.79 (m,2,olefinic H), 6.58-7.57 (m,7,ArH).

Anal. Calcd. for $C_{23}H_{26}S_2O_3$: C, 66.63; H, 6.32. Found: C, 66.72; H, 6.39.

► *(E)-1-Phenyl-1-(p-toluenesulfonyl)-6-[2-(3-methyl-2--cyclopenten-1-onyl)]-hex-3-ene (26b).*

In analogy to 26a. The product solidified on partly evaporating the aqueous solution. It was filtered, washed with water, ice cold isopropyl alcohol and diisopropyl ether and afforded upon air-drying 95% of 26b having mp 113-114 °C. Recrystallization from isopropyl alcohol gave analytical material; mp 116-117 °C. ^{1}H NMR δ ($CDCl_3$): 1.66-3.17 (m,10,aliphatic H), 1.90 (s,3,CH_3), 2.36 (s,3,TosCH_3), 3.81-4.20 (dd,1,CHTos), 4.70-5.66 (m,2,olefinic H), 6.79-7.51 (m,9,ArH).

Anal. Calcd. for $C_{25}H_{28}SO_3$: C, 73.50; H, 6.91. Found: C, 73.27; H, 7.10.

► *(E)-1-(2-Thienyl)-1-(p-toluenesulfonyl)-6-[2-(3-methyl-2--cyclopenten-1-olyl)]-hex-3-ene (27a).*

To a slurry of 0.24 g of LAH (0.0063 mol) in 10 mL of THF was carefully added, at 0 °C, 0.27 g (0.002 mol) of powdered $AlCl_3$. The mixture was stirred for 1 h at room temperature, and was then dropped at -5 °C to a slurry of 2.2 g of 26a (0.005 mol) in 10 mL of dry THF. After 45 min at 0 °C, 0.24 mL of 5N NaOH was added. The mixture was filtered and evaporated to give 2.0 g of 27a (91%). ^{1}H NMR δ ($CDCl_3$): 1.18-3.41 (m,11,aliphatic H and OH), 1.54 (s,3,CH_3C=C), 2.40 (s,3,TosCH_3), 4.03-4.50 (dd, 1.CHTos), 4.24-4.70 (br,1,OCH), 4.84-5.76 (m,2,olefinic H), 6.54-7.63 (m,7,ArH). IR: ν = 3500 cm^{-1} (OH); no C=O.

The product was used immediately for cyclization experiments.

► *(E)-1-Phenyl-1-(p-toluenesulfonyl)-6-[2-(3-methyl-2-cyclopenten-1-olyl)]-hex-3-ene (27b).*

Similar to 27a. The product solidified upon evaporation of the solvent. Trituration with diisopropyl ether gave 80% of 27b melting at 77-78 °C. ^{1}H NMR δ ($CDCl_3$): 1.36-3.17 (m,11, aliphatic H and OH), 1.51 (s,3,C=CCH_3), 2.40 (s,3,TosCH_3), 3.86-4.26 (dd,1,CHTos), 4.26-4.75 (br,1,OCH), 4.75-5.92 (m, 2,olefinic H), 6.85-7.48 (m,9,ArH). IR: ν = 3500 cm^{-1} (OH); no C=O.

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CHAPTER VI

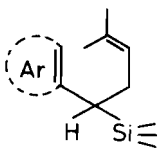
The TMS Group as Removable Enantioselectivity Inducing Fragment during Natural-product directed Cationic Polycyclization Processes

VI.1 Introduction

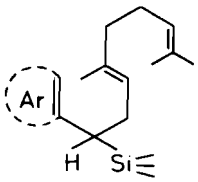
The explosive growth of organosilicon chemistry over the past 15 years has demonstrated its considerable synthetic potential[1-3] which stems chiefly from the ability of silicon to activate a substrate to certain types of reaction, to direct the course of some reactions, or to protect a substrate from unwanted reactions. Of the organosilanes, the most frequently encountered ones contain the trimethylsilyl (TMS) fragment. Sterically this resembles a *tert.*-butyl group, being sp^3-hybridized around its central silicon atom, and differing only in the longer Si-C bonds (1.98 Å). Of considerable significance in synthesis is the ease of TMS removal from vinylic or allylic systems and, in some instances, from benzylic substrates. Such behavior is in marked contrast with that of the *tert.*-butyl fragment, whose removal appears to be limited to detachment from aromatic systems only.[4]

To our knowledge there exists no precedent for the TMS fragment ever having found use as enantioselectivity-inducing fragment during cationic cyclization reactions, this being in contrast with the *tert.*-butyl group which has recently been shown to bring about absolute enantioselectivity during some steroid-directed ring closures.[5] It was therefore decided to investigate whether the TMS functionality could be made to serve a similar purpose, the difference being that the chance of desilylating the produced cyclic materials were deemed, *a priori*, to be reasonably good. This would provide another example of using silicon-containing intermediates to furnish ultimately silicon-free end products.

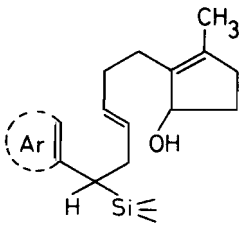
The projected plan of action would require access to substantial quantities of structures of type III. As before attention was to be directed first to preparing such simple models as I and II. The experience gained on preparing comparably tosylated systems described in Chapters III-V was thought to be applicable in the present proposals. As with the sulfonyl fragments, the ability of TMS fragments to stabilize adjacent carbanions was considered to facilitate the synthetic realizations of objectives I-III. If successful and if selectivity was indeed to be attained on cyclizing racemates of II and III, identical transformations performed on the optically pure systems, followed by ultimate de-trimethylsilylation would provide ready access to enantiomerically homogeneous polycyclic systems.



I



II



III

In practice, the presence of TMS fragments is readily ascertained via the ^{1}H NMR singlet around 0.00 ppm. The total concept would derive its merits from considerations of economics, simplicity of operation and directness of purpose.

This chapter describes the preparation and cyclization of olefins I-III. The possibility of the TMS fragment inducing enantioselectivity on cyclization of II and III constitutes the central issue. A novel benzylic desilylation method[6] is developed and discussed.

VI.2 Synthesis and De-trimethylsilylation of 1,1-Dimethyl--4-trimethylsilyl-1,2,3,4-tetrahydronaphthalenes

VI.2.1 Synthesis of compounds 3a and b

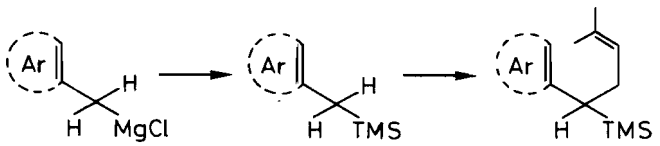
Elaboration of the set goals presupposes easy access to olefins 3a,b. These correspond to tosyl compounds 2a-d, described in Chapter III, so that by analogy a route involving prenylation of suitable benzyltrimethylsilanes would constitute the most logical approach. This, in turn, necessitated the preparation of 2a,b.

Literature examination revealed that trimethylsilyl fragments are best introduced onto benzylic positions via an electrophilic process[7a,b] involving treatment of benzyl organometallic species with chlorotrimethylsilane. To this effect benzylmagnesium chloride 1a, generated according to Benkeser,[8] gave with chlorotrimethylsilane compound 2a in 83% yield. A similar transformation performed on m-methoxybenzylmagnesium chloride gave 2b in equally good yield. Numerous attempts to obtain the related 2-thenyl analog 2c were to no avail. The 2-thenyl Grignard reagent gave, under circumstances as above, compound 2c contaminated with large amounts of the 3- and the 5-TMS analogs. Such anomalies are common in thiophene chemistry.[9a,b] Barbier conditions, involving direct trapping of the magnesium complex with chlorotrimethylsilane, produced a similar mixture. Another tactic proceeded via the intermediacy of the 2-thenyl radical anions generated by the addition of sodium naphthalene.[10] On quenching with chlorotrimethylsilane, isomer-free 2c was indeed obtained but its severe contamination with naphthalene made large-scale purification an unsavory prospect. The study of thiophene-containing systems was therefore discontinued.

Prenylation of 2a,b was achieved via the corresponding anions. A strong base, such as the n-butyllithium-tetramethylethylenediamine complex (BuLi-TMEDA),[11a-c] is capable of deprotonating even tetramethylsilane.[11c] When an α-silyl carbanion is flanked by a second anion stabilizing fragment, anion formation is facilitated. Benzyltrimethylsilane, for instance, has been metalated by methyllithium in hexamethylphosphoramide

(HMPA), the organometallic being subsequently brought into reaction with carbonyl compounds.[12] Oddly enough, alkylation of α-silyl carbanions in general has drawn little attention, short of the reaction of phenylselenotrimethylsilyllithium with primary alkyl bromides or iodides.[13] These precedents augured well for the intended prenylations of 2a,b.

Anionization of the benzylsilanes 2a,b was accomplished by treatment with 2 equivs of freshly prepared ethereal BuLi/TMEDA at room temperature. Subsequent addition of prenyl bromide provided after 18 h, besides low boiling components, 42-46% of 3a,b.



1a-c 2a-c 3a-c

a: Ar = phenyl
b: Ar = m-anisyl
c: Ar = 2-thienyl

VI.2.2 Compounds 4a-c: Synthesis via Cyclization and Desilylation Studies

Treatment of compound 3a with excess trifluoroacetic acid in methylene chloride at room temperature caused facile cycloalkylation to produce after distillation, GLC-pure 4a in 80% yield. Such conditions produced from 3b a mixture of *ortho*- and *para*-cyclized 4b and 4c. These were chromatographically separated to give 4b and 4c (26 and 39%) and identified by the aromatic NMR pattern with the *ortho* cyclized 4b showing a complex pattern of three *vicinal* protons and the *para* cyclized 4c, having only two *vicinal* protons, displaying simpler signals.

Although replacement of allylic or olefinic TMS groups by hydrogen constitutes a general tactic in synthesis,[1-3] cleavage of benzyltrimethylsilanes has hitherto been restricted to desilylation of systems 6a-c by sodium- or potassium amide in refluxing ammonia to give 90% of 7a-c, and sodium ethoxide or potassium hydroxide in refluxing ethanol to give acceptable

yields of 7b and 7c only.[14] In the present studies, 4a, on treatment with sodium amide, gave de-trimethylsilylated 5a quantitatively which was found to be identical to material obtained on detosylating its tosyl analog (compound 5d in Chapter III). By its nature, however, the method is not viable

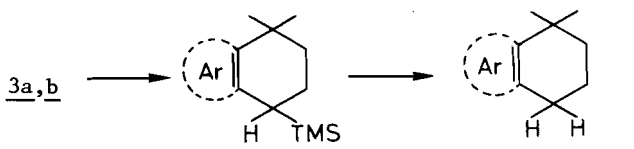
6a-c 7a-c

a: $R_1 = R_2 = H$

b: $R_1 = H$; R_2 = phenyl

c: $R_1 = R_2$ = phenyl

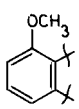
for infinite upscaling, thus prompting a search for a more practical desilylation mode. This was ultimately found in the use of potassium *tert.*-butoxide in dry DMSO.[15] On stirring 4a in 1.1 equiv of K-t-OBu for 15 min, followed by aqueous work-up and fractional distillation, 81% of desilylated 5a, identical with earlier obtained material, was isolated. K-t-OBu induced de-trimethylsilylation of 4b,c afforded 98%--GLC-pure 5b,c in essentially quantitative yields.



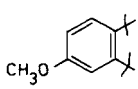
4a-c 5a-c

a: Ar =

b: Ar =



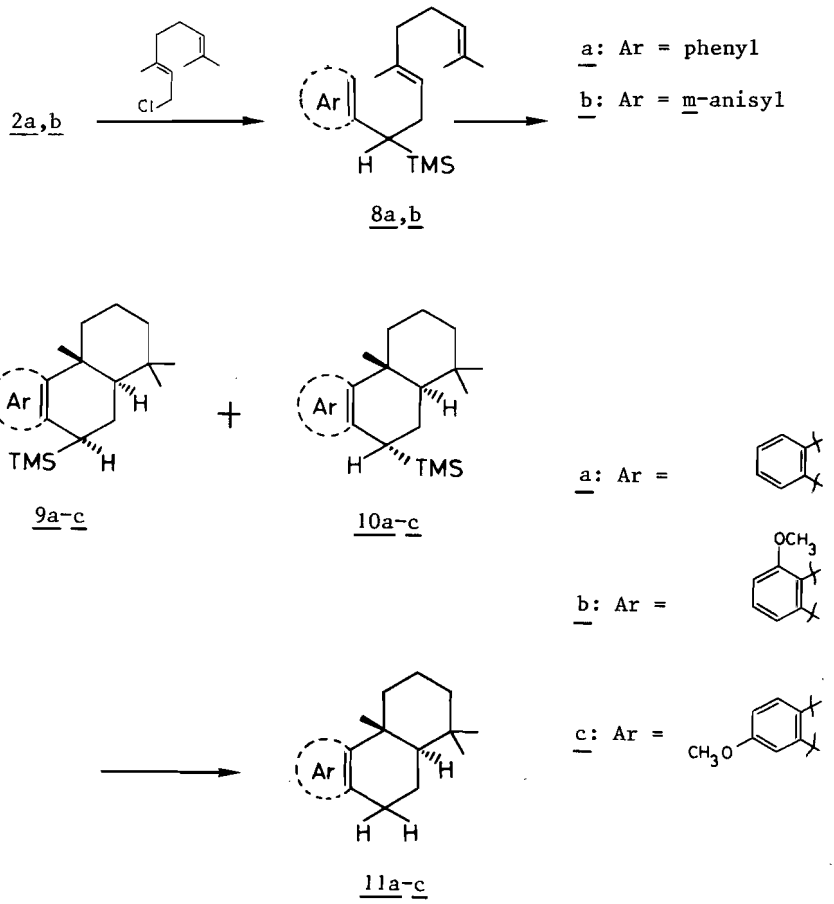
c: Ar =



VI.3 Aromatic Resin-acid Related Systems 11a-c via Desilylation of Polyene-cyclization Derived Structures

The above results, hinging on the preparation of benzyltrimethylsilanes, stimulated further efforts to extend the methodology to include aromatic resin acid models for purposes of probing the enantioselectivity inducing potential of the

TMS group. These efforts were to be limited to the synthesis and cyclization of geranyl systems 8a,b to *trans* annelated silylated structures 9-/10a-c and their subsequent desilylation to afford tricyclic resin acid related frameworks 11a-c.



Benzyltrimethylsilane 2a was anionized as above and was then treated with geranyl chloride[16] to give 62% of distilled 8a. Similarly 40% of 8b was obtained from m-methoxy analog 2b. The use of CF_3COOH, instrumental in bringing about formation of bicycles 4a-c, failed to effect cyclization of the geranylated systems. On using $SnCl_4$, however, cyclization did occur with best results being obtained on treatment of 8a with 4 equiv of freshly distilled stannic chloride in methylene chloride

for 2 h at -78 °C to give 51% of a GLC-determined 85:15 epimeric mixture of 9-/10a. The major isomer was designated as having the β-configuration in analogy to reasoning pursued in the earlier obtained tosylated versions (Chapter IV). The mixture was triturated with methanol to afford 29% of solid β-isomer 9a melting sharply at 83-84 °C.

Cyclization of 8b under identical conditions yielded both *ortho* and *para*-ring closed materials which were separated chromatographically to give 5% of GLC-pure 9b and 46% of a GLC-binary 77/23 mixture of 9-/10c. Compound 9b solidified on standing and had, after trituration with methanol, mp 108-109 °C.

The ring closure of 8a when conducted under the drastic FSO_3H/SO_2 conditions as employed for the comparable tosyl compounds, gave upon FSO_3H addition a gum immediately. After 15 min at -78 °C work-up afforded only 25% of a GLC 68/32 mixture of 9-/10a.

The experiments in the resin acid models show TMS to effect enantioselectivity ranging from a 77/23 mixture in *para* cyclization of 8b to an absolute enantioselectivity for *ortho* ring closure thereof. The enantioselectivity is ascribed to 1,3-diaxial interactions between TMS and the angular H in the pro-cyclization conformation of the geranyl system. In case of 9b the angular CH_3-methoxy interaction might well add to it resulting in absolute selectivity, but also giving a much lower yield when compared to 9-/10c. Cyclization conditions may well exert their effect on the enantiomeric ratio as demonstrated in the FSO_3H/SO_2 ringclosure of 8a. The relatively low enantiomeric excesses upon ring closure of tosyl compounds IV-4a-c possibly stem from such interactions.

Desilylation of the tricyclic systems 9-/10a,c using the K-t-OBu/DMSO reagent gave, upon filtration of the crude material through silica (hexane) GLC pure tricycles 11a,c in 80% yield (Table II). Their CH_3-NMR signals correspond to those of related *trans*-ring closed detosylated compounds IV--11-13 and also to IV-16, previously described by Wenkert *et al.*[17]

VI.4 Steroids via a Polyene Cyclization-desilylation Tactic: a New Synthesis of (±)-Estrone.

VI.4.1 Introduction

Results presented in Chapter III showed reaction conditions for cyclizing tosylated olefinic substrate models to require the use of a super-acid system such as FSO_3H/SO_2. These findings were rationalized by assuming the SO_2 to function as cation-solvating medium, thus prolonging the lifespan of critical cationic species sufficiently for polycyclization-productive molecular conformations to be attained. Conditions as these turned out to be superfluous for effecting cyclizations of silylated substrates such as 3a,b and 8a,b for which the use of CF_3COOH or $SnCl_4$ was found to be sufficient and, in fact, superior. The tosylated pro-steroidal substrates 27a,b described in Chapter V, on the other hand failed to respond satisfactorily to the FSO_3H/SO_2 treatment, producing mostly incomplete cyclized materials.

Attention was therefore turned to preparing pro-C-6 trimethylsilylated analogs 15a,b. Related studies, aimed at preparing 6-*tert*.-butyl thiophene A-ring containing estrone types, had used the $SnCl_4$-mediated ring closure of the cyclopentenol precursor to the desired system.[5] This cyclization, as the many others before it,[18] obeyed the Stork-Eschenmoser principles to provide *trans-anti-trans* annelated systems exclusively with the *tert*.-butyl group bringing about 100% enantioselectivity and ending up in the α-configuration.[5] Synthesis of the cyclization precursor used Johnson's route[19] and is outlined in Figure VI. 1. The concept suffers from hinging on a sensitive and always capricious Wittig-Schlosser olefination step at a late stage in the synthesis. Secondly, whereas the *tert*.-butyl group had clearly demonstrated its enantioselectivity-inducing potential, there presently exists no methodology for its ultimate detachment from sp^3-hybridized carbon.

These considerations prompted an alternative course of action whereby 2a,b were to be alkylated with fragment 12, both units being amply accessible. In combination with the by now established K-t-OBu/DMSO desilylation procedure, the

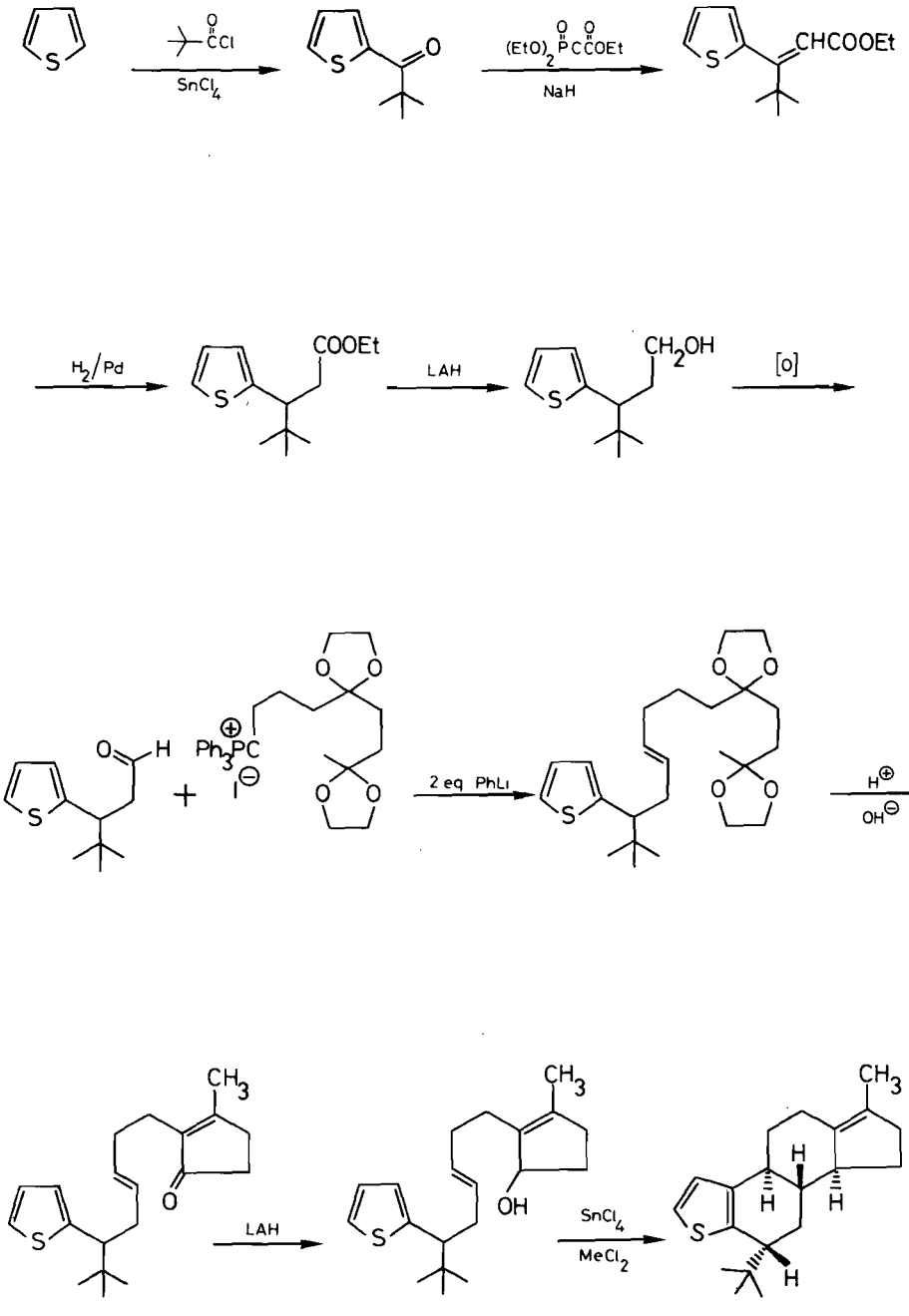
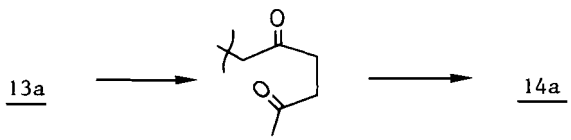

SnCl4
(EtO)2PCCOEt
NaH
CHCOOEt
H2/Pd
COOEt
LAH
CH2OH
[o]
2 eq PhLi
H⊕
OH⊖
CH3
LAH
OH
SnCl4
MeCl2
H

Figure VI. 1

advantages of the proposed strategy would lie in its brevity, its directness of purpose and, of course, the circumvention of the difficult Wittig-Schlosser step to arrive at *trans*--olefinic precursors. By its nature it would open the way to a host of A-ring variations in the ultimate produced steroidal systems since this segment is to be incorporated quite late in the sequence.

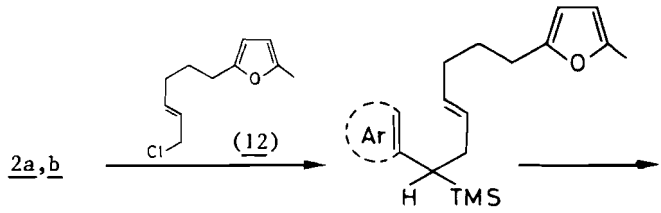
IV.4.2 Synthesis of Estrone Directed Steroids

Treatment of 2a-anion with 12, a structural unit already described in Chapter V, gave 46% of 13a after distillation. This was further elaborated into allylic alcohol 15a via conversions described earlier. This included acid-induced furan ring opening and base catalyzed intramolecular aldolization of the intermediate 1,4 diketone i to give 87% of TLC-



i

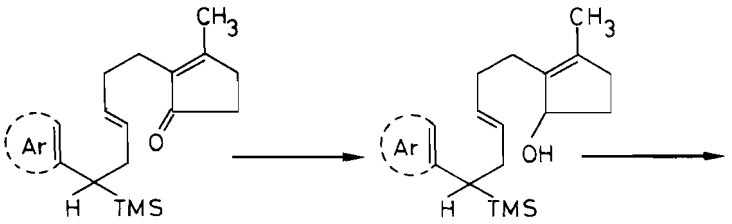
-pure 14a. Literature precedent[5,18a-f,20] called for enone→ →enol reduction by means of the nucleophilic $LiAlH_4$; in the present investigation, enone 14a was treated with the electrophilic AlH_3,[21] thus suppressing unwanted 1,4-reduction and giving NMR-pure alcohol 15a. This, because of its dehydration tendency, was immediately subjected to cyclization conditions. Experiments were conducted at -78 °C in methylene chloride containing 1.3 equiv of stannic chloride and gave cleanly and efficiently 67% of the totally ring closed, diastereomerically pure α-isomer 16a with none of the configurationally opposite β-isomer 17a being detectable by GLC. Assignment of the α configuration to 16a was based on literature analogies,[5,18a,f] on data gained earlier on similar cyclizations leading to tricyclic systems 9-/10a-c and, of course, on the observation of one GLC peak only. Such chromatographic data do not preclude,



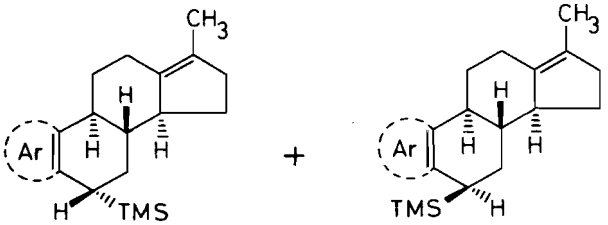
13a,b

a: Ar = phenyl

b: Ar = m-anisyl



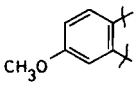
14a,b 15a,b

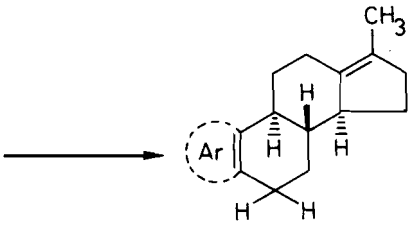


16a-c 17a-c

a: Ar = 

b: Ar = 

c: Ar = 



18a-c

however, the presence of components exhibiting a coinciding retention time. To prove 16a to be unequivocally free of β-isomer 17a, it was subjected to epimerization conditions. This involved proton abstraction by means of 2 equiv of BuLi--TMEDA for 5 h at room temperature and subsequent aqueous quenching. GLC examination of the product so obtained clearly showed emergence of a second adjacent peak indicative of production of β-isomer 17a under the equilibration circumstances. The absence of this component in the original cyclization harvest provided conclusive proof of the original product having been homogeneous 16a only. The TMS segment had elicited, in this case at least, 100% enantioselectivity during the cationic cyclization process.

The methoxy-substituted cyclization precursor 15b was prepared similarly to 15a and commenced with alkylation of m-methoxybenzyltrimethylsilane 2b with 12 and subsequent elaboration of the furan unit in the produced 13b into the enone segment found in 14b. Cyclopentenol 15b was obtained therefrom on reduction with AlH_3. Its cyclization was brought about by means of $SnCl_4$ in CH_2Cl_2 and gave rise to both the *ortho*- and *para*-methoxy-derived ring systems. These lent themselves to separation via column chromatography to provide 19% of *ortho*-cyclized material,consisting of configurationally differing α/β isomers 16-/17b in a 91:9 ratio and 34% of *para*-cyclized but epimerically homogeneous 16c. Characterization of the positional methoxy isomers was based on the NMR data, which showed identical aromatic patterns as for the corresponding bicycles 5b and 5c. Enantioselectivity data were derived from GLC analyses. The main cyclization component 16c solidified on standing and was triturated with diisopropyl ether to melt at 91-93 °C. It is considered to be fortuitous that this particular homogeneous major fraction is the one lying on the projected route to estrone.

Desilylation of the steroidal frameworks was performed with the system K-t-OBu/DMSO under conditions previously shown to be successful in desilylating bi- and tricyclic models. Compound 16a thus afforded 72% of solid 18a, identified spectrally and melting at 59-60 °C in agreement with the literature.[18d]

The 16-/17b mixture likewise gave desilylated 18b[18c] exclusively; this also applied to the desilylation of 16c to 18c,[18c] *thus forging the remaining link in a new approach to (±)-estrone and opening enticing vistas to possibilities of preparing enantiomerically pure estrone types.*

VI.5 Summary

The ability of a C-substituted trimethylsilyl fragment to serve as removable enantioselectivity inducing moiety during cyclization processes has been examined. The concept centers on the availability of benzylsilanes such as 2a,b. Prenylation converts these to 3a,b which are then cycloalkylated in CF_3COOH-containing CH_2Cl_2 to give 4a and a mixture of 4b,c respectively. Treatment with $NaNH_2/NH_3$ or K-*tert.*-OBu/DMSO brings about facile desilylation to 5a-c. Geranylation of 2a,b gives 8a,b which undergo stereospecific polycyclization with $SnCl_4$ in CH_2Cl_2. Hereby phenylsystem 8a has provided a 85:15 ratio of 9-/10a. m-Anisyl analog 8b gives mainly 9-/10c as a 77:23 mixture plus minor amounts of epimerically homogeneous *ortho* cyclized 9b. Desilylation of the cyclized systems 9-/10a,c by K-*tert.*-OBu/DMSO gives TLC pure 11a,c spectrally resembling compounds 11, 13 and 16 of Chapter IV. The reaction of benzylsilanes 2a,b with 12 (denoted as 23 in Chapter V) gives rise to 13a,b which are subsequently elaborated into 15a,b via furan transformation to cyclopentenones 14a,b and AlH_3 reduction to the cited allylic alcohols. Compound 15a is polycyclized in $SnCl_4$-containing CH_2Cl_2 at -78 °C to give 67% isolated yield of diastereomerically pure α-isomer 16a only. Anisyl system 15b gives, under these circumstances 19% of *ortho* cyclized 16-/17b in a 91:9 ratio and 34% of epimerically homogeneous *para*-ring closed material 16c. All cyclized systems are desilylated in the system K-*tert.*-OBu/DMSO to give 18a-c. This route to 18c is especially important in that it constitutes a new synthesis to d,l-estrone. Its prime importance lies in the fact that it opens new ways for large-scale preparation of enantiomerically pure steroids.[23]

VI.6 Experimental Section

Nuclear resonance spectra (NMR) were recorded on a Varian EM 360A spectrometer. Tetramethylsilane was used as external standard for those compounds containing a trimethylsilyl group; for other compounds tetramethylsilane was used as internal standard. Melting points (recorded on a Fisher--Johns block) and boiling points are uncorrected. GLC data were obtained on a carbowax column (fused silica; CP Wax 51) of 25 m and 0.23 mm diameter at 220-235 ^{o}C.

► *Phenyltrimethylsilyl methane (2a).*

The benzyl Grignard reagent was prepared according to directions of Benkeser:[8] An apparatus containing 39 g (1.6 mol) of nitrogen-covered magnesium was thoroughly flame-dried. To it was then added 90 mL of dry ether and a solution of 50.6 g (0.4 mol) of benzyl chloride in 135 mL of dry ether was dropped to it, maintaining a gentle reflux. The mixture was stirred for an additional hour, whereupon 43.4 g (0.4 mol) of freshly distilled chlorotrimethylsilane was added. The mixture was stirred overnight and was then poured onto 200 mL of ice-water. It was then filtered through Hy-Flow (Celite 545) and the organic phase was washed with water, diluted hydrogen chloride solution (0.1N), bicarbonate solution and again with water until neutral. Drying of the organic layer on magnesium sulfate and evaporation of the ether left 61.4 g of crude product which was fractionated to give 54 g (83%) of 2a; bp 88-90 ^{o}C/18 mm. ^{1}H NMR δ (CCl_4): 0.00 (s,9,$Si(CH_3)_3$), 2.03 (s,2,CH_2), 6.70--7.33 (m,5,ArH).

► *3-Methoxy-trimethylsilyl methane (2b).*

In analogy to 2a; yield 77%; bp 92-93 ^{o}C/9 mm. ^{1}H NMR δ (CCl_4): 0.00 (s,9,$Si(CH_3)_3$), 1.95 (s,2,CH_2), 3.62 (s,3,OCH_3), 6.23-7.10 (m,4,ArH).

The preparation procedure leading to compounds 3b, 8a,b and 13a,b (Table I) is given in detail for 3a.

► *1-Phenyl-1-trimethylsilyl-4-methyl-pent-3-ene (3a).*

To a freshly prepared solution of 0.2 mol of n-butyllithium in ether[22] was quickly added at 0-10 °C 23.2 g (0.2 mol) of N,N,N',N'-tetramethylethylene diamine (TMEDA). After stirring for half an hour at 0 °C, 16.4 g (0.1 mol) of 2a was added and the anion was allowed to form on stirring for 5 h at ambient temperature. On dropping 16.4 g (0.11 mol) of 90% pure prenyl bromide to the yellow reaction mixture a highly exothermic reaction occurred. The mixture was stirred for an additional 18 h, whereupon it was poured onto water. Separation of the organic layer and washing with respectively water, diluted hydrogen chloride solution (0.1N), sodium bicarbonate solution and water gave after drying over $MgSO_4$ and solvent evaporation 27.0 g of crude product. The low boiling, foaming components were thoroughly removed on distilling from 60-100 °C at 35 mm. The residue, 14.0 g, was then fractionated at 3.5 mm giving 10.7 g (46%) of product boiling at 103-105 °C. ^{1}H NMR δ (CCl_4): 0.00 (s,9,$Si(CH_3)_3$), 1.64 (s,6,2 CH_3), 1.83-2.33 (m,2,CH_2), 2.47 (t,1,CH), 4.99 (t,1,olefinic H), 6.78-7.33 (m,5,ArH).

► *(E)-1-Trimethylsilyl-6[-2(3-methyl-2-cyclopenten-1-onyl)]--hex-3-ene (14a).*

A mixture of 5 g (0.0153 mol) of 13a in 150 mL of ethanol and 75 mL of 0.5 N of aqueous hydrogen chloride was refluxed for 24 h. The solution was then rendered alkaline by addition of 4.0 mL of 50% (w/w) aqueous sodium hydroxide solution and refluxed for another 2 h. The solvent was then partly evaporated. To the residue was added water and ether and the organic layer was washed with brine until neutral. Drying over magnesium sulfate and expelling of the ether left 5 g of crude material. Filtering through 25 g of silica, using hexane-10% acetone as eluent gave 4.35 g (87%) of TLC and NMR pure material. (R_f in hexane-10% acetone = 0.32). ^{1}H NMR δ (CCl_4): 0.00 (s,9,$Si(CH_3)_3$), 1.15-2.90 (m,9,aliphatic H), 2.26 (s,3,CH_3), 5.02-5.58 (m,2, olefinic H), 5.55-5.80 (m,2,FuH), 6.67-7.36 (m,5,ArH).

► *(E)-1-(3-Methoxyphenyl)-1-trimethylsilyl-6-[2-(3-methyl--2-cyclopenten-1-onyl)]-hex-3-ene (14b).*

Analogous to 14a; yield 86%; R_f in hexane-10% acetone = 0.26. ^{1}H NMR δ (CCl_4): 0.04 (s,9,$Si(CH_3)_3$), 1.68-2.71 (m,11,aliphatic H), 1.93 (s,3,CH_3), 3.71 (s,3,OCH_3), 4.83-5.72 (m,2,olefinic H), 6.34-7.26 (m,4,ArH).

► *(E)-1-Phenyl-1-trimethylsilyl-6-[2-(3-methyl-2-cyclopenten--1-olyl)]-hex-3-ene (15a).*

To a slurry of 0.27 g of LAH (0.007 mol) in 10 mL of dry ether was carefully added, at 0 °C, 0.30 g (0.0022 mol) of powdered $AlCl_3$. The mixture was stirred for 1 h at room temperature and was then dropped at -5 °C to a solution of 2.94 g of 14a (0.009 mol) in 18 mL of dry ether. After stirring for 45 min at -5 °C, 0.9 mL of 5N sodium hydroxide solution was added, the mixture was filtered and evaporated at aspirator pressure below 40 °C, to give the allylic alcohol 15a quantitatively and NMR pure. ^{1}H NMR δ (CCl_4): 0.00 (s,9,$Si(CH_3)_3$), 1.17-2.79 (m,14,aliphatic H and OH), 1.60 (s br,3,CH_3), 4.23-4.75(br,1, OCH), 5.07-5.50 (m,2,olefinic H), 6.72-7.37 (m,5,ArH). IR: no C=O. The crude material was immediately subjected to cyclization experiments.

► *(E)-1-(3-Methoxyphenyl)-1-trimethylsilyl-6-[2-(3-methyl--2-cyclopenten-1-olyl)]-hex-3-ene (15b).*

Analogous to 15a, quantitatively, NMR pure. ^{1}H NMR δ (CCl_4): -0.04 (s,9,$Si(CH_3)_3$), 0.66-2.76 (m,12,aliphatic H and OH), 1.53 (s,3,CH_3), 3.73 (s,3,OCH_3), 4.10-4.67 (m,1,OCH), 4.83--5.60 (m,2,olefinic H), 6.20-7.30 (m,4,ArH). IR: no C=O.

► *1-Trimethylsilyl-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene (4a).*

To 11.5 g (0.05 mol) of 3a in 25 mL of methylene chloride was dropped, at room temperature, 37 g (0.325 mol) of trifluoro acetic acid in 75 mL of methylene chloride. After stirring for half an hour at ambient temperature, the mixture was poured onto water. The organic layer was washed with a saturated sodium bicarbonate solution and water until neutral, dried

over magnesium sulfate and evaporated to yield 11.5 g of crude material. Fractionation gave 9.2 g (80%) of pure product boiling at 96-99 °C/2.1 mm. ^{1}H NMR δ (CCl_4): 0.00 (s,9,$Si(CH_3)_3$), 1.13-2.18 (m,4,2 CH_2), 1.18 and 1.27 (2 s,6,2 CH_3), 2.30 (t,1, CHSi), 6.62-7.31 (m,4,ArH).

► *1- and 3-Methoxy-5-trimethylsilyl-8,8-dimethyl-5,6,7,8--tetrahydronaphthalene (4b and 4c).*

Analogous to 4a; the crude mixture was chromatographed through silica using as eluent hexane-1% acetone and yielded 4b and 4c in 26 respectively 39%. R_f in hexane-1% acetone = 0.56 resp. 0.21.
4b: ^{1}H NMR δ (CCl_4): 0.14 (s,9,$Si(CH_3)_3$), 1.26-2.75 (m,5,aliphatic H), 1.46 and 1.54 (2 s,6,s CH_3), 3.84 (s,3,OCH_3), 6.39-7.14 (m; 3 *vic* H,3,ArH).
4c: ^{1}H NMR δ (CCl_4): 0.14 (s,9,$Si(CH_3)_3$), 1.10-2.66 (m,5,aliphatic H), 1.33 and 1.42 (2 s,6,2 CH_3), 3.76 (s,3,OCH_3), 6.33-7.33 (m; 2 *vic* H,3,ArH).

► *d,l-1,2,3,4,4a,9,10,10aα-Octahydro-1,1,4aβ-trimethyl-9β--trimethylsilyl-phenanthrene (9a).*

To a solution of 3.6 g (0.0125 mol) of 8a in 50 mL of methylene chloride was added, at -78 °C, 6.25 mL (0.05 mol) of freshly distilled $SnCl_4$ in 25 mL of methylene chloride. The mixture was stirred for 2 h at -78 °C whereupon 31.2 mL of 8% (w/v) NaOH in methanol was dropped in at such rate to maintain the temperature below -70 °C. The mixture was then allowed to come to room temperature and 20 mL of water was added. The organic phase was separated, dried over potassium carbonate, and evaporated. The crude material was chromatographed over silica using hexane as eluent (R_f = 0.53) and yielded 1.83 g (51%) of an 85:15 mixture of pure 9a (β-trimethylsilyl) as was gas chromatographically established. Trituration of this mixture with methanol afforded 1.05 g (29%) of solid 9a, having mp 83-84 °C. Analytical material was obtained on recrystallization from methanol and had mp 86--87 °C. ^{1}H NMR δ (CCl_4): 0.00 (s,9,$Si(CH_3)_3$), 0.87, 0.95 and 1.07 (3 s,9,3 CH_3), 1.07-2.75 (m,10, aliphatic H), 6.61-7.25 (m,4,ArH).

Anal. Calcd. for $C_{20}H_{32}Si$: C, 79.92; H, 10.73. Found: C, 79.91; H, 10.93.

► *d,l-5- and 7-Methoxy-1,2,3,4,4a,9,10,10aα-octahydro-1,1,4aβ--trimethyl-9β-trimethylsilyl-phenanthrene (9b and 9c).*

Analogous to 9a. Chromatography through silica using hexane--1% acetone gave 5.2% of gas chromatographically pure 9b. Change of eluent to hexane-2% acetone afforded 26.2% of a gas chromatographically pure mixture of 9-/10c (ratio 77.5% of β-trimethylsilyl 9c and 22.5% of α-TMS-10c). Compound 9b solidified on standing, having after trituration with methanol mp 108-109 °C. Analytical material obtained from methanol had mp 108-109 °C.

Anal. Calcd. for $C_{21}H_{34}OSi$: C, 76.30; H, 10.37. Found: C, 76.41; H, 10.40.

R_f of 9b in hexane-1% acetone = 0.47; R_f of 9-/10c in hexane--1% acetone = 0.36.

9b: ^{1}H NMR δ (CCl_4): 0.25 (s,9,$Si(CH_3)_3$), 1.13, 1.21 and 1.43 (3 s,9,3 CH_3), 0.91-2.79 (m,10,aliphatic H), 3.95 (s,3,OCH_3), 6.50-7.40 (m; 3 *vic* H,3,ArH).

9c: ^{1}H NMR δ (CCl_4): 0.23 (s,9,$Si(CH_3)_3$), 0.97-2.80 (m,10,aliphatic H), 1.09, 1.19 and 1.27 (3 s,9,3 CH_3), 3.83 (s,3,OCH_3), 6.40-7.37 (m; 2 *vic* H,3,ArH).

► *d,l-6α-Trimethylsilyl-17-methyl-1,3,5(10),13(17)-gonatetraene (16a).*

To a solution of 2.95 g (0.009 mol) of crude alcohol 15a in 36 mL of methylene chloride was added dropwise, at -78 °C, a solution of 1.35 mL (0.0115 mol) of freshly distilled $SnCl_4$ in 18 mL of methylene chloride. The blood-red solution was stirred for half an hour at -78 °C whereupon 7.75 mL of 8% (w/v) NaOH in methanol was added at such rate to maintain the reactions' temperature below -70 °C. The mixture was allowed to come to room temperature and 20 mL of water were introduced. The organic phase was separated, dried over K_2CO_3, filtered and evaporated. The residue was chromatographed over silica using hexane as eluent to yield 1.86 g (67%) of gas chromatographically pure, isomer-free 16a as an oil.

R_f in hexane = 0.42. ^{1}H NMR δ (CCl_4): 0.09 (s,9,$Si(CH_3)_3$), 0.77--2.97 (m,14,aliphatic H), 1.73 (s.3.CH_3), 6.77-7.52 (m,4,ArH).

► *d,l-1- and 3-Methoxy-6α-trimethylsilyl-17-methyl-1,3,5(10),13(17)-gonatetraene (16b and 16c).*

Analogous to 16a. Chromatography through silica, using hexane as eluent, gave 18.6% of *ortho* cyclized material, consisting of a 91:9 mixture of 16-/17b as was gas chromatographically established. Change of eluent to hexane-2% acetone yielded 34.3% of gas chromatographically pure *para* cyclized 16c.
16-/17b: R_f in hexane = 0.38; in hexane-2% acetone = 0.68.
16c: R_f in hexane = 0.24; in hexane-2% acetone = 0.53.
16-/17b: ^{1}H NMR δ (CCl_4): -0.03 (s,9,$Si(CH_3)_3$), 0.52-3.23 (m,14,aliphatic H), 1.58 (s,3,CH_3), 3.70 (s,3,OCH_3), 6.22-7.13 (m,3 *vic* H,3,ArH).
16c: ^{1}H NMR δ (CCl_4): -0.03 (s,9,$Si(CH_3)_3$), 0.41-2.78 (m,14, aliphatic H), 1.48 (s,3,CH_3), 3.55 (s,3,OCH_3), 6.10-7.12 (m,2 *vic* H,3,ArH).
Compound 16c solidified on standing, having after trituration with ice cold diisopropyl ether mp 91-93 °C. Analytical material was obtained from diisopropyl ether and had mp 94-95 °C.

Anal. Calcd. for $C_{22}H_{32}OSi$: C, 77.58; H, 9.47. Found: C, 77.67; H, 9.41.

Desilylation experiments leading to compounds 5b,c, 11a,c and 18a-c (Table II) are typified by elimination of 4a.

► *1,1-Dimethyl-1,2,3,4-tetrahydronaphthalene (5a).*

To a thoroughly stirred mixture of 2.5 g (0.022 mol) of potassium-*tert*.-butoxide in 5 mL of dry DMSO was added, at room temperature 4.6 g (0.02 mol) of 4a. A slightly exothermic reaction occurred. After 15 min 50 mL of ether were added and the mixture was scrubbed with water and dried over magnesium sulfate. Evaporation of the ether left 3.55 g of crude, completely desilylated 5a, Fractionation at 17 mm afforded 2.6 g (81%) of pure product, having bp 99-101 °C; identical to material obtained via detosylation of 1-p-toluenesulfonyl--4,4-dimethyl-1,2,3,4-tetrahydronaphthalene (Chapter III).

Table I. Alkylation results of 2a,b

compd	bp, °C (mm)	yield (%)	^{1}H NMR δ (CCl_4)
3b	112-115 (0.1)	42	0.00 (s,9,Si(CH_3)$_3$), 1.63 (s,6,2 CH_3), 1.79-2.27 (m,2,CH_2), 2.44 (t,1,SiCH), 3.72 (s,3,OCH_3), 4.78-5.20 (m,1,olefinic H), 6.33-7.24 (m,4,ArH).
8a	167-169 (3.0)	62	0.00 (s,9,Si(CH_3)$_3$), 1.54 and 1.57 (2 s, 3 and 6, 3 CH_3), 1.66-2.71 (m,6,3 CH_2), 2.42 (t,1,CHSi), 4.64-5.16 (m,2,olefinic H), 6.66-7.30 (m,5,ArH).
8b	160-164 (0.03)	40	0.00 (s,9,Si(CH_3)$_3$),1.47-2.70 (m,7,aliph H), 1.57 and 1.64 (3 s,9,3 CH_3), 3.73 (s,3,OCH_3), 4.67-5.27 (m,2,olefinic H), 6.36-7.29 (m,4,ArH).
13a	142-146 (0.02)	46	0.00 (s,9,Si(CH_3)$_3$), 1.15-2.90 (m,9,aliph H), 2.26 (s,3,CH_3), 5.02-5.58 (m,2,olefinic H), 5.55-5.80 (m,2,FuH), 6.67-7.36 (m,5, ArH).
13b	158-162 (0.005)	49	0.00 (s,9,Si(CH_3)$_3$), 1.28-2.81 (m,9,aliph H), 2.29 (s,3,CH_3), 3.77 (s,3,OCH_3), 5.05--5.52 (m,2,olefinic H), 5.84-5.94 (m,2,FuH).

Table II. Desilylation results as for 3a

compd	yield (%)	mp, °C	^{1}H NMR δ (CCl_4)
5b	95	liquid[a]	1.22-1.47 (m,4,CH_2CH_2), 1.22 (s,6,2 CH_3), 2.30-2.80 (m,2,$ArCH_2$), 3.63 (s,3,OCH_3), 6.24-6.95 (m;3 *vic.* H,3,ArH).
5c	95	liquid[a]	1.10 (s,6,2 CH_3), 1.31-1.96 (m,4,CH_2CH_2), 2.32-2.76 (m,2,$ArCH_2$), 3.53 (s,3,OCH_3), 6.17-7.08 (m;2 *vic.* H,3,ArH).
11a	80	liquid[a]	0.71-2.53 (m,9,aliph H), 0.93, 0.93 and 1.18 (3 s,9,3 CH_3), 2.63-3.07 (m,2,$ArCH_2$), 6.72--7.27 (m,4,ArH).
11c	79	liquid[a]	0.74-3.07 (m,11,aliph H), 0.96, 0.96 and 1.18 (3 s,9,3 CH_3), 3.68 (s,3,OCH_3), 6.29-7.24 (m;2 *vic.* H,3,ArH).
18a	72	59-60[18d]	0.75-2.76 (m,15,aliph H), 1.68 (s,3,=CCH_3), 6.70-7.43 (m,4,ArH).
18b	70	109-110[18c]	0.73-2.90 (m,15,aliph H), 1.62 (s,3,=CCH_3), 3.70 (s,3,OCH_3), 6.45-7.12 (m;3 *vic.* H,3,ArH).
18c	73	79-80[18c]	0.71-2.95 (m,15,aliph H), 1.61 (s,3,=CCH_3), 3.66 (s,3,OCH_3), 6.38-7.26 (m;2 *vic.* H,3,ArH).

[a]98% GLC-pure compounds.

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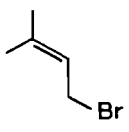
Summary

Preceeding Chapters have included sections "summary", recapitulating the essence of each of the topics discussed. This summary will endeavor to interrelate and unify all the previously reported results and surveys the authors' four years of doctoral research.

Representative examples of I-/IIIa,b are readily synthesized via base-induced alkylation of $ArCH_2Tos$ and $ArCH_2TMS$ with compounds 1-3. Types I- and IIa undergo (poly)cyclization in FSO_3H/SO_2 at -78 °C to give IV- and Va. The corresponding TMS analogs I-/IIIb are likewise converted to IVb by means of CF_3COOH in CH_2Cl_2 and to V- and VIb on using $SnCl_4$ in CH_2Cl_2. In these cyclizations the group X elicits significant enantioselectivity, giving predominately or exclusively epimers Va,b/VIb featuring X in configurations least impeded by energetically disfavoring 1,3-interactions. Of paramount importance is the polycyclization of IIIb (Ar = m-anisyl) to *para*-cyclized VIb proceeding with absolute TMS-induced enantioselectivity. Cleavage of X from IV- and Va is readily achieved by brief treatment with Dibal-H in toluene, furnishing IV- and Vc. The TMS moiety of IV-/VIb is best removed by means of K-*tert*.-OBu/DMSO to provide IV-/VIc.



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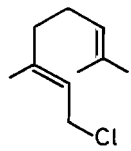

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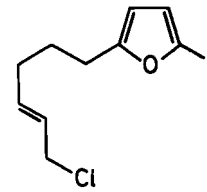

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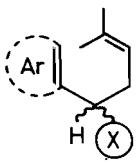
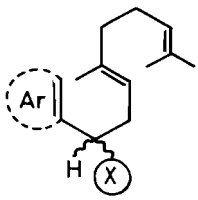
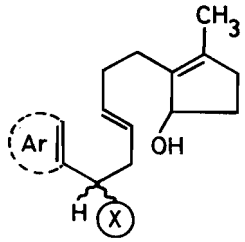


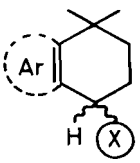
Ia,b



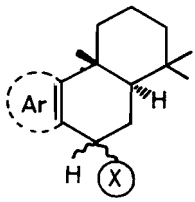
IIa,b



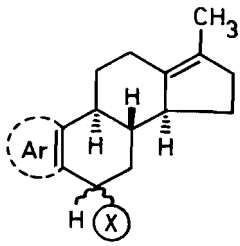
IIIa,b



IVa-c



Va-c



VIa-c

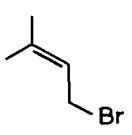
a: X = tosyl (Tos); b: X = trimethylsilyl (TMS); c: X = H

Major emphasis has been placed on the elaboration of new reactions and their application in practical organic synthesis. This has included the enantioselective polycyclization of aliphatically tosylated and trimethylsilylated substrates and subsequent Dibal-H or K-*tert*.-OBu removal of the respective controller groups. The methodologies have been optimized for yield, economics, ease of operation and industrial applicability. The new reactions have led to a new synthesis of d,l--estrone and have uncovered inviting perspectives for preparing optically active steroids.

Samenvatting

In de secties "summary" van de voorgaande hoofdstukken is de essentie van elk van de behandelde onderwerpen gerecapituleerd. In het volgende overzicht worden deze met elkaar in verband gebracht en verenigd, en wordt het promotieonderzoek van de schrijver in de afgelopen vier jaar op beknopte wijze weergegeven.

Enkele typische voorbeelden van I-/IIIa,b worden op eenvoudige wijze via base-geinduceerde alkylering van $ArCH_2Tos$ en $ArCH_2TMS$ met 1-3 gesynthetiseerd. Typen I- en IIa ondergaan (poly)cyclisatie in FSO_3H/SO_2 bij -78 °C tot IV- en Va. De soortgelijke TMS analoga I-/IIIb worden op overeenkomstige wijze tot IVb omgezet o. i. v. CF_3COOH in CH_2Cl_2 en tot V- en VIb m. b. v. $SnCl_4$ in CH_2Cl_2. In deze cyclisatie brengt de groep X aanzienlijke enantioselectiviteit teweeg waarbij hoofdzakelijk of uitsluitend epimeren Va,b/VIb gevormd worden met X in de minimaal door 1,3-interacties gestoorde configuratie. Uiterst belangrijk in dit werk is de polycyclisatie van IIIb (Ar = m-anisyl) naar *para*-gecycliseerd VIb welke met volledige TMS geïnduceerde enantioselectiviteit verloopt. Verwijdering van X uit IV- en Va is gemakkelijk te verwezenlijken middels korte behandeling met Dibal-H in tolueen en levert IV- en Vc. Het TMS fragment van IV-/VIb wordt o. i. v. K-*tert*.-OBu/DMSO



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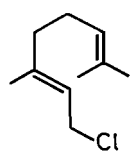

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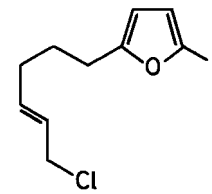

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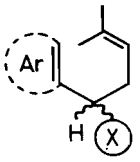
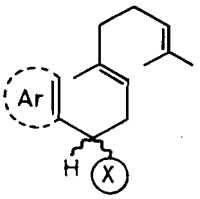
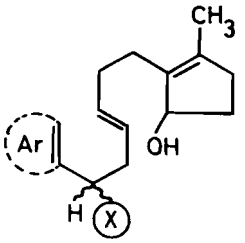


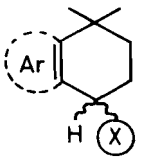
Ia,b



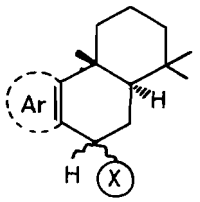
IIa,b



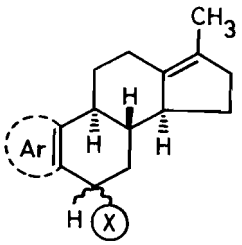
IIIa,b



IVa-c



Va-c



VIa-c

a: X = tosyl (Tos); b: X = trimethylsilyl (TMS); c: X = H

afgesplitst en verschaft dan IV-/VIc.

In dit werk is sterke nadruk gelegd op het ontwikkelen van nieuwe reacties en hun toepassingmogelijkheden in de practische organische synthese. Dit omvat o. m. de enantioselectieve polycyclisatie van alifatisch getosyleerde en getrimethylsilyleerde substraten en de daarop volgende Dibal-H of K-*tert.*-OBu geïnduceerde verwijdering van de "sturende" groepen. De methodologieën zijn geoptimaliseerd wat betreft opbrengst, economische aantrekkelijkheid, eenvoud in uitvoering en mogelijke industriële toepassingen. De nieuwe reacties hebben geleid tot een nieuwe synthese van het d,l oestron en bieden uiterst aantrekkelijke perspectieven voor het bereiden van optisch zuivere steroiden.

Curriculum vitae

De auteur van dit proefschrift werd op 9 september 1951 geboren te Schaesberg. Aan de Petrus en Paulus Mulo, aldaar, werd in 1968 het eindexamen Mulo A + B afgelegd. De studie werd voortgezet aan de HTS te Heerlen alwaar in juni 1973 het eindexamen Chemische Techniek cum laude werd behaald. In hetzelfde jaar werd de studie Scheikundige Technologie aan de Technische Hogeschool te Eindhoven begonnen. Het afstudeerwerk werd verricht bij de vakgroep Organische Chemie onder leiding van dr. E. F. Godefroi en prof. dr. H. M. Buck. In februari 1978 werd het ingenieursexamen cum laude afgelegd.

Vanaf augustus 1978 werd, onder leiding van prof. dr. E. F. Godefroi, het onderzoek zoals beschreven staat in dit proefschrift, uitgevoerd. Daarnaast werd een deel van deze tijd besteed aan het begeleiden van studenten in diverse fasen van hun studie.

Met ingang van 1 oktober 1982 is een post-doctorate aanstelling bij prof. dr. R. E. Ireland aan het California Institute of Technology te Pasadena (U.S.A.) aanvaard.

Dankwoord

Ik dank degenen die op directe of indirecte wijze hebben bijgedragen aan het totstandkomen van dit proefschrift. Enkelen wil ik met name noemen.

Prof. dr. E. F. Godefroi voor zijn enthousiasme, betrokkenheid, stimulerende inzet en voor de goede persoonlijke contacten die hierdoor gegroeid zijn.

Afstudeerders: ir. L. Simons, ir. P. van Herwijnen en A. Hendriks voor hun practische bijdragen.

Voor- en nakandidaatsstudenten voor hun prettige manier van samenwerken: P. Beaufort, H. van den Bersselaar, J. Boerekamp, S. Bouwens, M. Brekelmans, M. Dekkers, F. Dirne, P. Ernsting, P. Eijsbouts, C. Fidder, A. Gaykema, K. van Gool, J. Dela Haye, J. Hermans, R. Hermans, M. Hetum, G. Hoedemakers, H. van Houtum, R. Janssen, H. Kaskens, T. Kastelijn, G. Kastelijns, B. Klawer, P. de Kok, J. Kremers, A. Kuin, M. Kuyken, G. Mambi, J. Meesters, I. Merkelbach, P. Mertens, J. Naus, L. Paulissen, A. Peeters, P. Peeters, W. Peynenburg, J. Reinders, M. Schatorjé, P. Schoenmakers, R. Severins, W. van Son, M. Theunisse, M. Verkuylen, W. de Vet, S. Vleeshouwers, J. Vriens en P. Vollenberg.

Leden van het wetenschappelijk- en niet-wetenschappelijk personeel: G. Bezemer, P. van den Bosch, C. Bijdevier, H. Eding, J. de Haan, P. van Lier, P. Schipper en L. van de Ven.

Gaarne dank ik ook familie, vrienden en bekenden die van hun belangstelling tijdens mijn promotieonderzoek hebben blijkgegeven.

Stellingen

Het induceren van optische activiteit β- t.o.v. een aldehyde functie middels 1,4-Grignard additie aan het enantiomeer zuivere α,β onverzadigde *tert.*-leucine imine verlegt in de practijk het probleem naar de synthese van het moeilijk toegankelijke optisch zuivere *tert.*-leucine.

S-i Hashimoto, S-i Yamada and K. Koga, J. Amer. Chem. Soc., *98*, 7450 (1976).

De gepresenteerde anti-Markownikow additie van allylchloride met zuur chloriden is strijdig met de experimenteel waargenomen bevindingen.

N. N. Mushkalo and L. K. Mushkalo, Ukr. Khim. Zh., *36*, 915 (1970). (Russ.). Chem. Abstr., *74*, 53749k (1971).

"Onbekend maakt onbemind". Het veelvuldig aanwenden van HMPA als reactiemilieu doet, ten onrechte, volledige bekendheid met dit oplosmiddel vermoeden.

J. A. Zapp, Jr., Science, *190*, 422 (1975).

De uitvinding van het plakband heeft in aanzienlijke mate aan het tot stand komen van dissertaties bijgedragen.

Er wordt te weinig aandacht besteed aan het feit dat extrapolatie van de Debije-Hückel theorie ook bij toepassing van hogere ionsterkten en grotere moleculaire systemen toch relevante fysische informatie kan opleveren.

D. Solomon, P. Peretz and M. Faraggi., J. Phys. Chem., *86*, 1842 (1982).

Literatuurverwijzingen dienen als onvervangbaar hulpmiddel in het vergaren van achtergrondinformatie. Indien, evenwel, een sleutel referentie met de reeds onder ogen liggende bron blijkt overeen te komen, kan men een misplaatst gevoel voor humor vermoeden.

W. Nagata, T. Wakabayashi and Y. Hayase, Org. Synth., *53*, 44 (1973); ref. 5.

Het uitbeelden van saccharide hemiacetalen als planaire, sterk vertekende rechthoeken vertegenwoordigt het vasthouden aan de 19^{e} eeuwse voorstellingswijze, doet voor oningewijden de invoering van 2 extra koolstofatomen vermoeden, en hoort niet meer thuis in de moderne organisch-chemische studieboeken.

Het algemeen gangbare, maar foutieve, gebruik van de term "to optimize" in plaats van het linguistisch correcte "to optimalize" verleent een blijmoedig tintje aan de Engelstalige vakliteratuur.

Het aanbrengen van "randjes vet" aan de slijpstukken van micro glaswerk geeft, bij tijde, een te optimistische interpretatie van de rendementen van hierin uitgevoerde processen.

Cornelus G. M. Janssen

Eindhoven, 21 september 1982