cyclopentadienone epoxides

synthesis and properties

Adrie A. M. Houwen-Claassen

CYCLOPENTADIENONE EPOXIDES
SYNTHESIS AND PROPERTIES

ISBN 90-9003252-5

CYCLOPENTADIENONE EPOXIDES
SYNTHESIS AND PROPERTIES

EEN WETENSCHAPPELIJKE PROEVE OP HET GEBIED VAN DE NATUURWETENSCHAPPEN, IN HET BIJZONDER DE CHEMIE

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE KATHOLIEKE UNIVERSITEIT TE NIJMEGEN,
VOLGENS BESLUIT VAN HET COLLEGE VAN DECANEN
IN HET OPENBAAR TE VERDEDIGEN OP
DONDERDAG 1 FEBRUARI 1990, DES NAMIDDAGS TE 3.30 UUR

DOOR

ADRIANA ARNOLDA MARIA HOUWEN-CLAASSEN
GEBOREN TE HAPERT

NIJMEGEN
1990

Promotor: Prof. Dr. B. Zwanenburg
Co-promotor: Dr. A. J. H. Klunder

DANKWOORD

Het onderzoek, dat in dit proefschrift beschreven staat, was geen individuele aangelegenheid. Velen waren erbij betrokken en hebben door:

morele support (Bertus Thijs, en ook Ietje Dorhout)

stimulerende discussies (medepromovendi)

daadwerkelijke bijdragen (studenten, stagiaires, en ook de analyse-, massa- en nmr-specialisten: Peter van Gaal, Peter Weyers en Ad Swolfs)

een helpende technische hand (Wim van Luyn (ook bij tekenwerk voor dit proefschrift), Pieter van de Meer, Ruud Zwijnen)

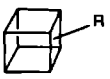
de voortgang en afronding van het onderzoek bevorderd, dan wel mogelijk gemaakt. Hen allen wil ik voor hun bijdragen van harte bedanken.

Een speciaal woord van dank wil ik richten tot mijn promotor en copromotor. Het deeltijd-experiment had kunnen mislukken. Ik ben hen erkentelijk voor het in mij gestelde vertrouwen. De vrijheid, die mij in het onderzoek gelaten werd, heb ik zeer gewaardeerd.

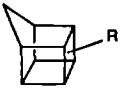
CONTENTS

Background and aim of research

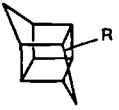
In the past three decades much effort has been devoted to the synthesis and study of strained cage compounds. Such a study is of general interest for synthetic and physical organic chemistry, because it provides valuable information on chemical reactivity. In the Department of Organic Chemistry of the University of Nijmegen there is a continuing programme on the chemistry of strained compounds with the particular objective to study the relationship between cage strain and chemical behaviour of bridgehead substituted cubanes **1**, homocubanes **2**, bis-homocubanes **3** and basketanes **4**. Results in this area have recently been reviewed[1,2].



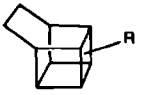
1



2



3



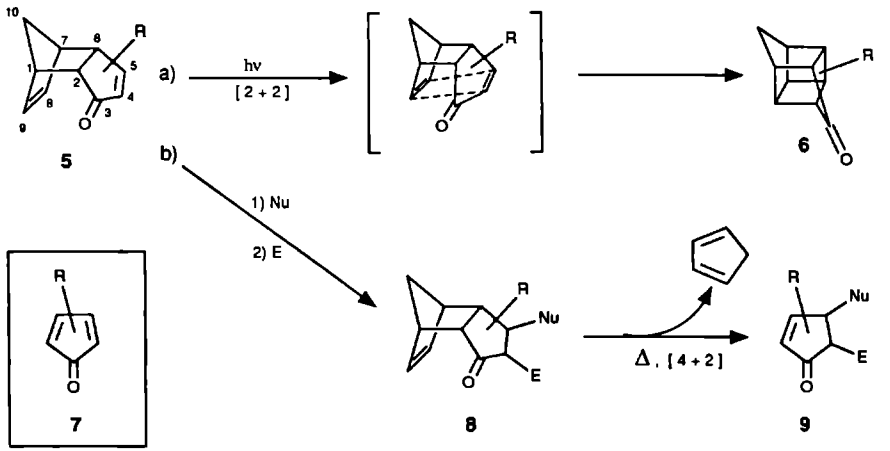
4

The various cage compounds **1-4** used in this study, are generally prepared from appropriately functionalized *endo*-tricyclodecadienones **5**. Photo-induced [2 + 2] cycloaddition reactions of these tricyclic compounds **5** readily produce bis-homocubanones **6** (Scheme 1, path a), which can be transformed into **1-4** by cage contraction and expansion reactions and appropriate functional group transformations.

It is of interest that the structures **5**, which fulfil a key role in the synthesis of strained cage compounds, can also be considered as synthetic equivalents of cyclopentadienones. In essence, these compounds **5** are Diels-Alder adducts of cyclopentadiene and cyclopentadienones **7** and as such they in fact mask one of the enone parts of **7**. Reaction of the free enone moiety in these adducts, by conjugate addition of a nucleophile followed by a reaction with an electrophile produces compounds of type **8**, which can undergo a thermal [4 + 2] cycloreversion to form cyclopentenones **9** (Scheme 1, path b). Hence, the products **9** can formally be considered as being obtained from cyclopentadienone by a reaction with only one enone part of this molecule.

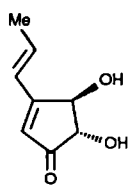
Synthetic procedures that give access to a wide variety of functionalized cyclopentenones are of particular interest because many biologically active compounds are in fact cyclopentenoids[3-6]. The synthesis of cyclopentenones **9** from tricyclodecadienones **5** proceeds in a stereocontrolled

Scheme 1

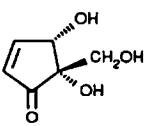


fashion, which makes this synthetic sequence even more valuable. The rigid, tricyclic structure of **5** prevents approach of the enone moiety by the reagent from the crowded *endo*-side, where the C-4, C-5 enone double bond is shielded by the C-8, C-9 double bond. Reactants will therefore preferentially enter from the least hindered *exo*-face[7-9], syn to the C-10 methylene bridge. As a consequence, the stereochemistry of the newly introduced groups in compounds **8** will usually be well defined. The stereochemical relationship present in the cyclopentenone part of **8** is retained during the thermal cycloreversion reaction, which is a synchronous stereospecific process.

The relevance of this strategy for the stereoselective synthesis of cyclopentenoids, given by route b (Scheme 1), was demonstrated by the total syntheses of the naturally occurring cyclopentenones, terrein **10** and pentenomycin **11**, carried out by Bos[10] and Verlaak[11], respectively. The scope of the method could even be extended to enantiospecific syntheses using optically pure tricyclodecadienones **5**[12] as the starting substrates.



10

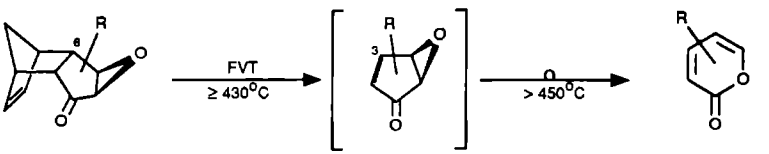


11

In all these syntheses the thermal cycloreversion of **5** was performed in the gas phase, using Flash Vacuum Thermolysis (FVT) conditions. This thermolytic procedure involves sublimation or distillation of the substrate *in vacuo* through an oven heated quartz tube, which is connected with a cold trap. Typical conditions are a pressure of *ca.* 10^{-2} - 10^{-1} mbar, an oven temperature of *ca.* 500°C and a tube length and diameter of *ca.* 20 x 1.5 cm. Vacuum and tube dimensions guarantee a short contact time in the hot zone. The low pressure implies a low concentration of substrate and products, which virtually excludes intermolecular reactions in the hot zone. The cold trap, immediately behind the oven, prevents the occurrence of further reactions of the products. The method is particularly suited for the generation of highly reactive species. Synthetic merits and technical aspects of the procedure are given in several reviews[13-16]. A detailed description of the equipment, used in this study, is presented in ref. 9.

A drawback of the FVT technique may be, at least in some cases, the relatively high temperatures, that are required to accomplish the desired fragmentations. For thermo-labile products, for example, this can cause problems if undesired thermal reactions already occur before the product leaves the hot zone. The result may then be a substantial loss in yield. Such complications were encountered, when some tricyclodecadienone epoxides **12**, as part of the syntheses of terrein and pentenomycin, were subjected to Flash Vacuum Thermolysis. The temperatures needed for the thermolysis of these epoxides appeared[9] to vary between 430°-500°C. Above 450°C, however, the desired cyclopentadienone epoxides **13**, which were formed as the initial products, rapidly rearranged to 2-pyrones **14** (Scheme 2). Only those tricyclodecadienone epoxides **12** with an

Scheme 2



12 **13** **14**

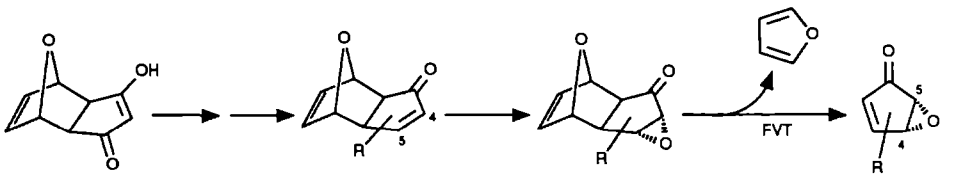
unsaturated substituent at C-6, *i.e.* **12** (R=6-CHO; R=6-COOEt; R=6-CH=CHCH$_3$), could efficiently be thermolysed at such a low temperature (*ca.* 430°C) that the corresponding 3-substituted cyclopentadienone epoxides **13** (R=3-CHO; R=3-COOEt; R=3-CH=CHCH$_3$) were practically obtained without pyrone contamination[10,17].

These results clearly show that the synthetic strategy for the preparation of cyclopentadienone epoxides **13**, using tricyclodecadienone epoxides **12** as synthetic equivalent of cyclopentadienone, need improvement, particularly to extend its scope. To this end the synthetic concept shown in Scheme 1, path b, was modified by taking the furan derived 10-oxatricyclodecadienone **16** as synthetic equivalents for cyclopentadienone. It may be expected that epoxides **17** will

undergo cycloreversion considerably more easy than the carbon analogues **12** because the eliminated furan has an aromatic character. Support for this supposition is the observation reported by Oda *et al*[18] that compound **17** (R=H) can efficiently be thermolysed under reduced pressure (300 mm Hg) at 120-140°C affording the parent cyclopentadienone epoxide **13** (R=H) in nearly quantitative yield. The polycyclic epoxide **17** (R=H), needed for this synthesis, can readily be obtained from the Diels-Alder adduct **15** of furan and cyclopentene-1,4-dione.

This Diels-Alder adduct **15** is an attractive substrate for the preparation of variety of differently functionalized 10-oxatricyclodecadienones **16**, provided that substituents can conveniently be introduced. Epoxidation of these tricyclic enones **16** can lead to various 10-oxatricyclodecadienone epoxides **17**, which on Flash Vacuum Thermolysis hopefully give access to the desired cyclopentadienone epoxides **13** under more favourable thermal conditions than the 10-carbon analogues **12** (Scheme 3). Encouraged by the result of Oda *et al*, it was decided to explore the use of

Scheme 3



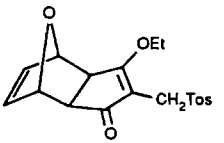
15 **16** **17** **13**

15 for the synthesis of cyclopentadienone epoxides. The results of the efforts to develop a general synthesis of functionalized cyclopentadienone epoxides as well as a subsequent study of the chemical behaviour of these compounds are presented in this thesis.

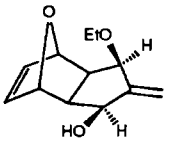
Outline of this thesis

In *Chapter 1* the preparation of several 4- and 5-substituted 10-oxatricyclodecadienones **16**, starting from adduct **15** is described. A key role in these syntheses is played by sulphone **18**. The combination of a β-alkoxy enone moiety and an allylic sulphonyl group gives this compound **18** some special properties. In this chapter particular attention is given to the nucleophilic displacement of the tosyl group. It will be shown that this group can readily be replaced by an ether or a thioether function. The mechanism of this displacement is discussed in detail.

In *Chapter 2* the conversion of the various 10-oxatricyclodecadienones **16** into 4- and 5-substituted cyclopentadienone epoxides **13** is described and the thermal stability of these epoxides is discussed.



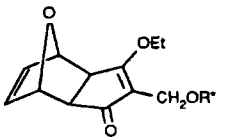
18



19

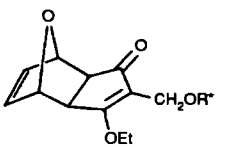
In *Chapter 3* an interesting spin-off, connected with the special reactivity of sulphone **18**, is presented. On treatment with LAH, **18** is converted into the exo-cyclic methylene compound **19**. The mechanism and the scope of this reduction have been investigated. Its application for the synthesis of exo-methylene cyclopentenoids has been explored.

In *Chapter 4* it is demonstrated that the synthetic strategy presented in Scheme 3 can also be employed for the synthesis of optically pure products. Displacement of the tosyl group in sulphone **18** by the chiral (-)menthoxy group leads to a diastereomeric mixture of the (-)menthyl ethers **20a** and **20b**, which can be separated by crystallization. The conversion of **20a** and **20b** into optically



20a

R^* = (-) menthyl

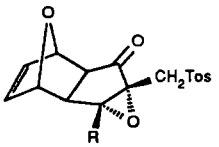


20b

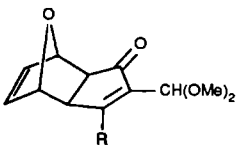
pure **16** (R=4-CH_2OMe) and the synthesis of optically pure **13** (R=5-CH_2OMe) therefrom is described. The absolute configurations of the intermediates (-)**16** (R=4-CH_2OMe) and (-)**17** (R=4-CH_2OMe) have been determined by X-Ray diffraction analysis. By correlation, the absolute structures of starting material and other intermediates in the synthesis of optically pure (+)**13** (R=5-CH_2OMe) and (-)**13** (R=5-CH_2OMe) as well as those of the products (+)**13** (R=5-CH_2OMe) and (-)**13** (R=5-CH_2OMe) have been deduced.

Chapter 5 surveys the results of a study of the chemical behaviour of cyclopentadienone epoxides **13**. Nucleophilic transformations, *viz.* hydrolyses, methanolyses and epoxidation reactions, using acid, neutral or alkaline conditions are investigated. It will be shown that depending on reaction conditions and substitution pattern a highly selective reaction can be accomplished with either the epoxide function or the enone moiety. The regio- and stereochemistry of these reactions is analysed and mechanistic aspects are discussed.

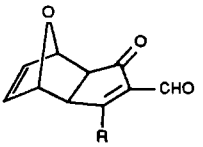
Chapter 6 deals with the cleavage of the epoxide ring in the sulphonylmethyl substituted tricyclodecadienone epoxides **21**. Upon treatment with sodium methanolate in methanol these epoxides are smoothly converted into the dimethyl ketals **22**. The essential role of the tosyl group in this transformation is elucidated. The hydrolysis of **22** leading to the aldehydes **23** is also described.



21



22



23

Part of the work presented in this thesis has already appeared in preliminary form[19,20]. The contents of the *Chapters 1-3* were recently published in *Tetrahedron*[21-23]. The contents of *Chapters 4-6* have been submitted for publication.

References

1. Klunder, A. J. H.; Zwanenburg, B. *Chem. Rev.* **1989**, *89*, 1035.
2. Zwanenburg, B.; Klunder, A. J. H. *Strain and Its Implications in Organic Chemistry*, de Meyere, A.; Blechert, S. Eds.; Kluwer Academic, **1989**, 405.
3. Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic, New York, **1977**.
4. Roberts, S. M.; Scheinmann, F. *New Synthetic Routes to Prostaglandins and Thromboxanes*; Academic, New York, **1982**.
5. Paquette, L. A. *Recent Synthetic Developments in Polyquinane Chemistry*; Topics in Current Chemistry 119; Springer, Berlin, **1984**.
6. Smith III, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855.
7. Bugel, J. P.; Ducos, P.; Gringore, O.; Rouessac, F. *Bul. Soc. Chim. Fr.* **1972**, 4371.
8. Chapman O. L.; Hess, T. C. *J. Org. Chem.* **1979**, *44*, 962.
9. Verlaak, J. M. J. *Ph.D. Thesis*, University of Nijmegen, The Netherlands, Febr. **1983**.
10. Klunder, A. J. H.; Bos, W.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4557.
11. Verlaak, J. M. J.; Klunder, A. J. H.; Zwanenburg, B. *Ibid.* **1982**, *23*, 5463.
12. Klunder, A. J. H.; Bos, W.; Verlaak J. M. J.; Zwanenburg, B. *Ibid.* **1981**, *22*, 4553.
13. Brown, R. F. C. *Pyrolytic Methods in Organic Chemistry*; Organic Chemistry Monographs, Vol. 41; Academic, New York, **1980**.
14. Wiersum, U. E. in *Aldrichimica Acta*, Vol. 17, No.2, **1984**.
15. Lasne, M. C.; Ripoll, J. L. *Synthesis*, **1985**, 121.
16. Ichihara, A. *Synthesis*, **1987**, 207.
17. Klunder, A. J. H.; Huizinga, W. B.; Sessink, P. J. M.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 357.

18. Oda, M.; Kawanishi, S. *Jap. Patent* 53-127495, **1978**; *Chem. Abstr.* 90, P137666z.
19. Klunder, A. J. H.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 1329;
20. Klunder, A. J. H.; Crul, M. J. F. M.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *Ibid.* **1987**, *28*, 3147.
21. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Kooy, M. G.; Steffann, J.; Zwanenburg, B. *Tetrahedron*, **1989**, *45*, 7109.
22. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Zwanenburg, B. *Ibid.*, **1989**, *45*, 7134.
23. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Zwanenburg, B. *Ibid.*, **1989**, *45*, 7149.

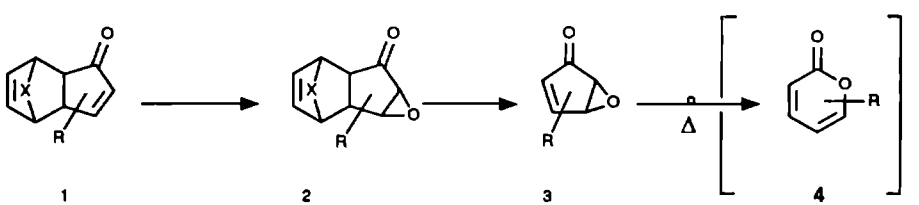
CHAPTER 1: SYNTHESIS OF 4- AND 5-SUBSTITUTED 10-OXATRICYCLO[5.2.1.$0^{2,6}$]-DECADIENONES. FUNCTIONALIZATION OF THE CYCLO-ADDUCT OF FURAN AND CYCLOPENTEN-1,4-DIONE[1].

1.1 Introduction

Functionalized cyclopentenones constitute important structures, both as synthetic intermediates and as ultimate goals in natural product synthesis[2]. A conceivable entry to this class of compounds from cyclopentadienones is blocked, because of the fast dimerization of these substrates[3]. In search of alternative approaches, we found that tricyclodecadienones **1** (X=CH_2,O) are appropriate precursors for the synthesis of a wide variety of cyclopentenones. These tricyclic enones can be considered as cyclopentadiene or furan derived Diels Alder adducts of cyclopentadienone and accordingly they in fact mask one of the double bonds of the cyclopentadienone unit. The remaining enone can therefore be subjected to selective transformations and the protected double bond can subsequently be regenerated by a thermal cycloreversion reaction to produce the desired functionalized cyclopentenones. The rigid 3-dimensional structure of these tricyclic synthetic equivalents of cyclopentadienones influences the stereochemical course of functionalizations as well as any further transformations and as a consequence these structures can be applied for stereocontrolled syntheses of a variety of cyclopentenoids[4,5].

Recently, we reported on the synthesis of various functionalized cyclopentenones, both racemic and optically active, using the synthetic strategy outlined above, in which the retro-Diels

Scheme 1

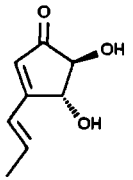


1 2 3 4

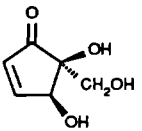
Alder reaction was carried out employing flash vacuum thermolysis[5,6]. It was then shown that cyclopentadienone epoxides **3**, synthesized according to the sequence given in Scheme 1, are key

intermediates in the approach to highly oxygenated cyclopentenoids.

During our study[6a,b] of the synthesis of terrein **5** and pentenomycin **6**, we found that the thermal cleavage of polycyclic epoxides **2**, derived from cyclopentadiene adducts **1** (X=CH_2), often requires such a high temperature that, under the conditions of the thermolysis, the initially formed cyclopentadienone epoxides **3** readily rearrange to α-pyrones **4**, via a [π4a + π2a] cycloreversion reaction[5a]. Notwithstanding the short reaction times, a substantial amount, if not all, of the cyclopentadienone epoxides was lost due to this rearrangement reaction.



5



6

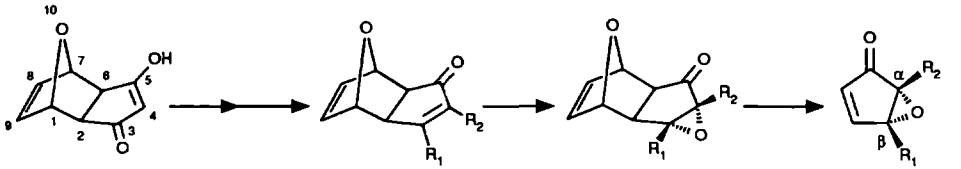
Similar results were obtained by Chapman and Hess[4c] when they tried to prepare the parent cyclopentadienone epoxide **3** (R=H) by flash vacuum thermolysis of the unsubstituted polycyclic epoxide **2** (X=CH_2; R=H) at 440°.

In order to make the synthesis of functionalized cyclopentadienone epoxides using the above strategy generally applicable, polycyclic precursors **2** are needed, that undergo the required cycloreversion at a temperature at which the rearrangement to α-pyrones does not take place. Epoxides **2**, that give an aromatic compound as one of the products in the retro Diels Alder reaction seem appropriate for this purpose. Indeed, Chapman and Hess[4c] eventually obtained their target compound **3** (R=H) from a precursor **2** with X is C(COOMe)=C(COOMe) and R=H, which eliminates dimethyl phthalate by flash vacuum thermolysis at 180°C, while Oda et al[7a] prepared the same cyclopentadienone epoxide **3** (R=H) from the furan derived tricyclic epoxide **2** (X=O; R=H) via sublimation under reduced pressure (300 mm Hg) at 120-140°C.

The polycyclic epoxide **2** (X=O; R=H) is readily available[7] from the Diels-Alder adduct of furan and cyclopentene-1,4-dione, **7**. The prospects of this adduct **7** for the preparation of functionalized cyclopentadienone epoxides prompted us to study Oda's synthesis[7a] of the parent cyclopentadienone epoxide, using flash vacuum thermolysis conditions. At a pressure of 10^{-3} torr no conversion was found below 250°C. At 375°C all of the starting material **2** (X=O; R=H) had reacted to give the cyclopentadienone epoxide **3** (R=H), without any formation of the corresponding pyrone **4** (R=H). A further increase of the temperature however, led to appreciable amounts of the α-pyrone.

This encouraging result initiated our investigation on the further exploration of the oxa-bridged polycyclic system **1** (X=O) as synthetic equivalent of cyclopentadienone. The objective of this study is to develop a general synthetic route to α- and/or β-substituted cyclopentadienone epoxides, based on the cycloadduct **7**, as outlined in Scheme 2.

Scheme 2



7 8 9 10

In this chapter we report on the functionalization of this adduct at C-4 and C-5, to form 4- and 5-substituted tricyclic enones **8**. The ultimate conversion to cyclopentenoids such as epoxides **10**, via the polycyclic epoxides **9**, will be the subject of the next chapter.

1.2 The furan adduct of cyclopenten-1,4-dione.

Furan is a poor Diels-Alder diene due to its aromatic character[8a,b]. Under normal pressure it forms only cycloadducts with very reactive dienophiles such as maleic anhydride and dimethyl acetylenedicarboxylate[8a,c]. As cyclopentene-1,4-dione is four times less dienophilic than maleic anhydride[8d], the Diels-Alder reaction with furan proceeds rather slow. The preparation of **7** on gram scale, by stirring cyclopenten-1,4-dione at room temperature in excess of furan, required 1-2 weeks. To speed up the reaction, heating at reflux, as described by Oda et al[7b], was considered but eventually rejected as the purity of the crude product obtained from the reaction at room temperature was higher and no further purification was needed.

The *exo*-enol structure of **7** has been deduced from spectral data[7a,b]. The enol structure follows from the absence of any ^{1}H-NMR signal between δ 3.0 and δ 4.4 ppm, as expected for the α-protons of the β-diketo form[9]. The absence of a significant absorption at ~1750 cm^{-1} in the IR spectrum confirms that in the solid phase the adduct is also completely enolic[10]. The broad weak bands between 2900 and 1700 cm^{-1} indicate that the enolic proton, involved in H-bonding, is only loosely bound[10], which is also suggested by its downfield position at δ 8.82 ppm in the ^{1}H-NMR spectrum. The *exo*-configuration of **7**, which is suggested by the absence of an observable spin coupling between the juncture and bridgehead protons[7a,b], was unambiguously proven by an X-Ray analysis of a derivative (*vide infra*).

Presumably due to the isomerization of the initially formed diketo-adduct to the more stable enol tautomer **7**, the furan adduct of cyclopenten-1,4-dione does not display the usual cycloreversion[8a]. Direct cycloreversion from **7** will be unfavourable since this would lead to a highly energetic hydroxy-cyclopentadienone. The fact that only the *exo*-isomer is found suggests that the cyclorever-

sion of the *endo*-diketo adduct (if formed at all, which as yet not can be excluded[8e,f] but might be questioned as it has never been observed) must be much faster than the isomerization to the corresponding *endo*-enol tautomer.

1.3 Functionalization at C-4

Synthesis of Sulphone **13**.

The active centre at C-4 in adduct **7** can be exploited for the introduction of a substituent. With the objective to synthesize eventually *epi*-pentenomycins, we were in particular interested in the introduction of a hydroxymethyl group. However, a direct condensation of **7** with formaldehyde following a standard hydroxymethylation procedure[11] failed. Therefore, an indirect strategy was explored by which a sulphonylmethyl group was introduced by an acid catalyzed condensation with formaldehyde and *p*-toluenesulphinic acid (Scheme 3). The tosyl group of the resulting 4-tolyl-

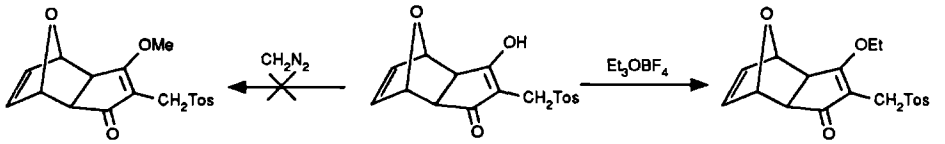
Scheme 3

7 **13**

sulphonylmethyl derivative **13** was intended to be displaced later by a desired substituent. The synthesis of **13** was based on a method, described by Hellmann and Müller[12a]. After careful experimentation[12b], optimum conditions (glacial acetic acid, DMF, 0°C → rt) were established, yielding **13** in ca 85%.

Sulphone **13** is poorly soluble in most of the common solvents, therefore, conversion into a convenient derivative was appropriate. In view of the ultimate transformations, such a displacement of the tosyl group and reductive removal of one of the carbonyl groups (*vide infra*), the synthesis of an enol ether of **13** was attempted. Treatment with an excess of diazomethane[4a] failed to give any methylation, due to insolubility of the substrate. However, O-alkylation with Meerwein's salt[4b,13] was successful and led to the O-ethylated sulphone **14** in 90% yield (Scheme 4). As will be demonstrated, this sulphone **14** is a versatile synthon from which a wide range of interesting products can be obtained.

Scheme 4



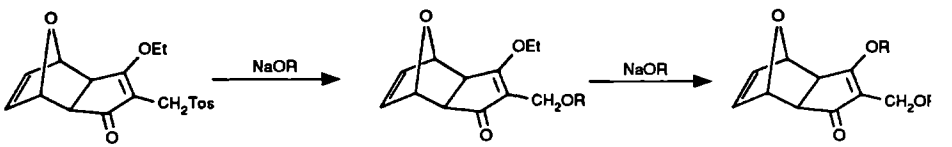
13 **14**

Displacement of the tosyl group by an ether or thioether function.

The displacement of the tosyl group of **14** by an ether function could easily be accomplished by treating this sulphone with sodium- or potassium alcoholates (Scheme 5).

Refluxing **14** with *ca* 1.5 eq of sodium ethanolate in ethanol for 10 min led to the 4-ethoxymethyl derivative **16** in 71% yield. Similarly, treatment of sulphone **14** with sodium methanolate in methanol resulted initially in the formation of **15** (87%). However, when longer reaction times were applied the bis-methoxy derivative **20** gradually appeared in the reaction mixture. Compound **20** was the only product, albeit in a much lower yield (ca 56%), when an excess of sodium methanolate was used and refluxing was continued overnight. With secondary alcoholates similar results were obtained. The reaction with sodium 2-propanolate in refluxing 2-propanol afforded **17** as the primary product (94%). When the reaction time and the amount of reagent were increased, **21** was obtained

Scheme 5



14

15 R=Me
16 R=Et
17 R=iPr
18 R=(-)menthyl
(**19** R=tBu)

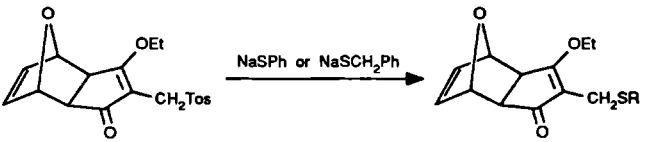
20 R=R'=Me
21 R=R'=iPr

as the sole product, however in a very poor yield of only 14%. With sodium (-)menthoxide sulphone **14** was smoothly converted into the (-)menthoxymethyl derivative **18** (88%). The last mentioned synthesis, which has been exploited for the preparation of optically active products, required somewhat modified reaction conditions. These will be described in detail in a separate publication[14]. The

reaction of sulphone **14** with potassium *tert*-butoxide in refluxing *tert*-butylalcohol (20 min), led to a mixture of the *tert*-butyl derivative **19** and a small amount of starting material (^{1}H-NMR data). On attempts to isolate **19** by preparative TLC considerable decomposition took place. No further efforts to obtain this sensitive compound were made.

Thiolates, derived from thiophenol and benzylthiol, also smoothly reacted with sulphone **14** to give the corresponding thioethers **22** and **23** respectively, in 43% and 74% yield (Scheme 6).

Scheme 6



22 R=Ph
23 R=CH_2Ph

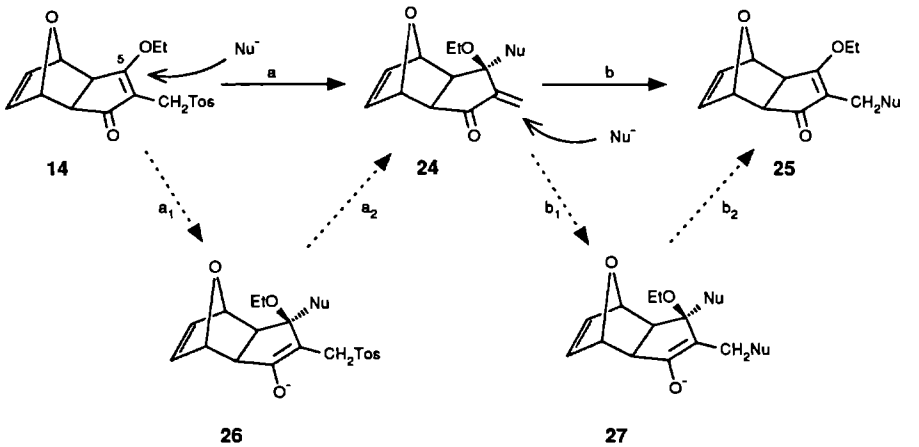
Attempts to prepare 4-aminomethyl derivatives from **14** by treatment with aqueous dimethylamine[15] or with dimethylamine in ethanol containing 2.5 eq of sodium ethanolate, were unsuccessful. Although in the last mentioned reaction the starting material was consumed no distinct compound could be isolated.

The mechanism of the displacement of the tosyl group in **14**.

The tosyl group is not recognized as a good leaving group under S_N1 or E1 conditions[16]. However, assistance from the ethoxy group at C-5 might facilitate the first order cleavage of the allyl-sulphone bond in **14**. Allylic sulphones have been reported to undergo a facile acid catalyzed 1,3-migration in which a transient tight ion pair, consisting of an allylic cation and a sulphinate anion, is proposed. The 1,3-rearrangement of an allylic sulphone group under neutral conditions is expected to start with a light or heat induced cleavage of the allylic sulphone bond[17-19]. These reports suggest that a first order process in the above tosyl displacement can *a priori* not be ruled out.

To investigate the possible occurrence of an S_N1 pathway, sulphone **14** was subjected to methanolysis under neutral conditions. After heating at reflux for 6 hrs, sulphone **14** was recovered quantitatively. In contrast, the conversion of **14** into the methoxymethyl ether **15** with sodium methanolate in methanol is almost instantaneous. These observations definitely rule out an S_N1 type displacement for this reaction. A direct S_N2 type substitution of the tosyl group is highly unlikely on steric and electronic grounds[20], implying that an indirect pathway via a distinct intermediate will be operative (Scheme 7). This intermediate **24** is generated in the first reaction-step, by elimination of the tosyl group. This elimination can in principle be achieved either via an S_N2' (path a) or via a

Scheme 7



conjugate addition-elimination route (paths $a_1 + a_2$). In both cases the reaction is initiated by attack of the nucleophile at C-5 of **14** from the least hindered *exo*-face of the molecule, i.e. *anti* to the oxa-bridge. Evidence that the S_N2' reaction (a) is the actual pathway could be deduced from the stereochemical course of the second step of the reaction-sequence. In this second step **24** reacts rapidly with the nucleophile to form enone **25**. In theory also this second transformation can proceed via an S_N2' (b) or an addition-elimination reaction ($b_1 + b_2$). However, evidence can now be accumulated (see below) that only the S_N2' pathway is involved.

In all the primary products, **15-19**, **22** and **23** the C-5 ethoxy group is retained. In case of the thioethers **22** and **23** the retention of this ethoxy group might be explained by a difference in leaving ability, favouring the elimination of a thiolate group from C-5 over the elimination of the ethoxy group. But for the formation of the alkylethers **15-19** such an explanation can not be valid since the differences in leaving ability of the alkoxides involved are far too small[21] to be decisive in the chemoselective outcome of the second step. Here, the retention of the C-5 ethoxy group clearly points to the stereocontrolled S_N2' process (b). It rules out the possibility of the conjugate mechanism ($b_1 + b_2$), as this would involve initial formation of enolate **27** and subsequent product formation therefrom would only be governed by differences in leaving ability and not by stereochemical factors. With a better leaving group at C-5 the S_N2' reaction (b) will compete more efficiently with the conjugate addition (b_1). Therefore the S_N2' route will certainly be followed in the formation of thioethers **22** and **23** from intermediate **24**.

In an S_N2' process incoming and leaving group occupy the same side of the molecule[22]. This implies here that the incoming nucleophile in the second step (b) as in the first (a), enters from the

exo-face of the tricyclic substrate. The observed retention of the C-5 ethoxy group in **15-19**, **22** and **23** therefore indicates, that reaction of the nucleophile with the exo-methylene function from the *endo*-face, i.e *syn* to the oxa bridge, is sterically unfavourable. Apparently, in spite of its remote position, the stereocontrol of the oxa-bridge is still very effective.

In essence the second step (b) is the reverse of the first step (a). Microscopic reversibility will thus dictate identical pathways for both these processes. This leads to the conclusion that also in the first step the S_N2' route is followed. The difference in leaving groups can hardly be used to argue against this conclusion. The better leaving ability of the tosyl group will in fact promote its S_N2' displacement and therefore disfavour the conjugate addition of the nucleophile to give enolate **26**. The steric demands connected with the S_N2' type displacement of the tosyl group explain why the reaction with a bulky nucleophile, such as the *tert*-butoxide anion, did not lead to complete conversion of the substrate in the usual reaction time.

The role of the carbonyl group in this double S_N2' process is presumably limited to an increase of the electron deficiency at the sites of attack enhancing the reaction rates. Allylic sulphones bearing only alkyl substituents have been reported to undergo a facile allylic displacement of the sulphone group, which is accelerated by Lewis acids[23]. Thus, without the carbonyl group the tosyl displacement is probably much slower if it does take place at all. A substrate lacking this activating carbonyl group is sulphone **34**, which was prepared by the DIBAL reduction of **14** (*vide infra*, Scheme 11). Treatment of **34** with sodium methanolate in refluxing methanol for 16 hrs failed to give any reaction.

In summary, the overall reaction sequence involves two consecutive S_N2' displacements and can be termed as a *bis*-β-β'-*allylic substitution*. As such, this sequence can be considered as a variant of the bis-β-β'-conjugate addition to α,β-enones, that possess a heteroatom substituent on the β'-carbon[24].

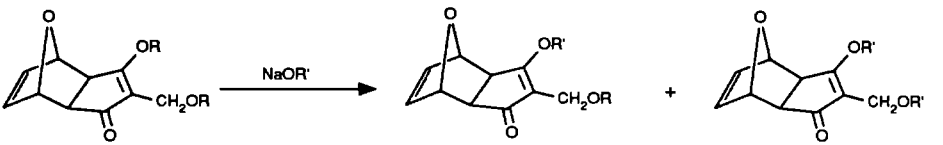
Trans-esterification and trans-etherification processes.

The displacement of the tosyl group by an alkyl ether described above is a very fast process. Full conversion of sulphone **14** on mmol scale requires less than 10 min. The resulting ethers however, are not stable under the applied conditions but suffer from vinylogous trans-esterification and trans-etherification reactions.

The *trans-esterification* was encountered when longer reaction times were applied (see Scheme 5). Compared with the tosyl displacement, this vinylogous trans-esterification is a slow process. It requires excess of alcoholate and reflux overnight. Under these conditions also degradation takes place, probably as a result of a base promoted β-elimination of the 10-oxa bridge[25]. Ultimate yields were therefore moderate (**20**) or poor (**21**). In the latter reaction degradation is obviously more competetive as a result of the increase in basicity and steric demands of the applied nucleophile.

The vinylogous *trans-etherification* process was studied by subjecting the bis-methyl ether **20** to a reaction with sodium ethanolate in ethanol. This led to a mixture of **15** and **16**, the former being the result of trans-esterification only, the latter of both a trans-esterification and a trans-etherification (Scheme 8). The product ratio being in favour of **15** indicated that compared with the trans-esterification, the trans-etherification is the slowest process. The product of trans-etherification only, *i.e.* the 5-ethoxy-4-methoxymethyl derivative **28**, was not observed. The absence of **28** in this reaction was unambiguously established using the analytical and spectral characteristics of an authentic sample. This was prepared by heating **16** with sodium methanolate in methanol, which afforded **28** together with the bis-methoxy derivative **20** as the only products in a ratio of 4:1 (Scheme 8).

Scheme 8



20 R=Me
16 R=Et

15 R=Me; R'=Et
28 R=Et; R'=Me

16 R'=Et
20 R'=Me

The vinylogous transesterification clearly takes place via a conjugate 1,4-addition and a subsequent 1,4-elimination. In order to explain the transetherification, the exo-methylene compound **24** must be invoked (Scheme 7), and as a consequence this conversion will proceed via two consecutive S_N2' substitution reactions.

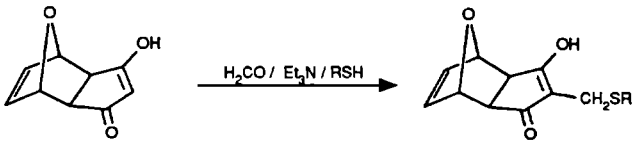
Direct introduction of the phenyl- and benzyl-thiomethyl substituents.

The conversion of **7** into the thiomethyl derivatives **22** and **23**, via the sulphones **13** and **14**, respectively, seems rather circuitous. Direct thiomethylation of **7** with formaldehyde and thiophenol or benzylthiol, followed by O-ethylation might give the same products in a shorter, more efficient manner.

In the literature several methods for the introduction of a thiomethyl group into active methylene compounds are described[26]. Before taking resort to one of these methods, the procedure applied in the tosylmethylation of **7**, using sodium thiophenolate instead of sodium *p*-toluene-sulphinate, was attempted, but in vain. Use of the method described by Poppelsdorf and Holt[26a] for the thiomethylation of indole failed as well, presumably due to the insolubility of **7** in the acidic solvent. Under basic conditions on the contrary, using triethylamine to dissolve **7** in ethanol[26a], the desired derivatives **29** and **30** could be obtained in yields of 68% and 79%, respectively, by reaction

with aqueous formaldehyde in the presence of thiophenol or benzylthiol (Scheme 9).

Scheme 9



7

29 R=Ph
30 R=CH_2Ph

The O-ethylation of **29** and **30** was subsequently carried out again using Meerwein's reagent (*cf* Scheme 4). This afforded the thioethers **22** and **23**, however in low and variable yields (17%-49%). Analysis of the crude reaction mixtures showed the presence of ethyl phenyl sulphide and benzyl ethyl sulphide respectively, suggesting that undesirable S-alkylation also had taken place[13,27]. As the indirect route to **22** and **23** gave satisfactory results (yields over 3 steps of 34% and 59%, respectively) we did not yet investigate other O-alkylation methods.

1.4 Transformations at C-5

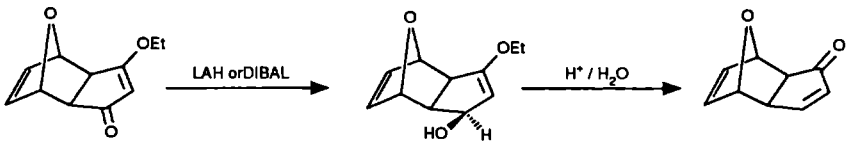
Reductions with DIBAL.

The conversion of β-alkoxy enones into α,β-unsaturated carbonyl compounds by treatment with complex metal hydrides[28] involves initial 1,2-reduction of the carbonyl group to produce γ-hydroxy enol ethers. Under the usual acidic work-up conditions these ethers then rapidly react to form α,β-unsaturated ketones, either through hydrolysis of the enol ether and subsequent elimination of water[29a] or via an allylic rearrangement followed by hydrolysis of the resulting hemiacetal[29b]. However, when alkaline or neutral work-up conditions are used, these ethers sometimes can be isolated.

When Oda's synthesis[4b] of the parent 10-oxatricyclodecadienone **1** (X=O; R=H) by the reduction of **31** with lithium aluminium hydride (LAH) was repeated, the intermediate alcohol **32** was obtained in 86% yield, using NH_4Cl as the hydrolyzing agent (Scheme 10). The subsequent hydrolysis in aqueous acetic acid[3b] however, afforded **1** (X=O; R=H) in an unsatisfactory yield of 49%. A similar moderate overall yield (52%) was reported by Oda et al[4b]. Remarkably, the use of di-*iso*-butyl aluminium hydride (DIBAL) as the reducing agent and 3% HCl for the acidic work-up, provided **1** (X=O; R=H) in an excellent overall yield of 95%. This different result is not fully understood. It indicates that success of such a reduction not only depends on the applied hydride.

The reduction of sulphone **14** with LAH took a totally different course leading to the exo-

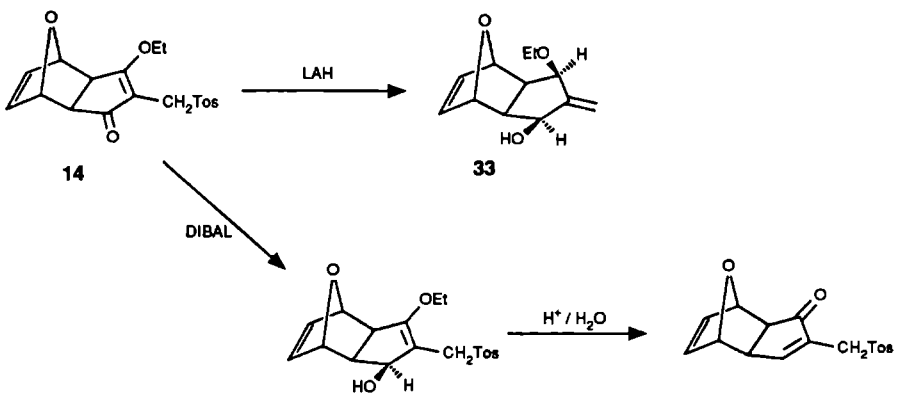
Scheme 10



31 **32** **1** (X=O; R=H)

cyclic methylene derivative **33** as the only product (Scheme 11). This surprising result has been the subject of a preliminary communication[5c], a detailed account will follow in due time. With DIBAL sulphone **14** behaved as expected and was smoothly converted into the desired enone **35**. The intermediate alcohol **34** could be isolated by applying an alkaline instead of an acid hydrolysis. The formation of this alcohol not only confirmed the 1,2-selectivity of the reducing agent[30] but also the overall reaction sequence as given in Scheme 11. The yield of this reduction, at best being 75%, was

Scheme 11

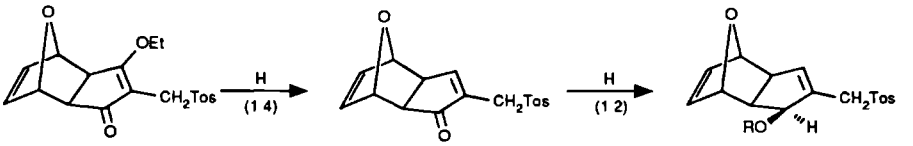


14 **33** **34** **35**

critically depending on the amount of DIBAL. When an excess of DIBAL was used, the reaction also afforded product **36**. The formation of this by-product can be explained by initial 1,4-hydride conjugate addition and concomitant elimination of the ethoxide to form *in situ* enone **35**. Subsequent 1,2-reduction of **35** then leads to **36** (Scheme 12). The loss in yield, caused by this side reaction, could be diminished to some extent by treatment of the crude mixture of **35** and **36** with activated manganese dioxide[28b]. By this treatment **36** was smoothly oxidized to **35**.

The sulphones **35** and **36** could not be separated by crystallization or chromatography.

Scheme 12

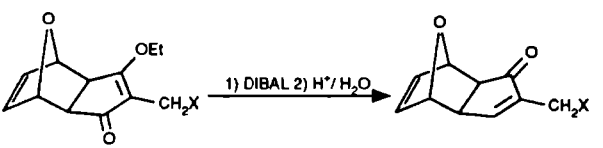


14 **35** **36** R=H
37 R=Ac

However, when a mixture of **35** and **36** was subjected to alkaline epoxidation[31], **36** did not react whereas **35** was converted into its epoxide Sulphone **36** could now readily be isolated Since its spectral data did not allow an unambiguous assignment of its structure, it was acylated and the resulting acetate **37** was subjected to an X-Ray analysis This analysis confirmed the *exo*-configuration of the oxatricyclodecadienone skeleton and revealed in particular the configuration at C-5[32] In conformity with the characteristic reaction pattern of the tricyclic adducts **1**, the hydride addition had occurred stereospecifically at the less hindered *exo*-face of the substrate **35** to produce the *endo*-alcohol **36**

In view of the good results obtained with DIBAL in the reductions of **31** and **14**, this same reagent was also chosen to reduce the tricyclic ethers **15-17** This provided the desired oxatricyclodecadienones **38-40** in high yields (*ca* 90%) (Scheme 13) Here no 1,4-reduction products were

Scheme 13



15 X=OMe
16 X=OEt
17 X=OiPr
22 X=SPh
23 X=SCH_2Ph

38 X=OMe
39 X=OEt
40 X=OiPr
41 X=SPh
42 X=SCH_2Ph

detected, when an excess of DIBAL was used The reduction of **17** was also investigated using LAH as the reducing agent In contrast to sulphone **14**, the tricyclic ether **17** behaved as anticipated and afforded **40** in excellent yield

The exceptional behaviour of sulphone **14** upon treatment with LAH or excess of DIBAL, is most likely associated with the electron withdrawing capacity of the tosyl group This generates a substantial electron deficiency at C-5, promoting hydride attack at that centre In case of the DIBAL reaction 1,4-addition follows as a result of the efficient complexation of this reagent with the

carbonyl group[33], whereas in the LAH reduction the S_N2' pathway, involving the removal of the tosyl group, is taken For the alkyl ethers **15-17** the electron deficiency at C-5 is much smaller than in sulphone **14** Accordingly, hydride attack on C-5 will be disfavoured for these substrates and their reduction to **38-40** will follow the 1,2-pathway (Scheme 10)

The reduction of the thioethers **22** and **23** with DIBAL to give the enones **41** and **42** (Scheme 13) required more time and the amount of DIBAL had to be chosen very carefully Too great an excess led to complex mixtures presumably resulting from overreduction after 1,4-hydride addition as described for sulphone **14** After extensive elaboration yields up to 80% were reached

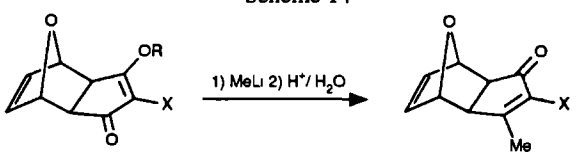
The reductions of **22** and **23** with LAH were even more problematic However, reductive fission of the thioether group, comparable with the elimination of the tosyl group in **14** leading to the exocyclic methylene derivative **33** (Scheme 11), was not observed

As an alternative reducing agent Red-Al ($NaAlH_2(OCH_2CH_2OCH_3)_2$) was tested in the reduction of **22** With this reagent full conversion was achieved in only 3 hrs, which was considerably shorter than the 3 days needed for the DIBAL reaction The yield of 65% however, was less satisfactory.

Reactions with organometallic reagents

When organometallic reagents are used instead of metal hydrides it is expected that the β-alkoxy enones are transformed into β-substituted enones The reaction of **31** with MeMgI afforded the β-methyl derivative **43** in a moderate yield (ca 47%) Similar treatment of sulphone **14** provided sulphone **44**[35] in 32% yield, whereas the reaction of MeMgI with a mixture of the alkyl ethers **15** and **20** led to the methyl derivative **45** in 71% yield (Scheme 14) The disappointing yields are probably

Scheme 14



31 X=H
14 X=CH_2Tos
15, 20 X=CH_2OMe

43 X=H
44 X=CH_2Tos
45 X=CH_2OMe

due to the competitive 1,4-addition, giving a complex mixture of products An NMR analysis of the product mixture obtained from the methylation of **15** and **20** confirmed this view

When MeLi was used instead of MeMgI the methylated products were obtained in almost quantitative yields (*ca* 90%) This result corresponds with the reported high 1,2-selectivity of alkyllithium reagents[34] The mechanism of these conversions is analogous to that of the reduction with DIBAL (Scheme 10)

1.5 Concluding remarks

The results presented above show that the furan adduct **7** can readily be functionalized at C-4 and C-5. Introduction of the 4-tosylmethylgroup followed by O-alkylation produces the synthon **14** in which two reactive moieties, both susceptible to nucleophilic reagents, are combined, *viz.* a β-alkoxy enone and an allylic sulphone group. The allylic sulphone group of **14** can efficiently and selectively be replaced by an ether or thioether group. This transformation proceeds via two consecutive S_N2' displacements. The selective transformation of the β-alkoxy enone moiety of sulphone **14** and its derivatives, via metal hydride reduction or alkylation with organo metallic reagents provides the corresponding enones and β-alkyl substituted enones, respectively, in high yields when 1,2-selective reagents are applied. The choice of the metal hydride in the 1,2-carbonyl reduction of sulphone **14** requires extra consideration as for this substrate hydride attack at C_β, promoted by the electron withdrawing property of the tosyl group, is strongly competing. The DIBAL reduction of **14** has been found to proceed stereospecifically at the least hindered *exo*-face of the substrate, in conformity with the stereocontrol imposed by the tricyclic structure. As yet, no exceptions on this characteristic stereocontrol were observed for the 10-oxatricyclodecadienone system.

1.6 Experimental section

General remarks

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were taken on a Perkin Elmer 298 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 or a Bruker WH-90 spectrometer and ^{13}C-NMR were measured on a Bruker WP-60 (15.08 MHz, FT), using TMS as internal standard. For mass spectra a Varian SM-1B or a double focussing VG 7070E mass spectrometer was used. Column chromatography under normal pressure was performed using Merck Kieselgel 60F 254. Column chromatography under light pressure ("flash chromatography"[36]) was carried out at a pressure of *ca* 1.5 bar, a column length of *ca* 15 cm and a column diameter of 1-4 cm, using Merck Kieselgel 60 H or Merck Aluminium Oxid 150 neutral (Typ T). For preparative TLC precoated Kieselgel plates Merck 60-F254 were used.

5-Hydroxy-exo-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**7**).

The tricyclic enone was prepared by stirring cyclopentene-1,4-dione[37] (*ca* 5 g; 52 mmol) in excess of furan (50 ml) at room temperature, under nitrogen. The enone separated out as a white solid, which occasionally was filtered off. After a reaction time of 2 weeks, a total amount of 7.3 g

(85%) was obtained. Crystallization from methanol afforded an analytically pure sample, mp 160-161°C (dec) (lit 156-157°C[6b], 160-162°C[6c]). IR(KBr) ν: 2900-2100/2100-1700 (two broad absorption bands(w)) and 1570(s)(hydrogen bonded enolized 1,3-diketone[10c]), 1430(m), 1325(s), 1309(s), 1260(m), 1242(m), 1185(m), 860(m), 810(s), 720(s) cm^{-1}. ^{1}H-NMR(DMSO-d_6) δ: 2.50(2H,s;H_2,H_6), 4.82(2H,s;H_1,H_7), 5.03(1H,s;H_4), 6.49(2H,s;H_8,H_9), 8.82(1H,br s;OH). MS(70 eV) m/e: 164(M^+), 135, 122, 107, 96(-furan), 68(furan$^+$). (Found: C 65.85, H 4.80. Calc. for $C_9H_8O_3$: C 65.85, H 4.91%.)

5-Hydroxy-4-(p-tolylsulphonyl)methyl-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**13**).

The applied procedure was a modification of a β-sulphonylmethylation method of 1,3-diketones, described by Hellmann and Müller[12a]. To a suspension of paraformaldehyde (2.0 g; 67 mmol of formaldehyde) in freshly distilled DMF (55 ml) was added 15 ml of glacial acetic acid. The mixture was stirred for 2 hrs while heated in an oil bath at 70°C. The glassy solution was then cooled on ice and sodium-*p*-toluenesulphinate (4.9 g; 27 mmol) and **7** (4.1 g; 24 mmol) were successively added. The resulting suspension was stirred for 3 hrs at 0°C, then overnight at room temperature. Precipitated product was collected by filtration through a Büchner funnel, washed with ethanol and dried in vacuo (60°C; 5 hrs) affording 5.5 g (69%) of pure, white **13**, mp ~ 180°C (dec). An additional amount of **13** was obtained from the DMF filtrate by evaporating the solvent (oil pump) and treating the oily residue with THF. The precipitate was filtered off, washed with ethanol and dried as above, yielding 1.6 g (19%) of **13** as a pale brown solid. This material appeared to be pure enough for the subsequent reaction with Meerwein's reagent (see **14**). Purification by crystallization or chromatography was not possible because of the poor solubility of **13**. N.B. The crude product can also be washed with water instead of ethanol. However, then immediate work-up and isolation of **13** is a necessity, since standing of **13** in an aqueous medium leads to decomposition[12b]. IR(KBr) ν(s): 1680-1510(enolic 1,3-diketone), 1305/1295/1280, 1260, 1135(SO_2), 1090, 1065, 1012, 890, 820/810, 765, 630 cm^{-1}. ^{1}H-NMR(DMSO-d_6) δ: 2.27(2H,s;H_2,H_6), 2.38(3H,s;ArCH_3), 3.80(2H,s;CH_2Tos), 4.74(2H,s;H_1,H_7), 6.48(2H,s;H_8,H_9), 7.37(d)/7.72(d)(J=9Hz;4ArH). MS(70 eV) m/e: 332(M^+), 298, 284, 278, 264(-furan), 246, 217, 156($CH_3C_6H_4SO_2H^+$), 139($CH_3C_6H_4SO^+$), 109, 92($C_6H_5CH_3^+$), 91($C_7H_7^+$), 68(furan$^+$), 64, 54. (Found: C 59.52, H 4.67. Calc. for $C_{17}H_{16}O_5S$: C 61.43, H 4.85%.)

5-Ethoxy-4-(p-tolylsulphonyl)methyl-exo-*10-oxatricyclo[5.2.1.0^{2,6}] deca-4,8-dien-3-one* (**14**).

The applied procedure was an adaptation of the method reported by Oda *et al*[4b]. To a vigorously stirred suspension of sulphone **13** (1.95 g; 5.86 mmol) in dichloromethane (25 ml, dried over CaH_2 and filtered through a short Al_2O_3 column to remove any alcohol additive) was added 1 ml (*ca* 7 mmol) of dry triethylamine. After 15 min, 10 ml of a 1 M solution of triethyloxonium tetrafluoroborate[13] in dichloromethane was injected. The reaction mixture was stirred for 3 hrs at room temperature. The resulting clear, yellow/green coloured solution was then neutralized by

adding dilute $NaHCO_3$. The aqueous layer was extracted with dichloromethane (5x). The combined organic layers were washed with a small amount of water (1x) and dried over $MgSO_4$. After removal of dichloromethane in vacuo, the crude product was purified by flash chromatography (silicagelethyl acetate), yielding 1.91 g (5.29 mmol;90%) of **14**. Crystallization from ethyl acetate afforded an analytically pure sample, mp 170-172°C. IR(KBr) ν(s): 1695(C=O), 1630(C=COEt), 1370, 1350, 1310, 1300, 1287, 1255, 1238, 1132, 1020, 888, 855, 820, 755, 680 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.36(3H,t,J=7Hz;OCH_2CH_3), 2.40(4H,s+d;$ArCH_3$,H_2), 2.84(1H,d,J=7Hz;H_6), 4.07(2H,s;CH_2Tos), 4.45(2H,q,J=7Hz;OCH_2CH_3), 4.90(1H,s)/4.96(1H,s)(H_1,H_7), 6.50(2H,m;H_8,H_9), 7.28(d)/7.78(d) (J=9Hz;4ArH). MS(70 eV) m/e: no M^+ peak, 292(-furan), 245, 205(-Tos), 137(-Tos,-furan), 109, 91($C_7H_7^+$), 81, 68(furan$^+$). (Found: C 63.24, H 5.54. Calc. for $C_{19}H_{20}O_5S$: C 63.32, H 5.59%.)

Displacement of the tosyl group in sulphone **14** *by an ether function: general procedure.*

To a stirred, gently refluxing 0.05-0.1 M solution of **14** in the appropriate alcohol is added *ca* 1.5 equiv. of the corresponding sodium alcoholate. Heating at reflux is continued during the indicated period. After cooling to room temperature, the excess of alcoholate is neutralized with 1 ml of saturated NH_4Cl. The solvents are evaporated, and water and dichloromethane are added to the residue. The aqueous layer is extracted with dichloromethane (3x). The combined organic layers are washed with water (1x), dried ($MgSO_4$), filtered and evaporated. The crude, generally almost pure product is further purified by crystallization from hexane-ethyl acetate and/or by flash chromatography over SiO_2 or Al_2O_3 using a hexane-ethyl acetate mixture as the eluent.

5-Ethoxy-4-methoxymethyl-exo-*10-oxa-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**15**).

Sulphone **14** (360 mg; 1.0 mmol) was converted according to the *general procedure* into 207 mg (87%) of **15**, applying sodium methoxide in refluxing methanol for 10 min. The Bruker WH-90 ^{1}H-NMR spectrum of the crude product revealed no signals of the closely related 5-methoxy-4-methoxymethyl compound **20** (see below). An analytically pure sample was obtained by crystallization from hexane, mp 93.5-94.5°C. IR(KBr) ν(s): 1685(C=O), 1610(br;C=COEt), 1410, 1390, 1325, 1265, 1085, 1012, 948, 890, 875, 730, 708 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.44(3H,t,J=7Hz; OCH_2CH_3), 2.54(1H,d,$J_{2,6}$=6Hz;H_2), 2.79(1H,d,$J_{6,2}$=6Hz;H_6), 3.30(3H,s;CH_2OCH_3), 4.09(2H,s; CH_2OCH_3), 4.53(2H,q,J=7Hz;OCH_2CH_3), 4.94(1H,s)/5.03(1H,s)(H_1,H_7), 6.46(2H,s;H_8,H_9). MS(70eV) m/e: 236(M^+), 204(-CH_3OH), 176(-CH_3OH,-CO), 168(-furan), 139, 109, 97, 81, 68(furan$^+$), 45($CH_2OCH_3^+$). (Found: C 66.28, H 6.81. Calc. for $C_{13}H_{16}O_4$: C 66.09, H 6.83%.)

When repeating this synthesis on gram scale, reaction times of at least 20 min were needed for complete conversion. Then mixtures of **15** and **20** were obtained. Increasing the reaction time led to an increase of the relative amount of **20**, but to a decrease in total yield. Crude mixtures of **15** and **20** could be purified chromatographically, but separation of **15** and **20** was not possible by chromatography or crystallization. For subsequent reactions (reduction with DIBAL (see **38**) or

alkylation with MeLi (see **45**)) such a separation was not needed.

5-Methoxy-4-methoxymethyl-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**20**).

Refluxing sulphone **14** (1.30 g; 3.6 mmol) with excess of sodium methoxide (10 eq) in methanol for 15 hrs and subsequent workup as described in the *general procedure* afforded **20** as the only product. No signals of **15** could be detected in the ^{1}H-NMR spectrum of the crude material. The crude yield measured 450 mg (*ca.* 56%). Crystallization in hexane-ethyl acetate (1:1) gave analytically pure **20** as white crystals, mp 96-97°C. IR(KBr) ν(s): 1678(C=O), 1610(C=COMe), 1388, 1332, 882, 702 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.52(1H,d,$J_{2,6}$=6Hz;H_2), 2.80(1H,d,$J_{6,2}$=6Hz;H_6), 3.30(3H,s;CH_2OCH_3), 4.10(2H,s;CH_2OCH_3), 4.20(3H,s;C(5)-OCH_3), 4.95(1H,s)/5.03(1H,s)(H_1,H_7), 6.48 (2H,s;H_8,H_9). MS(CI) m/e(%): 223(44;M+1$^+$), 191(8;-CH_3OH), 154(10;-furan), 123(100;-furan, -CH_3OH). (Found: C 64.89, H 6.36. Calc. for $C_{12}H_{14}O_4$: C 64.85, H 6.35%.)

5-Ethoxy-4-ethoxymethyl-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**16**).

Sulphone **14** (499 mg; 1.4 mmol) was converted according to the *general procedure* in 250 mg (71%) of **16**, applying sodium ethoxide in refluxing ethanol for 10 min. Purification by flash chromatography (Al_2O_3/hexane-ethyl acetate (1:2)) followed by crystallization from hexane-ethyl acetate (1:2) afforded analytically pure **16** as white needlets, mp 86-88°C. IR(melted film) ν_{max}: 1690(C=O), 1620(C=COEt) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.18(3H,t,J=7Hz;$CH_2OCH_2CH_3$), 1.43(3H,t, J=7Hz;C(5)-OCH_2CH_3), 2.53(1H,d,$J_{2,6}$=5.5Hz;H_2), 2.78(1H,d,$J_{6,2}$=5.5Hz;H_6), 3.48(2H,q,J=7Hz; $CH_2OCH_2CH_3$), 4.14(2H,s;CH_2OEt), 4.56(2H,q,J=7Hz;C(5)-OCH_2CH_3), 4.94(1H,s)/5.03(1H,s) (H_1,H_7), 6.46(2H,s;H_8,H_9). MS(70eV) m/e: 250(M$^+$), 204(-EtOH), 182(-furan), 176(-EtOH,-CO), 153, 138, 125, 109, 97, 81, 68(furan$^+$). (Found: C 67.18, H 7.26. *C*alc.for $C_{14}H_{18}O_4$: C 67.21, H 7.25%.)

5-Ethoxy-4-iso-*propyloxymethyl*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**17**).

Sulphone **14** (1.19 g; 3.3 mmol) was converted according to the *general procedure* into 767 mg (94%) of **17**, applying sodium *iso*-propoxide in refluxing 2-propanol for 30 min. Purification of the crude product by flash chromatography (SiO_2/hexane-ethyl acetate (1:4)) and crystallization from cyclohexane afforded an analytically pure sample, mp 70-71.5°C. IR(KBr) ν(s): 1688(C=O), 1620(C=CO-iPr), 1418, 1380, 1370, 1340, 1320/1310, 1265, 1042, 1020/1010, 888, 870, 722, 703 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.17(6H,d,J=6Hz;$OCH(CH_3)_2$), 1.42(3H,t,J=7Hz;OCH_2CH_3), 2.49(1H,d, $J_{2,6}$=6Hz;H_2), 2.73(1H,d,$J_{6,2}$=6Hz;H_6), 3.60(1H,sept,J=6Hz;$OCH(CH_3)_2$), 4.14(2H,s;CH_2O-iPr), 4.57(2H,q,J=7Hz;OCH_2CH_3), 4.93(1H,s)/5.03(1H,s)(H_1,H_7), 6.47(2H,s;H_8,H_9). MS(EI) m/e(%): 264(10;M$^+$), 196(22;-furan), 176(9;-iPrOH,-CO), 154(53;-furan,-C_3H_6), 138(90), 137(61;-furan,-OC_3H_7), 125(95), 109(100), 98(38), 97(28), 81(20), 68(35;furan$^+$), 55(11), 43(32;$C_3H_7^+$), 29(24;$C_2H_5^+$). (Found: C 68.05, H 7.62. Calc. for $C_{15}H_{20}O_4$: C 68.16, H 7.63%.)

5-iso-Propyloxy-4-iso-propyloxymethyl-exo-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**21**).

When in the above synthesis of **17** an excess of sodium *iso*-propoxide was used and refluxing was continued over a longer period, the initially formed **17** gradually was converted into **21**. Starting with 360 mg (1 mmol) of sulphone **14** and 3 mmol of sodium *iso*-propoxide in 20 ml of 2-propanol, complete conversion to **21** was realized in 24 hrs, yielding 40 mg (14%) of **21**. Purification of the crude product by flash chromatography (SiO_2/hexane-ethyl acetate (1:3)) and subsequent crystallization from hexane afforded analytically pure **21**, as white crystals, mp 52-54°C. IR(KBr) ν(s): 2980, 1685(C=O), 1600(C=CO-iPr), 1412, 1385, 1370, 1318, 1305, 1270/1260, 1090, 1040, 1018, 960, 932, 725, 700 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.13(6H,d,J=6.6Hz;$CH_2OCH(CH_3)_2$), 1.33(d, J=6Hz)/1.37(d,J=6Hz)(6H;C(5)-OCH(CH_3)$_2$), 2.47(1H,d,$J_{2,6}$=7Hz;H_2), 2.71(1H,d,$J_{6,2}$=7Hz;H_6), 3.57(1H,sept,J=6.6Hz;CH_2-OCH(CH_3)$_2$), 3.93-4.23(2H,AB_q,J_{AB}=11Hz;CH_2O-iPr), 4.87(1H,s)/5.00 (1H,s)(H_1,H_7), 5.17(1H,sept,J=6Hz;C(5)-OCH(CH_3)$_2$), 6.44(2H,s;H_8,H_9). MS(EI) m/e(%): 278(7;M^+), 210(16;-furan), 168(20;-furan,-C_3H_6), 152(28;-furan,-C_3H_6O), 126(100), 125(32), 110(61), 109(46), 108(52), 98(22), 68(17;furan$^+$). (Found: 69.33, H 8.03. Calc. for $C_{16}H_{22}O_4$: C 69.04, H 7.97%.)

5-Ethoxy-4-phenylthiomethyl-exo-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**22**).

A solution of sulphone **14** (4.27 g; 11.9 mmol) and sodium thiophenolate[38] (4.82 g; 36.5 mmol) in methanol (100 ml) was heated at reflux for 4 hrs and subsequently stirred overnight at room temperature. After evaporation of the solvent, dichloromethane was added to the residue. The resulting mixture was stirred for 10 min. Non dissolved material was filtered off. The filtrate was washed with water, dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product by flash chromatography (silicagel/ethyl acetate) afforded 1.6 g (43%) of pure (^{1}H-NMR) **22**, as a thick colourless oil. IR(CCl_4) ν: 1695(s;C=O), 1630(s:C=COEt), 1372(m), 1345(m), 1328(s), 1020(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.30(3H,t,J=6Hz;OCH_2CH_3), 2.45(1H,d,J=5Hz;H_2), 2.75(1H,d,J=5Hz;H_6), 3.62(2H,s;CH_2SPh), 4.20(2H,m,diasterotopic protons;OCH_2CH_3), 4.86 (1H,s)/5.00(1H,s)(H_1,H_7), 6.45(2H,s;H_8,H_9), 7.14-7.50(m;5ArH). MS(EI) m/e(%): 314(2;M^+), 270(8;-CH_3CHO), 246(16;-furan), 202(36;-furan,-CH_3CHO), 161(100;-CH_3CHO,-SPh), 137(93; -furan,-SPh), 109(85;SPh$^+$), 93(63), 77(23;$C_6H_5^+$), 68(12;furan$^+$). HRMS(EI) m/e: 314.0972 (calc. for $C_{18}H_{18}O_3S$ (M^+): 314.0977)

4-Benzylthiomethyl-5-ethoxy-exo-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**23**).

The procedure applied by Kowalski[15] for the thiomethylation of 3-(mesyloxy)-2-cyclohexen-1-one was followed. A dispersion of NaH in oil (50%; 490 mg; 10.2 mmol of NaH) was washed with pet.ether$^{40\text{-}60}$, decanted and dried under a flow of nitrogen. Then dry ether (25 ml) and benzylmercaptan (1.32 g; 10.6 mmol) were added and after the mixture had been stirred for 10 min, a

solution of sulphone **14** (1.47 g; 4.08 mmol) in a few ml of dry dichloromethane was injected. Stirring was continued for 5.5 hrs. Thereafter the reaction mixture was diluted with dichloromethane (60 ml) and consecutively washed with saturated NH_4Cl (20 ml), water (20 ml) and brine (20 ml) and finally dried on $MgSO_4$. After removal of the drying agent and evaporation of the solvents, the residue was purified by column chromatography (silicagel/hexane-ethyl acetate (1:1)) to give **23** as an oil, which crystallized on standing in the refrigerator. Recrystallization from pentane afforded 994 mg (74%) of **23**, as pale yellow crystals, mp 90.5-91.5°C. IR(KBr) ν: 1683(s;C=O), 1610(s; C=COEt), 1375(m), 1325(s), 1250(m), 1012(m), 705(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.36(3H,t, J=7.0Hz;OCH_2CH_3), 2.50(1H,d,J=5.4Hz;H_2), 2.77(1H,d,J=5.4Hz;H_6), 3.28(2H,s;SCH_2Ph), 3.74(2H, s;CH_2SBz), 4.35(2H,ABX_3multiplet,J_{AB}=2.4Hz,J_{AX}=J_{BX}=7Hz;OCH_2CH_3), 4.89(1H,s)/5.03(1H,s) (H_1,H_7), 6.46(2H,s;H_8,H_9), 7.29(m;5ArH). MS(70eV) m/e: 328(M^+), 260(-furan), 204(-HSBz), 169(-furan,-Bz), 138($BzSCH_3^+$), 137($BzS{=}CH_2^+$), 109, 91($C_7H_7^+$), 81, 68($furan^+$). (Found: C 68.92, H 6.10. Calc. for $C_{19}H_{20}O_3S$: C 69.48, H 6.14%.)

Vinylogous transesterification and transetherification of **20**.

To a solution of **20** (110 mg; 0.5 mmol) in ethanol (20 ml) was added 2 ml of a 1.5 M solution of sodium ethoxide in ethanol. The resulting mixture was heated at reflux for 3 hrs and then stirred at room temperature for 20 hrs. The conversion was monitored by means of TLC (AL_2O_3/ hexane-ethyl acetate (1:1)). After 3 hrs, TLC showed only the presence of **15** and **16**. TLC's later on revealed that, notwithstanding the long reaction time, complete conversion of **15** into **16** had not been reached. Work-up as usual (see *general procedure*), followed by preparative TLC (SiO_2/ethyl acetate) afforded 12 mg of a colourless oil, consisting of a mixture of **15** and **16** in a ratio of 1.2:1 (^{1}H-NMR). The total yield of **15** and **16** amounted to 10%. No trace of **28** was detected, neither by TLC, nor by ^{1}H-NMR analysis. In particular, no signal at δ 4.21 ppm for the 5-methoxy-group of **28** (*vide infra*) was observed.

Vinylogous transesterification and transetherification of **16**.

To a solution of **16** (294 mg; 1.2 mmol) in methanol (30 ml) was added 8 ml of a 0.7 M solution of sodium methoxide in methanol. The resulting mixture was heated in an oil bath at 75°C for 14 hrs until TLC indicated that complete conversion of the starting material had been reached. Work-up as usual (see *general procedure*) afforded 57 mg of crude product which contained, besides a small amount of impurities, *4-Ethoxymethyl-5-methoxy-exo-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**28**) and **20** in a ratio of *ca* 4:1 (^{1}H-NMR). The total yield of **28** and **20** did not exceed 20%. Further purification of **28** was not attempted. ^{1}H-NMR($CDCl_3$) δ: 1.17(3H,t,J=7Hz; OCH_2CH_3), 2.50(1H,d,$J_{2,6}$=5.5Hz;H_2), 2.74(1H,d,$J_{6,2}$=5.5Hz;H_6), 3.46(2H,q,J=7Hz;OCH_2CH_3), 4.13(2H,s;CH_2OEt), 4.21(3H,s;OCH_3), 4.91(1H,s)/5.00(1H,s)(H_1,H_7), 6.44(2H,s;H_8,H_9).

5-Hydroxy 4 phenylthiomethyl exo *10 oxatricyclo[5 2 1 $0^{2,6}$]deca-4,8- dien-3 one* (**29**)

The applied procedure was an adaptation of a thiomethylation method described by Poppelsdorf and Holt[26a] To a suspension of **7** (2 27 g, 13 8 mmol) in ethanol (30 ml) were successively added thiophenol (1 41 ml, 13 8 mmol), triethylamine (2 87 ml, 20 7 mmol) and 37% aqueous formaldehyde (1 68 ml, 20 7 mmol) The resulting solution was stirred for 24 hrs, while heated in an oil bath at 70°C After cooling, acidification (3% HCl), extraction with ether (4x) and evaporation of the combined ethereal extracts, a brown coloured residue was isolated, which was washed with small amounts of water (2x) and ether (2x) and dried in vacuo, affording 2 7 g (*ca* 68%) of **29** as a white solid Further purification was not carried out IR(KBr) ν 3000-2500(two broad absorptions bands(m)) and 1570(s(br)) (hydrogen bonded enolized 1,3-diketone), 1370(s(br)), 1290(m), 1268(m), 1240(m), 1152(m), 1012(m), 883(m), 850(m), 695(m) cm $^{-1}$ ^{1}H-NMR($d_6$acetone) δ 2 64(2H,s,H_2,H_6), 3 65(2H,s,CH_2SPh), 4 88(2H,s,H_1,H_7), 6 46(2H,s,H_8,H_9), 7 26(m,5ArH) MS(CI) m/e(%) 287(1,M+1$^+$), 219(9,-furan), 141(20,-furan,-C_6H_6), 123(4,CH_2SPh$^+$), 111(100, (PhSH+1)$^+$), 110(20,PhSH$^+$), 109(38,-furan,-PhSH), 79(5,(C_6H_6+1)$^+$), 69(64,(furan+1)$^+$) HRMS(CI) m/e 287 0744 (calc for $C_{16}H_{15}O_3S$ (M+1) 287 0742)

Reactions of **29** with Meerwein's reagent (*ca* 1 2 eq), applying the procedure described for the preparation of **14** from **13**, led to complex product mixtures containing the O-ethylated product **22** in variable yields According to the ^{1}H-NMR spectra of the crude products also ethyl phenyl sulphide was formed However, no efforts to obtain this sulphide were made Tedious flash chromatography of the crude materials on Al_2O_3 or SiO_2 using hexane-ethyl acetate (1 1) as the eluent, afforded **22** in 17-49% yield

4-Benzylthiomethyl 5 hydroxy-exo-*10-oxatricyclo[5 2 1 $0^{2,6}$]deca-4,8 dien-3-one* (**30**)

To a suspension of **7** (2 1 g, 12 8 mmol) in ethanol (30 ml) were successively added benzylthiol (1 51 ml, 12 8 mmol), triethylamine (2 66 ml, 19 2 mmol) and 37% aqueous formaldehyde (1 56 ml, 19 2 mmol) The resulting solution was refluxed for 24 hrs, then cooled to room temperature and acidified with 3% HCl (50 ml) A first amount of **30** precipitated immediately This was filtered off, rinsed with ether and dried in vacuo From the filtrate gradually some more product separated, which was treated in the same way as the first isolated material Further purification was not attempted The total yield of **30** amounted to 3 0 g (*ca* 79%) IR(KBr) ν 3000-2500(two broad absorption bands (m)) and 1555(s(br)) (hydrogen bonded enolized 1,3-diketone), 1365(s(br)), 1262(s), 1012(s), 883(s), 848(s), 708(s), 698(s) cm $^{-1}$ ^{1}H NMR($d_6$acetone) δ 2 64(2H,s,H_2,H_6), 3 18(2H,s,CH_2Ph), 3 73(2H,s,CH_2SBz), 4 91(2H,br s,H_1,H_7), 6 49(2H,br s,H_8,H_9), 7 30(m,5ArH) MS(CI) m/e(%) 301(<1%,M+1$^+$), 233(5,-furan), 215(4,-furan,-H_2O), 124(21,BzSH$^+$), 109(55,-furan,-BzSH), 91(100,Bz$^+$), 69(100,furan+1$^+$) HRMS(CI) m/e 301 0893 (calcd for $C_{17}H_{17}O_3S$ (M+1) 301 0898)

The subsequent reaction of **30** (468 mg, 1 56 mmol) with Meerwein's reagent (2 34 mmol),

applying the procedure described for the preparation of **14** from **13**, led to a complex product mixture[27]. This provided after flash chromatography (Al_2O_3/hexane-ethyl acetate (3:1)) 231 mg (45%) of the O-ethylated derivative **23**, besides 59 mg (25%) of benzyl ethyl sulphide.

5-Ethoxy-exo-*10-oxatricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one* (**31**).

This tricyclic enone was prepared by O-alkylation of **7** with Meerwein's salt according to the procedure described by Oda *et al*[4b]. Flashchromatography (silicagel/hexane-ethyl acetate (1:1)) of the crude product afforded pure **31** in 95% yield.

5-Ethoxy-exo-*10-oxatricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien*-endo-*3-ol* (**32**).

This alcohol was prepared by a modification of the procedure of Oda *et al*[4b] for the reduction of **31** to **1** (X=O; R=H). To an ice cooled suspension of lithium aluminium hydride (30 mg; 0.8 mmol) in ether (12 ml), was added slowly, with stirring a solution of **31** (172 mg; 0.9 mmol) in THF (10 ml). After the addition was complete, the reaction mixture was stirred for 2 hrs at room temperature. Then water was added cautiously and the resulting mixture was neutralized with solid NH_4Cl. Precipitated material was removed by filtration through a sintered glass funnel. The organic layer was separated from the filtrate, washed with water (2x), dried ($MgSO_4$) and evaporated, affording 150 mg (86%) of **32** as a white solid, which after crystallization from cyclohexane melted at 108-110°C. IR(KBr) ν(s): 3320, 3030, 2870, 1640 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.31(3H,t,J=6.8Hz; OCH_2CH_3), 1.89(1H,br m;OH), 2.33-2.62(2H,m;H_2(2.43 ppm,dd,$J_{2,6}$=8.1Hz,$J_{2,3}$=9.9Hz),H_6(2.57 ppm,d,$J_{6,2}$=8.1Hz)), 3.81(2H,q,J=6.8Hz;OCH_2CH_3), 4.64/4.74(2H,s+d($J_{3,2}$=9.9 Hz);H_1 or H_7 and H_3), 4.81(1H,s;H_4), 5.15(1H,s;H_1 or H_7), 6.34(2H,br s;H_8,H_9). MS(70 eV) m/e: 194(M^+), 176(-H_2O), 165(-C_2H_5), 128, 126(-furan), 97, 91, 70, 68(furan$^+$). Alcohol **32** was smoothly converted into enone **1** (X=O; R=H) by stirring in aqueous acetic acid as described by Oda et al[4b] (42% overall yield).

Reductions of the tricyclic β-alkoxy-enones **14-17, 20** *and* **31** *with Di*-Iso-*Butyl Aluminium Hydride*: *general procedure*.

To an ice cooled suspension or solution of the β-alkoxy-enone in ca 30 ml of dry benzene, under nitrogen, is added dropwise by means of a syringe, 1.0-1.5 equiv. of DIBAL (1 M solution in hexane; Aldrich 19.030-6). The mixture is stirred for 0.5-1 hr at 0°C and then allowed to warm up to room temperature. The conversion is monitored by TLC. If required, some more DIBAL is injected and stirring is continued for another 30 min at room temperature. Dichloromethane (30 ml) and 3% HCl (30 ml) are added. The resulting mixture is stirred vigorously during 20-30 min. The layers are separated. The aqueous phase is extracted with dichloromethane (3x30 ml). The combined organic solutions are washed with water (3x), dried ($MgSO_4$), filtered and evaporated. The crude product is purified by crystallization and/or flash chromatography or preparative TLC.

exo-*10-Oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one*, **1** (X=O; R=H).

Reduction of **31** (2.21 g; 11.4 mmol) with DIBAL as described in the *general procedure* afforded 1.60 g (95%) of enone **1** (X=O; R=H). An analytically pure sample was obtained by crystallization from hexane-ethyl acetate (1:1), mp 71-73°C (lit[4b]: 69-70°C).

4-(p-Tolylsulphonyl)methyl-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**35**).

The DIBAL reduction of sulphone **14** (903 mg; 2.51 mmol) to give the tricyclic enone **35** was carried out as described in the *general procedure* with a slight modification, namely instead of 3% HCl, saturated NH_4Cl was used for the acid hydrolysis. Crystallization of the crude product (815 mg) from ethyl acetate and subsequent flash chromatography of the mother liquor (SiO_2/hexane-ethyl acetate (1:3)) afforded 591 mg (75%) of pure **35**, mp 182-183°C. IR(KBr) ν(s): 1690(C=O), 1310/1305, 1287, 1275, 1162, 1145, 1130(SO_2), 1085, 908, 868, 850, 815, 755, 718, 630 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.36(1H,d,$J_{2/6}$=5Hz;H_2), 2.43(3H,s;$ArCH_3$), 2.99(1H,ddd,$J_{6,5}$=2.6Hz,$J_{6,2}$=5Hz,-$J_{6,5'}$=1.2Hz;H_6), 3.96(2H,br s;CH_2Tos), 4.81(2H,br s;H_1,H_7), 6.40(1H,dd)/6.54(1H,dd)($J_{8,9}$=5.6Hz, $J_{8,7}$=$J_{9,1}$=1.5Hz;H_8,H_9), 7.30(d,J=6.7Hz;2ArH), 7.72(m+d(J=6.7Hz);H_5+2ArH). MS(EI) m/e(%): 316(1;M$^+$), 249(1;-furan), 161(100;-Tos), 155(16;Tos$^+$), 133(13), 93(37;-Tos,-furan), 91(28;$C_7H_7^+$), 68(9;furan$^+$), 65(36), 39(18). (Found: C 63.98, H 5.11. Calc. for $C_{17}H_{16}O_4S$: C 64.54, H 5.10%.)

If in this DIBAL reduction of **14**, the hydrolysis was carried out with 10% NaOH instead of saturated NH_4Cl, then the intermediate alcohol *5-Ethoxy-4-(p-tolylsulphonyl)methyl*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien*-endo-*3-ol* (**34**) was obtained. Subsequent crystallization of the crude product from hexane/ethyl acetate (1:2) afforded then analytically pure **34**, mp 137.5-138°C. IR(KBr) ν(s): 3380(OH), 1680(C=COEt), 1343, 1315/1305, 1180, 1153, 1130(SO_2), 1100/1090, 1070, 910, 890/880, 815, 700 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.00(3H,t,J=7Hz;OCH_2CH_3), 1.57(1H,br s;OH), 2.43(4H,m(d+s);H_2,$ArCH_3$), 2.64(1H,d,J=6Hz;H_6), 3.42-3.85(2H,m,ABX_3system; OCH_2CH_3), 3.96(2H,s;CH_2Tos), 4.68(2H,br s;H_1,H_7), 5.24(1H,br s;H_3), 6.38(2H,s;H_8,H_9), 7.32(d)/7.75(d)(J=9Hz;4ArH). MS(CI) m/e(%): no signal for M+1$^+$, 345(3;-H_2O), 317(18;-EtOH), 295(69;-furan), 249(100;-furan,-EtOH), 189(21;-HTos), 161(40(-HTos,-EtOH), 157(H_2TosS^+), 139(94;-furan,-HTos), 69(65;furan$^+$). (Found: C 62.62, H 6.13. Calc. for $C_{19}H_{22}O_5S$: C 62.96, H 6.12%.). Alcohol **34** could smoothly be converted into enone **35**, by stirring it in a 1:3 mixture of 3% HCl and dichloromethane.

Attempted displacement of the tosyl group in sulphone **34**.

Sulphone **34** (158 mg; 0.43 mmol) was refluxed overnight with sodium methoxide (0.7 mmol) in methanol (*ca.* 5 ml). After cooling to room temperature, water (2 ml) was added and such an amount of dichloromethane that a good separation between the aqueous and organic layers was obtained. The layers were separated. The aqueous phase was extracted with dichloromethane (2x). The combined organic extracts were washed with water (1x), dried ($MgSO_4$), filtered and

evaporated. This afforded 152 mg (*ca.* 100%) of sulphone **34** in return. No indications of any other product were found in the ^{1}H-NMR spectrum of this material.

4-(p-Tolylsulphonyl)methyl-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien*-endo-*3-ol* (**36**).

If in the synthesis of **35** as described above, excess of DIBAL was applied, then alcohol **36** was formed as a by-product. The isolation of this alcohol was complicated by the fact that **35** and **36** could not be separated by chromatography or crystallization. However, on treatment of a mixture of **35** and **36** with alkaline hydrogen peroxide, enone **35** was converted into the corresponding epoxide[31] whereas **36** was not affected. In this stage **36** could be isolated readily by flash chromatography (SiO_2/hexane-ethyl acetate (1:1)). ^{1}H-NMR($CDCl_3$) δ: 2.23-2.43(5H,m;OH(2.23 ppm,br m),H_6(2.37 ppm,tr(dd,$J_{6,2}$=$J_{6,5}$=7.2Hz),$ArCH_3$(2.43 ppm,s)), 2.67(1H,br d,$J_{6,2}$=7.2Hz;H_2), 3.73-4.13(2H,AB_q,J_{AB}=14Hz;CH_2Tos), 4.52/4.60(2H,s+d($J_{5,6}$=7.2Hz);H_1 or H_7;H_5), 5.10(1H,s;H_1 or H_7), 5.67(1H,s;H_3), 6.37(2H,br s;H_8,H_9), 7.32(d)/7.76(d)(J=8Hz;4ArH). MS(CI) m/e(%): no M+1$^+$peak, 301(63;-H_2O), 251(18;-furan), 185(6), 157(29;HTos+1$^+$), 145(100), 139(24), 95(26;-furan,-HTos), 69(12;furan+1$^+$). The structure of **36** was elucidated by the X-Ray analysis of its acylated derivative **37** (see below).

endo-*5-Acetoxy-4-(p-tolylsulphonyl)methyl*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-3,8-diene* (**37**).

To a solution **36** (54 mg; 0.17 mmol) in dichloromethane (10 ml) were successively added acetic anhydride (37 mg; 0.36 mmol), triethylamine (37 mg; 0.37 mmol) and DMAP (2 mg; 0.02 mmol). The resulting mixture was stirred for 1.5 hr and then diluted with water (15 ml). The aqueous layer was extracted with dichloromethane (3x15 ml). The combined organic extracts were washed with 3% HCl (2x5 ml) and water (3x10 ml), dried ($MgSO_4$), filtered and evaporated. Flash chromatography (SiO_2/hexane-ethyl acetate (1:1)) of the crude product afforded 46 mg (75%) of **37** as a colourless oil which solidified in the freezer. Subsequent crystallization from hexane-ethyl acetate (3:1) provided analytically pure **37**, as glittering white platelets, mp 118-120°C. X-Ray analysis[32] of these crystals established the structure of **37**, as given in Scheme 12. IR(KBr) ν: 1730(s;C=O), 1313 (m), 1300(m), 1288(m), 1240(s), 1160(s), 1125(s), 1083(s), 1070(m), 1003(m), 895(s), 755(m), 703(m), 618(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.09(3H,s;CH_3acyl), 2.44(3H,s;$ArCH_3$), 2.56(1H,tr(dd), $J_{6,2}$=6.5Hz,$J_{6,5}$=8.0Hz;H_6), 2.78(1H,br d,$J_{2,6}$=6.5Hz;H_2), 3.89(2H,s;CH_2Tos), 4.58(1H,s)/4.63(1H,s) (H_1,H_7), 5.53 (1H,d,$J_{5,6}$=8.0Hz;H_5), 5.84(1H,br s;H_3), 6.32(2H,s;H_8,H_9), 7.33(d)/7.74(d)(J=9Hz; 4ArH). MS(CI) m/e(%): no M+1$^+$ peak, 301(16;-CH_3COOH), 293(8;-furan), 251(20;-furan, -CH_2CO), 185(14), 157(13;HTos+1$^+$), 145(24), 139(64), 137(27), 95(46;-furan,-HTos,-CH_2CO), 69(100;furan+1$^+$). (Found: C 63.18, S 9.13. Calc. for $C_{19}H_{20}O_5S$: C 63.32, H 5.59, S 8.90%.)

4-Methoxymethyl-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**38**).

A 3:1 mixture of **15** and **20** (485 mg; 2.1 mmol of substrate) was reduced as described in the

general procedure. The crude product (401 mg; 99%) was crystallized from hexane affording analytically pure **38**, mp 76-81°C. IR(KBr) ν: 3065(w), 2985(m), 2920(w), 2815(w), 1690(s(br)), 1660(w), 1400(m), 1312/1305(m), 1200(m), 1118(m), 1098(s), 1050(m), 950(m), 908(s), 870(s), 818(m), 710(s), 680(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.46(1H,d,$J_{2,6}$=4.4Hz;H_2), 2.93(1H,br m;H_6), 3.37(3H,s;OCH_3), 4.08(2H,narrow m,J=1.7Hz;CH_2OCH_3), 4.73(1H,br s)/4.98(1H,br s)(H_1,H_7), 6.40(dd)/6.50(dd)(2H,ABXY system,J_{AB}=5.1Hz,J_{AX}=J_{BY}=1.5Hz;H_8,H_9), 7.41(1H,m;H_5). MS(70eV) m/e: 192(M^+), 160(-CH_3OH), 132(-CH_3OH,-CO), 104, 96, 91, 81, 68(furan$^+$), 53, 45(CH_2=OCH_3^+). (Found: C 68.67, H 6.30. Calc. for $C_{11}H_{12}O_3$: C 68.74, H 6.29%.)

4-Ethoxymethyl-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**39**).

The reduction of **16** (410 mg;1.64 mmol) was carried out as described in the *general procedure*, affording 273 mg (70%) of **39**. An analytically pure sample was obtained after crystallization from hexane, mp 54.5-55.5°C. IR(KBr) ν: 1688, 1640 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.22(3H,t,J=7Hz;OCH_2CH_3), 2.47(1H,d,$J_{2,6}$=4.8Hz;H_2), 2.94(1H,br m;H_6), 3.55(2H,q,J=7Hz; CH_2OCH_3), 4.13(2H,narrow m,J=1.7Hz;CH_2OEt), 4.74(1H,br s)/5.00(1H,br s)(H_1,H_7), 6.40(dd)/ 6.53(dd)(2H,ABXY system,J_{AB}=5.7Hz,J_{AX}=J_{BY}=1.5Hz;H_8,H_9), 7.44(1H,m;H_5). MS(70eV): 206(M^+), 177(-C_2H_5), 160(-C_2H_5OH), 147(-CH_2=OC_2H_5), 132(-C_2H_5OH,-CO), 94, 82, 68(furan$^+$). (Found: C 69.12, H 6.86. Calc. for $C_{12}H_{14}O_3$: C 69.89,H 6.84%.)

4-iso-*Propyloxymethyl*-exo-*10-oxatricyclo[5.2.1 0^{2,6}]deca-4,8-dien-3-one* (**40**).

The reduction of **17** (806 mg; 3.1 mmol) was carried out as described in the *general procedure*, yielding 637 mg (93%) of **40**. An analytically pure sample was obtained by crystallization from hexane, mp 68-70°C. IR(KBr) ν: 2990(m), 2970(m), 2850(m), 1690(s(br)), 1635(w), 1380(m), 1370(m), 1340(m), 1128(s), 1090(m), 1025(m), 950(s), 902(s), 872(s), 835(s), 702(s), 668(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.19(6H,d,6.1Hz;$OCH(CH_3)_2$), 2.47(1H,d,$J_{2,6}$=5Hz;H_2), 2.93(1H,br m;H_6), 3.63(1H,sept,J=6.1Hz;$OCH(CH_3)_2$), 4.13(2H,narrow m,J=1.7Hz;CH_2O-iPr), 4.74 (1H,br s)/4.99(1H,br s)(H_1,H_7), 6.41(dd)/6.53(dd)(2H,ABXY system,J_{AB}=5.7Hz,J_{AX}=J_{BY}=1.5Hz; H_8,H_9), 7.47(1H,m;H_5). MS(CI) m/e(%): 221(24;M+1$^+$), 161(25;-iPrOH), 153(49;-furan), 132(24; -iPrOH,-CO), 111(100;-furan,-C_3H_6), 93(44), 82(8), 69(7;furan+1$^+$). (Found: C 70.59, H 7.33. Calc. for $C_{13}H_{16}O_3$: C 70.89, H 7.32%.)

40 *by reduction of* **17** *with Lithium Aluminium Hydride*.

A solution of **17** (221 mg; 0.82 mmol) in dry ether (2 ml), was added slowly to a stirred suspension of LAH (27 mg; 0.7 mmol) in dry ether (5 ml). The resulting mixture was refluxed for 20 min and then allowed to cool to room temperature. After the addition of acetone (3 ml), the mixture was stirred for 10 min and subsequently concentrated in vacuo. Then dichloromethane (25 ml) and 3% HCl (10 ml) were added and work-up was carried out as in the DIBAL reduction, see the above

general procedure. This afforded 173 mg (*ca* 95%) of crude **40** as a thick, white oil. The ^{1}H-NMR spectrum of this material did not differ significantly from the ^{1}H-NMR spectra of the crude products obtained from the DIBAL reduction of **17**.

4-Phenylthiomethyl-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**41**).

To a solution of **22** (160 mg; 0.5 mmol) in freshly distilled benzene (20 ml) was added 0.5 mmol of DIBAL (0.5 ml of a 1 M solution in hexane). The resulting mixture was stirred under nitrogen during 3 days. Then water (15 ml), dichloromethane (15 ml) and 3% HCl (5 ml) were added and stirring was continued for 1 hr. After the usual work-up (see *general procedure*) the crude product was purified by flash chromatography (Al_2O_3/hexane-ethyl acetate mixtures ranging from 10:1 to 100% ethyl acetate). This afforded 110 mg (80%) of **41** as a solid. IR(CCl_4) ν: 3067/ 3068(m), 3000(m), 2955/2920(s), 2850(m), 1705(br s), 1478(s), 1438(s), 1335(s), 1308(s), 1148(m), 1090(s), 1050(m), 1025(m), 1010(m), 948(s), 910(s), 870(s), 690(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.43(1H,d,$J_{2,6}$=4.5Hz;H_2), 2.79(1H,m,;H_6), 3.60(2H,s;CH_2S), 4.59(1H,s)/4.97(1H,s)(H_1,H_7), 6.35(dd)/6.44(dd)(2H,ABXY system,J_{AB}=5.6Hz,J_{AX}=J_{BY}=1.6Hz;H_8,H_9), 7.12(1H,br s;H_5), 7.24(5H,br s;ArH). ^{13}C-NMR($CDCl_3$) δ: 27.98(C_{11}), 46.62/51.12(C_2,C_6), 78.56/80.20(C_1,C_7), 126.46/128.70/130.28 (ArC), 135.44/136.90(C_8,C_9), 145.19(C_4), 158.03(C_5), 205.77(C_3). MS(EI) m/e(%): 270(8;M$^+$), 202(34;-furan), 161(100;-PhS), 160(48;-PhSH), 132(30), 109(17;PhS$^+$), 110(10;PhSH$^+$), 93(59;-furan,-PhS), 77(20;Ph$^+$), 68(8;furan$^+$). HRMS(EI) m/e: 270.0721 (calcd.for $C_{16}H_{14}O_2S$ (M$^+$): 270.0715). (Found: C 70.47, H 5.15. Calc. for $C_{16}H_{14}O_2S$: C 71.08, H 5.22%.).

41 *by reduction of* **22** *with Lithium Aluminium Hydride*.

The reduction of **22** (598 mg; 1.8 mmol) with LAH (20 mg; 0.53 mmol) was carried out similar to the LAH reduction of **17**, the only difference being the reaction time. Instead of only 20 min of reflux, 30 min of reflux were applied followed by overnight stirring at room temperature. The crude product (102 mg) was purified by flash chromatography over Al_2O_3 using hexane-ethyl acetate (1:3) as the eluent. This afforded 68 mg (14%) of **41**.

41 *by reduction of* **22** *with Red-Al* ($NaAlH_2(OCH_2CH_2OCH_3)_2$).

To an ice cooled solution of **22** (188 mg; 0.60 mmol) in dry benzene was added Red-Al (0.19 ml of a 3.44 M solution in toluene). The resulting mixture was stirred for 3 hrs at room temperature. Then water (10 ml), 3% HCl (5 ml) and dichloromethane (10 ml) were added and stirring was continued for 1.5 hr. Subsequent work-up as usual (see *general procedure*), followed by flash chromatography (Al_2O_3/hexane-ethyl acetate (1:2)), afforded 105 mg (65%) of **41**.

4-Benzylthiomethyl-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**42**).

The reduction of **23** (492 mg; 1.5 mmol) with DIBAL (1.5 mmol) to give **42**, was carried out

in the same way as the DIBAL reduction of **22** (see **41**, first described procedure). Purification of the crude product by flash chromatography (SiO_2/hexane-ethyl acetate (1:1)) afforded 340 mg (80%) of pure (^{1}H-NMR) **42**, as a colourless oil. IR(CCl_4) ν: 1708(s), 1308(m), 1090(m), 949(m), 911(m), 870(m), 700(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.42(1H,d,$J_{2,6}$=4.8Hz;H_2), 2.84(1H,m;H_6), 3.13(2H,d, J=1.2Hz;CH_2Ph), 3.69(2H,s;CH_2SBz), 4.69(1H,s)/4.96(1H,s)(H_1,H_7), 6.38(dd)/6.49(dd)(2H,ABXY system,J_{AB}=5.8Hz,J_{AX}=J_{BY}=1.2Hz;H_8,H_9), 7.27(6H,br s;H_5+ArH). MS(EI) m/e(%): 284(5;M^+), 216(6;-furan), 160(25;-BzSH), 132(25), 123(47;BzS^+), 94(40), 91(100;Bz^+), 84(11), 77(12;$C_6H_5^+$), 68(10;furan$^+$). HRMS(EI) m/e: 284.0873 (calc. for $C_{17}H_{16}O_2S$ (M^+): 284.0871).

5-Methyl-exo-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**43**).

To a solution of **31** (1.40 g; 7.3 mmol) in dry benzene (40 ml), cooled with crushed ice/salt and under nitrogen, was added 5 ml of a 1.6 M solution of MeLi in hexane. The reaction mixture was stirred for 1.5 hr. Then 3% HCl (30 ml) and dichloromethane (30 ml) were added and stirring was continued for 2 hrs. The ice bath was removed and the mixture was allowed to reach room temperature. The aqueous layer was separated and extracted with dichloromethane (3x). The combined organic solutions were washed successively with cold dilute $NaHCO_3$ (3x) and water (2x) and dried over $MgSO_4$. Removal of the solvents under reduced pressure left 1.15 g (97%) of **43**, as a white solid. This material was sufficiently pure for use in a following experiment (When MeMgI instead of MeLi was used in this synthesis the yield was much lower and the crude product had to be purified by chromatography). An analytically pure sample was obtained by crystallization from hexane-ethyl acetate (3:1), mp 70.0-71.8°C. IR(KBr) ν(s): 2987, 1680(br), 1617, 1430, 1376, 1330, 1288, 1270, 1200/1195, 1012, 950, 930, 900/895, 870, 855, 835, 810, 720, 668, 610 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.17(3H,br s;CH_3), 2.46(1H,d,$J_{2,6}$=4.8Hz;H_2), 2.81(1H,d,$J_{6,2}$=4.8Hz;H_6), 4.81(1H,br s)/4.98(1H,br s)(H_1,H_7), 5.94(1H,m;H_4), 6.44(2H,m;H_8,H_9). MS(EI) m/e(%): 162(76;M^+), 134(10,-CO), 133(17), 105(15), 94(13;-furan), 91(20), 77(11), 68(100;furan$^+$), 66(31;-CO,-furan), 65(12), 40(13), 39(35). (Found: C 73.87, H 6.09. Calcd. for $C_{10}H_{10}O_2$: C 74.06, H 6.21%.)

4-Methoxymethyl-5-methyl-exo-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**45**).

A solution of 433 mg of a 1:1 mixture of **15** and **20** (1.9 mmol of substrate) in dry benzene (20 ml) was treated with 1.5 ml of a 1.6 M solution of MeLi in ether in exactly the same way as described for the synthesis of **43**. This afforded **45** as a white solid (337 mg; 86%). Crystallization from hexane-ethyl acetate (1:1) gave an analytically pure sample, mp 84-86°C. IR(KBr) ν(s): 3070, 2922, 2885, 1685, 1640, 1395, 1323, 1310, 1092, 1065, 1008, 950, 930, 908, 875, 838, 802, 725, 645, 620 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.23(3H,s;C(5)-CH_3), 2.44(1H,d,$J_{2,6}$=6.8Hz;H_2), 2.77(1H,d,$J_{6,2}$=6.8 Hz;H_6), 3.32(3H,s;OCH_3), 4.07(2H,s;CH_2OCH_3), 4.82(1H,s)/5.00(1H,s)(H_1,H_7), 6.48(2H,m; H_8,H_9). MS(EI) m/e(%): 206(5;M^+), 174(64;-CH_3OH), 146(100;-CH_3OH,-CO), 138(18;-furan), 131 (31),

117(14), 110(56), 109(20), 107(27), 95(64), 91(15), 79(58), 78(26), 77(30), 68(47; furan$^+$), 67(35), 45(45;$CH_2OCH_3^+$), 39(41). (Found: C 69.87,H 6.87. Calc. for $C_{12}H_{14}O_3$: C 69.89, H 6.84%.).

1.7 References and notes

1. This chapter was recently published in Tetrahedron, **1989**, 45, 7149. Parts not included in the Tetrahedron article are inserted at the end of the chapter under the heading Addendum.
2. (a) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic, New York, 1977; (b) Roberts, S. M.; Scheinmann, F. *New Synthetic Routes to Prostaglandins and Thromboxanes*; Academic, New York, 1982; (c) Paquette, L. A. *Recent Synthetic Developments in Polyquinane Chemistry*; Topics in Current Chemistry 119; Springer, Berlin, 1984; (d) Wiel, J. B.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1979**, II-273; (e) Smith III, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855.
3. (a) Maier, G.; Franz, L. H.; Hartan, H. G.; Lanz, K.; Reisenauer, H. P. *Chem. Ber.* **1985**, *118*, 3196; (b) Ogliaruso, M. A.; Romanelli, M. G.; Becker, E. I. *Chem. Rev.* **1965**, *65*, 261; (c) Onishchenko, A. S. *Diene Synthesis*; Israel Program for Scientific Translations; Oldbourne, London, 1964; p 330; (d) Chapman, O. L.; McIntosh, C. L. *J. Chem. Soc., Chem. Commun.* **1971**, 770.
4. (a) Bugel, J. P.; Ducos, P.; Gringore, O.; Rouessac, F. *Bul. Soc. Chim. Fr.* **1972**, 4371; (b) Oda, M.; Kanao, Y.; Kasai, M.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1977**, *45*, 2497; (c) Chapman O. L.; Hess, T. C. *J. Org. Chem.* **1979**, *44*, 962; (d) Verlaak, J. M. J. *Ph.D. Thesis*, University of Nijmegen, Febr. 1983.
5. (a) Klunder, A. J. H.; Bos, W.; Verlaak J. M. J.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4553; (b) Klunder, A. J. H.; Huizinga, W. B.; Sessink, P. J. M.; Zwanenburg, B. *Ibid.* **1987**, *28*, 357; (c) Klunder, A. J. H.; Crul, M. J. F. M.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *Ibid.* **1987**, *28*, 3147; (d) Lange, J. H. M.; Klunder, A. J. H.; Zwanenburg, B. *Ibid.* **1989**, *30*, 127.
6. (a) Klunder, A. J. H.; Bos, W.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4557; (b) Verlaak, J. M. J.; Klunder, A. J. H.; Zwanenburg, B. *Ibid.* **1982**, *23*, 5463; (c) Klunder, A. J. H.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *Ibid.* **1987**, *28*, 1329.
7. (a) Oda, M.; Kawanishi, S. *Jap. Patent* 53-127495, 1978; *Chem. Abstr.* 90, P137666z. We thank prof. dr. M. Nakagawa for translating the relevant pages of this patent; (b) Oda, M.; Kasai, M.; Kitahara, Y. *Chem. Lett.* **1977**, 307; (c) Wolfbeis, O. S. *Monatsh. Chem.* **1981**, *112*, 369.

8. (a) ref 2c, p 556 ; (b) Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6893; (c) Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999; (d) DePuy, C. H.; Zaweski, E. F. *J. Am. Chem. Soc.* **1959**, *81*, 4920; (e) Jurczak, J.; Koźluk, T.; Filipek, S.; Eugster, C. H. *Helv. Chim. Acta* **1983**, *66*, 222; Jurczak, J.; Kawczyński, A. L.; Koźluk, T. *J. Org. Chem.* **1985**, *50*, 1106; (f) Fox, M. A.; Cardona, R.; Kiwiet, N. J. *J. Org. Chem.* **1987**, *52*, 1469.
9. Hesse, M.; Meier, H.; Zeeh, B. *Spektroskopische Methoden in der organischen Chemie*, 3. Auflage; Georg Thieme: Stuttgart-New York, 1987; p 109.
10. (a) Rasmussen, R. S.; Tunnicliff, D. D.; Brattain, R. R. *J. Am. Chem. Soc.* **1949**, *71*, 1068; (b) Dolphin, D.; Wiek, A. *Tabulation of infrared spectral data*; Wiley & Sons: New York, 1977; pp 15, 180; (c) Rao, C. N. R. *Chemical Applications of infrared spectroscopy*; Academic: New York-London, 1963; pp 186, 193, 210.
11. Hünig-Märkl-Sauer *Integriertes Organisches Praktikum*; Verlag Chemie: Weinheim-New York, 1979; p 373.
12. (a) Hellmann, H.; Müller, K. *Chem. Ber.* **1965**, *98*, 638; (b) See Addendum 1, at the end of this chapter, about a derailment of this condensation.
13. Meerwein, H.; Hinz, G.; Hofmann, P.; Kroning, E.; Pfeil, E. *J. Prakt. Chemie* **1937**, *147*, 257; Meerwein, H. In *Organic Syntheses*; Wiley: New York, 1966; Vol. 46, p 113.
14. Houwen-Claassen A. A. M.; Klunder, A. J. H.; Zwanenburg, B.; Beurskens, P. T.; Moers, F. G.; Beurskens, G., submitted for publication.
15. Kowalski, C. J.; Fields, K. W. *J. Org. Chem.* **1981**, *46*, 197.
16. (a) *The Chemistry of Sulphones and Sulphoxides*, Patai, S.; Rappoport, Z.; Stirling, C. J. M. Eds.; Wiley: New York; 1988; (b) Durst, T. In *Comprehensive Organic Chemistry*; Barton, D. H. R.; Ollis, W. D. Eds.; Pergamon, 1979; Vol. 3, pp 171-195.
17. Ogura, K.; Iihama, T.; Kiuchi, S.; Kajiki, T.; Koshikawa, O.; Takahashi, K.; Iida, H. *J. Org. Chem.* **1986**, *51*, 700.
18. Padwa, A.; Bullock, W. H.; Dyszlewski, A. *Tetrahedron Lett.* **1987**, *28*, 3193.
19. Barre, V.; Uguen, D. *Ibid.* **1987**, *28*, 6045.
20. (a) Strating, J. In *Organic Sulfur Compounds* I, Kharash, N., Ed.; New York, 1961; pp 146-153; (b) Bordwell, F. G.; Cooper, G. D. *J. Am. Chem. Soc.* **1951**, *73*, 5184; (c) Meyers, C. Y. *Tetrahedron Lett.* **1962**, *24*, 1125.
21. March, J. *Advanced Organic Chemistry*, 2nd ed; McGraw Hill: New York, 1977; pp 325-331.
22. (a) Stork, G.; White, W. N. *J. Am. Chem. Soc.* **1956**, *78*, 4609; (b) Kagan, H. B. *Organische Stereochemie*; Georg Thieme, 1977; p 174; (c) Anh, N. T. *Die Woodward-Hofmann-Regeln und ihre Anwendung*; Verlag Chemie, 1972; p 207.
23. Julia, M.; Nel, M.; Uguen, D. *Bull. Soc. Fr.* **1987**, 487.
24. Smith III, A.B.; Wexler, B. A.; Slade, J. S. *Tetrahedron Lett.* **1980**, *21*, 3237.

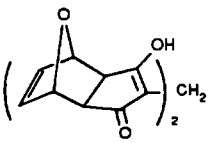
25. (a) Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299; (b) Grieco, P. A.; Zabrowski, D. A.; Lis, R.; Finn, J. *J. Org. Chem.* **1984**, *49*, 1454.
26. (a) Poppelsdorf, F.; Holt, S. J. *J. Chem. Soc.* **1954**, 1124; (b) Richer, J.-C.; Perelman, D. *Can. J. Chem.* **1966**, *44*, 2003; (c) Kirk, D. N.; Petrow, V. *J. Chem. Soc.* **1962**, 1091; (d) Smissmann, E. E.; Sorensen, J. R.; Albrecht, W. A.; Creese, M. W. *J. Org. Chem.* **1970**, *35*, 1357.
27. A more detailed analysis of this reaction is presented in Addendum 2, at the end of this chapter.
28. (a) Gannon, W. F.; House, H. O. In *Organic Syntheses*; Wiley: New York, 1973; Coll. Vol. V, p 294; (b) Funk, R. L.; Vollhardt, K. P. *Synthesis* **1980**, 118; (c) Gill, M.; Herlt, A. J.; Richards, R. W. *Tetrahedron* **1982**, *38*, 3527.
29. (a) Wenkert, E.; Strike, D. P. *J. Am. Chem. Soc.* **1964**, *86*, 2044; (b) Stiles, M.; Longroy, A. L. *J. Org. Chem.* **1967**, *32*, 1095.
30. (a) Winterfeldt, E. *Synthesis* **1975**, 617; (b) Wilson, K. E.; Seidner, R. T.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1970**, 213.
31. Houwen-Claassen, A. A. M.; Klunder, A. J. H; Vriends, J. J. T.; Zwanenburg, B., submitted for publication.
32. Smits, J. M. M.; Beurskens, P. T.; Smits, J. R. M.; Parthasarathi, V.; Houwen-Claassen, A. A. M.; Klunder, A. J. H. *J. Cryst. Spectrosc. Res.* **1988**, *18*, 1.
33. House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, California, 1972; p 67.
34. Schöllkopf, U. *Methoden zur Herstellung und Umwandlung von lithium-organischen Verbindungen,* Houben-Weyl XIII/1, 4th edition (1970), p 87-253.
35. The C-5 alkylated derivatives of sulphone **14**, such as **44**, have exceptional properties. Details about their preparation and chemistry will be given in a separate paper, see ref 31.
36. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
37. Cyclo-penten-1,4-dione was prepared in two steps starting from cyclopentadiene (50% overall), see (a) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876; (b) Rasmussen, G. H.; House, H. O.; Zaweski, E. F.; DePuy, C. H. *Org. Synth. Coll. Vol.* V, (1973), p 324.
38. Oae, S.; Takata T.; Kim, Y. H. *Tetrahedron* **1981**, *37*, 37.

1.8 Addendum 1

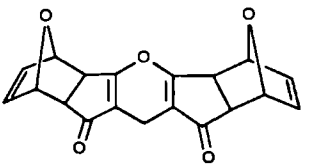
Complications in the tosylmethylation of **7**

The trickiness of the tosylmethylation, described in par. 1.3 (Scheme 3), is strikingly demonstrated by the following incident. On one occasion the sulphone was not isolated, as usual, immedi-

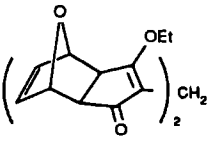
ately after the reaction but left overnight in excess of water to remove the last traces of DMF and acetic acid. After work-up, the IR and ^{1}H-NMR spectra of the crude product revealed that neither sulphone **13** nor unreacted **7** was obtained. In the IR spectrum the characteristic absorption of the sulphone group at 1135 cm^{-1} was lacking as were the signals for the tosyl group at δ 7.72 and 7.37 ppm in the ^{1}H-NMR spectrum. Singlet signals at δ 6.4 and 4.7 ppm showed that the isolated compound still possessed the 10-oxatricyclic skeleton related to **7**. The absence of a signal at δ 5.0 ppm, characteristic for the C-4 proton of **7**, pointed to a derivative in which C-4 is substituted. Furthermore, the IR spectrum suggested a hydrogen bonded enolized 1,3-dicarbonyl unit. Attempts to acylate the presumed enolic hydroxyl group with acetic anhydride and triethylamine, using DMAP as a catalyst failed. Instead a polycyclic compound was obtained, to which on the basis of spectral data structure **47** was assigned. Most likely its precursor had been bis-adduct **46**, which upon



46



47

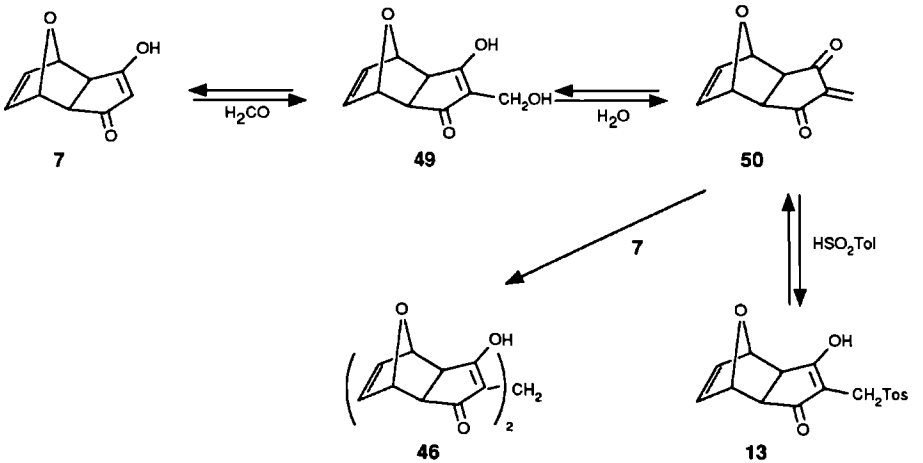


48

reaction with acetic anhydride, DMAP and triethylamine had been converted into this internal vinylogous anhydride **47**. The spectral data of the unknown product were compatible with structure **46**. To confirm the structure of **46**, O-alkylation with Meerwein's salt was attempted. This indeed provided the expected bis-ethoxy derivative **48**.

The formation of **46** can be rationalized by considering the mechanism of the tosylmethylation of **7** (Scheme 14). The first step of this reaction involves an acid catalyzed condensation of **7** with formaldehyde to give the 4-hydroxymethyl derivative **49**. Subsequent dehydration leads *in situ* to the exocyclic methylene derivative **50**, which will be highly susceptible to Michael addition and will react readily with sulphinic acid to afford the sulphone **13**. On standing in water **13** undergoes a retro-Michael reaction with the elimination of sulphinic acid, to give the reactive intermediate **50**. This reaction is probably catalyzed by a trace of dimethylamine originating from a residual amount of DMF and acetic acid (dimethylamine at least will have assisted in dissolving the sulphone). Similar eliminations in hydroxylic media have been reported for Mannich bases, derived from 1,3-diketones[39]. Under the applied aqueous conditions **50** equilibrates via **49** with the initial substrate **7**. The latter, being a much more reactive nucleophile than sulphinic acid, reacts on its turn in a Michael fashion with enone **50** to form the bis-adduct **46**. Such bis-adducts are often found in base catalyzed aldol or related condensations if an excess of the active methylene compound is applied[39-41]. The formation of **46** from **13** demonstrates the reactive nature of the intermediate 4-hydroxymethyl substituted 10-oxatricyclodecadienone **49**. The reactivity of this

Scheme 14



compound apparently impedes its isolation and it explains the failure of the direct hydroxymethylation of **7** with formaldehyde.

Experimental section

4,4'-Methylen-bis-5-hydroxy-exo-*10-oxatricyclo[5.2.1.$0^{2,6}$]deca-4,8- dien-3-one* (**46**).

Paraformaldehyde (1.52 g; 50.5 mmol of formaldehyde), freshly distilled DMF (60 ml), acetic acid (12 ml), sodium p-toluenesulphinate (1.16 g; 33.5 mmol) and **7** (5.14 g; 31.3 mmol) were treated as described for **13**. After filtration and subsequent washing of the precipitated product the crude solid was suspended in water to remove the last traces of DMF and acetic acid. After 16 hrs the material was filtered and subsequently dried in a desiccator during 5 days, yielding 3.44 g (*ca* 65%) of **46**. The poor solubility of the product prevented further purification. IR(KBr) ν: 3060-2740/ 2740-2360 (two broad absorption bands(m)) and 1570(s(br))(hydrogen bonded enolized 1,3-diketone), 1370(s(br)), 1290(m), 1268(m), 1150(m), 1012(m), 917(m), 883(m), 848(m), 727(m) cm^{-1}. ^{1}H-NMR(DMSO-d_6) δ: 2.38(br s)/2.51(br s)/2.68(br s)(>6H;CH_2,H_2,H_6,H_2',H_6', partially obscured by methyl protons of incomplete deuterated DMSO), 3.98(br s;trace of H_2O in DMSO), 4.76(4H,br s;H_1,H_7,H_1',H_7'), 6.44(4H,br s;H_8,H_9,H_8',H_9').

4,4'-Methylen-5,5'-oxy-bis-exo-*10-oxatricyclo[5.2.1.$0^{2,6}$]deca-4,8 -dien-3-one* (**47**).

To a stirred suspension of **46** (238 mg: 0.7 mmol) in dichloromethane (10 ml) was added a mixture of triethylamine (310 mg; 3.0 mmol), acetic acid anhydride (339 mg; 3.3 mmol) and DMAP

(16 mg; 0.13 mmol). The resulting clear solution was stirred for 2 hrs and then diluted with 20 ml of water. The aqueous layer was extracted with dichloromethane (3x20 ml). The combined extracts were washed successively with 3% HCl (3x10 ml) and water (4x15 ml) and subsequently dried over $MgSO_4$. The solvent was removed in vacuo leaving 299 mg of a crude mixture which, as indicated by its ^{1}H-NMR spectrum, hardly contained any acylated product. Purification by TLC (Al_2O_3/ethyl acetate) was attempted on 150 mg of the crude product, but failed. Crystallization from ethanol of the remaining part afforded a pale yellow powder, decomposing at about 220°C. No attempts were made to obtain an analytically pure sample. IR(KBr) ν: 1700(s;C=O), 1670(s;C=O), 1625(m (shoulder);C=COR), 1618(m;C=COR), 1380(s), 1225(m), 1198(s), 1185(m), 880(m) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.66(2H,d,J=5Hz;H_2,$H_{2'}$), 2.87(br s)/2.96(shoulder)(4H;H_6,$H_{6'}$,CH_2), 4.98(s)/5.06(s) (4H;H_1,H_7,$H_{1'}$,$H_{7'}$), 6.49(4H,br s;H_8,H_9,$H_{8'}$,$H_{9'}$). The assignment of the structure of **47** followed from comparison of its spectral data with the ^{1}H-NMR and IR spectra of **46** and **48**. The amorphness of the crystallized product, combined with the double set of IR signals at 1700/1625 and 1670/1618 cm^{-1} suggested strongly a mixture of both diastereomers.

4,4'-Methylen-bis-5-ethoxy-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-di en-3-one* (**48**).

To a suspension of **46** (191 mg; 0.56 mmol) in dichloromethane (12 ml) was added 871 mg (8.7 mmol) of triethylamine. The mixture was stirred for a few min. during which it turned into an almost clear solution. Then 6 ml of a 1M solution of triethyloxonium tetra fluoroborate[13] in dichloromethane was added and stirring was continued overnight. After the addition of 20 ml of water, the mixture was extracted with dichloromethane (3x10 ml). The combined extracts were washed with water (3x15 ml) and dried over $MgSO_4$. Removal of the solvent in vacuo left 155 mg of a white solid, being most probably a mixture of both diastereomers (double triplet of ethoxy groups at 1.35 ppm in the ^{1}H-NMR spectrum). Crystallization from ethyl acetate, followed by recrystallization from ethanol afforded only one diastereomer as colourless needles, decomposing at 217°C. IR(KBr) ν: 1678(s(br);C=O), 1618(s(br);C=COEt), 1380(s), 1355(m), 1330(s), 1280(s), 1260(m), 1018(m), 872(m), 720(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.40(6H,t,J=7.2Hz;2xOCH$_2$C$\underline{H}_3$), 2.44(2H,d,J=5.5Hz; H_2,$H_{2'}$), 2.78(2H,d,J=5.5Hz;H_6,$H_{6'}$), 3.08(2H,s;CH_2), 4.09-4.60(4H,m,ABX$_3$system; 2xOC$\underline{H}_2$CH$_3$), 4.86(2H,s)/4.98(2H,s)(H_1,H_7,$H_{1'}$,$H_{7'}$), 6.44(4H,s;H_8,H_9,$H_{8'}$,$H_{9'}$). MS(CI) m/e(%): 397(67;M+1$^+$), 329(24;-furan), 260(7;-furan,-(furan+1)), 137(38), 111(34), 89(81), 69(61;(furan+1)$^+$), 68(100; furan$^+$), 47(25). (Found: C 68.83, H 6.06. Calc. for $C_{23}H_{24}O_6$: C 69.68, H 6.10%.)

References

39. Bolte, M. L.; Crow, W. D.; Yoshida, S. *Austr. J. Chem.*, **1982**, 1421.
40. (a) Hellmann, H.; Aichinger, G. *Chem.Ber.*, **1959**, 2122; (b) Hellmann, H.; Aichinger, G.; Wiedemann, H.-P. *Ibid.*, **1959**, 35.

41. Smissmann, E. E.; Sorensen, J. R.; Albrecht, W. A.; Creese, M. W. *J.Org.Chem.*, **1970**, 1357.

1.9 Addendum 2

The reactions of **29** *and* **30** *with Meerwein's reagent*

The ^{1}H-NMR spectra of the crude reaction mixtures, resulting form the reactions of the thioethers **29** and **30** (Scheme 9) with Meerwein's reagent, revealed that, in addition to the respective O-alkylated derivatives **22** and **23**, two other compounds were formed, *viz.* a polycyclic product in which the thioether group was lacking and the already mentioned ethyl phenyl- or benzyl-ethyl sulphide. The polycyclic compound resisted purification and isolation due to its polar character. The spectral data suggested for this compound the dimeric structure of **46**. Its occurrence was established unambiguously by treating the crude reaction product, obtained from **30**, with Meerwein's reagent (see below). This afforded the ethylated bis-adduct **48**.

The formation of **46** in this alkylation reaction of **29** and **30** can be understood in essentially the same way as its formation during the hydrolysis of sulphone **13** (Scheme 14). The strong alkylating power of Meerwein's reagent causes not only alkylation of oxygen but also of sulphur[13]. Although in these reactions the nucleophilicity of oxygen was enhanced through deprotonation by triethylamine, some S-alkylation could apparently not be avoided. This S-alkylation of **29** and **30** leads to the corresponding sulphonium salts, which rapidly undergo an elimination reaction to form the exocyclic methylene compound **50** and the respective sulphides. Water addition and equilibration lead then to the bis-adduct **46**. Clearly, ethylation of **29** and **30** with Meerwein's reagent is not the appropriate method to obtain the 5-ethoxy derivatives of **22** and **23**.

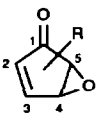
Experimental section

The crude product resulting from the Meerwein's reaction of **30** was treated with Meerwein's reagent as described for the preparation of **48** from **46** (*vide supra*). After work-up a brown tinted oil was obtained, from which on treatment with a small amount of methanol and ether a white solid precipitated. The ^{1}H-NMR and IR spectra of this precipitate were in full agreement with those of the ethylated bis-adduct **48**.

CHAPTER 2: SYNTHESIS OF CYCLOPENTADIENONE EPOXIDES FROM 10-OXATRICYCLODECADIENONES[1].

2.1 Introduction

The unique combination of an epoxide ring, a vinyl system and a carbonyl group within a compact, small ring system makes the cyclopentadienone epoxides **1** a fascinating class of compounds. Mutual interaction of these functional groups will be inevitable and special chemical behaviour may thus be expected. As these functionalities and their combinations all are susceptible for both nucleophilic and electrophilic attack, a well defined choice of reagents and reaction conditions will presumably be necessary to attain chemo- and regioselectivity.



1

In the literature so far only a few members of this class of compounds have been described. Especially their photochemistry has been studied in detail. Tri- and tetraphenyl substituted cyclopentadienone epoxides have been observed to equilibrate with pyrylium oxides on irradiation[3,4]. Photochemically induced rearrangements to 2-pyrones have been reported for the parent compound **1** (R=H)[5] and for the alkyl- and phenylsubstituted compounds **1** (R=2,5-dimethyl; R=3,4-diphenyl; R=2,3,4,5-tetraphenyl)[6-9]. The frequently postulated intermediacy of cyclopentadienone epoxides in the photo-isomerisation of 4-pyrones to 2-pyrones has unambiguously been established for **1** (R=2,5-dimethyl)[6]. Moreover, phenyl-, alkyl- and otherwise substituted cyclopentadienone epoxides have been found to rearrange to 2-pyrones on heating[3,5,10-12]. The parent compound **1** (R=H) has been reported to decompose in acidic or basic media[5]. Only a few reports mention a synthetic application of these epoxides[2,13,14].

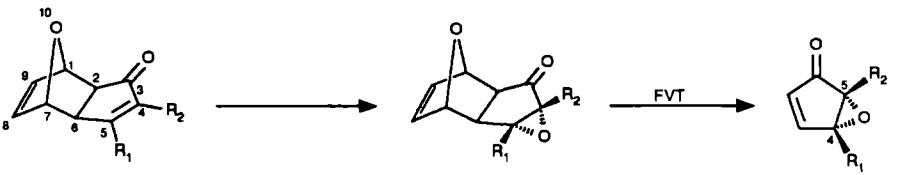
It is clear that a systematic study of cyclopentadienone epoxides was hampered by the difficult accessibility of these substrates. A general entrée to these compounds not only would allow a systematic study of their chemical behaviour but would also have a considerable synthetic impact, as these epoxides are potentially valuable synthons for the preparation of highly oxygenated cyclopentenoid natural products. Their apparent chemical sensitivity presumably will prevent a general preparation using normal chemical procedures. But, thanks to the development of advanced

thermolysis techniques[15] neutral synthetic methods are now available, which can be applied in preparing epoxides of type **1**.

In the preceding chapter we presented our strategy towards cyclopentenones via Flash Vacuum Thermolysis (FVT) of appropriately functionalized tricyclic precursors. We selected 10-oxatricyclodecadienones **2** as potential synthons for the FVT mediated synthesis of substituted cyclopentadienone epoxides and described *in extenso* the preparation of such tricyclic enones from the Diels-Alder adduct of furan and cyclopentene-1,4-dione.

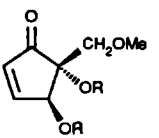
In this chapter we focus on the utilisation of these oxatricyclodecadienones for the synthesis of 4- and/or 5-substituted cyclopentadienone epoxides **4**, according to the pathway indicated in Scheme 1.

Scheme 1



2 **3** **4**

To illustrate the synthetic potential of such epoxides in the field of natural product synthesis, we here also describe the selective cleavage of the epoxide ring of **4** (R_1=H; R_2=CH_2OMe) leading to the *epi*-pentenomycin analogues **5a,b**.



5a R=H

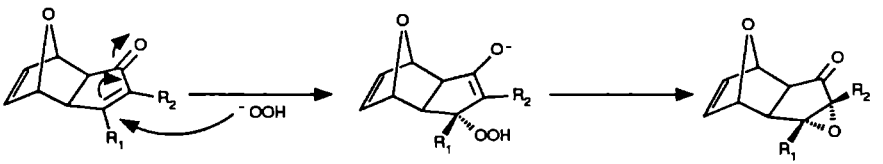
5b R=Ac

2.2 Results and Discussion

Alkaline epoxidation of 10-oxatricyclodecadienones **2**.

The ultimate conversion of the tricyclic enones **2** into the epoxides **4** involves two transformations (Scheme 1). The first one is a regioselective epoxidation of the electron poor double bond between C-4 and C-5 of the substrates **2**, to afford the corresponding epoxy ketones **3**. This epoxidation was carried out with alkaline hydrogen peroxide, which is the common reagent for such a nucleophilic epoxidation (Scheme 2). Yields were generally close to quantitative, see Table 1.

Scheme 2



2 3

Some attention had to be payed to the amount of hydrogen peroxide in the epoxidation of the thioethers **2e** and **2f**. Too great an excess presumably also brings about some oxidation on sulphur, as is suggested by the lower yields obtained for **3e** and **3f**.

Table 1

substr. no.	R_1	R_2	product no.	yield[a] [%]
2a	H	H	**3a**	94
2b	H	CH_2OMe	**3b**	98
2c	H	CH_2OEt	**3c**	95
2d	H	CH_2OiPr	**3d**	94
2e	H	CH_2SPh	**3e**	60[b]
2f	H	CH_2SBz	**3f**	77[b]
2g	Me	H	**3g**	93
2h	Me	CH_2OMe	**3h**	100

a. Except for **3e** and **3f** the yields given refer to crude products (purity *ca* 95%)
b. Yield after flash chromatography.

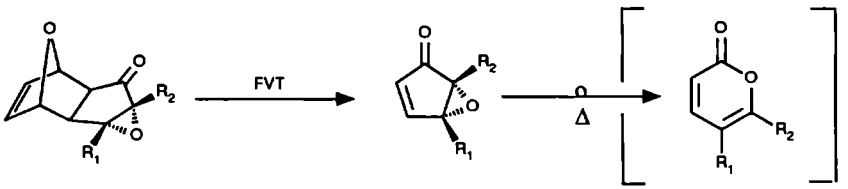
The alkaline epoxidation turned out to be a stereospecific process. In all cases only one diastereomer was formed as was indicated by melting points, ^{1}H-NMR and capillary GC data. In conformity with the stereochemistry postulated[2,5,17-19] and found[16,20] for such tricyclic enones, the peroxide anion is expected to enter stereospecifically from the least hindered side of the molecule, *anti* to the oxa-bridge, adding in a conjugate fashion to the enone moiety of **2** (Scheme 2). In the products **3** the epoxide ring will thus be orientated as indicated in Scheme 2. To remove any doubts about this mechanism and about the final structure of the products, epoxide **3b** was subjected to an X-Ray analysis. This structure determination indeed confirmed the anticipated *exo*-configuration of the epoxide ring[21]. It is most likely that for the oxatricyclodecadienones **2** the steric bulk and the

electronegative nature of the oxa-bridge cooperate in the steric approach control of incoming nucleophiles.

Flash vacuum thermolysis of the 10-oxatricyclodecadienone epoxides **3**.

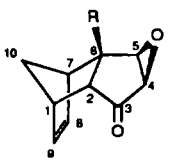
The second step in the route to cyclopentadienone epoxides **4** is a retro Diels-Alder reaction of the furan adducts **3** (Scheme 1). In view of the aromatic nature of furan, moderate cycloreversion temperatures were anticipated. We hoped that at these temperatures the thermally induced rearrangement of the epoxides **4** to the corresponding 2-pyrones **6** would not take place (Scheme 3).

Scheme 3



3 **4** **6**

Thermal cycloreversions can be accomplished under various conditions. We chose to employ the FVT technique since in previous work[12,13,17] excellent results had been obtained for the FVT cycloreversions of the 10-carbon analogues **7**. It should be noted however, that other techniques may



7

be applied as well to accomplish the thermal cycloreversion of the 10-oxatricyclodecadienone epoxides **3**. This is demonstrated by Oda et al[22] who performed the thermolysis of **3a** to afford **4a** by sublimation under reduced pressure (300 mm Hg) in a short path distillation apparatus at 120~140°C. In our FVT set-up[23] (quartz pyrolysis tube (16x1.3 cm), P~10^{-2} mbar) the thermal conversion of **3a** was brought about at 375°C and 0.05 mbar, affording the parent cyclopentadienone epoxide **4a** in 90% yield as the sole product (see Table 2, entry 1). Lower temperatures resulted in incomplete or no conversion, while higher temperatures soon led to substantial amounts of pyrone **6a**. Already at 425°C a 1:1 mixture of **4a** and **6a** was obtained in 90% total yield (compare entry 1 and 1*, respectively). The thermolyses of the 4-substituted tricyclodecadienone epoxides **3b-f** were carried out

using the same equipment. To avoid undesired pyrone formation small adjustments in temperature and pressure had to be made, but, having established those optimum conditions, the epoxides **4b,c,e,f** were obtained in virtually quantitative yields (entry 2,3,5,6). For **3d** the reaction conditions were not optimized. We expect however, that a thermolysis temperature between 300° and 340°C will give **4d** as the only product (compare entries 2,3,5 and 6). With the equipment indicated, the pyrone formation could not be avoided during the syntheses of the 4-substituted epoxides **4g** and **4h** from **3g** and **3h**, respectively. To minimize the pyrone production, a longer pyrolysis tube (25x1.3 cm) and oven were chosen, while the vacuum was kept at the same level. The longer contact time resulting therefrom allowed a lower thermolysis temperature, however, not low enough to avoid the pyrone formation completely. The conditions affording optimum yields for **4g** and **4h** are included in Table 2, *viz.* entry 7 and 8, respectively. The high yields obtained in the above thermolyses demonstrate that furan derived adducts, such as **2**, are excellent precursors for an FVT mediated synthesis of cyclopentadienone epoxides.

Table 2

		thermolysis conditions		composition of the pyrolysate[b]					
	substr.	P	T_2/T_1[c]	products				substr.	
entry[a]	no.	[mbar]	[°C]	no.	[%]	no.	[%]	no.	[%]
1.	**3a**	0.05	375/75	**4a**	90	**6a**	-	**3a**	<5
1*.		0.06	425/75		45		45		-
2.	**3b**	0.06-0.08	360/90	**4b**	90	**6b**	<5	**3b**	<5
3.	**3c**	0.05	340/90	**4c**	≥90	**6c**	<5	**3c**	-
3*.		0.06	525/110				84		-
4.	**3d**	0.05-0.06	350/70[d]	**4d**	75[d]	**6d**	25[d]	**3d**	-
5.	**3e**	0.2	300/135	**4e**	95	**6e**	-	**3e**	-
6.	**3f**	0.2	300/135	**4f**	95	**6f**	-	**3f**	-
7.	**3g**	0.09-0.15	355/65	**4g**	85	**6g/6g***	15	**3g**	-
8.	**3h**	0.08-0.09	310/70	**4h**	84	**6h**	11	**3h**	<5

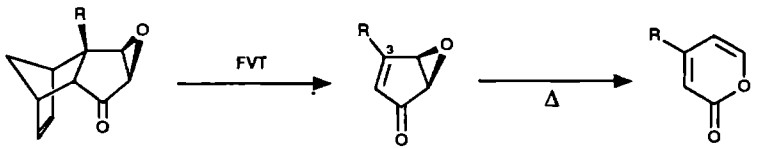
a. The thermolyses 1-6 were carried out in a short oven (16 x 1.3 cm), for the thermolyses 7 and 8 a longer oven (25 x 1.3 cm) was used. b. The compositions of the pyrolysates were calculated from their ^{1}H-NMR spectra. c. T_1 = preheating temp, T_2 = thermolysis temp. d. Conditions not optimized, see text.

In the thermolysates obtained from **3g**, two pyrones, *viz.* 5-methyl-2-pyrone (**6g**) and 3-methyl-2-pyrone (**6g***), were found instead of the single pyrone observed in the other thermolyses. The formation of all these pyrones **6a-h** from the corresponding cyclopentadienone epoxides **4a-h** is explained in Scheme 5 (*vide infra*).

The 10-oxatricyclodecadienone epoxides **3** were found, as expected to undergo the [4+2]

cycloreversion at considerably lower temperatures than their carbon analogues **7**. Whereas the flash vacuum thermolyses of the former led to complete conversion at temperatures ranging from 300-375°C, the thermolyses of the latter required generally temperatures up to or even higher than 500°C. Only in those cases, in which the resulting cyclopentadienone epoxide possessed a π-substituent at C-3, the temperature needed for the cycloreversion was lower, *viz. ca* 430°C (Scheme 4)[12,13]. Such a π-substituent enhances the thermodynamic stability of the products **8** by

Scheme 4



7a R: COOEt **8a** **9a**
7b R: CHO **8b** **9b**
7c R: CH=CHMe **8c**

extending the conjugation of the enone moiety and as a result thereof the E_{act} of the cycloreversion is appreciably lowered. The E_{act} of the thermal rearrangement to 2-pyrones, however, is increased by this same stabilisation. This increase is apparently sufficiently large to allow the isolation of the cyclopentadienones **8**, even when relatively high thermolysis temperatures are applied. In the absence of such a π-substituent the temperatures of these cycloreversions are too high (≥ 500°C) to allow the isolation or even detection of the cyclopentadienone epoxides. Then only 2-pyrones are obtained[17].

An additional and significant factor influencing the temperature of the cycloreversion is the relative steric energy of the polycyclic epoxides **3**. The data collected in Table 2 suggest that an increase in size of the substituent at C-4 considerably facilitates the cycloreversion process. This is particularly striking for the thioethers **3e** and **3f** for which the optimum FVT temperatures are about 50°C lower than for the ethers **3b-d**. Since the C-4 substituent is positioned *syn* with respect to the 10-oxa-bridge, this observation may be rationalized by assuming a considerable enhancement in the steric energy of **3** as a result of an increased interaction with the 10-oxa-bridge. The fact that this change in steric energy is apparently large enough to facilitate the cycloreversion process is another demonstration of the proximity effect of the 10-oxa-bridge in tricyclic structures such as **2** and **3**.

The influence of a substituent at C-5 was not studied in detail. Such a substituent will experience a smaller steric influence from the 10-oxa-bridge than a substituent at C-4 and will therefore presumably hardly reduce the temperature of the cycloreversion.

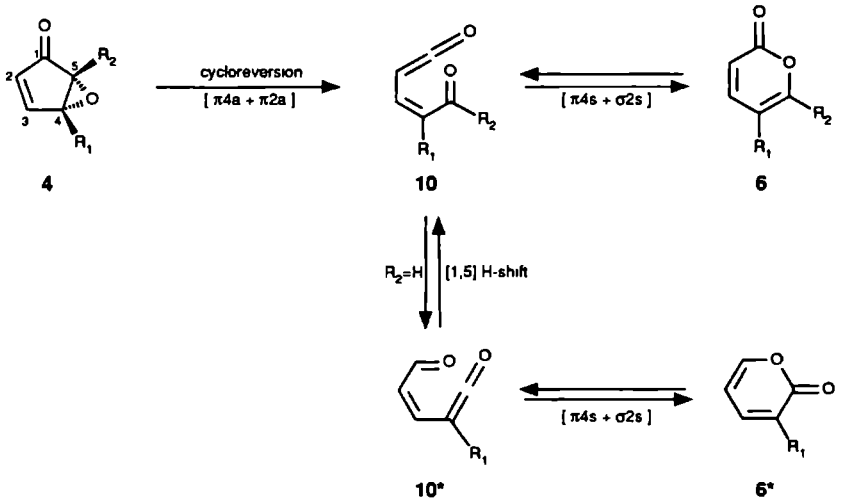
The epoxides **4a-h** appeared much easier to handle than anticipated from the literature.[4-7] They could be stored in the freezer without noticeable deterioration and were not affected during

purification using flash chromatography. During their isolation their relatively high volatility had to be taken into account.

Their spectral features are characteristic for their structure. The IR absorption for the carbonyl group appears at 1732 cm^{-1}. In the ^{1}H-NMR spectra a typical[24] set of (double) doublets is found for the olefinic protons, H_3 and H_2, at δ 7.5 ± 0.1 and δ 6.0 ± 0.1 ppm, respectively. The signal for H_4 (m or d) appears at δ 4.0 ± 0.2 ppm and the (double) doublet for H_5 at δ 3.6 ± 0.1 ppm. These ^{1}H-NMR data are in agreement with the reported[5] resonances of the parent compound **4a**. The relatively low field position of H_4, as compared with H_5, is remarkable. The electron density at C-4 is apparently lower than at C-5. It shows that the electronegative influence of the carbonyl group efficiently is transferred by the C-2, C-3 double bond.

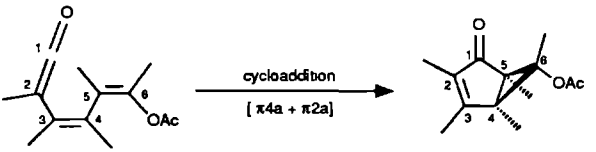
Previously[12a], the thermally induced rearrangement of cyclopentadienone epoxides to 2-pyrones has briefly[12b] been discussed and was suggested to proceed by a sequence of thermal pericyclic reactions, as presented in Scheme 5[12]. This mechanism is supported by the observation of

Scheme 5



Pirkle and Turner[25] that ketene aldehydes **10** (R_2=H) at elevated temperatures reversibly close to 2-pyrones or undergo reversible [1,5] sigmatropic H-shifts (Scheme 5). The occurrence of such 1,5-shifts explains the concomitant formation of pyron **6g*** in the thermal rearrangement of epoxide **4g** to pyron **6g**. Furthermore, the initial [π4a + π2a] cycloreversion reaction to ketene aldehyde **10** is in fact related to the conversion of ketene **11** into the bicyclic compound **12** (Scheme 6), for which transformation a similar [π4a + π2a] pericyclic pathway has been posited by Morris and Waring[26].

Scheme 6

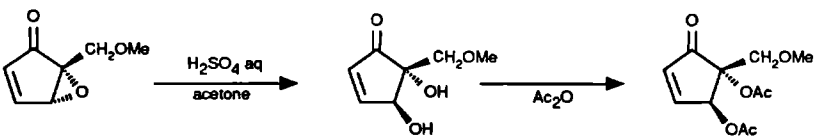


11 **12**

Selective opening of the epoxide ring of **4b**. *Synthesis of* epi-*pentenomycin analogues*, **5a** *and* **5b**.

As indicated in the introduction, subtle conditions are probably necessary to achieve a selective reaction with the epoxide function in cyclopentadienone epoxides. Previous work[13] on **8c** (*vide supra*) had revealed that the epoxide group of this particular substrate is significantly less sensitive to acid hydrolysis than anticipated. Its epoxide ring was not affected by treatment with 0.4 N H_2SO_4 in ether. However, in acetone containing 1% 5N H_2SO_4 a selective opening leading to a trans diol was accomplished. Application of the last mentioned acidic conditions to **4b** led to a smooth cleavage of the epoxide ring, affording the methyl protected *epi*-pentenomycin, **5a** (Scheme 7)[27].Comparison of the ^{1}H-NMR spectra of the resulting diol **5a** and its acylated derivative **5b**, with

Scheme 7



4b **5a** **5b**

the spectra of their epimers[17], confirmed unambiguously the *trans*-configuration of the diol group. The overall yield of this conversion appeared to vary between 30% and 55%. Presumably, both the high solubility of diol **5a** in water and the reactive nature of **4b** and **5a** disfavour a high and reproducible yield.

2.3 Concluding remarks

The results presented in this chapter demonstrate that the 10-oxatricyclodecadienones **2** offer a general and stereospecific route to 4- and/or 5-substituted cyclopentadienone epoxides **4**. In most cases the competing formation of 2-pyrones can almost completely be suppressed by an appropriate choice of the FVT conditions. The versatility of the cyclopentadienone epoxides **4** for the synthesis

of cyclopentenoid natural products is demonstrated by the synthesis of the *epi*-pentenomycin analogues **5a** and **5b**.

2.4 Experimental section

General remarks

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were taken on a Perkin Elmer 298 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 or a Bruker WH-90 spectrometer using TMS as internal standard. For mass spectra a Varian SM-1B or a double focussing VG 7070E mass spectrometer was used. Column chromatography under light pressure ("flash chromatography"[28]) was carried out at a pressure of *ca* 1.5 bar, a column length of *ca* 15 cm and a column diameter of 1-4 cm, using Merck Kieselgel 60 H or Merck Aluminium Oxid 150 neutral (Typ T).

Oxa-tricyclodecadienone epoxides **3a-h** *via alkaline epoxidation of oxatricyclodecadienones* **2a-h**: *general procedure*[29].

To a 0.5-0.1 M solution of **2a-h**[16] in a 1:1 mixture of methanol and dichloromethane were successively added, 35% hydrogen peroxide (2-3 eq) and 0.2 N sodium hydroxide (0.04-0.06 eq). The mixture was stirred vigorously for *ca*. 3 hrs and then diluted with dichloromethane and water (CH_2Cl_2:H_2O = 2:1). The aqueous phase was extracted with dichloromethane (3x). The combined organic solutions were washed with water (3x), dried ($MgSO_4$), filtered and evaporated. The crude epoxides were generally sufficiently pure (^{1}H-NMR and capillary GC data) for further use. Analytically pure samples were obtained by crystallization or flash chromatography.

Exo-*4,5-epoxy*-exo-*10-oxatricyclo[5.2.1.0^{2,6}] deca-8-en-3-one* (**3a**).

The epoxidation of **2a**[16] (1.4 g; 9.1 mmol) was carried out as described in the general procedure, yielding 1.47 g (94%) of **3a**. The capillary GC diagram of the crude product showed 3 peaks, belonging to epoxy-cyclopentenone **4a** (6.1%), pyrone **6a** (3.3%) and epoxide **3a** (90%), respectively. The first two compounds are not impurities, but result from thermolysis of **3a** in the injection port of the capillary GC. The ^{1}H-NMR soectrum confirmed the purity (≥ 95%) of the crude sample. Crystallization from n-hexane afforded analytically pure **3a**, mp 87-88°C (white needles). IR(KBr) ν(s): 1730(br,C=O), 1372, 1325/1315, 1262, 1219/1210/1202, 1190, 1042, 1020/1012, 950/935/928, 910, 880, 860/850, 832, 810/802, 715/705, 610 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.31(1H,dd,$J_{6,5}$=1.1Hz,$J_{6,2}$=5.9Hz;H_6), 2.69(1H,d,$J_{2,6}$=5.9Hz;H_2), 3.58(1H,dd, $J_{4,2}$=0.8Hz,$J_{4,5}$=2Hz;H_4), 3.86(1H,m,$J_{5,4}$=2Hz;H_5), 5.07(2H,s;H_1,H_7), 6.42(1H,dd,J=1.5 resp 6Hz)/6.55(1H,dd, J=1.5 resp 6Hz)(H_8,H_9). The signals for H_2, H_4, H_5 and H_6 were assigned after

spin decoupling. MS(CI) m/e(%): 165(24;M+1$^+$), 147(9;-H_2O), 137(8;-CO), 125(14), 111(8), 97(49;-furan), 91(16), 81(7),69(60;furan+1$^+$), 68(100;furan$^+$). (Found: C 65.68, H 5.01. Calc. for $C_9H_8O_3$: C 65.85, H 4.91%.)

Exo-*4,5-epoxy*-endo-*4-methoxymethyl*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8-en-3-one* (**3b**).

The epoxidation of **2b**[16] (780 mg; 4.0 mmol) was carried out as described in the general procedure, yielding 813 mg (98%) of **3b**. The ^{1}H-NMR spectrum of the crude product showed no contaminants. Flash chromatography (Al_2O_3/hexane-ethyl acetate (3:1)) afforded analytically pure **3b** as a thick white oil, which solidified in the freezer (capillary GC output: 3 peaks, epoxy-cyclopentenone **4b** (45%), pyrone **6b** (1%) and epoxide **3b** (52%), respectively). IR(CCl_4) ν(s): 1742 (C=O), 1122, 1090(C-O), 1028, 870, 700 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.35(1H,br d,$J_{6,2}$=5.8Hz;H_6), 2.57(1H,d,$J_{2,6}$=5.8Hz;H_2), 3.34(3H,s;OCH_3), 3.60/3.74/3.83/3.97(2H,AB_q,J_{AB}=12.6Hz;CH_2OMe), 3.92(1H,br s;H_5), 5.05(2H,br s;H_1,H_7), 6.41(dd,J=1.8 and 5.4Hz)/6.54(dd,J=1.8 and 5.4Hz)(2H; H_8,H_9). MS(CI) m/e(%)[30]: 209(1;M+1$^+$), 169(11), 141(17;-furan), 109(100; -furan,-CH_3OH), 95(25;M$^+$-furan,-CH_2OCH_3), 81(45;-furan,-CH_3OH,-CO), 68(23;furan$^+$), 45(19;$CH_2OCH_3^+$). HRMS(CI) m/e: 209.0803 (calc. for $C_{11}H_{13}O_4$(M+1): 209.0814).

Exo-*4,5-epoxy*-endo-*4-ethoxymethyl*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8-en-3-one* (**3c**).

The epoxidation of **2c**[16] (206 mg; 1.0 mmol) was carried out as described in the general procedure, yielding 210 mg (95%) of **3c**. The ^{1}H-NMR spectrum of the crude product showed no contaminants. Flash chromatography (Al_2O_3/hexane-ethyl acetate(5:1)) afforded analytically pure **3c** as a colourless oil (capillary GC output: 2 peaks, epoxy-cyclopentenone **4c** (32%) and epoxide **3c** (68%)). IR(film) ν(s): 1732(C=O), 1115, 1090(C-O), 870, 703, 610 cm^{-1}.^{1}H-NMR($CDCl_3$) δ: 1.11(3H,t,J=6.5Hz;OCH_2CH_3), 2.32(1H,dd,$J_{6,5}$=1.1Hz, $J_{6,2}$=6Hz;H_6), 2.57(1H,d,$J_{2,6}$=6Hz;H_2), 3.49(2H,q,J=6.5Hz;OCH_2CH_3), 3.65/3.78/3.83/3.97(2H,AB_q,J_{AB}=13Hz;CH_2OEt), 3.89(1H,d, $J_{5,6}$=1.1Hz;H_5), 5.00(2H,br s;H_1,H_7), 6.35(1H,dd,J=1.5 and 5.8Hz)/6.48(1H,dd,J=1.5 and 5.8Hz)(H_8,H_9). The assignment of the signals for H_5 and H_6 was confirmed by spin decoupling.

Exo-*4,5-epoxy*-endo-*4-isopropoxymethyl*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8-en-3-one* (**3d**).

The epoxidation of **2d**[16] (402 mg; 1.8 mmol) was carried out as described in the general procedure, yielding 400 mg (94%) of **3d**, as a thick, white oil. The ^{1}H-NMR spectrum of this product showed no contaminants. Crystallization from n-pentane failed. IR(film) ν(s): 2960/2920/2865(sat C-H), 1738(C=O), 1380/1370(i-Pr), 1150, 1125, 1090(C-O), 905, 870, 805, 703, 610 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.05(6H,d,J=6Hz;$CH(CH_3)_2$), 2.33(1H,dd,$J_{6,5}$=1.3Hz,$J_{6,2}$=5.8Hz;H_6), 2.54 (1H,d,$J_{2,6}$=5.8Hz;H_2), 3.75(1H,septet,J=6Hz;$CH(CH_3)_2$), 3.67/3.79/3.82/3.96(2H,AB_q,J_{AB}=12.5Hz; CH_2OiPr), 3.89(1H,d,$J_{5,6}$=1.3Hz;H_5), 4.74(2H,br s;H_1,H_7), 6.31(1H, dd,J=1.5 and 5.6Hz)/6.44(1H, dd,J=1.5 and 5.6Hz)(H_8,H_9). MS(CI) m/e(%)[30]: 237(30;M+1$^+$), 177(24;-C_3H_7OH), 169(100;-furan),

145(38),127(79;-furan,-C_3H_6), 110(22;-furan,-OC_3H_7), 109(22;-furan,-C_3H_7OH), 95(16;M^+-furan, -CH_2OiPr), 81(20;-furan,-C_3H_7OH,-CO), 68(13;furan$^+$). HRMS(CI) m/e: 237.1123 (calc. for $C_{13}H_{17}O_4$(M+1): 237.1127).

Exo-*4,5-epoxy*-endo-*4-phenylthiomethyl*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8-en-3-one* (**3e**).

The epoxidation of **2e**[16] (115 mg; 0.43 mmol) was carried out as described in the general procedure, yielding 100 mg (*ca.* 82%) of crude **3e**. Purification by flash chromatography (Al_2O_3/hexane-ethyl acetate (5:1)) left 73 mg (60%) of pure product. IR(KBr) ν: 1738(s), 1700(m), 1470(m), 1440(m), 1408(m), 1198(m), 1143(m), 1098(m), 1028(m), 1008(m), 920(m), 872(s), 802(m), 755(s), 695(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.40(1H,dd, $J_{6,7}$=0.8Hz,$J_{6,2}$=6.1Hz;H_6), 2.52(1H,d,$J_{2,6}$=6.1Hz;H_2), 3.13/3.30/3.50/3.67(3H,AB_q+ s,J_{AB}=15.2Hz;CH_2SPh + H_5 (3.67 ppm)), 4.80(1H,d,$J_{7,6}$=0.8Hz;H_7), 5.10(1H,br s;H_1), 6.38(1H,dd,J=1.4 and 5.6Hz)/6.51(1H,dd,J=1.4 and 5.6Hz)(H_8,H_9), 7.28(5H,m;ArH). MS(EI) m/e(%)[30]: 286(27;M^+), 218(51;-furan), 123(2;CH_2SPh^+), 109(88; -furan,-SPh and/or SPh^+), 95(100;-furan,-CH_2SPh), 77(23;$C_6H_5^+$), 68 (16;furan$^+$). (Found: C 66.80, H 4.87. Calc. for $C_{16}H_{14}O_3S$: C 67.11, H 4.93%.)

Endo-*4-benzylthiomethyl*-exo-*4,5-epoxy*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8-en-3-one* (**3f**).

The epoxidation of **2f**[16] (354 mg; 1.3 mmol) was carried out as described in the general procedure, yielding 353 mg (*ca.* 94%) of crude **3f**. Purification by flash chromatography (SiO_2/ethyl acetate), afforded 287 mg (77%) of pure **3f** as a colourless oil. IR(CCl_4) ν: 1743(s), 1452(w), 1408(w), 1312(w), 1262(w), 1150(w), 1090(w), 1028(m), 910(m), 870(m), 700(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.40(1H,dd,$J_{6,5}$=1.2Hz,$J_{6,2}$=6.0Hz;H_6), 2.57(1H,d,$J_{2,6}$=6.0Hz;H_2), 2.64/2.81/ 2.91/3.09(2H,AB_q,J_{AB}=15.4Hz;CH_2Ph), 3.73(2H,s;CH_2SBz), 3.84(1H,d,$J_{5,6}$=1.2Hz;H_5), 4.98(1H,d, J=1.4Hz)/5.08(1H,d,J=1.4Hz)(H_1,H_7), 6.40(1H,dd,J=1.4 and 5.6Hz)/6.53(1H,dd,J=1.4 and 5.6Hz) (H_8,H_9), 7.27(5H,br s;ArH). MS(CI) m/e(%): 301(6;M+1), 233(24;M+1-furan), 215(10;M+1-furan, -H_2O), 126(28), 110(10;M+1-furan,-SBz), 91(100;Bz^+), 69(15;(furan+1)$^+$). HRMS(CI) m/e: 301.0899 (calc. for $C_{17}H_{17}O_3S$ (M+1): 301.0898).

Exo-*4,5-epoxy*-endo-*5-methyl*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8-en-3-one* (**3g**).

The epoxidation of **2g**[16] (725 mg; 2.4 mmol) was carried out as described in the general procedure, yielding 734 mg (93%) of **3g**, as a white solid. The ^{1}H-NMR spectrum of the crude product showed no contaminants. Crystallization from hexane-ethyl acetate (4:1) afforded analytically pure **3g**, mp 85-87°C. IR(KBr) ν(s): 2940, 1750(C=O), 1400, 1255, 1232, 1192, 1110, 1075, 1022, 990, 852, 805, 715, 675, 615 cm^{-1}. ^{1}H-NMR($CDCl_3$/CCl_4) δ: 1.63(3H,s;CH_3), 2.27(1H,d, $J_{6,2}$=6Hz;H_6), 2.46(1H,d,$J_{2,6}$=6Hz;H_2), 3.30(1H,s;H_4), 4.98(br s)/5.04(br s)(2H;H_1,H_7), 6.44(2H,m; H_8,H_9). MS(EI) m/e(%): 178(0.7;M^+), 177(1.1;M-1), 149(1.5;M-1, -CO), 110(36;-furan), 82(48; -furan,-CO), 68(100;furan$^+$). (Found: C 67.49, H 5.66. Calc. for $C_{10}H_{10}O_3$: C 67.41, H 5.66%.)

Exo-*4,5-epoxy*-endo-*4-methoxymethyl*-endo-*5-methyl*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8-en-3-one* (**3h**).

The epoxidation of **2h**[16] (676 mg; 3.3 mmol) was carried out as described in the general procedure, yielding 740 mg (100%) of **3h**, as a white solid. The ^{1}H-NMR spectrum of the crude product showed no contaminants. Crystallization from hexane-ethyl acetate (3:1) afforded analytically pure **3h**, mp 60-63°C. IR(KBr) ν(s): 1735(C=O), 1120, 1015, 915, 870,720 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.71(3H,s;CH_3), 2.38(1H,d,$J_{6,2}$=6.3Hz;H_6), 2.54(1H,d,$J_{2,6}$=6.3Hz;H_2), 3.37(3H, s;OCH_3), 3.56/3.69/3.89/4.02(2H,AB_q,J_{AB}=11.7Hz;CH_2OMe), 5.02(1H,br s)/5.10(1H,br s)(H_1,H_7), 6.46(2H,m;H_8,H_9). MS(CI) m/e(%)[30]: (no M^+, M+1 or M-1 peak), 205(11;M+1-H_2O), 155(33;M+1 -furan), 123(100;M+1-furan,-CH_3OH), 109(17;M^+-furan,-CH_2OCH_3), 95(18; M+1-furan, -CH_2OCH_3,-CH_3), 68(furan$^+$). (Found: C 64.70, H 6.39. Calc. for $C_{12}H_{14}O_4$: C 64.85, H 6.35%.)

Flash-vacuum thermolysis of oxatricyclodecadienone epoxides, **3a-h**: *general remarks*.

The polycyclic epoxides **3a-h** were distilled or sublimed in vacuo through a hot quartz tube (16 or 25 x 1.3 cm). The pyrolysates were collected immediately after the pyrolysis tube in a cold trap at -78°C[23]. By carefully varying the pressure (P),the preheating temperature (T_1) and the oven temperature (T_2) optimum conditions were established for the majority of the reactions. Usually several runs were needed before the best conditions were found. The pyrolysates then often consisted of a mixture of unreacted substrate and products. The composition of these mixtures was at best deduced from ^{1}H-NMR data, as cap GC data sometimes gave a slightly distorted picture due to cycloreversion and rearrangement reactions taking place in the injection port of the capillary GC. The products could easily be isolated from the pyrolysates by flash chromatography on silicagel using a hexane-ethyl acetate mixture as the eluent. The isolation of the cyclopentadienone epoxides from the eluates required some care as these epoxides are rather volatile. In the experimentals below generally those conditions, that led to optimum yields of epoxides **4a-h** are given.

4,5-Epoxy-2-cyclopentenone (**4a**).

Flash vacuum thermolysis (16 cm tube/T_1 75°C/T_2 375°C/P 0.05 mbar/1.5 hr) of **3a** (164 mg; 1 mmol) provided 86 mg (*ca.* 90%) of **4a**. Only a small trace of **3a** (≤ 5%) was detected in the ^{1}H-NMR spectrum of the pyrolysate. Flash chromatography (SiO_2/hexane-ethyl acetate (3:1)) of crude product mixtures (see: *general remarks)* afforded pure **4a** as a colourless oil. IR(CCl_4)[5] ν: 1735(s;C=O), 1332(m), 1175(w)/1165(w), 1082(w)/1072(w), 993(w),960(w), 938(w), 845(s) cm^{-1}. ^{1}H-NMR($CDCl_3$)[5] δ: 3.67(dd;H_5), 4.14(m;H_4), 6.02(ddd;H_2), 7.63(dd;H_3).

Further elution afforded successively **3a** and *2H-pyran-2-one* (**6a**) (colourless oil). IR(CCl_4)[5] ν: 1745(s;C=O), 1245(m), 1192(m), 1112(w), 1080(m), 1060(w) cm^{-1}. ^{1}H-NMR(CCl_4) δ: 6.05-6.17(1H,m;H_5), 6.17-6.33(1H,m;H_3), 7.13-7.39(1H,m;H_4), 7.39-7.42(1H,m;H_6).

The thermolysis of **3a** (61 mg; 0.4 mmol) at an oven temperature of 425°C (other conditions unchanged) led to a 1:1 mixture of epoxide **4a** and pyrone **6a** (32 mg; 90% total yield).

4,5-Epoxy-5-methoxymethyl-2-cyclopentenone (**4b**).

Flash vacuum thermolysis (16 cm tube/T_1 90°C/T_2 360°C/P 0.06-0.08 mbar/1.5 hr) of **3b** (99 mg; 0.5 mmol) provided 59 mg (*ca.* 90%) of **4b**. Only small traces (≤ 5%) of **3b** and pyrone **6b** were detected in the ^{1}H-NMR spectrum of the pyrolysate. Flash chromatography (SiO_2/hexane-ethyl acetate (3:2)) of crude product mixtures (see: *general remarks)* afforded pure **4b** as a colourless oil. IR(CCl_4) ν: 1732(s;C=O), 1332(m), 1198(w), 1135(m), 1103(m), 828(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 3.40(3H,s;OCH_3), 3.73/3.87/3.99/4.16(2H,AB_q, J_{AB}=12Hz;CH_2OMe), 4.13(1H,br s;H_4), 6.00(1H,dd,$J_{2,4}$=2.2Hz,$J_{2,3}$=6Hz;H_2), 7.60(1H,dd,$J_{3,4}$=1.5Hz, $J_{3,2}$=6Hz;H_3). MS(EI) m/e(%): 140(2;M^+), 125(3;-CH_3), 110(5), 95(100;-CH_2OCH_3), 45(15;$CH_2OCH_3^+$). HRMS(EI) m/e: 140.0475 (calc. for $C_7H_8O_3$(M): 140.0473).

Further eluation afforded successively **3b** and *6-Methoxymethyl-2H-pyran-2-one* (**6b**) (colourless oil). IR(CCl_4) ν: 1745(s;C=O), 1640(w), 1560(m), 1200(w), 1125(m), 1090(m) cm^{-1}. ^{1}H-NMR(CCl_4) δ: 3.40(3H, s;OCH_3), 4.15(2H,s;CH_2OMe), 6.02(1H,d,$J_{5,4}$=9.6Hz;H_5), 6.13(1H,d(d),$J_{3,4}$=6.2Hz,(J=1.3Hz);H_3), 7.18(1H,dd, $J_{4,3}$=6.2Hz,$J_{4,5}$=9.6Hz;H_4).

4,5-Epoxy-5-ethoxymethyl-2-cyclopentenone (**4c**).

Flash vacuum thermolysis (16 cm tube/T_1 90°C/T_2 340°C/P 0.05 mbar/4 hr) of **3c** (141 mg; 0.6 mmol) provided *ca.* 95 mg (≥ 90%) of **4c**. Only a small trace of pyrone **6c** (≤ 5%) was detected in the ^{1}H-NMR spectrum of the pyrolysate. Flash chromatography (SiO_2/hexane-ethyl acetate (3:2)) of crude product mixtures (see: *general remarks)* afforded pure **4c** as a colourless oil. ^{1}H-NMR($CDCl_3$) δ: 1.20(3H,tr,J=6.6Hz;OCH_2CH_3), 3.54(2H,q,J=6.6Hz;OCH_2CH_3), 3.75/3.89/4.05/4.18(2H,AB_q, J_{AB}=13Hz;CH_2OEt), 4.15(1H,m;H_4), 6.04(1H,dd,$J_{2,4}$=2.4Hz,$J_{2,3}$=6Hz;H_2), 7.60(1H,dd,$J_{3,4}$=1.5Hz, $J_{3,2}$=6Hz;H_3). MS(70eV) m/e: 154(M^+), 125(-C_2H_5), 109(-OC_2H_5), 95(-CH_2OEt), 59(CH_2OEt^+). HRMS m/e: 154.063 (calc. for $C_8H_{10}O_3$(M): 154.066).

Further eluation afforded successively **3c** and *6-Ethoxymethyl-2H-pyran-2-one* (**6c**) (colourless oil). IR(CCl_4) ν: 2978(m), 2920(m), 2860(m), 1740(s;C=O), 1640(m), 1560(m), 1315(m), 1195(,m), 1175(m), 1122(s), 1088(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.24(3H,tr,J=7Hz;OCH_2CH_3), 3.58(2H,q,J=7Hz;OCH_2CH_3), 4.23(2H,br s;CH_2OEt), 6.21(1H,d,$J_{5,4}$=10Hz;H_5), 6.25(1H,d(d), $J_{3,4}$=6Hz,(J=1.2Hz);H_3), 7.29(1H,dd,$J_{4,3}$=6Hz, $J_{4,5}$=10Hz;H_4).

The thermolysis of **3c**, preheated at 110°C, at an oven temperature of 525°C and a pressure of 0.06 mbar led to pyrone **6c** as the only product in 84% yield.

4,5-Epoxy-5-iso-propoxymethylcyclopentenone (**4d**).

Flash vacuum thermolysis (16 cm tube/T_1 70°C/T_2 350°C/P 0.05-0.06 mbar/3 hr) of **3d** (223

mg; 0.9 mmol) produced a 3:1 mixture of epoxide **4d** and pyrone **6d** (131 mg; 87% total yield). Optimization of thermolysis conditions was not carried out. Flash chromatography (SiO_2/hexane-ethyl acetate (3:1)) of the pyrolysate afforded pure **4d** as a colourless oil (75%). IR(film) v: 3070(w), 2968(s), 2922(m), 2868(m), 1722(s;C=O), 1380(m), 1368(m), 1335(s), 1178(m), 1125(s), 1080(s), 840(s), 825(s) cm^{-1}. ^{1}H-NMR(CCl_4) δ: 1.14(6H,d,J=6.7Hz;$CH(CH_3)_2$), 3.57(1H,septet,J=6.7Hz; $CH(CH_3)_2$), 3.57/3.70/4.00/4.13(2H,AB_q,J_{AB}=11.4Hz; CH_2OiPr), 4.00(1H,br s;H_4), 5.97(1H,dd, $J_{2,4}$=1.9Hz,$J_{2,3}$=6Hz;H_2), 7.53(1H,dd,$J_{3,4}$=1.5Hz,$J_{3,2}$=6Hz;H_3). MS(CI) m/e(%): 169(59;$M+1^+$), 127(100;-C_3H_6), 109(34;-C_3H_7OH), 95(31;M^+-CH_2OiPr), 81(68;-C_3H_7OH,-CO), 73(5;CH_2OiPr^+), 43(12;$C_3H_6^+$). HRMS(CI) m/e: 169.0873 (calc. for $C_9H_{13}O_3$(M+1): 169.0865).

Further eluation afforded *6-iso-Propoxymethyl-2H-pyran-2-one* (**6d**) as a pale tinted oil. ^{1}H-NMR(CCl_4) δ: 1.17(6H,d,J=6.8Hz;$CH(CH_3)_2$), 3.63(1H,septet,J=6.8Hz;$CH(CH_3)_2$), 4.17(2H,br s;CH_2OiPr), 6.01(1H,d,$J_{5,4}$=9.6Hz;H_5), 6.11(1H,d,$J_{3,4}$=7.1Hz;H_3), 7.17(1H,dd,$J_{4,3}$=7.1Hz, $J_{4,5}$=9.6Hz;H_4).

4,5-Epoxy-5-phenylthiomethyl-2-cyclopentenone (**4e**).

Flash vacuum thermolysis (16 cm tube/T_1 135°C/T_2 300°C/P 0.2 mbar/5 hr) of **3e** (95 mg; 0.33 mmol) provided 69 mg (95%) of epoxide **4e** as the only product. This epoxide was obtained as an oil. IR(CCl_4) v: 3070/3050(w), 2955(w), 2923(w), 1736(s;C=O), 1480(w), 1438(w), 1332(w), 692(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 3.22/3.38/3.61/3.77(2H,AB_q,J_{AB}=14.4Hz;CH_2SPh), 3.83(1H,dd,$J_{4,3}$=1.6Hz,$J_{4,2}$=2.0Hz;H_4), 6.07(1H,dd, $J_{2,4}$=2.0Hz,$J_{2,3}$=6Hz;H_2), 7.34(5H,m;ArH), 7.45(1H,dd,$J_{3,4}$=1.6Hz,$J_{3,2}$=6Hz;H_3). MS(EI) m/e(%): 218(57;M^+), 123 (16;CH_2SPh^+), 109(68;-SPh and/or SPh^+), 95(100;-CH_2SPh), 81(10), 77(10;$C_6H_5^+$), 65(15), 45(22), 39(31). HRMS(EI) m/e: 218.0391 (calc. for $C_{12}H_{10}O_2S$ (M): 218.0402).

5-Benzylthiomethyl-4,5-epoxycyclopentenone (**4f**).

Flash vacuum thermolysis (16 cm tube/T_1 135°C/T_2 300°C/P 0.2 mbar/6.5 hr) of **3f** (102 mg; 0.34 mmol) provided 75 mg (95%) of epoxide **4f** as the only product. This epoxide was obtained as an oil. IR(CCl_4) v: 3060(w), 3025(w), 2918(w), 1734(s;C=O), 1452(m), 1408(m), 1333(m), 1028(m), 910(m), 700(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.74/2.91/3.06/3.22(2H,AB_q,J_{AB}=15Hz;SCH_2Ph), 3.75 (2H,br s;CH_2SBz), 3.90(1H,dd,$J_{4,3}$=1.4Hz,$J_{4,2}$=2.2Hz;H_4), 5.99(1H,dd,$J_{2,4}$=2.2Hz,$J_{2,3}$=6Hz;H_2), 7.26(5H,br s;ArH), 7.47(1H,dd,$J_{3,4}$=1.4Hz,$J_{3,2}$=6Hz;H_3). MS(EI) m/e(%): 232(2;M^+), 141(5; -$CH_2C_6H_5$), 126(54), 123(21;$SCH_2C_6H_5^+$), 122(13), 110(27), 95(27;-$CH_2SCH_2C_6H_5$), 91(100; $CH_2C_6H_5^+$), 82(12), 65(20), 45(17), 39(39). HRMS(EI) m/e: 232.0565 (calc. for $C_{13}H_{12}O_2S$ (M+1): 232.0558).

4,5-Epoxy-4-methyl-2-cyclopentenone (**4g**).

Flash vacuum thermolysis (25 cm tube/T_1 65°C/T_2 355°C/P 0.09-0.15 mbar/2 hr) of **3g** (320

mg; 1.8 mmol) provided 192 mg (97%) of a mixture of epoxide **4g** (85%), and pyrones **6g** and **6g*** (15%; *ca.* 2:3). Flash chromatography (SiO_2/hexane-ethyl acetate (4:1)) of crude product mixtures (see: *general remarks)* afforded pure **4g** as a colourless oil. IR(CCl_4) ν: 1745(s)/1722(s)(C=O), 1442(m), 1410(s), 1330(m), 1165(m), 1088(s), 1065(m), 900(s), 868(m), 700(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.76(3H,s;CH_3), 3.54(1H,d,$J_{5,2}$=1.8Hz;H_5), 5.91(1H,dd,$J_{2,5}$=1.8Hz,$J_{2,3}$=6.1Hz; H_2), 7.46(1H,d,$J_{3,2}$=6.1Hz;H_3). MS(CI) m/e(%): 111(100;M+1$^+$), 85(17;-CO), 57(12). HRMS(CI) m/e: 111.0448 (calc. for $C_6H_7O_2$(M+1): 111.0446).

Further eluation afforded *3-Methyl-2H-pyran-2-one* (**6g***), ^{1}H-NMR(CCl_4)[25] δ: 2.00(3H,s;CH_3), 6.00(1H,tr,J=6Hz;H_5), 6.98(1H,d,$J_{4,5}$=6Hz;H_4), 7.32(1H,d,$J_{6,5}$=6Hz;H_6) and *5-Methyl-2H-pyran-2-one* (**6g**). IR(CCl_4) ν: 1748(s)/1725(m) (C=O), 1655(w)/1645(w), 1540(w), 1240(w), 1210(w), 1138(w), 1115(w) cm^{-1}. ^{1}H-NMR(CCl_4)[25] δ: 1.93(3H,s;CH_3), 6.16(1H, d,$J_{3,4}$=9.8Hz;H_3), 7.08(1H,dd,$J_{4,6}$<2Hz,$J_{4,3}$=9.8Hz;H_4), 7.20(1H,br s;H_6).

4,5-Epoxy-5-methoxymethyl-4-methyl-2-cyclopentenone (**4h**).

Flash vacuum thermolysis (25 cm tube/T_1 70°C/T_2 310°C/P 0.08-0.09 mbar/10 hr) of **3h** (161 mg; 0.72 mmol) provided 105 mg (*ca.* 95%) of a mixture of epoxide **4h** (84%) and pyrone **6h** (11%). Also a small trace (≤ 5%) of **3h** was detected in the ^{1}H-NMR spectrum of the pyrolysate. Flash chromatography (SiO_2/hexane-ethyl acetate (3:1)) of crude product mixtures (see: *general remarks)* afforded pure **3h** as a colourless oil. IR(CCl_4) ν: 2990(w), 2920(m), 2822(w), 1732(s;C=O), 1450(w), 1388(m), 1330(m), 1300(w), 1195/1190(m), 1132(m), 1108(s), 1088(m), 1043(m), 950(w), 902(w) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.73(3H,s;CH_3), 3.40(3H,s;OCH_3), 3.61/3.73/4.04/4.18(2H,AB_q, J_{AB}=11Hz;CH_2OMe), 5.96(1H,d,$J_{2,3}$=6.3Hz;H_2), 7.44(1H,d,$J_{3,2}$=6.3Hz;H_3). MS(CI) m/e(%): 155 (74;M+1$^+$), 123(100;-CH_3OH), 109(19;M$^+$-CH_2OCH_3), 95(70;-CH_2OCH_3,-CH_3), 45(15; $CH_2OCH_3^+$). HRMS(CI) m/e: 155.0710 (calc. for $C_8H_{11}O_3$(M+1): 155.0708).

Further eluation afforded *6-Methoxymethyl-5-methyl-2H-pyran-2-one* (**6h**). IR(CCl_4) ν: 2990(w), 2920(m), 2820(w), 1742(s;C=O), 1645(m), 1550(w), 1450(w), 1387(w), 1367(w), 1305(m), 1205(w), 1192(m), 1128(m), 1088(s), 1005(m), 862(m) cm^{-1}. ^{1}H-NMR(CCl_4) δ: 2.04(3H,s;CH_3), 3.38(3H,s;OCH_3), 4.16(2H,s; CH_2OMe), 6.18(1H,d,$J_{3,4}$=9Hz;H_3), 7.03(1H,d,$J_{4,3}$=9Hz;H_4). MS(CI) m/e(%): 155(100;M+1$^+$), 123(20;-CH_3OH), 109(4;M$^+$-CH_2OCH_3), 57(11), 45(10;$CH_2OCH_3^+$). HRMS(CI) m/e: 155.0706 (calc. for $C_8H_{11}O_3$(M+1): 155.0708).

(4R,5S*)-4,5-dihydroxy-5-methoxymethyl-2-cyclopentenone* (**5a**).

A solution of **4b** (86 mg; 0.6 mmol) in acetone (25 ml, containing 1% 5N H_2SO_4) was stirred for 2 days. Then $NaHCO_3$ (5 g) and $MgSO_4$ (5 g) were added and stirring was continued overnight. The solids were filtered off and carefully rinsed with acetone. The combined filtrates were concentrated to give 86 mg of crude **5a**, as a pale yellow oil. Purification of this material was not attempted. IR(film) ν: 3700-3040 (s;OH), 2980(m), 2920(m), 1710(s;C=O), 1635(s;C=C), 1100(s)

cm^{-1}. ^{1}H-NMR(CD_3OD) δ: 3.33(3H,s;CH_2OCH_3), 3.57(2H,s; CH_2OCH_3), 4.73(1H,br s;H_4), 6.27(1H,br d,$J_{2,3}$=6Hz;H_2), 7.53(1H,dd,$J_{3,4}$=1.5Hz,$J_{3,2}$=6Hz;H_3).

Instead of purificaton, the crude diol **5a** was acylated by stirring it for 3 hrs in a solution of dichloromethane (4 ml) with Et_3N (0.3 ml), Ac_2O (0.2 ml) and DMAP (10 mg). After the usual work-up the crude product (151 mg, brown tinted oil) was purified by flash chromatography (SiO_2/ethyl acetate) to afford 78 mg of *(4R*,5S*)-4,5-diacetoxy-5-methoxymethyl-2-cyclopentenone* (**5b**), as a colourless oil (54% overall yield). IR(CCl_4) ν: 1735(broad s;C=O), 1370(m), 1245(s), 1220(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.10(s)/2.13(s) (6H;2xCH_3), 3.33(3H,s;CH_2OCH_3), 3.55(2H,s;CH_2OCH_3), 6.26(1H,t,$J_{4,3}$=$J_{4,2}$=2Hz;H_4), 6.47(1H,dd,$J_{2,4}$=2Hz,$J_{2,3}$=6Hz;H_2), 7.40(1H,dd,$J_{3,4}$=2Hz,$J_{3,2}$=6Hz;H_3). MS(EI) m/e(%): 242 (0.71;M^+), 158(10;-2xCH_2CO), 140(51; -CH_2CO,-CH_3COOH), 113(19;-2xCH_2CO,-CH_2OMe), 95(63;-CH_2CO,-CH_3COOH,-CH_2OMe), 45(43;CH_2OMe^+), 43(100;CH_3CO^+). HRMS(EI) m/e: 242.0787 (calc. for $C_{11}H_{14}O_6$(M): 242.0790).

2.5 References and notes

1. This chapter was recently published in *Tetrahedron* **1989**, *45*, 7134. A part not included in the Tetrahedron article has been inserted at the end of this chapter under the heading Addendum. A preliminary account of this work is presented in ref 2.
2. Klunder, A. J. H.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 1329.
3. Ullman, E. F. *J. Am. Chem. Soc.* **1963**, *85*, 3529.
4. Dunston, J. M.; Yates, P. *Tetrahedron Lett.* **1964**, *5*, 505.
5. Chapmann, O. L.; Hess, T. C. *J. Org. Chem.* **1979**, *44*, 962.
6. Baltrop, J. A.; Colin Day, A. C.; Samuel, C. J. *J. Chem. Soc., Chem. Comm.* **1977**, 598 and references cited therein.
7. Padwa, A. *Tetrahedron Lett.* **1964**, *5*, 813.
8. Padwa, A.; Hartman, R. *J. Am. Chem. Soc.* **1966**, *88*, 1518.
9. Pütter, P.; Dilthey, W. *J. Prakt. Chem.* **1937**, *150*, 49.
10. Ando, W.; Miyazaki, H.; Ueno, K.; Nakanishi, H.; Sakurai, T.; Kobayashi, K. *J. Am. Chem. Soc.* **1981**, *103*, 4949.
11. Takata, T.;Tajima, R.; Ando, W. *Chem. Lett.* **1985**, 665.
12. (a) Klunder, A. J. H.; Bos, W.; Verlaak J. M. J.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4553; (b) See the Addendum at the end of this chapter for an extended discussion.
13. Klunder, A. J. H.; Bos, W.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4557.
14. Hua, D. H.; Venkataraman, S.;Chan-Yu-King, R.;Paukstelis, J. V. *J. Am. Chem. Soc.* **1988**, *110*, 4741.

15. For recent reviews on this technique and its synthetic scope see: (a) Brown, R. F. C. *Pyrolytic Methods in Organic Chemistry*; Organic Chemistry Monographs, Vol. 41; Academic: New York, 1980; (b) Wiersum, U. E. in *Aldrichimica Acta*, Vol. 17, No.2, 1984; (c) Lasne, M. C.; Ripoll, J. L. *Synthesis*, **1985**, 121; (d) Ichihara, A. *Synthesis*, **1987**, 207.
16. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Kooy, M. G.; Steffann, J.; Zwanenburg, B. *Tetrahedron*, **1989**, 45, 7109.
17. Verlaak, J. M. J. *Ph.D. Thesis*, University of Nijmegen, Febr. 1983.
18. Oda, M.; Kanao, Y.; Kasai, M.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1977**, *45*, 2497.
19. Klunder, A. J. H.; Crul, M. J. F. M.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 3147.
20. (a) Smits, J. M. M.; Beurskens, P. T.; Smits, J. R. M.; Parthasarathi, V.; Houwen-Claassen, A. A. M.; Klunder, A. J. H. *J. Cryst. Spectrosc. Res.* **1988**, *18*, 1; (b) Smits, J. M. M.; Beurskens, P. T.; Klunder, A. J. H.; Crul, M. J. F. M. *J. Cryst. Spectrosc. Res.* **1986**, *16*, 665; (c) Noordik, J. H.; Luinge, H. J.; Klunder, A. J. H. *Cryst. Struct. Commun.* **1981**, *12*, 143.
21. Houwen-Claassen A. A. M.; Klunder, A. J. H.; Zwanenburg, B.; Beurskens, P.T.; Moers, F. G.; Beurskens, G. *Submitted for publication.*
22. Oda, M.; Kawanishi, S. *Jap. Patent* 53-127495, 1978; *Chem. Abstr.* 90, P137666z.
23. A detailed description of the FVT equipment is given in ref. 17, p 154.
24. Williams, D. N.; Fleming, I. *Spektroskopische Methoden zur Strukturaufklärung*; Thieme: Stuttgart, 1975; p 138.
25. Pirkle, W. H.; Turner, W. V. *J. Org. Chem.* **1975**, *40*, 1617.
26. Morris, M. R.; Waring, A. J. *J. Chem. Soc., Chem. Commun.* **1969**, 526.
27. See for other approaches to *epi*-pentenomycins: (a) Shono, T.; Matsumura, Y.; Yamnae, S.; Suzuki, M. *Chemistry Letters* **1980**, 1619; (b) Smith, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855.
28. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
29. The procedure is based on the alkaline epoxidation of dicyclopentadiene-3-one, reported by Chapman and Hess[5].
30. The underscored signals are also found in the corresponding mass spectrum of the derived cyclopentadienone epoxide.

2.6 Addendum

The thermal rearrangement of cyclopentadienone epoxides to 2-pyrones epoxides appears to be highly dependent on their substitution pattern. Careful monitoring of the thermolyses of the polycyclic epoxides **7** (Scheme 4) revealed that the resulting cyclopentadienone epoxides **8** did not

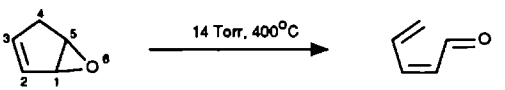
rearrange at temperatures as high as 420-430°C[12,13]. These epoxides owe their relative stability to the extended conjugation by the π-substituent at C-3. The data included in Table 2 indicate that the parent compound **4a** is the next stable cyclopentadienone epoxide. Its formation from **3a** at 375°C is attended by only a small trace of pyrone **6a**. The 5-monosubstituted epoxides **3b-d** are only a slightly more labile than parent compound **3a**. They resist pyrone formation up to *ca.* 350°C. The thermal stability of the thioethers **3e** and **3f** was not studied. The 4-substituted epoxides **3g** and **3h** are thermally the least stable members of the group of epoxides considered. We had to adjust the thermolysis equipment for these epoxides, to avoid excessive pyrone formation. The enhanced lability of the 4,5-disubstituted epoxide **3h** is not surprising. It can be explained by steric strain generated by the eclipsed 4-methylgroup and the 5-methoxymethylsubstituent. However, the higher lability of the 4-monosubstituted epoxide **3g**, as compared with the 5-monosubstituted epoxides **3b-d**, is remarkable.

The thermally induced rearrangement of cyclopentadienone epoxides to 2-pyrones can be rationalized by assuming the sequence of thermal pericyclic reactions shown in Scheme 5.

The occurence of the initial [π4a + π2a] cycloreversion reaction is supported by the report of Morris and Waring[26], who proposed a synchronous thermally allowed intramolecular [π4a + π2a] cyclisation to explain the formation of bicyclo[3.1.0]hexene **12** from ketene **11** (Scheme 6). On the basis of the strong solvent effects observed, these authors propose an asymmetric transition state in which bonding between C-5 and C-1 in the ketene **11** leads bonding between C-4 and C-6. Applying the principle of microscopic reversibility on the reverse reaction, which is actually the initial process in Scheme 5, then bond breaking between C-4 and C-6 is expected to take place before bond breaking between C-5 and C-1.

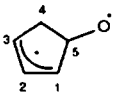
Schiess et al (Schiess, P. and Radimerski, P. *Helv. Chim. Acta* **1974**, *57*, 2583; Schiess, P. and Chia, H. L. *Ibid* **1970**, *53*, 485) studied the thermal conversion of the closely related cyclopentadiene epoxide **13**. This epoxide rearranges smoothly to cis-pentadienal **14** under FVT conditions (Scheme 7). Both a synchronous mechanism, in which the bonds between C-1 and C-6,

Scheme 7



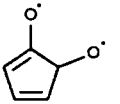
13 **14**

and C-4 and C-5 are broken simultaneously, and a radical mechanism, involving biradical **15**, were considered as possible pathways. The alternative involving radical **16** was excluded by the stereospecific formation of the cis-aldehyde.



15

16



17

On the basis of these reports, we expect that in a radical process the initial step in the rearrangement of the cyclopentadienone epoxides will involve cleavage of the C_4-O bond, to form a delocalised diradical **17.** The intermediacy of such a diradical **17** (R=H) was postulated by Chapman and Hess[5] in the light induced rearrangement of the parent cyclopentadienone epoxide **1** (R=H). A similar structure has been proposed for the photoinduced rearrangement of substituted epoxides **1** (R=2,5-dimethyl; R=3,4-diphenyl)[6-8].

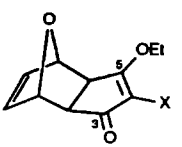
Both a concerted pathway, involving the proposed unsymmetric transition state, and a diradical mechanism, via diradical **17**, will be supported by an electron releasing substituent on C-4. This possibly explains the relative ease of pyrone formation from the 4-methyl substituted epoxide **4g**. More experimental information will be necessary to decide unequivocally about the actual mechanistic payhway.

The intermediacy of the ketene aldehydes **10** (Scheme 5) in the pyrone formation is supported by the work of Pirkle et al[25]. The methyl substituted keten aldehyde **10** (R_1= Me; R_2= H) resulting from [π4a + π2a] cycloreversion of **4g** can either cyclize immediately, to give pyrone **6g,** or rearrange to **10*** (R_1= Me), before ring closure to **6g***. If the pyrones spend sufficient time in the hot zone an equilibrium mixture will be produced. Pirkle et al[25] report an equilibrium ratio for **6g** and **6g*** of 1:3, indicating that **6g*** is the more stable pyrone. The occurrence of a similar mixture as minor product of the thermolysis of **3g** confirms not only the intermediacy of keten aldehyde **10** (R_1= Me; R_2= H) in the thermal rearrangement of epoxide **4g** but shows also, that under the thermal conditions, needed to realize an efficient cycloreversion of **3g**, the contact time is long enough to establish in part the equilibrium between **10g** and the respective pyrones **6g** and **6g***. An indication that the electrocyclic ring closure of the intermediate keten **10g** to pyrone **6g** is faster than the [1,5] sigmatropic H-shift, was obtained, more or less fortuitously, when purified epoxide **4g** was subjected to capillary GC analysis. Only pyron **6g**, resulting from cycloreversion in the injection port of the cap GC, was detected as a minor product together with unrearranged **4g**. No trace of **6g*** was present.

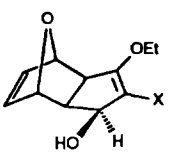
CHAPTER 3: SELECTIVE BIS-HYDRIDE REDUCTION OF TOSYLMETHYL-SUBSTITUTED TRICYCLIC ENONES BY LITHIUM ALUMINIUM HYDRIDE. SYNTHESIS OF α-METHYLENE CYCLOPENTENOIDS[1].

3.1 Introduction

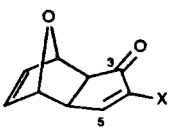
Functionalized cyclopentenones are of general interest in natural product synthesis. In several papers we have showed that a broad range of cyclopentenones can conveniently be obtained from appropriately substituted tricyclo[5.2.1.$0^{2,6}$]decadienones[2]. In connection with studies on the synthesis of cyclopentadienone epoxides[3,4], we needed to convert the tosylmethyl substituted 10-oxatricyclo[5.2.1.$0^{2,6}$]decadienone **1** into the tricyclic sulphone **3**. Such a transformation, which actually involves the conversion of a β-alkoxy enone into an α,β-unsaturated carbonyl compound, can in principle be achieved via complex metal hydride reduction of the ketone function followed by acid hydrolysis of the resulting γ-hydroxy enol ether[5-7]. The Lithium Aluminium Hydride (LAH) reduction of tricyclodecadienone **4** indeed follows this course. This was demonstrated by the isolation of the intermediate enol ether **5** and its subsequent hydrolysis to enone **6**[3,8]. We expected that the LAH reduction of the structurally related tricyclic sulphone **1** would proceed in the same way and thus would lead to the desired sulphone **3**, or to the intermediate enolether **2**, if neutral or alkaline hydrolysis conditions were applied.



1 X=CH_2Tos
4 X=H



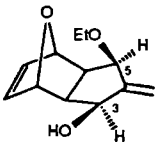
2 X=CH_2Tos
5 X=H



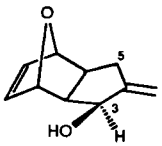
3 X=CH_2Tos
6 X=H

Most unexpectedly, however, the reduction of sulphone **1** with LAH provided neither **2** nor its hydrolyzed derivative **3**. Instead, an entirely different compound was obtained, *viz.* the exo-cyclic methylene derivative **7**. The intended conversion of **1** into sulphone **3** could eventually be achieved by applying Di-iso-Butyl Aluminium Hydride (DIBAL) as the reducing agent[3]. Treatment of sulphone **3** with LAH also resulted in the formation of an exo-cyclic methylene compound, *viz.* **8**. The surprising outcome of these LAH reductions led us to investigate this deviant reduction process

in more detail. In this chapter we will elucidate the crucial role of the allylic tosyl group in the whole process. Furthermore, we will demonstrate that the formation of the α-methylene alcohols **7** and **8** offers a unique entry to α-alkylidene-cyclopentenols and α-alkylidene-cyclopentenones.



7



8

3.2 Results and Discussion

The LAH reductions of sulphones **1** *and* **3.**

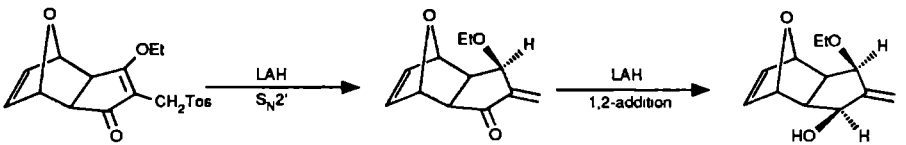
The LAH reduction of sulphone **1** was carried out in THF/ether (3:2), at room temperature. Neutral work up with sat NH_4Cl aq afforded **7** as the only product in 70% yield. No trace of **3** or its precursor **2** was found in the crude reaction mixture.

The basic structure of **7** could be deduced from its spectral data. A strong OH absorption at 3365 cm^{-1} and the absence of a C=O band in the IR spectrum indicated complete reduction of the ketone function. The absence of the tosyl group was apparent from the ^{1}H-NMR spectrum. As its spectral data did not allow an unambiguous assignment of the configuration at C-3 and C-5, the product was subjected to an X-Ray diffraction analysis[9]. This structure determination confirmed the reduction of the carbonyl function and the reductive elimination of the tosyl group. In addition, it revealed that both these processes had taken place with complete stereospecifity, implying hydride attack from the least hindered *exo*-face of the substrate, *anti* to the 10-oxa bridge. This stereo control is in agreement with previous observations for the *exo*-10-oxa-tricyclodecadienone system[3,4]. The conceivable involvement[10] of the 10-oxa bridge in the complexation of LAH, favouring the formation of a product with the opposite stereochemistry at C-3 and C-5, was not observed.

In order to rationalize the formation of **7** from **1** by reduction with LAH, initial attack at either of the two electrophilic centres in the substrate, C-3 or C-5, can be envisaged. Attack at C-3 would lead to the alcoholate of sulphone **2**. In the next step this alcoholate must then undergo a reductive S_N2' type substitution of the tosyl group in order to arrive at the final product **7**. This reaction sequence, however, could be excluded by subjecting sulphone **2**, obtained from the reduction of **1** with DIBAL[3], to the reaction conditions of the LAH reduction. Sulphone **2** was not affected by this treatment and was recovered almost quantitatively[11]. Even excess of LAH and a prolonged reaction time did not produce the slightest trace of **7**. This result convincingly proves that the first step in the LAH reduction of **1** does *not* involve C-3 attack leading to reduction of the

ketone group. The primary process is apparently the reductive elimination of the tosyl group, initiated by hydride attack at C-5. This elimination leads to the unsaturated ketone **9**, which then *in situ* is reduced, in a 1,2-fashion, to form the exo-cyclic methylene compound **7** (Scheme 1).

Scheme 1

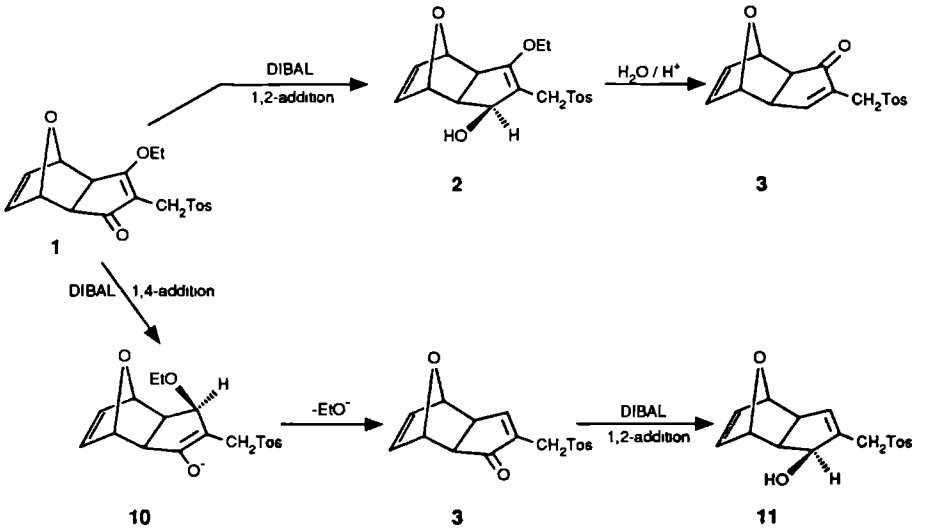


1 **9** **7**

The regioselectivity of the second step is certainly not trivial, since cyclic enones possessing an exo-cyclic double bond have been reported to be reactive Michael acceptors[12-14]. Evidence for the 1,2-selectivity of this step was obtained independently from the LAH reduction of enone **9**, which could be prepared by MnO_2 oxidation of the allylic alcohol **7** (*vide infra*). Under conditions identical to the LAH reduction of sulphone **1**, enone **9** was converted regioselectively and quantitatively into alcohol **7**.

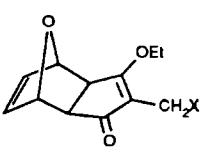
The mechanistic course of the first step is supposed to proceed via the S_N2' pathway. The occurrence of such an S_N2' process has been established for the nucleophilic displacement of the tosyl group in **1** by other nucleophiles such as alcoholates and thiolates[3]. Strong evidence against the alternative pathway, involving initial conjugate addition of the hydride to the enone moiety of sulphone **1** to form the intermediate enolate **10**, was provided by an observation during the investigation of the DIBAL reduction of this sulphone. In contrast to LAH, DIBAL was found to reduce **1** preferentially in a 1,2-fashion to afford **2** as the major product. The acid hydrolysis of **2** subsequently led to enone **3** (Scheme 2). However, when excess of DIBAL was applied in this reaction, some bis-reduction product **11** was isolated also. The formation of **11** can only be explained by assuming initial 1,4-hydride addition, leading to the formation of enolate **10**. This enolate eliminates *in situ* the C-5 ethoxy group to give enone **3**, which is then, under the conditions of the reaction, converted into alcohol **11** via a regioselective 1,2-reduction (Scheme 2). If such a conjugate addition in the LAH reduction of sulphone **1** would play a role of any importance, then formation of **11** would certainly have been observed. However, no trace of **11** was found in the crude reaction mixture of the LAH reduction. In the DIBAL reductions on the other hand no α-methylene product **7** was observed. This allows the conclusion that in the LAH- and 1,4-DIBAL reduction we are dealing with two different processes, both involving initial hydride attack at C-5. The different results with DIBAL, as compared with LAH, after the attack at C-5 can be explained by assuming that DIBAL coordinates more strongly with the carbonyl group[15], thus promoting the 1,4-addition. For LAH, which

Scheme 2



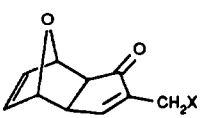
coordinates less efficiently, both the 1,2- and the 1,4-addition are overruled by the S_N2' displacement of the tosyl group. The absence of any **7** in the product mixtures of the DIBAL reactions not only excludes the S_N2' pathway for the DIBAL reduction, it also proves that elimination of the tosyl group from enolate **10** does not take place. The exclusive elimination of the C-5 ethoxy group from **10** can be explained by an enhanced leaving ability of the ethoxy group due to complexation with the excess of DIBAL. On the other hand strain factors, favouring the formation of an endo-cyclic enone system instead of a cyclic enone with an exo-cyclic olefinic bond also may be involved.

Both the mechanistic course and the regiospecifity of the first step in this LAH reduction are exceptional. In contrast to sulphone **1**, the analogous alkoxymethyl and thiomethyl substituted tricyclic enones **12a** and **12b** undergo exclusively 1,2-reduction of the carbonyl group when treated with LAH, to afford the corresponding α,β-unsaturated enones **13a** and **13b**, respectively. In these



12a X=OiPr

12b X=SPh



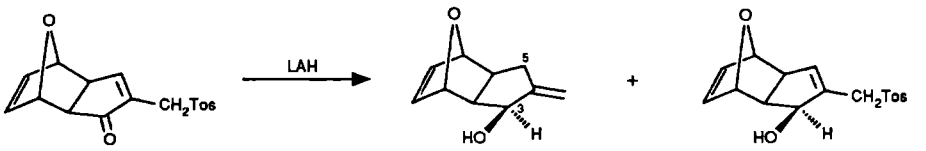
13a X=OiPr

13b X=SPh

LAH reductions the formation of **7** was not observed[3]. Hence, the exceptional regiospecifity of the LAH reduction of sulphone **1** is attributable to the presence of the tosyl group. Most likely, this is connected with the strongly electronegative character of the sulphonyl group which causes a substantial electron deficiency at C-5 of sulphone **1**.

In order to investigate the influence of the C-5 ethoxy group on this reductive process, sulphone **3**, lacking this substituent, was treated with LAH under conditions as applied for sulphone **1**. This afforded the bis-hydride reduction product **8** and sulphone **11**[3], in a ratio of 4:1 (Scheme 3).

Scheme 3



3 **8** **11**

Compound **11** was isolated by chromatography. The amount of this by-product could be diminished by performing the reduction at a lower temperature (0°C). In that case, only a negligible amount of **11** was formed (≤ 5%).

Apart from the signals for the substituents at C-5, the ^{1}H-NMR features of **8** resemble those of **7**. The assignment of the configuration at C-3 is based on the assumption that the stereochemical course of this bis-hydride reduction is the same as that of the LAH reduction of sulphone **1**.

The decreased regioselectivity in the LAH reduction of sulphone **3**, as compared with the LAH reduction of sulphone **1**, can be explained as follows. Due to the absence of the electron releasing C-5 ethoxy group, the electron deficiency at C-3 in sulphone **3** will be more pronounced than at C-3 in sulphone **1**. This electronic effect, favouring 1,2-reduction, is apparently large enough to bring about some competition between hydride attack at C-3 and C-5 in **3**.

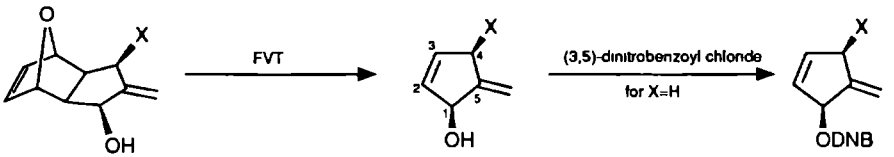
Synthesis of α-methylene cyclopentenoids.

The finding of an efficient and stereospecific route to the tricyclic α-methylene alcohols **7** and **8** offers an interesting possibility to synthesize the α-methylene cyclopentenols, **14** and **15**, and the α-methylene cyclopentenones, **17** and **18**.

For the preparation of **14** and **15** only a cycloreversion reaction had to be accomplished. This was carried out by subjecting **7** and **8**, respectively, to Flash Vacuum Thermolysis (FVT) (see Scheme 4).

Sublimation of **7** at 0.1 mbar through a quartz pyrolysis tube (16 x 1.3cm), heated at 400°C, afforded **14** as the only product (81% yield). Under these conditions the conversion of **8** into **15** was

Scheme 4



7 X=OEt
8 X=H

14 X=OEt
15 X=H

16 X=H

not entirely complete. Apparently, a longer contact time or a higher thermolysis temperature was needed in this case. Employment of a longer pyrolysis tube (25 x 1.3 cm) without changing the other thermolysis parameters indeed provided alcohol **15** (86% yield) without any substrate **8** left.

The spectral data of the α-methylene cyclopentenols **14** and **15** are characteristic for their structure. Both compounds display a strong broad OH absorption in the IR spectrum at ~ 3300 cm^{-1}. For **15** also a less intense OH band at 3595 cm^{-1}, indicative of a free OH group, is found.

The ^{1}H-NMR spectrum of **14** reveals a typical pattern for the ring protons, *viz.* a singlet for H_2 and H_3 at δ 6.12 ppm, a broad singlet for H_1 at δ 4.81 ppm and a broad singlet for H_4 at δ 4.71 ppm. The assignment of the last two signals is based on the different downward shifts caused by a hydroxy (*ca.* 1.7 ppm) and an alkoxy substituent (*ca.* 1.5 ppm)[16], respectively. For the α-methylene protons of **14** a set of two broad singlets is found at δ 5.52 and δ 5.47 ppm. The configuration at C-1 and C-4, which could not be deduced from ^{1}H-NMR data, is assumed to be the same as that at C-3 and C-5, respectively, in precursor **7**.

Despite its simplicity, the ^{1}H-NMR pattern of **15** did not immediately allow a definite assignment. The olefinic ring protons H_2 and H_3, which in contrast to **14** are clearly distinguishable from each other due to the absence of the C-4 ethoxy group, appear at δ 6.04 and δ 5.89 ppm, respectively. As compared with the H_4 proton of **14**, the protons H_{4A} and H_{4B} of **15** have shifted upfield (*ca.* 1.7 ppm) and are found at δ 3.03 ppm. For H_1 and both α-methylene protons a set of three singlets is observed at δ 5.39, δ 5.17 and δ 5.01 ppm. In order to assign these latter resonances, cyclopentenol **15** was converted into its dinitrobenzoate **16**. Comparison of the ^{1}H-NMR spectrum of **16** with that of **15** revealed a downfield shift for all the ring protons, except for one of the H_4 protons. For this particular proton an upfield shift of 0.36 ppm was observed. This upfield shift is most likely due to a shielding effect of the dinitrobenzoate group. This proton must thus be the proton, that is in *cis*-position towards the benzoate group (H_{4A}). The resonances for H_1 and the α-methylene protons were found at δ 6.30 and δ 5.16/5.04 ppm respectively. On the basis of this information the singlet at δ 5.39 ppm in the ^{1}H-NMR spectrum of **15** was assigned to H_1 and the remaining singlets at δ 5.17 and δ 5.01 ppm to the α-methylene protons.

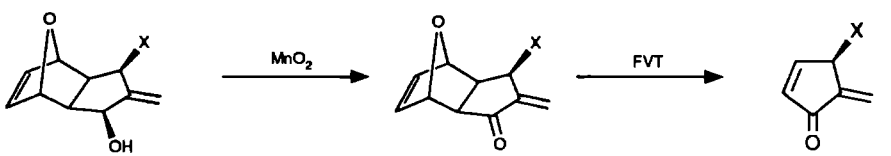
Cyclopentenol **14** decomposes slowly, even when stored in the freezer. In its IR spectrum a

strong absorption band at ~ 1730 cm^{-1} and a weaker one at 1650 cm^{-1} gradually appeared, while in the ^{1}H-NMR spectrum an extra set of doublets at δ 7.53 and δ 6.48 ppm was observed along with three new singlets at resp δ 6.21, δ 5.70 and δ 5.04 ppm. Both the IR data and the low field ^{1}H-NMR signals pointed to an α,β-unsaturated carbonyl system. GCMS(EI)-analysis of the new structure revealed a mass loss of only two m/e units as compared with the molecular mass of **14**. On the basis of these data we tentatively assigned structure **17** to this compound, which was confirmed in a later stage by an independent synthesis (*vide infra*).

This apparent oxidation of **14** to **17** is typical for **14**. Cyclopentenol **15** was found to be much more stable on storage in the freezer. This suggests that the C-4 ethoxy group plays a role in the formation of **17** from **14**.

The synthesis of the α-methylene cyclopentenones, **17** and **18**, from the tricyclic precursors **7** and **8** respectively required, apart from a cycloreversiom step, the oxidation of the allylic alcohol group at C-3. The precursor for **17** *viz.* **9**, was readily prepared from **7** by an MnO_2 oxidation (Scheme 5, *cf.* discussion of Scheme 1). Similarly, **19** was obtained from **8** in good yield.

Scheme 5



7 X = OEt
8 X = H

9 X = OEt
19 X = H

17 X = OEt
18 X = H

Both enones appeared to be sensitive compounds. Attempts to obtain an analytically pure sample of **19**, using various chromatographic techniques, failed due to decomposition of the product. Flash chromatography of enone **9** over SiO_2 also led to considerable decomposition. Most unexpectedly, in this case, besides enone **9**, a small amount of the cycloreversion product **17** was isolated[17]. Since the purity of both **9** and **19**, as obtained directly from the oxidation, was sufficient for the subsequent thermolyses, no further attempts were made to prepare analytically pure samples. The spectral data obtained for **9** and **19** were in full accord with their structures.

The cycloreversions of enones **9** and **19** to give **17** and **18**, respectively, were carried out under FVT conditions. When **9** was subjected to the same thermolysis conditions (400°C, 0.1 mbar), that had been applied on its precursor **7** in the synthesis of **14**, it was quantitatively converted into a mixture of the desired cyclopentenone **17** and an unknown by-product in a ratio of *ca.* 3:1 (capillary GC and ^{1}H-NMR data). Comparison of the^{1}H-NMR data of the mixture with those obtained for **14** and **18** (*vide infra*), confirmed the presence of structure **17** as the major product. The structure of the

by-product has not been elucidated yet. In order to prevent the formation of a similar by-product in the thermolysis of **19**, or at least to diminish its relative amount, the cycloreversion of enone **19** was attempted at a lower temperature, *viz.* 310°C instead of 400°C. This experiment afforded cyclopentenone **18** as the only product.

Both α-methylene cyclopentenones **17** and **18** are characterized by their spectral properties. Most typical are the ^{1}H-NMR resonances of the endo-cyclic H_β protons at low field, *viz.* δ 7.59 and δ 7.61 ppm, respectively, and those of the exo-cyclic H_β protons at much higher field, *viz.* δ 5.69/6.23 ppm and δ 5.44/6.12 ppm, respectively. The ^{1}H-NMR data of **18** are in agreement with those reported by Siwapinyoyos and Thebtaranonth[18] for this compound. Both cyclopentenones appeared to be stable on storage in the freezer. No indications of a spontaneous polymerization[18] were found.

3.3 Concluding remarks

The bis-hydride reduction of the sulphones **1** and **3** by LAH involves the initial S_N2' displacement of the tosyl group and subsequent 1,2-reduction of the carbonyl function. Both these processes proceed stereocontrolled from the *exo*-side of the substrate molecule, *anti* with respect to the oxa-bridge. This special behaviour of the sulphones **1** and **3** during LAH reductions finds its origin in the electron attracting character and the leaving ability of the allylic tosyl group.

The reduction products, *i.e.* the alcohols **7** and **8**, are excellent precursors for the stereospecific synthesis of functionalized α-methylene cyclopentenols and α-methylene cyclopentenones, using the FVT technique for the required cycloreversions. Such cyclopentenoids, in particular the α-methylene cyclopentenones, are potentially valuable synthons in natural product synthesis[18,19].

3.4 Experimental section

General remarks

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were taken on a Perkin Elmer 298 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 or a Bruker WH-90 spectrometer using TMS as internal standard. For mass spectra a Varian SM-1B or a double focussing VG 7070E mass spectrometer was used. Column chromatography under light pressure ("flash chromatography"[20]) was carried out at a pressure of *ca* 1.5 bar, a column length of *ca* 15 cm and a column diameter of 1-4 cm, using Merck Kieselgel 60 H or Merck Aluminium Oxid 150 neutral (Typ T).

Endo-*5-ethoxy-4-methylene*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8-ene*-endo-*3-ol* (**7**).

Sulphone **1**[3] (450 mg; 1.25 mmol) was added to 57 mg of LAH (1.50 mmol), suspended in a mixture of dry ether (12 ml) and dry THF (18 ml), under nitrogen, at room temperature. After 40 min of stirring, acetone (1 ml) was added to decompose the excess of LAH. The mixture was stirred for another 5 min and was then diluted with saturated NH_4Cl (5 ml). Stirring was continued for 15 min. Then more water was added to obtain a better separation between the organic and the aqueous layer. The aqueous phase was extracted with dichloromethane (3x60 ml). The combined organic layers were washed with water(3x), dried ($MgSO_4$), filtered and concentrated. The crude product (247 mg, purity *ca*, 90%) was crystallized in hexane-ethyl acetate (5:1) to give 108 mg of pure **7**, mp 132-134°C. Flash chromatography (SiO_2/hexane-ethyl acetate (3:1)) of the mother liquor afforded an additional amount of pure **7** (83 mg) (70% total yield). IR(KBr) v: 3365(s), 3020(w), 2975(m), 2885(m), 1430(br w), 1372(w), 1350(w), 1308(m), 1230/1225(m), 1160(w), 1145(w), 1123(m), 1100/1088(s), 1073(m), 1008(m), 948(m), 918(m), 905/898(s), 830(m), 698(s) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21(3H,t,J=7Hz;OCH_2CH_3), 2.11-2.31(2H,m;H_6,H_2), 2.42(1H,br d,J=8Hz;OH), 3.57(2H,q,J=7Hz;OCH_2CH_3), 4.10(1H,m;H_5), 4.40(1H,m;H_3), 4.92(d,J=1.8Hz)/4.97(d,J=1.8Hz) ($C=CH_2$)[21]//4.99(br s;H_7)/5.07(br s;H_1)(4H in all), 6.28(2H,m;H_8,H_9). MS(CI) m/e(%): 209(43;M+1$^+$), 191(16;-H_2O), 163(14;-C_2H_5OH), 162(13;M$^+$-C_2H_5OH), 147(14), 146(24), 145(100), 141(10;-furan), 139(12), 137(14), 123(42;-H_2O,-furan), 117(19), 113(62), 95(23;-furan,-C_2H_5OH), 85(20), 68(15;furan$^+$). (Found: C 69.55, H 7.86. Calc. for $C_{12}H_{16}O_3$: C 69.21, H 7.74%.)

Attempted reduction of sulphone **2** *with LAH.*

Sulphone **2**[3] (206 mg; 0.57 mmol) was stirred with LAH (24 mg; 0.63 mmol) in a mixture of dry ether (4 ml) and dry THF (6 ml), under nitrogen, at room temperature, for 2.5 hr. About half the amount of the reaction mixture was then treated with acetone (0.5 ml; 5 min of stirring) to decompose the excess of LAH. Subsequent hydrolysis was carried out with 10% NaOH. The aqueous layer was extracted with dichloromethane (3x3 ml). The combined organic extracts were washed with water (1x), dried ($MgSO_4$) and concentrated, affording 147 mg of sulphone **2**. No trace of **7** was found in this product (^{1}H-NMR). The remaining part of the reaction mixture was stirred overnight with an extra amount of LAH (8 mg). Subsequent work-up in the same way as above, afforded 40 mg of sulphone **2**. Although its purity was less than that of the first batch, again no trace of **7** could be detected (^{1}H-NMR).

4-Methylene-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8-ene*-endo-*3-ol* (**8**).

Reduction of sulphone **3**[3] (187 mg; 0.6 mmol) with LAH (30 mg; 0.8 mmol) in a mixture of dry ether (6 ml) and dry THF (9 ml), as described above for sulphone **1** (see **7**), afforded 117 mg of a crude product mixture, containing alcohol **8** and sulphone **11**[3] in a ratio of 4:1 (combined yield *ca.* 100%). Separation of the products was accomplished by flash chromatography over SiO_2, using

hexane-ethyl acetate (3:1) as the eluent. An analytically pure sample of **8**, mp 104-106°C, was obtained by subsequent crystallization in hexane-ethyl acetate (3:1). With the above eluent, sulphone **11** severely dragged behind and could not be collected. However, by applying a more polar eluent, this sulphone indeed could be isolated. By performing the reduction at 0°C instead of room temperature, the relative amount of **11** was substantially reduced. IR(KBr) ν: 3405(s), 3000(m), 2965(m), 2885(m), 1428(m), 1310(m), 1110/1105(s), 1005/998(m), 945(m), 905(s), 880(s), 862(s), 830(s), 678(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.80-2.68(5H,m; *endo*-H_5,H_6,H_2,OH,*exo*-H_5), 4.48(1H,br m;H_3), 4.65(1H,s;H_7), 4.85(d,J~1Hz)/4.93(d,J~1Hz)(2H;C=CH_2)[21], 5.12(1H,s;H_1), 6.36(2H,narrow m;H_8,H_9). (Found: C 72.55, H 7.46. Calc. for $C_{10}H_{12}O_2$: C 73.15, H 7.37%.)

Endo-*5-ethoxy-4-methylene*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8-ene-3-one* (**9**).

A mixture of **7** (108 mg; 0.52 mmol), activated MnO_2 (1851 mg; 21.2 mmol) and dry ether (15 ml) was stirred for 3 hrs at room temperature. Subsequent filtration and evaporation afforded 51 mg of **9** as an almost pure (^{1}H-NMR), pale tinted oil (50% yield). Attempts to purify the product by flash chromatography (SiO_2/hexane-ethyl acetate (3:1)) afforded two fractions, the first of which was **17** (9 mg) (^{1}H-NMR and capillary GC data identical to those of **17**, *vide infra*), while the second consisted of pure **9** (18 mg; colourless oil). IR(CCl_4) ν: 2980(w), 2872(w), 1725(s;C=O), 1645(w; C=C), 1145(w), 1120/1110(s), 1015(w), 955/945(w), 918(w), 898(w), 870(w), 855(w), 683(m) cm^{-1}. ^{1}H-NMR(CCl_4) δ: 1.33(3H,t,J=7Hz;OCH_2CH_3), 2.39(2H,m;H_6,H_2), 3.44-3.83(2H,m,ABX_3 system, J_{AX}=J_{BX}=7Hz;OCH_2CH_3), 4.53(1H,m;H_5), 4.97(1H,br s;H_7), 5.13(1H,br s;H_1), 5.37(1H,dd,J~1.5Hz, J_{gem}=3Hz)/5.91(1H,dd,J~1.5Hz,J_{gem}=3Hz)(C=CH_2)[21], 6.35(d,$J_{8,9}$=5.4Hz)/6.44(dd,J=1.5Hz, $J_{8,9}$=5.4Hz)(2H;H_8,H_9).

Conversion of **9** *into* **7** *via LAH reduction*.

Enone **9** (29 mg; 0.14 mmol) was treated with LAH (5 mg; 0.13 mmol) in a mixture of dry ether (2 ml) and dry THF (4 ml), under nitrogen, at room temperature. After 5 min all starting material had reacted (TLC). Acetone (0.5 ml) was added to quench the reaction. Work-up was carried out as described above for **7**. This afforded 28 mg (*ca.* 100%) of crude **7**, as a thick white oil. The IR spectrum of this product showed no carbonyl absorption. Crystallization from hexane-ethyl acetate (5:1) gave analytically pure **7**.

4-Methylene-exo-10-oxatricyclo[5.2.1.0^{2,6}]deca-8-ene-3-one (**19**).

A mixture of **8** (90 mg; 0.55 mmol), activated MnO_2 (7.6 mg; 8 mmol) and dry ether (12 ml) was stirred for 2.5 hr at room temperature. The mixture was then filtered and evaporated to give 88 mg (98% yield) of **19** as a colourless oil, which solidified in the freezer. Attempts to obtain an analytically pure sample by means of preparative TLC (SiO_2/ethyl acetate) or flash chromatography (Al_2O_3/hexane-ethyl acetate (3:1)) failed, due to decomposition of the product during these purifi-

cations. IR(CCl_4) ν: 3000(w), 2965(w), 2935(w), 1722(s;C=O), 1638(m;exocyclic C=C), 1270(s), 1148(s), 1112(m), 1020(m), 940(s), 920/910/902(m), 875(s), 690(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.24-2.57(~2H,m;H_6,H_2 and upfield part of ABXY pattern of *endo*-H_5), 2.67(~1H,narrow q, $J_{5,5'}$~3Hz;downfield part of ABXY pattern of *endo*-H_5), 2.77-3.21(1H,m;*exo*-H_5), 4.83(1H,br s;H_7), 5.10(1H,br s;H_1), 5.25(1H,narrow t, $J_{5',5}$~3Hz)/5.94(1H,narrow t,$J_{5',5}$~3Hz)($C=CH_2$)[21], 6.41(2H, narrow m;H_8,H_9). MS(CI) m/e(%): 163(3;M+1$^+$), 162(7;M$^+$), 145(12), 135(10;-CO), 123(17), 117(24), 95(100;-furan), 68(furan$^+$).

Flash vacuum thermolysis: general procedure.

The substrate is sublimed or distilled in vacuo, at moderate temperature (T_1) through a quartz pyrolysis tube (25 or 16 x 1.3 cm; oven heated (T_2)). The pyrolysate is collected immediately after the tube in a cold trap at -78°C. After the reaction the cold trap is disconnected from the equipment[22] and allowed to warm up under nitrogen. The product is then obtained by rinsing the cold trap with a suitable solvent, followed by removal of the solvent in vacuo.

Cis-*4-ethoxy-5-methylene-2-cyclopentenol* (**14**).

Flash vacuum thermolysis (16 cm tube/0.1 mbar/80°C(T_1)/400°C(T_2)) of **7** (106 mg; 0.50 mmol) provided **14** (57 mg; 81% yield) as a colourless oil (GLC: one peak, 99%). IR(film) ν: 3380(br s;OH), 2970(m), 2870(m), 1390(m), 1350(m), 1060(s), 1010(s), 990(s), 900(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.18(3H,t,J=7Hz;OCH_2CH_3), 1.97(1H,br m;OH), 3.53(2H,q,J=7Hz;OCH_2CH_3), 4.71(1H,br s;H_4), 4.81(1H,br s;H_1), 5.47(1H,br s)/5.52(1H,br s)($C=CH_2$)[21], 6.12(2H,s;H_2,H_3). MS(EI) m/e(%): 140(2;M$^+$), 139(10;M-1), 123(17;-OH), 112(23;-CO), 111(49;-C_2H_5), 95(100; -OC_2H_5), 83(36), 77(11;C_6H_6), 67(48), 55(60), 41(48), 39(59). HRMS(EI) m/e: 140.0839 (calc. for $C_8H_{12}O_2$(M): 140.0837).

5-Methylene-2-cyclopentenol (**15**).

Flash vacuum thermolysis (25 cm tube/0.06 mbar/80°C(T_1)/420°C(T_2)) of **8** (46 mg; 0.28 mmol) provided **15** (23 mg; 86% yield) as a colourless oil. IR(CCl_4) ν: 3595(m;free OH), 3500-3200(br m), 3060(m), 2985(w), 2900(m), 2825(w), 1432(w), 1380(m), 1110(m), 1040(m), 1000(s), 960(m), 910(s), 837(m), 715(m), 688(w) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.72(1H,s;OH), 3.03(2H,narrow m;H_{4A},H_{4B}), 5.01(1H,br s)/5.17(1H,br s)($C=CH_2$)[21], 5.39(1H,br s;H_1), 5.89(1H,d,$J_{3,2}$=6.7Hz;H_3), 6.04(1H,d,$J_{2,3}$=6.7Hz;H_2).

5-Methylene-2-cyclopentenyl 3,5-dinitrobenzoate (**16**).

Benzoylation of **15** (21 mg; 0.21 mmol) with 50 mg of 3,5-dinitrobenzoyl chloride (0.22 mmol) and a catalytic amount of DMAP (9 mg; 0.08 mmol) in a mixture of dichloromethane (5 ml) and triethylamine (5 drops) at 0°C during 1 hr, afforded, after the usual work-up, repeated flash

chromatography (SiO_2/hexane-ethyl acetate (3:1); SiO_2/hexane-ethyl acetate (9:1)) followed by crystallization (hexane), 11 mg of pure, white **16**, mp 103-106°C. IR(KBr) v: 3080(w;vinyl H), 1720(s;C=O), 1623(m;C=C), 1540(s;NO_2), 1342(s;NO_2), 1268(s), 1160(s), 730(m), 720(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.57(d,$J_{4A,3}$~2Hz)/2.76(d,$J_{4A,3}$~2Hz)//3.04(br d,$J_{4B,3}$=6.7Hz)/3.24(br d,$J_{4B,3}$=6.7Hz)(2H,ABX system,J_{AB}=18Hz;H_{4A},H_{4B}), 5.04(1H,br s)/5.16(1H,br s)(C=CH_2)[21], 6.16(m,$J_{3,2}$~$J_{3,4B}$=6-7Hz,$J_{3,4A}$~2Hz;H_3)/6.30(br s;H_1)(2H), 6.59(1H,d,$J_{2,3}$=6.2Hz;H_2), 9.16(3H,m;ArH). NB H_{4A} is the proton at C-4 that is in *cis*-position towards the dinitrobenzoate group. (Found: C 53.67, H 3.44, N 9.50. Calc. for $C_{13}H_{10}N_2O_6$: C 53.80, H 3.47, N 9.65%.)

4-Ethoxy-5-methylene-2-cyclopentenone (**17**).

Flash vacuum thermolysis (16 cm tube/0.03 mbar/80°C(T_1)/400°C(T_2)) of **14** (17 mg; 0.08 mmol) afforded a mixture (11 mg) containing **17** as major component (73%). Since the amount of product material was rather small, no attempts to separate cyclopentenone **17** from the by-product were made. Its spectral data could easily be deduced from the spectra of the crude pyrolysate. IR(CCl_4) v: 1728(s;C=O) and 1652(w;exocyclic C=C) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.22(3H,t,J=7Hz;OCH_2CH_3), 3.57(2H,q,J=7Hz;OCH_2CH_3), 5.04(1H,br s;H_4), 5.69(1H,br s)/6.23(1H,br s)(C=CH_2)[21], 6.50(1H,d,$J_{2,3}$=6Hz;H_2), 7.59(1H,d(d),$J_{3,2}$=6Hz;H_3). GCMS(EI) m/e(%): 138(48;M^+), 110(81;-CO), 109(52;-C_2H_5), 94(27), 93(72;-OC_2H_5), 82(81), 81(53), 65(100), 55(99), 39(99), 27(84).

5-Methylene-2-cyclopentenone (**18**).

Flash vacuum thermolysis (16 cm tube/0.03 mbar/60°C(T_1)/310°C(T_2)) of **19** (12-20 mg; 0.07-0.12 mmol) provided **18** as the only product (colourless oil; capillary GC: one peak (99%)). IR(CCl_4) v: 1708(s;C=O), 1650(m;exocyclic C=C), 1582(w), 1428/1415/1402/1388(w), 1342(w), 1250(m), 1195(m), 1135(m), 1080(w), 950(m), 937(s), 838(m), 698(m) cm^{-1}. ^{1}H-NMR($CDCl_3$)[18] δ: 3.24(2H,narrow m; H_{4A},H_{4B}), 5.44(1H,br s)/6.12(1H,br s)(C=CH_2)[21], 6.42(1H,br d,$J_{2,3}$=6Hz;H_2), 7.61(1H,m;H_3). MS(CI) m/e(%): 95(100;M+1$^+$), 79(18), 68(29), 57(21). HRMS(CI) m/e: 95.0500 (calc. for C_6H_7O(M+1): 95.0497).

3.5 References and notes

1. Part of this work was published as a short communication: Klunder, A. J. H.; Crul, M. J. F. M.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 3147. The detailed account, as presented in this chapter, has recently appeared: Houwen-Claassen, A. A. M; Klunder, A. J. H. and Zwanenburg, B. *Tetrahedron*, **1989**, *45*, 7149.

2. (a) Klunder, A. J. H.; Bos, W.; Verlaak J. M. J.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4553; (b) Klunder, A. J. H.; Bos, W.; Zwanenburg, B. *Ibid.* **1981**, *22*, 4557; (c) Verlaak, J. M. J.; Klunder, A. J. H.; Zwanenburg, B. *Ibid.* **1982**, *23*, 5463; (d) Klunder, A. J. H.; Huizinga, W. B.; Sessink, P. J. M.; Zwanenburg, B. *Ibid.* **1987**, *28*, 357; (e) Klunder, A. J. H.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *Ibid.* **1987**, *28*, 1329; (f) Lange, J. H. M.; Klunder, A. J. H.; Zwanenburg, B. *Ibid.* **1989**, *30*, 127.
3. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Kooy, M. G.; Steffann, J.; Zwanenburg, B. *Tetrahedron,* **1989**, *45*, 7109.
4. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron,* **1989**, *45*, 7134.
5. Gannon, W. F.; House, H. O. In *Organic Syntheses*; Wiley, New York, 1973; Coll. Vol. V, p 294.
6. Funk, R. L.; Vollhardt, K. P. *Synthesis* **1980**, 118.
7. Gill, M.; Herlt, A. J.; Richards, R. W. *Tetrahedron* **1982**, *38*, 3527.
8. Oda, M.; Kanao, Y.; Kasai, M.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1977**, *45*, 2497.
9. Smits, J. M. M.; Beurskens, P. T.; Klunder, A. J. H.; Crul, M. J. F. M. *J. Cryst. Spectrosc. Res.* **1986**, *16*, 665.
10. For an example of the participation of an oxygen containing functionality in the reduction of a carbonyl group, see: Klunder, A. J. H.; de Valk, W. C. G. M.; Verlaak, J. M. J.; Schellekens, J. W. M.; Noordik, J. H.; Parthasarathi, V.; Zwanenburg, B. *Tetrahedron,* **1985**, *41*, 963.
11. Previously, we mentioned also an inertness of sulphone **2** on treatment with sodium methanolate in refluxing methanol[3].
12. Siwapinyoyos, T.; Thebtaranonth, Y. *Tetrahedron Lett.* **1984**, *25*, 353.
13. Smith III, A. B.; Wexler, B. A.; Slade, J. S. *Tetrahedron Lett.* **1980**, *21*, 3237.
14. Verlaak, J. M. J. *Ph.D. Thesis*, University of Nijmegen, Febr. 1983; Chpt. 3.3.
15. House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin, Menlo Park, California, 1972; p 67.
16. Hesse, M.; Meier, H.; Zeeh, B. *Spektroskopische Methoden in der organischen Chemie*, 3. Auflage; Georg Thieme: Stuttgart-New York, 1987; p 114.
17. A similar result has recently been reported by Marchand and Vidyasagar, who demonstrated that the tricyclic enones, *exo*-2-carbomethoxy-*exo*-3-methyl- and *exo*-2-carbomethoxy-*exo*-3,7-dimethyl-tricyclo[5.2.1.$0^{2,6}$]deca-8-en-5-one undergo a rapid, Lewis acid promoted cycloreversion at room- or even lower temperatures (Marchand, A. P.; Vidyasagar, V. *J. Org. Chem.* **1988**, *53*, 4412). Their explanation for this acid catalyzed fragmentation may also be applicable to the SiO_2 mediated cycloreversion of **13**.
18. Siwapinyoyos, T.; Thebtaranonth, Y. *J. Org. Chem.* **1982**, *47*, 598.

19. (a) Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1987**, *28*, 333; (b) Shibasaki, M.; Ogawa, Y. *ibid.* **1985**, *26*, 3841; (c) Nagaoka, H.; Miyakoshi, T; Yamada, Y. *ibid.* **1984**, *25*, 3621; (d) Smith III, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855; (e) Nakanishi, K. *Natural Product Chemistry;* Nakanishi, K. Ed.; 1983; Vol. 3.

20. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

21. Increment calculations (ref 16, p 115) lead to the conclusion that the highest field signal of this pair should be assigned to the *exo*-cyclic H_β proton, that is in *cis*-position to the carbonyl group.

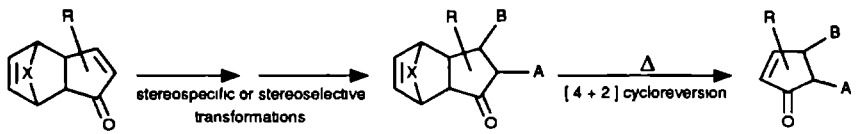
22. ref 14, p 154.

CHAPTER 4: MENTHOL MEDIATED OPTICAL RESOLUTION OF 10-OXATRICYCLO-DECADIENONES. APPLICATION IN THE ENANTIOSELECTIVE SYNTHESIS OF CYCLOPENTENOIDS.

4.1 Introduction

Tricyclodecadienones **1** (X = CH_2, O) can be employed as versatile substrates for the synthesis of functionalized cyclopentenones. Conjugate addition to their enone moiety, followed by electrophilic substitution and appropriate functional group transformations, allows the introduction of various functional groups. The resulting tricyclodecenones **2** (X = CH_2, O) can subsequently be converted into the desired cyclopentenones **3** by a thermal [4+2] cycloreversion[1,2]. This reaction sequence, which is summarized in Scheme 1, constitutes a stereoselective synthetic method for the

Scheme 1

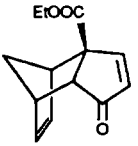


1 **2** **3**

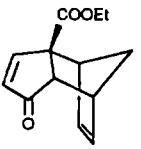
preparation of cyclopentenoids **3**, since both the formation of **2** from **1** and the thermal cyclo-reversion to **3** proceed in a stereocontrolled fashion. Control of stereochemistry during the formation of **2** is associated with the characteristic tricyclic structure of the substrate and intermediate products, which enforces reactants to enter exclusively from the least hindered *exo*-face of the molecule[1,2]. The stereospecifity of the cycloreversion is inherent to the mechanism of the retro-Diels-Alder reaction.

The stereoselectivity of the method and, as a consequence, its interest for natural product synthesis, is demonstrated by our syntheses of the naturally occurring cyclopentenoids: terrein, pentenomycin, *epi*-pentenomycins and sarkomycins[2].

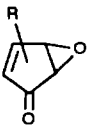
In order to extend the scope of this method to *enantioselective syntheses*, several ways to obtain enantiomerically pure tricyclodecadienones **1** were investigated. We previously reported[3] the efficient separation of the tricyclic ester **4** by enantioselective enzymatic hydrolysis using pig liver esterase. Both enantiomers, (+)**4** and (-)**4**, were obtained in high optical and chemical yield and various optically pure cyclopentenones have since been prepared from these esters, using the strategy



(+) 4



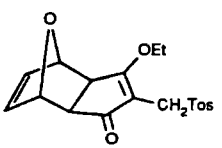
(-) 4



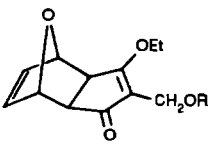
5

given in Scheme 1[4].

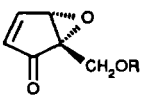
In this chapter the attention is focussed on the resolution of furan derived tricyclodecadienones, **1** (X = O). As has recently been reported [5,6] these 10-oxatricyclodecadienones are excellent precursors for cyclopentadienone epoxides **5**, which are of interest for the preparation of highly oxygenated cyclopentenoid natural products[2b,2c,6]. In our synthesis of functionalized cylopentadienone epoxides an essential role is played by tricyclic sulphone **6**. This sulphone, which is readily available from the Diels Alder adduct of furan and cyclopentene-1,4-dione, owes its versatility as synthon primarily to its special behaviour towards nucleophilic reagents[5,7]. On treatment with sodium alcoholates it undergoes a facile displacement of the tosyl group resulting in the formation of tricyclic ethers **7**[5]. These ethers, in turn, can efficiently be transformed into



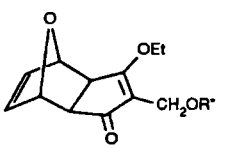
6



7



8



9a,b R* = (-) menthyl

alkoxymethyl substituted cyclopentadienone epoxides **8**, successively by a metalhydride reduction[5], an alkaline epoxidation and a thermal cycloreversion[6].

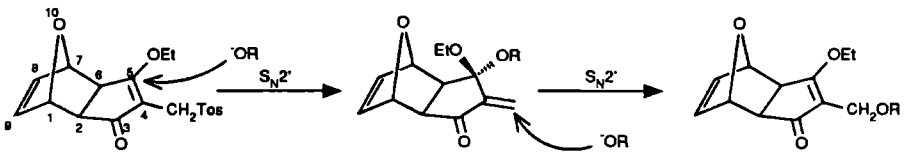
The displacement of the tosyl group in **6** by alkoxides offers an interesting possibility to achieve the desired optical resolution of the 10-oxatricyclodecadienone system. If in this displacement reaction optically pure alcoholates are employed, a mixture of diastereomeric ethers will be obtained. Separation of the diastereomers and subsequent removal of the chiral auxiliary should then eventually lead to enantiomerically pure cyclopentadienone epoxides.

In this chapter the preparation and separation of a diastereomeric mixture of menthyl ethers **9a,b** and the subsequent transformation into enantiomerically pure products is presented. The enantioselective synthesis of functionalized cyclopentenoids will be illustrated by the preparation of enantiomerically pure **8** (R = Me). Furthermore, the absolute configuration of the diastereomers **9a** and **9b** and their respective derivatives will be elucidated.

Synthesis and separation of the menthyl ethers **9a** *and* **9b**.

The formation of the tricyclic ethers **7** from sulphone **6** on treatment with sodium alcoholate, proceeds via two consecutive S_N2' reactions. The first one involves the substitution of the allylic tosyl group by attack of the alcoholate at C-5 of sulphone **6**. This leads to a reactive intermediate **10**, which then reacts with a second alcoholate molecule at the exo-cyclic methylene carbon in an S_N2' fashion to give compound **7** (Scheme 2). Details of this process have recently been reported[5].

Scheme 2



6 **10** **7**

The experimental procedure for the preparation of **7** (R = Me, Et, iPr) involves heating of sulphone **6** under reflux with *ca.* 1.5 equiv. of sodium alcoholate in a solution of the appropriate alcohol for 15-30 min. This procedure could not be used in the preparation of the menthyl ethers **9a,b**, because (-)menthol (mp 43-45°C) is not a practical solvent. The polar aprotic solvent DMF seemed a suitable solvent since both reactants readily dissolved in this medium. The desired tosyl displacement reaction took place readily, even at room temperature. The formation of the menthyl ethers **9a,b**, however, was accompanied by a considerable degradation leading to undefined polymeric by-products and low, irreproducable yields (15-40%). Such a substantial degradation had not been observed[5] during the preparations of the related ethers **7** (R = Me, Et, iPr).

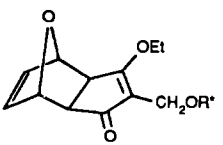
In DMF the menthylate anion may act as a reactive nucleophile but also as a strong base. It can cause deprotonation in substrate and products, either at C-2 or C-6, which may lead to β-elimination of the 10-oxa bridge[8,9]; α-deprotonation in sulphone **6** may be another cause for deviating reactions.

To avoid these interfering deprotonations several co-solvents decreasing the polarity of the reaction medium, such as dichloromethane, THF and ether, were tested, however, without success. After some experimentation it was found that addition of an extra equivalent of (-)menthol to the solution of sodium menthylate in DMF resulted in a substantially improved yield (88%). The extra amount of (-)menthol most probably suppresses undesired deprotonation reactions. The excess of the (-)menthol was readily removed by flash chromatography. The retention times of the diastereomers

9a and **9b** differed only slightly and crystallization was therefore used to separate these isomers. It was found that one of the diastereomers, **9a** (mp 127-128°C; $[\alpha]_D^{rt}$= -71.5° (c=0.6; chloroform)), could be obtained in pure form by one single crystallization from hexane-ethyl acetate (5:1). The efficiency of this crystallization averaged around 50-55%, implying an absolute yield of *ca.* 27%. The mother liquor gave on careful chromatography the other diastereomer **9b** (mp 94.5-96.5°C; $[\alpha]_D^{rt}$= -72.8° (c=0.6; chloroform)) in *ca.* 15% absolute yield (*ca.* 30% efficiency). No further efforts were made to separate the residual mixture of diastereomers.

The structures of both diastereomers were secured by IR, ^{1}H-NMR and mass spectra. The IR and mass spectra of **9a** and **9b** are nearly identical. The same holds for the majority of their ^{1}H-NMR resonances. Only the resonance pattern of the $\underline{CH_2}O$(-)menthyl protons differs distinctly. These protons appear as an AB quartet at $\delta \sim 4.17$ ppm. The size and shape of these quartets are characteristic for the particular diastereomer and can be used for a rapid identification.

An attempt to establish the absolute configuration of **9a** by means of an X-Ray analysis failed as no suitable single crystal could be obtained. Fortunately, X-Ray analyses of derivatives of diastereomer **9b** could be made (*vide infra*). These revealed the absolute configuration of **9b** and indirectly also that of **9a**.

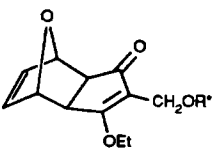


9a

mp 127-128°C

$[\alpha]_D$ = -71.5° (chloroform)

R* = (-) menthyl



9b

mp 94.5-96.5°C

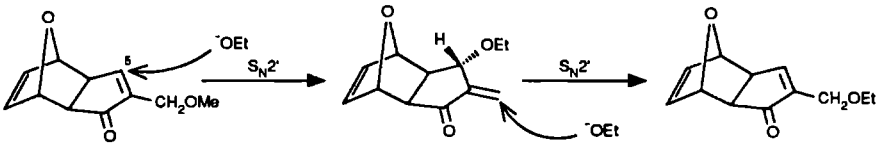
$[\alpha]_D$ = -72.8° (chloroform)

Removal of the menthyl group. Conversion of the menthyl ethers **9a** *and* **9b** *into enantiomerically pure methyl ethers* **(+)11** and **(-)11**.

In view of a possible application in the enantioselective synthesis of *epi*-pentenomycins[2d,6], removal of the chiral auxiliary using a displacement of the menthyl group by a methyl group was investigated. Such a transformation, *i.e.* a trans-etherification, can in principle be achieved by means of a reaction with sodium methoxide in methanol. Previous observations[5], that such alkoxide exchange reactions of the tricyclic ethers **7** (R = Me, Et) were accompanied by substantial deterioration (yields ≤ 5%), suggested that the menthyl ethers **9a**,**9b** might not be appropriate substrates for this displacement reaction. The trans-etherification of **7** (R = Me, Et) involves two consecutive S_N2' substitution reactions, comparable with those occurring in the conversion of sulphone **6** into **7** (Scheme 2). Assuming that the C-5 ethoxy group in **7** (R = Me, Et) might have an unfavourable influence on the first of these S_N2' displacement reactions, the trans-etherification of

compound **11**[5], lacking this C-5 substituent, was studied as a model compound. Treatment of **11** with *ca.* 1.2 equiv. of sodium ethanolate in boiling ethanol resulted in ethyl ether **12** (Scheme 3). The

Scheme 3

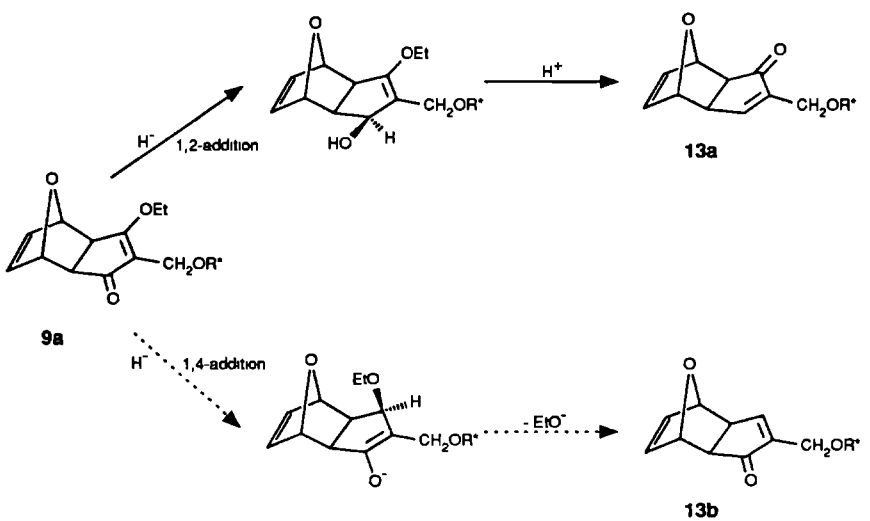


11 **12**

yield of this reaction(33%) indeed was higher than that obtained in the trans-etherifications of **7** (R = Me, Et), but still modest, indicating that β-elimination of the 10-oxa bridge efficiently competed. On the basis of similarity in structures of **7** (R = Me, Et) and **11**, it is suggested that the trans-etherification of **11** also proceeds via two consecutive S_N2' displacements, as shown in Scheme 3. From the result of this reaction it is evident that the planned displacement of the menthyl group can better be attempted with the menthyl ethers **13a**, **13b**, lacking the C-5 ethoxy substituent, than with **9a**, **9b**.

The ethers, **13a** and **13b**, were prepared by DIBAL reduction of **9a** and **9b**, respectively. The applied procedure was identical to that of the DIBAL reductions of the analogous compounds **7** (R = Me, Et, iPr)[5] and afforded **13a** and **13b** in quantitative yield. This DIBAL reduction proceeds via a

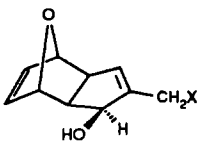
Scheme 4



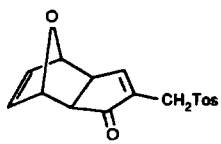
13a

13b

highly selective (1,2) hydride addition to the enone moiety and subsequent acid hydrolysis of the resulting γ-hydroxy-enolether. The (1,2) selectivity of the reduction step is absolutely essential for the conservation of chiral integrity, since (1,4) hydride addition followed by elimination of the ethoxy group will lead to the other diastereomer (Scheme 4) and, in consequence, will produce the opposite enantiomer after displacement of the menthyl group. If both routes take place racemisation will occur. Although DIBAL is known to reduce α,β-unsaturated enones preferentially in a (1,2) fashion[10,11], it is not trivial that this DIBAL reduction of **9a** and **9b** proceeds with complete regiocontrol. Our work[5] and that of others[12] revealed that β-alkoxy-enones sometimes also undergo (1,4) reduction on treatment with DIBAL. For example, when excess of DIBAL was applied in the reduction of sulphone **6**, a by-product **14** (X = Tos) was obtained, which is indicative of a (1,4) reduction. The formation of this product also shows that enone **15**, if initially formed as a result of (1,4) reduction, is converted *in situ* into **14** (X = Tos) by a selective (1,2) reduction (compare ref 12). Since similar by-products, **14** (X = OAlkyl), were neither observed in the DIBAL reductions of **7** (R = Me, Et, iPr), nor in that of **9a** and **9b**, we may conclude that during the conversion of **9** into **13** the chiral integrity is not endangered by the reduction with DIBAL. The (1,4) DIBAL reduction is apparently restricted to sulphone **6**.



14



15

The menthyl ethers **13a** and **13b** display nearly identical ^{1}H-NMR and IR spectra, which are entirely consistent with their structures. The individual diastereomers could not be separated by chromatographic techniques. Attempts to separate them by crystallization also failed, blocking resolution of the 10-oxatricyclodecadienone system in this stage. The pure diastereomers **13a** and **13b**, obtained from the respective diastereomers **9a** and **9b**, differ considerably in their crystallizability. Whereas diastereomer **13a**, derived from **9a** (mp 127-128°C), is isolated as a solid (mp 111-113°C), the other one, **13b**, is obtained as a viscous oil, which partially crystallizes on standing in the refrigerator. Their diastereomeric purity was confirmed by their conversion into optically pure (+)**11** and (-)**11** (*vide infra*). The absolute configurations of **13a** and **13b**, as given in Scheme 4, could be deduced from X-Ray diffraction analyses of derivatives of **13b** (*vide infra*).

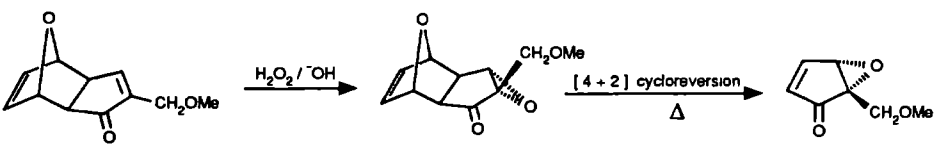
The trans-etherification of **13a** and **13b** was first tested on the diastereomeric mixture **13a,b**. Heating of this mixture under reflux in methanol with *ca.* 3 equiv. of sodium methanolate provided **11** in only 23% yield. Application of a smaller amount (1.4 equiv) of methanolate led to a substantial

improvement in yield (53%). The ^{1}H-NMR analysis of **11** using optical shift reagent Eu(hfc)$_3$[13] revealed a downfield shift for all the resonances and a prominent 1:1 splitting of the methyl singlet of the methoxymethyl group, which was suitable for a fast and accurate determination of the optical purity. Treatment of diastereomerically pure **13a** with sodium methoxide under the above optimal conditions afforded enantiomerically pure (+)**11**, mp 104-106.5°C[13], $[\alpha]_D^{24}$= +77.5° (c=0.6; chloroform). No trace of the other enantiomer was observed in the ^{1}H-NMR spectrum of the crude product upon analysis with Eu(hfc)$_3$. This confirmed the enantiomeric purity of the product and also the diastereomeric purity of the substrate. The antipode, (-)**11**, mp 104-106.2°C[13], $[\alpha]_D^{22}$= -78.4° (c=0.55; chloroform), was similarly prepared from **13b**. It was, however, also possible and in fact much easier, to obtain (-)**11** by methanolysis of partially resolved **13**, enriched in **13b**. Such a sample was obtained by DIBAL reduction of the mother liquor, that had been retained from the first resolving crystallization of **9a,b** (*vide supra*). Methanolysis of this partially resolved **13** resulted in an enantiomeric mixture enriched in (-)**11**. ^{1}H-NMR analysis of this mixture with Eu(hfc)$_3$ revealed an enantiomeric ratio (-)**11**:(+)**11** = 3:1. Crystallization of this material from hexane gave enantiomerically pure (-)**11**. This finding demonstrates that maximum diasteromeric purity of the key menthyl ethers, **9a** and **9b**, is not an absolute prerequisite to obtain the methylethers **11** in an enantiomerically pure state[15]. Crystals of (-)**11** were subjected to an X-Ray diffraction analysis to establish the absolute structure of this compound (*vide infra*).

Preparation of (+)-4,5-epoxy-5-(methoxymethyl)-cyclopentenone.

The next step in the sequence aiming at optically pure *epi*-pentenomycins involves the conversion of both antipodes of **11** into optically pure 4,5-epoxy-5-(methoxymethyl)-cyclopentenone **8** (R = Me). This transformation requires an alkaline epoxidation and a subsequent thermal cycloreversion, as shown in Scheme 5 for (-)**11**. Both reactions have recently[6] been described for racemic **11**. Therefore, the discussion will here be confined to the optical purity of the respective products.

Scheme 5



(-)**11**	(-)**16**	(+)**17**
mp 104-106.5°C	mp 56-59°C	oil
$[\alpha]_D$ = -78.4° ($CHCl_3$)	$[\alpha]_D$ = -234° ($CHCl_3$)	$[\alpha]_D$ = +330° ($CHCl_3$)

The alkaline epoxidation of (-)**11** afforded (-)**16** as a white solid in nearly quantitative yield. No trace of the antipode (+)**16** was detected in the ^{1}H-NMR spectrum of the crude product. Crystallization from hexane-ethyl acetate provided analytically pure (-)**16** as fine needles, mp 56-59°C[16], $[\alpha]_D^{22}$= -234° (c=0.53; chloroform), which were subjected to an X-Ray diffraction analysis. Atomic parameters are given in Table 1. The molecular configuration and the crystallographic numbering scheme are shown in Figure 1.

Table 1

Fractional positional and thermal parameters (with esd's).

Atom	x	y	z	100.Ueq(Å)
C(1)	-0.764(4)	-0.0959(17)	-0.6505(10)	5.9(8)
C(2)	-0.630(3)	-0.2124(20)	-0.6802(11)	6.1(7) *
C(3)	-0.796(4)	-0.3305(22)	-0.7097(12)	6.5(7) *
C(4)	-0.738(3)	-0.4566(18)	-0.6516(11)	5.0(8)
C(5)	-0.542(3)	-0.4059(18)	-0.6043(11)	4.8(5) *
C(6)	-0.473(3)	-0.2624(18)	-0.6195(9)	4.0(5) *
C(7)	-0.561(3)	-0.1622(20)	-0.5555(13)	7.1(9)
C(8)	-0.482(6)	-0.0169(22)	-0.5897(13)	8.6(12)
C(9)	-0.590(4)	0.0138(27)	-0.6377(14)	8.0(11)
O(10)	-0.8084(27)	-0.1512(15)	-0.5837(8)	7.3(5) *
O(11)	-0.4925(27)	-0.4940(17)	-0.6632(8)	8.8(7)
O(12)	-0.963(3)	-0.3305(17)	-0.7420(8)	10.0(7)
C(13)	-0.910(3)	-0.5575(16)	-0.6399(10)	4.3(7)
O(14)	-0.859(3)	-0.6422(16)	-0.5902(8)	10.2(8)
C(15)	-1.023(5)	-0.7475(25)	-0.5723(21)	15.5(16)

* Isotropic temperature factors.

This structure determination confirmed the general structure of (-)**16**, in particular, the position of the epoxide ring at the least hindered *exo*-face of the molecule, *anti* to the oxa-bridge[6]. The absolute configuration of (-)**16** could be established to a very high confidence level. Nevertheless, because of the rather poor quality of the crystals we cannot be sure that the assumption of a Gaussian error distribution is correct. Therefore, also crystals of its precursor (-)**11** were subjected to an X-Ray diffraction analysis. Atomic parameters are given in Table 2. The molecular configuration and the crystallographic numbering scheme are presented in Figure 2. Selected molecular geometries are collected in Table 3.

Figure 1

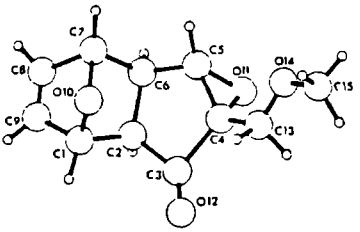


Figure 2

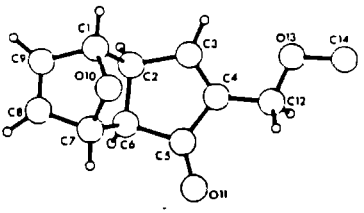


Table 2

Atomic positional and vibrational parameters (with esd's)

Atom	x	y	z	100 x U (Å)
C1	0.9473(5)	0.2085(9)	0.6145(5)	7.98(24)
C2	1.1040(5)	0.1126(8)	0.7261(5)	7.50(22)
C6	1.1228(5)	0.2620(9)	0.8630(4)	7.49(22)
C7	0.9768(5)	0.4104(10)	0.8050(5)	7.96(24)
C8	0.8572(5)	0.2097(11)	0.7753(5)	8.73(25)
C9	0.8398(6)	0.0867(10)	0.6584(6)	8.60(25)
O10	0.9516(3)	0.4762(6)	0.6608(3)	7.62(14)
C3	1.2277(5)	0.2181(10)	0.6997(5)	8.11(24)
C4	1.3069(5)	0.4055(9)	0.7948(5)	7.37(22)
C5	1.2537(5)	0.4440(10)	0.9001(5)	7.99(23)
O11	1.2974(4)	0.6065(8)	0.9977(4)	10.84(19)
C12	1.4309(6)	0.5569(11)	0.8020(5)	8.8(3)
O13	1.4373(4)	0.5402(10)	0.6740(4)	13.22(26)
C14	1.5458(7)	0.7111(15)	0.6678(7)	13.6(4)

Table 3

Bond lengths (Å) and angles (°) of the molecular skeleton of (-)**11**

C1-C2	1.556(6)	C6-C5	1.526(7)	C4-C5	1.450(9)
C1-C9	1.513(9)	C7-C8	1.513(8)	C4-C12	1.461(8)
C1-O10	1.440(6)	C7-O10	1.440(6)	C5-O11	1.221(6)
C2-C6	1.547(7)	C8-C9	1.305(8)	C2-C3	1.518(8)
C3-C4	1.341(6)	C6-C7	1.527(7)		

C2-C1-C9	106.9(4)	C7-C6-C5	112.6(4)	C3-C4-C5	110.0(5)
C2-C1-O10	100.9(3)	C6-C7-C8	107.3(4)	C3-C4-C12	128.7(6)
C9-C1-O10	101.4(4)	C6-C7-O10	100.9(4)	C5-C4-C12	121.3(4)
C1-C2-C6	99.9(4)	C8-C7-O10	102.3(3)	C6-C5-C4	109.0(4)
C1-C2-C3	114.3(4)	C7-C8-C9	105.0(6)	C6-C5-O11	123.9(6)
C6-C2-C3	103.9(4)	C1-C9-C8	106.6(4)	C4-C5-O11	126.9(5)
C2-C6-C7	101.8(3)	C1-O10-C7	95.3(3)	C2-C6-C5	104.2(4)
C2-C3-C4	112.7(5)				

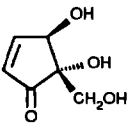
Although also this X-ray analysis was hampered by decomposition of the crystals during the measurements, the quality of the data was good enough to allow the determination of the absolute configuration with a very high confidence level. The result for (-)**16** confirms the result for (-)**11**. The definite assignments of the absolute structures of (-)**11** and (-)**16** are given in the figures 1 and 2, respectively. The absolute structures of the preceding menthylethers **9b** and **13b** and, in consequence, also those of the corresponding diastereomers **9a** and **13a** can now immediately be derived. The conversion of **9b** into **13b** proceeds, with respect to the tricyclic skeleton, with inversion of configuration. The trans-etherification of **13b** to give (-)**11** on the other hand does not affect this moiety. Hence, the tricyclic structure of **9b** must be the mirror image of that of (-)**11**, whereas **13b** and (-)**11** will have identical tricyclic structures.

The thermal cycloreversion of (-)**16**, which was carried out under Flash Vacuum conditions, afforded (+)**17**, as an oil, in 68% yield. Again no trace of the antipode (-)**17** was observed in the ^{1}H-NMR spectrum of this product. This confirms the stereochemical integrity of the thermal cycloreversion. The absolute configuration of (+)**17**, as shown in Scheme 5, follows from the absolute structure of its precursor (-)**16**.

Conversion of (+)**17** *into an enantiomericallly pure* epi-*pentenomycin.*

As stated in the introduction, cyclopentadienone epoxides may be useful synthons for the

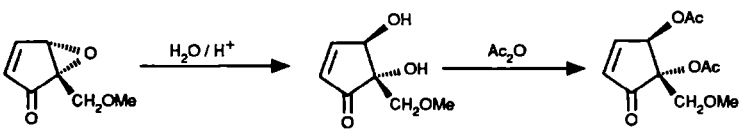
preparation of highly oxygenated cyclopentenoids, *e.g. epi*-pentenomycin (**18**). The trans-diol moiety of **18** can retrosynthetically be regarded as an epoxide ring and accordingly cyclopentadienone epoxide **17** may be a suitable precursor for this compound, provided that its epoxide ring can be hydrolyzed in trans-fashion. As has been demonstrated[6] previously, this trans-opening of the epoxide



18

ring can be achieved by an acid catalyzed hydrolysis and the resulting *epi*-pentenomycin analogue **19** can conveniently be characterized as its diacetate **20.** (Scheme 6). When homochiral **(+)17** was

Scheme 6



(+)17 **(+ or -)19** **(+)20**

subjected to this acid hydrolysis and subsequent acylation, optically active **20** was obtained. ^{1}H-NMR analysis of this product with Eu(hfc)$_3$ unequivocally established its enantiomeric purity. Similar to racemic **20**, a downfield shift for all the resonances was found, however, in contrast to racemic **20** here no splitting of the singlets of the methyl groups of the acetate moieties and the methylene protons of the methoxymethyl group was observed. This implies that the acid catalyzed epoxide ring opening of **17** to give **19** is a stereo- as well as a regio-specific process and, that under the conditions of the acylation neither epimerization nor racemization takes place. Despite repeated chromatography the preparation of an analytically pure sample failed. The actual specific rotation of **(+)20** will probably be *ca.* 5° higher than the measured optical rotation of the material obtained: +55° (c=0.32; chloroform) (see experimental). A conclusion about the precise site of the epoxide ring opening, being either C-4 or C-5, can in this stage not be drawn. Evidence, obtained later, indicating that the epoxide ring of **17** under acidic conditions opens regiospecifically at C-4, will be presented in a forthcoming paper. The implication of this regiochemistry for the absolute structure of **(+)20** is already included in Scheme 6.

4.3 Concluding remarks

The results presented in this chapter demonstrate that the conversion of sulphone **6** into the menthyl ethers **9a,9b** gives access to homochiral 10-oxatricyclodecadienones, which enantioselectively can be transformed into enantiomerically pure cyclopentenoids. Removal of the chiral menthyl group by trans-etherification can best be carried out on the reduced menthyl ethers **13a** and **13b**.

4.4 Experimental section

General remarks

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were taken on a Perkin Elmer 298 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 or a Bruker WH-90 spectrometer, using TMS as internal standard. For mass spectra a Varian SM-1B or a double focussing VG 7070E mass spectrometer was used. Flash column chromatography was carried out at a pressure of *ca* 1.5 bar, a column length of *ca* 15 cm and a column diameter of 1-4 cm, using Merck Kieselgel 60 H or Merck Aluminium Oxid 150 neutral (Typ T). For preparative TLC precoated Kieselgel plates Merck 60-F254 were used. All solvents used were dried and distilled by standard procedures.

5-ethoxy-4-(-)menthyloxymethyl-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca -4,8-dien-3-one* (**9a,b**).

A solution of sodium (-)mentholate in DMF[17] (4.5 ml; *ca.* 2M) was added to a solution of sulphone **6**[5] (1.8 g; 5.0 mmol) and (-)menthol (801 mg; 5.1 mmol) in dichloromethane (70 ml). The resulting mixture was stirred for 1 hr at room temperature. Then sat NH_4Claq was added (50 ml) and stirring was continued for a few min. The mixture was filtered and the organic phase was washed with water (1x50 ml). The combined aqueous layers were extracted with dichloromethane (4x50 ml). The organic extracts were dried ($MgSO_4$), filtered and evaporated. The residue (4.2 g) was purified by flash chromatography (SiO_2/hexane-ethyl acetate mixtures ranging from 3:1 to 1:1) affording 1.6 g (88%) of **9a,b** as a pale tinted solid. Subsequent crystallization from hexane-ethyl acetate (5:1; *ca.* 15 ml) gave 480 mg (26% absolute yield; 53% efficiency) of analytically and diastereomerically pure *(2R,6S)-5-ethoxy-4-(-)menthyloxymethyl-10-oxatricyclo[5.2.1.0^{2,6}] deca-4,8-dien-3-one* (**9a**), white platelets, mp: 127-128°C. $[\alpha]_D^n$= -71.5° (c=0.6; chloroform). IR(KBr) ν_{max}: 2955, 2920, 2870, 1685 (C=O), 1618(C=COEt), 1382, 1352, 1328, 1085, 1015 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.71(3H,d, J=7Hz;CH_3), 0.86(3H,d,J=7Hz;CH_3), 0.91(3H,d,J=6Hz;CH_3), 0.69-1.07(3H,m)/1.07-1.79(4H,m), 1.42(3H,t,J=7Hz;OCH_2CH_3), 2.00-2.38(2H,m), 2.53(1H,d,$J_{2,6}$=6Hz;H_2), 2.77(1H,d,$J_{6,2}$=6Hz;H_6), 3.10(1H,dt,J=4Hz,J=10Hz), 3.98/4.12/4.25/4.38(2H,AB_q,J_{AB}=11Hz;CH_2O(-)menthyl), 4.58(2H, q,J=7Hz;OCH_2CH_3), 4.94(1H,s)/5.04(1H,s)(H_1,H_7), 6.45(2H,s;H_8,H_9). MS(EI) m/e(%): 360(10;M^+),

292(32;-furan), 204(23;-menthol), 176(16;-menthol,-CO), 156 (88;menthol$^+$), 155(23), 154(52), 138(100), 137(86), 125(17), 110(21), 109(85), 83(15), 81(14), 69(15), 68(14;furan$^+$). (Found: C 72.96, H 8.91. Calc. for $C_{22}H_{32}O_4$: C 73.30, H 8.95%.)

Careful flash chromatography of the mother liquor (SiO_2/hexane-ethyl acetate (3:1)), followed by crystallization of the first fraction from hexane-ethyl acetate (5:1) afforded in *ca.* 15% absolute yield (30% efficiency) *(2S,6R)-5-ethoxy-4-(-)menthyloxymethyl-10-oxatricyclo[5.2.1.0^{2,6}]-deca-4,8-dien-3-one* (**9b**), glittering white needlets, mp: 94.5-96.5°C. $[\alpha]_D^n$= -72.8° (c=0.6; chloroform). IR(KBr) ν_{max}: 2980, 2925, 1690(C=O), 1618(C=COEt), 1378, 1328, 1045, 1018, 872, 722, 705 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.70(3H,d,J=7Hz;CH_3), 0.89(3H,d,J=7Hz;CH_3), 0.90(3H,d,J=6Hz;CH_3), 0.64-1.09(3H,m)/1.09-1.80(4H,m), 1.40(3H,t,J=7Hz;OCH_2CH_3), 1.96-2.33(2H,m), 2.52(1H,d, $J_{2,6}$=6Hz;H_2), 2.75(1H,d,$J_{6,2}$=6Hz;H_6), 3.05(1H,dt,J=4Hz,J=10Hz), 4.02/4.14/4.17/4.31(2H,AB_q, J_{AB}=12Hz;CH_2O(-)menthyl), 4.39-4.73(2H,ABX_3 multiplet,J_{AB}=10Hz,J_{AX}=J_{BX}=7Hz;OCH_2CH_3), 4.92(1H,s)/5.00(1H,s)(H_1,H_7), 6.43(2H,s;H_8,H_9). MS(EI) m/e(%): same fragmentation pattern as **9a**. (Found: C 73.02, H 9.00. Calc. for $C_{22}H_{32}O_4$: C 73.30, H 8.95%.)

*Preparation of 4-ethoxymethyl-*exo*-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**12**), *from 4-methoxymethyl-*exo*-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**11**).

A solution of sodium ethanolate in ethanol (1.5 ml; 0.5 M) was added to a boiling solution of **11**[5] (115 mg; 0.6 mmol) in ethanol (15 ml). The reaction mixture was allowed to attain room temperature. After 1 hr of stirring, the solvent was evaporated and dichloromethane (20 ml) and water (20 ml) were added. The aqueous phase was extracted with dichloromethane (3x15 ml). The combined organic extracts were washed with water (3x25 ml), dried ($MgSO_4$), filtered and evaporated. The residue was purified by preparative TLC (SiO_2/ethyl acetate) to afford 41 mg (33%) of pure **12**, as a colourless oil which solidified in the freezer. The ^{1}H-NMR spectrum of this material was identical to that of previously synthesized **12**[5].

*4-(-)menthyloxymethyl-*exo*-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**13a,b**).

A solution of Di-iso-Butyl Aluminium Hydride (DIBAL) in hexane (*ca.* 3 ml; 1 M) was added to a solution of **9a,b** (509 mg; 1.4 mmol) in dry benzene (25 ml), under nitrogen and cooled on ice. The resulting mixture was stirred for 30 min at 0°C and was then allowed to warm up to room temperature. Stirring was continued for 1 hr. Ether (40 ml) and 3% HCl (20 ml) were added and the resulting two phase system was stirred vigorously for 1 hr. The aqueous layer was separated and extracted with ether (3x40 ml). The combined organic layers were washed with water (3x20 ml), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography (SiO_2/hexane-ethyl acetate (3:1)) to afford 460 mg (100%) of **13a,b**, as a thick white oil. In the ^{1}H-NMR spectrum of **13a,b** no distinct resonance pattern, indicative of a mixture of diastereomers, was observed. The diastereomers could neither be differentiated on TLC or capillary GC. The

^{1}H-NMR and IR spectra of **13a,b** were identical to those of **13a** and **13b** (*vide infra*).

(2S,6R)-4-(-)menthyloxymethyl-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**13a**).

The reduction of **9a** (853 mg; 2.4 mmol) with DIBAL (3 mmol) was carried out as described for **9a,b** (see **13a,b**). This afforded 743 mg of crude **13a** as a white solid (*ca.* 100% yield). An analytically pure sample was obtained by flash chromatography (SiO_2/hexane-ethyl acetate (3:2)) and subsequent crystallization from pet. ether$^{40\text{-}60}$/ether (3:1) and recrystallization from hexane. mp: 111-113°C. IR(KBr) ν_{max}: 3000, 2960/2920/2870, 1690(broad;C=O), (1620(w;conj C=C)), 1125/1115, 1082, 1052, 1010, 955, 908/902, 870, 708 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.74(3H,d,J=6.4Hz; CH_3), 0.86(3H,d,J=6.6Hz;CH_3), 0.89(3H,d,J=6.6Hz;CH_3), 1.02-1.71 (7H,m), 1.98-2.36(2H,m), 2.44(1H,d,$J_{2,6}$=4.4Hz;H_2), 2.91(1H,m,$J_{6,5}$=2.6Hz,$J_{6,2}$=4.4Hz;H_6), 3.11(1H,dt,J=4Hz,J=10Hz), 3.91(t)/4.05(t)/4.22(t)/4.38(t)(2H,AB system,J_{AB}=14Hz,$J_{A,6}$=2Hz,$J_{B,6}$=1.4Hz;CH_2O(-)menthyl), 4.69(1H,br s)/4.97(1H,br s)(H_1,H_7), 6.39(1H,dd,J=1.7Hz,J=4.8Hz)/6.52(1H,dd,J=1.7Hz,J=4.8Hz) (H_8,H_9), 7.45 (1H,m,$J_{5,6}$=2.6Hz;H_5). MS(EI) m/e(%): 316(0.12;M$^+$), 248(1.09;-furan), 1.78(72;-menthene), 160(87;-menthol), 132(55;-menthol,-CO), 110(24;-menthene,-furan), 94(40), 83(100), 68(17;furan$^+$). (Found: C 75.53, H 8.96. Calc. for $C_{20}H_{28}O_3$: C 75.91, H 8.92%.)

(2R,6S)-4-(-)menthyloxymethyl-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (**13b**).

The reduction of **9b** (352 mg; 0.98 mmol) with 1.5 mmol of DIBAL, was carried out as described for **9a,b** (see **13a,b**). After flash chromatography (SiO_2/hexane-ethyl acetate (3:2)), 307 mg (99%) of **13b** was obtained, as a colourless oil, which on standing for months in the freezer slowly crystallized. The diasteromeric purity of this product was confirmed by its subsequent conversion into enantiomerically pure (-)**11**. IR(CCl_4) ν_{max}: 2960/2925/2870, 1705(C=O), 1118, 1090, 1050, 950, 912, 875, 700/690 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: identical to the ^{1}H-NMR spectrum of **13a**. MS(CI) m/e(%): 317(24;M+1$^+$), 179(100;-menthene), 161(31; -menthol), 139(70;menthyl$^+$), 137(46;menthene-1$^+$), 111(66;-furan,-menthene), 83(50), 81(29), 69(36;furan+1$^+$). HRMS(CI) m/e: 317.2101 (calc. for $C_{20}H_{29}O_3$ (M+1): 317.2117).

Preparation of racemic **11** *by trans-etherification of* **13a,b**.

A solution of **13a,b** (405 mg; 1.3 mmol) in methanol (30 ml) was heated under reflux with 1.8 ml of a 1 M solution of sodium methanolate in methanol. After one hour an extra amount (1.8 mmol) of sodium methanolate was added and reflux was continued overnight. The reaction mixture was cooled to room temperature and concentrated in vacuo. Work-up was carried out as usual (see related preparation of **12** from **11**). This afforded 375 mg of a dark coloured oil, containing a mixture of (-)menthol and **11** (^{1}H-NMR data). Flash chromatography (SiO_2/hexane ethyl acetate (1:1)) gave as the first fraction 182 mg of (-)menthol (*ca.* 92%). The second fraction left 58 mg (23%) of pure **11**. The spectral data of this material were in full accord with those reported previously[5]. ^{1}H-NMR

analysis of this material with the optical shift reagent $Eu(hfc)_3$[13] revealed a downfield shift for all the resonances and a prominent 1:1 splitting of the methyl signal of the methoxymethyl group.

Preparation of (+)**11** *from* **13a**.

A solution of sodium methanolate in methanol (2 ml; *ca.* 1.7 M) was added to a solution of **13a** (634 mg; 2 mmol) in methanol (25 ml). The resulting mixture was heated under reflux for 20 hrs and then worked-up as described for racemic **11**. The crude product was purified by flash chromatography (SiO_2/hexane-ethyl acetate (1:1)). The resulting, not entirely pure (TLC and ^{1}H-NMR data) (+)**11** (yield not determined) was subsequently subjected to preparative TLC (SiO_2/ethyl acetate). This provided 78 mg (20%) of enantiomerically pure (+)**11**, which after two crystallizations (hexane-ether) afforded fine needlets, mp: 104-106.5°C[14], $[\alpha]_D^{24}$= +77.5°(c=0.6; chloroform). (Found: C 68.39, H 6.03. Calc. for $C_{11}H_{12}O_3$: C 68.74, H 6.29%.)

Preparation of (-)**11** *from partially resolved* **13**.

A mixture of **13b** and **13a** (467 mg; 1.4 mmol of substrate, obtained by DIBAL reduction of the mother liquor retained after crystallization of **9a,b**; main constituent **13b**) was dissolved in 20 ml of methanol. After the addition of 0.5 ml of a 4 M solution of sodium methanolate in methanol the solution was heated under reflux for 17.5 hrs. Subsequent work-up was carried out as described for racemic **11**. Flash chromatography (SiO_2/hexane-ethyl acetate (1:1)) of the crude product afforded 141 mg (52%) of a mixture of (-)**11** and (+)**11**. Part of this mixture was crystallized from hexane. The rest was subjected to ^{1}H-NMR analysis to determine the enantiomeric ratio. Treatment of this sample with $Eu(hfc)_3$ revealed a ratio of 3:1 ± 10%. The crystallized material gave optically and analytically pure (-)**11**, mp: 104-106,2°C[14], $[\alpha]_D^{22}$= -78.4°(c=0.55; chloroform). (Found: C 68.51, H 6.28. Calc. for $C_{11}H_{12}O_3$: C 68.74, H 6.29%.)

*(-)-*exo*-4,5-epoxy-*endo*-4-methoxymethyl-*exo*-10-oxatricyclo[5.2.1.0^{2,6}]deca-8-en-3-one*, (-)**16**.

The epoxidation of (-)**11** (109 mg; 0.57 mmol) was carried out with 35% H_2O_2 (0.2 ml) and 0.2 N NaOH (0.2 ml) in a mixture of dichloromethane (1.5 ml) and methanol (1.5 mml) as described previously[6]. This afforded 120 mg (*ca.* 100% yield) of crude (-)**16** as a white solid. Subsequent crystallization from hexane-ethyl acetate gave crystalline (-)**16**, as fine needlets, mp 56-59°C[16], $[\alpha]_D^{22}$= -234°(c=0.53; chloroform). Its spectral data were entirely identical to those of racemic **16**, reported previously[6].

(+)-4,5-epoxy-5-methoxymethyl-2-cyclopentenone, (+)**17**.

Flash vacuum thermolysis[6,18] (16 cm quartz tube/0.14 mbar/preheating temp 75°C/oven temp 360°C) of (-)**16** (103 mg; 0.5 mmol) and subsequent flash chromatography (SiO_2/hexane-ethyl acetate (2:1)) of the crude pyrolysate gave 48 mg (68%) of (+)**17**. The ^{1}H-NMR spectrum of this

material showed, in contrast to racemic **17**, no splitting of the methyl singlet of the methoxy methyl group on treatment with $Eu(hfc)_3$. Since its capillary GC output revealed small impurities, it once again was subjected to flash chromatography (SiO_2/hexane-ethyl acetate (3:2)). This afforded *ca.* 40 mg (*ca.* 57%) of analytically (capillary GC data) pure (+)**17**, $[\alpha]_D^{22}$= +330°(c=0.7; chloroform)[19]. Its spectral data were entirely identical to those of racemic **17**, reported previously[6].

(+)-(trans-4,5-diacetoxy)-5-methoxymethyl-2-cyclopentenone, **(+)20.**

The hydrolysis of (+)**17** (*ca.* 40 mg; 0.28 mmol) and subsequent acylation of the resulting diol was carried out as described previously[6]. Column chromatography (SiO_2/ethyl acetate) of the crude product afforded 44 mg (*ca.* 65% overall yield) of (+)**20**. ^{1}H-NMR analysis with $Eu(hfc)_3$ established the optical purity of this product. Its chemical purity however was insufficient for a reliable determination of optical rotation. A second chromatography (SiO_2/hexane-ethyl acetate (1:1)) left only 19 mg of (+)**20**, that still contained a persistent contamination[20] (*ca.* 15%; capillary GC data). This impurity was presumably an achiral compound, since it revealed only a shift but no splitting of its ^{1}H-NMR signals on treatment with $Eu(hfc)_3$. The twice purified material displayed a specific rotation of +55° (c=0.32; chloroform). Further purification was not attempted. The spectral data, belonging to (**20**), were identical to those of racemic **20**, reported previously[6].

X-Ray analysis of **(-)16**

A small crystall was analyzed using Mo-Kα radiation on a Picker four-circle diffractometer. Standard experimental details and methods for structure solution and refinement are given elsewhere[20]. The crystals are orthorhombic, space group $P2_1\,2_1\,2_1$ with unit cell a = 5.685(1), b = 9.780(3), c = 18.157(5) Å and Z = 4. The intensity data of 1643 reflections were measured (half a sphere up to Θ = 25°), with 834 unique reflections of which 486 were observed, with $I > 3\sigma(I)$, R_{merge}= 0.078 for all reflections and 0.022 for the observed reflections only. The early Bijvoet coefficient was negative, and therefore the structure was inverted. Because of the small number of data, the central atoms were refind with isotropic temperature factor. The hydrogen atoms, except for the hydrogens of the methyl group, were put on calculated positions with fixed isotropic temperature factors. At the end of the refinement the Bijvoet coefficient for 100 Friedel pairs was 0.38(7) which confirms that the absolute configuration of the molecule is correct to a confidence level better than 0.9999. Due to the weak scattering power of the crystals, and the small anomalous scattering of the oxygen atoms, the absolute configuration can not be considered to be reliable. The final conventional agreement factor was Rc = 0.096, for 486 'observed' reflections and 111 variables. Programs used: DIFABS (Walker & Stuart), MULTAN (Main *et al.*), SHELX (Sheldrick), BIJVOET, and PLUTO (Motherwell); program references are given in ref 20.

X-Ray analysis of (-)**11**

A small crystal was analyzed using Cu-Kα radiation. Standard experimental details and methods for structure solution and refinement are given elsewhere[21]. The crystals are monoclinic, space group P21 with unit cell a = 10.266(2), b = 5.093(1), c = 10.419(2), β = 118.02(2)° with Z = 2. The intensity data of 3585 reflections were measured (a full sphere up to Θ = 70°) with 1810 unique reflections of which 1012 were observed with I > 3σ(I), R_{merge} = 0.127 for all reflections and 0.037 for the observed reflections only. The drift-correction curve, however, showed a very severe decomposition, and we decided to remove the second half of all data, leaving 1023 independent reflections of which 669 with I > 3σ (I); decomposition so far gave an intensity reduction down to 70 %. The structure was solved by MULTAN, which (by chance) gave the same absolute structure for the molecular skeleton as was obtained by the analysis of (-)**16**.

All hydrogen atoms were located from a difference Fourier synthesis and during the refinement they were kept at fixed positions, except the hydrogens of the CH_2 group which were put at calculated positions and refined in riding mode. The hydrogen atoms had isotropic temperature factors, and all other atoms were refined with anisotropic temperature factors. The final conventional agreement factor was R = 0.046 for 680 observed reflections and 139 variables.

Unfortunately, the rejected part of the data contained all the Bijvoet opposites, so this data set could not be used for the determination of the absolute configuration. Thus, another crystal was selected, and used for measurements such that Bijvoet pairs were measured prior to the symmetry dependent reflections. This crystal showed decomposition as well, but the resulting data set (collected 6942 reflections, last part rejected, left over 5634 reflections with intensity decrease down to 75 %; 1809 independent data of which 702 with I > 3σ (I)) was succesfully used for the determination of the absolute structure. The Bijvoet coefficient for this data set was B = 0.39(13) for 55 Bijvoet pairs, establishing the absolute configuration with a confidence level of better than 0.9999. The latter data set was less good than the former data set (final conventional agreement factor R = 0.051), and the corresponding parameter set has been rejected.

Programs used: MULTAN (Main et al.), SHELX(Sheldrick), DIFABS(Walker and Stuart), BIJVOET, PARST (Nardelli), and PLUTO (Motherwell); program references are given in ref. 20.

Acknowledgements: We are grateful to the Institute of Crystallography of the University Karlsruhe, Germany, for collecting part of the X-Ray data and to Mr. Mattern for his support and to Dr. H. Behm and Mr. J. M. M. Smits for valuable assistance.

4.5 References and notes

1. (a) Bugel, J. P.; Ducos, P.; Gringore, O.; Rouessac, F. *Bul. Soc. Chim. Fr.* **1972**, 4371; (b) Oda, M.; Kanao, Y.; Kasai, M.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1977**, *45*, 2497; (c) Chapman O. L.; Hess, T. C. *J. Org. Chem.* **1979**, *44*, 962.
2. (a) Klunder, A. J. H.; Bos, W.; Verlaak J. M. J.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4553; (b) Klunder, A. J. H.; Bos, W.; Zwanenburg, B. *Tetrahedron Lett.*, **1981**, *22*, 4557. (c) Verlaak, J. M. J.; Klunder, A. J. H.; Zwanenburg, B. **1982**, *23*, 5463; (d) Klunder, A. J. H.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *ibid.* **1987**, *28*, 1329; (e) Klunder, A. J. H.; Lange, J. H. M.; Zwanenburg, B. *ibid.* **1987**, *28*, 3027; (f) Klunder, A. J. H.; Crul, M. J. F. M.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *ibid.* **1987**, *28*, 3147;(g) Lange, J. H. M.; Klunder, A. J. H.; Zwanenburg, B. *ibid.* **1989**, *30*, 127.
3. Klunder, A. J. H.; Huizinga, W. B.; Hulshof, A. J. M.; Zwanenburg, B. *Tetrahedron Lett.* **1986**, *27*, 2543.
4. Klunder, A. J. H.; Huizinga, W. B.; Sessink, P. J. M.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 357.
5. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Kooy, M. G.; Steffann, J.; Zwanenburg, B. *Tetrahedron*, **1989**, *45*, 7109.
6. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron*, **1989**, *45*, 7134.
7. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron*, **1989**, *45*, 7149.
8. Brion, F. *Tetrahedron Lett.* **1982**, *23*, 5299.
9. Grieco, P. A.; Zabrowski, D. A.; Lis, R.; Finn, J. *J. Org. Chem.* **1984**, *49*, 1454.
10. Winterfeldt, E. *Synthesis* **1975**, 617.
11. Wilson, K. E.; Seidner, R. T.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1970**, 213.
12. Funk, R. L.; Vollhardt, K. P. *Synthesis* **1980**, 118. These authors mention the formation of 2-methyl-2-cyclopentenol, resulting from 1,4-reduction and subsequent 1,2-reduction, as a side reaction of the DIBAL reduction of 3-*iso*-butyloxy-2-methyl-2-cyclopentenone, which affords 2-methyl-2-cyclopentenone as the main product.
13. Tris[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]europium^{III}.
14. This melting point is about 25°C higher than that of racemic **11**. The racemate displays a rather broad melting traject between 76-81°C, which is indicative of a racemic crystal structure (see: Kagan,H.B. *Organische Stereochemie*; Thieme: Stuttgart, 1977; p 92.)
15. The observation that it is often possible to obtain the pure enantiomer by one crystallization of a partially resolved mixture is discussed in Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates and Resolutions*; Wiley & Sons: New York, 1981; p 423.

16. Racemic **18** is a thick white oil at room temperature.
17. The sodium mentholate solution can best be prepared shortly before the reaction. This preparation involves stirring of NaH (80% suspension in oil) in dried DMF under a nitrogen atmosphere with a slight excess of (-)menthol, until a glassy, grey/green solution is obtained (*ca.* 2 hrs).
18. A detailed description of the FVT equipment is given in Verlaak, J. M. J. *Ph.D. Thesis*, University of Nijmegen, Febr 1983; p 154.
19. A similar high rotation was found for a structurally related compound, *viz.* (+)-4,5-epoxy-3,3-dimethoxy-1-cyclopenten-1-carbaldehyde, see ref 4.
20. Smits, J. M. M.; Behm, H.; Bosman, W. P.; Beurskens, P. T. *J. Cryst. Spectrosc. Res.*, **1988**, *181*, 447.

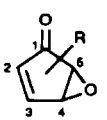
CHAPTER 5: SELECTIVE NUCLEOPHILIC TRANSFORMATIONS OF CYCLOPENTADIENONE EPOXIDES

5.1 Introduction

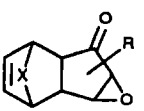
Cyclopentadienone epoxides **1** are challenging species to explore chemoselectivity and control of reactivity because the various functional groups present in these small molecules all are susceptible to the same reagents. A study of the chemical behaviour of these multifunctionalized compounds is of interest for general strategies in organic synthesis and for possible applications[1,2] in the synthesis of natural products, particularly highly oxygenated cyclopentenoids.

Until recently no practical synthesis of cyclopentadienone epoxides **1** was available and therefore their chemistry has but sporadically been described. Only their photochemistry was studied in some detail. Tri- and tetraphenyl substituted cyclopentadienone epoxides equilibrate with pyrylium oxides on irradiation[3,4]. Photochemical induced rearrangements to 2-pyrones were reported for the parent compound **1** (R=H)[5] and for the alkyl- and phenylsubstituted epoxides **1** (R=2,5-dimethyl; R=3,4-diphenyl; R=2,3,4,5-tetraphenyl)[6-8]. The postulated intermediacy of cyclopentadienone epoxides in the photo-isomerisation of 4-pyrones to 2-pyrones was unambiguously proven for **1** (R=2,5-dimethyl)[6]. Phenyl-, alkyl- and otherwise substituted cyclopentadienone epoxides rearrange to 2-pyrones on heating[3,5,9-13]. The parent compound **1** (R=H) decomposes in acidic or basic media[5]. Only a few reports deal with synthetic applications. These involve either a reaction with the enone moiety[14] or a reaction with the epoxide function[1,2].

A general synthesis of the cyclopentadienone epoxides **1**, using normal chemical procedures



1

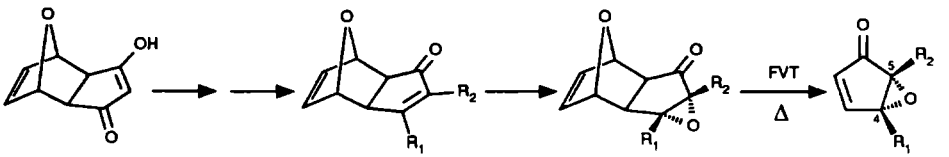


2

involving acid or basic reaction or work-up conditions, is frustrated by their inherent sensitivity to acids and bases. An alternative synthetic approach, in which these epoxides are generated by gas phase thermolysis (Flash Vacuum Thermolysis, FVT) of cyclopentadiene derived polycyclic epoxides **2** (X=CH_2,O) is limited by the thermal instability of **1**. These thermolyses of **2** (X=CH_2) often require rather high temperatures (430°-500°C), at which the thermal rearrangement of **1** to

2-pyrones hardly can be avoided[5,11,12]. Recently we demonstrated[13], however, that furan derived **2** (X=O) are excellent substrates for the FVT mediated synthesis of cyclopentadienone epoxides **1**. This type of polycyclic epoxides can efficiently be thermolysed at temperatures as low as 300-375°C, to give **1** without concomitant formation of pyrones. The polycyclic epoxides **2** (X=O),in turn, can conveniently be obtained from the Diels-Alder adduct **3** of furan and 2-cyclopentene-1,4-dione[13,15]. Starting from this adduct **3**, various 4- and 5-substituted cyclopentadienone epoxides **4** were prepared using the sequence of reactions shown in Scheme 1. These cyclopentadienone

Scheme 1



3 **4**

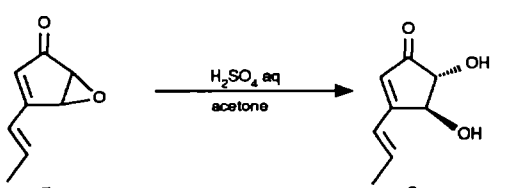
epoxides **4** were used to uncover the chemistry of this interesting class of compounds. In this chapter we focus on nucleophilic transformations of **4**, *viz.* hydrolyses, methanolyses and epoxidations, under acid, neutral and alkaline conditions. It will be shown that, depending on reaction conditions and substitution pattern, a highly selective reaction with either the epoxide function or the enone moiety can be accomplished. The regio- and stereochemistry of these reactions is analysed and mechanistic aspects are discussed.

5.2 Results and Discussion

Acid-catalysed hydrolysis of the epoxide function.

In a previous communication[1] we reported that selective hydrolysis of the epoxide function of **5** required more drastic acidic conditions than expected. In an ethereal solution, containing 10%

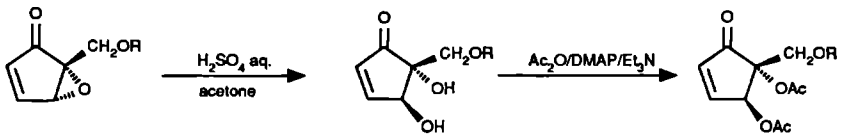
Scheme 2



5 **6**

0.4N H_2SO_4 aq, no reaction took place. It was found, after careful experimentation, that the desired epoxide ring opening could conveniently be achieved in acetone, containing 1% 0.5 N H_2SO_4 aq. Under these conditions the epoxide function of **5** was stereospecifically transformed into a *trans*-diol group, to give terrein **6** in 55% yield[1] (Scheme 2).When these same hydrolytic conditions were applied to the 5-alkoxymethyl substituted epoxides **7** and **8**, followed by an immediate acylation, the acyl-protected *epi*-pentenomycins **9** and **10** were obtained in 54% and 30% yield, respectively (Scheme 3). The *trans* configuration of these *epi*-pentenomycin diacetates **9** and **10** followed

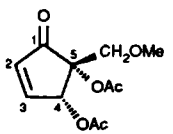
Scheme 3



7 R=Me
8 R=Et

9 R=Me
10 R=Et

unequivocally from comparison of their ^{1}H-NMR spectra with that of the epimer of **9**, *i.e.* **11**[12]. The signals for the ring protons, H_2, H_3 and H_4 of **9** and **10** were found at δ 6.47-6.45, δ 7.40-7.35 and δ 6.26-6.25 ppm, respectively, whereas the resonances of the corresponding protons of **11** were observed at δ 6.35, δ 7.25 and δ 5.75 ppm. The signals for H_4 in **9** and **10** were particularly indicative



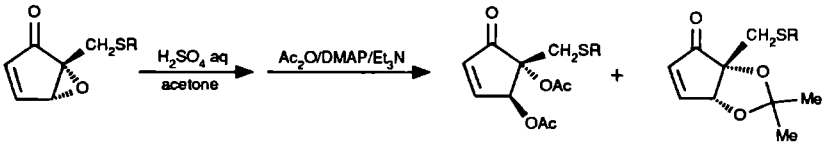
11

of the *trans* configuration. They were observed approximately 0.5 ppm downfield as compared with the resonance for H_4 in **11**.

Surprisingly, treatment of cyclopentadienone epoxides **12** and **13**, containing a phenyl- or benzyl-thiomethyl group instead of an alkoxymethyl group, with the same mixture of acetone and aqueous H_2SO_4, followed by acylation, also provided, in addition to the expected *trans*-diacetates **14** (36%) and **15** (38%), respectively, the acetonides **16** (32%) and **17** (32%) (Scheme 4). It should be emphasized that during the hydrolyses of **7** and **8** no such acetonides were observed.

Another unexpected result was obtained when cyclopentadienone epoxide **18** was subjected to these same hydrolysis conditions. After acylation of the resulting product mixture no identifiable compound was isolated. The spectral data of the crude mixture suggested that the initial products,

Scheme 4



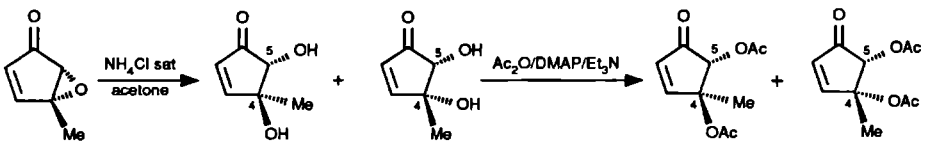
12 R=Ph
13 R=Bz

14 R=Ph
15 R=Bz

16 R=Ph
17 R=Bz

despite the mild acidic conditions of the hydrolysis, were converted *in situ* into other unstable materials. The hydrolysis of **18** was therefore tried again, but now in the absence of acid, *viz.* in acetone only containing 5% of water. However, under these conditions, epoxide **18** did not react. In a third attempt, epoxide **18** was stirred in a 10:1 mixture of acetone and saturated NH_4Cl aq. According to its ^{1}H-NMR spectrum, the product mixture now consisted of *trans*-diol **19** and *cis*-diol **20**, in a ratio of 1.8:1, and a trace of unreacted **18**. Subsequent acylation provided the corresponding diacetates **21** and **22**, in 22% overall yield (Scheme 5). These acetates were also obtained in the ratio of 1.8:1, implying that during the acylation no epimerisation had taken place. The formation of **20** by epimerisation of **19**, or *vice versa*, during the hydrolysis of epoxide **18** must therefore be considered as highly unlikely. During this hydrolysis of **18** a considerable amount of *cis*-diol was formed. Formation of an acetonide, similar to **16** and **17**, had, however, not occurred. This underlines the extremely mild acidic conditions needed to accomplish the opening of the epoxide ring of **18**. The

Scheme 5



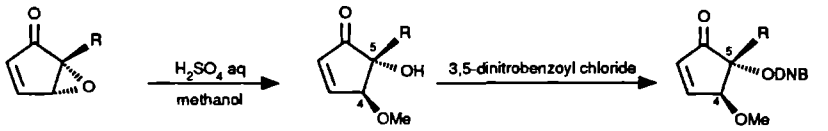
18 **19** **20** **21** **22**

configurations of **19** and **20** were deduced from the relative ^{1}H-NMR resonances of the respective H_5 protons. The most downfield H_5 signal, *viz.* at δ 4.30 ppm, was assigned to the *trans*-diol **19**, because in this isomer the C_4-OH group will exert a considerable deshielding effect on the adjacent, *cis*-orientated H_5 proton. Such an effect is obviously absent in *cis*-diol **20** and the H_5 signal of **20** is accordingly observed at higher field, *viz.* δ 3.87 ppm. A similar difference in chemical shift was found for the H_5 protons of the respective diacetates **21** and **22**, which were observed at δ 5.84 and δ 5.14 ppm, respectively.

Acid-catalysed methanolysis of the epoxide function.

Hydrolysis and methanolysis reactions of epoxides are usually mechanistically very similar. The latter, however, provide valuable information about the regiochemistry of these solvolyses. Methanolysis of the parent cyclopentadienone epoxide **23** was performed using the same concentration of acid as applied during the hydrolyses of the cyclopentadienone epoxides **5**, **7**, **8**, **12** and **13**. Under these conditions **23** was quantitatively converted into the *trans*-methoxyalcohol **24**. Subsequent treatment with 3,4-dinitrobenzoyl chloride gave product **25** (Scheme 6). Cyclopentadienone epoxide **7** similarly afforded the corresponding *trans*-products **26** (88% yield) and **27** (70% overall), respectively. No trace of the respective *cis*-methoxy epimers was observed in these cases. The

Scheme 6



23 (R=H)
7 (R=CH_2OMe)

24 (R=H)
26 (R=CH_2OMe)

25 (R=H)
27 (R=CH_2OMe)

DNB = 3,5-dinitro benzoyl

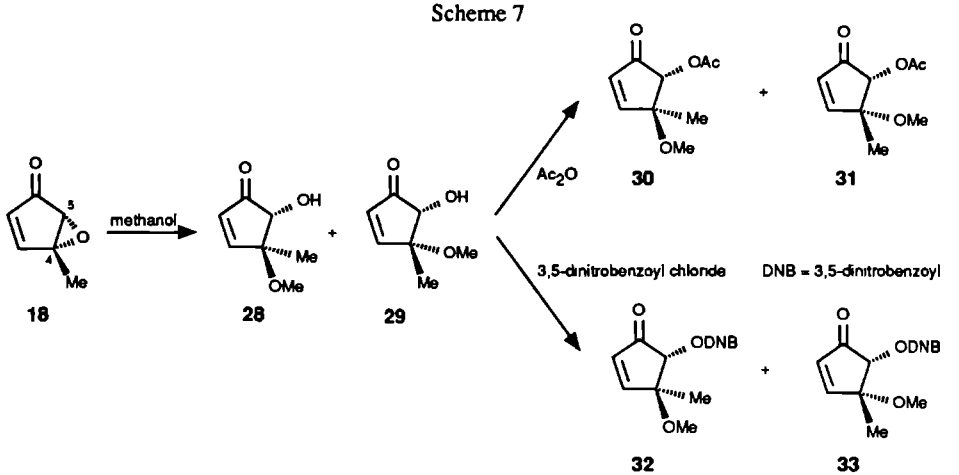
^{1}H-NMR spectra of **24-27** clearly established the 4-position of the methoxy group as well as the *trans* relationship between the methoxy and the hydroxy group. The particular position of the methoxy group in **24-27** was deduced from the following ^{1}H-NMR data. Upon benzoylation the doublet for the H_5 proton of **24** shifted downfield by 1.32 ppm. Such a shift is characteristic for a proton attached to a hydroxylated carbon that is converted into a benzoate[16]. Benzoylation of **26** led to a downfield shift of 0.57 ppm for the H_4 proton, implying that this proton was not situated at a carbon, carrying a hydroxyl group. Both observations indicated that the methoxy group in **24-27** is present at C-4. The relatively small coupling constants of 2.7 Hz and 3.0 Hz, observed for H_4 and H_5 in the ^{1}H-NMR spectra of **24** and **25**, respectively, are indicative of a *trans* relationship between these vicinal protons. In terrein **6** this coupling is similar, *viz.* 2.5 Hz[1], whereas in its epimer, *iso*-terrein, a much larger coupling of 6 Hz is found[17] for the *cis* H_4 and H_5 protons . These data confirm the *trans* structure of **24** and **25**. The *trans* configurations of **26** and **27** followed from comparison of their ^{1}H-NMR spectra with those of **9** and its diol-precursor (Scheme 3).

Methanolyses under neutral conditions.

In view of the very mild acidic conditions required for the hydrolysis of **18**, methanolysis of **18** was attempted without acid catalysis. Stirring of this epoxide in a solution of methanol at room temperature resulted in a smooth cleavage of the epoxide ring affording a 3.3:1 mixture of the *trans*- and *cis*-methoxy-alcohols **28** and **29**, respectively, in almost quantitative yield (Scheme 7).

Subsequent acylation gave acetates **30** and **31**, respectively, which failed to crystallize. Benzoylation with 3,5-dinitrobenzoyl chloride, however, afforded solid derivatives, *viz.* **32** and **33**, respectively. Crystals of the predominant isomer **32** were subjected to an X-Ray diffraction analysis. This structure determination unambiguously revealed that the methoxy group in **32** is located at C-4, *trans* to the C-5-dinitrobenzoate group[18]. With the spectral features of **32** as a reference, the structures of **28-33** could be established with certainty.

Scheme 7



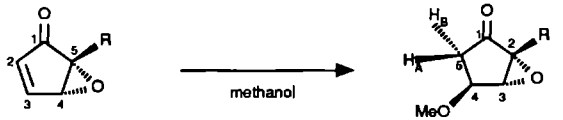
The acetates, **30** and **31**, as well as the benzoates, **32** and **33**, were obtained in the same ratio as the alcohols **28** and **29**, *viz.* 3.3:1, indicating that during acylation and benzoylation no epimerisation had taken place. Comparison of the *trans/cis* product ratios obtained in the hydrolysis and the methanolysis of **18** shows that the preference for *trans*-epoxide-opening in the latter case is slightly larger.

The above results show that the opening of the epoxide ring of **18** in neutral methanol takes place regioselectively at C-4, with some preference for the *trans* stereochemistry.

The parent cyclopentadienone epoxide **23** and the 5-alkoxymethylsubstituted epoxides **7** and **34** were also subjected to methanolysis under neutral conditions. Stirring of **23** in methanol for one week at room temperature gave a single product, which, however, as ascertained by capillary GC, was not alcohol **24** but cyclopentenone epoxide **35** (Scheme 8). The rather low yield of 39% must be attributed to considerable loss of material during the removal of the solvent. Similar treatment of the cyclopentadienone epoxides **7** and **34** led to the corresponding cyclopentenone epoxides **36** and **37**, in excellent yields of 82% and 100%, respectively.

The structures of the products **35-37** were deduced from their ^{1}H-NMR data. The splitting pattern of the signal for H_4 was particularly decisive for the assignment of the configurations. This proton has a medium range coupling of 5-6 Hz with one of the H_5 protons and a very small (for **35**)

Scheme 8

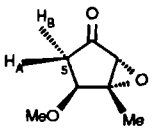


23 (R=H)
7 (R=CH_2OMe)
34 (R=CH_2OiPr)

35 (R=H)
36 (R=CH_2OMe)
37 (R=CH_2OiPr)

or even no (for **36**, **37**) coupling with the other H_5 proton. In all cases no coupling was observed with H_3. The coupling of 5-6 Hz was attributed (Karplus equation) to spin-spin interaction of H_4 with the *cis*-orientated H_5 proton, *i.e* H_B. The absence of spin coupling between H_4 and H_3 indicates that H_3 is *trans*-orientated to H_4. The methoxy group and the epoxide ring were therefore also positioned *trans* to each other. The resonances for H_3 and H_2 in the ^{1}H-NMR spectrum of **35**, at δ 3.36 ppm and δ 3.94 ppm, respectively, were assigned by comparison with the positions of the H_3 signals of **36** and **37**, which were present at δ 4.00 ppm and δ 4.03 ppm.

The substrates, shown in Scheme 8, all gave, in fact unexpectedly, exclusive addition of methanol to the enone system leaving the epoxide group in tact. In view of these results the ^{1}H-NMR spectrum of the crude product mixture, obtained from **18** under neutral methanolysis conditions, was scrutinized for the presence of the methanol addition product **38**. A weak AB pattern in the 1.8 - 2.4



38

ppm region was indeed observed, which was assigned to the H_5 protons of **38**, by comparison with the ^{1}H-NMR spectra of **35-37**. This means that also some conjugate addition of methanol to **18** had taken place to give **38** (yield ≤ 5%).

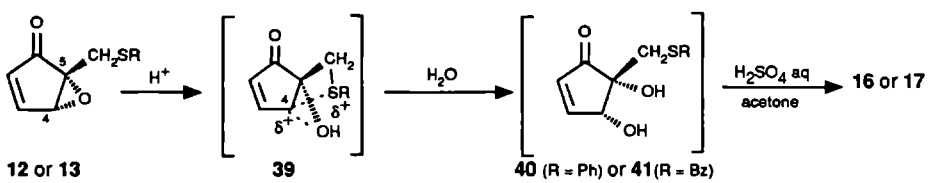
It is, in principle, conceivable that the products **28** and **29** from **18** (Scheme 7) are the result of an initial conjugative methanol addition to give **38**, followed by epoxide opening and elimination of methanol to produce the actual products isolated. A similar sequence can be envisaged for the formation of the products **24** and **26**, during the acid-catalysed methanolysis of **23** and **7** (Scheme 6). To test this hypothesis, compound **35** was treated with methanol containing a trace of acid. Instead of compound **24**, however, a fatty polymeric material was obtained (100%). This observation rules out the just mentioned involvement of an initial conjugative methanol addition. The epoxide opening and enone addition are clearly independent processes.

Mechanistic aspects of the (acid-catalyzed) opening of the epoxide ring.

In the discussion of the mechanism of the opening of the epoxide ring two aspects need to be covered, *viz.* the regiochemistry and the stereochemical course. The methanolysis reactions, shown in Schemes 6 and 7, clearly indicate that the nucleophilic solvent attacks at C-4. Because of the similarity in results between the above epoxide hydrolyses and methanolyses, it is justified to conclude that also the hydrolyses proceed by nucleophilic attack at C-4. It should be noted that this also holds for epoxide **18**, with a methyl substituent at C-4 (Scheme 5). The stereochemistry of the epoxide hydrolysis of the precursor **5** of terrein follows the general pattern[19-23] of epoxide opening reactions, implying exclusive formation of *trans*-diols (Scheme 2). Consistent herewith are the hydrolyses and methanolyses of the parent compound **23** and the 5-substituted cyclopentadienone epoxides **7** and **8**, which also proceed exclusively with *trans* stereochemistry (Schemes 3 and 6). This *trans* opening of the epoxide ring takes place with inversion of configuration at C-4. Confirming evidence for this stereo- and regio-chemistry is the observation[24] that the acid-catalysed hydrolysis and subsequent acylation of homochiral cyclopentadienone epoxide **7** lead to enantiomerically pure diacetate **9**.

This seemingly consistent picture of the stereochemistry of the epoxide opening needs reconsideration for the cyclopentadienone epoxides **12** and **13**. The formation of the acetonides **16** and **17** during the hydrolyses of these epoxides (Scheme 4) can only be reconciled by the involvement of *cis*-diols. In view of the exclusive C-4 epoxide opening, observed for the other cyclopentadienone epoxides, it is justified to assume that for these two compounds the epoxide opening also occurs at C-4. The interference of the sulphur containing substituent at C-5 allows a plausible explanation for *cis*-diol formation in these hydrolyses. The sulphur atom of this group can serve as an internal nucleophilic centre and assist in the opening of the epoxide ring[25]. Its role here is presumably restricted to anchimeric shielding of the cationic centre, that is generated at C-4 by stretching of the C-O bond in the protonated epoxide (see structure **39** in Scheme 9). The rear side of

Scheme 9



12 or **13** **39** **40** (R = Ph) or **41** (R = Bz)

the epoxide function is in this manner blocked for attack of the nucleophilic solvent molecule and, in consequence, *cis*-opened products, *i.e.* diols **40** or **41**, will be produced. Under the applied reaction conditions these diols are trapped by acetone to produce the acetonides **16** and **17**, respectively. This

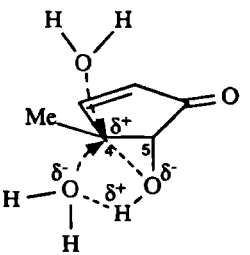
rationale in fact conforms with the generally accepted mechanism[26] of the acid-catalysed hydrolysis of epoxide rings, according to which this reaction has a considerable cationic character with the nucleophile entering rather late in the transition state, when the C-O bond cleavage has already progressed to a great extent (borderline A_2 mechanism).

Alternatively, a four-membered thietanium ion, resembling structure **39**, can be envisaged as an actual intermediate. If this were the case, then the *cis*-diol formation is readily explained by a two stage process involving double inversion. However, a true four-membered thietane would involve considerable annelation strain. Moreover, in that case the methylene carbon would *a priori* have been a more logical site for nucleophilic attack leading to entirely different products.

The anchimeric shielding is only partly effective as can be judged from the observed diacetate-acetonide ratio of *ca* 1:1 (Scheme 4). It is noteworthy that the alkoxymethyl substituents in the epoxides **7** and **8** are apparently ineffective in exerting an anchimeric shielding for nucleophilic epoxide opening from the rear side.

The formation of *cis*-diol **20** on hydrolysis of **18** (Scheme 5) can clearly not be explained by neighbouring group participation. On the basis of the general mechanism of the acid-catalysed hydrolysis of epoxides (*vide supra*), it is conceivable that the epoxide ring opening in this case has a high degree of S_N1 character, because the methyl substituent can stabilize the cationic centre at C-4. This implies that C-4 is close to sp^2 hybridisation and as a consequence thereof the methyl group has moved towards the plane of the five membered ring. The nucleophilic solvent can now enter the transition state from either side of the five membered ring producing a mixture of *cis*- and *trans*-diols. The respective arrangements are shown in Figure 1. Similar arrangements explain the

Figure 1



formation of the *trans*- and *cis*-products, **28** and **29**, in the methanolysis of **18** (Scheme 7). In this case the solvated epoxide is involved in the transition state, rather than the protonated oxirane.

Comparison of the stereochemistry of the epoxide opening in the substrates **23** and **18** (see methanolysis reactions in Schemes 6 and 7, respectively) reveals that the methyl group at C-4 has a remarkable influence. When this group is lacking no *cis*-opening is observed. The extremely mild

conditions under which the hydrolysis and methanolysis of this compound take place are also noteworthy. They illustrate the high reactivity of this particular cyclopentadienone epoxide.

In the literature sofar only a few examples of *cis*-epoxide-opening reactions, not involving double inversion are reported[19,27-30]. These epoxide openings were observed under acid-catalysed conditions for epoxides carrying alkenyl or aryl groups. Such unsaturated substituents can stabilize the incipient cationic centre resulting from the C-O bond stretching. This stabilizing effect apparently allows the introduction of the nucleophilic solvent from the front as well as the rear side.

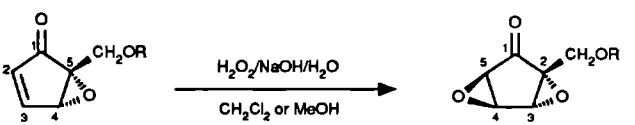
The results obtained with the epoxide opening of the respective cyclopentadienone epoxides investigated here, clearly demonstrate the great influence of the substituents on the stereochemical course of the reaction. The regiochemistry on the other hand is the same for all substrates. It involves exclusive nucleophilic attack at C-4.

Alkaline epoxidation of the double bond.

The enone moiety in cyclopentadienone epoxides is considerably reactive as is demonstrated by the conjugate addition of methanol (Scheme 8). It is of interest to investigate other reactions of the enone part. In view of the interesting structures of the expected products, the nucleophilic epoxidation was explored.

Treatment of the 5-substituted cyclopentadienone epoxides **7** and **8** with alkaline hydrogen peroxide in dichloromethane or methanol afforded the bis-epoxides **42** and **43** in 25% and 64% yield, respectively (Scheme 10). These bis-epoxides are rather labile compounds. They slowly decompose,

Scheme 10



7 (R=Me)
8 (R=Et)

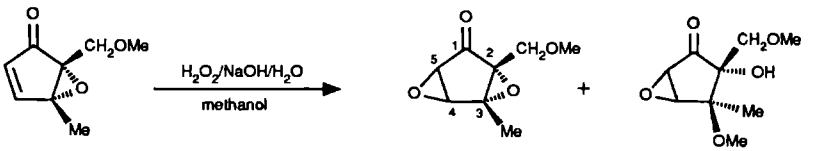
42 (R=Me)
43 (R=Et)

even on storage in the freezer. The IR spectra of the crude products sometimes displayed strong OH absorptions, indicating that epoxide opening already had occurred during the reaction.

The alkaline epoxidation of cyclopentadienone epoxide **44** in a mixture of dichloromethane and methanol provided a 3:1 mixture of the bis-epoxide **45** and the mono-epoxide **46**, in *ca* 50% yield (Scheme 11). The bis-epoxide could be obtained in pure state by filtration of the crude product over silicagel. In order to establish its intermediacy in the formation of mono-epoxide **46**, it was stirred in methanol. This led to a mixture of **45** and **46**, in a ratio of 1:3. An attempt to prepare the acyl derivative of **46** by treatment of this mixture with acetic anhydride, DMAP and triethylamine failed. Instead, a larger amount of the bis-epoxide **45** was obtained than initially had been intro-

duced. Under the conditions of this acylation the mono-epoxide **46** was apparently reconverted into its precursor **45**.

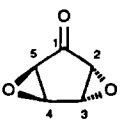
Scheme 11



44 **45** **46**

Attempts to prepare the bis-epoxide, derived from **18**, were frustrated by the lability of the product. To avoid decomposition *in situ* of this bis-epoxide, less alkaline conditions than applied in the other epoxidations were tested. This however resulted only in the formation the diols **19** and **20**.

The parent compound **23** smoothly reacted with alkaline hydrogen peroxide in dichloromethane. The isolation of the resulting bis-epoxide **47**, however, was troublesome due to the high volatility of this compound. So far, we only succeeded to obtain this bis-epoxide in solution.



47

The above epoxidations all afforded only one single diastereomer, *i.e* either the anti- or the syn-bis-epoxide. The configuration of **42** and **43** was deduced from the ^{1}H-NMR spectra of these compounds, which showed negligible spin coupling between H_4 and H_3, indicating the *trans* orientation of these protons. For the *cis* orientated protons, H_5 and H_4, a distinct spin coupling of *ca.* 2.5 Hz was observed. In consequence, both epoxide rings in **42** and **43** are positioned in an anti fashion.

The spectral data of **45** and **47** did not reveal the relative position of the epoxide rings with certainty. It is reasonable to assume that the epoxidizing agent in the reaction with **23** approaches from the same side as methanol in the conjugate addition to this compound (Scheme 8). Therefore the anti-bis-epoxide structure is proposed for **47**. In the case of **44** the steric course of the epoxidation is unpredictable, because both sides of the five membered ring carry substituents of comparable size.

The ^{1}H-NMR positions of the protons H_3, H_4 and H_5 in all bis-epoxides could readily be assigned by comparison with the ^{1}H-NMR spectrum of the methanol adduct **35**. In this adduct the H_2 proton absorbs at higher field than H_3, *viz.* at δ 3.36 ppm and δ 3.94 ppm, respectively. Accordingly, for the bis-epoxides the high field resonance at *ca* 3.39 ppm was assigned to H_5 (and H_2 for **47**) and the low field resonances at *ca.* 4.0-4.2 ppm to H_3 and H_4.

The results of the alkaline epoxidation reactions of the investigated cyclopentadienone epoxides show that under basic conditions the enone moiety is more prone to react with nucleophiles than the epoxide function. This observation is consistent with the selective reaction of methanol with the cyclopentadienone epoxides **23**, **7** and **34** under neutral conditions, where preferential enone addition is observed (Scheme 8).

5.3 Concluding remarks

The results presented in this chapter demonstrate that the epoxide function in cyclopentadienone epoxides allows a selective acid-catalysed hydrolysis or methanolysis reaction in which the nucleophilic solvent attacks at C-4. The stereochemical course of the epoxide ring opening strongly depends on the substitution pattern of the substrates and the nature of the substituents. Opening in *trans* fashion is usually preferred. However, depending on the substituents, considerable amounts of *cis*-opened products are obtained. These results can in part be explained by invoking a participation of the substituents in the solvolysis reaction. Selective reactions of the enone moiety of some substrates could be accomplished, *viz.* conjugate methanol addition under neutral and nucleophilic epoxidation under alkaline conditions.

5.4 Experimental section

General remarks

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were taken on a Perkin Elmer 298 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 or a Bruker WH-90 spectrometer using TMS as internal standard. For mass spectra a Varian SM-1B or a double focussing VG 7070E mass spectrometer was used. Column chromatography ("flash chromatography") was carried out at a pressure of *ca* 1.5 bar, a column length of *ca* 15 cm and a column diameter of 1-4 cm, using Merck Kieselgel 60 H. For preparative TLC precoated Kieselgel plates Merck 60-F254 were used.

The relative configurations of the products are specified by means of the prefixes R* and S*. The asterisks (*) indicate that the products consist of racemic mixtures[31].

(4S,5R*)-4,5-Diacetoxy-5-methoxymethyl-2-cyclopentenone* (**9**)[32].

A solution of cyclopentadienone epoxide **7**[13] (86 mg; 0.6 mmol) in acetone containing 1 vol. % 5N H_2SO_4aq (25 ml) was stirred at room temperature for 2 days. Then, $NaHCO_3$ (5g) and $MgSO_4$ (5g) were added and the resulting slurry was stirred overnight. The mixture was filtered. The solids

were carefully washed with acetone and the combined filtrates were concentrated in vacuo to give 86 mg of crude *(4S*,5R*)-4,5-dihydroxy5-methoxymethyl-2-cyclopentenone*, as a yellow oil. IR(film) v: 3700-3040 (s;OH), 2980(m), 2920(m), 1710(s;C=O), 1635(s;C=C), 1100(s) cm^{-1}. ^{1}H-NMR($CD_3OD/CDCl_3$) δ: 3.33(3H,s;CH_2OCH_3), 3.57(2H,s;CH_2OCH_3), 4.73(1H,br s;H_4), 6.27 (1H,br d,$J_{2,3}$=6Hz;H_2), 7.53(1H,dd,$J_{3,4}$=1.5Hz,$J_{3,2}$=6Hz;H_3). Without further purification, the crude diol was acylated in a mixture of dichloromethane (4 ml), Ac_2O (0.2 ml), DMAP (10 mg) and Et_3N (0.2 ml). After stirring at room temperature for 3 hrs, the reaction was quenched with water (10 ml). The aqueous layer was extracted with dichloromethane (3x5 ml). The combined organic solutions were successively washed with 3% HCl (3x5 ml) and water (3x5 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2/ethyl acetate) to afford 78 mg (54% overall) of **9**, as a colourless oil. IR(CCl_4) v: 1735(broad s;C=O), 1370(m), 1245(s), 1220(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.10(s)/2.13(s)(6H;2xCH_3CO), 3.33(3H,s;CH_2OCH_3), 3.55(2H,s;CH_2OCH_3), 6.26(1H,t,$J_{4,3}$=$J_{4,2}$=2Hz;H_4), 6.47(1H,dd,$J_{2,4}$=2Hz,$J_{2,3}$=6Hz;H_2), 7.40(1H, dd,$J_{3,4}$=2Hz,$J_{3,2}$=6Hz;H_3). MS(EI) m/e(%): 242(0.71;M^+), 158(10;-2xCH_2CO), 140(51;-CH_2CO, -CH_3COOH), 113(19;-2xCH_2CO,-CH_2OMe), 95(63;-CH_2CO,-CH_3COOH,-CH_2OMe), 45(43; CH_2OMe^+), 43(100;CH_3CO^+). HRMS(EI) m/e: 242.0787 (calc. for $C_{11}H_{14}O_6$(M): 242.0790).

(4S,5R*)-4,5-Diacetoxy-5-ethoxymethyl-2-cyclopentenone* (**10**).

The hydrolysis of cyclopentadienone epoxide **8**[13] (60 mg; 0.39 mmol) and subsequent acylation were carried out as described for the conversion of **7** into **9**. Crude **10** was purified by preparative TLC (SiO_2/ethyl acetate-petroleum ether 40°-60°(1:1)). Crystallization from ethyl acetate-petroleum ether 40°-60° provided analytically pure **10** (30 mg; 30%), mp: 48-52°C. IR(CCl_4) v(s): 1740(C=O), 1550 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.11(3H,t,J=7Hz;OCH_2CH_3), 2.06(s)/2.08(s)(6H; 2xCH_3CO), 3.50(q,J=7Hz)/3.58(s)(4H;OCH_2CH_3 and CH_2OEt), 6.25(1H,t,$J_{4,3}$=$J_{4,2}$=2Hz;H_4), 6.45 (1H,dd,$J_{2,4}$=2Hz,$J_{2,3}$=6.5Hz;H_2), 7.35(1H,dd,$J_{3,4}$=2Hz,$J_{3,2}$=6.5Hz; H_3). MS(70eV) m/e: 256(M^+), 214(-CH_2CO), 197(257-CH_3COOH), 172(-2xCH_2CO), 154(-CH_2CO,-CH_3COOH), 126, 110, 95 (-CH_2CO,-CH_3COOH,-CH_2OEt), 84, 68, 59(CH_2OEt^+). HRMS m/e: 256.0946 (calc. for $C_{12}H_{16}O_6$ (M): 256.0945). (Found: C 56.3, H 6.2. Calc. for $C_{12}H_{16}O_6$: C 56.25, H 6.29%.)

Acid-catalysed hydrolysis and subsequent acylation of **12**.

The hydrolysis of cyclopentadienone epoxide **12**[13] (55 mg; 0.25 mmol) and subsequent acylation were carried out as described for the conversion of **7** into **9**. Purification of the crude product by flash chromatography (SiO_2/hexane-ethyl acetate (3:1)) afforded 29 mg (36%) of *(4S*,5R*)-4,5-diacetoxy-5-phenylthiomethyl-2-cyclopentenone* (**14**), as a colourless oil. IR(CCl_4) v: 1748(s;C=O), 1728(s;C=O), 1440(w), 1370(m), 1230/1215 (broad;s), 1042/1022(broad;m), 690(w) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.00(6H,s;2xCH_3CO), 4.16/4.29/4.53/4.65(2H,ABq,J_{AB}=11.4Hz; CH_2SPh), 5.99(1H,dd,$J_{4,2}$=1.5Hz,$J_{4,3}$=2.6Hz;H_4), 6.31(1H,dd,$J_{2,4}$=1.5Hz,$J_{2,3}$=6Hz;H_2), 7.4(6H,m;5

ArH and H_3). MS(EI) m/e(%): 320(15;M^+), 211(5;-SPh), 169(38;-SPh,-CH_2CO), 110(23), 109(48; SPh^+), 91(6), 81(11), 65(11), 43(100;CH_3CO^+). HRMS(EI) m/e: 320.0716 (calc. for $C_{16}H_{16}O_5S$ (M): 320.0718).

Furthermore, 22 mg (32%) of *(4R*,5R*)-4,5-iso-propylidenedioxy-5-phenylthiomethyl-2-cyclopentenone* **(16)** was obtained, as a colourless oil. IR(CCl_4) ν: 2987(m), 1720(s;C=O), 1438(m), 1380/1370(s), 1260(m), 1220(s), 1187(s), 1168(m), 1105(s), 1025(m), 868(m), 692(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.31(3H,s)/1.42(3H,s)(2xCH_3), 3.85(2H,s;CH_2SPh), 4.76(1H,dd,$J_{4,2}$=1Hz, $J_{4,3}$=2.6Hz;H_4), 6.29(1H,dd,$J_{2,4}$=1Hz,$J_{2,3}$=6Hz;H_2), 7.41(6H,m;5 ArH and H_3); MS(EI) m/e(%): 276 (6;M^+), 218(13;-$(CH_3)_2CO$), 123(10), 109(8;SPh^+), 95(100), 81(8), 77(6), 65(7), 45(11), 39(26). HRMS(EI) m/e: 276.0815 (calc. for $C_{15}H_{16}O_3S$ (M): 276.0820).

Acid-catalysed hydrolysis and subsequent acylation of **13**.

The hydrolysis of cyclopentadienone epoxide **13**[13] (86 mg; 0.37 mmol) and subsequent acylation were carried out as described for the conversion of **7** into **9**. Purification of the crude product by flash chromatography (SiO_2/hexane-ethyl acetate (3:1)) afforded 43 mg (38%) of *(4S*,5R*)-5-benzylthiomethyl-4,5-diacetoxy-2-cyclopentenone* **(15)**, as a colourless oil. IR(CCl_4) ν: 1750(s;C=O), 1720(s;C=O), 1450(w), 1370(m), 1230(broad;s), 1042/1028(m), 702(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.00(3H,s)/2.08(3H,s)(2xCH_3CO), 3.95(2H,brs;SCH_2Ph), 4.16/4.27/4.60/4.73 (2H,ABq,J_{AB}=12Hz;CH_2SCH_2Ph), 5.75(1H,dd,$J_{4,2}$=1.2Hz,$J_{4,3}$=2.6Hz;H_4), 6.37(1H,dd,$J_{2,4}$=1.2Hz, $J_{2,3}$=6Hz;H_2), 7.27(m)/7.40(dd,$J_{3,4}$=2.6Hz,$J_{3,2}$=6Hz)(6H;5 ArH and H_3, respectively). MS(EI) m/e(%): 334(0.21;M^+), 212(29;M+1-SCH_2Ph), 152(100;M+1-SCH_2Ph,-CH_3CO_2H), 123(30; SCH_2Ph), 110(100), 91(100;CH_2Ph), 82(14), 65(25), 45(24), 43(100;CH_3CO^+). HRMS(EI) m/e: 334.0868 (calc. for $C_{17}H_{18}O_5S$ (M): 334.0875).

Furthermore, 34 mg (32%) of *(4R*,5R*)-5-benzylthiomethyl-4,5-iso-propylidenedioxy--2-cyclopentenone* **(17)** was obtained as a colourless oil. IR(CCl_4) ν: 1715(s;C=O), 1450(w), 1381/ 1372(m), 1222(s), 1190(m), 1168(w), 1108(s), 1030(w), 870(w), 702(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.31(3H,s)/1.40(3H,s)(2xCH_3), 3.87 (4H,s;CH_2SCH_2Ph), 4.55(1H,dd,$J_{4,2}$=0.9Hz,$J_{4,3}$=2.6Hz;H_4), 6.38(1H,dd,$J_{2,4}$=0.9Hz,$J_{2,3}$=6Hz;H_2), 7.25(br s;5 ArH), 7.52(1H,dd,$J_{3,4}$=2.6Hz,$J_{3,2}$=6Hz;H_3). ^{13}C-NMR($CDCl_3$) δ: 23(q)/26(q)((CH_3)$_2$C), 32(t;CH_2SBz), 52(s;$(CH_3)_2C$), 61(t;SCH_2Ph), 77.6(d; C(4)), 100.4(s;C(5)), 126.8(d)/128.1(d)/128.8(d)(p-,m- and o-ArC, respectively), 135(d;C(2)), 136.6(s;qrt. ArC), 158.6(d;C(3)), 203(s;C(1)). MS(CI) m/e(%): no M+1 signal, 233(32;-$(CH_3)_2CO$), 215(77,-$(CH_3)_2C(OH)_2$), 119(14), 110(13), 91(96), 59(19;$(CH_3)_2COH^+$), 41(100). HRMS(EI, direct inlet) m/e: 290.0981 (calc. for $C_{16}H_{18}O_3S$ (M): 290.0977).

Acid-catalysed hydrolysis and subsequent acylation of **18.**

Cyclopentadienone epoxide **18**[13] (92 mg; 0.84 mmol) was stirred at room temperature in a mixture of acetone (5 ml) and satd NH_4Cl aq (0.5 ml) for ca 20 hrs. The reaction mixture was then

diluted with dichloromethane (5 ml) and $MgSO_4$ (5 g) was added. Stirring was continued for 3 hrs, whereupon the mixture was filtered and concentrated in vacuo, leaving ca 71 mg of an oily residue, consisting of a 1.8:1 mixture of *(4S*,5R*)-* and *(4R*,5R*)-4,5-dihydroxy-4-methyl-2-cyclopentenone* (**19**) and (**20**). ^{1}H-NMR($CDCl_3$) δ: 1.37(s;CH_3(19)), 1.52(s;CH_3(20)), 3.87(s;H_5(20)), 4.30(s;H_5(19)), 6.16/6.23(overlapping doublets ($J_{2,3}$=6Hz) of H_2(19) and H_2(20)), 7.49(d,$J_{3,2}$=6Hz;H_3(19) and H_3(20)). Without further purification the diols **19** and **20** were subjected to acylation as usual, see the preparation of **9**. Purification of the crude product (82 mg) was carried out by flash chromatography (SiO_2/hexane-ethyl acetate (3:1)) to afford 39 mg (22% overall) of a colourless oil, consisting of a 1.8:1 mixture of the di-acetates *(4S*,5R*)-* and *(4R*,5R*)-4,5-diacetoxy-4-methyl-2-cyclopentenone* (**21**) and (**22**). IR(CCl_4) (**21** + **22**) ν: 1740(s;C=O), 1370(m), 1230(broad;s), 1095(m), 1055(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) (**21** + **22**) δ: 1.49(s;C(4)-CH_3(**21**)), 1.77(s;C(4)-CH_3(**22**)), 2.00(s;CH_3CO(**22**)), 2.07(s;CH_3CO(**21**)), 2.22(s;CH_3CO(**22**)), 2.23(s;CH_3CO(**21**)), 5.14(s;H_5(**22**)) 5.84(s;H_5(**21**)), 6.27(d, $J_{2,3}$=8Hz;H_2(**21**)), 6.34(d,$J_{2,3}$=6.5Hz;H_2(**22**)), 7.72(d,$J_{3,2}$=8Hz;H_3(**21**)), 7.86(d,$J_{3,2}$=6.5Hz;H_3(**22**)). GCMS(CI), 100°-150°C, 5°C.min^{-1}, m/e(%): **22** (rt 3'59"): 153(25;-AcOH), 139(5), 125(9), 111(100;-AcOH,-CH_2CO), 95(43), 83(12), 71(12), 69(15), 61(42;$AcOH_2^+$), 57(39), 55(28), 45(21); **21** (rt 4'20"): 153(54;-AcOH), 139(12), 125(24), 111(100;-AcOH,-CH_2CO), 95(53), 83(14), 71(13), 69(15), 61(76;$AcOH_2^+$), 57(39), 55(27), 45(25). MS(CI, direct inlet) m/e(%): 213(1.8;M+1$^+$), 153(46), 139(6), 125(10), 111(100), 95(19), 61(43). HRMS(CI, direct inlet) m/e: 213.0758 (calc. for $C_{10}H_{13}O_5$ (M+1): 213.0763). No attempts were made to separate **21** and **22**.

(4S,5R*)-5-(3,5-Dinitrophenylcarbonyloxy)-4-methoxy-2-cyclopentenone* (**25**).

A solution of cyclopentadienone epoxide **23**[13] (70 mg; 0.73 mmol) in methanol, containing 1 vol.% 5N H_2SO_4 aq (5 ml), was stirred at room temperature for 30 min. Then, $NaHCO_3$ (2 g) and $MgSO_4$ (2 g) were added and the resulting thick slurry was diluted with dichloromethane (14 ml). Stirring was continued overnight, whereupon the mixture was filtered and concentrated in vacuo to leave *ca* 100 mg (~100 %) of crude *(4S*,5R*)-5-hydroxy-4-methoxy-2-cyclopentenone* (**24**) as a colourless oil (purity ~ 90%). IR(CCl_4) ν: 3420(m;OH), 1750(m)/1728(s)(C=O), 1200(m), 1125(s), 982(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 3.58(3H,s;OCH_3), 4.18(1H,d,$J_{5,4}$=2.7Hz;H_5), 4.35(1H,m;H_4), 6.28(1H,dd,$J_{2,4}$=1.2Hz,$J_{2,3}$=6.0Hz;H_2), 7.48(1H,dd,$J_{3,4}$=2.0Hz, $J_{3,2}$=6.0Hz;H_3). Part of this material (85 mg; ~ 0.66 mmol) was dissolved in dichloromethane (7 ml) and at 0°C were successively added: 3,5-dinitrobenzoyl chloride (159 mg; 0.69 mmol), DMAP (15 mg) and Et_3N (100 mg; 1.0 mmol). The resulting mixture was stirred for 20 min, whereupon the cooling bath was removed. After an additional 2 hrs the reaction mixture was diluted with water (5 ml). The aqueous layer was extracted with dichloromethane (3x12 ml). The combined organic solutions were successively washed with 3% HCl (2x12 ml) and water (3x12 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2/hexane-ethyl acetate mixtures ranging from 3:1 to 1:1) to afford 108 mg (51%) of **25** as a thick oil. Attempts to crystallize this oil failed. IR(CCl_4) ν:

1745(m)/1735(s)(C=O), 1545(s;NO_2), 1340(s;NO_2), 1195(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 3.53(3H,s; OCH_3), 4.79(1H,m;H_4), 5.50(1H,d,$J_{5,4}$=3.0Hz;H_5), 6.45(1H,dd,$J_{2,4}$=1.4Hz,$J_{2,3}$=6.2Hz;H_2), 7.64(1H, dd,$J_{3,4}$=2.0Hz,$J_{3,2}$=6.2Hz;H_3), 9.2(m;3ArH). MS(EI) m/e(%): 322(48;M^+), 195(95;dinitrophenyl-carbonyl$^+$), 149(32;195-NO_2), 127(60;-dinitrophenylcarbonyl), 110(18), 99(38;-dinitrophenyl-carbonyl,-CO), 84(69), 75(52), 68(45), 49(97). HRMS(EI) m/e: 322.0448 (calc. for $C_{13}H_{10}O_8N_2$ (M): 322.0437).

(4S,5R*)-5-(3,5-Dinitrophenylcarbonyloxy)-4-methoxy-5-methoxymethyl-2-cyclopentenone* (**27**).

The acid-catalyzed methanolysis of cyclopentadienone epoxide **7**[13] (35 mg; 0.25 mmol) was carried out similar to that of **23** (see the preparation of **25**). This afforded 37 mg (88%) of *(4S*,5R*)-5-hydroxy-4-methoxy-5-methoxymethyl-2-cyclopentenone* (**26**), as a colourless oil (purity ~ 100% (capillary GC)): ^{1}H-NMR($CDCl_3$) δ: 3.33(3H,s;CH_2OCH_3), 3.53(2H,s;CH_2OCH_3), 3.57(3H,s; C(4)-OCH_3), 4.37(1H,br s;H_4), 6.30(1H,br d,$J_{2,3}$=6Hz;H_2), 7.63(1H,br d,$J_{3,2}$=6Hz;H_3). Benzoylation of this material with 3,5-dinitrobenzoyl chloride was performed as described for **24**, see the preparation of **25**. The purification of the crude product was carried out by flash chromatography (SiO_2/ hexane-ethyl acetate (3:1)) yielding 56 mg (70%) of **27**. Recrystallization in hexane-ethyl acetate (3:1) provided an analytically pure sample, mp: 133-135°C. IR(CCl_4) ν(s): 1730(broad;C=O), 1548 (NO_2), 1342(NO_2), 1285, 1198, 1168 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 3.44(3H,s;CH_2OCH_3), 3.60(3H,s; C(4)-OCH_3), 3.74/3.85/3.91/4.01(2H,AB_q,J_{AB}=10.3Hz;CH_2OCH_3), 4.94(1H,m;H_4), 6.49(1H,dd, $J_{2,4}$=1.7Hz,$J_{2,3}$=6.5Hz;H_2), 7.58(1H,dd,$J_{3,4}$=2.0Hz,$J_{3,2}$=6.5Hz;H_3), 9.2(m;3ArH). MS(EI) m/e(%): 366(12;M^+), 321(34;-CH_2OCH_3), 195(36;dinitrophenylcarbonyl$^+$), 171(4;-dinitrophenylcarbonyl), 154(8;-dinitrophenylcarbonyl,-CH_2OCH_3), 149(16;195-NO_2), 139(14), 123(6), 115(19), 98(12), 75(26), 45(100;$CH_2OCH_3^+$). (Found: C 49.18, H 3.90, N 7.54. Calc. for $C_{15}H_{14}N_2O_9$: C 49.19, H 3.85, N 7.67%.)

Methanolysis of **18**

A solution of cyclopentadienone epoxide **18**[13] (125 mg; 1.1 mmol) in 5 ml of methanol was stirred at room temperature for 2 days. (To avoid any acid-catalysis the reaction vessel used, had been rinsed with NH_4OHaq in order to remove possible traces of acid absorbed on the glass wall.) Subsequent concentration in vacuo left 180 mg (~ 100%) of a colourless oil consisting of a 3.3:1 mixture of *(4S*,5R*)*- and *(4R*,5R*)5-hydroxy-4-methoxy-4-methyl-2-cyclopentenone* (**28**) and (**29**). ^{1}H-NMR($CDCl_3$) (**28** + **29**) δ: 1.28(s;C(4)-CH_3 (**28**)), 1.53(s;C(4)-CH_3(**29**)), 3.23(s;OCH_3(**29**)), 3.35(s;OCH_3(**28**)), 3.70(s;H_5(**29**)), 4.27(s;H_5(**28**)), 6.21(d,$J_{2,3}$=6.0Hz;H_2(**28**)), 6.38(d,$J_{2,3}$=6.0Hz; H_2(**29**)), 7.32(d,$J_{3,2}$=6.0Hz;H_3(**29**)), 7.48(d,$J_{3,2}$=6.0Hz;H_3(**28**)).

Acylation of **28** *and* **29**.

Part of the above mixture of alcohols **28** and **29** (80 mg; 0.56 mmol) was subjected to the

acylation procedure described for the preparation of **9**. Purification of the resulting product by tedious flash chromatography (SiO_2/hexane-ethyl acetate mixtures ranging from 10:1-3:1) afforded 30 mg (29%) of *(4S*,5R*)-5-acetoxy-4-methoxy-4-methyl-2-cyclopentenone* (**30**) as a colourless oil. IR(film) ν: 2920(s), 2845(m), 1730(broad;s), 1455(m), 1440(m), 1375(m), 1230(broad;s), 1110(s), 1095(s), 1048(s), 908(w), 888(w), 800(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.35(3H,s;C(4)-CH_3), 2.20(3H, s;CH_3CO), 3.33(3H,s;C(4)-OCH_3), 5.63(1H,s;H_5), 6.27(1H,d,$J_{2,3}$=6.0Hz;H_2), 7.47(1H,d,$J_{3,2}$=6.0Hz; H_3). MS(CI) m/e(%): 185(15;M+1$^+$), 171(21), 153(59;-CH_3OH), 143(78;-H_2C=C=O), 142(25; -CH_3C=O), 125(23), 111(100;-CH_3OH,-H_2C=C=O), 95(13), 83(6), 61(17). HRMS(CI) m/e: 185.0810 (calc. for $C_9H_{13}O_4$ (M+1): 185.0814).

Furthermore, 9 mg (9%) of *(4R*,5R*)-5-acetoxy-4-methoxy-4-methyl-2-cyclopentenone* (**31**) was obtained: colourless oil; IR and mass spectra : nearly identical to those of **30**; ^{1}H-NMR(CCl_4) δ: 1.49(3H,s; C(4)-CH_3), 2.16(3H,s;CH_3CO), 3.03(3H,s;C(4)-OCH_3), 4.97(1H,s;H_5), 6.37(1H,d, $J_{2,3}$=6.0Hz;H_2), 7.20(1H,d,$J_{3,2}$=6.0Hz;H_3).

Each of these acetates **30** and **31** was stirred in methanol at room temperature during several weeks to investigate possible epimerisation. However, no reaction was observed; the acetates were recovered quantitatively.

Benzoylation of **28** *and* **29**.

Part of the above mixture of alcohols **28** and **29** (53 mg; 0.37 mmol) was treated with 3,5-dinitrobenzoyl chloride according to the procedure given for **25**. Purification of the resulting product mixture by flash chromatography (SiO_2/hexane-ethyl acetate (3:1)) afforded 41 mg of *(4S*,5R*)-5-(3,5-dinitrophenylcarbonyloxy)-4-methoxy-4-methyl-2-cyclopentenone* (**32**)[18] as a white solid. Crystallization from hexane-ethyl acetate (4:1) provided an analytically pure sample (fine needlets), mp: 133-135°C. IR(KBr) ν: 1742(s;C=O), 1720(s;C=O), 1550(s), 1538(s;NO_2), 1348(s;NO_2), 1285(s), 1178(s), 1120(m), 1042(m), 797(m), 738(s), 722(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.47(3H,s;C(4)-CH_3), 3.36(3H,s;C(4)-OCH_3), 5.91(1H,s;H_5), 6.36(1H,d,$J_{2,3}$=7.2Hz;H_2), 7.60(1H,d, $J_{3,2}$=7.2Hz;H_3), 9.17(m;3ArH). (Found: C 50.09, H 3.62, N 8.24. Calc. for $C_{14}H_{12}N_2O_8$: C 50.01, H 3.60, N 8.33%.). Furthermore, 57 mg of a 3:2 mixture of **32** and its epimer: *(4R*,5R*)-5-(3,5-dinitrophenylcarbonyloxy)-4-methoxy-4-methyl-2-cyclopentenone* (**33**) was obtained. No further attempts were made to separate **33** from **32**. The ^{1}H-NMR resonances of **33** followed from comparison with the ^{1}H-NMR spectrum of **32**: ^{1}H-NMR($CDCl_3$) δ: 1.66(3H,s;C(4)-CH_3), 3.18(3H,s;C(4)-OCH_3), 5.35(1H,s;H_5), 6.51(1H,d,$J_{2,3}$=6.7Hz;H_2), 7.46(1H,d,$J_{3,2}$=6.7Hz;H_3), 9.2(m;3ArH). The total yield of this benzoylation reaction ammounted to 98 mg (79%). The products **32** and **33** were obtained in a ratio of 3.3:1.

(2R,3R*,4S*)-2,3-Epoxy-4-methoxycyclopentanone* (**35**).

A solution of cyclopentadienone epoxide **23**[13] (20 mg; 0.2 mmol) in methanol (3 ml) was

stirred at room temperature during 1 week. Subsequent concentration in vacuo left only 10 mg (39%) of **35**, as the only product. This low yield is probably due to the volatility of **35**. The product was obtained as a colourless oil. IR(CCl_4) ν: 2985(w), 2925(m), 2895(m), 2850(w), 2820(m), 1760(s; C=O), 1460/1455(w), 1398(w), 1342(m), 1202(m), 1172(m), 1152(m), 1108(s), 1088(s), 948(m), 860(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.94(br s)/2.16(br s)(1H,upfield half of ABX system,J_{AB}=18Hz; H_{5A}), 2.38(d,$J_{5B,4}$=6Hz)/2.60(d,$J_{5B,4}$=6Hz)(1H,downfield half of ABX system,J_{AB}=18Hz;H_{5B}), 3.36 (4H,s+d($J_{2,3}$~3Hz);OCH_3+H_2), 3.94(1H,d,$J_{3,2}$=3.4Hz;H_3), 4.19(1H,br d,$J_{4,5B}$=6Hz;H_4). MS(EI) m/e(%): 128(64;M^+), 101(37;-CO), 97(51;-OCH_3), 85(80), 74(29), 69(51), 66(64), 58(100), 41(96). HRMS(CI) m/e: 129.0559 (calc. for $C_6H_9O_3$ (M+1): 129.0552).

(2R,3R*,4S*)-2,3-Epoxy-4-methoxy-2-methoxymethylcyclopentanone* (**36**).

A solution of cyclopentadienone epoxide **7**[13] (59 mg; 0.42 mmol) in methanol (3 ml) was stirred at room temperature for 4 days. (To avoid any acid-catalysis, the reaction vessel used, had been rinsed with 25% NH_4OH in order to remove traces of acid adsorbed on the glass wall.) Subsequent concentration in vacuo afforded 59 mg (82%) of **36** as a colourless oil[33]. IR(CCl_4) ν: 2985(w), 2925(m), 2890(m), 2822(m), 1748(s;C=O), 1450(w), 1343(w), 1200(m), 1120(s)/1108(s)/ 1090(s), 992(w), 940(w) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.06(s)/2.26(s)(1H,upfield half of ABX system, J_{AB}=18.6Hz;H_{5A}), 2.50(d,$J_{5B,4}$=5Hz)/2.71(d,$J_{5B,4}$=5Hz)(1H,downfield half of ABX system, J_{AB}=18.6 Hz;H_{5B}), 3.37(6H,s;2xOCH_3), 3.67/3.80/3.83/3.98(2H,AB_q,J_{AB}=12.5Hz;CH_2OCH_3), 4.00 (1H,s;H_3), 4.12(1H,d,$J_{4,5B}$=5Hz;H_4). MS(EI) m/e(%): 172(5;M^+), 140(17;-CH_3OH), 125(6), 110(13), 95(58;-CH_3OH,-CH_2OCH_3), 85(63), 68(59), 58(26), 45(100;$CH_2OCH_3^+$). HRMS(EI) m/e: 172.0731 (calcd. for $C_8H_{12}O_4$ (M): 172.0736).

(2R,3R*,4S*)-2,3-Epoxy-2-*iso*-propoxymethyl-4-methoxycyclopentanone* (**37**).

A solution of cyclopentadienone epoxide **34**[13] (41 mg; 0.24 mmol) in methanol (3 ml) was stirred at room temperature for 2.5 week. Subsequent concentration in vacuo afforded 53 mg (~ 100%) of **37** as a colourless oil[38]. IR(CCl_4) ν: 2970(s), 2925(m), 2885(m), 2824(w), 1750(s;C=O), 1467/1455(w), 1380(m), 1368(m), 1340(m), 1200(m), 1100(broad;s), 945(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.13(6H,d,J=6Hz;$CH(CH_3)_2$), 2.05(s)/2.26(s)(1H,upfield half of ABX system,J_{AB}=19Hz;H_{5A}), 2.53(d,$J_{5B,4}$=6Hz)/2.74(d,$J_{5B,4}$=6Hz)(1H,downfield half of ABX system,J_{AB}=19 Hz;H_{5B}), 3.38(3H,s; OCH_3), 3.62(1H,septet,J=6Hz;$CH(CH_3)_2$), 3.73/3.87/3.90/4.03(2H,AB_q,J_{AB}=12Hz;CH_2OiPr), 4.03 (1H,s;H_3), 4.14(1H,d,J=$6_{4,5B}$Hz;H_4). MS(CI) m/e(%): 201 (100;M+1$^+$), 169(40;-CH_3OH), 159(63; -iPr), 141(50;-iPrOH), 131(32;-iPr,-CO), 127(49), 113(49), 109(18), 99(30), 95(8), 85(27), 81(71), 73(11), 71(45), 59(29), 55(11). HRMS(CI) m/e: 201.1117 (calc. for $C_{10}H_{17}O_4$ (M+1): 201.1127).

anti-*(2,3)-(4,5)-Bisepoxy-2-methoxymethylcyclopentanone* (**42**).

A mixture of cyclopentadienone epoxide **7**[13] (41 mg; 0.29 mmol), dichloromethane (8 ml),

35% H_2O_2 (0.9 ml) and 0.2 N NaOH (0.9 ml) was vigorously stirred at room temperature for 20 min. The aqueous phase was then carefully extracted with dichloromethane (4x). The combined organic layers were washed with water (2x), dried ($MgSO_4$), filtered and concentrated in vacuo to give 12 mg (~ 25%) of **42** as a colourless oil. The capillary GC diagram of this material indicated a purity of *ca* 88%. It also revealed a distinct contaminant (*ca* 4%), the amount of which gradually increased on storage, even in the freezer. An attempt to remove this impurity by flash chromatography (SiO_2/hexane-ethyl acetate mixtures ranging from 3:1 to 1:1) failed. IR(CCl_4) ν: 2930(m), 1760(s), 1740(m), 1370(w), 1240(m), 1190(s), 1125(m), 860(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 3.37(3H,s;OCH_3), 3.42(1H,d,$J_{5,4}$=2.6Hz;H_5), 3.59/3.73/3.87/4.00(2H,AB_q,J_{AB}=12Hz;CH_2OCH_3), 4.13(1H,d, $J_{4,5}$=2.7Hz;H_4), 4.25(1H,br s;H_3). MS(EI) m/e: 156(M^+), 139, 127, 111, 97, 85, 84, 71, 69, 55, 45. HRMS(EI) m/e: 156.0427 (calcd. for $C_7H_8O_4$ (M): 156.0422).

anti-*(2,3)-(4,5)-Bisepoxy-2-ethoxymethylcyclopentanone* (**43**).

A mixture of cyclopentadienone epoxide **8**[13] (52 mg; 0.33 mmol), dichloromethane (0.6 ml), methanol (0.6 ml), 35% H_2O_2 (0.05 ml) and 0.2 N NaOH (0.05 ml) was stirred for 30 min. Subsequent work-up as described for **42** afforded 36 mg (*ca* 64%) of **43** as a colourless oil: purity *ca* 94% (capillary GC data). IR(film) ν: 2980(m), 2930(m), 2875(m), 1760/1750(s), 1445(m), 1380(m), 1305(m), 1200(m), 1115(s), 870(s), 810(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.16(3H,t,J=7Hz;OCH_2CH_3), 3.42(d,$J_{5,4}$=2.5Hz;H_5)/3.53(q,J=7Hz;OCH_2CH_3)(3H), 3.65/3.78/3.93/4.07(2H,AB_q,J_{AB}=12.5Hz; CH_2OEt), 4.16(1H,d,$J_{4,5}$=2.5Hz;H_4), 4.27(1H,br s;H_3). HRMS(CI) m/e: 171.0653 (calc. for $C_8H_{11}O_4$ (M+1): 171.0657). Compound **43** gradually decomposed, despite storage in the freezer.

Alkaline epoxidation of **44**.

A mixture of cyclopentadienone epoxide **44**[13] (61 mg; 0.40 mmol), dichloromethane (3 ml), methanol 0.5 ml, 35% H_2O_2 (0.2 ml) and 0.2 N NaOH (0.2 ml) was stirred for 30 min. Subsequent work up as described for **42** afforded 38 mg of a crude mixture, containing *(2,3)-(4,5)-bisepoxy-2-methoxymethyl-3-methylcyclopentanone* (**45**) and *(4,5)-epoxy-2-hydroxy-2-methoxymethyl-3-methoxy-3-methyl-cyclopentan one* (**46**) in a ratio of *ca* 3:1 (^{1}H-NMR data). Alcohol **46** and other contaminants could be removed by stirring the crude product for a few minutes in a CCl_4 solution, to which a pinch of SiO_2 was added. Subsequent filtration followed by concentration in vacuo provided pure **45**, as a colourless oil. IR(CCl_4) ν: 2920(m), 1762(s;C=O), 1195(m), 1130(m), 1100(m), 867(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.73(3H,s;C(3)-CH_3), 3.36(4H,s+d($J_{5,4}$=2.7Hz);CH_2OCH_3 and H_5, respectively), 3.39/3.53(1H,upfield part of AB_q,J_{AB}=12Hz;$CH_AH_BOCH_3$), 3.93/4.07(downfield part of AB_q,J_{AB}=12Hz)/3.98(d,J=2.7Hz)(2H;$CH_AH_BOCH_3$ and H_4, respectively). MS(CI) m/e(%): 171(4; $M+1^+$), 155(15), 139(13;-CH_3OH), 125(16;-CH_3OCH_3), 111(40), 85(16), 83(15), 45(100; $CH_2OCH_3^+$). HRMS(CI) m/e: 171.0657 (calcd. for $C_8H_{11}O_4$ (M+1): 171.0657).

A methanolic solution of **45** was subsequently stirred at room temperature for 18 hrs and then

concentrated in vacuo. This yielded an mixture of **45** and **46** in a ratio of 1:3. Since **46** now formed the main constituent, its ^{1}H-NMR pattern could easily be deduced by comparison of the ^{1}H-NMR spectrum of this mixture with that of **45**: ^{1}H-NMR($CDCl_3$) δ: 1.50(s;C(3)-CH_3), 3.08/3.19(upfield part of AB_q,J_{AB}=10Hz; $CH_AH_BOCH_3$), 3.24(d,$J_{5,4}$=3Hz;H_5), 3.38(s;CH_2OCH_3), 3.51(s;C(3)-OCH_3), 3.70(d,$J_{4,5}$=3Hz;H_4), 4.17/4.29 (downfield part of AB_q,J_{AB}=10Hz;$CH_AH_BOCH_3$).

(2,3)-(4,5)-Bisepoxy-cyclopentanone (**47**).

A mixture of cyclopentadienone epoxide **23**[13] (75 mg; 0.78 mmol), dichloromethane (4 ml), 35% H_2O_2 (0.12 ml) and 0.2 N NaOH (0.12 ml) was stirred at 0°C for 30 min. In view of the volatility of the product, the organic layer was, after the usual work-up (see **42**), only partially concentrated in vacuo. The yield could therefore not be established. ^{1}H-NMR ($CDCl_3$/CH_2Cl_2) δ: 3.37(t,J=2.0Hz;H_2 and H_5), 4.20(t,J=2.0Hz;H_3 and H_4), (5.3 (s) CH_2Cl_2). GCMS(CI) m/e: 113($M+1^+$), 97, 84, 69, 57, 49. HRMS(CI) m/e: 113.0243 (calc. for $C_5H_5O_3$ (M+1): 113.0239).

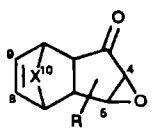
5.5 References and notes

1. Klunder, A. J. H.; Bos, W.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4557.
2. Klunder, A. J. H.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *Ibid.* **1987**, *28*, 1329.
3. Ullman, E. F. *J. Am. Chem. Soc.* **1963**, *85*, 3529.
4. Dunston, J. M.; Yates, P. *Tetrahedron Lett.* **1964**, *5*, 505.
5. Chapmann, O. L.; Hess, T. C. *J. Org. Chem.* **1979**, *44*, 962.
6. Baltrop, J. A.; Colin Day, A. C.; Samuel, C. J. *J. Chem. Soc., Chem. Commun.* **1977**, 598 and references cited therein.
7. Padwa, A. *Tetrahedron Lett.* **1964**, *5*, 813; Padwa, A.; Hartman, R. *J. Am. Chem. Soc.* **1966**, *88*, 1518.
8. Pütter, P.; Dilthey, W. *J. Prakt. Chem.* **1937**, *150*, 49.
9. Ando, W.; Miyazaki, H.; Ueno, K.; Nakanishi, H.; Sakurai, T.; Kobayashi, K. *J. Am. Chem. Soc.* **1981**, *103*, 4949.
10. Takata, T.;Tajima, R.; Ando, W. *Chem. Lett.* **1985**, 665.
11. Klunder, A. J. H.; Bos, W.; Verlaak J. M. J.; Zwanenburg, B. *Tetrahedron Lett.* **1981**, *22*, 4553.
12. Verlaak, J. M. J. *Ph.D. Thesis*, University of Nijmegen, The Netherlands, Febr. 1983.
13. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron*, **1989**, *45*, 7134.

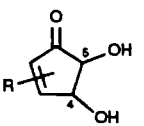
14. Hua, D. H.; Venkataraman, S.;Chan-Yu-King, R.; Paukstelis, J. V. *J. Am. Chem. Soc.* **1988**, *110*, 4741.
15. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Kooy, M. G.; Steffann, J.; Zwanenburg, B. *Tetrahedron*, **1989**, *45*, 7109.
16. Hesse, M.; Meier, H.; Zeeh, B. *Spektroskopische Methoden in der organischen Chemie*, 3. Auflage; Georg Thieme, Stuttgart-New York, 1987; p.114.
17. Barton, D. H. R. and Hulshof, L. *J. Chem. Soc.,Perkin. Trans. 1* **1977**, 1103.
18. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Behm, H.; Moers, F. G.; Beurskens, P. T.; Heydenrijk, D. and Schenk, H. *J. Cryst. Spectrosc. Res.* **1989**, *19*, 223.
19. Parker, R.E.; Isaacs, N.S. *Chem. Rev.* **1959**, *59*, 737.
20. House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, California, 1972; p 300.
21. Bartok, M. and Lang, K. L. *Heterocyclic compounds*: *Small Ring Heterocycles*;A. Hassner: Wiley, New York, 1985; Vol. 42, part 3.
22. Gorzynski Smith, J. *Synthesis*, **1984**, 629.
23. Addy, J. K. and Parker, R. E. *J. Chem. Soc.* **1963**, 915.
24. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Zwanenburg, B.; Beurskens, P. T.; Moers, F. G. and Beurskens, G., submitted for publication.
25. For a review of neighbour participation of sulphur-containing groups, see, Gündermann, K.D. *Angew. Chem.* **1963**, *24*, 1194.
26. (a) Biggs, J.; Chapman, N. B.; Finch, A. F. and Wray, V. *J. Chem. Soc. (B)*, **1971**, 55; (b) Biggs, J.; Chapman, N. B. and Wray, V. *Ibid.* **1971**, 63, 66 and 71.
27. Battistini, C.; Berti, G.; Crotti, P.; Ferreti, M. and Macchia, F. *Tetrahedron*, **1977**, *33*, 1629.
28. Berti, G.; Bottari, F.; Lippi, G. and Macchia, F. *Tetrahedron*, **1968**, *24*, 1959.
29. Robert, A. and Foucaud, A. *Bull. Soc. Chim. Fr.* **1970**, *37*, 212.
30. Brewster, J. H. *J. Am. Chem. Soc.* **1956**, *78*, 4061.
31. *J. Org. Chem.*, **1970**, *35*, 2849.
32. Although the synthesis of **9** has been described previously[13], it is repeated here because the procedure is used as reference for the other syntheses.
33. A trace (*ca* 2.5%) of 6-methoxymethyl-2-pyrone was observed in the capillary GC output of the product. This pyrone arises most probably from a thermally induced rearrangement of **7**, see ref 13.
34. A trace (*ca* 4%) of 6-*iso*-propoxymethyl-2-pyrone was observed in the capillary GC output of the product. This pyrone arises most probably from a thermally induced rearrangement of **37**, see ref 13.

6.1 Introduction

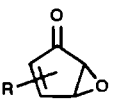
Tricyclodecadienone epoxides **1** (X=O,CH_2) are suitable precursors for a stereoselective synthesis of both *trans*- and *cis*-4,5-dihydroxy-2-cyclopentenones **2**. This has has been demonstrated previously during the syntheses of pentenomycin[1], terrein[2] and *epi*-pentenomycin[3]. The conversion



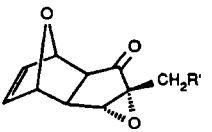
1



2



3



4 R' = OEt
5 R' = $SO_2C_6H_4CH_3$

of **1** into **2** requires two essential transformations, *viz.* a thermal [4 + 2] cycloreversion and an epoxide ring opening. In a recent paper[4] we showed that the thermal reaction of 10-oxatricyclodecadienone epoxides **1** (X=O) to give cyclopentadienone epoxides **3** is conveniently accomplished using the technique of Flash Vacuum Thermolysis. The hydrolysis of the epoxide function in **3** can subsequently readily be achieved under mild acidic conditions and leads usually to *trans*-4,5-dihydroxy-2-cyclopentenones **2**[5].

The ease with which the epoxide ring in **3** is converted into a diol considerably contrasts with the reluctance of the tricyclodecadienone epoxides **1** (X=CH_2; R=4-CH_2OMe; R=4-Me) to undergo epoxide opening[1,6]. These tricyclic epoxides completely fail to react under conditions that normally result in a smooth reaction of the epoxide ring of α,β-epoxy ketones. Their inertness to undergo epoxide ring opening is ascribed to the typical structural feature that the reactive rear side of the epoxide ring is shielded against nucleophilic attack, by either the C_8-C_9 ethylene bridge in the *endo* form or the C_{10} methylene bridge in the *exo* form.

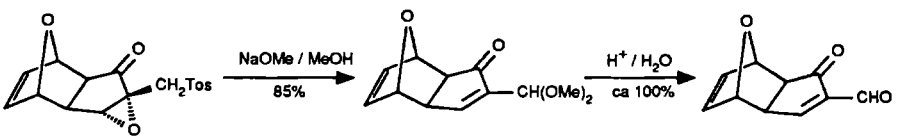
As various 10-oxatricyclodecadienone epoxides **1** (X=O) became recently conveniently accessible[4,7], we decided to investigate whether these compounds would show a similar reluctance to epoxide ring opening as the related 10-carbon analogues **1** (X=CH_2). The substrates selected for this study were the 4-ethoxymethyl- and 4-tosylmethyl-substituted epoxides, **4** and **5**[4], respectively. In

this chapter we report that β-epoxy sulphone **5** in contrast to its ethoxymethyl substituted congener **4** rapidly reacts under basic methanolysis conditions. It will be shown that compound **5** undergoes an exceptional desulphonylation reaction.

6.2 Results and Discussion

Treatment of **4** with 2.2 eq of sodium methanolate in boiling methanol for 24 hrs did not give any product indicative of an epoxide ring opening. The substrate was recovered in *ca.* 80% yield. The loss of material was most probably due to decomposition initiated by β-elimination of the 10-oxa bridge. When epoxy sulphone **5**[8] was treated in the same way as **4** an entirely different result was obtained. Complete conversion of the substrate was observed within 1.5 hrs. After work-up a single product was isolated, which by means of its IR and ^{1}H-NMR spectrum was identified as the dimethylketal **6** (*ca.* 85% yield) (Scheme 1). The characteristic absorption in the IR spectrum at 1710

Scheme 1



5 **6** **7**

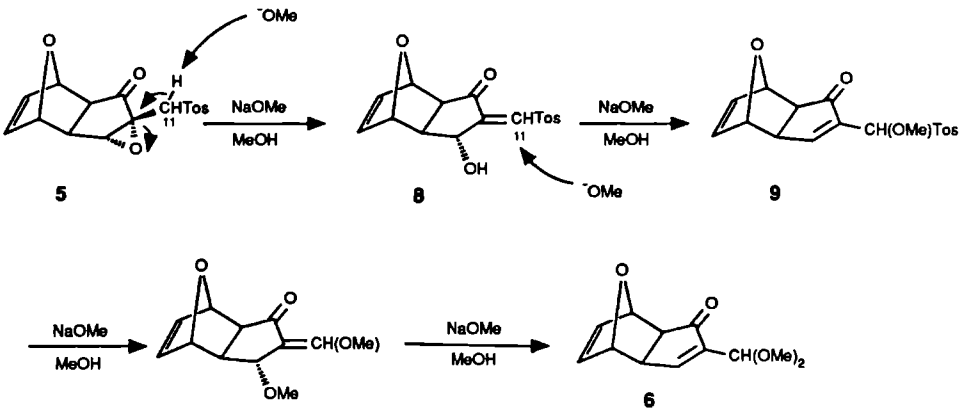
cm^{-1} and a typical low field resonance for the β-enone proton at δ 7.61 ppm in the ^{1}H-NMR spectrum clearly established the presence of the enone moiety. The ^{1}H-NMR spectrum revealed further the absence of the tosyl group, the presence of a dimethoxy unit and the retention of the tricyclic skeleton (see Table). Independent prove that the dimethoxy moiety was an acetal was obtained from the acid catalysed hydrolysis of **6** in a 2:1 mixture of dichloromethane and 3% HClaq. This hydrolysis produced the expected aldehyde **7** as a crystalline solid in almost quantitative yield.

The reluctance of epoxide **4** to undergo epoxide ring opening under the above conditions must be attributed to a shielding effect of the 10-oxa bridge, similar to that exerted by the C_8-C_9 ethylene or C_{10} methylene bridge in the *endo-* or *exo*-tricyclodecadienone epoxides **1** (X=CH_2). It is highly unlikely that this shielding effect of the 10-oxa bridge in sulphone **5** would be less pronounced. Direct bimolecular epoxide ring opening as the initial step in the formation of **6** from **5** can therefore be excluded.

An essential difference between the substrates **4** and **5** is that the latter has an active methylene group, adjacent to the sulphone function, which permits a reaction of compound **5**

commencing with proton abstraction. In view of this, the conversion of **5** into **6** can satisfactorily be rationalized as follows. Initial deprotonation at C_{11}, followed by intramolecular opening[9] of the

Scheme 2



epoxide ring, generates alcohol **8** (Scheme 2). Subsequent attack[10] of a methoxide anion at C_{11} in **8** leads to sulphone **9**, most probably by a reaction involving an S_N2' type substitution[11]. Sulphone **9** is then converted into dimethyl acetal **6** by two consecutive S_N2' displacement reactions, as indicated in Scheme 2.

To extend the scope of this interesting transformation, epoxy sulphones **13** and **14** were prepared and treated with NaOMe in MeOH in the same way as epoxy sulphone **5**. Both compounds **13** and **14** were readily obtained from sulphone **10**[7] via alkylation with MeLi or n-BuLi, followed by alkaline epoxidation of the resulting enones **11** and **12**, respectively (Scheme 3). The subsequent transformation into the corresponding dimethyl acetals **15** and **16** took place smoothly. Complete conversion was reached in less than 1 hr. Both ketals **15** and **16** are stable crystalline compounds. They were unequivocally characterized by their ^{1}H-NMR spectra (see Table). Treatment with HClaq in dichloromethane led, as in the case of **6**, to a rapid and quantitative formation of aldehydes **17** and **18**, respectively (see Table for ^{1}H-NMR data).

The aldehydes **7**, **17** and **18** are thermolabile compounds. They slowly decompose on standing at room temperature. These aldehydes are interesting structures, which are expected to be highly reactive Michael acceptors and dienophiles. They deserve further synthetic elaboration, particularly when is taken into account that these tricyclic compounds in combination with Flash Vacuum Thermolysis can be considered as synthetic equivalents of α-formyl cyclopentadienones.

Scheme 3

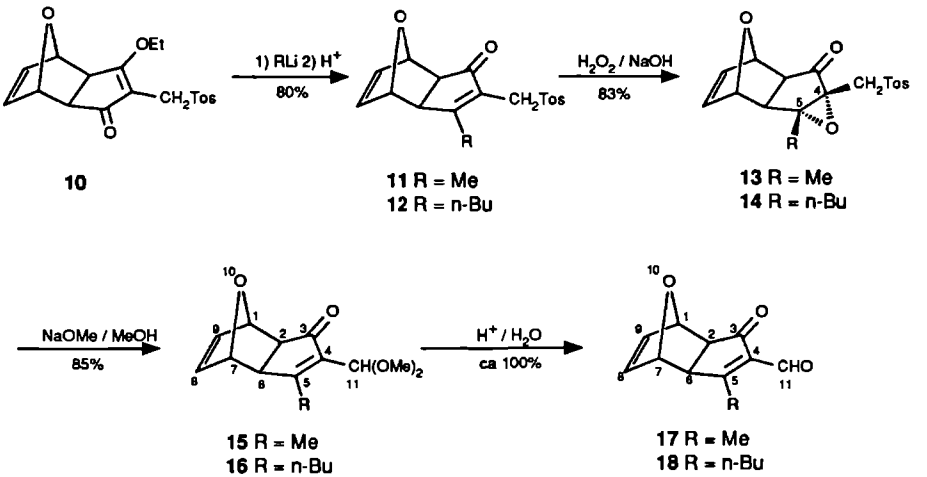


Table. ^{1}H-NMR spectra[a] of 4-dimethoxymethyl- and 4-formyl-10-oxatricyclodecadienones

no.	H_2	H_6	$(OMe)_2$	H_1/H_7	H_{11}	H_8/H_9	C_5-R
6	2.49(d)	2.98(m)	3.28(s)	4.74(s)	5.11(s)	6.42(dd)	R=H
			3.34(s)	5.02(s)		6.56(dd)	7.61(d)
15	2.42(d)	2.75(d)	3.30(s)	4.82(s)	5.13(s)	6.49(m)	R=Me
			3.40(s)	5.00(s)			2.32(s)
16	2.43(d)	2.90(d)	3.27(s)	4.80(d)	5.07(s)	6.41(dd)	R=n-Bu
			3.36(s)	4.98(s)		6.53(dd)	0.95(t); 1.47(m)
							2.43(d); 3.09(m)
7	2.58(d)	3.10(m)		4.87(s)	9.84(s)	6.43(dd)	R=H
				5.09(s)		6.58(dd)	8.23(d)
17	2.52(d)	2.90(d)		4.89(s)	9.90(s)	6.48(m)	R=Me
				5.23(s)			2.52(s)
18	2.48(d)	3.00(d)		4.88(s)	9.93(s)	6.47(m)	R=n-Bu
				5.07(s)			0.93(t); 1.50(m)
							2.48(m); 3.29(m)

a The spectra were measured in $CDCl_3$/TMS. Chemical shifts are recorded in ppm.

6.3 Experimental section

General remarks

Melting points were measured with a Reichert Thermopan microscope and are uncorrected. IR spectra were taken on a Perkin Elmer 298 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 or a Bruker WH-90 spectrometer, using TMS as internal standard. For mass spectra a Varian SM-1B or a double focussing VG 7070E mass spectrometer was used. Flash column chromatography was carried out at a pressure of *ca* 1.5 bar, a column length of *ca* 15 cm and a column diameter of 1-4 cm, using Merck Kieselgel 60 H or Merck Aluminium Oxid 150 neutral (Typ T). For preparative TLC precoated Kieselgel plates Merck 60-F254 were used. All solvents used were dried and distilled by standard procedures.

Exo-*4,5-epoxy-4-(p-tolylsulphonylmethyl)*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-8-en-3-one* (**5**).

To a solution of 4-*p*-tolylsulphonylmethyl-*exo*-10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one[7] (192 mg; 0.53 mmol) in a mixture of dichloromethane (3 ml) and methanol (2 ml) were successively added 35% H_2O_2 (1 ml) and 0.2 N NaOH (1.5 ml). The resulting two phase system was stirred vigorously for 1 hr. The layers were then separated. The aqueous phase was extracted with dichloromethane (3x10 ml). The combined organic layers were washed with water (5 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*, yielding 159 mg (90%) of **5**, as a white solid. Crystallization from hexane-ethyl acetate (1:1) afforded an analytically pure sample, mp: 163.5-165°C. IR(KBr) ν: 1745(s), 1320-1300(s), 1160(s), 1140(s), 1085(m), 1010(m), 880/875(s), 820(s), 780(m), 720(m), 635(m), 620(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.33(1H,d,$J_{2,6}$=7Hz;H_6 or H_2), 2.46(3H,s;Ar-CH_3), 2.63(1H,d,$J_{2,6}$=7Hz;H_6 or H_2), 3.33/3.50/4.00/4.16(2H,AB_q,J_{AB}=15Hz;CH_2Tos), 4.25(1H,br s;H_5), 4.97(1H,br s)/5.10(1H,br s)(H_1,H_7), 6.38(dd)/6.56(dd)(2H,$J_{8,7}$=$J_{9,1}$=1.5Hz, $J_{8,9}$=6Hz;H_8,H_9), 7.33(d,J=8.5Hz;2ArH), 7.83(d,J=8.5Hz;2ArH). MS(CI) m/e(%): 265(74;-furan), 177(14;-HTos), 155(41;Tos$^+$), 139(100), 127(6), 109(23;-furan,-HTos), 91(12;$C_7H_7^+$), 81(8), 68(30;furan$^+$). (Found: C 61.16, H 4.87. Calc. for $C_{17}H_{16}O_5S$: C 61.43, H 4.85%.)

*4-Dimethoxymethyl-*exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one* (**6**).

A solution of sulphone **5** (138 mg; 0.42 mmol) and sodium methoxide (0.9 mmol) in methanol (40 ml) was heated under reflux for 1.5 hr. After cooling to room temperature, the mixture was neutralized with sat NH_4Cl aq and concentrated *in vacuo*. The residue was dissolved in dichloromethane (30 ml) and water (10 ml). The layers were separated. The aqueous phase was extracted with dichloromethane (3x20 ml). The combined organic layers were washed with water (2x), dried ($MgSO_4$), filtered and concentrated. The crude product was subsequently purified by flash chromatography (Al_2O_3/hexane-ethyl acetate (3:1)), yielding 75 mg (80%) of **6** as a thick, colourless oil, which crystallized in the freezer. Recrystallization from hexane afforded an analytically pure

sample, mp: 78-81°C. IR(CCl_4) ν: 1710(s), 1640(m), 1385(br m), 1310/1300(m), 1210(m). 1195(m), 1150(m), 1120(s), 1090(s), 1075/1060/1035(s), 950(s), 910(s), 870(m), 690(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.49(1H,d,$J_{2,6}$=4.5Hz;H_2), 2.98(1H,m;H_6), 3.28(3H,s;OCH_3), 3.34(3H,s;OCH_3), 4.74(1H,br s;H_1), 5.02(1H,br s;H_7), 5.11(1H,br s;C<u>H</u>$(OMe)_2$), 6.42(dd)/6.56(dd)(2H,$J_{8,7}$=$J_{9,1}$=1.5Hz, $J_{8,9}$=6Hz;H_8,H_9), 7.61(1H,d,$J_{5,6}$=2Hz;H_5). MS(CI) m/e(%): 223(1.2;M+1$^+$), 191(100;-CH_3OH), 162(44), 161(21), 123(36;-CH_3OH,-furan), 111(11), 75(13), 68(6;furan$^+$). (Found: C 64.66, H 6.39. Calc. for $C_{12}H_{14}O_4$: C 64.85, H 6.35%.)

In a test experiment **6** (73 mg; 0.33 mmol) was subjected to acid hydrolysis in a mixture of dichloromethane (8 ml) and 3% HCl (4 ml). After 3 hrs of stirring, the layers were separated. The aqueous phase was extracted with dichloromethane (3x15 ml). The combined organic layers were washed with water (1x15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. This afforded 49 mg (84%) of almost pure *5-Oxo*-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-3,8-dien-4-carbaldehyde* (**7**) as a solid. An attempt to prepare an analytically pure sample by recrystallization failed, due to decomposition on heating. ^{1}H-NMR($CDCl_3$) δ: 2.58(1H,d,$J_{2,6}$=4Hz;H_2), 3.10(1H,m;H_6), 4.87(1H,s)/5.09 (1H,s)(H_1,H_7), 6.43(dd)/6.58(dd)(2H,$J_{8,7}$=$J_{9,1}$=1.8Hz,$J_{8,9}$=6Hz;H_8,H_9), 8.23(1H,d,$J_{5,6}$~2Hz;H_5), 9.84(1H,s;CH=O).

5-Methyl-4-(p-tolylsulphonylmethyl)-exo-*10-oxatricyclo[5.2.1.0^{2,6}]de ca-4,8-dien-3-one* (**11**).

A solution of MeLi in hexane (1.2 ml, 1.6 M) was added to a solution of sulphone **10**[7] (340 mg; 0.94 mmol) in dry benzene (15 ml), under nitrogen and cooled on ice. The resulting mixture was vigorously stirred for 1.5 hr and was then allowed to warm up to room temperature. After the addition of 3% HClaq (15 ml) and dichloromethane (15 ml), stirring was continued for 3 hrs. The layers were then separated. The aqueous phase was extracted with dichloromethane (3x10 ml). The combined organic layers were washed with dilute $NaHCO_3$ (3x25 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*, yielding 277 mg (89%) of **11** as a white solid. An analytically pure sample was obtained by crystallization from hexane-ethyl acetate (2:1). mp: 164.5-165°C. IR(KBr) ν(s): 1692, 1640, 1310/1300, 1290, 1160, 1140, 1020, 875, 860, 815, 760 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.21(3H,s;C(5)-CH_3), 2.27(1H,d,$J_{2,6}$=5Hz;H_2), 2.39(3H,s;Ar-CH_3), 2.77(1H,d,$J_{6,2}$=5Hz;H_6), 3.96(2H,s;CH_2Tos), 4.77(1H,br s)/4.85(1H,br s)(H_1,H_7), 6.40(dd)/6.53(dd)(2H,$J_{8,7}$=$J_{9,1}$=2Hz, $J_{8,9}$=5Hz;H_8,H_9), 7.30(d,J=8Hz;2ArH), 7.73(d,J=8Hz;2ArH). MS(CI) m/e(%): 331(22;M+1$^+$), 263(17;-furan), 175(100;-Tos), 107(100;-furan,-Tos), 91(58;$C_7H_7^+$), 79(53), 68(31;furan$^+$).

5-n-Butyl-4-(p-tolylsulphonylmethyl)-exo-*10-oxatricyclo[5.2.1.0^{2,6}]deca-4,8 dien-3-one* (**12**).

A solution of n-BuLi in hexane (2.5 ml, *ca* 1.6 M) was added to a solution of sulphone **10**[7] (672 mg; 1.87 mmol) in freshly distilled THF (30 ml), under nitrogen and cooled at -78°C. The resulting mixture was stirred for 1 hr and was then allowed to warm up to room temperature. After addition of 3% HClaq (15 ml) and dichloromethane (20 ml), stirring was continued for 1 hr. The

layers were then separated. The aqueous phase was extracted with dichloromethane (3x30 ml). The combined organic layers were washed with water (3x30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2/ethyl acetate), yielding 506 mg (73%) of **12** as a white solid, which was recrystallized from hexane-ethyl acetate (2:1), mp: 113-114.5°C. IR(KBr) ν(s): 1695, 1630, 1320, 1300, 1290, 1140, 880, 850, 770 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.97(3H,br t,J=7Hz;$(CH_2)_3CH_3$), 1.56(4H,m;$CH_2(CH_2)_2CH_3$), 2.29(1H,d, $J_{2,6}$=5Hz;H_2), 2.42(3H,s;Ar-CH_3), 2.42-2.93(2H,m;$CH_2(CH_2)_2CH_3$), 2.93(1H,d,$J_{6,2}$=5Hz;H_6), 3.99 (2H,s;CH_2Tos), 4.71(1H,br s)/4.83(1H,br s)(H_1,H_7), 6.38(dd)/6.51(dd)(2H,$J_{8,7}$=$J_{9,1}$=2Hz,$J_{8,9}$=6Hz; H_8,H_9), 7.25(d,J=8Hz;2ArH), 7.70(d,J=8Hz;2ArH). MS(CI) m/e(%): 373(14;M+1$^+$), 305(6;-furan), 217(52;-HTos), 149(100;-furan,-HTos), 131(13), 107(33), 91(33;$C_7H_7^+$), 79(14), 68(20;furan$^+$).

Exo-*4,5-epoxy-5-methyl-4-(p-tolylsulphonylmethyl)*-exo-*10-oxatri-cyclo[5.2.1.0^{2,6}]deca-8-en-3-one* **(13)**.

A mixture of sulphone **11** (202 mg; 0.61 mmol), dichloromethane (3 ml), methanol(2 ml), 35% H_2O_2 (1 ml) and 0.2 N NaOH (1.3 ml) was stirred overnight. Work-up was then carried out as described for **5**. This afforded 180 mg (85%) of **13**, as a white solid. Crystallization from hexane-ethyl acetate (1:3) afforded an analytically pure sample, mp: 157-157.5°C. IR(KBr) ν: 1740(s), 1600(m), 1390(m), 1325(s), 1145(s), 1090(m), 1020(m), 920(s), 880(s), 715(m), 640(m), 612(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.68(3H,s;C(5)-CH_3), 2.26(1H,d,$J_{2,6}$=6.6Hz;H_6 or H_2), 2.44/2.51(4H,s+d($J_{2,6}$=6.6Hz);Ar-CH_3 + H_6 or H_2), 3.29/3.46/3.86/4.03(2H,AB_q,J_{AB}=15Hz; CH_2Tos), 4.91(1H,s)/5.07(1H,br s)(H_1,H_7), 6.40(dd)/6.53(dd)(2H,$J_{8,7}$=$J_{9,1}$=1.8Hz,$J_{8,9}$=6Hz;H_8,H_9), 7.31(d,J=8Hz;2ArH), 7.87(d,J=8Hz;2ArH). MS(CI) m/e(%): 347(3;M+1$^+$), 279(100;-furan), 191(10;-HTos), 155(23;Tos$^+$), 139(53), 123(100;-furan,-HTos), 95(68), 68(38;furan$^+$). (Found: C 62.09, H 5.32. Calc. for $C_{18}H_{18}O_5S$: C 62.41, H 5.24%.)

5-n-Butyl-exo-*4,5-epoxy-4-(p-tolylsulphonylmethyl)*-exo-*10-oxatri-cyclo[5.2.1.0^{2,6}]deca-8-en-3-one* **(14)**.

Sulphone **12** (506 mg; 1.4 mmol) was dissolved in a few drops of dichloromethane. To this solution were successively added methanol (5 ml), 35% H_2O_2 (5 ml) and 0.2 N NaOH (5 ml). The resulting mixture was stirred for 18 hrs and was then diluted with dichloromethane (20 ml). Work-up was carried out as described for **5**. This afforded 417 mg (80%) of **14**, as a white solid. An analytically pure sample was obtained by crystallization from hexane-ethyl acetate (5:1), mp: 142.5-144°C. IR(KBr) ν: 1735(s), 1595(w), 1320(m), 1305(m), 1175(m), 1140(s), 1090(m), 1010(m), 950(m), 910(m), 880(m), 820 (m), 810(s), 770(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.95(3H,br t,J=6.5Hz; $(CH_2)_3CH_3$), 1.51(6H,br m;$(CH_2)_3CH_3$), 2.27(1H,d,$J_{2,6}$=7.5Hz;H_6 or H_2), 2.44(3H,s;Ar-CH_3), 2.56 (1H,d,$J_{2,6}$=7.5Hz;H_6 or H_2), 3.33/3.48/3.87/4.03(2H,AB_q,J_{AB}=14Hz;CH_2Tos), 4.87(1H,br s)/ 5.00(1H,br s)(H_1,H_7), 6.38(dd)/6.53(dd)(2H,$J_{8,7}$=$J_{9,1}$=1.6Hz,$J_{8,9}$=6Hz;H_8,H_9), 7.29(d,J=8Hz;2ArH),

7.83(d,J=8Hz;2ArH). MS(EI) m/e(%): 320(39;-furan), 233(10;-Tos), 166(70;-furan,-Tos), 149 (21), 139(6), 123(100;-furan,-Tos,-C_3H_6), 109(26;-furan,-Tos,-nBu), 91(74;$C_7H_7^+$), 81(15), 68(53;furan$^+$). (Found: C 64.74, H 6.28. Calc. for $C_{21}H_{24}O_5S$: C 64.93, H 6.23%.)

4-Dimethoxymethyl-5-methyl-exo-*10-oxatricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one* (**15**).

Heating of sulphone **13** (156 mg; 0.45 mmol) in refluxing methanol with sodium methoxide (0.97 mmol) for 45 min and subsequent work-up, as described for **6**, provided 93 mg (88%) of **15**, as a white solid, which was recrystallized from hexane, mp: 130-134°C. IR(KBr) v: 1690(s), 1635(m), 1400(br m), 1290(m), 1125(m), 1075/1055/1040(s), 1015(m), 915(m), 885(m), 850(s), 720(m) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.32(3H,s;C(5)-CH_3), 2.42(1H,d,$J_{2,6}$=5Hz;H_2), 2.75(1H,d,$J_{6,2}$=5Hz;H_6), 3.30(3H,s;OCH_3), 3.40(3H,s;OCH_3), 4.82(1H,s;H_1), 5.00(1H,s;H_7), 5.13(1H,s;CH(OMe)$_2$), 6.49(2H,m;H_8,H_9). MS(CI) m/e(%): 204(11;-CH_3OH), 189(54;-CH_3OH,-CH_3), 176(59), 137(100;-CH_3OH,-furan), 125(58), 75(39), 68(58;furan$^+$).

Acid hydrolysis of **15** (143 mg; 0.61 mmol) in a mixture of dichloromethane (15 ml) and 3% HClaq (6 ml) (1.5 hr of stirring and work-up as described for **7**) yielded 113 mg (99%) of almost pure *3-Methyl-5-oxo*-exo-*10-oxatricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-4-carbaldehyde* (**17**) as a pale tinted solid. Careful recrystallization from hexane-ethyl acetate (10:1) afforded an analytically pure sample. mp: 79°C (dec). IR(KBr) v: 1720(s), 1660(s), 1605(m), 1380(s), 1345(s), 1305(m), 1290(m), 1010(m), 905(m), 870(s), 725(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 2.52(4H,s+d($J_{2,6}$=4.5Hz);CH_3+H_2), 2.90(1H,d,$J_{6,2}$=4.5Hz;H_6), 4.89(1H,s)/5.23(1H,s)(H_1,H_7), 6.48(2H,m;H_8,H_9), 9.90(1H;CH=O). (Found: C 69.35, H 5.34. Calc. for $C_{11}H_{10}O_3$: C 69.46, H 5.30%.)

5-n-Butyl-4-dimethoxymethyl-exo-*10-oxatricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-one* (**16**)

Heating of sulphone **14** (212 mg; 0.55 mmol) in refluxing methanol (50 ml) with sodium methoxide (1.1 mmol) for 45 min and subsequent work-up, as described for **6**, provided 125 mg (82%) of **16**, as a white solid. An analytically pure sample was obtained by crystallization from hexane. mp: 46-48°C. IR(KBr) v: 1690(s), 1620(m), 1395(m), 1310(m), 1285(m), 1120(m), 1050(br s), 845(s), 815(s) cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.95(3H,br t,J=7Hz;$(CH_2)_3CH_3$), 1.47(4H,m; $CH_2(CH_2)_2CH_3$), 2.43(2H,m+d($J_{2,6}$=5Hz);C$H_AH_B$$(CH_2)_2CH_3$ and H_2), 2.90(1H,d,$J_{6,2}$=5Hz;H_6), 3.09 (1H,m;C$H_AH_B$$(CH_2)_2CH_3$), 3.27(3H,s;$OCH_3$), 3.36(3H,s;$OCH_3$), 4.80(1H,d,J<0.8Hz;$H_1$), 4.98(1H, br s;$H_7$), 5.07(1H,s;C$H(OMe)_2$), 6.41(dd)/6.53(dd)(2H,$J_{8,7}$=$J_{9,1}$=0.9Hz,$J_{8,9}$=7Hz;$H_8$,$H_9$). MS(CI) m/e(%): 247(16;M+1-CH_3OH), 246(16;M-CH_3OH), 231(47), 218(39), 217(22), 179(100; M+1-CH_3OH,-furan), 167(17), 140(26), 139(15), 123(16), 75(25), 68(13;furan$^+$). (Found: C 68.90, H 7.90. Calc. for $C_{16}H_{22}O_4$: C 69.04, H 7.97%.)

Acid hydrolysis of **16** (147 mg; 0.53 mmol) in a mixture of dichloromethane (15 ml) and 3% HCl aq (6 ml) (1.5 hr of stirring and work-up as described for **7**) yielded 126 mg (*ca.* 100%) of almost pure *3-n-Butyl-5-oxo*-exo-*10-oxatricyclo[5.2.1.$0^{2,6}$]deca-3,8-dien-4-carbaldehyde* (**18**) as an

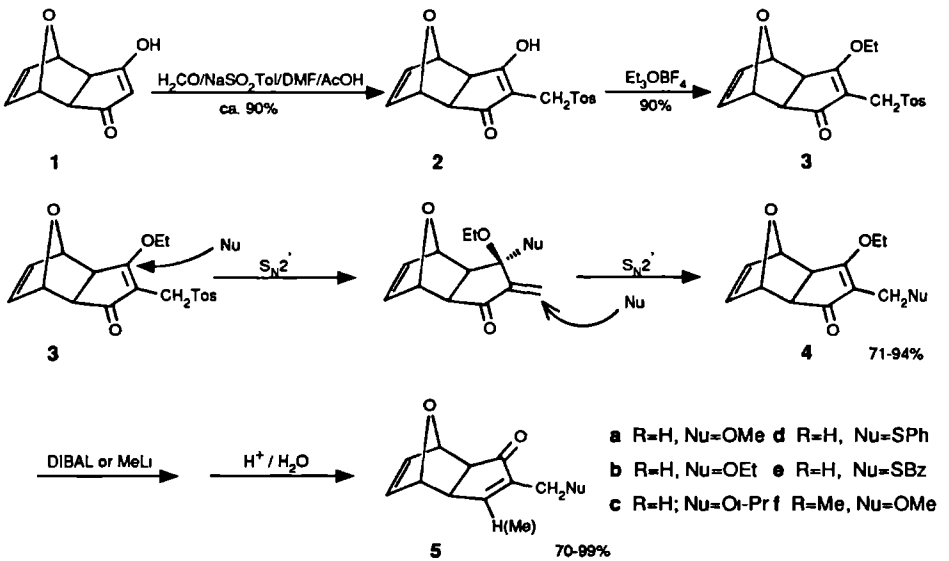
oil. This compound appeared unstable. It slowly decomposed on standing at room temperature. Attempts to prepare an analytically pure sample by careful recrystallization or thin layer chromatography failed. ^{1}H-NMR($CDCl_3$) δ: 0.93(3H,br t,J=6Hz;$(CH_2)_3C\underline{H}_3$), 1.50(4H,m;$CH_2(C\underline{H}_2)_2CH_3$), 2.48(2H, m+d($J_{2,6}$=4.5Hz);$C\underline{H}_AH_B(CH_2)_2CH_3$ and H_2), 3.00(1H,d,$J_{6,2}$=4.5Hz;H_6), 3.29(1H,m; $CH_A\underline{H}_B(CH_2)_2CH_3$), 4.88(1H,s)/5.07(1H,s)(H_1,H_7), 6.47(2H,m;H_8,H_9), 9.93(1H,s;CH=O).

6.4 References and notes

1. Verlaak, J. M. J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1982**, *23*, 5463.
2. Klunder, A. J. H.; Bos, W.; Zwanenburg, B. *Ibid.* **1981**, *22*, 4557.
3. Klunder, A. J. H.; Houwen-Claassen, A. A. M.; Kooy, M. G.; Zwanenburg, B. *Ibid.* **1987**, *28*, 1329.
4. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron*, **1989**, *45*, 7134.
5. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron*, submitted for publication.
6. Verlaak, J. M. J. *Ph.D. Thesis*, University of Nijmegen, The Netherlands, Febr. 1983.
7. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Kooy, M. G.; Steffann, J.; Zwanenburg, B. *Tetrahedron*, **1989**, *45*, 7109.
8. This compound was prepared by alkaline epoxidation of 4-*p*-tolylsulphonylmethyl-*exo*-10-oxatricyclo[5.2.1.$0^{2,6}$]deca-4,8 -dien-3-one[7].
9. Similar base-promoted epoxide opening reactions of β-epoxysulphones have been reported by (a) Bordwell, F. G.; Sokol, P. J.; Spainhour, J. D. *J. Am. Chem. Soc.* **1960**, *82*, 2881; (b) Conrad, P. C.; Fuchs, P. L. *Ibid.* **1978**, *100*, 346; (c) Donaldson, R. E.; Saddler, J. C.; Byrn, S.; McKenzie, A. T.; Fuchs, P. l. *J. Org. Chem.* **1983**, *48*, 2167.
10. Although the tosyl group discourages nucleophilic attack at an adjacent carbon, such an attack cannot be excluded here, since the carbon involved is an sp^2 centre and therefore less susceptible to steric and electronic shielding.
11. For evidence see ref 7.

Chapter 1

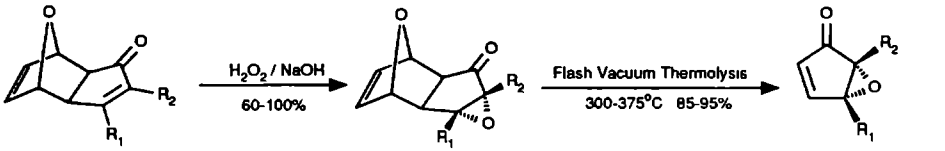
Tosylmethylation of the furan derived cycloadduct **1** of cyclopentene-1,4-dione, followed by O-ethylation, leads to 5-ethoxy-4-(*p*-tolylsulphonyl)methyl-*exo*-10-oxatricyclo[5.2.1.$0^{2,6}$]-deca-4,8-dien-3-one **3**. This sulphone undergoes a rapid displacement of the tosyl group by an ether or thioether function, when treated with alcoholates or thiolates. This displacement involves two consecutive S_N2' substitutions, taking place stereospecifically at the least hindered *exo*-face of the substrate molecule, *i e* anti to the 10-oxa bridge. Subsequent reduction with Di-iso-Butyl Aluminium Hydride (DIBAL) or reaction with Methyl Lithium (MeLi) produces 4- and/or 5-substituted 10-oxatricyclo[5.2.1.$0^{2,6}$]decadienones **5**.



Chapter 2

The alkaline epoxidation of **5a-h** affords the corresponding polycyclic epoxides **6a-h** in fair (**6d**: 60%, **6e**: 77%) to good (**6a-c,f-h**: 93-100%) yields. In this reaction the epoxide ring is

stereoselectively introduced at the *exo*-face of the substrate molecule. The products **6a-h** are efficiently (*ca* 85-90%) converted into cyclopentadienone epoxides **7a-h**, using the Flash Vacuum Thermolysis technique.



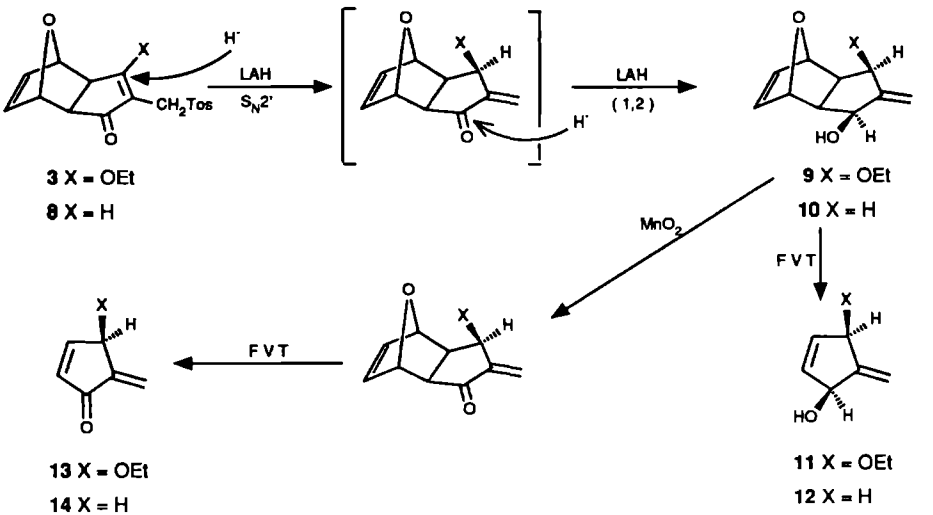
5a-f
5g $R_1 = R_2 = H$
5h $R_1 = Me$; $R_2 = H$

6a-f
6g $R_1 = R_2 = H$
6h $R_1 = Me$; $R_2 = H$

7a-f
7g $R_1 = R_2 = H$
7h $R_1 = Me$; $R_2 = H$

Chapter 3

On treatment with Lithium Aluminium Hydride (LAH) the tricyclic sulphones **3** and **8** undergo two consecutive, regioselective and stereoselective reductions. The first reduction constitutes an S_N2' displacement of the allylic tosyl group, the second a (1,2) reduction of the resulting *exo*-cyclic enone to form the α-methylene cyclenols **9** and **10**, respectively. These products are smoothly converted into α-methylenecyclopentenols **11** and **12**, and α-methylene-cyclopentenones **13** and **14**, respectively, using the Flash Vacuum Thermolysis technique for the required cycloreversion.



3 X = OEt
8 X = H

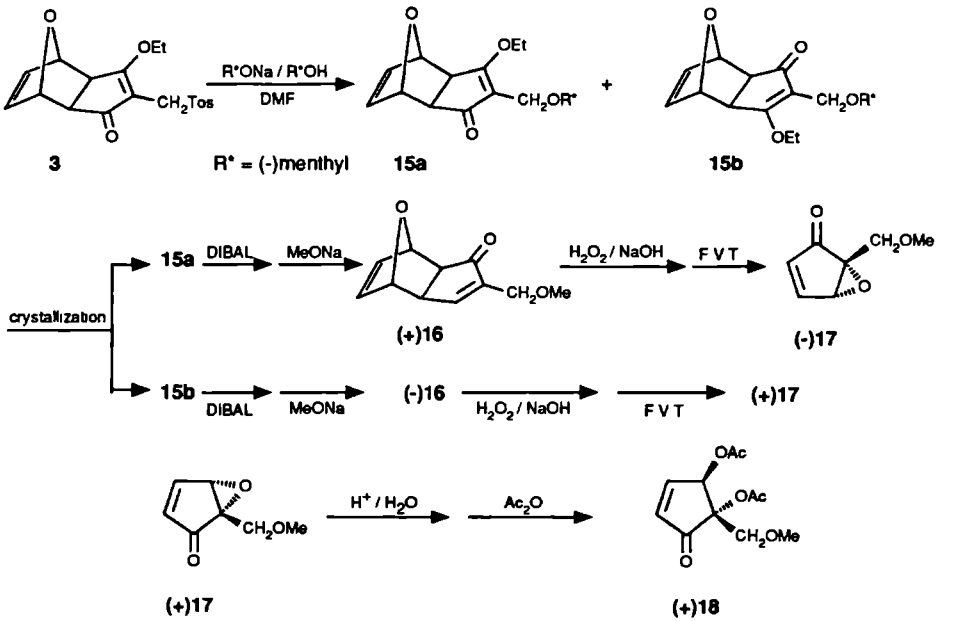
9 X = OEt
10 X = H

11 X = OEt
12 X = H

13 X = OEt
14 X = H

Chapter 4

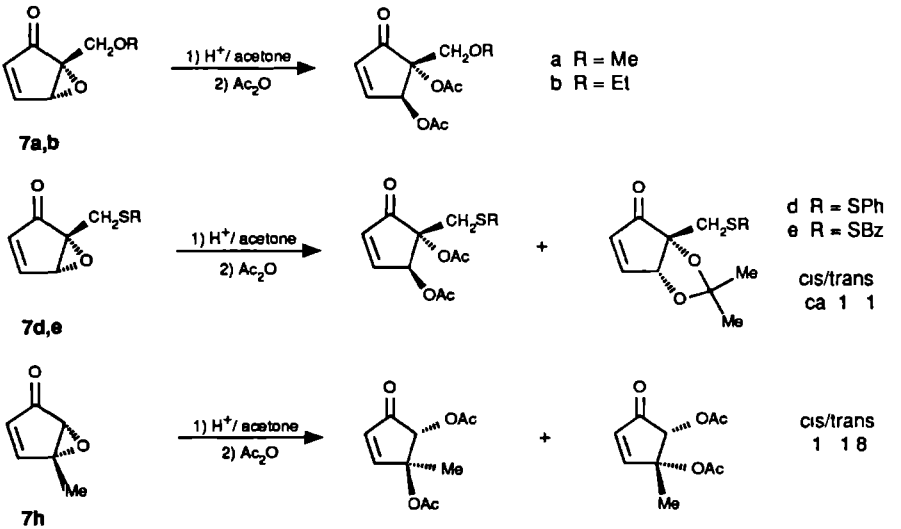
The reaction of sulphone **3** with sodium menthylate leads to a diastereomeric mixture of the (-)menthyl ethers, **15a** and **15b** in 88% yield. Separation of these ethers, followed by reduction with DIBAL and trans-etherification with NaOMe affords the enantiomerically pure methoxymethyl substituted 10-oxatricyclodecadienones **(+)16** and **(-)16**. These tricyclodecadienones are enantiospecifically converted into the cyclopentadienone epoxides **(-)17** and **(+)17**, respectively, by successive alkaline epoxidation and Flash Vacuum Thermolysis. The absolute configurations of the compounds **15-17** is deduced by correlation with structure **(-)16**, which has been determined by X-Ray diffraction analysis. The synthetic use of a homochiral cyclopentadienone epoxide is demonstrated by the enantiospecific conversion of **(+)17** into enantiomerically pure **(+)18**, which is a precursor for *epi*-pentenomycin.



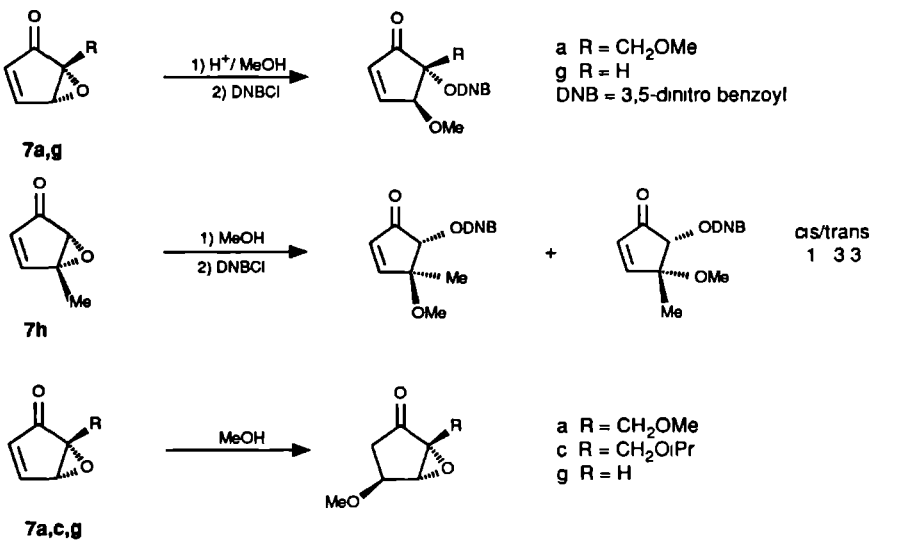
Chapter 5

The acid-catalysed hydrolysis and methanolysis of 4- or 5-substituted cyclopentadienone epoxides have been investigated. In all cases the nucleophilic solvent reacts at the 4-position, however, the stereochemistry of these solvolyses is strongly dependent on the nature of the substituent. Hydrolysis of the epoxides **7a,b** exclusively affords *trans*-diols (or the *trans*-diacetates

Hydrolyses

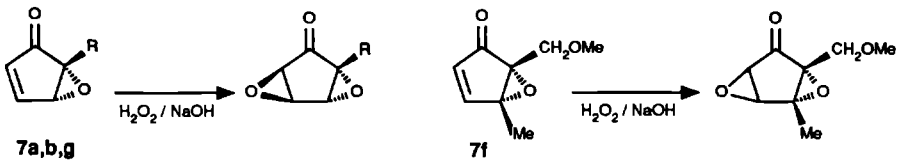


Methanolyses



after acylation). Unexpectedly, the hydrolysis of epoxides **7d,e** give *cis*- and *trans*-diols in almost equal yields. The *cis*-diols are trapped by the solvent acetone to produce acetonides, whereas the *trans*-diols are converted into the corresponding *trans*-diacetates by subsequent acylation. The formation of the *cis*-diols is rationalized by assuming that attack of the nucleophilic solvent from the rear side of the epoxide group is anchimerically shielded by the thiomethyl group at C-5. The acid-catalysed hydrolysis of epoxide **7h** yields a mixture of *cis*- and *trans*-diols in a ratio of 1:1.8. Neutral methanolysis of this epoxide produces a 1:3.3 mixture of *cis*- and *trans*-opened products. This stereochemistry can be understood by invoking a high degree of cationic character in the transition state of the solvolysis reaction. Methanolysis of epoxides **7a,c,g** under neutral conditions leads to conjugate methanol addition to the enone moiety. Under basic conditions the enone moiety is the preferred reactive unit, as can be deduced from the alkaline epoxidations of **7a,b,f,g**.

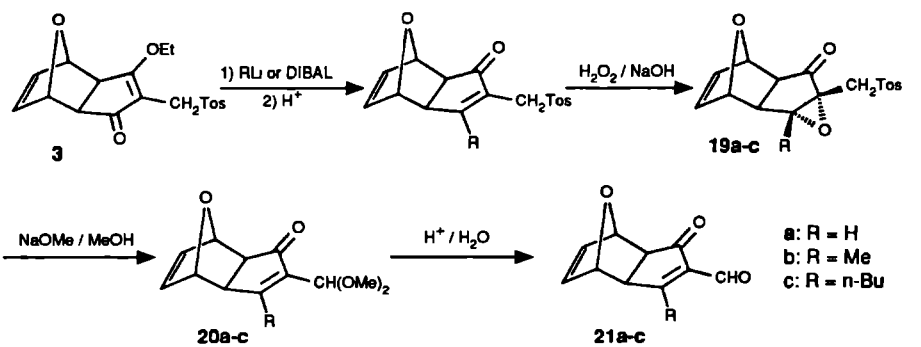
Alkaline epoxidations



7a,b,g **7f**

Chapter 6

The reaction of sulphone **3** with DIBAL or alkyl lithium reagents, followed by nucleophilic epoxidation, affords the tosylmethyl substituted tricyclodecadienone epoxides **19** (*ca.* 70% overall yield). Treatment of these epoxides with sodium methanolate in methanol and subsequent acid hydrolysis of the resulting ketals **20**, leads in high yield to 4-formyl-10-oxatricyclo[5.2.1.$0^{2,6}$]-8-en-3-ones **21**. The reaction sequence involves, successively, a base induced epoxide ring opening of a β-epoxy sulphone, three consecutive S_N2' type reactions and a hydrolysis of a dimethyl acetal.

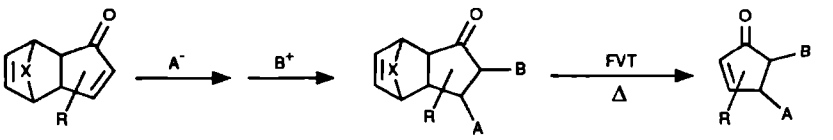


3 **19a-c** **20a-c** **21a-c**

SAMENVATTING

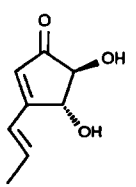
Het onderzoek dat in deze dissertatie beschreven staat, maakt deel uit van een breed researchprogramma, dat is gericht op de toepassing van tricyclodecadienonen **1** ($X=CH_2,O$) in de bereiding van gefunctionaliseerde cyclopentenonen **3**. Het algemene concept, dat aan dit project ten grondslag ligt, is weergegeven in Schema 1. Het aantrekkelijke van de geschetste route is, dat de

Schema 1

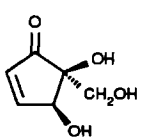


1 **2** **3**

omzetting van **1** naar **2** op stereogecontroleerde wijze verloopt. Dit geldt eveneens voor de daarop volgende cyclo-reversie van **2** naar **3**. Laatstgenoemde omzetting kan door middel van thermolyse in de gasfase bij een druk van ca. 0.1 mbar (Flits Vacuum Thermolyse) op een efficiënte manier worden gerealiseerd. Langs deze weg kunnen derhalve diverse cyclopentenonen **3** worden gesynthetiseerd, met een goed gedefinieerde structuur. De methode leent zich om die reden uitstekend voor toepassing in de synthese van natuurproducten. De bruikbaarheid voor dit doel was, voor de aanvang van het hier beschreven onderzoek, reeds aangetoond door de bereiding van de twee interessante cyclopentenoide natuurstoffen, terreïne **4** en pentenomycine **5**.



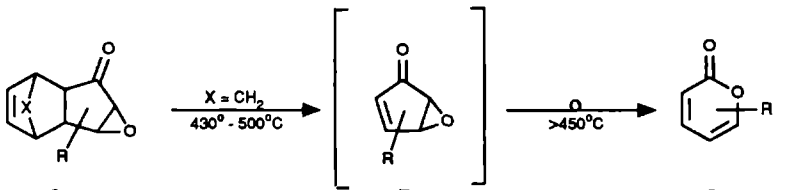
4



5

In de synthese van **4** zowel als **5**, werd in een bepaald stadium gebruik gemaakt van een polycyclisch epoxide **6** (X=CH_2). Bij oriënterend onderzoek naar het thermolytisch gedrag van dit type verbindingen bleek, dat een vrij hoge temperatuur (ca. 430°-500°C) nodig is om de gewenste cycloreversie tot stand te brengen. De cyclopentadienonepoxiden **7**, die daarbij in eerste instantie worden gegenereerd, reageerden echter vanaf ca. 450°C snel door tot 2-pyronen **8** en konden daardoor in de praktijk vaak niet geïsoleerd worden (Schema 2). Om deze verbindingen **7** toch goed

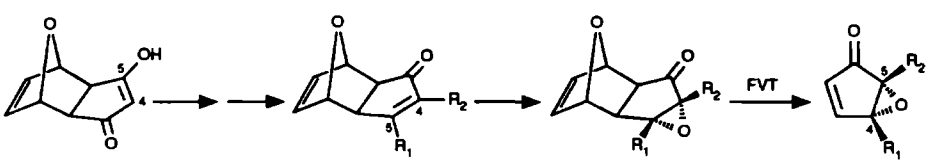
Schema 2



6 **7** **8**

in handen te kunnen krijgen, via de in Schema 1 geschetste route, werd gezocht naar alternatieven voor **6** (X=CH_2), die bij een relatief lage temperatuur, bij voorkeur lager dan 400°C, zouden kunnen worden gethermolyseerd. Hoge verwachtingen werden in dit verband gekoesterd van de 10-oxatricyclodecadienon-epoxiden **6** (X=O). Deze verbindingen splitsen bij de cyclo-reversie furan af. Gezien het aromatische karakter van furan mocht worden verwacht, dat dit proces bij relatief lage temperatuur kan worden gerealiseerd. De realiseerbaarheid van deze benadering werd duidelijk geïllustreerd door een voorbeeld uit de literatuur, waarin gewag werd gemaakt van de bereiding van de stamverbinding **7** (R=H) door middel van vacuümsublimatie van **6** (X=O; R=H) bij 120-140°C. De in de betreffende synthese toegepaste verbinding **6** (X=O; R=H) bleek eenvoudig toegankelijk vanuit het Diels-Alder adduct **9** van furan en cylopenteen-1,4-dion. Aangezien dit adduct **9** aantrekkelijke mogelijkheden biedt tot functionalisatie, met name op de 4- en 5-positie, lag het voor de hand om na te gaan of het te gebruiken zou zijn voor een algemene synthese van 4- en 5-gesubstitueerde cyclopentadienon-epoxiden **12**, via de in Schema 3 weergegeven route. Bij

Schema 3



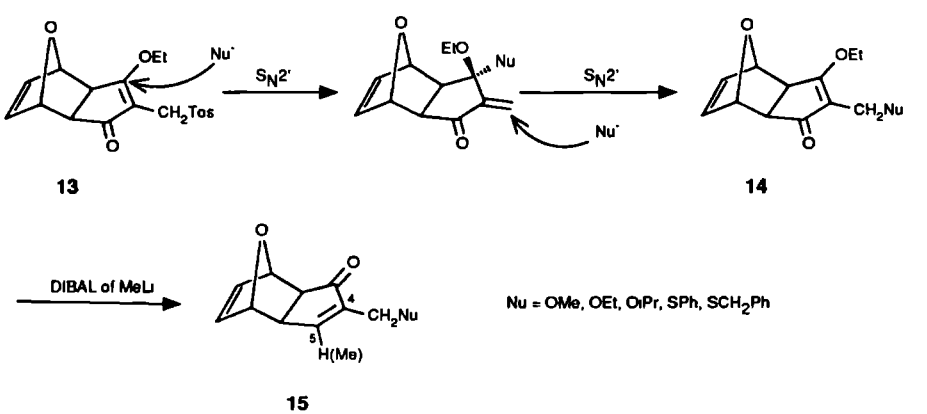
9 **10** **11** **12**

welslagen zou vervolgens een begin kunnen worden gemaakt met een systematisch onderzoek naar het chemisch gedrag van dit type verbindingen.

Cyclopentadienon-epoxiden vormen een interessante, betrekkelijk nieuwe klasse van verbindingen. Binnen een klein ringsysteem zijn een drietal functionele groepen geconcentreerd, namelijk een epoxide functie, een vinyl- en een carbonyl-groep, die, ieder voor zich en ook in combinatie met elkaar, alle gevoelig zijn voor de zelfde nucleofiele en electrofiele reagentia. Het is interessant en ook, met het oog op algemene strategieën in de organische synthese, van groot belang om na te gaan of dergelijke hoog gefunctionaliseerde systemen selectieve reacties met slechts één van de aanwezige reactieve groepen kunnen ondergaan. Mocht dit het geval zijn dan dient zich de volgende vraag aan of de reactieomstandigheden zo kunnen worden gekozen dat desgewenst de ene danwel de andere functionele groep in reactie gebracht kan worden. Nader onderzoek aan cyclopentadienon-epoxiden is verder van belang in verband met mogelijke toepassing in natuurstofsyntheses.

Het eerste onderdeel van het onderzoek, inhoudende de omzetting van het Diels-Alder adduct **9** in 4- en 5-gesubstitueerde 10-oxatricyclodecadienonen **10**, staat beschreven in *hoofdstuk 1*. Via een condensatie met formaldehyde in aanwezigheid van *p*-tolueensulfinezuur, gevolgd door O-alkylering met Meerwein's zout kon **9** in hoge opbrengst worden omgezet in sulfon **13**. De tosylgroep van dit sulfon was op eenvoudige wijze te vervangen door een ether- of thioether-functie. Het mechanisme van deze vervanging werd opgehelderd. Vastgesteld werd dat in eerste instantie de tosylgroep via een S_N2'-reactie wordt gesubstitueerd en dat in de tweede stap, eveneens via een S_N2'-substitutie, de in het begin geïntroduceerde groep weer wordt afgesplitst (Schema 4). Vervolgens werden de

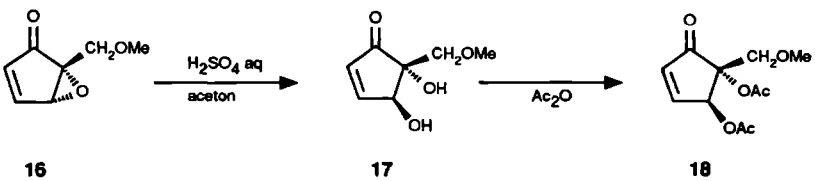
Schema 4



verkregen derivaten **14** via reductie met Di-iso-Butyl-Aluminiumhydride (DIBAL) of alkylering met methyllithium overgevoerd in de gewenste 4- en 5-gesubstitueerde 10-oxatricyclodecadienonen **15**. Vanuit **15** werden de overeenkomstige 4- en/of 5-gesubstitueerde cyclopentadienon-epoxiden **12** verkregen via een stereoselectieve nucleofiele epoxidatie, gevolgd door Flits-Vacuum-Thermolyse (Schema 3). De twee laatst genoemde omzettingen worden behandeld in *hoofdstuk 2*.

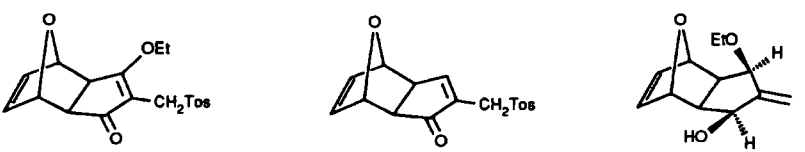
De resultaten van de Flits-Vacuum-Thermolyse bevestigden de aan het begin van het onderzoek geformuleerde verwachting, dat 10-oxatricyclodecadienon-epoxiden inderdaad bij een relatief lage temperatuur (300-375°C) kunnen worden gethermolyseerd. Hoewel bij de betrokken thermolyses de temperatuur niet ongestraft kon worden opgevoerd en aanpassingen in de apparatuur soms noodzakelijk waren om de kritische grens, waarbij pyronvorming begon op te treden, niet te passeren, kan geconcludeerd worden dat de methode een goede entree biedt tot een breed scala aan 4- en 5-gesubstitueerde cyclopentadienon-epoxiden **12**. Een eerste demonstratie van de bruikbaarheid van dit type verbindingen op het gebied van de natuurstofsynthese werd geleverd door de stereospecifieke omzetting van het 5-methoxymethyl-gesubstitueerde cyclopentadienon-epoxide **16** in de *epi*-pentenomycine-analoga **17** en **18** (Schema 5).

Schema 5



16 **17** **18**

Alvorens de studie van de chemie van deze interessante moleculen ter hand te nemen, werd aandacht besteed aan een verrassende reactie die gevonden werd bij een poging om sulfon **13** te reduceren tot sulfon **19**. Behandeling van **13** met Lithium Aluminium Hydride (LAH) leverde een volstrekt ander product op dan het verwachte **19**, namelijk de verbinding **20**. De vorming van **20** uit

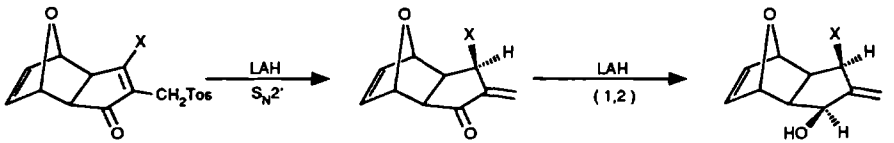


13 **19** **20**

13 kan in principe via twee verschillende wegen worden verklaard. Beide werden onderzocht. Dit leidde tot de conclusie dat slechts één bepaalde route wordt gevolgd. Deze begint met de regioselectieve en stereospecifieke S_N2'-substitutie van de tosylgroep leidend tot het reactieve

intermediair **21**, dat vervolgens in situ een regioselectieve en stereoselectieve (1,2)-reductie ondergaat, resulterend in de vorming van **20** (Schema 6). De reactie werd vervolgens ook geprobeerd

Schema 6

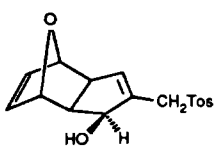


13 X = OEt
19 X = H

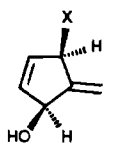
21 X = OEt
23 X = H

20 X = OEt
22 X = H

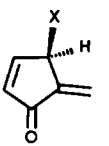
op sulfon **19**, dat uit **13** kon worden verkregen door middel van een reductie met DIBAL. De behandeling van sulfon **19** met LAH leverde als hoofdproduct de aan **20** verwante verbinding **22** op. Daarnaast werd als nevenproduct ook sulfon **24** verkregen, dat is ontstaan door directe (1,2)-reductie van **19**. De hoeveelheid van dit bijproduct kon worden geminimaliseerd (≤ 5%) door de reactie bij 0°C uit te voeren. De verbindingen **20** en **22** werden daarna door middel van thermolyse, dan wel MnO_2 oxidatie gevolgd door thermolyse, omgezet in de interessante cyclopentenoiden **25** en **26**, respectievelijk **27** en **28**. Bovenstaande resultaten staan beschreven in *hoofdstuk 3*.



24

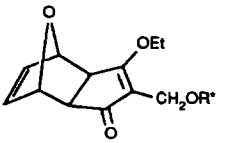


25 X = OEt
26 X = H



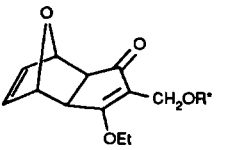
27 X = OEt
28 X = H

Een nadere uitwerking van de in hoofdstuk 1 en 2 beschreven chemie, speciaal gericht op de synthese van optisch actieve verbindingen, wordt behandeld in *hoofdstuk 4*. Vervanging van de tosylgroep in sulfon **13** door een menthylether-functie, op de wijze zoals in Schema 4 is aangegeven, leverde een mengsel van de diastereomere menthylethers **29a** en **29b** op. Deze diastereomeren konden worden gescheiden door middel van kristallisatie. De hierop aansluitende reductie met DIBAL, gevolgd door om-ethering met natriummethanolaat in methanol, leverde vervolgens de optisch zuivere methylethers (+)-**30**, respectievelijk (-)-**30** op. Deze verbindingen werden daarna op enantiospecifieke wijze, via de in hoofdstuk 2 beschreven procedures, overgevoerd in de optisch zuivere cyclopentadienon-epoxiden (-)-**16**, respectievelijk (+)-**16**. De absolute configuratie van de structuren (-)-**30** en het daarvan afgeleide polycyclische epoxide (-)-**31** kon worden vastgesteld met

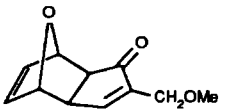


29a

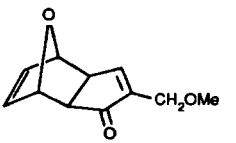
R* = (-) menthyl



29b

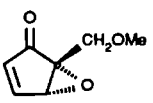


(+)-30

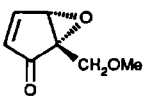


(-)-30

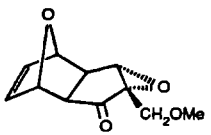
behulp van Röntgendiffractie-analyses. Hiermee lagen ook de absolute structuren van de uitgangsverbindingen, **29a** en **29b**, en de eindproducten, **(-)-16** en **(+)-16**, ondubbelzinnig vast.



(-)-16



(+)-16

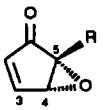


(-)-31

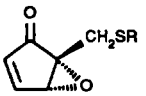
Hydrolyse van **(+)-16**, gevolgd door acylering, zoals aangegeven in Schema 5, leverde optisch zuiver **18**. Uit dit gegeven kon worden afgeleid dat de hydrolyse van **16** volledig regioselectief verloopt en dat bovendien tijdens de erop volgende acylering geen racemisatie of epimerisatie plaats vindt.

In *hoofdstuk 5* wordt het chemisch gedrag van de verkregen cyclopentadienon-epoxiden nader onder de loep genomen. Onderzocht werden nucleofiele reacties in mild zuur, neutraal en basisch milieu, met name: hydrolyses, methanolyses en epoxidaties. Vastgesteld kon worden dat de stamverbinding **7** (R=H) en de 5-alkoxymethyl-gesubstitueerde cyclopentadienon-epoxiden **32** en **33** in zuur milieu uitsluitend opening van de epoxide-ring geven. Deze epoxide-opening vindt regioselectief plaats vanuit C-4 en leidt stereospecifiek tot trans-geopende producten. In de zuur gekatalyseerde hydrolyse van de 5-thiomethyl-gesubstitueerde cyclopentadienon-epoxiden **34** en **35** vindt naast trans- ook cis-opening van de epoxide-ring plaats. Onder neutrale condities, in methanol, ondergaan **7** en **32** methanol-additie aan de dubbele band. Methanol hecht daarbij aan op C-3, trans ten opzichte van de epoxide-ring. Deze zelfde regio- en stereo-chemie werd ook waargenomen bij de basische epoxidaties van deze verbindingen. Genoemde epoxidaties leverden de interessante, in de

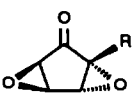
literatuur nog niet eerder beschreven, structuren **36-38** op.



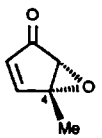
7 R = H
32 R = CH_2OMe
33 R = CH_2OEt



34 R = Ph
35 R = Bz



36 R = H
37 R = CH_2OMe
38 R = CH_2OEt

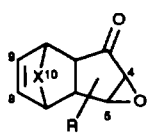


39

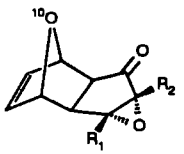
Het 4-methyl-gesubstitueerde cyclopentadienon-epoxide **39** bleek nauwelijks of geen zure katalyse nodig te hebben om ringopening van de epoxide-functie te ondergaan. Ook hier werd uitsluitend opening door reactie op C-4 waargenomen. In tegenstelling tot de stamverbinding **7** en de 5-gesubstitueerde cyclopentadienon-epoxiden **32** en **33** trad in dit geval ook cis-opening op. Bovendien bleek dit epoxide in neutrale methanol nauwelijks (≤ 5%) methanol-additie aan de dubbele band te ondergaan. In basisch milieu, bij epoxidatie, vond wel een reactie met de dubbele band plaats. Het verwachte bis-epoxide werd echter, als gevolg van ontleding tijdens de reactie, niet verkregen.

Bovenstaande resultaten tonen aan dat de cyclopentadienon-epoxiden, ondanks de veelheid aan reactieve groepen, een zeer ordelijk reactiepatroon vertonen, dat sterk afhankelijk is van substitutiepatroon en reactiecondities. De implicaties van bovenstaande resultaten voor het mechanisme van de epoxide-ringopening worden in dit hoofdstuk 5 nader geanalyseerd.

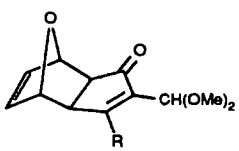
Epoxide-openingen komen ook ter sprake in *hoofdstuk 6*. Bij onderzoek naar mogelijke openingen van de epoxide-functie in de tricyclodecadienon-epoxiden **6** (X=CH_2; R=4-Me; R=4-CH_2OMe) was eerder vastgesteld dat de gebruikelijke omstandigheden, waarbij epoxyketonen



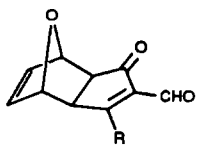
6



40 R_1= H; R_2= CH_2OEt
41 R_1= H; R_2= CH_2Tos
42 R_1= Me; R_2= CH_2Tos
43 R_1= n-Bu; R_2= CH_2Tos



44 R = H
45 R = Me
46 R = n-Bu



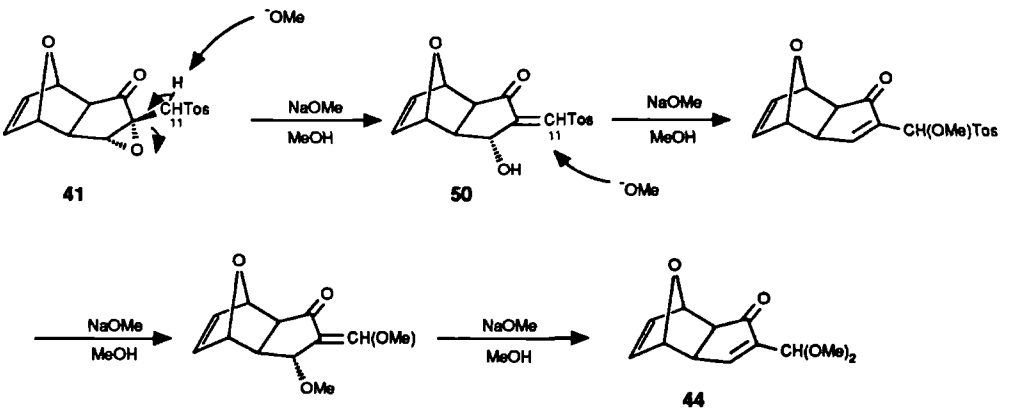
47 R = H
48 R = Me
49 R = n-Bu

epoxide-ringopening ondergaan, niet krachtig genoeg zijn om in deze verbindingen de gewenste reactie tot stand te brengen. Dit werd toegeschreven aan het feit dat de reactieve zijde van de epoxide-functie in deze polycyclische structuren efficiënt wordt afgeschermd door de

C_8-C_9-ethyleenbrug, in de *endo*-vorm, of door de C_{10}-methyleenbrug, in de *exo*-vorm. Voor de 10-oxatricyclodecadienon-epoxiden **6** (X=O) werd eenzelfde afschermend effect verwacht van de 10-oxabrug. Om deze verwachting te toetsen, werden **40** en **41** behandeld met natrium-methanolaat in kokende methanol. Eerstgenoemde verbinding vertoonde het verwachte resultaat: geen reactie. Het sulfon **41** daarentegen, bleek wel te reageren. Dit leverde in hoge opbrengst het ketaal **44**. De verwante sulfonen **42** en **43** gaven onder dezelfde reactiecondities de overeenkomstige verbindingen **45** en **46**. Onder mild zure condities konden de ketalen **44-46** kwantitatief worden gehydrolyseerd tot de overeenkomstige aldehyden **47-49**.

Het feit, dat **40** onder de genoemde condities niet reageerde, bevestigde de afschermende werking van de 10-oxabrug. De vorming van de ketalen kan derhalve niet met een directe epoxide-ringopening, vanuit C-4 of C-5, worden verklaard. De meest plausibele verklaring voor de vorming van **44-46** uit **41-43** is voor verbinding **44** weergegeven in Schema 7. De eerste stap,

Schema 7



inhoudende deprotonering van C-11 gevolgd door een β-eliminatieve epoxide-opening, wordt mogelijk gemaakt door de op C-11 aanwezige tosylgroep. Deze groep kan negatieve lading op een buuratoom uitstekend stabiliseren. Een ethoxygroep, zoals in **40** op C-11 aanwezig, mist dit stabiliserend vermogen en de voor bovenstaande reactie essentiële beginstap kan derhalve met **40** niet gezet worden. Uit het allylalcohol **50**, dat in eerste instantie wordt gegenereerd, wordt **44** via drie op elkaar volgende S_N2' substituties verkregen.

Kortom: het hier beschreven onderzoek heeft een bruikbare methode opgeleverd voor de bereiding van cyclopentadienon-epoxiden. De gegeven aanzet tot een systematische studie van de chemie van deze verbindingen heeft een verrassend ordelijk reactiepatroon aan het licht gebracht, dat een interessante grondslag vormt voor verder onderzoek.

Adrie A. M. Houwen-Claassen, geboren te Hapert, volgde middelbaar onderwijs aan het gymnasium 'Sint Angela', te Venray. Na het behalen van het diploma gymnasium β, studeerde zij één jaar biologie aan de Katholieke Universiteit te Nijmegen en stapte vervolgens over op de studie wis- en natuurkunde. Na in deze vakken het candidaats examen te hebben afgelegd, koos zij wiskunde als hoofdrichting. De doctoraal studie kon door privé verplichtingen niet worden voltooid. Op grond van het candidaats examen en het daarna gevolgde programma algemene didaktiek en vakdidaktiek van de wiskunde werd haar de MoA lesbevoegdheid wiskunde verleend. Gebruikmakend hiervan gaf zij vervolgens één jaar wiskunde aan de Scholengemeenschap Nebo-Marienbosch-Gabrielkollege te Nijmegen-Mook.

Zij hervatte haar studie toen de huiselijke omstandigheden het toelieten. Aanvankelijk volgde zij een verkort programma MoA natuur- en scheikunde. Begin 1975 verwierf zij het betreffende diploma. Daarna zette zij de studie in de scheikunde voort. Medio 1976 werd het candidaats examen (S1) afgelegd, met als aantekening 'met zeer veel genoegen'. De daarop volgende doctoraal studie omvatte Organische Chemie (Prof. dr B. Zwanenburg, onderwerp: reacties van α,β-epoxysulfonen met aromatische en alifatische aminen) als hoofdvak, Katalyse (Prof. Dr. Ir. J. W. E. Coenen, onderwerp: CO_2 vorming tijdens de methanering van CO op een nikkel katalysator) en Muziekwetenschappen (Prof. Dr. Etty M. Mulder, onderwerpen: geschiedenis van de muziek en algemene muziektheorie) als bijvakken, en de capita Quantumchemie (Dr. Ir. P. E. S. Wormer) en Organometaalchemie (Prof. Dr. Ir. J. J. Steggerda) als aanvulling van de bijvakken. In juni 1982 werd het doctoraal examen afgelegd, met als judicium 'cum laude'.

Half juli 1982 volgde een deeltijd aanstelling (20 uur per week) tot wetenschappelijk medewerker bij de afdeling Organische Chemie van de Katholieke Universiteit te Nijmegen. Deze aanstelling liep door tot 30 september 1988. In deze periode werd bij prof. dr. B. Zwanenburg en onder de directe leiding van dr. A. J. H. Klunder een promotie onderzoek verricht op het gebied van de synthese en de reactiveit van cyclopentadienon-epoxiden.

Tijdens de doctoraal fase assisteerde zij gedurende een viertal semesters bij 1^e en 2^e jaars practica Organische Chemie. Ook werd in deze periode les gegeven in natuur- en scheikunde aan de Gemeentelijke Avondscholen Gemeenschap Nijmegen. Gedurende het promotie-onderzoek begeleidde zij diverse hoofdvak-, bijvak- en HBO-studenten. Daarnaast verrichtte zij, op stedelijk niveau, algemeen organisatorisch werk als bestuurslid van de Stichting Moderne Muziek te Nijmegen en als voorzitter van het Stedelijk Muziek Overleg. Zij is thans lid van het Stedelijk Netwerk Nijmegen.

PUBLICATIES

1. A. A. M. Houwen-Claassen, J. W. McFarland, B. H. M. Lammerink, L. Thijs, B. Zwanenburg, *Synthesis* **1983**, 628. A convenient synthesis of β-sulfonylenamines from α,β-epoxysulfones.
2. A. J. H. Klunder, A. A. M. Houwen-Claassen, M. G. Kooy and B. Zwanenburg, *Tetrahedron Lett.* **1987**, *28*, 1329. Sulfone mediated synthesis of cyclopentadienone epoxides from 10-oxatricyclo[5.2.1.$0^{2,6}$]decadienones. A oonvenient route to *epi*-pentenomycins.
3. A. J. H. Klunder, M. J. F. M. Crul, A. A. M. Houwen-Claassen, M. G. Kooy and B. Zwanenburg, *Tetrahedron Lett.* **1987**, *28*, 3147. Remote electronic control in the $LiAlH_4$ reduction of tricyclic *p*-tolylsulfonylmethyl enones.
4. J. M. M. Smits, Paul T. Beurskens, J. R. M. Smits, V. Parthasarathi, A. A. M. Houwen-Claassen and A. J. H. Klunder, *J. Cryst. Spectrosc. Res.* **1988**, *18*, 1. Crystal and molecular structure of *endo*-5-acetoxy-4-(*p*-tolylsulfonyl)methyl-*exo*-10-oxatricyclo-[5.2.1.$0^{2,6}$]deca-3,8-diene, $C_{19}H_{20}O_5S$.
5. A. A. M. Houwen-Claassen, A. J. H. Klunder, H. Behm, F. G. Moers, Paul T. Beurskens, D. Heydenrijk and H. Schenk, *J. Cryst. Spectrosc. Res.* **1989**, *19*, 223. Crystal and molecular structure of (4R*,5S*)-5-(3,5-dinitrophenylcarbonyloxy)-4-methoxy-4-methyl-2-cyclo-penten-1-one, $C_{14}H_{12}O_8N_2$.
6. Adrie A. M. Houwen-Claassen, A. J. H. Klunder, M. G. Kooy, J. Steffann and B. Zwanenburg, *Tetrahedron*, **1989**, *45*, 7109. Synthesis of 4- and 5-substituted 10-oxatricyclo[5.2.1.$0^{2,6}$]deca-3,8-dienones. Functionalization of the cyclo-adduct of furan and cylopenten-1,4-dione.
7. Adrie A. M. Houwen-Claassen, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, **1989**, *45*, 7134. Synthesis of cyclopentadienone epoxides from 10-oxatricyclodecadienones.
8. Adrie A. M. Houwen-Claassen, A. J. H. Klunder and B. Zwanenburg, *Tetrahedron*, **1989**, *45*, 7149. Selective bis-hydride reduction of tosylmethyl substituted tricyclic enones by Lithium Aluminium Hydride. Synthesis of α-methylene cyclopentenoids.
9. Adrie A. M. Houwen-Claassen, A. J. H. Klunder, B. Zwanenburg, Paul T. Beurskens, F. G. Moers and Gezina Beurskens, *submitted for publication.* Menthol mediated optical resolution of 10-oxatricyclodecadienones. Application in the enantioselective synthesis of cyclopentenoids.
10. Adrie A. M. Houwen-Claassen, A. J. H. Klunder and B. Zwanenburg, *submitted for publication.* Selective nucleophilic transformations of cyclopentadienone epoxides.
11. Adrie A. M. Houwen-Claassen, A. J. H. Klunder, J. J. T. Vriends and B. Zwanenburg, *submitted for publication.* Exceptional desulphonylation of β-epoxy sulphonyl containing 10-oxatricyclodecenones.

COLOFON

Omslag ontwerp	Marga Janssen
Papier omslag	110 grams Elefantenhaut koper van Bührmann-Ubbens
Lettertype omslag	Optima
Tekstprogramma binnenwerk	ChemText version 1.20 04/11/88
Printer binnenwerk	Apple Laser Writer Plus
Lettertype binnenwerk	Roman en Helvetica
Papier binnenwerk	80 grams houtvrij offset papier
Drukkerij	Sneldruk Enschede

STELLINGEN

I

De promovendus, die - nu de verplichting stellingen aan een proefschrift toe te voegen is vervallen - desniettemin stellingen in zijn of haar proefschrift opneemt, wordt opgezadeld met het negatieve imago van uitslover: een geraffineerd en venijnig effect dat het definitieve einde van een aardige traditie ten zeerste zal bespoedigen.

II

In de discussie[1] over de wenselijkheid om aan de universiteiten in Nederland Engels als voertaal te introduceren is tot nu toe niet gepreciseerd welk Engels bedoeld wordt.
Het gehanteerde argument dat de Nederlandse universiteiten bij invoering van Engels aantrekkelijker zouden worden voor buitenlandse studenten impliceert dat invoering van Broken English (B. E.)[2] het meest profijtelijk zal zijn.

1. Chemisch Weekblad: 21 sept **1989**. De Volkskrant: 14-16 dec **1989**.
2. H. B. G. Casimir, *Haphazard Reality*, Harper & Row, New York, **1983**, pp 122-125, of H. B. G. Casimir, *Het Toeval en de Werkelijkheid*, Meulenhoff informatief bv, Amsterdam, **1983**, pp 146-150.

III

Nu het traditionele handrekenen door de ontwikkeling van goedkope zakrekenmachientjes een overbodige vaardigheid lijkt te worden, is het zaak op de lagere school extra aandacht aan het hoofdrekenen te besteden, opdat de leerlingen het vermogen behouden uitkomsten van berekeningen te controleren. De in onderstaande stellingen[1,2] aanbevolen vermenigvuldigingsmethode correleert hoofd- en hand-rekenen en kan daardoor een bijdrage leveren tot de gewenste versterking van het hoofdrekenen.

1. Stelling IX bij het proefschrift van W. H. Keesom, *Isothermen van mengsels van zuurstof en koolzuur*, Amsterdam, **1904**: "Het is wenschelijk, dat men van den aanvang af, reeds bij het lager onderwijs, invoert de gewoonte, bij het vermenigvuldigen te beginnen met het eerste cijfer links van den vermenigvuldiger."
2. Stelling X bij het proefschrift van A. P. Keesom, *Enkele thermische eigenschappen van vloeibaar en vast helium*, Leiden, **1938**: "Het ware gewenst, dat reeds bij het lager onderwijs werd ingevoerd de gewoonte om bij het vermenigvuldigen van getallen te beginnen met het eerste cijfer links van de vermenigvuldiger."

IV

De thematische manier, waarop de scheikunde in de door de Ministeriële Commissie Modernisering Leerplan Scheikunde ontwikkelde methode voor het VWO wordt gepresenteerd, vormt voor vele, gestructureerd denkende leerlingen een reden om dit vak niet in het eindexamen pakket op te nemen of na het eindexamen als studierichting te kiezen.

V

De ^{1}H-NMR gegevens van diverse cyclopentenoide α,β-epoxyketonen, gesynthetiseerd door Verlaak[1] en Hua *et al*[2], zijn niet toereikend om de posities van het α- en β-proton vast te stellen. Hetzelfde geldt voor de tricyclische α,β-epoxyketonen, gesynthetiseerd door Lange[3]. De voor de hand liggende toewijzing die deze auteurs geven: H_α bij laag en H_β bij hoog veld wordt door de in dit proefschrift gepresenteerde resultaten gelogenstraft.

1. Verlaak, J. M. J. '*Synthese van Cyclopentenoïde Natuurstoffen met behulp van Flits Vacuüm Thermolyse*', proefschrift KUN, febr **1983**.
2. Hua, D. H.; Venkataraman, S.; Chan-Yu-King, R.; Paukstelis, J. V. *Journ. Am. Chem. Soc.* **1988**, *110*, 4741.
3. Lange J. H. M. '*Structural Variations of Tricyclodecadienones in Synthetic Perspective*', proefschrift KUN, dec **1989**.

VI

De kloof tussen de moderne muziek en het publiek kan enigszins worden overbrugd door de concerten, waarin modern repertoire is geprogrammeerd, te openen met een mondelinge toelichting op de te brengen werken. Het zicht op de ernst van de communicatiestoornis tussen deze muziek en het publiek wordt aldus echter verhuld.

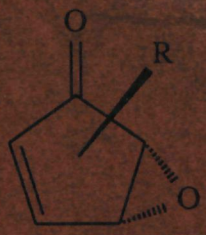
VII

Met het oog op de zorg voor het milieu zouden instellingen en bedrijven, werkzaam op het gebied van de chemie, het zich eigen moeten maken in hun jaaroverzichten ook de stofbalans te presenteren.

VIII

Het zou van goede smaak getuigen, wanneer operatiescènes, tijdens journaaluitzendingen op de televisie, niet in kleur maar in zwart-wit zouden worden vertoond.

Nijmegen, 17 dec 1989


O
R
O