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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.

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*Abstract: Tosylmethylation of the furan derived cyclo-adduct 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-d ien-3-one* **14**. *This sulphone undergoes a smooth 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 oxa-bridge. Subsequent reduction with DIBAL or reaction with MeLi provides 4- and/or 5-substituted 10-oxatricyclo[5.2.1.$0^{2,6}$]deca-dienones.*

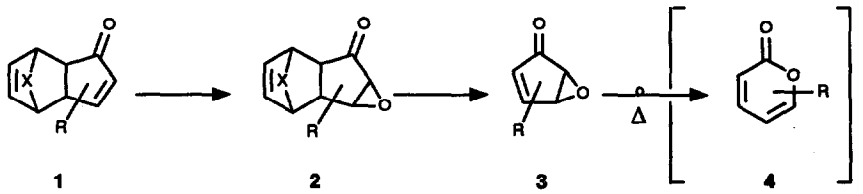
Introduction

Functionalized cyclopentenones constitute important structures, both as synthetic intermediates and as ultimate goals in natural product synthesis[1]. A conceivable entry to this class of compounds from cyclopentadienones is blocked, because of the fast dimerization of these substrates[2]. 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[3,4].

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 Alder reaction was carried out employing flash vacuum thermolysis[4,5]. 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[5a,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**

Scheme 1



1 **2** **3** **4**

readily rearrange to α-pyrones **4**, via a [π4a + π2a] cycloreversion reaction[4a]. 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[3c] 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°.

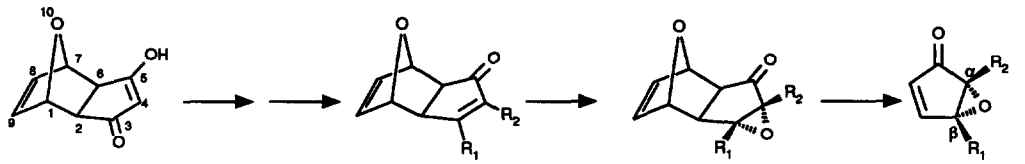
In order to make the synthesis of functionalized cyclopentadienone epoxides using the above strategy generally applicable, polycyclic precursors **2** are needed, that undergo the required cycloreversion at a temperature at which the rearrangement to α-pyrones does not take place. Epoxides **2**, that give an aromatic compound as one of the products in the retro Diels Alder reaction seem appropriate for this purpose. Indeed, Chapman and Hess[3c] 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[6a] 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[6] 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[6a] 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 oxabridged 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 paper 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 accompanying paper[7].

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 cyclo-adducts 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[6b], 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[6a,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[6a,b], was unambiguously proven by an X-Ray analysis of a derivative (*vide infra*).

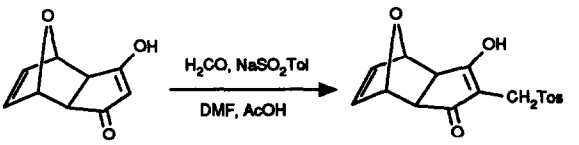
Presumably due to the isomerization of the initially formed diketo-adduct to the more stable enol tautomer **7**, the furan adduct of cyclopenten-1,4-dione does not display the usual cycloreversion[8a]. Direct cycloreversion from **7** will be unfavourable since this would lead to a highly energetic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

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).

Scheme 3

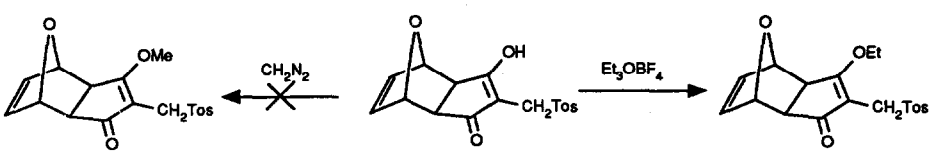


7 **13**

The tosyl group of the resulting 4-tolylsulphonylmethyl 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[12]. After careful experimentation, 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 as 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[3a] failed to give any methylation, due to insolubility of the substrate. However, O-alkylation with Meerwein's salt[3b,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



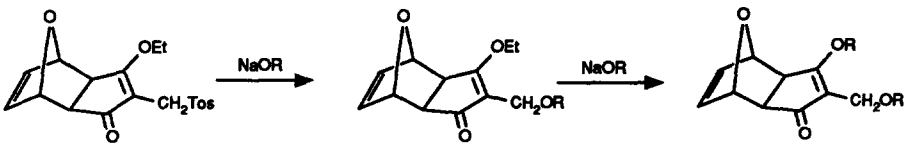
13 **14**

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

Scheme 5



14

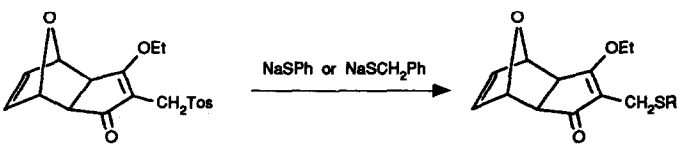
15 R=Me
16 R=Et
17 R=iPr
18 R=(-)menthyl
(**19** R=tBu)

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

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 as the sole product, however in a 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 were made to obtain this sensitive compound.

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



14

22 R=Ph
23 R=CH_2Ph

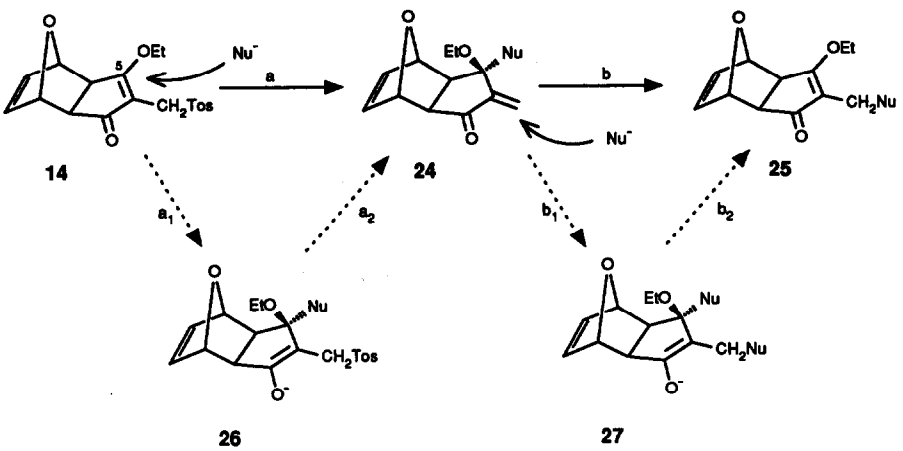
Attempts to prepare 4-aminomethyl derivatives from **14** by treatment with aqueous dimethylamine[15] or with dimethylamine in ethanol containing 2.5 eq of sodium ethanolate, were unsuccessful. Although in the last mentioned reaction the starting material was consumed no distinct compound could be isolated.

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 sulfinate 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

Scheme 7



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 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.

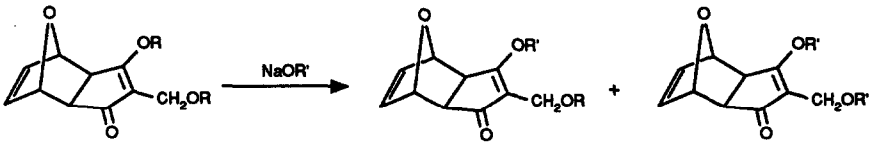
The displacement of the tosyl group by an alkyl ether described above is a very fast process. Full conversion of sulphone **14** on mmol scale requires less than 10 min. The resulting ethers however, are not stable under the applied conditions, but suffer from vinylogous trans-esterification and trans-etherification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

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

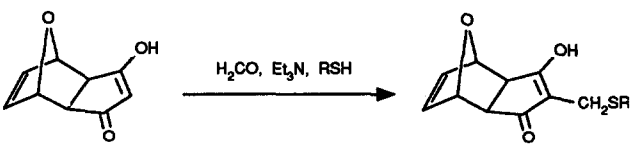
The vinylogous transesterification clearly takes place via a conjugate 1,4-addition and a subsequent 1,4-elimination. In order to explain the transetherification, the exo-methylene compound **24** must be invoked (Scheme 7), and as a consequence this conversion will proceed via two consecutive S_N2' 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 tosyl-methylation of **7**, using sodium thiophenolate instead of sodium *p*-toluenesulphinate, 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 consider other O-alkylation methods.

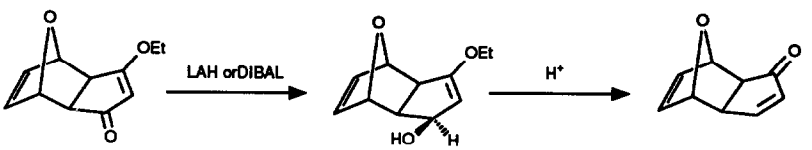
Transformations at C-5

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 conditions of acidic work-up 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[3b] 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]

Scheme 10

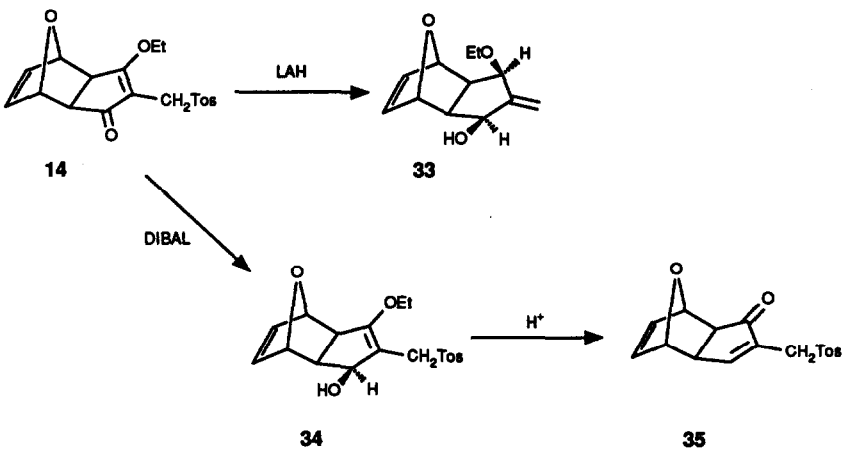


31 **32** **1** (X=O; R=H)

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[3b]. 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.

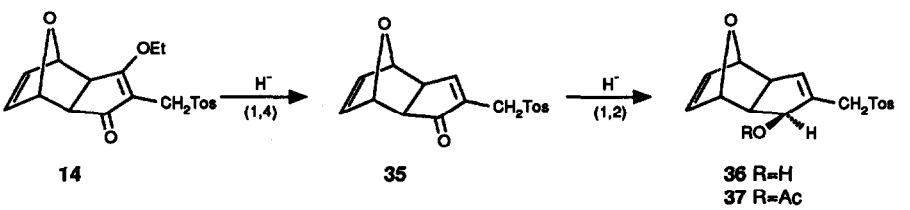
The reduction of sulphone **14** with LAH took a totally different course leading to the exo-cyclic methylene derivative **33** as the only product (Scheme 11). This surprising result has been the subject of a preliminary communication[4c], a detailed account will follow in due time. With DIBAL sulphone **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 critically depending on the amount of DIBAL. When an excess of DIBAL

Scheme 11



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

Scheme 12



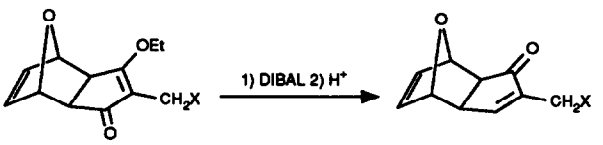
diminished to some extent by treatment of the crude mixture of **35** and **36** with activated manganese dioxide[28b]. By this treatment **36** was smoothly oxidized to **35**.

The sulphones **35** and **36** could not be separated by crystallization or chromatography. 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 detected, when an excess of DIBAL was

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

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 results because 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 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.

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

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).

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 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 of this characteristic stereocontrol were observed for the 10-oxatricyclodecadienone system.

In the accompanying paper the epoxidation of the above oxatricyclodecadienones will be described, as well as the preparation of cyclopentadienone epoxides using the FVT technique.

Experimental

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[12]. 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. 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*[3b]. 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 (silicagel/ethyl 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. Calc. 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;$OCH_2\underline{CH_3}$), 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. 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*[3b]. 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*[3b] 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[3b] (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[3b]: 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) v: 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) v: 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,$J_{6,2}$=6.8Hz;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%.).

References and notes

1. (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.
2. (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.
3. (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.
4. (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.
5. (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.
6. (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.
7. Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Zwanenburg, B. See accompanying paper. For a preliminary communication on this work see ref 5c.
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. Hellmann, H.; Müller, K. *Chem. Ber.* **1965**, *98*, 638.

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.; Moers, F. G.; Behm, H.; Beurskens, P.T.; Zwanenburg, B. To be published.
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 Houwen-Claassen, A. A. M. *Ph.D. Thesis*, University of Nijmegen, 1990.
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, H.; Zwanenburg, B. to be published.
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.