Acetals of 1-aryl-2,2-dimethyl-1,3-propanediols synthesis and use as chiral auxiliary

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CHAPTER 2
CYCLIC ACETALS OF 2-PHENYL- AND 2(o-CHLOROPHENYL)-2,2-DIMETHYL-1,3-PROPANEDIOL:
DIASTEREOSELECTIVITY OF FORMATION AND ABSOLUTE CONFIGURATION

2.1 INTRODUCTION

Acetals* have been synthesized in a number of ways.1,2 The most common and general approach is the acid catalyzed reaction of alcohols with aldehydes or ketones (Scheme 2.1). The equilibrium of this process is shifted to the right by removal of the water formed, either azeotropically or by means of an added drying agent, for instance molecular sieves.3 A derived method is the trans-acetalization of an acetal of a low molecular weight alcohol with an alcohol of higher molecular weight.

\[
\begin{align*}
\ce{R_1C=O + R_2-OH &\leftrightarrow R_1C\backslash\text{OH}} &\quad \ce{H^+} &\quad \ce{H^+/R_2\cdot OH &\leftrightarrow R_1C\backslash OR_2} \\
2.1 & & & 2.2
\end{align*}
\]

Scheme 2.1 Acetal formation

Cyclic acetals are formed in reactions between carbonyl compounds and diols. Most commonly used are 1,2- and 1,3-diols, which lead to stable five and six membered rings. These cyclic products are named: 1,3-dioxolanes and 1,3-dioxanes,

* An acetal is defined as the product of the reaction of two molecules of an alcohol with a carbonyl compound. In modern nomenclature no distinction is made between the adducts derived from aldehydes or ketones; both adducts are named acetals. Therefore, the name ketal is archaic. In this thesis the term ketal will occasionally be used to emphasize different properties of aldehyde and ketone derived acetals.
The equilibrium in these types of reactions lies further to the right than in reactions with "mono"-alcohols. The difference between a "mono"-alcohol and a diol emerges during the addition of a second molecule of an alcohol to the hemiacetal 2.1 (Scheme 2.1). In the case of a diol this reaction is unimolecular and therefore the entropy change is more favourable than in the bimolecular reaction between the hemiacetal and a "mono"-alcohol.

One principal feature of acetals is their stability under basic conditions. It is this property that makes acetals suitable for use as a protecting group in synthetic reactions under basic conditions.4

2.2 DIASTEREOMER FORMATION IN THE SYNTHESIS OF CHIRAL CYCLIC ACETALS

When the diol is chiral, diastereomers will be formed in the reaction with a prochiral carbonyl compound. In case the chiral diol possesses a C-2 axis of symmetry, only one diastereomer is formed (Scheme 2.2). In such a case, transposition of the non-oxygen ligands at the acetal center leads to the same compound. Chiral C-2 symmetric diols that have been used as chiral auxiliaries are, for instance: 2,4-pentanediol5,6 (2.7), 2,4-butane diol7 (2.8) and diethyl tartrate8 (2.9) (Fig. 2.1). The regular stream of publications that describes various uses of C-2 symmetric ligands or protecting groups confirms the great advantage of C-2 symmetry.9

![C-2 symmetric diols](image)

Fig. 2.1 C-2 symmetric diols

In acetalization reactions of chiral non-C-2 symmetric diols, the formation of one diastereomer is often favoured over the formation of the other one. As will be seen in Section 2.4, substituents usually tend to arrange themselves equatorially in cyclic acetals; thus leading to an excess of this diastereomer during the acetal
formation. In most cases separation of the two diastereomers is possible by crystallization or column chromatography.

![2.10](image)

![2.11](image)

![2.12](image)

**Fig. 2.2** Non C-2 symmetric diols

Examples of chiral non-C-2 symmetric diols are: 1,4-butanediol\(^1\) (2.10), mandelic acid\(^1\) (2.11) and \(\beta\)-hydroxybutanoic acid\(^2\) (2.12) (Fig. 2.2). Dioxalanones are formed on condensation of \(\alpha\)- and \(\beta\)-hydroxy acids with aldehydes and ketones. The diastereomeric ratios in these reactions are somewhat disappointing. Nevertheless, the reaction with pivaldehyde proceeds in a satisfactory diastereomeric ratio (Scheme 2.3).\(^{13a,b}\)

![Scheme 2.3](image)

The reason for this selectivity is the steric hindrance of the large t-butyl substituent at
the acetal center, favouring one diasteromer over the other to a reasonable extent. Acetals of 1,4-butane-2,10 are formed with a good to excellent diastereoselectivity.\textsuperscript{10}

2.3 SYNTHESIS OF ACETALS DERIVED FROM CHIRAL 1-ARYL 2,2-DIMETHYL 1,3-PROPANEDIOLS 2.18

2.3.1 Introduction

We expected the formation of six-membered cyclic acetals of 1-aryl-2,2-dimethyl-1,3-propanediols (2.18) with aldehydes to proceed in high diastereoselectivity. This expectation was based on literature precedents on acetal formation of non-\textsuperscript{C-2} symmetric diols.\textsuperscript{11,13} Our hypothesis was that the diastereomer with the 4-aryl and the 2-acetal substituent arranged equatorially would be formed in excess. This hypothesis will be substantiated with literature examples in paragraph 2.5.

Predictions about the diastereoselectivity in the formation of ketals is unfeasible. Formation of these ketals could be difficult due to a large steric hindrance of the two acetal carbon substituents.

2.3.2 Chiral 1-aryl 2,2-dimethyl 1,3-propanediols 2.18

\begin{equation}
\begin{array}{c}
\text{2.15} \\
\text{2.16}
\end{array}
\end{equation}

Scheme 2.4 Synthesis of 1-aryl-2,2-dimethyl-1,3-propanediols 2.18.

Kulka et al. have synthesized 1-aryl-2,2-dimethyl-1,3-propanediols 2.18 as shown in Scheme 2.4.\textsuperscript{14} Substituted benzaldehydes were allowed to react with two equivalents of isobutyraldehyde, under basic conditions to yield the 1,3-propane diols (2.18). The reaction sequence consists of an aldol condensation and a crossed Cannizzaro reaction. A variety of substituents on the benzaldehydes are possible. Reaction with phosphorous oxychloride and treatment with potassium hydroxide resulted in cyclic phosphoric acid derivatives 2.17. These phosphoric acids have been resolved by Ten
Hoeve and Wynberg\textsuperscript{15} (Scheme 2.5).

The enantiomerically pure diols can be obtained by treatment of the phosphor acids 2.17 with glycol-potassium hydroxide or with lithium aluminum hydride. Both enantiomers are obtainable by this method.

\[ \text{HO} \quad \text{OH} \quad \text{POCl}_3 \quad \text{NaOH} \quad \text{HCl} \quad \text{Resolution} \quad (+) \text{ and } (-)-2.17 \]

\[ \text{HO} \quad \text{OH} \quad \text{KOH/glycol} \quad \text{or LiAlH}_4 \quad (+) \text{ or } (-)-2.17 \quad (+) \text{ or } (-)-2.18 \]

Scheme 2.5

The optically pure phosphoric acids have proven their value as acidic resolving agents for amines and amino acids. For a great variety of substrates, these resolutions worked out very efficiently.\textsuperscript{15}

2.3.3 The absolute configuration of 1-aryl-2,2-dimethyl-1,3-propanediols (2.18)

To understand the mechanism of the asymmetric induction in a synthetic process which makes use of a chiral auxiliary, knowledge of the absolute configuration of the particular auxiliary is desirable. The absolute configurations of 1-phenyl-2.18a and 1-(o-chlorophenyl)-2,2-dimethyl-1,3-propanediol 2.18b are known. The absolute configuration of 1-phenyl-2,2-dimethyl-1,3-propanediol (2.18a) was established as is depicted in Scheme 2.6.

Mosher et al. have related the known absolute configuration of (S)-(+)–hydratropic acid (2.22),\textsuperscript{16} by chemical means, to the absolute configuration of (R)-(−)–t-butylphenylacetic acid (2.20). They converted both components to (S)-(−)-2,2-dimethyl-3-cyclohexylbutane 2.21.\textsuperscript{17} In the same paper Mosher has also related the absolute configuration of (R)-(+)–phenyl-t-butylcarbinol (2.23) to t-butylphenylacetic acid and hence to hydratropic acid. Mattell has resolved\textsuperscript{18} 2,2-dimethyl-3-hydroxy-3-
phenylpropionic acid (2.24) and Guetté et al. reduced this acid to 1-phenyl-2,2-dimethyl-1,3-propanediol (2.18). Guetté also established the absolute configurations of 2.18 and 2.24 to be (R) by converting them to (R)-(+) t-butylphenyl carbinol (2.23) that was known to possess a (R) configuration.

Through these sequences the absolute configuration of (R)-(−)-1-phenyl-2,2-dimethyl-1,3-propanediol (2.18) was related to the absolute configuration of (S)-(−)-hydratropic acid (2.22). The absolute configuration of (−)-1-(o-chlorophenyl)-2,2-dimethyl 1,3-propanediol (2.18b) was expected to be (S). A X-ray structure determination of the salt of the (−)-phosphoric acid and (−)-p-hydroxy phenylglycine confirmed a (S) absolute configuration for the phosphoric acid 2.17b and the diol
In Figure 2.3 the structures with the absolute configuration of (S)-(+)\(\cdot\)1-phenyl and (S)-(−)\(\cdot\)1-(o-chlorophenyl)-2,2-dimethyl-1,3-propanediol are shown. Note that these diols have a (pseudo) enantiomeric relationship.

![Structures 2.18a and 2.18b](image)

Fig. 2.3

### 2.3.4 Formation of Acetals 2.19

Acetals of enantiomerically pure 1-phenyl-2,2-dimethyl-1,3-propanediol (2.18a) and 1-(o-chlorophenyl)-2,2-dimethyl-1,3-propanediol (2.18b) were synthesized by reactions of these diols with a number of aldehydes (see Table 2.1).

The reactions were carried out in refluxing benzene and were catalyzed by p-toluenesulfonic acid. The water formed was removed by means of a Dean-Stark trap. The reaction was completed in about four to six hours. A very small amount of acid catalyst, approximately 0.5-1.0 mol %, was used. When larger quantities of acid were used a deeply coloured solution was obtained and the yield of product was lower. Perhaps this is the result of sensitivity of the benzylic hydroxyl group to acid. After protonation and loss of water a relative stable benzylic cation would be formed.

After a normal work-up procedure the products were purified by bulb-to-bulb distillation or column chromatography. Yields, after purification, are generally high (70-90%). Most of the acetals were thick, gluey oils, some of which solidified upon standing. Aliphatic, aromatic aldehydes as well as \(\alpha,\beta\)-unsaturated aldehydes gave good yields.

The ease of formation of these highly substituted acetals is remarkable. An explanation for this observation could lie in the Thorpe-Ingold (the gem-dialkyl) effect.\(^{20-22}\) In a wide variety of compounds ring closure is facilitated when gem dialkyl substituents are present in the open chain compound. This effect originates from a
combined action of a lower enthalpy of the cyclized compound, and an entropy loss in the cyclization step that is smaller for substituted than for unsubstituted compounds.\textsuperscript{23,24}

\[
\begin{array}{c}
\text{HO} \\
\text{OH} \\
\text{p-MeO-C}_6\text{H}_5- \\
\text{p-MeO-C}_6\text{H}_5- \\
\text{i-Propyl} \\
\text{(E)-Ph-CH=CH-} \\
\text{(E)-Ph-CH=CH-} \\
\text{(E)-(p-NO}_2\text{-PhCH=CH-} \\
\text{(E)-CH}_3\text{-CH=CH-} \\
\text{(E)-CH}_3\text{-CH=CH-} \\
\text{(E)-CH}_3\text{(CH}_2\text{),CH=CH-} \\
\text{(E)-PhCH=CH(CH}_3\text{) -} \\
\text{p-NO}_2\text{-Ph} \\
\text{H} \\
\text{R} \\
\text{H} \\
\text{O} \\
\text{ benzene} \\
\text{p-TsOH} \\
\text{+} \\
\text{O} \\
\text{2.18} \\
\text{2.19}
\end{array}
\]

<table>
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<tr>
<th>entry</th>
<th>diol</th>
<th>R</th>
<th>cy (%)</th>
<th>$[\alpha]_{578}$</th>
<th>c (CHCl$_3$)</th>
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<tr>
<td>a</td>
<td>2.18a</td>
<td>p-MeO-C$_6$H$_5$-</td>
<td>91</td>
<td>+18.8</td>
<td>0.41</td>
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<tr>
<td>b</td>
<td>2.18b</td>
<td>p-MeO-C$_6$H$_5$-</td>
<td>81</td>
<td>-8.6</td>
<td>0.41</td>
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<tr>
<td>c</td>
<td>2.18a</td>
<td>i-Propyl</td>
<td>92</td>
<td>+55.8</td>
<td>0.64</td>
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<td>d</td>
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<td>78</td>
<td>+38.3</td>
<td>0.59</td>
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<tr>
<td>e</td>
<td>2.18b</td>
<td>(E)-Ph-CH=CH-</td>
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<td>-2.60</td>
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<tr>
<td>f</td>
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<td>53</td>
<td>+10.4</td>
<td>0.41</td>
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<tr>
<td>g</td>
<td>2.18b</td>
<td>(E)-(p-NO$_2$)-PhCH=CH-</td>
<td>55</td>
<td>-42.3</td>
<td>0.35</td>
</tr>
<tr>
<td>h</td>
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<td>87</td>
<td>+108</td>
<td>0.62</td>
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<tr>
<td>i</td>
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<td>+85.3</td>
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<tr>
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</tr>
<tr>
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<td>79</td>
<td>-19.2</td>
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<td>+101</td>
<td>0.52</td>
</tr>
<tr>
<td>o</td>
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<td>p-NO$_2$-Ph</td>
<td>72</td>
<td>+27.2</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Table 2.1 Synthesis of acetals 2.19
Aldehydes reacted very fast with 1,3-propanediols (2.18a) or (2.18b), but ketones reacted sluggishly, if at all. Reactions were attempted with acetophenone and acetone. After twenty-four hours of reflux in benzene most of the diol and the ketones were recovered. These observations contradict the results of Kulka,\textsuperscript{14} who claimed to have synthesized a number of ketals derived from acetone and amyl methyl ketone and 1-aryl-2,2-dimethyl-1,3-propanediols 2.18. Unfortunately, no convincing structural proofs were given for any of the compounds of Kulka et al.\textsuperscript{14}

Space filling models show that the acetals 2.19 are very compact. In the case of ketals, one substituent is forced into an axial position, resulting in considerable steric crowding. Further conformational aspects will be discussed in the following paragraph. Ketal formation is clearly a slow process. However, we have no evidence whether this is a thermodynamic or a kinetic problem. The chemical yields of the acetalization reactions were good to excellent, but the question of the diastereoselectivity remains.

Fig. 2.4
In most cases 300 MHz $^1$H- and $^{13}$C-NMR spectra revealed only one diastereomer. This is indicated by the acetal- and benzylic-hydrogen signals in the $^1$H-spectra. The $^{13}$C-spectra reveal only one signal for every carbon atom. The $^1$H- and $^{13}$C-spectra of the p-nitrobenzaldehyde acetals 2.19p are shown in Fig. 2.4. Glc analysis of the p-methoxybenzaldehyde acetals confirmed a diastereoselectivity of at least 95%. Only acetals of $\alpha$-methyl-trans-cinnamaldehyde (Table 2.1 entry 1 and m), appeared to be mixtures of diastereomers with de's of 49 and 67%. Even after column chromatography $^1$H-NMR and $^{13}$C-NMR spectra revealed the presence of the second diastereomer in approximately 10%.

2.4 CONFORMATIONAL ANALYSIS

2.4.1 Chair conformations in substituted 1,3-dioxanes

Like cyclohexane, 1,3-dioxane exists largely in a chair conformation. The chair to chair inversion barriers for both unsubstituted compounds are approximately the same, about 40-42 kJ/mole. Substituted members of both classes of compounds tend to have apolar groups in equatorial positions. According to Riddell, trans 2,5-disubstituted compounds favour the 2-equatorial conformation over the 5-equatorial conformation. Investigations, carried out by Eliel, confirm these findings. Aksnes and coworkers have shown that a 2-substituent in an axial arrangement destabilizes a 1,3-dioxane ring (Scheme 2.7).

![Scheme 2.7 Formation of five- and six-membered cyclic acetals of glycerol](image-url)
The formation of the six-membered cyclic acetal is strongly disfavoured in the condensation of glycerol with acetone, compared to the condensation of glycerol with acetaldehyde (Scheme 2.7).30

Diaxial repulsions are sometimes unavoidable in poly-substituted 1,3-dioxanes. The ring strain that originates from these repulsions can lead to distortions in the ring from the perfect chair conformation.32

2.4.2 NOESY-NMR and conformational analysis

NMR-spectroscopy is an important tool in conformational analysis of organic compounds in general. Especially, conformations of various six-membered cyclic compounds were established by NMR-methods. Vicinal H-H coupling constants provide direct information about the cis or trans relationship between those protons.29 13C-NMR chemical shifts appear to correlate well with conformations of members in a class of compounds.31

The so called Nuclear Overhauser effect (NOE) provides an important method to obtain information about the conformation of a compound. The NOE is the change in the intensity of the absorption of a specific nuclear spin when another spin is saturated by irradiation.33,34 The effect is observed for both coupled and uncoupled pair of spins, provided that uncoupled spins are in each others proximity. The magnitude of the observed NOE gives qualitative information about the intramolecular proton-proton distances. NOE's can be measured between nuclei at distances of approximately 2-4.5 Å, and detailed information of the molecular geometry can be obtained in this way.33-36 The effect has been used to discriminate between trans 2.27a and cis 2.27b,37 and between conformations 2.28a and 2.28b (see Fig. 2.5).

A NOESY (Nuclear Overhauser Exchange Spectroscopy) is a 2D-homonuclear shift correlation technique. Through space NOE's between all sets of protons are observed in one experiment.32 Large molecules that tumble slowly in solution, like proteins, and small rigid molecules are best suited for NOESY analysis. For these kind of molecules, NOE's have time to build up; relaxation time and time that protons are actually in close proximity, are factors that determine the extent of the NOE build up.

23
As was discussed in the previous section the NOESY-NMR technique is an important tool in the determination of the conformation of small and rigid cyclic compounds. On the basis of information given in section 2.5.1 we expect that the acetals 2.19 would have the conformation depicted in Fig. 2.6. This means that the 2- and 4-aryl substituents both have assumed an equatorial position. With this hypothesis in mind a strong cross-peak, due to axial H-2 axial H-4 interaction, was anticipated.

To test the above mentioned hypothesis a number of NOESY spectra were recorded in chloroform-d1 (Table 2.2). The spectrum of 2.19g is given as example (Fig. 2.7).
The anticipated cross-peaks between H-2 and H-4 are readily identified. These peaks
are denoted in the spectra with \( \Delta \); and they clearly demonstrate the mutual diaxial relationship between H-2 and H-4.

Three other conformational relationships between H-2 and H-4 are possible. Namely: (a) eq H-2 - ax H-4, (b) ax H-2 - eq H-4, (c) eq H-2 - eq H-4. The cross peaks which are expected in these three case are between: (a) the axial 2-substituent and both axial H-4 and axial H-6, (b) the axial 4-aryl substituent and the axial H-6 and between 4-aryl and the axial H-2, (c) the axial 2-substituent and the axial 4-substituent.

None of these cross-peaks are seen in the spectrum. Although the absence of certain cross-peaks does not necessarily prove that no interaction exists, it is likely that they would have been present if the mentioned conformational relationships a to c were realistic. CPK spacefilling models show that these three conformations a to c are highly unlikely, as a consequence of large unavoidable steric hindrance by axial substituents.

Fig. 2.8

The NOESY spectra of the unsaturated acetals 2.19 reveal also information about the conformation of the 2-alkenyl substituents. Two rotamers can in principle exist (Fig. 2.8). In structure I, with the carbon-carbon double bond folded back to the ring, the axial H-2 interacts with H\(_a\). On the other hand in structure II the axial H-2 interacts with H\(_b\). Both cross-peaks are indeed present in the spectra and are denoted B and C in the example of 2.19g (Fig. 2.7). Both rotamers exists and there is no obvious reason why one should prevail over the other.

All other cross-peaks in Fig. 2.7 are the consequence of normal and expected interactions. The two separated doublets of the p-nitro substituted phenyl ring gave us the possibility to differentiate between the two phenyl substituents. It is clear that both aryl groups show no interaction with each other, and that the equatorial 4-aryl substituent shows no interaction with the carbon-carbon double bond of the
unsaturated acetals. Because the $^1$H- and $^{13}$C-NMR spectra of all synthesized acetals resemble each other closely, we assume that all these compounds exist in the same conformation: a chair conformation with the substituents at C-2 and C-4 assuming an equatorial position.

2.5 ASSIGNMENT OF STEREOCHEMISTRY

The diols used in this thesis are (S)-(+-)1-phenyl-2,2-dimethyl-1,3-propanediol (2.18a) and (S)-(--)1-(o-chlorophenyl)-2,2-dimethyl-1,3-propanediol (2.18b). Their absolute configurations have been established.15-19 The conformations of the derived acetals 2.19 have been established by NOESY NMR. With this knowledge the absolute configuration at the acetal centers can be assigned (Fig. 2.9). The acetals derived from (+)-2.18a have absolute configuration of (2R,4S), and the acetals derived from (-)-2.18b the absolute configuration of (2S,4S).

Fig. 2.9

2.6 CONCLUDING REMARKS

In the previous paragraphs we have discussed that enantiomerically pure (S)-(+)-1-phenyl-2,2-dimethyl-1,3-propanediol (2.18b) and (S)-(--)1-(o-chlorophenyl)-2,2-dimethyl-1,3-propanediol (2.18b) condense with aldehydes to form 1,3-dioxanes 2.19 (acetals). From NMR ($^1$H- and $^{13}$C-) and GLC analysis it was seen that these condensations proceed in a highly diastereomeric manner ($\geq 95\%$). With a 2-D homonuclear correlation NMR technique (NOESY), it was established that the acetals
exist in a chair conformation with equatorial substituents on C-2 and C-4.

2.7 EXPERIMENTAL

General remarks
Commercially available solvents and reagents were purchased and used as such. Thiophene-free benzene (Janssen) was used. The (+)-phenyl- and (-)-o-chlorophenyl-phosphoric acids were kindly provided by Dr. W. ten Hoeve. All aldehydes were commercially available except p-nitrocinnamaldehyde, which was synthesized by Drs. F. Leusink according to a literature procedure. Melting points are uncorrected and were determined on a Reichert microscope. Boiling points are also uncorrected.

$^1$H-NMR spectra were recorded on a Jeol C-60 HL spectrometer (60 MHz) or on a Nicolet NT-200 spectrometer (200 MHz), or on a Varian XL-300 (300 MHz). Chemical shifts are denoted in $\delta$ units (ppm) relative to tetramethylsilane. $^{13}$C-NMR spectra were recorded on a Nicolet NT-200 (at 50.32 MHz) or on a Varian XL-300 (75.48 MHz). Chemical shifts are denoted in $\delta$ units (ppm) relative to CDCl$_3$ ($\delta$ 76.9). Splitting patterns are designated as: s (singlet); d (doublet); t (triplet); q (quartet); b (broad); m (multiplet). NOESY spectra were recorded in CDCl$_3$ on a Varian XL-300 (300 MHz). Infrared spectra were recorded on a Perkin Elmer 177. Optical rotations were measured with a Perkin Elmer Model 241 polarimeter at a concentration of c in g/100ml at room temperature. Elemental analyses were carried out at the Microanalytical Department of the University. Mass spectra were recorded on an AEI MS 902 apparatus.

Synthesis of diols 2.18a and 2.18b
These diols were obtained by hydrolysis of the optically pure cyclic phosphoric acid derivatives 2.17a and 2.17b. In 100 ml of ethyleneglycol were dissolved 10 g of the phosphoric acid and 15 g of potassium hydroxide. This mixture was stirred magnetically at approximately 150°C during 8 h. After cooling, water was added and extraction with chloroform (100-150 ml) was carried out three times. The organic layer was dried over MgSO$_4$, filtered and evaporated to give an oily residue. Bulb-to-bulb distillation gave the optically pure diol in 60%-70% yield. 2.18a has $[\alpha]_{D}^{28}$ 46.8° (CHCl$_3$, c 0.60), and 2.18b has $[\alpha]_{D}^{28}$ -43.1° (CHCl$_3$, c 0.47).

4-Nitrocinnamaldehyde dimethylacetal
4-Nitrocinnamaldehyde (6.0 g, 34 mmoles) was dissolved in 15 ml of methanol and 15 ml of trimethyl orthoformate. One drop of concentrated hydrochloric acid was added and this mixture was stirred at room temperature for one hour. The solvent was then evaporated and a dark residue remained. Bulb-to-bulb distillation at 160° (0.05 mm Hg) gave 7.4 g (33 mmoles) of the product as a yellow solid (98% yield). mp 61°-63°C

$^1$H-NMR (CDCl$_3$): $\delta$ 3.45 (s, 6H); 5.15 (d, 1H, $^3$J=4.2Hz); 6.3-6.8 (m, 2H); 7.83 (d, 2H, $^3$J=9.6Hz); 8.60 (d, 2H, $^3$J=9.6Hz).

General procedure for synthesis of acetics 2.19
Diol 2.18a or 2.18b (10 mmoles) 11-12 mmoles of an aldehyde and 10-20 mg of
p-toluenesulphonic acid (0.5-1.0 mol-%) were dissolved in 100 ml of benzene. This mixture was stirred magnetically and refluxed during six hours. The water formed during the reaction was removed azeotropically by means of a Dean-Stark trap. After cooling, the mixture was washed with a saturated NaHSO₃ solution and with a saturated brine solution. After drying the benzene layer over MgSO₄, the solution was filtered and concentrated in vacuo. The resulting oil was purified by bulb-to-bulb distillation or by column chromatography (silica gel, hexane/ethyl acetate). In a few cases the crude product solidified in which case the solid was recrystallized. The pure compounds were oils that occasionally solidified upon standing. In a few cases the acetalization reaction was carried out with the dimethylacetal of the aldehyde. In those cases the methanol that was formed during the trans-acetalization was removed azeotropically with benzene.

(2R,4S)-(+)2-(p-Methoxyphenyl)-4-phenyl-5,5-dimethyl-1,3-dioxane (2.19a)

Diol 2.18a (1.62 g, 8.27 mmoles), p-methoxybenzaldehyde (1.50 g, 11.4 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure 2.21g of 2.19a (7.54 mmoles, 91%).

Bp 195°C (0.1 mm Hg).

'H-NMR (CDCl₃) δ 0.73 (s, 3H); 1.05 (s, 3H); 3.80 (s, 3H); 3.82 (s, 2H); 4.67 (s, 1H); 5.65 (s, 1H); 6.75-7.55 (m, 9H).

'C-NMR (CDCl₃) δ 18.6 (q); 21.7 (q); 33.9 (s); 55.1 (q); 78.6 (t); 87.1 (d); 101 (d); 114 (d); 127.0 (d); 127.3 (d); 131.1 (s); 138.0 (s); 160.0 (s).

Exact mass: calc. 298.380, found 298.382

[α]₅₇₅ +18.8° (CHCl₃, c 0.41)

(2S,4S)-(−)2-(p-Methoxyphenyl)-4-(o-chlorophenyl)-5,5-dimethyl-1,3-dioxane (2.19b)

Diol 2.18b (2.04 g, 9.49 mmoles), p-methoxybenzaldehyde (1.38 g, 9.78 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure 2.56 g of 2.19b (7.69 mmoles, 81%).

Bp 200°C (0.1 mm Hg).

'H-NMR (CDCl₃) δ 0.85 (s, 3H); 1.20 (s, 3H); 3.85 (s, 3H); 3.97 (s, 2H); 5.25 (s, 1H); 5.68 (s, 1H); 6.80-7.70 (m, 8H).

'C-NMR (CDCl₃) δ 19.3 (q); 21.7 (q); 35.2 (s); 55.1 (q); 78.9 (t); 87.1 (d); 102 (d); 113.5 (d); 126.1 (d); 127.4 (d); 128.6 (d); 130.5 (d); 132.7 (s); 135.8 (s); 159.9 (s).

Exact mass: 332.825, found 332.826

[α]₅₇₅ -8.6° (CHCl₃, c 0.41)

(2R,4S)-(+)2-Isopropyl-4-phenyl-5,5-dimethyl-1,3-dioxane (2.19c)

Diol 2.18a (1.73 g, 9.61 mmoles), isobutyraldehyde (0.76 g, 10.8 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure 2.07g of 2.19c (0.85 mmoles, 92%), as a mixture of diastereomers.

Bp 125°C (0.5 mm Hg).

'H-NMR (CDCl₃) δ 0.72 (s, 3H); 0.95 (s, 3H); 1.15 (d, 6H, 3J= 7.2Hz); 2.05 (m, 1H); 3.70 (2xd, 2H, 3J=11.2Hz); 4.40 (s, 1H0; 4.50 (d, 1H, 3J=7.2 Hz); 7.55 (s, 5H).

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$^{13}$C-NMR (CDCl$_3$) $\delta$ 16.7 (q); 18.5 (q); 21.7 (q); 33.9 (s); 78.1 (t); 86.3 (d); 105.5 (d); 127.1 (d); 127.3 (d); 127.4 (d); 138.4 (s).

$[\alpha]_{578}^{25} +55.8^\circ$ (CHCl$_3$, c 0.64)

Exact mass: calc. 234.337, found 234.338.

(2R,4S)-(+)\-2-(2'-Phenyl-1'-ethenyl)-4-phenyl-5,5-dimethyl-1,3-dioxane (2.19d)

Diol 2.18a (3.21 g, 17.8 mmoles), trans cinnamaldehyde (2.51 g, 19.0 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure 4.05 g of 2.19d (13.8 mmoles, 78%). Column chromatography (silica gel, hexane/ethyl acetate 2:1) gave a slightly higher yield. Bp 200°C (0.1 mm Hg).

$^1$H-NMR (CDCl$_3$) $\delta$ 0.82 (s, 3H); 0.95 (s, 3H); 3.70 (2xd, 2H, $^2$J= 14.2Hz); 4.45 (s, 1H); 5.15 (d, 1H, $^3$J= 6.3Hz; 6.30 (dd, 1H, $^3$J= 6.3Hz, $^3$J= 15.8Hz); 6.75 (d, 1H, $^3$J= 15.8Hz) 7.20-7.45 (m, 10H).

$^{13}$C-NMR (CDCl$_3$) $\delta$ 18.5 (q); 21.7 (q); 33.9 (s); 78.3 (t); 86.9 (d); 101 (d); 125.5 (d); 126.6 (d); 127.3 (d); 127.9 (d); 128.0 (d); 128.3 (d); 131.0 (d); 133.1 (d); 135.9 (s); 137.6 (s).

$[\alpha]_{578}^{25} +38.3^\circ$ (CHCl$_3$, c 0.57)

Exact mass: calc. 294.392, found 294.391

(2S,4S)-(\-)-2-(2'-Phenyl-1'-ethenyl)-4-(o-chlorophenyl)-5,5-dimethyl-1,3-dioxane (2.19e)

Diol 2.18b (2.12 g, 9.86 mmoles), trans cinnamaldehyde (1.35 g, 10.2 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure 2.88 g of 2.19e (8.75 mmoles, 89%). Column chromatography (silica gel, hexane/ethyl acetate 2:1) gave a slightly higher yield. The purified product solidified upon standing. Bp 210°C (0.1 mm Hg).

$^1$H-NMR (CDCl$_3$) $\delta$ 0.75 (s, 3H); 1.15 (s, 3H); 3.70 (2xd, 2H, $^2$J= 14.2Hz); 4.45 (s, 1H); 5.15 (d, 1H, $^3$J= 6.0Hz; 6.35 (dd, 1H, $^3$J= 6.0Hz, $^3$J= 16.5Hz); 6.85 (d, 1H, $^3$J= 16.5Hz) 7.20-7.70 (m, 9H).

$^{13}$C-NMR (CDCl$_3$) $\delta$ 19.2 (q); 21.8 (q); 35.3 (s); 78.6 (t); 81.9 (d); 101 (d); 125.3 (d); 126.2 (d); 128.0 (d); 128.7 (d); 130.3 (d); 132.8 (d); 133.4 (s); 135.7 (s); 135.9 (s).

$[\alpha]_{578}^{25} -2.60^\circ$ (CHCl$_3$, c 0.58)

Mass spectrum: M$^+$ 329

Elemental analysis: calc. for C$_20$H$_{21}$O$_2$Cl: C 73.05%, H 6.44%, Cl 10.78%; found C 72.95%, H 6.47%, Cl 10.38%.

(2R,4S)-(\+)-2-(2'-Nitrophenyl-1'-ethenyl)-4-phenyl-5,5-dimethyl-1,3-dioxane (2.19f)

Diol 2.18a (0.93 g, 5.16 mmoles), trans-4-nitrocinnamaldehyde dimethylacetal (1.15 g, 5.16 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure a light yellow solid, which was recrystallized from hexane/dichloromethane. Yield of light yellow needles: 0.927 g of 2.19f (2.73mmoles, 53%).
Mp. 111°-112°C

$^1$H-NMR (CDCl$_3$) δ 0.80 (s, 3H); 1.00 (s, 3H); 3.75 (2xd, 2H, $^3$J=13.6Hz); 4.60 (s, 1H); 5.35 (d, 1H, $^3$J= 3.4Hz); 6.45 (dd, 1H, $^3$J= 3.4Hz, $^3$J= 15.7Hz); 6.90 (d, 1H, $^3$J= 15.7Hz) 7.15 (m, 5H); 7.60 (d,2H, $^3$J= 10.2Hz); 8.20 (d, 2H, $^3$J= 10.2Hz).

$^{13}$C-NMR (CDCl$_3$) δ 18.6 (q); 21.7 (q); 34.1 (s); 78.5 (t); 87.1 (d); 103.3 (d); 123.8 (d); 126.8 (d); 127.3 (d); 130.6 (d); 137.4 (d); 142.2 (s); 147.2 (s).

$[\alpha]_{378}^{10.4}$ (CHCl$_3$, c 0.41)

Elemental analysis: calc. for C$_{20}$H$_{21}$NO$_4$: C 70.77%, H 6.24%, N 4.13%; found C 70.26%, H 6.28%, N 4.09%.

(2S,4S)-(−)-2-(2′-Nitrophenyl-1′-ethenyl)-4-(o-chlorophenyl)-5,5-dimethyl-1,3-dioxane (2.19g)

Diol 2.18b (1.12 g, 5.20 mmoles), trans-4-nitrocinnamaldehyde dimethylacetal (1.16 g, 5.20 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure a light yellow solid, which was recrystallized from hexane/dichloromethane.

Yield of light yellow needles: 1.09 g of 2.19g (2.91 mmole, 55%).

Mp. 76.5°-78°C

$^1$H-NMR (CDCl$_3$) δ 0.77 (s, 3H); 1.00 (s, 3H); 3.75 (s, 2H); 5.05 (s, 1H); 5.15 (d, 1H, $^3$J= 3.4Hz); 6.35 (dd, 1H, $^3$J= 3.4Hz, $^3$J= 13.6Hz); 7.05-7.40 (m, 4H) 7.45 (d, 2H, $^3$J= 8.9Hz); 9.05 (d,2H, $^3$J= 8.9Hz);

$^{13}$C-NMR (CDCl$_3$) δ 19.2 (q); 21.7 (q); 35.4 (s); 78.7 (t); 81.1 (d); 100.5 (d); 123.8 (d); 126.3 (d); 127.3 (d); 128.8 (d); 129.1 (d); 129.9 (d); 130.2 (d); 131.0 (d); 132.8 (s); 135.4 (s); 142.4 (s); 147.1 (s).

$[\alpha]_{378}^{578}$ -42.3° (CHCl$_3$, c 0.35)

Elemental analysis: calc. for C$_{20}$H$_{21}$NO$_4$: C 64.26%, H 5.39%, Cl 9.48, N 3.75%; found C 64.18%, H 5.45%, Cl 9.36%, N 3.78%.

(2R,4S)-(−)-2-(1′-Propenyl)-4-phenyl-5,5-dimethyl-1,3-dioxane (2.19h)

Diol 2.18a (2.25 g, 12.5 mmoles), crotonaldehyde (1.10 g, 15.7 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure 2.52 g of 2.19h (10.9 mmoles, 87%).

bp 180°C (0.1 mm Hg).

$^1$H-NMR (CDCl$_3$) δ 0.70 (s, 3H); 0.83 (s, 3H); 1.69 (d, 3H, $^3$J= 8.1Hz); 3.72 (s, 2H); 5.07 (s, 1H); 5.10 (d, 1H); 5.60-6.15 (m, 2H); 7.4 (s, 5H).

$^{13}$C-NMR (CDCl$_3$) δ 17.3 (q); 19.7 (q); 20.9 (q); 33.8 (s); 78.2 (t); 81.4 (d); 101.5 (d); 126.2 (d); 126.6 (d); 127.0 (d); 131.0 (d); 131.1 (d); 132.4 (s).

$[\alpha]_{378}^{10.8}$ (CHCl$_3$, c 0.62).

Exact mass: calc. 232.321, found 232.321

(2S,4S)-(−)-2-(1′-Propenyl)-4-(o-chlorophenyl)-5,5-dimethyl-1,3-dioxane (2.19i)

Diol 2.18b (2.36 g, 11.0 mmoles), crotonaldehyde (0.890 g, 12.7 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure 2.53 g of 2.19i (9.48 mmoles, 86%).

bp 150°C (0.05 mm Hg).
$^1$H-NMR (CDCl$_3$) δ 0.75 (s, 3H); 1.00 (s, 3H); 1.75 (d, 3H, $^3$J = 8.0Hz); 3.70 (s, 2H); 5.05 (s, 1H); 5.10 (d, 1H, $^3$J = 6.4Hz); 5.50-6.10 (m, 2H); 7.10-7.80 (m, 4H).

$^{13}$C-NMR (CDCl$_3$) δ 17.6 (q); 19.2 (q); 21.8 (q); 35.2 (s); 78.6 (t); 81.8 (d); 102.0 (d); 126.3 (d); 126.5 (d); 127.0 (d); 130.5 (d); 131.0 (d); 132.5 (s); 136.5 (s).

$[\alpha]_{578}^0$ -67.9$^\circ$ (CHCl$_3$, c 0.42).

Exact mass: calc. 265.273, found 265.274

(2R,4S)-(++)-2-(1'-Pentenyl)-4-phenyl-5,5-dimethyl-1,3-dioxane (2.19j)

Diol 2.18a (2.12 g, 11.8 mmoles), trans hexenal (1.23 g, 12.5 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure and column chromatography (silica gel, hexane/ethyl acetate 2:1), 2.10 g of 2.19j (8.08 mmoles, 96%).

$^1$H-NMR (CDCl$_3$) δ 0.70 (s, 3H); 0.95 (t, 3H); 1.07 (s, 3H); 1.50 (m, 2H); 2.15 (m, 2H); 3.78 (s, 2H); 4.60 (s, 1H); 5.27 (d, 1H, $^3$J = 5.4Hz); 5.80-6.30 (m, 2H); 7.40 (s, 4H).

$^{13}$C-NMR (CDCl$_3$) δ 12.8 (q); 18.7 (q); 21.9 (q); 22.5 (t); 33.2 (t); 34.8 (s); 78.2 (t); 81.4 (d); 101.8 (d); 126.2 (d); 126.6 (d); 127.8 (d); 128.1 (d); 129.9 (d); 130.9 (s).

$[\alpha]_{578}^0$ +85.3$^\circ$ (CHCl$_3$, c 0.34).

Exact mass: calc. 260.178, found 260.177

(2S,4S)-(--)2-(1'-Pentenyl)-4-(o-chlorophenyl)-5,5-dimethyl-1,3-dioxane (2.19k)

Diol 2.18b (1.47 g, 6.84 mmoles), trans hexenal (0.710 g, 7.23 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure and column chromatography (silica gel, hexane/ethyl acetate 2:1), 1.80 g of 2.19k (6.10 mmoles, 89%).

$^1$H-NMR (CDCl$_3$) δ 0.70 (s, 3H); 0.95 (t, 3H); 1.07 (s, 3H); 1.40 (m, 2H); 2.05 (m, 2H); 3.75 (s, 2H); 5.05 (s, 1H); 5.12 (d, 1H, $^3$J = 6.2Hz); 5.60 (m, 1H); 5.95 (m, 1H); 7.10-7.60 (m, 4H).

$^{13}$C-NMR (CDCl$_3$) δ 13.6 (q); 19.1 (q); 21.7 (q); 22.0 (t); 34.1 (t); 35.2 (s); 78.6 (t); 81.8 (d); 102.1 (d); 126.2 (d); 126.5 (d); 128.6 (d); 129.0 (d); 129.1 (d); 130.4 (s) 135.8 (s).

$[\alpha]_{578}^0$ -61.7$^\circ$ (CHCl$_3$, c 0.52).

Exact mass: calc. 294.177, found 294.177

(2R,4S)-(++)-2-(1'-Methyl-E-2'-phenyl-1'-ethenyl)-4-phenyl-5,5-dimethyl-1,3-dioxane (2.19l)

Diol 2.18a (1.64 g, 9.11 mmoles), methyl-E-cinnamaldehyde (1.46 g, 10.0 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure and column chromatography (silica gel, hexane/ethyl acetate 2:1) 2.30 g of 2.19l (7.47 mmoles, 82%) as a 2.8:1 mixture of diastereoisomers.

$^1$H-NMR (CDCl$_3$) δ major diastereoisomer 0.75 (s, 3H); 0.95 (s, 3H); 2.05 (s, 3H); 3.75 (2xd, 2H, $^2$J = 17.3Hz); 4.55 (s, 1H); 5.10 (s, 1H); 6.70 (s, 1H); 7.1-7.3 (m, 10H);

minor diastereoisomer 0.65 (s, 3H); 0.70 (s, 3H); 2.15 (s, 3H); 3.65 (2xd, 2H, $^2$J=
15.0Hz); 4.35 (s, 1H); 5.40 (s, 1H); 6.50 (s, 1H); 7.1-7.3 (m, 10H).

13C-NMR (CDCl₃) δ major diastereoisomer 12.8 (q); 18.6 (q); 21.7 (q); 33.8 (s); 78.2 (t); 86.6 (d); 105.6 (d); minor diastereoisomer 12.8 (q); 17.7 (q); 18.5 (q); 33.8 (s) 77.6 (t); 86.0 (d); 99.4 (d). The two diastereoisomers together showed 14 alkene and aromatic signals: 126.6 (d); 127.3 (d); 127.4 (d); 128.5 (d); 129.3 (d); 129.7 (d) 129.8 (d); 135.0 (s) 135.5 (s); 136.7 (s); 137.8 (s).

[a]₁₅₀ +76.2° (CHCl₃, c 0.37).

Exact mass: calc. 308.178, found 308.178

(2S,4S)-(-)-2-(1'-Methyl-E-2'-phenyl-1'-ethenyl)-4-(o-chlorophenyl)-5,5-dimethyl-1,3-dioxane (2.19m)

Diol 2.18b (1.52 g, 7.07 mmoles), methyl-E-cinnamaldehyde (1.17 g, 8.00 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure and column chromatography (silicagel hexane/ethyl acetate 2:1) 2.29 g of 2.19m (6.41 mmoles, 79%) as a 5:1 mixture of diastereoisomers.

1H-NMR (CDCl₃) δ major diastereoisomer 0.85 (s, 3H); 1.15 (s, 3H); 2.05 (s, 3H); 3.85 (s, 2H); 5.20 (s, 1H); 6.75 (s, 1H); 7.2-7.7 (m, 10H).

13C-NMR (CDCl₃) δ major diastereoisomer 12.8 (q); 19.3 (q); 21.8 (q); 35.3 (s); 78.4 (t); 81.8 (d); 105.8 (d); minor diastereoisomer 10.8 (q); 19.3 (q); 21.8 (q); 33.8 (s) 77.9 (t); 81.2 (d); 99.6 (d). The two diastereoisomers together showed 14 alkene and aromatic signals: 126.2 (d); 126.6 (d); 127.8 (d); 128.5 (d); 127.9 (d); 128.2 (d) 128.5 (d); 128.6 (d) 129.4 (d); 129.8 (d); 130.2 (d); 132.7 (s); 134.8 (s); 135.8 (s); 136.6 (s).

[a]₁₅₀ -19.2° (CHCl₃, c 0.74).

Exact mass: calc. 342.159, found 342.158

(2R,4S)-(+)-2-Ethenyl-4-phenyl)-5,5-dimethyl-1,3-dioxane (2.19n)

Diol 2.18a (2.05 g, 11.4 mmoles), acroleine (1.00 g, 17.8 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure 2.29 g of 2.19n (7.76 mmoles, 68%) as a light yellow oil.

Bp. 150°C (0.1mm Hg).

1H-NMR (CDCl₃) δ 0.75 (s, 3H); 0.95 (s, 3H); 3.75 (2xd, 2H, J= 21Hz); 4.50 (s, 1H); 5.12 (d, 1H, J= 4.6Hz); 5.31 (dd, 1H, J₂= 10.4Hz, J₁= 1.7Hz); 5.96 (oct, 1H, J₃= 4.6Hz, J₄= 3.1= 16.1Hz); 7.2-7.4 (m, 5H).

13C-NMR (CDCl₃) δ 18.5 (q); 21.7 (q); 33.9 (s); 78.2 (t); 88.8 (d); 101.1 (d); 118.3 (t); 126.6 (d); 127.3 (d); 134.7 (s); 137.7 (s).

[a]₁₅₀ +108° (CHCl₃, c 0.52).

Exact mass: calc. 218.131, found 218.130

(2R,4S)-(+)2-(4-Nitrophenyl)-5,5-dimethyl-1,3-dioxane (2.19o)

Diol 2.18a (1.60 g, 8.89 mmoles), 4-nitrobenzaldehyde (1.36 g, 9.00 mmoles) and a catalytic amount of p-toluenesulphonic acid were dissolved in 100 ml of benzene and gave after reaction and work-up according to the general procedure gave a light yellow solid, that was recrystallized from hexane. Yield of 2.19o (2.00g, 6.39mmoles, 72%).
Mp. 76.5°-78°C

$^1$H-NMR (CDCl$_3$) $\delta$ 0.75 (s, 3H); 0.90 (s, 3H); 3.80 (2xd, 2H, $^2$J= 12.8Hz); 4.60 (s, 1H); 5.65 (s, 1H); 7.25 (m, 5H); 7.70 (d, 2H, $^2$J= 8.3Hz); 8.15 (d, 2H, $^2$J= 8.3Hz).

$^{13}$C-NMR (CDCl$_3$) $\delta$ 18.5 (q); 21.7 (q); 36.0 (s); 78.5 (t); 87.2 (d); 100.2 (d); 123.1 (d); 126.7 (d); 127.1 (d); 127.2 (d); 127.5 (d) 137.2 (s); 144.8 (s); 147.9 (s).

[a]$_{578}^0$ 27.7° (CHCl$_3$, c 0.60).

Elemental analysis: calc for C$_{18}$H$_{19}$NO$_4$ C 68.99%, H 6.11%, N 4.47%; found C 69.06%, H 6.21%, N 4.49%.

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