SELECTIVE CONVERSION OF ALDEHYDES TO FUNCTIONAL ESTERS UTILIZING THE TISHCHENKO REACTION

Olli Törmäkangas

Abstract

Different modifications of the Tishchenko reaction were studied in order to develop new catalysts and technology to produce 1,3-diol monoester derivatives. Related monoesters are the most common coalescing agents in paint industry with over 100 kilo tonnes total global annual production. The products can also be utilized as solvents and lubricants.

During this project a selective process for the preparation of 1,3-diol monoesters with aldol-Tishchenko type mixed Tishchenko reaction via 1,3-dioxan-4-ols was developed and optimized to give a selective and economical method that can be scaled up to industrial scale. The 1,3-dioxan-4-ol type intermediates were initially prepared by dimerization of the isolated β-hydroxy aldehyde and another monofunctional aldehyde. New information concerning the formation, isolation and stability of 1,3-dioxan-4-ol type structures was also obtained. Due to the instability of 1,3-dioxan-4-ol like intermediates the method is temperature sensitive and should be conducted at relatively low temperatures. The catalyst studies in the esterification of 1,3-dioxan-4-ols indicated that the basic nature of the catalyst is essential for the initiation of the reaction. Also sufficient Lewis acidity is required due to the coordination of the counter cation to the oxygens of dioxanol and the formation of the transition state. New 1,3-diol based catalysts were found to give esterification rates of 1,3-dioxan-4-ols faster than previously used metal hydroxides. High yields were obtained without observable product hydrolysis.

Another process developed was the homo aldol-Tishchenko reaction of monofunctional enolizable aldehydes to 1,3-diol monoesters under water free reaction conditions. The use of 1,3-diol based monoalcoholate catalysts and one of the formed side products as the solvent provides an advantageous and economical process as the costs due to the formation of wastes are minimized. This work focused on the production of the most important paint industry coalescing agents (2,2-dimethyl-3-hydroxyl-1-isopropyl-propyl)-2-methylpropionate and (3-hydroxy-2,2,4-trimethylpentyl)-2-methyl-propionate with the highest yields reported ever.

Finally, a new pathway to synthesize a Taxol™ A-ring building block was investigated. In the final step of the synthesis different forms of formaldehyde were utilized successfully as the electrophiles in the Shapiro reaction. The synthesis developed gives the Taxol™ A-ring in good stepwise yields and is clearly superior to the previously described pathways.

Acknowledgements

during my studies. The last and the warmest thanks belong to Oili for her great help, encouragement and love during this 'everlasting' work. Your support was irreplaceable. I also wish to thank our lovely daughter Katri for waking me up for work punctually every morning.

Helsinki, November 2001   Olli Törmäkangas

Symbols and abbreviations

Ac   acetyl
DIBAL-H   diisobutylaluminium hydride
DMF   *N,N*-dimethylformamide
HPA   hydroxypivalaldehyde (2,2-dimethyl-3-hydroxy-propanal)
KHMDS   potassium hexamethyldisilazane
LDA   lithium diisopropylamide
MMFF   Merck Molecular Force Field
MPV   Meerwein-Ponndorf-Verley reaction
PPTS   pyridinium *p*-toluenesulfonate
THF   tetrahydrofuran
TMS   tetramethylsilane
Trs   trisyl (2,4,6-triisopropylbenzenesulfonyl)
Ts   tosyl (*p*-toluenesulfonyl)

List of Original Papers

This thesis consists of the following papers, which are placed at the end of this thesis and are referred by the Roman numerals I-V.

I   Törmäkangas, O. P.; Koskinen, A. M. P., 'The Tishchenko Reaction and Its Modifications in Organic Synthesis', *Recent Res. Devel. Organic Chem* **2001**, *5*, 225-255.

II   Törmäkangas, O. P.; Saarenketo, P.; Koskinen, A. M. P., 'Selective Mixed Tishchenko Reaction via Substituted 1,3-Dioxan-4-ols', *Org. Proc. Res. & Dev.* **2002**, *6*, 125-131.

III Törmäkangas, O. P.; Koskinen, A. M. P., 'Monoalcoholates of 1,3-Diols as Effective Catalysts in the Tishchenko Esterification of 1,3-dioxan-4-ols' *Tetrahedron Lett.* **2001**, *42*, 2743-2746.

IV   Törmäkangas, O. P.; Koskinen, A. M. P., 'Fast Aldol-Tishchenko Reaction Utilizing 1,3-Diol Monoalcoholates as the Catalysts', *Org. Proc. Res. & Dev.* **2001**, *5*, 421-425.

V   Törmäkangas, O. P.; Toivola, R. J.; Karvinen, E. K.; Koskinen, A. M. P., 'A Short and Convenient Way to Produce the Taxol™ A-Ring Utilizing the Shapiro Reaction' *Tetrahedron* **2002**, *58*, 2175-2181.

Table of Contents

Preface

This work was initiated in 1997 in co-operation with Neste Co (Later Neste Chemicals Co. and then Dynea Co.) and TEKES (National Technology Agency of Finland) in the project called 'Aldehyde Activation', part of a larger national technology program called 'Marketing Molecules'. It was expected to foster co-operation between the Finnish chemical industry and the universities and create new know-how for the needs of industry. The main theme for this particular project was to find out new ways to piggyback the aldehydes formed as hydroformylation products of propen which is one of the raw oil refinement side products (Figure 1).
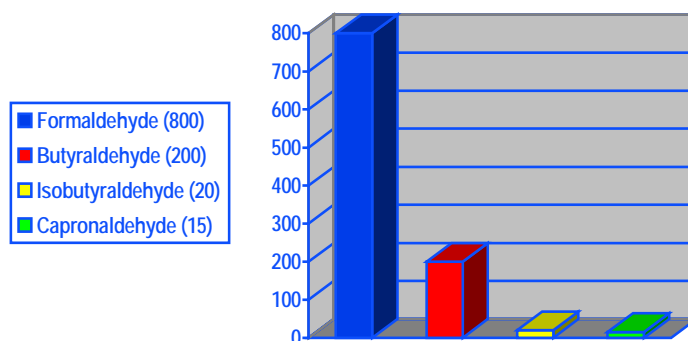
Figure 1. Annual production of the most common aldehydes at Neste (tn/a)

A more detailed goal for this particular work was to investigate the Tishchenko reaction in order to obtain new information on the effects of the catalysts and the reaction conditions on the selectivity between the Tishchenko reaction and the side reactions.

Later on the work focused on producing new monoesters of 1,3-diols from aldehydes by means of the Tishchenko reaction. Another goal was to create a method, which gives mixed monoesters in a selective manner without significant side reactions. Such a process was successfully developed and a patent application (FI981488; 'A method for

preparation 1,3-diol monoesters') was submitted. The most important application of 1,3-diol monoesters is their use as paint ingredients. Therefore, a method accomplishing large scale production at low cost, is needed. This goal sets several limitations for the reagents and methods, to be used in the process. The methods should also be as simple as possible with only few separate operations. These requirements made the work challenging and demand new ways of thinking about organic synthesis.

1. Introduction

In the Tishchenko reaction aldehydes or an aldehyde and a ketone are converted to esters usually with moderate to high yields. The reaction can be considered as a typical redox reaction between the aldehydes where a hydride shift takes place to give the product. There are several different modifications of the Tishchenko reaction that lead to different esters.

- The traditional Tishchenko reaction
- Mixed Tishchenko reaction
- The Aldol-Tishchenko reaction
- The Evans-Tishchenko reaction

These modifications have been discussed in details in our review article considering the Tishchenko reaction (I). With the *traditional Tishchenko reaction* an aldehyde can be converted to a simple monofunctional ester usually in high yields in the presence of strong Lewis acid catalysts, typically aluminium alkoxides. The *mixed Tishchenko reaction* proceeds in a similar way but between two different aldehydes giving usually a mixture of esters of all possible combinations. The *aldol Tishchenko reaction* can be divided in two different modifications: homo and hetero aldol-Tishchenko. The former one proceeds only for one enolizable aldehyde usually in the presence of a basic catalyst to give 1,3-diol monoesters. In the latter case an enolate or ketone reacts with an aldehyde also to give 1,3-diol monoesters. The *Evans-Tishchenko reaction* is closely related to the hetero aldol-Tishchenko giving 1,3-diol monoesters as the products usually in high yields and excellent stereoselectivity. The reaction is usually catalyzed by lanthanoids (e.g. SmI_2) and a readily available β-hydroxy ketone is used as the starting material.

In some cases two modifications can be competitive with each other but the selectivity can be adjusted with the choice of the reaction conditions. The selectivity can steered with proper choice of reaction temperature, catalyst and solvent. Additionally, there exist several possible side reactions in the modifications of Tishchenko reaction. It is usually more difficult to avoid the competitive reactions under the conditions typical to different modifications of the Tishchenko reaction and complicated product mixtures can result as well as difficulties in isolation of the products, especially on large scales. The most

common side reactions are aldol reaction (1) (with basic catalysts), Meerwein-Pondorff-Verley reduction (MPV) (2) (with Lewis acidic alkyl alcoholates), Oppennauer oxidation (3), hydrolysis (4) and Cannizzaro reaction (5) (with strongly basic alkaline metal hydroxides), transesterification (6) (catalysts having strongly coordinating counter cation) and Tollen's reaction (7) (with $Ca(OH)_2$).

The product esters are usually used as solvents, lubricants or paint coalescing agents (8). The use of different esters especially as lubricants has grown lately due to their relatively good biodegradation.

Aldehydes can also react as electrophiles with several alkyl lithium compounds usually in high yields. The Shapiro reaction is one convenient way to convert ketones to alkenes allowing substitution both at the α-position and the carbonyl carbon with various electrophiles (9). The ketone is first converted to a hydrazone followed by the formation of the dianion and decomposition to a reactive vinyl lithium compound. In our studies especially the different forms of formaldehyde were studied in the Shapiro reaction.

2. The chemistry of the 1,3-dioxan-4-ols

The very first goal of this work was to find out if it is possible to prepare mixed 1,3-dioxan-4-ols from a β-hydroxy aldehyde type aldol products and another aldehyde and then carry out a Tishchenko esterification of the formed dioxanols to the corresponding 1,3-diol monoesters. This pathway has not been investigated earlier in detail. If both steps were successful, it would provide an advantageous method to prepare selectively new monoesters with the mixed Tishchenko reaction without significant side reactions. The existing information on the chemistry of 1,3-dioxan-4-ols was found to be limited and several problems were encountered in the beginning of the work in the preparation and isolation of the dioxanols.

2.1. Existing methods for preparation of 1,3-dioxan-4-ols

There are three competitive methods for the preparation of 1,3-dioxan-4-ols. Seebach *et al.* (10) have prepared 1,3-dioxan-4-ones **3** from β-hydroxy acids **1** and monofunctional aldehydes **2** by acid catalyzed azeotropic distillation (Scheme 1.). Rychnovsky *et coll.* (11) further reduced such dioxanones with DIBAL-H to the corresponding dioxanols **4** where aluminium is attached to the hydroxyl group and thus stabilizes the structure. Conversion of **3** to monoester **5** has not been studied previously.
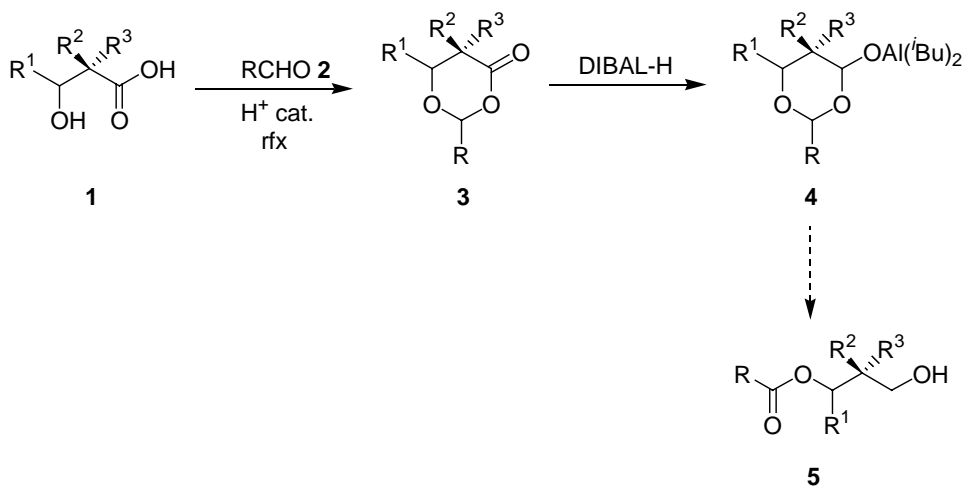
Scheme 1.

The route described in Scheme 1 was considered as an alternative method to produce the 1,3-diol monoesters if the Tishchenko esterification of **4** were successful. 5,5-Dimethyl-2-isopropyl-1,3-dioxan-4-one **3** (R = *i*-Pr, R^1 = H, R^2 = R^3 = Me) was prepared in the presence of 1 mol-% of PPTS in 66% isolated yield as a solid stable product. 2,2-Dimethyl-3-hydroxy propionic acid was prepared in 36% yield in the presence of 10M KOH with the initial Tishchenko esterification of dimeric 3-hydroxy-pivalaldehyde HPA to monoester followed by immediate hydrolysis. DIBAL-H reduction of **3** was carried out in THF and the Al-dioxanol aggregate **4** partly precipitated out. Decomposition of **4** to dioxanol did not succeed, and thus a further Tishchenko esterification cannot be carried out. However, this method would have been uneconomical in industrial scale because a stoichiometric amount of reducing agent would have been needed and large amount of waste would have been produced. Furthermore, strong precipitation during the reaction would also be problematic in larger scales.

Our second strategy was based on the work of Uehira *et al*. (12), who have studied the formation of 1,3-dioxan-4-ol derivatives **8** by a procedure similar to ours. They started with an initial conjugate addition of iodide to acrolein **6** giving an enolate which reacts with an aldehyde to give aldol product **7** with exclusive *syn* stereoselectivity (Scheme 2). The aldol product can be converted to the hemiacetal **8** by treatment with excess aldehyde at -78°C. However, they discovered that the dioxanol **8** decomposes and elimination of the aldol product **7** takes place at temperatures above 0°C. Decomposition was most probably caused by the presence of water but also the electron donating nature of the iodine may be crucial in the process.
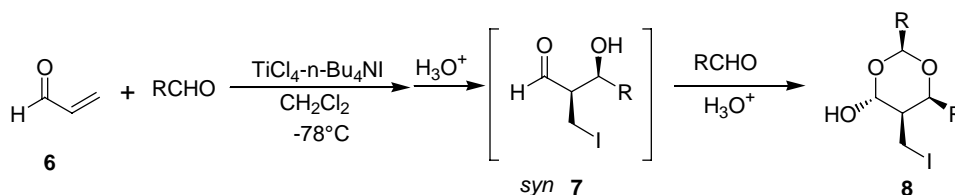
Scheme 2. Conjugate addition-aldol reaction-hemiacetal formation

Since the economical aspects and possibilities to scale up the reaction played a significant role in this work, both methods described above were considered unadvantageous, especially if they had to be scaled up to industrial (ton) scale.

The third method proved out to be suitable for our strategy. In 1943 Späth *et al.* had succeeded in preparing a few 'mixed' 1,3-dioxan-4-ol dimers by stirring the monomeric aldol product in excess of simple liquid aldehyde for three days (13). They did not study the ensuing esterification. This method would also be easy and inexpensive to carry out in large scale and was therefore further investigated.

2.2. Selective preparation of 'mixed' 1,3-dioxan-4-ols

Some aldol products of type **10** dimerize to form 1,3-dioxan-4-ol structures of type **9** (14). The Tishchenko reaction of dimeric aldol products to the corresponding 1,3-diol monoesters has been reported (15).

In this work the basic tenet was to monomerize the dimeric aldol product **9** to β-hydroxyaldehyde **10** and convert it to a new 'mixed' dimer, 4-hydroxy-1,3-dioxane **11** with another aldehyde (Scheme 3). Only one earlier paper describes a similar process.
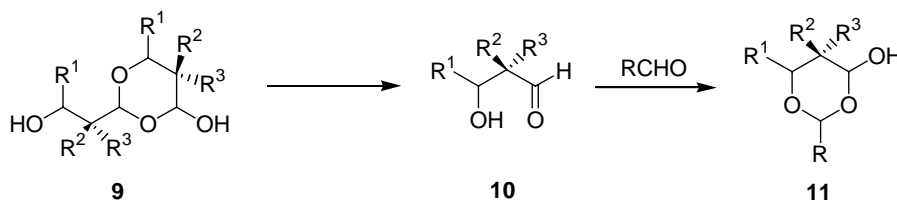
Scheme 3. Selective preparation of mixed dimer type 1,3-dioxan-4-ols

The formation of 1,3-diol monoester from β-hydroxy aldehyde and another aldehyde has been mentioned by Duke *et al.* (16). In their method vigorous reaction conditions were used. The reaction took place without a catalyst at +160° under 3.5 MPa pressure in 8 hours to give for example 2,2-dimethyl-3-hydroxypropyl isobutyrate in 77% yield. This method was not studied due to the vigorous and thus uneconomical reaction conditions.

Based on the few literature examples we concluded that this reaction sequence has potential for further experiments. If the isolation and the Tishchenko esterification of mixed dimers were possible, the products could be modified by changing substituents of the aldehydes. Several side reactions could be avoided if the dioxanols were isolated before esterification.

Our initial target was (2,2-dimethyl-3-hydroxylpropyl)-2-methylpropionate which was suspected to be an excellent coalescing agent Several problems were faced in the preparation and isolation of the corresponding dioxanol intermediate **11** (R = i-Pr, R^1 = H, $R^2 = R^3 = CH_3$) (II). These facts prompted us to study more carefully the chemistry of dioxanols which is reported in the following chapters.

2.2.1. *Solvent effect in monomerization of dimeric HPA*

The monomerization of dimeric HPA **12** and the formation of 1,3-dioxan-4-ols **14** was studied by of ^{1}H-NMR (II). The solvents and the temperature were found to have a significant effect on monomer-dimer equilibration. When dimeric HPA was dissolved in an apolar solvent ($CDCl_3$) at room temperature dimeric **12** was obtained exclusively. When the temperature was raised to +35°C HPA was partly (9%) monomerized and at +50°C the monomerization was complete. In polar (protic) solvents (D_2O) at rt HPA was 56% monomeric and at a slightly elevated temperature (+35°C) all HPA was in monomeric form. This effect was utilized later in this work in the cases where a solvent was needed in the formation of 1,3-dioxan-4-ols. For example, isooctane was used as a cosolvent in the preparation of dimeric HPA in order to accelerate the dimerization. When the samples were cooled back to room temperature partial dimerization of HPA was observed especially in $CDCl_3$. Monomerization of **12** in polar protic solvent was most probably due to the ability of the monomer **13** to form a hemiacetal type conjugate with the solvent.

2.2.2. *Effect of the reaction temperature*

Temperature effect has already been mentioned within the ^{1}H-NMR solvent studies. In order to prepare mixed dimers the dimeric HPA was first monomerized by heating in excess free aldehyde followed by cooling in order to prepare new mixed dimer, i.e. substituted 1,3-dioxan-4-ol. Optimal time for the completion of monomerization was three hours at +65 °C. When the mixture was cooled to room temperature the equilibrium between the monomeric and dimeric forms was reached in three days with still a significant amount of monomeric of HPA in the mixture. Cooling the reaction mixture from +65 °C directly to 0 °C shifted the equilibrium towards dimeric form and eventually the formation of 1,3-dioxan-4-ols was complete in 2½ hours and no monomeric HPA was observed in ^{1}H-NMR.

If the monomerization was carried out at too high temperatures the decomposition of the monomeric aldol product via retroaldol took place. When dimeric HPA was

attempted to be monomerized by heating in the absence of solvent, monomerization took place at the melting point (+91°C for HPA) and partial retroaldol reaction was observed already at +75°C. The presence of solvent or a simple liquid aldehyde promotes the monomerization at lower temperatures (typically +65 °C) and HPA can be fully monomerized without any retroaldol.

2.2.3. Effect of the aldehyde 2

In our optimized system to prepare mixed dioxanols **14**, dimeric HPA **12** was monomerized in 3 hours at +65 °C to β-hydroxyaldehyde **13** in excess liquid monofunctional aldehyde without a solvent (Scheme 4.) (II). An optimal amount of aldehyde was found to be 1000 mol-% compared to the dimeric HPA **12**. If a smaller excess was used monomer **13** dimerized readily back to **12**. After complete monomerization the mixture was cooled to 0 °C for 3 hours in order to complete the formation of **14**. The product mixture contained in most cases mainly dioxanols **14** and some **12** but also some monomeric HPA **13**.
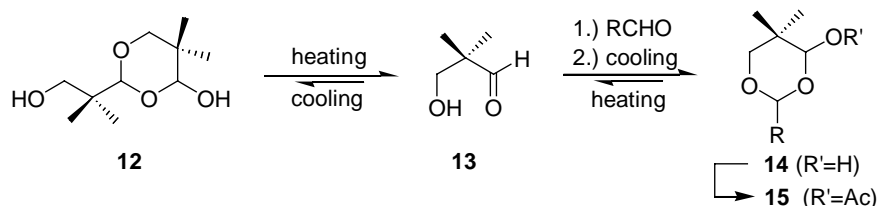
Scheme 4.

Electronic properties of substituents in the aldehyde also affects the formation of dioxanol **14**. The effect of the structure of different aldehydes **2** in the product distribution is shown in Table 1.

Table 1. Formation of mixed 1,3-dioxan-4-ol dimers (II)

Entry		Aldehyde 2	R	13 (mol-%)[a]	14 (mol-%)[a, b] trans	14 (mol-%)[a, b] cis	12 (mol-%)[a] (diastereomers)
1	a	Propanal	Et	0	22	48	30 (40:60)
2	b	2-methylpropanal	i-Pr	0	25	50	25 (41:59)
3	c	Pivalaldehyde	t-Bu	0	32	60	8 (40:60)
4	d	2-ethylhexanal	1'-Et-pentyl	0	38	49	13 (31:69)
5	e	Crotonaldehyde	CH=CHMe	62	0	0	38 (41:59)
6	f	Benzaldehyde	Ph	51	6	9	34 (40:60)
7	g	Cyclohexylcarboxaldehyde	C$_6$H$_{11}$	0	28	54	18 (40:60)

[a] The product distribution was determined by ^{1}H-NMR

[b] Relative stereochemistry has been determined by X-ray crystallography of acetylated **14c**

Electron releasing substituents R in aldehyde **2** increase the amount of mixed dimer **14** compared to **12** (entries 1-4 and 7). On the other hand, electron attracting alkyl groups (conjugation) disfavor the formation of 1,3-dioxan-4-ol acetals (entries 5 and 6). The *cis / trans* ratio of the dioxanols does not seem to depend on the steric effects caused by the R substituent.

2.2.4. Stability of the 1,3-dioxan-4-ols

We attempted to isolate some of the dioxanols, however, without success. The dioxanol decomposed during flash chromatography and vacuum distillation even at 0 °C. Our NMR studies (*vide supra*) showed that the formation and stability of 1,3-dioxan-4-ols is very temperature dependent. At 0 °C the monomerization is very slow. Thus, dioxanols like **14** slowly decompose under reduced pressure (< 1 mmHg) and the liberated HPA dimerizes to **12** during evaporation.

Späth *et al.* have isolated some 1,3-dioxan-4-ols after acetylation (13). Thus, we were able to study the formed dioxanol diastereomers from the reaction mixture with ^{1}H-NMR experiments in CDCl$_3$. The 1,3-dioxanols were acetylated and isolated with high purities. Alternatively, the protection can be carried out with *para*-nitrobenzoyl chloride giving a yellowish solid product.

A series of ^{1}H-NMR experiments was performed in different solvents in order to find out how the solvent affects on the mixed dimers of structure **14**. Dioxanol **14b** was used as a test compound and the decomposition was followed as a function of time at room temperature. After three days **14b** was partly decomposed in CDCl$_3$ (61%) and benzene-d$_6$ (33%) but hardly no decomposition was observed in DMSO-d$_6$ (< 1%). DMSO is believed to coordinate with hydroxyl group of the dioxanol and thus stabilize the structure.

Dimers of aldol products having 1,3-dioxan-4-ol structure are rather stable and can be stored at room temperature without decomposition. This was an interesting observation as the mixed dioxanols prepared in this work were highly unstable. One possible explanation might be an intramolecular hydrogen bonding in the dimer of aldol product between the ring oxygen and the hydroxyl group of the side chain at position 2. The possibility was studied by molecular modeling (17) and the minimum energy structure showed potential hydrogen bonding with 1.864 Å bond length (Figure 1). Additionally, the hydrogen bonding creates a 6-membered ring in chair like conformation.
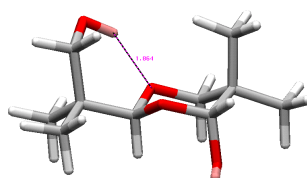
Figure 1. Suggested stabilizing intramolecular hydrogen bonding in dimeric HPA

2.2.5. Stereochemistry of the formed 1,3-dioxan-4-ols

The 1,3-dioxan-4-ols were obtained as a mixture of diastereomers. Despite their thermal instability, the ratio of the diastereomers was successfully determined with ^{1}H-NMR (in CDCl$_3$).

Most of the prepared dioxanols and their acetylated derivatives were oily products. However, 4-acetoxy-5,5-dimethyl-2-t-butyl-1,3-dioxane (Figure 2) was obtained as a solid product. The diastereomers were separated by column chromatography and crystallized from H$_2$O/MeOH. The stereochemistry was assigned through X-ray structure analysis of the major diastereomer which showed the cis enantiomers (2R*,4S*) to be the main products (see Table 1). The unit cell contained both enantiomers of **14c** which are shown in the Figure 2.
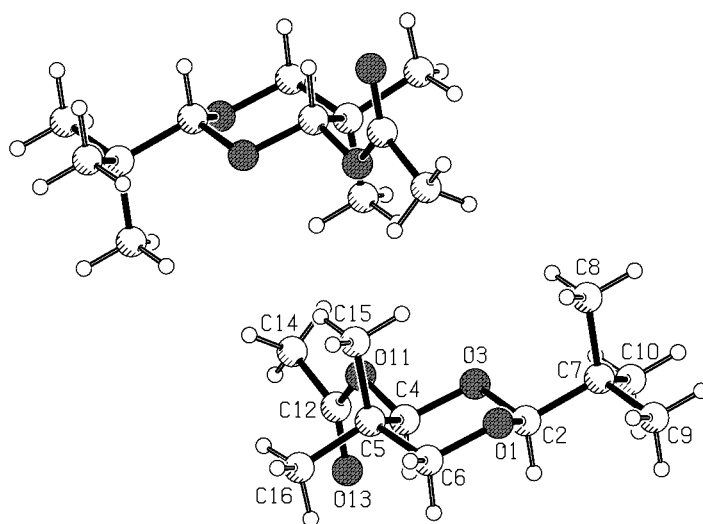
Figure 2.   X-ray crystal structure of 4-acetoxy-5,5-dimethyl-2-*t*-butyl-1,3-dioxane 14c.

The structure of **14c** was in accordance with the results obtained by molecular modeling. Calculations suggested that C2 the alkyl substituent takes equatorial position at the ring and the hydrogen, to be shifted as the hydride in Tishchenko reaction from C2, is always axially positioned (17).The calculations gave two diastereomers with relatively low energies compared to other conformations (Figure 3). Based on their energy difference they should be formed in ratio of 70 to 30 ((*S,R*)* : (*R,R*)*) which is close to experimental results (73:27).
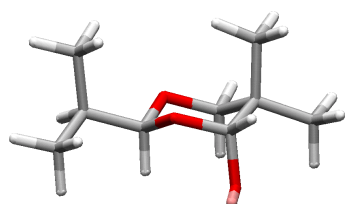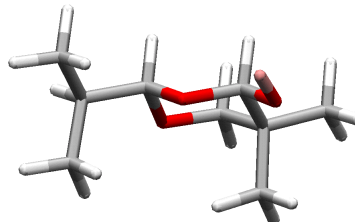
(*S*,*R*)* -171.6 kJ/mol   (*R*,*R*)* -166.7 kJ/mol

Figure 3.

The ratio of *cis* / *trans* diastereomers of **14** remained nearly constant (2:1 in Table 1) regardless of the size of the C2 alkyl group R. Similar results were obtained also by molecular modeling. The substituent at C2 was always equatorially oriented. It is known that the bulkier substituents preferequatorial orientation. In 1,3-dioxane structures the oxygen-carbon bond is shorter than a C-C bond and the equatorial orientation is even more preferred to avoid 1,3-diaxial interactions.

3. Tishchenko esterification of 1,3-dioxan-4-ols

In the homo aldol-Tishchenko reaction, aldoxans (structurally related to **14**) have been suggested as intermediates before conversion to the esters (18). These results provided the starting point for our initial catalyst studies.

3.1. Used reaction conditions

After successful preparation of mixed 1,3-dioxan-4-ols **14**, their further Tishchenko esterification to **16** was investigated (Scheme 5) (II). The reaction can be termed as mixed Tishchenko reaction since an ester is formed between two different aldehydes.
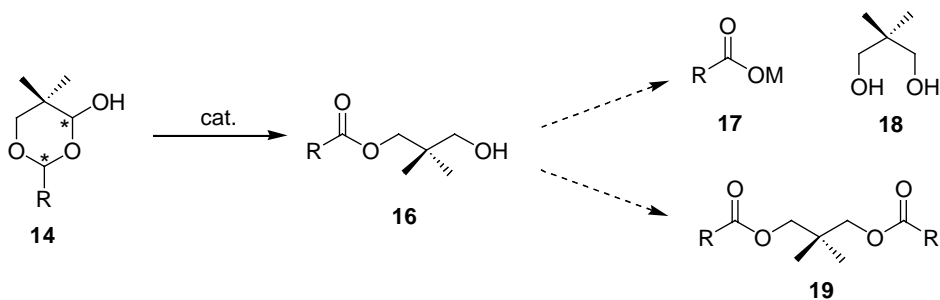
Scheme 5.

Before addition of the catalyst excess aldehyde should be removed to avoid side reactions. Especially the homo aldol-Tishchenko reaction of the enolizable aldehyde excess would give large quantity of several side products which could be difficult to isolate from the desired ones. This limits the spectrum of aldehydes that can be utilised. Higher boiling aldehydes (>100°C) are not practical, as exemplified by 2-ethylhexanal: the dimer **14d** completely decomposed before excess aldehyde was removed.

Progress of the evaporation should also be monitored during the evaporation. If the system was set under reduced pressure (1-2 mmHg at 0 °C) for too long time, the dioxanol **14** started to decompose liberating free, easily evaporating aldehyde. The evaporation was usually followed by GC and sometimes by ^{1}H-NMR.

Leaks in the reaction apparatus cause a partial oxidation of free aldehyde to corresponding acid. This should be taken into account by using larger amount of basic catalyst. The esterification proceeds usually well in the presence of 20-30 mol-% of catalyst.

3.2. The catalyst studies

3.2.1. Studies with the previously used and traditional catalysts

An exceptional Tishchenko esterification of the dimeric HPA in the absence of a catalyst has been reported by Finch (19). In that particular system the reaction was carried out in water and at a rather high temperature. In the patent by Duke *et al.* a related system was used to prepare 1,3-diol monoesters with mixed Tishchenko reaction in good yields but under extreme conditions: high temperature, pressure and long reaction time were used (16). Thus, such methods are not applicable here in the esterification of the mixed 1,3-dioxan-4-ols due to their high instability at elevated temperatures and in the presence of the water.

Alkali and alkali earth metal hydroxides have also been used as the catalysts in Tishchenko esterification (20). With these catalysts a fast hydrolysis of the product esters decrease the yields (step **16**→**17** & **18** in Scheme 5). The cases have been reported usually in Tishchenko esterification of dimeric HPA **12** to corresponding monoester which is commercially available product for needs of polymer technology.

We studied some metal hydroxides in order to find out a catalyst capable of catalyzing the esterification step but not hydrolyzing the formed esters (III). Dimeric HPA was used as the test compound due to its good stability and easy reaction monitoring. We suspected that as the cationic nature of the metal in hydroxides increases (Li > Na > K) hydrolysis is accelerated . Surprisingly $Ba(OH)_2 \times 8H_2O$ gave the fastest reaction out of the tested alkali metal and earth alkali metal hydroxides. However, with metal hydroxides only low isolated yields were obtained, typically 0-35%, and the hydrolysis could not be avoided with any of these hydroxides.

The most common catalysts in the traditional Tishchenko reaction between two monofunctional aldehydes are Lewis acids, typically aluminium alcoholates like $Al(O^iPr)_3$. This catalyst was found to be ineffective in the esterification of dimeric HPA which indicates that sufficient Lewis acidity is not the only requirement for the catalyst. Also SmI_2 which is typical catalyst in Evans-Tishchenko esterification (1.0 M solution in THF) was tested but no esterification was observed.

3.2.2. 1,3-Diol based monoalcoholates

The 1,3-diol based monoalcoholate catalysts were found to solve the problem of hydrolysis of product monoesters (III). These catalysts also give very fast esterification of 1,3-dioxan-4-ols to the desired esters (step **14**→**16** in Scheme 5). For comparison, when 4.5 M LiOH solution was used as the catalyst, the esterification was complete in 45 minutes but in the case of monoalcoholates the completion was achieved in 15 minutes giving very clean reaction and high yields up to 93%. Only a trace of side products from homo aldol-Tishchenko reaction were observed and no hydrolysis of the product esters. The most important target molecule **16** (R = *i*-Pr) was obtained in 86% isolated yield when a monolithium alcoholate of 2,2-dimethyl-1,3-propandiol **20** was used as the catalyst (30 mol-% in THF).

It was soon observed that these diol based alcoholate catalysts react with rather fast transesterification with the product monoester. Therefore it is essential that the structure of the used diol of the catalyst is exactly the same as the diol part of the product monoester. This was proven with deuterium labeled 1,3-diol monoalcoholate catalyst. If the alcoholate catalyst is bearing a different structure than diol part of the product ester the transesterification gives a new ester as a side product. Additionally, in the case of similar 1,3-diol structure in the product ester and in the catalysts the counter cation can be interchanged between these due to similar acidity of the hydroxyl proton. This leads to the formation of diester via transesterification (step **16**→**19** in Scheme 5). The amount of diester **19** slowly increases if the product mixture is heated for longer time in the presence of the catalyst.

The efficiency of the 1,3-diol based monoalcoholate catalysts is most probably due to the intramolecular hydrogen bonding which makes the coordination of the lithium to oxygen weaker and the reactivity of the catalyst higher. The possible isomers of the catalyst have been presented in Scheme 6 where **20a** is believed to be the most reactive one.

20a	**20b**	**20c**
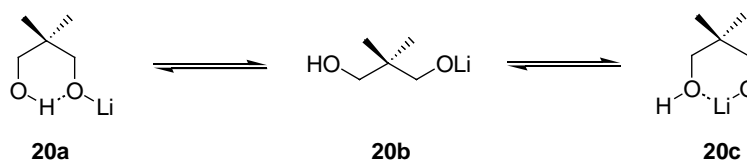
Scheme 6.

3.3. Discussion of the mechanism of esterification of the 1,3-dioxan-4-ols

Previously Merger and co-workers have suggested that the intramolecular Tishchenko esterification 1,3-dioxan-4-ols to takes place via open chain hemiacetal type transition state (18a). However, the existence of such an open chain hemiacetal was not observed in our NMR experiments. During this work we observed that the Lewis acidity of the catalysts alone is not enough to proceed Tishchenko esterification of the 1,3-dioxan-4-ols

but strongly basic catalysts like alkali metal and earth alkali metal hydroxides and alcoholates were needed. This indicates that the initial step of the mechanism is the deprotonation of the C4 hydroxyl group of **14**. The cation then coordinates to the ring 3-oxygen to give **21** and activates the intramolecular hydride shift via a bicyclic [6,6]-membered transition state **22** to give the 1,3-diol monoester **16** (Scheme 7). Similar bicyclic transition state has been reported (21).
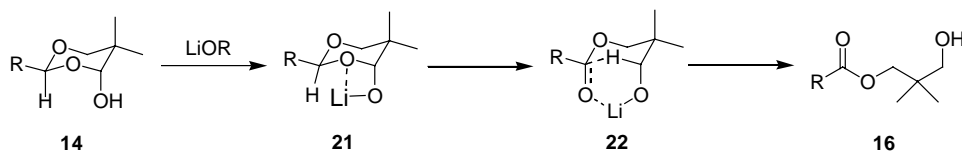
Scheme 7.

4. The aldol-Tishchenko reaction

Aldol Tishchenko reaction can be further divided in two sub classes: hetero and homo aldol-Tishchenko. In the former one, two different aldehydes or an aldehyde and a ketone are used to produce monoester of 1,3-diols. In the latter case, only one enolizable aldehyde is used which reacts first to aldol product and then to monoester. In this work we focused on the homo aldol-Tishchenko reaction due to its importance for the paint industry and easiness to scale up. The mechanism and kinetic studies have been reported previously by Streiwieser (22).

4.1. Homo aldol-Tishchenko reaction

We decided to utilize 1,3-diol monoalcoholates as catalysts in the preparation of 1,3-diol monoesters with homo aldol-Tishchenko reaction starting from enolizable monofunctional aldehydes. Our work was focused on the reaction of isobutyraldehyde **23** to (2,2-dimethyl-3-hydroxyl-1-isopropyl-propyl)-2-methylpropionate **28** and (3-hydroxy-2,2,4-trimethylpentyl)-2-methylpropionate **29** because these two are consumed in huge volumes in the paint industry (Scheme 8) (IV). These monoesters have been earlier prepared in the presence of several different catalysts with varying yields: $LiWO_2$ (55%) (23), $Fe_3(CO)_{12}$ in pyridine (83%) (24), KOH (45%) (25), 10% NaOH in H_2O (78%) (26), $Mg(Al(OC_4H_9)_4)_2$ (45%) (27), $MgAl^nBu$ (21%) (28). The stereochemistry and the effect of chiral catalysts on this reaction have also been studied by Mäeorg, but no clear stereoselectivity has been obtained due to reversibility of the steps (29).
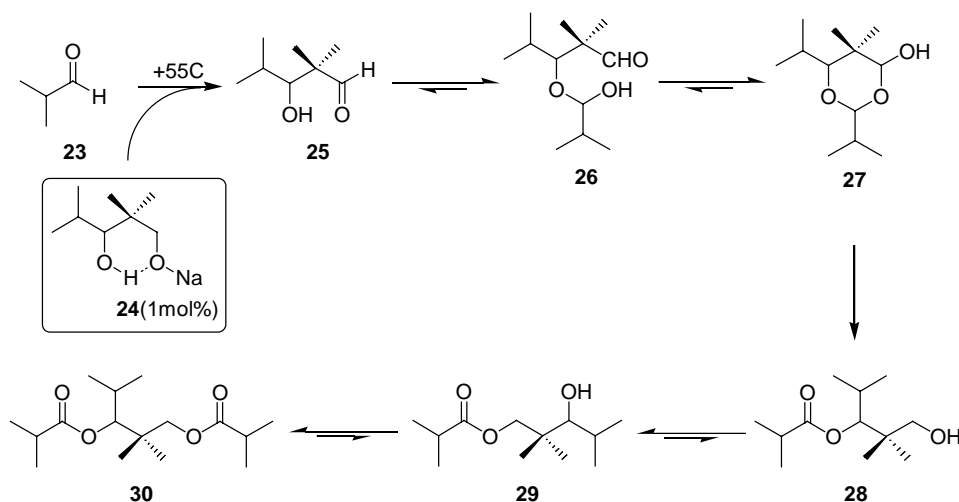
Scheme 8.

In industrial cases the reaction is usually carried out in water solution of the alkali metal hydroxides, typically in 78% yield (26). However, such reaction environment gives a fast and irreversible hydrolysis of the product esters and extra costs arise from treatment of waste water. In some processes diluted alkali metal hydroxide catalyst solutions have been used in order to diminish the hydrolysis, but still the amount of formed waste water is quite significant (30). In the system developed during this work both hydrolysis and the formation of waste water were avoided giving the product monoesters in the highest yield reported so far.

During the work we found that there are two literature examples closely related to our method but both are quite narrow in scope and have some disadvantages. Schwenk *et al.* have studied previously the same reaction under water free conditions by using 2-propanol as the solvent and sodium isopropionate as the catalyst (31). Hagemeyer Jr. *et al.* have also patented the use of sodium isopropoxide in isopropanol to give diol monoesters in 90% yield (32). However, in their method the transesterification product between the product ester and the catalyst reduces the yield giving isobutyl isobutyrate in 3.7-47% yields (depending on the reaction temperature). The reaction was studied only with one catalyst and in one solvent. Additionally, they used longer reaction times and higher temperatures.

The results of our most representative experiments are collected in the Table 2 (IV). As expected, the reaction was both solvent and counter cation dependent but also sensitive towards acid and water content of the aldehyde used. Also, the diol moiety in the catalyst must be the same as the diol part in final product monoester to avoid transesterification. The addition time of the aldehyde and the reaction time were optimized (for example entries 1-3 in Table 2). The aldehyde should be added as quickly as possible (in two minutes in laboratory experiments) and the reaction temperature should be kept stable at +55 °C (±3 °C) with external cooling and later with heating.

After a 30 minutes holdup time the reaction was quenched with a small amount of 2M HCl.

The solvent effect was investigated by using 2,2,4-trimethyl-1,3-pentanediol based monoalcoholates as the catalyst. The polarity of the solvent had a significant role and the best conversion of the aldehyde to products was obtained in polar aprotic THF. In THF the counter cation of the enolate is strongly solvated which makes the enolate more reactive and gives a faster aldol step. In apolar solvents (e.g. hexanes) the conversion of the aldehyde to the product monoesters was lower due to the slower aldol step.

Another problem to be solved was the cation interchange and further transesterification between the product ester **28** and the catalyst giving diester **30** as an undesired side product. This prompted us to study different counter cations in order to minimize the rate of the transesterification of the monoesters **28** and **29** to diester **30**. The catalysts examined (Figure 4) gave clear differences on the product distribution. Some results of these experiments are collected in Table 2.
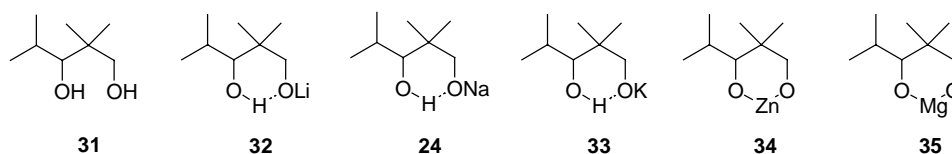

Figure 4.

When the coordination of the counter cation becomes weaker the formation of the diester **30** gets slower. This can be clearly seen from entries 5-7 in Table 2. In the case of potassium the formation of **30** was not observed at all but the rate of the aldol reaction was also slower giving lower overall conversion of isobutyraldehyde **23**.

Table 2. Homo-aldol-Tishchenko reaction of isobutyraldehyde (IV)

Entry	Cat.[a]		Solv.	Addition Time	Time (reaction)	31[b]	28[b]	29[b]	30[b]	23[b,c]	Yield[d] (28 & 29)
1	**32**	0.067M	Hex	2.5 min.	40 min.	14.9	22.2	36.5	8.7	17.7	73%
2	**32**	0.1M	Hex	2 min.	60 min.	15.0	23.8	36.1	14.8	10.3	65%
3	**32**	0.1M	Hex	2 min.	30 min.	6.6	32.4	40.8	1.3	19.0	87%
4	**24**	0.25M	THF	3.5 min.	20 min.	5.1	22.8	34.0	1.3	36.7	76%
5	**32**	0.1M	THF	2 min.	30 min.	10.6	23.7	45.9	9.4	10.5	77%
6	**24**	0.1M	THF	2 min.	30 min.	8.3	27.2	50.8	3.1	10.6	92%
7[e]	**33**	0.1M	THF	2 min.	30 min.	4.3	17.1	29.1	0.0	49.5	41%
8	**34**	0.1 M	THF	2 min.	33 min.	1.6	23.2	32.5	0.0	43.0	57%

[a] 1.0 mol-% of catalyst was used in every experiment

[b] mol-% of the product mixture (measured by ^{1}H-NMR)

[c] contains both unreacted free aldehyde and aldoxan (measured by ^{1}H-NMR)

[d] (wt)% of **28** & **29** (compared to theoretical yield if all **23** would have reacted to **28** & **29**)

[e] prepared from diol **31** and KHMDS in THF

In the series of experiments with alkali metals the best conversion was obtained with the lithium catalyst **32** and the worst with the potassium **33**. However, the rate of the formation of diester **30** was the fastest with lithium and the slowest with potassium counter cations.

The zinc alcoxide catalyst **34** was suspected to give slower ester interchange due to its weaker coordination to the carbonyl oxygen of the product esters **28** and **29**. After 35 minutes reaction time only a trace of the diester **30** was formed but the conversion of isobutyraldehyde to monoesters was also low, only 57%. The preparation of the catalyst **35** was unsuccessfull.

As a conclusion, in laboratory scale the sodium catalyst was found to give the best yields in reasonable time. In larger scale (2000 cm^3 reactor) the cooling capacity was found to be a limiting factor. The culprit is the very exothermic aldol reaction. Based on our results, this problem could be solved by using a less active potassium alcoholate 33 which would give more sluggish aldol reaction. Also the use of a non polar solvent, like hexanes instead of THF, in the catalyst solution would give slower aldol reaction and make the temperature control of the reactor more facile. Additionally, the aldehyde used in the reaction should be acid and water free in order to avoid destruction of the catalyst and the formation of detrimental precipitation in the reactor.

5. Utilization of aldehydes in a new Taxol™ A-ring synthesis route via Shapiro reaction

Taxol™ **36** is the most effective anticancer drug in the market towards e.g. ovarian and breast cancers (33). The compound has been originally isolated from the bark of *Taxus Brevifolia* in low concentrations. In our work a short synthesis route to produce Taxol™ A-ring has been created and especially formaldehyde can be utilized in a final step of the Shapiro reaction to produce vinyl alcohol moiety. Previously used strategies to synthesize A-ring moiety can be divided into three main approahes: Diels-Alder reaction (34), modification of cyclohexanones (35) and ene reaction (36).
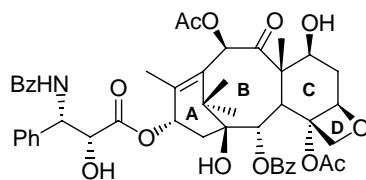
36

Our pathway to produce Taxol™ **36** A-ring in an efficient way is presenteded in Scheme 9 (V). This synthesis route developed is the shortest one reported so far: only four reaction steps in 38 % overall yield from 2-methyl-1,3-cyclohexadione **37** to alcohol **42**.
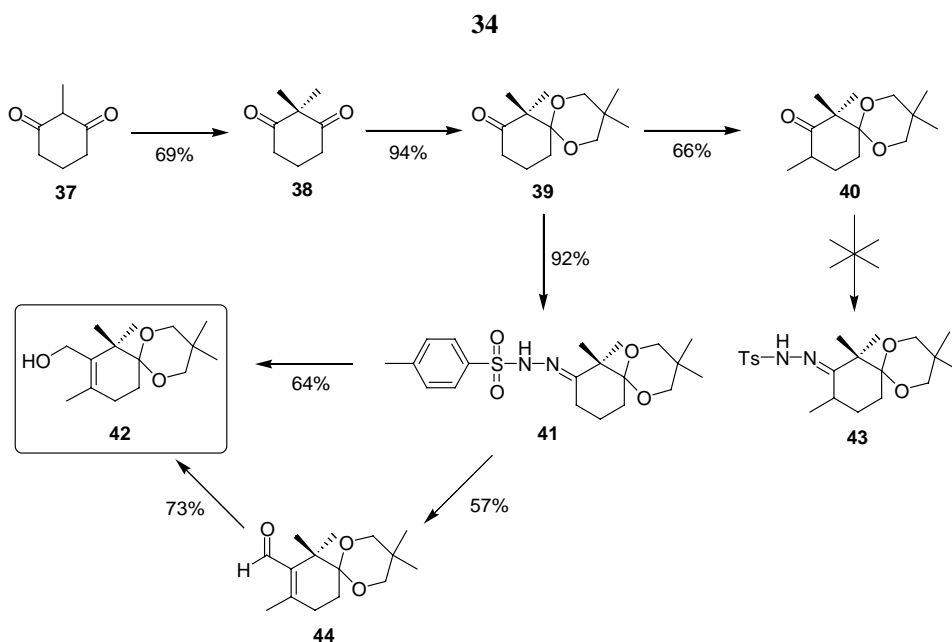
Scheme 9. A new synthetic pathway to prepare Taxol™ A-ring moiety

The reaction steps **37** → **38** → **39** are also a part of an earlier approach reported by our group (37). The Shapiro reaction was utilized as the key step in this new pathway allowing the use of various different electrophiles, like aldehydes, as the electrophiles leading to the desired functionality in the product. Ketone **39** was converted to different arylsulfonylhydrazones in high yields (79-94 %) and these were studied in the Shapiro reaction (step **41** → **42** in Scheme 9). Tosylhydrazone **41** was found to be an ideal choice because of sufficient stability of its dianion.

The tosylhydrazone **41** was first converted to its dianion **45** at –55 °C by treatment with *n*-BuLi followed by exhaustive methylation with CH₃I (Scheme 10). Addition of another equivalent of *n*-BuLi gave again a dianion which was allowed to decompose to the vinyl anion **46** by heating up to room temperature. When the decomposition of **45** was carried out at lower temperatures (0-10 °C) the formation of vinyl anion was incomplete before the addition of electrophile and a significant amount of methylated hydrazone was obtained as the side product.
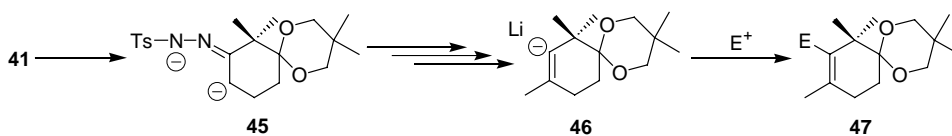
Scheme 10. The Shapiro reaction of tosylhydrazone 41

Formaldehyde was introduced as the electrophile to the vinyl anion **46** giving the target alcohol **42** directly. Different forms of formaldehyde were studied and the use of excess paraformaldehyde gave the highest 64% isolated yield of **42**. Desired alcohol **42** was obtained also with other isomers of formaldehyde but in lower yields (with gaseous CH_2O 28% and with trioxane 22%).

Alternative pathways with different electrophiles towards **42** were also attempted. As seen in Scheme 9 a two step procedure via **44** was successful. Vinyl anion **46** of tosylhydrazone was converted to aldehyde **44** in 57% yield upon reaction with DMF. The aldehyde was then reduced to **42** with $LiAlH_4$ in 73% yield. Danishefsky and co-workers have prepared A-ring block via an aldehyde related to **44**. In their pathway the aldehyde was prepared in 7 steps with 13 % overall yield (38).

Lithio vinyl anions can be basic enough to deprotonate solvent THF slowly and with increasing rate at elevated temperatures (39). This was always observed also in our experiments. With different arylsulfonylhydrazones we observed that even the first dianion of trisylhydrazone partly decomposed to its vinyl anion even at –78 °C. This leads to incomplete methylation of the dianion. Therefore, trisylhydrazone could be used in an alternative pathway where methylation of the dianion is not required. We attempted to prepare an arylhydrazone of readily methylated ketone **40** (steps **39** → **40** → **43** in Scheme 9.) which could be converted to its dianion and rapidly decomposed to the vinyl anion. However, the formation of even the tosylhydrazone **43** from ketone **40** was found to be impractical. Obviously, increased steric hindrance plays a crucial role in the reaction, as some highly reactive electrophiles (e.g. dimethylcarbonate and methylchloroformiate) refused to react with the vinyl anion in the step from **41** to **42**.

6. Summary

A new and selective method to produce 1,3-diol monoesters with crossed Tishchenko reaction with high yields has been developed. Aldol products are used as starting materials with some volatile, monofunctional aldehydes in the presence of 1,3-diol monoalcoholate based catalysts. This work also provides new information on the possibilities and limitations in preparing and isolating the 1,3-dioxan-4-ol products as well as on their stereochemistry, stability and further Tishchenko esterification. The product 1,3-diol monoesters can be utilized for example as the coalescing agents in paint industry, but also as building blocks in the synthesis of more complex molecules.

Another significant entirety in this thesis is a process to produce 1,3-diol monoesters from enolizable α-alkylated aldehydes under water free reaction conditions utilizing homo aldol-Tishchenko reaction. The process gives the highest yields reported so far. The aldehyde utilized should be water and acid free in order to keep the amount of the 1,3-diol monoalcoholate catalyst as low as possible.

In both of these topics the 1,3-diol based alcoholate catalysts play a key role to give faster and more selective reaction. These catalysts are also considerably more advantageous compared to previously used metal hydroxides which give fast and irreversible hydrolysis and large amount of waste waters. The catalyst experiments also gave new knowledge and tools to control not only the homo aldol-Tishchenko reaction but also the Tishchenko esterification of 1,3-dioxan-4-ols to corresponding 1,3-diol monoesters.

During the studies a new pathway to Taxol™ A-ring building block was also developed. The Shapiro reaction was utilized as the key step which allows the use of aldehydes as the electrophiles providing the shortest and maybe the best way to prepare the target alcohol. Especially, different forms of formaldehydes were investigated and the best yields were obtained with paraformaldehyde.

7. References and notes

I   Törmäkangas, O. P.; Koskinen, A. M. P., 'The Tishchenko Reaction and Its Modifications in Organic Synthesis', *Recent Res. Devel. Organic Chem.* **2001**, *5*, 225-255.

II   Törmäkangas, O. P.; Saarenketo, P.; Koskinen, A. M. P., 'Selective Mixed Tishchenko Reaction via Substituted 1,3-Dioxan-4-ols', *Org. Proc. Res. & Dev.* **2002**, *6*, 125-131.

III Törmäkangas, O. P.; Koskinen, A. M. P., 'Monoalcoholates of 1,3-Diols as Effective Catalysts in the Tishchenko Esterification of 1,3-dioxan-4-ols', *Tetrahedron Lett.* **2001**, *42,* 2743-2746.

IV Törmäkangas, O. P.; Koskinen, A. M. P., 'Fast Aldol-Tishchenko Reaction Utilizing 1,3-Diol Monoalcoholates as the Catalysts', *Org. Proc. Res. & Dev.* **2001**, *5*, 421-425.

V   Törmäkangas, O. P.; Toivola, R. J.; Karvinen, E. K.; Koskinen, A. M. P., 'A Short and Convenient Way to Produce the Taxol™ A-Ring Utilizing the Shapiro Reaction', *Tetrahedron* **2002**, *58*, 2175-2181.

1.   a) Casiraghi, C.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* 2000, *100* (6), 1929-1972. b) Machajewski, T. D.; Wong, C.-H.; Lerner, R. A. *Angew. Chem., Int. Ed.* 2000, *39* (8), 1352-1374. c) Mahrwald, R. *Chem. Rev.* 1999, *99* (5), 1095-1120. d) Cowden, C.; Paterson, I. *Org. React.* 1997, *51*, 1-200.

2.   a) de Graauw, C. F.; Peters, J. A.; van Bekkum, H.; Huskens, J. *Synthesis* 1994, 10, 1007-1017. b) Pickart, D. E.; Hancock, C. K. *J. Am. Chem. Soc.* 1955, *77*, 4642-4643.

3.   Woodward, R. B.; Wendler, N. L.; Brutschy, F. J. *J. Am. Chem. Soc.* 1945, *67* (9), 1425-1429.

4.   a) Bowden, K. *Chem. Soc. Rev.* 1995, *24* (6), 431-435. b) Cordes, E. H.; Bull, H. G. *Chem. Rev.* 1974, *74* (5), 581-603.

5.   a) Kharasch, M. S.; Snyder, R. H. *J. Org. Chem.* 1949, *14*, 819-835. b) Pfeil, E. *Ber.* 1951, *84* (2), 229-245.

6.   a) March, J. *Advanced Organic Chemistry; Reactions, Mechanisms and Structure*, 4th ed., 1993, John Wiley & Sons., p. 397. b) Otera, Yano, Kawabata, Nozaki *Tetrahedron Lett.* 1986, *27*, 2383.

7. Similar to aldol but usually in presence of formaldehyde, March, J. *Advanced Organic Chemistry; Reactions, Mechanisms and Structure*, 4th ed., 1993, John Wiley & Sons., p. 955.

8. Kirk, R. E.; Othmer, D. F. *Encyclopedia of Chemical Technology*, 3rd ed., Wiley Interscience, New York, 1984, vol. 11, p. 966-967.

9. Chamberlin, R. A.; Bloom, S. H. *Org. React.* 1990, *39*, 1-83.

10. a) Amberg, W.; Seebach, D. *Chem. Ber.* 1990, 2413-2428. b) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Act.* 1987, *70*, 448-464.

11. Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* 1996, *61*, 8317-8320.

12. Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* 1999, *1* (9), 1383-1385.

13. Späth, E.; v. Szilâgyi, I. *Ber. Dtsch. Chem. Ges.* 1943, *76* (9), 949-956.

14. Kula, J.; Quang, T. B.; Sikora, M. *Tetrahedron: Asymmetry* 2000, 11, 943-950.

15. Merger, F.; Duembgen, G.; Fuchs, W. (BASF A.-G.) Ger. Offen. 2,233,357, 1974; *Chem. Abstr.* 1974, *80*, 95282g.

16. Duke, R. B.; Perry, M. A. FR Pat. 1414216 (Eastman Kodak Co), 1963; *Chem. Abstr.* 1966, *64*, p11090c.

17. MacroModel 6.0; Monte Carlo, solvent $CDCl_3$, MMFF.

18. a) Fouquet, G.; Merger, F.; Platz, R. *Liebigs Ann. Chem.* 1979, *46*, 1591-1601. b) Villani, F. J.; Nord, F. F. *J. Am. Chem. Soc.* 1946, *68*, 1674-1675. c) Kirk, R. E.; Othmer, D. F. *Encyclopedia of Chemical Technology*, 3rd ed.; Wiley-Interscience: New York 1984; vol. 4, p 379.

19. Finch, G. K. *J. Org. Chem.* 1960, *25*, 2219-2220.

20. a) Merger, F. Duembgen, G. (BASF A.-G.) Ger. Offen. 2,233,897, 1974; *Chem. Abstr.* 1974, *81*, 25110w. b) Fr. 1,578,477, 1969; *Chem. Abstr.* 1970, *72*, 110827u.

21. a) Originally presented in SmI_2 promoted Reformatsky-type reactions: Molander, G. A.; Etter, J. B. *J. Am. Chem. Soc.* 1987, *109*, 6556-6558. b) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* 1990, *112*, 6447-6449.

22. Abu-Hasanayn, F.; Streitwieser, A. *J. Org. Chem.* 1998, *63*, 2954-2960.

23. Villacorta, G, M.; San Filippo, Jr., J. *J. Org. Chem.* 1983, *48* (8),1151-1154.

24. Ito, K.; Kamiyama, N.; Nakanishi, S.; Otsuji, Y. *Chem. Lett.* 1983, 657-660.

25. McCain, J. H.; Theiling, L. F. Trisubstituted hydroxyalkyl alkanoates, U.S. Pat. 3718689, 27.2.1973. *Chem. Abstr.* 1973, *78*, *135*694k.

26. Perry, M. A.; Hagemeyer Jr., H. J. U.S. Pat. 3291821 (Eastman Kodak Co.), 1966; *Chem. Abstr.* 1967, *66*, p37420a.

27. Villani, F. J.; Nord, F. F. *J. Am. Chem. Soc.* 1947, *69*, 2605-2607.

28. Kuplinnski, M. S.; Nord, F. F. *J. Org. Chem.* 1943, *8*, 256-270.

29. Loog, O.; Mäeorg, U. *Tetrahedron Asymmetry* 1999, *10*, 2411-2415.

30. Heinola, K.; Kulmala, K.; Lindfors, L.-P.; Hakanpää-Laitinen, H.; Rintala, L.; Lehtinen, V.-M. (Neste Oy) WO 9824752 A1 19980611. *Chem. Abstr.* 1998, 394313.

31. Schwenk, U.; Becker, A. *Liebigs Ann. Chem.* 1972, *756*, 162-169.

32. Hagemeyer, Jr., H. J.; Wright, Jr., H. W. U.S. Pat. 3091632 (Eastman Kodak Co.), 1963; *Chem. Abstr.* 1963, *59*, p13828g.

33. a) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* 1994, *33*, 15-44. b) Kingston, D. G. I. *Pharmac. Ther.* 1991, *52*, 1-34.

34. a) Carballares, S.; Craig, D.; Lane, C. A. L.; MacKenzie, A. R.; Mitchell, W. P.; Wood, A. *Chem. Commun.* 2000, 1767-1768. b) Funk, R. L.; Yost, III, K. J. J. Org. Chem. 1996, *61*, 2598-2599. c) Frost, C.; Linnane, P.; Magnus, P.; Spyvee, M. *Tetrahedron Lett.* 1996, *37* (51), 9139-9142. d) Nicolaou, K. C.; Liu, J.-J.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* 1995, *117*, 634-644. e) Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* 1992, *57*, 4043-4047. f) Lin, J.; Nikaido, M. M.; Clark, G. J. *J. Org. Chem.* 1987, *52*, 3745-3752.

35. a) Nivlet, A.; Dechoux, L.; Martel, J.-P. Proess, G.; Mannes, D.; Alcaraz, L.; Harnett, J. J.; Le Gall, T.; Mioskowski, C. *Eur. J. Org. Chem.* 1999, 3241-4249. b) Bourgeois, D.; Lallemand, J.-Y.; Pancrazi, A.; Prunet, J. *Synlett*, 1999, 10, 1555-1558. c) Karvinen, E. K.; Koskinen, A. M. P. *Tetrahedron* 1995, *51* (27), 7555-7560. d) Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* 1993, *58*, 4989-4992.

36. a) Wennerberg, J.; Polla, M.; Frejd, T. *J. Org. Chem.* 1997, *62*, 8735-8740. b) Polla, M.; Frejd, T. *Tetrahedron*, 1993, *49* (13), 2701-2710.

37. Toivola, R. J.; Koskinen, A. M. P. *Synlett* 1996, 1159-1161.

38. Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* 1993, *58*, 4989-4992.

39. Stemke, J. E.; Bond, T. F. *Tetrahedron Lett.* 1975, 22+23, 1815-1818.

Original Papers

The original papers have been reprinted with permission from

Transworld Research Network
        Recent Research Developments in Organic Chemistry (paper I)

The Royal Society of Chemistry and American Chemical Society
        Organic Process Research and Development (papers II & IV)

Elsevier Science Ltd.
        Tetrahedron Letters (paper III)
        Tetrahedron (paper V)