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Hydride Reduction of a Lactate Ester: Optimisation and Scale-Up

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Abstract:

The two-step synthesis of (2*S*)-2-(tetrahydropyran-2-yloxy)-propane-1-ol was selected for fine chemical scale-up. The first step, an acid-catalyzed protection of ethyl (*S*)(−)-lactate with 3,4-dihydro-2H-pyran, could be performed without solvent. The reaction enthalpy was determined to be −48 kJ/mol ethyl (*S*)-(−)-lactate, ensuring safe scale-up. The crude reaction mixture was used in the second step, the hydride reduction. For the reduction of the protected ester a clear solution of 1 M $LiAlH_4$ in THF was used. The reaction enthalpy was determined to be −313 kJ/mol ethyl (2*S*)-2-(tetrahydropyran-2-yloxy)propionate, and the work-up was optimised with experimental design techniques. Combination of all experimental and theoretical results resulted in a master recipe for a 10-dm^3 scale synthesis of (2*S*)-2-(tetrahydropyran-2-yloxy)propane-1-ol.

Introduction

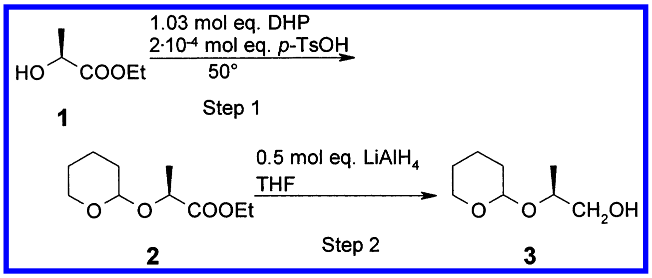
Fine chemical process research and development limits itself in various aspects. In contrast to bulk chemicals, fine chemicals are usually produced with multi-purpose (semi) batch-wise operated equipment and have a relatively short lifetime. The demands for a short time-to-market of new fine chemicals asks for a challenging batch process design. The fine chemical process research and development requires a fast and a systematic approach in the scale-up of fine chemical processes leading to an early recognition of scale-up surprises. This can lead to thorough understanding of the failures and key issues for scaling-up processes prior to (pilot) plant implementation.

To design tools and a methodology for fine chemical scale-up the synthesis of a chiral synthon, (2*S*)-2-(tetrahydropyran-2-yloxy)propane-1-ol (**3**), was selected. This chiral building block can be used in the synthesis of liquid crystalline disc-shaped molecules[1]

For the two-step synthesis[2] of (**3**), as depicted in Scheme 1, ethyl (*S*)(−)-lactate (**1**) was used as starting material. In the first step **1** is protected with 3,4-dihydro-2H-pyran using *p*-toluene sulphonic acid as the acid catalyst. In the second step the protected lactate ester **2** is reduced with $LiAlH_4$.

(*S*)(+)-Propane-1,2-diol being an interesting chiral C_3-synthon for other applications can also be synthesised by deprotection of **3**. This indirect route is preferred over the direct reduction of ethyl (*S*)(−)-lactate (**1**). Advantages of the indirect synthesis of (*S*)(+)-propane-1,2-diol are the absence of hydrogen production, lower solubility of intermediates in water, and less consumption of the expensive $LiAlH_4$.

Scheme 1



An extensive study was initiated to design the optimal process for the production of (2*S*)-2-(tetrahydropyran-2-yloxy)propane-1-ol (**3**) on a 10-dm^3 scale in a fully automated (semi)batch-wise operated miniplant. In this design study the reactions are optimised, taking into account process safety as well as environmental considerations.

Synthesis

For the optimisation and scale-up study literature recipes had to be adjusted and further investigated. Diethyl ether is generally used[2−4] as a solvent in both acid-catalyzed protection reactions and reduction reactions with $LiAlH_4$. However, in a large-scale protection (step 1) and reduction reaction (step 2) diethyl ether is not a suitable solvent due to its flammability and potential peroxide formation. Since both the protection as well as the reduction with $LiAlH_4$ are exothermic reaction steps, the reaction enthalpy for both steps had to be determined.

To select the best solvent for the acid-catalyzed protection of ethyl (*S*)(−)-lactate (**1**) tetrahydrofuran (THF), *tert*-butyl methyl ether (MTBE), and toluene were screened as alternative solvents on small scale (100 mL). The concentration of ethyl (*S*)(−)-lactate (**1**) was 5 kmol/m^3 solvent and that of the catalyst was 0.02 mol % based on **1**. The reaction temperature was kept at 50 °C by dropwise addition of 3,4-dihydro-2H-pyran. Thus, the reaction proceeded under

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"starving conditions". To force the reaction to complete conversion of **1** an excess of 3% 3,4-dihydro-2H-pyran was added. Reactions using THF or MTBE as solvent were much slower than those using toluene. This presumably results from hydrogen bonding between the catalyst and the two former solvents.

To reduce the number of operations and the amount of solvent the protection reaction was also investigated in the absence of solvent. In that case the crude reaction mixture might be used as such in the subsequent reduction step. Performing the reaction without solvent did not induce product loss. The crude yield determined by GC analysis was 97%. The only difference with the reactions in a solvent was a stronger temperature rise during the reaction due to the higher concentration.

To ensure proper chemical control of the reaction on a larger scale, the reaction enthalpy was determined for a 1-dm^3 isothermal reaction at 323 K to be −48 kJ/mol ethyl (*S*)-(−)-lactate (**1**). Since the reaction takes place under "starving conditions", the maximum allowed reaction temperature of 50 °C will be maintained by the addition rate of 3,4-dihydro-2H-pyran.

Optimisation of the reduction step started with 100-mL-scale experiments. Addition of a clear solution of 1 M $LiAlH_4$ in THF to the crude reaction mixture gathered from the protection reaction was chosen due to three main advantages. First it is commercially available, second the addition of a transparent solution is easier than the addition of a suspension, and finally, the risk of accumulation of the reductant during the addition is limited. The initial temperature for the reduction step was 0 °C. The feed rate of the $LiAlH_4$ solution determined the temperature rise of the reaction mixture. To safely scale up this instantaneous reaction the reaction enthalpy of the reduction was determined first. It amounted to be −313 kJ/mol protected ester (**2**) for a 1 dm^3 reaction at 50 °C. Since the reaction takes place under "starving conditions", the maximum reaction temperature will be governed by the addition rate of the $LiAlH_4$ solution. To force the reaction to completion an excess of 1 mol % of $LiAlH_4$ was used.

To obtain pure (2*S*)-2-(tetrahydropyran-2-yloxy)propane-1-ol (**3**), the reaction mixture was subjected to an effective work-up and subsequent purification by distillation. The method to work up the reaction mixture described in the literature is by adding per kilogram consumed $LiAlH_4$: 1 dm^3 water, 1 dm^3 15% caustic soda, and 3 dm^3 water, in the given sequence.[5] Although gel formation was observed with this work-up procedure, a perfectly filterable suspension was obtained after vigorous stirring. The solid particles were separated by filtration, and the solid residue was washed with four equal amounts of THF. The solvent was evaporated, and the residual product was purified by distillation. The yield after distillation was 96%.

Fractional Factorial Design

An instantaneous reaction has no advantages if the work-up is slow or difficult or when a lot of product is lost. The effect of the stirring speed, the temperature, and the used base on the yield and the filtration time was not known. To maximize the yield, implying a good filterability, the process conditions during work-up were optimised using a fractional factorial design.

Table 1. **Variables and minimum and maximum levels used in the factorial design**

X_i	variable	(+)	0	(−)
X_1	stirring speed (rpm)	400	300	200
X_2	base	LiOH	LiOH/NaOH (1:1)	NaOH
X_3	temperature (°C)	50	37	25
X_4	stirring afterward (min)	30	2	2

Table 2. **Fractional factorial design: experimental matrix and results**

	variables					responses	
expt	X_1	X_2	X_3	X_4	t_{filt} (min)	WE_{ff} %	Y_{tot} %
1	−	−	−	−	3	85	95
2	+	−	−	+	3	92	93
3	−	+	−	+	6	84	88
4	+	+	−	−	4	84	92
5	−	−	+	−	7	93	85
6	+	−	+	+	2	89	95
7	−	+	+	−	2.75	85	97
8	+	+	+	+	2.5	88	84
9	0	0	0	−	2	88	95
2*	+	−	−	+	3	91	92

The selected variable process parameters for a 2^{4-1} fractional factorial design were stirring speed (*N*) of the pitched-blade stirrer, temperature (*T*), and the base used in the work-up (B). Neglecting the three-factor interaction of *N*, B, and *T*, the stirring time *R* was introduced as a fourth variable in an eight experiments factorial design. The stirring time *R* is the time between the visual change of the gel into a suspension and the discharge of the reaction vessel.

The chosen variables and the minimum and maximum considered values of these variables are depicted in Table 1. In the central column the "centre point" experiments are shown. The values are used for 1-dm^3-scale reactions. Because of practical problems during scale-up the values of the variables were partially fixed. A stirring speed lower than 200 rpm was expected to cause problems due to the thickness of the gel, while a translation of energy input to larger scale was considered impossible with a stirring speed exceeding 400 rpm. Temperatures above 50 °C were considered not suitable in view of the close boiling point of THF. NaOH was chosen as a base since it is generally used for the work-up of lithium aluminum hydride reductions and it is cheap. LiOH was chosen as a substitute since lithium salts are already present in the reaction mixture.

In the four variables fractional factorial design three responses were studied: the mean filtration time of four washing steps when triturating the filter cake after every washing step (t_{filt}), the washing efficiency after the first washing step (WE_{ff}), and the total yield after four washing steps (Y_{tot}).

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Table 3. **Model equations per response**[a]

	model equation	R^2	Q^2	RSD
t_{filt}	$3.6 - 0.9X_1 + 0.2X_2 - 0.1X_3 + 1.0X_4 - 0.4X_1X_3 - 0.9X_2X_3$	0.93	0.31	0.77
$\mathrm{WE}_{\mathrm{ff}}$	$87.8 + 0.8X_1 - 2.2X_2 + 1.2X_3 - 1.5X_4 - 0.9X_1X_3$	0.95	0.75	1.07
Y_{tot}	$91.3 - 1.2X_2 - 0.8X_3 - 3.9X_4 - 2.1X_1X_2 + 1.2X_2X_3$	0.98	0.62	1.09

[a] R^2 = correlation coefficient; Q^2 = predictability of model; RSD = residual standard deviation.

Table 4. **Optimal configuration per response**

	N (rpm)	B	T (°C)	R (min)	predicted optimum
t_{filt} (min)	400	LiOH	50	2	0.4
$\mathrm{WE}_{\mathrm{ff}}$ (%)	300	NaOH	50	30	93.0
Y_{tot} (%)	400	NaOH	25	2	100.4

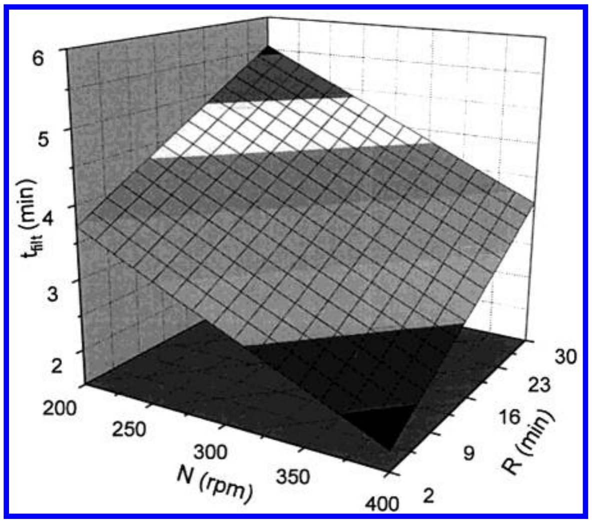

Figure 1. **Response surface X_1 (stirring speed N from 400 to 200 rpm) versus X_4 (stirring time R from 2 to 30 min) for the filtration time. Other variables $X_i = 0$.**

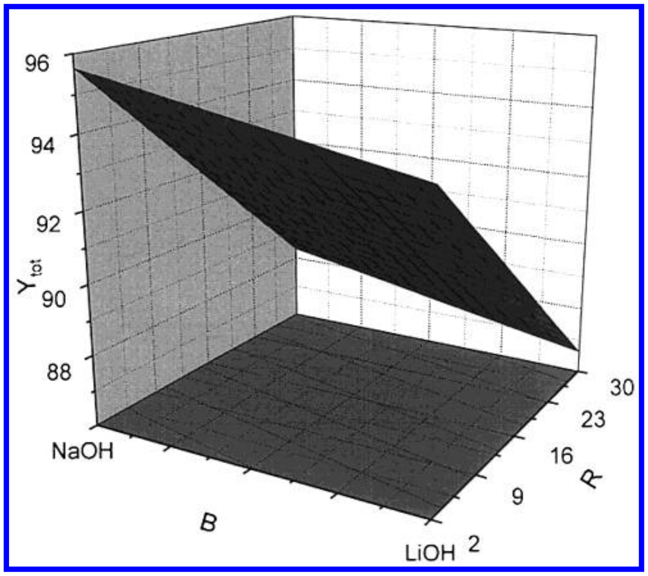

Figure 2. **Response surface X_2 (nature of the base B, NaOH (−1) and LiOH (+1)) versus X_4 (stirring time R from 2 to 30 min) for the total yield. Other variables $X_i = 0$.**

For large-scale experiments it is of upmost importance that the filtration time (t_{filt}) can be influenced. The washing efficiency after one washing step ($\mathrm{WE}_{\mathrm{ff}}$) multiplied by the isolated yield (Y_{tot}) demonstrates the yield after one washing step. All three responses determine the productivity of the process during scale-up. However, reduction of washing steps or volume of washing fluids gives a more sustainable process. Therefore, the most important response is the yield after one washing step.

The influence of the four variables was studied at 1-dm^3-scale with eight experiments, a centre point experiment, and a duplicate experiment. In Table 2 the experimental matrix and the results are depicted showing the measured values for the five chosen responses. Experiment 9 is the "centre point" experiment and experiment 2* is the duplicate experiment of experiment 2.

The regression analysis—using the Modde program[6]—of this factorial design resulted into models that would fit the experimental data as given in the model equations shown in Table 3. It can be concluded that the equations for filtration time, washing efficiency, and total yield describe the experimental values best and that the predictability of the model is varying. The most optimal configuration per response according to the model equations is depicted in Table 4 and Figures 1 and 2.

The experiment using a stirring speed of 400 rpm, NaOH as the base, a temperature of 50 °C and a stirring time of 2 min ($X_1 = 1$, $X_2 = -1$, $X_3 = 1$, $X_4 = -1$) is the theoretically best experiment when the filtration time (t_{filt}), and both yields ($\mathrm{WE}_{\mathrm{ff}}$ and Y_{tot}) are assumed to be the crucial responses. The experimental and calculated results of the optimal experiment[7] are shown in Table 5. The experimental values correspond well with the calculated values.

Large-Scale Synthesis. The insights and results of the small-scale experiments and the theoretically best work-up experiment for the reduction step (N = 400 rpm, B = NaOH, T = 50 °C, R = 2 min) were translated into a master recipe for the 10-dm^3-scale process.

For the first step, 3,4-dihydro-2H-pyran was added automatically within 2 h under "starving conditions" to the 10-dm^3 reactor, charged with a mixture of ethyl (S)(−)-lactate and p-toluene sulphonic acid. For the hydride reduction step, the reactor was filled with the crude reaction mixture from the first step. The hydride solution was also added with the aid of a membrane pump under "starving conditions" within 3 h. To complete the reaction the reaction mixture was stirred for 1 h at 50 °C. The reaction mixture was worked up by adding consecutively water, caustic soda, and water. After addition of the final amount of water a perfectly filterable suspension was obtained. The suspension was filtered on a

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(6) Modde 4.0, Umetri AB, Umeå, Sweden.

(7) The optimal experiment was selected as the best practical one in our case.

Table 5. **Validation optimal experiment**

experiment (1,−1,1,−1)	predicted	RSD	experimental
t_{filt} (min)	2.0	0.77	2
$\mathrm{WE}_{\mathrm{ff}}$ (%)	92.5	1.24	89
Y_{tot} (%)	96.4	1.09	95

Table 6. **Filterability and cake resistance**

experiment (1,−1,1,−1)	predicted	RSD	scale	
			1 dm^3	10 dm^3
t_{filt} (min)	2.0	0.77	2	7
Y_{tot} (%)	96.4	1.09	95	99
filter area (m^2)			6.36×10^{-3}	4.91×10^{-2}
cake resistance (1/m^2)			5×10^{13}	9.9×10^{13}
filterability (m^3/kg)			7.3×10^{-11}	3.6×10^{-11}

Büchner filter, and the residue was washed with four equal amounts of THF. The filtration time was 7 min, and the filterability was calculated to be 3.6×10^{-11} m^3/kg. The washing efficiency ($\mathrm{WE}_{\mathrm{ff}}$) was 87%. To obtain the crude product the filtrate was evaporated. The product was isolated in 99% yield.

The cake resistance and filterability on 10-dm^3-scale were compared with the 1 dm^3 results showing a longer filtration time for reactions on 10-dm^3-scale, as can be seen in Table 6. Isolation by centrifuge on 6-m^3-scale would not be suitable in view of these results (relatively high cake resistance and a factor 2 deterioration in filtration performance) and instead a belt filter is recommended for large-scale synthesis.[8]

Conclusions

The synthesis of (2*S*)-2-(tetrahydropyran-2-yloxy)propan-1-ol (**3**) was successfully optimised and scaled up to a 10-dm^3 reactor. The work-up of the hydride reduction was optimised by using a fractional factorial design. Experience with the centrifuge performance of many large-scale processes gave valuable insight in the best choice of the proper isolation equipment.[8] The above example illustrates that important scale-up features can be identified on lab-scale and can be reliably translated to larger scale.

The results of this research are useful to expand the current fine chemical scale-up methodology to industrial scale.

Experimental Section

All reagents and solvents were used without further purification. All NMR spectra were recorded on a Varian 300 MHz spectrometer with TMS as internal standard. GLC was conducted with a Perkin-Elmer Autosystem instrument with FID equipped with a CP-SIL 8 column (15 m × 0.25 mm × 0.1 μm). Optical rotations were determined with a Jasco polarimeter at 20 °C. Reaction calorimetry was performed with a Mettler Toledo RC1*e* reaction calorimeter equipped with a 2-dm^3 HP60 stainless steel high-pressure reactor with a pitched-blade impeller. The 1-dm^3-scale reactions were performed in a glass reactor with a 45° pitched-blade impeller with six blades (diameter impeller = 5 cm; diameter reactor = 10 cm; clearance = 1 cm). The large-scale reaction was carried out in a 10-dm^3 fully automated (semi)batch-operated Belatec reactor equipped with a 45° pitched-blade impeller with six blades (diameter impeller = 10 cm; diameter reactor = 20 cm; clearance = 2 cm). The reactor is controlled by a PLC, a special computer monitoring physical data (batch history), and securing optimal process and safety conditions.

Ethyl (2*S*)-2-(tetrahydropyran-2-yloxy)propionate (2). Ethyl (*S*)(−)-lactate (**1**) (228.5 mL, 236.3 g, 2.00 mol) and *p*-toluene sulphonic acid monohydrate (80 mg, 0.42 mmol, 0.02 mol %) were added to toluene (400 mL). The reaction mixture was heated to 50 °C. Within 60 min 3,4-dihydro-2H-pyran (188.0 mL, 173.3 g, 2.06 mol) was added dropwise to the reaction mixture. Then, the reaction mixture was washed with saturated $\mathrm{NaHCO_3}$ solution (100 mL). Drying of the toluene layer with $\mathrm{Na_2SO_4}$ (10 g, 0.07 mol) and evaporation of the toluene yielded the crude product. Distillation (75−77°C; 1.6 mbar) yielded pure (**2**) as a colourless oil (385 g, 1.90 mol, 95%).

^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz) δ 4.65 (1H, m, O-C$\underline{\mathrm{H}}$R-O), 4.35 (0.7H, q, O-C$\underline{\mathrm{H}}'$-(COOEt)CH$_3$), 4.2−4.1 (2.3H, m, O-C$\underline{\mathrm{H}}_2$-CH$_3$ and O-C$\underline{\mathrm{H}}''$-(COOEt)CH$_3$), 3.9−3.35 (4H, m, RCH$_2$-C$\underline{\mathrm{H}}_2$-O of DHP-group), 1.95−1.45 (12H, m, O-CH$_2$-(C$\underline{\mathrm{H}}_2$)$_3$-CHO$_2$ of the THP-group), 1.4−1.3 (6H, dd, CH-C$\underline{\mathrm{H}}_3$-(COOEt)), 1.25 (6H, m, O-CH$_2$-C$\underline{\mathrm{H}}_3$); ^{13}C NMR ($\mathrm{CDCl_3}$, 100 MHz) δ 173.2 and 173.1 (C═O), 98.1 and 97.4 (O-$\underline{\mathrm{C}}$HR-O), 72.4 and 69.8 (O-$\underline{\mathrm{C}}$H(COOEt)CH$_3$), 62.3 and 62.1 ($\underline{\mathrm{C}}$H$_2$-O-CHR-O), 60.7 and 60.6 (O-$\underline{\mathrm{C}}$H$_2$-CH$_3$), 30.3 and 30.2 (CH-$\underline{\mathrm{C}}$H$_2$), 25.3 and 25.2 ($\underline{\mathrm{C}}$H$_2$-CH$_2$-O), 19.0 and 18.9 (CH-CH$_2$-$\underline{\mathrm{C}}$H$_2$-CH$_2$-CH$_2$O), 18.6 and 17.9 (O-CH(COOEt)$\underline{\mathrm{C}}$H$_3$), 14.1 and 14.0 (O-CH$_2$-$\underline{\mathrm{C}}$H$_3$).

$[\alpha]^{20}_{\mathrm{D}} = -61.7°$ (*c* 3.19, $\mathrm{CHCl_3}$) (lit. $[\alpha]^{20}_{\mathrm{D}} = -60.7°$ (*c* 3.19, $\mathrm{CHCl_3}$)).[9]

The reaction conditions of the reaction for the 1-dm^3-scale reactor without solvent are identical. The amounts of reactants are: ethyl (*S*)(−)-lactate (430.0 mL, 444.6 g, 3.76 mol); *p*-toluene sulphonic acid (0.1433 g, 0.753 mmol, 0.02 mol %); 3,4-dihydro-2H-pyran (354.0 mL, 326.4 g, 3.88 mol).

(2*S*)-2-(Tetrahydropyran-2-yloxy)propan-1-ol (3). Through crude (**2**) (195.0 g, containing 0.96 mol ethyl (2*S*)-2-tetrahydropyran-2-yloxy)propionate, 0.01 mol 3,4-dihydro-2H-pyran and 0.19 mmol *p*-toluene sulphonic acid) argon was bubbled for half an hour. Then, 1 M $\mathrm{LiAlH_4}$ solution in THF (500 mL, 0.50 mol) was added dropwise to the reaction mixture within 1 h. The clear reaction mixture was allowed to react at room temperature for an additional hour after the addition of the $\mathrm{LiAlH_4}$ solution. The reaction mixture was quenched by adding water (19.0 mL), 15% caustic soda (19.0 mL), and water (57.0 mL), in that order. In the beginning, the reaction mixture turned white and formed a gel-like mass. After thorough stirring a filterable suspension was formed. The reaction mixture was filtered, and the residue was

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(8) Hulshof, L. A. Challenges in Fine Chemical Scale-Up: The Battle of Tweedledee and Tweedledum. Fifth International Conference on Organic Process Research and Development, New Orleans, LA, U.S.A., November, 2001.

washed with THF (150 mL) four times. The filtrate was evaporated, and the crude product was distilled (83−85 °C; 6.1 mbar) from Na_2CO_3 (20 g), to obtain the pure colourless product (147.5 g, 0.92 mol, 96%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.65 and 4.45 (2H, m, O-C$\underline{H}$R-O), 4.0−3.6 (4H, m), 3.55−3.3 (6H, m), 2.55 (1H, m, O$\underline{H}$), 1.85−1.4 (13H, m, OH and O-CH_2-(C$\underline{H}_2$)$_3$-CH of the DHP-group), 1.1−0.9 (6H, dd, O-CH(C$\underline{H}_3$)-(CH_2OH)). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 99.6 and 98.9 (O-$\underline{C}$HR-O), 77.3 and 74.6 (O-$\underline{C}$H(CH_2OH)CH_3), 67.0 and 66.0 ($\underline{C}H_2$-O-CHR-O), 64.3 and 62.9 (O-CH($\underline{C}H_2$OH)CH_3), 31.4 and 30.9 (CH-$\underline{C}H_2$), 25.2 and 24.9 ($\underline{C}H_2$-CH_2-O), 20.7 and 19.9 (CH-CH_2-$\underline{C}H_2$-CH_2-CH_2O), 17.6 and 17.0 (O-CH_2-$\underline{C}H_3$).

$[\alpha]^{20}_D = -8.3°$ (*c* 3.15, $CHCl_3$) (lit. $[\alpha]^{20}_D = -8.6°$ (*c* 3.15, $CHCl_3$).[9]

Master Recipe To Synthesise (2*S*)-2-(Tetrahydropyran-2-yloxy)propan-1-ol (3) on 10-dm^3 Scale. A 10-dm^3 fully automated Belatec reactor was charged with ethyl (*S*)-(−)-lactate (**1**) (2521 g, 21.34 mol) and *p*-toluene sulphonic acid monohydrate (1.0 g, 5.26 mmol). The reactor was heated to 50 °C and stirred at 400 rpm. With the aid of a membrane pump 3,4-dihydro-2H-pyran (1813 g, 21.55 mol) was added under "starving conditions" within 2 h. The acidic, colourless, clear solution was neutralised by addition of $LiAlH_4$ (200 mL 1.0 M in THF, 0.2 mol). The reactor was discharged and rinsed with THF (50 mL). The slightly pale mixture contained 92.0% (**2**) and 7.5% THF according to GLC and ^{1}H NMR analysis.

For the reduction the reactor was charged with the crude reaction mixture from the protection reaction (1999.7 g). To obtain maximum heat transfer, additional solvent (THF, 2.0 dm^3) was added, and the mixture was stirred at 400 rpm. The reactor was cooled to 15 °C, and then a clear solution of $LiAlH_4$ (4260 g, 1.0 M in THF, 4.73 mol) was added with the aid of a membrane pump under "starving conditions" within 3 h. The reaction mixture was stirred to completion for 1 h at 50 °C. Water (60 mL) was added in 10 min via a membrane-dosing pump under argon ventilation, and little hydrogen gas production was observed. Consecutively, water (120 mL) in 2 min, 15% NaOH (180 mL) in 2 min, and water (540 mL) were added, while maintaining the temperature at 50 °C. During the addition of the first portion of water, a white gel-like mass was formed. Continuous stirring for 2 min during the last phase of the work-up gave a good filterable suspension. The suspension was filtered using a Büchner filter in 7 min, and the residue was washed with THF (1500 mL) four times. The washing efficiency was 87%. The filtrate was evaporated, and the pure colourless product (**3**) was obtained in 99% yield (based on **1**) in a purity of 98% according to GC and ^{1}H NMR analysis.

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