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Enantioselective hydrogenation of pyrrolidine-2,3,5-triones over the Pt–cinchonidine system

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Abstract

1- and 4-Substituted pyrrolidine-2,3,5-triones **5**, **6** and **9** have been synthesized and hydrogenated to 3-hydroxy derivatives **10**–**12** with 17–91% ee using a 5 wt% Pt/Al_2O_3 catalyst in the presence of small amounts of cinchonidine. The influence of substituents on the enantioselectivity is discussed.

1. Introduction

Enantioselective hydrogenation of carbonyl compounds is one of the most intensively studied areas of asymmetric catalysis.[1] An efficient strategy to achieve reasonable enantioselectivity over solid catalysts is the modification of an active metal by a preadsorbed homochiral compound.[2] Since the first application of cinchona-modified Pt,[3] considerable effort has been made to broaden the application range of this catalyst system. Good to high ees were obtained in the hydrogenation of α-ketoesters (97.5%),[4] α-ketoacids (85%)[5] and ketopantolactone (91.6%).[6] The hydrogenation of other types of activated carbonyl compounds such as α-diketones, trifluoroacetophenone and pyruvamides was less successful, affording only 60% ee or less.[7]

We have reported recently[8] that a cyclic imidoketone could be hydrogenated to the corresponding alcohol with 91% ee, using the Pt–cinchonidine system. The aim of the present work is to reveal the influence of the structure of cyclic ketoimides on the enantiodifferentiation. A series of 1- and 4-substituted pyrrolidine-2,3,5-triones was prepared and hydrogenated with a cinchonidine-modified Pt/Al_2O_3 catalyst. The simple and economical procedure, starting from easily available racemic compounds, seems to be a promising method for the preparation of chiral alcohols. It has been reported that enantiomerically pure alcohols such as (*S*)-*N*-methyl-2-hydroxysuccinimide are excellent chiral auxiliaries for Lewis acid catalyzed enantioselective Diels–Alder reactions of enolates.[9]

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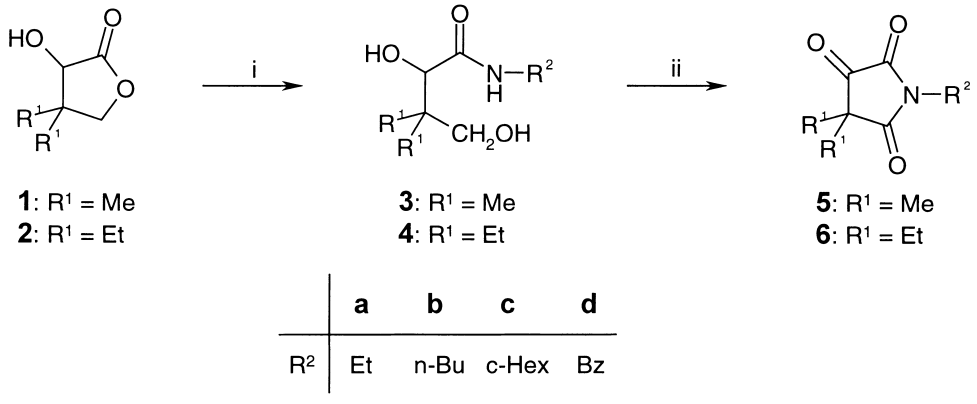
2. Results and discussion

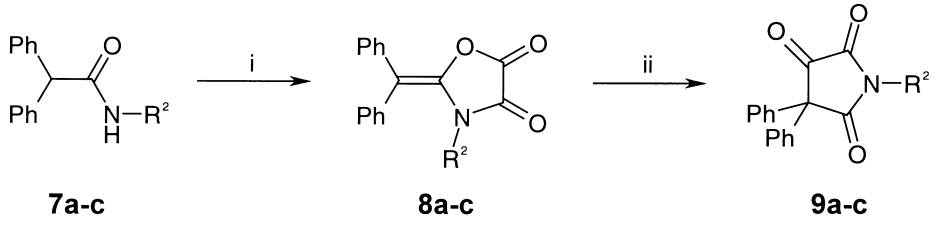
2.1. Synthesis of substrates 5, 6 and 9

Most of the cyclic ketoimides were prepared from the racemic lactones **1** and **2**, according to Scheme 1. The lactone ring was cleaved by an amine and the amides **3** and **4** were oxidized with pyridinium dichromate (PDC)[10] in DMF solution affording the cyclic ketoimides **5** and **6**.



Scheme 1. (i) R^2NH_2/MeOH, reflux, 2 h; (ii) PDC/DMF, RT, 24 h

Compounds **9a–c** were synthesized by an alternative route starting from the corresponding diphenyl acetamides **7a–c**, as shown in Scheme 2. The oxazolinediones **8** formed in the reaction of amides with oxalyl chloride were rearranged to **9a–c** by refluxing in ethanolic solutions in the presence of catalytic amounts of pyridine.[11]

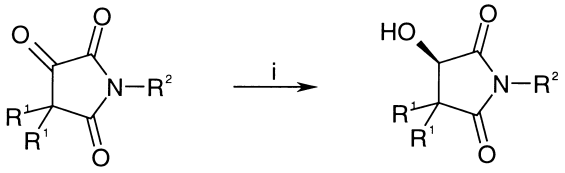


Scheme 2. (i) Oxalylchloride/benzene, 60°C, 12 h; (ii) pyridine/EtOH, reflux, 12 h

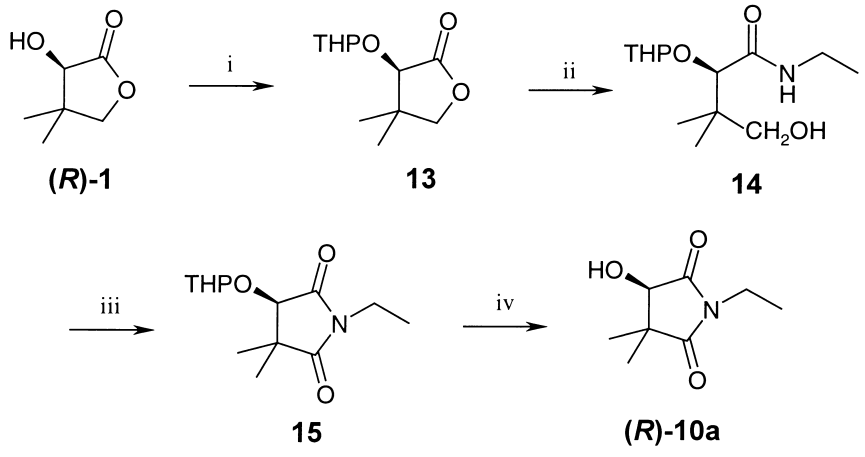
2.2. Product conformation

The enantioselective hydrogenation of 1-ethyl-4,4-dimethylpyrrolidine-2,3,5-trione (**5a** in Scheme 3) over cinchona-modified Pt/Al_2O_3 afforded **10a** in over 90% ee.[8] Taking the hydrogenation of other α-functionalized carbonyl compounds with the same catalyst as analogies, it is likely that the (*R*)-isomer of **10a** was formed in excess.

For the determination of the absolute configuration of the hydroxyimide **10a**, the pure (*R*)-isomer (*R*)-**10a** has been synthesized from (*R*)-pantolactone [(*R*)-**1** according to Scheme 4]. The hydroxyl function of (*R*)-**1** was protected by a tetrahydropyranyl group. After treatment with ethylamine the resulting hydroxyamide was oxidized with PDC in DMF. Deprotection in the presence of TsOH gave (*R*)-**10** in enantiomerically pure form. Gas chromatographic analysis using a chiral column corroborated that (*R*)-**10** is identical with the main product obtained in the hydrogenation of **5a**.



Scheme 3. (i) $H_2/Pt/Al_2O_3$, cinchonidine, toluene, 10°C



Scheme 4. (i) 3,4-Dihydro-2*H*-pyran, HCl/dioxane, RT, 2 h; (ii) $EtNH_2$/MeOH, RT, 2 h; (iii) PDC, DMF, RT, 24 h; (iv) TsOH, MeOH, RT, 2 h

2.3. Enantioselective hydrogenation

Preliminary experiments revealed that good ee could be achieved only if the catalyst was pretreated in hydrogen at elevated temperatures (Table 1, entries 1 and 2). This behaviour and similar observations[6,12] in the hydrogenation of other carbonyl compounds with cinchona-modified Pt may be explained by some surface restructuring of the metal particles during the reductive heat treatment. Entry 3 in Table 1 shows that an oxidative treatment subsequent to the reductive treatment at the same temperature, causes a drop in selectivity to the initial value of the untreated catalyst. (Note that the 'untreated' Pt/Al_2O_3 was stored in air and the surface was in an oxidized state.) Apparently, the transformation of the metal particles at 400°C from 'unselective' to 'selective' structures and vice versa is reversible.

It was found[8] to be important to apply rather low modifier concentrations, in the range of 50–200 μmol l^{-1}. The modifier is simply added to the reaction mixture and during the initial period of the reaction a steady state seems to be reached on the metal surface. It is assumed that the modifier competes for the metallic active sites (Pt^0) with hydrogen, substrate and product. Both too high and too low cinchonidine concentrations diminish the final ee. For example, in the hydrogenation of **5a** the ee decreased by 10% when the cinchonidine concentration was higher than 1 mmol l^{-1} or lower than 1 μmol l^{-1}. The optimum corresponds to a substrate/modifier molar ratio of almost 70 000.

As shown in Fig. 1, the solvent plays a crucial role in the enantioselective hydrogenation of pyrrolidine-2,3,5-triones. The ee increased with decreasing solvent polarity, except for strongly apolar solvents such as cyclohexane or *n*-hexane, in which media the reactant and modifier are only sparsely soluble. Acidic solvents (acetic acid, formic acid) afforded significantly higher ees than expected on the basis of their

Table 1
Influence of catalyst pretreatment at 400°C on the enantiomeric excess at full conversion of **5a**. Conditions: 3.2 mmol *N*-ethyl-4,4-dimethylpyrrolidine-2,3,5-trione, 60 mg 5 wt% Pt/Al_2O_3, 2 mmol l^{-1} cinchonidine, 5 ml toluene, 30 bar, 15°C, reaction time: 60 min

Entry	Pretreatment procedure[a]	Enantiomeric excess /%
1	No pretreatment	40
2	90 min in H_2	80
3	90 min in H_2 followed by 30 min in Air	43

[a] Each pretreatment was preceded by heating to 400 °C in N_2 in 30 min, and followed by cooling in 30 min to RT in the same medium used in the preceding heat treatment.

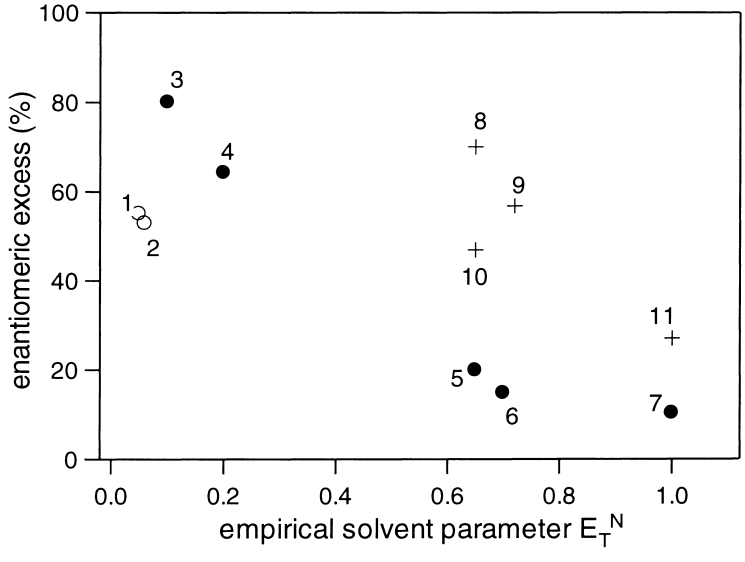


Figure 1. Influence of the empirical solvent parameter E_T^N on the ee in the hydrogenation of **5a**. Conditions: 3.2 mmol *N*-ethyl-4,4-dimethylpyrrolidine-2,3,5-trione, 70 bar, 15 C, 60 mg catalyst, 2 mmol l^{-1} cinchonidine, 5 ml solvent (1: cyclohexane, 2: *n*-hexane, 3: toluene, 4: THF, 5: ethanol, 6: *N*-methylformamide, 7: water, 8: acetic acid, 9: formic acid, 10: ethanol+1.3 wt% acetic acid, 11: water+1 wt% acetic acid)

polarity, characterized by the empirical solvent parameter E_T^N.[13] Similarly, addition of small amounts of acetic acid to protic polar solvents enhanced the ee remarkably. We have found very recently[14] that the conformation of cinchonidine changes with solvent polarity. Apolar solvents or protonation of the quinuclidine N of cinchonidine enhances the proportion of the 'open 3' conformation.[15] Molecular modelling indicated[2d,6a] that this conformation affords the highest ee via interaction with the activated carbonyl compound reactant on the Pt surface.

Another crucial parameter was the surface hydrogen concentration. Good ees could be achieved only above 30 bar hydrogen pressure.[8] The positive effect of high hydrogen concentration may be attributed to the rapid removal of some surface contamination at the beginning of the reaction (as has been shown for the enantioselective hydrogenation of ethyl pyruvate),[16] but other effects can also play a role.

The enantioselectivity decreased gradually with increasing reaction temperature. This small but

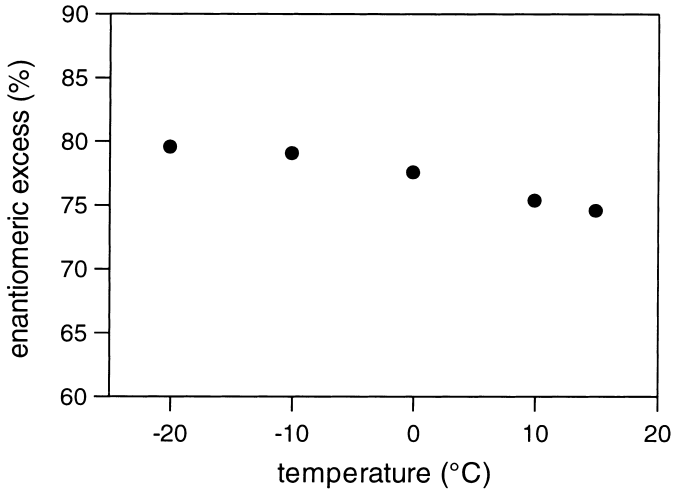


Figure 2. Influence of temperature on the ee in the hydrogenation of **5a**. Conditions: 3.2 mmol *N*-ethyl-4,4-dimethyl-pyrrolidine-2,3,5-trione, 70 bar, 60 mg catalyst, 10 mmol l^{-1} cinchonidine, 5 ml toluene

significant effect is illustrated in Fig. 2 by the example of the hydrogenation of **5a**. A similar correlation was observed in the hydrogenation of α-ketoesters[17,18] and α-ketopantolactone.[6]

For the study of the influence of substituents in the 1 and 4 positions, 10 different pyrrolidine-2,3,5-triones **5**, **6** and **9** have been hydrogenated under identical conditions. The results are collected in Table 2. The highest ee (85%) was obtained in the reduction of **6d**. It is hoped that by optimizing the reaction conditions, the ees can be significantly improved. For example, variation of some important parameters afforded 91.2±0.5% ee in the hydrogenation of **5a**. [Conditions: 80 bar, 10°C, in 5 ml toluene and 12 mmol l^{-1} acetic acid, 7.2 μmol l^{-1} cinchonidine and 60 mg catalyst (5 wt% Pt/Al_2O_3).[8]]

It seems from Table 2 that methyl and phenyl groups in the R^1 position lead to higher ees, compared to ethyl groups, except when R^2 is cyclohexyl. For the R^2 groups the selectivity order is Bn≥Et>*n*-Bu>*c*-Hex. Apparently, bulky alkyl and cycloalkyl substituents disfavour the enantiodifferentiation, but the electron-rich aromatic and alkyl-aromatic substituents are exceptions. This conclusion requires further confirmation due to the presence of small amounts of impurities in substrates **5**, **6** and **9**. For comparison, in the most selective reaction the chiral modifier cinchonidine was present in 15 ppm relative to the substrate **5a**. If traces of cinchonidine can result in dramatic changes in stereoselectivity, we cannot exclude the possible influence of (unknown) impurities present in the substrates in much higher concentrations (up to 0.1–0.5 wt%).

On the basis of the high ee achieved in the hydrogenation of **6d** (Table 2) we suggest that the *N*-benzyl group contributes to favourable adsorption of the substrate on the platinum surface and seems to enhance enantiodifferentiation. Based on our previous theoretical studies on the structure of the enantiodifferentiating complex[6a,2d] in α-ketoester hydrogenations we propose the complex shown in Fig. 3 to be relevant. The top-side view of the half-hydrogenated state of **6d**, stabilized by an H-bond interaction with the quinuclidine N-atom of cinchonidine is presented. The minimum energy conformations of **6d** and cinchonidine ('open 3')[15] have been determined independently using the 'Hyperchem' program. Note that the structure shown is not optimized, some deviations may be possible. Optimization, including the metal surface interaction is targeted in future work.

Bulky substituents in the 1 and 4 positions are assumed to hinder the appropriate adsorption of the substrate and diminish the ee. The best example of this case is the hydrogenation of **9c**. A comparison of substrates **6d** and **9c** can explain the 68% difference in ee in their hydrogenation. In **6d** the electron-rich

Table 2
Enantiomeric excess in the hydrogenation of 1- and 4-substituted pyrrolidine-2,3,5-triones according to Scheme 3. Conditions: 60 bar, 10°C, 60 mg catalyst, 10 μmol l^{-1} cinchonidine, 5 ml toluene, reaction time: 60 min. Conversion was always 100%

Substrate		Code	Ee
R^1	R^2		%
Methyl	Ethyl	**5a**	82
Methyl	Butyl	**5b**	58
Methyl	Cyclohexyl	**5c**	61
Ethyl	Ethyl	**6a**	40
Ethyl	Butyl	**6b**	33
Ethyl	Cyclohexyl	**6c**	69
Ethyl	Benzyl	**6d**	85
Phenyl	Ethyl	**9a**	81
Phenyl	Butyl	**9b**	58
Phenyl	Cyclohexyl	**9c**	17

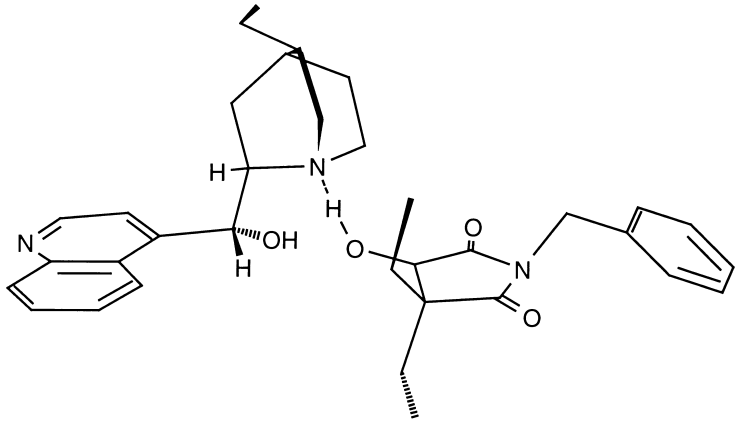


Figure 3. Top-side view of the half-hydrogenated state of **6d**, stabilized by cinchonidine via an H-bond interaction. The benzyl group may strengthen the adsorption of **6d** on the metal surface

N-benzyl group can strongly interact with the Pt surface (soft acid). Besides, the benzyl and the two ethyl groups possess enough flexibility to adopt the appropriate adsorption geometry on the surface of the Pt particle. On the contrary, the bulky phenyl and cyclohexyl groups are assumed to hinder the adsorption of the reducible carbonyl group parallel to the metal surface (Fig. 4). An η^2 di-σ adsorption mode was found to be the preferred adsorption geometry for carbonyl compounds on Pt by molecular modelling.[19] Also, this adsorption mode was suggested by a theoretical study of cinchonidine–ethyl pyruvate and cinchonidine–ketopantolactone activated complexes.[6a]

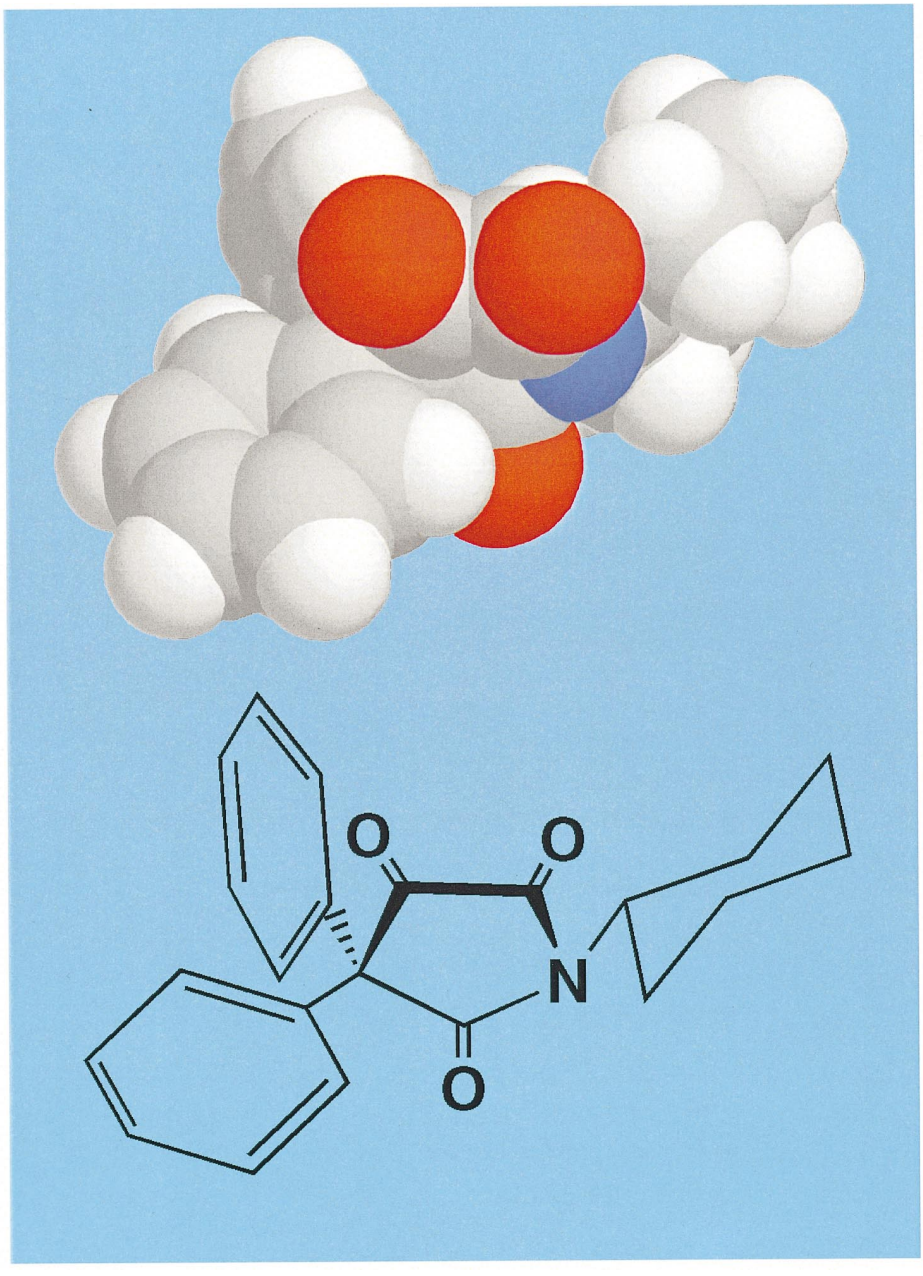


Figure 4. Space-filled model of **9c** (bottom-side view). Bulky substituents in the 1 and 4 positions represent steric barriers for appropriate adsorption of the carbonyl group to be hydrogenated

3. Conclusions

Hydrogenations of pyrrolidine-2,3,5-triones represent an extension of the application range of cinchona-modified Pt to a new class of reactants. Similarly to the former successful applications of this catalyst system,[3–7] the carbonyl groups in **5**, **6** and **9** are activated by an electron-withdrawing group in the α-position. The present work provides the first detailed investigation on the influence of reactant

structure on the enantiomeric excess over chirally modified Pt. It is hoped that this study will contribute to a better understanding of the mechanism of enantiodifferentiation.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DPX300 instrument at 300.13 and 75.48 MHz in $CDCl_3$ (internal standard: TMS). IR data were obtained on a Perkin–Elmer 2000 FT-IR spectrometer in CCl_4 solution. The optical purity of the compounds prepared and enantiomeric excess of hydroxyimides formed in the hydrogenation were determined by gas chromatography (**10a**–**c**, **11a**–**c**, WCOT cyclodextrin-β-2,3,6-M-19 Chrompack column) or NMR spectroscopy using (1*R*)-10-camphorsulphonic acid (**10d**, ^{1}H-NMR) or (*R*)-MTPA (**12a**–**c**, ^{19}F-NMR) derivatives. Acylation was performed with the acid chloride (1.5 equiv.) in dichloromethane solution in the presence of DMAP and triethylamine.[20]

4.2. 4,4-Diethyl-4,5-dihydro-3-hydroxy-2(3H)-furanone **2**

4,4-Diethyl-4,5-dihydrofuran-2,3-dione[21] (15.6 g, 0.10 mol) was hydrogenated in toluene (20 cm^3) in the presence of a 5 wt% Pt/C catalyst (200 mg) at room temperature under 60 bar pressure for 48 h. The catalyst was filtered off and the solvent was evaporated under reduced pressure. Recrystallization of the crude crystalline product from *tert*-butyl methyl ether and hexane (1:1) gave white platelets (14.6 g, 92%). Mp 76–78°C; IR (cm^{-1}) 3700–2800, 1780; ^{1}H-NMR 4.24 (*s*, 1H), 4.14 (*d*, J=9.3 Hz, 1H), 3.91 (*d*, J=9.3 Hz, 1H), 3.07 (br *s*, 1H), 1.65–1.52 (*m*, 4H), 0.98 (*t*, J=7.5 Hz, 3H), 0.91 (*t*, J=7.5 Hz, 3H); ^{13}C-NMR 178.6, 74.6, 73.2, 46.5, 28.1, 21.5, 8.4, 8.1. Anal. calcd for $C_8H_{14}O_3$ (158.2) C 60.74, H 8.92; found C 60.66, H 8.97.

4.3. Preparation of N-alkyl-2,4-dihydroxy-3,3-dialkylbutyramides **3**, **4**: general procedure

A solution of 4,4-dialkyl-4,5-dihydro-3-hydroxy-2(3*H*)-furanone (0.05 mol) in 20 cm^3 methanol was cooled with ice water and the corresponding alkylamine (0.06 mol) was added. After stirring at room temperature for 3 h, the solvent was evaporated under reduced pressure. White crystalline materials **3a**–**d** were obtained after recrystallization of the crude products from *tert*-butyl methyl ether and hexane. Column chromatography (silica gel, *tert*-butyl methyl ether) of **4a**–**c** resulted in colourless oils.

4.4. N-Ethyl-2,4-dihydroxy-3,3-dimethylbutyramide **3a**

Yield 95%; mp 62–63°C; IR (cm^{-1}) 3700–3200, 3419, 3100–2800 and 1657; ^{1}H-NMR 7.03 (br *s*, 1H), 4.81 (br *s*, 1H), 4.30 (br *s*, 1H), 3.99 (*d*, J=4.6 Hz, 1H), 3.48 (*qa*, J=7.2 Hz, 2H), 3.41–3.20 (*m*, 2H), 1.16 (*t*, J=7.2 Hz, 3H), 0.98 (*s*, 3H), 0.91 (*s*, 3H); ^{13}C-NMR 173.5, 77.3, 77.2, 49.3, 33.9, 21.2, 20.2, 14.8. Anal. calcd for $C_8H_{17}NO_3$ (175.2) C 54.84, H 9.78, N 7.99; found C 54.85, H 9.81, N 7.89.

4.5. N-*Butyl-2,4-dihydroxy-3,3-dimethylbutyramide* ***3b***

Yield 89%; mp 40–42°C; IR (cm^{-1}) 3500–3200, 3000–2820, 1653; ^{1}H-NMR 7.02 (*t*, J=5.7 Hz, 1H), 4.80 (br *s*, 1H), 4.32 (br *s*, 1H), 4.00 (*s*, 1H), 3.47 (*s*, 2H), 3.25 (*m*, 2H), 1.51 (*qa*, J=8.6 Hz, 2H), 1.35 (*sex*, J=8.6 Hz, 2H), 1.19 (*s*, 3H), 0.93 (*t*, J=8.6 Hz, 3H), 0.91 (*s*, 3H); ^{13}C-NMR 173.6, 76.6, 71.2, 49.4, 39.3, 31.5, 21.3, 20.1, 20.0, 13.7. Anal. calcd for $C_{10}H_{21}NO_3$ (203.3) C 59.09, H 10.41, N 6.89; found C 59.33, H 10.44, N 6.62.

4.6. N-*Cyclohexyl-2,4-dihydroxy-3,3-dimethylbutyramide* ***3c***

Yield 90%; mp 100–103°C; IR (cm^{-1}) 3700–3200, 3100–2800, 1655; ^{1}H-NMR 6.88 (*d*, J=8.4 Hz, 1H), 4.42 (br *s*, 2H), 3.97 (*s*, 1H), 3.75 (*m*, 1H), 3.47 (*s*, 2H), 1.90–1.10 (*m*, 10H), 0.98 (*s*, 3H), 0.90 (*s*, 3H); ^{13}C-NMR 172.6, 76.4, 71.2, 47.9, 39.3, 25.5, 24.8, 24.7, 24.6, 21.3, 18.9, 14.1. Anal. calcd for $C_{12}H_{23}NO_3$ (229.3) C 62.85, H 10.11, N 6.11; found C 62.70, H 10.03, N 6.11.

4.7. N-*Benzyl-2,4-dihydroxy-3,3-dimethylbutyramide* ***3d***

Yield 93%; mp 101–104°C; IR (cm^{-1}) 3700–3200, 3000–2850, 1653; ^{1}H-NMR 7.34–7.22 (*m*, 5H), 4.42 (*dqa*, J=6.1 and 12.3 Hz, 2H), 4.05 (*s*, 1H), 3.46 (*s*, 2H), 0.97 (*s*, 3H), 0.91 (*s*, 3H); ^{13}C-NMR 173.4, 137.8, 128.7, 127.7, 127.6, 77.6, 71.3, 43.1, 39.4, 21.2, 20.3. Anal. calcd for $C_{13}H_{20}NO_3$ (237.3) C 65.80, H 8.07, N 5.90; found C 65.75, H 7.85, N 5.99.

4.8. N-*3,3-Triethyl-2,4-dihydroxybutyramide* ***4a***

Yield 85%; IR (cm^{-1}) 3600–3050, 3020–2800, 1653; ^{1}H-NMR 7.03 (br *s*, 1H), 4.14 (*s*, 1H), 3.61 (*s*, 2H), 3.32 (*qi*, J=3.5 Hz, 2H), 1.48 (*qa*, J=7.5 Hz, 4H), 1.17 (*t*, J=7.3 Hz, 3H), 0.88 and 0.86 (overlapping *t*s, J=7.5 Hz, 6H); ^{13}C-NMR 174.2, 76.2, 66.8, 43.8, 34.1, 24.4, 23.2, 14.7, 7.9, 7.6. Anal. calcd for $C_{10}H_{21}NO_3$ (203.3) C 59.08, H 10.41, N 6.89; found C 58.87, H 10.38, N 6.93.

4.9. N-*Butyl-2,4-dihydroxy-3,3-diethylbutyramide* ***4b***

Yield 92%; IR (cm^{-1}) 3600–3200, 3000–2830, 1653; ^{1}H-NMR 6.91 (br *s*, 1H), 4.16 (*s*, 1H), 3.62 (*s*, 2H), 3.30 (*m*, 2H), 1.60–1.30 (*m*, 8H), 0.93, 0.89 and 0.87 (overlapping *t*s, J=7.4 Hz, 9H); ^{13}C-NMR 173.9, 76.3, 67.0, 43.9, 39.0, 31.5, 24.5, 23.3, 20.1, 13.7, 7.9, 7.6. Anal. calcd for $C_{12}H_{25}NO_3$ (231.3) C 62.31, H 10.89, N 6.06; found C 62.44, H 10.67, N 6.02.

4.10. N-*Cyclohexyl-2,4-dihydroxy-3,3-diethylbutyramide* ***4c***

Yield 90%; IR (cm^{-1}) 3700–3200, 3050–2850, 1654; ^{1}H-NMR 6.70 (*d*, J=8.1 Hz, 1H), 4.13 (*s*, 1H), 3.80 (*m*, 1H), 3.62 (*s*, 2H), 1.94–1.10 (*m*, 14H), 0.90 and 0.86 (overlapping *t*s, J=7.3 Hz, 6H); ^{13}C-NMR 173.1, 76.1, 66.9, 48.1, 43.9, 33.0, 32.8, 25.5, 24.8, 24.7, 24.6, 23.3, 7.9, 7.6. Anal. calcd for $C_{14}H_{27}NO_3$ (257.4) C 65.33, H 10.57, N 5.44; found C 65.25, H 10.50, N 5.61.

4.11. Preparation of pyrrolidine-2,3,5-triones **5**, **6**: general procedure

The corresponding *N*-alkyl-2,4-dihydroxy-3,3-dialkylbutyramide (0.03 mol) and pyridinium dichromate (PDC, 67.7 g, 0.18 mol) were dissolved in 120 cm^3 dry DMF and the mixture was stirred for 24 h at room temperature. The solution was poured into 10 volumes of water and then extracted with *tert*-butyl methyl ether. After drying of the combined organic layers over $MgSO_4$ the solvent was removed under reduced pressure. The crude product was purified by Kugelrohr distillation **5a**–**b**, **6a**–**c** or recrystallization **5c**–**d** from *tert*-butyl methyl ether.

4.12. 1-Ethyl-4,4-dimethylpyrrolidine-2,3,5-trione **5a**

Pale yellow oil; yield 55%; IR (cm^{-1}) 3050–2800, 1775, 1717; ^{1}H-NMR 3.78 (*qa*, J=7.2 Hz, 2H), 1.37 (*s*, 6H), 1.28 (*t*, J=7.2 Hz, 3H); ^{13}C-NMR 197.3, 176.6, 160.0, 45.6, 34.2, 19.8, 12.8. Anal. calcd for $C_8H_{11}NO_3$ (169.2) C 56.80, H 6.55, N 8.28; found C 56.67, H 6.71, N 8.28.

4.13. 1-Butyl-4,4-dimethylpyrrolidine-2,3,5-trione **5b**

Pale yellow oil; yield 80%; IR (cm^{-1}) 3000–2850, 1777, 1724, 1701; ^{1}H-NMR 3.70 (*t*, J=7.3 Hz, 2H), 1.62 (*qi*, J=7.5 Hz, 2H), 1.33 (*s*, 6H), 1.32 (*sex*, J=7.4 Hz, 2H), 0.92 (*t*, J=7.3 Hz, 3H); ^{13}C-NMR 197.3, 176.8, 160.2, 45.7, 39.0, 29.6, 20.0, 13.5. Anal. calcd for $C_{10}H_{15}NO_3$ (197.2) C 60.90, H 7.67, N 7.10; found C 60.63, H 7.73, N 7.13.

4.14. 1-Cyclohexyl-4,4-dimethylpyrrolidine-2,3,5-trione **5c**

Pale yellow crystals; yield 78%; mp 91–93°C; IR (cm^{-1}) 3020–2830, 1775, 1718; ^{1}H-NMR 4.20 (*tt*, J=3.8 and 12.3 Hz, 1H), 2.30–1.15 (*m*, 16H); ^{13}C-NMR 197.3, 176.9, 160.0, 52.3, 45.2, 28.8, 25.6, 24.8, 20.0. Anal. calcd for $C_{12}H_{17}NO_3$ (223.3) C 64.55, H 7.67, N 6.27; found C 64.38, H 7.60, N 6.44.

4.15. 1-Benzyl-4,4-dimethylpyrrolidine-2,3,5-trione **5d**

White crystals; yield 75%; mp 108–110°C; IR (cm^{-1}) 3250–2800, 1778, 1723, 1700; ^{1}H-NMR 7.47–7.23 (*m*, 5H), 4.87 (*s*, 2H), 1.34 (*s*, 6H); ^{13}C-NMR 197.0, 176.4, 159.8, 134.6, 128.9, 128.8, 128.4, 45.9, 42.7, 19.9. Anal. calcd for $C_{13}H_{13}NO_3$ (231.3) C 67.52, H 5.67, N 6.06; found C 67.62, H 5.79, N 6.12.

4.16. 1,4,4-Triethylpyrrolidine-2,3,5-trione **6a**

Pale yellow oil; yield 70%; IR (cm^{-1}) 3020–2820, 1774, 1719, 1701; ^{1}H-NMR 3.83 (*qa*, J=7.3 Hz, 2H), 1.89 (*qa*, J=7.5 Hz, 4H), 1.29 (*t*, J=7.3 Hz, 3H), 0.83 (*t*, J=7.5 Hz, 6H); ^{13}C-NMR 199.4, 176.0, 160.6, 55.8, 34.2, 27.9, 13.2, 9.0. Anal. calcd for $C_{10}H_{15}NO_3$ (197.2) C 60.91, H 7.67, N 7.10; found C 61.04, H 7.76, N 7.05.

4.17. 1-Butyl-4,4-diethylpyrrolidine-2,3,5-trione **6b**

Pale yellow oil; yield 80%; IR (cm^{-1}) 3000–2800, 1774, 1719; ^{1}H-NMR 3.78 (*t*, J=7.3 Hz, 2H), 1.88 (*qa*, J=7.5 Hz, 4H), 1.67 (*qi*, J=7.5 Hz, 2H), 1.37 (*sex*, J=7.4 Hz, 2H), 0.96 (*t*, J=7.2 Hz, 3H), 0.83 (*t*,

J=7.5 Hz, 6H); ^{13}C-NMR 199.3, 176.1, 160.7, 55.7, 38.9, 29.8, 27.8, 20.0, 13.4, 8.9. Anal. calcd for $C_{12}H_{19}NO_3$ (225.3) C 63.97, H 8.50, N 6.22; found C 63.76, H 8.59, N 6.14.

4.18. 1-Cyclohexyl-4,4-diethylpyrrolidine-2,3,5-trione ***6c***

Pale yellow oil; yield 81%; IR (cm^{-1}) 3000–2820, 1773, 1714; ^{1}H-NMR 4.26 (*tt*, J=3.8 and 12.3 Hz, 1H), 2.23 (*m*, 2H), 1.85 (*qa*, J=7.5 Hz, 4H), 1.70 (*m*, 4H), 1.34 (*m*, 4H), 0.92 (*m*, 2H), 0.81 (*t*, J=7.5 Hz, 6H); ^{13}C-NMR 199.6, 176.3, 160.7, 55.3, 52.6, 29.1, 28.1, 27.0, 25.7, 24.9, 8.9. Anal. calcd for $C_{14}H_{21}NO_3$ (251.3) C 66.91, H 8.42, N 5.57; found C 66.82, H 8.32, N 5.70.

4.19. Preparation of pyrrolidine-2,3,5-triones ***9a–c****: general procedure*

(i) A solution of *N*-alkyl-2,2-diphenyl acetamide (0.025 mol) in dry benzene (30 cm^3) was heated to 60°C and oxalylchloride (2.7 cm^3, 0.031 mol) was added dropwise. The resulting yellow solution was stirred at the same temperature overnight. After cooling to room temperature, water (50 cm^3) was added, the mixture was stirred for 15 min then 100 cm^3 *tert*-butyl methyl ether was added. The organic layer was separated, washed with water (2×50 cm^3) and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the yellow solid residue was crystallized from *tert*-butyl methyl ether and hexane (1:1) resulting in the corresponding diphenylmethyleneoxazoline-4,5-dione **8a–c**.

(ii) Diphenylmethyleneoxazoline-4,5-dione derivative **8a–c** (0.015 mol) was dissolved in abs. ethanol (50 cm^3) and 2 drops of pyridine were added. The mixture was refluxed gently overnight (the yellow colour of the solution turned to pale yellow). Ethanol was evaporated after cooling and the product was crystallized from the appropriate solvent **9a**,**c** or chromatographed (**9b**, silica gel, *tert*-butyl methyl ether/hexane).

4.20. 3-Ethyl-2-diphenylmethyleneoxazoline-4,5-dione ***8a***

Yellow crystals; yield 83%; mp 163–165°C; IR (cm^{-1}) 1828, 1751, 1653; ^{1}H-NMR 7.45–7.21 (*m*, 10H), 3.36 (*qa*, J=7.1 Hz, 2H), 0.94 (*t*, J=7.1 Hz, 3H); ^{13}C-NMR 154.7, 151.7, 137.3, 136.8, 135.4, 130.8, 130.0, 129.0, 128.8, 128.2, 127.8, 108.3, 78.7, 38.7, 13.0. Anal. calcd for $C_{18}H_{15}NO_3$ (293.3) C 73.71, H 5.16, N 4.78; found C 73.51, H 5.26, N 4.90.

4.21. 3-Butyl-2-diphenylmethyleneoxazoline-4,5-dione ***8b***

Yellow crystals; yield 80%; mp 122–123°C; IR (cm^{-1}) 1828, 1750, 1653; ^{1}H-NMR 7.45–7.20 (*m*, 10H), 3.29 (*t*, J=8.0 Hz, 2H), 1.33 (*qa*, J=8.0 Hz, 2H), 0.86 (*sex*, J=7.6 Hz, 2H), 0.69 (*t*, J=7.2 Hz, 3H); ^{13}C-NMR 154.7, 151.8, 137.6, 136.9, 135.5, 131.0, 130.0, 128.9, 128.7, 128.3, 127.9, 108.3, 78.7, 43.4, 29.7, 19.5, 13.3. Anal. calcd for $C_{20}H_{19}NO_3$ (321.4) C 74.74, H 5.96, N 4.36; found C 74.58, H 6.08, N 4.31.

4.22. 3-Cyclohexyl-2-diphenylmethyleneoxazoline-4,5-dione ***8c***

Yellow crystals; yield 85%; mp 204–205°C; IR (cm^{-1}) 3000–2830, 1822, 1750, 1653; ^{1}H-NMR 7.45–7.20 (*m*, 10H), 2.97 (*tt*, J=3.6 and 12.0 Hz, 1H), 2.19 (*m*, 2H), 1.58 (*m*, 4H), 1.40 (*m*, 1H), 1.04 (*m*, 1H), 0.50 (*m*, 2H); ^{13}C-NMR 155.0, 151.7, 137.8, 137.1, 136.4, 130.0, 130.0, 128.9, 128.8, 128.2,

127.7, 107.8, 78.7, 57.3, 27.7, 25.5, 24.4. Anal. calcd for $C_{22}H_{21}NO_3$ (347.4) C 76.06, H 6.09, N 4.03; found C 75.81, H 6.34, N 4.14.

4.23. 1-Ethyl-4,4-diphenylpyrrolidine-2,3,5-trione ***9a***

Pale yellow crystals; yield 84%; mp 84–86°C (*tert*-butyl methyl ether/hexane); IR (cm^{-1}) 3000–2820, 1773, 1719; ^{1}H-NMR 7.4–7.2 (*m*, 10H), 3.91 (*qa*, J=7.3 Hz, 2H), 1.34 (*t*, J=7.3 Hz, 3H); ^{13}C-NMR 192.9, 172.8, 159.8, 135.1, 129.2, 128.9, 128.8, 128.7, 128.3, 63.3, 35.0, 13.0. Anal. calcd for $C_{18}H_{15}NO_3$ (293.3) C 73.71, H 5.16, N 4.78; found C 73.96, H 5.29, N 4.99.

4.24. 1-Butyl-4,4-diphenylpyrrolidine-2,3,5-trione ***9b***

Yellow oil; yield 61%; IR (cm^{-1}) 3050–2850, 1773, 1718, 1703; ^{1}H-NMR 7.40–7.30 (*m*, 10H), 3.85 (*t*, J=7.4 Hz, 2H), 1.70 (*qi*, J=7.4 Hz, 2H), 1.40 (*sex*, J=7.4 Hz, 2H), 0.95 (*t*, J=7.3 Hz, 3H); ^{13}C-NMR 192.9, 173.1, 157.9, 135.2, 129.1, 129.0, 128.9, 128.8, 128.4, 63.1, 39.7, 29.6, 20.0, 13.5. Anal. calcd for $C_{20}H_{19}NO_3$ (321.4) C 74.74, H 5.96, N 4.36; found C 74.47, H 6.17, N 4.18.

4.25. 1-Cyclohexyl-4,4-diphenylpyrrolidine-2,3,5-trione ***9c***

Pale yellow crystals; yield 86%; mp 108–109°C (EtOH); IR (cm^{-1}) 3000–2830, 1773, 1717, 1700; ^{1}H-NMR 7.45–7.15 (*m*, 10H), 4.34 (*tt*, J=3.8 and 12.3 Hz, 1H), 2.34–1.20 (*m*, 10H); ^{13}C-NMR 192.9, 173.1, 160.0, 135.3, 129.1, 128.7, 128.4, 62.9, 53.2, 28.9, 25.7, 24.9. Anal. calcd for $C_{22}H_{21}NO_3$ (347.4) C 76.06, H 6.09, N 4.03; found C 75.80, H 6.17, N 4.02.

4.26. 1-Ethyl-3-hydroxy-4,4-dimethylpyrrolidine-2,5-dione ***10a***

Colourless oil; 82% ee; IR (cm^{-1}) 3600–3100, 3050–2800, 1705; ^{1}H-NMR 4.29 (*s*, 1H), 3.54 (*qa*, J=7.2 Hz, 2H), 1.37 (*s*, 3H), 1.22 (*s*, 3H), 1.17 (*t*, J=7.2 Hz, 3H); ^{13}C-NMR 180.7, 177.7, 75.4, 45.2, 33.6, 22.3, 19.8, 12.8. Anal. calcd for $C_8H_{13}NO_3$ (171.2) C 56.12, H 7.65, N 8.18; found C 56.00, H 7.47, N 7.97.

4.27. 1-Butyl-3-hydroxy-4,4-dimethylpyrrolidine-2,5-dione ***10b***

Colourless oil; 58% ee; IR (cm^{-1}) 3700–2800, 1784, 1702; ^{1}H-NMR 4.30 (*s*, 1H), 3.49 (*t*, J=7.5 Hz, 2H), 1.55 (*qi*, J=7.5 Hz, 2H), 1.37 (*s*, 3H), 1.30 (*sex*, J=7.5 Hz, 2H), 1.22 (*s*, 3H), 0.92 (*t*, J=7.4 Hz, 3H); ^{13}C-NMR 180.8, 177.9, 75.4, 45.2, 38.5, 29.6, 22.4, 20.0, 19.9, 13.6. Anal. calcd for $C_{10}H_{17}NO_3$ (199.3) C 60.27, H 8.60, N 7.03; found C 60.03, H 8.60, N 7.10.

4.28. 1-Cyclohexyl-3-hydroxy-4,4-dimethylpyrrolidine-2,5-dione ***10c***

White crystals; 61% ee; mp 101–102°C; IR (cm^{-1}) 3700–2800, 1773, 1709; ^{1}H-NMR 4.21 (*s*, 1H), 3.92 (*tt*, J=3.9 and 12.3 Hz, 1H), 2.17–1.15 (*m*, 10H), 1.37 (*s* in *m*), 1.18 (*s* in *m*); ^{13}C-NMR 180.6, 177.9, 75.4, 51.6, 45.2, 29.2, 28.5, 25.8, 25.0, 25.7, 22.2, 20.0. Anal. calcd for $C_{12}H_{19}NO_3$ (225.3) C 63.98, H 8.50, N 6.22; found C 64.02, H 8.43, N 6.27.

4.29. 1-Benzyl-3-hydroxy-4,4-dimethylpyrrolidine-2,5-dione **10d**

White crystals; 85% ee; mp 61–65°C; IR (cm^{-1}) 3700–2800, 1772, 1716; ^{1}H-NMR 7.31 (*m*, 5H), 4.63 (*s*, 2H), 4.26 (*s*, 1H), 1.36 (*s*, 3H), 1.17 (*s*, 3H); ^{13}C-NMR 180.4, 177.4, 135.4, 128.7, 128.6, 128.5, 128.0, 75.6, 45.4, 42.3, 22.3, 19.8. Anal. calcd for $C_{13}H_{15}NO_3$ (233.3) C 66.93, H 6.48, N 6.00; found C 66.86, H 6.39, N 5.93.

4.30. 1,4,4-Triethyl-3-hydroxypyrrolidine-2,5-dione **11a**

Colourless oil; 40% ee; IR (cm^{-1}) 3700–3000, 3020–2800, 1773, 1700; ^{1}H-NMR 4.39 (*s*, 1H), 3.57 (*qa*, J=7.2 Hz, 2H), 1.77 (*m*, 4H), 1.19 (*t*, J=7.2 Hz, 3H), 0.95 (*t*, J=7.5 Hz, 3H), 0.85 (*t*, J=7.5 Hz, 3H); ^{13}C-NMR 179.2, 178.6, 72.2, 52.8, 33.6, 27.3, 25.8, 13.1, 9.3, 8.6. Anal. calcd for $C_{10}H_{17}NO_3$ (199.3) C 60.27, H 8.60, N 7.03; found C 60.05, H 8.68, N 7.12.

4.31. 1-Butyl-3-hydroxy-4,4-diethylpyrrolidine-2,5-dione **11b**

Colourless oil; 33% ee; IR (cm^{-1}) 3700–3000, 3050–2800, 1773, 1701; ^{1}H-NMR 4.38 (*s*, 1H), 3.48 (*t*, J=7.5 Hz, 2H), 1.75 (*m*, 4H), 1.55 (*qi*, J=7.5 Hz, 2H), 1.30 (*sex*, J=7.5 Hz, 2H), 0.93 and 0.91 (overlapping *t*s, J=7.3 Hz, 6H), 0.84 (*t*, J=7.5 Hz, 3H); ^{13}C-NMR 179.4, 178.8, 72.2, 52.8, 38.4, 29.8, 27.2, 25.7, 20.1, 13.6, 9.3, 8.5. Anal. calcd for $C_{12}H_{21}NO_3$ (227.3) C 63.41, H 9.31, N 6.16; found C 62.50, H 9.37, N 5.85.

4.32. 1-Cyclohexyl-3-hydroxy-4,4-diethylpyrrolidine-2,5-dione **11c**

Colourless oil, 69% ee; IR (cm^{-1}) 3700–3100, 3050–2800, 1773, 1700; ^{1}H-NMR 4.30 (*s*, 1H), 4.00 (*tt*, J=3.8 and 12.4 Hz, 1H), 2.20–1.54 (*m*, 10H), 1.36–1.23 (*m*, 4H), 0.93 and 0.84 (overlapping *t*s, J=7.4 Hz, 6H); ^{13}C-NMR 179.3, 178.8, 72.0, 52.5, 51.7, 29.4, 28.7, 27.4, 25.9, 25.8, 25.7, 25.0, 9.4, 8.5. Anal. calcd for $C_{14}H_{23}NO_3$ (253.3) C 66.39, H 9.16, N 5.53; found C 66.30, H 9.10, N 5.71.

4.33. 1-Ethyl-3-hydroxy-4,4-diphenylpyrrolidine-2,5-dione **12a**

81% ee; mp 59–60°C; IR (cm^{-1}) 3700–2800, 1750, 1716; ^{1}H-NMR 7.66 (*m*, 2H), 7.43–7.22 (*m*, 6H), 7.01 (*m*, 2H), 5.15 (*s*, 1H), 3.71 (*q*a, J=7.2 Hz, 2H), 1.25 (*t*, J=7.2 Hz); ^{13}C-NMR 176.0, 175.3, 139.1, 137.5, 128.9, 128.8, 128.7, 128.3, 128.1, 128.0, 75.0, 61.8, 34.2, 12.8. Anal. calcd for $C_{18}H_{17}NO_3$ (295.3) C 73.21, H 5.80, N 4.74; found C 73.45, H 5.90, N 4.56.

4.34. 1-Butyl-3-hydroxy-4,4-diphenylpyrrolidine-2,5-dione **12b**

White crystals; 58% ee; mp 100–104°C; IR (cm^{-1}) 3700–2850, 1772, 1700; ^{1}H-NMR 7.66 (*d*, J=7.2 Hz, 2H), 7.43–7.26 (*m*, 6H), 7.03 (*d*, J=7.9 Hz, 2H), 5.16 (*s*, 1H), 3.65 (*t*, J=7.2 Hz, 2H), 1.63 (*qi*, J=7.2 Hz, 2H), 1.32 (*sex*, J=7.3 Hz, 2H), 0.93 (*t*, J=7.3 Hz, 3H); ^{13}C-NMR 176.3, 175.5, 139.2, 137.5, 129.0, 128.9, 128.8, 128.7, 128.3, 128.1, 128.0, 75.1, 63.2, 39.1, 29.6, 20.1, 13.6. Anal. calcd for $C_{20}H_{21}NO_3$ (323.4) C 74.28, H 6.55, N 4.33; found C 74.42, H 6.59, N 4.20.

4.35. 1-Cyclohexyl-3-hydroxy-4,4-diphenylpyrrolidine-2,5-dione ***12c***

White crystals; 17% ee; mp 156–159°C; IR (cm^{-1}) 3750–2830, 1777, 1700; ^{1}H-NMR 7.66 (*m*, 2H), 7.44–7.26 (*m*, 6H), 7.02 (*m*, 2H), 5.13 (*s*, 1H), 4.12 (*tt*, J=12.3 and 3.8 Hz, 1H), 2.19 (*m*, 3H), 1.88–1.67 (*m*, 4H), 1.42–1.18 (*m*, 3H); ^{13}C-NMR 176.2, 175.2, 139.2, 137.7, 128.9, 128.8, 128.7, 128.4, 128.0, 127.9, 74.6, 61.6, 52.4, 29.3, 28.5, 25.8, 25.7, 25.0. Anal. calcd for $C_{22}H_{23}NO_3$ (349.4) C 75.62, H 6.64, N 4.01; found C 75.42, H 6.69, N 4.00.

4.36. Determination of the absolute configuration of ***10a***

(3*R*)-4,5-Dihydro-4,4-dimethyl-3-(2-tetrahydropyranyloxy)-2(3*H*)-furanone **13** was prepared and purified by the method of Ito and Kibayashi[22] starting from (*R*)-pantolactone and 3,4-dihydro-2*H*-pyran.

*4.37. (*R*)-*N*-Ethyl-4-hydroxy-3,3-dimethyl-2-(2-tetrahydropyranyloxy)butyramide* ***14***

A solution of (3*R*)-dihydro-4,4-dimethyl-3-(2-tetrahydropyranyloxy)-2(3*H*)-furanone (4.28 g, 0.020 mol) in 20 cm^3 methanol was cooled with ice water and ethylamine (1.13 g, 0.025 mol) was added. After stirring for 3 h at room temperature the solvent was evaporated under reduced pressure. The crude product was purified by Kugelrohr distillation. Colourless oil; yield 92%; IR (cm^{-1}) 3750–2750, 1653; ^{1}H-NMR 6.39 (br *s*, 1H), 4.40 (*t*, J=7.3 Hz, 1H), 4.13 (*s*, 1H), 3.50–3.25 (*m*, 4H), 1.90–1.50 (*m*, 6H), 1.19 (*t*, J=8.4 Hz, 3H), 1.02 (*s*, 3H), 0.90 (*s*, 3H); ^{13}C-NMR 171.6, 99.8, 81.4, 70.1, 65.1, 39.4, 33.8, 31.4, 27.0, 24.9, 21.0, 20.9, 15.0. Anal. calcd for $C_{13}H_{25}NO_4$ (259.3) C 60.22, H 9.72, N 5.40; found C 60.04, H 9.65, N 5.47.

*4.38. (*R*)-1-Ethyl-4,4-dimethyl-3-(2-tetrahydropyranyloxy)pyrrolidine-2,5-dione* ***15***

(2*R*)-*N*-Ethyl-4-hydroxy-3,3-dimethyl-2-(2-tetrahydropyranyloxy)butyramide (1.03 g, 0.004 mol) and pyridinium dichromate (7.5 g, 0.02 mol) were dissolved in 20 cm^3 dry DMF and the mixture was stirred for 24 h at room temperature. The solution was poured into 10 volumes of water and then extracted with *tert*-butyl methyl ether. After drying of the combined organic layers over $MgSO_4$ the solvent was removed under reduced pressure. The product was purified by Kugelrohr distillation. Colourless oil; yield 63%; IR (cm^{-1}) 3010–2820, 1772, 1716; ^{1}H-NMR 5.20 (*m*, 1H), 4.28 (*s*, 1H), 3.53 (*m*, 4H), 1.50–1.80 (*m*, 6H), 1.36 (*s*, 3H), 1.25 (*s*, 3H), 1.16 (*t*, J=7.3 Hz, 3H); ^{13}C-NMR 180.7, 176.0, 98.6, 78.9, 62.4, 44.6, 33.4, 30.1, 25.3, 22.8, 20.2, 19.0, 12.9. Anal. calcd for $C_{13}H_{21}NO_4$ (255.3) C 61.16, H 8.29, N 5.49; found 61.09, H 8.13, N 5.40.

*4.39. (*R*)-1-Ethyl-3-hydroxy-4,4-dimethylpyrrolidine-2,5-dione (*R*)-***10a***

(*R*)-1-Ethyl-4,4-dimethyl-3-(2-tetrahydropyranyloxy)pyrrolidine-2,5-dione (1.02 g, 0.004 mol) was dissolved in methanol (10 cm^3). To this solution $TsOH \cdot H_2O$ (10 mg) was added and the mixture was stirred at room temperature for 4 h. After evaporation of the solvent, the residue was dissolved in dichloromethane, washed with 5% aqueous $NaHCO_3$ solution and water, and dried over $MgSO_4$. The solvent was removed and the crude product was purified by Kugelrohr distillation. Colourless oil; yield 90%; IR (cm^{-1}) 3600, 3050–2800, 1705; ^{1}H-NMR 4.29 (*s*, 1H), 3.54 (*qa*, J=7.2 Hz, 2H), 1.37 (*s*, 3H), 1.22 (*s*, 3H), 1.17 (*t*, J=7.2 Hz, 3H); ^{13}C-NMR 180.7, 177.7, 75.4, 45.2, 33.6, 22.3, 19.8, 12.8. Anal. calcd for $C_8H_{13}NO_3$ (171.2) C 56.12, H 7.65, N 8.18; found C 55.98, H 7.61, N 8.15.

4.40. Hydrogenation of pyrrolidine-2,3,5-triones: general procedure

For all experiments a 5 wt% Pt/Al_2O_3 catalyst (Engelhard 4759) was used. The catalyst was pretreated in a fixed bed reactor by flushing with 12.5 ml min^{-1} nitrogen (O_2 <10 ppm) at 400°C for 30 min followed by a reductive treatment in 30 ml min^{-1} hydrogen (O_2 <2 ppm) for another 90 min. The catalyst was then cooled to room temperature in hydrogen and transferred into the autoclave under exclusion of oxygen. The catalyst was first contacted with the solvent containing the appropriate amount of modifier.

Hydrogenation of the pyrrolidine-2,3,5-triones was carried out in a 100 ml stainless steel autoclave (Baskerville) with a 50 ml glass liner and PTFE cover, to provide clean conditions. Under standard conditions 60 mg pretreated catalyst, 10 μmol l^{-1} cinchonidine, 3.2 mmol substrate and 5 ml toluene were used at 60 bar and 10°C.

The enantiomeric excess was determined by gas chromatographic analysis using a chiral column in the case of **10a**–**d** and **11a**–**c** (WCOT Cyclodextrin-β-2,3,6-M-19 Chrompack column), and ^{1}H-NMR spectroscopy via the corresponding MTPA esters for **12a**–**c**. Concerning the chemoselectivity of the hydrogenation reactions, no other products beside the alcohols **10a**–**d** and **11a**–**c** could be detected by GC analysis.

4.41. Molecular modelling

As molecular modelling software, the program ‘Hyperchem’ was used. The minimum energy conformations of cinchonidine and substrate molecules were determined independently using molecular mechanics (MM+) method.

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