Asymmetric Hydrogenation of Substituted 2-Pyrones

Matthias J. Fehr,[†] Giambattista Consiglio,*[,†] Michelangelo Scalone,[‡] and Rudolf Schmid[‡]

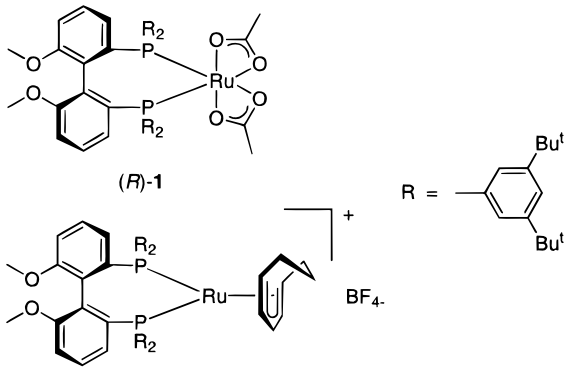
Swiss Federal Institute of Technology, Department of Industrial and Engineering Chemistry, ETH Zentrum, CH-8092 Zurich, Switzerland, and Pharmaceutical Division, Process Research & Catalysis, F. Hoffmann-La Roche Ltd., CH-4070 Basel, Switzerland

Received November 5, 1998

Various substituted 2-pyrones have been hydrogenated with high enantioselectivity (up to 97% ee) to the corresponding 5,6-dihydropyrones using cationic ruthenium catalysts containing the (6,6′-dimethoxybiphenyl-2,2′diyl)bis[3,5-di(*tert*-butyl)phenylphosphine] ligand. When substituents at position 3 are absent, 5,6-dihydropyrones are further hydrogenated to the fully saturated δ-lactones. In the case of 4,6-dimethyl-2*H*-pyran-2-one, the diastereoselectivity of the second hydrogenation step was determined by the chirality of the applied catalyst, while for the 4,5,6-trimethyl-2*H*-pyran-2-one a double asymmetric induction effect was observed. Other cyclic substrates with endo- or exocyclic double bonds were hydrogenated, although with substantially lower enantioselectivity with respect to the 2-pyrones.

Introduction

Enantioselective homogeneous hydrogenation using Ru(II) catalysts is a well-investigated method for stereoselective synthesis.[1−4] High enantioselectivities have been achieved for the hydrogenation of functionalized olefins such as α-(acylamino)acrylic acids,[5] enamides,[6,7] α,β- or β,γ-unsaturated carboxylic acids,[8−12] and allylic and homoallylic alcohols,[13] especially when using complexes containing atropisomeric bidentate phosphine ligands such as Binap,[14] Biphemp, and MeO−Biphep.[15,16] Other exocyclic olefinic substrates with aprotic functions as α,β-unsaturated carbonyl compounds, alkylidene lactones, alkenyl esters,[17] 3-alkylidene-2-piperidones,[18] and α-methylendioxolanones[19] have been hydrogenated with high enantioselectivity using Ru(II)−Binap catalysts.



The hydrogenation of the α-pyrone **3a** was the first example of a regio- and enantioselective reduction of an endocyclic enol ester type double bond.[1,20] The hydrogenation of this type of substrate represents an interesting and straightforward method for synthesizing optically active 5,6-dihydro-2-pyrones and, if complete, δ-lactones, which show interesting pharmaceutical properties.[21−26]

[†] ETH Zentrum.
[‡] F. Hoffmann-La Roche Ltd.

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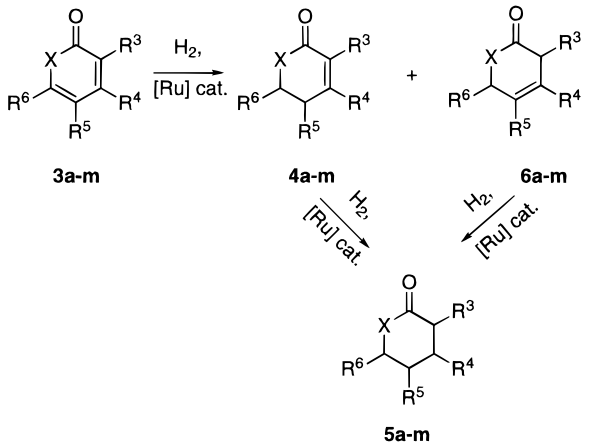
10.1021/jo982215l CCC: $18.00
Published on Web 07/14/1999

In fact, tetrahydrolipstatin, a potent antiobesity drug that is accessible starting from lactone (3*S*,4*S*,6*R*)-**5a**, has recently been introduced in the market.[1,20,27−29] When the catalyst precursor **1** (with the atropisomeric ligand (6,6′-dimethoxybiphenyl-2,2′-diyl)bis([3,5-di(*tert*-butyl)-phenylphosphine]) was used in the presence of HBF_4, the 5,6-dihydropyrone **4a** was obtained in high enantiomeric excess (96% ee). The use of other MeO−Biphep ligands gave substantially lower enantioselectivities.[1,20] The sterically demanding *tert*-butyl groups lead to effective hydrogenation of **3a**. The high enantioselectivity was attributed to the comparatively high rigidity and the slightly larger chiral pockets of complexes bearing the above-mentioned ligand.[30] NMR studies of selected complexes revealed restricted rotation around several of the P−C(ipso) bonds of the phosphorus substituents containing the bulky 3,5-di-*tert*-butyl groups.[30−32] This effect, which also led to improved enantioselectivity of several other catalytic reactions,[33−36] was named *3,5-dialkyl meta effect* by Pregosin and co-workers. Several other ruthenium complexes containing the above-mentioned ligand, e.g., $[Ru(acetone)_4(P\wedge P)](BF_4)_2$, $[Ru(DMF)_4(P\wedge P)](BF_4)_2$, or $[RuH(i\text{-}PrOH)_2(P\wedge P)]BF_4$, although bearing only weakly coordinating solvent molecules, exhibited no catalytic activity for the hydrogenation of **3a** in the absence of HBF_4.[20] Therefore, the addition of HBF_4 seems to be essential, not only for the abstraction of the coordinated acetate, but also for lowering the pH value to enable high catalytic activity.

Furthermore, the synthesis and characterization of the ruthenium hydrido complexes $[RuH(i\text{-}PrOH)_2(P\wedge P)]BF_4$[31] and $[RuH(cymene)(P\wedge P)]BF_4$[30] (where P∧P represents (6,6′-dimethoxybiphenyl-2,2′-diyl)bis[3,5-di(*tert*-butyl)-phenylphosphine]) suggest possible coordination modes of the 2-pyrone **3a** during hydrogenation and possible intermediates involved in the catalytic cycle. To explore the potential of this atropisomeric ligand, different substituted 2-pyrones (Scheme 1) and other substrates with endocyclic C−C double bonds were synthesized and subjected to hydrogenation. Here we present detailed results of the catalytic hydrogenation using the catalysts **1** and **2** in the presence of HBF_4. Some of the results concerning the stereochemistry of the stepwise reduction of pyrone **3g** have been published in a preliminary form.[37]

Scheme 1



	R^3	R^4	R^5	R^6	
a:	*n*-C_6H_{13}	OH	H	*n*-$C_{11}H_{23}$	X = O
b:	*n*-C_6H_{13}	OH	H	*n*-C_6H_{13}	
c:	CH_3	OH	H	*n*-$C_{11}H_{23}$	
d:	CH_3	OH	H	CH_3	
e:	H	OH	H	CH_3	
f:	H	OCH_3	H	CH_3	
g:	H	CH_3	H	CH_3	
h:	H	CH_3	CH_3	CH_3	
i:	H	CH_3	COOEt	CH_3	
k:	H	Ph	H	Ph	
l:	H	CH_3	H	CH_3	X = NH
m:	H	CH_3	H	CH_3	X = NCH_3

Table 1. Asymmetric Hydrogenation of Pyrone 3a with 1 or 2

					product **4a**		
entry	s/c[a]	[HBF_4]/[Ru][b]	catalyst	convn [%][c]	sel [%]	ee [%][d]	confign
1	50	2	(*S*)-**1**	100	86	95.5	*R*
2	500	10	(*S*)-**1**	99	>99	94.7	*R*
3	333	10	(*S*)-**1**	99	>99	96.2	*R*
4	500	2	(*S*)-**1**	6			
5	500	0	(*R*)-**2**	7			
6	500	10	(*R*)-**2**	98	>99	94.2	*S*
7	500	2.6	(*R*)-**1**	90	>99	92.7	*S*
8	1000	3	(*R*)-**1**	73	>99	91.8	*S*
9	500	10	(*S*)-**1**	100	80	96.4	*R*

[a] Molar substrate-to-catalyst ratio. [b] Molar equivalents of HBF_4 (50% aqueous) added. [c] Reaction time: 20 h. [d] See Experimental Section.

Results and Discussion

Enantioselective Hydrogenation of 4-Hydroxy-2-pyrones. Suitable reaction conditions were found in screening experiments using pyrone **3a** (see Table 1).[1] Hydrogenation reactions were usually carried out at 60 °C under 60 bar of hydrogen pressure in order to achieve complete conversion within 20 h. The chosen solvent was 2-propanol.[1] To achieve high catalytic activity, the addition of HBF_4 to the reaction was essential when the acetate complex **1** or the cyclooctadienyl complex **2** was used. While for hydrogenations at a low substrate-to-catalyst ratio (hereafter indicated as s/c) of 50, 2 molar equiv of HBF_4 have already produced good results, for higher s/c ratios excess HBF_4 had to be added to the reaction mixture before high catalytic activity was observed (entries 2−4 and 6, Table 1).

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Scheme 2

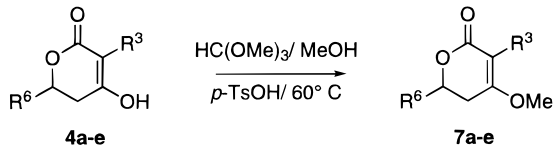

Table 2. Asymmetric Hydrogenation of Pyrones 3a−3d with Complex 1

entry		s/c[a]	[HBF_4]/ [Ru][a]	catalyst	convn [%][b]		sel [%]	ee [%][c]	product config[d]
1	**3a**	50	2	(*S*)-**1**	>99	**4a**	86	95.5	*R*(−)
2	**3a**	500	10	(*S*)-**1**	99	**4a**	>99	94.7	*R*(−)
3	**3b**	250	10	(*S*)-**1**	>99	**4b**	96	97.2	*R** (−)
4	**3c**	50	2	(*R*)-**1**	88	**4c**	91	91.4	*S** (+)
5	**3d**	50	2	(*R*)-**1**	75	**4d**	95	93.0	*S** (+)

[a] See Table 1. [b] Reaction time: 20 h. [c] See Experimental Section. [d] Where the absolute configuration was not determined, the expected absolute configuration is given (*). Sign of optical rotation is given in parentheses.

Table 3. Asymmetric Hydrogenation of Pyrone 3e with Complex 1

entry	[HBF_4]/ [Ru][a]	catalyst	convn [%][b]	sel. [%]	**4e** ee [%]	config[c]	**5e** sel. [%] *cis*	**5e** sel. [%] *trans*
1[d]	10	(*S*)-**1**	93	9	73	*R*	11	38
2	0	(*S*)-**1**	92	25	75	*S*	32	35

[a] See Table 1. [b] Reaction time: 20 h. [c] Based on the sign of the optical rotation of derivatized **7e**.[38] [d] Low selectivity to **5e** is due to acid-catalyzed reaction with 2-propanol (see text).

However, with smaller solvent volumes good activity with somewhat lower enantioselectivitiy was obtained with a smaller amount of acid (entries 7 and 8, Table 1). Therefore, a certain acidity of the reaction mixture seems to be essential for catalytic activity. Enantioselectivity in the formation of **4a** reached up to 96% ee, as determined after derivatization to the 5,6-dihydro-4-methoxy-2-pyrone **7a** (Scheme 2). The hydrogenation proceeds selectively to the dihydropyrone. Further hydrogenation of the second double bond of the dihydropyrone **4a** is much slower. After 5 days (compare entry 9, Table 1) only 12% of tetrahydropyrone **5a** (and 8% of 5,6-dihydro-3-hexyl-4-(2-propyloxy)-6-undecyl-2H-pyran-2-one from reaction of **4a** with the solvent 2-propanol) was formed.

To investigate the steric influence of the substituents, differently substituted 4-hydroxy-2-pyrones (**3b**−**e**) were synthesized and hydrogenated using either (*R*)- or (*S*)-**1**. An excess of HBF_4 was used for reactions at s/c ratios higher than 50 (vide infra). The results are shown in Tables 2 and 3. Pyrone **3b** (with two *n*-hexyl substituents in positions 3 and 6) is hydrogenated with comparable or somewhat higher enantioselectivity (97.2% ee) with respect to **3a**.

Substrates **3c** and **3d**, both bearing a methyl group in position 3 of the pyrone ring, are hydrogenated with lower enantioselectivity to the corresponding dihydropyrones (91.4 and 92.9% ee). Thus, the substitution of the *n*-hexyl substituent at position 3 for a methyl group has an favorable effect on enantioselectivity.

4-Hydroxy-6-methylpyrone (**3e**) was hydrogenated under identical conditions and gave the fully hydrogenated tetrahydropyrone **5e** as the main product, in contrast to the pyrones **3a**−**d**. The two hydrogenation reactions shown in Table 3 were carried out under identical conditions except that in entry 2 no additional acid was used. The catalytic reaction proceeded even in the absence of HBF_4, unlike in the case of 4-hydroxy-2-pyrones **3a**−**d**, and gave mainly the *cis*- and *trans*-tetrahydropyrones **5e**. Pyrone **3e** has a higher acidity (pK_a = 4.73, see experimental part) than the pyrones bearing an alkyl substituent in position 3 (pK_a **3d** = 5.12). The calculated pK_a values (see experimental part) for the pyrones **3e**, **3d**, and **3b** were 4.96, 5.24, and 5.77, respectively, and show the growing inductive and likewise shielding effect going from no substituent to methyl and to *n*-hexyl.

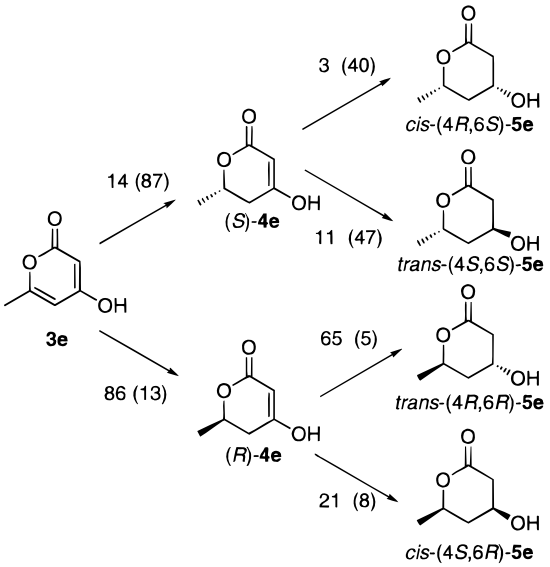

Figure 1. Different stereoselectivitiy for the hydrogenation of **3e** (given as relative concentrations in percent) using the catalyst (*S*)-**1** with or without (values in brackets) HBF_4.

The higher acidity of **3e** may in itself lead to a higher proton concentration in the solution and allows for effective hydrogenation even in the absence of HBF_4. The low selectivity for the tetrahydropyrones in entry 1 (Table 3) is due to the slowly progressing acid-catalyzed alcoholysis of the lactone **5e** to give isopropyl 3,5-dihydroxyhexanoate. The progressing formation of the latter compound makes the alternative mechanistic possibility of hydrogenation of a β-keto ester, formed by ring opening, followed by ring closure rather unlikely. Surprisingly, the hydrogenation of **3e** took place preferentially from the opposite enantioface of the C−C double bond when no acid was used, but occurred with comparable, although relatively lower enantioselectivity in both cases (73−76% ee). Kinetic resolution effects in the second hydrogenation step, as shown by the enantioselectivity in the formation of *cis*- and *trans*-**5e**, do not significantly influence these enantioselectivity values. The absolute configuration of dihydropyrone **4e** was determined through derivatization to **7e** (according to Scheme 2), determination of its optical rotation value and comparison with literature data.[38] The hydrogenation of either enantiomer of dihydropyrone **4e**, shown in detail in Figure 1, takes place with only very low diastereoselectivity in favor of *trans*-**5e** in the presence of HBF_4 (entry 1, Table 3). In the absence of HBF_4 (entry 2, Table 3) essentially no diastereoselectivity of the second hydrogenation step is observed.

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Table 4. Asymmetric Hydrogenation of Pyrone 3g and 3h with (*R*)-1[a]

substrate	H_2 [bar]	*T* [°C]	*t* [min]	convn [%][b]	ee [%][c]	de [%][d]	de [%][e]	% ee *cis*-**5g/h**
3g	40	40	83	99	86.9	88.1	62.7	97.3
3g	60	40	77	99	88.2	89.3	65.3	97.8[f]
3g	40	50	56	98	87.5	86.5	60.8	97.2
3h	40	40	220	93	92.2[g]	>98[h]	>98[h]	94.2

[a] s/c = 250 for substrate **3g**, s/c = 100 for substrate **3h**, conversion and product selectivity determined after complete conversion by means of GC. [b] Conversion of dihydropyrones **4g** or **4h**. [c] Enantioselectivity in the hydrogenation of **3g** to **4g** (Figure 3). The value was calculated as {[(4*R*,6*S*)-**5g**] + [(4*S*,6*S*)-**5g**] − [(4*R*,6*R*)-**5g**] − [(4*S*,6*R*)-**5g**]}/{Σ**5g**} at complete conversion. [d] Diastereoselectivity in the hydrogenation of (*S*)-**4g** to **5g** (Figure 3). The de value was calculated as {[(4*R*,6*S*)-**5g**] − [(4*S*,6*S*)-**5g**]}/{[(4*R*,6*S*)-**5g**] + [(4*S*,6*S*)-**5g**]} at complete conversion. [e] Diastereoselectivity in the hydrogenation of (*R*)-**4g** to **5g** (Figure 3). The de value was calculated as {[(4*R*,6*R*)-**5g**] − [(4*S*,6*R*)-**5g**]}/{[(4*R*,6*R*)-**5g**] + [(4*S*,6*R*)-**5g**]} at complete conversion. [f] E.g., for the second entry, the diastereomeric product ratio for **5g** (see Figure 3) is (4*S*,6*R*)/(4*R*,6*R*)/(4*S*,6*S*)/(4*R*,6*S*) = 1.0:4.9:5.0:89.1. [g] Initial enantiomeric excess (at 55% conversion with respect to **3h**). [h] Relative concentrations of other diastereomers of **5h** were less then 1%.

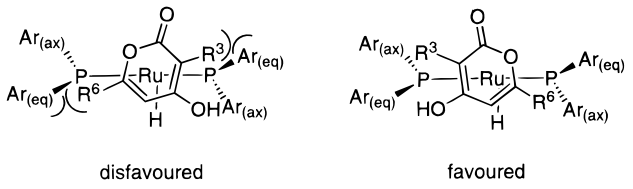


Figure 2. Possible geometry of the adduct between 4-hydroxy-2-pyrone and a ruthenium hydride complex with C_2-symmetric atropisomeric (*S*)-diphosphine (side view, ruthenium behind the ring).

In contrast to the observed differences in chemoselectivity for the hydrogenation of pyrone **3e**, **3f** (the methyl ether thereof) selectively gives the corresponding dihydropyrone **4f** with enantiomeric excess between 86 and 90% upon hydrogenation under identical conditions.[37] The fact that pyrone **3e** was fully hydrogenated to the tetrahydropyrone **5e**, while 4-hydroxy-2-pyrones with alkyl substituents in position 3 (**3a**−**d**) and the 4-methoxy-2-pyrone **3f** stop at the corresponding dihydropyrone, can be accounted for by assuming a possible chemoselective hydrogenation of a keto group of the tautomer of dihydropyrone **4e**. The keto form is, in fact, not accessible to dihydropyrone **4f** due to the methylation of the hydroxy group and to the dihydropyrones **4a**−**d** due to the steric hindrance of the 3-alkyl substituent. The lower enantioselectivities for the hydrogenation of 4-hydroxy-2-pyrones with substituents at position 3, going from *n*-hexyl to methyl and hydrogen, can be understood on the basis of a coordination of the substrate like that shown in Figure 2. This coordination is analogous to that shown by the η^6-coordinated cymene found in the crystal structure of [RuH(cymene)(P∧P)]BF_4[30] (where P∧P represents 6,6′-dimethoxybiphenyl-2,2′diyl)bis[3,5-di(*tert*-butyl)phenylphosphine), where the methyl and isopropyl substituents of the ring are located in the region of the axial phenyl rings bound to the phosporus atoms. The para-type substitution pattern of the alkyl substituents (R^3 and R^6) of the planar pyrone ring in combination with the nearly C_2-symmetry of the backbone of a possible ruthenium hydrido adduct complex, leads to a discrimination effect influenced by the interaction of both substituents.

Enantioselective Hydrogenation of 4-Alkyl-2-pyrones. The hydrogenation of 4,6-dimethylpyrone (**3g**), together with the catalyst (*R*)-**1**, gives the corresponding *cis*-(4*R*,6*S*)-tetrahydro-2-pyrone **5g** as the main product in up to 98% ee.[37] The hydrogenation proceeds stepwise from pyrone **3g** to give the 5,6-dihydropyrone **4g** as well as smaller amounts of the 3,6-dihydropyrone, both of which are hydrogenated further to the corresponding

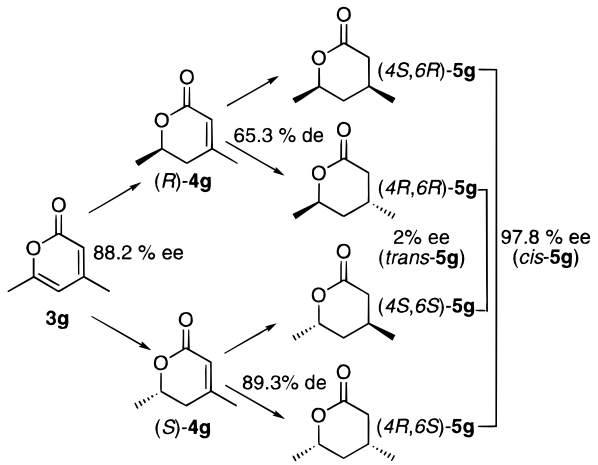


Figure 3. Enantiomeric and diastereomeric excesses in the hydrogenation of pyrone **5g** using the catalyst (*R*)-**1**/HBF_4 leading to an ee of up to 98% of the main product *cis*-**5g** (entry 2, Table 4).

tetrahydropyrones **5g** (Figure 3). Kinetic effects led to an increase in the ee of **4g** and *cis*-**5g** during the reaction, thus making it difficult to compare the actual stereoselectivity of the hydrogenation with other pyrones. From the ratio of the four stereomers of **5g** at complete conversion, the enantioselectivity of the hydrogenation of pyrone **3g** and the diastereoselectivity of the hydrogenation of the two enantiomers **4g** was calculated (see Table 4 and Figure 3). The enantioselectivity of the first hydrogenation step is around 88% ee and lies in the region of the value for pyrone **3f**. The diastereoselective hydrogenation of the major enantiomer **4g** occurs with diastereomeric excess between 86 and 89% de and yields preferably the *cis*-**5g** tetrahydropyrone, while the minor enantiomer is hydrogenated with somewhat lower diastereoselectivity (60−65% de) mainly to the trans-stereomer of **5g**. In contrast, when starting with pyrone **3h** (4,5,6-trimethyl-2*H*-pyran-2-one), the diastereoselectivity of the second hydrogenation step is overwhelmingly determined by the asymmetry of the substrate. The first hydrogenation step leads, with 80% selectivity and 94% ee, to the corresponding 5,6-dihydropyrone **4h**, while 20% 3,6-dihydropyrone **6h** with close to 81% ee were formed. Therefore, the additional methyl group leads to an increase in the enantioselectivity of the hydrogenation compared to pyrone **3g** (88 to 94% ee). The hydrogenation proceeds smoothly, despite the double bond being tetrasubstituted. Unlike the hydrogenation of **4g**, both enantiomers of dihydropyrone **4h** are hydrogenated diastereospecifically to the corresponding *all-cis*-**5h** tetrahydropyrone. Isolated dihydropyrone **4h** was hydro-

Table 5. Asymmetric Hydrogenation of Compounds 8, 9, 11 and 12 by (*R*)-1

entry	substrate	H_2 [bar]	*T* [°C]	s/c	t [h]	convn [%]	product	ee [%]
1[a]	**8**	60	40	100	24	>99	(*S*)-**10**	65
2[a]	**9**	60	40	100	20	>99	(*S*)-**10**	56
3[b]	**11**	40	40	250	0.5	17	(*R*)-**13**[c]	76
4[a]	**12**	60	60	150	0.5	46	(*R*)-**14**[c]	69

[a] Two equivalents of HBF_4 (50% aqueous) used. [b] Four equivalents of HBF_4 (50% aqueous) used. [c] Determined at low conversion (no fully hydrogenated alcohol present).

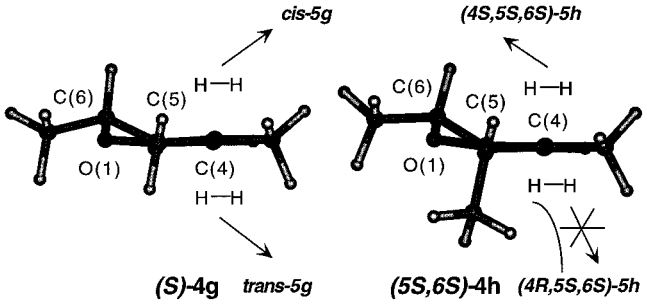
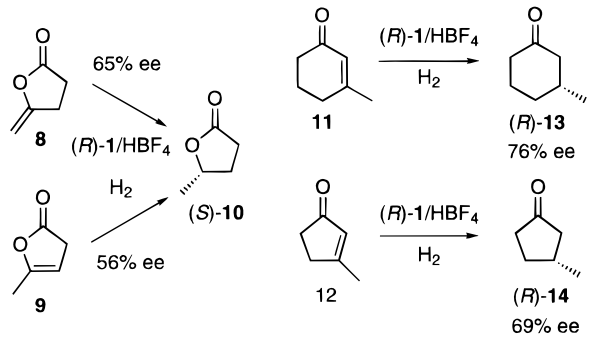


Figure 4. Free energy minimized structure (consistent valence force field) of the single molecule (*S*)-**4g** and (5*S*,6*S*)-**4h** (view along the C(4)−C(3) bond).

genated using the opposite enantiomeric catalyst ((*R*)-**1** and (*S*)-**1**) to give in all cases formation of *all-cis*-**5h** only. 3,6-Dihydropyrone **6h** is not hydrogenated further. As found for **4g**,[37] kinetic resolution effects play an important role in the second hydrogenation step from **4h** to **5h**. The major enantiomer of **4h** is hydrogenated faster than its mirror image, resulting in a decrease in the enantiomeric excess of **4h** with increasing conversion. At complete conversion, the enantiomeric excess of *all-cis*-**5h** amounts to 94% ee. The diastereoselectivity of the second hydrogenation step, which occurs as a result of the additional methyl group at position five of the pyrone, can be accounted for by looking at the structures of dihydropyrone **4g** and **4h** (Figure 4). The methyl group in allylic position to the C(4)−C(3) double bond of dihydropyrone **4h** is in a pseudoaxial position and hinders a second hydrogenation to give the corresponding tetrahydropyrone (4*R*,5*S*,6*S*)- or (4*S*,5*R*,6*R*)-**5h**. In contrast, for the hydrogenation of the 5,6-dihydropyrone **4g**, attack on both diastereofaces is possible, and the diastereoselectivity is instead determined by the chirality of the catalyst to give the *trans*- or *cis*-tetrahydropyrone **5g**.

In the hydrogenation of the pyrone **3g**, solvent, and acid have a strong influence on the reaction rate. Use of methanol as the solvent resulted in a 15 times lower reaction rate than with 2-propanol, while hydrogenation in *tert*-butyl alcohol showed a 1.5 times higher reaction rate. The reaction was also carried out in 50/50 v/v % mixture of 2-propanol and water and was as slow as that in methanol. Using dichloromethane as the solvent, no catalytic activity was observed. When CF_3SO_3H was used instead of HBF_4, the reaction proceeded at a similar rate, while when H_2SO_4 was used the reaction rate decreased by a factor of 10. When HCl or *p*-TsOH was used as the acid, no catalytic hydrogenation was observed. Thus, the importance of using strong acids with weakly coordinating counteranions was shown. Applying higher hydrogen pressure led to an increase in the chemoselectivity for the formation of 5,6-dihydropyrone **4h** against 3,6-dihydropyrone **6h**. At 5 bar of hydrogen pressure, the chemoselectivity was around 75%, while above 20 bar of H_2 the chemoselectivity was between 90 and 95%.

Scheme 3



Hydrogenation of Other Substrates. In contrast with pyrones described above, hydrogenation experiments with the substrates ethyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-carboxylate (**3i**) and 4,6-diphenyl-2-pyrone (**3k**), using the catalytic system **1**, resulted in no hydrogenation even when low s/c ratios were applied. Steric hindrance of the substituents may have prevented the formation of an adduct complex and thus a catalytic hydrogenation. Despite their structural similarity to the 2-pyrones, the two 2-pyridones (**3l** and **3m**) did not exhibit comparable results in terms of activity and selectivity when used in the asymmetric hydrogenation. While the 4,6-dimethyl-2-pyridone (**3l**) could not be hydrogenated at all, 1,4,6-trimethyl-2-pyridone (**3m**) was hydrogenated only slowly to the corresponding piperidone. After 46 h at 60 °C /60 bar H_2 and s/c = 25, complete conversion was possible. The *cis*-piperidone **5m** was formed with 84% selectivity as the main product but with a very low enantioselectivity of about 10% ee. The *trans*-piperidone, which was formed with around 16% selectivity, showed 60% ee. The reason for the comparatively low activity and enantioselectiviy for the hydrogenation of these substrates is not yet clear. However the lack of reactivity for hydrogenation of pyridone **3l** could be due to the predominant existence of the pyridinol tautomeric form. This form is not possible for the *N*-methyl-substituted compound **3m**.

Hydrogenation of other related unsaturated heterocycles with catalyst **1** was also studied (Scheme 3, Table 5). Hydrogenation of substrate **8** with an exocyclic and substrate **9** with an endocyclic C−C double bond gave the (*S*)-γ-valerolactone (*S*)-**10** in 65 and 56% enantiomeric excess, respectively, when the (*R*)-**1** catalyst was used. This values are substantially lower than the enantiomeric excess reached for the hydrogenation of 2-pyrones. Using Ru(II)−binap complexes, Takaya and co-workers found 94 and 20% ee for the resulting product after the hydrogenation of **8** and **9** respectively.[17] This was explained with the difficulty of substrates bearing endocyclic double bonds to give chelate coordination as is the case for substrate **9**. In our case for substrate **9** (as well as for all of the hydrogenated 2-pyrones), the ee is substantially higher, although only endocylic bonds are present for an adduct formation with the Ru(II) species.

This might be explained by assuming a more rigid structure of complex **1** with respect to the analogous binap species. Hydrogenation of the α,β-unsaturated cyclic ketones **11** and **12** succeeded with 76 and 69% ee, respectively, yielding preferentially the (*R*)-enantiomer when (*R*)-**1** catalyst was used. The enantiomeric excess was determined at low conversion due to the subsequent hydrogenation of the keto group, which led to kinetic resolution effects changing the ee of **13** and **14** with progressing reaction. The relative topicity for the hydrogenation of these two substrates was the same as for the hydrogenation of (*R*)- or (*S*)-**4g** using the (*R*)-catalyst, which gave the *trans*-(4*R*,6*R*)-**5g** and *cis*-(4*R*,6*S*)-**5g** diastereomers.

Conclusion

The enantioselective hydrogenation of 3,6-dialkyl-4-hydroxy-2-pyrones with the cationic ruthenium complex of (6,6′-dimethoxybiphenyl-2,2′diyl)bis[3,5-di(*tert*-butyl)-phenylphosphine] takes place selectively at positions 5 and 6 with generally high enantioselectivity (up to 97% ee). Substitution at position 3 influences the enantioselectivity of the process and renders further hydrogenation of the double bond at positions 3 and 4 much slower, thus bringing about good chemoselectivity. In the absence of substitution at C(3), further hydrogenation to tetrahydropyrones takes place. 4,6-Dialkyl-2-pyrones undergo complete consecutive hydrogenation, first at the 5,6 and then at the 3,4 double bond. Additional substitution at position 5 strongly changes the diastereoselectivity of the complete process causing selective formation of the *all-cis*-product. An aspect which deserves further investigation is represented by the apparent 1,4-hydrogenation for which precedents in the literature are rather scarce.

Experimental Section

General Remarks. All hydrogenation reaction solutions were prepared and transferred to the autoclave in a glovebox under nitrogen (<1.5 ppm of oxygen). For homogeneous hydrogenation reactions, a 60-mL steel autoclave with a mechanical stirrer (stirring speed 700 rpm) and a pressflow gas controller were used. Solution NMR spectra were measured using Bruker AM-300, AMX-400, or AMX-500 spectrometers with a TMS internal standard. 2D NMR methods were used for confirmation of structures. Optical rotation was measured with a Perkin-Elmer polarimeter 241 using a 1-dm quartz glass cell. Elemental analyses were performed at the Laboratory of Organic Chemistry at ETHZ. Gas chromatographic analyses were carried out on a Hewlett-Packard 5890 II GC equipped with a flame ionization detector on a Restek Rtx 200 capillary column (30 m). Enantiomeric excess was determined by means of GC using a Lipodex C or Lipodex D (50m), α-, β-, and γ-dex-120 (30m) column or a column with heptakis (6-*O*-TBDMS-2,3-*O*-methyl)-β-cyclodextrin as the stationary phase or by means of HPLC on a Hewlett-Packard HP 1050 using Chiralcel OD-H, OJ, and OB-H columns. GC-MS analyses were conducted on a Hewlett-Packard 5890 II GC equipped with a quadrupole mass spectrometer. B. Wagner, Hoffmann-La Roche, kindly determined the pK_a values of 4-hydroxy-2-pyrones in water by potentiometric titration with 0.5 M HCl using a 0.1 M KNO_3 electrolyte. Calculations of pK_a values were made using the program *Pallas 2.0* (*CompuDrug Chemistry Ltd.*). For minimization of the free energy of the single molecules (*S*)-**4g** and (6*S*)-**4h** a consistent valence force field[39] was applied using the program Cerius[2] (version 3.5).

Chemicals. All solvents were dried using standard methods and distilled under argon prior to use. All substrates were purified by recrystallization or kugelrohr distillation. Fluoroboric acid solution (50% in water), palladium on activated charcoal, and 2-propanol were purchased from Fluka. Hydrogen gas (purity 99.9999%) was used. The catalysts $[Ru(OAc)_2$-((*S*)- and (*R*)-3,5-di(*tert*-butyl)-MeO-Biphep)] ((*S*)-**1** and (*R*)-**1**) and 2-hexylacetoacetate were kindly provided by F. Hoffmann-La Roche. [Ru(η^5-cyclo-C_8H_{11})((*R*)-3,5-di(*tert*-butyl)-MeO-Biphep)]BF_4 was synthesized as reported earlier.[32]

3-Hexyl-4-hydroxy-6-undecyl-2*H*-pyran-2-one (**3a**) was kindly provided by F. Hoffmann- La Roche. 4,6-Dimethyl-2*H*-pyran-2-one(**3g**),[40] 4-methoxy-6-methyl-2*H*-pyran-one(**3f**),[41] 4,6-dimethylpyridone (**3l**),[42] 1,4,6-trimethylpyridone (**3m**),[43] and 5,6-dihydro-4-hydroxy-6-methyl-2*H*-pyran-2-one (**4e**)[44,45] were prepared according to published methods. 4-Hydroxy-6-methyl-2*H*-pyran-2-one (**3e**), ethyl isodehydracetate (**3i**), 4,6-diphenyl-2*H*-pyran-2-one (**3k**), 4,5-dihydro-5-methylene-2(3*H*)-furanone (**8**), 4-hydroxy-3-pentenoic acid γ-lactone (α-angelicalactone) (**9**), 3-methyl-2-cyclohexenone (**11**), and 3-methyl-2-cyclopentenone (**12**) were purchased from Fluka, Aldrich, Acros, or Interchim S. A. and were purified by recrystallization or kugelrohr distillation prior to use. Reference compounds of the hydrogenation products γ-valerolactone (**10**), (*R*)-γ-valerolactone ((*R*)-**10**), 3-methylcylcohexanone (**13**), (*R*)-3-methylcylcohexanone ((*R*)-**13**), 3-methylcyclopentanone (**14**), and (*R*)-3-methylcyclopentanone ((*R*)-**14**) were purchased from Fluka, Aldrich, or Acros. Synthesis and analytical data of 5,6-dihydro-4-methoxy-6-methyl-2*H*-pyran-2-one (**4f** respectively **7e**),[37,38] 5,6-dihydro-4,6-dimethyl-2*H*-pyran-2-one (**4g**), 3,6-dihydro-4,6-dimethyl-2*H*-pyran-2-one (**6g**), and *cis*- and *trans*- 4,6-dimethyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (**5g**) were described previously.[37]

Synthesis of Pyrones. 3-Hexyl-4-hydroxy-6-undecyl-2*H*-pyran-2-one (3a). The compound was recrystallized from diisopropyl ether under argon atmosphere prior to use. White solid: mp 83 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): 0.86 (d, 6H), 1.25−1.65 (m, 26H), 2.41−2.46 (t, 4H), 6.06 (s, 1H), 8.59 (br, 1H, *OH*). ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): 14.11 (*CH_3*), 22.69, 23.12, 26.86, 28.07, 29.08, 29.35, 29.52, 29.63, 31.83, 31.92, 33.56 (*CH_2*), 100.83, 103.43, 163.63, 167.08, 168.29. Anal. Calcd for $C_{22}H_{38}O_3$(350.54): C, 75.38; H, 10.93. Found: C, 75.18; H, 11.05.

3,6-Dihexyl-4-hydroxy-2*H*-pyran-2-one (**3b**). NaH (18.5 g, 0.44 mol, 55% pure in suspension in oil) was washed several times with absolute hexane and suspended in 250 mL of absolute THF in a three-necked flask with a mechanical stirrer. Freshly distilled methyl 2-hexylacetoacetate (80.1 g, 0.4 mol) was added dropwise at 0 °C. The suspension was cooled to −10 °C, and 260 mL (0.42 mol) of *n*-butyllithium (1.6 M in hexane) was added within an hour. The addition of 28.8 g (0.2 mol) of methyl heptanoate was done at 0 °C, also within an hour. The reaction mixture was then stirred for 1 h at 0 °C. The solution was cooled to − 30 °C and neutralized with 1 L of HCl (1.2 M) under vigorous stirring. The organic phase was separated, and the water phase extracted three times with 100 mL of diethyl ether. Organic phases were washed with saturated $NaHCO_3$ and water. The yellowish oil (methyl 3,5-dioxo-2-hexylundecanoate) was purified by silica gel filtration. Methyl 3,5-dioxo-2-hexylundecanoate (57.5 g, 0.184 mol) and 1.8-diazabicyclo[5.4.0]undec-7-ene (26 g, 0.17 mol) were refluxed in 200 mL of toluene for 1 h. The reaction mixture was cooled and neutralized with ice-cold diluted HCl. The organic

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layer was separated, and the water phase extracted three times with dichloromethane. Organic phases were washed with water and dried with Na_2SO_4. The solvent was evaporated, and the product was precipitated with hexane. Recrystallization from diisopropyl ether under argon gave 17 g **3b** as a white solid (30% yield based on methyl heptanoate): mp 99−100 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): 0.88 (t, 6H), 1.26−1.38 (m, 12H), 1.45−1.55 (m, 2H), 1.58−1.68 (m, 2H), 2.39−2.45 (t, 4H), 5.92 (s, 1H), 9−10 (br, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 °C): 13.99 (*CH*$_3$), 14.11 (*CH*$_3$), 22.47, 22.69, 23.12, 26.78, 28.09, 28.69, 29.37, 31.44, 31.83, 33.51 (*CH*$_2$), 101.12, 103.33, 163.48, 167.78, 168.54. Anal. Calcd for $C_{17}H_{28}O_3$ (280.41): C, 72.82; H 10.06. found C, 72.91; H, 10.11.

4-Hydroxy-3-methyl-6-undecyl-2*H*-pyran-2-one (3c). According to the synthesis of **3b**, 43.2 g (0.3 mol) of ethyl 2-methylacetoacetate, 14.4 g (0.33 mol, 55%) of NaH, 200 mL (0.31 mol) of *n*-butyllithium, and 34.3 g (0.15 mol) of ethyl dodecanoate gave after acid workup 48.5 g of the raw intermediate ethyl 3,5-dioxo-2-methylhexadecanoate, which was refluxed using 18.7 g (0.12 mol) of DBU in 200 mL of toluene for 120 min to give **3c**. Recrystallization from diisopropyl ether gave 11.1 g (26.4% yield based on ethyl dodecanoate) of **3c** as a white solid: mp 106−107 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): 0.87 (t, 3H), 1.26 (m, 16H), 1.62 (m, 2H), 1.97 (s, 3H), 2.44 (t, J = 7.5 Hz, 2H), 6.17 (s, 1H), 9.7 (br, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 °C): 8.09, 14.08 (*CH*$_3$), 22.66, 26.84, 28.98, 29.28, 29.31, 29.47, 29.59, 31.88, 33.48 (*CH*$_2$), 98.55, 100.65, 163.50, 166.88, 168.38. Anal. Calcd for $C_{17}H_{28}O_3$ (280.41): C, 72.82; H 10.06. found C, 72.57; H, 10.28.

3,6-Dimethyl-4-hydroxy-2*H*-pyran-2-one (3d).[46] 6-Methyl-4-hydroxy-2*H*-pyran-2-one (20.11 g, 0.16 mol) was suspended in 160 mL of acetic acid and heated to dissolve at 50 °C. Urea (9.6 g, 0.16 mol) dissolved in 25 mL of DMF was added. The solution was then heated to 60 °C and, within 10 min, 24.4 mL (0.223 mol) of trimethyl orthoformate was added dropwise. The solution was left for 30 min at 60 °C and then cooled to room temperature. The precipitated 6-methyl-3-ureidomethylen-2*H*-pyran-2-one was filtered off, washed with acetic acid and water, and dried under high vacuum. The colorless 6-methyl-3-ureidomethylen-2*H*-pyran-2-one (cis/trans mixture) (23.5 g, 0.12 mol) was suspended in 200 mL of acetic acid and warmed to 35 °C. Dimethylamineborane (9.18 g, 0.16 mol) in 200 mL acetic acid and added dropwise. After the addition, the solution was refluxed for 1 h. Most of the acetic acid was evaporated under high vacuum. After addition of ice-cold water the product precipitated and was filtered off. Recrystallization from dioxane/acetone gave 6.24 g (37.2% yield) **3d** as a colorless solid: mp 210 °C. ^{1}H NMR (200 MHz, DMSO, 25 °C): 1.74 (s, 3H), 2.14 (s, 3H), 5.98 (s, 1H), 11.08 (br, 1H, *OH*). ^{13}C NMR (50.32 MHz, DMSO, 25 °C): 8.24 (C(3)-*CH*$_3$), 19.11 (C(6)-*CH*$_3$), 96.21 (C(3)-*C*), 99.66 (C(5)-*CH*), 159.25, 164.84, 165.01. Anal. Calcd for $C_7H_8O_3$ (140.14): C, 60.00; H 5.75. Found C, 59.95; H, 5.79.

4,5,6-Trimethyl-2*H*-pyran-2-one (3f).[47] Iodomethane (6.84 g, 48 mmol) was added to 3.7 g (30 mmol) of pyrone **3g** in 10 mL of sodium methoxide solution (30% in methanol) over 10 min. The reaction mixture was stirred for 2 h at 50 °C and neutralized by adding concentrated acetic acid. After 10 mL of water was added, the reaction mixture was extracted three times with dichloromethane. The organic phases were dried with $NaSO_4$ and evaporated to dryness. The product was purified by kugelrohr distillation from higher boiling side products followed by column chromatography using ethyl acetate/dichloromethane (1:5). Recrystallization from hexane gave 600 mg (15% yield) of a colorless solid: mp 74 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C):1.92 (s, 3H, C(5)-*CH*$_3$), 2.10 (s, 3H), 2.22 (s, 3H), 6.00 (s, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 °C): 12.36 (C(5)-*CH*$_3$), 17.60 (C(6)-*CH*$_3$), 20.55 (C(4)-*CH*$_3$), 111.47, 111.53, 156.90 (C(6)), 157.39 (C(4)), 162.77 (C(2)). EI-MS: 138 (M^+, 64), 110 (100), 95 (52), 67 (95), 43 (70). Anal. Calcd for $C_8H_{10}O_2$ (138.17): C, 69.55; H, 7.29. Found: C, 69.48; H, 7.42.

Hydrogenation of the Substrates. General Procedure. Entry 2 (Table 1) is taken as an example. In an N_2 atmosphere in the glovebox, 1.5 mL of a solution of fluoroboric acid in 2-propanol (351 mg HBF_4 (50% in water) in 50 mL 2-propanol) was added to a solution of 7.5 mg (0.006 mmol) of [Ru((*S*)-**5**)-(OAc)$_2$] in 3.5 mL of 2-propanol. The solution was stirred for 1.5 h. 6-Hexyl-4-hydroxy-3-undecyl-2H-pyran-2-one (**3a**) (1.05 g, 3 mmol) was weighed into the glass insert of the autoclave, the catalyst solution was added, and the solution was filled up to 30 mL with 2-propanol. The autoclave was closed and pressurized at 60 bar of H_2 and heated to 60 °C. After 20 h the autoclave was cooled to room temperature and the residual gas was released. After the solvent was removed from the reaction mixture, the crude product was purified by silica gel filtration in order to remove the catalyst and acid. Conversion was determined by means of GC on a *rtx 200 (restek)* column after derivatization with MBTFA in pyridine for 10 h or directly by means of ^{1}H NMR. Slightly different conditions were used for the following entries: Table 1, entry 1, 1 mmol of **3a** in 10 mL of 2-propanol; Table 1, entry 7, 3 mmol of **3a** in 5 mL of 2-propanol; Table 1, entry 8, 3 mmol of **3a** in 3 mL of 2-propanol; Table 1, entry 9, the reaction was left for 5 days to check whether further hydrogenation takes places. The final reaction mixture composition was 12% **5a** and 8% 5,6-dihydro-3-hexyl-4-(2-propyloxy)-6-undecyl-2*H*-pyran-2-one from reaction of **4a** with 2-propanol were formed: Table 2, entry 3, 1.5 mmol of **3b** in 15 mL of 2-propanol; Table 2, entry 4, 0.5 mmol **3c** in 10 mL of 2-propanol; Table 2, entry 4, 1 mmol of **3d** in 10 mL of 2-propanol.

Characterization of Hydrogenation Products. (*S*)-5,6-Dihydro-3-hexyl-4-hydroxy-6-undecyl-2*H*-pyran-2-one (4a). Compound **4a** was isolated as a white solid (80%) after hydrogenation of 1.05 g (3 mmol) of pyrone **3a** in 2-propanol under 60 bar of hydrogen at 60 °C for 20 h in the presence of (*R*)-**2**/HBF_4 as the catalyst. Purification by column chromatography using dichloromethane gave a white solid: mp 112 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C, keto form): 0.88 (t, 6H), 1.26−1.97 (m, 30H), 2.36−2.46 (dd, J = 18.7, 11.6 Hz, 1H), 2.68−2.75 (dd, J = 18.8, 2.8 Hz, 1H), 3.40 (t, J = 5.4 Hz, 1H), 4.67 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C, keto form) 14.07 (*CH*$_3$), 14.13 (*CH*$_3$), 22.60, 22.69, 23.08, 24.74, 27.22, 29.27, 29.34, 29.42, 29.52, 29.61, 31.57, 31.92, 34.48, 43.63, 56.75, 74.08, 169.40 (C(2)), 201.39 (C(4)). $[\alpha]^{25}_D = +33$ (c = 0.53, MeOH, 94.2% ee). Anal. Calcd for $C_{22}H_{40}O_3$ (352.56): C, 74.95; H, 11.44. Found: C, 74.85; H, 11.45.

(−)-3,6-Dihexyl-5,6-dihydro-4-hydroxy-2*H*-pyran-2-one (4b). Compound **4b** was isolated as a white solid after hydrogenation of 0.42 g (1.5 mmol) of pyrone **3b** in 2-propanol under 60 bar of H_2 at 60 °C for 20 h in the presence of (*S*)-**1**/HBF_4 as the catalyst. It was purified by column chromatography using dichloromethane: mp 122 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C, keto form): 0.87 (t, 6H), 1.26−1.95 (m, 20H), 2.40 (dd, J = 18.7, 11.7 Hz, 1H), 2.70 (dd, J = 18.7, 2.9 Hz, 1H), 3.38 (t, J = 5.5 Hz, 1H), 4.65 (m, 1H), 9−10 (br, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 °C, keto form): 14.02 (*CH*$_3$), 22.21, 22.57, 23.06, 24.68, 27.20, 28.91, 29.34, 31.55, 31.57, 34.45, 43.60, 56.72, 74.05, 169.36, 201.37. $[\alpha]^{25}_D = -40$ (c = 0.49, MeOH, 97.2% ee). Anal. Calcd for $C_{17}H_{30}O_3$ (282.42): C, 72.30; H 10.71. found C, 72.07; H, 10.68.

(+)-5,6-Dihydro-4-hydroxy-3-methyl-6-undecyl-2*H*-pyran-2-one (4c). Compound **4c** was isolated as a white solid after hydrogenation of 0.14 g (0.5 mmol) of pyrone **3c** in 2-propanol under 60 bar of H_2 at 60 °C for 20 h in the presence of (*R*)-**1**/HBF_4 as the catalyst. Purification by column chromatography using dichloromethane gave a white solid: mp 115−116 °C.^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C, keto form): 0.88 (t, 3H), 1.27−1.89 (m, 20H), 2.43 (dd, J = 19.0, 11.8 Hz, 1H), 2.74 (dd, J = 19.0, 2.9 Hz, 1H), 3.57 (q, J = 6.7 Hz, 1H), 4.70 (m, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 °C, keto form): 7.78, 14.12 (*CH*$_3$), 22.69, 22.74, 29.27, 29.34, 29.42, 29.52, 29.61, 31.91, 34.44, 43.12, 51.66, 74.20, 170.00, 201.58. $[\alpha]^{25}_D = +$

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39 (c = 0.32, MeOH, 91.4% ee). Anal. Calcd for $C_{17}H_{30}O_3$ (282.42): C, 72.30; H, 10.71. Found C, 72.40; H, 10.94.

(+)-5,6-Dihydro-3,6-dimethyl-4-hydroxy-2*H*-pyran-2-one (4d). Compound **4d** was isolated as a white solid after hydrogenation of 0.28 g (2 mmol) of pyrone **3d** in 2-propanol under 60 bar of H_2 at 60 °C for 20 h in the presence of (*R*)-**1** as catalyst. It was purified by column chromatography using dichloromethane/ethyl acetate = 1: 1 to give a white solid: mp 151−153 °C.^{1}H NMR (200.13 MHz, DMSO, 25 °C): 1.28 (d, J = 6.3 Hz, 3H), 1.61 (s, 3H), 2.41−2.52 (dd, 2H), 4.30−4.47 (m, 1H), 10.66 (br, 1H). ^{13}C NMR (50.32 MHz, DMSO, 25 °C): 8.60 (C(3)-*CH*$_3$), 20.26 (C(6)-*CH*$_3$), 34.37 (C(5)-*CH*$_2$), 70.35 (C(6)-*CH*), 96.89 (C(3)), 165.32 (C(4)), 168.24 (C(2)). $[\alpha]^{25}_D$ = + 130 (c = 0.42, MeOH, 92.9% ee). Anal. Calcd for $C_7H_{10}O_3$ (142.15): C, 59.14; H, 7.09. Found C, 59.09; H, 7.17.

5,6-Dihydro-4-hydroxy-6-methyl-2*H*-pyran-2-one (4e). Compound **4e** was obtained according to literature methods.[44,45] Colorless solid: mp 118−120 °C. ^{1}H NMR (500.14 MHz, $CDCl_3$, 25 °C, keto form): 1.52 (d, J = 6.2 Hz, 3H), 2.47 (dd, J = 18.3, 11.4 Hz, 1H), 2.72 (d, J = 18.1 Hz, 1H), 3.43 (d, J = 18.8 Hz, 1H), 3.58 (d, J = 18.7 Hz, 1H), 4.81 (m, 1H). ^{13}C NMR (125.76 MHz, $CDCl_3$, 25 °C): 20.49 (*CH*$_3$), 45.01, 46.84, 71.97, 167.34 (C(2)), 200.07 (C(4)). Anal. Calcd for $C_6H_8O_3$ (128.13): C, 56.25; H, 6.29. Found: C, 56.08; H, 6.29.

***cis*- and *trans*-4-Hydroxy-6-methyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (5e).** A diastereomer mixture of *cis*- and *trans*-**5e** was isolated after hydrogenation of 126 mg (1 mmol) of pyrone **3e** in 2-propanol under 60 bar of H_2 at 60 °C for 20 h, in the presence of (*S*)-**1** as the catalyst. Purification by column chromatography using ethyl acetate gave 45 mg of a colorless liquid (73% *trans*-**5e**, 27% *cis*-**5e**).

trans-**5e**.[26] ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 1.39 (d, J = 6.4 Hz, 3H), 1.70 (ddd, J = 14.5, 11.3, 3.3 Hz, 1H), 2.00 (dddd, J = 14.5, 3.8, 3.2, 1.7 Hz, 1H), 2.61 (ddd, J = 18.4, 3.6, 1.7 Hz, 1H), 2.68 (dd, J = 18.4, 4.9 Hz, 1H), 4.35 (dddd, J = 4.9, 3.8, 3.6, 3.3 Hz, 1H), 4.85 (ddq, J = 11.1, 6.5, 3.1 Hz, 1H). ^{13}C NMR (125.76 MHz, $CDCl_3$, 25 °C): 21.38 (CH3), 37.42 (C(5)), 38.31 (C(3)), 62.42 (C(4)), 72.74 (C(6)), 171.51 (C(2)).

cis-**5e**.[26] ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 1.41 (d, J = 6.4 Hz, 3H), 1.57 (ddd, J = 13.8, 11.6, 9.1 Hz, 1H), 2.28 (dddd, J = 13.8, 5.6, 3.0, 1.3 Hz, 1H), 2.44 (dd, J = 17.1, 7.6 Hz, 1H), 2.87 (ddd, J = 17.1, 6.0, 1.3 Hz, 1H), 4.24 (dddd, J = 9.2, 7.6, 5.6, 5.9 Hz, 1H), 4.35 (ddq, J = 11.6, 6.5, 3.0 Hz, 1H). ^{13}C NMR (125.76 MHz, $CDCl_3$, 25 °C): 21.38 (CH3), 39.21 (C(3)), 39.43 (C(5)), 63.52 (C(4)), 74.03 (C(6)), 171.70 (C(2)).

(−)-5,6-Dihydro-4,5,6-trimethyl-2*H*-pyran-2-one (4f).[48] Compound **4f** was isolated from a hydrogenation of 138 mg (1 mmol) of pyrone **3f** in 2-propanol under 10 bar of hydrogen at 40 °C for 3 h in the presence of (*S*)-**1** as the catalyst. Purification by column chromatography (hexane/ethyl acetate 1: 1) gave 40 mg of a colorless liquid. $[\alpha]^{25}_D$ = − 23 (c = 0.76, MeOH) (89% ee by GC (γ-dex-120). ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): 1.07 (d, J = 7.1, 3H), 1.36 (d, J = 6.6, 3H), 2.00 (d, J = 1.4 Hz, 3H), 2.10 (qd, J = 7.1, 3.2 Hz, 1H), 4.56 (dq, J = 6.6, 3.2 Hz, 1H), 5.75 (q, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 °C): 10.40, 17.19, 21.47, 38.24, 75.94, 115.50, 163.63, 165.39. EI-MS: 140 (M^+, 2), 96 (100), 95 (30), 81 (34), 67 (25), 53 (16), 43 (16).

3,6-Dihydro-4,5,6-trimethyl-2*H*-pyran-2-one (6f). Compound **6f** was isolated after hydrogenation of 138 mg (1 mmol) of pyrone **3f** in 2-propanol under 10 bar of H_2 at 40 °C for 3 h in the presence of (*S*)-**1** as the catalyst. Purification by column chromatography (hexane/ethyl acetate 1: 1) gave 10 mg of a colorless liquid. ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): 1.41 (d, J = 6.7, 3H), 1.69 (s, 6H), 2.96 (d, 2H), 4.79 (q, J = 6.7 Hz, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 °C): 17.89, 20.44, 35.23, 53.46, 79.90, 121.47, 126.58, 170.27. EI-MS: 140 (M^+, 21), 125 (17), 112 (12), 97 (42), 81 (22), 43 (100).

***all-cis*-(−)-3,4,5,6-Tetrahydro-4,5,6-trimethyl-2*H*-pyran-2-one (5f).** Compound **5f** was isolated after hydrogenation of 138 mg (1 mmol) of pyrone **3f** in 2-propanol under 60 bar of H_2 at 60 °C for 5 h in the presence of (*R*)-**1** as the catalyst. Purification by kugelrohr distillation gave 80 mg of a colorless liquid. $[\alpha]^{25}_D$ = − 24 (c = 0.23, MeOH) (88% ee by GC (Lipodex D)).^{1}H NMR (500.14 MHz, $CDCl_3$, 25 °C): 0.84 (d, J = 7.2 Hz, 3H), 1.02 (d, J = 6.5 Hz, 3H), 1.33 (d, J = 6.6 Hz, 3H), 1.75 (m, 1H), 2.14 (dd, J = 17.0, 12.5 Hz, 1H), 2.20 (m, 1H), 2.54 (dd, J = 17.0, 4.7 Hz, 1H), 4.52 (dq, J = 6.6, 2.5 Hz, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 °C): 4.50, 18.91, 18.98, 31.95, 33.88, 36.39, 81.02, 171.67. EI-MS: 142 (M^+, 2), 98 (26), 70 (13), 56 (100), 43 (21). Anal. Calcd for $C_8H_{14}O_2$ (142.20): C, 67.57; H, 9.92. found: C, 67.37; H, 10.18.

1,4,6-Trimethylpiperidone (5m). Compound **5m** was isolated after hydrogenation of 69 mg (0.5 mmol) of pyridone **3m** in 2-propanol under 60 bar of H_2 at 60 °C for 46 h in the presence of (*S*)-**1** as the catalyst. Purification by chromatography (dichloromethane/ethyl acetate 1:1) gave 57 mg of a colorless liquid (84:16 *cis*/*trans*). Yield: 57 mg (80%, 84% *cis*-**5m**). ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): 0.97 (d, J = 6.1 Hz, 3H), 1.15 (m, 1H), 1.24 (d, J = 6.3 Hz, 3H), 1.72 (m, 1H), 1.85 (dd, 1H), 1.90 (m, 1H), 2.45 (dd, 1H), 3.42 (m, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 °C): 21.20, 21.78, 26.62, 31.09, 40.819, 40.844, 54.25, 170.63. EI-MS: 141 (M^+, 33), 126 (100), 73 (10), 69 (74), 58 (28), 42 (23). Anal. Calcd for $C_8H_{15}NO$ (141.21): C, 68.04; H, 10.71; N, 9.92. Found: C, 66.15; H, 9.00; N, 9.53.

Determination of Enantiomeric Excess. 5,6-Dihydro-4-hydroxy-2*H*-pyran-2-ones (4a−e) (compare Scheme 2). A sample of the hydrogenation products **4a**−**e** (0.5 mmol) was refluxed in 5 mL of methanol, 400 mg (3.8 mmol) of trimethyl orthoformate, and 10 mg (0.05 mmol) of *p*-toluenesulfonic acid monohydrate for 10 h. The solvent of the reaction mixture was evaporated, and the raw products 5,6-dihydro-4-methoxy-2*H*-pyran-2-ones **7a**−**e** were purified by column chromatography. Determination of enantiomeric excesses was achieved by means of GC or HPLC using chiral columns. Racemic reference mixtures of **4a**−**e** were obtained by hydrogenation of **3a**−**e** in ethanol with Pd on charcoal as catalyst at room temperature and 1−5 bar of hydrogen pressure for a few hours. Derivatization of the racemic **4a**−**e** gave correspondent **7a**−**e** as above-described.

7a. White solid; mp 62 °C. ^{1}H NMR (200.13 MHz, $CDCl_3$, 25 °C): 0.88 (t, 6H), 1.26−1.95 (m, 28H), 2.28 (t, 2H), 2.30−2.60 (dd, 2H), 3.76 (s, 3H), 4.23−4.35 (m, 1H). ^{13}C NMR (50.32 MHz, $CDCl_3$, 25 °C): 22.36 (*CH*$_3$), 23.15, 24.60, 28.31, 28.78, 28.88, 29.03, 29.13, 29.19, 29.26, 29.32, 31.44, 31.60. 34.60 (*CH*$_2$), 55.00 (*OCH*$_3$), 74.33 (*CH*), 107.93 (*C(3)*), 165.65, 168.22. $[\alpha]^{25}_D$ = + 26 (c = 0.21, MeOH) ((*S*)-**7a**, 92.5% ee). Enantiomeric excess determined by HPLC (Chiralcel OD-H, hexane/2-propanol 99:1, 0.8 mL/min, UV(254 nm), (*R*)-enantiomer eluted first).

7b. ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): 0.89 (t, 6H), 1.27−1.90 (m, 18H), 2.28 (t, J = 6.6 Hz, 2H), 2.43 (dd, J = 16.9, 11.4 Hz, 1H), 2.54 (dd, J = 16.9, 4.3 Hz, 1H), 3.76 (s, 3H), 4.28 (m, 1H), 5.13 (d, J = 1.5 Hz, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$, 25 °C): 14.06, 14.13 (*CH*$_3$), 22.55, 22.66, 23.53, 24.85, 28.65, 29.08, 29.12, 29.21, 31.67, 31.76, 34.93 (*CH*$_2$), 55.25 (*OCH*$_3$), 74.51 (C(6)-*CH*), 108.74 (C(3)), 165.37 (*C(4)*), 168.29 (*C(2)*). $[\alpha]^{25}_D$ = −26 (c = 0.08, MeOH) (97.2% ee). Enantiomeric excess determined by HPLC (Chiralcel OJ, hexane/2-propanol 165:1, 0.4 mL/min, UV(254 nm), (+)-enantiomer eluted first).

7c. ^{1}H NMR (500.14 MHz, $CDCl_3$, 25 °C): 0.88 (t, J = 6.8 Hz, 3H), 1.26−1.92 (m, 20H), 1.78 (s, 3H), 2.43 (dd, J = 17.0, 11.9 Hz, 1H), 2.54 (dd, J = 17.0, 4.0 Hz, 1H), 3.78 (s, 3H), 4.30 (m, 1H). ^{13}C NMR (125.76 MHz, $CDCl_3$, 25 °C): 8.87, 14.12 (*CH*$_3$), 22.70, 24.91, 29.20, 29.35, 29.40, 29.49, 29.57, 29.62, 29.64, 31.93, 34.93 (*CH*$_2$), 55.40 (*OCH*$_3$), 74.67 (C(6)-*CH*), 103.49 (C(3)), 165.56 (*C(4)*), 169.00 (*C(2)*). $[\alpha]^{25}_D$ = + 23 (c = 0.08, MeOH) (91.4% ee). Enantiomeric excess determined by HPLC (Chiralcel OD-H, hexane/2-propanol = 99:1, 0.7 mL/min, UV(254 nm), (+)-enantiomer eluted first).

7d. ^{1}H NMR (200.13 MHz, $CDCl_3$, 25 °C): 1.46 (d, J = 6.3 Hz, 3H), 1.78 (s, 3H), 2.34−2.51 (m, J = 17.0, 11.3 Hz, 1H), 2.58 (dd, J = 17.0, 4.4 Hz, 1H), 3.78 (s, 3H), 4.37−4.54 (m, 1H). ^{13}C NMR (50.32 MHz, $CDCl_3$, 25 °C): 8.85 (C(3)-*CH*$_3$), 20.80 (C(6)-*CH*$_3$), 30.86 (C(5)-*CH*$_2$), 55.39 (OCH_3), 70.95 (C(6)),

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125.89 (C(3)), 165.26, 168.70. $[\alpha]^{25}_{D} = +98$ ($c = 0.09$, MeOH) (92.9% ee).Enantiomeric excess determined by GC (6-*O*-TBDMS-2,3-*O*-methyl)-*β*-cyclodextrin, (+)-enantiomer eluted first).

7e.[38] ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): 1.44 (d, $J = 6.3$, 3H), 2.35 (dd, $J = 17.0$, 4.0, 1H), 2.47 (ddd, $J = 17.0$, 11.6, 1.6, 1H), 3.75 (s, 3H), 4.53 (ddq, $J = 11.6$, 4.0, 6.3 Hz, 1H), 5.14 (d, $J = 1.5$ Hz, 1H). ^{13}C NMR (100.61 MHz, $CDCl_3$, 25 °C): 20.54 (CH_3), 34.58 (C(5)), 55.98 (OCH_3), 72.24 (C(6)), 90.23 (C(3)), 167.34, 172.74. $[\alpha]^{25}_{D} = -123$ ($c = 0.53$, MeOH) ((*R*)-**7e**,[38] 89% ee). Enantiomeric excess determined by GC (6-*O*-TBDMS-2,3-*O*-methyl)-*β*-cyclodextrine, (*S*)-(+)-enantiomer eluted first).

5,6-Dihydro-4-methoxy-2*H*-pyran-2-ones (4f). As dihydropyrone **7e** (see above).

5,6-Dihydro-4,6-dimethyl-2*H*-pyran-2-one (4g). Enantiomeric excess determined by GC (Lipodex C, (*S*)-(+)-enantiomer eluted first).[37]

3,6-Dihydro-4,6-dimethyl-2*H*-pyran-2-one (6g). Enantiomeric excess determined by GC (Lipodex C, (*S*)-enantiomer eluted first).[37]

***trans*-4,6-Dimethyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (5g).** Enantiomeric excess determined by GC (*γ*-Dex-120, (4*S*,6*S*)-(−)-enantiomer eluted first).[37]

***cis*-4,6-Dimethyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one (5g)**. Enantiomeric excess determined by GC (Lipodex C, (4*S*,6*R*)-(+)-enantiomer eluted first).[37]

5,6-Dihydro-4,5,6-trimethyl-2*H*-pyran-2-one (4h). Enantiomeric excess determined by GC (Lipodex C, (+)-enantiomer eluted first).

3,6-Dihydro-4,5,6-trimethyl-2*H*-pyran-2-one (6h). Enantiomeric excess determined by GC (Lipodex D).

***all-cis*-3,4,5,6-Tetrahydro-4,5,6-trimethyl-2*H*-pyran-2-one (5f).** Enantiomeric excess determined by GC (Lipodex D, (+)-enantiomer eluted first).

1,4,6-Trimethyl-2-piperidone (5m). Enantiomeric excesses of cis- and trans-diastereomers were determined by GC (*γ*-Dex-120). Absolute configuration and optical rotation values could not be determined.

***γ*-Valerolacton (10).** Enantiomeric excess determined by GC (Lipodex C, (*R*)-(+)-enantiomer eluted first).

3-Methylcyclohexanone (13). Enantiomeric excess determined by GC (α-Dex-120, (*R*)-enantiomer eluted first).

3-Methylcyclopentanone (14). Enantiomeric excess determined by GC (α-Dex-120, (*R*)-enantiomer eluted first).

Acknowledgment. The pioneering work of Dr. E. Broger on the asymmetric hydrogenation of 2-pyrones is gratefully acknowledged. We thank also Dr. U. Widmer for helpful discussions. M.J.F. is grateful to Hoffmann-La Roche for the generous support of his Ph.D. work.

JO982215L