# 165. Synthesis and Ruthenium-Catalyzed Enantioselective Hydrogenation of 3-*O*-Substituted 1,3-Dihydroxypropan-2-ones

Part 2[1])

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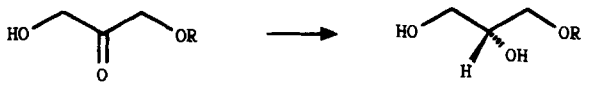
A number of 3-*O*-substituted 1,3-dihydroxypropan-2-ones have been synthesized in view of their potential use as prochiral precursors of optically active glycerols. Indeed, the oxo-ethers have been reduced to the corresponding 3-*O*-substituted glycerols *via* chiral Ru complexes derived from (*S*)-binap, (= (−)-(*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene) with enantiomeric excesses up to 93%. The steric course of the catalytic reduction appears to be essentially dependent on the steric encumbrance of the substituents; indeed, a dramatic increase of the enantiomeric excess is observed when the bulky trityl group is substituted by the less encumbering benzyl or octadecyl groups.

**Introduction.** – 3-*O*-Substituted glycerols are versatile intermediates in organic synthesis due to the presence, on a $C_3$ unit, of three vicinal chemically different O-atoms. Their importance is even more evident, considering that the glycerol skeleton constitutes the basic subunit of many biologically active compounds synthetically obtainable from 3-*O*-substituted glycerols [2], in which the ether acts as a protecting group or a definitive substituent.

On the basis of the reports on enantioselective chemical [3] and biological [4] reductions of α-hydroxy ketones and of our previous investigations concerning the enantioselective hydrogenation of 1,3-*O*-disubstituted 1,3-dihydroxypropan-2-ones [1] [5], the mono-ethers of the same dihydroxy-ketone were considered as potential precursors for optically active 3-*O*-substituted glycerols.

This paper focuses on the preparation of a number of such prochiral ketones, in particular the compounds **1a–e**, which have been selected as target molecules, considering their importance as synthons of the respective glycerol derivatives and on the catalytic reduction with chiral Ru complexes. The catalysts chosen are the dimeric complex $[Ru_2((S)\text{-binap})_2Cl_4]NEt_3$ [6] (**3**) and the 'preformed' $[Ru((S)\text{-binap})Cl_2]$ (**4**), recently developed by the *Noyori*'s group [7].

[1]) Part 1: [1].

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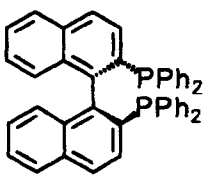
**a** R = $PhCH_2$
**b** R = $Ph_3C$
**c** R = $[(4\text{-}MeO)C_6H_4]Ph_2C$
**d** R = $C_{18}H_{37}$
**e** R = $CH_2{=}CHCH_2$




((*S*)-binap)

**3** $[Ru_2((S)\text{-binap})_2Cl_4]NEt_3$
**4** $[Ru((S)\text{-binap})Cl_2]_n$
(from $[Ru(Benzene)Cl_2]_n$ and ((*S*)-binap)

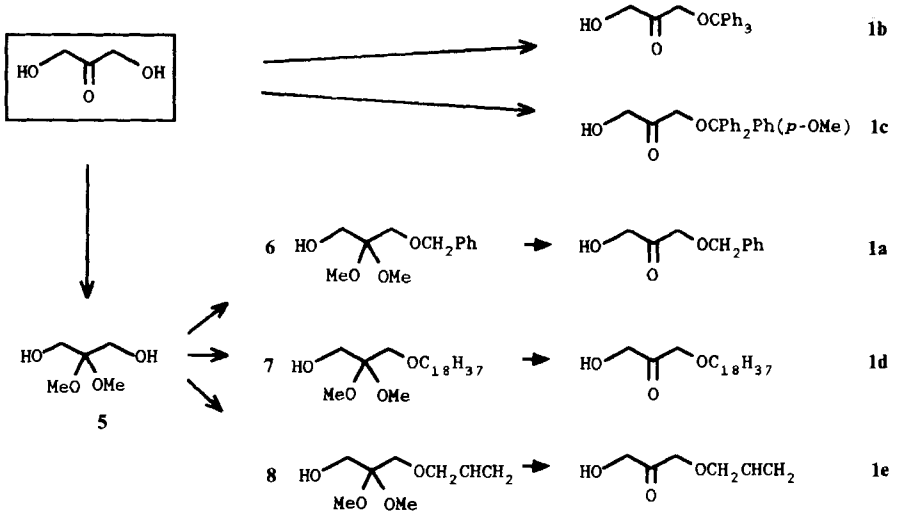
**Results and Discussion.** – The literature methods for the synthesis of 3-*O*-substituted 1,3-dihydroxypropan-2-ones are based on: *a*) the rearrangement of 3-*O*-substituted glyceraldehydes in hot pyridine [8]; *b*) the chemical or biological oxidation of 3-*O*-substituted glycerols [9] [10]; *c*) the replacement of the halogen with an OH moiety in 1-alkoxy-3-chloropropan-2-ones [11] [12]; *d*) the oxidation of glycerol derivatives bearing an ester and an ether group at C(1) and C(3), followed by a sequence of appropriate transformations of the keto, ester, and ether moieties [13]; *e*) the etherification of 1-*O*-trityl-2,2-dimethoxy-3-hydroxypropane, prepared from acetyl dihydroxyacetone dimethyl ketal, and the successive removal of trityl and ketal groups [14].

More simply, our approach involves the 3-*O*-substitution of 1,3-dihydroxypropan-2-one or of its easily obtainable dimethyl ketal. To date, the only example of such a strategy in the literature is the low-yield (17%) monotritylation of 1,3-dihydroxypropan-2-one [15]. Nevertheless, it seemed worthwhile to explore the practicability of this synthetic route further, on account of its attractive shortness.

The sequence of reactions used to synthesize the title compounds is outlined in the *Scheme*.

1,3-Dihydroxypropan-2-one was directly converted to **1b** and **1c** by treatment with trityl chloride and (*p*-anisyl)(chloro)diphenylmethane, respectively, in the presence of pyridine and a catalytic amount of 4-(dimethylamino)pyridine. To prepare **1a**, **1d**, and **1e**, 1,3-dihydroxypropan-2-one was previously transformed into the dimethyl ketal **5** by reaction in MeOH, with TsOH as a catalyst. The successive treatment of **5** with $PhCH_2Cl$, allyl bromide, and octadecyl methanesulfonate in *t*-BuOH in the presence of *t*-BuOK

*Scheme*




gave the mono-ethers **6**–**8**, which were converted finally into **1a**, **1d**, and **1e** by hydrolysis of the protecting ketal function.

The yields of the 3-*O*-substitution, which represent the critical step of the whole synthetic sequence, range between 45 and 55%.

The results of the enantioselective hydrogenation of 3-*O*-substituted 1,3-dihydroxypropan-2-ones **1a**–**e** are compiled in the *Table*.

Table. *Enantioselective Hydrogenation of 3-O-Substituted 1,3-Dihydroxypropan-2-ones*[a])

| *Entry* | Catalyst | Substrate | Solvent | *t* [h] | Conversion [%][b]) | e.e. [%][c]) | Configuration[d]) |
|---|---|---|---|---|---|---|---|
| *1* | **3** | **1a** | $CH_2Cl_2$ | 24 | > 98 | 87 | (*R*) |
| *2* | **4** | **1a** | $CH_2Cl_2$ | 48 | > 98 | 93 | (*R*) |
| *3* | **4** | **1a** | EtOH | 40 | > 98 | 70 | (*R*) |
| *4* | **3** | **1b** | $CH_2Cl_2$ | 72 | > 98 | 0 | – |
| *5*[e]) | **3** | **1b** | $CH_2Cl_2$ | 72 | > 98 | 0 | – |
| *6*[f]) | **4** | **1b** | $CH_2Cl_2$ | 70 | 95 | 6.5 | (*R*) |
| *7* | **4** | **1b** | $CH_2Cl_2$ | 45 | 54 | 0 | – |
| *8* | **3** | **1c** | $CH_2Cl_2$ | 90 | > 98 | 0 | – |
| *9*[f]) | **4** | **1c** | $CH_2Cl_2$ | 45 | 50 | 0 | – |
| *10* | **4** | **1d** | $CH_2Cl_2$ | 45 | 83 | 76[g]) | (*R*) |
| *11* | **4** | **1e** | $CH_2Cl_2$ | 90 | – | – | – |

[a]) Substrate concentrations 0.1M; catalyst concentration 0.001M; molar substrate/catalyst ratio 100:1; pressure 100 Kgw·cm$^{-2}$ (1 Kgw·cm$^{-2}$ = 9.81 × 10$^4$ Pa).
[b]) Isolated yield after flash chromatography.
[c]) Determined by HPLC on chiral stationary phase.
[d]) Determined by the sign of rotation.
[e]) 2 equiv. of $NEt_3$ with respect to the catalyst.
[f]) 1 equiv. of $NEt_3$ with respect to the catalyst.
[g]) Specific optical rotation (+)-(*R*)-**2d**: $[\alpha]_D^{25}$ = +2.36 (*c* = 7, THF) [16].

1-(Benzyloxy)-3-hydroxypropan-2-one (**1a**) is reduced to the corresponding alcohol **2a** by the dimer **3** and by the complex **4** in excellent yields with a remarkably high e.e.% (*Entries 1* and *2*). In EtOH, however, the enantioselectivity is somewhat lower (*Entry 3*), confirming that protic solvents are not the medium of choice when hydrogenating substrates which do not coordinate strongly [5]. A good enantioselectivity is obtained also in the reduction of 3-hydroxy-1-(octadecyloxy)propan-2-one (**1d**; *Entry 10*). Due to the absence of cromophores in **2d**, making UV detection impossible in HPLC, instead of the e.e.%, the optical purity is given, calculated on the specific optical rotation of (+)-(*R*)-**2d**: $[\alpha]_D = +2.36$ ($c = 7$, THF) [16].

Rather surprisingly, the substrates 3-hydroxy-1-trityloxypropan-2-one (**1b**) and 3-hydroxy-1-[(4-methoxyphenyl)diphenylmethoxy]propan-2-one (**1c**) are reduced in high yields but without enantioselectivity (*Entries 4–9*). Only the catalyst **4** reduces **1b** with a moderate 6.5% e.e. in the presence of 1 equiv. of $NEt_3$ as co-catalyst (*Entry 6*). It is worth mentioning that, albeit with disappointingly low enantioselectivities, the cleavage of the O-trityl bond in both the substrates **1b** and **1c** occurs in traces in $CH_2Cl_2$ (less than 2%) both in the presence and in the absence of $NEt_3$ as cocatalyst.

The substrate 1-allyloxy-3-hydroxypropan-2-one (**1e**) undergoes a different fate: only the C=C bond is selectively reduced after 90 h giving the corresponding 3-hydroxy-1-(propyloxy)propan-2-one (*Entry 11*) in 50% yield. The reduction of the C=C bond is not accompanied by the hydrogenation of the C=O group as one could expect; indeed it would seem as if the reduction of the C=C bond is followed by the inactivation of the catalyst towards the reduction of the C=O group. Recently, it has been shown that similar catalytic systems can affect ketone reduction without alkene hydrogenation in selected $\beta$-keto-esters [17]. Such chemoselectivity is coupled with a high enantioselectivity in spite of the slightly elevated temperatures at which the reactions are performed. All these results seem to confirm our previous observations on the non-innocent role of the substrate in directing the equilibrium mixture of different catalitically active Ru species towards the prevalence of one species over the others [5]. It is also very likely that the different substrates can drive the reaction between the Ru-phosphine complexes and the hydrogen towards the irreversible formation of different catalytic species.

In spite of the fact that $\alpha$-hydroxy-ketones have been generally considered good substrates in the enantioselective hydrogenation [2] [7], our results seem to indicate that this statement can only be true when the substituents are not particularly sterically hindering; the presence of bulky trityloxy groups in fact leads to a dramatic and apparently inexplicable decrease in the enantioselectivity.

These findings remind one of the earlier observations in the field of asymmetric syntheses catalyzed by transition-metal complexes: the interaction between a chiral complex and a prochiral or achiral substrate consists of a total interaction, reflected in the $\Delta G^{\neq}$, and a part, necessarily lower, which is the diastereotopic interaction $\Delta\Delta G^{\neq}$ [18]. Maximization of the total interaction increasing the hindrance of the substituents, does not affect necessarily the diastereotopic interaction $\Delta\Delta G^{\neq}$ to whom the stereochemical control is related; indeed this term may become so small with respect to the total interaction that the intermediates fail to 'see' a difference in reaction pathway and produce a racemic mixture. Thus, increasing the steric hindrance of the substituents does not necessarily lead to an increased efficiency in the asymmetric synthesis.

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## Experimental Part

*General.* (−)-(*S*)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene, ((−)-(*S*)-binap) is commercially available and was purchased from *Fluka AG*. The Ru complexes used in enantioselective reduction were prepared according to literature procedures: they were the dimer $[Ru_2((S)\text{-binap})_2Cl_4]NEt_3$ (**3**) [6] and the 'preformed' $[Ru((S)\text{-binap})Cl_2]_n$ (**4**), prepared from the combination of (*S*)-binap and $[Ru(benzene)Cl_2]_2$ in DMF [7]. All reactions with air- and moisture-sensitive solvents and reagents were carried out under a positive pressure of dry Ar. Solvents were distilled under dry $N_2$ and degassed with Ar prior to use. Solvent mixtures for TLC and column flash chromatography are specified by volume-to-volume ratio. HPLC analyses were performed on a *Chiralcel-OD* column (250 × 4.6 mm i.d.) from *Daicel*. $^1$H-NMR were recorded on a *Bruker WP80* and a *Varian XL200* in $CDCl_3$ with TMS as an internal standard.

*3-O-Substituted 1,3-Dihydroxypropan-2-ones. 1-Hydroxy-3-(triphenylmethoxy)propan-2-one* (**1b**) [15]. Freshly distilled 1,3-dihydroxypropan-2-one (0.52 g, 5.75 mmol), trityl chloride (1.72 g, 6.16 mmol), and 4-(dimethylamino)pyridine (54 mg) were dissolved in pyridine and stirred at r.t. for 15 h. After removing pyridine *in vacuo*, $H_2O$ and AcOEt were added. The org. layer was separated and concentrated. The resulting residue was chromatographed on silica gel (hexane/AcOEt 75:25) yielding 0.86 g (2.59 mmol; 45%) of **1b** as a colorless oil, which solidified on standing. $^1$H-NMR (200 MHz, $CDCl_3$): 3.0 (*t*, OH); 3.9 (*s*, $CH_2OTr$); 4.6 (*d*, $CH_2OH$); 7.2–7.5 (*m*, 3 Ph).

*1-Hydroxy-3-[(4-Methoxyphenyl)diphenylmethoxy]propan-2-one* (**1c**). Freshly distilled 1,3-dihydroxypropan-2-one (1 g, 11.1 mmol), (*p*-anisyl)(chloro)diphenylmethane (3.43 g, 11.1 mmol) and 4-(dimethylamino)pyridine (100 mg) were dissolved in pyridine and stirred at r.t. for 2 h. Workup was carried out as described for the preparation of **1b** and was followed by chromatography on silica gel (hexane/AcOEt 80:20), giving 1.95 g (5.38 mmol; 48.5%) of **1c** as a colorless oil, which solidified on standing. $^1$H-NMR (200 MHz, $CDCl_3$): 3.0 (*t*, OH); 3.8 (*s*, $CH_3O$); 3.9 (*s*, $CH_2OC(4\text{-}MeO\text{-}C_6H_4)Ph_2$); 4.6 (*d*, $CH_2OH$); 6.85, 7.25–7.45 (*d* and *m*, $(4\text{-}MeO\text{-}C_6H_4)Ph_2$).

*2,2-Dimethoxypropane-1,3-diol* (**5**). A mixture of 1,3-dihydroxypropan-2-one dimer (25 g, 138.8 mmol), trimethyl orthoformate (30 ml, 0.274 mmol), and TsOH (100 mg) in MeOH (300 ml) was shaken at r.t. overnight. After adding $Na_2CO_3$ (300 mg), the soln. was concentrated and the resulting residue chromatographed on silica gel ($CH_2Cl_2$/MeOH 93:7) yielding 28.6 g (210.1 mmol; 75.7%) of **5** as a white waxy solid. $^1$H-NMR (200 MHz, $CDCl_3$): 2.55 (*t*, 2 OH); 3.3 (*s*, $2CH_3$); 3.7 (*d*, $2CH_2$).

*3-(Benzyloxy)-2,2-dimethoxypropan-1-ol* (**6**). $PhCH_2Cl$ (2.79 ml, 24.3 ml) was added dropwise to a stirred mixture of **5** (3 g, 22.03 mmol) and *t*-BuOK (2.97 g, 26.5 mmol) in *t*-BuOH at 40° over 20 min. The mixture was shaken for 30 min at that temp. and then refluxed for 30 min more. After cooling to r.t., $Et_2O$, $H_2O$ were added and the layers separated. The aq. phase was extracted twice with $Et_2O$. The combined $Et_2O$ layers were dried ($Na_2SO_4$) and evaporated under reduced pressure. The resulting residue was chromatographed on silica gel (cyclohexane/AcOEt 65:35) yielding 2.73 g (12.1 mmol; 54.8%) of **6** as a colorless oil. $^1$H-NMR (200 MHz, $CDCl_3$): 2.0 (*t*, OH); 3.3 (*s*, $2CH_3$); 3.55 (*s*, $CH_2OBn$); 3.7 (*d*, $CH_2OH$); 4.6 (*s*, $CH_2Ph$); 7.35 (*m*, Ph).

*2,2-Dimethoxy-3-(octadecyloxy)propan-1-ol* (**7**) [19]. Octadecyl methanesulfonate (5.63 g, 16.2 mmol) dissolved in THF was added dropwise to a stirred mixture of **5** (2 g, 14.7 mmol) and *t*-BuOK (1.98 g, 17.6 mmol) in *t*-BuOH at 40°. The mixture was refluxed for 30 min and then cooled to r.t. $(i\text{-}Pr)_2O$ and $H_2O$ were added. The upper phase was evaporated and the residue chromatographed on silica gel (hexane/AcOEt 70:30) yielding 2.58 g (6.6 mmol; 45.2%) of **7** as a white solid. $^1$H-NMR (80 MHz, $CDCl_3$): 0.9 (*t*, $CH_2CH_3$); 1.3 (br. *s*, $16CH_2$); 2.3 (OH); 3.3 (*s*, $2CH_3O$); 3.35–3.8 ($CH_2OCH_2$, $CH_2OH$).

*3-(Allyloxy)-2,2-dimethoxypropan-1-ol* (**8**). Allyl bromide (1.4 ml, 16.2 mmol) was added dropwise to a stirred mixture of **5** (2 g, 14.7 mmol) and *t*-BuOK (1.98 g, 17.6 mmol) in *t*-BuOH at 40°. The mixture was shaken for 15 min at that temp. and then cooled to r.t. AcOEt and $H_2O$ were added and the layers separated. The aq. phase was extracted twice with AcOEt. The combined org. extracts were dried ($Na_2SO_4$) and concentrated. The residue was chromatographed on silica gel (hexane/AcOEt 60:40), yielding 1.25 g (7.1 mmol; 48.3%) of **8** as a colorless oil. $^1$H-NMR (80 MHz, $CDCl_3$): 2.65 (OH); 3.3 (*s*, $2CH_3$); 3.55 (*s*, $CH_2O(allyl)$); 3.7 (*s*, $CH_2OH$); 4.05 (*d*, $CH_2CH{=}CH_2$); 5.1–5.5 (*m*, $CH{=}CH_2$); 5.7–6.1 (*m*, CH).

*1-(Benzyloxy)-3-hydroxypropan-2-one* (**1a**). The compound **6** (0.55 g, 2.43 mmol) was dissolved in 3N HCl (15 ml) and shaken at r.t. for 30 min. The mixture was neutralized with $NaHCO_3$, extracted with AcOEt, and the extract dried ($Na_2SO_4$). Filtration and removal *in vacuo* of the solvent afforded 0.43 g (2.39 mmol; 98%) of **1a** as a colorless oil, which solidified on standing. $^1$H-NMR (200 MHz, $CDCl_3$): 3.0 (*t*, OH); 4.2 (*s*, $CH_2OBn$); 4.5 (*d*, $CH_2OH$); 4.6 (*s*, $CH_2Ph$); 7.35 (*m*, Ph).

*1-Hydroxy-3-(octadecyloxy)propan-2-one* (**1d**) [14]. The compound **7** (0.98 g, 2.52 mmol) was dissolved in dioxane (20 ml). 3N HCl (3 ml) was added and the mixture stirred at r.t. for 2 h. After adding $H_2O$ and $NaHCO_3$ (2 g), the mixture was extracted with $CHCl_3$. The org. extracts were concentrated *in vacuo* yielding 0.83 g (2.42

mmol; 96%) of **1d** as a white waxy solid. $^1$H-NMR (200 MHz, $CDCl_3$): 0.9 (*t*, $CH_3$); 1.3 (br. *s*, $15CH_2$); 1.6 (*m*, $OCH_2CH_2$); 3.05 (*t*, OH); 3.5 (*t*, $OCH_2CH_2$); 4.15 (*s*, $CH_2OC_{18}H_{37}$); 4.45 (*d*, $CH_2OH$).

*1-(Allyloxy)-3-hydroxypropan-2-one* (**1e**). The compound **8** (1.2 g, 6.81 mmol) was dissolved in 3N HCl (15 ml) and shaken at r.t. for 30 min. Workup as described for the preparation of **1a** gave 0.82 g (6.30 mmol; 93%) of **1e** as a colorless oil. $^1$H-NMR (200 MHz, $CDCl_3$): 3.0 (br. *s*, OH); 4.05 (*dt*, $CH_2CH{=}CH_2$); 4.2 (*s*, $CH_2O$(allyl)); 4.45 (*s*, $CH_2OH$); 5.15–5.4 (*m*, $CH{=}CH_2$); 5.8–6.0 (*m*, CH).

*Catalytic Reduction.* A weighed amount of catalyst was dissolved in a known amount of the solvent in a *Schlenk* tube under Ar. In another *Schlenk* tube, more than 1 mmol of the substrate was dissolved in the same solvent under Ar. With a syringe, 1.1 mmol of the substrate and 0.011 mmol of the catalyst were transferred into a third *Schlenk* tube, the solvent was added to obtain 11 ml of soln. which was stirred for 30 min under Ar. A stainless steel autoclave was pressurized to 100 Kgw/cm$^2$ and vented five times; 10 ml of the substrate/catalyst soln. were introduced into the autoclave with a syringe through a serum cap; the autoclave was pressurized to 100 Kgw/cm$^2$ and stirred in a thermoregulated oil bath at 20°. After the reaction, the autoclave was carefully vented, the resulting orange-yellow soln. was concentrated on a rotatory evaporator, and the oily residue was separated by column flash chromatography. The workup conditions were as follows:

*3-(Benzyloxy)propane-1,2-diol* (**2a**) [16]: AcOEt/toluene 85:15. $^1$H-NMR (200 MHz, $CDCl_3$, $D_2O$): 3.60 (*m*, 4H); 3.80 (*m*, 1H); 4.46 (*s*, 2H); 7.33 (*s*, Ph).

*3-(Triphenylmethoxy)propane-1,2-diol* (**2b**) [20]: AcOEt/toluene 1:1. $^1$H-NMR (200 MHz, $CDCl_3$, $D_2O$): 3.25 (*m*, 2H); 3.6 (*m*, 2H); 3.8 (*m*, 1H); 7.2–7.4 (*m*, 15H).

*3-[(4-Methoxyphenyl)diphenylmethoxy]propane-1,2-diol* (**2c**) [21]: AcOEt/toluene 1:1. $^1$H-NMR (200 MHz, $CDCl_3$, $D_2O$): 3.3 (*m*, 2H); 3.67 (*m*, 1H); 3.80 (*s*, 3H); 3.92 (*m*, 2H); 6.8–6.9 (*d*, 2H); 7.3 (*m*, 12H).

*3-(Octadecyloxy)propane-1,2-diol* (**2d**) [16]: AcOEt/toluene 1:1. $^1$H-NMR (200 MHz, $CDCl_3$, $D_2O$): 0.9 (*t*, 3H); 1.26 (br. *m*, 32H); 3.40–3.70 (*m*, 7H).

*1-Hydroxy-3-propyloxypropan-2-one* from the reduction of *1-(allyloxy)-3-hydroxypropan-2-one* (**1e**). AcOEt/hexane 7:3. $^1$H-NMR (200 MHz, $CDCl_3$, $D_2O$): 0.9 (*t*, 3H); 1.39 (*q*, 2H); 3.0 (br. *s*, OH); 4.05 (*t*, 2H); 4.2 (*s*, 2H); 4.45 (*s*, 2H).

The enantiomeric composition was determined by HPLC on a chiral stationary phase under the following conditions: **2a–c**: hexane/i-PrOH 9:1, flow rate: 1 ml/min.

The enantiomeric composition of **2d** was determined by comparing the optical rotation value with that reported in [16].

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