

Combined epimerisation and acylation: Meerwein–Ponndorf–Verley–Oppenauer catalysts in action

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A practical racemisation–epimerisation method for chiral secondary alcohols has been developed. Meerwein–Ponndorf–Verley–Oppenauer catalysts such as neodymium(III) isopropoxide are able to racemise these alcohols with retention of other stereocentres in the molecule. This is particularly useful for the recycling of the undesired products of kinetic resolutions of alcohols. By combination of such a racemisation with an acylation using isopropenyl or ethoxyvinyl esters as acyl donors, a fast straightforward recycling of starting materials may be achieved. The combined epimerisation and acylation process is demonstrated for the steroid estradiol methyl ether.

Introduction

The synthesis of complex chiral compounds is becoming increasingly important. However, not all conversions can be performed enantiospecifically. In these cases, the unwanted stereoisomer is separated from the desired compound and is often discarded, even at a relatively late stage of an elaborate reaction sequence. It is, therefore, desirable to have available gentle and selective racemisation and epimerisation reactions, which allow recycling of the undesired isomer, thus reducing the loss of valuable material.

In this paper, a mild procedure for the epimerisation of secondary alcohols is presented. It exploits the reversible Meerwein–Ponndorf–Verley–Oppenauer (MPVO) reduction–oxidation reactions.^{1–5} The MPV-reduction of ketones and the Oppenauer-oxidation of alcohols have been widely studied and typically both reactions can be performed under very mild reaction conditions.^{6–9} Their mechanisms have recently been shown to proceed exclusively *via* a carbon-to-carbon hydride transfer.¹⁰ Combination of the two reactions results in a convenient racemisation procedure. Originally, aluminium(III) isopropoxide was used as the catalyst for the MPV reduction and Oppenauer oxidation. Through the years, several improved catalysts have been developed.^{11–13} In the present study several catalytic systems were tested for their activity in racemisations of secondary alcohols.

Most reactions have been performed with 1-phenylethanol (**1**) as a model compound. The best catalyst was then tested in the epimerisation of the estradiol derivative **2** (Fig. 1). Estradiol is a steroid hormone from the family of estrogens, which can be prepared by reduction of the corresponding ketone. Achiral reducing reagents, such as NaBH₄ or LiAlH₄, give the epimers α -estradiol and β -estradiol in a ratio of typically 1 : 4.¹⁴ Since it is difficult to obtain the desired β -estradiol in high yields, the epimerisation of estradiol is an interesting test case for the scope of the newly developed methodology.

Additionally, recycling of unwanted isomers of alcohols produced during enzymatic kinetic resolutions of esters is a further example of a process where racemisations are important. It may be particularly useful to convert the racemised alcohols

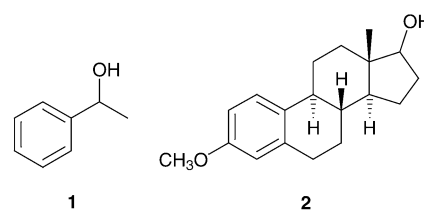


Fig. 1 The model compound 1-phenylethanol (**1**) and the steroid estradiol methyl ether (**2**).

directly into the appropriate esters so as to be able to use them again in a subsequent kinetic resolution.

The catalytic systems that are proposed for the racemisation and epimerisation are also known to be active for the acylation of alcohols.¹⁵ Therefore, we studied a one-pot reaction for the combined racemisation and acylation of secondary alcohols. For the acylation, isopropenyl and ethoxyvinyl esters (**3** and **4**) were applied as activated acyl donors (Fig. 2).^{16–18}

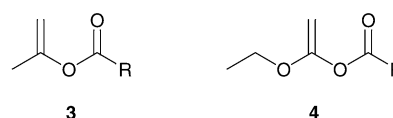
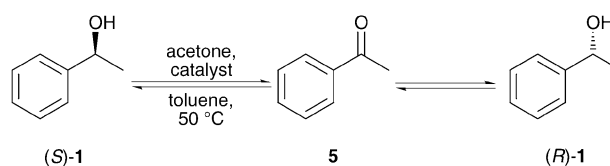


Fig. 2 Isopropenyl ester (**3**) and ethoxyvinyl ester (**4**).

Results and discussion

Selection of the catalyst

Several racemisation reactions of (*S*)-1-phenylethanol ((*S*)-**1**) were performed using 2 mol% of a metal isopropoxide as the catalyst and acetone as the initial oxidant (Scheme 1, Table 1).



Scheme 1 Racemisation of (*S*)-1-phenylethanol ((*S*)-**1**).

Aluminium(III) isopropoxide is the traditional catalyst for MPV reductions and Oppenauer oxidations. When catalytic amounts are used the racemisation reactions are very slow

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Table 1 Racemisation of (*S*)-1-phenylethanol ((*S*)-1) with different MPVO catalysts^a

Entry	Catalyst	Additive ^b	Time/h	Ee (<i>S</i>)-1 (%) ^c	Reaction rate/h ^{-1d}
1	—	—	24	>99	0.0
2	—	NaA	24	>99	0.0
3	—	NdA(180)	24	>99	0.0
4	—	NdA(400)	24	>99	0.0
5	Na(OCH(CH ₃) ₂) ₃	—	24	99	0.0
6	Na(OCH(CH ₃) ₂) ₃	NaA	24	99	0.0
7	Al(OCH(CH ₃) ₂) ₃	NaA	24	92	1.3
8	Zr(OCH(CH ₃) ₂) ₄	NaA	24	92	3.5
9	La(OCH(CH ₃) ₂) ₃	NaA	24	93	0.9
10	Nd(OCH(CH ₃) ₂) ₃	—	6 ^e	87	14.9
11	Nd(OCH(CH ₃) ₂) ₃	NaA	20	0	17.1
12	Nd(OCH(CH ₃) ₂) ₃	NdA(180)	24	13	17.3
13	Nd(OCH(CH ₃) ₂) ₃	NdA(400)	24	13	17.4
14	Sm(OCH(CH ₃) ₂) ₃	NaA	24	0	15.4
15	Gd(OCH(CH ₃) ₂) ₃	—	6 ^e	84	18.6
16	Gd(OCH(CH ₃) ₂) ₃	NaA	6	45	20.9
17	Gd(OCH(CH ₃) ₂) ₃	NaA	16	0	20.9
18	Yb(OCH(CH ₃) ₂) ₃	NaA	24	50	18.5
19	Nd(OCH(CH ₃) ₂) ₃	— ^f	24	>99	0.0
20	Nd(OCH(CH ₃) ₂) ₃	NaA ^g	24	99	0.0

^a Toluene (4 mL), (*S*)-1-phenylethanol (0.24 mL, 2 mmol), acetone (0.15 mL, 2 mmol, 1 equiv.), 1,3,5-triisopropylbenzene (int. std.) (0.1 mL) and the catalyst (0.04 mmol, 0.02 equiv.) were stirred at 50 °C. ^b Zeolite NaA (30 mg, dried at 400 °C) or NdA(T) (30 mg, where T is the activation temperature in °C) were added. ^c Ee (starting material) >99%. ^d Reaction rate during first 30 min. in [mol substrate]/[mol catalyst]/hour. ^e Reaction stopped due to deactivation of the catalyst. ^f In the presence of diacetone alcohol (0.22 mL, 2 mmol).

(entry 7); thus, it is commonly used in stoichiometric amounts. Catalysts based on lanthanide ions (entries 9–18), however, are generally more active, most likely because the ligand-exchange rates for lanthanide complexes are higher than those for aluminium complexes. Fig. 3 shows a typical plot of the conversion as a function of time. The reaction slows down within a short period of time and does not follow straightforward kinetics. Small amounts of diacetone alcohol were detected in the reaction mixture. This compound can be formed by an aldol reaction from acetone. Diacetone alcohol may bind the metal ion in a bidentate fashion and, therefore, inhibit the catalyst. Furthermore, the aldol condensation produces water, which destroys the Ln-isopropoxide catalyst. To verify this, the reactions were also performed in the presence of one equivalent of diacetone alcohol (entries 19 + 20). Indeed, the reaction was suppressed almost completely. This inhibition is prevented by the addition of activated zeolite NaA (3 Å molecular sieves, compare entries 10 + 15 with 11 + 16). In its presence, the conversions were much faster. Complete racemisation was achieved with Gd-isopropoxide in the presence of zeolite NaA within 16 h (entry 17).

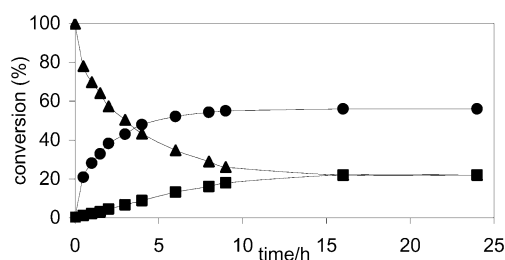


Fig. 3 Conversion versus time in the racemisation of (*S*)-1 (▲) into (*R*)-1 (■) and 5 (●) with Gd(OCH(CH₃)₂)₃ under the conditions described in Table 1, entry 17.

It is known that in aqueous suspensions, the Na⁺ counterions in zeolite NaA readily exchange for lanthanide ions. Such a transmetalation reaction between Ln-isopropoxide and zeolite NaA may also occur in the present system. In order to rule out that catalysis is taking place by exchanged sodium from the zeolite, experiments were performed with zeolite NaA, neodymium exchanged zeolite A, sodium isopropoxide and combinations thereof (entries 2–6). None of these appeared to be active as a catalyst in the racemisation reaction. Furthermore,

when using neodymium exchanged zeolites¹⁹ (entries 12 + 13) instead of zeolite NaA as the additive to the reaction, only a slight increase of initial reaction rate was observed: in the absence of an isopropoxide neither NdA(180) nor NdA(400) showed any catalytic activity (entries 3 + 4, the number in brackets is the activation temperature in °C). Obviously, the role of zeolite NaA in these reactions is important. It suppresses the negative effects of diacetone alcohol, possibly by absorbing it; additionally it removes any water formed by aldol condensations of acetone. Due to the larger counterion, NdA is less efficient in absorbing water and the aldol product.

Solvent effects

The results of experiments with various solvents (Table 2) show a general trend towards lower reactivities upon the increase of Lewis basicity of the solvent. The higher the Lewis basicity, the better the solvent can coordinate to the catalytic metal ion. This is supported by the observation that a change of colour occurs from blue (typically, the colour of a Nd(OCH(CH₃)₂)₃ solution) to green–yellow of an ethereal solution of the Nd-triisopropoxide catalyst upon standing. This yellow solution does not show any catalytic activity in the racemisation reaction. In view of these findings, further experiments were carried out with heptane or toluene as the solvent.

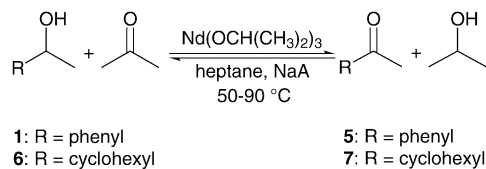
Table 2 Racemisation of (*S*)-1-phenylethanol ((*S*)-1) in different solvents^a

Entry	Solvent	Time/h	Ee ^b (%)
1	acetonitrile	>48	>99
2	dioxane	5	28
3	THF	3.5	0
4	diisopropyl ether	3.5	0
5	MTBE	3.5	0
6	toluene	3	0
7	hexane	2	0
8	heptane	2	0

^a Solvent (12 mL), zeolite NaA (30 mg, dried at 400 °C), (*S*)-1-phenylethanol (0.24 mL, 2 mmol), acetone (0.15 mL, 2 mmol, 1 equiv.), 1,3,5-triisopropylbenzene (int. std.) (0.2 mL) and neodymium(III) isopropoxide (120 mg, 0.37 mmol, 0.185 equiv.) were stirred at 50 °C. ^b Ee (starting material) >99%.

Oxidant–substrate ratio

The rate of racemisation and the yield of racemised alcohol depend not only on the catalyst and solvent, but also on the amount of the oxidant (acetone) used. The optimal conditions will also depend on the nature of the alcohol, since that determines the thermodynamics of the overall MPVO equilibrium (Scheme 2 and Table 3).⁸



Scheme 2 Racemisation of **1** and **6**.

The shortest reaction time for the racemisation of (*S*)-**1** was achieved with 1 equivalent of acetone (entry 1). However, in this case the amount of acetophenone (**5**) formed is 50%. A good compromise was achieved with a 0.1 equivalent of acetone; although longer reaction times were required, a considerably higher yield of the racemic alcohol was obtained (entry 3). Under comparable conditions, the racemisation of **6** was much slower and produced smaller amounts of ketone **7**. The difference in behaviour of **1** and **6** in the racemisation reaction can be explained by the difference in the equilibrium constants for the two reactions. Since acetophenone (**5**) is stabilised by conjugation, the equilibrium between alcohol **1** and ketone **5** lies further on the ketone side than the corresponding equilibria for **6** and **7**.

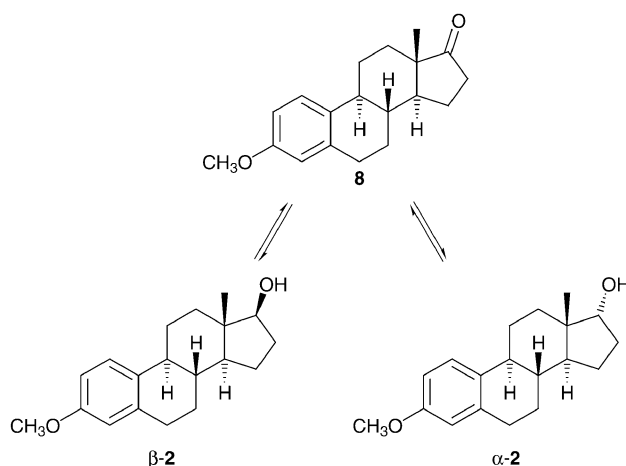
In conclusion, secondary alcohols can be racemised smoothly with Ln(III) isopropoxides (Ln = Nd → Yb) in the presence of 3 Å molecular sieves (zeolite NaA) with heptane as the solvent and an appropriate amount of acetone as the oxidant.

Epimerisation

As mentioned in the introduction, the reduction of **8** with NaBH₄ or LiAlH₄ gives mixtures of α -**2** and β -**2** in a molar ratio of about 1 : 4. A similar ratio was obtained with a MPV reduction using neodymium triisopropoxide as the catalyst in isopropanol. We assume that these products are determined by kinetic control. The epimerisation of estradiol methyl ether (**2**) *via* estrone methyl ether (**8**) is therefore an interesting test case for our racemisation–epimerisation methodology (Scheme 3).

The reaction was carried out as described for the racemisation above, however, toluene was used as solvent. To improve the solubility of estradiol its methyl ether **2** was used for the epimerisation.

With 0.5 equivalents of acetone in toluene, the epimerisation successfully proceeded in 16 h, giving a 3 : 2 ratio of the epimerised product and the ketone. None of the other stereocentres was affected, demonstrating the selectivity of



Scheme 3 Epimerisation of β - and α -estradiol methyl ether **2**.

the epimerisation. All products could readily be separated by column chromatography and recycled. As expected, the equilibrium shifted towards the alcohol upon use of less acetone (6 : 1 ratio with 0.1 equivalent instead of a 3 : 2 ratio with 0.5 equivalent). This occurs, however, at the expense of a longer reaction time. The α -**2** : β -**2** ratio after epimerisation was 2 : 3 and is independent of the amount of acetone used. This ratio is much more favourable for recycling procedures than the 1 : 4 α -**2** : β -**2** ratio obtained after the reduction of **8** with neodymium(III) isopropoxide in isopropanol.

Racemisations and acylations

Since the lanthanide isopropoxides are not only versatile redox catalysts, but also catalyse acylations,¹⁵ their potential for a one-pot racemisation and acylation was investigated. Acylation studies were carried out with the same alcohol to catalyst ratio as in the racemisation. To the mixture of a racemic alcohol, 1.1 equivalent of an acyl donor, isopropenyl ester (**3**) or ethoxyvinyl ester (**4**), was added (Fig. 4). These acyl donors release acetone or ethyl acetate as leaving groups. Both by-products are inactive in the acylation reaction and can readily be removed. The acyl donors used were synthesised *via* well-established procedures.^{20–22} Typically, the acylations of **1** proceeded within 15 minutes without any trace of side-products (Scheme 4). The

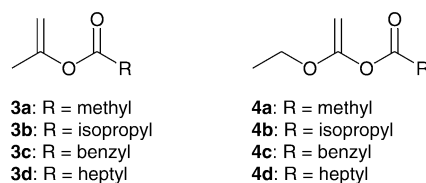
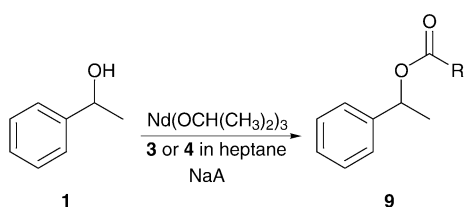


Fig. 4 The synthesised acyl donors **3** and **4**.

Table 3 Racemisation of (*S*)-1-phenylethanol (**1**) and (*S*)-1-cyclohexylethanol (**6**) with varying amounts of acetone^a

Entry	Substrate	Catalyst	Acetone (equiv.) ^b	Time/h ^c	Ketone (5/7) formed (%) ^d
1	(<i>S</i>)- 1	Nd(OCH(CH ₃) ₂) ₃	1	1.5	50 (5)
2	(<i>S</i>)- 1	Nd(OCH(CH ₃) ₂) ₃	0.2	2.5	12 (5)
3	(<i>S</i>)- 1	Nd(OCH(CH ₃) ₂) ₃	0.1	3	10 (5)
4	(<i>S</i>)- 1	Nd(OCH(CH ₃) ₂) ₃	0.05	>6	6 (5)
5	(<i>S</i>)- 1	Nd(OCH(CH ₃) ₂) ₃	0.025	>6	3 (5)
6	(<i>S</i>)- 6	Nd(OCH(CH ₃) ₂) ₃	1	2.5	25 (7)
7	(<i>S</i>)- 6	Nd(OCH(CH ₃) ₂) ₃	0.5	4	10 (7)
8	(<i>S</i>)- 6	Nd(OCH(CH ₃) ₂) ₃	0.1	>7	9 (7)

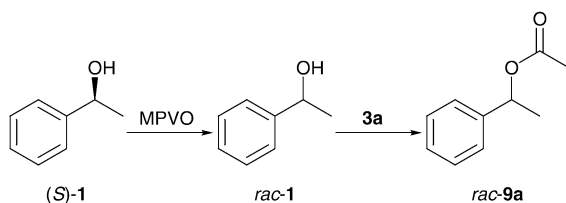
^a Heptane (12 mL), zeolite NaA (30 mg, dried at 400 °C), (*S*)-**1** or (*S*)-**6** (0.24 mL, 2 mmol, *ee* > 99%), acetone as in the table, 1,3,5-triisopropylbenzene (int. std.) (0.2 mL) and the catalyst (0.37 mmol, 0.185 equiv.) were stirred at 50 °C. After 30 min. the temperature was increased to 90 °C. ^b Equivalents of acetone with respect to the substrate. ^c Time needed for complete racemisation. ^d After complete racemisation (ketone formed in brackets).



Scheme 4 $\text{Nd}(\text{OCH}(\text{CH}_3)_2)_3$ catalysed acylation with **3** and **4**.

reaction times were independent of the type of acyl donor and the reaction is much faster than the racemisation. After purification, the racemic esters were obtained in good yields (71–88%), again the type of acyl donor showed little influence. It should be noted that in the absence of the catalyst, no reaction was observed.

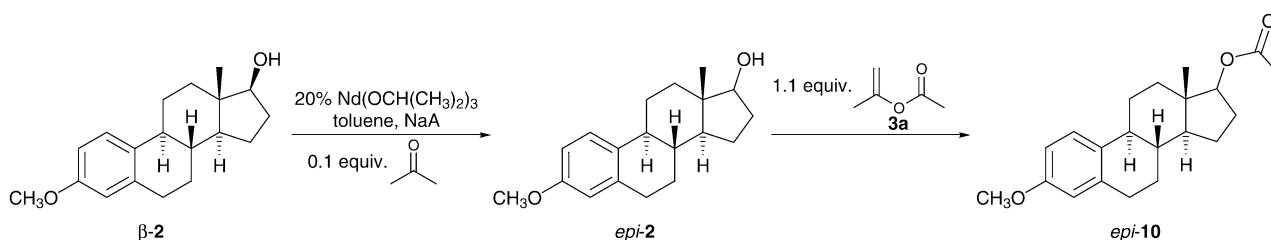
With the two above-described reactions, the racemisation and the acylation, it is possible to recycle the “wrong” enantiomer that is obtained as undesired side-product after an enzymatic kinetic resolution. For this purpose, it is of particular interest to perform these reactions in a one-pot two-step sequence by adding the acyl donor once the racemisation is complete. Since the acylation (15 min for **1**) is significantly faster than the racemisation (16 h), the influence of by-products released by the acylation (acetone or ethyl acetate) is negligible. When (*S*)-**1** was racemised under standard conditions and **3a** was added, racemic **9a** was obtained in good yield (88%; Scheme 5). The ester is not susceptible to reactions catalysed by neodymium(III) isopropoxide, as was shown by an attempt to racemise (*R*)-**9a** with this catalyst.



Scheme 5 Recycling of unwanted chiral alcohol to racemic acetate.

To investigate whether catalytic activity in the acylation was similar to that in the racemisation, two promising catalysts, samarium(III) isopropoxide and gadolinium(III) isopropoxide, were tested in this reaction too. Although the racemisation catalysed by Gd^{III} is faster than the racemisation catalysed by other catalysts (see also Table 1), no significant rate difference is observed in the acylation. The same was observed when **6** was acylated either by the Nd^{III} , Sm^{III} or Gd^{III} catalysts: the acylation is fast and proceeds within 20 minutes.

Ultimately, this one-pot two reaction sequence was applied to β -**2**. Subsequent to the epimerisation **3a** was added. Complete acylation proceeded within 1 hour yielding epimeric **10**. No other diastereoisomers of **10** were detected in the reaction mixture, proving the high selectivity of the developed methodology (Scheme 6). After column chromatography 40% of β -**10** and 33% of α -**10** were obtained.



Scheme 6 Epimerisation and acylation of β -**2**.

Conclusions

Neodymium triisopropoxide is a powerful and selective catalyst for the racemisation of secondary alcohols. Product inhibition due to aldol reactions can be suppressed by the use of zeolite NaA. The same catalytic system is very effective in the acylation of alcohols with the use of activated acyl donors including isopropenyl and ethoxyvinyl esters. Combination of the racemisation and acylation in a one-pot two-step sequence allows a mild and rapid recycling of undesired products from kinetic resolutions. The procedure proves to be selective for alcohol functions as was proven by the epimerisation of estradiol methyl ester **2**.

Experimental

All experiments were performed in dried glassware under a nitrogen atmosphere unless stated otherwise. All chemicals were purchased from Aldrich or Acros. Anhydrous solvents and solids were used as received, liquids were dried and distilled prior to use. Enantiopure alcohols (*S*)-**1** and (*S*)-**6** were prepared as described earlier.¹⁰ Zeolite NaA (3 Å molecular sieves) was dried overnight at 400 °C unless stated otherwise. Zeolite NdA was prepared according to a literature procedure.¹⁹ Enantiomeric excesses were determined and reactions were followed by gas chromatography by using a Hewlett-Packard 5890 Series II gas chromatograph, equipped with a 40 m × 0.25 mm chiral column Chiraldex™ B-PH (β -cyclodextrins permethylated hydroxypropyl), split injector (1/100) at 220 °C, a Flame Ionisation Detector at 250 °C and using He as carrier gas. In the catalytic reactions 1,3,5-triisopropylbenzene was used as internal standard. Retention times (min) at 120 °C isotherm: 1,3,5-triisopropylbenzene (11.0), acetophenone (11.5), (*S*)-1-methylbenzyl acetate (14.5), (*R*)-1-methylbenzyl acetate (15.0), (*R*)-1-phenylethanol (23.0), (*S*)-1-phenylethanol (23.5) or a Shimadzu GC-17A gas chromatograph, equipped with a 25 m × 0.32 mm chiral column Chrompack™ Chirasil-Dex CB, split injector (1/97) at 220 °C, a Flame Ionisation Detector at 220 °C and He as carrier gas. Retention times (min) at 120 °C isotherm: 1,3,5-triisopropylbenzene (4.0), (*S*)-1-phenylethanol (4.3), (*R*)-1-phenylethanol (4.5). NMR spectra were recorded on a Varian VXR-400S or a Varian Unity Inova-300 spectrometer at 25 °C. Some coupling constants were determined by spin iteration with the SpinWorks 1.2 program, using the NUMARIT²³ or NUMMRIT²⁴ algorithm. Mass spectra were recorded with a VG SE spectrometer at 70 eV. For column chromatography Fluka silica gel 60 was used and Merck aluminium sheets with silica gel 60 F₂₅₄ were used for TLC. Elution was carried out with mixtures of petroleum ether 40–65 °C (PE), diethyl ether (Et_2O) and *tert*-butyl methyl ether (MTBE).

General procedure for the racemisation of (*S*)-**1** with various catalysts

The catalyst (0.04 mmol) was dissolved in toluene (4 mL). In some experiments, zeolite (30 mg) was added. Then, 1,3,5-triisopropylbenzene (0.1 mL) and acetone (0.15 mL, 2.0 mmol) were added to this solution and the temperature was raised to 50 °C. Subsequently, (*S*)-**1** (0.24 mL, 2.0 mmol) was added

and samples of 20 μ L, which were analysed by chiral GC, were taken at regular time intervals. When diacetone alcohol (0.22 mL, 2 mmol) was added to the reaction mixture, it was added before raising the temperature. For results, see Table 1.

General procedure for the racemisation of (S)-1 in various solvents

Zeolite NaA (30 mg) was suspended in a solution of neodymium(III) isopropoxide (120 mg, 0.37 mmol) in the appropriate solvent (12 mL). 1,3,5-Triisopropylbenzene (0.2 mL) and acetone (0.15 mL, 2.0 mmol) were added and the temperature was raised to 50 °C. Subsequently, (S)-1 (0.24 mL, 2.0 mmol) was added and samples of 20 μ L, which were analysed by chiral GC, were taken at regular time intervals. For results, see Table 2.

General procedure for the racemisation of (S)-1 and (S)-6 with varying amounts of acetone

Zeolite NaA (30 mg) was added to a solution of neodymium(III) isopropoxide (120 mg, 0.37 mmol) in heptane (12 mL). 1,3,5-Triisopropylbenzene (0.2 mL) and the appropriate amount of acetone were added and the temperature was raised to 50 °C. Subsequently, (S)-1 or (S)-6 (0.24 mL, 2.0 mmol) was added and after 30 minutes the temperature was increased to 90 °C. Samples of 20 μ L were taken at regular time intervals and analysed by chiral GC. For results, see Table 3.

Estrone methyl ether (8)

Method 1: An aqueous solution of sodium hydroxide (12.5 mM, 0.25 mL, 3.13 mmol) was added to a mixture of estrone (0.50 g, 1.85 mmol), phenyltrimethylammonium chloride (0.43 g, 2.52 mmol) and toluene (4.9 mL).^{25,26} The mixture was refluxed for 2 h and then cooled to 50 °C. Water (4.9 mL) and acetic acid (93 μ L, 1.61 mmol) were added and after 15 min the volatiles were evaporated. The solids were washed with water and diethyl ether, giving 0.45 g (1.57 mmol, 85%) of the methylated estrone **8**.²⁷ Method 2: To a solution of estrone (500 mg, 1.85 mmol) in a mixture of dry acetone (15 mL) and dry 1,4-dioxane (10 mL), water free potassium carbonate (256 mg, 1.85 mmol) and dimethyl sulfate (0.18 mL, 1.85 mmol) were added. After refluxing the mixture overnight the reaction was quenched with an aqueous 1 M NaOH solution (15 mL). After evaporation of the solvents and redissolving with dioxane, the product was purified by column filtration (MTBE : PE = 1 : 1) giving 0.42 g (1.48 mmol, 80%) of the product **8**. δ_{H} (400 MHz, dioxane-*d*₈, Me₄Si) 0.86 (s, 3H, C-CH₃), 1.25–1.68 (m, 7H, C(14)H, C(6)H₂, C(12)HH, C(7)HH, C(11)HH, C(15)HH), 1.78–1.88 (m, 1H, C(12)HH), 1.88–2.10 (m, 3H, C(15)HH, C(7)HH, C(16)HH), 2.10–2.30 (m, 1H, C(9)H), 2.30–2.46 (m, 2H, C(11)HH, C(16)HH), 2.85–2.90 (m, 1H, C(8)H), 3.70 (s, 3H, OCH₃), 6.58 (d, *J* = 2.80 Hz, 1H, C(4)H), 6.65 (dd, *J* = 8.40, 2.80 Hz, 1H, C(2)H), 7.17 (d, *J* = 8.40, 1H, C(1)H); δ_{C} (75 MHz, CDCl₃, Me₄Si) 13.76 (C-CH₃), 22.00 (C(15)), 26.50 (C(11)), 27.25 (C(7)), 30.20 (C(8)), 32.35 (C(12)), 35.58 (C(16)), 39.17 (C(6)), 44.81 (C(9)), 48.18 (C(13)), 50.89 (C(14)), 55.05 (O-CH₃), 112.05 (C(2)), 114.28 (C(4)), 126.84 (C(1)), 132.75 (C(10)), 138.06 (C(5)), 158.47 (C(3)), 218.82 (C(17)).

Estradiol methyl ether (2)

To a solution of estrone methyl ether (**8**) (400 mg, 1.41 mmol) in 2-propanol (20 mL), neodymium(III) isopropoxide (46 mg, 0.14 mmol) was added. The mixture was refluxed overnight. Toluene was added (20 mL), the organic layer was washed with 1 M HCl in water (20 mL), dried over MgSO₄ and the solvent was evaporated under vacuum. With ¹H-NMR (methyl signals at 0.76 and 0.69 ppm) the ratio β -2 : α -2 was determined to be 78 : 22. The two epimers were separated by column chromatography (MTBE : PE 1 : 3) giving 0.18 g (0.63 mmol, 45%) of the major epimer (β -2), 0.05 g (0.17 mmol, 12%) of the minor epimer (α -2) and 0.16 g of a mixture of the epimers (0.55 mmol,

39%).²⁷ β -2: δ_{H} (400 MHz, dioxane-*d*₈, Me₄Si) 0.73 (s, 3H, C-CH₃), 1.10–1.50 (m, 6H, C(14)H, C(6)H₂, C(12)HH, C(7)HH, C(11)HH), 1.58–1.70 (m, 1H, C(15)HH), 1.80–2.00 (m, 3H, C(12)HH, C(15)HH, OH), 2.10–2.18 (m, 1H, C(7)HH), 2.25–2.35 (m, 1H, C(16)HH), 2.50–2.60 (m, 2H, C(9)H, C(11)HH), 2.70–2.88 (m, 2H, C(16)HH, C(8)H), 3.24 (d, *J* = 4.76 Hz 1H, C(17)H), 3.69 (s, 3H, OCH₃), 6.56 (d, *J* = 2.80 Hz, 1H, C(4)H), 6.63 (dd, *J* = 2.80, 8.40 Hz, 1H, C(2)H), 7.14 (d, *J* = 8.40 Hz, 1H, C(1)H); δ_{C} (100 MHz, dioxane-*d*₈, Me₄Si) 11.36 (C(13)CH₃), 23.62 (C(15)), 26.98 (C(7)), 27.99 (C(11)), 30.29 (C(8)), 30.96 (C(16)), 37.60 (C(12)), 39.70 (C(6)), 43.85 (C(13)), 44.79 (C(9)), 50.78 (C(14)), 55.01 (OCH₃), 81.65 (C(17)), 111.97 (C(2)), 114.21 (C(4)), 126.71 (C(1)), 133.13 (C(10)), 138.22 (C(5)), 158.30 (C(3)); α -2: δ_{H} (400 MHz, dioxane-*d*₈, Me₄Si) 0.67 (s, 3H, C-CH₃), 1.16–1.68 (m, 7H, C(14)H, C(6)H₂, C(12)HH, C(7)HH, C(11)HH, C(15)HH), 1.74–2.40 (m, 7H, C(12)HH, C(15)HH, C(7)HH, C(16)HH, OH, C(9)H, C(11)HH), 2.72–2.85 (m, 2H, C(16)HH, C(8)H), 3.21 (dd, *J* = 5.60, 11.20 Hz, 1H, C(17)H), 3.69 (s, 3H, OCH₃), 6.57 (d, *J* = 2.80 Hz, 1H, C(4)H), 6.64 (dd, *J* = 2.80, 8.40 Hz, 1H, C(2)H), 7.17 (d, *J* = 8.80 Hz, 1H, C(1)H); δ_{C} (75 MHz, dioxane-*d*₈, Me₄Si) 17.36 (C(13)CH₃), 24.78 (C(15)), 26.93 (C(7)), 28.84 (C(11)), 30.42 (C(8)), 32.28 (C(16)), 33.00 (C(12)), 39.99 (C(6)), 44.47 (C(13)), 46.11 (C(9)), 48.23 (C(14)), 55.03 (OCH₃), 79.70 (C(17)), 111.97 (C(2)), 114.17 (C(4)), 126.77 (C(1)), 133.30 (C(10)), 138.29 (C(5)), 158.27 (C(3)).

Epimerisation of β -estradiol methyl ether (β -2)

Zeolite NaA (10 mg) was added to a solution of neodymium(III) isopropoxide (8.4 mg, 0.064 mmol per 0.77) in toluene (2.2 mL). Acetone (2.6 μ L, 0.04 mmol) was added and the temperature was raised to 50 °C. Subsequently, β -2 (100 mg, 0.35 mmol) was added and after 30 min the temperature was increased to 90 °C. After 24 h, the mixture was cooled to room temperature and washed with aqueous 1 M HCl (5 mL), dried and concentrated. The product was purified by column chromatography (MTBE : PE = 1 : 1) yielding 69.3 mg of the epimeric mixture of alcohols **2** (0.24 mmol, 69%) and 13.4 mg of ketone **8** (0.046 mmol, 13%). With ¹H-NMR the ratio β -2 : α -2 was determined to be 58 : 42.

General procedure for the synthesis of isopropenylesters (3)²⁰

A 30 wt% potassium hydride dispersion in mineral oil was washed with pentane. The pure KH was suspended in DME. The mixture was cooled down to 0 °C, after which acetone was added carefully. After 30 minutes the mixture was added to an ice cooled solution of the acid chloride in DME. The mixture was allowed to warm up to room temperature and was stirred overnight. Then, diethyl ether and water were added and the layers were separated. The organic fraction was dried over magnesium sulfate and concentrated. After distillation the desired compound was obtained.

Isopropenyl isobutyrate (3b)

Compound **3b** was synthesised according to the general procedure using KH (8.43 g, 0.21 mol) in DME (160 mL), acetone (11.6 g, 0.19 mol) and freshly distilled isobutyryl chloride (20.2 g, 0.19 mol) in DME (180 mL). After distillation (115–124 °C, 1.2 mbar) 7.4 g (55 mmol, 29%) of the product was obtained.²⁸ δ_{H} (300 MHz, CDCl₃, Me₄Si) 1.21 (d, *J* = 6.96 Hz, 6H, C(CH₃)₂), 1.92 (dd, *J* = 1.19, 0.58 Hz, 3H, =CCH₃), 2.62 (sept, *J* = 6.96 Hz, 1H, CH), 4.66 (dq, *J* = 1.21, 0.58 Hz, 1H, =C(H)H), 4.70 (dq, *J* = 1.21, 1.19 Hz, 1H, =C(H)H); δ_{C} (75 MHz, CDCl₃, Me₄Si) 18.86 (2 $\times$ CH₃), 19.46 (CH), 34.08 (=C-CH₃), 101.76 (CH₂=), 153.13 (C=), 175.26 (C=O).

Isopropenyl phenylacetate (3c)

Compound **3c** was synthesised according to the general procedure using KH (4.82 g, 0.12 mol) in DME (145 mL), acetone

(7.3 g, 0.12 mol) and freshly distilled phenylacetyl chloride (17.0 g, 0.11 mol) in DME (165 mL). After distillation (85 °C, 1.1 mbar) 10.3 g (57 mmol, 52%) of the product was obtained as an oil that solidified upon standing at 4 °C. δ_{H} (300 MHz, CDCl_3 , Me_4Si) 1.89 (dd, $J = 1.10$, 0.54 Hz, 3H, CH_3), 3.68 (s, 2H, CH_2), 4.69 (dq, $J = 1.27$, 0.54 Hz, 1H, $=\text{C}(\text{H})\text{H}$), 4.68 (dq, $J = 1.27$, 1.10 Hz, 1H, $=\text{C}(\text{H})\text{H}$), 7.20–7.33 (m, 5H, arH); δ_{C} (75 MHz, CDCl_3 , Me_4Si) 19.41 (CH_3), 40.94 (CH_2), 102.08 ($\text{H}_2\text{C}=\text{C}$), 127.22 (arC-4), 128.65 (arC-3,5), 129.22 (arC-2,6), 133.61 (arC-1), 153.04 ($\text{C}=\text{C}$), 176.80 ($\text{C}=\text{O}$).

Isopropenyl octanoate (3d)

Compound **3d** was synthesised according to the general procedure using KH (2.4 g, 61 mmol) in DME (52 mL), acetone (3.5 g, 61 mmol) and octanoyl chloride (9.3 g, 57 mmol) in DME (55 mL). After distillation (85 °C, 1.4 mbar) 3.1 g (17 mmol, 29%) of the product was obtained as an oil.²⁹ δ_{H} (300 MHz, CDCl_3 , Me_4Si) 0.89 (t, $J = 6.82$ Hz, 3H, CH_3), 1.20–1.40 (m, 8H, CH_2), 1.58–1.72 (m, 2H, CH_2), 1.92 (dd, $J = 0.60$, 1.22 Hz, 3H, $=\text{C}-\text{CH}_3$), 2.38 (t, $J = 7.50$ Hz, 2H, $\text{CH}_2\text{C}=\text{O}$), 4.67 (dq, $J = 1.21$, 0.59 Hz, 1H, $=\text{C}(\text{H})\text{H}$), 4.69 (dq, $J = 1.22$, 1.21 Hz, 1H, $=\text{C}(\text{H})\text{H}$); δ_{C} (75 MHz, CDCl_3 , Me_4Si) 14.06 (CH_3), 19.58 (CH_2), 22.60 (CH_2), 24.93 (CH_2), 28.91 (CH_2), 29.04 ($=\text{C}-\text{CH}_3$), 31.67 (CH_2), 34.39 (CH_2), 101.91 ($\text{CH}_2=\text{C}$), 153.06 ($\text{C}=\text{C}$), 171.97 ($\text{C}=\text{O}$).

Ethoxy acetylene³⁰

At -70 °C $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (0.5 g, 2.1 mmol) was dissolved in liquid ammonia (500 mL). Freshly cut sodium (38 g, 1.7 mol) was added and allowed to react completely. Within 20 min, chloroacetaldehyde diethyl acetal (76.5 g, 0.5 mol) was added to the reaction mixture. After the addition was complete, the flask was allowed to warm up to room temperature to evaporate the ammonia. The flask and its solid contents were cooled again to -70 °C and brine (325 mL) at -20 °C was added rapidly. The set-up was then equipped with a distillation bridge and the flask was carefully heated to distil off the product. The organic fraction was neutralised with a saturated aqueous solution of NaH_2PO_4 . After freezing the water layer the organic fraction was decanted, dried over CaCl_2 (4 g) and distilled (48–50 °C). The product was obtained as a colourless oil in a yield of 26.4 g (0.38 mol, 75%). δ_{H} (300 MHz, CDCl_3 , Me_4Si) 1.39 (t, $J = 7.20$ Hz, 3H, CH_3), 1.54 (s, 1H, $\equiv\text{CH}$), 4.13 (q, $J = 7.20$ Hz, 2H, CH_2); δ_{C} (75 MHz, CDCl_3 , Me_4Si) 14.22 (CH_3), 26.44 ($\text{O}-\text{C}=\text{C}$), 74.61 (CH_2), 90.85 ($\equiv\text{CH}$).

General procedure for the synthesis of 1-ethoxyvinylesters (4)^{21,22}

Ethoxy acetylene (3.43 g, 49 mmol) and Bennet's ruthenium complex ($[\text{RuCl}_2(p\text{-cymene})]_2$) (0.16 mmol, 100 mg) were dissolved in diisopropyl ether (200 mL). The mixture was cooled to 0 °C and a solution of freshly distilled acid in diisopropyl ether (150 mL) was added dropwise. The reaction was allowed to warm up to room temperature and was stirred overnight. After concentration the product was distilled from the residue.

1-Ethoxyvinyl acetate (4a)

Compound **4a** was synthesised following the general procedure using acetic acid (1.80 g, 30 mmol). After distillation (80 °C, 0.4 mbar) the desired product was obtained as a colourless oil in a yield of 2.67 g (20 mmol, 67%).²¹ δ_{H} (300 MHz, CDCl_3 , Me_4Si) 1.33 (t, $J = 7.02$ Hz, 3H, CH_3-CH_2), 2.16 (s, 3H CH_3-CO_2), 3.76 (d, $J = 3.7$ Hz, 1H, $\text{HCH}=\text{CO}_2$), 3.82 (d, $J = 3.7$ Hz, 1H, $\text{HCH}=\text{CO}_2$), 3.86 (q, $J = 7.02$ Hz, 2H, CH_2); δ_{C} (75 MHz, CDCl_3 , Me_4Si) 14.12 (CH_3-CH_2), 20.64 ($\text{CH}_3\text{C}=\text{O}$), 64.85 (CH_2), 71.75 ($\text{CH}_2=\text{C}$), 157.22 ($\text{C}=\text{C}$), 168.13 ($\text{C}=\text{O}$).

1-Ethoxyvinyl isobutyrate (4b)

Compound **4b** was synthesised following the general procedure using isobutyric acid (2.64 g, 30 mmol). After distillation (70–

72 °C, 0.4 mbar) the desired product was obtained as a colourless oil in a yield of 3.06 g (20 mmol, 67%).³¹ δ_{H} (300 MHz, CDCl_3 , Me_4Si) 1.23 (d, $J = 6.90$ Hz, 6H, CH_3), 1.33 (t, $J = 6.78$ Hz, 3H, CH_3-CH_2), 2.65 (sept, $J = 6.90$ Hz, 1H, CH), 3.75 (d, $J = 3.58$ Hz, 1H, $=\text{CHH}$), 3.80 (d, $J = 3.58$ Hz, 1H, $=\text{CHH}$), 3.87 (q, $J = 6.78$ Hz, 2H, CH_2); δ_{C} (75 MHz, CDCl_3 , Me_4Si) 14.12 (CH_2CH_3), 18.69 ($2 \times \text{CH}_3$), 33.83 (CH), 64.81 (CH_2), 71.53 ($\text{C}=\text{C}$), 157.46 ($\text{CH}_2=\text{C}$), 174.34 ($\text{C}=\text{O}$).

1-Ethoxyvinyl phenylacetate (4c)

Compound **4c** was synthesised following the general procedure using phenylacetic acid (4.08 g, 30 mmol). After distillation (210 °C, 0.4 mbar) the desired product was obtained as a colourless oil in a yield of 2.67 g (15 mmol, 50%).³² δ_{H} (300 MHz, CDCl_3 , Me_4Si) 1.25 (t, $J = 7.12$ Hz, 3H, CH_3CH_2), 2.03 (s, 2H, $\text{C}_6\text{H}_5\text{CH}_2$), 3.75 (d, $J = 3.60$ Hz, 1H, $\text{HCH}=\text{C}$), 3.80 (d, $J = 3.60$ Hz, 1H, $\text{HCH}=\text{C}$), 3.84 (q, $J = 7.12$ Hz, 2H, CH_2), 7.12–7.38 (m, 5H, arH); δ_{C} (75 MHz, CDCl_3 , Me_4Si) 14.20 (CH_3), 42.06 (PhCH_2), 64.90 (CH_2CH_3), 71.86 ($\text{C}=\text{C}$), 157.00 ($\text{CH}_2=\text{C}$), 128.56 (arC), 128.65 (arC), 129.40 ($2 \times \text{arC}$), 129.55 ($2 \times \text{arC}$), 171.15 ($\text{C}=\text{O}$).

1-Ethoxyvinyl octanoate (4d)

Compound **4d** was synthesised following the general procedure using octanoic acid (4.33 g, 30 mmol). After distillation (190 °C, 0.4 mbar) the desired product was obtained as a colourless oil in a yield of 5.43 g (27 mmol, 89%).¹⁸ δ_{H} (300 MHz, CDCl_3 , Me_4Si) 0.88 (t, $J = 6.78$ Hz, 3H, CH_3CH_2), 1.20–1.40 (m, 11H, $4 \times \text{CH}_2 + \text{CH}_3$), 1.55–1.75 (m, 2H, CH_2), 2.41 (t, $J = 7.51$ Hz, 2H, $\text{CH}_2\text{C}=\text{O}$), 3.75 (d, $J = 3.57$ Hz, 1H, $\text{HCH}=\text{C}$), 3.80 (d, $J = 3.57$ Hz, 1H, $\text{HCH}=\text{C}$), 3.86 (q, $J = 7.08$ Hz, 2H, CH_2); δ_{C} (75 MHz, CDCl_3 , Me_4Si) 14.06 (CH_3), 14.12 (OCH_2CH_3), 22.59 (CH_2), 24.63 (CH_2), 28.88 (CH_2), 28.94 (CH_2), 31.63 (CH_2), 33.93 (CH_2), 64.79 (OCH_2), 71.65 ($\text{CH}_2=\text{C}$), 157.28 ($\text{C}=\text{C}$), 171.07 ($\text{C}=\text{O}$).

Procedure for the acylation of rac-1

Neodymium(III) isopropoxide (120 mg, 0.37 mmol) and zeolite NaA (30 mg, dried at 400 °C) were dissolved and suspended in heptane (12 mL). 1,3,5-Triisopropylbenzene (0.2 mL) and **1** (0.24 mL, 2.0 mmol) were added and the temperature was raised to 50 °C. Subsequently, an acyl donor (**3** or **4**) (2.2 mmol) was added. After 15 min, 1 M aqueous HCl (6 mL) was added and the two layers were separated. The aqueous layer was washed with heptane (10 mL) and the combined organic layers were dried over MgSO_4 and concentrated under vacuum. After column filtration with PE : Et_2O 4 : 1 mixture over silica gel, the acylated product could be recovered in almost quantitative yield.

Acetic acid 1-phenyl-ethyl ester (9a)

This compound was prepared as described above with **3a** (0.24 mL, 2.2 mmol) as acyl donor yielding 317 mg (1.76 mmol, 88%) or **4a** (286 mg, 2.2 mmol) yielding 257 mg (1.42 mmol, 71%) of the product as a colourless oil. δ_{H} (300 MHz, CDCl_3 , Me_4Si) 1.53 (d, $J = 6.61$ Hz, 3H, CHCH_3), 2.06 (s, 3H, $\text{C}(\text{O})\text{CH}_3$), 5.88 (q, $J = 6.61$ Hz, 1H, CH), 7.22–7.38 (m, 5H, arH).

Isobutyric acid 1-phenyl-ethyl ester (9b)

This compound was prepared as described above with **3b** (282 mg, 2.2 mmol) as acyl donor yielding 363 mg (1.78 mmol, 89%) of the product as a colourless oil. δ_{H} (300 MHz, CDCl_3 , Me_4Si) 1.16 (dd, $J = 7.80$, 6.90 Hz, 6H, $2 \times \text{CH}_3$), 1.52 (d, $J = 6.60$, 3H, CH_3-CH), 2.56 (sept, $J = 6.90$ Hz, 1H, $\text{CH}-\text{C}=\text{O}$), 5.87 (q, $J = 6.60$, 1H, $\text{CH}-\text{O}$), 7.22–7.36 (m, 5H, arH).

Octanoic acid 1-phenyl-ethyl ester (9c)

This compound was prepared as described above with **3c** (405 mg, 2.2 mmol) as acyl donor yielding 398 mg (1.50 mmol,

75%) or **4c** (471 mg, 2.2 mmol) yielding 439 mg (1.66 mmol, 83%) of the product as a colourless oil. δ_{H} (300 MHz, CDCl_3 , Me_4Si) 0.88 (t, $J = 3.60$ Hz, 3H, CH_3), 1.20–1.40 (m, 8H, $4 \times \text{CH}_2$), 1.53 (d, $J = 6.45$, 3H, $\text{CH}_3\text{-CH}$), 2.32 (dt, $J = 7.50$, 0.90 Hz, 2H, C(O)CH_2), 5.89 (q, $J = 6.45$, 1H, CH-O), 7.23–7.38 (m, 5H, ArH).

Phenyl-acetic acid 1-phenyl-ethyl ester (**9d**)

This compound was prepared as described above with **3d** (388 mg, 2.2 mmol) as acyl donor yielding 489 mg (1.60 mmol, 80%) of the product as a colourless oil. δ_{H} (300 MHz, CDCl_3 , Me_4Si) 1.50 (d, $J = 6.61$, 3H, $\text{CH}_3\text{-CH}$), 3.62 (s, 2H, CH_2), 5.89 (q, $J = 6.61$, 1H, CH), 7.19–7.35 (m, 10H, ArH).

Procedure for the one-pot racemisation and acylation of (*S*)-**1** or (*S*)-**6**

Neodymium(III), samarium(III) or gadolinium(III) isopropoxide (0.37 mmol) and zeolite NaA (30 mg, dried at 400 °C) were dissolved and suspended in heptane (12 mL). 1,3,5-Triisopropylbenzene (0.2 mL) and acetone (15 μL , 0.20 mmol) were added and the temperature was raised to 50 °C. (*S*)-**1** or (*S*)-**6** (0.24 mL, 2.0 mmol) was added. The reaction was followed by GC. After complete racemisation (less than 18 h) isopropenyl acetate (**3a**) (0.24 mL, 2.2 mmol) was added. Alcohol **1** was converted into the racemic acetate *rac*-**9a** in 15 minutes. Alcohol **6** was converted into its racemic acetate in 20 minutes. The reaction mixture was concentrated *in vacuo* and the product was purified by column chromatography (PE : Et_2O 4 : 1).

Nd^{III} + (*S*)-**1** yielded 288 mg (1.76 mmol, 88%) of the racemic acetate, Sm^{III} + (*S*)-**1** yielded 284 mg (1.74 mmol, 87%), Gd^{III} + (*S*)-**1** yielded 295 mg (1.80 mmol, 90%), Nd^{III} + (*S*)-**6** yielded 296 mg (1.74 mmol, 87%), Sm^{III} + (*S*)-**6** yielded 289 mg (1.70 mmol, 85%), Gd^{III} + (*S*)-**6** yielded 306 mg (1.80 mmol, 90%).

Procedure for one-pot epimerisation and acylation of β -**2**

Neodymium(III) isopropoxide (8.4 mg, 0.064 mmol) and zeolite NaA (10 mg, dried at 400 °C) were added to toluene (2.2 mL). Acetone (2.6 μL , 0.04 mmol) was added and the temperature was raised to 50 °C. β -**2** (90 mg, 0.32 mmol) was dissolved in the reaction mixture. After 1 h the temperature was raised to 90 °C and after 24 h isopropenyl acetate (**3a**) (38 μL , 0.35 mmol) was added. The reaction was monitored by TLC. Complete acylation was achieved after 1 h. The mixture was cooled, washed with an aqueous 1 M HCl solution (5 mL), dried over MgSO_4 and concentrated. Column chromatography (PE : MTBE 3 : 1) yielded 41 mg of β -**10** (0.12 mmol, 40%) and 34 mg of α -**10** (0.10, 33%), both as white solids.³³ β -**10**: δ_{H} (300 MHz, CDCl_3 , Me_4Si) 0.81 (s, 3H, C-CH_3), 1.10–1.60 (m, 7H, C(14)H, C(6)H₂, C(12)HH, C(7)HH, C(11)HH, C(15)HH), 1.60–1.80 (m, 1H, C(12)HH), 1.80–2.00 (m, 2H, C(15)HH, C(7)HH), 1.93 (s, 3H, $\text{CH}_3\text{-CO}$), 2.05–2.22 (m, 2H, C(16)HH, C(9)H), 2.22–2.40 (m, 1H, C(11)HH), 2.70–2.90 (m, 2H, C(16)HH, C(8)H), 3.68 (s, 3H, O-CH_3), 4.66 (dd, $J = 7.61$, 8.91 Hz, 1H, C(17)H), 6.56 (d, $J = 2.70$ Hz, 1H, C(4)H), 6.64 (dd, 1H, $J = 2.70$, 8.40 Hz C(2)H), 7.14 (d, $J = 8.40$ Hz, 1H, C(1)H); δ_{C} (75 MHz, dioxane-*d*₈, Me_4Si) 12.36 (C(13)CH₃), 20.65 ($\text{CH}_3\text{-CO}$), 23.61 (C(15)), 26.96 (C(7)), 27.97 (C(11)), 30.27 (C(8)), 30.93 (C(16)), 37.57 (C(12)), 39.68 (C(6)), 43.83 (C(13)), 44.76 (C(9)), 50.23 (C(14)), 55.01 (OCH_3), 81.64 (C(17)), 111.96 (C(2)), 114.20 (C(4)), 126.69 (C(1)), 133.12 (C(10)), 138.20 (C(5)), 158.27 (C(3)), 170.76 (C=O); α -**10**: δ_{H} (300 MHz, CDCl_3 , Me_4Si) 0.67 (s, 3H, C-CH_3), 1.10–1.70 (m, 7H, C(14)H, C(6)H₂, C(12)HH, C(7)HH, C(11)HH, C(15)HH), 1.70–1.95 (m, 3H, C(12)HH, C(15)HH, C(7)HH), 1.99 (s, 3H, $\text{CH}_3\text{-CO}$), 2.00–2.40 (m, 3H,

C(16)HH, C(9)H, C(11)HH), 2.75–2.85 (m, 2H, C(16)HH, C(8)H), 4.10–4.20 (m, 1H, C(17)H), 6.56 (d, $J = 2.75$ Hz, 1H, C(4)H), 6.63 (dd, $J = 2.75$, 8.42 Hz, 1H, C(2)H), 7.16 (d, $J = 8.42$ Hz, 1H, C(1)H); δ_{C} (75 MHz, dioxane-*d*₈, Me_4Si) 17.38 (C(13)CH₃), 20.44 ($\text{CH}_3\text{-CO}$), 24.80 (C(15)), 26.95 (C(7)), 28.86 (C(11)), 30.45 (C(8)), 32.31 (C(16)), 33.08 (C(12)), 40.01 (C(6)), 44.49 (C(13)), 46.13 (C(9)), 48.24 (C(14)), 55.02 (OCH_3), 79.67 (C(17)), 111.98 (C(2)), 114.18 (C(4)), 126.77 (C(1)), 133.31 (C(10)), 138.29 (C(5)), 158.30 (C(3)), 170.79 (C=O).

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