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New class of β-aminoalcohol ligands derived from isosorbide and isomannide: application in hydrogen transfer reduction of prochiral ketones

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ABSTRACT

Starting from isosorbide and isomannide, two by-products from the starch industry, a family of chiral functionalized β-aminoalcohols presenting a THF ring has been synthesized as potential ligands for hydrogen transfer reduction of prochiral ketones. Under optimal conditions, more than 70% ee with an excellent conversion were obtained for the HTR of the acetophenone.

1. Introduction

Chiral secondary alcohols are one of the most valuable intermediates in organic synthesis. For their formation, one of the most attractive route, which has recently emerged consists in catalytic asymmetric transfer hydrogenation reduction (HTR) of ketones using mainly isopropanol as the hydrogen donor. This reduction, occurring under very mild conditions, is a very useful alternative to the classical catalytic reduction of ketones using molecular hydrogen and is able to give very high enantioselectivities in some examples.[1–4]

Close to the use of chiral monotosylated diamine/Ru(II)-complexes leading to enantioelectivities higher than 90%,[2,5–12] Noyori showed that the use of β-aminoalcohols as ligand could accelerate the reaction rate.[13–15] Thus, numerous β-aminoalcohols/Ru(II) systems have been performed because these ligands are ready available and easy to functionalize. In general, they have shown height enantioselectivities and activities.[16] Moreover, some of them have been heterogeneized in order to isolate the catalytic system from the reaction mixture and to reuse it.[17]

To the best of our knowledge, no carbohydrate-derived β-aminoalcohols have been used as ligands in the asymmetric transfer hydrogenation reaction.

Our goal in this work was to promote biomass products for catalysis, particularly isosorbide and isomannide, two by-products from the starch industry. The dinitro derivative of isosorbide has been extensively used in medicine as vasodilator[18–20] and some aminoalcohol derivatives have shown glycosidase inhibitory activity.[21] Otherwise, isosorbide and isomannide derivatives were considered as factor Xa inhibitors[22,23] and isommanide pseudopeptides derivatives as serine protease inhibitors.[24] Isosorbide and isomannide were also used in the synthesis of biodegradable polymers,[25–28] amphiphiles,[29] chiral auxiliaries[30–34] or as starting material for catalyst used for enantioselective alkylation[35,36] or in chiral phase transfer catalysis.[37,38] Isomannide has found application as precursor of chiral ionic liquids for chiral discrimination and optical resolution of racemates.[39,40]

We present here their rapid and easy transformation into a large series of modular unsymmetrical chiral β-aminoalcohols ligands and their applications in hydrogen transfer reduction of various prochiral ketones.

2. Results and discussion

In 2001, we developed an efficient method to prepare chiral epoxides **3** and **4**, respectively, from isosorbide and isomannide.[29,41,42] Reacting these readily available epoxides with various primary amines at 40 °C in methanol led to a series of β-aminoalcohols **5**–**11** with moderate to good reaction yields (Scheme 1, Table 1). We have only observed the product resulting from the ring opening reaction at the less hindered carbon. It is

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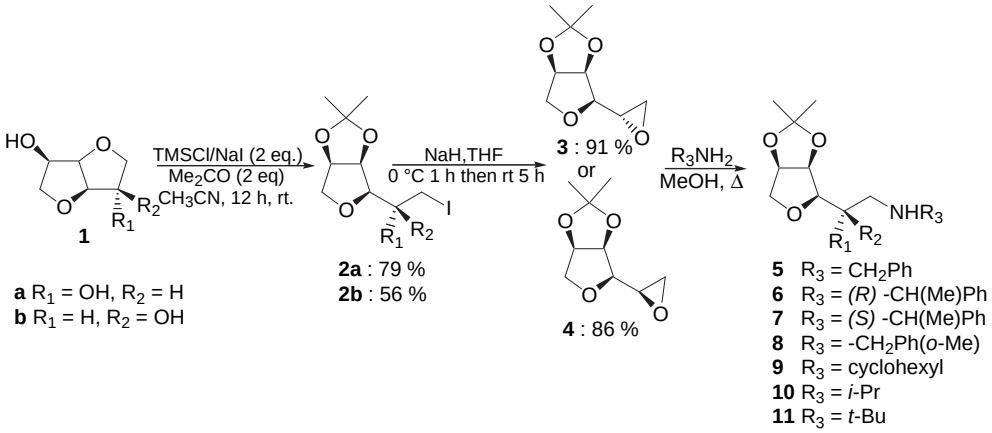


Scheme 1. β-Aminoalcohol syntheses.

Table 1
Formation of β-aminoalcohols by epoxide ring opening with various amines (2 equiv)

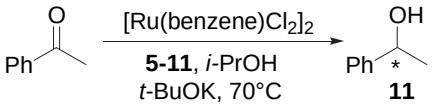
Entry	Substrate	Amine	Ligand	Time (h)	Yield (%)
1	**3**	$PhCH_2NH_2$	**5a**	16	66
2	**4**	$PhCH_2NH_2$	**5b**	16	56
3	**3**	$PhCH(Me)NH_2$ (*R*)	**6a**	21	80
4	**4**	$PhCH(Me)NH_2$ (*R*)	**6b**	21	87
5	**3**	$PhCH(Me)NH_2$ (*S*)	**7a**	21	95
6	**4**	$PhCH(Me)NH_2$ (*S*)	**7b**	16	85
7	**3**	(*o*-Me)$PhCH_2NH_2$	**8a**	21	64
8	**4**	(*o*-Me)$PhCH_2NH_2$	**8b**	21	65
9	**3**	Cyclohexylamine	**9a**	16	85
10	**4**	Cyclohexylamine	**9b**	16	88
11	**3**	*i*-$PrNH_2$	**10a**	21	77
12	**4**	*i*-$PrNH_2$	**10b**	21	65[a]
13	**3**	*t*-$BuNH_2$	**11a**	21.5	69
14	**4**	*t*-$BuNH_2$	**11b**	21.5	67

[a] 86% yield is obtained with 5 equiv of amine.

noteworthy that the moderate yields observed with the benzylamine derivatives **5** and **8** are due to the difficulties encountered during the chromatography purifications (entries 1, 2, 7, and 8). For isopropylamine and *tert*-butylamine derivatives **10** and **11**, the yields have not been optimized (entries 11–14). The volatility of the amine reagent is responsible of the moderate yields observed: if the ring opening reaction is performed with 5 equiv of isopropylamine the resulting product was formed in 86% yield (Table 1, entry 12 note a).

The pure β-aminoalcohols from the **a**[43] and **b** series were isolated and fully characterized via ^1H and ^{13}C NMR spectroscopic methods, high resolution mass spectrometry, and microanalysis. These compounds from the **a** and **b** series differ only in the configuration of the hydroxyl group on the side chain of the THF ring, the three stereocenters of the ring presenting the same absolute configuration.

The ruthenium complexes of these aminoalcohols were prepared in situ, under argon, by reacting $[Ru(benzene)Cl_2]_2$ with 2 equiv of these corresponding ligands in anhydrous isopropanol at 70 °C for 1 h. Color changes were observed from yellow to deep orange or deep red, showing the formation of the complex. The so-formed complexes with $[Ru(benzene)Cl_2]_2$ were then studied for the asymmetric HTR reaction of acetophenone (Scheme 2, Table 2). The catalysis was carried out under argon at 70 °C for 21 h, under free water conditions, in isopropanol in the presence of *t*-BuOK with a ratio of acetophenone/Ru/ligand/*t*-BuOK of 100:1:2:2. For ligand **5a**, this ratio gave the best results in terms of catalytic activity and enantioselectivity.[43]



Scheme 2. Hydrogen transfer reduction of acetophenone.

Table 2
Ruthenium assisted asymmetric HTR of acetophenone catalyzed by $[Ru(benzene)Cl_2]_2$ associated with ligands **5**–**11**

Entry	Ligand	Conv.[a] (%)	ee[a] (%) (config.)
1	**5a**	97	66 (*R*)
2	**5b**	94	70 (*S*)
3	**6a**	83	21 (*R*)
4	**6b**	79	34 (*S*)
5	**7a**	90	18 (*R*)
6	**7b**	89	54 (*S*)
7	**8a**	93	57 (*R*)
8	**8b**	57	5 (*S*)
9	**9a**	67	24 (*R*)
10	**9b**	48	51 (*S*)
11	**10a**	83	30 (*R*)
12	**10b**	75	29 (*S*)
13	**11a**	67	<5 (*R*)
14	**11b**	71	<5 (*S*)

[a] Determined by GC analyses on Rt-βDEX sm™ column.

All ligands (**5**–**11**, Table 2) were shown to be rather efficient in the asymmetric HTR reaction under the reaction conditions used. Conversion of 1-phenylethanol ranged from 48 to 97%.

The stereogenic center bearing the hydroxyl group, located in the side chain part of the THF ring, is responsible of the absolute configuration of the 1-phenylethanol, ligands **5a**–**11a** leading mainly to the *R* isomer, whereas ligands **5b**–**11b** gave the *S* one (Table 2 entries 1, 3, 5, 7, 9, 11, 13 and 2, 4, 6, 8, 10, 12, 14, respectively). The same phenomenon was already observed with chiral 2-methylamino-1,2-phenylethanol[44] or with β-aminoalcohols ligands derived from tartaric acid[45] in the case of HTR of prochiral ketones.

Moreover, it is noteworthy that in our case, the stereochemistry of the chiral center located on the position 2 of the THF ring of **a** and **b** series seemed to have no influence on the enantioselectivity of the HTR of ketones, as it has been observed by Paolucci and Rosini for the asymmetric addition of diethylzinc to benzaldehyde[36] with THF ring substituted in position 2 with β-aminoalcohol functionality.

Except for ligands **8** and **9**, a similar catalytic activity is observed for ligands **a** and **b** bearing the same amino group (Table 2 entries 1 and 2, 3 and 4, 5 and 6, 11 and 12, 13 and 14).

For ligands **5**–**7**, the enantioselectivity depends not only on the absolute configuration on the hydroxyl group but also on the presence or the absence of a methyl group in the benzylic position of the amino group. It is noteworthy that isomannide ligands (series **b**) gave higher enantioselectivities than isosorbide ones (series **a**) (entries 1–6).

Moreover, the presence of the methyl group resulted in a detrimental effect on the enantioselectivity of the ligand but this effect is less important with ligand **7b**.

Contrary to ligands **6a** and **7a** (entries 3 and 5), presenting, respectively, 21% and 18% ee, a match/mismatch effect was noticed with ligands **6b** and **7b** (entries 4 and 6), which gave, respectively, 34% and 54% ee.[46]

For ligands **8a** and **8b**, which contain a methyl group located on the *ortho* position of the phenyl group of the benzyl moiety, an important difference in the catalytic activities and in the enantioselectivities have been observed: 93% and 57% conversions and 57% and 5% ee, respectively (entries 7 and 8). This is probably the result of a steric hindrance due to the methyl group.

It is also noteworthy that the influence of the alkylamine moiety on the catalytic activity and enantioselectivity depends on whether the ligands belong to the isosorbide or the isomannide series.

For ligands **10** and **11**, containing a linear alkylamine moiety, conversions and enantioselectivities are similar: around 80% of conversion and 30% ee for **10a** and **10b**, and around 70% of conversion and quite no stereoselection for **11a** and **11b** (entries 11, 12 and 13, 14 respectively). If ligands present a cyclic amine moiety such as ligands **9**, a drastic decrease in conversion from 67% to 48% is observed along an important rise in enantioselection from 24% to 51% ee for **9a** and **9b**, respectively (entries 9 and 10). To summarize, these observed activity differences are probably due to steric factors.

We then studied the influence of the nature of the catalytic precursor. We observed that [Ru(*p*-cymene)Cl_2]$_2$ or [Ru(benzene)Cl_2]$_2$ associated with ligands **5a** or **5b** do not have the same influence on the catalytic activity and selectivity (Table 3). [Ru(*p*-cymene)Cl_2]$_2$ is less efficient in terms of enantioselectivity and conversion than [Ru(benzene)Cl_2]$_2$ in combination with ligand **5a** (entries 1 and 2) contrary to what was observed with ligand **5b**, which gave similar efficiency but with a better selectivity (entries 3 and 4). Previous results have reported this phenomenon with 2-methylamino-1,2-diphenylethanol as ligands.[44]

Table 3
Influence of the nature of the catalyst precursor associated with ligands **5** on the reaction rate and selectivity of the HTR of acetophenone. Reaction conditions: Ru/**5**/*t*-BuOK/ketone=1/2/2/100 at 70 °C for 21 h

Entry	Ligand	Precursor	Conv.[a] (%)	ee[a] (%) (config.)
1	**5a**	[Ru(benzene)Cl_2]$_2$	97	66 (*R*)
2		[Ru(*p*-cymene)Cl_2]$_2$	84	53 (*R*)
3	**5b**	[Ru(benzene)Cl_2]$_2$	94	70 (*S*)
4		[Ru(*p*-cymene)Cl_2]$_2$	96	75 (*S*)

[a] Determined by GC analyses on Rt-βDEX sm™ column.

The influence of the temperature and the reaction time have also been examined with ligand **7b** associated with [Ru(benzene)Cl_2]$_2$ (Table 4) with a ratio of acetophenone/Ru/ligand/*t*-BuOK of 100:1:2:2. After 21 h at 25 °C, conversion did not exceed 57% for 71% ee contrary to the experiment performed at 70 °C where 89% of conversion was observed with only 54% ee (entries 1 and 2). At 25 °C, a change of the reaction time has no effect on the enantioselectivity and no significative increase of the conversion is found (entries 2–4).

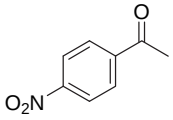
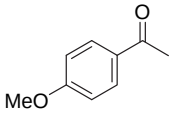
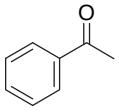
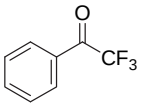
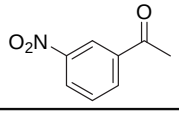
Table 4
Influence of the temperature and the reaction time on the enantioselective HTR of acetophenone

Entry	Ligand	Time (h)	*T* (°C)	Conv.[a](%)	ee[a] (%)
1	**7b**	21	70	89	54 (*S*)
2		21	25	57	71 (*S*)
3		63	25	59	71 (*S*)
4		116	25	60	71 (*S*)

[a] determined by chiral GC column: Rt-βDEX sm™.

We finally study the efficiency of the best ligand **5** of isomannide series using [Ru(benzene)Cl_2]$_2$ as the catalytic precursor on the asymmetric HTR of various prochiral ketones: acetophenone, *p*-methoxy, *p*- and *m*-nitro and trifluoromethylacetophenone (Table 5).

Table 5
Asymmetric HTR of various prochiral ketones catalyzed by [Ru(benzene)Cl_2]$_2$, associated with ligand **5b**. Reaction conditions: Ru/**5b**/*t*-BuOK/ketone=1/2/2/100 at 70 °C for 21 h

Entry	Substrate	Conv. (%)	ee (%)
1		100[a]	37[a]
2		29[a]	<5[a]
3		94[a]	70[a]
4		100[b]	41[b]
5		63[c]	<5[c]

[a] determined by chiral GC column: Rt-βDEX sm™.
[b] determined by chiral GC column: Rt-γDEX.
[c] determined by chiral HPLC chiracel-OD column (isooctane/*i*-PrOH 99:1).

Compared to the HTR of acetophenone, a drastic decrease in the stereoselection was observed if an electrodonating group or an electrowithdrawing group is present at the *para* position of the phenyl group (entries 1–3). Compared to the acetophenone HTR, an electrowithdrawing group such as a nitro gave similar conversion with moderate enantioselectivity (100% conv., 37% ee), and an electrodonating group, such as methoxy, led to a drastic decrease in conversion and also in enantioselection (29% conv., <5% ee). Introduction of a trifluoromethyl group instead of the methyl group of the acetophenone gave almost the same result as the one obtained with the *para* nitro group: total conversion with moderate enantioselectivities (respectively 37% ee and 41% ee, entries 1 and 4). In the case of a nitro group at the *meta* position the conversion is moderate with very low enantioselectivity (entry 5).

3. Conclusion

In conclusion, we have developed two series of epimeric β-aminoalcohols easily prepared from isosorbide and isomannide. Their Ru(II) complexes have been synthesized and evaluated for the reduction of acetophenone and other prochiral ketones. The complexes have shown modest to interesting enantioselectivity.

Ligands **5a** and **5b** with *N*-benzyl amino group gave rise to catalysts that induced the best enantioselectivities. 75% ee has been reached when ligand **5b** associated with Ru[(*p*-cymene)Cl_2]$_2$ was used for the reduction of acetophenone. The search for more active and selective ligands derived from these dianhydrohexitols for asymmetric catalysis is ongoing in our laboratory.

4. Experimental

4.1. General

Unless otherwise stated, commercial reagents were used without purification. Acetonitrile, isopropanol, methanol were distilled over calcium hydride and acetone over calcium sulfate. Dry THF was obtained by filtration through an activated alumina gel of a Glass Technology GTS100All apparatus. *t*-BuOK was sublimated.

Analytical thin-layer chromatography (TLC) was carried out on Macherey–Nagel Polygram®sil G/UV_{254}. Column chromatography was performed on silica gel 60 (40–63 μm, Merck). Air- and moisture-sensitive reactions were performed under inert atmosphere techniques. Melting points were determined on a Reichert Thermoval apparatus and are uncorrected. FT-IR spectra were performed on a Nicolet AVATAR 370 DTGS Thermo Electron Corporation apparatus and band positions are given in cm^{-1}. NMR spectra were recorded with a Bruker Avance 400 spectrometer, in $CDCl_3$ and referenced as following: ^1H (400 MHz) ^{13}C (100.6 MHz), internal $SiMe_4$ at δ=0.00 ppm. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br s (broadened singlet). High resolution mass spectra were recorded on a Waters Micromass® GCT Premier™. Optical rotations values were recorded using a Perkin–Elmer 343 polarimeter. Conversion and enantiomeric excesses were determined by GC using a capillary Rt-βDEX sm™ column (30 m×0.5 mm×0.25 μm) or a capillary Rt-γdex (30 m×0.25 mm×0.25 μm) column or by HPLC using a chiracel-OD (25 cm×0.46 cm) column.

Epoxides **3** and **4** were prepared, respectively, from isosorbide and isomannide according to the literature procedure.[29,41,42]

4.2. General procedure for the synthesis of chiral β-aminoalcohols 5–10

A solution of epoxide **3** or **4** (1 equiv) and amine (2–5 equiv) were heated at 40 °C in methanol (3 mL/mmol of epoxide) for 16–21 h. Solvent was then removed and the crude product was purified by column chromatography.

3,6-Anhydro-(1-benzylamino)-1-deoxy-4,5-*O*-isopropylidene D-sorbitol **5a**, 3,6-anhydro-(1(*R*)-phenyl ethylamino)-1-deoxy-4,5-*O*-isopropylidene D-sorbitol **6a**, 3,6-anhydro-(1(*S*)-phenyl ethylamino)-1-deoxy-4,5-*O*-isopropylidene D-sorbitol **7a**, 3,6-anhydro-(1-cyclohexylamino)-1-deoxy-4,5-*O*-isopropylidene D-sorbitol **9a**, 3,6-anhydro-(1-isopropylamino)-1-deoxy-4,5-*O*-isopropylidene D-sorbitol **10a**, 3,6-anhydro-(1-terbutylamino)-1-deoxy-4,5-*O*-isopropylidene D-sorbitol **11a**, already been described, were prepared according to the literature procedure using epoxide **3**.[43]

*4.2.1. 3,6-Anhydro-1-(benzylamino)-1-deoxy-4,5-O-isopropylidene D-mannitol **5b**.* Reagent amounts: epoxide **4** (297.6 mg, 1.60 mmol), benzylamine (384 μL, 3.50 mmol); time 16 h. Column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 56%; orange solid, mp=52.5–55.3 °C; R_f=0.26 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$ −28.2 (*c* 1.085, $CHCl_3$).

^1H NMR: δ 1.34 (s, 3H), 1.48 (s, 3H), 2.5–2.6 (br s, 2H), 2.78 (dd, 1H, *J*=12.2, 8.1), 2.99 (dd, 1H, *J*=12.2, 3.4), 3.34 (dd, 1H, *J*=7.9, 3.5), 3.47 (dd, 1H, *J*=10.7, 3.4), 3.83 (d, 1H, *J*=13.3), 3.85 (d, 1H, *J*=13.3), 4.02 (d, 1H, *J*=10.7), 4.04 (ddd, 1H, *J*=8.1, 7.9, 3.4), 4.76 (dd, 1H, *J*=6.3, 3.4), 4.79 (dd, 1H, *J*=6.3, 3.5), 7.2–7.4 (m, 5H); ^{13}C NMR: δ 24.7, 26.0, 52.3, 53.8, 67.6, 72.9, 80.6, 80.7, 83.8, 112.1, 127.1, 128.2, 128.4, 139.7; IR (cm^{-1}) (ATR): 3000–3300, 2916, 2841, 1495, 1455, 1380, 1271, 1204, 1168, 1095, 1065, 1052, 1029, 987, 909, 891, 861, 810; HRMS: (CI^+ NH_3) *m*/*z* found: 294.1688, $C_{16}H_{24}NO_4$ $[M+H]^+$ requires: 294.1705.

*4.2.2. 3,6-Anhydro-1-((1R)-phenylethylamino)-1-deoxy-4,5-O-isopropylidene D-mannitol **6b**.* Reagent amounts: epoxide **4** (300 mg, 1.61 mmol), (+)-(*R*)-(α)-méthylbenzylamine (413 μL, 3.22 mmol), time 21 h. Column chromatography (CH_2Cl_2/MeOH 98:2). Yield: 87%; viscous colorless oil; R_f=0.30 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$ +3.6 (*c* 0.495, $CHCl_3$).

^1H NMR: δ 1.32 (s, 3H), 1.37 (d, 3H, *J*=6.6), 1.46 (s, 3H), 2.55 (dd, 1H, *J*=12.1, 8.3), 2.6–2.8 (br s, 2H), 2.84 (dd, 1H, *J*=12.1, 3.4), 3.25 (dd, 1H, *J*=8.1, 3.5), 3.40 (dd, 1H, *J*=10.8, 3.5), 3.79 (q, 1H, *J*=6.6), 3.97 (d, 1H, *J*=10.8), 4.01 (ddd, 1H, *J*=8.3, 8.1, 3.4), 4.72 (dd, 1H, *J*=6.2, 3.5), 4.75 (dd, 1H, *J*=6.2, 3.5), 7.1–7.4 (m, 5H); ^{13}C NMR: δ 24.3, 24.7, 26.0, 50.6, 58.1, 68.0, 72.9, 80.7, 80.8, 83.8, 112.2, 126.5, 126.9, 128.5, 145.3; IR (cm^{-1}) (film): 3200–3600, 2977, 2934, 2849, 1493, 1452, 1371, 1270, 1206, 1165, 1098, 1077, 1059, 988, 964, 910, 884, 860, 815; HRMS: (CI^+ NH_3) *m*/*z* found: 308.1859, $C_{17}H_{26}NO_4$ $[M+H]^+$ requires: 308.1862.

*4.2.3. 3,6-Anhydro-1-((1S)-phenylethylamino)-1-deoxy-4,5-O-isopropylidene D-mannitol **7b**.* Reagent amounts: epoxide **4** (205 mg, 1.10 mmol), (−)-(*S*)-(α)-methylbenzylamine (284 μL, 2.20 mmol), time 16 h. Column chromatography (CH_2Cl_2/MeOH 98:2). Yield: 85%. White solid, mp 87.9–89.8 °C; R_f=0.30 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$ −67.2 (*c* 0.555, $CHCl_3$).

^1H NMR: δ 1.32 (s, 3H), 1.39 (d, 3H, *J*=6.6), 1.45 (s, 3H), 2.3–2.5 (br s, 2H), 2.64 (dd, 1H, *J*=11.9, 8.1), 2.80 (dd, 1H, *J*=11.9, 3.5), 3.31 (dd, 1H, *J*=8.0, 2.8), 3.44 (dd, 1H, *J*=10.7, 3.1), 3.78 (q, 1H, *J*=6.6), 3.92 (ddd, 1H, *J*=8.1, 8.0, 3.5), 3.99 (d, 1H, *J*=10.7), 4.7–4.8 (m, 2H), 7.2–7.3 (m, 1H), 7.3–7.4 (m, 4H); ^{13}C NMR: δ 24.3, 24.6, 26.0, 51.0, 58.6, 68.3, 72.8, 80.7–80.8, 83.7, 112.2, 126.6, 126.9, 128.5, 145.4; IR (cm^{-1}) (ATR): 3306, 2980, 2968, 2932, 2843, 1456, 1368, 1253,1212, 1161, 1111, 1100, 1086, 1057, 1027, 1005, 981, 964, 914, 872, 852, 832; HRMS: (CI^+ NH_3) *m*/*z* found 308.1857, $C_{17}H_{26}NO_4$ $[M+H^+]$ requires: 308.1862.

*4.2.4. 3,6-Anhydro-1-(2-methyl-benzylamino)-1-deoxy-4,5-O-isopropylidene D-sorbitol **8a**.* Reagent amounts: epoxide **3** (207 mg, 1.11 mmol), 2-methyl benzylamine (280 μL, 2.25 mmol), time 21 h. Column chromatography (CH_2Cl_2/MeOH 97:3 then 95:5). Yield: 64%, visquous yellowish oil; R_f=0.33 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{20}$ −42.5 (*c* 1.0, $CHCl_3$).

^1H NMR: δ 1.29 (s, 3H), 1.47 (s, 3H), 2.32 (s, 3H), 2.5–2.6 (br s, 2H), 2.82 (dd, 1H, *J*=12.1, 7.6), 2.98 (dd, 1H, *J*=12.1, 3.7), 3.42 (dd, 1H, *J*=6.2, 3.6), 3.48 (dd, 1H, *J*=10.7, 3.8), 3.78 (d, 1H, *J*=13.3), 3.86 (d, 1H, *J*=13.3), 4.05 (d, 1H, *J*=10.7), 4.14 (ddd, 1H, *J*=7.5, 6.3, 3.8), 4.66 (dd, 1H, *J*=6.2, 3.6), 4.78 (dd, 1H, *J*=6.2, 3.7), 7.14–7.20 (m, 3H), 7.29–7.34 (m, 1H); ^{13}C NMR: δ 19.0, 24.6, 26.0, 51.2, 51.4, 69.1, 72.7, 80.8, 81.3, 83.5, 112.3, 126.0, 127.2, 128.6, 130.3, 136.4, 137.7; IR (cm^{-1}) (ATR): 3200–3500, 2984, 2935, 2854, 1605, 1456, 1372, 1272, 1206, 1165, 1098, 1059, 987, 911, 857, 815, 740; HRMS: (FD^+) *m*/*z* found 307.1797$C_{17}H_{25}NO_4$ requires: 307.1784.

*4.2.5. 3,6-Anhydro-1-(2-methyl-benzylamino)-1-deoxy-4,5-O-isopropylidene D-mannitol **8b**.* Reagent amounts: epoxide **4** (201 mg, 1.07 mmol), 2-methyl benzylamine (268 μL, 2.16 mmol), time 21 h. Column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 65%, visquous yellowish oil; R_f 0.25 (CH_2Cl_2/MeOH 90:10); $[\alpha]_D^{20}$ −14.5 (*c* 1.07, $CHCl_3$).

^1H NMR: δ 1.34 (s, 3H), 1.49 (s, 3H), 2.2–2.4 (br s, 2H), 2.35 (s, 3H), 2.81 (dd, 1H, *J*=12.2, 8.1), 3.02 (dd, 1H, *J*=12.2, 3.4), 3.35 (dd, 1H, *J*=8.0, 3.4), 3.48 (dd, 1H, *J*=10.8, 3.4), 3.79 (d, 1H, *J*=13.2), 3.84

(d, 1H, *J*=13.2), 4.04 (ddd, 1H, *J*=7.8, 7.8.3.4), 4.76 (dd, 1H, *J*=6.1, 3.4), 4.79 (dd, 1H, *J*=6.1, 3.4), 7.1–7.2 (m, 3H), 7.2–7.3 (m, 2H); ^{13}C NMR: *δ* 19.3, 24.7, 26.0, 58.4, 58.7, 66.8, 73.0, 80.7, 80.8, 83.8, 112.2, 125.8, 127.4, 130.2, 130.5, 136.4, 137.2; IR (cm^{-1}) (ATR): 3200–3500, 2934, 2854, 1605, 1456, 1372, 1270, 1207, 1165, 1095, 987, 963, 909, 859, 815, 742; HRMS: (FD^+) *m*/*z* found 307.1791 $C_{17}H_{25}NO_4$ requires: 307.1784.

4.2.6. 3,6-Anhydro-1-(cyclohexylamino)-1-deoxy-4,5-O-isopropylidene D*-mannitol* ***9b***. Reagent amounts: epoxide **4** (305 mg 1.64 mmol), cyclohexylamine (400 μL, 3.48 mmol), time 16 h. Column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 88%. White solid, mp 83.7–86.9 °C; R_f 0.34 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$ −30.9 (*c* 0.97, $CHCl_3$).

^{1}H NMR: *δ* 1.0–1.4 (m, 5H), 1.34 (s, 3H), 1.49 (s, 3H), 1.5–1.9 (m, 5H), 2.42 (tt, 1H, *J*=10.4, 3.8), 2.4–2.6 (br s, 2H), 2.69 (dd, 1H, *J*=12.1, 8.4), 2.99 (dd, 1H, *J*=12.1, 3.5), 3.31 (dd, 1H, *J*=8.4, 3.5), 3.48 (dd, 1H, *J*=10.8, 3.5), 3.95 (ddd, 1H, *J*=8.4, 8.4, 3.5), 4.02 (d, 1H, *J*=10.4), 4.76 (dd, 1H, *J*=6.3, 3.5), 4.80 (dd, 1H, *J*=6.3, 3.5); ^{13}C NMR: *δ* 24.6, 25.0, 26.0, 26.1, 33.6, 49.7, 56.7, 67.6, 73.0, 80.7, 80.8, 84.0, 112.1; IR (cm^{-1}) (ATR): 3050–3200, 2975, 2924, 2848, 1450, 1384, 1370, 1325, 1301, 1272, 1250, 1210, 1168, 1100, 1078, 1057, 1030, 988, 902, 853, 842, 812; HRMS: (FI) *m*/*z* found 285.1961, $C_{15}H_{27}NO_4$ $[M]^+$ requires: 285.1940.

4.2.7. 3,6-Anhydro-1-(isopropylamino)-1-deoxy-4,5-O-isopropylidene D*-mannitol* ***10b***. Reagent amounts: epoxide **4** (347 mg, 1.86 mmol), *iso*propylamine (800 μL, 9.30 mmol), time 21 h. Column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 86%, visquous yellow oil; R_f 0.26 (CH_2Cl_2/MeOH 85:15); $[\alpha]_D^{20}$ −36.1 (*c* 0.985, $CHCl_3$).

^{1}H NMR: *δ* 1.10 (d, 6H, *J*=6.3), 1.34 (s, 3H), 1.49 (s, 3H), 2.71 (dd, 1H, *J*=12.1, 8.4), 2.8–2.9 (br s, 2H), 2.85 (sept, 1H, *J*=6.3), 2.98 (dd, 1H, *J*=12.1, 3.4), 3.34 (dd, 1H, *J*=8.1, 3.5), 3.49 (dd, 1H, *J*=10.5, 3.5), 4.00 (ddd, 1H, *J*=8.4, 8.1, 3.4), 4.03 (d, 1H, *J*=10.5), 4.77 (dd, 1H, *J*=6.3, 3.5), 4.81 (dd, 1H, *J*=6.3, 3.5); ^{13}C NMR: *δ* 22.8, 22.9, 24.6, 26.0, 48.9, 50.1, 67.7, 73.0, 80.7, 80.8, 83.9, 112.2; IR (cm^{-1}) (ATR): 3200–3600, 2964, 2933, 2849, 1456, 1371, 1338, 1270, 1208, 1166, 1098, 1073, 989, 964, 909, 855, 815; HRMS: (CI^+ NH_3) *m*/*z* found 246.1701, $C_{12}H_{24}NO_4$ $[M+H]^+$ requires: 246.1705.

4.2.8. 3,6-Anhydro-1-(tert-butylamino)-1-deoxy-4,5-O-isopropylidene D*-mannitol* ***11b***. Reagent amounts: epoxide **4** (55 mg, 0.3 mmol), *tert*-butylamine (63 μL, 0.60 mmol), time 21 h. Column chromatography (CH_2Cl_2/MeOH 95:5). Yield: 67%, visquous colorless oil; R_f 0.30 (CH_2Cl_2/MeOH 95:5); $[\alpha]_D^{20}$ −26.9 (*c* 0.405, $CHCl_3$).

^{1}H NMR: *δ* 1.18 (s, 9H), 1.34 (s, 3H), 1.48 (s, 3H), 2.73 (dd, 1H, *J*=11.9, 8.4), 3.01 (dd, 1H, *J*=11.9, 3.4), 3.36 (dd, 1H, *J*=8.0, 3.4), 3.49 (dd, 1H, *J*=10.6, 3.5), 3.5–3.7 (br s, 2H), 4.0–4.1 (m, 1H), 4.02 (d, 1H, *J*=10.6), 4.76 (dd, 1H, *J*=6.1, 3.5), 4.80 (dd, 1H, *J*=6.1, 3.4); ^{13}C NMR: *δ* 24.6, 26.0, 28.5, 45.5, 51.7, 67.3, 73.0, 80.6 (2C), 84.0, 112.2; IR (cm^{-1}) (ATR): 3200–3500, 2965, 2850, 1728, 1574, 1456, 1371, 1270, 1207, 1165, 1096, 1050, 1027, 988, 964, 911, 860, 816; HRMS: (CI^+ NH_3) *m*/*z* found calcd 260.1851, $C_{13}H_{26}NO_4$ $[M+H]^+$ requires: 260.1862.

4.3. Typical asymmetric HTR of ketones

In a Schlenk tube, under Ar $[Ru(benzene)Cl_2]_2$ (8.5 μmol (4.3 mg)) or $[Ru(p\text{-cymene})Cl_2]_2$ (8.5 μmol (5.2 mg)) and β-aminoalcohol (**5**–**11**, 34 μmol) are dissolved in 8.5 mL of anhydrous and degassed isopropanol. This reaction mixture is stirred and heated at 70 °C for 1 h. After cooling to room temperature, a solution of *t*-BuOK 0.1 M in isopropanol (34 μmol, 340 μL) is added. Then, after 10 more minutes, the prochiral ketone (1.7 mmol) is added. The mixture is allowed to stir for a few hours at 70 °C or 25 °C. A 0.5 mL aliquot was taken off and filtered through a pad of silica gel in order to follow the advancement of the reaction. After dilution in acetone (1 mL), GC or HPLC analysis of the sample is carried on in order to determine the conversion and the enantiomeric excess.

For the reduction of the acetophenone chiral GC conditions are: Rt-βDEX sm™ column, oven: 120 °C for 0.5 min then 0.6 °C/min to 125 °C, 1 min at that temperature: t_R=5.9 min, t_S=6.1 min.

For the reduction of the *p*-nitroacetophenone chiral GC conditions are: Rt-βDEX sm™ column, oven: 100 °C for 2 min then 1 °C/min to 180 °C, 2 min at that temperature: t_R=58.7 min, t_S=59.3 min.

For the reduction of the *p*-methoxyacetophenone chiral GC conditions are: Rt-βDEX sm™ column, oven: 80 °C for 5 min then 1 °C/min to 140 °C, 1 min at that temperature: t_R=43.5 min, t_S=44.0 min.

For the reduction of the *p*-trifluoromethylacetophenone chiral GC conditions are: column Rt-γDEX, oven: 100 °C for 5 min then 1 °C/min to 140 °C, 1 min at that temperature: t_R=31.4 min, t_S=33.7 min.

For the reduction of the *m*-nitroacetophenone chiral HPLC conditions are: HPLC chiracel-OD column; isooctane/*i*-PrOH 99:1, 1 mL/min, 254 nm, t_r are 102.8 min and 111.0 min.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.060. These data include MOL files and InChiKeys of the most important compounds described in this article.

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