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A novel case of 1,3-asymmetric induction in rhodium-catalyzed hydroformylation of an allylic double bond using perbenzylated C-glucosides as chiral directors

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Abstract—1-(2′,3′,4′,6′-Tetra-*O*-benzyl-α-D-glucopyranosyl)-2-propene **1a** and 1-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)-2-propene **1b** were hydroformylated at different temperatures affording linear and branched aldehydes in either a 1:1 or 2:1 regioisomeric ratio, depending on the stereochemistry of the starting substrate. The diastereoisomeric ratio of the branched isomer depended on the reaction temperature as well as the alkene structure, the highest value (85:15) being obtained in the case of hydroformylation of the α-isomer at 0 °C.

1. Introduction

The hydroformylation of olefins is an attractive synthetic transformation that introduces an aldehyde function by means of atom economic formation of a C–C bond, which represents a starting point for additional carbon skeleton expanding operations.[1] Furthermore, addition of CO and H_2 can lead to the formation of one or even two new stereocenters, depending on the stereochemical features of the olefin substrate. Stereoselectivity can be induced using chiral diphosphines[2] as ligands of rhodium (I), as well as via substrate control by a chiral starting alkene.[3] Substrate control has been realized using chiral conformationally defined bicyclic structures, for example, in the diastereoselective hydroformylation of α-pinene,[4] or by introducing catalyst directing groups on the alkene skeleton. This is a group that is able to precoordinate the catalytically active species, giving rise to the selective positioning of the catalyst at one of the two diastereotopic faces of the olefin, such as in the case of methallylic alcohols.[5] Sugar derivatives have also been used as chiral architectures for substrate controlled stereoselective hydroformylation.[6] The good stereoselectivity obtained in the hydroformylation of glucals[6a] and *C*-vinyl glucosides[6b] also suggests that sugar derivatives containing a different kind of double bond could be stereoselectively hydroformylated.

Prompted by these considerations, we became interested in investigating the hydroformylation of 1-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-glucopyranosyl)-2-propene and 1-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)-2-propene **1a** and **1b** (Fig. 1),[7] where a methylene group separates the alkene function from the C-glucoside. Much effort has been devoted to the functionalization of the allylic appendage of C-glycosides, such as oxidative degradation,[8] palladium-mediated oxidation,[9] or hydroxyiodination.[10] In this context, the possibility offered by the hydroformylation reaction to perform a one-pot

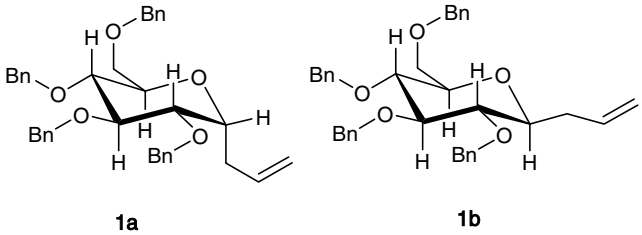

Figure 1.

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reaction able to elongate or branch the allylic residue is very attractive.

Our experience in the field of stereoselective hydroformylation indicates that a good level of asymmetric induction can be achieved with open chain olefin substrates possessing a stereogenic center in β to the double bond, provided additional electronic factors are present, such as in the case of vinyl ethers.[11] In this regard, the use of chiral substrates **1a** and **1b** is also of interest in order to check the possibility of obtaining good levels of 1,3-asymmetric induction in the hydroformylation of an isolated terminal double bond.

2. Results and discussion

2.1. Hydroformylation

Taking into account the well-known high reactivity of allyl-substrates against unmodified rhodium catalysts,[12] hydroformylation of **1a** and **1b** was carried out with $Rh_4(CO)_{12}$ at 80 atm of CO and H_2 (1:1) and low temperatures (0–40 °C). These mild reaction conditions can be adapted to investigate the influence of substrate structure on both regioselectivity and diastereoselectivity of the reaction. Since the rate determining step of the hydroformylation reaction is the formation of the catalytically active Rh–H species,[13] to perform the runs at 0 °C, this species was generated by reacting $Rh_4(CO)_{12}$ with CO (40 atm) and H_2 (40 atm) at 40 °C for 30 min, then freezing the reaction mixture at 0 °C and introducing the substrate at that temperature.

As expected, the hydroformylation of the two substrates gives the linear **3** and branched **2** regioisomers, the last one being formed as a mixture of diastereoisomers. The results obtained are reported in Table 1.

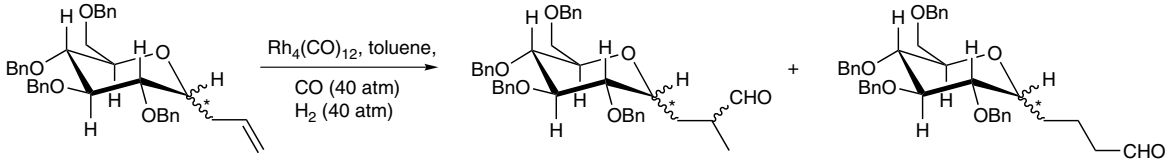
Complete substrate conversion was obtained after 7 h at 40 °C, while at 0 °C much more time was necessary (24 h). Both regioisomeric and diastereoisomeric ratios were determined by ^{1}H NMR spectra at 600 MHz in $CDCl_3$, carried out directly on the crude reaction mixture after removing the reaction solvent and catalyst. This determination is straightforward because the proton resonances of the formyl group of linear and branched aldehydes are well separated as well as those of the two diastereoisomeric products. The reaction is regioselective in the case of **1b**, affording a prevalence of the branched isomer (regioisomeric ratio **2b/3b** ≅ 2), while a similar amount of the two isomers is obtained starting from **1a**. Reaction temperature does not affect the regioisomeric ratio to a significant extent with either substrate, at least within the examined range (0–40 °C). In both cases, the linear aldehyde can be easily separated from the branched one, by flash chromatography, also allowing a complete characterization of both regioisomers. As far as the diastereoselectivity is concerned, a significant prevalence of one diastereomer is observed in both cases. C-Glucoside **1a** afforded a prevalence of the diastereomer whose CH=O proton resonates at lower NMR frequencies. In contrast, starting from **1b** a prevalence of the diastereomer whose CH=O proton resonates at higher NMR frequencies is achieved.

Reaction temperature significantly influenced the diastereoisomeric ratio in the case of **1a**: by lowering the temperature from 40 to 0 °C the diastereomeric ratio increased from 70:30 (entry 1) to 85:15 (entry 3). Conversely, the temperature did not affect the diastereoselectivity of **1b** hydroformylation, which afforded the same diastereoisomeric ratio in passing from 40 to 0 °C (entries 4–6).

2.2. Configuration assignment

The assignment of the absolute configuration of the new stereocenter was determined by NMR after oxidation of aldehydes **2a** and **2b** with $NaClO_2/NaH_2PO_4$[14] to the corresponding carboxylic acids **4a** and **4b**, respectively, and subsequent double derivatization with phenylglycine methyl esters (PGME) in both the enantiomeric forms [(*R*)-PGME and (*S*)-PGME] to derivatives **5** and **6**, respectively (Scheme 1).

Table 1. Hydroformylation of **1a** and **1b**



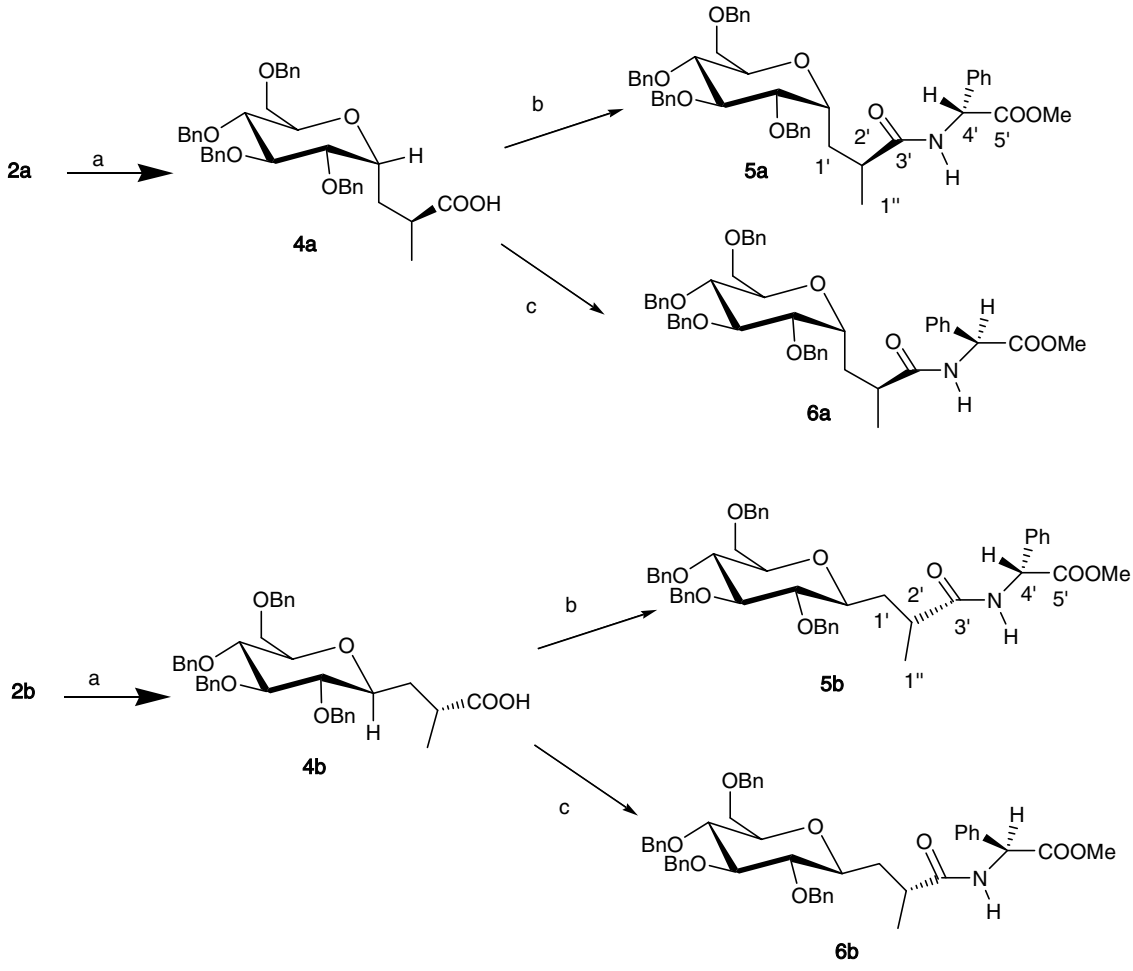
1a: * = α
1b: * = β

2a: * = α
2b: * = β

3a: * = α
3b: * = β

Entry	Alkene	Temp (°C)	Time (h)[a]	**2/3** ratio[b]	Diastereomeric ratio of **2**[b] (*S*/*R*)
1	**1a**	40	7	47/52	70:30
2	**1a**	25	7	50/50	80:20
3	**1a**	0	24	50/50	85:15
4	**1b**	40	7	64/36	30:70
5	**1b**	25	7	66/34	30:70
6	**1b**	0	24	66/34	30:70

[a] All the reactions were carried out to complete substrate conversion.
[b] Determined by ^{1}H NMR analysis.



Only the absolute configuration of the prevailing stereoisomer is indicated

Scheme 1. Reagents and conditions: (a) $NaClO_2$, 1.25 M aq NaH_2PO_4, CH_3CN; (b) (*R*)-PGME·HCl, PyBroP, DIPEA, DMF; (c) (*S*)-PGME·HCl, PyBroP, DIPEA, DMF.

NOEs experiments on compounds **5** and **6** are in agreement with a planar arrangement of the C-2′-C-5′ chain, as depicted in Figure 2 for the (*R*)-PGME derivatives, as already reported with different PGME derivatives.[15] Given this conformation, R_1 protons will be more shielded by the phenyl group in the (*R*)-PGME derivatives then those of the (*S*)-PGME, hence the absolute configuration of the stereocenter can be determined. Chemical shifts of the relevant protons and $\Delta\delta(\delta_{(S)} - \delta_{(R)})$ values for derivatives **5** and **6** are reported in Table 2; an (*S*)-configuration was determined for the major isomer **4a**, hence aldehyde **2a**, and an (*R*)-configuration for derivative **4b**, and aldehyde **2b**.

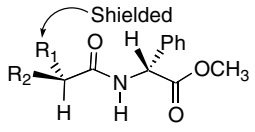


Figure 2.

Table 2. Chemical shifts (ppm) of the relevant protons of derivatives **5** and **6** for the configuration assignment

	H1″	H-1′a	H-1′b
5a	1.21	1.81	1.93
6a	1.15	1.89	1.97
$\Delta\delta(\delta_{(S)} - \delta_{(R)})$	−0.06	+0.08	+0.04
5b	1.03	1.34	2.02
6b	1.07	1.27	1.96
$\Delta\delta(\delta_{(S)} - \delta_{(R)})$	+0.04	−0.07	−0.08

3. Conclusion

1-(2′,3′,4′,6′-Tetra-*O*-benzyl-α-D-glucopyranosyl)-2-propene **1a** and 1-(2′,3′,4′,6′-tetra-*O*-benzyl-β-D-glucopyranosyl)-2-propene **1b** have proven to be suitable chiral synthons for the 1,3-asymmetric induction in the stereoselective hydroformylation, providing diastereoisomeric excesses up to 70%. The extent of diastereoselectivity as well as the sense of asymmetric induction depends on the absolute configuration of the C-anomeric center. Starting from the α-anomer, a higher diastereoisomeric

ratio (85:15) was achieved with the newly formed stereogenic center of the prevalent diastereomer having an (*S*)-absolute configuration. The β-isomer affords lower prevalence (70:30) of the diastereomer having an (*R*)-configuration at the new stereogenic center. Conversely little or no regioselectivity was observed; although the separation by flash chromatography of the regioisomers allowed us to obtain isomerically pure products. These results open new perspectives concerning the use of different glycosides as chiral synthons for the 1,3-asymmetric induction in the stereoselective hydroformylation of their *C*-allyl derivatives. Studies are currently in progress on this topic aimed at using the hydroformylation of the *C*-allyl glycosides not only to study the stereoselectivity of the reaction but also to obtain sugar derivatives, which can be further functionalized as well as linked to solid matrixes.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on either a Varian Gemini-200 MHz, a Varian Mercury-400 MHz or a Varian Inova-600 MHz NMR spectrometers, using TMS as an internal standard. The following abbreviations are used: s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet, br = broad. TLC analyses were performed on silica gel 60 Macherey-Nagel sheets; flash chromatography separations were carried out on adequate dimension columns using silica gel 60 (230–400 mesh). Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Toluene was dried over molecular sieves and distilled under nitrogen. $Rh_4(CO)_{12}$ was prepared according to a known procedure.[16] *C*-Allyl glucosides were prepared as described elsewhere and matched the reported characteristics.[7] Unless otherwise stated, the reagents were used without any further purification.

4.2. Hydroformylation of *C*-allyl glucosides 1a and 1b: general procedure

A solution of *C*-allyl glucoside **1a** or **1b** and $Rh_4(CO)_{12}$ (ratio substrate/Rh = 100/1) in toluene was introduced by suction into an evacuated 25 mL stainless steel reaction vessel. Carbon monoxide was introduced and the autoclave then rocked, while being kept at the desired temperature with hydrogen introduced rapidly to 100 atm ($CO/H_2 = 1:1$) total pressure. The reaction was monitored by TLC (SiO_2, CH_2Cl_2/acetone = 98:2). After removing the solvent at reduced pressure the crude products were purified by flash chromatography (SiO_2, CH_2Cl_2/acetone = 98/2) affording the pure aldehydes as brown solids (80% yield).

4.2.1. Characterization of 2a. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.09 (d, $J = 7.2$ Hz, 3H, $CH_{3\text{-minor diastereomer}}$), 1.15 (d, $J = 7.2$ Hz, 3H, $CH_{3\text{-major diastereomer}}$), 1.76–1.82 (m, 4H, $-CH_2$), 2.12 (m, 2H, C*H*–CH_3), 3.55–3.78 (m, 8H, CH_{ring}), 4.06 (m, 1H, anomericH$_{major\ diastereomer}$), 4.16 (m, 1H, anomericH$_{minor\ diastereomer}$), 4.45–4.94 (m, 20H, CH_2–Ph, CH_2–O), 7.32 (m, 40H, Ar), 9.64 (d, $J = 0.8$ Hz, 1H, $CHO_{major\ diastereomer}$), 9.66 (d, $J = 0.8$ Hz, 1H, $CHO_{minor\ diastereomer}$).

^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 30.0, 42.6, 69.2, 71.7, 72.1, 73.3, 73.8, 75.3, 75.7, 80.0, 82.3, 97.3, 127.9–128.7, 138.3–138.9, 204.5.

4.2.2. Characterization of 3a. $[\alpha]_D^{22} = +36.8$ (*c* 1.1, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.61–1.75 (m, 4H, CH_2), 2.47–2.40 (m, 2H, CH_2), 3.78–3.55 (m, 4H, CH_{gluc}), 4.00 (m, 1H, anomericH), 4.94–4.45 (m, 10H, CH_2–Ph, CH_2–O), 7.32 (m, 20H, Ar.), 9.74 (t, $J = 1.4$ Hz, 1H, CHO) ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.1, 24.0, 43.3, 69.1, 71.1, 73.2, 73.4, 73.8, 75.0, 75.4, 78.1, 80.1, 82.4, 127.5–128.4, 138–138.7, 202.2.

4.2.3. Characterization of 2b and 3b. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.07 (d, $J = 6.6$ Hz, 3H, $CH_{3\text{-minor diastereomer}}$), 1.10 (d, $J = 6.6$ Hz, 3H, $CH_{3\text{-major diastereomer}}$), 1.65–1.86 (m, 4H), 2.19–2.15 (m, 2H), 2.57–2.42 (m, 6H), 3.72–3.23 (m, 15H, CH_{ring}), 4.93–4.49 (m, 30H, CH_2–Ph, CH_2–O), 7.3 (m, 60H, Ar), 9.59–9.58 (d, $J = 2$ Hz, 1H, $CHO_{minor\ diastereomer}$), 9.62–9.61 (d, $J = 2$ Hz, 1H, $CHO_{major\ diastereomer}$), 9.72 (t, $J = 1.8$ Hz, 1H, CHO_{linear}). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 18.3, 30.9, 33.0, 42.9, 43.7, 68.9, 69.1, 73.5, 74.9, 75.1, 75.2, 75.5, 76.5, 78.4, 78.6, 78.9, 82.0, 87.2, 87.3, 127.6–128.4, 138.1–138.5, 202.5, 204.5.

4.3. Oxidation of aldehydes 2a and 2b: general procedure

Aldehyde **2a** or **2b** (0.151 mmol) was dissolved in CH_3CN (2 mL), then $NaClO_2$ (5 equiv) and a 1.25 M aqueous solution of $NaH_2PO_4{\cdot}2H_2O$ (5 equiv) were added. The solution was stirred for 1 h, the reaction quenched with sodium thiosulfate and the solvent reduced in vacuo. The residue was diluted with diethyl ether, filtered, and the solution evaporated to dryness affording **4a** or **4b** as a colorless oil (0.092 g, quantitative yield). The crude acids, as a mixture of diastereoisomers, were used for the subsequent derivatization without any further purification.

NMR data refers to the major isomer (aromatic signals are omitted).

4.3.1. Characterization of 4a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, 3H, $J = 6.9$ Hz, H-1″), 1.75 (ddd, 1H, $J = 13.5$, 12.0, 3.8 Hz, H-1′a), 2.03 (ddd, 1H, $J = 13.5$, 10.3, 3.0 Hz, H-1′b), 2.59–2.65 (m, 1H, H-2′), 3.46–3.70 (m, 6H, H-2, H-3, H-4, H-5, H-6), 4.13 (ddd, 1H, $J = 12.0$, 5.0, 3.0 Hz, H-1), 4.36–4.48 (m, 2H, PhC*H*$_2$O), 4.51–4.58 (m, 3H, PhC*H*$_2$O), 4.65–4.74 (m, 2H, PhC*H*$_2$O), 4.85 (d, 1H, $J = 10.8$ Hz, PhC*H*$_2$O). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 18.7 (q, C-1″), 28.6 (t, C-1′), 35.8 (d, C-2′), 69.3, 73.2, 73.9, 75.5, 75.9 (5t, 4PhCH_2O, C-6), 71.8, 72.3, 78.3, 80.0, 82.5 (5 d, C-1, C-2, C-3, C-4, C-5), 182.0 (s, C═O).

4.3.2. Characterization of 4b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, 3H, $J = 7.1$ Hz, H-1″), 1.42 (ddd, 1H, $J = 13.9$, 10.0, 4.0 Hz, H-1′a), 2.12 (ddd, 1H,

$J = 13.9$, 10.0, 2.5 Hz, H-1′b), 2.63–2.70 (m, 1H, H-2′), 3.14–3.29 and 3.52–3.68 (m, 7H, H-1, H-2, H-3, H-4, H-5, H-6), 4.35–4.90 (m, 8H, PhCH_2O). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 18.4 (q, C-1″), 36.0 (t, C-1′), 36.3 (d, C-2′), 69.3, 73.8, 75.2, 75.5, 75.9 (5t, 4PhCH_2O, C-6), 78.7, 79.1, 79.3, 82.6, 87.5 (5 d, C-1, C-2, C-3, C-4, C-5), 182.1 (s, C=O).

4.4. Preparation of PGME amides: general procedure

Acids **4a** and **4b** (1 equiv) and phenylglycine methyl esters (1.2 equiv) were dissolved in dry DMF (0.3 mL), after which PyBroP (1.5 equiv) and DIPEA (4.5 equiv) were added sequentially. After 1 h, the reaction mixture was concentrated to dryness. Purification by flash chromatography (SiO_2, light petroleum/EtOAc = 7/3) afforded amides **5** and **6**.

4.4.1. Characterization of 5a. Compound **4a** (0.052 mmol) was treated with (*R*)-PGME following the general procedure to afford **5a** as white solid (0.022 g, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, 3H, $J = 6.8$ Hz, H-1″), 1.81 (ddd, 1H, $J = 14.9$, 12.0, 3.8 Hz, H-1′a), 1.93 (ddd, 1H, $J = 14.9$, 11.5, 3.9 Hz, H-1′b), 2.54–2.59 (m, 1H, H-2′), 3.84 (t, 1H, $J = 9.5$ Hz, H-4), 3.50 (dd, 1H, $J = 9.9$, 6.0 Hz, H-6a), 3.57–3.78 (m, 7H, H-2, H-3, H-5, H-6b, $COOCH_3$), 3.87 (ddd, 1H, $J = 11.5$, 5.3, 3.9 Hz, H-1), 4.37 and 4.44 (ABq, 2H, $J = 11.4$ Hz, PhCH_2O), 4.49 and 4.55 (ABq, 2H, $J = 12.4$ Hz, PhCH_2O), 4.73 and 4.89 (ABq, 2H, $J = 11.0$ Hz, PhCH_2O), 4.77 and 4.80 (ABq, 2H, $J = 10.8$ Hz, PhCH_2O), 5.59 (d, 1H, $J = 7.2$ Hz, H-4′), 6.98 (d, 1H, $J = 7.2$ Hz, NH). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 18.7 (q, C-1″), 30.1 (t, C-1′), 36.4 (d, C-2′), 53.0 (d, C-4′), 56.8 (q, COOCH_3), 69.8, 72.6, 73.7, 75.4, 75.8 (5t, 4PhCH_2O, C-6), 71.0, 71.6, 78.6, 79.9, 82.5 (5 d, C-1, C-2, C-3, C-4, C-5), 171.3, 175.3 (2s, C=O).

4.4.2. Characterization of 5b. Compound **4b** (0.031 mmol) was treated with (*R*)-PGME following the general procedure, to afford **5b** as a white solid (0.024 g, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, 3H, $J = 6.8$ Hz, H-1″), 1.34 (ddd, 1H, $J = 14.7$, 12.0, 3.8 Hz, H-1′a), 2.02 (ddd, 1H, $J = 14.7$, 12.7, 3.0 Hz, H-1′b), 2.59–2.64 (m, 1H, H-2′), 3.15 (t, 1H, $J = 9.1$ Hz, H-2), 3.35 (t, 1H, $J = 9.1$ Hz, H-4), 3.40 (dd, 1H, $J = 10.0$, 4.3 Hz, H-6a), 3.47 (ddd, 1H, $J = 12.0$, 9.1, 3.0 Hz, H-1), 3.57 (dd, 1H, $J = 10.0$, 1.7 Hz, H-6b), 3.63 (s, 3H, COOCH_3), 3.67–3.73 (m, 2H, H-5, H-3), 4.21 (br s, 2H, PhCH_2O), 4.42 and 4.74 (ABq, 2H, $J = 10.8$ Hz, PhCH_2O), 4.58 and 4.75 (ABq, 2H, $J = 10.8$ Hz, PhCH_2O), 4.82 (br s, 2H, PhCH_2O), 5.51 (d, 1H, $J = 7.8$ Hz, H-4′), 6.77 (d, 1H, $J = 7.8$ Hz, NH). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 18.1 (q, C-1″), 30.1 (t, C-1′), 36.5 (d, C-2′), 52.9 (d, C-4′), 56.6 (q, COOCH_3), 69.8, 73.3, 75.3, 75.4, 75.9 (5t, 4PhCH_2O, C-6), 75.8, 77.9, 79.4, 83.6, 87.3 (5 d, C-1, C-2, C-3, C-4, C-5), 171.5, 175.5 (2s, C=O).

4.4.3. Characterization of 6a. Compound **4a** (0.044 mmol) was treated with (*S*)-PGME following the general procedure, affording **6a** as white solid (0.031 g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, 3H, $J = 6.8$ Hz, H-1″), 1.89 (ddd, 1H, $J = 15.0$, 12.3, 4.3 Hz, H-1′a), 1.97 (ddd, 1H, $J = 15.0$, 11.0, 4.5 Hz, H-1′b), 2.54–2.60 (m, 1H, H-2′), 3.47 (ddd, 1H, $J = 11.0$, 5.4, 4.3 Hz, H-1), 3.53 (dd, 1H, $J = 9.5$, 6.2 Hz, H-6a), 3.60–3.84 (m, 8H, H-2, H-3, H-4, H-5, H-6b, $COOCH_3$), 4.35 and 4.39 (ABq, 2H, $J = 12.0$ Hz, PhCH_2O), 4.47 and 4.83 (ABq, 2H, $J = 10.8$ Hz, PhCH_2O), 4.58 and 4.69 (ABq, 2H, $J = 11.5$ Hz, PhCH_2O), 4.78 and 4.96 (ABq, 2H, $J = 11.0$ Hz, PhCH_2O), 5.40 (d, 1H, $J = 6.5$ Hz, H-4′), 7.08 (d, 1H, $J = 6.5$ Hz, NH). ^{13}C NMR (100.57 MHz, $CDCl_3$) δ 18.3 (q, C-1″), 30.1 (t, C-1′), 35.8 (d, C-2′), 52.9 (d, C-4′), 57.3 (q, COOCH_3), 70.1, 72.7, 73.6, 75.4, 75.8 (5t, 4PhCH_2O, C-6), 70.8, 71.6, 78.7, 80.1, 82.6 (5 d, C-1, C-2, C-3, C-4, C-5), 171.4, 175.5 (2s, C=O).

4.4.4. Characterization of 6b. Compound **4b** (0.049 mmol) was treated with (*S*)-PGME following the general procedure, affording **6b** as white solid (0.037 g, quantitative yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, 3H, $J = 6.8$ Hz, H-1″), 1.27 (ddd, 1H, $J = 14.0$, 11.3, 4.2 Hz, H-1′a), 1.96 (ddd, 1H, $J = 14.0$, 10.1, 3.0 Hz, H-1′b), 2.56–2.62 (m, 1H, H-2′), 2.67–2.71 (m, 1H, H-5), 2.87 (ddd, 1H, $J = 11.3$, 9.0, 3.0 Hz, H-1), 3.05 (t, 1H, $J = 9.0$ Hz, H-2), 3.20–3.38 (m, 4H, H-3, H-4, H-6) 3.63 (s, 3H, COOCH_3), 4.34–4.82 (m, 8H, PhCH_2O), 5.59 (d, 1H, $J = 6.5$ Hz, H-4′), 6.71 (d, 1H, $J = 6.5$ Hz, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.3 (q, C-1″), 30.1 (t, C-1′), 36.9 (d, C-2′), 52.9 (d, C-4′), 56.4 (q, COOCH_3), 69.3, 73.6, 74.9, 75.3, 75.8 (5t, 4PhCH_2O, C-6), 76.5, 78.3, 78.9, 83.1, 87.1 (5 d, C-1, C-2, C-3, C-4, C-5), 171.5, 175.2 (2s, C=O).

References

1. Van Leeuwen, P. W. N. M.; Claver, C. *Rhodium Catalyzed Hydroformylation*; Kluwer Academic Publishers, 2000.
2. Agbossou, F.; Carpentier, J. F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485.
3. Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264.
4. Siegel, H.; Himmele, W. *Angew. Chem., Int. Ed.* **1980**, *19*, 178.
5. Breit, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2835.
6. (a) Fernandez, E.; Ruitz, A.; Claver, C.; Castillòn, S.; Polo, A.; Piniella, J. F.; Alvarez-Larena, A. *Organometallics* **1998**, *17*, 2857; (b) Takahashi, T.; Ebata, S.; Yamada, H. *Synlett* **1998**, 381.
7. Lewis, D. M.; Kun Cha, J.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
8. Cupp, T. L.; Wise, D. S.; Towsend, L. B. *J. Org. Chem.* **1982**, *47*, 5115.
9. Cipolla, L.; La Ferla, B.; Lay, L.; Peri, F.; Nicotra, F. *Tetrahedron: Asymmetry* **2000**, *11*, 295.
10. La Ferla, B.; Cipolla, L.; Peri, F.; Nicotra, F. *J. Carbohydr. Chem.* **2001**, *7&8*, 667.
11. Lazzaroni, R.; Pucci, S.; Bertozzi, S.; Pini, D. *J. Organomet. Chem.* **1983**, *C56*, 247.
12. Lazzaroni, R.; Pertici, P.; Bertozzi, S.; Fabrizi, G. *J. Mol. Catal.* **1990**, *58*, 75.
13. (a) Lazzaroni, R.; Uccello-Barretta, G.; Benetti, M. *Organometallics* **1989**, *8*, 2323; (b) Alagona, G.; Ghio, C.; Lazzaroni, R.; Settambolo, R. *Organomettalics* **2001**,

20, 5394; (c) Alagona, G.; Ghio, C.; Lazzaroni, R.; Settambolo, R. *Inorg. Chim. Acta* **2004**, *357*, 29.
14. Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637.
15. (a) Yabuuchi, T.; Kusumi, T. *J. Org. Chem.* **2000**, *65*, 397; (b) Nagai, Y.; Kusumi, T. *Tetrahedron Lett.* **1995**, *36*, 1853; (c) Yabuuchi, T.; Ooi, T.; Kusumi, T. *Chirality* **1997**, *9*, 550.
16. (a) McCleverty, J. A.; Wilkinson, G. *Inorg. Synth.* **1966**, *8*, 211; (b) Cattermole, P. E.; Osborne, G. A. *Inorg. Synth.* **1977**, *17*, 115.