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Hydroformylation of Olefinic Derivatives of Isosorbide and Isomannide

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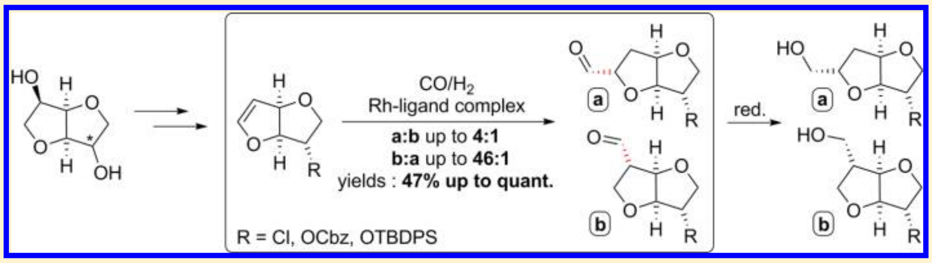
Ⓢ *Supporting Information*



ABSTRACT: The first time application of hydroformylation on olefinic derivatives of isosorbide and isomannide is shown by which a new carbon−carbon bond is formed. Depending on the ligand and reaction conditions used, the C6 regioisomer **a** can be obtained in 4:1 ratio and excellent yield, whereas C5 isomer **b** is achieved in almost complete regioselectivity (46:1) and good yield. In the majority of cases only the *exo* orientation is observed for the obtained aldehydes, and the method is easily applicable also on a 1 g scale.

INTRODUCTION

In recent decades the search for renewable resources for chemicals has intensified due to environmental issues and depletion of petrol resources. Biomass, especially lignocellulosic biomass, is the obvious source for sustainable carbon compounds.[1] A group of the platform molecules from biomass receiving increased interest are 1,4:3,6-dianhydrohexitols[2]—isosorbide[3] (**1a**, Figure 1) and its diastereomers, isomannide[4] **1b**, and isoidide[5] **1c**. These are rigid bicyclic compounds bearing two hydroxyl groups, with either *endo* or *exo* orientation.[6] The isohexides can be obtained from different carbohydrates, e.g., isosorbide can be derived from cellulose by double dehydration of sorbitol, and the stereoisomers can also be interconverted by catalytic isomerization.[7] They are attractive compounds due to rigidity, chirality, relative stability, and nontoxicity.[8]

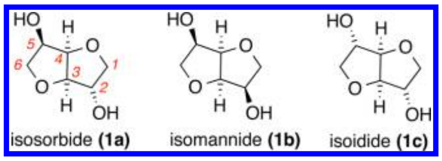


Figure 1. Platform molecules from biomass—isosorbide (**1a**) and its diastereomers, isomannide (**1b**), and isoidide (**1c**).

Isosorbide derivatives have found several applications.[9] In most of these, the sugar derivative has been functionalized through the hydroxyl groups at C2 and/or C5, while fewer efforts have been expended on preparing analogs in which the C−O bonds have been replaced with C−C bonds.[10]

Our goal was to develop novel isosorbide and isomannide derivatization strategy through selective C−C bond formation at C2/C5 and C1/C6. Hydroformylation, a powerful method for the formation of aldehydes from alkenes, was chosen for that transformation.[11] If successful, this C−C chain elongation methodology would considerably expand the potential usability of corresponding isohexide derivatives, especially in the synthesis of interesting bioactive targets and novel polymeric materials.[12] Furthermore, to best of our knowledge, isohexide derivatives have not been selectively derivatized in C1 and C6 positions previously.

Our general synthetic strategy is outlined in Scheme 1. Prerequisite for hydroformylation is the regioselective formation of mono-olefin of the type **2**.

We speculated that in isosorbide (**1a**) the 2-*exo* and 5-*endo* hydroxyls should have different reactivity enabling the selective formation of mono-olefin **2** via elimination. Subsequent hydroformylation of **2** would then afford the target aldehydes **3a** and **3b** (path A). It is reasonable to assume that due to different electronic and steric properties at carbons C6/C5, a regioselective (C6 vs C5) hydroformylation could in principle be achieved if suitable catalyst, ligand, and reaction conditions are identified.

Isomannide (**1b**) as a starting material with *endoendo* configuration can be expected to yield symmetrical bis-olefin **4**, which would subsequently yield symmetrical hydroformylation product **5** (path B).

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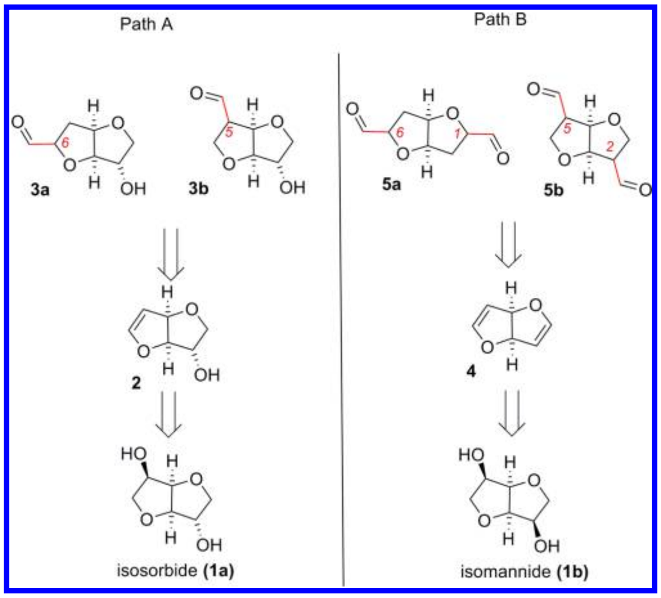
Scheme 1. Synthetic Strategies for C−C Bond Formations of Isohexides[a]

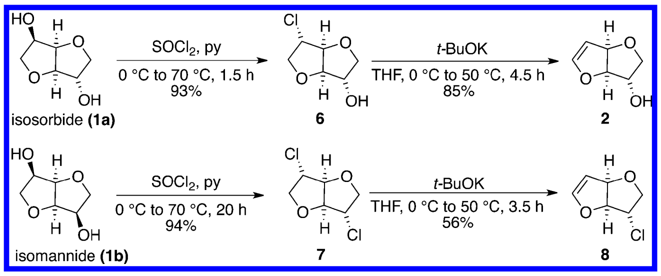


[a]Path A: regioselective conversion of isosorbide into **3a** and **3b**. Path B: symmetrical derivatization of isomannide.

RESULTS AND DISCUSSION

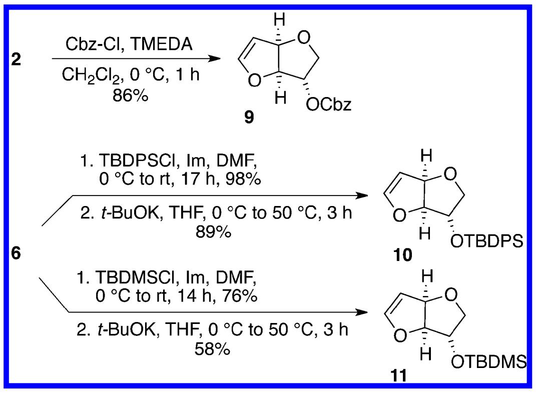
We started our investigation by exploring the *β*-elimination to obtain a mono-olefin **2**. When isosorbide **1a** was treated with thionyl chloride and pyridine, only *endo* hydroxyl at C5 was converted into corresponding chloride **6** in high yield and clean inversion of configuration (Scheme 2). The subsequent elimination with *t*-BuOK afforded the desired olefin **2** in good yield. In a similar fashion we tested chlorination of isomannide **1b**, and *exoexo* dichloride **7** was obtained as expected in high yield. However, surprisingly, during the following elimination, only single chloride was eliminated to yield **8**. This unexpected elimination enables the use of C2 *exo* chloro derivative **8** as a substrate for hydroformylations as well. Both **2** and **8** proved to be relatively unstable and prone to partial decomposition under prolonged heating and storage.[13]

Scheme 2. Olefinic Derivatives 2 and 8 from Isosorbide and Isomannide



In order to improve stability, the hydroxyl group of alcohol **2** was protected. Cbz- and two different silyl groups were chosen for their ease of application, and we speculated that their diverse electronic and steric properties might lead to different selectivities in hydroformylation reactions. Cbz-protected derivate **9** (Scheme 3) was achieved from **2** in the presence of Cbz-Cl and TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) in good yield. A silyl group was added to **6** using TBDPSCl or TBDMSCl in the presence of imidazole, followed by *β*-elimination of the chloride to afford **10** or **11**, respectively. A lower yield of **11** can be explained by some desilylation observed during the elimination step.

Scheme 3. Synthesis of *O*-Protected Isosorbide Derivatives 9, 10, and 11



To study the hydroformylation of the alkenes, two rhodium precursors ($Rh(CO)_2acac$ and $[RhCl(cod)]_2$) in combination with nine ligands [$P(ODBP)_3$, (*R*,*R*)-Ph-BPE, (*S*,*S*)-Ph-BPE, Nixantphos, (*S*,*S*,*S*)-DiazaPhos-PPE, (*S*,*S*′,*R*,*R*′)-Tangphos, (*R*,*R*)-Chiraphite, (*R*,*S*)-Binaphos, and (*R*,*R*)-Binaphos] (Figure 2) were explored in toluene using synthetic gas ($CO:H_2$, 1:1, 1−40 bar) at different temperatures (50−80 °C). The choice of ligands was based on their reported performance in hydroformylations, structural diversity, and availability.[14] The more promising results were achieved with a $Rh(CO)_2acac$ precursor along with different ligands and are discussed below. The results with $[RhCl(cod)]_2$ precursor along with other unsatisfactory results are shown in the Supporting Information. The aldehyde products can be purified by column chromatography; however, we observed some aldehyde epimerization on silica gel. The direct reduction of aldehyde functionality into corresponding alcohol followed by chromatography eliminates the epimerization concern. Thus, a one-pot method was devised where first the alkene is subjected to hydroformylation conditions followed by reduction of the formed aldehyde into a corresponding primary alcohol. The regioselectivity and *endo*/*exo* preference was routinely determined from crude hydroformylation spectra and in all cases of potential interest also verified on corresponding purified alcohol obtained after reduction. No change in regioisomeric and diastereomeric ratio was observed during the reduction; regioisomers were inseparable on conventional flash chromatography. The conversion and crude yield of hydroformylations were determined directly from crude NMR spectra unless described otherwise.

First we investigated the hydroformylation of chloro-olefin **8** (Table 1). We were pleased that in spite of limited shelf life, chloro-olefin **8** could still be successfully hydroformylated in high yield and good regioselectivity. When **8** was treated with $Rh(CO)_2acac$ in the presence of bulky ligand $P(ODBP)_3$ at 60 °C, 40 bar, and 12 h, a mixture of inseparable aldehydes **12a** and **12b** was obtained in low regioselectivity (1:2) but good yield (entry 1). Surprisingly, lowering the pressure changed the regiopreference favoring C6 regioisomer **12a** instead (entries 2−4). Gratifyingly, the reaction time could be shortened from 12 to 2 h without a drop in yield. When the temperature was increased to 80 °C, both the regioselectivity toward **12a** and the

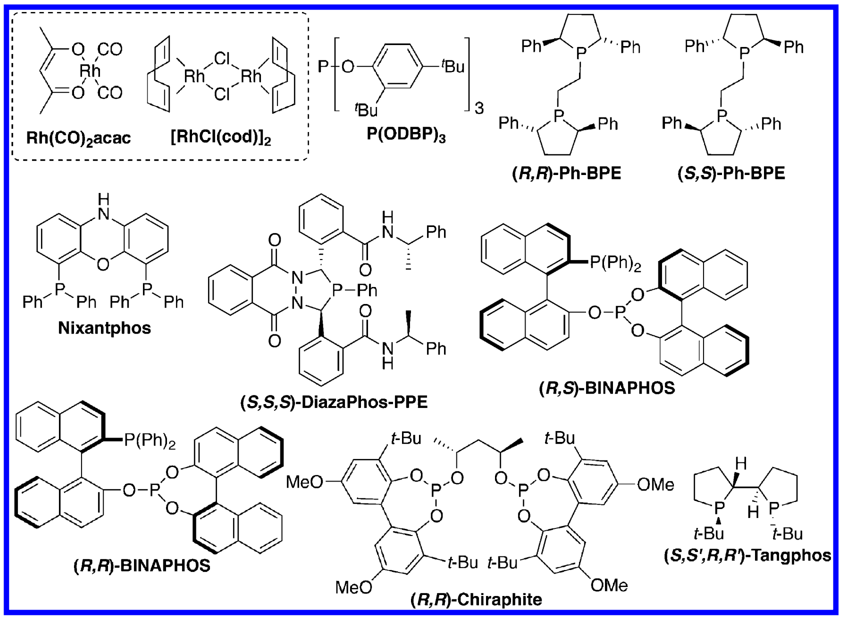
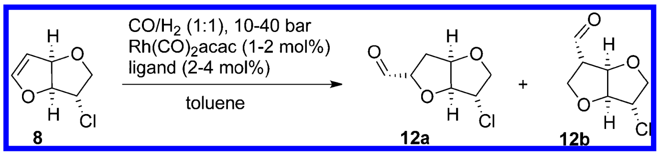


Figure 2. Precatalysts and ligands used in this study.

Table 1. Hydroformylation of Olefin 8[a]



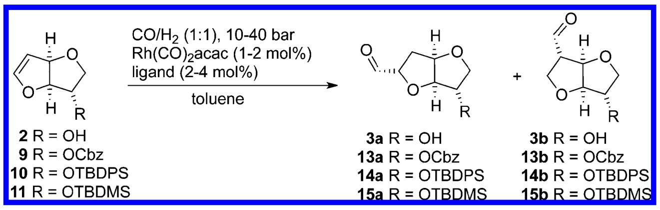
entry	alkene	ligand	*T* (°C)	P (bar)	time (h)	product	product ratio (*a*:*b*)[b]	conversion (%)	yield (*a* + *b*) (%)[c]
1	**8**	P(ODBP)$_3$	60	40	12	**12a/b**	1:2	83	74
2	**8**	P(ODBP)$_3$	60	20	2	**12a/b**	1.2:1.0	85	80
3	**8**	P(ODBP)$_3$	60	10	14	**12a/b**	2:1	>99	78
4	**8**	P(ODBP)$_3$	60	10	2	**12a/b**	2:1	>99	65
5	**8**	**P(ODBP)$_3$**	**80**	**10**	**2**	**12a/b**	**4:1**	**>99**	**93**
6	**8**	(*S,S,S*)-DiazaPhos-PPE	80	10	2	**12a/b**	1:2	50	50
7	**8**	(*S,S,S*)-DiazaPhos-PPE	80	40	4	**12a/b**	1:1.6	>99	60
8	**8**	(*S,S*)-Ph-BPE	80	10	2	**12a/b**	1:8	73	24
9	**8**	**(*S,S*)-Ph-BPE**	**80**	**40**	**4**	**12a/b**	**1:26**	**75**	**35**
10	**8**[d]	**(*S,S*)-Ph-BPE**	**80**	**30**	**5**	**12a/b**	**1:46**	**70**	***47***
11	**8**	(*R,R*)-Ph-BPE	80	30	5	**12a/b**	1:1.1	89	86

[a] Reaction conditions: mixture of alkene, Rh(CO)$_2$acac precursor if not otherwise stated (1−2 mol %) and ligand (2−4 mol %) in toluene (1−1.5 mL) was placed into the high-pressure reactor under synthetic gas environment. [b] Product (*a*:*b*) ratio was determined by ^{1}H NMR of the crude reaction mixture. [c] Isolated yield of aldehyde product or yield determined from crude by ^{1}H NMR against tetramethylsilane as internal standard (in italics). [d] Large scale (1 g alkene).

yield improved considerably (4:1, 2 h, 10 bar, 93%, entry 5). When ligand (*S,S,S*)-DiazaPhos-PPE was employed, C5 regioisomer **12b** was obtained as the main product instead of C6, but unfortunately the usefully high yields were accompanied by low regioselectivities (entries 6−7). Also with (*S,S*)-Ph-BPE ligand, C5 regioisomer **12b** was the main product in all conditions tested. In 2 h at 10 bar and 80 °C the **12b** was obtained in 8:1 selectivity, albeit in low yield (24%, entry 8). Increasing the pressure to 40 bar and prolonging the reaction time significantly improved the selectivity (26:1 toward **12b**) and increased the yield to 35% (entry 9). After additional fine-tuning, the **12b** was achieved in essentially complete regioselectivity (46:1) and acceptable yield as shown on large scale (1 g, entry 10). In all cases, only *exo* stereoisomer could be detected by NMR analysis. Interestingly, when (*R,R*)-Ph-BPE ligand was used in the same conditions, higher aldehyde yield was obtained, however, with almost no regioselectivity (entry 11).

Next we turned our attention to olefin **2** and its *O*-protected derivatives **9−11** (Table 2). Olefin **2**, furnished with unprotected alcohol group, did not perform well in hydroformylations (entries 1−3). At best we were able to achieve 1:2 regioselectivity favoring C5 regioisomer **3b**, but as yields remained low in all cases probably due to decomposition of starting material we did not explore this substrate further. When the Cbz-furnished alcohol **9** was subjected to our previously found optimal conditions in the presence of (*S,S*)-Ph-BPE ligand, the yield remained high but the regiopreference favored the C6 isomer **13a** (entry 4). Interestingly, with (*R,R*)-Ph-BPE ligand negligible regiopreference was observed toward **13b** (entry 5). Continuing with (*S,S*)-Ph-BPE, we were surprised to see that lowering the pressure from 40 to 10 bar

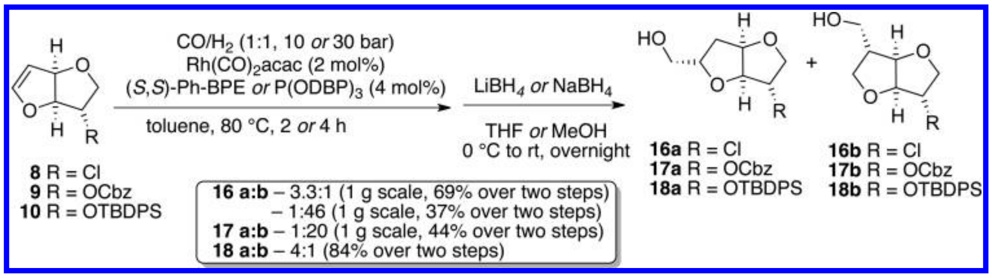
Table 2. Hydroformylation of 2 and *O*-Protected Olefins 9−10.[a]



entry	alkene	ligand	*T* (°C)	*P* (bar)	time	product	product ratio (*a*:*b*)[b]	conversion (%)	yield (*a* + *b*) (%)[c]
1	**2**	P(ODBP)$_3$	60	40	16	**3a/b**	1:2	50	12
2	**2**	P(ODBP)$_3$	60	40	2	**3a/b**	1:1.6	>99	30
3	**2**	P(ODBP)$_3$	60	20	2	**3a/b**	n.d.[g]	50	30
4	**9**	(*S*,*S*)-Ph-BPE	80	40	4	**13a/b**	1.9:1	n.d.[f]	90
5	**9**	(*R*,*R*)-Ph-BPE	80	40	4	**13a/b**	1:1.2	>99	98
6	**9**[d]	**(*S*,*S*)-Ph-BPE**	**80**	**10**	**2**	**13a/b**	**1:20**	**40**	***38***
7	**9**[d]	**(*S*,*S*)-Ph-BPE**	**80**	**10**	**2.75**	**13a/b**	**1:17.3**	**70**	***68***
8	**9**	P(ODBP)$_3$	80	10	2	**13a/b**	3.5:1	n.d.[f]	90
9	**9**	(*S*,*S*,*S*)-DiazaPhos-PPE	80	10	2	**13a/b**	1:2	60	54
10	**9**	(*S*,*S*,*S*)-DiazaPhos-PPE	80	40	4	**13a/b**	mixture[e]	>99	<99
11	**10**	(*S*,*S*,*S*)-DiazaPhos-PPE	80	10	2	**14a/b**	1.9:1	n.d.[f]	<99
12	**10**	(*S*,*S*)-Ph-BPE	80	10	2	**14a/b**	>1:20 (d.m. 7:1)	85	70
13	**10**	P(ODBP)$_3$	80	10	2	**14a/b**	4:1	>99	>99
14	**11**	P(ODBP)$_3$	80	10	4	**15a/b**	3.7:1	n.d.[f]	86

[a] Reaction conditions: see Table 1. [b] Product (*a*:*b*) ratio was determined by ^{1}H NMR of the crude reaction mixture; [c] Isolated yield of aldehyde product or yield determined from crude by ^{1}H NMR against tetramethylsilane as internal standard (in italics). [d] Large scale (1 g alkene). [e] Complex mixture of regio- and diastereomers. [f] n.d.—not determined.

Scheme 4. Synthesis of Primary Alcohols 16a/b−18a/b via One-Pot Hydroformylation and Aldehyde Reduction Sequence



resulted in a considerable increase in regioselectivity toward **13b** (1:20, entry 6), albeit with lower conversion and yield. After fine-tuning the reaction time, we employed the optimized conditions on a larger scale (1 g of alkene **9**), and the regiosiomer **13b** was obtained in comparable reagioselectivity and good yield (68%, entry 7). Additionally increasing the reaction time lead to a slight drop in regio- and diastereoselectivity. As it was for alkene **8**, also in this case the use of P(ODBP)$_3$ ligand turned the regiopreference toward the C6 regioisomer giving **13a** as the prevalent product (entry 8) albeit in lower selectivity. Ligand (*S*,*S*,*S*)-DiazaPhos-PPE in turn gave clean conversion to the product; however, at 10 bar and 2 h the regioselectivity was poor (entry 9), but running the reaction at 40 bar resulted in a product with poor selectivity as a complex mixuture of regio- and diastereoisomers was obtained (entry 10). (*S*,*S*,*S*)-DiazaPhos-PPE ligand provided high yield also for OTBDPS furnished olefin **10**, although in low regioselectivity (entry 11). The highest C5 regioselectivity was again obtained with (*S*,*S*)-Ph-BPE ligand (entry 12) as only one regioisomer could be detected by NMR; however, in this case **14b** was a 7:1 mixture of *exo*/*endo* diastereomers. Pleasingly, in the presence of ligand P(ODBP)$_3$ selectivity 4:1 toward C6 regioisomer **14a** was observed in excellent yield (entry 13). Also TBDMS-*O*-protected **11** performed similarly to the previous silyl compound giving **15a** as the main aldehyde (entry 14).

With optimized hydroformylation conditions at hand, we now turned to develop a method where the epimerization of the aldehyde product during purification could be circumvented. Here a one-pot procedure is shown where the hydroformylation of alkene **8**, **9**, or **10** is followed by reduction of the formed crude aldehyde into a corresponding primary alcohol **16**, **17**, or **18** with lithium or sodium borohydride (Scheme 4). In all cases the corresponding alcohols could be isolated with retained regioselectivity and diastereomeric ratio in moderate to good yield.

In summary, we have developed a high yielding, diastereo- and regioselective hydroformylation for olefinic isosorbide and isomannide derivatives. Excellent regioselectivity of 46:1 was achieved toward C5 hydroformylation and 4:1 for C6 hydroformylation; in both cases only *exo* diastereomer was deteced. Also a facile one-pot procedure in 1 g scale was shown where the hydroformylation of the olefinic isohexide was followed by a subsequent reduction of the aldehyde into a corresponding primary alcohol, which could be isolated with retained high regioselectivity and diastereomeric ratio.

■ EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were recorded at 400.1 and 100.6 MHz, respectively. For compounds **12**, **13**, and **14**, some of the ^{1}H and ^{13}C NMR spectra were recorded at 800.1 and 201.2 MHz, respectively. The chemical shifts for the ^{1}H and ^{13}C NMR spectra are given in ppm and are calibrated using residual solvent signals (for ^{1}H, CDCl$_3$: δ = 7.26 ppm, or toluene methyl group δ = 2.16 ppm. For ^{13}C, CDCl$_3$: δ = 77.0 ppm, or toluene methyl group δ = 21.4 ppm). The following abbreviations are used for multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Reactions were monitored by thin-layer chromatography (TLC), and TLC plates were visualized either by UV detection or by staining with KMnO$_4$, vanilla, or phosphomolybdic acid solution. Purification of reaction products was done by flash chromatography using silica gel 60 (0.040−0.063 mm, 230−400 mesh). Hydroformylation reactions were carried out in a high-pressure reactor (stainless steel vessel, 450 mL) in a 2 or 4 mL open glass vial using a synthetic gas (syngas) mixture of 1:1 CO/H$_2$ under pressures 1−40 bar. For hydroformylations on 1 g scale, a 25 mL flask was used instead of a vial. The reactor was heated inside a rigid heating jacket with a temperature controller and a thermocouple. The gas inlet was controlled by internal analog pressure gauge. For HRMS analysis, an LTQ Orbitrap analyzer was used. An FTIR spectrophotometer (ATR) was used for IR analysis. All reagents and solvents were obtained from commercial sources and were used without further purification. BINAPHOS ligands were synthesized according to a reported method.,[15,16]

General Procedure for Hydroformylation of Olefins. A mixture of an alkene (0.1 mmol), rhodium complex (1−2 mol %), and ligand (2−4 mol %) in toluene (1−2 mL) was placed into the high-pressure reactor in a 2 or 4 mL open glass vial.[17] For larger scale experiments (~1 g of olefin), a 25 mL flask and 15 mL of tolune were typically used. After degassing with water jet vacuum pump, the reactor was filled to the appropriate syngas pressure (see Tables 1 or 2, CO/H$_2$, 1:1). The reaction was stirred for a given time under rapid stirring (500−600 rpm) at a desired temperature. Then the pressure was reduced to atmospheric level, and the heater was turned off. The crude ^{1}H NMR spectra were taken directly from the cooled and aired reaction mixtures in order to determine regio- and diastereoselectivity. The isolated yields for the oily products were obtained after column chromatography on silica (2% MeOH/CH$_2$Cl$_2$) or were determined from crude by ^{1}H NMR analysis against tetramethylsilane as an internal standard.

General Procedure for Reduction of Aldehydes. To the crude untreated hydroformylation reaction mixture in toluene (including NMR solvent) containing the aldehydes **a**,**b** (0.1 mmol) was added THF (2 mL), and the solution was cooled to 0 °C. To the cooled solution was added LiBH$_4$ or NaBH$_4$ (0.7 mmol), and it was stirred overnight at rt. After consumption of the starting material (monitored by TLC analysis), the mixture was diluted with NaHCO$_3$ (aq. satd., 3 mL) and EtOAc (4 mL). Then the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 4 mL). The collected organic phases were dried over MgSO$_4$, filtrated, concentrated in vacuo, and purified by flash chromatography.

(3S,3aR,6aR)-2,3,3a,6a-Tetrahydrofuro[3,2-b]furan-3-ol (**2**).[18] To the cooled solution of **6** (2.82 g, 17.1 mmol) in THF (10 mL) was added *t*-BuOK (4.80 g; 42.8 mmol) in THF (13 mL) dropwise at 0 °C. The reaction was stirred at 50 °C for 4.5 h. Then the reaction was quenched with H$_2$O (50 mL) at 0 °C and EtOAc added (30 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The collected organic phases were dried over MgSO$_4$, filtrated, and concentrated to dryness in vacuo. The crude product **2** was purified by column chromatography on silica (2% MeOH/CH$_2$Cl$_2$) to yield the product as a pale yellow solid (1.86 g, 85%). To minimize decomposition, **2** was stored at −20 °C in EtOAc. Mp 77−78 °C; $[\alpha]^{23}_{D}$ = −103.1 (*c* 1.1, CHCl$_3$); ^{1}H NMR (400.1 MHz, CDCl$_3$) δ 6.51 (ddd, *J* = 2.6, 0.7, 0.3 Hz, 1H), 5.45 (ddm, *J* = 6.4, 2.6 Hz, 1H), 5.02 (dddd, *J* = 2.6, 2.6, 0.7, 0.4 Hz, 1H), 4.75 (dm, *J* = 6.4 Hz, 1H), 4.28 (ddm, *J* = 7.2, 2.7 Hz, 1H), 3.82 (ddd, *J* = 10.4, 1.1, 0.4 Hz, 1H), 3.47 (ddd, *J* = 10.4, 2.7, 0.6 Hz, 1H), 2.36 (d, *J* = 7.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, CDCl$_3$) δ 149.9, 99.6, 88.4, 83.6, 75.7, 69.7 ppm. IR (ATR) ν_{max} (cm^{-1}): 3387, 3086, 1612, 1061; HRMS (ESI): calcd for C$_6$H$_8$O$_3$Na [M + Na]$^+$ 151.0366, found 151.0361.

*(2S,3aR,6S,6aR)-6-Hydroxyhexahydrofuro[3,2-b]furan-2-carbaldehyde (Regioisomer **3a**), (3S,3aR,6S,6aR)-6-Hydroxyhexahydrofuro[3,2-b]furan-3-carbaldehyde (Regioisomer **3b**).* Prepared from **2** according to the general procedure for hydroformylation of olefins.

Isomer **3a**: ^{1}H NMR (400.1 MHz, toluene + CDCl$_3$) δ 9.38 (d, *J* = 1.1 Hz, 1H), 4.78 (dm, *J* = 3.6 Hz, 1H), 4.55 (m, 1H), 4.07 (m, 1H), 3.86 (dd, *J* = 9.4, 3.9 Hz, 1H), 3.79 (dm, *J* = 10.5 Hz, 1H), 3.73 (dd, *J* = 10.5, 3.6 Hz, 1H), 3.65 (dd, *J* = 9.4, 6.8 Hz, 1H), 2.86 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, CDCl$_3$) δ 198.9, 88.8, 82.5, 76.2, 74.4, 67.3, 59.2 ppm.

Isomer **3b**: ^{1}H NMR (400.1 MHz, toluene + CDCl$_3$) δ 9.32 (d, *J* = 1.9 Hz, 1H), 4.54 (m, 1H), 4.37 (dm, *J* = 3.7 Hz, 1H), 4.22 (dm, *J* = 3.7 Hz, 1H), 4.05 (m, 1H), 3.67 (dd, *J* = 10.5, 3.6 Hz, 1H), 3.63 (dm, *J* = 10.5 Hz, 1H), 2.28 (m, 1H), 1.67 (ddd, *J* = 13.5, 9.8, 4.9 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, CDCl$_3$) δ 200.2, 90.1, 82.9, 82.1, 76.4, 74.9, 35.2 ppm.

IR (ATR) ν_{max} (cm^{-1}): 3371, 2958, 2071, 1809, 1492, 1188, 1080, 968. HRMS (ESI): calcd for C$_7$H$_{11}$O$_4$ [M + H]$^+$ 159.0652, found 159.0648.

(3S,3aR,6S,6aS)-6-Chlorohexahydrofuro[3,2-b]furan-3-ol (**6**).[18,19] To a cooled solution of 1,4:3,6-dianhydro-D-sorbitol (3.02g, 20.7 mmol) and pyridine (4.9 mL, 62.0 mmol) was added SOCl$_2$ (3.3 mL, 45.5 mmol) dropwise at 0 °C. Then the reaction was stirred at 70 °C for 1.5 h. After completion of the reaction the mixture was cooled to 0 °C and quenched with H$_2$O (10 mL). Then NaCl (aq. satd., 30 mL) and EtOAc (30 mL) were added, the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The collected organic phases were dried over MgSO$_4$, filtrated, and concentrated in vacuo. The crude product **6** was obtained as a beige waxy solid (3.16 g, 93%). ^{1}H NMR (400.1 MHz, CDCl$_3$) δ 4.79 (dm, *J* = 3.6 Hz, 1H), 4.67 (m, *J* = 3.6 Hz, 1H), 4.36 (m, 1H), 4.32 (m, 1H), 4.04 (ddm, *J* = 10.6, 1.6 Hz, 1H), 4.02 (ddm, *J* = 10.6, 3.1 Hz, 1H), 3.90 (dm, *J* = 10.2 Hz, 1H), 3.86 (ddm, *J* = 10.2, 3.3 Hz, 1H), 2.32 (bs, 1H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, CDCl$_3$) δ 88.0, 87.4, 75.7, 75.4, 74.8, 60.4 ppm.

(3S,3aS,6S,6aS)-3,6-Dichlorohexahydrofuro[3,2-b]furan (**7**).[4a,20] To a cooled solution of 1,4:3,6-dianhydro-D-mannitol (2.23 g, 15.3 mmol) and pyridine (3.1 mL, 38.2 mmol) was added SOCl$_2$ (2.8 mL, 38.2 mmol) dropwise at 0 °C. The reaction was stirred at 70 °C overnight. Then the mixture was cooled to room temperature and quenched with H$_2$O (5 mL), added brine (15 mL), and EtOAc (20 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The collected organic phases were dried over MgSO$_4$, filtrated, and concentrated in vacuo. The crude product **7** was obtained as a beige waxy solid (2.61 g, 94%). ^{1}H NMR (400.1 MHz, CDCl$_3$) δ 4.84 (m, 2H), 4.33 (m, 2H), 4.07 (dd, *J* = 10.7, 1.2 Hz, 2H), 4.03 (dd, *J* = 10.7, 3.4 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, CDCl$_3$) δ 87.9, 75.5, 60.1 ppm.

(3S,3aS,6aR)-3-Chloro-2,3,3a,6a-tetrahydrofuro[3,2-b]furan (**8**). To the compound **7** (1.23 g, 6.74 mmol) in THF (3 mL) was added *t*-BuOK (1.95 g; 17.41 mmol) in THF (7 mL) dropwise at 0 °C under argon atmosphere. Then the reaction was brought to 50 °C and stirred for 3.5 h. The reaction was quenched with H$_2$O (30 mL) at 0 °C. To the mixture was added EtOAc (30 mL). Then the phases were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The collected organic phases were dried over MgSO$_4$, filtrated, and carefully concentrated in vacuo. While evaporating solvents the water bath temperature was kept below 25 °C to avoid possible decomposition of **8**—the oily crude may transform into unidentified solid compounds if heated. The crude oil was either directly used in a subsequent hydroformylation reaction or stored in solvent (EtOAc) at −20 °C. The crude product **8** was obtained as a light brown oil (550 mg, 56%). ^{1}H NMR (400.1 MHz, CDCl$_3$) δ 6.49 (dm, *J* = 2.7 Hz, 1H), 5.49 (ddm, *J* = 6.3, 2.6 Hz, 1H), 5.04 (ddm, *J* = 2.6, 2.6 Hz, 1H), 4.92 (dm, *J* = 6.3 Hz, 1H), 4.30 (dm, *J* = 3.1 Hz, 1H), 3.95 (dm, *J* =

10.8 Hz, 1H), 3.70 (ddm, *J* = 10.8, 3.1 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 149.7, 99.9, 89.1, 83.7, 70.1, 60.2 ppm. IR and HRMS analyses were not obtained due to the labile nature of compound.

*Benzyl ((3S,3aS,6aR)-2,3,3a,6a-Tetrahydrofuro[3,2-b]furan-3-yl) Carbonate (**9**).* To a solution of **2** (551 mg, 4.3 mmol) in CH_2Cl_2 (3 mL) was added *N,N,N′,N′*-tetramethylethylenediamine (390 μL, 2.6 mmol) and benzyl chloroformate (800 μL, 5.6 mol) at 0 °C. After 1 h and consumption of the starting material, the mixture was diluted with CH_2Cl_2 (15 mL), and H_2O (5 mL) and NaCl (aq. satd., 15 mL) added. Then the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The collected organic phases were dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude product was purified by column chromatography on silica (10% EtOAc/p.ether) to afford **9** as a clear colorless oil (966 mg, 86%): $[\alpha]^{23}_D$ = +16.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.41−7.31 (m, 5H), 6.51 (ddd, *J* = 2.7, 0.8, 0.4 Hz, 1H), 5.46 (ddddd, *J* = 6.6, 2.5, 0.8, 0.6, 0.6 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.17 (d, *J* = 12.2 Hz, 1H), 5.09 (dm, *J* = 3.0 Hz, 1H), 5.04 (dddd, *J* = 2.7, 2.5, 0.7, 0.4 Hz, 1H), 4.87 (dm, *J* = 6.6 Hz, 1H), 4.01 (ddd, *J* = 11.2, 1.1, 0.5 Hz, 1H), 3.56 (ddd, *J* = 11.2, 2.9, 0.6 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 154.1, 149.6, 134.8, 128.6, 128.5, 128.3, 99.9, 86.0, 84.0, 81.0, 69.9, 67.4 ppm. IR (ATR) ν_{max} (cm^{-1}): 2962, 1744, 1612, 1250, 1049, 736, 698; HRMS (ESI): calcd for $C_{14}H_{14}O_5Na$ [M + Na]$^+$ 285.0733, found 285.0727.

*(3S,3aS,6aR)-3-{[tert-Butyl(diphenyl)silyl]oxy}-2,3,3a,6a-tetrahydrofuro[3,2-b]furan (**10**).* To a cooled solution of **6** (584 mg, 3.6 mmol) in DMF (1.0 mL) was added imidazole (604 mg, 8.9 mmol) in DMF (1.5 mL) and TBDPSCl (1170 mg, 4.3 mmol, 1 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 17 h. After that the reaction was diluted with EtOAc (20 mL) and NaCl (aq.satd., 20 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The collected organic phases were dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude was purified by column chromatography on silica (1% EtOAc/p.ether) to afford the silylated product as a clear colorless oil (1.41 g, 98%). This silylated compound (657 mg, 1.6 mmol) was then redissolved in THF (1 mL) and *t*-BuOK (457 mg, 4.1 mmol) in THF (3.0 mL) added dropwise at 0 °C. The reaction was heated to 50 °C and stirred for 3 h. Then the mixture was brought to room temperature and diluted with EtOAc (15 mL), and H_2O (10 mL) and NaCl (aq. satd., 15 mL) added. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The collected organic phases were dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude was purified by column chromatography on silica (8% EtOAc/p. ether) to afford **10** as a clear colorless oil (534 mg, 89%): $[\alpha]^{23}_D$ = −1.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.74−7.67 (m, 4H), 7.46−7.36 (m, 6H), 6.40 (dm, *J* = 2.7 Hz, 1H), 5.47 (ddm, *J* = 6.4, 2.6 Hz, 1H), 5.01 (ddm, *J* = 2.7, 2.6 Hz, 1H), 4.73 (dm, *J* = 6.4 Hz, 1H), 4.31 (ddm, *J* = 2.9, 0.8 Hz, 1H), 3.75 (ddd, *J* = 10.0, 0.8, 0.6 Hz, 1H), 3.30 (dd, *J* = 10.0, 2.9 Hz, 1H), 1.10 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 149.3, 135.68, 135.67, 134.8, 129.91, 129.87, 127.81, 127.76, 127.70, 100.3, 89.3, 83.7, 77.6, 70.2, 26.8, 19.1 ppm. IR (ATR) ν_{max} (cm^{-1}): 3071, 2958, 1612, 1111, 817, 702; HRMS (ESI): calcd for $C_{22}H_{26}O_3SiNa$ [M + Na]$^+$ 389.1543, found 389.1535.

*(3S,3aS,6aR)-3-{[tert-Butyl(dimethyl)silyl]oxy}-2,3,3a,6a-tetrahydrofuro[3,2-b]furan (**11**).*[16] To a cooled solution of **6** (360 mg, 2.18 mmol) in DMF (1.0 mL) was added imidazole (372 mg, 5.47 mmol) in DMF (1 mL) and *tert*-butyl(chloro)dimethylsilane (395 mg, 2.62 mmol) in DMF (1 mL) at 0 °C under argon atmosphere. The reaction was allowed to warm to room temperature and stirred for 14 h. Then the reaction was diluted with EtOAc (25 mL) and NaCl (aq. satd., 20 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The collected organic phases were dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude was purified by column chromatography on silica (5% EtOAc/p.ether) to afford the silylated product as a beige oil (466 mg, 76%). This silylated compound (370 mg, 1.32 mmol) was then redissolved in THF (3 mL) and *t*-BuOK (372 mg, 3.32 mmol) in THF (3.0 mL) added dropwise at 0 °C. The reaction was heated to 50 °C and stirred for 3 h. Then the mixture was brought to room temperature and H_2O (5 mL), EtOAc (15 mL), and NaCl (aq. satd., 15 mL) were added. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The collected organic phases were dried over $MgSO_4$, filtrated, and concentrated in vacuo. The crude was purified by column chromatography on silica (5−10% EtOAc/p. ether) to afford **11** as a clear colorless oil (185 mg, 58%). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 6.48 (dm, *J* = 2.7 Hz, 1H), 5.42 (ddm, *J* = 6.5, 2.6 Hz, 1H), 5.04 (dddd, *J* = 2.7, 2.6, 0.6, 0.4 Hz, 1H), 4.66 (dm, *J* = 6.5 Hz, 1H), 4.28 (dm, *J* = 3.1 Hz, 1H), 3.72 (ddd, *J* = 9.8, 1.1, 0.8 Hz, 1H), 3.47 (ddm, *J* = 9.8, 3.1 Hz, 1H), 0.91 (s, 9H), 0.124 (s, 3H), 0.117 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 149.3, 100.4, 89.7, 83.6, 77.0, 70.6, 25.8, 18.2, 4.8 ppm. IR (ATR) ν_{max} (cm^{-1}): 2932, 1612, 1253, 1146; HRMS (ESI): calcd for $C_{12}H_{22}O_3SiNa$ [M + Na]$^+$ 265.1230, found 265.1222.

*(2S,3aR,6S,6aS)-6-Chlorohexahydrofuro[3,2-b]furan-2-carbaldehyde (Regioisomer **12a**), (3S,3aR,6S,6aS)-6-Chlorohexahydrofuro[3,2-b]furan-3-carbaldehyde (Regioisomer **12b**).* Prepared from **8** according to the general procedure for hydroformylation of olefins.

Isomer **12a**: ^{1}H NMR (800.1 MHz, toluene + $CDCl_3$) δ 9.15 (d, *J* = 2.2 Hz, 1H), 4.42 (dd, *J* = 4.7, 3.6 Hz, 1H), 4.28 (dm, *J* = 3.6 Hz, 1H), 3.89 (dm, *J* = 3.8 Hz, 1H), 3.85 (ddd, *J* = 10.2, 6.7, 2.2 Hz, 1H), 3.67 (dm, *J* = 10.6 Hz, 1H), 3.62 (dd, *J* = 10.6, 3.8 Hz, 1H), 1.89 (dd, *J* = 13.6, 6.7 Hz, 1H), 1.34 (ddd, *J* = 13.6, 10.2, 4.7 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (201.2 MHz, toluene + $CDCl_3$) δ 199.0, 90.6, 83.6, 82.3, 74.9, 60.9, 35.0 ppm.

Isomer **12b**: ^{1}H NMR (800.1 MHz, toluene + $CDCl_3$) δ 9.01 (d, *J* = 0.8 Hz, 1H, C<u>H</u>O), 4.77 (dd, *J* = 4.1, 1.6 Hz, 1H), 4.28 (m, 1H), 3.85 (m, 1H), 3.73 (dd, *J* = 9.3, 3.2 Hz, 1H), 3.67 (dm, *J* = 10.6 Hz, 1H), 3.60 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.42 (dd, *J* = 9.3, 6.7 Hz, 1H), 2.54 (ddm, *J* = 6.7, 3.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (201.2 MHz, toluene + $CDCl_3$) δ 197.7, 89.2, 82.6, 74.6, 67.5, 60.7, 59.0 ppm.

IR (ATR) ν_{max} (cm^{-1}): 2870, 1724, 1076, 1007, 737, 687; HRMS (ESI): calcd for $C_7H_{10}Cl_1O_3$ [M + H]$^+$ 177.0313, found 177.0311.

*Benzyl (2S,3aR,6S,6aS)-2-Formylhexahydrofuro[3,2-b]furan-6-yl Carbonate (Regioisomer **13a**), Benzyl (3S,3aR,6S,6aS)-3-Formylhexahydrofuro[3,2-b]furan-6-yl Carbonate (Regioisomer **13b**).* Prepared from **9** according to the general procedure for hydroformylation of olefins.

Isomer **13a**: ^{1}H NMR (800.1 MHz, toluene + $CDCl_3$) δ 9.21 (d, *J* = 2.0 Hz, 1H), 4.93 (dddd, *J* = 3.6, 1.2, 0.7, 0.6 Hz, 1H), 4.91 (m, 2H), 4.35 (dddm, *J* = 4.8, 3.7, 0.7 Hz, 1H), 4.28 (dd, *J* = 3.7, 1.2 Hz, 1H), 3.91 (dddd, *J* = 9.9, 6.7, 2.0, 0.7 Hz, 1H), 3.71 (ddm, *J* = 10.9, 0.7 Hz, 1H), 3.69 (dd, *J* = 10.9, 3.6 Hz, 1H), 1.93 (ddm, *J* = 13.6, 6.7 Hz, 1H), 1.40 (ddd, *J* = 13.6, 9.9, 4.8 Hz, 1H), Ph signals were overlapping with toluene signals of the crude mixture; ^{13}C{^{1}H} NMR (201.2 MHz, toluene + $CDCl_3$) δ 199.5, 154.4, 135.22, 128.69, 128.58, 128.53, 87.5, 83.1, 82.5, 81.3, 72.3, 69.9, 35.0 ppm.

Isomer **13b**: ^{1}H NMR (800.1 MHz, toluene + $CDCl_3$) δ 9.06 (d, *J* = 1.0 Hz, 1H), 4.91 (m, 2H), 4.88 (ddddd, *J* = 3.9, 1.6, 1.1, 0.6, 0.5 Hz, 1H), 4.68 (dd, *J* = 4.3, 1.6 Hz, 1H), 4.26 (dm, *J* = 4.3 Hz, 1H), 3.74 (dd, *J* = 9.3, 3.5 Hz, 1H), 3.76 (dm, *J* = 10.9 Hz, 1H), 3.65 (dd, *J* = 10.9, 3.9 Hz, 1H), 3.50 (ddm, *J* = 9.3, 6.8, 0.5 Hz, 1H), 2.60 (m, 1H) ppm, Ph signals were overlapping with toluene signals of the crude mixture; ^{13}C{^{1}H} NMR (201.2 MHz, $CDCl_3$) δ 198.0, 154.2, 135.18, 128.73, 128.68, 128.67, 86.1, 82.8, 81.3, 71.9, 69.9, 67.1, 59.0 ppm.

IR (ATR) ν_{max} (cm^{-1}): 2962, 2873, 1748, 1385, 1242, 1095, 752, 694. HRMS (ESI): calcd for $C_{15}H_{17}O_6$ [M + H]$^+$ 293.1020, found 293.1011.

*(2S,3aR,6S,6aS)-6-{[tert-Butyl(diphenyl)silyl]oxy}hexahydrofuro[3,2-b]furan-2-carbaldehyde (Regioisomer **14a**), (3S,3aR,6S,6aS)-6-{[tert-Butyl(diphenyl)silyl]oxy}hexahydrofuro[3,2-b]furan-3-carbaldehyde (Regioisomer **14b**).* Prepared from **10** according to the general procedure for hydroformylation of olefins.

Isomer **14a**: ^{1}H NMR (800.1 MHz, toluene + $CDCl_3$) δ 9.17 (d, *J* = 2.1 Hz, 1H), 4.55 (dd, *J* = 4.5, 3.7 Hz, 1H), 4.35 (dm, *J* = 3.7 Hz, 1H), 4.26 (dddd, *J* = 3.7, 2.3, 1.4, 0.6 Hz, 1H), 3.84 (dddd, *J* = 10.3, 6.5, 2.1, 0.6 Hz, 1H), 3.63 (dd, *J* = 9.7, 1.4 Hz, 1H), 3.45 (dd, *J* = 9.7, 3.7 Hz, 1H), 1.95 (ddm, *J* = 13.5, 6.5 Hz, 1H), 1.39 (dddd, *J* = 13.5, 10.3, 4.5, 0.6 Hz, 1H), 1.07 (s, 9H) ppm, Ph signals were overlapping with toluene signals of the crude mixture; ^{13}C{^{1}H} NMR (201.2 MHz, toluene + $CDCl_3$) δ 199.9, 135.88, 135.85, 133.6, 133.33, 128.12, 128.05, 127.8, 90.6, 82.9, 82.4, 78.1, 75.2, 35.3, 26.97, 19.2 ppm.

Isomer **14b**: ^{1}H NMR (800.1 MHz, toluene + $CDCl_3$) δ 9.09 (d, J = 1.0 Hz, 1H), 4.88 (ddm, J = 4.2, 1.4 Hz, 1H), 4.34 (dm, J = 4.2 Hz, 1H), 4.22 (dddd, J = 3.7, 2.2, 1.4, 0.5 Hz, 1H), 3.70 (dd, J = 9.2, 3.3 Hz, 1H), 3.61 (ddd, J = 9.6, 2.2, 0.6 Hz, 1H), 3.43 (dd, J = 9.6, 3.7 Hz, 1H), 3.41 (ddd, J = 9.2, 6.7, 0.5 Hz, 1H), 2.59 (m, 1H), 1.06 (s, 9H) ppm, Ph signals were overlapping with toluene signals of the crude mixture; ^{13}C{^{1}H} NMR (201.2 MHz, toluene + $CDCl_3$) δ 198.5, 135.86, 135.76, 133.7, 133.25, 128.10, 128.02, 127.9, 89.2, 82.7, 78.0, 74.6, 66.8, 59.2, 26.96, 19.1 ppm.

IR (ATR) ν_{max} (cm^{-1}): 2931, 2852, 1427, 1111, 1080, 736, 702; HRMS (ESI): calcd for $C_{23}H_{29}O_4Si$ [M + H]$^+$ 397.1830, found 397.1821.

*(2S,3aR,6S,6aS)-6-{[tert-Butyl(dimethyl)silyl]oxy}hexahydrofuro-[3,2-b]furan-2-carbaldehyde (Regioisomer **15a**), (3S,3aR,6S,6aS)-6-{[tert-Butyl(dimethyl)silyl]oxy}hexahydrofuro[3,2-b]furan-3-carbaldehyde (Regioisomer **15b**), (3R,3aR,6S,6aS)-6-{[tert-Butyl-(dimethyl)silyl]oxy}hexahydrofuro[3,2-b]furan-3-carbaldehyde (Regioisomer **15c**).* Prepared from **11** according to the general procedure for hydroformylation of olefins.

Isomer **15a**: ^{1}H NMR (700.1 MHz, $CDCl_3$) δ 9.62 (d, J = 2.0 Hz, 1H), 4.82 (ddm, J = 4.5, 3.6 Hz, 1H), 4.47 (ddm, J = 3.6, 1.3 Hz, 1H), 4.35 (dddd, J = 10.3, 6.5, 2.0, 0.8 Hz, 1H), 4.33 (m, 1H), 3.93 (ddd, J = 9.6, 3.8, 0.4 Hz, 1H), 3.73 (dm, J = 9.6 Hz, 1H), 2.37 (dddd, J = 13.5, 6.5, 1.5, 0.8 Hz, 1H), 1.94 (dddd, J = 13.5, 10.3, 4.5, 0.7 Hz, 1H), 0.89 (s, 9H), 0.09 (s, 6H) ppm; ^{13}C{^{1}H} NMR (176.0 MHz, $CDCl_3$) δ 200.4, 90.8, 83.0, 82.1, 77.0, 75.7, 35.3, 25.70, 18.02, −4.84 ppm.

Isomer **15b**: ^{1}H NMR (700.1 MHz, $CDCl_3$) δ 9.75 (d, J = 1.1 Hz, 1H), 5.02 (dd, J = 4.2, 1.3 Hz, 1H), 4.30 (ddm, J = 4.2, 1.3 Hz, 1H), 4.26 (ddddd, J = 3.7, 2.0, 1.3, 0.6, 0.6 Hz, 1H), 4.18 (dddd, J = 9.2, 3.3, 0.4, 0.3 Hz, 1H), 3.94 (ddm, J = 9.2, 6.3 Hz, 1H), 3.89 (ddm, J = 9.5, 3.7 Hz, 1H), 3.74 (ddm, J = 9.5, 2.0 Hz, 1H), 3.22 (dddddd, J = 6.3, 3.3, 1.3, 1.1, 0.6, 0.6 Hz, 1H), 0.88 (s, 9H), 0.10 (s, 6H) ppm; ^{13}C{^{1}H} NMR (176.0 MHz, $CDCl_3$) δ 199.2, 89.2, 82.5, 76.8, 75.1, 67.0, 59.1, 25.71, 18.04, −4.83 ppm.

Isomer **15c**: ^{1}H NMR (700.1 MHz, $CDCl_3$) δ 9.80 (d, J = 1.4 Hz, 1H), 5.12 (ddddd, J = 5.3, 3.7, 0.5, 0.5, 0.5 Hz, 1H), 4.36 (m, 1H), 4.28 (m, 1H), 4.15 (dddd, J = 9.0, 8.6, 0.5, 0.4 Hz, 1H), 3.96 (dd, J = 9.0, 8.1 Hz, 1H), 3.85 (ddd, J = 9.5, 3.6, 0.4 Hz, 1H), 3.75 (dm, J = 9.5 Hz, 1H), 3.17 (ddddd, J = 8.6, 8.1, 5.3, 1.4, 0.6 Hz, 1H), 0.888 (s, 9H), 0.08 (s, 6H) ppm; ^{13}C{^{1}H} NMR (176.0 MHz, $CDCl_3$) δ 198.2, 90.3, 83.0, 76.3, 76.0, 66.9, 57.1, 25.68, 18.03, −4.82 ppm.

IR (ATR) ν_{max} (cm^{-1}): 2932, 1736, 1470, 1080, 837. HRMS (ESI): calcd for $C_{13}H_{25}O_4Si$ [M + H]$^+$ 273.1517, found 273.1513.

*(3S,3aS,5S,6aR)-3-Chloro-5-hydroxymethyl-hexahydrofuro[3,2-b]furan (Regioisomer **16a**), (3S,3aS,6S,6aR)-3-Chloro-6-hydroxy-methyl-hexahydrofuro[3,2-b]furan (Regioisomer **16b**).* The hydroformylation step was run according to the general procedure for hydroformylation of olefins. To get **12a** as major product see conditions in Table 1, entry 5.

To get **12b** as major product use alkene **8** (800 mg, 5.5 mmol), $Rh(CO)_2acac$ (27 mg, 0.1 mmol) and (*S,S*)-Ph-BPE (99 mg, 0.2 mmol) in toluene (13 mL) at 80 °C, 30 bar for 4 h. The reduction step was run according to the general procedure for reduction of aldehydes with **12a,b** (2.6 mmol) and $LiBH_4$ (354 mg, 16.3 mmol) in THF (45 mL). Purification by flash chromatography (75% EtOAc/p. ether) afforded **16** as a beige oil (inseparable mixture of regioisomers **a** and **b**, 363 mg, yield 37% over 2 steps). Isomer **16a**: ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 4.87 (ddm, J = 4.6, 3.8 Hz, 1H), 4.62 (ddm, J = 3.8, 1.3 Hz, 1H), 4.28 (ddm, J = 3.9, 1.8 Hz, 1H), 4.12 (m, 1H), 4.11 (ddd, J = 10.5, 3.9, 0.5 Hz, 1H), 3.96 (ddm, J = 10.5, 1.8 Hz, 1H), 3.70 (dm, J = 12.0 Hz, 1H), 3.43 (ddd, J = 12.0, 5.5, 5.0 Hz, 1H), 2.60 (dd, J = 6.0, 5.5 Hz, 1H), 2.08 (ddddd, J = 13.6, 5.5, 0.9, 0.8, 0.8 Hz, 1H), 1.85 (dddd, J = 13.6, 10.4, 4.6, 0.7 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 89.3, 83.1, 81.0, 75.0, 63.7, 61.0, 35.1 ppm. Isomer **16b**: ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 4.71 (dd, J = 4.1, 1.5 Hz, 1H), 4.55 (dm, J = 4.1 Hz, 1H), 4.27 (m, 1H), 4.06 (ddd, J = 10.5, 3.8, 0.5 Hz, 1H), 3.94 (dm, J = 10.5 Hz, 1H), 3.90 (ddd, J = 9.0, 6.2, 0.5 Hz, 1H), 3.73 (dd, J = 9.0, 3.3 Hz, 1H), 3.54 (bs, 1H), 3.53 (bs, 1H), 2.67 (bs, 1H), 2.47 (m, 1H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 88.7, 84.9, 74.3, 70.9, 61.8, 60.8, 48.9 ppm. IR (ATR) ν_{max} (cm^{-1}): 3422, 1072, 1042, 833. HRMS (ESI): calcd for $C_7H_{12}Cl_1O_3$ [M + H]$^+$ 179.0469, found 179.0465.

*Benzyl (3S,3aS,5S,6aR)-5-Hydroxymethylhexahydrofuro[3,2-b]-furan-3-yl Carbonate (Regioisomer **17a**), Benzyl (3S,3aS,6S,6aR)-6-Hydroxymethylhexahydrofuro[3,2-b]furan-3-yl Carbonate (Regioisomer **17b**).* The hydroformylation step was run according to the general procedure for hydroformylation of olefins starting from alkene **9** (1.2 g, 4.6 mmol), $Rh(CO)_2acac$ (24 mg, 0.09 mmol) and (*S,S*)-Ph-BPE (84 mg, 0.18 mmol) in toluene (15 mL) at 80 °C, 10 bar for 2 h. The reduction step was run according to the general procedure for reduction of aldehydes with aldehydes **13a,b** (3.1 mmol) and $NaBH_4$ (408 mg, 18.6 mmol) in MeOH (90 mL). Purification by flash chromatography (75% EtOAc/p. ether) afforded **17** as a yellow oil (inseparable mixture of regioisomers **a** and **b**, 586 mg, yield 44% over 2 steps). Isomer **17a**: ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.42–7.32 (m, 5H), 5.19–5.13 (m, 2H), 5.11–5.06 (m, 1H), 4.81 (ddm, J = 4.4, 4.0 Hz, 1H), 4.59 (dm, J = 4.0 Hz, 1H), 4.16 (dddd, J = 10.4, 5.4, 4.8, 2.8 Hz, 1H), 4.07 (dd, J = 10.8, 4.1 Hz, 1H), 3.94 (dm, J = 10.8 Hz, 1H), 3.63 (dd, J = 10.7, 6.7 Hz, 1H), 3.59 (dd, J = 10.7, 6.9 Hz, 1H), 2.10 (dd, J = 13.5, 5.6 Hz, 1H), 1.90 (ddd, J = 13.5, 10.2, 4.8 Hz, 1H), 1.82 (bs, 1H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 154.23, 134.83, 128.70, 128.64, 128.42, 86.4, 81.8, 81.5, 80.2, 71.7, 70.02, 63.8, 35.2 ppm. Isomer **17b**: ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.42–7.32 (m, 5H), 5.19–5.13 (m, 2H), 5.11–5.06 (m, 1H), 4.65 (ddm, J = 4.4, 1.5 Hz, 1H), 4.53 (dm, J = 4.4 Hz, 1H), 4.03 (dd, J = 10.9, 3.9 Hz, 1H), 3.96 (dd, J = 8.9, 6.2 Hz, 1H), 3.94 (dm, J = 10.9 Hz, 1H), 3.79 (dd, J = 11.8, 2.8 Hz, 1H), 3.77 (dd, J = 8.9, 3.6 Hz, 1H), 3.49 (dd, J = 11.8, 4.7 Hz, 1H), 2.50 (m, 1H), 1.82 (bs, 1H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 154.21, 134.81, 128.67, 128.63, 128.41, 85.7, 85.2, 83.5, 72.4, 70.5, 69.98, 62.3, 49.0 ppm. IR (ATR) ν_{max} (cm^{-1}): 3445, 1744, 1249, 1042. HRMS (ESI): calcd for $C_{15}H_{18}O_6Na$ [M + Na]$^+$ 317.0996, found 317.0981.

*(3S,3aS,5S,6aR)-3-{[tert-Butyl(diphenyl)silyl]oxy}-5-hydroxymethylhexahydrofuro[3,2-b]furan (Regioisomer **18a**), (3S,3aS,6S,6aR)-3-{[tert-Butyl(diphenyl)silyl]oxy}-6-hydroxymethylhexahydrofuro[3,2-b]furan (Regioisomer **18b**).* The hydroformylation step was run according to the general procedure for hydroformylation of olefins starting from alkene **10** (for condtitions see Table 2, entry 12). The reduction step was run according to the general procedure for reduction of aldehydes with aldehydes **14a,b** (0.1 mmol) $LiBH_4$ (16 mg, 0.7 mmol) in THF (2 mL). Purification by flash chromatography (2% MeOH/CH_2Cl_2) afforded **18** as a yellow oil (inseparable mixture of regioisomers **a** and **b**, 27 mg, yield 84% over 2 steps). Isomer **18a**: ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.68–7.61 (m, 4H), 7.48–7.34 (m, 6H), 4.88 (dd, J = 4.4, 4.0 Hz, 1H), 4.46 (ddm, J = 3.8, 1.3 Hz, 1H), 4.35–4.26 (m, 1H), 4.02 (dddd, J = 10.3, 5.3, 5.0, 2.8 Hz, 1H), 3.76–3.66 (m, 3H), 3.43 (dd, J = 11.8, 5.0 Hz, 1H), 2.05 (ddm, J = 13.4, 5.4 Hz, 1H), 1.82 (ddd, J = 13.4, 10.3, 4.5 Hz, 1H), 1.73 (bs, 1H), 1.07 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 135.69, 135.63, 133.57, 133.32, 129.86, 129.84, 127.77, 127.73, 89.2, 83.3, 79.7, 78.2, 75.1, 64.0, 35.3, 26.8, 19.1 ppm. Isomer **18b**: ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 7.68–7.61 (m, 4H), 7.48–7.34 (m, 6H), 4.71 (dm, J = 4.1 Hz, 1H), 4.43 (dm, J = 4.1 Hz, 1H), 4.30 (m, 1H), 3.81 (dd, J = 8.9, 6.1 Hz, 1H), 3.76–3.66 (m, 2H), 3.65 (dd, J = 9.6, 3.6 Hz, 1H), 3.62 (dd, J = 10.6, 6.8 Hz, 1H), 3.56 (dd, J = 10.6, 7.0 Hz, 1H), 2.44 (m, 1H), 1.73 (bs, 1H), 1.07 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ 135.66, 135.62, 133.63, 133.29, 129.86, 129.83, 127.77, 127.72, 88.7, 84.9, 77.9, 74.4, 70.1, 62.5, 49.2, 26.8, 19.1 ppm.

IR (ATR) ν_{max} (cm^{-1}): 3437, 1111, 1076, 702. HRMS (ESI): calcd for $C_{23}H_{30}O_4SiNa$ [M + Na]$^+$ 421.1806, found 421.1786.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01179.

Copies of ^{1}H and ^{13}C NMR spectra, additional experimental procedures, and details about determination of regio- and diastereoselectivity (PDF)

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Notes

The authors declare no competing financial interest.

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