Synthesis of chiral enantioenriched tetrahydrofuran derivatives

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Abstract
A simple and short synthetic pathway to novel chiral enantioenriched 2,2-disubstituted tetrahydrofuran derivatives, starting from enantiomeric lactone acids in 2 steps was developed in 36-54% overall yield. The method enables also to obtain enantioenriched 2,3'-spiro ditetrahydrofuran (1,7-dioxaspiro[4.4]nonane) starting from the spirodilactone (*R*-1,7-dioxaspiro[4.4]nonane-2,6-dione).

Keywords: Asymmetric oxidation, chiral tetrahydrofuran derivatives, reduction, 1,7-dioxaspiro[4.4]nonane

Introduction

The tetrahydrofuran structural elements are an essential part in many naturally occurring compounds, like communiols,[1] acetogenins,[2,3] polycyclic ethers,[4,5,6] lignans[7] etc. Derivatives of 2,2-disubstituted tetrahydrofurans have elicited attention as antitumor agents[8] and potent VLA-4 antagonists,[9,10] which could be useful in the treatment of various VLA-4 dependent inflammatory diseases such as asthma, multiple sclerosis and arthritis. 1,7-Dioxaspiro[4.4]nonane (spiro-ditetrahydrofuran) skeleton exists in the naturally occurring prehispanolones,[11] leopersins,[12] syringolides.[13] Also, this structural element is an essential part in synthetic spironucleosides[14] and fructose derived molecular scaffolds.[15]

Although, there exist many diastereoselective[16-19] and enantiospecific[16,20] methods for synthesizing differently substituted tetrahydrofurans, only a few methods exist to obtain chiral 2,2-disubstituted tetrahydrofuran derivatives.[21-24] Also, the synthesis of the spiro tetrahydrofuran skeleton, has been realized by many different routes,[5,25-27] however, only in a few cases has an asymmetric method been used to accomplish this goal.

In recent years our group has developed a simple and enantioselective method for synthesizing chiral lactone carboxylic acids (Scheme 1).[28,29] This approach has been applied in the synthesis of 2-alkyl-substituted 2-hydroxyglutaric acid γ-lactones[30] homocitric acid[31], and nucleoside analogues.[32,33] The easy access and wide possible structural variability of that chiral building block **2** motivated us to broaden the practical scope of the compounds - to use the lactone carboxylic acids for the synthesis of chiral tetrahydrofuran derivatives. In this paper, we report a convenient method for obtaining several novel chiral tetrahydrofurans **3** and **7** from the corresponding lactone acids **2** and spiro ditetrahydrofuran from spirodilactone **2g**.
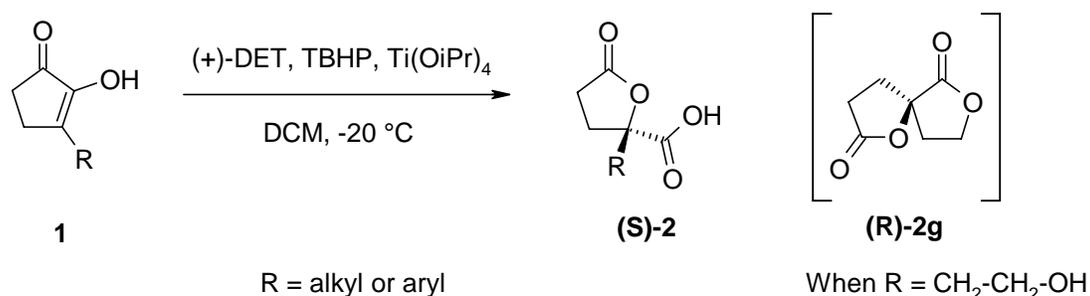
Scheme 1. Asymmetric synthesis of chiral lactone carboxylic acids.

Results and Discussion

To transform the lactone acid skeleton to the tetrahydrofuran ring we made an attempt to use a direct reduction approach proposed by Verma *et al.*[34] for triarylsubstituted dihydrofuranones with neat $BH_3 \cdot Me_2S$ (11 eq). However, with methylsubstituted lactone **2a** this single step procedure at room temperature gave us a two component mixture – hydroxymethyl tetrahydrofuran alcohol **3a** and triol **4a** with 77% combined isolated yield in a 1:1 ratio (Scheme 2). Also, with benzyloxyethyl lactone acid **2e** the reaction was not selective, resulting in tetrahydrofuran alcohol **3e** and triol **4e** with 90% overall isolated yield, in a 1:1.4 ratio. Using different borane complexes as reductive agents e.g. $BH_3 \cdot NH_3$, $BH_3 \cdot THF$, $BH_3 \cdot Me_2S/BF_3 \cdot Et_2O$ did not afford ether **3a** from **2a**.

Scheme 2. Direct reduction of carboxylic acids.

To improve the yield of the target tetrahydrofuran derivatives, we applied a two step sequence involving the reduction of lactone carboxylic acid **2** in the first step and reduction of the formed lactone alcohol **5** to the ether alcohol **3** in the second step. For the reduction of the free carboxylic group we used a protocol proposed by Ravid *et al.*[35] For compounds **2a-e** the isolated yields of the resulted lactone alcohols **5a-e** were in a range of 68-77% (Scheme 3, Table 1).

R = a) and f) -CH$_3$, b) -C$_2$H$_5$, c) -Bn, d) -CH$_2$OBn, e) -C$_2$H$_4$OBn
R' = a-b) -Bn, f) -TBDMS

Scheme 3. Synthetic routes to chiral THF-derivatives.

Table 1. Synthesis of tetrahydrofuran derivatives

Entry	Substrate	5	3	7†
1	**2a**	74%		
2	**2b**	73%		
3	**2c**	71%		
4	**2d**	68%		
5	**2e**	77%		
6	**5a**			48%
7	**5b**			57%
8	**5c**		75%	
9	**5d**		64%	
10	**5e**		70%	

†The yields over two steps (protection and reduction).

There are several options to transform the lactones into cyclic ethers, e.g. $NaBH_4/BF_3 \cdot Et_2O$,[36] $DIBALH/Et_3SiH/BF_3 \cdot Et_2O$,[37] manganese acetyl complexes/$PhSiH_3$,[38] titanocene complexes/ $PMHS/Et_3SiH/Amberlyst$ 15,[39] and $TiCl_4/TMSOTf/Et_3SiH$,[40] ruthenium complexes/ $EtMe_2SiH$.[41] The most promising, according to us, is a method, described by Kraus *et al*.[37] where DIBALH at −78ºC with Et_3SiH and $BF_3 \cdot Et_2O$ in DCM is used.

The latter conditions were applied to the starting material **5a**, affording in the first attempt a low yield – <20% according to GC analysis. The reason may be a low boiling point of the formed product which makes separation of the compound from the reaction mixture complicated when small quantities of starting material (100 mg) are used. Therefore, we protected the hydroxyl group in **5a** with a TBDMS protecting group (87-93% yield) and reduced the protected alcohol with $DIBALH/Et_3SiH/BF_3 \cdot Et_2O$ at -78 ºC in DCM. The reduction proceeds smoothly, however, under the reaction conditions some cleavage of the TBDMS group occurred in the silane reduction step, giving rise to a mixture of the expected TBDMS ether **7f** together with free alcohol **3a** with 77% combined yield[47] (Scheme 3).

To avoid undesired deprotection of the starting material, we turned to the more stable benzyl protecting group. So, starting materials **5a** and **5b** were protected with benzyl bromide in the presence of an equimolar amount of NaH in DMF in 62% and 73% yield respectively and were then subjected to reduction with $DIBALH/Et_3SiH/BF_3 \cdot Et_2O$ at -78 ºC in DCM (Scheme 3). As a result, the target tetrahydrofuran derivatives **7a** and **7b** were obtained with 77% and 78% yield. The overall yield starting from lactone alcohols **5a** and **5b** were 48% and 57% respectively.

The protection/deprotection steps are often complicating the synthetic technologies. Therefore, starting materials **5c-e** with an unprotected hydroxyl group were subjected to DIBALH and then $Et_3SiH/BF_3 \cdot Et_2O$ reduction (Scheme 3). The obtained yield of the reduction step was somewhat lower than in the case of the protected compounds. During the direct Lewis acid promoted silane reduction of **5** intermolecular acetalization of the product **3** with the starting

compound **5** was observed, leading to byproducts **8c-e** in 7-10% yield. This reaction transforms some amount of the starting material to an unreactive acetal and so, diminishes the yield. The byproduct itself is easily separable from the target product by simple chromatography. However, the yields of the target tetrahydrofuran derivatives **3c-e** were higher (64–75%) than the overall yield of compounds **7a** and **7b** with the corresponding protection steps (48% and 57%) (Table 1). Unmasking to obtain **3a** and **3b** would additionally decrease the yield of the whole reaction sequence. So, for the synthesis of compounds **3** the protection-free approach is favourable.

THF derivative **3d** is a key intermediate for the synthesis of the bioactive compound (S)-SRI-62-834 **14** (Scheme 4), an antitumor agent[8], that has been obtained previously by a multistep sequence that includes enzymatic resolution of the acetylated tetrahydrofuran-2,2-methanol.[24]
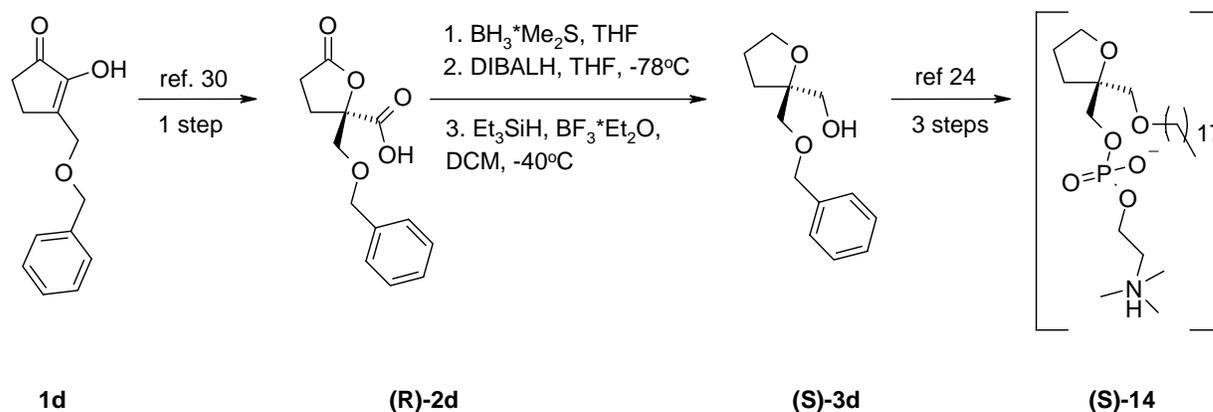
Scheme 4. Formal synthesis of (S)-SRI-62-834 14.

Spirodilactone **2g** was obtained from substituted lactone **2f** by simple lactonisation.[42] We made an attempt to apply the above described methodology to the reduction of spirodilactone **2g** in order to obtain spiro tetrahydrofuran compound **3g**. Thus, we pursued the reduction of **2g** with DIBALH and obtained a mixture of diastereomeric acetal **9** and hemiacetal diols **10** and **11** as determined by NMR analysis of the crude product (Scheme 5).[43] These results lead us to search more suitable methods for reducing spirodilactone **2g**. A similar over reduction problem was also observed in the synthesis of conformationally restricted spirocyclic nucleosides by Paquette *et al.*[44] and they solved the problem by using a low DIBALH concentration in the presence of an excess of Lewis acid (4.5 eq Me₃SiCl). We applied that method to spirodilactone **2g** and obtained lactol **9** together with bicyclic acetal **12** as a single diastereomer (up to 45% yield; Scheme 5).
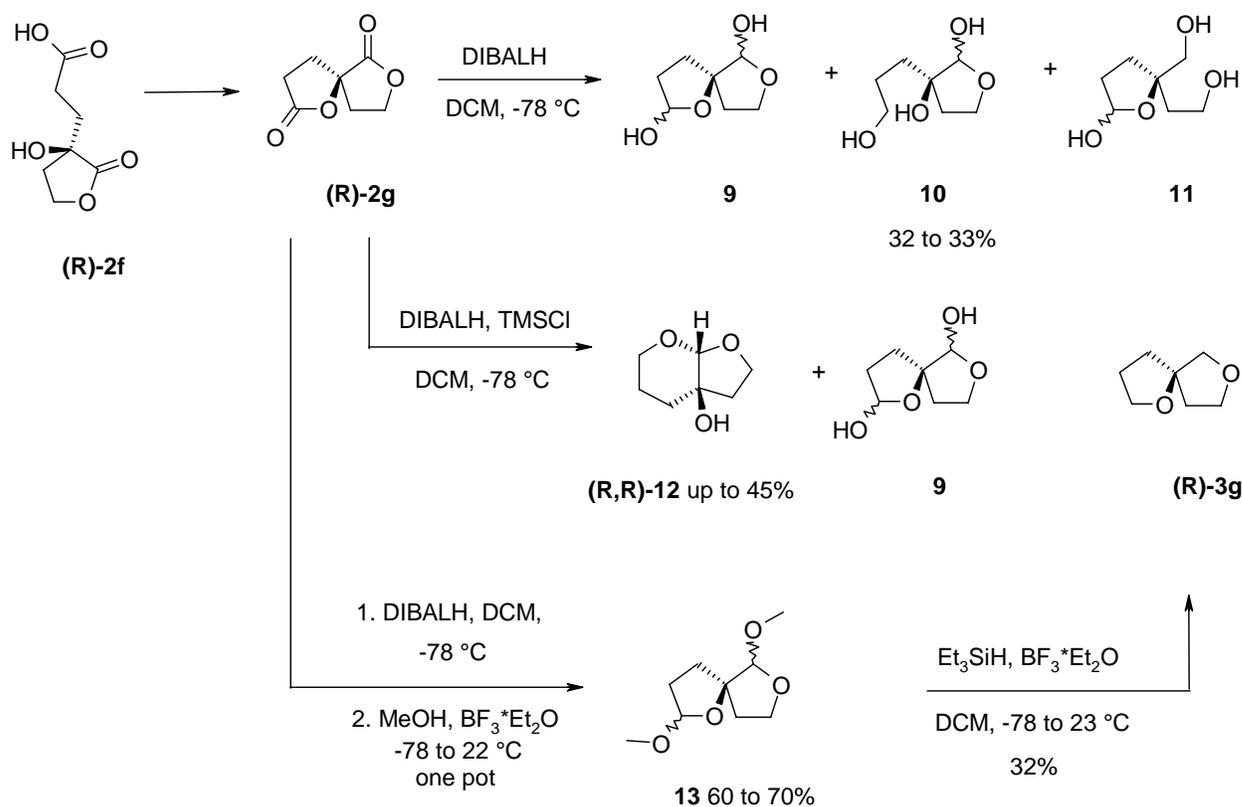
Scheme 5. Synthesis of spirodiether.

Separation of the lactols from the reaction mixture after hydrolysis (containing Al(OH)$_3$) appeared to be complicated. In order to improve the yield of acetal **9** (to extract it from the aluminium hydroxide) we used an in situ trapping of the formed lactols as methylacetals **13** by quenching the DIBALH reaction with an excess of dry MeOH in the presence of 1 equiv of BF$_3$·Et$_2$O. This method afforded stable yields of **13** (~70%). This compound was used in the following step without purification. Silane reduction[45,46] of **13** proceeded smoothly (with a modification of the original protocol: a stoichiometric amount of BF$_3$·Et$_2$O was used at -45 ºC to rt instead of a catalytic amount at rt) to furnish the volatile spiro tetrahydrofuran **3g** exclusively in 32% isolated yield after purification (the product partly co-evaporated during solvent removal) (Scheme 5).

In conclusion a short and convenient method for the synthesis of different 2,2-substituted chiral tetrahydrofuran derivatives was developed. The two step sequence gave better overall yield than the direct reduction of the chiral carboxylic acid – 54% and 37% respectively. In the case of starting material **2g**, the conversion of the hemiacetal **9** to the methyl acetal **13** contributes to the extraction of the latter from the reaction mixture and improves the yield of the reduction step. Subsequent silane reduction gave cleanly the desired compound **3g** with 32% yield.

Experimental Section

General. Chemicals were purchased from Aldrich Chemical Co or Alfa Aesar and were used as received. DCM and DMF were distilled over CaH_2 and stored on the 3Å molecular sieve pellets. THF and ether were distilled over $LiAlH_4$. Precoated silica gel 60 F254 plates from Merck were used for TLC, whereas for column chromatography silica gel KSK40-100 μm was used. NMR spectra were determined in $CDCl_3$ on Bruker AMX-500 or Bruker Avance USLA 400 spectrometer. Solvent peaks were used as references. 2D FT methods were used for the analysis of synthesized compounds. IR spectra were measured on a Perkin-Elmer Spectrum BX FTIR spectrometer. Mass spectra were recorded on a Hitachi M80B spectrometer using EI (70eV) or a Shimadzu GCMSQP2010 spectrometer using EI (70eV). Optical rotations were obtained using a Krüss Optronic GmbH Polarimeter P 3002. Elemental analyses were performed on a PerkinElmer C, H, N, S-Analyzer 2400. All reactions sensitive to the moisture or oxygen were carried out under Ar atmosphere in oven-dried glassware. Chiral acids **2a-e** were synthesized according to previously published methods and each exhibited physical and spectroscopic properties in accordance with data given in literature.[34,36]

Direct reduction of carboxylic acids 2a and 2e. To the carboxylic acid (1.5 mmol) at -30 °C was added neat 10M $BH_3 \cdot Me_2S$ (1.5 mL, 15 mmol) dropwise and the resulting mixture was stirred at 22 °C for 17 h. Then dry MeOH (3.0 mL) was added dropwise at -20 °C. After stirring at 22 °C for 1 h the volatiles were removed and the residue was purified by flash chromatography (petroleum ether/acetone 10:1 to 2:1) to give cyclic ether alcohol along with triol. Tetrahydrofuran **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 3.1, 3H, CH_3), 1.62 (ddd, J = 11.2, 10.0, 6.0, 1H, H-3), 1.82– 2.01 (m, 3H, H-3 and H-4), 3.42 – 3.46 (m, 2H, CH_2O), 3.77 – 3.90 (m, 2H, H-5), ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.33 (CH_3), 26.47 (C-4), 33.48 (C-3), 68.07 (C-5), 68.53 (CH_2O), 82.95 (C-2); triol **4a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 3H, CH_3), 1.52 – 1.48 (m, 1H, H-4), 1.54 (dt, J = 7.0, 2.1, 1H, H-4), 1.69 – 1.57 (m, 2H, H-3), 3.38 – 3.35 (m, 2H, H-5), 3.59 – 3.53 (m, 2H, H-1), 4.90 (s, 3H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.89 (CH_3), 27.86 (C-4), 35.88 (C-3), 63.71 (C-5), 70.46 (C-1), 73.56 (C-2). Tetrahydrofuran **3e**: see below. Triol **4e**: ^{1}H NMR (500 MHz, DMSO-D_6) δ 1.35 (m, 2H, H-3), 1.44 (m, 2H, H-4), 3.19 (d, 2H, H-1), 3.35 (m, 2H, H-5), 3.54 (t, 2H, CH_2O), 4.03 (s, 1H, OH-2), 4.38 (s, 1H, OH-5), 4.43 (s, 2H, Bn CH_2), 4.46 (s, 1H, OH-1), 7.31 (m, 5H, Bn *p, o, m*); ^{13}C NMR (DMSO-D_6) δ 26.50 (C-4), 33.38 (C-3), 36.14 (C-1'), 61.65 (C-5), 66.23 (C-2'), 66.76 (C-1), 71.95 (Bn CH_2), 72.43 (C-2), 127.28 (Bn *p*), 127.39 (Bn *o*), 128.20 (Bn *m*), 138.72 (Bn *i*).

General method for synthesis of lactone alcohols 5a-e. 2-(*S*)-lactone carboxylic acid **2a** (3 g, 20.8 mmol) was dissolved in dry THF (15 mL) and cooled on ice bath to 4 °C after which, $BH_3 \cdot Me_2S$ (2.37 mL, 24.0 mmol) was added dropwise over period of 20 min. The resulting mixture was stirred at 23 °C for 1.5 h to 2.0 h (endpoint was confirmed by TLC). Then MeOH (1.25 mL) was carefully added to destroy borane complex. The solvents were removed *in vacuo*, then MeOH (1.25 mL) was added and the volatiles were removed – the procedure was repeated

once to yield the crude product as light yellow viscous oil. Purification was achieved by flash chromatography (SiO$_2$, petroleum ether /EtOAc 3:1 to 1:1).

(*S*)-5-Hydroxymethyl-5-methyl-dihydro-furan-2-one 5a. The title compound was synthesized in 20.8 mmol scale and recrystallization from petroleum ether/Et$_2$O obtained as white solid (2.01 g, 15.5 mmol, 74%). [α]$_D$^{23}= +12.7 (*c* 3.47, AcOEt); ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.36 (s, 3H, CH$_3$), 1.92 (ddd, 1H, H-4), 2.36 (ddd, 1H, H-4), 2.58 (ddd, 1H, H-3), 2.69 (ddd, 1H, H-3), 2.73 (bs, 1H, OH) 3.51 (d, 1H, CH2-OH), 3.70 (d, 1H, CH2-OH); ^{13}C NMR (125 MHz, CDCl$_3$): δ 23.01 (CH$_3$), 29.54 (C-4), 29.57 (C-3), 68.31 (C-OH), 86.66 (C-5), 177.38 (C-2); IR (KBr) 3412, 2978, 2938, 1759, 1649, 1459, 1419, 1384, 1304, 1213, 1162, 1130, 1099, 1061, 1011, 945; MS (m/z): 131(M+1)$^+$, 115, 99 (base), 71, 56.

(*S*)-5-Ethyl-5-hydroxymethyldihydrofuran-2-one 5b. The title compound was synthesized in 0.7 mmol scale in good yield to obtain a colorless oil (73 mg, 73%), which solidified upon smearing with glass stick. [α]$_D$^{25}= +11.5 (*c* 3.29, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): δ 0.94 (t, *J*=2×7.5 Hz, 3H, CH$_3$), 1.69 (dt, *J*=3×7.5, 14.2, 1H, CH$_2$), 1.71 (dt, *J*=3×7.5, 14.2, 1H, CH$_2$), 1.98 (ddd, *J*=7.3, 10.7, 13.0 Hz, 1H, H-4), 2.26 (ddd, *J*=5.8, 10.8, 13.0 Hz, 1H, H-4), 2.55 (ddd, *J*=5.8, 10.7, 18.2 Hz, 1H, H-3), 2.70 (ddd, *J*=7.3, 10.8, 18.2 Hz, 1H, H-4), 3.01 (bs, 1H, OH), 3.54 (d, *J*=12.1 Hz, 1H, CH$_2$OH), 3.73 (d, *J*=12.1 Hz, 1H, CH$_2$OH); ^{13}C NMR (125 MHz, CDCl$_3$): δ 7.42 (Et CH$_3$), 26.87 (C-4), 28.97 (Et CH$_2$), 29.62 (C-3), 66.93 (*CH$_2$*OH), 89.39 (C-5), 177.90 (C-2); IR (KBr) 3433(OH), 2974, 2944, 2886, 1766(C=O), 1464, 1418, 1331, 1219, 1160, 1120, 1069, 976, 936; MS m/z: 145 (M+1)$^+$, 127, 113 (base), 98, 95, 71, 57, 55, 41; anal. calcd. for C$_7$H$_{12}$O$_3$: C, 58.32; H, 8.39. Found C, 57.95; H, 8.49.

(*R*)-5-Benzyl-5-hydroxymethyldihydrofuran-2-one 5c. The title compound was synthesized in 0.45 mmol scale to yield the title compound as white solid (67 mg, 0.33 mmol, 71%). [α]$_D$^{23}= +56.6 (*c* 6.58, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.96 (m, 1H, H-3), 2.07 (m, 1H, H-4), 2.21 (ddd, *J*=7.2, 10.4, 12.5 Hz, 1H, H-4), 2.45 (ddd, *J*=5.1, 10.4, 17.5 Hz, 1H, H-3), 2.85 (d, *J*=14.0 Hz, 1H, Bn CH$_2$), 3.06 (d, *J*=14.0 Hz, 1H, Bn CH$_2$), 3.60 (d, *J*=12.1 Hz, 1H, CH$_2$OH), 3.76 (d, *J*=11.9 Hz, 1H, CH$_2$OH), 7.29 (m, 5H, Bn *m, p, o*); ^{13}C NMR (100 MHz, CDCl$_3$): δ 26.63 (C-4), 29.25 (C-3), 41.97 (Bn CH$_2$), 67.63 (CH$_2$OH), 88.19 (C-5), 127.21 (Bn *p*), 128.64 (Bn *m*), 130.43 (Bn *o*), 134.76 (Bn *i*), 177.15 (C-2); IR (film) 3434(OH), 2929, 1767(C=O), 1496, 1456, 1416, 1187, 1061, 942, 705; MS m/z: 206 (M)$^+$, 188, 175, 129, 115 (base), 91, 77, 65, 55, 41; HRMS calcd. for (M)$^+$ C$_{12}$H$_{14}$O$_3$: 206.0942; found: 206.0944.

(*S*)-5-Benzyloxymethyl-5-hydroxymethyldihydro-furan-2-one 5d. The title compound wa synthesized in 0.46 mmol scale to yield the title compound as light yellow liquid (74 mg, 0.31 mmol, 68%). [α]$_D$^{23}= +8.1 (*c* 3.29, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.14 (m, 2H, H-4), 2.61 (m, 2H, H-3), 3.55 (dd, *J*=10.2, 21.9 Hz, 2H, CH$_2$O), 3.70 (dd, *J*=12.0, 53.0 Hz, 2H, CH$_2$OH), 4.53 (s, 2H, Bn CH$_2$), 7.31 (m, 5H, Bn *m, p, o*); ^{13}C NMR (100 MHz, CDCl$_3$): δ 25.82 (C-4), 29.31 (C-3), 65.62 (CH$_2$OH), 72.55 (CH$_2$O), 73.84 (Bn CH$_2$O), 87.67 (C-5), 127.74 (Bn *o*), 128.01 (Bn *p*), 128.62 (Bn *m*), 137.63 (Bn *i*), 177.47 (C-2); IR (neat) 3020, 2400, 1773, 1216, 752, 669; MS m/z: 205 (M-31)$^+$, 130, 115, 91, 55, 41; HRMS calcd. for (M-106)$^+$ C$_6$H$_{10}$O$_3$: 130.0630, found: 130.0635.

(R)-5-Benzyloxyethyl-5-hydroxymethyl-dihydrofuran-2-one 5e. The tilte compound was synthesized in 0.18 mmol scale yielded title compound as light yellow syrup (35 mg, 0.14 mmol, 77%). $[\alpha]_D^{24}$= -7.0 (*c* 7.63, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 2.01 (m, 2H, Et CH$_2$), 2.06 (m, 1H, H-4), 2.27 (m, 1H, H-4), 2.56 (m, 2H, H-3), 3.58 (m, 2H, Et CH$_2$O), 3.60 (s, 2H, C*H*$_2$OH), 3,65 (m, 1H, Et CH$_2$O), 4.48 (s, Bn CH$_2$O), 7.30 (m, 5H, Bn); ^{13}C NMR (100 MHz, CDCl$_3$): δ 28.97 (C-3), 29.03 (C-4), 36.91 (Et CH$_2$), 65.77 (Et CH$_2$O), 66.85 (CH$_2$OH), 73.73 (Bn CH$_2$O), 87.63 (C-5), 128.03 (Bn *o*), 128.19 (Bn *p*), 128.77 (Bn *m*), 137.63 (Bn *i*), 177.06 (C-2); IR (neat) 3444, 2928, 2871, 1769, 1208, 1097; MS m/z: 219 (M-31)$^+$, 172, 159 (M-91), 126, 107, 91 (Base), 79, 65, 44; HRMS: calcd. for (M-91)$^+$ C$_7$H$_{11}$O$_4$: 159.0656; found: 159.0653.

Benzylation of 5a and 5b. To the lactone **5a** (100 mg, 0.77 mmol) dissolved in dry DMF (1.5 mL), sodium hydride (27 mg, 1.15 mmol) and BnBr (165 uL, 1.39 mmol) were added at 0 °C. The resulting solution was stirred at 23 °C for 48 h, after which water (0.5 mL) was added dropwise on ice bath to quench the reaction. Then DCM (2.5 mL) was added and the layers separated. Water phase was extracted with DCM (2×2.5 mL) and the organics washed with brine (1.0 mL), then dried over MgSO$_4$, filtered and concentrated to yield crude product, which was purified by flash chromatography (SiO$_2$, petroleum ether /EtOAc 3:1 to 1:1) giving compound (105 mg, 62%) as a colorless oil.

(*S*)-5-Benzyloxymethyl-5-methyldihydrofuran-2-one 6a. Synthesis in 0.77 mmol scale gave the title compound (105 mg, 62%) as a colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.39 (s, 3H, CH$_3$), 1.94 (ddd, *J*=8.4, 10.3, 12.8 Hz, 1H, H-4), 2.35 (ddd, *J*=4.8, 10.4, 12.8 Hz, 1H, H-4), 2.54 (ddd, *J*=4.8, 10.4, 17.9 Hz, 1H, H-3), 2.74 (ddd, *J*=8.4, 10.4, 17.9 Hz, 1H, H-3), 3.44 (d, *J*=10.1 Hz, 1H, CH$_2$O), 3.52 (d, *J*=10.1 Hz, 1H, CH$_2$O), 4.53 (d, *J*=12.1 Hz, 1H, Bn CH$_2$), 4.59 (d, *J*=12.1 Hz, 1H, Bn CH$_2$), 7.31 (m, 3H, *p*, *o*), 7.36 (m, 2H, *m*); ^{13}C NMR (125 MHz, CDCl$_3$): δ 23.74 (CH$_3$), 29.68 (C-3), 30.73 (C-4), 73.52 (Bn CH$_2$), 75.82 (*C*H$_2$O), 85.30 (C-5), 127.48 (o-Bn), 127.73 (*p*-Bn), 128.41 (*m*-Bn), 137.68 (*i*-Bn), 177.13 (C-2); IR (neat) 4060, 3520, 3089, 3064, 3032, 2977, 2936, 2867, 1958, 1772, 1604, 1497, 1454, 1416, 1381, 1367,1286, 1231, 1212, 1158, 1099, 1028, 1011, 943; MS m/z: 220 (M)$^+$, 114, 99 (base), 91, 71, 65, 55, 43; anal. calcd. for C$_{13}$H$_{16}$O$_3$: C, 70.89; H, 7.32; found: C, 70.41; H, 7.29.

(*S*)-5-Benzyloxymethyl-5-ethyldihydrofuran-2-one 6b. Synthesis in 0.48 mmol scale gave benzyl ether (82 mg, 0.35 mmol, 73%) as colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.89 (t, *J*=7.5, 3H, CH$_3$), 1.66 (m, 2H, CH$_2$), 1.93 (ddd, *J*=8.5, 10.6, 12.9, 1H, H-4), 2.20 (ddd, *J*=4.5, 10.6, 12.9, 1H, H-4), 2.44 (ddd, *J*=4.5, 10.6, 15.1, 1H, H-3), 2.67 (ddd, *J*=8.5, 10.6, 18., 1H, H-3), 3.46 (q, *J*=10.1, 2H, CH$_2$O), 4.50 (q, *J*=12.0, 2H, Bn CH$_2$), 7.27 (m, 5H, Bn *o*, *p*, *m*); ^{13}C NMR (100 MHz, CDCl$_3$): d 7.62 (5-CH$_3$), 28.37 (C-4), 29.78 (5-CH$_2$), 29.84 (C-3), 73.75 (5-CH$_2$O), 74.73 (Bn-CH$_2$), 87.98 (C-5), 127.65 (*o*), 127.87 (*p*), 128.58 (*m*), 137.93 (*i*), 177.50 (C-2); IR 3030, 2972, 2926, 1770, 1496, 1454, 1416, 1366, 1221, 1158, 1100, 940, 738, 699; MS m/z: 205 (M-29)$^+$, 179, 159, 143, 128, 113 (base), 107, 91, 71, 57; anal. calcd. for C$_{14}$H$_{18}$O$_3$: C, 71.77; H, 7.74; found: C, 72.16; H, 7.72.

General method for synthesis of tetrahydrofurans 7a-b and 3c-e. Lactone benzyl ether **6a** (0.27 mmol) was dissolved in DCM (1.0 mL) and cooled to -78 °C, then DIBALH was added

dropwise and the resulting solution stirred for 3 h. Reaction mixture was quenched with water (200 uL) and the temperature was allowed to reach 0 °C, then DCM (2.5 mL) was added. The resulting mixture was stirred at 22 °C for 1 h, filtered through Celite and the solids were washed with DCM (3×2.5 mL). TLC showed presence of one product. After removal of solvents, the residue was dissolved in DCM (1.0 mL) and Et_3SiH (70 uL, 0.41 mmol) was added. Then the reaction mixture was cooled to -45 °C and $BF_3 \cdot Et_2O$ (40 uL, 0.31 mmol) was added dropwise. After stirring for 3 h, the reaction was quenched with aq. $NaHCO_3$ solution (10%, 0.5 mL). The layers were separated and the water phase was extracted with DCM (3×2.5 mL). The combined organics were dried over $MgSO_4$ and concentrated to give crude product. Further purification was achieved by flash chromatography (petroleum ether /EtOAc 5:1 to 1:1).

(2S)-2-[(Benzyloxy)methyl]-2-methyltetrahydro-furan 7a Obtained as a colorless liquid (43 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, J=6.6, 3H, CH_3), 1.60 (m, 1H, H-1), 1.76 (m, 3H, H-1, H-5), 3.33 (dd, J=9.71, 2H, CH_2O), 3.84 (m, 2H, H-4), 4.56 (dd, 2H, J=12.35, 13.45, Bn CH_2O), 7.28 (m, 5H, Bn o, p, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.32 (CH_3), 26.37 (C-5), 34.63 (C-3), 68.19 (C-5), 73.62 (Bn CH_2), 76.53 (CH_2O), 82.40 (C-2), 127.61 (p-Bn), 127.68 (o-Bn), 128.48 (m-Bn), 138.84 (i-Bn); IR (neat) 3088, 3064, 3030, 2970, 2866, 1810, 1604, 1497, 1454, 1370, 1310, 1272, 1206, 1103, 1050, 736, 698, 606; MS (m/z): 206 (M)[+], 191, 175, 148, 135, 119, 107, 91, 85 (base), 77, 65, 43; anal. calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80; found: C, 75.56; H, 8.78.

(S)-5-Benzyloxymethyl-5-ethyltetrahydrofuran 7b. Synthesis in 0.26 mmol scale yielded the title compound as a colorless liquid (45 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (m, 3H, Et CH_3), 1.63 (m, 3H, H-3 and Et CH_2), 1.86 (m, 3H, H-3 and H-4), 3.33 (q, J=9.5, 2H, CH_2O), 3.82 (q, J=6.1, 2H, H-5), 4.55 (m, 2H, Bn CH_2), 7.27 (m, 5H, Bn o,p,m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.53 (Et CH_3), 26.53 (C-4), 29.73 (Et CH_2), 32.37 (C-3), 68.37 (C-5), 73.59 (Bn CH_2), 74.55 (CH_2O), 84.82 (C-2), 127.58 (p-Bn), 127.67 (o-Bn), 128.43 (m-Bn), 138.83 (i-Bn); IR (film): 3440, 3085, 3061, 3028, 2949, 2868, 1950, 1880, 1813, 1758, 1604, 1583, 1496, 1454, 1400, 1330, 1296, 1200, 1147, 1123, 1087, 1039, 957, 702; MS (m/z): 191 (M-29)[+], 161, 149, 114, 99 (base), 91, 57; anal. calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; found: C, 75.98; H, 9.21.

((R)-2-Benzyltetrahydrofuran-2-yl)-methanol 3c. Synthesis in 0.46 mmol scale yielded the title compound as a colorless liquid (66 mg, 75%).$[α]_D^{23}$= -1.5 (c 12.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (m, 2H, H-3, H-4), 1.83 (m, 2H, H-3, H-4), 2.13 (bs, 1H, OH), 2.80 (m, 2H, Bn CH_2), 3.49 (m, 2H, CH_2OH), 3.79 (m, 2H, H-5), 7.28 (m, 5H, Bn o, p, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.53 (C-4), 31.35 (C-3), 42.38 (Bn CH_2), 67.35 (CH_2OH), 68.63 (C-5), 85.69 (C-2), 126.47 (p-Bn), 128.39 (o-Bn), 130.75 (m-Bn), 137.82 (s-Bn); IR ($CHCl_3$): 3440, 3085, 3061, 3028, 2949, 2868, 1950, 1880, 1813, 1758, 1604, 1583, 1496, 1454, 1400, 1330, 1296, 1200, 1147, 1123, 1087, 1039, 957, 702; MS (m/z): 192 (M)[+], 161, 128, 115, 101 (base), 91, 83, 65; HRMS calcd. for (M)[+] $C_{12}H_{16}O_2$: 192.1149; found 192.1156; anal. calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; found: C, 74.72; H, 8.44.

((S)-2-Benzyloxymethyltetrahydrofuran-2-yl)-methanol 3d. Synthesis in 0.19 mmol scale yielded the title compound as a colorless liquid (23 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ

1.85 (m, 4H, H-3 and H-4), 2.10 (s, 1H, OH), 3.43 (dd, J=9.4, 39.4, 2H, CH_2O), 3.56 (dd, J=11.3, 37.0, 2H, CH_2OH), 3.84 (t, J=6.4, 2H, H-5), 4.54 (q, J=12.2, 2H, Bn CH_2O), 7.30 (m, 5H, Bn o, p, m); ^{13}C NMR (100 MHz, CDCl$_3$): δ 26.38 (C-4), 30.67 (C-3), 66.43 (C-5), 68.86 (CH$_2$OH), 73.43 (CH$_2$O), 73.80 (Bn CH$_2$O), 84.39 (C-2), 127.80 (o-Bn), 127.85 (p-Bn), 128.60 (m-Bn), 138.38 (s-Bn); IR (neat): 3439, 3089, 3064, 3031, 2927, 2868, 1497, 1454, 1406, 1365, 1208, 1096, 1056, 737, 699; MS (m/z): 222 (M)[+], 207, 191, 181, 161, 143, 131, 116, 101, 91, 83, 65, 55, 43; HRMS: calcd. for (M-31)[+] C$_{12}$H$_{15}$O$_2$: 191.1071; found: 191.1064.

{(2R)-2-[2-(Benzyloxy)-ethyl]-tetrahydrofuran-2-yl}-methanol 3e. Synthesis in 0.49 mmol scale yielded THF-derivative as a colorless liquid (76 mg, 70%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.74 (m, 1H, H-3), 1.89 (m, 5H, H-3, H-4, Et CH$_2$), 2.71 (bs, 1H, OH), 3.45 (m, 2H, CH$_2$OH), 3.57 (m, 1H, CH$_2$O), 3.65 (m, 1H, CH$_2$O), 3.82 (m, 2H, H-5), 4.51 (m, 2H, Bn CH$_2$), 7.32 (m, 5H, Bn o, p, m); ^{13}C NMR (100 MHz, CDCl$_3$): 26.11 (C-5), 33.15 (C-3), 36.86 (Et CH$_2$), 66.86 (Et CH$_2$O), 67.01 (C-5), 67.88 (CH$_2$OH), 73.33 (Bn CH$_2$), 84.35 (C-2), 127.65 (p-Bn), 127.76 (o-Bn), 128.46 (m-Bn), 137.91 (s-Bn); IR (neat): 3444, 3088, 3063, 3030, 2947, 2868, 1496, 1454, 1366, 1308, 1206, 1098, 1053, 926, 738, 698; MS (m/z): 205 (M-31)[+], 187, 169, 159, 143, 129, 113, 99, 91 (base), 81, 65; HRMS: calcd. for (M-31)[+] C$_{13}$H$_{17}$O$_2$: 205.1227; found: 205.1226; anal. calcd. for C$_{14}$H$_{20}$O$_3$: C, 71.16; H, 8.53; found: C, 70.89; H, 8.60.

(5R)-1,7-Dioxaspiro[4.4]nonane-2,6-dione 2g. Spirodilactone **2g** was synthesized with slight modification to previously reported method: To the solution of Ti(OiPr)$_4$ (7.1 mL, 23.2 mmol) and (+)-DET (5.0 mL, 29.0 mmol) in DCM (180 mL) at -20 °C 2-hydroxy-3-(2-hydroxyethyl)cyclopent-2-en-1-one (3.3 g, 23.2 mmol) was added carefully. After stirring for 0.5 h t-BuOOH (9.4 mL, 58.0 mmol) was added dropwise over 20 min. The resulting mixture was kept at -20 °C for 68 h. The reaction was quenched with water (145 mL), then the mixture was stirred for 1 h and 10N NaOH solution (29 mL) was added. After stirring for 1 h the layers were separated and water phase was treated with 5.5N HCl solution (110 mL), then the water phase was extracted with DCM (10×100 mL). The extracts were dried over MgSO$_4$, filtered and the solvents evaporated to give 3.37 g of crude as yellow crystals, which upon crystallization from EtOAc/Et$_2$O mixture (1:4) gave spirodilactone **2g** as white solids (2.75 g, 17.6 mmol, 75%), which physical and spectroscopic properties were in accordance with data given in literature[42].

(R)-1,7-dioxaspiro[4,4]nonane 3g. Spirodilactone **2g** (786 mg, 5.04 mmol) was dissolved in DCM (200 mL, solution was 0.025M in substrate, dried over 4Å MS, amylenes as stabilizers) under Ar atmosphere. Resulting solution was cooled to -78 ºC and then DIBALH (7.0 mL, 10.6 mmol, 1.5M in toluene) was added dropwise. After 2 h stirring, MeOH (40 mL, dried over 3Å MS) and BF$_3$·Et$_2$O (1.48 mL, 12.0 mmol) were added sequentially and the reaction mixture was kept at -78 ºC for 14 h and then stirred 2 h at 23 ºC. The reaction was quenched with aq NaHCO$_3$ (30 mL, 10%) at +4 ºC and agitated for 1 h, after which the layers were separated and the aqueous phase was extracted with DCM (6×50 mL). Organic phase was dried over MgSO$_4$, filtered and the solvents were evaporated to yield methylacetal **13** (565 mg, 3.0 mmol, 60%) as yellow viscous oil, which was used in the next synthetic step without further purification. The crude and Et$_3$SiH (2.9 mL, 18.0 mmol) were dissolved in DCM (60 mL, 0.05M in substrate),

then the resulting solution was cooled to -78 ºC and BF$_3$·Et$_2$O (750 uL, 6.01 mmol) was added. The thus obtained reaction mixture was stirred for 3 h at -78 ºC and then the temperature was slowly allowed to reach 23 ºC (4 h). The reaction was quenched by adding aq NaHCO$_3$ (5.0 mL, 10%). The layers were separated and the water phase was extracted with DCM (4×30 mL). The organics were dried over MgSO$_4$, filtered and the solvents evaporated. Purification of the crude by flash chromatography (SiO$_2$, petroleum ether /acetone, 20:1 to 16:1) gave the title compound (123 mg, 0.96 mmol, 32%) as light yellow oil. Caution! The volatility of title compound is of concern! $[\alpha]_D^{21}$= -2.4 (*c* 12.4, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.85 – 1.92 (m, 1H, H-9), 1.89 – 2.01 (m, 2H, H-3), 1.90 – 1.97 (m, 2H, H-4), 2.02 – 2.10 (m, 1H, H-9), 3.59 (d, *J*=9.1 Hz, 1H, H-6), 3.77 (d, *J*=9.1 Hz, 1H, H-6), 3.78 – 3.88 (m, 2H, H-2), 3.87 – 3.97 (m, 2H, H-8) and ^{13}C (100 MHz, CDCl$_3$): δ 25.97 (C-3), 33.29 (C-4), 38.51 (C-9), 67.37 (C-2), 67.99 (C-8), 76.90 (C-6), 89.16 (C-5); IR (CHCl$_3$): 2971, 2870, 1461, 1059, 911; MS(m/z): 128, 98, 83, 70, 56 (base), 42, 27; HRMS calcd. for (M)$^+$ C$_7$H$_{12}$O$_2$: 128.0836; found 128.0827.

(3a*R*,7a*R*)-Tetrahydro-4*H*-furo[2,3-*b*]pyran-3a(7a*H*)-ol 12. Spirodilactone **2g** (156 mg, 1.0 mmol) was dissolved in dry DCM (40 mL, 0.025M in substrate) under Ar atmosphere. Then, to the obtained solution TMSCl (1.70 mL, 9.0 mmol) was added and the mixture was cooled to -78 ºC after which DIBALH (1.15 mL, 2.5 mmol) was added dropwise. Reaction mixture was stirred at -78 °C for 2 h and carefully quenched with aq NaHCO$_3$ (10%, 0.46 mL) and the temperature rised slowly to 23 ºC. Na$_2$SO$_4$ (2.28 g) was added and the stirring was continued for further 2 h. The solids were filtered off and washed with EtOAc (3×10 mL). Combined organics were concentrated and purified by flash chromatography (SiO$_2$, PE/acetone 10:1 to 3:1) to yield title compound as clear liquid (65 mg, 0.45 mmol, 45%). $[\alpha]_D^{21}$= -7.8 (*c* 9.1, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.56 (m, 1H, H-4e), 1.64 (m, 1H, H-4a), 1.71 (m, 1H, H-7), 1.76 (m, 1H, H-5a), 2.13 (m, 1H, H-5e), 2.24 (m, 1H, H-7), 2.86 (bs, 1H, OH), 3.39 (m, 1H, H-3a), 3.83 (m, 1H, H-3e), 4.10 (m, 2H, H-8), 4.61 (s, 1H, H-1) and ^{13}C NMR (100 MHz, CDCl$_3$): 23.02 (C-4), 31.61 (C-5), 33.04 (C-7), 64.29 (C-3), 67.21 (C-8), 77.15 (C-6), 105.03 (C-1); IR (neat): 3428, 2948, 2899, 2862, 1447, 1252, 1213, 1128, 1100, 1070, 1034, 991, 966, 932, 726, 601, 588; MS (m/z): 144 (M)$^+$, 126, 116, 98, 97, 70 (base), 56; HRMS: calcd. for (M)$^+$ C$_7$H$_{12}$O$_3$: 144.0785; found: 144.0783.

Acknowledgements

References and Notes

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47. According to Kraus' work (see ref 37) the TBDMS group should be stable under the reaction conditions described.