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Preparation and stereoselective hydrogenation of chiral (4-hydroxy-tetrafuranylidene)carboxylates: a new formal entry to functional *anti*- and *syn*-3,5-dihydroxyesters

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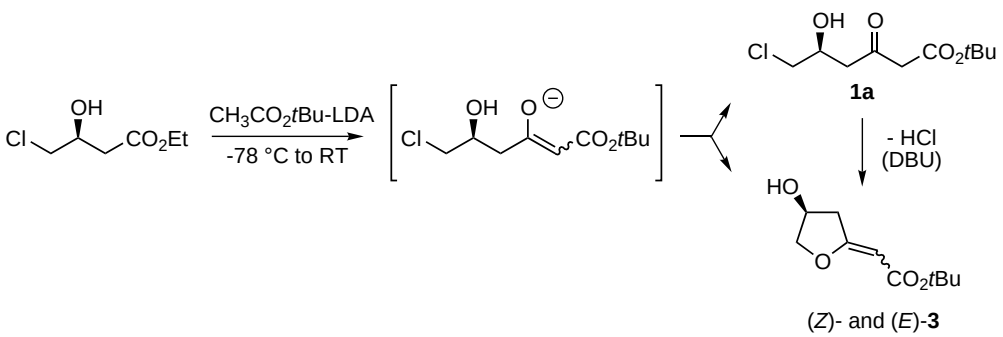
Abstract—New *tert*-butyl (*Z*)- and (*E*)-((*S*)-4-hydroxy-tetrafuranylidene)carboxylates have been prepared from (*S*)-4-chloro-3-hydroxybutyrate and AcO*t*Bu-LDA enolate, and hydrogenated with various achiral and chiral catalysts to give the (2*S*,4*S*)- and (2*R*,4*S*)-diastereomers of (4-hydroxy-tetrahydrofuranyl)acetates in up to 93% de and 83% yield, and 80% de and 31% yield, respectively.

Chiral 6-halogeno-3,5-dihydroxyhexanoates (**2**) are advanced building blocks in the synthesis of natural and biologically active products, in particular for the preparation of mevinic type HMG-CoA reductase inhibitors of industrial interest.[1] We have recently reported a catalytic preparation of optically active functional diols **2** by transfer hydrogenation of 2-propanol to optically pure 5-hydroxy-3-oxohexanoates (**1**), that provides an attractive alternative to traditional borane reagents.[2] This process proved, however, inefficient for the reduction of *tert*-butyl 6-chloro-5-hydroxy-3-oxohexanoate (**1a**) because the chloro function of this aldol inhibits the catalytically active ruthenium species.[2] During the preparation of (*S*)-**1a** from ethyl (*S*)-4-chloro-3-hydroxybutyrate and AcO*t*Bu-LDA enolate,[1] we observed the formation of significant amounts of two side-products (Scheme 1). The latter were isolated by column chromatography in 17 and 15% yields and formally identified, on the basis of NMR and MS data, as the (*Z*)- and (*E*)-stereoisomers of *tert*-butyl ((*S*)-4-



Scheme 1.

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hydroxy-tetrafuranylidene)carboxylate (**3**), respectively.† The structure of the (*Z*)-stereoisomer was confirmed from an X-ray diffraction study (Fig. 1). Among the variety of (tetrahydrofuranylidene)carboxylate derivatives which are known,[3–11] compounds with an heterosubstituent at the 4-position of the furane ring only a few have been documented.[11] The formation of (*Z*)- and (*E*)-**3** most likely involves intramolecular substitution of the chloro atom by the enolate anion of aldol (*S*)-**1a** as outlined in Scheme 1.[8–11] Accordingly, treatment of pure (*S*)-**1a**† with 2 equiv. of DBU in THF[11] afforded **3** in 62% yield (*Z*:*E*=21/79), raising to 63% the overall isolated yield in **3** (based on (*S*)-4-chloro-3-hydroxybutyrate).

We gained interest in compounds (*Z*)- and (*E*)-**3** because, upon chemo- and stereoselective hydrogenation to the corresponding 4-hydroxy-tetrahydrofuranylacetates **4**,[12] the furane ring of the latter can be easily and regioselectively cleaved with organoboron bromide reagents such as Me_2BBr to give the valuable corresponding chiral 6-bromo-3,5-dihydroxyhexanoates (**2a**) (Scheme 2).[13–15] Therefore, we investigated the hydrogenation of both isomers of **3** and paid special attention first to simple achiral catalysts since the presence of a chiral center in the substrate may allow for a diastereoselective process.

As shown in Scheme 2 and Table 1, the hydrogenation of **3** did not prove necessarily chemoselective for the expected product **4**. Upon using particular reaction conditions and/or catalysts, significant amounts of side products formed, of which three were regularly observed and could be unambiguously identified. Thus, *tert*-butyl 2-(tetrahydrofuranyl)acetate (**5**) may arise either from the direct hydrogenolysis of the C–OH bond in **3** followed by hydrogenation of the *exo* C=C bond or from dehydration of **3** and subsequent hydrogenation. In the absence of identified intermediates, hydrogenolysis appears as the most likely route for the formation of **5** considering that: (i) heterogeneous catalysts, traditionally associated to hydrogenolysis pro-

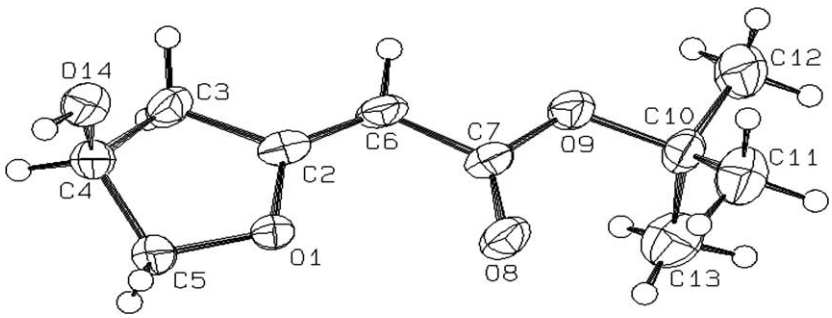
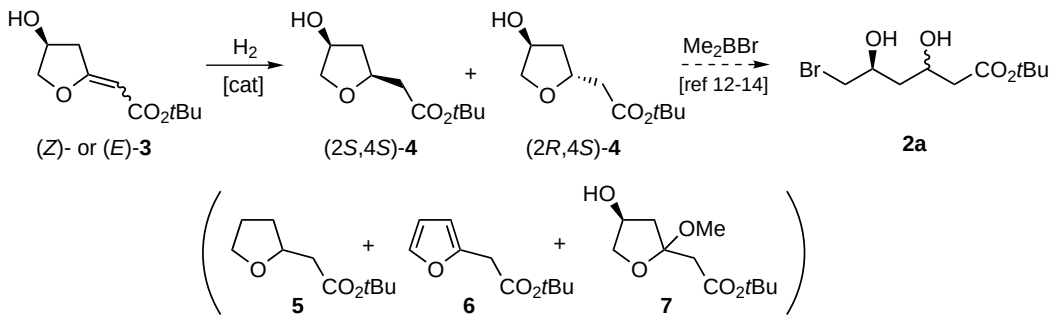


Figure 1. Crystal structure of (*Z*,4*S*)-**3** (ORTEP drawn at 50% probability).



Scheme 2.

† To a stirred solution of iPr$_2$NH (7.07 g, 70 mmol) in THF (100 mL) kept at −78°C were added dropwise, under N_2, *n*-BuLi (36 mL of a 1.66 M solution in hexanes, 60 mmol) and a solution of AcO*t*Bu (6.97 g, 60 mmol) in THF (10 mL). After 10 min, a solution of ethyl (*S*)-4-chloro-3-hydroxybutyrate (3.33 g, 20 mmol, 99% ee) in THF (10 mL) was added and the reaction mixture was stirred for 1.5 h at −50°C and 15 min at −15°C. Ice water (100 mL) was added and the mixture was extracted with Et_2O (2×50 mL). Organic layers were washed with a saturated $NaHCO_3$ solution, then with water, dried over Na_2SO_4 and volatiles were removed in vacuo. The oily residue was chromatographed over silica (AcOEt/heptane, 3:2) to give pure **1a** as a pale yellow oil (2.40 g, 50%; R_f=0.54), (*E*)-**3** as a colorless oil (0.60 g, 15%; R_f=0.29) and (*Z*)-**3** as colorless crystals (0.68 g, 17%; soluble in pure AcOEt). Full assignment of NMR resonances was made on the basis of ^{1}H,^{1}H-COSY and ^{13}C,^{1}H-HETCOR experiments; (*E*)-**3**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.25 (s, 1H, C*H*=C), 4.56 (m, 1H, C*H*OH), 4.18 (d, 1H, ^2J=10.1 Hz, CH*H*O), 4.11 (dd, 1H, ^2J=10.1, ^3J=3.7, C*H*HO), 3.31 (dd, 1H, ^2J=18.6, ^3J=1.0, CH*H*-C=CH), 2.94 (ddd, 1H, ^2J=18.7, ^3J=5.6, ^4J=2.2, C*H*H-C=CH), 1.42 (s, 9H, *t*Bu); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.9 (CH=*C*), 168.1 (CO_2), 92.4 (*C*H=C), 79.1 (*C*Me$_3$), 78.1 (*C*H$_2$O), 68.9 (*C*HOH), 39.7 (*C*H$_2$C=CH), 28.1 (C*Me*$_3$). MS (EI) m/z (%): 200 (M^+, 7), 169 (6), 144 (42), 127 (100), 109 (27), 84 (65), 69 (23), 57 (65). $[\alpha]_D^{25}$ (c=1, $CHCl_3$)=−25. HRMS, calcd for $C_{10}H_{17}O_4$: 201.1127, found: 201.1128. (*Z*)-**3**: ^{1}H NMR ($CDCl_3$): δ 4.87 (s, 1H, C*H*=C), 4.51 (m, 1H, C*H*OH), 4.43 (d, 1H, ^2J=10.2, CH*H*O), 4.36 (dd, 1H, ^2J=10.2, ^3J=3.6, C*H*HO), 2.86 (dd, 1H, ^2J=17.1, ^3J=5.1, ^4J=1.7, CH*H*-C=CH), 2.67 (d, 1H, ^2J=17.5, C*H*H-C=CH), 2.63 (s br, 1H, CHO*H*), 1.46 (s, 9H, *t*Bu); ^{13}C NMR ($CDCl_3$): δ 170.3 (CH=*C*), 165.9 (CO_2), 91.0 (*C*H=C), 80.9 (*C*H$_2$O), 79.3 (*C*Me$_3$), 68.2 (*C*HOH), 41.1 (*C*H$_2$C=CH), 28.3 (C*Me*$_3$). $[\alpha]_D^{25}$ (c=0.7, $CHCl_3$)=−27. MS identical to (*E*)-**3**; HRMS, calcd for $C_{10}H_{17}O_4$: 201.1127, found: 201.1128. Full details for the X-ray crystal structure determination of (*Z*)-**3** have been deposited with the Cambridge Crystallographic Data Centre with the number CCDC 175686.

cesses, lead to much larger amounts of **5** than homogeneous systems do (entries 2 and 11); (ii) the formation of *tert*-butyl (2-furanyl)acetate (**6**), selectively obtained with $RuCl_2(PPh_3)_3$ as the catalyst precursor and CH_2Cl_2 as the solvent (entries 17 and 18), suggests that once dehydration of **3** has occurred, isomerization of the intermediate to **6** proceeds faster than hydrogenation to **5**. Also, the use of an alcohol as solvent such as methanol induces the formation of the Michael addition product (**7**), a major pathway with Wilkinson catalyst $RhCl(PPh_3)_3$, even under smooth conditions (entries 1, 2 and 7).

Chemoselective hydrogenation of **3** to **4** appeared to be best conducted in THF (or toluene) with Ru, Rh and Pt catalysts. With all of the catalyst systems investigated, (*E*)-**3** turned much less reactive than its (*Z*) isomer (compare entries 1/2, 3/4, 12/13, 14/15); thus, as a consequence of slow isomerization between (*Z*)-**3** and (*E*)-**3** under the reaction conditions, hydrogenation required prolonged times to reach completion. 4-Hydroxy-tetrahydrofuranylacetates **4** were obtained in >80% GLC yields and reasonable times from (*Z*)-**3** using Rh/C, Pt/C and PtO_2. The latter catalyst provided with an enriched mixture of **4** in 77% de, from which the major diastereomer crystallized out.‡ The absolute configuration of the major diastereomer produced from these achiral catalysts was thus shown by X-ray crystallography (Fig. 2) to be (2*S*,4*S*)-**4**; i.e. the product leading to *anti*-diol **2** upon ring-opening with

Table 1. Hydrogenation of (*Z*)- and (*E*)-*tert*-butyl ((*S*)-4-hydroxy-tetrafuranylidene)carboxylate (**3**)[a]

Entry	Subst. **3**	Catalyst	Solvent	Temp. (°C)	Time[b] (h)	Conv. **3**[c] (%)	Yield **4**[c] (%)	De **4**[d] (%)	Others[c,e] (%)
1	(*Z*)	Pd/C 10%	MeOH	20	15	72	53	74	1 (**5**); 18 (**7**)
2	(*E*)	Pd/C 10%	MeOH	40	15	95	14	72	42 (**5**); 11 (**7**)
3	(*Z*)	Pd/C 10%	THF	20	15	42	36	69	3 (**5**)
4	(*E*)	Pd/C 10%	THF	20	43	15	6	58	3 (**5**)
5	(*Z*)	Rh/C 5%	THF	20	66	94	86	48	8 (**5**)
6	(*E*)	$RhCl(PPh_3)_3$	PhMe	40	68	49	49	4	–
7	(*E*)	$RhCl(PPh_3)_3$	MeOH	40	66	84	6	0	78 (**7**)
8	(*Z*)	$RhCl(PPh_3)_3$	THF	20	62	38	36	0	–
9[f]	(*Z*)	PtO_2	PhMe	40	18	89	80	30	–
10[f]	(*Z*)	PtO_2	THF	20	39	81	80 (72)	77	1 (**5**)
11[f]	(*Z*)	PtO_2	CH_2Cl_2	20	63	88	8	88	36 (**5**); 27 (**6**)
12	(*Z*)	Pt/C 10%	THF	20	48	94	94	61	–
13	(*E*)	Pt/C 10%	THF	20	43	20	11	80	2 (**5**)
14	(*Z*)	Ru/C 10%	THF	20	19	61	58	53	2 (**5**)
15	(*E*)	Ru/C 10%	THF	20	43	20	19	50	1 (**5**)
16	(*Z*)	RuO_2/C 10%	THF	20	19	26	22	72	2 (**5**)
17	(*Z*)	$RuCl_2(PPh_3)_3$	THF	50	41	84	5	50	4 (**5**); 72 (**6**)
18	(*Z*)	$RuCl_2(PPh_3)_3$	CH_2Cl_2	40	43	100	1	ns	1 (**5**); 97 (**6**)
19	(*Z*)	$RuCl_2$((*S*)-Binap)	THF	20	42	90	83 (71)	93	7 (**6**)
20	(*Z*)	$RuCl_2$((*R*)-Binap)	THF	20	46	34	31	–80	3 (**6**)

[a] Unless otherwise stated, reactions were carried out using 2 mol% of metal catalyst under 50 bar of H_2; see footnote ‡ for a typical procedure.
[b] Reaction time was not necessarily optimized.
[c] Conversion (mol%) of **3** and yields (mol%) in **4** (2*S*,4*S*+2*R*,4*S*), **5**–**7** as determined by quantitative GLC analysis; data in parentheses are isolated yields of **4** (2*S*,4*S*+2*R*,4*S*).
[d] Diastereomeric excess as determined by GLC and/or ^1H NMR of isolated **4**. The major diastereomer is 2*S*,4*S*, except in entry 20: 2*R*,4*S*.
[e] Two other products so far unidentified mainly account for the balance.
[f] 5 mol% of catalyst was used.

‡ In a typical experiment (entry 10), a degassed solution of (*Z*)-**3** (100 mg, 0.50 mmol) in THF (10 mL) was introduced under N_2 into a 50 mL stainless steel autoclave containing PtO_2 (5.6 mg, 5 mol%). The reactor was pressurized with H_2 (50 bar) and magnetic stirring was started. The reaction was monitored by quantitative GLC analysis of aliquots using a BPX5 column. After 39 h, gas were evacuated, the solution was filtered over Celite and the filtrate was concentrated under vacuum. The oily residue was then chromatographed over silica (AcOEt/heptane) to give **4** (36 mg, 72%) as a mixture of diastereomers in 77% de from which the 2*S*,4*S*-stereoisomer was selectively recrystallized from methanol. Hydrogenations carried out with homogeneous (Rh, Ru) catalysts were performed in a similar way, by introducing under N_2 into the autoclave a solution of **3** and the catalyst precursor in the appropriate solvent. (2*S*,4*S*)-**4**: ^1H NMR ($CDCl_3$): δ 4.40 (m, 1H, C*H*OH), 4.16 (m, 1H, C*H*CH$_2$COOO), 3.87 (d, 1H, ^2J=9.8 Hz, CH(OH)C*H*HO), 3.64 (dd, 1H, ^2J=9.8, ^3J=3.8 Hz, CH(OH)CH*H*O), 2.90 (d, 1H, ^3J=7.0, CHO*H*), 2.63 (d, 2H, ^3J=5.7, CHC*H*$_2$COO), 2.39 and 1.74 (2m, 2×1H, CH(OH)C*HH*CHO), 1.44 (s, 9H, *t*Bu); ^{13}C NMR ($CDCl_3$): δ 171.0 (CO_2), 81.1 (*C*Me$_3$), 76.6 (O*C*H$_2$CHOH), 74.7 (*C*HCH$_2$), 72.4 (*C*HOH), 40.9 (*C*HCH$_2$CO$_2$), 40.1 (CHOH*C*H$_2$CH), 28.1 (C*Me*$_3$). $[\alpha]_D^{25}$ (c=0.45, $CHCl_3$)=+7. MS (EI) m/z (%): 202 (M^+, 7), 183 (8), 146 (17), 127 (48), 111 (17), 102 (15), 87 (67), 69 (17), 57 (100); anal. calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97; found: C, 59.61; H, 8.92. Full details for the X-ray crystal structure determination of (2*S*,4*S*)-**4** have been deposited with the Cambridge Crystallographic Data Centre with the number CCDC 175685. (2*R*,4*S*)-**4**: ^1H NMR ($CDCl_3$): δ 4.46 (m, 1H, C*H*CH$_2$COOO), 4.43 (m, 1H, C*H*OH), 3.96 (dd, 1H, ^2J=9.8, ^3J=5.5, CH(OH)C*H*HO), 3.70 (d, 1H, ^2J=9.8, CH(OH)CH*H*O), 3.05 (s br, CHO*H*), 2.50 (d, 2H, ^3J=5.7, CHC*H*$_2$COO), 2.06 and 1.74 (2m, 2×1H, CH(OH)C*HH*CHO), 1.44 (s, 9H, *t*Bu); ^{13}C NMR ($CDCl_3$): δ 171.0 (CO_2), 80.8 (*C*Me$_3$), 75.9 (O*C*H$_2$CHOH), 74.4 (*C*HCH$_2$), 72.4 (*C*HOH), 41.6 (*C*HCH$_2$CO$_2$), 41.3 (CHOH*C*H$_2$CH), 28.1 (C*Me*$_3$).

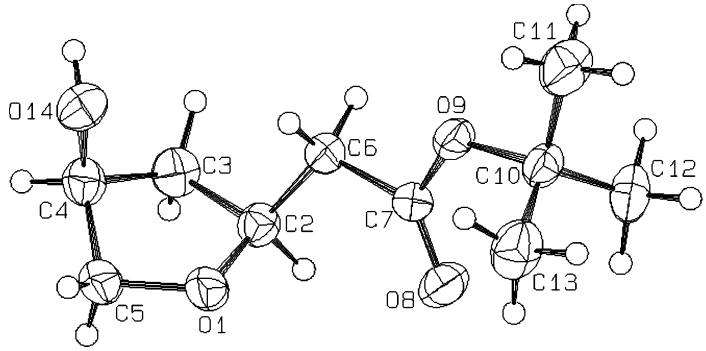


Figure 2. Crystal structure of (2*S*,4*S*)-**4** (ORTEP drawn at 50% probability).

Me_2BBr.[13–15] To enforce the opposite diastereoselectivity during hydrogenation and in turn to potentially obtain the valuable *syn*-diol **2**, we investigated the use of the commercially available chiral catalyst $RuCl_2$(Binap) (entries 19 and 20). The reactions in THF were found to proceed with good chemoselectivity for **4**. $RuCl_2$((*S*)-Binap) gave (2*S*,4*S*)-**4** in 93% de and 82% GLC yield,[‡] whilst the (*R*)-Binap catalyst led to the (2*R*,4*S*)-diastereomer in 80% de but with poor activity.

In conclusion, these results show that stereoselective hydrogenation of chiral (4-hydroxy-tetrafuranylidene)-carboxylates can be controlled and may thus afford a new entry toward chiral functional *anti* and *syn* 3,5-dihydroxyesters. Current efforts are aimed at improving activity and stereoselectivity of homogeneous catalysts as well as at investigating the hydrogenation of derivatives of **3**.

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