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REGIOSELECTIVE PROTECTION OF *THREO*-2,3-DIHYDROXYBUTANOIC ESTERS

Andreas Kirschning,* Monika Kreimeyer, Hans-Peter Blanke

Institut für Organische Chemie der Technischen Universität Clausthal, Leibnizstraße 6, D-38678 Clausthal-Zellerfeld, Germany

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Abstract: Monoprotected derivatives of optically pure diolester 1 are regioselectively constructed by lipase-based methodologies as well as via the stannylene acetal of 1.

Methods for the preparation of optically active methyl 2,3-dihydroxybutanoates have lately attained considerable interest.[1] As their isopropylidene and cyclohexylidene protected derivatives they have been widely employed in the synthesis of 6-deoxy sugars[2] as well as complex natural products.[3]

As part of our studies directed toward the de-novo synthesis of labelled carbohydrates, it has been necessary to develop synthetic pathways which differentiate between the two hydroxy groups of (2S, 3R) - dihydroxybutanoic acid methyl ester **1**. Regioselective α-O-sulfonylation and α-bromination of **1** have recently been described by *Sharpless et al.*[4] Here we report on the preparation of optically active monoprotected methyl *threo* dihydroxybutanoates by enzymatic means and compare the results with conventional chemical methods based on the chemistry of stannylene acetals.

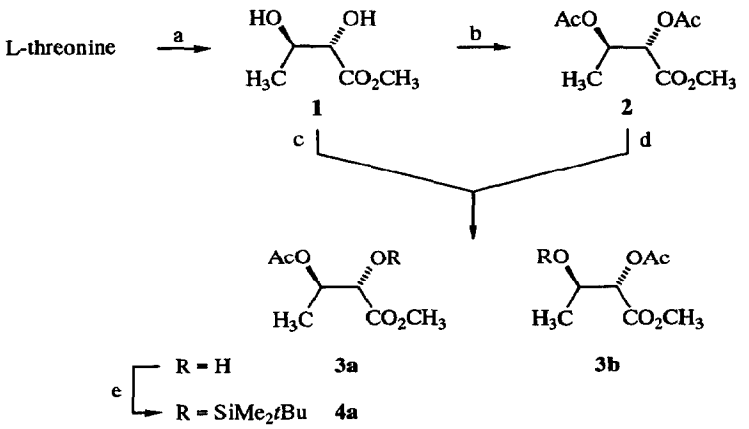
The optical purity of **1**, which is easily accessable from L-threonine in two steps,[2d] was established by converting it into its isopropylidene derivative followed by gc-analysis on a chiral 6-O-methyl-γ-cyclodextrin column. Comparison with the racemate of **1** revealed an ee >99%.[5]

The use of lipases as routine chiral catalysts for esterification and ester hydrolysis is well documented.[6] Both substrates, diol **1** ($[\alpha]_D^{22}$ = +8.8 (c 1.2; $CHCl_3$)) and diacetate **2** ($[\alpha]_D^{22}$ = +19 (c 1.08; $CHCl_3$)) may be employed for this methodology as outlined in Scheme 1. The latter was easily prepared in high yield under standard acylating conditions[1b] or by irreversible transesterification using vinylacetate / dichloromethane (4:1) in the presence of lipase PS[7]. We studied a wide variety of enzymes[7] in different organic solvents at varying temperatures for the selective monoacetylation of **1**. The best results were obtained with lipase AY 20[7] in vinylacetate / dichloromethane (4:1) at 22 °C which left less than 5% unreacted material. As shown in Scheme 1 regioselective ester hydrolysis of **2** was also achieved with lipase AY 20 in 0.1 M phosphate buffer at 22 °C. Under these conditions, 18% of **2** remained unreacted. Surprisingly, both experiments predominantly gave the 3-acetoxy derivative **3a**[8] (Scheme 1). We checked the ratio of both regioisomers **3a** and **3b** at each stage of purification by gc- and ^1H NMR analysis. We found that acetyl migration which is a facile process commonly observed in polyols, did occur during work up under acidic conditions, e.g. chromatographic separation on silica gel usually gave uniform mixtures of monoacetates **3a** and **3b** in a ratio of 4:1. In contrast, we did not observe any acetyl migration for **3a** under the typical silylating conditions which afforded **4a** (oil; $[\alpha]_D^{22}$= -1.0 (c 1.27; $CHCl_3$)).

In addition we studied lipase-catalysed regioselective acetylation and deacetylation of the (2R, 3S)-enantiomers of diolester **1** and its diacetate **2**. For *ent*-**1** none of the lipases used[7] gave satisfactory results whereas *ent*-**2** could regioselectively be transformed under hydrolyzing conditions with lipase AY 20 (0.1 M

phospate buffer, pH 7, 2d, 35°C, 82 %: (2R, 3S) **3a** : **3b** = 16:1) or lipase CC (0.1 M phospate buffer, pH 7, 7d, 35°C, 92 %: (2R,3S) **3a** : **3b** >20:1).

Scheme 1

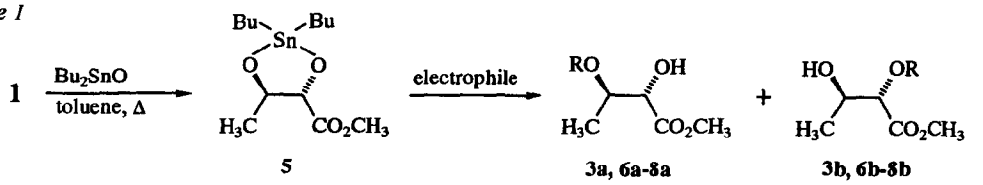


a. $NaNO_2$, H_2SO_4, 0°C, 12h; then MeOH, HCl, 80°C, 4h, 54%; b. Ac_2O, pyridine, rt, 12h, 89% or lipase PS, CH_2=CHOAc / CH_2Cl_2 4:1, rt, 4d, 92%; c. lipase AY 20, CH_2=CHOAc, CH_2Cl_2 4:1, rt, 24d, (2S, 3R) **3a** : **3b** 5:1, 79%; d. lipase AY 20, 0.1M phosphate buffer pH 7, rt, 2.5d, (2S, 3R) **3a** : **3b** 6:1, 87%; e. ^{t}BuMe$_2$SiCl, imidazole, DMF, rt, 12h, 91%.

Another general and efficient method for monofunctionalization of diols is by electrophilic attack on O,O'-dibutylstannylene acetals.[9] Acetylation of the O,O'-dibutylstannylene acetal **5** provided the monoacetylated esters **3a** and **3b** in a ratio of 11:1 in moderate yield (Table 1) When pivaloyl chloride was employed as the acylating agent the regioselectivity dropped to 2:1 in favor of **6a**.[8] However, the ratio was dramatically improved by quantitatively converting **6b** into **6a** in refluxing toluene in the presence of a trace of silica gel.

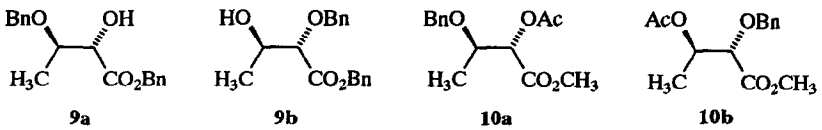
In contrast, when **5** was benzylated in refluxing toluene in the presence of one equivalent of tetrabutylamonium iodide (TBAI), a complex mixture formed from which the 2- and 3-monobenzylated methyl esters **7a**[10] (oil; $[\alpha]_D^{23}$ = -26.4 (c 1.26; $CHCl_3$)) and **7b**[10] (oil; $[\alpha]_D^{23}$ = -89.5 (c 1.4; $CHCl_3$)) were isolated by column chromatography as well as both regioisomeric benzyloxy-hydroxy-benzylesters **9a,b**. In accordance with *Ohno* and *Nagashima*[10] , activation of **5** by CsF via a pentacoordinated tin complex followed by benzylation with benzyl bromide and TBAI in DMF at rt afforded both monobenzylated methyl esters **7a** and **7b** in a ratio of 1.5:1. The regioselectivity was proven unambigously by acetylation of the remaining hydroxyl group of both isolated regioisomers under standard conditions giving **10a** and **10b**. In both cases H-2 and H-3 are shifted downfield in the ^{1}H NMR spectrum by about 1.1- 1.3 ppm in comparison to the starting material.

Table 1



entry	electrophile	conditions	R	ratio		yield %[a]
1	1.1 equ. AcCl, toluene	rt, 2h	Ac	**3a:3b**	11:1	60
2	1.1 equ. PivCl, toluene	rt[b]	Piv	**6a:6b**	2:1	58
3	CsF, BnBr, Bu_4NI, toluene	rt[b]	Bn	**7a:7b**	1.5:1	69
4	CsF, MEMCl, toluene	-18°C[b]	MEM	**8a:8b**	1:1	63

[a] isolated yields from 1; [b] ovemight.



In an analogous fashion, alkylation of **5** with methoxyethoxymethyl chloride (MEMCl) took place. In the absence of CsF, again a complex mixture of alkylated products was formed whereas activation by fluoride at -18°C in DMF afforded both monoacetals **8a** (oil; $[\alpha]_D^{22}$ = -22.5 (c 1.27, $CHCl_3$) and **8b** (oil $[\alpha]_D^{22}$ = -69.3 (c 1.18, $CHCl_3$) in a ratio of about 1:1 (Table 1).

In summary, the methods described here give access to fully differentiated optically pure methyl 2,3-dihydroxybutanoates and further enhance their synthetic utility.

Acknowledgements

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(5) In contrast *Schurig* and coworkers encountered an anchimeric assistance imposed by the 3-hydroxy group during the diazotization of **1** in the presence of chloride to afford a mixture of 2- and 3-chloro-hydroxybutanoic acid esters: Hintzer, K.; Koppenhoefer, B.; Schurig, V. *J. Org. Chem.* **1982**, *47*, 3850.

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(7) Following lipases were used: PS from *Pseudomonas fluorescens* and AY-20 from *Candida cylindracea* (Amano Pharmaceutical Co.), CC from *Candida cylindracea* and PP from *Porcine Pancreas*, type II (Sigma Chemical Co.) and OF (Meito Sangyo Co., Ltd).

(8) Esters **3a** and **3b** were separated by subliming the major fraction **3a** from the crude product leaving behind the minor fraction **3b**.

(2S, 3R) **3a**: mp= 41°C; $[\alpha]_D^{22}$ = +54 (c 1.2, $CHCl_3$) and $[\alpha]_D^{21}$ = -50 (c 1.05; $CHCl_3$) for the (2R, 3S) enantiomer; ^{1}H-NMR ($CDCl_3$; TMS= 0.0 ppm)δ: 5.23 (dq, *J*= 2.2, 6.4 Hz, 1H, 3-*H*), 4.13 (dd, *J*= 2.2, 7.6 Hz, 1H, 2-*H*), 3.78 (s, 3H, CO_2CH_3), 2. 90 (d, *J*= 7.6 Hz, 1H, O*H*), 2.02 (s, 3H, OAc), 1.36 (d, *J*= 6.4 Hz, 3H, 4-*H*); **3b** (mixed with **3a**): oil; ^{1}H-NMR ($CDCl_3$; TMS= 0.0 ppm)δ: 4.97 (d, *J*= 3.6 Hz, 1H, 2-*H*), 4.27 (dq, *J*= 6.8, 3.6 Hz, 1H, 3-*H*), 3.78 (s, 3H, CO_2CH_3), 2.54 (d, *J*= 7.6 Hz, 1H, O*H*) 2.20 (s, 3H, OAc), 1.28 (d, *J*= 6.8 Hz; 3H, 4-*H*).

Esters **6a** and **6b** were separated by column chromatography on silica gel (hexane/ ethylacetate 4:1): (2S, 3R) **6a**: mp= 36.5°C-38.5°C; $[\alpha]_D^{22}$ = +42 (c 0.99, $CHCl_3$); ^{1}H-NMR ($CDCl_3$; TMS= 0.0 ppm)δ: 5.18 (dq, *J*= 2.6, 6.6 Hz, 1H, 3-*H*), 4.16 (dd, *J*= 2.6, 7.2 Hz, 1H, 2-*H*), 3.77 (s, 3H, CO_2CH_3), 2. 88 (d, *J*= 7.2 Hz, 1H, O*H*), 1.35 (d, *J*= 6.6 Hz, 3H, 4-*H*), 1.10 (s, 9H, ^{t}Bu); **6b**: oil, $[\alpha]_D^{22}$ = -29 (c 1.07, $CHCl_3$); ^{1}H-NMR ($CDCl_3$; TMS= 0.0 ppm)δ: 4.96 (d, *J*= 3.6 Hz, 1H, 2-*H*), 4.29 (dq, *J*= 6.6, 3.6 Hz, 1H, 3-*H*), 3.78 (s, 3H, CO_2CH_3), 2.15 (b, 1H, O*H*) 1.29 (s, 9H, ^{t}Bu), 1.28 (d, *J*= 6.6 Hz; 3H, 4-*H*).

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