A Four-Step Route from Aldehydes to C_2-Elongated Enantiomerically Pure α,β-Unsaturated γ-Hydroxy Esters

Christian Harcken,[a] Reinhard Brückner*[b]

[a] Present address: Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, USA

[b] Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität, Albertstr. 21, 79104 Freiburg, Germany

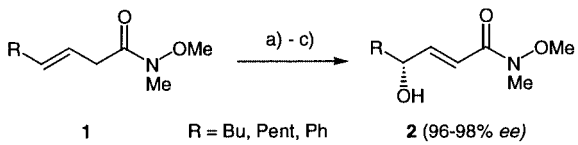
Fax +49-761-2036100; E-mail: reinhard.brueckner@organik.chemie.uni-freiburg.de; charcken@mail.cm.utexas.edu

Received 12 March 2001

Abstract: Asymmetric dihydroxylation of β,γ-unsaturated esters **4** provided β-hydroxy-γ-lactones **3** or *ent*-**3**. Methanolysis acetonide formation and LDA-mediated fragmentation of the resulting esters **5**/*ent*-**5** furnished the γ-chiral acrylates **6**/*ent*-**6** containing disubstituted C = C bonds (93-99% *ee*). Also, β-hydroxy-γ-lactones *ent*-**3a** and **3b** were α-butylated and α-brominated, respectively, prior to methanolysis, acetonide formation, and fragmentation which led to the γ-chiral acrylates **9** and **12** with trisubstituted C = C bonds (94 and 95% *ee*, respectively).

Key words: acetonides, asymmetric dihydroxylation, chiral acrylates, γ-chiral α,β-unsaturated esters, β-hydroxy-γ-lactones

Many reactions with acyclic stereocontrol exploit the minimization of allylic strain.[1] Accordingly, substrates with stereodirecting allylic oxygen[2] or nitrogen substituents[3] are frequently encountered in stereoselective synthesis. Enantiomerically pure type-**6** α,β-unsaturated γ-hydroxy esters are particularly versatile in this regard,[4] although they are not accessible very generally. The most common starting point are an enantiopure unprotected or protected α-hydroxyaldehyde and a stabilized phosphorane.[5,6] The limited supply of such aldehydes from the „chiral pool" and the possibility of stereorandomization at C-α hinder this approach. More widely applicable but lengthier are Sharpless epoxidation and photolysis of the derived epoxydiazoketone.[7] A promising yet little explored route is the enzymatic resolution of the racemic hydroxyester.[8] A one-step synthesis of type-**6** esters is the reaction between aldehydes and enantiomerically pure sulfinyl esters unfortunately, *ee*'s are only 50-75% and five equivalents of the aldehyde are required to obtain good yields.[9]



1 R = Bu, Pent, Ph **2** (96-98% *ee*)

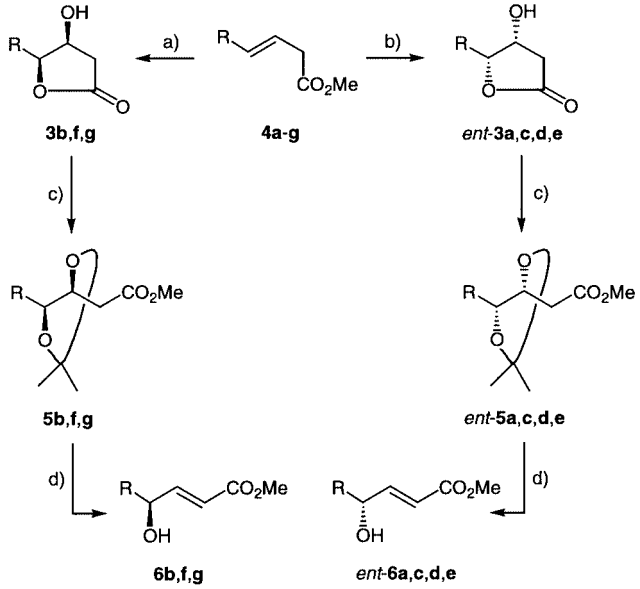
Scheme 1 a) Modified AD mix-β® [containing 1 mol-% $K_2OsO_3(OH)_2$ and 5 mol-% $(DHQD)_2PHAL$], $MeSO_2NH_2$; 81-84%.[10]– b) $SOCl_2$, NEt_3, CH_2Cl_2.[11]– c) DBU; 87-92% over the two steps.[11]

A highly stereocontrolled synthesis of the Weinreb amide analogs **2** of type-**6** esters appeared in the literature, too (Scheme 1): Dihydroxylation of the β,γ-unsaturated amides **1** with AD mix-β®[10] followed by conversion of the resulting diols into cyclic sulfites and β-elimination/fragmentation.[11] However, it is unlikely that this route can be extended to obtaining γ-hydroxy amides with trisubstituted $C^{\alpha} = C^{\beta}$ bonds – while our approach described below delivers esters of that substitution pattern. Moreover, it is doubtful that the amides of Scheme 1 react like the corresponding esters. Therefore, we adopted the strategy of Scheme 1 for the conversion of different dihydroxylation products – the hydroxylactones **3** or their enantiomers *ent*-**3** – into type-**6** esters and reduced the step requirement (Schemes 2-4).[12] These esters may contain two or three substituents at the $C^{\alpha} = C^{\beta}$ bond. The crucial hydroxylactones **3**/*ent*-**3** are accessible[13,14] through asymmetric dihydroxylation (AD) of β,γ-unsaturated esters **4**. They were already used as precursors for many saturated and unsaturated γ-lactones[15-19] as well as simple alcohols[20] and 1,2-diols[17] in our hands.

The *trans*-configured β,γ-unsaturated ester **4a** is commercially available. Unsaturated esters **4b, d, e, g** were prepared in 71-77% yield and *trans*-selectively by decarboxylative Knoevenagel condensations between an appropriate aldehyde and monomethyl malonate.[21,22] Ester **4c** was prepared by a decarboxylative Knoevenagel condensation between phenylacetaldehyde and malonic acid[23] followed by TsOH-catalyzed esterification of the β,γ-unsaturated ester intially obtained.

AD of esters **4b-g** under standard conditions delivered *S,S*- and *R,R*-configured hydroxylactones **3** and *ent*-**3**, respectively, depending on whether AD mix-α® was employed – which contains $(DHQ)_2PHAL$ – or AD mix-β® – which contains $(DHQD)_2PHAL$; the lactones resulted with 93-99% *ee* in 74-90% yield (Scheme 2, Table). The AD reaction of ester **4a** was performed using 10 mol-% $(DHQD)_2PHAL$ and 2 mol-% $K_2OsO_3(OH)_2$, providing hydroxylactone *ent*-**3a** with 94% *ee* (69% yield) while standard AD conditions led to 80% *ee* and 38% yield.[17]

The conversion of lactones **3**/*ent*-**3** into acetonide-protected β,γ-dihydroxy esters **5**/*ent*-**5** succeeded under the conditions described for such a reaction of γ-(hydroxymethyl)-γ-lactone[24] [under which, however, β-hydroxy-γ-(hydroxymethyl)-γ-lactone failed to ring-open[25]]: Lactones **3**/*ent*-**3** in excess 2,2-dimethoxypropane / methanol



Scheme 2 a) AD mix-α®, tBuOH/H_2O 1:1, $MeSO_2NH_2$ (1.0 equiv.), 0 °C, 36-72 h.– b) AD mix-β®, tBuOH/H_2O 1:1, $MeSO_2NH_2$ (1.0 equiv.; for the exceptional case of **4a** see ref.[17]), 0 °C, 36-72 h.– c) $Me_2C(OMe)_2$ (10 equiv.), MeOH (8 equiv.), Amberlyst 15 (20 mg/mmol), room temp., 36 h.– d) LDA (2.2 equiv., 3.2 equiv. for **6f** and **g**), THF, -78 °C, 10 min.

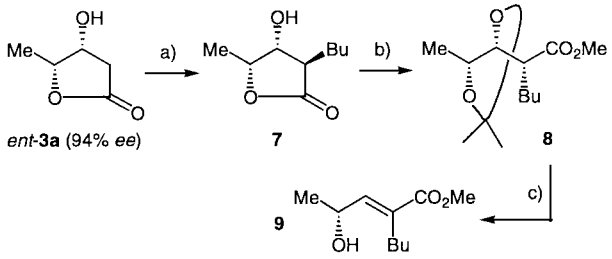
Table Yields of Compounds **3**/*ent*-**3**, **5**/*ent*-**5**, **6**/*ent*-**6**

	R	**3**/*ent*-**3** % Yield	**3**/*ent*-**3** % *ee*	**5**/*ent*-**5** % Yield	**6**/*ent*-**6** % Yield	Total yield from **4**
a	Me	69	94[b]	87	78	47
b	Oct	90	95[c]	86	92	71
c	Ph	78	99[b]	91	97	69
d	$PhCH_2$	88	96[b]	98	92	73
e	iPr	84	96[d]	96	86	69
f	$HO(CH_2)_{10}$ [a]	- [a]	97[d]	82	58	- [a]
g	$HC{\equiv}C\text{-}CH_2$	74	93[d]	92	95	65

[a] Lactone **3f** was prepared by desilylation of the corresponding *tert*-butyldiphenylsilylether.[17] [b] Determined by chiral GC. [c] Determined by chiral GC of the corresponding β-elimination product. [d] Determined by ^{1}H-NMR spectroscopic analysis of the Mosher ester

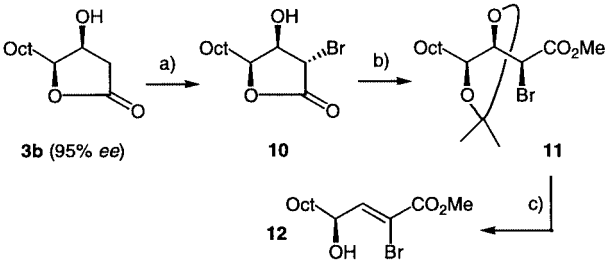
reacted at room temperature within 36 h giving the desired acetonide esters **5**/*ent*-**5** in essentially quantitative yields (Table).[26] After filtration and removal of the solvent they could be used in the next reaction without further purification; the yield of material purified by flash chromatography on silicagel[27] was 82-98%.

At -78 °C the acetonide esters **5**/*ent*-**5** and 2.2 equivalents of LDA reacted to completion within 10 min to give the desired γ-hydroxy α,β-unsaturated esters **6**/*ent*-**6** with ≥98:2 *trans*-selectivity.[28-30] The second equivalent of LDA deprotonates the acetone released in the reaction, since otherwise the acetone reprotonates the **5**- or *ent*-**5**-enolate, rendering the fragmentation incomplete. The yields were 78-97% except starting from the OH-containing ester acetonide **5f** which was fragmented with 3.2 equivalents of LDA and furnished 58% yield (Table). The terminal alkyne group of acetonide ester **5g** also required an additional equivalent of LDA for clean acrylate formation (95% yield). The *ee* of esters **6**/*ent*-**6** should be unaltered compared with the precursor lactones **3**/*ent*-**3**; ^{1}H NMR spectroscopy of the Mosher of *ent*-**6e** revealed *ee* = 95% compared to 96% *ee* in *ent*-**5e** (determined by GC). When the AD reactions **4** → **3**/*ent*-**3** were performed in the absence of $MeSO_2NH_2$ – which increased the reaction times – the three-step sequences **4** → **3**/*ent*-**3** → **5**/*ent*-**5** → **6**/*ent*-**6** could be performed with unpurified intermediates.



Scheme 3 a) LDA (2.5 equiv.), THF, -78 °C, 2 h; BuI (1.2 equiv.), THF/DMPU 1:1, -35 °C, 20 h; 84%.– b) $Me_2C(OMe)_2$ (10 equiv.), MeOH (16 equiv.), Amberlyst 15 (20 mg/mmol), room temp., 3 d; 44%.– c) LDA (2.2 equiv.), THF, -78 °C, 10 min; 79%.

The β-hydroxylactone *ent*-**3a** was α-butylated in THF/DMPU with complete *trans*-selectivity[31] and the β-hydroxylactone **3b** α-brominated *trans*-selectively. Thereby, we obtained the trisubstituted γ-lactones **7** (Scheme 3) and **10** (Scheme 4), respectively. These, too, were subjected to methanolysis and acetonide formation by treatment with dimethoxypropane in acidic methanol. These reactions – other than those with their disubstituted counterparts **3**/*ent*-**3** – did not go to completion, not even after prolonged reaction times (3 d) or working at 40 °C rather than at room temperature. Since we isolated the desired acetonide



Scheme 4 a) LDA (2.5 equiv.), THF, -78 °C, 2 h; Br_2 (2.0 equiv.), THF/DMPU 1:1, -35 °C, 20 h; 48%.– b) $Me_2C(OMe)_2$ (10 equiv.), MeOH (16 equiv.), Amberlyst 15 (20 mg/mmol), room temp., 3 d; 41%.– c) LDA (2.2 equiv.), THF, -78 °C, 10 min; 77%.

esters **8** and **11** in 44% and 41% yield, respectively, and retrieved the residual starting material in 49% and 45% yield, respectively, this means that the third substituent in the lactone turned methanolysis/ketalization into thermodynamically indifferent reactions. The LDA-induced fragmentation of acetonide esters **8** and **11** afforded the corresponding α-butylated and α-brominated γ-hydroxy acrylates **9** and **12** isomerically pure and in 79% and 77% yield, respectively. In both compounds the CO_2Me group and the hydroxyalkyl substituent assume *trans* positions at the C = C bond as they did in the α-unsubstituted esters **6**/*ent*-**6**. However, as a consequence of the CIP priority rules, the C = C configuration is *E* in **9** and *Z* in **12**.

We are convinced that this catalytically asymmetric synthesis − entailing four steps from aliphatic aldehydes if α-unsubstituted hydroxy acrylates and five steps if α-substituted hydroxy acrylates are desired − will facilitate the use of type-**6** γ-hydroxy acrylates in synthesis.

Acknowledgement

This work was supported by the *Deutsche Forschungsgemeinschaft* for which we are very grateful. We are indebted to *BASF AG* (Ludwigshafen) and *Chemmetall GmbH* (Langelsheim) for donating chemicals.

References and Notes

(1) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841-1860.
(2) a) Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761-1795.− b) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191-1223.
(3) Reetz, M. T., *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531-1546.
(4) Leading references: Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357-2384.− Muray, E.; Alvarez-Larena, A.; Piniella, J. F.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2000**, *65*, 388-396.− Ref. 2b.− Ferreira, A. R. G.; Dias, A. G.; Pinto, A. C.; Costa, P. R. R.; Miguez, E.; da Silva, A. J. R. *Tetrahedron Lett.* **1998**, *39*, 5305-5308.− Krief, A.; Provins, L.; Froidbise, A. *Tetrahedron Lett.* **1998**, *39*, 1437-1440.− Adam, W.; Renze, J.; Wirth, T. *J. Org. Chem.* **1998**, *63*, 226-227.− Chambers, M. S.; Thomas, E. J.; *J. Chem. Soc., Perkin Trans. 1* **1997**, 417-431.− Yechezkel, T.; Ramesh, N. G.; Hassner, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2423-2436.
(5) Craig, D.; Daniels, K.; MacKenzie, A. R. *Tetrahedron* **1993**, *49*, 11263-11304.
(6) Ambrosi, H.-D.; Duczek, W.; Ramm, M.; Gründemann, E.; Schulz, B.; Jähnisch, K. *Liebigs Ann. Chem.* **1994**, 1013-1018.
(7) van Aar, M. P. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 11223-11234.
(8) Burgess, K.; Henderson, I. *Tetrahedron: Asymmetry* **1990**, *1*, 57-60.
(9) For example: Burgess, K.; Cassidy, J.; Henderson, I. *J. Org. Chem.* **1991**, *56*, 2050-2058.
(10) Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2079-2082.
(11) Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2083-2086.
(12) C. Harcken, PhD Thesis, Universität Göttingen **2000**.
(13) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B.; Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *Tetrahedron Lett.* **1992**, *33*, 6407-6410.
(14) Miyazaki, Y.; Hotta, H.; Sato, F. *Tetrahedron Lett.* **1994**, *35*, 4389-4392.
(15) Harcken, C.; Brückner, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2750-2752.
(16) Harcken, C.; Brückner, R.; Rank, E. *Chem.–Eur. J.* **1998**, *4*, 2342-2352 (*corrigendum ibid.* 2390).
(17) Harcken, C.; Brückner, R. *New J. Chem.* **2001**, 40-54.
(18) Berkenbusch, T.; Brückner, R. *Tetrahedron* **1998**, *54*, 11461-11470.
(19) Braukmüller, S.; Diploma work, Universität Göttingen **1998**.
(20) Berkenbusch, T.; Brückner, R. *Tetrahedron* **1998**, *54*, 11471-11480.
(21) Yamanaka, H.; Yokoyama, M.; Sakamoto, T.; Shiraishi, T.; Sagi, M.; Mizugaki, M. *Heterocycles* **1983**, ***20***, 1541-1544.
(22) All new compounds gave satisfactory ^{1}H NMR and IR spectra as well as correct combustion analyses (except compound **12**).
(23) Ragoussis, N. *Tetrahedron Lett.* **1987**, *28*, 93-96.
(24) Larcheveque, M.; Lalande, J. *Tetrahedron* **1984**, *40*, 1061-1065.
(25) Han, S. Y.; Joullié, M. M.; Petasis, N. A.; Bigorra, J.; Corbera, J.; Font, J.; Ortuño, R. M. *Tetrahedron* **1993**, *49*, 349-362.
(26) Representative procedure: **Methyl 2-[(4*S*,5*S*)-2,2-Dimethyl-5-octyl-1,3-dioxolan-4-yl]acetate (5b)**: A solution of β-hydroxylactone **3b** (2.14 g, 10.0 mmol) in MeOH (8.0 equiv.) was treated with 2,2-dimethoxypropane (10.0 equiv.) and amberlyst 15 ion-exchange resin (200 mg). The mixture was stirred for 36 h at room temperature. During this time the solution darkened. The catalyst was filtered off and the solvent was removed. The crude product could be directly used in the next reaction or was purified by flash chromatography[27] (petroleum ether/*t*BuOMe 20:1) giving a colorless liquid (2.43 g, 86%).− $[\alpha]_D^{25}$ = 22.8 (*c* = 0.80 in $CHCl_3$; *ee* = 95%).− ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, $J_{8'',7''}$ = 6.8, 8''-H_3), 1.25-1.60 (m, 1''-H_2 – 7''-H_2), partially superimposed by 1.38 and 1.40 (2 s, 2'-Me_2), AB signal (δ_A = 2.55, δ_B = 2.58, J_{AB} = 15.5, additionally split by $J_{A,4'}$ = 4.9, $J_{B,4'}$ = 7.2, 2-H_2), 3.72 (s, OMe), superimposed by 3.70 (m_c, 5'-H), 4.04 (ddd, $J_{4',5'} \approx J_{4',2\text{-H(B)}}$ = 7.2, $J_{4',2\text{-H(A)}}$ = 5.1, 4'-H).− ^{13}C NMR (75 MHz): δ = 14.04 (C-8''), − 22.59, − 25.91, − 29.17, − 29.39, − 29.64, − 31.79, − 32.52 and −38.09 (C-2, C-1'' - C-7''), 27.04 and 27.28 (2'-Me_2), 51.76 (OMe), 76.89 and 80.47 (C-4', C-5'), −108.53 (C-2'), − 171.05 (C-1).− IR (neat): ν = 2985, 2930, 2855, 1745, 1440, 1375, 1240, 1170, 1100, 1065 cm^{-1}.− $C_{16}H_{30}O_4$ (286.4) calc. C 67.10 H 10.56 found C 67.22 H 10.32.
(27) W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923-2925.
(28) Representative procedure: **Methyl (4*S*)-*trans*-4-Hydroxy-2-dodecenoate (6b[29])**: *n*BuLi (1.6 M in hexane, 2.2 equiv.) was added to a solution of *i*Pr_2NH (2.3 equiv.) in THF (30 mL) at -78 °C. After 30 min a solution of acetonide ester **5b** (2.43 g, 8.50 mmol) in THF (20 mL) was added dropwise. After 10 min the reaction was terminated by the addition of aqueous HCl (1 M, 5.0 equiv.). After extraction of the aqueous layer with *t*BuOMe (3 × 20 mL) the combined organic phases were dried over $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography[27] (petroleum ether/*t*BuOMe 3:1) to yield **6b** (1.81 g, 92%) as a colorless liquid.− $[\alpha]_D^{25}$ = 19.8 (*c* = 0.62 in $CHCl_3$; *ee* = 95%) {ref.[29] for the *R*-isomer: $[\alpha]_D^{25}$ = -18.0 (*c* = 1.00 in $CHCl_3$; *ee* = 88%)}.− ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, $J_{12,11}$ = 6.6, 12-H_3), 1.22-1.46 (m, 6-H_2 - 11-H_2), 1.58 (m_c, 5-H_2), 1.70 (br s, OH), 3.75 (s, OMe), 4.31 (tdd, $J_{4,5} \approx J_{4,3} \approx$ 5.8, $^4J_{4,2}$ = 1.5, 4-H),

6.04 (dd, J_{trans} = 16.1, $^4J_{2,4}$ = 1.4, 2-H), 6.97 (dd, J_{trans} = 16.2, $J_{3,4}$ = 4.9, 3-H). ^{13}C NMR (75 MHz): δ = 13.99 (C-12), − 22.55, − 25.14, − 29.15, − 29.40 (double intensity), − 31.75 and − 36.52 (C-5 - C-11), 51.54 (OMe), 70.92 (C-4), 119.41 (C-2), 150.80 (C-3), − 167.09 (C-1).

(29) Compound *ent*-**6b** was previously prepared: Allevi, P.; Anastasia, M.; Ciuffreda, P.; Sanvito, A. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1397-1400.

(30) Compound **6a** was previously prepared: Ainsworth, P. J.; Craig, D.; Reader, J. C.; Slawin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1995**, *42*, 11601-11622.

(31) Procedure: Ref.15,16

Article Identifier:
1437-2096,E;2001,0,05,0718,0721,ftx,en;G04901ST.pdf