ORGANIC LETTERS

2009
Vol. 11, No. 18
4032−4035

A Novel One-Pot Procedure for the Stereoselective Synthesis of α-Hydroxy Esters from Ortho Esters

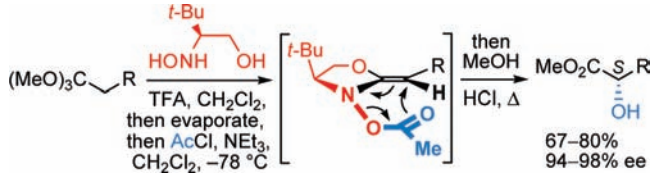
Matthias Breuning,* Tobias Häuser, and Eva-Maria Tanzer

Universität Würzburg, Institut für Organische Chemie, Am Hubland, 97074 Würzburg, Germany

breuning@chemie.uni-wuerzburg.de

Received May 29, 2009

ABSTRACT



A novel one-pot procedure for the stereoselective synthesis of α-hydroxy esters from ortho esters was developed. Key steps were multi-heteroatom Cope rearrangements of *O*-acylated *N*-hydroxy-L-*tert*-leucinol-derived oxazoline *N*-oxides leading to α-acyloxy oxazolines and, after methanolysis, to the target molecules in 67−80% yield and 94−98% ee.

Enantiomerically pure α-hydroxy acids and esters are important synthetic building blocks.[1] Only a few methods are currently known for the stereoselective preparation of such compounds from the corresponding acid derivatives. The α-oxidation of methyl esters with the enzyme extract of peas gives *R*-configured α-hydroxy esters with excellent stereocontrol (>99% ee),[2] but this biocatalytic transformation is often hampered by low yields. The stereoselective α-hydroxylation of enolates with oxaziridines is well studied.[3] While enantioselective variants of this reaction, usually with (+)- or (−)-(camphorylsulfonyl)oxaziridine as the chiral oxygen source, suffer from moderate stereocontrol,[4] good to excellent asymmetric inductions are achieved in diastereoselective α-oxidations of chirally modified amide or ester enolates.[5] Disadvantages of the latter method are the incompatibility of the oxaziridine with some functional groups[6] and the additional steps required to attach and remove the chiral auxiliary.

A first step toward a conceptually different approach[7] that does not rely on an electrophilic oxygen source was presented in 1998 by Dalko and Langlois (Scheme 1):[8] Condensation of the *N*-hydroxyisoborneol **1** with ortho esters afforded the oxazoline *N*-oxides **2**, which upon *O*-acylation underwent [3,3]-sigmatropic rearrangements leading to the α-acyloxy oxazolines **3** in 41−67% yield and high 92−95% de. The

(1) Coppola, G. M.; Schuster, H. F. α-*Hydroxy Acids in Enantioselective Synthesis*; VCH: Weinheim, 1997.

(2) (a) Adam, W.; Boland, W.; Hartmann-Schreier, J.; Humpf, H.-U.; Lazarus, M.; Saffert, A.; Saha-Möller, C. R.; Schreier, P. *J. Am. Chem. Soc.* **1998**, *120*, 11044. (b) Adam, W.; Lazarus, M.; Saha-Möller, C. R.; Schreier, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2287.

(3) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.

(4) (a) Chen, B.-C.; Weismiller, M. C.; Davis, F. A. *Tetrahedron* **1991**, *47*, 173. (b) Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, *55*, 3715. (c) Davis, F. A.; Serajul Haque, M.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402. (d) Boschelli, D.; Smith, A. B. *Tetrahedron Lett.* **1981**, *22*, 4385.

(5) (a) Raghavan, S.; Ganapathy Subramanian, S.; Tony, K. A. *Tetrahedron Lett.* **2008**, *49*, 1601. (b) Gaich, T.; Karig, G.; Martin, H. J.; Mulzer, J. *Eur. J. Org. Chem.* **2006**, 3372. (c) Williams, D. R.; Nold, A. N.; Mullins, R. J. *J. Org. Chem.* **2004**, *69*, 5374. (d) Wei, Y.; Bakthavatchalam, R.; Jin, X.-M.; Murphy, C. K.; Davis, F. A. *Tetrahedron Lett.* **1993**, *34*, 3715. (e) Gamboni, R.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 615.

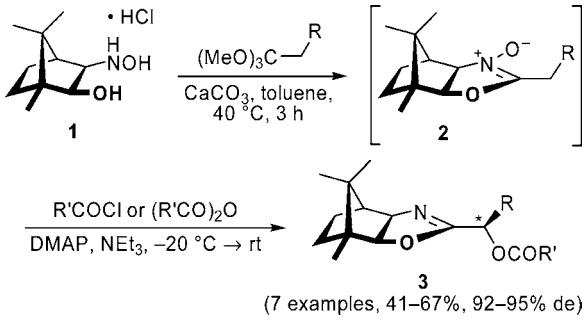
(6) Alkenes, for example, react with oxaziridines to give epoxides; see: (a) Michaelis, D. J.; Ischay, M. A.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 6610. (b) Armstrong, A.; Edmonds, I. D.; Swarbrick, A. E. *Tetrahedron Lett.* **2005**, *46*, 2207.

(7) For a two-step sequence that includes an asymmetric Sharpless dihydroxylation of ketene *O*,*O*- or *S*,*O*-acetals, see: (a) Kirschning, A.; Dräger, G.; Jung, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 253. (b) Monenschein, H.; Dräger, G.; Jung, A.; Kirschning, A. *Chem.—Eur. J.* **1999**, *5*, 2270.

(8) Dalko, P. I.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 2107.

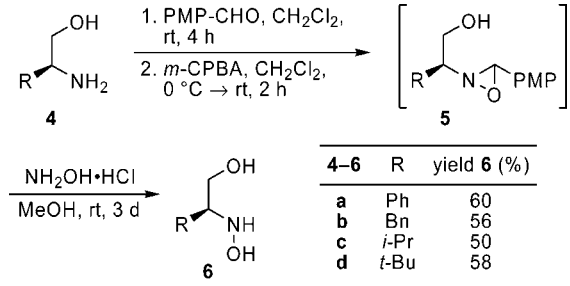
10.1021/ol901214n CCC: $40.75
Published on Web 08/19/2009

Scheme 1. Multiheteroatom Cope Rearrangements of Chiral Oxazoline *N*-Oxides According to Dalko and Langlois[8]



possibility to convert **3** into α-hydroxy esters was also demonstrated on one example (R = Bn, R′ = Me: three steps, 42% yield). Variations of the chiral auxiliary and further attempts to optimize the hydrolysis of **3** were not done, even though this sequence might allow a versatile alternative access to chiral α-hydroxy esters. Herein we report on a highly efficient method for the one-pot transformation of ortho esters into α-hydroxy methyl esters of ≥94% ee that includes a multiheteroatom Cope rearrangement[9] of an *O*-acylated *N*-hydroxy-L-*tert*-leucinol-derived oxazoline *N*-oxide as the stereochemical key step.

Scheme 2. Preparation of the *N*-Hydroxy *β*-Amino Alcohols **6**[a]

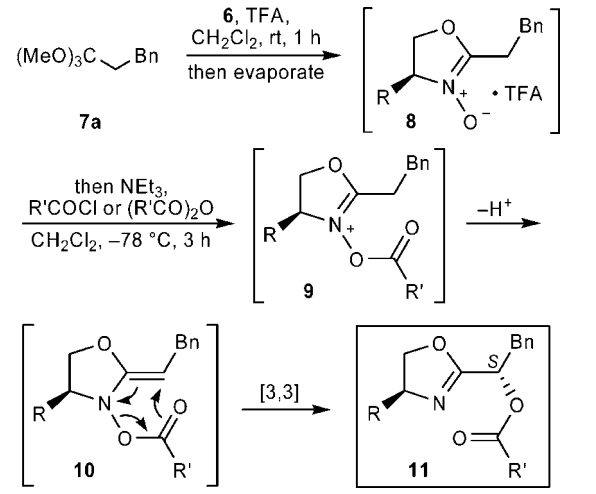


4–6	R	yield **6** (%)
a	Ph	60
b	Bn	56
c	*i*-Pr	50
d	*t*-Bu	58

[a] PMP = 4-MeOPh; *m*-CPBA = *m*-chloroperoxybenzoic acid.

Since the preparation of the isoborneol derivative **1** requires expensive camphorquinone as the starting material, we explored whether the structurally simpler, nonbicyclic *N*-hydroxy *β*-amino alcohols of type **6** (Scheme 2) are also suited as chiral auxiliaries and induce highly diastereoselective rearrangements. The synthesis of **6a**−**d** (R = Ph, Bn, *i*-Pr, *t*-Bu)[11] was straightforward from the commercially available *β*-amino alcohols **4a**−**d** using a slightly modified variant of a known three-step procedure.[12] Simple extraction with diethyl ether in the last step furnished **6a**−**d** in

Scheme 3. General Scheme for the Preparation and Multiheteroatom Cope Rearrangement of Chiral Oxazoline *N*-Oxides



enantiomerically and analytically pure form and 50−60% overall yield.

Initial screening experiments on the condensation−acylation−rearrangement sequence were performed with the ortho ester **7a** as the model substrate (Scheme 3). Reaction of 3 equiv of **7a** with **6** in the presence of TFA and evaporation quantitatively afforded the protonated oxazoline *N*-oxides **8**, as determined by ^{1}H NMR. Subsequent treatment of **8** with an acid chloride or anhydride and triethylamine in CH_2Cl_2 at −78 °C led to the *O*-acylated intermediates **9** and, after loss of a proton, to the ketene *N*,*O*-acetals **10**, which smoothly underwent [3,3]-sigmatropic multiheteroatom Cope rearrangements to give the *S*-configured[13] α-acyloxy oxazolines **11**.

For high yields of **11** it was crucial to remove the methanol freed in the initial preparation of the oxazoline *N*-oxide **8**. Otherwise, it will add to the acylated intermediate **9** to give methanol adducts of type **12** (Figure 1) in varying amounts, as evidenced from ^{1}H NMR investigations of the crude reaction mixtures. These compounds were stable under basic conditions, thus inhibiting the formation of the required Cope systems **10**, but usually decomposed or partially rearranged upon aqueous workup. In the reaction of **7a** with **6a** and AcCl, for example, the intermediate **12a** was found as the sole primary product. In contrast to all other derivatives of **12**, **12a** possessed a decent stability and was isolated as a single diastereomer in 43% yield after chromatography.

The diastereomeric excess in the products **11** strongly depended on the steric demand of the substituent R of the

(9) For reviews about asymmetric Cope and Claisen rearrangements, see: (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Nubbemeyer, U. *Synthesis* **2003**, 961.

(10) (a) Dirat, O.; Kouklovsky, C.; Mauduit, M.; Langlois, Y. *Pure Appl. Chem.* **2000**, *72*, 1721. (b) Baldwin, S. W.; McFadyen, R. B.; Aubé, J.; Wilson, J. D. *Tetrahedron Lett.* **1991**, *32*, 4431.

(11) The *N*-hydroxy *β*-amino alcohol **6a** and the HCl salt of **6c** are known compounds; see: (a) Tamura, O.; Gotanda, K.; Yoshino, J.; Morita, Y.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Mita, N.; Yamashita, M.; Ishibashi, H.; Sakamoto, M. *J. Org. Chem.* **2000**, *65*, 8544. (b) Aurich, H. G.; Biesemeier, F.; Geiger, M.; Harms, K. *Liebigs Ann. Org. Bioorg. Chem.* **1997**, 423.

(12) (a) Wovkulich, P. M.; Uskokoviæ, M. R. *Tetrahedron* **1985**, *41*, 3455. (b) Połoñski, T.; Chimiak, A. *Tetrahedron Lett.* **1974**, *28*, 2453. (c) See also ref 11b.

(13) The *S*-configuration of the products **15a**,**b**,**e**,**f** and **16** was established from the sign of their known optical rotations or by comparison with the known retention times on HPLC on chiral phase.

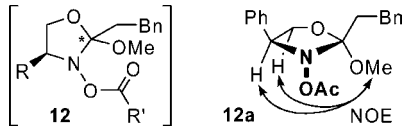


Figure 1. Methanol adducts **12** and **12a**.

chiral *N*-hydroxy β-amino alcohol **6** (Table 1, entries 1−4). Only moderate 62−83% de's were achieved with **6a**−**c** (R = Ph, Bn, *i*-Pr), whereas excellent 96% de were obtained with the L-*tert*-leucinol-derived auxiliary **6d** possessing the bulky *tert*-butyl group. Thus, the use of bicyclic *N*-hydroxy β-amino alcohols like **1** is not required for a highly diastereoselective rearrangement step.

The influence of the acylating reagent as studied on the reaction of **7a** with **6d** is small (Table 1, entries 4−7). With Ac_2O, AcCl, BzCl, and PivCl, the products **11d**−**f** were isolated in good 78−88% yield and 95−98% de. No rearrangement occurred with the less reactive Boc_2O (entry 8).

Table 1. Influence of the Chiral *N*-Hydroxy β-Amino Alcohol **6** and the Acylating Reagent on the Transformation of **7a** into **11**

entry	**6**	R	R′COCl/(R′CO)$_2$O	**11**	R′	yield[a] (%)	de[b](%)
1	**a**	Ph	AcCl	**a**	Me	68	83
2	**b**	Bn	AcCl	**b**	Me	48	62
3	**c**	*i*-Pr	AcCl	**c**	Me	59	63
4	**d**	*t*-Bu	AcCl	**d**	Me	78	96
5	**d**	*t*-Bu	Ac_2O	**d**	Me	80	96
6	**d**	*t*-Bu	BzCl	**e**	Ph	88	95
7	**d**	*t*-Bu	PivCl	**f**	*t*-Bu	86	98
8	**d**	*t*-Bu	Boc_2O	**g**	O*t*-Bu	0	

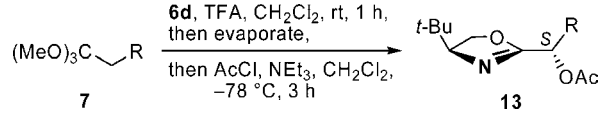
[a] Isolated yields refer to the limiting reagent **6**; the ortho ester **7a** was used in a 2-fold excess. [b] Determined by ^{1}H NMR.

The substrate scope of this transformation was evaluated next (Table 2). Condensation of **6d** with the ortho esters **7b**−**i** and subsequent rearrangement upon addition of acetyl chloride provided the α-acetoxy oxazolines **13b**−**i** in good 70−83% yield and ≥96% de. It should be noted that a contamination of **7** with even large amounts of the corresponding methyl or ethyl esters, which are usually formed as side products in the preparation of ortho esters from nitriles, has no negative effect on the outcome of the reaction. For example, similar results were obtained with analytically pure **7i** and with a 53:47 mixture of **7i** and the corresponding methyl ester (entries 7 and 8). A time-consuming purification of **7** is thus not necessary.

The highly preferential formation of the (*S*)-configured[13] products **13** suggests that the rearrangement is a concerted process[14] via the *Z*-ketene *N*,*O*-acetal **14A** (Figure 2), in

(14) The high stereoselectivities obtained strongly support a concerted [3,3]-sigmatropic rearrangement. Non-concerted processes involving short-lived radicals or ionic species, however, cannot fully be excluded; see also: Cummins, C. H.; Coates, R. M. *J. Org. Chem.* **1983**, *48*, 2070.

Table 2. Substrate Scope



entry	**7**	purity[a] (%)	R	**13**	yield[b] (%)	de[c] (%)
1	**b**[d]	45	CH_2Bn	**b**	76	97
2	**c**[d]	100	Me	**c**	74	97
3	**d**	100	*n*-Pr	**d**	71	97
4	**e**	40	*n*-Pent	**e**	80	97
5	**f**	82	$(CH_2)_{10}Me$	**f**	83	97
6	**g**	52	$(CH_2)_{11}Me$	**g**	77	96
7	**h**	>90	$(CH_2)_2OBn$	**h**	74	97
8	**i**	100	$(CH_2)_4Br$	**i**	77	96
9	**i**	53	$(CH_2)_4Br$	**i**	70	96

[a] Contaminated by the corresponding ester. [b] Isolated yields refer to the limiting reagent **6d**; the ortho esters **7** were used in a 2-fold excess. [c] Determined by ^{1}H NMR. [d] The triethyl orthoate was used.

which the bulky *tert*-butyl group induces a transient stereogenic center at the nitrogen atom that, in turn, defines the chairlike conformation of the Cope system. The alternative arrangement **14B** is strongly disfavored due to the repulsion of the *tert*-butyl group with the oxygen atom of the N−O moiety.

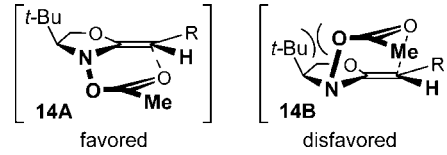


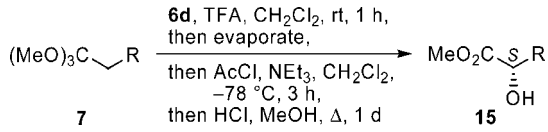
Figure 2. Proposed transition states.

The primary goal of our investigations, the one-pot conversion of ortho esters into chiral α-hydroxy methyl esters, was achieved by an additional methanolysis step (Table 3). Thus, condensation of **7a**,**b**,**e**−**i** with **6d**, evaporation, acetylation followed by the multiheteroatom Cope rearrangement, and final methanolysis delivered the products **15a**,**b**,**e**−**i** in good 67−80% yield and excellent 94−98% ee. Any significant racemization at the newly formed stereogenic center in α-position was not observed, as was obvious from the high enantiopurities of **15**. The fatty acid derivatives **15e** and **15g** are the methyl esters of the natural products (*S*)-2-hydroxyonanthic acid and (*S*)-2-hydroxymyristic acid.

By the same procedure, but with a final hydrolysis step in 6 N HCl, the corresponding α-hydroxy acids are in principle available, as exemplarily demonstrated on the one-pot transformation of **7a** into L-phenyllactic acid (**16**, 81% yield, 97% ee, Scheme 4).

In summary, we developed a novel one-pot procedure for the conversion of ortho esters into highly enantioenriched

Table 3. One-Pot Synthesis of the α-Hydroxy Methyl Esters **15**



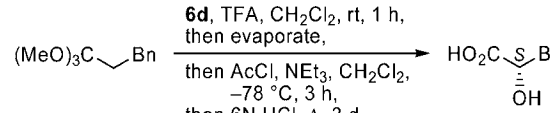
7 15

entry	7	purity[a] (%)	R	15	yield[b] (%)	ee (%)
1	**a**	100	Bn	**a**	80	96[c]
2	**b**[d]	45	CH_2Bn	**b**	72	96[e]
3	**e**	40	*n*-Pent	**e**	75	94[e]
4	**f**	82	$(CH_2)_{10}Me$	**f**	71	98[e]
5	**g**	52	$(CH_2)_{11}Me$	**g**	73	96[e]
6	**h**	>90	$(CH_2)_2OBn$	**h**	67	98[e]
7	**i**	53	$(CH_2)_4Br$	**i**	70	97[e,f]

[a] Contaminated by the corresponding ester. [b] Isolated yields refer to the limiting reagent **6d**; the ortho esters **7** were used in a 2-fold excess. [c] Determined by HPLC on chiral phase. [d] The triethyl orthoate was used. [e] Determined by ^{1}H NMR of the Mosher ester. [f] Ac_2O was used in the acylation step and HBr in MeOH for hydrolysis to avoid a Cl/Br exchange.

(94−98% ee) α-hydroxy esters and acids. The stereochemical information in the α-position was introduced via a multi-heteroatom Cope rearrangement of an *O*-acylated *N*-hydroxy-L-*tert*-leucinol-derived oxazoline *N*-oxide intermediate. Further extension of this method toward the preparation of chiral α-amino acids is in progress.

Scheme 4. One-Pot Procedure for the Synthesis of L-Phenyllactic Acid (**16**) from the Ortho Ester **7a**



7a **16**
81%, 97% ee[a]

[a] Determined by HPLC on chiral phase after conversion of **16** into **15a**.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft DFG.

Supporting Information Available: Full experimental procedures, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901214N