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Asymmetric Meerwein–Ponndorf–Verley reduction of long chain keto alkanoic acid methyl esters

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Abstract: 3-, 7- and 13-Monoketo tetradecanoic acid methyl esters carrying a keto group at the ends and at the middle of the chain with 14 carbon atoms were reduced by a Meerwein–Ponndorf–Verley reaction in the presence of *R*-(+)-1,1'-binaphthalene-2,2'-diol, 1,2:5,6-D-di-*O*-isopropylidene-D-mannitol and L-(–)-menthol. The highest enantiomeric purity of 65% *ee* was found for 13-hydroxy ester isomer. The enantiomeric excess was determined by ^{1}H-NMR shift with Eu(tfc)$_3$ and by optical rotation.

Keywords: asymmetric Meerwein–Ponndorf–Verley reduction, monoketo tetradecanoic acid, *R*-(+)-1,1'-binaphthalene-2,2'-diol (BINOL), 1,2:5,6-D-di-*O*-isopropylidene-D-mannitol, L-(–)-menthol.

INTRODUCTION

Several long chain alkanoic acids occur frequently in nature as constituents of natural lipids, various natural waxes (caranday, carnauba, licuri, conifer, jalop, tree-bark waxes, wool wax and beeswax), brain lipids (cerebrosides) and some seed fats.[1] Most of the naturally occurring hydroxy acids are optically active and they are essential biological molecules, as well as intermediates for organic synthesis.[2]

Methyl 3-, 7-, 13-monohydroxy tetradecanoates were preferred in this work. 3-Hydroxytetradecanoic acid is the major component of Lipid A.[3] 7-Hydroxytetradecanoic acid is found in the hairpencils of male *Amauris* butterflies and in secretions from the male of African milkweed butterflies[4,5] and 13-hydroxytetradecanoic acid was determined in white-fir bark.[6]

The Meerwein–Ponndorf–Verley (MPV) reduction of carbonyl compounds using a secondary alcohol as a hydrogen donor and the carbonyl group as a hydrogen acceptor is one of the important reactions in synthetic organic chemistry. Stoichiometric amounts of metal alkoxides are generally required to obtain good yields of the desired alcohols.[7]

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The aim of this study was to synthesize the enantiomers of 3-, 7-, 13-hydroxy tetradecanoic acid methyl esters of high enantiomeric excess at atmospheric pressure by asymmetric Meerwein–Ponndorf–Verley reduction. *R*-(+)-1,1'-Binaphthalene-2,2'-diol (BINOL) (**1**), 1,2:5,6-D-di-*O*-isopropylidene-D-mannitol (**2**) and L-(–)-menthol (**3**) were used as chiral auxiliaries in this reduction (Scheme 1). The optimal reduction conditions giving the highest enantiomeric purity were determined. The aim was targeted at investigating the effectiveness of the positions of the induction agents, such as keto group and chiral compounds (**1, 2, 3**) in the asymmetric MPV reduction.

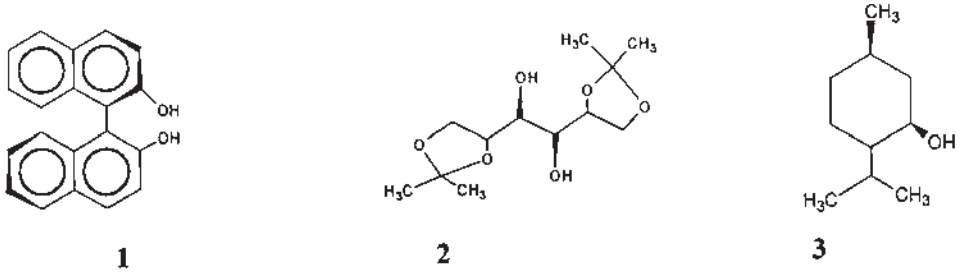
There is no data in the literature concerning the asymmetric MPV synthesis of methyl 3-, 7- and 13-hydroxy tetradecanoates. Only the reduction of several ketones by different asymmetric MPV reduction methods were found.[8,9]

The *S*-enantiomer of 3-hydroxytetradecanoate was obtained by Raney-Nickel,[10,11] ruthenium catalyst[12] and multi-step synthesis.[13] (*S*)-3-Hydroxy- and (*S*)-13-hydroxy- tetradecanoates and their acids were synthesized by chiral $NaBH_4$ reduction.[14]

According to the literature, the synthesis of the 7-hydroxy isomer has not been investigated before. Therefore, enantiomerically enriched 7-hydroxy isomer was synthesized in this work for the first time by asymmetric MPV reduction.

The asymmetric MPV reduction of chiral modified by **1, 2, 3** was applied to the long chain keto esters for the first time in this study.

The development of metal hydrides have diminished the importance of MPV reduction, but it is still a useful and convenient reduction method because of its chemoselectivity, mild reaction conditions and use of an inexpensive hydride source.



1 **2** **3**

Scheme 1.

RESULTS AND DISCUSSION

3-, 7- and 13-Monoketo tetradecanoic acid methyl esters carrying a keto group at the beginning, at the middle and at the end of a chain with 14 carbon atoms were chosen as the prochiral compounds in order to study the influence of the keto position on the asymmetric MPV reduction and enantiomeric excess. Chiral ligands **1, 2, 3** were used in the amount of 1, 1 and 2 mol for 1 mol $Al(O^iPr)_3$, respectively, in the presence of a 2-propanol/THF mixture for the preparation of the chiral aluminium isopropoxide catalyst. Keto ester isomers were reduced by these chiral catalysts at room temperature (Tables I and II).

The asymmetric MPV reductions of the three keto esters studied in this work are postulated in Schemes 2 and 3.

In a previous study[15] an attempt was made to reduce the 3-keto ester by normal MPV reduction at high temperature, which was however unsuccessful. The chiral modified MPV reduction of 3-keto ester was carried out in this work at room temperature, but again no reduction was obtained for this β-keto position. It was found that the building of the enol form of similar compounds led to resistance against reduction.

The 13-keto ester, with a keto group at the end of the chain, provided higher enantiomeric excesses (65 % *ee*) than the 7-keto ester with the keto group in the middle of the chain, in the presence of **1** and **3** (Tables I and II, entries 1 and 3).

TABLE I. Effects of different chiral alcohols (**1, 2, 3**) on the asymmetric reduction of 7-oxotetradecanoic acid methyl ester

Entry	Chiral alcohol	$Al(O^iPr)_3$/chiral alcohol/keto ester (mole ratios)	Temp./Time	Yield %	$[\alpha]_D^{20}$ (c=1, $CHCl_3$)	*ee* %	Abs. conf.
1	**1**	3/3/1	Room temp./3days	60	– 4.58°	52	*R*
2	**2**	3/3/1	Room temp./3days	10	+4,1°	50	*S*
3	**3**	3/6/1	Room temp./3days	12	– 4.7°	54	*R*

Enantiomeric excess (*ee*/%) was determined by the ^{1}H-NMR-shift reagent.

TABLE II. Effects of different chiral alcohols (**1, 2, 3**) on the asymmetric reduction of 13-oxotetradecanoic acid methyl ester

Entry	Chiral alcohol	$Al(O^iPr)_3$/chiral alcohol/keto ester (mole ratios)	Temp./Time	Yield %	$[\alpha]_D^{20}$ (c=1, $CHCl_3$)	*ee* %	Abs. conf.
1	**1**	3/3/1	Room temp./3days	70	– 15°	65	*R*
2	**2**	3/3/1	Room temp./3days	11	+ 9.16°	39	*S*
3	**3**	3/6/1	Room temp./3days	21	– 15°	65	*R*

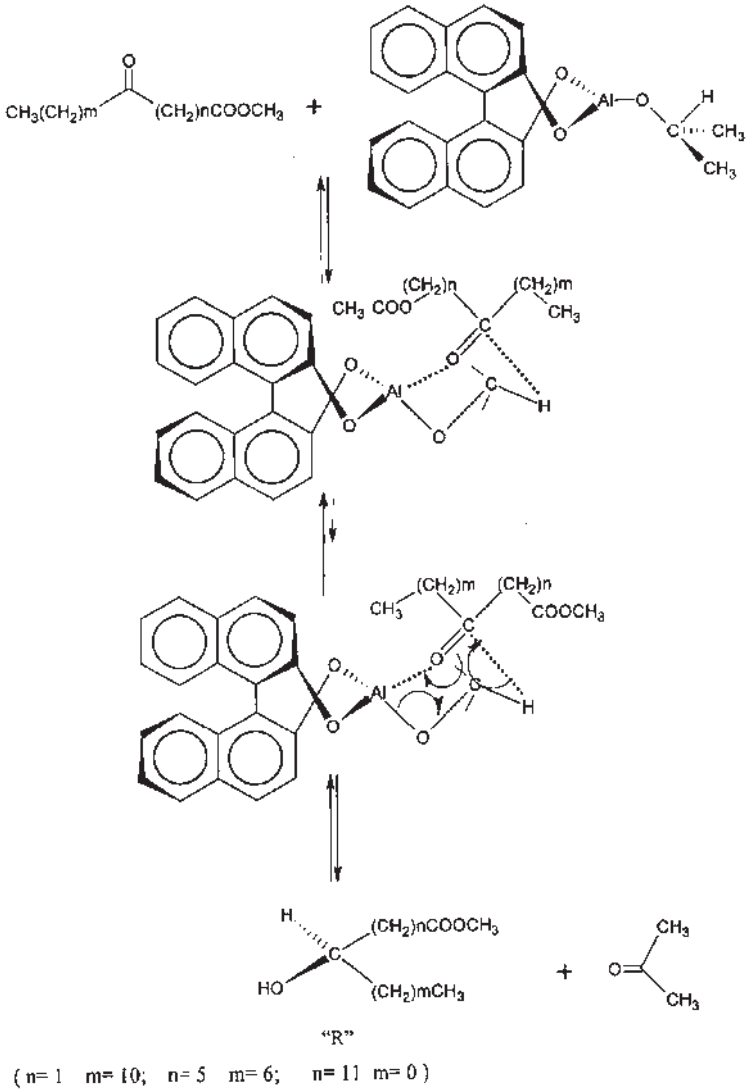
The absolute configuration was determined according to the sign of the optical rotation measured in a previous work[14]

A hydride shift through the six-membered-ring aluminium complex is proposed as the mechanism of MPV reduction,[8] which can also be seen in Schemes 2 and 3.

BINOL (**1**), an atropisomeric compound gave the highest asymmetric MPV reduction yield for the 7- and 13-keto ester isomers (Tables I and II, entry 1). Ligands **2** and **3**, with no aromatic character, inhibited the hydride transfer; therefore, lower reduction yields were obtained for the 7-and 13-keto ester isomers (Tables I and II, entries 2 and 3).

Enantiomeric excess values are higher for the ω1 position showing a chiral difference for **1, 3** with one methyl group and eleven methylene groups. The chiral

aluminium isopropoxide catalysts modified by **1** and **3**, with their more bulkiness in structures, showed higher enantiomeric excesses than **2**. Ligand **1** built with $Al(O^iPr)_3$ has a seven-membered ring. On the other hand, with ligand **2**, a five membered ring is thermodynamically more stable and decreases the ability of Al to form a complex with a keto ester. Therefore, the induction of **2** for the ω1 position is lower than **1**. Ligand **3** formed with the Al catalyst has no ring system. In this way, **3** increased the complexing of the Al centered structure with the keto ester. Thus, higher enantiomeric values could be obtained. The middle of the chain, being hindered from one side by five methylenes carrying the ester group and from the other side by six methylenes with a methyl group at the end shows no difference

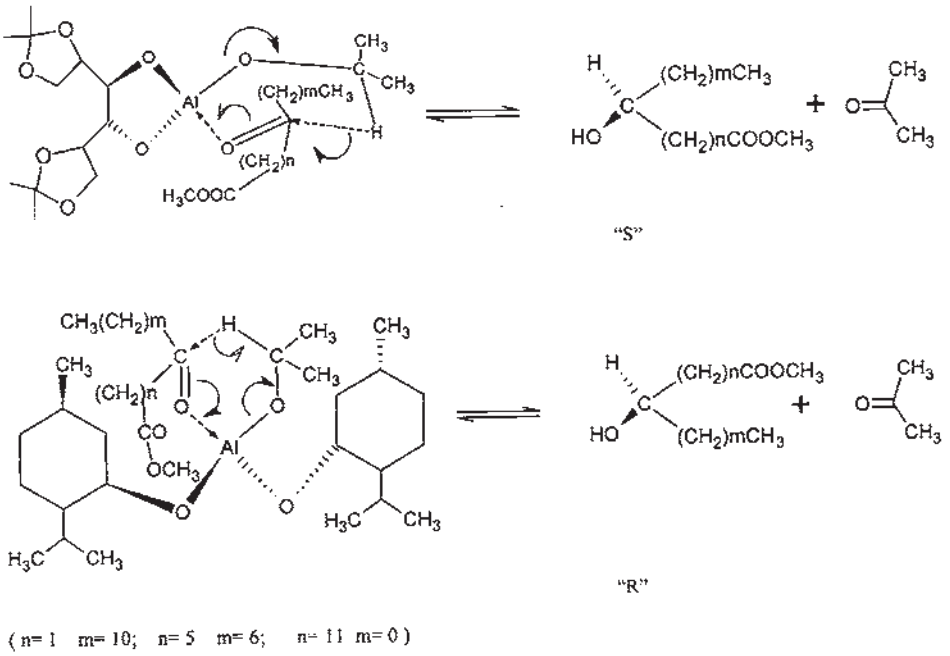


Scheme 2. Postulated working model using ligand **1**.

for **1, 2, 3** and, therefore, the *ee* values of the middle position are very similar to each other (Tables I and II, entries 1, 2, 3).

The ester group of the keto ester also played role through binding to aluminium. The ester group is oriented to Al through the less sterically hindered side. Hence **1** and **3** gave the *R* isomers and **2** the *S* isomer (Schemes 2 and 3).

The absolute configuration of the mentioned enantiomerically enriched hydroxy esters were assigned as *R* and *S* due to the sign of their optical rotation and the literature.[12,14,16,17] In the literature,[14] the configuration of the ω1 position was determined by the chiral HPLC method *via* Daicel OD. The configuration of the middle position was explained by the ^{1}H-NMR shift method with $Eu(tfc)_3$. The difference in the chemical shifts of the split methoxy singlet was distinguishable for the *R* and *S* enantiomers in the presence of the chiral shift reagent $Eu(tfc)_3$. Based on their chemical shifts and the intensity of each signal, the configuration and *ee* values were determined for establishing the absolute configuration. The optical rotation signs obtained in this study were compared with those in the literature.[12,14,16,17] The *R* isomers gave a negative rotation sign, whereas the *S* isomers were positive. Therefore, in this study the enantiomerically enriched hydroxy esters with negative rotation signs are assigned to the *R* configuration. In the ^{1}H-NMR shift, the *S* enantiomer was observed before the *R* enantiomer.



Scheme 3. Postulated working model using ligands **2** and **3**.

EXPERIMENTAL

Enantiomerically pure L-(–)-menthol, 1,2:5,6-di-*O*-isopropylidene-D-mannitol and *R*-(+)-1,1'-binaphthalene-2,2'-diol were obtained from Merck. Of the keto tetradecanoic acid methyl ester isomers used in the asymmetric reduction, the 3- and 13-keto esters were synthesized using acetoacetester reaction[18] and the 7-keto ester by the Blaise reaction.[19] Melting points were determined with Gallenkamp model melting point apparatus and are uncorrected. Refractive indices were measured with 60/70 Model Abbe refractometer. The optical rotations were measured with a AA-5 Automatic Polarimeter. The IR spectra were recorded on a Mattson 1000 series FTIR (as 1% KBr pellets). All asymmetric reduction reactions were carried out at room temperature. The ^{1}H-NMR spectra were recorded on a Bruker Model 400 MHz spectrometer. The chemical shifts are given in ppm relative to the internal standard TMS (δ=0 ppm). Eu(tfc)$_3$=tris[3-(trifluoromethyl-hydroxymethylene)-*d*-camphorato]europium (III) was used as shift reactive in the ^{1}H-NMR method. The asymmetric MPV reductions were controlled by TLC (toluen:ethylacetate/ 8:2).

General procedure for the asymmetric reduction of the prochiral keto esters by chiral-modified MPV[20]

A mixture of Al(O^{i}Pr)$_3$ (5.85 mmol), THF (10 ml), and HO^{i}Pr (5 ml) was stirred until a clear solution was obtained. After a chiral diol (5.85 mmol) had been added and the mixture stirred for another 2 h, a keto compound (1.95 mmol) and 4 Å sieves (0.05 g) were added and the mixture was stirred for a given time at a given temperature. Acetone was removed by distillation for 10 min once every 12 h under reduced pressure followed by the addition of 2–5 ml of 2-propanol. The reaction was quenched by the addition of aqueous HCl (5 %, 20 ml). The mixture was extracted two times with ether (50 ml each time). The combined ether layers were washed with saturated aqueous Na_2CO_3 solution (20 ml) and then with water (30 ml). The organic layer was dried over $MgSO_4$. The products were isolated by a bulb-to-bulb distillation after filtration, in which chiral diols were also recovered (yield > 95%). Rotation measurements on the chiral diols showed there was no racemization and also no structural change during the reduction processes. The hydroxy ester isomers were also purified by column chromatography (toluen:ethylacetate/ 8:2).

7-Hydroxytetradecanoic acid methyl ester: M.p. 36.2–37 °C, n_D^{70} = 1.4343, $[\alpha]_D^{20}$ = –4.58° (*c* = 1, $CHCl_3$) (*R* form) 52 % *ee**, $[\alpha]_D^{20}$ = –4.7° (*c*=1, $CHCl_3$), (*R* form) 54 % *ee***, $[\alpha]_D^{20}$= + 4.1° (*c*=1 $CHCl_3$) (*S* form) 50 % *ee****, IR (KBr, cm^{-1}): 3334 (–OH), 1754 (C=O), 1185 (C–O), ^{1}H-NMR ($CDCl_3$, ppm): 0.88 (*t*, 3H, –CH_3), 1.2–1.35 (*m*, 12H, (–CH_2–)$_6$), 1.35–1.55 (*m*, 8H, (CH_2)$_4$), 1.7 (*s/d*, 1H, –OH), 2.32 (*t* ,2H, –CH_2–CO–), 3.60 (*s,* 1H, –C*H*(OH)), 3.67 (*s*, 3H, –OCH_3).

13-Hydroxytetradecanoic acid methyl ester: M.p. 49–49.8 °C, n_D^{70} = 1.4349, $[\alpha]_D^{20}$ = –15 (*c*=1, $CHCl_3$) (*R* form) 65 % *ee**, $[\alpha]_D^{20}$= –15° (*c*=1, $CHCl_3$) (*R* form) 65 % *ee****, $[\alpha]_D^{20}$ = + 9.16° (*c*=1, $CHCl_3$) (*S* form) 39 % *ee***, IR (KBr, cm^{-1}): 3434 (–OH), 1754 (C=O), 1185 (C–O), ^{1}H-NMR ($CDCl_3$, ppm): 1.19–1.27 (*d*, 3H, –CH_3), 1.35–1.56 (*m*, 20H, (–CH_2)$_{10}$), 1.6 (*s*/*m*), 1H, –OH), 2.3 (*t*, 2H, –CH_2–CO–), 3.67 (*s*, 3H, –OCH_3), 3.79 (*s/m*, 1H,–CH(OH)).

Induction of **1***, **2****, **3*****

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ИЗВОД

АСИМЕТРИЧНА MEERWEIN-PONNDORF-VERLEY-EВА РЕДУКЦИЈА МЕТИЛ-ЕСТАРА ДУГОЛАНЧАНИХ КЕТО-АЛКАНСКИХ КИСЕЛИНА

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Метил-естри 3-, 7- и 13-монокето-тетрадеканских киселина, са кето-групом на крајевима и у средини ланца са 14 угљеникових атома редуковани су Meerwein-Pon-

ndorf-Verley-евом реакцијом у присуству *R*-(+)-1,1'-бинафтален-2,2'-диола, 1,2:5,6- ди-*O*-изопропилиден-D-манитола и L-(–)-ментола. Највећа енантиомерна чистоћа од 65 % *ee* добијена је код естра 13-хидрокси изомера. Оптичка чистоћа је одређена преко ^{1}H-NMR померања у присуству $Eu(tfc)_3$ и оптичке ротације.

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REFERENCES

1. S. Coffey, in *Rood's Chemistry of Carbon Compounds,* Elsevier, Amsterdam, 1965; Vol. 1, Part D, p. 65
2. K. S. Markley, *Fatty Acids*, *Their Chemistry and Physical Properties*, Interscience, New York, 1947, p. 69
3. C. Galanos, O. Luderitz, E. Rietschel, O. Westphal, in *International review of biochemistry*: *biochemistry of lipids II,* T. W. Goodwin, Ed., University Park Press, Baltimore, 1977, Vol. 14, p. 239
4. S. Schulz, W. Francke, M. Boppre, *Biol. Chem. Hoppe-Seyler* **369** (1988) 633
5. S. Schulz, M. Boppre, R. Vane-Wright, *Philos. Trans. R. Soc. London*, **342** (1993) 161
6. H. L. Herget, *Forest Prods. J.* **8** (1958) 335
7. C. F. Graauw, J. A. Peters; H. van Bekkum, J. Huskens, *Synthesis* (1994) 1007
8. K. Nishide, M. Node, *Chirality,* **14** (2002) 759
9. C. R. Graves, E. J. Campbell, S. T. Nuyen, *Tetrahedron Asymmetry* **16** (2005) 3460
10. T. Akira, N. Masaaki, H. Tadao, I. Yoshiharu, *Chem. Lett.* (1980) 1125
11. N. Masaaki, I. Motomasa, O. Hiroshi, H. Tadao, T. Akira, *Bull. Chem. Soc. Jpn.* **55** (1982) 2186
12. M. Bork, T. H. Gregory, S. C. Kalberg, *J. Am. Chem. Soc.* **117** (1995) 4423
13. K. Matsuyama, M. Ikunaka, *Tetrahedron Asymmetry.* **10** (1999) 2945
14. B. Hasdemir, A. Yusufoğlu, *Tetrahedron Asymmetry,* **15** (2004) 65
15. H. Lund, *Ber. Dtsch. Chem. Ges.* **70** (1937) 1520
16. A. Yusufoğlu, *Chim. Acta Turcia* **23** (1995) 107
17. A. Yusufoğlu, H. Çelik, *Chim. Acta Turcica* **24** (1996) 29
18. S. Stallberg-Stenhagen, *Ark. Kemi Mineralo. Geol.* **A20** (1945) 1
19. E. E. Blaise, *C. R. Acad Sci. Hebd*, *Seances* **157** (1913) 1440
20. H. Xianming, R. M. Kellogg, *Rec. Trav. Chim. Pays-Bas* **115** (1996) 410.