Tetrahedron Letters 52 (2011) 4017–4020

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Lead(IV) acetate oxidative ring-opening of 2,3-epoxy primary alcohols: a new entry to optically active α-hydroxy carbonyl compounds

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ARTICLE INFO

Article history:
Received 30 March 2011
Revised 24 May 2011
Accepted 25 May 2011
Available online 1 June 2011

Keywords:
Hydroxycarbonyl compounds
Allyl alcohols
Asymmetric synthesis
Lead tetraacetate

ABSTRACT

The treatment of 2,3-epoxy primary alcohols with lead(IV) acetate (LTA) leads to α-acetoxy aldehydes or α-acetoxy ketones, through the nucleophilic ring-opening of an intermediate oxonium and the subsequent carbon–carbon bond cleavage. This reaction represents a new route to optically active α-hydroxy carbonyl compounds.

1. Introduction

The α-hydroxy carbonyl group occupies a prominent place in organic chemistry. It is found in a wide variety of biologically active natural products,[1a–e] such as the farnesyl-transferase inhibitor kurosain A.[1e] Chiral α-hydroxy ketones (acyloins) are also versatile synthetic intermediates in asymmetric synthesis.[2]

Numerous methods for introducing a hydroxyl group into the α-position to a carbonyl moiety have been reported. These include the direct oxidation of ketone/enol[3] or the most widely used procedure, involving enolates.[4] Most of the above cited methods are restricted to ketones. The corresponding α-hydroxylation of aldehydes is often complicated by undesired self-condensation of the enolates and the instability of the hydroxylated products.[4c] Frequently, α-hydroxy carbonyl compounds are made using multistep transformations.[5]

Several chemical methods for the preparation of chiral α-hydroxy carbonyl compounds have been described in the literature,[6] including stereoselective versions of some of the above methods.[7,8] More recently, the desymmetrization of *meso*-diols through acylation and oxidation,[9] the asymmetric reductive coupling of alkynes and aldehydes,[10] or the asymmetric dihydroxylation of substituted allenes,[11] have been utilized for synthesizing chiral α-hydroxy ketones. An alternative procedure to obtain enantiomerically pure acyloins involves their chemoenzymatic dynamic kinetic resolution (DKR).[12]

Lead(IV) acetate (LTA, lead tetraacetate) has long been considered one of the most useful reagents in organic chemistry because of its ability to bring about various reactions under mild conditions and its low cost.[13] LTA is commonly used for oxidative cleavage (C–C bond cleavage),[14] decarboxylations,[15] acetoxylation,[16] and formation of cyclic ethers (C–O bond formation).[17] It is less often used for C–C bond formation,[18] and C–N bond formation.[19] The use of LTA for the oxidation of allylic alcohols and α,β-epoxy alcohols to the corresponding carbonyl compounds has been reported.[20] More recently, some new applications have been reported, such as the preparation of aryl lead triacetate, utilized in the direct arylation of nucleophiles[21] and a very interesting multistage hetero-domino transformation;[22] both examples allow the construction of unique carbon substitution patterns. Very recently an interesting LTA mediated oxidative fragmentation of homoallylic alcohols[23] and an oxidative cleavage of allyl alcohols induced by the O_3/LTA system[24] have been reported.

In this Letter, we communicate a lead(IV) acetate (LTA) oxidative ring-opening of 2,3-epoxy alcohols leading to α-acetoxy aldehydes or α-acetoxy ketones with complete regioselectivity. The use of asymmetric Sharpless epoxidation allows the enantioselective synthesis of α-acetoxy carbonyl compounds from the corresponding allyl alcohols.

2. Results and discussion

During our research on the synthesis of bioactive natural products we found that 2,3-epoxy alcohols were transformed into

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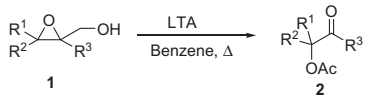
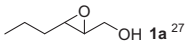
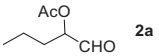
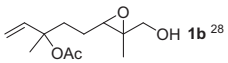
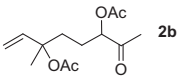
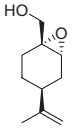
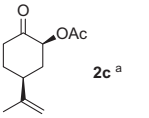
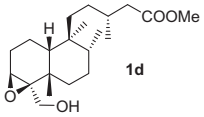
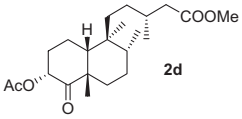
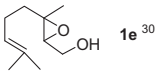
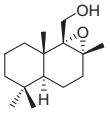
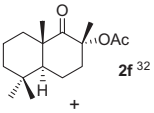
doi:10.1016/j.tetlet.2011.05.116

Table 1
Reaction of 2,3-epoxy alcohols with LTA



1 2

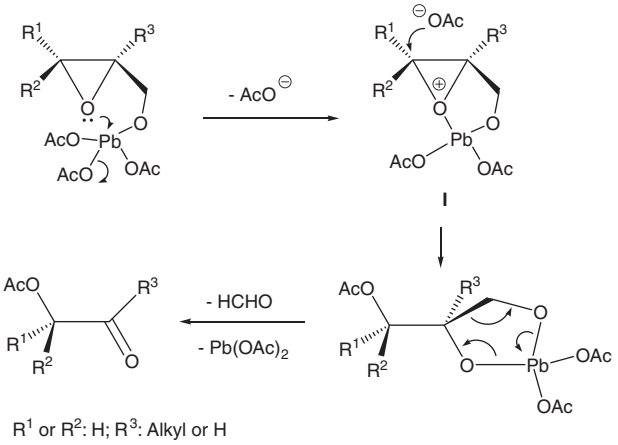
Entry	Epoxy alcohol[26]	Time	Product[26]	%
1	 **1a** [27]	20 min	 **2a**	73
2	 **1b** [28]	1 h	 **2b**	96
3	 **1c** [a, 29]	1.5 h	 **2c** [a]	94
4	 **1d**	2 h	 **2d**	97
5	 **1e** [30]	2 h	Complex mixture	
6	 **1f** [31]	2 h	 **2f** [32] + Complex mixture	26

Synthesis of α-acetoxy aldehydes and α-acetoxy ketones.
[a] Diastereomeric ratio: 6:1.

α-acetoxy aldehydes or α-acetoxy ketones with complete regioselectivity, after treating with one equivalent of LTA in benzene with heating. The oxidation leading to aldehydes was performed at 50 °C and the reaction leading to ketones was carried out at reflux. When 2,3-epoxyhexanol (**1a**) was treated with $Pb(OAc)_4$ in benzene at 50 °C for 20 min 2-acetoxypentanal (**2a**) was obtained in 73% yield.[25] In order to establish the scope and limitations of this reaction a series of 2,3-epoxy alcohols was studied; Table 1 shows some representative examples. 2,3-Epoxyalcohols bearing an alkyl group on the C-2 (compounds **1b–d**) led to the corresponding α-acetoxy ketones **2b–d**; cyclic epoxides of this type (compounds **1c–d**) gave cyclohexanone derivatives (ketones **2c–d**). 3,3-Dialkyl-2,3-epoxyalcohols (**1e–f**) showed a different behaviour to that of the above mentioned epoxy alcohols, affording a mixture of products. Acyclic compounds, such as alcohol **1e**, always produced a complex mixture, whereas the more rigid cyclic epoxy alcohols, such as the bicyclic alcohol **1f**, led to a mixture of compounds including the α-acetoxy ketone **2f** as a minor constituent.

The results obtained when chiral non-racemic epoxy alcohols (entries 3 and 4) were utilized as the substrate reaction deserve special mention. The enantiopure compound **1d** was transformed into the α-acetoxy ketone **2d** as the only isomer. Epoxy alcohol **1c**, a 6:1 mixture of diasteroisomers, gave a mixture of diastereomeric acetoxy ketones **2c** in identical proportion. In both cases an inversion of configuration on α-carbon was observed. However, the 3,3-dialkyl-2,3-epoxyalcohol **1f** afforded the minor α-acetoxy ketone **2f** with retention of the configuration on the α-carbon.

A possible mechanism for this new reaction, which is in agreement with the observed regio- and stereoselectivities, is depicted in Scheme 1. The complete stereoselectivity exhibited by chiral epoxydes, such as compounds **1c–d**, can be explained by the nucleophilic attack of acetate anion in the intermediate oxonium **I**. The

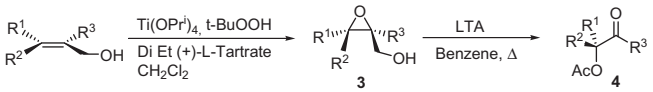


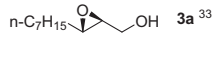
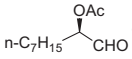
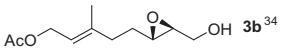
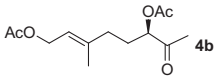
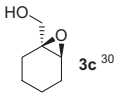
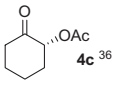
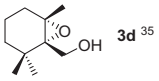
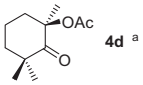
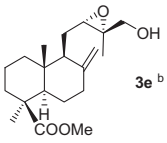
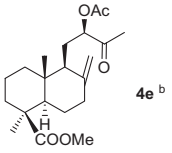
Scheme 1. Mechanism of the reaction of 2,3-epoxy alcohols with LTA.

unsatisfactory results provided by the 3,3-dialkyl-2,3-epoxyalcohols, such as compounds **1e–f**, can be attributed to the formation of a tertiary carbenium ion resulting from the oxonium ring opening, which undergoes different side reactions. The retention of configuration observed in the formation of compound **2f** is presumably the result of nucleophilic attack at the less hindered face of the carbenium ion (entry 6).

In view of the complete stereoselectivity observed for chiral compounds **1c–d**, the enantioselective synthesis of α-acetoxy carbonyl compounds from allylic alcohols, via epoxides obtained through Sharpless reaction,[30] was investigated. Epoxy alcohols **3a–d** were prepared, with >95% enantiomer excess,[37] with the

Table 2
Enantioselective synthesis of α-acetoxy aldehydes and α-acetoxy ketones



Entry	Epoxy alcohol[26]	Time	Product[26]	%
1	 **3a** [33]	20 min	 **4a**	93
2	 **3b** [34]	1 h	 **4b**	95
3	 **3c** [30]	1 h	 **4c** [36]	59
4	 **3d** [35]	4 h	 **4d** [a]	81
5	 **3e** [b]	45 min	 **4e** [b]	92

[a] 70% ee.
[b] Diastereomeric ratio: 6:1.

Sharpless L-(+)DET reagent (Table 2). Treatment of these compounds with $Pb(OAc)_4$ in benzene under heating afforded in high yield the corresponding α-acetoxy carbonyl derivatives **4a–d**. Compounds **4a–c** were obtained with >95% enantiomer excess, as it could be expected. The acetoxy cyclohexanone derivative **4d** resulted in only 70% enantiomer excess; the lower enantioselectivity observed in this case can be attributed to the 3,3-dialkyl substitution pattern of epoxy alcohol **3d**, which can react via carbocationic intermediate. Epoxy alcohol **3e**, a 6:1 mixture of diastereomers obtained after the Sharpless epoxidation of the corresponding enantiopure allyl alcohol, led to a mixture of α-acetoxy ketones **4e** in the approximate 6:1 ratio. The absolute configuration of compounds **2c–f** and **4a–e** was proposed on the basis of the reaction mechanism; compounds **2f** and **4c**, showed similar $[\alpha]_D$ values to those reported in the literature.[32,36]

3. Conclusions

In summary, the treatment of 2,3-epoxy alcohols with $Pb(OAc)_4$ causes a carbon–carbon cleavage which proves to be a useful synthetic tool. α-Acetoxy aldehydes or α-acetoxy ketones can be efficiently synthesized by treating 2,3-epoxy alcohols with lead tetraacetate in benzene under heating. The reaction, which proceeds with complete regio- and high stereoselectivities facilitates the enantioselective synthesis of α-acetoxy carbonyl compounds from allyl alcohols, via Sharpless epoxidation. In order to explore the scope of this reaction, the behaviour of larger cyclic ethers is being studied.

Acknowledgements

The authors thank the Spanish Ministry of Science and Innovation (Project CTQ2009-09932) and the Regional Government of Andalucia (Project P07-FQM-03101 and assistance to the FQM-348 group) for financial support. H.B. thanks the Spanish Agency for the International Cooperation and Development (AECID) for the predoctoral grant provided.

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25. Typical procedure for the reaction of 2,3-epoxy alcohols with lead (IV) acetate: To a solution of epoxy alcohols (1 mmol) in dry benzene (10 mL) was added lead (IV) acetate (1.3 mmol) and the reaction mixture was heated at 50 °C or at reflux for the specified time (monitorized by TLC). Then, the reaction was quenched with 5% Na_2SO_3, extracted with Et_2O, washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (hexanes/ether) to give acetoxy carbonyl compounds.
26. All new compounds were fully characterized spectroscopically and had satisfactory high resolution mass spectroscopy data. Selected data:
Compound **1d**: Colourless oil. $[\alpha]_D^{25}$ = +4.8 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.76 (d, *J* = 6.6 Hz, 3H), 0.79 (s, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.24 (dd, *J* = 3.9, 3.9 Hz, 1H), 1.08 (s, 3H), 1.12 (m, 1H), 1.17 (s, 3H), 1.13 (m, 1H), 1.22–1.34 (m, 3H), 1.34–1.42 (m, 2H), 1.46–1.60 (m, 2H), 1.80–1.89 (m, 3H), 1.97 (m, 1H), 2.04 (m, 1H), 2.13 (dd, *J* = 14.8, 8.1 Hz, 1H), 2.31 (dd, *J* = 14.8, 6.0 Hz, 1H), 3.29 (d, *J* = 3.2 Hz, 1H), 3.63. (dd, *J* = 12.3, 8.7 Hz, 1H), 3.64 (s, 3H), 3.99 (dd, *J* = 12.3, 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.7 (CH_3), 16.7 (CH_2), 19.6 (CH_3), 19.9 (CH_3), 22.7 (CH_3), 29.08 (CH_2), 29.14 (CH_2), 29.26 (CH_3), 31.1 (CH), 34.5 (CH_2), 34.6 (C), 35.6 (CH_2), 37.5 (CH), 39.0 (C), 41.6 (CH_2), 44.3 (CH), 51.4 (CH_3), 57.5 (CH), 61.2 (CH_2), 63.9 (C), 173.6 (C); IR (film): 3450, 1739, 1716, 1699, 1684, 1558, 1507, 1457, 1306, 1233, 1038, 897, 788, 747 cm^{-1}. HRMS (EI) M^+ *m*/*z*: calcd for $C_{21}H_{36}O_4$ 352.2614, found: 352.2608.
Compound **2a**: Colourless oil. $[\alpha]_D^{25}$ = −7.2 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.93 (t, *J* = 7.3 Hz, 3H), 1.34–1.52 (m, 2H), 1.61–1.86 (m, 2H), 2.15 (s, 3H), 4.98 (dd, *J* = 8.4, 4.6 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.8 (CH_3), 18.3 (CH_2), 20.6 (CH_3), 30.7 (CH_2), 78.2 (CH), 170.7 (C), 198.3 (C); IR (film): 1737, 1729, 1468, 1372, 1247, 1105, 1017, 799, 750 cm^{-1}.
Compound **2d**: Colourless oil. $[\alpha]_D^{25}$ = +16.4 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.66 (s, 3H), 0.73 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 1.33 (s, 3H), 1.42 (ddd, *J* = 13.3, 13.3, 3.5 Hz, 1H), 1.45 (ddd, *J* = 13.2, 13.3, 3.6 Hz, 1H), 1.80 (m, 1H), 1.85 (m, 1H), 1.95 (m, 1H), 2.13 (s, 3H), 2.29 (dt, *J* = 13.4, 3.5 Hz, 1H), 2.31 (dd, *J* = 14.9, 6.1 Hz, 1H), 3.66 (s, 3H), 5.65 (dd, *J* = 11.3, 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 15.6 (CH_3), 18.9 (CH_2), 19.1 (CH_3), 19.8 (CH_3), 20.7 (CH_3), 27.3 (CH_2), 28.9 (CH_2), 30.1 (CH_3), 30.9 (CH), 30.95 (CH_2), 35.05 (CH_2), 35.12 (CH_2), 37.2 (CH), 40.1 (C), 41.4 (CH_2), 48.2 (C), 49.8 (CH), 51.4 (CH_3), 72.4 (CH), 170.2 (C), 173.5 (C), 209.6 (C); IR (film): 1746, 1722, 1462, 1437, 1373, 1238, 1173, 1089, 1013, 984, 789, 753 cm^{-1}. HRMS (EI) M^+ *m*/*z*: calcd for $C_{22}H_{36}O_5$ 380.2563, found: 380.2572.
Compound **2f**: Colourless oil. $[\alpha]_D^{25}$ = +72.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.87 (s, 3H), 0.93 (s, 3H), 1.12 (s, 3H), 1.44 (s, 3H), 1.14–1.67 (m, 7H), 3.49 (br d, *J* = 12.3 Hz, 1H), 1.84 (m, 1H), 1.96 (dt, *J* = 12.8, 3.2 Hz, 1H), 2.02 (s, 3H), 2.31 (ddd, *J* = 13.2, 13.2, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 18.2 (CH_2), 19.3 (CH_2), 19.7 (CH_3), 21.5 (CH_3), 22.1 (CH_3), 26.7 (CH_2), 33.0 (CH_3), 33.9 (C), 34.2 (CH_2), 37.2 (CH_2), 41.1 (CH_2), 49.5 (CH), 81.6 (C), 170.0 (C), 214.3 (C). HRMS (EI) M^+ *m*/*z*: calcd for $C_{16}H_{26}O_3$ 266.1882, found: 266.1894.
Compound **3e**: Colourless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.54 (s, 3H), 0.93–1.04 (m, 2H), 1.11 (s, 3H), 1.22 (s, 3H), 1.44 (m, 1H), 1.55–1.96 (m, 9H), 2.10 (br d, *J* = 13.5 Hz, 1H), 2.35 (m, 1H), 2.94 (dd, *J* = 6.8, 4.1 Hz, 1H), 3.44 (d, *J* = 12.1 Hz, 1H), 3.54 (s, 3H), 3.60 (d, *J* = 12.1 Hz, 1H), 4.67 (s, 1H), 4.86 (s, 1H); signals assignable to minor isomer: 3.53 (s, 3H, OCH_3), 4.40 (s, 1H, C=CH_2), 4.80 (s, 1H, C=CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 12.4 (CH_3), 14.4 (CH_3), 20.0 (CH_2), 23.3 (CH_2), 26.1 (CH_2), 28.8 (CH_3), 38.2 (CH_3), 38.6 (CH_2), 39.4 (CH_2), 40.2 (C), 44.3 (C), 51.2 (CH_3), 54.3 (CH), 56.2 (CH), 62.2 (CH), 59.9 (C), 60.1 (CH), 65.6 (CH_2), 107.5 (CH_2), 180.9 (C); IR (film): 3446, 1724, 1645, 1449, 1384, 1154, 1033, 891 cm^{-1}. HRMS (EI) M^+ *m*/*z*: calcd for $C_{20}H_{32}O_4$ 336.2301, found: 336.2308.
Compound **4a**: Colourless oil. $[\alpha]_D^{25}$ = +15.2 (*c* 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.87 (t, *J* = 7.2 Hz, 3H), 1.22–1.35 (m, 8H), 1.36–1.45 (m, 2H), 1.67–1.76 (m, 1H), 1.77–1.86 (m, 1H), 2.17 (s, 3H), 4.98 (dd, *J* = 8.4, 4.8 Hz, 1H), 9.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.1 (CH_3), 20.6 (CH_2), 22.6 (CH_2), 25.0 (CH_2), 28.7 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 31.7 (CH_2), 78.4 (CH), 170.3 (C), 198.4 (C); IR (film): 1742, 1371, 1233, 1045 cm^{-1}. HRMS (EI) M^+ *m*/*z*: calcd for $C_{11}H_{20}O_3$ 200.1412, found: 200.1406.
Compound **4c**: Colourless oil, $[\alpha]_D^{25}$ = +76.0 (*c* 1.2, MeOH). ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.57 (ddd, 13.3, 13.3, 4.1 Hz, 1H), 1.64–1.76 (m, 2H), 1.91 (m, 1H), 2.02 (m, 1H), 2.09 (s, 3H), 2.23 (m, 1H), 2.39 (ddt, *J* = 13.7, 6.1, 1.0 Hz, 1H), 2.51 (m, 1H), 5.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 20.7 (CH_3), 23.8 (CH_2), 27.1 (CH_2), 33.1 (CH_2), 40.7 (CH_2), 76.5 (CH), 170.0 (C), 204.5 (C). HRMS (EI) M^+ *m*/*z*: calcd for $C_8H_{12}O_3$ 156.0786, found: 156.0795.
Compound **4e**: Colourless oil. $[\alpha]_D^{25}$ = +14.1 (*c* 1.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ: 0.50 (s, 3H), 1.06 (ddd, *J* = 13.3, 13.3, 4.0 Hz, 1H), 1.07 (ddd, *J* = 13.8, 13.8, 3.0 Hz, 1H), 1.18 (s, 3H), 1.33 (dd, *J* = 12.5, 3.1 Hz, 1H), 1.53 (m, 1H), 1.70–1.94 (m, 8H), 2.00 (m, 1H), 2.13 (s, 3H), 2.17 (s, 3H), 2.42 (dt, *J* = 11.7, 3.1 Hz, 1H), 3.61 (s, 3H), 4.59 (s, 1H), 4.94 (s, 1H), 4.97 (d, 10.0 Hz, 1H); signals assignable to minor isomer: 3.60 (s, 3H, OCH_3), 4.62 (s, 1H, C=CH_2), 4.90 (s, 1H, C=CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 12.7 (CH_3), 19.9 (CH_2), 20.8 (CH_3), 25.2 (CH_3), 26.17 (CH_3), 26.20 (CH_2), 28.8 (CH_3), 38.2 (CH_2), 38.6 (CH_2), 39.1 (CH_2), 40.1 (C), 44.4 (C), 51.3 (CH_3), 51.6 (CH), 56.3 (CH), 77.8 (CH), 107.0 (CH_2), 147.3 (C), 170.8(C), 177.6 (C), 205.9 (C); IR (film): 1750, 1725, 1644, 1445, 1374, 1248, 1227, 1155, 1046, 983, 893, 756 cm^{-1}. HRMS (EI) M^+ *m*/*z*: calcd for $C_{21}H_{32}O_5$ 364.2250, found: 364.2242.
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37. The enantiomeric excesses were determined by ^1H NMR, utilizing europium (III) tris [3-(heptafluoropropylhydroxymethylene)-*d*-camphorate] [Eu(hfc)$_3$] as chiral shift reagent.
Typical experimental procedure: 10 mg of Europium(III) tris[3-(heptafluoropropylhydroxymethelene)-*d*-camphorate] (Eu(hfc)$_3$) was added to a solution of benzoates obtained from alcohols **3a–d** (15 mg) in $CDCl_3$ (0.5 mL) containing 1% of TMS, and the resulting yellow solution was stand for 15 min. Then, the solution was added to an NMR tube and the ^1H NMR spectrum recorded. The relative intensities (peak heights or peak areas) of the resonance signal of oxygenated methylene protons were measured and the percentage of each enantiomer in the sample calculated.
Chemical shifts of signals for the oxygenated methylene groups on benzoate derivatives of **3a–d** (δ, ppm):
3a benzoate: Racemic mixture: 6.61 (br s, 1H), 6.67 (br s, 1H) and 6.74 (br s, 1H), 6.92 (br s, 1H); chiral compound (>95%): 6.71 (br s, 1H) and 6.87 (br s, 1H).
3b benzoate: Racemic mixture: 6.87 (br s, 1H), 6.97 (br s, 1H) and 7.04 (br s, 1H), 7.11 (br s, 1H); chiral compound (>95%): 6.98 (br s, 1H) and 7.06 (br s, 1H).
3c benzoate: Racemic mixture: 6.52 (br s, 1H), 6.57 (br s, 1H) and 6.64 (br s, 1H), 6.69 (br s, 1H); chiral compound (>95%): 6.62 (br s, 1H) and 6.66 (br s, 1H).
3d benzoate: Racemic mixture: 6.77 (br s, 1H), 6.80 (br s, 1H) and 6.85 (br s, 1H), 6.91 (br s, 1H); chiral compound (>95%): 6.93 (br s, 1H) and 7.01 (br s, 1H).