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

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ABSTRACT

The treatment of 2,3-epoxy 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 pre-eminent place in organic chemistry. It is found in a wide variety of biologically active natural products, [1a-e] such as the pharnesyl-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-hydroxycarbonyl 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 the chemoenzymatic dynamic kinetic resolution (DKR) of these.[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] More recently, some new applications have been reported, such as the preparation of aryl lead triacetate, utilized in the direct arylation of nucleophiles,[20] and a very interesting multistage hetero-domino transformation;[21] both of examples allow the construction of unique carbon substitution patterns. Very recently an interesting LTA mediated oxidative fragmentation of homoallylic alcohols[22] and an oxidative cleavage of allyl alcohols induced by the O_3/LTA system[23] 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 assymmetric Sharpless epoxidation facilitates 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 are transformed into α-acetoxy aldehydes or α-acetoxy ketones with complete regioselectivity, after treating with one equivalent of LTA in benzene with heating. When 2,3-epoxyhexanol (**1a**) was treated with $Pb(OAc)_4$ in benzene at 50 ºC for 20 min 2-acetoxypentanal (**2a**) was obtained in 73% yield.[24] 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

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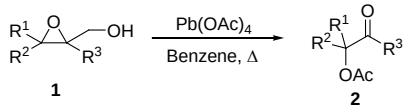
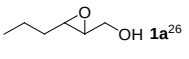
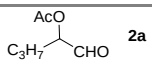
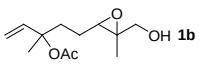
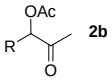
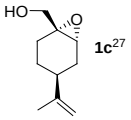
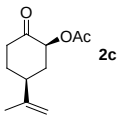
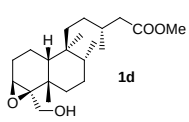
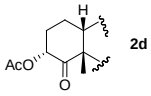
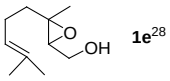
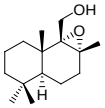
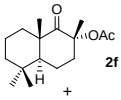
mixture, whereas the more rigid cyclic epoxy alcohols, such as the bicyclic alcohol **1f**, led to a mixture of compounds including the α-acetoxy ketone **2f** as a minor constituent.

Table 1. Reaction of 2,3-epoxy alcohols with $Pb(OAc)_4$. Synthesis of α-acetoxy aldehydes and α-acetoxy ketones.

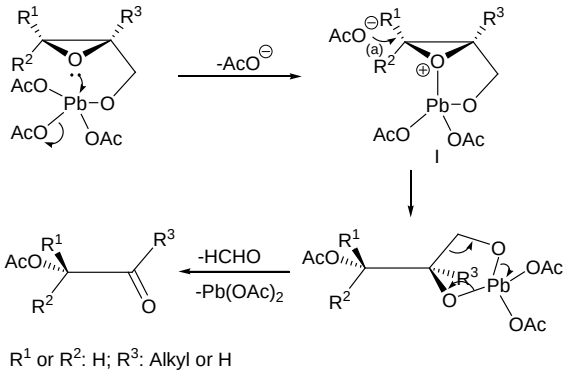


Entry	Epoxy alcohol[25]	Time	Product[25]	%
1	 **1a**[26]	20 min	 **2a**	73[a]
2	 **1b**	1 h	 **2b**	96[b]
3	 **1c**[27]	1.5 h	 **2c**	94[b]
4	 **1d**	2 h	 **2d**	97[b]
5	 **1e**[28]	2 h	Complex mixture[b]	
6	 **1f**	2 h	 **2f** + Complex mixture	26[b]

[a]Run at 50 ºC. [b]Run under reflux.

The results obtained when chiral 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. 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.

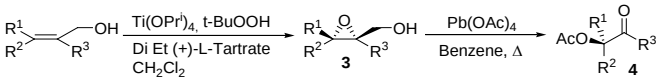
A possible mechanism for this new reaction, which is in agreement with the observed regio- and stereoselectivities, is depicted in Scheme 1. The complete stereoselectivity exhibited by chiral epoxydes, such as compounds **1c-d**, can be explained by the dorsal attack of acetate anion in the intermediate oxonium **I**. The 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 carbocation resulting from the oxonium ring opening, which undergoes different side reactions; the observed retention in the α carbon configuration for compound **2f**, which results after the attack of an acetate anion on the cationic carbon by the less hindered α side, seems to corroborate this assumption (entry 6).

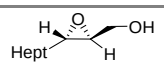
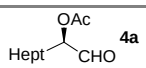
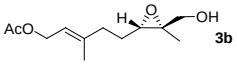
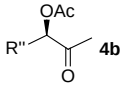
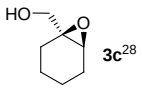
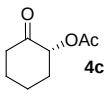
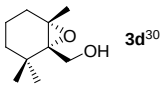
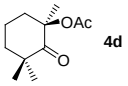
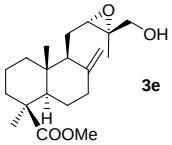
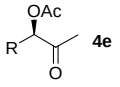


Scheme 1. Mechanism of the reaction of 2,3-epoxy alcohols with $Pb(OAc)_4$.

In view of the complete stereoselectivity observed for chiral compounds **1c-d**, the enantioselective synthesis of α-acetoxy carbonyl compounds from allyl alcohols, *via* Sharpless epoxidation, was investigated. Epoxy alcohols **3a-d** were prepared, with >95% enantiomer excess,[29] with the Sharpless L-(+)DET reagent (Table 2). Treatment of these compounds with

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



Entry	Epoxy alcohol[25]	Time	Product[25]	%
1	 **3a**	20 min	 **4a**	93[a]
2	 **3b**	1 h	 **4b**	95[b]
3	 **3c**[28]	1 h	 **4c**	59[b]
4	 **3d**[30]	4 h	 **4d**	81[b]
5	 **3e**	45 min	 **4e**	92[b]

[a]Run at 50 ºC. [b]Run under reflux.

$Pb(OAc)_4$ 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.[29] 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.

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 stereoselectivity 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.

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24. 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 ºC 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.
25. All new compounds were fully characterized spectroscopically and had satisfactory high resolution mass spectroscopy data. Selected data:
Compound **1d**: $[\alpha]_D^{25}$ = +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}.
Compound **2a**: $[\alpha]_D^{25}$ = -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**: $[\alpha]_D^{25}$ = +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}.
Compound **3e**: ^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); ^{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}.
Compound **4a**: $[\alpha]_D^{25}$ = +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}.
Compound **4e**: $[\alpha]_D^{25}$ = +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); ^{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}.

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