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On the Susceptibility of Organic Peroxy Bonds to Hydride Reduction

Hong-Xia Jin, He-Hua Liu, Qi Zhang, and Yikang Wu*

State Key Laboratory of Bioorganic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

yikangwu@mail.sioc.ac.cn

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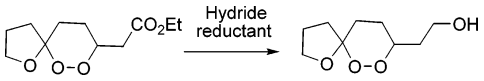

Reduction of organic molecules that contain a peroxy bond is broadly considered as a "risky" and uncertain operation when cleavage of the peroxy linkage is not desired. For this reason, such reduction steps are normally avoided at the planning stage of the synthesis when possible. As a natural consequence, the information in the literature about the susceptibility of organic peroxy bonds to reducing species is scant. In this work the tolerance of organic peroxy bonds to some common hydride reductants was examined systematically for the first time. Using reduction of ester group to alcohol as a probe, $LiAlH_4$, $LiAlH(O^tBu)_3$, $LiBHEt_3$, and $LiBH_4$ were found to be significantly better than other reductants examined when taking into consideration both the completeness of the reduction of ester groups and the peroxy bond survival rate. $LiBH_4$ appeared to be the most suitable reductant for the reduction under discussion, not only because of the high reduction yields/excellent compatibility with peroxy bonds, but also because of the advantages in practical aspects. The results disclosed herein may (hopefully) provide a handy reference for dealing with reduction of other peroxy bond-containing molecules in the future.

Introduction

Peroxy bonds are among the most "fragile" covalent bonds found in organic compounds, with an average[1a] bond energy of only 34 kcal/mol (less than half of that for C−C single bond). Apart from heat and UV light, they are also sensitive to various reducing species. Therefore, reduction of any functional group in the presence of a peroxy functionality is considered by most chemists as a potentially insecure/risky operation when cleavage of the peroxy bond is not desired. As a consequence, the number of existing examples of such reductions in the literature is rather limited. Because "reduction without cleaving peroxy bonds" has not been covered by the major reference books[1b−e] on organic peroxides and has never been designed as an entry point in documentation, retrieval of the scant relevant information in the literature is also a time-consuming task.

The earliest one appeared to be the NaBH4 reduction[2a] of qinghaosu[2b] (an outstanding antimalarial agent, known as artemisinin in the West), where the six-membered lactone functionality was smoothly reduced to lactol in high yield. It should be noted, however, that this reductant usually is not powerful enough to reduce acyclic ester functionality. Treatment of qinghaosu with $LiAlH_4$ led[3] to substantial cleavage of the peroxy linkage. Reduction of the lactone carbonyl to the alcohol level is also known, either using the one-pot procedure ($NaBH_4/BF_3{\cdot}OEt_2$) reported[4] by Jung and co-workers or the two-step procedure (first DIBAL-H ($^iBu_2AlH$)/−78 °C then $Et_3SiH/BF_3{\cdot}OEt_2$) developed by Avery[5] and co-workers. Ziffer and co-workers[6] also used DIBAL-H to reduce an ester group (to corresponding aldehyde and alcohol in 50% and

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29%yield, respectively) in the side-chain of a qinghaosu analogue. Their results showed that at least 79% of the peroxy bond was not broken at −78 °C after 1.5 h.

In their efforts to establish the structure of some marine sponges metabolites, Stierle and Faulkner[7] successfully reduced an ester group (88% yield on a 20-mg scale) with $LiAlH(O^tBu)_3$ (a mild reductant often used to reduce ketones/aldehydes but normally not esters) in refluxing diethyl ether without breaking the peroxy bond in the molecule. Later, the same reagent was also employed by Kitagawa[8] in reduction of a similar peroxy bond-containing ester but without giving any information about the yield or experimental details.

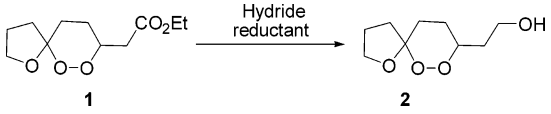
Reduction of ester groups with[9] $LiAlH_4$ without cleaving the co-present peroxy bond was also known. In one case[9a] (on a 20 mg scale) the yield was essentially quantitative, and in another case[9b] the yield was not reported. Slight variation in, for example, the stereochemistry of the substrate might lead[9c] to substantially changed yields. Prolonged reaction time from 3 to 7 h also led to high levels of peroxy bond-breaking products.

Dussault[10] and co-workers examined $LiAlH_4$/−78 °C or 0 °C, $NaBH_4$/rt or 0 °C, and DIBAL-H/−78 °C in the reduction of a peroxy-containing aldehyde. The yield with $LiAlH_4$ at −78 °C was excellent. However, the reduction required very careful operation and did not work so well with another closely related substrate. DIBAL-H was also successfully employed by Porter[11] and co-workers in reducing an ester group in the presence of a hindered (with a tertiary carbon on each side of the peroxy linkage) peroxy bond.

Reduction of peroxy bond-containing ketones (51−62% yield)/cyclic carbonate (yield not specified) with LiBH4 was briefly communicated by Xu[12a] and co-workers. Very recently, in a major breakthrough[12b,c] in developing novel antimalarial agents Vennerstrom and co-workers cleanly reduced[12d] an ethyl ester functionality in a highly stable ozonide (with an adamantanyl and a cyclohexanyl on the two terminals of the peroxy bond, respectively) with $LiBH_4$ in the presence of 10 mol % of $LiBHEt_3$.

Because in most of the above-mentioned investigations the reductions were performed either as part of structural elucidation of natural products or a single step of a total synthesis, the available information on the susceptibility of peroxy bonds to the reductants is rather limited. In the past, when organic peroxides were useful to most organic chemists mainly as radical initiators, such a knowledge deficiency perhaps did not cause much inconvenience (because at that time there were rarely occasions, where a reduction must be done in the presence of a peroxy functionality). Now, as organic peroxides become an important[13] class of antimalarial agents (many other activities are also known) and synthesis of new organic peroxides is already a commonplace, the implicit yet strongly influencing "no reduction" convention perhaps deserves reconsideration—is it really necessary and worthy for a synthesis to take extra steps and a roundabout route just for avoiding involvement of a reduction step? Given the large number of the syntheses of organic peroxides in recent years and obvious absence of convincing experimental data showing how sensitive the peroxy bonds are to for instance the hydride reductants, we believe efforts to find out an answer to this question are well-warranted now.

SCHEME 1



To gain a general knowledge of the stability of peroxy linkage to commonly employed hydride reducing agents, we conducted a systematic investigation. The main results are reported below, which hopefully may serve as a quick reference for dealing with other peroxy bond-containing substrates in the future when a reducing agent is involved.

Results and Discussion

Reduction of Peroxy Ester 1 with Various Common Reducing Agents. Our investigation on the stability of peroxy bonds to hydride reductants started with reduction of compound **1** (Scheme 1). We chose ester functionality here for the reaction because on one hand this type of transformations is very common in organic synthesis, and on the other, such reductions usually need more forcing conditions than reduction of aldehydes or ketones. Thus, if a combination of reagent/conditions can successful reduce an ester to alcohol without breaking the peroxy bond, it is probably also safe and effective for reducing similar peroxy-containing aldehdes/ketones to corresponding alcohols. Some reductants that are known to be able to convert ester groups into alcohols were then tested (Table 1). Because reaction temperature was also an important parameter in the present context, for those potentially useful reductants, the reduction was often examined at several temperatures commonly employed in synthesis.

$LiAlH_4$ is one of the most common reagents for reducing esters. Therefore, in the present work we first

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TABLE 1. Reaction of the Peroxy Ester 1 to 2 with Various Hydride Reducing Agents[a]

entry	reductant (mol equiv)	solvent	temperature	time	yield of **2**
1	$LiAlH_4$ (2.0)	THF	0 °C	13 min	89%
2	$LiAlH_4$ (2.4)	THF	0 °C	35 min	80%
3	$LiAlH_4$ (2.1)	THF	24 °C	15 min	55%[b]
4	Red-Al (1.5)	THF	0 °C∼29 °C	2.3 h	48%[c]
5	DIBAL-H (4.5)	CH_2Cl_2	−78 °C	3.6 h	53%[d]
6	$LiAlH(O^tBu)_3$[e](6.7)	Et_2O[f]	20 °C	25 min	83%[g]
7	$LiAlH(O^tBu)_3$[e](6.7)	Et_2O[f]	Reflux	15 min	80%[h]
8	$LiAlH(O^tBu)_3$[e](6.7)	THF	40∼55 °C	32 min	52%[i]
9	BH_3-THF (2.0)	THF	Reflux	3 h	Traces[j]
10	L-Selectride (3.0)	THF	−78 °C	25 min	Traces[k]
11	L-Selectride (2.5)	THF	−78 °C	2.8 h	66%
12	L-Selectride (2.5)	THF	0 °C	50 min	59%
13	L-Selectride (2.3)	THF	30 °C	1 h	29%
14	K-Selectride (2.0)	THF	−100 °C	30 min	–[l]
15	K-Selectride (2.0)	THF	−78 °C	15 min	–[l]
16	$LiBHEt_3$ (2.5)	THF	0 °C	25 min	86%[m]
17	$LiBHEt_3$ (2.5)	THF	33 °C	14 min	76%
18	$NaBH_4/HSC_2H_4SH$ (1.5)	THF	30∼40 °C	1 h	–[l]
19	$NaBH_4/HSC_2H_4SH$ (1.5)	THF	29 °C	30 min	N. R.[n]
20	$LiBH_4$ (2.0)	Et_2O	29 °C	1 h	89%[o]
21	$LiBH_4$ (2.0)	Et_2O	reflux	8 min	87%[p]
22	$LiBH_4$ (2.0)	Et_2O	0 °C	25 min	91%
23	LiCl+KBH_4 (3.4)	Et_2O	29 °C	2 h	85%

[a] For the general procedure see Experimental Section. [b] The starting **1** disappeared on TLC within 5 min. [c] The starting **1** was recovered in 7% yield. [d] Some aldehyde was still left after reduction at −78 °C for 3.6 h. Warming to room temperature for 10 min led to full reduction to alcohol. [e] About 30% solution in THF. [f] Final reaction medium was 1:4 THF (from the reagent solution)/Et_2O (the added solvent). [g] About 5% of the starting **1** was recovered. [h] The starting **1** disappeared on TLC within 4 min. [i] About 22% of the starting **1** was recovered. [j] The reaction mixture comprised mainly the starting **1**. [k] The starting **1** was near quantitatively recovered. [l] The product mixture was very complicated. [m] The starting **1** disappeared on TLC after 14 min. [n] No reaction. [o] TLC showed disappearance of **1** within 15 min. [p] About 5% of the starting **1** was recovered.

examined the tolerance of peroxy bond to $LiALH_4$ reduction closely. The highest yield (89%) of **2** was obtained at 0 °C with the reaction terminated within 13 min (entry 1). Longer reaction time or higher reaction temperature all led to substantially reduced yields (entries 2 and 3). In all these runs, the starting **1** was fully consumed, which suggested that the mass imbalance was most likely caused by cleavage of the peroxy bond/over reduction (leading to highly polar/water soluble polyols and thus lost in the aqueous workup). The yield of the isolated peroxy alcohol therefore reflected the survival rate of the peroxy bond in the reduction.

Reduction of **1** with Red-Al ($NaAlH_2(OCH_2CH_2OMe)_2$, a reagent that has not been employed in reductions of peroxy bond containing substrates) in THF was very sluggish at 0 °C. At high temperatures (up to 29 °C) the reaction proceeded substantially faster. After 2 h, more than 90% of the starting **1** was consumed. The yield of **2**, however, was only 48% (along with 7% of recovered **1**, entry 4). Thus, in this case the overall survival rate of the peroxy bond was only about 55%.

DIBAL-H did not work so well in the reduction of **1**. When using 3 equiv of DIBAL-H to reduce **1** at −78 °C, substantial amounts of the intermediate aldehyde remained in the reaction mixture after reaction for up to 3.6 h. Quenching the reaction at this stage always led to extensive formation of side-products. Addition of another 1.5 equiv of DIBAL-H did not make much difference. Warming the reduction mixture from −78 °C to the ambient temperature (then kept at the same temperature for 10 min.) before the workup helped to transform all intermediate aldehyde to alcohol. The yield of **2**, however, was still not so good (entry 5), signaling substantial cleavage of the peroxy bond.

$LiAlH(O^tBu)_3$ normally reduces[14] ketones and aldehydes but not esters. However, apart from the examples[7,8] mentioned above, Ayers[15] successfully utilized $LiAlH(O^tBu)_3$ (THF solution, not the commonly employed powder) to reduce malonates into β-hydroxy propionates. For comparison with other reducing agents, we also examined this reductant with **1**. We observed that the reducing power of $LiAlH(O^tBu)_3$ depended on the state/form of the reagent (we are unaware of any records of similar observations in the literature). The reagent that came as THF solution was apparently more powerful than the powdered one (vide infra). It is also interesting to note that addition of diethyl ether to the reaction system significantly facilitated the reduction of ester group, although the solubility of $LiAlH(O^tBu)_3$ in THF is much higher than in diethyl ether. For instance, in 1:4 Et_2O-THF at 20 °C (entry 6) the starting **1** was reduced to **2** in 83% yield within 25 min, along with ca. 5% of recovered **1** (i.e., 88% of the starting peroxy bond survived or 12% of the peroxy bond was cleaved). Treatment of **1** in the same media at refluxing for 15 min led to full consumption of the starting ester, giving the alcohol **2** in 80% yield (entry 7). In the absence of Et_2O, 22% of the **1** remained intact after reaction at 40−55 °C for 32 min and the yield of **2** was only 52% (entry 8). The "survival rate" of the starting peroxy bond in this case was 77%.

The reaction with L-Selectride ($LiBH(^iBu)_3$) at 30, 0, −20, and −78 °C showed very similar TLC chromatogram after 5−10 min' reaction, with the product **2** being the only spot developed away from the origin. In all runs the

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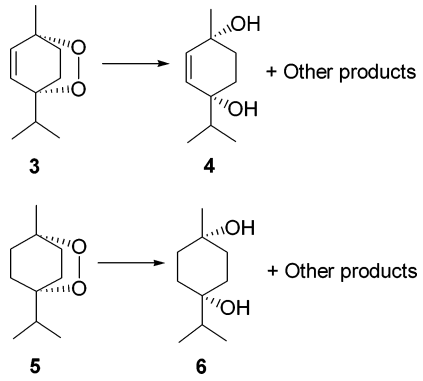
starting **1** completely disappeared soon. However, more careful inspection revealed that the rapid disappearance of **1** on TLC observed with this reductant did not necessarily mean consumption of **1**, because most of the starting **1** was recovered (entry 10) after reaction at −78 °C for 25 min and oxidative workup (H_2O_2/NaOH). Extending the reduction time from 25 min to 2.8 h led to substantially increased yield of **2** (66%, entry 11). If running the reduction at 0 °C for 50 min, **2** was isolated in 59% yield (entry 12). Raising the reaction temperature to 30 °C lowered the yield of **2** even further (29%, entry 13). These results showed that L-Selectride could be tolerated by the peroxy linkage only at low temperatures. Because of the difficulty in monitoring the reaction, relatively tedious workup (compared with e. g., $LiBH_4$ mentioned below), and requirement for low-temperature cooling facility, we did not continue with this reagent any further.

K-Selectride ($KBH(^iBu)_3$) appeared to be much less suitable than L-Selectride. Even at −100 °C the reaction mixture was also rather complicated, while the starting **1** was still present in substantial quantities on TLC. These observations showed that the peroxy bond was significantly cleaved (entry 14). At −78 °C, the mixture became even more complicated, although **1** disappeared on TLC (entry 15). In contrast, $LiBHEt_3$ (super-hydride, which alone has not been examined on any peroxy bond-containing substrate to our knowledge) seemed to be better than L-Selectride. At 0 °C the starting **1** was fully consumed after 14 min's reaction and the alcohol **2** could be isolated in 86% yield. Running the same reaction at 33 °C for 14 min lowered the yield to 76% (entry 17). Formation of side products also became apparent. Similar to what is mentioned above for L-Selectride, $LiBHEt_3$ also tended to coordinate with the substrates (rapid disappearance of **1** on TLC) and thus made the TLC following of the progress of the reduction rather difficult.

We also examined $NaBH_4/HSCH_2CH_2SH$, which could[16] satisfactorily reduce esters according to Guida and coworkers. Reduction of **1** with $NaBH_4/HSCH_2CH_2SH$ at the ambient temperature (ca. 29 °C) resulted in essentially no reactions within time up to 30 min (entry 18). Raising the reaction temperature to 40 °C (oil bath) for 1 h led to complete disappearance of **1**. However, the product mixture was too complicated to allow for isolation of the expected **2**.

Lithium borohydride ($LiBH_4$) is a well-known reagent that is capable of reducing ester functionality to alcohol. It is hence interesting to see whether peroxy bonds can tolerate this hydride. We were very pleased to find that treatment of **1** with 2 mol equiv of $LiBH_4$ in Et_2O at the ambient temperature (ca. 29 °C) for 1 h resulted in the expected alcohol **2** in 89% yield after chromatographic isolation (entry 20). The reaction was quite clean and the workup was very simple. More importantly, the yield was apparently not so sensitive to the variation in temperature/reaction time (entries 21−22) as observed with, e.g., $LiAlH_4$ or $LiBHEt_3$. The possibility of performing the reduction at the ambient temperature without special precautions against moisture/air during the addition of the reagent (cf. DIBAL-H, $LiBHEt_3$ and L/K-Selectride all required syringe operation) was also a great advantage. Finally, it should be mentioned that the $LiBH_4$ prepared in situ from KBH_4 and LiCl (entry 23) gave more or less the same results as the commercially available powder reagent.

SCHEME 2



Tolerance of Ascaridole to Hydride Reduction. To gain further knowledge of tolerance of peroxy bonds to hydride reduction, we next examined the reaction (Scheme 2) of ascaridole **3**[17a,b] (or dihydroascaridole **5**[17c,d]) with some of the most promising hydride reductants according to the results mentioned above (with **4**[17e] or **6**[17f,g] as the peroxy bond cleaved product, respectively). Table 2 summarizes the main results. Here a higher recovery rate of the starting peroxy substrate (or lower yields of the diol/side-products) corresponds to a set of safer reduction conditions for the peroxy bond. In some of the experiments, an equal molar amount of phenylethyl pivalate was introduced to the reaction system to serve as an indicator for the extent of exposure[18] to the hydride (showing relative ease of reduction of ester functionality and cleavage of the peroxy bond).

As observed in the earlier experiments, $LiAlH_4$ was most satisfactorily used for reduction of esters at 0 °C (Table 2, entry 1). Under such conditions the ester function was often completely reduced, whereas the peroxy bond was only partially cleaved (91% vs 8%). More forcing conditions led to substantially increased cleavage of the peroxy bond (entries 2−4).

$LiBH_4$ was remarkably milder and safer than $LiAlH_4$. Treatment of ascaridol (or dihydroascaridol) with this reductant at 25 °C in diethyl ether for 3.3 h led to only negligible amounts of peroxy bond cleaved products and most of the starting peroxy substrate could be recovered (entry 5). The peroxy bond cleavage, however, became more evident with time. If extending the reaction time to 16 h, the survived starting substrate dropped from 92% to 60% (entry 6), and the yield of the diol and other

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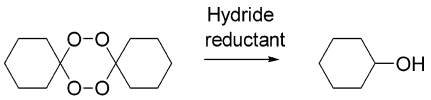
(18) The conditions that allowed for full reduction of the added pivalate using $LiALH_4$ or DIBAL-H were 18 °C/18 min or −78 °C/1 h, respectively. With $LiBH_4$ or $LiALH(O^tBu)_3$ as the reductant, however, 3−4 h at the ambient temperature was required.

TABLE 2. Treatment of Ascaridol with $LiAlH_4$, $LiBH_4$, DIBAL-H, $LiALH(O^tBu)_3$, and $LiBHEt_3$

entry	reductant (mol equiv)	solvent	temp. (°C)	time (h)	substrate recovery	diol **4**	other products[a]
1[b,c]	$LiAlH_4$ (1.5)	THF	0	1.0	79%	8%	
2[b,c]	$LiAlH_4$ (1.5)	THF	25	2.0	65%	13%	~7%
3	$LiAlH_4$ (1.5)	THF	32	6.5	57%	23%	~8%
4	$LiAlH_4$ (1.5)	THF	reflux	2.0	16%	40%	~24%
5[b,d]	$LiBH_4$ (2.0)	Et_2O	25	3.3	92%	traces **6**	
6	$LiBH_4$ (2.0)	Et_2O	25	15.8	60%	17%	~10%
7	$LiBH_4$ (2.0)	Et_2O	32	6.5	65%	14%	~7%
8	$LiBH_4$ (2.0)	Et_2O	reflux	5.8	70%	11%	~7%
9	$LiBH_4$ (2.0)	THF	reflux	2.0	83%	6%	~5%
10[b,e]	DIBAL-H (3.0)	CH_2Cl_2	−78	1.0	80%	3%	~3%
11	DIBAL-H (3.0)	CH_2Cl_2	−78	2.7	78%	6%	~6%
12	DIBAL-H (3.0)	CH_2Cl_2	−30	1.0	15%	26%	~48%
13[b,f]	$LiAlH(O^tBu)_3$ (6.7)	Et_2O/ THF	25	5.8	86%	traces	
14	$LiAlH(O^tBu)_3$ (6.7)	Et_2O/ THF	30	13.9	56%	32%	
15[b,f]	$LiBHEt_3$ (2.0)	THF	0	1.7	75%	7%	4%
16	$LiBHEt_3$ (2.0)	THF	19	6.5	50%	14%	10%
17	$LiBHEt_3$ (2.0)	THF	reflux	2.5	21%	50%	15%

[a] Weight percentage with respect to the substrate. [b] Competition experiment (i.e., reduction of the Piv ester vs cleavage of the peroxy bond) run in the presence of an equal molar amount of $PhCH_2CH_2OPiv$ (Piv = pivaloyl). [c] The yield of $PhCH_2CH_2OH$ was 91%. [d] With dihydroascaridole **5** as the substrate. [e] The yield of $PhCH_2CH_2OH$ was 74% (along with 11% of recovered starting $PhCH_2CH_2OPiv$). [f] The yield of $PhCH_2CH_2OH$ was 92%.

SCHEME 3



products climbed drastically. Raising the temperature did not have so profound effects as extending the reaction time. As shown by entries 7 and 8, substantially more peroxy substrate survived at higher temperatures but within shorter reaction time.

DIBAL-H was a very powerful reductant. Even at −78 °C, after reaction for 1 h, the yield of the diol and other products was already more than negligible. When the reaction temperature increased to −30 °C, most of the peroxy bond was already broken within 1 h.

The results with $LiAlH(O^tBu)_3$ were more or less similar to those observed in the reductions with $LiBH_4$. At the ambient temperature, the majority of the starting ascaridol remained intact for several hours (entry 13), which was long enough for complete reduction of the pivalate. However, if the exposure time was longer than 10 h, the cleavage products also became significant (entry 14).

The profile of peroxy bond cleavage by $LiBHEt_3$ was examined in a similar way. This reagent was more powerful than $LiBH_4$, but less powerful than $LiALH_4$. After treatment with $LiBHEt_3$ at 0 °C for 1.7 h, the recovery yield of intact **3** was 75%. Raising the temperature and extending the reaction time increased the percentage of peroxy bond cleavage further as clearly shown by the raised yields of the diol and other products.

Tolerance of a Teraoxane to Hydride Reduction. We also briefly examined the hydride reduction compatibility with tetraoxane **7**[19] (Scheme 3, Table 3), a robust compound readily prepared from cyclohexanone. Perhaps because the peroxy bonds were somewhat more hindered than those in compound **1** or ascaridole **3**, **7** was rather stable to $LiAlH_4$. In sharp contrast to what was observed with the other peroxy substrates, the survival rate for **7** was essentially the same at 0 and 28 °C (the ambient temperature).

TABLE 3. Treatment of 7 with $LiAlH_4$, $LiBH_4$, DIBAL-H, $LiBHEt_3$, and $LiAlH(O^tBu)_3$

entry	reductant mol equiv)	solvent	temp. (°C)	time (h)	substrate recovery[a]
1	$LiAlH_4$ (1.5)	THF	0	2.0	88%
2	$LiAlH_4$ (1.5)	THF	28	2.0	85%
3	$LiAlH_4$ (1.5)	THF	19	11	64%
4	$LiAlH_4$ (1.5)	THF	50	2.0	64%
5	$LiBH_4$ (2.0)	Et_2O	19	11	86%
6	$LiBH_4$ (2.0)	Et_2O	reflux	10	85%
7	DIBAL-H (3.0)	CH_2Cl_2	26	3.0	42%
8	$LiBHEt_3$ (2.0)	THF	0	2.0	95%
9	$LiBHEt_3$ (2.0)	THF	18	22	90%
10	$LiBHEt_3$ (2.0)	THF	reflux	2.0	83%
11	$LiAlH(O^tBu)_3$ (6.7)	Et_2O/THF	19	19	86%

[a] Because of its relatively low boiling point., it was not convenient to calculate the yield of **8**.

Similarly, stirring with $LiBH_4$ at the ambient temperature (19 °C) for a few hours did not led to any discernible changes. Even after refluxing for 11 h, the starting **7** still could be recovered in 85% yield. DIBAL-H, however, cleaved **7** much more effectively. Only 42% of the starting **7** was recovered after treatment with DIBAL-H at 26 °C for 3 h (entry 7). $LiBHEt_3$ and $LiAlH(O^tBu)_3$ were all well-tolerated as expected (entries 8−11).

Tolerance of the Peroxy Bond in a Plakoric Acid Analogue to Hydride Reduction. The three experiments (Table 4) with a plakoric acid analogue (Scheme 4) carried out under parallel conditions provided an even closer comparison of the peroxy-bond cleavage power of $LiAlH_4$, $LiBH_4$, and $LiAlH(O^tBu)_3$, these three promising reductants.

The reactions (reduction of the ester group and the cleavage of the peroxy bond) with $LiAlH_4$ proceeded remarkably faster than with the other two reagents. The peroxy bond-cleavage products appeared on TLC within minutes. Apparently, utilization of this reductant on peroxy bond-containing substrates requires greater care

(19) (a) Sanderson, J. R.; Paul, K.; Story, P. R.; Denson, D. D.; Alford, J. A. *Synthesis* **1975**, 159−161. (b) Xu, W.-L.; Chen, Y.-F.; Zhang, S.-L. *Chem. Res. Chin. Univ.* **1999**, *15*, 329−332.

TABLE 4. Comparison of $LiAlH_4$, $LiBH_4$, and $LiAlH(O^tBu)_3$ in Reduction of 9 (cf Scheme 4)

entry	reductant (mol equiv)	solvent	temp. (°C)	time (min)	10	side products[a]
1	$LiAlH_4$ (2.0)	THF	0	13	81%	18%
2	$LiBH_4$ (2.0)	Et_2O	0	39	86%	20%
3	$LiAlH(O^tBu)_3$ (6.7)	Et_2O/THF	0	52[b]	50%[c]	20%

[a] Weight percentage with respect to the substrate. [b] Then stirred at 34 °C for 106 min before workup. [c] Along with ca. 30% of recovered starting **9**.

than using other reagents. To minimize over-reduction, monitoring the progress of the reaction must be done soon after the addition of all reactants, especially for those substrates where the peroxy bond is not highly hindered.

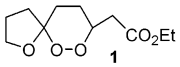
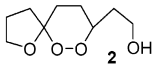
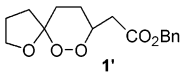
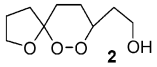
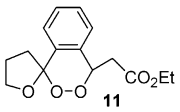
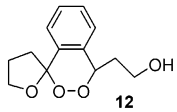
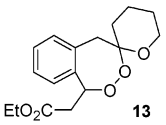
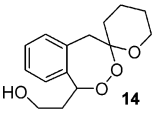
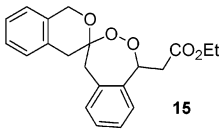
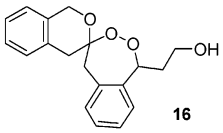
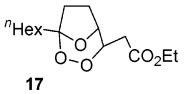
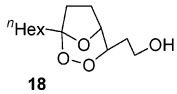
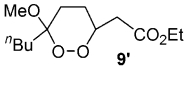
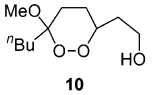
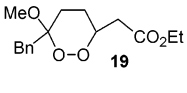
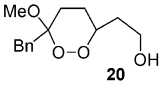
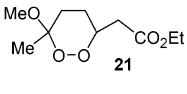
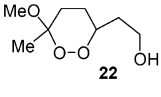
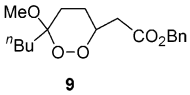
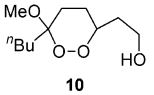
$LiBH_4$ was well-tolerated by the peroxy bond while reducing the ester group effectively as observed with other substrates, demonstrating again the great potential of this reductant.

SCHEME 4

9 **10**

The reducing power of $LiAlH(O^tBu)_3$ was remarkably lower than $LiAlH_4$ or $LiBH_4$ here. Even under the most suitable conditions (using the reagent came as THF solution and reacting in a mixture of Et_2O−THF), the reaction was very sluggish at 0 °C. Raising the temperature to 34 °C after stirring at 0 °C for 52 min still failed to drive the reaction to complete (ca. 30% of starting **9** was recovered). On the other hand, the peroxy bond cleaved products were as much as observed with the

TABLE 5. Reduction of Some Plakoric Acid Analogues with $LiBH_4$[a]

entry	substrate	temp. (°C)	time (min)	product	yield%
1[b]	 **1**	0	24	 **2**	91
2	 **1'**	26	51	 **2**	89
3	 **11**	25	20	 **12**	97
4	 **13**	26	19	 **14**	97
5	 **15**	29	60	 **16**	94
6	 **17**	30	12	 **18**	92
7	 **9'**	0	34	 **10**	85
8	 **19**	27	20	 **20**	87
9	 **21**	28	18	 **22**	88
10[c]	 **9**	0	39	 **10**	86

[a] All starting esters (except for **11**, **17**, and **21**, which were single diastereomer isolated by column chromatography) employed in the reduction were a mixture of the two diastereomers (almost inseparable on TLC). As the chiral centers were not touched during the reduction, the products were presumably also mixtures of diastereomers. However, the diastereomeric mixtures served equally well as far as the compatibility of the peroxy bond to hydride reductants was concerned. [b] Data taken from Table 1 for comparison. [c] Data taken from Table 4 for comparison.

TABLE 6. Reduction of $PhCH_2CO_2Me$ with $LiAlH(O^tBu)_3$ (6.7 mol equiv) under Different Conditions

entry	reagent[a]	solvent[b]	temperature/time	ratio[c]
1	A	3:2 Et_2O/THF	20 °C/30 min	100:0
2	A	THF	20 °C/30 min	76:24
3	A	3:2 Et_2O/THF	25 °C/15 min	100:0
4	A	1:1 Et_2O/THF	20 °C/15 min	100:0
5	B	Et_2O	20 °C/4 h	21:79
6	B	THF	20 °C/4 h	28:62
7	B	Et_2O	19 °C/14.5 h	31:69
8	B	THF	19 °C/14.5 h	75:25
9	B	THF	20 °C/1 h then reflux 2 h	75:25
10[d]	B	2:1 Et_2O/THF	20 °C/1 h then reflux 2 h	55:45
11[e]	B	2:1 Et_2O/THF	30 °C/1 h then reflux 2 h	69:31
12[f]	B	5:4 Et_2O/THF	28 °C/1 h then reflux 2 h	39:61

[a] A, $LiAlH(O^tBu)_3$ solution in THF; B, $LiAlH(O^tBu)_3$ powder. [b] Final composition of the reaction medium after adding Et_2O. [c] The ratio of $PhCH_2CH_2OH/PhCH_2CO_2Me$ in the product mixture as estimated from the integrals in ^1H NMR of the product mixture. [d] The $LiAlH(O^tBu)_3$ powder was suspended in THF at the ambient temperature. [e] The $LiAlH(O^tBu)_3$ powder was refluxed in THF (still a suspension) for 0.5 h before cooling down and introducing the Et_2O. [f] The $LiAlH(O^tBu)_3$ powder was refluxed in THF for 2 h (still a suspension) before cooling down and introducing the Et_2O.

other two more powerful reductants. The results here are in sharp contrast to the reduction of ethyl (**1**, cf. Table 1) or methyl esters (cf. ref 7 and the results in the last section of this paper), indicating that the ease of the reduction with this reagent may depend significantly on the alkyl group in the ester functionality.

Reduction of the Ester Functionality in Some Plakoric Acid Analogues with $LiBH_4$. The results above show that among all the reductants tested, $LiAlH_4$, $LiAlH(O^tBu)_3$, $LiBHEt_3$, and $LiBH_4$ gave the best results. Because $LiBH_4$ was particularly attractive when taking all aspects into consideration, we next examined this reductant with a number of other peroxy substrates (Table 5).

The yields are generally high. As observed in reduction of other substrates, variation of the temperature or time did not have much influence on the yield. Benzyl ester was also reduced satisfactorily. Compared with $LiAlH(O^tBu)_3$ (which is only effective for methyl/ethyl esters but not the benzyl esters even under the optimal conditions), the application scope of $LiBH_4$ is apparently broader. Taking the reducing power, compatibility with peroxy functionality, convenience of operations as well as reagent handling into consideration, $LiBH_4$ is evidently superior to all the other reductants in the reduction of peroxy bond-containing substrates.

On the Reducing Power of $LiAlH(O^tBu)_3$. We have mentioned in the first section that the reducing power of $LiAlH(O^tBu)_3$ seemed to be dependent on the state/form of the reagent. Addition of diethyl ether to the reaction medium (THF) appeared to have an accelerating effect on the reduction. As we were unable to find related reports in the literature, it would be interest to see whether this effect occurred only in the presence of a peroxy bond or existed generally. Hence, we also briefly tested $LiAlH(O^tBu)_3$ on an ordinary ester that did not contain any peroxy functionality. For convenience of monitoring the progress of the reduction, methyl phenylacetate was chosen as the substrate. The reduction was conducted under different conditions as shown in Table 6. The substrate/product ratio was then measured by ^1H NMR (taken on the crude product mixture after simple workup).

Again, in the presence of Et_2O the reduction (with the commercially available $LiAlH(O^tBu)_3$ THF solution as the reductant) of $PhCH_2CO_2Me$ proceeded rather fast and complete (Table 6, entries 1, 3, and 4). In the absence of Et_2O, only 76% of the starting ester was reduced under the otherwise the same conditions (entry 2). Powdered $LiAlH(O^tBu)_3$ was much less active. At the ambient temperature for 4 h, the reduction was still rather incomplete in either Et_2O or THF (entries 5 and 6). Prolonged reaction time did not help much if the reaction medium was Et_2O alone (entry 7). In THF (in which the solubility of the reductant is significantly higher than in Et_2O), however, the yield could be raised to 75% after 14.5 h (entry 8). Finally, it is interesting to note that reflux of the powdered reagent in THF before the reduction and with the added Et_2O still could not gave the same reactivity as observed with the commercially available $LiAlH(O^tBu)_3$ THF solution (entries 10−12).

Conclusions

We have conducted a systematic investigation on the tolerance of organic peroxy bonds to some hydride reducing agents commonly utilized in organic synthesis. Using reduction of ester group to the corresponding alcohol as a reference reaction to define the end point of exposure to the reducing agent, we measured the survival rate of organic peroxy bonds after treatment with each individual reducing agent selected. The results show that $LiAlH_4$, $LiAlH(O^tBu)_3$, $LiBHEt_3$, and $LiBH_4$ are significantly better than other reductants examined when taking into consideration both the efficiency of the ester reduction and survival of the peroxy bond. Reduction with $LiAlH_4$ requires careful control (best carried out at 0 °C for only a few minutes in most cases). Slight increase in temperature or reaction time may lead to significantly increased over-reductions (cleavage of the peroxy bond). The powdered $LiAlH(O^tBu)_3$ could not reduce ester functionality to any synthetically useful extents without breaking the peroxy bond present in the substrate. The commercially available $LiAlH(O^tBu)_3$ solution in THF is a reagent powerful enough to reduce methyl or ethyl esters while still weak enough to be tolerated by the peroxy bonds. The presence of Et_2O facilitates the reduction of esters with the $LiAlH(O^tBu)_3$ solution in THF, although the solubility of the reagent is much higher in THF than in ether. $LiBHEt_3$ is also a potentially useful reagent for the reduction of the peroxy-esters. $LiBH_4$ is much more attractive than all other reagents so far tested. Apart from the excellent reducing power and peroxy bond compatibility, the advantages in practical aspects over the other reductants are also very impressive. It is hoped that the results disclosed herein may add a useful piece to the existing knowledge of organic peroxides and provide a quick reference for dealing with other peroxy bond-containing molecules when a hydride reducing agent is involved.

Experimental Section

Typical Procedure 1 (Reduction of 1 with L-Selectride, Preparation of 2-(1,6,7-Trioxa-spiro[4.5]dec-8-yl)-ethanol (2)). L-Selectride (1.0 M, 0.85 mL) was added (via a

syringe) to a solution of **1** (78 mg, 0.34 mmol) in dry THF (2.3 mL) stirred at −78 °C under N_2. After stirring at the same temperature for 2.75 h, MeOH (0.2 mL) was added to the reaction mixture. The −78 °C bath was then replaced by an ice−water bath. Aqueous NaOH (10%, 3 mL) was introduced slowly, followed by H_2O_2 (30%, 2 mL). The stirring was continued at the ambient temperature for another 4.5 h. The phases were separated and the aqueous layer was back-extracted with Et_2O. The combined organic layers were washed in turn with H_2O, saturated $NaHSO_3$ solution, brine, and dried over anhydrous Na_2SO_4. The residue after removal of the solvents was purified by column chromatography on silica gel (2:1 Et_2O/hexanes) to give alcohol **2** (42 mg, 65.7%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35−4.26 (m, 1H), 4.12−4.01 (m, 2H), 3.82−3.72 (m, 2H), 2.05−1.66 (m, 11H); IR (film): 3425, 2949, 1440, 1357, 1164, 1110, 1043 cm^{-1}; ESI-MS (*m/z*): 189 ($[M + H]^+$); ESI−HRMS calcd. for $C_9H_{16}O_4Na$ ($[C_9H_{16}O_4Na]^+$) 211.0937, found 211.0941. Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.44; H, 8.73.

Typical Procedure 2 (Reduction of 1 with Red-Al). Red-Al (wt 65% in toluene, 0.14 mL) was added dropwise (via a syringe) to a solution of the **1** (74 mg, 0.32 mmol) in dry THF (3.2 mL) stirred at 0 °C under N_2. The stirring was continued at the ambient temperature for 2.3 h. With cooling in ice−water bath aqueous NaOH (10%, 4 mL) was added dropwise. The phases were separated and the aqueous phase was back-extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent left an oily residue, which was purified by column chromatography on silica gel to give **2** (29 mg, 48%).

Typical Procedure 3 (Reduction of 1 with DIBAL-H). DIBAL-H (1.0 M solution in cyclohexane, 2.3 mL) was added (via a syringe) to a solution of **1** (174 mg, 0.76 mmol) in dry CH_2Cl_2 (3.8 mL) stirred at −78 °C under N_2. The stirring was continued at −78 °C for 3.6 h. Then the bath was allowed to warm to the ambient temperature. MeOH (0.02 mL) was added, followed by aqueous saturated potassium sodium tartrate solution (5 mL) and Et_2O (7 mL). The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were filtered and washed with copious amount of H_2O and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel to give **2** (75 mg, 53%).

Typical Procedure 4 (Reduction of 1 with $LiAlH_4$). With stirring and cooling (0 °C), $LiAlH_4$ (20 mg) was added in portions to a 1.0 M solution of **1** (59 mg, 0.26 mmol) in dry THF (2.5 mL). The resulting mixture was stirred at the same temperature until TLC showed complete disappearance of **1**. Saturated aqueous NH_4Cl was added, followed by EtOAc. Acidification of the mixture with aqueous HCl (2 N, two drops) led to disappearance of the gray precipitates. The phases were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel to give **2** (43 mg, 89%).

Typical Procedure 5 (Reduction of 1 with $LiAlH(O^tBu)_3$). A 30% solution of $LiAlH(O^tBu)_3$ in THF (1.3 g) was added dropwise (via a syringe) to a solution of **1** (54 mg, 0.23 mmol) in dry Et_2O (4.6 mL) stirred at the ambient temperature. When TLC showed complete disappearance of **1**, the reaction was quenched with H_2O. The mixture was acidified with aqueous HCl (2 N, two drops, which turned the reaction mixture into a clear solution) before the phases were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel to give **2** (36 mg, 83%).

Typical Procedure 6 (Reduction of 1 with $LiBH_4$). $LiBH_4$ (13 mg) was added to a 1.0 M solution of **1** (66 mg, 0.287 mmol) in anhydrous Et_2O stirred at the ambient temperature. The mixture was stirred until TLC showed complete disappearance of **1**. The reaction was quenched with saturated aqueous NH_4Cl with cooling (ice−water bath). The phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel to give **2** (49 mg, 91%).

Typical Procedure 7 (Reduction of 1 with $LiBHEt_3$). $LiBHEt_3$ (1.0 M, 0.5 mL) was added (via a syringe) to a solution of **1** (57 mg, 0.25 mmol) in dry THF (2.0 mL) stirred at 0 °C under N_2. The stirring was continued at the same temperature until TLC showed complete disappearance of **1**. The reaction was quenched with saturated aqueous NH_4Cl, followed by aqueous HCl (2 N, two drops). The phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel to give **2** (40 mg, 86%).

Reduction of Plakoric Acid Analogues 9′, 11, 13, 15, 17, 19, and 21 with $LiBH_4$ (Preparation of 2-(6-Butyl-6-methoxy-1,2-dioxinan-3-yl)-ethanol (10), 2-(Spiro[2,3-dioxo-benzocyclohexane-4,2′- tetrahydrofuran]-1-yl)-ethanol (12), 2-(Spiro[5-dihydro-2,3-dioxo-benzocycloheptane-4,2′- tetrahydropyran]-1-yl)-ethanol (14), 2-(Spiro-[5-dihydro-2,3-dioxo-benzocycloheptane-4,2′- (3′,6′-dihydro)-benzotetrahydropyran]-1-yl)-ethanol (16), 2-(4-Hexyl-2,3,7-trioxa- bicyclo[2.2.1]hept-1-yl)-ethanol (18), 2-(6-Benzyl-6-methoxy-1,2-dioxinan-3-yl)-ethanol (20), and 2-(6-Methoxy-6-methyl-1,2-dioxinan-3-yl)-ethanol (22)). The procedure was the same as that for the reduction of **1** with $LiBH_4$ described above (Typical Procedure 6). The reaction temperature/time and the yield for each individual substrate are listed in Table 5.

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Note Added after ASAP Publication. An oxygen atom was missing in the structure of the starting material in the abstract/toc graphic in the version posted April 26, 2005; the corrected version posted April 28, 2005.

Supporting Information Available: The general remarks for the Experimental Section, the data for all new compounds not mentioned in the Experimental Section, reduction of **3**, **7**, and **9**, ^{1}H NMR of **9**, **9′**, **17**, and ^{13}C NMR spectra of compounds **18** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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