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Article

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Stabilization of $NaBH_4$ in Methanol Using a Catalytic Amount of NaOMe. Reduction of Esters and Lactones at Room Temperature without Solvent-Induced Loss of Hydride

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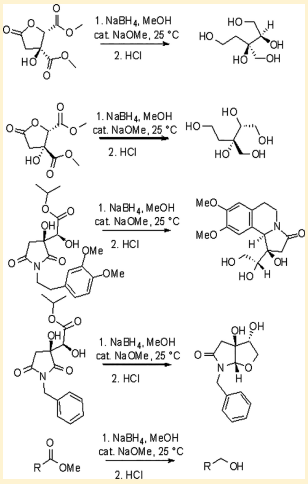
Supporting Information

ABSTRACT: Rapid reaction of $NaBH_4$ with MeOH precludes its use as a solvent for large-scale ester reductions. We have now learned that a catalytic amount of NaOMe (5 mol %) stabilizes $NaBH_4$ solutions in methanol at 25 °C and permits the use of these solutions for the reduction of esters to alcohols. The generality of this reduction method was demonstrated using 22 esters including esters of naturally occurring chiral γ-butyrolactone containing dicarboxylic acids. This method permits the chemoselective reductions of esters in the presence of cyano and nitro groups and the reductive cyclization of a pyrrolidinedione ester to a fused five-membered furo[2,3-*b*]pyrrole and a (−)-crispine A analogue in high optical and chemical yields. Lactones, aliphatic esters, aromatic esters containing electron-withdrawing groups, and heteroaryl esters are reduced more rapidly than aryl esters containing electron-donating groups. The ^{11}B NMR spectrum of the NaOMe-stabilized $NaBH_4$ solutions showed a minor quartet due to monomethoxyborohydride ($NaBH_3OMe$) that persisted up to 18 h at 25 °C. We postulate that $NaBH_3OMe$ is probably the active reducing agent. In support of this hypothesis, the activation barrier for hydride transfer from $BH_3(OMe)^-$ onto benzoic acid methyl ester was calculated as 18.3 kcal/mol.



INTRODUCTION

Reduction of carboxylic esters to the corresponding alcohols is an important transformation in synthetic organic chemistry and is generally carried out using powerful reducing agents, such as lithium aluminum hydride ($LiAlH_4$) and lithium borohydride ($LiBH_4$). Even though these reagents are very effective for ester reductions, they are highly moisture sensitive and cannot tolerate most of the other reducible groups typically present in multifunctional molecules.[1] Unlike other hydrides, sodium borohydride ($NaBH_4$) is attractive since it is cost-effective and less moisture sensitive. However, sodium borohydride is normally sluggish toward reducing esters, and only in special cases, such as high temperatures or with electronically modified[2] ester carbonyls, can the reductions be achieved. Carrying out the reduction of esters using sodium borohydride at room temperature would be highly desirable since $NaBH_4$ is extensively used in chemical industry.[3] $NaBH_4$ easily reduces aldehydes and ketones to the corresponding alcohols.[4−6] It also reduces electrophilic carbonyls like ketoesters,[7] anhydrides,[8,9] acid chlorides,[10] and imides.[11] Reduction of carbonyl groups that are less reactive than these highly reactive systems is always a major challenge when carbonyls with different electron demands are present in a substrate. The poor solubility of $NaBH_4$ in common ethereal solvents poses an additional challenge for using $NaBH_4$ for routine reductions.

The reduced electrophilicity of the ester carbonyl group makes $NaBH_4$ a less preferred reducing agent for the reduction of esters.[12] Scheme 1 summarizes the known methods for the reduction of esters with $NaBH_4$ in methanol. Addition of metal salts, such as LiCl, LiBr, $MgCl_2$, $CaCl_2$, $ZnCl_2$, and $AlCl_3$, to sodium borohydride increases its reduction capabilities (Scheme 1, entry 1).[13−16] There are also reports of the reduction of esters using $NaBH_4$ in the presence of Ce[17] or Co[18] catalyst (Scheme 1, entry 2) supported on cationic surfaces.[12] Under reflux conditions, $NaBH_4$ has been reported to reduce esters in protic solvents (Scheme 1, entry 3).[1,19−21] Esters bearing substituents like hydroxyl/oxo/amino in the α- or β-positions have been reduced by $NaBH_4$ via intramolecular hydride transfer (Scheme 1, entry 4).[22−25] Unfortunately, alcohol solvents, such as methanol, are not compatible with $NaBH_4$ at elevated temperatures because decomposition of $NaBH_4$ becomes competitive with the reduction. Under such conditions, a large amount of $NaBH_4$ is often required.[26] In reality, $NaBH_4$ quickly reacts with MeOH and necessitates the

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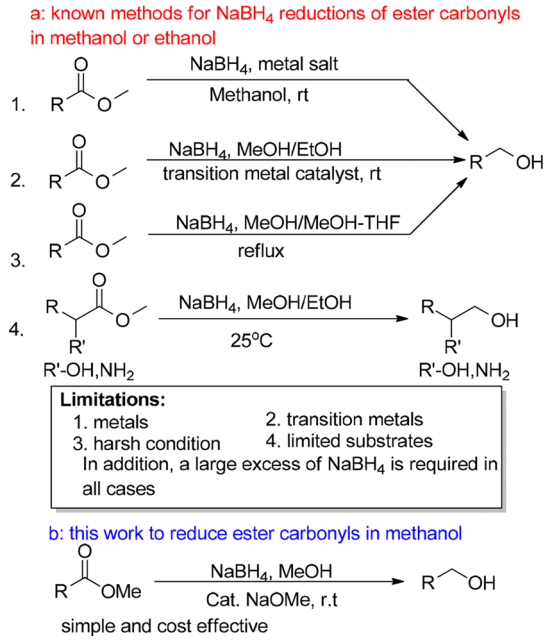
Scheme 1. Methods for $NaBH_4$ Reduction of Esters in Alcohol Solvents



use of a large excess of $NaBH_4$ when MeOH is used as the reaction solvent. When working on a small-scale reaction, researchers tend to ignore the rapid reaction of $NaBH_4$ with MeOH and use a large excess of $NaBH_4$ to compensate for the solvent-induced loss of hydride. On large-scale reactions, this is not only a waste of material but also a safety hazard as copious amounts of hydrogen gas are generated during the reaction. We have now learned to stabilize $NaBH_4$ solutions in methanol using a catalytic amount of NaOMe (5 mol %). Herein, we report the results of our study on the reduction of esters and lactones at room temperature using $NaBH_4$ in methanol stabilized by a catalytic amount of sodium methoxide.

RESULTS AND DISCUSSION

As a part of our synthetic program utilizing naturally occurring (2*S*,3*S*)- and (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acids (garcinia and hibiscus acids, **1** and **2**, respectively, Figure 1),[27] for the preparation of enantiomerically

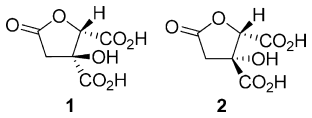
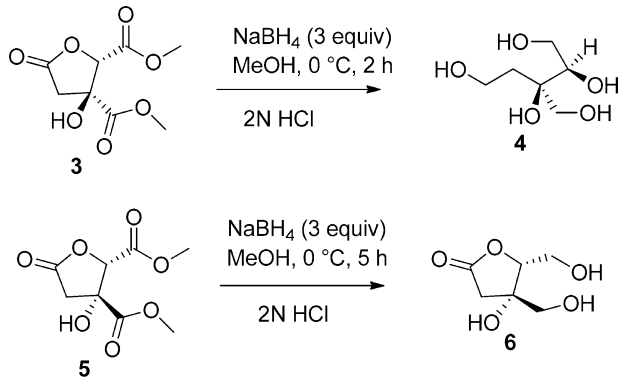


Figure 1. Structure of garcinia and hibiscus acids.

pure precursor molecules aimed at natural product and synthetic targets, we were interested in developing mild and chemoselective reductions of carbonyl groups present in **1** and **2**. After screening several reducing agents, we selected $NaBH_4$, a tunable reducing agent, to effect the selective reduction of carbonyl groups of **1** and **2** and their derivatives at ambient conditions in methanol.

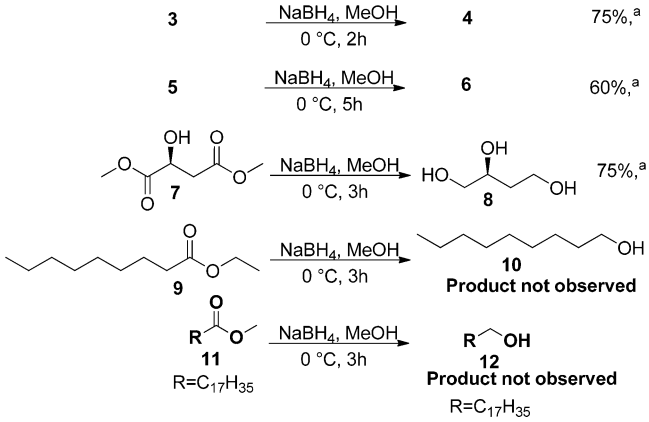
We started our study with the reduction of methyl esters of **1** and **2**[28] using $NaBH_4$ and MeOH at 0 °C. It has been reported that the $BH_3(OMe)^-$ ion is mainly responsible for the enhanced reactivity of $NaBH_4$ in mixed solvents containing methanol at 0 °C.[29] Scheme 1 clearly indicates the limitations of using $NaBH_4$ as a reducing agent for the reduction of esters in protic solvents. The reduction of the methyl esters of **1** and **2** proceeds at an acceptable rate at 0 °C. It is too slow below 0 °C, and $NaBH_4$ reacts with MeOH rapidly above 0 °C. Interestingly, $NaBH_4$ in methanol exhibited a controlled and tandem reduction leading to the formation of **4** and **6** (Scheme 2). The chemoselectivity observed during the reduction of ester **5** is due to steric-screening of both *re* and *si* faces of the lactone carbonyl by the ester moieties.

Scheme 2. Reduction of Garcinia and Hibiscus Esters Using $NaBH_4$ in MeOH at 0 °C



This encouraging observation warranted further investigations of $NaBH_4$ in MeOH as a viable reducing system at 0 °C. To optimize the reaction conditions and to delineate the generality of this reduction, we also included several examples of simple esters in our study. The results are summarized in Scheme 3. While this method worked well for esters **3**, **5**, and **7**,

Scheme 3. $NaBH_4$ Reduction of Esters in Methanol at 0 °C[a]



[a]Isolated yields.

which reacted rapidly, it was not effective for esters of fatty acids (**9** and **11**). These long chain fatty acid esters react slower with $NaBH_4$ in MeOH at 0 °C, possibly due to formation of micelles under the reaction conditions. We also observed that $NaBH_4$ rapidly degrades at 0 °C in MeOH preventing reduction of less reactive esters.

With the objective of circumventing the difficulty associated with carrying out reductions at 0 °C using $NaBH_4$ in MeOH and to generalize the procedure for the reduction of esters at ambient temperature, we investigated the reaction of $NaBH_4$ in MeOH by variable-temperature ^{11}B NMR spectroscopy. We

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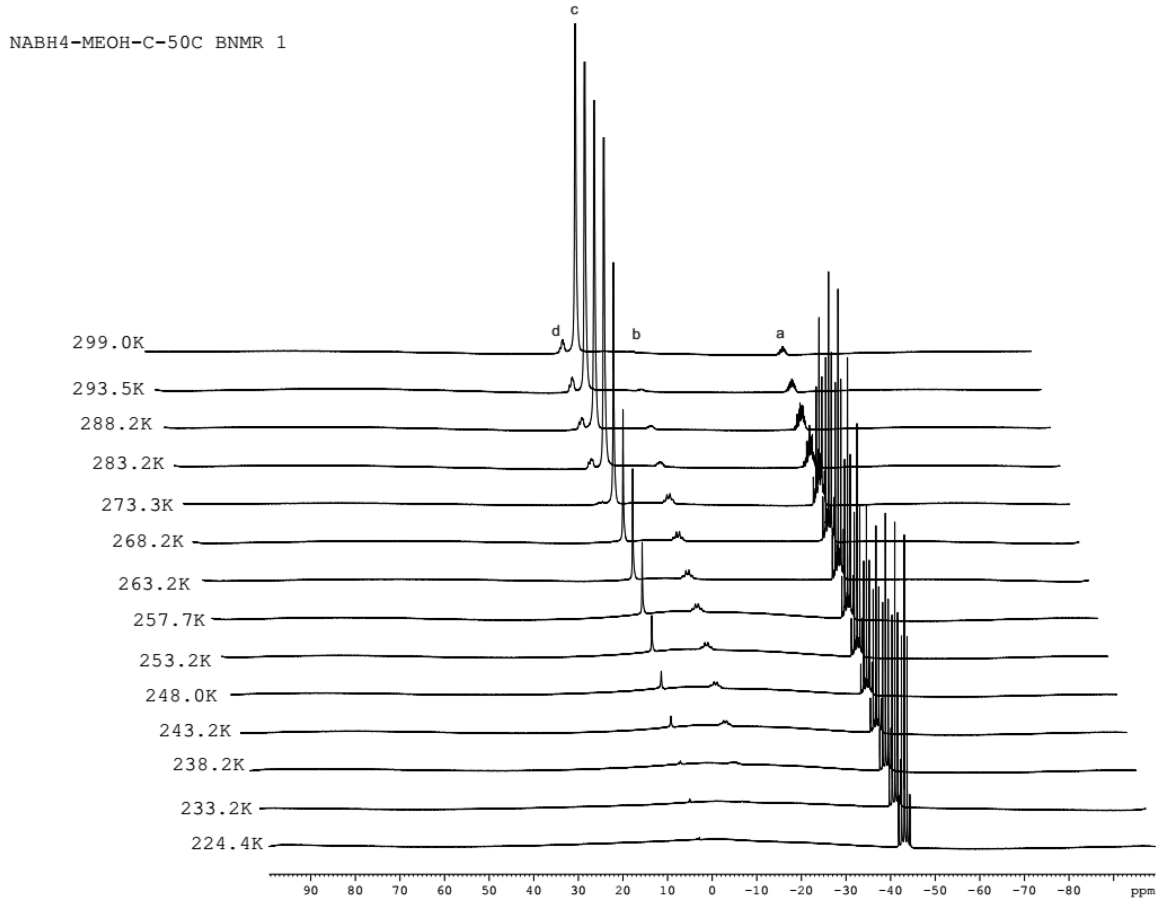

Figure 2. Variable-temperature ^{11}B NMR study of the reaction of $NaBH_4$ and methanol. (a) Quintet of $NaBH_4$ (−42 ppm) (referenced to BF_3·OEt). (b) Quartet of $NaBH_3(OMe)$ (−9 ppm). (c) Singlet of $NaB(OMe)_4$ (3 ppm). (d) Doublet of $NaBH(OMe)_3$ (+6 ppm) not observed until 0 °C. $NaBH_2(OMe)_2$ not observed.

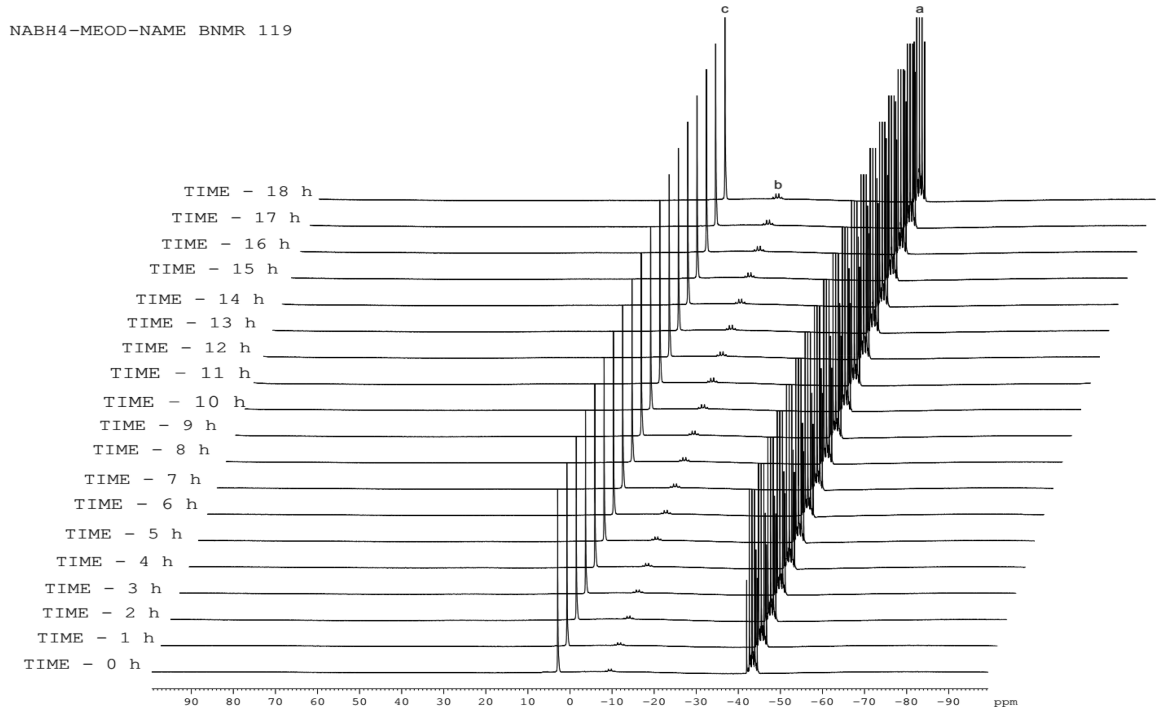

Figure 3. ^{11}B NMR study of the reaction of $NaBH_4$ and methanol with a catalytic amount of NaOMe at 25 °C. (a) Qunitet of $NaBH_4$ (−42 ppm) (referenced to BF_3−OEt). (b) Quartet of $NaBH_3(OMe)$(−9 ppm). (c) Singlet of $NaB(OMe)_4$ (3 ppm). $NaBH(OMe)_3$ (+6 ppm) not observed even at 25 °C. $NaBH_2(OMe)_2$ not observed.

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initiated our study by monitoring a solution of $NaBH_4$ in methanol by ^{11}B NMR spectroscopy; as the solution gradually warmed from −50 to +25 °C, its ^{11}B NMR spectrum was recorded at every 5 °C temperature increase (Figure 2). It has been reported that $NaBH_4$ forms various alkoxyborohydrides, such as $BH_3(OMe)^-$, $BH_2(OMe)_2^-$, and $BH(OMe)_3^-$,[29] when dissolved in methanol and that these species are implicated in reductions using $NaBH_4$ in MeOH.[17]

$$NaBH_4 + MeOH \rightarrow NaBH_3(OMe) + NaBH_2(OMe)_2 + NaBH(OMe)_3 + NaB(OMe)_4$$

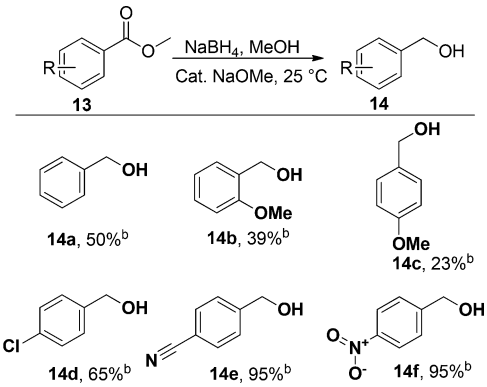
The variable-temperature ^{11}B NMR study revealed that $NaBH_4$ solution in MeOH is stable at −50 °C and starts degrading at −30 °C, producing monomethoxyborohydride, $BH_3(OMe)^-$ (−9 ppm) ion, and $B(OMe)_4^-$ (+3 ppm) ion. No signals due to the other alkoxyborohydrides were visible below 0 °C. Sodium monomethoxyborohydride, $BH_3(OMe)^-$ (−9 ppm) ion, is stable only up to 0 °C. The ^{11}B NMR signal corresponding to dimethoxyborohydride, $BH_2(OMe)_2^-$, was not observed at any temperature from −50 to +25 °C. It is most likely that dimethoxyborohydride, if formed, rapidly disproportionates to $NaBH_4$ and $B(OMe)_4^-$. Apparently, above 0 °C, both $NaBH_4$ and $NaBH_3(OMe)$ react rapidly with MeOH to give nonhydridic $NaB(OMe)_4$ (+3 ppm). Sodium borohydride usually does not reduce esters.[2] Since sodium monomethoxyborohydride is the only other hydride reagent detectable below 0 °C, it is very likely that $NaBH_3(OMe)$ is involved in the reduction of esters at or below 0 °C. In support of this hypothesis, the activation barrier for hydride transfer from $BH_3(OMe)^-$ onto benzoic acid methyl ester was calculated as 18.3 kcal/mol using DFT computational methods (see SI). It is possible that a single methoxy group in $NaBH_3(OMe)$ may make the boron atom a better hydride donor, compared to $NaBH_4$, through back bonding.[30] Similar back bonding promoted powerful hydride donation has been observed in aminoborohydrides, MBH_3NMe_2.[31] Unfortunately, both $NaBH_3(OMe)$ and $NaBH_4$ rapidly degrade in MeOH at temperatures above 0 °C. At this point, our efforts were directed toward stabilizing both $NaBH_3(OMe)$ and $NaBH_4$ at ambient temperature.

During our quest to stabilize $NaBH_4$ solutions in MeOH, we observed that a catalytic amount of NaOMe stabilizes $NaBH_4$ solutions in MeOH even at 25 °C probably due to the reduction in the amount of trace $MeOH_2^+$. Earlier kinetic studies indicated that base and low temperature slow the reaction of $NaBH_4$ with MeOH.[32] We wanted to verify experimentally that, by controlling the basicity of the medium using a catalytic amount of NaOMe, $NaBH_4$ reductions could be carried out in methanol at ambient conditions. We initiated our study by monitoring a mixture of $NaBH_4$ and a catalytic amount of NaOMe (5 mol %) in methanol at 25 °C using ^{11}B NMR; a spectrum was recorded every hour (Figure 3). Apparently, $NaBH_3OMe$ is in equilibrium with $NaBH_4$ and $NaB(OMe)_4$ in methanolic solution containing 5 mol % of NaOMe. Since $NaBH_4$ is incapable of reducing esters and since $NaBH_3OMe$ is the only other hydride containing species in solution, we postulated that $NaBH_3OMe$ is the active reducing agent. Even if the concentration of $NaBH_3OMe$ is low, we believe that the reduction is going through $NaBH_3OMe$ as it has a low activation barrier (18 kcal/mol) for ester reduction. This fits well with the Curtin−Hammett principle. However, we could not rule out the possibility of another species present at avery low concentration that is the most reactive species.

$$NaBH_4 + MeOH \xrightarrow[25\ ^\circ C]{\text{cat. NaOMe}} NaBH_3(OMe) + NaB(OMe)_4$$

We were pleased to find that a catalytic amount of NaOMe did slow down the methanolysis of both $NaBH_3(OMe)$ and $NaBH_4$ at 25 °C for at least 18 h. Under comparable conditions, without the added NaOMe, the ^{11}B NMR spectrum showed the total conversion of $NaBH_4$ to $NaB(OMe)_4$ essentially within 60 min (see the SI). None of the other alkoxyborohydrides were detected by ^{11}B NMR spectra in the NaOMe-stabilized $NaBH_4$ solution in MeOH. This prompted us to study the reductions of various esters and lactones, including esters of naturally occurring garcinia and hibiscus acids, with NaOMe stabilized methanolic $NaBH_4$ at 25 °C. As a model substrate, we studied the reduction of methyl benzoate using $NaBH_4$ (2 equiv) in methanol (5 mL) with sodium methoxide (5 mol %) at 25 °C. The reaction was slow and afforded benzyl alcohol in moderate yield after 3 h. Similarly, the reduction of methyl 2-methoxy and 4-methoxybenzoates was also sluggish. Fortunately, reductions of esters containing electron-withdrawing substituents, such as methyl 4-cyanobenzoate and methyl 4-nitrobenzoate, were facile and gave the corresponding benzyl alcohols in excellent yields under similar conditions. Scheme 4 summarizes the reductions of various substituted aromatic esters.

Scheme 4. $NaBH_4$ Reduction of Aromatic Esters in Methanol with 5 mol % of NaOMe at 25 °C[a]



[a]Reaction conditions: ester (5 mmol), $NaBH_4$ (10 mmol), NaOMe (5 mol %), MeOH (5 mL), 25 °C, 3 h. [b]Isolated yields.

From the data in Scheme 4, we concluded that reductions of simple aromatic esters afforded moderate yields of the corresponding alcohols. Compared with electron-donating substituents (Scheme 4, compounds **14b**, **14c**, and **14d**), esters bearing electron-withdrawing substituents (Scheme 4, compounds **14e** and **14f**) furnished the corresponding alcohols in good yields. The study demonstrated the high chemoselectivity of the NaOMe−$NaBH_4$ reagent, permitting the rapid reduction of the ester group in the presence chloro, cyano, and nitro groups. Similar chemoselectivity cannot be achieved by reductions using lithium aluminum hydride. We then extended our study to include the reductions of heteroaromatic esters, aliphatic esters, and lactones.

Pyridine and pyrazine heteroaromatic esters were reduced to the corresponding alcohols in excellent yields. The electro-

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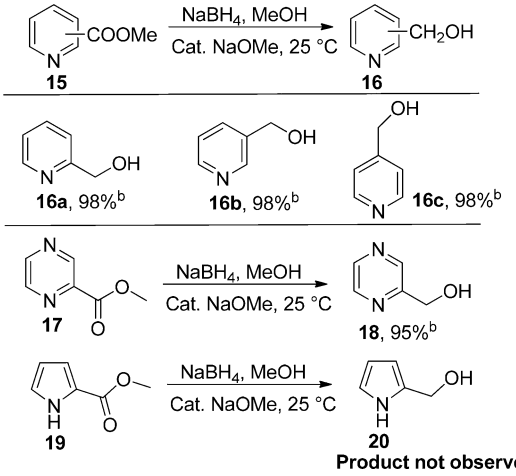
negative N atom in the ring makes these esters more reactive compared to methyl benzoate (Scheme 5).

Scheme 5. $NaBH_4$ Reduction of Heteroaromatic Esters in Methanol with 5 mol % of NaOMe at 25 °C[a]



[a]Reaction conditions: ester (5 mmol), $NaBH_4$ (10 mmol), NaOMe (5 mol %), MeOH (5 mL), 25 °C, 3 h. [b]Isolated yields.

In contrast, electron-donating pyrrole esters remain unreacted under the reaction conditions. This may be due to the formation, under the reaction conditions, of an enolate ion **21** which inhibits the reduction of the ester carbonyl group (Figure 4).

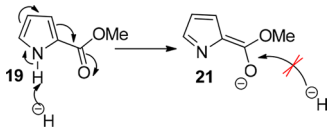


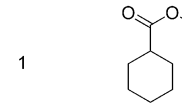
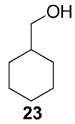
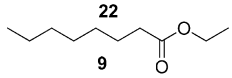
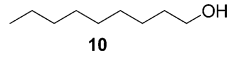
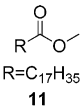
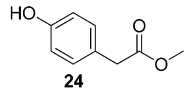
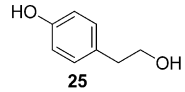
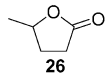
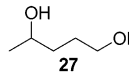
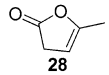
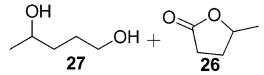
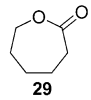
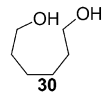
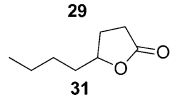
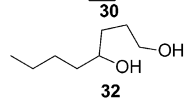
Figure 4. Plausible mechanistic explanation for the resistance of **19** to undergo reduction.

Aliphatic esters and lactones were reduced to the corresponding alcohols in good yields, and the results are summarized in Table 1. The lower yield for the reduction of long chain esters **9** and **11** may be due to micelle formation. However, the yield of **12** was increased to 60% with 3 equiv of $NaBH_4$. Esters containing an acidic proton (Table 1, entry 4) are not suitable for the reduction because the rate of methanolysis competed over ester reduction.[32] It is also possible that this ester forms the corresponding enolate which prevents the reduction of the ester group. The unsaturated lactone **28** (Table 1, entry 6) probably undergoes base-catalyzed isomerization of the double bond followed by Michael addition of hydride to give the γ-lactone **26**, which finally gets reduced to give a mixture of 1,4-diol **27** and the γ-lactone **26** in a 3:1 ratio (Figure 5). Fortunately, reduction of **28** with 3 equiv of $NaBH_4$ furnished **27** exclusively.

To further ascertain the stabilizing effect of NaOMe, a comparative study of the reduction of esters and lactones using sodium borohydride in pure methanol and in methanol containing sodium methoxide (5 mol %) was carried out at 25 °C. The results are summarized in Table 2.

The results summarized in Table 2 clearly demonstrate that NaOMe (5 mol %) stabilizes $NaBH_4$ in MeOH at 25 °C and

Table 1. $NaBH_4$ Reduction of Aliphatic Esters and Lactones in Methanol with 5 mol % of NaOMe at 25 °C[a]

entry	substrate	product	yield
1			90%[b]
2			60%[b]
3			35%[b]
4			0%[b]
5			98%[b]
6			78%[b]+22%[b]
7			85%[b]
8			85%[b]

[a]Reaction conditions: ester (5 mmol), $NaBH_4$ (10 mmol), NaOMe (5 mol %), MeOH (5 mL), 25 °C, 3 h. [b]Isolated yields.

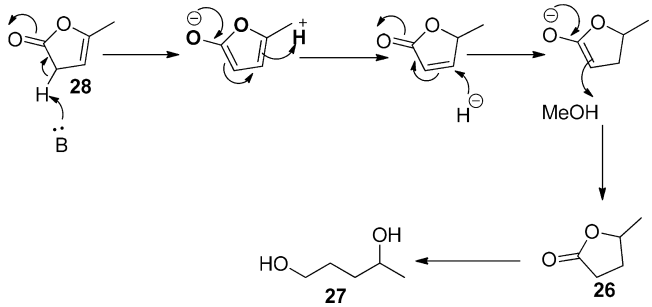


Figure 5. Tentative mechanism for the reduction of **28** using $NaBH_4$ in methanol with 5 mol % of NaOMe at 25 °C.

reduces unreactive esters more effectively than $NaBH_4$ in pure methanol at 25 °C. The lower yield of reduced product in pure methanol at 25 °C is consistent with reported results using an excess of $NaBH_4$.[7]

To further understand the reactivity of $NaBH_4$ for the reduction of esters in ethanol and 2-propanol, reactions were carried out and compared with the results in Table 2.

Lower yields and trans-esterified products were obtained for reduction of esters and lactones in ethanol (Scheme 6), which is consistent with the reported results.[33] These results and the ^{11}B NMR spectrum in ethanol at 25 °C (see the SI) support the hypothesis that the monoalkoxyborohydrides are more efficient reducing species compared to $NaBH_4$. While sodium borohydride forms monoethoxyborohydride with ethanol, sodium borohydride does not form monoisopropoxyborohydride in 2-propanol (see the SI). Consequently, $NaBH_4$ in 2-propanol is inefficient in reducing esters at 25 °C (Scheme 6). This is expected because hydride transfer should be more

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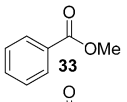
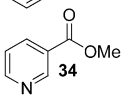
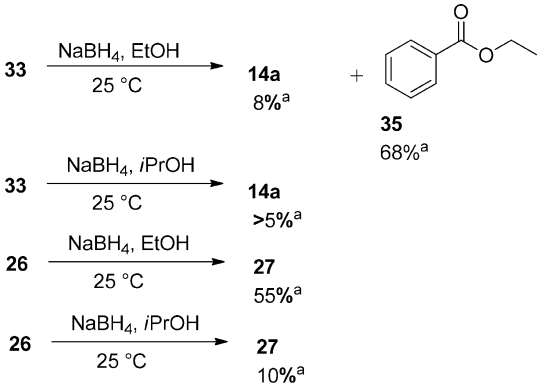
Table 2. Comparative Study of $NaBH_4$ Reduction of Esters/Lactones in Pure Methanol and in Methanol with 5 mol % of Sodium Methoxide at 25 °C

entry	substrate	product	Yield in various reduction system	
			methanol[b]	methanol-NaOMe(5mol%)[c]
1	 **33**	**14a**	15(%)[a]	51(%)[a]
2	 **34**	**16b**	95(%)[a]	98(%)[a]
3	**22**	**23**	30(%)[a]	89(%)[a]
4	**26**	**27**	72(%)[a]	98(%)[a]

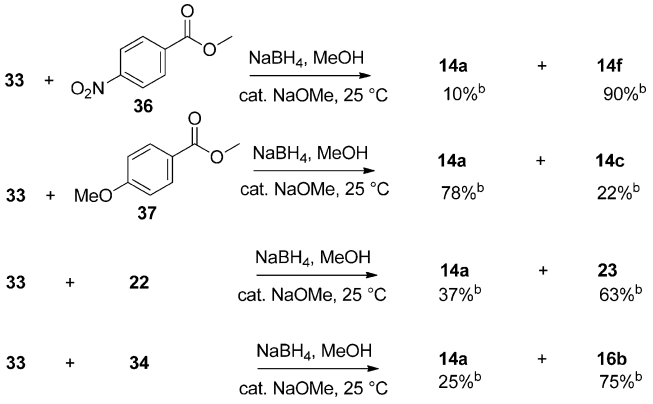
[a]Isolated yields. [b]Reaction conditions: ester (5 mmol), $NaBH_4$ (10 mmol), MeOH (5 mL), 25 °C, 3 h. [c]Reaction conditions: ester (5 mmol), $NaBH_4$ (10 mmol), NaOMe (5 mol %), MeOH (5 mL), 25 °C, 3 h.

Scheme 6. Comparative Study of $NaBH_4$ Reduction of Esters in Pure Ethanol[b] and 2-Propanol[c] at 25 °C



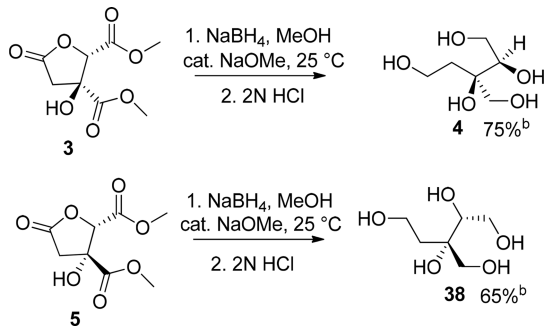
[a]Isolated yields. [b]Reaction conditions: ester (5 mmol), $NaBH_4$ (10 mmol), EtOH (5 mL), 25 °C, 3 h. [c]Reaction conditions: ester (5 mmol), $NaBH_4$ (10 mmol), *i*-PrOH (5 mL), 25 °C, 3 h.

Scheme 7. Selective and/or Competitive Reduction of Esters by $NaBH_4$ in Methanol Containing 5 mol % of NaOMe at 25 °C[a]



[a]Reaction conditions: ester **A** (2.5 mmol), ester **B** (2.5 mmol), $NaBH_4$ (10 mmol), NaOMe (5 mol %), MeOH (5 mL), 25 °C, 3 h. [b]Yield determined by ^1H NMR spectroscopy.

Scheme 8. Reduction of Garcinia and Hibiscus Esters Using $NaBH_4$ in MeOH with 5 mol % of NaOMe at 25 °C[a]



[a]Reaction conditions: ester (5 mmol), $NaBH_4$ (15 mmol), NaOMe (5 mol %), MeOH (5 mL), 25 °C, 3 h. [b]Isolated yields.

difficult from a stronger Lewis acid, such as BH_3, than from a weaker Lewis acid, such as $BH_2(OR)$. This is consistent with our inability to locate a transition state for hydride transfer from $NaBH_4$ onto the substrate by DFT calculations. These results show that pure methanol, ethanol, and 2-propanol are not good solvents for the reduction of esters using $NaBH_4$ at 25 °C.

In order to explore the synthetic potential of sodium methoxide stabilized $NaBH_4$ in methanol, we examined the competitive or selective reductions of various substituted esters. The results are shown in Scheme 7.

Aromatic ester **36** bearing an electron-withdrawing substituent and pyridinecarboxylic ester **34** are readily reduced selectively over the simple aromatic ester **33**. While the reduction of methyl 4-methoxybenzoate **37** and methyl benzoate showed 78% selectivity toward **33**, aliphatic ester **22** was reduced with 2:1 selectivity over simple aromatic ester **33**.

To further expand the viability of the current methodology to the reduction of chiral esters, methyl esters of **1** and **2** were reduced using sodium methoxide and $NaBH_4$ in methanol. Thus, tandem reductions of **3** and **5** resulted in the formation of **4** and **38** (Scheme 8).

The reduction-induced cyclization of chiral pyrrolidinedione **39** afforded compound **40** containing a fused five membered furo[2,3-*b*]pyrrole framework (Scheme 9),[42,43] found in natural products, such as millingtonine A,[34,35] diazonamide A,[36−38] and physovenine.[39−41]

The Pictet−Spengler cyclization of the *N*-acyliminium ion intermediate **42** obtained from **39** via 5-*exo*-*trig* ring closure yielded **40** as a single diastereomer. Despite having three chiral centers, the preferential cis-fusion of the bicyclic furo[2,3-*b*]pyrrole ring system permits only the formation of a single diastereomer (Scheme 10).

Synthesis of pyrrolo[2,1-*a*]isoquinoline derivative **44** was also carried out employing the current methodology. Pyrrolo-[2,1-*a*]isoquinoline-based *N*-heterocyclic scaffolds comprise the key structural feature of a wide range of naturally occurring molecules.[42−44] This ring system is present in numerous structurally diverse natural products exhibiting a wide range of biological and pharmacological activities.[45,46] Highly functionalized 3-substituted pyrrolidinedione **43** derived from **1** was converted to **44** [(−)-crispine A analogue] via diastereoselective intramolecular *N*-acyliminium ion cyclization Scheme 11.

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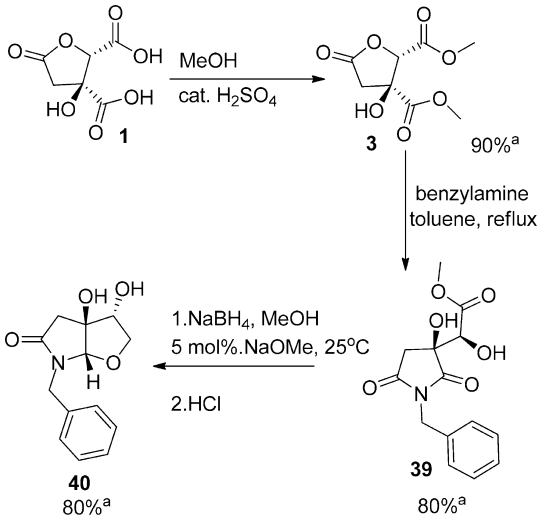
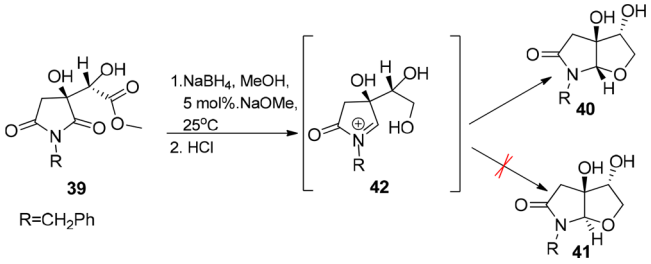
Scheme 9. Synthesis of Furo[2,3-*b*]pyrrole 40

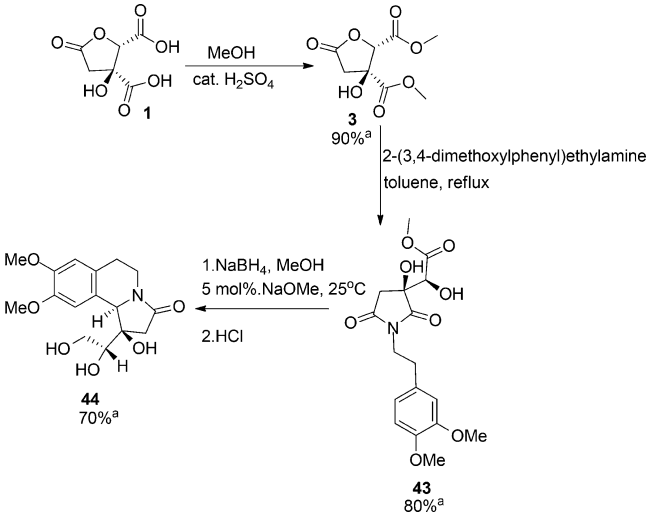


[a]Isolated yields.

Scheme 10. Intermediate Pictet–Spengler Cyclization



Scheme 11. Synthesis of (−)-Crispine A Analogue 44



[a]Isolated yields.

CONCLUSION

In summary, we have described a simple and efficient method to reduce esters and lactones to the corresponding alcohols and diols, respectively, under ambient conditions. The success of our strategy hinges upon using catalytic amounts of NaOMe as a stabilizer for sodium borohydride in MeOH. Sodium methoxide stabilizes $NaBH_3OMe$, which is the most likely intermediate responsible for ester reduction at room temperature. The method is simple and efficient, does not require a large excess of sodium borohydride, and can be carried out at ambient temperature. This procedure extends the existing use of sodium borohydride for the reduction of aldehydes, ketones, acid chlorides, anhydrides, and imides to include the reductions of esters and lactones under ambient and salt-free conditions. The work described in this paper expands the versatility of sodium borohydride as demonstrated by using 22 examples of aliphatic, aryl, and heteroaryl esters. This reduction system was used in the tandem reduction of esters of naturally occurring diastereomeric (2*S*,3*S*)- and (2*S*,3*R*)-tetrahydro-3-hydroxy-5-oxo-2,3-furandicarboxylic acids (garcinia and hibiscus acids) and the reduction-induced conversion of two pyrrolidinediones to a fused five-membered furo[2,3-*b*]pyrrole and a (−)-crispine A analogue in high optical and chemical yields. In order to gain structural information on the species present in the methanolic solution of sodium borohydride, variable-temperature ^{11}B NMR spectroscopy was used. In MeOH, monomethoxyborohydride is in equilibrium with $NaBH_4$ and $NaB(OMe)_4$. Since $NaBH_4$ is incapable of reducing esters, and since $NaBH_3OMe$ is the only other hydride containing species detectable in solution, we suggest that monomethoxyborohydride is the reactive intermediate. In support of this hypothesis, the activation barrier for hydride transfer from $BH_3(OMe)^-$ to benzoic acid methyl ester was calculated to be 18.3 kcal/mol.

EXPERIMENTAL SECTION

General Experimental Details. All operations were carried out under a nitrogen atmosphere. All glassware, syringes, and needles were oven-dried and cooled under a nitrogen gas before use. Anhydrous MeOH was freshly distilled from magnesium turnings. Toluene was distilled from sodium wire. All substrates and reagents were purchased from Sigma-Aldrich or Alfa Aesar and used without further purification. The $^1H/^{13}C$ NMR spectra of the samples were recorded at 400/100 MHz or at 300/75 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) relative to TMS (δ = 0), and coupling constants are reported as hertz (Hz). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), coupling constant, and integration. Boron NMR samples were recorded in $CDCl_3$ at 128.4 MHz and are reported relative to external standard $BF_3{\cdot}Et_2O$ (δ = 0). Melting points were determined with an electrically heated melting point apparatus and were uncorrected. IR spectra were recorded on a FT-ATR spectrometer and are reported as wavenumbers (cm^{-1}). HRMS were recorded under ESI Q-TOF conditions. Column chromatography was carried out with Merck product silica (silica gel 60–120 mesh), and thin-layer chromatography was carried out with Merck product silica (silica gel G for TLC).

(2R,3R)-3-(Hydroxymethyl)pentane-1,2,3,5-tetraol (**4**). The following procedure is representative for the tandem reduction of α-hydroxy esters. A 100 mL two-necked round-bottom flask, equipped with a magnetic stir bar and fitted with a rubber septum, was charged with a solution of diester **3** (1.0 g, 3.65 mmol) and methanol at 0 °C. Powdered $NaBH_4$ (414 mg, 10.95 mmol) was added in one portion to the reaction mixture with constant stirring. The progress of the reaction was followed by ^{11}B NMR analysis. The mixture was stirred for 2 h at 0 °C. The reaction was quenched by the addition of 2 N HCl (*Caution! Hydrogen evolution*). The resultant solution was evaporated on a rotary evaporator, and the residue was extracted with dry acetone. After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel ($CHCl_3$/MeOH, 9:1) to afford **4** as a colorless oil (539 mg, 3.75 mmol) in 75% yield: $[\alpha]_D^{26}$ +2.8 (*c* 0.40, MeOH); IR (ATR) 3307, 2950, 1645, 1416, 1011 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 3.71 (m, 7H), 1.87 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 76.9, 75.3, 66.0, 63.2, 58.8, 37.0; ^{11}B NMR (128.37 MHz, $CDCl_3$) δ +10 (s), +19 (s); HRMS (ESI) *m*/*z* calcd for $C_6H_{14}O_5Na$ $[M + Na]^+$ 189.0739, found 189.0735.

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*(4S,5R)-4-Hydroxy-4,5-bis(hydroxymethyl)dihydrofuran-2-one (**6**).* Following the representative procedure, ester **5** was reduced to give **6** as a colorless oil (450 mg, 3 mmol) in 60% yield: $[\alpha]_D^{26}$ +30.0 (*c* 0.40, MeOH); IR (ATR) 3410, 1731, 1212, 1094 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 4.47 (m, 1H), 3.90 (m, 2H), 3.66 (m, 2H), 2.87 (d, *J* = 17.6 Hz, 1H), 2.43 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 175.7, 89.1, 79.1, 65.0, 61.0, 40.7; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{22}O_9S_2$ $[M + H]^+$ 471.0778, found 471.0782.

*(2S)-Butane-1,2,4-triol (**8**).* Following the representative procedure, ester **7** was reduced to give **8** as a colorless oil (344 mg,3.25 mmol) in 75% yield: $[\alpha]_D^{26}$ −27.0 (*c* 0.40, MeOH); IR (ATR) 3299, 2926, 1651, 1417, 1049 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 3.71 (m, 2H), 3.44 (m, 2H), 3.03 (bs, 2H), 1.65 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 71.3, 61.4, 60.2, 37.1.

General Procedure for Reduction of Esters/Lactones by $NaBH_4$ in Methanol at 0 °C. A 100 mL two-necked round-bottom flask, equipped with a magnetic stir bar and fitted with a rubber septum, was charged with ester (5 mmol) and methanol (5 mL) at 0 °C. Powdered $NaBH_4$ (567 mg, 15 mmol) was added in one portion to the reaction mixture with constant stirring. The progress of the reaction was followed by TLC. The mixture was stirred for 3 h at 0 °C. The reaction was quenched by the addition of excess methanol/2 N HCl (5 mL) (*Caution! Hydrogen evolution*). The resulting solution was evaporated on a rotovap, and the residue was extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was evaporated on a rotovap to obtain the crude reaction product.

General Procedure for Reduction of Esters/Lactones by $NaBH_4$ in Methanol with 5 mol % of NaOMe at 25 °C. A 100 mL two-necked round-bottom flask, equipped with a magnetic stir bar and fitted with a rubber septum, was charged with ester (5 mmol), methanol (5 mL), and 5 mol % of NaOMe (0.25 mmol) at 25 °C. Powdered $NaBH_4$ (378 mg, 10 mmol) was added in one portion to the reaction mixture with constant stirring. The progress of the reaction was followed by TLC. The mixture was stirred for 3 h at 25 °C. The reaction was quenched by the addition of excess methanol. The resultant solution was evaporated on a rotary evaporator at reduced pressure, and the residue was extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was evaporated on a rotovap to obtain the crude reaction product.

Procedure for the Comparative Study of $NaBH_4$ Reduction of Esters/Lactones in Various Protic Solvents. A dry 100 mL two-necked round-bottom flask, equipped with a magnetic stir bar and fitted with a rubber septum, was charged with ester (5 mmol) and methanol/ethanol/2-propanol (5 mL) at 25 °C. After being stirred at room temperature for 5 min, powdered $NaBH_4$ (378 mg, 10 mmol) was added in one portion to the reaction mixture with constant stirring. The progress of the reaction was followed by TLC. Upon stirring for 3 h at 25 °C, the reaction was quenched by the addition of excess methanol. The resultant solution was evaporated on a rotary evaporator and the residue was extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was evaporated on a rotovap to obtain the crude reaction product.

Procedure for the Study of Competitive Reduction of Esters by $NaBH_4$ in Methanol with 5 mol % of NaOMe at 25 °C. A 100 mL two-necked round-bottom flask, equipped with a magnetic stir bar and fitted with a rubber septum, was charged with ester **A** (2.5 mmol), ester **B** (2.5 mmol), methanol (5 mL), and 5 mol % of NaOMe (0.25 mmol) at 25 °C. Powdered $NaBH_4$ (378 mg, 10 mmol) was added in one portion to the reaction mixture with constant stirring. The progress of the reaction was followed by TLC. The mixture was stirred for 3 h at 25 °C. The reaction was quenched by the addition of excess methanol. The resultant solution was evaporated under reduced pressure on a rotary evaporator, and the residue was extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried over anhydrous sodium sulfate, and the solvent was evaporated on a rotovap to obtain the crude reaction product. The product ratio was determined by ^1H NMR spectral analysis of the crude reduction product.

^{11}B NMR Spectroscopic Study of $NaBH_4$ Reaction with Methanol at Variable Temperatures. Sodium borohydride (0.4 mmol) was added to 1 mL of CD_3OD cooled at −50 °C in an NMR tube, and the ^{11}B NMR spectrum was recorded at −50 °C. The progress of the reaction was measured by recording the ^{11}B NMR spectra every 5 °C increase from −50 to +25 °C. The studies revealed that the $BH_3(OCD_3)^-$ ion is stable only up to 0 °C. Above 0 °C, it rapidly reacts with CD_3OD to give less reactive $BH(OCD_3)_3^-$ and nonreactive $B(OCD_3)_4^-$: ^{11}B NMR at +25 °C (128.37 MHz, CD_3OD) δ +6.6 (d, *J* = 114.7 Hz, $BH(OCD_3)_3^-$), +2.8 (s, $B(OCD_3)_4^-$), −9.2 (q, *J* = 83.9 Hz, $BH_3(OCD_3)^-$), −43.1 (p, *J* = 322.2 Hz, BH_4^-). The peak at δ +6.6 does not appear until 0 °C. Below 0 °C, only the signals due to BH_4^- ion, $BH_3(OMe)^-$ ion, and $B(OMe)_4^-$ are visible in the spectra.

^{11}B NMR Spectroscopic Study of $NaBH_4$ Reaction with Methanol with 5 mol % of NaOMe at 25 °C. Sodium borohydride (0.4 mmol) was added to 1 mL of CD_3OD with 5 mol % of NaOMe at 25 °C in an NMR tube. The progress of the reaction was measured by recording the ^{11}B NMR spectrum at every 1 h interval. The studies revealed that $BH_3(OCD_3)^-$ ion is stable at 25 °C for up to 18 h: ^{11}B NMR (128.4 MHz, CD_3OD) δ +2.8 (s, $B(OCD_3)_4^-$), −9.2 (q, *J* = 83.9 Hz, $BH_3(OCD_3)^-$), −43.1 (p, *J* = 322.2 Hz, BH_4^-).

*(2R,3S)-3-(Hydroxymethyl)pentane-1,2,3,5-tetrol (**38**).* A nitrogen-flushed, dry 100 mL two-necked round-bottom flask, equipped with a magnetic stir bar and fitted with a rubber septum, was charged with ester **5** (5 mmol), methanol (5 mL), and 5 mol % of NaOMe (0.25 mmol) successively at 25 °C. Powdered $NaBH_4$ (576 mg, 15 mmol) was added in one portion to the reaction mixture with constant stirring. The mixture was stirred for 3 h at 25 °C. The reaction was quenched by the addition of 2 N HCl (*Caution! Hydrogen evolution*). The resultant solution was evaporated on a rotary evaporator at reduced pressure, and the residue was extracted with acetone (5 × 10 mL). After evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel ($CHCl_3$/MeOH, 9:1) to afford **38** as a yellow oil (151.5 mg, 3.24 mmol) in 65% yield: $[\alpha]_D^{26}$ −78.2 (*c* 0.23, MeOH); IR (ATR) 3354, 2946, 2838, 1643, 1456 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 1.67−1.84 (m, 2H), 3.47−3.55 (m, 3H), 3.61−3.74 (m, 4H); ^{13}C NMR (100 MHz, D_2O) δ 35.0, 57.2, 61.9, 64.0, 74.7, 75.3; HRMS (ESI) *m*/*z* calcd for $C_6H_{14}O_5Na$ $[M + Na]^+$ 189.0739, found 189.0735.

*(S)-Isopropyl 2-((S)-1-benzyl-3-hydroxy-2,5-dioxopyrrolidin-3-yl)-2-hydroxyacetate (**39**).* To a solution of garcinia diester **3** (1.0 g, 4.6 mmol) in toluene (10 mL) was added dropwise benzylamine (0.50 mL, 4.6 mmol). The reaction mixture was refluxed for 5 h and concentrated in vacuum, and the residue was purified by silica gel column chromatography (hexane/EtOAc 90:10) to afford **39** as colorless crystals (1.25g, 4.2 mmol) in 93% yield: mp 106−107 ° C; $[\alpha]_D^{20}$ +11.1 (*c* = 0.12, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.26 (m, 5H), 4.70−4.61 (m, 2H), 4.32 (s, 1H), 3.81 (s, 3H), 3.16 (d, 1H, *J* = 18.0 Hz), 2.76 (d, 1H, *J* = 18.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 173.5, 171.8, 135.1, 128.7, 128.5, 128.0, 76.2, 72.1, 53.8, 42.6, 39.7; IR (ATR) 3432, 2949, 1775, 1743, 1695 cm^{-1}; HRMS (TOF MS ES+) *m*/*z* calcd for $C_{14}H_{16}NO_6$ $(M + H)^+$ 294.0978, found 294.0980.

*(3R,3aS,6aS)-6-Benzyl-3,3a-dihydroxytetrahydro-2H-furo[2,3-b]-pyrrol-5(3H)-one (**40**).* A 100 mL two-necked round-bottom flask, equipped with a magnetic stir bar and fitted with a rubber septum, was charged with pyrrolidinedione **39** (5 mmol), methanol (5 mL), and 5 mol % of NaOMe (0.25 mmol) at 25 °C. Powdered $NaBH_4$ (378 mg, 10 mmol) was added in one portion to the reaction mixture with constant stirring. The mixture was stirred for 4 h at 25 °C. The reaction was quenched with 2 M HCl (*Caution! Hydrogen evolution*) and concentrated under vacuum, followed by dissolving the residue in acetone. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography over silica gel (60−120 mesh) using $CHCl_3$/MeOH (1−3% MeOH) mixture as eluent to afford **40** as a yellow oil (0.995 mg, 4.0 mmol) in 80% yield: $[\alpha]_D^{20}$ −46.2 (c = 0.10, MeOH); ^1H NMR (CD_3COCD_3, 400 MHz) δ

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7.35−7.25 (m, 5H), 4.96 (s, 1H), 4.93 (br s, 1H), 4.85 (br s, 1H), 4.77 (d, 1H, J = 15.2 Hz), 4.28 (t, 1H, J = 7.4 Hz), 4.09−4.01 (m, 2H), 3.39 (t, 1H, J = 8.8 Hz), 3.19 (d, 1H, J = 17.6 Hz), 2.33 (d, 1H, J = 18.0 Hz); ^{13}C NMR (100 MHz, CD_3COCD_3) δ 172.6, 137.9, 129.3, 129.0, 128.1, 98.2, 82.8, 78.3, 71.4, 43.8, 38.9; IR (KBr) 3373, 1671, 1452 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{13}H_{15}NaNO_4$ $(M + Na)^+$, 272.0893, found 272.0907.

*(S)-Methyl 2-((S)-1-(3,4-Dimethoxyphenethyl)-3-hydroxy-2,5-dioxopyrrolidin-3-yl)-2-hydroxyacetate (**43**).* To a solution of garcinia diester **3** (1.0 g, 4.6 mmol) in toluene (10 mL) was added dropwise 2-(3,4-dimethoxyphenyl)ethanamine (0.50 mL, 4.6 mmol). The reaction mixture was refluxed for 5 h and concentrated in vacuum, and the residue was purified by silica gel column chromatography (hexane/EtOAc 90:10) to afford **43** as yellow oil (1.55g, 4.2 mmol) in 92% yield: $[\alpha]_D^{20}$ +16.9 (c = 0.17, acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.80−6.72 (m, 3H), 4.26 (s, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.75−3.71 (m, 2H), 3.11 (d, J = 18.0 Hz, 1H), 2.83 (t, J = 7.4 Hz, 2H), 2.69 (d, J = 18.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 173.8, 171.7, 148.9, 147.8, 129.9, 129.9, 112.1, 111.2, 77.3, 76.1, 72.1, 55.9, 53.7, 40.2, 39.6, 32.8; IR (ATR) 3466, 2952, 1790, 1739, 1700 cm^{-1}; HRMS (TOF MS ES+): m/z calcd for $C_{17}H_{22}NO_8$ $(M + H)^+$ 368.1340, found 368.1333.

*(1R,10bR)-1-((R)-1,2-Dihydroxyethyl)-1-hydroxy-8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one (**44**).* A dry and nitrogen-flushed 100 mL, two-necked round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was charged with pyrrolidinedione (**43**) (0.92g, 2.5 mmol), methanol (5 mL), and 5 mol % of NaOMe (0.125 mmol) at 25 °C. Powdered $NaBH_4$ (283.7 mg, 7.5 mmol) was added in one portion to the reaction mixture with constant stirring. After the mixture was stirred for 4 h at 25 °C, the reaction was quenched with 2 M HCl (5 mL) (*Caution! Hydrogen evolution*) and concentrated under vacuum followed by dissolving the residue in methanol. The solvent was removed under reduced pressure and the crude residue was purified by column chromatography over silica gel (60−120 mesh) using a $CHCl_3$/MeOH (1−3% MeOH) mixture as eluent to afford **44** as a white solid (0.616 mg, 0.19 mmol) in 70% yield: $[\alpha]_D^{20}$ −156.6 (c = 0.11. methanol); mp 99−102 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.42 (s, 1H), 6.71 (s, 1H), 5.06 (s, 1H), 4.30−4.26 (m, 1H), 3.95 (dd, J = 6.8, 4.8 Hz, 1H), 3.87−3.83 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.74−3.69 (m, 1H), 2.92−2.79 (m, 3H), 2.63 (d, J = 14.8 Hz, 1H), 2.34 (d, J = 17.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.6, 149.3, 148.7, 130.1, 125.1, 113.7, 113.3, 80.1, 77.4, 66.5, 64.3, 56.5, 56.4, 44.1, 39.0, 29.9; IR (KBr) 3330, 2934, 1661 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{16}H_{21}NO_6Na$ $(M + Na)^+$ 346.1261, found 346.1256.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02993.

^{1}H, ^{11}B, and ^{13}C NMR spectra and computational data (PDF)

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Notes

The authors declare no competing financial interest.

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