Tetrahedron 66 (2010) 3995–4001

Contents lists available at ScienceDirect

Tetrahedron

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

Reduction of aromatic and aliphatic keto esters using sodium borohydride/MeOH at room temperature: a thorough investigation

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ARTICLE INFO

Article history:
Received 12 March 2010
Received in revised form 9 April 2010
Accepted 14 April 2010
Available online 18 April 2010

Keywords:
Alcohols
Reduction
Esters
Keto esters
Sodium borohydride

ABSTRACT

Reduction of keto esters is a valuable alternative to produce diols. Sodium borohydride/MeOH system at room temperature and short reaction time efficiently reduced α, β, γ, and δ-keto esters having α-keto esters as the most reactive. The ester functionality was reduced effectively due to the presence of oxo group that somehow facilitates the formation of ring intermediate. As expected, the chemoselective experiments showed that ester functionality was not reduced using this system. This study presents a simple, easy, and benign reduction process of various keto esters to its corresponding diols.

1. Introduction

Reduction is one of the most important transformations in organic synthesis and sodium borohydride as reducing agent is the most common since its conception.[1] It has been effective for the selective reduction of aldehydes and ketones[2] but it shows lower reactivity for esters and other relatively difficult to reduce functionalities. However, due to its relatively cheaper cost and ease of handling, modification to augment its reducing power has never stopped. This includes changing the reaction conditions such as varying the solvent, increasing its amount, adding additives or even using catalysts. For instance, sodium borohydride/methanol system can reduce ester provided the reaction was done under refluxing THF and/or used large excess of sodium borohydride at a relatively longer time.[3] Others used several metal borohydrides[4] while others used additive such as aluminum chloride,[5] magnesium bromohydride,[6] zinc chloride,[7] polyethylene glycol,[8] and a lot more. Refluxing in ethereal solvents and inert conditions are commonly employed in the above-mentioned reactions. Furthermore, there have been reports also that reduction of esters proceeded using sodium or potassium borohydride provided a neighboring functional group such as oxo, hydroxyl or carboxylic acid is present.[9] However, there is no detail investigation of this matter.

Recently, we have experienced on reduction of ethyl benzoylacetate to diol using sodium borohydride in methanol at room temperature.[10] Diols especially 1,2-diols and 1,3-diols have become an important building blocks in various synthetic applications. It has been used as precursor and intermediates in the synthesis of active pharmaceutical ingredients,[11] organic transformations,[12] polymer synthesis,[13] and among others. There are many methods available for diol formation and reduction of keto esters is one of them as we have demonstrated.[10] There have been few reports on the reduction of α-keto esters[14] and β-keto esters[15] using sodium borohydride in ethanol solvent. The yields are quite low and the reaction time is sometimes too long. Furthermore, these reports do not specifically demonstrate the effectiveness of sodium borohydride in the reduction of keto esters. Thus, we report herein a detailed investigation of the reduction of various keto esters using sodium borohydride in methanol at room temperature at a shorter period. This could be a valuable alternative for the formation of diols, which has enormous application.

2. Results and discussion

Previously, we found 1-phenylpropane-1,3-diol as a precursor for Tolterodine, which we obtained from reduction of ethyl benzoylacetate using 3.0 M equiv of sodium borohydride in methanol at room temperature for 30 min.[10] It was surprising that an ester

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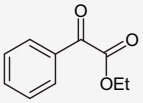
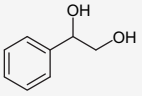
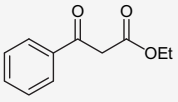
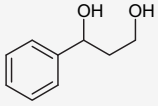
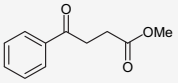
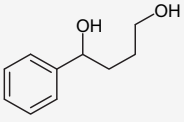
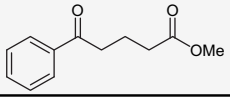
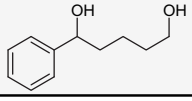
doi:10.1016/j.tet.2010.04.062

moiety was reduced using $NaBH_4$/MeOH system at room temperature in such a short period; thus, we decided to investigate on this matter and check the general applicability of this protocol by doing further experimentation.

To check this finding systematically, we verified the amount of $NaBH_4$ necessary for this reaction to proceed and indeed 3.0 M equiv was necessary. This was checked using α-keto ester; reducing the amount of $NaBH_4$ to 1.0 or 2.0 M equiv gave lower yield. During the reaction, hydrogen gas evolution was evident. Several other keto esters were considered to check the reactivity of this protocol. As shown in Table 1, the reactivity of keto esters decreased as the number of carbon between the keto and the ester group increased. We found that using 0.20 M reaction solution concentration will give hydroxy ester by product (Table 1, entries 2–4). From these results, we considered varying the concentration of the reaction solution. We found that in order to obtain a quantitative yield of diol from keto esters having methylene unit/s spacer (Table 1, entries 2–4) it was necessary to increase the concentration of the reaction solution. Figure 1 showed the optimum concentration for each keto esters necessary to give a quantitative yield.

Table 1
Reactivity of keto esters

Entry	Keto esters	Product structure	Yield[a] (%)
1			Quant
2[b]			77
3[c]			45
4[d]			49

[a] Isolated yield using 0.2 M solution and 3.0 M equiv $NaBH_4$ at rt for 10 min.
[b] Obtained 17% hydroxy methyl ester.
[c] Obtained 29% hydroxy ester and 25% lactone.
[d] Obtained 49% hydroxy ester.

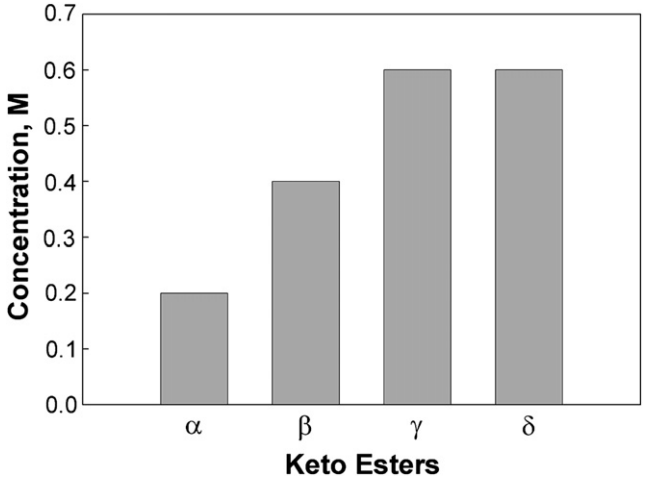


Figure 1. Optimum reaction concentration of various keto esters.

From these findings, we predicted that this reaction proceeded via a ring formation. During the reaction, $NaBH_4$ was slowly decomposed in methanol to give trimethoxy borane and sodium alkoxyborohydride species[8] that readily reduced the ketone moiety. The trimethoxy borane in situ generated then reacted with the alkoxy anion forming an alkoxyborane and acted as a Lewis acid that activated the carbonyl moiety of the ester unit forming a ring intermediate as shown in Figure 2. By virtue of this activation, the ester unit was then easily reduced. We presumed that this hypothesis explained the reactivity of keto esters as predicted by other groups several years ago.[9] The capability of the keto ester to form the ring intermediate dictated its reactivity. In the case of α and β-keto ester, the latter easily form the six-membered ring however; the former was more reactive because of pronounced inductive effect. On the other hand, γ and δ-keto esters required greater concentration of reaction solution because seven and eight-membered ring intermediates were less probable to form.

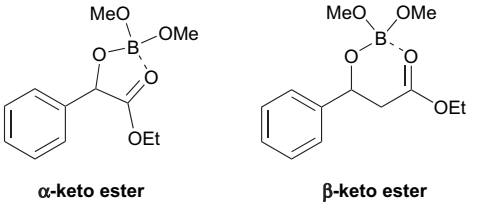
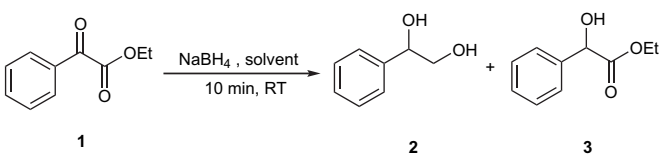


Figure 2. Possible ring intermediate.

To further check the influence of alkoxyborane in this reaction, several alcohol solvents were considered using the condition shown in Scheme 1. Data shown in Table 2 implied that trimethoxy borane was formed easily in situ from the decomposition of sodium borohydride in methanol and acts as Lewis acid unlike with that of ethanol (triethoxyborane) and IPA (triisopropoxyborane) that was probably due to steric hindrance. Furthermore, it was noticeable that a very low yield of diol was obtained using IPA solvent. Previous study reported that IPA does not react with sodium borohydride,[16] thus, presumably isopropoxyborane that will supposedly act as Lewis acid was hardly generated and instead the isopropoxide moiety generated attacks the ester group and transesterification occurred instead. On the other hand, to counter check the effect of trimethoxy borane, we considered a comparative experiment using a non-alcohol solvent THF. According to entry 5 of Table 2, using THF solvent alone would give only 4% of diol and much of hydroxy ester (89%); however, if 3.0 equiv of B $(OCH_3)_3$ was added the amount of diol formed significantly increased. This data proved that in using methanol as solvent, the B $(OCH_3)_3$ formed in situ acted as a Lewis acid that facilitated the reduction of the ester moiety. In fact, it was previously reported that $B(OCH_3)_3$ catalyzed the reduction of esters by sodium borohydride in ether at 25 °C.[17] Our finding was in accordance with this observation.



Scheme 1.

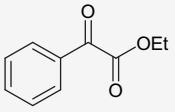
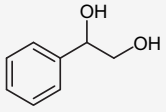
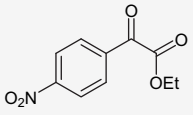
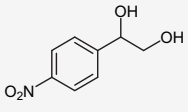
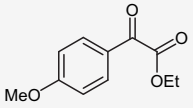
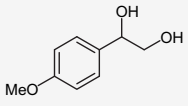
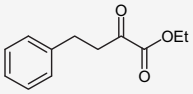
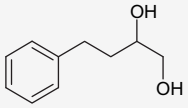
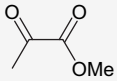
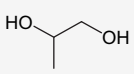
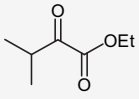
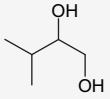
Table 2
Influence of solvent

Entry	Solvent	Yield[a] (%)	
		Diol, **2**	Hydroxy ester, **3**
1	MeOH	Quant	—
2	EtOH	30	60
3[b]	IPA	9	22
4[c]	H_2O	43	31
5	THF	4	89
6[d]	THF	57	33

[a] Isolated yield using 0.2 M solution and 3.0 M equiv $NaBH_4$.
[b] Obtained 59% of isopropyl hydroxy ester (trans-esterification).
[c] Recovered 18% SM.
[d] Used 3.0 equiv $B(OCH_3)_3$.

To validate further our protocol, several α-keto esters were considered as shown in Table 3. All entries both aromatic and aliphatic α-keto esters gave excellent yield except for entry 6. The bulkiness of the isopropyl moiety probably hinders the formation of the ring transition state; thus, it required higher solution concentration (0.40 M) to get higher yield (90%).

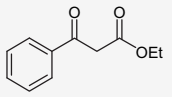
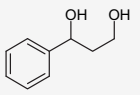
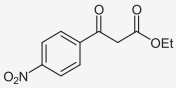
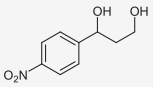
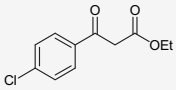
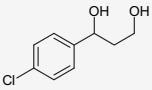
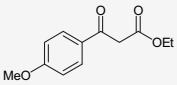
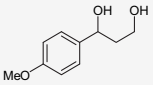
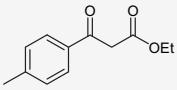
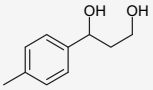
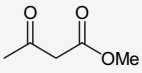
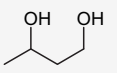
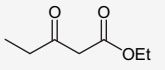
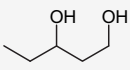
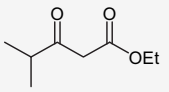
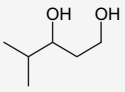
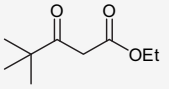
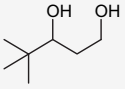
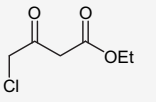
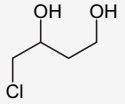
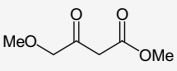
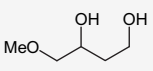
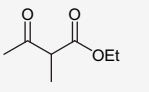
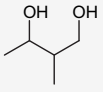
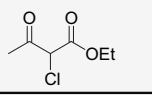
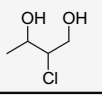
Table 3
Reduction of various α-keto esters

Entry	Starting α-keto esters	Product structure	Yield[a] (%)
1			Quant
2			Quant
3			Quant
4			91
5			93
6[b]			64

[a] Isolated yield using 0.2 M solution and 3.0 M equiv $NaBH_4$ at rt for 10 min.
[b] Obtained 27% hydroxy ester; the yield was 90% when 0.4 M solution was used.

Moreover, several β-keto esters were also checked using this protocol as depicted in Table 4. Aromatic β-keto esters (Table 4, entries 1–5) gave excellent yield regardless of the nature of the substituents present on the aromatic ring. The planarity of the ring did not inhibit the formation of the six-membered intermediate and thus even though the ring was bulky the yields were still excellent. However, it is noteworthy that the presence of electron withdrawing groups on the ring (Table 4, entries 2 and 3) make the reaction faster (shorter reaction time) compared to that having electron donating groups (Table 4, entries 4 and 5). This was due to the inherent inductive effect. On the other hand, the reactivity of aliphatic β-keto esters was influenced significantly by the nature of substituents. As the substituents became bulkier (Table 4, entries 6–9), the more difficult it became to form the six-membered intermediate due to steric hindrance. Thus, the yield for diol decreased and hydroxy ester by-product increased. For entries 10–13, the yield was influenced by the nature of substituents. The Cl atom and OMe unit in entries 10 and 11, respectively both gave excellent yield because of its electronic effect induced on the adjacent oxo unit. This electronic effect also explained the significant difference in the yields of entries 12 and 13. Though these units entailed steric hindrance at the α-carbon, the electronic effect prevailed in the case of Cl atom (entry 13) thereby giving excellent yield. On the other hand, in the case of methyl unit steric effect predominated arising to a significant decrease in yield.

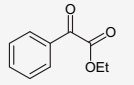
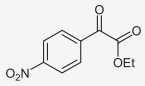
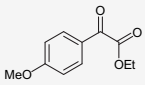
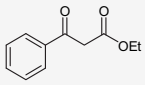
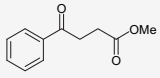
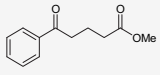
Table 4
Reduction of various β-keto esters

Entry	Starting β-keto esters	Time (h)	Product Structure	Yield[a] (%)
1		0.5		97
2		1		94
3		0.5		94
4		3		94
5		3		94
6		0.5		92
7[b]		0.5		74
8[c]		0.5		72
9[d]		0.5		58
10		0.5		94
11		0.5		93
12[e]		0.5		71
13		0.5		96

[a] Isolated yield using 0.4 M solution and 3.0 M equiv $NaBH_4$ at rt for 10 min.
[b] Obtained 8% of hydroxy methyl ester and 8% of hydroxy ethyl ester.
[c] Obtained 10% of hydroxy methyl ester and 8% of hydroxy ethyl ester.
[d] Obtained 17% of hydroxy methyl ester and 18% of hydroxy ethyl ester.
[e] Obtained 21% hydroxy ethyl ester.

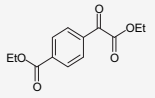
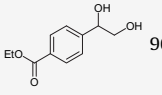
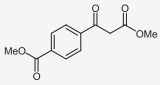
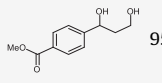
In addition, we also checked the chemoselectivity of this protocol. In Table 5, we demonstrated the inter-chemoselective reduction of keto esters in the presence of ethyl benzoate. It was evident that only keto esters were reduced to diol while almost all of the starting ethyl benzoate was recovered at the end of the reaction. We also tried the reduction of ethyl benzoylformate and ethyl benzoylacetate with aliphatic esters, ethyl phenylacetate, and ethyl hydrocinnamate, respectively. As expected, the starting ethyl phenylacetate and ethyl hydrocinnamate were recovered in 96 and 98% along with 1,2- and 1,3-diol in 95 and 94% yield, respectively. On the other hand, the intra-chemoselective reduction was shown in Table 6. Results showed that the isolated ester moiety remained unreduced while the keto ester moiety was reduced to diol.

Table 5
Inter-chemoselective reduction of keto esters with ethyl benzoate

Entry	Starting keto ester	Solution concn (M)	Time (min)	Product yield[a] (%)	
				Diol	Ethyl benzoate
1		0.20	5	97	96
2		0.20	10	96	98
3		0.20	5	96	97
4		0.40	10	98	97
5		0.60	30	84	93
6		0.60	30	86	95

[a] Isolated yield using 3.0 M equiv $NaBH_4$ at rt.

Table 6
Intra-chemoselective reduction of keto esters

Entry	Starting keto ester	Solution concn (M)	Time (min)	Product structure	Yield[a] (%)
1		0.20	15		96
2		0.40	30		95

[a] Isolated yield using 3.0 M equiv $NaBH_4$ at rt.

3. Conclusion

We have thoroughly investigated the reducing ability of sodium borohydride/MeOH system at room temperature for various types of keto esters. The protocol presented offers a mild reaction condition for the formation of several diols that have widespread application in synthetic chemistry.

4. Experimental section

4.1. General procedure for the reduction of keto ester

In a flask, the starting material α-keto ester (1 mmol) was dissolved in methanol (5 mL for α-keto ester and 2.5 mL for β-keto ester). Then $NaBH_4$ (3.0 equiv) was added portion wise. The reaction mixture was stirred at room temperature until the reaction was completed based on TLC monitoring. Upon completion of the reaction, the mixture was acidified using 5.0 M HCl until pH 6. The solvent was then evaporated using rotary evaporator. For alkyl case: The residue was dissolved in methanol and column filtered thru a short pad of silica using methanol/chloroform (1:4) as eluent to obtain the crude product. This material was purified with column chromatography using various hexane/EtOAc eluent systems. For aromatic case: the residue was dissolved in brine solution and the crude material was extracted using EtOAc as many times necessary. The organic layer was dried using anhydrous Na_2SO_4, filtered, and the solvent was evaporated. The residue was purified via column chromatography using various hexane/EtOAc eluent systems.

4.1.1. 1-Phenylethane-1,2-diol (Table 1, entry 1)[18]. White solid; yield: quantitative (0.138 g). ^{1}H NMR ($CDCl_3$): δ=7.34 (m, 5H, Hs at aromatic ring), 4.85 (dt, J=7.8, 3.7 Hz, 1H, H at C1), 3.77 (m, 1H, H at C2), 3.69 (m, 1H, H at C2), 2.49 (d, J=3.3 Hz, 1H, H at C1 OH), 2.03 (dd, J=7.5, 4.8 Hz, 1H, H at C2 OH).

4.1.2. 1-Phenylpropane-1,3-diol (Table 1, entry 2)[19]. Colorless gummy solid; yield: 97% yield (0.147 g). ^{1}H NMR ($CDCl_3$): δ=7.33 (m, 5H, Hs at aromatic ring), 4.98 (dt, J=8.1, 3.9 Hz, 1H, H at C1), 3.88 (td, J=5.4, 5.2 Hz, 2H, Hs at C3), 2.69 (d, J=3.0 Hz, 1H, H at C1 OH), 2.23 (t, J=4.8 Hz, 1H, H at C3 OH), 2.00 (m, 2H, Hs at C-2).

4.1.3. Methyl 3-hydroxy-3-phenylpropanoate (Table 1, entry 2)[20]. Colorless liquid; yield: 17% (0.031 g). ^{1}H NMR ($CDCl_3$): δ=7.34 (m, 5H, Hs at aromatic ring), 5.15 (dd, J=8.6, 4.1 Hz, 1H, H at C3), 3.73 (s, J=5.4, 5.2 Hz, 3H, Hs at OCH_3), 3.27 (br s, 1H, H at OH), 2.77 (dd, J=16.2, 8.4 Hz, 1H, H at C2), 2.72 (dd, J=16.2, 4.2 Hz, 1H, H at C2).

4.1.4. Phenylbutane-1,4-diol (Table 1, entry 3)[21]. White solid; yield: quantitative (0.332 g). ^{1}H NMR ($CDCl_3$): δ=7.31 (m, 5H, Hs at aromatic ring), 4.74 (t, J=6.3 Hz, 1H, H at C1), 3.69 (m, 2H, Hs at C4), 2.52 (br s, 1H, H at C1 OH), 2.03 (br s, 1H, H at C4 OH), 1.80 (td, J=6.9, 6 Hz, 2H, Hs at C2), 1.70 (m, 2H, Hs at C3).

4.1.5. Methyl 4-hydroxy-4-phenylbutanoate (Table 1, entry 3)[22]. Colorless liquid; yield: 29% (0.056 g). ^{1}H NMR ($CDCl_3$): δ=7.31 (m, 5H, Hs at aromatic ring), 4.75 (t, J=6.5 Hz, 1H, H at C4), 3.67 (s, 3H, Hs at OCH_3), 2.44 (t, J=7.4 Hz, 2H, Hs at C2), 2.07 (q, J=7.0 Hz, 2H, Hs at C3), 2.32 (d, J=3.0 Hz, 1H, H at OH).

4.1.6. 5-Phenyltetrahydro-2-furanone (Table 1, entry 3)[23]. Colorless liquid; yield: 25% (0.041 g). ^{1}H NMR ($CDCl_3$): δ=7.37 (m, 5H, Hs at aromatic ring), 5.52 (t, J=6.9 Hz, 1H, H at C5), 2.66 (m, 3H, Hs at C3), 2.20 (m, 1H, H at C4).

4.1.7. Phenylpentane-1,5-diol (Table 1, entry 4)[24]. White solid; yield: 96% (0.346 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.32 (m, 5H, Hs at aromatic ring), 4.69 (t, J=6.3 Hz, 1H, H at C1), 3.63 (t, J=6.5 Hz, 2H, Hs at C5), 1.62 (m, 8H, Hs at C2, C3, C4, C1 OH, C5 OH).

4.1.8. Methyl 5-hydroxy-5-phenylpentanoate (Table 1, entry 4)[23]. Colorless liquid; yield: 49% (0.102 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.31 (m, 5H, Hs at aromatic ring), 4.68 (m, 1H, H at C5), 3.65 (s, 3H

Hs at OCH_3), 2.34 (t, J=6.5 Hz, 2H, Hs at C2), 2.03 (d, J=3.3 Hz, 1H, H at OH), 1.74 (m, 4H, Hs at C3, C4).

4.1.9. Ethyl 2-hydroxy-2-phenylacetate (Table 2, entry 3)[25]. Colorless liquid; yield: 22% (0.040 g). ^{1}H NMR ($CDCl_3$): δ=7.37 (m, 5H, Hs at aromatic ring), 5.16 (d, J=5.1 Hz, 1H, H at C2), 4.22 (m, 2H, Hs at OCH_2CH_3), 3.49 (d, 1H, J=5.7 Hz, H at OH), 1.23 (t, J=7.1 Hz, 3H, Hs at OCH_2CH_3).

4.1.10. Isopropyl mandelate (Table 2, entry 3)[26]. Colorless liquid; yield: 59% (0.115 g). ^{1}H NMR ($CDCl_3$): δ=7.37 (m, 5H, Hs at aromatic ring), 5.08 (m, 2H, Hs at C2, $OCH(CH_3)_2$), 3.49 (d, J=5.7 Hz, 1H, H at OH), 1.28 (d, J=6.3 Hz, 3H, Hs at $OCH(CH_3)_2$), 1.11 (d, J=6.3 Hz, 3H, Hs at $OCH(CH_3)_2$).

4.1.11. 1-(4-Nitrophenyl)-1,2-ethanediol (Table 3, entry 2)[27]. White solid; yield: quantitative (0.164 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.23 (d, J=9 Hz, 2H, Hs at aromatic ring), 7.57 (d, J=9 Hz, 2H, Hs at aromatic ring), 4.96 (dt, J=7.8, 3.6 Hz, 1H, H at C1), 3.85 (m, 1H, H at C2), 3.65 (m, 1H, H at C2), 2.82 (d, J=3.3 Hz, 1H, H at C1 OH), 2.10 (d, J=5.6 Hz, 1H, H at C2 OH).

4.1.12. 1-(4-Mhoxyphenyl)ethane-1,2-diol (Table 3, entry 3)[28]. White solid; yield: quantitative (0.168 g). ^{1}H NMR ($CDCl_3$): δ=7.30 (d, J=8.1 Hz, 2H, Hs at aromatic ring), 6.90 (d, J=9 Hz, 2H, Hs at aromatic ring), 4.79 (dt, J=8.4, 4.2 Hz, 1H, H at C1), 3.81 (s, 3H, Hs at OCH_3), 3.68 (m, 2H, Hs at C2), 2.41 (d, J=2.7 Hz, 1H, H at C1 OH), 2.02 (dd, J=7.4, 5.0 Hz, 1H, H at C2 OH).

4.1.13. 4-Phenyl-1,2-butanediol (Table 3, entry 4)[29]. Light yellow viscous oil; yield: 91% (0.151 g). ^{1}H NMR ($CDCl_3$): δ=7.25 (m, 5H, Hs at aromatic ring), 3.73 (m, 1H, H at C2), 3.65 (dd, J=11.1, 3.3 Hz, 1H, H at C1), 3.46 (dd, J=11.1, 7.5 Hz, 1H, H at C1), 2.74 (m, 2H, Hs at C4), 2.30 (br s, 1H, H at C2 OH), 2.09(br s, 1H, H at C1 OH), 1.75(m, 2H, Hs at C3).

4.1.14. Propane-1,2-diol (Table 3, entry 5)[30]. Colorless liquid; yield: 93% (0.071 g). ^{1}H NMR ($CDCl_3$): δ=3.91 (m, 1H, H at C2), 3.62 (d, J=10.8 Hz, 1H, H at C1), 3.39 (dd, J=11.0, 8.0 Hz, 1H, H at C1), 3.07 (br s, 2H, Hs at OH), 1.16 (d, J=6.3 Hz, 3H, Hs at C3).

4.1.15. 3-Methylbutane-1,2-diol (Table 3, entry 6)[31]. Colorless liquid; yield: 90% (0.094 g). ^{1}H NMR ($CDCl_3$): δ=3.70 (d, J=10.2 Hz, 1H, H at C1), 3.47 (m, 2H, Hs at C1, C2), 2.40 (br s, 2H, Hs at OH), 1.71 (m, 1H, H at C3), 0.98 (d, J=6.9 Hz, 3H, Hs at C4), 0.92 (d, J=6.9 Hz, 3H, Hs at C4).

4.1.16. Ethyl 2-hydroxy-3-methylbutanoate (Table 3, entry 6)[32]. Colorless liquid; yield: 27% yield (0.040 g). ^{1}H NMR ($CDCl_3$): δ=4.26 (m, 2H, Hs at OCH_2CH_3), 4.03 (dd, J=3.3, 3.3 Hz 1H, H at C2), 2.71 (d, J=6.3 Hz 1H, H at OH), 2.08 (m, 1H, H at C3), 1.31 (t, J=7.2 Hz, 3H, Hs at OCH_2CH_3), 1.03 (d, J=7.2 Hz, 3H, Hs at C3 CH_3), 0.87 (d, J=6.9 Hz, 3H, Hs at C4).

4.1.17. 1-(4-Nitrophenyl)propane-1,3-diol (Table 4, entry 2)[33]. Yellow solid; yield: 94% (0.185 g). ^{1}H NMR ($CDCl_3$): δ=8.23 (d, J=8.7 Hz, 2H, Hs at aromatic ring), 7.57 (d, J=8.7 Hz, 2H, Hs at aromatic ring), 5.12 (m, 1H, H at C1), 3.95 (td, J=5.2, 5.1 Hz, 2H, Hs at C-3), 3.43 (d, J=3.3 Hz, 1H, H at C1 OH), 2.01 (1H, H at C3 OH), 2.01 (m, 2H, Hs at C2).

4.1.18. 1-(4-Chlorophenyl)propane-1,3-diol (Table 4, entry 3)[34]. Colorless gummy solid; yield: 94% (0.175 g). ^{1}H NMR ($CDCl_3$): δ=7.31 (m, 4H, Hs at aromatic ring), 4.94 (t, J=4.2 Hz, 1H, H at C1), 3.85 (m, 2H, Hs at C-3), 3.2 (d, J=2.4 Hz, 1H, H at C1 OH), 2.46 (br s, 1H, H at C3 OH), 1.94 (m, 2H, Hs at C2).

4.1.19. 1-(4-Methoxyphenyl)-1,3-propanediol (Table 4, entry 4)[35]. White solid; yield: 94% (0.171 g). ^{1}H NMR ($CDCl_3$): δ=7.29 (d, J=8.7 Hz, 2H, Hs at aromatic ring), 6.89 (d, J=8.7 Hz, 2H, Hs at aromatic ring), 4.91 (dt, J=8.7, 3.0 Hz, 1H, H at C1), 3.85 (q, J=5.4 Hz, 2H, Hs at C3), 3.81 (s, 3H, Hs at OCH_3), 3.00 (d, J=3.0 Hz, 1H, H at C1 OH), 2.72 (t, J=5.0 Hz, 1H, H at C3 OH), 1.95 (m, 2H, Hs at C-2).

4.1.20. 1-(4-Methylphenyl)-1,3-propanediol (Table 4, entry 5)[36]. Colorless gummy solid; yield: 94% (0.156 g). ^{1}H NMR ($CDCl_3$): δ=7.26 (d, J=7.8 Hz, 2H, Hs at aromatic ring), 7.17 (d, J=8.4 Hz, 2H, Hs at aromatic ring), 4.93 (dd, J=8.7, 3.3 Hz, 1H, H at C1), 3.85 (t, J=5.4 Hz, 2H, Hs at C3), 2.66 (s, 2H, Hs at C1 OH), 2.35 (s, 4H, Hs at CH_3, C3 OH), 1.97 (m, 2H, Hs at C-2).

4.1.21. 1,3-Butanediol (Table 4, entry 6)[37]. Colorless liquid; yield: 92% (0.083 g). ^{1}H NMR ($CDCl_3$): δ=4.09 (m, 1H, H at C3), 3.86 (m, 2H, Hs at C1), 2.76 (br s, 2H, Hs at C1 OH, C3 OH), 1.70 (m, 2H, Hs at C2), 1.25 (d, J=6.3 Hz, 3H, Hs at C4).

4.1.22. Pentane-1,3-diol (Table 4, entry 7)[38]. Colorless liquid; yield: 74% (0.077 g). ^{1}H NMR ($CDCl_3$): δ=3.84 (m, 3H, Hs at C1, C3), 2.54 (br s, 2H, Hs at C1 OH, C3 OH), 1.68 (m, 2H, Hs at C2), 1.53 (m, 2H, Hs at C4), 0.95 (t, J=7.4 Hz, 3H, Hs at C5).

4.1.23. Methyl 3-hydroxypentanoate (Table 4, entry 7)[39]. Colorless liquid; yield: 8% (0.011 g). ^{1}H NMR ($CDCl_3$): δ=3.94 (m, 1H, H at C3), 3.71 (s, 3H, Hs at OCH_3), 2.94 (d, J=3.9 Hz, 1H, H at OH), 2.52 (dd, J=16.7, 3.5 Hz, 1H, H at C2), 2.41 (dd, J=16.4, 9.2 Hz, 1H, H at C2), 1.52 (m, 2H, Hs at C4), 0.96 (t, J=7.2 Hz, 3H, Hs at C5).

4.1.24. Ethyl 3-hydroxypentanoate (Table 4, entry 7)[40]. Colorless liquid; yield: 8% (0.012 g). ^{1}H NMR ($CDCl_3$): δ=4.18 (q, J=7.2 Hz, 2H, Hs at OCH_2CH_3), 3.94 (m, 1H, H at C3), 2.98 (d, J=3.9 Hz, 1H, H at OH), 2.52 (dd, J=16.4, 3.2 Hz, 1H, H at C2), 2.40 (dd, J=16.5, 9.0 Hz, 1H, H at C2), 1.53 (m, 2H, Hs at C4), 1.28 (t, J=7.2 Hz, 3H, Hs at OCH_2CH_3), 0.97 (t, J=7.5 Hz, 3H, Hs at C5).

4.1.25. 4-Methyl-1,3-pentanediol (Table 4, entry 8)[35]. Colorless liquid; yield: 72% yield (0.085 g). ^{1}H NMR ($CDCl_3$): δ=3.86 (m, 2H, Hs at C1), 3.63 (m, 1H, H at C3), 2.56 (br s, 1H, H at C1 OH), 2.41 (br s, 1H, H at C3 OH), 1.69 (m, 3H, Hs at C2, C4), 0.93 (dd, J=6.6, 5.1 Hz, 6H, Hs at C4, C5 $2CH_3$).

4.1.26. Methyl 3-hydroxy-4-methylpentanoate (Table 4, entry 8)[11e]. Colorless liquid; yield: 10% (0.015 g). ^{1}H NMR ($CDCl_3$): δ=3.78 (m, 1H, H at C3), 3.71 (s, 3H, Hs at OCH_3), 2.87 (d, J=3.3 Hz, 1H, H at OH), 2.51 (dd, J=16.4, 3.2 Hz, 1H, H at C2), 2.41 (dd, J=15.9, 9.3 Hz, 1H, H at C2), 1.71 (m, 1H, H at C4), 0.95 (d, J=7.2 Hz, 3H, Hs at C4 CH_3), 0.92 (d, J=6.6 Hz, 3H, Hs at C5).

4.1.27. Ethyl 3-hydroxy-4-methylpentanoate (Table 4, entry 8)[41]. Colorless liquid; yield: 8% (0.013 g). ^{1}H NMR ($CDCl_3$): δ=4.18 (q, J=7.2 Hz, 2H, Hs at OCH_2CH_3), 3.78 (m, 1H, H at C3), 2.94 (d, J=3.9 Hz, 1H, H at OH), 2.50 (dd, J=16.2, 3 Hz, 1H, H at C-2), 2.4 (dd, J=16.2, 9.3 Hz, 1H, H at C2), 1.71 (m, 1H, H at C4), 1.28 (t, J=7.2 Hz, 3H, Hs at OCH_2CH_3), 0.95 (d, J=6.9 Hz, 3H, Hs at C4 CH_3), 0.93 (d, J=6.9 Hz, 3H, Hs at C5).

4.1.28. 4,4-Dimethylpentane-1,3-diol (Table 4, entry 9)[42]. White solid; yield: 58% (0.077 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.87 (m, 2H, Hs at C1), 3.50 (d, J=10.2 Hz, 1H, H at C3), 2.66 (br s, 1H, H at C3 OH), 2.44 (d, J=3.3 Hz, 1H, H at C1 OH), 1.66 (m, 2H, Hs at C2), 0.91 (s, 9H, Hs at C4, C5, $3CH_3$).

4.1.29. Methyl 3-hydroxy-4,4-dimethylpentanoate (Table 4, entry 9)[40]. Colorless liquid; yield: 17% yield (0.027 g). ^{1}H NMR ($CDCl_3$): δ=3.73 (m, 1H, H at C3), 3.72 (s, 3H, Hs at OCH_3), 2.88 (d, J=3.9 Hz,

1H, H at OH), 2.54 (dd, J=16.1, 2.6 Hz, 1H, H at C2), 2.37 (dd, J=16.2, 10.3 Hz, 1H, H at C2), 0.93 (s, 9H, Hs at C4, C5, $3CH_3$).

4.1.30. Ethyl 3-hydroxy-4,4-dimethylpentanoate (Table 4, entry 9)[43]. Colorless liquid; yield: 18% (0.031 g). ^{1}H NMR ($CDCl_3$): δ=4.18 (q, J=7.2 Hz, 2H, Hs at OCH_2CH_3), 3.71 (dt, J=10.5, 2.7 Hz, 1H, H at C3), 2.91 (d, J=3.3 Hz, 1H, H at C3 OH), 2.53 (dd, J=16.1, 2.0 Hz, 1H, H at C2), 2.35 (dd, J=16.4, 10.4 Hz, 1H, H at C2), 1.28 (t, J=7.1 Hz, 3H, Hs at OCH_2CH_3), 0.93 (s, 9H, Hs at C4, C5, $3CH_3$).

4.1.31. 4-Chlorobutane-1,3-diol (Table 4, entry 10)[44]. Colorless liquid; yield: 94% yield (0.117 g). ^{1}H NMR ($CDCl_3$): δ=4.07 (m, 1H, H at C3), 3.86 (m, 2H, Hs at C1), 3.58 (m, 2H, Hs at C4), 3.36 (d, J=5.4 Hz, 2H, Hs at C1 OH, C3 OH), 1.80 (m, 2H, Hs at C2).

4.1.32. 4-Methoxybutane-1,3-diol (Table 4, entry 11)[45]. Colorless liquid; yield: 93% (0.112 g). ^{1}H NMR (DMSO): δ=4.51 (d, J=5.1 Hz, 1H, H at C3 OH), 4.32 (t, J=5.1 Hz, 1H, H at C1 OH), 3.68 (m, 1H, H at C3), 3.48 (dd, J=6.2 Hz, 2H, Hs at C1), 3.24 (s, 3H, Hs at OCH_3), 3.20 (d, J=5.1 Hz, 2H, Hs at C4), 1.54 (m, 1H, H at C2), 1.40 (m, 1H, H at C2).

4.1.33. 2-Methylbutane-1,3-diol (Table 4, entry 12)[46]. Colorless liquid; yield: 71% yield (0.074 g). ^{1}H NMR ($CDCl_3$): δ=4.04 (m, 1H, H at C3 A), 3.72 (m, 2H, Hs at C1 B), 3.72 (m, 2H, Hs at C1 A), 3.61 (m, 1H, H at C1 B), 3.14 (m, 1H, H at C-3 OH), 2.70 (d, J=26.4 Hz, 1H, H at C1 OH), 1.82 (m, 1H, H at C2 A), 1.66 (m, 1H, H at C2 B), 1.24 (d, J=6.3 Hz, 3H, Hs at C4 A), 1.20 (d, J=6.6 Hz, 3H, Hs at C4 B), 0.90 (d, J=7.5 Hz, 3H, Hs at C2 CH_3 A), 0.85 (d, J=6.9 Hz, 3H, Hs at C-2 CH_3 B).

4.1.34. Ethyl 3-hydroxy-2-methylbutanoate (Table 4, entry 12)[47]. Colorless liquid; yield: 21% (0.031 g). ^{1}H NMR ($CDCl_3$): δ=4.18 (q, J=7.2 Hz, 2H, Hs at OCH_2CH_3 A), 4.18 (q, J=7.2 Hz, 2H, Hs at OCH_2CH_3 A), 4.07 (m, 1H, H at C3 B), 3.89 (m, 1H, H at C3 A), 2.74 (d, J=6.0 Hz, 1H, H at OH A), 2.64 (d, J=4.8 Hz, 1H, H at OH B), 2.50 (m, 1H, H at C2 B), 2.44 (m, 1H, H at C2 A), 1.28 (t, J=7.2 Hz, 3H, Hs at OCH_2CH_3 A), 1.28 (t, J=7.2 Hz, 3H, Hs at OCH_2CH_3 A), 1.23 (d, J=6.3 Hz, 3H, Hs at $CHCH_3$ A), 1.23 (d, J=6.3 Hz, 3H, Hs at $CHCH_3$ A), 1.20 (d, J=3.0 Hz, 3H, Hs at C4 B), 1.18 (d, J=2.4 Hz, 3H, Hs at C4 A).

4.1.35. 2-Chloro-1,3-butanediol (Table 4, entry 13)[48]. Colorless liquid; yield: 96% (0.120 g). ^{1}H NMR ($CDCl_3$): δ=4.09 (m, 1H, H at C3), 3.94 (m, 3H, Hs at C1, C2), 2.32 (m, 1H, Hs at C3 OH), 2.25 (m, 1H, H at C1 OH), 1.36 (d, J=6.6 Hz, 3H, Hs at C4 A), 1.33 (d, J=6.6 Hz, 3H, Hs at C4 B).

4.1.36. 1-(4-Ethoxycarbonylphenyl)-1,2-ethanediol. White solid; yield: 87% (0.182 g); mp 65–67 °C. ^{1}H NMR ($CDCl_3$): δ 8.02 (d, J=8.1 Hz, 2H, Hs at aromatic ring), 7.43 (d, J=8.4 Hz, 2H, Hs at aromatic ring), 4.88 (m, 1H, H at C1), 4.37 (q, J=7.0 Hz, 2H, Hs at OCH_2CH_3), 3.78 (d, J=11.1 Hz, 1H, H at C-2), 3.63 (m, 1H, H at C2), 3.02 (br s, 1H, H at C1 OH), 2.43 (br s, 1H, H at C2 OH), 1.39 (t, J=7.1 Hz, 3H, Hs at OCH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 145.7, 130.1, 129.9, 126.1, 74.5, 68.0, 61.3, 14.5; IR (KBr, cm^{-1}): 3380 (OH), 1714 (C=O), 1281 (C–O). HRMS m/z calcd for $C_{11}H_{15}O_4$ 211.0970, found 211.0972.

4.1.37. 4-(1,3-Dihydroxypropyl)benzoic acid methyl ester (Table 6, entry 2)[49]. White solid; yield: 95% (0.040 g). ^{1}H NMR ($CDCl_3$): δ=8.02 (d, J=9 Hz, 2H, Hs at aromatic ring), 7.45 (d, J=8.1 Hz, 2H, Hs at aromatic ring), 5.05 (m, 1H, H at C-1), 3.92 (s, 3H, Hs at OCH_3), 3.88 (m, 2H, Hs at C3), 3.21 (br s, 1H, H at C1 OH), 2.28 (br s, 1H, H at C3 OH), 1.97 (m, 2H, Hs at C-2).

Acknowledgements

J.K., K.A.D.C., and M.L. acknowledge financial support from the Korean Ministry of Education through the 2nd stage of the BK21 project for the Hanyang University graduate program and M.L. also acknowledges Seoul Metropolitan Government for Seoul Science Fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.04.062.

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