JOC*Note*

Efficient and Selective Reduction Protocols of the 2,2-Dimethyl-1,3-benzodioxan-4-one Functional Group to Readily Provide Both Substituted Salicylaldehydes and 2-Hydroxybenzyl Alcohols

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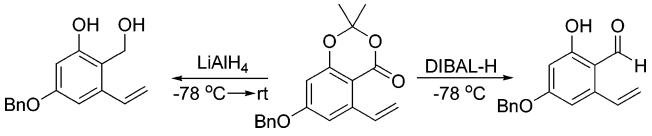
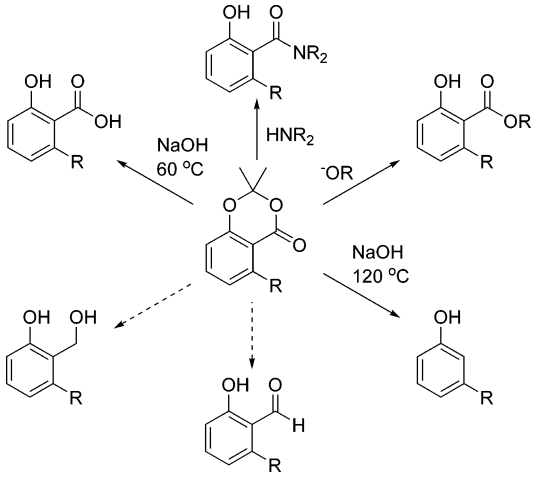


Two complementary procedures have been developed that selectively allow for the synthesis of either substituted salicylaldehydes or the corresponding 2-hydroxylbenzyl alcohols upon treatment of the 2,2-dimethyl-1,3-benzodioxan-4-one functional group with DIBAL-H or LAH, respectively.

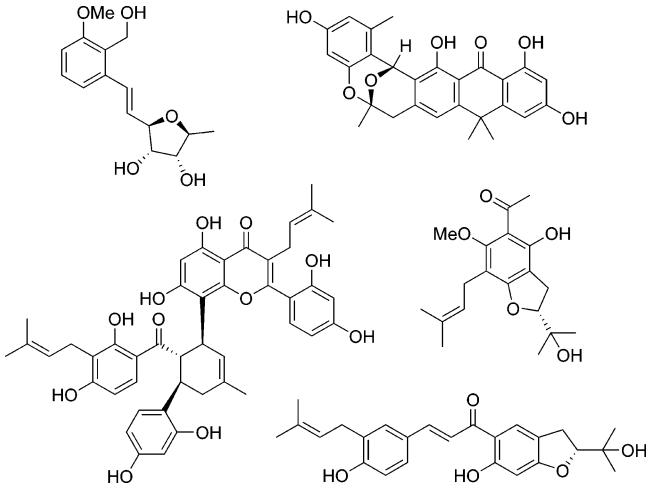
Due to the ubiquitous nature of aromatic natural products, the development of new methods for the synthesis of highly functionalized and substituted benzene building blocks is of tremendous significance. One specific subunit that is used frequently in aromatic natural product synthesis is the 2,2-dimethyl-1,3-benzodioxan-4-one functional group, which concomitantly masks both the carboxylic acid and free hydroxyl moieties. As shown in Scheme 1, selective manipulation of such a protecting group to provide the phenolic acid, ester, amide, and decarboxylated phenol has been developed and is frequently used in target-based synthesis.[1]

While most research laboratories utilize the 2,2-dimethyl-1,3-benzodioxan-4-one functional group as a phenolic ester surrogate,[2] a wide range of biologically active natural products could readily be derived from the reduction of such an aromatic subunit to either the aldehyde or diol intermediates as highlighted in Scheme 2.[3] As part of our research program aimed at the total synthesis of resorcinol-type natural products, we were interested in developing two reduction protocols for the selective syntheses of both substituted salicylaldehydes as well as the corresponding 2-hydroxybenzyl alcohol subunits. If successful, these protocols offer direct entrance into the mentioned moieties in a one-step procedure, whereas existing technologies require a minimum of at least two steps from the 2,2-dimethyl-1,3-benzodioxan-4-one functional group.

SCHEME 1. Selective Manipulation of the 2,2-Dimethyl-1,3-benzodioxan-4-one Functional Group



SCHEME 2. Selected Natural Products that Could Be Derived from the Reduction of a Substituted 2,2-Dimethyl-1,3-benzodioxan-4-one Subunit



With this idea in mind, we initially chose to investigate the reduction of 2,2-dimethyl-1,3-benzodioxan-4-one (**1a**)[4] with a variety of nucleophilic and electrophilic reagents. As shown in Table 1, the reduction of **1a** did not proceed at room temperature with the weakly nucleophilic reagents $NaBH_4$ and $LiAl(OtBu)_3H$ to provide either salicylaldehyde (**1b**) or 2-hydroxybenzyl alcohol (**1c**), but afforded only the recovered starting material. Likewise, treatment of **1a** with Red-Al in toluene did not lead to any of the reduced products **1b** or **1c** at room temperature, but further heating to reflux decomposed the starting material.

(1) (a) Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1992**, *114*, 655. (b) Soltani, O.; De Brabander, J. K. *Angew. Chem., Int. Ed*. **2005**, *44*, 1696.

(2) For some recent examples in natural product total synthesis, see: (a) Bolshakov, S.; Leighton, J. L. *Org. Lett*. **2005**, *7*, 3809. (b) Soltani, O.; De Brabander, J. K. *Org. Lett*. **2005**, *7*, 2791.

(3) (a) Malmstrom, J.; Christophersen, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. *J. Nat. Prod*. **2002**, *65*, 364. (b) Herath, K. B.; Jayasuriya, H.; Guan, Z.; Schulman, M.; Ruby, C.; Sharma, N.; MacNaul, K.; Menke, J. G.; Kodali, S.; Galgoci, A.; Wang, J.; Singh, S. B. *J. Nat. Prod*. **2005**, *68*, 1437. (c) Oshima, Y.; Konno, C.; Hikino, H.; Matsushita, K. *Heterocycles* **1980**, *14*, 1287. (d) Su, C.-R.; Kuo, P.-C.; Wang, M.-L.; Liou, M.-J.; Damu, A. G.; Wu, T.-S. *J. Nat. Prod*. **2003**, *66*, 990. (e) Ngameni, B.; Ngadjui, B. T.; Folefoc, G. N.; Watchueng, J.; Abegaz, B. M. *Phytochemistry* **2004**, *65*, 427.

(4) Mowry, D. T.; Yanko, W. H.; Ringwald, E. L. *J. Am. Chem. Soc*. **1947**, *69*, 2358.

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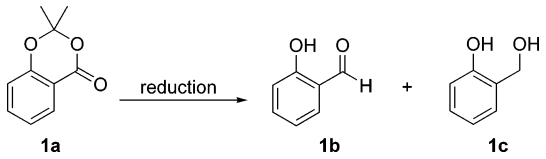
TABLE 1. Reduction of 1a with Various Reducing Reagents[a]

No.	reagent	equiv	solvent	temp	product	yield %
1	$NaBH_4$	2	EtOH	rt	**1a**	NR
2	Red-Al	2	toluene	rt → 110 °C	decomposed	NA
3	$LiAl(OtBu)_3H$	2	THF	rt	**1a**	NR
4	$LiAlH_4$	1	THF	−78 °C → rt	**1b** and **1c** (1:1)	81
5	$LiAlH_4$	4	THF	rt	**1c**	84
6	$LiBH_4$	4	THF	rt	**1c**	83
7	$BH_3{\bullet}SMe_2$	2	THF	rt	**1a**	NR
8	DIBAL-H	1.5	toluene	−78 °C	**1b**	45
9	DIBAL-H	1.5	CH_2Cl_2	−78 °C	**1b**	45
10	DIBAL-H	3	CH_2Cl_2	−78 °C	**1b**	68

[a] Yields are of the isolated and purified compound. NR = no reaction.

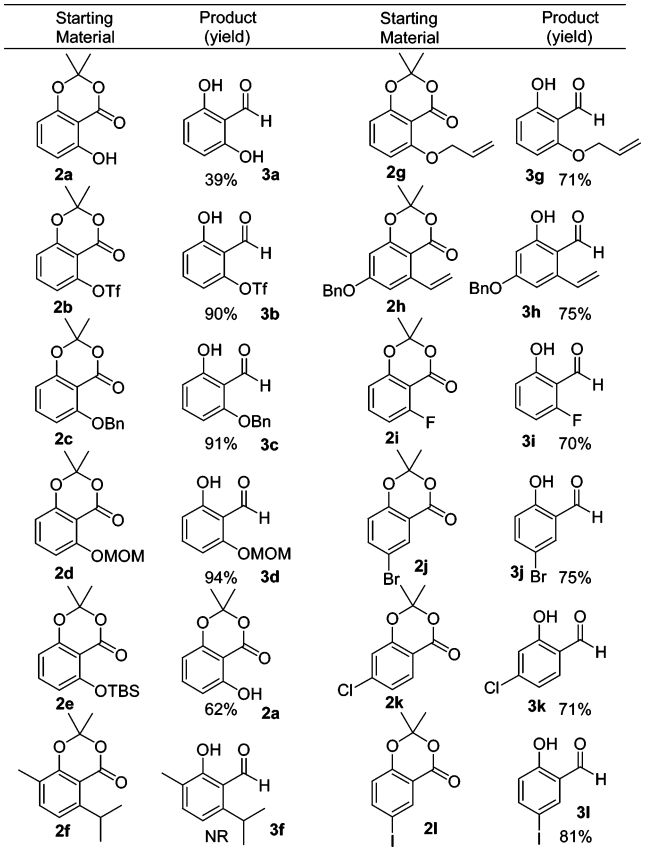
Initial attempts aimed at the reduction of **1a** with lithium aluminum hydride (LAH) at −78 °C furnished mixed results. When the reaction was left at −78 °C for 0.5 h and then warmed to room temperature with 1 equiv of LAH in THF, we observed consumption of the starting material and a 1:1 mixture of **1b** and **1c**. Additional attempts to reduce **1a** with an excess of LAH at room temperature readily led to the formation of **1c** as the sole product in 84% yield. Similarly, reduction of **1a** with excess $LiBH_4$ (4 equiv) at room temperature furnished solely diol **1c** in a yield very compatible to that of LAH.



Upon the observation that 1 equiv of LAH would only partially reduce **1a** at −78 °C, we surmised that treatment of **1a** with an electrophilic reducing reagent such as borane or DIBAL might selectively afford **1b**. However, the reduction of **1a** did not proceed as predicted at room temperature with borane dimethyl sulfide, and only starting material was recovered. Conversely, treatment of **1a** with 1.5 equiv of DIBAL-H at low temperature provided aldehyde **1b** but with only a 45% yield. Switching the medium from toluene to dichloromethane (DCM) furnished **1b** with an identical yield of 45%. Much to our delight, addition of 3 equiv of DIBAL-H in DCM to **1a** at −78 °C afforded aldehyde **1b** with a respectable 68% yield. It should be noted that the yield was lower than anticipated due to the unexpected volatility of **1b**, which hindered its isolation and purification.

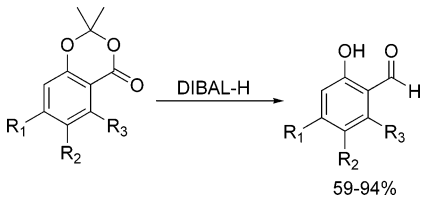
With the two complementary and efficient protocols for the selective reduction of **1a** in hand, we next turned our attention to defining the scope and limitations of these methodologies. As described in Table 2, we investigated the stability of a variety of functional groups and orthogonally protected phenols toward the DIBAL-H reduction procedure. Thus, the reduction of the phenol-substituted 2,2-dimethyl-1,3-benzodioxan-4-one (**2a**)[5] with 3 equiv of DIBAL-H proceeded to provide 2,6-dihydroxybenzaldehyde (**3a**)[6] in 39% yield, with the remaining material balance as the starting material **2a**. We surmised that the initial diisobutyl aluminum alkoxide severely hindered the addition of a second equivalent of DIBAL-H and was responsible for the low yield of **3a**. Much to our delight, protection of the free hydroxyl group of **2a** as a benzyl (**2c**),[7] methoxymethyl (**2d**),

TABLE 2. Reduction of 2a−l with DIBAL-H[a−c]



[a] Reactions ran at −78 °C with 3 equiv of DIBAL-H (1 M in CH_2Cl_2) for 2 h. [b] Yields are of the isolated and purified compound. [c] NR = no reaction.

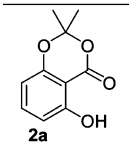
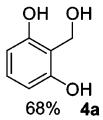
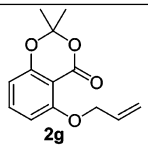
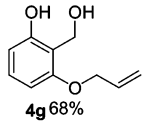
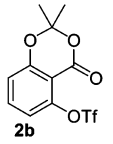
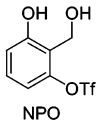
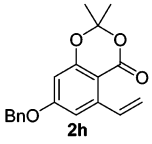
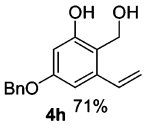
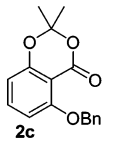
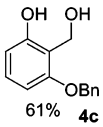
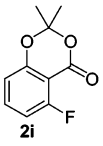
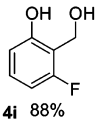
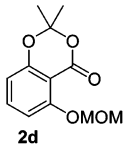
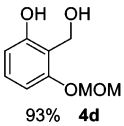
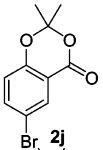
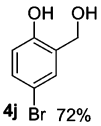
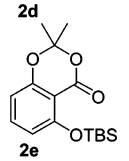
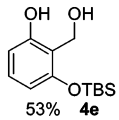
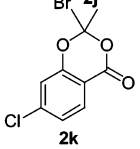
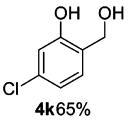
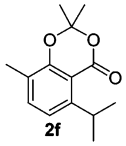
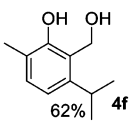
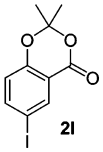
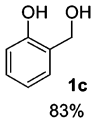
or allyl (**2g**) ether allowed for the reduction of the 2,2-dimethyl-1,3-benzodioxan-4-one functional group to provide the resultant aldehydes **3c**, **3d**, and **3g** in very good yields ranging from 71 to 94%.[8−10] The fluoro, bromo, chloro, and iodo-substituted 2,2-dimethyl-1,3-benzodioxan-4-ones (**2i**−**2l**) readily underwent reduction with DIBAL-H to afford the corresponding aldehydes (**3i**−**3l**)[11−14] (70−81% yield) with no over-reduction of the halide susbtituents. Likewise, a triflate (**2b**)[15] and vinyl (**2h**) functional group was tolerant of the standard conditions employed at −78 °C, and the matching aldehydes (**3b** and **3h**) were isolated in good yields of 91 and 75%, respectively. Unfortunately, the sterically hindered 2,2-dimethyl-1,3-benzodioxan-4-one **2f** did not undergo reduction with DIBAL to provide the corresponding aldehyde **3f**.



However, the reduction of the TBS-protected phenolic 2,2-dimethyl-1,3-benzodioxan-4-one (**2e**) did not lead to any of the

(5) Furstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett*. **2000**, *2*, 3731.
(6) Felber, B.; Diederich, F. *Helv. Chim. Acta*. **2005**, *88*, 120.
(7) Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc*. **2004**, *126*, 10313.
(8) Shipchandler, M.; Soine, T. O.; Gupta, P. K. *J. Pharm. Sci*. **1970**, *59*, 67.
(9) Zacharie, B.; Attardo, G.; Barriault, N.; Penney, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2925.

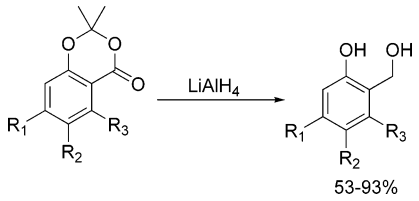
TABLE 3. Reduction of 2a−l with LAH[a−d]

Starting Material	Product (yield)	Starting Material	Product (yield)
 **2a**	 68% **4a**	 **2g**	 **4g** 68%
 **2b**	 NPO	 **2h**	 **4h** 71%
 **2c**	 61% **4c**	 **2i**	 **4i** 88%
 **2d**	 93% **4d**	 Br **2j**	 **4j** Br 72%
 **2e**	 53% **4e**	 Cl **2k**	 **4k** 65%
 **2f**	 62% **4f**	 **2l**	 **1c** 83%

[a] For specific reaction conditions, see the Experimental Section. [b] Yields are of the isolated and purified compound. [c] NPO = no product observed. [d] Reduction of **2b** and **2l** with $LiBH_4$ provided the matching diols **4b** and **4l** in 67 and 71% yields.

desired product aldehyde **3e**, but unfortunately provided mostly compound **2a** and aldehyde **3a** with isolated yields of 62 and 35%, respectively. In accordance with Corey's previous report,[16] we observed that DIBAL-H readily desilylated the TBS-protected phenol of **2e** at −78 °C. Additionally, the corresponding diisobutyl aluminum alkoxide most likely impeded the reduction of the 2,2-dimethyl-1,3-benzodioxan-4-one subunit to **3a** as previous described for **2a**.

With the successful partial reduction of the 2,2-dimethyl-1,3-benzodioxan-4-one subunit containing a variety of substituted functional groups to the resultant substituted salicylaldehyde products with DIBAL, our focus was then shifted to examining the reduction of such compounds to the corresponding benzyl alcohol derivatives with LAH. As illustrated in Table 3, we investigated the stability of a variety of functional groups and orthogonally protected phenols toward the LAH reduction protocol. Accordingly, treatment of **2a** with excess LAH (4 equiv) at −78 °C for 2 h readily allowed for the formation of the corresponding diol **4a**[17] with a 68% yield. By utilizing a large excess of LAH, the free hydroxyl moiety of **2a** did not hinder the reaction progress as observed during the DIBAL-H reduction procedure.



Gratifyingly, protection of the free hydroxyl group of **2a** as a variety of orthogonal protecting groups such as the benzyl (**2c**), methoxymethyl (**2d**), *tert*-butyldimethylsilyl (**2e**), or allyl (**2f**) ether allowed for the reduction of the 2,2-dimethyl-1,3-benzodioxan-4-one functional group to provide the resultant substituted 2-hydroxybenzylic alcohols **4c**, **4d**, **4e**, and **4f** in good yields ranging from 53 to 93%. Correspondingly, the fluoro, bromo, and chloro-substituted 2,2-dimethyl-1,3-benzodioxan-4-ones (**2h**−**2j**)[18−20] readily underwent reduction with LAH to afford the corresponding 2-hydroxybenzylic alcohols (**4h**−**4j**) (65−88% yield) with no over-reduction of the halide susbtituents. Likewise, the conjugated vinyl (**2g**) functional group was tolerant of the standard LAH conditions employed at −78 °C, and the matching diol (**4g**) was isolated with a good yield of 71%.[21] The sterically hindered 2,2-dimethyl-1,3-benzodioxan-4-one **2f** also readily underwent reduction with LAH to provide the corresponding diol **4f** in good yield. Unfortunately, carbonyl and halide reduction of the iodo-substituted 2,2-dimethyl-1,3-benzodioxan-4-one (**2l**) was observed, and diol **1c** was isolated in 83% yield. Attempted reduction of the triflate-substituted 2,2-dimethyl-1,3-benzodioxan-4-one **2b** under a variety of conditions with LAH led to complete decomposition of the starting material and provided none of the desired compound **4b**. However, reduction of both **2b** and **2l** could be successfully carried out when utilizing $LiBH_4$ to provide the corresponding diols **4b** and **4l**[22] with yields of 67 and 71%, respectively.

In conclusion, we have developed two complementary procedures that provide either substituted salicylaldehydes or the corresponding 2-hydroxylbenzyl alcohols upon treatment of the 2,2-dimethyl-1,3-benzodioxan-4-one functional group with DIBAL-H or LAH (and in some cases $LiBH_4$), respectively. These two methodologies should readily allow for the production of indispensable aromatic subunits that could be utilized during the total synthesis of biologically active natural products. Efforts in that direction are currently underway and will be reported in due course.

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Experimental Section

General Procedure for the Preparation of Aldehydes 3a−3l. A solution of substituted 2,2-dimethyl-1,3-benzodioxan-4-one (1 mmol) in CH_2Cl_2 at −78 °C was treated with DIBAL-H (3 mmol, 1 M solution in CH_2Cl_2). The reaction mixture was stirred at −78 °C for 2 h and then quenched with 1 M HCl and MeOH. After warming to room temperature, H_2O was added, and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. Chromatography on silica gel with hexanes−EtOAc (95:5) as the eluent afforded the targeted aldehyde compounds **3a**−**3j**.

Procedure for the Preparation of Diols 4a, 4d, and 4g−4l. A solution of substituted 2,2-dimethyl-1,3-benzodioxan-4-one (1 mmol) in THF at −78 °C was treated with LAH (4 mmol, 1 M solution in THF). The reaction mixture was stirred at −78 °C until completion (generally 2 h) as determined by TLC. The cooling bath was then removed, and the reaction mixture was quenched with 1 M HCl and MeOH followed by extraction of the aqueous layer with Et_2O. The combined organic layers were washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. Chromatography on silica gel with hexanes−EtOAc (9:1 → 8:2) as the eluent afforded the targeted diol compounds **4a**, **4d**, and **4g**−**4j**.

Procedure for the Preparation of Diols 4c, 4e, and 4f. A solution of substituted 2,2-dimethyl-1,3-benzodioxan-4-one (1 mmol) in THF at −78 °C was treated with LAH (5 mmol, 1 M solution in THF). The reaction mixture was kept at −78 °C for 2 h followed by warming to room temperature and further stirring for 12 h. The reaction was then quenched with 1 M HCl and MeOH followed by extraction of the aqueous layer with Et_2O. The combined organic layer was then washed with water and brine, dried with $NaSO_4$, and concentrated in vacuo. Chromatography on silica gel with hexanes−EtOAc (9:1 → 8:2) as the eluent afforded the targeted diol compounds **4c**, **4e**, and **4f** in good yields.

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Supporting Information Available: Experimental procedures for the preparation of the substituted 2,2-dimethyl-1,3-benzodioxan-4-ones and full characterization data for all new compounds. ^1H NMR spectral data for the previously reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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