Stereoselective Synthesis of Substituted 5-Hydroxy-1,3-dioxanes

David C. Forbes,* Doina G. Ene, Michael P. Doyle[1]
Department of Chemistry, Trinity University, San Antonio, Texas 78212, USA
E-mail: dforbes@u.arizona.edu

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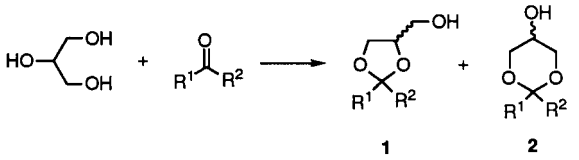
Abstract: A series of 5-hydroxy-1,3-dioxanes has been synthesized using a practical three-step strategy beginning with acetal/ketal formation of tris(hydroxymethyl)aminomethane followed by oxidative cleavage of the amino alcohol. After the ketone was revealed, stereoselective reduction with common hydride reagents, $LiAlH_4$ for the *trans* isomers and L-Selectride for the *cis* analogues, gave the target compounds in high yield.

Key words: 5-hydroxy-1,3-dioxanes, synthesis, cyclization, sodium periodate oxidation, stereoselective reduction

The synthesis of 2-substituted 5-hydroxy-1,3-dioxanes has been achieved by a laborious process initiated with the acetalization of glycerol.[2] Four isomeric products are formed upon treatment of glycerol with aldehydes: *cis*- and *trans*-2-alkyl-4-hydroxymethyl-1,3-dioxolanes **1** together with *cis*- and *trans*-2-alkyl-5-hydroxy-1,3-dioxanes **2**. Ketalization of glycerol leads to 4-hydroxymethyl-1,3-dioxolanes **1** virtually exclusively.

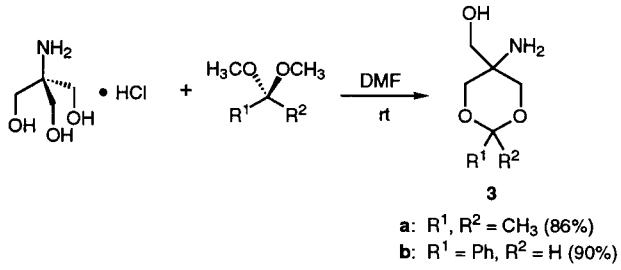


1 **2**

Although there is considerable interest in their properties and uses as synthetic intermediates,[2,3] 5-hydroxy-1,3-dioxanes have required labor-intensive separation schemes for their isolation[4] that, even with recently reported transacetalization/recrystallization[5] and chemoselective derivatization[6] methodologies, result in low isolated product yields (17–40%). We wish to report a new synthetic methodology for the construction of 2-substituted 5-oxo-1,3-dioxanes which is a considerable improvement to the current technology[7,8] that also incorporates, for the first time, the synthesis of 2,2-disubstituted 5-hydroxy-1,3-dioxanes.

Recognizing the general limitations of glycerol as the starting material for the synthesis of **2**, we selected commercially available tris(hydroxymethyl)aminomethane which as the hydrochloride salt is readily converted by transacetalization or transketalization to **3**. Periodate oxidation of **3** forms the corresponding 1,3-dioxan-5-ones **4** which undergo stereoselective reduction or alkylation. The major advantages of this approach are: (1) the exclusive formation of the dioxane and not the dioxolane, a complication noted in previously reported syntheses,[5,6] (2) a stereoselective reduction of the ketonic moiety to provide either the *cis* or *trans* diastereomer, and (3) complete control of substitution at positions C-2 and C-5.

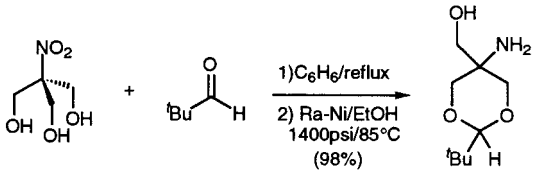
Using 2,2-dimethoxypropane as the starting ketal, the desired amino alcohol **3a** was obtained as a low melting solid in 86% yield after neutralization of the reaction mixture with triethylamine and removal of the excess DMF. When the dimethyl acetal derived from benzaldehyde was employed under the same reaction conditions, cyclization afforded the desired phenyl acetal **3b** in 90% yield.



a: R^1, R^2 = CH_3 (86%)
b: R^1 = Ph, R^2 = H (90%)

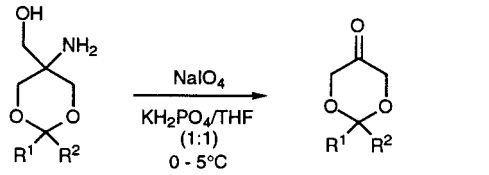
Because all attempts to prepare the corresponding *tert*-butyl acetal from tris(hydroxymethyl)aminomethane in reproducibly high yields failed, we examined modifications to the existing protocol. Thus we replaced tris(hydroxymethyl)aminomethane with the corresponding nitro derivative. Although ketal/acetal formation with this nitro compound, a process previously reported in the literature,[7] adds one step to the synthetic route described to give **5**, it does permit the incorporation of sterically demanding residues at C-2. Treatment of pivaldehyde with tris(hydroxymethyl)nitromethane in refluxing benzene using a Soxlet apparatus for the extraction of water afforded the desired cyclized product in 98% yield. Reduction of the nitro moiety using catalytic Raney nickel under 1400 psi of hydrogen at 85 °C afforded the desired *tert*-butyl acetal **3c** quantitatively.

Sodium periodate cleavage of amino alcohols **3a–c** gave the desired ketones **4** in 85–98% yield as either clear and colorless oils or solids after purification. Using THF, ei-



3c

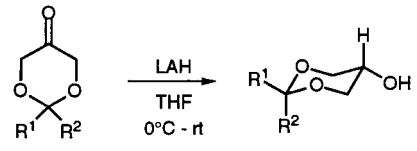
ther as a cosolvent or exclusively, greatly improved the yields with the more lipophilic amino alcohols. This two-step sequence has been used on a multigram scale in high yields for the production of the desired ketones **4a–c**, beginning with commercially available triol, which is a substantial advancement to the previously reported approach.[6–8] Overall yields from the triol increased from 35% to 73% (**4a**), 23% to 66% (**4b**), and 45% to 98% (**4c**).[7]



3 **4**

a: R^1, R^2 = CH_3 (85%)
b: R^1 = Ph, R^2 = H (90%)
c: R^1 = ^{t}Bu, R^2 = H (98%)

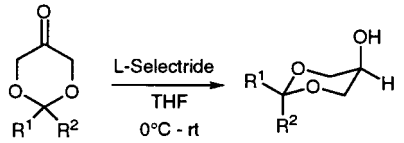
Synthesis of the target molecules was completed with the stereoselective reduction of each symmetrical ketone **4**. For the dimethyl ketal **4a**, $LiAlH_4$ was found to be effective in providing the desired hydroxydioxane **5a** in 97% yield. Since the requisite hydroxydioxanes **5b** and **5c** are diastereomeric, stereoselective reductions were performed. Upon treatment of either the phenyl- **4b** or *tert*-butyl- **4c** substituted ketone with $LiAlH_4$, a mixture of diastereomers (GC analysis) in 87% and 90% yield, respectively, favoring the desired isomer (86:14 and 87:13, *trans/cis*) was obtained. The pure diastereomer was isolated after silica gel chromatography in 50% yield for *trans*-**5b** and 83% yield for *trans*-**5c.**[9]



4 **5**

a: R^1, R^2 = CH_3 (97%)
trans-**b**: R^1 = Ph, R^2 = H (50%)
trans-**c**: R^1 = ^{t}Bu, R^2 = H (83%)

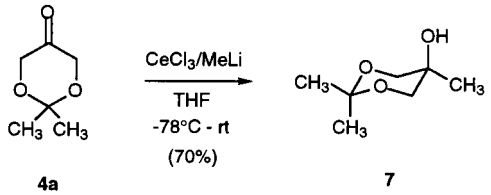
The diastereomeric counterparts *cis*-**5b** and *cis*-**5c** mandate an equatorial addition of hydride to the ketonic moiety at C-5. The bulky reductant L-Selectride was chosen and found to yield, in very high levels of stereoselectivity, the *cis* isomers based on GC analysis. The phenyl-substituted acetal **4b** was reduced to afford *cis*-**5b** in 94% yield as a 92:8 mixture of diastereomers favoring the desired *cis* analogue (50% isolated yield) whereas with the *tert*-butyl acetal **4c**, the *cis* diastereomer **5c** was formed exclusively (75% isolated yield).[9]



4 **5**

cis-**b**: R^1 = Ph, R^2 = H (50%)
cis-**c**: R^1 = ^{t}Bu, R^2 = H (75%)

Application of this synthetic protocol allows for the preparation of both secondary and tertiary 5-hydroxy-1,3-dioxanes by way of organometallic additions to the ketone moiety. Accordingly, methyl-substituted alcohol **7** was prepared using anhydrous cerium trichloride and methyllithium in 70% yield. This process was found to be optimal when compared to other classical methodologies such as Grignard-based additions.



4a **7**

The most attractive features of this three-step strategy, as illustrated, are the relative ease of preparation and exclusive formation of the hydroxy-1,3-dioxane template in high yield, which has been problematic in previous methodologies. Substitution at both C-2 and C-5 has been achieved providing novel 2,2-disubstituted 5-hydroxy-1,3-dioxanes both stereoselectively and, again, in high yields.

^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were obtained as solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ) downfield from internal TMS. MS were obtained using electron ionization (70 eV) on a quadrupole instrument. IR were recorded as a thin film on NaCl plates or in a KBr pellet as indicated, and absorptions are reported in wavenumbers (cm^{-1}). Mps are uncorrected. Anhyd THF was distilled from Na/benzophenone under N_2. Anhyd CH_2Cl_2 was dried over CaH_2 for 24 h and then distilled prior to use. $CeCl_3 \cdot 7\ H_2O$ was dried prior to use (150 °C/30 Torr) for 12 h. Both tris(hydroxymethyl)aminomethane hydrochloride and tris(hydroxymethyl)nitromethane were purchased from Aldrich. Analytical data listed for amino alcohols **3**, ketones **4** and hydroxydioxanes **5** and **7** are in agreement with those previously reported.[7, 8, 10]

5-Amino-5-hydroxymethyl-2,2-dimethyl-1,3-dioxane (3a); Typical Procedure:

A general procedure[7, 8] was followed for the preparation of **3a** and **3b**. The preparation of **3a** is representative. To a solution of tris(hydroxymethyl)aminomethane hydrochloride (20.0 g, 125 mmol) in an-

hyd DMF (140 mL) was added PTSA (1.8 g, 6.0 mmol, 0.050 equiv) followed by 2,2-dimethoxypropane (16.9 mL, 138 mmol, 1.1 equiv) in one portion. The resulting clear and colorless solution was allowed to stir overnight (12 h) at which time Et_3N (1.0 mL, 7.0 mmol, 0.060 equiv) was added and allowed to stir for an additional 10 min. The mixture was next concentrated in vacuo and treated with Et_3N (13.7 mL, 98.0 mmol) and EtOAc (500 mL). The white precipitate which was formed upon addition of the base was removed via filtration and the filtrate was purified by bulb-to-bulb distillation [85 °C/0.7 Torr (air-bath temp)] to afford 17.4g (108 mmol, 86% yield) of **3a** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.44 (s, 3 H), 2.36 (br s, 3 H), 3.49 (s, 2 H), 3.53 (d, *J* = 11.8 Hz, 2 H), 3.78 (d, *J* = 11.9 Hz, 2 H).

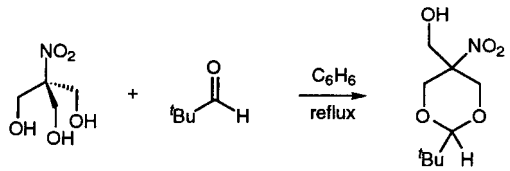
^{13}C NMR (100 MHz, $CDCl_3$): δ = 22(q), 25(q), 50(t), 64(t), 67(t), 98(s).

5-Amino-5-hydroxymethyl-2-phenyl-1,3-dioxane (**3b**):

From the combination of tris(hydroxymethyl)aminomethane hydrochloride (20.0 g, 127 mmol), PTSA (1.1 g, 6.0 mmol), benzaldehyde dimethyl acetal (22.3 g, 139 mmol), and Et_3N (13.9 mL, 99.0 mmol), acetal **3b** was obtained after purification by bulb-to-bulb distillation [70 °C/0.3 Torr (air-bath temp)] in 19.5 g (93 mmol, 90% yield) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.03 (s, br, 3 H), 3.93 (s, 2 H), 3.84 (d, *J* = 11.4 Hz, 2 H), 3.93 (d, *J* = 11.4 Hz, 2 H), 5.41 (s, 1 H), 7.33–7.51 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 51(t), 64(s), 74(t), 101(d), 125(d), 128(d), 129(d), 137(s).



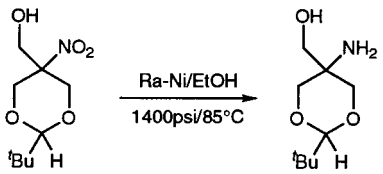
6

5-Amino-2-*tert*-butyl-5-hydroxymethyl-1,3-dioxane (3c):

2-tert-*Butyl-5-hydroxymethyl-5-nitro-1,3-dioxane* **(6)**:

From the combination of tris(hydroxymethyl)nitromethane (7.6 g, 50 mmol), PTSA (0.9 g, 5 mmol), and pivaldehyde (6.6 g, 50 mmol) in benzene (150 mL) using the typical procedure for **3a**, acetal **6** was obtained in 11.0 g (50 mmol, quantitative yield) as a white solid that required no further purification.

^{1}H NMR (400 MHz, $CDCl_3$) minor: δ = 0.92 (s, 9 H), 1.85 (br s, 1 H), 4.00 (d, *J* = 11.5 Hz, 2 H), 4.11 (s, 1 H), 4.28 (s, 2 H), 4.28 (d, *J* = 11.5 Hz, 2 H); major: δ = 0.88 (s, 9 H), 1.26 (t, *J* = 4.2 Hz, 1 H), 3.81 (s, 2 H), 3.82 (d, *J* = 12.7 Hz, 2 H), 4.13 (s, 1 H), 4.86 (d, *J* = 12.9 Hz, 2 H).



6 **3c**

5-Amino-2-tert-*butyl-5-hydroxymethyl-1,3-dioxane* **(3c)**:

The following procedure[7] required the use of a Parr reactor, a high pressure autoclave which allows for both external heating and stirring. Acetal **6** (6.5 g, 30 mmol) was dissolved in EtOH (75 mL) at which time a solution of Raney nickel[11] (8 mL, 0.6 g/mL in EtOH) was added. The mixture was fitted into the setup, charged with 1400 psi of H_2 and allowed warm to 85 °C for a period of 4 h with stirring. Upon cooling the mixture, the slurry was filtered through a cotton plug, and concentrated in vacuo to afford 5.4 g (29 mmol, 98% yield) of amino alcohol **3c** as a white solid that required no further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (s, 9 H), 2.29 (br s, 3 H), 3.41 (s, 2 H), 3.61 (d, *J* = 11.3 Hz, 2 H), 3.88 (d, *J* = 11.3 Hz, 2 H), 4.06 (s, 1 H).

2,2-Dimethyl-5-oxo-1,3-dioxane (4a); Typical Procedure:

A general procedure[7, 8] was followed for the preparation of **4a–c**. The preparation of **4a** is representative. To a cold (5 °C) solution containing 5-amino-5-hydroxymethyl-2,2-dimethyl-1,3-dioxane (9.7 g, 60 mmol) and KH_2PO_4 (8.2 g, 60 mmol, 1.0 equiv) in water (200 mL) was added dropwise via addition funnel a solution of $NaIO_4$ (12.8 g, 60.0 mmol, 1.00 equiv) in water (175 mL). Upon completion, ca. 3 h, the mixture was allowed to stir for an additional hour at 5 °C and then 5 h at r.t. $Na_2S_2O_3$ (14.8 g, 60.0 mmol, 1.00 equiv) was next added, and the resulting solution was allowed to stir for approximately 15 min at which time it was extracted with CH_2Cl_2 (15 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by bulb-to-bulb distillation [85 °C/20 Torr (air-bath temp)] to afford 6.6 g (51 mmol, 85% yield) of **4a** as a clear and colorless oil.

IR ($CHCl_3$): ν = 1755 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 6 H), 4.15 (s, 4 H).

5-Oxo-2-phenyl-1,3-dioxane (**4b**):

From the combination of amino alcohol **3b** (4.6 g, 21.8 mmol), KH_2PO_4 (3.0 g, 22 mmol), $NaIO_4$ (4.6 g, 22 mmol), and $Na_2S_2O_3$ (5.4 g, 22 mmol), ketone **4b** was obtained in 3.5 g (20 mmol, 90% yield) as a white solid that required no further purification.

IR($CHCl_3$): ν = 2864, 1745 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, C_6D_6): δ = 4.03 (d, *J* = 17.3 Hz, 2 H), 5.28 (s, 1 H), 7.10–7.49 (m, 5 H).

^{13}C NMR (100 MHz, C_6D_6): δ = 72(t), 99(d), 127(d), 128(d), 129(d), 134(s), 138(s).

2-tert-*Butyl-5-oxo-1,3-dioxane* (**4c**):

From the combination of amino alcohol **3c** (4.7 g, 25 mmol), KH_2PO_4 (4.1 g, 30 mmol, 1.2 equiv), $NaIO_4$ (6.4 g, 30 mmol, 1.2 equiv), and $Na_2S_2O_3$ (7.4 g, 30 mmol) while using THF as solvent (120 mL), ketone **4c** was obtained in 4.2 g (26 mmol, quantitative yield) as a pale yellow solid that required no further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (s, 9 H), 4.25 (dd, *J* = 18.0, 0.9 Hz, 2 H), 4.41 (s, 1 H), 4.42 (dd, *J* = 18.0, 0.9 Hz, 2 H).

5-Hydroxy-2,2-dimethyl-1,3-dioxane (5a); Typica1 Procedure:

A general procedure was followed for the preparation of **5a–c.** The preparation of **5a** is representative. To a cold (0 °C) solution of 2,2-dimethyl-5-oxo-1,3-dioxane (6.0 g, 46 mmol) in THF (120 mL) was added via syringe 1.0 M $LiAlH_4$ in THF (46 mL, 46 mmol, 1.0 equiv) dropwise. The resulting solution was allowed to warm to r.t. and stir for 1 h at which time the mixture was diluted with Et_2O (300 mL). Quenching the mixture began with a cautious addition of water (1.8 mL) followed by 10% aq NaOH (1.8 mL) and finally water (5.3 mL). The precipitate was removed via gravity filtration, and the filtrate was concentrated in vacuo to afford, after purification by chromatography (silica gel, hexanes/EtOAc 1:1), 5.9 g (45 mmol, 97% yield) of **5a** as a clear and colorless oil. Spectral data are in agreement with those previously reported.[7]

IR (neat): ν = 3445 (OH), 2993, 2874, 1647 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 0.6 Hz, 3 H), 1.46 (d, *J* = 0.6 Hz, 3 H), 2.89–2.92 (m, 1 H), 3.53 (br s, OH), 3.73–3.75 (m, 1 H), 3.77–3.79 (m, 1 H), 4.05–4.06 (m, 1 H), 4.09–4.10 (m, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.6, 25.9, 62.9, 64.9, 98.0.

trans-*5-Hydroxy-2-phenyl-1,3-dioxane* (***trans*-5b)**:
From the combination of ketone **4b** (5.0 g, 28 mmol) and 1.0 M $LiAlH_4$ in THF (28 mL, 28 mmol), alcohol **5b** was obtained in 87% yield as a mixture of diastereomers. The *cis*/*trans* mixture (14:86) was separated by chromatography (deactivated silica gel, hexanes/EtOAc 1:1) to afford 2.5 g (14 mmol, 50% yield) of *trans*-**5b** as a white solid. Spectral data are in agreement with those previously reported.[5c]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (d, *J* = 5.8 Hz, 1 H), 3.58–3.63 (m, 2 H), 3.96–4.05 (m, 1 H), 4.32 (dd, *J* = 11.3, 4.9 Hz, 1 H), 5.43 (s, 1 H), 7.35–7.49 (m, 5 H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 61(d), 71(t), 71(t), 100(d), 126(d), 128(d), 129(d), 137(s).

trans-*2*-tert-*Butyl-5-hydroxy-1,3-dioxane* (***trans*-5c)**:
From the combination of ketone **4c** (3.6 g, 23 mmol) and 1.0 M $LiAlH_4$ in THF (23 mL, 23 mmol), alcohol **5c** was obtained in 90% yield as a mixture of diastereomers. The reaction was quenched by the cautious addition of 10% aq NaOH. This addition proceeded until the formation of a white precipitate was observed. The *cis*/*trans* mixture (13:87) was separated by chromatography (silica gel, hexanes/EtOAc 1:1) to afford 3.0 g (19 mmol, 83% yield) of *trans*-**5c** as a white solid. Spectral data are in agreement with those previously reported.[7]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 9 H), 1.56 (d, *J* = 5.6 Hz, 1 H), 3.33 (t, *J* = 10.1 Hz, 1 H), 3.84 (ddd, *J* = 15.4, 10.5, 5.3 Hz, l H), 3.99 (s, 1 H), 4.19 (dd, *J* = 5.2, 1.4 Hz, 1 H).

***cis*-5-Hydroxy-2-phenyl-1,3-dioxane (*cis*-5b); Typical Procedure:**
To a cold (–78 °C) solution of 1.0 M L-Selectride in THF (56 mL, 56 mmol) was added 5-oxo-2-phenyl-1,3-dioxane (**4b**) (5.0 g, 28 mmol) as a solution in THF (14 mL) dropwise. The mixture was allowed to stir for 3 h at which time it was quenched with water (2.0 mL) and extracted with Et_2O (3 × 30 mL). The combined organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Analysis of the crude product revealed a 92:8 (*cis*/*trans*) mixture of diastereomers in 94% yield. Purification by chromatography (silica gel, hexanes/EtOAc 1:1) afforded 2.6 g (14 mmol, 50% yield) of *cis*-**5b** as a white solid. Spectral data are in agreement with those previously reported.[5c]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.06 (d, *J* = 11.1 Hz, 1 H), 3.63 (d, *J* = 11.0 Hz, 1 H), 4.11–4.20 (m, 4 H), 5.56 (s, 1 H), 7.35–7.51 (m, 5 H).
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 65(s), 72(d), 101(d), 125(d), 128(d), 129(d), 137(s).

cis-*2*-tert-*Butyl-5-hydroxy-1,3-dioxane* (***cis*-5c**):
From the combination of ketone **4c** (2.0 g, 13 mmol) and 1.0 M L-Selectride in THF (22 mL, 22 mmol), alcohol **5c** was purified by chromatography (silica gel, hexanes/EtOAc 1:1) to afford 1.6 g (9.4 mmol, 75% yield) of *cis*-**5c** as a white solid. Spectral data are in agreement with those previously reported.[5d]
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 9 H), 2.87 (d, *J* = 11.5 Hz, 1 H), 3.35 (d, *J* = 10.5 Hz, 1 H), 3.85 (d, *J* = 10.5 Hz, 2 H), 4.17 (d, *J* = 10.5 Hz, 2 H), 4.15 (s, 1 H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 24(q), 35(s), 64(d), 72(t), 72(t), 107 (d).

5-Hydroxy-2,2,5-trimethyl-1,3-dioxane (7):
To a cold (–78 °C) solution consisting of anhyd $CeCl_3$ (26 g, 60 mmol, 2.0 equiv) in anhyd THF (20 mL) was added 1.5 M MeLi in THF (40 mL, 60 mmol, 2.0 equiv) dropwise. As the MeLi was added to the mixture, the initially white $CeCl_3$ solution turned black over a period of 30 min. At this time, 2,2-dimethyl-5-oxo-1,3-dioxane (**4a**) (4.0 g, 30 mmol, 1.0 equiv) was added neat. The mixture was stirred for an additional 4 h at –78 °C. During this time, a white/beige precipitate was observed. The mixture was warmed to r.t., quenched with water (10 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phase was dried (anhyd $MgSO_4$), filtered and concentrated in vacuo to afford 2.5 g of **7** as a clear and colorless oil that required no further purification. An additional 0.55 g of **7** (21 mmol, 70% combined yield) was obtained via continuous extraction (Et_2O). Spectral data are in agreement with those previously reported.[10]
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (s, 3 H), 1.44 (s, 6 H), 3.30 (br s, 1 H), 3.53 (d, *J* = 11.7 Hz, 2 H), 3.79 (d, *J* = 11.7 Hz, 2 H).

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(1) Current address: The University of Arizona, Department of Chemistry, Chemistry Building, P. O. Box 210041, Tucson, AZ 85721-0041, USA
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