Bromination of 2,2,6-Trialkyl-1,3-dioxan-4-ones. Application of the Deuterium Isotope Effect to the Synthesis of a Chiral Trialkyldioxinone

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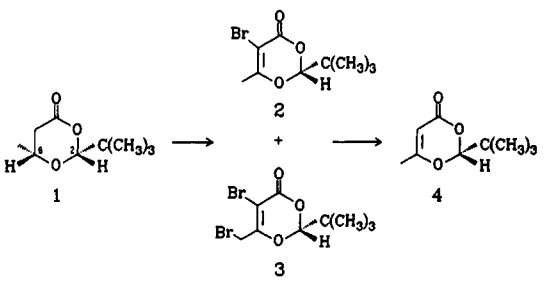
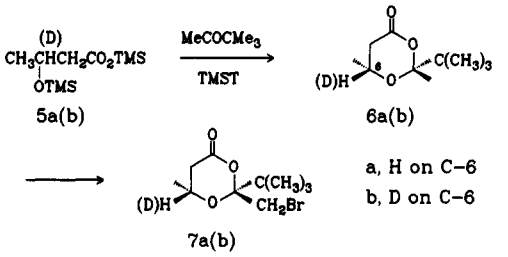
Free-radical bromination (2 equiv of NBS) of 2-*tert*-butyl-2,6-dimethyl-1,3-dioxan-4-one (**6a**) gives the 2-bromomethyl product **7a**. By contrast, bromination of 2-*tert*-butyl-2-methyl-1,3-dioxan-4-one (**1**) is reported to occur at the 6-position. Deuterium-labeling experiments established that **7a** is formed by direct substitution at the 2-methyl group of **6a** and not by abstraction of H-6 followed by hydrogen atom transfer from the 2-methyl group and bromination of the resultant primary radical **12**. When 2-*tert*-butyl-6-methyl-2-(methyl-d_3)-1,3-dioxan-4-one (**13**) is reacted with 4 equiv of NBS, the course of the reaction is altered dramatically and the major product formed in high yield is dioxinone **16**. Thus, a trideuteriomethyl group directs bromination away from the 2-methyl site to H-6. Bromination at the 6-position followed by loss of HBr, addition of Br_2, and loss of a second HBr gives **16**. Dioxinone **14**, a valuable substrate for asymmetric induction studies, is formed in high yield by reductive debromination of **16**. When (*R*)-3-hydroxybutyric acid is used in the preparation of **13**, optically pure (−)-**14** is obtained using the sequence described.

Substituted 1,3-dioxin-4-ones (e.g., **4**) have been employed as substrates for a variety of reactions including cuprate additions, hydrogenations, and photoadditions.[1-4] Several groups have pursued asymmetric induction studies using optically enriched dioxinones in which C-2 is chiral[1,5] These substrates may be prepared in two ways: (1) directly by reaction of acetoacetate with an optically active ketone such as menthone[5] or (2) indirectly by reaction of an optically active 3-hydroxyalkanoic acid with an aldehyde or ketone to give a dioxanone which is then converted to an optically active dioxinone.[1] A specific example of the latter approach involved the reaction of (*R*)-3-hydroxybutanoic acid with pivaldehyde under acidic catalysis to give the 1,3-dioxanone **1**,[6] which upon treatment with slightly over 2 equiv of *N*-bromosuccinimide (NBS) gave a mixture of **2** and **3**[7] (Scheme I). It is proposed that **2** is formed by free-radical bromination of **1** at C-6 followed by loss of HBr, addition of Br_2, and loss of a second HBr.[7] **3** is formed by allylic bromination of **2**. Reductive debromination of the mixture of **2** and **3** with H_2–Pd/C gave the desired optically active 1,3-dioxin-4-one **4**.[7] Herein we describe our efforts to conduct the same bromination–dehydrobromination sequence on 2,2,6-trialkyl-1,3-dioxanone **6a** and the unexpected but synthetically valuable results that were obtained using a selectively deuterated substrate.

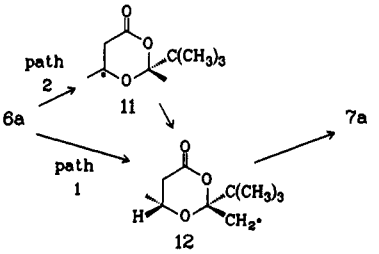
Scheme I



Scheme II



Scheme III



Results and Discussion

Dioxanone **6a** was prepared in high yield by reacting pinacolone and the bis(trimethylsilyl) derivative of 3-hydroxybutyric acid (**5a**) in the presence of trimethylsilyl triflate (TMST) catalyst[8] (Scheme II). Only one isomer, in which the two methyl groups are trans, was observed in the ^{1}H NMR spectrum of the crude and sublimed products. Bromination of **6a** using the standard conditions employed by Seebach,[7] with slightly more than 2 equiv of NBS, gave in 51% yield the unexpected bromo product **7a**.[9] Thus, replacement of a hydrogen by a methyl group at C-2 in these dioxanones has dramatically changed the site of bromination. To determine if other 2,2-dialkylated

(1) Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763.
(2) Kaneko, C.; Sato, M.; Sakaki, J.; Abe, Y. *J. Heterocycl. Chem.* **1990**, *27*, 25.
(3) Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852.
(4) Baldwin, S. W.; Wilkinson, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 3634.
(5) Demuth, M.; Palomer, A.; Sluma, H.-D.; Dey, A. K.; Kruger, C.; Tsay, Y.-H. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1117.
(6) Seebach, D.; Zimmermann, J. *Helv. Chim. Acta* **1986**, *69*, 1147.
(7) Zimmermann, J.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1104.
(8) (a) Schreiber, S. L.; Reagan, J. *Tetrahedron Lett.* **1986**, *27*, 2945. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.

(9) A base such as triethylamine or potassium carbonate was normally included in the bromination reaction mixture to suppress any acid-catalyzed reactions.

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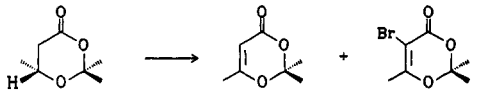
derivatives give this type of product, we examined the bromination of the 2,2-dimethyldioxanone (8). Using the standard conditions, a mixture of dioxinones 9 and 10 was formed in moderate yield. These products were similar to those obtained by bromination of 1, and we can conclude that 8 reacts in the "normal" manner.



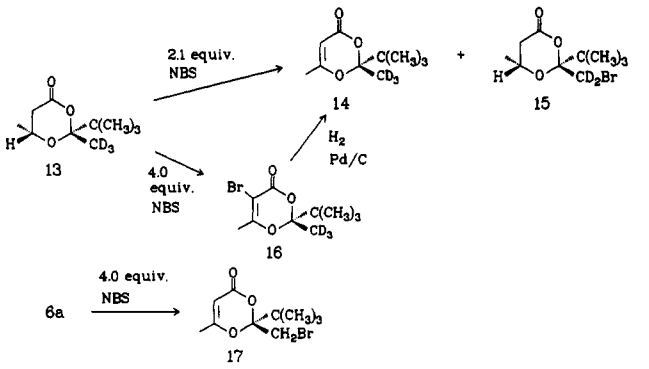
8 9 10

Two explanations could be offered for the unexpected product formed in the bromination of **6a**: (1) the 2-methyl group hinders abstraction of H-6 (the two groups are cis and diaxial) and radical **12** (Scheme III) is formed by direct abstraction of a hydrogen atom from that methyl group or (2) radical **11** is formed as usual but the proximate 2-methyl group transfers a hydrogen atom to C-6 to give indirectly radical **12**, which then yields the brominated product **7a**. To distinguish between these two pathways, the 6-deuterio derivative **6b** was synthesized by reacting pinacolone with the bis-silyl derivative of 3-deuterio-3-hydroxybutyric acid (**5b**). If explanation 1 is correct, the deuterium label will remain on C-6 and **7b** will be formed; if explanation 2 is operative, the label will be lost during the formation of radical **11** and the product will be **7a**. Bromination of **6b** gave **7b**[10] (75%) in which the deuterium label was retained. Thus, the reaction must be proceeding via pathway 1.

Next, we investigated bromination of **13**, in which the 2-methyl group in **6a** was replaced by a trideuteriomethyl substituent (Scheme IV). **13** was prepared by reacting the bis-silyl derivative of 3-hydroxybutyric acid (**5a**) with 1,1,1-trideuteriopinacolone.[11] Bromination of **13** with slightly more than 2 equiv of NBS gave a mixture of dioxinone **14** and bromo derivative **15**,[12] but if 4 equiv of NBS were employed the bromoenone **16** was formed in excellent yield (95%).[13] We assume **16** is formed in the same manner as previously described for the conversion of **1** → **2**.[7] Reductive debromination of **16** with H_2–Pd/C[7] gave the dioxinone **14** (96%) that we initially desired. Reaction of nondeuteriated substrate **6a** with 4 equiv of NBS gave in 53% yield enone **17** formed by substitution of both a 2-methyl hydrogen and H-6 (followed by dehydrobromination). The difference in bromination regioselectivity between **6a** and **13** appears to be the result of a deuterium isotope effect.[14] Substitution of a CH_3 by a CD_3 at C-2 retards bromination at this site and thus enhances the substitution at C-6 which ultimately leads to the excellent yield of **16**.

The relatively facile preparation of dioxinone **14** in good yield (75% overall from **5a**) has important synthetic consequences. If (*R*)-3-hydroxybutyric acid, which is ready available by hydrolysis of poly-(*R*)-3-hydroxybutyrate,[15] is employed in the preparation of **13**, then essentially optically pure (–)-**14** is obtained using the methodology described herein. Thus, the versatile substrate **14** is now readily available for studies in the area of asymmetric synthesis. Our investigations, which will be published separately, indicate significant differences in the face selectivity of **14** as compared with **4**.

Scheme IV



Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded on 200- and 400-MHz spectrometers ($CDCl_3$ solvent, TMS internal standard). The multiplicities of the ^{13}C spectra were determined by the attached proton test (ATP), which produced positive (+) quaternary C and CH_2 signals and negative (–) CH and CH_3 signals. IR spectra were recorded on an FTIR spectrophotometer in CCl_4 solution using NaCl solution cells. Mass spectra were obtained using electron-impact ionization (EIMS) at 50 eV. Products were purified by medium-pressure liquid chromatography (MPLC) using 230–400 mesh silica gel. Analytical thin-layer chromatography (TLC) was performed on silica gel GF 254 with a thickness of 0.25 mm. The solvent system used for the MPLC purifications was that which gave the product of interest an R_f of 0.35 on TLC analysis. Melting points are uncorrected.

CH_2Cl_2, CCl_4, and triethylamine were distilled over CaH_2 prior to use. NBS (*N*-bromosuccinimide) was recrystallized from water and AIBN (azobisisobutyronitrile) from methanol. All reactions sensitive to air or moisture were conducted under argon. Reaction vessels for moisture-sensitive reactions were flame dried and allowed to cool under an argon atmosphere.

General Procedure for Synthesis of the Dioxanones. The procedure follows that of Schreiber[8a] and Noyori.[8b] A solution of the bis(trimethylsilyl) derivative of 3-hydroxybutyric acid (**5a**) (8–12 mmol) and the desired ketone (2 equiv) in dry CH_2Cl_2 (20 mL) was cooled to –78 °C, and trimethylsilyl trifluoromethanesulfonate (5–10 mol %) was added. The mixture was maintained at –78 °C for 3 h, warmed to 0 °C over 2 h, and held at that temperature for 3 h. It was then cooled to –78 °C, and triethylamine (200 μL) followed by methanol (200 μL) were added. After the reaction was warmed to 0 °C, the solvent was removed in vacuo. Final purification of the product was achieved either by sublimation or distillation.

The bis(trimethylsilyl) derivative **5a** used in the above procedure was obtained by heating at reflux for 12 h a solution of the sodium salt (or acid)[16] of 3-hydroxybutyrate (10.0 g, 79 mmol), triethylamine (24.0 g, 238 mmol, 3.0 equiv), and trimethylsilyl chloride (25.8 g, 238 mmol, 3.0 equiv) in dry THF (250 mL). The mixture was cooled to 0 °C and pentane added to precipitate the salts. After filtration and solvent removal, the product was purified by distillation (75 °C, 4 Torr) to yield 18.5 g (93%) of **5a**.

2-*tert*-Butyl-2,6-dimethyl-1,3-dioxan-4-one (6a).[17,18] Pinacolone (2.43 g, 24 mmol) and **5a** (3.00 g, 12 mmol) gave a crude

(10) The 75% yield of **6b** (using K_2CO_3 as base) is significantly higher than the 51% yield of **6a** (using triethylamine as base). If K_2CO_3 is used as base in the preparation of **6a** the yield is even lower (43%).

(11) Kaye, P. T.; Meakins, G. D.; Willbe, C.; Williams, P. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2335.

(12) In these bromination reactions there was considerable variation in the yields of the products. Seebach encountered similar variability in his bromination studies.[7]

(13) It is not clear why 2.1 equiv of NBS resulted in some substitution at the CD_3 group while 4 equiv gave no such substitution.

(14) The kinetic isotope effect (k_H/k_D) for the reaction of ethane with $Cl^\bullet$ is 5.8: Parmar, S. S.; Benson, S. W. *J. Am. Chem. Soc.* **1989**, *111*, 57. The isotope effect for bromination would be expected to be larger than that for chlorination: Wiberg, K. B.; Slaugh, L. H. *J. Am. Chem. Soc.* **1958**, *80*, 3033.

(15) Seebach, D.; Zuger, M. *Helv. Chim. Acta* **1982**, *65*, 495. Seebach, D.; Beck, A. K.; Breitschuh, R.; Job, K. *Org. Synth.* submitted.

(16) 3-Hydroxybutyric acid may be substituted for the sodium salt without appreciable change in the yield of the product.

(17) Compound **6a** was prepared previously in 25% yield by reaction of pinacolone with 3-hydroxybutyric acid in acidic medium.[18]

(18) Ayras, P.; Pihlaja, K. *Tetrahedron* **1973**, *29*, 1311.

product which was purified by sublimation (bath 80 °C, 15 Torr) to yield **6a** (1.90 g, 85%) as white needles: mp 42–43 °C (lit.[18] mp 41–43 °C); ^{1}H NMR ($CDCl_3$) δ 4.22 (m, 1 H, H-6), 2.55 (dd, J = 17.5, 3.5 Hz, 1 H, H-5β), 2.23 (dd, J = 17.5, 11.0 Hz, 1 H, H-5α), 1.50 (s, 3 H, 2-CH_3), 1.28 (d, J = 6.1 Hz, 3 H, 6-CH_3), 1.01 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) (APT) δ 168.4 (+, C-4), 111.1 (+, C-2), 63.4 (–, C-6), 39.5 (+, C(CH$_3$)$_3$), 37.6 (+, C-5), 24.4 (–, C(CH$_3$)$_3$), 21.1 (–, 6-CH$_3$), 18.7 (–, 6-CH$_3$); IR (CCl_4) 1739, 1548, 1292, 1208, 1124 cm^{-1}; EIMS 50 eV m/z (rel int) 187 [M + 1]$^+$ (2.1), 171 [M – CH$_3$]$^+$ (4.2), 129 [M – t-butyl]$^+$ (30), 100 [pinacolone]$^+$ (31), 69 (100), 57 (67), 43 (87).

2-*tert*-Butyl-6-deuterio-2,6-dimethyl-1,3-dioxan-4-one (6b). Procedure as for **6a** using pinacolone (1.60 g, 16 mmol) and **5b**[19] (2.00 g, 8 mmol) gave **6b** (1.27 g, 85%): mp 41–42 °C; ^{1}H NMR ($CDCl_3$) δ 2.50 (d, J = 17.0 Hz, 1 H, H-5β), 2.18 (dt, J = 17.0, 1.2 Hz, 1 H, H-5α), 1.46 (s, 3 H, 6-CH_3), 1.24 (s, 3 H, 2-CH_3), 0.97 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) (APT) δ 168.3 (+, C-4), 111.1 (+, C-2), 39.5 (+, C(CH$_3$)$_3$), 37.4 (+, C-5), 24.3 (–, C(CH$_3$)$_3$), 21.0 (–, 6-CH$_3$), 18.7 (–, 2-CH$_3$); IR (CCl_4) 2135, 1739, 1547, 1283, 1128 cm^{-1}.

2,2,6-Trimethyl-1,3-dioxan-4-one (8).[20] Acetone (2.37 g, 40 mmol) and **5a** (4.00 g, 16 mmol) gave after distillation (75 °C, 3.8 Torr) a clear, colorless liquid **8** (1.52 g, 66%): ^{1}H NMR spectrum was that reported;[16] ^{13}C NMR ($CDCl_3$) (APT) δ 167.3 (+, C-4), 105.7 (+, C-2), 63.4 (–, C-6), 36.6 (+, C-5), 28.8 and 24.5 (–, 2-CH$_3$'s), 20.9 (–, 6-CH$_3$); IR (CCl_4) 1745, 1388, 1288, 1154 cm^{-1}.

2-*tert*-Butyl-6-methyl-2-(methyl-d_3)-1,3-dioxan-4-one (13). Pinacolon-d_3[11] (2.50 g, 24 mmol) and **5a** (3.00 g, 12 mmol) gave **13** (1.86 g, 82%): mp 39–40 °C; ^{1}H NMR ($CDCl_3$) δ 4.21 (m, 1 H, H-6), 2.48 (dd, J = 18.1, 3.6 Hz, 1 H, H-5β), 2.22 (dd, J = 18.1, 10.7 Hz, 1 H, H-5α), 1.29 (d, J = 6.1 Hz, 3 H, 6-CH_3), 1.01 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) (APT) δ 168.5 (+, C-4), 111.0 (+, C-2), 63.2 (–, C-6), 39.3 (+, C(CH$_3$)$_3$), 37.3 (+, C-5), 24.1 (–, C-(CH$_3$)$_3$), 20.9 (–, 6-CH$_3$); IR (CCl_4) 1741, 1209, 1124, 985 cm^{-1}; EIMS 50 eV m/z (rel int) 190 [M + 1]$^+$ (21.8), 146 [M – COCH$_3$]$^+$ (16), 105 (30), 86 (38), 69 (100), 57 (66), 43 (73).

General Procedures for Bromination of Dioxanones. A solution of dioxanone (0.4–1.1 mmol), NBS (2.1–2.6 equiv), and a base (triethylamine or anhydrous K_2CO_3, 0.5–2.0 equiv) in CCl_4 (15 mL) was stirred at room temperature for 20 min, AIBN (5 mg) was added, and the mixture was heated at reflux for 3 h. The reaction mixture was cooled to 0 °C and filtered and the solvent removed in vacuo. Products were separated by MPLC.

2-(Bromomethyl)-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one (7a). A mixture of **6a** (200 mg, 1.1 mmol), NBS (396 mg, 2.2 mmol), and triethylamine (75 μL, 0.5 equiv) gave **7a** (148 mg, 51%), as a pale yellow oil, after purification by MPLC (15% EtOAc/hexanes): ^{1}H NMR ($CDCl_3$) δ 4.63 (m, 1 H, H-6), 3.78 (s, 2 H, 2-CH_2Br), 2.60 (dd, J = 17.0, 2.6 Hz, 1 H, H-5β), 2.24 (dd, J = 17.0, 11.1 Hz, 1 H, H-5α), 1.30 (d, J = 6.1 Hz, 3 H, 6-CH_3), 1.06 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) (APT) δ 166.9 (+, C-4), 107.1 (+, C-2), 65.4 (–, C-6), 40.9 (+, C(CH$_3$)$_3$), 37.3 (+, C-5), 32.7 (–, 2-CH$_2$Br), 24.9 (–, C(CH$_3$)$_3$), 21.0 (–, 6-CH$_3$); IR (CCl_4) 1754, 1280, 1210, 1175, 999, 963 cm^{-1}; EIMS 50 eV m/z (rel int) 267 [M + 1 (Br = 81)]$^+$ (97), 265 [M + 1 (Br = 79)]$^+$ (100), 249 [M – CH$_3$]$^+$ (13), 247 [M – CH$_3$]$^+$ (13), 122 (28).

2-(Bromomethyl)-2-*tert*-butyl-6-deuterio-6-methyl-1,3-dioxan-4-one (7b). A mixture of **6b** (75 mg, 0.40 mmol), NBS (148 mg, 0.83 mmol), and K_2CO_3 (80 mg, 0.58 mmol) gave **7b** (80 mg, 75%) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 2 H, 2-CH_2Br), 2.55 (d, J = 17.5 Hz, 1 H, H-5β), 2.21 (dt, J = 17.5, 1.3 Hz, 1 H, H-5α), 1.26 (s, 3 H, 6-CH_3), 1.02 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) (APT) δ 167.0 (+, C-4), 107.1 (+, C-2), 40.8 (+, C(CH$_3$)$_3$), 37.2 (+, C-5), 32.7 (–, 2-CH$_2$Br), 24.9 (–, C(CH$_3$)$_3$), 20.8 (–, 6-CH$_3$); IR (CCl_4) 1753, 1274, 1217, 1132, 999, 963 cm^{-1}; EIMS 50 eV m/z (rel int) 268 [M (Br = 81)]$^+$ (99), 266 [M (Br = 79)]$^+$ (100), 198 (38), 196 (38), 182 (7), 123 (17). Anal. Calcd for $C_{10}H_{16}O_3DBr$: C, 45.28; H, 6.44. Found: C, 44.66; H, 6.66.

Bromination of 8. **8** (75 mg, 0.52 mmol), NBS (195 mg, 1.1 mmol), and K_2CO_3 (104 mg, 0.75 mmol) gave **9** (28 mg, 38%) as a colorless oil and **10** (30 mg, 26%) as a pale yellow oil after purification by MPLC (15% EtOAc/hexanes).

2,2,6-Trimethyl-1,3-diox-5-in-4-one (9). Spectral data showed good agreement with literature values.[21]

5-Bromo-2,2,6-trimethyl-1,3-diox-5-in-4-one (10): ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3 H, 6-CH_3), 1.66 (s, 6 H, 2-CH_3's); ^{13}C NMR ($CDCl_3$) δ 166.4 (+, C-4), 157.2 (+, C-6), 106.5 (+, C-2), 89.9 (+, C-5), 24.8 (–, 2-CH$_3$'s), 20.2 (–, 6-CH$_3$); IR (CCl_4) 1739, 1611, 1379, 1316, 1260, 1034 cm^{-1}; EIMS 50 eV m/z (rel int) 222 [M (Br = 81)]$^+$ (58), 220 [M (Br = 79)]$^+$ (59), 164 [M – acetone (Br = 81)]$^+$ (99), 162 [M – acetone (Br = 79)]$^+$ (100), 122 (53), 120 (54); HRMS calcd for $C_7H_9O_3Br$ 219.9736, found 219.9746 (where Br = 79). Anal. Calcd for $C_7H_9O_3Br$: C, 37.66; H, 4.10. Found: C, 36.94; H, 3.95.

Bromination of 13 with 2.1 equiv of NBS. **13** (75 mg, 0.40 mmol), NBS (148 mg, 0.83 mmol), and K_2CO_3 (110 mg, 0.58 mmol) gave, after purification by MPLC (15% EtOAc/hexanes), two crystalline solids, **14** (21 mg, 28%) and **15** (46 mg, 43%).

2-*tert*-Butyl-6-methyl-2-(methyl-d_3)-1,3-diox-5-in-4-one (14): mp 36–37 °C; ^{1}H NMR ($CDCl_3$) δ 5.20 (br s, 1 H, H-5), 1.98 (br s, 3 H, 6-CH_3), 1.08 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) (APT) δ 168.7 (+, C-4), 151.7 (+, C-6), 111.8 (+, C-2), 93.6 (–, C-5), 39.1 (+, C(CH$_3$)$_3$), 24.6 (–m, C(CH$_3$)$_3$), 20.3 (–, 6-CH$_3$); IR (CCl_4) 1735, 1638, 1386, 1119 cm^{-1}; EIMS (50 eV m/z (rel int) 189 [M + 2]$^+$ (47), 188 [M + 1]$^+$ (100), 187 [M]$^+$ (51). Anal. Calcd for $C_{10}H_{13}O_3D_3$: C, 64.18; H, 8.70. Found: C, 64.11; H, 8.48.

2-(Bromomethyl-d_2)-2-*tert*-butyl-6-methyl-1,3-dioxan-4-one (15): mp 50–51 °C; ^{1}H NMR ($CDCl_3$) δ 4.60 (m, 1 H, H-6), 2.57 (dd, J = 17.3, 3.3 Hz, 1 H, H-5β), 2.22 (dd, J = 17.3, 11.3 Hz, 1 H, Hh5α), 1.28 (d, J = 6.1 Hz, 3 H, 6-CH_3), 1.04 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) (APT) δ 167.5 (+, C-4), 107.6 (+, C-2), 66.0 (–, C-6), 41.4 (+, C(CH$_3$)$_3$), 37.9 (+, C-5), 25.4 (–, C(CH$_3$)$_3$), 21.5 (–, 6-CH$_3$); IR (CCl_4) 2165, 1745, 1385, 1283, 1098, 1008 cm^{-1}; EIMS 50 eV m/z (rel int) 269 [M + 1 (Br = 79)]$^+$ (80), 268 [M (Br = 81)]$^+$ (81), 267 [M + 1 (Br = 79)]$^+$ (100), 266 [M (Br = 79)]$^+$ (74). Anal. Calcd for $C_{10}H_{15}O_3D_2Br$: C, 45.11; H, 6.44. Found: C, 44.70; H, 6.65.

Bromination of 13 with 4.0 equiv of NBS. Reaction of **13** (1.42 g, 7.5 mmol), NBS (5.36 g, 30 mmol, 4 equiv), K_2CO_3 (2.06 g, 15 mmol), and AIBN (94 mg, 0.57 mmol) in CCl_4 (100 mL) gave, after purification by MPLC (10% EtOAc/hexanes), an amorphous solid **16** (1.89 g, 95%): mp 43–44 °C; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3 H, 6-CH_3), 1.02 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) (APT) δ 166.9 (+, C-4), 162.4 (+, C-6), 112.2 (+, C-2), 91.8 (+, C-5), 39.4 (+, C(CH$_3$)$_3$), 24.8 (–, C(CH$_3$)$_3$), 20.9 (–, 6-CH$_3$); IR (CCl_4) 1744, 1613, 1342, 1122 (br) cm^{-1}.

Preparation of 14 by Catalytic Hydrogenation of 16. To a solution of **16** (2.40 g, 9.0 mmol) in triethylamine (4.1 mL) and absolute ethanol (50 mL) was added 10% Pd/C (576 mg). The suspension was stirred vigorously in an atmosphere of H_2, and the progress of the reaction was followed by TLC. After 72 h the mixture was filtered and the solvent removed in vacuo. The residue was suspended in cold ether and the ammonium salt was removed by filtration. After evaporation of the solvent, the crude product was purified by MPLC (15% EtOAc/hexane) to give **14** (1.62 g, 96%). The data for compound **14** are listed above. When (*R*)-3-hydroxybutyric acid[15] was used in the preparation of **13**, the rotation of (–)-**14** was $[\alpha]^{22}_D$ –31.5° (c 1.25, $CHCl_3$).

Bromination of 6a with 4.0 equiv of NBS. **6a** (75 mg, 0.40 mmol), NBS (283 mg, 1.6 mmol), and K_2CO_3 (110 mg, 0.60 mmol) in CCl_4 (5 mL) gave, after purification by MPLC (10% EtOAc/hexane), an oil, **17** (57 mg, 53%): ^{1}H NMR ($CDCl_3$) δ 5.10 (br s, 1 H, H-5), 3.78 (s, 2 H, CH_2Br), 2.01 (s, 3 H, 6-CH_3), 1.11 (s, 9 H, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$) (APT) δ 169.1 (+, C-4), 159.4 (+, C-6), 109.8 (+, C-2), 92.0 (–, C-5), 41.4 (+, C(CH$_3$)$_3$), 34.0 (+, CH$_2$Br), 24.8 (–, C(CH$_3$)$_3$), 19.8 (–, 6-CH$_3$); IR (CCl_4) 1743, 1647, 1386, 1344, 1146 cm^{-1}. Anal. Calcd for $C_{10}H_{15}O_3Br$: C, 45.80; H, 5.73. Found: C, 45.91; H, 5.73.

(19) Prepared by reduction of ethyl acetoacetate with $NaBD_4$ followed by saponification and bis-silylation.

(20) Compound **8** was prepared previously in 10% yield by reaction of 2,2-dimethoxypropane with 3-hydroxybutyric acid in acidic medium.[18]

(21) Bader, A. R.; Gutowsky, H. S.; Heeschen, J. P. *J. Org. Chem.* **1956**, *21*, 821.