

HETEROCYCLES, Vol. 96, No. 1, 2018, pp. 127 - 136. © 2018 The Japan Institute of Heterocyclic Chemistry
 Received, 13th September, 2017, Accepted, 17th November, 2017, Published online, 28th November, 2017
 DOI: 10.3987/COM-17-13814

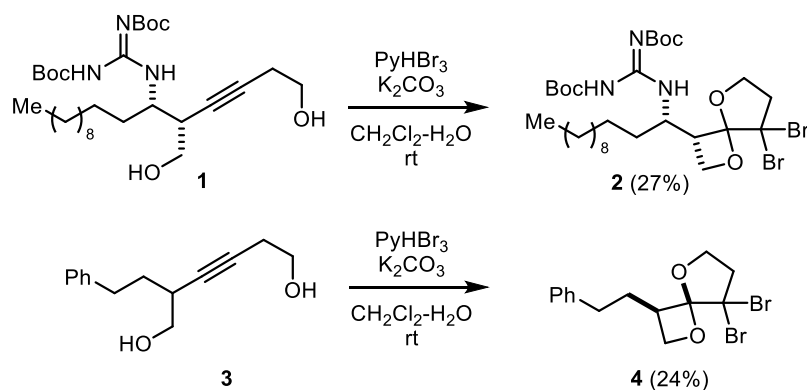
SYNTHESIS OF DIBROMO COMPOUNDS CONTAINING 2,6-DIOXABICYCLO[3.1.1]HEPTANE SIMILAR TO CORE MOIETY OF THROMBOXANE A₂

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Abstract – Thromboxane A₂, a potent platelet aggregation factor, contains a labile 2,6-dioxabicyclo[3.1.1]heptane as the core moiety. Dibromo compounds with a similar core structure were synthesized by the cyclization of tribromides derived from D-glucal.

While investigating the synthesis of crambescine B, a guanidine-containing marine alkaloid,¹ we accidentally observed the formation of *spiro*-oxetane acetal **2** when intermediate **1** was treated with PyHBr₃ and K₂CO₃ in CH₂Cl₂-H₂O,² a condition of cascade cyclization developed in our laboratory (**Scheme 1**).³ Although the yield was low, to our surprise, the product was stable enough to allow for purification by column chromatography using a neutralized silica gel. A similar reaction was also observed in the case of a simpler substrate **3**, indicating that the guanidine group was not responsible for this cyclization. To our knowledge, these compounds are the first and only examples of oxetane acetal with a 1,5-dioxaspiro[3.4]octane ring system synthesized to date.⁴ The unusual stability of the strained oxetane acetal can be attributed to the strong electron-withdrawing characteristics of the bromo substitutions.



Scheme 1. Formation of *spiro*-oxetane acetal by Br⁺-triggered cascade reaction

These observed reactions reminded us of the synthesis of thromboxane A₂ (TXA₂) by Still in 1985⁵ and prompted us to investigate the construction of the core structure of TXA₂ by a similar bromocyclization. This paper describes our efforts towards the synthesis of an oxetane acetal with a structure similar to that of the core of TXA₂.

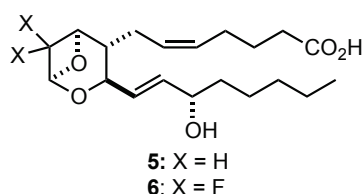
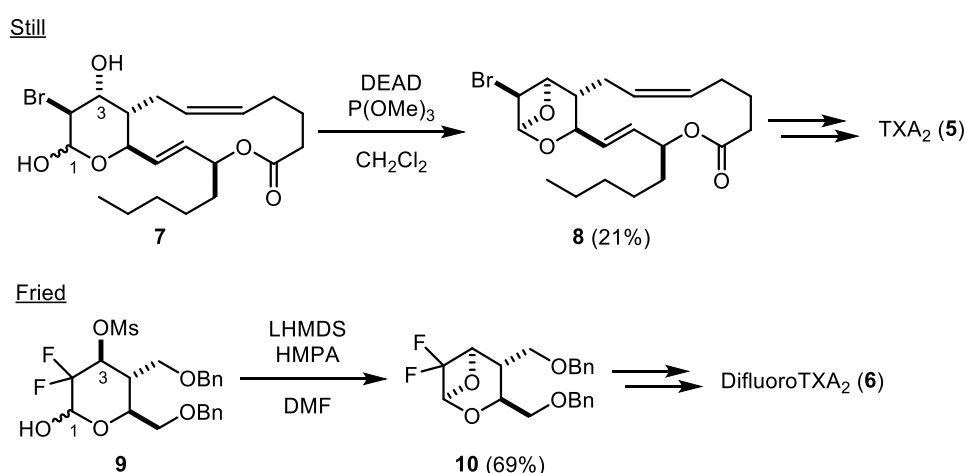


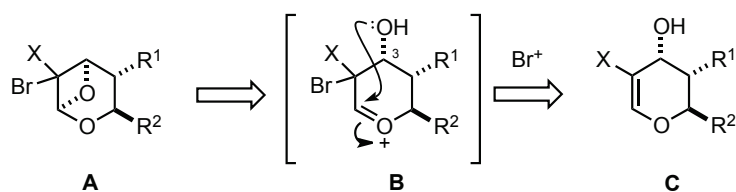
Figure 1. Thromboxane A₂ (TXA₂, **5**) and its difluoro analogue **6**

Thromboxane A₂ (**5** in **Figure 1**) is an endogenous potent platelet aggregation factor that is enzymatically synthesized from arachidonic acid through prostaglandin H₂.⁶ Because of its strained oxetane acetal structure, TXA₂ is highly unstable and degrades to thromboxane B₂ (TXB₂), an inactive form, in a few minutes (half-life at 37 °C is approximately 30 s). Therefore, it was believed that the chemical synthesis of TXA₂ (**5**) would be difficult. However, in 1985, Still was able to synthesize TXA₂ through bromo-substituted TXA₂, in which the oxetane-acetal moiety was constructed by an intramolecular Mitsunobu type reaction (**Scheme 2**). Fried also developed the same synthetic strategy and synthesized difluoroTXA₂ (**6**), a stable analogue of TXA₂, by an intramolecular Williamson ether synthesis.⁷



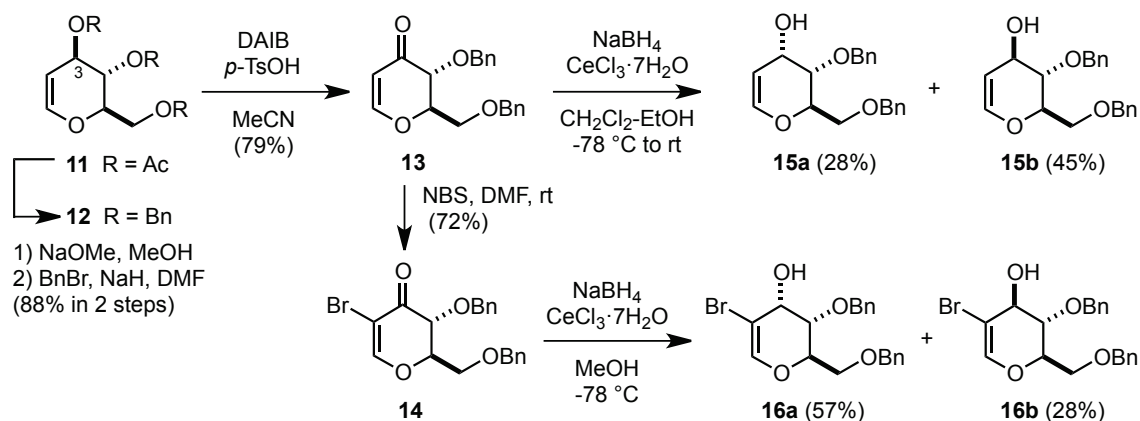
Scheme 2. Previous synthesis of the oxetane-acetal moiety of TXA₂ (**5**) and its difluoro analogue **6**

We assumed that it would be possible to construct the core structure **A** of TXA₂ through an attack of the internal hydroxy group at the C-3 position at the oxonium carbon of intermediate **B**, which could be generated from glycol **C** by a bromo cation (**Scheme 3**). The bromo substituent(s) of the products should stabilize the strained oxetane acetal of product **A**. Substrate **C** could be synthesized from D-glucal, a readily available starting material.



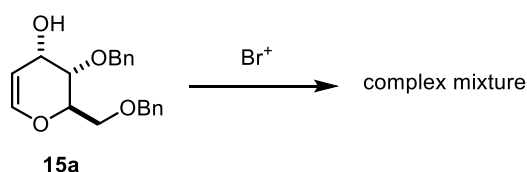
Scheme 3. Plan for synthesis of acetal moiety of TXA₂

The syntheses of the substrates as **C** for the bromocyclization are shown in **Scheme 4**. Tri-*O*-acetyl-D-glucal (**11**), a commercially available starting material, was transformed into the corresponding tribenzyl ether **12** in two steps by conventional protecting-group manipulation. Based on a study by Kirschning,⁸ compound **12** was transformed into **15a** and **15b** in two steps, namely, selective oxidation with (diacetoxyiodo)benzene (DAIB) and subsequent Luche reduction in CH₂Cl₂-EtOH as the solvents.^{9,10} The corresponding 2-bromo substrates **16a** and **16b** were prepared by the reduction of compound **14**, which was obtained by the bromination of **13** with NBS. The Luche reduction of **14** in MeOH gave **16a** and **16b** in yields of 57% and 28%, respectively.¹¹



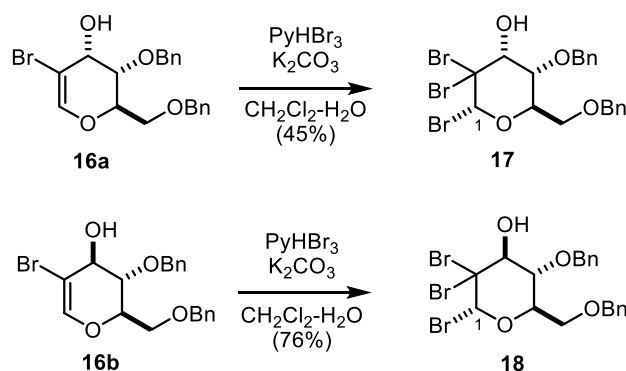
Scheme 4. Preparation of substrates **15** and **16** for bromocyclization

With these substrates in hand, the bromocyclization of **15a** was attempted first. When **15a** was treated with PyHBr₃ and K₂CO₃ in CH₂Cl₂-H₂O—as stated above, these conditions for the cascade bromocyclization were developed in our laboratory—a complex mixture was obtained (**Scheme 5**). Unfortunately, despite an extensive examination of the conditions, the desired cyclized product could not be obtained.



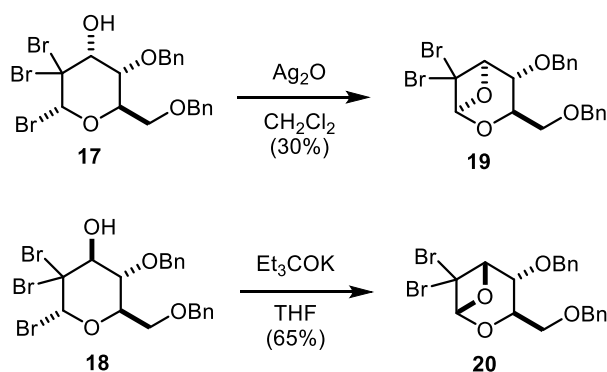
Scheme 5. Attempted bromocyclization of **15a**

Next, we investigated the cyclization of **16a** and **16b** as substrates. Substrate **16a** was treated with PyHBr_3 under the above-mentioned conditions; this resulted in the unexpected tribromide **17** (45%) as a single isolable product (**Scheme 6**). When the diastereomer **16b** was exposed to the same conditions, tribromide **18** was obtained in a 76% yield. Tribromides **17** and **18** were both obtained as a single diastereomer. The unusual stability of these products may also be attributed to bromo substitution at the C-2 position. Although the configurations at the C-1 position were not determined, we propose α configuration of bromo atom at the C-1 position due to the anomeric effect as well as axial attack of bromide from the less hindered α -face to the oxonium ion intermediates generated.¹² In order to suppress the competitive addition of the bromide ion (Br^-) to the oxonium ion intermediates, other bromination reagents that did not contain Br^- were examined. No reaction was observed when NBS in CH_2Cl_2 was used, while reactions with *N*-bromosaccharin and $\text{Br}(\text{collidine})_2\text{PF}_6$ in CH_2Cl_2 resulted in complex mixtures. These results imply that oxonium ion intermediates were generated. However, trapping by the intramolecular hydroxy group at the C-3 position was difficult, probably because of the highly strained structure of the oxetane acetal of the desired cyclized products.



Scheme 6. Attempted bromocyclization of **16a** and **16b** (configurations at the C-1 position are proposed)

Since tribromides **17** and **18** were obtained readily from the above reactions, several types of cyclizations using these tribromides were explored. We found that the intramolecular Koenigs-Knorr synthesis of **17** with Ag_2O produced oxetane acetal **19** in a yield of 30% (**Scheme 7**). On the other hand, the intramolecular Williamson ether synthesis of **18** with Et_3COK resulted in **20** in a good yield,¹³ while the reaction of **17** under the conditions for the Williamson ether synthesis process did not produce the cyclized product **19** at all. The resulting oxetane-acetal products **19** and **20** were stable enough to allow for purification by silica gel chromatography, as anticipated.



Scheme 7. Synthesis of oxetane acetals **19** and **20**

In summary, we investigated the synthesis of the oxetane acetal core structure of TXA₂ using a bromocyclization process developed in our laboratory. Unfortunately, the reactions of 3-hydroxyglycals under the above-described conditions did not yield the desired oxetane acetals but produced tribromides instead. However, these tribromides could eventually be transformed into the desired oxetane acetals **19** and **20** under the Koenigs-Knorr and Williamson ether synthesis conditions, respectively. To our knowledge, the Koenigs-Knorr condition is the first example for construction of the strained oxetane acetal. This study should provide an easy route for the synthesis of a variety of dibromo compounds containing oxetane acetal structures similar to TXA₂ from readily available glycals.

EXPERIMENTAL

General: Melting points (MP) were recorded on a Yanaco MP-S3 melting point apparatus and are not corrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded on a Bruker AVANCE-400 (400 MHz) spectrometer. NMR samples were dissolved in CDCl₃ or C₆D₆, and chemical shifts are reported in ppm relative to the residual undeuterated solvent (CDCl₃ as $\delta = 7.26$ ppm, C₆D₆ as $\delta = 7.16$ ppm). ¹H NMR data were reported as follows; chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broadened, m = multiplet), coupling constant, and assignment. Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Bruker AVANCE-400 (100 MHz) spectrometer. The samples were dissolved in CDCl₃ or C₆D₆, and chemical shifts are reported in ppm relative to the residual undeuterated solvent (CDCl₃ as $\delta = 77.1$ ppm, C₆D₆ as $\delta = 128.0$ ppm). All NMR were measured at 300 K. High resolution mass spectra (HRMS) were recorded on an Applied Biosystems Mariner Biospectrometry Workstation and reported in *m/z*. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel coated glass plate 60 F₂₅₄ (Merck, #1.05715). Silica gel 60 (spherical, particle size 40-50 μm , Kanto Chemical Co., Inc.) was used for flash-column chromatography. Unless otherwise noted, non-aqueous reactions were carried out in flame-dried glasswares under nitrogen or argon. Dry CH₂Cl₂

and THF were purchased from Kanto Chemical Co., Inc. All other commercially available reagents were used as received.

(2R,3R)-3-Benzyloxy-2-benzyloxymethyl-5-bromo-3,4-dihydropyran-4-one (14). A two-necked round-bottomed flask was charged with enone **13** (0.972 g, 3.00 mmol) and dry DMF (10 mL). To the solution was added NBS (561 mg, 3.15 mmol) at 0 °C and then stirred at 0 °C for 1.5 h. Stirring was continued at room temperature for an additional 2 h. The reaction was quenched with sat. aq. NaHCO₃ solution (30 mL), and extracted with AcOEt (15 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to afford crude product. The same reaction was conducted using 0.324 g of enone **13** under the same procedure. The combined crude product was purified by flash column chromatography (silica gel 100 g, AcOEt/hexane 1:4 to 2:1) to afford bromo enone **14** (1.16 g, 72%) as a colorless oil.

$[\alpha]_D^{22} +351$ (*c* 1.00, CHCl₃). ¹H NMR (400 MHz, C₆D₆) δ 3.26 (1H, dd, *J* = 11.0, 2.5 Hz, H-7), 3.33 (1H, dd, *J* = 11.0, 3.5 Hz, H-7), 3.90 (1H, ddd, *J* = 11.0, 3.5, 2.5 Hz, H-2), 3.99 (1H, d, *J* = 11.0 Hz, H-3), 4.08 (1H, d, *J* = 12.0 Hz, -OCH_aH_bPh), 4.15 (1H, d, *J* = 12.0 Hz, -OCH_aH_bPh), 4.42 (1H, d, *J* = 11.0 Hz, -OCH_aH_bPh), 5.03 (1H, d, *J* = 11.0 Hz, -OCH_aH_bPh), 6.89 (1H, s, H-6), 7.04-7.19 (8H, m, Ph), 7.23-7.27 (2H, m, Ph). ¹³C NMR (100 MHz, CDCl₃) δ 67.8, 73.4, 74.6, 74.9, 81.9, 100.5, 127.9, 128.2, 128.6, 128.7, 138.0, 138.2, 160.5, 186.2. HR-MS (ESI, positive): calcd. for C₂₀H₁₉O₄BrNa [M+Na]⁺: 425.0359; found, 425.0369.

(2R,3S,4R)-3-Benzyloxy-2-benzyloxymethyl-5-bromo-3,4-dihydropyran-4-ol (16a) and (2R,3S,4S)-3-Benzyloxy-2-benzyloxymethyl-5-bromo-3,4-dihydropyran-4-ol (16b). A two-necked round-bottomed flask was charged with bromo enone **14** (179 mg, 0.444 mmol) and cerium(III) chloride heptahydrate (280 mg, 0.752 mmol), and connected to a vacuum/nitrogen line. The flask was evacuated and then filled with nitrogen. MeOH (5 mL) was added to the mixture and then the mixture was stirred at -78 °C for 30 min. NaBH₄ (19.0 mg, 0.502 mmol) was added to the mixture at -78 °C and then the reaction mixture was stirred at -78 °C for 1.5 h. The reaction was quenched with sat. aq. NH₄Cl solution (10 mL), and extracted with AcOEt (15 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 10 g, Et₂O/hexane 1:2 to 1:1) to afford alcohol **16a** (104 mg, 57%) and its diastereomer **16b** (51.6 mg, 28%) as a colorless solid, respectively.

16a: $[\alpha]_D^{23} +153$ (*c* 1.00, CHCl₃). Mp 53-55 °C. ¹H NMR (400 MHz, CDCl₃) δ 2.62 (1H, d, *J* = 2.0 Hz, -OH), 3.81 (2H, d, *J* = 3.0 Hz, H-7), 3.92 (1H, dd, *J* = 10.5, 4.0 Hz, H-3), 4.07 (1H, dt, *J* = 10.5, 3.0 Hz, H-2), 4.28 (1H, dd, *J* = 4.0, 2.0 Hz, H-4), 4.55 (1H, d, *J* = 12.0 Hz, -OCH_aH_bPh), 4.60 (1H, d, *J* = 11.0 Hz, -OCH_aH_bPh), 4.63 (1H, d, *J* = 12.0 Hz, -OCH_aH_bPh), 4.64 (1H, d, *J* = 11.0 Hz, -OCH_aH_bPh), 6.69 (1H, s, H-6), 7.24-7.37 (10H, m, Ph). ¹³C NMR (100 MHz, CDCl₃) δ 66.8, 68.1, 72.3, 72.7, 73.8, 74.0, 97.8,

128.0, 128.1, 128.2, 128.5, 128.6, 128.8, 137.1, 137.9, 145.4. HR-MS (ESI, positive): calcd. for $C_{20}H_{21}O_4BrNa$ $[M+Na]^+$: 427.0515; found, 427.0500.

16b: $[\alpha]_D^{23} +75$ (*c* 1.00, $CHCl_3$). Mp 72-77 °C. 1H NMR (400 MHz, $CDCl_3$) δ 2.65 (1H, d, $J = 5.5$ Hz, -OH), 3.78 (2H, brd, $J = 3.5$ Hz, H-7), 3.86 (1H, dd, $J = 7.5, 5.0$ Hz, H-3), 4.13 (1H, dt, $J = 7.5, 3.5$ Hz, H-2), 4.30 (1H, t, $J = 5.0$ Hz, H-4), 4.55 (1H, d, $J = 12.0$ Hz, $-OCH_aH_bPh$), 4.60 (1H, d, $J = 12.0$ Hz, $-OCH_aH_bPh$), 4.66 (1H, d, $J = 12.0$ Hz, $-OCH_aH_bPh$), 4.83 (1H, d, $J = 12.0$ Hz, $-OCH_aH_bPh$), 6.67 (1H, s, H-6), 7.24-7.38 (10H, m, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.9, 71.3, 73.5, 73.9, 77.1, 101.5, 127.97, 128.04, 128.08, 128.11, 128.6, 128.7, 137.6, 137.9, 144.0. HR-MS (ESI, positive): calcd. for $C_{20}H_{21}O_4BrNa$ $[M+Na]^+$: 427.0515; found, 427.0505.

(4R,5S,6R)-5-Benzyloxy-6-benzyloxymethyl-2,3,3-tribromotetrahydropyran-4-ol (17). A two-necked round-bottomed flask was charged with alcohol **16a** (60.0 mg, 0.148 mmol), CH_2Cl_2 (5 mL) and water (5 mL), and cooled at 0 °C. To the solution were added K_2CO_3 (204 mg, 1.48 mmol) and $PyHBr_3$ (236 mg, 0.738 mmol). The reaction mixture was stirred at 0 °C for 8 min, and then quenched by addition of aqueous Na_2SO_3 solution (1 M, 1 mL) and sat. aq. $NaHCO_3$ solution (1 mL). The resulting mixture was extracted with AcOEt (10 mL x 2) and dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 10 g, AcOEt/hexane 1:4 to 2:1) to afford tribromide **17** (38.4 mg, 45%) as a colorless oil.

$[\alpha]_D^{23} +151$ (*c* 1.00, C_6H_6). 1H NMR (400 MHz, C_6D_6) δ 2.71 (1H, d, $J = 3.0$ Hz, -OH), 3.41 (1H, d, $J = 11.5$ Hz, H-7), 3.60 (1H, dd, $J = 11.5, 3.0$ Hz, H-7), 4.12 (1H, d, $J = 11.0$ Hz, $-OCH_aH_bPh$), 4.20 (1H, d, $J = 11.0$ Hz, $-OCH_aH_bPh$), 4.23 (1H, d, $J = 12.0$ Hz, $-OCH_aH_bPh$), 4.33 (1H, brs, H-4), 4.40 (1H, d, $J = 12.0$ Hz, $-OCH_aH_bPh$), 4.38-4.44 (1H, m, H-6), 4.58 (1H, dd, $J = 10.5, 3.5$ Hz, H-5), 6.45 (1H, s, H-2), 7.05-7.16 (8H, m, Ph), 7.23 (2H, d, $J = 7.5$ Hz, Ph). ^{13}C NMR (100 MHz, C_6D_6) δ 67.1, 68.1, 70.7, 71.0, 71.5, 73.6, 74.6, 89.4, 127.9, 128.18, 128.23, 128.6, 128.7, 137.6, 138.8. HR-MS (ESI, positive): calcd. for $C_{20}H_{21}Br_3O_4Na$ $[M+Na]^+$: 584.8882; found, 584.8881.

(4S,5S,6R)-5-Benzyloxy-6-benzyloxymethyl-2,3,3-tribromotetrahydropyran-4-ol (18). A two-necked round-bottomed flask was charged with alcohol **16b** (30 mg, 0.074 mmol), CH_2Cl_2 (2 mL) and water (2 mL), and cooled at 0 °C. To the solution were added K_2CO_3 (61 mg, 0.44 mmol) and $PyHBr_3$ (71 mg, 0.22 mmol). The reaction mixture was stirred at 0 °C for 5 min, and then quenched by addition of aqueous Na_2SO_3 solution (1 M, 1 mL). The resulting mixture was extracted with AcOEt (10 mL x 2) and dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 5 g, AcOEt/hexane 1:9 to 1:3) to afford tribromide **18** (32 mg, 76%) as a colorless oil.

$[\alpha]_D^{24} +155$ (*c* 1.00, C_6H_6). 1H NMR (400 MHz, C_6D_6) δ 2.11 (1H, d, $J = 5.0$ Hz, -OH), 3.36 (1H, dd, $J = 11.5, 2.0$ Hz, H-7), 3.57 (1H, dd, $J = 11.5, 3.5$ Hz, H-7), 4.07-4.13 (2H, m, H-3 and H-5), 4.17-4.23 (1H,

m, H-6), 4.21 (1H, d, $J = 12.0$ Hz, $-\text{OCH}_a\text{H}_b\text{Ph}$), 4.38 (1H, d, $J = 12.0$ Hz, $-\text{OCH}_a\text{H}_b\text{Ph}$), 4.45 (1H, d, $J = 11.5$ Hz, $-\text{OCH}_a\text{H}_b\text{Ph}$), 4.77 (1H, d, $J = 11.5$ Hz, $-\text{OCH}_a\text{H}_b\text{Ph}$), 6.48 (1H, s, H-2), 7.04-7.26 (10H, m, Ph). ^{13}C NMR (100 MHz, C_6D_6) δ 67.8, 72.0, 73.5, 75.4, 76.9, 77.4, 77.7, 93.4, 127.9, 128.2, 128.6, 138.7. HR-MS (ESI, positive): calcd. for $\text{C}_{20}\text{H}_{21}\text{Br}_3\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 584.8882; found, 584.8860.

(1R,3R,4R,5R)-4-Benzyloxy-3-benzyloxymethyl-7,7-dibromo-2,6-dioxabicyclo[3.1.1]heptane (19). A two-necked round-bottomed flask was charged with tribromide **17** (24 mg, 0.042 mmol), finely powdered molecular sieves 4 Å (0.12 g) and CH_2Cl_2 (6 mL). To the solution was added Ag_2O (29 mg, 0.13 mmol), and the reaction mixture was stirred at room temperature for 12.5 h. The reaction was quenched with sat. aq. NaHCO_3 solution (5 mL). The resulting mixture was extracted with AcOEt (10 mL x 2) and dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 4 g, AcOEt/hexane 1:9 to 1:4) to afford oxetane **19** (5.7 mg, 30%) as a colorless oil.

$[\alpha]_D^{24} +20$ (c 0.29, C_6H_6). ^1H NMR (400 MHz, C_6D_6) δ 3.60 (1H, dd, $J = 11.0, 4.0$ Hz, H-8), 3.69 (1H, dd, $J = 11.0, 6.0$ Hz, H-8), 3.93 (1H, d, $J = 12.0$ Hz, $-\text{OCH}_a\text{H}_b\text{Ph}$), 4.01 (1H, d, $J = 12.0$ Hz, $-\text{OCH}_a\text{H}_b\text{Ph}$), 4.03 (1H, d, $J = 6.5$ Hz, H-4), 4.36 (2H, s, $-\text{OCH}_a\text{H}_b\text{Ph}$), 4.49 (1H, td, $J = 6.5, 3.5$ Hz, H-3), 4.76 (1H, d, $J = 4.0$ Hz, H-5), 5.37 (1H, d, $J = 4.0$ Hz, H-1), 7.04-7.16 (8H, m, Ph), 7.26 (2H, d, $J = 7.5$ Hz, Ph). ^{13}C NMR (100 MHz, C_6D_6) δ 57.0, 69.9, 71.6, 73.3, 74.9, 77.5, 92.0, 110.0, 127.9, 128.2, 128.57, 128.63, 129.0. HR-MS (ESI, positive): calcd. for $\text{C}_{20}\text{H}_{20}\text{Br}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 506.9777; found, 506.9760.

(1S,3S,4R,5R)-4-Benzyloxy-3-benzyloxymethyl-7,7-dibromo-2,6-dioxabicyclo[3.1.1]heptane (20). A two-necked round-bottomed flask was charged with 3-ethyl-3-pentanol (20 mg, 0.17 mmol), dry THF (1 mL) and the powdered potassium hydride (6.0 mg, 0.14 mmol). The reaction mixture was stirred for 10 min at room temperature. To the mixture were added tribromide **18** (26 mg, 0.046 mmol) and THF (1 mL) and stirred for 10 min at room temperature. The reaction was quenched with sat. aq. NaCl solution (5 mL). The resulting mixture was extracted with AcOEt (10 mL x 2) and dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel 5 g, AcOEt/hexane 1:9 to 1:1) to afford oxetane **20** (15 mg, 65%) as a colorless oil.

$[\alpha]_D^{24} +45$ (c 1.0, C_6H_6). ^1H NMR (400 MHz, C_6D_6) δ 3.38 (1H, dd, $J = 10.5, 5.5$ Hz, H-8), 3.43 (1H, dd, $J = 10.5, 5.0$ Hz, H-8), 4.04 (1H, dd, $J = 5.5, 4.0$ Hz, H-4), 4.14 (1H, d, $J = 12.0$ Hz, $-\text{OCH}_a\text{H}_b\text{Ph}$), 4.18 (1H, d, $J = 12.0$ Hz, $-\text{OCH}_a\text{H}_b\text{Ph}$), 4.25 (1H, d, $J = 12.0$ Hz, $-\text{OCH}_a\text{H}_b\text{Ph}$), 4.29 (1H, d, $J = 12.0$ Hz, $-\text{OCH}_a\text{H}_b\text{Ph}$), 4.61 (1H, t, $J = 3.5$ Hz, H-5), 4.85 (1H, q, $J = 5.0$ Hz, H-3), 5.43 (1H, d, $J = 3.5$ Hz, H-1), 7.04-7.18 (8H, m, Ph), 7.22 (2H, d, $J = 7.5$ Hz, Ph). ^{13}C NMR (100 MHz, C_6D_6) δ 51.6, 72.2, 72.3, 73.4, 76.5, 76.9, 89.1, 110.9, 127.8, 127.9, 128.2, 128.6, 128.7, 138.2, 138.6. HR-MS (ESI, positive): calcd. for $\text{C}_{20}\text{H}_{20}\text{Br}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 506.9777; found, 506.9760.

ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid for Scientific Research (B) from the Japan Society for the Promotion of Science (JSPS) and by the Sumitomo Chemical Co., Ltd.

REFERENCES AND NOTES

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9. The configurations of the C-3 position of **15a** and **15b** were determined by the following experiment: benzylation of **15b** gave tribenzyl ether **12**, thus **15a** are the diastereomer at the C-3 position of **15b**.
10. Synthesis of **15a** and **15b** by Luche reduction of **13** were reported by two groups such as Kirshnig (Ref. 8(b)) and Sridhar (Ref. 8(c)). Kirshnig reported that reduction of **13** with CeCl₃ and NaBH₄ in EtOH-CH₂Cl₂ gave a mixture of **15a** and **15b** in 38% yield (**15a** : **15b** = 1 : 1.5) respectively, while Sridhar reported the same reaction in MeOH as a solvent gave **15a** as a single diastereomer in 90% yield. We are not able to reproduce the result of Sridhar.
11. The configurations of the C-3 position of **16a** and **16b** were determined by transformation to the corresponding tribenzyl ethers (prepared using NaH, BnBr in DMF, rt) and comparing the ¹H NMR spectra reported in the following paper. See: S. Dharuman and Y. D. Vankar, *Org. Lett.*, 2014, **16**,

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