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SYNTHESIS OF (±)-3-AMINO-2,4-DIHYDROXY-6-HYDROXYMETHYL-8-OXABICYCLO[3.2.1]OCTANE DERIVATIVES, AND THEIR ANHYDRO-RING-MIGRATION WITH HYDROGEN BROMIDE–ACETIC ACID

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ABSTRACT

Nitromethane-mediated cyclization of the dialdehyde generated by periodate oxidation of (±)-2*exo*,3*exo*-dihydroxy-5*endo*-hydroxymethyl-7-oxabicyclo[2.2.1]-heptane (**2**) in methanolic sodium methoxide afforded, after neutralisation, three diastereoisomers (**4a–6a**) of (±)-2,4-dihydroxy-6-hydroxymethyl-3-nitro-8-oxabicyclo[3.2.1]octane in 52% combined yield. Their structures were assigned on the basis of ^{1}H-n.m.r. spectra of the respective triacetates (**4b–6b**). Hydrogenation of the nitro compounds in methanol–acetic anhydride with Raney nickel followed by acetylation gave the corresponding *N*-acetyl derivatives (**4c–6c**), treatment of which with 15% hydrogen bromide–acetic acid at 80° replaced the primary acetoxyl group with bromine, giving the monobromo derivatives **4d–6d**. Migration of the anhydro rings also occurred with **4c** and **6c**, yielding the respective isomers (1*RS*,2*RS*,4*SR*,5*RS*,6*RS*,7*SR*)-7-acetamido-2,6-diacetoxy-4-bromomethyl-8-oxabicyclo[3.2.1]octane (**7**) and (1*RS*,2*RS*,4*SR*,5*RS*,6*SR*,7*SR*)-6-acetamido-4,7-diacetoxy-2-bromomethyl-8-oxabicyclo[3.2.1]octane (**8a**). The mechanism of these reactions is considered.

INTRODUCTION

Since five- and six-membered carbocyclic analogues of sugars (pseudo-sugars) occur in Nature as components of several biologically active substances, such as antibiotics[1] and enzyme inhibitors[2], much attention has been focused on their chemical and biochemical properties[3]. We have been engaged in the synthesis[4] of pseudo-hexopyranose derivatives by acid-catalysed cleavage of 2,3-dihydroxy-5-hydroxymethyl-7-oxabicyclo[2.2.1]heptane derivatives. Attempts to construct pseudo-septanoses have been made by the preparation of appropriately functionalised 6-hydroxymethyl-8-oxabicyclo[3.2.1]octanes and cleavage of the anhydro ring with hydrogen bromide in acetic acid or by acetolysis.

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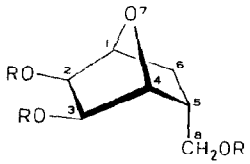
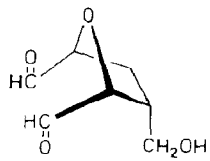
RESULTS AND DISCUSSION

Nitromethane-mediated cyclisation[5] of the dialdehyde **3** generated by periodate oxidation of (±)-2*exo*,3*exo*-dihydroxy-5*endo*-hydroxymethyl-7-oxabicyclo[2.2.1]heptane (**2**), derived from the known triacetate[4] **1**, gave, after chromatography, the diastereoisomers **4a** (18%), **5a** (10%), and **6a** (24%) of (±)-2,4-dihydroxy-6-hydroxymethyl-3-nitro-8-oxabicyclo[3.2.1]octane. Treatment of **4a–6a** severally with acetic anhydride–boron trifluoride etherate gave the respective triacetates **4b–6b** in good yields. Hydrogenation of **4a–6a** severally in methanol–acetic anhydride in the presence of Raney nickel T-4[6] and then treatment with acetic anhydride–pyridine afforded the crystalline tetra-*N*,*O*-acetyl derivatives **4c** (77%), **5c** (73%), and **6c** (82%), respectively.

Each newly formed nitro group was oriented in the thermodynamically stable position[7]. Assuming that the boat conformer of the 8-oxabicyclo[3.2.1]octane structure depicted in the formulae with the 3-nitro or 3-acetamido group in the *exo*-position to be more favourable, the ^{1}H-n.m.r. parameters were interpreted as in Table I. Chair conformers with the 3-substituents in the *endo*-position are



1 R = Ac
2 R = H



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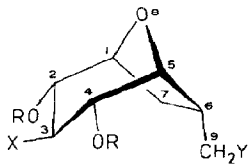
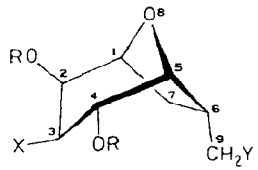
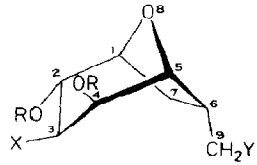


4a-g



5a-d



6a-d

	R	X	Y
a	H	NO_2	OH
b	Ac	NO_2	OAc
c	Ac	NHAc	OAc
d	Ac	NHAc	Br
e	Ms	NHAc	OMs
f	Ms	NHAc	Br
g	Ms	NHAc	OAc

possible, and there was no evidence to rule out those structures involving the boat conformation of the six-membered ring for which the above assignments of the configurations at C-2,3,4 would be inverted.

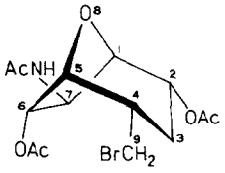
Thus, the spectrum of **4b** contained signals at δ 5.51 and 5.41 (2 dd, J 4.8 and 9.6 Hz), indicating H-2,4 to be *endo*. The spectrum of **5b** contained signals at δ 5.86 (dd, J 4.5 and 10.5 Hz) and 5.42 (dd, J 2.1 and 4.8 Hz) attributable to H-4*endo* and H-2*exo*, respectively. The spectrum of **6b** contained signals at δ 5.77 (dd, J 4.4 and 10.3 Hz) and 5.53 (dd, J 1.7 and 5.3 Hz) due to H-2*endo* and H-4*exo*, together with a signal at δ 4.45 (dd, J 1.7 and 7 Hz, H-5) coupled with the latter. The ^{1}H-n.m.r. data for **4c–6c** further supported the structures assigned.

In order to generate a cycloheptane ring, **4c–6c** were each treated with 15% hydrogen bromide in acetic acid in a sealed tube at 80° for 3 days. Two bromides **4d** (39%) and **7** (54%) were obtained from **4c, 5c** gave a single bromide **5d** (94%), and **6c** gave three bromides **6d** (9%), **8a** (46%), and **8b** (16%). Compound **8b** was, perhaps, derived from the initially formed di-*O*-acetyl amine hydrobromide via $O \rightarrow N$ acetyl group migration during isolation (under basic conditions), and was convertible into **8a** by acetylation.

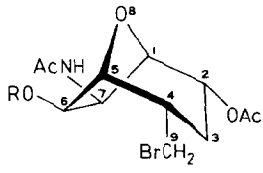
The structures of **4d–6d** were established by comparison of their ^{1}H-n.m.r. spectra with those of **4c–6c** respectively. The presence of the anhydro rings in **7a** and **8a** suggested that acid-catalysed migration of the rings had occurred. The ^{1}H-n.m.r. (270 MHz) spectrum of **7** contained signals at δ 5.20 (dd, J 3.4, 6.3 Hz), 4.93 (ddd, J 4.4, 6, 10.6 Hz), 4.50 (dd, J 3.3, 6.3 Hz), 4.31 (dd, J 3.4, 3.8 Hz), and 4.20 (dd, J 3.4, 4.4 Hz), assigned to H-6,2,5,7,1, respectively. The spectrum of **8a** contained signals at δ 4.83 (ddd, J 4.4, 6.6, 10.6 Hz), 4.42 (d, J 7 Hz), 4.34 (d, J 7 Hz), 4.30 and 4.23 (2 d, J 4.4 Hz) due to H-2,7,6,1,5 respectively.

The reactions of **4c–6c** with hydrogen bromide can be explained on the basis of the structures assigned. Thus, **4c** gives **4d**, the protonated anhydro ring of which can be opened at C-1 with the assistance of AcO-2 to give an intermediate cyclic acetoxonium ion from which **7** can be obtained. Stereomodels suggest that the formation of a 4,5-cyclic acetoxonium ion from **4d** would be sterically hindered by the 6-bromomethyl group and, for this reason, no isomerised product was obtained from **5d**. For **6c**, the ratio of products seems to denote that the isomer **8a** is thermodynamically more stable than **6d**.

The anhydro ring of **4c** was stable under acidic conditions. Thus, after



7



8a R = Ac
8b R = H

treatment with boiling aqueous 30% hydrobromic acid or on acetolysis (acetic anhydride–acetic acid–conc. sulfuric acid, 110°), **4c** was recovered unchanged after acetylation.

When the trimesylate (**4e**), derived from **4a**, was subjected to the bromination conditions, the bromide **4f** was obtained, only the primary mesylate group being substituted. On the other hand, treatment of **4e** with excess of sodium acetate in 2-methoxyethanol or *N,N*-dimethylformamide at 120° gave only the monoacetate **4g**. These results indicate that a *trans*-vicinal acetoxyl group is needed for migration of the anhydro ring, and that participation involving O-8 or AcNH-3 does not occur under basic conditions.

EXPERIMENTAL

General methods. — Melting points were determined with a MEL-TEMP capillary melting-point apparatus and are uncorrected. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Jeol JNM-FX90A (90 MHz) or GSX-270 (270 MHz) instrument. T.l.c. was performed on Silica Gel 60 F_{254} (Merck) with detection by charring with sulfuric acid. Column chromatography was conducted on Wakogel C-300 (300 Mesh, Wako Co., Osaka). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated at <50° under diminished pressure.

(±)-*2*exo,*3*exo-*Dihydroxy-5*endo-*hydroxymethyl-7-oxabicyclo[2.2.1]heptane* (**2**). — To a mixture of (±)-*2exo*,*3exo*-diacetoxy-*5endo*-acetoxymethyl-7-oxabicyclo-[2.2.1]heptane[4] (**1**; 8.16 g, 28.5 mmol) and methanol (60 mL) was added methanolic M sodium methoxide (0.5 mL). The mixture was stirred at room temperature for 2 h, then neutralised with Amberlite IR-120B (H^+) resin, and concentrated to give **2** (4.56 g, ~100%) as plates, m.p. 98–101° (from ethanol).

Anal. Calc. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.47; H, 7.38.

*(1*SR,*2*SR,*3*RS,*4*RS,*5*RS,*6*RS)- (**4a**), *(1*SR,*2*RS,*3*RS,*4*RS,*5*RS,*6*RS)- (**5a**), *and (1*SR,*2*SR,*3*RS,*4*SR,*5*RS,*6*RS)-*2,4-Dihydroxy-6-hydroxymethyl-3-nitro-8-oxabicyclo[3.2.1]octane* (**6a**). — Compound **2** (150 mg, 0.94 mmol) was treated with sodium metaperiodate (352 mg, 1.6 mmol) in water (1.5 mL) at room temperature for 1.5 h. Ethanol (20 mL) was added to the mixture which was then filtered and concentrated. The residue was treated with ethanol again to give the syrupy dialdehyde **3**. To a solution of **3** in methanol (7 mL) was added nitromethane (0.15 mL, 2.77 mmol) and methanolic M sodium methoxide (0.94 mL), and the mixture was stirred at room temperature for 24 h. T.l.c. (chloroform–methanol, 1:8) then revealed two major components (R_F 0.45, 0.24) and one minor component (R_F 0.38). The mixture was neutralised with Amberlite IR-120B (H^+) resin and concentrated. Column chromatography (chloroform–methanol, 15:1) of the residue gave **4a** (36 mg, 18%) and **5a** (20 mg, 10%), isolated as syrups, and **6a** (50 mg, 24%), m.p. 168–170° (from chloroform–methanol).

Anal. Calc. for $C_8H_{13}NO_6$: C, 43.84; H, 5.98; N, 6.39. Found: **4a** C, 43.49;

H, 5.85; N, 6.35; **6a** C, 43.61; H, 5.80; N, 6.32. Calc. for $C_8H_{15}NO_6 \cdot 0.5H_2O$: C, 42.11; H, 6.18; N, 6.14. Found: **5a** C, 42.21; H, 6.31; N, 5.92.

Compound **4a** (29 mg, 0.13 mmol) was treated with acetic anhydride (1 mL) and boron trifluoride etherate (one drop) at 0° for 30 min. The mixture was poured into ice–water (15 mL) and extracted with chloroform, the extract was dried and concentrated, and the residue was crystallised from ethanol to give the triacetate **4b** (30 mg, 65%) as needles, m.p. 116–118°.

Acetylation of **5a** (20 mg, 0.09 mmol) gave the triacetate **5b** (21 mg, 66%) as plates, m.p. 126–129° (from ethanol).

Acetylation of **6a** (37 mg, 0.17 mmol) gave the triacetate **6b** (51 mg, 88%) as needles, m.p. 120–122° (from ethanol).

The ^{1}H-n.m.r. data for **4a–6a** are listed in Table I.

Anal. Calc. for $C_{14}H_{19}NO_9$: C, 48.70; H, 5.55; N, 4.06. Found: **4b** C, 48.57; H, 5.38; N, 3.97; **5b** C, 48.88; H, 5.42; N, 4.07; **6b** C, 48.69; H, 5.41; N, 4.07.

(1SR,2SR,3RS,4RS,5RS,6RS)-3-Acetamido-2,4-diacetoxy-6-acetoxymethyl-8-oxabicyclo[3.2.1]octane (**4c**). — A solution of **4b** (60 mg, 0.27 mmol) in methanol (7 mL) containing acetic anhydride (50 μL, 0.53 mmol) was hydrogenated in the presence of Raney nickel T-4 (0.5 mL) in a Parr apparatus (initial hydrogen pressure, 3.4 kg.cm^{-2}) for 15 h at room temperature, then filtered, and concentrated. The residue was treated conventionally with acetic anhydride in pyridine at room temperature overnight. The product was eluted from a column of silica gel (4 g) with ethanol–toluene (1:10) to give **4c** (75 mg, 77%) as prisms, m.p. 145–145.5° (from ethanol). The ^{1}H-n.m.r. data are shown in Table I.

Anal. Calc. for $C_{16}H_{23}NO_8$: C, 53.78; H, 6.49; N, 3.92. Found: C, 53.68; H, 6.38; N, 4.00.

(1SR,2RS,3RS,4RS,5RS,6RS)-3-Acetamido-2,4-diacetoxy-6-acetoxymethyl-8-oxabicyclo[3.2.1]octane (**5c**). — Compound **5b** (80 mg, 0.37 mmol) was hydrogenated and acetylated as described above, to give **5c** (95 mg, 73%) as needles, m.p. 172.5–173.5° (from ethanol). The ^{1}H-n.m.r. data are listed in Table I.

Anal. Calc. for $C_{16}H_{23}NO_8$: C, 53.78; H, 6.49; N, 3.92. Found: C, 53.66; H, 6.29; N, 3.93.

(1SR,2SR,3RS,4SR,5RS,6RS)-3-Acetamido-2,4-diacetoxy-6-acetoxymethyl-8-oxabicyclo[3.2.1]octane (**6c**). — Compound **6b** (1.6 g, 7.3 mmol) was hydrogenated and acetylated as described above, to give **6c** (2.14 g, 82%) as plates, m.p. 174–176° (from ethanol). The ^{1}H-n.m.r. data are listed in Table I.

Anal. Calc. for $C_{16}H_{23}NO_8$: C, 53.78; H, 6.49; N, 3.92. Found: C, 53.87; H, 6.40; N, 3.97.

Reaction of **4c–6c** *with 20% hydrogen bromide–acetic acid at 80°.* — A mixture of **4c** (200 mg, 0.56 mmol), acetic acid (2 mL), and 30% hydrogen bromide–acetic acid (3 mL) was heated in a sealed tube for 3 days at 80°. The cooled mixture was poured into ice–water (20 mL) and extracted with chloroform (45 mL). The extract was washed successively with saturated aq. sodium hydrogencarbonate and water, dried, and concentrated. The residue was eluted from a column of silica gel

TABLE I

FIRST-ORDER N.M.R. PARAMETERS FOR COMPOUNDS **4–6**[a]

Compound	*Chemical shifts (δ)*								
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-9*	*H-9'*	$COCH_3$	*NH*
4b[b]	4.70–4.45	5.51dd	4.90t	5.41dd	4.70–4.45	4.51dd	4.20dd	2.08 2.07 2.03	
4c[b]	4.51–4.28	4.97dd	4.45bq	4.91dd	4.51–4.28		4.50–4.27	2.10 2.05 2.00 1.93	6.25d
4d[c]	4.39ddd	4.97dd	4.44bq	4.89dd	4.34dd	3.82dd	3.73dd	2.09 2.06 1.92	5.56d
5b[b]	4.70–4.51	5.42dd	4.99dd	5.86dd	4.70–4.51	4.45dd	4.15dd	2.16 2.15 2.13	
5c[b]	4.80–4.20	4.87dd	4.80–4.20	5.15dd	4.80–4.20		4.80–4.20	2.16 2.09 2.03 1.95	5.65d
5d[b]	4.75–4.25	4.85dd	4.75–4.25	5.17dd	4.75–4.25	3.83dd	3.67dd	2.19 2.01 1.96	5.75d
6b[c]	4.63ddd	5.77dd	4.88dd	5.53dd	4.45dd	4.38dd	4.25dd	2.17 2.08 2.07	
6c[c]	4.50–4.40	5.08dd	4.48ddd	5.01dd	4.50–4.40		4.50–4.40	2.16 2.12 2.06 1.93	5.69d
6d[c]	4.41–4.32	5.08dd	4.41–4.32	5.08dd	4.41–4.32	3.60dd	3.57dd	2.16 2.06 1.94	5.76d

	Coupling constants (Hz)										
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{1,7}$	$J_{1,7'}$	$J_{6,9}$	$J_{6,9'}$	$J_{9,9}$	$J_{3,NH}$
4b[b]	4.8	9.6	9.6	4.8				8.1	7	11.1	
4c[b]	4.5	10.3	10.3	4.5							9.1
4d[c]	4.4	10.3	10.3	4.4	6.2	6.4	2.9	8.8	8.1	10.3	9.5
5b[b]	2.1	4.8	10.5	4.5				7.1	8	11.7	
5c[b]	2.2	4.5	10.6	4.7							9.1
5d[b]	2.1	4.6	10.6	4.6				3	2	8	9
6b[c]	4.4	10.3	5.3	1.7	7	5.9	1.5	5.7	7.7	12.1	
6c[c]	4	10.3	4.4	~0							8.8
6d[c]	4.2	10.5	4.6	1.7				2.2	1.8	~0	8.4

[a]Measured on solutions in $CDCl_3$. [b]At 90 MHz. [c]At 270 MHz.

(20 g) with ethanol–toluene (1:12) to give, first, (1*SR*,2*SR*,3*RS*,4*RS*,5*RS*,6*RS*)-3-acetamido-2,4-diacetoxy-6-bromomethyl-8-oxabicyclo[3.2.1]octane (**4d**; 82 mg, 39%) as needles, m.p. 169–169.5° (from ethanol). The ^{1}H-n.m.r. data are listed in Table I.

Anal. Calc. for $C_{14}H_{20}BrNO_6$: C, 44.45; H, 5.33; N, 3.70. Found: C, 44.45; H, 5.16; N, 3.66.

Eluted second was (1*RS*,2*RS*,4*SR*,5*RS*,6*RS*,7*SR*)-7-acetamido-2,6-diacetoxy-4-bromomethyl-8-oxabicyclo[3.2.1]octane (**7**; 114 mg, 54%), m.p. 174–176° (from ethanol). ^{1}H-N.m.r. data (270 MHz, $CDCl_3$): δ 6.05 (bd, 1 H, $J_{7,NH}$ 3.8 Hz, NH), 5.20 (dd, 1 H, $J_{5,6}$ 6.3, $J_{6,7}$ 3.4 Hz, H-6), 4.93 (ddd, 1 H, $J_{1,2}$ 4.4, $J_{2,3}$ 10.6, $J_{2,3'}$ 6 Hz, H-2), 4.50 (bdd, 1 H, $J_{4,5}$ 3.3 Hz, H-5), 4.31 (dd, 1 H, H-7), 4.20 (dd, 1 H, $J_{1,7}$ ~0 Hz, H-1), 3.47 (dd, 1 H, $J_{4,9}$ 8.1, $J_{9,9}$ 9.9 Hz, H-9), 3.30 (dd, 1 H, $J_{4,9'}$ 8.1 Hz, H-9′), 2.52–2.29 (m, 2 H, H-5,6), 2.13 and 1.98 (2 s, 6 and 3 H, NAc and 2 OAc).

Anal. Found: C, 44.40; H, 5.14; N, 3.72.

Compound **5c** (100 mg, 0.28 mmol) was treated with acetic acid (0.7 mL) and 30% hydrogen bromide–acetic acid (1 mL) at 80° for 3 days. The mixture was processed as described above. Column chromatography (ethanol–toluene, 1:8) of the chloroform-soluble product gave (1*SR*,2*RS*,3*RS*,4*RS*,6*RS*)-3-acetamido-2,4-diacetoxy-6-bromomethyl-8-oxabicyclo[3.2.1]octane (**5d**, 15 mg), isolated as a syrup. Acetylation of the water-soluble product and similar chromatography gave more **5d** (80 mg, total 94%). The ^{1}H-n.m.r. data are listed in Table I. Analytical sample was very hygroscopic and formed a hemihydrate.

Anal. Calc. for $C_{14}H_{20}BrNO_6 \cdot 0.5H_2O$: C, 43.42; H, 5.47; N, 3.62. Found: C, 43.40; H, 5.07; N, 3.50.

Compound **6c** (300 mg, 0.84 mmol) was treated with 20% hydrogen bromide–acetic acid (5 mL) as described above. Column chromatography (ethanol–toluene, 1:12) of the chloroform-soluble product gave (1*SR*,2*SR*,3*RS*,4*SR*,5*RS*,6*RS*)-6-acetamido-4-acetoxy-2-bromomethyl-7-hydroxy-8-oxabicyclo[3.2.1]octane (**8b**; 40 mg, 16%), m.p. 165–166° (from acetone–hexane). The ^{1}H-n.m.r. data (270 MHz, $CDCl_3$): δ 6.53 (d, 1 H, $J_{7,NH}$ 6.6 Hz, NH), 4.83 (ddd, 1 H, $J_{1,2}$ 4.4, $J_{2,3}$ 6.6, $J_{2,3'}$ 10.6 Hz, H-2), 4.42 (dd, 1 H, $J_{1,7}$ ~0, $J_{6,7}$ 7 Hz, H-7), 4.34 (d, 1 H, H-6), 4.30 and 4.23 (2 d, each 1 H, $J_{4,5}$ 4.4 Hz, H-1,4), 3.29 (dd, 1 H, $J_{4,9}$ 8.4, $J_{9,9}$ 10.6 Hz, H-9), 3.22 (dd, 1 H, $J_{4,9'}$ 6.6 Hz, H-9′), 2.35–2.15 (m, 2 H, H-3,4), 2.10 (s, 3 H, OAc), 2.04 (s, 3 H, NAc), 1.05 (bq, J ~12 Hz, H-3′).

Anal. Calc. for $C_{12}H_{18}BrNO_5$: C, 42.87; H, 5.40; N, 4.17. Found: C, 42.74; H, 5.19; N, 4.18.

Acetylation of the water-soluble product and column chromatography (chloroform–ethyl acetate, 1:2) gave, first, (1*SR*,2*SR*,3*RS*,4*SR*,5*RS*,6*RS*)-3-acetamido-2,4-diacetoxy-6-bromomethyl-8-oxabicyclo[3.2.1]octane (**6d**; 29 mg, 9%) as prisms, m.p. 158–159.5°. The ^{1}H-n.m.r. data are listed in Table I.

Anal. Calc. for $C_{14}H_{20}BrNO_6$: C, 44.45; H, 5.33; N, 3.70. Found: C, 44.29; H, 5.32; N, 3.45.

Eluted second was (1*RS*,2*RS*,4*SR*,5*RS*,6*SR*,7*SR*)-6-acetamido-4,7-diacetoxy-

2-bromomethyl-8-oxabicyclo[3.2.1]octane (**8a**; 146 mg, 46%) as plates, m.p. 206–209° (from ethanol). ^{1}H-N.m.r. data (270 MHz, $CDCl_3$): δ 6.00 (d, 1 H, $J_{7,NH}$ 8.1 Hz, NH), 5.15 (d, 1 H, $J_{5,6}$ ~0, $J_{6,7}$ 7.7 Hz, H-6), 4.85 (ddd, 1 H, $J_{1,2}$ 4, $J_{2,3}$ 10.6, $J_{2,3'}$ 5.9 Hz, H-2), 4.73 (t, 1 H, H-7), 4.23 (d, 2 H, $J_{4,5}$ 4, $J_{1,7}$ ~0 Hz, H-1,5), 3.44 (dd, $J_{4,9}$ 7.3, $J_{9,9}$ 10.6 Hz, H-9), 3.26 (dd, 1 H, $J_{4,9'}$ 7, H-9'), 2.75–2.25 (m, 2 H, H-3,4), 2.13, 2.11, and 2.01 (3 s, each 3 H, NAc and 2 OAc).

Anal. Found: C, 44.51; H, 5.23; N, 3.69.

(1SR,2RS,3SR,4SR,5SR,6RS)-3-Acetamido-2,4-dimesyloxy-6-mesyloxymethyl-8-oxabicyclo[3.2.1]octane (**4e**). — A solution of **4c** (100 mg, 0.28 mmol) in methanol (3 mL) containing methanolic M sodium methoxide (0.3 mL) was stirred for 1 h at room temperature, then neutralised with Amberlite IR–120B (H^+) resin, and concentrated. The residue was treated with methanesulfonyl chloride (0.15 mL, 1.94 mmol) in pyridine (3 mL) in the presence of a catalytic amount of 4-dimethylaminopyridine for 12 h at room temperature. More methanesulfonyl chloride (0.15 mL) was added, and the mixture was stirred for 9 h and then concentrated. Column chromatography (chloroform–methanol, 20:1) of the residue gave **4e** (75 mg, 58%) as plates, m.p. 192–194.5° (from ethanol). ^{1}H-N.m.r. data (90 MHz, $CDCl_3$): δ 7.67 (d, 1 H, $J_{3,NH}$ 8.9 Hz, NH), 4.90 (dd, 1 H, $J_{1,2}$ 5, $J_{2,3}$ 9.3 Hz, H-2), 4.85 (dd, 1 H, $J_{3,4}$ 9, $J_{4,5}$ 4 Hz, H-4), 4.72–4.05 (m, 5 H, H-1,2,5, and CH_2O), 3.10, 3.09, and 3.07 (3 s, each 3 H, 3 OMs), 2.03 (s, 3 H, NAc).

Anal. Calc. for $C_{13}H_{23}NO_{11}S_3$: C, 33.54; H, 4.98; N, 3.00. Found: C, 33.15; H, 4.74; N, 2.80.

(1SR,2RS,3SR,4SR,5SR,6RS)-3-Acetamido-6-bromomethyl-2,4-dimesyloxy-8-oxabicyclo[3.2.1]octane (**4f**). — A mixture of **4e** (70 mg, 0.15 mmol) and 20% hydrobromic acid–acetic acid (1.7 mL) was heated in a sealed tube for 40 h at 85°, then concentrated. Column chromatography (chloroform–methanol, 20:1) of the residue gave **4f** (65 mg, 96%), m.p. 193–194° (from ethyl acetate–hexane). ^{1}H-N.m.r. data (90 MHz, $CDCl_3$): δ 7.38 (d, 1 H, $J_{3,NH}$ 9 Hz, NH), 4.95 (dd, 1 H, $J_{1,2}$ 4, $J_{2,3}$ 9.5 Hz, H-2), 4.90 (dd, 1 H, $J_{3,4}$ 9, $J_{4,5}$ 3.8 Hz, H-4), 4.70–4.10 (m, 3 H, H-1,3,5), 3.92–3.52 (m, 2 H, CH_2Br), 3.09 and 3.08 (2 s, each 3 H, 2 OMs), 2.00 (s, 3 H, NAc).

Anal. Calc. for $C_{12}H_{20}BrN_8S_2$: C, 32.01; H, 4.48; N, 3.11. Found: C, 32.05; H, 4.37; N, 3.01.

When reaction time was prolonged, no products other than **4f** were formed.

(1SR,2RS,3SR,4SR,5SR,6RS)-3-Acetamido-6-acetoxymethyl-2,4-dimesyloxy-8-oxabicyclo[3.2.1]octane (**4g**). — A mixture of **4e** (45 mg, 0.10 mmol), anhydrous sodium acetate (50 mg, 0.61 mmol), and aqueous 90% 2-methoxyethanol (3 mL) was heated at 120° for 53 h, then concentrated, and the residue was acetylated. Column chromatography (chloroform–methanol, 15:1) of the product gave amorphous **4g** (38 mg, 90%), m.p. 62–75° (from ethyl acetate–hexane). ^{1}H-N.m.r. data (90 MHz, $CDCl_3$): δ 7.25 (d, 1 H, $J_{3,NH}$ 9 Hz, NH), 4.95 (dd, 1 H, $J_{1,2}$ 4.5, $J_{2,3}$ 10 Hz, H-2), 4.90 (dd, 1 H, $J_{3,4}$ 9, $J_{4,5}$ 4 Hz, H-4), 4.75–4.00 (m, 5 H, H-1,3,5, and CH_2O), 3.10 and 3.05 (2 s, each 3 H, 2 OMs), 2.12 and 2.02 (2 s, each 3 H, NAc and OAc).

Anal. Calc. for $C_{14}H_{23}NO_{10}S_2$: C, 39.15; H, 5.40; N, 3.26. Found: C, 39.63; H, 5.30; N, 2.81.

When the solvent was replaced with *N,N*-dimethylformamide, only **4f** was obtained in 52% yield.

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