Synthesis of New Cyclopropano Furanosides: Construction of a 2-Oxabicyclo[3.1.0]hexane Skeleton by a One-Pot 1,2-Diol Monosulfonate Rearrangement–Cyclopropanation Reaction

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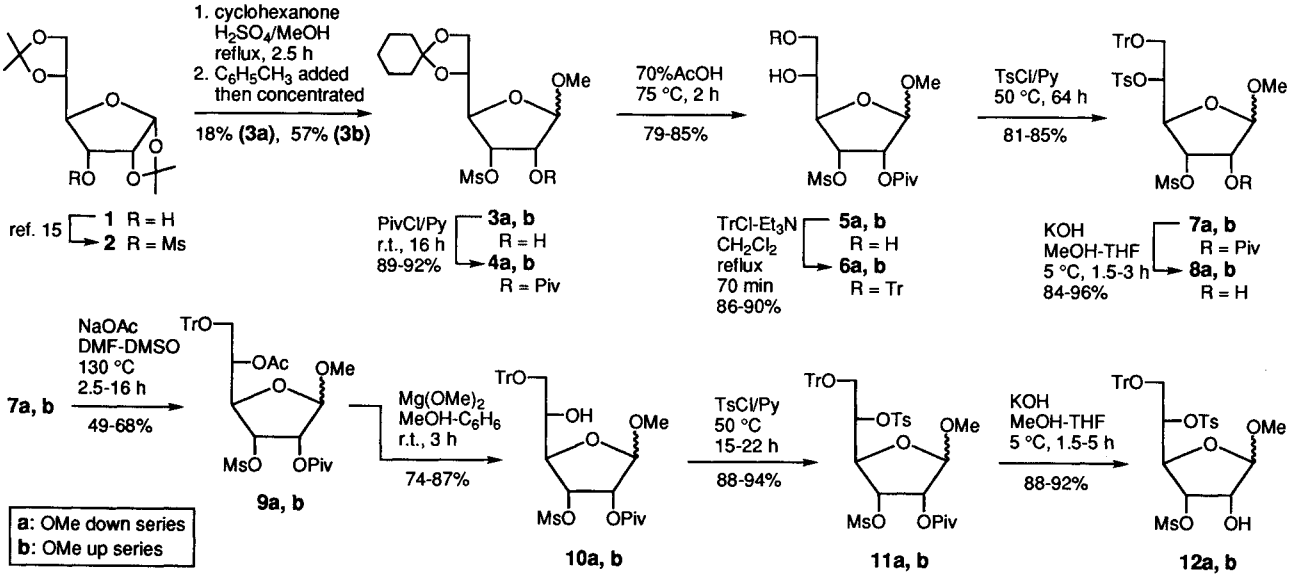
This paper is dedicated to the memory of Professor Sakae Emoto.

The synthesis and characterization of new methyl cyclopropano furanosides are described. A fused cyclopropane ring bearing a hydroxymethyl group was constructed at the 3,4-positions of the furanose ring by a consecutive 1,2-hydride shift–enolization–cyclopropanation reaction starting from a sugar disulfonate under mild reaction conditions with $Mg(OMe)_2$ in a one-pot manner.

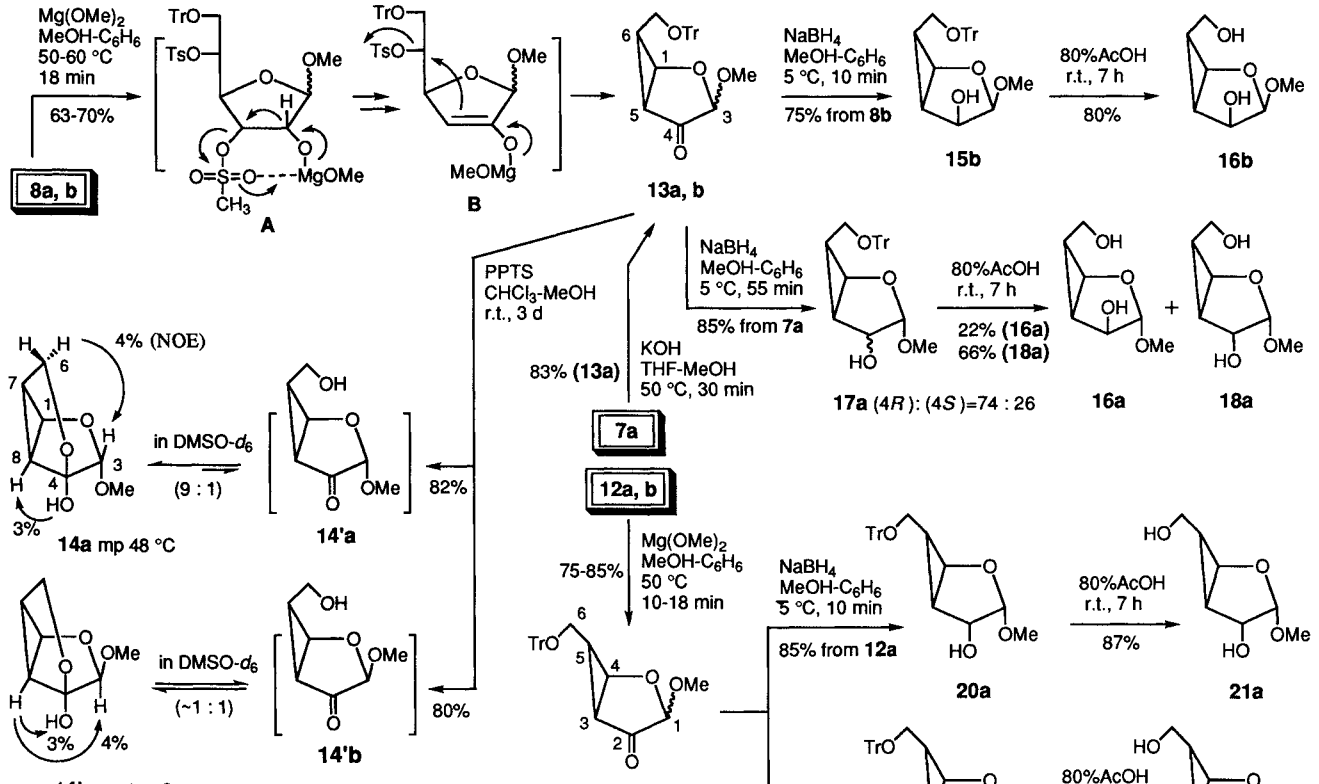
The development of efficient methods for the deoxygenation of hydroxyl functions has attracted considerable attention in carbohydrate chemistry.[2] In 1975, we discovered a novel deoxygenation involving a 1,2-hydride shift with a concomitant functional group conversion,[3] and its synthetic utilities have been demonstrated by us[4–7] and others.[8,9] For example, sugar or nucleoside derivatives containing a monosulfonylated *cis*-1,2-diol system underwent the 1,2-hydride shifts in the presence of a Grignard[6,8] or Wittig[5] reagent or a reducing[4,7,9] agent. The hydroxyl group adjacent to the sulfonyloxy function in the diol moiety was converted into a carbonyl group, while in a concerted manner the sulfonyloxy group was substituted with the hydride. The resulting deoxy ketones then reacted with these reagents in a one-pot manner to provide modified deoxy sugars[4,5] or nucleosides.[6–9] This 1,2-diol monosulfonate rearrangement strategy has recently been extended to a deoxygenative framework-transformation of ribonucleosides by combining the rearrangement with a cyclopropanation[10] in a one-pot fashion (**A** and **B**, Scheme 2).[11] Herein we report an application of the one-pot cyclopropanation reaction to the synthesis of new methyl cyclopropano furanosides,[12] which are potentially useful for synthesis of modified nucleosides[13] as well as for preparation of chiral cyclopropane-based synthons.[14]

Initially, commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-*allo*-furanose (**1**) was converted into the corresponding mesylate **2** according to the published method[15] (Scheme 1). A modified methanolysis[3] of **2** in the presence of cyclohexanone as an additive gave a ca. 3:7 mixture of methyl 5,6-*O*-cyclohexylidene-3-*O*-mesyl-α- and -β-D-*allo*-furanosides (**3a** and **3b**) in 92% combined yield. The 5,6-*O*-cyclohexylidenation was completed at a workup stage of the methanolysis of **2** by distilling off methanol and the 2,2-dimethoxypropane liberated from the isopropylidene groups. The anomers **3a,b**, which exposed the C-2 hydroxyl groups to triggers for the 1,2-hydride shift rearrangements, were isolated by fractional crystallizations and used separately for further reactions. Pivaloylation of **3a,b** with pivaloyl chloride followed by decyclohexylidenation of pivaloylates **4a,b** with acetic acid gave diols **5a,b** in good yields. The selective tritylation of the primary hydroxyl groups in **5a,b** was performed with trityl chloride (2.5 equiv) in refluxing CH_2Cl_2 in the presence of triethylamine to afford trityl ethers **6a,b**. Treatment of **6a,b** with tosyl chloride (5 equiv) gave key intermediates, methyl 3-*O*-mesyl-2-*O*-pivaloyl-5-*O*-tosyl-6-*O*-trityl-α- and -β-D-*allo*-furanosides (**7a** and **7b**), which were deprotected with KOH (2.5 equiv) at 5°C to afford D-*allo*-hydroxymesylates **8a,b**.

To obtain the corresponding L-*tallo*-hydroxymesylates **12a,b** an S_N2 type (Walden) inversion of the hydroxyl



Scheme 1



Scheme 2

groups at C-5 in the key intermediates **7a,b** was carried out using sodium acetate to give acetates **9a,b** in moderate yields. No compound substituted at C-3 in **7a,b** was detected. The stereochemistry at C-5 in **9a,b** could safely be assumed to be L-*tallo* from the mode of formation. Selective removal of the acetyl groups in **9a,b** without affecting the pivaloyl groups at C-2 was difficult even when mild hydrazine hydrate[16] was used for the deacetylation. However, we found that magnesium methoxide [$Mg(OMe)_2$] was the reagent of choice. Upon treatment with $Mg(OMe)_2$ (5 equiv) at room temperature for 40 minutes, **9a,b** furnished alcohols **10a,b** in extremely high regioselectivity in 74–87% yields. Conventional tosylation of **10a,b** gave methyl 3-*O*-mesyl-2-*O*-pivaloyl-5-*O*-tosyl-6-*O*-trityl-α- and -β-L-*tallo*-furanosides (**11b** and **11a**). Mild treatment of **11a,b** with KOH under conditions similar to those used for the preparation of **8a,b** gave the L-*tallo* isomers **12a,b**.

The synthetic application of our cyclopropanation to the *allo* compounds **8a,b** was achieved under mild and simple conditions, which comprised heating a methanolic solution of each compound at 50–60 °C in the presence of freshly prepared $Mg(OMe)_2$ (20 equiv)[17] for 18 minutes (Scheme 2). The reactions proceeded very nicely through presumed species **A** and **B** to afford (1*R*,3*S* and *R*,5*S*,6*S*)-3-methoxy-6-trityloxymethyl-2-oxabicyclo[3.1.0]hexan-4-ones (**13a** and **13b**) in 63–70% yields without detectable anomerization at C-1; except for the nomenclature of the bi- and tricyclic (*vide infra*) compounds, a "carbohydrate-like" numbering system (see **19a,b**) was adopted for convenience. Similarly the *tallo* derivatives **12a,b** produced (3*S*,6*R*)- and (3*R*,6*R*)-isomers (**19a** and **19b**) in good yields, respectively.

Strongly oxygenophilic but weakly basic $Mg(OMe)_2$ could not trigger the 1,2-hydride shift rearrangements starting from the C-2 hydroxyl protected pivaloylates **7a,b** and **11a,b** even at elevated temperatures (~ 60 °C). The use of KOH[7] instead of $Mg(OMe)_2$, however, made both the deprotection of the C-2 pivaloyl groups and the initiation of the 1,2-hydride shifts possible. Thus treatment of **7a** with methanolic KOH (10 equiv) at 50 °C for 30 minutes provided **13a** in 83% yield. Under similar reaction conditions, **11a** resulted in an approximately 1:1 anomeric mixture of **19** in 71% combined yield.

Other substrates, **7b** and **11b**, required stronger conditions (60 °C; 1 h for **11b**, 1.5 h for **7b**) than those for **7a** or **11a** to complete the one-pot reaction, giving ca. 6:4 (α/β) anomeric mixtures of **13** and **19**, respectively, along with unidentified products (< 10%, by TLC and ^{1}H NMR analyses). The KOH induced 1,2-hydride shift rearrangement for the OMe-up **7b** or **11b** proceeded very slowly in comparison with that for the OMe-down **7a** or **11a** as judged by TLC analysis, the reason being not clear at this time.

The ^{1}H NMR spectra of **13a,b** and **19a,b** showed, in each case, one set of signals at a higher field (~ 2 ppm), characteristic to the ring methine protons of a cycloprop-

Table 1. Compounds **3–23** Prepared

Product	Yield[a] (%)	mp (°C) (Recryst Solvent)	Molecular Formula[c] or Lit. mp (°C)	$[\alpha]_D^{25}$ (*c*, $CHCl_3$) [Lit.]	^{1}H NMR Coupling Constants/Hz[b] H-1	H-2	H-3	H-4	H-5	H-6	H-6′	OH	IR (KBr) ν (C=O) cm^{-1}
3a	18	117–118 (*i*-$Pr_2OC_6H_6$)	118–119[3] (*i*-$Pr_2OC_6H_6$)	+97.5 (0.95)[d], [+97.7 (1)[e]][3]									
3b	57	137–139 (MeOH)	138–140[3] (MeOH)	−44.4 (1.01)[d], [−44.6 (1)[f]][3]									
4a	89	glass	$C_{19}H_{32}O_9S \cdot 0.2H_2O$	+94.5 (0.34)	4.6	4.6, 7.0	2.4, 7.0	2.4, 6.4	m	6.4, 8.2	4.6, 8.2	–	
4b	92	106–107 (hexane)	$C_{19}H_{32}O_9S$ (436.5)	−19.6 (0.91)	1.2	1.2, 5.0	m	m	m	m	m	–	
5a	79	syrup	$C_{13}H_{24}O_9S \cdot 0.5H_2O$ (365.4)	+117 (0.89)	4.3	4.3, 7.0	2.8, 7.0	2.8, 5.2	m	m	m	–	
5b	85	syrup	$C_{13}H_{24}O_9S \cdot 0.2H_2O$	−29.9 (0.71)	1.2	1.2, 5.2	5.2	5.6	m	m	m	4.3 (d), 6.0 (t)	
6a	90	foam	$C_{32}H_{38}O_9S$ (598.7)	+67.6 (0.42)	4.3	4.3, 7.2	2.9, 7.2	2.9, 7.2	m	m	m	4.9	
6b	86	foam	$C_{32}H_{38}O_9S$ (598.7)	+0.2 (0.61)	~1	1.0, 4.9	5.4	5.4, 7.3	m	3.4, 9.8	m	3.9	
7a	81	146–147 (MeOH)	$C_{39}H_{44}O_{11}S_2$ (752.9)	+56.9 (0.89)	4.4	4.4, 6.8	2.4, 6.8	3.2	m	5.9, 10.7	5.6, 10.7	–	
7b	85	foam	$C_{39}H_{44}O_{11}S_2$ (752.9)	+14.6 (0.90)	s	4.9	5.6	6.1	m	4.4		–	
8a	96	foam	$C_{34}H_{36}O_{10}S_2$ (668.8)	+53.1 (1.03)	4.9	4.6, 6.9, 11.1	m	2.4	m	6.4, 10.6	5.5, 10.7	11.3	
8b	84	foam	$C_{34}H_{36}O_{10}S_2$ (668.8)	+10.2 (0.96)	0.9	0.9, 4.4	5.0	5.6, 7.7	m	m	m	4.3	
9a	49	foam	$C_{34}H_{40}O_{10}S$ (640.7)	+67.8 (0.68)	4.6	4.6, 7.0	3.4, 7.0	3.4	m	5.5		–	
9b	68	foam	$C_{34}H_{40}O_{10}S$ (640.7)	+10.1 (1.03)	s	4.4	4.4, 7.8	2.9, 7.8	m	7.8, 9.8	4.9, 9.8	–	
10a	74	foam	$C_{32}H_{38}O_9S \cdot 0.2H_2O$	+65.5 (0.93)	4.4	4.4, 7.3	3.4, 7.3	2.2, 3.2	m	m	m	7.3	
10b	87	foam	$C_{32}H_{38}O_9S$ (598.7)	−7.3 (1.11)	s	1.0, 5.3	5.8	2.2, 6.1	m	7.4, 9.3	5.9, 9.2	8.3	
11a	88	foam	$C_{39}H_{44}O_{11}S_2$ (752.9)	+53.3 (1.03)	4.4	4.4, 7.3	3.2, 7.3	2.9	m	6.3, 9.8	5.2, 9.8	–	
11b	94	foam	$C_{39}H_{44}O_{11}S_2$ (752.9)	+4.8 (0.6)	s	4.9	4.9, 7.3	2.1, 7.3	2.1, 6.5	m	m	–	
12a	92	foam	$C_{34}H_{36}O_{10}S_2$ (668.8)	+47.9 (0.92)	4.4	4.4, 6.8, 11.2	2.2, 6.8	~2	m	7.3, 9.8	5.4, 9.8	11.7	
12b	88	foam	$C_{34}H_{36}O_{10}S_2$ (668.8)	−10.8 (0.79)	s	3.8	4.2, 7.6	2.1, 7.6	2.1, 6.1	m	m	~4	
13a	63 83 (from **7a**)	81–82 (*i*-PrOH)	$C_{26}H_{24}O_4$ (400.5)	+54.5[d] (0.97)	br s	–	3.9, 10.8	1.4, 4.4	m	8.2, 10.3	6.3, 10.3	–	1761 (st)
13b	70	125–126 (EtOH)	$C_{26}H_{24}O_4$ (400.5)	−8.7 (1.07)	1.5	–	1.5, 4.2, 11.7	4.2	m	8.5, 10.2	4.8, 10.2	–	1754 (st)
14a[g]	82	45–46 (sintered), 48 °C (melt) (CCl_4—cyclohexane)	$C_7H_{10}O_4$ (158.2)	+217[d] (0.5, DMSO)	s	–	6.1, 7.6	3.2, 7.6	m	7.8	4.4, 7.8	s	1748 (w)
14b	80	84–86 (CH_2Cl_2—cyclohexane)	$C_7H_{10}O_4$ (158.2)	+22.9[d] (18 min) → +11.6 (6 h) (0.96, DMSO)	s	–	6.4, 8.3	6.4	4.4, 8.3	m	4.6 8.1	s	

Table 1. (continued)

Product	Yield[a] (%)	mp (°C) (Recryst Solvent)	Molecular Formula[c] or Lit. mp (°C)	$[\alpha]_D^{25}$ (c, $CHCl_3$) [Lit.]	^{1}H NMR Coupling Constants/Hz[b] H-1	H-2	H-3	H-4	H-5	H-6	H-6′	OH	IR (KBr) ν (C=O) cm^{-1}
14′a	not isolated				br s	–	4.2, 10.6	1.5, 4.1	m	m	m	5.6	1748 (w)[h]
14′b	not isolated				br s	–	1.6, 4.2, 11.8	4.2	m	m	m	5.4	1748 (st)[i]
15b	75	133–135	$C_{26}H_{26}O_4$ (402.5)	−58.3 (0.86)	6.5	6.6, 10.3	6.4, 9.8	5.4	m	8.3, 11	9.1, 11.0	10.2	
16a	22	syrup	$C_7H_{12}O_4 \cdot 0.3H_2O$	+189 (0.49)	s	~1, 7	5.5, 7.0, 9.2	0.9, 5.2	5.1, 7.2, 9.5	7.0, 12.2	10.4, 11.9	br s, br s	
16b	80	83.5–84.5 (*i*-PrOH—cyclohexane)	$C_7H_{12}O_4$ (160.2)	−21.8 (0.48)	5.8	3.1, 6.0	5.8, 6.7, 9.5	4.9, 5.9	4.9, 7.0, 9.8	7.0, 9.2, 12.2	3.4, 10.1, 12.2	3.1 (d), 3.4 (dd), 9.5 (dd)	
(4*R*)-**17a**	85[j]	syrup			4.4	4.9, 8.8	1.0, 5.4, 10.0	4.7	m	7.3, 10.2	8.3, 10.3	8.8	
(4*S*)-**17a**					s	4.9	6.3, 7.3, 7.9	7.3, 11.2	m	7.3, 10.2		4.6	
18a	66	71–72 (*i*-PrOH—cyclohexane)	$C_7H_{12}O_4$ (160.2)	+302 (0.75)	4.4	m	1.0, 5.4, 9.8	m	m	6.8, 11.7	8.8, 11.7	8.8 (d), br m	
19a	85	glass	$C_{26}H_{24}O_4 \cdot H_2O$ (418.5)	+11.0 (0.33)	2.0	–	3.9	1.5, 1.5, 3.9	1.5	5.4, 10.2	5.9, 10.2	–	1752 (st)
19b	70	101–102 (EtOH)	$C_{26}H_{24}O_4$ (400.5)	−113 (0.41)	1.4	–	1.2, 4.2	1.9, 3.9	m	5.3, 10.2	5.1, 10.2	–	1750 (st)
20a	85	syrup	$C_{26}H_{26}O_4$ (402.5)	+92.7 (0.66)	4.4	1.0, 4.4, 8.3	m	1.1, 5.6	~1	6.1, 10.2	6.8, 10.2	8.3	
21a	87	syrup	$C_7H_{12}O_4 \cdot 0.5H_2O$ (169.2)	+223 (0.67)	4.3	~1, 4.3, 8.0	1.1, 4.3, 5.8	1.2, 5.8	1.2, 4.0, 7.2	m	m	8.2 (d), br s	
22b	87	glass	$C_{26}H_{26}O_4$ (402.5)	−46.0 (0.43)	5.9	5.8, 9.7	m	1.0, 5.9	m	5.9, 9.8	6.4, 9.8	9.2	
23b	76	syrup	$C_7H_{12}O_4 \cdot 0.2H_2O$	−72.4 (0.47)	5.9	5.9, 8.7	3.9, 5.9	1.5, 5.9	1.5, 4.4, 7.1	m	m	9.3 (d), br s	

[a] Yield of isolated product.
[b] A "carbohydrate-like" numbering system (see, **19a, b**) was adopted for **13–23**.
[c] Satisfactory microanalyses obtained: C ±0.29, H ±0.27, S ±0.26.
[d] 20 °C.
[e] 22 °C.
[f] 24 °C.
[g] A ca. 9 : 1 mixture of **14a** and **14′a**.
[h] Amorphous film; an equilibrated mixture of **14a** and **14′a**.
[i] Amorphous film; an equilibrated mixture of **14b** and **14′b**.
[j] Combined yield of (4*R*)- and (4*S*)-isomers.

Table 2. ^{1}H NMR Data of Products **4–23** ($CDCl_3$/TMS), δ (ppm)[a,b]

Product	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	OCH_3 (s)	Ms (s)	CH_3 Ts (s)	Piv (s)	OH	Aromatic Protons (m)
4a	5.13 d	4.85 dd	5.14 dd	4.16 dd	4.07–4.11 m	4.13 dd	3.96 dd	3.39	3.07	–	1.27	–	1.28–1.69
4b	4.87 d	5.22 dd	5.17–5.20 m		4.10–4.15 m		3.94–4.00 m	3.36	3.05	–	1.25	–	1.30–1.70
5a	5.15 d	4.82 dd	5.28 dd	4.26 dd	3.80–3.87 m		3.72–3.86 m	3.41	3.10	–	1.26	2.35 (t) 2.87 (d)	–
5b	4.92 d	5.22 dd	5.35 t	4.27 t	3.80–3.87 m		3.72–3.87 m	3.42	3.06	–	1.25	2.23 (t) 3.03 (d)	–
6a	5.08 d	4.76 dd	5.12 dd	4.22 dd	3.67–3.71 m		3.32–3.36 m	3.37	2.96	–	1.25	2.56 d	7.24–7.43
6b	4.82 br d	5.20 dd	5.26 t	4.19 dd	3.86–3.92 m	3.40 dd	3.24–3.28 m	3.26	2.94	–	1.24	2.69 d	7.23–7.45
7a	4.82 d	4.56 dd	5.12 dd	4.47 t	4.77–4.81 m	3.42 dd	3.27 dd	3.31	2.86	2.42	1.22	–	7.23–7.75
7b	4.78 s	5.15 d	5.21 t	4.57 t	4.78–4.82 m		3.27 d	3.13	3.02	2.40	1.24	–	7.21–7.75
8a	4.62 d	4.01 ddd	4.84–4.87 m	4.40 t	4.84–4.87 m	3.39 dd	3.29 dd	3.40	2.93	2.40	–	2.64 d	7.21–7.75
8b	4.83 d	4.33 td	5.18 t	4.57 dd	4.71–4.74 m		3.23–3.29 m	3.14 or 3.16		2.40	–	2.59 d	7.19–7.72
9a	5.05 d	4.79 dd	5.10 dd	4.49 t	5.25–5.28 m		3.31 d	3.33	3.04	2.16 (Ac)	1.23	–	7.23–7.43
9b	4.78 s	5.17 d	4.95 dd	4.34 dd	5.21–5.25 m	3.51 dd	3.32 dd	3.28	2.99	2.15 (Ac)	1.23	–	7.23–7.44
10a	5.11 d	4.82 dd	5.20 dd	4.35 dd	3.99–4.04 m		3.24–3.32 m	3.36	3.03	–	1.28	2.22 d	7.23–7.47
10b	4.88 s	5.18 dd	5.31 t	4.41 dd	3.84–3.90 m	3.34 dd	3.22 dd	3.31	2.99	–	1.25	2.41 d	7.22–7.47
11a	5.01 d	4.69 dd	5.25 dd	4.57 t	4.85–4.88 m	3.33 dd	3.11 dd	3.30	3.07	2.41	1.23	–	7.21–7.76
11b	4.76 s	5.18 d	5.22 dd	4.44 dd	4.76 dt		3.40 m	3.05 or 3.07		2.41	1.24	–	7.22–7.77
12a	4.80 d	4.12 ddd	4.92 dd	4.58 br t	4.78–4.82 m	3.31 dd	3.07 dd	3.41	3.08	2.41	–	2.68 d	7.22–7.72
12b	4.80 s	4.30 t	5.10 dd	4.42 dd	4.73 td		3.35–3.42 m	3.16	3.06	2.41	–	2.48 br d	7.22–7.77
13a	4.06 br s	–	2.19 dd	4.80 td	1.82–1.90 m	3.25 dd	3.19 dd	3.37	–	–	–	–	7.22–7.45
13b	4.83 d	–	2.16 ddd	4.66 t	1.82–1.90 m	3.60 dd	3.41 dd	3.17	–	–	–	–	7.20–7.46
14a[c]	4.27 s	–	2.30 dd	4.08 dd	1.99–2.04 m	4.09[d] dd	3.66[e] d	3.27	–	–	–	7.01 s	–
14b[f]	4.69 s	–	2.33 dd	3.86 t	1.97 dt	4.06 dd	3.68–3.75 m	3.36	–	–	–	7.11 s	–
14′a[c]	4.72 br s	–	2.23 dd	4.80 td	1.78–1.88 m		3.44–3.58 m	3.31	–	–	–	4.96 t	–
14′b[f]	5.02 br s	–	2.22 ddd	4.66 t	1.75–1.82 m	3.68–3.75 m	3.57–3.63 m	3.39	–	–	–	4.78 t	–
15b	4.98 d	4.68 dt	2.07 dt	3.92 t	1.17–1.25 m	3.79 dd	3.47 dd	3.09	–	–	–	3.89 d	7.21–7.50
16a	4.73 s	4.61 dd	2.00 ddd	4.29 td	1.29 tdd	4.19 dd	3.66 dd	3.37	–	–	–	3.14 (br s) 4.10 (br s)	–
16b	5.23 d	4.71 br t	1.98 ddd	3.97 dd	1.41 tdd	4.04 ddd	3.86 ddd	3.53	–	–	–	2.81 (dd) 3.18 (d)	–
(4*R*)-**17a**[g]	4.37 d	3.87 ddd	1.68 ddd	4.06 t	1.22–1.30 m	3.32 dd	2.81 dd	3.39	–	–	–	2.81 d	7.20–7.49
(4*S*)-**17a**	4.36 s	4.17 t	2.06 ddd	3.94 dd	1.09–1.13 m		3.33 dd	3.24	–	–	–	3.87 d	7.21–7.49
18a	4.90 d	4.12 m	1.73 ddd	4.12 m	1.28–1.35 m	3.71 dd	3.61 dd	3.49	–	–	–	1.7–1.8 (br m) 2.99 (d)	–
19a	4.63 d	–	2.12 t	4.62 ddd	1.84–1.88 dm	3.18 dd	3.07 dd	3.44	–	–	–	–	7.21–7.45
19b	4.64 d	–	2.03 td	4.54 dd	2.39–2.44 m	3.16 dd	3.07 dd	3.45	–	–	–	–	7.22–7.39

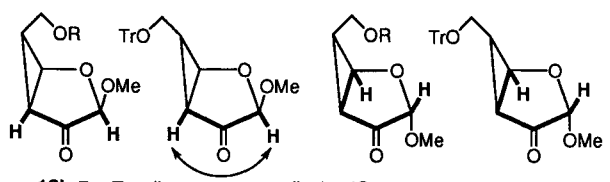
Table 2. (continued)

Product	H-1	H-2	H-3	H-4	H-5	H-6	H-6′	OCH_3 (s)	Ms (s)	CH_3 Ts (s)	Piv (s)	OH	Aromatic Protons (m)
20a	4.78 d	4.10 ddd	1.52–1.55 m	3.89 dd	1.05–1.09 dm	2.96 dd	2.83 dd	3.48	–	–	–	2.86 d	7.20–7.42
21a	4.79 d	4.11 ddd	1.57 ddd	3.91 dd	1.15 tdd	3.36–3.43 m		3.48	–	–	–	1.7–1.8 (br s) 2.97 (d)	–
22b	4.84 d	4.65 dt	1.65–1.68 m	3.83 dd	1.75–1.79 m	2.96 dd	2.81 dd	3.42	–	–	–	2.62 d	7.09–7.49
23b	4.87 d	4.67 dt	1.71 dt	3.85 dd	1.88 tdd	3.39–3.45 m	3.28–3.55 m	3.42	–	–	–	1.84 (br s) 2.87 (d)	–

[a] A "carbohydrate-like" numbering system (see **19a, b**) was adopted for **13–23**.
[b] The corresponding coupling constants were summarized in Table 1.
[c] A 9 : 1 equilibrated mixture of **14a** and **14′a** in DMSO-d_6.
[d] An *exo*-proton.
[e] An *endo*-proton.
[f] A 54 : 46 equilibrated mixture of **14b** and **14′b** in DMSO-d_6.
[g] A 74 : 26 mixture of (4*R*)- and (4*S*)-isomers.

yl ketone together with signals due to other protons (Tables 1 and 2).[10,11] The presence of a five-membered carbonyl group adjacent to the cyclopropane ring in each product was confirmed by its IR spectrum, which displayed an intense conjugated carbonyl absorption band[10,11,18] at 1750–1761 cm^{-1}.

To obtain more structural information on the bicyclic ketones, **13a,b** were deprotected with pyridinium *p*-toluenesulfonate (PPTS),[6,19] yielding crystalline compounds. On the basis of spectroscopic (IR, ^1H NMR, NOE) and analytical data for these products, it was concluded that the hygroscopic compound obtained from **13a** was a > 9:1 mixture of (1*R*,3*S*,4*S*,7*S*,8*S*)-4-hydroxy-3-methoxy-2,5-dioxatricyclo[3.3.0.$0^{1,7}$]octane **(14a)** and its keto form **14′a**, whereas the compound from **13b** was a (3*R*)-isomer **14b**. Compound **14b** showed mutarotation in DMSO to reach an equilibrium between the keto **(14′b)** and its internal hemiketal **(14b)** forms[20] at 20 °C within 6 hours. The presence of the two species was demonstrated clearly by the ^1H NMR of their equilibrated solution in DMSO-d_6; a ratio of **14b** to **14′b** was approximately 1:1. In the case of **14a**, neither mutarotation nor change in ^1H NMR was observed since a rapid equilibrium was attained before the beginning of the measurements (90 sec for rotation and 10 min for ^1H NMR). The ^1H NMR of an equilibrated solution of **14a** in DMSO-d_6 showed that a ratio of **14a** to **14′a** was 9:1. It is evident from these results that the trityloxymethyl side chain in **13a,b** disposed inside (*endo*) of the cyclopropyl keto framework. The observed long-range couplings (J, ~ 1.5 Hz)[21] between *cis*-1,3- **(13b, 14′b, 19b)** or *trans*-1,4-protons **(13a, 14′a, 19a)** (Scheme 3) and the downfield shifts (~ 0.8 ppm) of the signals due to H-4's



13b R = Tr **14′b** R = H (long-range coupling) **19b** **13a** R = Tr **14′a** R = H **19a**

Scheme 3

in **14′a,b** compared with **14a,b** also indicated the presence of the cyclopropyl ketone structure in these compounds.

Stereoselective reduction of **13b** and **19a,b** was carried out starting from **8b** and **12a,b**, respectively, by adding $NaBH_4$ to the corresponding cyclopropanation reaction mixture without isolation of the ketone to give alcohols **15b**, **20a**, and **22b** in 75–87% yields. On the other hand **13a** (from **7a**) gave an inseparable 74:26 mixture **(17a)** of (4*R*)- and (4*S*)-isomers in 85% combined yield.

Lastly, deprotection of **15b** with 80% acetic acid afforded an *endo*-hydroxymethyl diol **16b** in 80% yield. In a similar manner, epimers **17a** yielded a mixture of *endo*-diols **16a** and **18a**, which could be separated by chromatography. Upon treatment with 80% acetic acid, **20a** and **22b** also gave *exo*-diols **21a** and **23b** in good yields, respectively.

The configurations of the C-2 hydroxyl groups in **15–18** and **20–23** were determined by ^1H NMR spectroscopy. The compounds bearing *cis*-1,2 oriented functional groups showed relatively large values (4.3–6.5 Hz) of the couplings between H-1 and H-2, whereas the corresponding couplings for the ones having a *trans*-1,2 relationship were not observed in conformity with literature observations of methyl furanosides.[22] In addition, the signals attributable to H-2's in **17a** (4*R*), **18a**, **20a**, and **21a** were strongly shielded by the cyclopropane ring.[11] On the contrary, the signals due to H-5's in **22b** and **23b** were deshielded by their oxygen functions at C-1 and C-2. These observations fully supported the assigned structures.

In summary, we have developed a general procedure for the synthesis of the new methyl furanosides fused with a cyclopropane ring carrying a hydroxymethyl side chain by the one-pot 1,2-diol monosulfonate rearrangement–cyclopropanation reaction under simple and mild reaction conditions. In this reaction, there was no need for cumbersome preparation and isolation of an enolate species **(B)** used for the stepwise protocol.

Melting points were determined with a Yamato micro melting-point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. IR spectra were obtain-

ed with a Shimadzu FTIR-8100M spectrophotometer. ^{1}H NMR and NOE difference spectra were recorded on JEOL JNM-GX 400 (400 MHz) and 500 (500 MHz) spectrometers, respectively. Reactions were monitored by TLC on a HPTLC plate (silica gel 60 F_{254}, Merck). Detection of the TLC was done by UV (254 nm) or spraying the plates with a solution of MeOH–H_2SO_4–*p*-anisaldehyde (85:15:5, v/v/v), followed by heating them on an electric plate. Column chromatography was performed on silica gel 60 (70–230 mesh, Merck). Solvents were reagent grade and used without purification. Dry solvents were prepared over molecular sieves 4 Å. Compound **1** was purchased from Kyowa Junyaku Kogyo Co., Ltd. (Tokyo).

Methyl 5,6-*O*-Cyclohexylidene-3-*O*-mesyl-α- and -β-D-*allo*-furanosides (3a and 3b):
To a stirred mixture of **2**[15] (14.5 g, 40 mmol) and cyclohexanone (5 mL, 49 mmol) in MeOH (120 mL) was added H_2SO_4 (0.2 mL) and the mixture was gently refluxed at 80 °C (oil-bath temp.) for 2.5 h. Toluene (100 mL) was added and the mixture was cooled to r.t., and concentrated to ca. 60 mL below 40 °C in vacuo until the residue began to solidify. A solution of Et_3N (1.1 mL) in $CHCl_3$ (50 mL) was added and the mixture was diluted with $CHCl_3$ (450 mL), washed with sat. aq $NaHCO_3$ (100 mL) and then with H_2O (200 mL) and dried ($MgSO_4$). The solvents were removed by evaporation in vacuo and the residue was triturated in hot hexane (100 mL) and allowed to stand at r.t. for 4 h. The resulting undissolved materials were collected by filtration, washed with hexane (100 mL), and air-dried at r.t. to give an anomeric mixture of **3** (13.0 g, 92%). Recrystallization from a mixture of benzene (50 mL) and isopropyl ether (100 mL) gave **3b** (8.06 g, needles). The mother liquor was concentrated in vacuo and the residue was recrystallized from a mixture of benzene (10 mL) and isopropyl ether (50 mL) to afford **3a** (2.57 g, prisms). The physical properties (mp, optical rotation, and ^{1}H NMR) of **3a** and **3b** were almost identical with those published.[3]

Methyl 5,6-*O*-Cyclohexylidene-3-*O*-mesyl-2-*O*-pivaloyl-α- and -β-D-*allo*-furanosides (4a and 4b):
Pivaloyl chloride (3.7 mL, 30 mmol) was added to a stirred solution of **3a** or **3b** (3.52 g, 10 mmol) in dry pyridine (25 mL) at r.t. and the mixture was stirred at r.t. for 16 h. After cooling (5 °C), the mixture was quenched with crushed ice (ca. 10 mL) and H_2O (10 mL) and extracted with Et_2O (200 mL). The extract was washed successively with H_2O (80 mL), sat. aq $NaHCO_3$ (80 mL), and H_2O (80 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The pyridine was removed by repeated co-evaporation with toluene. The crude product was then chromatographed on silica gel (170 g) with $CHCl_3$–MeOH (100:0.2) as the eluent to give **4a** (3.9 g) or **4b** (4.0 g).

Methyl 3-*O*-Mesyl-2-*O*-pivaloyl-α- and -β-D-*allo*-furanosides (5a and 5b):
A stirred mixture of **4a** or **4b** (6.56 g, 15 mmol) in 70% AcOH (65 mL) was heated at 75 °C (oil-bath temp.) for 2 h, and H_2O (75 mL) was added. After cooling, the mixture was extracted several times with hexane–Et_2O (4:1, 4 × 75 mL), and the aqueous layer was concentrated at 45 °C in vacuo. The AcOH was removed by repeated co-evaporation with EtOH–toluene. The residue was chromatographed on silica gel (400 g). Elution with $CHCl_3$–MeOH (99:1) gave **5a** (4.2 g) or **5b** (4.53 g).

Methyl 3-*O*-Mesyl-2-*O*-pivaloyl-6-*O*-trityl-α- and -β-D-*allo*-furanosides (6a and 6b):
Trityl chloride (6.98 g, 25 mmol) was added to a stirred solution of **5a** or **5b** (3.56 g, 10 mmol) in a mixture of dry CH_2Cl_2 (35 mL) and dry Et_3N (8 mL). The mixture was refluxed for 70 min with stirring. After cooling (15 °C), MeOH (10 mL) was added and the mixture was stirred at r.t. for 30 min and diluted with Et_2O (100 mL). The solution was washed with H_2O (3 × 50 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (400 g) with $CHCl_3$–MeOH (100:0.3) as the eluent to give **6a** (5.4 g) or **6b** (5.15 g).

Methyl 3-*O*-Mesyl-2-*O*-pivaloyl-5-*O*-tosyl-6-*O*-trityl-α- and -β-D-*allo*-furanosides (7a and 7b):
Tosyl chloride (9.55 g, 50 mmol) was added to a stirred solution of **6a** or **6b** (6.0 g, 10 mmol) in dry pyridine (45 mL) at r.t. and the mixture was heated at 50 °C (oil-bath temp.) for 64 h with stirring. After cooling (5 °C), the mixture was quenched with crushed ice (ca. 20 mL) and extracted with Et_2O (200 mL). The extract was washed successively with H_2O (80 mL), sat. aq $NaHCO_3$ (2 × 80 mL), and H_2O (80 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The pyridine was removed by repeated co-evaporation with toluene. The crude product was then chromatographed on silica gel (200 g) with hexane–EtOAc (9:1, 8:2, and then 7:3) as the successive eluents to give **7a** (6.1 g) or **7b** (6.43 g).

Methyl 3-*O*-Mesyl-5-*O*-tosyl-6-*O*-trityl-α- and -β-D-*allo*-furanosides (8a and 8b) and Their Respective L-Isomers (12b and 12a):
A solution of KOH (280 mg, 5 mmol) in MeOH (2.5 mL) was added to an ice-cooled and stirred solution of **7a**, **7b**, **11a**, or **11b** (1.51 g, 2 mmol) in a mixture of THF (4 mL) and MeOH (4 mL). After the mixture had been stirred at 5 °C for 1.5 h (for **7a** or **11a**), 3 h (for **7b**), or 5 h (for **11b**), $CHCl_3$ (75 mL) was added and the solution was washed with H_2O (3 × 15 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (100 g) with $CHCl_3$–MeOH (100:0.1) as the eluent to give **8a** (1.29 g), **8b** (1.04 g), **12a** (1.23 g), or **12b** (1.18 g).

Methyl 5-*O*-Acetyl-3-*O*-mesyl-2-*O*-pivaloyl-6-*O*-trityl-α- and -β-L-*tallo*-furanosides (9b and 9a):
A stirred suspension of **7a** or **7b** (3.01 g, 4 mmol) and NaOAc (3.28 g, 40 mmol) in a mixture of dry DMF (40 mL) and dry DMSO (20 mL) was heated at 130 °C (oil-bath temp.) for 2.5 h (for **7a**) or 16 h (for **7b**). After cooling (5 °C), crushed ice (ca. 100 mL) and H_2O (100 mL) were added and the mixture was extracted with Et_2O (400 mL). The water layer was then extracted with Et_2O (3 × 200 mL) and the combined extracts were washed with H_2O (3 × 60 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (200 g) with hexane–EtOAc (8:2) as the eluent to give **9a** (1.26 g) or **9b** (1.75 g).

Methyl 3-*O*-Mesyl-2-*O*-pivaloyl-6-*O*-trityl-α- and -β-L-*tallo*-furanosides (10b and 10a):
A mixture of Mg turnings (480 mg, 20 mmol) and MeOH (20 mL) was stirred for 40 min at r.t. under a dry N_2 atmosphere and the resulting solution of $Mg(OMe)_2$ was diluted with benzene (4 mL). A solution of **9a** or **9b** (2.57 g, 4 mmol) in benzene (12 mL) was added and the mixture was stirred at r.t. for 3 h. After cooling (5 °C), Celite (6 g) and cold H_2O (10 mL) were added with vigorous stirring. The mixture was diluted with $CHCl_3$–MeOH (9:1, 40 mL) and the suspension was filtered through a Celite pad and washed with the same solvents (200 mL). The combined filtrates were concentrated in vacuo and the water was removed by co-evaporation with EtOH. The residue was chromatographed on silica gel (200 g) with hexane–EtOAc (85:15 and then 7:3) as the successive eluents to give **10a** (1.78 g) or **10b** (2.09 g). For analytical purposes a quantity of **10** was purified by silica gel column chromatography using $CHCl_3$–MeOH (100:0.3) as the eluent.

Methyl 3-*O*-Mesyl-2-*O*-pivaloyl-5-*O*-tosyl-6-*O*-trityl-α- and -β-L-*tallo*-furanosides (11b and 11a):
Tosyl chloride (1.9 g, 9.9 mmol) was added to a stirred solution of **10a** or **10b** (1.15 g, 1.9 mmol) in dry pyridine (12 mL) at r.t. and the mixture was heated at 50 °C (oil-bath temp.) for 15 h (for **10a**) or 22 h (for **10b**) with stirring. After cooling (5 °C), the mixture was quenched with crushed ice (ca. 10 mL) and extracted with Et_2O (100 mL). The extract was washed successively with H_2O (20 mL), sat. aq $NaHCO_3$ (20 mL), and H_2O (20 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The pyridine was removed by repeated co-evaporation with toluene. The residue was then chromatographed on silica gel (60 g) with hexane–EtOAc (85:15) as the eluent to give **11a** (1.26 g) or **11b** (1.34 g).

(1*R*,3*S* and *R*,5*S*,6*S*)-3-Methoxy-6-trityloxymethyl-2-oxabicyclo[3.1.0]hexan-4-ones (13a and 13b) and Their Respective (6*R*)-Isomers (19a and 19b):

With $Mg(OMe)_2$. A freshly prepared solution of $Mg(OMe)_2$ (4.6 mmol) in MeOH (5 mL) was diluted with benzene (2 mL). A solution of **8a**, **8b**, **12a**, or **12b** (155 mg, 0.23 mmol) in benzene (1.5 mL) was added at r.t. under a dry N_2 atmosphere with stirring. The mixture was heated at 50 °C (for **8b**, **12a**, **12b**) or 60 °C (for **8a**) for 10 min (for **12b**), 18 min (for **8a**, **8b**), 25 min (for **12a**), immediately after which it was cooled to 5 °C. Celite (1.5 g) and cold H_2O (0.5 mL) were added with vigorous stirring. The mixture was diluted with $CHCl_3$–MeOH (9:1, 10 mL) and the suspension was filtered through a Celite pad and washed with the same solvent system (30 mL). The combined filtrates were concentrated below 30 °C in vacuo and the water was removed by evaporation with EtOH. The residue was chromatographed on silica gel (50 g) with hexane–EtOAc (95:5 and then 7:3) as the successive eluents to afford **13a** (58 mg), **13b** (64 mg), **19a** (78 mg), or **19b** (64 mg).

With KOH. A solution of KOH (140 mg, 2.5 mmol) in MeOH (1 mL) was added to a stirred solution of **7a** (188 mg, 0.25 mmol) in a mixture of THF (0.5 mL) and MeOH (2.5 mL) at r.t. and the mixture was heated at 50 °C for 30 min. After cooling (5 °C), a solution of AcOH (90 mg) in MeOH (0.5 mL) was added and the mixture was diluted with Et_2O (70 mL), washed with H_2O (3 × 5 mL), and dried ($MgSO_4$). The solvents were removed by evaporation below 30 °C in vacuo. The residue was chromatographed on silica gel (50 g) with hexane–EtOAc (95:5 and then 7:3) as the successive eluents to give **13a** (83 mg).

(1*R*,3*S*,4*S*,7*S*,8*S*)-4-Hydroxy-3-methoxy-2,5-dioxatricyclo-[3.3.0.0^{1,7}]octane (14a):

To a stirred solution of **13a** (800 mg, 2 mmol) in a mixture of $CHCl_3$ (9 mL) and MeOH (3 mL) was added PPTS (1.51 g, 6 mmol) and the mixture was stirred at r.t. for 66 h. After cooling (5 °C), Et_3N (1.7 mL, 12 mmol) was added and the mixture was concentrated below 30 °C in vacuo. The residue was chromatographed on silica gel (60 g) using hexane–EtOAc (6:4) as the eluent to give hygroscopic **14a** (260 mg), which contained a small amount (< 10%) of (1*R*,3*S*,5*S*,6*S*)-6-hydroxymethyl-3-methoxy-2-oxabicyclo[3.1.0]hexan-4-one (**14'a**), judging from the IR and ^{1}H NMR spectroscopic analyses.

(1*R*,3*R*,4*S*,7*S*,8*S*)-4-Hydroxy-3-methoxy-2,5-dioxatricyclo-[3.3.0.0^{1,7}]octane (14b):

A solution of **13b** (292 mg, 0.73 mmol) and PPTS (552 mg, 2.2 mmol) in a mixture of $CHCl_3$ (4.5 mL) and MeOH (1.5 mL) was treated as described for the synthesis of **14a**. The crude product was chromatographed on silica gel (80 g) with hexane–EtOAc (6:4) as the eluent to give **14b** (92 mg).

(1*R*,3*R*,4*S*,5*R*,6*S*)-4-Hydroxy-3-methoxy-6-trityloxymethyl-2-oxabicyclo[3.1.0]hexane (15b) and the Corresponding (3*S*,4*R*,6*R*)- and (6*R*)-Isomers (20a and 22b):

A solution of **8b**, **12a**, or **12b** (335 mg, 0.5 mmol) in benzene (3 mL) was treated with $Mg(OMe)_2$ (10 mmol) as described for the synthesis of **13b** or **19a,b**. After completion of the reaction, the mixture was cooled to 5 °C and $NaBH_4$ (76 mg, 2 mmol) was added. The mixture was stirred at 5 °C for 10 min and quenched with acetone (1 mL). Celite (3 g) and cold H_2O (1 mL) were added with vigorously stirring. The mixture was diluted with $CHCl_3$–MeOH (9:1, 20 mL) and the suspension was filtered through a Celite pad and washed with the same solvents (60 mL). The combined filtrates were diluted with $CHCl_3$ (40 mL) and washed with H_2O (3 × 10 mL) and dried ($MgSO_4$). The solvents were removed below 30 °C in vacuo and the residue was chromatographed on silica gel (50 g) with hexane–EtOAc (9:1, 8:2, and then 7:3) as the successive eluents to give **15b** (150 mg), **20a** (170 mg), or **22b** (175 mg).

(1*R*,3*S*,4*RS*,5*R*,6*S*)-4-Hydroxy-3-methoxy-6-trityloxymethyl-2-oxabicyclo[3.1.0]hexane (17a):

A solution of **7a** (188 mg, 0.25 mmol) in a mixture of THF (0.5 mL) and MeOH (2.5 mL) was treated with a solution of KOH (140 mg, 2.5 mmol) in MeOH (1 mL) as described for the synthesis of **13a** with KOH. After addition of a solution of AcOH (90 mg) in MeOH (0.5 mL), the mixture was diluted with MeOH (3 mL). To this cooled mixture was added $NaBH_4$ (38 mg, 1 mmol) and the mixture was stirred at 5 °C for 15 min. Another portion of $NaBH_4$ (19 mg, 0.5 mmol) was added and the stirring was continued for another 40 min. The mixture was quenched with acetone (0.4 mL), diluted with Et_2O (60 mL), washed with H_2O (3 × 5 mL), and dried ($MgSO_4$). The solvents were removed by evaporation in vacuo. The residue was chromatographed on silica gel (40 g) with hexane–EtOAc (9:1, 8:2, and then 7:3) as the successive eluents to give a 74:26 mixture [**17a** (86 mg)] of (4*R*)- and (4*S*)-isomers.

(1*R*,3*R*,4*S*,5*R*,6*S*)-4-Hydroxy-6-hydroxymethyl-3-methoxy-2-oxabicyclo[3.1.0]hexane (16b) and Its (3*S*,4*R*,6*R*)- and (6*R*)-Isomers (21a and 23b):

To a solution of **15b**, **20a**, or **22b** (177 mg, 0.44 mmol) in AcOH (1.2 mL) was added H_2O (0.28 mL) and the mixture was stirred at r.t. for 7 h. The resulting crystals were removed by filtration and washed with H_2O (5 mL). The combined filtrate and washings were diluted with H_2O (5 mL) and extracted with hexane–Et_2O (1:1, 2 × 25 mL). The water layer was concentrated in vacuo and AcOH was removed by repeated co-evaporation with EtOH. The residue was chromatographed on silica gel (26 g) with $CHCl_3$–MeOH (98:2) as the eluent to provide **16b** (56 mg), **21a** (61 mg), or **23b** (53 mg).

(1*R*,3*S*,4*S* and *R*,5*R*,6*S*)-4-Hydroxy-6-hydroxymethyl-3-methoxy-2-oxabicyclo[3.1.0]hexanes (16a and 18a):

To a solution of **17a** (370 mg, 0.92 mmol) in AcOH (2.5 mL) was added H_2O (0.6 mL) and the mixture was stirred at r.t. for 7 h. The resulting crystals were removed by filtration and washed with H_2O (10 mL). The combined filtrate and washings were diluted with H_2O (10 mL) and extracted with hexane–Et_2O (1:1, 2 × 50 mL). The water layer was concentrated in vacuo and AcOH was removed by repeated co-evaporation with EtOH. The residue was chromatographed on silica gel (60 g) using hexane–EtOAc (3:7) and then hexane–EtOAc–MeOH (3:7:0.2) as the successive eluents to give **16a** (32 mg) and **18a** (97 mg).

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