Carbohydrate Research, 146 (1986) 160–166
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

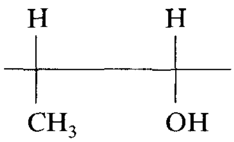
Ring-opening reactions of some branched-chain anhydro sugars using hydride and azide as nucleophiles*

NOBUYA KAWAUCHI, HIRONOBU HASHIMOTO, AND JUJI YOSHIMURA

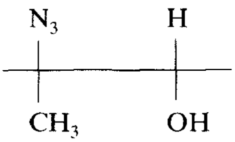
Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Nagatsuta, Midoriku, Yokohama 227 (Japan)

(Received January 28th, 1985; accepted for publication, May 18th, 1985)

Ring-opening reactions of five branched-chain anhydro sugars (**1**[2], **3**[1], **4**[1], **6**[1], and **9**[1]) with lithium aluminium hydride and tetraethylammonium azide were examined to construct such branched-chain structures as A and B in the hexopyranoside system. The former structure is often encountered in the skeleton of such natural products as[3] macrolides and ansa compounds, while the latter can be readily converted into branched-chain sugars, such as[4] vancosamine and evernitrose, having amino or nitro group at the branching carbon atom. The branched-chain anhydro sugars used in this study, except **3**, have conformations that favor attack of the nucleophile at the branching carbon atom, if the *trans*-diaxial ring-opening follows the stereoelectronic rationale of the so-called Fürst–Plattner rule[5].

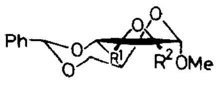


A

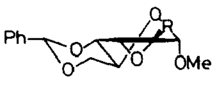


B

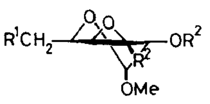
The anhydro sugars **4**, **6**, and **9** were treated with lithium aluminium hydride



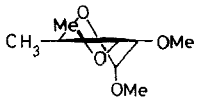
1 R^1=Me, R^2=H
2 R^1=R^2=H
3 R^1=H, R^2=Me



4 R=Me
5 R=H



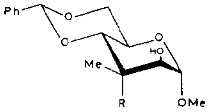
6 R^1=OBn, R^2=Me
7 R^1=OH, R^2=H
8 R^1=R^2=H



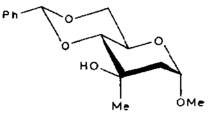
9

---

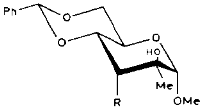
*Branched-chain sugars, Part XXXVIII. For Part XXXVII, see, ref. 1



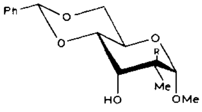
10 R = H
11 R = N_3



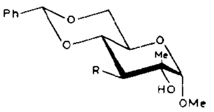
12



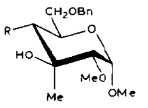
13 R = H
14 R = N_3



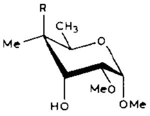
15 R = H
16 R = N_3



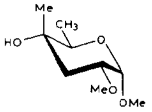
17 R = H
18 R = N_3



19 R = H
20 R = N_3



21 R = H
22 R = N_3



23

under the same condition as previously reported[2] for **1** (in boiling 1,4-dioxane). The results are summarized in Table I together with the observed data. The structures of the ring-opening products were determined from the ^{1}H-n.m.r. data (Table II). Both conformationally rigid 2,3-anhydro sugars (**1** and **4**) gave two isomers (**10** and **12**, and **15** and **17**, respectively), with slight predominance of the former, that is, the products of diaxial ring-opening. These results, when compared with those reported for the analogous anhydro sugars (**2** and **5**)[6] lacking the methyl branch, indicate that introduction of methyl branch onto the oxirane ring retards the nucleophilic attack of hydride at the branching carbon atom. This tendency became more clear with the conformationally more-flexible 3,4-anhydro sugars (**6** and **9**), which give almost exclusively the anti-Fürst–Plattner products (**19** and **23**), respectively. Because analogs of **6** such as **7** (ref. 7) and **8** (ref. 8) have been reported to give mainly the dixial ring-opening products, this tendency to give the diequatorial products despite the stereoelectronic effect is noteworthy. In contrast, the reactions of **3**, where the stereoelectronic effect favors the less sterically hindered, secondary carbon atom, showed an apparent regioselectivity to give exclusively the 3-substituted products (**13** and **14**, respectively), as shown in Table I. In this case, the stereoelectronic effect also favors attack of the nucleophile at the secondary carbon atom.

For azidolysis of the branched-chain anhydro sugar **4**, the conventional method using sodium azide and ammonium chloride in boiling 2-methoxyethanol–water was not efficient. After 4 days, only 30% of azidolysis product (**16**, 19% and **18**, 11%) was obtained and most of the **4** was recovered (65%). However, azidolysis with tetraethylammonium chloride present in *N,N*-dimethylformamide[9] proved to be much more efficient. The azidolysis of **4** for 4 days at 95° gave **16** and **18** in 69 and 22% yields, respectively. The azidolysis products of other branched-chain anhydro sugars (**1**, **6**, and **9**) under similar conditions are also summarized in Table I. The stereochemistry of the products could be established by ^{1}H-n.m.r. data and by selective acetylation of the secondary hydroxyl group. Here again, the attack of azide ion at the branching carbon atom proved to be more or less hindered

TABLE I

RING-OPENING REACTIONS OF BRANCHED-CHAIN ANHYDRO SUGARS

Anhydro sugars	*Nucleophiles*	*Solvents*	*Temperature and reaction time*	*Products (%)*				*Recovered (%)*	
				Diaxial[a]		*Diequatorial*[b]			
1	$LiAlH_4$	1,4-Dioxane	reflux, 6 h	**10**	47[c]	**12**	40[c]		
	Et_4NN_3[d]	DMF	90°, 5 d	**11**	55		[e]	**1**	41
3	$LiAlH_4$	1,4-Dioxane	reflux, 8 h	**13**	49		[e]		
	Et_4NN_3	DMF	90°, 4 d	**14**	91		[e]		4.2
4	$LiAlH_4$	1,4-Dioxane	reflux, 8 h	**15**	48	**17**	37		
	NaN_3 (NH_4Cl)	ME[f]-H_2O	reflux, 4 h	**16**	19	**18**	11	**4**	65
	Et_4NN_3	DMF	95°, 4 d	**16**	69	**18**	22	**4**	1.6
6	$LiAlH_4$	1,4-Dioxane	reflux, 8 h		[e]	**19**	80		
	Et_4NN_3	DMF	65°, 2 d		[e]	**20**	44	**6**	44
9	$LiAlH_4$	1,4-Dioxane	reflux, 8 h	**21**	3.9	**23**	86		
	Et_4NN_3	DMF	65°, 2 d	**22**	61(84)[g]		[e]		

[a] Diaxial ring-opening product (Furst–Plattner product). [b] Diequatorial ring-opening product (anti-Fürst–Plattner product). [c] Lit. 2. [d] Prepared *in situ* from tetraethylammonium chloride and sodium azide. [e] Not detected. [f] 2-Methoxyethanol. [g] Isolated as the acetate.

TABLE II

^{1}H-N M R DATA^a OF REACTION PRODUCTS AT 100 MHz IN $CDCl_3$

Compounds	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*		*C-CMe*	*O-Me*	*Ph-CH*	*Ph*	*Others*
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6}$	$J_{6,6'}$	$J_{CH,Me}$				
11^b	4 29d	3 30bs	—	3.46d	3.92–4 46m (2 H)		3.60t	1.38t	3 07s	5 24s	7.3–7.5m	
	1.6	—	—	10 0	^{c}	8.2	8 2					
2-Acetate	4 49bs	5 05bs	—	3.65d	4.38m	4 11dd	3 45t	1 22s	3.02s	5 25s	7 3–7 6m	1.57s (OAc)
of **11**	0	—	—	9.6	4 2	10 0	10 0					
13	4 33bs	—	1 9–2 1m (2 H)	3 8–4 1m (4 H)				1.29s	3 47s	5 60s	7 3–7 6m	
	—	—	^{c}	^{c}	^{c}	^{c}	^{c}					
14^b	3 98s	—	3 46d	3 9–4 4m (3 H)			3 54t	1 14s	3.00s	5 34s	7.0–7 7m	
	—	—	3 8	^{c}	^{c}	9 8	9 8	—				
15	4 60d	2.02ddq	4 03m	3.59dd	3 97m	4 28m	3 80t	1 16d	3.46s	5 64s	7 3–7.64m	2 86bd (OH)
	4 6	7 4	3 8	9 8	^{c}	9 6	9 6	7 8				
16	4 42d	—	3 83dd	4 35dd	3 72–4 00m	3 94–4 28m		1 52s	3 44s	5 63s	7.3–7.6m	
	$J_{1,3}$ 1.2	—	3 6	8.0	^{c}	^{c}	^{c}	—				
3-Acetate	4 16s	—	5 52d	3 96dd	4 09m	4 28dd	3.54t	1.17s	2 95s	5 28s	7 3–7.5m	1.68s (OAc)
of **16**	—	—	3 6	10 0	4 4	9 4	9 4	—				
17	4 31s	—	ax 1 93t	3 56–4 03m (3 H)			4 28m	1 37s	3 47s	5.52s	7 26–7 6m	
			eq 2 10dd									
	—	—	4 8	^{c}	^{c}	^{c}	^{c}	—				
18^b	4 04s	—	3 65d	3 23dd	3 52m	4 03dd	3.33t	1 28s	2 85s	5 17s	7 3–7 6m	
	—	—	9 6	10 0	4 2	9 8	9 8	—				
19	4 96d	3 32d	—	1.75bd (2 H)	3.95m	3.57s (2 H)		1 44s	3 46s	—	7 42bs	4 62s (2 H) (PhCH$_2$)
	3.8	—	—	6.4	^{c}	^{c}	^{c}	—	3.55s			
20	4.96d	3 38d	—	3.4m (2 H)		3 47ABq		1.40s	3 43s	—	7 36bs	3 65ABq (PhCH$_2$)
	3 9	—	—	^{c}	^{c}	—	6.9	—	3 55s			
21	4 98d	3 9–4 1m		2 34m	4 18m	1 21d (3 H)		1 23d	3 49s (6 H)	—	—	
	4 0	^{c}	^{c}	2 2	7 6	—	—	8.0				
22	4 84dd^d	3 66t	3 82dd	—	3 97q	1 24d (3 H)		1 40s	3 43s	—	—	
	2 9	2 9	—	—	6.6	—	—	—	3 47s			
3-Acetate	4 77d	3 67dd	5 36b	—	3 97q	1 21d (3 H)		1 24s	3 42s (6 H)	—	—	2 13s (OAc)
of **22**	4.4	3 7	—	—	6 4	—	—	—				
3-Acetate	4.61d	3 56t	5 42d	—	3.96q	1 05d (3 H)		0 94s	3 11s	—	—	1 90s (OAc)
of **22**^{b}	4 0	4.0	—	—	7 6	—	—	—	3 16s			
23	4 75d	3 34m	ax 1 94	—	3 72q	1 18d (3 H)		1.23s	3 44s	—	—	
			eq 1 75					3 49s				
	3 8	^{e}	—	—	6 6	—	—	—				

^{a}Chemical shifts in δ and coupling constants in Hz Abbreviations b, broad, d, doublet, m, multiplet, q, quartet; s, singlet, t, triplet ^{b}Measured in C_6D_6 ^{c}Could not be analyzed $^dJ_{1,3}$ 0 9 $^eJ_{2,3a}$ 6 2, $J_{2,3e}$ 3 8, $J_{3a,3e}$ 12 0

TABLE III

PHYSICAL PROPERTIES AND ANALYTICAL DATA OF THE PRODUCTS

Products	*m.p.* °*C*	$[\alpha]_D$(c) *degrees*	*Found (%)*			*Calc. (%)*			*Eluants for column chromatography*[a]
			C	*H*	*N*	*C*	*H*	*N*	
11[b]	123.5–124	+41.8(1.3)	56.26	5.85	13.25	56.06	5.96	13.08	H:A = 6:1
2-Acetate of **11**	syrup	+44.6(0.86)	56.16	5.93	11.77	56.19	5.83	11.57	
13	syrup	+148.9(0.86)	64.28	7.34	—	64.27	7.19	—	H:E = 9:1
14[b]	142–143	+99.5(0.76)	55.94	6.06	13.02	56.06	5.96	13.08	B:H:A = 7:2:1
15	syrup	+127.4(1.4)	63.99	7.16	—	64.27	7.19	—	H:T:A = 14:4:1
17	syrup	+109.1(1.5)	64.35	7.22	—	64.27	7.19	—	
16[b]	172.5–173	+26.1(0.87)	56.32	5.95	12.92	56.06	5.96	13.08	H:E = 6:1
18[b]	syrup	+124.7(3.3)	56.34	6.09	13.14	56.06	5.96	13.08	
3-Acetate of **16**	syrup	+29.0(1.6)	56.19	5.83	11.68	56.19	5.83	11.57	
19	syrup	+78.0(0.71)	64.61	7.87	—	64.84	8.16	—	H:A = 7:3
20[b]	syrup	+26.7(0.61)	57.03	6.65	12.31	56.96	6.87	12.46	H:E = 4:1
21	syrup	+12.2(0.55)	56.84	9.78	—	56.82	9.54	—	H:E = 8:1
23	syrup	+109.5(1.1)	56.70	9.33	—	56.82	9.54	—	
22	syrup	+112.8(0.61)	47.42	6.38	18.55	47.15	6.60	18.33	
3-Acetate of **22**	syrup	+146.6(0.35)	48.71	6.28	15.58	48.70	6.32	15.49	

[a] A, acetone, B, benzene, E: ethyl acetate, H: hexane, T: toluene. [b] I.r. absorption (cm^{-1}) for azido group: **11**, 2200; **14**, 2210, **18**, 2220, **20**, 2200, 3-acetate of **22**, 2210.

by the introduction of a methyl branch in comparison with the results of the analogous anhydro sugars lacking the methyl branch **2** (ref. 10), **5** (ref. 10), and **8** (ref. 11). An interesting difference in regioselectivity was observed in the reaction of **9**, and may be attributed to the difference in effective bulkiness of the azide and aluminum hydride ions. Thus the stereoelectronic effect controls the regioselectivity more effectively in the reaction of the branched-chain anhydro sugars with azide than with hydride, whereas in the case of **6**, diequatorial ring-opening occurred exclusively for both nucleophiles.

EXPERIMENTAL

General methods. — These were the same as previously described[1]. ^{1}H-N.m.r. data and physical properties of the products described here are summarized in Tables II and III, respectively.

Reaction of the branched-chain sugars with lithium aluminium hydride. — To a solution of a branched-chain sugar (1.5 mmol) in 1,4-dioxane (10 mL) was added lithium aluminium hydride (6.0 mmol), and the suspension was boiled under reflux for 8 h. The mixture was poured into water and the precipitate was filtered off. The filtrate was extracted with dichloromethane, and the extract was washed with water and evaporated. The residue was either fractionated or purified on a column of silica gel to give one or a mixture of two deoxy branched-chain sugars. The deoxy branched-chain sugar was acetylated conventionally with acetic anhydride in pyridine overnight at room temperature.

Reaction of the branched-chain sugar with tetraethylammonium azide. — To a solution of a branched-chain sugar (1 mmol) in *N,N*-dimethylformamide (1 mL) was added sodium azide (10 mmol) and tetraethylammonium chloride (5 mmol), and the suspension was heated at the temperature given in Table I for a few days. The reaction was poured into water and extracted with dichloromethane. The extract was processed as already described. The branched-chain azido sugar was acetylated as already described.

Reaction of **4** *with sodium azide.* — To a solution of **4** (150 mg, 0.55 mmol) in 2-methoxyethanol–water (19:1, 2.5 mL) was added sodium azide (150 mg, 2.7 mmol) and ammonium chloride (60 mg, 1.1 mmol), and the mixture was boiled under reflux for 4 days. The residue obtained by evaporation of the mixture was fractionated on a column of silica gel to give **16, 18**, and unreacted **4**.

REFERENCES

1 J. Yoshimura, N. Kawauchi, T. Yasumori, K. Sato, and H. Hashimoto, *Carbohydr. Res.*, 133 (1984) 255–274.

2 M. Funabashi, N. Hong, H. Kodama, and J. Yoshimura, *Carbohydr. Res.*, 67 (1978) 139–145.

3 S. Hanessian, *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon Press, Oxford, 1983, pp. 239–278.

4 J. Yoshimura, *Adv. Carbohydr. Chem. Biochem.*, 42 (1984) 69–134.

5 N. R. Williams, *Adv. Carbohydr. Chem. Biochem.*, 25 (1970) 109–179.

6 D. A Prins, *J. Am. Chem. Soc.*, 70 (1948) 3955–3957

7 K. Čapel, J Nemec, and J. Jary, *Collect. Czech Chem. Commun* , 33 (1968) 1758–1767.

8 E J. Hedgley, R A. C. Rennie, and W. G. Overend, *J. Chem. Soc.*, (1963) 4701–4711

9 S. Hanessian and J Vatele, *Tetrahedron Lett* , 22 (1981) 3579–3582

10 R. D. Guthrie and D Murphy, *J Chem. Soc.*, (1963) 5288–5294.

11 K. Čapek and J Jary, *Collect. Czech Chem. Commun* , 31 (1966) 2558–2564