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Definitive Synthesis of Methyl α-kedarosaminide, a Sugar Component of the Antitumor Antibiotic Kedarcidin+

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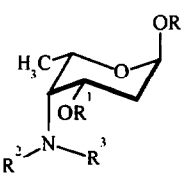
Abstract: The first definitive synthesis and physical data of the α-methyl glycoside (methyl α-kedarosaminide **2**) of kedarosamine (**1**), the aminodeoxy sugar component of the antibiotic kedarcidin is presented.

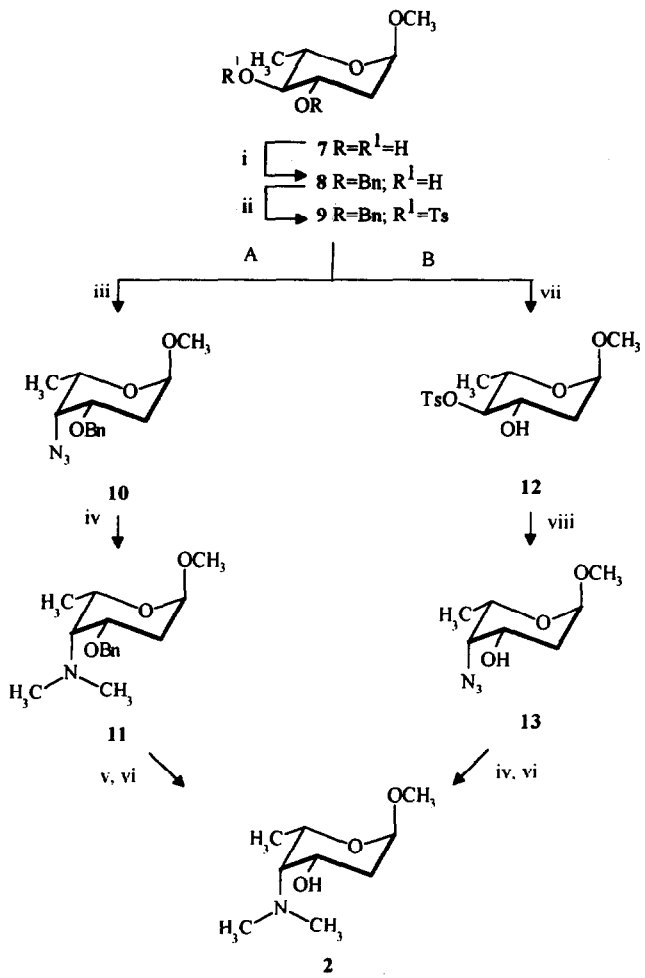
Kedarosamine (**1**), a most recently discovered representative of the naturally occurring aminodeoxy sugars, has been isolated[1] as an anomeric mixture of the α- and β-methyl glycosides[2] (now called methyl α- and β-kedarosaminide, respectively) from the antitumor chromoprotein antibiotic kedarcidin. On the basis of NMR and X-ray studies[1] kedarosamine (**1**) has been identified as 4-(dimethylamino)-2,4,6-trideoxy-L-*lyxo*-hexopyranose, i.e. a structural isomer of L-rhodosamine[3], which is the aminosugar moiety of several members of the anthracycline-glycoside antibiotic family.



1 R=R^1=H; R^2=R^3=CH_3
2 R^1=H; R=R^2=R^3=CH_3
3 R=R^1=R^2=H; R^3=$COCF_3$
4 R=Bn; R^1=R^2=H; R^3=Ts
5 R=R^1=CH_3; R^2=R^3=H
6 R=R^1=CH_3; R^2=H; R^3=Ac

A few derivatives (**3-6**) of the parent aminosugar (4-amino-2,4,6-trideoxy-L-*lyxo*-hexopyranose) have been prepared both from carbohydrates[4] and non-sugar precursors[5,6]. The present report describes the definitive synthesis of methyl α-kedarosaminide(**2**), starting from methyl 2,6-dideoxy-α-L-*arabino*-hexopyranoside (**7**), a common intermediate of the syntheses[7] of numerous antibiotic aminodeoxy sugars.

*Dedicated to the 80th birth anniversary of the late Professor Rezső Bognár



i. 1. Bu_2SnO, in toluene, 6 hrs, rt; 2. BnBr, Bu_4NI, in toluene, 24 hrs, rt (See Ref. 8.)
ii. TsCl, in abs. pyr., 48 hrs, 25 °C
iii. NaN_3, in HMPA, 18 hrs, 100 °C
iv. 10 % Pd/C, H_2, 25 : 1 MeOH-HCHO
v. 10 % Pd/C, H_2, 8 : 2 H_2O-AcOH
vi. column chromatography: Silica Gel 60 (0.063-0.2), 10 : 2 : 0.2 CH_2Cl_2-CH_3COCH_3-NH_4OH
vii. 10 % Pd/C, H_2, 8 : 2 MeOH-AcOH
viii. NaN_3, in DMSO, 3 hrs, 130 °C

By means of the stannilydene-acetal protocol[8] **7** was converted into the known 3-O-benzyl ether **8**. Subsequent tosylation readily afforded the crystalline 4-O-tosylate **9**[9], whose enantiomer was similarly synthesized by Binkley et al[10]. Azide displacement of **9** furnished the C-4 azidosugar **10**[11] which was then subjected to reductive methylation. Although under these conditions the azido group of **10** could be conveniently

converted into a dimethylamino function, to obtain **11**[12], simultaneous removal of the 3-O-benzyl protection failed. To overcome these difficulties, in parallel experiments **9** was smoothly debenzylated upon catalytic hydrogenation and the resulting **12** was converted into the azide **13**. Finally, the target methyl α-kedarosaminide (**2**) was obtained either from **11** or **13** by means of hydrogenation under slightly acidic conditions and reductive methylation, respectively. The overall yield of reaction route B (37 %) was more than twice as high as that of route A (15 %).

The obtained EI-MS data[15] and ^{1}H- and ^{13}C-NMR parameters (Table 1.) clearly proved that the constitution, conformation and the glycosidic linkage of the amino sugar component of the antibiotic kedarcidin correspond to structure **2**. The specific optical rotation value of the natural (isolated) sample was not given by Leet et al.[1] We found for the extremely volatile "synthetic" **2** $[\alpha]_D^{22} = -149.5°$ (c= 1.04 $CHCl_3$).

Table 1. ^{1}H and ^{13}C-NMR Data of Methyl α-L-Kedarosaminide
/coupling constants (Hz) are given in parenthesis/

Sugar carbons	^{13}C-NMR (ppm)		Sugar protons	^{1}H-NMR (ppm)		
	Natural sample[a]	**2**[b]		Natural sample[a]	**2**[b]	
$O\underline{C}H_3$	54.9	54.94	$OC\underline{H}_3$	3.30	3.33	
C-1	97.9	97.98	H-1	4.80	4.83	($J_{1,2}$=$J_{1,2e}$ 3)
C-2	35.5	35.66	H-2 (ax)	1.76	1.79	($J_{2a,3}$ 10, $J_{2e,2a}$ 14)
			H-2 (eq)	1.90	1.94	($J_{2e,3}$ 6)
C-3	63.3	63.47	H-3	3.93	3.97	($J_{3,4}$ 6)
C-4	63.8	64.10	H-4	2.48	2.54	($J_{4,5}$ 3)
C-5	67.6	67.69	H-5	4.10	4.13	($J_{5,6}$ 7)
C-6	18.0	18.04	H-6	1.40	1.43	
$N(\underline{C}H_3)_2$	44.8	44.88	$N(C\underline{H}_3)_2$	2.59	2.64	

(a) See Ref. 1.. (b) Recorded at 25 °C in $CDCl_3$ (200/50.3 MHz)

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9. Each new compound gave satisfactory elemental analyses. Selected physical and spectral data for **9**: m.p. 72-73 °C, $[\alpha]_D^{25}$ -69° (*c*, 0.76, $CHCl_3$), δ_H ($CDCl_3$) 1.32 (3H, d, $J_{5,6}$ 6.5 Hz, 6Me); 1.65 (1H, ddd, $J_{2a,3}$ 11.5 Hz, $J_{1,2a}$ 3.5 Hz, H-2a); 2.17 (1H, ddd, $J_{2e,3}$ 5 Hz, $J_{1,2e}$ 1 Hz, H-2e); 3.27 (3H, s, OCH_3); 3.7-3.87 (2H, m, H-3, H-5); 4,7 (1H, t, $J_{4,5}$,$J_{3,4}$ 9 Hz, H-4); 4,7 (1H, dd, H-1).
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11. Selected physical and spectral data for **10**: $[\alpha]_D^{25}$ -111° (*c*, 1.19, $CHCl_3$), ν_{max} 2104 (N_3), δ_H ($CDCl_3$) 1.27 (3H, d, $J_{5,6}$ 6.5 Hz, 6Me); 1.9-2.1 (2H, m, H-2a, H-2e); 3.3 (3H, s, OCH_3); 3.71 (1H, dd, $J_{4,5}$ 1.5 Hz, $J_{3,4}$ 3 Hz, H-4); 3.85 (1H, dq, H-5); 4,01 (1H, ddd, $J_{2a,3}$ 10 Hz, $J_{2e,3}$ 6.5 Hz, H-3). 4,84 (1H, t, $J_{1,2a}$,$J_{1,2e}$ 3 Hz, H-1).
12. Physical and spectral data for **11**: $[\alpha]_D^{25}$ -89° (*c*, 0.65, $CHCl_3$), δ_H ($CDCl_3$) 1.36 (3H, d, $J_{5,6}$ 7 Hz, 6Me); 1.87 (1H, ddd, $J_{1,2e}$ 4 Hz, $J_{2e,3}$ 5 Hz, H-2e); 2.17 (1H, ddd, $J_{1,2a}$ 4 Hz, $J_{2a,3}$ 10 Hz, H-2a); 2.58 (6H, s, $N(C\underline{H}_3)_2$); 2.62 (1H, dd, $J_{3,4}$ 5 Hz, $J_{4,5}$ 3 Hz, H-4); 3.33 (3H, s, OCH_3); 4.0 (1H, dt, H-3); 4.08 (1H, dq, H-5); 4,84 (1H, t, H-1).
13. Most important physical and spectral data for **12**: m.p. 122-123 °C, $[\alpha]_D^{25}$ -106° (*c*, 1.01, $CHCl_3$), δ_H ($CDCl_3$) 1.18 (3H, d, $J_{5,6}$ 6.5 Hz, 6Me); 1.72 (1H, ddd, $J_{1,2a}$ 3.5 Hz, $J_{2a,3}$ 9 Hz, H-2a); 2.24 (1H, ddd, $J_{1,2e}$ 1 Hz, $J_{2e,3}$ 5 Hz, H-2e); 3.3 (3H, s, OCH_3); 3.73 (1H, dq, $J_{4,5}$ 9 Hz, H-5); 4.08 (1H, m, $J_{3,4}$ 9 Hz, H-3); 4.16 (1H, t, H-4); 4,72 (1H, dd, H-1).
14. Selected physical and spectral data for **13**: m.p. 119-120 °C, $[\alpha]_D^{25}$ -158° (*c*, 1.1, $CHCl_3$), ν_{max} 2104 (N_3), δ_H ($CDCl_3$) 1.33 (3H, d, $J_{5,6}$ 6.5 Hz, 6Me); 1.74-1.97 (2H, m, H-2e, H-2a); 3.3 (3H, s, OCH_3); 3.95 (1H, dq, H-5); 4.2 (1H, dq, $J_{2e,3}$ 6 Hz, $J_{2a,3}$ 11 Hz, H-3); 4.77 (1H, dd, $J_{1,2a}$ 3 Hz, $J_{1,2e}$ 1 Hz, H-1).
15. EI-MS data for **2** (70 eV, $T_{ion\ source}$ 110 °C, sample inlet through the septum): m/z (%): 189, M$^+$ (20); 188, M-H (3); 186, M-H-H_2 (10); 158, M-OCH_3 (12); 143 (6); 115 (30); 101 (40); 87, $(CH_3)_2NCH{=}CHOH$ (100); 85, $(CH_3)_2NCCOH$ (44); 72 (30); 58 (22); 45, $(CH_3)_2NH$ (75).

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