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Diastereoselective Synthesis of Methyl α-Kedarosaminide, a Carbohydrate Moiety of the Enediyne Antitumor Antibiotic Kedarcidin Chromophore

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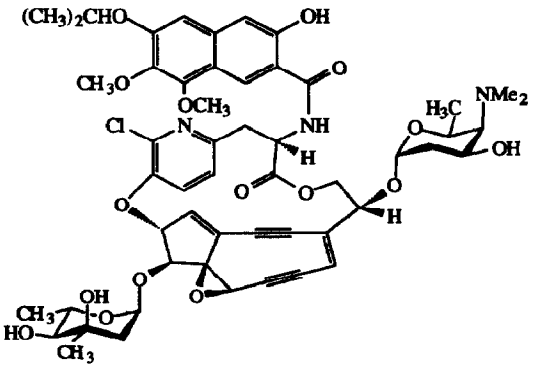
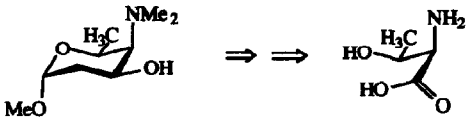
Abstract: Methyl α-kedarosaminide (**9**), a carbohydrate moiety of the enediyne antitumor antibiotic kedarcidin chromophore, was synthesised from D-threonine. Stereoselective reduction of the allyl ketone **5** derived from D-threonine was a key step in the synthesis, which was achieved by using $Me_4NBH(OAc)_3$ for intramolecular hydride delivery.

The enediyne antitumor antibiotics have attracted much attention as highly specific and potent antitumor agents which cleave both strands of DNA[1]. Most of the enediynes isolated from nature contain highly unusual oligosaccharide moieties, and the oligosaccharide fragment of the enediyne calicheamicin was recently shown to play a critical role in specific binding to DNA[2]. Kedarcidin chromophore is another member of the family of enediyne antitumor antibiotics which contains the novel aminodeoxy sugar kedarosamine[3]. Development of synthetic routes to kedarosamine is essential in order to reveal its role in the biological activity of kedarcidin chromophore. A synthesis of methyl α-kedarosaminide (**9**) from a 2-deoxy-L-rhamnoside was recently described[4], and syntheses of two kedarosamine analogues have also been reported[5,6]. Here we present a diastereoselective synthesis of methyl α-kedarosaminide (**9**) starting from D-threonine, which relies on the stereoselective reduction of an allyl ketone by intramolecular hydride delivery.

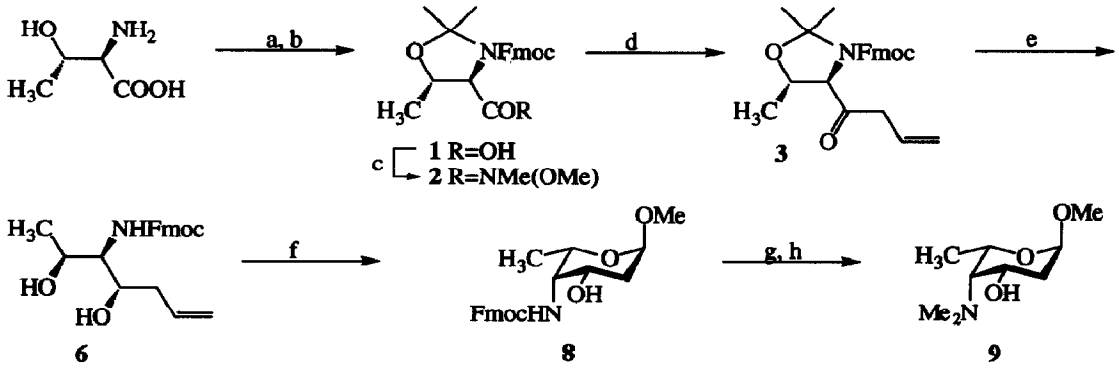


Kedarcidin chromophore



9 D-Threonine

Treatment of D-threonine with Fmoc-Cl followed by 2,2-dimethoxypropane gave the N^{α},O^{β}-protected derivative **1** (Scheme 1). The acid **1** was converted into the corresponding acid chloride with cyanuric chloride[7], and then into the Weinreb amide[8] **2**. Coupling of amide **2** with allylmagnesium bromide gave the ketone **3** in 79% yield.

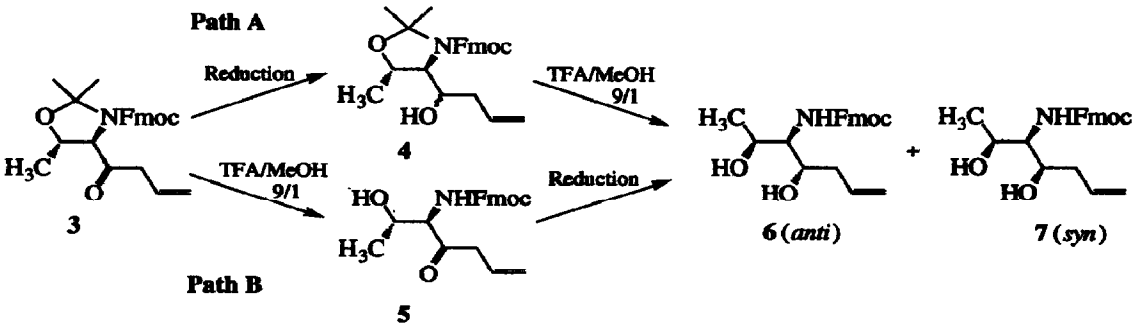


Scheme 1. a) Fmoc-Cl, 10% aq. Na_2CO_3, dioxane, 100% b) 2,2-dimethoxypropane, pTsOH, benzene, reflux, 81% c) i. cyanuric chloride, pyridine, CH_2Cl_2 ii. N,O-dimethylhydroxylamine hydrochloride, pyridine, CH_2Cl_2, 51% d) allylmagnesium bromide, THF, -78°C, 79% e) i. TFA/MeOH; 9/1 ii. $Me_4NBH(OAc)_3$, CH_3CN/HOAc 1/1, -40°C, 73% f) i. O_3, Me_2S, -78°C ii. pTsOH, MeOH, 60% g) 10% Pd/C, $Pd(OAc)_2$, NH_4HCO_2, MeOH, 45% h) 10% Pd/C, H_2, HCHO, MeOH/H_2O 1/1, 62%.

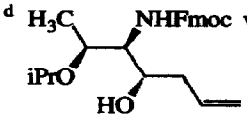
Conversion of ketone **3** to the diol **6** requires a key stereoselective reduction and cleavage of the isopropylidene protective group. This was attempted both by reduction of **3** to give **4** followed by methanolysis of the isopropylidene group (Table 1, path A), and by performing the reduction on **5** obtained after removal of the protective group (Table 1, path B). Non-chelation controlled reduction of **3** and **5** was expected to give a diastereomeric mixture, with the undesired *syn* isomer **7** predominating, as was recently reported for similar systems[9]. In agreement with this expectation reduction of **3** with $NaBH_4$ selectively gave the *syn* isomer whereas reduction of **5** with $NaBH_3CN$ was nonselective (Table 1). Reduction of **3** with DIBAL was high yielding, but non-selective. In contrast, 1,2-chelation controlled reduction of **3** and **5** should give the desired *anti* isomer **6**. Accordingly, reduction of the fully protected **3** with $Zn(BH_4)_2$[10] in diethyl ether, was found to be higly *anti* selective, but proceeded in low yield due to accompanying reductive opening of the isopropylidene group (Table 1, entry 4). The reductive opening was assumed to reflect too strong chelation of Zn^{2+} to the substrate, and ether was therefore replaced by the stronger donor THF. Isopropylidene opening was then suppressed but a significant loss in diastereoselectivity in the reduction was also observed. For the β-hydroxy ketone **5** reduction with $Zn(BH_4)_2$ was not stereoselective, which could result from competing 1,2- and 1,3-chelation to the Fmoc-amino and hydroxyl groups, respectively. Almost complete *anti*-selectivity was reported[11] in the reduction of N-benzyloxycarbonyl protected α-amino ketones with triethylsilane and titanium tetrachloride, but in our hands **3** and **5** could not be reduced with these reagents. Evans et al.[12] have described high *anti* stereoselectivity, based on intramolecular hydride delivery, in reductions of β-hydroxy ketones with $Me_4NBH(OAc)_3$. Applying this protocol to ketone **5** resulted in a smooth formation of the desired *anti* alcohol **6**[13] in 73% yield and as a single diastereomer.

The unsaturated *anti* alcohol **6** was then cleaved quantitatively by ozonolysis and subsequent ring closure to the corresponding hemiacetal occurred spontaneously. On treatment of this hemiacetal with acidic methanol an anomeric mixture (α/β, 4/1) of methyl glycosides was obtained, from which the α-anomer **8**[14] was isolated in 60% yield (Scheme 1). The stereochemistry of the new stereocenters at C-1 (methyl glycoside formation) and C-3 (ketone reduction) was conclusively determined for compound **8** using COSY and NOESY NMR spectroscopy. In this analysis the possibility for **8** and its stereoisomers to exist in different chairlike conformations was taken into account. The NOE observed between H-5 and H-3 ruled out an axial configuration for the hydroxyl group at C-3. The presence of an NOE between H-5 and the methyl glycoside, and the absence of NOE:s between H-1 and H-3, and H-1 and H-5, which were expected for the β-glycoside, confirmed the anomeric configuration as α.

Table 1. Conversion of the Ketone **3** to the *Anti* and *Syn* Alcohols **6** and **7**.



Reducing agent, Solvent	Path A		Path B	
	6:7[a]	Yield(%)[b]	6:7[a]	Yield(%)[b]
$NaBH_4$, MeOH	1:9	46	-	-[c]
$NaBH_3CN$, MeOH	-	-[c]	1:1	62
DIBAL, hexane	2:1	90	1:1	16
$Zn(BH_4)_2$, ether	17:1	30[d]	1:1	40
$Zn(BH_4)_2$, THF	2:1	60	-	-[c]
$Et_3SiH/TiCl_4,CH_2Cl_2$	-	0	-	0
$Me_4NBH(OAc)_3$, CH_3CN/HOAc 1/1	-	-[c]	>300:1	73

[a]The anti:syn ratio was determined by HPLC.
[b]Combined yield of **6** and **7** after the two steps and purification by flash column chromatography.
[c]The reduction was not attempted.
[d]  was isolated in 29% yield.

Cleavage of the Fmoc group in the amino glycoside **8** with piperidine gave unsatisfactory yields. Instead Fmoc deprotection was performed by catalytic transfer hydrogenolysis with ammonium formate and freshly precipitated palladium on charcoal[15]. Attempted reductive dimethylation of the resulting amine with formaldehyde in methanol over palladium on charcoal resulted in predominant formation of two oxazolidines[16]. Replacement of methanol as solvent by 50% aqueous methanol in the reductive methylation suppressed formation of these side products and **9** was obtained in 62% yield from the preceding amine. The ^{1}H and ^{13}C NMR data for the synthetic methyl α-kedarosaminide (**9**) were in good agreement with data previously reported for **9** isolated from natural sources[3] and synthesised by Hornyák et al[4].

Acknowledgements. This work was funded by the *Swedish National Board for Industrial and Technical Development* and the *Swedish Natural Science Research Council.*

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13. Compound **6**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.29 (m, 8H, Ar), 5.89-5.76 (m, 1H, C<u>H</u>=CH_2), 5.53 (d, 1H, *J*=9.3 Hz, NH), 5.21-5.16 (m, 2H, CH=C<u>H</u>$_2$), 4.49-4.42 (m, 2H, C<u>H</u>$_2$(Fmoc)), 4.36 (bq, 1H, *J*=6.4 Hz, C<u>H</u>(OH)CH_3), 4.23 (t, 1H, *J*=6.8 Hz, C<u>H</u>(Fmoc)), 3.88-3.82 (m, 1H, C<u>H</u>(OH)allyl), 3.46 (ddd, 1H, *J*=9.3, 4.4, 1.2 Hz, C<u>H</u>NH), 2.79 (bs, 1H, OH), 2.43-2.24 (m, 3H, OH, C<u>H</u>$_2$CH=CH_2) and 1.18 (d, 1H, *J*=6.4 Hz, CH_3).
14. Compound **8**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.30 (m, 8H, Ar), 5.08 (d, 1H, *J*=9.2 Hz, NH), 4.73 (d, 1H, *J*=3.6 Hz, H-1), 4.49 (dd, 1H, *J*=10.8, 7.1 Hz, C<u>H</u>$_2$(Fmoc)), 4.42 (dd, 1H, *J*=10.8, 6.6 Hz, C<u>H</u>$_2$(Fmoc)), 4.22 (t, 1H, *J*=6.8 Hz, C<u>H</u>(Fmoc)), 4.13-4.08 (m, 1H, H-3), 4.01 (bq, 1H, *J*=6.4 Hz, H-5), 3.86 (dd, 1H, *J*=9.2, 2.9 Hz, H-4), 3.29 (s, 3H, OMe), 2.51 (bs, 1H, OH), 1.94 (bdd, 1H, *J*=13.3, 5.0 Hz, H-2e), 1.57 (ddd, 1H, *J*=13.3, 12.3, 3.6 Hz, H-2a) and 1.14 (d, 3H, *J*=6.4 Hz, H-6).
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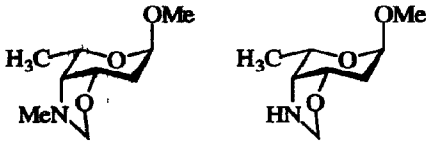
16. Oxazolidines formed in the reductive methylation in methanol:



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