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Asymmetric Synthesis of 2,3-Epoxyamides by Reacting Monosaccharide Derivatives with Stabilised Sulphur Ylides Generated in-situ: Two-Phase Method and Configurational Assignations.

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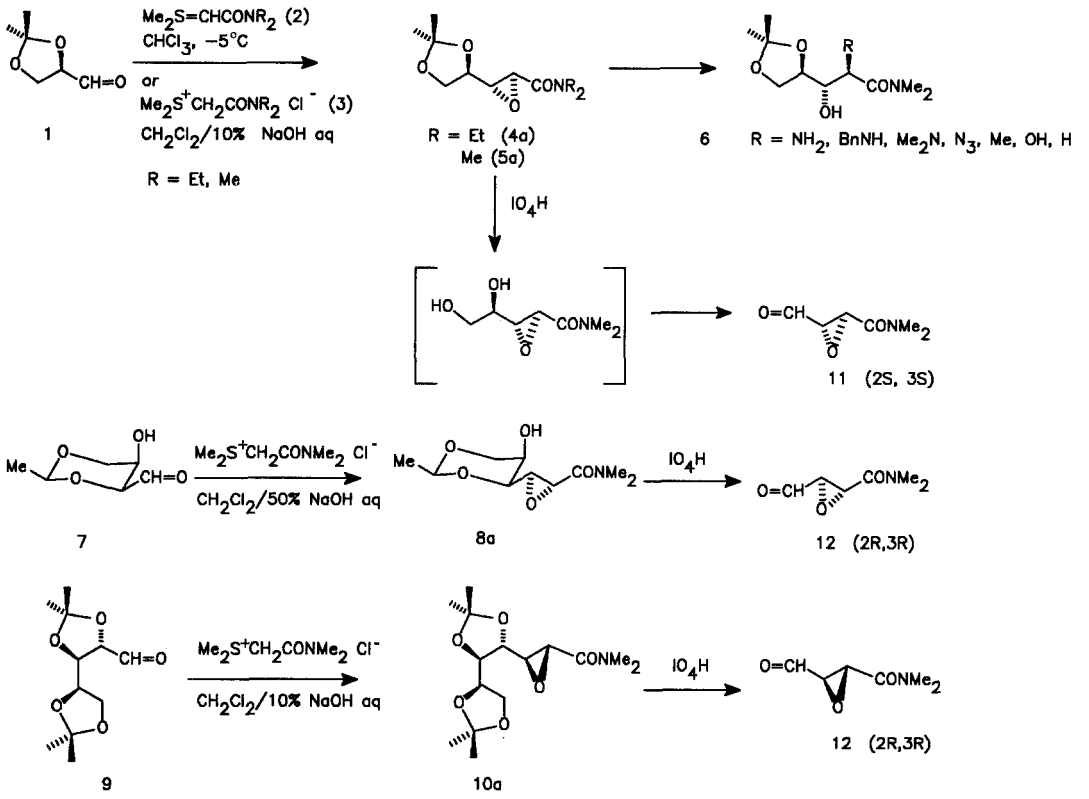
Abstract: The reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde **1** , 2,4-ethylidene-D-threose **7** , or 2,3:4,5-di-*O*-isopropylidene-D-arabinose **9** with N,N-dimethyl-carbamoylmethyl dimethyl sulphonium chloride and a 10-50% solution of sodium hydroxyde gave the corresponding 2,3-epoxyamides **5**, **8** and **10**, and the reaction of **1**, or 5-*O*-trityl-2,3-*O*-isopropylidene-D-ribofuranose **13** with N,N-diethyl-carbamoylmethyl dimethyl sulphonium chloride and a 10-50% solution of sodium hydroxyde gave the corresponding 2,3-epoxyamides **4** and **14**, respectively, with high yields and variable stereoselectivity.

Epoxides play an important rôle in the synthesis of many interesting natural and synthetic products.[1] Since the discovery of the asymmetric epoxidation of allylic alcohols by Sharpless,[2] researchers have employed the epoxide group to synthesize many asymmetric products. However, the regioselective opening of these 2,3-epoxy alcohols[3] can often be a problem. Several procedures are suggested to resolve this difficulty,[4] and also that of the undesirable Payne rearrangement,[5] that include the oxidation of the hydroxyl group to the carboxyl or another group to increase the asymmetry around the epoxide group and favour the complete regio-control of the opening processes.

We reported the synthesis[6] and later the completely regio-selective opening on C-2[7] of N,N-dimethyl-2,3-anhydro-4,5-O-isopropylidene-D-arabinonamide **5** by carbon, nitrogen, oxygen and hydrogen nucleophiles to produce the compounds **6**. The resulting 2,3-epoxyamides **4** and **5** have now become interesting chiral templates for many syntheses. In this way we were able to carry out our first highly-selective syntheses of **4** and **5**[6] by reaction of 2,3-O-isopropylidene-D- glyceraldehyde **1** with the N,N-dimethyl- or N,N-diethyl-sulphuranylidene acetamide **2a** or **2b** (100%, 96:4 D-*arabino*: D-*xylo*). However, we thought that their preparation should be simplified to increase their usefulness.

The use of **2** (prepared from the corresponding sulphonium salt), because of its reactivity with some solvents ($CHCl_3$, alcohols, water, etc.) might present some problems. For example, when **2** was prepared from **3** by treating it with sodium hydride in acetonitrile, the preparation did not go well if the solvent was very dry and we found we had to first add a few drops of water to the acetonitrile to produce powdered sodium hydroxide, the actual base (probably to minimise the reaction of the hydride with the solvent or, perhaps for other reasons).

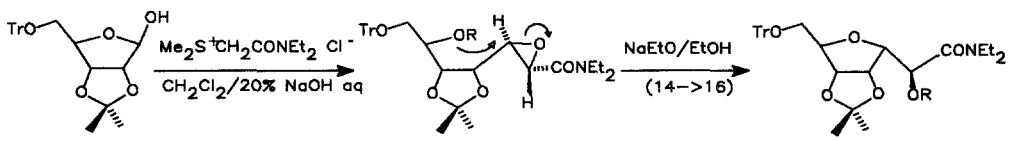
Consequently, we decided to use the "two-phase method"[8] to try to generate the ylide in-situ by adding an aqueous solution of sodium hydroxide (10-50%) to a mixture of the sulphonium salt **3** and the corresponding aldehyde-sugar dissolved in an organic solvent like dichloromethane while stirring strongly the mixture between 0ºC and 25ºC. In this way, **4** and **5** were conveniently prepared with 100% yields and good stereoselectivity; (D-*arabino*:D-*xylo* 96:4 to 85:15). The method was applied to other aldehyde-sugars previously reacted with the ylides mentioned above, **2a** and **2b,** and they gave the corresponding products with yields and stereoselectivities similar to those published[9] and therefore the "two-phase method" is the method of choice for these syntheses.



The configuration of the two new stereogenic carbons of compounds **4a** and **5a** were established previously[6] by chemical correlation with 2-deoxy-D-ribono-γ-lactone, and it was established that the major isomers had the *arabino* configuration, while the minor isomers had the *xylo*. However, the enantiomeric purity remains to be established. We are now obliged to establish the enantiomeric excess of both starting and final products because we employ a more basic medium that might provoke the racemization of **1**. Thus, we determined the optical purity of the starting aldehyde **1** ($[\alpha]_D^{18} = 64$ (2.35, C_6H_6), literature:[10a] $[\alpha]_D^{21} = 64{,}9$ (5.73, C_6H_6)). When the reaction had finished the ^{1}H-NMR spectrum revealed the presence of only two compounds that corresponded to the previously-published trans-epoxides ($J_{2,3}$= 2.1 Hz) and, consequently, they should present a relative configuration of *arabino* and *xylo*. The D-*arabino* absolute configuration for the major compound and its enantiomeric excess, were established by transforming a chromatographically pure fraction of **5a** in the corresponding γ-aldonolactone and using NMR spectroscopy and specific rotation determination to ensure we were dealing with enantiomerically pure 2-deoxy-D-ribono-γ-lactone ($[\alpha]_D^{25} = 18{,}05$ (c 0.41, H_2O), literature:[10b] $[\alpha]_D^{20} = 18{,}5$ (c 0.35, H_2O). On the other hand,

the enantiomeric purity of products **7** and **9** is confirmed by their spectroscopic data and ensured by the preparation method.[11,12] The trans configuration of all the resulting epoxides **8a:8b** and **10a:10b** was established by ^{1}H-NMR ($J_{2,3}$= 2.1 Hz)[6]. Nevertheless, the absolute configuration of the two new stereogenic centres had not yet been established. We used a very simple procedure to do this. Firstly, we treated a small amount of **4a**, with an excess of periodic acid in D_2O,. This provoked the hydrolysis of the acetal group and the oxidation of the resulting polyhydroxy-derivate to **11**, the rotatory power of which was negative. The course of these reactions was followed at the same time by studying the variation of their spectra of ^{13}C-NMR in D_2O, and these showed that carbons C-3 and C-4, and the acetalic carbons, had completely disappeared, while the signals that corresponded to the rest of the epoxyamide remained. The method was also applied to the epoxyamides **8** y **10**, and the sign of the final rotatory power was positive in both cases. This indicated the formation of **12**, the enantiomer of **11**, revealing the configurations of the major components like D-*ido* **8a** and D-*glycero*-D-*galacto* **10a** , respectively. In this way we concluded that the conditions employed in this "two-phase method" caused neither epimerization nor racemization of the products involved. This we attributed to the low solubility of these compounds in the aqueous alkaline solution and also to the short reaction-times and the low temperatures employed. The application of this method to carbonyl compounds more soluble in water, the use of higher temperatures, and employing longer reaction times, could cause epimerizations that could be confirmed by studying the stereochemistry of the resulting products.

The method was also applied to derivatives of cyclohemiacetalic reducing-sugars. For example, the 5-O-trityl-2,3-O-isopropylidene-D-ribose **13**, that produced with complete stereoselectivity only one product that we characterised as **14**. We determined the *trans* -2,3-epoxyamide structure of this compound by spectroscopic methods and by cyclation to **16** after treatment with 0.1 N ethanolic sodium ethoxyde. The ^{1}H-NMR spectrum of **15** was consistent with a *trans*-epoxide ($J_{2,3}$= 2 Hz). Our determination of the structure of the C-glycoside **16** was based on its ^{1}H-NMR data ($J_{5,6}$= 0 Hz) and this value is consistent with an α-D-ribofuranosyl anomer,[13a,b] and with a comparative study with many other α- and β-D-ribofuranosyl-C-glycosides.[13c,d] As usual, in these cyclation processes, we assumed that the formation of one product only **16** from **14**, was likely to be the result of a stereospecific opening of the epoxide group by a completely regio-selective attack on C-3, with inversion of the configuration, to give only the anomer α **16**, that implies a 3(R) configuration in **14**, and the configuration trans of the epoxide group implies, in turn, a 2(S) configuration. Moreover, these compounds, **14** and **16**, were transformed into the corresponding monoacetates **15** (C-6) and **17** (C-2), with NMR data according to these structures.



13

14 R = H
15 R = Ac

16 R = H
17 R = Ac

Finally, the results of applying this reaction to the 2,3:5,6-di-O-isopropylidene-D-mannofuranose were not good, even after we employed more energetic reaction conditions (50ºC, benzene-water. 20% NaOH) . These conditions only produced varying mixtures of products. We reasoned that this was due to the lower reactivity of this D-mannose derivative compared with those of D-ribose derivatives. Under these more drastic conditions, the ylide underwent a complete hydrolysis that impeded the slower formation of this compound. Our work in this field continues and we plan to apply the reaction to other derivatives with pyranose and furanose structures.

EXPERIMENTAL

Melting points are given uncorrected. ^{1}H- and ^{13}C-NMR spectra were obtained at 200 and 50 MHz respectively, on a Bruker WP 200 SY, using $CDCl_3$ as solvent. Chemical shifts (δ, ppm) are referred to the residual $CHCl_3$ (7.24 ppm), notations indicate signal multiplicity (s, singlet; d doublet; t triplet; q quadruplet; m, multiplet). Coupling constants are expressed as J values in Hz units. Mass spectra were recorded on a Hewlett-Packard 5988A instrument. Microanalyses were performed by the "Servicio de Microanálisis de la Universidad de Málaga". Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Preparative thin layer chromatography was performed on Merck silica-gel 60 No. 7747. High-resolution MS were performed by the "Servicio de Espectrometría de Masas de la Universidad de Sevilla".

N,N-Diethyl-2,3-anhydro-4,5-*O*-isopropylidene-D-*arabino*- and D- *xylo*-pentonamides 4a and 4b . To a solution of **1**[10a] (7 g, 53.9 mmol) in dichloromethane (140 mL) was added the sulphonium salt **3 (R=Et)**[14] (13.7 g, 9.2 mmol) and 10% aqueous NaOH (35 mL). The reaction mixture was stirred at room temperature for 1 h. Water (140 mL) was then added and the organic phase separated. The aqueous phase was extracted twice with dichloromethane (2 x 140 mL). The organic layers were washed twice with water, dried with sodium sulphate and evaporated in vacuo (rotatory evaporator, cold bath) to obtain **4a:4b**[6] (13 g, quantitative yield, 85:15, (2S, 3R):(2R, 3S)).

N,N-Dimethyl-2,3-anhydro-4,5-*O*-isopropylidene-D-*arabino*- and D-*xylo*-pentonamides 5a and 5b . To a cold (0 °C) solution of **1**[10a] (1 g, 7.7 mmol) in dichloromethane (20 mL) was added the sulphonium salt **3b** (1.95 g, 9.2 mmol) and 10% aqueous NaOH (5 mL at 0 °C). The reaction mixture was stirred at 0 °C for 1 h. Water (20 mL) was then added and the organic phase separated. The aqueous phase was extracted twice with dichloromethane (2 x 20 mL). The organic layers were washed twice with water, dried with sodium sulphate and evaporated in vacuo to obtain **5a:5b**[6] (1,8 g, quantitative yield, 95:5, (2S, 3R):(2R, 3S)).

Acid hydrolysis and periodic oxidation of a 96:4 mixture of N,N-Diethyl-2,3-anhydro-4,5-*O*-isopropylidene-D-*arabino*- and D-*xylo*-pentonamides 4a:4b . To a solution of 106 mg (0.436 mmol) of **4a:4b** (96:4 (2S, 3R):(2R, 3S)) in 1 mL of D_2O, 0,12 mg (0.526 mmol) of periodic acid were added. After 5 min, ^{13}C-NMR spectra showed the disappearance of the starting product and the only presence of the hydrated aldehydes **11** and **12**.

^{13}C-NMR, $CDCl_3$ (δ) of **4a**, **4b**, **11** and **12**

Compound	CO	$\underline{C}Me_2$	C4	C5	C3	C2	$N\underline{C}H_2CH_3$	$C\underline{Me}_2$	$NCH_2\underline{C}H_3$
4a	166.80	109,98	72.80	65.10	56.97	50.62	41.37, 40.69	24.95, 23.37	13.06, 11.49
4b	166.80	110.12	73.42	65.09	56.97	50.00	41.37, 40.69	24.66, 23.76	13.17, 11.49
11 and **12**	166.59		80.97		57.84	49.83	41.22, 40.50		12.78, 11.27

The rotatory power for the resulting mixture was determined: $[\alpha]^{20}_D$ = -8,9 (c 3,7, D_2O) which shows the principal isomer **11** has a negative rotatory power. Similar treatment of a small amount of **5a**, give also a negative rotatory power, as corresponding to the same epoxy configuration (2S,3R).

N,N-Dimethyl-2,3-anhydro-4,5-*O*-(S)-ethylidene-D-*galacto*- and D-*ido*-hexonamides 8a and 8b . To a solution of **7**[11] (110 mg, 0,75 mmol) in dichloromethane (4 mL) was added the sulphonium salt **3 (R=Me)**[14] (207 mg, 0,96 mmol) and 50% aqueous NaOH (1 mL). The reaction mixture was stirred at room temperature and followed by TlC (10:1 ethyl acetate-methanol), showing, after 15 min, the disappearence of the starting product **7**. Water (4 mL) was then added and the organic phase separated. The aqueous phase was extracted with tert-buthylmethyl ether (5 x 2 mL). The organic layers were washed twice with water, dried with sodium sulphate and evaporated in vacuo (rotatory evaporator, cold bath) to obtain **8a:8b**[9] (170 mg, 98%, 3:2, (2R, 3S):(2S, 3R)). Treatment of a small amount of a **8a** enriched mixture of **8a:8b** with periodic acid in water, give a solution with a positive rotatory power, showing the 2R,3S configuration of the principal epoxy derivative **8a**.

N,N-Dimethyl-2,3-anhydro-4,5:6,7-di-*O*-isopropylidene-D-*glycero*-D-*galacto*- and D-*glycero*-D-*ido*-heptonamides 10a and 10b . To a solution of **9**[12] (47 mg, 0.2 mmol) in dichloromethane (1 mL) was added the sulphonium salt **3 (R=Me)**[14] (84 mg, 0.4 mmol) and 10% aqueous NaOH (0.26 mL). The reaction mixture was stirred at room temperature and monitored by TLC (1:2 hexane-ethyl acetate, Rf: **9** (0.5) and **10** (0.22)), showing, after 3 h, the disappearence of the starting product **9**. Water (10 mL) and dichloromethane (10 mL) were then added and the organic phase separated. The aqueous phase was extracted with dichloromethane (2 x 10 mL). The organic layers were washed twice with water, dried with sodium sulphate and evaporated in vacuo (rotatory evaporator, cold bath) to obtain **10a:10b**[9] (84 mg, quantitative yield, 2:1, (2R, 3S):(2S, 3R)). Treatment of a small amount of a **10a** enriched mixture of **10a:10b** with periodic acid in water, give a solution with a positive rotatory power, showing the 2R,3S configuration of the principal epoxy derivative **10a**.

N,N-Diethyl 2,3-anhydro-4,5-*O*-isopropylidene-7-*O*-trityl-D-*glycero*-D-*altro*-heptonamide 14 . To a solution of **13**[15] (485 mg, 1.12 mmol) in CH_2Cl_2 (8mL) were added the sulphonium salt **3 (R=Et)**[14] (290 mg, 1.37 mmol) and 20% aqueous NaOH (4 mL). The reaction was stirred at room temperature for 8 h. Water (20 mL) was added and the organic phase was decanted. The aqueous phase was extracted with ether (2x20 mL). The combined organic solution were washed with water (2x20 mL) and dried with sodium sulphate. The solvent was evaporated to give **14** (599 mg, 98%) as a foam, virtually pure. Some recristallyzation attemps to obtain good crystals for m.p. determination, gave the cyclic product **16**. Treatment of a small amount of **14** with periodic acid in water and traces of TFA, gives a solution with a negative rotatory power, showing the 2S, 3R configuration of **14**.

Compound **14**: $[\alpha]^{20}_D$ = -10.4 (c 1, MeOH), $[\alpha]^{20}_D$ = -8 (c 1, $CHCl_3$). Rf 0.33 (1:1 hexane-ethyl acetate). **^{1}H-NMR**, $CDCl_3$ (δ): 5.09 (ddd, 1H, J 9.2, 3.6 and 3.0 Hz, H-6), 4.69 (dd, 1H, J 9.2 and 5.7 Hz, H-5), 4.02 (dd, 1H, J 6.1 and 5.7 Hz, H-4), 3.53 (d, 1H, J 2.0 Hz, H-2), 3.27 (dd, 1H, J 6.1 and 2.0 Hz, H-3), 3.50-3.30 (m, 6H, $2CH_2$ and H-7a,7b), 1.34 and 1.33 (2s, 2x3H, CMe_2), 1.22 and 1.11 (2t, 2x3H, $CH_2\underline{C}H_3$), 7.5-7.10 (Tr). **^{13}C-NMR**, $CDCl_3$ (δ): 166.70 (CO), 144.01, 128.72, 127.67 and 127.82 (Tr), 109.28 ($\underline{C}Me_2$), 86.43 (Tr), 77.28, 74.91 (C-5,4), 68.65, 65.30 (C-6,7), 55.75 (C-3), 51.76 (C-2), 41.56 and 40.39 ($\underline{C}H_2CH_3$), 27.47 and 25.38 ($C\underline{Me}_2$), 14.52 and 12.68 ($CH_2\underline{C}H_3$). EIMS *m/z* (%): 527 (M^+-18) (1), 302 (M^+-Tr) (5), 272 (16), 244 (Tr+1) (21), 243 (Tr) (100), 242 (11), 228 (6), 214 (5), 196 (6), 165 (36), 100 ($CONEt_2$) (52), 72 (27). *Anal.* calcd. for $C_{33}H_{39}NO_6$: C, 72.64; H, 7.20; N, 2.57. Found: C, 72.55; H, 7.14; N, 2.41.

N,N-Diethyl-6-*O*-acetyl-2,3-anhydro-4,5-*O*-isopropylidene-7-*O*-trityl-D-glycero-D-altro-heptonamide 15 . To a mixture of Ac_2O (1 mL) and pyridine (2.5 mL) was added **14** (200 mg, 0.36 mmol) and kept at room

temperature overnight. After the usual treatment, the crude product was purified by preparative TLC (4:1hexane-ethyl acetate) yielding **15** (170 mg, 79%).

Compound **15**, Rf: 0.37 (1:1 hexane-ethyl acetate). **^{1}H-NMR**, $CDCl_3$ (δ): 5.09 (ddd, 1H, J 9.2, 3.6, 3.0 Hz, H-6), 4.69 (dd, 1H, J 9.2 and 5.7 Hz, H-5), 4.02 (dd, 1H, J 6.1 and 5.7 Hz, H-4), 3.53 (d, 1H, J 2 Hz, H-2), 3.27 (dd, 1H, J 6.1 and 2.0 Hz, H-3), 3.50-3.30 (m, 6H, $2CH_2$ and H-7a,7b), 1.34 and 1.33 (2s, 2x3H, CMe_2), 1.22 and 1.11 (2t, 2x3H, CH_2CH_3), 7.5-7.10 (Tr). **^{13}C-NMR**, $CDCl_3$ (δ): 169.85 and 165.44 (CON and $\underline{C}OCH_3$), 143.79, 128.62, 127.71 and 126.96 (Tr), 109.27 ($\underline{C}Me_2$), 86.40 (Tr), 77.01 (C-6), 74.58 (C-7), 70.41 (C-5), 62.23 (C-4), 54.38 (C-3), 51.23 (C-2), 41.49 and 40.84 ($\underline{C}H_2CH_3$), 27.65 and 25.25 ($C\underline{Me}_2$), 21.01 (Ac), 14.70 and 12.84 ($CH_2\underline{C}H_3$). EIMS *m/z* (%): 344 (M^+-Tr) (4), 244 (Tr+1) (21), 243 (Tr) (100), 228 (3), 166 (3), 165 (17), 100 ($CONEt_2$) (14), 72 (9). High-resolution MS *m/z* Calcd $C_{35}H_{40}NO_7$ (M^+): 586.2805, Found: 586.2859.

N,N-Diethyl-3,6-anhydro-4,5-*O*-isopropylidene-7-*O*-trityl-D-*glycero*-D-*manno*-heptonamide 16 .- A solution of **14** (203 mg, 0.37 mmol) in ethanolic sodium ethoxyde 0.1 N was kept at room temperature. Monitorization by ^{1}H-RMN showed the progressive disappearance of the signals of **14** and the formation of a new product whose signals corresponded to the cyclic product **16**. After a day, the solution was diluted with ether and neutralized with saturated aqueous solution of potassium bisulfate. The organic phase was washed with water and evaporated to yield **16** (173 mg, 85%). Further purification was done on preparative TLC (3:1hexane-ethyl acetate).

Compound **16**: $[\alpha]^{20}_D = +18$ (c 0.8, MeOH), m.p.: 171-172 C. Rf: 0.69 (1:1 hexane-ethyl acetate).**^{1}H-NMR**, $CDCl_3$ (δ): 4.90 (dd, 1H, J 6 and 3.7 Hz, H-4), 4.76 (d, 1H, J 8.9 Hz, H-2), 4.56 (d, 1H, J 6.0 Hz, H-5), 4.19 (dd, 1H, J 5.9 and 4.1 Hz, H-6), 3.99 (dd, 1H, J 8.9 and 3.7 Hz, H-3), 3.70 and 3.25 (2m, 2x2H, $2CH_2$), 3.06 (dd, 1H, J 10.1 and 5.9, H-7a), 2.98 (dd, 1H, J 10.1 and 4.1H-7b), 1.33 and 1.23(2s, 2x3H, CMe_2), 1.19 and 1.13 (2t, 2x3H, CH_2CH_3). **^{13}C-NMR**, $CDCl_3$ (δ): 172.14 (CO), 143.53, 128.53, 127.90 and 127.06 (Tr), 112.38 ($\underline{C}Me_2$), 87.20 (Tr), 84.00, 83.90, 82.47, 81.45 (H 6,5,4 and 3), 65.44 (C-7), 63.63 (C-2), 41.27 and 40.56 ($\underline{C}H_2CH_3$), 26.49 and 24.77 ($C\underline{Me}_2$), 13.86 and 12.80 ($CH_2\underline{C}H_3$). EIMS *m/z* (%): 303 (M^+-Tr+1)(1), 302 (M^+-Tr) (9), 272(7), 244 (Tr+1) (22), 243 (Tr) (100), 228 (4), 213(7), 196(12), 165 (29), 130 (10), 105(8), 100 ($CONEt_2$) (33). *Anal.* calcd. for $C_{33}H_{39}NO_6$: C, 72.64; H, 7.20; N, 2.57. Found: C, 72.57; H, 7.26; N, 2.56.

N,N-Diethyl- 2-*O*-acetyl-3,6-anhydro-4,5-*O*-isopropylidene-7-*O*-trityl-D-*glycero*-D-*manno*-heptonamide 17 . The acetylation procedure above described was followed for **16** (200 mg, 0.36 mmol) giving **17** (178 mg, 83 %)

Compound **17**: Rf 0.64 (1:1 hexane-ethyl acetate).**^{1}H-NMR**, $CDCl_3$ (δ): 5.48 (d, 1H, J 9.5 Hz, H-2), 4.78 (dd, 1H, J 6.0 and 3.8 Hz, H-4), 4.56 (d, 1H, J 6.0 Hz, H-5), 4.44 (dd, 1H, J 9.5 and 3.8 Hz, H-3), 4.21 (dd, 1H, J 5.0 and 4.7 Hz, H-6), 3.80-3.20 (2m, 2x2H, $2CH_2$), 3.12 (dd, 1H, J 10.0 and 5.0, H-7a), 3.03 (dd, 1H, J 10.0 and 4.7 H-7b), 1.47 and 1.30 (2s, 2x3H, CMe_2), 1.29 and 1.11 (2t, 2x3H, $CH_2C\underline{H}_3$), 7.5-7.10 (Tr). **^{13}C-NMR**, $CDCl_3$ (δ): 169.94 and 167.67 ($\underline{C}ON$ and $\underline{C}OCH_3$), 143.42, 128.52, 127.86 and 126.99 (Tr), 112.40 ($\underline{C}Me_2$), 86.95 (Tr), 83.75, 82.79, 80.80(2C) (C-6,5,4 and 3), 67.47 (C-7), 63.53 (C-2), 41.85 and 40.88 (CH_2CH_3), 26.35 and 24.89 ($C\underline{Me}_2$), 20.69 ($\underline{C}H_3CO$), 13.62 and 12.69 ($CH_2\underline{C}H_3$). EIMS *m/z* (%): 344 (M^+-Tr) (3), 314 (8), 244 (Tr+1) (20), 243 (Tr) (100), 228 (3), 213 (5), 196 (8), 166 (3), 165 (16), 100 ($CONEt_2$) (18), 72 (16).High-resolution MS *m/z* Calcd $C_{35}H_{40}NO_7$ (M^+): 586.2805. Found: 586.2828.

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