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Studies on reactivity of azidoamides, intermediates in the synthesis of tetrahydroxypipecolic acid derivatives

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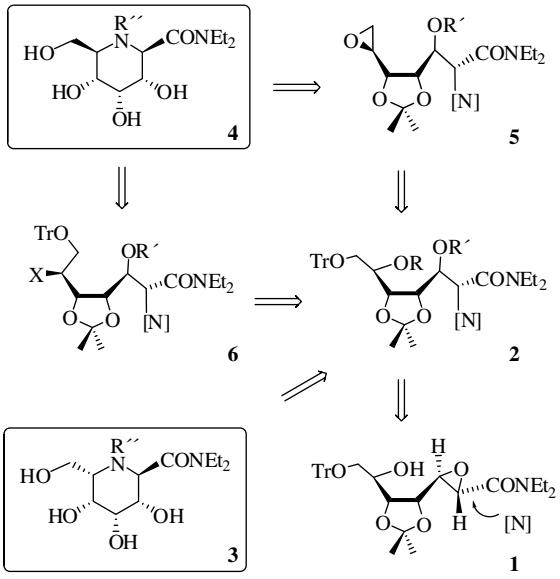
Abstract—Azido group reduction was observed by the treatment of a 2-azido-3-triisopropylsilyloxy heptonamide derivative with NaI in DMSO. The process allowed us to obtain a tetrahydroxypipecolic acid amide derivative. The same azido amide was treated with LiCl in DMSO, but desilylation occurred to give 3,6-anhydro-2-azido heptonamide.

1. Introduction

Iminoalditols (also known as iminosugars or azasugars) are valuable glycosidase inhibitors.[1,2] They have attracted interest as potential therapeutic agents against HIV infection,[3] cancer,[4] diabetes[5] and other genetic or metabolic disorders.[6] However, at the moment, their use is limited because of a lack of commercially viable syntheses. Additionally, new structures with higher selectivities are needed.[7]

As part of our ongoing work on the preparation of glycosidase inhibitors, we are interested in stereoselective methods for synthesizing iminoalditols from 2,3-epoxyamides.[8] In 2,6-iminoheptitols, the presence of an additional α- or β-hydroxymethyl group often leads to an increase in either their potency and/or specificity as inhibitors. Polyhydroxy pipecolic acid analogues have attracted a number of approaches to their synthesis because of their potential biological properties.[9] In a communication,[8a] we described a route to form the piperidine framework from an epoxide **1**, obtained from a D-ribose derivative. This strategy was based on the regioselective epoxide opening by nitrogen nucleophiles, followed by selective hydroxyl group protection (Scheme 1). Intermediates of type **2** gave us the possibility of synthesizing C-6 epimers **3** and **4**. In order to obtain the 6-(*R*) isomers, an azido epoxide of type **5** was obtained, but its reduction and subsequent cyclization led to a mixture of imino derivatives with different ring sizes.



Scheme 1. Retrosynthetic analysis of 2,6-dideoxy-2,6-imino-heptonamides (pipecolic acid amide derivatives).

Thus, polyhydroxy piperidine and azepane derivatives could be obtained.[8a] We then planned other transformations to change the configuration at C-6 in an intermediate of type **2**.[8e]

We chose an azido derivative because azides have several advantages as amino protecting groups. Azido groups offer low steric hindrance, uncomplicated NMR spectra and

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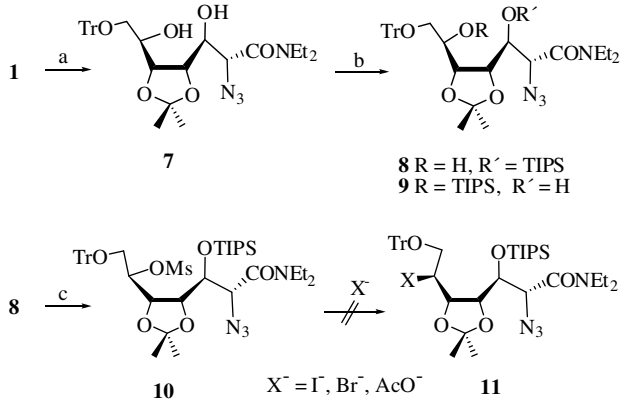
good solubility. Moreover, azides are resistant to many reaction conditions and can be easily reduced to amines. Much effort has been devoted to obtain efficient azido reduction methods,[10] and some of them have found application in carbohydrate area.[11] Besides the well-known methods such as hydrogenation, or the use of hydrides or triphenyl phosphine, there are a variety of reagents described in the literature for the reduction of azides, including $FeSO_4/NH_3$,[12] SmI_2 or Sm/I_2,[13] $Sm/NiCl_2$[14] and $FeCl_3/Zn$.[15] The inexpensive NaI has usually been employed in combination with other halides: $FeCl_3/NaI$[16] or TMSCl/NaI.[17] Additionally, the treatment of arylazides with NaI in acetic acid or formic acid gave *N*-arylacetamides or *N*-arylformamides, respectively.[18] To the best of our knowledge the use of NaI in DMSO has not previously been reported for the reduction of the azide functionality.

Herein, we report the unexpected results obtained in displacement reactions with 2-azido amide derivatives, containing suitable nucleofuges at C-6, when they were treated with halides. The conditions which provoked azido reduction and/or internal displacement are described.

2. Results and discussion

2-Azido amide **7** was obtained by regioselective epoxide opening of epoxiamide **1**, with NaN_3 in DMF, with acetic acid as catalyst. Next, we had to selectively protect the hydroxyl group at C-3 in **7**. The best results were obtained with TIPSOTf (triisopropyl silyl triflate) and lutidine giving **8** as the principal isomer (Scheme 2). With the appropriate substrate **8** in hand, the next stage was the conversion of the free hydroxyl group into a good leaving group. The C-6 hydroxyl group was mesylated giving **10**, but unfortunately, it could not be displaced by nucleophiles such as Br^-, I^- or AcO^-.



Scheme 2. Reagents: (a) NaN_3, DMF, cat. AcOH; (b) TIPSOTf, 2,6-lutidine, CH_2Cl_2; (c) MsCl, py.

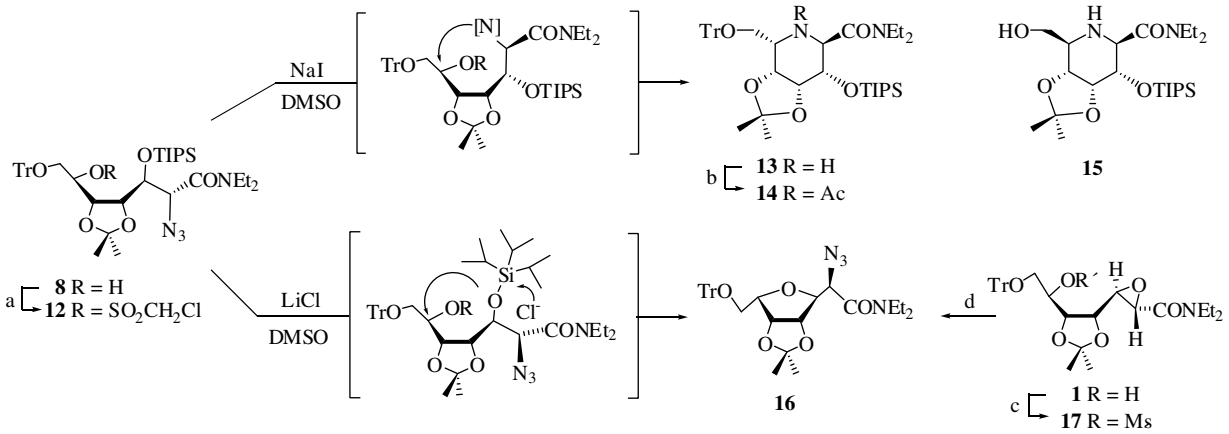
Different results were found with the chloromesylated derivative **12**, as it is depicted in Scheme 3. Compound **12** was easily obtained in 45 min and isolated after usual work-up without the need for further purification. NMR data confirmed its structure. Several reactions were performed by treating **12** with different nucleophiles and solvents. With NaI in acetone or LiCl in THF, after 48 h at rt, the starting material was recovered. With NaI in DMSO, after 48 h at rt, a new, more polar product **13** was observed, which was isolated and purified by column chromatography. NMR data (δ ppm) of compound **13** allowed us to confirm a pyrimidine ring (C-6: 50.8 and C-2: 53.4). The protons H-6, 7–7′ and 2 appeared at higher field (2.94, 3.03 and 3.74) compared with the data of the previous compound **12**. Acetylation of **13** gave the N-acetylated **14** with higher values of δ for H-6, 7–7′ and 2. The slow rate of the acetylation reaction (several days) can be attributed to steric hindrance with nearby trityl and amide group. The *cis*-configuration of the substituents at C-5 and C-6 was assigned by a comparison with the detritylated C-6 epimer **15**,[19] obtained from epoxide **5** (R′: TIPS, [N]: N_3).[8a] Compound **13** showed NMR data different to that of **15**, confirming the direct displacement of $-OSO_2CH_2Cl$ by [N]. Whereas the epimer **15** had $J_{5,6} = 8.6$ Hz (*trans*-axial relationship); in **13** the smaller coupling constant could not be measured directly but it could be in the acetylated **14** ($J_{5,6} = 4.8$ Hz).

In Scheme 3 the formation of **13** is shown. Firstly, the iodide causes azido group reduction and thus, [N] is free to attack at C-6, provoking the cyclization to the piperidine **13**. The reduction mechanism is unknown; it is not clear if an intermediate amine is formed or another reduced species. The evidence is that the chloromesylate group is displaced to give the iminosugar derivative. Kamal et al. employed $FeCl_3/NaI$ or TMSCl/NaI combinations to reduce azides to amines.[16,17] The role of NaI in these processes is unclear and it could involve the participation of in situ generated FeI_3 or TMSI, respectively. But in our case, there is no additional halide added, but only DMSO.

On the other hand, the reaction of **12** with LiCl in DMSO gave, after 30 h at rt, a new, more polar product **16**, which was isolated and purified by column chromatography. NMR data showed the disappearance of the silyl group and the presence of a furanose ring. Lithium chloride provoked the desilylation of **12** and the intramolecular cyclization. Product **16** was also obtained by the reaction of **17** with NaN_3 in DMF. These 2-azido amides are valuable products to obtain synthetic aminoacids,[20] which can be used for the modification of bioactive glycopeptides.

3. Conclusion

In conclusion, these results confirmed to us the importance of the solvent in these transformations, DMSO being the solvent that permits a better reactivity. To the best of our knowledge, there has not been any previous description of azido group reduction with NaI in DMSO. This combination is a mild, suitable and inexpensive system for the efficient synthesis of **13.** With regard to the role of LiCl in DMSO, it promoted desilylation and further cyclization by the internal displacement of the nucleofuge. The failed attempts of direct substitution on C-6 by external nucleophiles may be due to the large steric hindrance of the trityl group.



Scheme 3. Reagents: (a) chloromethanesulfonyl chloride, py; (b) Ac_2O, py; (c) MsCl, py; (d) NaN_3, DMF, cat. AcOH.

4. Experimental

4.1. General

All reactions were carried out under either an argon or nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on E. Merck silica gel plates (0.25 mm) and visualized using UV light (254 nm) and/or heating with 7% ethanolic phosphomolybdic acid solution. Flash chromatography was performed on E. Merck Silica Gel (60, particle size 0.040–0.063 mm). After chromatographic purification, the formation of solid foam is favoured by dissolving syrupy products in some Et_2O and evaporating in vacuo. NMR spectra were recorded on a Bruker WP200SY spectrometer at room temperature. Mono- and bidimensional experiments (SEFT, COSY and gHMQC) were performed to elucidate the new structures. Chemical shifts (ppm) are reported relative to the residual solvent peak. Multiplicities are designated as singlet (s), doublet (d), triplet (t) and multiplet (m). Coupling constants are expressed as *J* values in Hertz units. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Elemental analyses were performed by the Microanalyses service of the University of Málaga. High resolution mass spectra (HRMS) were recorded on a Micromass AutoSpecQ instrument of the University of Granada or on a Kratos MS-80RFAa of the University of Seville.

4.2. 2-Azido-*N*,*N*-diethyl-4,5-*O*-isopropylidene-7-*O*-trityl-D-*glycero*-D-*allo*-heptonamide 7

To a stirred solution of epoxiamide **1**[21,8a] (2.58 g, 4.7 mmol) in DMF (31.5 mL) were added NaN_3 (0.46 g, 7.1 mmol) and AcOH (0.13 mL, 2.3 mmol). The mixture was left at rt and monitored by TLC. After 4 d, more NaN_3(1.5 equiv) and AcOH (0.5 equiv) were added and the reaction was left for 4 d.[22] Then, the mixture was diluted with ethyl ether and washed with aq NH_4Cl and then with water. The organic layer was dried over $MgSO_4$ and the solvents were evaporated in vacuo. Purification by column chromatography gave **7** (1.71 g) as a white foam and 500 mg of **1** (80% total yield over recovered starting material). R_f: 0.5 (7:3 hexane/ethyl acetate), $[\alpha]_D^{21} = -28$ (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.60–7.20 (m, 15H, Ph), 4.36 (dd, 1H, $J_{5,6} = 9.7$, H-5), 4.15 (dd, 1H, H-3), 4.04 (dd, 1H, $J_{4,5} = 5.4$, $J_{4,3} = 10.0$, H-4), 3.96 (m, 1H, H-6), 3.93 (d, 1H, $J_{2,3} = 3.0$, H-2), 3.51–3.32 (m, 5H, H-7 and $2CH_2CH_3$), 3.26 (dd, 1H, $J_{7',6} = 5.5$, $J_{7,7'} = 9.7$, H-7′), 1.25–1.17 (m, 12H, CH_3). ^{13}C NMR δ (100 MHz, $CDCl_3$): 168.8 (*C*O), 144.1, 128.8, 127.7 and 126.8 (Ph), 108.8 (CMe_2), 86.4 (CPh_3), 77.7 (C-4, 5), 73.2 (C-3), 68.5 (C-6), 65.2 (C-7), 55.0 (C-2), 42.6 and 41.0 (CH_2CH_3), 27.9 and 25.2 [$C(CH_3)_2$], 14.2 and 13.0 (CH_2CH_3). HRMS (FAB): *m*/*z* 611.2845 $[M+Na]^+$ ($C_{33}H_{40}N_4NaO_6$ requires 611.2845). Elemental Anal. Calcd for $C_{33}H_{40}N_4O_6$: C, 67.33; H, 6.85; N, 9.52. Found: C, 67.47; H, 6.97; N, 9.15.

4.3. 2-Azido-*N*,*N*-diethyl-4,5-*O*-isopropylidene-3-*O*-triisopropylsilyl-7-*O*-trityl-D-*glycero*-D-*allo*-heptonamide 8 and 2-azido-*N*,*N*-diethyl-4,5-*O*-isopropylidene-6-*O*-triisopropylsilyl-7-*O*-trityl-D-*glycero*-D-*allo*-heptonamide 9

To a stirred solution of **7** (518 mg, 0.87 mmol) in anhydrous CH_2Cl_2 (2.5 mL) at 0 °C under an argon atmosphere were added 2,6-lutidine (0.25 mL, 2.19 mmol) and triisopropylsilyl triflate (0.26 ml, 0.96 mmol). After 20 min MeOH was added (5 mL). The reaction mixture was diluted with ethyl ether and washed with aq NH_4Cl and then with water. Organic solvents were evaporated in vacuo and the residue was purified by column chromatography to give silylated **8** (390 mg, 60%) and **9** (130 mg, 20%) as white solid foams. Compound **8** had R_f: 0.7 (6:1 hexane/ethyl acetate). $[\alpha]_D^{22} = -10$ (*c* 0.3, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.60–7.20 (m, 15H, Ph). 4.98 (dd, 1H, H-3), 4.51 (d, 1H, $J_{2,3} = 9.3$, H-2), 4.34 (dd, 1H, $J_{4,3} = 2.3$, H-4), 4.24 (dt, 1H, H-6), 3.95 (dd, 1H, $J_{5,4} = 5.5$, $J_{5,6} = 9.9$, H-5), 3.65 and 3.54 (2m, 2H, CH_2CH_3), 3.43 (dd, 1H, $J_{7,6} = 2.1$, H-7), 3.25 and 3.15 (2m, 2H, CH_2CH_3), 3.08 (dd, 1H, $J_{7,7'} = 9.2$, $J_{7',6} = 7.6$, H7′), 1.32 and 1.29 (s, 3H, $C(CH_3)_2$), 1.22 (t, 3H, CH_2CH_3), 1.16 (t, 3H, CH_2CH_3), 1.07–1.12 (m, 21H, $Si[CH(CH_3)_2]_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.3 (*C*O). 144.1, 128.8, 127.6 and 126.8 (Ph), 107.3 [$C(CH_3)_2$], 86.5 (CPh_3), 78.12 (C-4), 77.1 (C-5), 70.4 (C-3), 68.9 (C-6), 65.3 (C-7), 58.7 (C-2), 42.5 and

41.4 ($2CH_2CH_3$), 27.4 and 25.3 [$C(CH_3)_2$], 18.3–18.0 ($Si[CH(CH_3)_2]_3$), 14.9, 13.1 and 12.9 ($Si[CH(CH_3)_2]_3$ and $2CH_2CH_3$). HRMS (FAB): *m/z* 767.4180 $[M+Na]^+$ ($C_{42}H_{60}N_4NaO_6Si$ requires 767.4180). Elemental Anal. Calcd for $C_{42}H_{60}N_4O_6Si$: C, 67.71; H, 8.12; N, 7.52. Found: C, 67.61; H, 8.12; N, 7.34. Compound **9** had R_f: 0.6 (6:1 hexane/ethyl acetate). $[\alpha]_D^{22} = -12.5$ (*c* 0.2, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.6–7.2 (Ph), 4.87 (d, 1H, OH, $J_{OH,3} = 10$), 4.53 (m, 1H, H-6), 4.41 (dd, 1H, H-5), 4.1 (dt, 1H, H-3), 3.92 (dd, 1H, $J_{4,3} = 9.7$, $J_{4,5} = 7.0$, H-4), 3.62 (d, $J_{2,3} = 3.1$, 1H, H-2), 3.24–3.52 (m, 6H, H-7′, H-7, $2CH_2CH_3$), 1.23–1.09 (m, 33H, $Si[CH(CH_3)_2]_3$, $2CH_2CH_3$, $C(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.7 (*C*O), 144.0, 128.8, 127.7 and 126.8, (*Ph*), 107.8 [$C(CH_3)_2$], 86.8 (CPh_3), 80.4 (C-5), 77.2 (C-4), 71.9 and 72.0 (C-6 and C-3), 66.3 (C-7), 55.7 (C-2), 42.5 and 40.8 ($2CH_2CH_3$), 26.44 and 24.34 [$C(CH_3)_2$], 18.0–18.3 ($Si[CH(CH_3)_2]_3$), 14.2 and 13.0 ($2CH_2CH_3$), 12.5 ($Si[CH(CH_3)_2]_3$). HRMS (FAB): *m/z* 767.4182 $[M+Na]^+$ ($C_{42}H_{60}N_4NaO_6Si$ requires 767.4180). Elemental Anal. Calcd for $C_{42}H_{60}N_4O_6Si$: C, 67.71; H, 8.12; N, 7.52. Found: C, 67.68; H, 8.13; N, 7.44.

4.4. 2-Azido-*N*,*N*-diethyl-4,5-*O*-isopropylidene-6-*O*-mesyl-3-*O*-triisopropylsilyl-7-*O*-trityl-L-*glycero*-D-*allo*-heptonamide 10

To a stirred solution of **8** (351 mg, 0.47 mmol) in anhydrous pyridine (1.2 mL) at 0 °C under an argon atmosphere was added mesyl chloride (0.04 mL, 0.61 mmol). The reaction mixture was left to reach rt. After 15 h, TLC showed the completion of the reaction, and the reaction mixture was diluted with methanol. The mixture was partitioned between diethyl ether and water. The organic solvents were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography to give compound **10** (346 mg, 90%) as a white foam. R_f: 0.4 (4:1 hexane/ethyl acetate). $[\alpha]_D^{20} = +24$ (*c* 0.37, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.47–7.22 (m, 15H, *Ph*). 5.36 (dt, 1H, H-6), 4.95 (dd, 1H, $J_{3,2} = 2.5$, $J_{3,4} = 7.3$, H-3), 4.60 (t, 1H, $J_{5,4} = 6.8$, $J_{5,6} = 7.1$, H-5), 4.47–4.43 (m, 2H, H-4 and H-2), 3.63–3.54 (m, 3H, H-7′, H-7 and CH_2CH_3), 3.51–3.44 (m, 1H, CH_2CH_3), 3.39–3.30 (m, 2H, CH_2CH_3), 2.78 (s, 3H, OSO_2CH_3), 1.34 and 1.31 [2s, $2 \times 3H$, $C(CH_3)_2$], 1.22 and 1.15 (t, $2 \times 3H$, $2CH_2CH_3$), 1.08 (m, 21H, $Si[CH(CH_3)_2]_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5 (*C*O), 127.1, 127.7, 129.0 and 143.1 (*Ph*), 107.4 [$C(CH_3)_2$], 87.0 (CPh_3), 81.0 (C-6), 79.0 (C-4), 75.4 (C-5), 70.2 (C-3), 62.2 (C-7), 60.3 (C-2), 42.1 and 41.0 ($2CH_2CH_3$), 39.42 (OSO_2CH_3) 26.6 and 24.6 [$C(CH_3)_2$], 18.1 ($Si[CH(CH_3)_2]_3$), 14.6, 13.1 and 12.7 ($Si[CH(CH_3)_2]_3$ and $2CH_2CH_3$). HRMS (FAB): *m/z* 845.3954 $[M+Na]^+$ ($C_{43}H_{62}N_4NaO_8SSi$ requires 845.3955). Elemental Anal. Calcd for $C_{43}H_{62}N_4O_8SSi$: C, 62.74; H, 7.59; N, 6.81; S, 3.90. Found: C, 62.76; H, 6.69; N, 6.79; S, 3.76.

4.5. Chloromesylation of compound 8

To a dried flask under an argon atmosphere with compound **8** (70 mg, 0.093 mmol) were added pyridine (0.7 mL) and chloromethanesulfonyl chloride (0.01 mL, 0.12 mmol) at 0 °C, and the solution was stirred for 45 min. The reaction was quenched by the addition of methanol, diluted with ethyl ether and filtered through a small amount of silica gel. The filtrated solution was washed with water, dried over anhydrous $MgSO_4$, and concentrated giving pure **12** (80 mg, 100%) as a white foam. R_f: 0.6 (hexane/ethyl acetate, 4:1). $[\alpha]_D^{22} = +26$ (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.50–7.20 (m, 15H, Ph). 5.39 (dt, 1H, H-6), 4.95 (dd, 1H, $J_{3,2} = 7.0$, H-3), 4.47 (t, 1H, $J_{5,4} = 5.8$, $J_{5,6} = 3.5$, H-4), 4.38 (d, 1H, H-2), 4.34 (dd, 1H, H-5), 4.16 (2d, 2H, SO_2CH_2Cl), 3.52 (m, 2H, H-7, H-7′), 3.32 (m, 4H, $2CH_2CH_3$), 1.27 and 1.24 [s, 3H, $C(CH_3)_2$], 1.15 and 1.08 (t, 3H, CH_2CH_3), 1.01–0.98 (m, 21H, $Si[CH(CH_3)_2]_3$). ^{13}C NMR δ (100 MHz, $CDCl_3$): 166.3 (*C*O), 142.7, 128.8, 127.8 and 127.2 (Ph), 107.4 [$C(CH_3)_2$], 87.3 (CPh_3), 82.9 (C-6), 78.5 (C-4), 75.0 (C-5), 70.1 (C-3), 62.2 (C-7), 60.4 (C-2), 54.9 (OSO_2CH_2), 42.1 and 41.0 ($2CH_2CH_3$), 26.8 and 24.8 [$C(CH_3)_2$], 18.1 ($Si[CH(CH_3)_2]_3$), 14.5, 13.0 and 12.8 ($Si[CH(CH_3)_2]_3$ and $2CH_2CH_3$). HRMS (FAB): *m/z* 879.3567 $[M+Na]^+$.

4.6. *N*,*N*-Diethyl-2,6-dideoxy-2,6-imino-4,5-*O*-isopropylidene-3-*O*-triisopropylsilyl-7-*O*-trityl-L-*glycero*-D-*allo*-heptonamide 13

To a solution of compound **12** (30 mg, 0.034 mmol) in DMSO (0.5 mL) was added NaI (6.81 mg, 0.045 mmol, 1.3 equiv) with stirring. The reaction was monitored by TLC. After 48 h, the solution was diluted with ethyl ether, washed with water, dried over anhydrous $MgSO_4$, and concentrated. Purification by column chromatography afforded piperidine **13** (18.5 mg, 75%) as a white solid foam. R_f: 0.4 (hexane/ethyl acetate, 4:1). $[\alpha]_D^{22} = -10.5$ (*c* 0.26, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.10 (m, 15H, Ph), 4.47–4.44 (m, 3H, H-3, 4 and 5), 3.74 (d, 1H, $J_{2,3} = 8.80$, H-2), 3.25 (m, 4H, $2CH_2CH_3$), 3.04–2.95 (m, 3H, H-6, 7 and 7′), 1.37 and 1.28 [2s, $2 \times 3H$, $C(CH_3)_2$], 1.11–0.98 (m, 21H, $Si[CH(CH_3)_2]_3$, $2CH_2CH_3$). ^{13}C NMR δ (100 MHz, $CDCl_3$): 171.9 (*C*O), 144.15, 128.8, 127.5 and 126.7 (Ph), 108.5 [$C(CH_3)_2$], 86.4 (CPh_3), 75.7 (C-4), 74.5 (C-5), 68.7 (C-3), 63.5 (C-7), 53.4 (C-2), 50.8 (C-6), 41.9 and 40.9 ($2CH_2CH_3$), 26.3 and 23.9 [$C(CH_3)_2$], 17.9 ($Si[CH(CH_3)_2]_3$), 14.8 and 12.7 ($2CH_2CH_3$), 12.6 ($Si[CH(CH_3)_2]_3$). HRMS (FAB): *m/z* 701.4316 $[M+H]^+$ ($C_{42}H_{61}N_2O_5Si$ requires 701.4349).

4.7. Acetylation of piperidine 13

To a stirred solution of piperidine **13** (13 mg, 0.018 mmol) in dried pyridine (0.5 mL) was added acetic anhydride (0.4 mL). The reaction was monitored by TLC which showed the slow formation of a more polar product. After 6 d, the solvent is concentrated and the residue chromatographed to give unreacted **13** (5 mg) and pure **14** (7 mg) as a white solid foam, 82% total yield over recovered starting material. R_f: 0.33 (4:1 hexane/ethyl acetate). ^1H NMR δ (400 MHz, $CDCl_3$): 7.42–7.12 (m, 15H, Ph), 5.10 (d, 1H, $J_{2,3} = 6.1$, H-2), 4.60 (dd, 1H, $J_{5,4} = 7.9$; $J_{5,6} = 4.8$, H-5), 4.50 (m, 2H, $J_{3,4} = 3.05$. H-3 and 6), 4.30 (dd, 1H, H-4), 3.84 (dd, 1H, H-7), 3.53 (m, 4H, $2CH_2CH_3$), 3.24 (m, 1H, H-7′), 1.86 (s, 3H, $COCH_3$), 1.38 [s, 3H, $C(CH_3)_2$], 1.31 [m, 6H, CH_2CH_3, $C(CH_3)_2$], 1.13 (t, 3H, CH_2CH_3), 1.06 (m, 21H, $Si[CH(CH_3)_2]_3$). ^{13}C NMR δ (100 MHz,

$CDCl_3$): 171.9 (*C*ONEt$_2$), 170.0 (*C*OCH$_3$), 143.7, 128.8, 127.7 and 126.9 (Ph), 109.6 [*C*(CH$_3$)$_2$], 86.9 (*C*Ph$_3$), 73.9 (C-4), 72.5 (C-5), 68.4 (C-3), 64.1 (C-7), 57.0 (C-2), 56.8 (C-6), 42.3 and 40.7 (2*C*H$_2$CH$_3$), 25.6 and 23.8 [C(*C*H$_3$)$_2$], 23.1 (CO*C*H$_3$), 17.9 (Si[CH(*C*H$_3$)$_2$]$_3$), 14.1 and 12.8 (2CH$_2$*C*H$_3$), 12.7 (Si[*C*H(CH$_3$)$_2$]$_3$). HRMS (FAB): *m*/*z* 743.4453 [M+H]$^+$ ($C_{44}H_{63}N_2O_6Si$ requires 743.4455).

4.8. 3,6-Anhydro-2-azido-*N*,*N*-diethyl-4,5-*O*-isopropiliden-7-*O*-trityl-L-*glicero*-D-*allo*-heptonamide 16

To a solution of **12** (50 mg, 0.058 mmol) in DMSO (0.8 mL) was added LiCl (3.2 mg, 0.075 mmol) with stirring at rt. After 30 h, a unique more polar product was observed (TLC). The mixture was diluted with ethyl acetate and washed with water. Organic solvents were concentrated in vacuo to give **16** (26.8 mg, 81%) as a white solid, which was characterized by NMR spectroscopy. mp: 169 °C. R_f: 0.3 (hexane/ethyl acetate, 4:1). $[\alpha]_D^{21} = +7.5$ (*c* 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42–7.12 (m, 15H, Ph), 4.92 (dd, 1H, $J_{4,5} = 6.3$, H-4), 4.68 (dd, 1H, $J_{5,6} = 3.7$, H-5), 4.35 (dd, 1H, $J_{3,4} = 1.6$, H-3), 4.11 (m, 1H, H-6), 3.92 (d, 1H, $J_{2,3} = 6.9$, H-2), 3.46 (m, 1H, C*H*$_2$CH$_3$), 3.38–3.23 (m, 5H, H-7,7′, C*H*$_2$CH$_3$), 1.28 [s, 3H, C(C*H*$_3$)$_2$], 1.24 [s, 3H, C(C*H*$_3$)$_2$], 1.18 and 1.10 (2t, 2 × 3H, CH$_2$C*H*$_3$). ^{13}C NMR δ (100 MHz, $CDCl_3$): 166.3 (*C*O), 143.7, 128.8, 127.7 and 126.9 (Ph), 112.9 [*C*(CH$_3$)$_2$], 86.9 (*C*Ph$_3$), 84.3 (C-4), 82.6 (C-5), 81.7 (C-4), 81.3 (C-3), 62.5 (C-7), 58.7 (C-2), 42.0 and 41.0 (2*C*H$_2$CH$_3$), 26.3 and 25.3 [C(*C*H$_3$)$_2$], 14.8 and 12.9 (2CH$_2$*C*H$_3$). HRMS (FAB): *m*/*z* 593.2738 [M+Na]$^+$ ($C_{33}H_{38}N_4NaO_5$ requires 593.2740).

4.9. Mesylation of compound 1

To a stirred solution of **1** (500 mg, 0.9 mmol) in the anhydrous pyridine (2 mL) at 0 °C under an Argon atmosphere was added mesyl chloride (0.2 mL, 2.5 mmol). The reaction mixture was left to reach rt. After 5 h, the mixture was partitioned between diethyl ether and water. The organic layer was washed with aq ammonium chloride and then with water. Organic solvents were dried over $MgSO_4$ and concentrated in vacuo to give a residue which was purified by column chromatography to give **17** (433 mg, 76%) as a white solid foam, mp 58 °C. R_f: 0.3 (hexane/ethyl acetate, 1:1). $[\alpha]_D^{20} = -6$ (*c* 1.01, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55–7.20 (m, 15H, Tr), 5.06 (m, 1H, H-6), 4.59 (dd, 1H, $J_{5,6} = 6.6$, H-5), 3.88 (dd, 1H, $J_{4,5} = 6.5$, H-4), 3.64 (dd, 1H, $J_{7,6} = 2.9$, H-7), 3.55 (dd, 1H, $J_{7',7} = 9.3$, $J_{7',6} = 2.9$, H-7′), 3.50 (d, 1H, H-2), 3.49–3.37 (m, 4H, 2C*H*$_2$CH$_3$), 3.31 (dd, 1H, $J_{3,2} = 1.7$, $J_{3,4} = 7.1$, H-3), 3.10 (s, 3H, OSO$_2$C*H*$_3$), 1.33 and 1.32 [2s, 2 × 3H, C(C*H*$_3$)$_2$], 1.25 and 1.16 (2t, 2 × 3H, 2CH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2 (CO, 25.0 (C(CH$_3$)$_2$)), 143.3, 128.7, 127.8 and 127.1 (*Ph*), 109.4 (*C*Me$_2$), 87.2 (*C*Ph$_3$), 78.3 (C-6), 77.1 (C-5), 75.6 (C-4), 62.5 (C-7), 54.3 (C-3), 52.7 (C-2), 41.4 (OSO$_2$*C*H$_3$), 40.7 and 38.2 (*C*H$_2$CH$_3$), 27.2 [C(*C*H$_3$)$_2$], 14.7 and 12.8 (CH$_2$*C*H$_3$). HRMS (FAB): *m*/*z* 646.2454 [M+Na]$^+$ ($C_{34}H_{41}NNaO_8S$ requires 646.2451).

4.10. Formation of compound 16 from mesylated epoxiamide 17

To a stirred solution of **17** (50 mg, 0.080 mmol) in DMF (1 mL) were added NaN_3 (18 mg, 0.277 mmol) and acetic acid (0.04 mL). The reaction mixture was heated at 60 °C for one week. Then, the mixture was diluted with ethyl ether and washed with aq NH_4Cl and then with water. The organic layer was dried over $MgSO_4$ and the solvents were evaporated in vacuo. Purification by column chromatography gave **16** (35 mg, 76%) which showed the same spectroscopic data as above.

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19. *Compound* **15**: $[\alpha]_D^{20} = -27$ (*c* 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 4.41 (dd, 1H, $J_{4,5} = 4.1$, H-4), 4.21 (dd, 1H, $J_{3,4} = 3.5$, $J_{3,2} = 9.4$, H-3), 3.79–3.74 (m, 3H, H-7, 2 and 5), 3.65 (m, 1H, CH_2CH_3), 3.44–3.30 (m, 3H, H-7′, CH_2CH_3), 3.20 (m, 1H, CH_2CH_3), 2.75 (ddd, 1H, $J_{5,6} = 8.6$, $J_{6,7} = 3.4$, $J_{6,7'} = 9.2$, H-6), 1.52 and 1.32 [2s, 2 × 3H, $C(CH_3)_2$], 1.22 and 1.11 (t, 2 × 3H, CH_2CH_3), 1.04 (m, 21H, $Si[CH(CH_3)_2]_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2 ($CONEt_2$). 109.8 [$C(CH_3)_2$], 75.0 (C-5) 76.8 (C-4), 71.4 (C-3), 63.1 (C-7), 58.0 (C-6), 55.2 (C-2), 42.4 and 41.1 ($2CH_2CH_3$), 28.6 and 26.1 [$C(CH_3)_2$], 18.1 ($Si[CH(CH_3)_2]_3$), 15.0 and 13.1 ($2CH_2CH_3$), 12.8 ($Si[CH(CH_3)_2]_3$).
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22. With layer reaction times, the product of cyclization **1** (see Ref. 8a) was obtained in addition to the main product **7**.