Synthesis of bis-(oxabicyclic tetrazole) polyoxyethylene *via* an intramolecular [2+3] cycloaddition of bis-(azidonitrile) polyoxyethylene derivatives

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(Received: 16 July 2015, accepted: 31 December 2015)

Abstract: Oligoethylene glycol diglycidyl ethers **1** were converted by the action of sodium azide in the hydro-methanolic medium into the corresponding (azido alcohols) **2**. The latter react with 2-chloroacetonitrile in the presence of potassium *t*-butoxide in one pot, leading to new condensed ring systems 1,5-tetrazole **4** via an intramolecular [2+3] cycloaddition reaction. The present method avoids the formation and isolation of azido nitrile **3** generated *in situ* and also the use of any catalyst.

Keywords: oligoethylene glycol diglycidyl ether, tetrazole, sodium azide, chloroacetonitrile, potassium t-butoxide, intramolecular [2+3] cycloaddition reaction.

Résumé: Les oligoéthylèneglycol diglycidyl éthers **1** ont été converties par action de l'azoture de sodium dans un milieu hydro-methanolique en bis-(azido alcohols) **2** correspondants. Ces derniers réagissent avec le 2-chloroacétonitrile en présence de tertiobutylate de potassium en une seule étape conduisant à des nouveaux systèmes cycliques condensés 1,5-tétrazoliques **4** via une réaction de cycloaddition[2+3] intramoléculaire. La présente méthode évite la formation et l'isolation de l'azido nitrile **3** généré *in situ* ainsi que l'utilisation d'un catalyseur.

Mots Clés : Oligoéthylène glycol diglycidyl éther, tetrazole, azoture de sodium, chloroacetonitrile, tertiobutylate de potassium, réaction de cycloaddition [2+3] intramoléculaire.

INTRODUCTION

Tetrazole compounds are widely employed as surrogates for carboxylic acids and as pharmaceuticals section [1-3]. They are also found several applications in the industrial fields [4,5] and as precursors in the synthesis of heterocyclic compounds [6,7]. The classical synthetic approach towards disubstituted tetrazoles involves an intermolecular cyclization process of non activated-nitriles and azides [8,9] using polar and aprotic solvents at elevated temperatures. Oximes and amides were frequently used in these preparations [10]. Fused cyclic tetrazole compounds are generally carried out *via* intramolecular [2+3] cycloaddition reaction in DMF or DMSO at temperatures greater than 100 °C [11]. From the literature survey, Bliznets *et al.* [12] have reported the preparation of 3-(tetrazol-5-yl)-pyridine tricyclic systems by intramolecular reaction of cyanopyridines and azides.

Recently, diversely functionalised oxabicyclic tetrazoles were obtained by a facile Lewis acid induced cycloaddition reaction of TMSCN with azido aryl dioxolane in the presence of BF_3OEt_2 [13]. More recently, we have reported the synthesis of a

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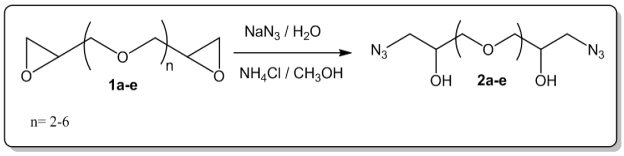


Scheme 1: Preparation of bis-(azido alcohols) **2**

series of polyoxyethylene bis- oxazolidinones from polyoxyethylene diglycidyl ethers and simple isocyanates in the presence of lithium bromide as catalyst [14]. In continuation of our research studies on polyoxyethylene chain derivatives [15], we report in this article the synthesis of a series of new bis-(oxabicyclic tetrazoles) bridged by a polyoxyethylene chain starting from the bis-(azido alcohol) polyoxyethylenes.

RESULTS AND DISCUSSION

Our approach started with the synthesis of bis-(azido alcohols) **2** from oligoethylene glycol diglycidyl ethers **1** [16] and sodium azide in the presence of ammonium chloride at 80°C in a mixture of methanol-water as solvent in 45-67% yield after purification with flash column chromatography as shown in scheme 1**.** The bis-(azido alcohol) polyoxyethylenes **2a-d** synthesized are summarized in table 1.

The first attempts to develop a new series of bis-(oxabicyclic tetrazole), were conducted from bis-(azido alcohol) polyoxyethylenes **2** and 2-chloroacetonitrile in the presence of several couples base/solvent. The use of sodium hydroxide in dichloromethane or sodium hydride in dry THF provides a complex mixture of products. In the presence of triethylamine in acetone or pyridine base and solvent, the reaction does not take place and we recovered the starting product.

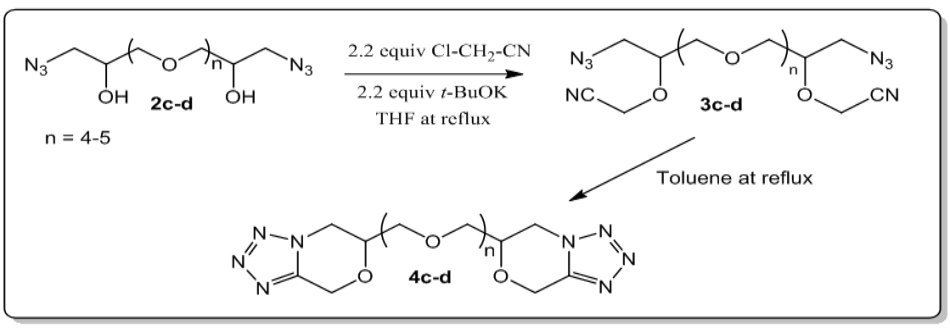
Nevertheless, the key step for this work consist when two equivalents of *t*-BuOK were employed, the *O*-alkylation of azido alcohol **2** with 2-chloroacetonitrile afforded in this case only the corresponding bis-(azido nitriles) **3c-d** in 75-82% yields and we have avoided the formation of the complex mixture of products. The reaction was conducted in dry THF under reflux for 48h. The bis-(azido nitriles) was also converted *via* intramolecular [2+3] cyclization reaction in refluxing toluene for 55 h minotoride by TLC with ethyl acetate to lead bis-(oxabicyclic tetrazoles) **4** in moderate yields (65-72%) as shown in scheme 2.

In order to improve this method, we have carried out the reaction in a one-pot procedure.

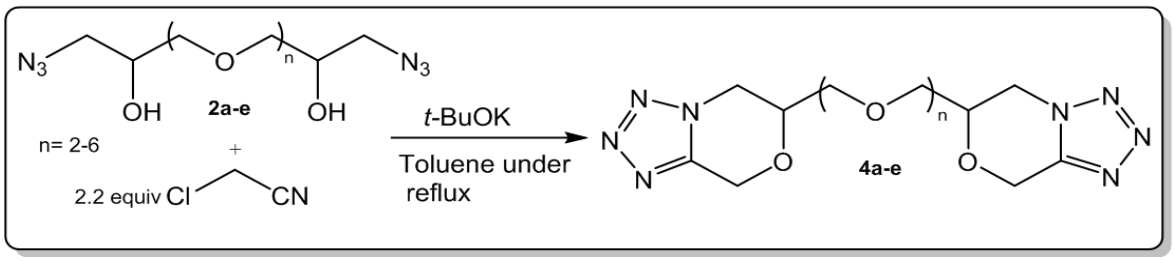
Table I: Synthesis of bis-(azido alcohols)polyoxyethylene **2a-d**.

Bis-(azidoalcohol **2)**	**2a**	**2b**	**2c**	**2d**	**2e**
Chain length	n=2	n=3	n=4	n=5	n=6
Yield (%) [a]	45	57	59	61	67

[a] Isolated yield after purification with flash column chromatography.



Scheme 2: Synthesis of tetrazoles **4** in two steps via isolation and purification of azido nitriles **3**.



Scheme 3: One pot synthesis of tetrazoles **4**

Although the reaction proceeds in one step and this allows us to avoid the isolation and purification of azido alcohols **2**, the reaction presents some anomaly such as longer duration of reaction time and lower yield. We also noticed that 20 % of the azido nitrile **3** is not converted into bis-(oxabicyclic tetrazoles) **4** and it was recovered at the end of the reaction. To overcome these difficulties on yield and reaction time, the same procedure was repeated using 4 equivalents of potassium *t*-butoxide afforded bis-(oxabicyclic tetrazole) **4** with good at excellent yields as shown in table 3.

It should be noted that the use of four equivalents of *t*-butoxide allows reduce significantly the reaction time and increase the reaction yield. Indeed, the used of two equivalents previously are not enough fully to realize the *O*-alkylation reaction between azido alcohols and chloroacetonitrile and thus we recovered at the end of the reaction about 20% of azido alcohols. The extension of the reaction time in the case of two equivalents is necessarily due to the lower quantity of *t*-butoxide.

The plausible mechanism for the synthesis of bis-(oxabicyclic tetrazoles) **4**

Table II: One-pot preparation of bis-(oxabicyclic tetrazoles) **4** [a] from bis(azido alcohols) **2** with two equivalent of *t*-butoxide.

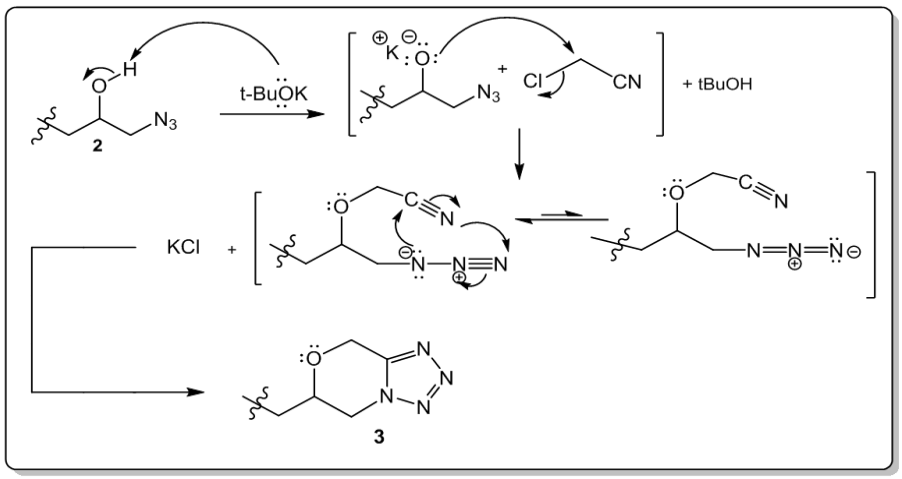
Entry	Bis-(azido alcohol) 2	Bis-(oxabicyclic tetrazole) 4	Time (h)	Yield (%) [a]
1, n=2	**2a**	**4a**	40	67
2, n=3	**2b**	**4b**	48	68
3, n=4	**2c**	**4c**	52	70
4, n=5	**2d**	**4d**	58	72
5, n=6	**2e**	**4e**	62	74

[a] Isolated yield after purification with columns chromatography.

Table III: One-pot preparation of bis-(oxabicyclic tetrazoles) **4** [a] from bis-(azido alcohols) **2** with four equivalent of *t*-butoxide.

Entry	Bis-(azido alcohol) 2	Bis-(oxabicyclic tetrazole) 4	Time (h)	Yield (%) [a]
1, n=2	**2a**	**4a**	5	77
2, n=3	**2b**	**4b**	7	81
3, n=4	**2c**	**4c**	10	85
4, n=5	**2d**	**4d**	12	87
5, n=6	**2e**	**4e**	14	90

[a] Isolated yield after purification with columns chromatography.



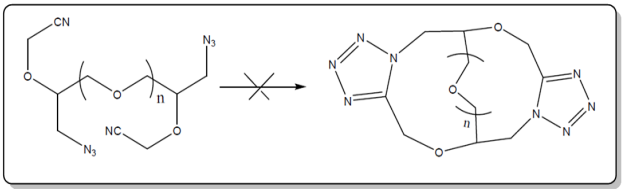
Scheme 4: Plausible mechanism for the synthesis of bis-(oxabicyclic tetrazoles) **4**

started first with the *O*-alkylation of chloroacenitrile with azido alcoholate generated *in situ* by the action of potassium *t*-butoxide on bis-(azido alcohol) **2**. The intermediate azido nitriles formed previously was converted via an intramolecular cycloaddition [2+3] reaction between the azide and nitrile groups neighbors to lead a target compounds bis-(oxabicyclic tetrazoles) **4** as shown in scheme 4.

We have shown that bis-(azido alcohols) **2** bridged by a polyoxyethylene chain undergo intramolecular cycloaddition reactions, affording a new bis-(oxabicyclic tetrazoles) **4**. This can be interpreted by the favorable arrangements of cyano and azido groups at the ends of polyoxyethylene chains which make the cycloaddition step possible. We can also mention that the intramolecular cyclization reaction leading to the *endo-isomer* does not occur since involves both nitrile and azide groups very distant from each other.

The structures of compounds **2**, **3** and **4** were fully characterized by ^{1}H and ^{13}C NMR and High-resolution mass spectrometry. For instance, ^{1}H NMR spectrum of compound **2c** shows a multiplet centred at 3.34 ppm corresponding to azidomethyl group and another multiplet at 3.95 ppm related to the proton carried by the hydroxylated carbon. The ^{1}H NMR spectrum of compound **3c** present an AB system ($^{2}J_{AB}$=18.0 Hz) centred at 4.5 ppm related to the cyanomethyl group and another multiplet between 3.40 and 3.42 ppm attributed to azidomethyl group. The ^{13}C NMR spectrum of compound **3c** shows the presence of a singlet at 53.34 ppm corresponding to the carbon of the azidomethyl moiety. Carbon of nitrile group resonates as a singlet at 116.47 ppm.

The analysis of the ^{1}H NMR spectrum of compound **4c**, shows the presence of a signal between 4.95 and 5.30 ppm which resonates as a corresponding AB system of CH_2O group adjacent to the tetrazole ring ($^{2}J_{AB}$=15.0Hz). The methylene group CH_2N in α of tetrazole system resonates between 4.25-4.63 ppm and represents the AB part of an ABX system which $^{2}J_{AB}$ coupling constant in the order of 12 Hz. The ^{13}C NMR spectrum of compound **3c** contained a singlet at 149.53 attributed to the tetrazole carbon.



CONCLUSION

A novel series of bis-(oxabicyclic tetrazole) system bridged by a polyoxyethylene chain **4** was elaborated in one pot under free-catalyst via an intramolecular [2+3] dipolar cycloaddition process of azido

nitrile generated *in situ* from starting materials azido alcohol and chloroacetonitrile. The new bis-(oxabicyclic tetrazoles) **4** could have interesting biological properties which are under investigation in our laboratory.

EXPERIMENTAL

All commercially available reagents were used without further purification. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on silica gel (230-400 mesh). Analytical thin layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Fluka 40-60 mm). The developed chromatogram was analyzed by UV lamp (254 nm). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 at 300 and 75 MHz, respectively. Deuterochloroform ($CDCl_3$), unless otherwise noted, on a 300 MHz instrument. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s =singlet, d = doublet, t = triplet, q = quartet, and m = multiplet) and coupling constant in hertz (Hz). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sep = septet, m = multiplet, br = broad), coupling constant in hertz (Hz), and integration. High-Resolution mass spectra (HMRS) were obtained from FINIGAN MAT 95 SBE.

1. Preparation of bis-(azido alcohol) polyoxyethylenes 2a-e: Typical procedure

To a solution of oligoethylene glycol diglycidyl ether **2** (30 mmol) in a mixture of Methanol-water (100 /24 mL) were added 15.5g (240 mmol) of sodium azide and 6g (120 mmol) of ammonium chloride. The mixture was heated at 80 °C for 48 h. The reaction was monitored with TLC with diethyl ether. At the end of the reaction, the mixture was cooled and the solvents were evaporated under reduced pressure. The concentrated mixture was diluted with water (40 mL), extracted with chloroform (4x40 mL) and dried over $MgSO_4$. The solvent was removed and the residue was purified on column chromatography with diethyl ether as eluent to yield the bis-(azido alcohol)polyoxyethylenes **2** as colorless viscous oils.

1,10-Diazido-4,7-dioxadecan-2,9-diol (2a): IR ($CHCl_3$): ν 3414 (OH), 2119 (N_3) cm^{-1}. ^{1}H NMR ($CDCl_3$,300 MHz), δ(ppm): 3.33-3.34 (m, 4H, $2xCH_2N_3$), 3.46-3.58 (m, 4H, $2C\underline{H}_2CHOH$), 3.60-3.68 (m, 4H, $2CH_2O$), 3.80 -3.90 (m, 2H, 2 C<u>H</u>OH); ^{13}C NMR ($CDCl_3$,75 MHz), δ(ppm): 53.22 (s, 2C, $2xCH_2N_3$), 69.51 (s, 2C, 2CHOH), 69.70-70.29 (s, 2C, $2CH_2O$), 72.31 (s, 2C, $2\underline{C}H_2OCHOH$). HRMS (ESI) for $C_8H_{16}O_4N_6Na$, $[M+Na]^+$ calculated: 283,1131, found: 283.1134; Δ(mmu)=0.3.

1,13-Diazido-4,7,10-trioxatridecan-2,12-diol (2b): IR ($CHCl_3$): ν 3419 (OH), 2125 (N_3) cm^{-1}. ^{1}H NMR ($CDCl_3$,300 MHz), δ (ppm): 3.33-3.35 (m, 4H, $2xCH_2N_3$), 3.48-3.59 (m, 4H, $2C\underline{H}_2O$ CHOH), 3.62-3.67 (m, 8H, $4CH_2O$), 3.94-3.98 (m, 2H, 2 C<u>H</u>OH); ^{13}C NMR ($CDCl_3$,75 MHz), δ(ppm): 53.35 (s, 2C, $2xCH_2N_3$), 69.49 (s, 2C, 2CHOH), 70.59-70.95 (m, 4C, $4CH_2O$), 72.86 (s, 2C, $2\underline{C}H_2OCHOH$). HRMS (ESI) for $C_{10}H_{20}O_5N_6Na$, $[M+Na]^+$ calculated value: 327,1393, found value: 327.1395; Δ(mmu) =0.2.

1,16-Diazido-4,7,10,13-tetraoxahexadecan-2,15-diol (2c): IR ($CHCl_3$): ν 3417 (OH), 2120 (N_3) cm^{-1}. ^{1}H NMR ($CDCl_3$,300 MHz), δ(ppm): 3.33-3.34 (m, 4H, $2xCH_2N_3$), 3.47-3.58 (m, 4H, $2C\underline{H}_2O$ CHOH), 3.62-3.66 (m, 12H, $6CH_2O$), 3.93-3.96 (m, 2H, 2 C<u>H</u>OH); ^{13}C NMR ($CDCl_3$,75 MHz), δ(ppm): 53.26 (s, 2C, $2xCH_2N_3$), 69.56 (s, 2C, 2CHOH), 70.26-72.99 (m, 6C, $6CH_2O$), 73.02 (s, 2C, $2\underline{C}H_2OCHOH$). HRMS (ESI) for $C_{12}H_{24}O_6N_6Na$, $[M+Na]^+$ calculated value: 371,1655, found value: 371.1656; Δ (mmu)=0.1.

1,19-Diazido-4,7,10,13,16-pentaoxanonadecan-2,18-diol (2d): IR ($CHCl_3$): *v* 3421 (OH), 2118 (N_3) cm^{-1}. ^1H NMR ($CDCl_3$,300 MHz), δ(ppm): 3.32-3.34 (m, 4H, $2xCH_2N_3$), 3.44-3.54 (m, 4H, $2C\underline{H}_2O$ CHOH), 3.61-3.67 (m, 16H, $8CH_2O$), 3.91-3.98 (m, 2H, 2 C<u>H</u>OH); ^{13}C NMR ($CDCl_3$,75 MHz), δ(ppm): 53.29 (s, 2C, $2xCH_2N_3$), 69.47 (s, 2C, 2CHOH), 70.35-72.89 (m, 8C, $8CH_2O$), 72.76 (s, 2C, $2\underline{C}H_2OCHOH$). HRMS (ESI) for $C_{14}H_{28}N_6O_7Na$, $[M+Na]^+$ calculated value: 415,1917, found value: 415,1919; Δ (mmu)=0.2.

1,22-Diazido-4,7,10,13,16,19-hexaoxadocosan-2,21-diol (2e): IR ($CHCl_3$): *v* 3421 (OH), 2118 (N_3) cm^{-1}. ^1H NMR ($CDCl_3$,300 MHz), δ(ppm): 3.32-3.34 (m, 4H, $2xCH_2N_3$), 3.45-3.57 (m, 4H, $2C\underline{H}_2O$ CHOH), 3.61-3.64 (m, 20H, $10CH_2O$), 3.92-3.98 (m, 2H, 2 C<u>H</u>OH); ^{13}C NMR ($CDCl_3$,75 MHz), δ (ppm): 53.28 (s, 2C, $2xCH_2N_3$), 69.49 (s, 2C, 2CHOH), 70.32-72.91 (m, 6C, $6CH_2O$), 72.82 (s, 2C, $2\underline{C}H_2OCHOH$). HRMS (ESI) for $C_{16}H_{32}O_8N_6Na$, $[M+Na]^+$ calculated value: 459,2179, found value: 459,2182; Δ(mmu) =0.3.

2. General procedure for the preparation of bis-(azidonitrile) (3)

To a solution of azido alcohol **2** (7.6 mmol) in 50 mL of dry THF were added 1.87g (16.72 mmol) of potassium *t*-butoxide and 1.26 g (16.72 mmol) of 2-chloroacetonitrile. The mixture was heated at reflux for 48 h. The reaction was monitored with TLC with diethyl ether. At the end of the reaction, the mixture was cooled, diluted with water (40 mL), extracted with CH_2Cl_2 (4x40 mL) and dried over $MgSO_4$. The solvent was removed and the residue was purified with column chromatography with diethyl ether and then with ethyl acetate as eluents to yield the bis-(azido nitrile) polyoxyethylenes **3**.

4,17-Diazidomethyl-3,6,9,12,15,18-hexaoxaeicosannitrile (3c): Yield: 75 %, viscous oil. IR ($CHCl_3$): *v* 2224 (CN), 2115 (N_3) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm), *J* (Hz): 3.39-3.41 (m, 4H, $2xCH_2N_3$), 3.47-3.58 (m, 4H, $2C\underline{H}_2CHO$), 3.62-3.66 (m, 12H, $6CH_2O$), 3.85-3.89 (m, 2H, 2CHO); 4.45-4.58 (AB system, 4H, $2OCH_2CN$, $^2J_{HH}$= 18 Hz). ^{13}C NMR ($CDCl_3$,75 MHz), δ(ppm): 51.77 (s, 2C, $2CH_2N_3$), 69.34-71.29 (m, 6C, $6CH_2O$), 72.87 (s, 2C, $2\underline{C}H_2OCHO$), 78.77 (s, 2C, $2\underline{C}H_2OCN$), 116.45 (s, 2C, 2CN). HRMS (ESI) for $C_{16}H_{26}O_6N_8Na$, $[M+Na]^+$ calculated value: 449,1873, found value: 449,1876; Δ (mmu)=0.3.

4,17-Diazidomethyl-3,6,9,12,15,18-hexaoxaei cosannitrile (3d): Yield: 82 %, viscous oil. IR ($CHCl_3$): *v* 2227 (CN), 2117 (N_3) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ (ppm), *J* (Hz): 3.39-3.41 (m, 4H, $2xCH_2N_3$), 3.50-3.53 (m, 4H, $2C\underline{H}_2CHO$), 3.61-3.64 (m, 16H, $8CH_2O$), 3.85-3.89 (m, 2H, 2CHO); 4.45-4.59 (AB system, 4H, $2OCH_2CN$, $^2J_{HH}$= 18 Hz). ^{13}C NMR ($CDCl_3$,75 MHz), δ(ppm): 51.65 (s, 2C, $2CH_2N_3$), 68.07-71.88 (m, 8C, $8CH_2O$), 72.87 (s, 2C, $2\underline{C}H_2OCHO$), 78.91 (s, 2C, $2\underline{C}H_2OCN$), 116.58 (s, 2C, 2CN). HRMS (ESI) for $C_{18}H_{30}O_7N_8Na$, $[M+Na]^+$ calculated value: 493,2135, found value: 493,2137; Δ (mmu)=0.2.

3. Preparation of bis-(oxabicyclic tetrazole) (4) from azido nitrile (3): General procedure

A solution of azido nitrile **3** (7.6 mmol) in 50 mL of dry toluene was heated at reflux for 55 h. The reaction was monitored with TLC (ethyl acetate). At the end of the reaction, the mixture was cooled, the solvent was removed and the residue was purified with column chromatography with ethyl acetate as eluent to yield the bis-(oxabicyclic tetrazole) polyoxyethylenes **4** as yellow viscous oils.

4. One pot preparation of bis-(oxabicyclic tetrazole)polyoxyethylenes (4a-e) using 4 equivalent of *t*-butoxide : General procedure

To a solution of azido alcohol **2** (7.6 mmol) dissolved in 50 mL of dry toluene was added 3.4 g (30.4 mmol) of potassium *t*-butoxide and 1.26 g (16.72 mmol) of 2-chloroacetonitrile. The mixture was heated at reflux for 5-14 h (Table 3) and the reaction

was monitored with TLC (ethyl acetate). At the end of the reaction, the mixture was cooled, diluted with water (40 mL) and then extracted with dichloromethane (4x40 mL) and dried on $MgSO_4$. The solvent was removed and the residue was purified on column chromatography with ethyl acetate as eluent to obtain the bis-(oxabicyclic tetrazoles) **4** as yellow viscous oils.

1,6-Bis(5,6-dihydro-8H-tetrazolo[1,4]oxazin-6-yl)-2,5-dioxahexane (4a): ^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm), J (Hz): 5.35-4.92 (AB system, 4H, 2 OCH_2-C=N, $^2J_{HH}$= 15.1Hz), 4.61-4.24 (m, 4H, $2CH_2N$, $^2J_{HH}$= 12.2Hz), 4.23-4.11 (m, 2H, 2CHO), 3.91-3.75 (m, 4H, 2C$\underline{H_2}$O-CHO), 3.75-3.65 (m, 4H, $2CH_2O$). ^{13}C NMR ($CDCl_3$,75 MHz), δ(ppm) : 149.54 (s, 2C, 2C=N), 72.50-70.49 (m, 6C, $6CH_2O$), 61.93 (s, 2C, 2CHO), 47.03 (m, 2C, $2CH_2N$). HRMS (ESI) for $C_{12}H_{18}O_4N_8Na$, $[M+Na]^+$ calculated value: 361.1348, found value: 361.1350; Δ(mmu)=0.2.

1,9-Bis(5,6-dihydro-8H-tetrazolo[1,4]oxazin-6-yl)-2,5,8-trioxanonane (4b): ^{1}H NMR ($CDCl_3$, 300 MHz), δ(ppm), J (Hz): 5.32 -4.94 (AB system, 4H, $2OCH_2$-C=N, $^2J_{HH}$= 15.3Hz), 4.64-4.27 (m, 4H, $2CH_2N$, $^2J_{HH}$= 12.4Hz), 4.21-4.12 (m, 2H, 2CHO), 3.90-3.78 (m, 4H, 2C$\underline{H_2}$O-CHO), 3.72-3.64 (m, 8H, $4CH_2O$). ^{13}C NMR ($CDCl_3$, 300MHz), δ(ppm): 149.57 (s, 2C, 2C=N), 72.52-70.50 (m, 8C, $8CH_2O$), 61.91 (s, 2C, 2CHO), 47.05 (m, 2C, $2CH_2N$). HRMS (ESI) for $C_{14}H_{22}O_5N_8Na$, $[M+Na]^+$ calculated value: 405.1610, found value: 405.1613, Δ(mmu)=0.3.

1,12-Bis(5,6-dihydro-8H-tetrazolo[1,4]oxazin-6-yl)-2,5,8,11-tetraoxadidecane (4c): ^{1}H NMR ($CDCl_3$, 300 MHz), δ(ppm), J (Hz): 5.30-4.95 (AB system, 4H, 2 OCH_2-C=N, $^2J_{HH}$= 15.0Hz), 4.63-4.25 (m, 4H, $2CH_2N$, $^2J_{HH}$= 12.0Hz), 4.20-4.13 (m, 2H, 2CHO), 3.89 -3.77 (m, 4H, 2C$\underline{H_2}$O-CHO), 3.74-3.65 (m, 12H, $6CH_2O$). ^{13}C NMR ($CDCl_3$, 300MHz), δ (ppm) : 149.53 (s, 2C, 2C=N), 72.56-70.54 (m, 10C, $10CH_2O$), 61.96 (s, 2C, 2CHO), 47.06 (m, 2C, $2CH_2N$). HRMS (ESI) for $C_{16}H_{26}O_6N_8Na$, $[M+Na]^+$ calculated value: 449.1872, found value: 449.1871, Δ(mmu) = -0.1.

1,15-Bis(5,6-dihydro-8H-tetrazolo[1,4]oxazin-6-yl)-2,5,8,11,14-pentaoxapentadecane (4d): ^{1}H NMR ($CDCl_3$, 300MHz), δ (ppm), J (Hz): 5.33-4.93 (AB system, 4H, 2 OCH_2-C=N, $^2J_{HH}$= 15.2Hz), 4.62-4.28 (m, 4H, $2CH_2N$, $^2J_{HH}$= 12.1Hz), 4.19-4.11 (m, 2H, 2CHO), 3.92-3.78 (m, 4H, 2C$\underline{H_2}$O-CHO), 3.73 -3.63 (m, 16H, $8CH_2O$). ^{13}C NMR ($CDCl_3$, 300MHz), δ(ppm) : 149.59 (s, 2C, 2C=N), 72.53-70.51 (m, 12C, $12CH_2O$), 61.92 (s, 2C, 2CHO), 47.01 (m, 2C, $2CH_2N$). HRMS (ESI) for $C_{18}H_{30}O_7N_8Na$, $[M+Na]^+$ calculated value: 493.2135, found value: 493.2137; Δ(mmu) =0.2.

1,18-Bis(5,6-dihydro-8H-tetrazolo[1,4]oxazin-6-yl)-2,5,8,11,14,17-hexaoxaoctadecane (4e): ^{1}H NMR ($CDCl_3$, 300MHz), δ(ppm), J (Hz): 5.31-4.91 (AB system, 4H, 2 OCH_2-C=N, $^2J_{HH}$= 15.5Hz), 4.65-4.26 (m, 4H, $2CH_2N$, $^2J_{HH}$= 12.3Hz), 4.21-4.12 (m, 2H, 2CHO), 3.90-3.76 (m, 4H, 2C$\underline{H_2}$O-CHO), 3.71 -3.62 (m, 16H, $8CH_2O$). ^{13}C NMR ($CDCl_3$, 300MHz), δ(ppm) : 149.56 (s, 2C, 2C=N), 72.51-70.53 (m, 14C, $14CH_2O$), 61.94 (s, 2C, 2CHO), 47.04 (m, 2C, $2CH_2N$). HRMS (ESI) for $C_{20}H_{34}O_8N_8Na$, $[M+Na]^+$ calculated value: 537.2397, found value: 537.2398, Δ(mmu) =0.1.

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