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Expeditious synthesis of enantiopure symmetrical macroheterocycles by ring-closing metathesis of ether and tether-linked 1,2-*O*-isopropylidenefuranosides

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Abstract—Bis-olefinic symmetrical carbohydrate derivatives were prepared by joining two 1,2-*O*-isopropylidenefuranose units either through an ether linkage or by a tether of variable size. The ring-closing metathesis (RCM) of these substrates using Grubbs' first-generation catalyst led to the synthesis of enantiopure symmetrical macroheterocycles containing nine- to twenty-five-membered rings fused to the 1,2-*O*-isopropylidenefuranose ring.

Keywords: Synthesis; Enantiopure; Macroheterocycles; Ring-closing metathesis; Tether-linked 1,2-*O*-isopropylidenefuranosides

1. Introduction

The emergence of ring-closing metathesis (RCM) as a tool for constructing various sizes of cyclic compounds has made phenomenal impact on organic synthesis.[1–5] The synthesis of otherwise difficultly accessible cyclic skeletons, including medium and large ring carbocycles and heterocycles, has been possible with the use of this reaction.[1–10] Application of RCM and cross metathesis has also been noteworthy in the carbohydrate area.[11–16] Macrocyclic structures are frequently encountered in naturally occurring compounds. RCM has proved to be an efficient method for the synthesis of carbohydrate-based macrocyclic natural products such as woodrosin I[17] and tricolorin G[18] as well as non-carbohydrate macrocyclic compounds.[5] The use of macrocyclic skeletons as hosts in the recognition of ionic and neutral molecules is well known.[19] Recently the importance of macrocyclic structures, including nucleosides as antibacterial agents based on novel targets and as gene and drug-delivery systems, has led to the application of RCM for the synthesis of such systems.[20–22] This is why the development of strategies for the synthesis of macrocycles remains an ever-important task for synthetic chemists. Particularly important is the construction of chiral macrocyclic frameworks from chiral precursors, because chirality has a profound influence on the biological activity of drugs and related molecules.[23] In this context it was of interest to synthesize macrocyclic structures having two carbohydrate fragments in the periphery so that these molecules will be useful for conjugation with other biologically important molecules through glycosylation leading to biologically relevant materials such as antibacterial agents. Alternatively, conversion of these carbohydrate-derived macrocycles to nucleosides having aforementioned biological importance is a distinct possibility. Moreover, the resulting C_2-symmetric molecules will be potentially important as precursors for novel chiral ligands in asymmetric catalysis. We report herein a general strategy for such symmetrical macroheterocycles from carbohydrate derivatives by RCM using Grubbs' first-generation catalyst **1**.[24] We envisioned that RCM using **1** can be applied to **A**, a bis-olefinic ether-linked pseudodisaccharide[25] or a tether-linked disaccharide derivative, leading to the formation of an enantiopure chiral

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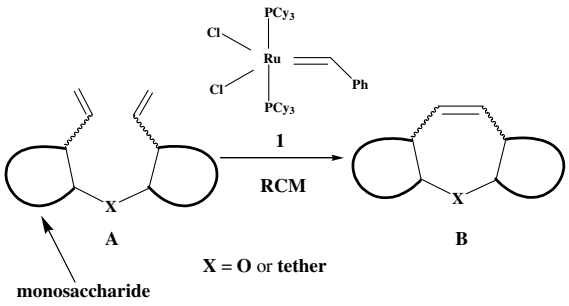


Scheme 1. The strategy for the synthesis of chiral symmetrical macroheterocycles.

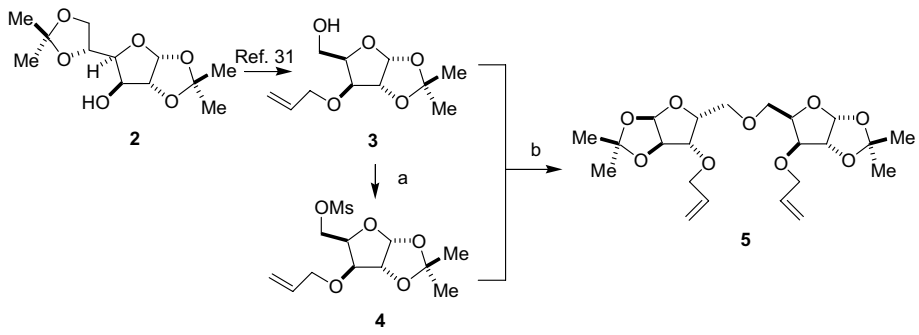
macrocycle **B** (Scheme 1). Recently the 1,2-*O*-isopropylidenefuranose scaffold, readily available from the well-known 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) (Scheme 2), has provided the template for a variety of reactions resulting in the synthesis of diverse types of enantiomerically pure skeletons.[26–28] The use of this carbohydrate scaffold will enable the future conjugation with other molecules via glycosylation at the anomeric centre. Another advantage of the occurrence of the *O*-isopropylidene protected furanoside rings in the macrocycles **B** is the future conversion of this ring system to a nucleoside. As an example, a sequence of reactions involving removal of the *O*-isopropylidene group, acetylation of the resulting diol intermediate and glycosylation of the diacetate with a base following well-established procedures has been frequently used to prepare nucleosides from 1,2-*O*-isopropylidene protected furanosides.[29,30]

2. Results and discussion

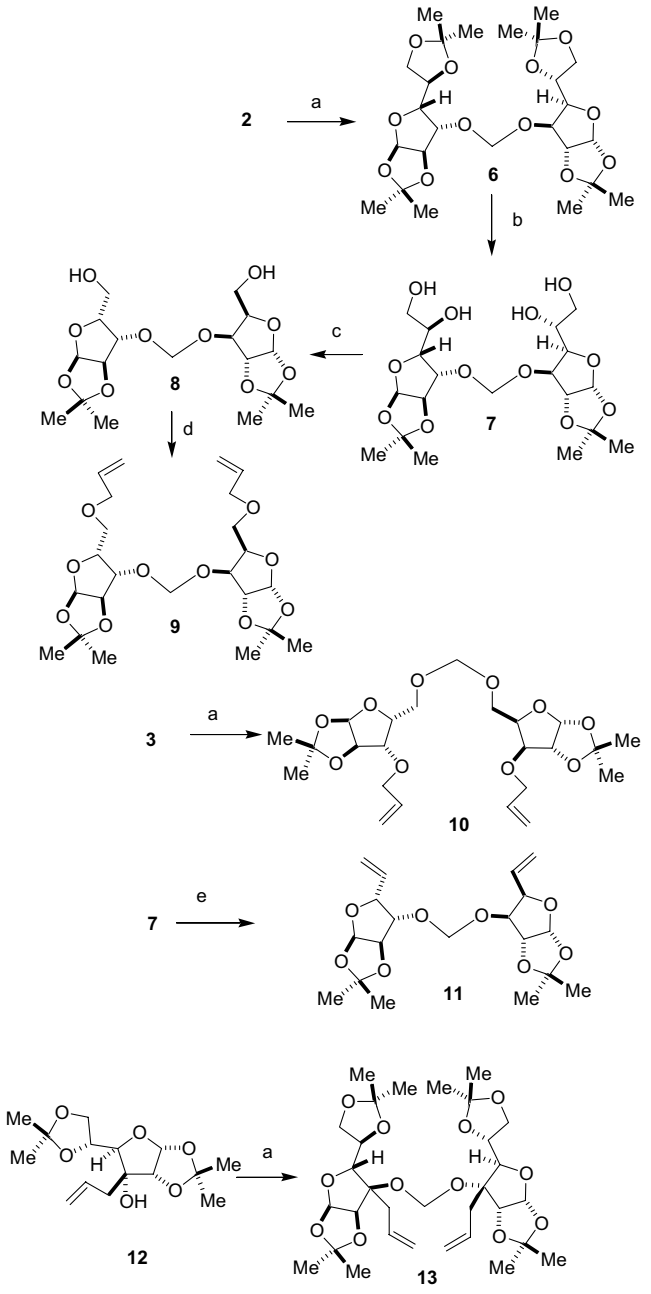
The symmetrical substrates required for this work were prepared from known carbohydrate derivatives. The general strategy for the synthesis of these substrates involved the coupling of two carbohydrate units either by an ether linkage or by a tether. The intermediates prepared by the former method represent examples of ether-linked pseudodisaccharide derivatives bearing alkene units. The synthesis of the pseudodisaccharide derivative, bis(3-*O*-allyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)ether (**5**), was achieved by heating the known[31] alcohol **3** with its mesyl derivative **4** in aqueous sodium hydroxide in the presence of tetrabutylammonium bromide (Scheme 2). It should be mentioned that although 5,5′-linked pseudodisaccharide derivatives have been made[25] by using the corresponding triflates instead of the less sensitive mesylates, the present method utilizing the latter derivatives in aqueous medium provides an operationally simpler method for the synthesis of ether-linked pseudodisaccharides.

The tether-linked symmetrical substrates were prepared by the coupling of two carbohydrate units by reaction with a bifunctional unit and carrying out further transformations to provide the bis-olefinic substrates. The smallest tether used in this work was a methylene unit, which was introduced by stirring the carbohydrate derivative in 50% aq sodium hydroxide–dichloromethane in the presence of tetrabutylammonium bromide, and bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl)methane (**6**), bis(3-*O*-allyl-1,2-*O*-isopropylidene-α-D-xylofuranos-5-*O*-yl)methane (**10**) and bis(1,2:5,6-di-*O*-isopropylidene-3-deoxy-3-*C*-allyl-α-D-glucofuranos-3-*O*-yl)methane (**13**) were prepared by applying this procedure (Scheme 3). The RCM substrate bis(5-*O*-allyl-1,2-*O*-isopropylidene-α-D-xylofuranos-3-*O*-yl)methane (**9**) was prepared by phase-transfer catalyst-mediated allylation[32] of **8**, which was obtained from **6** by sequential deprotection to **7**, vicinal diol cleavage with sodium metaperiodate and reduction with sodium borohydride (Scheme 3). Intermediate **7** was converted to the bis-vinyl derivative, bis(5,6-dideoxy-5,6-didehydro-1,2-*O*-isopropylidene-α-D-xylohexofuranos-3-*O*-yl)methane (**11**) by treatment with triphenylphosphine, iodine and imidazole.[33]

The substrates incorporating longer tethers were prepared according to the process shown in Scheme 4. Alkylation of the known carbohydrate derivative **14** with 1,3-dibromopropane afforded the propylene tethered *N*,*N*′-di-*p*-toluenesulfonyl-*N*,*N*′-bis(1,2:5,6-di-*O*-isopropylidene-3-deoxy-α-D-glucofuranos-3-yl)-1,3-



Scheme 2. Preparation of the pseudodisaccharide substrate **5**. Reagents and conditions: (a) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 25 °C, 2 h, 95%; (b) 50% aq NaOH, Bu_4NBr, 70 °C, 72 h, 71%.



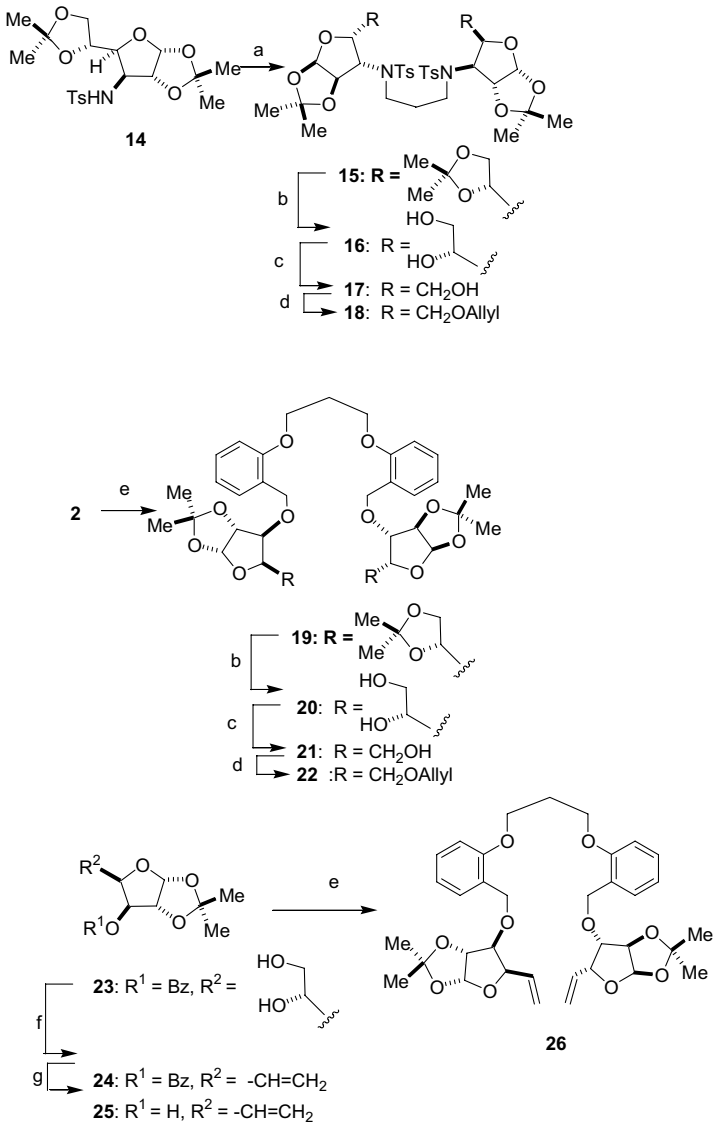
Scheme 3. Synthesis of the methylene acetal-tethered substrates **9**–**11** and **13**. Reagents and conditions: (a) CH_2Cl_2–50% aq NaOH, Bu_4NBr, 25 °C, 48 h, 95% (**6**), 80% (**10**), 83% (**13**); (b) 75% aq AcOH, 25 °C, 12 h, 93%; (c) i. $NaIO_4$, MeOH–H_2O, 0–25 °C, 2 h; ii. $NaBH_4$, MeOH, 25 °C, 12 h, 76% two steps; (d) allyl bromide, CH_2Cl_2–50% aq NaOH, Bu_4NBr, 25 °C, 12 h, 91%; (e) imidazole, I_2, Ph_3P, toluene, reflux, 5 h, 78% (Ref. 33).

diaminopropane (**15**), which was converted to the bis-olefinic substrate *N*,*N*′-di-*p*-toluenesulfonyl-*N*,*N*′-bis(5-*O*-allyl-1,2-*O*-isopropylidene-3-deoxy-α-D-xylofuranos-3-yl)-1,3-diaminopropane (**18**) following the usual protocol mentioned earlier for the preparation of **9**. A longer tether was used in 1,3-bis[2-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl)methylphenoxy]propane (**19**), which was prepared from **2** by alkylation with readily available 1,3-di(2-bromomethylphenoxy)propane,[†] in the presence of NaH and then converted to 1,3-bis[2-(5-*O*-allyl-1,2-*O*-isopropylidene-α-D-xylofuranos-3-*O*-yl)methylphenoxy]propane (**22**) by the usual method (Scheme 4). The vinyl compound 1,3-bis-[2-(5,6-didehydro-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-xylohexofuranos-3-*O*-yl)methylphenoxy]propane (**26**) was prepared by alkylating 5,6-didehydro-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-xylohexofuranose (**25**) with the aforementioned bis-bromomethylphenoxypropane (Scheme 4).

The general procedure for carrying out the RCM reactions involved stirring a 10^{-3} M solution of the substrate in CH_2Cl_2 either at 25 °C or under reflux for 10–36 h in the presence of 10–50 mol % of the catalyst. The results of the RCM reactions are presented in Table 1. Structures of the products are shown in Figure 1.

The RCM of the bis-olefinic 5,5′-linked pseudodisaccharide derivative **5** furnished an inseparable (3:7) mixture of the *E* and *Z* isomers of the 13-membered oxygen heterocycle, (1*R*,5*R*,7*R*,8*R*,9*S*,16*S*,17*R*,18*R*)-(7,8:17,18-diisopropylidenedioxy)-3,6,10,15,19-pentaoxatricyclo[14.3.0.0^{5,9}]nonadec-12-ene (**27**), in 43% yield. Substantial amount of the starting material was recovered from the reaction, and employment of higher temperature or increased catalyst concentration did not improve the yield. The occurrence of the (M+H) peak at *m*/*z* 415 in the FAB mass spectrum of the mixture indicated the formation of the heterocycle **27**. The presence of two geometrical isomers in the mixture was apparent from the ^{1}H NMR spectrum, which exhibited two sets of two-proton multiplets at δ 6.02 and 5.82 due to the olefinic protons, as well as from the appearance of two peaks at δ 130.67 and 130.62 due to the olefinic carbon atoms in the ^{13}C NMR spectrum. The C_2-symmetry of the molecules was indicated by the presence of single sets of peaks due to the symmetry-related protons and the carbon atoms in the ^{1}H and ^{13}C NMR spectra. However, on account of the symmetrical nature of the isomers, the assignment of stereochemistry to the olefinic bonds of the respective isomers could not be made on the basis of NMR spectral data. Although the formation of nine-membered rings by RCM is well-known[8–10,16] attempts to achieve the RCM of **11** in the presence of Grubbs' first-generation catalyst **1** did not result in the formation of any nine-membered ring product. The starting material was recovered unchanged along with some intractable materials under various conditions of solvent, temperature, catalyst concentration or even after using the Grubbs' second-generation catalyst. The reluctance of the formation of a nine-membered ring by RCM is not unprecedented,[16]

[†] Salicylaldehyde was treated with 1,3-dibromopropane in the presence of K_2CO_3 in methanol under reflux, and the product was reduced with $NaBH_4$, followed by treatment with PBr_3.



Scheme 4. Preparation of the tethered substrates **18**, **22** and **26**. Reagents and conditions: (a) $(CH_2)_3Br_2$, K_2CO_3, DMF, 80–120 °C, 8 h, 66%; (b) 75% aq AcOH, 25 °C, 12 h, 85% (**16**), 93% (**20**); (c) i. $NaIO_4$, MeOH–H_2O, 0–25 °C, 2 h; ii. $NaBH_4$, MeOH, 25 °C, 12 h, 87% (**17**), 92% (**21**) two steps; (d) allyl bromide, CH_2Cl_2–50% aq NaOH, Bu_4NBr, 25 °C, 12 h, 86% (**18**), 91% (**22**); (e) 1,3-di(2-bromomethylphenoxy)propane, NaH, THF, reflux, 8 h, 69% (**29**), 78% (**26**); (f) imidazole, I_2, Ph_3P, toluene, reflux, 5 h, 76% (Ref. 33); (g) LiOH, 50% aq MeOH, 25 °C, 12 h, 90%.

and it is probable that a deleterious steric crowding in the metathesis activation complex due to the particular environment adjacent to the reacting olefinic moieties is responsible for the failure of the reaction. In contrast, the olefinic sites in **13** are relatively free from such steric congestion, and the RCM in the presence of **1** afforded the bis-spiro nine-membered heterocycle, (1*R*,3*R*,4*R*,5*R*,9*R*,10*R*,12*R*,13*R*)-(3,4:12,13-di-*O*-isopropylidenedioxy)-1,10-bis(1,2-isopropylidenedioxyethyl)-2,6,8,11-tetraoxadispiro[4.3.4.4]heptadec-15-ene (**28**), in 85% yield. The mass and NMR spectra of **28** were consistent with the structure, and the *Z* stereochemistry of the olefin was assigned on the basis of reported examples.[8–10,16] The pentose substrates **9** and **10** have the positions of the methylene tethers and olefinic moieties interchanged. It was found that there was no significant difference in their behaviour towards RCM using **1**, and the 15-membered oxygen heterocycles, (1*S*,5*S*,6*R*,7*R*,9*R*,18*R*,20*R*,21*R*)-(6,7:20,21-diisopropylidenedioxy)-2,4,8,11,16,19-hexaoxatricyclo[16.3.0.0^{5,9}]heneicos-13-ene (**29**) and (1*R*,7*R*,9*R*,10*R*,11*S*,18*S*,19*R*,20*R*)-(9,10:19,20-diisopropylidenedioxy)3,5,8,12,17,21-hexaoxatricyclo[16.3.0.0^{7,11}]heneicos-14-ene (**30**), were obtained as mixtures of *E*/*Z* isomers in 90% and 95% yields from the respective substrates. Hydrogenation of **29** in the presence of 10% Pd/C in EtOH led to the formation of the C_2-symmetric molecule, (1*S*,5*S*,6*R*,7*R*,9*R*,18*R*,20*R*,21*R*)-(6,7:20,21-diisopropylidenedioxy)-2,4,8,11,16,19-hexaoxatricyclo[16.3.0.0^{5,9}]heneicosane (**34**), in 98% yield. The bis-olefinic amino sugar derivative **18** on

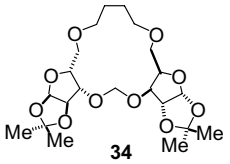
Table 1. Ring-closing metathesis (RCM) of symmetrical bis-olefinic carbohydrate derivatives

Substrate	Product[a]	Yield (%)[b]	Conditions				
			Substrate concn ($M \times 10^{-3}$)	Solvent	Catalyst concn (mol %)	Temperature (°C)	Reaction time (h)
5	**27** (*E*:*Z* = 3:7)[c]	43[d]	6	CH_2Cl_2	10	25	24
11	—	—	6–7	CH_2Cl_2, benzene, toluene	10–50	40–110	24–60
13	**28**[e]	85	1	CH_2Cl_2	25	Reflux	36
9	**29** (*E*:*Z* = 2.3)[c]	90	6	CH_2Cl_2	10	Reflux	10
10	**30** (*E*:*Z* = 3:7)[c]	95	6	CH_2Cl_2	10	25	24
18	**31**[e]	78	6	CH_2Cl_2	10	25	36
26	**32** (*E*:*Z* = 1:2)[c]	95	6	CH_2Cl_2	12	Reflux	10
22	**33**[e]	70	1	CH_2Cl_2	15	Reflux	10

[a] Structures are shown in Figure 1.
[b] Yields are for isolated products.
[c] The ratio of the *E* and *Z* isomers was determined by integration of the ^1H NMR peaks of the olefinic protons.
[d] Yield based on 50% recovered **5**.
[e] Single isomer.

RCM using **1** gave the 17-membered diaza-dioxa heterocycle, (1*S*,7*S*,8*R*,9*R*,11*S*,20*S*,22*R*,23*R*)-8,9:22,23-diisopropylidenedioxy-2,6-bis-(*p*-toluenesulfonyl)-10,13,18,21-tetraoxa-2,6-diazatricyclo[18.3.0.$0^{7,11}$]tricos-15-ene (**31**), as a single stereoisomer in 78% yield as evident from the ^1H and ^{13}C NMR spectra, which exhibited only one set of peaks for the olefinic protons and carbon atoms as well as the anomeric protons and carbon atoms. Unlike the methylene acetal tethered bis-vinyl substrate **11**, which failed to undergo RCM, **26** having a similar scaffold incorporating a rather longer tether gave the 19-membered heterocycle, (2*R*,3*R*,3a*S*,20a*S*,21*R*,22*R*,23a*R*,25a*R*)-2,3:21,22-diisopropylidenedioxy-2,3,3a,20a,21,22,23a,25a-octahydrodibenzo[*c*,*j*]difuro[2,3-*n*:3,2-*r*][1,5,9,13]tetraoxacyclononadeca-5a,14a,20a,24,25a-pentaene (**32**), as a mixture of *E*/*Z* isomers in 95% yield. The appreciably increased size of the ring in **32** helped in offsetting the unfavourable steric crowding encountered in the attempted RCM of **11**. The synthesis of a larger ring was demonstrated by the RCM of the tethered substrate **22**, leading to the formation of a single stereoisomer of the twenty-five-membered oxa-heterocycle, (2*S*,3*S*,3a*R*,20a*R*,21*S*,22*S*,23a*S*,31a*S*)-(2,3:21,22-diisopropylidenedioxy)-2,3,5,3a,20a,21,22,23a-octahydrodibenzo[*c*,*j*]difuro[2,3-*c*:3,2-*r*][1,5,9,13,17,21]hexaoxacyclopentacosa-7a,14a,20a,27,31a-pentaene (**33**), in 70% yield. The structure was consistent with the mass and NMR spectra, which also exhibited single sets of peaks due to the symmetry-related protons and carbon atoms.

Grubbs' first-generation catalyst was used for all the successful RCM reactions throughout this study, and both the Grubbs' first- and second-generation catalysts



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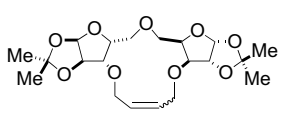

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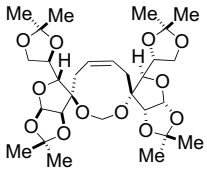

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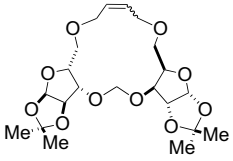

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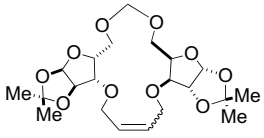

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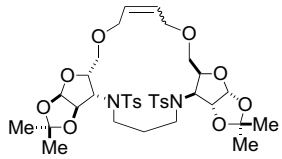

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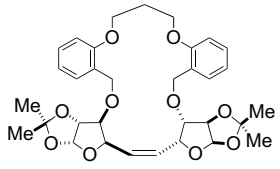

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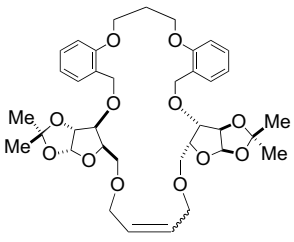

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Figure 1. Structures of the symmetrical products from the ring-closing metathesis (RCM) of symmetrical, bis-olefinic carbohydrate derivatives **5**, **9**–**11**, **13**, **18**, **22** and **26**.

failed to bring about the RCM of **11**. However, it has been demonstrated that Grubbs' second-generation catalyst improved those RCM reactions that proceeded sluggishly with the first-generation catalyst.[5] So, it is expected that many of the metathesis reactions described in this work will furnish better results by switching to Grubbs' second-generation and other RCM catalysts.

The macrocycles described above have multiple heteroatoms in the ring, and hence some of them may possess crown ether like properties. In a preliminary study, the ability of **33** to extract sodium or potassium picrate from aqueous solutions was explored using the recently reported method of Mlinarić-Majerski and Kragol.[34] However, the experiments indicated that **33** was unable to extract the above metal salts from aqueous solution with dichloromethane.

In conclusion, this work described the preparation of symmetrical bis-olefinic compounds by tethering two 1,2-*O*-isopropylidenefuranose units and their RCM providing an expedient strategy for the synthesis of enantiopure symmetrical macroheterocycles. These macrocyclic compounds are expected to be potentially important due to their amenability to transformations to other biologically significant materials.

3. Experimental

3.1. General

Melting points are uncorrected. Unless otherwise mentioned ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. Assignments of CH_3, CH_2, CH and quaternary (q) carbon atoms in the ^{13}C NMR spectra were based on DEPT analyses. Reactions were monitored by thin-layer chromatography using E. Merck Silica Gel 60 F_{254} precoated plates (No 1.05554). Organic extracts were dried over anhydrous sodium sulfate. Unless otherwise mentioned, 60–120 mesh silica gel was used for column chromatography. Solvents were distilled and dried prior to use. Petroleum ether refers to a fraction boiling between 60 and 80 °C.

3.2. Bis(3-*O*-allyl-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-5-yl)ether (5)

To a solution of **3**[31] (0.60 g, 2.8 mmol) in CH_2Cl_2 containing Et_3N (0.7 mL) at 0 °C was added dropwise with stirring CH_3SO_2Cl (0.2 mL). The mixture was then stirred at 25 °C for 2 h. Water at 0 °C was added and the mixture was stirred for 0.5 h. It was diluted with CH_2Cl_2 and washed with water, satd aq $NaHCO_3$ solution and finally water. Removal of the solvent from the organic layer afforded **4** (0.76 g, 95%) as a pale-yellow oil, which was used without further purification, ^{1}H NMR: δ 5.94 (d, *J* 3.6 Hz, 1H), 5.85 (m, 1H), 5.32–5.22 (m, 2H), 4.58 (d, *J* 3.6 Hz, 1H), 4.51–4.37 (m, 3H), 4.17–4.11 (m, 1H), 4.00–3.94 (m, 2H), 3.07 (s, 3H), 1.50 (s, 3H), 1.33 (s, 3H).

A mixture of the alcohol **3** (0.39 g, 1.68 mmol), the mesylate **4** (1.04 g, 3.37 mmol) prepared as described above, Bu_4NBr (0.1 g, 0.33 mmol), 50% aq NaOH (1.6 mL) was stirred at 70 °C for 72 h. The mixture was then extracted with CH_2Cl_2, and the combined organic layers were washed with water and brine. Removal of the solvent afforded a syrupy liquid that was chromatographed using 1:9 EtOAc–petroleum ether as eluent to give **5** (0.55 g, 71%) as a colourless sticky liquid: $[\alpha]_D^{25}$ −54.0 (*c* 1.07, $CHCl_3$); IR (Neat): 2932, 1647, 1377 cm^{-1}; ^{1}H NMR: δ 5.91 (d, *J* 3.9 Hz, 2H), 5.89–5.79 (m, 2H), 5.28 (dd, *J* 7.8, 1.5 Hz, 2H), 5.19 (dd, *J* 10.5, 1.5 Hz, 2H), 4.54 (d, *J* 3.9 Hz, 2H), 4.43–4.35 (m, 2H), 4.15–4.09 (m, 2H), 4.02–3.95 (m, 2H), 3.89 (d, *J* 3.1 Hz, 2H), 3.79 (dd, *J* 10.2, 5.4 Hz, 2H), 3.69 (dd, *J* 10.1, 6.5 Hz, 2H), 1.49 (s, 6H), 1.31 (s, 6H); ^{13}C NMR: δ 133.8 (CH), 117.3 (CH_2), 111.3 (q), 104.8 (CH), 82.2 (CH), 81.4 (CH), 79.0 (CH), 70.8 (CH_2), 68.8 (CH_2), 26.5 (CH_3), 26.0 (CH_3); FABMS: *m*/*z* 465 (M+Na), 443 (M+H), 427 (M−Me); Anal. Calcd for $C_{22}H_{34}O_9$: C, 59.71; H, 7.74. Found: C, 59.48; H, 7.51.

3.3. General procedure for the synthesis of bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl)methane (6), bis(3-*O*-allyl-1,2-*O*-isopropylidene-α-D-xylofuranos-5-*O*-yl)methane (10) and bis(1,2:5,6-di-*O*-isopropylidene-3-*C*-allyl-α-D-glucofuranos-3-*O*-yl)methane (13)

The general procedure for the above compounds is illustrated by the preparation of **6**.

A mixture of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**2**) (5.0 g, 19.2 mmol), CH_2Cl_2 (20 mL), 50% aq NaOH (20 mL) and tetrabutylammonium bromide (0.62 g, 1.9 mmol) was stirred vigorously at 25 °C for 48 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried and evaporated to give an oil, which was chromatographed using 1:10 EtOAc–petroleum ether as eluent to give **6** (4.86 g, 95%) as a colourless thick liquid: $[\alpha]_D^{25}$ −22.7 (*c* 0.98, $CHCl_3$); IR (KBr): 2986, 2935, 1376 cm^{-1}; ^{1}H NMR: δ 5.90 (d, *J* 3.6 Hz, 2H), 4.86 (s, 2H), 4.55 (d, *J* 3.6 Hz, 2H), 4.34–4.28 (m, 4H), 4.16 (dd, *J* 7.2, 2.7 Hz, 2H), 4.10 (dd, *J* 8.7, 6.0 Hz, 2H) 4.00 (dd, *J* 8.4, 5.7 Hz, 2H), 1.50 (s, 6H), 1.43 (s, 6H), 1.35 (s, 6H), 1.32 (s, 6H); ^{13}C NMR: δ 111.8 (q), 108.9 (q), 105.1 (CH), 92.7 (CH_2), 82.9 (CH), 80.9 (CH), 78.7 (CH), 72.4 (CH), 67.0 (CH_2), 26.7 (CH_3), 26.6 (CH_3), 26.1 (CH_3), 25.2 (CH_3); FABMS: *m*/*z* 555 (M+Na); Anal. Calcd for $C_{25}H_{40}O_{12}$: C, 56.38; H, 7.57. Found: C, 56.42; H, 7.29.

The above procedure was used to prepare the methylene acetal derivatives **10** and **13** from **3** and **12**,[31] respectively.

3.3.1. Compound **10**: Colourless viscous liquid: yield 80%; $[\alpha]_D^{25}$ −72.0 (*c* 0.71, $CHCl_3$); IR (Neat): 3081, 1644, 1378 cm^{-1}; ^1H NMR: δ 5.92 (d, *J* 3.6 Hz, 2H), 5.92–5.79 (m, 2H), 5.28 (d, *J* 16.5 Hz, 2H), 5.20 (d, *J* 10.2 Hz, 2H), 4.76 (s, 2H), 4.55 (d, *J* 3.6 Hz, 2H), 4.40–4.35 (m, 2H), 4.12 (dd, *J* 12.9, 5.1 Hz, 2H), 3.97 (dd, *J* 13.8, 5.1 Hz, 2H), 3.89 (d, *J* 2.7 Hz, 2H), 3.86–3.74 (m, 4H), 1.49 (s, 6H), 1.32 (s, 6H); ^{13}C NMR: δ 133.8 (CH), 117.4 (CH_2), 111.5 (q), 105.0 (CH), 96.0 (CH_2), 82.2 (CH), 81.6 (CH), 78.9 (CH), 70.8 (CH_2), 65.5 (CH_2), 26.7 (CH_3), 26.2 (CH_3); ESIMS (positive ion): *m*/*z* 495 (M+Na); Anal. Calcd for $C_{23}H_{36}O_{10}$: C, 58.46; H, 7.68. Found: C, 58.42; H, 7.52.

3.3.2. Compound **13**: Colourless syrupy liquid: yield 83%; $[\alpha]_D^{25}$ +98.1 (*c* 1.19, $CHCl_3$); IR (KBr): 3075, 2987, 1375 cm^{-1}; ^1H NMR: δ 6.06–5.97 (m, 2H), 5.57 (d, *J* 3.6 Hz, 2H), 5.16–5.09 (m, 4H), 5.09 (s, 2H), 4.45 (d, *J* 3.6 Hz, 2H), 4.22 (t, *J* 6.3 Hz, 2H), 4.13–4.02 (m, 4H), 3.88 (t, *J* 7.3 Hz, 2H), 2.85 (dd, *J* 14.4, 8.1 Hz, 2H), 2.60 (dd, *J* 15.0, 6.6 Hz, 2H), 1.56 (s, 6H), 1.40 (s, 6H), 1.33 (s, 6H), 1.31 (s, 6H); ^{13}C NMR: δ 133.1 (CH), 118.4 (CH_2), 112.1 (q), 109.2 (q), 103.8 (CH), 89.9 (CH_2), 84.4 (q), 82.0 (CH), 81.6 (CH), 72.8 (CH), 67.9 (CH_2), 37.7 (CH_2), 26.8 (CH_3), 26.4 (CH_3), 26.3 (CH_3), 25.4 (CH_3); EIMS: *m*/*z* 612 (M), 597 (M−CH_3); Anal. Calcd for $C_{31}H_{48}O_{12}$: C, 60.77; H, 7.90. Found: C, 60.80; H, 7.92.

3.4. Bis(5-*O*-allyl-1,2-*O*-isopropylidene-α-D-xylofuranos-3-*O*-yl)methane (9)

A solution of **6** (4.0 g, 8.84 mmol) in aq AcOH (75% v/v, 20 mL) was stirred for 12 h at 25 °C. The mixture was then concentrated, and the residue was repeatedly coevaporated with toluene (3 × 40 mL) yielding **7** (3.16 g, 93%) as a colourless liquid: $[\alpha]_D^{25}$ −106.1 (*c* 1.23, $CHCl_3$); IR (KBr): 3434, 1382 cm^{-1}; ^1H NMR: δ 5.88 (d, *J* 3.6 Hz, 2H), 4.90 (s, 2H), 4.57 (br m, 2H), 4.51 (d, *J* 3.6 Hz, 2H), 4.36 (d, *J* 2.1 Hz, 2H), 4.11 (dd, *J* 9.0, 2.4 Hz, 2H), 3.99 (m, 2H), 3.84 (br d, *J* 10.1 Hz, 2H), 3.69 (dd, *J* 11.3, 5.5 Hz, 2H), 3.57 (br m, 2H), 1.50 (s, 6H), 1.31 (s, 6H); ^{13}C NMR: δ 111.8 (q), 104.8 (CH), 91.7 (CH_2), 82.0 (CH), 79.5 (CH), 78.6 (CH), 68.0 (CH), 63.9 (CH_2), 26.4 (CH_3), 26.0 (CH_3); FABMS: *m*/*z* 475 (M+Na), 453 (M+H).

To a solution of this material (2.30 g, 5.08 mmol) in MeOH (40 mL) was added dropwise with stirring a solution of $NaIO_4$ (3.26 g, 15.26 mmol) in water (10 mL) at 0 °C. Stirring was continued at 25 °C for 2 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 and dried, and removal of the solvent afforded a syrupy material that was dissolved in methanol (10 mL) and cooled to 0 °C. To this solution $NaBH_4$ (0.52 g) was added in portions with stirring, and the mixture was further stirred for 12 h at 25 °C.The mixture was then acidified with 1:1 AcOH–H_2O and extracted with CH_2Cl_2. Removal of the solvent afforded **8** (1.51 g, 76%) as a viscous liquid: $[\alpha]_D^{25}$ −110.3 (*c* 0.60, $CHCl_3$); IR (KBr): 3452, 2985, 1379 cm^{-1}; ^1H NMR: δ 5.91 (d, *J* 3.6 Hz, 2H), 4.84 (s, 2H), 4.55 (d, *J* 3.6 Hz, 2H), 4.35–4.29 (m, 2H), 4.27 (d, *J* 3.3 Hz, 2H), 3.88 (d, *J* 6.0 Hz, 4H), 2.68 (br m, 2H), 1.51 (s, 6H), 1.33 (s, 6H); ^{13}C NMR: δ 111.9 (q), 104.7 (CH), 91.6 (CH_2), 82.5 (CH), 79.9 (CH), 78.7 (CH), 59.2 (CH_2), 26.6 (CH_3), 26.2 (CH_3); FABMS: *m*/*z* 415 (M+Na).

A mixture of the above material (3.30 g, 4.60 mmol) in CH_2Cl_2 (50 mL), 50% NaOH solution (40 mL), tetrabutylammonium bromide (0.15 g, 0.46 mmol) and allyl bromide (1.16 mL, 13.8 mmol) was vigorously stirred for 12 h at 25 °C. Water (50 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with water and dried, and the solvent was removed under reduced pressure to afford **9** (3.40 g, 91%) as a colourless syrupy liquid: $[\alpha]_D^{25}$ −24.0 (*c* 0.77, $CHCl_3$); IR (KBr): 3082, 2985, 1375 cm^{-1}; ^1H NMR: δ 5.91 (d, *J* 3.6 Hz, 2H), 5.97–5.84 (m, 2H), 5.28 (dd, *J* 17.1, 1.5 Hz, 2H), 5.19 (dd, *J* 10.2, 1.2 Hz, 2H), 4.78 (s, 2H), 4.56 (d, *J* 3.6 Hz, 2H), 4.41–4.36 (m, 2H), 4.18 (d, *J* 3.3 Hz, 2H), 4.08–3.95 (m, 4H), 3.72–3.61 (m, 4H), 1.50 (s, 6H), 1.32 (s, 6H); ^{13}C NMR: δ 134.2 (CH), 117.2 (CH_2), 111.5 (q), 104.7 (CH), 92.2 (CH_2), 82.3 (CH), 78.6 (CH), 78.5 (CH), 72.2 (CH_2), 66.9 (CH_2), 26.5 (CH_3), 26.0 (CH_3); FABMS: *m*/*z* 495 (M+Na); Anal. Calcd for $C_{23}H_{36}O_{10}$: C, 58.46; H, 7.68. Found: C, 58.32; H, 7.41.

3.5. Bis(5,6-didehydro-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-xylohexofuranos-3-*O*-yl)methane (11)

To a solution of **7** (0.76 g, 1.40 mmol) in toluene (10 mL), imidazole (0.80 g, 11.2 mmol) and triphenyl phosphine (2.93 g, 11.2 mmol) were added, and the mixture was heated under reflux. At the initiation of reflux, iodine (2.84 g, 11.2 mmol) was added in portions over a period of 1 h. After completion of addition, reflux was continued for 5 h. The solution was then cooled and transferred to a separatory funnel. The organic layer was separated and washed successively with satd sodium thiosulfate solution (30 mL), followed by 1 M NaOH solution (10 mL) and water (3 × 100 mL), respectively. Removal of the solvent gave a syrupy material that was chromatographed using 1:13 EtOAc–petroleum ether as eluent to give **11** (0.52 g, 78%) as a viscous liquid: $[\alpha]_D^{25}$ −56.9 (*c* 1.30, $CHCl_3$); IR (KBr): 3083, 2987, 1376 cm^{-1}; ^1H NMR: δ 5.94 (d, *J* 3.6 Hz, 2H), 5.92–5.82 (m, 2H), 5.42 (d, *J* 17.4 Hz, 2H), 5.30 (d, *J* 10.5 Hz, 2H), 4.73 (s, 2H), 4.64–4.62 (m, 2H), 4.57 (d, *J* 3.6 Hz, 2H), 4.13 (d, *J* 3.0 Hz, 2H), 1.52 (s, 6H), 1.32 (s, 6H); ^{13}C NMR: δ 131.7 (CH), 119.1(CH_2),

111.5 (q), 104.5 (CH), 92.3 (CH_2), 82.8 (CH), 80.9 (CH), 80.4 (CH), 26.5 (CH_3), 26.0 (CH_3); FABMS: *m/z* 407 (M+Na), 385 (M+H); Anal. Calcd for $C_{19}H_{28}O_8$: C, 59.36; H, 7.34. Found: C, 59.60; H, 7.13.

3.6. *N,N′*-Di-*p*-toluenesulfonyl-*N,N′*-bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl)-1,3-diaminopropane (15)

A mixture of **14**[35] (1.0 g, 2.4 mmol), K_2CO_3 (0.69 g) and DMF (5 mL) was heated at 80 °C for 1 h and to it was added 1,3-dibromopropane (0.25 mL), and the mixture was stirred at 120 °C for 8 h. It was diluted with water (30 mL) and extracted with CH_2Cl_2. The combined organic layer was washed with water and brine and dried. Removal of the solvent afforded a syrupy material that was chromatographed using 1:10 EtOAc–petroleum ether as eluent to give **15** (0.66 g, 66%) as a foam: $[\alpha]_D^{25}$ −22.4 (*c* 0.52, $CHCl_3$); IR (KBr): 2987, 2938, 1598, 1456, 1379 cm^{-1}; ^1H NMR: δ 7.75 (d, *J* 8.2 Hz, 4H), 7.29 (d, *J* 8.0 Hz, 4H), 6.02 (d, *J* 3.5 Hz, 2H), 4.86 (br s, 2H), 4.13 (br s, 2H), 3.98 (dd, *J* 9.1, 4.2 Hz, 2H), 3.86 (d, *J* 4.5 Hz, 4H), 3.66 (br s, 2H), 3.36 (m, 2H), 3.16 (m, 2H), 2.43 (s, 6H), 2.07 (m, 2H), 1.49 (s, 6H), 1.30 (s, 12H), 1.15 (s, 6H); ^{13}C NMR: δ 143.6 (q), 137.1 (q), 129.4 (CH), 127.8 (CH), 111.1 (q), 109.5 (q), 105.1 (CH), 84.3 (CH), 80.3 (CH), 71.7 (CH), 67.6 (CH), 65.5 (CH_2), 61.3 (CH_2), 46.2 (CH_2), 26.6 (CH_3), 26.3 (CH_3), 25.8 (CH_3), 25.0 (CH_3), 21.5 (CH_3); FABMS: *m/z* 889 (M+Na), 867 (M+H); Anal. Calcd for $C_{41}H_{58}N_2O_{14}S_2$: C, 56.80; H, 6.74; N, 3.23. Found: C, 57.06; H, 6.53; N, 3.50.

3.7. *N,N′*-Di-*p*-toluenesulfonyl-*N,N′*-bis(5-*O*-allyl-3-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranos-3-yl)-1,3-diaminopropane (18)

The compound **15** (1.04 g, 1.2 mmol) was subjected to the same procedure as described for the conversion of **6** to **7** affording **16** (0.88 g, 85%) as a foam: $[\alpha]_D^{25}$ −35.7 (*c* 0.46, $CHCl_3$); IR (KBr): 3495, 2986, 1598, 1335 cm^{-1}; ^1H NMR: δ 7.75 (d, *J* 7.5 Hz, 4H), 7.37 (d, *J* 7.8 Hz, 4H), 5.89 (d, *J* 3.5 Hz, 2H), 4.36–4.30 (m, 4H), 4.04 (dd, *J* 9.0, 3.7 Hz, 2H), 3.84 (br m, 4H), 3.68–3.64 (m, 4H), 3.45–3.42 (m, 2H), 3.33 (m, 2H), 2.46 (s, 6H), 2.44 (m, 2H), 2.17–2.01 (m, 2H), 1.47 (s, 6H), 1.22 (s, 6H); ^{13}C NMR: δ 144.4 (q), 135.8 (q), 130.1 (CH), 127.2 (CH), 111.6 (q), 104.7 (CH), 82.5 (CH), 79.8 (CH), 68.5 (CH), 64.5 (CH), 64.3 (CH_2), 45.4 (CH_2), 32.1 (CH_2), 26.2 (CH_3), 25.8 (CH_3), 21.6 (CH_3); FABMS: *m/z* 809 (M+Na).

The procedure described for the conversion of **7** to **8** was used to convert **16** (0.37 g, 0.47 mmol) to **17** (0.33 g, 86%) as a foam: $[\alpha]_D^{25}$ −29.2 (*c* 0.63, $CHCl_3$); IR (KBr): 3509, 2985, 1598, 1381 cm^{-1}; ^1H NMR: δ 7.73 (d, *J* 8.2 Hz, 4H), 7.37 (d, *J* 8.1 Hz, 4H), 5.89 (d, *J* 3.6 Hz, 2H), 4.49 (d, *J* 3.3 Hz, 2H), 4.35–4.25 (m, 4H), 3.72 (br s, 2H), 3.63 (br m, 2H), 3.26 (m, 2H), 3.04 (m, 2H), 2.46 (s, 6H), 2.08 (m, 2H), 1.49 (s, 6H), 1.25 (s, 6H); ^{13}C NMR: δ 144.2 (q), 136.2 (q), 130.1 (CH), 127.1 (CH), 111.6 (q), 104.4 (CH), 83.3 (CH), 79.8 (CH), 64.1 (CH), 59.8 (CH_2), 45.1 (CH_2), 31.8 (CH_2), 26.3 (CH_3), 25.9 (CH_3), 21.6 (CH_3); FABMS: *m/z* 750 (M+Na+H).

Allylation of the above material with allyl bromide following the procedure described for the conversion of **8** to **9** yielded **18** (0.29 g, 86%) as a syrupy liquid: $[\alpha]_D^{25}$ −12.2 (*c* 0.69, $CHCl_3$); IR (KBr): 2986, 1645, 1598, 1341 cm^{-1}; ^1H NMR: δ 7.72 (d, *J* 7.4 Hz, 4H), 7.34 (d, *J* 7.2 Hz, 4H), 5.93 (d, *J* 3.6 Hz, 2H), 5.88–5.77 (m, 2H), 5.22 (d, *J* 17.6 Hz, 2H), 5.17 (d, *J* 11.3 Hz, 2H), 4.53 (d, *J* 3.0 Hz, 2H), 4.38–4.31 (m, 4H), 3.88 (m, 4H), 3.44 (dd, *J* 10.6, 6.8 Hz, 2H), 3.29 (dd, *J* 10.3, 3.4 Hz, 2H), 3.20 (m, 2H), 3.02 (m, 2H), 2.44 (s, 6H), 2.00 (m, 2H), 1.49 (s, 6H), 1.27 (s, 6H); ^{13}C NMR: 143.8 (q), 136.9 (q), 134.2 (CH), 129.8 (CH), 127.2 (CH), 117.4 (q), 111.3 (CH_2), 104.5 (CH), 83.6 (CH), 78.6 (CH), 72.3 (CH_2), 67.6 (CH_2), 64.5 (CH), 44.9 (CH_2), 31.5 (CH_2), 26.3 (CH_3), 25.8 (CH_3), 21.5 (CH_3); FABMS: *m/z* 829 (M+Na), 807 (M+H); Anal. Calcd for $C_{39}H_{54}N_2O_{12}S_2$: C, 58.05; H, 6.74; N, 3.47; Found: C, 58.31; H, 6.53; N, 3.68.

3.8. 1,3-Bis[2-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-*O*-yl)methylphenoxy]propane (19)

To a suspension of NaH (0.24 g, 10 mmol) in THF (50 mL) cooled to 0 °C was added a solution of **2** (2.0 g, 7.7 mmol) with stirring, followed by addition of 1,3-di(2-bromomethylphenoxy)propane (1.60 g, 3.85 mmol) at 0 °C. The mixture was then heated under reflux for 8 h. Excess NaH was destroyed by careful addition of ice, and the THF was removed under reduced pressure. The residue was extracted with CH_2Cl_2, washed with H_2O and dried. Removal of the solvent yielded a colourless syrup that was chromatographed using 1:9 EtOAc–petroleum ether as eluent yielding **19** (2.5 g, 69%) as a foam: $[\alpha]_D^{25}$ −25.2 (*c* 1.07, $CHCl_3$); IR (KBr): 2983, 2933, 1599, 1377 cm^{-1}; ^1H NMR: δ 7.38 (d, *J* 6.9 Hz, 2H), 7.25 (t, *J* 7.2 Hz, 2H), 6.95 (t, *J* 7.2 Hz, 2H), 6.88 (d, *J* 8.1 Hz, 2H), 5.88 (d, *J* 3.6 Hz, 2H), 4.73 (d, *J* 12.6 Hz, 2H), 4.63 (d, *J* 12.6 Hz, 2H), 4.58 (d, *J* 3.6 Hz, 2H), 4.40–4.33 (m, 2H), 4.21–4.15 (m, 6H), 4.11–3.98 (m, 6H), 2.32 (m, 2H), 1.49 (s, 6H), 1.41 (s, 6H), 1.34 (s, 6H), 1.29 (s, 6H); ^{13}C NMR: δ 155.9 (q), 129.2 (CH), 128.7 (CH), 126.0 (q), 120.4 (CH), 111.5 (q), 110.7 (CH_2), 108.7 (q), 105.1 (CH), 82.4 (CH), 81.8 (CH), 81.1 (CH), 72.5 (CH_2), 66.6 ($2\times CH_2$), 64.3 (CH), 29.6 (CH_2), 26.7 (CH_3), 26.6 (CH_3), 26.1 (CH_3), 25.3 (CH_3); FABMS: *m/z* 795 (M+Na); Anal. Calcd for

$C_{41}H_{56}O_{14}$: C, 63.72; H, 7.30. Found: C, 63.57; H, 7.47.

3.9. 1,3-Bis[2-(5-*O*-allyl-1,2-*O*-isopropylidene-α-D-xylofuranos-3-*O*-yl)methylphenoxy]propane (22)

The deprotection of the **19** (2.0 g, 2.59 mmol) using the procedure described for the conversion of **6** to **7** afforded **20** (1.66 g, 93%) as a sticky liquid: $[\alpha]_D^{25}$ −28.9 (*c* 1.22, $CHCl_3$); IR (KBr): 3458, 2935, 1379 cm^{-1}; ^1H NMR: δ 7.34–7.28 (m, 4H), 6.99–6.94 (m, 4H), 5.93 (d, *J* 3.5 Hz, 2H), 4.70 (d, *J* 11.1 Hz, 2H), 4.66 (d, *J* 3.6 Hz, 2H), 4.54 (d, *J* 11.1 Hz, 2H), 4.25–4.10 (m, 8H), 3.93 (br m, 2H), 3.73 (d, *J* 11.4 Hz, 2H), 3.56 (dd, *J* 11.4, 5.7 Hz, 2H), 3.36 (br m, 2H), 2.75 (hump, 2H), 2.39–2.35 (m, 2H), 1.47 (s, 6H), 1.32 (s, 6H); ^{13}C NMR: δ 156.5 (q), 130.2 (CH), 129.7 (CH), 125.1 (q), 120.7 (CH), 111.5 (CH), 111.5 (q), 105.1 (CH), 82.0 (CH), 81.7 (CH), 79.5 (CH), 69.6 (CH), 67.6 (CH_2), 64.9 (CH_2), 64.0 (CH_2), 28.8 (CH_2), 26.6 (CH_3), 26.0 (CH_3); FABMS: *m*/*z* 715 (M+Na), 693 (M+H).

The tetrahydroxy compound **20** (1.50 g, 2.16 mmol) was subjected to the procedure for the conversion of **7** to **8** to yield **21** (1.26 g, 92%) as a colourless viscous liquid: $[\alpha]_D^{25}$ −46.2 (*c* 1.42, $CHCl_3$); IR (KBr): 3489, 1378 cm^{-1}; ^1H NMR: δ 7.32–7.26 (m, 4H), 6.94 (dd, *J* 14.6, 7.5 Hz, 4H), 5.96 (d, *J* 3.6 Hz, 2H), 4.71 (d, *J* 11.7 Hz, 2H), 4.65 (d, *J* 3.6 Hz, 2H), 4.52 (d, *J* 11.7 Hz, 2H), 4.26 (dd, *J* 9.0, 5.1 Hz, 2H), 4.21 (t, *J* 6.0 Hz, 4H), 4.04 (d, *J* 3.6 Hz, 2H), 3.88–3.77 (m, 4H), 2.39–2.31 (m, 2H), 2.20 (br m, 2H), 1.48 (s, 6H), 1.32 (s, 6H); ^{13}C NMR: δ 156.5 (q), 129.7 (CH), 129.5 (CH), 125.2 (q), 120.7 (CH), 111.5 (q), 111.2 (CH), 105.1 (CH), 82.8 (CH), 82.3 (CH), 79.8 (CH), 67.3 (CH_2), 64.6 (CH_2), 60.7 (CH_2), 29.0 (CH_2), 26.7 (CH_3), 26.2 (CH_3); FABMS: *m*/*z* 655 (M+Na), 633 (M+H).

Allylation of **21** (3.3 g, 7.11 mmol) by the procedure described for the conversion of **8** to **9** yielded **22** (3.26 g, 91%) as a syrup: $[\alpha]_D^{25}$ −58.3 (*c* 0.83, $CHCl_3$); IR (Neat): 2983, 1643, 1599, 1377 cm^{-1}; ^1H NMR: δ 7.34 (d, *J* 7.5 Hz, 2H), 7.26 (t, *J* 7.2 Hz, 2H), 6.95 (t, *J* 7.2 Hz, 2H), 6.88 (d, *J* 7.5 Hz, 2H), 5.92 (d, *J* 3.6 Hz, 2H), 5.94–5.81 (m, 2H), 5.24 (dd, *J* 17.1, 1.5 Hz, 2H), 5.15 (dd, *J* 10.5, 1.5 Hz, 2H), 4.70 (d, *J* 12.6 Hz, 2H), 4.60 (d, *J* 3.6 Hz, 2H), 4.55 (d, *J* 12.6 Hz, 2H), 4.40–4.35 (m, 2H), 4.18 (t, *J* 6.0 Hz, 4H), 4.07–3.92 (m, 6H), 3.75–3.65 (m, 4H), 2.33–2.29 (m, 2H), 1.48 (s, 6H), 1.29 (s, 6H); ^{13}C NMR: δ 155.9 (q), 134.5 (CH_2), 128.8 (CH_2), 128.7 (CH), 126.0 (q), 120.5 (CH), 117.0 (CH_2), 111.5 (q), 110.8 (CH), 105.0 (CH), 82.2 (CH), 82.0 (CH), 79.3 (CH), 72.3 (CH_2), 67.5 (CH_2), 66.8 (CH_2), 64.3 (CH_2), 29.3 (CH_2), 26.7 (CH_3), 26.2 (CH_3); FABMS: *m*/*z* 735 (M+Na); Anal. Calcd for $C_{39}H_{52}O_{12}$: C, 65.71; H, 7.35. Found: C, 65.57; H, 7.63.

3.10. 5,6-Didehydro-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-xylohexofuranose (25)

3-*O*-Benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**23**)[36] was subjected to the procedure used for the conversion of **7** to **11** leading to the vinyl derivative **24** (76%) as a colourless syrup, which could not be separated from traces of triphenyl phosphine and other unidentified aromatic compounds and was used directly for the next step: ^1H NMR: δ 8.02 (d, *J* 7.3 Hz, 2H), 7.59 (t, *J* 7.5 Hz, 1H), 7.45 (t, *J* 7.5 Hz, 2H), 6.04 (d, *J* 3.6 Hz, 1H), 5.89 (m, 1H), 5.49 (d, *J* 17.7 Hz, 1H), 5.45 (d, *J* 2.7 Hz, 1H), 5.28 (d, *J* 10.5 Hz, 1H), 4.87 (br d, *J* 3.6 Hz, 1H), 4.69 (d, *J* 3.6 Hz, 1H), 1.57 (s, 3H), 1.35 (s, 3H). A mixture of **24** (4.13 g, 14.24 mmol), prepared as described above, MeOH (10 mL) and 50% aq LiOH (10 mL) was stirred at 25 °C for 12 h. The solvent was removed, and the residue was extracted with ether. The combined organic layer was washed with water and dried. Removal of the solvent gave **25** (2.38 g, 90%) a white crystalline solid: mp 59–60 °C (EtOAc–petroleum ether); $[\alpha]_D^{25}$ −57.6 (*c* 0.77, $CHCl_3$); IR (KBr): 3426, 2928, 1381 cm^{-1}; ^1H NMR: δ 5.95 (d, *J* 3.6 Hz, 1H), 5.95–5.84 (m, 1H), 5.53 (d, *J* 17.1 Hz, 1H), 5.41 (d, *J* 10.8 Hz, 1H), 4.72 (br m, 1H), 4.57 (d, *J* 3.6 Hz, 1H), 4.09 (d, *J* 2.4 Hz, 1H), 2.08 (s, 1H), 1.51 (s, 3H), 1.32 (s, 3H); ^{13}C NMR: δ 131.1 (CH), 119.4 (CH_2), 111.6 (q), 104.5 (CH), 84.8 (CH), 80.8 (CH), 75.6 (CH), 26.6 (CH_3), 26.1 (CH_3); FABMS: *m*/*z* 187 (M+H); Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.25; H, 7.37.

3.11. 1,3-Bis[2-(5,6-didehydro-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-xylohexofuranos-3-*O*-yl)methylphenoxy]-propane (26)

Alkylation of **25** (0.20 g, 1.08 mmol) with 1,3-di(2-bromomethylphenoxy)propane (0.22 g, 0.53 mmol) according to the method used for the conversion of **2** to **19** gave **26** (0.26 g, 78%) as a colourless viscous liquid: $[\alpha]_D^{25}$ −57.5 (*c* 0.47, $CHCl_3$); IR (Neat): 3077, 1689, 1377 cm^{-1}; ^1H NMR: δ 7.33 (d, *J* 7.5 Hz, 2H), 7.25 (t, *J* 7.8 Hz, 2H), 6.94 (t, *J* 7.5 Hz, 2H), 6.87 (d, *J* 7.8 Hz, 2H), 6.08–5.96 (m, 2H), 5.94 (d, *J* 3.6 Hz, 2H), 5.41 (d, *J* 17.2 Hz, 2H), 5.28 (d, *J* 9.3 Hz, 2H), 4.69–4.53 (m, 8H), 4.17 (t, *J* 6.0 Hz, 4H), 3.91 (d, *J* 3.0 Hz, 2H), 2.32–2.26 (m, 2H), 1.50 (s, 6H), 1.30 (s, 6H); ^{13}C NMR: δ 155.9 (q), 132.2 (CH), 128.70 (CH), 128.66 (CH), 125.9 (q), 120.4 (CH), 118.8 (CH_2), 111.2 (q), 110.7 (CH), 104.6 (CH), 83.6 (CH), 82.7 (CH), 81.5 (CH), 66.9 (CH_2), 64.2 (CH_2), 29.1 (CH_2), 26.6 (CH_3), 26.0 (CH_3); MS (positive ion ESI): *m*/*z* 647 (M+Na); Anal. Calcd for $C_{35}H_{44}O_{10}$: C, 67.29; H, 7.10. Found: C, 67.30; H, 7.07.

3.12. General procedure for the ring-closing metathesis

The general procedure for the above compounds is illustrated by the RCM of **9**.

3.12.1. (1*S*,5*S*,6*R*,7*R*,9*R*,18*R*,20*R*,21*R*)-(6,7:20,21-Diisopropylidenedioxy)-2,4,8,11,16,19-hexaoxatricyclo-[16.3.0.0^{5,9}]heneicos-13-ene (29). To a solution of **9** (0.10 g, 0.21 mmol) in degassed CH_2Cl_2 (30 mL), **1** (0.018 g, 10 mol %) was added and refluxed for 10 h in an Ar atmosphere. The solvent was evaporated, and the residue was chromatographed using 1:9 EtOAc–petroleum ether as eluent to yield **29** (0.084 g, 90%) as a foam: IR (KBr): 1648, 1377 cm^{-1}; ^{1}H NMR (2:3-mixture of *E*, *Z* isomers): δ 5.93 (d, *J* 3.6 Hz, 1.2H), 5.90 (d, *J* 3.9 Hz, 0.8H), 5.85 (m, 0.8H), 5.78 (m, 1.2H), 4.81 (s, 0.8H), 4.79 (s, 1.2H), 4.46 (d, *J* 3.6 Hz, 0.8H), 4.45 (d, *J* 3.9 Hz, 1.2H), 4.41–4.36 (m, 2.4H), 4.31 (dd, *J* 12.3, 1.8 Hz, 1.6H), 4.20 (d, *J* 3.0 Hz, 0.8H), 4.17–4.03 (m, 2.4H), 3.95–3.89 (m, 0.8H), 3.87 (dd, *J* 10.5, 3.6 Hz, 1.2H), 3.80 (dd, *J* 10.5, 5.7 Hz, 0.8H), 3.67 (dd, *J* 10.5, 6.0 Hz, 0.8H), 3.46 (dd, *J* 10.5, 6.3 Hz, 1.2H), 1.50 (s, 2.4H), 1.41 (s, 3.6H), 1.31 (s, 6H); ^{13}C NMR (2:3-mixture of *E*, *Z* isomers): δ 132.5 (CH), 129.9 (CH), 111.9 (q), 105.0 (CH), 94.3 (CH_2), 92.3 (CH_2), 82.8 (CH), 82.6 (CH), 82.1 (CH), 80.1 (CH), 79.3 (CH), 78.7 (CH), 70.5 (CH_2), 67.1 (CH_2), 66.4 (CH_2), 65.6 (CH_2), 26.7 (CH_3), 26.3 (CH_3), 26.2 (CH_3); MS (EI) *m*/*z* 444 (M); Anal. Calcd for $C_{21}H_{32}O_{10}$: C, 56.75; H, 7.26. Found: C, 56.48; H, 7.43.

3.12.2. (1*R*,5*R*,7*R*,8*R*,9*S*,16*S*,17*R*,18*R*)-(7,8:17,18-Diisopropylidenedioxy)-3,6,10,15,19-pentaoxatricyclo-[14.3.0.0^{5,9}]nonadec-12-ene (27). Colourless syrup: yield 43% based on 50% recovered starting material, IR (KBr): 1635, 1378 cm^{-1}; ^{1}H NMR (3:7-mixture of *E*, *Z* isomers): δ 6.02 (br t, *J* 3.0 Hz, 1.4H), 5.90 (d, *J* 3.9 Hz, 0.6H), 5.89 (d, *J* 3.9 Hz, 1.4H), 5.82 (br t, *J* 3.9 Hz, 0.6H), 4.57 (d, *J* 3.9 Hz, 0.6H), 4.54 (d, *J* 3.6 Hz, 1.4H), 4.43–4.32 (m, 2H), 4.26 (d, *J* 13.8, 2.9 Hz, 1.4H), 4.13 (dd, *J* 11.7, 3.6 Hz, 0.6H), 4.04 (d, *J* 3.6 Hz, 0.6H), 4.01 (d, *J* 3.3 Hz, 1.4H), 3.90–3.74 (m, 4H), 3.70–3.62 (m, 2H), 1.49 (s, 6H), 1.32 (s, 6H); ^{13}C NMR (3:7-mixture of *E*, *Z* isomers): δ 130.67 (CH), 130.62 (CH), 111.9 (q), 111.8 (q), 83.7 (CH), 83.5 (CH), 81.0 (CH), 77.7 (CH), 77.1 (CH), 69.2 (CH_2), 67.0 (CH_2), 66.2 (CH_2), 65.9 (CH_2), 26.9 (CH_3), 26.8 (CH_3), 26.4 (CH_3), 26.2 (CH_3); FABMS: *m*/*z* 415 (M+H); Anal. Calcd for $C_{20}H_{30}O_9$: C, 57.96; H, 7.30. Found: C, 58.09; H, 7.42.

3.12.3. (1*R*,3*R*,4*R*,5*R*,9*R*,10*R*,12*R*,13*R*)-(3,4:12,13-Diisopropylidenedioxy)-1,10-bis(1,2-isopropylidenedioxyethyl)-2,6,8,11-tetraoxadispiro[4.3.4.4]heptadec-15-ene (28). Colourless, viscous liquid: yield 85%, single isomer $[\alpha]_D^{25}$ +109.1 (*c* 0.77, $CHCl_3$); IR (Neat): 2935, 1374 cm^{-1}; single isomer; ^{1}H NMR: δ 5.78–5.76 (m, 2H), 5.68 (d, *J* 3.3 Hz, 2H), 5.33 (s, 2H), 4.51 (d, *J* 3.0 Hz, 2H), 4.22 (dd, *J* 12.3, 6.0 Hz, 2H), 4.09 (m, 4H), 3.93 (dd, *J* 8.1, 6.3 Hz, 2H), 2.41 (m, 4H), 1.55 (s, 6H), 1.43 (s, 6H), 1.36 (s, 6H), 1.33 (s, 6H); ^{13}C NMR: δ 127.8 (CH), 113.0 (q), 109.2 (q), 103.2 (CH_2), 89.9 (CH_2), 84.8 (q), 82.9 (CH), 82.4 (CH), 73.5 (CH), 67.4 (CH_2), 30.3 (CH_2), 27.0 (CH_3), 26.6 (CH_3), 26.5 (CH_3), 25.5 (CH_3); MS (positive ion ESI) *m*/*z* 607 (M+Na); Anal. Calcd for $C_{29}H_{44}O_{12}$: C, 59.58; H, 7.59. Found: C, 59.70; H, 7.42.

3.12.4. (1*R*,7*R*,9*R*,10*R*,11*S*,18*S*,19*R*,20*R*)-(9,10:19,20-Diisopropylidenedioxy)3,5,8,12,17,21-hexaoxatricyclo-[16.3.0.0^{7,11}]heneicos-14-ene (30). Pale-yellow viscous liquid: yield 95%; IR (KBr): 2986, 1614 cm^{-1}; ^{1}H NMR (3:7-mixture of *E*, *Z* isomers): δ 5.92 (d, *J* 3.6 Hz, 1.4H), 5.87–5.83 (m, 2.6H), 4.78 (s, 0.6H), 4.73 (s, 1.4H), 4.56 (d, *J* 3.6 Hz, 2H), 4.36–4.28 (m, 4H), 4.09–3.98 (m, 2H), 3.95 (d, *J* 2.7 Hz, 0.6H), 3.92 (d, *J* 3.0 Hz, 1.4H), 3.80–3.74 (m, 2H), 3.55 (dd, *J* 9.0, 4.5 Hz, 0.6H), 3.42 (dd, *J* 9.0, 6.0 Hz, 1.4H), 1.49 (s, 6H), 1.32 (s, 6H); ^{13}C NMR (3:7-mixture of *E*, *Z* isomers): δ 130.9 (CH), 130.0 (CH), 111.6 (q), 104.9 (CH), 104.5 (CH), 97.2 (CH_2), 94.9 (CH_2), 83.0 (CH), 82.7 (CH), 82.5 (CH), 81.0 (CH), 78.7 (CH), 78.5 (CH), 70.3 (CH_2), 66.1 (CH_2), 64.8 (CH_2), 64.3 (CH_2), 26.6 (CH_3), 26.2 (CH_3); ESIMS (positive ion): *m*/*z* 467 (M+Na); Anal. Calcd for $C_{21}H_{32}O_{10}$: C, 56.75; H, 7.26. Found: C, 56.82; H, 7.32.

3.12.5. (1*S*,7*S*,8*R*,9*R*,11*S*,20*S*,22*R*,23*R*)-8,9:22,23-Diisopropylidenedioxy-2,6-bis-(*p*-toluenesulfonyl)-10,13,18,21-tetraoxa-2,6-diazatricyclo[18.3.0.0^{7,11}]tricos-15-ene (31). Pale-yellow needles: mp 198–200 °C ($CHCl_3$-petroleum ether); yield 78%, single isomer; $[\alpha]_D^{25}$ −30.3 (*c* 0.92, $CHCl_3$); IR (KBr): 2988, 2937, 1597, 1380, 1340 cm^{-1}; ^{1}H NMR: δ 7.73 (d, *J* 8.2 Hz, 4H), 7.36 (d, *J* 8.1 Hz, 4H), 5.96 (d, *J* 3.6 Hz, 2H), 5.80 (br s, 2H), 4.42–4.40 (m, 2H), 4.30–4.25 (m, 6H), 3.83–3.79 (m, 2H), 3.69 (dd, *J* 10.5, 8.2 Hz, 2H), 3.41 (dd, *J* 10.5, 2.2 Hz, 2H), 3.20–3.10 (m, 2H), 2.87–2.77 (m, 2H), 2.45 (s, 6H), 2.24 (m, 2H), 1.48 (s, 6H), 1.21 (s, 6H); ^{13}C NMR: δ 144.0 (q), 135.9 (q), 130.9 (CH), 129.9 (CH), 127.5 (CH), 111.2 (q), 104.7 (CH), 82.5 (CH), 79.1 (CH), 71.0 (CH_2), 67.1 (CH_2), 64.7 (CH), 44.7 (CH_2), 33.3 (CH_2), 26.4 (CH_3), 25.9 (CH_3), 21.5 (CH_3); FABMS: *m*/*z* 779 (M+H); Anal. Calcd for $C_{37}H_{50}N_2O_{12}S_2$: C, 57.05; H, 6.47; N, 3.60. Found: C, 56.97; H, 6.28; N, 3.32.

3.12.6. (2*R*,3*R*,3a*S*,20a*S*,21*R*,22*R*,23a*R*,25a*R*)-2,3:21,22-Diisopropylidenedioxy-2,3,3a,20a,21,22,23a,25a-octahydrodibenzo[*c*,*j*]difuro[2,3-*n*:3,2-*r*][1,5,9,13]tetraoxa-cyclononadeca-5a,14a,20a,24,25a-pentaene (32). Colourless, sticky liquid: yield 95%; IR (KBr): 2983, 1689, 1378 cm^{-1}; ^{1}H NMR (1:2-mixture of *E*, *Z* isomers):

7.39–7.26 (m, 4H), 7.01–6.87 (m, 4H), 6.12 (d, *J* 4.5 Hz, 1.33H), 5.93 (d, *J* 4.5 Hz, 0.67H), 5.88–5.85 (m, 2H), 4.99 (m, 2H), 4.69–4.48 (m, 6H), 4.19–4.15 (m, 4H), 3.90 (d, *J* 2.4 Hz, 1.33H), 3.73 (d, *J* 2.4 Hz, 0.67H), 2.41–2.37 (m, 1.33H), 2.26–2.22 (m, 0.67H), 1.47 (s, 6H), 1.31 (s, 6H); ^{13}C NMR: δ 157.4, 155.6, 131.1, 129.6, 128.6, 128.5, 127.3, 126.0, 121.1, 120.7, 112.5, 112.3, 111.4, 104.9, 86.2, 83.7, 83.5, 83.2, 81.2, 76.4, 68.9, 68.3, 65.8, 65.6, 29.5, 29.0, 26.4, 26.2; ESIMS (positive ion): *m*/*z* 619 (M+Na); Anal. Calcd for $C_{33}H_{40}O_{10}$: C, 66.43; H, 6.76. Found: C, 66.60; H, 6.47.

3.12.7. (2*S*,3*S*,3a*R*,20a*R*,21*S*,22*S*,23a*S*,31a*S*)-(2,3:21,22-Diisopropylidenedioxy)-2,3,5,3a,20a,21,22,23a-octahydrodibenzo[*c*,*j*]difuro[2,3-*c*:3,2-*r*][1,5,9,13,17,21]hexaoxacyclopentacosa-7a,14a,20a,27,31a-pentaene (33).

Yellowish-white viscous liquid: yield 70%, single isomer; $[\alpha]_D^{25}$ −32.5 (*c* 0.73, $CHCl_3$); IR (KBr): 2929, 1377 cm^{-1}; ^{1}H NMR: δ 7.25–7.35 (m, 4H), 6.89–6.98 (m, 4H), 5.91 (d, *J* 3.6 Hz, 2H), 5.57 (br m, 2H), 4.67 (d, *J* 12.3 Hz, 2H), 4.61 (d, *J* 3.6 Hz, 2H), 4.54 (d, *J* 12.3 Hz, 2H), 4.31 (m, 2H), 4.18 (m, 4H), 3.96 (d, *J* 2.7 Hz, 2H), 3.89 (d, *J* 10.2, 5.7 Hz, 2H), 3.76 (d, *J* 10.2 Hz, 2H), 3.64–3.54 (m, 4H), 2.33 (m, 2H) 1.49 (s, 6H), 1.32 (s, 6H); ^{13}C NMR: δ 156.2, 129.5, 129.3, 129.0, 126.4, 120.7, 111.7, 111.3, 104.9, 83.0, 81.8, 78.9, 71.1, 67.7, 66.5, 64.8, 29.2 26.8, 26.3; ESIMS (positive ion) *m*/*z* 707 (M+Na); Anal. Calcd for $C_{37}H_{48}O_{12}$: C, 64.90; H, 7.07. Found: C, 65.00; H, 7.07.

3.13. (1*S*,5*S*,6*R*,7*R*,9*R*,18*R*,20*R*,21*R*)-(6,7:20,21-Diisopropylidenedioxy)-2,4,8,11,16,19-hexaoxatricyclo[16.3.0.0^{5,9}]heneicosane (34)

A mixture **29** (0.20 g, 0.45 mmol) and Pd–C (10%) (0.020 g) in EtOH (20 mL) was stirred under hydrogen for 4 h at 25 °C. Then the mixture was filtered. Removal of the solvent afforded a syrupy residue that was chromatographed using 1:10 EtOAc–petroleum ether as eluent to give **34** (0.20 g, 98%) as a colourless thick liquid, $[\alpha]_D^{25}$ −108.4 (*c* 0.75, $CHCl_3$); IR (Neat): 1378 cm^{-1}; ^{1}H NMR: δ 5.87 (d, *J* 3.6 Hz, 2H), 4.85 (s, 2H), 4.53 (d, *J* 3.6 Hz, 2H), 4.35–4.31 (m, 2H), 4.26 (d, *J* 2.4 Hz, 2H), 3.83 (t, *J* 9.6 Hz, 2H), 3.59–3.52 (m, 6H), 1.78 (br m, 2H), 1.60 (br m, 2H), 1.51 (s, 6H), 1.32 (s, 6H); ^{13}C NMR: δ 111.8 (q), 104.5 (CH), 91.2 (CH_2), 82.4 (CH), 78.8 (CH), 78.2 (CH), 71.2 (CH_2), 66.0 (CH_2), 26.7 (CH_3), 26.2 (CH_3), 25.8 (CH_2); ESIMS (positive ion): *m*/*z* 469 (M+Na); Anal. Calcd for $C_{21}H_{34}O_{10}$: C, 56.49; H, 7.68. Found: C, 56.69; H, 7.47.

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