Novel Crown Ether Assemblies: The Role of Isobenzofurans for Attaching Crown Ethers to Rigid Molecular Racks in a Geometrically Precise Fashion

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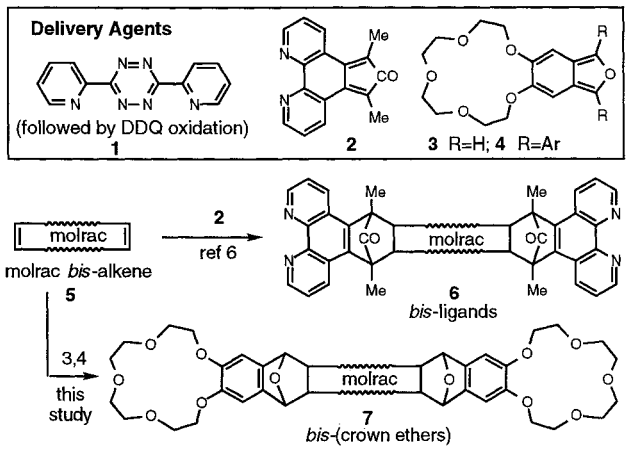
Abstract: Rigid polyalicyclic nanostructures with extended and U-shaped geometry and functionalised with 15-crown-5 rings have been prepared from molrac mono or *bis*alkenes and new crown ether isobenzofurans; substituents in the 1,3-position of the isobenzofuran are used to modify stereospecifities in the cycloaddition process thereby acting as geometrical control agents in the construction process.

Crown ethers in which the ionophoric groups are fixed in relationship to each other offer prospects for evolving new guest, host chemistry.[1] Rigid molecular racks (molracs), already successful as spacer systems for energy transfer studies[2] and as hosts for host, guest chemistry,[3] are employed as the geometric spacer in the present study. This work highlights a developing synthetic protocol[4] where preformed molrac *bis*-alkenes, represented as **5** in Scheme 1, are treated with functionalised cycloaddition reagents such as delivery reagents **1**[5] or **2**[6] to form the target molecule, eg *bis*-ligands **6**, where the shape of the starting *bis*-alkene and the stereospecificity of the cycloaddition govern the shape of the *bis*-functionalised product.

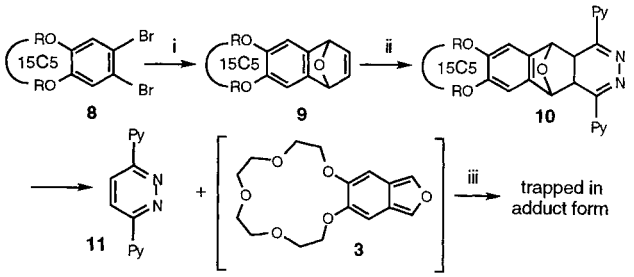
In the present context, the isobenzofuran crown ethers **3** or **4** are reacted with rigid molrac *bis*-alkene **5** to form nanosized bis(crown ethers) **7** which exemplify polyalicyclic nanostructures.



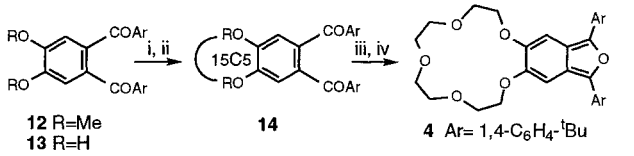
Scheme 1

The parent isobenzofuran crown **3** was prepared as outlined in Scheme 2. The known dibromide **8**[7] was treated with nBuLi in the presence of furan to afford the benzo-7-oxanorbornadiene **9**. Reaction of dienophile **9** with 3,6-di(2-pyridyl)*s*-tetrazine **1**[8] in DMSO yielded the unstable dihydropyridazine **10** which was isolated as a yellow-coloured solid.[9] Warming solutions of **10** in the presence of a dienophile allowed trapping of the first-generated isobenzofuran **3** in adduct(s) form. Typically, isobenzofuran **3** formed a 10:1 mixture of *endo* and *exo*-adducts with *N*-methyl maleimide.

Preparation of the 1,3-*bis*-(3-*tert*.butylphenyl)isobenzofuran crown **4** followed traditional lines for stable isobenzofurans (Scheme 3). The appropriately substituted catechol **13**, readily prepared by boron tribromide demethylation of **12**,[10] was converted to the disodium salt by reaction with sodium hydroxide and alkylated with 1,11-dichloro-3,6,9-trioxaundecane[11] to afford **14**. Conversion to 1,3-*bis*-(4-*tert*.butylphenyl)isobenzofuran crown **4** was achieved using Zn in aqKOH/EtOH followed by cyclisation in acid.



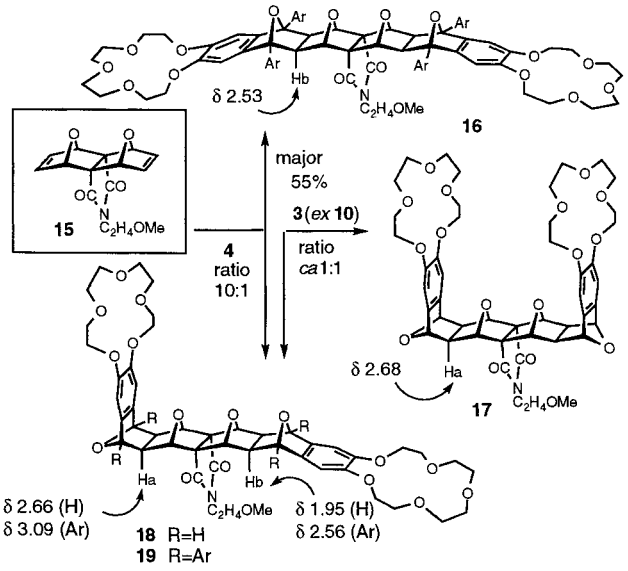
Scheme 2. *Reagents and conditions:* i) BuLi, furan, ether, -50 °C, 34% ii) *s*-tetrazine 1, DMSO, RT, unstable iii) *N*-methyl maleimide, *endo, exo* ratio 9:1



Scheme 3. *Reagents and conditions:* i) BBr_3, CH_2Cl_2, -80 °C, 100% ii) aq NaOH, BuOH, 1,11-dichloro-3,6,9-trioxaundecane, 81% iii) KOH,aq EtOH, Zn iv) acidify carefully to pH 7 with H_2SO_4, 90 %

The current methodology for the construction of inner-functionalised nanostructures further functionalised at the termini with 15-crown-5 functionality is illustrated using a series of *bis*-alkenes **15**, **20**, **22** which contain norbornene, 7-oxanorbornene and cyclobutene-1,2-diester type dienophiles respectively. These *bis*-alkenes have been selected as they contain between them, all the major dienophilic end-groups present in molrac alkenes. Consequently, they should act as prototypes for other molrac alkene systems.

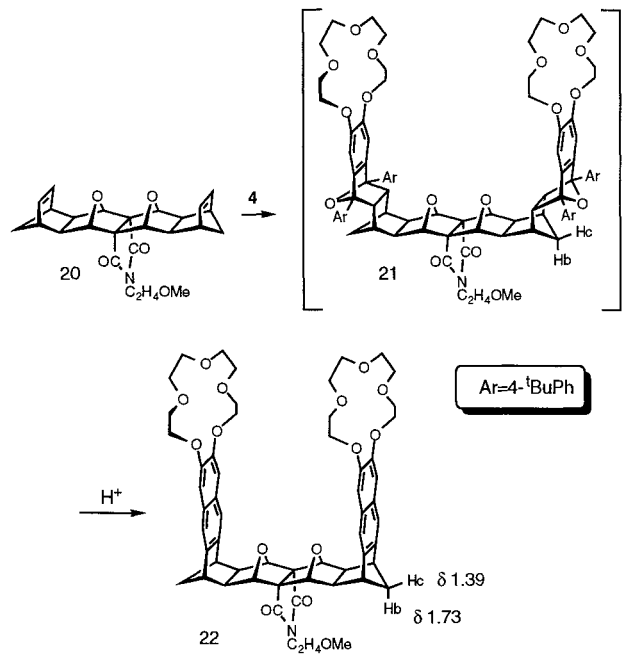
Reaction between *bis*-alkene **15** and the 1,3-*bis*-(4-*tert*.-butyl phenyl)isobenzofuran crown ether **4** gave two 1:2-adducts: a C_{2v}-symmetrical product which dominated 10:1 over the minor one (Scheme 4). The isolation of this minor product **19** was critical as it held the key to the stereochemical assignment to the major product since, being unsymmetrical, it contained both types of stereo-definitive protons Ha, Hb which occurred at δ 3.09 and δ 2.56. Here the higher field resonance is attributed to the extended stereochemistry where the benzene component of the basic isobenzofuran ring provides the ring-current for shielding. This indicates that the major product has the extended structure **16**. Using reference to Ha and Hb chemical shifts in the unsubstituted counterparts **17** and **18** is quite misleading in this case. The shielding contribution in this unsubstituted series (δHb-δHa= 0.71 ppm) compares favourably with that in **19** (0.53 ppm); the absolute difference between individual proton chemical shifts in the two series reflects the *deshielding* effect of the bridgehead aryl rings, a factor not readily assessed *a priori*, because of their conformational mobility.



Scheme 4

Reaction of *bis*-alkene **15** with the parent crown isobenzofuran **3**, generated by thermal decomposition of **10**, forms two out of the three possible isomers from *exo*-face attack on **15** (Scheme 4). Coupling data allow definitive stereochemical assignments on the basis of the vicinal coupling with the oxygen bridge methine protons which occur in the δ 4-5 region of the ^{1}H NMR spectrum (extended isomers show no coupling, bent isomers display coupling). This shows that the U-shaped *bis*-adduct **17** and the unsymmetrical *bis*-adduct **18** can be accessed via this route which emphasises the opportunity to control stereochemical outcomes by variation of the 1,3-substituents on the isobenzofuran .

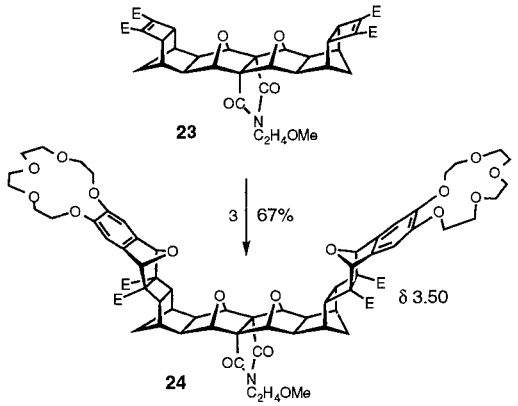
Direct access to another class of U-shaped cavity with crown ether walls was achieved by reaction of the 1,3-*bis*-(4-*tert*.butylphenyl) isobenzofuran crown **4** with *bis*-alkene **20**. A high-symmetry product was obtained where the chemical shift of the methylene protons Hb (δ1.73) and Hc (δ1.39) was indicative of the final outcome and immediately ruled out 1:2 adduct **21**, since there is much evidence to



Scheme 5

expect resonances of *ca* δ 0.5 and δ 2.5 for such protons.[12] In practice, loss of the newly formed ether-bridges in **21** has occurred to yield the related naphthalene **22**, a process clearly aided by the aryl-substituents and promoted by a trace of acid during reaction or work-up.

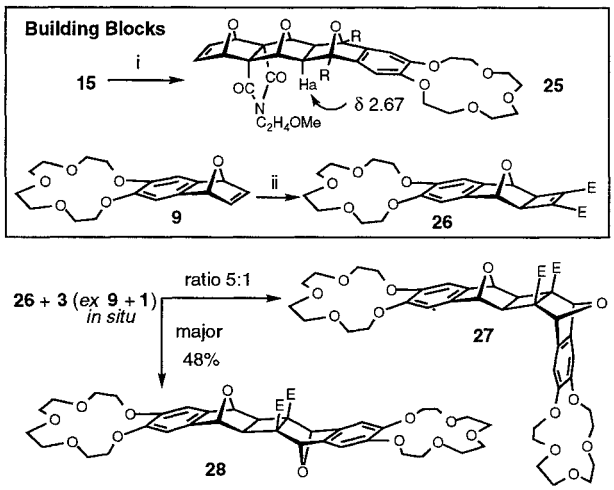
Following the guideline offered by the model study,[13] synthesis of the extended *bis*-crown ether **24** was achieved from *bis*-cyclobutene-1,2-diester **23** using the parent crown isobenzofuran **3** (Scheme 6). The high-symmetry was apparent in both the ^{1}H NMR and ^{13}C NMR spectrum for *bis*-adduct **24** and the stereochemistry was assigned using the chemical shift of the ester-methyl groups as the monitor.[13]



Scheme 6

Controlled reaction between *bis*-alkene **15** and crown isobenzofuran **4** allowed formation of the 1:1-adduct **25** (Ha=δ 2.67, confirmed the extended stereochemistry). Compound **25**, the parent isobenzofuran precursor **9** and the cyclobutene-1,2-diester **26** derived from **9** (Scheme 7) offer a bank of crown ether building blocks for future use in polyalicyclic nanostructure development.[14] The cycloaddition of the parent crown isobenzofuran **3** with **26** yields two new *bis*-crown ethers: **28**, in which the relative orientations of the two crown ether units are roughly parallel and **27** where they are at right angles to one another.

Spectroscopic data and melting points for representative new compounds are reported in the reference section.[15]



Scheme 7. *Reagents and conditions:* i) $CHCl_3$, sealed vessel, 80 °C, 7h ii) DMAD, $RuH_2CO(PPh_3)_3$ catalyst, C_6H_6, 12 h, 56%

Molecular modelling of these systems has been complicated by the size and conformational mobility of the crown ether moieties, so they have been omitted in the trimmed down versions of U-shaped cavity structures **29** (R=H and Ph) for **21** and **30** (R=H and Ph) for **17**; the

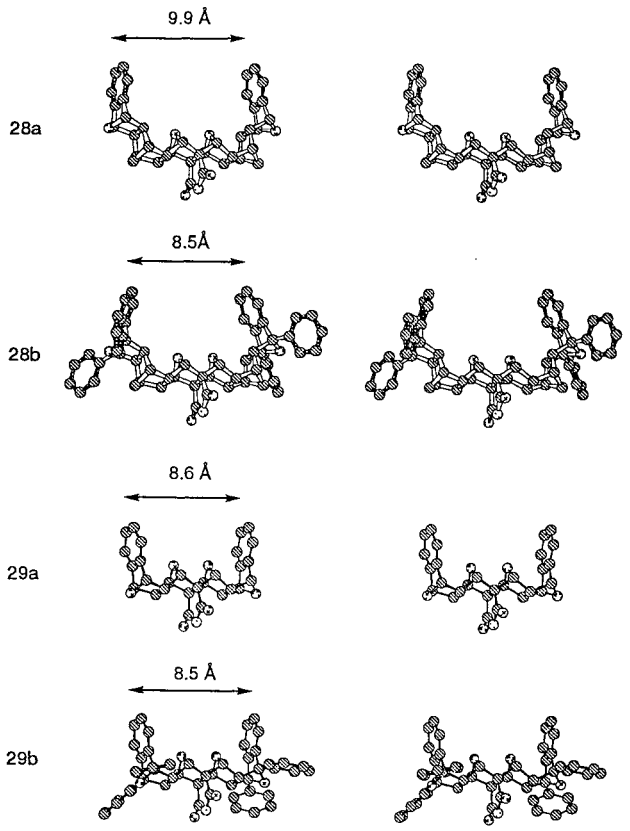


Figure 1. Stereoview of cavity molecules **29** and **30**: a) without substituents, b) with phenyl substituents. H atoms omitted from figures for visual reasons. The geometries have been optimised using the AM1 Hamiltonian.

N-substituent has been replaced by H for similar reasons. These structures have been minimised using AM1 and are shown in stereoview in Figure 1 for a) the parent and b) the phenyl substituted systems. The most significant difference occurs in **29** following introduction of the phenyl substituents as these cause the walls to converge by around 1Å.

This study demonstrates the value of 1,3-substituents in isobenzofurans to control stereochemistry, and illustrates the role of functionalised isobenzofurans to act as delivery reagents for introducing 15-crown-5-subunits into molecular assemblies. The use of the U-shaped *bis*-crown **22** in guest, host studies and the extended *bis*-crown **24** in self assembly studies will be presented in due course.

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References and Notes

(1) "Crown Compounds: Towards Future Applications", Ed S. R. Cooper, VCH, NY, 1992.

(2) *inter alia* Lawson, J. M.; Craig, D. C.; Oliver, A. M.; Paddon-Row, M. N. *Tetrahedron* **1995**, *51*, 3841 and references therein. Kumar, K.; Tepper, R. J.; Zeng, Y.; Zimmt, M. B. *J. Org. Chem.* **1995**, *60*, 4051 and references therein.

(3) Klarner, F.-G.; Benkhoff, J.; Boese, R.; Burkert, U.; Kamieth, M.; Naatz, U. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1130. Benkhoff, J.; Boese, R.; Klarner, F.-G; Wigger, A. E. *Tetrahedron Lett.* **1994**, *35*, 73.

(4) While not explicitly stating it at the time, this protocol was used by us earlier to form space-separated molrac bis(ligands) where 3,6-di(2-pyridyl)-*s*-tetrazine (DDQ) acted as the delivery agent for the 3,6-di(2-pyridyl)-pyridazine ligand.[5]

(5) Warrener, R. N.; Elsey, G. M.; Sankar, I. V.; Butler, D. N.; Pekos, P.; Kennard, C. H. L. *Tetrahedron Lett.*. **1994**, *35*, 6745.

(6) Warrener, R. N.; Houghton, M. A.; Schultz, A. C.; Keene, F. R.; Kelso, L. S.; Dash, R.; Butler, D. N. *Chem. Commun.* **1996**, 1151. Warrener, R. N.; Ferreira, A. B. B.; Schultz, A. C.; Butler, D. N.; Keene, F. R.; Kelso, L. S. *Angew. Chem.* **1996**, *108*, 2651. Warrener, R. N.; Schultz, A. C.; Houghton, M. A.; Butler, D. N. *Tetrahedron*, **1997**, *in press.*

(7) Sielcken, O. E.; van Tilborg, M. M.; Roks, M. F. M.; Hendriks, R.; Drenth, W.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1987**, *109*, 4261.

(8) Geldard, J. F.; Lions, F. *J. Org. Chem.* **1965**, *30*, 318.

(9) Where isobenzofurans are being reacted with ring-strained substrates, eg **15**, which themselves react with *s*-tetrazines, then it is necessary to use the isolated dihydropyridazine **10** as the isobenzofuran source; where substrates, eg **25**, are not reactive towards *s*-tetrazines, *in situ* generation of isobenzofuran can be used in a one-pot reaction containing epoxynaphthalene, *s*-tetrazine and the substrate to undergo cycloaddition.
Warrener, R. N. *J. Am. Chem. Soc.* **1971**, *93*, 2346. Russell, R. A.; Longmore, R. W.; Warrener, R. N. *J. Chem. Ed.* **1992**, *69*, 16410.

(10) Prepared by dehydrogenation (DDQ, 51%, m.p. 169-170 °C) of the [4π+2π]adduct of 2,3-dimethoxy-1,3-butadiene and 1,4-di(4-*tert*-butylphenyl)-but-2-en-1,4-dione (75%, m.p. 176-177 °C).

(11) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7071.

(12) Precedent for such dehydrations have been found in other U-shaped cavity systems, Warrener, R. N.; Fairlie, D. P.; Russell, R. A., *unpublished results.*

(13) Warrener, R. N.; Wang, S.; Butler, D. N.; Russell, R. A. *Synlett.* **1997**, 44.

(14) We have recently discovered a new coupling process for stereospecifically assembling polyalicyclic nanostructures from the reaction of smaller functionalised carbocyclic dienophiles with fused epoxycyclobutanes and these crown compounds are admirably suited building blocks for this procedure.

(15) Data on selected compounds discussed herein.
4. *m/z* 573 (M^+, 100%) ^{1}H NMR ($CDCl_3$) δ 1.38 (18H, s), 3.80-4.20 (16H, m), 6.95 (2H, s), 7.50 (4H, dt, *J* = 8.6 Hz, 2.1 Hz), 7.80 (4H, dt, *J* = 8.6 Hz, 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 31.28, 34.61, 68.32, 69.28, 70.35, 71.24, 97.63, 118.37, 124.15, 125.76, 129.36, 142.18, 149.28, 150.09.
9. m.p. 72-74 °C. m/z 335 (M^+, 13%), ^{1}H NMR ($CDCl_3$) δ 3.73-4.12 (16H, m, CH_2CH_2), 5.64 (2 H, t, *J* = 1.0 Hz), 6.93 (2H, s), 7.01 (2 H, t, *J* = 1.0 Hz); ^{13}C NMR ($CDCl_3$) δ 69.71, 69.89, 70.62, 70.81, 82.49, 109.73, 142.39, 143.18, 146.05.
16. m.p. 245-247 °C. ^{1}H NMR δ 1.36 (36 H, s), 2.53 (4H, s), 2.60 (3H, s), 3.31-3.50 (4H, m), 3.46-4.01 (32H, m), 4.41 (4H, s), 6.54 (4H, s), 7.46 (16H, d, *J* = 2.8 Hz).
19. m.p. 279-281 °C ^{1}H NMR ($CDCl_3$) δ 1.33 (18H, s), 1.40 (18H, s, ^{t}Bu x2), 2.56 (2H, s), 2.75 (3H, s, OCH_3), 3.09 (2H, s), 3.39 (2H, t, *J* = 5.0 Hz), 3.59 (2H, t, *J* = 5.0 Hz), 3.68 (16H, sbr), 3.76 (4H, m), 3.81 (4H, m), 3.91 (4H, m), 4.02 (4H, m), 4.30 (2H, s), 4.42 (2H, s), 6.29 (2H, s), 6.66 (2H, s), 7.41 (8H, d, *J* = 8.3 Hz), 7.49 (8H, d, *J* = 9.3 Hz).
22. 32% ^{1}H NMR ($CDCl_3$) δ 1.39 (2H, d, *J* = 8.4 Hz), 1.48 (36H, s), 1.73 (2H, d, *J* = 8.4 Hz), 1.58 (4H, s), 2.27 (4H, m), 3.24 (3H, s, OCH_3), 3.36-3.96 (32H, m), 4.05 (4H, s), 6.88 (4H, s), 7.22-7.60 (16H, m).
24 m.p. 292-294 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (2H, d, *J* = 10.8 Hz), 2.11 (4H, m), 2.15 (2H, d, *J* = 10.6 Hz), 2.40 (4H, m), 2.52 (4H, s), 3.27 (3H, s), 3.50 (12H, s, OCH_3), 3.57 (4H, m), 3.73-4.10 (32H, m), 4.72 (4H, s), 5.10 (4H, s), 6.71 (4H, s); ^{13}C NMR ($CDCl_3$) δ 36.80, 38.11, 40.57, 43.24, 47.22, 51.01, 58.59, 59.58, 68.32, 69.31, 69.39, 70.38,

72.76, 72.23, 81.23, 85.45, 107.57, 135.42, 148.46, 168.77, 174.65.

25 m.p. 194-196 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (18H, s), 2.67 (2H, s), 2.78 (3H, s), 3.31 (2H, t, *J* = 5.2 Hz), 3.43 (2H, t, *J* = 5.2 Hz), 3.67-3.99 (16H, m), 4.56 (2H, s), 5.07 (2H, t, *J* = 0.7 Hz), 6.39 (2H, t, *J* = 0.7 Hz), 6.65 (2H, s), 7.54 (8H, d, *J* = 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 31.40, 34.62, 38.20, 54.86, 58.33, 68.22, 68.47, 69.59, 69.85, 70.57, 70.87, 80.60, 82.19, 89.82, 106.77, 125.66, 125.68, 137.12, 142.20, 148.34, 150.51, 133.23, 174.27 (carbonyl).

26. m.p. 200-202 °C; Mass spectrum m/z 477 (M+, 6.3%), ^{1}H NMR ($CDCl_3$) δ 2.86 (2H, s), 3.84 (6H, s, OCH_3), 3.74-4.13 (16H, m), 5.12 (2H, s), 6.92 (2H, s).

27. ^{1}H NMR ($CDCl_3$) δ 1.32 (2H, s, H2,26), 3.82 (6H, s, OCH_3), 3.71-4.09 (32H, m), 5.56 (2H, s), 5.61 (2H, s), 6.66 (2H, s), 6.87 (2H, s).

28. ^{1}H NMR ($CDCl_3$) δ 2.35 (2H, s), 3.55 (6H, s), 3.74-4.14 (32H, m), 5.22 (2H, s), 5.41 (2H, s), 6.82 (2H, s), 6.86 (2H, s); ^{13}C NMR ($CDCl_3$) δ 46.55, 51.37, 58.75, 69.23, 69.31, 69.43, 70.33, 70.45, 70.76, 79.44, 85.49, 107.00, 107.92, 135.64, 137.21, 148.18, 148.37, 168.89.