

HETEROCYCLES, Vol. 68, No. 1, 2006, pp. 125 – 136. © The Japan Institute of Heterocyclic Chemistry
Received, 13th October, 2005, Accepted, 2nd December, 2005, Published online, 6th December, 2005. COM-05-10592

SYNTHESIS OF DIBENZO-FUSED 10-MEMBERED CYCLIC ETHERS FROM ISOVANILLIN VIA RING-CLOSING META-THESIS

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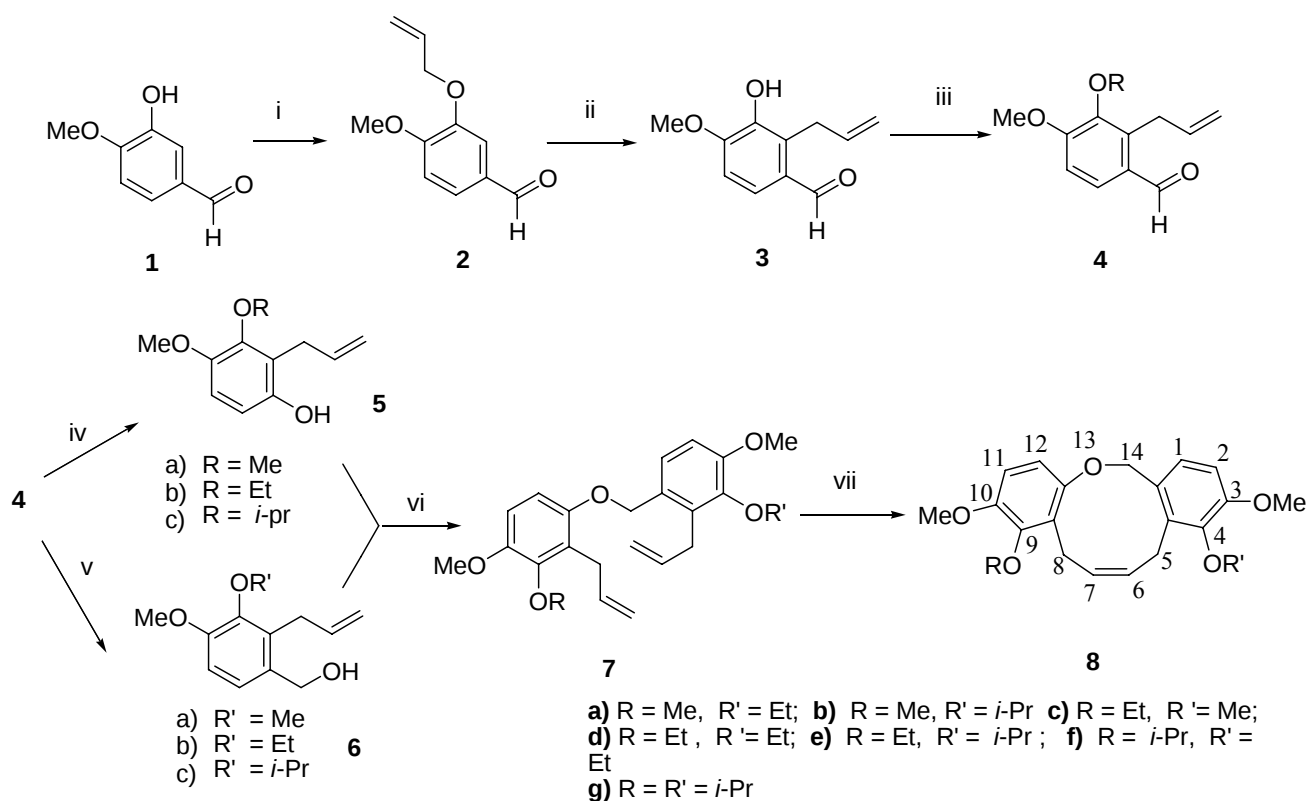
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Abstract –A synthesis of substituted dibenzo-fused 10-membered cyclic ethers is described. 2-Allylbenzyl alcohols and 2-allylphenols derived from isovanillin were coupled by the Mitsunobu reaction to construct intramolecular dienes with ether linkage. The resulting dienes were subsequently treated with Grubbs' catalyst to undergo ring-closing metathesis to give the desired cyclic ethers.

INTRODUCTION

Interest in the synthesis of medium macrocyclic ethers has increased because of their occurrence in nature and their biological activities.¹ The cyclic ethers such as seven-membered,² eight-membered,³ and nine-membered cyclic ethers⁴ which were prepared from ring-closing metathesis (RCM) have been reported in the previous studies. However the synthesis of ten-membered cyclic ethers has paid no attention. Recently, we have based on RCM and used the powerful catalyst developed by Grubbs⁵ to synthesize benzo[*b*]oxepines,⁶ benzo[*c*]oxocines,⁷ and benzofurans.⁸ In this our continuing study, we disclose the synthesis of a series of novel dibenzo-fused 10-membered macrocyclic ethers. The strategy was started from isovanillin which was transformed it to the requisite aryl benzyl ethers with dienes functionality by the Mitsunobu reaction.⁹ Subsequent treatment of these aryl benzyl ethers with Grubbs' catalyst yielded a series of novel substituted dibenzo-fused 10-membered cyclic ethers in moderate yield,

respectively (**Scheme 1**). Their structures were assigned rationally by spectral data. In addition the olefinic double bonds of these giving cyclic ethers (**8a-g**) were confirmed as *cis*-configuration by either $^1\text{H-NMR}$ spectra or X-Ray crystallography.



Scheme 1. Reagents and conditions: i) allyl bromide / K_2CO_3 / acetone, reflux, 8 h, 87%; ii) heated to 180°C , 3 h, 92%; iii) RX / K_2CO_3 / acetone, reflux, 8 h, 80-98%; iv) H_2O_2 / MeOH/ H^+ , rt, 1.5 h, 71-75%; v) NaBH_4 / EtOH, rt, 30 min, 93-98%; vi) DIAD / TPP, 0°C to rt, 12 h, 50-57%; vii) 1st generation Grubbs' catalyst / CH_2Cl_2 , 1.5 days, 41-50%

RESULTS AND DISCUSSION

3-Allyloxy-4-methoxybenzaldehyde (**2**), prepared from isovanillin (**1**) and allyl bromide, was subjected to the Claisen rearrangement at 180°C to give 2-allyl-3-hydroxy-4-methoxybenzaldehyde (**3**) in 92 % yield.¹⁰ The resulting compound (**3**) was reacted with various either alkyl iodide or bromide to undergo O-alkylation to produce 2-allyl-3-alkoxy-4-methoxybenzaldehydes (**4a-c**) in 80-98% yield.¹⁰ Compounds (**4a-c**) were converted into corresponding phenols (**5a-c**) in yield of 71-75% by Dakin oxidation.⁶ On the other hand, compounds (**4a-c**) were reduced with sodium borohydride to give the corresponding benzyl alcohols (**6a-c**) in yield of 93-98% by a reported procedure.⁷ Subsequently, compounds (**5a-c**) and (**6a-c**) were subjected to the Mitsunobu reaction to undergo intermolecular dehydration to produce the aryl benzyl ethers with dienes functionality (**7a-g**) in yield of 50-57%. The structures of **7a-g** were confirmed according to their spectral data. For example, the $^1\text{H-NMR}$ spectrum of **7a** exhibited one singlet signal with six protons at δ 3.82 which indicated the overlap of two methoxy groups; one singlet signal with three protons at δ 3.85 indicating the presence of one another methoxy group; one triplet signal of three

protons at δ 1.38 with coupling constant $J = 6.8$ Hz and one quartet signal of two protons at δ 4.02 with $J = 6.8$ Hz indicating the presence of one ethoxy group; one singlet signal of two protons at δ 4.90 indicating the presence of benzylic protons and the success of the formation of ether linkage from phenol and benzyl alcohol via the Mitsunobu reaction. Furthermore two double triplet signals with two protons in each were observed, one at δ 3.45 with coupling constant $J = 6.4, 1.6$ Hz, and the other one at δ 3.53 with coupling constant $J = 6.0, 1.6$ Hz indicating the presence of two allylic protons. In addition, twenty four carbons found in ^{13}C -NMR spectrum matched the structure of **7a**, $\text{C}_{24}\text{H}_{30}\text{O}_5$. Furthermore, the molecular ion, m/z 398 (M^+) in EI-MS (70 eV) and m/z 398.2090 in the HRMS spectrum were found that is coincident with the calculated one, 398.2088 for $\text{C}_{24}\text{H}_{30}\text{O}_5$. Subsequent treatment of the dienes (**7a-g**) with 1st generation Grubbs' catalyst furnished the substituted dibenzo-fused 10-membered cyclic ethers (**8a-g**) in yield of 41-50%, respectively. The structure of **8a-g** was verified based on their spectral data such as ^1H -NMR, ^{13}C -NMR, EI-MS, and NOESY spectra. The combination of data from ^1H -NMR and NOESY spectra enabled us to assign their structures unequivocally. For example, the NOESY correlations of **8c** showed the signal of O-CH₂ of ethoxy group at δ 4.03 has two cross peaks; one at δ 3.64 indicating H-8 and the other one at δ 3.86 indicating the methoxy group at C-10. The signal at δ 5.59, which is the cross peak of H-8, was assigned as H-7. The signal at δ 5.49, which is the cross peak of H-7, was assigned as H-6. The proton at δ 4.01 was assigned as H-5 for its cross-linking with H-6. The typical benzylic proton, H-14 at δ 4.94 has two cross peaks; H-1 at δ 6.94 and H-12 at δ 6.73. The signal of H-12 was assigned because of its no cross-linking with methoxy group. Therefore two other aromatic protons, which were overlapped, could be assigned at δ 6.72. Thus, the assignment of the ^1H -NMR spectrum of **8c** was accomplished. Based on the information of NOESY spectrum, the characteristic signals of dibenzo-fused 10-membered cyclic ethers (**8a-g**) could be deduced and were summarized in **Table 1**. Furthermore, the stereochemistry of dibenzo-fused 10-membered cyclic ether (**8a-g**) was respectively certified as *cis*-configuration on the basis of their olefinic coupling constants (10.0 ~ 10.8 Hz) in ^1H -NMR spectra. In addition the structure of **8c** is further confirmed by X-Ray crystallography (**Figure 1**). The X-Ray crystal data for **8c** revealed that the selected bond length ($\text{\AA}$) between olefinic carbons C(6)-C(7) is 1.327. The selected bond angles of C(5)-C(6)-H(6), C(5)-C(6)-C(7), C(7)-C(6)-H(6), C(6)-C(7)-C(8), C(6)-C(7)-H(7), and C(8)-C(7)-H(7) were 116.2°, 127.4°, 116.4°, 127.2°, 116.3°, and 116.4°, respectively. Thus, the coplanar of H(6)-C(6)-C(7)-H(7) was observed and further confirmed the olefinic double bond of the structure (**8c**) as *cis*-configuration.

On the other hand, the ^1H - ^{13}C HETCOR spectra provide the further information for the identification of characteristic carbons at compound (**8a-g**). For example, in the molecule of **8c**, the methyl carbon of

Table 1. The characteristic protons of 10-membered cyclic ethers (**8a-g**) in $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) spectra*

Compds	H-5	H-8	H-6	H-7	H-14
8a	4.01 (d, $J = 7.2$ Hz)	3.63 (d, $J = 8.0$ Hz)	5.49(dt, $J = 10.4, 8.0$ Hz)	5.58 (dt, $J = 10.4, 8.0$ Hz)	4.94 (s)
8b	4.05 (d, $J = 8.0$ Hz)	3.99 (d, $J = 8.0$ Hz)	5.46 (d, $J = 10.4, 8.0$ Hz)	5.57 (dt, $J = 10.8, 8.4$ Hz)	4.92 (s)
8c	3.99 (d, $J = 8.0$ Hz)	3.64 (d, $J = 8.0$ Hz)	5.49 (dt, $J = 10.8, 7.8$ Hz)	5.59 (dt, $J = 10.4, 8.2$ Hz)	4.94 (s)
8d	4.01 (d, $J = 8.8$ Hz)	3.64 (d, $J = 8.0$ Hz)	5.48 (dt, $J = 10.0, 7.8$ Hz)	5.57 (dt, $J = 10.8, 7.8$ Hz)	4.93 (s)
8e	4.05 (d, $J = 8.4$ Hz)	3.64 (d, $J = 8.4$ Hz)	5.44 (dt, $J = 10.4, 7.6$ Hz)	5.56 (dt, $J = 10.4, 8.0$ Hz)	4.91(s)
8f	4.02 (d, $J = 7.2$ Hz)	3.66 (d, $J = 8.4$ Hz)	5.45 (dt, $J = 10.4, 7.6$ Hz)	5.58 (dt, $J = 10.4, 8.2$ Hz)	4.92 (s)
8g	4.05 (d, $J = 8.0$ Hz)	3.65 (d, $J = 8.4$ Hz)	5.42 (dt, $J = 10.8, 7.8$ Hz)	5.56 (dt, $J = 10.4, 8.0$ Hz)	4.91 (s)

*Other chemical shifts are described in EXPERIMENTAL

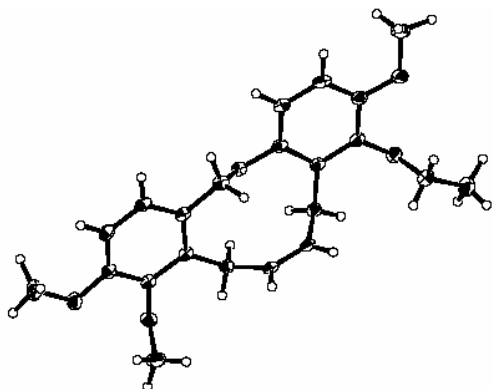


Figure 1. ORTEP plot of the X-Ray crystal of **8c**

ethoxy group was assigned at 15.67 (OCH_2CH_3) for its linking with the corresponding proton at δ 1.40 (OCH_2CH_3). Based on the same technique, the other carbons of **8c** were assigned as follows: δ 22.44 (C-8), 24.77 (C-5), 55.62 (OCH_3), 56.01 (OCH_3), 60.86 (OCH_3), 69.24 (OCH_2CH_3), 75.52 (C-14), 109.06 (C-11), 110.08 (C-2), 115.19 (C-12), 125.41 (C-1), 126.48 (C-6), 127.51 (C-7). Thus, the characteristic carbons of **8a-g** could be assigned and compiled in **Table 2**.

CONCLUSION

We have established a method for the construction of dibenzo-fused 10-membered cyclic ethers from isovanillin *via* the Mitsunobu's reaction and RCM. Furthermore, the olefinic double bond of those resulting cyclic ethers was identified as *cis*-configuration. In addition, the assignment of each proton and typical carbons of those cyclic ethers was achieved by NOSEY and HETCOR spectra, respectively.

Table 2. The characteristic carbons of 10-membered cyclic ethers (**8a-g**) in ^{13}C -NMR spectra (CDCl_3 , 100 MHz)

Compds	C-8	C-5	C-14	C-2	C-11	C-12	C-1	C-6	C-7
8a	22.21	24.94	75.73	108.93	109.98	115.55	125.23	126.56	127.36
8b	22.49	25.32	76.27	108.93	110.05	115.96	124.91	126.47	127.37
8c	22.44	24.77	75.52	109.06	110.08	115.19	125.41	126.48	127.52
8d	22.49	24.95	75.82	108.98	110.05	115.45	125.23	126.51	127.45
8e	22.50	25.26	76.24	108.91	110.06	115.73	124.83	126.35	127.39
8f	22.90	24.95	75.96	109.04	110.15	115.34	125.19	126.48	127.44
8g	22.86	25.26	76.31	108.91	110.07	115.55	124.76	126.29	127.38

*Other chemical shifts are described in EXPERIMENTAL

EXPERIMENTAL

Melting points (Yanaco micro melting-point apparatus) were uncorrected. ^1H -NMR and ^{13}C -NMR spectra were obtained on a Varian Gemini-200 or Varian Unity plus 400 Spectrometer. Chemical shifts were measured in parts per million with respect to TMS. Elemental analyses were recorded on a Heraeus CHN-O Rapid analyzer. MS spectra were recorded on a Chem/hp/middle spectrometer connected to a Hewlett Packard series II model gas-liquid chromatograph. HRMS spectra were performed on a JEOL JMS SX/SX 102A instrument. Silica gel (230-400 mesh) for column chromatography and precoated silica gel plates (60 F-254) for TLC were purchased from E. Merck Co. UV light (254 nm) was used to detect spots on TLC plates after development.

Crystal structure analysis of **8c**

The crystal structure of compound (**8c**) has been determined by single-crystal X-Ray diffraction techniques and refined by full-matrix least-squares procedures to give R value of 0.043. The crystals are colorless prism, space group $\text{P2}_1/\text{c}$ (#14) with lattice parameters, $a = 9.5067(8) \text{ \AA}$, $b = 6.6759(5) \text{ \AA}$, $c = 29.995(2) \text{ \AA}$ and $Z = 4$. A crystal of $0.20 \times 0.20 \times 0.20 \text{ mm}$ was chosen. The data were collected on a Rigaku AFC8 diffractometer with graphite monochromated Mo (μ) K ($0.71070 \text{ \AA}$) radiation. The CIF file has been deposited at the Cambridge Crystallographic Center (CCDC), UK, and received the number as CCDC 281587.

Starting material and key intermediates: Isovanillin (**1**) was purchased from TCI, Japan. 3-Allyloxy-4-methoxybenzaldehyde (**2**), 2-allyl-3-hydroxy-4-methoxybenzaldehyde (**3**), 3-alkoxy-2-allyl-4-methoxybenzaldehyde (**4**), 4-alkoxy-2-allyl-3-methoxyphenols (**5a-c**), and 4-alkoxy-2-allyl-3-

methoxybenzyl alcohols (**6a-c**) were respectively prepared by previous paper.^{6,7,10}

General procedure for the preparation of 3',4'-dialkoxy-2'-allylbenzyloxy-2-allyl-3,4-dialkoxybenzenes (7a-g)

A mixture of dialkoxy-2-allylphenols (**5a-c**) (7 mmol), dialkoxy-2-allylbenzyl alcohols (**6a-c**) (7 mmol), and triphenylphosphine (2.2 g, 8.4 mmol) in THF (20 mL) was cooled to 0 °C and stirred for few min. The resulting clear solution was continually stirred at ice bath and added to diisopropyl azodicarboxylate (1.67 mL, 8.4 mmol) in drops. Then, the resulting solution was allowed to warm to rt and was stirred continually for 12 h. Subsequently, the reaction mixture was concentrated *in vacuo* to remove THF. The giving residue was subjected to silica gel column chromatography (EtOAc: *n*-hexane = 1: 20) to afford 3',4'-dialkoxy-2'-allylbenzyloxy-2-allyl-3,4-dialkoxybenzenes (**7a-g**), respectively.

1-(2'-Allyl-3'-ethoxy-4'-methoxy)benzyloxy-2-allyl-3,4-dimethoxybenzene (7a)

7a (1.48 g, 53%) was obtained as light reddish color crystals, mp 59 °C (EtOAc + *n*-hexane), R_f = 0.48 (EtOAc: *n*-hexane = 1: 5), ¹H-NMR (CDCl₃, 400 MHz) δ 1.38 (t, J = 6.8 Hz, 3H, OCH₂CH₃), 3.45 (dt, J = 6.4, 1.6 Hz, 2H, ArCH₂CH=CH₂), 3.53 (dt, J = 6.0, 1.6 Hz, 2H, ArCH₂CH=CH), 3.82 (s, 6H, OCH₃), 3.85 (s, 3H, OCH₃), 4.02 (q, J = 6.8 Hz, 2H, OCH₂CH₃), 4.90 (s, 2H, ArOCH₂Ar), 4.94 (m, 4H, ArCH₂CH=CH₂), 5.96 (m, 2H, ArCH₂CH=CH₂), 6.61 (d, J = 8.8 Hz, 1H, ArH), 6.72 (d, J = 8.8 Hz, 1H, ArH), 6.80 (d, J = 8.4 Hz, 1H, ArH), 7.14 (d, J = 8.4 Hz, 1H, ArH); ¹³C-NMR (CDCl₃, 100 MHz) δ 15.73, 28.37, 30.32, 55.64, 56.19, 60.89, 68.60, 68.87, 107.02, 110.02, 110.20, 114.59, 114.98, 123.61, 124.15, 128.71, 132.00, 136.82, 137.19, 146.51, 147.38, 148.09, 151.41, 152.59; EI-MS (70eV) m/z (rel. intensity, %): 398 (M⁺, 2), 206 (14), 205 (100), 177 (39), 176 (6), 147 (11), 146 (11), 145 (41), 117 (24), 115 (9); HRMS (EI, m/z): Calcd for C₂₄H₃₀O₅: 398.2088. Found: 398.2090; Anal. Calcd for C₂₄H₃₀O₅: C, 72.34; H, 7.59. Found: C, 72.19; H, 7.68.

1-(2'-Allyl-3'-isopropoxy-4'-methoxy)benzyloxy-2-allyl-3,4-dimethoxybenzene (7b)

7b (1.59 g, 55%) was obtained as light yellow color crystals, mp 47 °C (EtOAc + *n*-hexane), R_f = 0.47 (EtOAc: *n*-hexane = 1: 5), ¹H-NMR (CDCl₃, 400 MHz) δ 1.28 (t, J = 6.4 Hz, 6H, OCH(CH₃)₂), 3.45 (dt, J = 6.0, 1.6 Hz, 2H, ArCH₂CH=CH), 3.55 (dt, J = 6.0, 1.6 Hz, 2H, ArCH₂CH=CH), 3.81 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 4.52 (sept., J = 6.4 Hz, 1H, OCH(CH₃)₂), 4.91 (s, 2H, ArOCH₂Ar), 4.94 (m, 4H, ArCH₂CH=CH₂), 5.94 (m, 2H, ArCH₂CH=CH₂), 6.60 (d, J = 8.8 Hz, 1H, ArH), 6.72 (d, J = 8.8 Hz, 1H, ArH), 6.79 (d, J = 8.4 Hz, 1H, ArH), 7.13 (d, J = 8.4 Hz, 1H, ArH); ¹³C-NMR (CDCl₃, 100 MHz) δ 22.57, 28.31, 30.51, 55.47, 56.08, 60.80, 68.55, 74.52, 106.89, 109.84, 110.08, 114.52, 114.98, 123.46, 123.63, 128.77, 132.11, 136.54, 137.10, 144.90, 147.24, 147.96, 151.34, 152.46; EI-MS (70eV) m/z (rel. intensity, %): 412 (M⁺, 2), 220 (5), 219 (38), 178 (15), 177 (100), 17 (5),

146 (11), 145 (49), 117 (33), 115 (10); HRMS (EI, m/z): Calcd for $C_{25}H_{32}O_5$: 412.2250. Found: 412.2244; Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.65; H, 7.91.

1-(2'-Allyl-3', 4'-dimethoxy)benzyloxy-2-allyl-3-ethoxy-4-methoxybenzene (7c)

7c (1.59 g, 57%) was obtained as light reddish color crystals, mp 39 °C (EtOAc + *n*-hexane), R_f = 0.45 (EtOAc: *n*-hexane = 1: 5), 1H -NMR ($CDCl_3$, 400 MHz) δ 1.38 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 3.45 (dt, J = 6.4, 1.6 Hz, 2H, $ArCH_2CH=CH$), 3.52 (dt, J = 6.0, 1.6 Hz, 2H, $ArCH_2CH=CH$), 3.80 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.02 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.91 (s, 2H, $ArOCH_2Ar$), 4.95 (m, 4H, $ArCH_2CH=CH_2$), 5.96 (m, 2H, $ArCH_2CH=CH_2$), 6.60 (d, J = 8.8 Hz, 1H, ArH), 6.71 (d, J = 8.8 Hz, 1H, ArH), 6.82 (d, J = 8.4 Hz, 1H, ArH), 7.16 (d, J = 8.4 Hz, 1H, ArH); ^{13}C -NMR ($CDCl_3$, 100 MHz) δ 15.68, 28.54, 30.10, 55.59, 56.19, 60.83, 68.47, 68.85, 106.77, 110.06, 110.12, 114.41, 115.03, 123.68, 124.34, 128.74, 131.85, 136.76, 137.18, 147.25, 147.48, 151.40, 152.44; EI-MS (70eV) m/z (rel. intensity, %): 398 (M^+ , 8), 192 (14), 191 (100), 176 (7), 161 (11), 160 (37), 159 (7), 145 (5), 121 (4), 91 (4); HRMS (EI, m/z): Calcd for $C_{24}H_{30}O_5$: 398.2088. Found: 398.2091; Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.13; H, 7.62.

1-(2'-Allyl-3'-ethoxy-4'-methoxy)benzyloxy-2-allyl-3-ethoxy-4-methoxybenzene (7d)

7d (1.48 g, 53%) was obtained as colorless crystals, mp 59 °C (EtOAc + *n*-hexane), R_f = 0.48 (EtOAc: *n*-hexane = 1: 5), 1H -NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.38 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 3.46 (d, J = 6.4 Hz, 2H, $ArCH_2CH=CH$), 3.53 (dt, J = 6.0, 1.6 Hz, 2H, $ArCH_2CH=CH$), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.02 (q, J = 7.2 Hz, 4H, OCH_2CH_3), 4.90 (s, 2H, $ArOCH_2Ar$), 4.94 (m, 4H, $ArCH_2CH=CH_2$), 5.96 (m, 2H, $ArCH_2CH=CH_2$), 6.60 (d, J = 8.8 Hz, 1H, ArH), 6.71 (d, J = 8.8 Hz, 1H, ArH), 6.80 (d, J = 8.4 Hz, 1H, ArH), 7.14 (d, J = 8.4 Hz, 1H, ArH); ^{13}C -NMR ($CDCl_3$, 100 MHz) δ 15.61, 28.49, 30.21, 55.49, 56.08, 68.45, 68.74, 68.75, 106.68, 109.89, 110.02, 114.35, 114.85, 123.57, 124.07, 128.62, 131.87, 136.72, 137.10, 146.37, 147.17, 147.38, 151.34, 152.46; EI-MS (70eV) m/z (rel. intensity, %): 412 (M^+ , 8), 206 (15), 205 (100), 178 (13), 177 (50), 147 (14), 146 (15), 145 (33), 144 (10), 117 (29), 115 (12); HRMS (EI, m/z): Calcd for $C_{25}H_{32}O_5$: 412.2244. Found: 412.2247; Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.48; H, 7.90.

1-(2'-Allyl-3'-isopropoxy-4'-methoxy)benzyloxy-2-allyl-3-ethoxy-4-methoxybenzene(7e)

7e (1.49 g, 50%) was obtained as colorless crystals, mp 44 °C (EtOAc + *n*-hexane), R_f = 0.51 (EtOAc: *n*-hexane = 1: 5), 1H -NMR ($CDCl_3$, 400 MHz) δ 1.28 (d, J = 6.4 Hz, 6H, $OCH(CH_3)_2$), 1.38 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 3.45 (d, J = 6.0 Hz, 2H, $ArCH_2CH=CH$), 3.55 (dt, J = 5.6, 1.6 Hz, 2H, $ArCH_2CH=CH$), 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.02 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.52 (sept., J = 6.4 Hz, 1H, $OCH(CH_3)_2$), 4.91 (s, 2H, $ArOCH_2Ar$), 4.94 (m, 4H, $ArCH_2CH=CH_2$), 5.94 (m, 2H, $ArCH_2CH=CH_2$),

6.59 (d, $J = 8.8$ Hz, 1H, ArH), 6.71 (d, $J = 8.8$ Hz, 1H, ArH), 6.79 (d, $J = 8.4$ Hz, 1H, ArH), 7.13 (d, $J = 8.4$ Hz, 1H, ArH); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 15.67, 22.59, 28.56, 30.53, 55.50, 56.16, 68.54, 68.83, 74.55, 106.71, 109.86, 110.07, 114.41, 114.99, 123.64, 128.85, 132.16, 136.57, 137.16, 144.92, 147.20, 147.41, 151.43, 152.47; EI-MS (70eV) m/z (rel. intensity, %): 426 (M^+ , 3), 220 (5), 219 (36), 178 (13), 177 (100), 147 (6), 146 (11), 145 (45), 117 (31), 115 (9); HRMS (EI, m/z): Calcd for $\text{C}_{26}\text{H}_{34}\text{O}_5$: 426.2401. Found: 426.2403; Anal. Calcd for $\text{C}_{26}\text{H}_{34}\text{O}_5$: C, 73.21; H, 8.03. Found: C, 73.18; H, 8.07.

1-(2'-Allyl-3'-ethoxy-4'-methoxy)benzyloxy-2-allyl-3-isopropoxy-4-methoxybenzene (7f)

7f (1.61 g, 54%) was obtained as light pink crystals, mp 35 °C (EtOAc + *n*-hexane), $R_f = 0.49$ (EtOAc: *n*-hexane = 1: 5), ^1H -NMR (CDCl_3 , 400 MHz) δ 1.27 (d, $J = 6.4$ Hz, 6H, $\text{OCH}(\text{CH}_3)_2$), 1.38 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 3.45 (d, $J = 6.0$ Hz, 2H, $\text{ArCH}_2\text{CH}=\text{CH}_2$), 3.53 (dt, $J = 6.0, 1.6$ Hz, 2H, $\text{CH}_2=\text{CHCH}_2\text{Ar}$), 3.70 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.01 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 4.53 (sept, $J = 6.4$ Hz, 1H, OCHMe_2), 4.91 (s, 2H, ArOCH_2Ar), 4.94 (m, 4H, 2 x $\text{CH}_2\text{CH}=\text{CH}_2$), 5.95 (m, 2H, 2 x $\text{CH}_2\text{CH}=\text{CH}_2$), 6.58 (d, $J = 8.8$ Hz, 1H, ArH), 6.70 (d, $J = 8.8$ Hz, 1H, ArH), 6.80 (d, $J = 8.4$ Hz, 1H, ArH), 7.15 (d, $J = 8.4$ Hz, 1H, ArH); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 14.13, 15.65, 22.59, 28.88, 30.25, 55.54, 56.09, 68.39, 68.78, 74.57, 106.29, 109.92, 110.00, 114.46, 114.88, 123.90, 124.06, 128.73, 131.86, 136.76, 136.90, 145.78, 146.38, 147.45, 151.55, 152.46; EI-MS (70eV) m/z (rel. intensity, %): 426 (M^+ , 4), 206 (14), 205 (100), 178 (7), 177 (44), 176 (7), 147 (12), 146 (10), 145 (46), 117 (25), 115 (9), 91 (7); HRMS (EI, m/z): Calcd for $\text{C}_{26}\text{H}_{34}\text{O}_5$: 426.2401. Found: 426.2403; Anal. Calcd for $\text{C}_{26}\text{H}_{34}\text{O}_5$: C, 73.21; H, 8.03. Found: C, 72.89; H, 7.99.

1-(2'-Allyl-3'-isopropoxy-4'-methoxy)benzyloxy-2-allyl-3-isopropoxy-4-methoxybenzene (7g)

7g (1.79 g, 58%) was obtained as light pink crystals, mp 54 °C (EtOAc + *n*-hexane), $R_f = 0.67$ (EtOAc: *n*-hexane = 1: 5), ^1H -NMR (CDCl_3 , 400 MHz) δ 1.27 (d, $J = 6.4$ Hz, 6H, $\text{OCH}(\text{CH}_3)_2$), 1.28 (d, $J = 6.4$ Hz, 6H, $\text{OCH}(\text{CH}_3)_2$), 3.45 (dt, $J = 6.0, 1.6$ Hz, 2H, $\text{ArCH}_2\text{CH}=\text{CH}_2$), 3.55 (dt, $J = 6.0, 1.6$ Hz, 2H, $\text{CH}_2=\text{CHCH}_2\text{Ar}$), 3.78 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.52 (sept, $J = 6.0$ Hz, 1H, OCHMe_2), 4.91 (s, 2H, ArOCH_2Ar), 4.94 (m, 4H, 2 x $\text{ArCH}_2\text{CH}=\text{CH}_2$), 5.93 (m, 2H, 2 x $\text{ArCH}_2\text{CH}=\text{CH}_2$), 6.57 (d, $J = 8.8$ Hz, 1H, ArH), 6.70 (d, $J = 8.8$ Hz, 1H, ArH), 6.79 (d, $J = 8.4$ Hz, 1H, ArH), 7.14 (d, $J = 8.4$ Hz, 1H, ArH); ^{13}C -NMR (CDCl_3 , 100 MHz) δ 22.59, 22.62, 28.93, 30.54, 55.50, 56.12, 68.46, 74.54, 74.62, 106.28, 109.85, 110.00, 114.48, 114.98, 123.63, 123.89, 128.91, 132.10, 136.57, 136.93, 144.88, 145.77, 147.44, 151.60, 152.44; EI-MS (70eV) m/z (rel. intensity, %): 440 (M^+ , 2), 219 (33), 178 (12), 177 (100), 146 (12), 145 (40), 117 (25), 115 (8); HRMS (EI, m/z): Calcd for $\text{C}_{27}\text{H}_{36}\text{O}_5$: 440.2557. Found: 440.2560; Anal. Calcd for $\text{C}_{27}\text{H}_{36}\text{O}_5$: C, 73.61; H, 8.24; Found: C, 73.79; H, 8.22.

General procedure for the preparation of 4-alkoxy-5,14-dihydro-8H-13-oxadibenzo[*a,f*]cyclode-

cene (8a-g)

Substituted 2'-allylbenzyloxy-2-allylbenzenes (**7a-g**) (2 mmol) dissolved in CH₂Cl₂ (40 mL) was added 1st generation Grubbs' catalyst (80 mg, 0.1 mmol), respectively. The resulting mixture was stirred at rt for 1.5 days. Then, the mixture was concentrated under reduced pressure to remove solvent. The resulting residue was distilled from micro-distilled apparatus (Eyela Co.) under high vacuum (~0.5 mmHg). The distillate was subjected to silica gel column chromatography (EtOAc: *n*-hexane = 1: 25) to give pure 4-alkoxy-5,14-dihydro-8*H*-13-oxadibenzo[*a,f*]cyclodecene (**8a-g**), respectively.

4-Ethoxy-3,9,10-trimethoxy-5,14-dihydro-8*H*-13-oxadibenzo[*a,f*]cyclodecene (8a)

8a (0.36 g, 48%) was obtained as colorless crystals, mp 128 °C (EtOAc + *n*-hexane), *R*_f = 0.32 (EtOAc: *n*-hexane = 1: 5), ¹H-NMR (CDCl₃, 400 MHz) δ 1.41 (t, *J* = 7.0 Hz, 3H, OCH₂CH₃), 3.63 (d, *J* = 8.0 Hz, 2H, H-8), 3.83 (s, 3H, 1 x OCH₃), 3.84 (s, 6H, 2 x OCH₃), 4.00 (q, *J* = 7.0 Hz, 2H, OCH₂CH₃), 4.01 (d, *J* = 7.2 Hz, 2H, H-5), 4.94 (s, 2H, H-14), 5.49 (dt, 1H, *J* = 10.4, 8.0 Hz, H-6), 5.58 (dt, 1H, *J* = 10.4, 8.0 Hz, H-7), 6.71 (d, *J* = 8.4 Hz, 1H, H-2), 6.73 (d, *J* = 8.6 Hz, 1H, H-11), 6.86 (d, *J* = 8.6 Hz, 1H, H-12), 6.92 (d, *J* = 8.6 Hz, 1H, H-1); ¹³C-NMR (CDCl₃, 100 MHz) δ 15.60 (OCH₂CH₃), 22.21 (C-8), 24.94 (C-5), 55.59 (OCH₃), 55.92 (OCH₃), 61.17 (OCH₃), 68.98 (OCH₂CH₃), 75.73 (C-14), 108.93 (C-2), 109.98 (C-11), 115.55 (C-12), 125.23 (C-1), 126.56 (C-6), 127.36 (C-7), 128.40, 128.56, 133.34, 146.83, 147.00, 149.06, 152.28, 153.27; EI-MS (70eV) *m/z* (rel. intensity, %): 370 (M⁺, 5), 204 (33), 203 (100), 202 (18), 191 (14), 190 (11), 175 (34), 143 (25), 115 (12); HRMS (EI, *m/z*): Calcd for C₂₂H₂₆O₅: 370.1775. Found: 370.1777; Anal. Calcd for C₂₂H₂₆O₅: C, 71.33; H, 7.07. Found: C, 71.25; H, 7.03.

4-Isopropoxy-3,9,10-trimethoxy-5,14-dihydro-8*H*-13-oxadibenzo[*a,f*]cyclodecene (8b)

8b (0.32 g, 42%) was obtained as colorless crystals, mp 113 °C (EtOAc + *n*-hexane), *R*_f = 0.35 (EtOAc: *n*-hexane = 1: 5), ¹H-NMR (CDCl₃, 400 MHz) δ 1.31 (d, *J* = 6.0 Hz, 6H, OCH(CH₃)₂), 3.63 (d, *J* = 8.4 Hz, 2H, H-8), 3.83 (s, 3H, OCH₃), 3.84 (s, 6H, 2 x OCH₃), 3.99 (d, *J* = 8.0 Hz, 2H, H-8), 4.05 (d, *J* = 8.0 Hz, 2H, H-5), 4.42 (sept, *J* = 6.0 Hz, 1H, OCH(CH₃)₂), 4.92 (s, 2H, H-14), 5.46 (dt, *J* = 10.8, 8.0 Hz, 1H, H-6), 5.57 (d, *J* = 10.8, 8.4 Hz, 1H, H-7), 6.70 (d, *J* = 8.0 Hz, 1H, H-2), 6.74 (d, *J* = 8.8 Hz, 1H, H-11), 6.88 (d, *J* = 8.8 Hz, 1H, H-12), 6.91 (d, *J* = 8.0 Hz, 1H, H-1); ¹³C-NMR (CDCl₃, 100 MHz) δ 22.31 (OCH(CH₃)₂), 22.49 (C-8), 25.32 (C-5), 55.59 (OCH₃), 55.97 (OCH₃), 61.24 (OCH₃), 74.98 (OCH(CH₃)₂), 76.27 (C-14), 108.93 (C-2), 110.05 (C-11), 115.96 (C-12), 124.91 (C-1), 126.47 (C-6), 127.37 (C-7), 128.67, 128.72, 133.61, 145.55, 147.01, 149.19, 152.61, 153.41; EI-MS (70eV) *m/z* (rel. intensity, %): 384 (M⁺, 1), 342 (12), 218 (11), 217 (42), 191 (12), 176 (39), 175 (100), 174 (16), 152 (11), 144 (11), 143 (26), 115 (11); HRMS (EI, *m/z*): Calcd for C₂₃H₂₈O₅: 384.1931. Found: 384.1933; Anal. Calcd for C₂₃H₂₈O₅: C, 71.85; H, 7.34. Found: C, 71.55; H, 7.52.

9-Ethoxy-3,4,10-trimethoxy-5,14-dihydro-8H-13-oxadibenzo[*a,f*]cyclodecene (8c)

8c (0.37 g, 50%) was obtained as colorless crystals, mp 143 °C (EtOAc + *n*-hexane), R_f = 0.30 (EtOAc: *n*-hexane = 1: 5), $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 1.41 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 3.64 (d, J = 8.0 Hz, 2H, H-8), 3.81 (s, 6H, 2 x OCH_3), 3.86 (s, 3H, OCH_3), 3.99 (d, J = 8.0 Hz, 2H, H-5), 4.03 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.94 (s, 2H, H-14), 5.49 (dt, J = 10.8, 7.8 Hz, 1H, H-6), 5.59 (dt, J = 10.4, 8.2 Hz, 1H, H-7), 6.72 (d, J = 8.8 Hz, 2H, H-2 and H-11), 6.84 (d, J = 8.8 Hz, 1H, H-12), 6.94 (d, J = 8.0 Hz, 1H, H-1); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 15.67 (OCH_2CH_3), 22.44 (C-8), 24.77 (C-5), 55.62 (OCH_3), 56.01 (OCH_3), 60.86 (OCH_3), 69.24 (OCH_2CH_3), 75.52 (C-14), 109.06 (C-2), 110.08 (C-11), 115.19 (C-12), 125.41 (C-1), 126.48 (C-6), 127.52 (C-7), 128.53, 128.75, 133.30, 146.24, 147.79, 149.20, 152.25, 153.17; EI-MS (70eV) m/z (rel. intensity, %) 370 (M^+ , 15), 205 (9), 190 (29), 189 (100), 188 (14), 174 (17), 159 (9.0); HRMS (EI, m/z): Calcd for $\text{C}_{22}\text{H}_{26}\text{O}_5$: 370.1775. Found: 370.1777; Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{O}_5$: C, 71.33; H, 7.07. Found: C, 71.59; H, 7.11.

4,9-Diethoxy-3,10dimethoxy-5,14-dihydro-8H-13-oxadibenzo[*a,f*]cyclodecene (8d)

8d (0.31 g, 41%) was obtained as colorless crystals, mp 114 °C (EtOAc + *n*-hexane), R_f = 0.36 (EtOAc: *n*-hexane = 1: 5), $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 1.41 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 3.64 (d, J = 8.0 Hz, 2H, H-8), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.00 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.01 (d, J = 8.8 Hz, 2H, H-5), 4.03 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.93 (s, 2H, H-14), 5.48 (dt, J = 10.0, 7.8 Hz, 1H, H-6), 5.57 (dt, J = 10.8, 7.8 Hz, 1H, H-7), 6.71 (d, J = 8.4 Hz, 1H, H-2), 6.72 (d, J = 8.8 Hz, 1H, H-11), 6.85 (d, J = 8.8 Hz, 1H, H-12), 6.93 (d, J = 8.4 Hz, 1H, H-1); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 15.63 (OCH_2CH_3), 15.68 (OCH_2CH_3), 22.49 (C-8), 24.95 (C-5), 55.64 (OCH_3), 56.02 (OCH_3), 69.04 (OCH_2CH_3), 69.29 (OCH_2CH_3), 75.82 (C-14), 108.98 (C-2), 110.05 (C-11), 115.45 (C-12), 125.23 (C-1), 126.51 (C-6), 127.45 (C-7), 128.65, 128.71, 133.39, 146.21, 146.86, 149.23, 152.43, 153.30; EI-MS (70eV) m/z (rel. intensity, %) 384 (M^+ , 22), 207 (12), 205 (14), 204 (32), 203 (100), 202 (21), 190 (9), 176 (11), 175 (23), 143 (18), 115 (8); HRMS (EI, m/z): Calcd for $\text{C}_{23}\text{H}_{28}\text{O}_5$: 384.1931. Found: 384.1934; Anal. Calcd for $\text{C}_{23}\text{H}_{28}\text{O}_5$: C, 71.85; H, 7.34. Found: C, 71.87; H, 7.34.

9-Ethoxy-4-isopropyl-3,10-dimethoxy-5,14-dihydro-8H-13-oxadibenzo[*a,f*]cyclodecene (8e)

8e (0.37 g, 47%) was obtained as colorless crystals, mp 132 °C (EtOAc + *n*-hexane), R_f = 0.39 (EtOAc: *n*-hexane = 1: 5), $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 1.31 (d, J = 6.0 Hz, 6H, $\text{OCH}(\text{CH}_3)_2$), 1.41 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 3.64 (d, J = 8.4 Hz, 2H, H-8), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.03 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.05 (d, J = 8.4 Hz, 2H, H-5), 4.42 (setp, J = 6.0 Hz, 1H, $\text{OCH}(\text{CH}_3)_2$), 4.91 (s, 2H, H-14), 5.44 (dt, J = 10.4, 7.6 Hz, 1H, H-6), 5.56 (dt, J = 10.4, 8.0 Hz, 1H, H-7), 6.70 (d, J = 8.4 Hz, 1H, H-2), 6.73 (d, J = 8.8 Hz, 1H, H-11), 6.86 (d, J = 8.8 Hz, 1H, H-12), 6.91 (d, J = 8.4 Hz, 1H, H-1); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ 15.63 (OCH_2CH_3), 22.45 $\text{OCH}(\text{CH}_3)_2$, 22.50 (C-8), 25.26 (C-5), 55.55

(OCH₃), 55.99 (OCH₃), 69.29 (OCH₂CH₃), 74.96 (OCH(CH₃)₂), 76.24 (C-14), 108.91 (C-2), 110.06 (C-11), 115.73 (C-12), 124.83 (C-1), 126.35 (C-6), 127.39 (C-7), 128.74, 128.88, 133.58, 145.52, 146.15, 149.28, 152.66, 153.36; EI-MS (70eV) *m/z* (rel. intensity, %): 398 (M⁺, 16), 356 (11), 218 (12), 217 (48), 205 (11), 177 (11), 176 (35), 175 (100), 174 (17), 153 (11), 143 (25); HRMS (EI, *m/z*): Calcd for C₂₄H₃₀O₅: 398.2088. Found: 398.2090; Anal. Calcd for C₂₄H₃₀O₅: C, 72.34; H, 7.59. Found: C, 72.10; H, 7.76.

4-Ethoxy-9-isopropyl-3,10-dimethoxy-5,14-dihydro-8H-13-oxadibenzo[*a,f*]cyclodecene (8f)

8f (0.39 g, 49%) was obtained as colorless crystals, mp 124 °C (EtOAc + *n*-hexane), R_f = 0.39 (EtOAc: *n*-hexane = 1: 5), ¹H-NMR (CDCl₃, 400 MHz) δ 1.32 (d, *J* = 6.4 Hz, 6H, OCH(CH₃)₂), 1.41 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 3.66 (d, *J* = 8.4 Hz, 2H, H-8), 3.81 (s, 3H, OCH₃), 3.84 (s, 3H, OCH₃), 3.99 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 4.02 (d, *J* = 7.2 Hz, 2H, H-5), 4.67 (setp, *J* = 6.4 Hz, 1H, OCH(CH₃)₂), 4.92 (s, 2H, H-14), 5.45 (dt, *J* = 10.4, 7.6 Hz, 1H, H-6), 5.58 (dt, *J* = 10.4, 8.2 Hz, 1H, H-7), 6.71 (d, *J* = 8.0 Hz, 1H, H-2), 6.72 (d, *J* = 8.8 Hz, 1H, H-11), 6.84 (d, *J* = 8.8 Hz, 1H, H-12), 6.93 (d, *J* = 8.0 Hz, 1H, H-1); ¹³C-NMR (CDCl₃, 100 MHz) δ 15.66 (OCH₂CH₃), 22.65 (OCH₂(CH₃)₂), 22.90 (C-8), 24.95 (C-5), 55.70 (OCH₃), 56.04 (OCH₃), 69.12 (OCH₂CH₃), 75.02 (OCH(CH₃)₂), 75.96 (C-14), 109.04 (C-2), 110.15 (C-11), 115.34 (C-12), 125.19 (C-1), 126.48 (C-6), 127.44 (C-7), 128.93, 129.14, 133.42, 145.02, 146.87, 149.41, 152.73, 153.32; EI-MS (70eV) *m/z* (rel. intensity, %): 398 (M⁺, 15), 356 (13), 217 (10), 204 (30), 203 (100), 202 (19), 190 (13), 177 (14), 176 (16), 175 (41), 153 (13), 143 (24); HRMS (EI, *m/z*): Calcd for C₂₄H₃₀O₅: 398.2088. Found: 398.2090; Anal. Calcd for C₂₄H₃₀O₅: C, 72.34; H, 7.59. Found: C, 72.31; H, 7.54.

4,9-Diisopropyl-3,10-dimethoxy-5,14-dihydro-8H-13-oxadibenzo[*a,f*]cyclodecene (8g)

8g (0.37 g, 45%) was obtained as colorless crystals, mp 86 °C (EtOAc + *n*-hexane), R_f = 0.48 (EtOAc: *n*-hexane = 1: 5), ¹H-NMR (CDCl₃, 400 MHz) δ 1.31 (d, *J* = 6.4 Hz, 6H, OCH(CH₃)₂), 1.32 (d, *J* = 6.4 Hz, 6H, OCH(CH₃)₂), 3.65 (d, *J* = 8.4 Hz, 2H, H-8), 3.81 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 4.05 (d, *J* = 8.0 Hz, 2H, H-5), 4.41 (setp, *J* = 6.4 Hz, 1H, OCH(CH₃)₂), 4.46 (setp, *J* = 6.4 Hz, 1H, OCH(CH₃)₂), 4.91 (s, 2H, H-14), 5.42 (dt, *J* = 10.8, 7.8 Hz, 1H, H-6), 5.56 (dt, *J* = 10.4, 8.0 Hz, 1H, H-7), 6.70 (d, *J* = 8.4 Hz, 1H, H-2), 6.72 (d, *J* = 8.8 Hz, 1H, H-11), 6.85 (d, *J* = 8.8 Hz, 1H, H-12), 6.91 (d, *J* = 8.4 Hz, 1H, H-1); ¹³C-NMR (CDCl₃, 100 MHz) δ 22.46 (OCH(CH₃)₂), 22.58 (OCH(CH₃)₂), 22.86 (C-8), 25.26 (C-5), 55.58 (OCH₃), 55.97 (OCH₃), 75.00 (2 x OCH(CH₃)₂), 76.31 (C-14), 108.91 (C-2), 110.07 (C-11), 115.55 (C-12), 124.76 (C-1), 126.29 (C-6), 127.38 (C-7), 128.88, 129.36, 133.58, 144.90, 145.48, 149.40, 152.86, 153.36; EI-MS (70eV) *m/z* (rel. intensity, %): 412 (M⁺, 21), 307 (14), 328 (21), 219 (11), 218 (14), 217 (68), 216 (14), 178 (12), 177 (29), 176 (71), 175 (100), 163 (12), 144 (13), 143 (34), 115 (11); HRMS (EI, *m/z*): Calcd for C₂₅H₃₂O₅: 412.2244. Found: 412.2248; Anal. Calcd for C₂₅H₃₂O₅: C, 72.79; H, 7.82.

Found: C, 72.85; H, 7.93.

ACKNOWLEDGEMENTS

We are grateful to NSC, Taiwan for financial support (NSC 93-2113-M-037-009). We are also thankful to Professor Hiroki Takahata, Tohoku Pharmaceutical University, Japan for encouragement and to Mr. Wen-Hsiung Lu, and Mrs. Chi-Jia Wang for taking NMR spectra, to Miss Chia-Jen Tsai for measuring elemental analysis and to Mr. Min-Yuan Hung for running GC-EI/MS.

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