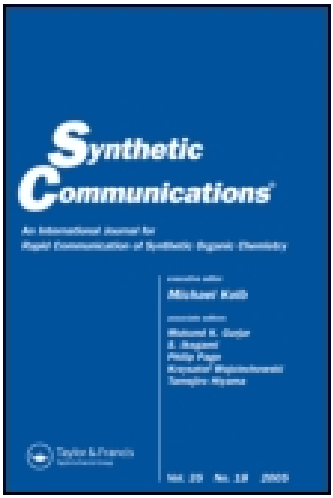

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Diels-Alder Reactions of Furo [3,4-b] 1,4-benzodioxins: An Efficient Approach to Substituted Dibenzo [b,e][1,4] Dioxins

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DIELS-ALDER REACTIONS OF FURO [3,4-*b*] 1,4-BENZODIOXINS : AN EFFICIENT APPROACH TO SUBSTITUTED DIBENZO [*b,e*][1,4] DIOXINS

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Abstract: In view of their potential biological properties, different substituted dibenzo [*b,e*][1,4] dioxins have been synthesized using Diels-Alder reactions. This required the preparation of furobenzodioxins and further dehydration of the bicyclo-adducts of the cycloaddition.

The dibenzo [*b,e*][1,4] dioxins and benzo [*b*] naphto [2,3-*e*][1,4] dioxins have attracted increasing interest over the past few years, because of their biological (antitumoral activity[1], ecotoxicity[2]) and electrochemical[3] properties. Several syntheses of these linear oxygenated heterocyclic systems have recently been described[1c,2,4]. However, very few of these allowed access to multi-substituted derivatives with good regioselectivity.

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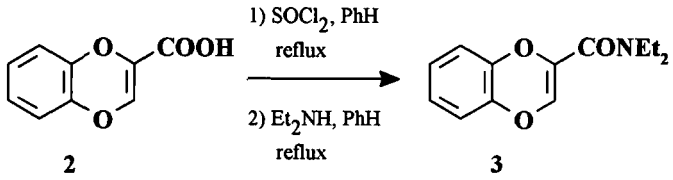
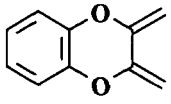


2 3

Scheme 1

As part of a continuing study on the chemistry of 1,4-benzodioxin[5], our aim was to design a new approach to substituted dibenzodioxins of biological interest.

We have already described the synthesis of such tri and tetracyclic systems, using a Diels-Alder reaction involving 2,3-dihydro-2,3-dimethylene-1,4-benzodioxins **1**[6].

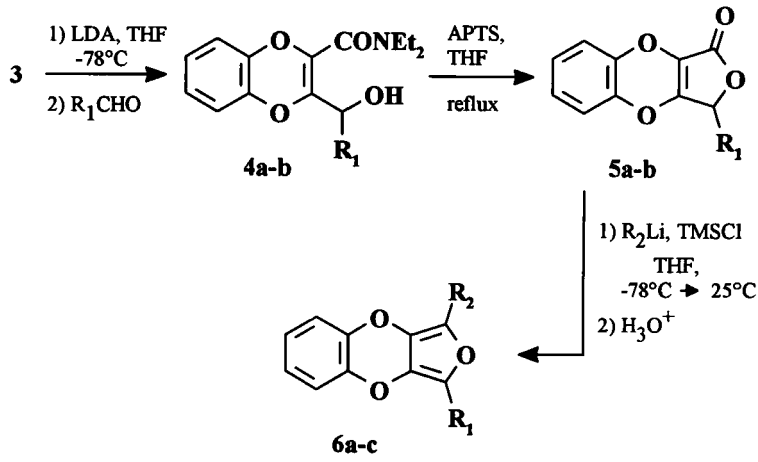


1

Unfortunately this method proved unsuccessful when used for the preparation of substituted dienic systems. We decided then to prepare new furobenzodioxins which could act as diene in cycloaddition reactions. This was achieved starting from 2-carboxy-1,4-benzodioxin **2**.

Acid **2** was obtained in 4 steps from catechol as described by Coudert et al.[7]. Compound **2** was treated by thionyl chloride, and subsequent treatment of the acid chloride by diethylamine gave the corresponding amide **3** in quantitative yield (scheme 1).

The amide was then lithiated (LDA, 2 eq, -78°C, 3h30) and the 3-lithioderivative was condensed on several aldehydes providing hydroxyamides

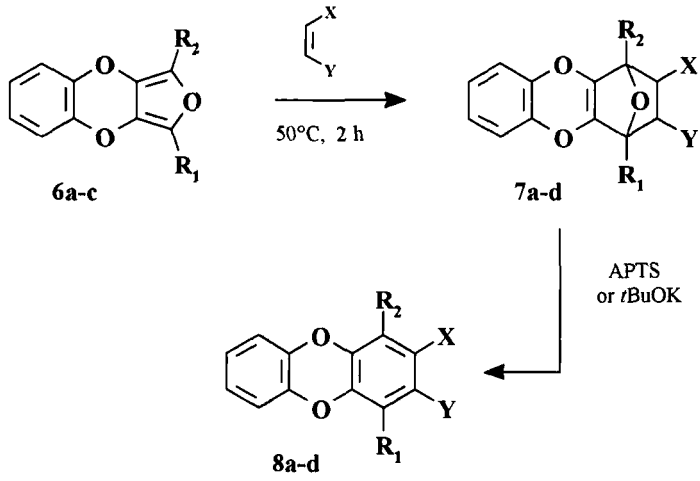


Scheme 2

Table 1 : Synthesis of furobenzodioxinic dienes

R_1	R_2	**4** : Yield (%)	**5** : Yield (%)	**6** : Yield (%)
CH_3	CH_3	**4a**: 95	**5a**: 90	**6a**: 77
CH_3	C_4H_9	**4a**: 95	**5a**: 90	**6b**: 55
C_4H_9	CH_3	**4b**: 90	**5b**: 60	**6b**: 70
C_4H_9	C_4H_9	**4b**: 90	**5b**: 60	**6c**: 50

4a-b. These were converted into lactones **5a-b** using acidic conditions (APTS cat.)[8]. In the following step, the lactones were submitted to the nucleophilic attack of the appropriate organolithium R_2Li (3 eq, -78°C, 30 mn) in the presence of Me_3SiCl (6 eq) according to Cooke's procedure[9]. After acidic workup, and purification, furobenzodioxins **6a-c** were obtained in good yields (scheme 2, table 1).



Scheme 3

Table 2 : Diels-Alder reactions of furobenzodioxins and dehydration of the adducts

Diene		Dienophile			7 Yield (%)	8 Yield (%)
R_1	R_2	X	Y			
CH_3	CH_3	H	CN	**a**	90	95[b]
CH_3	CH_3	$COOCH_3$	$COOCH_3$	**b**	90	95[b](70[a])
CH_3	C_4H_9	$COOCH_3$	$COOCH_3$	**c**	65	70[a]
C_4H_9	C_4H_9	H	CN	**d**	72	91[b]

a) APTS cat., toluene, reflux, 15 mn.
b) *t*BuOK, THF, RT, 15 mn.

Furobenzodioxins **6a-c** appeared to be very reactive in the course of Diels-Alder reactions (scheme 3). They reacted very easily with several dienophiles to afford cycloaddition adducts **7a-d** in high yields (a mixture of *endo* and *exo* adducts was obtained; these could be separated only in the case of **7a**[10]). These adducts were then submitted to dehydration using either acidic[11] or basic[12] medium, to give very good yields of the desired dibenzo [*b,e*][1,4] dioxins **8a-d**, (table 2).

To sum up, the use of furobenzodioxinic dienes in Diels-Alder reactions proved to be a new and very effective method to prepare regioselectively substituted dibenzo [*b,e*][1,4] dioxins. The transformation of some of these derivatives into compounds with interesting biological properties will be described further.

Experimental section

General procedure for the functionalization of amide 3.

A THF solution of amide **3** (2 g, 8.6 mmol) was slowly added, at -78°C, to a stirred solution of LDA (2 M in THF/heptan, 16 mmol) in THF (10 ml), under Argon atmosphere. After stirring the latter solution for 3.5 hours at that temperature, a THF solution of the appropriate aldehyde (17.2 mmol) was added dropwise. The reaction mixture was then allowed to warm up to room temperature overnight. The reaction mixture was poured into a stirred saturated aqueous NH_4Cl solution, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated, and purified by column chromatography (petroleum ether/ethyl acetate 7/3 (v/v)) to give hydroxy-amides **4**. **4a** : IR (neat) 3400-2980, 1735, 1690, 1260 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.24 (m, 6H, C**H**$_3$-CH_2-N-), 1.40 (d, 3H, *J*=6.6 Hz, **CH**$_3$-CH-OH), 3.44 (m, 4H, CH_3-C**H**$_2$-N-), 4.43 (q, 1H, **CH**-OH, *J*=6.6 Hz, *J*=12.5 Hz), 6.80 (m, 4H, H_5,H_6,H_7,H_8); ^{13}C NMR ($CDCl_3$) δ 12.1/13.8 (CH_3, CH_3-CH_2-N-), 18.3 (CH_3, CH_3-CH-OH), 39.7/43.0 (CH_2, CH_3-CH_2-N-), 63.7 (CH, CH_3-CH-OH), 115.6/116.3 (CH, $C_{5,8}$), 124.3 (CH, $C_{6,7}$), 129.1 (C, C_2), 141.8, 142.3/142.4 (C, $C_{3,4a,8a}$), 163.1 (C, $C_{C=O}$). **4b** : IR

(neat) 3600-3100, 1665 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (m, 3H, CH_2-CH_2-CH_2-**CH_3**), 1.19/1.28 (t, 3H, **CH_3**-CH_2-N-, *J*=7.3 Hz), 1.36 (m, 4H, CH_2-**CH_2**-**CH_2**-CH_3), 1.73 (m, 2H, **CH_2**-CH_2-CH_2-CH_3), 3.43 (m, 4H, CH_3-**CH_2**-N-), 4.21 (m, 1H, **CH**-OH), 6.69/6.77 (m, 2H, H_5,H_8), 6.87 (m, 2H, H_6,H_7).

*General procedure for the formation of lactones **5a-b**.*

APTS (50% weight) was added to a stirred solution of hydroxy-amides **4a—b** (10 mmol) in THF (100 ml), under Argon atmosphere, and the reaction was refluxed overnight. After cooling, the reaction mixture was diluted with ethyl acetate (100 ml), and washed with water (3 x 60 ml). The organic layer was dried over MgSO4, concentrated, and purified by column chromatography (petroleum ether/ethyl acetate 9/1 (v/v)), to give pure lactones **5**. **5a** : mp 130°C ; IR (KBr) 1775, 1730, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (d, 3H, **CH_3**-C_3, *J*=6.6 Hz), 4.95 (q, 1H, **CH**-O, *J*=6.6 Hz, *J*=13.5 Hz), 6.93 (m, 4H, H_5,H_6,H_7,H_8); ^{13}C NMR ($CDCl_3$) δ 17.5 (CH_3, CH_3-C_3), 71.6 (CH, C_3), 117.6/118.1 (CH, $C_{5,8}$), 122.5 (C, C_{9a}), 125.4/125.6 (CH, $C_{6,7}$), 140.7/141.7 (C, $C_{4a,8a}$), 156.2 (C, C_{3a}), 168.2 (C, $C_{C=O}$); **5b** : mp 64°C; IR (KBr) 1770, 1720, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, **CH_3**-CH_2-CH_2-CH_2-, *J*=7 Hz), 1.37 (m, 4H, CH_3-**CH_2**-**CH_2**-CH_2-), 1.68 (m, 2H, CH_3-CH_2-CH_2-**CH_2**-), 4.83 (dd, 1H, H_3, *J*=4.5 Hz, *J*=7.5 Hz), 6.92 (m, 4H, H_5,H_6,H_7,H_8).

*General procedure for the formation of dienes **6a-c**.*

Under Argon atmosphere, a solution of organolithium (1.6 M in THF/ether, 29.3 mmol) was added dropwise to a stirred THF solution of lactones **5a-b** (9.7 mmol) and trimethylsilyl chlorid (7.4 ml, 58.6 mmol), at -78°C. After stirring at that temperature for 30 minutes, the reaction mixture was allowed to warm up to room temperature, and quenched with a 2 M HCl solution (50 ml). The reaction mixture was stirred another 30 minutes at room temperature, and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography (petroleum ether/ethyl acetate 9/1 (v/v)) afforded dienes **6**. **6a** : mp 51°C; IR (KBr) 1690, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.20 (s, 6H, **CH_3**-C-), 6.93 (m, 4H, H_5,H_6,H_7,H_8); ^{13}C NMR ($CDCl_3$) δ 10.7 (CH_3, CH_3-C), 117.9 (CH, $C_{5,8}$), 128.3 (CH, $C_{6,7}$), 128.8/129.3 (C, $C_{1,3,3a,9a}$), 140.9 (C, $C_{4a,8a}$); **6b** : mp 42°C; IR (KBr) 1680, 1260, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H,

CH$_3$-CH$_2$-CH$_2$-CH$_2$-, *J*=7.7 Hz), 1.38 (2H, CH$_3$-**CH$_2$**-CH$_2$-CH$_2$-), 1.62 (qt, 2H, CH$_3$-CH$_2$-**CH$_2$**-CH$_2$-, *J*=7.7 Hz, *J*=15.6 Hz, *J*=22.5 Hz), 2.20 (s, 3H, **CH$_3$**-C), 2.56 (t, 2H, CH$_3$-CH$_2$-CH$_2$-**CH$_2$**-, *J*=7.7 Hz), 6.93 (m, 4H, H$_5$,H$_6$,H$_7$,H$_8$); ^{13}C NMR (CDCl$_3$) δ 10.7 (CH$_3$, **CH$_3$**-C), 13.8 (CH$_3$, C$_{4'}$), 22.3 (CH$_2$, C$_{3'}$), 25.2 (CH$_2$, C$_{2'}$), 29.7 (CH$_2$, C$_{1'}$), 117.3/117.4 (CH, C$_{5,8}$), 128.5/129.0 (C, C$_{1,3}$), 129.2 (CH, C$_{6,7}$), 133.1 (C, C$_{3a,9a}$), 140.9 (C, C$_{4a,8a}$); **6c** : IR (neat) 1690, 1255 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.9 (t, 6H, **CH$_3$**-CH$_2$-CH$_2$-CH$_2$-, *J*=7.9 Hz), 1.39 (m, 4H, CH$_3$-**CH$_2$**-CH$_2$-CH$_2$-), 1.61 (m, 4H, CH$_3$-CH$_2$-**CH$_2$**-CH$_2$-), 2.55 (t, 2H, CH$_3$-CH$_2$-CH$_2$-**CH$_2$**-C$_4$, *J*=7.3 Hz), 2.82 (t, 2H, CH$_3$-CH$_2$-CH$_2$-**CH$_2$**-C$_1$, *J*=7.0 Hz), 6.91 (m, 4H, H$_5$,H$_6$,H$_7$,H$_8$); ^{13}C NMR (CDCl$_3$) δ 13.6 (CH$_3$, C$_{4'}$), 22.5 (CH$_2$, C$_{3'}$), 25.4 (CH$_2$, C$_{2'}$), 29.6 (CH$_2$, C$_{1'}$), 117.5 (CH, C$_{5,8}$), 128.8 (C, C$_{1,3}$), 129.1 (CH, C$_{6,7}$), 132.8 (C, C$_{3a,9a}$), 140.9 (C, C$_{4a,8a}$)

General procedure for the cycloaddition reactions.

A mixture of diene **6a-c** (1 mmol) and dienophile (1.5 mmol) was heated at 60°C in a closed atmosphere during 2 hours (overnight for **7b-c**). After cooling, the crude reaction mixture was dissolved in CH_2Cl_2 and purified by column chromatography (petroleum ether/ethyl acetate 8/2 (v/v)) to give pure Diels Alder adducts **7**. **7a** : mp 144°C; IR (KBr) 2240, 1730, 1220 cm^{-1} broad signal; **7a *exo*** : ^{1}H NMR (CDCl$_3$) δ 1.61 (s, 3H, **CH$_3$**-C$_4$), 1.76 (s, 3H, **CH$_3$**-C$_1$), 2.17 (dd, 1H, H$_{3exo}$, $J_{3exo\text{-}2}$=3.7 Hz, $J_{3endo\text{-}3exo}$=11.7 Hz), 2.40 (dd, 1H, H$_{3endo}$, $J_{3endo\text{-}2}$=8.1 Hz, $J_{3endo\text{-}3exo}$=11.7 Hz), 2.94 (dd, 1H, H$_2$, $J_{3exo\text{-}2}$=3.7 Hz, $J_{3endo\text{-}2}$=8.1 Hz), 6.74 (m, 2H, H$_6$,H$_9$), 6.89 (m, 2H, H$_7$,H$_8$); ^{13}C NMR (CDCl$_3$) δ 14.2 (CH$_3$, **CH$_3$**-C$_1$), 15.8 (CH$_3$, **CH$_3$**-C$_4$), 37.4 (CH, C$_2$), 42.5 (CH$_2$, C$_3$), 83.4 (C, C$_1$), 84.5 (C, C$_4$), 117.5 (CH, C$_{6,9}$), 122.7 (C, C$_{C\equiv N}$), 125.0 (CH, C$_{7,8}$), 135.7 (C, C$_{10a}$), 139.0 (C, C$_{4a}$), 142.5 (C, C$_{5a,9a}$); **7a *endo*** : ^{1}H NMR (CDCl$_3$) δ 1.58 (s, 3H, **CH$_3$**-C$_4$), 1.71 (s, 3H, **CH$_3$**-C$_1$), 2.17 (dd, 1H, H$_{3endo}$, $J_{2\text{-}3endo}$=3.7 Hz, $J_{3endo\text{-}3exo}$=11.7 Hz), 2.31 (dd, 1H, H$_{3exo}$, $J_{2\text{-}3exo}$=8.8 Hz, $J_{3endo\text{-}3exo}$=11.7 Hz), 2.96 (dd, 1H, H$_2$, $J_{2\text{-}3endo}$=3.7 Hz, $J_{2\text{-}3exo}$=8.8 Hz), 6.81 (m, 2H, H$_6$,H$_9$), 6.88 (m, 2H, H$_7$,H$_8$); ^{13}C NMR (CDCl$_3$) δ 15.4 (CH$_3$, **CH$_3$**-C$_1$), 15.9 (CH$_3$, **CH$_3$**-C$_4$), 37.9 (CH, C$_2$), 42.1 (CH$_2$, C$_3$), 83.6 (C, C$_1$), 85.1 (C, C$_4$), 117.4/117.9 (CH, C$_{6,9}$), 119.0 (C, C$_{C\equiv N}$), 124.8/125.2 (CH, C$_{7,8}$), 135.8 (C, C$_{10a}$), 139.1 (C, C$_{4a}$), 142.8 (C, C$_{5a,9a}$); **7b** : mp 92°C; IR (KBr) 1750, 1720, 1230 cm^{-1}broad signal; ^{1}H NMR (CDCl$_3$) δ 1.63 (s, 6H, **CH$_3$**-C), 3.36 (s, 2H, H$_2$,H$_3$), 3.57 (s, 6H, O**CH$_3$**), 6.72/6.82 (m, 4H, H$_6$,H$_7$,H$_8$,H$_9$); ^{13}C

NMR ($CDCl_3$) δ 15.7 (CH_3, CH_3-C_1-**CH_3**-C_4-), 51.8 (CH, $C_{2,3}$), 56.7 (CH_3, -**OCH_3**), 84.3 (C, $C_{1,4}$), 117.1 (CH, $C_{6,9}$), 124.4 (CH, $C_{7,8}$), 137.6 (C, $C_{4a,10a}$), 143.0 (C, $C_{5a,9a}$), 169.8 (C, $C_{C=O}$); **7c** : IR (neat) 1750, 1710, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, **CH_3**-CH_2-CH_2-CH_2-, *J*=7.3 Hz), 1.44 (m, 2H, CH_3-**CH_2**-CH_2-CH_2), 1.75 (m, 2H, CH_3-CH_2-**CH_2**-CH_2), 1.61 (s, 3H, **CH_3**-C_4), 2.08 (m, 2H, CH_3-CH_2-CH_2-**CH_2**), 3.28 (d, 1H, H_3, *J*=9.5 Hz), 3.38 (d, 1H, H_2, *J*=9.5 Hz), 3.52 et 3.53 (s, 6H, **CH_3**-O-), 6.70 (m, 2H, H_6,H_9), 6.80 (m, 2H, H_7,H_8); **7d** : IR (neat) 2220, 1720, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (m, 6H, **CH_3**-CH_2-CH_2-CH_2-), 1.45 (m, 4H, CH_3-**CH_2**-CH_2-CH_2-), 2.86 (m, 4H, CH_3-CH_2-**CH_2**-CH_2-), 2.15 (m, 1H, H_3), 2.31 (m, 1H, $H_{3'}$), 2.91 (m, 1H, H_2), 3.76 (t, 4H, CH_3-CH_2-CH_2-**CH_2**-, *J*=7.3 Hz), 6.82 (m, 4H, H_6,H_7,H_8,H_9).

General procedure for the dehydration reaction of Diels-Alder adducts 7.

Method a : APTS (50% weight) was added to a stirred solution of the adduct **7b** or **7d** (0.5 mmol) in toluene (15 ml), under Argon atmosphere, in the presence of molecular sieves 4Å, and the reaction was refluxed for 10 minutes. After cooling, and filtring, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, concentrated and purified by column chromatography (petroleum ether/ethyl acetate 8/2 (v/v)) to give dibenzodioxins **8b**, **8d**.

Method b : Potassium tertbutylate (1.2 mmol) was added to a stirred solution of the adducts **7a-c** (1 mmol) in THF (10 ml), under Argon atmosphere, and the reaction mixture was stirred at room temperature for 5 minutes. The reaction mixture was poured into water (10 ml), neutralized with aqueous 0.1 M HCl solution, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated and purified by column chromatography (petroleum ether/ethyl acetate 8/2 (v/v)) to afford pure dibenzodioxins **8a-c**. **8a** : mp 144°C; IR (KBr) 2210, 1590, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.22 (s, 3H, **CH_3**-C_4), 2.38 (s, 3H, **CH_3**-C_1), 6.91 (m, 4H, H_6,H_7,H_8,H_9), 7.03 (s, 1H, H_3); ^{13}C NMR δ 13.4 (CH_3, CH_3-C_1), 14.8 (CH_3, CH_3-C_4), 107.3 (C, C_2), 116.3 (CH, $C_{6,9}$), 117.7 (C, $C_{C\equiv N}$), 123.0 (C, C_4), 124.2/124.4 (CH, $C_{7,8}$), 127.0 (C, C_1), 129.0 (CH, C_3), 140.3 (C, C_{10a}), 141.1/141.3 (C, $C_{5a,9a}$), 143.9 (C, C_{4a}); **8b** : mp 150°C; IR (KBr) 1730, 1580, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (s, 6H, **CH_3**-C_1, **CH_3**-C_4), 3.85 (s, 6H, **CH_3**-O-), 6.90 (m, 4H, H_6,H_7,H_8,H_9); ^{13}C NMR ($CDCl_3$) δ 12.1 (CH_3, CH_3-C_1, CH_3-C_4), 52.3 (CH_3, CH_3-O-), 116.2 (CH,

$C_{6,9}$), 122.9 (C, $C_{2,3}$), 124.1 (CH, $C_{7,8}$), 127.8 (C, $C_{1,4}$), 141.3/141.4 (C, $C_{4a,5a,9a,10a}$), 167.8 (C, $C_{C=O}$); **8c** : mp 70°C; IR (KBr) 1700, 1580, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (t, 3H, CH_3-CH_2-CH_2-CH_2-, J=7.7 Hz), 1.41 (m, 2H, CH_3-CH_2-CH_2-CH_2), 1.58 (m, 2H, CH_3-CH_2-CH_2-CH_2), 2.28 (s, 3H, CH_3-C_4), 2.69 (t, 2H, CH_3-CH_2-CH_2-CH_2, J=7.7 Hz), 3.86 (s, 6H, CH_3-O), 6.93 (m, 4H, H_6,H_7,H_8,H_9); ^{13}C NMR ($CDCl_3$) δ 12.2 (CH_3, CH_3-CH_2-CH_2-CH_2), 13.9 (CH_3, CH_3-C_4), 22.6 (CH_2, CH_3-CH_2-CH_2-CH_2), 32.2 (CH_2, CH_3-CH_2-CH_2-CH_2), 52.3 (CH_3, CH_3-O), 116.3 (CH, $C_{6,9}$), 123.3 (C, $C_{2,3}$), 124.2 (CH, $C_{7,8}$), 127.9 (C, $C_{1,4}$), 141.4/141.5/141.6 (C, $C_{4a,5a,9a,10a}$), 168.0 (C, $C_{C=O}$) ; **8d** : IR (neat) 2210, 1490, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (m, 6H, CH_3-CH_2-CH_2-CH_2-), 1.43 (m, 4H, CH_3-CH_2-CH_2-CH_2-), 1.46 (m, 4H, CH_3-CH_2-CH_2-CH_2-), 2.61 (t, 2H, CH_3-CH_2-CH_2-CH_2-C_4, J=7.3 Jz), 2.82 (t, 2H, CH_3-CH_2-CH_2-CH_2-C_1, J=7.0 Hz), 6.95 (m, 4H, H_6,H_7,H_8,H_9); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 22.3/22.4/27.8/ 28.5/31.5/31.8, (CH_2), 107.1 (C, C_2), 116.3 (CH, C_3), 117.9 (C, $C_{C\equiv N}$), 124.2/124.4 (CH, $C_{6,9}$), 127.7 (CH, $C_{7,8}$), 129.3 (C, C_{4a}), 132.3 (C, C_1), 140.3 (C, C_{10a}), 141.4/141.6 (C, $C_{5a,9a}$), 143.7 (C, C_{4a}).

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