

Ring-Closure Reactions. 8.¹ Synthesis and Ultraviolet Spectra of Macrocyclic Aromatic Ethers

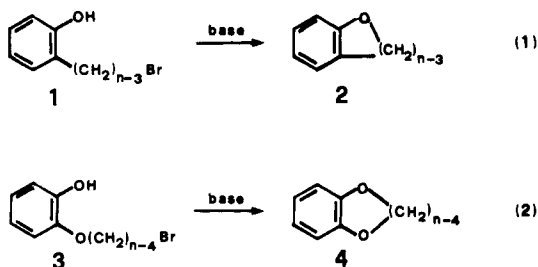
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Macrocyclic mono- and diethers have been prepared in fairly good yields by means of a very convenient, straightforward procedure starting from the open-chained bifunctional precursors, namely, *o*- ω -bromoalkyl and *o*- ω -bromoalkoxyphenols. In some cases small amounts of the dimeric cycles were also isolated. The present work provides a further example of the effectiveness of the NaOH–Me₂SO base–solvent system in promoting ring formation via intramolecular Williamson synthesis. The UV spectral data of the present compounds, when combined with those of the already available lower homologues, exhibit significant ring-size dependent effects, which are discussed in some detail.

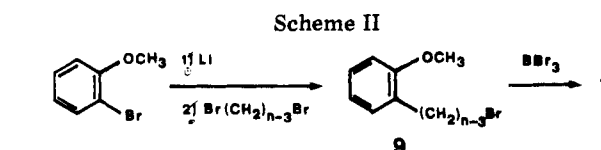
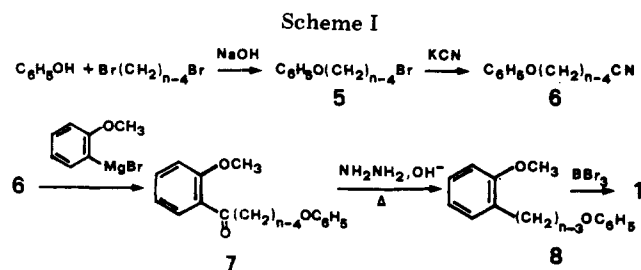
In connection with our studies on ring-closure reactions we have undertaken an extensive investigation of the cyclization reactions 1 and 2,^{2,3} leading to the aromatic mono- and diethers 2 and 4, respectively, by intramolecular Williamson



synthesis.⁴ The scope of these studies includes physical and mechanistic aspects as well as the attainment of better insight for the improvement of synthetic procedures for ring compounds. The preparation of the eight-, nine-, and ten-membered monoethers 2 by means of an extremely convenient cyclization procedure has already been described.⁵ We report now the extension of the above procedure to the synthesis of compounds 2, $n = 11, 14,$ and $16,$ and 4, $n = 11, 12, 13, 14, 16,$ and $24.$ The UV absorption spectra of the above compounds and of the lower homologues in both series were recorded and compared with those of suitable open-chained models. The observed ring-size dependent features provide an insight into the conformational restrictions imposed by the different ring structures to the degree of coplanarity of the chromophoric groups.

Syntheses of the Open-Chain Precursors. *o*- ω -Bromoalkoxyphenols 3 were prepared by mono-O-alkylation of catechol with the appropriate α,ω -dibromoalkane. Yields, physical constants, and analytical data of the synthesized compounds are listed in Table I.

For the preparation of the *o*- ω -bromoalkylphenols 1, $n = 11, 14,$ and $16,$ the five-step synthetic procedure (Scheme I) previously developed for the smaller members of the series was followed in the early part of this work. Poor yields of the desired compounds were obtained by this method (method A), probably due at least in part to the difficulties encountered



in the isolation and purification of the low-melting, high-boiling long-chain compounds. A more convenient procedure was developed subsequently (method B), involving a two-step reaction scheme (Scheme II) from the same commercially available starting materials, i.e., *o*-bromoanisole and the appropriate α,ω -dibromoalkane. The lithiation of *o*-bromoanisole with lithium metal proceeds smoothly in dry ether at room temperature. When 1 mol of the lithium derivative was treated with 1 mol of dibromo compounds the monoalkylated products were isolated in 31–35% yield, satisfactory for a reaction of a monofunctional reagent with an equimolar amount of a bifunctional one. The desired *o*- ω -bromoalkylphenols 1 were obtained by simple cleavage with BBr₃ of the methoxyl group of 9. It is apparent from Table I, where the pertinent yield data are shown, that the latter procedure is definitely better than the former one.

It is worth noting that the interaction of aromatic lithium derivatives with alkylating agents appears to have been carried out previously but seldom with reagents other than methyl derivatives or ethylene oxide. In fact, we are aware of only one case in which a long-chain alkyl halide has been employed for the alkylation of an aryllithium compound.⁶ Moreover, ortho alkyanisoles (and phenols) are not easily prepared. Most of the available synthetic procedures lead to mixtures of ortho and para derivatives. Lately a new method for the synthesis of ortho-alkylated phenols from phenols and dialkyl sulfides has been published.⁷ However, this method, which appears to be far superior to previously reported ones, suffers from the general unavailability of the cyclic polymethylene sulfides which are required for the introduction of alkyl groups other than methyl.

It seems therefore that the reaction sequence of Scheme II has the potential of providing a convenient general synthetic route to ortho-alkylated anisoles (and phenols) from readily available starting materials.

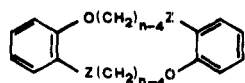
Cyclization Reactions. In a previous paper of this series we have shown that compounds 1, $n = 8, 9,$ and $10,$ could be conveniently cyclized to the corresponding macrocycles 2 by treatment with a suspension of excess concentrated aqueous NaOH in Me₂SO solution at 55 °C.⁵ This simple procedure, successfully applied in the present work, avoided the long reaction times and large volume of solvent usually required for the synthesis of macrocycles according to the Ziegler high-dilution technique. Typically, a few grams of a given bifunctional precursor were cyclized employing 150 mL of

Table I. Yields and Physical Constants for the Preparation of *o*- ω -Bromoalkylphenols 1, *o*- ω -Bromoalkoxyphenols 3, Cyclic Monoethers 2, and Cyclic Diethers 4^a

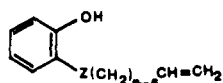
Registry no.	Compd	<i>n</i>	Yield, %	Mp, °C, or <i>n</i> _D ²⁰
62587-18-2	1 ^b	11	3.3 (A), 21 (B)	1.5386
62587-19-3		14	7.2 (A), 23 (B)	27.5–30
62587-20-6		16	2.6 (A), 25 (B)	41–43.5
62587-21-7	3	11	26	29–31 ^c
62587-22-8		12	34	1.5261
62587-23-9		13	29	23–24.5 ^d
62587-24-0		14	26	1.5197
62587-25-1		16	22	25.5–26.5
62587-26-2		24	35 ^e	51–52.5
62587-27-3	2	11	70	1.5416
62609-07-8		14	79	1.5328 ^f
62587-28-4		16	79	1.5247 ^g
7125-07-7	4	11	70	1.5384
7125-08-8		12	62	41–43 ^h
7198-62-1		13	58	54–56 ⁱ
7198-63-2		14	62	1.5356
62587-29-5		16	73	46.5–48
62587-30-8		24	69 ^e	55–56

^a Analytical data were within $\pm 0.3\%$ in all cases, with the sole exception of 3, *n* = 24. For the latter compound: Anal. Calcd for C₂₆H₄₅BrO₂: C, 66.51; H, 9.66. Found: C, 67.25; H, 9.83. ^b Yields reported are overall yields. For the meaning of the symbols A and B see text. ^c From pentane at 5 °C, lit.⁴ mp 32 °C. ^d From pentane at 5 °C, lit.⁴ mp 19°. ^e Yields not comparable with others. See text. ^f Bp 120–125 °C (1.5 mm). ^g Bp 158 °C (1.8 mm). ^h Lit.⁴ mp 46 °C. ⁱ Lit.⁴ mp 58 °C.

solvent and reaction times of 1 h or so. Fair to good yields of cyclic compounds in both series were obtained (Table I). In some cases minor amounts of the dimeric cycles 10 were iso-



10, Z = O, CH₂



11, Z = O, CH₂

lated. No trace was found of the isomeric open-chain alkenyl derivatives 11 which were found to accompany the eight- and nine-membered ring formation in both series^{2,3,5} and which were attributed to a competing intramolecularly assisted elimination reaction of the E₂ type. Since on increasing molecular weight purification became more difficult, the cyclization of compound 3, *n* = 24, was run in the presence of K₂CO₃ in aqueous ethanol, under conditions similar to those of the kinetic runs,³ and to those previously adopted for the cyclization of compounds 3, *n* = 8 and 9.² A small amount of the dimeric 48-membered tetraether 10, Z = O, *n* = 24, was also isolated in this case. Apart from the diethers with ring size up to 14,⁴ none of the ring compounds has been reported in the literature. Structure assignments were based mainly on elemental analyses (Table I) and ¹H NMR spectrometry. In the ¹H NMR spectra of the diethers 4 the protons are grouped in three areas at δ 6.7 (singlet, aromatic protons), 3.8–4.1 (broad triplet, CH₂ next to oxygen), and 1.2–2.0 (multiplet, "central" methylene protons). The latter signal is broad, but a prominent sharp peak stands out at ca. δ 1.4 in the 13- and higher membered rings. A similar situation appears in the ¹H NMR spectra of the monoethers 2, for which the corresponding signal is a broad and featureless multiplet at δ 1.0–2.0 for ring size 11, while the 14- and 16-membered rings exhibit a signal at δ 1.3–2.0, with a prominent peak at δ 1.4. In all the monoethers the benzylic and ethereal methylenes appear as partially resolved triplets at ca. δ 2.5–2.8 and 3.8–4.1, respectively. In addition, the aromatic protons are shown as a com-

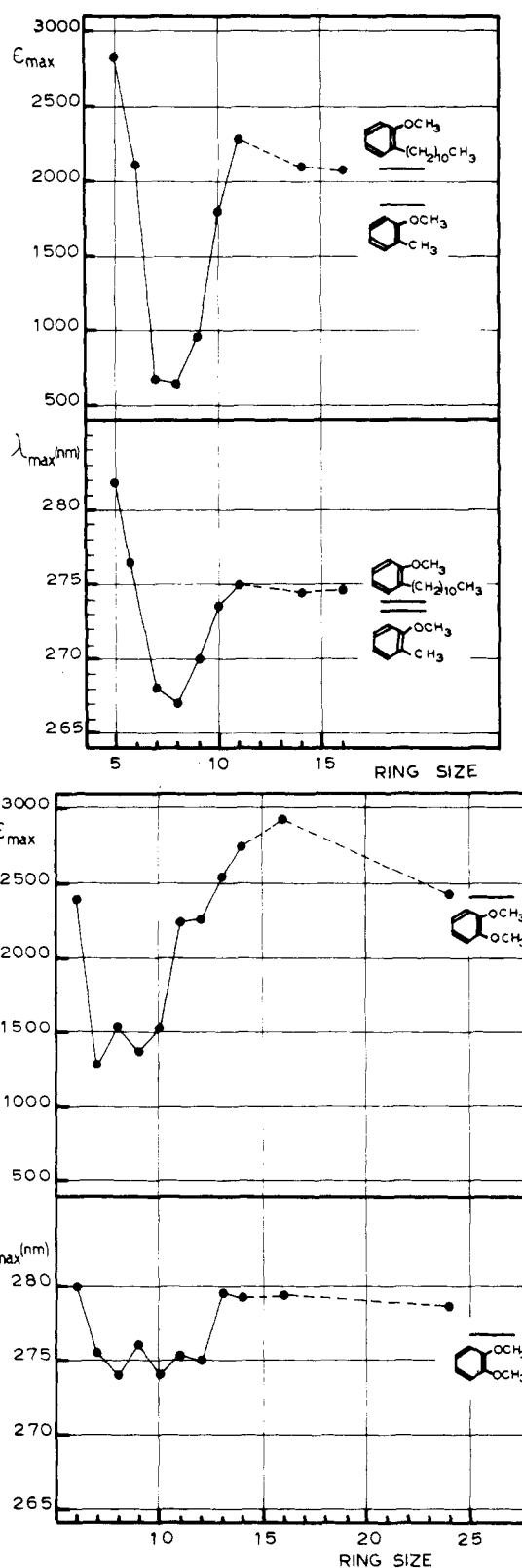


Figure 1. Ultraviolet spectral data for the monoethers 2 (top) and diethers 4 (bottom) in ethanol solution. The pertinent data of open-chained model compounds are also shown.

plex multiplet at δ 6.4–7.2. In all cases the intensity ratios are as expected, and no extra peak is present.

Structure assignment to the dimeric cycles was based mainly on molecular weight determinations by means of mass spectrometry, since their ¹H NMR spectra are expected to be quite similar to those of the corresponding monomeric cycles.

Table II. Ultraviolet Spectral Data for the Monoethers 2, Diethers 4, and Open-Chained Model Compounds in Ethanol Solution

Registry no.	Compd	<i>n</i>	λ_{\max} , nm		ϵ_{\max} , cm ⁻¹ M ⁻¹		ϑ , deg		
496-16-2	2	5	289*	281.8	274*	2829	0		
493-08-3		6	284.4	276.5	270*	2079	2122	30	
6169-78-4		7	274.0	268.0	261*	665	670	61	
51060-43-6		8	273.5	267.0	261*	651	651	61	
51795-92-7		9	275.0	270.0	262*	882	961	54	
51795-93-8		10	279.6	273.6	267*	1669	1794	37	
		11	281.4	274.9	267*	2198	2289	26	
		14	280.5	274.4	267*	1972	2105	30	
		16	280.8	274.7	267*	1922	2083	31	
578-58-5		<i>o</i> -Methyl-anisole		279.2	273.2	267*	1711	1825	37
20056-62-6		<i>o</i> -Undecyl-anisole		279.8	273.8	267*	1938	2081	31
493-09-4		4	6	286.0	280.0	274*	2130	2392	
7216-18-4			7	283*	275.5	271*		1285	
7124-91-6			8	282*	274.0	268*		1539	
7124-99-4			9		276.1	272*		1364	
7198-60-9			10	280*	274.0			1527	
	11		280.6	275.3	267*	2024	2241		
	12		280.0	275.0		2249	2258		
	13		285*	279.5	276.9		2540	2020	
	14		285*	279.2	276*		2748		
	16		285*	279.4	276*		2929		
	24		284*	278.6	276.0		2415	2385	
	91-16-7		Veratrole		282*	276.7		2400	

* Shoulder.

UV Spectra of the Ring Compounds. Inspection of space-filling molecular models indicates that the degree of coplanarity between the benzene ring and the O-C_{aliph} chromophore(s) in both mono- and diethers is affected to a significant extent by the size of the ring. A particularly severe hindrance to planarity is apparent in the neighborhood of ring size 8 and 9. Since maximum conjugative interaction between the chromophoric groups requires a planar arrangement, it is expected that increasing the degree of twist results in both an increasing hypochromic effect and hypsochromic shift relative to the spectrum of a planar model.⁸ Compounds in which a chromophoric group attached to a benzene ring has been incorporated into cyclic structures, mostly in the ring size range 5–8, have been reported to exhibit ring-size dependent spectral features, in accordance with the above arguments.^{9–11}

The UV spectral data of the cyclic compounds prepared in this work, together with those of the lower homologues in both series and of suitable open-chained reference compounds, are presented in Table II and plotted in Figure 1 as a function of ring size. None of the given compounds displays a simple absorption band; generally either a second closely spaced maximum and a shoulder or two shoulders are present besides the principal maximum. The trends in both λ_{\max} and ϵ_{\max} can be interpreted in terms of the varying degree of coplanarity of the O-C_{aliph} moiety with the aromatic ring for different ring sizes. Steric hindrance to coplanarity appears to be a maximum for ring size 7–9, while the conformations of the strainless or nearly strainless large rings are closely akin to those of the open-chained models. In the case of the monoethers the angle of twist ϑ has been calculated by means of the relationship $\epsilon^{\vartheta}/\epsilon^0 = \cos^2 \vartheta$,⁸ where ϵ^0 refers to ϵ_{\max} of coumaran (2, *n* = 5), in which the chromophoric groups are required to be coplanar because of steric reasons. However, it must be noted that the simple $\cos^2 \vartheta$ relationship is expected to hold mainly in cases where a hypochromic effect is not accompanied by a relevant hypsochromic shift.¹² Moreover, such a relationship cannot account for any effect due to possible geometrical

distortions in the aromatic portion caused by the annelation with a strained ring. No doubt the latter effect plays some role, as shown by the fact that the five- to eight-membered cycloalkenobenzenes have been reported¹³ to exhibit UV spectral data markedly dependent on ring size. In the latter compounds steric inhibition to conjugation, if any, is likely to give but a small contribution. The observed effect has been explained on the basis of strain on the π -electron sextet both in the ground and excited state.¹³ It is thus concluded that the ϑ values reported in Table II are probably not meaningful as such, but should rather be regarded as providing a rough indication of steric hindrance to coplanarity in the various ring compounds.

Experimental Section

Most apparatuses were as previously described.² IR and ¹H NMR spectra were taken in CCl₄ solutions. UV spectra were measured in ethanol solution on a Beckman DB GT spectrometer, fitted with a W+W 1100 recorder. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach über Engelskirchen, West Germany. All melting points are uncorrected.

Materials. Catechol (Erba RPE) and Veratrole (Fluka) were commercial samples and used as such. *o*-Bromoanisole (Schuchardt) and *o*-methylanisole (Schuchardt) were redistilled before use. All the α,ω -dibromoalkanes up to C₁₂ were from Fluka and used without further purification. All the cyclic mono-^{3,5} and diethers² up to ring size ten and 1,20-dibromoeicosane¹ were available from previous investigations. 1,13-Dibromotridecane was obtained in 53% yield from 14-bromotetradecanoic acid¹ by the Cason and Welb's modification (procedure P)¹⁴ of the Hunsdiecker reaction, bp 138–142 °C (0.05 mm), n_{D}^{25} 1.4881 (lit.¹⁵ n_{D}^{27} 1.4880).

***o*- ω -Bromoalkoxyphenols (3, *n* = 11, 12, 13, 14, 16, and 24).** All the compounds except that with *n* = 24 were prepared according to a previously described procedure,² with the sole difference that increasing times were required on increasing chain length of the dibromo compound in order to achieve complete reaction, namely, 3.5, 7, 15, 24, and 40 h for *n* = 11, 12, 13, 14, and 16, respectively. With the aim of avoiding inconveniently long reaction times, the alkylation reaction with 1,20-dibromoeicosane (*n* = 24) was run under different reaction conditions, namely, in homogeneous solution of boiling ethanol, where the reaction was complete in 4 h. The compounds were purified by

chromatography on silica gel, with CHCl_3 -light petroleum (1:1) as eluent. For analytical purposes the products were further purified by microdistillation under vacuum with the ball tube. The ^1H NMR spectra were in all cases consistent with the expected structures.

***o*- ω -Bromoalkylphenols (1, $n = 11, 14,$ and 16).** **Method A.** The identity of all intermediates and final products was checked by ^1H NMR spectroscopy. The ^1H NMR spectra were analogous to those of the lower homologues,⁵ with the obvious difference of an increased intensity of the signal due to the "central" methylene protons. ω -Phenoxy bromides **5** were obtained by reacting sodium phenoxide (1 mol) with the appropriate α,ω -dibromoalkane (1 mol) in refluxing ethanol (4 h). After standard workup, the pure compounds were obtained by chromatography on silica gel, using CCl_4 -light petroleum (3:1) as eluent: $n = 11$, 28% yield, n_{D}^{21} 1.5229; $n = 14$, 34% yield, mp 31–31.5 °C; $n = 16$, 29% yield, mp 37–40 °C. The conversions **5** \rightarrow **6**, **6** \rightarrow **7**, **7** \rightarrow **8**, and **8** \rightarrow **1** were carried out as previously described.⁵ For each compound the pertinent yields and physical constants, when available, are reported below in the given order. All nitriles **6** and ketones **7** showed the expected IR bands at 2250 and 1680 cm^{-1} , respectively. Compounds **6**: $n = 11$, 92%, oil (crude); $n = 14$, 96%, mp 25–27 °C (crude); $n = 16$, 87%, mp 33–35 °C (crude). Compounds **7**: $n = 11$, 88%, oil (crude); $n = 14$, 89%, oil (crude); $n = 16$, 68%, oil (crude). Compounds **8** were purified by chromatography on silica gel, with CHCl_3 -light petroleum (1:1) as eluent: $n = 11$, 26%, n_{D}^{24} 1.5365; $n = 14$, 30%, mp 30–32 °C; $n = 16$, 33%, mp 41–43 °C. Compounds **1**, $n = 11, 14,$ and 16 , were repeatedly chromatographed on silica gel with CHCl_3 -light petroleum (1:2) and/or CHCl_3 until pure by TLC. For analytical purposes the compounds were microdistilled with the ball tube under vacuum (0.05 mm or less).

Method B. All operations before aqueous workup were carried out under argon. 2-Lithioanisole was prepared from *o*-bromoanisole (1 mol) and freshly cut small pieces of lithium metal (2 mol) in dry ether. After the dissolution of lithium was complete, the solution was filtered through glass wool with the aid of an argon overpressure. To the clear filtrate the appropriate α,ω -dibromoalkane was added dropwise. The resulting solution was refluxed for 2 h. In order to ensure complete reaction the solvent was evaporated and the residue was heated for additional 2 h at 120 °C. After cooling, water was added and the aqueous mixture was neutralized with H_2SO_4 and extracted with CHCl_3 . The latter was dried over Na_2SO_4 and evaporated. Compound **9**, $n = 11$, was isolated by fractional distillation of the residue in 35% yield, bp 120–130 °C (0.3 mm). Compound **9**, $n = 14$, was obtained likewise in 35% yield, bp 154–164 °C (0.1 mm). In the latter case a small amount (ca. 1%) of 2,2'-dimethoxybiphenyl separated on standing from the forerun as white crystals, mp 150–152 °C from EtOH, lit.¹⁵ mp 155 °C, ^1H NMR as expected. Compound **9**, $n = 16$, was obtained in 31% yield by column chromatography on silica gel using benzene-light petroleum (1:1) as eluent. All three compounds were pure by TLC and gave ^1H NMR spectra consistent with the expected structure. Cleavage of the methoxy group afforded compounds **1**, $n = 11, 14,$ and 16 , in 72, 60, and 79% yield, respectively.

Cyclic ethers 2, $n = 11, 14,$ and $16,$ and 4, $n = 11, 12, 13, 14, 16,$ and $24,$ were synthesized by cyclization of the corresponding open-chained precursor as outlined in the general part. After aqueous workup and ether extraction the crude products were eluted on silica gel with CHCl_3 -light petroleum (1:2), then further purified either by distillation or sublimation under vacuum. In some cases the dimeric cycles **10** separated as white, crystalline solids from solutions of the

crude products in light petroleum (compounds **10**, $Z = \text{CH}_2$, $n = 14$ and 16) or light petroleum- CHCl_3 (2:1) (compound **10**, $Z = \text{O}$, $n = 24$). The solids were collected by filtration and thoroughly washed with light petroleum. Compound **10**, $Z = \text{CH}_2$, $n = 14$, 1.2% yield, mp 124.5–126 °C, M^+ m/e 492. Compound **10**, $Z = \text{CH}_2$, $n = 16$, 2% yield, mp 130.5–132 °C, M^+ m/e 548. Compound **10**, $Z = \text{O}$, $n = 24$, 4% yield, mp 143.5–145 °C, M^+ m/e 776.

***o*-Undecylanisole** was obtained as an unexpected product on attempted bishomologation of **9**, $n = 14$, via the interaction of the Grignard reagent derived therefrom with ethylene oxide. After standard workup, the title compound was obtained in 10% yield by chromatography on silica gel, using CHCl_3 -light petroleum (1:2) as eluent: n_{D}^{19} 1.4922; ^1H NMR δ 7.2–6.5 (m, 4 H, nuclear protons), 3.8 (s, 3 H, OCH_3), 2.8–2.4 (distorted t, 2 H, benzylic CH_2), 1.9–0.7 (m, 21 H, central methylene and terminal methyl protons). The recovery was not quantitative, since several fractions containing the given compound in a less pure form were discarded.

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Registry No.—**5** ($n = 11$), 51795-98-3; **5** ($n = 14$), 2033-87-6; **5** ($n = 16$), 62587-31-9; **6** ($n = 11$), 62587-32-0; **6** ($n = 14$), 62587-33-1; **6** ($n = 16$), 62587-34-2; **7** ($n = 11$), 62587-35-3; **7** ($n = 14$), 62587-36-4; **7** ($n = 16$), 62587-37-5; **8** ($n = 11$), 62587-38-6; **8** ($n = 14$), 62587-39-7; **8** ($n = 16$), 62587-40-0; **9** ($n = 11$), 62587-41-1; **9** ($n = 14$), 62587-42-2; **9** ($n = 16$), 62587-43-3; **10** ($Z = \text{CH}_2$; $n = 14$), 62587-44-4; **10** ($Z = \text{CH}_2$, $n = 16$), 62587-45-5; **10** ($Z = \text{O}$, $n = 24$), 62587-46-6; 1,8-dibromooctane, 4549-32-0; 1,11-dibromoundecane, 16696-65-4; 1,13-dibromotridecane, 31772-05-1; 1,7-dibromoheptane, 4549-31-9; 1,10-dibromodecane, 4101-68-2; 1,12-dibromododecane, 3344-70-5; *o*-bromoanisole, 578-57-4; phenol, 108-95-2; 1,20-dibromoeicosane, 14296-16-3.

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