Facile Access to Versatile Polyaromatic Building Blocks: Selectively Protected Benzocyclobutenedione Derivatives *via* Regioselective [2 + 2] Cycloaddition of α-Alkoxybenzyne and Ketene Silyl Acetal

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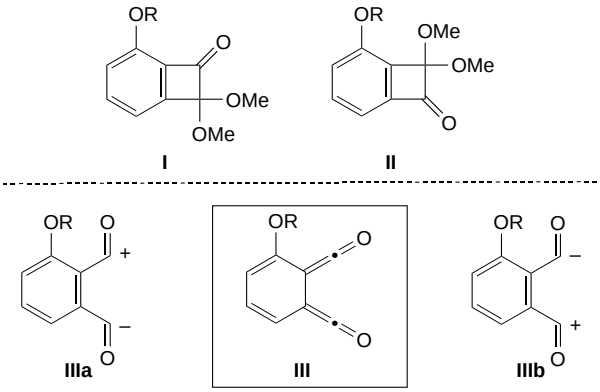
Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

A facile, divergent access to highly oxygenated benzocyclobutene derivatives was developed *via* the regioselective [2 + 2] cycloaddition of α-alkoxybenzynes and ketene silyl acetals. The cycloadducts could be converted to selectively protected alkoxybenzocyclobutenediones, an attractive class of compounds for the synthesis of polyaromatic compounds. As one possible application, divergent access to a regioisomer pair of sulfonylphthalides for the *Hauser* approach to polyaromatic compounds is described.

Introduction. – Retrosynthetic analysis by considering *latent polarity* is now a standard method in planning organic synthesis [1]. Logical disconnection by assigning donor/acceptor characteristics greatly aids one in systematically recognizing possible precursor structures that may be well-precedented but might be overlooked, unknown, or deserve development. The state-of-the-art in current organic synthesis greatly owes the *umpolung* concept of *Seebach* [2], which spurred the development of various charge-inverted (umpoled) species, providing wider possibilities of synthetic pathways. As a consequence of rapid advancement along these lines, an ironic situation may well arise today, such that one might carry out a synthetic transformation even without being aware of whether it is a *natural* one or an *umpoled* one. Another implication is the concept of synthetic equivalents possessing variable polarities, facilitating the formulation of versatile reagents or building blocks as a new repertoire for synthetic transformations.

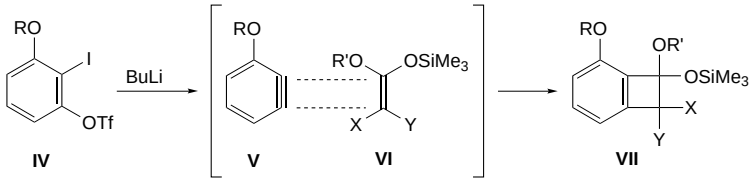
With respect to these concepts, we wish to describe a regioselective approach to a set of isomeric compounds **I** and **II**. These are the selectively masked forms of an intriguing species **III** with multiple potential reactivities, *i.e.*, inherent polarities **IIIa** or **IIIb** and two additional carbonyl groups.

Benzocyclobutene derivatives display unique reactivities arising from their inherent strain [3], and, among numerous possibilities, the facile pericyclic opening to give *o*-quinodimethane species [4] is key to various useful synthetic reactions. Even greater opportunities can be expected from the congeners with a higher oxidation state, *i.e.*, benzocyclobutenones and benzocyclobutenediones. The utility of some of these has been proven by pioneering studies (for selected examples, see [5]). The progress in this area, however, is limited by the accessibility to such highly oxidized benzocyclobutene derivatives.



In our continuing studies on the synthesis of polyarene structures, we have established an efficient, divergent access to benzocyclobutenedione derivatives. The three key features of our approach are illustrated in *Scheme 1: a*) efficient generation of benzyne species from *o*-iodo triflate precursor **IV** by treatment with butyllithium at low temperature [6], *b*) the viability of the [2 + 2] cycloaddition of the α-alkoxybenzyne **V**, thus generated, to ketene silyl acetal **VI**, and *c*) the rigorous regioselectivity consistently observed to provide a single adduct **VII** [7]. Importantly, all of these aspects proved to be applicable to all substrate combinations tested, including ones with multiple O-functionalities, thereby allowing direct access to a class of selectively protected or selectively elaborated alkoxybenzocyclobutenediones. These, in turn, serve as building blocks for the completed [8] or currently targeted [9] synthesis of the polyaromatic natural products shown in the *Figure*.

Scheme 1



Results and Discussion. – For the preparation of iodo triflate derivatives **3m** and **3b**[1]), two possible routes are shown in *Scheme 2*. In the three-step method, conversion of 2-iodoresorcinol (**1**) [10] to the corresponding bis-triflate (Tf_2O, $^iPr_2NEt$, CH_2Cl_2), followed by the cleavage of one of the two sulfonyl groups by treatment with cesium carbonate in 1,2-dimethoxyethane, cleanly afforded phenol **2** in virtually quantitative yield. Subsequent methylation (Me_2SO_4, K_2CO_3, acetone) or benzylation (BnBr, K_2CO_3, DMF) of **2** produced iodo triflate **3m** or **3b** in high yield, respectively. This

[1]) Throughout this article, the suffix **m** or **b** designates a series of compounds having a **m**ethyl or a **b**enzyl protecting group.

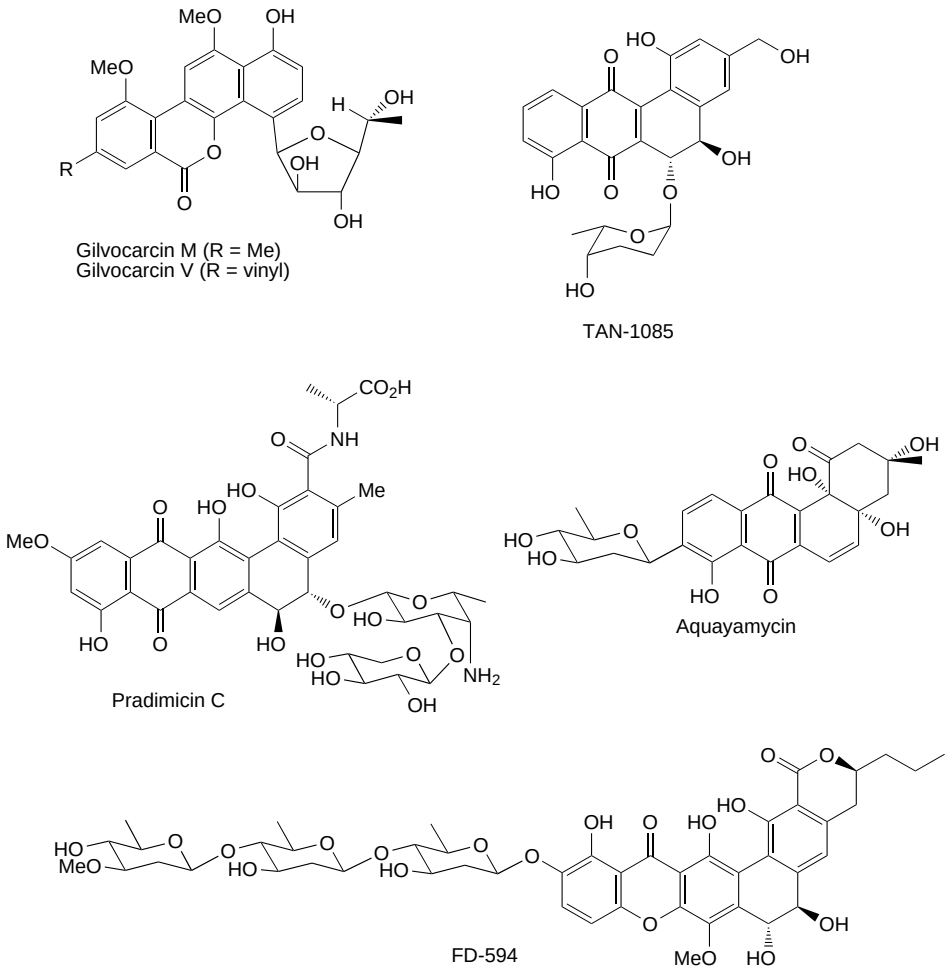


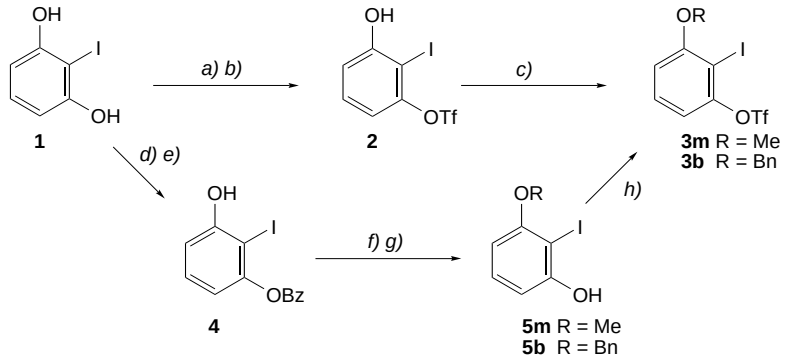
Figure. *Polyaromatic natural products synthesized or to be synthesized from alkoxybenzocyclobutenediones*

protocol is attractive in terms of simplicity, applicability to large-scale synthesis, and high yield, excep for the drawback that a molar equivalent of triflate is 'wasted'.

An alternative, presumably more economical, five-step route involved dibenzoylation of **1** followed by selective monosaponification to benzoate **4**. Methylation or benzylation of **4** followed by hydrolysis afforded methyl ether **5m** or benzyl ether **5b**, which was converted to **3m** or **3b**, respectively.

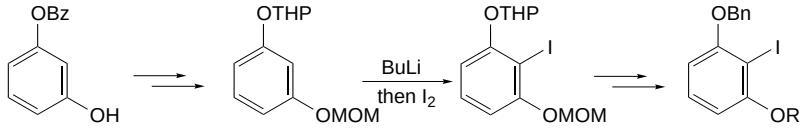
Previously, we utilized a directed metallation–iodination protocol for the synthesis of this class of compounds (see, *e.g.*, *Scheme 3*), which had problems of longer steps and difficulty in scaling up. On the other hand, the ready availability of 2-iodoresorcinol (**1**) by direct iodination of resorcinol [10] enabled us to open a more-facile access to the benzyne precursors.

Scheme 2



a) Tf_2O, $^iPr_2NEt$, CH_2Cl_2, $-78°$ (99%). *b*) Cs_2CO_3, 1,2-dimethoxyethane, 80° (quant.). *c*) For **2** → **3m**: $(MeO)_2SO_2$, K_2CO_3, acetone (88%); for **2** → **3b**: BnBr, K_2CO_3, DMF (82%). *d*) BzCl, pyridine, *N,N*-dimethylpyridin-4-amine (DMAP). *e*) 2M NaOH, 1,4-dioxane (83%, 2 steps from **1**). *f*) For **4** → **5m**: $(MeO)_2SO_2$, K_2CO_3, acetone (98%); for **4** → **5b**: BnBr, K_2CO_3, DMF (99%). *g*) 1M NaOH, 1,4-dioxane (92% for **4** → **5m**; 97% for **4** → **5b**). *h*) Tf_2O, $^iPr_2NEt$, CH_2Cl_2, $-78°$ (94% for **5m** → **3m**; 90% for **5b** → **3b**).

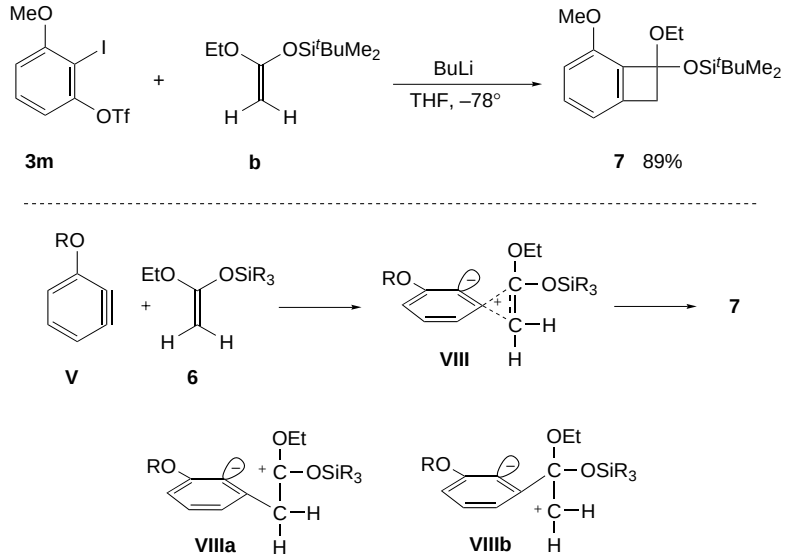
Scheme 3



Divergent Access to Isomeric Benzocyclobutenedione Derivatives. The starting point is the [2+2] cycloaddition of an α-alkoxybenzyne to an olefin as exemplified in *Scheme 4* by **V** + **6** → **7** [7]. Several points deserve comments: *a*) Ketene silyl acetals (KSAs), easily available from the enolization–silylation of various esters [11a,b] (KSAs **8**, **13**, and **20** were prepared by the *Yamamoto* method [11c]), proved to show excellent reactivity as an olefinic component, which can be ascribed to the high HOMO level of KSA. *b*) The relevant frontier orbital of benzyne is the unusually low-lying LUMO, which is made even lower by the inductively electron-withdrawing alkoxy group [12]. These two aspects are the origin of excellent reactivities and yields observed for these reaction partners in comparison with the parent system, *i.e.*, ethylene and benzyne.

Such electronic perturbation in these partners is also the origin of the remarkably rigorous regioselectivity (see *Scheme 4*). The cycloaddition gives product **7**, in which the silyl acetal moiety is located near the MeO group. The rationale shown in *Scheme 4* is based on the two-step mechanism by the *Fukui–Hoffmann* interpretation on this particular, *thermally* allowed [2+2] process [12]. The site where the primary orbital interaction occurs for the benzyne side is distal from the RO group, and the attack of the olefinic π-system forms a three-membered ring intermediate **VIII** that collapses to the final four-membered ring of **7**. Obvious preference in the two canonical forms, **VIIIa** over **VIIIb**, clearly explains the regiochemical outcome. Alternatively, the two oxy functions may offer cation stabilization sufficient for the direct generation of an

Scheme 4



open zwitterion **VIIIa**. However, experiments showed that the (*E*)/(*Z*) ratio of KSA is perfectly reflected in the *cis*/*trans* composition in the product [7b], suggesting a short lifetime of such an open zwitterion if involved[2]).

Leaving the rationale aside, the key aspect is that the regioselectivity proved to persist for a variety of oxygenated KSAs, thereby enabling access to various benzocyclobutenes of synthetic versatility as shown in *Scheme 5*. Upon treatment of iodo triflate **3m** in the presence of KSA **8** with BuLi (THF, $-78°$), cycloadduct **9m** was immediately formed as a single product by the [2 + 2] cycloaddition of α-alkoxybenzyne **V** and KSA **8**. The perfect regioselectivity applied also in the corresponding reaction of iodo triflate **3b**, having a benzyl protecting group, to give cycloadduct **9b**.

Amazingly, the more oxygenated KSA **13** also showed complete regioselectivity. This is an intriguing observation in view of the high symmetry in tetraoxyethene **13**, which, nonetheless, gave a single cycloadduct **14m** (*Scheme 5*). Experimentally, Et_2O (rather than THF) was the solvent of choice for the reaction of fully oxygenated olefin **13**. When THF was used, though the regioselectivity remained perfect, giving only **14m**, the yield was lower (56%). Again, for the reaction with the benzyl derivative **3b**, complete regioselectivity was observed to give **14b**.

The synthetic implication of these findings is that a pair of cycloadducts **9m** and **14m**, and their benzyl-protected congeners **9b** and **14b**, are formally differentially protected alkoxybenzocyclobutenediones. Such an aspect became obvious by successful conversion of these compounds to a pair of monoprotected derivatives **12m** and

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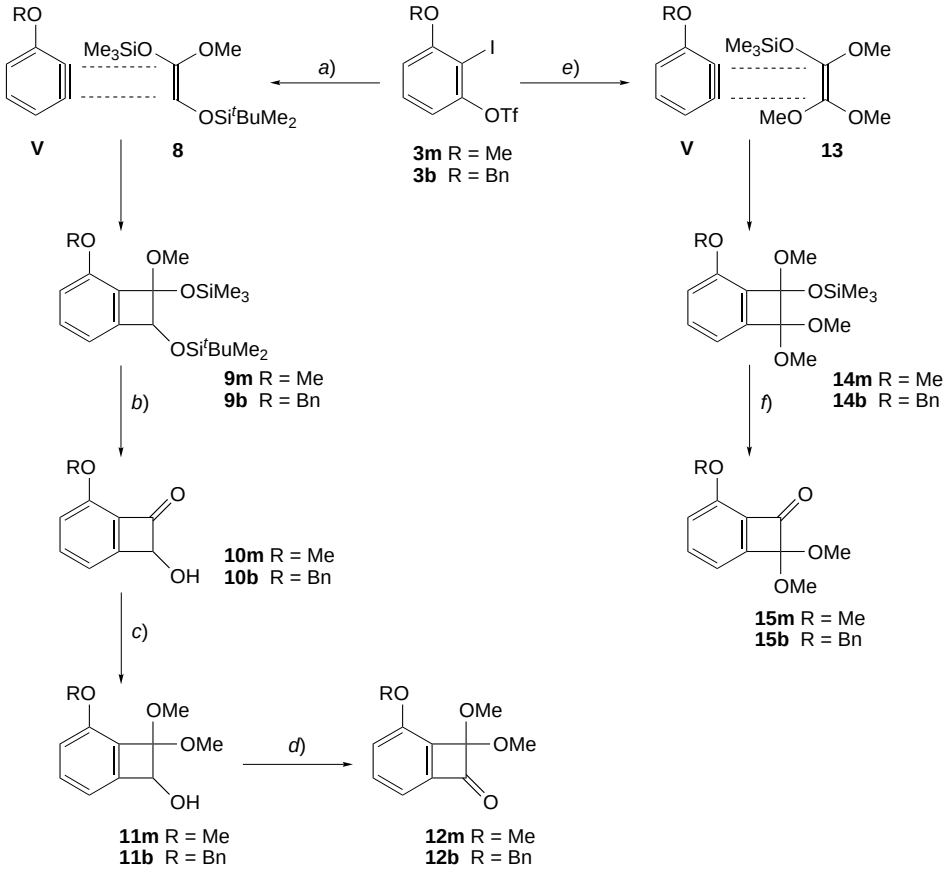
[2]) Theoretical calculation showed that these two cases are very close to each other, and the relative stability delicately depends on molecular geometry as well as on the calculation level (unpublished results of Prof. *Yoshihiro Osamura* and Mr. *Kazuhiko Sato* [13]).

Scheme 5

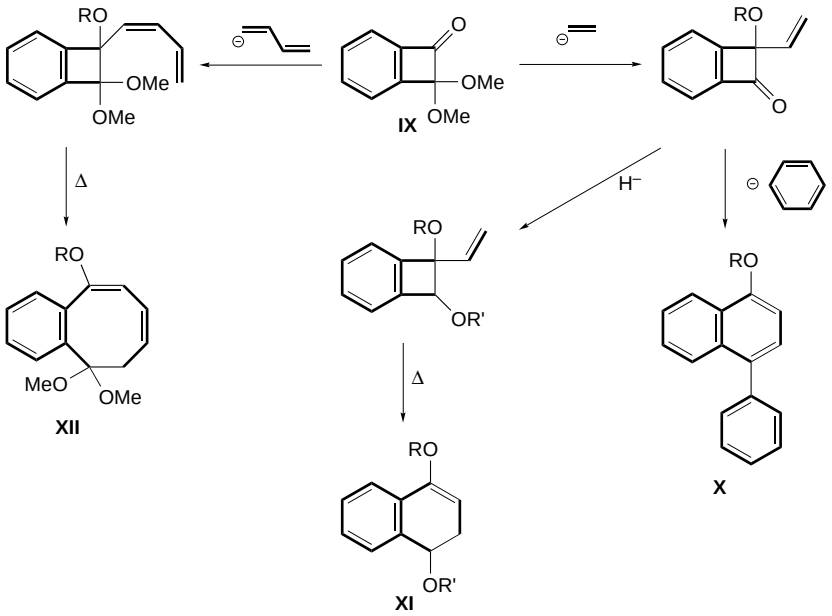


a) **8**, BuLi, THF, −78°. *b*) 46% aq. HF soln., MeCN, 0→25° (**10m**: 68%; **10b**: 75%; 2 steps). *c*) TsOH, $(MeO)_3CH$, MeOH (**11m**: 92%; **11b**: 96%). *d*) Et_3N, $SO_3 \cdot$ pyridine, DMSO (**12m**: 94%; **12b**: 95%). *e*) **13**, BuLi, Et_2O, −78°. *f*) Sat. aq. KF soln., Bu_4NCl, MeCN, 25° (**15m**: 72%; **15b**: 80%; 2 steps).

15m, as well as to their benzyl counterparts, **12b** and **15b**. Thus, the cycloadduct **14m** was easily converted to the corresponding mono-one **15m** by treatment with aqueous KF solution in MeCN (cat. Bu_4NCl, 25°). Similarly, the benzyl congener **14b** was hydrolyzed to mono-one **15b** in high yield. On the other hand, cycloadducts **9m** and **9b** could be converted in high yields to the regioisomeric mono-ones **12m** and **12b**, by treatment with aqueous HF solution and MeCN (0→25°) (→ hydroxy ketones **10m**, **b**) and subsequent acetalization and oxidation ($SO_3 \cdot$ pyridine, Et_3N, DMSO).

We now have a facile entry into these attractive benzocyclobutene derivatives that are highly oxygenated, yet selectively protected, and are, therefore, promising building blocks awaiting synthetic utilization. Indeed, starting from benzocyclobutenone **IX**, we have reported pericyclic accesses to various compounds, such as 1-arylnaphthalenes **X**, including highly *hindered* ones [14], dihydronaphthalenes **XI** [15], and also eight-membered rings **XII** [16] as illustrated in *Scheme 6*.

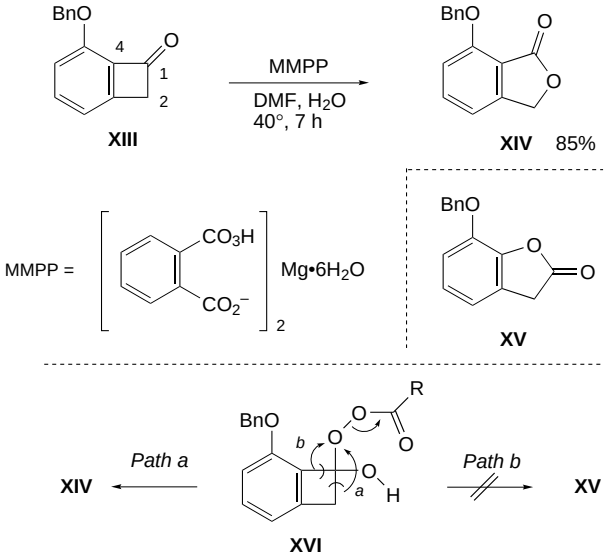
Scheme 6



Synthesis of 3-(Phenylsulfonyl)phthalides. Another synthetic utility of these selectively protected benzocyclobutene derivatives can be found in relation to the *Hauser* reaction, one of the most important annelation reactions in polyaromatic synthesis [17]. The key was our previous finding that the *Baeyer–Villiger* oxidation of benzocyclobutenones proceeds regioselectively with the O-insertion into the C(1)–C(2) bond (*Path a*) rather than the C(1)–C(4) bond (*Path b*) (see *Scheme 7*, **XIII** → **XIV**). This is remarkable in view of the general order of migratory aptitude in this class of anionotropic reaction, *aryl* > *alkyl*. This general difference in the migratory aptitudes is explained by the presence or absence of π-participation at the stage of the *Criegee* intermediate [18]. In the present *Criegee* intermediate **XVI**, however, π-participation is inhibited by the geometrical constraints imposed by the bicyclic structure [19]. Thus, the effect of hybridization becomes decisive, making the benzylic C-atom (sp^3) a better migrator rather than the aromatic C-atom (sp^2).

Although we were unsure prior to this study whether such a tendency is valid for the more-oxygenated benzocyclobutenones, it turned out to be the case. *Scheme 8* shows the facile syntheses of a pair of regioisomeric 3-(phenylsulfonyl)phthalides **19m** (and its benzyl congener **19b**) and **23m**. Thus, reduction of ketone **15m** with $NaBH_4$ followed by acid hydrolysis gave hydroxy ketone **16m** in 94% yield, which was converted to the corresponding *tert*-butyldimethylsilyl ether **17m** (^{t}BuMe$_2$SiCl, 1*H*-imidazole, DMF). Upon treatment with MMPP (magnesium monoperoxyphthalate) in the presence of Na_2HPO_4, silyloxy ketone **17m** underwent *Baeyer–Villiger* oxidation in a fully regioselective manner to give phthalide **18m**. None of the regioisomeric product, the

Scheme 7



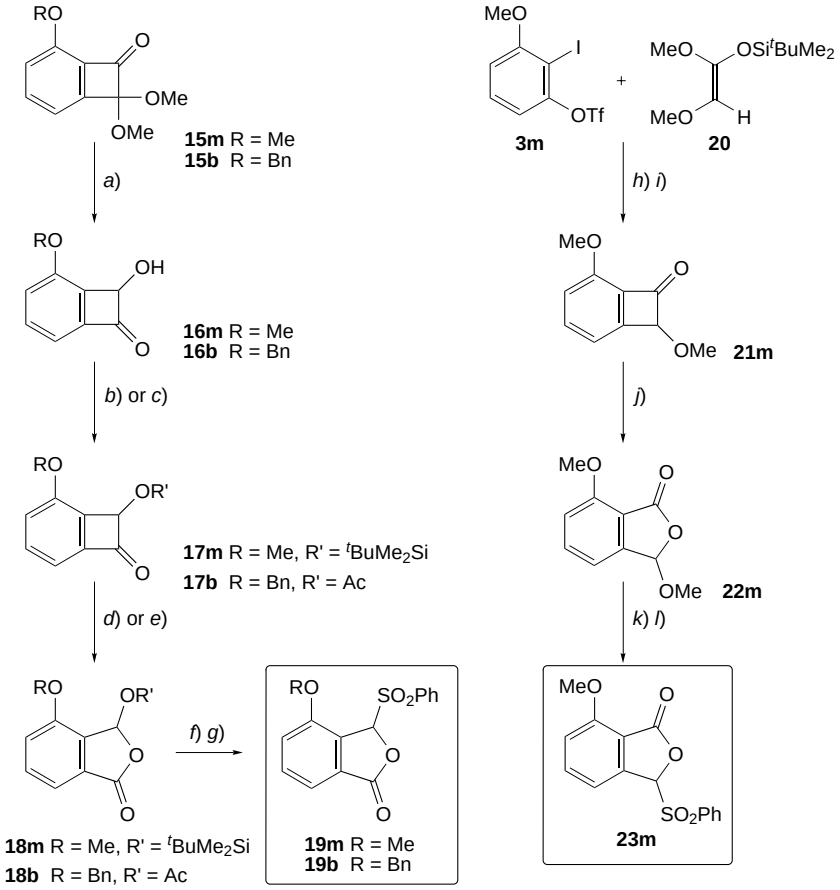
benzofuran-2(3*H*)-one, was observed. Replacement of the [(*tert*-butyl)dimethylsilyl]-oxy group in **18m** by a phenylthio group proceeded smoothly by reaction with PhSH under acidic conditions, and oxidation of the resulting sulfide with *m*CPBA afforded 3-(phenylsulfonyl)phthalide **19m** in high yield. In a similar manner, the benzyl congener **15b** was also converted to the corresponding phthalide **19b** in high overall yield. Two differences should be noted, *a*) use of an acetate protection at the stage of **17b**, and *b*) use of *m*CPBA as the oxidant for **17b**, which gave a better overall yield to phthalide **18b**.

For the synthesis of the isomeric sulfonylphthalide **23m**, benzocyclobutenone **21m** was used as the starting material, itself prepared by the cycloaddition of α-methoxybenzyne (*vide supra*) to KSA **20** followed by acid hydrolysis. *Baeyer–Villiger* oxidation of **21m** with MMPP proceeded again regioselectively, giving phthalide **22m** in 85% yield as a sole product. Treatment of **22m** with PhSH under acidic conditions, followed by oxidation of the resulting sulfide with *m*CPBA, afforded 3-(phenylsulfonyl)phthalide **23m** in high yield.

Thus, by exploiting the selective protection patterns in the isomeric benzocyclobutenedione derivatives, we have developed a facile, divergent access to regioisomeric (phenylsulfonyl)phthalides, which are versatile intermediates for the synthesis of polyaromatic compounds *via* the *Hauser* annelation reaction [17]. Indeed, these aspects were fully exploited in the first total synthesis of aquayamycin [8c], the first aryl *C*-glycoside antibiotic discovered [20][21], as outlined in *Scheme 9*. *C*-Glycosylated iodo triflate **XVII** served as the starting point to carry out the synthetic transformations discussed in this paper [8c], culminating in the long-sought target, aquayamycin (**XVIII**), with high total efficiency.

In conclusion, we have developed a facile, divergent access to highly oxygenated benzocyclobutene derivatives, *via* the [2 + 2] cycloaddition of α-alkoxybenzynes and

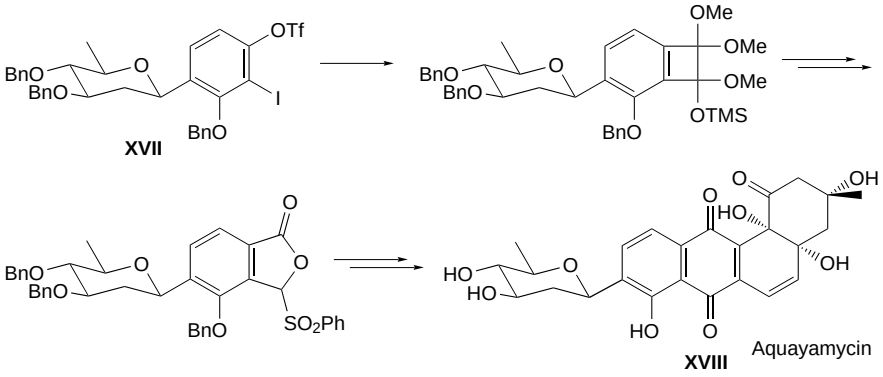
Scheme 8



a) $NaBH_4$, MeOH, 0°, then 2M aq. HCl (**16m**: 94%; **16b**: 92%). *b*) ^{t}BuMe$_2$SiCl, 1*H*-imidazole, DMF (**16m** → **17m**: 95%). *c*) Ac_2O, DMAP, pyridine (**16b** → **17b**: 99%). *d*) MMPP (see *Scheme 7*), Na_2HPO_4, DMF, H_2O, 40° (**17m** → **18m**: 83%). *e*) 3-Chloroperbenzoic acid (*m*CPBA), Na_2HPO, CH_2Cl_2 (**17b** → **18b**: 85%). *f*) PhSH, TsOH, benzene reflux. *g*) *m*CPBA, CH_2Cl_2 (**19m**: 92% 2 steps from **18m**; **19b**: 83% 2 steps from **18b**. *h*) BuLi, THF, −78° (81%). *i*) Aq. HF soln., MeCN, 25° (93%). *j*) MMPP, Na_2HPO_4, DMF, H_2O, 40° (85%). *k*) PhSH, TsOH, benzene reflux. *l*) *m*CPBA, CH_2Cl_2 (89% 2 steps from **22m**).

ketene silyl acetals. The cycloadducts and their derivatives are promising candidates for the selective synthesis of various classes of compounds, particularly those including polyaromatic systems. Although we have described only one example of applications in relation to the *Hauser* approach, various further possibilities of these compounds would be uncovered by careful polarity considerations.

Scheme 9



Experimental Part

General. Ethereal solvents were distilled from benzophenone ketyl (=oxidodiphenylmethyl) immediately before use. CH_2Cl_2 was distilled successively from P_2O_5 and CaH_2, and stored over 4-Å molecular sieves. M.p.: *Yanako MP-S3* instrument; uncorrected. Flash column chromatography (FC): silica gel *60* (Art 7734, 70–230 mesh) from *Merck*. TLC: *Merck* precoated plates, silica gel *60* F_{254} (Art 5715, 0.25 mm). Prep. TLC: *Merck* silica gel *60* PF_{254} (Art 7747). ^{1}H- and ^{13}C-NMR Spectra: *Jeol JNM-lambda-300*; or *JNM-lambda-400* spectrometer; δ in ppm, J in Hz. IR Spectra: *Perkin-Elmer 1600-FT/IR-200* spectrometer; in cm^{-1}.

2-Iodoresorcinol (**1**) [10]. To a soln. of resorcinol (=benzene-1,3-diol; 66.1 g, 0.600 mol) and I_2 (163 g, 0.642 mol) in H_2O (450 ml) was slowly added $NaHCO_3$ (56.5 g, 0.667 mmol) in portions at 0° with vigorous stirring (strong evolution of CO_2). After warming to r.t., the mixture was stirred for a further 10 min. The mixture was extracted with Et_2O (3×), and the extract dried (Na_2SO_4) and evaporated. The crude product, consisting predominantly of **1**, was triturated in $CHCl_3$ at −10° for 1 h, and filtered: pure **1** (103 g, 72.3%). White solid. M.p. 91.2–92.5° ([10]: 107–109° (H_2O)]. ^{12}C-NMR ((D_6)acetone): 6.45 (*d*, *J* = 8.1, 2 H); 6.99 (*t*, *J* = 8.1, 1 H); 8.81 (*s*, 2 H). ^{1}H-NMR ((D_6)acetone): 75.2; 106.9; 130.2; 158.6. IR (KBr): 3546, 3354, 1582, 1490, 1456, 1354, 1304, 1278, 1249, 1185, 1158, 1022, 994, 783. Anal. calc. for $C_6H_5IO_2$ (236.01): C 30.54, H 2.14; found: C 30.75, H 2.10.

2-Iodoresorcinol Bis(trifluoromethanesulfonate). To a soln. of **1** (49.3 g, 0.209 mol) in CH_2Cl_2 (300 ml) were added ^{i}Pr$_2$NEt (88 ml, 0.51 mol) and Tf_2O (82 ml, 0.49 mol) at −78°. After 10 min, the reaction was quenched with H_2O, the mixture extracted with Et_2O (2×), dried (Na_2SO_4), and evaporated, and the residue purified by FC (silica gel, hexane/AcOEt 92:8): title compound (103 g, 99.0%). Recrystallization from hexane gave a white solid. M.p. 34.3–36.2°. ^{1}H-NMR ($CDCl_3$): 7.38 (*d*, *J* = 8.3, 2 H); 7.56 (*t*, *J* = 8.3, 1 H). ^{13}C-NMR ($CDCl_3$): 87.6, 118.7 (*q*, *J*(C,F) = 320.7); 121.5; 131.0; 151.6. IR (KBr): 3101, 1573, 1447, 1426, 1220, 1141, 970, 880, 800, 758. Anal. calc. for $C_8H_3F_6IO_6S_2$ (545.11): C 19.21, H 0.60, S 12.81; found: C 19.30, H 0.36, S 12.56.

3-Hydroxy-2-iodophenyl Trifluoromethanesulfonate (**2**). To a soln. of 2-iodoresorcinol bis(trifluoromethanesulfonate) (103 g, 0.209 mol) in 1,2-dimethoxyethane (400 ml) was added Cs_2CO_3 (104 g, 0.319 mol) at r.t. The mixture was warmed to 80° and stirred further for 3 h. After cooling to r.t., the reaction was quenched with sat. aq. NH_4Cl soln. the mixture extracted with Et_2O (2×), the extract dried (Na_2SO_4) and evaporated, and the residue purified by FC (silica gel, hexane/AcOEt 7:3): **2** (82.2 g, quant.). Colorless oil. ^{1}H-NMR ($CDCl_3$): 6.45 (*s*, 1 H); 6.90 (*d*, *J* = 8.3, 1 H); 6.94 (*d*, *J* = 8.3, 1 H); 7.27 (*dd*, *J* = 8.3, 8.3, 1 H). ^{13}C-NMR ($CDCl_3$): 81.6; 113.9; 114.6; 118.6 (*q*, *J*(C,F) = 320.1); 130.6; 150.2; 157.1. IR (KBr): 3487, 1595, 1571, 1462, 1451, 1418, 1297, 1175, 1137, 1028, 975, 841, 784, 731. Anal. calc. for $C_7H_4F_3SIO_4$ (368.07): C 22.84, H 1.10, S 8.71; found: C 22.98, H 0.94, S 8.87.

2-Iodo-3-methoxyphenyl Trifluoromethanesulfonate (**3m**). To a soln. of **2** (82.1 g, 0.223 mol) in acetone (400 ml) were added dimethyl sulfate (104 g, 0.319 mol) and K_2CO_3 (63.2 g, 0.457 mmol) at 0°. After warming to r.t., the mixture was further stirred for 1 h. The inorg. material was filtered off. For removal of excess dimethyl

sulfate, Et_2NH (5.5 ml) was added at 0°, and the mixture was allowed to stand for 30 min. After addition of 2M HCl, the mixture was extracted with AcOEt (2×), the combined org. extract washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (silica gel, hexane/AcOEt 8:2): **3m** (75.0 g, 88.0%). Recrystallization from hexane gave colorless prisms. M.p. 33.2–33.8°. ^{1}H-NMR ($CDCl_3$): 3.93 (*s*, 3 H); 6.82 (*dd*, *J* = 8.3, 1.0, 1 H); 6.96 (*dd*, *J* = 8.3, 1.0, 1 H); 7.38 (*dd*, *J* = 8.3, 8.3, 1 H). ^{13}C-NMR ($CDCl_3$); 57.0; 82.7; 110.1; 114.2; 118.8 (*q*, *J*(C,F) = 320.6); 130.4; 151.3; 160.4. IR (KBr) 2960, 1590, 1470, 1425, 1290, 1270, 1230, 1210, 1130, 1060, 1020, 930, 830, 785. HR-MS: 381.8987 ($C_8H_6F_3IO_4SH^+$, M^+; 381.8984).

3-(Benzyloxy)-2-iodophenyl Trifluoromethanesulfonate (**3b**). To a soln. of **2** (64.9 g, 0.176 mol) in DMF (200 ml) were added BnBr (28 ml, 0.24 mol) and K_2CO_3 (32.5 g, 0.235 mol) at 0°. The mixture was warmed to r.t. and stirring was continued for 17 h. For removal of excess BnBr, Et_2NH (12 ml) was added at 0°, and the mixture was allowed to stand for 30 min. After addition of H_2O, the mixture was extracted with Et_2O (2×) and the combined extract washed with 2M HCl, sat. aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated. The residue, almost pure product, was recrystallized from hexane: **3b** (66.1 g, 81.8%). White solid. M.p. 84–85°. ^{1}H-NMR ($CDCl_3$): 5.18 (*s*, 2 H); 6.84 (*d*, *J* = 8.3, 1 H); 6.96 (*d*, *J* = 8.3, 1 H); 7.34 (*dd*, *J* = 8.3, 8.3, 1 H); 7.32–7.36 (*m*, 1 H); 7.38–7.43 (*m*, 2 H); 7.47–7.50 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 71.5; 83.4; 111.7; 114.4; 118.7 (*q*, *J*(C,F) = 320.6); 127.0; 128.2; 128.7; 130.3; 135.7; 151.3; 159.4. IR (KBr): 3080, 2940, 1580, 1500, 1470, 1450, 1420, 1400, 1390, 1295, 1275, 1230, 1210, 1140, 1080, 1060, 1020, 950, 850, 830, 790, 740. Anal. calc. for $C_{14}H_{10}F_3IO_4S$ (368.07): C 36.70, H 2.20, S 7.00; found: C 36.81, H 2.14, S 7.30.

Ketene Silyl Acetal **13**: *Typical Procedure* [11c]. To a soln. of tetramethylpiperidine (22.8 g, 1.61 mmol) in THF (100 ml) was slowly added 1.56M BuLi in hexane (100 ml, 156 mmol) at 0°. This mixture was stirred for 15 min and subsequently cooled to −78°. Me_3SiCl (19.2 g, 177 mmol) in THF (40 ml) was added, and then a soln. of the ester (18.0 g, 134 mmol) in THF (90 ml) was slowly added over 1.2 h. The mixture was stirred for 10 min at −78° and subsequently was allowed to reach r.t. After stirring for 1 h, the soln. was diluted with hexane (450 ml). The mixture was filtered through a *Celite* pad and the filtrate evaporated. Distillation of the residue at 70–75°/15 Torr gave **13** (19.9 g, 71.7%). ^{1}H-NMR ((D$_6$)acetone): 0.18 (*s*, 9 H); 3.46 (*s*, 3 H); 3.489 (*s*, 3 H); 3.493 (*s*, 3 H). ^{13}C-NMR ((D$_6$)acetone): 0.08; 57.2; 57.4; 58.5; 137.4; 140.2. IR (neat): 2961, 2938, 2834, 1463, 1442, 1237, 1195, 1127, 1049, 999, 955, 878, 848, 758.

8-Hydroxy-5-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**10m**). To a mixture of **3m** (6.39 g, 16.7 mmol) and ketene silyl acetal **8** (6.44 g, 23.3 mmol) in THF (60 ml) was added 1.58M BuLi in hexane (15 ml, 24 mmol) at −78°. After 10 min, the reaction was stopped by adding H_2O. Extractive workup (AcOEt) followed by evaporation gave crude cycloadduct **9m**. To a soln. of cycloadduct **9m** (9.14 g) in MeCN (60 ml) was added 46% aq. HF soln. (8.0 ml) at 0°. After warming to r.t., the mixture was further stirred for 4 h. The reaction was stopped by adding sat. aq. $NaHCO_3$ soln., the mixture extracted with AcOEt, the combined org. extract washed with brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 7:3): **10m** (1.98 g, 72.1%). Recrystallization from hexane/AcOEt gave colorless prisms. M.p. 81.6–82.5°. ^{1}H-NMR ($CDCl_3$): 3.46 (*d*, *J* = 7.3, 1 H); 4.10 (*s*, 3 H); 5.74 (*d*, *J* = 7.3, 1 H); 6.93 (*d*, *J* = 8.3, 1 H); 7.26 (*d*, *J* = 7.4, 1 H); 7.54 (*dd*, *J* = 7.4, 8.3, 1 H). ^{13}C-NMR ($CDCl_3$): 59.8; 85.1; 115.1; 117.8; 131.7; 138.6; 154.6; 156.4; 187.2. IR (KBr): 3280, 3170, 1771, 1610, 1568, 1484, 1436, 1322, 1284, 1194, 1161, 1124, 943, 812, 778. Anal. calc. for $C_9H_8O_3$ (164.16): C 65.58, H 4.90; found: C 65.72, H 4.88.

2,8,8-Trimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-ol (**11m**). To a soln. of **10m** (545 mg, 3.32 mmol) in MeOH (34 ml) were added trimethyl orthoformate (3.5 ml, 32 mmol) and $TsOH \cdot H_2O$ (63 mg, 0.33 mmol) at r.t. After 4 h, the reaction was quenched with sat. aq. $NaHCO_3$, soln., the mixture extracted with Et_2O (3×), dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 7:3): **11m** (657 mg, 94.1%). Recrystallization from hexane/Et_2O gave colorless prisms. M.p. 72.0–72.5°. ^{1}H-NMR ((D$_6$)acetone): 3.39 (*s*, 3 H); 3.48 (*s*, 3 H); 3.84 (*s*, 3 H); 4.31 (*d*, *J* = 10.0, 1 H); 5.01 (*d*, *J* = 10.0, 1 H); 6.90 (*d*, *J* = 8.3, 1 H); 6.92 (*d*, *J* = 7.3, 1 H); 7.34 (*dd*, *J* = 7.3, 8.3, 1 H). ^{13}C-NMR ((D$_6$)acetone): 52.1; 52.2; 56.0; 78.9; 108.2; 112.6; 116.2; 131.6; 132.9; 148.9; 154.7. IR (neat): 3426, 2976, 2946, 2839, 1603, 1486, 1464, 1439, 1414, 1344, 1271, 1234, 1172, 1103, 1068, 1043, 1025, 1002, 919, 799, 764, 742, 708. Anal. calc. for $C_{11}H_{14}O_4$ (210.23): C 62.84, H 6.71; found: C 62.82, H 6.82.

2,8,8-Trimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**12m**). To a soln. of **11m** (1.07 g, 5.09 mmol) in DMSO (11.0 ml) were added $SO_3 \cdot$pyridine (2.03 g, 12.7 mmol) and Et_3N (3.6 ml, 26 mmol) at r.t., and further stirred for 2 h. The reaction was quenched with H_2O, and the mixture extracted with Et_2O (3×), dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 94:6): **12m** (977 mg, 92.2%). Recrystallization from hexane/Et_2O gave colorless prisms. M.p. 33.2–33.8°. ^{1}H-NMR ($CDCl_3$): 3.58 (*s*, 6 H); 3.98 (*s*, 3 H); 7.06 (*d*, *J* = 8.1, 1 H); 7.16 (*d*, *J* = 7.6, 1 H); 7.53 (*dd*, *J* = 7.6, 8.1, 1 H). ^{13}C-NMR ($CDCl_3$): 53.6; 56.7; 113.3; 117.0;

119.0; 133.9; 145.6; 149.5; 155.4; 191.5. IR (KBr): 2974, 2943, 1771, 1594, 1506, 1489, 1457, 1350, 1272, 1232, 1053, 1018, 948, 904, 826, 808, 756, 715. Anal. calc. for $C_{11}H_{12}O_4$ (208.21): C 63.45, H 5.81; found: C 63.61, H 5.62.

5-(Benzyloxy)-8-hydroxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**10b**). To a mixture of **3b** (27.8 g, 60.7 mmol) and ketene silyl acetal **8** (21.8 g, 78.8 mmol) in THF (70 ml) was slowly added 1.57M BuLi in hexane (46.5 ml, 73 mmol) at $-78°$ over 40 min. After 20 min, the reaction was stopped by adding pH 7 phosphate buffer. Extractive workup (Et_2O) followed by evaporation gave crude cycloadduct **9b**. To a soln. of this material in MeCN (200 ml) was added 46% aq. HF soln. (13 ml) at 0°. After warming to r.t., the mixture was further stirred for 12 h. After dilution with H_2O, the mixture was extracted with Et_2O, the combined org. extract washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 8:2 → 7:3): **10b** (11.0 g, 75.5%). Recrystallization from hexane/Et_2O gave colorless prisms. M.p. 75–78°. ^{1}H-NMR ($CDCl_3$): 1.76–1.78 (*m*, 1 H); 3.36–3.48 (*m*, 1 H); 5.35 (*d*, *J* = 12.2, 1 H); 5.49 (*d*, *J* = 12.2, 1 H); 7.01 (*d*, *J* = 8.3, 1 H); 7.26 (*d*, *J* = 7.0, 1 H); 7.29–7.45 (*m*, 5 H); 7.54 (*dd*, *J* = 7.0, 8.3, 1 H). ^{13}C-NMR ($CDCl_3$): 74.0; 85.0; 115.3; 118.5; 127.8; 128.3; 128.5; 131.9; 136.1; 138.7; 153.4; 156.3; 187.3. IR (KBr): 3372, 1744, 1604, 1567, 1471, 1270, 1131, 756, 702. Anal. calc. for $C_{15}H_{12}O_3$ (240.26): C 74.99, H 5.03; found: C 75.02, H 5.13.

2-(Benzyloxy)-8,8-dimethoxybicyclo[4.2.0]-1,3,5-trien-7-ol (**11b**). To a soln. of **11b** (11.0 g, 7.76 mmol) in MeOH (500 ml) were added trimethyl orthoformate (90 ml) and $TsOH \cdot H_2O$ (880 mg, 4.63 mmol) at r.t. After 6 h, the reaction was quenched with sat. aq. $NaHCO_3$, soln. the mixture extracted with Et_2O (4×), dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 8:2 → 7:3): **11b** (12.1 g, 92.0%). Recrystallization from hexane/Et_2O gave colorless prisms. M.p. 72.0–72.5°. ^{1}H-NMR ($CDCl_3$): 2.87 (*d*, *J* = 10.5, 1 H); 3.49 (*s*, 3 H); 3.63 (*s*, 3 H); 5.14 (*d*, *J* = 10.5, 1 H); 5.15 (*d*, *J* = 12.2, 1 H); 5.20 (*d*, *J* = 12.2, 1 H); 6.85 (*d*, *J* = 8.5, 1 H); 7.02 (*d*, *J* = 7.3, 1 H); 7.29–7.42 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$): 52.2; 52.7; 70.4; 76.9; 106.5; 113.4; 116.1; 127.1; 127.9; 128.5; 130.7; 132.4; 136.7; 147.7; 152.7. IR (KBr): 3424, 2941, 1604, 1482, 1454, 1384, 1343, 1273, 1243, 1070, 1028, 763. Anal. calc. for $C_{17}H_{18}O_4$ (286.33): C 71.31, H 7.34; found: C 71.47, H 6.63.

2-(Benzyloxy)-8,8-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**12b**). To a soln. of **11b** (12.1 g, 42.3 mmol) in DMSO (110 ml) were added $SO_3 \cdot$pyridine (16.2 g, 102 mmol) and Et_3N (31 ml, 224 mmol) at r.t., and the mixture was further stirred for 1 h. The reaction was quenched with ice water, the mixture extracted with Et_2O (3×), dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 9:1): **12b** (11.7 g, 97.4%). Recrystallization from hexane/Et_2O gave colorless prisms. M.p. 53–56°. ^{1}H-NMR ($CDCl_3$): 3.58 (*s*, 6 H); 5.26 (*s*, 2 H); 7.10 (*d*, *J* = 8.1, 1 H); 7.17 (*d*, *J* = 7.6, 1 H); 7.32–7.48 (*m*, 5 H); 7.50 (*dd*, *J* = 7.6, 8.1, 1 H). ^{13}C-NMR ($CDCl_3$): 53.7; 71.6; 113.7; 117.1; 120.7; 127.5; 128.2; 128.6; 133.9; 136.1; 145.8; 149.6; 154.6; 191.8. IR (KBr): 1766, 1596, 1484, 1277, 1232, 1093, 955, 754, 701. Anal. calc. for $C_{17}H_{16}O_4$ (284.31): C 71.82, H 5.67; found: C 72.12, H 5.92.

5,8,8-Trimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**15m**). To a mixture of **3m** (12.9 g, 33.7 mmol) and ketene silyl acetal **13** (8.34 g, 40.4 mmol) in Et_2O (100 ml) was slowly added 1.56M BuLi in hexane (28 ml, 44 mmol) at $-78°$ over 1 h. After 10 min, the reaction was quenched with pH-7 phosphate buffer. Extractive workup (Et_2O) followed by evaporation gave crude cycloadduct **14m**. To a soln. of this material in MeCN (120 ml) were added sat. aq. KF soln. (4.2 ml) and Bu_4NCl (0.94 g, 3.37 mmol) at r.t. After 24 h, the reaction was stopped by adding sat. aq. $NaHCO_3$ soln. the mixture extracted with Et_2O (3×), dried (Na_2SO_4), and evaporated, and the residue purified by FC (silica gel, hexane/AcOEt 9:1): **15m** (4.95 g, 70.5%). Recrystallization from hexane gave colorless prisms. M.p. 39.2–39.5°. ^{1}H-NMR ($CDCl_3$): 3.59 (*s*, 6 H); 4.14 (*s*, 3 H); 6.97 (*d*, *J* = 8.3, 1 H); 7.23 (*d*, *J* = 7.3, 1 H); 7.53 (*d*, *J* = 7.3, 8.3, 1 H). ^{13}C-NMR ($CDCl_3$): 52.6; 59.9; 113.8; 114.9; 118.5; 132.9; 138.1; 155.3; 157.8; 185.8. IR (KBr): 2950, 2840, 1755, 1600, 1565, 1485, 1440, 1360, 1270, 1250, 1125, 1070, 1040, 1015, 980, 890, 800. Anal. calc. for $C_{11}H_{12}O_4$ (208.21): C 63.45, H 5.81; found: C 63.40, H 5.77.

5-(Benzyloxy)-8,8-dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**15b**). To a mixture of **3b** (20.8 g, 45.4 mmol) and ketene silyl acetal **13** (14.5 g, 70.2 mmol) in Et_2O (170 ml) was slowly added 1.54M BuLi in hexane (34.1 ml, 52.5 mmol) at $-78°$ over 30 min. After 10 min, the reaction was quenched by adding pH-7 phosphate buffer. Extractive workup (Et_2O) followed by evaporation gave crude cycloadduct **14b**. To a soln. of this material in MeCN (180 ml) were added Bu_4NCl (608 mg, 2.19 mmol) and sat. aq. KF soln. (5.5 ml, 87 mmol) at 0°. The mixture was stirred at r.t. for 1.5 h, and sat. aq. $NaHCO_3$ soln. was poured into this mixture at 0°. MeCN was removed by azeotropic distillation with benzene. The mixture was extracted with Et_2O (3×), the combined extract washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 95:5 → 93:7 → 91:9): **15b** (10.3 g, 79.8%). Recrystallization from hexane gave colorless needles. M.p. 53.5–54.0°. ^{1}H-NMR ($CDCl_3$): 3.59 (*s*, 6 H); 5.47 (*s*, 2 H); 7.05 (*d*, *J* = 8.3, 1 H); 7.24 (*d*, *J* = 6.9, 1 H); 7.30–7.57 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$): 52.6; 74.3; 114.0; 114.8; 119.1; 127.9; 128.3; 128.5; 133.0; 136.0; 138.2; 154.0; 157.7; 185.9. IR (KBr): 2940, 2850, 1765, 1600, 1565, 1450, 1415, 1390, 1355,

1260, 1205, 1130, 1055, 1015, 970, 840, 810, 760. Anal. calc. for $C_{17}H_{16}O_4$ (284.31): C 71.81, H 5.67; found: C 71.70, H 5.79.

5,8-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**21m**). To a mixture of **3m** (1.21 g, 3.17 mmol) and ketene silyl acetal **20** (972 mg, 4.45 mmol) in THF (10 ml) was added 1.60M BuLi in hexane (4.0 ml, 6.4 mmol) at −78°. After 10 min, the reaction was stopped by adding pH-7 phosphate buffer. The mixture was extracted with Et_2O and the combined org. extract washed successively with brine, dried (Na_2SO_4), and evaporated. The residue was purified by FC (hexane/Et_2O 96:4): cycloadduct (838 mg, 81.4%). Colorless oil. ^{1}H-NMR ($CDCl_3$): −0.14 (*s*, 3 H); 0.04 (*s*, 3 H); 0.94 (*s*, 9 H); 3.51 (*s*, 3 H); 3.56 (*s*, 3 H); 3.86 (*s*, 3 H); 4.73 (*s*, 1 H); 6.84 (*d*, *J* = 8.3, 1 H); 6.96 (*d*, *J* = 6.8, 1 H); 7.32 (*dd*, *J* = 6.8, 8.3, 1 H). ^{13}C-NMR ($CDCl_3$): −4.5; −4.0; 18.5; 25.9; 52.2; 55.5; 57.8; 86.8; 104.9; 112.3; 116.1; 132.1; 132.5; 144.6; 153.4. IR (neat): 3090, 2970, 2950, 2900, 2860, 2850, 1620, 1500, 1480, 1460, 1455, 1420, 1380, 1360, 1290, 1265, 1230, 1180, 1155, 1135, 1100, 1085, 1070, 1030, 990, 970, 935, 890, 860, 830, 820, 800, 785, 770, 745, 710. HR-MS: 323.1677 ($C_{17}H_{28}O_8Si^+$, M^+; calc. 323.1677).

To a soln. of the cycloadduct (161 mg, 0.496 mmol) in MeCN (1.6 ml) was added 46% aq. HF soln. (0.3 ml, 6 mmol) at 0°. After warming to r.t., the mixture was further stirred for 1 h. The reaction was stopped by adding sat. aq. $NaHCO_3$ soln., the mixture extracted with AcOEt the combined org. extract washed successively with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated, and the residue purified by prep. TLC (hexane/AcOEt 7:3): **21m** (82.6 mg, 93.1%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 3.55 (*s*, 3 H); 4.13 (*s*, 3 H); 5.52 (*s*, 1 H); 6.94 (*d*, *J* = 8.3, 1 H); 7.24 (*d*, *J* = 6.8, 1 H); 7.52 (*dd*, *J* = 6.8, 8.3, 1 H). ^{13}C-NMR ($CDCl_3$): 56.8; 59.8; 92.0; 115.5; 117.8; 132.4; 138.1; 154.3; 155.1; 186.1. IR (neat): 3525, 3050, 3000, 2950, 2825, 1765, 1605, 1580, 1500, 1450, 1430, 1380, 1295, 1220, 1080, 1135, 1070, 1020, 970, 940, 835, 820, 800, 745. HR-MS: 178.0626 ($C_{10}H_{10}O_3^+$, M^+; calc. 178.0628).

*3,7-Dimethoxyisobenzofuran-1(3*H*)-one* (**22m**). To a soln. of **21m** (76.7 mg, 0.430 mmol) in DMF (3.0 ml) and H_2O (0.5 ml) were added $Na_2HPO_4 \cdot 12\,H_2O$ (369 mg, 1.03 mmol) and MMPP (*ca.* 80% purity; 441 mg, 0.71 mmol) at r.t. After warming to 40°, the mixture was further stirred for 3 h. The reaction was stopped by adding 10% aq. $Na_2S_2O_3$ soln., the mixture extracted with Et_2O (3×), dried (Na_2SO_4), and evaporated, and the residue purified by prep. TLC (hexane/AcOEt 5:5): **22m** (71.0 mg, 84.9%). Recrystallization from hexane/AcOEt gave colorless needles. M.p. 62.3–63.1°. ^{1}H-NMR ($CDCl_3$): 3.60 (*s*, 3 H); 4.00 (*s*, 3 H); 6.21 (*s*, 1 H); 7.02 (*d*, *J* = 8.3, 1 H); 7.12 (*d*, *J* = 7.8, 1 H); 7.66 (*dd*, *J* = 7.8, 8.3, 1 H). ^{13}C-NMR ($CDCl_3$): 56.1; 56.3; 101.7; 112.6; 114.2; 115.0; 136.7; 147.2; 158.3; 166.5. IR (KBr): 3050, 2950, 2875, 1785, 1620, 1500, 1465, 1450, 1390, 1360, 1325, 1300, 1255, 1200, 1135, 1080, 1070, 1040, 995, 970, 945, 880, 840, 805, 780, 700. Anal. calc. for $C_{10}H_{10}O_4$ (194.19): C 61.80, H 5.20; found: C 61.85, H 5.19.

*7-Methoxy-3-(phenylthio)isobenzofuran-1(3*H*)-one.* To a soln. of **22m** (27.1 mg, 0.140 mmol) in benzene (3.0 ml) were added benzenethiol (120 mg, 1.09 mmol) and $TsOH \cdot H_2O$ (108 mg, 0.568 mmol) at r.t. The soln. was heated under reflux in a *Dean–Stark* apparatus for 2 h. The cooled mixture was successively washed with 1M NaOH and brine, dried (Na_2SO_4), and evaporated, and the residue purified by prep. TLC (hexane/AcOEt 5:5): title compound (35.2 mg, 92.6%). White powder. ^{1}H-NMR ((D$_6$)acetone): 3.91 (*s*, 3 H); 6.90 (*s*, 1 H); 7.10 (*d*, *J* = 8.8, 1 H); 7.26 (*d*, *J* = 7.8, 1 H); 7.30–7.76 (*m*, 6 H). ^{13}C-NMR ((D$_6$)acetone): 56.4; 85.3; 112.9; 114.3; 116.0; 129.5; 129.9; 131.7; 134.0; 137.4; 149.8; 159.3; 166.6. IR (KBr): 3075, 3000, 2850, 1780, 1605, 1500, 1440, 1300, 1255, 1215, 1195, 1095, 1070, 1020, 970, 835, 780, 745. HR-MS: 272.0496 ($C_{15}H_{12}O_3S^+$, M^+; calc. 272.0505).

*7-Methoxy-3-(phenylsulfonyl)isobenzofuran-1(3*H*)-one* (**23m**). To a soln. of 7-methoxy-3-(phenylthio)-isobenzofuran-1(3*H*)-one (132 mg, 0.483 mmol) in CH_2Cl_2 (2.0 ml) was added *m*CPBA (*ca.* 80% (*w*/*w*); 302 mg, 1.2 mmol) at r.t. After 1 h, the solid 3-chlorobenzoic acid was removed by filtration, the filtrate was washed with 10% aq. $Na_2S_2O_3$ soln., sat. aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 5:5): **23m** (136 mg, 92.6%). Recrystallization from hexane/acetone gave colorless prisms. M.p. 187.7–188.0°. ^{1}H-NMR ($CDCl_3$): 3.96 (*s*, 3 H); 6.10 (*s*, 1 H); 7.05 (*d*, *J* = 8.3, 1 H); 7.50–7.87 (*m*, 7 H). ^{13}C-NMR ($CDCl_3$): 56.2; 89.8; 113.2; 113.3; 116.5; 129.2; 129.7; 134.6; 134.9; 137.1; 141.6; 158.7; 165.4. IR (KBr): 3200, 2875, 1790, 1600, 1495, 1465, 1450, 1335, 1300, 1245, 1210, 1195, 1160, 1090, 1075, 1040, 1000, 950, 825, 785, 775, 755, 730. HR-MS: 304.0388 ($C_{15}H_{12}O_5S$, M^+; calc. 304.0404).

8-Hydroxy-2-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**16m**). To a soln. of $NaBH_4$ (116 mg, 3.07 mmol) in MeOH (1 ml) was added ketone **15m** (382 mg, 1.83 mmol) in MeOH (5.0 ml) at 0°. After the consumption of **15m** (TLC monitoring), 4M HCl (2.2 ml) was added to the mixture at 0°. After 20 min, the mixture was neutralized with sat. aq. $NaHCO_3$ soln., and extracted with AcOEt, the combined org. extract washed successively with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 7:3): **16m** (281 mg, 93.3%). Recrystallization from hexane/Et_2O gave colorless prisms. M.p. 83.0–83.6°. ^{1}H-NMR ($CDCl_3$): 4.00 (*d*, *J* = 7.8, 1 H); 4.05 (*s*, 3 H); 5.87 (*d*, *J* = 7.8, 1 H); 7.05 (*d*, *J* = 7.8, 1 H); 7.07 (*d*, *J* = 7.8, 1 H); 7.47 (*dd*, *J* = 7.8, 7.8, 1 H). ^{13}C-NMR ($CDCl_3$): 57.3; 85.6; 113.5; 121.8; 133.4; 141.4; 148.8;

156.6; 191.7. IR (KBr): 3400, 3100, 3000, 2960, 2860, 1745, 1605, 1590, 1500, 1445, 1350, 1270, 1245, 1180, 1165, 1095, 1060, 1050, 985, 900, 840, 815, 780, 735. Anal. calc. for $C_9H_8O_3$ (164.16): C 65.58, H 4.90; found: C 65.85, H 4.91.

*8-{[(*tert*-Butyl)dimethylsilyl]oxy}-2-methoxybicyclo[4.2.0]octa-1,3,5-trien-7-one* (**17m**). To a soln. of **16m** (102 mg, 0.621 mmol) in DMF (4 ml) were added ^{t}BuMe$_2$SiCl (357 mg, 1.30 mmol) and 1*H*-imidazole (123 mg, 1.81 mmol) at 0°. After 40 min, the reaction was stopped by pouring the mixture into pH-7 phosphate buffer at 0°. The mixture was extracted with Et_2O, the combined org. extract washed with brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 9:1): **17m** (165 mg, 95.4%). Colorless oil. ^{1}H-NMR ($CDCl_3$): 0.20 (*s*, 3 H); 0.21 (*s*, 3 H); 0.94 (*s*, 9 H); 4.01 (*s*, 3 H); 5.85 (*s*, 1 H); 7.02 (*d*, *J* = 7.8, 1 H); 7.06 (*d*, *J* = 7.3, 1 H); 7.44 (*dd*, *J* = 7.3, 7.8, 1 H). ^{13}C-NMR ($CDCl_3$): −5.0; −4.4; 18.2; 25.7; 57.2; 86.0; 113.3; 121.2; 133.0; 142.2; 148.8; 156.6; 190.7. IR (neat): 2950, 2900, 2870, 1775, 1605, 1580, 1490, 1465, 1440, 1415, 1395, 1355, 1275, 1235, 1195, 1170, 1110, 1060, 1040, 1010, 985, 945, 875, 845, 810, 790. HR-MS: 278.1341 ($C_{15}H_{22}O_3Si^+$, M^+; calc. 278.1337).

*3-{[(*tert*-Butyl)dimethylsilyl]oxy}-4-methoxyisobenzofuran-1(3*H*)-one* (**18m**). To a soln. of **17m** (48.1 mg, 0.173 mmol) in DMF (1.2 ml) and H_2O (0.5 ml) were added $Na_2HPO_4 \cdot 12H_2O$ (185 mg, 0.517 mmol) and MMPP (*ca.* 80% purity; 128 mg, 0.21 mmol) at r.t. After 15 min, the reaction was stopped by pouring the mixture into pH-7 phosphate buffer at 0°. The mixture was extracted with Et_2O, the combined org. extract washed successively with sat. aq. $Na_2S_2O_3$ soln., sat. aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated, and the residue purified by prep. TLC (hexane/AcOEt 8:2): **18m** (42.1 mg, 82.8%). Recrystallization from hexane gave colorless prisms. M.p. 75.4–76.2°. ^{1}H-NMR ($CDCl_3$): 0.20 (*s*, 3 H); 0.26 (*s*, 3 H); 0.96 (*s*, 9 H); 3.91 (*s*, 3 H); 6.63 (*s*, 1 H); 7.11 (*d*, *J* = 8.3, 1 H); 7.43 (*d*, *J* = 7.3, 1 H); 7.51 (*dd*, *J* = 7.3, 8.3, 1 H). ^{13}C-NMR ($CDCl_3$): −5.2; −4.5; 18.1; 25.4; 55.5; 96.7; 115.9; 116.9; 128.7; 132.3; 135.1; 155.2; 168.9. IR (KBr): 2940, 2860, 1790, 1775, 1620, 1500, 1470, 1390, 1360, 1315, 1290, 1280, 1260, 1215, 1190, 1125, 1055, 1010, 965, 905, 860, 845, 815, 790, 755, 710. Anal. calc. for $C_{15}H_{22}O_4Si$ (294.42): C 61.19, H 7.53; found: C 61.06, H 7.60.

*4-Methoxy-3-(phenylthio)-isobenzofuran-1(3*H*)-one.* To a soln. of **18m** (104 mg, 0.354 mmol) in benzene (3.5 ml) were added benzenethiol (202 mg, 1.84 mmol) and $TsOH \cdot H_2O$ (90.1 mg, 0.474 mmol) at r.t., and the soln. was heated under reflux in a *Dean–Stark* apparatus. After 40 min, the soln. was cooled to r.t., and diluted with Et_2O (15 ml). The org. phase was washed with 1M NaOH, dried (Na_2SO_4), and evaporated. Purification by prep. TLC (hexane/AcOEt 6:4) gave the title compound (93.9 mg, 97.6%). Recrystallization from hexane gave colorless needles. M.p. 88.2–88.5°. ^{1}H-NMR ($CDCl_3$): 4.00 (*s*, 3 H); 6.66 (*s*, 1 H); 7.10 (*d*, *J* = 7.8, 1 H); 7.19–7.28 (*m*, 3 H); 7.32 (*d*, *J* = 7.3, 1 H); 7.41–7.47 (*m*, 3 H). ^{13}C-NMR ($CDCl_3$): 55.9; 84.8; 115.7; 117.0; 128.1; 128.9; 128.9; 130.0; 131.9; 133.4; 134.4; 154.3; 169.0. IR (KBr): 3070, 3010, 2950, 2850, 1780, 1610, 1495, 1470, 1440, 1350, 1275, 1230, 1180, 1090, 1065, 1035, 970, 905, 880, 825, 780, 770, 755, 740. Anal. calc. for $C_{15}H_{12}O_3S$ (272.32): C 66.16, H 4.44; found: C 65.95, H 4.59.

*4-Methoxy-3-(phenylsulfonyl)isobenzofuran-1(3*H*)-one* (**19m**). To a soln. of 4-methoxy-1(3*H*)-isobenzofuran-3-(phenylthio)-one (159 mg, 0.585 mmol) in CH_2Cl_2 (5.0 ml) was added *m*CPBA (*ca.* 80% (*w*/*w*); 372 mg, *ca.* 1.5 mmol) at r.t. After 1.5 h, the reaction was stopped by adding 10% aq. $Na_2S_2O_3$ soln. The mixture was extracted with AcOEt, the combined org. extract washed successively with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 5:5): **19m** (168 mg, 94.5%). Recrystallization from AcOEt gave colorless prisms. M.p. 185.1–185.3°. ^{1}H-NMR ($CDCl_3$): 3.99 (*s*, 3 H); 6.31 (*s*, 1 H); 7.24 (*d*, *J* = 8.3, 1 H); 7.42 (*d*, *J* = 7.3, 1 H); 7.51–7.56 (*m*, 2 H); 7.59 (*dd*, *J* = 7.3, 8.3, 1 H); 7.65–7.70 (*m*, 1 H); 7.86–7.89 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$): 56.4; 90.2; 117.0; 117.7; 127.0; 128.3; 129.2; 129.8; 133.5; 134.7; 135.4; 156.0; 167.6. IR (KBr): 3100, 2990, 2890, 1800, 1620, 1590, 1505, 1470, 1450, 1345, 1330, 1305, 1290, 1185, 1170, 1100, 1090, 1040, 1020, 925, 835, 800, 775, 760, 740. HR-MS: 304.0380 ($C_{15}H_{12}O_5S^+$, M^+; calc. 304.0404).

2-(Benzyloxy)-8-hydroxybicyclo[4.2.0]octa-1,3,5-trien-7-one (**16b**). To a soln. of $NaBH_4$ (3.06 g, 72.6 mmol) in MeOH (60 ml) was added **15b** (10.3 g, 36.2 mmol) in THF (60 ml) at −78° over 20 min. The mixture was warmed to 0° over 75 min, and stirring was continued for 20 min. After the consumption of **15b** (TLC monitoring), 4M HCl (90 ml) was added at 0°, and the mixture was warmed to r.t. After 30 min. sat. aq. $NaHCO_3$ soln. was poured into this mixture at 0°. After MeOH was removed by azeotropic distillation with benzene, the mixture was extracted with AcOEt (3×), the combined extract washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 76:24): **16b** (8.03 g, 92.3%). Recrystallization from hexane/AcOEt gave white needles. M.p. 94–95°. ^{1}H-NMR ($CDCl_3$): 4.03–4.12 (*m*, 1 H); 5.40 (*d*, *J* = 12.2, 1 H); 5.49 (*d*, *J* = 12.2, 1 H); 5.76 (*d*, *J* = 7.6, 1 H); 7.06 (*d*, *J* = 7.6, 1 H); 7.13 (*d*, *J* = 8.3, 1 H); 7.31–7.48 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$): 71.6; 85.7; 113.8; 122.9; 127.2; 128.2; 128.7; 133.4; 136.6; 141.3; 148.7; 155.7; 191.5. IR (KBr): 3346, 3095, 3059, 2923, 1769, 1604, 1568, 1483, 1448, 1384, 1346, 1264, 1231, 1142, 1041, 1028. Anal. calc. for $C_{15}H_{12}O_3$ (240.26): C 74.98, H 5.04; found: C 74.76, H 5.26.

8-(Acetoxy)-2-(benzyloxy)bicyclo[4.2.0]octa-1,3,5-trien-7-one (**17b**). To a soln. of **16b** (8.03 g, 33.5 mmol) in pyridine (25 ml) were added Ac_2O (6.2 ml, 65.6 mmol) and a cat. amount of DMAP (204 mg, 1.68 mmol) at 0°. After the mixture was stirred for 15 min, the reaction was quenched by adding a small amount of H_2O. The soln. was diluted with AcOEt, the org. layer washed with sat. aq. $CuSO_4$ soln. and sat. aq. Na_2SO_4 soln., dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 8:2 → 75:25): **17b** (9.38 g, 99.3%). Colorless oil (solidified in a refrigerator as a white solid). M.p. 43–45°. ^{1}H-NMR ($CDCl_3$): 2.14 (*s*, 3 H); 5.19 (*s*, 2 H); 6.77 (*s*, 1 H); 7.14 (*d*, *J* = 7.9, 1 H); 7.17 (*d*, *J* = 7.9, 1 H); 7.32–7.41 (*m*, 5 H); 7.52 (*dd*, *J* = 7.9, 7.9, 1 H). ^{13}C-NMR ($CDCl_3$): 20.7; 71.0; 84.2; 113.8; 122.2; 127.0; 128.2; 128.7; 133.9; 135.9; 137.8; 150.1; 155.2; 169.4; 185.3. IR (neat): 2940, 1770, 1735, 1600, 1480, 1210, 1025. Anal. calc. for $C_{17}H_{14}O_4$ (282.30): C 72.33, H 5.00; found: C 72.06, H 5.28.

*3-Acetoxy-4-(benzyloxy)isobenzofuran-1(3*H*)-one* (**18b**). To a suspension of *m*CPBA (*ca.* 80% (*w*/*w*); 3.91 g, 18.1 mmol) and $Na_2HPO_4 \cdot 12\,H_2O$ (8.34 g, 22.7 mmol) in CH_2Cl_2 (17 ml) was added **17b** (4.26 g, 15.1 mmol) in CH_2Cl_2 (30 ml) at 0°. After the mixture was stirred for 10 min, 10% aq. $Na_2S_2O_3$ soln. was added. The mixture was stirred for 10 min and then diluted with AcOEt. Sat. aq. $NaHCO_3$ soln. was added, the mixture extracted with AcOEt (3×), the combined extract washed with 10% aq. $Na_2S_2O_3$ soln., sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 8:2): **18b** (3.81 g, 84.6%). Recrystallization from hexane/AcOEt gave white needles. M.p. 126.5–127.5°. ^{1}H-NMR ($CDCl_3$): 2.13 (*s*, 3 H); 5.21 (*s*, 2 H); 7.20 (*d*, *J* = 8.1, 1 H); 7.34–7.42 (*m*, 5 H); 7.49–7.59 (*m*, 3 H). ^{13}C-NMR ($CDCl_3$): 20.6; 70.3; 91.0; 117.50; 117.54; 126.9; 128.3; 128.4; 128.7; 131.9; 133.2; 135.6; 154.1; 167.9; 169.0. IR (KBr): 2945, 1884, 1790, 1758, 1616, 1490, 1393, 1283, 1221, 1052, 1016. Anal. calc. for $C_{17}H_{14}O_5$ (298.30): C 68.45, H 4.73; found: C 68.51, H 4.65.

*4-(Benzyloxy)-3-(phenylthio)isobenzofuran-1(3*H*)-one.* A soln. of **18b** (3.72 g, 12.5 mmol), benzenethiol (6.4 ml, 62 mmol), and $TsOH \cdot H_2O$ (387 mg, 2.03 mmol) in benzene (100 ml) was refluxed for 2.2 h in a *Dean–Stark* apparatus. To this mixture was added $TsOH \cdot H_2O$ (600 mg, 3.15 mmol), and the reaction was completed by stirring for another 50 min under reflux. The soln. was cooled to 0°, diluted with Et_2O, washed with 0.5M NaOH and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 8:2): title compound (3.87 g, 89.1%). Recrystallization from hexane/AcOEt gave white needles. M.p. 92.5–93.5°. ^{1}H-NMR ($CDCl_3$): 5.24 (*d*, *J* = 12.2, 1 H); 5.30 (*d*, *J* = 12.2, 1 H); 6.69 (*s*, 1 H); 7.15–7.58 (*m*, 13 H). ^{13}C-NMR ($CDCl_3$): 70.4; 85.2; 117.0; 117.2; 127.2; 128.3; 128.3; 128.7; 128.87; 128.90; 130.2; 131.9; 133.8; 134.4; 135.9; 153.2; 169.0. IR (KBr): 3089, 3084, 3025, 2899, 2857, 1760, 1613, 1498, 1466, 1295, 1275, 1089, 1039. Anal. calc. for $C_{21}H_{16}O_3S$ (348.42): C 72.39, H 4.63, S 9.20; found: C 72.14, H 4.84, S 9.09.

*4-(Benzyloxy)-3-(phenylsulfonyl)isobenzofuran-1(3*H*)-one* (**19b**). To a soln. of 4-(benzyloxy)-3-(phenylthio)isobenzofuran-1(3*H*)-one (3.72 g, 10.7 mmol) in CH_2Cl_2 (70 ml), *m*CPBA (*ca.* 80% (*w*/*w*); 6.22 g, 28.9 mmol) was slowly added at 0°. The mixture was stirred for 1 h at r.t., and 10% aq. $Na_2S_2O_3$ soln. was added at 0°. After the mixture was stirred for 5 min and diluted with AcOEt, sat. aq. $NaHCO_3$ soln. was added, the mixture extracted with AcOEt (3×), the combined extract washed with 10% aq. $Na_2S_2O_3$ soln., sat. aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated, and the residue purified by FC (hexane/AcOEt 7:3 → 6:4): **19b** (3.77 g, 92.8%). Recrystallization from hexane/AcOEt gave a white solid. M.p. 131–132°. ^{1}H-NMR ($CDCl_3$): 5.26 (*d*, *J* = 12.2, 1 H); 5.34 (*d*, *J* = 12.2, 1 H); 6.34 (*s*, 1 H); 7.26 (*d*, *J* = 8.3, 1 H); 7.85–7.90 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 70.9; 90.2; 117.8; 118.2; 127.3; 128.3; 128.7; 129.1; 129.8; 133.4; 134.7; 135.2; 135.6; 155.0; 167.5. IR (KBr): 2965, 1780, 1610, 1500, 1335, 1145, 1015. Anal. calc. for $C_{21}H_{16}O_5S$ (380.42): C 66.30, H 4.24, S 8.43; found: C 66.19, H 4.44, S 8.29.

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