# Synthesis of Benzodioxepinone Analogues *via* a Novel Synthetic Route with Qualitative Olfactory Evaluation

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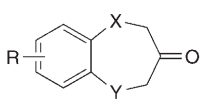
Marine odorants represent a minor yet diverse class of substances within the fragrance industry, of which 7-methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one (**1**) is commercially known as *Calone 1951*®, a synthetic first in the area of marine-fragrance chemistry. To determine the extent to which the characteristic marine odor of *Calone 1951*® corresponds to the substitution at the benzo portion of the molecule, a variety of aromatic substituents were incorporated into the benzodioxepinone structure (*Scheme 1*, *Table 3*). In light of the difficulty experienced in applying patented literature to deriving the analogues **12**–**18**, particularly those with electron-withdrawing substituents, an alternative synthetic scheme was implemented for the construction of all analogues in favorable yields (*Scheme 4*, *Table 3*). Formation of the hydroxy-protected dihalo alkylating agent **24** *via* epoxide cleavage of epichlorohydrin (*Scheme 3*) allowed etherification favoring dihalo displacement and subsequent intramolecular ring closure (→**26a**–**g**). THP Deprotection followed by oxidation of the alcohols **27a**–**g** to the ketones **12**–**18** provided a general pathway to the benzodioxepinone products. The influence of the substituent nature on odor activity revealed a diverse scope of olfactory character (*Table 4*).

**Introduction.** – The distinct marine-odor character and substantivity of *Calone 1951*® (=7-methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one; **1**), first synthesized by *Beereboom*, *Cameron*, and *Stephens* (*Pfizer*) [1] has contributed to its incorporation in the fragrance industry. *Calone 1951*® is used for seabreeze accords in fragrances such as 'Escape' (*C. Klein*, 1991), 'Polo Sport Woman' (*R. Lauren*, 1996), and 'Cool Water Woman' (*Davidoff*, 1997) [2]. Amongst traditional fragrance groups such as woody and floral, *Calone 1951*® has become an prominent compound in an atypical, formerly unestablished marine-fragrance category.

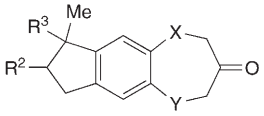
The novel properties of *Calone 1951*® render it suitable as a template for structure–odor-relationship (SOR) applications. The significant olfactory influence of the heterocycle O-atoms is evident in the contrast of odor character between the benzoxepinone **2** and the annulenone structures **3**–**5** or benzodioxepines **1** and **6**. Some olfactory data for analogues of **1** are presented in *Table 1*.

Olfactory analysis of the benzoxepinone **2**, also prepared by *Beereboom et al.* [1], was restricted to the term 'watermelon ketone', and $\alpha$-keto-substituted derivatives of both **1** and **2** were assigned the same odor description. The annulenone analogue **3** was prepared by *Kubota* and *Isemura* in 1931 and described as exhibiting a bitter almond/peppermint odor [3]. More recently, benzocycloheptanones **4** and **5** were synthesized by *Yoshii* and co-workers [4] who defined them as possessing a lily-of-the-valley fragrance, with the presence of a marine accord in **5**, the carbocyclic equivalent of **1**.

Table 1. *Molecular Features of some Benzodioxepinone Odorants*




**1 – 7**




**8**

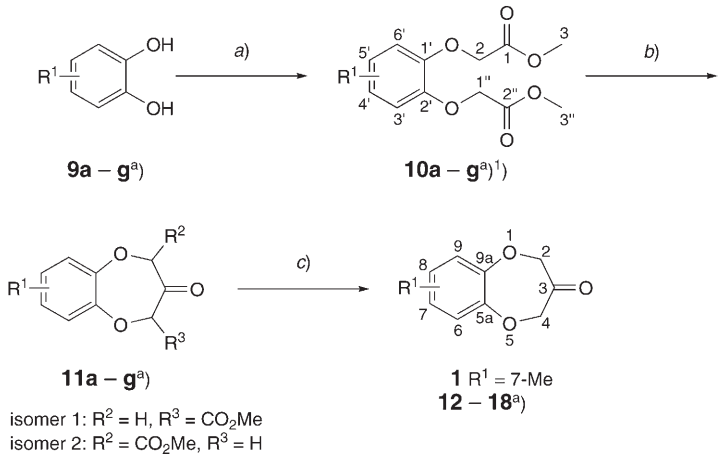
| | X | Y | R | $R^2$, $R^3$ | Odor character |
|---|---|---|---|---|---|
| **1** | O | O | 7-Me | | marine, floral nuance |
| **2** | O | $CH_2$ | H | | watermelon, green |
| **3** | $CH_2$ | $CH_2$ | H | | bitter almond, peppermint |
| **4** | $CH_2$ | $CH_2$ | 7-$^t$Bu | | lily-of-the-valley |
| **5** | $CH_2$ | $CH_2$ | 7-Me | | lily-of-the-valley, marine |
| **6** | O | O | 7-*n*-Pr | | aldehydic |
| **7** | O | O | 7-straight-chain and branched alkyl | | marine, floral, aldehydic, fruity, with ozone, animalic, and ink-like appearances |
| **8** | O | O | | H, Me | marine, aldehydic, floral, with citrus, nutty, and lichen facets |

The 7-propyl-2*H*-1,5-benzodioxepin-3(4*H*)-one (**6**) was prepared by *Gaudin* and *Blanc* [5], and a range of other 7-substituted varieties **7** have been designed by *Kraft* [6] for which olfactory accords are dominated by marine, floral, aldehydic, and fruity notes. Tricyclic indenodioxepinone structures **8**, also synthesized by *Kraft*, provided novel and reasonably intense marine analogues with the occasional citrus inflection, and singular nutty, moss, and animalic/civet appearances.

In our current studies pertaining to the odor properties of benzodioxepinone systems, we considered the modification of substitution and functionality at the aromatic ring and supported by qualitative olfactory analysis for consideration in ongoing SOR (structure – odor-relationship) studies by our group [7]. Preparation of benzodioxepinones substituted at the benzo moiety required introduction of an alternate broadly applicable synthetic pathway due to the diverse nature of the substituents. Limitations of the current approach (see below, *Scheme 1*) are examined, and the application of a simple but novel methodology towards benzodioxepinone syntheses (see below, *Scheme 4*) will be discussed.

**Results and Discussion.** – The current synthetic methodology for the preparation of benzodioxepinone structures is presented in *Scheme 1* (*Procedure A*) [1]. Our previous studies suggested that the *Williamson* ether synthesis conducted under microwave irradiation can lead to improvements in yield and purity of dietherified intermediates [8]. This is advantageous in the preparation of fragrance chemicals, as structurally related impurities are often difficult to remove and can persist in the benzodioxepinone products, causing erroneous olfactory evaluation. A range of benzodioxepinone analogues, *i.e.*, **12** – **18** were prepared under *Williamson* reaction conditions from the corresponding *ortho*-dihydroxy-substituted aromatics **9a** – **g** (*Table 2*) and a 2 mol-equiv. excess of methyl bromoacetate (*Scheme 1*). Differences in reactivity were observed in the formation of diester derivatives **10a** – **g**, depending on the method of

Scheme 1. *Procedure A*




*a*) $K_2CO_3$, $BrCH_2COOCH_3$, DMF. *b*) KO$^t$Bu, THF. *c*) 2M HCl, aq. EtOH.

[a]) For $R^1$, see *Tables 2* (**9a**–**g** and **10a**–**g**) and *3* (**12**–**18**)

heating used, *i.e.*, microwave or conventional heating (*Table 2*). Yields for **10d** and **10e** [9] obtained from the catechols (= benzene-1,2-diols) **9d** and **9e** containing electron-withdrawing substituents were improved with microwave heating. The degree of influence of substitution at the benzo moiety on the remainder of the molecule was evident in the NMR data of intermediates **10a**–**g**, **11a**–**g** (see below), and benzodioxepinones **12**–**18** (see below)[1]).

Table 2. *Microwave* vs. *Conventional Methods for the* Williamson *Etherification*. Highest yields are given.

| $R^1$ | **9** | Yield [%] of **10** | Purity [%] of **10**[a]) |
|---|---|---|---|
| 3-Me | **a** | 92[b]) | 95 |
| 3-MeO | **b** | 66[b]) | 98 |
| H | **c** | 88[b]) | 98 |
| 4-$NO_2$ | **d** | 74[c]) | 100 |
| 4-CHO | **e** | 79[c]) | 91 |
| 4-$^t$Bu | **f** | 75[b]) | 98 |
| (C(4))–CH=CH–CH=CH–(C(5)) | **g** | 96[b]) | 97 |

[a]) Purity determined by GC/MS prior to column chromatography. [b]) Yield of isolated product obtained by the conventional method (90–100°, 2 h). [c]) Yield of isolated product obtained by the microwave method (200 W, 4 min).

Heteronuclear HMBC data verified the connectivity of the $CH_2$ and benzene moieties of all analogues of **10**. The $^1$H- and $^{13}$C-NMR chemical shifts of the $CH_2$ groups of **11** and target analogues **12**–

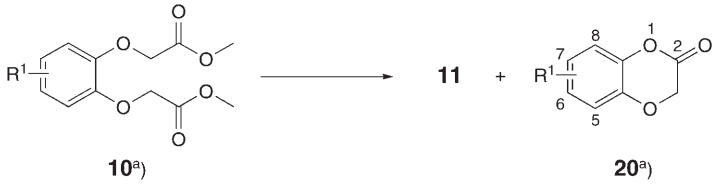
[1]) Arbitrary atom numbering; for systematic names, see *Exper. Part.*

**18** (see below) were established by HMQC and HMBC analysis. The nonequivalence of the two $CH_2$ and the two MeO groups in the $^1$H- and $^{13}$C-NMR spectra of **10** established that the inductive electronic effect of the $R^1$ substituent influences the entire molecular structure. As expected, this is evident in *ortho*-substituted derivatives **10a** ($\delta$(H) 4.69 ($CH_2$(1″)) and 4.60 ($CH_2$(2))) and **10b** ($\delta$(H) 4.65 ($CH_2$(1″)) and 4.64 ($CH_2$(2))[1])). The inductive effect on the terminal MeO groups from 4′-substitution is prominent in the NMR data of **10d** ($\delta$(H) 3.82 (Me(3)O) and 3.81 (Me(3″)O); $\delta$(H) 4.83 ($CH_2$(2)) and 4.80 ($CH_2$(1″))), whereby the lone pair of the $NO_2$ group enhanced electron-donating resonance effects. The inductive strength of the aldehyde moiety in **10e** ($\delta$(H) 4.81 ($CH_2$(1″)) and 4.78 ($CH_2$(2))) did not match the effect of the nitro group and seemed restricted to the $CH_2$ groups, as did the influence of the *t*-butyl group in **10f** ($\delta$(H) 4.72 ($CH_2$(1″)) and 4.68 ($CH_2$(2))).

The subsequent *Dieckmann* condensation reaction of the symmetrical hetero-ester chains of **10** resulted in regioisomer mixtures **11**. Preliminary experiments have been published previously [8]. Our trials to form the $\beta$-keto esters returned varying yields of cyclized products **11** with KO$^t$Bu in THF. Cyclization attempts to produce **11** mediated by the presence of a *Lewis* acid ($TiCl_4$) [10] gave no product after 48 h at 80°. The symmetrical side chains prevented ring closure despite the use of 0.5 mol-equiv. of $TiCl_4$ to encourage formation of the mono- rather than di-titanium enolate. *Rosnati* and *De Marchi* likewise reported unsuccessful efforts to prepare the oxobenzodioxepine-carboxylate structure by *Dieckmann* cyclization [11]. We noticed that the formation of isomers **11** with KO$^t$Bu/THF required **10** to be $\geq$98% pure; the presence of minor impurities led to decomposition and poor product yields (30–50%). The separation of the regioisomers was unnecessary since subsequent decarbomethoxylation of both isomers led to the desired benzodioxepinone products. The *Dieckmann* condensation for the cyclization of substituted diesterified catechols was not as general as we had anticipated. Diesters **10a**–**c**, **f** provided good yields of cyclized material **11a**–**c**, **f** (82–87%); however, the yields of diesters **11d**, **e**, **g** were irreproducible and complex product mixtures were formed.

The formation of bicyclic benzodioxane impurities 6- and 7-$R^1$-benzo[1,4]dioxin-2-one **20** [8] (*Scheme 2*), first noticed during the synthesis of the *Calone 1951*® precursors ($R^1$ = Me) were the major recurring by-products appearing in highly variable yields in the product mixtures of the *Dieckmann* condensation. Product mixtures containing both **11** and the major impurities **20** ($R^1$ = Me) are a viscous resin and difficult to separate, which *Carter et al.* [12] also discovered in their quest to synthesize acetic acid derivatives of catechol, resorcinol, and quinol. Rudimentary

Scheme 2. *Major Impurities of the* Dieckmann *condensation of* **10**: *6- and 7-R$^1$-benzo[1,4]dioxin-2-one*

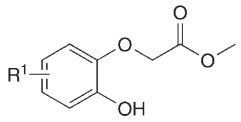



**10**[a]) **20**[a])

isomer 1: $R^1$ at C(6) (or C(5))
isomer 2: $R^1$ at C(7) (or C(8))

[a]) For $R^1$, see *Table 2*

isolation of **20a** ($R^1 = Me$) revealed it as a red resin, devoid of olfactory character, that forms a brittle solid on prolonged exposure to the atmosphere. Corresponding analogues **20a–g** (for **a–g**, see *Table 2*) exhibited similar physical properties of which **20b** [13], **20c** [14], **20d** [14], **20f** [13], and **20g** [15] have previously been prepared. Initially it was suspected that the main impurity appearing in the synthesis of all analogues **11** were substituted derivatives **20**. Complex cyclization mixtures obtained for **11d,e** required separation by HPLC, and inconsistencies arose when NMR data of the isolated by-products were compared with GC/MS results. HPLC Separation was also employed to purify the target products **15**, **16**, and **18**, establishing by subsequent NMR analysis that these impurities were the ether-cleavage products **21** (*Fig. 1*) [16]. Conclusions that KO$^t$Bu-mediated *Dieckmann* condensation caused the formation of a mono-alkylated catechol that thermally cyclized in the GC injector port to the sterically favored 6-membered heterocyclic ring were concordant with both NMR and GC/MS data. On-column transesterification of **21** to the ethyl ester derivative provided a compound which was resistant to cyclization under GC conditions, thus confirming the formation of a mono-alkylated species from **10d,e** under *Dieckmann* cyclization conditions.




**21**

$R^1 = NO_2$, CHO

Fig. 1. *Monoalkylated impurities present in the product mixtures containing* **11d** *and* **11e**

We established by means of rudimentary ChemDraw models (MM2 and PM3 optimized), that aromatic substitution of the benzodioxepinone system has a significant influence on the geometric conformation adopted by the heterocyclic ring. The dependence of perceptible 1D-NMR shift differences on the kind and position of the functional groups in intermediates **10a–g** and **11a–g** and in benzodioxepinones **12–18** supported this. *Archer* and *Claret* [17] published results on the twist angle ($\theta$) along the bond between the aromatic ring and the O-atoms of the heteroalicyclic ring obtained from the extinction coefficients in the UV spectra indicative of $\pi \rightarrow \pi^*$ transitions. Their modelling investigations led to the conclusion that the heteroalicyclic ring adopts either a more stable, rigid chair form or a flexible skewed pseudo twist-boat conformation, and that the boat conformation is only adopted by a negligible percentage of the compound due to steric constraints.

Semi-empirical calculations (MOPAC; AM1 followed by PM3) and *ab initio* models with HOMO/LUMO predictions were used to interpret differences in reactivity. Presenting compound **10d** as a representative in *Fig. 2*, the difficulty for compounds **10d** and **10e**, and to an extent for **10c** [18] and **10g**, to cyclize became evident. LUMO Hybridization is towed away from the alicyclic portion and concentrated around the aromatic ring, unlike those with electron-donating alkyl substituents as demonstrated by the 4-methyl isomer **10** ($R^1 = 4$-Me; *Fig. 3*). Based on

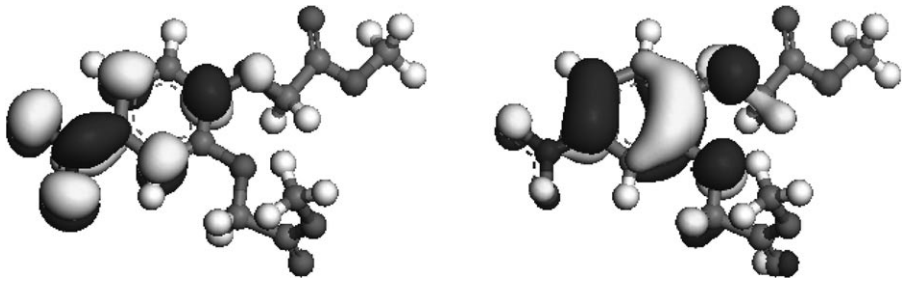


Fig. 2. *LUMO* (left) *and HOMO* (right) *representations of the 4-nitro compound* **10d** ($R^1 = 4\text{-}NO_2$)

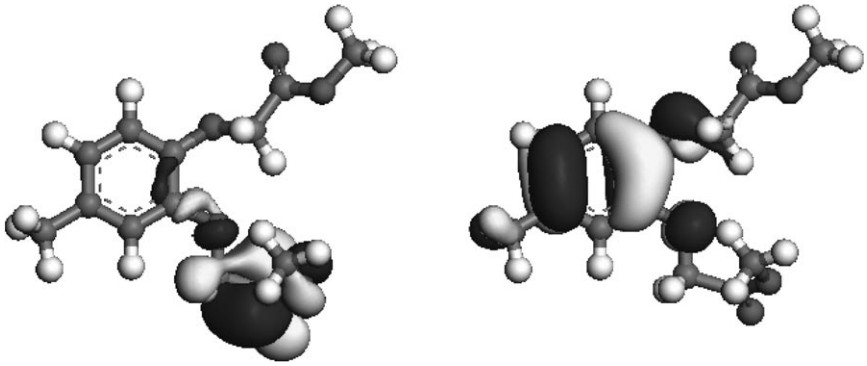
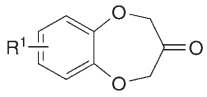


Fig. 3. *LUMO* (left) *and HOMO* (right) *representations of compound the 4-methyl isomer* **10** ($R^1 = 4$-Me)

these models, intramolecular cyclization is substantially hindered for **10d** due to a lack of available orbitals for acceptance of electrons required in the formation of a new $\sigma$ bond. For the decarbomethoxylation (*Scheme 1*) in the absence of LUMO around the reaction site, the energy required for bond breaking and forming for the saponified side chain is much greater than that offered by external HOMO. Other factors such as polarization and potential tautomerism may also contribute. Electron-donating aromatic substituents present in compounds **10a**, **b**, **f** assist in localizing the charge of the O-atoms and destabilization of the aromatic ring. Conversely the electron-withdrawing substituents of **10d**, **e** and the conjugated naphthodioxepine system of **10g** contribute to resonance stabilization of the aromatic ring, resulting in hindered cyclization. Of compounds **11a**–**g**, the MeO derivative **11b** is the only product obtained as a solid and the only intermediate for which the NMR data shows no distinguishable regioisomers, although GC/MS data reveals an 81 : 19 isomer ratio. The isomeric ratios for **11a**, **11d**, **11e**, and **11f** are 30 : 70, 57 : 43, 100 and 51 : 49, respectively. Signals due to the enol form of compounds **11a**–**g** were not observed in the $^1$H-NMR or FT-IR spectra, and CH and $CH_2$ signals were confirmed by DEPT-135, COSY, and HMQC analysis.

For the liberation of the target benzodioxepinones **12**–**18** (*Table 3*) a single-step acidic decarbomethoxylation of **11** (*Scheme 1*) afforded more desirable results than

Table 3. *Yields of Target Analogues* **12**–**18**



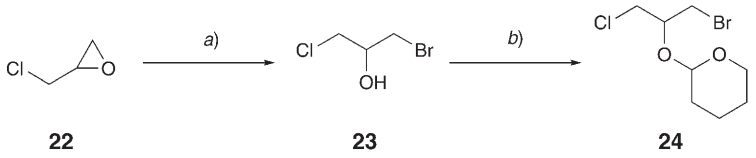
| | $R^1$ | *Procedure A* | | *Procedure B* | |
|---|---|---|---|---|---|
| | | Yield [%][a]) | Purity [%][b]) | Yield [%][a]) | Purity [%][b]) |
| **12** | 6-Me | 14 | 97 | 56 | 78 |
| **13** | 6-MeO | 95 | 99 | 87 | 86 |
| **14** | H | 10 | 87 | 60 | 98 |
| **15** | 7-$NO_2$ | 2 | 53 | 84 | 99 |
| **16** | 7-CHO | 11 | 69 | 52 | 93 |
| **17** | 7-$^t$Bu | 84 | 95 | 73 | 94 |
| **18** | (C(7))−CH=CH−CH=CH−(C(8)) | 7 | 81 | 61 | 58 |

[a]) Yield following purification with respect to **11** (*Procedure A*) or **27** (*Procedure B*). [b]) Purity by GC/MS prior to purification by column chromatography or HPLC.

initial saponification under basic conditions followed by acidic decarboxylation. In agreement with our electronic considerations, those variants **10** with an electron-withdrawing substituent at the aromatic moiety were more susceptible to nucleophilic alkoxy attack during the formation of **11d** and **11e**, and as a result, the latter were also less vulnerable to decarbomethoxylation. Purification of the decarbomethoxylated analogues **12**–**18** was dependent on the type of aromatic substituent present. Analogues with electron-donating aromatic substituents such as **12**, **13**, and **17** could be effectively purified by vacuum distillation, whereas those with an electron-withdrawing substituent or no electron-donating contributor, *i.e.*, **14** [19], **15**, **16**, and **18**, demanded separation by HPLC. Analysis of the $^1$H-NMR data of the benzodioxepinone target analogues revealed a characteristic $CH_2$ *s* for the unsubstituted aromatic products **14** and **18**, and two separate $CH_2$ signals for compounds containing aromatic substitution (see *Exper. Part*).

The low yields of **15** and **16** (*Table 3*) and the inherent instability of compounds **11d** and **11e** required a more viable approach to the ketone ring to access the broader scope of analogues containing reactive or strongly electron-withdrawing aromatic substituents. Single-step trials to form the benzodioxepinone adduct by *Rosnati et al.* [11] have included the reaction between catechol and 1,3-dichloroacetone in the presence of *N*,*N*-dimethylpyridin-4-amine (DMAP) with no success. A study by these authors on the alkaline condensation of catechol with 1,3-dichloropropan-2-ol briefly described the formation of the 1,5-benzodioxepin ring as a minor impurity. Modification of this generally unutilized approach was applied to our current studies with the incorporation of a protected 1,3-dihalo alcohol. Our group has successfully applied this novel synthetic route (*Procedure B*) to generate analogues **12**–**18** (*Table 3*). Thus, 1-bromo-3-chloropropan-2-ol was prepared by acid-catalyzed epoxide opening of epichlorohydrin (**22**; *Scheme 3*) with HBr to give the secondary alcohol **23** exclusively. anti-*Markovnikov*-type regioselectivity is commonly encountered for these ambident substrates (*Shargi* and co-workers) [20]. The trimethylsilyl group was initially

*Scheme 3*



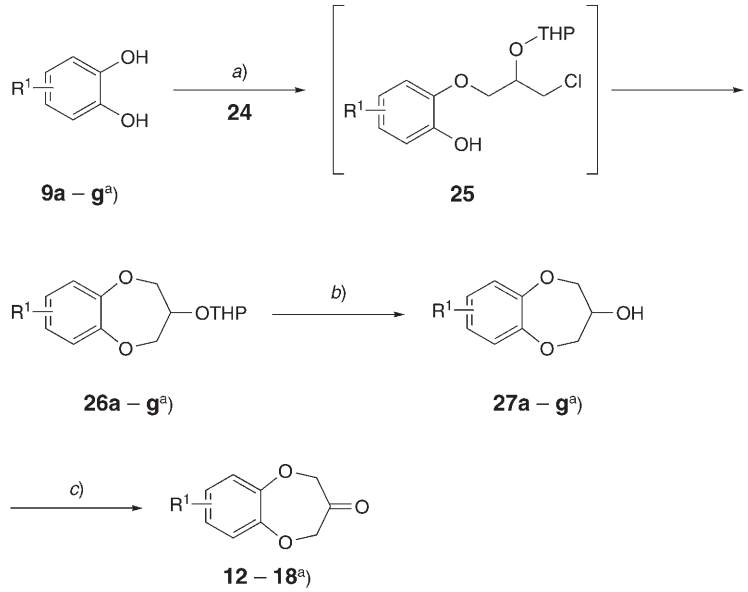

**22** **23** **24**

*a*) HBr (48%), r.t. *b*) DHP, $P_2O_5$, r.t.

implemented as a protecting group for **23**; however, it proved too labile for etherification reactions even at milder temperatures. Thus, the robust (under basic conditions) protecting group tetrahydropyran (THP) was introduced by reaction of **23** with 3,4-dihydro-2*H*-pyran (DHP) and $P_2O_5$ as catalyst under solvent-free conditions [21], to produce **24** as a distillable colorless oil in 91% yield.

The experimental approach employed in *Procedure B* (*Scheme 4*) involved initial reaction of the benzene-1,2-diols **9a**–**g** with an equimolar amount of alkylating agent **24** to expediently form the stable monoalkylated intermediate **25** by chemoselective displacement of the Br-atom as shown by GC/MS. Intramolecular etherification of the second OH group with the chloroalkane moiety gave the cyclized 7-membered ring upon prolonged heating in DMF. Although the Cl-displacement required 24 h, no dimeric structures or polymeric material were formed. Initial trials involved the use of

Scheme 4. *Procedure B*




**9a – g**[a]) **25** **26a – g**[a]) **27a – g**[a]) **12 – 18**[a])

*a*) $K_2CO_3$, DMF, reflux. *b*) $V_2O_5$, $H_2O_2$, 70°. *c*) $KMnO_4$, 4% KOH soln., r.t. (for $R^1 = NO_2$ or CHO, oxalyl chloride, DMSO, $Et_3N$, −78°).

[a]) For $R^1$, see *Tables 2* (**9a**–**g**) and *3* (**12**–**18**)

NaH but produced inferior results to $K_2CO_3$ in DMF, which was sufficient to deliver clean mixtures of the cyclized products **26** in excellent yields. Deprotection of **26** with silica chloride [22] according to a protocol by *Firouzabadi et al.* was successful in the removal of THP, but was accompanied by significant decomposition. A trial of a dual oxidative deprotection with $\beta$-cyclodextrin (deprotection) and *N*-bromosuccinimide (NBS; oxidation) in $H_2O$/acetone [23] resulted in a small yield of the $\alpha$-bromo carbonyl compound after 15 min, and with incorporation of a Br-scavenger returned only the starting alcohol. A $KMnO_4/CuSO_4$ hydrate with an alcohol catalyst [24] was attempted, also to no avail. A $NaBrO_3/NH_4Cl$ reagent [25] in aqueous MeCN, recommended for oxidative deprotection of silyl ethers resulted in attack at the fusion atoms forming over-oxidized catechol derivatives. Deprotection of the THP group (*Scheme 4*) with $V_2O_5$ catalyst under conditions developed by *Patel* and co-workers [26] produced the alcohol in quantitative yield under mild conditions. The aldehyde derivative **26e** was also successfully deprotected with $V_2O_5$ avoiding over-oxidation and polymerization. Esterification of the aldehyde was avoided by the use of MeCN rather than MeOH as solvent as suggested by *Patel* and co-workers. The $^1$H-NMR signal for the proton at the stereogenic center C(3) of **26a**–**g** characteristically overlapped with the diastereotopic $CH_2(2)$ and $CH_2(4)$ protons. The ambiguous $^1$H-NMR resonance was clarified by COSY and HMQC experiments in each case.

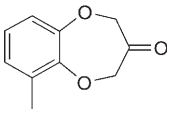
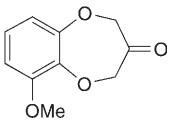
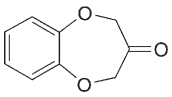
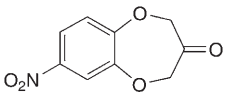
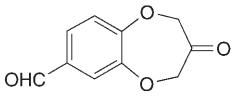
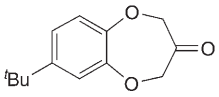
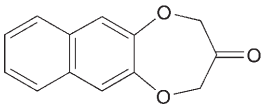
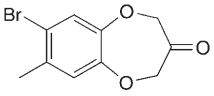
Oxidation of the secondary alcohols **27** (*Scheme 4*) with $KMnO_4$ in benzene and under PTC-assisted biphasic conditions (PTC = phase-transfer catalyst) failed to provide the oxidized product in greater than 5% yield. Aqueous basic conditions suggested by *Rosnati et al.* were found to be optimal for the oxidative activity of $KMnO_4$ and provided the ketone products **12**–**14** and **17**–**18** at room temperature in good yields (*Table 3*). Surprisingly, the aqueous acidic workup resulted in chlorinated by-products when $CH_2Cl_2$ was used as extraction solvent, so $Et_2O$ was used instead. Permanganate was not a suitable oxidizing agent for the formation of benzodioxepinone analogues with electron-withdrawing aromatic substituents. Application of *Swern*-oxidation conditions by using oxalyl chloride and DMSO gave reproducible formation of the nitro and aldehyde derivatives **15** and **16** in 84% and 52%, respectively and in favorable purity (99% and 93%, resp., *Table 3*). HMQC and HMBC couplings established $CH_2$/fusion atom correlations for all target analogues (including **19**, see below) and the intermediates **26** and **27** [27].

Halogenated compounds rarely appear in the fragrance-chemistry arena, in part due to their inherent toxicity. In determining the importance of the aromatic moiety to the *Calone 1951*® headspace, the accessible aromatic halo-substitution product **19** provided an informative addition to the analogue group. Bromination of *Calone 1951*® (**1**) gave **19**, the single molecule in this series not derived from a catechol. This bromination was based on a system developed by *Kikuchi*, *Sakaguchi*, and *Ishii* [28] (*Scheme 5*), *i.e.*, a two-phase system for the *in situ* generation of hypobromous acid (HOBr) from $NaBrO_3/NaHSO_3$ in the aqueous phase, which is suspected to form a cationic bromine species. Bromination of the aromatic ring occurred selectively at the *ortho* position to the Me group as predicted by the activating Me group.

**Olfactory Evaluation.** – The diverse range of synthesized analogues incorporated many which maintained the original marine-odor attribute of **1**, namely **12**, **13**, **17**, and

**19** and to a lesser extent **15** and **16** (*Tables 4* and *5*). In all cases, the odor threshold was largely increased compared to **1**, as indicated by a low perceived intensity for the range of analogues. Aromaticity, particularly as benzylic functionality is prevalent in compounds used for their fragrant properties. The patent released by *Pfizer* allocated a general olfactory assessment of 'watermelon green' to a range of benzodioxepinone

Table 4. *Olfactory Data for Analogues* **12**–**19**

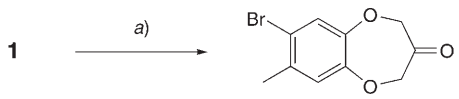
| | | Qualitative olfactory data[a]) |
|---|---|---|
| **12** |  | Fresh, floral-aldehydic odor of green and woody-marine tonality |
| **13** |  | Sweet-spicy, green-marine, floral, slightly earthy, walnut-like nuances, relatively weak |
| **14** |  | Green-floral, balsamic odor in the direction of Peru and Tolu balsam resinoid, a slight marine salty aspect |
| **15** |  | Fruity-spicy, balsamic odor with a slight woody inflection and a distant powdery-vanillic sweetness, weak |
| **16** |  | Sweet, powdery scent reminiscent of vanilla with a spicy-balsamic undertone |
| **17** |  | Fresh, marine, ozony odor, a green and walnut-like nuance, slightly floral |
| **18** |  | Oily, floral-green, and a slightly metallic odor, a very weak watery-floral, Calone-like inflection, weak |
| **19** |  | Marine-ozony, ethereal, walnut-like odor, with salty aspects and a floral-fruity, geranium-like inflection, slightly earthy; same intensity and tenacity as **17** |

[a]) Data provided by *Philip Kraft* and *Alain E. Alchenberger*, *Givaudan Switzerland AG*, Fragrance Research.

Table 5. *Graphic Representation of Olfactory Characteristics of Compounds* **12**–**19**. Black: present; grey: present but weak; white: absent.

| | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** |
|---|---|---|---|---|---|---|---|---|
| $R^1$ | Me | MeO | H | $NO_2$ | CHO | *t*Bu | Benzo | 7-Me, 8-Br |
| marine | | | | | | | | |
| green | | | | | | | | |
| floral | | | | | | | | |
| aldehyde | | | | | | | | |
| woody/earthy | | | | | | | | |
| nutty | | | | | | | | |
| fruity | | | | | | | | |
| vanillic | | | | | | | | |
| balsamic | | | | | | | | |
| metallic | | | | | | | | |
| salty | | | | | | | | |
| oily | | | | | | | | |
| spicy | | | | | | | | |

*Scheme 5*




**19**

*a*) $NaBrO_3$, $NaHSO_3$, $H_2O$/cyclohexane, 85%.

compounds including **14** and **17** of our work. Compound **14** and **18** exhibit similar odor profiles concordant with their comparable molecular attributes: a benzo and a naphtho fusion component, respectively. The green note is preserved, however, the marine aspect is weakened for both structures, indicating the importance of aromatic substitution to the typical *Calone 1951*® olfactory character. Interestingly, complete absence of substitution converts the fragrance emanated to a sweet array, particularly by the reference to balsam of Peru and Tolu that typically exhibit deep, rich sweetness. Both the nitro and aldehyde derivatives **15** and **16**, respectively, displayed individual olfactory characteristics. The marine character is completely removed in both cases, with introduction of fruity, sweet, balsamic tonalities, with a hint of spiciness for **15**. The steric bulk introduced by the *t*Bu and Br groups in **17** and **19**, respectively, may contribute to the walnut inflection perceived for both. Compound **18** serves as an interesting comparison, maintaining the marine aspect understandably as the entire *Calone 1951*® molecular skeleton is preserved for this analogue. The marine odor is steered in a more salty direction, accompanied by floral notes, as also often detected in the headspace from **1**. To preserve the characteristic *Calone 1951*® odor, substitution is not restricted to the 7-position as demonstrated when comparing compounds **12**, **13**, **16**, and **18**. The type of functionality present at the aromatic ring, rather than its position, is more active in deconstructing the marine-odor character, as exhibited by the qualitative assessment of **14**–**16**.

**Conclusion.** – The presence of the aromatic Me substituent in *Calone 1951®* complements but is not critical for the essential marine odor characteristic. In conjunction with the presence of the C=O group in the aliphatic ring which was previously studied [7], it is evident from our observations that aromatic-ring substitution modifies the odor perception of the marine character of *Calone 1951®*.

Financial support from the School of Applied Science, RMIT University, is acknowledged. Utmost thanks to *Daniel Dias* for technical assistance with HPLC, and *Nicole Benedek* for *ab initio* molecular modelling. We are indebted to *Philip Kraft* and *Alain E. Alchenberger* (*Givaudan*, Switzerland) for olfactory evaluation. We also thank *Julie Niere* for assistance with NMR, in conjunction with *Paul Morrison* and *Frank Antolasic* for support with GC and GC/MS instrumentation. Appreciation for technical assistance and advice related to gas chromatography/olfactometry (GCO) to *Jean-Pierre Dufour* and *Graham Eyres*, University of Otago, New Zealand. We are grateful to *Michael Malcmann* (*Warlock Engineering*) and *Raymond Lingham* for provision of microwave apparatus.

## Experimental Part

1. *General.* Potassium *tert*-butoxide and methyl bromoacetate were supplied by *Merck*. Otherwise, all reagents were obtained from *Aldrich Chemical Co.* and used without further purification. THF was dried over $CaH_2$, followed by distillation from sodium/benzophenone. DMF was dried over $CaH_2$, followed by distillation over molecular sieves (4 Å). Synthesis of *Calone 1951®* (**1**) by means of the microwave heating procedures has been discussed previously [8], and intermediates **10d** and **10e** were more efficiently prepared by the microwave methodology. Microwave experiments were performed in a prototype microwave applicator '*MDV2.4*' and with a *0-700 W* variable power microwave source (*2m172*)[2]). FC: *Merck* silica gel *60* (0.040–0.063 μm). CC = Column chromatography. TLC: *Merck* silica gel *60* $F_{254}$ (particle size 5–40 μm, layer thickness 0.2 mm on aluminium, 20 × 20 cm); visualization by UV light (254 nm). Semiprep. HPLC: *Varian Prostar* (model *210*); *Phenomenex* column (250 × 10 mm, 5μ ODS (3)); MeCN/$H_2O$ 33:67; 3.5 ml/min flow rate; UV/VIS detection. IR: *Perkin-Elmer Spectrum-2000 Fourier*-transform IR spectrophotometer. NMR: *Bruker Avance-300* (300 MHz) spectrometer, *Varian Gemini-200* (200 MHz) spectrometer, referenced to $SiMe_4$ with the solvent resonance as the internal standard ($CHCl_3$: $\delta$(H) 7.26) unless otherwise stated. MS/GC: *Hewlett-Packard 6890* GC with *BPX-5* column/*5973* mass-selective detector.

2. *Calculations.* Molecular-model calculations were performed by using density functional theory (DFT), as implemented in the Dmol[3] program package. The PBE functional was used in combination with the DNP basis set (double numerical plus polarization). All calculations were all-electron and spin-restricted. Each model was charge-neutral. The geometry of each model was optimized, without constraints. Electron-density maps, HOMOs and LUMOs were calculated for the relaxed structures.

3. *Calone 1951®* (**1**) *and Analogues* **12**–**18**: *General Procedure A. 2,2′-[(4-Methyl-1,2-phenylene)bis(oxy)]bis[acetic Acid] Dimethyl Ester* (**10**; $R^1$ = 4-Me). *Conventional Method:* Ground, oven-dried $K_2CO_3$ (9.00 g, 65.12 mmol) and methyl bromoacetate (6.00 ml, 63.38 mmol) were added sequentially to a soln. of **9** ($R^1$ = 4-Me; 2.00 g, 16.11 mmol) in anh. DMF (100 ml). The soln. was heated to 120° for 2 h, then the hot mixture was poured into ice/$H_2O$ (200 ml) and extracted with $CH_2Cl_2$ (3 × 100 ml). The combined org. phase was washed with 5% aq. NaOH soln. (2 × 50 ml) followed by $H_2O$ (2 × 50 ml), dried ($MgSO_4$), and concentrated. The obtained yellow oil was purified by vacuum CC (silica gel (short column), pentane, then AcOEt/pentane 1:9 → 3:7) followed by bulb-to-bulb distillation: **10** ($R^1$ = 4-Me; 3.37 g, 78%). White solid. M.p. (pentane) 43–44°.

*Microwave Procedure:* The reagents were combined as described for the conventional procedure, and the soln. was irradiated for 4 min at 200 W under $N_2$. Workup of the mixture was performed according to the conventional procedure: **10** ($R^1$ = 4-Me; 3.60 g, 83%).

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[2]) Provided on trial by *Warlock Engineering*: www.warlock.com.au/chemreactor.htm.

*Methyl 3,4-Dihydro-7-methyl-3-oxo-2*H*-1,5-benzodioxepine-2-carboxylate* (**11**; $R^1$ = 7-Me). Under an inert atmosphere, a soln. of **10** (3.72 g, 13.88 mmol) in anh. THF (35 ml) was added within 5 min to a stirred mixture of KO*t*Bu (3.11 g, 27.71 mmol) in anh. THF (35 ml) with cooling in an ice/$H_2O$ bath. The soln. was then transferred to an oil bath at 70° and heated for 30 min before quenching in a stirred mixture of 0.2M HCl (200 ml) in ice (200 g). The acidic soln. was extracted with $CH_2Cl_2$ (3 × 100 ml) and the combined org. phase washed with $H_2O$ (2 × 150 ml) and concentrated: **11** ($R^1$ = 7-Me; 3.00 g, 92%). Viscous yellow-brown oil consisting of a mixture of regioisomers and requiring storage at −20°. After prolonged storage, purification by CC (silica gel, hexane/AcOEt 1:1) was necessary prior to use.

*7-Methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**1**). To a soln. of **11** ($R^1$ = 7-Me; 1.00 g, 4.24 mmol) in EtOH (10 ml) was added 2M HCl (50 ml), and the soln. was heated at 90° while stirring in an oil bath. After 2 h, the mixture was poured into ice/$H_2O$ (100 ml) and extracted with $CH_2Cl_2$ (3 × 100 ml). The combined org. extract was washed with $H_2O$ (1 × 200 ml), dried ($MgSO_4$), and concentrated and the obtained brown semi-solid subjected to bulb-to-bulb distillation (70°/0.5 Torr): **1** (0.59 g, 78%). White crystalline solid. M.p. (pentane) 38–39° (lit.[3]) 38–40°).

4. Calone 1951® (**1**) *and Analogues* **12**–**18**. *General Procedure B. 1-Bromo-3-chloropropan-2-ol* (**23**). A 48% HBr soln. (28.3 g) was added dropwise to neat epichlorohydrin (= 2-(chloromethyl)oxirane; **22**; 15.0 g, 162 mmol) within 2 h under vigorous stirring. The soln. was stirred for an additional 45 min, then mixed with $Et_2O$ (150 ml) and washed with sat. $NaHCO_3$ soln. (3 × 50 ml). The org. phase was dried ($MgSO_4$) and concentrated and the residue distilled under vacuum (54–56°/5 Torr): **23** (20.0 g, 71%). Clear oil. IR (neat): 3380*s* (br.), 2961*m*, 2894*w*, 1625*w*, 1426*s*, 1382*m*, 1344*m*, 1295*m*, 1261*s*, 1225*m*, 1135*m*, 1088*s*, 1067*s*, 1039*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 4.03 (*quint.*, *J* = 5.3, H−C(2)); 3.70 (*d*, *J* = 5.7, $CH_2$(3)); 3.56 (*d*, *J* = 5.3, $CH_2$(1)); 2.64 (*s*, OH). $^{13}$C-NMR (75 MHz, $CDCl_3$): 70.3 (C(2)); 46.4 (C(3)); 34.7 (C(1)). $^1$H,$^1$H-COSY ($CDCl_3$): 3.98 (H−C(2))/3.63 (H−C(3)); 3.98 (H−C(2))/3.51 (H−C(1)); 3.65 (H−C(1), H−C(3))/2.58 (OH). $^1$H,$^{13}$C-HMQC ($CDCl_3$): H−C(2)/C(2) (70.5); $CH_2$(3)/C(3) (46.7); $CH_2$(1)/C(1) (34.9). EI-MS: 125 (96), 123 (100), 95 (6), 93 (6), 81 (18), 79 (50).

*2-[2-Bromo-1-(chloromethyl)ethoxy]tetrahydro-2*H*-pyran* (**24**). To 3,4-dihydro-2*H*-pyran (5.30 g, 63.00 mmol), **23** (10.0 g, 57.66 mmol) was added neat, followed by a cat. amount of $P_2O_5$ (0.10 g, 0.35 mmol). The soln. was warmed to 60° in a water bath for 1 h and then allowed to reach r.t. and stirred for an additional hour. The resulting mixture was dissolved in $Et_2O$ (150 ml) and washed with sat. $NaHCO_3$ soln. (3 × 50 ml), the org. phase dried ($MgSO_4$) and concentrated, and the residue distilled under vacuum (101–102°/50 Torr): **24** (13.5 g, 91%). Clear oil. IR (neat): 2940*m*, 2868*w*, 2853*w*, 1437*w*, 1395*w*, 1382*w*, 1344*w*, 1323*w*, 1284*w*, 1261*w*, 1199*m*, 1178*w*, 1148*w*, 1122*m*, 1075*m*, 1054*s*, 1029*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 4.78–4.77 (*m*, H−C(2)); 4.06–3.98 (*m*, $ClCH_2CH$); 3.92–3.48 (*m*, $CH_2$(6)); 3.83–3.48 (*m*, $ClCH_2$, $BrCH_2$); 1.82–1.50 (*m*, $CH_2$(3), $CH_2$(4), $CH_2$(5)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 98.8 (C(2)); 75.5 (CH); 62.7 (C(6)); 44.2 ($ClCH_2$); 31.9 ($BrCH_2$); 30.5 (C(3)); 25.2 (C(5)); 19.2 (C(4)). $^1$H,$^{13}$C-HMQC ($CDCl_3$): $CH_2$(2)/C(2) (99.1); H−C(1)/C(1) (75.6); $CH_2$(6)/C(6) (62.7); $H_a$−C(1)/$ClCH_2$ (44.7); $H_b$−C(1)/$ClCH_2$ (44.6); $CH_2$(2)/C(2) (32.4); $CH_2$(3)/C(3) (30.3); $CH_2$(5)/C(5) (25.3); $CH_2$(4)/C(4) (19.2). EI-MS: 257 (10, $M^+$), 255 (8), 209 (2), 207 (2), 203 (2), 202 (2), 201 (2), 200 (3), 157 (16), 155 (12), 137 (4), 135 (4), 121 (5), 101 (4), 95 (3), 93 (2), 85 (100), 77 (6), 75 (18), 67 (7), 56 (20).

*3,4-Dihydro-7-methyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-1,5-benzodioxepine* (**26**; $R^1$ = 7-Me). Ground oven-dried $K_2CO_3$ (2.22 g, 16.06 mmol) was added in one portion to a soln. of **9** (0.50 g, 4.03 mmol) in DMF, and the soln. was heated to 100°. Then a soln. of **24** (0.70 g, 2.72 mmol) in DMF was added dropwise over 30 min and the soln. stirred at 120° for 24 h. The hot soln. was poured into a stirred ice/$H_2O$ (200 ml) mixture and saturated with NaCl before extraction with $CH_2Cl_2$ (3 × 75 ml). The combined org. phase was washed with $H_2O$ (2 × 100 ml), dried ($MgSO_4$), and concentrated: **26** (0.98 g, 92%). Deep brown viscous oil. IR (neat): 3436 (br.), 3031*w*, 2942*s*, 2871*s*, 2738*w*, 2660*w*, 2578*w*, 2251*w*, 2227*w*, 2052*w*, 2017*w*, 1871*w*, 1724*w*, 1614*w*, 1579*m*, 1505*s*, 1455*m*, 1442*m*, 1415*w*, 1381*w*, 1355*m*, 1305*s*, 1262*s*, 1201*s*, 1185*m*, 1150*m*, 1128*s*, 1075*s*, 1034*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.91–6.66 (*m*, H−C(6), H−C(8), H−C(9)); 4.74 (*t*, *J* = 3.5, H−C(2′)); 4.42–4.00 (*m*, $CH_2$(2), H−C(3), $CH_2$(4)); 3.93–3.86 (*m*, $H_a$−C(6′)); 3.57–3.50 (*m*, $H_b$−C(6′)); 2.23 (*s*, Me); 1.89–1.50 (*m*, $CH_2$(3′), $CH_2$(4′), $CH_2$(5′)). $^{13}$C-NMR

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[3]) Material safety data sheet of 7-methyl-3,4-dihydro-2*H*-1,6-benzodioxepine-3-one (*Calone 1951*®); *Ganone Agan Aroma and Fine Chemicals Ltd*.

(75 MHz, $CDCl_3$): 149.6 (C(9a)); 147.8 (C(5a)); 132.7 (C(7)); 124.4 (C(8)); 123.4 (C(9)); 121.2 (C(6)); 98.4 (C(2′)); 74.4 (C(3)); 73.0 (C(4)); 72.1 (C(2)); 62.7 (C(6′)); 30.7 (C(3′)); 25.3 (C(5′)); 20.5 (Me); 19.41 (C(4′)). $^1$H,$^1$H-COSY ($CDCl_3$): 4.66 (H−C(2′))/1.61 ($CH_2$(3′)); 3.81 ($H_b$−C(6′))/3.45 ($H_a$−C(6′)); 3.81 (H−C(6′))/1.49 ($CH_2$(5′)). $^1$H,$^{13}$C-HMQC ($CDCl_3$): H−C(3)/C(3) (74.5); $CH_2$(4)/C(4) (73.4); $CH_2$(2)/C(2) (72.1); $CH_2$(6′)/C(6′) (62.7). EI-MS: 264 (77, $M^+$), 236 (3), 208 (4), 206 (2), 180 (20), 162 (22), 149 (7), 135 (35), 11 (133), 124 (8), 123 (9), 105 (7), 99 (6), 91 (7), 85 (100), 77 (10), 67.1 (19), 57 (23), 55 (10).

*3,4-Dihydro-7-methyl-2*H*-1,5-benzodioxepin-3-ol* (**27**). Vanadium pentoxide (14 mg, 0.11 mmol) was added to a 30% $H_2O_2$ soln. (0.90 ml), and the mixture was stirred at 0° for 10 min. The catalyst mixture was then added to a soln. of **26** (0.50 g, 1.89 mmol) in MeCN (20 ml) and heated at 70° for 15–20 min, or until the soln. ceased effervescing and became dark green. The MeCN was evaporated and the crude material solubilized in 2M $NaHCO_3$ (50 ml). Extraction of the product was achieved with $CH_2Cl_2$ (3 × 40 ml), and the org. phase washed with sat. $NaHCO_3$ soln. (1 × 60 ml) and concentrated: opaque resin which solidified upon cooling to give **27** (0.26 g, 76%). White solid. M.p. (heptane) 56–58°. IR (KBr): 3210 (br.), 3083*m*, 2988*m*, 2961*m*, 2922*m*, 2866*m*, 2714*w*, 1611*w*, 1578*m*, 1509*s*, 1443*m*, 1414*w*, 1383*w*, 1360*w*, 1344*s*, 1300*s*, 1290*s*, 1275*s*, 1261*s*, 1202*m*, 1151*m*, 1137*s*, 1116*m*, 1103*w*, 1042*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.89 (*d*, *J* = 8.1, H−C(9)); 6.80 (*s*, H−C(6)); 6.78 (*d*, *J* = 8.1, H−C(8)); 4.35–4.25 (*m*, $H_a$−C(2), $H_a$−C(4)); 4.08–3.99 (*m*, $H_b$−C(4), H−C(3), $H_b$−C(2)); 2.78 (*s*, OH); 2.24 (*s*, Me). $^{13}$C-NMR (75 MHz, $CDCl_3$): 150.2 (C(9a)); 148.3 (C(5a)); 133.0 (C(7)); 123.7 (C(8)); 121.5 (C(9)); 120.7 (C(6)); 74.6 (C(2)); 74.4 (C(4)); 69.1 (C(3)); 20.3 (Me). $^1$H,$^1$H-COSY ($CDCl_3$): 4.30 ($H_a$−C(2))/4.03 ($H_b$−C(2)); 4.30 ($H_a$−C(4))/4.03 ($H_b$−C(4)). $^1$H,$^{13}$C-HMQC ($CDCl_3$): $CH_2$(2)/C(2) (74.5); $CH_2$(4)/C(4) (74.4); H−C(3)/C(3) (69.2). EI-MS: 180 (100, $M^+$), 161 (2), 149 (11), 135 (51), 123 (28), 109 (11), 107 (5), 106 (5), 95 (8), 94 (9), 91 (10), 78 (13), 77 (14), 66 (10), 65 (6) 57 (2), 51 (6).

*7-Methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**1**). To a 4% aq. KOH soln. (20 ml) and $KMnO_4$ (1.75 g, 11.07 mmol) at 0–5° was added **27** (0.40 g, 2.22 mmol) in one portion. The soln. was stirred for 2.5 h, then the $MnO_2$ was removed by vacuum filtration and the filter cake washed with $Et_2O$ (2 × 20 ml). The filtrate was acidified by the dropwise addition of conc. HCl soln. to pH 2, and then extracted with $Et_2O$ (3 × 30 ml). The combined org. phase was washed with sat. $NaHCO_3$ soln. (1 × 50 ml), dried ($MgSO_4$), and concentrated and the obtained yellow resin purified by bulb-to-bulb distillation (70°/0.5 Torr): **1** (0.35 g, 87%). Crystalline white solid. M.p. (pentane) 38–39°. IR (KBr): 3448*w*, 3057*w*, 2991*w*, 2920*w*, 2859*w*, 1742*s*, 1614*w*, 1582*w*, 1506*s*, 1466*w*, 1435*m*, 1414*w*, 1303*s*, 1265*s*, 1207*m*, 1150*m*, 1119*m*, 1053*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.90–6.75 (*m*, H−C(6), H−C(8), H−C(9)); 4.70 (*s*, $CH_2$(4)); 4.67 (*s*, $CH_2$(2)); 2.27 (*s*, Me). $^{13}$C-NMR (75 MHz, $CDCl_3$): 204.8 (C(3)); 147.9 (C(9a)); 146.1 (C(5a)); 133.8 (C(7)); 124.3 (C(8)); 121.2 (C(9)); 120.6 (C(6)); 75.8 (C(2)); 75.5 (C(4)); 20.5 (Me). EI-MS: 178 (100, $M^+$), 150 (2), 149 (3), 135 (24), 122 (6), 108 (8), 94 (89), 91 (17), 89 (12), 77 (17), 66 (74), 63 (14), 51 (18), 39 (21).

5. *Benzodioxepinone* **12** *by* Procedure A. *2,2′-[(3-Methyl-1,2-phenylene)bis(oxy)]bis[acetic Acid] Dimethyl Ester* (**10a**). As described in *Exper. 3* (conventional method), with **9a** (1.00 g, 8.05 mmol). Purification involved bulb-to-bulb distillation (160°/0.4 Torr) performed twice: **10a** (1.99 g, 92%). Clear pale yellow oil. The microwave procedure provided **10a** in 36% yield. IR (neat): 3002*m*, 2955*s*, 2853*m*, 2112*w*, 1774*s*, 1749*s*, 1646*w*, 1604*m*, 1587*m*, 1488*s*, 1440*s*, 1380*m*, 1304*m*, 1262*m*, 1183*m*, 1114*m*, 1070*m*, 1027*m*. $^1$H-NMR (300 MHz, $CDCl_3$)[1]): 6.89–6.60 (*m*, H−C(4′), H−C(5′), H−C(6′)); 4.69 (*s*, $CH_2$(1″)); 4.60 (*s*, $CH_2$(2)); 3.74 (*s*, Me(3″)O); 3.72 (*s*, Me(3)O); 2.28 (*s*, arom. Me). $^{13}$C-NMR (75 MHz, $CDCl_3$)[1]): 169.9 (C(2″)O); 168.9 (C(1)O); 149.8 (C(1′)); 145.9 (C(2′)); 132.3 (C(3′)); 124.1 (C(4′)); 123.7 (C(5′)); 111.5 (C(6′)); 69.0 $CH_2$(1″)); 65.6 ($CH_2$(2)); 51.6 (Me(3)O, Me(3″)O); 15.8 (arom. Me). EI-MS: 268 (16, $M^+$), 209 (5), 207 (3), 195 (11), 176 (11), 163 (12), 149 (15), 135 (75), 121 (3), 109 (17), 91 (19), 77 (21), 65 (17), 63 (5), 59 (9), 51 (10), 45 (100).

*Methyl 3,4-Dihydro-6-methyl-3-oxo- and 3,4-Dihydro-9-methyl-3-oxo-2*H*-1,5-benzodioxepine-2-carboxylate* (**11a**). As described in *Exper. 3*, with **10a** (1.00 g, 3.73 mmol): **11a** (0.72 g, 82%). Caramel-colored oil. IR (neat): 3474*m*, 2956*s*, 2572*w*, 1742*s*, 1677*m*, 1632*w*, 1594*m*, 1477*s*, 1440*s*, 1337*m*, 1274*s*, 1250*m*, 1217*s*, 1202*s*, 1100*s*, 1071*m*, 1045*m*. $^1$H-NMR (300 MHz, $CDCl_3$): *Regioisomer 1:* 6.93–6.83 (*m*, H−C(7), H−C(8), H−C(9)); 5.36 (*s*, H−C(2)); 4.81 (*d*, *J* = 16.7, $H_a$−C(4)); 4.62 (*d*, *J* = 16.7, $H_b$−C(4)); 3.86 (*s*, MeO); 2.22 (*s*, arom. Me); *Regioisomer 2:* 6.93–6.83 (*m*, H−C(7), H−C(8), H−C(9)); 5.37 (*s*,

H–C(4)); 4.87 (*d*, *J* = 16.7, $H_a$–C(2)); 4.56 (*d*, *J* = 16.7, $H_b$–C(2)); 3.85 (*s*, MeO); 2.28 (*s*, arom. Me). $^{13}$C-NMR (75 MHz, $CDCl_3$): *Regioisomer 1:* 199.7 (C(3)); 165.4 ($CO_2$); 147.1 (C(9a)); 145.9 (C(5a)); 130.7 (C(6)); 125.2 (C(7)); 124.0 (C(8)); 118.1 (C(9)); 81.8 (C(2)); 76.4 (C(4)); 52.9 (MeO); 15.9 (arom. Me); *Regioisomer 2:* 199.6 (C(3)); 165.4 ($CO_2$); 147.3 (C(9a)); 145.4 (C(5a)); 130.0 (C(6)); 126.4 (C(7)); 122.8 (C(8)); 118.8 (C(9)); 81.8 (C(4)); 76.4 (C(2)); 58.4 (MeO); 18.2 (arom. Me). EI-MS: 236 (100, $M^+$), 204 (4), 177 (22), 149 (66), 135 (48), 121 (22), 105 (5), 94 (47), 77 (28), 66 (34), 51 (13), 39 (18).

*6-Methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**12**). As described in *Exper. 3*, with **11a** (1.02 g, 4.32 mmol). The obtained brown oily **12** (0.56 g, 72%) which was bulb-to-bulb distilled at 50–60°/0.2 Torr: **12** (0.11 g, 14%). Clear oil. IR (KBr): 3024*w*, 2964*w*, 2939*w*, 2906*w*, 2839*w*, 1790*m*, 1738*s*, 1613*w*, 1592*m*, 1492*m*, 1475*s*, 1440*m*, 1419*w*, 1380*w*, 1324*m*, 1296*m*, 1274*s*, 1258*s*, 1205*m*, 1191*m*, 1101*s*, 1080*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.86 (br. *s*, H–C(7), H–C(8), H–C(9)); 4.74 (*s*, $CH_2$(4)); 4.70 (*s*, $CH_2$(2)); 2.23 (*s*, Me). $^{13}$C-NMR (75 MHz, $CDCl_3$): 205.1 (C(3)); 148.4 (C(9a)); 146.9 (C(5a)); 130.4 (C(6)); 125.4 (C(7)); 123.0 (C(8)); 118.6 (C(9)); 75.6 (C(4)); 75.5 (C(2)); 16.1 (Me). EI-MS: 178 (100, $M^+$), 150 (5), 135 (32), 122 (2), 108 (5), 94 (82), 77 (17), 66 (77), 51 (17), 39 (19).

6. *Benzodioxepinone* **12** *by* Procedure B. *3,4-Dihydro-6-methyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-1,5-benzodioxepine* (**26a**). As described in *Exper. 4*, with **9a** (0.50 g, 4.03 mmol): **26a** (0.95 g, 90%). Brown viscous oil. IR (neat): 3452 (br.), 3075*w*, 3017*w*, 2943*s*, 2870*s*, 2739*w*, 1906*w*, 1835*w*, 1724*w*, 1649*w*, 1624*w*, 1593*m*, 1477*s*, 1455*m*, 1440*m*, 1402*w*, 1379*w*, 1355*m*, 1302*s*, 1272*s*, 1248*m*, 1194*s*, 1159*m*, 1128*s*, 1084*s*, 1034*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.77 (*s*, H–C(7), H–C(8), H–C(9)); 4.75 ('*t*', H–C(2′)); 4.45–4.23 (*m*, $CH_2$(2), H–C(3), $CH_2$(4)); 3.95–3.87 (*m*, $H_a$–C(6′)); 3.57–3.50 (*m*, $H_b$–C(6′)); 2.21 (*s*, Me); 1.90–1.51 (*m*, $CH_2$(3′), $CH_2$(4′), $CH_2$(5′)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 150.0 (C(9a)); 148.5 (C(5a)); 130.0 (C(6)); 124.4 (C(7)); 122.0 (C(8)); 118.4 (C(9)); 98.4 (C(2′)); 74.4 (C(3)); 72.9 (C(2)); 71.9 (C(4)); 62.7 (C(6′)); 30.7 (C(3′)); 25.3 (C(5′)); 19.5 (C(4′)); 16.2 (Me). EI-MS: 264 (58, $M^+$), 236 (6), 208 (3), 206 (1), 180 (14), 162 (21), 149 (8), 135 (38), 124 (5), 123 (6), 105 (5), 99 (5), 94 (5), 91 (7), 85 (100), 77 (10), 67 (18), 57 (22), 55 (8).

*3,4-Dihydro-6-methyl-2*H*-1,5-benzodioxepin-3-ol* (**27a**). As described in *Exper. 4*, with **26a** (0.70 g, 2.65 mmol): **27a** (0.41 g, 85%). Clear oil which solidified to a white solid upon cooling. M.p. (heptane) 34–38°. IR (KBr): 3265 (br.), 2964*m*, 2920*m*, 2860*w*, 1589*w*, 1528*w*, 1477*s*, 1438*m*, 1377*w*, 1343*w*, 1292*s*, 1278*s*, 1247*m*, 1196*s*, 1161*w*, 1138*s*, 1087*s*, 1045*s*, 1011*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.86 (*s*, H–C(7), H–C(8), H–C(9)); 4.35–4.25 (*m*, H–C(3)); 4.08–3.99 (*m*, $CH_2$(2), $CH_2$(4)); 2.60 (br. *s*, OH); 2.24 (*s*, Me). $^{13}$C-NMR (75 MHz, $CDCl_3$): 151.4 (C(9a)); 149.7 (C(5a)); 131.0 (C(6)); 125.5 (C(7)); 123.2 (C(8)); 119.2 (C(9)); 74.8 (C(2)); 74.4 (C(4)); 69.7 (C(3)); 16.1 (Me). EI-MS: 180 (100, $M^+$), 161 (3), 149 (16), 136 (22), 135 (62), 124 (21), 123 (24), 109 (12), 107 (4), 105 (5), 95 (5), 94 (9), 91 (12), 89 (2), 78 (11), 77 (16), 66 (11), 57 (3), 52 (5), 51 (7).

*6-Methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**12**). As described in *Exper. 4*, with **27a** (0.40 g, 2.22 mmol). The obtained yellow resin was purified by bulb-to-bulb distillation at 50–60°/0.2 Torr: **12** (0.22 g, 56%). Clear oil.

7. *Benzodioxepinone* **13** *by* Procedure A. *2,2′-[(3-Methoxy-1,2-phenylene)bis(oxy)]bis[acetic Acid] Dimethyl Ester* (**10b**). As described in *Exper. 3* (conventional method), with **9b** (2.51 g, 17.9 mmol). Purification involved bulb-to-bulb distillation (190°/0.5 Torr) performed twice: **10b** (3.35 g, 66%). Clear oil. The microwave procedure provided **10b** in 45% yield. IR (KBr): 2954*w*, 2918*w*, 2843*w*, 1757*s*, 1602*m*, 1499*m*, 1479*s*, 1445*m*, 1397*w*, 1387*w*, 1306*m*, 1259*m*, 1217*s*, 1182*m*, 1125*s*, 1093*m*, 1069*m*. $^1$H-NMR (300 MHz, $CDCl_3$)[1]): 6.94–6.45 (*m*, H–C(4′), H–C(5′), H–C(6′)); 4.65 (*s*, $CH_2$(1″)); 4.64 (*s*, $CH_2$(2)); 3.79 (*s*, arom. MeO); 3.75 (*s*, Me(3″)O); 3.72 (*s*, Me(3)O). $^{13}$C-NMR (75 MHz, $CDCl_3$)[1]): 169.4 (C(1)O); 169.1 (C(2″)O); 153.3 (C(1′)); 151.2 (C(3′)); 137.3 (C(2′)); 123.8 (C(5′)); 107.8 (C(4′)); 106.7 (C(6′)); 69.5 ($CH_2$(2)); 66.6 ($CH_2$(1″)); 56.1 (arom. MeO); 51.6 (Me(3)O, Me(3″)O). EI-MS: 284 (85, $M^+$), 252 (2), 211 (64), 192 (12), 165 (20), 153 (87), 137 (9), 125 (40), 107 (29), 95 (32), 77 (15), 65 (12), 51 (16), 45 (100).

*Methyl 3,4-Dihydro-6-methoxy-3-oxo- and 3,4-Dihydro-9-methoxy-3-oxo-2*H*-1,5-benzodioxepine-2-carboxylate* (**11b**). As described in *Exper. 3*, with **10b** (3.32 g, 11.69 mmol). Trituration with EtOH provided **11b** (2.50 g, 85%). White crystalline solid. M.p. (EtOH) 117–119°. IR (KBr): 2962*m*, 2897*w*, 2847*w*, 1767*s*, 1741*s*, 1596*m*, 1486*s*, 1473*s*, 1441*m*, 1435*m*, 1416*w*, 1345*m*, 1319*m*, 1277*s*, 1259*m*, 1246*m*, 1214*s*, 1204*s*, 1176*s*, 1105*s*, 1080*s*, 1068*m*, 1034*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.92–6.60 (*m*, H–C(7),

H–C(8), H–C(9)); 5.36 (*s*, H–C(2)); 4.75 (*d*, *J* = 16.6, $H_a$–C(4)); 4.54 (*d*, *J* = 16.6, $H_b$–C(4)); 3.88 (*s*, arom. MeO); 3.84 (*s*, COOMe). $^{13}$C-NMR (75 MHz, $CDCl_3$): 198.9 (C(3)); 164.9 ($CO_2$); 150.9 (C(9a)); 148.3 (C(6)); 137.0 (C(5a)); 122.6 (C(8)); 113.4 (C(7)); 108.0 (C(9)); 82.4 (C(2)); 76.9 (C(4)); 56.4 (arom. MeO); 52.9 (COO*Me*). EI-MS: 252 (97, $M^+$), 209 (16), 193 (15), 165 (28), 151 (30), 137 (9), 110 (46), 95 (100), 79 (19), 65 (16), 51 (31), 39 (53).

*6-Methoxy-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**13**). As described in *Exper. 3*, with **11b** (1.10 g, 4.36 mmol) in a minimum amount of EtOH/$CH_2Cl_2$ 2:1 for 2.5 h. Aq. workup involved neutralization with $NaHCO_3$ prior to extraction: **13** (0.81 g, 95%). White crystals. M.p. (pentane) 130–132°. IR (KBr): 3030*w*, 2962*m*, 2897*w*, 2847*w*, 1767*s*, 1740*s*, 1596*m*, 1486*s*, 1474*s*, 1441*m*, 1435*m*, 1415*w*, 1345*w*, 1319*m*, 1277*m*, 1259*m*, 1247*m*, 1214*s*, 1204*s*, 1176*m*, 1105*s*, 1080*m*, 1068*m*, 1034*w*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.94–6.62 (*m*, H–C(7), H–C(8), H–C(9)); 4.87 (*s*, $CH_2$(4)); 4.73 (*s*, $CH_2$(2)); 3.87 (*s*, MeO). $^{13}$C-NMR (75 MHz, $CDCl_3$): 204.2 (C(3)); 151.5 (C(6)); 149.4 (C(9a)); 138.4 (C(5a)); 122.9 (C(8)); 113.1 (C(7)); 106.7 (C(9)); 76.2 (C(2)); 75.6 (C(4)); 56.3 (MeO). EI-MS: 194 (100, $M^+$), 166 (2), 151 (63), 137 (3), 123 (5), 110 (32), 107 (18), 95 (75), 79 (10), 77 (5), 65 (10), 51 (15), 39 (21). HR-ESI-MS: 195.0650 ($C_{10}H_{10}O_4^+$, $[M+1]^+$; calc. 195.0657).

8. *Benzodioxepinone* **13** *by* Procedure B. *3,4-Dihydro-6-methoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-1,5-benzodioxepine* (**26b**). As described in *Exper. 4*, with **9b** (0.50 g, 3.57 mmol): **26b** (0.91 g, 91%). Brown viscous oil. IR (neat): 3436 (br.), 2944*s*, 2873*m*, 2853*m*, 2744*w*, 2251*w*, 1673*m*, 1652*m*, 1598*m*, 1588*m*, 1489*s*, 1476*s*, 1456*m*, 1441*m*, 1387*w*, 1356*w*, 1311*m*, 1273*m*, 1248*m*, 1202*s*, 1183*w*, 1162*w*, 1119*s*, 1103*s*, 1077*s*, 1093*s*, 1024*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.87–6.78 (*m*, H–C(8)); 6.62–6.51 (*m*, H–C(7), H–C(9)); 4.96–4.43 (*m*, $H_a$–C(2), $H_a$–C(4)); 4.56–4.04 (*m*, $H_b$–C(2), H–C(3), $H_b$–C(4)); 5.10 (*t*, *J* = 3.5, H–C(2′)); 3.84 (*s*, MeO); 3.56–3.49 (*m*, $CH_2$(6′)); 1.87–1.53 (*m*, $CH_2$(3′), $CH_2$(4′), $CH_2$(5′)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 151.2 (C(6)); 143.9 (C(9a)); 139.8 (C(5a)); 120.6 (C(8)); 113.2 (C(9)); 110.4 (C(7)); 98.0 (C(2′)); 74.1 (C(3)); 72.3 (C(2)); 70.2 (C(4)); 62.9 (C(6′)); 56.1 (MeO); 30.7 (C(3′)); 25.3 (C(5′)); 23.2 (C(4′)). EI-MS: 280 (50, $M^+$), 252 (13), 224 (4), 196 (29), 178 (18), 165 (7), 151 (36), 149 (11), 140 (12), 125 (5), 107 (14), 95 (18), 85 (100), 77 (5), 67 (20), 57 (29), 55 (15), 51 (6).

*3,4-Dihydro-6-methoxy-2*H*-1,5-benzodioxepin-3-ol* (**27b**). As described in *Exper. 4*, with **26b** (0.77 g, 2.75 mmol): **27b** (0.41 g, 76%). Yellow resin. IR (neat): 3459 (br.), 3099*w*, 2941*m*, 2840*w*, 1721*m*, 1646*w*, 1598*m*, 1588*m*, 1489*s*, 1475*s*, 1442*m*, 1361*w*, 1321*w*, 1304*w*, 1272*s*, 1249*s*, 1207*m*, 1183*m*, 1092*s*, 1076*s*, 1029*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.89 (*t*, *J* = 8.3, H–C(8)); 6.67–6.61 (*m*, H–C(7), H–C(9)); 4.41–4.26 (*m*, $H_a$–C(4), $H_a$–C(2)); 4.16–4.09 (*m*, $H_b$–C(4), H–C(3), $H_b$–C(2)); 3.86 (*s*, MeO); 2.01 (br. *s*, OH). $^{13}$C-NMR (75 MHz, $CDCl_3$): 152.3 (C(6)); 151.9 (C(9a)); 140.8 (C(5a)); 122.9 (C(8)); 113.7 (C(9)); 107.0 (C(7)); 75.2 (C(2)); 74.9 (C(4)); 69.7 (C(3)); 56.3 (MeO). EI-MS: 196 (100, $M^+$), 177 (1), 165 (9), 151 (38), 140 (25), 125 (15), 110 (11), 107 (26), 95 (21), 93 (17), 81 (4), 77 (5), 68 (2), 66 (2), 6.3 (3), 57 (4), 55 (4), 51 (10).

*6-Methoxy-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**13**). As described in *Exper. 4*, with **27b** (0.40 g, 2.04 mmol). The obtained yellow resin was bulb-to-bulb distilled at 65°/0.2 Torr: **13** (0.34 g, 87%). Clear crystals.

9. *Benzodioxepinone* **14** *by* Procedure A. *2,2′-[1,2-Phenylenebis(oxy)]bis[acetic Acid] Dimethyl Ester* (**10c**). As described in *Exper. 3* (conventional method), with **9c** (0.50 g, 4.54 mmol). Bulb-to-bulb distillation (180°/0.05 Torr) performed twice afforded **10c** (1.01 g, 88%). White solid. M.p. (pentane) 44–48°. The microwave procedure provided **10c** in 48% yield. IR (KBr): 3012*w*, 2961*m*, 1752*s*, 1708*w*, 1596*m*, 1507*s*, 1456*m*, 1434*m*, 1372*m*, 1334*m*, 1275*m*, 1233*s*, 1197*s*, 1180*s*, 1163*m*, 1138*s*, 1088*w*, 1068*m*, 1020*w*. $^1$H-NMR (300 MHz, $CDCl_3$)[1]: 6.94–6.86 (*m*, H–C(3′), H–C(4′), H–C(5′), H–C(6′)); 4.71 (*s*, $CH_2$(1″), $CH_2$(2)); 3.77 (*s*, Me(3)O, Me(3″)O). $^{13}$C-NMR (75 MHz, $CDCl_3$)[1]: 169.3 (C(1)O, C(2″)O); 147.9 (C(1′), C(2′)); 122.6 (C(4′), C(5′)); 115.3 (C(3′), C(6′)); 66.5 ($CH_2$(1″), $CH_2$(2)); 52.1 (Me(3)O, Me(3″)O). EI-MS: 254 (32, $M^+$), 222 (2), 193 (10), 162 (33), 149 (3), 135 (14), 121 (29), 107 (2), 95 (10), 77 (16), 63 (8), 52 (10), 45 (100).

*Methyl 3,4-Dihydro-3-oxo-2*H*-1,5-benzodioxepine-2-carboxylate* (**11c**). As described in *Exper. 3*, with **10c** (3.65 g, 14.37 mmol): **11c** (2.78 g, 87%). Pale brown oil. IR (neat): 3472*m*, 2956*m*, 1746*s*, 1682*m*, 1634*w*, 1594*m*, 1494*s*, 1456*m*, 1439*s*, 1396*w*, 1338*m*, 1273*s*, 1250*m*, 1228*s*, 1157*m*, 1106*m*, 1081*m*, 1025*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.11–6.95 (*m*, H–C(6), H–C(7), H–C(8), H–C(9)); 5.36 (*s*, H–C(2));

4.82 (*d*, *J* = 16.8, $H_a$–C(4)); 4.60 (*d*, *J* = 16.8, $H_b$–C(4)); 3.85 (*s*, MeO). $^{13}$C-NMR (75 MHz, $CDCl_3$): 199.3 (C(3)); 165.2 ($CO_2$); 147.2 (C(5a)); 147.0 (C(9a)); 125.0 (C(7)); 123.6 (C(9)); 121.4 (C(8)); 120.5 (C(6)); 81.8 (C(2)); 76.8 (C(4)); 52.9 (MeO). EI-MS: 222 (99, $M^+$), 190 (6), 163 (17), 146 (3), 135 (100), 121 (61), 107 (24), 92 (4) 91 (4), 80 (52), 77 (38), 69 (11), 65 (26), 63 (26), 52 (41), 43 (30).

*2*H-*1,5-Benzodioxepin-3(4*H*)-one* (**14**). As described in *Exper. 3*, with **11c** (0.65 g, 2.93 mmol) in EtOH/$CH_2Cl_2$ 2:1. The obtained yellow-brown semi-solid **14** (0.45 g, 94%) was triturated with $CH_2Cl_2$: **14** (0.05 g, 10%). White crystalline solid. M.p. ($CH_2Cl_2$) 64–65°. IR (KBr): 3408*w*, 2957*m*, 1741*s*, 1631*m*, 1586*w*, 1495*s*, 1459*w*, 1303*m*, 1263*s*, 1181*w*, 1153*w*, 1097*m*, 1052*s*, 1025*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.90 (*s*, H–C(6), H–C(7), H–C(8), H–C(9)); 4.08 (*s*, $CH_2$(2), $CH_2$(4)). $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$): 204.3 (C(3)); 152.2 (C(5a), C(9a)); 124.9 (C(7), C(8)); 122.7 (C(6), C(9)); 79.4 (C(2), C(4)). EI-MS: 164 (100, $M^+$), 136 (2), 121 (27), 108 (10), 94 (3), 80 (75), 63 (13), 52 (27), 32 (22).

10. *Benzodioxepinone* **18** *by* Procedure B. *3,4-Dihydro-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-1,5-benzodioxepine* (**26c**). As described in *Exper. 4*, with **9c** (0.50 g, 4.54 mmol): **26c** (0.99 g, 87%). Yellow-brown viscous oil. IR (neat): 3436 (br.), 3069*w*, 3036*w*, 2942*s*, 2871*m*, 2852*m*, 2741*w*, 2661*w*, 2223*w*, 1932*w*, 1737*w*, 1600*w*, 1583*m*, 1492*s*, 1464*m*, 1455*m*, 1442*w*, 1403*w*, 1379*w*, 1356*w*, 1303*s*, 1258*s*, 1248*s*, 1202*w*, 1181*w*, 1160*m*, 1122*m*, 1104*m*, 1074*s*, 1043*s*, 1022*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.01–6.86 (*m*, H–C(6), H–C(7), H–C(8), H–C(9)); 4.74 (*t*, *J* = 3.6, H–C(2′)); 4.45–4.10 (*m*, $CH_2$(2), H–C(3), $CH_2$(4)); 3.94–3.87 (*m*, $H_a$–C(6′)); 3.57–3.50 (*m*, $H_b$–C(6′)); 1.89–1.50 (*m*, $CH_2$(3′), $CH_2$(4′), $CH_2$(5′)). $^{13}$C-NMR (75 MHz, $(CD_3)_2CO$): 150.0 (C(5a), C(9a)); 124.0 (C(8)); 122.9 (C(7)); 121.5 (C(6)); 120.8 (C(9)); 98.5 (C(2′)); 74.4 (C(3)); 73.1 (C(2)); 72.0 (C(4)); 62.7 (C(6′)); 30.8 (C(3′)); 25.3 (C(5′)); 19.4 (C(4′)). EI-MS: 250 (43, $M^+$), 222 (2), 194 (2), 166 (18), 148 (23), 135 (7), 121 (37), 109 (5), 107 (1), 103 (1), 99 (5), 91 (4), 85 (100), 77 (7), 67.1 (15), 57 (18), 55 (11).

*3,4-Dihydro-2*H*-1,5-benzodioxepin-3-ol* (**27c**). As described in *Exper. 4*, with **26c** (0.82 g, 3.28 mmol). The obtained clear oil partially solidified to a white semi-solid upon cooling. Evaporative crystallization from $Et_2O$/pentane gave **27c** (0.49 g, 91%). Clear crystals. M.p. (pentane) 48–50°. IR (KBr): 3266 (br.), 2964*w*, 2917*w*, 2856*w*, 1594*w*, 1579*w*, 1523*w*, 1494*m*, 1455*w*, 1402*w*, 1375*w*, 1261*s*, 1182*w*, 1132*m*, 1098*m*, 1040*s*, 1019*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.04–6.94 (*m*, H–C(6), H–C(7), H–C(8), H–C(9)); 4.31–4.26 (*m*, $H_a$–C(4), $H_a$–C(2)); 4.12–4.07 (*m*, $H_b$–C(4), H–C(3), $H_b$–C(2)); 2.61 (br. *s*, OH). $^{13}$C-NMR (75 MHz, $CDCl_3$): 151.1 (C(5a), C(9a)); 124.0 (C(7), C(8)); 121.6 (C(6), C(9)); 74.8 (C(2), C(4)); 69.7 (C(3)). EI-MS: 166 (100, $M^+$), 147 (3), 135 (19), 122 (26), 121 (77), 110 (30), 109 (12), 95 (15), 81 (9), 77 (14), 63 (13), 52 (9).

*2*H-*1,5-Benzodioxepin-3(4*H*)-one* (**14**). As described in *Exper. 4*, with **27c** (0.39 g, 2.35 mmol). The obtained pale yellow oil was purified by CC (silica gel (short column), $CH_2Cl_2$): **14** (0.23 g, 60%). White crystalline solid. M.p. ($CH_2Cl_2$) 64–65°.

11. *Benzodioxepinone* **15** *by* Procedure A. *2,2′-[(4-Nitro-1,2-phenylenebis(oxy)]bis[acetic Acid] Dimethyl Ester* (**10d**). As described in *Exper. 3* (microwave procedure), with **9d** (0.50 g, 3.22 mmol). Purification by vacuum CC (silica gel (short column), pentane, then AcOEt/pentane 1:9 → 3:7 gradient), followed by bulb-to-bulb distillation (215°/0.1 Torr) provided **10d** (0.71 g, 74%). Bright yellow solid. The conventional method provided **10d** in 53% yield. M.p. (pentane) 84–86°. IR (KBr): 3087*w*, 2960*w*, 1757*s*, 1590*w*, 1520*m*, 1505*m*, 1437*w*, 1373*w*, 1347*m*, 1309*w*, 1286*m*, 1242*w*, 1207*s*, 1174*m*, 1145*w*, 1109*m*, 1085*m*, 1062*m*. $^1$H-NMR (300 MHz, $CDCl_3$)[1]): 7.93–6.85 (*m*, H–C(3′), H–C(5′), H–C(6′)); 4.83 (*s*, $CH_2$(2)); 4.80 (*s*, $CH_2$(1″)); 3.82 (*s*, Me(3)O); 3.81 (*s*, Me(3″)O). $^{13}$C-NMR (75 MHz, $CDCl_3$)[1]): 168.3 (C(1)O); 168.1 (C(2″)O); 153.0 (C(1′)); 147.4 (C(2′)); 142.2 (C(4′)); 118.7 (C(6′)); 113.0 (C(5′)); 109.8 (C(3′)); 66.1 ($CH_2$(2)); 66.0 ($CH_2$(1″)); 52.5 (Me(3)O); 52.4 (Me(3″)O). EI-MS: 299 (22, $M^+$), 267 (10), 240 (10), 207 (5), 194 (8), 180 (15), 166 (16), 151 (3), 135 (5), 120 (6), 107 (5), 92 (3), 79 (17), 63 (9), 51 (13), 45 (100), 30 (3).

*Methyl 3,4-Dihydro-7-nitro-3-oxo- and 3,4-Dihydro-8-nitro-3-oxo-2*H*-1,5-benzodioxepine-2-carboxylate* (**11d**). As described in *Exper. 3*, with **10d** (0.71 g, 2.37 mmol): crude **11d** (0.43 g, 68%). Bright red/yellow oil as a complex mixture. IR (neat): 3413*m*, 2924*s*, 2725*w*, 2255*w*, 2128*w*, 1740*m*, 1645*m*, 1590*w*, 1519*m*, 1460*s*, 1376*m*, 1342*m*, 1278*m*, 1051*s*, 1026*s*, 1005*s*. EI-MS: 267 (100, $M^+$), 235 (11), 207 (22), 194 (6), 180 (8), 166 (29), 162 (10), 149 (8), 134 (66), 119 (21), 107 (24), 101 (7), 92 (16), 79 (53), 77 (18), 75 (32), 69 (19), 65 (11), 63 (31), 59 (32), 53 (23), 51 (48), 45 (38), 39 (14).

*7-Nitro-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**15**). As described in *Exper. 3*, with **11d** (0.81 g, 3.03 mmol) for 2.5 h. The obtained brown semi-solid (0.28 g) was purified by semi-prep. HPLC ($t_R$ 11.7 min; $\lambda_{max}$ 239 and 311 nm): **15** (16 mg, 2%). Orange oil. IR (KBr): 3452*w*, 3080*w*, 2925*w*, 2853*w*, 1801*w*, 1736*s*, 1587*m*, 1517*s*, 1491*m*, 1429*w*, 1346*s*, 1315*m*, 1274*s*, 1176*w*, 1122*w*, 1098*w*, 1080*w*, 1036*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 8.03–7.11 (*m*, H–C(6), H–C(8), H–C(9)); 4.98 (*s*, $CH_2$(2)); 4.91 (*s*, $CH_2$(4)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 202.1 (C(3)); 153.7 (C(9a)); 147.9 (C(5a)); 143.3 (C(7)); 121.3 (C(9)); 119.8 (C(8)); 117.6 (C(6)); 76.3 (C(2)); 75.3 (C(4)). EI-MS: 209 (100, $M^+$), 193 (2), 167 (4), 166 (3), 163 (3), 151 (14), 135 (15), 120 (4), 107 (55), 105 (8), 90 (3), 79 (37), 77 (12), 75 (14), 63 (12), 51 (23). HR-ESI-MS: 209.0325 ($C_9H_7O_5N^+$, $M^+$; calc. 209.0324).

12. *Benzodioxepinone* **15** *by* Procedure B. *3,4-Dihydro-7-nitro-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-1,5-benzodioxepine* (**26d**). As described in *Exper. 4*, with **9d** (0.50 g, 3.22 mmol): **26d** (0.81 g, 85%). Deep orange viscous oil. IR (neat): 3428 (br.), 3081*w*, 2945*s*, 2870*m*, 2605*w*, 2243*w*, 1994*w*, 1809*s*, 1720*w*, 1586*m*, 1520*s*, 1494*m*, 1463*w*, 1424*w*, 1347*s*, 1322*m*, 1281*s*, 1265*s*, 1202*w*, 1182*w*, 1159*w*, 1123*s*, 1073*s*, 1033*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.80–7.77 (*m*, H–C(8), H–C(6)); 7.00–6.97 (*m*, H–C(9)); 4.71 ('*t*', H–C(2′)); 4.54–4.27 (*m*, $CH_2$(2), H–C(3), $CH_2$(4)); 3.92–3.84 (*m*, $H_a$–C(6′)); 3.57–3.50 (*m*, $H_b$–C(6′)); 1.86–1.51 (*m*, $CH_2$(3′), $CH_2$(4′), $CH_2$(5′)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 155.5 (C(9a)); 149.5 (C(5a)); 142.6 (C(7)); 120.8 (C(9)); 118.8 (C(8)); 116.9 (C(6)); 98.9 (C(2′)); 74.4 (C(3)); 73.0 (C(2)); 72.1 (C(4)); 62.8 (C(6′)); 30.6 (C(3′)); 25.1 (C(5′)); 19.4 (C(4′)). EI-MS: 295 (11, $M^+$), 211 (19), 193 (19), 180 (1), 166 (12), 147 (3), 134 (1), 120 (4), 107 (2), 91 (3), 85 (100), 79 (5), 67 (10), 63 (3), 57 (11), 55 (4), 51 (3).

*3,4-Dihydro-7-nitro-2*H-*1,5-benzodioxepin-3-ol* (**27d**). As described in *Exper. 4*, with **26d** (0.76 g, 2.57 mmol). The obtained yellow resin was crystallized from $Et_2O$: **27d** (0.28 g, 52%). Pale yellow solid. M.p. ($Et_2O$) 74–78°. IR (KBr): 3453 (br.), 3105*w*, 3076*w*, 2953*w*, 1802*w*, 1721*w*, 1587*w*, 1518*s*, 1496*m*, 1466*w*, 1422*w*, 1351*s*, 1325*m*, 1283*s*, 1270*m*, 1186*w*, 1126*w*, 1103*w*, 1077*m*, 1020*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.87–7.82 (*m*, H–C(6), H–C(8)); 7.05 (*d*, *J* = 8.7, H–C(9)); 4.36–4.21 (*m*, $CH_2$(2), H–C(3), $CH_2$(4)); 2.12 (br. *s*, OH). $^{13}$C-NMR (75 MHz, $CDCl_3$): 155.9 (C(9a)); 150.1 (C(5a)); 143.2 (C(7)); 121.5 (C(9)); 119.4 (C(8)); 117.5 (C(6)); 74.9 (C(2)); 74.6 (C(4)); 69.0 (C(3)). EI-MS: 211 (100, $M^+$), 192 (2), 180 (14), 167 (11), 166 (11), 155 (9), 152 (4), 137 (12), 134 (5), 121 (11), 107 (20), 94 (4), 91 (6), 79 (15), 77 (4), 75 (4), 65 (16), 63 (16), 57 (15), 51 (13).

*7-Nitro-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**15**). At −78° under $N_2$, DMSO (0.42 g, 5.37 mmol) in $CH_2Cl_2$ (5 ml) was added dropwise over 20 min to oxalyl chloride (0.34 g, 2.68 mmol) in $CH_2Cl_2$ (40 ml), and the mixture was stirred for 15 min. Then **27d** (0.25 g, 1.18 mmol) in $CH_2Cl_2$ (5 ml) was added dropwise over 30 min followed by stirring at −78° for 90 min. $Et_3N$ (0.68 g, 6.72 mmol) was then added dropwise over 15 min, and the soln. was stirred for a further 2 h at −78°. THF/$H_2O$ 1:1 (10 ml) was added while maintaining the temp. of the mixture below −60°. The soln. was then allowed to reach 0° followed by addition of $CH_2Cl_2$ (40 ml). The org. mixture was washed with 2M HCl (2 × 60 ml), dried ($MgSO_4$), and concentrated and the crude resin crystallized from MeCN: **15** (0.21 g, 84%). Bright yellow semi-solid. M.p. (MeCN) 110–112°.

13. *Benzodioxepinone* **16** *by* Procedure A. *2,2′-[(4-Formyl-1,2-phenylene)bis(oxy)]bis[acetic Acid] Dimethyl Ester* (**10e**). As described in *Exper. 3* (microwave procedure), with **9e** (1.00 g, 7.24 mmol). Purification by bulb-to-bulb distillation (210°/0.1 Torr) gave **10e** (1.61 g, 79%). White solid. The conventional method gave **10e** in 55% yield. M.p. (pentane) 84–86°. IR (KBr): 2957*w*, 1765*m*, 1751*s*, 1682*m*, 1598*m*, 1588*m*, 1520*m*, 1442*m*, 1428*m*, 1404*w*, 1392*w*, 1380*w*, 1340*m*, 1332*m*, 1290*m*, 1218*s*, 1175*m*, 1133*s*, 1080*w*, 1060*m*. $^1$H-NMR (300 MHz, $CDCl_3$)[1]): 9.83 (*s*, CHO); 7.50–6.91 (*m*, H–C(3′), H–C(5′), H–C(6′)); 4.81 (*s*, $CH_2$(1″)); 4.78 (*s*, $CH_2$(2)); 3.80 (*s*, Me(3)O, Me(3″)O). $^{13}$C-NMR (75 MHz, $CDCl_3$)[1]): 190.4 (CHO)); 168.4 (C(1)O, C(2″)O); 152.8 (C(1′)); 148.1 (C(2′)); 131.0 (C(4′)); 126.9 (C(5′)); 113.3 (C(6′)); 112.6 (C(3′)); 65.9 ($CH_2$(1″), $CH_2$(2)); 52.3 (Me(3)O, Me(3″)O). EI-MS: 282 (38, $M^+$), 250 (11), 223 (7), 193 (4), 177 (5), 163 (18), 149 (35), 135 (4), 119 (8), 105 (5), 95 (6), 77 (11), 63 (8), 51 (10), 45 (100).

*Methyl 7-Formyl-3,4-dihydro-3-oxo- and 8-Formyl-3,4-dihydro-3-oxo-2*H-*1,5-benzodioxepine-2-carboxylate* (**11e**). As described in *Exper. 3*, with **10e** (0.30 g, 1.06 mmol): crude **11e** (0.13 g, 50%). Yellow oil as a complex mixture. IR (neat): 3425*m*, 2956*m*, 2361*w*, 1742*s*, 1688*m*, 1599*m*, 1509*m*, 1440*m*, 1276*s*,

1212*s*, 1163*m*, 1130*m*, 1063*m*. EI-MS: 178 (56), 149 (100), 121 (25), 103 (1), 91 (6), 79 (6), 63 (14), 51 (12), 42 (8).

*3,4-Dihydro-3-oxo-2*H*-1,5-benzodioxepine-7-carboxaldehyde* (**16**). As described in *Exper. 3*, with **11e** (0.17 g, 0.68 mmol). Extraction was performed without $NaHCO_3$ neutralization: yellow oily **16** (0.11 g, 85%). The sample was purified by semi-prep. HPLC ($t_R$ 7.8 min, $\lambda_{max}$ 270 nm): **16** (12 mg, 11%). Yellow semi-solid. IR (KBr): 3437 (br.), 3041*w*, 2923*w*, 2852*w*, 2836*w*, 2735*w*, 1802*w*, 1736*s*, 1704*w*, 1683*s*, 1605*w*, 1575*s*, 1508*m*, 1438*w*, 1421*w*, 1383*w*, 1359*w*, 1341*w*, 1314*m*, 1299*m*, 1283*s*, 1269*s*, 1236*w*, 1208*w*, 1162*w*, 1109*w*, 1044*m*, 1027*w*, 1017*w*. $^1$H-NMR (300 MHz, $CDCl_3$): 9.85 (*s*, CHO); 7.53–7.50 (*m*, H–C(6), H–C(8)); 7.10 (*d*, $J$ = 8.8, H–C(9)); 4.79 (*s*, $CH_2$(2)); 4.71 (*s*, $CH_2$(4)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 203.0 (C(3)); 190.2 (CHO); 153.5 (C(9a)); 148.6 (C(5a)); 132.4 (C(7)); 126.0 (C(8)); 122.7 (C(9)); 121.6 (C(6)); 76.1 (C(2)); 75.2 (C(4)). EI-MS: 192 (100, $M^+$), 163 (81), 149 (6), 135 (13), 121 (5), 108 (15), 91 (4), 79 (26), 63 (12), 51 (19), 42 (6), 39 (5).

14. *Preparation of* **16** *by* Procedure B. *3,4-Dihydro-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-1,5-benzodioxepine-7-carboxaldehyde* (**26e**). As described in *Exper. 4*, with **9e** (0.50 g, 3.62 mmol): **26e** (0.74 g, 74%). Caramel brown viscous oil. IR (neat): 3422 (br.), 3063*w*, 2943*m*, 2869*m*, 2733*w*, 1803*w*, 1686*s*, 1601*s*, 1573*m*, 1501*s*, 1432*m*, 1389*w*, 1356*w*, 1316*m*, 1281*s*, 1201*w*, 1158*m*, 1127*s*, 1074*s*, 1033*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 9.77 (*s*, CHO); 7.42–6.95 (*m*, H–C(6), H–C(8), H–C(9)); 4.72 ('*t*', H–C(2′)); 4.59–4.22 (*m*, $CH_2$(4), H–C(3), $CH_2$(2)); 4.01–3.78 (*m*, $H_a$–C(6′)); 3.56–3.51 (*m*, $H_b$–C(6′)); 1.80–1.18 (*m*, $CH_2$(5′), $CH_2$(4′), $CH_2$(3′)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 190.6 (CHO); 155.3 (C(9a)); 150.1 (C(5a)); 131.7 (C(7)); 125.2 (C(8)); 121.4 (C(9)); 121.3 (C(6)); 98.7 (C(2′)); 74.0 (C(3)); 72.9 (C(2)); 72.0 (C(4)); 62.8 (C(6′)); 30.7 (C(3′)); 25.2 (C(5′)); 19.5 (C(4′)). EI-MS: 278 (22, $M^+$), 250 (1), 222 (2), 194 (30), 176 (19), 164 (16), 149 (30), 137 (4), 121 (3), 119 (4), 113 (3), 109 (2), 105 (1), 103 (1), 99 (1), 93 (1), 91 (5), 85 (100), 79 (5), 67 (13), 57.1 (14), 55 (7), 51 (3).

*3,4-Dihydro-3-hydroxy-2*H*-1,5-benzodioxepine-7-carboxaldehdye* (**27e**). As described in *Exper. 4*, with **26e** (0.56 g, 2.01 mmol): **27e** (0.35 g, 89%). Yellow resin. IR (neat): 3440 (br.), 3078*w*, 2939*m*, 2856*m*, 2735*w*, 2620*w*, 1794*w*, 1731*m*, 1688*s*, 1599*s*, 1588*m*, 1574*m*, 1505*s*, 1434*s*, 1394*w*, 1359*w*, 1338*w*, 1317*m*, 1280*s*, 1169*m*, 1138*m*, 1099*w*, 1035*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 9.82 (*s*, CHO); 7.47–7.45 (*m*, H–C(6), H–C(8)); 7.06 (*d*, $J$ = 8.8, H–C(9)); 4.32–4.14 (*m*, $CH_2$(2), H–C(3), $CH_2$(4)); 2.87 (br. *s*, OH). $^{13}$C-NMR (75 MHz, $CDCl_3$): 190.6 (CHO); 155.8 (C(9a)); 150.8 (C(5a)); 132.2 (C(7)); 125.7 (C(8)); 122.6 (C(9)); 121.8 (C(6)); 74.7 (C(2)); 74.5 (C(4)); 69.1 (C(3)). EI-MS: 194 (100, $M^+$), 175 (3), 163 (17), 149 (65), 137 (21), 121 (13), 119 (6), 109 (6), 105 (3), 95 (6), 91 (5), 79 (8), 77 (8), 65 (9), 63 (11), 57 (7), 51 (9).

*3,4-Dihydro-3-oxo-2*H*-1,5-benzodioxepine-7-carboxaldehyde* (**16**). As described in *Exper. 4*, with **27e** (0.25 g, 1.29 mmol). The crude resin was crystallized from MeCN: **16** (0.13 g, 52%). White solid. M.p. (MeCN) 110–112°.

15. *Benzodioxepinone* **17** *by* Procedure A. *2,2′-{[4-(*tert*-Butyl)-1,2-phenylene]bis(oxy)}bis[acetic Acid] Dimethyl Ester* (**10f**). As described in *Exper. 3* (conventional method), with **9f** (1.00 g, 6.02 mmol). Bulb-to-bulb distillation (190°/0.3 Torr) performed twice afforded **10f** (1.40 g, 75%). Clear oil. IR (neat): 2908*s*, 2956*s*, 2870*m*, 2111*w*, 1762*s*, 1608*m*, 1592*m*, 1583*m*, 1510*s*, 1440*s*, 1414*m*, 1376*m*, 1364*m*, 1294*s*, 1201*s*, 1153*s*, 1110*m*, 1068*s*, 1028*m*, 1005*m*. $^1$H-NMR (300 MHz, $CDCl_3$)[1]): 6.96–6.77 (*m*, H–C(3′), H–C(5′), H–C(6′)); 4.72 (*s*, $CH_2$(1″)); 4.68 (*s*, $CH_2$(2)); 3.78 (*s*, Me(3)O, Me(3″)O); 1.26 (*s*, $^t$Bu). $^{13}$C-NMR (75 MHz, $CDCl_3$)[1]): 169.5 (CO(1), CO(2″)); 147.3 (C(1′)); 145.9 (C(2′), C(4′)); 119.4 (C(5′)); 114.9 (C(6′)); 114.2 (C(3′)); 67.2 ($CH_2$(2)); 66.7 ($CH_2$(1″)); 52.1 (Me(3)O); 52.0 (Me(3″)O); 34.3 ($Me_3C$); 31.3 ($Me_3C$). EI-MS: 310 (23, $M^+$), 295 (100), 222 (2), 205 (1), 191 (1), 177 (4), 163 (11), 149 (3), 133 (5), 121 (2), 117 (2), 105 (4), 91 (6), 77 (5), 65 (2), 59 (2), 51 (1), 45 (32).

*Methyl 7-(*tert*-Butyl)-3,4-dihydro-3-oxo- and 8-(*tert*-Butyl)-3,4-dihydro-3-oxo-2*H*-1,5-benzodioxepine-2-carboxylate* (**11f**). As described in *Exper. 3*, with **10f** (2.42 g, 7.81 mmol): **11f** (1.89 g, 87%). Clear brown oil. IR (neat): 3456*m*, 2958*s*, 2870*s*, 2566*m*, 2085*w*, 1741*s*, 1582*m*, 1504*s*, 1473*m*, 1437*s*, 1414*s*, 1364*m*, 1269*s*, 1206*s*, 1149*s*, 1126*s*, 1102*m*, 1079*m*. $^1$H-NMR (300 MHz, $CDCl_3$): *Regioisomer 1:* 7.11–6.94 (*m*, H–C(6), H–C(8), H–C(9)); 5.40 (*s*, H–C(2)); 4.82 (*d*, $J$ = 16.4, $H_a$–C(4)); 4.60 (*d*, $J$ = 16.6, $H_b$–C(4)); 3.87 (*s*, MeO); 1.28 (*s*, $^t$Bu); *Regioisomer 2:* 7.11–6.94 (*m*, H–C(6), H–C(8), H–C(9)); 5.36 (*s*, H–C(2)); 4.81 (*d*, $J$ = 17.1, $H_a$–C(4)); 4.58 (*d*, $J$ = 16.8, $H_b$–C(4)); 3.86 (*s*, MeO); 1.28 (*s*, $^t$Bu). $^{13}$C-NMR (75 MHz, $CDCl_3$): *Regioisomer 1:* 199.6 (C(3)); 165.5 ($CO_2$); 148.5 (C(9a)); 146.4 (C(5a));

144.5 (C(7)); 120.8 (C(8)); 119.8 (C(9)); 117.5 (C(6)); 81.7 (C(2)), 76.7 (C(4)); 52.9 (MeO); 34.4 ($Me_3C$); 31.3 ($Me_3C$); *Regioisomer 2:* 199.6 (C(3)); 165.4 ($CO_2$); 147.2 (C(9a)); 145.7 (C(5a)); 144.8 (C(7)); 121.8 (C(8)); 120.6 (C(9)); 118.2 (C(6)); 81.9 (C(4)); 76.8 (C(2)); 52.9 (MeO); 34.2 ($Me_3C$); 31.3 ($Me_3C$). EI-MS: 278 (22, $M^+$), 263 (100), 235 (5), 219 (3), 205 (6), 191 (3), 175 (5), 163 (3), 147 (4), 133 (2), 121 (3), 115 (4), 105 (3), 91 (6), 77 (5), 65 (2), 55 (2), 41 (2), 32 (5).

*7-(*tert-*Butyl)-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**17**). As described in *Exper. 3*, with **11f** (1.24 g, 4.46 mmol) for 2.5 h, with the aq. workup involving neutralization with aq. $NaHCO_3$ soln. prior to extraction. The obtained brown oil was bulb-to-bulb distilled at 100–105°/0.2 Torr: **17** (0.82 g, 84%). White crystalline solid. M.p. (pentane) 66–68°. IR (KBr): 2965*s*, 2950*m*, 2901*m*, 2868*m*, 1791*w*, 1742*s*, 1577*m*, 1504*s*, 1477*m*, 1461*m*, 1438*m*, 1424*m*, 1409*m*, 1394*w*, 1367*w*, 1359*w*, 1347*w*, 1300*s*, 1274*s*, 1248*m*, 1206*m*, 1189*m*, 1127*m*, 1098*w*, 1045*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.02–6.79 (*m*, H–C(6), H–C(8), H–C(9)); 4.72 (*s*, $CH_2$(2)); 4.69 (*s*, $CH_2$(4)); 1.26 (*s*, $^t$Bu). $^{13}$C-NMR (75 MHz, $CDCl_3$): 204.9 (C(3)); 147.6 (C(9a)); 147.4 (C(5a)); 145.8 (C(7)); 120.7 (C(8)); 120.3 (C(9)); 117.8 (C(6)); 75.7 (C(2)); 75.6 (C(4)); 34.3 ($Me_3C$); 31.3 ($Me_3C$). EI-MS: 220 (26, $M^+$), 205 (100), 177 (11), 149 (3), 135 (4), 121 (4), 105 (4), 91 (7), 77 (7), 6.5 (3), 55 (2), 41 (3).

16. *Benzodioxepinone* **17** *by* Procedure B. *7-(*tert-*Butyl)-3,4-dihydro-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-1,5-benzodioxepine* (**26f**). As described in *Exper. 4*, with **9f** (0.5 g, 3.01 mmol): **26f** (0.90 g, 98%). Light brown viscous oil. IR (neat): 3435 (br.), 3039*w*, 2952*s*, 2870*m*, 2741*w*, 2662*w*, 1727*w*, 1625*w*, 1613*w*, 1574*m*, 1505*s*, 1463*m*, 1455*m*, 1442*w*, 1412*w*, 1393*w*, 1363*w*, 1355*w*, 1306*s*, 1274*m*, 1263*m*, 1239*m*, 1202*m*, 1185*w*, 1161*w*, 1122*s*, 1097*w*, 1076*s*, 1034*s*, 1023*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.96–6.86 (*m*, H–C(6), H–C(8), H–C(9)); 4.74 (*t*, $J$ = 2.8, H–C(2′)); 4.46–4.21 (*m*, $CH_2$(2), H–C(3), $CH_2$(4)); 3.95–3.86 (*m*, $H_a$–C(6′)); 3.57–3.49 (*m*, $H_b$–C(6′)); 1.90–1.43 (*m*, $CH_2$(3′), $CH_2$(4′), $CH_2$(5′)); 1.26 (*s*, $^t$Bu). $^{13}$C-NMR (75 MHz, $CDCl_3$): 147.5 (C(9a)); 146.3 (C(5a), (C(7)); 120.9 (C(8)); 120.1 (C(9)); 119.7 (C(6)); 98.4 (C(2′)); 74.5 (C(3)); 73.0 (C(2)); 71.9 (C(4)); 62.6 (C(6′)); 34.1 ($Me_3C$); 31.3 ($Me_3C$); 30.8 (C(3′)); 25.3 (C(5′)); 19.4 (C(4′)). EI-MS: 306 (77, $M^+$), 291 (58), 263 (3), 261 (2), 250 (2), 248 (1), 235 (13), 222 (19), 207 (81), 204 (5), 193 (5), 189 (24), 177 (12), 163 (6), 161 (6), 151 (10), 147 (3), 133 (10), 121 (4), 119 (4), 117 (3), 115 (3), 105 (12), 91 (12), 85 (100), 77 (11), 67 (17), 57 (25), 55 (17), 51 (36).

*7-(*tert-*Butyl)-3,4-dihydro-2*H-*1,5-benzodioxepin-3-ol* (**27f**). As described in *Exper. 4*, with **26f** (0.80 g, 2.61 mmol): **27f** (0.47 g, 81%). White solid. M.p. (pentane) 48–50°. IR (KBr): 3459 (br.), 2962*m*, 2866*w*, 1578*w*, 1503*s*, 1460*w*, 1447*w*, 1409*m*, 1390*w*, 1364*w*, 1311*s*, 1274*s*, 1252*m*, 1236*s*, 1204*w*, 1184*w*, 1118*m*, 1090*m*, 1057*m*, 1042*s*, 1022*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.04–6.95 (*m*, H–C(6), H–C(8), H–C(9)); 4.32–4.23 (*m*, $H_a$–C(2), $H_a$–C(4)); 4.09–4.04 (*m*, $H_b$–C(2), H–C(3), $H_b$–C(4)); 2.70 ('*s*', OH); 1.27 (*s*, $^t$Bu). $^{13}$C-NMR (75 MHz, $CDCl_3$): 150.4 (C(9a)); 148.5 (C(5a)); 147.5 (C(7)); 120.9 (C(8)); 120.8 (C(9)); 118.6 (C(6)); 74.7 (C(2), C(4)); 69.7 (C(3)); 34.2 ($Me_3C$); 31.3 ($Me_3C$). EI-MS: 222 (29, $M^+$), 207 (100), 163 (4), 151 (9), 133 (5), 123 (5), 105 (7), 91 (5), 77 (6), 65 (2).

*7-(*tert-*Butyl)-2*H-*1,5-benzodioxepin-3(4*H*)-one* (**17**). As described in *Exper. 4*, with **27f** (0.41 g, 1.85 mmol). The obtained clear oil was purified by bulb-to-bulb distillation at 100–105°/0.2 Torr: **17** (0.30 g, 73%). Crystalline solid M.p. (pentane) 66–68°.

17. *Benzodioxepinone* **18** *by* Procedure A. *2,2′-[Naphthalene-2,3-diylbis(oxy)]bis[acetic Acid] Dimethyl Ester* (**10g**). As described in *Exper. 3* (conventional method), with **9g** (2.00 g, 12.49 mmol). Purification was achieved by continuous trituration with $CH_2Cl_2$ until an ivory solid appeared: **10g** (3.56 g, 96%). The microwave procedure gave **10g** in 75% yield. M.p. ($CH_2Cl_2$) 78–80°. IR (KBr): 2975*w*, 2953*m*, 1751*s*, 1737*s*, 1629*w*, 1603*w*, 1585*w*, 1510*m*, 1488*s*, 1460*m*, 1447*m*, 1436*m*, 1410*w*, 1380*m*, 1339*w*, 1284*s*, 1247*s*, 1228*s*, 1189*m*, 1168*s*, 1123*m*, 1078*w*, 1047*m*, 1034*w*, 1024*m*. $^1$H-NMR (300 MHz, $CDCl_3$)[1]): 7.67 (*dd*, $J$ = 6.1, 3.1, H–C(5′), H–C(8′)); 7.35 (*dd*, $J$ = 6.1, 3.5, H–C(6′), H–C(7′)); 7.12 (*s*, H–C(1′), H–C(4′)); 4.83 (*s*, $CH_2$(2), $CH_2$(1″)); 3.82 (*s*, Me(3)O, Me(3″)O). $^{13}$C-NMR (75 MHz, $CDCl_3$)[1]): 169.1 (C(1)O, C(2″)O); 147.7 (C(2′), C(3′)); 129.5 (C(4a), C(8a)); 126.5 (C(5′), C(8′)); 124.8 (C(6′), C(7′)); 109.6 (C(1′), C(4′)); 66.2 ($CH_2$(2), $CH_2$(1″)); 52.3 (Me(3)O, MeO(3″)). EI-MS: 304 (100, $M^+$), 272 (8), 243 (23), 213 (8), 203 (5), 185 (26), 171 (87), 147 (6), 127 (26), 115 (36), 102 (25), 88 (6), 76 (6), 63 (6), 45 (67).

*3,4-Dihydro-methyl-3-oxo-2*H*-naphtho[2,3-*b*][1,4]dioxepine-2-carboxylate* (**11g**). As described in *Exper. 3*, with **10g** (1.39 g, 4.57 mmol): **11g** (1.16 g, 93%). Caramel brown oil. A portion of this sample was purified by semi-prep. HPLC ($t_R$ 29.9 min, $\lambda_{max}$ 230 nm): **11g** (21 mg, 2%). Light brown oil. IR (KBr):

3453*m*, 3056*w*, 2954*w*, 1744*s*, 1635*w*, 1602*w*, 1505*s*, 1469*s*, 1363*m*, 1277*s*, 1225*s*, 1172*s*, 1117*m*, 1072*m*, 1024*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.70 (*dd*, *J* = 6.0, 3.2, H–C(7), H–C(10)); 7.54 (*s*, H–C(11)); 7.45 (*s*, H–C(6)); 7.39 (*dd*, *J* = 6.7, 3.1, H–C(8), H–C(9)); 5.41 (*s*, H–C(2)); 4.96 (*d*, *J* = 17.1, $H_a$–C(4)); 4.81 (*d*, *J* = 17.1, $H_b$–C(4)); 3.86 (*s*, MeO). $^{13}$C-NMR (75 MHz, $CDCl_3$): 199.5 (C(3)); 165.3 ($CO_2$); 147.2 (C(11a)); 146.5 (C(5a)); 131.0 (C(10a)); 130.0 (C(6a)); 125.7 (C(8)); 125.3 (C(9)); 126.7 (C(10)); 126.8 (C(7)); 118.0 (C(11)); 116.7 (C(6)); 81.7 (C(2)); 76.5 (C(4)); 53.0 (MeO). EI-MS: 272 (3, $M^+$), 243 (12), 213 (5), 185 (17), 171 (61), 157 (2), 147 (3), 127 (19), 115 (28), 102 (20), 88 (6), 76 (5), 63 (6), 45 (100).

*2*H-*Naphtho[2,3-*b*][1,4]dioxepin-3(4*H*)-one* (**18**). As described in *Exper. 3*, with **11g** (0.33 g, 1.21 mmol) in a minimal amount of EtOH/AcOEt 2:1 for 2.5 h. Quenching of the reaction soln. in aq. $NaHCO_3$ soln. and usual workup gave brown semi-solid **18** (0.17 g, 65%). A portion of the sample was purified by semi-prep. HPLC ($t_R$ 15.1 min, $\lambda_{max}$ 230 nm): **11g** (18 mg, 7%). Light brown crystalline solid. M.p. (MeCN) 70–72°. IR (KBr): 3442*m*, 2960*s*, 2925*s*, 2854*s*, 1737*m*, 1599*w*, 1504*m*, 1470*m*, 1413*w*, 1363*m*, 1330*w*, 1289*m*, 1262*s*, 1169*w*, 1151*w*, 1098*m*, 1046*s*, 1030*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.51 (*dd*, *J* = 6.4, 3.2, H–C(7), H–C(10)); 7.19 (*dd*, *J* = 6.4, 3.1, H–C(8), H–C(9)); 7.07 (*s*, H–C(6), H–C(11)); 4.60 (*s*, $CH_2$(2), $CH_2$(4)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 204.8 (C(3)); 148.2 (C(5a), C(11a)); 130.4 (C(6a), C(10a)); 126.7 (C(7), C(10)); 125.4 (C(8), C(9)); 117.2 (C(11), C(6)); 75.4 (C(2), C(4)). EI-MS: 214 (100, $M^+$), 186 (6), 171 (58), 160 (4), 142 (2), 130 (33), 114 (32), 102 (63), 88 (12), 76 (15), 63 (20), 51 (16), 39 (7). HR-ESI-MS: 215.0715 ($C_{13}H_{10}O_3^+$, $[M+1]^+$; calc. 215.0629).

18. *Benzodioxepinone* **18** *by* Procedure B. *3,4-Dihydro-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-naphtho[2,3-*b*][1,4]dioxepine* (**26g**). As described in *Exper. 4*, with **9g** (0.5 g, 3.12 mmol): **26g** (0.77 g, 82%). Brown viscous oil. IR (neat): 3331 (br.), 3056*w*, 2943*s*, 2870*m*, 1708*m*, 1670*s*, 1631*w*, 1602*w*, 1503*s*, 1472*s*, 1453*s*, 1386*m*, 1359*m*, 1290*s*, 1260*s*, 1247*s*, 1201*m*, 1172*m*, 1159*m*, 1125*s*, 1074*s*, 1031*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.67–7.61 (*m*, H–C(7), H–C(10)); 7.36 (*s*, H–C(6), H–C(11)); 7.33–7.30 (*m*, H–C(8), H–C(9)); 4.77 ('*t*', H–C(2′)); 4.51–4.30 (*m*, $CH_2$(2), H–C(3), $CH_2$(4)); 4.05–3.83 (*m*, $H_a$–C(6′)); 3.59–3.44 (*m*, $H_b$–C(6′)); 1.90–1.20 (*m*, $CH_2$(3′), $CH_2$(4′), $CH_2$(5′)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 151.1 (C(11a)); 150.2 (C(5a)); 130.2 (C(6a), C(10a)); 126.5 (C(7), C(10)); 124.8 (C(8), C(9)); 116.9 (C(6), C(11)); 98.5 (C(2′)); 74.6 (C(3)); 73.0 (C(2)); 71.9 (C(4)); 62.7 (C(6′)); 30.7 (C(3′)); 25.3 (C(5′)); 19.4 (C(4′)). EI-MS: 300 (65, $M^+$), 272 (14), 244 (8), 216 (31), 198 (17), 185 (10), 181 (2), 171 (44), 169 (14), 160 (18), 141 (9), 131 (11), 128 (11), 127 (14), 115 (22), 114 (17), 102 (22), 85 (100), 77 (4), 76 (4), 67 (18), 57 (28), 55 (11).

*3,4-Dihydro-2*H*-naphtho[2,3-*b*][1,4]dioxepin-3-ol* (**27g**). As described in *Exper. 4*, with **26g** (0.65 g, 2.16 mmol). Crystallization of the residue from $^t$BuOMe yielded **27g** (0.34 g, 73%). Red solid. M.p. ($^t$BuOMe) 79–80°. IR (KBr): 3420 (br.), 3056*w*, 2925*w*, 1777*w*, 1726*m*, 1627*w*, 1598*m*, 1503*s*, 1474*m*, 1458*w*, 1445*w*, 1432*w*, 1394*w*, 1360*m*, 1341*w*, 1289*m*, 1263*s*, 1173*m*, 1151*w*, 1109*m*, 1069*w*, 1031*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.71–7.68 (*m*, H–C(7), H–C(10)); 7.46 (*s*, H–C(6), H–C(11)); 7.39–7.36 (*m*, H–C(8), H–C(9)); 4.41–4.36 (*m*, $H_a$–C(2), $H_a$–C(4)); 4.14–4.09 (*m*, $H_b$–C(2), H–C(3), $H_b$–C(4)); 2.30 ('*s*', OH). $^{13}$C-NMR (75 MHz, $CDCl_3$): 151.1 (C(5a), C(11a)); 130.7 (C(6a), C(10a)); 126.8 (C(7), C(10)); 125.3 (C(8), C(9)); 118.1 (C(6), C(11)); 75.3 (C(2), C(4)); 69.8 (C(3)). EI-MS: 216 (100, $M^+$), 197 (1), 185 (13), 172 (16), 171 (32), 160 (33), 145 (5), 131 (16), 127 (13), 115 (22), 114 (23), 102 (13), 88 (5), 77 (4), 76 (4), 63 (4).

*2*H-*Naphtho[2,3-*b*][1,4]dioxepin-3(4*H*)-one* (**18**). As described in *Exper. 4*, with **27g** (0.31 g, 1.43 mmol): **18** (0.19 g, 61%). Grey-white solid. M.p. (MeCN) 70–74°.

19. *7-Bromo-8-methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one* (**19**). Sodium bromate (2.54 g, 16.83 mmol) was added to **1** (1.00 g, 5.62 mmol) dissolved in cyclohexane/$H_2O$ 4:3 (70 ml). Then sodium metabisulfite (0.98 g, 5.15 mmol) in $H_2O$ (10 ml) was added dropwise, and the mixture was stirred at 50° for 8 h. The deep yellow soln. was quenched with ice/$H_2O$ (250 ml) and extracted with $Et_2O$ (3 × 100 ml) and the combined org. phase washed with $H_2O$ (2 × 200 ml), dried ($MgSO_4$), and concentrated: **19** (1.23 g, 85%). Pale yellow powdery solid. M.p. (pentane) 88–90°. IR (KBr): 2930*w*, 2900*w*, 1737*s*, 1602*w*, 1566*m*, 1480*s*, 1451*m*, 1428*m*, 1416*m*, 1378*w*, 1294*s*, 1266*m*, 1230*w*, 1178*m*, 1152*s*, 1052*s*, 1036*s*. $^1$H-NMR (300 MHz, $CDCl_3$): 7.17 (*s*, H–C(6)); 6.87 (*s*, H–C(9)); 4.67 (*s*, $CH_2$(2)); 4.66 (*s*, $CH_2$(4)); 2.28 (*s*, Me). $^{13}$C-NMR (75 MHz, $CDCl_3$): 203.8 (C(3)); 147.3 (C(9a)); 146.6 (C(5a)); 133.3 (C(8)); 124.2 (C(6)); 122.3 (C(9)); 117.4 (C(7)); 75.7 (C(2)); 75.5 (C(4)); 21.9 (Me). EI-MS: 258 (89, $M^+$), 257 (10), 256 (92), 215 (12), 213

(12), 202 (3), 200 (4), 174 (25), 172 (28), 149 (30), 135 (5), 121 (6), 105 (3), 93 (100), 77 (18), 65 (14), 51 (12), 39 (10). HR-ESI-MS: 256.9812 ($C_{10}H_9O_3Br^+$, $M^+$; calc. 256.9813).

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