# Synthesis and Qualitative Olfactory Evaluation of Benzodioxepine Analogues

by **Britta Drevermann**, **Anthony R. Lingham**, **Helmut M. Hügel***, and **Philip J. Marriott**

School of Applied Sciences (Chemistry), RMIT University, GPO Box 2476V, Melbourne, Victoria 3001, Australia
(phone: +(613)99252626; fax: +(613)99253747; e-mail: helmut.hugel@rmit.edu.au)

Marine fragrances, particularly *Calone 1951®* (= 7-methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one; **1**) has carved a minor but distinct niche in the broad field of fragrance chemistry. By focusing on the polar structure fragment of the benzodioxepinone parent compound, we set out to determine the molecular influence on the dominant marine note attributed to the *Calone 1951®* structure. A selection of one-step modifications of the ketone **1** resulted in a range of odor-active conformers with diverse olfactory attributes. The synthesis of a range of benzodioxepine analogues, *i.e.*, of **3**–**11**, is presented alongside olfactory evaluation (*Tables 2* and *3*). Removal of the carbonyl group of **1** and increasing the size of the aliphatic ring portion (see **6** and **7**) introduced sweetness and a predominant loss of the marine character.

**Introduction.** – *Calone 1951®* (= 7-methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one; **1**; *Scheme*) is now integrated within the fragrance industry and offers an interesting molecular framework for structure–odor-relationship (SOR) research due to its nonpolar, semipolar, and polar regions.

A patent released by *Beereboom*, *Cameron*, and *Stephens* (*Pfizer*) [1] in 1966 incorporated the syntheses of benzodioxepinone and benzoxepinone systems. Benzodioxepinones, including *Calone 1951®*, generally exhibit a pronounced marine note with a watermelon tonality, and in contrast, the sister benzoxepinone compounds emanate watermelon/green character.

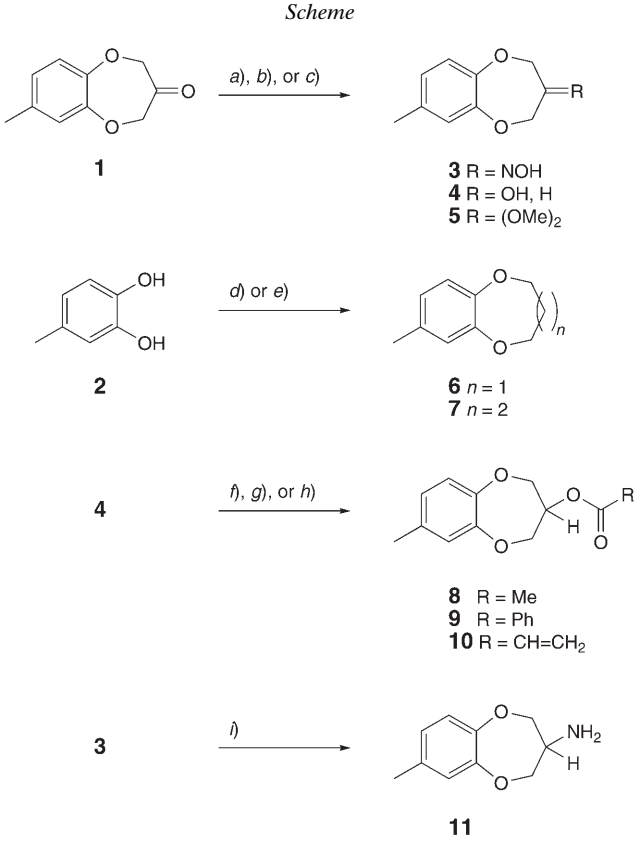
A range of benzodioxepinone and benzodioxepine analogues was prepared and described in the patent literature; however, no olfactory characteristics were described. The polar region of *Calone 1951®*, more specifically the ketone group has been hypothesized as fundamental to the olfactory character of the molecule. Dramatic olfactory changes from tailored manipulations of this moiety performed by our group support this premise. Limited olfactory reports on 7-membered benzodioxepine analogues with modification to the polar region of the structure prompted us to construct a range of C(3)-substituted structures for olfactory evaluation. Elimination of the odor-active carbonyl group of **1** to form a benzodioxepine was also achieved, alongside an 8-membered homologue, both contributing to the analogue data set. Related studies by our group have focused on specific modification of the nonpolar aromatic region of benzodioxepinones [2].

Structure–odor-relationship (SOR) analysis becomes increasingly universal and prognostic as the compound data set expands. Primarily, incorporation of a diverse

range of functionality contributes valuable information on the molecular aspects that determine the archetypal marine character of *Calone 1951®*. Here we present the preparation of *Calone 1951®* analogues **3**–**11** including spectroscopic and olfactory details to contribute to the sparse marine fragrance arena.

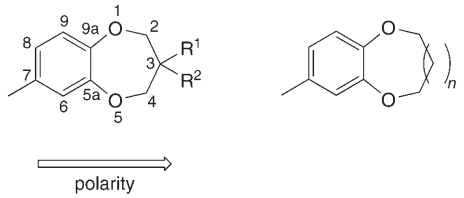
**Results and Discussion.** – Target molecules **3**–**5** were generated by direct manipulation of the carbonyl group of **1**, **6**, and **7** were formed from 4-methylcatechol (=4-methylbenzene-1,2-diol; **2**) by alkylation, **8**–**10** were obtained from **4** and the corresponding acid chloride, and **11** was formed by reduction of **3**. The yields and purities of **3**–**11** are given in *Table 1*. The $^1$H- and $^{13}$C-NMR resonances of $CH_2$(2) and $CH_2$(4) and the fusion atoms C(5a) and C(9a) for all analogues **3**–**11** were verified with HMQC and HMBC data.

*Scheme*




*a*) $NH_2OH \cdot HCl$, AcONa, $H_2O$/MeCN, 50°, 24 h; 94% of **3**. *b*) $NaBH_4$, $H_2O$/MeOH, r.t., 4 h; 89% of **4**. *c*) $CH(OMe)_3$, MeOH, cat. $CF_3SO_3H$, $MeNO_2$, 100°, 3 h; 72% of **5**. *d*) $K_2CO_3$, DMF, $Br(CH_2)_3Br$, 120°, 2 h; 30% of **6**. *e*) $K_2CO_3$, DMF, $Br(CH_2)_4Br$, 120°, 2 h; 65% of **7**. *f*) $Et_3N$, $Et_2O$, AcCl, r.t., 2 h; 88% of **8**. *g*) $Et_3N$, $Et_2O$, benzoyl chloride, r.t., 2 h; 45% of **9**. *h*) $Et_3N$, $Et_2O$, acryloyl chloride, r.t., 2 h; 22% of **10**. *i*) $NaBH_4$, $TiCl_4$, $MeOCH_2CH_2OMe$, r.t., 24 h; 54% of **11**.

Table 1. *Yields of* Calone 1951® *Analogues* **3**–**11**




| | $R^1$ | $R^2$ | *n* | Yield [%] | Purity [%] |
|---|---|---|---|---|---|
| **3** | =NOH | – | – | 94 | 100 |
| **4** | OH | H | – | 90 | 100 |
| **5** | MeO | MeO | – | 72 | 100 |
| **6** | – | – | 1 | 30[a]) | 97 |
| **7** | – | – | 2 | 65[a]) | 96 |
| **8** | MeC(=O)O | H | – | 88 | 100 |
| **9** | PhC(=O)O | H | – | 45 | 99 |
| **10** | $CH_2$=CHC(=O)O | H | – | 22 | 97 |
| **11** | $NH_2$ | H | – | 54 | 98 |

[a]) Isolated yield after purification.

Oximes are an untapped but potentially abundant functionality for studies on odor-active species due to their accessibility *via* direct conversion of ketones. Formation of ketoxime **3** (*Scheme*) was based on the conditions of *Grigg* and co-workers [3]. Gentle heating (50°) of **1** for 12 h enabled isolation of **3** as pure crystalline material upon quenching in ice/$H_2O$ (yield 94%). The $^1$H-NMR splitting of the $CH_2$(2) and $CH_2$(4) signals confirmed that the oxime was locked in two alternate geometrical conformations in equivalent amounts (isomers **3a** and **3b**). More commonly, the isomer arrangement will favor one of the (*E*) or (*Z*) forms both in aliphatic [4] and alicyclic [5] oxime compounds. Distinguishable isomer signals of **3** were evident in the HMBC plot (coupling of H–C(2) and H–C(4) to the fusion atoms C(9a) and C(5a), see the *Exper. Part*).

Similar to oximes, alcohols provide H-bonding capabilities for which a protein-structured biological receptor will demonstrate affinity. The benzodioxepinol **4** (*Scheme*) was prepared in 89% isolated yield by simple reduction of **3** with $NaBH_4$ in MeOH/$H_2O$.

The HMQC data of **4** revealed the overlapping of the H–C(3) signal with the *m* at 4.0–4.1 of 1 H–C(2) and 1 H–C(4). The second-order nature of the diastereotopic $CH_2$ protons observed in the 300-MHz $^1$H-NMR spectrum was substantiated by the 500-MHz $^1$H-NMR data, revealing the signals as *dd*s. The OH signal at $\delta$ 1.33 was verified by HMBC.

The dimethyl acetal **5** was easily obtained by modification of **1**. Initial attempts to form the diethyl acetal by treatment of an ethanol solution of **1** with HCl gas failed to produce any acetal product [6], but the dimethyl acetal **5** was conveniently prepared from **1** in 72% isolated yield by using a 10 mol-equiv. excess of both MeOH and

trimethyl orthoformate in the presence of a catalytic amount of triflic acid [7] (*Scheme*), followed by bulb-to-bulb distillation (purity > 98% GC/MS). The absence of the C=O signal and appearance of characteristic $^{13}$C-NMR dimethyl acetal signals ($\delta$ 100.8 (C(3)) and 48.6 (MeO) (DEPT-135)) confirmed the structure of **5**.

Since the carbonyl O-atom was suspected to be a primary requisite for the benzodioxepinone marine odor, removal of this moiety would provide evidence for this supposition and contribute a valuable analogue for olfactory studies. Thus, the cyclic diethers **6** and **7** were prepared by *Williamson* etherification of 4-methylcatechol (**2**) (*Scheme*). Reaction of **2** with 1,3-dibromopropane in DMF at 120° for 2 h gave **6** in a crude mixture containing dialkylated and monoalkylated catechol ether impurities as indicated by GC/MS analysis. An alternative procedure, with sodium and an etherified ethylene glycol as solvent, based on the protocol of *Jamrozik* and co-workers [8], provided similar yields. Microwave heating of **2** and 1,3-dibromopropane in DMF gave **6** in 55% yield as a 'clean' mixture after 2 min at 200 W. Removal of brominated impurities was effectively achieved by precipitation with $Et_3N$ as the quaternary ammonium salts. Our NMR data of **6** complies with that of *Archer* and *Claret* [9] whereby in solution at room temperature, the benzodioxepine **6** exhibits clean $^1$H-NMR signal splitting, eluding to a fixed chair conformation of the dioxepine moiety similar to that observed in **1**. Microwave and conventional heating methods were both also applied to generate **7** (24% and 65%, resp.). Conventional heating encouraged formation of the dialkylated catechol ether, whereas microwave heating provided the monoalkylated catechol preferentially.

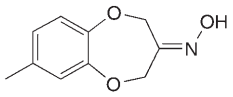
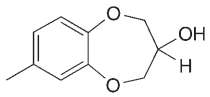
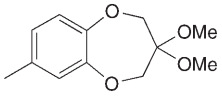
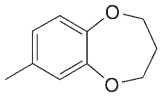
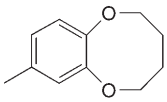
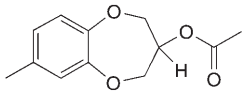
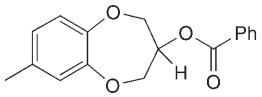
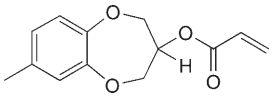
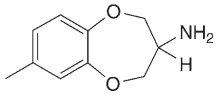
Acylation of **4** with the appropriate acid chloride produced carboxylic esters **8**–**10** (*Scheme*). The acrylate **10** formed in significantly lower yields and had a tendency to polymerize. Coupling to the quaternary C(5a) and C(9a) fusion atoms in the HMBC plot corroborates the $\delta$(H) of $CH_2$(2), H–C(3), and $CH_2$(4) of **8**–**10**.

The reactivity of zinc metal in AcOH, sodium metal in EtOH, $NaBH_4$, $LiAlH_4$, and reduction with *Baker*'s yeast proved insufficient for the reduction of **3** to form amine **11** (*Scheme*). A $NaBH_4/TiCl_4$ [10] reduction system, developed by *Kano* and co-workers for the reduction of oximes presented the most promising results with 1,2-dimethoxyethane as solvent. Chloro displacement of the borohydride-activated titanium(IV) chloride reducing complex was identified by a characteristic blue-violet color. Subsequent addition of **3** at room temperature gave a clean reduction to the amine **11** in moderate yields (54%), a product which required purification by HPLC. As the broad $NH_2$ signal in the $^1$H-NMR spectrum of **11** (*s* at $\delta$ 4.1) overlapped with the signals of $CH_2$(2), H–C(3), and $CH_2$(4), a COSY and HMQC analysis was required to establish the $\delta$(H) correlations which, as expected, resembled that of the OH analogue **4**.

**Olfactory Evaluation.** – Ketones are typically odor-active, and *Calone 1951*® is no exception. The essential nature of the carbonyl moiety to the unique marine-odor attributes exhibited by **1** became increasingly evident as C(3) modified analogues were evaluated for their olfactory properties (*Tables 2* and *3*).

Maintaining an electron-rich O-containing moiety with altered connectivity and hybridization allowed assessment of how C(3) substitution alters the familiar marine-odor character of the parent species. The marine tonality remains detectable upon

Table 2. *Olfactory Data for* Calone 1951 *Analogues* **3**–**11**

| | | Qualitative olfactory data[a]) |
|---|---|---|
| **3** |  | Fresh, marine-ozony odor with a green nuance, slightly aldehydic, weak |
| **4** |  | Marine, ozony, aldehydic, fruity-floral nuances, weak |
| **5** |  | Marine, ozony, watery, floral-green facets and a metallic character, weak |
| **6** |  | Naphthalinic, balsamic-sweet, spicy-medical odor in the direction of guaiacol, green-floral, vanilla-type nuances |
| **7** |  | Sweet, powdery, balsamic, aromatic odor in the direction of origanum and thyme oil, a slightly woody and marine inflection and slight spicy nuances |
| **8** |  | Floral-balsamic, slightly green, spicy and smoky facets, with a woody inflection, weak |
| **9** |  | Salty, green with spicy-balsamic, slight floral-marine, weak |
| **10** |  | Chemical, fruity, green and garlic-like, marine, woody and smoky-leathery inflections |
| **11** |  | Marine, green-mossy, with medicinal, animalic and slightly woody facets |

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

removal of the carbonyl group, and in addition, more dominant accords begin to arise such as aldehydic, sweet, and floral-fruity. Most notable is the transition from a potent odor (0.031 ng/l) [11] to a significantly weaker odor for both structures **3** and **4**. It seems

Table 3. *Graphical Representation of Olfactory Characteristics of Analogues* **3**–**11**. Black: present; grey: present but weak; white: absent.

| | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** |
|---|---|---|---|---|---|---|---|---|---|
| $R^1$ | =NOH | OH | MeO | H | H | MeC(=O)O | PhC(=O)O | $CH_2$=CHC(=O)O | $NH_2$ |
| $R^2$ | | H | MeO | H | H | H | H | H | H |
| *n* | | | | 1 | 2 | | | | |
| marine | | | | | | | | | |
| ozone | | | | | | | | | |
| green | | | | | | | | | |
| aldehyde | | | | | | | | | |
| floral | | | | | | | | | |
| fruity | | | | | | | | | |
| chemical | | | | | | | | | |
| spicy | | | | | | | | | |
| balsamic | | | | | | | | | |
| woody | | | | | | | | | |
| herbal | | | | | | | | | |
| smoky | | | | | | | | | |
| salty | | | | | | | | | |
| garlic | | | | | | | | | |
| metallic | | | | | | | | | |
| sweet | | | | | | | | | |
| medicinal | | | | | | | | | |
| animalic | | | | | | | | | |

the olfactory receptor binding pocket is quite specifically delineated for a ketone on the adjoining dioxepin ether ring, with an $sp^2$ to $sp^3$ conversion perhaps contributing to the potent-to-weak alteration of the odor intensity. Products **3**–**5** demonstrate that replacement of the cyclic ketone with functionality of similar electronegativity but differing connectivity results in a dramatic decrease in intensity. As oxime groups are effective at binding glyco compounds and peptides [12], one would predict that **3** is a potent odor analogue. This was not the case, and our observation suggests that the introduction of the OH substituent at the polar region of the molecule may generally result in a perceptible weakening of the odor. The slightly higher odor potency of **4** and **5** with $sp^3$ OH and acetal substituents, respectively, suggests that the receptor binding pocket exhibits conformational selectivity.

Absence of functionality at the cyclic ether moiety of **6** and **7** introduces a perceptible sweet nuance to the accord, with the larger cyclic portion of **7** providing a slight decrease in spiciness. Compound **6**, the CH(3) analogue of **1**, was completely devoid of marine character, drawing a direct correlation between C(3) substitution and marine odor. The 8-membered ring (compound **7**) features a marine nuance, although MM2- and PM3-energy minimized models of **7** suggest a nonplanar ring conformation unlike 7-membered variants **3**–**6** and **8**–**11**. Synthesis of **8**–**10** allowed geometric considerations when contemplating olfactory changes from the introduction of steric bulk at the oxygenated portion of the ring. Replacement of the carbonyl group with an acetyloxy (**8**) or benzoyloxy (**9**) moiety weakens overall olfactory properties. As an exception, **10** possessed moderate odor potency, possibly explained by the terminal allyl

group the presence of which typically results in odor-active compounds, such as allyl amylglycolate (=2-hydroxyheptanoic acid prop-2-enyl ester) with a strong fruity odor or the strong fruity herbal-green odor of allyl ionone (=1-(2,6,6-trimethylcyclohex-2-en-1-yl)hepta-1,6-dien-3-one). Despite contrasting R groups, the acyloxy attachments of **8**–**10** altered perceivably qualitative characteristics by the introduction of more pronounced green, spicy-herby, and smoky connotations. It is worth noting the contrast in molecular makeup, yet collective balsamic-odor attribute of acetylated and benzoylated derivatives **8** and **9**, and alicyclic compounds **6** and **7**.

Primary and secondary amines are prevalent as food components and are less utilized in perfumery. The medicinal, animalic nuances for amine **11** were, therefore, expected. Amines are typically potent odorants although odor activity becomes increasingly indiscriminate as molecular size increases. In the absence of the O-functionality, an $sp^2$ O-atom is replaced with an $sp^3$ primary amine for **11**, further illustrating the correlation of the marine character to small C(3) substituents. In conjunction with compounds **3**–**5**, compound **11** unexpectedly preserves the marine character.

**Conclusion.** – Modification of the C=O group of *Calone 1951*® (**1**) leads to significant deviation in character from the prototypical marine odor and a decrease in overall potency. Replacement of the C=O functionality with a $CH_2$ moiety results in a complete absence of marine character, which is present in small C(3)-heterosubstituted compounds and much weaker in the C(3) ester analogues.

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## Experimental Part

*General.* Unless otherwise stated, all reagents were obtained from *Aldrich Chemical Co.* and used without further purification. $Et_3N$ was distilled and stored over KOH pellets. $Et_2O$ was dried over $CaH_2$, followed by distillation from sodium/benzophenone. *Calone 1951*® (=7-methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one, **1**) was purchased from *Agan Aroma and Fine Chemicals Ltd.* (Ashdod, Israel) under the name *Ganone*. Microwave experiments were performed in a prototype microwave applicator *MDV2.4* and with a 0–700-W variable power microwave source (*2m172*)[1]). FC: *Merck* silica gel *60* (0.040–0.063 μm). TLC: *Merck* silica gel *60* $F_{254}$ (particle size 5–40 μm, layer thickness 0.2 mm on aluminium, 20 × 20 cm); visualisation by UV light of 254 nm. IR: *Perkin-Elmer Spectrum-2000 Fourier*-transform IR spectrophotometer; in $cm^{-1}$. NMR: *Bruker Avance-300* (300 MHz) spectrometer; $\delta$ in ppm referenced to $SiMe_4$ with the solvent resonance as the internal standard ($CHCl_3$: $\delta$ 7.26), unless otherwise stated. MS: *Hewlett-Packard 6890 GC* with *BPX-5* column/*5973* mass-selective detector; in *m*/*z* (rel. %).

*7-Methyl-2*H*-1,5-benzodioxepin-3(4*H*)-one Oxime* (**3**). To a soln. of **1** (3.00 g, 16.85 mmol) in MeCN (60 ml) and $H_2O$ (20 ml), AcONa (2.07 g, 25.23 mmol) was added followed by hydroxylamine

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

hydrochloride (1.37 g, 19.71 mmol), and the mixture was stirred at 50° for 24 h or until reaction was complete (GC/MS control). The clear soln. was poured into ice/$H_2O$ (300 ml), and the white precipitate was isolated by vacuum filtration. The filter cake was washed with ice cold $H_2O$ (2 × 50 ml): **3** (3.05 g, 94%). Fluffy white solid. M.p. 98–100° ($H_2O$). IR (KBr): 3289*m*, 3026*w*, 2921*m*, 2858*w*, 1582*w*, 1509*s*, 1448*m*, 1422*m*, 1358*w*, 1311*s*, 1266*m*, 1204*m*, 1151*w*, 1115*m*, 1056*m*, 1028*m*, 1001*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.89–6.66 (*m*, H–C(6), H–C(8), H–C(9)); 5.05 (*s*, 1 H, $CH_2$(4), **3a**); 5.03 (*s*, 1 H, $CH_2$(4), **3b**); 4.91 (*s*, 1 H, $CH_2$(2), **3a**); 4.88 (*s*, 1 H, $CH_2$(2), **3b**); 2.24 (*s*, arom. Me). $^{13}$C-NMR (75 MHz, $CDCl_3$): **3a**: 157.3 (C(3)); 146.9 (C(9a)); 145.0 (C(5a)); 132.2 (C(7)); 125.1 (C(8)); 122.5 (C(9)); 119.6 (C(6)); 68.7 (C(2)); 68.3 (C(4)); 20.3 (arom. Me); **3b**: 157.3 (C(3)); 148.3 (C(9a)); 146.5 (C(5a)); 134.6 (C(7)); 122.9 (C(8)); 122.0 (C(9)); 120.2 (C(6)); 68.4 (C(2)); 68.1 (C(4)); 20.6 (arom. Me). $^1$H,$^{13}$C-HMBC ($CDCl_3$): H–C(2) and H–C(4) (**3a**)/C(9a) (146.9) and C(5a) (145.8); H–C(2) and H–C(4) (**3b**)/C(9a) (148.4) and C(5a) (147.5). EI-MS: 193 (100, $M^+$), 176 (54), 148 (49), 135 (17), 123 (26), 121 (14), 105 (5), 95 (16) 77 (14), 66 (15), 54 (7), 39 (9). HR-ESI-MS: 194.0812 ($C_{10}H_{12}NO_3^+$, $[M+H]^+$; calc. 194.0817).

*3,4-Dihydro-7-methyl-2*H*-1,5-benzodioxepin-3-ol* (**4**). To a suspension of **1** (1.00 g, 5.62 mmol) in $H_2O$ (20 ml), MeOH (40 ml) was added until **1** was completely solubilized. $NaBH_4$ (0.42 g, 11.10 mmol) was added portion-wise with cooling in an ice bath. The soln. was stirred at r.t. for 4 h and then quenched with 0.1M HCl (150 ml). The soln. was then extracted with $CH_2Cl_2$ (3 × 50 ml) and the combined org. phase washed with $H_2O$ (2 × 100 ml), dried ($MgSO_4$), and concentrated: **4** (0.90 g, 89%). Low-melting white solid. M.p. 56–58° (heptane). 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)); 4.25 (*m*, $H_a$–C(2), $H_a$–C(4)); 4.04 (*m*, $H_b$–C(2), H–C(3), $H_b$–C(4)); 2.24 (*s*, arom. Me); 1.33 (*s*, OH). $^{13}$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 (arom. Me). EI-MS: 180 (100, $M^+$), 149 (11), 135 (48), 123 (27), 109 (11), 94 (8), 91 (9), 77 (12), 66 (8), 51 (5), 39 (4). HR-ESI-MS: 203.0682 ($C_{10}H_{12}NaO_3^+$, $[M+Na]^+$; calc. 203.0684).

*3,4-Dihydro-3,3-dimethoxy-7-methyl-2*H*-1,5-benzodioxepine* (**5**). Trimethyl orthoformate (2.46 ml, 22.48 mmol) was added to a soln. of **1** (0.40 g, 2.25 mmol) in $MeNO_2$ (20 ml) cooled to 0°. MeOH (0.90 ml, 22.19 mmol) was added, followed by the addition of catalytic amounts of trifluoromethane sulfonic acid (0.04 ml, 0.45 mmol), and the mixture was heated to 100° under $N_2$ for 3 h. The clear purple soln. was cooled to r.t. and then poured into a sat. aq. $NaHCO_3$ soln. (100 ml). The aq. mixture was extracted with $Et_2O$ (3 × 40 ml), the combined org. extract washed with $H_2O$ (1 × 75 ml), dried ($MgSO_4$), and concentrated, and the transparent yellow oil purified by bulb-to-bulb distillation (80–90°/0.2 Torr): **5** (0.36 g, 72%). Colourless oil. IR (KBr): 2925*s*, 2856*s*, 2730*w*, 1867*w*, 1743*w*, 1615*w*, 1583*w*, 1505*m*, 1460*s*, 1377*m*, 1305*m*, 1270*m*, 1165*m*, 1146*m*, 1121*w*, 1092*m*, 1071*m*, 1025*w*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.67–6.83 (*m*, H–C(6), H–C(8), H–C(9)); 4.20 (*s*, $CH_2$(2)); 4.19 (*s*, $CH_2$(4)); 3.33 (*s*, 2 MeO); 2.23 (*s*, arom. Me). $^{13}$C-NMR (75 MHz, $CDCl_3$): 149.1 (C(9a)); 147.2 (C(5a)); 132.8 (C(7)); 123.5 (C(8)); 120.9 (C(6)); 120.2 (C(9)); 100.8 (C(3)); 71.7 (C(2)); 71.5 (C(4)); 48.6 (2 MeO); 20.4 (arom. Me). EI-MS: 224 (100, $M^+$), 193 (8), 179 (11), 165 (4), 163 (5), 161 (3), 149 (36), 135 (87), 119 (40), 105 (19), 91 (34), 71 (22), 59 (7), 45 (24). HR-ESI-MS: 247.0946 ($C_{12}H_{16}NaO_4^+$, $[M+Na]^+$; calc. 247.0946).

*3,4-Dihydro-7-methyl-2*H*-1,5-benzodioxepine* (**6**). *a*) Ground, oven-dried $K_2CO_3$ (3.34 g, 24.15 mmol) and 1,3-dibromopropane (2.45 ml, 24.13 mmol) were added sequentially to a soln. of 4-methylbenzene-1,2-diol (**2**; 1.00 g, 8.05 mmol) in anh. DMF (50 ml). The soln. was irradiated under $N_2$ (200 W, 2 min) with vigorous stirring. Upon cooling (15 min), the soln. was poured into ice/$H_2O$ (200 ml). The aq. soln. was extracted with $CH_2Cl_2$ (3 × 100 ml) and the combined org. extract washed with 5% aq. NaOH soln. (2 × 50 ml) followed by $H_2O$ (2 × 50 ml), dried ($MgSO_4$), and concentrated. The obtained crude yellow oil was dissolved in MeCN (12.0 ml) and $Et_3N$ (6.0 ml) and stirred at r.t. for 48 h. The ammonium bromide salts were removed by using a syringe filter (0.45 μm), and the filtrate was stored at −20° until no more precipitate was formed. After final removal of the precipitate, the filtrate was subjected to FC (heptane): **6** (0.73 g, 55%). Colourless oil.

*b*) The reaction conducted by heating for 2 h at 120° in a conventional oil bath, followed by workup as described above, provided **6** in 30% yield. IR (neat): 3031*w*, 2953*m*, 2867*m*, 1865*w*, 1726*w*, 1613*w*, 1578*m*, 1505*s*, 1461*m*, 1416*m*, 1388*m*, 1360*w*, 1349*w*, 1305*s*, 1260*s*, 1232*w*, 1201*m*, 1149*m*, 1117*m*, 1102*m*,

1054*s*. $^1$H-NMR (300 MHz, ($CDCl_3$): 6.92–6.70 (*m*, H–C(6), H–C(8), H–C(9)); 4.10 (*t*, *J* = 5.3, $CH_2$(2)); 4.08 (*t*, *J* = 5.1, $CH_2$(4)); 2.21 (*s*, arom. Me); 2.11 (*quint.*, *J* = 5.5, $CH_2$(3)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 153.2 (C(9a)); 151.3 (C(5a)); 134.6 (C(7)); 125.5 (C(8)); 123.8 (C(9)); 123.1 (C(6)); 72.4 (C(2)); 72.3 (C(4)); 34.1 (C(3)); 21.5 (arom. Me). $^1$H,$^1$H-COSY ($CDCl_3$): 3.96 ($CH_2$(2), $CH_2$(4))/1.97 ($CH_2$(3)). EI-MS: 164 (100, $M^+$), 135 (85), 123 (26), 108 (11), 94 (27), 77 (19), 66 (35), 51 (16), 39 (30).

*2,3,4,5-Tetrahydro-8-methyl-1,6-benzodioxocine* (**7**). *a*) $K_2CO_3$ (3.34 g, 24.20 mmol), **2** (1.00 g, 8.06 mmol), and 1,4-dibromobutane (2.86 ml, 23.95 mmol) were added sequentially to DMF (50 ml), and the mixture was heated to 120° for 2 h. Workup as described for **6** gave a crude yellow oil which was treated with $Et_3N$. The filtrate was subjected to FC (gradient heptane → $CH_2Cl_2$/heptane 5 : 95): **7** (0.93 g, 65%). Clear pale yellow oil.

*b*) The reaction involving microwave irradiation as described for **6** provided **7** in 24% yield. IR (neat): 2925*w*, 2867*w*, 1360*w*, 2342*w*, 1726*w*, 1613*w*, 1578*w*, 1504*s*, 1470*w*, 1444*w*, 1382*w*, 1304*s*, 1255*m*, 1230*m*, 1194*w*, 1153*w*, 1118*w*, 1085*w*, 1055*w*, 1006*w*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.87–6.72 (*m*, H–C(7), H–C(9), H–C(10)); 4.29 (*t*, *J* = 5.5, $CH_2$(2)); 4.21 (*t*, *J* = 5.5, $CH_2$(5)); 2.26 (*s*, arom. Me); 1.88–2.08 (*m*, $CH_2$(3), $CH_2$(4)). $^{13}$C-NMR (75 MHz, $CDCl_3$): 149.5 (C(10a)); 146.6 (C(6a)); 133.5 (C(8)); 123.8 (C(9)); 122.6 (C(10)); 122.3 (C(7)); 73.1 (C(2)); 72.2 (C(5)); 27.3 (C(4)); 26.4 (C(3)); 20.6 (arom. Me). $^1$H,$^1$H-COSY ($CDCl_3$): 4.23 ($CH_2$(5))/1.82 ($CH_2$(4)); 3.96 ($CH_2$(2))/1.95 ($CH_2$(3)). EI-MS: 178 (100, $M^+$), 150 (2), 135 (75), 124 (100), 106 (12), 94 (17), 78 (39), 66 (48), 55 (96), 39 (73).

*3,4-Dihydro-7-methyl-2*H*-1,5-benzodioxepin-3-yl Acetate* (**8**). $Et_3N$ (0.20 ml, 1.43 mmol) was added to a soln. of **4** (0.20 g, 1.11 mmol) in anh. $Et_2O$ (20 ml). AcCl (0.097 ml, 1.36 mmol) was added dropwise, and the mixture was stirred at r.t. for 2 h. The precipitate was removed by vacuum filtration and the filtrate dissolved in $Et_2O$ (50 ml) and washed with aq. 2M HCl (3 × 50 ml) followed by sat. aq. $NaHCO_3$ soln. (3 × 50 ml). The combined org. extract was dried ($MgSO_4$) and concentrated: **8** (0.22 g, 88%). Low-melting yellow solid of >95% purity (GC/MS). M.p. 43–44° (pentane). IR (KBr): 2969*m*, 2947*w*, 2926*w*, 1736*s*, 1694*w*, 1579*w*, 1509*m*, 1445*m*, 1396*w*, 1379*m*, 1338*w*, 1296*m*, 1276*m*, 1252*s*, 1206*m*, 1154*w*, 1109*m*, 1056*s*, 1028*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.83 (*d*, *J* = 8.1, H–C(9)); 6.76 (*s*, H–C(6)); 6.71 (*d*, *J* = 8.1, H–C(8)); 5.26 (*tt*, *J* = 5.1, 4.3, H–C(3)); 4.37 (*dd*, *J* = 12.8, 4.3, $H_a$–C(2)); 4.35 (*dd*, *J* = 12.8, 4.3, $H_b$–C(2)); 4.28 (*dd*, *J* = 12.8, 5.1, $H_a$–C(4)); 4.26 (*dd*, *J* = 12.8, 5.1, $H_b$–C(4)); 2.24 (*s*, arom. Me); 2.13 (*s*, MeCO). $^{13}$C-NMR (75 MHz, $CDCl_3$): 170.3 (C=O); 149.4 (C(9a)); 147.5 (C(5a)); 133.2 (C(7)); 123.8 (C(8)); 121.2 (C(9)); 120.5 (C(6)); 71.5 (C(3)); 71.4 (C(2)); 71.2 (C(4)); 20.9 (*Me*CO); 20.4 (arom. Me). $^1$H,$^1$H-COSY ($CDCl_3$): 5.17 (H–C(3))/4.23 ($CH_2$(2), $CH_2$(4)). EI-MS: 222 (23, $M^+$), 162 (46), 161 (39), 149 (6), 135 (52), 133 (6), 124 (13), 123 (10), 105 (8), 94 (17), 91 (14), 77 (19), 66 (25), 51 (13), 43 (100), 39 (24).

*3,4-Dihydro-7-methyl-2*H*-1,5-benzodioxepin-3-yl Benzoate* (**9**). As described for **8**, with benzoyl chloride (0.142 ml, 1.22 mmol): **9** (0.14 g, 44%). Low-melting white solid of >95% purity (GC/MS). M.p. 54–56° (heptane). IR (KBr): 2931*w*, 1714*s*, 1613*w*, 1601*w*, 1582*m*, 1506*s*, 1463*m*, 1450*m*, 1416*w*, 1392*w*, 1361*w*, 1331*m*, 1308*m*, 1287*s*, 1264*s*, 1253*s*, 1209*m*, 1195*m*, 1174*m*, 1151*m*, 1117*s*, 1085*m*, 1070*m*, 1041*m*, 1033*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 8.10 (*s*, H–C(2′), H–C(6′)); 7.59 (*t*, *J* = 7.3, H–C(4′)); 7.45 (*t*, *J* = 7.8, H–C(3′), H–C(5′)); 6.86 (*d*, *J* = 8.1, H–C(9)); 6.79 (*s*, H–C(6)); 6.73 (*d*, *J* = 8.1, H–C(8)); 5.53 (*tt*, *J* = 5.1, 4.3, H–C(3)); 4.51 (*dd*, *J* = 12.8, 4.3, $H_a$–C(2)); 4.50 (*dd*, *J* = 12.8, 4.3, $H_b$–C(2)); 4.43 (*dd*, *J* = 12.8, 5.1, $H_a$–C(4)); 4.42 (*dd*, *J* = 12.8, 5.1, $H_b$–C(4)); 2.26 (*s*, arom. Me). $^{13}$C-NMR (75 MHz, $CDCl_3$): 165.8 (CO); 149.4 (C(9a)); 147.6 (C(5a)); 133.4 (C(4′)); 133.2 (C(7)); 129.8 (C(6′)); 129.5 (C(2′)); 128.4 (C(3′), C(5′)); 123.8 (C(8)); 121.2 (C(6)); 120.5 (C(9)); 71.9 (C(3)); 71.6 (C(2)); 71.3 (C(4)); 20.5 (arom. Me). $^1$H,$^1$H-COSY ($CDCl_3$): 8.01 (H–C(2′), H–C(6′))/7.38 (H–C(3′), H–C(5′)), 7.52 (H–C(4′))/7.38 (H–C(3′), H–C(5′)), 5.45 (H–C(3))/4.40 (H–C(2), H–C(4)). $^1$H,$^{13}$C-HMQC ($CDCl_3$): H–C(2′) and H–C(6′)/C(2′) and C(6′) (129.8); H–C(4′)/C(4′) (133.5); H–C(3) and H–C(5′)/C(3′) and C(5′) (128.5); H–C(3)/C(3) (72.1); $CH_2$(2) and $CH_2$(4)/C(2) and C(4) (71.7). EI-MS: 284 (49, $M^+$), 162 (100), 149 (3), 135 (32), 123 (3), 105 (71), 94 (7), 77 (40), 66 (7), 51 (8), 39 (4).

*3,4-Dihydro-7-methyl-2*H*-1,5-benzodioxepin-3-yl Prop-2-enoate* (**10**). As described for **8**, with prop-2-enoylchloride (0.099 ml, 1.22 mmol): **10** (0.057 g, 22%). Clear pale yellow oil of >95% purity (GC/MS). IR (neat): 3106*w*, 3036*m*, 1955*w*, 1873*w*, 1732*s*, 1635*m*, 1619*w*, 1581*m*, 1505*s*, 1462*w*, 1445*w*, 1406*s*, 1306*s*, 1295*s*, 1259*s*, 1185*s*, 1150*m*, 1115*m*, 1075*m*, 1050*s*, 1012*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.83 (*d*, *J* = 8.1, H–C(9)); 6.76 (*s*, H–C(6)); 6.72 (*d*, *J* = 8.1, H–C(8)); 6.49 (*d*, $J_{trans}$ = 17.3, $H_a$–C(3′)); 6.18 (*dd*,

$J = 17.3, 10.4$, H–C(2′)); 5.90 (*d*, $J_{cis} = 10.4$, $H_b$–C(3′)); 5.35 (*tt*, $J = 5.1, 4.3$, H–C(3)); 4.34 (*dd*, $J = 12.8, 4.3$, $H_a$–C(2)); 4.33 (*dd*, $J = 12.8, 4.3$, $H_b$–C(2)); 4.25 (*dd*, $J = 12.8, 5.1$, $H_a$–C(4)); 4.23 (*dd*, $J = 12.8, 5.1$, $H_b$–C(4)); 2.24 (*s*, arom. Me). $^{13}$C-NMR (75 MHz, $CDCl_3$): 165.4 (C=O); 149.3 (C(9a)); 147.5 (C(5a)); 133.2 (C(3′)); 132.0 (C(7)); 127.8 (C(2′)); 123.8 (C(8)); 121.2 (C(9)); 120.5 (C(6)); 71.5 (C(3)); 71.4 (C(2)); 71.2 (C(4)); 20.4 (arom. Me). $^1$H,$^1$H-COSY ($CDCl_3$): 6.43 ($H_a$–C(3′))/6.11 (H–C(2′)); 6.14 (H–C(2′))/5.85 ($H_b$–C(3′)); 5.28 (H–C(3))/4.30 ($CH_2$(2), $CH_2$(4)). $^1$H,$^{13}$C-HMQC ($CDCl_3$): $H_b$–C(3′)/C(3′) (133.1); $H_a$–C(3′)/C(3′) (130.9); H–C(2′)/C(2′) (128.4); H–C(3)/C(3) (71.6); $CH_2$(2)/C(2) (70.5); $CH_2$(4)/C(4) (70.2). EI-MS: 234 (66, $M^+$), 162 (100), 149 (8), 135 (54), 123 (56), 105 (8), 94 (13), 77 (10), 66 (13), 55 (45), 39 (6).

*3,4-Dihydro-7-methyl-2*H*-1,5-benzodioxepin-3-amine* (**11**). Under a dry $N_2$ atmosphere, $NaBH_4$ (1.64 g, 43.33 mmol) was added portionwise to freshly distilled $TiCl_4$ (2.39 ml, 21.79 mmol) in anh. 1,2-dimethoxyethane (100 ml) at 0°. The blue soln. was stirred for 10 min followed by the addition of **3** (1.00 g, 5.18 mmol), then the mixture was warmed to r.t. and stirred for 24 h. The reaction was quenched in ice/$H_2O$ (200 ml) and then the mixture washed with $CH_2Cl_2$ (5 × 50 ml). The aq. phase was then basified to pH 8 and extracted with $CH_2Cl_2$ (3 × 70 ml). The combined org. extract was dried ($MgSO_4$) and concentrated and the obtained yellow resin subjected to semi-prep. HPLC ($t_R$ 10.2 min, $\lambda_{max}$ 231, 275 nm): **11** (0.50 g, 54%). Clear oil. IR (neat): 3361*w*, 3295*m*, 3033*w*, 2925*m*, 2878*w*, 1612*w*, 1578*w*, 1505*s*, 1459*w*, 1417*w*, 1394*w*, 1373*w*, 1305*m*, 1260*m*, 1202*w*, 1148*w*, 1114*w*, 1091*w*, 1033*m*. $^1$H-NMR (300 MHz, $CDCl_3$): 6.89–6.71 (*m*, H–C(6), H–C(8), H–C(9)); 4.14 (br. *s*, $NH_2$); 4.32–3.97 (*m*, $CH_2$(2), H–C(3), $CH_2$(4)); 2.24 (*s*, arom. Me). $^{13}$C-NMR (75 MHz, $CDCl_3$): 150.5 (C(9a)); 148.7 (C(5a)); 133.9 (C(7)); 124.1 (C(8)); 121.8 (C(9)); 121.0 (C(6)); 74.1 (C(2)); 74.0 (C(4)); 50.7 (C(3)); 20.5 (arom. Me). $^1$H,$^1$H-COSY ($CDCl_3$): 4.16 ($H_a$–C(2))/3.27 ($H_b$–C(2)); 4.16 ($H_a$–C(4))/3.27 ($H_b$–C(4)); 4.13 (H–C(2), H–C(4))/3.96 (H–C(3)). $^1$H,$^{13}$C-HMQC ($CDCl_3$): $CH_2$(2), $CH_2$(4)/C(4), C(2) (74.0); H–C(3)/C(3) (52.0). EI-MS: 179 (65, $M^+$), 162 (19), 151 (21), 150 (57), 135 (100), 123 (7), 121 (9), 105 (7), 91 (13), 78 (18), 77 (20), 66 (9), 65 (9), 63 (6), 56 (35), 51 (11). HR-ESI-MS: 180.1017 ($C_{10}H_{14}NO_2^+$, $[M+1]^+$; calc. 180.1024).

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