# 96. Synthesis of 1,3,4,5-Tetrahydro-2-benzoxepin Derivatives as Conformationally Restricted Analogues of Cyclamenaldehyde-Type Compounds and as Intermediates for Highly Odour-Active Homologues

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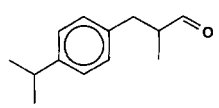
(12.III.96)

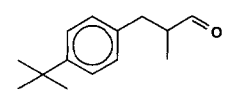
Nine 1,3,4,5-tetrahydro-2-benzoxepin derivatives have been prepared as mimics of the folded (*gauche*) conformation of cyclamenaldehyde (**1**) and related compounds, but none of them showed the typical lily-of-the valley (muguet) odour activity. However, conversion of these substances to previously unknown analogues of **1** having a Me substituent on the aromatic ring in an *ortho* position to the side chain led to new fragrance substances with remarkable properties. The results indicate that the extended (*anti*) conformation is more likely to be the 'bioactive' one at the receptor site(s).

**Introduction.** – The 3-(4-isopropylphenyl)-2-methylpropanal (**1**; cyclamenaldehyde) [1], 3-[4-(*tert*-butyl)phenyl]-2-methylpropanal (**2**; *Lilial*®[2])) [2] and 3-[4-(*tert*-butyl)-phenyl]-2-methylpropanol (**3**; *Bourgeonal*®[3])) [3] are widely used synthetic odorants of the floral class, having the appreciated lily-of-the-valley ('muguet') tonality [4]. Noteworthy, the two enantiomers of **2** have recently been prepared and both shown to be odour-active, the (−)-*R*-enantiomer being slightly stronger [5]. Moreover, compound **2** has also been used for experimental [6] and theoretical [7] studies of the primary event in olfaction, namely the odorant-olfactory receptor interaction.

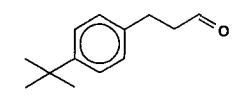
This floral class of odorants comprises various other types of compounds having, instead of an aldehyde, an alcohol functional group, *e.g.* **4** (*Mayol*®[4])) [8] and **5** (*Mugetanol*®[5])) [9], or both an aldehyde and an alcohol function, *e.g.* **6** (hydroxycitronellal), or



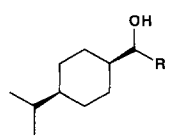
(±)-**1**



(±)-**2**

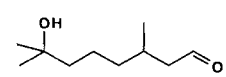


**3**

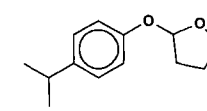


**4** R = H

(±)-**5** R = $CH_3$



(±)-**6**



(±)-**7**

[1]) Postdoctoral fellow at *Firmenich SA* (1991–1992).

[2]) Trade name registered by *Givaudan-Roure SA*.

[3]) Trade name registered by *Quest International*.

[4]) Trade name registered by *Firmenich SA*.

[5]) Trade name registered by *Haarman & Reimer GmbH*.

even an acetal functional group, *e.g.* **7** [10]; several studies have already been devoted to the structure-activity relationships within this group of fragrance substances [11–15].

In the present work, we have examined the structural conformational dependence of the odour-activity in a series of compounds related to aldehydes **1–3**. Our study was based on molecular mechanics (MM2) calculations, using the program MacroModel (v. 3.1 to 4.5) [16], which indicated that the aldehyde side chain in compounds **1–3** has two low-energy conformations: the extended (*anti*) and the folded (*gauche*) conformations, the latter-one being higher in energy for **3**, but *lower* in energy for **1** and **2** (see *Fig. 1*).

This intriguing result raised the question whether it was the extended or the folded form which was the 'bioactive' conformation at the receptor site(s).

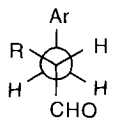
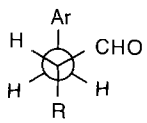
| | Extended (*anti*) | Folded (*gauche*) |
|---|---|---|
| |  |  |
| | $E_{MM2}$ [kJ/mol] | $E_{MM2}$ [kJ/mol] |
| **1** (R = Me) | 36.82 | 35.67 |
| **2** (R = Me) | 48.38 | 47.24 |
| **3** (R = H) | 38.25 | 39.76 |

Fig. 1. *Compared energies* (MM2 calculations) *of the two low-energy conformations of compounds* **1–3**

Given the commercial importance of **1** and **2**, we decided to investigate the relevance of the folded conformation for odour activity and to synthesize conformationally restricted analogues which would mimic the folded conformation of **1** and **2**[6]). We envisaged to imbed the O-function in a cycle, in the form of an ether functional group, and our first goal became to prepare the 1,3,4,5-tetrahydro-2-benzoxepin derivative (±)-**10a**, as a rigidified analogue of the preferred folded conformation of (±)-**2**[7]).

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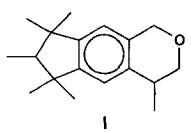
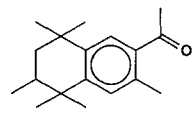
[6]) For a recent investigation of an olfactively active ring-like conformer of a chain-type odorant, see [17].

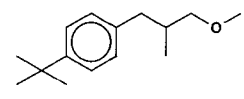
[7]) Ethers are generally more stable than aldehydes; apart from this fact, the reasoning for the design of an ether to mimic a carbonyl functional group was based on an analogous case well-known in the field of musk-type odorants: ether **I** (*Galaxolide*®, trade name registered by *International Flavor and Fragrances*) and ketone **II** (*Tonalid*®, trade name registered by *Polak's Frutal Works*) have indeed very similar odours. On the other hand, it should be mentioned that compound **III**, the ring-opened analogue of **10a**, had been prepared by Mr. *H. Pamingle* (*Firmenich SA*, unpublished results) in another context and was found to have no *Lilial*-type odour activity, despite the fact that its lowest-energy conformer also has the chain in a folded (*gauche*) conformation (MM2 calculations with MacroModel and the Monte Carlo procedure); however, the accessibility of the ether O-atom in compound **III** (averaged over the low-energy conformations) is much smaller than in the bicyclic compound **10a** (*cf.* [18]).



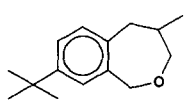
**I**



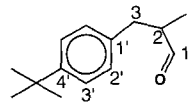
**II**



**III**



(±)-**10a**




(±)-**2**

Molecular modeling indicated that rigid superimposition of **2** and **10a** in their lowest-energy conformations by exact matching of their aromatic rings positioned the respective O-atoms at a distance of 2.93 Å from each other (when free rotation around the C(1)–C(2) bond in **2** was allowed; this distance ranged from 1.50 to 3.50 Å). Moreover, flexible superimposition of **2** and **10a** by exact matching of atoms C(1′), C(2′), C(4′), *and* O afforded conformations for **2** and **10a** which were 5.45 kJ/mol and 0.63 kJ/mol, respectively, above their lowest-energy conformations. The visualization of this result is illustrated in *Fig. 2*.

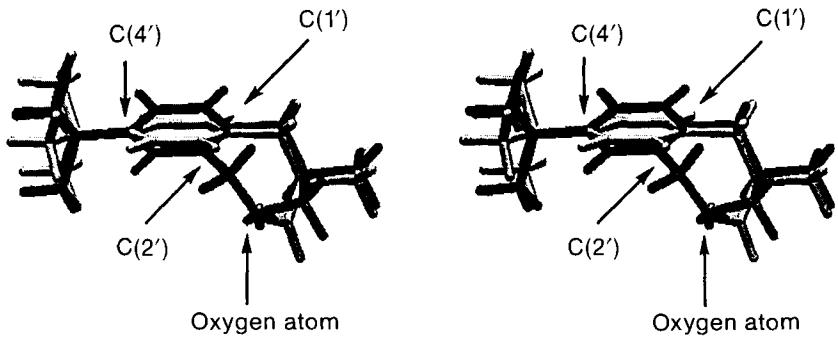


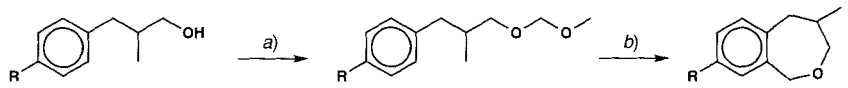

Fig. 2. *Stereoview of flexible superimposition of* (R)-**2** (in white) *and* (R)-**10a** (in black) *showing the atoms forced to match*

When the distance constraint for C(2′) was suppressed, the conformations for **2** and **10a** were calculated to be only 1.88 and 0.14 kJ/mol, respectively, above their lowest-energy conformations, but the planes of the aromatic rings became tilted by an angle of *ca.* 35° to each other.

**Results.** – The synthesis of the 1,3,4,5-tetrahydro-2-benzoxepin derivative **10a** started from alcohol **8a**. *Rieche* and *Gross* [19] have shown that tetrahydro-2-benzoxepins can be directly obtained from 3-phenylpropanols by cyclization of intermediate chloromethyl ethers in the presence of $AlCl_3$ in $CS_2$; in analogy to the synthesis of isochromans [20], we found it more convenient to work *via* the intermediate methoxymethyl ether **9a**, prepared by using a published procedure [21]. Indeed, **9a** was smoothly cyclized to the desired product **10a** in the presence of $AlCl_3$ in $CH_2Cl_2$ (see *Scheme 1*). Compound **10a** had not the slightest lily-of-the-valley odour activity and was described as 'weak and vague' by the perfumers.

We next decided to reduce the bulkiness of the alkyl group on the aromatic ring, thereby also diminishing the molecular weight and enhancing the volatility, and thus prepared the analogues **10b–d** by using the same methodology as employed for **10a** (see *Scheme 1*). These products also did not possess any typical lily-of-the-valley odour

*Scheme 1*



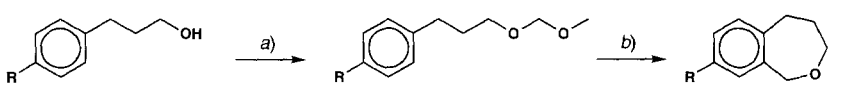
| | | | | | |
|---|---|---|---|---|---|
| **8a** | R = *t*-Bu | **9a** | R = *t*-Bu (87%) | **10a** | R = *t*-Bu (76%) |
| **b** | R = i-Pr | **b** | R = i-Pr (74%) | **b** | R = i-Pr (79%) |
| **c** | R = Et | **c** | R = Et (75%) | **c** | R = Et (87%) |
| **d** | R = Me | **d** | R = Me (64%) | **d** | R = Me (80%) |

*a*) $CH_2(OMe)_2$, LiBr, $TsOH \cdot H_2O$, r.t., 2–4 h. *b*) $AlCl_3$, $CH_2Cl_2$, 0–5°, 20 min.

activity; instead, only weak tonalities ranging from motor oil, metallic type to green, hydrocarbon and lactonic-type were registered by the perfumers.

The corresponding series of 1,3,4,5-tetrahydro-2-benzoxepins **13a–d**, without the Me group on the seven-membered ring, was then prepared following once again the same methodology (see *Scheme 2*). Except for **13a**, which possessed a slight white-flower note, compounds **13b–d** were also lacking the typical lily-of-the-valley odour.

*Scheme 2*



| | | | | | |
|---|---|---|---|---|---|
| **11a** | R = *t*-Bu | **12a** | R = *t*-Bu (90%) | **13a** | R = *t*-Bu (67%) |
| **b** | R = i-Pr | **b** | R = i-Pr (87%) | **b** | R = i-Pr (75%) |
| **c** | R = Et | **c** | R = Et (73%) | **c** | R = Et (79%) |
| **d** | R = Me | **d** | R = Me (71%) | **d** | R = Me (36%) |

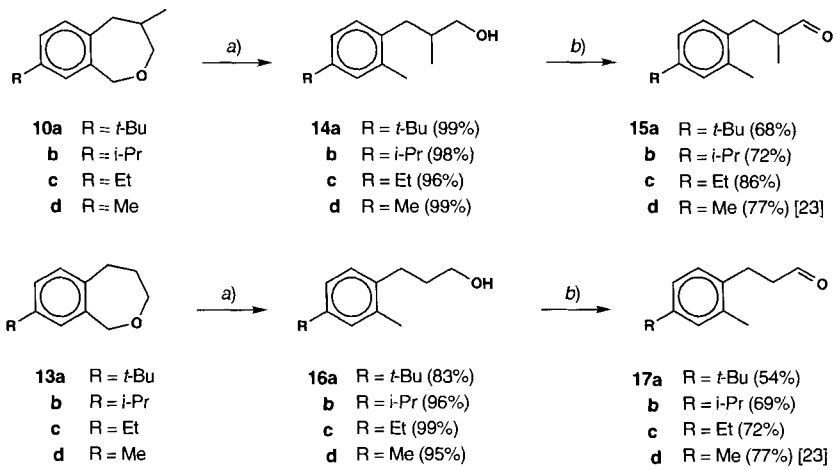
*a*) $CH_2(OMe)_2$, LiBr, $TsOH \cdot H_2O$, r.t., 2–4 h. *b*) $AlCl_3$, $CH_2Cl_2$, 0–5°, 20 min.

The next step was to employ these benzoxepin derivatives for the preparation of a series of new analogues of aldehydes **1–3** having an additional Me substituent on the aromatic ring in the *ortho*-position with respect to the aldehyde side chain, in order to examine the effect on both the conformation of the side chain and on the odour. Thus, the 1,3,4,5-tetrahydro-2-benzoxepin derivatives **10a–d** and **13a–d** were ring-opened by hydrogenolysis [22] to the alcohols **14a–d** and **16a–d** (all odourless), which were oxidized to the corresponding aldehydes **15a–d** and **17a–d** using pyridinium chlorochromate (PCC; see *Scheme 3*).

Aldehydes **15a–d** were subsequently alkylated (KO(*t*-Bu)/*t*-BuOH, followed by MeI) to give the corresponding α,α-dimethyl derivatives **18a–d** (see *Scheme 4*).

Furthermore, to evaluate the effect of another Me substituent on the aromatic ring in the second position *ortho* to the side chain, alcohol **16a** was converted to 1,3,4,5-tetrahydrobenzoxepin **19** and then to aldehyde **21**, using the same sequence of reactions as described above. Alternatively, aldehyde **21** was also obtained by direct coupling of 1-(*tert*-butyl)-3,5-dimethylbenzene (**22**) with acrolein diacetyl acetal, followed by hydrolysis, according to the method of *Scriabine* [24] (*Scheme 5*).

*Scheme 3*

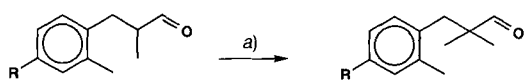



| | | | | | |
|---|---|---|---|---|---|
| **10a** | R = *t*-Bu | **14a** | R = *t*-Bu (99%) | **15a** | R = *t*-Bu (68%) |
| **b** | R = i-Pr | **b** | R = i-Pr (98%) | **b** | R = i-Pr (72%) |
| **c** | R = Et | **c** | R = Et (96%) | **c** | R = Et (86%) |
| **d** | R = Me | **d** | R = Me (99%) | **d** | R = Me (77%) [23] |

| | | | | | |
|---|---|---|---|---|---|
| **13a** | R = *t*-Bu | **16a** | R = *t*-Bu (83%) | **17a** | R = *t*-Bu (54%) |
| **b** | R = i-Pr | **b** | R = i-Pr (96%) | **b** | R = i-Pr (69%) |
| **c** | R = Et | **c** | R = Et (99%) | **c** | R = Et (72%) |
| **d** | R = Me | **d** | R = Me (95%) | **d** | R = Me (77%) [23] |

*a*) $H_2$, 5% Pd/C, AcOEt, EtOH, r.t., 12–15 h. *b*) PCC, $CH_2Cl_2$, r.t., 12–15 h.

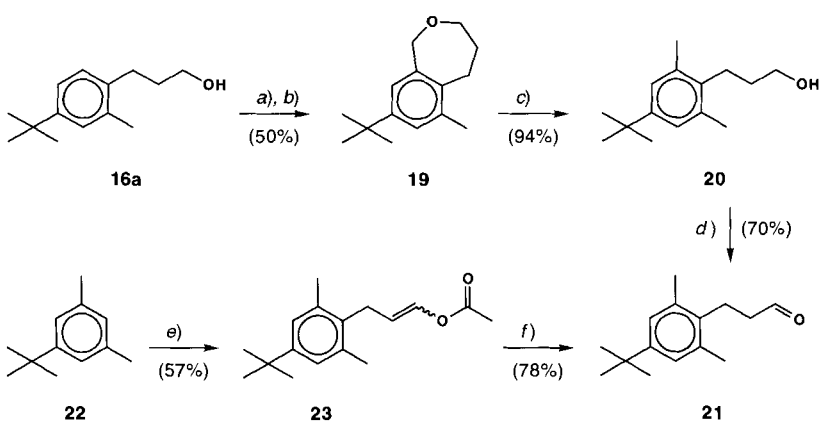
*Scheme 4*




| | | | |
|---|---|---|---|
| **15a** | R = *t*-Bu | **18a** | R = *t*-Bu (88%) |
| **b** | R = i-Pr | **b** | R = i-Pr (75%) |
| **c** | R = Et | **c** | R = Et (77%) |
| **d** | R = Me | **d** | R = Me (76%) |

*a*) 1. KO(*t*-Bu), *t*-BuOH, r.t., 20 min; 2. MeI, r.t., 1.5 h.

*Scheme 5*

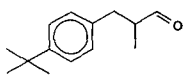
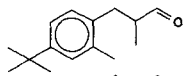
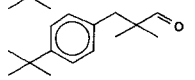
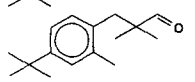



*a*) LiBr, $CH_2(OMe)_2$, TsOH; $H_2O$, r.t., 4 h. *b*) $AlCl_3$, $CH_2Cl_2$, 0–5°, 20 min. *c*) 5% Pd/C, $H_2$, AcOEt, r.t., 12 h. *d*) PCC, $CH_2Cl_2$, r.t., 12–15 h. *e*) $CH_2CHCH(OAc)_2$, $TiCl_4$, $CH_2Cl_2$, 5–10°, 15 min. *f*) 25% aq. $H_2SO_4$ soln., THF, 65°, 4 h.

Among the new aldehydes **15a–d**, **17a–d**, and **21** synthesized during this work, compound **17a** turned out to be a very valuable odorant [25], described as *Lilial*®-type, lily-of-the-valley, with a slight aniseed undertone; moreover, this compound was found to be much more stable towards aerial oxidation than the related aldehydes **2** and **3**. *E.g.*, the odour of **17a** on a smelling strip was still very well perceived after 44 days, whereas that of **2** had disappeared after 3 days, due to oxidation by air to the corresponding acid. Aldehydes **15a** and **21** were also found to have a Lilial®-type odour, though weaker than **17a** and with additional aniseed notes.

**Discussion.** – MM2 Calculations of the conformational preference of the side chain for the novel aldehydes described here confirmed that the aldehydes with a substituted side chain (**15a–d**, **18a–d**) prefer a folded (*gauche*) conformation, even when an *ortho*-Me group is present (see *Table 1*).

Table 1. *Conformational Energies* (MM2 calculation) *of Compounds with a Substituted Side Chain*

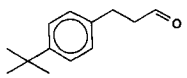
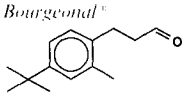
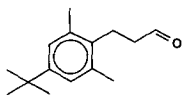
| | Compound | $E_{MM2}$ [kJ/mol] | | Odour description |
|---|---|---|---|---|
| | | folded | extended | |
| **2** |  *Lilial*® | 47.24 | 48.38 | 'Sweet, yet refreshing and intensely floral: green odour of considerable radiance'[a]) |
| **15a** |  | 52.25 | 54.09 | *Lilial*®, aromatic, somewhat fenchyl, pleasant |
| **24** [26] |  | 58.55 | 60.94 | fatty, aldehydic, metallic |
| **18a** |  | 67.11 | 70.67 | vague, slightly dirty not special |

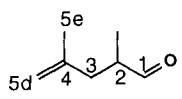
[a]) Taken from S. Arctander, 'Perfume and Flavor Chemicals', No. 496, published by the author, Montclair, N.J. (USA), 1969.

In contrast, the aldehydes possessing a non-substituted side chain and an *ortho*-positioned Me group (**17a–d**) favour an extended (*anti*) conformation (*e.g.* **17a**, $\Delta E_{MM2} \approx 4$ kJ/mol), a preference which is enhanced when two *ortho*-Me groups are present (*e.g.* **21**, $\Delta E_{MM2} \approx 6.5$ kJ/mol), as shown in *Table 2*.

Interestingly, *Pelzer et al.* [14] have recently proposed, based on computer-aided measurements of 41 carbonyl compounds with lily-of-the-valley odour activity, the presence of an odour-active side-chain fragment which should be substituted at C(2) by one or two Me groups (see *Fig. 3*). The dimensions indicated by these authors for this substituted side-chain fragment are in better agreement with the extended (*anti*) conformation, rather than with the folded (*gauche*) conformation which was favoured by our calculations; this discrepancy probably arises from the different methods of calculation used: AM1 (Ampac) in the work cited as opposed to MM2 (MacroModel) in the present work. Nevertheless, it is clear that such a substituted side-chain fragment can readily adopt an extended (*anti*) conformation at a relatively low energy cost, as indicated by our calculations ( < 4 kJ/mol, see *Table 1*).

Table 2. *Conformational Energies* (MM2 calculation) *of Compounds with a Non-Substituted Side Chain*

| | Compound | $E_{MM2}$ [kJ/mol] | | Odour description |
|---|---|---|---|---|
| | | folded | extended | |
| **3** |  *Bourgeonal*® | 39.76 | 38.25 | floral, lily of the valley, aldehydic, green |
| **17a** |  | 47.33 | 43.32 | green, *Lilial*® muguet with a slight anise |
| **21** |  | 57.26 | 50.75 | *Lilial*®, anise |




C(1)→ C(4) = 3.9 ± 0.3 Å

C(1) → C(5d) = 4.4 ± 0.3 Å

C(1) → C(5e) = 5.0 ± 0.3 Å

Fig. 3. *Structural fragment identified in floral fragrances with a carbonyl function* (from [14])

Thus, considering the loss of activity of the compounds conformationally locked in the folded form and the generally better performances of the compounds with a non-substituted side chain, it is tempting to conclude that the extended conformation is the 'bioactive' conformation at the receptor site(s).

Work is continuing to confirm this assumption, and the results will be reported in due course.

We wish to thank Dr. *F. Näf*, research director, *Firmenich SA*, for initiating this work. We gratefully acknowledge the collaboration of Prof. *N. Richards* (University of Florida, Gainesville), and the assistance of Dr. *A. Boschung* and Dr. *J. Y. de Saint Laumer*, *Firmenich SA*, in the computer-aided molecular-modeling work, of Mr. *W. Thommen* and Mr. *R. Brauchli*, *Firmenich SA*, for NMR analysis, and of Dr. *P.-A. Blanc*, *Firmenich SA*, for the evaluation of olfactive properties.

## Experimental Part

1. *General.* GLC: *Hewlett-Packard-5890* instrument equipped with a flame-ionization detector coupled to a *Hewlett-Packard-3392A* or *-3396A* integrator; capillary columns *Chrompack CP-Wax-52 CB* (10 m) and *CP-Sil-5 CB* (10 m). TLC: Silica gel *60* (*Merck F 254*, layer thickness 0.25 mm). Prep. CC: silica gel *60* (*Merck*, 0.063–0.2 mm, 70–270 mesh, ASTM). Bulb-to-bulb distillation: *Büchi-GKR-50* oven; b.p. correspond to the air temp. IR Spectra (liquid film): *Perkin-Elmer-297* spectrometer; $cm^{-1}$. NMR: *Bruker WH-360, Bruker AMX-360*; $^1H$ at 360 and $^{13}C$ at 90.5 MHz, in $CDCl_3$; chemical shifts $\delta$ in ppm rel. to $SiMe_4$ ( = 0 ppm), coupling constants $J$ in Hz. MS: *HP 5972 MSD* (70 eV ); *m/z* and intensities in % rel. to the base peak (100%).

2. *Computer-Aided Molecular Modeling.* Calculations were carried out on a *Silicon Graphics Iris 4D/35* computer system with the program MacroModel (versions 3.1 to 4.5) [16]. The Monte Carlo method [27] was used for conformational searching from an energy-minimized (MM2) starting conformation by using the automatic set-up from the MacroModel program.

3. *Starting Materials.* The known alcohols **8a–d** [28], **11a** [29], **11b** [30], and **11d** [31] were obtained by $LiAlH_4$ reduction of commercially available precursors or by a sequence similar to that described below for the preparation of the unreported alcohol **11c**.

*3-(4-Ethylphenyl)propan-1-ol* (**11c**). To a soln. of methyl 3-(4-ethylphenyl)prop-2-enoate (methyl *p*-ethylcinnamate) [32] (purity 91%; 16.7 g, 80 mmol) in AcOEt (150 ml) was added 5% Pd/C (2 g), and the mixture was shaken under $H_2$ at r.t. After 15 h, the catalyst was filtered off and the filtrate evaporated (17 g). Bulb-to-bulb distillation (0.1 mbar, oven temp.→130°) gave methyl 3-(4-ethylphenyl)propanoate (purity 94%; 16.7 g, 100%). Colourless oil. IR (neat): 2960, 1735, 1510, 1435, 1360, 1200, 1165, 840, 825. $^1$H-NMR: 7.11 (*s*, 4 H); 3.66 (*s*, 3 H); 2.91 (*t*, $J$ = 8, 2 H); 2.61 (*t*, $J$ = 8, 2 H); 2.61 (*q*, $J$ = 8, 2 H); 1.22 (*t*, $J$ = 8, 3 H). $^{13}$C-NMR: 173.4 (*s*); 142.2 (*s*); 137.7 (*s*); 128.2 (2*d*); 128.0 (2*d*); 51.6 (*q*); 35.8 (*t*); 30.6 (*t*); 28.5 (*t*); 15.6 (*q*). MS: 192 (42, $M^{+\cdot}$), 177 (3), 161 (6), 132 (100), 119 (76), 117 (64), 105 (17), 91 (33), 77 (14), 59 (9), 51 (6), 39 (5), 29 (4).

A soln. of this ester (purity 94%; 15.4 g, 75 mmol) in $Et_2O$ (100 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (2.5 g, 65 mmol) in $Et_2O$ (150 ml), while allowing the temp. to rise to 35° (reflux). After 10 min, the mixture was cooled to 4–5°, acetone (3 m) was added and then 1N aq. NaOH (12.5 ml). The mixture was allowed to reach r.t., $Na_2SO_4$ was added and the mixture filtered and evaporated (14 g). Bulb-to-bulb distillation (0.1 mbar, oven temp.→130°) gave **11c** (purity 95%; 12.5 g, 97%). Colourless oil. IR (neat): 3340 (br.), 2960, 2930, 2870, 1510, 1450, 1060, 1040, 840, 820. $^1$H-NMR: 7.11 (*s*, 4 H); 3.64 (*t*, $J$ = 5, 2 H); 2.66 (*t*, $J$ = 8, 2 H); 2.61 (*q*, $J$ = 8, 2 H); 1.90 (*s*, OH); 1.86 (*m*, 2 H); 1.22 (*t*, $J$ = 8, 3 H). $^{13}$C-NMR: 141.7 (*s*); 139.0 (*s*); 128.3 (2*d*); 127.9 (2*d*); 62.1 (*t*); 34.2 (*t*); 31.6 (*t*); 28.4 (*t*); 15.6 (*q*). MS: 164 (75, $M^{+\cdot}$), 146 (32), 131 (94), 119 (87), 117 (100), 105 (57), 91 (99), 77 (26), 65 (11), 51 (10), 39 (11), 31 (20).

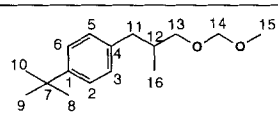
4. *General Procedure 1: Preparation of Methoxymethyl Ethers* **9** *and* **12** (*cf.* [21]). To a soln. of starting alcohol (200 mmol) in dimethoxymethane (100 ml) was added LiBr (870 mg, 10 mmol) and toluene-4-sulfonic acid hydrate (950 mg, 5 mmol). The mixture was stirred at r.t. during 15 h, then diluted with $Et_2O$, washed successively with sat. aq. $NaHCO_3$ soln. and brine, dried $K_2CO_3$), and evaporated. The residue was distilled under vacuum. There was always some starting alcohol in the distilled product, but this was used as such for the next step (cyclization). For anal. purpose, a sample was purified by CC (silica gel, cyclohexan/$Et_2O$ 4:1). Yields are given for the distilled product.

*(±)-1-(*tert*-Butyl)-4-[3-(methoxymethoxy)-2-methylpropyl]benzene* (**9a**): Yield 87% from **8a**. IR (neat): 2940, 2910, 1450, 1355, 1260, 1145, 1105, 1040, 915. $^1$H-NMR: 7.29 (*d*, $J$ = 8, 2 H); 7.09 (*d*, $J$ = 7, 2 H); 4.63 (*s*, 2 H); 3.44–3.33 (*m*, 2 H); 3.37 (*s*, 3 H); 2.76 (*dd*, $J$ = 14, 7, 1 H); 2.37 (*dd*, $J$ = 14, 7, 1 H); 2.09–1.96 (*m*, 1 H); 1.31

Table 3. *$^{13}$C-NMR Data of Compounds* **9a–d** *and* **12a–d**[a])

| C-Atom | 9a | 9b | 9c | 9d | 12a | 12b | 12c | 12d |
|---|---|---|---|---|---|---|---|---|
| C(1) | 148.6 | 146.4 | 141.6 | 135.2 | 148.6 | 146.3 | 141.7 | 135.2 |
| C(2) | 125.1 | 126.2 | 127.7 | 128.9 | 125.2 | 126.4 | 127.8 | 129.0 |
| C(3) | 128.8 | 129.1 | 129.1 | 129.1 | 128.1 | 128.3 | 128.4 | 128.3 |
| C(4) | 137.6 | 138.0 | 137.8 | 137.6 | 138.8 | 139.2 | 139.0 | 138.8 |
| C(5) | 128.9 | 129.1 | 129.1 | 129.1 | 128.1 | 128.3 | 128.4 | 128.3 |
| C(6) | 125.1 | 126.2 | 127.7 | 128.9 | 125.2 | 126.4 | 127.8 | 129.0 |
| C(7) | 34.4 | 33.7 | 28.4 | 21.0 | 34.3 | 33.7 | 28.4 | 21.0 |
| C(8) | 31.5 | 24.1 | 15.6 | – | 31.4 | 24.1 | 15.6 | – |
| C(9) | 31.5 | 24.1 | – | – | 31.4 | 24.1 | – | – |
| C(10) | 31.5 | – | – | – | 31.4 | – | – | – |
| C(11) | 39.5 | 39.6 | 39.5 | 39.5 | 31.9 | 32.0 | 32.0 | 32.0 |
| C(12) | 35.5 | 35.6 | 35.6 | 35.6 | 31.4 | 31.5 | 31.5 | 31.6 |
| C(13) | 72.8 | 72.8 | 72.6 | 72.7 | 67.2 | 67.2 | 67.2 | 67.2 |
| C(14) | 96.7 | 96.7 | 96.6 | 96.7 | 96.5 | 96.5 | 96.5 | 96.5 |
| C(15) | 55.2 | 55.1 | 55.1 | 55.1 | 55.1 | 55.2 | 55.2 | 55.2 |
| C(16) | 17.0 | 16.9 | 16.9 | 16.8 | – | – | – | – |

[a]) Arbitrary C-atom numbering:



(*s*, 9 H); 0.92 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 3*. MS: 250 (3), 218 (19), 203 (65), 188 (5), 173 (34), 147 (100), 145 (23), 132 (25), 131 (84), 117 (32), 105 (17), 91 (30), 77 (6), 57 (73), 45 (58).

*(±)-1-Isopropyl-4-[3-(methoxymethoxy)-2-methylpropyl]benzene* (**9b**): Yield 74% from **8b**. B.p. *ca.* 150°/0.2 mbar (bulb-to-bulb). IR (neat): 2940, 2900, 2860, 1500, 1450, 1375, 1210, 1150, 1100, 1040, 915, 840, 800. $^1$H-NMR: 7.14 (*d*, *J* = 7, 2 H); 7.08 (*d*, *J* = 7, 2 H); 4.63 (*s*, 2 H); 3.43–3.32 (*m*, 2 H); 3.38 (*s*, 3 H); 2.87 (*sept.*, *J* = 7, 1 H); 2.76 (*dd*, *J* = 14, 6, 1 H); 2.37 (*dd*, *J* = 14, 8, 1 H); 2.07–1.94 (*m*, 1 H); 1.24 (*d*, *J* = 7, 6 H); 0.92 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 3*. MS: 236 (1), 204 (14), 189 (8), 174 (12), 159 (19), 133 (100), 131 (45), 117 (23), 105 (25), 91 (45), 77 (4), 65 (2), 55 (5), 45 (33).

*(±)-1-Ethyl-4-[3-(methoxymethoxy)-2-methylpropyl]benzene* (**9c**): Yield 68% from **8c**. B.p. *ca.* 110°/0.2 mbar (bulb-to-bulb). IR (neat): 2960, 2920, 2870, 1510, 1450, 1150, 1125, 1050, 940. $^1$H-NMR: 7.11 (*d*, *J* = 8, 2 H); 7.08 (*d*, *J* = 8, 2 H); 4.62 (*s*, 2 H); 3.40 (*dd*, *J* = 10, 6, 1 H); 3.37 (*s*, 3 H); 3.35 (*dd*, *J* = 10, 6, 1 H); 2.76 (*dd*, *J* = 13, 6, 1 H); 2.62 (*q*, *J* = 8, 2 H); 2.37 (*dd*, *J* = 13, 8, 1 H); 2.02 (*m*, 1 H); 1.23 (*t*, *J* = 8, 3 H); 0.92 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 3*. MS: 222 (2, $M^{+}$), 190 (20), 160 (14), 145 (8), 131 (21), 119 (100), 91 (24), 77 (5), 65 (3), 45 (34).

*(±)-1-[3-(Methoxymethoxy)-2-methylpropyl]-4-methylbenzene* (**9d**): Yield 64% from **8d**. B.p. *ca.* 110°/0.2 mbar (bulb-to-bulb). IR (neat): 2940, 2910, 2860, 2800, 2740, 1500, 1450, 1375, 1210, 1145, 1100, 1070, 1040, 915, 840, 790, 750. $^1$H-NMR: 7.09 (*d*, *J* = 9, 2 H); 7.05 (*d*, *J* = 9, 2 H); 4.63 (*s*, 2 H); 3.45–3.31 (*m*, 2 H); 3.38 (*s*, 3 H); 2.75 (*dd*, *J* = 14, 6, 1 H); 2.37 (*dd*, *J* = 14.4, 9, 1 H); 2.32 (*s*, 3 H); 2.07–1.94 (*m*, 1 H); 0.91 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 3*. MS: 208 (1), 176 (14), 146 (12), 131 (23), 117 (5), 105 (100), 91 (10), 77 (8), 65 (3), 45 (30).

*1-(*tert*-Butyl)-4-[3-(methoxymethoxy)propyl]benzene* (**12a**): Yield 90% from **11a**. B.p. *ca.* 120°/0.2 mbar (bulb-to-bulb). IR (neat): 2950, 2860, 1500, 1455, 1355, 1260, 1150, 1110, 1040, 915. $^1$H-NMR: 7.30 (*d*, *J* = 8, 2 H); 7.13 (*d*, *J* = 8, 2 H); 4.63 (*s*, 2 H); 3.55 (*t*, *J* = 6, 2 H); 3.37 (*s*, 3 H); 2.67 (*dd*, *J* = 8, 7, 2 H); 1.92 (*m*, 2 H); 1.30 (*s*, 9 H). $^{13}$C-NMR: *Table 3*. MS: 236 (4, $M^{+}$), 204 (29), 180 (100), 159 (43), 147 (23), 131 (36), 117 (44), 105 (30), 91 (26), 57 (57), 45 (49), 41 (14), 29 (9).

*1-Isopropyl-4-[3-(methoxymethoxy)propyl]benzene* (**12b**): Yield 87% from **11b**. B.p. *ca.* 120°/0.2 mbar (bulb-to-bulb). IR (neat): 2980, 2900, 1520, 1470, 1390, 1160, 1125, 1050, 930, 850. $^1$H-NMR: 7.13 (*m*, 4 H); 4.63 (*s*, 2 H); 3.55 (*t*, *J* = 6, 2 H); 3.37 (*s*, 3 H); 2.88 (*sept.*, *J* = 7, 1 H); 2.68 (*dd*, *J* = 8, 6, 2 H); 1.91 (*m*, 2 H); 1.24 (*d*, *J* = 7, 6 H). $^{13}$C-NMR: *Table 3*. MS: 222 (5, $M^{+}$), 190 (5), 175 (22), 160 (33), 145 (80), 133 (65), 117 (100), 105 (58), 91 (82), 77 (14), 65 (7), 45 (72), 29 (12).

*1-Ethyl-4-[3-(methoxymethoxy)propyl]benzene* (**12c**): Yield 73% from **11c**. B.p. *ca.* 115°/0.2 mbar (bulb-to-bulb). IR (neat): 2960, 2940, 2875, 1510, 1450, 1150, 1115, 1045, 920, 840, 820. $^1$H-NMR: 7.11 (*s*, 4 H); 4.62 (*s*, 2 H); 3.54 (*t*, *J* = 6, 2 H); 3.37 (*s*, 3 H); 2.67 (*dd*, *J* = 8, 7, 2 H); 2.61 (*q*, *J* = 8, 2 H); 1.90 (*m*, 2 H); 1.22 (*t*, *J* = 8, 3 H). $^{13}$C-NMR: *Table 3*. MS: 208 (4, $M^{+}$), 176 (46), 163 (15), 146 (51), 133 (66) 119 (100), 117 (61), 105 (36), 91 (47), 77 (13), 65 (6), 45 (60), 29 (9).

*1-[3-(Methoxymethoxy)propyl]-4-methylbenzene* (**12d**): Yield 71% from **11d**. B.p. *ca.* 90°/92 mbar (bulb-to-bulb). IR (neat): 2940, 2920, 2870, 1510, 1445, 1150, 1110, 1040, 920, 800. $^1$H-NMR: 7.08 (*s*, 4 H); 4.62 (*s*, 2 H); 3.54 (*t*, *J* = 6, 2 H); 3.37 (*s*, 3 H); 2.67 (*dd*, *J* = 8, 7, 2 H); 2.31 (*s*, 3 H); 1.90 (*m*, 2 H). $^{13}$C-NMR: *Table 3*. MS: 194 (6, $M^{+}$), 162 (72), 149 (15), 132 (57), 119 (71), 117 (68), 105 (100), 91 (24), 77 (14), 65 (5), 45 (28), 31 (6).

5. *General Procedure 2: Preparation of 1,3,4,5-Tetrahydro-2-benzoxepins* **10** *and* **13** (*cf.* [19]). To a stirred suspension of $AlCl_3$ (70 mmol) in $CH_2Cl_2$ (200 ml) at 3–4° was added dropwise a soln. of the corresponding methoxymethyl ether (50 mmol) in $CH_2Cl_2$ (50 ml), and the mixture was stirred at 3–4° during 1 h. The mixture was diluted with $Et_2O$ (500 ml), washed with brine (2×) and sat. aq. $NaHCO_3$ soln., dried ($Na_2SO_4$), and evaporated. Boric acid (5–10 mmol, depending on the amount of alcohol present in the mixture) was added to the crude, and the mixture was heated to 120° at 30 mbar in the bulb-to-bulb oven until no more $H_2O$ was evolved. Distillation under vacuum gave the products as colourless oils.

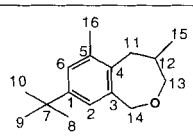
*(±)-8-(*tert*-Butyl)-1,3,4,5-tetrahydro-4-methyl-2-benzoxepin* (**10a**): Yield 76% from **9a**. M.p. 50–51° (from petroleum ether (30–50) at −30°). IR ($CHCl_3$): 3030, 2940, 2860, 1495, 1350, 1113, 1090. $^1$H-NMR: 7.20 (*dd*, *J* = 8, 2, 1 H); 7.16 (*d*, *J* = 2, 1 H); 7.09 (*d*, *J* = 8, 1 H); 4.69 (*s*, 2 H); 4.07 (*dd*, *J* = 11, 6, 1 H); 3.59 (*dd*, *J* = 11, 4, 1 H); 2.87–2.81 (*m*, 2 H); 2.0–1.9 (*m*, 1 H); 1.31 (*s*, 9 H); 0.89 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 4*. MS: 218 (29), 203 (100), 185 (12), 173 (24), 161 (54), 145 (41), 133 (22), 131 (25), 115 (23), 105 (21), 91 (32), 77 (12), 65 (10), 57 (32), 41 (20).

*(±)-1,3,4,5-Tetrahydro-8-isopropyl-4-methyl-2-benzoxepin* (**10b**): Yield 79% from **9b**. B.p. 72–74°/0.1 mbar (bulb-to-bulb). IR (neat): 2940, 2910, 2850, 1500, 1450, 1380, 1360, 1250, 1170, 1100, 1000, 970, 880, 820. $^1$H-NMR: 7.10–7.02 (*m*, 2 H); 7.00 (br. 1 H); 4.02 (*s*, 2 H); 4.06 (*dd*, *J* = 13, 5, 1 H); 3.57 (*dd*, *J* = 13, 10,1 H); 2.92–2.76 (*m*, 3 H); 2.01–1.86 (*m*, 1 H); 1.22 (*d*, *J* = 7, 6 H); 0.87 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 4*. MS: 204 (34), 189 (17), 186 (15), 171 (33), 161 (44), 159 (58), 147 (100), 143 (43), 131 (91), 119 (53), 117 (48), 115 (45), 105 (42), 91 (75), 77 (21), 71 (17), 65 (15), 51 (8), 43 (23), 41 (21).

Table 4. *$^{13}$C-NMR Data of Compounds* **10a–d**, **13a–d**, *and* **19**[a])

| C-Atom | **10a** | **10b** | **10c** | **10d** | **13a** | **13b** | **13c** | **13d** | **19** |
|---|---|---|---|---|---|---|---|---|---|
| C(1) | 149.1 | 146.8 | 142.1 | 135.6 | 149.0 | 146.7 | 142.0 | 135.6 | 148.4 |
| C(2) | 125.5 | 125.5 | 128.1 | 129.2 | 125.7 | 126.8 | 128.2 | 129.1 | 124.0 |
| C(3) | 139.4 | 139.8 | 139.8 | 139.7 | 139.6 | 139.8[b]) | 139.8[b]) | 139.6 | 139.9 |
| C(4) | 137.8 | 138.2 | 138.1 | 137.8 | 139.6 | 139.9[b]) | 139.9[b]) | 139.9 | 137.9 |
| C(5) | 129.5 | 129.7 | 129.7 | 129.6 | 128.9 | 129.1 | 129.1 | 129.4 | 135.0 |
| C(6) | 124.5 | 124.5 | 127.1 | 128.3 | 124.5 | 125.6 | 127.1 | 128.3 | 126.9 |
| C(7) | 34.3 | 34.2 | 28.3 | 20.8 | 34.3 | 33.6 | 28.3 | 20.8 | 34.2 |
| C(8) | 31.4 | 24.0 | 15.6 | – | 31.4 | 24.0 | 15.6 | – | 31.3 |
| C(9) | 31.4 | 24.0 | – | – | 31.4 | 24.0 | – | – | 31.3 |
| C(10) | 31.4 | – | – | – | 31.4 | – | – | – | 31.3 |
| C(11) | 42.7 | 42.7 | 42.7 | 42.7 | 35.0 | 35.1 | 35.1 | 35.0 | 28.8 |
| C(12) | 34.2 | 33.7 | 34.1 | 34.1 | 30.6 | 30.5 | 30.5 | 30.6 | 29.6 |
| C(13) | 81.5 | 81.4 | 81.4 | 81.4 | 75.7 | 75.7 | 75.7 | 75.7 | 75.3 |
| C(14) | 75.5 | 75.2 | 75.1 | 75.0 | 75.6 | 75.3 | 75.2 | 75.1 | 75.3 |
| C(15) | 17.8 | 17.8 | 17.8 | 17.7 | – | – | – | – | – |
| C(16) | – | – | – | – | – | – | – | – | 20.7 |

[a]) Arbitrary C-atom numbering:




[b]) Interchangeable.

*(±)-8-Ethyl-1,3,4,5-tetrahydro-4-methyl-2-benzoxepin* (**10c**): Yield 87% from **9c**. B.p. 110°/0.1 mbar (bulb-to-bulb). IR (neat): 3000, 2960, 2920, 2860, 2820, 1500, 1460, 1390, 1260, 1160, 1120, 1110, 1080, 1060, 1000, 960, 930, 880, 750. $^1$H-NMR: 7.07 (*d*, *J* = 7, 1 H); 7.01 (*d*, *J* = 7, 1 H); 6.98 (*s*, 1 H); 4.61 (*s*, 2 H); 4.05 (*dd*, *J* = 13, 4, 1 H); 3.58 (*dd*, *J* = 13, 9, 1 H); 2.89–2.78 (*m*, 2 H); 2.60 (*q*, *J* = 9, 2 H); 1.22 (*t*, *J* = 9, 3 H); 0.87 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 4*. MS: 190 (23), 172 (18), 161 (15), 157 (23), 145 (40), 143 (30), 133 (100), 131 (53), 117 (50), 105 (38), 91 (53), 77 (17), 65 (12), 51 (10), 41 (9).

*(±)-1,3,4,5-Tetrahydro-4,8-dimethyl-2-benzoxepin* (**10d**): Yield 80% from **9d**. B.p. 80°/0.1 mbar (bulb-to-bulb). IR (neat): 2980, 2940, 2920, 1490, 1450, 1240, 1150, 1120, 1100, 1070, 1000, 955, 900, 875, 815, 630. $^1$H-NMR: 7.04 (*d*, *J* = 7, 1 H); 8.98 (*d*, *J* = 7, 1 H); 6.95 (*s*, 1 H); 4.59 (*s*, 2 H); 4.04 (*dd*, *J* = 13, 5, 1 H); 3.58 (*dd*, *J* = 13, 9, 1 H); 2.87–2.76 (*m*, 2 H); 2.30 (*s*, 3 H). $^{13}$C-NMR: *Table 4*. MS: 176 (40), 158 (32), 143 (47), 131 (85), 119 (100), 105 (39), 91 (57), 77 (23), 65 (10), 51 (9), 39 (9).

*8-(*tert*-Butyl)-1,3,4,5-tetrahydro-2-benzoxepin* (**13a**): Yield 67% from **12a**. B.p. 92°/0.2 mbar (bulb-to-bulb). M.p. 49° (from petroleum ether (30–50) at −30°). IR (neat): 2940, 2880, 2820, 1500, 1445, 1430, 1355, 1250, 1220, 1100, 1095, 1030, 995, 970, 910, 895, 880, 830, 815, 750, 730, 670. $^1$H-NMR: 7.22–7.13 (*m*, 2 H); 7.10 (*d*, *J* = 7, 1 H); 4.66 (*s*, 2 H); 4.07–4.02 (*m*, 2 H); 2.99–2.93 (*m*, 2 H); 1.87–1.80 (*m*, 2 H); 1.30 (*s*, 9 H). $^{13}$C-NMR: *Table 4*. MS: 204 (17), 189 (100), 171 (15), 147 (24), 145 (55), 131 (21), 115 (22), 105 (24), 91 (28), 77 (12), 71 (9), 65 (10), 57 (25), 51 (4), 41 (20).

*8-Isopropyl-1,3,4,5-tetrahydro-2-benzoxepin* (**13b**): Yield 75% from **12b**. B.p. *ca.* 120°/0.2 mbar (bulb-to-bulb). IR (neat): 2990, 2870, 1515, 1470, 1395, 1375, 1270, 1190, 1120, 1050, 985, 845. $^1$H-NMR: 7.09 (*d*, *J* = 8, 1 H); 7.03 (*dd*, *J* = 8, 2, 1 H); 7.02 (br. *s*, 1 H); 4.64 (*s*, 2 H); 4.04 (*m*, 2 H); 2.96 (*m*, 2 H); 2.86 (*sept.*, *J* = 7, 1 H); 1.82 (*m*, 2 H); 1.23 (*d*, *J* = 7, 6 H). $^{13}$C-NMR: *Table 4*. MS: 190 (52, $M^{+\cdot}$), 175 (55), 157 (36), 147 (100), 129 (46), 117 (58), 115 (51), 105 (29), 91 (46), 77 (18), 65 (12), 51 (11), 39 (14).

*8-Ethyl-1,3,4,5-tetrahydro-2-benzoxepin* (**13c**): Yield 79% from **12c**. B.p. *ca.* 115°/0.2 mbar (bulb-to-bulb). IR (neat): 2960, 2930, 2830, 1500, 1455, 1260, 1105, 1035, 880, 830. $^1$H-NMR: 7.08 (*d*, *J* = 8, 1 H); 7.01 (*d*, *J* = 8, 1 H); 6.99 (*s*, 2 H); 4.62 (*s*, 2 H); 4.03 (*t*, *J* = 5); 2.95 (*t*, *J* = 4, 1 H); 2.95 (*d*, *J* = 11, 1 H); 2.60 (*d*, *J* = 8, 2 H); 1.81 (*m*, 2 H); 1.21 (*t*, *J* = 8, 3 H). $^{13}$C-NMR: *Table 4*. MS: 176 (78, $M^{+\cdot}$), 158 (35), 147 (88), 133 (84), 129 (86), 117 (100), 115 (68), 105 (52), 91 (76), 77 (28), 65 (16), 51 (15), 39 (16), 29 (10).

*8-Methyl-1,3,4,5-tetrahydro-2-benzoxepin* (**13d**): Yield 36% from **12d**. B.p. 40–50°/0.1 mbar (bulb-to-bulb). M.p. 49° (from petroleum ether (30–50) at −30°). IR (neat): 3000, 2940, 2840, 1500, 1460, 1440, 1380, 1360, 1250, 1155, 1125, 1100, 1045, 970, 900, 880, 830, 810, 640. $^1$H-NMR: 7.06 (*d*, *J* = 7, 1 H); 7.02–6.96 (*m*, 2 H); 4.62 (*s*,

2 H); 4.07–4.0 (*m*, 2 H); 3.0–2.92 (*m*, 2 H); 2.30 (*s*, 3 H); 1.86–1.77 (*m*, 2 H). $^{13}$C-NMR: *Table 4*. MS: 162 (48), 147 (31), 144 (78), 131 (38), 129 (70), 119 (97), 117 (93), 115 (67), 106 (65), 107 (75), 91 (100), 77 (42), 65 (23), 63 (18), 51 (20), 39 (12).

6. *General Procedure 3: Hydrogenolysis of 1,3,4,5-Tetrahydro-2-benzoxepins to* **4** *and* **16**. To a soln. of the corresponding 1,3,4,5-tetrahydro-2-benzoxepin (30 mmol) in AcOEt (30 ml) and EtOH (30 ml) was added 5% PdC (2 g), and the mixture was shaken under $N_2$ (1 atm.) at r.t. during 15 h. The catalyst was filtered off and the filtrate evaporated. Bulb-to-bulb distillation under vacuum afforded the corresponding alcohols as colourless oils.

*(±)-3-[4-(*tert*-Butyl)-2-methylphenyl]-2-methylpropan-1-ol* (**14a**): Yield 99% from **10a**. B.p. 130–140°/0.1 mbar (bulb-to-bulb). IR (neat): 3600, 3500, 2920, 1590, 1440, 1020. $^1$H-NMR: 7.15 (*s*, 1 H); 7.14 (*d*, *J* = 9, 2 H); 7.04 (*d*, *J* = 9, 2 H); 3.57 (*dd*, *J* = 11, 6.1, 1 H); 2.71 (*dd*, *J* = 14.0, 6.7, 1 H); 2.38 (*dd*, *J* = 14.0, 9, 1 H); 2.31 (*s*, 3 H); 1.98–1.87 (*m*, 1 H); 1.45 (*s*, 9 H); 0.95 (*d*, *J* = 6.7, 3 H). $^{13}$C-NMR: *Table 5*. MS: 220 (25), 205 (91), 187 (8), 173 (4), 161 (100), 145 (33), 131 (35), 119 (22), 115 (15), 105 (28), 77 (9), 57 (25), 41 (17).

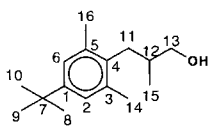
*(±)-3-(4-Isopropyl-2-methylphenyl)-2-methylpropan-1-ol* (**14b**): Yield 98% from **10b**. B.p. 120–130°/0.1 mbar (bulb-to-bulb). IR (neat): 3340, 2940, 2900, 2860, 1600, 1500, 1450, 1370, 1170, 1120, 1100, 1030, 980. $^1$H-NMR: 7.03 (*d*, *J* = 7, 1 H); 7.00 (*s*, 1 H); 6.97 (*d*, *J* = 7, 1 H); 3.54 (*dd*, *J* = 11, 5, 1 H); 3.46 (*dd*, *J* = 11, 7, 1 H); 2.83 (*sept.*, *J* = 7, 1 H); 2.70 (*dd*, *J* = 14, 7, 1 H); 2.36 (*dd*, *J* = 14, 9, 1 H); 2.30 (*s*, 3 H); 1.96–1.84 (*m*, 1 H); 1.63 (br., 1 H); 1.23 (*d*, *J* = 7, 6 H); 0.94 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 5*. MS: 206 (13), 191 (7), 173 (11), 159 (13), 147 (100), 131 (21), 119 (27), 117 (15), 105 (38), 91 (24), 77 (6), 55 (5), 41 (11).

*(±)-3-(4-Ethyl-2-methylphenyl)-2-methylpropan-1-ol* (**14c**): Yield 96% from **10c**. B.p. 120°/0.1 mbar (bulb-to-bulb). IR (neat): 3340, 2960, 2920, 2860, 1500, 1450, 1380, 1060, 970, 880, 860, 820. $^1$H-NMR: 7.03 (*d*, *J* = 7, 1 H); 6.98 (*s*, 1 H); 6.95 (*d*, *J* = 7, 1 H); 3.56 (*dd*, *J* = 11, 6, 1 H); 3.48 (*dd*, *J* = 11, 7, 1 H); 2.72 (*dd*, *J* = 14, 9, 1 H); 2.29 (*s*, 3 H); 1.98–1.84 (*m*, 1 H); 1.46 (br., 1 H); 1.22 (*t*, *J* = 9, 3 H); 0.94 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 5*. MS: 192 (13), 174 (2), 159 (3), 145 (6), 133 (100), 117 (8), 105 (25), 91 (12), 77 (4), 65 (3), 55 (2), 41 (4).

Table 5. *$^{13}$C-NMR Data of Compounds* **14a–d**, **16a–d**, *and* **20**[a])

| C-Atom | **14a** | **14b** | **14c** | **14d** | **16a** | **16b** | **16c** | **16d** | **20** |
|---|---|---|---|---|---|---|---|---|---|
| C(1) | 148.9 | 146.6 | 141.9 | 135.4 | 148.8 | 146.5 | 141.9 | 135.7 | 148.3 |
| C(2) | 127.3 | 128.6 | 129.9 | 131.1 | 127.2 | 128.4 | 129.8 | 131.0 | 125.1 |
| C(3) | 135.9 | 136.3 | 136.1 | 135.9 | 135.4 | 135.7 | 135.8 | 136.9 | 135.6 |
| C(4) | 135.6 | 136.0 | 136.1 | 136.0 | 136.9 | 137.3 | 137.2 | 135.4 | 135.7 |
| C(5) | 129.6 | 129.9 | 129.9 | 129.9 | 128.5 | 128.7 | 128.8 | 128.8 | 135.6 |
| C(6) | 122.6 | 123.7 | 125.2 | 126.4 | 122.8 | 123.9 | 125.4 | 126.6 | 125.1 |
| C(7) | 34.2 | 33.6 | 28.4 | 20.9 | 34.2 | 33.6 | 28.4 | 20.9 | 34.1 |
| C(8) | 31.4 | 24.0 | 15.6 | – | 31.4 | 24.1 | 15.7 | – | 31.4 |
| C(9) | 31.4 | 24.0 | – | – | 31.4 | 24.1 | – | – | 31.4 |
| C(10) | 31.4 | – | – | – | 31.4 | – | – | – | 31.4 |
| C(11) | 36.7 | 36.8 | 36.7 | 36.7 | 29.0 | 29.1 | 29.1 | 29.0 | 25.7 |
| C(12) | 36.7 | 36.8 | 36.8 | 36.8 | 33.0 | 33.1 | 33.1 | 33.1 | 32.2 |
| C(13) | 68.1 | 68.0 | 68.8 | 68.0 | 62.6 | 62.6 | 62.4 | 62.4 | 63.2 |
| C(14) | 19.8 | 19.6 | 19.5 | 19.4 | 19.6 | 19.4 | 19.3 | 19.2 | 20.1 |
| C(15) | 16.8 | 16.8 | 16.8 | 16.7 | – | – | – | – | – |
| C(16) | – | – | – | – | – | – | – | – | 20.1 |

[a]) Arbitrary C-atom numbering:




*(±)-3-(2,4-Dimethylphenyl)-2-methylpropan-1-ol* (**14d**): Yield 99% from **10d**. B.p. 110–120°/0.1 mbar (bulb-to-bulb). IR (neat): 3310, 2940, 2900, 2860, 2710, 1600, 1495, 1450, 1370, 1030, 980, 930, 860, 820, 800. $^1$H-NMR: 7.00 (*d*, *J* = 7, 1 H); 6.96 (*s*, 1 H); 6.92 (*d*, *J* = 7, 1 H); 3.54 (*dd*, *J* = 11, 7, 1 H); 3.45 (*dd*, *J* = 11, 6, 1 H); 2.70 (*dd*, *J* = 14, 7, 1 H); 2,35 (*dd*, *J* = 14, 7, 1 H); 2.35 (*dd*, *J* = 14, 9, 1 H); 2.28 (*s*, 3 H); 2.27 (*s*, 3 H); 1.95–1.83 (*m*, 1 H);

1.5 (br., 1 H); 0.93 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 5*. MS: 178 (13), 160 (3), 145 (10), 131 (4), 120 (15), 119 (100), 105 (10), 91 (18), 77 (10), 65 (5), 51 (3), 41 (5).

*3-[4-(*tert*-Butyl)-2-methylphenyl]propan-1-ol* (**16a**): Yield 83% from **13a**. B.p. 110°/0.1 mbar (bulb-to-bulb). IR (neat): 3300, 2940, 2850, 1500, 1460, 1350, 1270, 1050, 1030, 820, 810. $^1$H-NMR: 7.18–7.11 (*m*, 2 H); 7.07 (*d*, *J* = 9, 1 H); 3.7 (*t*, *J* = 7, 2 H); 2.68–2.64 (*m*, 2 H); 2.32 (*s*, 3 H); 1.89–1.79 (*m*, 2 H); 1.6 (br., 1 H); 1.31 (*s*, 9 H). $^{13}$C-NMR: *Table 5*. MS: 206 (23), 191 (65), 173 (15), 161 (5), 145 (100), 131 (90), 119 (18), 117 (17), 115 (20), 106 (24), 105 (47), 91 (30), 77 (15), 72 (4), 65 (8), 57 (42), 44 (12), 41 (35).

*3-(4-Isopropyl-2-methylphenyl)propan-1-ol* (**16b**): Yield 96% from **13b**. B.p. *ca.* 120°/0.2 mbar (bulb-to-bulb). IR (neat): 3330 (br.), 2960, 2870, 1500, 1455, 1380, 1060, 1045, 825. $^1$H-NMR: 7.08 (*d*, *J* = 8, 1 H); 7.01 (br. *s*, 1 H); 6.99 (*dd*, *J* = 8, 2, 1 H); 3.70 (*t*, *J* = 6, 2 H); 2.84 (*sept.*, *J* = 7, 1 H); 2,65 (*dd*, *J* = 8, 6, 2 H); 2.30 (*s*, 3 H); 1.84 (*m*, 2 H); 1.50 (br., OH); 1.23 (*d*, *J* = 6 H). $^{13}$C-NMR: *Table 5*. MS: 192 (74, $M^+$), 177 (100), 159 (42), 147 (88), 131 (73), 119 (47), 105 (70), 91 (45), 77 (19), 65 (10), 51 (8), 41 (16), 31 (26).

*3-(4-Ethyl-2-methylphenyl)propan-1-ol* (**16c**): Yield 99% from **13c**. B.p. *ca.* 110°/0.1 mbar (bulb-to-bulb). IR (neat): 3330 (br.), 2960, 2930, 2860, 1500, 1450, 1060, 1040, 880, 825. $^1$H-NMR: 7.06 (*d*, *J* = 8, 1 H); 6.98 (*s*, 1 H); 6.96 (*d*, *J* = 8, 1 H); 3.69 (*t*, *J* = 6, 2 H); 2.65 (*t*, *J* = 8, 2 H); 2.58 (*q*, *J* = 8, 2 H); 2.29 (*s*, 3 H); 1.83 (*m*, 2 H); 1.59 (br. *s*, OH); 1.22 (*t*, *J* = 8, 3 H). $^{13}$C-NMR: *Table 5*. MS: 178 (44, $M^+$), 160 (8), 145 (25), 133 (100), 131 (35), 119 (26), 117 (23), 115 (20), 105 (44), 91 (27), 77 (12), 65 (5), 51 (4), 41 (5), 31 (9).

*3-(2,4-Dimethylphenyl)propan-1-ol* (**16d**): Yield 95% from **13d**. B.p. 110–120°/0.2 mbar (bulb-to-bulb). IR (neat): 3340, 2950, 2870, 1500, 1450, 1060, 1045, 820. $^1$H-NMR: 7.02 (*d*, *J* = 8, 1 H); 6.95 (br. *s*, 1 H); 6.93 (br. *d*, *J* = 8, 1 H); 3.66 (*t*, *J* = 7, 2 H); 2.63 (*dd*, *J* = 8, 7, 2 H); 2.28 (*s*, 3 H); 2.27 (*s*, 3 H); 1.93 (*s*, OH); 1.81 (*m*, 2 H). $^{13}$C-NMR: *Table 5*. MS: 164 (36, $M^+$), 146 (8), 131 (40), 118 (100), 105 (20), 91 (24), 77 (10), 65 (4), 51 (3), 31 (4).

7. *General Procedure 4: Oxidation of Alcohols to Aldehydes* **15** *and* **17**. To a stirred suspension of pyridinium chlorochromate (PPC; 13.4 g, 62 mmol) in $CHCl_2$ (80 ml) at r.t. was added a soln. of the corresponding alcohol (41 mmol) in $CH_2Cl_2$ (20 ml), and the mixture was stirred at r.t. during 15 h. The mixture was diluted with $Et_2O$ (200 ml), filtered through *Celite* and then through a short column of *Florisil*® (*Fluka*), and evaporated. Bulb-to-bulb distillation under vacuum afforded the corresponding aldehyde as colourless oils.

*(±)-3-[4-(*tert*-Butyl)-2-methylphenyl]-2-methylpropanal* (**15a**): Yield 68% from **14a**. B.p. 100–110°/0.1 mbar (bulb-to-bulb). IR (neat): 3400, 2940, 2820, 2800, 2690, 1710, 1600, 1450. $^1$H-NMR: 9.71 (*d*, *J* = 3, 1 H); 7.17 (br. *s*, 1 H); 7.16 (*dd*, *J* = 8, 2, 1 H); 7.04 (*d*, *J* = 8, 1 H); 3.06 (*dd*, *J* = 14, 7, 1 H); 2.71–2.59 (*m*, 1 H); 2.53 (*dd*, *J* = 14, 9, 1 H); 2.31 (*s*, 3 H); 1.30 (*s*, 9 H); 1.11 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 6*. MS: 218 (18), 203 (57), 185 (8), 173 (3), 161 (100), 145 (27), 133 (23), 131 (24), 119 (13), 105 (16), 91 (16), 77 (8), 57 (15), 41 (13).

*(±)-3-(4-Isopropyl-2-methylphenyl)-2-methylpropanal* (**15b**): Yield 72% from **14b**. B.p. 145°/0.1 mbar. IR (neat): 2940, 2910, 2860, 2800, 2700, 1740, 1490, 1450, 1370. $^1$H-NMR: 9.70 (*d*, *J* = 3, 1 H); 7.03 (*d*, *J* = 7, 1 H); 7.01 (*s*, 1 H); 6.99 (*d*, *J* = 7, 1 H); 3.06 (*dd*, *J* = 14, 7, 1 H); 2.84 (*sept.*, *J* = 7, 1 H); 2.70–2.58 (*m*, 1 H); 2.53 (*dd*, *J* = 14, 9, 1 H); 2.3 (*s*, 3 H); 1.23 (*d*, *J* = 7, 6 H); 1.1 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 6*. MS: 204 (8), 186 (13), 171 (11), 161 (13), 147 (100), 143 (9), 131 (25), 119 (53), 105 (38), 91 (28), 77 (9), 71 (2), 65 (5), 55 (4), 43 (8), 41 (12).

*(±)-3-(4-Ethyl-2-methylphenyl)-2-methylpropanal* (**15c**): Yield 86% from **14c**. B.p. 120°/0.2 mbar (bulb-to-bulb). IR (neat): 2960, 2920, 2860, 2800, 2700, 1720, 1500, 1450, 1390, 1370, 1120, 930, 880, 840. $^1$H-NMR: 9.74 (*d*, *J* = 2, 1 H); 7.03 (*d*, *J* = 7, 1 H); 6.99 (*s*, 1 H); 6.96 (*d*, *J* = 7, 1 H); 3.06 (*dd*, *J* = 14, 6, 1 H); 2.70–2.48 (*m*, 4 H); 2.29 (*s*, 3 H); 1.21 (*t*, *J* = 9, 3 H); 1.10 (*d*, *J* = 7, 3 H). $^{13}$C-NMR: *Table 6*. MS: 190 (5), 172 (13), 161 (3), 157 (5), 143 (4), 133 (100), 120 (8), 117 (12), 115 (11), 105 (39), 91 (15), 77 (7), 65 (3), 51 (2), 41 (5).

*(±)-3-(2,4-Dimethylphenyl)-2-methylpropanal* (**15d**) [23]: Yield 77% from **14d**. B.p. 110°/0.2 mbar (bulb-to-bulb). IR (neat): 2960, 2900, 2850, 2800, 2700, 1715, 1600, 1500, 1450, 1385, 1370, 1120, 1030, 920, 860, 820, 800. $^1$H-NMR: 9.69 (*d*, *J* = 2.9, 1 H); 6.99 (*d*, *J* = 7.2, 1 H); 6.97 (*s*, 1 H); 6.93 (*d*, *J* = 7.2, 1 H); 3.05 (*dd*, *J* = 14.4, 7.2, 1 H); 2.68–2.56 (*m*, 1 H); 2.52 (*dd*, *J* = 14.4, 9, 1 H); 2.28 (*s*, 3 H); 2.26 (*s*, 3 H); 1.10 (*d*, *J* = 7.2, 3 H). $^{13}$C-NMR: *Table 6*. MS: 176 (6), 158 (15), 143 (8), 128 (84), 119 (100), 115 (8), 106 (10), 91 (18), 77 (9), 65 (5), 51 (4), 41 (6).

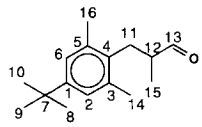
Table 6. *$^{13}$C-NMR Data of Compounds* **15a–d**, **17a–d**, *and* **21**[a])

| C-Atom | **15a** | **15b** | **15c** | **15d** | **17a** | **17b** | **17c** | **17d** | **21** |
|---|---|---|---|---|---|---|---|---|---|
| C(1) | 149.3 | 147.2 | 142.5 | 136.0 | 149.3 | 147.1 | 142.4 | 135.9 | 148.9 |
| C(2) | 127.4 | 128.8 | 130.1 | 131.3 | 127.4 | 128.6 | 130.0 | 131.2 | 125.3 |
| C(3) | 135.5 | 135.9 | 135.9 | 135.9 | 135.4 | 135.7 | 135.8 | 135.7 | 135.5 |
| C(4) | 134.0 | 134.4 | 134.2 | 134.0 | 135.4 | 135.7 | 135.6 | 135.3 | 134.0 |

*Table 6* (cont.)

| C-Atom | **15a** | **15b** | **15c** | **15d** | **17a** | **17b** | **17c** | **17d** | **21** |
|---|---|---|---|---|---|---|---|---|---|
| C(5) | 129.4 | 129.8 | 129.7 | 129.6 | 128.2 | 128.5 | 128.5 | 128.5 | 135.5 |
| C(6) | 122.9 | 124.0 | 125.4 | 126.7 | 123.1 | 124.1 | 125.6 | 126.8 | 125.3 |
| C(7) | 34.2 | 33.7 | 28.3 | 20.8 | 34.3 | 33.6 | 28.4 | 20.9 | 34.1 |
| C(8) | 31.4 | 24.0 | 15.5 | – | 31.4 | 24.0 | 15.6 | – | 31.4 |
| C(9) | 31.4 | 24.0 | – | – | 31.4 | 24.0 | – | – | 31.4 |
| C(10) | 31.4 | – | – | – | 31.4 | – | – | – | 31.4 |
| C(11) | 33.5 | 33.7 | 33.6 | 33.5 | 25.0 | 25.1 | 25.1 | 25.1 | 21.7 |
| C(12) | 46.8 | 46.9 | 47.0 | 47.0 | 44.0 | 44.1 | 44.2 | 44.2 | 43.2 |
| C(13) | 204.2 | 204.5 | 204.5 | 204.5 | 201.8 | 201.8 | 201.8 | 201.7 | 201.6 |
| C(14) | 19.7 | 19.6 | 19.5 | 19.4 | 19.6 | 19.4 | 19.3 | 19.2 | 20.1 |
| C(15) | 13.5 | 13.5 | 13.4 | 13.4 | – | – | – | – | – |
| C(16) | – | – | – | – | – | – | – | – | 20.1 |

[a]) Arbitrary C-atom numbering:




*3-[4-(*tert*-Butyl)-2-methylphenyl]propanal* (**17a**): Yield 54% from **16a**. M.p. 81–83° (from petroleum ether (30–50) at −30°). IR (neat): 2960, 2900, 2860, 2810, 2720, 1725, 1610, 1510, 1460, 1390, 1270, 1140, 1110, 1040, 885, 830. $^1$H-NMR: 9.83 (br., 1 H); 7.18 (*s*, 1 H); 7.16 (*d*, *J* = 9, 1 H); 7.06 (*d*, *J* = 9, 1 H); 2.95–2.87 (*m*, 2 H); 2.76–2.68 (*m*, 2 H); 2.31 (*s*, 3 H); 1.30 (*s*, 9 H). $^{13}$C-NMR: *Table 6*. MS: 204 (18), 189 (100), 171 (10), 161 (9), 145 (75), 133 (15), 131 (19), 130 (20), 119 (15), 115 (18), 105 (23), 91 (18), 87 (3), 77 (8), 65 (6), 57 (14), 41 (13).

*3-(4-Isopropyl-2-methylphenyl)propanal* (**17b**): Yield 69% from **16b**. B.p. 120°/0.2 mbar (bulb-to-bulb). IR (neat): 2960, 2930, 2870, 1725, 1500, 1455, 1380, 830. $^1$H-NMR: 9.84 (*t*, *J* = 1.5, 1 H); 7.05 (*d*, *J* = 8, 1 H); 7.02 (br. *s*, 1 H); 7.00 (*dd*, *J* = 8, 2, 1 H); 2.91 (*t*, *J* = 8, 2 H); 2.84 (*sept.*, *J* = 7, 1 H); 2.72 (*m*, 2 H); 2.30 (*s*, 3 H); 1.23 (*d*, *J* = 7, 6 H). $^{13}$C-NMR: *Table 6*. MS: 190 (42, $M^+$), 175 (55), 157 (31), 147 (100), 131 (63), 119 (77), 115 (36), 105 (39), 91 (43), 77 (18), 65 (9), 51 (7), 41 (11), 29 (14).

*3-(4-Ethyl-2-methylphenyl)propanal* (**17c**): Yield 72% from **16c**. B.p. *ca.* 120°/0.2 mbar (bulb-to-bulb). IR (neat): 2960, 2930, 2870, 2710, 1720, 1500, 1450, 1060, 830. $^1$H-NMR: 9.83 (*t*, *J* = 1, 1 H); 7.04 (*d*, *J* = 8, 1 H); 6.98 (*s*, H); 6.96 (*d*, *J* = 8, 1 H); 2.90 (*t*, *J* = 7, 2 H); 2.62 (*dt*, *J* = 1, 7, 2 H); 2.58 (*q*, *J* = 8, 2 H); 2.29 (*s*, 3 H); 1.21 (*t*, *J* = 8, 3 H). $^{13}$C-NMR: *Table 6*. MS: 176 (35, $M^+$), 158 (31), 147 (34), 133 (100), 129 (36), 120 (38), 117 (40), 115 (35), 105 (84), 91 (46), 77 (22), 65 (11), 51 (8), 39 (9), 29 (15).

*3-(2,4-Dimethylphenyl)propanal* (**17d**) [23]: Yield 77% from **16d**. B.p. 90–100°/0.2 mbar (bulb-to-bulb). IR (neat): 2920, 2820, 2720, 1725, 1500, 1450, 820. $^1$H-NMR: 9.82 (*t*, *J* = 1.5, 1 H); 7.00 (*d*, *J* = 8, 1 H); 6.97 (br. *s*, 1 H); 6.94 (br. *d*, 1 H); 2.89 (*t*, *J* = 8, 2 H); 2.69 (*m*, 2 H); 2.28 (*s*, 3 H); 2.27 (*s*, 3 H). $^{13}$C-NMR: *Table 6*. MS: 162 (22, $M^+$), 147 (9), 144 (37), 129 (23), 118 (100), 106 (35), 91 (46), 77 (18), 65 (9), 51 (8), 39 (10), 29 (9).

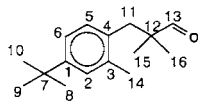
8. *General Procedure 5: Preparation of α,α-Dimethyl Derivatives* **18**. One equiv. of 3-(4-alkylphenyl)-2-methylpropanal was added to 1.1 equiv. of KO(*t*-Bu) in *t*-BuOH (1.1M) under $N_2$ at 30°. Upon addition of the aldehyde, a golden yellow soln. was formed. After 20 min, addition of MeI caused the disappearance of the golden yellow colour. After 1½ h, the mixture was treated with a sat. $NH_4Cl$ soln. and extracted with $Et_2O$. The org. layer was washed with $H_2O$ and brine, dried ($Na_2SO_4$), and evaporated. Distillation or recrystallization at low temperature yielded the α,α-dimethyl-substituted aldehydes.

*3-[4-(*tert*-Butyl)-2-methylphenyl]-2,2-dimethylpropanal* (**18a**): Yield 88% from **15a**. M.p. 20–22° (from petroleum ether (30–50) at −30°). IR (neat): 2940, 2845, 2780, 2680, 1715, 1600, 1490, 1450, 1385, 1370, 1355, 1270, 1195, 875, 825. $^1$H-NMR: 9.59 (*s*, 1 H); 7.14 (*d*, *J* = 2, 1 H); 7.12 (*dd*, *J* = 9, 2, 1 H); 6.95 (*d*, *J* = 9, 1 H); 2.80 (*s*, 2 H); 2.29 (*s*, 3 H); 1.29 (*s*, 9 H); 1.09 (*s*, 6 H). $^{13}$C-NMR: *Table 7*. MS: 232 (5), 217 (5), 199 (2), 187 (2), 173 (2), 161 (100), 146 (15), 133 (17), 131 (25), 119 (12), 105 (12), 91 (8), 77 (5), 65 (2), 57 (5), 41 (15).

*3-(4-Isopropyl-2-methylphenyl)-2,2-dimethylpropanal* (**18b**): Yield 75% from **15b**. B.p. *ca.* 150°/0.2 mbar (bulb-to-bulb). IR (neat): 2940, 2910, 2850, 2780, 2700, 1720, 1600, 1490, 1455, 1370, 1355, 880, 830. $^1$H-NMR: 9.59 (*s*, 1 H); 6.99 (*s*, 1 H); 6.94 (br. *s*, 2 H); 2.81 (*sept.*, *J* = 7, 1 H); 2.78 (*s*, 2 H); 2.26 (*s*, 3 H); 1.21 (*d*, *J* = 7, 6 H);

Table 7. *$^{13}$C-NMR Data of Compounds* **18a**–**d**[a])

| C-Atom | **18a** | **18b** | **18c** | **18d** | C-Atom | **18a** | **18b** | **18c** | **18d** |
|---|---|---|---|---|---|---|---|---|---|
| C(1) | 149.5 | 147.2 | 142.5 | 136.1 | C(9) | 31.3 | 24.0 | – | – |
| C(2) | 127.6 | 128.8 | 130.2 | 131.4 | C(10) | 31.3 | – | – | – |
| C(3) | 136.2 | 136.6 | 136.6 | 136.5 | C(11) | 39.1 | 39.2 | 39.1 | 39.0 |
| C(4) | 132.3 | 132.6 | 132.5 | 132.2 | C(12) | 47.6 | 47.7 | 47.7 | 47.6 |
| C(5) | 130.7 | 131.0 | 131.0 | 130.9 | C(13) | 206.2 | 206.2 | 206.2 | 206.1 |
| C(6) | 122.6 | 123.7 | 125.2 | 126.4 | C(14) | 20.6 | 20.4 | 20.3 | 20.8 |
| C(7) | 34.2 | 33.6 | 28.3 | 20.2 | C(15) | 21.6 | 21.6 | 21.5 | 21.5 |
| C(8) | 31.3 | 24.0 | 15.5 | – | C(16) | 21.6 | 21.6 | 21.5 | 21.5 |

[a]) Arbitrary C-atom numbering: 


1.07 (*s*, 6 H). $^{13}$C-NMR: *Table 7*. MS: 218 (3), 200 (4), 185 (1), 173 (2), 157 (2), 147 (100), 131 (12), 119 (30), 105 (25), 91 (18), 87 (3), 77 (5), 65 (3), 55 (7), 41 (8).

*3-(4-Ethyl-2-methylphenyl)-2,2-dimethylpropanal* (**18c**): Yield 77% from **15c**. B.p. 100°/0.4 mbar (bulb-to-bulb). IR (neat): 2960, 2930, 2870, 2800, 2700, 1720, 1610, 1500, 1460, 1400, 1375, 1360, 1230, 1200, 915, 880, 835. $^1$H-NMR: 9.58 (*s*, 1 H); 6.98 (*s*, 1 H); 6.94 (br. *s*, 2 H); 2.79 (*s*, 2 H); 2.57 (*q*, *J* = 9, 2 H); 2.27 (*s*, 3 H); 1.21 (*t*, *J* = 9, 3 H); 1.07 (*s*, 6 H). $^{13}$C-NMR: *Table 7*. MS: 204 (2), 186 (4), 175 (1), 145 (2), 133 (100), 117 (6), 105 (22), 91 (12), 77 (5), 65 (3), 55 (4), 41 (5).

*3-(2,4-Dimethylphenyl)-2,2-dimethylpropanal* (**18d**): Yield 76% from **15d**. B.p. 120–130°/0.2 mbar (bulb-to-bulb). IR (neat): 2950, 2900, 2850, 2790, 2700, 1710, 1600, 1490, 1450, 1380, 1365, 1350, 1030, 870, 820. $^1$H-NMR: 9.58 (*s*, 1 H); 6.97 (*s*, 1 H); 6.92 (br. *s*, 2 H); 2.79 (*s*, 2 H); 2.28 (*s*, 3 H); 2.26 (*s*, 3 H); 1.08 (*s*, 6 H). $^{13}$C-NMR: *Table 7*. MS: 190 (3), 172 (6), 157 (1), 128 (2), 119 (100), 117 (4), 115 (4), 91 (13), 77 (6), 65 (3), 55 (3), 41 (4).

9. *Synthesis of* **21**. *8-(*tert*-Butyl)-1,3,4,5-tetrahydro-6-methyl-2-benzoxepin* (**19**). According to the *General Procedures 1* and *2* from **16a**. Yield 50%. B.p. *ca.* 92°/0.1 mbar (bulb-to-bulb). M.p. 40° (from petroleum ether (30–50) at −30°). IR (neat): 2960, 2910, 2850, 1600, 1460, 1420, 1380, 1360, 1220, 1100, 1090, 1040, 1000, 940, 880, 830. $^1$H-NMR: 7.10 (*s*, 1 H); 7.05 (*s*, 1 H); 4.65 (*s*, 2 H); 4.06–4.03 (*m*, 2 H); 3.01–2.95 (*m*, 2 H); 2.35 (*s*, 3 H); 1.83–1.74 (*m*, 2 H); 1.30 (*s*, 9 H). $^{13}$C-NMR: *Table 4*. MS: 218 (23), 203 (100), 185 (21), 174 (9), 170 (3), 161 (20), 159 (37), 147 (15), 143 (13), 133 (16), 131 (15), 129 (15), 119 (116), 115 (15), 105 (16), 91 (13), 77 (12), 65 (4), 57 (16), 41 (15).

*3-[4-(*tert*-Butyl)-2,6-dimethylphenyl]propan-1-ol* (**20**). According to the *General Procedure 3* from **19**. Yield 94%. B.p. *ca.* 110–120°/0.1 mbar (bulb-to-bulb). IR (neat): 3350, 2960, 2880, 1610, 1575, 1485, 1460, 1365, 1305, 1240, 1065, 1010, 875. $^1$H-NMR: 7.02 (*s*, 2 H); 3.74 (*t*, *J* = 6, 2 H); 2.67 (*m*, 2 H); 2.33 (*s*, 6 H); 1.75 (*m*, 2 H); 1.44 (br. *s*, OH); 1.29 (*s*, 9 H). $^{13}$C-NMR: *Table 5*. MS: 220 (23, $M^{+}$), 205 (100), 175 (33), 159 (30), 145 (27), 133 (15), 119 (33), 105 (17), 91 (17), 77 (10), 65 (4), 57 (14), 41 (11).

*3-[4-(*tert*-Butyl)-2,6-dimethylphenyl]propanal* (**21**) *from* **20**. According to the *General Procedure 4* from **20**. Yield 70%. M.p. 36–38° (from petroleum ether (30–50) at −30°). IR (neat): 2970, 2920, 2880, 2820, 2720, 1728, 1610, 1575, 1490, 1465, 1370, 1240, 880. $^1$H-NMR: 9.86 (br., 1 H); 7.04 (*s*, 2 H); 3.0–2.88 (*m*, 2 H); 2.68–2.56 (*m*, 2 H); 2.31 (*s*, 6 H); 1.3 (*s*, 9 H). $^{13}$C-NMR: *Table 6*. MS: 218 (18), 203 (100), 200 (13), 185 (23), 175 (30), 159 (74), 147 (35), 145 (28), 133 (20), 129 (25), 119 (23), 115 (16), 105 (18), 91 (15), 79 (10), 77 (8), 65 (5), 57 (8), 41 (14).

*(*E*)-3-[4-(*tert*-Butyl)-2,6-dimethylphenyl]prop-1-enyl Acetate* (**23**). To a soln. of 1-(*tert*-butyl)-3,5-dimethylbenzene ( = 5-(*tert*-butyl)-*m*-xylene; **22**; *Fluka purum*; 2 g, 12 mmol) in $CH_2Cl_2$ (10 ml) at 4–5° was added $TiCl_4$ (2.34 g, 12.2 mmol), and, after 10 min, dropwise prop-2-enal diacetyl acetal ( = acrolein diacetyl acetal; *Fluka purum*; 1,94 g, 12.2 mmol). After 15 min, the mixture was diluted with $Et_2O$, washed with $H_2O$ (2×), sat. aq. $NaHCO_3$ soln., dried ($Na_2SO_4$), and evaporated (2.9 g). Bulb-to-bulb distillation (0.2 mbar, oven temp.→160°) gave a colourless oil (purity 97%; 1.87 g, 57%) containing (by GC) 85% of (*E*)-**23**, 6% of (*Z*)-**23**, and 6% of **21**. IR (neat): 2970, 1760, 1370, 1225, 1100, 935, 870. $^1$H-NMR: 7.02 (*s*, 2 H); 7.00 (*dt*, *J* = 13, *J* = 2, 1 H); 5.48 (*dt*, *J* = 13, 7, 1 H); 3.30 (*dd*, *J* = 7, 2, 2 H); 2.31 (*s*, 6 H); 2.06 (*s*, 3 H); 1.29 (*s*, 9 H). $^{13}$C-NMR: 168.0 (*s*); 149.0 (*s*); 136.2 (*d*); 135.9 (2*s*); 132.7 (*s*); 125.3 (2*d*); 112.4 (*d*); 34.1 (*s*); 31.4 (3*q*); 27.3 (*t*); 20.6 (*q*); 20.1 (2*q*). MS: 260 (10, $M^{+}$), 245 (10), 218 (8), 203 (41), 185 (18), 161 (43), 147 (31), 128 (11), 119 (12), 91 (18), 57 (58), 43 (100).

*Propanal* (**21** *from* **23**). To a stirred soln. of **23** (purity 90%; 0.63 g, 2.1 mmol) in THF (10 ml) was added 25% aq. $H_2SO_4$ soln. (2 ml), and the mixture was heated under reflux (65°) during 4 h. The mixture was diluted with $Et_2O$, washed with brine, sat. aq. $NaHCO_3$ soln., and brine, dried ($Na_2SO_4$), and evaporated (0.51 g). Bulb-to-bulb distillation (0.3 mbar, oven temp.→175°) gave **21** (purity 89%; 0.40 g, 78%). Colourless oil.

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