Alternative Synthesis of 2-Hydroxy-3,5,5-trimethylcyclopent-2-en-1-one

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The 2-hydroxy-3,5,5-trimethylcyclopent-2-en-1-one (**1**) was synthesized in 42% yield by rearrangement of epoxy ketone **10** on treatment with $BF_3 \cdot Et_2O$ under anhydrous conditions. Intermediate **10** was available from the known enone **8**, either *via* direct epoxidation (60% H_2O_2, NaOH, MeOH; yield 50%), or *via* reduction to the corresponding allylic alcohol **14** ($LiAlH_4$, THF), followed by epoxidation ($[VO(acac)_2]$, ^{t}BuOOH) and reoxidation under *Swern* conditions, in 37% total yield.

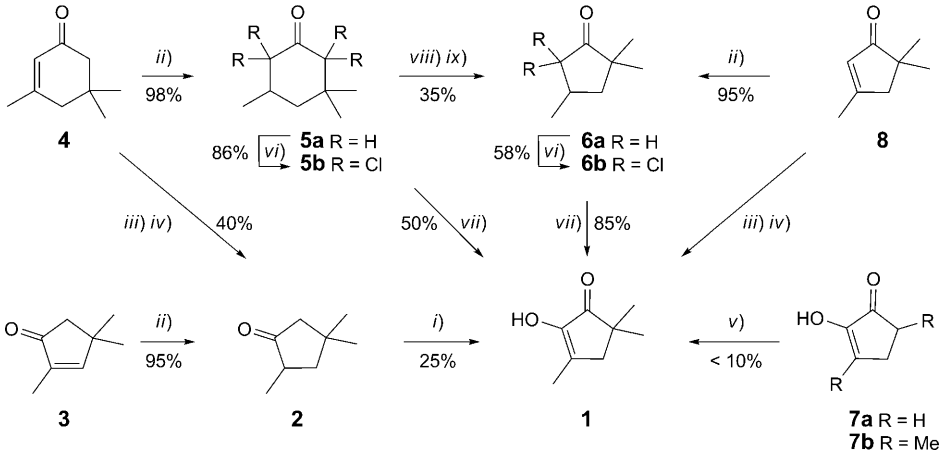
Introduction. – The title compound **1** was first isolated from the essential oil of *Backhousia angustifolia* in 1931 [1] and later identified in roasted coffee [2], as well as in the *Maillard* reaction of casein pancreatic hydrolyzate derived peptides with glucose [3]. Three syntheses have been published which are summarized in *Scheme 1*[1]). The first one consisted in the stoechiometric SeO_2 oxidation of 2,4,4-trimethylcyclopentanone (**2**) [5b–5d] giving **1** in 25% yield [5a].

Intermediate **2**[2]) is readily available, either *via* the corresponding enone **3** [6], by acidic cyclization of isobutyl methacrylate (=2-methylpropyl 2-methylprop-2-enoate) [7], followed by hydrogenation, or from isophorone **4**, *via* sequential $BF_3 \cdot Et_2O$ rearrangement and NaOH treatment of its corresponding epoxide [8]. Alternatively, hydrolytic NaOH treatment of either the tetrachlorocyclohexanone **5b**, with air oxidation, or dichlorocyclopentanone **6b**, afforded the desired compound **1** [9]. Finally, ingredient **1** was also unselectively obtained, as an inseparable mixture of mono- [10], di- [11], and trimethylated material, by alkylation of cyclotene **7a** *via* its ketimine derivative [12]. Nevertheless, none of these approaches is eligible for a viable industrial process for the safe production of a flavor, due to the toxicity of SeO_2, Cl_2, or trace amounts of halogenated materials in the last step. We thus decided to explore and present here an alternative approach, starting from cyclopentenone **8** [13], using classical scalable conditions.

Results and Discussion. – Alkylation of isobutyric acid **9a** with lithium diisopropylamide (LDA) and methallyl chloride (=3-chloro-2-methylprop-1-ene) afforded practically quantitatively the reported acid **9b** (95% yield) [14], which was cyclized with polyphosphoric acid into cyclopentenone **8**, with an improved yield of 83% [13f][15] (*Scheme 2*). Hydrogenation of enone **8** was already reported to afford

[1]) For the photolysis of **1**, see [4].
[2]) ^{13}C-NMR Data: 221.8 (*s*); 52.7 (*t*); 46.1 (*t*); 42.9 (*d*); 34.0 (*s*); 29.8 (*q*); 28.0 (*q*); 14.9 (*q*).

Scheme 1



i) SeO_2, EtOH, 78°. *ii*) H_2, Pd/C, EtOH. *iii*) 35% H_2O_2, NaOH, MeOH. *iv*) $BF_3 \cdot Et_2O$, then NaOH. *v*) $PhNH_2$, TsOH, then 2 equiv. of NaH, THF, MeI, then 15% HCl. *vi*) Cl_2, CCl_4, cat. DMF. *vii*) 3N NaOH, 100°. *viii*) HNO_3, NH_4VO_3. *ix*) Dist./$Ba(OH)_2$.

cyclopentanone **6a**[3]) [16] in 95% yield [13b,c] (*Scheme 1*). We unsuccessfully attempted the oxidation of **6a** with either SeO_2/EtOH or the more practical ^{t}BuOK/O_2 conditions [17]. We then came back to our initial strategy by epoxidizing the C=C bond (60% H_2O_2 solution, NaOH, MeOH), and could isolate the epoxy ketone **10**[4]) in 50% yield[5]) [19]. We also tried acidic *m*CPBA (3-chloroperbenzoic acid) conditions but, as expected, obtained the corresponding epoxy lactone **12** in a poor 12% yield[6]).

To oxidize the α-position of enone **8**, we also treated it with two equiv. of $BH_3 \cdot THF$. Thus, after oxidative NaOH/H_2O_2 workup, we isolated diol **13** in 61% yield. Further oxidation (pyridinium chlorochromate (PCC), CH_2Cl_2) furnished a sample of **1** in 17% yield. The efficiency of this process could be improved by using *Swern* conditions (oxalyl chloride, CH_2Cl_2, DMSO, Et_3N, 25% yield) during the last step[7]). This nonindustrial approach at least allowed us to obtain a sample of **1**, thus facilitating the

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[3]) MS Data: 126 (38, $M^{+\cdot}$), 111 (27), 83 (50), 69 (48), 56 (100), 41 (48).

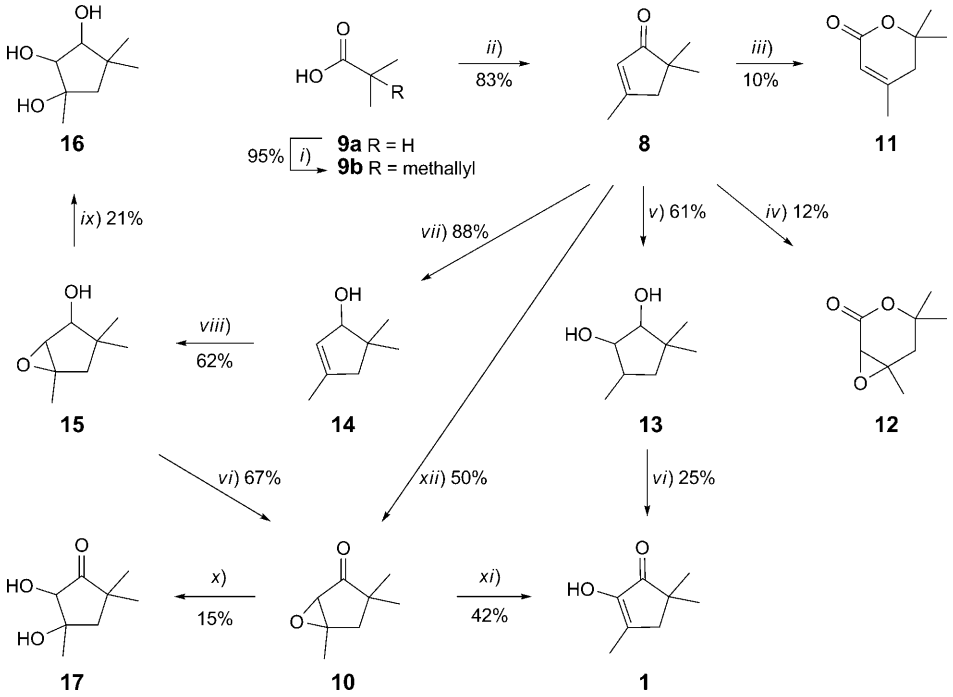
[4]) Both **8** and **10** possess very similar t_R on both polar and apolar capillary GC columns, and UV/TLC or GC/IR analyses are recommended to follow the reaction.

[5]) The known unsaturated lactone **11** was isolated as a by-product in 10% yield on using 30% H_2O_2 solution, beside **10** (30% yield). Phase-transfer conditions (30% H_2O_2 solution, Me_3BnNCl, CH_2Cl_2, H_2O, NaOH [10a]) were cleaner but also less efficient (35% yield), while (KF-Al_2O_3, ^{t}BuOOH [18]) gave only 15% partial conversion.

[6]) Alternative less industrial conditions, oxone [20] or F_2/H_2O/MeCN/CH_2Cl_2 [21], were not attempted.

[7]) *Dess–Martin* conditions gave the worst result (8% of **1**), besides numerous linear derivatives of 2,2,4-trimethylpentanedial [22]; data of 2,2,4-trimethylpentanedial: ^{1}H-NMR: 9.57 (*d*, *J* = 2, 1 H); 9.45 (*s*, 1 H); 2.42–2.35 (*m*, 1 H); 2.11 (*dd*, *J* = 7, 14, 1 H); 1.44 (*dd*, *J* = 5.5, 14, 1 H); 1.11 (*d*, *J* = 7, 3 H); 1.09 (*s*, 3 H); 1.08 (*s*, 3 H). ^{13}C-NMR: 205.3 (*d*); 203.8 (*d*); 45.7 (*s*); 42.8 (*d*); 37.2 (*t*); 22.2 (*q*); 21.7 (*q*); 15.6 (*q*). MS: 142 (1, $M^{+\cdot}$), 113 (5), 95 (16), 72 (32), 58 (48), 43 (100), 41 (35). For an untested alternative aerobic oxidative technique, see [23].

Scheme 2



i) LDA, THF, methallylCl ($ClCH_2C(Me)=CH_2$). *ii*) H_3PO_4. *iii*) 30% H_2O_2, NaOH, MeOH. *iv*) *m*CPBA, CH_2Cl_2, 0°. *v*) $BH_3 \cdot$ THF, THF. *vi*) $(COCl)_2$, DMSO, Et_3N, −10°. *vii*) $LiAlH_4$, THF, 0°. *viii*) ^{t}BuOOH, toluene, $[VO(acac)_2]$. *ix*) 15% HCl. *x*) 0.2% H_2SO_4, 100°. *xi*) $BF_3 \cdot Et_2O$, CH_2Cl_2. *xii*) 60% H_2O_2, NaOH, MeOH.

analysis of alternative processes. Since enone **8** seemed sensitive to oxidative conditions, and prone to *Bayer–Villiger* reaction, we also decided to reduce it ($LiAlH_4$, THF, 88% yield) to the corresponding allyl alcohol **14**. At this stage, we could readily and stereoselectively epoxidize the C=C bond (^{t}BuOOH, $[VO(acac)_2]$, 62% yield, [24]) to the *cis*-epoxy alcohol **15**[8]). This compound is also very sensitive and was readily transformed into triol **16** by a simple washing with 15% aqueous HCl solution during an extraction. *Swern* oxidation of **15** (oxalyl chloride, DMSO, Et_3N, 67% yield) afforded the desired epoxy ketone **10**. Following a known procedure, used for a monomethylated isomer [9], we attempted to isomerize **10** with 0.2% H_2SO_4 solution, but isolated instead of **1** the crystalline dihydroxy ketone **17** in 15% yield. Formally, a further dehydration at a more acidic pH should result in the target molecule [25], but

[8]) Due to the geometry of the five-membered ring, and even with the NOESY experiments in hand, we were unable to fully ascertain the relative *cis* or *trans* configuration of both OH groups in structures of **13**, **16**, and **17**, based on undisputable arguments. Simulated ^{1}H-NMR and IR spectra suggest the following relative configurations: *rel*-(1*RS*,2*SR*,5*SR*)-**13**; *rel*-(1*RS*,2*RS*,3*RS*)-**16**; *rel*-(4*RS*,5*SR*)-**17**; but in view of the absence of chirality in the final compound **1**, further derivatizations or X-ray structure analyses were not undertaken.

we preferred instead to directly isomerize epoxide **10** by treatment with $BF_3 \cdot Et_2O$ under anhydrous conditions. Thus, we readily obtained the desired crystalline flavor ingredient **1** in 42% yield[9]). Although this alternative approach is longer and globally less efficient than the direct epoxidation of enone **8**, this reduction/oxidation route could eventually be shortened by a direct access to the allyl alcohol **14**[10]).

Conclusion. – We could obtain pure **1** by rearrangement of epoxy ketone **10** with $BF_3 \cdot Et_2O$ under anhydrous conditions (42% yield)[9]). This latter intermediate is available from the reported enone **8**, either by direct 60% H_2O_2/NaOH epoxidation (50% yield)[11]) or, less efficiently (37% yield), *via* $[VO(acac)_2]$/^{t}BuOOH epoxidation of the corresponding allyl alcohol **14**, prior to reoxidation under *Swern* conditions. Another two-step transformation of **8**, involving a hydroboration/*Swern* oxidation sequence, is less industrial (15% global yield).

We are indebted to Dr. *Jean-Yves de Saint Laumer* for calculations of the coupling constants in theoretical ^{1}H-NMR analyses ($CDCl_3$) of **13** and **16**[12]).

Experimental Part

General. See [26]. All the chiral compounds presented here were obtained as racemates.

2-Hydroxy-3,5,5-trimethylcyclopent-2-en-1-one (**1**). $BF_3 \cdot Et_2O$ (1.6 g, 11 mmol) was added dropwise to a soln. of epoxy ketone **10** (15.5 g, 110 mmol) in CH_2Cl_2 (200 ml). After 2 h at 20°, the mixture was diluted with CH_2Cl_2 (100 ml) and washed with sat. aq. $NaHCO_3$ soln. to neutrality. The org. phase was dried (Na_2SO_4) and concentrated and the residue bulb-to-bulb distilled: pure **1** (42%). White crystals. M.p. (pentane) 84.5–85.5°. B.p. 77°/6 mbar. IR: 3501, 3421, 3329, 2968, 2928, 2869, 1756, 1695, 1651, 1460, 1404, 1358, 1299, 1234, 1197, 1177, 1147, 1087, 1055, 1028, 959, 932, 839, 781, 704, 658. ^{1}H-NMR: 2.30 (*q*, $J = 1.5$, 2 H); 2.00 (*t*, $J = 1.5$, 3 H); 1.30 (*s*, 6 H); 1.28 (*s*, OH). ^{13}C-NMR: 208.3 (*s*); 146.4 (*s*); 142.4 (*s*); 44.8 (*t*); 41.2 (*s*); 25.1 (2*q*); 14.2 (*q*). MS: 140 (100, $M^{+\bullet}$), 125 (85), 107 (22), 97 (26), 85 (15), 79 (18), 69 (23), 56 (20), 43 (22), 41 (27).

3,5,5-Trimethylcyclopent-2-en-1-one (**8**). A mixture of enone **9b** (17.8 g, 125 mmol) and polyphosphoric acid (85 g) was heated to 140° for 4 h. Ice (100 g) was added to the cold mixture which was then stirred for 1 h. The aq. phase was extracted with Et_2O (5×80 ml), the org. phase washed to neutrality with sat. aq. $NaHCO_3$ soln. and then H_2O, dried (Na_2SO_4), and concentrated, and the residue distilled: pure **8** (83%). B.p. 67°/8.5 to 62°/7.4 mbar. IR: 2960, 2926, 2867, 1701, 1624, 1432, 1378, 1323, 1302, 1224, 1128, 1099, 848, 720, 616. ^{1}H-NMR: 5.85 (*s*, 1 H); 2.44 (*s*, 2 H); 2.11 (*s*, 3 H); 1.11 (*s*, 6 H). ^{13}C-NMR: 214.6 (*s*); 175.5 (*s*); 128.0 (*d*); 49.7 (*t*); 44.6 (*s*); 25.0 (2*q*); 19.4 (*q*). MS: 124 (30, $M^{+\bullet}$), 109 (100), 81 (28), 79 (15), 53 (8), 41 (9), 39 (12).

2,2,4-Trimethylpent-4-enoic Acid (**9b**). Obtained in 95% yield according to [14] and [13f]. B.p. 80°/8 mbar. IR: 3076, 2972, 2931, 1696, 1474, 1448, 1407, 1366, 1311, 1279, 1221, 1163, 1137, 942, 893, 867, 825,

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9) Compound **1** is also very sensitive to purification conditions. For example, a column chromatography (SiO_2) with the eluent AcOEt should be avoided due to partial transesterification to the corresponding 2,4,4-trimethyl-5-oxocyclopent-1-en-1-yl acetate. MS: 182 (0, $M^{+\bullet}$), 140 (96), 125 (74), 112 (23), 107 (13), 97 (22), 85 (27), 69 (19), 56 (38), 43 (100), 41 (39).

10) Thus, for example, the intramolecular oxo–ene reaction of 2,2,4-trimethylpent-4-enal was already reported to form the endocyclic homoallyl alcohol, an analogue of **14** [13a].

11) This shorter access will be further optimized.

12) **13**: $^3J = 4.8$ *vs.* 8.5 Hz between *trans*-positioned H–C(1) and H–C(5) for *cis*- *vs. trans*-positioned OH–C(1) and OH–C(2), resp. **16**: $^3J = 5.2$ *vs.* 7.6 Hz between *trans*-positioned OH–C(1) and OH–C(2) for *cis*- *vs. trans*-positioned OH–C(3) and OH–C(2), resp.

788. ^{1}H-NMR: 12.0 (*s*, OH); 4.84 (*s*, 1 H); 4.71 (*s*, 1 H); 2.34 (*s*, 2 H); 1.72 (*s*, 3 H); 1.21 (*s*, 6 H). ^{13}C-NMR: 185.2 (*s*); 142.2 (*s*); 114.5 (*t*); 48.2 (*t*); 42.0 (*s*); 25.4 (2*q*); 23.6 (*q*). MS: 142 (10, $M^{+\bullet}$), 127 (16), 97 (100), 81 (14), 70 (15), 55 (52), 41 (23).

3,3,5-Trimethyl-6-oxabicyclo[3.1.0]hexan-2-one (**10**). DMSO (1.2 g, 15 mmol) was added dropwise at $-70°$ to a soln. of $(COCl)_2$ (981 mg, 7.7 mmol) in CH_2Cl_2 (14 ml). A soln. of alcohol **15** (1.0 g, 7 mmol) in CH_2Cl_2 (7 ml) was added dropwise, followed, after 0.25 h, by Et_3N (3.55 g, 35 mmol). The temp. was then slowly increased to 20° during 1 h, Et_2O (30 ml) was added, and the org. phase was washed to neutrality with aq. sat. NH_4Cl soln., dried, and concentrated. Bulb-to-bulb distillation afforded pure ketone **10** (67%). B.p. 71°/0.7 mbar. IR: 2967, 2930, 2869, 1741, 1470, 1450, 1410, 1382, 1360, 1268, 1226, 1144, 1126, 1060, 918, 865, 809, 774, 710, 682, 613. ^{1}H-NMR: 3.24 (*s*, 1 H); 2.20 (*d*, $J = 14.7$, 1 H); 1.84 (*d*, $J = 14.7$, 1 H); 1.56 (*s*, 3 H); 1.13 (*s*, 3 H); 1.06 (*s*, 3 H). ^{13}C-NMR: 214.7 (*s*); 64.0 (*s*); 62.2 (*d*); 43.4 (*t*); 43.2 (*s*); 27.6 (*q*); 25.9 (*q*); 18.2 (*q*). MS: 140 (95, $M^{+\bullet}$), 125 (9), 109 (18), 97 (65), 83 (75), 70 (100), 55 (68), 43 (72), 41 (80), 39 (45).

4,4,6-Trimethyl-3,7-dioxabicyclo[4.1.0]heptan-2-one (**12**). A soln. of enone **8** (300 mg, 2.4 mmol) in CH_2Cl_2 (5 ml) was added at 0° to a soln. of 70% *m*CPBA (600 mg, 2.4 mmol) in CH_2Cl_2 (5 ml). After 18 h at 20°, the mixture was diluted with CH_2Cl_2 and extracted with sat. aq. $NaHCO_3$ soln. The org. phase was washed to neutrality with H_2O, dried (Na_2SO_4), and concentrated and the residue purified by CC (SiO_2; Et_2O): pure **12** (12%). B.p. 75°/0.15 mbar. IR: 2980, 2934, 1725, 1445, 1419, 1386, 1372, 1362, 1303, 1281, 1198, 1133, 1075, 1018, 997, 984, 908, 855, 834, 808, 761, 735, 686. ^{1}H-NMR: 3.36 (*s*, 1 H); 2.20 (*d*, $J =$ 15, 1 H); 2.10 (*d*, $J = 15$, 1 H); 1.55 (*s*, 3 H); 1.48 (*s*, 3 H); 1.39 (*s*, 3 H). ^{13}C-NMR: 168.6 (*s*); 81.3 (*s*); 60.1 (*s*); 53.8 (*d*); 38.8 (*t*); 31.7 (*q*); 29.6 (*q*); 21.0 (*q*). MS: 156 (1, $M^{+\bullet}$); 100 (20), 97 (63), 83 (14), 69 (43), 55 (26), 43 (100), 41 (46).

3,3,5-Trimethylcyclopentane-1,2-diol (**13**). A soln. of $BH_3 \cdot THF$ complex (1.0M in THF; 32 ml, 32 mmol) was added dropwise at 0° to a soln. of enone **8** (2.0 g, 16 mmol) in THF (20 ml). After 1.5 h, a 15% aq. NaOH soln. (4 ml) was added, followed at 0° by 35% H_2O_2 soln. (2.0 ml). The mixture was diluted with Et_2O (30 ml) and washed to neutrality with H_2O. The org. phase was dried (Na_2SO_4) and concentrated and the residue purified by CC (SiO_2; cyclohexane/Et_2O 95:5 → 5:95): pure **13** (61%). This material crystallized from cyclohexane. M.p. 74–77°. IR: 3223, 2969, 2954, 2925, 2892, 2863, 1457, 1346, 1286, 1117, 1068, 1016, 999, 911, 843, 790, 715. ^{1}H-NMR: 3.72 (br. *s*, 2 OH); 3.46 (*d*, $J = 4.3$, 2 H); 1.80–1.70 (*m*, 2 H); 1.20–1.10 (*m*, 1 H); 1.05 (*d*, $J = 7$, 3 H); 1.04 (*s*, 3 H); 0.93 (*s*, 3 H). ^{13}C-NMR: 85.7 (*d*); 83.8 (*d*); 44.3 (*t*); 36.7 (*s*); 34.4 (*d*); 29.6 (*q*); 24.9 (*q*); 18.7 (*q*). MS: 144 (8, $M^{+\bullet}$), 126 (16), 111 (69), 88 (28), 83 (54), 71 (100), 69 (76), 57 (70), 43 (56), 41 (70).

3,5,5-Trimethylcyclopent-2-en-1-ol (**14**). A soln. of enone **8** (6.7 g, 53 mmol) in Et_2O (10 ml) was added dropwise at 0° to a suspension of $LiAlH_4$ (1.0 g, 27 mmol) in Et_2O (230 ml). After 2 h at 20°, H_2O (1 ml), 15% NaOH soln. (1 ml), and H_2O (10 ml) were successively added. The mixture was filtered and the filtrate dried ($MgSO_4$) and concentrated. Bulb-to-bulb distillation afforded pure **14** (88%). B.p. 68°/9.0 mbar. IR: 3337, 3045, 2953, 2911, 2866, 2839, 1658, 1466, 1440, 1378, 1363, 1322, 1195, 1154, 1038, 1020, 992, 942, 885, 865, 825, 671.^{1}H-NMR: 5.38 (*s*, 1 H); 4.13 (*s*, 1 H); 2.22 (*d*, $J = 16.2$, 1 H); 1.94 (*d*, $J = 16.2$, 1 H); 1.73 (*s*, 3 H); 1.26 (br. *s*, OH); 1.05 (*s*, 3 H); 1.04 (*s*, 3 H). ^{13}C-NMR: 145.0 (*s*); 126.4 (*d*); 85.2 (*d*); 50.4 (*t*); 42.2 (*s*); 28.7 (*q*); 22.8 (*q*); 17.1 (*q*). MS: 126 (8, $M^{+\bullet}$), 111 (100), 108 (30), 93 (99), 91 (55), 77 (43), 55 (20), 43 (20), 41 (18), 39 (20).

3,3,5-Trimethyl-6-oxabicyclo[3.1.0]hexan-2-ol (**15**). At 20°, 70% aq. *t*BuOOH soln. (9.0 g, 70 mmol) was added dropwise at 20° to a soln. of alcohol **14** (5.9 g, 47 mmol) and $[VO(acac)_2]$ (186 mg, 0.7 mmol) in toluene (80 ml). After 2 h at 20°, the mixture was diluted with Et_2O (120 ml) and extracted with sat. aq. $NaHCO_3$ soln. and H_2O to neutrality. The org. phase was dried (Na_2SO_4) and concentrated and the residue bulb-to-bulb distilled: pure **15** (62%). B.p. 78°/4.8 mbar. IR: 3423, 2954, 2929, 2868, 1469, 1448, 1426, 1383, 1362, 1309, 1221, 1169, 1150, 1088, 1051, 1029, 1000, 984, 965, 922, 882, 868, 832, 804, 693, 662. ^{1}H-NMR: 3.83 (*s*, 1 H); 3.38 (*s*, 1 H); 2.03 (br. *s*, OH); 1.89 (*d*, $J = 14.4$, 1 H); 1.59 (*d*, $J = 14.4$, 1 H); 1.40 (*s*, 3 H); 1.03 (*s*, 3 H); 1.00 (*s*, 3 H). ^{13}C-NMR: 80.7 (*d*); 67.3 (*d*); 62.9 (*s*); 45.8 (*t*); 39.2 (*s*); 30.1 (*q*); 24.7 (*q*); 18.4 (*q*). MS: 142 (11, $M^{+\bullet}$), 127 (10), 109 (33), 85 (100), 72 (33), 57 (41), 55 (35), 43 (65), 41 (38).

1,4,4-Trimethylcyclopentane-1,2,3-triol (**16**). A soln. of epoxy alcohol **15** (4.1 g, 29 mmol) in Et_2O (50 ml) was washed with 15% aq. HCl soln. (3 × 30 ml) and then with sat. aq. NH_4Cl soln. to neutrality. The org. phase was dried ($MgSO_4$) and concentrated and the residue bulb-to-bulb distilled: **16** (21%).

B.p. 73°/1.3 mbar. IR: 3395, 2961, 2933, 2870, 1700, 1656, 1469, 1448, 1407, 1378, 1366, 1306, 1259, 1224, 1202, 1140, 1093, 1028, 1011, 990, 948, 894, 854, 781, 698, 657. ^{1}H-NMR: 4.26 (*d*, *J* = 4.4, 1 H); 4.09 (*d*, *J* = 4.4, 1 H); 2.76 (br. *s*, 3 H); 2.11 (*s*, 2 H); 1.64 (*s*, 3 H); 1.21 (*s*, 3 H); 1.02 (*s*, 3 H). ^{13}C-NMR: 82.9 (*d*); 80.3 (*d*); 74.4 (*s*); 55.0 (*t*); 39.6 (*s*); 29.9 (*q*); 27.4 (*q*); 25.3 (*q*). MS: 160 (1, $M^{+\bullet}$), 142 (7), 109 (9), 83 (11), 72 (100), 57 (17), 43 (14).

4,5-Dihydroxy-2,2,4-trimethylcyclopentanone (**17**). A mixture of epoxy ketone **10** (200 mg, 1.4 mmol) in 0.2% H_2SO_4 soln. (0.9 ml) was heated to reflux for 1 h. The mixture was diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The org. phase was dried (Na_2SO_4) and concentrated and the residue purified by CC (SiO_2; cyclohexane/Et_2O 95:5): pure **17** (15%). White crystals. IR: 3358, 3270, 2974, 2963, 2931, 2866, 2843, 1742, 1464, 1448, 1389, 1378, 1359, 1315, 1302, 1231, 1182, 1144, 1102, 1058, 1033, 1001, 952, 945, 892, 827, 795, 678. ^{1}H-NMR: 4.53 (*s*, 1 H); 3.53 (br. *s*, OH); 3.26 (br. *s*, OH); 2.11 (*d*, *J* = 13.5, 1 H); 2.00 (*d*, *J* = 13.5, 1 H); 1.22 (*s*, 3 H); 1.19 (*s*, 3 H); 1.13 (*s*, 3 H). ^{13}C-NMR: 219.2 (*s*); 82.6 (*d*); 75.3 (*s*); 48.3 (*t*); 42.0 (*s*); 28.8 (*q*); 25.4 (*q*); 22.4 (*q*). MS: 158 (21, $M^{+\bullet}$), 140 (48), 125 (35), 101 (100), 88 (42), 74 (42), 55 (32), 43 (60), 41 (30).

REFERENCES

[1] R. S. Cahn, C. S. Gibson, A. R. Penfold, J. L. Simonsen, *J. Chem. Soc.* **1931**, 286.

[2] M. A. Gianturco, A. S. Giammarino, R. G. Pitcher, *Tetrahedron* **1963**, *19*, 2051; S. Mihara, O. Nishimura, *J. High Resolut. Chromatogr.* **1989**, *12*, 763; O. Nishimura, S. Mihara, *J. Agric. Food. Chem.* **1990**, *38*, 1038.

[3] Y. Zhang, B. Dorjpalam, C. T. Ho, *J. Agric. Food. Chem.* **1992**, *40*, 2467.

[4] G. Gowda, T. B. H. McMurry, *J. Chem. Soc., Perkin Trans. 1* **1979**, 274.

[5] a) M. A. Gianturco, P. Friedel, *Tetrahedron* **1963**, *19*, 2039; b) T. H. Koch, D. A. Brown, *J. Org. Chem.* **1971**, *36*, 1934; c) M.-H. Rei, *J. Org. Chem.* **1978**, *43*, 2173; d) J. A. Elings, H. E. B. Lempers, R. A. Sheldon, *Eur. J. Org. Chem.* **2000**, *10*, 1905.

[6] H. Ahlbrecht, A. Von Daacke, *Synthesis* **1987**, 24; I. N. Nazarow, S. S. Bukhmutskaya, *Izvest. Akad. Nauk SSSR, Ser. Khim.* **1947**, 205 (*Chem. Abstr.* **1948**, *42*, 36483); P. Yates, P. M. Burke, *Can. J. Chem.* **1987**, *65*, 1695.

[7] K. Mori, M. Sasaki, *Tetrahedron* **1980**, *36*, 2197.

[8] R. L. Wasson, H. O. House, *Org. Synth., Coll. Vol.* **1963**, *4*, 552; G. D. Ryerson, R. L. Wasson, H. O. House, *Org. Synth., Coll. Vol.* **1963**, *4*, 957; G. D. Ryerson, R. L. Wasson, H. O. House, *Org. Synth.* **1959**, *39*, 70.

[9] L. de Buyck, R. Verhé, N. De Kimpe, D. Courtheyn, N. Schamp, *Bull. Soc. Chim. Belg.* **1981**, *90*, 837.

[10] a) T.-L. Ho, S.-H. Liu, *Synth. Commun.* **1983**, *13*, 685; b) H. Stetter, W. Slenker, *Tetrahedron Lett.* **1980**, *21*, 3479.

[11] C. Binet du Jassonneix, *Bull. Soc. Chim. Fr.* **1975**, 758; S. Casson, P. Kocieński, *J. Chem. Soc., Perkin Trans. 1* **1994**, 1187; H. J. Wild, to *Givaudan SA*, US4892966A1, 09 Jan. 1990 (*Chem. Abstr.* **1990**, *113*, 23189).

[12] Y. Naoshima, Y. Hayashi, I. Ichimoto, H. Ueda, *Agric. Biol. Chem.* **1974**, *38*, 1393; J. Arnarp, C. Enzell, K. Petersson, T. Pettersson, *Acta Chem. Scand., Ser. B* **1986**, *40*, 839.

[13] a) N. H. Andersen, S. W. Hadley, J. D. Kelly, E. R. Bacon, *J. Org. Chem.* **1985**, *50*, 4144; b) O. Wallach, *Liebigs Ann. Chem.* **1887**, *241*, 307; c) O. Wallach, *Liebigs Ann. Chem.* **1915**, *408*, 205; d) H. Sargent, *J. Org. Chem.* **1942**, *7*, 154; e) F. Kienzle, R. E. Minder, *Helv. Chim. Acta* **1976**, *59*, 439; f) C. E. Davis, B. C. Duffy, R. M. Coates, *J. Org. Chem.* **2003**, *68*, 6935.

[14] P. Weyerstahl, H. Marschall, M. Schulze, I. Schwope, *Liebigs Ann. Chem.* **1996**, 799.

[15] Y. Hayashi, M. Nishizama, T. Sakan, *Tetrahedron* **1977**, *33*, 2513.

[16] S. F. Birch, E. A. Johnson, *J. Chem. Soc.* **1951**, 1493; G. Slomp Jr., M. Inatome, C. E. Bowers, J. M. Derfer, K. W. Greenlee, C. E. Boord, *J. Org. Chem.* **1960**, *25*, 514; H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, J. F. Simeone, *J. Am. Chem. Soc.* **1970**, *92*, 2800; J. B. Stothers, C. T. Tan, *Can. J. Chem.* **1974**, *52*, 308; T. Sato, M. Watanabe, T. Watanabe, Y. Onoda, E. Murayama, *J. Org. Chem.* **1988**, *53*, 1894; H. Beschke, H. Friedrich, H. Offermanns, to *DGSS* vormals *Roessler*,

US4332940, 16. Mar. 1978 (*Chem. Abstr.* **1978**, *88*, 190604); T. Markert, T. Bruns, K. Krause, H. Juergen, J. Penninger, M. Virnig, V. Falk, to *Henkel AG & Co.*, EP282795, 15 Sep. 1988 (*Chem. Abstr.* **1989**, *110*, 38654); W. Gramlich, W. Lengsfeld, to *BASF*, US5081309, 11 Sep. 1986 (*Chem. Abstr.* **1986**, *105*, 208511); M. Spagnol, L. Gilbert, to *Rhone-Poulenc Chimie*, US5618982, 24 May 1995 (*Chem. Abstr.* **1995**, *123*, 55424).

[17] H. Fuhrer, A. K. Ganguly, K. W. Gopinath, T. R. Govindachari, K. Nagarajan, B. R. Pai, P. C. Partharathy, *Tetrahedron* **1970**, *26*, 2371.

[18] V. K. Yadav, K. K. Kapoor, *Tetrahedron* **1996**, *52*, 3659.

[19] E. S. Greenwood, P. B. Hitchcock, P. J. Parsons, *Tetrahedron* **2003**, *59*, 3307; B. Bardili, H. Marschall-Weyerstahl, P. Weyerstahl, *Liebigs Ann. Chem.* **1985**, 275.

[20] G. Righi, P. Bovicelli, A. Sperandio, *Tetrahedron* **2000**, *56*, 1733.

[21] S. Rozen, E. Golan, *Eur. J. Org. Chem.* **2003**, *10*, 1915.

[22] G. W. K. Cavill, D. H. Solomon, *Aust. J. Chem.* **1960**, *13*, 121; G. W. K. Cavill, D. L. Ford, H. Hinterberger, D. H. Solomon, *Chem. Ind. (London)* **1958**, 292.

[23] I. Reile, A. Paju, M. Eek, T. Pehk, M. Lopp, *Synlett* **2008**, 347.

[24] C. Chapuis, M. Barthe, B. L. Muller, K. H. Schulte-Elte, *Helv. Chim. Acta* **1998**, *81*, 153.

[25] G. Traverso, G. P. Pollini, G. DeGiuli, A. Barco, A. Invernizzi Gamba, *Gazz. Chim. Ital.* **1971**, *101*, 225.

[26] C. Chapuis, R. Brauchli, *Helv. Chim. Acta* **1992**, *75*, 1527; C. Chapuis, M. Barthe, J.-Y. de Saint Laumer, *Helv. Chim. Acta* **2001**, *84*, 230.

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