Synthesis of *rac-ar*-Curcumen-15-al

Peter Weyerstahl* and Volker Schlicht

Institut für Organische Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, D-10623 Berlin, Germany

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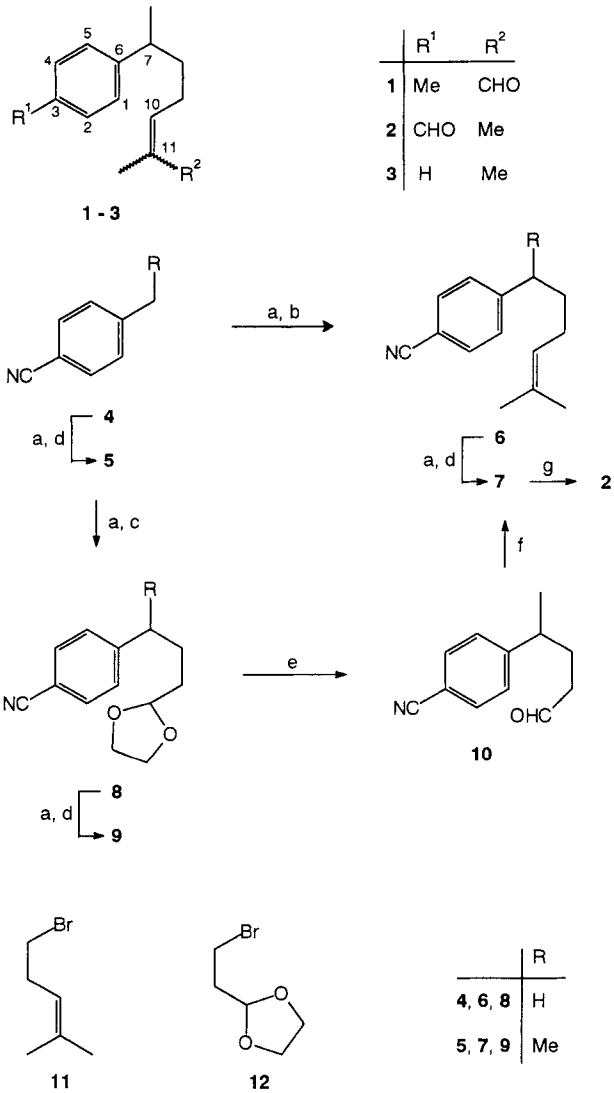
Starting from *p*-tolunitrile (**4**) via alkylation with the bromoacetal **12** (→ **8**), and with MeI (→ **9**), hydrolysis to **10**, Wittig reaction (→ **7**) and DIBAH reduction, the *rac-ar*-curcumen-15-al (**2**) was obtained. The cumin-like, citrus odor of *rac*-**2** is similar to that of the isolated (−)-**2**.

Among the aldehydes of the bisabolane group, (*E*)- and (*Z*)-nuciferal (**1**) are well investigated. Their isolation[1] and synthesis[2] were described previously. Within a research program to elucidate the typical constituents of Brazilian wood oils[3] we investigated the oil of *Lantana camara*[4]. From the medium-polar sesquiterpene fraction we obtained a mixture of three aldehydes that were difficult to separate. By comparison with literature data[1,2] we identified two of them to be the nuciferal isomers (*E*)- and (*Z*)-**1**. The purity of the third aldehyde could be increased up to 90% (with 10% of **1**) by repeated flash chromatography (FC). ^{1}H- and ^{13}C-NMR spectral data led to the structure of an *ar*-curcumen-15-al (**2**)[4]. The odor of the isolated material (90% of **2**, 10% of **1**) was evaluated as cumin-like, metallic and ozone-like. Since the sniffing GC also did not provide the odor of (−)-**2**, we decided to synthesize this aldehyde as a racemate to confirm the structure and to evaluate the odor.

Our first idea was to functionalize selectively the hydrocarbon **3**[5] in *p*-position. However, all our experiments failed. Various well-known methods for formylation catalyzed by Lewis acids gave the starting material only. The reason for this could be a chelating complexation of the Lewis acid by the additional double bond to lower the electron density of the aromatic system. Manifold variations of nitration were also unsuccessful: either tarry products or starting materials were obtained. Therefore, we decided to add the side chain to a corresponding functionalized benzene derivative. Despite variations of the reaction time and temperature, the direct alkylation of the benzylic anion of **4** or **5** with homoprenyl bromide (**11**) gave the substituted benzonitrile **6** or **7** in a yield of only 12 or 8%. Finally, the best method for the synthesis of **7** was found to be the alkylation of the anion of **4** with the bromoethyl dioxolane **12** to give **8** in 81% yield. Further methylation of **8** furnished **9** in 60% yield. This two-step sequence is superior to the direct alkylation of **5** with **12**, which provides **9** in only 15% yield. Obviously, these alkylations in general are very sensitive to steric effects. Hydrolysis of the acetal **9** to the aldehyde **10** and its Wittig reaction with the isopropylidene triphenylphosphorane occurred in very good yield to give the nitrile **7**. DIBAH reduction of **7** led to the target molecule **2**.



a: $NaNH_2$, liq. NH_3, Et_2O; b: **11**, −50 °C; c: **12**, −50 °C; d: MeI, −50 °C; e: PPTS, acetone/water, rfl.; f: $Ph_3P{=}CMe_2$, THF, r.t.; g: DIBAH, hexane, −70 °C.

The odor of pure *rac*-**2** was evaluated as cumin-like and citrus. This means the ozone-like tonality of the impure (−)-**2** must be assigned to nuciferal (**1**)[5]. However, any

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slight contamination could be responsible for the metallic sensation.

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Experimental Section

^{1}H NMR ($CDCl_3$): Bruker AM 400. – ^{13}C NMR ($CDCl_3$): Bruker AH 270 with DEPT programme. – GC-MS: Varian MAT 44 S (70 eV) combined with Varian 3700, 25 m CP Sil 5 CB column, carrier gas He. – GC: Packard 439 with a 25-m CP Sil 5 CB column, carrier gas N_2. – Flash chromatography (FC): ICN Biomedicals silica 32–63; elution light petroleum (PE, boiling range 40–60 °C) and increasing amounts of diethyl ether. – TLC: Silica gel 60 F_{254} (Merck no. 5554). – IR ($CDCl_3$): Perkin-Elmer 881. – Kugelrohr distillation (KRD): b.p. means the temp. of the air-bath. – Usual workup: The aqueous layer was extracted several times with diethyl ether; the combined organic phases were washed with dild. hydrochloric acid, $NaHCO_3$ and satd. NaCl solution, dried with $MgSO_4$, and concentrated in a rotatory evaporator. – For reactions where water had to be excluded, the vessels were flame-dried under N_2. The solvents were dried as usual and stored over molecular sieves. – All compounds are racemic. – For numbering, see scheme.

2-Methyl-6-phenylhept-2-ene (**3**): Prepared according to ref.[6]. – ^{1}H NMR: δ = 1.24 (d, *J* = 7.5 Hz, 7-Me), 1.52, 1.67 (2 s, br., 11-Me_2), 1.60 (m_c, 8-H_2), 1.85, 1.91 (ABddd, *J* = 15, 7.5, 7, 7 Hz, 9-H_2), 2.69 (qdd, *J* = 7.5, 7, 7 Hz, 7-H), 5.09 (tqq, *J* = 7.5, 1.5, 1.5 Hz, 10-H), 7.24 (tt, *J* = 7, 1.5 Hz, 3-H), 7.19 (d, br., *J* = 7.5 Hz, 1-, 5-H), 7.29 (m_c, 2-, 3-, 4-H). in agreement with the data (100 MHz) in ref.[6,7]. – ^{13}C NMR: δ = 17.6, 25.7 (2 q, 11-Me_2), 22.4 (q, 7-Me), 26.9 (t, C-9), 38.4 (t, C-8), 39.5 (d, C-7), 124.5 (d, C-10), 125.8 (d, C-3), 127.0 (d, C-1, -5), 128.3 (d, C-2, -4), 131.4 (s, C-11), 147.7 (s, C-6).

Alkylation of the p-Substituted Benzonitriles in the Benzylic Position. – General Procedure: According to ref.[8] 30 mmol of the substituted benzonitrile in 20 ml of Et_2O was added slowly to a freshly prepared $NaNH_2$ suspension in liquid NH_3 [prepared from 200 ml of NH_3, a spatula-tip of $FeCl_3$ and 0.76 g (33 mmol) of Na at −50 °C]. The mixture was stirred for 30 min at −50 °C and a solution of the corresponding halide in 50 ml of Et_2O was added rapidly. Stirring was continued (see below), then the NH_3 was allowed to evaporate. Usual workup and FC gave the products.

4-Ethylbenzonitrile (**5**): From 3.51 g (30 mmol) of *p*-tolunitrile (**4**) and 4.26 g (30 mmol) of MeI after 1 h. FC (PE/Et_2O, 98:2) yields 2.96 g (76%) of **5** as first fraction and 0.75 g of recovered **4** as second fraction. – ^{1}H NMR: δ = 1.25 (t, *J* = 7.5 Hz, Me), 2.71 (q, *J* = 7.5 Hz, CH_2), 7.29, 7.57 (2 d, br., *J* = 8 Hz, 4 Ar-H), ref.[8] 7.27, 7.52. – ^{13}C NMR: δ = 14.8 (q, Me), 28.9 (t, CH_2), 109.3 (s, C-1), 118.9 (s, CN), 128.5 (d, C-3, -5), 131.9 (d, C-2, -6), 149.6 (s, C-4). – GC MS: *m/z* (%) = 131 (24) [M^+], 116 (100), 103 (8), 89 (14), 77 (6).

4-(5-Methyl-4-hexenyl)benzonitrile (**6**): From 3.51 g (30 mmol) of **4** and 6.50 g (40 mmol) of homoprenyl bromide (**11**) after 48 h. FC (PE/Et_2O, 98:2) gives 3.07 g of recovered **4** as first fraction, 5.85 g of recovered **11** as second fraction, and 0.70 g (12%) of **6** as third fraction. – IR: $\tilde{\nu}$ = 2230 cm^{-1} (CN). – ^{1}H NMR: δ = 1.57, 1.70 (2 d, *J* = 1.5 Hz, 11-Me_2), 1.66 (tt, *J* = 7.5, 7 Hz, 8-H_2), 2.01 (dt, *J* = 7, 7 Hz, 9-H_2), 2.66 (t, *J* = 7.5 Hz, 7-H_2), 5.12 (tqq, *J* = 7, 1.5, 1.5 Hz, 10-H), 7.27, 7.56 (2 d, br., *J* = 8 Hz, 4 Ar-H). – ^{13}C NMR: δ = 17.7, 25.7 (2 q, 11-Me_2), 27.4 (t, C-9), 31.8 (t, C-8), 35.5 (t, C-7), 109.5 (s, C-3), 119.1 (s, CN), 123.7 (C-10), 129.2 (d, C-1, -5), 132.0 (d, C-2, -4), 132.2 (s, C-11), 148.4 (s, C-6). – GC MS: *m/z* (%) = 200 (3) [M^+ + 1], 199 (14) [M^+], 143 (8), 130 (18), 129 (64), 117 (15), 116 (18), 69 (53), 55 (100). – $C_{14}H_{17}N$ (199.3): calcd. C 84.37, H 8.60, N 7.03; found C 84.15, H 8.66, N 7.24.

4-(6-Methyl-5-hepten-2-yl)benzonitrile (**7**): From 2.62 g (20 mmol) of **5** and 3.19 g (24 mmol) of **11** after 60 h. FC (PE/Et_2O, 5:1) yields 2.33 g of recovered **5** as first fraction, 3.68 g of recovered **11** as second fraction and 0.36 g (9%) of **7** as third fraction. – IR: $\tilde{\nu}$ = 2230 cm^{-1} (CN). – ^{1}H NMR: δ = 1.24 (d, *J* = 7 Hz, 7-Me), 1.50, 1.66 (2 d, *J* = 1.5 Hz, 11-Me_2), 1.62 (td, *J* = 7, 7 Hz, 8-H_2), 2.01 (ABddd, *J* = 15, 7.5, 7, 7 Hz, 9-H_2), 2.76 (qdd, *J* = 7, 7, 7 Hz, 7-H), 5.05 (tqq, *J* = 7.5, 1.5, 1.5 Hz, 10-H), 7.28, 7.58 (2 d, br., *J* = 8 Hz, 4 Ar-H). – ^{13}C NMR: δ = 17.6, 25.6 (2 q, 11-Me_2), 21.8 (q, 7-Me), 25.9 (t, C-9), 37.9 (t, C-8), 39.5 (d, C-7), 109.6 (s, C-3), 119.2 (s, CN), 123.8 (d, C-10), 128.5 (d, C-1, -5), 131.6 (d, C-2, -4), 131.9 (s, C-11), 153.1 (s, C-6). – GC MS: *m/z* (%) = 213 (4) [M^+], 143 (45), 131 (17), 83 (23), 69 (29), 55 (100). – $C_{15}H_{19}N$ (213.3): calcd. C 84.46, H 8.98, N 6.57; found C 84.31, H 8.69, N 6.70.

4-[3-(1,3-Dioxolan-2-yl)propyl]benzonitrile (**8**): From 3.51 g (30 mmol) of **4** and 5.90 g (33 mmol) of 2-(2-bromoethyl)-1,3-dioxolane (**12**) after 72 h. FC (PE → 20% Et_2O) yields 5.25 g (81%) of **8**, which was used for the next step. – IR: $\tilde{\nu}$ = 2230 cm^{-1} (CN). – ^{1}H NMR: δ = 1.65–1.8 (m, 8-, 9-H_2), 2.72 (t, *J* = 7.5 Hz, 7-H_2), 3.8–4.0 (m, OCH_2CH_2O), 4.86 (t, *J* = 4.5 Hz, 10-H), 7.28, 7.56 (2 d, br., *J* = 8 Hz, 4 ArH).

4-[4-(1,3-Dioxolan-2-yl)butyl]benzonitrile (**9**): From 3.89 g (18 mmol) of **8** and 3.55 g (25 mmol) of MeI after 72 h. FC (PE/Et_2O, 5:1) gives 2.41 g (58%) of **9** as first fraction and 1.19 g of recovered **8** as second fraction. – IR: $\tilde{\nu}$ = 2230 cm^{-1} (CN). – ^{1}H NMR: δ = 1.26 (d, *J* = 7 Hz, 7-Me), 1.4–1.8 (m, 8-, 9-H_2), 2.78 (ddq, *J* = 7.5, 7, 7 Hz, 7-H), 3.8–4.0 (m, OCH_2CH_2O), 4.80 (t, *J* = 5 Hz, 10-H), 7.28, 7.57 (2 d, br., *J* = 8 Hz, 4 Ar-H).

4-(1-Methyl-4-oxobutyl)benzonitrile (**10**): A mixture of 9.24 g (40 mmol) of **9**, 4.6 g of pyridinium-*p*-toluenesulfonate (PPTS), 180 ml of acetone and 40 ml of water was refluxed for 12 h. Usual workup and FC (PE/Et_2O, 8:2→3:2) yields 5.82 g (78%) of **10**. – IR: $\tilde{\nu}$ = 2230 cm^{-1} (CN), 1725 (CHO). – ^{1}H NMR: δ = 1.28 (d, *J* = 7 Hz, 7-Me), 1.8–2.0 (m, 8-H_2), 2.31, 2.34 (ABddd, *J* = 17, 8, 7, 1.5 Hz, 9-H_2), 2.79 (dqd, *J* = 8, 7, 6 Hz, 7-H), 7.28, 7.60 (2 d, br., *J* = 8 Hz, 4 Ar-H), 9.71 (t, *J* = 1.5 Hz, CHO). – ^{13}C NMR: δ = 21.6 (q, 7-Me), 32.4 (t, C-8), 39.4 (d, C-7), 41.8 (t, C-9), 110.1 (s, C-3), 118.8 (s, CN), 127.8 (d, C-1, -5), 132.4 (d, C-2, -4), 151.8 (s, C-6), 201.6 (d, CHO). – GC MS: *m/z* (%) = 187 (2) [M^+], 144 (39), 143 (100), 130 (43), 116 (28), 103 (39), 77 (20). – $C_{12}H_{13}NO$ (187.2): calcd. C 76.98, H 7.00, N 7.48; found C 77.10, H 7.01, N 7.66.

Wittig Reaction of **10** *to* **7**: To an ylene solution prepared from 7.78 g (18 mmol) of isopropyl triphenylphosphonium iodide in 40 ml of dry THF and 11.9 ml (19 mmol) of *n*BuLi (1.6 M in hexane) after stirring for 1 h at room temp., a solution of 2.06 g (11 mmol) of **10** in 40 ml of dry THF was added dropwise. The mixture was stirred for 15 h. After usual workup 20 ml of PE was added and the solid Ph_3PO was removed. Thereafter FC (PE/Et_2O, 99:1) gives 2.09 g (89%) of **7** (GC: 98%). – Spectral data: See above.

4-(6-Methyl-5-hepten-2-yl)benzaldehyde (*rac-ar*-curcumen-15-al, **2**): 10 ml (10 mmol) of DIBAH (1 M in *n*-hexane) was added dropwise at −70 °C to a solution of 0.85 g (4.0 mmol) of **7** in 10 ml of dry *n*-hexane. Stirring was continued at −70 °C for 30 min, and then the mixture was allowed to warm to room temp. over 15 h.

Then 15 ml of a satd. NH_4Cl solution was added and the mixture stirred for 20 min. Finally 10 ml of 10% H_2SO_4 was added and the solution stirred for 30 min. Usual workup and FC (PE) gives 0.70 g (81%) of **2** (GC: 99%), b.p. 135°C/0.05 mbar. – IR: $\tilde{\nu}$ = 1730 cm^{-1} (CHO). – ^1H NMR: δ = 1.26 (d, *J* = 7 Hz, 7-Me), 1.50, 1.67 (2 d, *J* = 1.5 Hz, 11-Me_2), 1.64 (m_c, 8-H_2), 1.84, 1.90 (ABddd, *J* = 16, 7.5, 7, 7 Hz, 9-H_2), 2.79 (dqd, *J* = 7.5, 7, 7 Hz, 7-H), 5.07 (tqq, *J* = 7, 1.5, 1.5 Hz, 10-H), 7.34, 7.81 (2 d, br., *J* = 8 Hz, 4 Ar-H), 9.97 (s, CHO). – ^{13}C NMR: δ = 17.5, 25.5 (2 q, 11-Me_2), 21.8 (q, 7-Me), 25.8 (t, C-9), 37.9 (t, C-8), 39.6 (d, C-7), 123.9 (d, C-10), 127.6 (d, C-1, -5), 129.9 (d, C-2, -4), 131.6 (s, C-11), 134.4 (s, C-3), 155.1 (s, C-6), 192.0 (d, CHO). – GC MS: *m/z* (%) = 216 (22) [M^+], 187 (3), 146 (100), 134 (41), 133 (35), 105 (54), 91 (38), 83 (32), 69 (42), 55 (85). – $C_{15}H_{20}O$: calcd. 216.1514; found 216.1514 (HR MS). – All spectroscopic data are identical with those of (–)-*ar*-curcumen-15-al (**2**), $[\alpha]_D^{20}$ = –76.9 (*c* = 1.3, $CHCl_3$; GC: 90%), isolated from the essential oil of *Lantana camara*[4].

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