Notiz / Note

Improved Procedure for the Reductive Intermolecular Cyclodehalogenation of 2,6-Dibromocyclohexanones to Furan and Fulvenes

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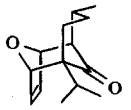
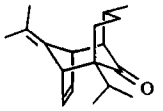
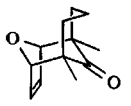
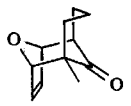
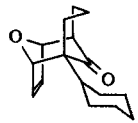
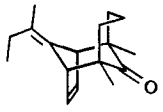
The preparation of tricyclo[4.3.1.1^{2,5}]undec-3-en-10-ones has been scaled up. By using the improved procedure a number of tricyclic compounds have been obtained for the first time.

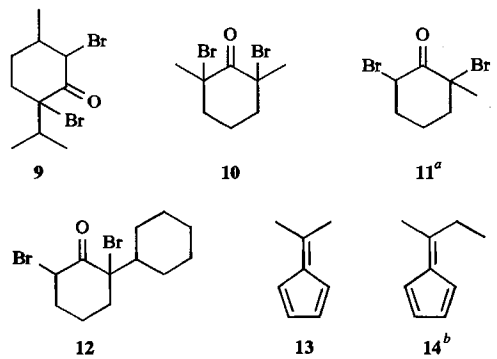
Alkylated 2,6-dibromocyclohexanones and furan enter into reductive intermolecular cyclodehalogenation, giving 11-oxatricyclo[4.3.1.1^{2,5}]undec-3-en-10-ones[1]. For practical applications it is often essential to scale up the reaction. We now show how this can be done and also report the preparation of some previously inaccessible tricyclic compounds. Using the old method of adding the dibromoketone to a suspension of sodium iodide in acetonitrile/furan, and increasing the scale from 5 to 150 mmol, yields dropped from 35 to 5%. As a result, the absolute amount of isolated cycloadduct did, unfortunately, not increase, when the reactions were carried out on a larger scale (Figure 1). However, we found it advantageous to predissolve the dibromoketone **9** in furan or vice versa, and to use as little acetonitrile as possible: tricyclic compound **1** (cymenth) was now obtained in 5 g per batch. Interestingly, ultrasonication stopped the reaction under the new conditions (TLC control). We speculate that the mixture of starting materials behaves as a *macroliquid* with high segregation, and, at the same time, a high *local concentration* of reactants is maintained throughout the reaction.

The new procedure is also advantageous for preparing the tricyclic compound **5**, which previously was obtained only by the triethyl borate/zinc method[1]. Furthermore, the crowded cycloadduct **7** has been prepared for the first time, and the new highly crowded fulvene adducts **2**, **4**, **6**, and **8** have been synthesized in respectable yields. Tricyclic alcohol **15** (Scheme 2) showed slight patchouly odor. The related tricyclic alcohol **22** was prepared advantageously by the reduction of cymenth (**1**) with DIBAH. Since the hydroxylic proton of **22** points into the cavity of the molecule,

Scheme 1. Improved procedure for the NaI/Cu-promoted intermolecular cyclodehalogenation of dibromoketones to furan and fulvenes

Cycloadduct	Cycloadduct
 **1**	 **2**
35%, 5 mmol, 0.385 g[a] 36%, 70 mmol, 5.53 g, (GC 90%)	17%, 10 mmol, 0.44 g colorless liquid, slow crystallization at -18°C
 **3**	 **4**
22%, 5 mmol, 0.21 g[a] 16%, 30 mmol, 0.92 g	23%, 13 mmol, 0.68 g yellowish crystals
 **5**	 **6**[b]
15%, 5 mmol, 0.13 g, $B(OEt)_3$/Zn method[a] 18%, 30 mmol, 1.05 g	25%, 20 mmol, 1.34 g regioisomeric mixture
 **7**	 **8**[b]
(Not accessible according ref. 1) 25%, 46 mmol, 2.52 g	14%, 25 mmol, 0.89 g

[a] Ref.[1]. — [b] Experimental data in ref.[3].



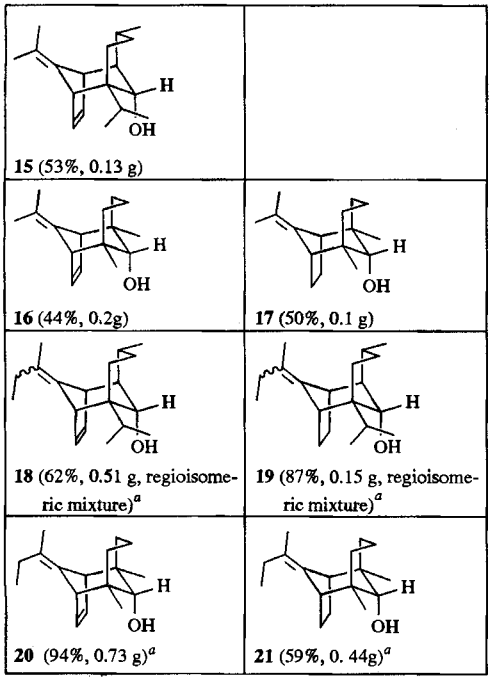
9 **10** **11**[a] **12** **13** **14**[b]

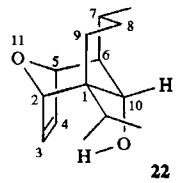
[a] Ref.[1]. — [b] Ref.[3].

  0009–2940/91/0707–1673 $ 3.50+.25/0

this alcohol is of interest as chiral proton donor[2]. Starting from (5*R*)-menthone and from (5*S*)-menthone, either **22** or its enantiomer are now readily available.

Scheme 2. Tricyclic alcohols from reduction of ketones





22

[a] Experimental data in ref.[3].

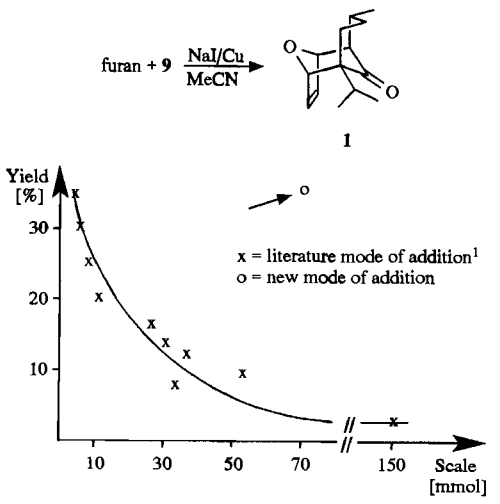


Figure 1. Preparation of **1**

We thank *Ulrike Eggert* for experimental assistance, the *Deutsche Forschungsgemeinschaft* and the *Fonds der Chemischen Industrie* for support of this work.

Experimental

General: Column chromatography (silica gel, 0.02–0.063 mm, Merck) was carried out under weak positive pressure. – TLC: Precoated plates, Macherey-Nagel, Merck. – Gas chromatography: FID, N_2, Varian A 1400. Glass capillary column (25 m, type OV 1 CB) and SE 54 CB (25 m fused silica, widebore). – Melting points: Büchi apparatus. – Optical rotations: Perkin-Elmer polarimeter 241. – IR: Electrophotometer 580 and FT spectrometer 1710, Perkin-Elmer. – ^{1}H NMR: WP 80, WH 90, WP 200 SY and AM 300, Bruker. – ^{13}C NMR: WP 200 SY, AM 300, Bruker. – MS: Spectrometer MAT 312, Finnigan. – Elementary analyses: Microanalytical laboratory of the Department of Organic Chemistry. – E: ether; EE: ethyl acetate; PE: petroleum ether; r.t.: room temperature.

Improved NaI/Cu Procedure: A three-necked flask equipped with reflux condenser, dropping funnel with septum, and glass stopper was charged, per mmol of dibromoketone, with Cu powder (0.32 g, 5 mmol) and NaI (1.50 g, 10 mmol). The apparatus was heated externally (blow-dryer) while being flushed internally with N_2. Commercial acetonitrile (Baker grade, 0.05% water) (3 ml per mmol of dibromoketone) was added by syringe to the magnetically stirred mixture. The dibromoketone (1 mmol) was dissolved in furan (0.48 g, 7 mmol) (for solid 4-π electron components and liquid dibromoketones, the procedure was modified accordingly); fulvenes were used equimolar (1 mmol), because an excess was difficult to separate on workup. If necessary, as little acetonitrile as possible was added as a cosolvent. The solution of the dibromoketone/cyclic diene (MeCN) was slowly added dropwise to the mixture, and the reaction was monitored by TLC (furan adducts: lilac spot with vanillin; fulvene adducts: blue spot with cerium ammonium nitrate). After complete addition, the reaction mixture was stirred for ca. 12 h and suction-filtered through a sintered glass funnel. If the product is not too volatile, aqueous workup may be simplified further by evaporating the acetonitrile beforehand. Filter cake and residue in the flask were washed with CH_2Cl_2. The organic phase was washed with concd. aq. NH_3 until the aqueous phase remained colorless. The NH_3 phase was reextracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), freed from solvent, and chromatographed.

Further Representative Cycloadditions. – 1-Isopropyl-11-isopropylidene-7-methyltricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (**2**): The dibromoketone **9** (3.12 g, 10 mmol) and the fulvene **13** (4.75 g, 45 mmol) were allowed to react for 1 d according to the general procedure, giving after chromatography [PE/EE (10:1)] **2**; 0.44 g (17%), colorless liquid. – IR ($CHCl_3$): $\tilde{\nu}$ = 2965 cm^{-1}, 1705, 1455, 1375. – ^{1}H NMR ($CDCl_3$): δ = 6.13 (dd, *J* = 1 Hz, *J* = 1 Hz, 2 H, 3-H, 4-H), 3.39 (m, 2 H, 2-H, 5-H), 2.13 (dd, *J* = 2 Hz, *J* = 5 Hz, 1 H, 6-H), 1.93 (m, 6 H), 1.78, 1.76 [s, 6 H, $=C(CH_3)_2$], 0.97, 0.96 [d, *J* = 7 Hz, 6 H, $CH(CH_3)_2$], 0.91 (d, *J* = 7 Hz, 3 H, $CHCH_3$). – ^{13}C NMR ($CDCl_3$): δ = 216.07 (s, C-10), 140.68, 117.62 [s, C-11, $=C(CH_3)_2$], 137.08, 136.44 (d, C-3, C-4), 59.30 (d, C-6), 57.94 (s, C-1), 48.87, 47.54 (d, C-2, C-5), 35.67, 30.57 [d, C-7, $CH(CH_3)_2$], 30.64, 29.80 (t, C-8, C-9), 23.79, 19.92 [q, $=C(CH_3)_2$], 16.29, 16.12, 15.25 (q, 3 CH_3). – MS (70 eV, r.t.): *m/z* (%) = 258 (56) [M^+], 243 (60), 91 (100).

$C_{18}H_{26}O$ Calcd. 258.1984 Found 258.1985 (MS)

11-Isopropylidene-1,6-dimethyltricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (**4**): The dibromoketone **10** (3.77 g, 13 mmol) and the fulvene **13** (1.38 g, 13 mmol) were allowed to react for 2 h according to the general procedure, giving after chromatography [PE/E (2:1)] **4**; 0.68 g (23%), yellowish, waxy crystals. – IR ($CHCl_3$): $\tilde{\nu}$ = 2920

cm $^{-1}$, 1700, 1450, 1370. – ^{1}H NMR ($CDCl_3$): δ = 6.26 (dd, *J* = 1 Hz, *J* = 1 Hz, 2 H, 3-H, 4-H), 3.15 (dd, *J* = 1 Hz, *J* = 1 Hz, 2 H, 2-H, 5-H), 2.0 (m, 2 H, 8-H), 1.75 [s, 6 H, $=C(CH_3)_2$], 1.57 (m, 2 H), 1.32 (m, 2 H), 0.99 (s, 6 H, 2 CH_3). – ^{13}C NMR ($CDCl_3$): δ = 217.44 (s, C-10), 140.93, 115.94 [s, $=C(CH_3)_2$, C-11], 137.97 (d, C-3, C-4), 52.83 (d, C-2, C-5), 51.99 (s, C-1, C-6), 38.76 (t, C-7, C-9), 22.80 [q, $=C(CH_3)_2$], 19.63 (q, CH_3), 18.45 (t, C-8). – MS (70 eV, r.t.): *m/z* (%) = 230 (21) [M^+], 215 (15), 187 (44), 125 (86), 91 (100).

$C_{16}H_{22}O$ Calcd. 230.1671 Found 230.1671 (MS)

1-Cyclohexyl-11-oxatricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (**7**): The dibromoketone **12** (15 g, 46 mmol) and furan (21.8 g, 320 mmol) were allowed to react according to the general procedure, giving after chromatography [PE/E, (2:1)] 7; 2.52 g (25%), crystals, mp 95°C. – IR (KBr): $\tilde{\nu}$ = 2930 cm^{-1}, 1718, 1444. – ^{1}H NMR ($CDCl_3$): δ = 6.33 (dd, *J* = 2 Hz, *J* = 6 Hz, 2 H, 3-H, 4-H), 4.84 (d, *J* = 2 Hz, 1 H, 2-H), 4.81 (dd, *J* = 2 Hz, *J* = 2 Hz, 1 H, 5-H), 2.4–1.0 (m, 17 H), 0.92 (br.t, *J* = 11 Hz, 1 H, cyclohexyl). – ^{13}C NMR ($CDCl_3$): δ = 214.86 (s, C-10), 135.06, 134.96 (d, C-3, C-4), 84.54, 83.73 (d, C-2, C-5), 60.21 (s, C-1), 52.15 (d, C-6), 39.80 (d, C-cyclohexyl), 33.79, 30.49 (t, C-7, C-9), 27.67, 27.67, 27.17, 26.91, 26.63 (t, C-cyclohexyl), 21.64 (t, C-8). – MS (70 eV, 60°C): *m/z* (%) = 246 (64) [M^+], 178 (46), 163 (100).

$C_{16}H_{22}O_2$ (246.2) Calcd. C 78.00 H 9.00
Found C 77.57 H 8.91

Calcd. 246.1620 Found 246.1620 (MS)

1-Isopropyl-11-isopropylidene-7-methyltricyclo[4.3.1.1^{2,5}]undec-3-en-10-ol (**15**): The cycloadduct **2** (0.28 g, 1.09 mmol) was reduced with $LiAlH_4$ (41 mg, 1.09 mmol), giving after chromatography [PE/E (2:1 → 1:1)] **15**; 0.13 g (53%), crystals, mp 58°C. – IR ($CHCl_3$): $\tilde{\nu}$ = 3637 cm^{-1}, 2958, 1455, 1374, 1069. – ^{1}H NMR ($CDCl_3$): δ = 6.49 (dd, *J* = 1 Hz, *J* = 1 Hz, 2 H, 3-H, 4-H), 3.73 (br.d, *J* = 12 Hz, 1 H- 10-H), 3.25 (m, 2 H, 2-H, 5-H), 2.8 (d, *J* = 12 Hz, 1 H, OH), 1.95 [dq, *J* = 7 Hz, *J* = 20 Hz, 1 H, $CH(CH_3)_2$], 1.68, 1.64 [s, 6 H, $=C(CH_3)_2$], 1.51 (dd, *J* = 4 Hz, *J* = 4 Hz, 1 H, 6-H), 1.30 (t, *J* = 8 Hz, 2 H, 9-H), 0.99, 0.95, 0.92 (d, *J* = 7 Hz, 9 H, 3 CH_3). – ^{13}C NMR ($CDCl_3$): δ = 142.96, 113.75 [C-11, $=C(CH_3)_2$], 140.40, 139.27 (C-3, C-4), 71.95 (C-10), 48.34, 47.79, 46.78 (C-2, C-5, C-6), 45.72 (C-1), 32.66, 31.76 [C-7, $CH(CH_3)_2$], 27.14, 25.94, (C-8, C-9), 23.60, 19.64 [$=C(CH_3)_2$], 19.48, 17.59, 16.26 (3 CH_3). – MS (70 eV, r.t.): *m/z* (%) = 260 (9) [M^+], 106 (100).

$C_{18}H_{28}O$ Calcd. 260.2140 Found 260.2132 (MS)

Evaluation of odor: relatively weak, first sweet, fresh, camphor, then earthy, potatoe-like, woody, slight patchouly.

11-Isopropylidene-1,6-dimethyltricyclo[4.3.1.1^{2,5}]undec-3-en-10-ol (**16**): The cycloadduct **4** (0.45 g, 1.89 mmol) was reduced with $LiAlH_4$ (72 mg, 1.89 mmol), giving after chromatography [PE/E (2:1)] **16**; 0.20 g (45%), crystals, mp 55°C. – IR (KBr): $\tilde{\nu}$ = 3570 cm^{-1}, 2932, 1451, 1371, 1076, 1012. – ^{1}H NMR ($CDCl_3$): δ = 6.54, 6.52 (d, *J* = 2 Hz, 2 H, 3-H, 4-H), 3.10 (br.s, 1 H, 10-H), 2.98, 2.96 (d, *J* = 2 Hz, 2 H, 2-H, 5-H), 2.32 (br.s, 1 H, OH), 1.87 (m, 2 H, 8-H), 1.61 [s, 6 H, $=C(CH_3)_2$], 1.39 (m, 4 H, 7-H, 9-H), 1.02 (s, 6 H, 2 CH_3). – ^{13}C NMR ($CDCl_3$): δ = 143.18, 112.34 [C-11, $=C(CH_3)_2$], 140.21 (C-3, C-4), 84.41 (C-10), 51.37 (C-2, C-5), 41.61 (C-1, C-6), 38.50 (C-7, C-9), 26.19 [$=C(CH_3)_2$], 19.24 (CH_3), 18.61 (C-8). – MS (70 eV, r.t.): *m/z* (%) = 232 (11) [M^+], 217 (9), 109 (100).

$C_{16}H_{24}O$ (232) Calcd. C 82.71 H 10.41
Found C 81.07 H 10.22

11-Isopropylidene-2,6-dimethyltricyclo[4.3.1.1^{2,5}]undecan-10-ol (**17**): The alcohol **16** (0.20 g, 0.86 mmol) was hydrogenated (10% Pd/C, 92 mg), giving after chromatography [PE/E (2:1)] **17**; 0.10 g (50%), crystals, mp 54°C. – IR ($CHCl_3$): $\tilde{\nu}$ = 3638 cm^{-1}, 3466, 1446, 1372, 1069. – ^{1}H NMR ($CDCl_3$): δ = 3.14 (s, 1 H, 10-H), 2.4 (ddd, *J* = 1 Hz, *J* = 1 Hz, *J* = 4 Hz, 2 H, 2-H, 5-H), 2.04 (d, *J* = 8 Hz, 2 H), 1.89 (m, 2 H), 1.64 [s, 6 H, $=C(CH_3)_2$], 1.5–1.2 (m, 7 H), 0.97 (s, 6 H, 2 CH_3). – ^{13}C NMR ($CDCl_3$): δ = 141.50, 114.98 [C-11, $=C(CH_3)_2$], 83.60 (C-10), 46.18 (C-2, C-5), 41.13 (C-1, C-6), 40.04 (C-7, C-9), 24.64 [$=C(CH_3)_2$], 24.20 (C-3, C-4), 20.06 (CH_3), 19.07 (C-8). – MS (70 eV, r.t.): *m/z* (%) = 234 (12) [M^+], 220 (5), 109 (100).

1-Isopropyl-7-methyl-11-oxatricyclo[4.3.1.1^{2,5}]undec-3-en-10-ol (**22**): The tricyclic compound **1** (220 mg, 1 mmol) was reduced with DIBAH (1.2 M solution in toluene, 1 ml, 1.2 mmol), giving the alcohol **22**; 150 mg (68%). For spectroscopic data see ref.[1].

CAS Registry Numbers

1: 133813-94-2 / **2**: 133752-63-3 / **3**: 129363-33-3 / **4**: 133752-64-4 / **5**: 129363-26-4 / **6**: 133752-65-5 / **7**: 133752-66-6 / **8**: 133752-67-7 / **9**: 18427-47-9 / **10**: 56829-67-5 / **11**: 41597-25-5 / **12**: 88974-55-4 / **13**: 2175-91-9 / **14**: 3141-02-4 / **15**: 133752-68-8 / **16**: 133752-69-9 / **17**: 133752-70-2 / **18**: 133752-71-3 / **19**: 133752-72-4 / **20**: 133752-73-5 / **21**: 133752-74-6 / **22**: 133814-62-7 / furan: 110-00-9

[1] H. M. R. Hoffmann, D. Wagner, R. Wartchow, *Chem. Ber.* **123** (1990) 2131, 2460; see also: M. R. Ashcroft, H. M. R. Hoffmann, *Org. Synth.* Coll. Vol. **6** (1988) 512.
[2] S. Hünig, personal communication and work in progress.
[3] T. Schottelius, *PhD Thesis*, University of Hannover, 1991.

[89/91]