Halogen/Metal vs. Hydrogen/Metal Exchange: General or Specific Site Selectivity as Exemplified in the Camphene Series

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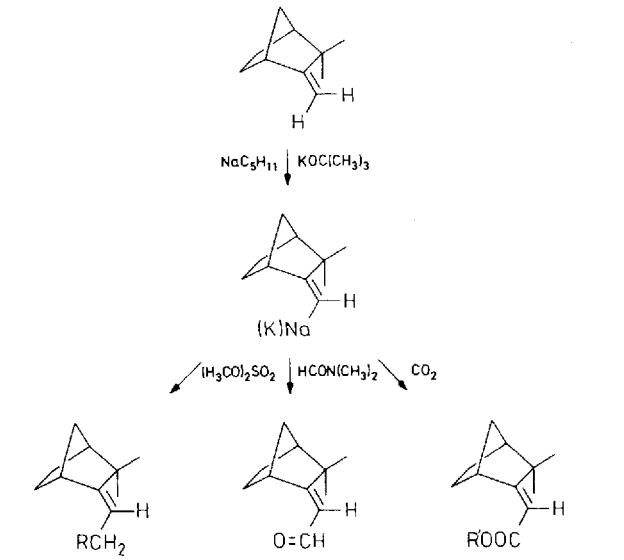
(Z)-(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)methyllithium can be readily generated by treatment of (Z)-3-bromomethylene-2,2-dimethylbicyclo[2.2.1]heptane with *tert*-butyllithium. At −75 °C, the organometallic intermediate is configurationally stable and reacts with a variety of electrophiles under stereochemical retention.

There are two prominent options for the introduction of metal into organic molecules. The *halogen*/lithium exchange[1] is regioselectively unbiased: the metal emerges at exactly the same position where the bromine or iodine has been located before its replacement. The situation is quite different when a *hydrogen*/metal exchange ("metalation") is performed. Although typical organic molecules carry hydrogen atoms at almost all positions, only a few of them, if any, are sufficiently mobile to be abstracted as protons. Consequently, the latter process lacks universality and can be executed only at privileged sites.

We wish to illustrate these principles taking camphene as the model. This monoterpene selectively exchanges the outward oriented olefinic hydrogen against alkali metal (sodium or potassium) when exposed to the action of pentylsodium in the presence of potassium *tert*-butoxide in hexane (1 h of stirring at 25 °C)[2]. The products obtained upon electrophilic trapping have exclusively the *E* configuration. Thus, with dimethyl sulfate, prenyl (3-methylbut-2-enyl) bromide, dimethylformamide and carbon dioxide as the electrophiles the following products were obtained: (*E*)-3-ethylidene-2,2-dimethylbicyclo[2.2.1]heptane (*E*-**1a**, 78%), (*E*)-isosantalene (*E*-**1b**, 61%), which is a putative[3] though elusive natural product, (*E*)-(3,3-dimethylbicyclo[2.2.1]-hept-2-ylidene)acetaldehyde (*E*-**2**, 71%) and (*E*)-(3,3-dimethylbicyclo[2.2.1]-hept-2-ylidene)acetic acid (*E*-**3**, 74%). The latter acid was converted into the methyl ester (*E*-**4a**, 93%) and isobutyl ester (*E*-**4b**, 82%).

Because of their unique geometry, the corresponding *Z* isomers are particularly intriguing targets. Obviously, a different approach had to be devised for making them accessible, the method of choice being this time a halogen/metal exchange. When (*Z*)-3-bromomethylene-2,2-dimethylbicyclo[2.2.1]heptane (*Z*-**5**) was consecutively treated with *tert*-butyllithium and the appropriate electrophile, the pure isomers *Z*-**1a** (79%), *Z*-**1b** (35%), *Z*-**2** (79%) and *Z*-**3** (63%) were indeed readily obtained. Esterification of the acid *Z*-**3** gave the esters *Z*-**4a** (92%) and *Z*-**4b** (53%). Reduction of the aldehyde with sodium borohydride led to (*Z*)-(3,3-dimethylbicyclo-[2.2.1]hept-2-ylidene)ethanol (*Z*-**6**, 64%).



***E*-1a:** R = H
***E*-1b:** R = $(H_3C)_2C{=}CH$

***E*-2**

***E*-3:** OR' = HO
***E*-4a:** OR' = H_3CO
***E*-4b:** OR' = $(H_3C)_2CHCH_2O$

The preparation of the starting material *Z*-**5** required a multi-step sequence. Addition of mercuric trifluoroacetate to camphene afforded 3-bis(trifluoroacetoxymercurio)-methylene-2,2-dimethylbicyclo[2.2.1]heptane (**7**, 81%) which reacted with elemental bromine to give 3-dibromomethylene-2,2-dimethylbicyclo[2.2.1]heptane[3] (**8**, 80%). Reduction of the latter compound with tributyltin hydride produced an inseparable 3:2 mixture of (*Z*)- and (*E*)-3-bromomethylene-2,2-dimethylbicyclo[2.2.1]heptane (**5**, 67%). Fortunately, the two stereoisomers exhibit considerable differences in their reactivity; only the (*E*) component was attacked by lithium dimethylcuprate. The resulting hydrocarbon *E*-**1** was readily removed by distillation from the unconsumed bromide *Z*-**5** and 3,3'-(ethanediylid-

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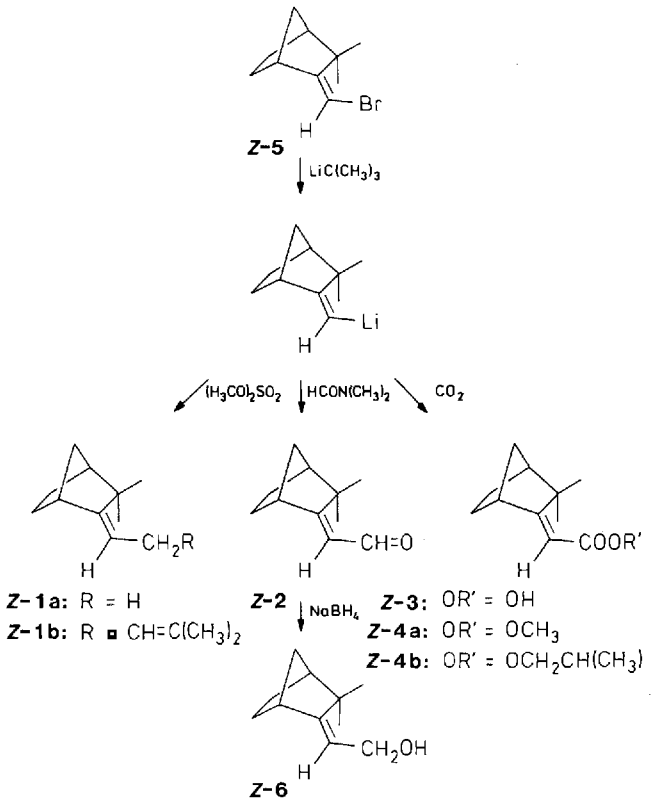

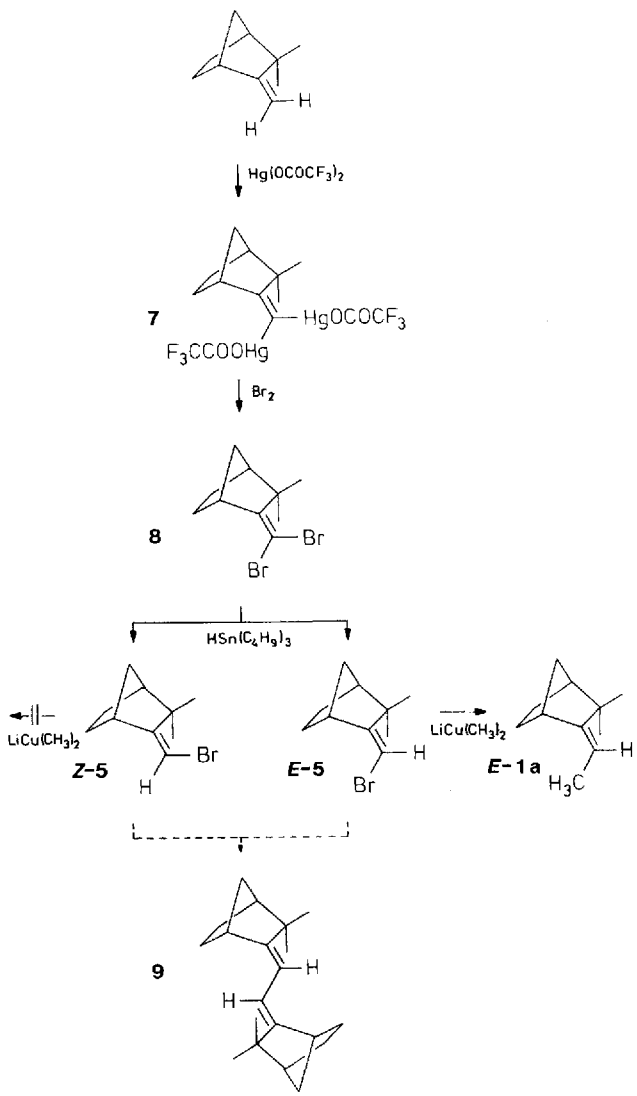

ene)bis(2,2-dimethylbicyclo[2.2.1]heptane) (**9**)[4], the latter by-product being formed in small amounts (3%) as a 2:1 mixture of *meso*- and *dl*-stereoisomers both having (*E*,*E*) configuration.

Bromides **5** were obtained with practically the same (*Z*/*E*) ratio when tris(trimethylsilyl)silane[5] rather than tributyltin hydride was employed to accomplish partial dehalogenation. This coincidence may be taken as evidence against a rapid equilibration occurring between the radicals *Z*-**10** and *E*-**10**. When tributyltin *deuteride* was used for the reduction of dibromide **8**, the entire isotope label was found to be incorporated into the olefinic positions of the stereoisomeric bromides (*Z*-**5**-d_1 and *E*-**5**-d_1) and no detectable trace of it in a methyl group. This rules out an intramolecular hydrogen transfer converting the radical intermediate *E*-**10** into the congener **11**.

Unlike unstrained 1-alkenyllithium species[6], (*Z*)-(3,3-dimethylbicyclo[2.2.1]hept-2-ylidene)methyllithium proved to be configurationally labile at temperatures around or above −50 °C, slowly switching into the (*E*) configuration. The equilibrium must be extremely in favor of the latter since the (*E*) isomer of the organometallic intermediate did not show any "structural leakage". This isomer was generated by halogen/metal exchange from (*E*)-3-iodomethylene-2,2-dimethylbicyclo[2.2.1]heptane (**12**)[2] and kept 2 h at 0 °C; it was then intercepted with carbon dioxide and the acid isolated. Subsequent treatment of the acid *E*-**3** with diazomethane yielded the ester *E*-**4a**.

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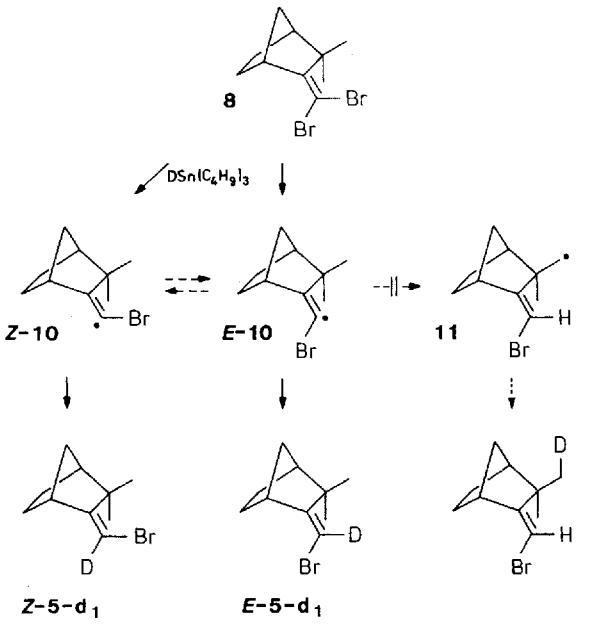

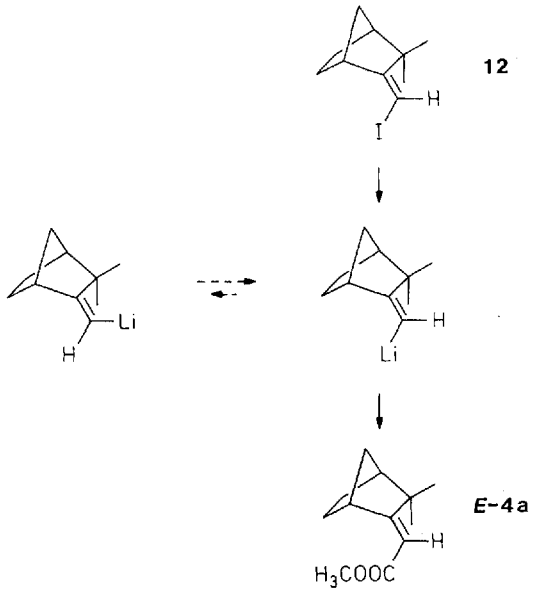

20-41'887-94) and a special program encouraging the collaboration with East European scientists (grant 7-UNP J-038635).

Experimental Section

General: For standard experimental practice and abbreviations see related articles[7] from this laboratory. – ^{1}H-NMR spectra were recorded of samples dissolved in deuterochloroform at 400 MHz or, if marked with an asterisk, at 600 MHz. – Only capillary columns were used for gas chromatography. The stationary phases employed were a silicone rubber blend (DB-1701), a polyalcohol (DB-Wax) and a polyester (DB-FFAP). – The mass peaks specified for compound **7** refer to the most abundant ^{202}Hg isotopomers, those of the dibrominated products **8** to the ^{81}Br isotopomers. – Elementary analysis were made by the institute of I. Beetz, D-96301 Kronach.

We have avoided specifying the rotatory powers for any of the products described below since none of them were enantiomerically pure. According to polarimetry and gas chromatography on a chiral phase (30 m, cyclodextrine "cyclodex", 50°C), the most frequently employed levorotatory (1*S*) stereoisomer (Fluka nr. 21290; chemical purity 85% or, after one recrystallization from ethanol, 95%) had an e.e. value of only 11%, the dextrorotatory (1*R*) antipode (Aldrich, nr. 37'659-0; chemical purity 94%) of 48%.

1. *Preparation of Starting Materials*

(E)-3-Iodomethylene-2,2-dimethylbicyclo[2.2.1]heptane[2] (**12**): A slurry of pentylsodium[8] (65 mmol), potassium *tert*-butoxide (11.2 g, 100 mmol) in pentane (0.15 l), wherein camphene (8.9 g, 65 mol) had been dissolved, was vigorously stirred for 2 h using a high-speed device[9] (5000 rpm). At −75°C, a solution of lithium bromide in tetrahydrofuran (0.10 l) and, after 5 min of stirring, iodine (12.7 g, 50 mmol) was added. At 0°C, it was poured onto ice (150 g) and the two phases were separated. The aqueous one was extracted with diethyl ether (2 × 40 ml), the combined organic layers were washed with 0.5 M aqueous solution (30 ml) of sodium thiosulfate, dried and concentrated. The resulting yellow oil was purified by distillation affording a colorless liquid, which was composed of the (*Z*) and (*E*) isomer in the ratio of 1:99 according to gas chromatography (30 m, DB-FFAP, 100°C; 30 m, DB-1701, 100°C); m.p. −5 to −4°C; b.p. 79−81/2 Torr; n_D^{20} = 1.5328; 10.9 g (64%). – ^{1}H NMR: δ = 5.50 (1H, s), 3.01 (1H, d, *J* = 3.5), 2.18 (1H, dq, *J* = 4.0, 1.5), 1.76 (1H, dquint, *J* = 10.0, 2.0), 1.7 (2H, m), 1.5 (1H, m), 1.3 (1H, m), 1.25 (1H, dt, *J* = 10.3, 1.5), 1.06 (3H, s), 1.05 (3H, s).

(Z)-3-Bromomethylene-2,2-dimethylbicyclo[2.2.1]heptane (*Z*-**5**) *Accompanied by (E)-Ethylidene-2,2-dimethylbicyclo[2.2.1]heptane* (*E*-**1a**) *and 3,3'-(Ethanediylidene)bis(2,2-dimethylbicyclo[2.2.1]-heptane)* (**9**): At −75°C, copper(I) iodide (8.2 g, 43 mmol) was added to 1.6 M solution of methyllithium (83 mmol) in diethyl ether (54 ml). After 5 min. of vigorous stirring, the temperature was raised to 0°C and a (*Z*/*E*) mixture (60:40) of "ω-bromocamphene" **5** (see below; 8.8 ml, 11.4 g, 53 mmol) was added. The dark-brown mixture was allowed to stand 36 h before being poured onto freshly crushed dry ice. The mixture was filtered and concentrated. Distillation of the remaining oil gave two colorless fractions (2.2 and 5.9 g). The residue, when triturated with acetone, solidified to form a white cake (0.5 g) which was further purified by sublimation. – (*Z*)-**5**: isomeric purity 99% (by gas chromatography; conditions as above); m.p. −37 to −35°C; b.p. 48−50°C/0.1 Torr; n_D^{20} = 1.5212; 5.8 g (51%). – ^{1}H NMR: δ = 5.83 (1H, s), 2.74 (1H, dd, *J* = 4.5, 1.5), 1.93 (1H, *J* = 4.0), 1.8 (1H, m), 1.73 (1H, quint, *J* = 10.3, 2.1), 1.64 (1H, tdd, *J* = 12.2, 5.0, 4.5), 1.40 (1H, tdd, *J* = 12.0, 5.0, 4.0), 1.31 (3H, s), 1.3 (1H, m), 1.26 (3H, s), 1.22 (1H, dt, *J* = 9.8, 1.5). – MS; *m/z* (%): 216 (5%, M^+), 135 (39%), 107 (100%). – $C_{10}H_{15}Br$ (215.13): calcd. C 55.83, H 7.03; found C 55.96, H 7.02. – (*E*)-**1**: isomeric purity 96%; b.p. 30−31°C/0.2 Torr; n_D^{20} = 1.4801; 2.2 g (28%). – ^{1}H NMR: δ = 4.95 (1H, q, *J* = 6.8), 2.94 (1H, dm, *J* = 3.5), 1.88 (1H, dm, *J* = 3.0), 1.65 (1H, dm, *J* = 10.2), 1.6 (2H, m), 1.60 (3H, d, *J* = 6.8), 1.4 (1H, m), 1.20 (1H, dm, *J* = 10.2), 1.2 (1H, m), 1.21 (3H, s), 0.99 (3H, s). – **9**[4]: a 3:2 mixture of diastereoisomers (gas chromatography: 30 m, DB-FFAP, 170°C); m.p. 173−175°C; 0.4 g (6%). – ^{1}H NMR: δ = 5.73 (0.8H, s), 5.71 (1.2H, s), 3.10 (0.8H, d, *J* = 3.5), 3.08 (1.2H, d, *J* = 4.0), 1.89 (2.0H, dm, *J* = 3.0), 1.7 (6.0H, m), 1.4 (2.0H, m), 1.22 (2.0H, d, *J* = 9.7), 1.2 (2.0H, m), 1.06 (3.6H, s), 1.05 (2.4H, s), 1.03 (3.6H, s), 1.03 (2.4H, s). – MS; *m/z* (%): 270 (100%, M^+). – $C_{20}H_{30}$ (270.46): calcd. C 88.82, H 11.18; found C 88.83, H 11.26%.

(Z/E)-3-Bromomethylene-2,2-dimethylbicyclo[2.2.1]heptane[10] ("ω-Bromocamphene"; **5**): ω,ω-Dibromocamphene (**8**; see below; 29 g, 0.10 mol) and tributyltin hydride (27 ml, 29 g, 0.10 mol) were mixed and heated for 1 h to 50°C. The product was isolated by distillation through a Vigreux column (10 cm long) as a 3:2 (*Z*/*E*) mixture (gas-chromatographic analysis: 30 m; DB-FFAP, 100°C; 30 m, DB-1701, 100°C); b.p. 52−53°C/0.2 Torr; n_D^{20} = 1.5235; 20.4 g (95%). – ^{1}H NMR: δ = 5.83 (0.6H, s), 5.61 (0.4H, s), 3.13 (0.4H, dq, *J* = 34.5, 1.5), 2.74 (0.6H, dq, *J* = 4.5, 1.5), 2.05 (0.4H, dm, *J* = 4.0), 1.93 (6.0H, d, *J* = 4.0), 1.8 (1.6H, m), 1.7 (1.4H, m), 1.4 (1H, m), 1.31 (3 × 0.6H, s), 1.3 (1.4H, m), 1.26 (0.6H, dt, *J* = 9.5, 1.5), 1.20 (3 × 0.6H, s), 1.08 (3 × 0.4H, s), 1.06 (3 × 0.4H, s). – $C_{10}H_{15}Br$ (215.13): calcd. C 55.83, H 7.03; found C 55.94, H 7.02%.

(Z/E)-3-(Bromodeuteriomethylene)-2,2-dimethylbicyclo[2.2.1]-heptane ("ω-Bromo-ω-deuteriocamphene", **5**-d_1): In the same way a 55:45 (*Z*/*E*) mixture of the isotopically labelled bromocamphene was obtained when tributyltin deuteride was employed; b.p. 56−58°C/0.3 Torr; n_D^{20} = 1.5239; 0.5 g (67%). – ^{1}H NMR: δ = 3.13 (0.45H, dq, *J* = 4.5, 1.5), 2.74 (0.55H, dq, *J* = 4.5, 1.5), 2.05 (0.45H, dm, *J* = 4.0), 1.93 (0.55H, dm, *J* = 3.5), 1.8 (1.55H, m), 1.7 (1.45H, m), 1.4 (1H, m), 1.31 (3 × 0.55H, s), 1.45H, m), 1.26 (0.55H, dt, *J* = 9.5, 1.5), 1.20 (3 × 0.55H, s), 1.08 (3 × 0.45H, s), 1.06 (3 × 0.45H, s). – $C_{10}H_{14}DBr$ (216.14): calcd.C 55.57, H 7.05; found C 55.66, H 7.04%.

3-Dibromomethylene-2,2-dimethylbicyclo[2.2.1]heptane ("ω,ω-Dibromocamphene", **8**): At 0°C, bromine (21 ml, 64 g, 0.40 mol) was added dropwise to a solution of 3,3-bis(trifluoroacetoxymercurio)methylene-2,2-dimethylbicyclo[2.2.1]heptane (**7**; see below; 76 g, 0.10 mol) in diethyl ether (0.50 l). The precipitate formed was removed by filtration and the solvent evaporated. The residue was purified by chromatography on silica gel, hexane being the eluent, and by distillation to give a colorless liquid; m.p. −3 to −2°C; b.p. 85−86°C/1 Torr (lit.[3]: 130°C/0.5 Torr); n_D^{20} = 1.5594; 23.5 g (80%). − ^{1}H NMR*: δ = 3.13 (1H, dq, *J* = 4.7, 1.5), 2.05 (1H, dm, *J* = 4.5), 1.8 (2H, m), 1.65 (1H, tm, *J* = 11.8), 1.43 (1H, tdd, *J* = 12.5, 5.5, 4.0), 1.4 (1H, m), 1.30 (3H, s), 1.25 (3H, s), 1.22 (1H, dt, *J* = 10.0, 1.5). − MS; *m/z* (%): 294 (78%, M^+), 251 (86%). − $C_{10}H_{14}Br_2$ (294.03): calcd. C 40.85, H 4.80; found C 40.90, H 4.86%.

2,2-Dimethyl-3,3-bis(trifluoroacetoxymercurio)methylenebicyclo[2.2.1]heptane (**7**): Mercury (II) trifluoroacetate (0.19 kg, 0.44 mol) was dissolved in 50% aqueous tetrahydrofuran (0.80 l) whereupon the solution turned orangered. Solid camphene (27 g, 0.20 mol) was added. After a few minutes of vigorous shaking, complete decoloration was observed and two phase had formed. The aqueous phase was separated and extracted with diethyl ether (3 × 0.15 l). The combined organic layers were washed with water (1 × 50 ml), dried and evaporated to dryness. The residue was taken up in chloroform (0.50 l) and the insoluble mass (unconsumed mercuric salts, 25 g) removed by filtration. The solution was concentrated, diluted with hexane (0.25 l) and stored in a refrigerator. Overnight, the product crystallized in form of tiny white needles which were collected by filtration; m.p. 186.5−187.5°C (after recrystallization from a 1:1 mixture of diethyl ether and pentane); 122 g (81%). − ^{1}H NMR: δ = 2.73 (1H, d, *J* = 3.5), 1.08 (1H, s, broad), 1.9 (3H, m), 1.52 (1H, tdd, *J* = 12.0, 5.0, 4.0), 1.4 (1H, m), 1.34 (3H, s), 1.28 (3H, s). − MS; *m/z* (%): 781 (4%, $M^+ + NH_3$), 764 (1%, M^+), 594 (78%), 354 (100%). − $C_{14}H_{14}F_6Hg_2O_4$ (761.43): calcd. C 22.08, H 1.85; found C 22.13, H 1.93%.

2. *ω-Bromocamphene": Halogen/Metal Exchange and Trapping Reactions*

(Z)-3-Ethylidene-2,2-dimethylbicyclo[2.2.1]heptane (*Z*-**1a**): At −75°C, a 1.5 M solution of *tert*-butyllithium (30 mmol) in pentane (10 ml) and, 15 min later, dimethyl sulfate (1.4 ml, 1.9 g, 15 mmol) were added to a solution of (*Z*)-ω-bromocamphene (*Z*:*E* ratio of 99:1, 2.5 ml, 3.2 g, 15 mmol) in tetrahydrofuran (60 ml). The product was isolated by distillation as a colorless liquid; b.p. 31−32°C/0.2 Torr; n_D^{20} = 1.4808; 1.8 g (81%). − ^{1}H NMR: δ = 5.15 (1H, q, *J* = 7.0), 2.05 (1H, dd, *J* = 4.0, 0.8), 1.83 (1H, dm, *J* = 2.5), 1.7 (2H, m), 1.63 (3H, d, *J* = 7.0), 1.6 (1H, m), 1.30 (1H, tdd, *J* = 12.0, 5.5, 4.0), 1.2 (1H, m), 1.20 (3H, s), 1.15 (3H, s), 1.13 (1H, dm, *J* = 9.5). − $C_{11}H_{18}$ (150.26): calcd. C 87.93, H 12.07; found C 87.74, H 12.22%.

(Z)-2,2-Dimethyl-3-(2-methylpent-2-en-5-ylidene)-bicyclo-[2.2.1]heptane [(*Z*)-Isosantalene, *Z*-**1b**]: (*Z*)-ω-bromocamphene (*Z*-**5**; 1.7 ml, 2.1 g, 10 mmol) was treated with *tert*-butyllithium (20 mmol) exactly as described above and subsequently with 3-methylbut-2-enyl bromide (1.1 ml, 1.4 g, 10 mmol). Immediate distillation afforded a colorless liquid; b.p. 85−87°C/0.5 Torr; n_D^{20} = 1.4933; 0.7 g (35%). − The (*Z*/*E*) ratio was 96:4 according to gas chromatography (30 m, DB-FFAP, 110°C; 30 m DB-1701, 110°C). − ^{1}H NMR: δ = 5.08 (1H, tsept, *J* = 7.1, 1.4), 5.00 (1H, t, *J* = 7.5), 2.73 (2H, tm, *J* = 7.5), 2.51 (1H, dq, *J* = 4.3, 1.2), 1.81 (1H, d, *J* = 2.6), 1.7 (2H, m), 1.69 (3H, q, *J* = 1.2), 1.63 (3H, s), 1.6 (1H, m), 1.35 (1H, tdd, *J* = 12.5, 5.0, 4.5), 1.23 (1H, dddd, *J* = 14.5, 11.4, 5.0, 22.5), 1.19 (3H, s), 1.13 (3H, s), 1.1 (1H, m). − $C_{15}H_{24}$ (204.36): calcd. C 88.16, H 11.84; found C 87.76, H 11.83%.

(Z)-(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)acetaldehyde (*Z*-**2**): At −75°C, ω-Bromocamphene (4.2 ml, 5.4 g, 25 mmol) was treated with *tert*-butyllithium (see above; 50 ml) and, 5 min later, anhydrous *N*,*N*-dimethylformamide (2.3 ml, 2.2 g, 30 mmol). When the mixture had reached 25°C, it was poured into water (0.10 l) and extracted with diethyl ether (3 × 25 ml). The organic layer was evaporated and the residue absorbed on silica gel (10 ml). Elution from a column filled with more silica gel (100 ml) with a 1:2 (v:v) mixture of diethyl ether and hexane gave a colorless oil which was purified by distillation in a Hickmann flask; m.p. −3 to −2°C; b.p. 56−58°C/0.2 Torr; n_D^{20} = 1.5230; 2.9 g (79%). − The (*Z*/*E*) ratio was 98:2 according to gas chromatography (30 m, DB-FFAP, 110°C, 30 m, DB-1701, 110°C). − ^{1}H NMR: δ = 10.05 (1H, d, *J* = 8.8), 5.81 (1H, d, *J* = 8.8), 2.82 (1H, d, *J* = 4.5), 1.99 (1H, s, broad), 1.8 (2H, m), 1.7 (1H, m), 1.48 (1H, tt, *J* = 12.5, 4.8), 1.4 (1H, m), 1.38 (3H, s), 1.34 (3H, s), 1.3 (1H, m). − $C_{11}H_{16}O$ (164.25): calcd. C 80.44, H 9.82; found C 80.39, H 9.56%.

(Z)-(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)acetic Acid (*Z*-**3**): At −75°C, *tert*-butyllithium (see above; 100 mmol) was added to ω-bromocamphene (50 mmol) and, 5 min later, the mixture was poured on an excess of freshly crushed dry ice. A 0.5 M aqueous solution (0.10 l) of sodium hydroxide was added. After having been washed with diethyl ether (3 × 25 ml), the solution was acidified to pH 4 and extracted with diethyl ether (3 × 25 ml). The combined organic layers were dried and evaporated to dryness. The remaining crude product (which had formed in almost quantitative yield) was crystallized from pentane (20 ml); m.p. 116−118°C; 6.6 g (73%). − ^{1}H NMR*: δ = 5.72 (1H, s), 2.74 (1H, dm, *J* = 4.2), 1.95 (1H, d, *J* = 2.2), 1.8 (3H, m), 1.4 (1H, m), 1.31 (3H, s), 1.3 (2H, m), 1.29 (3H, s). − $C_{11}H_{16}O_2$ (180.25): calcd. C 73.30, H 8.95; found C 73.31, H 9.07%.

Methyl (Z)-(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)acetate (*Z*-**4a**): Acid *Z*-**3** (0.90 g, 50 mmol) was treated with an ethereal solution of diazomethane until the yellow color persisted. Immediate distillation gave a colorless oil; b.p. 82−83°C/0.02 Torr, n_D^{20} = 1.4943; 8.9 g (92%). − The (*Z*/*E*) ratio was 99:1 according to gas chromatography (30 m, DB-FFAB, 125°C; DB-WAX, 130°C). − ^{1}H NMR: δ = 5.67 (1H, s), 3.66 (3H, s), 2.69 (1H, dm, *J* = 3.2), 1.94 (1H, d, *J* = 2.0), 1.7 (3H, m), 1.4 (1H, m), 1.32 (3H, s), 1.3 (2H, m), 1.29 (3H, s). − $C_{12}H_{18}O_2$ (194.27): calcd. C 74.19, H 9.34; found C 74.03, H 9.29%.

Isobutyl (Z)-(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)acetate (*Z*-**4b**): Acid *Z*-**3** (2.7 g, 15 mmol) and *N*,*N'*-carbonyldiimidazole (2.4 g, 15 mmol) were conjointly dissolved in tetrahydrofuran (10 ml). After 15 min of standing, a solution of sodium 2-methylpropanolate (15 mmol) in 2-methylpropan-1-ol (isobutanol, 5.0 ml) was added. The mixture was heated for 2 h to reflux before being poured into water (0.10 l) and extracted with diethyl ether (3 × 15 ml). The combined organic layers were washed with water (3 × 10 ml) and brine (2 × 10 ml), then dried and concentrated. Upon distillation, a colorless liquid was collected; b.p. 82−84°C/0.02 Torr; n_D^{20} = 1.4947; 1.9 g (53%). − The (*Z*/*E*) ratio was 97:3 (by gas chromatography: 30 m, DB-FFAP, 170°C; 30 m, DB-1701, 170°C). − ^{1}H-NMR: δ = 6.99 (H, s), 3.85 (1H, d, *J* = 7.5), 3.84 (1H, d, *J* = 7.5), 2.69 (1H, dq, *J* = 4.0, 1.2), 1.92 (1H, nonet, *J* = 7.5), 1.9 (1H, m), 1.8 (3H, m), 1.4 (1H, m), 1.32 (3H, s), 1.3 (1H, m), 1.29 (3H, d, s), 1.27 (1H, dt, *J* = 10.1, 1.2), 0.94 (3H, d, *J* = 7.5). − $C_{15}H_{24}O_2$ (236.35): calcd. C 76.23, H 10.23; found C 76.23, H 10.16%.

(Z)-(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)ethanol (*Z*-**6**): At 25°C, sodium borohydride (0.57 g, 15 mmol) was added, under stirring, to a solution of aldehyde *Z*-**2** (2.9 ml, 2.5 g, 15 mmol) in

a 1:9 (v:v) mixture (30 ml) of methanol and diethyl ether. After 1 h, water (20 ml) was added and the stirring was continued for 30 min. The aqueous phase was extracted with diethyl ether (2 × 10 ml). The organic layers were combined, washed with brine (2 × 10 ml), dried and concentrated. Distillation afforded a colorless liquid; m.p. 13.5–14.5°C; b.p. 58–60°C/0.1 Torr (lit.[11,12] b.p. of *Z/E* mixtures: 87–88°C/2 Torr, 110–115°C/5 Torr); n_D^{20} = 1.5012; 1.6 g (64%). – The (*Z/E*) ratio was 98:2 (by gas chromatography: 30 m, DB-FFAP, 130°C; 30 m, DB-WAX, 140°C). – ^{1}H NMR: δ = 5.33 (1H, t, *J* = 7.4), 4.18 (2H, d, *J* = 7.4), 2.58 (1H, dm, *J* = 3.5), 1.85 (1H, dm, *J* = 2.5), 1.7 (3H, m), 1.38 (1H, tt, *J* = 13.0, 4.0), 1.3 (1H, m), 1.2 (1H, m), 1.18 (3H, s), 1.14 (1H, s). – $C_{11}H_{18}O$ (166.26): calcd. C 78.62, H 10.91; found C 79.17, H 10.69%.

4. *Camphene: Metalation and Trapping Reactions*

(E)-3-Ethylidene-2,2-dimethylbicyclo[2.2.1]heptane (*E*-**1a**)[2]: At 25°C, a mixture of camphene (8.7 g, 65 mmol), pentylsodium[8] (65 mmol) and potassium *tert*-butoxide (11.2 g, 100 mmol) in pentane (0.15 l) was submitted during 2 h to high-speed stirring (5000 rpm)[9]. Under continuing stirring, but at −75°C, dimethyl sulfate (9.5 ml, 12.5 g, 100 mmol) was added dropwise. The mixture was centrifuged and the supernatant liquid decanted. Upon distillation, some camphene (6%; b.p. 84–86°C/12 Torr) and the product *E*-**1a** were collected; (*Z/E*) ratio 1:99; b.p. 90–92°C/12 Torr (lit.[13] b.p. of a *Z/E* mixture: 95°C/45 Torr); n_D^{20} = 1.4816; 7.6 g (78%).

(E)-2,2-Dimethyl-3-(2-methylpent-2-en-5-ylidene)bicyclo-[2.2.1]heptane ["(*E*)-isosantalene"; *E*-**1b**]: Camphene (65 mmol) was treated with pentylsodium and potassium *tert*-butoxide as described above. At −75°C and under vigorous stirring, lithium bromide (13 g, 0.15 mol) in tetrahydrofuran (0.10 l) and, 5 min later, 3-methylbut-2-enyl bromide (10 ml, 13 g, 87 mmol) were added. When it had reached 25°C, the mixture was centrifuged. The supernatant solution was decanted and evaporated. Distillation of the residue, a yellow oil, gave a colorless liquid; (*Z/E*) ratio 9:91; b.p. 84–86°C/0.5 Torr (lit.[4] b.p. of a presumable *Z/E* mixture: 130–135°C/4 Torr); n_D^{20} = 1.4927; 8.1 g (61%). – ^{1}H NMR: δ = 5.07 (1H, tsept, *J* = 7.3, 1.5), 4.83 (1H, t, *J* = 7.3), 2.93 (1H, d, *J* = 4.0), 2.67 (2H, t, *J* = 7.3), 1.87 (1H, d, *J* = 4.0), 1.71 (3H, q, *J* = 1.3), 1.63 (3H, s), 1.6 (3H, m), 1.4 (1H, m), 1.2 (1H, m), 1.18 (1H, dt, *J* = 9.5, 1.5), 1.01 (3H, s), 0.98 (3H, s). – $C_{15}H_{24}$ (204.36): calcd. C 8.16, H 11.84; found C 87.89, H 11.91%.

(E)-3-Dimethylbicyclo[2.2.1]hept-2-ylidene)acetaldehyde (*E*-**2**): As described in the preceding paragraph, camphene (65 mmol) was consecutively treated with pentylsodium in the presence of potassium *tert*-butoxide and lithium bromide dissolved in tetrahydrofuran. Still at −75°C, *N,N*-dimethylformamide (23 ml, 20 g, 0.12 mol) was added. When the mixture had reached 25°C, it was poured onto ice (0.2 kg). The aqueous phase was extracted with diethyl ether (2 × 50 ml). The combined organic layers were concentrated and absorbed on silica gel (25 ml). Elution with a 1:2 (v:v) mixture of diethyl ether and hexane from a column filled with more silica gel (250 ml) and evaporation afforded a yellowish oil which was further purified by distillation and crystallization at −75°C (from pentane); (*Z/E*) ratio 2:98; m.p. 3–4°C; b.p. 57–59°C/0.2 Torr (lit.[15] b.p. of a presumable *Z/E* mixture: 105–112°C/6 Torr); n_D^{20} = 1.5228; 7.6 g (71%). – ^{1}H NMR: δ = 9.90 (1H, d, *J* = 8.4), 5.74 (1H, d, *J* = 8.4), 3.69 (1H, d, *J* = 4.8), 2.05 (1H, dm, *J* = 4.0), 1.89 (1H, tdd, *J* = 12.5, 4.8, 4.0), 1.82 (1H, dp, *J* = 10.3, 2.0), 1.72 (1H, dddd, *J* = 12.5, 9.0, 4.0, 3.1), 1.52 (1H, tdd, *J* = 12.5, 4.5, 4.0), 1.45 (1H, dt, *J* = 10.3, 1.2), 1.30 (1H, dddd, *J* = 12.5, 9.5, 4.5, 2.0), 1.13 (3H, s), 1.10 (3H, s). – $C_{11}H_{16}O$ (164.25): calcd. C 80.44, H 9.82; found C 80.44, H 9.77%.

(E)-(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)acetic Acid (*E*-**3**): After the treatment of camphene (65 mmol) with pentylsodium and potassium *tert*-butoxide (see above), the mixture was poured on an excess of freshly crushed dry ice. At 25°C, water (0.10 l) was added. The aqueous phase was separated and acidified to pH 4. Extraction with diethyl ether (3 × 25 ml), washing with brine (2 × 15 ml), drying and evaporation left a yellowish oil behind which crystallized from pentane (20 ml); m.p. 126–128°C (lit.[16] m.p.: 126–127°C); 8.7 g (74%). – ^{1}H NMR: δ = 5.47 (1H, s), 3.98 (1H, d, *J* = 5.0), 1.96 (1H, dm, *J* = 4.2), 1.83 (1H, tdd, *J* = 12.3, 5.3, 4.0), 1.73 (1H, dp, *J* = 10.4, 1.8), 1.65 (1H, ddt, *J* = 12.3, 9.1, 3.2), 1.48 (1H, tdd, *J* = 12.3, 5.3, 4.0), 1.35 (1H, d, *J* = 10.4), 1.3 (1H, m), 1.09 (3H, s), 1.07 (3H, s).

Methyl (E)-(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)acetate (*E*-**4a**): As described for the (*Z*) isomer (see above), acid *E*-**3** (15 mmol) was converted into the methyl ester by treatment with ethereal diazomethane and isolated by distillation; (*Z/E*) ratio 2:98; b.p. 82–83°C/0.02 Torr (lit.[11,17] b.p.: 112–118°C/14 Torr, 94°C/4 Torr); n_D^{20} = 1.4943; 2.7 g (93%). – ^{1}H NMR: δ = 5.45 (1H, s), 3.96 (1H, d, *J* = 5.0), 3.69 (3H, s), 1.95 (1H, dm, *J* = 4.0), 1.81 (1H, tdd, *J* = 12.2, 5.0, 4.0), 1.72 (1H, dp, *J* = 10.2, 2.0), 1.63 (1H, dddd, *J* = 12.5, 9.5, 4.0, 3.0), 1.45 (1H, tdd, *J* = 12.5, 5.5, 4.0), 1.32 (1H, d, *J* = 10.2), 1.2 (1H, m), 1.08 (3H, s), 1.06 (3H, s).

Isobutyl (E)-(3,3-Dimethylbicyclo[2.2.1]hept-2-ylidene)acetate (*E*-**4b**): Acid *E*-**3** (3.4 g, 20 mmol), boron trifluoride diethyl etherate (2.5 ml, 2.8 g, 20 ml) and 2-methylpropan-1-ol (18 ml, 15 g, 0.20 mmol) was heated to reflux for 2 h. Immediate distillation gave a colorless liquid; (*Z/E*) ratio 1:99; b.p. 82–83°C/0.02 Torr; n_D^{20} = 1.4943; 3.9 g (82%). – ^{1}H NMR: δ = 5.45 (1H, s), 3.94 (1H, d, *J* = 4.7), 3.88 (1H, d, *J* = 6.5), 3.87 (1H, d, *J* = 6.5), 1.95 (1H, nonet, *J* = 6.5), 1.9 (1H, m), 1.80 (1H, tdd, *J* = 12.0, 5.0, 4.0), 1.71 (1H, dp, *J* = 10.1, 2.0), 1.63 (1H, dddd, *J* = 12.0, 9.5, 4.0, 3.5), 1.44 (1H, tdd, *J* = 12.2, 5.5, 4.0), 1.31 (1H, d, *J* = 10.1), 1.23 (1H, dddd, *J* = 12.2, 9.5, 5.5, 2.0), 1.08 (3H, s), 1.06 (3H, s), 0.95 (3H, d, *J* = 6.5), 0.95 (3H, d, *J* = 6.5). – $C_{15}H_{24}O_2$ (236.35): calcd. C 76.23, H 10.23; found C 76.21, H 10.10%.

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