SYNTHESIS OF 1,1,5,6-TETRAMETHYL- AND 7-ISOPROPYL-1,1-DIMETHYL-1,2,3,4-TETRAHYDRONAPHTHALENE

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4-(2,3-Dimethylphenyl)butanoic acid (4) was treated with excess of methyllithium to yield 5-(2,3-dimethylphenyl)-2-methylpentan-2-ol (6) which was cyclodehydrated using Dowex 50W-X8 resin, trifluoroacetic acid or polyphosphoric acid (PPA) to furnish 1,1,5,6-tetramethyl-1,2,3,4-tetrahydronaphthalene (1). The acid 4 was cyclized with PPA to furnish 5,6-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (5) which was converted into 1 by reaction with dimethylzinc and titanium tetrachloride. 4-(4-Isopropylphenyl)butanoic acid (7) on esterification followed by Grignard reaction with methylmagnesium iodide furnished 5-(4-isopropylphenyl)-2-methylpentan-2-ol (9), which was cyclodehydrated as above to yield 7-isopropyl-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (2).

Key words: 1,2,3,4-Tetrahydronaphthalenes; Friedel-Crafts reaction; Alkylation; Cyclization; Sesquiterpenoids.

Several sesquiterpenoids of interesting types have been discovered¹ in the steam-volatile oil of *Isocoma wrightii* along with 1,1,5,6-tetramethyl-1,2,3,4-tetrahydronaphthalene (1), a novel nordrimane sesquiterpene. Compound 1 has been obtained earlier from the degradative rearrangement of naturally occuring sesquiterpene, avarol². An analogous 1,2,3,4-tetrahydronaphthalene system has been obtained recently from some diterpene derivatives³. The 7-isopropyl-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (2) with the rearranged isolongifolene skeleton^{4,5} is another 1,1-dimethyl-1,2,3,4-tetrahydronaphthalene type known in the literature. Ionene (1,1,6-trimethyl-1,2,3,4-tetrahydronaphthalene) and its 3,4-dehydro derivative, a constituent of *Passiflora edulis* (ref.⁶) can also be regarded as members of the 1,1-dimethyl-1,2,3,4-tetrahydronaphthalene family of sesquiterpenes.

Murali and Krishna Rao⁷ reported the first synthesis of 1,1,5,6-tetramethyl-1,2,3,4-tetrahydronaphthalene. We now report a short synthesis of this compound. The Friedel–Crafts reaction of *o*-xylene with

butano-4-lactone⁸ at 0–5 °C yielded 4-(2,3-dimethylphenyl)butanoic acid (4) as a major product and 4-(3,4-dimethylphenyl)butanoic acid (3) as a minor product. The products were separated by fractional crystallization and the major product 4 was treated with excess of methyllithium⁴ to yield 5-(2,3-dimethylphenyl)-2-methylpentan-2-ol (6). This alcohol was cyclodehydrated using three different reagents, Dowex 50W-X8 resin, trifluoroacetic acid or polyphosphoric acid (PPA), to furnish 1,1,5,6-tetramethyl-1,2,3,4-tetrahydronaphthalene (1). The acid 4 was cyclized with PPA to furnish 5,6-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (5). Treatment of 5 with excess of dimethylzinc and titanium tetrachloride⁹ (Reetz reagent) yielded 1 (Scheme 1).



(i) AlCl₃, 0-5 °C; (ii) PPA; (iii) MeLi, Et₂O, r.t.; (iv) Dowex 50W-X8, benzene, reflux; (v) TFA, reflux; (vi) PPA, 90-95 °C; (vii) Me₂Zn, TiCl₄, CH₂Cl₂, -30 °C to r.t.

Scheme 1

The first synthesis of 7-isopropyl-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (**2**) was reported by Farnum *et al.*⁴. There are also several reports¹⁰⁻¹⁵ in the literature on the formation of this compound by rearrangement of longifolene or isolongifolene. We now report another synthesis of 7-isopropyl-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (**2**). The Friedel–Crafts reaction of isopropylbenzene with butano-4-lactone at 10 °C yielded 4-(4-isopropylphenyl)butanoic acid (**7**), which was converted into its methyl ester **8** using methanol and sulfuric acid. The ester **8** on Grignard reaction with methylmagnesium iodide furnished 5-(4-isopropylphenyl)-2-methylpentan-2-ol (**9**) which was cyclodehydrated using three different reagents, Dowex 50W-X8 resin, trifluoroacetic acid or polyphosphoric acid to yield 7-isopropyl-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene **2** (Scheme 2).



(i) AlCl₃, r.t.; (ii) MeOH, H⁺, reflux; (iii) MeMgI, Et₂O, reflux; (iv) Dowex 50W-X8, benzene, reflux; (v) TFA, reflux; (vi) PPA, 90-95 °C

SCHEME 2

EXPERIMENTAL

Melting and boiling points are uncorrected. Preparative thin-layer chromatography (PLC) was carried out on glass plate precoated (2.0 mm) with silica gel G (Merck). Materials were detected by visualization under an iodine chamber. Column chromatography was performed with silica gel (Merck) (60–120 mesh). The IR spectra (wavenumbers in cm⁻¹) were recorded on a Perkin–Elmer 783 spectrophotometer either as neat (liquids) or in KBr pellets (solids). ¹H NMR spectra were recorded on a JEOL spectrometer FX 90Q (90 MHz) in CDCl₃ solutions and chemical shifts were given in ppm (δ -scale).

4-(3,4-Dimethylphenyl)butanoic Acid (3) and 4-(2,3-Dimethylphenyl)butanoic Acid (4)

To a mechanically stirred solution of *o*-xylene (53 g, 0.5 mol) and butano-4-lactone (21.5 g, 0.25 mol), anhydrous aluminum chloride (85 g, 0.625 mol) was added at 0–5 °C during 2 h. The reaction mixture was stirred at room temperature for additional 5 h and decomposed with 15% ice-cold concentrated hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with a sodium hydrogencarbonate solution. Acidification of the alkaline extract with concentrated hydrochloric acid gave a mixture of acids 3 and 4. Yield 24.5 g (54%). The mixture of acids upon fractional crystallization from petroleum ether gave 4-(2,3-dimethylphenyl)butanoic acid (4), yield 8.6 g (35%), m.p. 99–100 °C (ref.⁸ gives m.p. 102 °C) and 4-(3,4-dimethylphenyl)butanoic acid (3), yield 1.7 g (7%), m.p. 54–55 °C (ref.⁸ gives m.p. 56 °C).

5,6-Dimethyl-3,4-dihydronaphthalen-1(2H)-one (5)

To a well stirred polyphosphoric acid, prepared from phosphorus pentoxide (90 g) and orthophosphoric acid (55 ml), was added 4-(2,3-dimethylphenyl)butanoic acid (4; 9.0 g, 46.9

mmol) and the reaction mixture was heated at 90–95 °C for 1.5 h. The cool reaction mixture was decomposed by pouring onto crushed ice (90 g) and extracted with diethyl ether. The ether extract was successively washed with water, a 10% sodium hydroxide solution, water and then dried with anhydrous sodium sufate. The residue after evaporation was chromatographed on silica gel (80 g). Slow elution with benzene gave pure 5, yield 6.85 g (84%), b.p. 171–175 °C/1 595 Pa (ref.¹⁶ gives b.t. 154–158 °C/1 064 Pa). IR (neat): 1 674. ¹H NMR (CDCl₃): 2.07 quintet, 2 H (CH₂); 2.22 s, 3 H (CH₃); 2.35 s, 3 H (CH₃); 2.6 t, 2 H (CH₂); 2.9 t, 2 H (CH₂); 7.1 d, 1 H, J = 8 (Ar-H); 7.75 d, 1 H, J = 8 (Ar-H).

5-(2,3-Dimethylphenyl)-2-methylpentan-2-ol (6)

To a stirred solution of methyllithium, prepared from lithium (1.18 g, 170 mmol) and methyl iodide (5.6 ml, 90 mmol) in dry ether (180 ml), a solution of 4-(2,3-dimethyl-phenyl)butanoic acid (4; 2.3 g, 12 mmol) in diethyl ether (20 ml) was added during 15 min. The reaction mixture was stirred at room temperature for 4 h and then kept overnight. It was decomposed by pouring into a cold saturated ammonium chloride solution (70 ml) and extracted with diethyl ether. The ether extract was successively washed with a saturated so-dium hydrogencarbonate solution, water and then dried with anhydrous sodium sulfate. Removal of the solvent yielded **6** (2.1 g, 85%), b.t. 132–137 °C/1 064 Pa (ref.⁷ gives b.t. 112–117 °C/665 Pa). IR (neat): 3 365 (broad, OH).

1,1,5,6-Tetramethyl-1,2,3,4-tetrahydronaphthalene (1)

A) Cyclodehydration of **6** with Dowex 50W-X8 resin. A mixture of **6** (0.3 g, 1.45 mmol) and Dowex 50W-X8 resin (1.0 g) in dry benzene (10 ml) was refluxed for 4 h. The cool reaction mixture was filtered off and the solvent was removed. The crude product was purified by preparative TLC (silica gel G, hexane) to give pure **1** (0.2 g, 73%), b.t. 100–105 °C/665 Pa (ref.⁷ gives 125–130 °C/1 595 Pa). IR (neat): 810. ¹H NMR (CDCl₃): 1.25 s, 6 H (CH₃); 1.7 m, 4 H (CH₂); 2.1 s, 3 H (Ar-CH₃); 2.22 s, 3 H (Ar-CH₃); 2.63 t, 2 H (CH₂); 7.03 and 7.08 AB quartet, 2 H, J = 8.5 (Ar-H). For C₁₄H₂₀ (188.3) calculated: 89.30% C, 10.70% H; found: 89.14% C, 10.46% H.

B) Cyclodehydration of **6** with trifluoroacetic acid. A mixture of **6** (0.2 g, 1 mmol) and trifluoroacetic acid (2 ml) was refluxed for 3 h, cooled, poured into water and extracted with diethyl ether. The ether extract was successively washed with water, a 5% aqueous sodium carbonate solution, water and then dried with anhydrous sodium sulfate. Removal of the solvent gave a crude product which was purified by preparative TLC (silica gel G, hexane) to give pure **1** (0.17 g, 93%).

C) Cyclodehydration of **6** with polyphosphoric acid. Compound **6** (0.17 g, 0.8 mmol) was added to a well stirred polyphosphoric acid, prepared from phosphorus pentoxide (0.4 g) and orthophosphoric acid (1.2 ml), and the reaction mixture was heated at 90–95 °C for 2 h, then cooled, poured onto crushed ice and extracted with diethyl ether. The extract was washed with water and dried with anhydrous sodium sulfate. Removal of the solvent gave a crude product which was purified by preparative TLC (silica gel G, hexane) to give pure **1** (0.135 g, 88%).

D) Compound 5 (1.76 g, 0.01 mol) was added at -30 °C under nitrogen atmosphere to the stirred Reetz reagent, prepared from dimethylzinc (1.9 g, 0.02 mol) and titanium tetrachloride (3.76 g, 0.02 mol) in dry methylene chloride (100 ml). The reaction mixture was stirred at -30 °C for 30 min and allowed to reach room temperature. The product was hydrolyzed

by a saturated sodium hydrogencarbonate solution (100 ml) and extracted with diethyl ether. The ether extract was washed with water and dried with anhydrous sodium sulfate. The residue after evaporation (1.3 g) was chromatographed on silica gel (20 g). Slow elution with hexane gave 1 (1.6 g, 85%).

4-(4-Isopropylphenyl)butanoic Acid (7)

To a mechanically stirred solution of isopropylbenzene (60 g, 0.5 mol) and butano-4-lactone (21.5 g, 0.25 mol), anhydrous aluminum chloride (85 g, 0.625 mol) was added at 10 °C during 2 h. The reaction mixture was stirred at this temperature for 5 h and decomposed with 15% ice-cold concentrated hydrochloric acid. The organic layer was separated and the aqueous layer extracted with diethyl ether. The combined organic extracts were washed with a sodium hydrogencarbonate solution. Acidification of the alkaline extract with concentrated hydrochloric acid (7), yield 25.0 g (49%), b.p. 162–165 °C/1 064 Pa (ref.¹⁷ gives b.p. 186 °C/1 595 Pa). IR (neat): 3 700–2 500.

Methyl 4-(4-Isopropylphenyl)butanoate (8)

To a solution of 7 (6.0 g, 29 mmol) in methanol (25 ml) was added concentrated sulfuric acid (1.5 ml) and the reaction mixture was refluxed for 6 h. Methanol was distilled off and the product poured into water, the mixture was extracted with diethyl ether and the ether extract was washed with a saturated sodium hydrogencarbonate solution, water and then dried with anhydrous sodium sulfate. The residue after evaporation was distilled to give **8** (5.3 g, 83%), b.p. 115–117 °C/266 Pa. IR (neat): 1 740. For $C_{14}H_{20}O_2$ (220.3) calculated: 76.33% C, 9.15% H; found: 76.10% C, 8.92% H.

5-(4-Isopropylphenyl)-2-methylpentan-2-ol (9)

A solution of **8** (2.16 g, 9.8 mmol) in diethyl ether (15 ml) was added during 30 min to a stirred solution of methylmagnesium iodide prepared from magnesium (1.28 g, 53 mmol) and methyl iodide (5.1 ml, 82 mmol) in dry ether (70 ml). The reaction mixture was stirred for 6 h and finally refluxed for 1 h. The reaction mixture was cooled to 0 °C and decomposed with a saturated ammonium chloride solution (50 ml). The product was extracted with diethyl ether and the extract was washed with water and dried with anhydrous sodium sulfate. Removal of solvent furnished **9** (1.9 g, 88%), b.t. 129–131 °C/665 Pa. IR (neat): 3 385 (broad, OH).

7-Isopropyl-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene (2)

A) Cyclodehydration of **9** with Dowex 50W-X8 resin. A mixture of **9** (0.5 g, 2.3 mmol) and Dowex 50W-X8 resin (1.5 g) in dry benzene (15 ml) was refluxed for 4 h. The benzene solution was filtered and the residue after evaporation was purified by preparative TLC (silica gel G, hexane) to give pure **2** (0.44 g, 95%), b.t. 124–125 °C/665 Pa (ref.⁵ gives b.p. 90–92 °C/133 Pa). IR (neat): 1 610, 890, 815. ¹H NMR (CDCl₃): 1.27 s, 6 H (CH₃); 1.22 d, 6 H, J = 7 (CH₃CH); 1.65 m, 4 H (CH₂); 2.65 m, 3 H (Ar-CH₂, Ar-CH); 6.81 s, 2 H (Ar-H); 7.0 bs, 1 H (Ar-H). For C₁₅H₂₂ (202.3) calculated: 89.05% C, 10.96% H; found: 88.85% C, 10.64% H.

B) Cyclodehydration of 9 with trifluoroacetic acid. A mixture of 9 (0.3 g, 1.36 mmol) and trifluoroacetic acid (2.5 ml) was refluxed for 3 h, then cooled, poured into water and ex-

tracted with diethyl ether. The ether extract was successively washed with water, a 5% aqueous sodium carbonate solution, water and then dried with anhydrous sodium sulfate. The residue after evaporation was purified by preparative TLC (silica gel G, hexane) to yield 2 (0.26 g, 95%).

C) Cyclodehydration of **9** with polyphosphoric acid. Compound **9** (0.15 g, 0.68 mmol) was added to a well stirred polyphosphoric acid, prepared from phosphorus pentoxide (0.3 g) and orthophosphoric acid (1.0 ml), and the reaction mixture was heated at 90–95 °C for 2 h. The mixture was cooled, poured onto crushed ice and extracted with diethyl ether. The ether extract was washed with water and dried with anhydrous sodium sulfate. The crude product after evaporation was purified by preparative TLC (silica gel G, hexane) to give **2** (0.12 g, 88%).

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