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Syntheses in the Isocamphane Series XLII [1]. Synthesis and Odour of 5-*exo*-Hydroxycamphene (Isonojigiku Alcohol)

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Summary. The synthesis of the title compound is described. Hydroxylation of the endocyclic double bond of 2-acetyl-3,3-dimethylnorborn-5-ene furnished a mixture of nojigiku alcohol and the title compound. A shorter route leads from 2,5-norbornadiene solely to the desired camphoraceous smelling new hydroxy derivative to which the name isonojigiku alcohol is assigned.

Keywords. 2-Acetyl-3,3-dimethylnorborn-5-ene; Bicyclo[2.2.1]heptane derivatives; Fragrance compounds; Nojigiku alcohol; Odour.

Synthesen in der Isocamphanreihe, 42. Mitt. [1]**. Synthese und Geruch von 5-*exo*-Hydroxycamphen (Isonojigikualkohol)**

Zusammenfassung. Die Synthese des bisher unbekannten 5-*exo*-Hydroxycamphens wird beschrieben. Hydroxylierung der Doppelbindung in 2-Acetyl-3,3-dimethylnorborn-5-en führt zu einem Gemisch der beiden isomeren Camphenalkohole Nojigikualkohol und der Titelverbindung. Ein kürzerer Syntheseweg, ausgehend von 2,5-Norbornadien, führt ausschließlich zur camphrig riechenden Titelverbindung, die mit Isonojigikualkohol bezeichnet wird.

Introduction

In the preceding paper of this series [1] we have described the synthesis of 7-*syn*-hydroxycamphene (**1**) which-on account of its warm, soft, and pleasant camphoraceous odour-could be a valuable constituent in fragrance compositions, especially of the woody type. Another hydroxycamphene compound, nojigiku alcohol (6-*exo*-hydroxycamphene, **2**) has been shown to be an important olfactory component of floral perfumes and fragrance compositions [2], especially because of its ''good aroma'' [3]. Besides its odour qualities, **2** was also found to be a suitable starting compound for the preparation of α-campholenic aldehyde (**3**) [4] from which many important synthetic sandalwood odorants can be obtained [5]. Therefore, it is not surprising that an economic synthesis of **2** has already been

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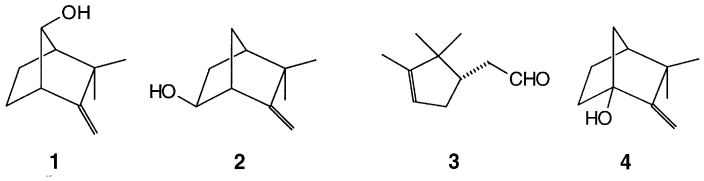
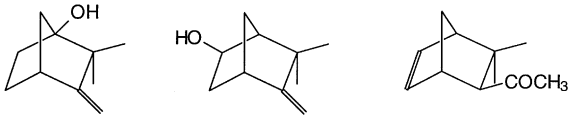
developed [6]. However, not only **1** and **2** are valuable for perfumery purposes, but also 1-hydroxycamphene (**4**) has been said to impart a pleasant fresh note to a perfume on account of its camphoraceous odour [7, 8]. Finally, also the synthesis of 4-hydroxy-camphene (**5**) has been described, but no olfactive properties given [9, 10]. Therefore, it seems logical to synthesize the ''missing link'' in the series of hydroxycamphenes, the hitherto unknown 5-*exo*-hydroxycamphene (**6**) to which we want to assign the name isonojigiku alcohol and to evaluate its olfactive properties.



1 **2** **3** **4**

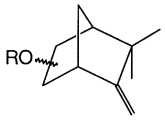


5 **6** **7**

Results and Discussion

2-Acetyl-3,3-dimethylnorborn-5-ene as starting substance

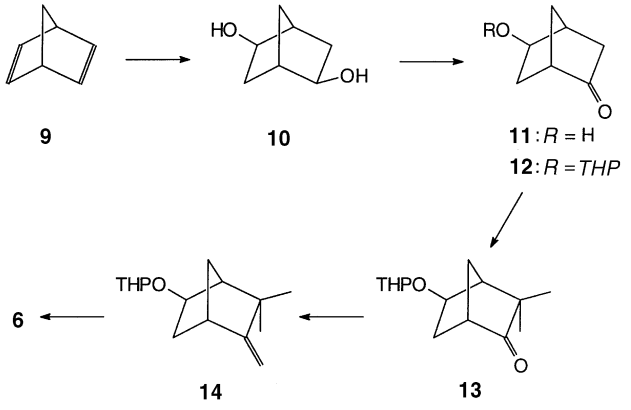
The easy access of 2-acetyl-3,3-dimethylnorborn-5-ene (**7**) by a *Diels-Alder* reaction of mesityl oxide and cyclopentadiene [11] and the versatility of this synthon for the preparation of a lot of biologically active compounds like fragrants (*e.g.* Ref. [12]), fungicides (*e.g.* Ref. [13]), or pharmaca (*e.g.* Ref. [14]) prompted us to use **7** in the synthesis of the target compound **6** as well. However, several attempts to prepare 5-hydroxycamphene (**6**) *via* hydroxylation of the endocyclic double bond of **7** followed by the already established reaction sequence to transform the side chain of **7** into the exocyclic double bond [1, 15] failed. An unseparable 1:2 mixture of the corresponding 5-hydroxy- and 6-hydroxy-dimethylnorbornane compounds was obtained using different hydroxyl protecting groups (*e.g.* *MEM* ether [16], pivaloyl ester [17]. Attempts to remove the *MEM* group from the corresponding *MEM*-camphene **8** furnished either **8** again or destroyed the molecule [16]. Also, various attempts to obtain pure **2** and **6** by chromatographical procedures proved to be useless. By HPLC, the 3,5-dinitrobenzoate ester mixture of **2** + **6** could be separated into its single esters indeed, but only on an analytical scale [17]. Multifold TLC on silica gel coated plates (0.25 mm) yielded only some mg of **2** but not the target molecule **6** [17]. Therefore, the idea to use synthon **7** for the preparation of this new terpenic alcohol proved to be impracticable and had to be dismissed.



8: $R = MEM$

2,5-Norbornadiene as starting substance

Because of the difficulties concerning the separation of the isomeric hydroxy derivatives, a strategy introducing the hydroxyl function selectively at C5 had to be developed. For this purpose, the commercially available bicyclo[2.2.1]heptadiene (**9**) proved to be the ideal starting material, because it could easily be transformed into the hydroxy ketone **11** *via* the 2,5-*bis*-*exo*-diol **10** with already correct positions of the functional groups at C2 and C5 [18, 19]. Hydroboration of **9** [20] with subsequent careful *Jones* oxidation furnished 5-*exo*-hydroxynorbornan-2-one (**11**). Before the next step, the geminal dimethylation, the hydroxyl group had to be protected which was performed using dihydropyrane, thus affording the tetrahydropyranyl ether **12**. This protecting group permits the application of basic conditions and can be removed without difficulties [21]. Geminal dimethylation in position 3 of the bicyclus using CH_3I/lithium cyclohexyl-isoproylamide/*THF* furnished a mixture of mono- and (mainly) dialkylated norbornanone derivative after 18 h of reflux which could be separated by preparative DC. By transformation of the keto function of **13** into the exocyclic methylene group using *Tebbe*'s reagent [22], a titanium-aluminum complex especially suited for sterically hindered ketones [23], we obtained the hydroxy derivative **14**. Cleavage of the tetrahydropyranyl ether with *PPTS*/EtOH [21] finally yielded isonojigiku alcohol (**6**).



6 possesses a not markedly pronounced camphoraceous odour with dry woody notes, not comparable with the warm, soft, and pleasant odour of 7-*syn*-hydroxycamphene (**1**) or with its isomer 6-*exo*-hydroxycamphene (nojigiku alcohol, **2**).

Experimental

^{1}H NMR spectra: Bruker AM 400 WB (400.13 MHz) and Bruker AC-80 (80 MHz), *TMS*, δ in ppm; ^{13}C NMR spectra: Bruker AM 400 WB (100.61 MHz); IR spectra: Perkin Elmer-237, Perkin Elmer

FT-IR-Spektrometer Spectrum 2000, ν in cm^{-1}; mass spectra: Hewlett Packard MSD (GC: 5890; MS: 5970); TLC: PSC-Fertigplatte Merck Art. Nr. 13793, silica gel 60 F_{254}S with concentration zone, 20×20 cm, layer thickness 2 mm, concentration zone 4×20 cm; DC aluminum foil, Merck Art. Nr. 5717, silica gel 60 F_{254}, 20×20 cm, layer thickness 0.2 mm; for further details, see Ref. [24].

5-exo-Hydroxybicyclo[2.2.1]heptan-2-one (**11**)

Compound **11** was prepared according to Ref. [18]. 9.20 g (100 mmol) bicyclo[2.2.1]hepta-2,5-diene (**9**), 100 ml dry *THF*, 100 ml borane-*THF* complex (100 mmol), 40 ml of a 2 *M* NaOH solution in water, 40 ml 30% H_2O_2; yield of **10**: 12.1 g (94.5%), white crystals, m.p.: 183–184°C (Ref. [18]: 183.5–184.5°C), $C_7H_{12}O_2$ (128.08). 0.50 g (3.89 mmol) **10**, 50 ml acetone, 1.8 ml of a 2 *M* CrO_3 solution in 30% H_2SO_4; purification of crude **11**: column chromatography on silica gel 60, solvent system: diethyl ether/methanol (100 ml/10 drops); yield of **22**: 0.23 g (46%), colourless oily liquid, $C_7H_{10}O_2$ (126.07). IR (NaCl, liquid film): 3430, 2974, 1744 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$): $\delta = 1.71$ (m, 3H), 1.86 (br s, 1H), 2.00 (m, 3H), 2.52 (m, 2H), 4.02 (d, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 33.5$ (CH_2), 35.4 (CH_2), 39.9 (CH_2), 43.1 (CH), 48.9 (CH), 7.22 (CH), 217.2 (C = O) ppm; MS: *m/z* (%) = 126 (M^+; 59), 108 (8), 97 (12), 82 (100), 79 (35), 70 (14).

5-(O-Tetrahydropyranyl)-bicyclo[2.2.1]heptan-2-one (**12**)

0.6 g (4.76 mmol) ketoalcohol **11** were dissolved in 33 ml dry dichloromethane und mixed slowly with 0.65 ml (7.14 mmol) dried dihydropyrane at room temperature. After addition of 0.12 g (0.48 mmol) *PPTS* and stirring for 6 h, the mixture was extracted with diethyl ether, followed by washing the ether extracts with brine and drying over $MgSO_4$. After evaporation of the solvent, 0.9 g (90%) of **12** were obtained .

$C_{12}H_{18}O_3$ (210.28); IR (NaCl, liquid film): 2943, 1751 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$): $\delta = 1.56$–1.94 (m, 13H), 2.74 (m, 1H), 3.45 (m, 1H), 3.86 (m, 2H), 4.63 (d, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 19.7$ (CH_2, C-4′), 25.4 (CH_2, C-5′), 31.0 (CH_2, C-3′), 33.9 (CH_2), 34.2 (CH_2), 39.4 (CH, C-4), 40.4 (CH_2, C-3), 48.7 (CH, C-1), 62.8 (CH_2, C-6′), 75.9 (CH, C-5), 97.5 (CH, C-2′), 215.1 (C, C-2) ppm; MS: *m/z* (%) = 210 (M^+; 2), 192 (1), 168 (1), 126 (3), 109 (13), 85 (100), 81 (25), 67 (17).

3,3-Dimethyl-5-(O-tetrahydropyranyl)-bicyclo[2.2.1]heptan-2-one (**13**)

0.38 ml (2.33 mmol) cyclohexylisopropylamide in 8 ml dry *THF* were slowly mixed with 1.4 ml (2.24 mmol) of a 1.6 *M* suspension of *n*-butyllithium in *n*-hexane at −10°C under argon and warmed up to ambient temperature. Then, 0.27 g (1.36 mmol) 5-(O-tetrahydropyranyl)-bicyclo[2.2.1]heptan-2-one (**12**) und 0.21 ml (3.41 mmol) methyliodide were added at room temperature and refluxed for 18 h. Subsequent hydrolyzation with saturated ammonium chloride solution, extraction with diethyl ether, and drying over Na_2SO_4 was followed by evaporation of the solvent. The same procedure was repeated in order to obtain a geminal methylation. Purification: prep. TLC, solvent system. ligroin/EtOAc = 80/20, twofold development.

Yield: 0.4 g (90%); oily liquid; $C_{14}H_{22}O_3$ (238.33); IR (NaCl, liquid film): 2943, 1748, 1454 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$): $\delta = 1.02$ (s, 3H), 1.03 (s, 3H), 1.48–1.85 (m, 12H), 3.44 (m, 1H), 3.81 (m, 2H), 4.58 (d, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 19.4$ (CH_2, C-4′), 21.2 (CH_3, C-2″), 23.4 (CH_3, C-3″), 25.5 (CH_2, C-5′), 31.2 (CH_2, C-3′), 33.1 (CH_2), 37.4 (CH_2), 43.2 (CH), 48.3 (CH), 61.5 (C, C-3), 63.3 (CH_2, C-6′), 78.1 (CH, C-5), 98.1 (CH, C-2′), 219.4 (C, C-2) ppm; MS: *m/z* (%) = 238 (M^+; 1), 210 (1), 196 (1), 154 (4), 109 (9), 85 (100), 71 (5), 67 (15).

3,3-Dimethyl-2-methylene-5-(O-tetrahydro-pyranyl)-bicyclo[2.2.1]heptane (**14**)

0.28 g (1.18 mmol) **13** were dissolved in 4 ml of dry *THF* and cooled to 0°C. Then, 2.36 ml (2.36 mmol) of a 0.5 *M* suspension of *Tebbe*'s complex in toluene were added and stirred for 30 min at 0°C and 5.5 h at room temperature. Upon addition of 15 ml diethyl ether and 20 drops of methanol, the solution reacts vigorously under precipitation of a yellow, viscous precipitate. This was filtered through Celite® and washed with about 60 ml of diethyl ether. Subsequent column chromatography over Al_2O_3 with diethyl ether as eluent and finally evaporation of the solvent furnished 0.24 g (88%) of crude **14** as a yellow residue which was purified by prep. TLC. (ligroin/diethyl ether = 90/10, twofold development).

$C_{15}H_{24}O_2$ (236.36); IR (NaCl, liquid film): 3068, 2959, 1663, 877 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$): $\delta = 1.00$ (s, 6H), 1.45–1.90 (m, 12H), 3.43 (m, 1H), 3.82 (m, 2H), 4.13 (d, 1H), 4.43 (s, 1H), 4.67 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 20.0$ (CH_2, C-4′), 25.5 (CH_2, C-5′), 25.52 (CH_3), 29.4 (CH_3), 31.4 (CH_2, C-3′), 34.1 (CH_2), 39.1 (CH_2), 40.1 (C, C-3), 44.8 (CH), 47.4 (CH), 62.9 (CH_2, C-6′), 79.3 (CH, C-5), 97.3 (CH, C-2′), 101.3 (CH_2, C-1″), 164.6 (C, C-2) ppm; MS: *m/z* (%) = 236 (M^+; 1), 194 (1), 135 (5), 199 (2), 107 (11), 85 (100), 77 (5), 67 (11).

3,3-Dimethyl-2-methylene-bicyclo[2.2.1]heptan-5-ol (**6**) *(5-exo-hydroxycamphene)*

A solution of 0.1 g *THP* ether **14** in dry ethanol was mixed 0.01 g (0.04 mmol) of *PPTS* and stirred for 3 h at 55°C (external temperature). After evaporation of the solvent, the residue (0.104 g, 80%) was purified by sublimation.

White needles with a camphoraceous and dry woody odour; m.p.: 60–63°C; $C_{10}H_{16}O$ (152.31); IR (NaCl, liquid film): 3320, 3065, 2959, 877 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$): $\delta = 1.00$ (s, 6H), 1.32–1.91 (m, 7H), 2.65 (s, C1-H), 4.55, 4.71 (2s, 2H, $=CH_2$), 3.73 (m, HC-OH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 25.3$ (CH_3), 29.4 (CH_3), 29.7 (CH_2, C-7), 33.4 (CH_2, C-6), 41.5 (C, C-3), 46.0 (CH), 56.1 (CH), 70.3 (CH, C-5), 100.1 (CH_2, C-1″), 160.0 (C, C-2) ppm; MS: *m/z* (%) = 152 (M^+; 10), 137 (11), 121 (12), 108 (96), 93 (100), 77 (5).

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References

[1] Buchbauer G, Spreitzer H, Worm A, Bauer W, Zabern S (1998) Monatsh Chem **129**: 711
[2] Kuraray Co Ltd, Osaka City (1983) Japan Kokai Koho 84-155308; Europ Pat appl 109773
[3] Uchio Y (1978) Bull Chem Soc Jpn **51**: 2342
[4] Nomura M, Fujihara Y (1987) Yukagaku **36**: 680; Chem Abstr (1988) **108**: 137677u
[5] Buchbauer G, Lebada Ph, Wiesinger L, Weiss-Greiler P, Wolschann P (1997) Chirality **9**: 380 and further references cited therein
[6] Uchida T, Matsubara Y, Nishiguchi I, Hirashima T, Ohnishi T, Kanehira K (1990) J Org Chem **55**: 2938
[7] Paukstelis JV, Macharia BW (1970) Chem Commun 131
[8] Libman J, Sprecher M, Mazur Y (1969) Tetrahedron Lett 1679
[9] Garcia Martinez A, Gomez Marin M, Subramanian LR (1978) An Quim **74**: 972
[10] Garcia Martinez A, Teso Vilar E, Garcia Fraile A, Ruano Franco R, Soto Salvador J, Subramanian LR, Hanack M (1987) Synthesis 321; Garcia Martinez A, Teso Vilar E, Garcia Fraile A, Osio Barcina J, Hanack M, Subramanian LR (1989) Tetrahedron Lett **30**: 1503

[11] Buchbauer G, Hana GW, Koch H (1976) Monatsh Chem **107**: 387
[12] Buchbauer G, Spreitzer H, Gruber A, Lux C, Wolfsberger A, Kalchhauser H (1994) Monatsh Chem **125**: 335
[13] Buchbauer G, Spreitzer H, Kneidinger M (1990) Monatsh Chem **121**: 549
[14] Buchbauer G, Hana GW, Koch H (1978) Arch Pharm **323**: 367
[15] Buchbauer G, Koch H (1978) Chem Ber **111**: 2533
[16] Wachter A (1989) Master thesis, University of Vienna
[17] Bauer I (1990) Master thesis, University of Vienna
[18] Gagnon R, Gagnon G, Roberts SM, Villa R, Willetts AJ (1995) J Chem Soc Perkin Trans 1, 1505
[19] Zweifel G, Nagase K, Brown HC (1962) J Am Chem Soc **84**: 183
[20] Brown HC, Knights EF, Scouten CS (1974) J Am Chem Soc **96**: 7765
[21] Miyashita M, Yoshikoshi A, Grieco PA (1977) J Org Chem **42**: 3727
[22] Pine SH, Shen GS, Hoang H (1991) Synthesis 165
[23] Tebbe FN, Parshall GW, Reddy GS (1978) J Am Chem Soc **100**: 3611
[24] Buchbauer G, Zechmeister-Machhart F, Weiß-Greiler P, Wolschann P (1997) Arch Pharm **330**: 112

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