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Alkynylborneol Derivatives and Their Spatial Structures

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Recently we took interest in chiral propargylic alcohols derived from (l-R)-(+)-camphor. We were amazed to find no less than 16 citations in the literature from 1929 to 1994, but a total confusion as to purity, melting points, and assignments of stereostructures for the camphor (**1**)/acetylene addition products **2** and **3**.Therefore, we decided to clarify the situation.

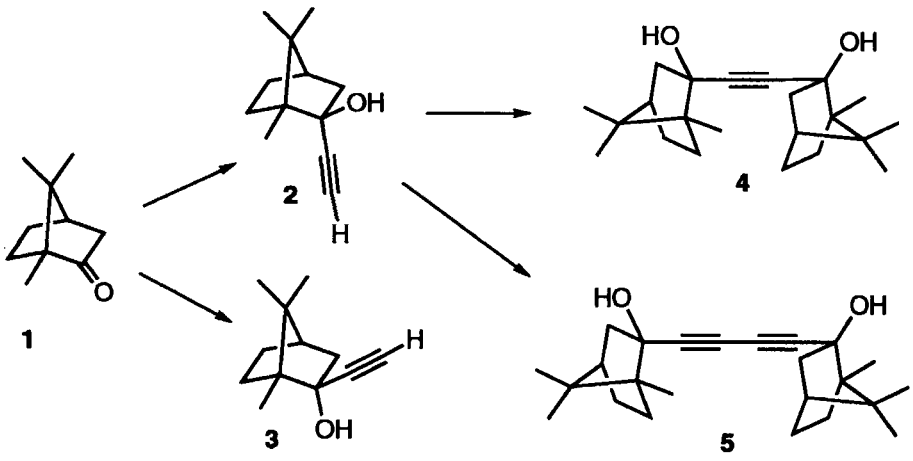
We find that adducts of **1** with alkali metal acetylide are rather difficult to purify. A major (m.p. 55 °C, positive rotation) and a minor stereoisomer (m.p. 121°C, negative rotation sence) are formed under most sets of conditions. They can be isolated by repeated careful column chromatography. Analysis by gas chromatography indicates, however, that in most cases small quantities of **1** (m.p. 179–181°C; $[a]_D^{25}$ +44.1°) are present in supposedly "pure" chromatographed and recrystallized samples of **2** and **3**. Another complication arises from the fact that (major compound) **2** can react a second time under the condition of its formation giving rise to **4** (m.p. 209–210 °C) as a further impurity. Even small concentrations of **1** and **4** have a profound influence on melting points. Table 1 presents the results from the literature along with our data (for configurational assignments, see below).

Reactions at room temperature and below in solvents such as THF and ether give mostly **2**. We can confirm that the addition of acetylene to **1** is reversible in the presence of powdered KOH in N-methylpyrrolidone and that **3** is formed in relatively higher concentration on prolonged interaction of **1** and acetylene/KOH in that solvent (cf. [11]). It is difficult, however, to control this specific reaction and to get reproducible results even if conditions are seemingly constant: The transformation of **2** back into **1** and then into **3** competes with the formation of **4**.

The C,H-COSY spectrum permitted the assignment of all ^1H and ^{13}C signals of **2**, but a total interpretation of the spec-

Table 1 Literature data on compounds **2** and **3**, compared to the present work

m.p. °C	α_D [°C]	Value	isomer assigned	year	lit.
205	–	+22.5° (50% in EtOH)	?	1929	[1]
85			?	1934	[2]
97–98			?	1937	[3]
56–60			?	1936	[4]
54–56			?	1944	[5]
63			?	1955	[6]
68–69	20	+16.35° (EtOH)	?	1958	[7]
55	20	+17.7° (c=20, EtOH)	?	1959	[8]
55	–	+19.3°	?	1959	[9]
87	–	–14.22°	?	1959	[9]
50	25	+15.31° (4% in EtOH)	**2**	1965	[10]
86	–	+15.3° (c=7.2, EtOH)	**2**	1968	[11]
122	25	–26.20° (EtOH)	**3**	1968	[11]
63.5–64.5			**2**	1981	[12]
207.5–209			**2**	1981	[13]
52–54			?	1982	[14]
61–62			**3**	1988	[15]
57.5–59.5			**3**	1994	[16]
55	21	+15.37° (c=20, EtOH)	**2**	this work	
121	20	–18.89° (c=0.7, EtOH)	**3**	this work	



tra of **3** was not possible due to overlapping multiplets. Even though differential anisotropic influences of OH and acetylene groups on the neighboring proton and carbon signals are apparent, these data do not allow safe assignments of relative configurations of **2** and **3**. In the recent literature [15, 16], *exo* attack of the acetylide (to give **3** as major product) was assumed. The older publications by Cadiot et al. [10, 11] reverse assignments. These authors refer to the stereochemically established *endo* addition of the methyl Grignard reagent to camphor [18]. The latter result has been the basis of many subsequent structural assignments in camphor addition chemistry.

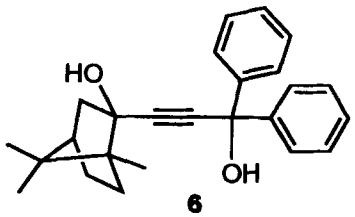
Lanthanide-induced shift experiments with $Eu(fod)_3$ were thought to clarify the situation [19]. When the ^1H NMR spectrum of the lower melting, major adduct was measured in the presence of three different concentrations $Eu(fod)_3$, strong downfield shifts were observed for (C-1)-methyl and endo-(C-7)-methyl, (C-3)H_{exo} (very strong shift), (C-3)H_{endo}, (C-6)H_{endo}, and (C-4)-H. The other, higher melting isomer exhibited strong shifts for (C-1)-methyl and endo-(C-7)-methyl, (C-3)H_{exo}, (C-3)H_{endo}, and (C-6)H_{endo}, the latter two being very strong. These effects can be explained best if one assumes association of the europium complex not only at the hydroxyl but also partially at the acetylene. The very strong influences on (C-3)H_{endo}, and (C-6)H_{endo} in the m.p. 121 °C compound are in line with the assigment of endo-OH (≡ **3**), as is the strongest shift of (C-3)H_{exo} with the exo-OH configuration (≡ **2**) in the m.p. 55 °C isomer.These absolute stereostructures fit also into the concept of preferred attack of the reagent from the bottom side.

Table 2 gives ^{13}C NMR results from the literature along with our data. We now identify the compound with a m.p. above 200 °C as **4** . Although this had been stated already in 1955 [6], a wrong structural appointment as **2** was published as late as 1981 [13].

Once the stereochemistry of **2** is granted, the configuration of the further products prepared in the present work from **2** and benzophenone, pivalophenone, and 2,4-dimethylpentandione (**4–8**) must be analogous. Best yields in the adduct formations were obtained if **2** was transformed into its THP ether prior to its conversion with butyl lithium and the ketones. A second center of chirality is present in **7**. Neverthe-

Table 2 ^{13}C Data of compounds **2**, **3**, and **4** as assigned by various authors

This work: **4**	Garratt et al. [13]: **2** (wrong)	This work: **3**	This work: **2**	Johnson et al.[15], Djuardi et al.[16]: **3**
87.6(**C**≡)	87.6(**C**≡CH)	89.3(**C**≡CH)	88.1(**C**≡CH)	88.1
78.0(C-2)	77.9(C-2)	76.0(C-2)	77.9(C-2)	77.8
—	77.9(H**C**≡C)	73.6(H**C**≡C)	71.5(H**C**≡C)	71.5
53.7(C-1)	53.7(C-1)	54.1(C-1)	53.4(C-1)	53.4
48.5(C-3)	48.5(C-3)	49.6(C-7)	48.1(C-3)	48.1
47.9(C-7)	47.9(C-7)	47.2(C-3)	47.9(C-7)	47.9
45.4(C-4)	45.4(C-4)	45.3(C-4)	45.4(C-4)	45.3
32.6(C-6)	32.6(C-5)	27.9(C-6/C-5)	32.4(C-6)	32.3
27.0(C-5)	27.0(C-6)	27.2(C-5/C-6)	26.9(C-5)	26.8
21.4(Me)	21.4(Me)	21.0(Me)	21.3(Me)	21.3
21.0(Me)	21.0(Me)	20.8(Me)	21.0(Me)	21.0
10.4(Me)	10.4(Me)	11.9(Me)	10.1(Me)	10.3



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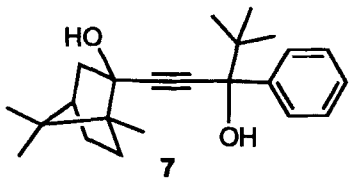

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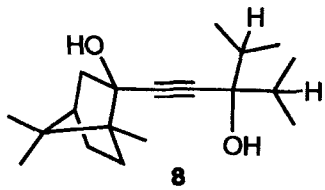

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less, the recrystallized compound was obtained as a single diastereomer, exhibiting only one *tert*-butyl group in the ^1H NMR and the expected 19 signals in the ^{13}C NMR spectrum.

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Experimental

Gas chromatography: 3m OV17 column at 100 °C, carrier gas N_2, 1 bar, Carlo Erba Fractovap 4200 instrument. Rentention times for **2**: 10.8; for **3**: 12.0 min.
^1H NMR spectra: Bruker AC 250-P (250 MHz) or AM 300 (300 MHz); ^{13}C NMR spectra: Bruker AC 250-P (62.9 MHz).

2-endo-Ethinyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-exo-ol (**2**) was prepared from **1** according to lit. methods: a) via ethinyl magnesium chloride in THF [15], b) via lithium acetylide in THF [16], or c) via sodium acetylide in liquid ammonia [9]. The crude material was purified as stated in the references via the silver salt, then chromatographed (silicagel, petroleum ether (b.p. 60 °C)/ether 4 : 1, and recrystallized. m.p. 55 °C. – ^1H NMR: δ 2.45 (s, 1 H, ethinyl-H), 2.22 (ddd, 1 H, J = 3.4, 4.1, 13.5 Hz, (C-3)H_{exo}), 1.97(s, 1H, OH), 1.95–1.85 (m, 1 H, (C-6)H_{endo}), 1.90–1.86 (m, 1 H, (C-3) H_{endo}), 1.76 (dd 1 H, J = 4.1, 4.5 Hz, (C-4)H), 1.72–1.63 (m, 1 H, (C-5)H_{exo}), 1.53–1.37 (m, 1 H, (C-6)H_{exo}), 1.24–1.08 (m, 1 H, (C-5)H_{endo}), 1.06 (s, 3 H, exo-(C-7)-CH_3), 0.96 (s, 3 H, (C-1)-CH_3), 0.88 (s, 3 H, endo-(C-7)-CH_3).

2-exo-Ethinyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-endo-ol (**3**) *and 1,2-Di(2-exo-hydroxy-2-endo-bornyl)ethyne* (**4**) (cf. [11]):

60 g (0.39 mol) of **1** were dissolved in 150 ml of freshly distilled N-methylpyrrolidone and a stream of acetylene gas was passed through for 2 h. 97 g (1.73 mol) of powdered KOH were added slowly within 30 min. in such a way that the temp. never exceeded 20 °C. The mixture was stirred for 90 h at room temperature. Within that period, more acetylene was introduced (twice for 1 h each time). In the end the reaction mixture was poured onto ice, and the precipitate was filtered and washed with saturated aqueous NH_4Cl. The brownish solid was taken up in ether and dried (Na_2S0_4). The relative proportions of **2**, **3**, and **4** varied strongly among parallel experiments. Typically 13–24% of **3** and up to 40% of **4** were obtained along with unreacted **1** and much **2**.
Repeated recrystallization of the crude product from petroleum ether furnished **4**, m.p. 209–210 °C, $[\alpha]_D^{24}$ = + 24.7° (c= 3.01, EtOH). – ^1H NMR (250 MHz): δ 6.23 (m, 2 H, (C-3 and C-3')H_{exo}), 2.03 (broad s, 2 H, OH), 1.89–1.63 (m, 8 H), 1.53–1.41 (m, 2 H, (C-6 and C-6')H_{exo}), 1.19–1.09 (m, 2 H, (C-5 and C-5')H_{endo}), 1.06 (s, 6 H, exo-(C-7 and C-7')-CH_3), 0.94 (s, 6 H, (C-1 and C-1')-CH_3), 0.87 (s, 6 H, endo-(C-7 and C-7')-CH_3).
The mother liquids of **4** were worked up by column chromatography (silica gel, petroleum ether (b.p. 60 °C)/ether 4:1). After **2**, **3** was eluted. m.p. 121 °C , $[\alpha]_D^{30}$ = –18.89° (c= 0.7, EtOH). – ^1H NMR (250 MHz): δ 2.59 (s, 1 H, ethinyl-H), 2.52–2.43 (m, 1 H, (C-3)H_{exo}), 2.16–2.05 (m, 1 H, (C-6)H), 1.95 (s, 1 H, OH), 1.81–1.69 (m, 2 H, (C-4)H, (C-5)H), 1.49 (d, 1 H; J=13.6 Hz, (C-3)H_{endo}), 1.43–1.29(m, 1 H, (C-6)H), 1.28–1.26 (m, 1 H, (C-5)H), 1.10 (s, 3 H, (C-7)-CH_3), 0.99 (s, 3 H, (C-1)-CH_3), 0.90 (s, 3 H,(C-7 CH_3).

1,4-Di(2-exo-hydroxy-endo-2-bornyl)butadiyne (**5**):

3 g (16.85 mmol) **2** in 80 ml of ethanol were dropped slowly into a solution of 6.8 g of NH_4Cl and 4.3 g of Cu_2Cl_2 in 50 ml of water. The mixture was warmed to 50 °C. Air was bubbled through at this temperature for 21 h (distributed over 3 d; in the nights the reaction was stirred at room temp., and three times 50 ml of ethanol each were added). In the end the mixture was cooled and extracted 4 times with 30 ml portions of ether. The aqueous phase was evaporated to dryness, and the residue was extracted repeatedly with boiling ether. The combined etheral extracts were dried (Na_2SO_4) and concentrated. The forming solid was recrystallized from petroleum ether to give 1.4 g (47%) of colorless **5**, m.p. 239–240 °C (lit. m.p. 242 °C [6]). – $[\alpha]_D^{30}$ = + 32.4°(c= 1, EtOH). – ^1H NMR (250 MHz): δ 2.26–2.18 (m, 2 H, (C-3 and C-3')H_{exo}), 2.05 (s, 2 H, OH), 1.91–1.65 (m, 8 H), 1.55–1.43 (m, 2 H, (C-6 and C-6')H_{exo}), 1.20–1.10 (m, 2 H, (C-5 and C-5')H_{endo}) 1.05 (s, 6 H, exo-(C-7 and C-7')-CH_3), 0.96 (s, 6 H, (C-1 and C-1')-CH_3), 0.87 (s, 6 H, endo-(C-7 and C-7')-CH_3). – ^{13}C NMR: δ 83.4 (ethinyl-C), 78.6 (C-2, C-2'), 68.1 (ethinyl-C), 54.1 (C-1, C-1'), 48.09 (C-3,C-3'), 48.07 (C-7, C-7'), 45.3 (C-4, C-4'), 32.4 (C-6, C-6'), 26.9 (C-5, C-5'), 21.3 (endo(C-7 and C-7')-C), 20.9 (exo-(C-7 and C-7')-C), 10.3 ((C-1 and C-1')-C).

Transformation of 2 into 6–8 (general procedure):

a) *Formation of the 2 THP ether*: 17.8 g (100 mmol) of **2** were treated with 9.24 g (110 mmol) of 3,4-dihydro-2H-pyrane and 0.5 ml of conc. aqueous HCl under cooling and stirring. After 12 h at room temp., 1 g solid KOH was added, and the mixture was filtered 15 min. later. The liquid was distilled in a kugelrohr at 80–120 °C/15 Torr and used as such.

b) *Li acetylide formation and carbonyl addition*: 3.9 g (15 mmol) of the THP ether was dissolved in 30 ml of dry THF, cooled to –70 °C, and 10 ml of a 1.6 M butyl lithium solution in pentane (16 mmol) was dropped in. After 15 min. of stirring at –70 °C, 15 mmol of the ketone in 10 ml of dry THF was added slowly. After continued stirring over night at room temperature, 25 ml of a saturated aqueous NH_4Cl solution was added. Usual workup was followed by cleavage of the THP ether: The residue was taken up in 30 ml of methanol and treated with 200 mg of p-toluene sulfonic acid (2h at 50 °C, 12 h at room temperature). Methanol was removed in vacuo, the residue was worked up with ether, and washed with aqueous Na_2CO_3. The aqueous phases were re-extracted with ether, the combined organic extracts were dried (Na_2SO_4) and concentrated. The crude products were purified by chromatography on silicagel with petroleum ether (b.p. 60 °C)/ether 1:1.

2-endo-(3-Hydroxy-3,3-diphenylprop-1-inyl)1,7,7-trimethylbicyclo[2.2.1]heptan-2-exo-ol (**6**)

m.p. 87–88 °C, $[\alpha]_D^{24}$ = +23.5° (c = 2, EtOH). – ^{1}H NMR (250 MHz): δ 7.61–7.56 (m, 4 H, $H_{arom.}$), 7.35–7.21 (m, 6 H, $H_{arom.}$), 2.80 (s, 1 H, OH), 2.27 (ddd, 1 H; J = 3.4, 4.1, 13.5 Hz, (C-3)H_{exo}), 2.04 (s, 1 H, OH), 1.96–1.11 (m, 6 H), 1.07 (s, 3 H, exo-(C-7)-CH_3), 0.97 (s, 3 H, (C-1)-CH_3), 0.88 (s, 3 H, endo-(C-7)-CH_3). – ^{13}C NMR: δ 145.1, 144.7, 128.33, 128.26, 127.6, 126.0, 125.92, 125.90 ($C_{arom.}$), 91.6, 90.1 (ethinyl-C), 86.3, 74.5 (C -2, C-OH), 53.8 (C-1), 48.3 (C-3), 48.0 (C-7), 45.4 (C-4), 32.5 (C-6), 27.0 (C-5), 21.3 (endo-(C-7)-C), 21.0 (exo-(C-7) C), 10.5 ((C-1)-C). – Anal. calcd. for $C_{25}H_{28}0_2$ (360.5): C 83.29 H 7.83; found C 83.01 H 7.50.

2-endo-(3-Hydroxy-4,4-dimethyl-3-phenylpent-1-inyl)1,7,7-trimethylbicyclo[2.2.1]heptan-2-exo-ol (**7**)

m.p. 95–98 °C, $[\alpha]_D^{24}$ = +15.18° (c = 2.02, EtOH). – ^{1}H NMR (250 MHz): δ 7.60–7.56 (m, 2 H, $H_{arom.}$), 7.33–7.27 (m, 3 H, $H_{arom.}$), 2.33 (s, 1 H, OH), 2.25 (ddd, 1 H; J = 3.5, 4.0, 13.4 Hz (C-3) H_{exo}), 2.03 (s, 1 H, OH), 1.95–1.88 (m, 2 H, (C-3)H_{endo}, (C-6)H_{exo}), 1.80–1.43 (m, 4 H, (C-4)H, (C-5)H_{endo}, (C-5)H_{exo}, (C-6)H_{endo}), 1.07 (s, 3 H, exo-(C-7)-CH_3) 1.00 (s, 9 H, *tert.*butyl), 0.97 (s, 3 H, (C-1)-CH_3), 0.89 (s, 3 H, endo-(C-7)-CH_3). – ^{13}C NMR: δ 142.3, 128.5, 126.5 ($C_{arom.}$), 90.0, 86.7 (ethinyl-C), 78.9, 78.2 (C-2, C-OH), 53.7 (C-1), 48.5 (C-3), 48.0 (C-7), 45.4 (C-4), 39.7 (quart. C of *tert.*butyl), 32.6 (C-6), 27.0 (C-5), 25.3 (Me of *tert.*butyl), 21.4 (endo-(C-7)-C), 20.9 (exo-(C-7)-C), 10.5 ((C-1)-C). Anal. calcd. for $C_{23}H_{32}O_2$ (340.5): C 81.13 H 9.47; found C 81.08 H 9.60.

2-endo-(3-Hydroxy-3-isopropyl-4-methylpent-1-inyl)1,7,7-trimethylbicyclo[2.2.1]heptan-2-exo-ol (**8**)

m.p. 89 °C, $[\alpha]_D^{24}$ = +10.61°(c= 1, EtOH). – ^{1}H NMR (250 MHz): δ 2.23 (ddd, 1 H; J = 3.4, 4.1, 13.4 Hz, (C-3)H_{exo}), 2.00–1.90 (m, 2 H, (C-3)H_{endo}, (C-6)H_{endo}), 1.86 (s, 1 H, OH), 1.81 (s, 1 H, OH), 1.78–1.63 (m, 4 H, (C-4)H, (C-5)H_{exo}, H of *i*-Pr), 1.53–1.41 (m, 1 H, (C-6)H_{exo}), 1.28–1.11 (m, 1 H, (C-5)H_{endo}), 1.06 (s, 3 H, exo-(C7)-CH_3), 1.03 (d, 3 H; J = 6.8 Hz, Me of *i*-Pr), 1.01 (d, 3 H; J = 6.8 Hz, Me of *i*-Pr), 1.00 (s, 3 H, (C-1)-CH_3), 0.97 (d, 3 H; J = 7.3 Hz, Me of *i*-Pr), 0.94 (d, 3 H; J = 7.3 Hz, Me of *i*-Pr), 0.87 (s, 3 H, endo-(C-7)-CH_3). – ^{13}C NMR: δ 89.6, 84.7 (ethinyl-C), 78.0, 77.5 (C-2, C-OH), 53.6 (C-l), 48.6 (C-3), 47.9 (C-7), 45.4 (C-4), 34.49, 34.46 (*tert.* C of *i*-Pr), 32.6 (C-6), 27.0 (C-5), 21.4 (endo-(C-7)-C), 21.0 (exo-(C-7)-C), 16.41, 16.37 (Me of *i*-Pr), 10.4 ((C-1)-C).
Anal. calcd. for $C_{19}H_{32}O_2$ (292.5): C 78.03 H 11.03; found C 77.48 H 11.17.

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[19] We thank a referee for suggesting these experiments, even if the outcome is not as clear-cut as expected

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