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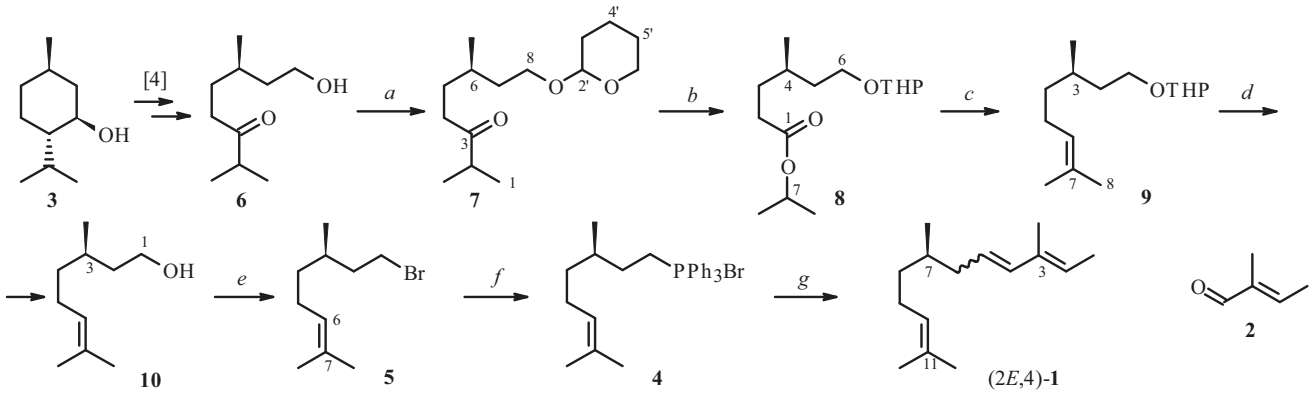
STEREOSELECTIVE SYNTHESIS OF THE ANTILEUKEMIC SESQUITERPENE (+)-CAPARRATRIENE FROM L-MENTHOL AND TIGLIC ALDEHYDE

V. A. Vydrina, A. A. Kravchenko, M. P. Yakovleva,*
N. M. Ishmuratova, and G. Yu. Ishmuratov

*A stereoselective synthesis of natural (+)-caparratriene was developed starting from commercially available L-menthol and tiglic aldehyde. The key step was a Wittig reaction of the latter with the triphenylphosphorane generated from (*R*)-(–)-citronellyl bromide. (+)-Caparratriene as a mixture (4:1) of 2*E*,4*E*- and 2*E*,4*Z*-stereoisomers is a known anticancer agent.*

Keywords: (+)-caparratriene, L-menthol, tiglic aldehyde, Wittig reaction, (*R*)-(–)-citronellyl bromide.

The sesquiterpenoid 3,7*R*,11-trimethyldodeca-2*E*,4*E*,10-triene [(+)-caparratriene, **1**] was isolated from the Colombian tree *Ocotea caparrapi* and possessed significant pharmacological activity including antileukemic [1]. It was prepared previously in racemic [2] and optically active forms [3] using (±)- and (+)-citronellal and tiglic aldehyde (**2**) as starting materials. Various modifications of the Wittig reaction were most often used in the key step of forming the (2*E*,4*E*)-diene fragment of the target caparratriene (**1**). The carbon skeleton of tiglic aldehyde (**2**) was incorporated after converting it through the corresponding alcohol, bromide, and phosphonium salt into the allylic triphenylphosphorane.



a. DHP/Et_2O; *b*. *m*-CPBA; *c*. 1. DIBAH/THF, –70°C, 2. Pr^iPPhI/Bu^nLi; *d*. PPTS/Et_2O; *e*. PBr_3/Py; *f*. PPh_3; *g*. 1. Bu^nLi/THF, 2. **2**, 20°C (DHP = 3,4-dihydro-2*H*-pyran; *m*-CPBA = *meta*-chloroperbenzoic acid; DIBAH = diisobutylaluminum hydride; PPTS = pyridinium *p*-toluenesulfonate)

A new synthetic scheme for an analog of **1**, 3,7*R*,11-trimethyldodeca-2*E*,4,10-triene [(2*E*,4)-**1**], was elaborated starting from L-menthol (**3**) and tiglic aldehyde (**2**). It was based on Wittig olefination using starting conjugated aldehyde **2** as the carbonyl component. The required ylide was generated from triphenylphosphonium salt **4** of (*R*)-(–)-citronellyl bromide (**5**) using *n*-butyllithium. In turn, optically pure bromide **5** was obtained via chemo- and regioselective transformations of ketoalcohol **6**, the preparation of which from L-menthol (**3**) in four steps through (–)-menthyl lactone was reported earlier by us [4]. Further transformations aimed at (*R*)-(–)-citronellyl bromide (**5**) included regiospecific Baeyer–Villager oxidation of tetrahydropyranyl (THP) derivative **7** of hydroxyketone **6**, one-pot low-temperature (–70°C) hydride reduction of the resulting

Ufa Institute of Chemistry, Russian Academy of Sciences, 71 Prosp. Oktyabrya, Ufa, 450054; e-mail: insect@anrb.ru.
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isopropyl ester **8**, olefination of the intermediate aldehyde by isopropylidenetriphenylphosphorane, and removal of the THP protection from **9** to give (*R*)-(+)-citronellol (**10**). The overall yield of target (2*E*,4)-**1** as a mixture (4:1) of the 2*E*,4*E*- and 2*E*,4*Z*-stereoisomers (according to GC and PMR data) calculated for L-menthol (**3**) was 16%.

EXPERIMENTAL

PMR and IR spectra were obtained on equipment of the Khimiya CUC at UfIC, RAS. IR spectra were recorded from thin layers on an IR-Prestige-21 FTIR spectrophotometer (Shimadzu). NMR spectra were taken in $CDCl_3$ solutions with TMS internal standard on a Bruker AM-300 spectrometer (operating frequency 300.13 MHz for ^1H and 75.47 MHz for ^{13}C). Chromatography was performed on Chrom-5 [1.2-m column, SE-30 silicone (5%) stationary phase on Chromaton N-AW-DMCS (0.16–0.20 mm, operating temperature 50–300°C] and Shimadzu GC-9A instruments (25-m quartz capillary column, OV-101 stationary phase, operating temperature 80–280°C) with He carrier gas. Optical rotation was measured on a Perkin-Elmer 241 MC polarimeter. TLC monitoring used Sorbfil SiO_2 (Russia). Tiglic aldehyde (99%) was purchased (Sigma-Aldrich). Isolation and chromatography used methyl-*t*-butylether (MTBE) and petroleum ether (40–70°C, PE).

2,6*R*-Dimethyl-8-(tetrahydro-2*H*-pyran-2-yloxy)octan-3-one (7). Hydroxyketone **6** (5.00 g, 29.1 mmol), which was prepared from L-menthol (**3**) in four steps in 75% yield [4], in Et_2O (38 mL) was treated with DHP (4.47 g, 53.2 mmol, 8.9 mL), and TsOH (0.10 g, 0.6 mmol), stirred for 24 h at room temperature, diluted with Et_2O (100 mL), washed successively with $NaHCO_3$ solution (10%) and saturated NaCl solution, dried over Na_2SO_4, and evaporated to afford **7** (7.22 g, 97%), $[\alpha]_D^{20}$ +18.0° (*c* 0.5, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.89 (3H, d, J = 6.2, CH_3-6), 1.06 (6H, d, J = 6.8, H-1, CH_3-2), 1.00–1.40 (1H, m, H-6), 1.40–1.70 (8H, m, H-5, 7, 4′, 5′), 1.80–2.20 (2H, m, H-3′), 2.43–2.52 (2H, m, H-4), 2.53 (1H, septet, J = 6.8, H-2), 3.60–3.70 (4H, m, H-8, 6′), 4.50 (1H, br.s, H-2′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 18.27 (CH_3, C-1, CH_3-2), 19.30 (CH_3, CH_3-6), 19.53 and 19.64 (CH_2, C-4′), 25.41 and 25.45 (CH_2, C-5′), 29.60 (CH, C-6), 29.78 (CH_2, C-5), 30.70 and 30.73 (CH_2, C-3′), 36.35 (CH_2, C-7), 37.80 (CH_2, C-4), 40.60 (CH, C-2), 62.28 and 62.80 (CH_2, C-6′), 65.70 (CH_2, C-8), 98.69 and 98.90 (CH, C-2′), 214.40 (C, C-3).

Isopropyl Ester of 4*R*-Methyl-6-(tetrahydro-2*H*-pyran-2-yloxy)hexanoic Acid (8). A suspension of a mixture (9.40 g) containing *m*-CPBA (75%, 35.0 mmol) in anhydrous $CHCl_3$ (94 mL) at room temperature was treated dropwise with a solution of **7** (7.10 g, 27.7 mmol) in anhydrous $CHCl_3$ (63 mL); stirred for 48 h; diluted with CH_2Cl_2 (100 mL); washed successively with saturated solutions of $NaHCO_3$, $Na_2S_2O_3$ and NaCl; dried over $MgSO_4$; and evaporated to afford **8** (6.41 g, 85%), $[\alpha]_D^{20}$ +2.6° (*c* 0.38, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, d, J = 6.2, CH_3-4), 1.21 (6H, d, J = 6.3, CH_3-7), 1.00–1.40 (1H, m, C-4), 1.50–1.70 (8H, m, H-3, 5, 4′, 5′), 1.80–2.20 (2H, m, H-3′), 2.20–2.35 (2H, m, H-2), 3.60–3.70 (4H, m, H-6, 6′), 4.96 (1H, septet, J = 6.3, H-7), 4.55 (1H, br.s, H-2′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 19.28 (CH_3, CH_3-4), 19.52 (CH_2, C-4′), 21.13 (CH_3, $2CH_3$-7), 25.41 (CH_2, C-5′), 29.58 (CH, C-4), 30.69 (CH_2, C-3′), 32.01 (CH_2, C-2), 32.34 (CH_2, C-3), 36.26 (CH_2, C-5), 62.80 (CH_2, C-6′), 65.71 (CH_2, C-6), 67.52 (CH, C-7), 98.70 (CH, C-2′), 173.58 (C, C-1).

3*R*,7-Dimethyloct-6-en-1-ol (10). A solution of isopropylidenetriphenylphosphorane was prepared by adding a solution of *n*-BuLi in hexane (21.9 mL, 25.6 mmol, 1.17 N) at –70°C (Ar) to a suspension of *i*-$PrPPh_3I$ (1.10 g, 25.6 mmol) [5] in anhydrous THF (59 mL), storing for 1 h at room temperature, adding successively at –70°C (Ar) a solution of **8** (6.30 g, 23.2 mmol) in anhydrous THF (20 mL) and a solution of DIBAH in toluene (11.8 mL, 47.2 mmol, 73%), storing (–70°C, 1 h; 20°C, 16 h), treating with cold H_2O (48 mL), and filtering through a Schott filter. The filtrate was dried over Na_2SO_4, filtered, and evaporated. The solid was dissolved in MTBE (100 mL), filtered through a thin layer of Al_2O_3 (5 cm), and evaporated. The solid was chromatographed over silica gel (PE–MBTE, 10:1→5:1) to afford **9** (3.06 g, 55%), R_f 0.6 (PE–MTBE, 2:1). The IR and PMR spectral data were identical to those reported earlier [6]. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 17.5 and 25.5 (CH_3, $2CH_3$-7), 19.6 (CH_3, CH_3-3), 19.6 (CH_2, C-4′), 24.8 (CH_2, C-5′), 25.4 (CH_2, C-5), 29.6 (CH, C-3), 30.7 (CH_2, C-3′), 37.2 (CH_2, C-2), 39.2 (CH_2, C-4), 62.1 (CH_2, C-6′), 65.8 (CH_2, C-1), 98.8 (CH, C-2′), 124.8 (CH, C-6), 130.3 (C, C-7). A solution of THP ester **9** (2.95 g, 12.3 mmol) and PPTS (0.31 g, 1.23 mmol) [7] in MeOH (98 mL) was stirred at 55°C for 3 h. The solvent was vacuum evaporated. The solid was chromatographed over silica gel to afford **10** (1.92 g, 97%), R_f 0.5 (PE–MTBE, 2:1), $[\alpha]_D^{22}$ +5.51° (neat), lit. $[\alpha]_D^{22}$ +5.52° (neat) [8]. IR, PMR, and ^{13}C NMR spectral data were identical to those reported earlier [9].

***R*-Citronellyl Bromide (5).** A solution of **10** (1.90 g, 12.2 mmol) and Py (0.17 mL, 2.1 mmol) in anhydrous Et_2O (12 mL) was treated dropwise at –15°C (Ar) with PBr_3 (0.4 mL, 4.1 mmol), stirred at –15°C for 2 h and at room temperature for 15 h, diluted with Et_2O (50 mL), poured into ice water (15 mL), and extracted with Et_2O. The combined extract was washed successively with saturated solutions of $NaHCO_3$ and NaCl, dried over $MgSO_4$, and evaporated. The solid was chromatographed (SiO_2, hexane) to afford **5** (2.45 g, 92%), $[\alpha]_D^{22}$ –6.61° (neat), lit. $[\alpha]_D^{22}$ –6.56° (neat) [6]. IR, PMR, and ^{13}C NMR spectral data were identical to those reported earlier [10].

Citronellyltriphenylphosphonium Bromide (4). Triphenylphosphine (2.66 g, 10.1 mmol) and bromide **5** (2.30 g, 10.5 mmol) were placed into a molybdenum-glass ampul that was sealed, heated at 150°C for 3 h, and cooled. The contents were rinsed on a Schott filter with petroleum ether to afford phosphonium salt **4** (4.63 g, 95%).

3,7*R*,11-Trimethyl-2*E*,4,10-dodecatriene [(2*E*,4)-1]. A solution of the alkylidenetriphenylphosphorane was prepared by adding *n*-BuLi in hexane (8.3 mL, 9.6 mmol, 1.17 M) at –70°C (Ar) to a suspension of **4** (4.60 g, 9.6 mmol) in anhydrous THF (22 mL), storing for 1 h at room temperature, adding at 0°C a solution of **2** (0.86 g, 10.2 mmol) in anhydrous THF (10 mL), storing at 20°C for 16 h, adding H_2O (10 mL), storing for 1 h, drying over Na_2SO_4, and evaporating. The solid was diluted with Et_2O (50 mL), filtered through a layer of Al_2O_3 (5 cm), and evaporated. The solid was chromatographed over silica gel (PE–Et_2O, 10:1→5:1) to afford the triene [(2*E*,4)-**1**, 1.14 g, 58%], R_f 0.74 (PE–MTBE, 2:1). ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): (value wite note * is related to 2*E*,4*Z*-isomer of compound **1**) 0.90 (3H, d, J = 7.0, CH_3-7), 1.10–1.25 (1H, m, Ha-8), 1.33–1.41 (1H, m, Hb-8), 1.47–1.60 (1H, m, H-7), 1.62 (2.4H, s, CH_3-3-*trans*), 1.66 (0.6H, s, CH_3-3-*cis*)*, 1.70 and 1.74 (6H, both s, $2CH_3$-11), 1.70 (0.6H, d, J = 7.1, H-1-*cis*)*, 1.72 (2.4H, d, J = 7.0, H-1-*trans*), 1.89–2.13 (3.8H, m, Ha-6, Hb-6-*trans*, H-9), 2.18–2.26 (0.2H, m, Hb-6-*cis*), 5.12 (1H, t, J = 7.0, H-10), 5.23–5.31 (0.2H, m, H-5-*cis*)*, 5.42 (0.2H, q, J = 7.1, H-2-*cis*)*, 5.45 (0.8H, q, J = 7.0, H-2-*trans*), 5.48–5.60 (0.8H, m, H-5-*trans*). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 12.09 (CH_3, CH_3-3), 13.53 (CH_3, C-1)*, 13.63 (CH_3, C-1), 16.45 (CH_3, CH_3-3)*, 17.59 and 25.09 (both CH_3, C-12, CH_3-11), 17.59 and 25.09 (both CH_3, C-12, CH_3-11)*, 19.47 (CH_3, CH_3-7), 19.58 (CH_3, CH_3-7)*, 25.64 (CH_2, C-9), 25.65 (CH_2, C-9)*, 33.10 (CH, C-7), 33.22 (CH, C-7)*, 35.50 (CH_2, C-6)*, 36.73 (CH_2, C-8), 36.73 (CH_2, C-8)*, 40.34 (CH_2, C-6), 124.27 (CH, C-2), 124.41 (CH, C-2)*, 124.92 (CH, C-10), 124.92 (CH, C-10)*, 125.67 (CH, C-5), 128.38 (CH, C-5)*, 130.98 (C, C-11), 130.98 (C, C-11)*, 133.55 (CH, C-4)*, 134.48 (C, C-3), 134.88 (C, C-3)*, 135.86 (CH, C-4).

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