First Total Synthesis of (+)–Caparratriene

Jing Li, Zuosheng Liu, Jiong Lan, and Yulin Li*
National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000, P.R.China

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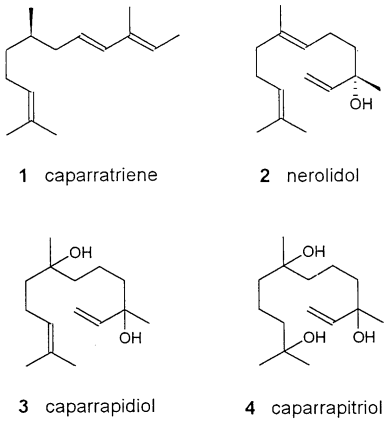
Caparratriene (**1**), a new sesquiterpene hydrocarbon with significant growth inhibitory activity against CEM leukemia cells, was first synthesized starting from (R)–(+)–citronellal through 3 steps in an overall yield of 17.5%. The absolute configuration at C_7 was determined as R.

The title compound caparratriene (**1**)[1] (Figure 1), a novel sesquiterpene hydrocarbon, was isolated from the oil of *Ocotea caparrapi* (Nates) Dugand (Lauraceae) along with other known structures such as nerolidol (**2**), caparrapi oxide, caparrapidiol (**3**) and caparrapitriol (**4**). The geometrical structure of **1**, determined by spectroscopic techniques, corresponded to (*E*,*E*)–3,7,11–trimethyl–2,4,10–dodecatriene. But its absolute stereochemistry at C_7 has not been determined yet. To our knowledge, although natural and synthetic sesquiterpene hydrocarbons isomeric with **1** have been reported in the literature,[2,3] none contains a conjugated diene substructure such as caparratriene. Besides, compound **1** expresses significant anticancer activity. In vitro testing using human leukemia cells (CEM), **1** displayed growth inhibitory activity with an IC_{50} of 3.0 ± 0.5 × 10^{-6} M (Although modest, this inhibitory value is significant given the fact that **1** was poorly soluble in the testing medium and its evaluation had to be performed as a suspension in DMSO).



1 caparratriene **2** nerolidol

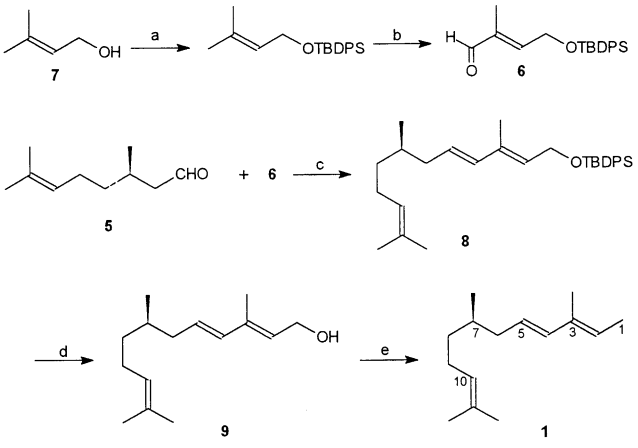
3 caparrapidiol **4** caparrapitriol

Figure 1.

As far as we know, the total synthesis of this compound has not been reported yet. In order to determine the absolute configuration of this compound and to penetrate into the studies on the biological activity of this compound and its derivatives, we select **1** as the target compound and complete the total synthesis of (+)–**1** from (R)–(+)–citronellal (**5**) through 3 steps.

The key step was the synthesis of unsymmetrical olefin by titanium (0) induced mixed carbonyl coupling reaction. It was reported by McMurry that mixed coupling reaction is particularly efficient in cases where an excess of one inexpensive carbonyl component could be used and where the major olefinic by product could be easily removed.[4,5] Thus, we selected 1 *eq.* commerically available (Aldrich Co.) (R)–(+)–citronellal **5** to couple with 3 *eq.* aldehyde **6**,[5,6] which was conveniently prepared from 3–methyl–2–buten–1–ol **7** through two steps. Fortunately, the desired product **8** was obtanied in 35% yield (evaluated basing on citronellal). Deprotection of silyl ether **8** with 1M n-$Bu_4N^+F^-$ / THF at room temperature gave allylic alcohol **9** in 96% yield.[7]

The last step was deoxygenation of allylic alcohol **9**. Compound **9** was first iodized by Ph_3P/imidazole/I_2, and then reduced by $NaBH_3CN$[8] to afford the title compound as a clear oil in 52% yield. The spectral data of key intermediate **8** and title compound **1** were compatible with the assigned structures.[9] And the specific rotation of synthetic compound **1** was determined as +19.2, which was identical with that of the natural occurring material **1** (+18.1). Since the chiral centre of (R)–(+)–citronellal was never affected in our synthetic route, the absolute stereochemistry of both the natural occurring material **1** and our synthetic compound **1** should be 7R configuration.



Scheme 1.

a) TBDPSCl, imidazole, DMF, r.t., 30 min, 100%; b) SeO_2, t-BuOOH, CH_2Cl_2, r.t., 12 h, 52%; c) $TiCl_4$/Zn, py, DME, reflux, 10 h, 35%; d) n-$Bu_4N^+F^-$ in THF (1 M), r.t., 5 h, 96%; e) 1. Ph_3P, imidazole, I_2, Et_2O/CH_3CN, 0 °C; 2. $NaBH_3CN$, HMPA, THF, Ar, 52%.

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References and Notes

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9 spectral data:
caparratriene **1** $[\alpha]_D^{20}$ +19.2 (*c* 0.1, CH_2Cl_2), (lit[1]: $[\alpha]_D^{25}$ +18.1 (*c* 0.1, CH_2Cl_2)); IR: 2957, 2924, 1643, 1455, 1377, 966 cm^{-1}; EIMS (m/z): 206(M^+, 1%), 191(11), 163(20), 149(10), 136(24), 121(52), 109(60), 95(62), 81(50), 69(100), 55(58), 41(85); ^{1}HNMR(400 MHz, $CDCl_3$): δ (ppm) 6.04 (d, J=15.7 Hz, 1H, CH=), 5.52 (dt, J=15.7 Hz, 7.9 Hz, 1H, CH=), 5.44 (q, J=6.4 Hz, 1H, CH=), 5.10 (t, J=7.4 Hz, 1H, CH=), 1.90-2.10 (m, 4H, $2CH_2$), 1.00-1.60 (m, 3H, CH_2, CH), 1.73 (s, 3H, CH_3), 1.72 (d, J=6.4 Hz, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 0.86 (d, J=6.6 Hz, 3H, CH_3)
Compound **8** $[\alpha]_D^{20}$ −2.38 (*c* 2.1, $CHCl_3$); IR: 2959, 2929, 2858, 1667, 1427, 1110, 704, 506 cm^{-1}; EIMS (m/z): 460(M^+, 2%), 403(3), 335(2), 293(2), 267(6), 253(4), 199(100), 183(7), 135(8), 105(4), 77(6), 55(3), 41(7); ^{1}HNMR (400 MHz, $CDCl_3$): δ (ppm) 7.40-7.75 (m, 10H, 2Ph-), 6.10 (d, J=15.6 Hz, 1H, CH=), 5.63 (dt, J=15.6 Hz, 7.3 Hz, 1H, CH=), 5.61 (t, J=6.3 Hz, 1H, CH=), 5.15 (t, J=7.3 Hz, 1H, CH=), 4.38 (d, J=6.3 Hz, 2H, CH_2O), 1.90-2.20 (m, 4H, $2CH_2$), 1.73 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.12-1.60 (m, 3H, CH_2, CH), 1.09 (s, 9H, Me_3C), 0.93 (d, J=6.6 Hz, 3H, CH_3).