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Note

An Efficient Total Synthesis of (2*E*,4*E*,7*R*)-Farnesa-2,4,10-triene from (*R*)-(+)-Citronellal

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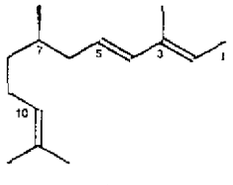
(2*E*,4*E*,7*R*)-farnesa-2,4,10-triene(Caparratriene) (**1**), a novel sesquiterpene hydrocarbon with significant growth inhibitory activity against CEM leukemia cells, was first synthesized from (*R*)-(+)-citronellal (**2**) by employing titanium-induced intermolecular carbonyl-coupling as the key step. The absolute configuration of (+)-Caparratriene was determined to be 7*R*.

INTRODUCTION

The title compound caparratriene (**1**), a novel sesquiterpene hydrocarbon, is a recently isolated compound from *Ocotea caparrapi* (Nates) Dugand (lauraceae),[1] whose oil has been used to treat many kinds of diseases such as insect and snake bites, skin ulcers, bronchitis, laryngitis, and cancerous tumors. Partial chemical studies of the oil appeared in the literature nearly one hundred years ago,[2] but no validation of components with therapeutic activity was reported until isolation of (+)-caparratriene (**1**) in 1996. 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 was not determined yet. To our knowledge, although natural and synthetic sesquiterpene hydrocarbons isomeric with **1** have been reported in the literature,[3,4] none contains a conjugated diene substructure such as caparratriene. More importantly, compound **1** exhibits significant anticancer activity.[1] We now report the total synthesis of (+)-caparratriene, which also allows the determination of its absolute configuration.



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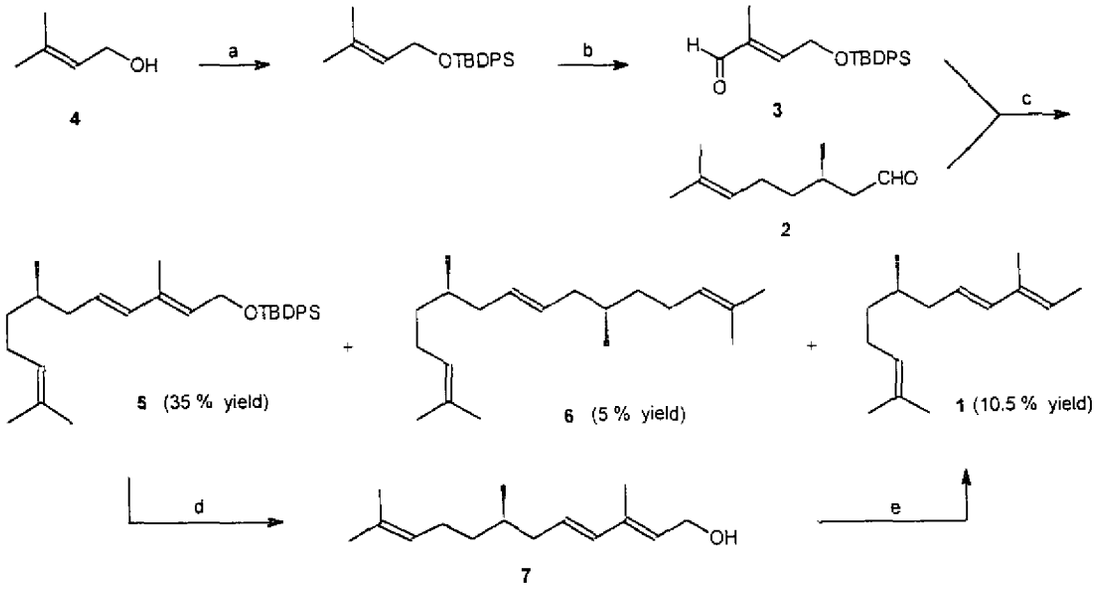
RESULTS AND DISCUSSION

Our synthetic strategy involved the synthesis of an unsymmetrical olefin by a titanium(0) induced mixed carbonyl coupling reaction. Although low-valent titanium induced carbonyl coupling reactions have been well reviewed by McMurry and some intermolecular mixed carbonyl coupling reactions were also reported,[5,6] the utilization of $TiCl_4$/Zn in the mixed carbonyl coupling of aldehydes to form unsymmetrical olefins was not investigated. Employing this coupling as the key step, we completed the total synthesis of (+)-**1** from (*R*)-(+)-citronellal (**2**) in three steps as shown in Scheme I.

It was reported by McMurry that the 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.[6] Thus, we selected 1 *eq.* commercially available (Aldrich Co.) (*R*)-(+)-citronellal **2** to couple with 3 *eq.* Aldehyde **3**,[6,7] which was conveniently prepared from 3-methyl-2-buten-1-ol (**4**) in two steps (protection with TBDPSCl, followed by oxidation with SeO_2/*t*-BuOOH). Fortunately, the desired product **5** was obtained in 35% yield (based on citronellal) along with a small amount of symmetrical olefinic products. Interestingly the title compound **1** was also obtained (10.5% yield) in this reaction. (It can be separated from **6** by HPLC). The reason is that the *tert*-butyldiphenylsiloxy protecting group can apparently be reductively removed from the product **5** during reflux with the $TiCl_4$/Zn system over a two hour period.

After deprotection of silyl ether **5** with 1 M *n*-$Bu_4N^+F^-$ in THF at room temperature, allylic alcohol **7** was afforded in 96% yield.[8] The last step was deoxygenation of allylic alcohol **7**. Compound **7** was first iodinated with Ph_3P/imidazole/I_2, and then reduced with $NaBH_3CN$[9] to afford the target compound **1** as a colorless oil in 52% yield. The spectral data of compound **1** was compatible with the assigned structure. The specific rotation of synthetic compound **1** was de-

Scheme I



(a) *tert*-Butylchlorodiphenylsilane(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, dimethoxyethane(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%.

termined as +19.2, which was almost identical to the naturally occurring material (+18.1).[1] Since the chiral center of starting material (*R*)-(+)-citronellal was never affected in our synthetic route, it is obvious that the absolute stereochemistry of both naturally occurring **1** and our synthetic **1** should be 7*R*.

Thus, a facile and efficient total synthesis of (+)-caparratriene **1** was achieved from readily available starting materials in three steps in 35% overall yield. The absolute configuration of (+)-**1** was determined by synthesis. Further investigations on the physiological activity of compound **1** and its precursors or derivatives such as compound **5**, **6**, and **7** are in progress in our laboratory.

EXPERIMENTAL SECTION

General Experimental Procedures

^{1}H NMR spectra were recorded on a Varian FT-80A or Bruker AM-400 spectrometer and ^{13}C NMR spectra were recorded on 100 MHz spectrometer in $CDCl_3$ solution using TMS as internal reference. IR spectra were obtained using a FT-170SX (film) spectrophotometer. Mass spectra were measured on a VG ZAB-HS spectrometer by direct inlet at 70 eV, and signals given in *m/z* with relative intensity (%) in brackets. Optical rotation measurements were carried out on a Perkin-Elmer 141 polarimeter. All solvents were freshly purified and dried by standard techniques prior to use. All reactions were routinely carried out under an inert atmosphere of Ar, and monitored by TLC. Purification of products was conducted by flash column chromatography (FCG) on silica gel (200~300 mesh) purchased from *Qing Dao Marine Chemical Co.* (*R*)-(+)-citronellal and 3-methyl-2-buten-1-ol were purchased from Aldrich Co. In the workup, all organic phases were washed with H_2O, then brine, dried ($MgSO_4$) and filtered prior to rotary evaporation of the solvent under reduced pressure.

(*E*)-4-(*tert*-Butyldiphenylsiloxy)-2-methyl-but-2-enal (3)

To a stirred mixture of 3-methyl-2-buten-1-ol **4** (860 mg, 10 mmol), imidazole (1.50 g, 22 mmol) in anhydrous DMF (5 mL) was added dropwise *tert*-butyldiphenylsilyl chloride (2.74 g, 10 mmol) at room temperature. After stirring for an additional 20 min, the resulting mixture was added to H_2O (5 mL) and extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with H_2O (3 × 5 mL), brine (5 mL) and dried. Evaporation of the solvent under vacuum gave the crude silyl ether, which without further purification was taken up in CH_2Cl_2 (15 mL), and then added dropwise to a stirred clear solution of SeO_2 (555 mg,

5 mmol) and *t*-BuOOH (75% *aq.* solution, 2.74 mL, 20 mmol) in CH_2Cl_2 (35 mL). After being stirred for 16 h at room temperature, the reaction mixture was diluted with Et_2O (50 mL) and then washed with 10% KOH aqueous solution (4 × 10 mL), H_2O, brine, then dried. Evaporation of the solvent under vacuum followed by purification by flash column chromatography afforded the enal **3** as a colourless oil; yield: 1.765 g, (52%). IR (film) 2959, 2932, 2857, 1692, 1469, 1427, 1379, 1332, 1201, 1111, 1061, 823, 787, 741, 705, 507 cm^{-1}; EIMS *m/z* 338 (M^+, 0.5), 323 (1), 295 (2), 281 (32), 263 (5), 251 (7), 223 (7), 199 (100), 175 (31), 139 (63), 105 (10), 91 (3), 77 (16), 57 (11), 41 (10); ^1H NMR ($CDCl_3$, 80 MHz) δ 9.66 (s, 1H, CHO), 7.60-8.05 (m, 10H, 2Ph-), 6.80 (t, *J* = 6.0 Hz, 1H, CH=), 4.80 (d, *J* = 6.0 Hz, 2H, CH_2), 1.88 (s, 3H, CH_3), 1.09 (s, 9H, Me_3C).

(2*E*,4*E*)-1-(*tert*-Butyldiphenylsiloxy)-3,7,11-trimethyl-2,4,10-dodecatriene (5) and (*E*)-2,6,11,15-tetramethyl-2,8,14-hexedecatriene (6)

To an anhydrous DME solution (50 mL) was added dropwise $TiCl_4$ (3.2 mL, 30 mmol) slowly by a dry syringe at -78 °C with efficient stirring over 10 min. After removal of cooling bath, to the resulting DME suspension of $TiCl_4$-DME complex was added zinc powder (3.9 g, 60 mmol) followed by the addition of pyridine (0.6 mL). The suspension mixture was then refluxed (2.5 h), when a solution of (+)-citronellal **2** (154 mg, 1 mmol) and enal **3** (1.01 g, 3 mmol) in dimethoxyethane (anhydrous, 30 mL) was slowly added by syringe over 14 h. After addition was complete, the reaction mixture was refluxed for an additional 3 h, then cooled to room temperature, diluted with Et_2O (30 mL) and quenched with 20% K_2CO_3 aqueous solution (2 mL). The organic phase was separated and then washed with H_2O and brine and dried. Evaporation of the solvent under reduced pressure gave an oily residue which was purified by flash column chromatography carefully to afford compound **5** (161 mg, 35%), and a mixture of **6** and **1**. This mixture was further separated by reversed-phase HPLC (ODS-silica column, 9.6 mm × 250 mm) using MeOH-H_2O (9:1) as the eluant to afford **6** (14 mg, 5%) and **1** (22 mg, 10.5%) separately. Compound **5**: $[\alpha]_D^{20}$ -2.38 (*c* = 2.1, $CHCl_3$); IR (film) 2959, 2929, 2858, 1667, 1590, 1467, 1427, 1383, 1110, 824, 739, 704 cm^{-1}; EIMS *m/z* 460 (M^+, 1), 403 (5), 335 (5), 267 (9), 253 (7), 227 (4), 199 (100), 183 (10), 135 (10), 121 (5), 105 (7), 77 (10), 55 (5), 41 (12); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73-7.75 (m, 4H, Ph-), 7.40-7.48 (m, 6H, Ph-), 6.10 (d, *J* = 15.6 Hz, 1H, CH=), 5.61-5.65 (m, 2H, 2CH=), 5.15 (t, *J* = 7.0 Hz, 1H, CH=), 4.38 (d, *J* = 6.3 Hz, 2H, =$CHCH_2O$), 1.97-2.16 (m, 4H, $2CH_2CH$=), 1.73 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.15-1.50 (m, 3H, CH_2, CH), 1.10 (s, 9H, Me_3C), 0.93 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.6 (4C), 135.3, 133.9, 132.5, 129.5 (3C), 128.8 (2C), 127.9, 127.6 (4C), 124.9, 61.1, 40.3, 36.7, 33.0, 27.3, 26.8 (3C), 25.7, 25.6, 19.5, 17.6, 12.7. Compound **6**: $[\alpha]_D^{20}$ +11.13 (*c* = 1.25, $CHCl_3$); UV (MeOH): λ_{max} = 228 nm (ε, 1130); IR (film) 2957, 2924, 2862, 1642, 1455, 1377, 967, 889 cm^{-1}; EIMS *m/z* 276 (M^+, 3), 233 (8), 177 (6), 163 (13), 149 (14), 137 (26), 123 (35), 109 (75), 95 (45), 81 (44), 69 (100), 55 (36), 41 (49); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.36 (t, *J* = 4.0 Hz, 2H, 2CH=), 5.10 (t, *J* = 6.9 Hz, 2H, 2CH=), 2.04-1.95 (m, 4H, $2CH_2CH$=), 1.88-1.81 (m, 4H, $2CH_2CH$=), 1.69 (s, 6H, $2CH_3C$=), 1.60 (s, 6H, $2CH_3C$=), 1.05-1.60 (m, 6H, $2CH_2$, 2CH), 0.86 (d, *J* = 5.9 Hz, 6H, $2CH_3$).

(*E*,*E*)-3,7,11-trimethyl-2,4,10-dodecatriene-1-ol (7)

The solution of compound **5** (138 mg, 0.3 mmol) in 1 M *n*-$Bu_4N^+F^-$/THF (1 mL) was stirred at room temperature under Ar atmosphere for 10 h, and then the reaction mixture was diluted with Et_2O. The organic phase was washed with H_2O, brine and dried. Evaporation of the solvent prior to purification by flash column chromatography yielded **7** as a colorless oil; yield 64 mg (96%). $[\alpha]_D^{20}$ +9.6 (*c* = 1.0, $CHCl_3$); IR (film) 3456, 2962, 2923, 1716, 1674, 1650, 1456, 1379, 1099, 998, 828 cm^{-1}; EIMS *m/z* 222 (M^+, 1), 207 (5), 191 (17), 179 (5), 161 (7), 149 (7), 135 (11), 123 (29), 109 (57), 95 (37), 81 (47), 69 (100), 55 (49), 41 (83); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.06 (d, *J* = 15.5 Hz, 1H, CH=), 5.65-5.72 (dt, *J* = 7.3 Hz, 15.5 Hz, 1H, CH=), 5.57 (t, *J* = 6.8 Hz, 1H, CH=), 5.10 (t, *J* = 7.0 Hz, 1H, CH=), 4.27 (d, *J* = 6.8 Hz, 2H, CH_2), 2.10-2.15 (m, 1H, CH_2), 1.91-1.98 (m, 3H, CH_2), 1.79 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.50-1.55 (m, 1H, CH), 1.13-1.39 (m, 2H, CH_2), 0.88 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.4, 135.1, 132.3, 129.1, 127.6, 124.8, 59.4, 40.3, 36.7, 33.0, 25.7, 25.6, 19.5, 17.6, 12.6.

(*E*,*E*)-3,7,11-trimethyl-2,4,10-dodecatriene (1)

To a stirred mixture of allylic alcohol **7** (50 mg, 0.23 mmol), Ph_3P (88 mg, 0.34 mmol) and imidazole (23 mg, 0.34 mmol) in a solvent mixture of Et_2O (1 mL) and MeCN (0.4 mL) was added I_2 (100 mg, 0.39 mmol) portionwise at 0 °C. The cooling bath was removed and the mixture was stirred for an additional 0.5 h at room temperature, diluted with Et_2O (40 mL) and washed with sat. $Na_2S_2O_3$, H_2O, brine and dried. Evaporation of the solvent under vacuum followed by flash column chromatography gave the allylic iodide, which was dissolved in anhydrous THF (1 mL). After HMPA (0.55 mL) and $NaBH_3CN$ (85%, 22 mg, 0.29 mmol) was added, the reaction mixture was further stirred

for 12 h at room temperature under Ar atmosphere. The resulting mixture was diluted with Et_2O (30 mL) and washed with H_2O (2 × 5 mL), then with brine. The solution was dried and concentrated on a rotary evaporator under reduced pressure to yield an oily residue. Purification of the residue by flash column chromatography yielded the title compound **1** as a colorless oil (24 mg, 52%). $[\alpha]_D^{20}$ +19.2 (c = 0.1, CH_2Cl_2). Lit.[1] $[\alpha]_D^{20}$ +18.1 (c = 0.1, CH_2Cl_2); UV (MeOH): λ_{max} = 232 nm (ε, 6232); IR (film) 2958, 2924, 2861, 1741, 1649, 1455, 1378, 1110, 963, 821 cm^{-1}; EIMS *m/z* 206 (M^+, 10), 191 (15), 177 (9), 163 (32), 149 (9), 136 (35), 121 (78), 109 (95), 95 (100), 81 (50), 69 (91), 55 (41), 41 (56); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.04 (d, J = 15.4 Hz, 1H, CH=), 5.49-5.56 (dt, J = 15.4 Hz, 7.4 Hz, 1H, CH=), 5.42-5.47 (q, J = 7.0 Hz, 1H, CH=), 5.10 (t, J = 6.7 Hz, 1H, CH=), 2.07-2.14 (m, 1H, CH_2CH=), 1.90-2.05 (m, 3H, CH_2CH=), 1.73 (s, 3H, CH_3), 1.71 (d, J = 7.0 Hz, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.44-1.53 (m, 1H, CH), 1.30-1.40 (m, 1H, CH_2), 1.10-1.19 (m, 1H, CH_2), 0.88 (d, J = 6.3 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.8, 135.6, 129.5, 125.8, 124.9, 124.3, 40.3, 36.7, 33.1, 25.7, 25.6, 19.5, 17.6, 13.7, 12.1.

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Key Words

Total synthesis; Caparratriene; Citronellal.

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