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SYNTHESIS OF (+)-CASSIOL, A POTENT ANTIULCEROGENIC COMPOUND†

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abstract -- (+)-Cassiol (**1**) [(*S*)-2,4-dimethyl-3-(4'-hydroxy-3'-hydroxymethyl-1'-butenyl)-4-hydroxymethyl-2-cyclohexen-1-one] was synthesized from methyl (*S*)-3-hydroxypentanoate in 5.6 % overall yield in 10 steps.

In 1988 Fukaya and his co-workers isolated 5.2 mg of cassioside (**2**), a potent antiulcerogenic compound, from aqueous extract of 50 kg of Cinnamoni Cortex (the dried stem bark of *Cinnamonum cassia* Blume).[1] Enzymatic hydrolysis of cassioside (**2**) with β-D-glucosidase afforded an aglycon named (+)-cassiol (**1**), with inhibited the ulceration in rats more strongly than **2**. The first synthesis of (+)-**1** was reported by Fukaya and co-workers in 1989.[2] Their synthesis afforded (+)-**1** in 14.6% overall yield in 15 steps from a commercially available chiral building block with a cyclohexane ring.[2] This paper describes a new synthesis of (+)-**1** starting from methyl (*S*)-3-hydroxypentanoate (**3**), a chiral and acyclic building block of microbial origin.[3] As shown in Scheme 1, cyclization of **9** to give **10** was the key-step of our synthesis.

Methyl (*S*)-3-hydroxypentanoate (**3**) was prepared according to the published procedure employing baker's yeast.[3] Its methylation according to Fráter yielded **4**, which was alkylated with 3,3-dimethoxypropyl iodide (**5**) and LDA to give **6**.[4,5,6] The depicted stereochemistry was deduced on the basis of Fráter's observation that the dianion alkylation of **3** or **4** would give *anti*-product predominantly. An attempt to alkylate **3** with the same iodide was unsuccessful, and a polar compound with an unknown structure was obtained instead of **13**.

Reduction of **6** with LAH furnished **7**, the primary OH group of which was silylated to give **8** as a single isomer, supporting the homogeneity of **6**. Swern oxidation of **8** yielded **14**, which was reduced with $NaBH_4$ to give a mixture of **8** and **8'**. These *syn*- and *anti*-isomers were separable by preparative TLC, and the starting **8** was shown to be the polar isomer. Jones oxidation of **8** afforded **9**, which was treated with NaH to effect cyclization. The resulting enolate was ethylated with EtI and K_2CO_3 to give **10** in 71% yield together with the minor and the more polar product **11** (8.5% yield). The major product was deduced to be **10**, because in its ^1H NMR spectrum the signal due to $C=C\underline{H}_3$ was observed at $\delta = 1.67$ as a 3H triplet ($J = 1.5$ Hz) due to the long-range coupling. In the case of **11**, that signal was observed as a 3H singlet at $\delta = 1.80$.

Addition of an alkenyllithium derived from the known stannane **12**[7] to the ketone **10** was followed by desilylation with HF to give (+)-cassiol (**1**), $[\alpha]_D^{20}$ +8.5°(MeOH), in 5.6% overall yield in 10 steps. The IR, ^1H NMR and ^{13}C NMR spectra as well as the CD spectrum of the synthetic (+)-**1** coincided with those of the natural (+)-**1**. The enantiomeric purity of our synthetic **1** was 99.2% e.e. as estimated by the HPLC analysis of the corresponding α-methoxy-α-trifluoromethylphenylacetates (MTPA esters), **15** and **16**.[8]

In summary, a new and shorter synthesis of (+)-cassiol (**1**) was achieved, although the overall yield was yet to be improved.

†Carotenoids and Degraded Carotenoids — 7. Part 6, Mori, K. and Tamura, H. *Tetrahedron* **1986**, *42*, 2643-2646.

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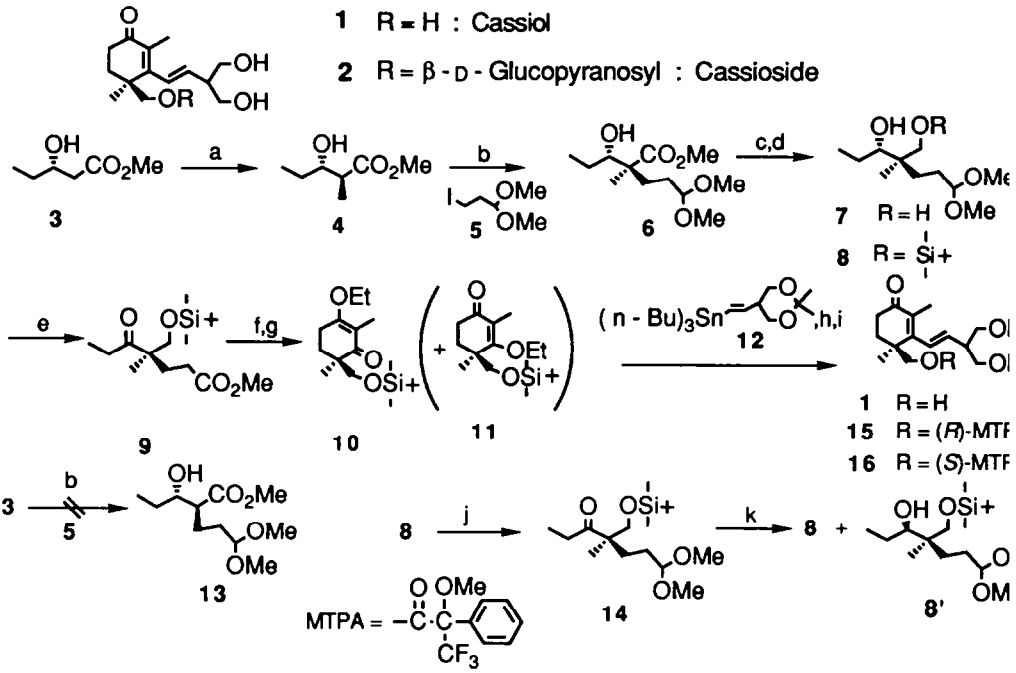

Reagents: (a) LDA, MeI/THF-HMPA (97%); (b) LDA, **5**/THF-HMPA (97%); (c) LAH (85%); (d) TBSCl, imidazole (86%) (e) Jones CrO_3; CH_2N_2 (61%) (f) NaH/benzene; (g) EtI, K_2CO_3/DMF (71%); (h) **12**, *n*-BuLi (97%); (i) 10% HF/ (33%) (j) $(COCl)_2$,DMSO,Et_3N (96%); (k)$NaBH_4$ (37% **8**, 42 % **8'**)

Scheme 1. Synthesis of (+)-cassiol (**1**).

EXPERIMENTAL

IR spectra were measured as films on a Jasco IRA-102 spectrometer unless otherwise stated. ^1H NMR spectra were rec with TMS as an internal standard at 100 MHz on a JEOL JNM FX-100 spectrometer unless otherwise stated. 250 MHz ^1H and 63 MHz ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer. Mass spectrum was recorded on a JMS-S spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. CD spectrum was measured on a Jasco spectropolarimeter. Merck Kieselgel 60 Art. 7734 was used for SiO_2 column chromatography.

Methyl (2S,3S)-2-methyl-3-hydroxypentanoate **4**. A soln of LDA was prepared by the dropwise addition of *n*-BuL (1.50 N in *n*-hexane, 48.8 ml, 73.2 mmol) to a stirred and cooled soln of $(i\text{-Pr})_2NH$ (10.2 ml, 7.36 g, 72.5 mmol) in dry THF (at -10 to -5°C under Ar. The mixture was stirred for 30 min at -10 to -5°C. To the stirred and cooled (-65°C) soln of LD added dropwise a soln of **3** (100% e.e., 4.00 g, 30.3 mmol) in dry THF (10 ml). The mixture was stirred for 1 hr at -30 to -20° this mixture was added a solution of CH_3I (2.26 ml, 5.15 g, 36.3 mmol) in dry HMPA (12 ml) at -40°C. The mixture was stirr 1 h at room temp. The mixture was quenched with sat. NH_4Cl soln and extracted with ether. The extract was washed with dried (Na_2SO_4) and concentrated *in vacuo* to give 5.1 g of a crude oil. This was distilled to give 3.32 g (75%) of **4**, b.p.79-8 Torr; n_D^{17} 1.4270; GLC (Column, OV-101, 50 m x 0.25 mm at 125°C; Carrier gas, N_2, 1.2 kg/cm^2): Rt 8.3 min (**3**, 11.6%), 9.6 m 68.1%), 9.9 min (*syn*-isomer of **4**, 19.8%), impurity (0.5%); νmax 3480 (s), 2980 (s), 2900 (m), 1740 (s), 1460 (s), 1440 (s), 12 1200 (s), 1180 (s), 1120 (s), 980 (s) cm^{-1}. This was employed in the next step without further purification.

(3S,4S)-4-Methyl-7,7-dimethoxy-4-methoxycarbonyl-3-heptanol **6**. A soln of LDA was prepared by the dropwise ad

of *n*-BuLi soln (1.54 N in *n*-hexane, 24.0 ml, 37.0 mmol) to a stirred and cooled soln of $(i\text{-Pr})_2NH$ (5.2 ml, 3.75 g, 37.0 mmol) in dry THF (10 ml) at -10 to -5°C under Ar. The mixture was stirred for 30 min at -10 to -5°C. To the stirred and cooled (-65°C) soln of LDA was added dropwise a soln of **4** (1.2 g, 8.2 mmol) in dry THF (2 ml). The mixture was stirred for 1 hr at -30 to -20°C. After the addition of HMPA (6.6 g), the mixture was cooled to -65°C. To this mixture was added a soln of 3,3-dimethoxypropyl iodide **5** (4.39 g, 20.5 mmol) in dry THF (3 ml) at -70 to -60°C. The mixture was stirred for 1 day at -20°C. The mixture was quenched with sat. NH_4Cl soln at -20°C and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (100 g). Elution with *n*-hexane-AcOEt (10:1-4:1) gave 1.30 g (72 %) of **6**, n_D^{17} 1.4490; $[\alpha]_D^{19}$ -2.8° (c = 1.10, MeOH); νmax 3530 (s), 2980 (s), 2860 (m), 1730 (s), 1460 (s), 1390 (s), 1320 (m), 1220 (m), 1200(m), 1130 (s), 1060 (s), 980 (s) cm^{-1}; δ ($CDCl_3$) 1.00 (3H, t, *J* = 7 Hz), 1.13 (3H, s), 1.2-1.8 (6H, m), 2.34 (1H, OH), 3.23 (6H, s), 3.50 (1H, m), 3.73 (3H, s), 4.32 (1H, t, *J* = 5 Hz). (Found: C, 57.79; H, 9.60. Calc for $C_{12}H_{24}O_5$: C, 58.04; H, 9.74%).

(3S,4R)-4-Hydroxymethyl-4-methyl-7,7-dimethoxy-3-heptanol **7**. To a stirred suspension of LAH (170 mg, 4.48 mmol) in ether (30 ml) was added a soln of **6** (1.10 g, 4.43 mmol) in ether (10 ml) at 0°C. After stirring for 1 hr at room temp, the reaction mixture was quenched by adding water (0.2 ml), 15% NaOH aq (0.2 ml) and water (0.5 ml) at 0°C. The ether soln was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (5 g). Elution with *n*-hexane-AcOEt (2:1) gave 840 mg (85%) of **7**, n_D^{17} 1.4568; $[\alpha]_D^{18}$ -14.9° (c = 1.1, MeOH); νmax 3440 (s), 2980 (s), 2910 (s), 2860 (s), 1460 (s), 1380 (s), 1240 (m), 1200 (m), 1130 (s), 1040 (s), 970 (s) cm^{-1}; δ ($CDCl_3$) 0.75 (3H, s), 1.03 (3H, t, *J* = 7 Hz), 1.2-1.8 (8H, m), 3.35 (6H, s), 3.35-3.8 (3H, m), 4.37 (1H, t, *J* = 7 Hz). (Found: C, 59.49; H, 10.99. Calc for $C_{11}H_{24}O_4$: C, 59.97; H, 10.98%).

(3S,4R)-4-(t-Butyldimethylsiloxymethyl)-4-methyl-7,7-dimethoxy-3-heptanol **8**. A mixture of **7** (780 mg, 3.54 mmol), imidazole (530 mg, 7.78 mmol) and *t*-$BuMe_2SiCl$ (600 mg, 3.98 mmol) in DMF (20 ml) was stirred overnight at room temp. The reaction mixture was poured into water and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (30 g). Elution with *n*-hexane-AcOEt (10:1) gave 1.02 g (86%) of **8**, n_D^{17} 1.4455; $[\alpha]_D^{17}$ +8.8° (c = 1.34, MeOH); νmax 3450 (s), 2990 (s), 2960 (s), 2880 (s), 1460 (s), 1390 (m), 1260 (s), 1130 (s), 1070 (s), 980 (s), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.07 (6H, s), 0.77 (3H, s), 0.90 (9H, s), 0.9-1.1 (3H, m), 1.2-1.8 (7H, m), 3.25 (1H, m), 3.33 (6H, s), 3.45 (1H, d, *J* = 10 Hz), 3.61 (1H, d, *J* = 10 Hz), 4.32 (1H, t, *J* = 6 Hz). (Found: C, 60.85; H, 11.53. Calc for $C_{17}H_{38}O_4Si$: C, 61.03; H, 11.45%).

(4R)-4-(t-Butyldimethylsiloxymethyl)-4-methyl-7,7-dimethoxy-3-heptanone **14**. To a soln of oxalyl chloride (0.020 ml, 28 mg, 0.22 mmol) in CH_2Cl_2 (2 ml) was added dropwise DMSO (0.032 ml, 35 mg, 0.45 mmol) at -70°C. After stirring for 10 min at -70°C, to this was added a soln of **8** (50 mg, 0.15 mmol) in CH_2Cl_2 (0.2 ml) and the mixture was stirred for 15 min. Then Et_3N (0.125 ml, 91 mg, 0.90 mmol) was added dropwise and the temp was gradually raised to room temp. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (3 g). Elution with *n*-hexane-AcOEt (8:1) gave 48 mg (96 %) of **14**. νmax 2960 (s), 2940 (s), 2850 (s), 1720 (s), 1460 (m), 1260 (m), 1100 (s), 840 (s), 780(m) cm^{-1}; δ ($CDCl_3$) 0.02 (6H, s), 0.88 (9H, s), 1.00 (3H, t, *J* = 7 Hz), 1.12 (3H, s), 1.2-1.7 (4H, m), 1.49 (2H, q, *J* = 7 Hz), 3.30 (6H, s), 3.50 (1H, d, *J* = 10 Hz), 3.62 (1H, d, *J* = 10 Hz), 4.29 (1H, m).

4-(t-Butyldimethylsiloxymethyl)-4-methyl-7,7-dimethoxy-3-heptanol **8**. To a soln of **14** (40 mg, 0.12 mmol) in MeOH (1 ml) was added $NaBH_4$ (9 mg, 0.24 mmol) at room temp. After stirring 3 h at room temp, the reaction mixture was concentrated. The residue was diluted with ice-water and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by prep TLC [Merck Kieselgel 60 F-254; developed with *n*-hexane-AcOEt (4:1)] to give 15 mg (37%) of **8** (Rf = 0.25). Its ^1H NMR spectrum was identical with that of authentic **8**; *syn*-isomer of **8** (Rf = 0.19), 17 mg (42%), δ ($CDCl_3$) 0.08 (6H, s), 0.82 (3H, s), 0.88 (9H, s), 0.8-1.1 (3H, m), 1.2-1.7 (7H, m), 3.31 (6H, s), 3.39 (1H, d, *J* = 10 Hz), 3.50 (1H, m), 3.58 (1H, d, *J* = 10 Hz), 4.28 (1H, t, *J* = 6 Hz).

Methyl (R)-4-(t-butyldimethylsiloxymethyl)-4-methyl-5-oxoheptanoate **9**. Jones CrO_3 (3 ml) was added to a soln of **8** (0.90 g, 2.7 mmol) in acetone (50 ml) with stirring and ice-cooling. The excess CrO_3 was destroyed with *i*-PrOH. The mixture was poured into ice-water and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was treated with ethereal CH_2N_2. The ether soln was washed with sat $NaHCO_3$ soln, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (50 g). Elution with *n*-hexane-AcOEt (20:1) gave 520 mg (61%) of **9**, n_D^{17} 1.4421; $[\alpha]_D^{17}$ -12.0° (c = 1.45, MeOH); νmax 2980 (s), 2900 (s), 1740 (s), 1710 (s), 1460 (m), 1260 (s), 1200 (m), 1100 (s), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.02 (6H, s), 0.86 (9H, s), 1.00 (3H, t, *J* = 7 Hz), 1.12 (3H, s), 1.6-2.3 (4H,

m), 2.50 (2H, q, J=7 Hz), 3.55 (1H, d, J=11 Hz), 3.62 (1H, d, J=11 Hz), 3.65 (3H, s). (Found: C, 60.32; H, 10.07. Calc $C_{16}H_{32}O_3Si$: C, 60.71; H, 10.19%).

***(R)-6-(t-Butyldimethylsiloxymethyl)-3-ethoxy-2,6-dimethyl-2-cyclohexen-1-one* 10.** A soln of **9** (100 mg, 0.32 mm NaH (60 %, 25 mg, 0.63 mmol) and EtOH (cat. amount) in benzene (5 ml) was heated under reflux for 3 h. The reaction mix was concentrated *in vacuo*. The residue was dissolved in DMF (5 ml), to this was added K_2CO_3 (44 mg, 0.32 mmol) and EtI mg, 0.96 mmol). After stirring for 2 h at room temp, the mixture was poured into water and extracted with ether. The ether was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (1(Elution with *n*-hexane-AcOEt (20:1) first yielded **10** (70.5 mg, 71%). n_D^{17} 1.4621; $[\alpha]_D^{26}$ -12.7° (c=1.37, MeOH); νmax 2970 2900 (s), 1740 (s), 1700 (m), 1650 (m), 1620 (s), 1460 (s), 1380 (s), 1360 (m), 1260 (s), 1240 (m), 1120 (m), 1100 (s), 840 (s), 78(cm^{-1}; δ (250 MHz, $CDCl_3$) 0.00 and 0.02 (total 6H, each s), 0.86 (9H, s), 1.02 (3H, s), 1.35 (3H, t, J=7 Hz), 1.67 (3H, t, J= Hz), 1.85 (1H, m), 2.10 (1H, m), 2.4-2.7 (2H, m), 3.45 (1H, d, J=9.6 Hz), 3.71 (1H, d, J=9.6 Hz), 4.06 (2H, q, J=7 Hz). (Fo C, 65.33; H, 10.59. Calc for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32%). Further elution afforded **11** (8.4 mg, 8.5%), νmax 2960 (s), 2 (s), 2850 (s), 1670 (s), 1620 (s), 1470 (m), 1300 (m), 1260 (s), 1180 (m), 1100 (s), 1030 (m), 840 (s), 780 (m) cm^{-1}; δ ($CDCl_3$) and 0.05 (total 6H, each s), 0.88 (9H, s), 1.10 (3H, s), 1.35 (3H, t, J=7 Hz), 1.80 (3H, s), 2.0-2.6 (4H, m), 3.40 (1H, d, J=11 H 3.77 (1H, d, J=11 Hz), 3.9-4.15 (2H, m).

***(S)-2,4-Dimethyl-3-(4'-hydroxy-3'-hydroxymethyl-1'-butenyl)-4-hydroxymethyl-2-cyclohexen-1-one* (*Cassiol*) 1.** soln of *n*-BuLi in *n*-hexane (1.57 M, 0.28 ml, 0.44 mmol) was added dropwise to a stirred and cooled soln of the vinylstannane (190 mg, 0.44 mmol) in dry THF (2 ml) at -70°C under Ar. The mixture was stirred for 1 h at -70 to -60°C. To the stirred mix was added dropwise a soln of **10** (68.9 mg, 0.22 mmol) in dry THF (0.2 ml) at -70°C and the temp was gradually raised to After stirring for 20 min at 0°C, the mixture was poured into sat NH_4Cl soln and extracted with ether. The extract was washed brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was dissolved in 10% HF aq (0.2 ml) and MeCN (1 ml), and mixture was stirred for 3 h at room temp. The mixture was neutralized by adding $NaHCO_3$ and concentrated *in vacuo*. residue was purified by prep TLC (Merck Kieselgel 60 F-254 Art. 5744) to give 18.2 mg (33%) of **1**, $[\alpha]_D^{20}$ +8.5° (c=0.37, MeO $[\theta]_{284}^{25.5}$ 1.0×10^4 (3.9×10^{-4}, MeOH), MS: *m/z* 254.1513 (M^+); Calc for $C_{14}H_{22}O_4$: 254.1518. νmax 3400 (s), 2940 (s), 2880 (s), 1 (s), 1600 (m), 1460 (m), 1420 (m), 1380 (m), 1360 (m), 1340 (m), 1300 (m), 1200 (m), 1040 (s), 980 (m) cm^{-1}; δ (250 MHz, D 0.92 (3H, s), 1.55 (1H, m), 1.60 (3H, s), 1.98 (1H, m), 2.3-2.55 (2H, m), 3.22 (1H, d, J=11.5 Hz), 3.4-3.6 (5H, m), 5.46 (1H, J=8.4, 16.3 Hz), 6.07 (1H, d, J=16.3 Hz); ^{13}C NMR (62.9 MHz, D_2O) δ 15.49, 23.12, 35.36, 35.92, 43.15, 50.14, 64.66, 70.51, 131 134.28, 138.99, 164.76, 207.05. Its IR, ^1H NMR and ^{13}C NMR spectral data were identical with those of the natural **1**.

***Determination of the enantiomeric purity of* 1.** According to the reported procedure,[8] (*R*)- and (*S*)-MTPA esters **15** **16** were prepared from **1**. HPLC [Column, CHIRALCEL OD, 25 cm x 4.6 mm x 2; Solvent, *n*-hexane-2-propanol-Et_2 (950:50:1), 1.0 ml/min; Detected at 254 nm] co-injection of (*R*)- and (*S*)-MTPA esters **15** and **16**; Rt 53.78 min and 59.39 m (*R*)-MTPA ester **15**: Rt 51.61 min (99.6%), (*S*)-MTPA ester **16**: Rt 57.01 min (0.4%). Therefore the enantiomeric purity of **1** determined to be 99.2 % e.e.

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