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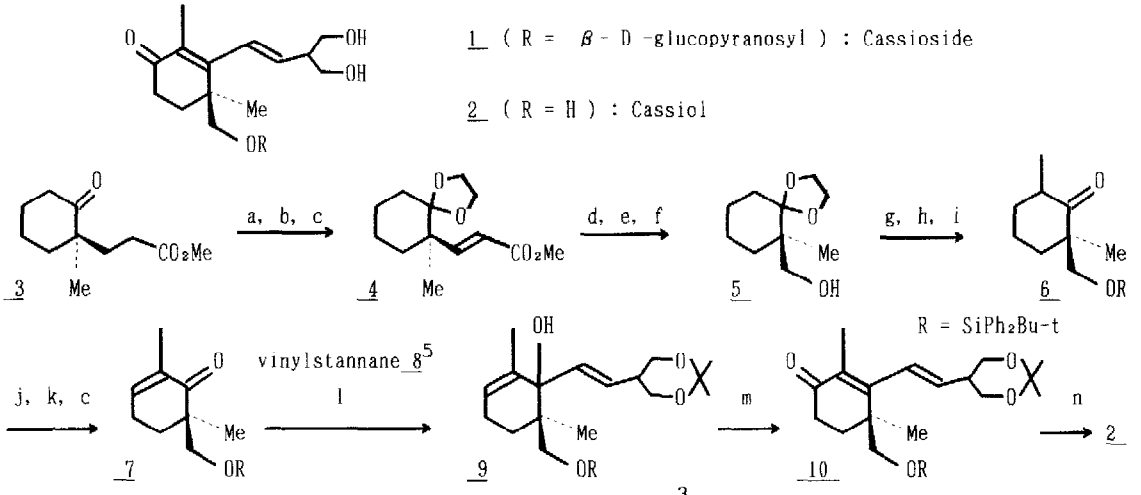
FIRST TOTAL SYNTHESIS OF (+)-CASSIOL. A POTENT ANTIULCEROGENIC COMPOUND

Tadahiro Takemoto, Chikara Fukaya* and Kazumasa Yokoyama.
Central Research Laboratory, The Green Cross Corporation,
2-1180-1, Shodai-Ohtani, Hirakata, Osaka 573, Japan.

Summary: The first total synthesis of (S)-(+)-Cassiol (2) is described.

Cassioside (1), isolated from aqueous extract of Cinnamoni Cortex (*Cinnamonum cassia* Blume; "Kannan Keihi" in Japanese)[1a], showed serotonin-induced antiulcerogenic activity[1b]. In this communication, we wish to report the first synthesis of cassiol (2), which inhibits the ulceration in rat more strongly than 1, from the optically active keto ester 3[2]. The keto ester 3 was converted into the crotonate 4 in 66 % yield in 3 steps (ketalization and subsequent formation of carbon-carbon double bond in the side chain). The crotonate 4 was subjected to osmylation followed by $NaIO_4$ oxidation to afford



(a) ethylene glycol, p-TsOH, PhH, reflux; (b) PhSeBr, LiICA[3], THF, -78℃; (c) 30 % H_2O_2 aq, CH_2Cl_2, 0℃; (d) OsO_4, Pyr, PhH, rt / then sat $NaHSO_3$ aq; (e) $NaIO_4$, Et_2O, rt; (f) $NaBH_4$, EtOH, 0℃; (g) ^{t}Bu Ph_2SiCl, imidazole, DMF; (h) p-TsOH, aq.THF, reflux; (i) MeI, LDA, HMPA, THF, -78℃; (j) TMSOTf, Et_3N, CH_2Cl_2, reflux; (k) PhSeCl, CH_2Cl_2, rt; (l) n-BuLi, THF, -50→-78℃ / -78→0℃; (m) PDC, CH_2Cl_2, rt; (n) 70 % HF-Pyr, Pyr-CH_3CN, 70 ℃.

the corresponding aldehyde, which was reduced with $NaBH_4$ to give the alcohol **5** in 74 % overall yield. The alcohol **5** was subjected to silylation followed by deprotection of ketal to afford a ketone (78 % yield), which was monomethylated by usual manner to give the methyl ketone **6** (75 % yield). The methyl ketone **6** was treated sequentially[4] with (1) $TMSOTf/Et_3N$ (2) PhSeCl (3) 30 %-H_2O_2 aq. to afford the desired enone **7**, $[\alpha]_D^{24}$ = -23.6° (c 1.80, MeOH), in 89 % overall yield. Selective vinylation (1,2-addition) of **7** was achieved by the reaction with (*E*)-vinyllithium reagent which was generated by the transmetalation of **8**[5] with n-BuLi to give the allylalcohol **9** in 94 % yield. Pyridinium dichromate mediated rearrangement of **9** proceeded at room temperature to afford the desired dienone **10** in 75 % yield (84.5 % yield based on recovered **9**, $[\alpha]_D^{24}$ = -14.9°, c 1.42, MeOH). Finally, treatment of **10** with 70 % HF-pyridine complex in pyridine-acetonitrile at 70°C resulted in concominant deprotection of silyl and acetonide groups to give cassiol (**2**) as an oil of more than 98 % optical purity[6] ($[\alpha]_D^{28.5}$ = +8.63°, c 0.35, MeOH) in 72 % yield. Synthetic cassiol was completely identical with an authentic sample of **2** in all respects.

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References and notes

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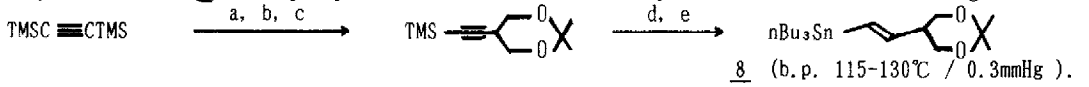
5. Vinylstannane **8** was prepared in 29 % overall yield as the following manner[7]:



8 (b.p. 115-130℃ / 0.3mmHg).

(a) MeLi-LiBr, THF, rt ; (b) diacetoxyacetone, THF, -78℃ / MsCl, -78 ℃; (c) LAH, ether, -15 ℃ then $Me_2C(OMe)_2$, acetone, H_2SO_4 ; (d) n-Bu_4NF, THF, rt ; (e) n-Bu_3SnH, AIBN(trace), 80 ℃

6. Optical purity of the synthetic sample was determined by ^1H-NMR analysis of the corresponding tri-MTPA ester: (i) J. D. Morrison, "Asymmetric synthesis" , ACADEMIC PRESS, 1983, chapter 7. (ii) J. A. Dale, D. L. Dull and H. S. Mosher, J. Org. Chem., 34, 2543(1969).
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