STUDIES ON HINDERED PHENOLS. III.[#]

Synthesis of (±)-5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-5-^{14}C-thiazolidine-2,4-dione (^{14}C-Labelled CS-045)

T. Yoshioka,* Y. Aizawa, T. Kanai, T. Fujita, and K. Kawai[a]

Medicinal Chemistry Research Laboratories and Analytical and Metabolic Research Laboratories,[a] SANKYO CO. LTD., 2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo 140, JAPAN

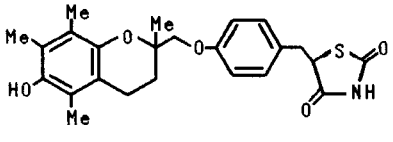
SUMMARY

A synthetic procedure for producing (±)-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-5-^{14}C-thiazolidine-2,4-dione (^{14}C-labelled CS-045) is described. The radiolabel is introduced using [5-^{14}C]thiazolidine-2,4-dione, as shown in the scheme.

Key Words: Carbon 14, CS-045, [^{14}C]CS-045.

INTRODUCTION

(±)-5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione, (CS-045), **1** is a new oral anti-diabetic agent (1)(2) which is effective in insulin-resistant diabetic animal models, such as the KK-mouse, ob/ob mouse, and Zucker fatty rat. In addition to this activity, **1** has a



1 (CS-045)

[#] Studies II: J. Med. Chem. in press.

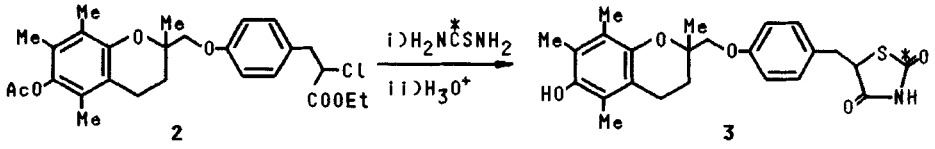
0362–4803/90/080911–10$05.00

Received December 11, 1989
Revised February 20, 1990

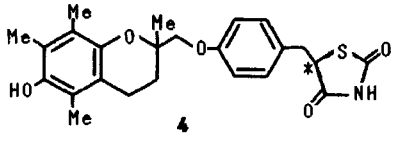
significant lipid peroxide lowering activity. So CS-045 is desired as a new type of pharmaceutical.

For use in metabolism and disposition studies of 1 in the development stage, it was necessary to prepare a ^{14}C-labelled compound.

We already reported several synthetic routes of 1 (1)(3). If we applied them, compound 1 might be labelled with carbon-14



in the 2-position of the thiazolidine ring by reaction of ethyl 3-[4-(6-acetoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)phenyl]-2-chloropropionate, 2, with [^{14}C]thiourea, followed by hydrolysis. However, during the hydrolysis procedure or the metabolic process, etc., the S-C bond cleavage in the labelled compound 3 may occur *a priori* to generate $^{14}CO_2$, although the contribution of the cleavage may be minimal. So we wished to avoid preparing compound 3 from the view of safety, and to instead prepare another compound, 4, with the label being introduced at the 5-

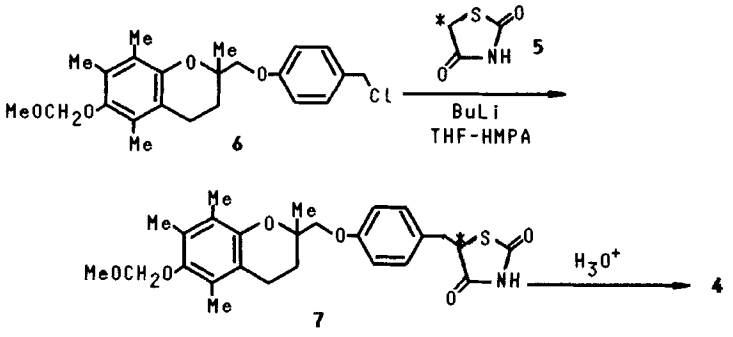


position of the thiazolidine ring.

RESULTS AND DISCUSSION

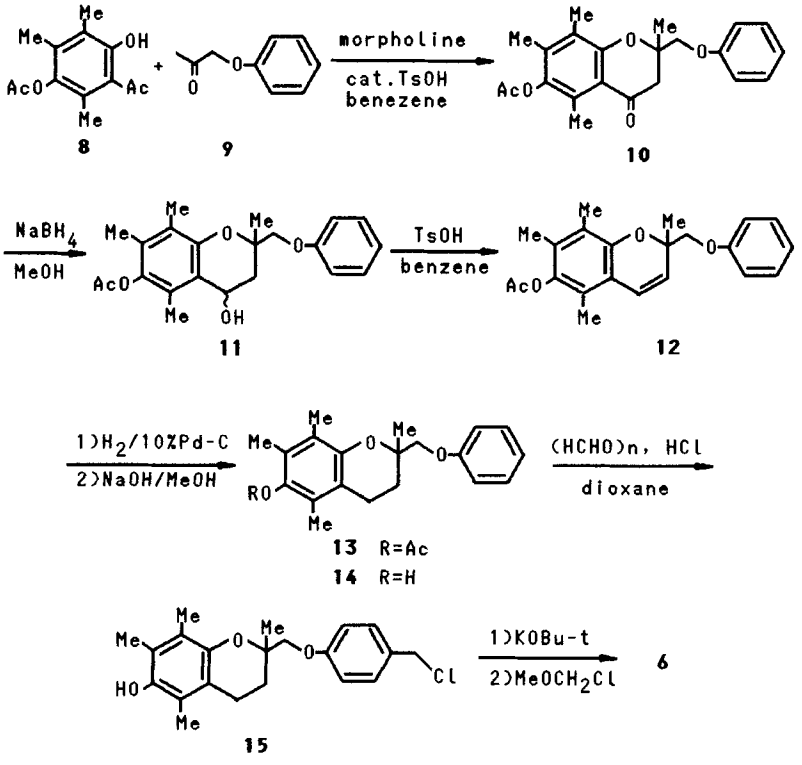
We developed a new synthetic route for preparing compound 4 by a method similar to that described by J.D.Taylor et al.

(4)(5), as shown in Scheme 1. A raw material, [5-^{14}C]thiazol-



Scheme 1

idine-2,4-dione, 5, was purchased from Amersham International plc., which was prepared by reacting [2-^{14}C]bromoacetic acid with



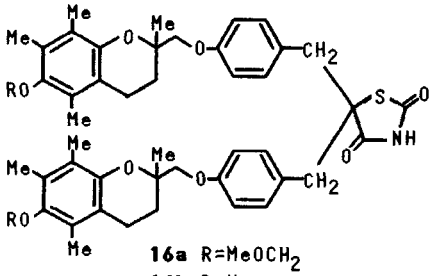
Scheme 2

thiourea by a method similar to that described by R. Deghenghi et al. (6) Another raw material, 4-(6-methoxymethoxy-

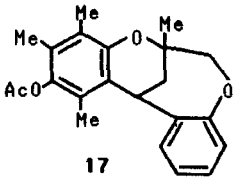
2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl chloride, 6, was prepared as shown in Scheme 2.

We obtained 1.29 g (907.4 MBq) of (±)-5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-5-^{14}C-thiazolidine-2,4-dione, 4 (specific activity: 703.4 kBq/mg), radiochemical purity greater than 99% (TLC), and 0.33 g (185 MBq) of the diluted compound, 4 (specific activity: 561.3 kBq/mg), radiochemical purity greater than 97.4% (TLC), in two steps from 178.9 mg (2.96 GBq) of the starting [5-^{14}C]thiazolidine-2,4-dione, 5, (specific activity: 16.80 MBq/mg, radiochemical purity greater than 98% (TLC), analyzed by Amersham International plc.), in an overall radiochemical yield of 36.9%.

We also obtained 5,5-bis[4-(6-methoxymethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]thiazolidine-2,4-dione, 16a, as a side product during the cold runs. This compound, 16a, was able to separate off easily from the desired intermediate 7 by reversed-phase column chromatography.



16a R=MeOCH$_2$
16b R=H



17

During the studies of preparing the benzyl chloride derivative 6, we found a dibenzobicyclo compound 17 in the dehydration procedure of 4-chromanol, 11, under the harder reaction conditions.

We will describe the chemistry and biological activity, etc., of both 16 and 17 in the following paper(s).

EXPERIMENTAL

Proton magnetic resonance (NMR) spectra were recorded on a 90-MHz Varian EM-390 spectrometer and are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (Me_4Si); the abbreviation nd means that precise identification of the signal was not possible because of overlap by other signals or the absorption of solvent. All NMR spectra were consistent with the structures assigned. Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected.

6-Acetoxy-2,5,7,8-tetramethyl-2-phenoxymethylchroman-4-one [10]

A mixture comprising 255 g (1.08 mol) of 5-acetoxy-2-hydroxy-3,4,6-trimethylacetophenone [8], 151.8 g (1.0 mol) of phenoxyacetone [9], 150 g (1.724 mol) of morpholine, 20 g (0.105 mol) of p-toluenesulfonic acid hydrate, and 750 ml of benzene was refluxed for 13 h attached with a water separator. After cooling, the solution was acidified (pH ca.1) with dil. hydrochloric acid and stirred for 30 min at room temperature. The organic layer was separated and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The resulting residue was subjected to silica gel column chromatography [eluent; hexane:ethyl acetate=6:1], to give 253 g of crude **10** [purity; 69% by GC]. This compound was not purified by chromatography, so the structure assignment was performed by 6-hydroxy compound obtained by hydrolysis of crude **10**. 6-Hydroxy-2,5,7,8-tetramethyl-2-phenoxymethylchroman-4-one melted at 103.5-104.5°C. NMR Spectrum (δ ppm, $CDCl_3$): 1.50 (3H, s), 2.13 (3H, s), 2.23 (3H, s), 2.57 (3H, s), 2.68 (1H, d, J=16 Hz), 3.07 (1H, d, J=16 Hz), 4.00 and 4.10 (2H, AB type, J=10 Hz), 4.62 (1H, s, disappeared by adding D_2O), 6.8-7.1 (3H, m), 7.15-7.45 (2H, m).

6-Acetoxy-4-hydroxy-2,5,7,8-tetramethyl-2-phenoxymethylchroman [11]

Compound 10 (233 g, purity 69%, 0.443 mol) was dissolved in 2 l of MeOH under a nitrogen atmosphere. To the solution was added 19 g (0.502 mol) of sodium borohydride in small portions at 15-20°C. The reaction mixture was stirred for 1 h at the same temperature, acidified with 10% hydrochloric acid, and concentrated under reduced pressure. The resulting residue was extracted with ethyl acetate. The extract was dried over sodium sulfate and evaporated under reduced pressure, to give the crude product as a pale orange solid. The solid was washed with hot cyclohexane, to give 62 g (38%) of 11 as colorless crystals, melting at 139-140°C. NMR Spectrum (δ ppm, $CDCl_3$): 1.55 (3H, s), 1.74 (1H, d, J=5 Hz, disappeared by adding D_2O), 2.0-2.5 (2H, nd), 2.04 (3H, s), 2.08 (3H, s), 2.19 (3H, s), 2.22 (3H, s), 3.97 and 4.03 (2H, AB type, J=10 Hz), 4.85-5.1 (1H, m, changed to 4.97 (1H, t, J=4 Hz) by adding D_2O), 6.85-7.1 (3H, m), 7.15-7.45 (2H, m).

2-Acetoxy-2,5,7,8-tetramethyl-2-phenoxymethyl-2H-chromene [12]

A mixture comprising 105.6 g (0.285 mol) of 11, 10 g (0.0526 mol) of p-toluenesulfonic acid hydrate, and 1 l of benzene was refluxed for 50 min. The reaction mixture was poured into ice and water, extracted with benzene, washed with sodium bicarbonate, and dried over sodium sulfate. The solvent was evaporated under reduced pressure, to give 99 g (99%) of 12 as an orange oil. NMR Spectrum (δ ppm, $CDCl_3$): 1.57 (3H, s), 2.02 (3H, s), 2.08 (6H, s), 2.31 (3H, s), 4.01 (2H, s), 5.76 (1H, d, J=10 Hz), 6.63 (1H, d, J=10 Hz), 6.8-7.1 (3H, m), 7.15-7.4 (2H, m).

6-Acetoxy-2,5,7,8-tetramethyl-2-phenoxymethylchroman [13]

Compound 12 (99 g, 0.28 mol) was dissolved in 500 ml of MeOH and hydrogenated for 7 h in atmospheric pressure at room temperature in the presence of 10 g of 10% Pd on carbon. The catalyst was filtered off and the solvent was evaporated under reduced

pressure. The resulting residue was purified by silica gel column chromatography [eluent; cyclohexane:ethyl acetate=12:1 to 10:1], to give 81.05 g (82%) of 13 as a colorless oil. NMR Spectrum (δ ppm, $CDCl_3$): 1.40 (3H, s), 1.8-2.4 (2H, nd), 1.95 (3H, s), 2.00 (3H, s), 2.06 (3H, s), 2.30 (3H, s), 2.60 (2H, br.t, J=7 Hz), 3.85 and 3.92 (2H, AB type, J=9 Hz), 6.7-7.1 (3H, m), 7.1-7.4 (2H, m).

6-Hydroxy-2,5,7,8-tetramethyl-2-phenoxymethylchroman [14]

A mixture comprising 41.15 g (0.116 mol) of 13, 4.8 g (0.12 mol) of sodium hydroxide, and 300 ml of MeOH was stirred for 30 min at room temperature. The mixture was acidified with dil. hydrochloric acid and concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate, washed with water, and dried over sodium sulfate. The solution was evaporated under reduced pressure, to give a dark orange oil, which was solidified by adding hexane. The resulting powder was filtered and washed with hexane, to give 24 g (66%) of 14, melting at 76.5-77.5°C. NMR Spectrum (δ ppm, $CDCl_3$): 1.41 (3H, s), 1.7-2.3 (2H, nd), 2.10 (6H, s), 2.15 (3H, s), 2.59 (2H, br.t, J=7 Hz), 3.86 and 3.98 (2H, AB type, J=10 Hz), 4.16 (1H, s, disappeared by adding D_2O), 6.8-7.1 (3H, m), 7.1-7.45 (2H, m).

4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl Chloride [15]

Into a mixture comprising 22 g (0.071 mol) of 14, 4.7 g (0.141 mol) of 90% paraformaldehyde, and 200 ml of dioxane, was passed dry hydrogen chloride for 3 h under ice cooling. The mixture was concentrated under reduced pressure, extracted with benzene, and washed with water. The extract was dried over sodium sulfate and concentrated under reduced pressure, to yield 25.6 g of 15 as a pale brown crude oil. This oil was used in the next step without further purification. NMR Spectrum (δ ppm, $CDCl_3$): 1.41 (3H, s), 1.65-2.3 (2H, nd), 2.10 (3H, s), 2.14 (3H, s), 2.62 (2H, br.t,

J=7 Hz), 3.7-4.6 (1H, br.), 3.86 and 3.97 (2H, AB type, J=9 Hz), 4.53 (2H, s), 6.88 (2H, d, J=9 Hz), 7.28 (2H, d, J=9 Hz).

4-(6-Methoxymethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl Chloride [6]

Compound 15 (25.6 g, 0.071 mol) was dissolved in 250 ml of tetrahydrofuran. To the solution was added dropwise a tetrahydrofuran (150 ml) solution of 12.3 g (0.119 mol) of potassium t-butoxide, and subsequently a tetrahydrofuran (100 ml) solution of 17.1 g (0.212 mol) of chloromethyl methyl ether in a dry-ice bath. The mixture was stirred for 2 h at room temperature. The reaction mixture was poured into ice and water, extracted with benzene, and dried over sodium sulfate. The solvent was removed under reduced pressure, to give the crude product as a reddish orange oil. This oil was subjected to silica gel column chromatography [eluent; hexane:ethyl acetate=13:1 to 11:1], to give 12.39 g (43%) of 6 as a colorless oil. NMR Spectrum (δ ppm, $CDCl_3$): 1.41 (3H, s), 1.7-2.3 (2H, nd), 2.07 (3H, s), 2.15 (3H, s), 2.19 (3H, s), 2.61 (2H, br.t, J=7 Hz), 3.60 (3H, s), 3.85 and 4.00 (2H, AB type, J=9 Hz), 4.53 (2H, s), 4.87 (2H, s), 6.89 (2H, d, J=9 Hz), 7.29 (2H, d, J=9 Hz).

5-[4-(6-Methoxymethoxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-5-^{14}C-thiazolidine-2,4-dione [7]

In 3 ml of the mixed solvent of dry tetrahydrofuran and dry hexamethylphosphoric triamide (4:1) was dissolved 178.9 mg (1.5 mmol, 2.96 GBq) of 5-^{14}C-thiazolidine-2,4-dione [5], and the solution was cooled in an ethanol dry-ice bath for 10 min. Into the solution was added 2 ml (3.2 mmol) of a 15% hexane solution of BuLi, dropwise, and the resulting solution was stirred for 1 h at the same temperature. Into the reaction mixture was added 790.6 mg (1.95 mmol) of 6 dissolved in 5 ml of the mixed solvent (4:1) in one portion. The resulting solution was stirred for 30 min in an ice bath. After quenching with 0.3 ml of conc. hydro-

chloric acid, 50 ml of water was added to the reaction mixture and the product was extracted with cyclohexane twice (50 ml and 20 ml). The extract was dried over sodium sulfate and evaporated under reduced pressure, to give 990 mg of the crude product as an orange oil. The oil was subjected to reversed-phase Lobar column chromatography [Merck, RP-18, 70 ml, eluent; MeCN:H_2O=4:1, 8 ml/min], to give 430 mg (59%) of **7** as a yellow oil.

5-[4-(6-Hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-5-^{14}C-thiazolidine-2,4-dione [4]

A mixture comprising 430 mg (0.887 mmol) of **7**, 10 ml of ethylene glycol mono methyl ether, and 1 ml of conc. hydrochloric acid, was heated at 130°C for 30 min. To the reaction mixture was added 50 ml of brine, and it was then extracted with ethyl acetate (50 ml x 2). The extract was dried over sodium sulfate and evaporated under reduced pressure, to give 750 mg of crude **4** as an oily substance. The oil was subjected to silica gel Lobar column chromatography [Merck, Si-60, 70 ml, eluent; benzene:ethyl acetate=4:1, 10 ml/min], to give 350 mg of **4** as a pale yellow oil. This oil was diluted with 1.3 g (2.948 mmol) of cold CS-045 [**1**], followed by recrystallization from benzene, to yield 1.29 g (2.925 mmol) of **4** (907.4 MBq, specific activity: 703.4 kBq/mg). To the mother liquor was added 0.2 g (0.454 mmol) of cold CS-045 [**1**], followed by recrystallization from benzene, to give 0.33 g (0.748 mmol) of **4** (185 MBq, specific activity: 561.3 kBq/mg).

REFERENCES

1) Yoshioka, T., Fujita, T., Kanai, T., Aizawa, Y., Kurumada, T., Hasegawa, K., and Horikoshi, H. - J. Med. Chem. 32: 421 (1989).

2) Fujiwara, T., Yoshioka, S., Yoshioka, T., Ushiyama, I., Horikoshi, H. - Diabetes, 37: 1549(1988).

3) Yoshioka, T., Kitazawa, E., Kurumada, T., Yamazaki, M., Hasegawa, K., and Fujita, T. - Eur. Pat. Appl. EP 207,581. [Chem. Abstr. 106, 119879r].

4) Taylor, J. D. and Wolfe, J. F. - Synthesis, 1970: 310.

5) Barrett, G. C. - Tetrahedron, 36: 2023 (1980).

6) Deghenghi, R and Daneault, G. - Can. J. Chem., 38: 1255 (1960).