SYNTHESIS OF (±)-trans-6-[4,4-bis(4-FLUOROPHENYL)-3-(1-METHYL-1H-TETRAZOL-5-YL)-1(E),3-[2-^{14}C]BUTADIENYL]-4-HYDROXY-3,4,5,6-TETRAHYDRO-2H-PYRAN-2-ONE

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SUMMARY

A convergent synthesis of the title compound (BMY-22089) is described. [^{14}C]Methyl iodide was used to alkylate 1,5-dimethyltetrazole which was added to 4,4'-difluorobenzophenone to give the tertiary alcohol 4. Dehydration gave the olefin 5 which was brominated and converted to the phosphonate 7 with trimethylphosphite. Coupling of the carbanion of 7 with cis-2,2-dimethyl-6-formyl-1,3-dioxane-4-acetic acid tert-butyl ester (8) produced the diene 9. Sequential hydrolysis steps using acid and base gave the dihydroxy acid 11 which was converted to the lactone 12 with the use of dicyclohexylcarbodiimide. The overall yield was 20%.

Key Words:

(±)-trans-6-[4,4-bis(4-fluorophenyl)-3-(1-methyl-1H-tetrazol-5-yl)-1(E),3-[2-^{14}C]butadienyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, HMG-CoA reductase inhibitor, hypocholesterolemic.

INTRODUCTION

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) is the rate limiting enzyme in the biosynthesis of cholesterol. Inhibition of this

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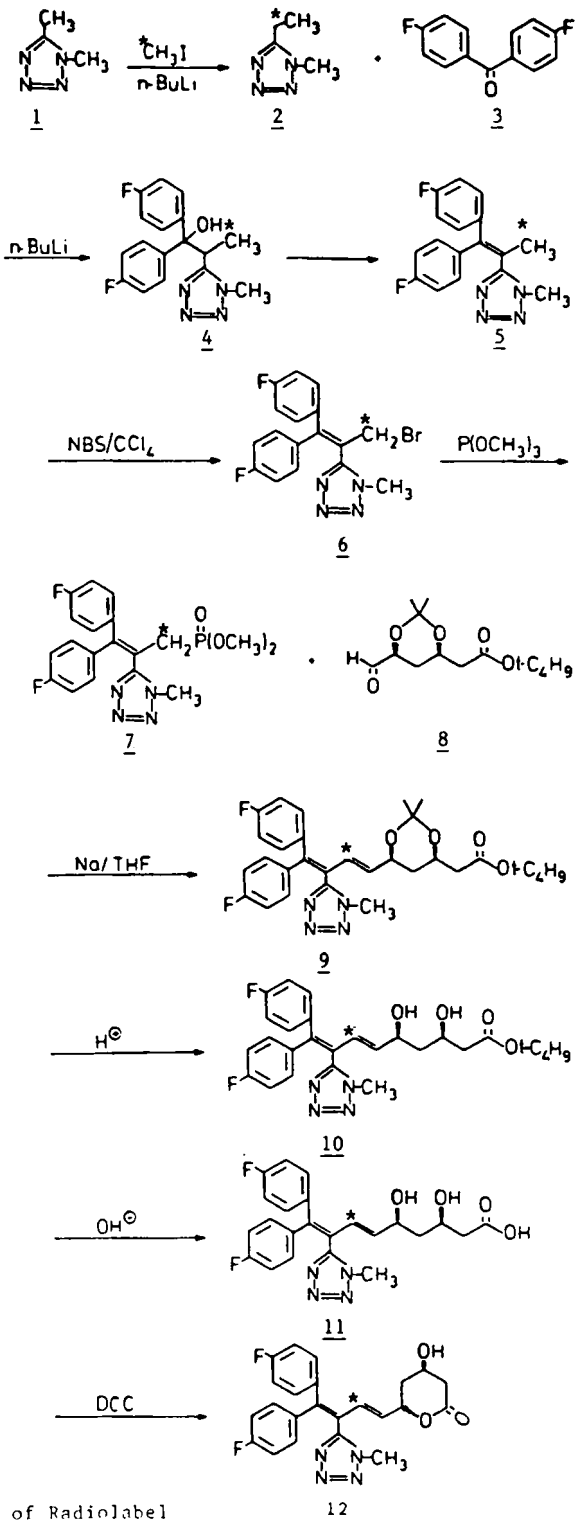
enzyme has proven to be an effective method for lowering serum cholesterol levels in both animals and man.[1] The search for synthetic compounds more potent than the natural products compactin or mevinolin as competive inhibitors of HMG-CoA reductase has led to the discovery of BMY-22089.[2] During the development of BMY-22089, pharmacokinetic and drug distribution studies were essential to understand its absorption in various animal models used in the investigation of safety and efficacy. This paper describes the preparation of (±)-trans-6-[4,4-bis(4-fluorophenyl)-3-(1-methyl-1H-tetrazol-5-yl)-1(E),3-[2-^{14}C]-butadienyl]-4-hydroxy-3,4,5,6-tetrahydro- 2H-pyran-2-one (12) ([^{14}C] BMY-22089).

DISCUSSION

The synthesis of [^{14}C] BMY-22089 was accomplished in nine steps following the reaction scheme shown. Although several different syntheses were possible[2], the one described here held several advantages from a radiochemical synthetic standpoint. First, the labeled carbon could be introduced using [^{14}C]methyl iodide which is relatively inexpensive and readily available. This also placed the label on a metabolically stable carbon. Second, by using a convergent synthesis, the right half of the molecule that results in the formation of the lactone ring could be prepared "cold" and coupled in one step. This was especially helpful since the intermediate 8 contains both of the chiral centers and a pure cis compound was necessary to produce a stereochemically pure product. Purification losses to obtain pure 8 were with "cold" material. Third, except for two steps using refluxing toluene (dehydration of 4 to 5 and formation of phosphonate 7), reaction conditions were very mild. In several of the alternate synthetic schemes, high temperatures and "neat" conditions were necessary which held the potential for significant radiolysis.

5-[2-^{14}C]Ethyl-1-methyltetrazole (2) was prepared in high yield by alkylation of 1,5-dimethyltetrazole with [^{14}C]methyl iodide. Treatment of 2 with n-butyllithium at -70°C produced the lithio anion which was condensed with 4,4-difluorobenzophenone to give the tertiary alcohol 4 in 55% yield. Acid catalyzed dehydration of 4 gave the olefin 5 which was brominated with N-bromosuccinimide and converted to the phosphonate 7 by reaction with trimethylphosphite in refluxing toluene. The last three reactions proceeded cleanly giving white crystalline products in yields of 87-97%. The phosphonate was then elaborated into the diene 9 following the general procedure of Wadsworth and Emmons.[3] The carbanion of 7 was formed very slowly at room temperature using sodium hydride in THF and reacted with aldehyde 8. The anion could be generated more rapidly at -70°C using n-butyllithium but the reaction product was not

REACTION SCHEME



*Position of Radiolabel

as clean. Cis-2,2-Dimethyl-6-formyl-1,3-dioxane-4-acetic acid tert-butyl ester had been synthesized separately in four steps starting from trans-cinnamaldehyde and tert-butyl acetoacetate. Flash chromotography of 9 on silica gel afforded pure diene as a white solid in 80% yield. The acetonide protecting group was removed under acid conditions followed by basic hydrolysis of the ester group to yield the dihydroxy acid 11. Lactonization was rapid in the presence of dicyclohexylcarbodiimide. Purification by flash chromatography and crystalization from toluene yielded [^{14}C] BMY-22089 (12) as a white powdery solid having a radiochemical purity of 96.7%.

EXPERIMENTAL

[^{14}C]Methyl iodide was purchased from Amersham Corporation, U.K. 1,5-Dimethyltetrazole was purchased from Dynamit Nobel AG. N-Bromosuccinimide was purchased from Pfaltz & Bauer, Inc. and recrystallized before using. Cis-2,2-Dimethyl-6-formyl-1,3-dioxane-4-acetic acid tert-butyl ester was synthesized and supplied by J.D. Catt, Bristol-Myers Squibb Research, Wallingford, CT. All other reagents were ACS grade or the highest quality commercially available.

Proton NMR spectra were recorded in $CDCl_3$ on a Bruker Model AM 360 spectrometer using TMS as an external standard. Radioactivity was measured by a Beckman LS9000 liquid scintillator. Radiochemical purity was determined by HPLC. TLC was carried out on precoated silica gel GF (250μ) plates (Analtech) and visualized using UV light (254nm). Flash chromatography was performed on silica gel (32-63μ) obtained from ICN Biochemicals.

All experimental conditions were optimized using non-radiolabelled materials. NMR spectra were obtained for each intermediate of the cold synthesis as well as melting points on crystalline products. In the radiolabelled synthesis only an NMR on the final product was recorded.

5-[2-^{14}C]Ethyl-1-methyltetrazole (2).

A solution of 1,5-dimethyltetrazole (1.54 g, 15.70 mmol) in dry tetrahydrofuran (14 ml) was cooled to -70°C and treated with n-butyllithium (6.30 ml of a 2.5M solution in hexanes) over 5 min under a nitrogen atmosphere. The resultant mixture as stirred at -70°C for 30 min and then a solution of [^{14}C]methyl iodide (300 mCi in 2 ml of tetrahydrofuran, 54 mCi/mmol) and unlabeled methyl iodide (1.576 g, 11.10 mmol) was added via syringe over 8 min to the anion. Stirring was

continued for an additional 40 min at -70°C. The cooling bath was removed and the mixture was diluted with water (5 ml) and ethyl acetate (14 ml). The organic layer was separated, washed once with sat'd brine solution and dried over Na_2SO_4. The brine and aqueous layers were combined, extracted further with methylene chloride (2 x 12 ml) and the extracts were added to the ethyl acetate extract. Evaporation of the solvents gave 1.562 g (89% yield) of a dark yellow liquid which was used directly in the next reaction without purification.

1,1-Bis(4-fluorophenyl)-2-(1-methyl-1H-tetrazol-5-yl)-[3-^{14}C]propanol (4).

To a solution of 2 (1.562 g, 13.93 mmol) in dry tetrahydrofuran (15 ml) was added n-butyllithium (5.57 ml of a 2.5M solution in hexanes) over 5 min at -70°C under a nitrogen atmosphere. The dark yellow solution was stirred for 20 min at -70°C and then added through an 18" double-ended needle to a well stirred solution of 4,4-difluorobenzophenone (3.04 g, 13.93 mmol) in dry tetrahydrofuran (15 ml) at -65°C. The dry ice/acetone cooling bath was freshened and the dark solution was stirred for 16 hr.

The reaction solution was added rapidly to a stirred mixture of ice (39.5 g), toluene (26 ml) and conc. HCl (2.50 ml). After 10 min the toluene layer was separated and the aqueous phase was extracted once with methylene chloride (20 ml). The combined extracts were dried (Na_2SO_4), concentrated *in vacuo* to about 15 ml and the syrupy residue was seeded with crystals of unlabeled 4. The slowly crystallizing mixture was stored at 5°C for 3 hr, filtered and the filter cake rinsed with cold toluene. Drying *in vacuo* yielded 2.546 g (55%) of 4 as a white solid.

1,1-Bis(4-fluorophenyl)-2-(1-methyl-1H-tetrazol-5-yl)-[3-^{14}C] propene-(5).

A slurry of the tertiary alcohol 4 (2.546 g, 7.70 mmol) and p-toluenesulfonic acid monohydrate (85 mg) in toluene (40 ml) was stirred and heated at reflux with a Dean-Stark trap for 16 hr. Sodium carbonate (504 mg) was added to the solution, stirred at ambient temperature for 20 min and filtered. The filtrate was concentrated to a slushy solid filtered, washed with cold xylene and air dried to a white solid. Yield: 2.235 g (93%).

1,1-Bis(4-fluorophenyl)-3-bromo-2-(1-methyl-1H-tetrozl-5-yl)-[3-^{14}C]propene (6).

A mixture of 5 (2.235 g, 7.16 mmol), N-bromosuccinimide (1.353 g, 7.60 mmol) and benzoyl peroxide (229 mg) in carbon tetrachloride (40 ml) was stirred and heated at reflux, under nitrogen, for 75 min. The reaction mixture was cooled to 35°C, filtered and the filtrate was concentrated to approximately 15 ml. After 17 hr at 5°C the precipitate was filtered, washed with cold carbon tetrachloride and dried in vacuo to a pale yellow solid. Yield: 2.456 g (87%).

Dimethyl 3,3-bis(4-fluorophenyl)-2-(1-methyl-1H-tetrazol-5-yl)-[1-^{14}C] propenylphosphonate (7).

A mixture of 6 (2.456 g, 6.28 mmol) and trimethylphosphite (842 mg, 6.78 mmol) in toluene (25 ml) was stirred and heated at reflux for 40 min under a nitrogen atmosphere. The solvent was evaporated at reduced pressure and the residual solid was triturated with cold 15% ethyl acetate in Skellysolve B. The mixture was cooled at 0°C for 2 hr, filtered and the filter cake rinsed with cold solvent to yield 2.479 g (97%) of 7 as a white solid.

cis-2,2-Dimethyl-6-[4,4-bis(4-fluorophenyl)-3-(1-methyl-1H-tetrazol-5-yl)-1(E),3-[2-^{14}C]butadienyl]-1,3-dioxane-4-acetic acid tert-butyl ester (9).

Phosphonate 7 (2.479 g, 6.07 mmol) was added to a stirred suspension of 60% sodium hydride (255 mg, 6.37 mmol) in dry tetrahydrofuran (25 ml) and the mixture was stirred at ambient temperature. After six hours cis-2,2-dimethyl-6-formyl-1,3-dioxane-4- acetic acid tert-butyl ester (8) (1.57 g, 6.07 mmol) was added and stirring was continued for 16 hr.

The yellow-brown solution was cooled in an ice bath and treated with ethyl acetate (25 ml) and 0.2N HCl (33 ml). The aqueous layer was separated, extracted once more with ethyl acetate (20 ml) and the combined extracts were washed with brine. After drying (Na_2SO_4), the solvents were evaporated to give a cloudy, pale yellow gum. The crude product was then purified by flash chromatography on silica gel using ether: Skellysolve B (1:1) as the eluent. Each fraction was assayed by tlc (silica gel, 3:2 ether/Skellysolve B) and the appropriate ones were combined and evaporated to dryness to give 2.671 g (80%) of the title compound as a white solid.

cis-9,9-Bis(4-fluorophenyl)-3,5-dihydroxy-8-(1-methyl-1H-tetrazol-5-yl)-6,8-[7-^{14}C]nonadienoic acid (11).

A suspension of 9 (2.671 g, 4.83 mmol) in methanol (45 ml) was treated with 0.2N HCl (4.5 ml) and the mixture was stirred at room temperature for 17 hr. To the resulting solution of the dihydroxy ester (10) was added water (11.7 ml) plus 1.0N NaOH (6.3 ml) and stirring was continued for 4 hr.

The methanol was removed at reduced pressure and the residue was diluted with water. The mixture was extracted with two portions of ether (discarded) and the aqueous layer was made acidic by the slow addition of 1.0N HCl (6.0 ml) with ice cooling. The separated gum was extracted into ethyl acetate (2 x 25 ml), dried over Na_2SO_4 and the solvent evaporated to yield 1.92 g (87%) of 11 as a slightly sticky, white solid. The acid was used directly in the next step.

(+)-trans-6-[4,4-Bis(4-fluorophenyl)-3-(1-methyl-1H-tetrazol-5-yl)-1(E),3-[2-^{14}C]butadienyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (12).

A mixture of the dihydroxy acid (11) (1.92 g, 4.21 mmol) and dicyclohexylcarbodiimide (1.17 g, 5.72 mmol) in dry ethyl acetate (40 ml) was stirred at ambient temperature for 3 hr. The mixture was filtered, concentrated to dryness and the residual gum was chromatographed under pressure on silica gel (50g). The column was eluted with ether: ethyl acetate (1:1) and the appropriate fractions were combined to give a white foam. Toluene (11.0 ml) was added and the cloudy mix was warmed to give a clear solution. This solution was seeded with unlabeled crystals of BMY-22089 and stirred at room temperature for 3 hr. The precipitated lactone was filtered, rinsed with cold toluene and dried *in vacuo* to a white, powdery solid. Yield: 1.367 g (74%). The product had a radiochemical purity of 96.7% and a specific activity of 31.4 μCi/mg.

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