Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1521–1526

TETRAHEDRON: *ASYMMETRY*

Synthesis of TAK-218 using (*R*)-2-methylglycidyl tosylate as a chiral building block

Kohji Fukatsu,* Nobuhiro Fujii and Shigenori Ohkawa

Pharmaceutical Research Division, Takeda Chemical Industries, Ltd, 17–85 Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan

Received 16 March 1999; accepted 2 April 1999

Abstract

We performed an asymmetric synthesis of (*S*)-2,3-dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperidinyl)-methyl]-5-benzofuranamine dihydrochloride (TAK-218, **1**), a compound used for the treatment of traumatic and ischemic central nervous system injuries. Oxirane **6**, which was synthesized from (*R*)-2-methylglycidyl tosylate, was treated with aqueous trifluoroacetic acid to afford benzofuranmethanol **7** with inversion of stereochemistry at the stereogenic center. Compound **7** was converted into **1** with high enantiomeric excess in four steps.

1. Introduction

Oxygen radicals and monoamines are possible secondary factors involved in delayed neuronal cell death. In a previous paper,[1] we demonstrated that a 2,3-dihydrobenzofuran (coumaran) derivative, (*S*)-2,3-dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperidinyl)methyl]-5-benzofuranamine dihydrochloride **1** has potent inhibitory activities on lipid peroxidation and dopamine release. These activities inhibited functional deficits in a brain injury model and improved the survival rate in a central ischemia model.

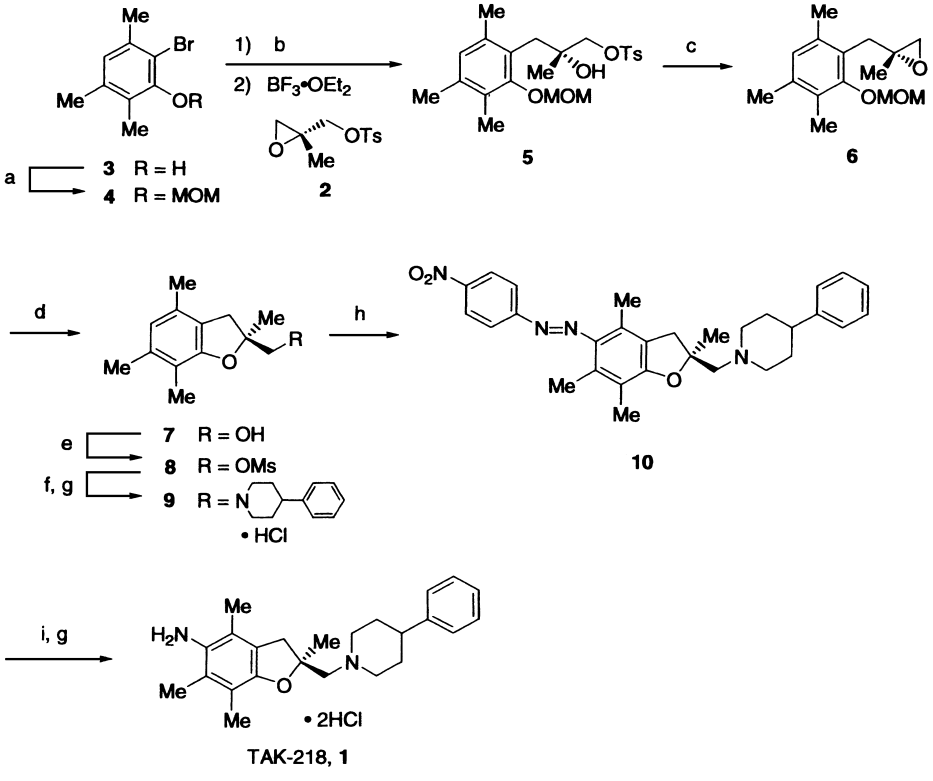
Coumaran derivatives having amino groups at position 5 are used as insecticides,[2] diuretics,[3] and analgesics,[4] however, the enantiomerically pure compounds have not been synthesized. Recently, Hayashi et al. accomplished a high enantioselective coumaran ring construction using a Wacker-type reaction of 2-allylphenols.[5] Harada et al. also reported the asymmetric synthesis of coumarans that have one substituent at position 2, using glycidyl phenyl sulfide as a chiral synthon.[6] Herein we report the asymmetric synthesis of **1**, employing (*R*)-2-methylglycidyl tosylate **2**[7] as a chiral building block.

* Corresponding author. Fax: +81 6 6300 6306; e-mail: fukatsu_kohji@takeda.co.jp

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00138-X

2. Results and discussion

The methoxymethyl ether **4**, prepared from bromophenol **3**, was lithiated, and then condensed with chiral oxirane **2**[7] (94% ee; evaluated by NMR shift analysis) in the presence of boron trifluoride etherate[8] to give tertiary alcohol **5** in 97% yield (Scheme 1). Treatment of the tertiary alcohol **5** with K_2CO_3 caused oxirane ring formation to provide **6** in 93% yield. Coumaran ring construction was achieved with aqueous trifluoroacetic acid to afford **7** in 82% yield with 93% ee. The enantiomeric excess was determined by chiral HPLC analysis using *rac*-**7**, prepared from *rac*-**2**,[9] as a racemic standard. Although the absolute configuration at position 2 could not be determined at this stage, chiral HPLC analysis indicated almost no change in enantiomeric excess after coumaran ring construction.



Scheme 1. Reagents: (a) MOMCl, NaH; (b) *n*-BuLi; (c) K_2CO_3; (d) aq. TFA; (e) MsCl, Et_3N; (f) 4-phenylpiperidine, K_2CO_3; (g) HCl; (h) 4-nitrobenzenediazonium chloride; (i) H_2/Raney-nickel

Introduction of the piperidine moiety was accomplished by methanesulfonylation of the alcohol **7** in quantitative yield, followed by condensation with 4-phenylpiperidine in the presence of K_2CO_3 in *N*,*N*-dimethylacetamide at 180°C. The free base of **9** thus obtained was crystallized as its hydrochloride, and recrystallization of **9** from ethanol/diethyl ether resulted in enrichment of enantiomeric purity (>99% ee) with a yield of 72% from **8**.†

Incorporation of an amino group into position 5 of **9** was accomplished using a two-step sequence; diazo coupling reaction with 4-nitrobenzenediazonium chloride,[10] followed by reductive cleavage of

† The chiral HPLC analysis of *rac*-**9** did not separate the enantiomers. We estimated the enantiomeric excess of **9** in relation to that of the free base of **1** prior to crystallization of its dihydrochloride. See Experimental.

the nitrogen–nitrogen bond using Raney-nickel as the catalyst. The product was crystallized as its dihydrochloride in 70% overall yield from **9**. Comparison of the specific rotation for the synthetic product **1**, $[\alpha]_D$ +27.5 (*c* 0.99, methanol), with the known compound,[1] $[\alpha]_D$ +27.8 (*c* 1.05, methanol), established its absolute stereochemistry as *S* indicating that oxirane **6** was converted to benzofuranmethanol **7** with inversion of stereochemistry at the stereogenic center. In conclusion, we have accomplished the efficient and stereospecific synthesis of enantiomerically pure **1** using the intramolecular cyclization reaction of chiral oxirane **6** as a key step.

3. Experimental

3.1. General methods

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) absorption spectra were recorded with a Shimadzu FTIR-8200PC spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-200 spectrometer (200 MHz) and ^{13}C NMR spectra were recorded on a Bruker DRX500 spectrometer (500 MHz), with tetramethylsilane as the internal standard. Optical rotations were determined with a JASCO DIP-370 digital polarimeter. Mass spectra were measured on a JEOL JMS-AX505W (EI) or a Hitachi M-2000 (SIMS) mass spectrometer. TLC analyses were carried out on Merck Kieselgel 60 F_{254} plates. Elemental analyses were carried out by Takeda Analytical Research Laboratories, Ltd. Tetrahydrofuran (THF) was distilled over calcium hydride prior to use, and other solvents and reagents were used without purification. Raney-nickel used was commercially available as NDHT-90 (Kawaken Finechemical Co. Ltd), and was washed with distilled water (three times) and ethanol (once) prior to use. Solutions in organic solvents were dried over anhydrous $MgSO_4$, and concentration of the organic solution was carried out under reduced pressure. Chromatographic purification was carried out on silica gel columns (Merck Kieselgel 60, 0.063–0.200 mm).

3.2. 2-Bromo-3-(methoxymethoxy)-1,4,5-trimethylbenzene *4*

To a solution of *tert*-butylamine (54 mL, 0.73 mol) in toluene (1.0 L) was added dropwise bromine (59 g, 0.37 mol) at −25°C. After the addition was complete, the mixture was cooled to −78°C. To the mixture was added a solution of 2,3,5-trimethylphenol (50 g, 0.37 mol) in CH_2Cl_2 (250 mL) and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with EtOAc, washed with aqueous $Na_2S_2O_4$ and brine, dried and concentrated to afford crude 2-bromo-3,5,6-trimethylphenol **3**. To a solution of crude **3** in *N*,*N*-dimethylformamide (100 mL) was added 66% NaH (8.2 g, 0.22 mol, dispersed in mineral oil) under a nitrogen current with cooling in an ice-water bath, and the mixture was stirred for 15 min. Then chloromethyl methyl ether (17 mL, 0.22 mol) was added and the mixture was stirred for an additional 30 min. The reaction mixture was poured into ice water and the mixture was extracted with hexane. The extract was washed with brine, dried and concentrated. The residue was distilled to give 31 g (32% yield, from 2,3,5-trimethylphenol) of **4** as a colorless oil: bp 94–96°C/0.2 mmHg; ^{1}H NMR ($CDCl_3$) δ 2.20 (3H, s), 2.24 (3H, s), 2.34 (3H, s), 3.66 (3H, s), 5.04 (2H, s), 6.85 (1H, s).

3.3. (R)-2-Hydroxy-3-[2-(methoxymethoxy)-3,4,6-trimethylphenyl]-2-methylpropyl 4-methylbenzenesulfonate **5**

Under an argon atmosphere, to a solution of **4** (9.6 g, 37 mmol) in THF (100 mL) at −78°C was added dropwise 1.7 M *n*-BuLi hexane solution (22 mL, 37 mmol), and the mixture was stirred for 15 min. Then a solution of (*R*)-2-methylglycidyl tosylate[7] (3.0 g, 12 mmol, 94% ee; evaluated by NMR shift analysis) in THF (5 mL) and boron trifluoride diethyl ether complex (4.7 mL, 37 mmol) were added, and the mixture was stirred for an additional 20 min. To the reaction mixture was added water, and the aqueous mixture was extracted with EtOAc. The extract was washed with brine, dried and concentrated. The residue was purified by column chromatography (EtOAc:hexane=1:4, followed by 1:3) to give 5.1 g (97% yield, based on (*R*)-2-methylglycidyl tosylate) of **5** as a colorless oil: $[\alpha]_D^{20}$ +8.7 (*c* 1.01, ethanol); IR (KBr): 3464, 2944, 1456, 1369, 1190, 1177, 984 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (3H, s), 2.13 (3H, s), 2.20 (3H, s), 2.24 (3H, s), 2.45 (3H, s), 2.83 (1H, d, *J*=14.2 Hz), 3.09 (1H, d, *J*=14.2 Hz), 3.59 (3H, s), 3.85 (2H, s), 4.88 (1H, d, *J*=5.6 Hz), 4.93 (1H, d, *J*=5.6 Hz), 6.81 (1H, s), 7.34 (2H, d, *J*=8.2 Hz), 7.80 (2H, d, *J*=8.2 Hz); MS (SIMS) *m/z*: 422 (M^+, 6), 391 (22), 361 (27), 189 (100), 149 (42).

3.4. (R)-2-[[2-(Methoxymethoxy)-3,4,6-trimethylphenyl]methyl]-2-methyloxirane **6**

A mixture of **5** (5.1 g, 12 mmol) and K_2CO_3 (1.7 g, 12 mmol) in methanol (40 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried and concentrated. The residue was purified by column chromatography (EtOAc:hexane=1:9) to yield 2.8 g (93% yield) of **6** as a colorless oil: $[\alpha]_D^{20}$ −47.2 (*c* 1.02, ethanol); IR (KBr): 2870, 1460, 1452, 1295, 1159, 1076, 1064, 1045, 981 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (3H, s), 2.15 (3H, s), 2.20 (3H, s), 2.26 (3H, s), 2.45 (1H, d, *J*=5.2 Hz), 2.50 (1H, d, *J*=5.2 Hz), 3.03 (1H, d, *J*=14.6 Hz), 3.11 (1H, d, *J*=14.6 Hz), 3.61 (3H, s), 4.91 (2H, s), 6.78 (1H, s); ^{13}C NMR ($CDCl_3$) δ 13.2, 20.0, 20.1, 22.3, 32.6, 53.0, 56.9, 57.4, 99.6, 126.1, 126.6, 127.8, 135.7, 136.3, 155.2; MS (EI) *m/z*: 250 (M^+, 25), 205 (10), 187 (22), 175 (100), 133 (12).

3.5. (S)-2,3-Dihydro-2,4,6,7-tetramethyl-2-benzofuranmethanol **7**

To a solution of **6** (2.8 g, 11 mmol) in THF (22 mL) cooled in an ice-water bath was added dropwise a cold solution of trifluoroacetic acid (4 mL) in water (4 mL), and the mixture was stirred for 30 min. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and the aqueous mixture was extracted with EtOAc. The extract was washed with brine, dried and concentrated. The residue was purified by column chromatography (EtOAc:hexane=1:4, followed by 1:3) to afford 1.9 g (82% yield) of **7** as a colorless solid. The analytical sample was recrystallized from hexane. The enantiomeric excess of **7** was determined to be 93% by LC/MS (column, CHIRALCEL OD-R, 4.6×250 mm, 20°C; eluent, MeCN−0.01 M $AcONH_4$ (1:1); flow rate, 1.0 mL/min; t_R of **7**, 8.8 min; t_R of enantiomer of **7**, 7.7 min), and did not improve after recrystallization from hexane: mp 54–57°C; $[\alpha]_D^{20}$ +2.4 (*c* 1.01, ethanol); IR (KBr): 3326, 2921, 1593, 1456, 1410, 1327, 1294, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (3H, s), 1.94 (1H, t, *J*=6.8 Hz), 2.08 (3H, s), 2.15 (3H, s), 2.19 (3H, s), 2.79 (1H, d, *J*=15.4 Hz), 3.13 (1H, d, *J*=15.4 Hz), 3.55–3.72 (2H, m), 6.51 (1H, s); ^{13}C NMR ($CDCl_3$) δ 11.6, 18.5, 19.3, 23.6, 37.3, 68.6, 88.0, 115.4, 122.5, 122.7, 131.3, 136.6, 157.1; MS (EI) *m/z*: 206 (M^+, 40), 175 (100), 160 (9), 149 (14), 136 (9). Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.45; H, 8.77.

3.6. (S)-(2,3-Dihydro-2,4,6,7-tetramethylbenzofuran-2-yl)methyl methanesulfonate **8**

To a solution of **7** (1.7 g, 8.3 mmol) and triethylamine (1.7 mL, 12 mmol) in THF (14 mL) cooled in an ice-water bath was added dropwise methanesulfonyl chloride (0.71 mL, 9.1 mmol), and the mixture was stirred for 15 min. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried and concentrated to yield 2.3 g (98% yield) of **8** as a colorless solid: mp 70–71°C; $[\alpha]_D^{20}$ +3.1 (*c* 1.00, ethanol); IR (KBr): 2940, 1460, 1366, 1175, 1001, 972, 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (3H, s), 2.05 (3H, s), 2.15 (3H, s), 2.19 (3H, s), 2.88 (1H, d, *J*=15.6 Hz), 3.02 (3H, s), 3.13 (1H, d, *J*=15.6 Hz), 4.26 (2H, s), 6.52 (1H, s); MS (EI) *m/z*: 284 (M^+, 52), 187 (19), 175 (100), 159 (11), 147 (13). Anal. calcd for $C_{14}H_{20}O_2S$: C, 59.13; H, 7.09; S, 11.28. Found: C, 58.86; H, 7.00; S, 11.26.

3.7. (S)-1-[(2,3-Dihydro-2,4,6,7-tetramethylbenzofuran-2-yl)methyl]-4-phenylpiperidine hydrochloride **9**

A mixture of **8** (1.0 g, 3.5 mmol), 4-phenylpiperidine (1.1 g, 7.0 mmol), and K_2CO_3 (0.97 g, 7.0 mmol) in *N*,*N*-dimethylacetamide (5 mL) was stirred under an argon atmosphere at 180°C for 5 h. After cooling, the reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried and concentrated. The residue was purified by column chromatography (EtOAc:hexane=1:19, followed by 1:9). The free base of **9** obtained (0.97 g) was dissolved in ethanol/EtOAc and 4 M HCl/EtOAc was added. The mixture was concentrated and the residue was recrystallized from ethanol/diethyl ether to yield 0.98 g (72% yield, from **8**) of **9** as a colorless solid: mp 178–182°C; $[\alpha]_D^{20}$ +13.1 (*c* 1.00, ethanol); IR (KBr): 2934, 2483, 1456, 1429, 1406, 1283, 1073 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.63 (3H, s), 1.85–2.42 (4H, m), 2.01 (3H, s), 2.13 (3H, s), 2.14 (3H, s), 2.73–3.01 (2H, m), 3.17–3.68 (6H, m), 3.82–3.91 (1H, m), 6.53 (1H, s), 7.22–7.36 (5H, m), 10.53 (1H, br s); MS (SIMS) *m/z*: 350 (MH^+ of free base, 97), 174 (100), 91 (9), 70 (13). Anal. calcd for $C_{24}H_{32}ClNO$: C, 74.68; H, 8.36; Cl, 9.19; N, 3.63. Found: C, 74.46; H, 8.37; Cl, 9.18; N, 3.91.

3.8. (S)-1-[[2,3-Dihydro-2,4,6,7-tetramethyl-5-[(4-nitrophenyl)azo]benzofuran-2-yl]methyl]-4-phenylpiperidine **10**

4-Nitroaniline (0.16 g, 1.1 mmol) was dissolved in 2 N HCl (3 mL) by heating, and the resulting solution was cooled in an ice-water bath. Then a solution of sodium nitrite (79 mg, 1.1 mmol) in water (0.5 mL) was added dropwise and the mixture was stirred for 15 min. The diazonium chloride solution obtained was added to a solution of **9** (0.40 g, 1.0 mmol) in acetic acid (3 mL), and the mixture was stirred at room temperature for 15 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$, and the aqueous mixture was extracted with EtOAc. The extract was washed with water and brine, dried and concentrated. The residue (0.55 g) was used in the next step without further purification.

3.9. (S)-2,3-Dihydro-2,4,6,7-tetramethyl-2-[(4-phenyl-1-piperidinyl)methyl]-5-benzofuranamine dihydrochloride **1**

A mixture of **10** (0.55 g, crude) and Raney-nickel (0.6 g) in ethanol (30 mL) was stirred under a hydrogen atmosphere (5 kgf/cm^2) at room temperature for 2 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (EtOAc:hexane=3:7, followed by 1:1) to afford 0.30 g of the free base of **1**. The enantiomeric excess of this compound

was determined as 99.4% by LC/MS (column, CHIRALCEL OD-R, 4.6×250 mm, 20°C; eluent, MeCN–phosphate buffer (pH 7) (1:1); flow rate, 1.0 mL/min; t_R of **1**, 21.6 min; t_R of enantiomer of **1**, 23.4 min). The free base was dissolved in ethanol and 4 M HCl/EtOAc was added to the solution. The acidic solution was concentrated, and the residue was recrystallized from ethanol/diethyl ether to yield 0.32 g (70% yield, from **9**) of **1** as a colorless crystal. The enantiomeric excess of **1** was determined as 99.8% by LC/MS (analytical condition was the same as used for the free base): mp 226–230°C (lit.[1], 226°C); $[\alpha]_D^{20}$ +27.5 (*c* 0.99, methanol) (lit.[1], $[\alpha]_D$ +27.8 (*c* 1.05, methanol)); IR (KBr): 2946, 2789, 1524, 1454, 1422, 1258, 1080 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.63 (3H, s), 1.82–2.43 (4H, m), 2.07 (3H, s), 2.23 (3H, s), 2.25 (3H, s), 2.74–2.86 (1H, m), 3.01–3.60 (7H, m), 3.78–3.86 (1H, m), 7.20–7.39 (5H, m), 9.93 (3H, br s), 10.62 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 12.0, 14.2, 14.9, 25.6, 29.1, 29.4, 53.5, 54.3, 62.7, 85.5, 116.2, 122.0, 123.0, 125.8, 126.4, 126.5, 128.4, 130.6, 144.4, 154.5; MS (SIMS) *m/z*: 365 (MH^+ of the free base, 96), 174 (46). Anal. calcd for $C_{24}H_{34}Cl_2N_2O$: C, 65.90; H, 7.83; Cl, 16.21; N, 6.40. Found: C, 65.72; H, 7.85; Cl, 15.95; N, 6.31.

Acknowledgements

We thank Mr. Norio Tada for chiral HPLC analyses.

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