AN EFFICIENT SYNTHESIS OF (*S*)-(–)-2,8-DIMETHYL-3-METHYLENE-1-OXA-8-AZASPIRO[4.5]DECANE BY COBALOXIME(I)-MEDIATED RADICAL CYCLIZATION

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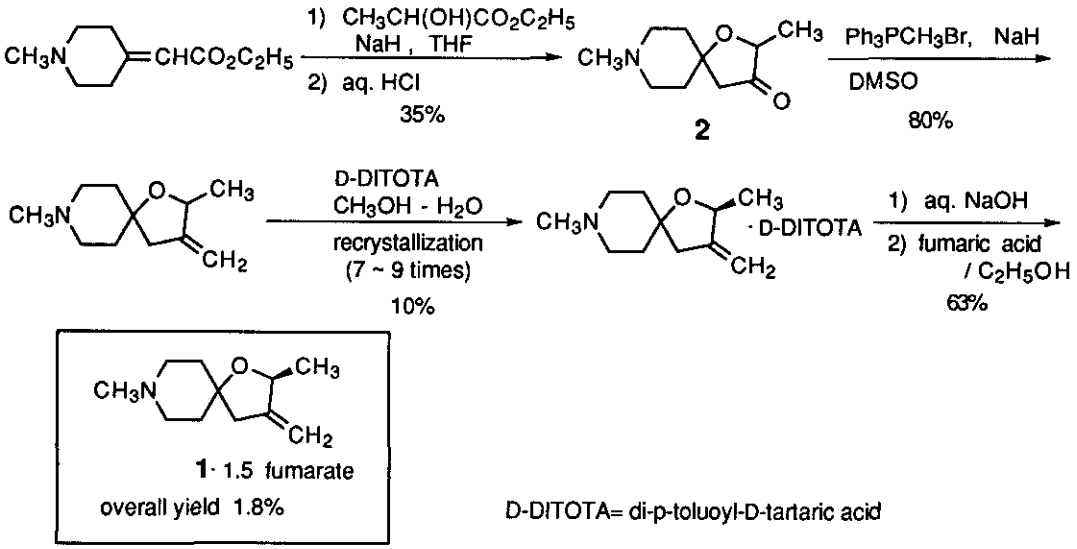
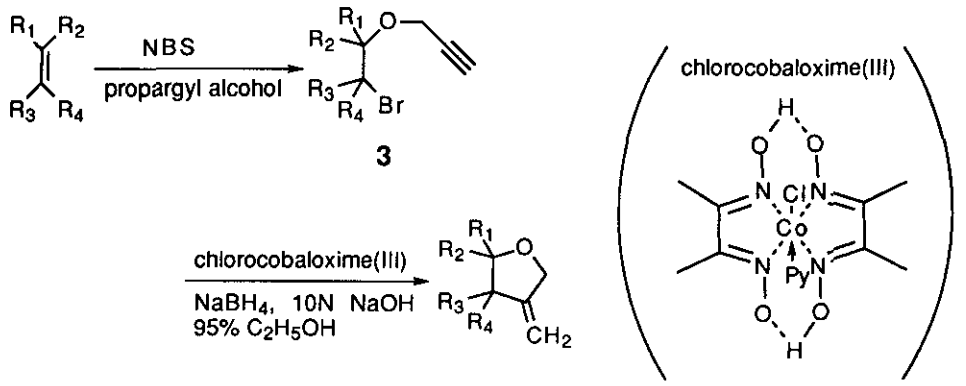
Abstract- Optically pure (*S*)-(–)-2,8-dimethyl-3-methylene-1-oxa-8-azaspiro[4.5]-decane (**1**) was synthesized by alkoxybromination of 1-ethoxycarbonyl-4-methylenepiperidine (**4**) with (*S*)-3-butyn-2-ol and *N*-bromosuccinimide followed by radical cyclization mediated by cobaloxime(I) in 15% overall yield. Reaction conditions for the alkoxybromination reaction were devised to reduce the requirement of the optically pure alcohol.

A novel spirotetrahydrofuran, (*S*)-(–)-2,8-dimethyl-3-methylene-1-oxa-8-azaspiro[4.5]decane (**1**),[1] is an M_1 muscarinic acetylcholine agonist and a potential therapeutic agent for senile dementia of Alzheimer type. The L-tartrate monohydrate of **1** is now under clinical studies as YM796. At first, compound (**1**) was prepared by resolution of the racemate (±**1**), which was prepared *via* the Michael addition-Dieckmann condensation sequence as shown in Scheme 1. Although ethyl (*S*)-(–)-lactate was used as a starting material, complete racemization had occurred during the addition-cyclization reaction. In addition, the resolution required nine-times recrystallizations and resulted in low yield probably due to the long distance between the stereogenic center and the basic nitrogen atom.[2] For preparation in large amounts of **1**, a more efficient method was needed.[3]

A variety of simple or fused 3-methylenetetrahydrofuran rings have been constructed *via* cobaloxime(I)- or tributyltin hydride-mediated reductive cyclization of 2-[(2-propynyl)oxy]ethyl bromide (**3**), which was prepared by treatment of olefines with *N*-bromosuccinimide (NBS) and an excess of propargyl alcohol (Scheme 2).[4-9] We



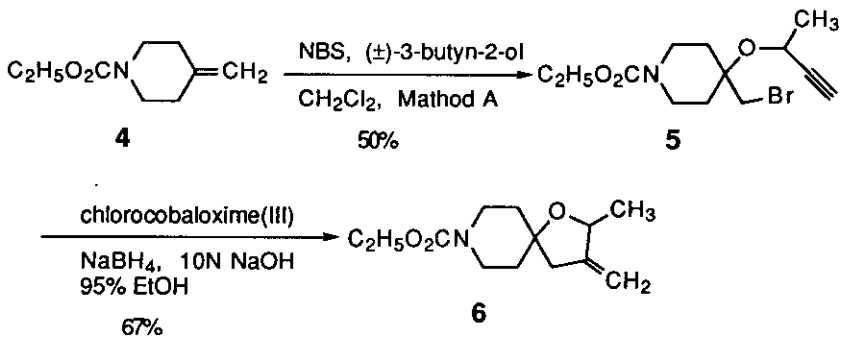
Scheme 1



Scheme 2

applied this method to the synthesis of 3-methylene-5-spirotetrahydrofuran (**1**), because the racemization seemed not to occur during the addition-cyclization reactions. To our knowledge, there are three papers published on the application of the reactions to the construction of spirotetrahydrofurans, which include 3-methylene-4-[7,8] and 3-methylene-2-spirotetrahydrofurans.[9]

First, the alkoxybromination-cyclization sequence was tested with racemic 3-butyn-2-ol by the method described in literatures (Scheme 3).[4,5] Addition of 1-ethoxycarbonyl-4-methylenepiperidine (**4**), which was obtained by Wittig reaction from 1-ethoxycarbonyl-4-piperidone, to a mixture of 2 equiv. of NBS and 18 equiv. of 3-butyn-2-ol in methylene chloride at –30 ℃ gave desired bromide (**5**) in 50% yield. It should be noted that moderate yields (52—61%) were reported for alkoxybromination of vinyl ether with secondary or tertiary propargyl alcohols,



Scheme 3

Table 1. Investigation of reaction conditions of the alkoxybromination reaction.

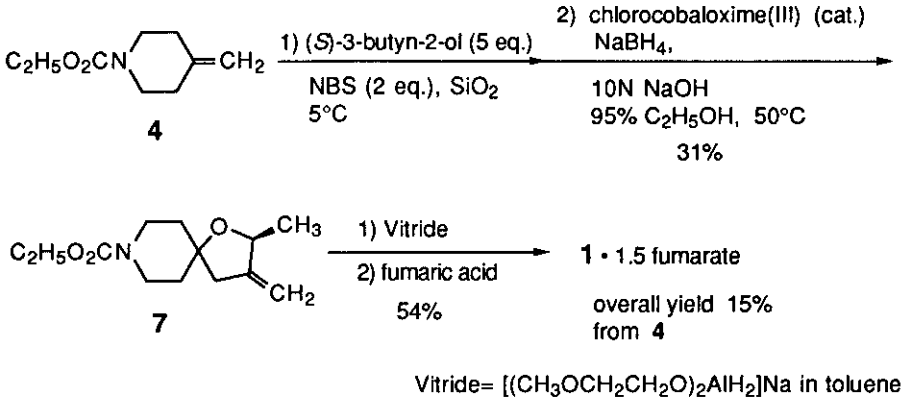
run	method	alcohol (equiv.)	NBS (equiv.)	solv.	temp.[a] (℃)	time[b] (h)	yield (%) based on 4	yield (%) based on alcohol
1	A[c]	18	2	CH_2Cl_2	–30	24	50	2.8
2	B[d]	18	2	CH_2Cl_2	–40	5	61	3.4
3	B	18	1	CH_2Cl_2	–40	7	39	2.2
4	B	10	2	—	5	5	54	5.4
5	B	10	3	—	5	5	50	5.0
6[e]	B	10	2	—	5	5	58	5.8
7	B	10	2	—	rt[f]	2	43	4.3
8	B	5	2	CH_2Cl_2	–40	20	37	7.4
9	B	5	2	CH_2Cl_2	5	9	35	7.0
10	B	5	2	—	5	6	44	8.8

a) Reagents were mixed at the cited temperature. b) The reaction mixture was stirred for the described time at room temperature. c) **4** was added to a mixture of (±)-3-bytyn-2-ol and NBS. d) NBS was added to a mixture of **4** and (±)-3-bytyn-2-ol. e) Silica gel (10 g / mol of **4**) was used. f) Room temperature

although the detailed experimental conditions were not described. The bromide (**5**) was treated with a catalytic

amount of bis(dimethylglyoximato)(pyridine)cobalt(III) chloride[10] [hereafter chlorocobaloxime(III) in the text and Schemes) and equimolar amount of sodium borohydride. The radical cyclization mediated by cobaloxime(I), which was generated in situ *via* the reduction of chlorocobaloxime(III) by sodium borohydride, proceeded smoothly in 5-exo-dig fashion to afford 3-methylene-5-spirotetrahydrofuran (**6**) in acceptable yield (67%). Thus, this strategy seemed to be promising, while some device was needed to reduce the requirement of the alcohol.

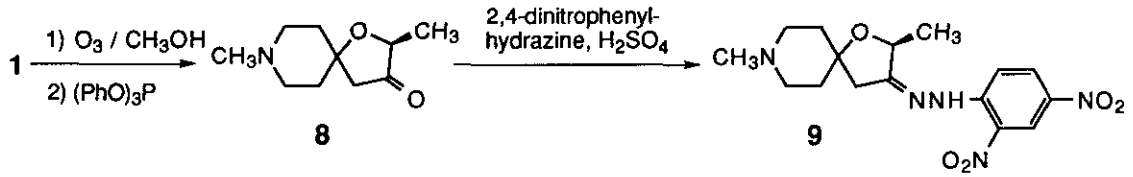
Next, the reaction conditions for the alkoxybromination reaction were investigated as described in Table 1. Both yields based on **4** and the alcohol were described. The order of mixing of reagents was not important (run 1 vs. 2). Two equiv. of NBS was optimum (run 2 vs. 3, 4 vs. 5). Interestingly, it was not necessary to cool the mixture below –30 ℃ for mixing of reagents. Cooling to 5 ℃ was acceptable (run 8 vs. 9). The yield based on the alcohol was a little improved when reaction was executed without solvent (run 9 vs. 10). On the other hand, use of tetrahydrofuran reduced the yield (data not shown). Reduction of the quantity of the alcohol from 18 equiv. to 5 equiv. decreased the yield based on **4**, whereas it increased that based on the alcohol. In some cases, addition of silica gel was reported to improve the yield of alkoxybromination.[5] But in this case, use of silica gel only little improve the yield (run 6). Consequently, combination of run 10 and the use of silica gel seemed to be practically optimum.



Scheme 4

Finally, by using the optimum conditions, the synthesis of **1** was performed as shown in Scheme 4. (*S*)-(–)-3-Butyn-2-ol was prepared by the method described in the literature[11] and the optical purity was confirmed by GLC analysis to be 99% ee (column; CP Cyclodex β 236 M). A mixture of **4**, (*S*)-(–)-3-butyn-2-ol, and silica gel was treated with NBS at 5 ℃ and the resulting crude bromoethyl ether was used for reductive cyclization reaction

without further purification to afford **7** in 31% yield based on **4**. Thus purification of the intermediate [(*S*)-**5**] was proved not to be necessary. The ethoxycarbonyl group was reduced to a methyl group with bis(2-methoxyethoxy)aluminum hydride and the obtained **1** was transformed to sesquifumarate in 54% yield. The optical purity of **1** was examined to be 98% ee by hplc of 2,4-dinitrophenylhydrazone (**9**) derived from **1** by usual methods as described in Scheme 5. Thus this method afforded optically pure **1** in 15% overalll yield in three steps from **4**.



Scheme 5

In summary, a new efficient synthetic method of optically pure **1** was accomplished by the alkoxybromination-radical cyclization sequence. This route has following advantages; 1) resolution is easy and is performed in the first stage; 2) the optical purity of the raw material is conserved in the final product; 3) all intermediates are able to be purified by distillation. This study also provides alkoxybromination reaction devised for sterically hindered substrates: a secondary alcohol and an exo-methylene group.

EXPERIMENTAL

All melting points were determined with a Yanaco MP-3 melting point apparatus and are uncorrected. ^{1}H-Nmr spectra were measured with either a JEOL FX90Q or a FX100 spectrometer; chemical shifts are recorded in parts per million (δ unit) using tetramethylsilane as an internal standard (in nmr description s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, and dq=double quartet). Mass spectra were recorded with a Hitachi M-80 or JEOL JMS-DX300 spectrometer. All solutions were dried over anhydrous magnesium sulfate and concentration was performed *in vacuo*.

(±)-4-Bromomethyl-1-ethoxycarbonyl-4-[(1-methyl-2-propynyl)oxy]piperidine (5). Reaction conditions were investigated by the following method A or B and factors were changed as described in Table 1.

Method A (run 1); NBS (1.12 g, 6.3 mmol) was added to (±)-3-butyn-2-ol (4.2 ml, 54 mmol) cooled to –30 ℃. To the mixture, a solution of 1-ethoxycarbonyl-4-methylenepiperidine (**4**, 0.51 g, 3 mmol) in methylene chloride (3 ml) was added dropwise during 1 h and the mixture was stirred for 24 h at room temperature. After

addition of 1N aqueous NaOH, the mixture was extracted with methylene chloride. The extract was washed with 1N aqueous NaOH, dried, and concentrated. The resulting residue was purified by silica gel column chromatography (ethyl acetate–*n*-hexane, 1:8, v/v) to give **5** (0.48 g, 50%), bp 96—98℃ (0.6 mmHg). Ms (m/z): 319, 317; ^{1}H-nmr ($CDCl_3$) δ: 1.23 (t, *J*=7.1 Hz, 3H), 1.48 (d, *J*=6.5 Hz, 3H), 1.5—2.2 (m, 4H), 2.40 (d, *J*=2.7 Hz, 1H), 2.9—3.8 (m, 6H), 4.14 (q, *J*=7.1 Hz, 2H), 4.28 (dq, *J*=2.7, 6.5 Hz, 1H).

Method B (run 2); A mixture of **4** (0.51 g, 3 mmol) and (±)-3-butyn-2-ol (4.2 ml, 54 mmol) was cooled to –40° C and NBS (1.12 g, 6.3 mmol) was added in small portions at the same temperature. The mixture was stirred for 5 h at room temperature. After addition of saturated aqueous $NaHCO_3$, the mixture was extracted with methylene chloride. The extract was dried and concentrated. The residue was purified by the same method as described above to give **5** (0.58 g, 61 %).

(±)-8-Ethoxycarbonyl-2-methyl-3-methylene-1-oxa-8-azaspiro[4.5]decane (6). Sodium borohydride (0.33 g, 9 mmol) was added to a solution of **5** (2.3 g, 7.2 mmol) and 10 N aqueous NaOH (0.72 ml) in 95% ethanol (72 ml). The mixture was flushed with argon gas, and 0.2 g (0.45 mmol) of chlorocobaloxime(III)[10] was added in small portions during 1 h at 50 ℃. The reaction mixture was stirred for 30 min at the same temperature and concentrated. Water was added to the residue and the mixture was extracted with ethyl acetate. The extract was washed with water and saturated aqueous NaCl, dried, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate–*n*-hexane, 1:9, v/v) to give **6** (1.15 g, 67%); bp 85—88℃ (0.8 mmHg). Ms (m/z) 239(M^+); ^{1}H-nmr ($CDCl_3$) δ: 1.25 (t, *J*=7.3 Hz, 3H), 1.29 (d, *J*=7.3 Hz, 3H), 1.45—1.85 (m, 4H), 2.44 (m, 2H), 3.2—3.8 (m, 4H), 4.13 (q, *J*=7.3 Hz, 2H), 4.3—4.6 (m, 1H), 4.85 (q, *J*=2.2 Hz, 1H), 4.96 (q, *J*=2.2 Hz, 1H).

(*S*)-8-Ethoxycarbony-2-methyl-3-methylene-1-oxa-8-azaspiro[4.5]decane (7). NBS (42.7 g, 0.24 mol) was added to a mixture of **4** (20.3 g, 0.12 mol), (*S*)-3-butyn-2-ol (42.1 g, 0.60 mol), and silica gel (1.2 g) at 0—5 ℃ and the resulting mixture was stirred for 8 h at room temperature. Saturated aqueous solution of $NaHCO_3$ was added to the reaction mixture and the mixture was extracted with methylene chloride. The extract was dried and concentrated to give crude (*S*)-4-bromomethyl-1-ethoxycarbony-4-[(1-methyl-2-propynyl)oxy]-piperidine (65 g). To a solution of the crude product in 95% EtOH (720 ml), 7.2 ml (72 mmol) of 10 N aqueous NaOH and sodium borohydride (13.6 g, 0.36 mol)were added. The solution was flushed with argon gas, and powdered chlorocobaloxime(III) (2.4 g, 6 mmol) were added in small portions over a period of 1 h at 50 ℃. After the completion of the addition, the reaction mixture was stirred for 1 h at 50 ℃. The reaction mixture was filtered and the filtrate was concentrated. The residue was mixed with water and extracted with ethyl acetate. The

combined organic layer was washed with water, 1 N HCl, water, and saturated aqueous NaCl and dried. After the evaporation of the solvents, the residue was purified by silica gel column chromatography (ethyl acetate–*n*-hexane, 1:10) to give **7** (8.8 g, 31% yield). $[\alpha]_D^{20}$ –39.2° (c=1.05, MeOH).

(*S*)-2,8-Dimethyl-3-methylene-1-oxa-8-azaspiro[4.5]decane (1) sesquifumarate. A mixture of **7** (8.4 g, 35 mmol), Vitride (70% toluene solution of sodium bis(2-methoxyethoxy)aluminum hydride; Nacalai Tesqui, Inc., 35 g), and toluene (70 ml) was stirred at room temperature overnight. To the reaction mixture, 150 ml of 2 N aqueous NaOH was added at 0—5 ℃ and the mixture was extracted with toluene. The toluene solution was concentrated and the residue was distilled under reduced pressure to give the free base of **1** (4.05 g, 64%), bp 99—103 ℃ (23 mmHg).

The obtained free base (3.98 g, 22 mmol) was treated with fumaric acid (3.75 g, 32 mmol) in acetonitril (60 ml) to give the sesquifumarate of **1** (6.1 g, 54% from **7**), $[\alpha]_D^{20}$ –27.6° (c=1.5, MeOH) ($[\alpha]_D^{20}$ –28.3° (c=1.1, MeOH for **1** sesquifumarate obtained by optical resolution[2]), mp 127—129 ℃. ^{1}H-Nmr (DMSO-d_6) δ: 1.20 (d, *J*=7.1 Hz, 3H), 1.6—2.0 (m, 4H), 2.48 (m, 2H), 2.58 (s, 3H), 2.9—3.1 (m, 4H), 4.40 (m, 1H), 4.87 (m, 1H), 4.95 (m, 1H), 6.50 (s, 3H), 10.96 (br s, 3H). Anal. Calcd for $C_{11}H_{19}NO{\cdot}C_6H_6O_6$: C; 57.45, H; 7.09, N; 3.94. Found: C; 57.32, H; 7.16, N; 3.78.

Analysis of optical purity was as follows. A methanol (25 ml) solution of the free base (18 mg, 0.1 mmol) of **1** was treated with ozone gas at –70 ℃. After excess ozone was expelled with argon gas, triphenylphosphite (0.89 g, 2.9 mmol) was added to the mixture and the mixture was stirred for 20 h at room temperature. Methanol was removed *in vacuo* and the residue was dissolved in water (20 ml) and treated with aqueous 2,4-dinitrophenylhydrazine (0.21 g, 1 mmol) and conc. sulfuric acid (2.5 ml) at 0—5 ℃ for 1 h. The solid deposited was collected by filtration on a glass filter and washed with water and diethyl ether to give 14 mg of solid. Thus obtained hydrazone was dissolved in methanol and analyzed by hplc; column: Resolvosil-BSA-7, eluent: 0.01 M phosphate buffer (pH 8.0)–*n*-propanol (95:5, v/v), flow rate: 1 ml/min. In a typical run, the retention time of the hydrazone derived from (+)-isomer of **1** was 6.29 min and that of the hydrazone derived from **1** was 9.90 min. In this method, the compound **1** obtained as described above exhibited 98% ee.[12]

ACKNOWLEDGEMENTS

We thank Drs. K.Murase, T. Mase, and S. Usuda for their helpful discussions. Thanks are also due to Mr. Kohinata for hplc analysis and Mr. Matsumoto for glc analysis of optical purity.

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Received, 27th March, 1995