Stereochemical Control in Microbial Reduction. 12. (*S*)-4-Nitro-2-butanol as a Source to Synthesize Natural Products

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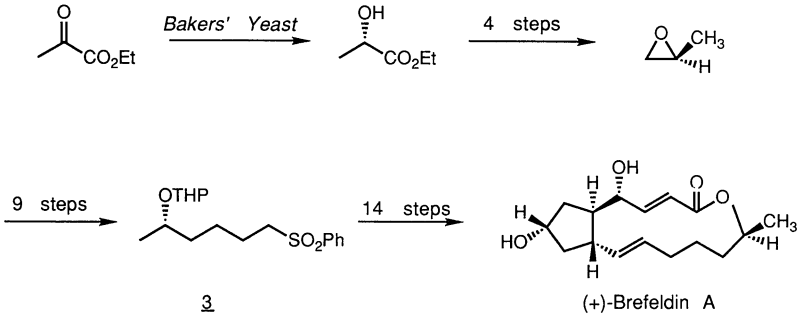
(*S*)-(+)-4-Nitro-2-butanol (**1**) obtained by the stereoselective reduction of 4-nitro-2-butanone by bakers' yeast was employed for the syntheses of natural products. A precursor of (+)-brefeldin A is synthesized starting from this chiral building block by 10 steps short-cut procedure compared with the shortest method so far reported. (*S*)-(+)-Sulcatol is obtained in much better enantiomeric purity than those reported. The reactivity of **1** in base-catalyzed condensations with Michael acceptors or aldehydes is largely affected by a base employed as the catalyst.

In a previous paper of the series from our laboratory, it was reported that enantiomerically pure (*S*)-(+)-4-nitro-2-butanol ((*S*)-**1**) and (*S*)-(+)-5-nitro-2-pentanol ((*S*)-**2**) are obtained easily from the corresponding nitro ketones by the reduction with bakers' yeast.[1] Since the electron-withdrawing property of a nitro group activates its α-position for the generation of a carbanion, **1** and **2** can be converted into various compounds with a variety of carbon skeltons. The nitro group is the strongest electron-withdrawing group among neutral functional groups.

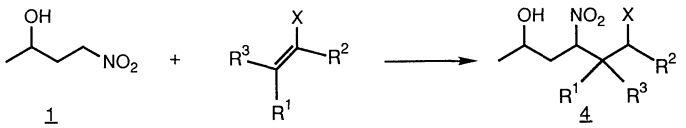
In order to demonstrate the utility of **1** and **2** as valuable chiral building blocks in organic syntheses, we attempted to synthesize several biologically active natural products starting from these compounds. The first example concerns with the synthesis of (+)-brefeldin A, in which the carbanion generated from **1** was subjected to the Michael addition to phenyl vinyl sulfone. (+)-Brefeldin A has been isolated from *Penicillium sp.* and other fungi.[2] The compound has been found to have a wide range of biological activity including antiviral,[3] anti-fugal,[4] antimitotic[5] as well as antitumor[6] activities. The structure was elucidated in 1971 by X-ray crystallography.[7] After the pioneering study by Corey and Wollenberg,[8] there appeared several reports concerning with the asymmetric total synthesis of this compound.[9–11] The shortest procedure so far reported may be that reported by Gais and Lied, where a key compound, 1-phenylsulfonyl-5-(tetrahydropyranyloxy)hexane (**3**), was prepared after 12 steps.[11] The process involves the stereoselective reduction of ethyl pyruvate by bakers' yeast and the conversion of the resulted ethyl (*S*)-lactate into (*S*)-2-methyloxirane.[12] The transformation of the last compound into **3** required additional 9 steps. When, on the other hand, **1** is subjected to the reduction mediated by bakers' yeast, the product, (*S*)-4-nitro-2-butanol (**1**), can afford **3** after only 3 steps; the Michael addition, reductive denitration, and tetrahydropyranylation. Thus, asymmetric synthesis of (+)-brefeldin A can be shorten by 10 steps, exemplifying that the nitro alcohol is much superior to the hydroxy ester in modifying the carbon skelton.

The second example is the total synthesis of (*S*)-(+)-sulcatol. A 65:35 mixture of (*R*)-(−)- and (*S*)-(+)-sulcatols is an aggregation pheromone of *Gnathotrichus sulcatus*.[13] After asymmetric syntheses of (*R*)-(−)- and (*S*)-(+)-sulcatols,[14,15] it was found that *Gnathotrichus retusus* responds only for the (*S*)-(+)-enantiomer.[16] The key process in this synthesis is the condensation of an α-nitro carbanion to an aldehyde which is followed by dehydration and reductive denitration to afford an olefinic alcohol. Although the process employed here is not surprisingly shorter than the other,[15] where the reduction of ethyl acetoacetate by bakers' yeast was employed, the enantiomer excess observed in the reduction of 4-nitro-2-butanone (99% e.e.)[1] is much higher than that of the β-keto ester (86—87% e.e.).[15,17]



Scheme 1.

Table 1. The Michael Addition of a Carbanion from 4-Nitro-2-butanol[a]



Compd.	Olefin R¹	R²	R³	X	Base	Equivalency	Yield of 4/%[b]
a	H	H	H	$CH_3C(=O)$	TMG	0.1	91.5
					TMG	0.3	75.5
					DBU	1.0	Decomp
					Et_3N	0.1	No react'n.
b	H	H	H	$CH_3OC(=O)$	TMG	0.1	76.3
					TMG	0.3	74.2
					DBU	0.3	37.5
					DBU	1.0	Decomp
					Et_3N	0.1	No react'n.
					Ph_3P	0.1	47.3
c	H	H	H	$C_2H_5OC(=O)$	TMG	0.1	83.3
					TMG	0.3	81.5
					DBU	0.3	31.3
					DBU	1.0	Decomp
					Et_3N	0.1	No react'n.
d	H	H	H	$PhSO_2$	TMG	0.1	77.6[c]
					Ph_3P	0.1	49.4[c]
e	H	H	H	$PhS(=O)$	TMG	0.1	No react'n.
					DBU	0.1	No react'n.
f	H	H	H	CN	TMG	0.1	49.5
g	H	CH_3	H	$CH_3OC(=O)$	TMG	0.1	39.6
					DBU	1.0	Decomp
					Ph_3P	0.1	No react'n.
h	CH_3	H	H	$CH_3OC(=O)$	TMG	0.1	No react'n.
					DBU	0.1	No react'n.
					DBU	1.0	12.6[d]
					Et_3N	0.1	No react'n.
					Ph_3P	0.1	No react'n.
i	CH_3	CH_3	H	$CH_3OC(=O)$	TMG	0.1	No react'n.
					DBU	1.0	Decomp
					DBU	1.0	No react'n.[d]
					Et_3N	0.1	No react'n.
					Ph_3P	0.1	No react'n.
j	H	H	$-(CH_2)_2C(=O)-$		TMG	0.1	58.9
					DBU	0.1	29.5
					DBU	1.0	Decomp
					Et_3N	0.1	No react'n.
k	H	H	$-(CH_2)_3C(=O)-$		TMG	0.1	26.5
					DBU	0.1	19.6
					DBU	1.0	Decomp
					DBU	1.0	No react'n.[d]
					Et_3N	0.1	No react'n.

a) Room temperature unless otherwise indicated. b) Decomp means that the starting materials were consumed completely, but no identifiable product was isolated. c) A mixture of two products. See text. d) At −18°C.

Results and Discussion

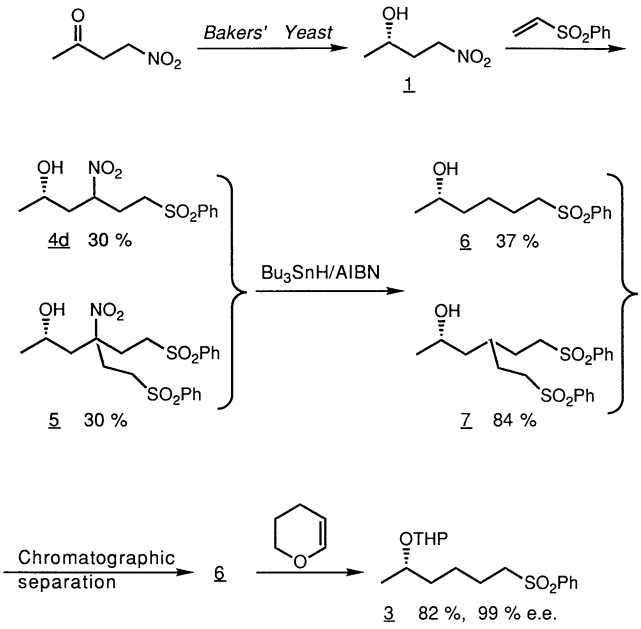
Synthesis of a Precursor to (+)-Brefeldin A. The Michael addition of primary and secondary nitro compounds to an electron-defficient olefin and subsequent substitution of the nitro group by a hydrogen have been reported of Ono and his co-workers.[19] According to their procedure, the γ-hydroxy nitro compound, 4-nitro-2-butanol (**1**), was reacted with phenyl vinyl sulfone under the catalysis of tetramethylguanidine (TMG, 0.1 equiv). It was found that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is too strong to be a base catalyst, but triethylamine and triphenylphosphine are too weak. Results from the Michael addition of **1** with various olefins are summarized in Table 1.

In contrast to other olefins, the product obtained from the reaction with phenyl vinyl sulfone is composed of a 1:1 mixture of 6-phenylsulfonyl-4-nitro-2-hexanol (**4d**), a 1:1 adduct, and 4,4-bis[2-(phenylsulfonyl)ethyl]-4-nitro-2-butanol (**5**), a 1:2 adduct, which was observable on an ^{1}H NMR spectrum. The ratio in amount of **4d**:**5** remained constant on the change of relative amounts of the starting materials or on the change of the order of their addition. Methyl vinyl ketone affords the 1:2 adduct when 2 equivalent amounts of this olefin are used. No other olefins afforded the adduct of this type under any reaction conditions.

The origin of this unexpected property of phenyl vinyl sulfone has not been clarified yet. We suppose that a delicate balance of basicities between the reactant α-nitro carbanion and the resulted composite carbanion plays a crucial role for the formation of the 1:2 adduct.

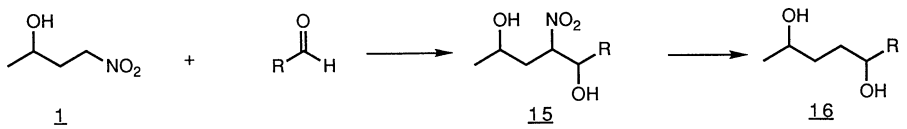
A mixture of **4d** and **5** were subjected, without being separated, to reductive denitration by the aid of tributyltin hydride–AIBN system[17] because of difficulty in separation of these two materials. Since the nitro groups in **4d** and **5** are secondary and tertiary, respectively, the denitration takes place more efficiently with **5** than with **4d** and the yields of the products, 6-phenylsulfonyl-2-butanol (**6**) and 4,4-bis[2-(phenylsulfonyl)ethyl]-2-butanol (**7**), were 37 and 84%, respectively, based on the amount of the each starting material. The mixture can now be separated quite easily by column chromatography and the resulted **6** was subjected to tetrahydropyranylation to afford the final product **3** in 82% yield. When (*S*)-(+)-**1** of 99% e.e. was employed as the starting material, (*S*)-(+)-**3** in 99% e.e. was isolated. The whole scheme of the reaction is shown in Scheme 2. The method to transform (*S*)-(+)-**3** into (+)-brefeldin A is straightforward.[11]

Synthesis of (*S*)-(+)-Sulcatol. The condensation of the carbanion with normal alkanals as well as benzaldehyde took place under the catalysis of triethylamine at room temperature or below 100 °C as



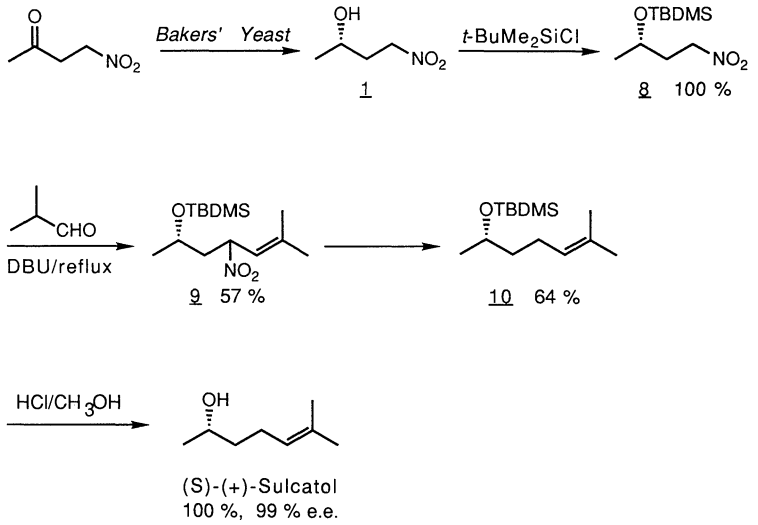
Scheme 2.

Table 2. Condensation of a Carbanion from 4-Nitro-2-butanol with Various Aldehydes[a]



Compd.	R in RCHO	Temp/°C[b]	Chemical yield of **15**/%	Chemical yield of **16**/%	d.e./%
a	CH_3–	r.t.[c]	71.5	64.9	—
b	CH_3CH_2–	r.t.[c]	77.1	61.3	23.0
c	$CH_3(CH_2)_2$–	r.t.[c]	82.1	—	—
d	$CH_3(CH_2)_3$–	90	77.0	—	—
e	$CH_3(CH_2)_5$–	90	79.7	—	—
f	C_6H_5–	90	57.1	67.1	15.4

a) The reaction was run in THF for 15 h under the catalysis of triethylamine for the condensation, and was run in benzene for 2 h at 90 °C for denitration. b) Reaction temperature for the condensation. c) Room temperature.



Scheme 3.

listed in Table 2. It was demonstrated that asymmetric induction followed the condensation, which was demonstrated by ^{1}H NMR spectroscopy on the resulted diols after the reductive denitration by tributyltin hydride–AIBN system. The diastereomer excess (d.e.) observed in the diols are also listed in Table 2. It was confirmed that the diastereoisomer formed in larger amount has the anti-configuration (see Experimental).

The condensation of the carbanion with 2-methylpropanal, a secondary alkyl aldehyde, however, did not take place under the same reaction conditions. Instead, the carbanion reacted with this aldehyde only when the system was refluxed in the presence of DBU, a stronger base than triethylamine. It was necessary, however, to protect the hydroxyl group in the carbanion under these revised reaction conditions, and, after several experiments, it was found that the protecting function has to be the *t*-butyldimethylsilyl group (TBDMS). Other protecting groups such as tetrahydropyranyl or acetyl group prevented the carbanion from the condensation.[18] The product obtained by the condensation in 57% yield was not the corresponding alcohol but was an olefin, 6-(*t*-butyldimethylsilyloxy)-2-methyl-4-nitro-2-heptene (**9**). The reductive denitration of **9** with tributyltin hydride–AIBN system[19] afforded the TBDMS derivative of (*S*)-(+)-sulcatol in 64% yield. The last compound was deprotected under acidic conditions in 100% chemical yield to give (*S*)-(+)-sulcatol of 99% e.e. Scheme 3 represents the whole reaction.

Experimental

Instruments. ^{1}H NMR spectra were recorded on a Varian VXR-200 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference or in D_2O with sodium 3-(trimethylsilyl)-1-propanesulfonate-1,1,2,2-d_4 (DSS) as an internal reference. IR spectra were recorded on a Hitachi EPI-S2 infrared spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

Materials. Organic reagents were purchased from Nacalai Tesque Co., Tokyo Kasei Co., and Aldrich Chemical Co., respectively, unless otherwise indicated. All products gave satisfactory results in elemental analyses.

4-Nitro-2-butanol (1). 4-Nitro-2-butanone[20] was reduced by sodium borohydride to obtain racemic 4-nitro-2-butanol, whereas the reduction of this nitro ketone with bakers' yeast afforded (*S*)-**1**: 1 mmol of 4-nitro-2-butanone was added to a suspension of bakers' yeast (10 g) and glucose (2 g) in water (200 ml) and the whole mixture was incubated at 30 °C for 4 days. Usual work-up gave a mixture of the starting material and the product, that were separated by column chromatography on silica gel with an eluent of a mixture of hexane (5 parts) and ethyl acetate (1 part) to afford (*S*)-**1** in 51% yield with 99% e.e. ($[\alpha]_D^{25}$ +40.6° (*c* 1.15, $CHCl_3$)). The enantiomer excess was determined by ^{1}H NMR analysis of the corresponding (+)-MTPA ester.

Michael Addition of the Carbanion from 1. A solution of **1** (0.1 g, 0.85 mmol) and an appropriate amount of a base in 5 ml of dry acetonitrile was added dropwise to methyl propenoate (86 mg, 1 mmol) at room temperature. The resulted solution was stirred for 15 h at room temperature, then poured into 20 ml water. The mixture was acidified by diluted hydrochloric acid (pH 1) and extracted with ether (3×10 ml). The combined ether layer was washed with water (3×10 ml), dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel with a 1:1 mixture of hexane and ethyl acetate as an eluent to yield the product **4**. The results are summarized in Table 1.

Reductive Denitration of 6-Phenylsulfonyl-4-nitro-2-hexanol (4d). A solution composed of a mixture (91 mg) of **4d** and 1,1-bis(2-phenylsulfonylethyl)-1-nitro-3-butanol (**5**) in 2 ml of dry benzene, 0.17 ml (0.64 mmol) of tributyltin hydride, and 26 mg (0.16 mmol) of AIBN was refluxed for 3 h. The solution was concentrated under reduced pressure. The residue was chromatographed on silica gel column using a 1:1 mixture of hexane and ethyl acetate as an eluent to isolate 1-phenylsulfonyl-5-butanol (**6**) and 1,1-bis(2-

phenylsulfonylethyl)-3-butanol (**7**), in 37% (11 mg) and 84% (42 mg) yields, respectively.

Tetrahydropyranylation of (*S*)-1-Phenylsulfonyl-5-butanol ((*S*)-6). A solution composed of 11 mg (0.045 mmol) of (*S*)-**6**, prepared as described above, 1 ml of dry tetrahydrofuran (THF), 0.011 ml (0.12 mmol) of 3,4-dihydro-2*H*-pyran, and 4 mg of pyridinium *p*-toluenesulfonate was stirred for 14 h at room temperature. The mixture was washed with saturated aqueous sodium hydrogencarbonate and brine, then dried over anhydrous sodium sulfate and concentrated to leave the crude product, which was chromatographed on a silica gel column using ethyl acetate as an eluent to afford (*S*)-1-phenylsulfonyl-5-(tetrahydropyranyloxy)hexane ((*S*)-**3**) in 82% yield (12 mg) with 99% e.e. ($[\alpha]_D^{24}$ +8.1° (*c* 0.72, $CHCl_3$)).

^1H NMR ($CDCl_3$) δ=1.19 (d, 3H, *J*=6.2 Hz), 1.45—1.91 (bs, 6H), 2.28—2.35 (m, 2H), 3.31—3.42 (m, 2H), 3.65—4.04 (m, 2H), 4.04—4.14 (m, 2H), 4.52—4.96 (m, 1H), and 7.55—7.93 (m, 5H).

Condensation of 1 with Normal Alkanals. A 10 ml solution of THF containing 500 mg (4.2 mmol) of **1**, 1.7 ml (8.4 mmol) of triethylamine, and an acetaldehyde (5 mmol) was stirred for 15 h at room temperature, then the mixture was poured into 10 ml of water. The whole mixture was acidified by diluted hydrochloric acid (pH 1) and extracted with ether (3×50 ml). The combined ether layer was washed with brine (3×50 ml), dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography over silica gel with an equivalent mixture of hexane and ethyl acetate as an eluent. The results are listed in Table 2.

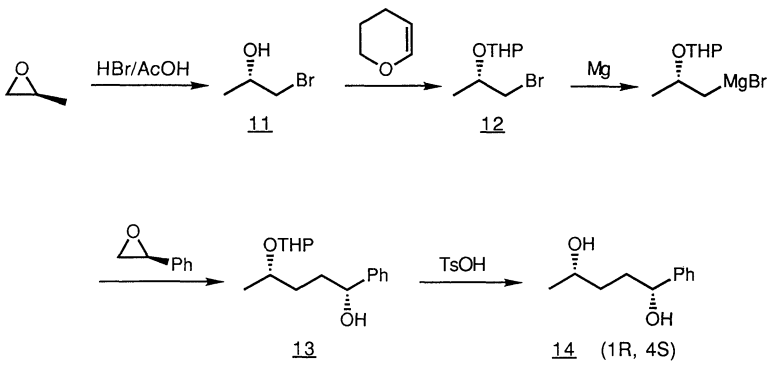
Determination of Absolute Configuration in the Condensation Product (16f). An acetic acid solution of hydrogen bromide (3.6 ml, 17.6 mmol) was added to (*S*)-2-methyloxirane (0.83 g, 14.3 mmol) dropwise at 0 °C and the mixture was stirred at 0 °C for 2 h. The reaction mixture was distilled at 145 °C to give a mixture of (*S*)-1-bromo-2-propanol (**11**) contaminated by small amount of (*S*)-2-bromo-1-propanol in 50% yield (982 mg). The mixture (250 mg, 1.8 mmol) was dissolved into 5 ml dry dichloromethane containing pyridinium *p*-toluenesulfonate (50 mg) and 3,4-dihydro-2*H*-pyran (0.33 ml, 3.6 mmol), and the whole mixture was stirred for 14 h at room temperature. The reaction mixture was subjected to column chromatography on silica gel using a mixture eluent (hexane:ethyl acetate= 1:1) to afford THP derivative of **11** (**12**) contaminated by small amount of its 2-bromo counterpart. A solution of 150 mg (0.68 mmol) of crude **12** in 3 ml of dry THF was added dropwise to 16.5 mg (0.68 mmol) of baked magnesium under argon atmosphere and the mixture was stirred for 1 h at 50 °C, then 0.078 ml (0.68 mmol) of (*R*)-styrene oxide was added dropwise to this reaction mixture and stirred for additional 6 h at room temperature. The whole reaction mixture was poured into 20 ml water and the organic materials were extracted with ether. The combined ether layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel with an equivalent amount mixture of hexane-ethyl acetate as an eluent to afford (1*R*,4*S*)-4-tetrahydropyranyloxy-1-phenyl-1-pentanol (**13**) (23 mg), which was deprotected by stirring with 200 mg of *p*-toluenesulfonic acid to yield (1*R*,4*S*)-1-phenyl-1,4-pentanediol (**14**). The reaction course is shown in Scheme 4.

The ^1H NMR spectrum of this authentic compound was compared with that of the product from the reaction of (*S*)-**1** with benzaldehyde to determine the stereochemistry of the latter: since the former had a doublet at δ 1.18, whereas the latter exhibited a larger doublet at δ 1.14 with a smaller doublet at δ 1.18, the predominant configuration of the latter was identified to be (1*S*,4*S*).

Condensation of 1 with 2-Methylpropanal. Imidazole (16 g, 0.24 mol) was added dropwise to a stirred 60 ml solution of *N*,*N*-dimethylformamide (DMF) containing 7.0 g (59 mmol) of (*S*)-**1** and 10 g of *t*-butyldimethylsilyl chloride (TBDMSCl) at 0 °C, then the stirring was continued for 3 h at room temperature. The reaction mixture was poured into 100 ml water and the organic materials were extracted with ether (3×100 ml). The combined ether layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with a mixture of hexane (5 parts) and ethyl acetate (1 part) as an eluent. 1-Nitro-3-(*t*-butyldimethylsilyloxy)butane (**8**) was obtained quantitatively (13.7 g) ($[\alpha]_D^{25}$ +31.4° (*c* 1.00, $CHCl_3$)).

^1H NMR ($CDCl_3$) δ=0.03, 0.04 (ds, 6H), 0.86 (s, 9H), 1.16 (d, 3H, *J*=7.0 Hz), 1.90—2.27 (m, 2H), 3.85—3.96 (m, 1H), and 4.40—4.50 (m, 2H). IR (neat): 1558 and 1382 cm^{-1}.

2-Methylpropanal (0.21 ml, 2.2 mmol) was added to a mixture of 0.5 g (2.2 mmol) of **8**, 0.33 ml (2.2 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and small amount of



Scheme 4.

dried Molecular Sieve 4A in 20 ml THF, and the mixture was refluxed for 16 h. The reaction mixture was poured into 15 ml water and acidified to pH 6—7 with acetic acid. The organic materials were extracted with ether (3×20 ml) and the combined ether layer was washed with water (3×20 ml), brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel. A mixture of hexane (5 parts) and ethyl acetate (1 part) was used as an eluent to afford (*S*)-(*t*-butyldimethylsilyloxy)-2-methyl-4-nitro-2-heptene (**9**) in 57% yield (0.36 g) ($[\alpha]_D^{25}$ −24.2° (*c* 1.03, $CHCl_3$)).

^1H NMR ($CDCl_3$) δ=−0.01—0.05 (m, 6H), 0.85—0.89 (m, 9H), 1.12—1.19 (dd, 3H, *J*=6.0 Hz), 1.58—1.72, 2.20—2.34 (m, 2H), 1.74—1.77 (m, 6H), 3.66—3.84 (m, 1H), and 5.26—5.52 (m, 2H). IR (neat): 2975, 1557, and 1380 cm^{-1}.

Convension of (*S*)-9 into (*S*)-(+)-Sulcatol. A solution composed of 120 mg (0.42 mmol) of **9**, 0.11 ml (0.42 mmol) of tributyltin hydride, 20 mg (0.15 mmol) of AIBN, and 3 ml dry benzene was refluxed for 2 h. The removal of the solvent from the solution remained a crude product, which was subjected to column chromatography on silica gel using a mixture of hexane and ethyl acetate (5:1) as an eluent. (*S*)-2-Methyl-6-(*t*-butyldimethylsiloxy)-2-heptene (**10**) was obtained in 64% yield (60 mg).

A concentrated hydrochloric acid (2 ml) was added dropwise to 10 ml methanol solution containing 60 mg (0.27 mmol) of **10**, and stirred for 2 h at room temperature. The reaction mixture was washed with saturated aqueous sodium hydrogencarbonate and brine, then dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel using a mixture of hexane and ethyl acetate (5:1) as an eluent to afford the final product in quantitatively yield (34.8 mg) with 99% e.e. ($[\alpha]_D^{25}$ +15.1° (*c* 0.75, $CHCl_3$)).

^1H NMR ($CDCl_3$) δ=1.14 (d, 3H, *J*=6.2 Hz), 1.38—1.50 (m, 2H), 1.58 (s, 3H), 1.65 (s, 3H), 1.84—1.95 (bs, 1H), 1.97—2.09 (td, 2H, *J*=7.2 and 7.8 Hz), 3.71—3.80 (tq, 1H, 6.2 and 6.2 Hz), and 5.05—5.13 (tt, 1H, *J*=7.8 and 7.8 Hz). IR (neat): 3400, 2975, 1450, and 1255 cm^{-1}. Found: C, 74.85; H, 12.75%. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58%.

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