DIASTEREOFACIAL SELECTIVITY OF RADICAL CYCLIZATION USING CHIRAL α,β-UNSATURATED ESTER AND AMIDE: INVESTIGATION OF A NEW CHIRAL SYNTHON SYNTHESIS†

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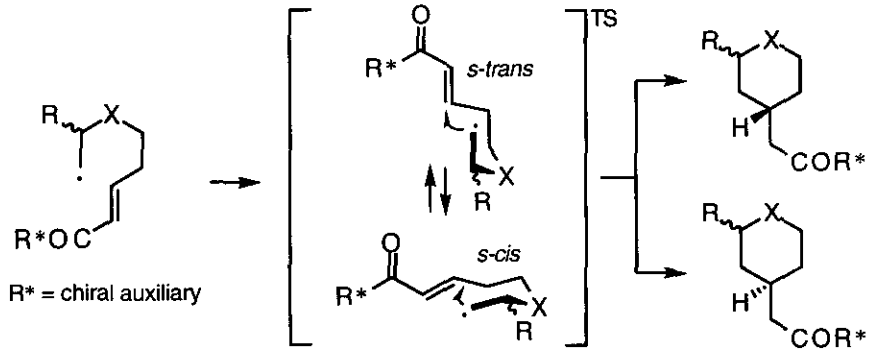
Abstract – The chiral α,β-unsaturated ester (**3a**) gave cyclic acetal (**4aA**) in a highly diastereoselective manner (>98% de) by radical cyclization, which was carried out in the presence of MAD. Furthermore, **4aA** was converted into chiral lactone (**9**), possessing the stereogenic center with three differentiated C-2 units.

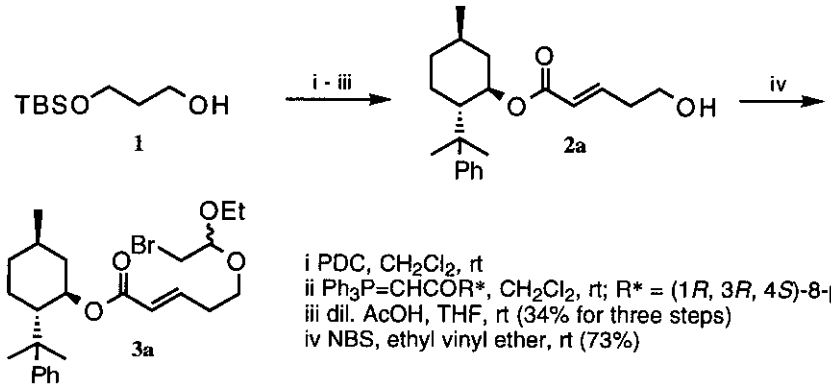
Recently, radical reactions have emerged as useful tools for carbon-carbon bond formation reaction in organic synthesis.[1] Furthermore, the generation of new stereogenic center using this methodology is shown much interest and, specially, diastereoselective radical addition or cyclization to chiral alkenes has been reported.[2] Previously, we demonstrated the construction of the stereoselective six-membered ring skeleton with excellent 1,2-asymmetric induction.[3] As an extension of this work, the *6-exo* type radical cyclization to chiral radical acceptor was studied; the diastereoselectivity depends on *s-trans* and *s-cis* conformations of α,β-unsaturated carbonyl part.[4] It is expected that stereoselective synthesis of chiral cyclic acetal can be achieved by the control of these two conformations (Scheme 1). Since (1*R*, 3*R*, 4*S*)-8-phenylmenthol[5] and (4*S*)-4-benzyl-2-oxazolidinone[6] had been used as efficient chiral auxiliary in asymmetric synthesis, we have examined radical cyclization of α,β-unsaturated ester and amide bearing these chiral auxiliaries.[7]



Scheme 1

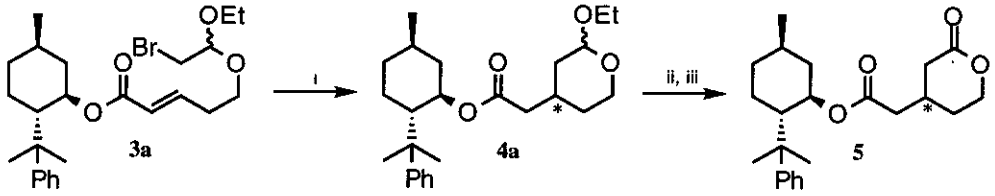
† Dedicated to the memory of the late Dr. Shun-ichi Yamada, Professor Emeritus of Tokyo University.

Radical Cyclization of (1*R*, 3*R*, 4*S*)-8-Phenylmenthyl Ester (3a): The substrate (**3a**) of the key reaction was prepared as follows (Scheme 2). 3-*tert*-Butyldimethylsilyloxypropanol (**1**)[8] was converted into **2a** by way of pyridinium dichromate (PDC) oxidation, Wittig reaction,[9] and desilylation. Treatment of **2a** with ethyl vinyl ether and *N*-bromosuccinimide (NBS)[10] furnished the bromoacetal (**3a**).



Scheme 2

Radical cyclization of **3a** was carried out under several conditions. Since the separation of the cyclized product from by-products was difficult, the overall yield was shown after conversion of **4a** into lactone (**5**) (Scheme 3, Table 1). The diastereomeric excess (de) was also determined by ^{1}H-NMR spectroscopy (300 MHz in C_6D_6) of **5**.



Scheme 3

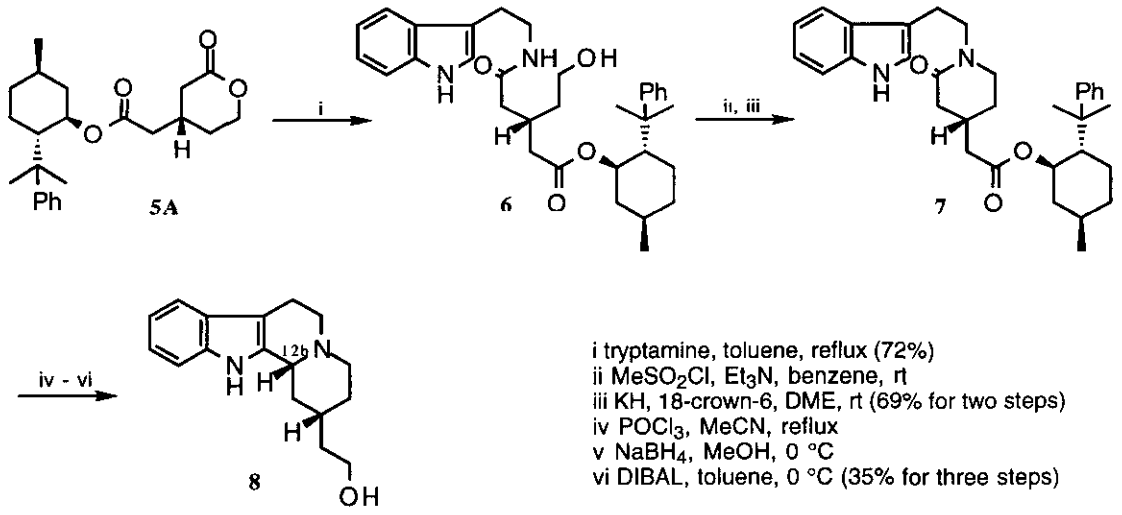
Heating **3a** with Bu_3SnH in the presence of azoisobutyronitrile (AIBN), followed by the two steps transformation, provided **5** in 70% overall yield. But the diastereoselectivity was poor (entry 1). Furthermore, in the case of reaction with Bu_3SnH using Et_3B[11] at –40 °C, **5** was obtained in 44% overall yield and 31% de (entry 2). The diastereoselectivity was improved when the reaction was carried out in the presence of Lewis acid.[12] A rather good selectivity (67% de) was obtained by addition of Me_3Al (entry 3) and the reaction in the presence of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[13] gave a single diastereoisomer (**4aA**) (>98% de, entry 4).

entry	conditions	yield of 5 (%)[a]	de (%)
1	Bu_3SnH, AIBN, benzene, reflux	70	13
2	Bu_3SnH, Et_3B, toluene, –40 °C	44	31
3	Bu_3SnH, Et_3B, Me_3Al, toluene, –40 °C	51	67
4	Bu_3SnH, Et_3B, MAD, toluene, –40 °C	38	> 98

[a] Overall yield for three steps from **3a**.

Table 1

The stereochemistry of the predominant isomer (**5A**) was established by transformation into (+)-12b-epidevinylantirhine (**8**) (Scheme 4). Treatment of the product (**5A**), obtained using MAD (Table 1, entry 4), with tryptamine in hot toluene afforded the amide (**6**), which was cyclized to the lactam (**7**) in two steps. The Bischler-Napieralski reaction of **7**, followed by reduction of the resulting iminium salt with $NaBH_4$, produced stereoselectively the indolo[2,3-*a*]quinolizine as a single stereoisomer, which was further reduced with DIBAL to provide (+)-**8**, $[\alpha]_D^{21}$ +12.3° (*c* 0.50, MeOH). The relative stereochemistry was deduced from the ^{1}H-NMR spectroscopic data.[14] The selective formation of the single isomer by the above reduction with $NaBH_4$ is explainable by stereoelectronic effects.[15] The *R* configuration at the 12b position was suggested by the circular dichroism (CD) spectrum, $[\theta]$ –3.14 x 10^3 (269 nm, MeOH).[16]



Scheme 4

The above result supports that α,β-unsaturated ester group is fixed in the *s-trans* conformation by addition of MAD and the radical cyclization proceeds with high diastereofacial selectivity (Figure 1).

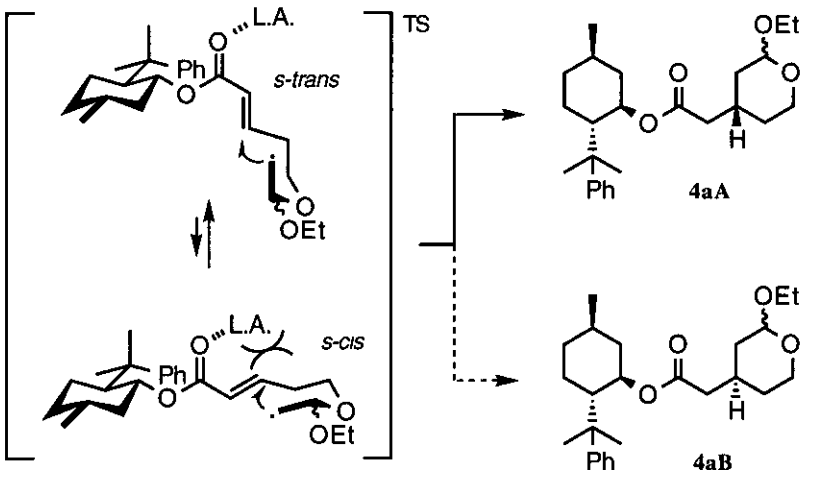


Figure 1

Radical Cyclization of (4*S*)-4-Benzyl-2-oxazolidinone (3b): In order to compare the effect of the chiral auxiliary, we next investigated the radical cyclization of (4*S*)-4-benzyl-2-oxazolidinone (**3b**). It was expected that the conformation of the amide group of **3b** during cyclization would be fixed in *s-cis* conformation due to the steric interaction between the oxazolidinone auxiliary and α,β-unsaturated olefin part in the presence of Lewis acid (Figure 2).[17]

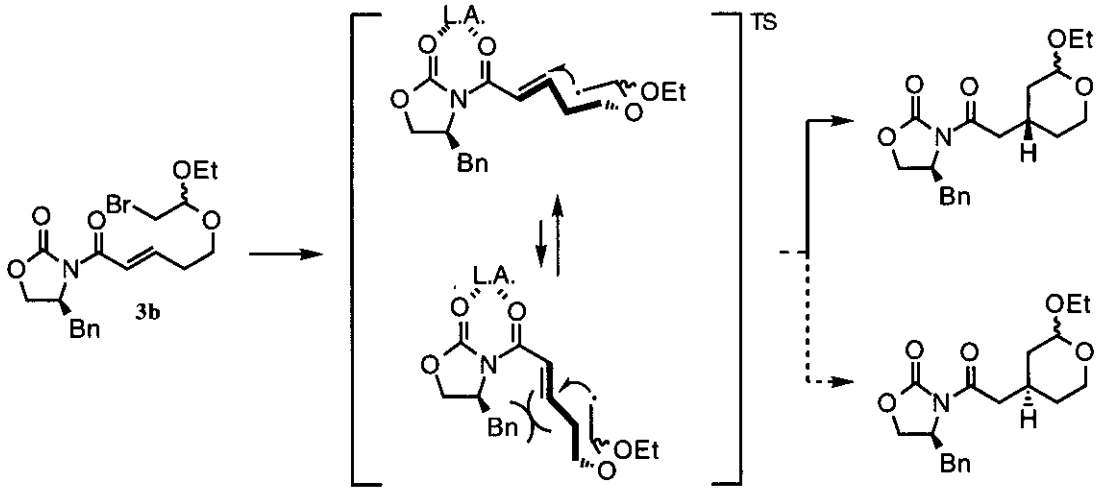
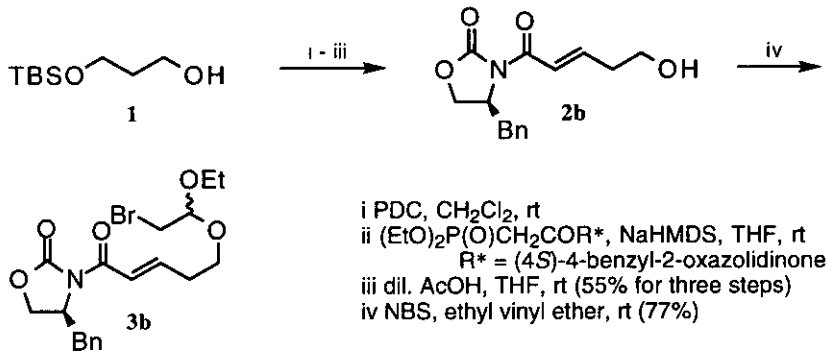
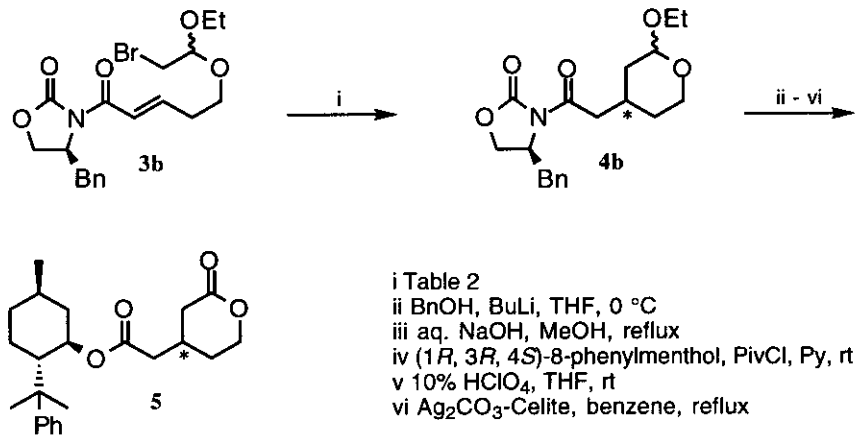


Figure 2

Results for the cyclization of **3b**, which was synthesized by a similar procedure (Scheme 5) as previous, under several conditions are summarized in Table 2. The cyclic acetal (**4b**) was transformed into the lactone (**5**) for the determination of diastereoselectivity. Since the direct hydrolysis of **4b** resulted in low yield, the removal of oxazolidinone was performed by way of benzyl ester[18] as shown in Scheme 6.



Scheme 5



Scheme 6

Unfortunately, no significant diastereoselectivities were not observed by the radical cyclization in spite of the presence of Lewis acids.

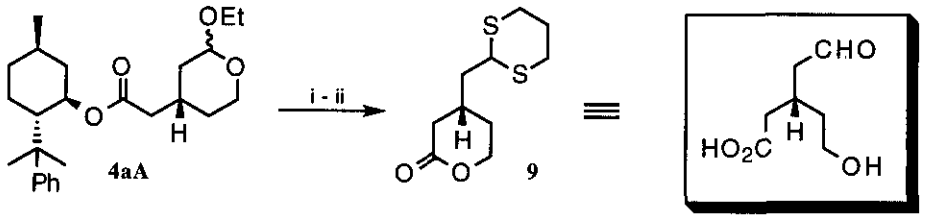
entry	conditions	yield of 5 (%)[a]	de (%)
1	Bu_3SnH, AIBN, toluene, reflux	19	9
2	Bu_3SnH, Et_3B, toluene, –40 °C	33	9
3	Bu_3SnH, Et_3B, Et_2AlCl, toluene, –40 °C	6	9
4	Bu_3SnH, Et_3B, $Yb(OTf)_3$, CH_2Cl_2, –40 °C	22	0

[a]Overall yield for six steps from **3b**.

Table 2

Synthesis of (+)-(3*R*)-3-(1,3-Dithian-2-ylmethyl)-5-pentanolide (9): The cyclic acetal

(**4aA**), obtained as a single diastereoisomer (Table 1, entry 4), was transformed into the lactone (**9**); the conversion of the cyclized product into dithioacetal using 1,3-propanedithiol and BF_3·OEt_2, followed by hydrolysis under alkaline conditions and lactonization (Scheme 7). This compound (**9**) possesses three C-2 units, whose oxidation levels are different, at the stereogenic center and is expected to be useful as a chiral synthon for the synthesis of natural products.



i $HS(CH_2)_3SH$, BF_3·OEt_2, CH_2Cl_2, rt
ii aq. NaOH, MeOH, reflux then dil. HCl

Scheme 7

EXPERIMENTAL SECTION

General Procedure. All reactions were carried out under a inert atmosphere of N_2 or Ar unless otherwise indicated. All new compounds are homogeneous on TLC, and their purities were further verified by 300 MHz ^{1}H-NMR spectra. NMR spectra were measured in $CDCl_3$ or C_6D_6 and referred to tetramethylsilane.

(1*R*, 3*R*, 4*S*)-8-Phenylmenthyl (2*E*)-5-Hydroxy-2-pentenoate (2a)

To a stirred solution of **1** (302 mg, 1.59 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C were added 4A molecular sieves (896 mg) and PDC (896 mg, 2.38 mmol), and the mixture was stirred for 1 h at rt. After dilution with Et_2O, followed by filtration through Celite, evaporation of the filtrate gave the crude aldehyde, which was used in the following reaction without purification.

To a stirred solution of [(1*R*, 3*R*, 4*S*)-8-phenylmenthyl(triphenylphosphoranylidene)acetate][9] (848 mg, 1.59 mmol) in dry CH_2Cl_2 (5 mL) at rt was added the above crude aldehyde in dry CH_2Cl_2 (10 mL). The mixture was then stirred for 1 h at rt. Evaporation of the mixture gave a solid, which was taken up into hexane. Evaporation of the solvent gave a residue, which was subjected to the next reaction without purification.

A mixture of the above product and AcOH-H_2O (3:1 v/v, 8 mL) in THF (2 mL) was stirred for 12 h at rt. After dilution with Et_2O, followed by neutralization with saturated $NaHCO_3$ under cooling with ice, the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Column chromatography of the product on silica gel with hexane-AcOEt (7:3 v/v) provided **2a** (178 mg, 34%) as a colorless oil: IR (neat, cm^{-1}) 3600-3200, 1710, 1655; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 6.6 Hz, 3H), 1.20 (s, 3H), 1.30 (s, 3H), 1.88-1.92 (m, 1H), 2.02-2.10 (m, 1H), 2.28-2.35 (m, 2H), 3.68-3.80 (m, 3H), 4.84 (ddd, J = 4.0, 10.6, 10.6 Hz, 1H), 5.33 (d, J = 15.7 Hz, 1H), 6.40-6.50

(m, 1H), 7.08-7.37 (m, 5H); HRMS calcd for $C_{21}H_{30}O_3$ (M^+) 330.2195, found 330.2176.

(4*S*)-4-Benzyl-3-[(2*E*)-5-hydroxypent-2-enoyl]oxazolidin-2-one (2b)

To a stirred solution of Emmons reagent[19] (7.20 g, 20.3 mmol) in dry THF (20 mL) at rt was added 1.0 M NaHMDS-hexane (18.3 mL, 18.3 mmol), and the mixture was stirred for 30 min at rt. After the addition of the crude aldehyde, prepared from **1** (4.56 g, 24.0 mmol) as above in dry THF (30 mL), the mixture was stirred for 12 h at rt. After dilution with Et_2O, the mixture was washed with H_2O and brine, dried ($MgSO_4$), and evaporated to give a residue, which was used in the next reaction without purification. Using the same procedure as for the preparation of **2a**, the above product was converted into **2b** (3.64 g, 55%) as a colorless oil: IR (neat, cm^{-1}) 3600-3200, 1770, 1680, 1640; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.07 (br s, 1H), 2.55-2.61 (m, 2H), 2.79 (dd, J = 9.6, 13.5 Hz, 1H), 3.34 (dd, J = 3.0, 13.5 Hz, 1H), 3.83 (t, J = 6.3 Hz, 2H), 4.16-4.25 (m, 2H), 4.70-4.76 (m, 1H), 7.18-7.37 (m, 7H); HRMS calcd for $C_{15}H_{17}NO_4$ (M^+) 275.1168, found 275.1158.

(1*R*, 3*R*, 4*S*)-8-Phenylmenthyl (2*E*)-5-(2'-Bromo-1'-ethoxyethoxy)-2-pentenoates (3a)

To a stirred solution of **2a** (105 mg, 0.318 mmol) in ethyl vinyl ether (5 mL) at 0 °C was slowly added NBS (170 mg, 0.955 mmol), and the mixture was stirred for 20 h at rt. Evaporation of the mixture gave a residue, which was taken up into Et_2O. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated. Column chromatography of the product on silica gel with hexane-AcOEt (9:1 v/v) provided **3a** (112 mg, 73%) as a colorless oil: IR (neat, cm^{-1}) 1710, 1660; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.6 Hz, 3H), 1.21 (s, 3H), 1.30 (s, 3H), 1.64-1.70 (m, 2H), 1.88-1.92 (m, 1H), 1.99-2.08 (m, 1H), 2.33-2.40 (m, 2H), 3.35-3.73 (m, 6H), 4.65-4.69 (m, 1H), 4.84 (ddd, J = 4.0, 10.6, 10.6 Hz, 1H), 5.34 (d, J = 15.8 Hz, 1H), 6.46-6.54 (m, 1H), 7.11-7.37 (m, 5H); MS *m/z* 480 (M^+). Anal. Calcd for $C_{25}H_{37}O_4Br$: C, 62.37; H, 7.75. Found: C, 61.94; H, 7.57.

(4*S*)-4-Benzyl-3-[(2*E*)-5-(2'-bromo-1'-ethoxyethoxy)pent-2-enoyl]oxazolidin-2-ones (3b)

Using the same means as above, **2b** (701 mg, 2.55 mmol) was transformed into **3b** (840 mg, 77%) as a colorless oil: IR (neat, cm^{-1}) 1770, 1680, 1640; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.25 (t, J = 4.1 Hz, 3H), 2.59-2.62 (m, 2H), 2.79 (dd, J = 9.6, 13.5 Hz, 1H), 3.39 (d, J = 5.5 Hz, 2H), 3.56-3.85 (m, 4H), 4.15-4.25 (m, 2H), 4.69-4.77 (m, 2H), 7.17-7.38 (m, 7H); MS *m/z* 380 (M^+–OEt). Anal Calcd for $C_{19}H_{24}NO_5Br$: C, 53.35; H, 5.67; N, 3.28. Found: C, 53.35; H, 5.68; N, 3.28.

(3*R*)- and (3*S*)-3-[(1*R*, 3*R*, 4*S*)-8-Phenylmenthyloxycarbonylmethyl]-5-pentanolides (5)

Table 1

entry 1: To a stirred solution of **3a** (554 mg, 1.15 mmol) in dry benzene (350 mL) at rt was added AIBN (94.5 mg, 0.575 mmol) and Bu_3SnH (371 μL, 1.38 mmol). The mixture was heated for 2 h under reflux. Evaporation of the mixture gave the crude **4a**, which was used in the following reaction without purification.

The crude **4a** was dissolved in THF (4 mL) and then treated with 10% $HClO_4$ (2 mL) for 24 h at rt. After dilution with Et_2O, the organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. The residue was not purified and used in the next reaction.

A mixture of the above product and Ag_2CO_3 on Celite (17:15 w/w 1.95 g, 1.95 mmol) in dry benzene (5 mL) was heated for 40 min under reflux. Filtration through Celite, followed by evaporation of the filtrate, afforded a residue, which was purified by column chromatography on silica gel. Elution with hexane-AcOEt (3:1 v/v) provided **5** (300 mg, 70% from **3a**) as a colorless oil.

entry 2: A mixture of **3a** (82.9 mg, 0.172 mmol) and Bu_3SnH (55.6 μL, 0.207 mmol) in dry toluene (50 mL) was slowly added 1.0 M Et_3B-hexane (0.207 mL, 0.207 mmol) at –40 °C, and the mixture was stirred for 2 h at –40 °C. Evaporation of the reaction mixture gave the crude **4a**, which was used in the next reaction without purification.

Using the same method as above, the crude **4a** was transformed into **5** (28.4 mg, 44% from **3a**) as a colorless oil.

entry 3: To a stirred solution of **3a** (51.6 mg, 0.110 mmol) in dry toluene (40 mL) were added Bu_3SnH (43.4 μL, 0.16 mmol), 1.0 M Me_3Al-hexane (0.22 mL, 0.22 mmol) and 1.0 M Et_3B-hexane (0.12 mL, 0.12 mmol) at –40 °C, and the mixture was stirred for 2 h at the same temperature. Evaporation of the mixture gave a residue, which was diluted with Et_2O. The organic layer was washed with 10% HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated. The crude **4a** was directly used in the next reaction.

Using the same method as above, the crude **4a** was transformed into **5** (20.4 mg, 51% from **3a**) as a colorless oil.

entry 4: To a mixture of **3a** (42.6 mg, 0.089 mmol) and Bu_3SnH (0.036 mL, 0.133 mmol) in dry toluene (20 mL) at rt was added 0.5 M MAD in toluene (0.186 mL, 0.093 mmol), and the mixture was stirred for 30 min at –40 °C. After addition of 1.0 M Et_3B-hexane (0.093 mL, 0.093 mmol) at –40 °C, the mixture was stirred for 1.5 h at the same temperature. After evaporation of solvents, followed by dilution with Et_2O, the resulting mixture was washed with 10% HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated. The crude **4aA** was used in the following reaction without purification.

Using the same procedure as above, the crude **4aA** was transformed into **5A** (12.6 mg, 38% from **3a**) as a colorless oil: $[\alpha]_D^{24}$ +3.9° (*c* 1.05, $CHCl_3$); IR (neat, cm^{-1}) 1735, 1725; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.6 Hz, 3H), 0.93-1.01 (m, 1H), 1.10-1.26 (m, 1H), 1.18 (s, 3H), 1.29 (s, 3H), 1.33-1.59 (m, 4H), 1.62-1.76 (m, 2H), 1.80-1.90 (m, 3H), 1.94-2.13 (m, 3H), 2.53-2.65 (m, 1H), 4.16-4.24 (m, 1H), 4.31-4.38 (m, 1H), 4.81 (ddd, J = 4.4, 10.7, 10.7 Hz, 1H), 7.09-7.31 (m, 5H); HRMS calcd for $C_{14}H_{21}O_4$ (M^+–CMe_2Ph) 253.1490, found 253.1440.

Table 2

entry 1: Using the same method (Table 1, entry 1), **3b** (115 mg, 0.27 mmol) was transformed into the crude **4b**, which was used in the next reaction without purification.

To a stirred solution of BnOH (70 μL, 0.67 mmol) in dry THF (3 mL) at 0 °C was added 1.56 M BuLi-hexane (0.35 mL, 0.56 mmol), and the mixture was stirred for 30 min at 0 °C. To the stirred mixture was

added a solution of the crude **4b** in dry THF (2 mL), and the mixture was stirred for 1.5 h at 0 °C. Evaporation of the reaction mixture gave the crude benzyl ester, which was directly used in the next reaction.

A mixture of the above product and 10% NaOH (2 mL) in MeOH (3 mL) was heated for 1 h under reflux. After concentration of the reaction mixture under pressure followed by dilution with $CHCl_3$, the mixture was acidified with 10% HCl and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated to give the crude carboxylic acid, which was used in the following reaction without purification.

To a stirred solution of (1*R*, 3*R*, 4*S*)-8-phenylmenthol (38.7 mg, 0.17 mmol) and the above product in dry pyridine (2 mL) at 0 °C was slowly added pivaloyl chloride (62 μL, 0.50 mmol). The mixture was stirred for 2 h at 0 °C to rt and then diluted with benzene. The resulting mixture was washed with 10% HCl and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The crude phenylmenthyl ester was directly used in the next reaction without purification.

Using the same procedure as above, the above product was transformed into **5** (16.4 mg, 19% from **3b**) as a colorless oil.

entry 2: Using the same method (Table 1, entry 2), **3b** (117 mg, 0.27 mmol) was transformed into the crude **4b**, which was used in the following reaction without purification.

By the same procedure as above, the crude **4b** was converted into **5** (32.9 mg, 33% from **3b**) as a colorless oil.

entry 3: 3b (104 mg, 0.24 mmol) was converted, using 1.0 M Et_2AlCl-hexane (0.50 mL, 0.50 mmol), into **5** (5.8 mg, 6% from **3b**) as a colorless oil.

entry 4: To a solution of **3b** (121 mg, 0.28 mmol) in dry CH_2Cl_2 (80 mL) at –40 °C was added $Yb(OTf)_3$ (352 mg, 0.58 mmol), dry THF (4 mL), Bu_3SnH (114 μL, 0.43 mmol), and 1.0 M Et_3B-hexane (312 μL, 0.31 mmol). The mixture was stirred for 2 h at –40 °C. After evaporation of solvents, followed by dilution with Et_2O, the resulting mixture was washed with 10% HCl, saturated $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated. The crude **4b** was used in the next reaction without purification.

According to the same procedure, the crude **4b** was transformed into **5** (22.6 mg, 22% from **3b**) as a colorless oil.

(+)-(3*S*)-5-Hydroxy-*N*-[2-(indol-3-yl)ethyl]-3-[(1*R*, 3*R*, 4*S*)-8-phenylmenthyloxycarbonylmethyl]pentanamide (6)

A mixture of **5A** (143 mg, 0.38 mmol) and tryptamine (123 mg, 0.77 mmol) in toluene (15 mL) was heated for 7 h under reflux. The reaction mixture was evaporated to give a residue, which was purified by column chromatography on silica gel. Elution with $CHCl_3$-AcOEt (1:4 v/v) afforded **6** (148 mg, 72%) as a colorless oil: $[\alpha]_D^{24}$ +1.8° (*c* 1.91, $CHCl_3$); IR (neat, cm^{-1}) 3500-3200, 1730-1700; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.6 Hz, 3H), 1.18 (s, 3H), 1.27 (s, 3H), 2.97 (t, J = 6.9 Hz, 2H), 3.45-3.65 (m, 4H), 4.77 (ddd, J = 4.4, 10.7, 10.7 Hz, 1H), 5.93-5.96 (m, 1H), 7.04-7.26 (m, 8H), 7.36-7.39 (m, 1H), 7.60-7.62 (m, 1H), 8.24-8.31 (br s, 1H); HRMS calcd for $C_{33}H_{44}N_2O_4$ (M^+) 532.3301, found 532.3333.

(–)-(4*S*)-4-[(1*R*, 3*R*, 4*S*)-8-Phenylmenthyloxycarbonylmethyl]-*N*-[2-(indol-3-yl)ethyl]-piperidin-2-one (7)

To a stirred mixture of **6** (91 mg, 0.17 mmol) and Et_3N (36 μL, 0.26 mmol) in dry benzene (10 mL) at 0 °C was added $MeSO_2Cl$ (17 μL, 0.22 mmol), and the mixture was stirred for 1 h at rt. After dilution with benzene, the mixture was washed with 10% HCl, saturated $NaHCO_3$, and brine. The benzene layers were dried ($MgSO_4$) and evaporated to give the crude mesylate, which was used in the next reaction without purification.

To a stirred suspension of KH (68 mg, 1.7 mmol) and 18-crown-6 (9.0 mg, 0.03 mmol) in dry 1,2-dimethoxyethane (DME) (4 mL) at 0 °C was added slowly a solution of the above mesylate in dry DME (6 mL). The mixture was stirred for 1.5 h, poured into saturated NH_4Cl, and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give a residue. Silica gel column chromatography of the residue with $CHCl_3$-AcOEt (2:1 v/v) as eluant afforded **7** (60 mg, 69% for two steps) as a colorless oil: $[\alpha]_D^{25}$ –10.2° (*c* 1.26, $CHCl_3$); IR (neat, cm^{-1}) 3475, 1700-1730; ^1H-NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 6.3 Hz, 3H), 1.17 (s, 3H), 1.28 (s, 3H), 2.01-2.10 (m, 1H), 2.40-2.44 (m, 1H), 2.95-3.19 (m, 4H), 3.56-3.74 (m, 2H), 4.79 (ddd, J = 4.4, 10.7, 10.7 Hz, 1H), 7.02-7.28 (m, 8H), 7.29-7.39 (m, 1H), 7.64-7.67 (m, 1H), 8.13-8.22 (br s, 1H); HRMS calcd for $C_{33}H_{42}N_2O_3$ (M^+) 514.3195, found 514.3173.

(+)-12b-Epidevinylantirhine (8)

A mixture of **7** (106 mg, 0.21 mmol) and distilled $POCl_3$ (1.2 mL, 12.3 mmol) in dry MeCN (10 mL) was heated for 1.5 h under reflux. After removal of the solvent under reduced pressure, the reagents were removed by azeotropic distillation with toluene to give the iminium salt, which was used for the next reaction without further purification.

To a stirred solution of the above salt in distilled MeOH (12 mL) at 0 °C was added $NaBH_4$ (78 mg, 2.1 mmol). After being stirred at the same temperature for 1 h, the reaction mixture was poured into H_2O, and the mixture was extracted with $CHCl_3$. The combined extracts were washed with brine, dried (K_2CO_3), and evaporated to give a residue, which was used in the following reaction with purification.

To a solution of the above product in dry toluene (4 mL) at 0 °C was added 1.01 M DIBAL-toluene (0.82 mL, 0.82 mmol) and the mixture was stirred for 40 min at the same temperature and then concentrated under reduced pressure. After being addition of H_2O (0.82 mL) followed by 12 h of stirring, the mixture was filtered through Celite, and evaporated. Purification of the residue by silica gel column chromatography with $CHCl_3$-MeOH (5:1 v/v) as eluant afforded **8** (19 mg, 35% for three steps) as a colorless solid: $[\alpha]_D^{21}$ +12.3° (*c* 0.50, MeOH); $[\theta]$ –3.14 x 10^3 (269 nm, MeOH), the physical properties of which were identical with those of the authentic compound.[14]

(+)-(3*R*)-3-(1,3-Dithian-2-ylmethyl)-5-pentanolide (9)

By the same procedure (Table 1, entry 4), **3a** (147 mg, 0.31 mmol) was converted into the crude **4aA**, which was used in the following reaction without purification.

To a stirred solution of the above product and 1,3-propanedithiol (29.6 μL, 0.30 mmol) at 0 °C was added

BF_3·OEt_2 (96.5 μL, 0.79 mmol). The mixture was stirred for 1.5 h at rt, and then evaporated to give a residue, which was directly used in the next reaction without purification.

A mixture of the above product and 10% NaOH (2 mL) in MeOH (3 mL) was heated for 2 h under reflux. The reaction mixture was concentrated under reduced pressure to remove solvent. After being diluted with $CHCl_3$, followed by acidification of the aqueous solution with 10% HCl, the mixture was stirred for 2 h at rt. The solution was extracted with $CHCl_3$, the combined organic phases were washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and the solvent was evaporated at reduced pressure. The crude product was purified by column chromatography on silica gel. Elution with hexane-AcOEt (3:1 v/v) provided **9** (21.3 mg, 30% from **3a**) as a colorless oil: $[\alpha]_D^{22}$ +46.14° (*c* 0.70, $CHCl_3$); IR (neat, cm^{-1}) 1730; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.50-1.53 (m, 2H), 1.68-1.92 (m, 2H), 1.93-2.05 (m, 1H), 2.09-2.19 (m, 1H), 2.21-2.42 (m, 1H), 2.74-2.94 (m, 5H), 4.06 (t, J = 7.4 Hz, 1H), 4.28 (dt, J = 3.6, 11.2 Hz, 1H), 4.39-4.47 (m, 1H); HRMS calcd for $C_{10}H_{16}O_2S_2$ (M^+) 232.0625, found 232.0592.

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REFERENCES

1. (a) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Oxford, 1986. (b) D. P. Curran, in *Comprehensive Organic Synthesis*, ed. by B. M. Trost, I. Fleming, and M. F. Semmelhack, Pergamon, Oxford, 1991, vol. 4, p. 715. (c) A. L. J. Beckwith, *Chem. Soc. Rev.*, 1993, 143. (d) G. Stork and N. H. Baine, *J. Am. Chem. Soc.*, 1982, **104**, 2321.
2. Review: N. A. Porter, B. Giese, and D. P. Curran, *Acc. Chem. Res.*, 1991, **24**, 296.
3. M. Ihara, K. Yasui, N. Taniguchi, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1469.
4. (a) W. Oppolzer, M. Kurth, D. Reichlin, C. Chapuis, M. Mohnhaupt, and F. Moffatt, *Helvetica Chem. Acta*, 1981, **64**, 2802. (b) D. P. Curran, B. H. Kim, H. P. Piyasena, R. J. Loncharich, and K. N. Houk, *J. Org. Chem.*, 1987, **52**, 2137.
5. (a) E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.*, 1975, **97**, 6908. (b) J. K. Whitesell, *Chem. Rev.*, 1992, **92**, 953.
6. D. A. Evans and A. E. Weber, *J. Am. Chem. Soc.*, 1986, **108**, 6757.
7. A part of this work has been preliminary communicated: M. Ihara, A. Katsumata, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1997, 991.
8. B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1980, **102**, 4743.
9. W. R. Roush, H. R. Gillis, and A. I. Ko, *J. Am. Chem. Soc.*, 1982, **104**, 2269.
10. Y. Ueno, K. Chino, M. Watanabe, O. Moriya, and M. Okawara, *J. Am. Chem. Soc.*, 1982, **104**, 5564.
11. K. Nozaki, K. Oshima, and K. Utimoto, *J. Am. Chem. Soc.*, 1987, **109**, 2547.
12. M. Nishida, E. Ueyama, H. Hayashi, Y. Ohtake, Y. Yamaura, E. Yanaginuma, O. Yonemitsu, A.

Nishida, and N. Kawahara, *J. Am. Chem. Soc.*, 1994, **116**, 6455.

13. K. Maruoka, T. Itoh, M. Sakurai, K. Nonoshita, and H. Yamamoto, *J. Am. Chem. Soc.*, 1988, **110**, 3588.
14. E. Wenkert, M. Guo, M. J. Pestchanker, Y.-J. Shi, and Y. D. Vankar, *J. Org. Chem.*, 1989, **54**, 1166.
15. P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Oxford, 1983.
16. G. Toth, O. Clauder, K. Gesztes, S. S. Yemul, and G. Snatzke, *J. Chem. Soc., Perkin Trans. 2*, 1980, 701.
17. M. P. Sibi, C. P. Jasperse, and J. Ji, *J. Am. Chem. Soc.*, 1995, **117**, 10779.
18. D. L. J. Clive, K. S. K. Murthy, A. G. H. Wee, J. S. Prasad, G. V. J. da Silva, M. Majewski, P. C. Anderson, C. F. Evans, R. D. Haugen, L. D. Heerze, and J. R. Barrie, *J. Am. Chem. Soc.*, 1990, **112**, 3018.
19. C. Broka and J. Ehrler, *Tetrahedron Lett.*, 1991, **32**, 5907.

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