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APPLICATION OF OXIDATIVE DESYMMETRIZATION OF *MESO*-TETRAHYDROFURANS: SYNTHESES OF FUNCTIONALIZED CHIRAL BUILDING BLOCKS AND OF (-)-ALLOYOHIMBANE

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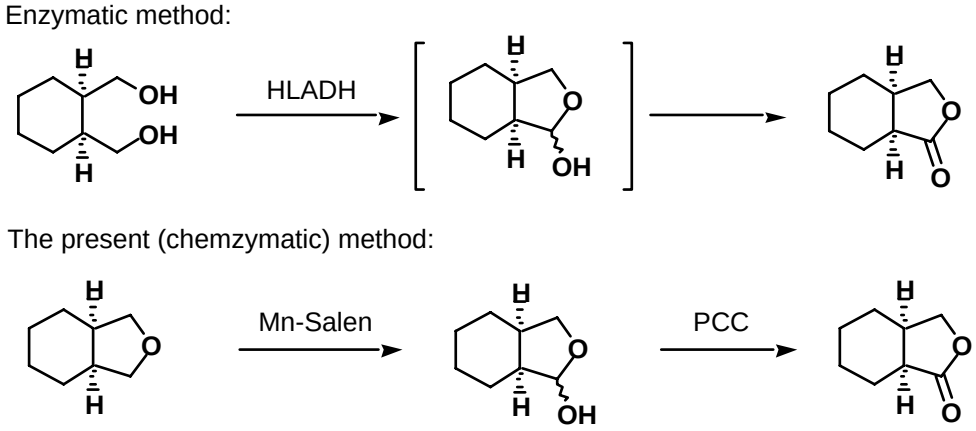
Abstract-Oxidative desymmetrization of oxygen functionalized *meso*-tetrahydrofurans was successfully achieved (up to 87% ee) through (salen)manganese(III) catalyzed enantiotopic selective C-H oxidation. The enantioselective synthesis of (-)-alloyohimbane (**12**) has also been achieved in a short step by using oxidative desymmetrization of *meso*-tetrahydrofuran as the key step.

Most of biologically active natural products have multi-stereogenic centers and their configurations have strong influences on biological activities of the natural products. Therefore, much effort has been directed toward exploitation of efficient methodologies for the construction of stereogenic center(s).[1] Among various methods reported to date, desymmetrization of *meso* compounds has some advantages from the synthetical view point: i) multi-asymmetric centers can be constructed by single manipulation, and ii) various types of *meso* compounds are available with ease. Oxidative desymmetrization provides another



Scheme 1. Oxidative desymmetrization of *meso* compounds

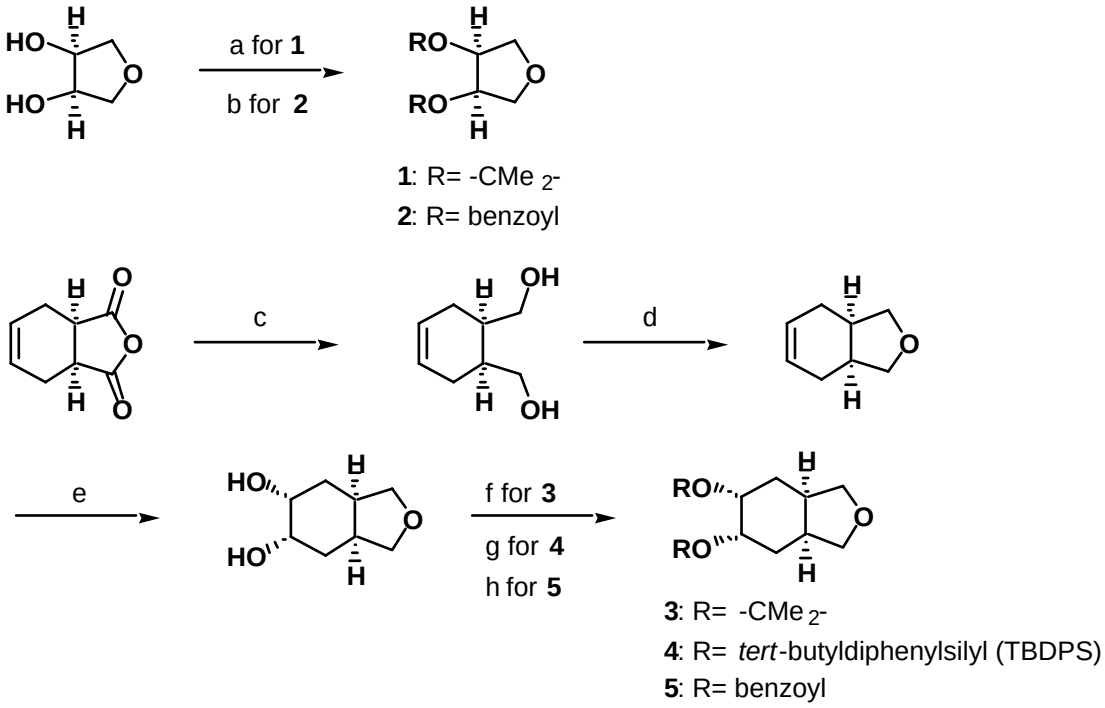
This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his seventy third birthday.

advantage that an extra oxygen functionality is endowed to the product through the process.This oxidative desymmetrization has so far been investigated by an enzymatic approach.[2] For example, it has been reported that horse liver alcohol dehydrogenase (HLADH) catalyzes enantiotopic selective oxidation of *meso*-diol to give the synthetically useful γlactone through the corresponding lactol intermediate (Scheme 1).[3] Enzymatic transformations generally show high enantioselectivity in the selected substrates, but the substrate-derivatization sometimes decreases enantioselectivity, because of high substrate-specificity of enzymes.

We have already demonstrated that chiral (salen)manganese(III) complexes (hereafter abbreviated as Mn-salen complexes) are excellent catalysts not only for asymmetric epoxidation of simple olefins[4] but also for enantioselective hydroxylation of prochiral benzylic carbon.[5] We expected that these Mn-salen complexes could be used as catalysts for enantiotopic selective C-H oxidation of *meso*-tetrahydrofurans.Actually,we could recently achieve high enantioselectivity (up to 90% ee) in desymmetrization of non-functionalized tetrahydrofurans giving the corresponding lactols (Scheme 1).[6] To expand the scope of this oxidative desymmetrization, we examined the reaction of *meso*-tetrahydrofurans bearing oxygen functionalities as substrates.

Syntheses of Functionalized *meso*-Tetrahydrofurans (1-5)

The requisite functionalized *meso*-tetrahydrofurans were prepared from commercial *cis*-3,4-dihydroxytetrahydrofuran and from *cis*-1,2,3,6-tetrahydrophthalic anhydride in a conventional manner (Scheme 2).

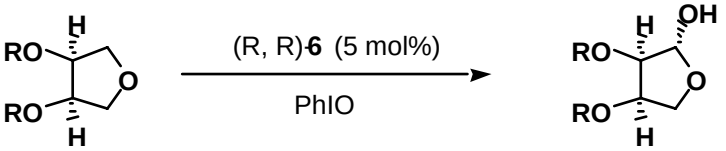


a) acetone, TsOH (61%) b) BzCl, Et_3N, DMAP (77%) c) LAH (99%) d) DMSO, 180°C (100%) e) $K_2OsO_4 \cdot 2H_2O$, $K_3Fe(CN)_6$, K_2CO_3, DABCO (63%) f) acetone, CSA (90%) g) TBDPSCl, Et_3N, DMAP (87%) h) BzCl, Et_3N, DMAP (72%)

Scheme 2

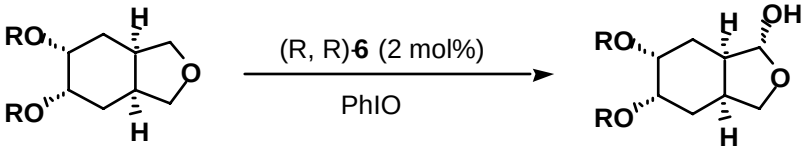
Oxidative Desymmetrization of Functionalized *meso*-Tetrahydrofurans

We first examined the oxidation of **1** in chlorobenzene using iodosylbenzene as a terminal oxidant in the presence of a catalytic amount of Mn-salen complex (**6**), which is the best conditions for oxidative desymmetrization of non-functionalized *meso*-tetrahydrofurans.[6] The results are summarized in Table 1. As expected, the reaction proceeded smoothly at -30˚C to give the corresponding lactol (**7**) of high enantiomeric excess of 84% ee (entry 1). Oxidation of **2** bearing benzoyl group was sluggish (entry 2). These results seemed to suggest that acetonide group does not affect enantioselectivity in desymmetrization.



1: R= -CMe_2-
2: R= benzoyl

7: R= -CMe_2-
8: R= benzoyl



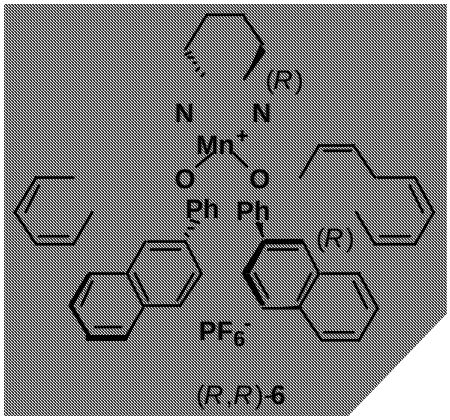
3: R= -CMe_2-
4: R= *tert*-butyldiphenylsilyl (TBDPS)
5: R= benzoyl

9: R= -CMe_2-
10: R= *tert*-butyldiphenylsilyl (TBDPS)
11: R= benzoyl

Table 1. Oxidative Desymmetrization of *meso*-tetrahydrofurans using Mn-salen complex as a catalyst.[a)]

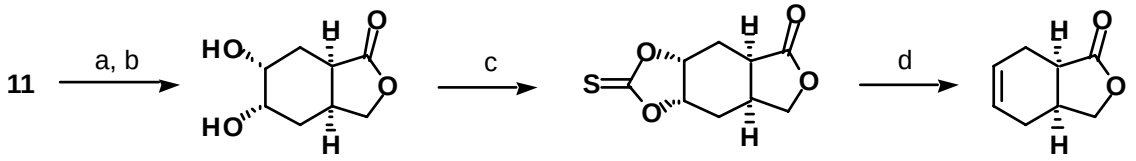
entry	substrate	time (h)	yield (%)	% ee
1	**1**	72	46	84[b)]
2	**2**	72	2	15[c)]
3	**3**	36	55	65[d)]
4	**4**	72	37	56[e)]
5	**5**	72	58	87[f)]

a) The reaction was carried out in chlorobenzene at -30˚C by using 1 equivalent of iodosylbenzene as an oxidant.
b) Determined by HPLC using optically active column (Daicel Chiralcel OD-H;hexane/*i*PrOH=1:1)after 3,5-dinitrobenzoylation.
c) Determined by HPLC using optically active column (Daicel Chiralcel OD-H;hexane/*i*PrOH=7:3)after *p*-nitrobenzoylation.
d) Determined by HPLC using optically active column (Daicel Chiralcel OD; hexane/*i*-PrOH=50:1)after benzylacetalization.
e) Determined by HPLC using optically active column (Daicel Chiralcel OD-H; hexane/*i*-PrOH =400:1) after benzylacetalization.
f) Determined by HPLC using optically active column (Daicel Chiralcel OD-H; hexane/*i*PrOH=9:1)after benzylacetalization.



(*R*,*R*)-**6**

Encouraged by this result, we next examined the oxidation of **3** bearing acetonide group under the same conditions, since oxidation of 8-oxabicyclo[4.3.0]nonane had shown high enantioselectivity of 90% ee.[6b] Contrary to our expects, oxidation of **3** exhibited poor enantioselectivity of 65% ee (entry 3).Oxidationof **4** bearing *tert*-butyldiphenylsiloxy group of poor coordinating ability was next examined but it also suffered enantioselectivity and chemical yield (entry 4). On the other hand, **5** protected as benzoyl ester exhibited high enantioselectivity of 87% ee together with moderate chemical yield, suggesting that the suitable protecting group varies with the structure of the substrate (entry 5). Ab solute configuration of **7** was determined to be 3*R*, 4*R* by the comparison of the specific rotation with the reported one,[7] after converted into the corresponding lactone by oxidation with pyridinium chlorochromate (PCC). Absolute configuration of **11** was determined to be 1*S*, 3*S*, 4*R*, 6*R* by chiroptical comparison with the published value[8] after its conversion to 8-oxabicyclo[4.3.0]non-3-en-7-one by the sequence: i) oxidation with PCC, ii) hydrolysis with K_2CO_3-methanol, iii) thiocarbonate formation and its pyrolysis in the presence of trimethyl phosphite.[9] (Scheme 3).



$[\alpha]_D^{24}$ +80.5 ° (*c* 1.18, acetone)

lit.,[8] (1*R*,6*S*) $[\alpha]_D^{20}$ -85.4 ° (*c* 2.63, acetone)

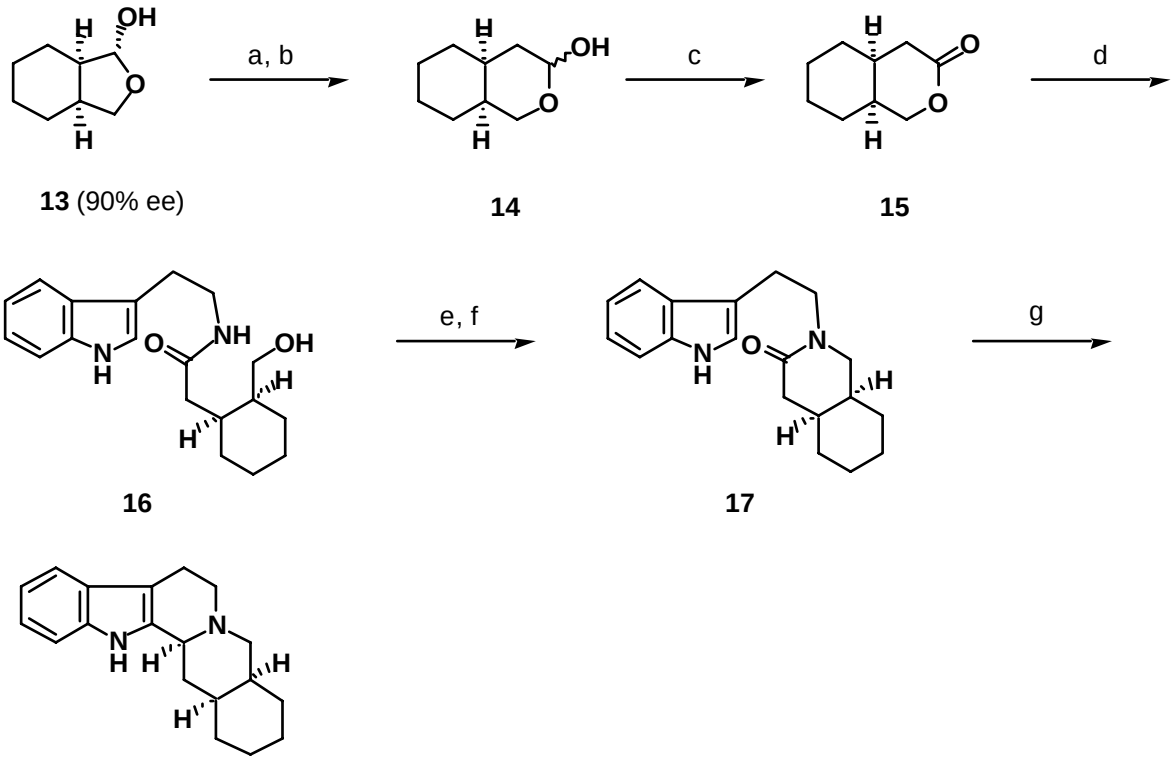
a) PCC (95%) b) K_2CO_3, MeOH (66%) c) $CSIm_2$ (60%) d) $P(OMe)_3$ (61%)

Scheme 3

Enantioselective Synthesis of (-)-Alloyohimbane (12)

To demonstrate the utility of the oxidative desymmetrization of *meso*-tetrahydrofurans in organic synthesis, we examined an enantioselective synthesis of (-)-alloyohimbane (**12**) (Scheme 4). (-)-Alloyohimbane that is one of the yohimbane family has the pentacyclic *cis* D/E skeleton. Yohimbane family of indole alkaloid has received much attention mainly due to their pharmacological interest such as antihypertensive activity.[10] Although some enantioselective syntheses of (-)alloyohimbane have been reported,[11] they use stoichiometric amount of chiral sources such as sugars or chiral auxiliaries, except for

enzymatic method.[11b] In particular, catalytic asymmetric synthesis using chiral molecular catalyst has not been reported.



13 (90% ee) **14** **15**

16 **17**

(-)-Alloyohimbane (**12**)

a) $Ph_3P^+CH_2OMe\ Cl^-$, *tert*-BuOK b) THF -1N HCl aq. (82% for 2 steps) c) PCC (84%)
d) tryptamine, xylene, 100°C (90%) e) Ph_3P, CCl_4, pyridine (52%) f) $LiN(TMS)_2$ (94%) g) $POCl_3$, $NaBH_4$ (83%

Scheme 4

Our synthesis started with 7-hydroxy-8-oxabicyclo[4.3.0]nonane (**13**) of 90% ee which is oxidative desymmetrization product of 8-oxabicyclo[4.3.0]nonane as previously reported.[6b] Wittigreaction of lactol (**13**) followed by the acid treatment of the resulting enol ether afforded the homologated lactol (**14**). Oxidation of lactol (**14**) with PCC gave lactone (**15**). Lactone (**15**) was heated with tryptamine in xylene at 100 ˚C to give amide alcohol (**16**). Conversion of amide alcohol (**16**) to lactam (**17**) was performed according to Isobe's method which was used for the synthesis of (-)-dehydroalloyohimbane.[11a,12] Thus, treatment of amide alcohol (**16**) with triphenylphosphine and carbon tetrachloride in a mixture of chloroform and pyridine (2:1) followed by the treatment of the resulting amide chloride with lithium bis(trimethylsilyl)amide gave the desired lactam (**17**). Final cyclization of lactam(**17**) in the conventional manner (Bischler-Napieralski cyclization[13]) gave (-)-alloyohimbane (**12**). All thespectroscopicdata of **12** are compatible with reported data. The specific rotation of **12** was $[\alpha]_D^{26}$ -151.9˚ (*c*0.41,pyridine)[lit.,[14] $[\alpha]_D^{21.5}$ -166.5˚ (*c* 0.4, pyridine)].

In conclusion, we were able to disclose the potential of oxidative desymmetrization of *meso*-tetrahydrofurans in organic synthesis by demonstrating the efficient synthesis of functionalized γ-lactol and

γ-lactone derivatives which are useful chiral building blocks and by performing the enantioselective synthesis of (-)-alloyohimbane, starting from oxidative desymmetrization product.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 270 MHz on a JEOL EX-270 and 400 MHz on a AVANCE DPX400 instruments. All signals were expressed as ppm down field from tetramethylsilane used as an internal standard (δ-value in $CDCl_3$), unless otherwise noted. IR spectra were obtainedwithaSHIMADZUFTIR-8600 instrument. Optical rotation was measured with a JASCO DIP-360 and JASCO P-1020 automatic digital polarimeters. High-resolution MS spectra were recorded on a JEOL JMSSX/SX 102A instrument. Column chromatography was conducted on Silica Gel BW-820MH, 70-200 mesh ASTM, available from FUJI SILYSIA CHEMICAL LTD. HPLC analysis of enantiomeric excess was carried out using Hitachi L-4000. The reaction temperature was controlled with EYELA COOL ECS 50. Solvents were dried and distilled shortly before use. Reactions were carried out under an atmosphere of nitrogen if necessary. Iodosylbenzene was purchased from Tokyo Chemical Industry Co., Ltd.

meso-Tetrahydrofurans (1-5)

They were prepared from commercially available *cis*-3,4-dihydroxytetrahydrofuran and from *cis*-1,2,3,6-tetrahydrophthalic anhydride in a conventional manner.[6] Their spectroscopic data (^{1}H NMR and IR) are given below.

cis-3,4-Isopropylidenedioxytetrahydrofuran (1)

A colorless oil. ^{1}H NMR: δ 4.76 (dd, *J*= 1.0, 2.3 Hz, 2H), 4.03 (d, *J*= 11.2 Hz, 2H), 3.45-3.40 (m, 2H), 1.50 (s, 3H), 1.34 (s, 3H). IR (neat): 2984, 2937, 2849, 1381, 1275, 1229, 1205, 1103, 1047, 858, 719 cm^{-1}.

cis-3,4-Dibenzoyltetrahydrofuran (2)

A colorless oil. ^{1}H NMR: δ 7.97-7.94 (m, 4H), 7.55-7.51 (m, 2H), 7.37-7.34 (m, 4H), 5.70-5.66 (m, 2H), 4.31-4.27 (m, 2H), 4.06 (dd, *J*= 4.0, 10.0 Hz, 2H). IR (neat): 1724, 1450, 1279, 1128, 1096, 1070, 710 cm^{-1}.

3,4-Isopropylidenedioxy-8-oxabicyclo[4.3.0]nonane (3)

A white solid. ^{1}H NMR: δ 4.41 (s, 2H), 3.91 (dd, *J*= 7.3, 8.9 Hz, 2H), 3.41 (dd, *J*= 4.3, 8.9 Hz, 2H), 2.49-2.44 (m, 2H), 1.94 (dd, *J*= 3.0, 14.5 Hz, 2H), 1.47 (s, 3H), 1.34 (s, 3H), 1.34-1.26 (m, 2H). IR (KBr): 2941, 2835, 1383, 1258, 1207, 1165, 1128, 1105, 1042, 1001, 934, 866 cm^{-1}.

3,4-Di-*t*-butyldiphenylsiloxy-8-oxabicyclo[4.3.0]nonane (4)

A colorless oil. ^{1}H NMR: δ 7.73-7.60 (m, 12H), 7.45-7.28 (m, 8H), 3.86 (d, *J*= 7.5 Hz, 2H), 3.49 (dd, *J*= 7.5, 7.5 Hz, 2H), 3.07 (dd, *J*= 5.1, 8.1 Hz, 2H), 2.32 (m, 2H), 1.87-1.84 (m, 2H), 1.13-1.01 (m, 2H), 1.07 (s, 18H). IR (KBr): 2932, 2856, 1427, 1113, 1063, 999, 854, 822, 741, 702, 507, 488 cm^{-1}.

3,4-Dibenzoyl-8-oxabicyclo[4.3.0]nonane (5)

A white solid. ^{1}H NMR: δ 8.02-8.00 (m, 4H), 7.58-7.54 (m, 2H), 7.44-7.40 (m, 4H), 5.51-5.49 (m, 2H), 3.95 (dd, *J*= 6.5, 8.0 Hz, 2H), 3.77 (dd, *J*= 5.0, 8.0 Hz, 2H), 2.67-2.62 (m, 2H), 2.35-2.29 (m, 2H), 2.01-1.96 (m, 2H). IR (KBr): 2943, 2864, 1717, 1450, 1121, 1065, 1024, 989, 961 cm^{-1}.

General procedure for oxidative desymmetrization using Mn-salen complex (*R*,*R*)-6 as a catalyst

To the stirred solution of **5** (54.4 mg, 0.15 mmol), Mn-salen complex (*R*,*R*)-**6** (3 mg, 0.3 μmol) and chlorobenzene (1.5 mL) was added iodosylbenzene (33 mg, 0.15 mmol) at -30 °C in air. The mixture was stirred for 72 h at the same temperature and quenched by adding dimethyl sulfide (10 μL, 0.14 mmol).The mixture was directly chromatographed on silica gel (hexane/ethyl acetate= 1/0 to 1/1) to give lactol (**11**) (33 mg, 58%) as a white solid. It was used for the next reaction without further purification.

Typical procedure for the determination of the enantiomeric excess of lactols

To a solution of lactol (**11**) in dichloromethane (0.2 mL) were added several drops of benzyl alcohol and catalytic amount of camphorsulfonic acid in air. After stirring for 2 h, the mixture was concentrated and chromatographed on silica gel to yield the corresponding benzylacetal as a white solid. The enantiomeric excess of the product was determined to be 87% by HPLC analysis (Daicel Chiralcel ODH; hexane/iPrOH = 9:1).

Identification and determination of absolute configuration of the desymmetrization products were carried out after they were oxidized to the corresponding lactones.

Oxidation of lactol (7) and determination of its configuration

To a stirred solution of lactol (**7**) (51 mg, 0.32 mmol) and Celite (200 mg) in 2 mLof dichloromethane was added PCC (345 mg, 1.6 mmol). After stirring at rt for 18 h, more Celite and ether were added to the suspension and the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residual mixture was subjected to column chromatography on silica gel (hexane/ethyl acetate= 7/3) to give pure (2*R*,3*R*)-2,3-*O*-isopropylidenerythronolactone (26 mg, 51%) as a white solid which gave spectroscopic data identical with the reported ones in any respect except for specific rotation. $[\alpha]_D^{25}$ -99.18° (*c* 1.00, H_2O) (lit.,[7] ((2*R*,3*R*)-(-)-2,3-*O*-Isopropylidenerythronolactone) $[\alpha]_D^{25}$ -113.8° (*c* 1.11, H_2O)). NMR: δ 4.89-4.87 (m, 1H), 4.75 (d, *J*= 6.0 Hz, 1H), 4.47 (d, *J*= 11.1 Hz, 1H), 4.41 (dd, *J*= 4.0, 11.1 Hz, 1H), 1.50 (s, 3H), 1.40 (s, 3H).

Oxidation of 11 to 3,4-dibenzoyl-8-oxabicyclo[4.3.0]nonan-7-one

To a stirred solution of lactol (**11**) (532 mg, 1.4 mmol) and Celite (1 g) in 20 mL of dichloromethane was added PCC (1.5 g, 7.0 mmol). After stirring at rt for 4 h, more Celite and ether were added to this suspension and the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residual mixture was subjected to column chromatography on silica gel

(hexane/ethyl acetate= 6/4) to give 3,4-dibenzoyl-8-oxabicyclo[4.3.0]nonan-7-one (507 mg, 95%) as white crystals. mp 172-174˚C. $[\alpha]_D^{23}$ +88.5˚ (*c* 1.13, $CHCl_3$). ^{1}H NMR: δ 8.05-8.03 (m, 2H), 7.95-7.92 (m, 2H), 7.62-7.58 (m, 1H), 7.52-7.46 (m, 3H), 7.39-7.35 (m, 2H), 5.66-5.65 (m, 1H), 5.15 (ddd, *J*= 2.5, 5.0, 11.0 Hz, 1H), 4.34 (dd, *J*= 5.0, 9.0 Hz, 1H), 4.08 (br d, *J*= 9.0 Hz, 1H), 3.04-3.02 (m, 1H), 2.91-2.83 (m, 1H), 2.57-2.51 (m, 1H), 2.47-2.38 (m, 2H), 1.84-1.76 (m, 1H). IR (KBr): 1763, 1450, 1375, 1313, 1285, 1178, 1159, 1117, 1069, 1043, 1026 cm^{-1}. Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30%. Found: C, 69.43; H, 5.29%.

Conversion of 3,4-dibenzoyl-8-oxabicyclo[4.3.0]nonan-7-one to (1*S*,6*R*)-8-oxabicyclo-[4.3.0]non-3-en-7-one and its structure determination

The mixture of 3,4-dibenzoyl-8-oxabicyclo[4.3.0]nonan-7-one (507 mg, 1.3 mmol) and K_2CO_3 (360 mg, 2.6 mmol) in 10 mL of methanol was stirred for 3 h at rt. After filtration, it was concentrated and subjected to column chromatography on silica gel (ether/methanol=8/2) to give a crude dihydroxy lactone. The lactone was dissolved in a small amount of methanol, and precipitated by dilution with the mixture of ether (2 mL) and hexane (5 mL). After decantation, the precipitate was washed three times with ether and hexane, to yield pure dihydroxy lactone (147 mg, 66%) as a white solid. ^{1}H NMR (methanol-d_4): δ 4.12 (dd, *J*= 5.0, 8.5 Hz, 1H), 3.81 (d, *J*= 8.5 Hz, 1H), 3.72-3.71 (m, 1H), 3.29-3.24 (m, 1H), 2.73 (m, 1H), 2.58-2.53 (m, 1H), 1.90-1.83 (m, 3H), 1.23 (ddd, *J*= 2.5, 12.0, 14.6 Hz, 1H).

The mixture of the above dihydroxy lactone (70.4 mg, 0.41 mmol) and 1,1'-thiocarbonyldiimidazole (73 mg, 0.41 mmol) in 4 mL of toluene was refluxed for 4 h. After cooled to rt, the resulting mixture was filtered off and washed with the mixture of methanol (1 mL) and ether (5 mL). It was dissolvedinasmall amount of CH_2Cl_2 and subjected to short column chromatography on silica gel (CH_2Cl_2 only to ether/methanol=30/1) to give the corresponding thiocarbonate (52.9 mg, 60%) as a white solid. ^{1}H NMR (CD_2Cl_2): δ 5.24-5.16 (m, 2H), 4.49 (dd, *J*= 7.5, 9.5 Hz, 1H), 4.04 (dd, *J*= 2.5, 9.5 Hz, 1H), 2.98-2.91 (m, 1H), 2.77-2.71 (m, 1H), 2.66 (ddd, *J*= 3.0, 8.5, 16.1 Hz, 1H), 2.20 (ddd, *J*= 2.0, 4.5, 15.6 Hz, 1H), 1.76 (ddd, *J*= 2.0, 10.5, 15.6 Hz, 1H), 1.65 (ddd, *J*= 3.0, 13.6, 16.1 Hz, 1H).

A solution of the above thiocarbonate (38 mg, 0.17 mmol) in 2 mL of trimethyl phosphite was refluxed for for 100 h. After the mixture was cooled to rt, the mixture was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (hexane/ethyl acetate=7/3) to give 8-oxabicyclo[4.3.0]non-3-en-7-one (14.3 mg, 61%) as a colorless oil. $[\alpha]_D^{24}$ +80.5˚ (*c* 1.18, acetone) (lit.,[8] (1*R*,6*S*) $[\alpha]_D^{20}$ -85.4˚ (*c* 2.63, acetone)). ^{1}H NMR : δ 5.75-5.74 (m, 2H), 4.32 (dd, *J*= 5.0, 8.5 Hz, 1H), 4.03 (dd, *J*= 2.1, 8.5 Hz, 1H), 2.79 (ddd, *J*= 3.0, 8.0, 8.0 Hz, 1H), 2.67-2.59 (m, 1H), 2.54-2.25 (m, 3H), 1.96-1.88 (m, 1H). Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30%. Found: C, 69.63; H, 7.33%. Comparison of specific rotation determined the configuration of the 3,4-dibenzoyl-8-oxabicyclo[4.3.0]nonan-7-one to be 1*S*,6*R*.

(1*S*, 6*S*)-4-Oxabicyclo[4.4.0]decan-3-one (15)

To the flask containing potassium *tert*-butoxide (2.54 g, 23 mmol) and methoxymethyltriphenyl-phosphonium chloride (7.92 g, 23 mmol) was added 40 mL of THF at -78 °C. The mixture was once

warmed to rt and re-cooled to -78 °C. To the mixture was added a solution of lactol (**13**) (657 mg, 4.6 mmol) in 10 mL of THF. The mixture was warmed slowly to -20 °C, quenched with 10 mL ofwater,and allowed to warm to room temperature. The mixture was extracted with 10 mL of ether threetimesandthe combined organic layers were dried with sodium sulfate. After filtration, the solvent was removedunder reduced pressure. The residue was dissolved in the mixture of THF and 1N HCl (30 mL, 1:1), stirredfor 1 h, and extracted with 5 mL of ether five times. The organic layer was washed with saturated aqueous $NaHCO_3$ and dried with sodium sulfate. After filtration, the solvent wasconcentratedandsubjectedto short column (hexane/ethyl acetate= 6/4) to remove most of the excess phosphonium salt and theresulting triphenylphosphine oxide and the filtrate was concentrated in *vacuo*. The residue was submitted againto column chromatography (silica gel, hexane/ethyl acetate=7/3) to yield lactol (**14**) (594 mg, 82%) as a colorless oil. To a stirred solution of lactol (**14**) (594 mg, 3.8 mmol) and Celite (3 g) in 40 mL of dichloromethane was added PCC (4.1 g, 19 mmol). After stirring at rt for 3 h, Celite (5 g) and ether (40 mL) were added to this suspension. The mixture was filtered through a pad of Celite and the filtrate was removed under reduced pressure. The residual mixture was subjected to columnchromatographyonsilica gel (hexane/ethyl acetate= 7/3) to give lactone (**15**) (492 mg, 84% from **13**) as a colorless oil. $[\alpha]_D^{24}$45.2˚ (*c* 1.56, $CHCl_3$). ^{1}H NMR: δ 4.31 (d, *J*= 5.3 Hz, 2H), 2.53 (dd, *J*= 5.4, 7.5 Hz, 2H), 2.25-2.17 (m, 1H), 2.01-1.94 (m, 1H), 1.64-1.35 (m, 8H). IR (neat) 2928, 2856, 1736, 1450, 1402, 1248, 1221, 1194, 1096, 1090, 1076, 1007, 953, 795 cm^{-1}. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15%. Found: C, 70.19; H, 9.25%.

3-[(1*S*,2*S*)-(2-Hydroxymethylcyclohexylmethylcarboxyamido)ethyl]indole (16)

A solution of lactone (**15**) (50.9 mg, 0.33 mmol) and tryptamine (79 mg, 0.49 mmol) in xylene (3 mL) was refluxed for 3 h. The mixture was directly chromatographed on silica gel (hexane/ethyl acetate= 7/3to 0/1) to give the amide alcohol (**16**) (94 mg, 90%) as a colorless oil. $[\alpha]_D^{24}$ -11.8˚ (*c* 1.73, $CHCl_3$). ^{1}H NMR: δ 8.23 (br s, 1H), 7.60 (d, *J*= 7.9 Hz, 1H), 7.38 (d, *J*= 8.2 Hz, 1H), 7.24-7.10 (m, 2H), 7.03 (d, *J*= 2.3 Hz, 1H), 5.79 (br s, 1H), 3.65-3.55 (m, 3H), 3.37-3.30 (m, 2H), 2.98 (t, *J*= 6.6 Hz, 2H), 1.94-1.71 (m, 2H), 1.90 (dd, *J*= 3.8, 14.3 Hz, 1H), 1.84-1.71 (m, 1H), 1.52-1.07 (m, 8H). IR (KBr): 3404, 3294, 2926, 2856, 1647, 1529, 1456, 1304, 1231, 1099, 1024, 743 cm^{-1}. HRFABMS m/z Calcd for $C_{19}H_{27}N_2O_2$ (M^++H): 315.2073. Found 315.2073.

3-[(4a*S*,8a*S*)-(3-Oxo-2-decahydroisoquinolinyl)ethyl]indole (17)

To a stirred solution of amide alcohol (**16**) (910 mg, 2.9 mmol), carbon tetrachloride (4.3 mL) and pyridine (4.3 mL) in 8.6 mL of chloroform was added a solution of triphenylphosphine (3.0 g, 11 mmol), tetrachloromethane (4.3 mL) and pyridine (4.3 mL) in 8.6 mL of chloroform over a period of 2 h at 70°C. After the mixture was cooled to rt, the mixture was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (hexane/ether= 1/3) to give the corresponding amide chloride (497 mg, 52%) as a white solid.

To a solution of amide chloride (54.8 mg, 0.16 mmol) in 1.6 mL of THF was added 200 μL of $LiN(TMS)_2$ (1.0 M solution in n-hexane, 0.2 mmol) at -78 °C and it was allowed to warm to rt. The reaction mixture was re-cooled to -78 °C and another 200 μL of $LiN(TMS)_2$ was added the mixture and

the reaction mixture was warmed to rt. This operation was repeated one more time. (Totally 600 µL of $LiN(TMS)_2$ was used for this reaction.) Saturated aqueous NH_4Cl (1 mL) was added and themixturewas extracted with ether (2 mL) three times and the organic phase was dried over magnesium sulfate. After filtration, the solvent was removed under reduced pressure. The residuewaschromatographedonsilicagel with ether to give lactam **17** (46.3 mg, 98%) as white crystals. mp 170-172˚C. $[\alpha]_D^{24}$ +7.5˚ (*c* 0.82, $CHCl_3$). ^{1}H NMR: δ 8.42 (brs, 1H), 7.66 (d, *J*= 7.9 Hz, 1H), 7.35 (d, *J*= 7.6 Hz, 1H), 7.20-7.08 (m, 2H), 7.02 (d, *J*= 2.3 Hz, 1H), 3.78-3.53 (m, 2H), 3.23-3.00 (m, 4H), 2.38 (dd, *J*= 3.8, 6.8 Hz, 2H), 2.00-1.90 (m, 2H), 1.55-1.26 (m, 8H). IR (KBr): 3244, 2926, 2855, 1618, 1501, 1340, 1300, 1009, 739, 590, 428 cm^{-1}. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45%. Found: C, 76.85; H, 8.19; N, 9.35%.

(-)-Alloyohimbane (12)

The mixture of lactam (**17**) (46.3 mg, 0.16 mmol) and phosphorus oxychloride (1.6 mL, 17.2 mmol) was refluxed for 3 h and allowed to cool to rt. After concentrated in *vacuo*, the residue was dissolved in mixture of methanol and water (1 mL, 9:1) and, to this solution was added sodium tetrahydroborate at0˚C until the solution become basic (pH > 7). 1 mL of saturated aqueous NH_4Cl and ice were added and the mixture was extracted with dichloromethane (3 x 1 mL). The organic layer was subsequently washed with water and brine and dried over sodium sulfate. After filtration, the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (hexane/ethyl acetate= 8/2) to give the (-)-alloyohimbane (**12**) (37.3 mg, 83%) as white crystals. An analytical sample was obtained by recrystallization from methanol. mp 155-157˚C (lit.,[14] mp 156-157˚C). $[\alpha]_D^{25}$ -151.9˚ (*c* 0.41, pyridine) (lit.,[14] $[\alpha]_D^{22}$ -166.5˚ (*c* 0.4, pyridine)). ^{1}H NMR: δ 7.71 (brs, 1H), 7.47 (d, *J*= 7.5 Hz, 1H), 7.30 (d, *J*= 7.5 Hz, 1H), 7.14-7.05 (m, 2H), 3.21-3.19 (m, 1H), 3.00-2.94 (m, 2H), 2.77 (dd, *J*= 2.0, 11.0 Hz, 1H), 2.71-2.66 (m, 1H), 2.55-2.50 (m, 2H) 1.99-1.91 (m, 3H), 1.72-1.60 (m, 5H), 1.43-1.23 (m, 4H). ^{13}CNMR($CDCl_3$):δ 135.9, 135.5, 127.5, 121.2, 119.3, 118.1, 110.7, 108.2, 62.0, 60.5, 53.4, 36.7, 34.8, 31.6, 30.5, 26.6, 26.5, 21.8, 20.8. IR (KBr): 3423, 2920, 2856, 2800, 1342, 1321, 1308, 1279, 1259, 1161, 1146, 1123, 1103, 1061, 1009, 737 cm^{-1}. Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99%. Found: C, 81.39; H, 8.60; N, 9.98%.

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