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Stereoselective Synthesis of Axially Chiral Natural Products, (−)-Steganone and *O*,*O*′-Dimethylkorupensamine A, Utilizing Planar Chiral (Arene)chromium Complexes

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Abstract—Palladium(0)-mediated Suzuki–Miyaura cross-coupling of planar chiral (2,6-disubstituted bromobenzene)chromium complexes with *o*-substituted arylboronic acids in the presence of sodium carbonate under refluxing in aqueous methanol gave stereoselectively axially chiral mono $Cr(CO)_3$-complexed biaryls. The axial stereochemistry of the cross-coupling products was found to be largely dependent on the steric bulkiness of *ortho* substituent of arylboronic acids and reaction conditions. The cross-coupling with *o*-alkyl or hydroxymethyl substituted arylboronic acids gave kinetically controlled products in which the *ortho* substituents were oriented in *syn*-configuration to the tricarbonylchromium fragment. On the other hand, *o*-formyl phenylboronic acid produced thermodynamically stable *anti*-coupling products under the same conditions. By utilizing these methodologies, biologically active axially chiral natural products, (−)-steganone and *O*,*O*′-dimethyl derivative of the natural product of korupensamine A, were stereoselectively synthesized.

Introduction

Axially chiral biaryls are of importance not only as chiral ligands or auxiliaries in asymmetric reactions but also for the synthesis of biologically active natural products. There is a considerable current interest in the development of efficient methodologies for the synthesis of biaryls with atropisomers in an enantiomerically pure form.[1] Nucleophilic displacement of an *ortho* methoxy group of chiral aryl oxazolines with aryl Grignard reagents has been widely employed in the asymmetric biaryl syntheses.[2] Copper-mediated Ullmann homo-coupling reaction has recently been observed for biaryl coupling of the chiral *ortho* bromo phenyloxazolines.[3] Nucleophilic aromatic substitution to the arene ring activated with other functional groups, e.g. ester, imine, has also been achieved for the preparation of chiral biaryl compounds.[4] For an intramolecular aryl coupling reaction[5] giving lignans and the related compounds, the bridge containing a chiral part is not only a constituent part of the target molecular but also at the same time it determines the steric course of the coupling reaction. Cyanocuprate mediated biaryl intramolecular coupling of a tethered nonracemic chiral compound is also elaborated.[6] Atrop-enantioselective biaryl synthesis as an unique method has been achieved by stereocontrolled torsion of flat achiral lactone precursors by means of optically active nucleophiles.[7] Other interesting methods including catalytic asymmetric coupling[8] have been reported to prepare biaryls in optically active form.

(η^6-Polysubstituted arene)chromium complexes exist in two enantiomeric forms based on a planar chirality when the arene ring is substituted at *ortho*- or *meta*-positions with different substituents. This fact in concert with ability of the tricarbonylchromium function to effectively block one face of the arene ring, has led to a rapid increase in the use of (arene)chromium complexes as the synthetic intermediates[9] and as the catalysts[10] for the asymmetric reactions. As part of our asymmetric exploration of the planar chiral arene chromium complexes, we have developed diastereoselective synthesis of axially chiral biaryls in enantiomerically pure form. In this paper, we wish to report further application of the palladium(0)-catalyzed cross-coupling of planar chiral arylhalide chromium complexes with arylboronic acids to the synthesis of biologically active axially chiral natural product and its derivative, (−)-steganone and *O*,*O*′-dimethylkorupensamine A.

Results and Discussion

Axially chiral biaryls utilizing planar chiral (arene)$Cr(CO)_3$ complexes

Cross-coupling reactions of aryl halides or aryl triflates with

Keywords: alkaloids; atropisomerism; chromium and compounds; coupling reactions.

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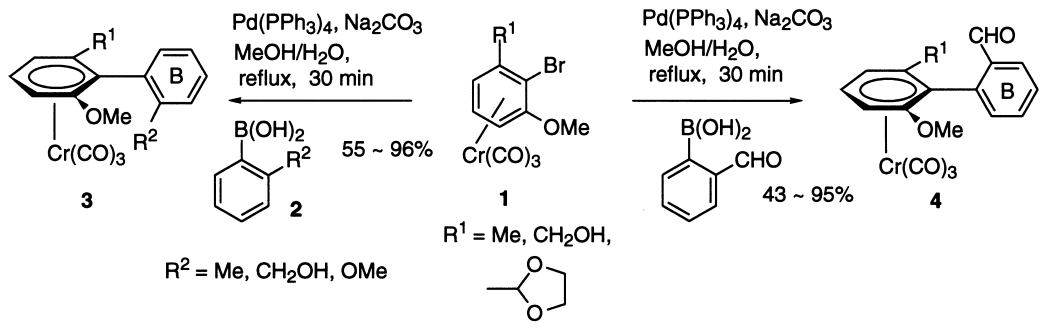


Scheme 1. Palladium-catalyzed cross-coupling of planar chiral (arene)$Cr(CO)_3$ complexes.

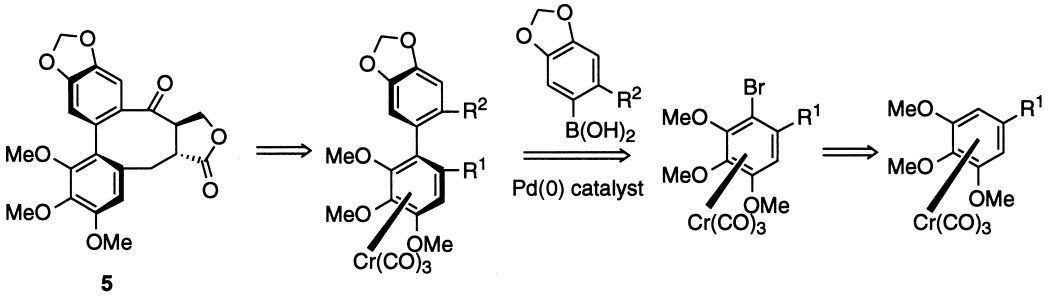
arylmetals catalyzed by palladium(0) are used for the preparation of biaryls. An oxidative addition of the carbon–halogen bond of the aryl halide to the palladium(0) is accelerated by a coordination of an electron withdrawing tricarbonylchromium fragment to the arene ring. Even chlorobenzene can be made susceptible to oxidative addition by utilizing the corresponding tricarbonylchromium complex to give cross-coupling products.[11] We have already reported[12] that the palladium(0)-mediated cross-coupling of planar chiral (*o*-substituted arylhalide)-chromium complexes with *o*-substituted arylboronic acids in the presence of sodium carbonate under refluxing in aqueous methanol gave stereoselectively axially chiral mono $Cr(CO)_3$-complexed biaryls. The axial stereochemistry of the cross-coupling products was found to be largely dependent on the nature of *ortho* substituent of arylboronic acids and reaction conditions.

For instance, the cross-coupling of *o*-alkyl, alkoxy or hydroxymethyl substituted phenylboronic acid **2** with the chromium complex **1** gave the *syn*-(S^*,S^*)-configurated[13] coupling products **3** (Scheme 1). The *ortho* substituent R^2 on the B-ring of *syn*-product **3** is directed toward the tricarbonylchromium fragment in spite of a severe steric interaction between $Cr(CO)_3$ group and the *ortho* substituents. On the other hand, *o*-formylphenylboronic acid produced diastereoisomeric *anti*-(S^*,R^*)-chromium complexes **4** as the only isolated coupling products under the same conditions. In some cases, the CO-inserted products, benzophenone chromium complexes were obtained in various ratios. Similarly, α-naphthylboronic acids were reacted with (2,6-disubstituted-1-bromobenzene)$Cr(CO)_3$ complexes **1** under the same conditions to give the *syn*-coupling products without formation of *anti*-isomer in good yields.[14] Furthermore, the *syn*-biphenyl chromium complexes **3** were easily isomerized to the corresponding thermodynamically stable *anti*-biphenyl complexes under refluxing in higher boiling solvents, e.g. toluene, xylene, mesitylene, since the *syn*-biphenyl chromium complexes **3** are kinetically controlled products. As the mono-$Cr(CO)_3$ complexes of biaryls have both axial and planar chiralities, the chromium-complexed biaryls can exist in an enantiomerically active form based on the planar chirality even when the central bond rotates. Consequently, we can easily prepare both atropisomers from a single planar chiral arene chromium complex by utilizing this diastereoselective cross-coupling and subsequent axial isomerization.[15]

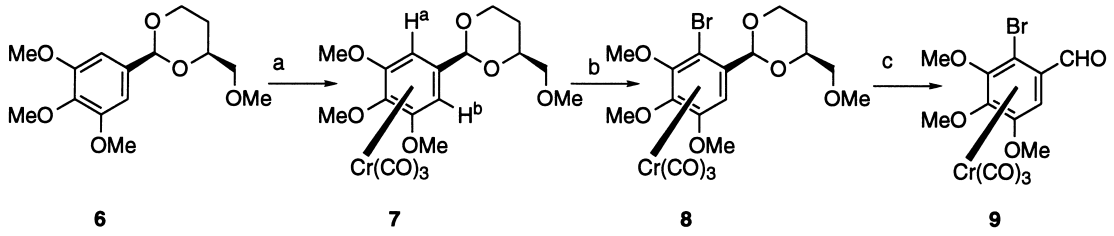
Synthesis of (−)-steganone

On the basis of above stereochemical results in the cross-coupling of planar chiral arene chromium complexes with arylboronic acids, we have next investigated total synthesis of biologically active axial natural products, e.g. (−)-steganone and *O*,*O′*-dimethylkorupensamine A. (−)-Steganone **5**, an antileukemic bisbenzocyclooctadiene lignan lactone, one of four isolated[16] *Steganotaenia araliacea* by Kupchan in 1973, has attracted considerable synthetic interest.[17] These ligands have demonstrated significant in vivo activity against P-338 leukemia in mice and have displayed significant in vitro activity against cells derived from human carcinoma of the nasopharynx. This natural product has the axial chirality between two phenyl rings and the chiral center derived from *trans*-fused γ-lactone. The novel feature of our strategy of total synthesis of (−)-steganone is to initially prepare an enantiomerically pure (arylhalide)-chromium complex with planar chirality via diastereoselective *ortho* lithiation, and subsequently to form the axial asymmetry of the biaryl bond (Scheme 2).[18]

Since optical resolution methods[19] for the preparation of planar chiral (arene)chromium complexes waste the



Scheme 2. Retrosynthesis of (−)-steganone.



Scheme 3. Synthesis of planar chiral bromobenzene chromium complex **9**. Reagents and conditions: (a) $Cr(CO)_6$, *n*-Bu_2O/THF (10/1), 140°C, 18 h, 62%; (b) *n*-BuLi, toluene, −78°C, then $BrCF_2CF_2Br$, 54%; (c) 6H-HCl, THF, 40°C, 30 min, 83%.

corresponding antipode (arene)chromium complex, we studied a diastereoselective *ortho* lithiation of tricarbonyl(3,4,5-trimethoxybenzaldehyde acetal)chromium complex for the preparation of planar chiral (arylhalide)-chromium complex. Initially, we examined the diastereoselective *ortho* lithiation of chiral C_2 symmetric acetal complex, e.g. tricarbonylchromium complex of (4*R*,5*R*)-[4,5-bis(α-methyl-α-methoxymethyl-2-(3′,4′,5′-trimethoxyphenyl)-1,3-dioxolane] derived from (+)-diethyl tartrate developed by Green and co-workers.[20] However, the diastereoselective *ortho* lithiation followed by bromination with 1,2-dibromo-1,1,2,2-tetrafluoroethane gave only 33% de in 69% yield. Therefore, we next turned our attention to another chiral benzaldehyde acetal auxiliary (Scheme 3). Dimethyl acetal of 3,4,5-trimethoxybenzaldehyde was reacted with (*S*)-(−)-1,2,4-butanetriol derived from L-malic acid followed by methylation with NaH/MeI to give stereoselectively 1,3-di-equatorial substituted dioxane structure **6** without formation of 5-membered acetal ring[21] in 73% overall yield. Tricarbonylchromium complexation of **6** with $Cr(CO)_6$ under usual thermal conditions gave the corresponding (arene)chromium complex **7** ($[\alpha]_D^{27}=-19.6$) in 67% yield. Diastereoselective *ortho* lithiation of **7** with butyl lithium followed by bromination and subsequent acidic hydrolysis of the acetal group afforded optically active (+)-(2-bromo-3,4,5-trimethoxybenzaldehyde)$Cr(CO)_3$ (**9**). Diastereoselectivity of the *ortho* lithiation was largely dependent upon the nature of lithiation solvent. Thus, the *ortho* lithiation in polar solvent was extremely low stereoselectivity owing to a coordination of the lithium with oxygen of solvent (e.g. 67% ee in ether, 3% ee in THF). Fortunately, a use of toluene as solvent with *n*-BuLi for the directed lithiation resulted in 90% ee of (+)-**9**. The optical purity of **9** was increased to >99% ee ($[\alpha]_D^{27}=+1036$) by one fractional crystallization of the brominated acetal compound **8** from ether/hexane and following acidic hydrolysis of the acetal. Although the yield of brominated product was moderate, the starting material could be easily recovered by flash chromatography before the acidic hydrolysis step. The stereochemistry of the planar chirality of **9** was assigned as shown in the text by the observed correlation with the sign of the specific rotations of related (*o*-halogenated benzaldehyde)$Cr(CO)_3$ complexes,[9a] and by analogy to the related diastereoselective lithiation with ferrocene homology.[22]

The observed diastereoselectivity for the directed *ortho* lithiation of **7** could be explained as follows (Fig. 1). Both tricarbonylchromium-complexed arene ring and methoxymethyl are equatorial. Among proposed transition states, a conformer **10** has a severe steric hindrance between tricarbonylchromium fragment and 1,3-dioxane part, and the other conformer **11** is free of hindrance with an *exo*-relationship between the chromium fragment and oxygen of dioxane. Therefore, the *ortho* lithiation would stereoselectively occur at H^a-position via a chelation of the lithium with oxygen atoms of the conformer **11** giving the planar chiral (+)-chromium complex **9**.

With an optically active planar chiral (arene)chromium complex in hand, the next stage of our effort was to form stereoselectively the axial chirality by the cross-coupling with *o*-substituted arylboronic acid. Reaction of (−)-(2-bromo-3,4,5-trimethoxybenzylalcohol)chromium (**12**) ($[\alpha]_D^{24}=+214$), derived from **9** by reduction, with 2-formyl-4,5-methylenedioxyphenylboronic acid (**13**) in the presence of 5mol % of $Pd(PPh_3)_4$ gave biaryl coupling product **14** ($[\alpha]_D^{25}=-161.5$) in 67% yield without formation of the corresponding atropisomer. The axial stereochemistry of **14** was assigned as (*R*)-configuration on the basis of the previous results[12b,c] that the coupling reactions of (*o*-substituted arene)$Cr(CO)_3$ complexes with *o*-formylphenylboronic acid gave stereoselectively the (*R*)-axial configuration products. At this axial juncture, the assignment was purely arbitrary, but this assumption proved to be correct as the synthesis reached its target molecule. Furthermore, the axial stereochemistry of **14** was confirmed by ^1H NMR spectra of diastereomeric chromium complexes as follows. The benzylic methylene protons of chromium-uncomplexed ring **15** obtained by reduction with $NaBH_4$

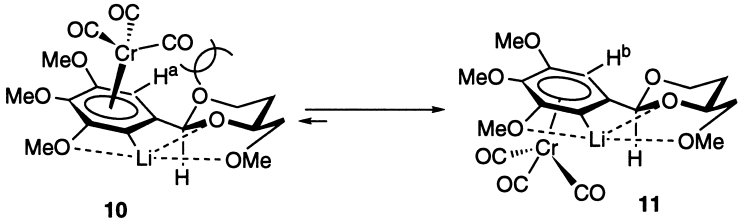


Figure 1. Transition state for diastereoselective *ortho* lithiation.

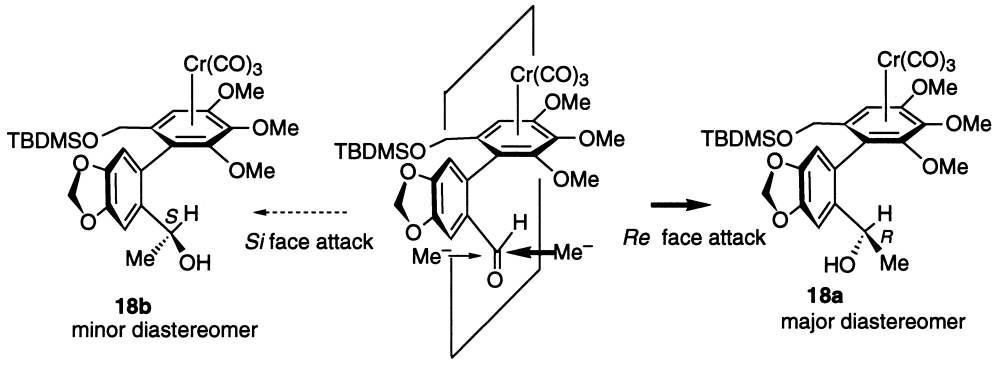
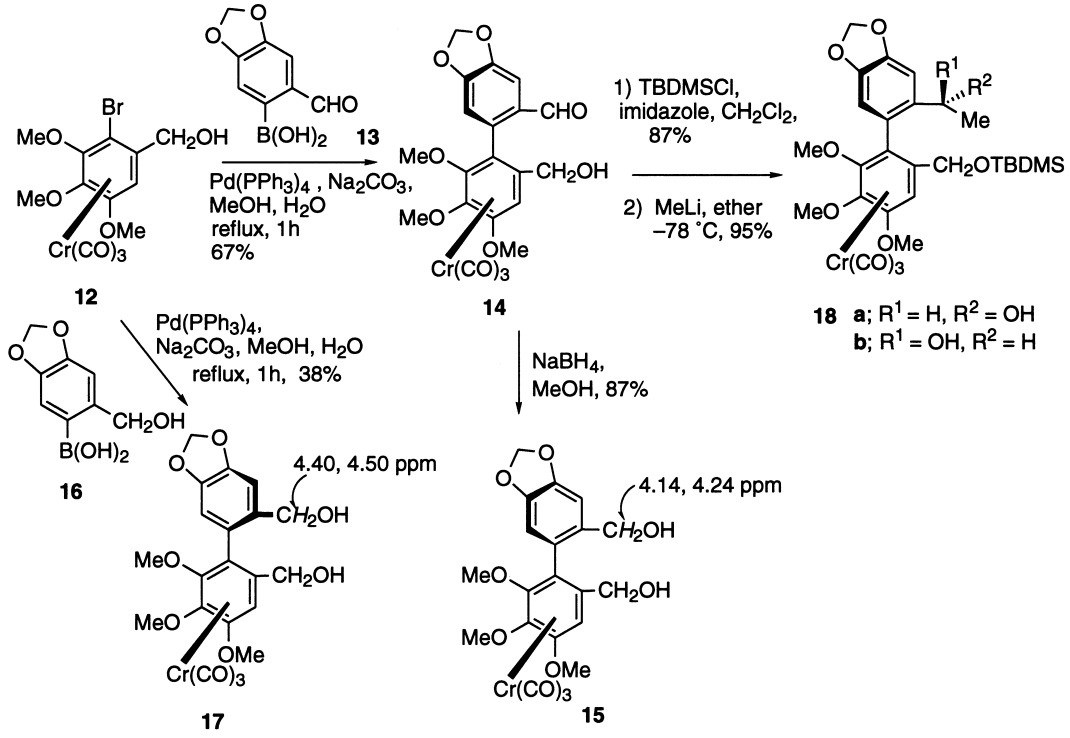


Figure 2.

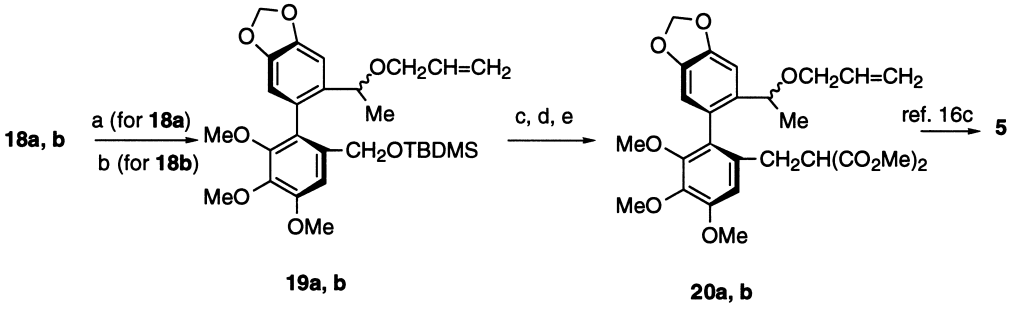
appeared at 4.14 and 4.24 ppm, while the corresponding methylene of cross-coupling product **17** with 2-hydroxymethyl-4,5-methylenedioxyphenylboronic acid **16** under the same conditions showed at 4.40 and 4.50 ppm as a double doublet. Generally, NMR signals of the benzylic proton *syn* to the $Cr(CO)_3$ fragment are shifted to lower field than those of the *anti* proton due to anisotropic effect.[23]

It was now necessary to elaborate the biaryl to the 8-membered ring present in steganone from the coupling product **14**. Protection of the hydroxyl group with *t*-butyldimethylsilyl chloride followed by treatment with methyllithium at −78°C afforded 5:1 diastereomeric mixture of secondary alcohols **18a**,**b** in 83% overall yield. This mixture was cleanly separated by flash chromatography, and each diastereomeric secondary alcohol could be used in the synthetic route since at a later stage in the synthesis this alcohol function was to be oxidized to a methyl ketone. The stereochemistry at newly created benzylic center could be easily predicted from the transition state as shown in Fig. 2. The carbonyl oxygen of axial biphenylchromium complex would be oriented *anti* to the chromium-complexed phenyl ring due to steric hindrance, and methyl lithium attack *re*-face of the carbonyl avoiding steric hindrance with *t*-$BuMe_2Si$ group to afford the *R*-configurated secondary alcohol **18a** (Scheme 4).

A more polar, major product **18a** (mp 148°C, $[\alpha]_D^{24}=-148.1$) was reacted with allylbromide and NaH followed by an air oxidative demetalation to give **19a** ($[\alpha]_D^{21}=+2.3$) in 57% overall yield. Desilylation of **19a** with *n*-Bu_4NF, bromination with CBr_4 and triphenylphosphine in CH_2Cl_2 at 0°C followed by treatment with sodium dimethylmalonate gave **20a** ($[\alpha]_D^{26}=+13.1$) in 45% overall yield which was already converted to (−)-steganone **5** by previously reported method.[17c] Spectral data of the compound **20a** are consistent with that of the reported compound. A less polar and minor fraction **18b**



Scheme 4.



Scheme 5. Reagents and conditions: (a) (i) CH_2=$CHCH_2Br$, NaH, THF, DMF, 63%; (ii) hν-O_2, ether, 90%; (b) (i) hν-O_2, ether; (ii) CH_2=$CHCH_2Br$, NaH, THF, DMF, 62% from **18b**; (c) *n*-Bu_4NF, THF, 98%; (d) CBr_4, PPh_3, CH_2Cl_2, 0°C; (e) $NaCH(CO_2Me)_2$, MeOH, 45%.

(mp 72°C, $[\alpha]_D^{25}=-139.4$) was treated with allylbromide and NaH to give desired allylated compound in less than 10% yield. The low yield would be contributed to the steric effect, and therefore, **18b** was first exposed to sunlight for de-tricarbonylchromium followed by treatment with NaH and allylbromide to give the corresponding **19b** ($[\alpha]_D^{25}=+55.8$) in 62% yield. Compound **19b** was converted to **20b** by the same reaction sequence, and all spectral data of **20b** are consistent with authentic sample (Scheme 5).[17c]

Synthesis of *O*,*O*′-dimethylkorupenamine A

Korupensamines and michellamines have been isolated from the tropical liana *Ancistrocladus korupensis* in Cameroon (Fig. 3), and some of these alkaloids possess significant pharmacological activities such as antimalarial properties,[24] and remarkable antiviral activity against human immunodeficiency virus strains HIV-1 and HIV-2.[25] Structurally, the korupensamines have a naphthyltetrahydroisoquinoline skeleton with an axial chirality between the naphthalene and tetrahydroisoquinoline rings, and the michellamines are atropisomerically dimeric alkaloids of korupensamines. Most biologically active alkaloid to strains HIV, michellamine B is formed by dimerization of axially isomeric korupensamine A and B. These alkaloids have been previously synthesized via the construction of the axial bond between the naphthalene and tetrahydroisoquinoline rings as a key step.[26,27] However, the palladium(0)-catalyzed cross-coupling[26] of two arene rings or nucleophilic addition[27]of aryl Grignards to the chiral *o*-methoxyaryl oxazoline compounds for the central bond formation of the naphthalene and tetrahydroisoquinoline rings gave usually various ratios of atropisomeric mixture. The other method for induction of the axial chirality other than central bond formation, e.g. enantioselective cleavage of lactone ring developed by Bringmann et al. is an attractive procedure for stereoselective synthesis of these alkaloids.[28]

As a further extension for the stereoselective axial bond formation, we next investigated the stereoselective synthesis of these alkaloids utilizing the planar chiral (arene)chromium complex.[29] At first, we have tried the synthesis of an enantiomerically pure (3,5-dialkoxy-2-bromobenzaldehyde)$Cr(CO)_3$ complex as a coupling partner. Since tricarbonylchromium complexation of 1-(3′,5′-dimethoxy-2′-bromophenyl)-1,2-propanediol gave a complexed mixture along with de-brominated compound as major product, we investigated diastereofacial tricarbonylchromium complexation of 1-(3′,5′-dimethoxy-2′-trimethylsilylphenyl)-1,2-propanediol (Scheme 6). The *threo*-diol **21** took place the ligand exchange with naphthalenechromium in THF at 70°C to give easily separable diastereomeric mixture in a ratio of 82:18. But, the corresponding *erythro*-diol **24** produced a single chromium complexation product **25** under the same conditions. This diastereoselective chromium complexation was based on the configuration of a benzylic hydroxyl group.[30] Sarker et al. reported[31] that potassium hydride reacted with tricarbonylchromium-complexed aryl trimethylsilanes to generate tricarbonylchromium complexed aryl anions which can be further trapped with some electrophiles. After protection of diol, the acetonide complex **26** was treated with potassium hydride under reported conditions followed by quenching

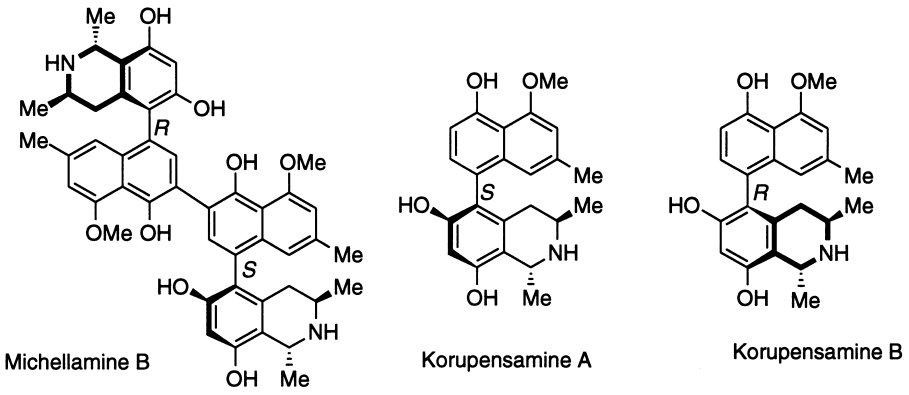
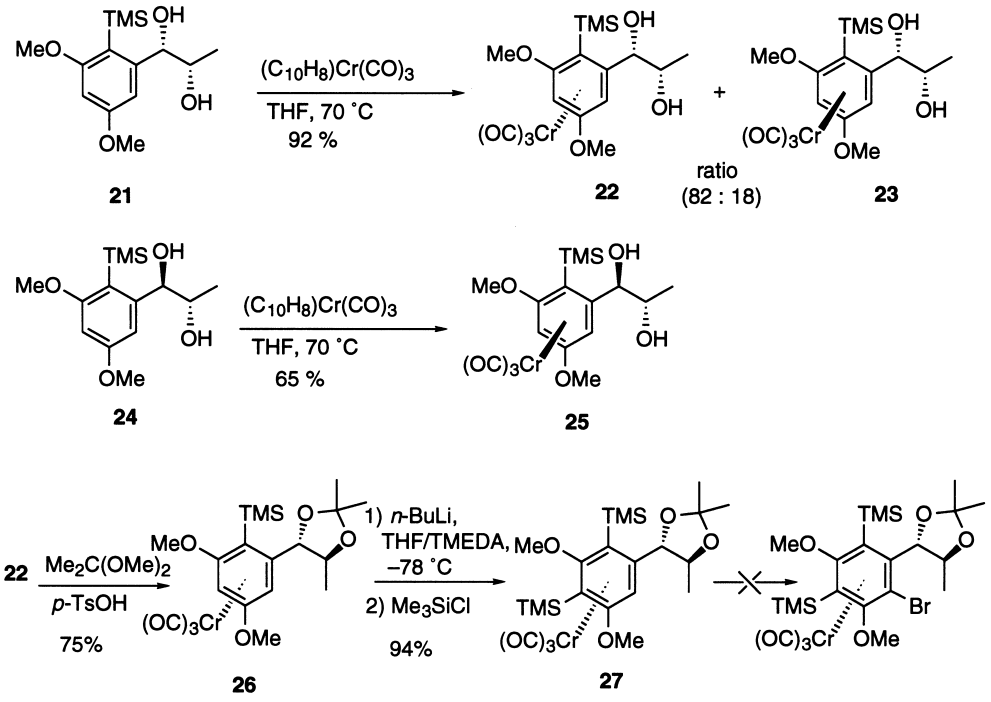


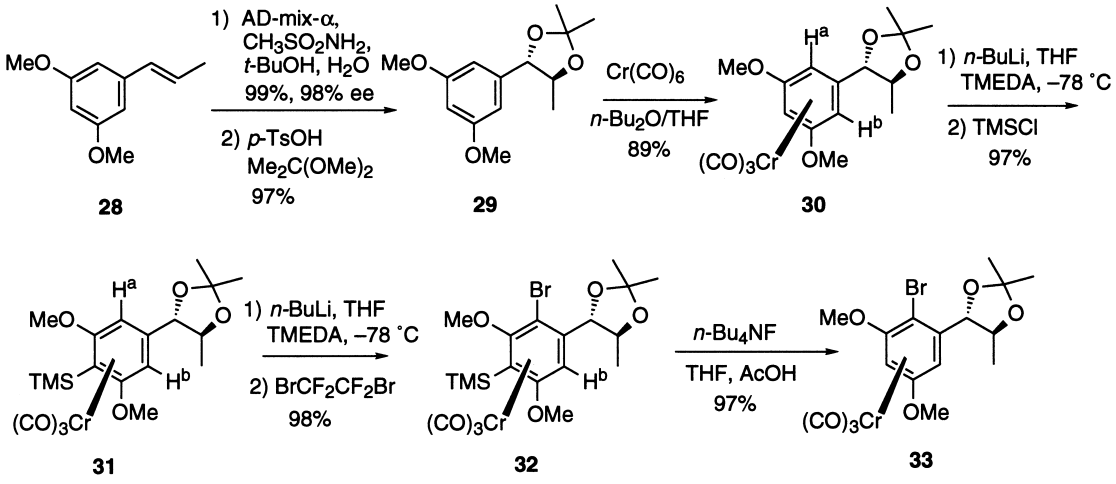
Figure 3.



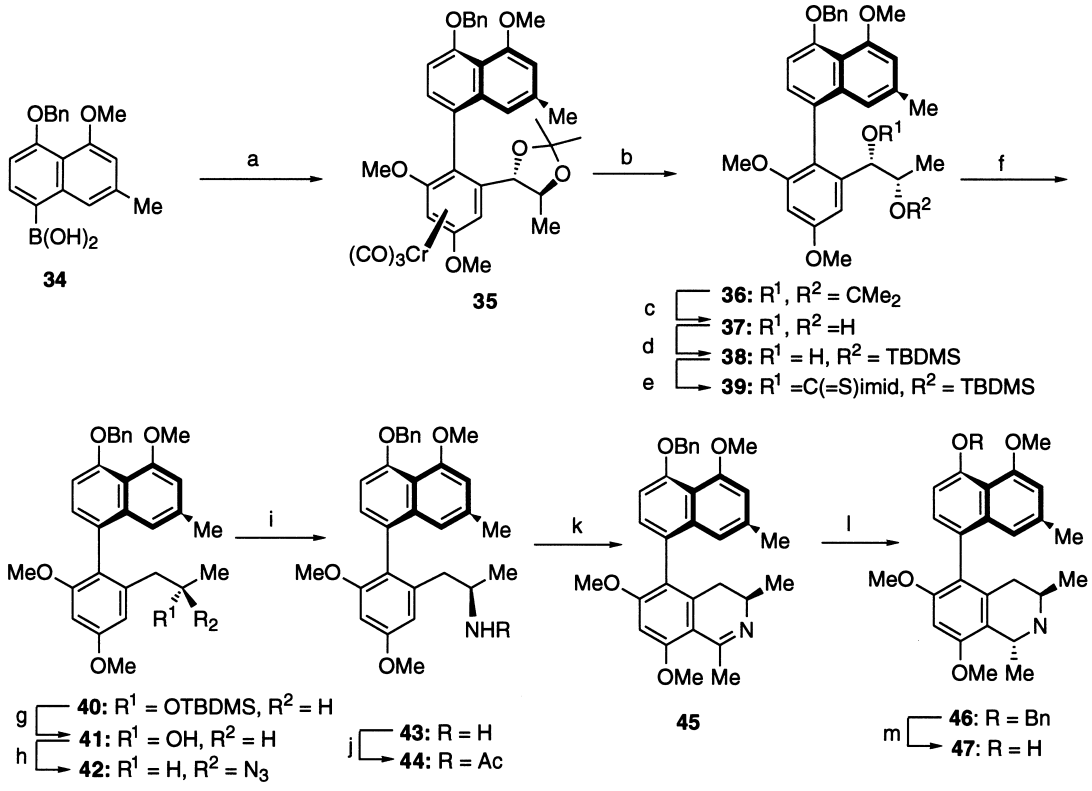
Scheme 6. Tricarbonylchromium complexation by ligand transfer with (naphthalene)$Cr(CO)_3$.

with various brominating agents. However, only de-silylation chromium complex was obtained.[32] Therefore, the directed lithiation of **26** was next tried for the introduction of bromine atom. The complex **26** was reacted with *n*-BuLi to give regioselectively bis-trimethylsilyl chromium complex **27**. But, the complex **27** was not further lithiated at C-6 position due to severe steric hindrance.

We next turned our attention to diastereoselective *ortho* lithiation of the chromium complex having a proper functional group at C-1 position for the introduction of bromine as follows (Scheme 7). An asymmetric catalytic dihydroxylation of (*E*)-(3,5-dimethoxyphenyl)propene **28** was treated with AD-mix-α,[33] and the resulting diol was subsequently protected with acetone dimethyl acetal to give the acetonide **29** ($[\alpha]_D^{27}=+23.8$) in 96% yield with >98% ee. Tricarbonylchromium complexation of **29** with $Cr(CO)_6$ under thermal conditions gave the corresponding (arene)chromium complex **30** ($[\alpha]_D^{26}=-4.0$) in 89% yield. In order to introduce the bromine atom at either *ortho* position of the C-1 side-chain group regioselectively, the C-4 position was initially protected by an introduction of an easily removable Me_3Si group. Thus, the lithiation of **30** with *n*-BuLi followed by treatment with trimethylsilylchloride afforded the trimethylsilylated complex **31** ($[\alpha]_D^{27}=-36.0$) in 97% yield. Subsequent diastereotopic lithiation[34] of **31** followed by quenching with 1,2-dibromo-1,1,2,2-tetrafluoroethane gave the brominated complex **32** at the H^a-position without regioisomeric chromium complex after detrimethylsilylation in 95% overall yield. This planar chirality of **33** was determined by X-ray crystallography. In this case, an extremely high



Scheme 7.



Scheme 8. Reagents and conditions: (a) **33**, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, H_2O, 70°C, 30 min, 90%; (b) hν-O_2, ether, 92%; (c) 1 M aq. HCl, THF, 50°C, 96%; (d) TBDMSCl, imidazole, DMF, 84%; (e) $(imd)_2C{=}S$. THF; (f) *n*-Bu_3SnH, AIBN, 62% from **38**; (g) *n*-Bu_4NF, THF, 96%; (h) $(PhO)_2PON_3$, DEAD, PPh_3, THF; (i) $SnCl_2$, MeOH; (j) Ac_2O, py, 66% from **40**; (k) $POCl_3$, MeCN; (l) $LiAlH_4$. Me_3Al, THF, −78 to 0°C, 70% from **44**; (m) Pd-black, HCO_2H, MeOH, 45°C, 91%.

diastereoselectivity of directed lithiation was achieved even in THF, while the *ortho* lithiation of the complex **7** was largely effected by solvent. Regioselective removal of diastereotopic H^a proton would be contributed to the coordination of lithium with nearby benzylic oxygen.

The planar chiral bromobenzene complex **33** was easily converted to *O*,*O*′-dimethylkorupensamine A as follows (Scheme 8). Palladium(0)-catalyzed cross-coupling of the planar chiral (arene)$Cr(CO)_3$ complex **33** with 4-benzyloxy-5-methoxy-6-methylnaphthylboronic acid **34**[26f] in the presence of sodium carbonate in aqueous MeOH at reflux for 30 min produced a single atropisomeric coupling product **35** in 90% yield without any formation of the atropisomers. The axial stereochemistry of the coupling product **35** was assigned to be the (*S*)-configuration by ^1H NMR spectra, in which the *peri*-proton of naphthalene ring appeared at a lower field (8.62 ppm) due to the anisotropic effect of the *syn*-$Cr(CO)_3$ fragment.[23] An oxidative demetalation of **35** and subsequent treatment with dilute HCl afforded the dihydroxyl compound **37**. Selective protection of the hydroxyl at the homobenzylic position of **37** with *tert*-butyldimethylsilyl chloride gave the mono-silylated compound **38** ($[\alpha]_D^{25}=+35.8$) in 84% yield. The benzylic hydroxyl of **38** was removed by Barton method[35] to give the deoxygenation compound **40** in 62% yield. The substitution of the hydroxyl to nitrogen atom with the stereochemical inversion was achieved under Mitsunobu conditions.[36] Thus, deprotection of the silyl ether **40** and subsequent treatment with $(PhO)_2PON_3$ in the presence of DEAD and PPh_3 produced the azide compound **42** which was reduced with $SnCl_2$ followed by acetylation to give the amide compound **44** in 66% overall yield. Bischler–Napieralski cyclization of **44** with $POCl_3$ in acetonitrile gave the naphthyldihydroisoquinoline compound **45**. Reduction[37] of the imine double bond of **45** with $LiAlH_4$ in the presence of Me_3Al afforded *trans*-dimethyl compound **46** along with small amount of the corresponding *cis*-isomer (ratio; 93:7) in 70% overall yield. Finally, debenzylation with Pd-black in a solution of 8.8% formic acid in MeOH gave *O*,*O*′-dimethylkorupensamine A **47** (R=H) in 91% yield.

In conclusion, we have demonstrated the asymmetric synthesis of axially chiral biaryl natural products by stereoselective Pd(0)-mediated cross-coupling method by using planar chiral arene chromium complexes.

Experimental

All manipulations involving organometallics were carried out under an atmosphere of nitrogen or argon and using an inert gas/vacuum double manifold techniques. All melting points were determined on a Yanagimoto MPJ-2 micro-melting point apparatus and were uncorrected. ^1H NMR spectra were measured on Hitachi R-90, JEOL GX-400, EX-270 instrument, and all NMR spectra were recorded in $CDCl_3$ solvent with tetramethylsilane as an internal reference. IR spectra were determined in $CHCl_3$ solution on a JASCO A-100 spectrometer. Elemental analyses were performed on a Perkin–Elmer Model 240 automatic analyzer. Mass spectra were determined on a JEOL

JMS-AM 500 with EI mode (70 eV). Optical rotations were obtained on a JASCO DIP-370 automatic polarimeter at wavelength 589 nm (sodium D line) using a 1.0-dm cell with a total volume of 3 mL. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl immediately before use.

Preparation of chromium complex 7. A mixture of 2-(3′,4′,5′-trimethoxyphenyl)-4-methoxymethyl-1,3-dioxane **6** (3.62 g, 12.2 mmol) and chromium hexacarbonyl (2.94 g, 13.8 mmol) in di-*n*-butyl ether (300 mL) and THF (30 mL) was heated at 140°C for 18 h under nitrogen. After evaporation of the solvent under reduced pressure, the residue was diluted with dichloromethane, filtered through Celite, and concentrated in vacuo. The crude, yellow solid was recrystallized from ether/hexane to give the (arene)chromium complex **7** (3.27 g, 62%) as yellow crystals. mp 103°C (dec); $[\alpha]_D^{27}=-19.6$ (c=1.88, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (1H, brd, J=12.2 Hz), 1.89 (1H, dq, J=4.9, 12.2 Hz), 3.42 (3H, s), 3.47 (1H, dd, J=4.3, 10.4 Hz), 3.55 (1H, dd, J=6.1, 10.4 Hz), 3.85 (6H, s), 3.88 (3H, s), 3.97 (1H, dt, J=1.8, 12.2 Hz), 4.04–4.12 (1H, m), 4.31 (1H, dd, J=4.9, 12.2 Hz), 4.31 (1H, dd, J=4.9, 12.2 Hz), 4.97 (1H, s), 5.06 (1H, s), 5.37 (1H, s); IR ($CHCl_3$) 1970, 1890, 1240, 1160, 1130 cm^{-1}; Anal. calcd for $C_{18}H_{22}O_9Cr$: C, 49.77; H, 5.10. Found: C, 49.85; H, 5.15.

Directed lithiation of 7. To a solution of (arene)chromium complex **7** (2.00 g, 4.60 mmol) in dry toluene (160 mL) was added *n*-BuLi (1.6 M in hexane, 7.20 mL, 11.5 mmol) at −78°C under argon. After stirring for 1 h at −78°C, 1,2-dibromo-1,1,2,2-tetrafluoroethane (1.60 mL, 13.8 mmol) was added at −78°C. The reaction mixture was warmed to −30°C, quenched with saturated aqueous NH_4Cl at 0°C, and extracted with ether. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography with hexane/ether to give (bromobenzene)-chromium complex **8** (1.28 g, 54%) as yellow crystals along with recovery of starting material (0.78 g): recrystallization from ether/hexane. mp 82–84°C; $[\alpha]_D^{27}=-128.0$ (c=1.65, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (1H, bd, J=12.2 Hz), 1.95 (1H, dq, J=4.9, 12.2 Hz), 3.39 (3H, s), 3.47 (1H, dd, J=4.3, 10.4 Hz), 3.51 (1H, dd, J=5.5, 10.4 Hz), 3.80 (3H, s), 3.93 (3H, s), 3.97 (3H, s), 4.06 (1H, dt, J=2.4, 12.2 Hz), 4.08–4.14 (1H, m), 4.37 (1H, dd, J=4.9, 12.2 Hz), 5.34 (1H, s), 5.55 (1H, s); IR ($CHCl_3$) 1960, 1880, 1100, 1000 cm^{-1}; Anal. calcd for $C_{18}H_{21}O_9CrBr$: C, 42.12; H, 4.12. Found: C, 42.14; H, 4.06.

(1*S*, 2*R*)-Tricarbonyl(2-bromo-3,4,5-trimethoxybenzaldehyde)chromium 9. A solution of chromium complex **8** (100 mg, 0.195 mmol) in aqueous 6 M HCl (5 mL) and THF (5 mL) was degassed by three freeze/vacuum/thaw cycles and warmed to 40°C for 30 min under argon. After cooling to room temperature, the reaction mixture was extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography with ether/hexane to give (benzaldehyde)chromium complex **9** (66 mg, 83%, >99% ee) as red crystals. An enantiomeric purity was determined by HPLC with Chiralcel OJ eluted with 10% 2-propanol in hexane; flow rate 1.0 mL/min; column temperature 40°C; UV detector 254 nm; retention time: 12.4 min for **9** and 19.0 min for enantiomer. mp 113°C; $[\alpha]_D^{19}=+1036$ (c=1.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (3H, s), 3.98 (3H, s), 4.03 (3H, s), 5.64 (1H, s), 9.99 (1H, s); IR ($CHCl_3$) 1980, 1910, 1680, 1300, 1000 cm^{-1}; Anal. calcd for $C_{13}H_{11}O_7CrBr$: C, 37.98; H, 2.70. Found: C, 38.08; H, 2.64.

Reduction of complex 9 to give 12. A solution of (benzaldehyde)chromium complex **9** (2.00 g, 4.87 mmol) in MeOH (80 mL) was added to a solution of sodium borohydride (0.370 g, 9.74 mmol) in MeOH (20 mL) under argon. The reaction mixture was stirred for 5 min and quenched with H_2O. The solvent was evaporated under reduced pressure. The residue was extracted with ether, and the extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography (35% ether in hexane) to give (benzylalcohol)chromium complex **12** (1.97 g, 98%) as yellow crystals. mp 130°C (dec); $[\alpha]_D^{24}=-214$ (c=1.42, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (1H, bd, J=6.1 Hz), 3.81 (3H, s), 3.95 (3H, s), 4.00 (3H, s), 4.69 (1H, dd, J=6.1, 14.0 Hz), 4.75 (1H, dd, J=6.1, 14.0 Hz), 5.24 (1H, s); IR ($CHCl_3$) 3600, 1960, 1880, 1310, 1020, 1000 cm^{-1}; Anal. calcd for $C_{13}H_{13}O_7CrBr$: C, 37.79; H, 3.17. Found: C, 37.85; H, 3.11.

Palladium(0)-mediated cross-coupling of 12 to give 14. A mixture of planar chiral (bromobenzylalcohol)chromium complex **12** (1.00 g, 2.42 mmol), phenylboronic acid **13** (0.940 g, 4.84 mmol), and $Pd(PPh_3)_4$ (140 mg, 0.12 mmol) in aqueous 1.0 M Na_2CO_3 (4 mL) and MeOH (40 mL) was degassed and refluxed for 1 h under argon. The solvent was evaporated in vacuo. The residue was extracted with ether. The extract was washed with aqueous 1 M NaOH and brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography with ether/hexane to give the cross-coupling product **14** (787 mg, 67%) as yellow crystals. mp 140–142°C; $[\alpha]_D^{25}=-161.5$ (c=2.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.86 (1H, bs), 3.72 (3H, s), 3.91 (3H, s), 3.94 (3H, s), 4.20 (2H, d, J=6.1 Hz), 5.13 (1H, s), 6.15 (2H, s), 7.00 (1H, s), 7.35 (1H, s), 9.74 (1H, s); IR ($CHCl_3$) 3600, 1960, 1880, 1310, 1020, 1000 cm^{-1}; Anal. calcd for $C_{21}H_{18}O_{10}Cr$: C, 52.29; H, 3.76. Found: C, 51.99; H, 3.86.

Protection of 14 with chloro *t*-butyldimethylsilane. To a solution of coupling product **14** (70 mg, 0.15 mmol) and imidazole (30 mg, 0.44 mmol) in dry CH_2Cl_2 was added a solution of chloro *t*-butyldimethylsilane (44 mg, 0.29 mmol) in dry CH_2Cl_2 (1 mL). The reaction mixture was stirred at 25°C for 2 h, and extracted with CH_2Cl_2. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography to give silyl ether (76 mg, 87%) as yellow crystals. mp 157°C (dec); $[\alpha]_D^{21}=-184.8$ (c=0.353, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ −0.05 (3H, s), 0.00 (3H, s), 0.86 (9H, s), 3.72 (3H, s), 3.89 (3H, s), 3.93 (3H, s), 4.13 (1H, d, J=12.8 Hz), 4.15 (1H, d, J=12.8 Hz), 5.10 (1H, s), 6.15 (2H, s), 6.99 (1H, s), 7.38 (1H, s), 9.72 (1H, s); IR ($CHCl_3$) 1950, 1880,

1680, 1260, 1240, 1200, 1100 cm^{-1}; Anal. calcd for $C_{27}H_{32}O_{10}CrSi$: C, 54.35; H, 5.41. Found: C, 54.38; H, 5.37.

MeLi addition to give complex 18a and 18b. To a solution of silyl ether complex (366 mg, 0.613 mmol) in dry ether (30 mL) was added MeLi (0.77 mL, 1.06 M in ether, 1.23 mmol) at −78°C under argon, and warmed to −50°C. The reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography to give alcohol **18a** (298 mg, 79%) and diastereomeric isomer **18b** (85 mg, 15%) as yellow crystals, respectively. First fraction **18b**. mp 71–73°C; $[\alpha]_D^{25}=-139.4$ (c=1.54, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.85 (9H, s), 1.37 (3H, d, J=6.1 Hz), 2.87 (1H, bs), 3.78 (3H, s), 3.88 (3H, s), 3.93 (3H, s), 4.13 (1H, d, J=11.6 Hz), 4.19 (1H, d, J=11.6 Hz), 4.58 (1H, q, J=6.1 Hz), 4.92 (1H, s), 6.02 (1H, s), 6.03 (1H, s), 6.83 (1H, s), 7.04 (1H, s); IR ($CHCl_3$) 3500–3100, 1950, 1870, 1240, 1140, 1100, 1080, 1040 cm^{-1}; Anal. calcd for $C_{28}H_{32}O_{16}CrSi$: C, 54.89; H, 5.92. Found: C, 54.97; H, 5.89. Second fraction **18a**; mp 147–149°C; $[\alpha]_D^{20}=-148.1$ (c=1.42, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (3H, s), 0.05 (3H, s), 0.90 (9H, s), 1.33 (3H, d, J=6.1 Hz), 2.17 (1H, bs), 3.87 (6H, s), 3.92 (3H, s), 4.02 (1H, d, J=13.4 Hz), 4.27 (1H, d, J=13.4 Hz), 4.58 (1H, q, J=6.1 Hz), 5.22 (1H, s), 6.03 (1H, s), 6.04 (1H, s), 6.84 (1H, s), 7.04 (1H, s); IR ($CHCl_3$) 3500–3100, 1950, 1870, 1240, 1140, 1100, 1080, 1040 cm^{-1}; Anal. calcd for $C_{28}H_{32}O_{16}CrSi$: C, 54.89; H, 5.92. Found: C, 55.05; H, 5.90.

Preparation of 19a. A solution of alcohol **18a** (224 mg, 0.367 mmol) in dry THF (5 mL) was added to a suspension of NaH (40 mg, 60% in oil, 0.55 mmol) in dry THF (5 mL) and DMF (2 mL) at 25°C under argon. The reaction mixture was stirred for 30 min, and then allyl bromide (0.073 mL, 0.84 mmol) was added. The mixture was stirred for 1 h, quenched with buffer solution (0.025 M aqueous KH_2PO_4, 0.025 M aqueous Na_2HPO_4), and extracted with ether. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography to give allyl ether complex (150 mg, 63%) as yellow oil. $[\alpha]_D^{20}=-165.4$ (c=1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.07 (3H, s), 0.91 (9H, s), 1.20 (3H, d, J=6.1 Hz), 3.73–3.84 (2H, m), 3.87 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 4.09 (1H, d, J=13.4 Hz), 4.21 (1H, q, J=6.1 Hz), 4.38 (1H, d, J=13.4 Hz), 5.12 (1H, dd, J=10.4, 1.5 Hz), 5.23 (1H, dd, J=18.9, 1.5 Hz), 5.27 (1H, s), 5.81–5.91 (1H, m), 6.03 (1H, s), 6.04 (1H, s), 6.81 (1H, s), 7.05 (1H, s); IR ($CHCl_3$) 1950, 1870, 1240, 1140, 940, 910 cm^{-1}; MS (relative intensity) m/z 652 (M^+, 14), 568 (13), 527 (100), 458 (66); HRMS calcd for $C_{31}H_{40}O_{10}CrSi$ 652.1796; found 652.1781. A solution of the allyl ether chromium complex (57 mg, 0.087 mmol) in ether (20 mL) was exposed to sunlight until the yellow solution became colorless. The precipitate was filtered off, and the solution was evaporated under reduced pressure and purified by silica gel chromatography to give demetalated compound **19a** (42 mg, 94%) as colorless oil. $[\alpha]_D^{25}=+2.3$ (c=1.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (3H, s), 0.03 (3H, s), 0.91 (9H, s), 1.13 (3H, d, J=6.1 Hz), 3.59 (3H, s), 3.75–3.81 (1H, m), 3.88 (3H, s), 3.85–3.91 (1H, m), 3.91 (3H, s), 4.13 (1H, d, J=13.6 Hz), 4.14 (1H, q, J=6.1 Hz), 4.36 (1H, d, J=13.6 Hz), 5.07 (1H, dd, J=1.8, 10.4 Hz), 5.23 (1H, dd, J=1.8, 17.1 Hz), 5.82–5.92 (1H, m), 6.00 (1H, s), 6.51 (1H, s), 6.98 (1H, s), 7.09 (1H, s); IR ($CHCl_3$) 1220, 1140, 1100, 930, 910 cm^{-1}; MS (relative intensity) m/z 516 (M^+, 3), 458 (72), 401 (10), 386 (100); HRMS calcd for $C_{28}H_{40}O_7Si$ 516.2543, found 516.2533.

Preparation of 20a. To a solution of demetalated compound **19a** (165 mg, 0.321 mmol) in THF (15 mL) was added n-Bu_4NF (0.6 mL, 1.0 M in THF, 0.6 mmol) at 0°C. The reaction mixture was stirred for 3 h at 0°C, quenched with buffer solution and extracted with ether. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography to give benzyl alcohol (125 mg, 0.311 mmol, 97%). To a solution of alcohol (125 mg, 0.311 mmol) and CBr_4 (129 mg, 0.389 mmol) in dry CH_2Cl_2 was added triphenylphosphine (122 mg, 0.467 mmol) at 0°C under argon. The reaction mixture was stirred for 5 min, and evaporated under reduced pressure. The residue was dissolved with ether. The precipitate was filtered off, and the solution was concentrated under reduced pressure. The residue was purified by silica gel chromatography to give a benzyl bromide. A solution of this benzyl bromide in dry MeOH (2 mL) was added to a solution of dimethyl sodiomalonate, prepared from dimethyl malonate (148 mg, 1.12 mmol) and sodium (79 mg, 3.42 mmol) in dry MeOH (2 mL), at 25°C under argon. The reaction mixture was stirred for 1 h, and was quenched with diluted aqueous HCl, and extracted with ether. Usual workup gave **20a** (57 mg, 36%) as colorless oil. $[\alpha]_D^{26}=+13.1$ (c=1.40, THF) lit.16c; $[\alpha]_D=+8.8$ (c=1.40, THF); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, d, J=6.1 Hz), 2.78 (1H, dd, J=14.7, 6.1 Hz), 2.93 (1H, dd, J=9.2, 14.7 Hz), 3.55–3.82 (3H, m), 3.62 (3H, m), 3.67 (3H, s), 3.68 (3H, s), 3.86 (6H, s), 4.06 (1H, q, J=6.1 Hz), 5.06 (1H, dd, J=1.2, 10.4 Hz), 5.20 (1H, dd, J=1.2, 17.1 Hz), 5.79–5.89 (1H, m), 6.00 (1H, d, J=1.2 Hz), 6.01 (1H, d, J=1.2 Hz), 6.54 (1H, s), 6.55 (1H, s), 7.09 (1H, s); IR ($CHCl_3$) 1750, 1730, 1230 cm^{-1}; MS (relative intensity) m/z 516 (M^+, 26), 458 (100), 427 (20), 327 (57); HRMS calcd for $C_{27}H_{32}O_{10}$ 516.1996, found 516.2025.

Complexation of *erythro*-diol 24 with (naphthalene)-$Cr(CO)_3$. A mixture of *erythro*-diol **24** (568 mg, 2.00 mmol) and (naphthalene)$Cr(CO)_3$ (581 mg, 2.20 mmol) in THF (20 mL) in sealed tube was degassed by three freeze/vacuum/thaw cycles and heated at 70°C for 3.0 h under argon. The precipitate was filtered off and the solution was evaporated under reduced pressure. The residue was purified by silica gel chromatography to give chromium complex **25** (547 mg, 65%) as yellow crystals. mp 127–131°C (dec); ^1H NMR (270 MHz, $CDCl_3$) δ 0.37 (9H, s), 1.20 (3H, d, J=6.4 Hz), 2.04 (1H, bd, J=5.3 Hz), 2.43 (1H, bd, J=3.7 Hz), 3.77 (3H, s), 3.80 (3H, s), 3.77–3.90 (1H, m), 4.95 (1H, t, J=3.7 Hz), 5.14 (1H, d, J=1.8 Hz), 5.21 (1H, d, J=1.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 2.6, 16.6, 55.5, 55.7, 66.0, 70.9, 72.0, 72.7, 83.0, 119.2, 144.0, 148.0, 234.3; IR ($CHCl_3$) 3600, 3000, 2400, 1950, 1860, 1530, 1210 cm^{-1}; Anal. calcd for $C_{17}H_{24}O_7CrSi$: C, 48.56; H, 5.75, Found: C, 48.46; H, 5.70.

Preparation of acetonide 29. To a stirred mixture of AD-mix-α (9.8 g, 1.4 g/mmol) and methane sulfonamide (0.667 g, 7.00 mmol) in *t*-BuOH (35 mL) and water (35 mL) was added (*E*)-1-(3,5-dimethoxyphenyl)-1-propene (**28**) (1.25 g, 7.00 mmol) at 25°C. The reaction mixture was stirred vigorously at 25°C for 2.0 h. Sodium thiosulfate (10 g) was added, and the mixture was stirred at 25°C for 30 min. The reaction mixture was extracted with EtOAc, washed with aqueous 2 M KOH (35 mL) and brine (35 mL). The extract was dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by silica gel chromatography to afford (1*S*,2*S*)-1-(3,5-dimethoxyphenyl)-1,2-propanediol (1.48 g, 99%, 98% ee) as colorless oil. $[\alpha]_D^{27}=+16.8$ (c=1.06, EtOH); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.07 (3H, d, J=6.9 Hz), 2.56 (1H, brs), 2.76 (1H, brs), 3.78 (6H, s), 3.83 (1H, q, J=6.9 Hz), 4.27 (1H, d, J=6.9 Hz), 6.39 (1H, t, J=2.3 Hz), 6.49 (2H, d, J=2.3 Hz); IR ($CHCl_3$) 3325, 2950, 1600, 1300, 1160, 1040 cm^{-1}; MS (relative intensity) m/z 212 (M^+, 76), 168 (100), 167 (86), 139 (97), 124 (44); HRMS calcd for $C_{11}H_{16}O_4$ 212.1003, found 212.1026. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.25; H, 7.68. A mixture of diol (1.43 g, 6.74 mmol) and catalytic amount of *p*-toluenesulfonic acid monohydrate in 2,2-dimethoxypropane (20 mL) was stirred at 25°C for 30 min. Usual workup gave acetonide **29** (1.65 g, 97%) as colorless oil. $[\alpha]_D^{27}=+23.8$ (c=1.12, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31 (3H, d, J=5.9 Hz), 1.51 (3H, s), 1.55 (3H, s), 3.80 (6H, s), 3.85 (1H, dq, J=5.9, 8.6 Hz), 4.41 (1H, d, J=8.6 Hz), 6.41 (1H, t, J=2.3 Hz), 6.54 (2H, d, J=2.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 16.4, 26.8, 27.4, 55.3, 79.0, 89.7, 99.8, 104.3, 108.5, 140.3, 160.9; IR ($CHCl_3$) 2950, 1600, 1160 cm^{-1}; MS (relative intensity) m/z 252 (M^+, 66), 237 (26), 208 (100), 193 (99) 177 (36) 149 (39). HRMS calcd for $C_{14}H_{20}O_4$ 252.1398, found 252.1369.

Preparation of chromium complex 30. Chromium complexation with $Cr(CO)_6$ was carried out under above method. Yield 89%; mp 150–152°C; $[\alpha]_D^{26}=-4.0$ (c=1.01, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.41 (3H, d, J=6.3 Hz), 1.51 (3H, s), 1.52 (3H, s), 3.75 (3H, s), 3.76 (3H, s), 3.89 (1H, dq, J=6.3, 8.2 Hz), 4.27 (1H, d, J=8.2 Hz), 4.69 (1H, bs), 5.09 (1H, bs), 5.14 (1H, t, J=2.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 17.0, 26.6, 27.3, 55.8, 67.9, 69.5, 71.1, 78.9, 82.2, 108.8, 109.3, 143.3, 143.4, 233.1; IR ($CHCl_3$) 1960, 1880, 1540, 1160 cm^{-1}; Anal. calcd for $C_{17}H_{20}O_7Cr$: C, 52.58; H, 5.19. Found: C, 52.44; H, 5.15.

Preparation of complex 31. To a solution of complex **30** (1.36 g, 3.50 mmol) and TMEDA (0.58 mL, 3.85 mmol) in dry THF (35 mL) was added *n*-BuLi (2.41 mL, 1.6 M in hexane, 3.85 mmol) at −78°C under argon atmosphere. The reaction mixture was stirred for 1.0 h at −78°C followed by addition of chlorotrimethylsilane (0.67 mL, 5.25 mmol), and usual workup afforded silylated chromium complex **31** (1.56 g, 97%) as yellow crystals. mp 159–161°C; $[\alpha]_D^{27}=-36.0$ (c=1.07, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.33 (9H, s), 1.43 (3H, d, J=5.9 Hz), 1.52 (3H, s), 1.53 (3H, s), 3.69 (3H, s), 3.71 (3H, s), 3.93 (1H, dq, J=5.9, 8.2 Hz), 4.35 (1H, d, J=8.2 Hz), 4.52 (1H, s), 4.97 (1H, s); IR ($CHCl_3$) 1960, 1880 cm^{-1}; Anal. calcd for $C_{20}H_{28}O_7CrSi$: C, 52.16; H, 6.13. Found: C, 52.21; H, 6.19.

Lithiation of 31 to give brominated complex 32. To a solution of complex **31** (1.50 g, 3.26 mmol) and TMEDA (0.74 mL, 4.89 mmol) in dry THF (33 mL) was added *n*-BuLi (3.06 mL, 1.6 M in hexane, 4.89 mmol) at −78°C under argon atmosphere. The reaction mixture was stirred for 1.0 h at −78°C followed by addition of 1,2-dibromo-1,1,2,2-tetrafluoroethane (0.78 mL, 6.52 mmol). After the addition, the reaction mixture was warmed to 25°C, quenched with saturated aqueous NH_4Cl at 0°C, and extracted with EtOAc. Usual purification gave **32** (1.73 g, 98%) as yellow crystals. mp 138–140°C; $[\alpha]_D^{27}=-35.6$ (c=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.42 (9H, s), 1.49 (3H, s), 1.55 (3H, s), 1.61 (3H, d, J=6.3 Hz), 3.71 (3H, s), 3.82 (3H, s), 3.87 (1H, dq, J=4.6, 6.3 Hz), 5.02 (1H, s), 5.16 (1H, d, J=4.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 1.5, 20.3, 28.3, 28.7, 55.8, 63.0, 70.7, 76.6, 82.7, 83.9, 87.9, 107.2, 110.8, 144.5, 145.0, 232.2; IR ($CHCl_3$) 1970, 1895 cm^{-1}; Anal. calcd for $C_{20}H_{27}O_7BrCrSi$: C, 44.53; H, 5.04. Found: C, 44.51; H, 5.02.

Cross-coupling of 33 to give 35. Cross-coupling was carried out under above conditions. Yield 90%. $[\alpha]_D^{28}=-142.9$ (c=1.11, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.08 (3H, d, J=5.9 Hz), 1.21 (3H, s), 1.31 (3H, s), 2.55 (3H, s), 3.64 (3H, s), 3.85 (3H, s), 3.96 (3H, s), 4.26 (1H, d, J=5.9 Hz), 4.37 (1H, qui, J=5.9 Hz), 5.23 (2H, s), 5.24 (1H, d, J=2.3 Hz,), 5.30 (1H, d, J=2.3 Hz), 6.76 (1H, s), 6.84 (1H, d, J=7.9 Hz), 7.17 (1H, d, J=7.9 Hz), 7.33 (1H, t, J=7.3 Hz), 7.42 (2H, t, J=7.3 Hz), 7.62 (2H, d, J=7.3 Hz), 8.62 (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.2, 21.7, 27.8, 28.1, 55.8, 56.1, 56.3, 65.7, 71.0, 72.1, 77.9, 81.3, 98.8, 106.0, 108.8, 110.2, 112.0, 116.0, 118.4, 119.6, 126.9, 127.5, 128.3, 132.0, 135.0, 136.5, 137.5, 141.2, 142.7, 156.8, 157.2, 233.3; IR ($CHCl_3$) 1960, 1870, 1580 cm^{-1}; MS (relative intensity) m/z 664 (M^+, 11), 618 (17), 580 (61), 565 (32), 544 (100); HRMS calcd for $C_{36}H_{36}O_9Cr$ 664.1728, found 664.1746; Anal. calcd for $C_{36}H_{36}O_9Cr$: C, 65.06; H, 5.46. Found: C, 64.74; H, 5.67.

Preparation of axial biaryl compound 37. A solution of **35** (1.33 g, 2.00 mmol) in ether (40 mL) was exposed to sunlight to give biaryl **36** (973 mg, 92%) as colorless foam. $[\alpha]_D^{26}=-39.3$ (c=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.54 (3H, d, J=5.9 Hz), 1.25 (3H, s), 1.51 (3H, s), 2.32 (3H, s), 3.60 (3H, s), 3.91 (3H, s), 3.91 (1H, m), 3.95 (3H, s), 4.23 (1H, d, J=8.3 Hz), 5.25 (2H, s), 6.55 (1H, d, J=2.3 Hz), 6.65 (1H, s), 6.66 (1H, s), 6.82 (1H, d, J=2.3 Hz), 6.94 (1H, d, J=7.9 Hz), 7.20 (1H, d, J=7.9 Hz), 7.32 (1H, t, J=7.3 Hz), 7.42 (2H, t, J=7.3 Hz), 7.64 (2H, d, J=7.3 Hz); IR ($CHCl_3$) 2860, 1580, 1460, 1380, 1160, 1080 cm^{-1}; Anal. calcd for $C_{33}H_{36}O_6$: C, 74.98; H, 6.86. Found: C, 74.87; H, 6.90. A solution of **36** (200 mg, 0.379 mmol) in THF (4 mL) and aqueous 1 M HCl (1 mL) was stirred at 50°C for 15 h. Usual workup gave diol **37** (1.77 mg, 96%) as pale yellow foam. $[\alpha]_D^{27}=+3.5$ (c=1.10, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.70 (3H, d, J=6.6 Hz), 1.70 (1H, bs), 2.20 (1H, bs), 2.31 (3H, d), 3.60 (3H, s), 3.80 (1H, qui, J=6.6 Hz), 3.90 (3H, s), 3.94 (3H, s), 4.08 (1H, d, J=6.6 Hz), 5.22 (2H, d), 6.54 (1H, d, J=2.3 Hz), 6.65 (1H, s), 6.67 (1H, s), 6.70 (1H, d,

J=2.3 Hz), 6.90 (1H, d, J=7.9 Hz), 7.15 (1H, d, J=7.9 Hz), 7.33 (1H, t, J=7.3 Hz), 7.42 (2H, t, J=7.3 Hz), 7.63 (2H, d, J=7.3 Hz); IR ($CHCl_3$) 3300, 1580, 1390, 1330, 1180 cm^{-1}; MS (relative intensity) m/z 488 (M^+, 52), 470 (41), 442 (81), 379 (50), 351 (100); HRMS, calcd for $C_{30}H_{32}O_6$ 488.2209, found 488.2204.

Preparation of 40. A solution of diol **37** (852 mg, 1.74 mmol), *t*-butylchlorodimethylsilane (316 mg, 2.09 mmol) and imidazole (238 mg, 3.49 mmol) in dry DMF (3.5 mL) was stirred at 25°C for 3 h under argon. Usual workup gave silylated compound **38** (888 mg, 84%) as colorless foam. $[\alpha]_D^{25}$=+35.8 (c=1.11, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.14 (6H, s), 0.53 (3H, d, J=6.0 Hz), 0.82 (9H, s), 2.32 (3H, s), 3.06 (1H, d, J=6.0 Hz), 3.54 (1H, dq, J=4.3, 6.0 Hz), 3.61 (3H, s), 3.91 (3H, s), 3.96 (3H, s), 4.27 (1H, dd, J=4.3, 6.0 Hz), 5.24 (2H, s), 6.52 (1H, d, J=2.3 Hz), 6.67 (1H, s), 6.72 (1H, s), 6.73 (1H, d, J=2.3 Hz), 7.07 (1H, d, J=7.9 Hz), 7.24 (1H, d, J=7.9 Hz), 7.33 (1H, t, J=7.3 Hz), 7.42 (2H, t, J=7.3 Hz), 7.64 (2H, d, J=7.3 Hz); IR ($CHCl_3$) 3300, 2950, 1580, 1460, 1380, 1320, 1180, 840 cm^{-1}; MS (relative intensity) m/z 602 (M^+, 100), 584 (13), 557 (8), 493 (13), 470 (30); HRMS calcd for $C_{36}H_{46}O_6Si$ 602.3120, found 602.3092. A solution of silylated compound **38** (888 mg, 1.48 mmol) and 1,1′-(thiocarbonyl)diimidazole (656 mg, 3.68 mmol) in THF (3 mL) was stirred at 25°C under argon. After 24 h, the reaction mixture was concentrated under reduced pressure, and the residue was purified to give the crude pale yellow foam of **39** (813 mg). ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.30 (3H, s), −0.16 (3H), 0.79 (9H, s), 0.86 (3H, d, J=6.0 Hz), 2.26 (3H, s), 3.60 (3H, s), 3.72 (1H, dq, J=3.6, 6.3 Hz), 3.85 (3H, s), 3.97 (3H, s), 5.27 (2H, s), 6.09 (1H, d, J=3.6 Hz), 6.56 (1H, d, J=2.3 Hz), 6.63 (1H, s), 6.63 (1H, d, J=2.3 Hz), 6.64 (1H, s), 6.98 (2H, m), 7.33 (1H, t, J=7.3 Hz), 7.41–7.46 (4H, m), 7.65 (2H, d, J=7.3 Hz), 8.21 (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.9, −4.8, 17.8, 21.2, 22.1, 25.6, 55.4, 56.0, 56.2, 69.7, 71.2, 87.3, 98.4, 105.3, 107.0, 108.4, 116.3, 117.7, 117.8, 121.2, 125.5, 127.0, 127.5, 128.4, 130.6, 136.1, 136.7, 137.1, 137.7, 137.8, 156.0, 157.3, 159.0, 159.9, 183.4, 217.3. To a solution of the crude thioimidazolide and trace amount of AIBN in dry toluene (20 mL) was added n-Bu_3SnH (0.95 mL, 3.42 mmol) at 25°C under argon. The reaction mixture was stirred for 3 h, and extracted with EtOAc. Usual workup gave deoxygenated compound **40** (540 mg, 62% from **38**) as colorless gum. $[\alpha]_D^{26}$=+11.9 (c=1.10, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.31 (3H, s), −0.23 (3H, s), 0.75 (9H, s), 0.83 (3H, d, J=6.6 Hz), 2.33 (3H, s), 2.38 (2H, d, J=6.6 Hz), 3.59 (1H, qui, J=6.6 Hz), 3.60 (3H, s), 3.88 (3H, s), 3.95 (3H, s), 5.23 (2H, s), 6.47 (1H, d, J=2.3 Hz), 6.56 (1H, d, J=2.3 Hz), 6.67 (1H, s), 6.74 (1H, s), 6.92 (1H, d, J=7.9 Hz), 7.12 (1H, d, J=7.9 Hz), 7.33–7.46 (3H, m), 7.63–7.65 (2H, m); IR ($CHCl_3$) 2925, 1580, 1460, 1370, 1320, 1160, 1070, 840 cm^{-1}; MS (relative intensity) m/z 586 (M^+, 87), 528 (7), 438 (31), 363 (84), 309 (100); HRMS calcd for $C_{36}H_{46}O_5Si$ 586.3133, found 586.3124.

Preparation of 41. A solution of compound **40** (166 mg, 0.283 mmol) and n-Bu_4NF (0.85 mL, 1.0 M in THF, 0.85 mmol) in THF (3 mL) was stirred at 25°C for 24 h. Usual workup afforded **41** (128 mg, 97%) as colorless foam. $[\alpha]_D^{25}$=+18.4 (c=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.83 (3H, d, J=5.9 Hz), 2.28 (1H, dd, J=8.3, 13.5 Hz), 2.32 (3H, s), 2.50 (1H, dd, J=13.5, 4.6 Hz), 3.60 (3H, s), 3.60–3.70 (1H, m), 3.89 (3H, s), 3.94 (3H, s), 5.23 (2H, s), 6.50 (1H, d, J=2.3 Hz), 6.55 (1H, d, J=2.3 Hz), 6.67 (1H, s), 6.68 (1H, s), 6.92 (1H, d, J=7.9 Hz), 7.13 (1H, d, J=7.9 Hz), 7.32 (1H, t, J=7.3 Hz), 7.42 (2H, t, J=7.3 Hz), 7.63 (2H, d, J=7.3 Hz); IR ($CHCl_3$) 3300, 2950 1580, 1370, 1320, 1160, 1080 cm^{-1}; MS (relative intensity) m/z 472 (M^+, 61), 454 (50), 381 (18), 363 (100), 335 (32); HRMS calcd for $C_{30}H_{32}O_5$ 472.2262, found 472.2256.

Preparation of acetamide compound 44. To a solution of **41** (419 mg, 0.888 mmol) and PPh_3 (279 mg, 1.06 mmol) in dry THF (2 mL) were added diethyl azodicarboxylate (0.42 mL, 40% in toluene, 1.1 mmol) and diphenylphosphorylazide (0.29 mL, 1.3 mmol) at 0°C under argon. The reaction mixture was stirred at 0°C for 2 h. The solvents were removed under reduced pressure and the residue was purified by silica gel chromatography to give the azide **42** (650 mg) as pale yellow oil. To a solution of the crude azide compound in MeOH (5 mL) was added $SnCl_2$ (842 mg, 4.44 mmol) and stirred at 25°C for 3 h. The solvent was removed under reduced pressure and the residue was acetylated with Ac_2O (1.5 mL) in pyridine (3.5 mL). Usual workup gave acetamide **44** (302 mg, 66% from **41**) as colorless foam. $[\alpha]_D^{27}$=+8.1 (c=1.05, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (3H, d, J=6.6 Hz), 1.67 (3H, s), 2.25 (1H, dd, J=6.6, 14.2 Hz), 2.33 (3H, s), 2.43 (1H, dd, J=8.3, 14.2 Hz), 3.60 (3H, s), 3.88 (3H, s), 3.96 (3H, s), 4.11–4.16 (1H, m), 4.86 (1H, d, J=7.9 Hz), 5.25 (2H, s), 6.47 (1H, d, J=2.3 Hz), 6.57 (1H, d, J=2.3 Hz), 6.69 (2H, s), 6.95 (1H, d, J=7.9 Hz), 7.14 (1H, d, J=7.9 Hz), 7.34 (1H, t, J=6.9 Hz), 7.43 (2H, t, J=6.9 Hz), 7.65 (2H, d, J=6.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.7, 22.2, 23.2, 39.4, 46.7, 55.3, 55.7, 56.1, 71.1, 97.1, 104.8, 107.1, 108.2, 116.3, 117.5, 122.4, 126.9, 127.4, 128.3, 129.4, 136.2, 136.7, 137.7, 139.9, 155.5, 157.3, 158.7, 159.9, 169.3; IR ($CHCl_3$) 3350, 2860, 1650, 1580 cm^{-1}; MS (relative intensity) m/z 513 (M^+, 86), 454 (12), 423 (9), 380 (39), 363 (100), 348 (12); HRMS calcd for $C_{32}H_{35}NO_5$ 513.2523, found 513.2519.

Preparation of naphthyltetrahydroisoquinoline compound 46. A solution of acetamide **44** (216 mg, 0.421 mmol) and $POCl_3$ (0.12 mL, 1.3 mmol) in dry acetonitrile (10 mL) was heated under reflux for 30 min under argon. The reaction mixture was concentrated under reduced pressure and the residue was extracted with EtOAc, washed with 10% aqueous NaOH and brine. Usual purification gave cyclization product **45** (200 mg) as pale yellow foam. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.13 (3H, d, J=6.6 Hz), 1.80 (1H, dd, J=11.9, 16.2 Hz), 2.19 (1H, dd, J=4.6, 16.2 Hz), 2.32 (3H, s), 2.52 (3H, d, J=1.6 Hz), 3.21–3.69 (1H, m), 3.70 (3H, s), 3.95 (3H, s), 3.97 (3H, s), 5.24 (2H, s), 6.51 (1H, s), 6.65 (1H, d), 6.68 (1H, s), 6.93 (1H, d, J=7.9 Hz), 7.13 (1H, d, J=7.9 Hz), 7.33 (1H, t, J=7.9 Hz), 7.43 (2H, t, J=7.9 Hz), 7.63 (2H, d, J=7.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 21.3, 22.1, 27.8, 31.7, 51.1, 55.5, 55.8, 56.2, 71.2, 93.8, 107.2, 108.4, 112.5, 116.4, 117.4, 120.4, 126.2, 126.9, 127.4, 128.3, 128.4, 136.2, 136.7, 137.8, 141.7, 155.7, 157.3, 158.4,

160.1, 163.5. A solution of the crude product in dry THF (5 mL) was added dropwise to a mixture of $LiAlH_4$ (169 mg, 4.40 mmol) and Et_3Al (2.20 mL, 2 M in hexane, 4.40 mmol) at −78°C. The suspension was stirred at −78°C for 1 h, and warmed to 0°C over 3 h. The reaction mixture was quenched with saturated aqueous sodium fluoride and the precipitate was filtered off. Usual workup gave **46** (158 mg, *trans*:*cis*=93:7). This mixture was dissolved in MeOH (2 mL), and treated with conc. HCl to transform it to its hydrochloride salt. After evaporation of the solvent in vacuo, the residue was recrystallized from $CHCl_3$/hexane. A solution of the product in MeOH (2 mL) was treated with 30 % aqueous ammonia, extracted with EtOAc, and concentrated in vacuo to give **46** as light brown gum. $[\alpha]_D^{23}=-20.6$ (c=1.15, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.96 (3H, d, J=6.3 Hz), 1.46 (3H, d, J=6.6 Hz), 1.75 (1H, br), 1.75 (1H, dd, J=10.9, 17.2 Hz), 2.32 (1H, dd, J=17.2, 4.0 Hz), 2.32 (3H, s), 3.16 (1H, m), 3.62 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 4.44 (1H, q, J=6.6 Hz), 5.24 (2H, s), 6.48 (1H, s), 6.67 (1H, d), 6.94 (1H, d, J=7.9 Hz), 7.12 (1H, d, J=7.9 Hz), 7.33 (1H, t, J=7.3 Hz), 7.42 (2H, t, J=7.3 Hz), 7.63 (2H, d, J=7.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 21.6, 22.1, 22.6, 35.0, 42.0, 47.3, 55.3, 56.2, 71.3, 93.3, 107.4, 108.4, 116.5, 117.6, 120.9, 121.3, 126.9, 127.4, 127.5, 128.1, 128.3, 136.0, 136.5, 138.0, 155.3, 156.1, 156.6 157.2; IR ($CHCl_3$) 3350, 2950, 1580, 1320, 1080, 920 cm^{-1}; MS (relative intensity) m/z 497 (M^+, 25), 482 (100), 402 (18), 391 (26); HRMS calcd for $C_{32}H_{35}NO_4$ 497.2594, found 497.2580.

Preparation of *O*,*O*′-dimethylkorupensamine A 47. A solution of **46** (109 mg, 0.22 mmol) in 8.8% HCO_2H–MeOH (2 mL) was added to palladium black (100 mg, 0.94 mmol) in 8.8% HCO_2H–MeOH (3 mL), and stirred at 45°C for 3 h under argon. After filtration the solution was concentrated under reduced pressure. The residue was dissolved in MeOH (2 mL) and treated with 30% aqueous ammonia. The mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure to give *O*,*O*′-dimethylkorupensamine A **47** (81 mg, 91%) as light brown gum. $[\alpha]_D^{22}=-29.1$ (c=0.81, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.95 (3H, d, J=6.3 Hz), 1.45 (3H, d, J=6.6 Hz), 1.54 (1H, br), 1.70 (1H, dd, J=10.9, 17.2 Hz), 2.31 (3H, s), 2.33 (1H, dd, J=4.0, 17.2 Hz), 3.16 (1H, m), 3.62 (3H, s), 3.92 (3H, s), 4.04 (3H, s), 4.43 (1H, q, J=6.6 Hz), 6.47 (1H, s), 6.59 (1H, d), 6.68 (1H, d), 6.87 (1H, d, J=7.9 Hz), 7.10 (1H, d, J=7.9 Hz), 9.38 (1H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 21.7, 22.2, 22.8, 35.2, 41.9, 47.3, 55.3, 56.0, 56.1, 93.2, 106.2, 109.4, 113.5, 118.6, 121.0, 121.1, 125.2, 129.5, 135.4, 135.7, 136.2, 153.6, 156.0, 156.1 156.7; IR ($CHCl_3$) 3350, 2900, 1590, 1430, 1320, 1090 cm^{-1}; MS (relative intensity) m/z 407 (M^+, 9), 392 (100), 377 (7), 362 (17); HRMS calcd for $C_{25}H_{29}NO_4$ 407.2061, found 407.2079.

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