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Stereoselective Synthesis of Atropisomeric Korupensamines A and B Utilizing Planar Chiral Arene Chromium Complex

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Naphthyl tetrahydroisoquinoline alkaloids, atropisomeric korupensamines A and B and *ent*-korupensamine B, were synthesized by syn-selective cross-coupling of a planar chiral arene chromium complex with naphthylboronic acid and subsequent axial isomerization or tricarbonylchromium migration to the inverted arene face as a key step. Palladium(0)-catalyzed cross-coupling of planar chiral arene chromium complex **12** with naphthylboronic acid **9** gave *syn*-biaryl coupling product **13**. *syn*-Biaryl chromium complex **13** was heated in 1:1 mixture of di-*n*-butyl ether and 1,2-dichloroethane to give a face-inverted *anti*-biaryl chromium complex **14** without axial isomerization. Korupensamine A was synthesized from the *syn*-biaryl chromium complex **13** via *o*-formyl *syn*-biaryl chromium complex **10**, and *ent*-korupensamine B was prepared from the face-inverted *anti*-biaryl chromium complex **14**. On the other hand, difluoro-substituted *syn*-biaryl chromium complex **40** with a formyl group afforded *anti*-biaryl chromium complex **41** containing a rotated central bond by heating in xylene. The chromium-complexed fluorine atom was easily substituted with an isopropoxy group by nucleophilic substitution. Use of these reactions allowed (+)-2-bromo-3,5-difluorobenzaldehyde chromium complex (**37**) as a single chiral source to be converted to atropisomeric korupensamines A and B, respectively.

Introduction

Axially chiral biaryls are of importance not only as chiral ligands or auxiliaries in asymmetric reaction but also for biologically active natural products. There is considerable current interest in the development of efficient methodologies for the synthesis of axial biaryls in an enantiomerically pure form.[1] Nucleophilic displacement of an *ortho*-methoxy group of chiral aryl oxazolines by aryl Grignard reagents has been widely employed in asymmetric biaryl syntheses.[2] Copper-mediated Ullmann homocoupling reaction has been reported 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 and imine, has been also achieved for the preparation of chiral biaryl compounds.[4] Cyanocuprate-mediated biaryl intramolecular coupling of a tethered nonracemic chiral compound is also elaborated.[5] Atrop-enantioselective biaryl synthesis as a unique method has been achieved by stereocontrolled torsion of flat achiral lactone precursors by means of optically active nucleophiles.[6] Other interesting methods, including catalytic asymmetric coupling,[7] have been reported for optically active axially chiral biaryls.

(η^6-Polysubstituted arene)chromium complexes exist in two enantiomeric forms based on planar chirality when the arene ring is substituted at the ortho or meta position

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with different substituents. This fact, in concert with ability of the tricarbonylchromium function to effectively block one face of the arene ring, has allowed the use of (arene)chromium complexes as synthetic intermediates, chiral auxiliaries, and ligands for the asymmetric reactions.[8,9] 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.[10] In this paper, we report full details of total syntheses of korupensamines A and B and *ent*-korupensamine B using stereoselective palladium(0)-catalyzed cross-coupling of planar chiral arylhalide chromium complexes with arylboronic acid and subsequent axial isomerization or stereoselective migration of the tricarbonylchromium fragment to an inverted arene face.

Results and Discussion

Synthesis of Korupensamine A and *ent*-Korupensamine B from a Common Arene Chromium Complex. Michellamine B, dimerization product of atropdiastereomeric korupensamines A and B, was found to be fully protective against both HIV-1- and HIV-2-infected CEMSS cells and identified by NCI for preclinical development.[11] These alkaloids have been isolated from the tropical liana *Ancistrocladus korupensis* in Cameroon and have a naphthyltetrahydroisoquinoline skeleton with axial chirality between the naphthalene and tetrahydroisoquinoline rings (Figure 1).[12] These alkaloids have been previously synthesized via construction of the axial bond between the naphthalene and tetrahydroisoquinoline rings as a key step. However, palladium(0)-catalyzed cross-coupling[13] of two arene rings or nucleophilic addition[14] of aryl Grignards to the chiral *o*-methoxyaryl oxazoline compounds for the formation of the central bond of the naphthalene and tetrahydroisoquinoline rings usually gave various ratios of an atropisomeric mixture.

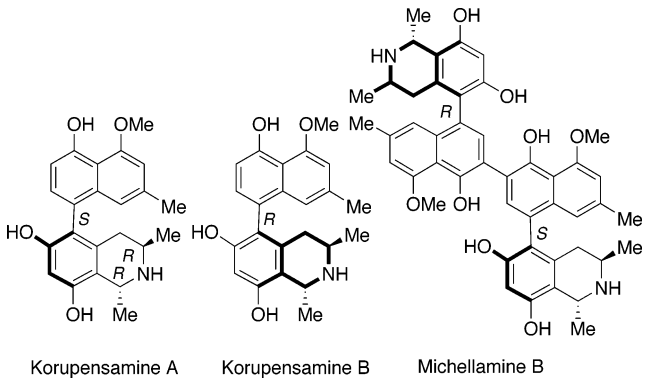

FIGURE 1. Axially chiral naphthyltetrahydroisoquinoline alkaloids.

Lipshutz et al. reported[15] that palladium(0)-catalyzed atropselective cross-coupling was achieved using a properly positioned internal phosphine group in the tetrahydroisoquinoline part as a coordinating ligand to afford a single biaryl atropisomer for korupensamine A. The other method for induction of the axial chirality other than central bond formation developed by Bringmann et al. is an attractive procedure for stereoselective synthesis of korupensamines A and B from a common precursor by a divergent lactone cleavage method with a chiral reducing agent.[16] As a further extension for the stereoselective axial bond formation utilizing the planar chiral (arene)chromium complex, we investigated total synthe-

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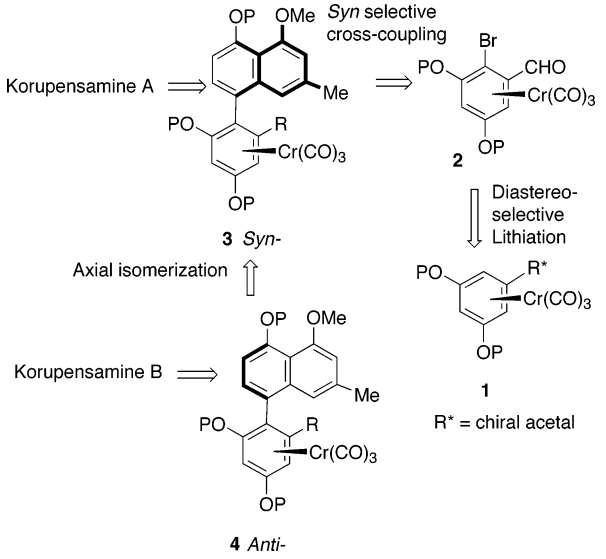
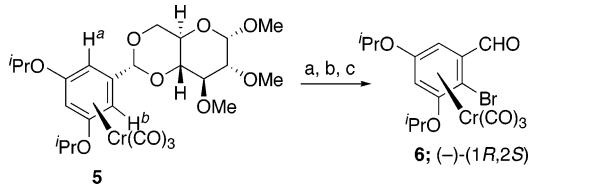
SCHEME 1. Retrosynthesis of Korupensamines A and B from Identical Planar Chiral Arene Chromium Complex.



sis of both atropisomeric korupensamines A and B starting from an identical planar chiral arene chromium complex. Our synthetic plan of atropisomeric korupensamines A and B is illustrated in Scheme 1. Planar chiral 3,5-dialkoxy-2-bromobenzaldehyde chromium complex **2** would produce *syn*-biaryl chromium complex **3** by palladium(0)-catalyzed cross-coupling with naphthylboronic acid under kinetic conditions. The obtained syn coupling product **3** would be isomerized to the corresponding thermodynamically stable anti isomer **4** with central bond rotation under thermal conditions.[10,17] The *syn*- and *anti*-biaryl chromium complexes, **3** and **4**, would be converted to korupensamines A and B, respectively, by stereoselective conversion of the formyl group to a tetrahydroisoquinoline skeleton.

Initially, an optically pure tricarbonyl(2-bromo-3,5-diisopropoxybenzaldehyde)chromium complex as a coupling partner was synthesized by diastereoselective ortho lithiation (Tables 1, 2).[18] According to reported procedure,[19] a tricarbonylchromium complex of chiral 3,5-diisopropoxybenzaldehyde acetal **5** was prepared from methyl α-D-glucopyranoside and 3,5-diisopropoxybenzaldehyde dimethylacetal in good yield. Directed lithiation of the complex **5** with *n*-BuLi in THF followed by quenching with 1,2-dibromo-1,1,2,2-tetrafluoroethane gave an ortho-brominated chromium complex in 76% yield along with 15% yield of a para bromination product

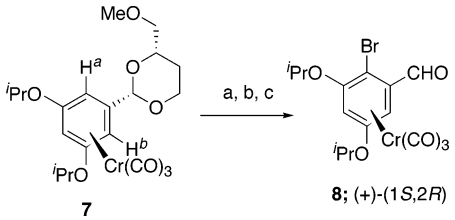
TABLE 1. Diastereoselective Lithiation of Methyl α-Glucopyranoside Chromium Complex 5[a]



	solvent	yield **6** (%)[b]	% ee **6**
1	THF	38 (76)[c]	78
2	ether	57 (98)	94

[a] Conditions for reaction depicted: (a) *n*-BuLi, solvent, 78 °C; (b) $BrCF_2CF_2Br$; (c) 50% aq H_2SO_4/acetone (1:1), reflux, 30 min. [b] Yield in parentheses is for the bromination product before the hydrolysis step. [c] *p*-Bromination product was obtained in 15% yield.

TABLE 2. Diastereoselective Lithiation of Chromium Complex 7[a]



	solvent	yield **8** (%)[b]	% ee **8**
1	THF	58 (90)	94
2	ether	64 (92)	96

[a] Conditions for reaction depicted: (a) *n*-BuLi, solvent, 78 °C; (b) $BrCF_2CF_2Br$; (c) $TiCl_4$, ether, 78 °C. [b] Yield in parentheses is for the bromination product before the hydrolysis step.

(Table 1). Hydrolysis of the bromination product was carried out with 50% aqueous sulfuric acid in refluxing acetone, and the yield of hydrolysis was 45−50% yield along with de-chromium tricarbonyl compound. The optical purity of (−)-(1*R*,2*S*)-tricarbonyl(2-bromo-3,5-diisopropoxybenzaldehyde)chromium complex (**6**) was found to be 78% ee by HPLC with Chiralcel OJ-H. Thus, the directed lithiation of **5** occurred at the H^b-position via chelation of the lithium metal with the nearby methoxy oxygen of the sugar moiety followed by regioselective removal of one of the diastereotopic *ortho*-hydrogens. Use of diethyl ether instead of THF as a solvent in the lithiation reaction increased both the diastereoselectivity and the yield of the bromination product. Thus, lithiation of **5** in ether followed by bromination and acidic hydrolysis gave the bromination product **6** in 57% overall yield with 94% ee without formation of the bromination product at the 4-position. The low diastereoselectivity of ortho lithiation of **5** in THF would be attributed to the competitive coordinative ability of THF oxygen with the lithium atom. We next investigated the diastereoselectivity in the directed lithiation of chiral benzaldehyde acetal chromium complex **7** derived from (*S*)-1,2,4-butanetriol as the chiral auxiliary (Table 2). Directed lithiation of **7** with *n*-BuLi at −78 °C followed by quenching with 1,2-dibromo-1,1,2,2-tetrafluoroethane was carried out under the same conditions. Hydrolysis of the bromination product was achieved by treatment with 1 equiv of titanium tetrachloride in ether at −78 °C, since

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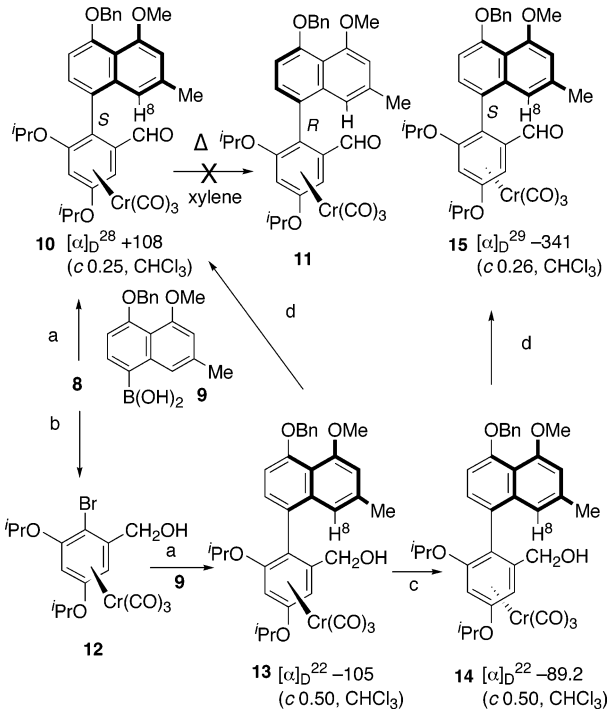
SCHEME 2[a]



[a] Reagents and conditions: (a) **9**, 5 mol % $Pd(PPh_3)_4$, 1 M aq Na_2CO_3/MeOH (1/10), 75 °C, 10−30 min (38% for **10**, 88% for **13**); (b) $NaBH_4$, MeOH/CH_2Cl_2 (2/1), 0 °C, 30 min (99%); (c) *n*-Bu_2O/$ClCH_2CH_2Cl$ (1/1), 120 °C, 30 min (80%); (d) $(CF_3CO)_2O$, DMSO, CH_2Cl_2, −78 °C, then Et_3N (80% for **10**, 93% for **15**).

the hydrolysis with aqueous sulfuric acid resulted in poor yield. The obtained benzaldehyde chromium complex **8** was an antipode (+)-isomer. In this case, directed lithiation took place at the H^a-position of **7**. In this way, both enantiomers of a planar chiral bromobenzaldehyde chromium complex were obtained by diastereoselective lithiation of 3,5-diisopropoxybenzaldehyde chiral acetal chromium complexes **5** and **7**. Of both enantiomers, (+)-3,5-diisopropoxybenzaldehyde chromium complex **8** was employed as a coupling partner for synthesis of korupensamines, since the overall chemical yield and the diastereoselectivity of ortho lithiation were superior to those of **6**.

Palladium(0)-catalyzed cross-coupling of planar chiral (+)-2-bromo-3,5-diisopoxybenzaldehyde chromium complex (**8**) with 4-benzyloxy-5-methoxy-7-methylnaphthylboronic acid (**9**)[20] in the presence of sodium carbonate under heating at 75 °C in aqueous MeOH for 10 min gave a kinetically controlled syn coupling product **10** ($[\alpha]_D^{28}$ +108° (*c* 0.25, $CHCl_3$)) in 38% yield without formation of the corresponding anti isomer (Scheme 2).[21] The axial stereochemistry of the syn cross-coupling product **10** is identical with that of korupensamine A. Toward the synthesis of atropisomeric korupensamine B, the axial isomerization of the syn coupling product **10** to *anti*-biaryl chromium complex **11** was next examined under thermal conditions. Unfortunately, refluxing of **10** in xylene gave a de-tricarbonylchromium biaryl compound as the major product. The low yield in the palladium(0)-catalyzed cross-coupling and unsatisfactory axial isomerization under thermal conditions might be attributed to the thermal lability of the chromium-complexed naphthyl benzaldehyde **10**. Therefore, the formyl group of **8** was reduced to a hydroxymethyl group. The planar chiral benzyl alcohol chromium complex **12** was coupled with naphthylboronic acid **9** under the same conditions to give syn coupling product **13** ($([\alpha]_D^{22}$ −105° (*c* 0.50, $CHCl_3$)) in 88% yield. Oxidation of **13** with TFAA/DMSO afforded the *syn*-formyl complex **10** in 80% yield. The peri protons (H^8) of the naphthalene ring of the tricarbonylchromium-complexed *syn*-biaryls, **10** and **13**, appeared at 8.29 and 8.65 ppm, respectively. The low field shift was attributed to an anisotropic effect of the tricarbonylchromium fragment.[22] The syn coupling product **13** was next heated in xylene for central bond rotation. However, (xylene)$Cr(CO)_3$ was only obtained without formation of the corresponding anti isomer. Therefore, a nonaromatic solvent was next employed for thermal isomerization. Heating of the *syn*-biaryl chromium complex **13** in 1:1 mixture of di-*n*-butyl ether and 1,2-dichloroethane at 120 °C for 30 min gave thermally isomerized chromium-complexed biaryl **14** ($[\alpha]_D^{22}$ −89.2° (*c* 0.50, $CHCl_3$)) in 80% yield. The stereochemistry of the thermal isomerized product **14** was easily presumed to be an anti isomer from the chemical shift (H^8; 6.68 ppm) of the corresponding peri proton of the naphthalene ring. However, the thermally isomerized *anti*-chromium complex **14** was found not to be the axially isomerized *anti*-biaryl chromium complex. Optical rotation of a de-tricarbonylchromium compound derived from the *syn*-coupling product **13** was consistent with that of a photooxidative demetalation product from the thermally isomerized *anti*-biaryl chromium complex **14**.[23] This result obviously indicates that thermal isomerization of **13** afforded stereoselective migration of the tricarbonylchromoium fragment to the reversed arene face giving *anti*-biaryl complex **14** without formation of the expected *anti*-biaryl complex with central bond rotation.[24] This stereoselective $Cr(CO)_3$ migration to the inverted arene face is an interesting reaction and would be useful for further asymmetric reactions utilizing the planar chirality. The face-inverted *anti*-chromium complex **14** was also oxidized to the *anti*-formyl chromium complex **15** ($[\alpha]_D^{29}$ −341° (*c* 0.26, $CHCl_3$)). In this way, the key intermediates **10** and **15** for synthesis of korupensamine A and *ent*-korupensamine B were stereoselectively prepared from identical planar chiral arene chromium complex **8** in enantiomerically pure form in good yields.

We next designed stereoselective addition of an acyl anion equivalent to the formyl group of the axial biaryl chromium complex **10** for construction of the dimethyl tetrahydroisoquinoline skeleton of korupensamine A (Scheme 3). Reaction of the *syn*-biaryl chromium complex

(20) Naphthylboronic acid **9** was prepared by a modified procedure of the following reference: Hoye, T. R.; Mi, L. *J. Org. Chem.* **1997**, *62*, 8586.

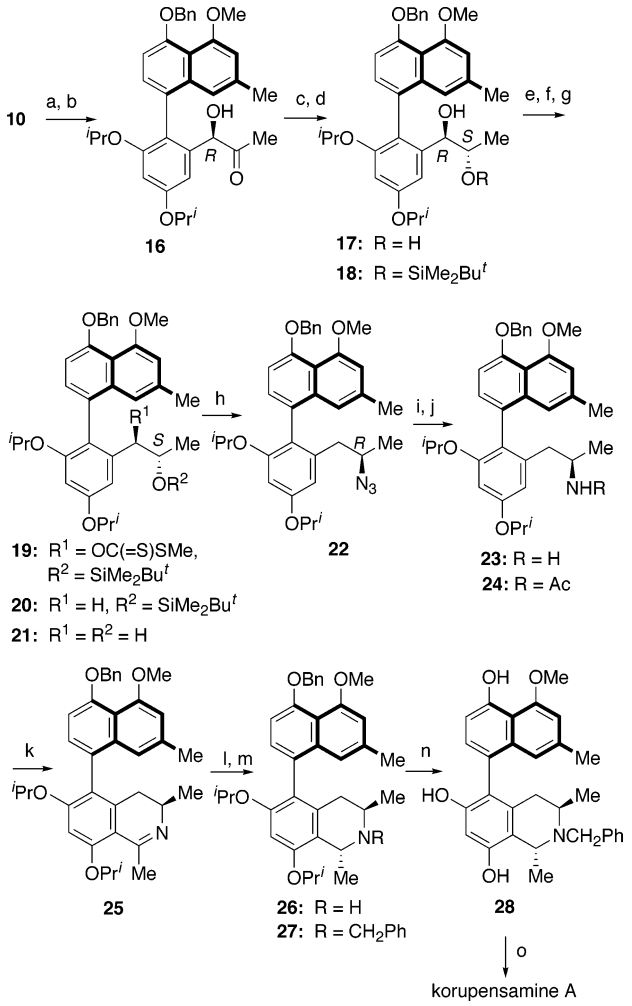
(21) Watanabe, T.; Shakadou, M.; Uemura, M. *Synlett* **2000**, 1141.

(22) (a) Uemura, M.; Nishimura, H.; Kamikawa, K.; Shiro, M. *Inorg. Chim. Acta* **1994**, *222*, 63. (b) Bringmann, G.; Göbel, L.; Peters, K.; Peters, E.-M.; Schnering, H. G. *Inorg. Chim. Acta* **1994**, *222*, 255.

(23) Optical rotation ($[\alpha]_D^{20}$ +49 (*c* 1.0, $CHCl_3$)) of de-tricarbonylchromium compound derived from thermally isomerized *anti*-biaryl chromium complex **14** by air oxidation was completely identical with that of de-tricarbonylchromium compound of the *syn*-biaryl complex **13**.

(24) (a) Kamikawa, K.; Sakamoto, T.;Uemura, M. *Synlett* **2003**, 516. (b) Tanaka, Y.; Sakamoto, T.; Kamikawa, K.; Uemura, M. *Synlett* **2003**, 519. (c) Kamikawa, K.; Sakamoto, T.; Tanaka, Y.; Uemura, M. *J. Org. Chem.* **2003**, *68*, 9356.

SCHEME 3[a]



[a] Reagents and conditions: (a) CH_2=C(OEt)Li, THF, −78 °C; (b) 10% aq HCl/THF (1/5), 25 °C, in air (79% from **10**); (c) $Zn(BH_4)_2$, THF, ether, −78 °C (99%); (d) Bu*t*Me_2SiOTf, Et_3N (95%); (e) NaH, CS_2, MeI, THF (90%); (f) *n*Bu_3SnH, AIBN, toluene, 100 °C, 15 min (94%); (g) *n*Bu_4NF (87%); (h) $(PhO)_2PON_3$, DEAD, PPh_3, THF, 0 °C (94%); (i) $SnCl_2 \cdot 2H_2O$, MeOH; (j) Ac_2O, pyr (86% from **22**); (k) $POCl_3$, MeCN, reflux (97%); (l) $LiAlH_4$, Me_3Al, THF, −78 to 0 °C; (m) BnBr, K_2CO_3, acetone, (64% from **25**); (n) BCl_3, CH_2Cl_2 (35%); (o) 10% Pd/C, H_2, MeOH (90%).

10 with α-ethoxy vinyllithium[25] followed by acidic hydrolysis under air gave a single demetalated (*R*)-α-hydroxy methyl ketone derivative **16** in 79% overall yield. Extremely high diastereoselectivity (>99:<1 dr) in the addition of vinyllithium would be attributed to an opposite face attack of the nucleophile to a preferred conformation of a chromium-complexed benzaldehyde from a tricarbonylchromium fragment, in which the carbonyl oxygen of the formyl group is well-known to be in anti orientation to the ortho substituent due to stereoelectronic effect.[8,26] Subsequent reduction of the ketone **16** with zinc borohydride produced *erythro*-(*R*,*S*)-diol **17** as a single product via a chelation-controlled transition state.[27] Regioselective protection of homobenzylic alcohol with *tert*-butyldimethylsilyl triflate followed by reduction of the benzylic hydroxyl via xanthate chemistry according to Barton's procedure,[28] followed by desilylation provided monoalcohol **21**. Conversion of the (*S*)-hydroxyl group of **21** to azide with stereochemical inversion was achieved under Mitsunobu conditions.[29] Thus, treatment with $(PhO)_2PON_3$ in the presence of DEAD and PPh_3 gave (*R*)-azido compound **22**, which was converted into amide **24** by reduction and subsequent acetylation. Cyclization of **24** followed by reduction with $LiAlH_4$ in the presence of trimethylaluminum[30] afforded predominantly *trans*-dimethyl naphthyltetrahydroisoquinoline **26** along with the corresponding cis isomer in a ratio of 76:24 and then **27** after protection of NH with benzyl bromide. Deprotection of the isopropoxy and *O*-benzyloxy groups of **27** with BCl_3 gave *N*-benzyl korupensamine A (**28**) in 35% yield along with a mixture of regioisomeric monoisopropyl ethers of *N*-benzyl korupensamine A (in 33% yield). Compound **28** was completely consistent with reported *N*-benzylkorupensamine A[12a] in the spectral data, including optical rotation, and converted to korupensamine A by treatment with Pd/C under a hydrogen atmosphere. Moreover, a regioisomeric mixture of the monoisopropyl ether of *N*-benzyl korupensamine A was treated with isopropyl bromide in the presence of $CsCO_3$ to give the triisopropyl ether of *N*-benzyl korupensamine A. The obtained triisopropyl ether of *N*-benzyl korupensamine A was finally converted to korupensamine A using a reported procedure, and all spectral data of the synthetic product were consistent with those of natural korupensamine A.[12a]

Similarly, the thermally isomerized *anti*-biaryl chromium complex **15** was converted to *ent*-korupensamine B by the same reaction sequence (Scheme 4). Synthetic korupensamine B was found to be *ent*-korupensamine B. Thus, optical rotation of the synthetic korupensamine B was −63° (*c* 0.09, MeOH), while natural korupensamine B shows a plus value of optical rotation.[31] In this way, korupensamine A and *ent*-korupensamine B were synthesized via a stereoselective Pd(0)-mediated cross-

(25) Braish, T. F.; Saddler, J. C.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 3647.

(26) Some representative references: (a) Pache, S.; Romanens, P.; Kündig, E. P. *Organometallics* **2003**, *22*, 377. (b) Wang, Q.; Foersterling, F. H.; Hossain, M. M. *Organometallics* **2002**, *21*, 2596. (c) Tanaka, Y.; Taniguchi, N.; Uemura, M. *J. Org. Chem.* **2002**, *67*, 9227. (d) Gibson, S. E.; Ibrahim, H. *Chem. Comm.* **2002**, *21*, 2465. (e) Rose-Munch, F.; Rose, E. *Eur. J. Inorg. Chem.* **2002**, 1269. (f) Tanaka, Y.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2002**, *4*, 835. (g) Netz, A.; Polborn, K.; Müeller, T. J. *J. Am. Chem. Soc.* **2001**, *123*, 3441. (h) Baldoli, C.; Del Buttero, P.; Perdicchia, D.; Pilati, T. *Tetrahedron* **1999**, *55*, 14089. (i) Rose-Munch, F.; Rose, E. *Curr. Org. Chem.* **1999**, *3*, 445. (j) Han, J. W.; Son, S. U.; Chung, Y. K. *J. Org. Chem.* **1997**, *62*, 8264. (k) Fretzen, A.; Kündig, E. P. *Helv. Chim. Acta* **1997**, *80*, 2023. (l) Alexakis, A.; Kanger, T.; Mangeney, P.; Rose-Munch, F.; Perrotey, A.; Rose, E. *Tetrahedron: Asymmetry* **1995**, *6*, 2135. (m) Baldoli, C.; Del Buttero, P. *J. Chem. Soc., Chem. Comm.* **1991**, 982. (n) Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A. *J. Chem. Soc., Chem. Comm.* **1987**, 762. (o) Schmalz, H.-G.; Siegel, S. In *Transition Metals for Fine Chemicals and Organic Synthesis*; Bolm, C., Beller, M., Eds.; VCH: Weinheim, 1998; Vol. 1.

(27) (a) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653. (b) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338.

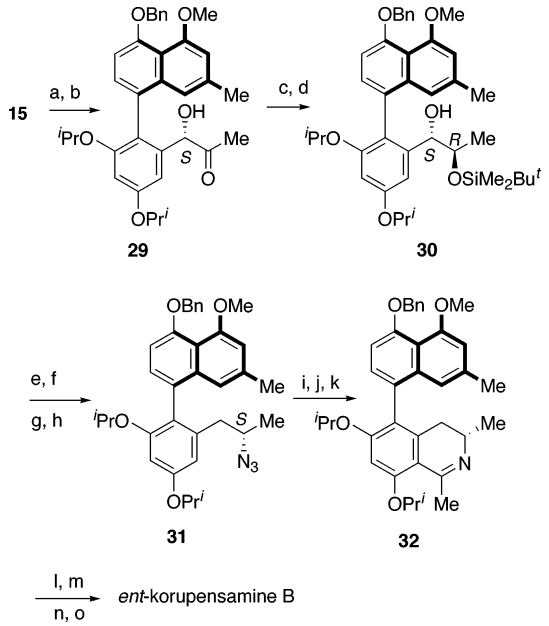
(28) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**. 1574.

(29) Mitsunobu, O. *Synthesis* **1981**, 1.

(30) (a) Bringmann, G.; Jansen, J. R.; Rink, H.-P. *Angew. Chem.* **1986**, *98*, 917. Bringmann, G.; Jansen, J. R.; Rink, H.-P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 913. (b) Bringmann, G.; Weirich, R.; Reusher, H.; Jansen, J. R.; Kinzinger, L.; Ortmann, T. *Liebigs. Ann. Chem.* **1993**, 877. (c) Maruoka, K.; Yamamoto, H. *Angew. Chem.* **1985**, *97*, 670. Maruoka, K.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 668.

(31) Optical rotation of natural korupensamine B is $[\alpha]_D$ +65 (*c* 0.76, MeOH): see ref 11d.

SCHEME 4[a]

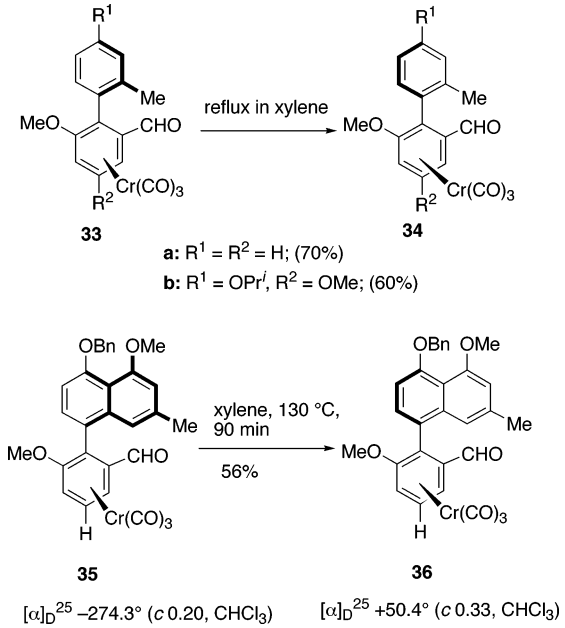


[a] Reagents and conditions: (a) CH_2=C(OEt)Li, THF, −78 °C; (b) 10% aq HCl/THF (1/5), 25 °C, in air (84% from **15**); (c) $Zn(BH_4)_2$, THF, ether, −78 °C (99%); (d) Bu*t*Me_2SiOTf, Et_3N, CH_2Cl_2 (92%); (e) NaH, CS_2, MeI, THF (97%); (f) *n*Bu_3SnH, AIBN, toluene, 100 °C, 15 min (99%); (g) *n*Bu_4NF (88%); (h) $(PhO)_2PON_3$, DEAD, PPh_3, THF, 0 °C (98%); (i) $SnCl_2.2H_2O$, MeOH; (j) Ac_2O, pyr, 94% from **31**; (k) $POCl_3$, MeCN, reflux (95%); (l) $LiAlH_4$, Me_3Al, THF, −78 to 0 °C; (m) BnBr, K_2CO_3, acetone, 65% from **32**; (n) BCl_3, CH_2Cl_2, (30%); (o) 10% Pd/C, H_2, MeOH (94%).

coupling and subsequent tricarbonylchromium migration to the inverted arene face under thermal conditions starting from the identical planar chiral arene chromium complex **8**.

Synthesis of Atropisomeric Korupensamines A and B from Common Arene Chromium Complex. As described above, we have succeeded in the total synthesis of korupensamine A and *ent*-korupensamine B from common planar chiral arene chromium complex by diastereoselective cross-coupling of 2-bromo-3,5-diisopropoxybenzaldehyde chromium complex **8** with naphthylboronic acid **9** and subsequent face inversion under heating in a mixture of di-*n*-butyl ether and 1,2-dichloroethane. Thermal isomerization of the *syn*-biaryl chromium complex **13** with a hydroxymethyl group gave *anti*-biaryl chromium complex **14** with inversion of planar chirality by stereoselective migration of the tricarbonylchromium fragment without central bond rotation as shown in Scheme 2. For the achievement of total synthesis of atropisomeric korupensamines A and B from an *identical arene chromium complex*, the axial isomerization of the *syn*-biaryl chromium complex should be required. From our previous results,[24] the *ortho*-formyl group is essential for the axial isomerization of *syn*-biaryl chromium complexes under thermal conditions. However, the *syn*-biaryl chromium complex **10** with an *ortho*-formyl group was a thermally labile chromium complex to give a decomposition product by heating in xylene. Therefore, further investigation of the axial isomerization was directed toward the total synthesis of both korupensamines A and B from an identical planar chiral arene chromium complex. 2-Formyl-substituted *syn*-chromium

SCHEME 5. Axial Isomerization of *syn*-Biaryl Chromium Complexes

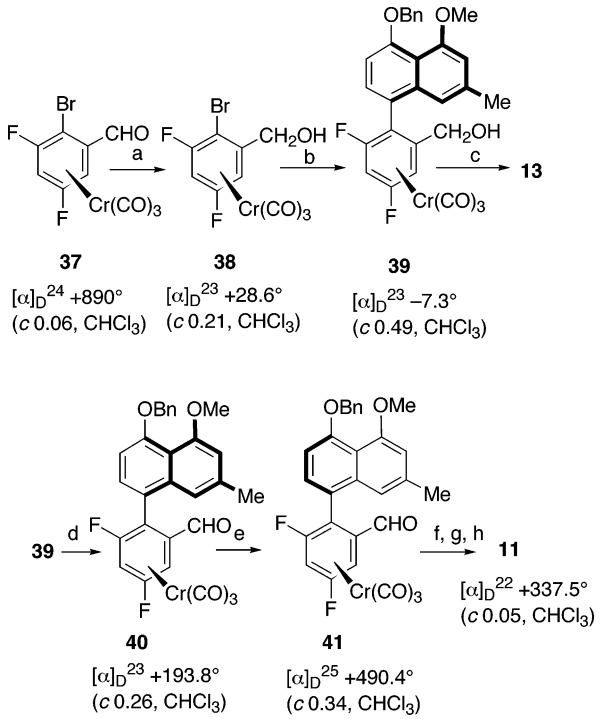


complex **33a** was heated in xylene to give the expected *anti*-biaryl chromium complex **34a**, containing a rotated central bond, in 70% yield (Scheme 5). Similarly, *syn*-biphenyl complex **33b** afforded axial isomerization product **34b** in 60% yield by refluxing in xylene. These *syn*-biaryl chromium complexes **33** are substituted with a phenyl ring instead of the naphthalene ring as the central bond. Construction of the functionalized-naphthalene ring for the korupensamine skeleton by conversion from the methyl-substituted phenyl ring of **33** and **34** is not so easy. Therefore, we next studied thermal isomerization of the *syn*-biaryl chromium complex with a naphthalene fragment. *syn*-Biaryl complex **35**, devoid of a *p*-methoxy group at the chromium-complexed arene ring, was heated in xylene to afford axially isomerized *anti*-biaryl chromium complex **36** in 56% yield. The progress of the axial isomerization of **35** is in sharp contrast to the *syn*-biaryl chromium complex **10**, which was a thermally labile complex. These results indicate that the thermal stability of the *syn*-biaryl chromium complexes with the formyl group would be attributed to an electronic effect on the arene ring. An electron-donating group of the chromium-complexed arene ring would destabilize the *syn*-biayl chromium complexes under thermal conditions. Therefore, the *syn*-biaryl chromium complex with an electron-withdrawing fluorine atom would be expected to be a thermally stable chromium complex for the axial isomerization.

In line with this idea, we selected enantiomerically pure 2-bromo-3,5-difluorobenzaldehyde chromium complex (**37**)[32] ($[\alpha]_D^{24}$ +890° (*c* 0.06, $CHCl_3$)) as a coupling partner. Furthermore, the chromium-complexed fluorine

(32) Enantiomerically pure (+)-2-bromo-3,5-difluorobenzaldehyde chromium complex (**37**) was obtained by optical resolution of the diastereomers prepared from the corresponding racemic chromium complex and *L*-valinol with column chromatography according to reported procedure: (a) Davies, S. G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans 1* **1989**, 192. (b) Davies, S. G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans 1* **1990**, 393. (c) Bromley, L. A.; Davies, S. G.; Goodfellow, C. L. *Tetrahedron Asymmetry* **1991**, *2*, 139.

SCHEME 6[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH (79%); (b) **9**, $Pd(PPh_3)_4$, 0.1 M aq K_3PO_4, toluene, 95 °C (74%); (c) *i*-PrOH, NaH, 18-crown ether-6, benzene, rt (93%); (d) TFAA, DMSO, CH_2Cl_2, then Et_3N (87%); (e) xylene, 120 °C, 1 h (65%); (f) $CH(OMe)_3$, *p*-TsOH, rt, 3 h (78%); (g) *i*-PrOH, NaH, 18-crown ether-6, benzene, rt (73%); (h) 50% aq H_2SO_4, acetone, 0 °C, 15 min (46%).

atom could be easily converted to alkoxybenzene by nucleophilic substitution.[8d] Since cross-coupling of (+)-difluoro-bromobenzaldehyde chromium complex **37** with naphthylboronic acid **9** under various conditions resulted in formation of complex mixtures, the formyl group was reduced to a hydroxymethyl group. Palladium(0)-catalyzed cross-coupling of 2-bromo-3,5-difluorobenzyl alcohol chromium complex **38** ($[\alpha]_D^{23}$ +28.6° (*c* 0.21, $CHCl_3$)) with **9** in aqueous methanol gave a complicated mixture. However, use of a mixture of toluene and water instead of methanol at 95 °C gave the desired *syn*-biaryl coupling product **39**[33] ($[\alpha]_D^{23}$ −7.3° (*c* 0.49, $CHCl_3$)) in 74% yield. The syn stereochemistry was confirmed by ^1H NMR spectra (peri H^8 proton; δ 8.42 ppm). Treatment of the *syn*-difluoro arene chromium complex **39** with 2-propanol and NaH in the presence of 18-crown ether-6 at room temperature gave diisopropoxy biaryl chromium complex **13** in 93% yield. Optical rotation ($[\alpha]_D^{22}$ −105° (*c* 0.50, $CHCl_3$)) was identical with that of the *syn*-biaryl chromium complex prepared by cross-coupling of planar chiral (−)-2-bromo-3,5-diisopropoxybenzyl alcohol chromium complex (**12**) with naphthylboronic acid **9** as shown in Scheme 2. The syn complex **13** was already converted to korupensamine A via formyl-substituted *syn*-biaryl chromium complex **10** as shown in Scheme 3. We next studied the axial isomerization of a difluoro-substitituted *syn*-biaryl complex. The hydroxymethyl group of **39** was initially oxidized to the formyl group. Heating of *syn*-biaryl chromium complex **40** ($[\alpha]_D^{23}$ +193.8° (*c* 0.26, $CHCl_3$)) in xylene at 120 °C for 1 h gave the expected *anti*-biaryl chromium complex **41** containing a rotated central bond ($[\alpha]_D^{25}$ +490.4° (*c* 0.34, $CHCl_3$)) in 65% yield along with de-chromium tricarbonyl product (25%). Peri H^8 proton of the *syn*-biaryl complex **40** appeared at 8.07 ppm, while the corresponding proton of the axially isomerized *anti*-complex **41** showed at 6.74 ppm. Protection[34] of the formyl group of the *anti*-biaryl chromium complex **41** as dimethyl acetal, followed by nucleophilic substitution with 2-propanol and finally acidic hydrolysis, afforded **11** ($[\alpha]_D^{22}$ +338° (*c* 0.05, $CHCl_3$)). The obtained *anti*-biaryl chromium complex **11** is an antipode of *anti*-biaryl chromium complex **15**; thus, the chromium complex **11** would be converted to korupensamine B by the same reaction sequence. In conclusion, we have demonstrated the total synthesis of korupensamines by diastereoselective cross-coupling of a planar chiral arene chromium complex with naphthylboronic acid and subsequent axial isomerization of the syn coupling product or stereoselective tricarbonyl chromium migration to the inverted arene face as key steps.

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Supporting Information Available: Experimental details for preparation of the all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(33) Reflux of difluoro-substituted *syn*-biaryl chromium complex **39** in a mixture of di-*n*-butyl ether and dichloroethane resulted in recovery of the starting material without tricarbonylchromium migration to the inverted arene face despite the benzyl alcohol function. This result would be attributed to the strong electron-withdrawing ability of the fluorine atom: see ref 24.

(34) Nucleophilic substitution reaction of the fluoro atom of **41** with sodium isopropoxide gave a complex mixture. The formyl group of **41** disappeared in this nucleophilc substitution reaction. Furthermore, nucleophilic substitution of an *anti*-difluorobenzyl alcohol chromium complex obtained from **41** by sodium borohydride reduction gave a monoisopropoxy-substituted chromium complex under the same conditions with *syn*-biaryl chromium complex **39**. The *ortho*-fluorine atom of the *anti*-biaryl chromium complex did not reacted with the nucleophile due to steric hindrance.