An Asymmetric Synthesis of an Axially Chiral Biaryl *via* an (Arene)chromium Complex: Formal Synthesis of (−)-Steganone

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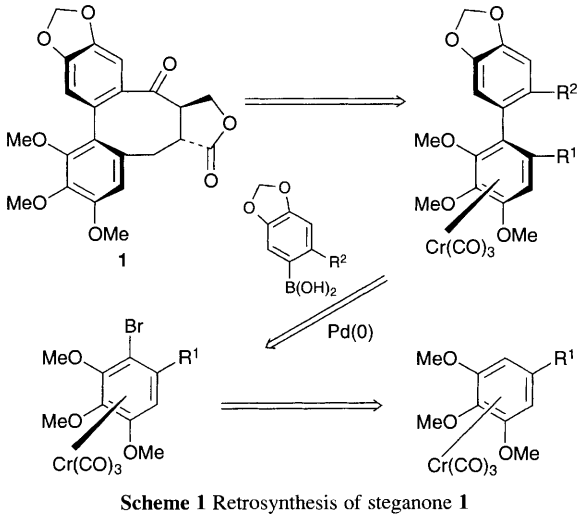
(−)-Steganone was formally synthesized by using the diastereoselective *ortho*-lithiation of a chiral acetal of tricarbonyl(3,4,5-trimethoxybenzaldehyde)chromium and subsequent cross-coupling of optically pure tricarbonyl(2-bromo-3,4,5-trimethoxybenzyl alcohol)chromium with arylboronic acid as key steps.

Biphenyls and binaphthyls with axial chirality are attractive compounds as chiral ligands in asymmetric reactions and also in the synthesis of biologically active natural products. There is a considerable current interest in the development of efficient methodologies for the synthesis of biphenyls which give the atropisomers in an enantiomerically pure form.[1] We have recently reported[2] that Suzuki cross-coupling reaction of tricarbonyl(substituted aryl halide)chromium complexes with *ortho*-substituted arylboronic acids catalysed by palladium(0) afforded stereoselectively mono-$Cr(CO)_3$ complexes of biphenyls with axial chirality depending upon the nature of the *ortho*-substituents of phenylboronic acids. We now report a formal synthesis of (−)-steganone utilizing the stereoselective cross-coupling of a planar chiral (arene)chromium complex.

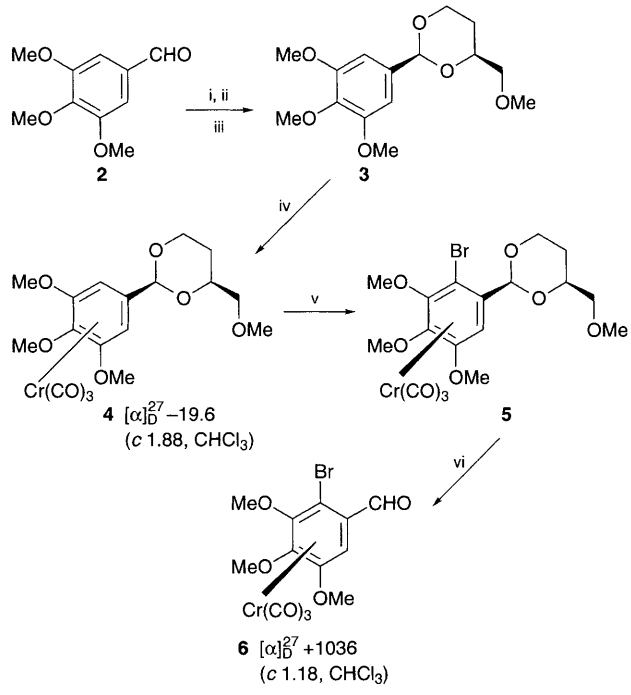
(−)-Steganone **1**, an antileukaemic bisbenzocyclooctadiene lignan lactone, one of four isolated[3] *Steganotaenia araliacea*, has attracted considerable synthetic interest. The novel feature of our strategy for the total synthesis of (−)-steganone is initially to prepare an enantiomerically pure (aryl halide)-chromium complex with planar chirality *via* diastereoselective *ortho*-lithiation, and subsequently to form the axial asymmetry of the biaryl bond (Scheme 1).

We initially investigated the diastereoselective *ortho*-lithiation of the chiral acetal of tricarbonyl(3,4,5-trimethoxybenzaldehyde)chromium for the preparation of a planar chiral (aryl halide)chromium complex as in Scheme 2. The dimethyl acetal of 3,4,5-trimethoxybenzaldehyde was treated with (*S*)-(−)-butane-1,2,4-triol derived from L-malic acid followed by methylation with NaH–MeI to give stereoselectively the 1,3-diequatorial substituted dioxane structure **3** without formation of a five-membered acetal ring, in 73% overall yield.[4] Chromium complexation of **3** gave the corresponding (arene)chromium complex **4** {$[\alpha]_D^{27}$ −19.6 (*c* 1.88, $CHCl_3$)} in 67% yield. Diastereoselective *ortho*-lithiation of **4** followed by bromination with 1,2-dibromo-1,1,2,2-tetrafluoroethane and then acidic hydrolysis of the acetal group afforded the optically active benzaldehyde complex (+)-**6** as shown in Table 1. The diastereoselectivity of the *ortho*-lithiation was largely dependent upon the nature of the solvent. Thus, the *ortho*-lithiation in a polar solvent, *e.g.* THF, led to extremely low stereoselectivity owing to coordination of the lithium with THF oxygen. The use of toluene as solvent with Bu^nLi for the directed lithiation followed by hydrolysis of the acetal resulted in 90% e.e.† of (+)-**6**. The optical purity of **6** was increased to >99% e.e. {$[\alpha]_D^{27}$ +1036 (*c* 1.18, $CHCl_3$)} by one fractional crystallizaton of the brominated acetal compound **5** from ether–hexane followed by acidic hydrolysis of the acetal. The stereochemistry of the planar chirality of **6** was assigned as shown by the commonly observed correlation with the sign of the specific rotations of related (*o*-halogenated benzaldehyde)$Cr(CO)_3$ complexes,[5] and by analogy with the related diastereoselective lithiation with ferrocene homologues.[6]

With the optically active planar chiral (arene)chromium complex in hand, the next stage was to form stereoselectively



Scheme 1 Retrosynthesis of steganone **1**



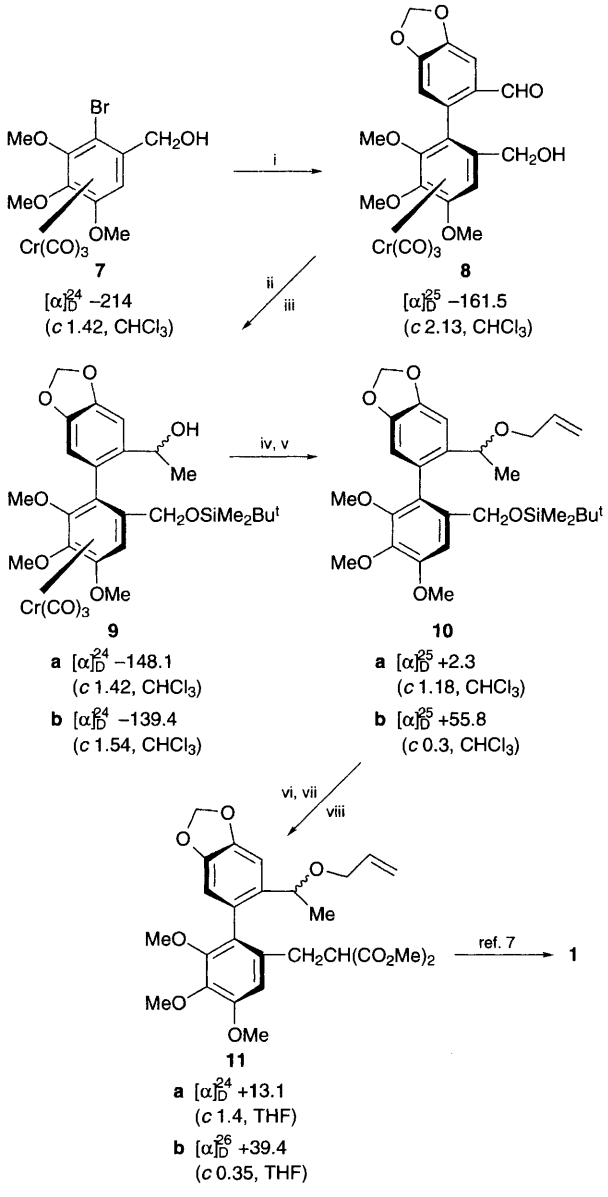
Scheme 2 *Reagents and conditions*: i, MeOH, $CH(OMe)_3$, TsOH, 98%; ii, (*S*)-butane-1,2,4-triol, TsOH, 79%; iii, MeI, NaH, THF, DMF, 94%; iv, $Cr(CO)_6$, butyl ether, heptane, THF, 130 °C, 24 h, 67%; v, see text, vi, HCl (TsOH = *p*-$MeC_6H_4SO_3H$)

Table 1 Diastereoselective *ortho*-lithiation of **4** (e.e., enantiomeric excess)

RLi	Solvent	Yield[a] (%) of **6**	% e.e. of **6**
Bu^tLi	Ether	45	71
Bu^tLi	THF	45	3
Bu^tLi	Toluene	62	77
Bu^nLi	Ether	70	67
Bu^nLi	THF	67	3
Bu^nLi	Toluene	47	90
Bu^nLi	Toluene–TMEDA	68	25

[a] Yield is not optimized.

the axial chirality by cross-coupling with an *ortho*-substituted arylboronic acid. Reaction of (−)-(2-bromo-3,4,5-trimethoxybenzyl alcohol)chromium **7**, derived from **6** by reduction, with 2-formyl-4,5-methylenedioxyphenylboronic acid in the presence of $Pd(PPh_3)_4$ (0.05 mol. equiv.) gave the biaryl coupling product **8** in 67% yield without formation of the corresponding atropisomer. The axial stereochemistry of **8** was assigned as (*R*) on the basis of results[2]‡ of previous studies in which the coupling reactions of (*o*-substituted arene)$Cr(CO)_3$ complexes with *o*-formylphenylboronic acid gave stereoselectively the (*R*)-axial products. At this axial juncture, the assignment was purely arbitrary, but this assumption proved to be correct as the synthesis reached its target molecule. It was now necessary to elaborate the biaryl to the 8-membered ring present in steganone from the coupling product **8**. Protection of the hydroxy group in **8** with *tert*-butyldimethylsilyl chloride followed by treatment with methyllithium at −78 °C afforded a 5 : 1 diastereoisomeric mixture of secondary alcohols **9a**,**b** in 83% overall yield. This mixture was cleanly separated by flash chromatography, and each diastereoisomeric 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.



Scheme 3 *Reagents and conditions*: i, 2-formyl-4,5-methylenedioxyphenylboronic acid, $Pd(PPh_3)_4$ (0.05 mol equiv.), aq. Na_2CO_3, MeOH, reflux, 1 h, 67%; ii, Bu^tMe_2SiCl, imidazole, CH_2Cl_2, 87%; iii, MeLi, diethyl ether, −78 °C, 95%; iv, allyl bromide, NaH, THF, DMF, 63%; v, *hv*, O_2, diethyl ether, 90%; vi, Bu^n_4NF, THF, 98%; vii, CBr_4, PPh_3, CH_2Cl_2, 0 °C; viii, $NaCH(CO_2Me)_2$, MeOH, 45% from **10**

The more polar, major fraction **9a** (mp 148 °C) was treated with allyl bromide and NaH followed by an oxidative demetallation in air to give **10a** in 57% overall yield. Desilylation of **10a** with Bu^n_4NF, and bromination with CBr_4 and triphenylphosphine in CH_2Cl_2 at 0 °C followed by treatment with sodium dimethylmalonate gave **11a** ($[\alpha]_D^{24}$ +13.1 (*c* 1.4, THF); lit.[7] $[\alpha]_D^{21}$ +8.8 (*c* 1.4, THF)} in 45% overall yield, which had already been converted to (−)-steganone **1** by a previously reported method.[7] Spectral data of compound **11a** are consistent with those of the reported compound. The less polar, minor fraction **9b** (mp 72 °C) was treated with allyl bromide and NaH to give the desired allylated compound in < 10% yield. The low yield is probably due to steric effects, and therefore **9b** was first exposed to sunlight for de-tricarbonylchromium followed by treatment with NaH and allyl bromide to give the corresponding **10b** in 62% yield. Compound **10b** was converted to **11b** by same reaction sequence, and all spectral data of **11b** are consistent with data for an authentic sample.[7]

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Footnotes

† The optical purity of **6** was determined by HPLC with a chiral stationary phase; Chiralcel OJ-H (eluted with 10% propan-2-ol in hexane); column temperature, 40 °C; retention time: 12.4 min for (+)-isomer; 19.0 min for (−)-isomer.

‡ The axial stereochemistry of the coupling product of the chromium complex **7** with 2-hydroxymethyl-4,5-methylenedioxyphenylboronic acid instead of the 2-formyl compound was different from that of the reduction compound derived from the coupling product **8**.

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