Total Synthesis of (−)-Steganone Utilizing a Samarium(II) Iodide Promoted 8-Endo Ketyl−Olefin Cyclization

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Abstract: A six-step synthesis of (±)-steganone from commercially available 3,4,5-trimethoxybenzyl alcohol features a samarium(II) iodide promoted 8-endo ketyl−olefin coupling to install, in a single transformation, the 8,5 ring system common to the lignan lactones. The racemic synthesis provided the basis for the construction of (−)-steganone, which exploited a chromium tricarbonyl moiety both to establish and protect the desired absolute stereochemistry through key transformations, including a SmI_2-promoted 8-endo radical cyclization and two palladium-catalyzed couplings.

Introduction

The 1973 article describing the isolation of steganone and steganacin (Figure 1) marked them as biologically active targets[1] and initiated synthetic studies culminating in the first published total syntheses in 1976.[2,3] Steganone continued to be a popular target through the next two decades because some natural and synthetic congeners of steganone, steganacin, and stegane inhibit tubulin polymerization both in vitro and in vivo.[4] Structure−activity relationships of synthetic congeners and new isolates continue to be investigated on steganone analogues.[5] Many synthetic studies have been conducted on these compounds and to date, nine total syntheses of steganone have been achieved. Two syntheses,[6,7] based on significant advances in stereoselective biaryl couplings, provided a fresh perspective on the construction of (−)-steganone. Both relied on a previously developed sequence to generate the 8−5 ring system.[8] To date, no synthesis has featured a radical ring closure to form the eight-membered ring and in all cases formation of the five- and eight-membered rings is separated by several synthetic transformations. Consequently, the 8−5 ring system of steganone presented itself as an appropriate challenge with which to explore the SmI_2-promoted 8-endo ketyl−olefin radical cyclization in total synthesis.

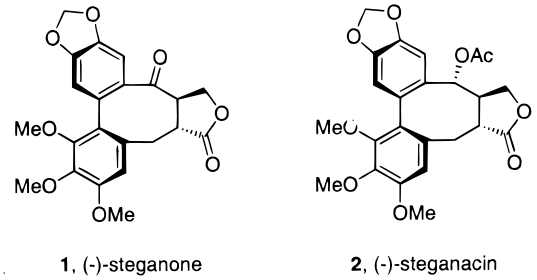

Figure 1. Cyclooctadiene lignan lactones steganone and steganacin.

Previous racemic syntheses of steganone reveal that the eight-membered ring can be generated by ring-expansion or ring-closing methods. Ring expansion from a 6,4 ring system produced by [2+2] cycloaddition to a phenanthroline unit[2,9] or an imaginative ring expansion from a 7,3 ring system[10] both yield substituted eight-membered rings requiring further elaboration to install the lactone ring of steganone. Ring-closing methods are represented by an alkylation, which generates the eight-membered ring after intermolecular biaryl coupling,[8,11] and by an intramolecular biaryl coupling,[3,12] which forms the eight-

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† University of Colorado.
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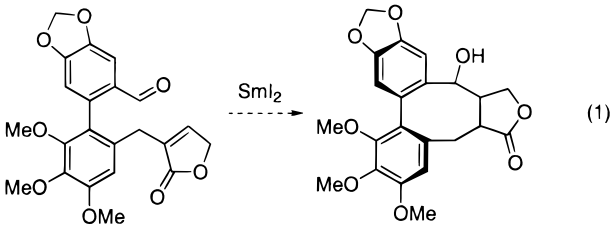
membered ring and biaryl linkage simultaneously, but without stereochemical control.

Both ring-expansion and ring-closing strategies[13] have been successfully applied to enantioenriched syntheses of steganone and/or steganacin, although the phenanthroline-based ring expansion requires a late-stage resolution.[14] A remote stereocenter can be utilized in the intramolecular and intermolecular biaryl couplings to produce the desired biaryl geometry, although in no case is the initial biaryl formation stereoselective.[15] The absolute stereochemistry of the remote stereocenter is ultimately relayed to the biaryl geometry by thermal equilibration after biaryl formation. Alternatively, a stereocontrolled, intermolecular biaryl coupling can be performed early in the synthesis, followed by eight-membered ring formation and concluding with the five-membered ring formation.[6,7] We sought to combine the advantages of a stereocontrolled biaryl coupling with the efficiency afforded by simultaneous construction of the eight- and five-membered rings of steganone utilizing a SmI_2-promoted ketyl−olefin radical cyclization protocol.

Results and Discussion

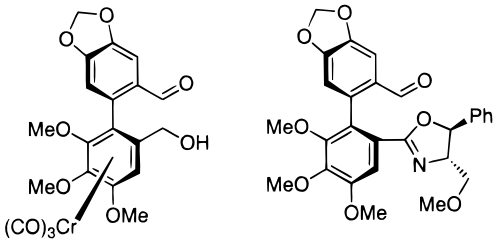
Excellent yields in SmI_2-promoted 8-endo ketyl−olefin cyclization can be attained in substrates in which the olefin component is substituted with an electron-withdrawing group.[16,17] A high degree of efficiency can be achieved when the electron-withdrawing group provides a portion of the carbon framework required in the target structure. Such is the case with butenolide **3** (eq 1), which was envisioned to undergo reductive coupling



3

with a samarium ketyl radical anion generated from an aromatic carbaldehyde moiety. To our knowledge, no coupling of this type has been described previously to generate an eight-membered ring.[18]

The skeleton common to steganone, steganacin, and stegane is well suited to the 8-endo cyclization for reasons addressed in detail throughout this contribution. First, the electronic characteristics of the aldehyde deserve comment. Often aldehydes, especially aromatic aldehydes, perform less well than ketones in reductive couplings because of the lower-lying



5, Uemura **6**, Meyers

Figure 2. Biaryl intermediates utilized in previous syntheses of (−)-steganone.

SOMO produced by their reduction.[19] In fact, there exists a correlation between the substitution pattern of the aromatic rings of aromatic carbaldehydes and their success in reductive couplings.[20] Electron-donating groups, such as the methylenedioxy substituent of **3**, favor coupling relative to simple reduction by raising the SOMO of the aldehyde. Despite the effect of these electron-donating groups on the reduction potential of the aldehyde, the notable selectivity of SmI_2 was expected to allow exclusive reduction of the aromatic aldehyde to its ketyl in the presence of the butenolide and of the product lactone.[21] Although SmI_2 rapidly reduces α,β-unsaturated esters to their saturated derivatives,[22] forcing conditions (strongly acidic or basic media) are required to reduce simple esters.[23]

The conformational bias imposed by the biaryl unit was anticipated to aid cyclization. The biaryl motif enforces folding of at least four of the eight carbons destined to be the eight-membered ring and partially counteracts the negative entropy of activation leading to slow formation of eight-membered rings, an effect evident in the success of the alkylation reaction featured in one steganone synthesis.[8,11] Alkylations forming eight-membered carbocycles are generally unsuccessful or low-yielding because intermolecular reactions are often faster. At the outset it was unknown as to whether the propensity of these biaryl systems to cyclize would be required for the SmI_2-promoted coupling between an aromatic aldehyde and α,β-unsaturated carbonyl partners, because other carbonyl/alkene pairings have shown no dependency on this feature.[24]

The novel late-stage features of the current synthesis made preliminary investigation of a racemic version prudent. Furthermore, the stereochemical outcome of the 8-endo cyclization was difficult to predict with regard to the stereocenters at the 8−5 ring juncture relative to the biaryl axis. All three stereochemical elements are potentially alterable after cyclization, but it was necessary to know which, if any, would require adjustment before proceeding with an enantioenriched synthesis. This information was used to determine the absolute stereochemistry of the biaryl juncture needed to produce the natural series.

The racemic biaryl hydroxy aldehyde **4**, which bears close resemblance to enantiopure biaryls **5** and **6** synthesized previously by Uemura[7] and Meyers (Figure 2),[6] respectively, was envisioned as an early intermediate (eq 2). To access **4**, we initially investigated an Ullmann coupling between 6-bromopip-

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(23) (a) Kamochi, Y.; Kudo, T. *Tetrahedron Lett.* **1991**, *32*, 3511. (b) Kamochi, Y.; Kudo, T. *Tetrahedron* **1992**, *48*, 4301.

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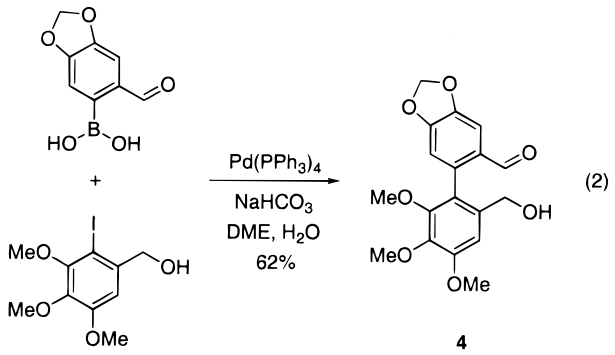
eronal and 2-iodo-3,4,5-trimethoxybenzyl alcohol protected as a TBDMS ether. Related reactions between 6-bromopiperonal and a bis(orthosubstituted) aryl iodide produced acceptable yields of a biaryl that was carried through to steganone by Robin and co-workers.[11a,d,15a] Using 2 equiv of the appropriate aryl iodide led to a disappointing 28% yield of biaryl **4** protected as the TBDMS ether based on 6-bromopiperonal. Although protection of the alcohol was required because free hydroxyl groups poison the Ullmann coupling, the easily removable TBDMS ether was capable of withstanding the 230 °C reaction temperature. However, the Ullmann coupling works best with a large excess (2−5 equiv) of the aryl iodide that is generally unrecoverable because of extensive homocoupling and reduction to the parent arene.

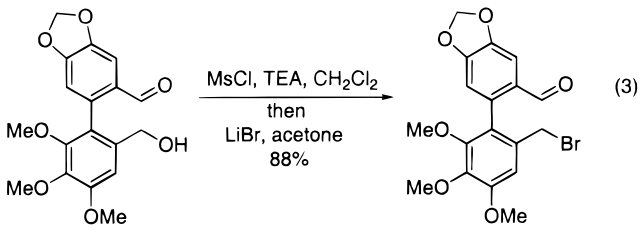
Although quick and operationally simple, the poor yields in the Ullmann coupling led us to explore a Suzuki coupling. Arylboronic acids and their esters perform well in palladium-[25] and nickel-catalyzed biaryl syntheses and are generally the best choice for the organometallic partner when sterically congested biaryls are desired.[26] For reasons that will be made clear in the ensuing discussion, we chose to convert 6-bromopiperonal into the arylboronic acid derivative. As is generally noted with arylboronic acids substituted with electron-withdrawing groups, the standard Suzuki conditions[27] employing aqueous Na_2CO_3 as a base led to extensive deboronation at the expense of coupling yields. Premature destruction of the carbon−boron bond can be slowed by utilizing milder bases[28] or nonaqueous conditions.[29] With $NaHCO_3$ as a base, Suzuki coupling proceeded slowly to the desired biaryl **4** in moderate yield (eq 2).



(2)

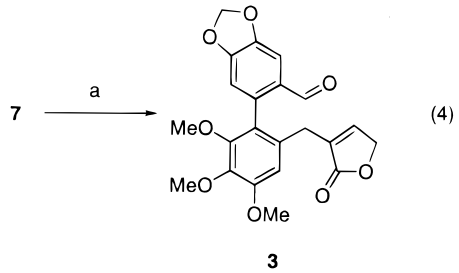
4

Conversion of benzyl alcohol **4** to the benzyl bromide **7** utilizing MsCl and Et_3N in CH_2Cl_2 followed by direct conversion of the resulting chloride to the bromide by the addition of excess LiBr in acetone provided **7**, which contained a useful handle to install the butenolide of **3** (eq 3). Many syntheses of 3-substituted furanones[30] require multiple transformations including condensations, alkylations, and/or retro-aldol transformations. Although butenolide **3** could be accessed by alkylation of the α-phenylselenyl-γ-butyrolactone, we focused on a palladium-catalyzed coupling with 3-tributylstannyl-(5*H*)-furan-2-one (eq 4).[31] This route, utilizing a stannylated butenolide, required no protection/deprotection sequence and resulted in no regiochemical ambiguity of the double bond. Consequently, it would likely function in the asymmetric version of the synthesis. In the event, desulfurative stannylation of the corresponding phenylthiobutenolide produced 3-tributylstannyl-(5*H*)-furan-2-one, which was known to undergo Pd-catalyzed couplings with aryl iodides.[31] Carbon−carbon bond formation occurred between the stannylated furanone and benzyl bromide **7** at 80 °C when $Pd_2(dba)_3$/trifurylphosphine (Pd:L 1:2) was used as a catalyst.[32] A fully conjugated isomer, formed by a thermal- or palladium-catalyzed mechanism, proved to be a minor component in the reaction mixture.



(3)

4 **7**



(4)

3

(a) 3-(tributylstannyl)-(*5H*)-furan-2-one, $Pd_2(dba)_3$, trifurylphosphine, DMA, 80 °C, 83%.

Treatment of substrate **3** with 2.2 equiv of SmI_2 in THF/HMPA at 0 °C using *t*-BuOH as a proton source gave two diastereomeric cyclized products isolated in a 3:1 ratio (Scheme 1). The minor diastereomer, epipicrosteganol **10**,[33] was identified by comparison of its spectral data to that reported in the literature, as five of the eight possible diastereomers are known. The major diastereomer was previously unknown. Both diastereomers were of the picro series (8−5 cis ring system), because neither were oxidized to the known trans compounds, steganone or isosteganone, by Dess−Martin periodinane. X-ray crystallographic data generated from the major diastereomer also support this assignment (Figure 3). Following the nomenclature for these systems, the major diastereomer **9** is called isopicrosteganol. The synthesis of isopicrosteganol from an epimer was attempted previously for structure activity determination because one member of the picro series had been demonstrated to be as potent as steganacin in in vitro studies.[4a]

In both intermediates (e.g., **8**), the oxygen of the reacting ketyl in the intermediates lies pseudoequatorially and the stereochemistry at the adjacent stereocenter is set by attack on either of the two diastereotopic faces of the butenolide (Scheme

(25) Benbow, J. W.; Martinez, B. L. *Tetrahedron Lett.* **1996**, *37*, 8829.
(26) For a review see: Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. See also: Johnson, M. G.; Foglesong, R. J. *Tetrahedron Lett.* **1997**, *38*, 7001.
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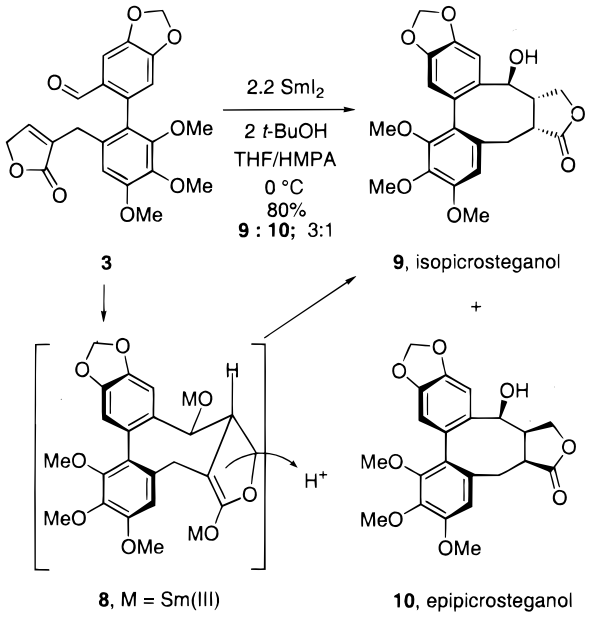
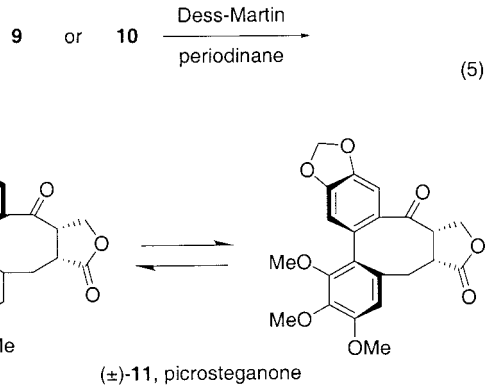
(33) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Chem. Pharm. Bull.* **1986**, *34*, 1501.

Scheme 1



1, only one isomer shown). Protonation from the convex side of the samarium(III) enolates yields the observed products.

Oxidation of **9** *or* **10** surprisingly provided an inseparable pair of diastereomeric ketones (eq 5). Neither ketone matched the spectral data reported for steganone or isosteganone (8−5 trans diastereomers), so we concluded that **11**, picrosteganone, exists as a mixture of atropisomers.



The remaining transformation of picrosteganone **11** to steganone utilized a well-established driving force.[34] Steganone, the target natural product, is the only diastereomer of the four possible that allows the ketone carbonyl to achieve planarity with the nearby arene ring as evidenced by its carbonyl stretching frequency [1667 cm^{-1} versus that of isosteganone (1707 cm^{-1})] and by the chemical shift of the aromatic proton ortho to the ketone (δ 7.53 ppm for steganone versus δ 6.71 ppm for isosteganone).[34] This thermodynamic driving force has been frequently used in total syntheses of steganone. Isosteganone was reported to be converted to steganone by either of the following two conditions: (1) by heating to reflux a solution of isosteganone in xylenes or (2) by heating to reflux a solution of isosteganone in MeOH or EtOH in the presence of NaOAc (eq 6). Only the first method has been utilized to convert enantioenriched isosteganone into enantioenriched steganone in

(34) Kende, A. S.; Liebeskind, L. S.; Kubiak, C.; Eisenberg, R. *J. Am. Chem. Soc.* **1976**, *98*, 6389.

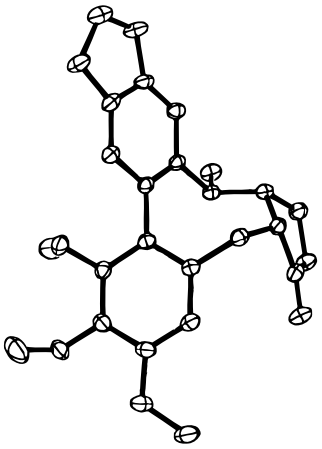
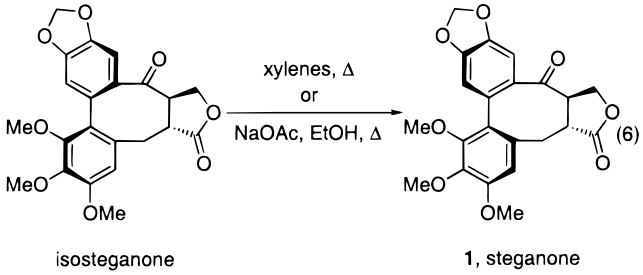
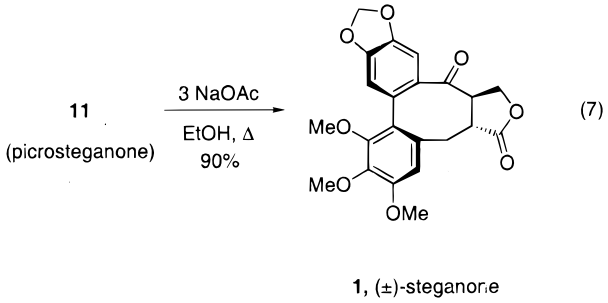


Figure 3. X-ray crystal structure of isopicrosteganol.

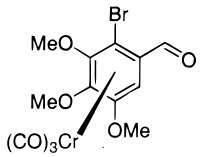
which the sense of absolute stereochemistry of the stereocenter α to the lactone carbonyl was retained.[15a]



Picrosteganone **11**, when heated to reflux in xylenes, did not yield steganone and led only to recovered starting material. By contrast, base-promoted conditions (NaOAc in EtOH) provided steganone from picrosteganone in 90% yield (eq 7). The



discrepancy between the behavior of picrosteganone and isosteganone under the equilibration conditions noted above may be explained by the requirement of picrosteganone to undergo enolate formation. The mechanism proposed for the facile isomerization of isosteganone to steganone under both sets of conditions involves a retro-Michael reaction followed by Michael reaction of the resultant carboxylic acid.[34] It is possible that the observed isomerization of isosteganone to steganone in hot xylenes involves only a simple thermal-promoted rotation about the biaryl axis, which is known to occur in a related system[6] and is facilitated by the presence of the sp^2-hybridized ortho carbon. For picrosteganone, rotation about the biaryl axis yields only the starting material: the two possible atropisomers of the picro series. Consequently, the base-promoted conditions are required and the significantly lower temperature at which isomerization occurs suggests that the retro-Michael/Michael manifold may be operating. Formation of a sodium enolate, followed by β-elimination to give the sodium carboxylate,



12

Figure 4. Uemura's enantiopure chromium tricarbonyl complex **12**.

produces a common intermediate enone from picrosteganone or isosteganone.

With this information in hand, we were prepared for the enantioselective synthesis of steganone via either of two routes for generating an enantioenriched biaryl intermediate using literature precedent.[6,7,35] We were especially intrigued by the opportunities presented by Uemura's method.[7] Although sensitive to oxidation, Cr^0 arene complexes were known to perform well in the reducing environment of SmI_2.[36] In some, but not all, cases the complexation of the chromium results in attack of the arene ring by radical intermediates. In others, the arene is preserved and the chromium moiety serves only as a tool for controlling stereochemistry.[35] It was in the second capacity that we envisioned exploiting the chromium tricarbonyl unit.

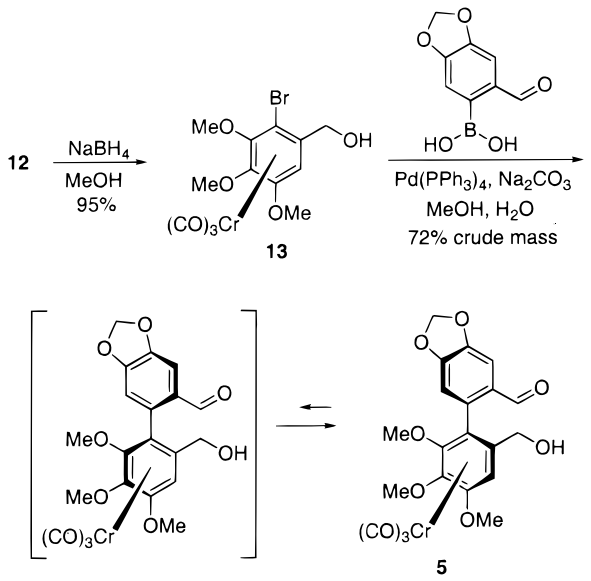
The difficulties associated with forming the biaryl unit as a single atropisomer early in the synthesis lie in the arene-substitution pattern. The thermal isomerization barrier for a steganone precursor that carries only three ortho substituents is highly sensitive to the exact identity of those substituents. When one of the three possible groups (e.g., a formyl moiety) adds only a small amount to the inversion barrier and a second substituent is also relatively small (e.g., a methoxy group), the barrier to inversion renders the biaryl stereochemically labile even at 0 °C.[35] At least one of three labile intermediates (including **6**) in the Meyers synthesis of steganone resulted in some loss of biaryl stereochemistry.[6] Even with careful handling, the enantiomeric excess of the product did not reflect the initial success of the biaryl formation.

With the chromium−arene complex intact in structure **5**, however, the lability of the biaryl system would pose no danger owing to its propensity to exist as the desired diastereomer. In biaryl **5**, the formyl group would position itself distal to the chromium tricarbonyl moiety. At best, the chromium-complexed biaryl **5** could be converted to a substrate for the SmI_2-promoted reductive coupling and carried through the synthesis of the 8−5 ring system. At worst, the SmI_2-based synthesis would involve only one labile intermediate. The potential for the chromium to serve as both a tool for forming and for protecting the desired biaryl atropisomer led us to explore this route.

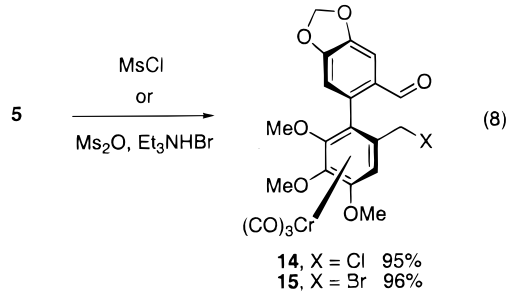
Construction of chromium-complexed biaryl **5** proceeded by Uemura's method,[7] generating enantiomerically pure chromium−carbonyl complex **12** in five steps from 3,4,5-trimethoxy benzaldehyde (Figure 4).

Reduction of benzaldehyde **12** with $NaBH_4$ proceeded smoothly to produce alcohol **13**, which was successfully coupled with 2-formyl-4,5-methylenedioxyboronic acid in the presence of $Pd(PPh_3)_4$ and aqueous Na_2CO_3 (Scheme 2). The observed diastereomer **5** is likely produced from the other possible diastereomer, itself the direct product of the Suzuki coupling. Rotation about the biaryl axis under the reaction conditions would provide the desired diastereomer. Some decomplexation

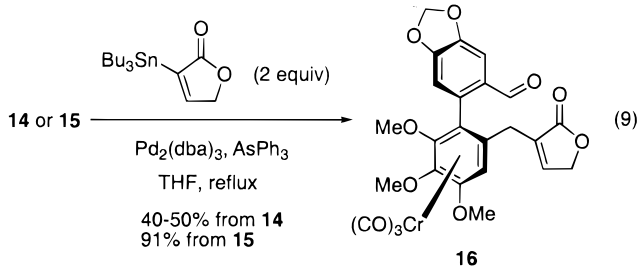
Scheme 2



of biaryl **5** occurred under the reaction conditions and during purification, so the alcohol was converted directly to the corresponding benzyl chloride **14** or bromide **15**, either of which could be purified and stored without incident. In contrast to the uncomplexed case, the synthesis of bromide **15** required the use of methanesulfonic anhydride to avoid formation of an intermediate chloride **14**, which could not be separated from or converted to bromide **15** by treatment with excess LiBr (eq 8).



Both halides **14** and **15** were successfully converted to the desired chromium-complexed substrate **16** for SmI_2-promoted coupling (eq 9). However, the more reactive benzyl bromide



15 provided superior yields. Optimized conditions singled out the weakly coordinating $AsPh_3$ as the ligand of choice for the coupling. The facility with which oxidative addition occurs to these chromium-complexed benzyl halides using a relatively electron poor palladium complex bears contrast to previously reported descriptions of palladium couplings with benzyl halides,[37] and to the one described in the present text that require

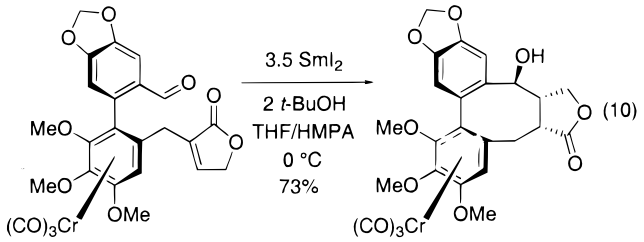
(35) Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 1375.

(36) (a) Schmaltz, H.-G.; Siegel, S.; Schwarz, A. *Tetrahedron Lett.* **1996**, *37*, 2947. (b) Taniguchi, N.; Hata, T.; Uemura, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1232.

(37) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.

a highly polar, coordinating solvent such as DMF, DMA, or NMP to facilitate oxidative addition. This high-yielding coupling utilizing the chromium-complexed benzyl halides represents a new application of the special reactivity at the benzylic position of chromium-complexed arenes.[38]

Unlike the SmI_2-promoted coupling performed on the uncomplexed, racemic substrate **3** that afforded diastereomers **9** and **10**, the chromium-complexed version **16** yielded a single diastereomer in 65−75% yield with the chromium arene moiety intact (eq 10). The relative stereochemistry between biaryl and



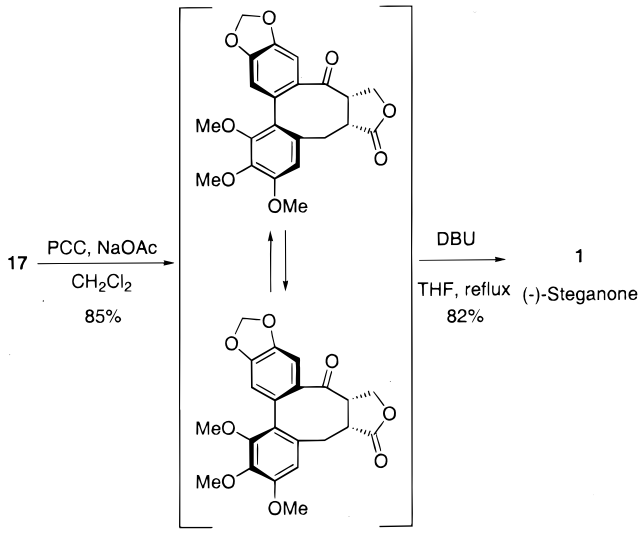
16 **17**

ring juncture stereocenters in the chromium-complexed product **17** fortunately corresponded to the major diastereomer **9** observed in the racemic synthesis. The conditions differed slightly from the racemic case, as a larger excess of SmI_2 was required.

Oxidation of the chromium-complexed isopicrosteganol **17** using PCC buffered with NaOAc in CH_2Cl_2 accomplished the deprotection/decomplexation reaction and the oxidation of the secondary carbinol to the corresponding ketone in one pot (Scheme 3). The Dess−Martin reagent used in the racemic synthesis also performed these two transformations, but generated an impurity that was not easily removed from the desired ketone **11**. As expected, oxidation to the ketone produced a 2:1 mixture of atropisomers, in which the absolute stereochemical information contained in alcohol **17** was retained only at the lactone ring juncture stereocenters in ketone **11**.

At this point, equilibration of the stereocenter α to the ketone carbonyl of enantiopure **11** was required to produce the desired trans stereochemistry at the ring juncture and the driving force to correct the stereochemistry of the biaryl. Although enantiomerically pure isosteganone had been previously converted to steganone by simply heating neat or in xylenes,[15a] this process required only rotation about the biaryl bond. Furthermore, the use of NaOAc in boiling EtOH had been employed only in the racemic series, and thus the effect of its application on the various enantiomerically enriched isomers of steganone was unknown. In fact, use of NaOAc in boiling EtOH to isomerize enantioenriched **11** led to an 87/13 mixture of (−)-steganone to (+)-steganone by chiral HPLC.[39] This loss of enantiomeric excess in the final product signaled a partial equilibration of the stereocenter α to the lactone carbonyl. The absolute stereochemistry at this center is set relative to the biaryl during the SmI_2-promoted cyclization and is ultimately necessary to relay all of the stereochemical information back to the remaining stereocenters in the final equilibration step. Fortunately, utilizing

Scheme 3



11

DBU in THF heated at reflux[40] afforded (−)-steganone from enantiopure picrosteganone **11** in 82% yield with an optical purity >99%.[39]

Conclusions

The total synthesis of steganone via an 8-endo radical cyclization allows direct construction of an 8−5 fused ring system without undue manipulation of functionality and translates to a high degree of synthetic efficiency. The racemic synthesis of steganone entails only six linear steps from commercially available compounds. Construction of (−)-steganone exploits the chromium tricarbonyl moiety both to establish and protect the desired sense of absolute stereochemistry through key transformations, including a SmI_2-promoted 8-endo radical cyclization and two palladium-catalyzed couplings. A new means of equilibration from picrosteganone to steganone suitable for the enantiomeric series of compounds has been introduced. Finally, this synthesis of steganone proceeds via a new compound, isopicrosteganol, whose synthesis had been attempted previously for structure−activity determination. There is significant interest in this latter compound because of its potential biological activity.

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Supporting Information Available: Full experimental details, ^1H and ^{13}C NMR spectra for **1** and **14**−**17** and X-ray structural data for **9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(38) Merlic, C. A.; Walsh, J. C.; Tantillo, D. J.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 3596.

(39) This ratio was determined by comparing the HPLC chromatogram of our compound with the chromatogram of racemic steganone. Conditions: Chiralcel OD, hexanes/EtOH 95/5, 2 mL/min. (−)-Steganone: t_R = 74 min. (+)-Steganone: t_R = 47 min.

(40) Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625.