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Total synthesis of haouamine A: the indeno-tetrahydropyridine core

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Dedicated to Professor Larry Overman for his pioneering work in organic chemistry

ABSTRACT

A full account of synthetic efforts toward the indeno-tetrahydropyridine core of haouamine A is presented. Initial failed strategies led to the unexpected discovery of a mild abnormal Chichibabin pyridine synthesis and provided knowledge and inspiration for the development of a cascade annulation that has enabled rapid and scalable access to the core in either racemic or enantiopure form.

1. Introduction

The haouamines are a structurally unique and intriguing class of natural products that originate from the ascidian *Aplidium haouarianum* collected off the coast of Tarifa in southern Spain. Zubía and co-workers[1] isolated haouamines A and B (**1** and **2**, Fig. 1) in 2003 and elucidated their structures using NMR and X-ray crystallographic analysis. In addition to displaying such an unprecedented molecular architecture, the authors showed haouamine A to have high and selective cytotoxic activity against HT-29 human colon carcinoma (IC_{50}=0.1 μg/mL), while haouamine B exhibited milder cytotoxicity against MS-1 mice endothelial cells (IC_{50}=5 μg/mL).

As seen in Figure 1, haouamine A (**1**) contains a total of seven cycles with an atypical *meta*-hydroxylation pattern on its four phenols. The core is an indeno-tetrahydropyridine, which has an imbedded all-carbon quaternary center at C26. Fused onto this is the hallmark structural feature of these natural products: a 3-aza-[7]-paracyclophane macrocycle (containing a bridgehead olefin) that is strained to such a point that one of its aromatic rings is bent out of planarity into a boat-like conformation. As seen in Figure 1, the two planes made from C9–C10–C14 and C11–C12–C13 are bent out of the C10–C11–C13–C14 plane by 13.63° and 13.91°, respectively. Haouamine B (**2**), isolated in a far smaller quantity than **1**, (and characterized as the peracetyl derivative due to the instability of the pentaphenol, possibly due to a greater propensity for oxidation in **2** as compared to **1**) differs in the presence of an additional *meta*-hydroxyl group at C21 of its westernmost arene. Both molecules exist in solution as an inseparable mixture of two interconverting isomers that is most likely due to slowed pyramidal inversion at nitrogen coupled with conformational reorganization of the tetrahydropyridine.[2,32]

These various features lay down a challenging synthetic gauntlet that was successfully navigated by our group in the case of haouamine A, first with a racemic synthesis[3] and later with an

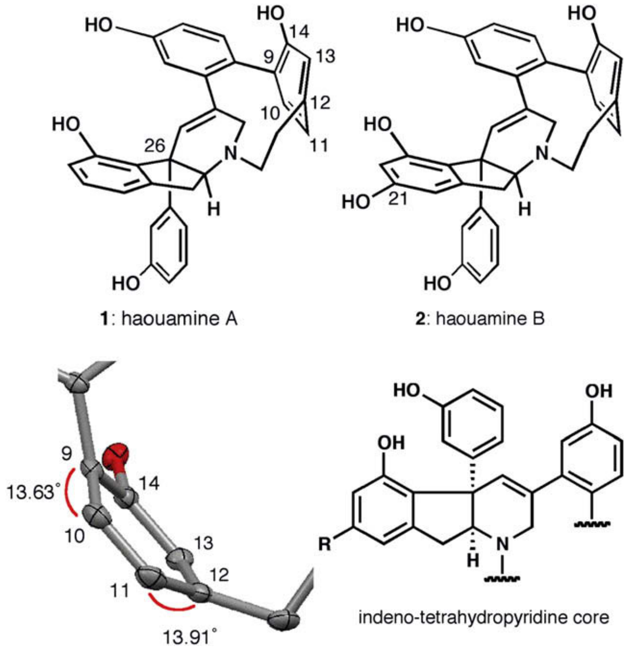

Figure 1. Haouamines A and B, their *boat* arene, and the indeno-tetrahydropyridine core.

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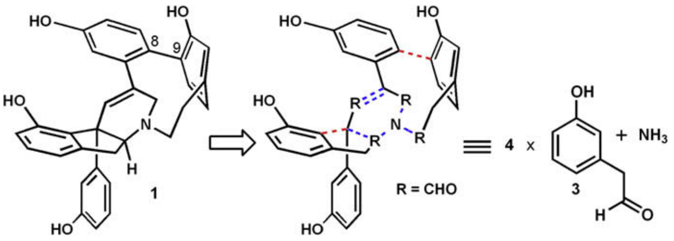
enantioselective version.[4] In addition to this work, the haouamine alkaloids have been pursued by at least seven other research groups: Rawal[5] and Trauner[6] have both reported routes to the core indeno-tetrahydropyridine, Wipf[7] has synthesized a model aza-paracyclophane, and Weinreb,[8] Fürstner,[9] and Ishibashi[10] have all completed a formal synthesis of haouamine A (**1**). Poupon[11] had reported initial progress toward a biomimetic synthesis of the haouamines following a similar biosynthetic hypothesis to our own. In this article, full details of efforts toward the indeno-tetrahydropyridine core of these molecules are reported, culminating in a concise and scalable route.

2. Results and discussion

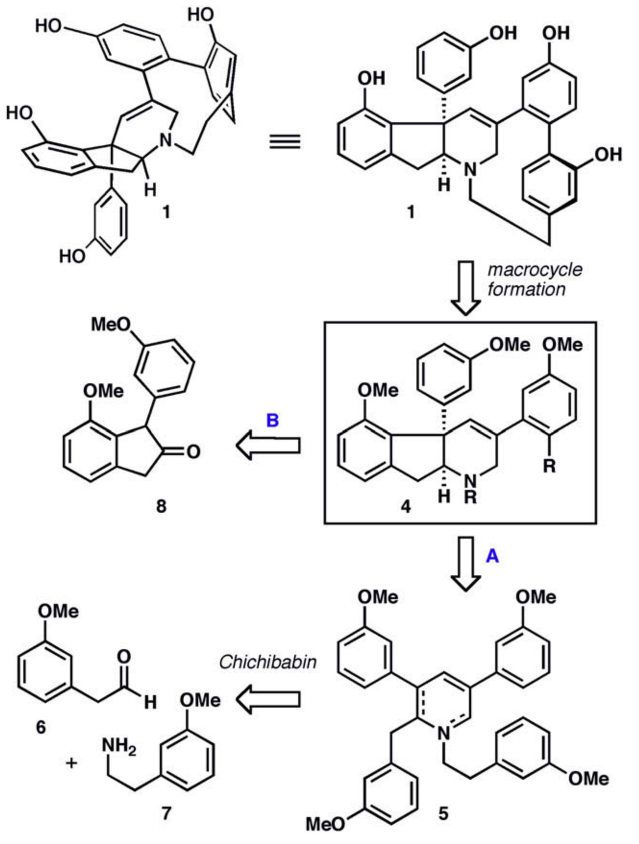
2.1. Retrosynthetic ruminations and initial strategies

From the outset of this project the question of the biological origin of these fascinating molecules was present, particularly in the context of trying to devise a feasible biomimetic synthesis. It is an intriguing notion that the entire haouamine skeleton can be traced back to 4 equiv of *meta*-hydroxyphenylacetaldehyde **3** and 1 equiv of ammonia through five condensations and two oxidative carbon–carbon bond forming events (Scheme 1). Of particular note in this sequence is the oxidative phenol coupling to close the paracyclophane between C8 and C9, for intermediates wherein one or both of these carbons is sp^3-hybridized appear to be considerably less strained than the bent arene-containing macrocycle. It is possible that this stepwise approach facilitates the bending of an aromatic ring during biosynthesis.

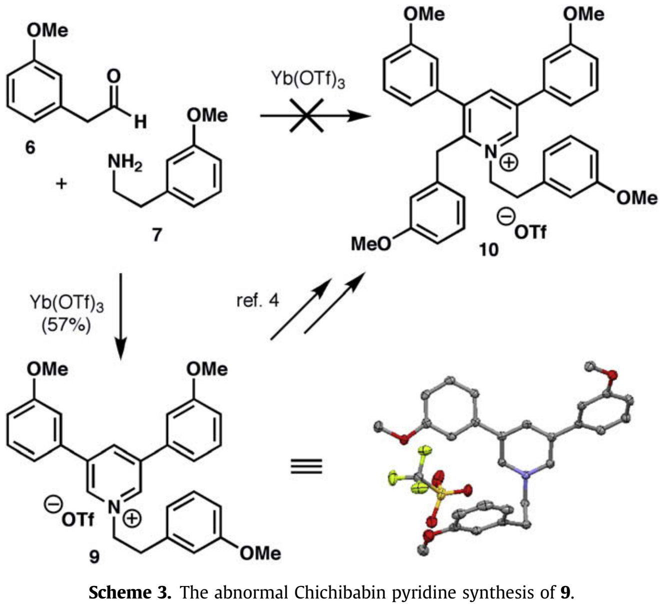


Scheme 1. Original biosynthetic proposal.

Such a phenylacetaldehyde-based origin had been proposed and studied by our group previously,[4] and this guided some of the initial, ultimately non-productive, strategies. A general retrosynthetic blueprint is outlined in Scheme 2. Since the paracyclophane macrocycle was anticipated to pose a significant challenge, its installation was deferred until the final steps. Thus, construction of an indeno-tetrahydropyridine of generalized structure **4** was the first goal. One strategy (pathway A) involved the tetrasubstituted pyridine **5** of unspecified oxidation state as the precursor to **4**. A pyridinium such as **5** was identified as the product of a Chichibabin pyridine synthesis[12] of *meta*-methoxyphenylacetaldehyde **6** with amino anisole **7**. The prospect of employing such a Chichibabin pyridine synthesis was additionally intriguing as it would allow *in a single step* the introduction of all of the atoms present in **1**. An alternate strategy (pathway B) was envisioned wherein **4** would arise from indanone **8** via three independent events: (1) installation of the all-carbon quaternary center, (2) introduction of the nitrogen, and (3) formation of the tetrahydropyridine ring.



Scheme 2. Haouamine A retrosynthetic analysis.

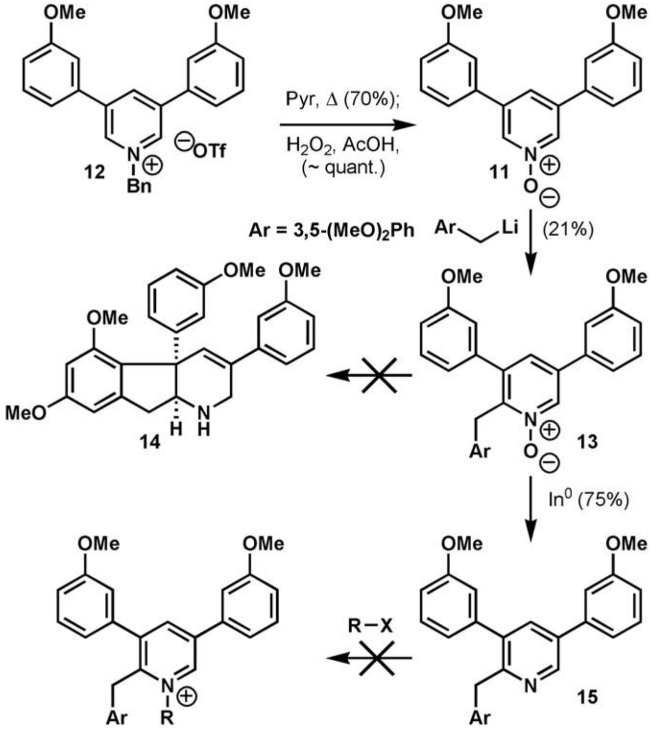


Scheme 3. The abnormal Chichibabin pyridine synthesis of **9**.

As reported previously,[4] Chichibabin pyridine syntheses of arylacetaldehydes do not follow the expected pathway but rather occur with the curious loss of an equivalent of benzaldehyde. These substrates thus generate not the expected 2-benzyl-3,5-diarylpyridiniums from such a reaction, but instead 3,5-diarylpyridiniums. This transformation is shown for the system most relevant to haouamine A in Scheme 3. When **6** and **7** are allowed to react in the presence of ytterbium triflate the exclusive product is pyridinium **9** as opposed to the previously reported[11] erroneous structure **10**. Confirmation of this assignment was obtained from the crystal structure of **9** and its subsequent transformation into **10**.

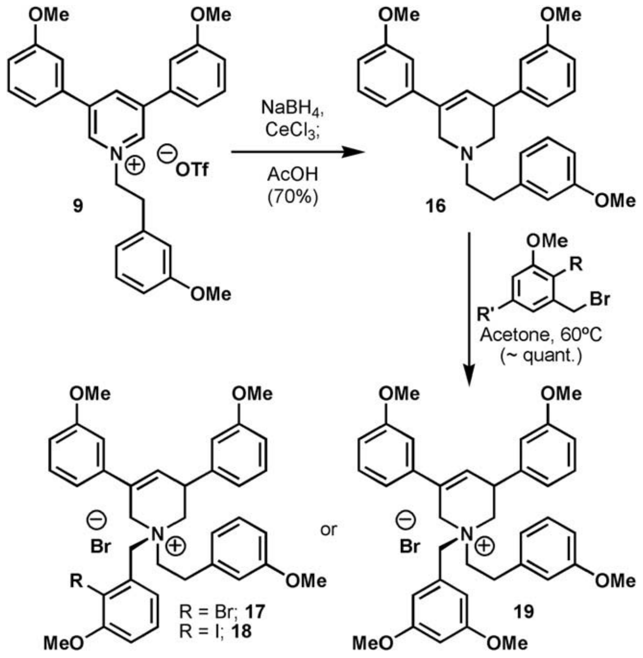
This type of abnormal Chichibabin pyridine synthesis with phenylacetaldehydes has been known in the literature since the 1950s, however the harsh conditions and low yields have rendered it essentially useless. For example, Eliel[13] reported that heating an ammonia-saturated solution of phenylacetaldehyde in ethanol to 235 °C at 1150 p.s.i. for 6 h yields 13.1% 3,5-diphenylpyridine, and later Eckroth[14] showed that the lithium aluminum hydride reduction of *meta*-methoxyphenylacetamide yields 17% 3,5-bis(*meta*-methoxyphenyl)pyridine. More recently, d'Ischia[15] reported that phenylalanine and tyrosine derivatives could be cyclotrimerized to 3,5-diarylpyridines in 3–15% isolated yield upon exposure to excess hypochlorous acid. This version of the reaction can be performed with mild reagents in either water or a water–1,4-dioxane mixture (when the starting aldehyde is a solid) at room temperature without an inert atmosphere and generally takes 18–24 h for completion. The largest drawback of this methodology is the typical instability of the phenylacetaldehyde reactants. They are prone to polymerization and should be made (usually by IBX or DMP oxidation of the alcohol) and used without prolonged storage.

As the production of **9** gave rise to none of the anticipated full haouamine skeleton **10**, other methods were sought to introduce the requisite 2-benzyl moiety. After some difficulty with attempts to add benzyl organometallic reagents into the *N*-alkyl pyridinium substrate, it was discovered that the addition of 3,5-dimethoxybenzyllithium to 3,5-diarylpyridine-*N*-oxide **11** (synthesized from the Chichibabin product **12** by removal of the *N*-benzyl by heating in pyridine and *N*-oxide formation) produced the benzyl-containing pyridine-*N*-oxide **13** with unanticipated retention of the *N*-oxide (Scheme 4). Unfortunately, however, attempts to either directly or indirectly convert this compound into the haouamine B indeno-tetrahydropyridine core **14** were unsuccessful. Also, reduction of the *N*-oxide to the free pyridine **15** resulted in a compound that was extremely averse to alkylation (no reaction was observed upon heating in neat iodomethane).



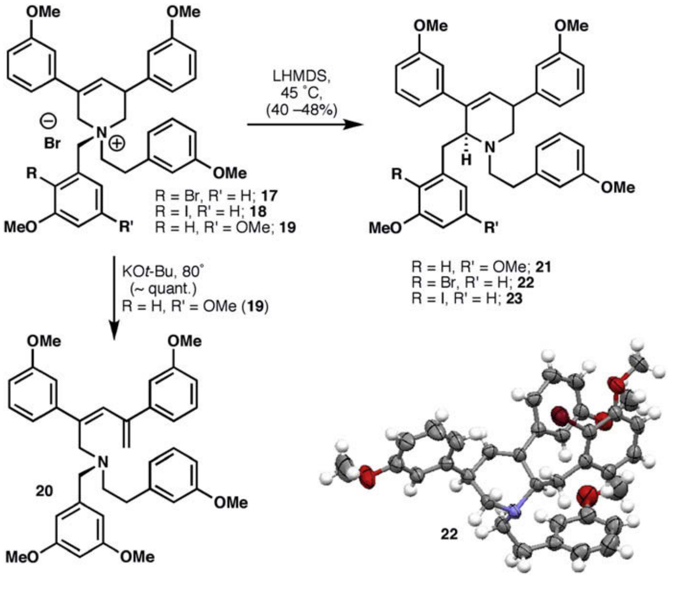
Scheme 4. Attempted use of a pyridine *N*-oxide.

A strategy to introduce the 2-benzyl group via a Stevens rearrangement[16] was next pursued in order to install it with the pyridine at a lower oxidation state (Scheme 5). Reduction of abnormal Chichibabin product **9** with sodium borohydride and acetic acid in the presence of cerium trichloride gave tetrahydropyridine **16**. Nitrogen alkylation could then be performed with a variety of benzyl electrophiles containing 2-bromo-3-methoxy, 2-iodo-3-methoxy, and 3,5-dimethoxy substitution to provide quaternary ammonium salts **17**, **18**, and **19**, respectively, as mixtures of diastereomers.



Scheme 5. Preparation of Stevens rearrangement substrates.

It was anticipated that a Stevens rearrangement would shift the *N*-benzyl substituent to the 2-position of the tetrahydropyridine, placing it proximal to the alkene for quaternary center formation. An initial attempt at this reaction (Scheme 6) was performed with haouamine B precursor **19**. Exposure to potassium *tert*-butoxide at 80 °C in toluene resulted in an instantaneous and quantitative Hofmann elimination[17] to diene **20** via deprotonation of the allylic–benzylic position of **19**. Altering these conditions to the rapid addition of 3 equiv of lithium hexamethyldisilazide to the substrate in a 45 °C solution of THF was found to produce the desired product

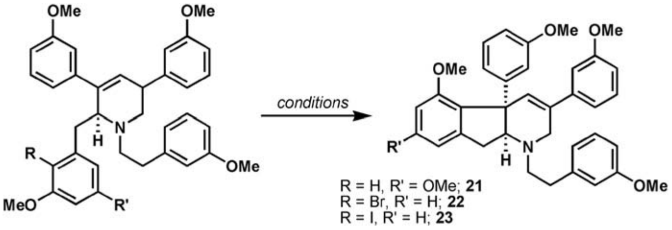


Scheme 6. Failure and success in the Stevens rearrangement.

21 as well as the Hofmann product **20** in an approximate 1:1 ratio. These conditions proved viable for the bromo- and iodo-substrates **17** and **18** as well, providing access to additional compounds **22** and **23** in which it was hoped the all-carbon quaternary center could be formed. X-ray crystallographic analysis of **22** confirmed the assigned structure of these products.

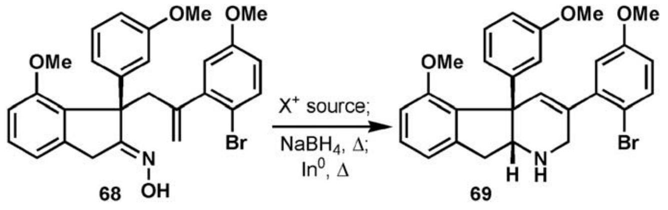
With compounds **21** to **23** in hand, attention was focused on forming the quaternary center at C26. A number of conditions were screened in order to effect this transformation, which ultimately proved unachievable (Table 1). Lewis and Brønsted acid-mediated Friedel–Crafts chemistry as well as oxidative Heck conditions were attempted on substrate **21** (Table 2, entries 1–7) leading to either recovered starting material or intractable mixtures. Arylbromide substrate **22** was submitted to a variety of Heck conditions (entries 8–19) including those of Fu[18] and Herrmann[19] as well as highly active Ni(0). In no instance was oxidative addition observed, with all conditions leading to recovered starting material. Radical conditions with tributyltin hydride resulted in loss of the bromide (entry 20), but none of the desired cyclization was observed. It was hoped that the iodoaryl substrate **23** would lead to more facile insertion of palladium(0), however standard conditions all led to recovered starting material (entries 22–25).

Table 1
Conditions attempted to form the C26 quaternary center

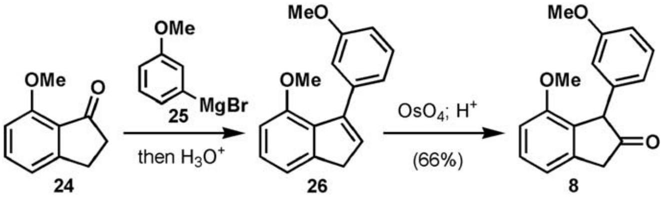


Entry	Substrate (Ar)	Conditions	Results
1	**21**	$Pd(OAc)_2$, AcOH, O_2	SM
2	**21**	$Pd(OAc)_2$, AcOH, Δ	decomp.
3	**21**	Montmorillonite K10	SM
4	**21**	*p*-TsOH, Δ	SM
5	**21**	2.5 N HCl/THF	SM
6	**21**	H_2SO_4/THF	SM
7	**21**	$AuCl_3$/AgOTf	SM
8	**22**	$Pd(OAc)_2$, AcOH, Et_3N	SM
9	**22**	$Pd(OAc)_2$, dppp, Et_3N	SM
10	**22**	$Pd(OAc)_2$, dppp, Ag_2CO_3	SM
11	**22**	$Pd(OAc)_2$, dppp, Ag_2CO_3	SM
12	**22**	$Pd(OAc)_2$, K_2CO_3, TBABr	SM
13	**22**	$Pd(PPh_3)_4$, Et_3N	SM
14	**22**	$Pd(PPh_3)_4$, DABCO	SM
15	**22**	$Pd_2(dba)_3$, $P(t\text{-}Bu)_3$, Cy_2NMe	SM
16	**22**	$Ni(COD)_2$, NaI	SM
17	**22**	Herrmann, NaOAc	SM
18	**22**	Herrmann, Bu_4NOAc	SM
19	**22**	$Pd_2(dba)_3$, Ag_3PO_4	SM
20	**22**	Bu_3SnH, AIBN	[H]
21	**22**	$(TMS)_3SiH$, AIBN	SM
22	**23**	$Pd(OAc)_2$, PPh_3, Et_3N	SM
23	**23**	$Pd(OAc)_2$, K_2CO_3, TBACl	SM
24	**23**	Herrmann, NaOAc	SM
25	**23**	$Pd(TFA)_2$, Et_3N	SM

Table 2
Optimization of cascade substrate **68**



Entry	X^+ source (equiv)	In^0 (equiv)	% Yield
1	NIS	—	—
2	*t*-BuOCl	2.0	—
3	BDCP	—	—
4	NBA (1.1)	5.0	23%
5	NBA (1.1)	2.0	33%
6	NBS (1.1)	2.0	37%
7	TBCHD (1.1)	2.0	43%
8	TBCHD (2.2)	2.0	57%

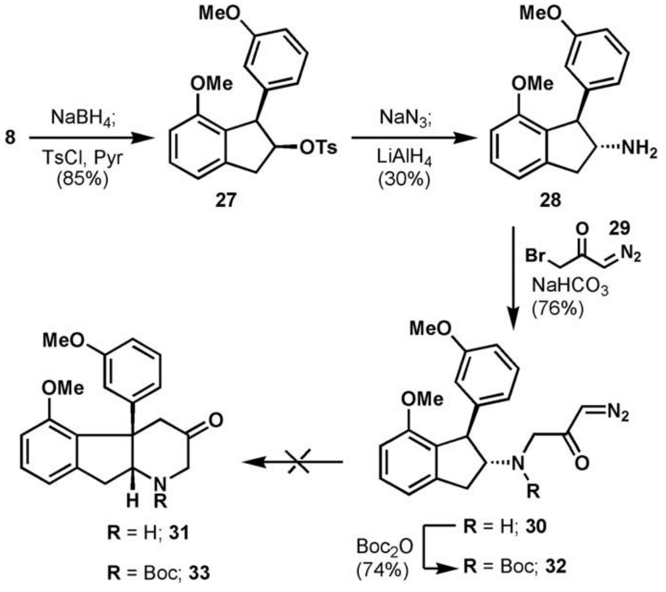


Scheme 7. Preparation of starting ketone **8**.

2.2. Initial indanone-based strategies to the core

In order to investigate the alternative strategy shown in Scheme 2 (pathway B) wherein tetrahydropyridine construction is delayed until after introduction of the quaternary center, **8** was prepared as shown in Scheme 7. 7-Methoxyindanone **24** (commercially available or readily synthesized on large scale from phenol by a tandem Fries/Friedel–Crafts reaction with 3-chloropropionoyl chloride followed by methylation[20]) was treated with 3-methoxyphenylmagnesium bromide **25** to give, following acid-mediated dehydration, aryl indene **26**. Dihydroxylation and a second acid-mediated dehydration provided the key starting ketone **8** on 40 g-scale.

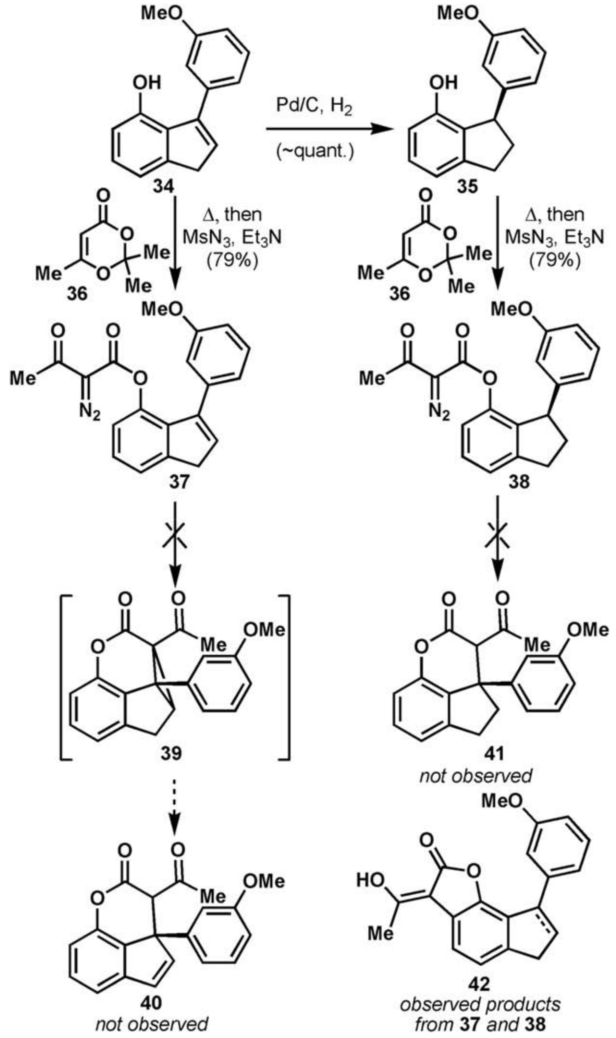
The next two approaches sought to utilize diazocarbonyl C–H insertion methodology to install the all-carbon quaternary center.[21] The first approach began with **8** (Scheme 8), which was reduced with sodium borohydride to the *syn* aryl secondary alcohol and activated as the tosylate **27** and displaced with sodium azide to install the required nitrogen. Lithium aluminum hydride reduction



Scheme 8. Failed diazocarbonyl chemistry 1.

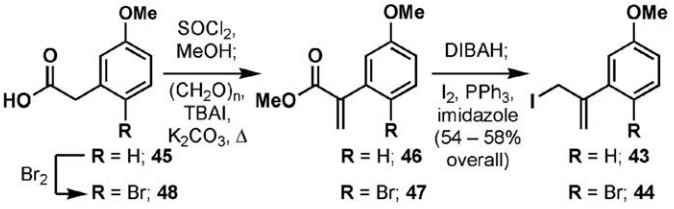
produced amine **28** that could be alkylated with 1-bromo-3-diazoacetone **29** to give diazoketone **30**, an appropriate substrate for a potential metal-mediated C–H insertion. Unfortunately, all attempts to synthesize piperidinone **31** via reaction of **30** with various rhodium or copper catalysts failed to produce detectable amounts, possibly due to competitive insertion alpha to the heteroatom or into the benzylic methylene group. Protection of the nitrogen as its *N*-Boc derivative **32** did not solve these problems (**33** was not observed in the reaction mixture).

Attention then turned to utilization of a phenol-tethered diazocarbonyl (Scheme 9) beginning initially from free phenol containing aryl indene **34** (synthesized analogously to **26** via temporary TBS protection of the phenol). Palladium on carbon hydrogenation produced aryl indane **35**. Heating these compounds (**34** or **35**) neat with acetylketene precursor **36** followed by exposure to methanesulfonyl azide led to diazoacetoacetates **37** and **38**. It was hoped that either indene **37** would undergo an initial intramolecular cyclopropanation to produce **39** with sufficient strain so as to fragment to quaternary center containing indene **40**, or that indane **38** would be posed for insertion into the doubly benzylic C–H bond to give **41**. Unfortunately, exposure of either **37** or **38** to known C–H insertion or cyclopropanation catalysts did not produce any **40** or **41** and only led to the observed compounds of type **42** wherein the metal carbenoid had inserted into the *ortho* aryl hydrogen.



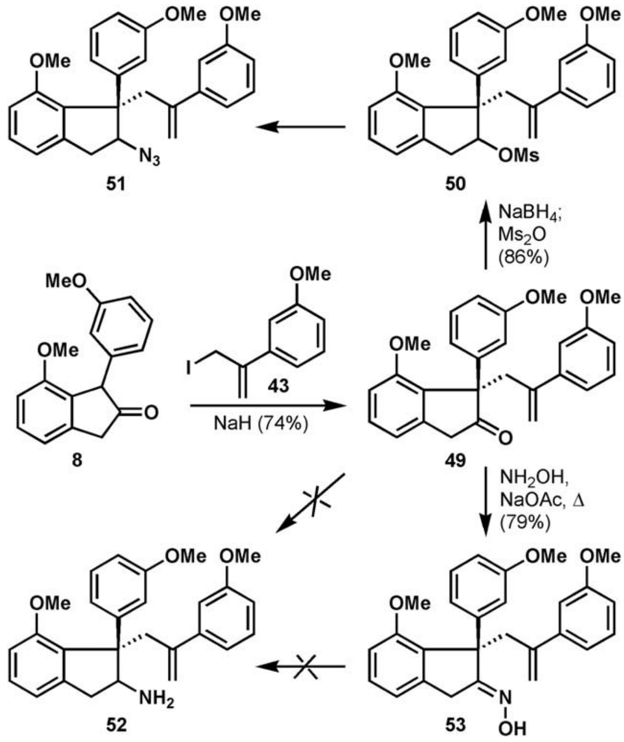
Scheme 9. Failed diazocarbonyl chemistry 2.

The subsequent plan then became the use of more reliable enolate alkylation chemistry in order to introduce the requisite all-carbon quaternary center. To this end, allyl iodide electrophiles **43** and **44** (Scheme 10) were synthesized containing either anisole or bromoanisole as a functional handle for further elaboration of the macrocycle. Fischer esterification of 3-methoxyphenylacetic acid **45** and methylenation with paraformaldehyde under phase-transfer conditions provided aryl propenoate **46** that could be reduced to the allylic alcohol with diisobutylaluminum hydride and further activated as the allyl iodide **43** with triphenylphosphine and iodine. Bromoarene allyl iodide **44** was synthesized identically via **47** starting from 6-bromo-3-methoxyphenylacetic acid **48** (the product of treating **45** with bromine).

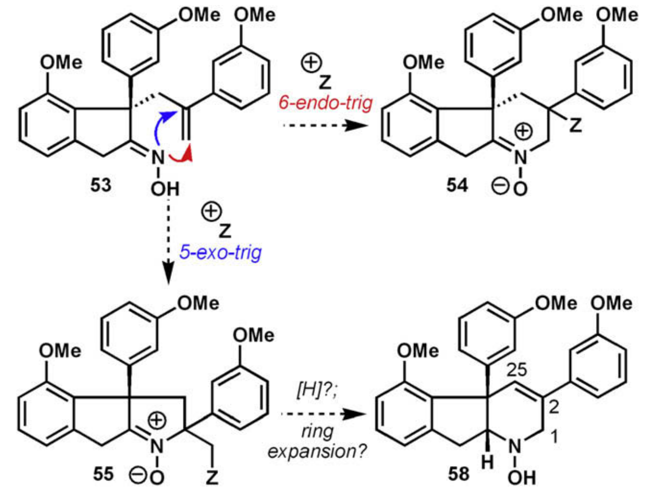


Scheme 10. Preparation of allyl iodide electrophiles.

The sodium enolate of aryl ketone **8** was reacted with allyl iodide **43** to produce, gratifyingly, quaternary center containing ketone **49** (Scheme 11). With the connectivity now established at this center, the next task became introduction of the sole haouamine nitrogen atom. Indanone **49** could be reduced to an undetermined single diastereomer with sodium borohydride and activated with methanesulfonic anhydride to mesylate **50**. However, attempts at displacing this neopentyl mesylate with azide to **51** resulted in either no reaction or elimination under forcing conditions. Direct reductive amination also failed to install the nitrogen as in **52**. Whereas oxime **53** was formed by heating **49** in



Scheme 11. Success in installation of the all-carbon quaternary center.



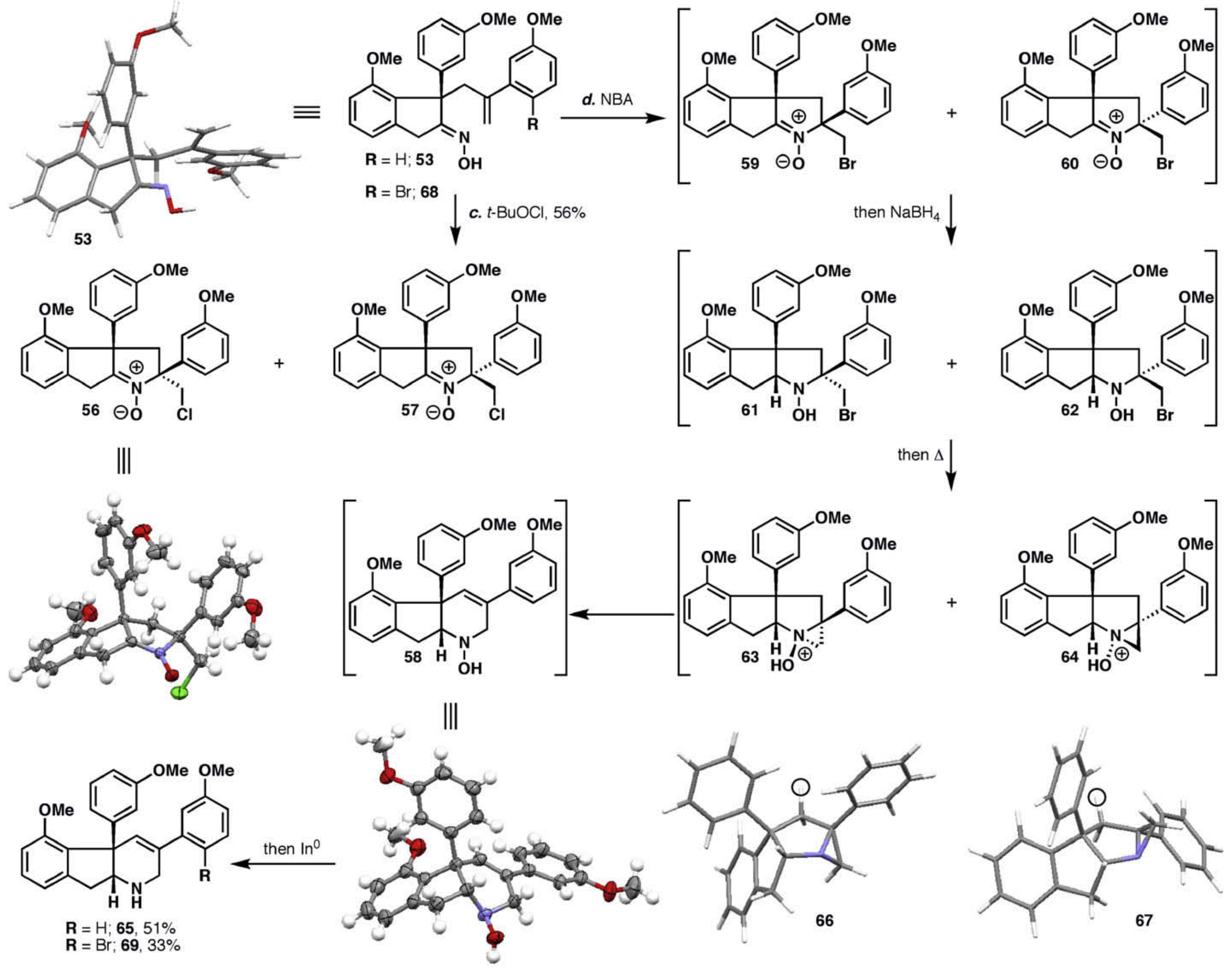
Scheme 12. Possible modes of cyclization for **53** and a possible ring expansion to **58**.

refluxing ethanol with a large excess of hydroxylamine hydrochloride and sodium acetate, it was also resistant to reduction (to deliver **52**). It thus became clear that initial annulation might be a wiser approach.

2.3. Development of a cascade annulation to synthesize the core

Inspection of three-dimensional models of oxime **53** (MM2 minimized structure, Scheme 13) provided evidence that alkene activation could promote cyclization onto the oxime nitrogen due to their spatial proximity. While a 6-*endo-trig* cyclization was desired (Scheme 12) in order to directly access a structure such as **54**, strong precedent from Grigg[22] suggested a probable 5-*exo-trig* pathway leading to **55**. Indeed, reaction of oxime **53** with *tert*-butyl hypochlorite resulted in a facile 5-*exo-trig* cyclization to give two diastereomeric five-membered chloronitrones **56** and **57** (Scheme 13), the structure of which was confirmed by X-ray crystallographic analysis. As opposed to seeing this undesired cyclization as a dead-end strategy en route to the indeno-tetrahydropyridine core, an idea was formulated consisting of the following: reduction of the nitrone functionality should occur stereospecifically to give a cis-fused *N*-hydroxypyrroloindane that is poised to undergo an intramolecular S_N2 reaction to produce an *N*-hydroxypyrroloaziridinium species that could fragment to *N*-hydroxytetrahydropyridine **58** with unsaturation at either C1–C2 or the desired C2–C25 position (haouamine numbering, Scheme 12).

In practice, the reaction of **53** with *N*-bromoacetamide (Scheme 13) produced bromonitrones **59** and **60** that, upon in situ reaction with



Scheme 13. Development of a cascade annulation sequence.

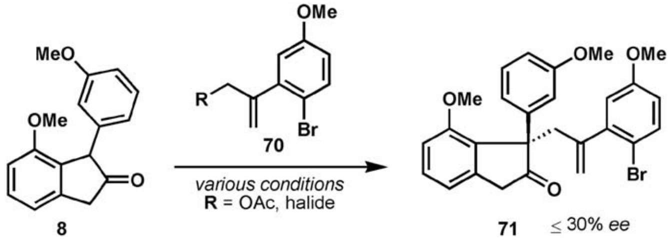
sodium borohydride at 50 °C underwent stereospecific reduction to **61** and **62**, supposed 3-*exo-tet* displacement to fleeting *N*-hydroxyaziridiniums **63** and **64** (not observed spectroscopically), and the desired regiospecific ring expansion to converge on *N*-hydroxytetrahydropyridine **58** (structure confirmed by X-ray). Exposure of this crude material to indium powder[23] chemoselectively reduced the *N*-hydroxy functional group to secondary amine **65**. Inspection of model aziridines **66** and **67** provide a clear stereoelectronic rationale for why none of the regioisomeric *N*-hydroxyenamine is produced in this fragmentation step. The preferential hydrogen in both diastereomers to be involved in this eliminative fragmentation (pointed out for clarity in **66** and **67**) is well aligned for donation into the C–N antibonding orbital that is breaking. Neither of the alternative hydrogens on the aziridinium ring possesses such overlap so as to preclude their involvement in this step.

This overall cascade sequence produces indeno-tetrahydropyridine **65** in 51% overall yield (average 87% yield per transformation) from oxime **53** in a single step as one diastereomer. A slight complication arose when applying this sequence to bromooxime **68** as the yield of the product bromoamine **69** fell to 33% utilizing the same conditions. Optimization of these conditions is shown in Table 2. Some halogen sources such as *N*-iodosuccinimide and bromonium dicollidine perchlorate failed to elicit initial nitrone formation (entries 1 and 3) and *tert*-butyl hypochlorite (entry 2) did not produce any product due to the lower nucleofugality of chlorine with respect to bromine in the hydroxyaziridinium-forming step. As mentioned earlier, the use of *N*-bromoacetamide with 2 equiv of indium resulted in a 33% yield (entry 5) while increasing the indium only lowered the yield to 23% (entry 4) due to competitive arylbromide reduction. *N*-Bromosuccinimide led to comparable yields (entry 6). Final success was achieved with the use of tetrabromocyclohexadienone as the bromonium source with 1.1 equiv resulting in a 43% yield (entry 7) and 2.2 equiv raising this to a satisfactory 57% (entry 8).

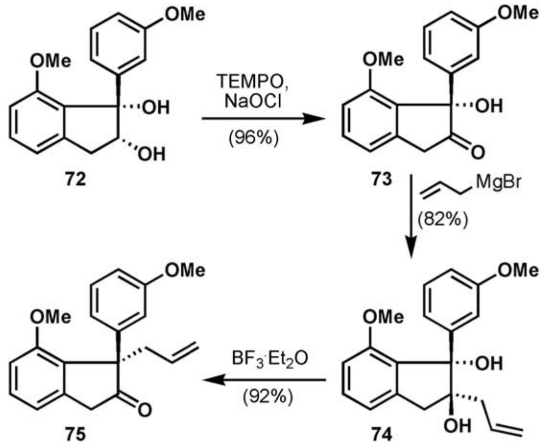
2.4. Enantioselective synthesis of the core

Whereas a route to the core of haouamine A (as well as a subsequent conversion of this into the natural product) that addressed the issues of chemo- and diastereoselectivity had now been developed,[3] it fell short of achieving absolute stereocontrol; as the absolute configuration of the haouamines was not known, the development of an asymmetric route was required. As all of the stereochemical information within our racemic synthesis is derived from the all-carbon quaternary center, it initially seemed that an asymmetric route to these molecules would be trivial since all that would be required is an enantioselective alkylation. However, attempts to achieve such a reaction from aryl ketone **8** (Scheme 14) with an electrophile **70** (R=halogen, OAc) using conditions such as Trost's palladium-catalyzed asymmetric allylic alkylation,[24] Enders' SAMP/RAMP hydrazone alkylation,[25] or asymmetric phase-transfer-catalysis[26] did not provide **71** with levels of enantiomeric excess above 30%.

Attention then turned to a less direct chirality transfer strategy in order to introduce the requisite asymmetry via a non-alkylative method. Specifically, installation of the allyl group nucleophilically (as opposed to electrophilically) was envisaged with the stereoselectivity resulting from addition to an already chiral substrate. A model study was thus performed starting from racemic diol **72** (Scheme 15). TEMPO/NaOCl oxidation[27] proved to be the only viable method of oxidation (this diol is particularly susceptible to oxidative glycol cleavage) providing alpha-hydroxy ketone **73**, which was treated with allyl magnesium bromide to give the homoallylic diol **74** with high diastereoselectivity as a likely result of direction by the neighboring alcohol. Exposure of this compound to stoichiometric boron trifluoride diethyl etherate at 0 °C then elicited a pinacol rearrangement[28] to produce the model quaternary ketone **75** in high yield. Even with these results, three further issues arose before a workable asymmetric route to the indeno-tetrahydropyridine core could be developed: access to enantiopure diol **72**, diastereoselective addition of a fully elaborated allyl substituent to the enantiopure alpha-hydroxy ketone, and a successful pinacol rearrangement occurring on this substrate without loss of stereochemical information.



Scheme 14. Failed asymmetric alkylation.

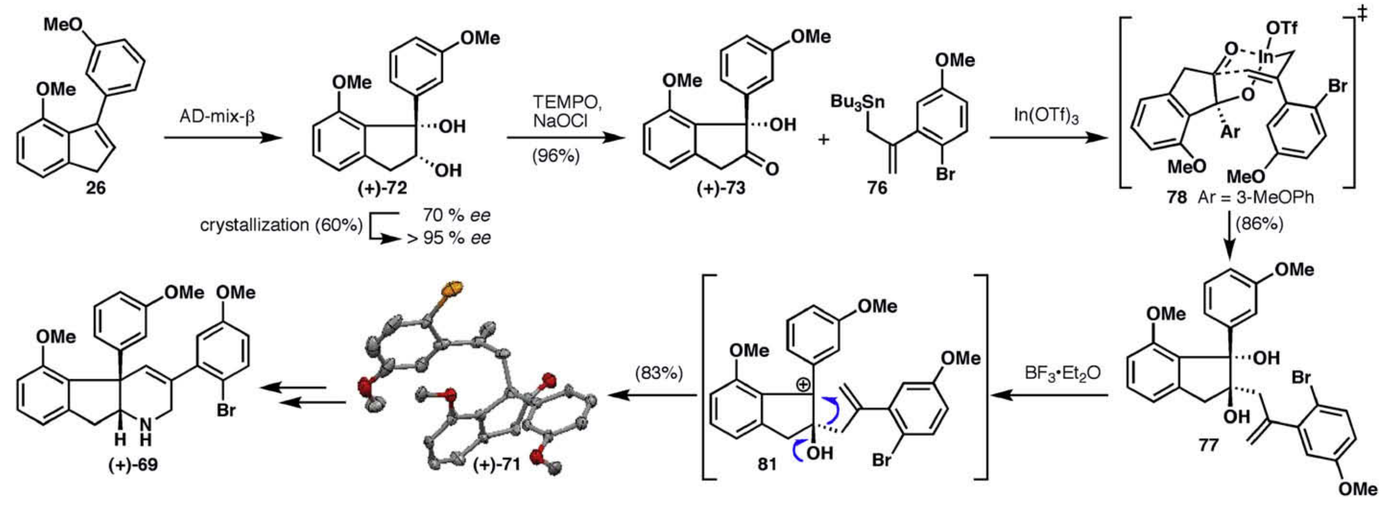


Scheme 15. Pinacol rearrangement model study.

Achievement of these goals is shown in Scheme 16. Sharpless asymmetric dihydroxylation[29] on aryl indene **26** achieved moderate levels of enantioselectivity yielding optically active diol (+)-**72** in 70% ee (ee determined by ^{1}H NMR analysis of the monoester derived from the *R*-Mosher acid). The racemic diol within this mixture (30% by weight) could then be selectively crystallized as the centrosymmetric racemate leaving the enantiopure diol in solution (isolated in 60% overall yield from **26**). According to the Sharpless mnemonic the diol produced in this reaction should have the 1*S*,2*R* absolute configuration as shown in Scheme 16. This compound was then oxidized as before to alpha-hydroxy ketone (+)-**73**, the substrate for incorporation of an appropriate allyl nucleophile. Attempts to synthesize an allyl Grignard reagent **70** (R=MgX) were complicated by the presence of an arylbromide in the substrate, and the appropriate allylsilane or allylboronate did not have sufficient reactivity for addition. Attention then turned to an allylindium species, in particular that formed via transmetalation from an organotin with indium(III).[30] Exposure of tributylallyltin **76** to (+)-**73** in the presence of indium(III) triflate gave the desired product **77** in 86% yield.

Furthermore, the pinacol rearrangement occurred smoothly on this fully functionalized diol to intercept the previous ketone (+)-**71**.

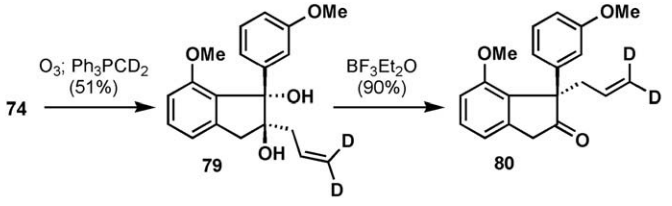
Additionally pleasing was the fact that there was no loss in stereochemical information throughout this sequence as deduced by reduction of (+)-**71** to a single alcohol diastereomer and ^{1}H NMR analysis of the ester derived from the (*R*)-Mosher acid and comparison to that with the racemic **71**. The absolute stereochemistry of (+)-**71** was established by X-ray crystallographic analysis and found



Scheme 16. A successful enantioselective route to ketone (+)-**71**.

to have the *R* configuration as shown in Scheme 16. This sequence thus renders the previously developed route enantioselective.

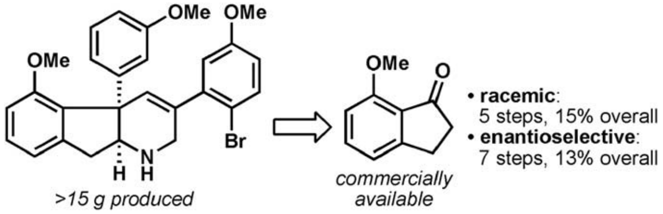
A question regarding the mechanism of the pinacol rearrangement still lingered and prompted an investigation. Assuming that the transition state of addition resembles **78** to give *anti* 1,2-diol in **77**, the shift of the allyl group must occur with facial retention across the cyclopentane of the indane. There was lack of clarity as to whether such a shift was occurring in a [1,2]-sense with or without allylic rearrangement. In order to differentiate between these two mechanisms, the model homoallylic diol **74** was ozonolyzed to the aldehyde (Scheme 17) and treated with a methylene-d_2 Wittig reagent to give **79** with 80% deuterium incorporation. When submitted to the pinacol rearrangement conditions the product **80** was found to still contain deuterium incorporation solely at the vinylic terminus. This evidence strongly suggests that a [1,2]-shift is transpiring without allylic rearrangement within this reaction as shown in **81** (Scheme 16).



Scheme 17. Mechanistic study of the pinacol rearrangement.

3. Conclusions

In summary, a full account of efforts toward the indeno-tetrahydropyridine of haouamine A (**1**) has been presented. Biosynthetic questions, failed routes, and necessity-driven invention have led to efficient routes that access the core of this natural product in either racemic or enantiopure fashion. The developed cascade annulation sequence is particularly enabling as it allows for the rapid construction of the heterocycle portion in a chemo- and stereoselective fashion in a single step from a readily available oxime intermediate. This chemistry has enabled the production of large quantities of the indeno-tetrahydropyridine core (>15 g to date) that is available from commercial material racemically in five steps (15% overall) or enantioselectively in seven steps (13% overall) (Scheme 18). In the former case, four steps form key skeletal bonds; two extra steps are required in the latter case (TEMPO oxidation and pinacol shift) while the dihydroxylation step is rendered enantioselective using Sharpless chemistry. This synthesis is short, scalable, high yielding, and compares favorably with other reported approaches.[5–10] However, one could imagine further improvements to the current approach if certain redox fluctuations could be avoided—particularly with regard to the oxidation state of the oxime in **68** (both the C=N and N–O bond are reduced).[31] Nevertheless, access to decagram quantities of **69** enabled both an initial[3,4] as well as a preparative-scale total synthesis of **1**.[32]



Scheme 18. Summary of synthetic efforts.

4. Experimental section

4.1. General

All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), diethyl ether, dichloromethane (DCM), benzene, toluene, methanol (MeOH), acetonitrile, 1,2-dimethoxyethane (DME), *N*,*N*-dimethylformamide (DMF), and triethylamine (Et_3N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates ($60F_{254}$) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate ($KMnO_4$), and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates ($60F_{254}$). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ at 7.26 ppm ^{1}H NMR, 77.0 ppm ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time-of-flight reflectron experiments. IR spectra were recorded on a Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12–144 melting point apparatus. Optical rotations were obtained on a Pekin–Elmer 431 Polarimeter.

4.2. 1-(3-Methoxyphenethyl)-3,5-bis(3-methoxyphenyl)-pyridinium triflate (9)

A solution of *m*-methoxyphenylacetaldehyde (324 mg, 2.16 mmol, 4.0 equiv) and 2-(*meta*-methoxyphenyl)-ethylamine hydrochloride (101 mg, 0.54 mmol) in water (1.1 mL, 0.5 M) was treated with ytterbium triflate (167 mg, 0.27 mmol, 0.5 equiv), and the reaction mixture was stirred vigorously for 24 h. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (2×20 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (silica gel, 99:1→95:5 DCM/MeOH) afforded **9** as a white solid (131 mg, 57%). Mp=158–160 °C; R_f=0.22 (silica gel, 9:1 DCM/MeOH); IR (film) ν_{max} 2937, 1735, 1594, 1583, 1488, 1454, 1255 (s), 1152, 1027, 783, 691, 636 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J*=1.6 Hz, 2H), 8.50 (t, *J*=1.6 Hz, 1H), 7.41 (t, *J*=8.0 Hz, 2H), 7.17–7.14 (m, 3H), 7.10 (t, *J*=2.0 Hz, 2H), 7.03 (dd, *J*=2.4, 8.3 Hz, 2H), 6.74 (dd, *J*=2.4, 8.2 Hz, 1H), 6.68 (t, *J*=2.1 Hz, 1H), 6.63 (d, *J*=7.7 Hz, 1H), 5.15 (t, *J*=6.5 Hz, 2H), 3.89 (s, 6H), 3.72 (s, 3H), 3.30 (t, *J*=6.5 Hz, 2H); ^{13}C-APT NMR (150 MHz, $CDCl_3$) δ 160.7, 141.4, 140.5, 139.9, 136.9, 134.0, 130.8, 130.2, 121.1, 119.6, 116.7, 114.2, 113.5, 112.4, 63.6, 55.7, 55.3, 37.9; HRMS (ESI) calcd for $C_{28}H_{28}NO_3$ [M$^+$] 426.2069, found 426.2062.

4.3. 2-(3-Methoxybenzyl)-1-(3-methoxyphenethyl)-3,5-bis(3-methoxyphenyl)pyridinium triflate (10)

The title compound was prepared from **9** in four steps[4] as a yellow solid. R_f=0.32 (silica gel, 9:1 DCM/MeOH); IR (film) ν_{max} 2926, 1600, 1584, 1490, 1468, 1258 (s), 1224, 1153, 1030, 787, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.96 (d, *J*=2.0 Hz, 1H), 8.36 (d, *J*=2.0 Hz, 1H), 7.41 (t, *J*=8.0 Hz, 1H), 7.37 (t, *J*=7.9 Hz, 1H), 7.26 (t, *J*=7.9 Hz, 1H), 7.20 (t, *J*=7.9 Hz, 1H), 7.16–7.14 (m, 2H), 7.04 (ddd, *J*=8.3, 2.4, 0.7 Hz, 1H), 7.01 (ddd, *J*=8.4, 2.5, 0.7 Hz, 1H), 6.93 (ddd, *J*=7.5, 1.4, 0.8 Hz, 1H), 6.89 (m, 1H), 6.83–6.79 (m, 2H), 5.00 (t, *J*=7.0 Hz, 2H), 4.29 (s, 2H), 3.91 (s, 3H), 3.761 (s, 3H), 3.760 (s, 3H), 3.75 (s, 3H), 3.02 (t, *J*=7.0, 2 Hz); ^{13}C-APT NMR (150 MHz, $CDCl_3$): δ 160.7, 160.5, 160.2, 159.9, 152.1, 144.0, 143.2, 139.0, 136.8, 136.7, 136.4, 133.5, 130.8, 130.7, 130.4, 130.3, 121.1, 120.7, 119.8, 119.6, 116.9, 115.7, 114.6, 114.1, 114.0, 113.4, 112.9, 112.3, 60.1, 55.8, 55.4, 55.33, 55.32, 37.1, 35.6; ^{13}C-APT NMR (150 MHz, CD_2Cl_2): δ 161.3, 161.1, 160.9, 160.6, 152.6, 144.8, 144.4, 144.3, 139.6, 137.4, 137.1, 136.8, 134.2, 131.4, 131.3, 131.0, 130.9, 121.7, 121.3, 120.3, 120.1, 117.0, 116.0, 115.2, 114.8, 114.6, 113.8, 113.5, 113.1, 60.8, 56.3, 55.95, 55.88, 55.8, 37.7, 36.1; HRMS (ESI) calcd for $C_{36}H_{36}NO_4$ [M$^+$] 546.2644, found 546.2635.

4.4. 1-(3-Methoxyphenethyl)-3,5-bis(3-methoxyphenyl)-1,2,3,6-tetrahydropyridine (16)

To a solution of pyridinium **9** (426 mg, 0.74 mmol) in methanol (3.7 mL) and DCM (3.7 mL) at 0 °C was added cerium trichloride (276 mg, 0.74 mmol, 1.0 equiv). Sodium borohydride was added CAUTIOUSLY (560 mg, 14.8 mmol, 20.0 equiv). A distinct bright color is observed upon addition. The reaction mixture was stirred for 20 min, and acetic acid (3.7 mL) was then added CAUTIOUSLY dropwise. A disappearance in color signified the completion of the reaction (more sodium borohydride was added if complete decoloration did not occur within 30 min). The reaction mixture was then diluted with 1.0 M NaOH (40 mL), and the aqueous layer was extracted with EtOAc (2×50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (silica gel, 5:1 hexanes/EtOAc) afforded **16** as a clear oil (229 mg, 72%). R_f=0.29 (silica gel, 3:1 hexanes/EtOAc); IR (film) ν_{max} 2930, 2827, 1598, 1580, 1484, 1462, 1451, 1429, 1285, 1259, 1148, 1045, 780, 691 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J*=7.9 Hz, 1H), 7.25 (d, *J*=8.0 Hz, 1H), 7.21 (t, *J*=7.8 Hz, 1H), 7.02 (d, *J*=7.7 Hz, 1H), 6.96 (s, 1H), 6.90 (d, *J*=7.5 Hz, 1H), 6.86–6.75 (m, 6H), 6.19 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.79 (m, 1H), 3.68 (d, *J*=15.8 Hz, 1H), 3.37 (dt, *J*=2.5, 15.6 Hz, 1H), 3.16 (dd, *J*=5.5, 11.2 Hz, 1H), 2.88 (dd, *J*=11.3, 9.4 Hz, 2H), 2.81 (dd, *J*=9.7, 10.9 Hz, 2H), 2.43 (dd, *J*=9.0, 11.1 Hz, 1H); ^{13}C-APT NMR (150 MHz, $CDCl_3$) δ 159.7, 159.6 (2C), 145.2, 141.9, 141.3, 136.1, 129.42, 129.35, 129.34, 126.2, 121.1, 120.5, 117.7, 114.5, 114.0, 112.5, 111.8, 111.3, 111.2, 59.8, 58.3, 55.23, 55.19, 55.1, 54.6, 43.2, 33.9; HRMS (ESI) calcd for $C_{28}H_{31}NO_3$ [M+H$^+$] 430.2377, found 430.2370.

4.5. 7-Methoxy-1-(3-methoxyphenyl)-1*H*-inden-2(3*H*)-one (8)

To 7-methoxyindanone **24** (37 g, 228 mmol) in THF (500 mL) at 0 °C was added a solution of 3-(methoxyphenyl)magnesium bromide **25** (500 mL, 319 mmol, 1.4 equiv) [prepared by adding 3-bromoanisole (40.4 mL, 319 mmol, 1.4 equiv) dropwise over the course of 1.5 h to a solution of magnesium turnings (38.9 g, 1.6 mol, 7 equiv) and 1,2-dibromoethane (0.1 mL) in THF (500 mL)]. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Saturated aqueous NH_4Cl (200 mL) was added and the mixture was extracted with Et_2O (3×250 mL), dried over $MgSO_4$, filtered, and concentrated. The resultant oil was dissolved in CH_3CN (500 mL), treated with H_2SO_4 (10%, 50 mL), and heated to 60° for 1 h. The reaction mixture was cooled to room temperature and stirred overnight. The mixture was then diluted with brine (200 mL) and extracted with DCM (3×250 mL); the combined extracts were dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (silica gel, 2:1 to 1:1 hexanes/DCM) afforded indene **26** (43 g, 170 mmol) as an unstable oil that was immediately dissolved in 9:1 acetone/H_2O (550 mL) and cooled to 0°. 4-Methylmorpholine-*N*-oxide (34.5 g, 255 mmol, 1.5 equiv) was added followed by osmium tetroxide (2.5% in *t*-BuOH; 21 mL, 1.7 mmol, 0.01 equiv) and the solution was warmed to room temperature and stirred for 7.5 h. Saturated aqueous $Na_2S_2O_3$ (100 mL) was added and the mixture was stirred for 1 h. Saturated aqueous $NaHCO_3$ (500 mL) was added and the aqueous mixture extracted with EtOAc (3×500 mL); the extracts were dried over $MgSO_4$, filtered, and concentrated. The dark oil was dissolved in benzene (500 mL) and treated with *p*-toluenesulfonic acid (3.2 g, 17.0 mmol, 0.1 equiv). The flask was equipped with a Dean–Stark trap and refluxed for 6 h. The reaction was cooled, diluted with EtOAc (500 mL), and washed subsequently with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL). The combined aqueous washings were back extracted with EtOAc (500 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (9:1 hexanes/EtOAc) afforded **8** as an off-white solid (40.4 g, 66% overall); mp 104–105 °C; R_f=0.35 (silica gel, 4:1 hexanes/EtOAc); IR (film) ν_{max} 2939, 2359, 1749 (s), 1598 (s), 1484 (s), 1290, 1265, 1135, 1047 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (t, *J*=7.9 Hz, 1H), 7.20 (t, *J*=7.9 Hz, 1H), 7.00 (d, *J*=7.5 Hz, 1H), 6.83 (d, *J*=8.3 Hz, 1H), 6.78 (dd, *J*=8.3, 2.2 Hz, 1H), 6.70–6.67 (m, 2H), 4.64 (s, 1H), 3.77 (s, 3H), 3.73–3.67 (m, 1H), 3.66 (s, 3H); ^{13}C-APT NMR (150 MHz, $CDCl_3$) δ 213.2, 159.6, 156.6, 138.9, 138.8, 129.4, 129.3, 128.4, 119.7, 116.9, 113.4, 112.1, 109.4, 57.3, 55.3, 55.1, 42.8; HRMS (ESI) calcd for $C_{17}H_{17}O_3$ [M+H$^+$] 269.1172, found 269.1171.

4.6. 2-(2-Bromo-5-methoxyphenyl)prop-2-en-1-ol (44a)

To a solution of 3-methoxyphenylacetic acid (30.2 g, 182 mmol) in DCM (250 mL) at 0 °C was added bromine (10.3 mL, 200 mmol, 1.1 equiv) dropwise. The solution was allowed to warm to room temperature and stirred for 2 h. Saturated aqueous $Na_2S_2O_3$ (200 mL) was added and the aqueous layer further extracted with DCM (2×200 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. The crude mixture was dissolved in methanol (200 mL) and treated dropwise with thionyl chloride (39.8 mL, 546 mmol, 3.0 equiv). The solution was heated to reflux for 4 h and then cooled and concentrated. This material was dissolved in toluene (500 mL) and treated with tetrabutylammonium iodide (66.5 g, 180 mmol, 1.0 equiv), potassium carbonate (49.8 g, 360 mmol, 2.0 equiv), and paraformaldehyde (27.3 g, 900 mmol, 5.0 equiv). The resulting mixture was heated to reflux for 8 h and then cooled and diluted with EtOAc (500 mL) and washed with water (500 mL) and brine (500 mL). The organic was dried over $MgSO_4$, filtered, and concentrated. This crude mixture was dissolved in toluene (700 mL) and cooled to −78 °C. A toluene solution of diisobutylaluminum hydride (345 mL, 1.5 M, 517 mmol, 3.0 equiv) was added and the solution stirred at −78 °C for 1 h. The reaction was quenched with EtOAc (200 mL) and allowed to warm to room temperature. Saturated aqueous potassium sodium tartrate (1.0 L) and Et_2O (1.0 L) were added and the solution stirred for 1 h. The layers were separated and the aqueous was further extracted with Et_2O (2×500 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (silica gel, 9:1 hexanes/EtOAc) afforded **44a** as a clear oil (23.4 g, 56% overall). R_f=0.19 (silica gel, 4:1 hexanes/EtOAc); IR (film) ν_{max} 3341 (br), 2360, 2341, 1590, 1567, 1464 (s), 1290, 1224 (s), 1039 (s), 1012 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J=8.8 Hz, 1H), 6.75 (d, J=3.1 Hz, 1H), 6.71 (dd, J=8.7, 3.1 Hz, 1H), 5.51 (d, J=1.5 Hz, 1H), 5.13 (d, J=1.3 Hz, 1H), 3.77 (s, 3H); ^{13}C-APT NMR (125 MHz, $CDCl_3$) δ 158.7, 149.1, 141.8, 133.3, 116.3, 115.0, 114.8, 112.6, 65.3, 55.4.

4.7. 1-Bromo-2-(3-iodoprop-1-en-2-yl)-4-methoxybenzene (44)

Allylic alcohol **44a** (13.9 g, 57.1 mmol) was dissolved in DCM (286 mL) and sequentially treated at 0° with triphenylphosphine (19.5 g, 74.2 mmol, 1.30 equiv), imidazole (5.44 g, 79.9 mmol, 1.4 equiv), and iodine (19.6 g, 77.1 mmol, 1.35 equiv). The solution was stirred at 0 °C for 30 min and quenched with saturated aqueous $Na_2S_2O_3$ (250 mL). Et_2O (500 mL) was added and the organic layer washed with water (200 mL) and brine (200 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated, and passed through a plug of silica gel eluting with 9:1 hexanes/Et_2O (1 L) to give allyl iodide **44** (19.5 g, 97%) as an unstable oil, which was used immediately or stored at −78 °C. R_f=0.44 (silica gel, 9:1 hexanes/Et_2O); IR (film) ν_{max} 1590, 1565, 1463, 1404, 1303, 1226, 1155, 1117, 1045, 1015, 916, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J=8.8 Hz, 1H), 6.84 (d, J=3.1 Hz, 1H), 6.76 (dd, J=8.8, 3.1 Hz, 1H), 5.65 (d, J=0.8 Hz, 1H), 5.15 (d, J=0.9 Hz, 1H), 4.31 (d, J=0.7 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 146.7, 141.4, 133.3, 119.6, 117.2, 115.1, 112.1, 55.5, 9.1.

4.8. 3-(2-Bromo-5-methoxyphenyl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-*b*]pyridine (69)

To a solution of oxime **68** (1.07 g, 2.11 mmol) in 1,2-dichloroethane (21.1 mL) at 0 °C was added 2,4,4,6-tetrabromo-2,5-cyclohexadienone (1.73 g, 4.22 mmol, 2.2 equiv) at once. Stirring was continued for 30 min at 0 °C and EtOH (21.1 mL) was then added followed by sodium borohydride (399 mg, 10.5 mmol, 5.0 equiv). The reaction mixture was heated to 50 °C for 1 h and then poured into 1:1 5% aqueous $NaHCO_3$/brine (100 mL) and extracted with DCM (3×100 mL). The combined organics were dried over $MgSO_4$, filtered, concentrated, and diluted with EtOH (14.0 mL). The solution was heated to reflux and indium powder (484 mg, 4.22 mmol, 2.0 equiv) was added followed by saturated aqueous NH_4Cl (7.0 mL). The reaction was heated to reflux for 3.5 h then cooled and diluted with EtOAc (100 mL) and 5% aqueous $NaHCO_3$ (100 mL). The aqueous layer was further extracted with EtOAc (3×100 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (silica gel, 4:1→2:1 hexanes/EtOAc) afforded **69** as a white foam (592 mg, 57%). Mp 57–61 °C; R_f=0.25 (silica gel, 1:1 hexanes/EtOAc); IR (film) ν_{max} 2935, 1587 (s), 1478 (s), 1463 (s), 1288, 1263 (s), 1080, 1051, 1028 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, J=8.7 Hz, 1H), 7.26 (t, J=8.7 Hz, 1H), 7.18 (t, J=7.9 Hz, 1H), 6.94 (d, J=7.4 Hz, 1H), 6.83 (s, 1H), 6.79–6.67 (m, 5H), 6.36 (s, 1H), 3.82 (d, J=17.0 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.68 (dd, J=6.8, 4.6 Hz, 1H), 3.60 (s, 3H), 3.53 (d, 17.0 Hz, 1H), 3.17 (dd, J=16.0, 6.9 Hz, 1H), 2.95 (dd, J=16.0, 4.3 Hz, 1H), 2.31 (br s, 1H); ^{13}C-APT NMR (150 MHz, $CDCl_3$) δ 159.5, 158.8, 157.4, 147.2, 143.6, 143.5, 139.0, 133.2, 132.3, 130.0, 129.1, 129.0, 119.4, 117.8, 116.0, 114.2, 113.1, 112.8, 111.3, 109.6, 66.4, 55.6, 55.5, 55.2, 55.1, 45.1, 36.0; HRMS (ESI) calcd for $C_{27}H_{27}BrNO_3$ $[M+H^+]$ 491.1169, found 492.1163.

4.9. (1*S*,2*R*)-7-Methoxy-1-(3-methoxyphenyl)-2,3-dihydro-1*H*-indene-1,2-diol ([+]-72)

To a solution of indene **26** (2.78 g, 11.0 mmol, synthesized as previously described) in *t*-BuOH (55 mL) was added sequentially methanesulfonamide (5.2 g, 55.0 mmol, 5.0 equiv), $(DHQD)_2PHAL$ (428.0 mg, 0.55 mmol, 0.05 equiv), K_2CO_3 (4.56 g, 33.0 mmol, 3.0 equiv), and H_2O (55.0 mL). This solution was cooled to 0 °C and treated with potassium ferricyanide (10.9 g, 33.0 mmol, 3.0 equiv) followed by osmium tetroxide (2.5% in *t*-BuOH; 1.38 mL, 0.11 mmol, 0.01 equiv). The reaction flask was placed in a 5 °C cold room and stirred for 44 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (100 mL) and allowed to warm to room temperature and stir for 1 h. The aqueous layer was then extracted with EtOAc (3×150 mL), dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (silica gel, 4:1→3:1 hexanes/EtOAc) afforded the diol (3.10 g, 98%). To the solid was added hexanes (40 mL) and EtOAc (10 mL), and the solution heated to a brief reflux with a heat gun in order to assure complete dissolution. The hot solution was then seeded with a sample of racemic diol and allowed to cool to room temperature. Clear needles of racemic diol crystallized out of the mixture, and the supernatant was then removed from the resulting crystals and concentrated to afford enantiomerically pure (+)-**72** as a thick oil (1.89 g, 60%). R_f=0.24 (silica gel, 2:1 hexanes/EtOAc); $[\alpha]_D$ +43.4 (*c* 0.53, $CHCl_3$); IR (film) ν_{max} 3447 (br), 2937, 2835, 1589, 1480 (s), 1262 (s), 1078 (s), 1044 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, J=8.1 Hz, 1H), 7.19 (t, J=8.0 Hz, 1H), 6.95 (d, J=7.5 Hz, 1H), 6.83–6.78 (m, 3H), 6.70–6.68 (m, 1H), 4.29 (d, J=4.6 Hz, 1H), 4.15 (s, 1H, D_2O exchangeable), 3.77 (s, 3H), 3.75 (s, 3H), 3.48 (s, 1H, D_2O exchangeable), 3.02 (dd, J=16.5, 4.5 Hz, 1H), 2.90 (d, J=16.4 Hz, 1H); ^{13}C-APT NMR (150 MHz, $CDCl_3$) δ 159.6, 156.7, 145.8, 143.6, 130.5, 130.0, 129.1, 118.3, 118.2, 112.5, 111.8, 109.1, 85.8, 80.5, 55.3, 55.1, 38.1; HRMS (ESI) calcd for $C_{17}H_{18}O_4$ $[M+Na^+]$ 309.1097, found 309.1092.

4.10. (*S*)-1-Hydroxy-7-methoxy-1-(3-methoxyphenyl)-1*H*-inden-2(3*H*)-one ([+]-73)

To a solution of (+)-**72** (599 mg, 2.09 mmol) in DCM (10.5 mL) at 0 °C was added sequentially: saturated aqueous $NaHCO_3$

(4.2 mL), potassium bromide (12.0 mg, 0.10 mmol, 0.05 equiv), TEMPO (16.0 mg, 0.10 mmol, 0.05 equiv), and aqueous sodium hypochlorite (6.2 mL, 4.18 mmol, 2.0 equiv). The reaction mixture was stirred at 0 °C for 30 min and quenched with saturated aqueous $NaHSO_4$ (10 mL) and allowed to warm to room temperature. The aqueous layer was extracted with EtOAc (3×30 mL), and the combined organics were washed once with brine (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (silica gel, 3:1 hexanes/EtOAc) afforded (+)-**72** as an off-white solid. Mp 117–119 °C; R_f=0.24 (silica gel, 2:1 hexanes/EtOAc); $[\alpha]_D$ +37.9 (*c* 0.43, DCM); IR (film) ν_{max} 3467 (br), 3011, 1744 (s), 1587 (s), 1484 (s), 1291 (s), 1053 (s) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.39 (t, *J*=8.0 Hz, 1H), 7.19 (t, *J*=8.0 Hz, 1H), 7.01 (d, *J*=7.6 Hz, 1H), 6.97 (m, 1H), 6.89 (d, *J*=8.3 Hz, 1H), 6.82 (m, 1H), 6.77 (dd, *J*=7.7, 0.8 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.67 (d, *J*=21.5 Hz, 1H), 3.58 (d, *J*=1.2 Hz, 1H), 3.49 (d, *J*=21.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 210.5, 160.0, 157.0, 141.7, 137.7, 130.9, 129.8, 129.6, 118.1, 117.5, 113.9, 111.5, 110.2, 82.4, 55.6, 55.4, 40.3; HRMS (ESI) calcd for $C_{17}H_{16}O_4$ $[M+Na^+]$ 307.0941, found 307.0929.

4.11. (*R*)-1-(2-(2-Bromo-5-methoxyphenyl)allyl)-7-methoxy-1-(3-methoxyphenyl)-1*H*-inden-2(3*H*)-one ([+]-71)

To a solution of α-hydroxy ketone (+)-**73** (490 mg, 1.72 mmol) and allyl stannane **76** (1.78 g, 3.45 mmol, 2.0 equiv) in THF (11.5 mL) at 0 °C was added indium(III) trifluoromethanesulfonate (1.16 g, 2.06 mmol, 1.2 equiv). After complete dissolution, the reaction mixture was allowed to warm to room temperature and stirred for 1.5 h. Saturated aqueous sodium potassium tartrate (20 mL) and EtOAc (50 mL) were added, and the organic layer was washed with brine (20 mL). The combined aqueous layers were back extracted with EtOAc (50 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (silica gel, 6:1→4:1 hexanes/EtOAc) afforded the homoallylic diol **77** as a clear oil (755 mg, 86%). To a solution of this diol (755 mg, 1.48 mmol) in DCM (14.8 mL) at 0 °C was added boron triflouride diethyl etherate (204 μL, 1.62 mmol, 1.1 equiv) dropwise. After stirring for 10 min at 0 °C, satd aq $NaHCO_3$ (20 mL) and EtOAc (20 mL) were added. The organic layer was washed with brine (20 mL), and the combined aqueous layers were back extracted with EtOAc (20 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (silica gel, 9:1→6:1 hexanes/EtOAc) afforded (+)-**71** as a white solid (603 mg, 83%). Mp=88–90 °C; R_f=0.39 (silica gel, 1:1 hexanes/Et_2O); $[\alpha]_D$ +6.8 (*c* 0.5, DCM); IR (film) ν_{max} 1749 (s), 1586 (s), 1482 (s), 1463 (s), 1289 (s), 1264 (s), 1050 (s), 1016 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J*=6.0 Hz, 1H), 7.23 (t, *J*=7.9 Hz, 1H), 7.16 (t, *J*=8.0 Hz, 1H), 6.91 (d, *J*=7.2 Hz, 1H), 6.79 (d, *J*=7.9 Hz, 1H), 6.76 (dd, *J*=8.4, 6.3 Hz, 1H), 6.74 (dd, *J*=8.1, 1.9 Hz, 1H), 6.53 (dd, *J*=8.8, 3.1 Hz, 1H), 6.51 (d, *J*=10.0 Hz, 1H), 5.63 (d, *J*=3.1 Hz, 1H), 5.24 (s, 1H), 4.88 (d, *J*=1.4 Hz, 1H), 3.91 (d, *J*=13.2 Hz, 1H), 3.74 (s, 3H), 3.72 (d, *J*=13.1 Hz, 1H), 3.57 (s, 3H), 3.48 (d, *J*=22.5 Hz, 1H), 3.42 (m, 3H), 3.11 (d, *J*=22.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 215.2, 159.6, 158.0, 157.3, 147.5, 143.7, 142.4, 138.5, 132.7, 130.3, 129.6, 129.3, 120.4, 119.2, 116.8, 115.6, 114.6, 113.2, 112.7, 111.8, 109.2, 63.4, 55.3, 55.2, 54.6, 42.9, 41.3; HRMS (ESI) calcd for $C_{27}H_{25}BrO_4$ $[M+H^+]$ 493.1014, found 493.0988.

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