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Synthesis of Isohasubanan Alkaloids via Enantioselective Ketone Allylation and Discovery of an Unexpected Rearrangement

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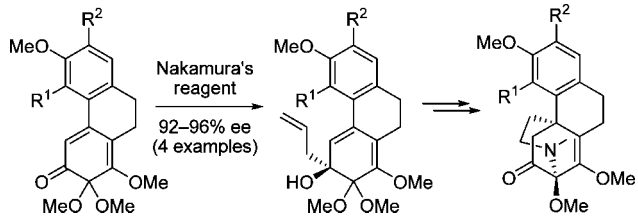

A synthesis of the hasubanan alkaloids hasubanonine, runanine, and aknadinine via a unified route was attempted. Construction of key phenanthrene intermediates by a Suzuki coupling−Wittig olefination−ring-closing metathesis sequence allowed a convergent and flexible approach. Conversion of the phenanthrenes into the target structures was projected to involve six steps including phenolic oxidation, ketone allylation, anionic oxy-Cope rearrangement, and acid-promoted cyclization. The final step was thwarted by a pinacol-like rearrangement that delivered the unnatural isohasubanan alkaloid skeleton. The structures of the products were established by exhaustive NMR experiments and confirmed by GIAO ^{13}C NMR calculations of runanine, isorunanine, and three other isomers. These computations revealed some inconsistencies with the benzene solvent correction which suggest that caution should be used in employing this algorithm. The racemic synthesis of isohasubanonine was transformed into an enantioselective synthesis by the discovery that Nakamura's chiral bisoxazoline-ligated allylzinc reagent mediates the enantioselective allylation of ketone **19** in 93% ee. This method could be extended to three other structurally related ketones (92−96% ee), and the enantioselective syntheses of two other isohasubanan alkaloids, isorunanine and isoaknadinine, were accomplished. Racemic isohasubanonine was found to be an ineffective analgesic agent.

Introduction

The hasubanan alkaloids are a family of over 40 natural products sharing a common tetracyclic skeleton which have been isolated from flowering plants of the genus *Stephania*.[1] The name of the family is derived from that of hasubanonine (**1**, Figure 1), the first member of this compound class to be discovered.[2] The hasubanan alkaloids have been the targets of numerous synthetic efforts that culminated in racemic products.[3,4]

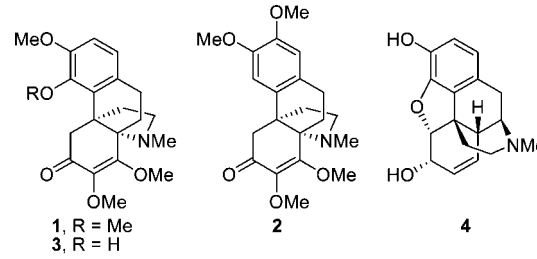

FIGURE 1. Hasubanan alkaloids (**1**−**3**) and morphine (**4**).

The first enantioselective total synthesis of a hasubanan alkaloid was reported by Schultz and Wang in 1998,[5] who noted the structural resemblance between the hasubanan alkaloids and the morphine alkaloids (see Figure 1). Although the two families are somewhat similar in architecture, a key difference is that the spatial relationship between the aromatic ring and the tertiary amine is opposite in the naturally occurring enantiomers. This

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(1) (a) Matsui, M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 33, pp 307−347. (b) Inubushi, Y.; Ibuka, T. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1977; Vol. 16, pp 393−430. (c) Bentley, K. W. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1971; Vol. 13, pp 131−143.

(2) (a) Tomita, M.; Ibuka, T.; Inubushi, Y.; Watanabe, Y.; Matsui, M. *Chem. Pharm. Bull.* **1965**, *13*, 538. (b) Tomita, M.; Ibuka, T.; Inubushi, Y.; Watanabe, Y.; Matsui, M. *Tetrahedron Lett.* **1964**, 2937. (c) Kondo, H.; Satomi, M.; Odera, T. *Ann. Rep. ITSUU Lab.* **1951**, *2*, 35.

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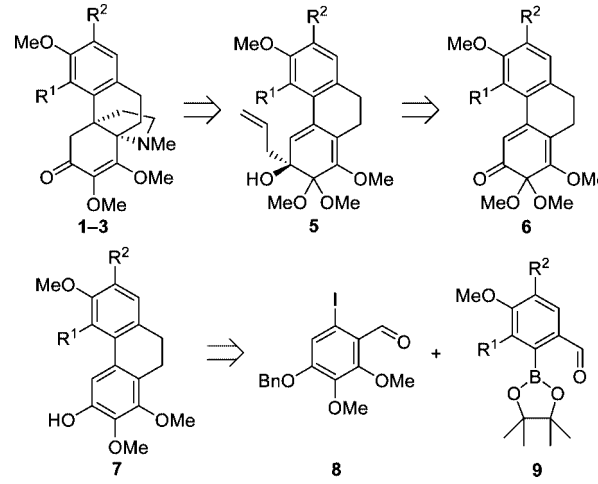
may explain why the hasubanan alkaloids do not share the potent analgesic activity of the morphine alkaloids.[1a] In addition, it has been demonstrated that the unnatural enantiomers of morphine alkaloids are devoid of painkilling properties.[6]

Recognizing the potential of the unnatural enantiomers of hasubanan alkaloids as analgesic agents, Schultz and Wang constructed the (+)-antipode of cepharamine.[5] However, to the best of our knowledge, no evaluation of the painkilling abilities of this material has been disclosed. Accordingly, our interest in determining the veracity of Schultz's hypothesis provided the impetus for launching a program directed at the enantioselective total synthesis of hasubanan alkaloids. Herein, we describe our efforts to construct hasubanonine (**1**), runanine (**2**), and aknadinine (**3**). We developed a synthetic route which appeared to deliver **1**;[7a] however, attempts to prepare **2** and **3** revealed that a previously undetected rearrangement had occurred in the final cyclization step.[7b] This process afforded an unnatural structure that we refer to as the isohasubanan skeleton. A significant aspect of this work was the discovery of an enantioselective ketone allylation which proceeds in good yield and excellent enantioselectivity (≥92% ee) with several complex ketones.

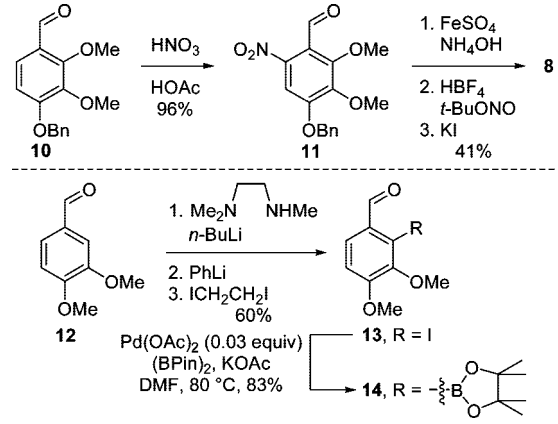
Results

Our retrosynthetic analysis of hasubanan alkaloids **1**−**3** is depicted in Scheme 1. Previously, we developed a route to the propellane-type[8] tricyclic core of the alkaloid acutumine which entailed annulation of a pyrrolidine ring onto an aromatic precursor. Key reactions in this sequence include a phenolic oxidation, an anionic oxy-Cope rearrangement, and a Michael-type cyclization.[9] Due to the similarities in structure between acutumine and the hasubanan alkaloids, we reasoned that this process would produce **1**−**3** from phenolic dihydrophenanthrenes of general structure **7** via the intermediacy of ketones **6** and homoallylic alcohols **5**. In order to accomplish an enantioselective synthesis of **1**−**3**, the asymmetric allylation of **6** to provide **5** would be required. Dihydrophenanthrenes **7** could be prepared from the corresponding phenanthrenes, which should be available in three simple steps from aryl iodide **8** and pinacolboronates **9** by means of Iuliano's method.[10] An advantage of employing this phenanthrene synthesis is that all three targeted compounds could be constructed from **8**. Moreover, additional hasubanan alkaloids and unnatural analogues would be readily accessible by simple modifications to either Suzuki coupling partner.

SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Synthesis of Iodide 8 and Boronate 14



At the outset, we identified two main synthetic objectives of this work. First, we wanted to determine if the five-step sequence developed for synthesis of the acutumine propellane core was directly applicable to preparation of the hasubanan skeleton or if modifications would be required. Second, we wished to evaluate the viability of ketones **6** as substrates for asymmetric allylations. We approached this second goal with some trepidation, as **6** differs significantly from ketones which are typically employed in asymmetric allylation studies (vide infra). Consequently, we initially focused on the first objective by embarking on a total synthesis of (±)-**1**.

This endeavor commenced with the preparation of aryl iodide **8** and aryl pinacolboronate **14** (Scheme 2). Nitration of 4-benzyloxy-2,3-dimethoxybenzaldehyde (**10**, available in two steps from commercially available 2,3-dimethoxyphenol)[11]

(3) Total syntheses: (a) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Chem. Pharm. Bull.* **1974**, *22*, 907. (b) Ibuka, T.; Tanaka, K.; Inubushi, Y. Tetrahedron Lett. 1972, *1393*. (c) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Chem. Pharm. Bull.* **1974**, *22*, 782. (d) Ibuka, T.; Tanaka, K.; Inubushi, Y. *Tetrahedron Lett.* **1970**, *4811*. (e) Kametani, T.; Nemoto, H.; Kobari, T.; Shishido, K.; Fukumoto, K. *Chem. Ind. (London)* **1972**, *538*. (f) Inubushi, Y.; Kitano, M.; Ibuka, T. *Chem. Pharm. Bull.* **1971**, *19*, 1820.

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(5) Schultz, A. G.; Wang, A. *J. Am. Chem. Soc.* **1998**, *120*, 8259.

(6) Iijima, I.; Minamikawa, J.; Jacobson, A. E.; Brossi, A.; Rice, K. *J. Org. Chem.* **1978**, *43*, 1462.

(7) Preliminary communication: (a) Jones, S. B.; He, L.; Castle, S. L. *Org. Lett.* **2006**, *8*, 3757. (b) Correction: Jones, S. B.; He, L.; Castle, S. L. *Org. Lett.* **2009**, *11*, 785.

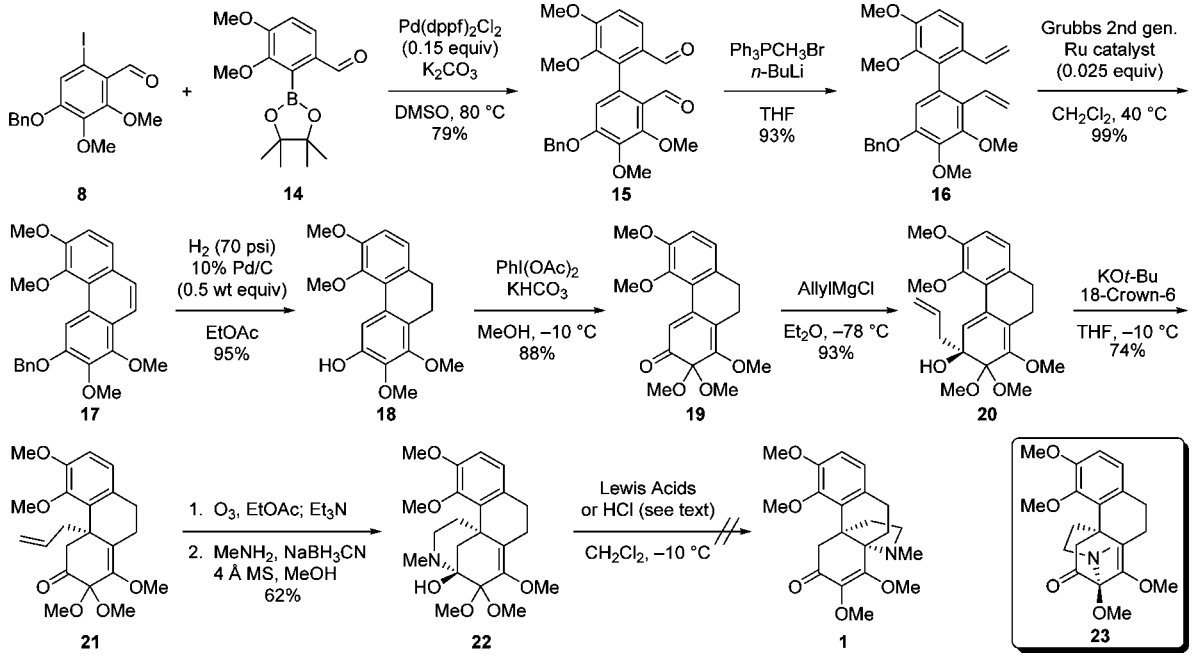
(8) For a review on the synthesis of propellane-containing natural products, see: Pihko, A. J.; Koskinen, A. M. P. *Tetrahedron* **2005**, *61*, 8769.

(9) Reeder, M. D.; Srikanth, G. S. C.; Jones, S. B.; Castle, S. L. *Org. Lett.* **2005**, *7*, 1089.

(10) Iuliano, A.; Piccioli, P.; Fabbri, D. *Org. Lett.* **2004**, *6*, 3711.

(11) Kurosawa, K.; Ollis, W. D.; Sutherland, I. O.; Gottlieb, O. R.; De Oliveira, A. B. *Phytochemistry* **1978**, *17*, 1389.

SCHEME 3. Coupling of 8 and 14 and Initial Attempts at Synthesizing 1



afforded **11**. The unusual regioselectivity of this reaction is precedented, as nitration of 2,3,4-trimethoxybenzaldehyde affords 2,3,4-trimethoxy-6-nitrobenzaldehyde.[12] The regiochemistry of nitro compound **11** was ultimately proven by its successful transformation into phenanthrene **17** (see Scheme 3); the biaryl adduct derived from the alternative nitro regioisomer would be unable to afford a phenanthrene via ring-closing metathesis. Then, a sequence of nitro reduction, diazotization, and iodination delivered aryl iodide **8** in 41% yield from **11**. Attempts at direct iodination of **10** afforded the undesired regioisomer of **8**; accordingly, we adopted the multistep protocol instead. The coupling partner of **8** was constructed in two steps from veratraldehyde (**12**). Thus, regioselective iodination according to the directed *ortho* metalation protocol of Comins[13] produced **13**, which was subjected to a Suzuki coupling with bis(pinacolato)diboron[14] to provide arylboronic ester **14**.

The Suzuki coupling of **8** and **14** was performed under a slight modification of conditions developed by Danishefsky and co-workers for the union of aryl iodides and aryl pinacolboronates (Scheme 3).[15] The resulting biaryl dialdehyde **15** was converted into diene **16** via Wittig olefination, and ring-closing metathesis of **16** with the Grubbs second-generation ruthenium catalyst[16] provided phenanthrene **17** in excellent yield. The three-step synthesis of **17** from **8** and **14**, which was inspired by the report of Iuliano and co-workers,[10] proceeded in 73% overall yield. This result is noteworthy given the hindered nature of the trisubstituted biaryl axis formed in the Suzuki coupling. Then, cleavage of the benzyl ether and reduction of the phenanthrene were simultaneously accomplished by high-pressure catalytic hydrogenation, affording phenolic dihydrophenanthrene **18** in 95% yield.

At this point, we applied our previously developed sequence for construction of the acutumine propellane core[9] to the transformation of **18** into **1**. Accordingly, addition of **18** to a solution of $PhI(OAc)_2$ in MeOH at low temperature caused a rapid (20 min) phenolic oxidation[17] that produced masked *o*-benzoquinone[18] **19**. 1,2-Addition of allylmagnesium chloride to **19** provided tertiary alcohol **20** in excellent yield. This alcohol was subsequently transformed into ketone **21** via an extremely facile anionic oxy-Cope rearrangement.[19] The reaction was complete at −10 °C within 15 min. It is likely that the presence of additional unsaturation in conjugation with the allylic alcohol moiety (i.e., methyl enol ether, aryl group) is responsible for the pronounced rate acceleration relative to typical anionic oxy-Cope rearrangements. Similar effects have been previously noted.[20] Ozonolysis of **21** was regioselective, affording the aldehyde derived from oxidative cleavage of the terminal olefin. However, frequent monitoring of the reaction by TLC was necessary in order to avoid oxidation of the electron-rich but hindered methyl enol ether. Reductive amination of the crude aldehyde with methylamine delivered a secondary amine, which cyclized to form hemiaminal **22**. This ozonolysis–reductive amination sequence was cleaner than our earlier work on the acutumine core, in which competitive oxidation of the tetrasubstituted methyl enol ether by ozone forced us to halt the reaction at ca. 50% conversion. Perhaps the less hindered nature of the terminal olefin of **21** compared to the corresponding olefin in the acutumine substrate[9] is responsible for the improved regioselectivity.

Surprisingly, exposure of **22** to our previously developed conditions (TMSOTf, 4 Å MS, CH_2Cl_2, −10 °C) for cyclization of an amine onto an α,β-unsaturated ketal[21] did not afford **1**. Rather, an isomer of **1** was obtained, as evidenced by HRMS.

(12) (a) Lin, A. J.; Pardini, R. S.; Lillis, B. J.; Sartorelli, A. C. *J. Med. Chem.* **1974**, *17*, 668. (b) Cherkaoui, M. Z.; Scherowsky, G. *New. J. Chem.* **1997**, *21*, 1203.

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(18) For a review on the chemistry of masked *o*-benzoquinones, see: Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383.

(19) (a) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971. (b) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

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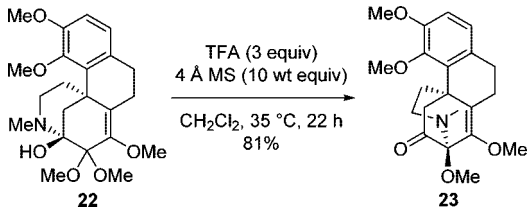
SCHEME 4. Conversion of 22 into 23

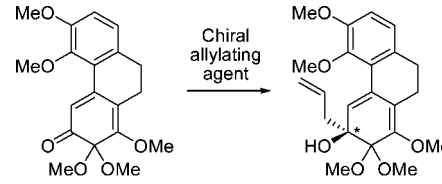


This compound was unstable to SiO_2, neutral alumina, basic alumina, and Florisil. It could be partially purified by rapid chromatography on SiO_2 that was pretreated with Et_3N or NaOH, but we were unable obtain a pure sample due to decomposition. Our inability to purify this product precluded us from precisely determining its structure. We tentatively assigned it as *N*,*O*-acetal **23** based on ^{1}H NMR spectra of partially purified samples, but that conclusion was later shown to be incorrect (vide infra). Formation of this undesired isomer of **1** was quite rapid (≤10 min) and could also be accomplished by treatment of **22** with BCl_3 or HCl. Unfortunately, attempts to convert this compound into **1** were fruitless, as it decomposed under all of the conditions examined.

After considerable experimentation, we discovered that trifluoroacetic acid facilitated the transformation of **22** into a compound whose spectral data matched reasonably well with the available data for **1**. Ultimately, we determined that this product did not have the structure of **1**. Instead, we are now confident that *N*,*O*-acetal **23** was produced from this reaction (Scheme 4).[7b] Nevertheless, this fact was initially unrecognized due to the paucity of NMR data available for **1**,[22] a compound whose structure was determined in 1964.[2b] Optimized conditions for the production of **23** entailed warming a solution of **22** in CH_2Cl_2 at 35 °C in the presence of 3 equiv of TFA and 10 weight equiv of 4 Å MS for 22 h (Scheme 4). Reactions conducted at room temperature were sluggish, proceeding to <50% completion after 24 h. To the best of our knowledge, the skeleton represented by **23** is not produced in nature. Hereafter, we refer to **23** and related compounds as isohasubanan alkaloids.

Convinced that we had successfully completed the total synthesis of racemic **1**, we set out to accomplish an enantioselective total synthesis. This required an enantioselective ketone allylation (**19**→**20**, Scheme 3). Recently, numerous methods for enantioselective ketone allylation have been reported.[23,24] However, to the best of our knowledge, none of these processes have been employed in a total synthesis; rather, the development of this methodology has primarily been conducted with simple acetophenone derivatives. We were anxious to determine which, if any, of the known enantioselective ketone allylation protocols were compatible with the sterically hindered, functional-group-laden substrates typically encountered in a total synthesis.

TABLE 1. Enantioselective Allylation of 19



entry	reagent[a]	result
1	**24**	complex mixture
2	**25**	byproduct[b]
3	**26**[c]	racemic
4	**27**	no reaction
5	**28**	racemic
6	**29**	no reaction
7	**30**	racemic
8	**31a**	25% ee[d]
9	**31b**	racemic
10	**31c**	5% ee[d]
11	**32**	76% yield, 93% ee[d]

[a] See Figure 2 for structures and references to reaction conditions. [b] An unidentified compound was obtained, and **20** was not observed. [c] Conditions: THF, −90 °C. [d] Determined by chiral HPLC (Chiralcel OD-H, 99:1 hexane/*i*-PrOH, 1 mL/min).

The structures of the chiral allylating reagents and catalysts which we tested are portrayed in Figure 2, and the results of our investigation are contained in Table 1. Application of the chromium-catalyzed procedure discovered by Sigman[23b] resulted in consumption of **19**, but a complex mixture was created from which **20** could not be identified (entry 1).[25] The Walsh protocol, which employs a Ti−BINOL catalyst in conjunction with tetraallyltin,[23d] gave a cleaner mixture, but the major product was neither **20** nor the 1,4-addition product **21** (entry 2). We attempted to modify this method by generating chiral allyltitanium reagent **26** via reaction of the Ti−BINOL complex with allylmagnesium chloride. The resultant species did react with **19** to form **20**; unfortunately, the allylic alcohol was produced in racemic fashion (entry 3). The asymmetric Sakurai−Hosomi allylation of Yamamoto[23g] and the copper-catalyzed enantioselective allylboration of Shibasaki[23k] also yielded racemic homoallylic alcohol **20** (entries 5 and 7). In our hands, the catalysts and reagents developed by Schaus[23e] and Loh[23j] were unreactive with **19** (entries 4 and 6). Our first promising result came from the TADDOL-modified Grignard reagents of

(21) These conditions (reported in ref 9) are based on the work of Matsumoto: Yasui, Y.; Koga, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2004**, *615*.

(22) We were able to locate two sets of partial low-field ^{1}H NMR data for **1** in the literature: Singh, R. S.; Kumar, P.; Bhakuni, D. S *J. Nat. Prod.* **1981**, *44*, 664, as well as refs 2a and 2b. Both sets of data only list chemical shift values for the aromatic hydrogens, the methoxy and *N*-methyl groups, and the α-ketone hydrogens. Interestingly, the two sets of data do not agree very well with each other; the differences in chemical shift range from 0.10 to 0.25 ppm. We attributed these discrepancies to the existence of multiple forms of **1** (i.e., different salts versus the free base). Our data matched more closely to that of Bhakuni. We also obtained COSY and HETCOR spectra which were consistent with the connectivity of atoms shown in **1**. We were unable to locate any ^{13}C NMR data for **1** in the literature, and a discrepancy between structure **1** and our ^{13}C NMR data was initially overlooked due to the overlapping of two signals (vide infra).

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(24) For reviews, see: (a) García, C.; Martín, V. S. *Curr. Org. Chem.* **2006**, *10*, 1849. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

(25) This experiment was conducted by Jeremie J. Miller in the Sigman laboratory at the University of Utah.

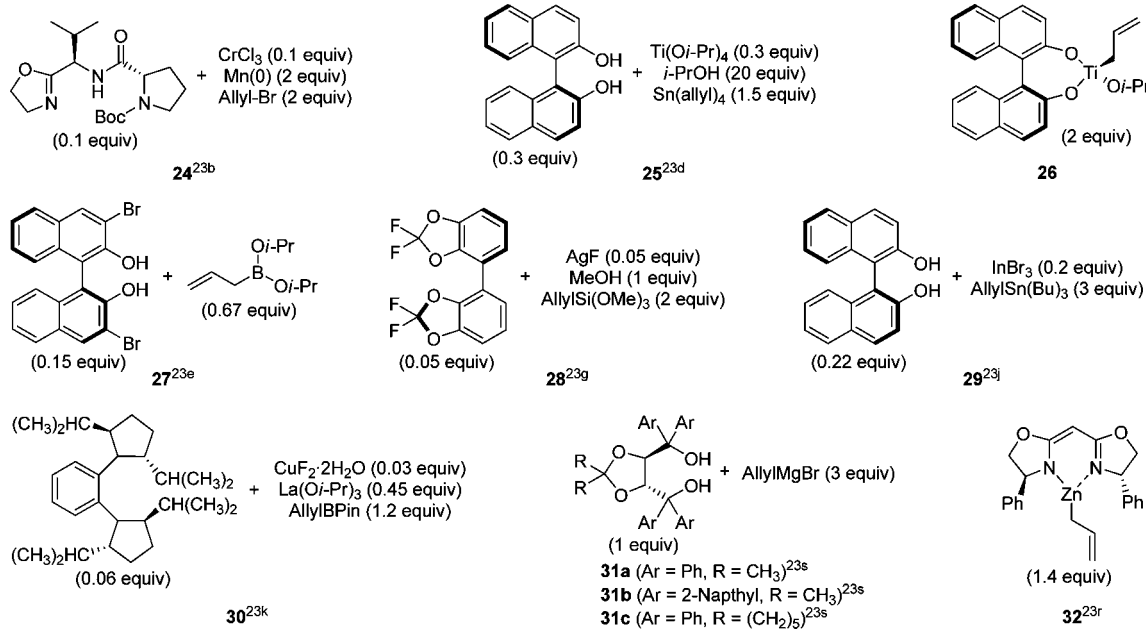
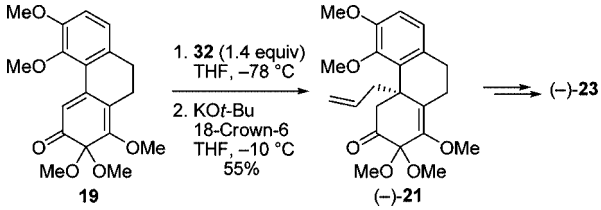


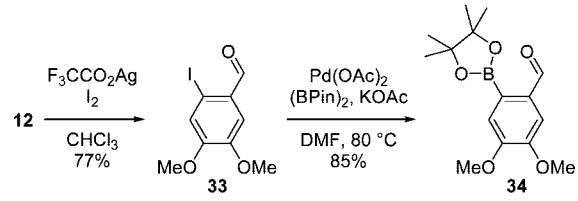
FIGURE 2. Catalysts and reagents used in enantioselective ketone allylation studies.

SCHEME 5. Enantioselective Synthesis of (−)-23[a]



[a] See Schemes 3 and 4 for conversion of **21** into **23**.

SCHEME 6. Synthesis of Boronate 34



Seebach.[23s] Use of the tetraphenyl TADDOL ligand **31a** provided alcohol **20** in modest enantiomeric excess (25% ee, entry 8). However, the reaction had to be conducted at −108 °C in order to achieve any enantioselectivity. Interestingly, the reaction was quite rapid (ca. 30 min) at this low temperature. Unfortunately, replacing TADDOL **31a** with either tetranaphthyl TADDOL **31b** or cyclohexanone-derived TADDOL **31c** led to poorer results (entries 9 and 10).

In 1998, the Nakamura group developed a bisoxazoline-ligated chiral allylzinc reagent (**32**, Figure 2) for the enantioselective allylation of alkynyl ketones.[23r] Despite its utility for this purpose, Nakamura's reagent has not found wide application in organic synthesis.[26] To our delight, **32** reacted cleanly with ketone **19**, affording (−)-**20** in 93% ee (entry 11). Separation of the bisoxazoline ligand from (−)-**20** was challenging but possible, affording a 76% yield of the desired product. In practice, we found it more convenient to perform the subsequent anionic oxy-Cope rearrangement on crude (−)-**20** and purify the resultant ketone (−)-**21** (Scheme 5). This intermediate was then converted into (−)-isohasubanonine ((−)-**23**) by means of the pathway outlined in Scheme 3 and 4. Chiral HPLC analysis of (−)-**23** indicated that no racemization occurred during the synthesis. At the time, we still believed we had synthesized hasubanonine instead of isohasubanonine. Accordingly, we compared our optical rotation value to those recorded in the literature for (−)-**1**. Interestingly, there is a discrepancy in the literature regarding the magnitude of the optical rotation of hasubanonine; values of −219 (*c* 0.78, EtOH),[2c] −214 (*c* 2.0, MeOH),[22] and −134 (*c* 0.82, MeOH)[27] have been reported. Our measurement ($[\alpha]^{25}_{D}$ −114 (*c* 0.45, MeOH)) was relatively close to that of Kupchan and co-workers.[27] Consequently, we thought we had synthesized the natural enantiomer of hasubanonine, and we attributed the varying optical rotation values to concentration and solvent effects.

We were anxious to determine the scope of the Nakamura asymmetric ketone allylation and the versatility of what we believed was a route to the hasubanan alkaloids. Accordingly, we next embarked upon a total synthesis of (−)-runanine[28] (**2**, Figure 1). The structural similarities between **1** and **2** allowed us to employ aryl iodide **8** as an intermediate in this new endeavor. However, an arylboronic ester isomeric to **14** was required. The preparation of this new building block was straightforward and is detailed in Scheme 6. Veratraldehyde (**12**), the precursor to **14**, was the starting point for this synthesis as well. Ag^{+}-mediated iodination of **12** afforded known aryl iodide **33**.[29] Borylation of **33** utilizing the procedure described in Scheme 2 for iodide **13** delivered the requisite arylboronic ester **34** in good yield. It is noteworthy that two isomeric aryl iodides (**13** and **33**) can be accessed from veratraldehyde via complementary iodination protocols.

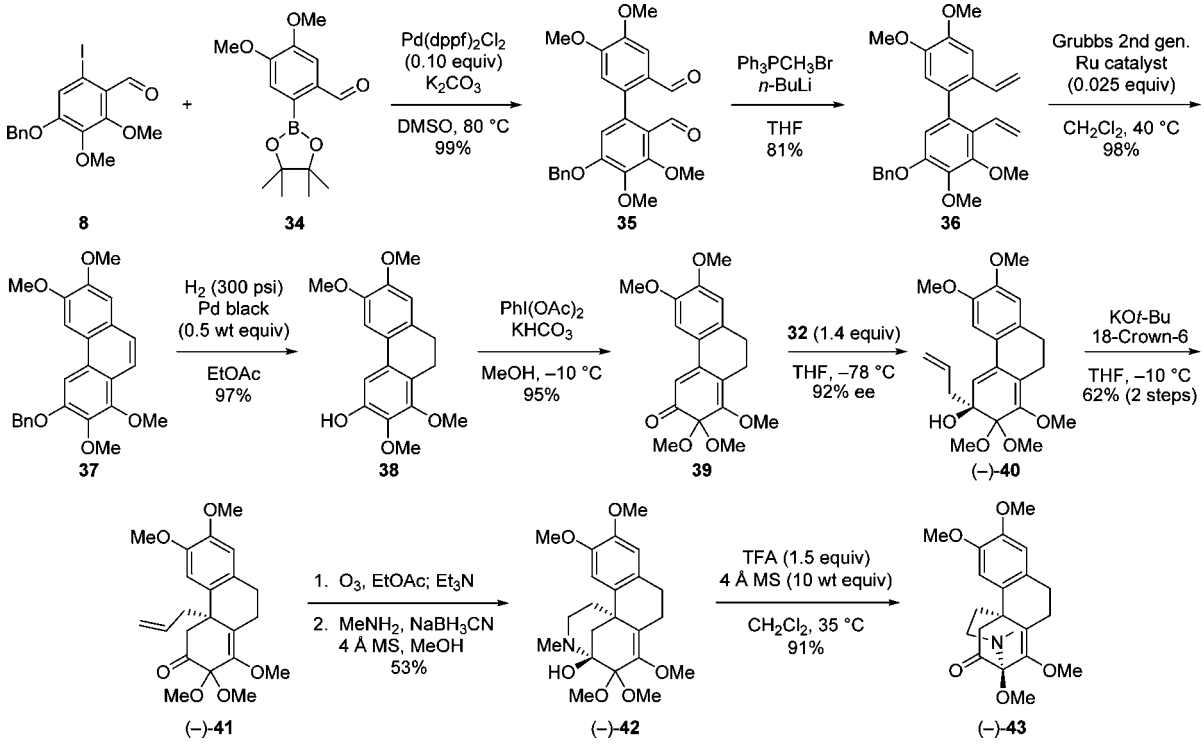
(26) A Scifinder Scholar search failed to turn up any examples of the use of **32** other than the reactions reported in ref 23r.

(27) Kupchan, S. M.; Suffness, M. I.; White, D. N. J.; McPhail, A. T.; Sim, G. A. *J. Org. Chem.* **1968**, *33*, 4529.

(28) Zhi-Da, M.; Ge, L.; Guang-Xi, X.; Iinuma, M.; Tanaka, T.; Mizuno, M. *Phytochemistry* **1985**, *24*, 3084 This paper contains a full set of ^{1}H NMR data for **2**, but no ^{13}C NMR data.

(29) (a) Ahmad-Junan, S. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, *675*. (b) Olivera, R.; SanMartin, R.; Domínguez, E.; Solans, X.; Urtiaga, M. K.; Arriortua, M. I. *J. Org. Chem.* **2000**, *65*, 6398.

SCHEME 7. Synthesis of (−)-Isorunanine ((−)-43)



Arylboronic ester **34** and iodide **8** were joined in a high-yielding Suzuki coupling, providing biaryl dialdehyde **35** (Scheme 7). We attribute the greater yield in this reaction relative to the analogous transformation in the isohasubanonine synthesis (99% vs 79%; see Scheme 3) to the less hindered nature of **34** compared to **14**. The subsequent Wittig reaction and ring-closing metathesis also proceeded well, delivering phenanthrene **37**. Surprisingly, **37** was considerably more resistant to reduction than its counterpart **17** from the isohasubanonine series. When **37** was exposed to the conditions used to convert **17** into phenolic dihydrophenanthrene **18** (70 psi H_2, Pd/C, EtOAc), the major product was the corresponding phenolic phenanthrene in which the extended aromatic system remained intact. Increases in both pressure (up to 1200 psi) and reaction time (up to 5 d) gave no more than minor amounts of desired dihydrophenanthrene **38**. The use of other protocols reported to reduce phenanthrenes to dihydrophenanthrenes (Li/NH_3,[30] $RhCl_3$/70 psi H_2,[31] PtO_2/300 psi H_2[32]) afforded complex mixtures presumably derived from over-reduction. Our standard hydrogenation conditions developed with phenanthrene **17** employed EtOAc as solvent due to insolubility of the starting material in MeOH, which is often the solvent of choice for hydrogenations. We found that the debenzylated phenanthrene derived from **37** was soluble in MeOH; accordingly, we attempted to hydrogenate the partially reduced compound in this solvent. Dihydrophenanthrene **38** was produced from these reactions; however, yields were low and variable (15−50%). Finally, an effective solution was provided by substituting Pd black for Pd/C. With this more active catalyst, **38** was obtained in a single step from **37** in excellent yield (97%). It is possible that the existence of steric strain between the C-5 methoxy group and the C-4 hydrogen of **17,** which is relieved upon reduction of the phenanthrene, renders this substrate more reactive than **37** to hydrogenation. The latter compound does not possess a methoxy group at C-5 and thus cannot benefit from a corresponding strain release upon reduction.[33]

Phenolic oxidation of **38** proceeded smoothly, providing masked *o*-benzoquinone **39** and setting the stage for the crucial asymmetric allylation. We were pleased to discover that Nakamura's reagent **32** facilitated a clean, highly enantioselective allylation, delivering homoallylic alcohol (−)-**40** in 92% ee. As in the (−)-isohasubanonine total synthesis, this intermediate was typically subjected to the anionic oxy-Cope rearrangement in crude form. In this way, a 62% yield of ketone (−)-**41** was produced from **39**. Then, ozonolysis, reductive amination, and Michael-type cyclization afforded (−)-isorunanine ((−)-**43**). Importantly, in the process of optimizing the cyclization, we found that it could be conducted with fewer equivalents of TFA than employed previously (1.5 vs 3.0).

Comparison of our ^{1}H NMR data for (−)-**43** to the data available in the literature for (−)-**2**[28] revealed numerous discrepancies. Moreover, our measured optical rotation for (−)-**43** ($[\alpha]^{25}_D$ −34 (*c* 0.38, $CHCl_3$)) was significantly lower than the reported value for (−)-**2** ($[\alpha]^{25}_D$ −400 (*c* 0.8, $CHCl_3$)).[28] Thus, at this point it was clear that we had not synthesized runanine. Furthermore, given the similarities in the ^{1}H and ^{13}C NMR spectra of **23** and **43**, we began to doubt that we had synthesized hasubanonine. Accordingly, we commenced a thorough structural investigation of the two products. Unfortunately, attempts to grow crystals suitable for X-ray diffraction were thwarted by decomposition of the material in solution over a period of days at room temperature. Both **23** and **43** are stable to long-term storage at −30 °C, and they do not decompose

(30) Broering, T. J.; Morrow, G. W. *Synth. Commun.* **1999**, *29*, 1135.
(31) Amer, I.; Amer, H.; Ascher, R.; Blum, J.; Sasson, Y.; Vollhardt, K. P. C. *J. Mol. Catal.* **1987**, *39*, 185.
(32) Bhandari, S. R.; Kapadi, A. H. *Indian J. Chem., Sect. B* **1985**, *24B*, 204.

(33) We thank the reviewers for this suggestion.

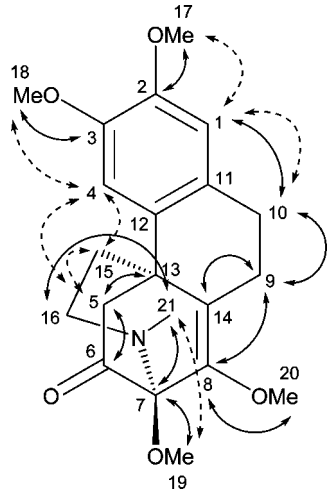


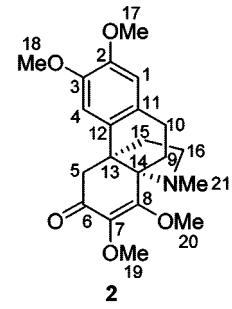
FIGURE 3. HMBC (solid arrows) and NOE (dashed arrows) correlations of **43**.

noticeably during purification or overnight NMR experiments. Nevertheless, their instability to standard crystallization conditions provides indirect evidence that they are not hasubanan alkaloids, as an X-ray structure of a hasubanan alkaloid has been obtained previously.[27]

Fortunately, NOE and 2D NMR experiments were informative and allowed us to determine the structures of our products. Isorunanine ((−)-**43**) was quite well-suited for NMR analysis, as the positioning of the aryl hydrogens allowed us to observe through-bond and through-space correlations across a large portion of the molecule. COSY, HMQC, HMBC, and NOE experiments were in strong agreement with the isorunanine structure, and the diagnostic HMBC and NOE correlations are shown in Figure 3. Particularly instructive are the H-19/C-7 and H-21/C-7 HMBC correlations as well as the H-19/H-21 NOE correlation, which demonstrate the presence of an *N*,*O*-acetal moiety. Furthermore, the relative positions of C-5, C-6, and C-15 are established by the H-5/C-6 HMBC correlation combined with NOE enhancements between H-4 and H-5, H-4 and H-15, and H-5 and H-15. An identical set of NMR experiments conducted on (−)-**23** were also in agreement with the proposed isohasubanan alkaloid skeleton.[34]

Comparison of the hasubanan and isohasubanan alkaloid skeletons (see Figures 1 and 3) reveals a fairly simple way to distinguish the two classes of compounds. The ^{13}C NMR spectra of **1** and **2** should show nine downfield signals (≥90 ppm) and twelve upfield signals (≤70 ppm), whereas 10 downfield and 11 upfield signals should be observed in the corresponding spectra of **23** and **43**. Unfortunately, the signals for C-12 and C-14 of **23** overlap precisely at 129.5 ppm. Therefore, we initially believed there were only nine downfield signals, and we assigned a small peak caused by an impurity at 29.9 ppm (presumably hydrocarbon grease) as the twelfth upfield signal. Fortunately, the C-12 and C-14 peaks in **43** are resolved (129.45 and 129.41 ppm), so proper interpretation of the ^{13}C spectrum of this compound was much simpler.

Additional evidence in support of the isorunanine structure was obtained from GIAO ^{13}C NMR calculations. This technique has been used by Bifulco,[35] Rychnovsky,[36] and others[37] as a



2

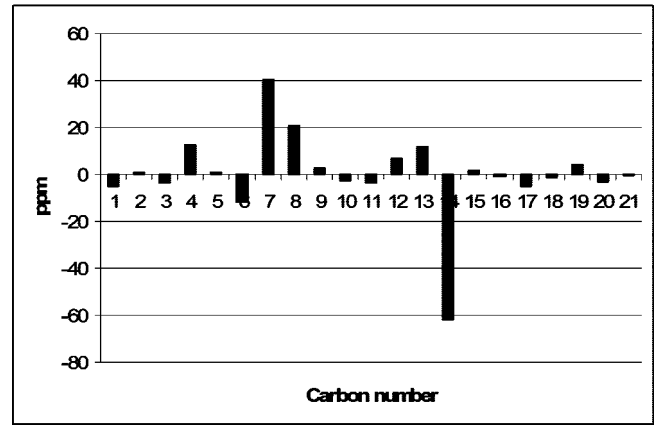


FIGURE 4. Difference between calculated and experimental ^{13}C NMR shifts for runanine (**2**). The average $|\Delta\delta|$ was 9.7 ppm, and the maximum was 61.7 ppm.

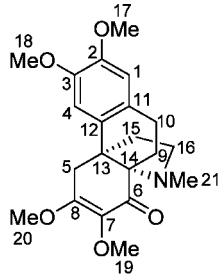
tool in the structural assignment of organic molecules. It has been particularly valuable in distinguishing between constitutional isomers. Accordingly, we turned to these calculations as a means of checking the validity of our proposed isorunanine structure. Thus, the geometries of runanine (**2**), isorunanine (**43**), and isomers **44**−**46** (see Figures 5–7 for structures) were optimized at the mPW1PW91/6-31G(d,p) level, and the resultant conformations were subjected to GIAO NMR calculations. Isomer **45**, which differs from runanine in the orientation of the pyrrolidine ring, was included in this exercise because we could envision a mechanism for its formation under the acidic cyclization conditions involving the 1,2-alkyl shift of a cationic intermediate. Although we could not formulate a reasonable mechanistic hypothesis for the production of compounds **44** and **46**, which are the carbonyl-transposed isomers of **2** and **45**, we recognized that both would possess identical spin systems to **2**, **43**, and **45**. Since structures **44** and **46** could possibly fit our NMR data, we included them in the computational exercise to ensure completeness. Our results are recorded in Figures 4−8. Clearly, structures **2** and **44**−**46** are not good fits for the experimentally obtained data. In particular, C-7 (*N*,*O*-acetal carbon in **43**, alkene carbon in other structures) and C-14 (alkene carbon in **43**, quaternary aliphatic carbon in other structures) exhibited significant error (ca. 40−60 ppm difference between calculated and observed chemical shifts). The average difference between the computed and observed chemical shifts for structures **2** and **44**−**46** ranged from 9.3 to 12.0 ppm. In contrast, the calculated ^{13}C NMR data for isorunanine (**43**) agreed much better with our observed data. The average deviation dropped to 3.8 ppm, and the maximum deviation was 9.8 ppm. C-4

(34) For details, see the Supporting Information.

(35) Bifulco, G.; Dambruoso, P.; Gomez-Paloma, L.; Riccio, R. *Chem. Rev.* **2007**, *107*, 3744.

(36) Rychnovsky, S. D. *Org. Lett.* **2006**, *8*, 2895.

(37) (a) Smith, S. G.; Paton, R. S.; Burton, J. W.; Goodman, J. M. *J. Org. Chem.* **2008**, *73*, 4053. (b) Braddock, D. C.; Rzepa, H. S. *J. Nat. Prod.* **2008**, *71*, 728.



44

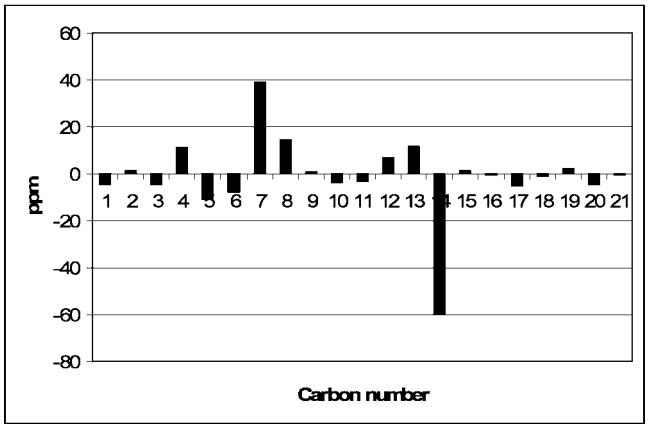
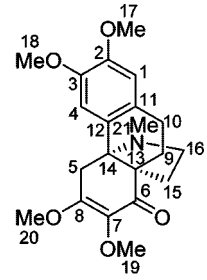


FIGURE 5. Difference between calculated and experimental ^{13}C NMR shifts for isomer **44**. The average $|\Delta\delta|$ was 9.3 ppm, and the maximum was 60.1 ppm.



46

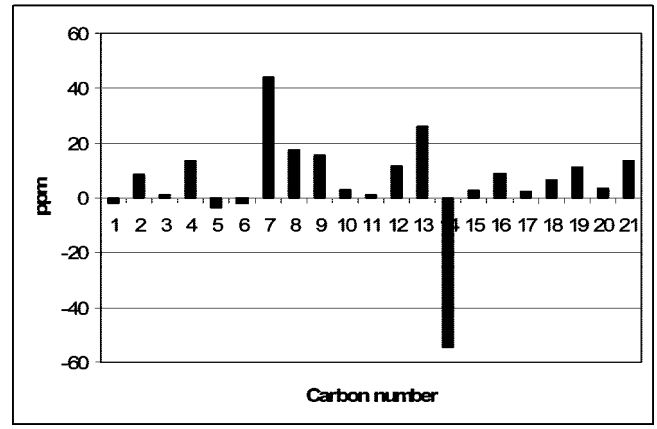
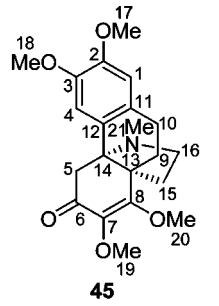


FIGURE 7. Difference between calculated and experimental ^{13}C NMR shifts for isomer **46**. The average $|\Delta\delta|$ was 12.0 ppm, and the maximum was 54.6 ppm.



45

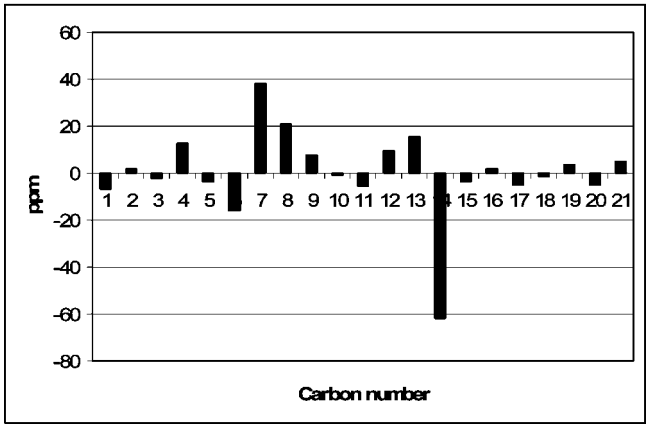
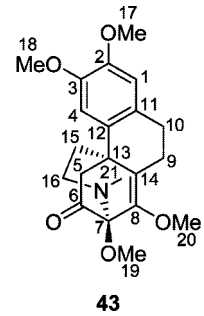


FIGURE 6. Difference between calculated and experimental ^{13}C NMR shifts for isomer **45**. The average $|\Delta\delta|$ was 10.9 ppm, and the maximum was 61.8 ppm.



43

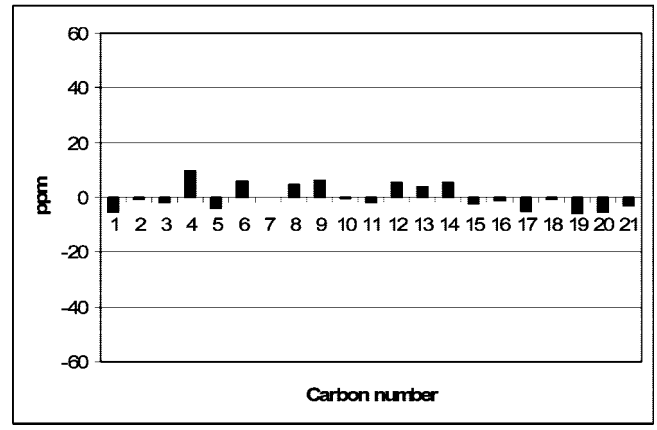
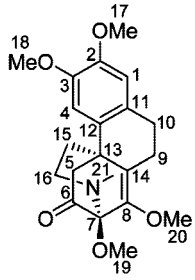


FIGURE 8. Difference between calculated and experimental ^{13}C NMR shifts for isorunanine (**43**). The average $|\Delta\delta|$ was 3.8 ppm, and the maximum was 9.8 ppm.

exhibited the largest difference, with the calculated value (118.3 ppm) being significantly higher than the experimental value (108.5 ppm, assignment verified by NOE and HMBC spectroscopy). Perhaps the neighboring bridged ring system in **43** exerts a shielding effect on this carbon which is not fully accounted for by the computer algorithm. Reassuringly, the calculated chemical shifts of C-7 and C-14 in structure **43** fit the experimental ^{13}C NMR data quite well, with differences of 0.1 and 5.6 ppm, respectively.



43

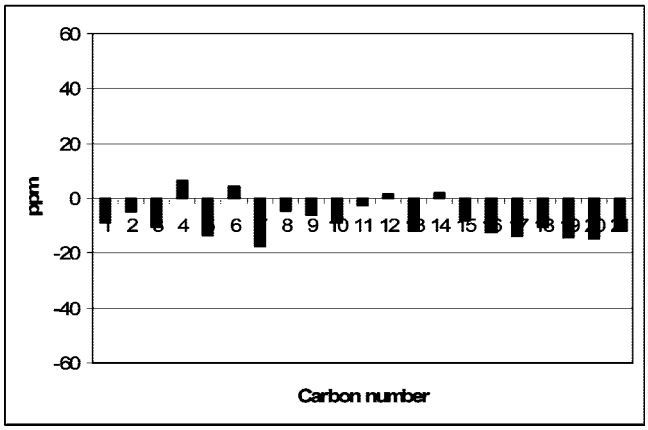


FIGURE 9. Difference between calculated and experimental ^{13}C NMR shifts for isorunanine (**43**) in benzene. The average $|\Delta\delta|$ was 9.1 ppm, and the maximum was 17.4 ppm.

The calculations described in Figures 4−8 were performed with a chloroform solvent correction. Since we also acquired the ^{13}C NMR spectrum of isorunanine in C_6D_6, we performed an identical set of calculations on all five structures with a benzene solvent correction. Surprisingly, the calculated chemical shifts for **43** in this case did not agree well with the experimentally determined data (Figure 9). Particularly telling was the fact that all aliphatic carbons bonded to heteroatoms exhibited calculated chemical shifts which were significantly lower than the observed values (−10.5 to −17.4 ppm deviations). The reasons for this unusual phenomenon are unclear. Experimentally, the differences in chemical shift between spectra of isorunanine acquired in $CDCl_3$ and C_6D_6 are slight (2.3 ppm maximum difference; <1.0 ppm difference for most carbons). Moreover, the differences in data calculated in both solvents were quite minor (<1.0 ppm for the vast majority of carbons) for structures **2** and **44**−**46**. It is possible that the benzene solvent correction algorithm is treating the bridged structure of **43** differently than it treats the fused propellane structures of **2** and **44**−**46**. Whatever the reason, it appears that the benzene solvent correction should be used cautiously when performing GIAO ^{13}C NMR calculations.

Prior to recognizing that our synthetic route did not provide hasubanan alkaloids, we set our sights on constructing (−)-aknadinine (**3**, Figure 1).[22,27,38] We expected **3** to be more challenging to prepare due to the presence of a free phenol on the aromatic ring. This would require differentiation of the two oxygen substituents on the arylboronic acid coupling partner. Accordingly, aryl iodide **47**[39] was coupled with bis(pinacolato)diboron, affording arylboronic ester **48** (Scheme 8). In contrast to previously performed couplings, the Suzuki coupling of **48** with aryl iodide **8** was sluggish, with increased quantities of $Pd(dppf)_2Cl_2$ required for good yields (0.25 equiv vs 0.10−0.15 equiv in earlier reactions). Presumably, the additional steric hindrance caused by the *o*-MOM group retards the reaction rate. Conversion of biaryl dialdehyde **49** into masked *o*-benzoquinone **53** proceeded in analogous fashion to the isohasubanonine synthesis. Fortunately, the hydrogenation of **51** was relatively facile and could be conducted with Pd/C. As with phenanthrene **17**, it is possible that strain release provides a driving force for the reduction of **51**. However, it was necessary to prewash the EtOAc with Na_2CO_3 and store it over K_2CO_3, as the use of untreated solvent led to concomitant cleavage of the MOM group.

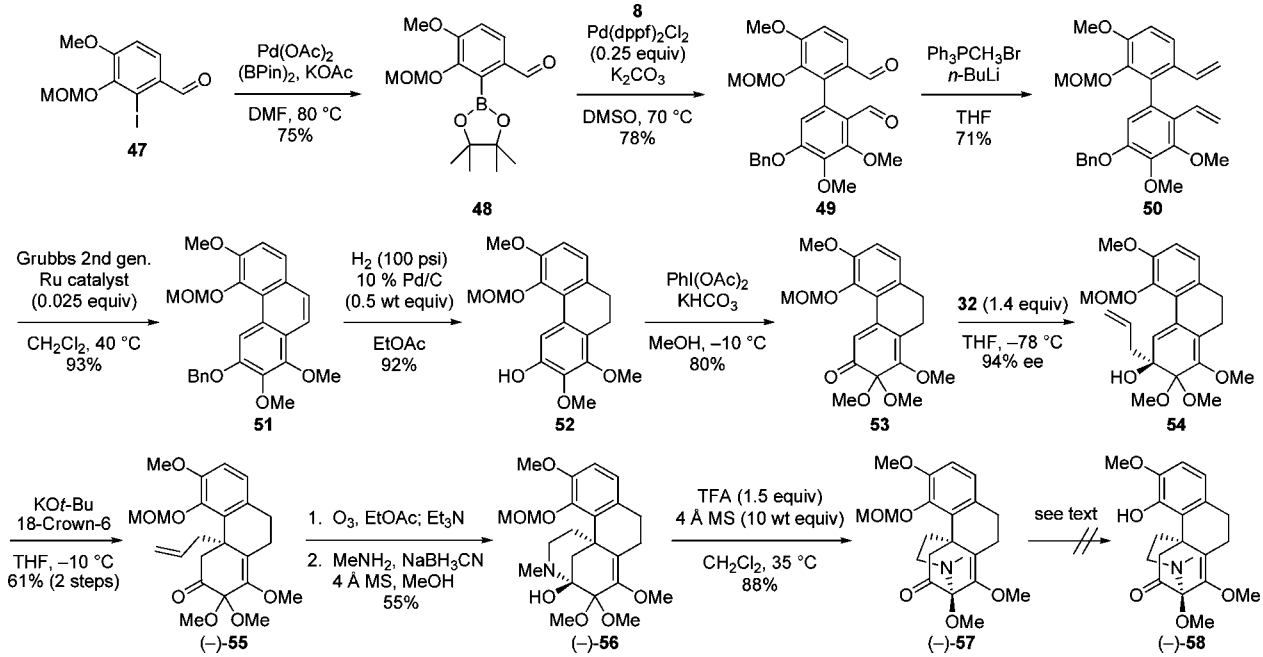
Gratifyingly, asymmetric allylation of ketone **53** with the Nakamura reagent proceeded with 94% ee. As before, separation of the product from the bisoxazoline ligand was accomplished most conveniently after the anionic oxy-Cope rearrangement. Then, ozonolysis/reductive amination and subsequent cyclization delivered MOM-protected isoaknadinine ((−)-**57**). Unfortunately, all attempts to cleave the phenolic MOM group were unsuccessful. Numerous Brønsted and Lewis acids were examined, and analysis of the cleaner reactions indicated that loss of a methyl ether was occurring in preference to MOM deprotection. This phenomenon provided yet another piece of evidence in favor of the isohasubanan skeleton, which possesses a relatively labile methyl enol ether. We were unable to remove the MOM moiety from intermediates **53**−**56** without damaging other acid-sensitive functional groups present in these compounds. Consequently, we were forced to resort to a swap of protecting groups.

We were reticent to introduce a group larger than the MOM moiety into an arylboronic ester of type **48** for fear of further impeding the Suzuki coupling. Thus, we maintained the existing route up to phenanthrene **51** and then removed the MOM group under standard conditions (Scheme 9). Protection of the resulting free phenol as its triethylsilyl ether afforded **60**, which was converted into masked *o*-benzoquinone **62** in quantitative yield over two steps. We were concerned that the additional steric demand of **62** relative to the other ketones employed in the Nakamura asymmetric allylation might be problematic. While we did need to increase the concentration of chiral allylzinc reagent **32** in order to obtain good yields (1.8 equiv vs 1.4 equiv used previously), we were pleased to find that alcohol **63** was produced in excellent ee (96%). When **63** was subjected to the anionic oxy-Cope rearrangement, rapid TES cleavage occurred, and the rearrangement was extremely sluggish. Therefore, the silyl ether was removed under conventional conditions, and the crude phenol was treated with KO*t*-Bu and 18-crown-6. However, the rearrangement still did not occur. Success was achieved by rapidly passing the crude phenol through a silica gel column and then performing the sigmatropic rearrangement. The presence of a free phenol in the substrate necessitated the use of additional base (2.4 equiv) and elevated temperature (40 °C) to promote the reaction. Unfortunately, a low yield of ketone (−)-**64** was obtained (28%). We believe that the bulk of the material was lost during the attempted purification of the intermediate phenol, as multiple colored bands resulted from application of the crude material to the column. Nevertheless,

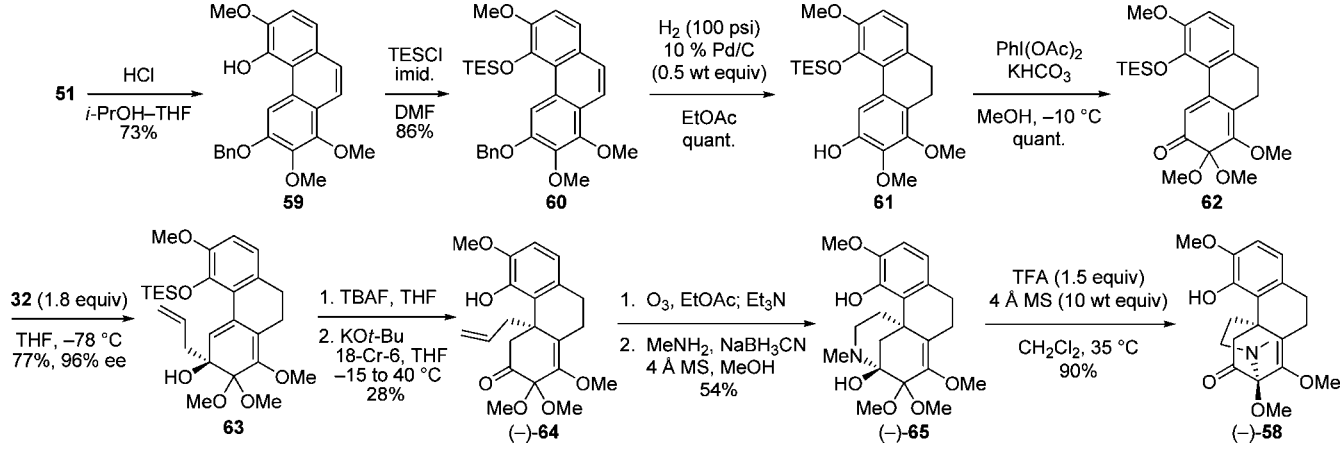
(38) (a) Moza, B. K.; Bhaduri, B.; Basu, D. K. *Chem. Ind. (London)* **1969**, *1178*. (b) Moza, B. K.; Bhaduri, B.; Basu, D. K.; Kunitomo, J.; Okamoto, Y.; Yuge, E.; Nagai, Y.; Ibuka, T. *Tetrahedron* **1970**, *26*, 427. (c) Kashiwaba, N.; Morooka, S.; Kimura, M.; Ono, M.; Toda, J.; Suzuki, H.; Sano, T. *J. Nat. Prod.* **1996**, *59*, 476.

(39) Markey, M. D.; Fu, Y.; Kelly, T. R. *Org. Lett.* **2007**, *9*, 3255.

SCHEME 8. Attempted Synthesis of (−)-Isoaknadinine ((−)-58)



SCHEME 9. Synthesis of (−)-Isoaknadinine ((−)-58)



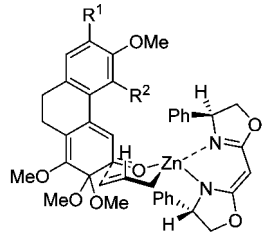
sufficient quantities of (−)-**64** were acquired to enable synthesis of isoaknadinine, so further optimization was not pursued. In fact, the next two steps proceeded in identical fashion to our earlier efforts, providing (−)-**58**. 1D and 2D NMR spectra of (−)-**58** exhibited strong similarities to spectra of (−)-**23** and (−)-**43** and possessed the characteristic features of the isohasubanan skeleton.[34]

Prior to discovery of the enantioselective ketone allylation, we accumulated sufficient quantities of racemic **23** for evaluation of its analgesic properties. At the time, we were under the impression that we had prepared hasubanonine. Racemic **23** did not exhibit any affinity for the μ, κ, or δ opioid receptors. In the mouse tail-flick assay, no painkilling activity was detected at concentrations of 10, 30, and 56 mg/kg. Some analgesia was observed (approximately 50% of maximum effect) at a high concentration of **23** (100 mg/kg). Thus, it appears that (±)-**23** possesses weak analgesic activity that is not mediated by opioid receptors. These results suggest that the isohasubanan alkaloids are not useful lead structures for new painkilling agents.

Discussion

Although these endeavors did not result in the total synthesis of hasubanan alkaloids, there are several interesting and useful facets of our work. Chief among them is the discovery that Nakamura's chiral zinc reagent **32** is extraordinarily effective in the enantioselective allylations of ketones **19**, **39**, **53**, and **62**. Despite the fact that asymmetric ketone allylation is currently an active area of research,[23,24] we are unaware of any previous examples of this reaction being performed on a complex ketone in the context of a multistep synthesis. Reagent **32** was designed specifically for use with alkynyl ketones, and it has not been utilized in organic synthesis.[26] Our finding that other, more elaborate ketones are excellent substrates for **32** may lead to increased usage of this reagent.

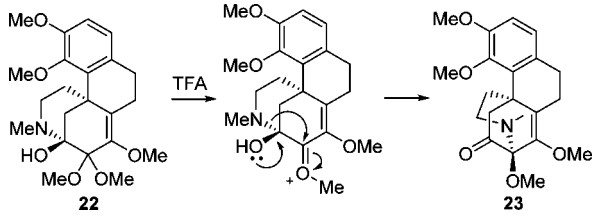
We have yet to construct any natural products or known compounds from the enantioenriched homoallylic alcohols, and attempts to grow crystals of isohasubanan ammonium salts possessing heavy atoms resulted in decomposition of the samples. Thus, at this time we are limited to speculation



19: R^1 = H, R^2 = OMe (93% ee)
39: R^1 = OMe, R^2 = H (92% ee)
53: R^1 = H, R^2 = OMOM (94% ee)
62: R^1 = H, R^2 = OTES (96% ee)

FIGURE 10. Proposed transition-state model.

SCHEME 10. Mechanistic Rationale for Isohasubanonine Formation



concerning the absolute configurations of the allylation adducts. Nakamura and co-workers proposed a cyclic six-membered transition state for allylations of alkynyl ketones by **32** in which the alkynyl and alkyl groups of the ketone occupy axial and equatorial positions, respectively. Computational studies lent some support to this model.[23r] Superimposing our substrates onto Nakamura's model (Figure 10) demonstrates that the bulky dimethyl ketal can occupy the equatorial position, whereas the axial position can be filled by the planar aryl group. The facial selectivity of the allylation is likely dictated by the fact that the aryl moiety of the substrate is significantly larger than the axial vinylic hydrogen of the allyl group. Thus, the aryl group resides in a location where it can avoid steric interactions with the phenyl group of the bisoxazoline ligand. If this model is correct, then alcohols **20**, **40**, **54**, and **63** each possess the (*S*)-configuration as drawn herein. It is noteworthy that ketones **53** and **62**, which incorporate sterically more demanding groups at the R^2 position than do **19** and **39**, undergo the allylation with excellent enantioselectivity. This observation bodes well for the scope of this reaction, which will be determined by further investigations.

A postulated mechanism explaining the formation of isohasubanonine (**23**) from hemiaminal **22** is illustrated in Scheme 10. In the presence of trifluoroacetic acid, it is possible that the dimethyl ketal moiety of **22** undergoes ionization while the hemiaminal remains intact. The presence of an electron-deficient oxocarbenium ion adjacent to a hemiaminal would permit a pinacol-like rearrangement to occur, forming a ketone and generating the bridged ring system of **23**. Presumably, this mechanism is operative in the production of each of the isohasubanan alkaloids.

Our early attempts at converting **22** into hasubanonine utilized Lewis acids (TMSOTf, BCl_3) or strong Brønsted acids (HCl) and afforded an unstable byproduct which we initially thought was **23** (see Scheme 3). Identification of the product of the TFA-mediated cyclizations as **23** forces us to revise this hypothesis. Unfortunately, our inability to purify and store the byproduct precluded us from characterizing it. We have identified it as an isomer of **23** and **1** based on HRMS, but the lack of additional data for this compound does not allow us to draw any further conclusions regarding its structure. It is remarkable that two different isomers of **1**, but not the natural product itself, could be produced from **22** under related conditions.

Conclusions

We designed a convergent, brief route to three hasubanan alkaloids which entailed constructing a dihydrophenanthrene and then annulating a pyrrolidine ring to fashion the propellane-type ring system. Syntheses of the final cyclization precursors were quite efficient, but the last step was thwarted in each case by an unanticipated pinacol-like rearrangement. Structures of the resultant isohasubanan alkaloids were established by NMR spectroscopy and confirmed by GIAO ^{13}C NMR calculations. This work adds to the growing body of examples in the literature where such calculations have proven to be a valuable aid to structure determination.[35−37] However, we also noted some inconsistencies in calculations employing the benzene solvent correction which suggest that caution should be used when applying this algorithm. Initially, the pinacol-like rearrangement went undetected because data for isohasubanonine fit well with the reported partial NMR data for hasubanonine. We recognized the structural discrepancies only after attempting to synthesize hasubanan alkaloids for which more complete NMR data were available. Thus, our experience serves as a cautionary tale regarding the pitfalls of relying on incomplete literature data for verification of structure.

In the course of this endeavor, we discovered that chiral allylzinc reagent **32**, which has been unused by synthetic chemists since its discovery in 1998 by Nakamura,[23r] is uniquely and remarkably effective in enantioselective allylations of ketones **19**, **39**, **53**, and **62**. Accordingly, reagent **32** has a scope which extends beyond its originally intended purpose of alkynyl ketone allylations. Studies to fully define the scope and limitations of this reagent are in progress and will be reported in due course. We hope that our work will serve as a catalyst for the use of **32** and other enantioselective ketone allylating agents in the synthesis of complex molecules.

Experimental Section

5-Benzyloxy-3,4,5′,6′-tetramethoxybiphenyl-2,2′-dicarbaldehyde (15). A solution of aryl iodide **8** (1.18 g, 2.96 mmol), arylboronic ester **14** (1.08 g, 3.70 mmol), K_2CO_3 (1.64 g, 11.8 mmol), and Pd(dppf)Cl_2·CH_2Cl_2 (362 mg, 0.44 mmol) in anhydrous DMSO (37 mL) was stirred at 80 °C under Ar for 16 h. The mixture was diluted with brine (20 mL) and EtOAc (25 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 30% EtOAc in hexanes elution) afforded **15** (1.02 g, 2.34 mmol, 79%) as a yellow solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 10.18 (s, 1H), 9.46 (s, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.41−7.32 (m, 5H), 7.05 (d, J = 9.0 Hz, 1H), 6.57 (s, 1H), 5.12 (s, 2H), 4.07 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 190.2, 189.3, 157.6, 157.5, 156.7, 145.9, 142.3, 138.5, 136.0, 132.0, 128.9 (2C), 128.6, 128.2, 127.6 (2C), 125.5, 123.1, 112.7, 111.7, 71.2, 62.7, 61.3, 60.7, 56.2; IR (film) ν_{max} 2940, 2841, 1684, 1586, 1560, 1276, 1254, 1109 cm^{-1}; HRMS (ESI) *m/z* 437.16032 (MH^+, $C_{25}H_{24}O_7H$ requires 437.15948).

5-Benzyloxy-3,4,2′,3′-tetramethoxy-2,6′-divinylbiphenyl (16). A suspension of methyltriphenylphosphonium bromide (purified by flash chromatography with 5−15% MeOH in CH_2Cl_2 gradient elution and then dried over P_2O_5 in a vacuum desiccator for 3 d,

3.20 g, 8.96 mmol) in anhydrous THF (100 mL) was cooled to 0 °C and treated dropwise with *n*-BuLi (6.40 mL, 1.6 M in hexanes, 10.24 mmol). The solution was warmed to rt, stirred for 2 h, then cooled to −78 °C and treated dropwise over 10 min with a solution of **15** (869 mg, 1.99 mmol) in anhydrous THF (90 mL + 2 × 5 mL rinses). The resultant mixture was stirred for 10 min and then warmed to rt and stirred for 1.5 h. The reaction was quenched by the addition of 2 N HCl (9 mL, 18 mmol), diluted with brine (100 mL), and extracted with EtOAc (3 × 70 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo. Flash chromatography (SiO_2, 5−15% EtOAc in hexanes gradient elution) afforded **16** (800.8 mg, 1.85 mmol, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43−7.25 (m, 6H), 6.92 (d, J = 9.0 Hz, 1H), 6.49 (s, 1H), 6.33 (dd, J = 11.7, 18.0 Hz, 1H), 6.21 (dd, J = 11.1, 17.4 Hz, 1H), 5.49 (d, J = 17.4 Hz, 1H), 5.43 (d, J = 17.7 Hz, 1H), 5.13−5.03 (m, 3H), 4.96 (d, J = 11.1 Hz, 1H), 3.98 (s, 3H), 3.90 (s, 6H), 3.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.7, 152.6, 151.2, 146.4, 142.4, 137.1, 135.0, 134.7, 131.6, 131.3, 130.3, 128.7 (2C), 128.1, 127.6 (2C), 124.3, 120.6, 117.7, 113.1, 112.0, 111.8, 70.8, 61.3, 60.8, 60.6, 56.0; IR (film) ν_{max} 2936, 2836, 1589, 1481, 1290, 1128, 912, 738 cm^{-1}; HRMS (ESI) *m*/*z* 433.20074 (MH^+, $C_{27}H_{28}O_5H$ requires 433.20095).

3-Benzyloxy-1,2,5,6-tetramethoxyphenanthrene (17). A solution of **16** (367 mg, 0.849 mmol) and the Grubbs second-generation ruthenium catalyst[16] (18.2 mg, 0.021 mmol) in anhydrous CH_2Cl_2 (83 mL) was stirred at 40 °C under Ar for 2 h. The solvent was removed in vacuo, and the residue was purified via flash chromatography to afford **17** (340 mg, 0.841 mmol, 99%) as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.11 (s, 1H), 7.91 (d, J = 9.3 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.57−7.52 (m, 3H), 7.44 (t, J = 7.8 Hz, 2H), 7.35−7.25 (m, 2H), 5.36 (s, 2H), 4.07 (s, 6H), 4.01 (s, 3H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.5, 151.2, 148.6, 146.7, 141.7, 137.4, 128.8 (2C), 128.6, 128.0, 127.3 (2C), 126.4, 125.3, 125.1, 124.3, 123.5, 118.8, 113.1, 107.0, 70.7, 61.9, 61.4, 60.1, 56.7; IR (film) ν_{max} 2933, 2830, 1597, 1501, 1276, 1113, 742 cm^{-1}; HRMS (ESI) *m*/*z* 427.15077 (MNa^+, $C_{25}H_{24}O_5Na$ requires 427.15159).

1,2,5,6-Tetramethoxy-9,10-dihydrophenanthren-3-ol (18). A flask containing **17** (340 mg, 0.841 mmol), 10% Pd/C (170 mg), and EtOAc (28 mL) was placed inside a Parr apparatus, pressurized to 70 psi with H_2, and stirred for 16 h. The mixture was filtered through a pad of Celite and concentrated in vacuo. Flash chromatography (SiO_2, 22% EtOAc/hexanes elution) afforded **18** (252 mg, 0.797 mmol, 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90 (s, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 5.57 (s, 1H), 3.99 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 3.74 (s, 3H), 2.76−2.71 (m, 2H), 2.68−2.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.3, 149.0, 147.4, 147.2, 139.1, 132.2, 129.0, 127.9, 124.8, 123.0, 111.3, 111.1, 61.1, 60.9, 60.4, 56.2, 29.7, 21.9; IR (film) ν_{max} 3421, 2937, 2834, 1568, 1096, 760 cm^{-1}; HRMS (ESI) *m*/*z* 317.13840 (MH^+, $C_{18}H_{20}O_5H$ requires 317.13835).

1,2,2,5,6-Pentamethoxy-9,10-dihydro-2*H*-phenanthren-3-one (19). A mixture of $KHCO_3$ (112.7 mg, 1.11 mmol), *I*,*I*-diacetoxyiodobenzene (164.8 mg, 0.512 mmol), and anhydrous CH_3OH (5 mL) was cooled to −10 °C and treated dropwise over 5 min with a solution of **18** (147 mg, 0.465 mmol) in anhydrous CH_3OH (5 mL + 1 mL rinse). The resultant mixture was stirred at −10 °C for 20 min and then diluted with brine (10 mL) and CH_2Cl_2 (15 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 2:8:90 Et_3N/EtOAc/hexanes elution) afforded **19** (141.6 mg, 0.409 mmol, 88%) as a yellow oil that solidified upon standing: ^{1}H NMR (C_6D_6, 500 MHz) δ 7.37 (s, 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 8.0 Hz, 1H), 3.91 (s, 3H), 3.57 (s, 3H), 3.42 (s, 6H), 3.27 (s, 3H), 2.58−2.55 (m, 2H) 2.43−2.40 (m, 2H); ^{13}C NMR (C_6D_6, 125 MHz) δ 195.1, 153.6, 152.9, 150.5, 146.3, 135.9, 128 (obscured by solvent peak), 126.9, 123.4, 120.3, 115.2, 95.0, 60.4, 59.8, 56.2, 51.2 (2C), 30.3, 23.4; IR (film) ν_{max} 2941, 2840, 1660, 1541, 1340, 1078 cm^{-1}; HRMS (ESI) *m*/*z* 369.13084 (MNa^+, $C_{19}H_{22}O_6Na$ requires 369.13086).

3-Allyl-1,2,2,5,6-pentamethoxy-2,3,9,10-tetrahydrophenanthren-3-ol (20). A solution of **19** (213 mg, 0.615 mmol) in anhydrous Et_2O (21 mL) at −78 °C under Ar was treated dropwise with allylmagnesium chloride (2.0 M in THF, 1.69 mL, 3.38 mmol). The resulting mixture was stirred at −78 °C for 1 h and then treated with brine (2 mL) and allowed to warm to rt. The mixture was diluted with additional brine (20 mL) and satd aq potassium tartrate (5 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 2:10:88 Et_3N/EtOAc/hexanes elution) afforded **20** (222 mg, 0.572 mmol, 93%) as a colorless oil: ^{1}H NMR (C_6D_6, 500 MHz) δ 7.10 (s, 1H), 6.64 (d, J = 8.5 Hz, 1H), 6.47 (d, J = 8.5 Hz, 1H), 6.31−6.22 (m, 1H), 5.12 (dd, J = 17.0, 2.0 Hz, 1H), 5.02 (dd, J = 10.5, 1.0 Hz, 1H), 3.71 (s, 3H), 3.62 (s, 3H), 3.45 (s, 3H), 3.34 (s, 3H), 3.23 (s, 3H), 3.05 (s, 1H), 2.91−2.85 (m, 1H), 2.79−2.74 (m, 1H), 2.54−2.45 (m, 3H), 2.43−2.37 (m, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ 153.1, 149.8, 136.5, 135.9, 135.5, 132.9, 127.7, 125.7, 125.4, 123.5, 117.8, 112.5, 101.8, 80.5, 61.2, 59.9, 56.3, 51.6, 51.0, 40.0, 30.5, 24.1; IR (film) ν_{max} 3582, 2937, 2835, 1480, 1261, 1218, 1053 cm^{-1}; HRMS (ESI) *m*/*z* 411.17711 (MNa^+, $C_{22}H_{28}O_6Na$ requires 411.17781).

(−)-20. A solution of bis((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)methane[40] (13.9 mg, 0.045 mmol) and 2,2′-dipyridyl (one crystal) in anhydrous THF (200 μL) under Ar at 0 °C was treated dropwise with *n*-BuLi (1.6 M in hexanes, 0.055 mL, 0.088 mmol) until the mixture turned a reddish brown color. The solution was warmed to rt and stirred for 1 h, then treated dropwise with allylzinc bromide (1.0 M in THF, 43.4 μL, 0.043 mmol) and cooled to −78 °C. A solution of **19** was added dropwise (0.7 M in THF, 42 μL, 0.029 mmol), and the resultant mixture was stirred at −78 °C under Ar for 80 min. The reaction was quenched by the addition of MeOH–H_2O (1:1, 0.5 mL), and the mixture was extracted with Et_2O (3 × 1 mL). The combined organic layers were washed with aq NaOH (0.5 M, 0.5 mL), dried (Na_2SO_4), and concentrated in vacuo. Preparative TLC (SiO_2, 2:20:78 Et_3N/EtOAc/hexanes elution) afforded (−)-**20** (9 mg, 0.022 mmol, 76%): $[\alpha]^{25}_D$ −76.1 (*c* 0.28, CH_2Cl_2). Chiral HPLC analysis (Chiralcel OD-H, 99:1 hexane/*i*-PrOH, 1 mL/min, t_R = 10.7 min, 26.1 min (major)) demonstrated that (−)-**20** was obtained in 93% ee.

(−)-4a-Allyl-1,2,2,5,6-pentamethoxy-4,4a,9,10-tetrahydro-2*H*-phenanthren-3-one ((−)-21). A mixture of KO-*t*-Bu (70 mg, 0.62 mmol), 18-crown-6 (169 mg, 0.64 mmol), and anhydrous THF (5 mL) at −10 °C under Ar was stirred for 10 min. A solution of **20** (80 mg, 0.206 mmol) in anhydrous THF (5 mL) was added to the mixture dropwise over 3 min, and the resultant mixture was stirred at −10 °C for 10 min. The solution was treated with brine (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 2:5:93 Et_3N/EtOAc/hexanes elution) afforded **21** (59.4 mg, 0.153 mmol, 74%) as a colorless oil: $[\alpha]^{25}_D$ −151.8 (*c* 0.61, CH_2Cl_2); ^{1}H NMR (C_6D_6, 500 MHz) δ 6.81−6.76 (m, 2H), 5.61−5.50 (m, 1H), 4.96 (d, J = 16.0 Hz, 1H), 4.90, (d, J = 10.0 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.59 (d, J = 14.0 Hz, 1H), 3.43 (s, 3H), 3.24 (s, 3H), 3.12−3.07 (m, 1H), 3.01−2.86 (m, 3H), 2.77 (td, J = 14.0, 5.0 Hz, 1H), 2.60 (dd, J = 14.0, 8.0 Hz, 1H), 2.17 (td, J = 14.0, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 203.1, 151.8, 148.3, 145.7, 135.6, 135.0, 134.9, 130.0, 124.1, 118.1, 111.9, 97.9, 62.3, 60.7, 56.1, 52.7, 51.3, 49.0, 46.4, 44.8, 31.7, 23.0; IR (film) ν_{max} 2939, 2836, 1731, 1483, 1275, 1089, 919, 808, 736 cm^{-1}; HRMS (ESI) *m*/*z* 411.17711 (MNa^+, $C_{22}H_{28}O_6Na$ requires 411.17781).

Hemiaminal (−)-22. A solution of **21** (30.0 mg, 0.0772 mmol) in EtOAc (7.5 mL) at −78 °C was treated with O_3 (bubbled slowly through the mixture) until the starting material was consumed as

(40) Hall, J.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1.

indicated by TLC. The solution was then stirred for 5 min before being treated with Et_3N (33.0 μL, 0.232 mmol). The resulting solution was stirred at rt for 16 h and then concentrated in vacuo to afford the crude aldehyde.

The aldehyde was then dissolved in anhydrous CH_3OH (1 mL) and treated with 4 Å MS (50 mg) followed by CH_3NH_2 (1.7 M in CH_3OH, 181 μL, 0.308 mmol). The mixture was stirred at rt for 30 min, then treated with $NaBH_3CN$ (9.7 mg, 0.154 mmol) and stirred for 5 h before being quenched with 0.1 N NaOH (0.5 mL), diluted with brine (0.5 mL), and extracted with EtOAc (4 × 1.5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 2:20:78 Et_3N/EtOAc/hexanes elution) afforded **22** (19.2 mg, 0.0474 mmol, 62%) as a colorless oil: $[\alpha]^{25}_D$ −190.1 (*c* 1.15, CH_2Cl_2); ^{1}H NMR (C_6D_6, 500 MHz) δ 6.64 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 3.85 (s, 3H), 3.67 (s, 3H), 3.58 (s, 3H), 3.37 (s, 3H), 3.32 (s, 3H), 3.29−3.24 (m, 1H), 3.09 (d, J = 12.5 Hz, 1H), 3.07−2.94 (m, 2H), 2.93 (s, 3H), 2.80−2.75 (m, 1H), 2.73−2.66 (m, 2H), 1.97 (d, J = 11.5 Hz, 1H), 1.81 (td, J = 13.0, 5.5 Hz, 1H), 1.40−1.24 (m, 1H), 1.18 (d, J = 12.5 Hz, 1H); ^{13}C NMR (C_6D_6, 125 MHz) δ 152.7, 150.3, 148.6, 135.8, 131.2, 131.0, 124.2, 112.2, 100.1, 86.4, 62.9, 60.8, 56.0, 52.4, 49.2, 42.6, 41.3, 37.3, 31.9, 30.6, 29.9, 22.3; IR (film) ν_{max} 3421, 2920, 2854, 1596, 1460, 1254, 1064 cm^{-1}; HRMS (ESI) *m*/*z* 406.2220 (MH^+, $C_{22}H_{31}NO_6H$ requires 406.2230).

(−)-Isohasubanonine ((−)-23). A solution of **22** (7.2 mg, 0.0178 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was treated with 4 Å MS (72 mg) and stirred at rt for 10 min. Trifluoroacetic acid (1.0 M in CH_2Cl_2, 53 μL, 0.053 mmol) was added slowly, and the resultant mixture was stirred at 35 °C for 22 h. The reaction was quenched by the addition of K_3PO_4 (50 mg), stirred for 5 min, filtered, and concentrated in vacuo. Flash chromatography (SiO_2, 2:20:78 Et_3N/EtOAc/hexanes elution) afforded **23** (5.4 mg, 0.0145 mmol, 81%) as a light yellow oil that solidified on standing: $[\alpha]^{25}_D$ −114 (*c* 0.45, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.82 (d, J = 8.5 Hz, 1H) 6.78 (d, J = 8.5 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.72 (s, 3H), 3.51 (s, 3H), 3.42−3.34 (m, 1H), 3.22 (d, J = 19 Hz, 1H), 3.01−2.95 (m, 1H), 2.95−2.88 (m, 1H), 2.84−2.77 (m, 2H), 2.65−2.58 (m, 1H), 2.41 (s, 3H), 2.33 (d, J = 19 Hz, 1H), 2.20−2.12 (m, 1H), 1.49−1.44 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 205.7, 152.0, 148.4, 146.2, 135.8, 129.5 (2C), 124.0, 111.2, 92.7, 61.8, 60.8, 56.1, 51.9, 49.4, 47.7, 39.4, 34.9, 30.5, 29.5, 22.5; IR (film) ν_{max} 2925, 2849, 1724, 1660, 1601, 1483, 1272 cm^{-1}; HRMS (ESI) *m*/*z* 374.19811 (MH^+, $C_{21}H_{27}NO_5H$ requires 374.19620).

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Supporting Information Available: Experimental procedures and characterization data for all new compounds not included in the Experimental Section, NMR spectra for all new compounds, chiral HPLC traces, description of GIAO ^{13}C NMR calculations, and description of analgesic assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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