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Dihydroxylation of Vinyl Sulfones: Stereoselective Synthesis of (+)- and (−)-Febrifugine and Halofuginone

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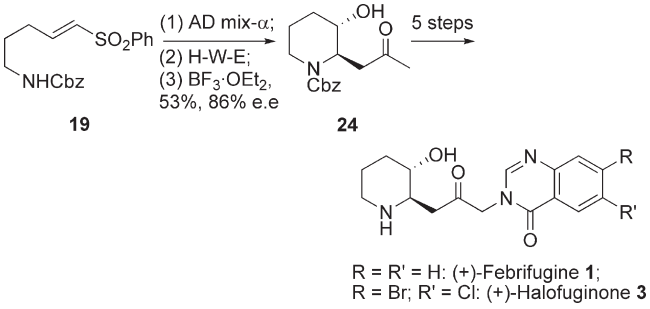

The asymmetric dihydroxylation of amino-functionalized vinyl sulfone **19** has been used for the 3-step preparation of 3-hydroxylpiperidine **24** in 86% enantiomeric excess. This enantiomerically enriched building block was used then to synthesize the naturally occurring antimalarial alkaloid febrifugine **1** and its antiangiogenic analogue, halofuginone **3**.

Febrifugine **1** and its isomer isofebrifugine **2** (Figure 1) were isolated from a Chinese medicinal plant, chang shan (*Dichroa febrifuga*), and were later found to be present in a popular garden plant, hydrangea.[1] Decoctions of chang shan have been used for over 2000 years for the treatment of a variety of aliments including stomach cancer and malaria.[2] More recently it has been shown that both **1** and **2** exhibit potent antimalarial activity in their own right in several models of this disease, which has been estimated to affect between 300 million and 500 million people each year.[2,3] Currently the mode by which these compounds elicit their activity is unknown[2] and interestingly, the antimalarial activities for **1** and **2** are surprisingly approximately equal.[1] The existence of these C-2 isomers and their comparable biological activities suggest that isomerization via a *retro*-conjugate−conjugate addition sequence may occur in vivo.[4] Although these compounds possess interesting biological profiles, possibly via a novel mechanism, and have been used historically as a herbal remedy, they do have serious side effects (including nausea, vomiting , and liver toxicity) which have precluded their use as antimalarial drugs.[3] The chemical structures of **1** and **2** were elucidated in 1950s following studies by Baker and co-workers.[5] However, the precise relative and absolute stereochemistry has historically caused confusion, and it was as recently as 1999 that the absolute stereochemistry of these compounds was finally unambiguously determined by total synthesis.[6] Since 1999 these targets have proved popular and several successful synthetic strategies toward **1** and **2**, in both racemic and enantioselective fashion, have been reported.[7] Halofuginone **3** (the active component of tempostatin and stenorol) is an analogue of **1**, in which the metabolically vulnerable aromatic protons have been replaced.[3,8] Stenorol has been used for more than 2 decades as an antiprotozoal agent in the poultry industry.[9] Issues concerning the optimal dose administered to chickens led to the discovery that **3** also inhibits type 1 collagen biosynthesis[10] and this observation in turn led to the

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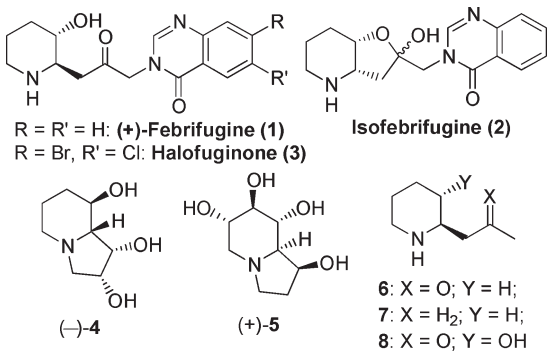
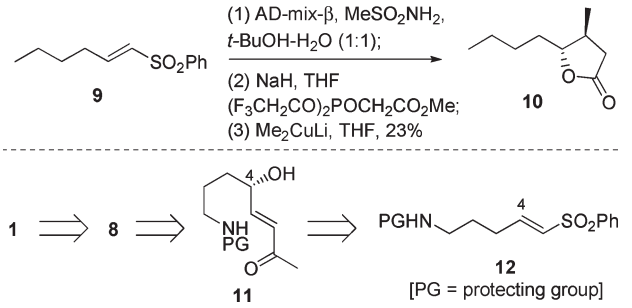


FIGURE 1. 2,3-Disubstituted piperidine natural products.

SCHEME 1. Retrosynthetic Analysis of Febrifugine Based on the Asymmetric Dihydroxylation of Vinyl Sulfones



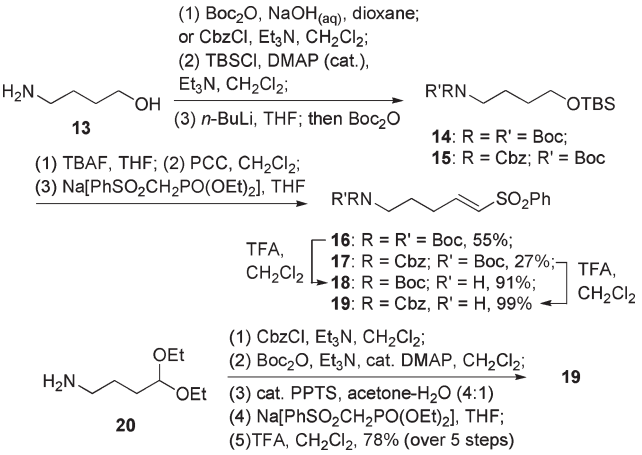
identification of **3** as a lead compound for the development of an antiangiogenic agent for the treatment of various cancers.[11]

The *trans*-2-alkyl-3-hydroxylpiperidine substitution pattern present in febrifugine is also found in several additional naturally occurring compounds. For example, the widely reported indolizidine alkaloids (−)-swainsonine **4** and (+)-castanospermine **5** contain the same structural motif and in a wider sense the piperidine alkaloids pelletierine **6** and coniine **7** (given above as the unnatural enantiomers) possess the type of stereogenic 2-propyl substituent exhibited by febrifugine.[12]

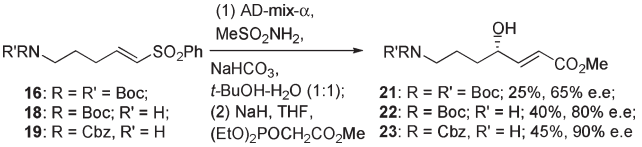
We wished to investigate the preparation of the 2-alkyl-3-hydroxyl-substituted piperidine motif found in the febrifugine family using our asymmetric dihydroxylation of vinyl sulfones (Scheme 1).[13] We have recently shown that this reaction enables the preparation of γ-hydroxyl α,β-unsaturated esters in good enantiomeric excesses and have used this method to prepare the quercus (Whiskey) lactone **10** and both (+)- and (−)-maritolide. More recently this method has been employed by Au and Pyne in a formal synthesis of (−)-**4**.[14]

Thus, it was envisaged that an acyclic precursor of the type **11**, possessing an appropriately protected nitrogen atom, would afford piperidine **8** in its *N*-protected form. This type of intramolecular heteroconjugate addition approach has been previously studied in the context of febrifugine synthesis.[7f,m−o] Notably, within these studies high levels of trans-stereoselective ring closure have been reported which

SCHEME 2. Vinyl Sulfone Synthesis



SCHEME 3. Dihydroxylation of Vinyl Sulfones 16, 18, and 19



may be tuned according to the identity of the stereogenic allylic subsituent and the reaction conditions.[7m]

A series of vinyl sulfone dihydroxylation precursors (of the type **12**) were accessed following the sequence of transformations outlined in Scheme 2. Thus, starting from either **13** or **20** amino protected vinyl sulfones **16**−**19** were obtained in good overall yields following modified literature procedures.[15] Regarding this sequence, it was notable that in order to perform the oxidation−olefination chemistry the amino group needed to be carried through to **16** or **17** in their diprotected form.

The behavior of **16**, **18**, and **19** under dihydroxylation conditions was next studied in the context of assembling the requisite γ-hydroxyl α,β-unsaturated cyclization precursors of the type **11** (Scheme 3). Treatment of **16** initially with AD-mix-α and then the crude product with the anion derived from methyl diethylphosphonoacetate gave *E*-**21** in a disappointing yield and enantiomeric excess even after attempts to optimize reaction parameters. Undeterred we considered the same process albeit with monoprotected precursors **18** and **19**. In both instances improvements in both chemical and optical yield were observed with the benzyloxy carbamate (Cbz) protected material **19** proving optimal.

With the identification of the favored substrate the two-step sequence was carried out with diethyl (2-oxopropyl)-phosphonate. In this case the anticipated γ-hydroxyl α,β-unsaturated ketone proved to be difficult to isolate and was consistently contaminated with the ultimately desired piperidine **24** (Scheme 4). Further investigation indicated that the conversion of the enone into **24** was facile, gradually occurring

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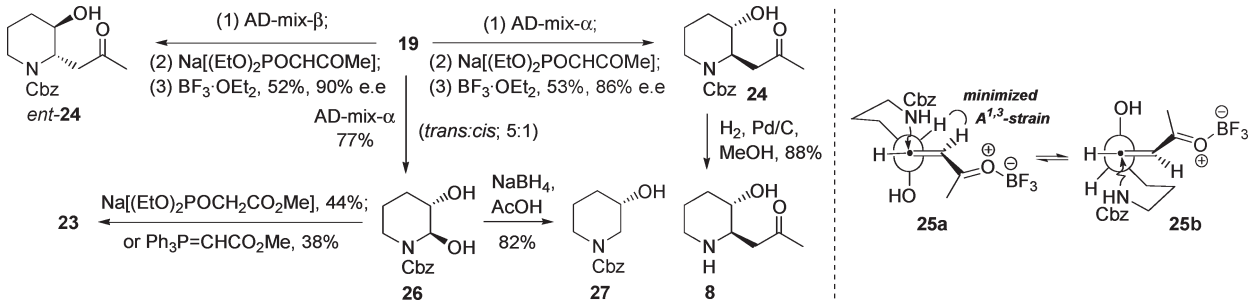
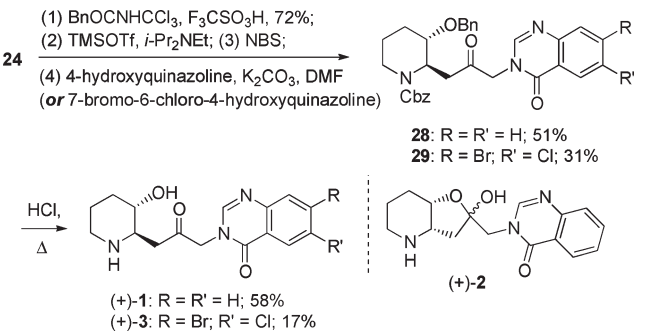
SCHEME 4. Synthesis of Piperidine 24 and Hemiaminal 26



SCHEME 5. Conversion of 24 to (+)-Febrifugine and (+)-Halofuginone



in $CDCl_3$ at rt for example. To maximize the efficiency of this process it was discovered that treatment of the crude material following Horner−Wadsworth−Emmons olefination with $BF_3 \cdot OEt_2$ (0.5 equiv)[7f,m] gave the desired material **24** in reasonable yield and 86% enantiomeric excess.

As previously reported,[7f,m] we observed that the formation of **24** occurred with high diastereoselectivity. Careful inspection of the proton NMR spectrum obtained for the crude material failed to indicate signals attributable to the cis-diastereoisomer, or its hemiketal.[16] Also worthy of mention was that the corresponding cyclization of the less reactive γ-hydroxyl α,β-unsaturated esters **22** and **23** was not observed under identical conditions. The stereochemical outcome of this cyclization is consistent with a Felkin−Ahn-type transition state in which the reactive conformer, affording *trans*-**24**, resembles **25a** as opposed to **25b** (Scheme 4).[17] The use of AD-mix-β gave *ent*-**24** in comparable yield and enantiomeric excess from vinyl sulfone **19** and the assignment of absolute stereochemistry of compounds **21**−**24** was made on the basis of previous work[13] and the later conversion of **24** into (+)-febrifugine (Scheme 5). Deprotection of **24** and *ent*-**24** (not shown) following hydrogenation gave the novel pelletierine analogues **8**.

In an attempt to explain the effect vinyl sulfone structure had on the outcome of reaction in terms of yield and enantioselectivity the crude product resulting from dihydroxylation was studied. On treatment of **19** with AD-mix-α and monitoring the reaction until starting material was consumed the hemiaminal **26** was isolated in good yield as predominantly the trans-diastereoisomer (dr 5:1).[18] On subsequent subjection of **26** to either H-W-E olefination or Wittig conditions, which gave **23**, it became evident that the moderate yields observed for this process partly reflect the recalcitrance of the hemiaminal **26** to undergo olefination. A poor yield was observed for the formation of **21** in the above sequence. In this instance the α-hydroxyl aldehyde intermediate is unable to form a cyclic hemiaminal of the type **26** and we speculate that loss of material stemmed from likely formation of the water-soluble *gem*-diol and oligomeric materials which may not participate in the subsequent olefination chemistry. In terms of enantiomeric excess it seems plausible that the in situ formation of **26** also may serve to protect the potentially epimerizable stereogenic center. Finally, it has been noted previously that steric effects often serve to diminish levels of stereoselectivity on asymmetric dihydroxylation.[19] Therefore, we speculate that in going from **16** to **18** to **19** the increase in enantioselectivity observed was based on a decrease in size of the alkene substituent. In relation to this, in our previous study[13] *n*-alkyl vinyl substituents gave higher levels of enantiomeric excess (95% ee) than observed in the current work.

Subsequent conversion of **24** into naturally occurring (+)-febrifugine **1** was achieved in five steps and was based on the previously reported regioselective bromination sequence (Scheme 5).[6] The spectroscopic data for synthetic **1** obtained accordingly, including rotation of plane polarized light, were in agreement with reported values.[6,7p] The overall stereoselective outcome served to prove that the dihydroxylation of **19** was also consistent with our previous work and Sharpless' predictive model in which the phenyl sulfonyl substituent represents the largest group.

It is notable that samples obtained following this sequence were obtained with minimal quantities of (+)-isofebrifugine **2**. However, care needed to be taken in terms of the length of exposure of **28** to the acidic conditions required for deprotection, and it was also noted that after prolonged storage of samples of (+)-**1** in $CDCl_3$ significant interconversion of (+)-**1** into (+)-**2** was observed.[4] This sequence presumably occurs via an α,β-unsaturated ketone; however, an intermediate resembling this was never detected. Following an identical

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(18) Stereochemistry assigned based on data reported for *cis*-**25**: Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809.

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sequence of reactions *ent*-**24** was converted into (−)-**1** with comparable yields (not shown). Similarly, by using 7-bromo-6-chloro-4-hydroxyquinazoline[20] (+)- and (−)-halofuginone **3** were obtained. Concerning the conversion of **29** into (+)-**3** a crude yield of 71% was initially isolated; however, following purification by flash column chromatography a low yield (17%) of purified material was isolated.

In summary, using the asymmetric dihydroxylation of an amino-functionalized vinyl sulfone **19** naturally occurring febrifugine was accessed in 12 linear steps in 12% overall yield in 86% ee. An identical sequence was employed to access both enantiomerically enriched forms of halofuginone. Our original objective was to reduce the length of this synthetic route utilizing phosphonates already bearing either the quinazolinone heterocycle or a leaving group.[7n] This would remove the requirement for the bromination−alkylation chemistry depicted in Scheme 5. However, our initial attempts to achieve this were unsuccessful and future work will involve further investigation of this convergent approach.

Experimental Section

(2*R*,3*S*)-3-Hydroxy-2-(2-oxopropyl)piperidine-1-carboxylic Acid Benzyl Ester 24. A solution of **19** (719 mg, 2.00 mmol, 1.00 equiv) in *t*-BuOH (10 mL) and H_2O (10 mL) was treated with sodium bicarbonate (504 mg, 6.00 mmol, 3.00 equiv) and methane sulfonamide (190 mg, 2.00 mmol, 1.00 equiv). AD mix-α (8.00 g) was added and the resulting mixture was stirred for 22 h. Dichloromethane (30 mL) and H_2O (30 mL) were added and the mixture was partitioned for 30 min. The resulting aqueous layer was further extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with brine (40 mL) and dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude aldehyde. At 0 °C a solution of diethyl (2-oxopropyl)phosphonate (778 mg, 4.01 mmol, 2.00 equiv) in dry THF (30 mL) was treated with 60% (w/w) sodium hydride in mineral oil (160 mg, 4.00 mmol, 2.00 equiv) for 30 min. The crude aldehyde in dry THF (10 mL) was added and the reaction was stirred for 15 h. Diethyl ether (40 mL) was added to dilute the reaction mixture, which was then washed with a saturated solution of NH_4Cl (2 × 40 mL) and brine (40 mL). The combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude product. At rt a solution of the crude olefin in acetonitrile (20 mL) was treated with boron trifluoride diethyl etherate (0.12 mL, 0.97 mmol, 0.49 equiv) and the mixture was stirred at rt for 10 min. The reaction mixture was washed with a saturated solution of $NaHCO_3$ (2 × 30 mL) and brine (30 mL). The combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent evaporation under reduced pressure afforded the crude product. Purification by flash column chromatography (c-Hex−EtOAc; 1:1) gave compound **24** (310 mg, 53% over 3 steps) as a colorless oil. R_f 0.15 (*c*-Hex−EtOAc; 1:1); $[\alpha]^{25}_D$ −18.4 (*c* 1.00, $CHCl_3$); ν_{max} (neat/cm^{-1}) 3599, 3046, 2973, 2950, 1698, 1439, 1355, 1278, 1137, 983, 688; HRMS calcd for $C_{16}H_{21}NO_4Na$ 314.1368, found 314.1369 (+0.2 ppm); δ_H (400 MHz, $CDCl_3$) 1.41−1.43 (1H, m), 1.67−1.75 (1H, m), 1.78−1.87 (1H, m), 1.89−1.92 (1H, m), 2.15 (3H, s), 2.65 (2H, d, J = 7.5 Hz), 2.86 (1H, t, J = 14.0 Hz), 3.81 (1H, br s), 4.06−4.07 (1H, m), 4.74 (1H, t, J = 7.5 Hz), 5.13 (2H, s), 7.28−7.34 (5H, m) ppm; δ_C (100 MHz, $CDCl_3$) 19.1, 26.0, 30.1, 39.7, 43.9, 54.3, 67.1, 67.5, 128.0, 128.1, 128.6, 136.8, 156.4, 206.3 ppm; HPLC analysis (IA column), heptane−EtOH 70:30 (1.0 cm^3/min): (2*R*,3*S*) t_r = 8.62 min, (2*S*,3*R*) t_r = 10.53 min; 86% ee. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.78; H, 7.24; N, 4.72.

(20) Obtained from Credimate Trading Ltd.: http://www.credimate.com.

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Supporting Information Available: Experimental details and copies of proton, carbon NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.