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Stereospecific, Enantiospecific Total Synthesis of the Sarpagine Indole Alkaloids (*E*)16-Epiaffinisine, (*E*)16-Epinormacusine B, and Dehydro-16-epiaffinisine

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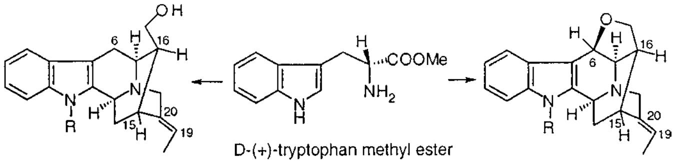
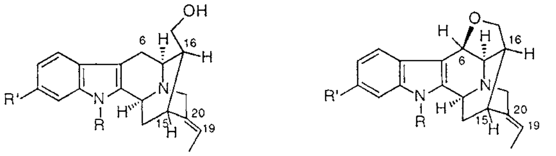
ABSTRACT



The first stereospecific total synthesis of the sarpagine indole alkaloids (*E*)16-epiaffinisine (1), (*E*)16-epinormacusine B (2), and dehydro-16-epiaffinisine (4) has been completed; this method has also resulted in the synthesis of dehydro-16-epinormacusine B (5). The formation of the required ether in both 4 and 5 was realized with complete control from the top face on treatment of the corresponding alcohols with DDQ/THF in 98% and 95% yields, respectively.

The sarpagine alkaloids (*E*)16-epiaffinisine (**1**), (*E*)16-epinormacusine B (**2**), and dehydro-16-epiaffinisine (**4**) were isolated from the leaves and root bark of *Ervatamia hirta*,[1] a 5−7 m tree from Malaysia. This plant comprises one of the ingredients in the preparation of poisoned arrows and was also used in traditional medicine for the treatment of ulcerations of the nose.[2] The structures of (*E*)16-epiaffinisine (**1**), (*E*)16-epinormacusine B (**2**), and dehydro-16-epiaffinisine (**4**) were elucidated on the basis of ^{1}H NMR and ^{13}C spectroscopic studies and were further supported by analysis of their 2D NMR spectral data as well as chemical correlations.[1] Several other sarpagine-related indole alkaloids in this class (Figure 1) have been isolated from *Gardneria nutans* by Haginiwa and Sakai et al.,[3] including gardnerine (**3**) and gardnutine (**6**). Although dihydro-16-epinormacusine B (**5**) has not yet been isolated from the plant, we postulated that it may serve as a biogenetic intermediate on the route toward **4**.

As illustrated in Figure 1, the common structural features of these indole alkaloids include the asymmetric centers at C-3(*S*), C-5(*R*), C-15(*R*), and C-16(*S*) as well as the



1 R = CH_3, R' = H, (*E*) 16-epiaffinisine
2 R = H, R' = H, (*E*) 16-epinormacusine B
3 R = H, R' = OCH_3, gardnerine

4 R = CH_3, R' = H, dehydro-16-epiaffinisine
5 R = H, R' = H
6 R = H, R' = OCH_3, gardnutine

Figure 1.

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[1] Clivio, P.; Richard, B.; Deverre, J.-R.; Sevenet, T.; Zeches, M.; Le Men-Olivier, L. *Phytochemistry* **1991**, *30*, 3785.

[2] Van Beek, T. A.; Verpoorte, R.; Baerheim Svendsen, A.; Leeuwenberg, A. J. M.; Bisset, N. G. *J. Ethnopharm.* **1984**, *10*, 1.

[3] Haginiwa, J.; Sakai, S.; Kubo, A.; Hamamoto, T. *Yakugaku Zasshi* **1967**, *87*, 1484.

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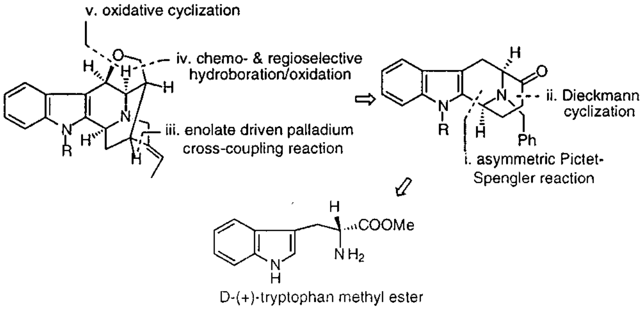
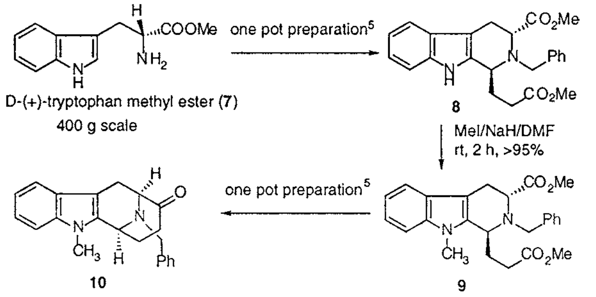
ethylidene double bond at C-19 and C-20 present in the less stable *E* configuration. To date, no biological activity for these specific alkaloids has been reported. Because of their unique structure and the paucity of alkaloidal material from natural sources, it was decided to prepare them in enantiospecific fashion for biological screening. No total synthesis of these alkaloids has been reported, to date. Magnus et al.[4] reported the synthesis of the enantiomer of **2**, which was employed as an intermediate in the total synthesis of (+)-koumine and (+)-taberpsychine. Herein, we wish to describe the first enantiospecific total synthesis of (*E*)16-epiaffinisine (**1**), (*E*)16-epinormacusine B (**2**), and dehydro-16-epiaffinisine (**4**). In addition, dehydro-16-epinormacusine B (**5**) was also prepared by extension of this approach and may provide a route for the synthesis of gardnutine (**6**) in the future. As shown in Scheme 1 (retrosynthetic analysis), the strategy here rested on the use of the asymmetric Pictet−Spengler reaction (>98% ee), the Dieckmann cyclization, the enolate-mediated palladium-catalyzed intramolecular cyclization, and a chemospecific hydroboration. The stereocenters at C(3), C(5), C(15), and C(16) as well as the C(19)−C(20) *E* ethylidene function were controlled in stereospecific fashion.

Scheme 1. Retrosynthetic Analysis



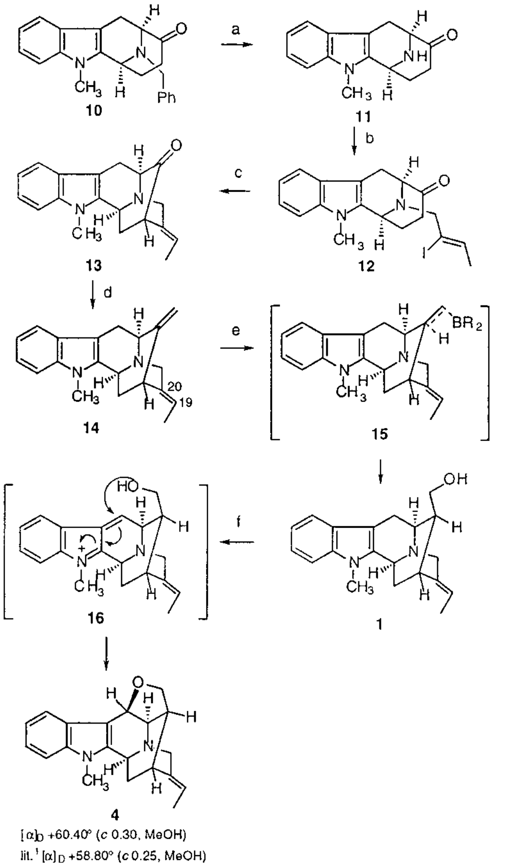
The synthesis of (*E*)16-epiaffinisine (**1**) and dehydro-16-epiaffinisine (**4**) began from the readily available (−)-N_a-methyl, N_b-benzyl tetracyclic ketone **10**, which was prepared in three reaction vessels from D-(+)-tryptophan methyl ester (**7**) (400 g scale) in greater than 98% ee (Scheme 2).[5] Liu et al.[6] recently reported a synthetic sequence for the preparation of the enantiomer of ketone **13** from the enantiomer of **7**. As a consequence, ketone **13** was obtained in stereospecific fashion via a similar route.[6] Minor modifications during the process of catalytic hydrogenation and the alkylation on treatment with the *Z*-1-bromo-iodo-2-butene in the presence of potassium carbonate (THF) as well as slight changes in the palladium-catalyzed intramolecular cross-coupling reaction were required (Scheme 3).[6−8] It is worthy of note that a decrease in the amount of $Pd(OAc)_2$ (from 5 mol % to 3 mol %) and an increase in the amount of PPh_3 (from 20 mol % to 30 mol %), as compared to the previous process,[6] resulted in a cleaner reaction although this took longer to go to completion. With the cyclized ketone **13** in hand, the desired diene **14** was obtained by stirring **13** with methyl-

Scheme 2[a]



[a] See ref 5 for details.

Scheme 3[a]



[a] Reagents and conditions: (a) 5% Pd/C, H_2, EtOH/HCl, rt, 5 h, 94%. (b) *Z*-1-bromo-2-iodo-2-butene, THF, K_2CO_3, reflux, 24 h, 85%. (c) 3 mol % $Pd(OAc)_2$, 30 mol % PPh_3, 1 equiv Bu_4NBr, 4 equiv K_2CO_3, DMF−H_2O (9:1), 65 °C, 30 h, 82%. (d) PPh_3CH_3Br, KO-*t*-Bu, benzene, rt, 4 h, 90%. (e) Sia_2BH; NaOH/H_2O_2, rt, or 9-BBN; NaOH/H_2O_2, rt, 75−80%. (f) DDQ, THF, reflux, 1 h, 98%.

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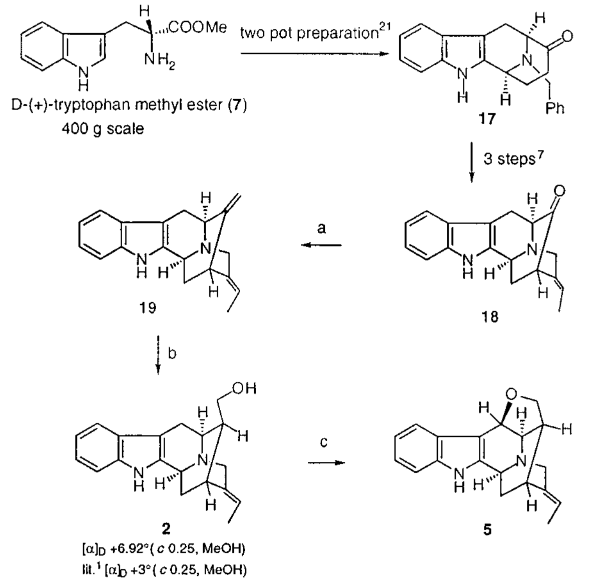
triphenylphosphonium bromide in benzene in the presence of potassium *tert*-butoxide. The Wittig reaction took place in 90% yield. Hydroboration/oxidation was employed to solve the problem of chemoselectivity between the olefinic centers. It was felt the less hindered C16−C17 double bond, relative to the C19−C20 site, would be attacked more readily by selective hydroborating agents. It had been documented[9] that the C19−C20 double bond of the enantiomer of **13** reacted with both BH_3·DMS and BH_3·THF, however, it did not react with thexyl borane or 9-BBN. Certainly, a key issue rested on the regiopreference for the desired attack at the C16−C17 double bond in contrast to the C19−C20 bond. Importantly, Magnus et al.[4] had previously demonstrated that C17 of the C16−C17 olefinic site could be selectively hydroborated to provide the 16(S) alcohol in the synthesis of (+)-koumine. From examination of the possible transition states,[10] attack from the convex face seemed more favorable, although it would be difficult to distinguish the outcome based solely on steric factors. Gratifyingly, (*E*)16-epiaffinisine (**1**) was obtained as the only detectable diastereomer when the hindered diisoamylborane or 9-BBN were employed as hydroborating agents, followed by oxidative workup. Further oxidative cyclization of **1** effected by DDQ in THF afforded dehydro-16-epiaffinisine (**4**) in 98% yield in stereospecific fashion. Although the vinylogous iminium ion **16** is depicted here as an intermediate, a number of possible mechanisms for the generation of **4** are possible.[11−20] The spectroscopic properties and optical rotations of synthetic **1** and **4** agree in all respects with those reported for the natural products.[1] Thus, a concise and stereospecific total synthesis of **1** and **4** has been carried out from commercially available D-(+)-tryptophan methyl ester (**7**) which involved only seven reaction vessels for **1** (25% overall yield) and eight reaction vessels for **4** (24% overall yield).

Recently, the synthesis of the *E*-ethylidene ketone **18** was completed by Wang and Cook[7] via an efficient enolate driven palladium-catalyzed cyclization as a key step (Scheme 4). This synthesis[7] permitted the conversion of the N_a-H, N_b-benzyl tetracyclic ketone **17**, which had been prepared in two reaction vessels from D-(+)-trypotophan methyl ester (**7**),[21] into the *E*-ethylidene ketone **18** in only three steps.

Scheme 4[a]



[a] Reagents and conditions: (a) PPh_3CH_3Br, KO-*t*-Bu, benzene, rt, 4 h, 92%. (b) Sia_2BH; $NaOH/H_2O_2$, rt, or 9-BBN; $NaOH/H_2O_2$, rt, 75−80%. (c) DDQ, THF, reflux, 1 h, 95%.

With the *E*-ethylidene ketone **18** in hand, the synthesis of **2** was completed via a Wittig reaction coupled with a chemospecific, regiospecific hydroboration/oxidation (74% yield for the two steps). (*E*)16-Epinormacusine B (**2**) was obtained as the sole diastereomer from this procedure. Consequently, (*E*)16-epinormacusine B (**2**) could be prepared in a short synthetic sequence from D-(+)-tryptophan methyl ester (**7**) in eight reaction vessels in 26% overall yield. The spectroscopic properties and optical rotation of synthetic **2** were in complete agreement with the natural product.[1] Finally, oxidative cyclization of alcohol **2** by treatment with DDQ in THF afforded the dehydro-16-epinormacusine B (**5**) in 95% yield (Scheme 4). The stereochemistry of the chiral centers in both **4** and **5** was determined by 2D NOESY experiments; they were present in the correct configuration at C(3), C(5), C(6), C(15), and C(16) as depicted in Figure 2.

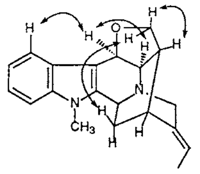


Figure 2. Selected NOESY's of dehydro-16-epiaffinisine (**4**).

In conclusion, the first stereospecific total synthesis of (−)-(*E*)16-epiaffinisine (**1**), (+)-(*E*)16-epinormacusine B (**2**), and (+)-dehydro-16-epiaffinisine (**4**) has been accomplished from commercially available D-(+)-tryptophan methyl ester

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(**7**) via the asymmetric Pictet−Spengler reaction. A stereocontrolled intramolecular enolate driven palladium-mediated cross-coupling reaction, and a chemospecific and regiospecific hydroboration/oxidation were also key steps in this approach. In these syntheses the stereochemistries at C(3), C(5), C(6), C(15), and C(16) and the geometry of the C(19)−C(20) *E* ethylidene were controlled completely. The synthesis of dehydro-16-epinormacusine B (**5**) was also completed and provides a model route to reliably access other sarpagine-related alkaloids including gardnutine (**6**).[3,9]

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