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The first enantiospecific total synthesis of the 3-oxygenated sarpagine indole alkaloids affinine and 16-epiaffinine, as well as vobasinediol and 16-epivobasinediol

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ABSTRACT

The first enantiospecific total synthesis of the 3-oxygenated sarpagine indole alkaloids affinine (**1**) and 16-epiaffinine (**2**) as well as the synthesis of vobasinediol (**3**) and 16-epivobasinediol (**4**) was accomplished from D-(+)-tryptophan methyl ester.

Affinine (**1**) was first isolated from *Peschiera affinis* (Muell. Arg.) Miers (Apocynaceae) in 1963 by Weisbach et al.,[1] while 16-epiaffinine (**2**) was isolated from the bark of *Pleiocarpa talbotii* Wernham.[2] These indole alkaloids belong to the family of 3-oxygenated sarpagine indole alkaloids which are a rare, but important group of bases because they comprise key components of a group of bisindole alkaloids shown to possess potent biological activity including antileishmanial activity.[3] The structures of a few of these bases are illustrated in Figure 1.

In the past few years, affinine (**1**) and 16-epiaffinine (**2**) have also been isolated from various other species.[3b,4,5] Vobasinediol (**3**), a derivative of affinine, was first synthesized from vobasine (**6**),[6] and later was also obtained from affinine.[2] 16-Epivobasinediol (**4**) was synthesized originally by Naranjo et al. from the alkaloid 16-epiaffinine (**2**).[2]

The structures of affinine (**1**) and 16-epiaffinine (**2**) were originally elucidated on the basis of NMR spectroscopy as well as a comparison with the data on related indole alkaloids.[2,4c,7,8] Common structural features of the 3-oxygenated sarpagine series include a 3-oxygenated 10-membered ring and the asymmetric centers at C-5(*R*), C-15(*R*), and C-16(*R*) or C-16(*S*), as well as the ethylidene double bond at C-19 and C-20 with the less stable *E* configuration. No enantiospecific total synthesis of members of this class of alkaloids has appeared, to date. Sakai and co-workers earlier reported the partial synthesis (from gardnerine) of 11-methoxy-16-epiaffinine, which contained a skeleton similar to that of 16-epiaffinine (**2**);[9] however, analysis of this work was not able to establish the C-16(*S*) stereochemistry, unequivocally for affinine. A skeleton similar to that of affinine was also synthesized by Shioiri et al. and Sundberg et al.[10] Data from this synthesis could not be employed to establish the configurations at the C(19)–C(20) double bond and at the substituents at C(16). Later, Kutney et al. reported the total synthesis of dregamine and epidregamine which also contained structures similar to affinine.[11] However, this work could not be used to determine the stereochemistry of the C(19)–C(20) double bond and of the C(16) substituents in the present series. Recently, an intramolecular palladium (enolate-mediated) cross coupling reaction has been developed to introduce the *E* configuration of the C(19)–C(20) double bond stereospecifically in 80% yield.[12] However, the chirality at C(16) in **1** and **2** still must be controlled to offer either the *S* or *R* stereochemistry at will.[13,14] Consequently in a retrosynthetic sense (Scheme 1), affinine (**1**) and 16-epiaffinine (**2**) were envisaged to arise from the alcohols normacu-

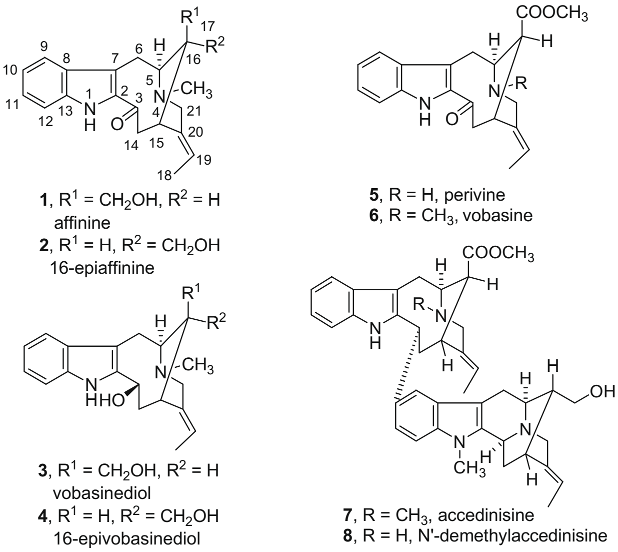

Figure 1. The structures of 3-functionalized indole alkaloids.

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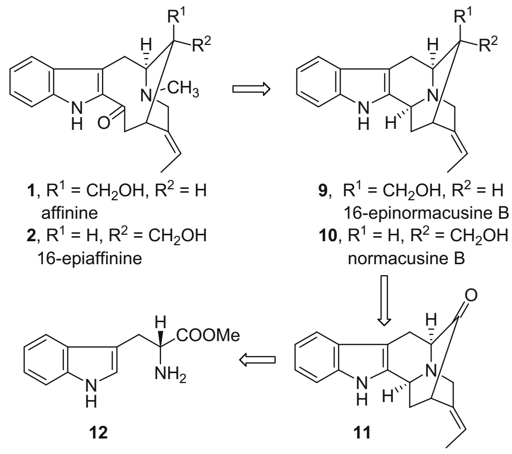
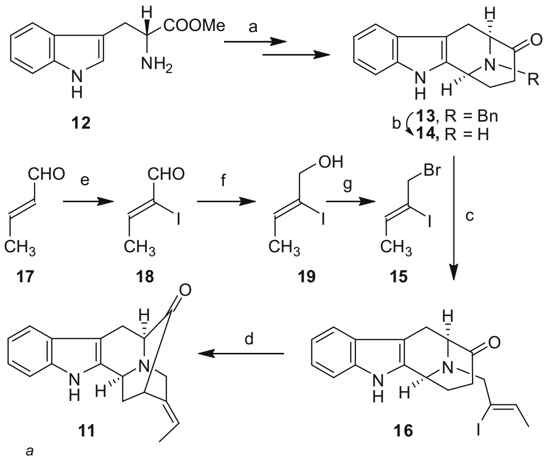


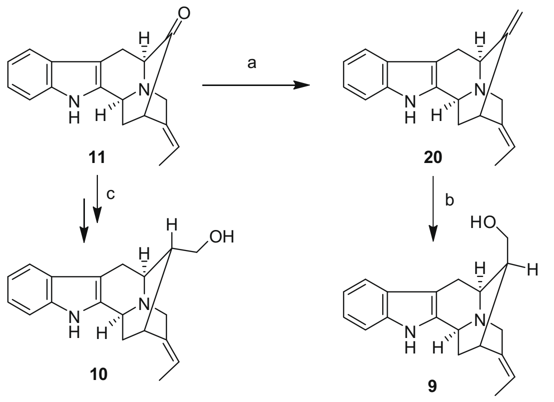
Scheme 1. Retrosynthetic analysis.

sine B (**10**) and 16-epinormacusine B (**9**), which presumably could be obtained from pentacyclic ketone (**11**).

The tetracyclic ketone (**13**) was obtained on a large scale in a two-pot process as reported previously via the asymmetric Pictet–Spengler/Dieckmann protocol.[15] The ketone (**13**) was converted into the iodoolefin (**16**),[12] in excellent yield employing debenzylation (Pd/C, H_2) and alkylation processes analogous to previous reports.[12] This olefin (**16**) was converted into the pentacyclic ketone (**11**) via an intramolecular enolate-driven Pd-mediated cross coupling (Scheme 2) or a Buchwald–Hartwig coupling.[12,13,16] The (*Z*)-1-bromo-2-iodo-butene (**15**) was a necessary component in this process.[13] This olefin had been used many times in the synthesis of other natural products.[17] In spite of the existing procedure, the stereoselectivity of this process was deemed unsatisfactory on a large scale.[18] About 5% of the *E* isomer was obtained in this reaction and the olefin had to be purified. Recently, Kraft et al. reported the α-iodination of α,β-unsaturated carbonyl compound (**17**) to offer the α-iodinated aldehyde (**18**) in 99% yield.[19,20] This was an important advancement in the large scale synthesis of olefin (**15**). Reduction of aldehyde (**18**) with $NaBH_4$ gave the alcohol (**19**)[21] and this was followed by bromination of the alcohol (**19**) to provide the desired olefin (**15**) in excellent yield on 500 gram scale.[17c,22] This improved procedure was cheaper, scalable, easier to handle, and stereospecific.



Scheme 2. Reagents and conditions: (a) see Ref. 15; (b) and (c) see Refs. 12,13; (d) 5 mol % $Pd_2(dba)_3$, 6 mol % DPEphos, 1.2 equiv NaO*t*Bu, THF, 65–75 °C, 75%; (e) see Ref. 19; (f) $NaBH_4$ (0.5 equiv), THF–H_2O (9:1), 0 °C, 95%; (g) see Refs. 17c, 21.



Scheme 3. Reagents and conditions: (a) see Ref. 14; (b) (i) 9-BBN, THF, rt; (ii) $NaBO_3·4H_2O$, THF–H_2O (1:1), rt, >90%; (c) see Ref. 13.

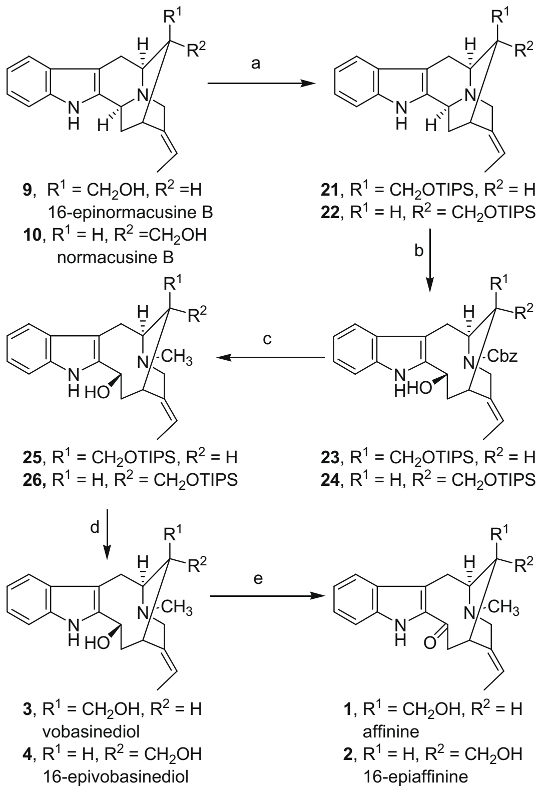
The intramolecular enolate coupling process was initially executed with the palladium source $Pd(OAc)_2$. Recently, Pd(0) was employed for this coupling reaction.[16] However, this process in the N_a–H series with (**16**) gave low yields under the reported conditions (2 mol % $Pd(dba)_2$, 2.4 mol % DPEphos, and 2.2 equiv NaO*t*Bu), as compared to the N_a-methyl substituted systems reported previously.[16]After many variations, conditions were found to be very sensitive to the amount of base and the longer the reaction time, the lower the yield.

In addition if more base was employed, more byproducts were formed. Finally, optimized conditions in the N_a–H series were found to be 5 mol % $Pd_2(dba)_3$, 6 mol % DPEphos, and 1.2 equiv NaO*t*Bu in dry THF at 65–75 °C for 3 h. This coupling furnished the desired ketone (**11**) in 70–75% isolated yield.

The synthesis of alcohols 16-epinormacusine B (**9**) and normacusine B (**10**) had been achieved recently from D-(+)-tryptophan methyl ester (Scheme 3).[12,14,23] Magnus et al. had earlier reported that the hydroboration of a related olefin intermediate (**20**) to generate a hydroxyl group at the β-axial position was particularly difficult.[24] The yields of hydroboration/oxidation process were not consistent with olefin (**20**) when the previous conditions were employed.[14,24] Consequently, the reaction conditions were modified slightly and less 9-BBN was employed; moreover, the oxidative workup was altered to Kabalka's sodium perborate ($NaBO_3$) instead of H_2O_2.[25] This modified procedure provided a higher yield (>90%) of alcohol **9** and on a consistent basis as compared to previous processes (Scheme 4).

The scission of the bond across the C(3)–N_b function in other systems has been reported.[26] However, an intramolecular C(6)–O(17) ether bond was formed when the C(3)–N_b bond was opened directly in 16-epinormacusine B (**9**).[27] Several attempts to directly cleave the C(3)–N_b bond of normacusine B (**10**) were unsuccessful. Because of this, the hydroxyl group at C(3) was protected by stirring with TIPSOTf.[23,28] The conversion of amines **21** and **22** into carbamates **23** and **24**, respectively, was carried out on treatment with Cbz–Cl.[26] Reduction of the Cbz group by $LiAlH_4$ at room temperature furnished the N_b-methyl derivatives **25** and **26**.[24] The TIPS group was removed (individually) with TBAF, to provide the diols **3** and **4**. Oxidation with activated MnO_2 gave the natural products affinine **1** and 16-epiaffinine **2** in 92% and 82% yields, respectively.[29] The spectral data for these alkaloids were in excellent agreement with the literature.[2,4c,7,8]

The first enantiospecific, stereospecific total syntheses of the 3-substituted sarpagine alkaloids vobasinediol (**3**) and affinine (**1**), as well as 16-epivobasinediol (**4**) and 16-epiaffinine (**2**) have been accomplished from commercially available D-(+)-tryptophan methyl ester. The palladium-mediated cross coupling process and



Scheme 4. Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, **21**: 85%, **22**: 82%; (b) Cbz–Cl, THF–H_2O, Na_2CO_3, **23**: 77%, **24**: 71%; (c) $LiAlH_4$, THF, rt, 12 h, **25**: 78%, **26**: 70%; (d) TBAF, THF, 0 °C, 3–4 h, **3**: 90%, **4**: 85%; (e) MnO_2, CH_2Cl_2, **1**: 92%, **2**: 82%.

the Cbz–Cl mediated scission were the key steps in these syntheses. The ability to stereospecifically prepare either epimer at C(16) at will was gratifying because the corresponding β-axial aldehyde is the thermodynamically less stable isomer. This approach should provide a general solution to the synthesis of 3-functionalized sarpagine-related indole alkaloids.

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