Enantiospecific Total Synthesis of the Sarpagine Related Indole Alkaloids Talpinine and Talcarpine: The Oxyanion−Cope Approach

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Interest in the macroline/sarpagine alkaloids originated as a result of folk tales that described the medicinal properties of the plants from which these alkaloids were isolated.[1−5] A number of alkaloids from *Alstonia angustifolia* were reported to possess antiprotozoal activity against *Entamoeba histolytica* or *Plasmodium falciparum* in vitro,[6] while other sarpagine alkaloids have been found to possess sedative, ganglionic blocking, hypoglycemic, or antibacterial activity.[2] Studies were begun to evaluate these alkaloids for activity against cancer[7] and HIV;[8,9] however, the paucity of isolable material from these species has retarded biological screening.

In 1972, Schmid et al.[10] reported the structures of the alkaloids talpinine **1** and talcarpine **2** (Figure 1), which had been isolated from the stem bark of *Pleiocarpa talbotii* Wernham. LeQuesne reported a series of interconversions between the *Alstonia* macroline-related alkaloids and **1** as well as **2**,[11] while Sakai[12] completed a partial synthesis of talcarpine **2** from ajmaline. At this time, the assignment of the chirality of the C(19) methyl group was established in talcarpine **2** and then related chemically to that in talpinine **1**.[12]

From examination of the transformations carried out by LeQuesne,[11] it was clear the macroline alkaloids[2] are related biosynthetically to the two bases from *P. talbotii*. The stereogenic centers of the sarpagine alkaloids at C(3), C(5), C(15), and C(16) are identical to those in **1** and **2**, while both series are antipodal to ajmaline at C(16). We wish to report the first stereocontrolled entry into the correct chirality of the sarpagine alkaloids at C(3), C(5), C(15), and C(16), which resulted in the enantiospecific total synthesis of **1** and **2**.

D-(+)-Tryptophan methyl ester **3** was diastereospecifically converted (via **4**) into azabicyclononone **5** in greater than 98% ee in a two-pot process on a multihundred gram scale. In contrast to the analogous process in the N_a-methyl

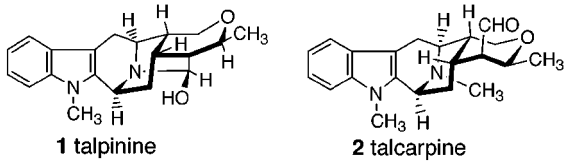

Figure 1.

series,[16] the cis diester in the N_aH series isomerized into the trans diester **4** so readily that none of the undesired cis diastereomer was observed on workup. The conditions of cyclization/isomerization (CH_2Cl_2, TFA, rt, 48 h)[17] at C(1) were much milder in the N_a-H case, as expected. The more rapid rate of isomerization (at C-1) of the cis diastereomer in the N_a-H series into the desired trans diastereomer **4** (>98% ee) was consistent with previous studies on the mechanism of this process.[13,14] Dieckmann cyclization of **4**, followed by acid-mediated decarboxylation in the second sequence, provided the desired tetracyclic ketone **5** in 80% yield. Five steps can now be executed in this two-pot process, which constitutes an important improvement over previous methods.[17] The reasons for this stem from the unique nature of N_a-H-substituted indoles in comparison to the previously reported N_a-methyl analogues.[16]

Conversion of the carbonyl function of (−)-**5** into the α,β-unsaturated aldehyde moiety of **6** via the spirooxirano-phenylsulfoxide[18,19] was accomplished in 87% overall yield by modification of the procedure of Fu.[20] The α,β-unsaturated aldehyde (−)-**6** contains the desired absolute configuration at C(3) as well as C(5) and serves as the key intermediate for the total synthesis of both **1** and **2** (see Scheme 1). From the beginning, an intramolecular sigmatropic rearrangement was envisaged to generate the correct chirality at C(15) for this series of alkaloids. An anionic oxy-Cope rearrangement would be expected to occur by the preferred chair transition state[21,22] from the bottom face of the azabicyclononene ring system (from **6**) to generate the correct chirality at C(15). However, the allylic carbanion required to provide allylic alcohol **8** would be expected to undergo an allylic rearrangement when stabilized as either the magnesium or lithium species. This obstacle was overcome by an important modification of the barium chemistry of Yamamoto et al.[23] Addition of a mixture of *trans*-1-bromo-2-pentene (**7**) and aldehyde **6** to freshly prepared barium metal at −78 °C generated the desired allylic carbanion. This barium-stabilized species added in situ at −78 °C in a 1,2-fashion to **6** in high yield without allylic rearrangement. The anionic oxy-Cope rearrangement took place in the N_a-H azabicyclononene system **8** almost exclusively from the

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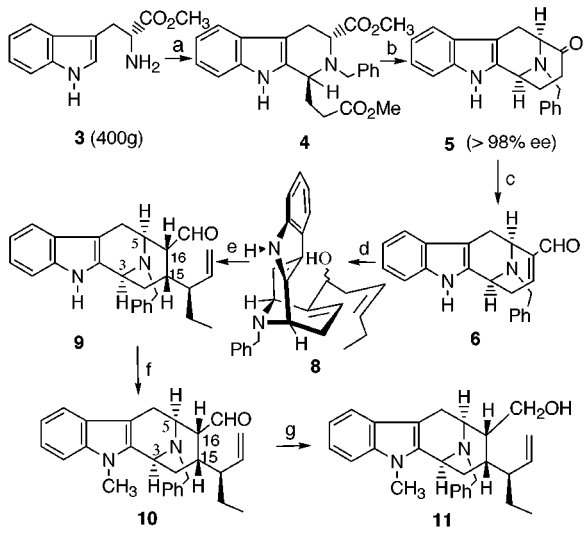
Scheme 1[a]



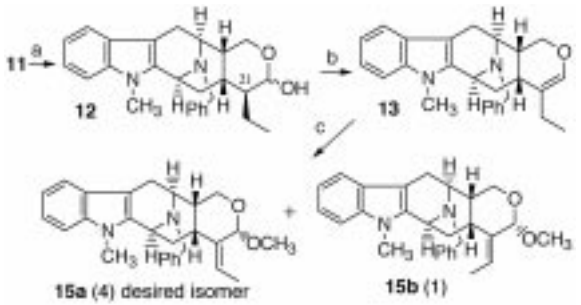
[a] Key: (a) PhCHO/CH_3OH, rt, 2 h; $NaBH_4$, −5 °C, 3 h; TFA (2.4 equiv)/CH_2Cl_2/$(CH_3O)_2CHCH_2CH_2CO_2Me$, Δ, 12 h, 83%; (b) NaH (8 equiv)/CH_3OH/reflux, 48 h; HOAc/HCl/H_2O/reflux, 10 h, 80%; (c) $ClCH_2SOPh$/LDA/THF, −78 °C; KOH, 6 h; $LiClO_4$/dioxane/reflux, 10 h, 87%; (d) a mixture of **6** and *trans*-1-bromo-2-pentene (**7**) was added to barium metal generated from Li/biphenyl/THF; dry BaI_2, −78 °C, 5 h, 90%; (e) KH/dioxane/18-crown-6/reflux, 14 h; CH_3OH, rt, 2 h, 85%; (f) NaH (1.1 equiv)/THF/MeI, rt, 6 h, 95%; (g) $NaBH_4$/MeOH, rt, 1 h, 96%.

desired bottom face of the C(15)−C(16) olefinic bond. The diastereoselectivity at C(15) was greater than 30:1 in this system to provide the correct chirality at C(15). Although the major diastereomer **9** (76%) contained the correct chirality at C(15) and C(16), it was accompanied by a minor diastereomer (12%) epimeric at the aldehydic carbon atom at C(16). This isomer, however, was completely converted into **9** on addition of methanol to the reaction mixture with continued stirring at room temperature for 2 h. The desired stereochemistry in **9** was obtained with high diastereoselectivity from **8** in 85% overall yield. The stereoselectivity of the oxy-anion Cope rearrangement here was increased significantly in comparison to the previously reported heptenyl[20] and pentenyl series in the N_a-methyl case. This sequence of reactions provides the first stereocontrolled entry into the correct chirality of the sarpagine alkaloids at C(3), C(5), C(15), and C(16). The N_a-H aldehydic olefin **9** was regiospecifically N_a-methylated in 95% yield to provide **10**, which was reduced with sodium borohydride in 95% yield to furnish monol **11**. Oxidative cleavage of the olefinic unit (latent aldehyde) in **11** gave hemiacetal **12**, which was converted into a single pure enol ether **13** on dehydration with *p*-TSA[12] in refluxing benzene.

As illustrated in Scheme 2, the regiospecific oxyselenation of olefin **13** was carried out with *N*-phenylselenophthalimide **14** in THF/methanol at 0 °C in the presence of *p*-TSA, and this was followed by treatment with $NaIO_4$. This process gave the mixture of olefins **15a** and **15b** in 90% yield with the desired isomer predominating in a ratio of 4:1. Attempts to convert the minor isomer **15b** into **15a** are currently underway.

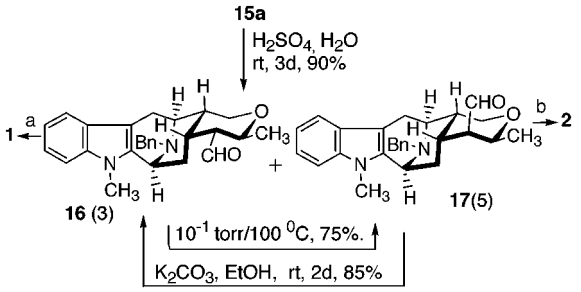
Acid-catalyzed[10,12] hydrolysis of **15a** was followed by the Michael addition of the C(17) hydroxyl group to the α,β-unsaturated aldehyde so generated to provide a mixture of N_b-benzyl-N_b-21-secotalpinine **16** and N_b-benzyltalcarpine **17** in a ratio of 3:5 in 90% yield. Both compounds obtained in this process are important, for aldehyde **16** was required for the synthesis of talpinine, while aldehyde **17** was necessary for the preparation of talcarpine. As shown in Scheme 3, the mixture of **16** and **17** was converted com-

Scheme 2[a]



[a] Key: (a) OsO_4/THF/py; $NaHSO_3$ $NaIO_4$, H_2O, MeOH, 0 °C, 3 h, 78%; (b) benzene/*p*-TSA/DST, reflux, 5 h, 95%; (c) *p*-TSA/MeOH/*N*-phenylselenophthalimide; $NaIO_4$/H_2O/THF/MeOH, 0 °C, 15 h, 90%.

Scheme 3[a]



[a] Key: combined yield from **15a**: **16** (82%) or **17** (80%); (a) EtOH/Pd/C (10 mol %), H_2, rt, 5 h, 92%; (b) MeOH/Pd/C (1.5 equiv), H_2, rt, 5 h, 90%.

pletely into the desired secotalpinine **16** on stirring in methanol in the presence of K_2CO_3. This provided the secotalpinine **16** required for the synthesis of **1** in 82% overall yield from **15a**. Conversely, **16** could be separated from **17** via flash chromatography and the secotalpinine **16** which remained then pyrolyzed[10] to provide aldehyde **17**. In this fashion, the overall yield of the necessary secotalcarpine **17** was increased to 80% (from **15a**). The process outlined in Scheme 3 is unique for either aldehyde **16** or aldehyde **17** and can be prepared in greater than 80% yield from **15a**, when desired, and in greater than 98% ee. When N_b-benzyl-N_b-21-secotalpinine **16** was subjected to the conditions of catalytic debenzylation (Pd/C, H_2) in ethanol, a 92% yield of talpinine **1** was realized. However, when **17** was stirred with excess Pd/C in methanol in the presence of hydrogen, analogous to the procedure of Fu,[20] the important N_b-benzyl-N_b-methyl transfer reaction took place to provide talcarpine **2** in 90% yield. This N_b-benzyl-N_b-methyl transfer reaction was observed in the raumacline series[20] and may have some utility in the synthesis of other N_b-methylazabicyclo[3.3.1]nonane-functionalized alkaloids. The spectral and physical properties including the optical rotations of **1** and **2** were in excellent agreement with the published values for the natural products talpinine and talcarpine, respectively.[3,10]

In conclusion, the enantiospecific total syntheses of **1** and **2** have been accomplished in 13 steps (11 reaction vessels) in 10% and 9.5% overall yields, respectively. D-(+)-Tryptophan has served here as both the chiral auxiliary and the starting material, which provides a facile route [from L-(−)-tryptophan] to the antipodes of these alkaloids, if desired.

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